European Journal of Heart Failure (2017) **19**, 1414–1423
doi:10.1002/ejhf.887

RESEARCH ARTICLE

Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry

Michel Komajda[1]*, Martin R. Cowie[2], Luigi Tavazzi[3], Piotr Ponikowski[4], Stefan D. Anker[5], and Gerasimos S. Filippatos[6], on behalf of the QUALIFY Investigators[†]

[1]Institute of Cardiometabolism and Nutrition (ICAN), Pierre et Marie Curie University, Paris VI, La Pitié-Salpétrière Hospital, Paris, France; [2]Imperial College London, Royal Brompton Hospital, London, UK; [3]Maria Cecilia Hospital, GVM Care & Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy; [4]Medical University, Faculty of Public Health, Wroclaw, Poland; [5]Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany; and [6]National and Kapodistrian University of Athens, School of Medicine, Athens University Hospital Attikon, Athens, Greece

Received 5 April 2017; revised 14 April 2017; accepted 17 April 2017; online publish-ahead-of-print 30 April 2017

Aims To evaluate the impact of physicians' adherence to guideline-recommended medications for heart failure with reduced ejection fraction (HFrEF), including ≥50% prescription of recommended doses, on clinical outcomes at 6-month follow-up.

Methods and results In QUALIFY, an international, prospective, observational, longitudinal survey, 6669 outpatients with HFrEF were recruited 1–15 months after heart failure (HF) hospitalization from September 2013 to December 2014 in 36 countries and followed up at 6 months. A global adherence to guidelines score was developed for prescription of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs) and ivabradine and their dosages. Baseline global adherence score was good in 23% of patients, moderate in 55%, and poor in 22%. At 6-month follow-up, poor adherence was associated with significantly higher overall mortality [hazard ratio (HR) 2.21, 95% confidence interval (CI) 1.42–3.44, *P*=0.001], cardiovascular mortality (HR 2.27, 95% CI 1.36–3.77, *P*=0.003), HF mortality (HR 2.26, 95% CI 1.21–4.2, *P*=0.032), combined HF hospitalization or HF death (HR 1.26, 95% CI 1.08–1.71, *P*=0.024) and cardiovascular hospitalization or cardiovascular death (HR 1.35, 95% CI 1.08–1.69, *P*=0.013). There was a strong trend between poor adherence and HF hospitalization (HR 1.32, 95% CI 1.04–1.68, *P*=0.069).

Conclusion Good adherence to pharmacologic treatment guidelines for ACEIs, ARBs, BBs, MRAs and ivabradine, with prescription of at least 50% of recommended dosages, was associated with better clinical outcomes during 6-month follow-up. Continuing global educational initiatives are needed to emphasise the importance of guideline recommendations for optimising drug therapy and prescribing evidence-based doses in clinical practice.

Keywords Adherence • Dosage • Guidelines • Heart failure with reduced ejection fraction • Medication • Outcomes

*Corresponding author. Institute of Cardiometabolism and Nutrition (ICAN), Department of Cardiology, Pierre et Marie Curie University, Paris VI, Pitié-Salpêtrière Hospital, AP-HP, 47–83 Boulevard de l'Hôpital, 75013 Paris, France. Tel: +33 1 42165514, Fax: +33 1 42163020, Email: michel.komajda@psl.aphp.fr
[†]See Supplementary material online, *Appendix S1*.
Clinical trial registration ISRCTN87465420.

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology

Introduction

Despite improvements in understanding of the pathophysiology of heart failure (HF) and significant progress in pharmacological therapy, the disease remains a substantial cause of morbidity and mortality and a considerable global burden for healthcare systems.[1–4] Prescription of evidence-based therapies recommended by international guidelines is the most effective way of ensuring that patients receive optimal care.[5] Although physicians are encouraged to implement such guidelines in practice, it has been repeatedly observed that a sizeable proportion of HF patients do not receive evidence-based treatments. A study analysing care delivered to over 15 000 HF patients in outpatient settings found that a median of 27% of patients received all HF therapies for which they were potentially eligible, and use of guideline-recommended therapies varied widely between practice settings.[6] More recently, data from the National Heart Failure Audit of nearly 57 000 HF admissions in England and Wales in 2014–2015 showed that only 42% of HF patients were discharged on angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs).[7]

There is some evidence that good adherence to guidelines can improve clinical outcomes. For example, in a multicentre, observational study on the medical management and cost of chronic HF carried out in six European countries between 2001 and 2002, adherence to treatment guidelines was a strong predictor of fewer cardiovascular (CV) hospitalizations.[8] However, even when prescription of guideline-based HF treatment is high, there is evidence of frequent failure to reach target doses[9] and there is evidence from some, though not all studies, that sub-optimal dosing may adversely influence outcomes.[10,11]

We therefore decided to gain a global perspective on the impact of adherence to guideline-recommended medication for HF, including prescription of recommended doses, on clinical outcomes. The international survey QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) assessed adherence to five classes of medications recommended for HF with reduced ejection fraction (HFrEF) by the European Society of Cardiology (ESC) guidelines, ACEIs, ARBs, BBs, MRAs and ivabradine.[12] We have previously reported baseline characteristics and guideline adherence scores for the study population at enrollment.[13] In the present analysis, we report the impact of physicians' adherence to the same guideline-recommended classes of HF medication, including prescription of recommended doses, on clinical outcomes at 6-month follow-up.

Methods

Study design and population

QUALIFY is an international, prospective, observational, longitudinal survey of outpatients with HFrEF treated at 547 centres in 36 countries in Africa, Asia, Australia, Europe, the Middle East, and North, Central and South America.

Survey participants were adult outpatients (>18 years old) with chronic HF diagnosed according to the participating investigator's clinical judgement, with left ventricular ejection fraction (LVEF) ≤40% (on the most recent echocardiogram, ≤2 years), who had been hospitalized for worsening HF within the previous 1–15 months. Information collected at baseline included demographics, medical history, CV risk factors and lifestyle, results of physical examination, current symptoms, most recently available investigations, including electrocardiogram, echocardiography and laboratory data, and current medical treatments. Details of the study design, baseline evaluation and data management have been published previously.[13] The survey involved physicians and we assessed physicians' adherence to guideline-recommended medications in HFrEF.[13]

Key clinical outcomes assessed at 6-month follow-up were all-cause mortality, CV death, HF death, HF hospitalization, HF hospitalization or HF death, CV hospitalization or CV death. Events were reported by investigators and were not centrally adjudicated. Between 10% and 15% of the centres in each country were audited as a means of face-to-face quality control (1397 patients in total at baseline and follow-up visits). Data in source documents were compared with data recorded and the results of the audit were satisfactory in most cases. When quality control problems occurred, a face-to-face discussion was organized with investigators and cross checks made between source documents and recorded data.

Global adherence to guideline score

The global adherence to guideline score used in QUALIFY was based on physicians' adherence to the latest ESC HF guideline recommendations at the time the study registry was established.[12] The score related to five classes of medications associated with significant improvement in morbidity or mortality in large randomised controlled trials (RCTs), and recommended by the ESC for reduction of 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, heart rate ≥70 or 75 b.p.m., NYHA class II–IV).[12] Having previously identified under-dosage of recommended medications as an issue in our baseline QUALIFY analysis,[13] we integrated adherence to target doses of recommended medications into the adherence score for the current 6-month outcome analysis.

The adherence score was 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 in ≥50% of recommended dosages (*Table S1*). The number of patients prescribed medication at ≥50% target dose was assessed using doses defined by the ESC guidelines when available;[12] for ivabradine, we used the therapeutic regimen used in the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT).[14]

The score was calculated for each patient by summing the points attributed as follows: 0 points for non-prescription in the absence of contraindications, 0.5 points for use of <50% of target dosage (<100% of target dose for MRA as the majority of patients were treated with ≥50% of target dose of MRA) or 1 point for use in ≥50% of target dosage (target dose for MRA). Non-administration of recommended drugs due to specific contraindications or intolerance was scored as adherence to guidelines. The score ranged from 0 (very poor) to 1 (excellent) and we defined three levels of adherence: good adherence (score =1); moderate adherence (score >0.5 to <1) and poor adherence (score ≤0.5). In this survey, our term 'adherence' relates solely to physicians following guidelines, not to patient compliance or persistence.

© 2017 The Authors

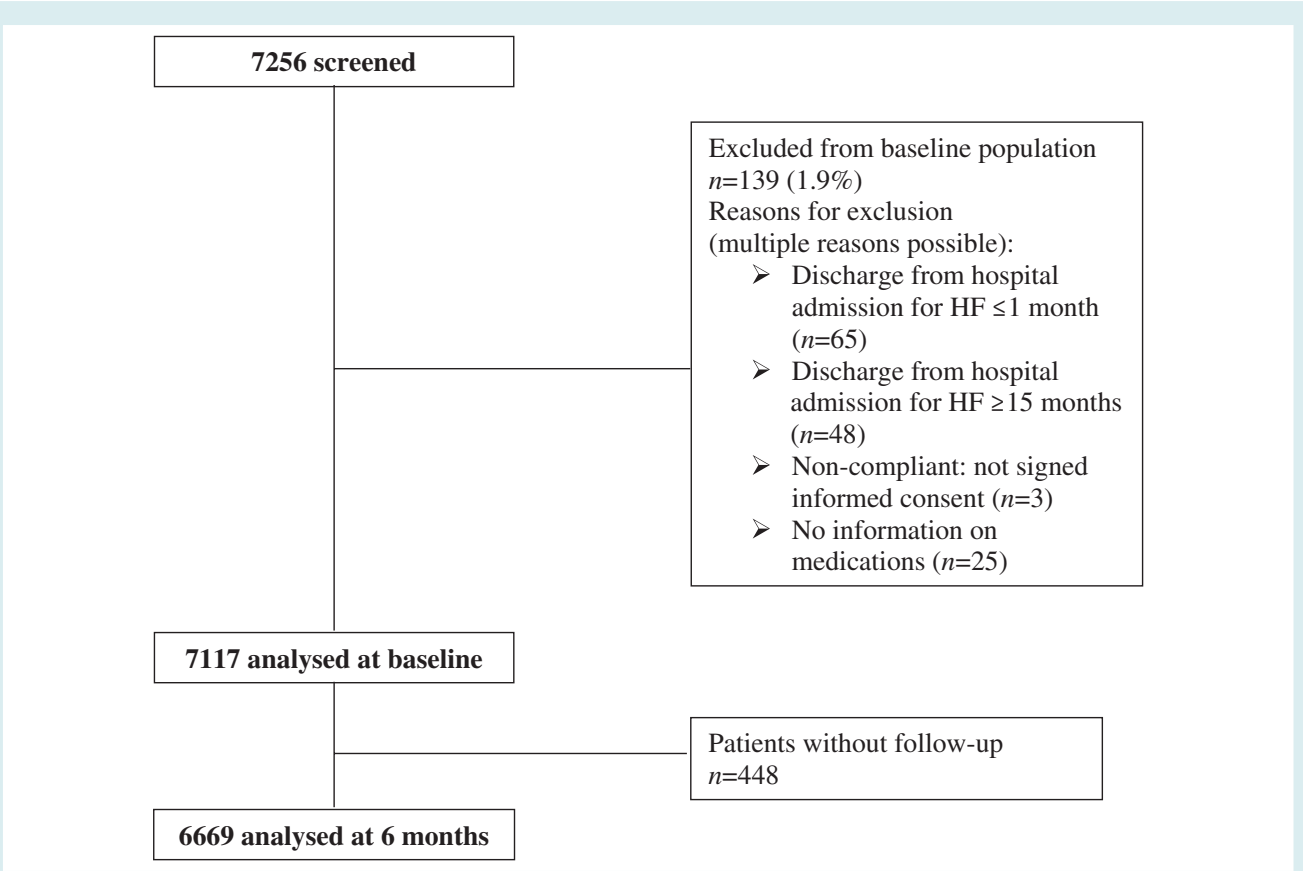

Figure 1 Study population. HF, heart failure.

The survey was conducted according to the rules of 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.

Statistical analysis

This analysis has been conducted in patients with 6-month follow-up information and known adherence score at baseline. Baseline characteristics for three adherence groups – good (score =1), moderate (score >0.5 to <1) and low (score ≤0.5) are presented using descriptive statistics as numbers and percentages for categorical variables, and means ± standard deviation or median for continuous variables. Baseline values were compared between groups using an analysis of variance (ANOVA) test for quantitative variables and chi-square test or Fisher's exact test for qualitative variables.

Individual and composite clinical outcomes were analysed based on the time to first event. The data were analysed using Cox proportional hazards regression models to calculate hazard ratios (HRs), corresponding 95% confidence intervals (CIs), and *P*-values, for each adherence group.

Univariate analysis was conducted using potential covariates such as age, gender, time to HF diagnosis, coronary artery disease, diabetes, hypertension, asthma/chronic obstructive pulmonary disease, chronic kidney disease, heart rate and LVEF. Significant covariates were selected with a threshold of 1% in the univariate analysis. Multivariate analysis was conducted using a stepwise method by selecting significant covariates with a threshold of 5%.

Statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 7256 patients were screened between September 2013 and December 2014 and baseline treatment adherence scores were analysed and reported for 7117 patients (data extraction July 2016) (*Figure 1*). Follow-up data were unavailable for 448 patients, and results are reported for the remaining 6669 patients.

The global adherence score at baseline (ACEIs/ARBs, BBs, MRAs and ivabradine) was good in 23% of patients, moderate in 55%, and poor in 22% (*Figure 2*). The influence of age, sex, ethnicity, co-morbidities and symptoms at baseline is shown in *Table 1*. Mean age was similar in groups with good, moderate or poor adherence scores, though there was a non-significant trend towards more patients ≥74 years in the poor adherence group ($P = 0.109$). Approximately three quarters of patients were male, with a slightly higher proportion of women in the poor adherence group than in the good or moderate groups ($P = 0.008$). Significantly more

© 2017 The Authors

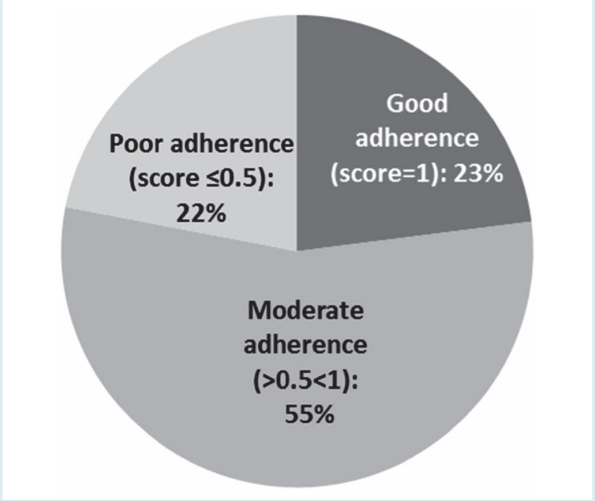

Figure 2 Global adherence to guideline score at baseline.

patients with a good adherence score were Caucasian than Asian (including Middle East population) ($P < 0.001$). A significantly higher proportion of patients with a good adherence score had atrial fibrillation/flutter ($P < 0.001$), coronary artery bypass graft ($P = 0.002$), diabetes mellitus ($P < 0.001$), dyslipidaemia ($P < 0.001$), or history of hypertension ($P < 0.001$). In addition, a significantly higher proportion had a medical history of asthma or chronic obstructive pulmonary disease ($P < 0.001$), or chronic kidney disease ($P < 0.001$). In contrast, a significantly higher proportion of patients with a poor adherence score had a history of cancer than those with a high score ($P = 0.043$). Amongst patients with a good adherence score, 49.3% had ≥3 co-morbidities, compared to 37.9% in the group with poor adherence score ($P < 0.001$). Body mass index and systolic and diastolic blood pressure were significantly higher in the group with a good adherence score than in the moderate or poor adherence groups ($P < 0.001$ for all parameters).

A higher proportion of patients in the good adherence group were in NYHA class I ($P < 0.001$) compared with patients in the poor adherence group, while slightly more patients in the poor adherence group had NYHA class IV compared with patients in the good adherence group ($P < 0.001$). Median LVEF was comparable across the high, moderate and poor adherence groups (32.2%, 31.6% and 32.3%, respectively; $P = 0.004$).

Adherence according to baseline medication

Table 2 and *Table S2* show adherence score to prescription of medication at baseline. In the group with poor adherence scores, significantly fewer patients were prescribed ACEIs ($P < 0.001$), BBs ($P < 0.001$), MRAs ($P < 0.001$), ivabradine ($P < 0.001$), diuretics ($P < 0.001$), anticoagulants ($P < 0.001$), and statins ($P < 0.001$). With the exception of BBs, patients in the good adherence group had highest prescribing levels for these classes of drugs. Beta-blockers were most commonly prescribed in the moderate adherence group.

There was also a trend towards greater use of devices in patients in the good adherence group, with significantly more patients having implantable cardioverter-defibrillators ($P = 0.001$).

Outcomes at 6 months

Good adherence score at baseline was consistently associated with better clinical outcomes at 6-month follow-up than moderate or poor adherence score (*Table 3* and *Figure 3*). Multivariate analysis showed that poor adherence score was associated with significantly higher all-cause mortality than good adherence score (HR 2.21, 95% CI 1.42–3.44, $P = 0.001$). Poor adherence score was also associated with significantly higher CV mortality (HR 2.27, 95% CI 1.36–3.77, $P = 0.003$), HF mortality (HR 2.26, 95% CI 1.21–4.2, $P = 0.032$), combined HF hospitalization or HF death (HR 1.26, 95% CI 1.08–1.71, $P = 0.024$) and CV hospitalization or CV death (HR 1.35, 95% CI 1.08–1.69, $P = 0.013$). In addition, there was a strong trend between poor adherence score and HF hospitalization (HR 1.32, 95% CI 1.04–1.68).

Discussion

Our current analysis showed that (i) adherence to five classes of medications recommended for HFrEF by the ESC at the time the study was initiated[12] was satisfactory; (ii) integration of dosages of these medications into the adherence assessment reduced significantly the proportion of patients with good adherence to 23%; (iii) good adherence to ESC guidelines for the prescription of ACEIs/ARBs, BBs, MRAs and ivabradine, with ≥50% of recommended dosages, was associated with improved clinical outcomes during 6-month follow-up.

Adherence versus outcomes: evidence from observational studies

As demonstrated by our initial analysis and in several observational studies including data from the British National HF audit, adherence to HF guidelines regarding use of appropriate classes of therapy has improved considerably over the past decade from approximately a quarter of prescriptions in 2008[6] to nearly two thirds in 2016.[7,13] However, our earlier analysis showed that simple calculation of the percentage of treated patients may not be an adequate measure to indicate the quality of healthcare provided for HF patients, and that under-dosing of recommended therapies is a major issue. In that analysis, the proportion of patients at target dose and ≥50% of target dose was low for most medications (28% and 63% for ACEIs, 7% and 39% for ARBs, 15% and 52% for BBs, 71% and 99% for MRAs, and 27% and 86% for ivabradine).[13] Data from the ESC Heart Failure Long-Term Registry reported in 2013 showed similar trends, with fewer than one-third of patients on guideline-recommended target dosages (29% for ACEIs, 24% for ARBs, 17% for BBs, and 30% for MRAs).[9]

Similarly, a recent European survey (BIOSTAT-CHF) conducted in 11 countries and enrolling 2500 patients showed that only a minority of patients reached the target dose of ACEIs and BBs recommended by the ESC guidelines.[15]

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology

Table 1 Characteristics of the study population

	Good ($n = 1543$)	Moderate ($n = 3631$)	Poor ($n = 1495$)	*P*-value
Demographic characteristics				
Age (years)	62.7 ± 12.2	63.0 ± 12.7	63.5 ± 12.6	0.218
Age ≥74 years	316 (20.5%)	803 (22.1%)	363 (24.3%)	0.109
Male	1152 (74.7%)	2731 (75.2%)	1063 (71.1%)	0.008
Ethnic origin				<0.001
Caucasian	1069 (69.3%)	2145 (59.1%)	703 (47.0%)	
Asian (including Middle East population)	301 (19.5%)	1029 (28.4%)	612 (40.9%)	
Other	158 (10.2%)	424 (11.7%)	163 (10.9%)	
Cardiac disease history/co-morbidities				
HF duration (years)	4.3 ± 4.8	4.1 ± 4.8	3.7 ± 4.8	0.008
Two or more HF hospitalizations (last 12 months)	490 (31.8%)	1113 (30.7%)	496 (29.3%)	0.765
Time since last HF discharge (months)	6.3 ± 2.9	6.2 ± 2.8	6.4 ± 2.9	0.092
Coronary artery disease	848 (55.3%)	1909 (52.9%)	757 (50.9%)	0.054
Atrial fibrillation/flutter	492 (31.9%)	1057 (29.2%)	374 (25.1%)	<0.001
Myocardial infarction	739 (48.2%)	1671 (46.3%)	634 (42.6%)	0.007
Percutaneous coronary intervention	406 (26.5%)	932 (25.8%)	361 (24.3%)	0.351
Coronary artery bypass graft	255 (16.6%)	471 (13.1%)	193 (13.0%)	0.002
Left bundle branch block	244 (18.2%)	660 (20.8%)	249 (19.3%)	0.102
Stroke or TIA	186 (12.1%)	383 (10.6%)	153 (10.3%)	0.192
Peripheral arterial disease	150 (9.8%)	349 (9.7%)	133 (8.9%)	0.666
Diabetes mellitus	598 (38.9%)	1210 (33.5%)	451 (30.3%)	<0.001
Dyslipidaemia	964 (62.8%)	2019 (56.0%)	714 (48.0%)	<0.001
Hypertension	1085 (71.0%)	2311 (64.2%)	865 (58.2%)	<0.001
Medical history				
Asthma or COPD	272 (17.7%)	489 (13.5%)	170 (11.4%)	<0.001
Chronic kidney disease	304 (19.8%)	663 (18.4%)	210 (14.1%)	<0.001
Depression	115 (7.5%)	227 (6.3%)	70 (4.7%)	0.006
Cancer	39 (2.5%)	110 (3.1%)	61 (4.1%)	0.043
Co-morbidities number				<0.001
≥2	783 (50.7%)	2083 (57.3%)	928 (62.1%)	
≥3	760 (49.3%)	1548 (42.6%)	567 (37.9%)	
Time of inclusion after HF hospitalization				0.341
<6 months after hospitalization for HF	808 (52.9%)	1963 (54.7%)	785 (52.9%)	
≥6 months after hospitalization for HF	720 (47.1%)	1626 (45.3%)	699 (47.1%)	
Clinical status/laboratory data				
Body mass index (kg/m^2)	29.13 ± 5.72	27.79 ± 5.17	26.94 ± 5.04	<0.001
Systolic blood pressure (mmHg)	128.9 ± 20.3	125.5 ± 20.0	125.4 ± 20.4	<0.001
Diastolic blood pressure (mmHg)	77.2 ± 12.3	76.0 ± 12.3	75.6 ± 12.4	<0.001
Resting heart rate (b.p.m.)	74.7 ± 14.1	76.6 ± 14.3	77.0 ± 14.6	<0.001
NYHA class				<0.001
I	244 (15.8%)	394 (10.9%)	189 (12.7%)	
II	669 (43.4%)	1684 (46.4%)	714 (47.8%)	
III	561 (36.4%)	1353 (37.3%)	491 (32.9%)	
IV	68 (4.4%)	195 (5.4%)	99 (6.6%)	
Fasting blood glucose (mmol/L)	6.81 ± 2.62	6.55 ± 2.60	6.42 ± 2.63	<0.001
Serum creatinine (μmol/L)	111.21 ± 66.18	109.39 ± 59.96	106.29 ± 70.46	0.132
Haemoglobin (g/L)	134.85 ± 20.75	134.90 ± 20.25	135.23 ± 20.92	0.874
BNP (pmol/L), outpatients value, median	87.45	123.16	123.02	0.631
NT-proBNP (pmol/L), outpatients value, median	265.32	242.73	177.12	0.166
LVEF	32.2 (6.8%)	31.6 (6.9%)	32.3 (7.6%)	0.004

BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, *N*-terminal proBNP; NYHA, New York Heart Association; TIA, transient ischaemic attack.

© 2017 The Authors

Table 2 Pharmacological treatments and devices

	Good ($n = 1543$)	Moderate ($n = 3631$)	Poor ($n = 1495$)	Total ($n = 6669$)	*P*-value
ACEIs	1129 (73.2%)	2484 (68.4%)	800 (53.5%)	4413 (66.2%)	<0.001
≥50% TD*	1128 (>99.9%)	1747 (70.4%)	319 (39.9%)	3194 (72.4%)	<0.001
ARBs	269 (17.4%)	809 (22.3%)	325 (21.7%)	1403 (21%)	<0.001
≥50% TD*	267 (99.3%)	326 (40.4%)	75 (23.1%)	668 (47.7%)	<0.001
Beta-blockers	1306 (84.6%)	3290 (90.6%)	1182 (79.1%)	5778 (86.6%)	<0.001
≥50% TD*	1306 (100%)	1447 (44.0%)	266 (22.5%)	3019 (52.2%)	<0.001
MRAs	1218 (78.9%)	2797 (77.0%)	617 (41.3%)	4632 (69.5%)	<0.001
100% TD*	1132 (92.9)	1923 (68.8%)	198 (32.1%)	3253 (70.2)	<0.001
Ivabradine	635 (43.6%)	1105 (35.3%)	156 (14.4%)	1896 (33.4%)	<0.001
≥50% TD*	595 (93.7%)	926 (83.8%)	116 (74.4)	1637 (86.3%)	<0.001
Digoxin	383 (24.9%)	979 (27.0%)	369 (24.7%)	383 (24.9%)	0.116
Diuretic	1349 (87.4%)	3097 (85.3%)	1119 (74.8%)	1349 (87.4%)	<0.001
Nitrate	354 (23.0%)	832 (23.0%)	335 (22.4%)	354 (23.0%)	0.902
Anticoagulant	545 (35.4%)	1156 (31.9%)	408 (27.3%)	545 (35.4%)	<0.001
Antiplatelet	989 (64.2%)	2412 (66.5%)	986 (66.0%)	989 (64.2%)	0.276
Amiodarone	196 (12.7%)	445 (12.3%)	180 (12.0%)	196 (12.7%)	0.839
ICD	185 (12.1%)	344 (9.5%)	123 (8.3%)	185 (12.1%)	0.001
CRT-P	43 (2.8%)	101 (2.8%)	23 (1.5%)	43 (2.8%)	0.024
CRT-D	110 (7.2%)	249 (6.9%)	85 (5.7%)	110 (7.2%)	0.209
Non-CRT pacemaker	93 (6.3%)	200 (5.7%)	95 (6.5%)	93 (6.3%)	0.517

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CRT-D, cardiac resynchronization with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; TD, target dose.
*Number of patients at TD or at ≥50% TD was assessed for doses defined by the current European Society of Cardiology guidelines when available.[12] For ivabradine, the TD was 7.5 mg b.i.d. based on the therapeutic regimen used in SHIFT.[14]

Several observational studies have explored the association between class adherence to guideline-recommended therapies and clinical outcomes in HF,[8,16] but the use of dosage as a marker of good adherence has been used less frequently.[15]

The Austrian Heart Failure Registry showed that improvement in guideline adherence related to dose escalation towards optimal levels is associated with reduced long-term mortality in ambulatory HFrEF subjects surviving 1 year after registration.[17] Similarly the BIOSTAT-CHF registry showed that patients receiving >50% or recommended doses of ACEIs and BBs had better outcomes than those taking lower doses.[15]

There is therefore evidence from observational studies that dosage of recommended therapies matters.

Dosage and outcomes: evidence from clinical trials

Several randomised clinical trials have explored the relationship between dosage and clinical outcomes. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial demonstrated that although there were no significant differences in all-cause or CV mortality in patients using higher versus lower doses of lisinopril, there was a lower relative risk of the composite endpoint of total mortality plus hospitalization for any reason, as well as for HF hospitalizations.[10] However, high doses of lisinopril were associated with more adverse events, such as hypotension, dizziness and worsening renal function. The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial evaluated three carvedilol doses in patients with HF.[18] Although this trial was not designed to evaluate the effect of carvedilol on survival, the lowest 6-month mortality was noted in the highest dose group. Finally, the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial showed that high-dose losartan, compared with low-dose losartan, can reduce mortality and readmission to hospital in patients with HF, supporting the value of up-titrating ARB doses to confer clinical benefit.[11]

Other large-scale HF trials have performed post-hoc analyses evaluating the effect of dose on mortality reduction. In the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), risk reduction was similar in the high- and low-dose subgroups which, at least partly, may be the result of similar beta-blockade as judged from the heart rate response.[19] The results support the idea of an individualised dose-titration regimen, which is guided by patient tolerability and the heart rate response. A similar outcome was reported in a secondary analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), showing significant and similar relative reductions in mortality by low, moderate and high daily doses of bisoprolol versus the corresponding randomised placebo groups.[20]

Although post-hoc analyses have limitations, these results together with those of the randomised trials mentioned above suggest that reaching a high dose of recommended medications may favourably influence clinical outcomes.

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology

Table 3 Relationship between adherence score and 6-month outcomes

Baseline adherence score	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*, group effect	HR (95% CI)	*P*, group effect
HF hospitalization or HF death		0.0170		0.024
Moderate vs. good	1.26 (1.05;1.52)		1.22 (1.01;1.47)	
Poor vs. good	1.34 (1.07;1;67)		1.36 (1.08;1.71)	
HF hospitalization		0.0574		0.069
Moderate vs. good	1.23 (1.02;1;49)		1.19 (0.98;1.45)	
Poor vs. good	1.29 (1.02;1.63)		1.32 (1.04;1.68)	
HF death		0.0199		0.032
Moderate vs. good	1.89 (1.11;3.22)		1.84 (1.07;3.18)	
Poor vs. good	2.31 (1.27;4.20)		2.26 (1.21;4.20)	
CV death		0.0056		0.003
Moderate vs. good	1.85 (1.23;2.81)		2.06 (1.32;3.20)	
Poor vs. good	2.08 (1.29;3.34)		2.27 (1.37;3.77)	
All-cause death		0.0048		0.001
Moderate vs. good	1.64 (1.14;2.34)		1.85 (1.26;2.72)	
Poor vs. good	1.96 (1.30;2.97)		2.21 (1.42;3.44)	
CV hospitalization or CV death		0.0094		0.013
Moderate vs. good	1.30 (1.09;1.55)		1.27 (1.06;1.53)	
Poor vs. good	1.32 (1.06;1.64)		1.35 (1.08;1.69)	

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

Adherence level: a multifactorial situation

Different factors, both medical (patients and physicians) and economic, play an important role in adherence level. Patient factors can influence the adherence level through contraindications, poor tolerability of recommended medications and poor compliance. We did indeed observe that poor adherence was more common in older patients, in patients with the most severe HF (NYHA class IV) and in those with cancer, suggesting that patient frailty may have played a role. In the BIOSTAT-CHF registry, it was observed that patients not reaching recommended doses owing to symptom severity, side effects and non-cardiac organ dysfunction had the highest mortality rate.[15] In the QUALIFY population, we found that more patients had co-morbidities in the good adherence group compared with moderate and poor adherence groups. This observation is counter-intuitive and in contrast with the perception that multimorbidity implies polypharmacy with a consequent poor adherence to treatments. However, research has shown that the relationship between the number of co-morbidities and adherence is inconsistent, due to conflicting results. Some data suggest that having more co-morbidity is related to a lower level of adherence,[21] whereas other studies have shown no impact of co-morbidities on adherence.[22,23] When analysed, drug adherence appears to be quite a complex phenomenon. A poor adherer to treatments is also a poor adherer to a healthy lifestyle and has characteristics of a phenotype carrying a high risk of premature death. In several RCTs and in a meta-analysis, patient non-adherers to placebo have a nearly 40% higher probability of dying than patient adherers to placebo.[24,25]

In addition, we could not exclude the fact that some patients were still in the uptitration phase of disease-modifying medications since the lower time window for inclusion in our registry was 1 month after hospitalization for HF. Data from the ESC-HF Long-Term Registry showed that in approximately one-third of patients not achieving target dosages, a drug up-titration was still ongoing, while for about another third of patients not achieving the target, a clear reason was not reported.[9] However, we did not find any significant differences in adherence score and dosages between patients included less than 6 months after previous hospitalization for HF and those included 6 months or later. Finally, if the achieved dosage provides useful information about the quality of care, it is not sufficient in isolation as it may be influenced by the fact that some patients tolerate higher doses because their cardiac reserve is better. Body mass index may also play a role and was, for example, lower in our Asian population than in other patient groups (data not shown).

Physicians' awareness is another important factor. It has been shown that dissemination of guidelines through communication campaigns improves the rate of prescription of recommended medications.[26] In the advanced elderly patient population with HF, physicians' reluctance to provide disease-modifying drugs and focus on symptom relief is well documented.[27]

Adherence to recommended clinical practices is also strongly related to access to treatments and affordability, which are the consequence of national economic status. The general organization of healthcare systems and the existence of reimbursement schemes, as well as incentives or obligations to comply with guideline recommendations, play an important role.[28,29] Inevitably, these factors influence any adherence score, particularly the use of expensive

© 2017 The Authors

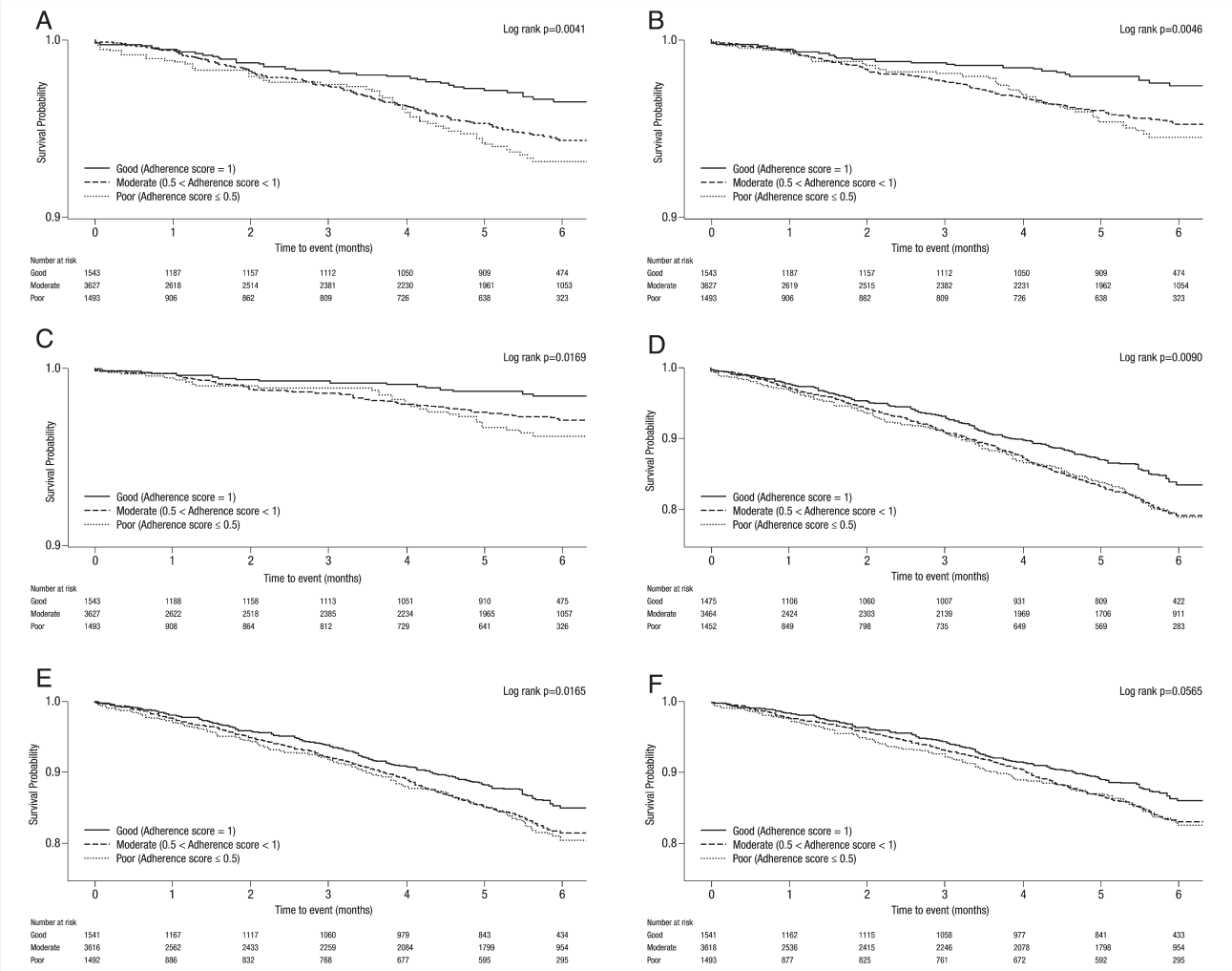

Figure 3 Event-free curves for overall mortality (*A*), cardiovascular (CV) mortality (*B*), heart failure (HF) mortality (*C*), CV hospitalization or CV death (*D*), HF hospitalization or HF death (*E*), and HF hospitalization (*F*) in HF patients with good, moderate and poor physicians' adherence to guidelines.

procedures such as implantable defibrillators or cardiac resynchronization therapy, which have demonstrated clear benefit in randomised trials. Overall use of these interventions was low in our survey, especially in countries with low income.

Limitations

The population enrolled in our survey was relatively young and this may not necessarily reflect the overall profile of HF in elderly patients.

As with all observational studies, the possibility for unmeasured bias exists, leading to overestimation or underestimation of treatment effects. In particular, adherence behaviour to treatments is known to influence outcomes in itself, as shown by measures of adherence to placebo.[30] Although the registry was conducted in five continents, some geographic areas are underrepresented such as Africa, South America and the United States, as well as some large European countries including the UK and Italy. As centres were selected by national coordinators, on a voluntary basis, selection bias cannot be excluded. Recommendations were made to each centre to recruit consecutively but we were unable to verify this procedure.

In particular, we may have underestimated the role of economic factors in countries with low gross national product per capita. This probably explains the low rate of use of devices such as implantable defibrillators and cardiac resynchronization therapy, which have demonstrated benefit in clinical trials.

The vast majority of the investigators were cardiologists, and our survey does not therefore necessarily reflect adherence to guidelines and drug dosage in patients in the care of general practitioners or internists.

We used our adherence score (good, moderate, poor) in relation to prescription and dosages of the five core therapies recommended for HFrEF at the time QUALIFY was initiated. It was therefore based on the ESC HF recommendations published in

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology

2012[12], and the use of angiotensin receptor neprilysin inhibitor therapy was not captured.

Although drug dosage was integrated into our adherence score, the current analysis of QUALIFY data does not include information about reasons for under-dosing, such as intolerance.

Clinical outcomes were reported by investigators and, although they were given guidance about how these should be assessed, we cannot exclude some variability in reporting.

Conclusion

Our analysis demonstrates that good adherence to contemporary pharmacologic treatment guidelines as determined by prescription of ACEIs/ARBs, BBs, MRAs and ivabradine, in dosages at least 50% of those recommended, is associated with improved mid-term clinical outcomes. Our results reinforce the importance of full implementation of guideline recommendations into clinical practice, and suggest that quality performance metrics for HF in hospitals or healthcare systems should involve global adherence to all medications and dosages. They provide further rationale for performance improvement, and the global use of educational initiatives and disease management programmes to support implementation of guideline-recommended HF therapies, at evidence-based target doses, into clinical practice. Further research is needed to investigate the common causes for failure to adhere to guideline recommendations for drug doses of HF medications, including the potential role of physician-related factors as well as patient-related factors including lack of awareness or intolerance.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. QUALIFY Investigators.

Table S1. Algorithms for global adherence to guideline score.

Table S2. Type and doses of evidence-based heart failure treatments.

Acknowledgements

Writing assistance was provided by Jenny Bryan and funded by Servier. The authors thank Dr Irina Elyubaeva for her support in the setup of the registry.

Funding

The study was supported by a research grant from Servier, France. The funding source had no role in the study design, in the analysis and interpretation of the data, and in the decision to submit the manuscript for publication but did assist with the setup, data collection, and management of the study in each country. The sponsor funded editorial support for editing and revision of the manuscript and received the manuscript for review before submission.

Conflict of interest: M.K. reports personal fees from AstraZeneca, BMS, Menarini, Novartis, Amgen, Servier, MSD, Novo Nordisk and Sanofi, outside the submitted work. M.R.C. reports personal fees from Servier and Novartis, outside the submitted work. L.T. reports personal fees from Servier as Trial Committee member, within the submitted work, and personal fees from Cardiorentis and CVIE Therapeutics for trial committee membership, outside the submitted work. P.P. reports grants, personal fees and other from Servier, during the conduct of the study; personal fees and other from Amgen, personal fees and other from Novartis; personal fees from Berlin Chemie, personal fees and other from Bayer; grants, personal fees and other from Vifor Pharma, grants, personal fees and other from Cibien; personal fees and other from Cardiorentis, personal fees and other from Respicardia; personal fees and other from Abbott Vascular, personal fees from Coridea, and personal fees from Celladon, outside the submitted work. S.D.A. reports fees for consultancy and/or speaking from Servier, Vifor, Bayer, Boehringer Ingelheim and Novartis, and support for research from Abbott Vascular, Vifor. G.S.F. reports that he was a committee member of trials and registries sponsored by Bayer, Novartis, Servier and Vifor.

References

1. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, Di Lenarda A, Mortara A, Oliva F, Maggioni AP; IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: the one-year follow-up results of IN-HF outcome registry. *Circ Heart Fail* 2013;**6:**473–481.
2. Maggioni AP, Dahlstrom 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. 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.
7. British Society for Heart Failure. *National Heart Failure Audit, April 2014–March 2015*. https://www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/heartfailurepublication14_15 (17 February 2017).
8. 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.
9. 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; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology

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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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 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.
16. 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.
17. 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, Keroe D, Groebner H, Auer J, Jakl G, Hallas A, EssM, 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.
18. 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.
19. 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.
20. 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.
21. Granger BB, Ekman I, Granger CB, Ostergren J, Olofsson B, Michelson E, McMurray JJ, Yusuf S, Pfeffer MA, Swedberg K. Adherence to medication according to sex and age in the CHARM programme. *Eur J Heart Fail* 2009;**11**:1092–1098.
22. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;**21**(11 Suppl):S212–S220.
23. Mathes T, Jaschinski T, Pieper D. Adherence influencing factors—a systematic review of systematic reviews. *Arch Public Health* 2014;**72**:37.
24. Yue Z, Cal C, Ai-Fang Y, Feng-Min T, Li C, Bin W. The effect of placebo adherence on reducing cardiovascular mortality: a meta-analysis. *Clin Res Cardiol* 2014;**103**:229–235.
25. Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJ, Yusuf S, Michelson EL, Pfeffer MA; CHARM Investigators. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. *Lancet* 2005;**366**:2005–2011.
26. De Groote P, Isnard R, Clerson P, Jondeau G, Galinier M, Assyag P, Demil N, Ducardonnet A, Thebaut JF, Komajda M. Improvement in the management of chronic heart failure since the publication of the updated guidelines of the European Society of Cardiology. The Impact-Reco-Programme. *Eur J Heart Fail* 2009; **11**:85–91.
27. 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.
28. Peterson PN, Chan PS, Spertus JA, Tang F, Jones PG, Ezekowitz JA, Allen LA, Masoudi FA, Maddox TM. Practice-level variation in use of recommended medications among outpatients with heart failure: insights from the NCDR PINNACLE program. *Circ Heart Fail* 2013;**6:**1132–1138.
29. Maggioni AP, Van Gool K, Biondi N, Urso R, Klazinga N, Ferrari R, Maniadakis N, Tavazzi L. Appropriateness of prescriptions of recommended treatments in Organisation for Economic Co-operation and Development Health Systems: findings based on the Long-Term Registry of the European Society of Cardiology on Heart Failure. *Value Health* 2015;**18:**1098–1104.
30. Tavazzi L, Borer JS, Tavazzi G. Use and disuse of observational research: the case of remote monitoring in heart failure. *Cardiology* 2016;**137**:14–19.

© 2017 The Authors
European Journal of Heart Failure © 2017 European Society of Cardiology