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ORIGINAL RESEARCH ARTICLE

Patient factors associated with titration of medical therapy in patients with heart failure with reduced ejection fraction: data from the QUALIFY international registry

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Abstract

Aims Failure to prescribe key medicines at evidence-based doses is associated with increased mortality and hospitalization for patients with Heart Failure with reduced Ejection Fraction (HFrEF). We assessed titration patterns of guideline-recommended HFrEF medicines internationally and explored associations with patient characteristics in the global, prospective, observational, longitudinal registry.

Methods and results Data were collected from September 2013 through December 2014, with 7095 patients from 36 countries [>18 years, previous HF hospitalization within 1–15 months, left ventricular ejection fraction (LVEF) ≤ 40%] enrolled, with dosage data at baseline and up to 18 months from 4368 patients. In 4368 patients (mean age 63 ± 17 years, 75% male) ≥ 100% target doses at baseline: 30.6% (ACEIs), 2.9% (ARBs), 13.9% (BBs), 53.8% (MRAs), 26.2% (ivabradine). At final follow-up, ≥100% target doses achieved in more patients for ACEI (34.8%), BB (18.0%), and ivabradine (30.5%) but unchanged for ARBs (3.2%) and MRAs (53.7%). Adjusting for baseline dosage, uptitration during follow-up was more likely with younger age, higher systolic blood pressure, and in absence of chronic kidney disease or diabetes for ACEIs/ARBs; younger age, higher body mass index, higher heart rate, lower LVEF, and absence of coronary artery disease for BBs. For ivabradine, uptitration was more likely with higher resting heart rate.

Conclusions The international QUALIFY Registry suggests that few patients with HFrEF achieve target doses of disease-modifying medication, especially older patients and those with co-morbidity. Quality improvement initiatives are urgently required.

Keywords Heart failure; Guidelines; Adherence; Medication; Dosage

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Introduction

Recent evidence shows that although heart failure (HF) survival has improved by approximately 20% since 1970, 1 and 5 year mortality rates remain high at 11% and 40%, respectively.[1] A recent study of temporal trends in 1 year HF mortality in the UK showed a modest decline from 13% in 2002–2004 to 10% in 2011–2013, with a 6% reduction in hospital admissions.[2] Almost half of the patients were over 80 years at diagnosis with multiple co-morbidities, and in this

group, there was less change in survival and hospitalizations, suggesting an urgent need to address the growing HF burden in our ageing population.[2]

Prescription of guideline recommended therapies for heart failure with reduced ejection fraction (HFrEF),[3,4] and uptitration to evidence-based dosages, remains one of the most effective ways to ensure that patients receive optimal care targeted at reducing the risk of recurrent HF hospitalization and cardiovascular mortality. For example, the composite of all-cause mortality or HF hospitalization is significantly improved with higher doses of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) compared with lower doses.[5]

Patients with HFrEF who are treated with <50% of recommended doses of ACE inhibitors/ARBs and beta-blockers (BBs) have been shown to be at greater risk of death and/or heart failure hospitalization than patients treated with ≥100% of recommended doses.[6,7]

US and European registries have shown that many patients do not receive recommended doses of HF medication,[8,9] but little is known about longer-term dose uptitration and the clinical factors that may affect HF prescribing in routine practice globally. In this context, the QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) registry provides a novel opportunity to describe the patterns of longitudinal titration of recommended therapies in real world practice across many countries.

QUALIFY was established to address the need for a longer-term, global perspective on physician adherence to five classes of medications recommended for HFrEF in the 2012 European Society of Cardiology (ESC) guidelines: ACEIs/ARBs, BBs, mineralocorticoid receptor antagonists (MRAs), and ivabradine[10] 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, and poor) for the study population at enrolment[11] and shown the beneficial impact of physicians' adherence to target doses of five guideline-recommended classes of HF medication on clinical outcomes.[12,13]

The current analysis investigates dosage patterns of these five classes of HF medications during 18 months' follow up.

Methods

QUALIFY is a global, prospective, observational, longitudinal survey of outpatients with chronic HFrEF [LVEF ≤40%, age >18 years, HF hospitalization (minimum of one overnight stay) within one to 15 months prior to enrolment] conducted in 36 countries. Details of the study design, baseline evaluation, and data management have been published previously.[11] QUALIFY was carried out in accordance with the Declaration of Helsinki and was approved by relevant ethics committees and/or regulatory bodies in participating countries. All patients gave written informed consent to participate.

The QUALIFY survey is registered in the ISRCTN registry of clinical trials under the number ISRCTN87465420. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data were collected from September 2013 through December 2014, with 7095 patients enrolled and fulfilling the inclusion criteria. Patients were recruited in Africa, Asia, Australia, Europe, the Middle East, and North, Central, and South America.[11] Follow-up examinations were conducted at 6, 12, and 18 months after baseline. Medication data were available for 4368 patients who attended all four visits.

For this analysis, we investigated dosage at baseline and subsequent titration to target doses of ACEIs, ARBs, BBs, MRAs, and ivabradine at 18 months. Target doses were as defined by the ESC guidelines relevant at the time of data collections.[10] We investigated associations between titration patterns and patient factors, including age, sex, body mass index (BMI), presence of co-morbidity [coronary artery disease (CAD), diabetes mellitus (DM), chronic kidney disease (CKD), asthma, chronic obstructive pulmonary disease (COPD), hypertension], resting heart rate, systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), and time since HF diagnosis.

Statistical analysis

Study participants with no follow-up data or with incomplete data for model fitting were excluded from the analysis. 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, χ^2 test, and the Fisher's exact test. Individual changes in doses for ACEIs, ARBs, BBs, MRAs, and ivabradine during the 18 month follow-up were plotted using alluvial diagrams. Associations between patient characteristics at baseline and uptitration at 18 months compared with baseline were assessed using log-binomial regression. Patients on an optimal dose of ACEI, ARB, BB, MRA, or ivabradine at baseline and patients who were not treated with a drug class due to documented contraindications, intolerances, or other clinical reasons were excluded from relevant analyses. Univariable analyses were conducted for age, sex, BMI, CAD, DM, CKD, asthma, COPD, resting heart rate, hypertension, SBP, LVEF, and time since HF diagnosis (Model 1), after adjustment for initial dose at

baseline (Model 2), and after adjustment for age, sex, and initial dose at baseline (Model 3).

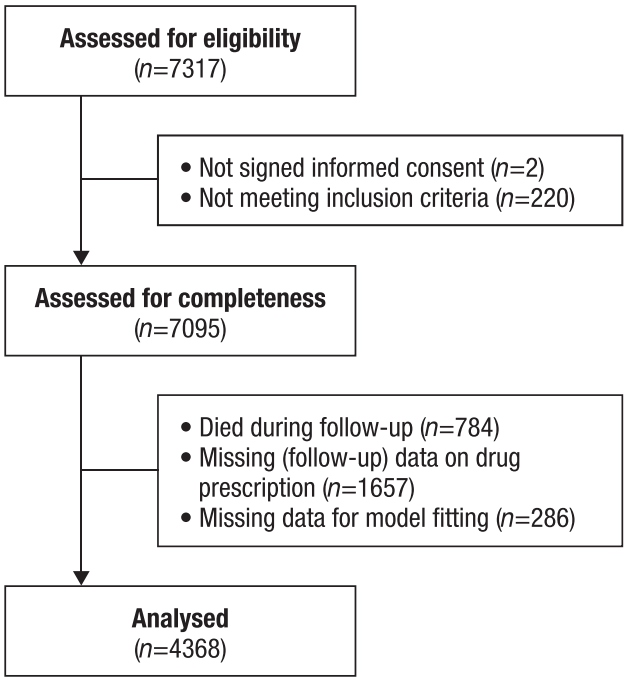
Significance level was set at 5% and the reported two-sided *P*-values were not adjusted for multiple comparisons due to the explorative nature of the investigation. All analyses were conducted using the BSW, ggplot2, ggalluvial, and stats packages in R version 4.0.0.[14,15]

Results

A total of 7095 patients from 549 centres in 36 countries who were enrolled in the QUALIFY survey between September 2013 and December 2014 met eligibility criteria. The final analysis dataset with at least 12 (maximum 18 month) follow-up with drug dosage information included 4368 patients. *Figure 1* shows the patient flow and disposition.

Characteristics of the patients with complete data, with a comparison of data for patients with incomplete data and for the total QUALIFY cohort, are shown in Supporting Information, *Table S1*. Mean age of the study cohort was 63 years, and 75.3% were men. Data showed that 58.9% were Caucasian, 28.4% were Asian, 0.7% were Black/African, and 12.0% were 'Other'. Forty-two per cent were in New York Heart Association class III–IV, and mean left ventricular ejection fraction (LVEF) was 34% (10%). Mean blood pressure was 125/78 mmHg, and mean resting heart rate was 74 bpm. Hypertension was reported in 65% of patients, CAD in 58%, atrial fibrillation in 28%, dyslipidaemia in 58%, DM in 34%, and CKD in 16%. Nine per cent had an implantable cardioverter-defibrillator, 8% had undergone cardiac resynchronization therapy, and 6% had a non-CRT pacemaker.

Figure 1 Enrolment and patient flow through study.



At baseline, 69.6% of patients were prescribed ACEIs, 20.8% were prescribed ARBs (thus 90.3% on either ACEI or ARB), 87.9% BBs, 70.6% MRAs, and 30.8% ivabradine. Data concerning the number of patients who did not receive treatment owing to contraindications, tolerability issues, lack of indications, or other clinically stated reasons are summarized in *Table 1*.

Full baseline patient characteristics by achieved dose of medication, by drug class, are shown in Supporting Information, *Table S2*, and similarly for data at 18 months in Supporting Information, *Table S3*.

Despite a high proportion of patients being prescribed the individual drug classes, the majority of patients did not receive target doses of recommended therapies at any point during the 18 month follow up (*Figure 2*).

At baseline, patients achieving at least 100% target doses were 30.6% (1337/4368) for ACEIs, 2.9% (128/4368) for ARBs, 13.9% (607/4368) for BBs, 53.8% (2352/4368) for MRAs, and 26.2% (1145/4368) for ivabradine. In general, there was a trend showing that patients who were on target dose of one drug at baseline were more likely to be on target doses of other drugs at baseline (Supporting Information, *Table S4*).

At 12–18 months, these dosages were achieved in 34.8% (1520/4368), 3.2% (141/4368), 18% (787/4368), 53.7% (2346/4368), and 30.5% (1332/4368) for patients prescribed with ACEIs, ARBs, BBs, MRAs, and ivabradine, respectively.

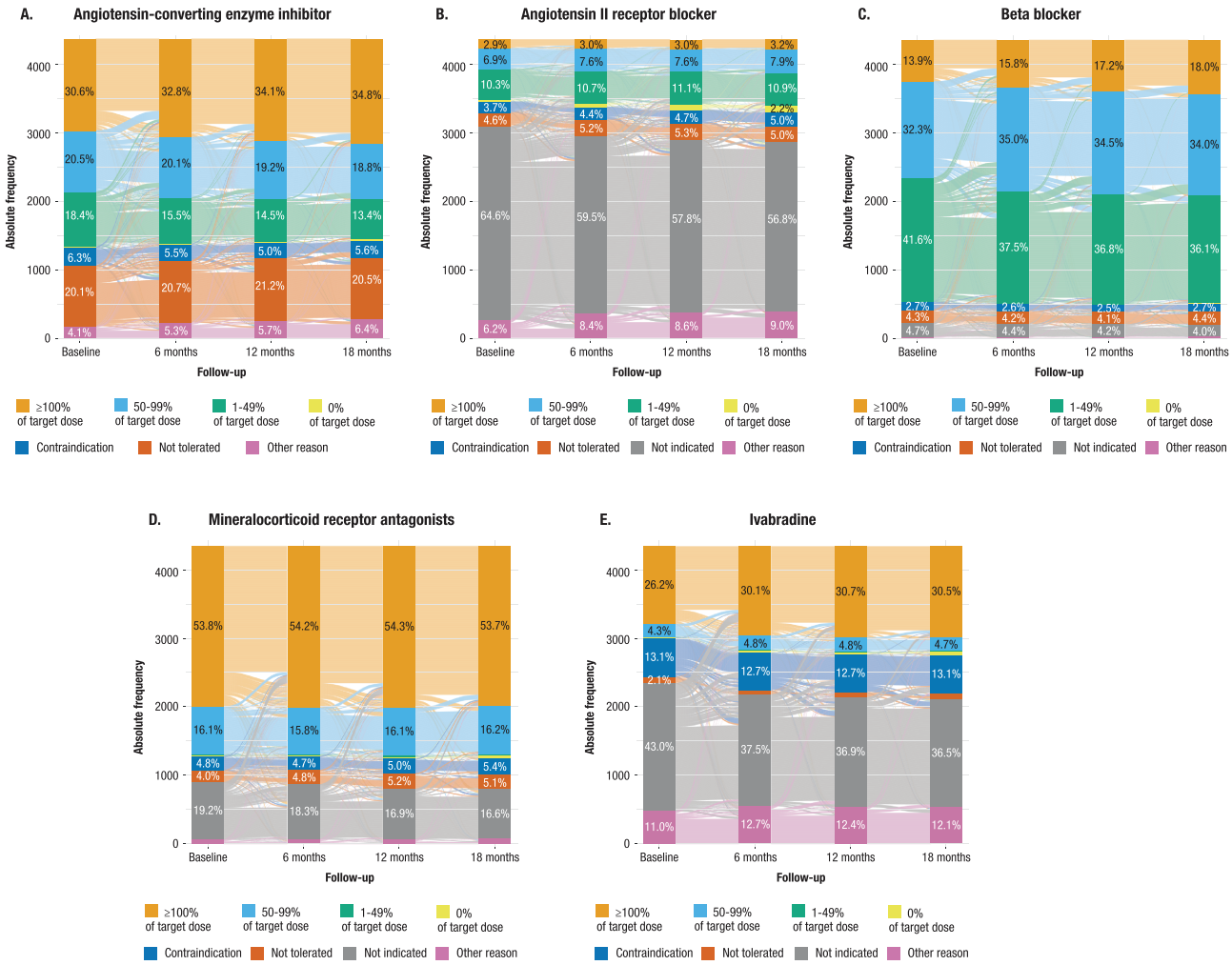
The clinical features associated with target drug usage at baseline are shown in *Table 2*. In brief, higher BMI, a history of hypertension or a higher systolic blood pressure, longer duration of HF, and a higher LVEF were associated with a higher likelihood of being on target dose of ACEI/ARB at baseline; for BBs, target dose at baseline was more likely in those who were younger, had a higher BMI, DM (49% more likely), a history of hypertension or a higher systolic blood pressure, or a lower LVEF. For MRAs, target dose at baseline was more likely if the patient did not have CKD, had a higher resting heart rate, a history of hypertension or a higher systolic blood pressure, or a higher EF. For ivabradine, this was more likely in younger patients, those with asthma, a higher resting heart rate, a higher EF, or a higher systolic blood pressure.

Associations between patient characteristics at baseline and likelihood of uptitration over 18 months are summarized in *Table 3*. After adjustment for baseline dosage (Model II), older patients were less likely to be uptitrated for ACEI/ARB therapy ($P = 0.01$) as were those with CKD ($P = 0.004$), T2DM ($P = 0.004$), or a lower SBP ($P < 0.001$). For BBs, uptitration was less likely in older patients ($P < 0.001$) and those with a lower BMI ($P < 0.001$), underlying CAD ($P < 0.001$), a lower resting heart rate ($P < 0.001$) or a higher LVEF ($P < 0.001$). For ivabradine, patients with a lower

Table 1 Absolute frequencies for prescription by drug class at baseline

n = 4368	Treated	Contraindication	Not tolerated	Not indicated	Other reason
Angiotensin converting enzyme inhibitor	3038	275	878	0	177
Angiotensin receptor blocker	908	162	203	2822	273
Beta-blocker	3838	120	188	204	18
Mineralocorticoid receptor antagonist	3084	208	173	839	64
Ivabradine	1346	574	91	1877	480

Figure 2 Alluvial diagram showing dose changes during follow up.



resting HR were less likely to be uptitrated ($P < 0.001$). The associations described earlier were unaltered after further adjustment for age and sex (Model III).

Discussion

In a contemporary population of patients with HFrEF who had recently been hospitalized in 36 countries, a high proportion of patients did receive guideline-directed medical therapy at baseline and throughout follow-up. At baseline, 90.3% were on an ACEI/ARB, 87.9% were on a BB, 70.6% were on an MRA, and 30.8% were on ivabradine. However, few patients reached 'target' doses of recommended therapies at any point during the 18 month follow up period, with little evidence of uptitration from baseline through 18 months: the initial dose of drug at baseline remaining unchanged for the majority of patients.

At baseline, patients treated with an ACEI were more likely to be on target dose compared with an ARB, and there was

Table 2 Associations between patient characteristics and target drug dosage, by class of drug, at baseline (log binomial analysis tables)

	Model I	
	RR [95% CI]	*P*
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker (*n* = 3893)		
Age (years)	1.000 [0.997; 1.003]	0.917
Asthma	1.061 [0.854; 1.318]	0.593
Body mass index (kg/m^2)	1.023 [1.016; 1.029]	<0.001
Chronic kidney disease	0.838 [0.739; 0.949]	0.006
Chronic obstructive pulmonary disease	1.040 [0.918; 1.180]	0.536
Coronary artery disease	1.094 [1.007; 1.188]	0.034
Diabetes mellitus	1.113 [1.024; 1.210]	0.012
Resting heart rate (bpm)	1.003 [1.001; 1.006]	0.017
Hypertension	1.412 [1.283; 1.554]	<0.001
Time since last hospitalization (months)	1.023 [1.009; 1.037]	0.002
Left ventricular ejection fraction (%)	1.018 [1.012; 1.024]	<0.001
Female	1.026 [0.935; 1.126]	0.584
Systolic blood pressure (mmHg)	1.011 [1.010; 1.012]	<0.001
Time since heart failure diagnosis (years)	1.007 [0.999; 1.015]	0.076
Beta-blocker (*n* = 3838)		
Age (years)	0.990 [0.984; 0.995]	<0.001
Asthma	1.223 [0.819; 1.826]	0.324
Body mass index (kg/m^2)	1.042 [1.030; 1.055]	<0.001
Chronic kidney disease	1.225 [1.021; 1.471]	0.029
Chronic obstructive pulmonary disease	1.183 [0.947; 1.478]	0.139
Coronary artery disease	0.887 [0.766; 1.026]	0.107
Diabetes mellitus	1.494 [1.291; 1.729]	<0.001
Resting heart rate (bpm)	0.997 [0.991; 1.002]	0.230
Hypertension	1.278 [1.087; 1.503]	0.003
Time since last hospitalization (months)	1.013 [0.987; 1.039]	0.338
Left ventricular ejection fraction (%)	0.983 [0.973; 0.994]	0.002
Female	0.928 [0.780; 1.103]	0.396
Systolic blood pressure (mmHg)	1.004 [1.000; 1.008]	0.032
Time since heart failure diagnosis (years)	1.010 [0.996; 1.025]	0.155
Mineralocorticoid receptor antagonist (*n* = 3080)		
Age (years)	0.999 [0.998; 1.001]	0.275
Asthma	1.031 [0.923; 1.151]	0.588
Body mass index (kg/m^2)	NA [NA; NA]	NA
Chronic kidney disease	0.933 [0.876; 0.993]	0.030
Chronic obstructive pulmonary disease	1.033 [0.974; 1.094]	0.279
Coronary artery disease	1.107 [1.063; 1.153]	<0.001
Diabetes mellitus	1.019 [0.978; 1.061]	0.374
Resting heart rate (bpm)	1.002 [1.001; 1.003]	<0.001
Hypertension	1.111 [1.063; 1.161]	<0.001
Time since last hospitalization (months)	1.007 [1.000; 1.014]	0.049
Left ventricular ejection fraction (%)	1.004 [1.001; 1.007]	0.009
Female	1.032 [0.987; 1.078]	0.166
Systolic blood pressure (mmHg)	1.003 [1.002; 1.003]	<0.001
Time since heart failure diagnosis (years)	1.003 [0.999; 1.006]	0.159
Ivabradine (*n* = 1343)		
Age (years)	0.997 [0.996; 0.999]	0.003
Asthma	1.111 [1.036; 1.192]	0.003
Body mass index (kg/m^2)	1.005 [1.001; 1.009]	0.006
Chronic kidney disease	0.929 [0.856; 1.009]	0.081
Chronic obstructive pulmonary disease	0.983 [0.914; 1.057]	0.643
Coronary artery disease	1.042 [0.993; 1.093]	0.096
Diabetes mellitus	1.011 [0.967; 1.058]	0.624
Resting heart rate (bpm)	1.002 [1.001; 1.003]	0.004
Hypertension	1.008 [0.962; 1.056]	0.739
Time since last hospitalization (months)	1.002 [0.994; 1.011]	0.557
Left ventricular ejection fraction (%)	1.004 [1.000; 1.007]	0.044
Female	1.011 [0.961; 1.062]	0.681
Systolic blood pressure (mmHg)	1.001 [1.000; 1.002]	0.038
Time since heart failure diagnosis (years)	0.997 [0.992; 1.003]	0.361

Table 3 Associations between clinical features at baseline and subsequent uptitration by 18 months of follow-up for the different classes of guideline-recommended therapy

	Model I		Model II		Model III	
	RR [95% CI]	*P*	RR [95% CI]	*P*	RR [95% CI]	*P*
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker (n = 2428)						
Age (years)	0.993 [0.990; 0.997]	0.001	0.995 [0.991; 0.999]	0.011	0.995 [0.991; 0.999]	0.010
Asthma	0.814 [0.582; 1.139]	0.230	0.994 [0.719; 1.375]	0.972	1.001 [0.725; 1.383]	0.995
Body mass index (kg/m^2)	1.004 [0.994; 1.014]	0.451	1.009 [0.999; 1.019]	0.066	1.008 [0.998; 1.017]	0.113
Chronic kidney disease	0.778 [0.664; 0.911]	0.002	0.799 [0.685; 0.932]	0.004	0.824 [0.704; 0.964]	0.015
Chronic obstructive pulmonary disease	1.078 [0.923; 1.260]	0.344	1.108 [0.954; 1.286]	0.178	1.138 [0.980; 1.323]	0.091
Coronary artery disease	1.034 [0.934; 1.146]	0.518	1.026 [0.929; 1.133]	0.614	1.061 [0.957; 1.175]	0.260
Diabetes mellitus	0.820 [0.731; 0.920]	<0.001	0.850 [0.760; 0.950]	0.004	0.859 [0.768; 0.961]	0.008
Resting heart rate (bpm)	1.003 [0.999; 1.006]	0.151	1.002 [0.999; 1.006]	0.206	1.001 [0.998; 1.005]	0.434
Hypertension	0.994 [0.895; 1.104]	0.917	1.078 [0.974; 1.194]	0.147	1.115 [1.004; 1.237]	0.041
Time since last hospitalization (months)	0.989 [0.971; 1.007]	0.237	0.987 [0.969; 1.005]	0.150	0.988 [0.970; 1.006]	0.179
Left ventricular ejection fraction (%)	0.994 [0.987; 1.001]	0.076	0.999 [0.992; 1.006]	0.744	0.999 [0.992; 1.006]	0.874
Female	0.960 [0.851; 1.082]	0.504	1.009 [0.898; 1.133]	0.885	1.028 [0.915; 1.156]	0.642
Systolic blood pressure (mmHg)	1.003 [1.000; 1.006]	0.032	1.005 [1.003; 1.008]	<0.001	NA [NA; NA]	NA
Time since heart failure diagnosis (years)	0.986 [0.974; 0.999]	0.033	0.987 [0.975; 0.999]	0.038	0.990 [0.978; 1.002]	0.103
New York Heart Association classification						
II vs. I	1.031 [0.882; 1.205]	0.703	1.001 [0.862; 1.161]	0.994	1.016 [0.875; 1.179]	0.837
III vs. I	0.878 [0.744; 1.037]	0.125	0.859 [0.733; 1.008]	0.062	0.870 [0.742; 1.021]	0.088
IV vs. I	0.859 [0.642; 1.149]	0.306	0.820 [0.619; 1.086]	0.166	0.805 [0.608; 1.067]	0.131
Atrial fibrillation	1.099 [0.986; 1.225]	0.088	1.116 [1.005; 1.239]	0.039	1.154 [1.038; 1.283]	0.008
Beta-blocker (n = 3231)						
Age (years)	0.992 [0.988; 0.996]	<0.001	0.993 [0.989; 0.996]	<0.001	0.992 [0.989; 0.996]	<0.001
Asthma	0.817 [0.575; 1.161]	0.259	0.854 [0.605; 1.205]	0.369	0.877 [0.622; 1.237]	0.454
Body mass index (kg/m^2)	1.016 [1.006; 1.025]	0.001	1.022 [1.013; 1.031]	<0.001	1.014 [1.005; 1.023]	0.004
Chronic kidney disease	0.851 [0.736; 0.984]	0.030	0.878 [0.761; 1.012]	0.073	0.925 [0.800; 1.070]	0.296
Chronic obstructive pulmonary disease	0.819 [0.681; 0.984]	0.033	0.865 [0.722; 1.037]	0.118	0.891 [0.743; 1.068]	0.212
Coronary artery disease	0.769 [0.698; 0.847]	<0.001	0.782 [0.712; 0.860]	<0.001	0.809 [0.734; 0.893]	<0.001
Diabetes mellitus	0.898 [0.807; 1.001]	0.051	0.917 [0.825; 1.019]	0.106	0.927 [0.835; 1.030]	0.160
Resting heart rate (bpm)	1.008 [1.005; 1.011]	<0.001	1.006 [1.003; 1.009]	<0.001	1.005 [1.002; 1.008]	0.003
Hypertension	0.892 [0.807; 0.985]	0.024	0.933 [0.846; 1.028]	0.162	0.968 [0.877; 1.070]	0.528
Time since last hospitalization (months)	0.984 [0.967; 1.002]	0.077	0.982 [0.965; 0.999]	0.041	0.983 [0.967; 1.001]	0.061
Left ventricular ejection fraction (%)	0.984 [0.977; 0.991]	<0.001	0.986 [0.980; 0.993]	<0.001	0.988 [0.981; 0.995]	<0.001
Female	1.036 [0.926; 1.157]	0.539	1.042 [0.935; 1.162]	0.455	1.080 [0.967; 1.205]	0.172
Systolic blood pressure (mmHg)	1.001 [0.998; 1.003]	0.469	1.002 [0.999; 1.004]	0.181	NA [NA; NA]	NA
Time since heart failure diagnosis (years)	0.991 [0.980; 1.002]	0.125	0.994 [0.983; 1.005]	0.270	0.999 [0.988; 1.010]	0.834
New York Heart Association classification						
II vs. I	0.894 [0.772; 1.034]	0.131	0.953 [0.827; 1.098]	0.506	0.973 [0.844; 1.120]	0.700
III vs. I	0.825 [0.709; 0.962]	0.014	0.830 [0.715; 0.962]	0.014	0.848 [0.731; 0.983]	0.029
IV vs. I	0.659 [0.490; 0.887]	0.006	0.635 [0.474; 0.850]	0.002	0.628 [0.470; 0.840]	0.002
Atrial fibrillation	1.178 [1.063; 1.307]	0.002	1.212 [1.096; 1.340]	<0.001	1.278 [1.153; 1.415]	<0.001
Mineralocorticoid receptor antagonist (n = 728)						
Age (years)	1.009 [0.998; 1.020]	0.099	1.000 [0.989; 1.012]	1.000	1.000 [0.989; 1.012]	1.000
Asthma	0.995 [0.412; 2.404]	0.991	1.000 [0.388; 2.579]	1.000	1.000 [0.387; 2.585]	1.000
Body mass index (kg/m^2)	1.058 [1.030; 1.085]	<0.001	1.001 [0.974; 1.030]	0.918	1.001 [0.973; 1.030]	0.919
Chronic kidney disease	1.490 [1.080; 2.056]	0.015	0.988 [0.750; 1.300]	0.929	0.988 [0.743; 1.312]	0.931
Chronic obstructive pulmonary disease	2.045 [1.483; 2.821]	<0.001	1.098 [0.787; 1.532]	0.583	1.098 [0.760; 1.587]	0.619

(*Continues*)

Table 3 (continued)

	Model I		Model II		Model III	
	RR [95% CI]	*P*	RR [95% CI]	*P*	RR [95% CI]	*P*
Coronary artery disease (Asian)	1.908 [0.969; 3.759]	0.062	1.000 [0.505; 1.981]	1.000	1.000 [0.501; 1.998]	1.000
Coronary artery disease (non-Asian)	0.865 [0.654; 1.145]	0.311	0.924 [0.684; 1.247]	0.604	0.928 [0.682; 1.262]	0.632
Diabetes mellitus	1.158 [0.866; 1.549]	0.322	0.998 [0.780; 1.276]	0.986	0.998 [0.776; 1.283]	0.986
Resting heart rate (bpm)	0.995 [0.984; 1.005]	0.331	1.000 [0.989; 1.011]	1.000	1.000 [0.989; 1.011]	1.000
Hypertension	1.703 [1.252; 2.317]	<0.001	1.244 [0.932; 1.659]	0.138	1.244 [0.924; 1.674]	0.150
Time since last hospitalization (months) (Asian)	1.077 [0.951; 1.220]	0.240	1.017 [0.893; 1.159]	0.796	1.016 [0.891; 1.158]	0.812
Time since last hospitalization (months) (non-Asian)	1.016 [0.969; 1.066]	0.509	1.017 [0.968; 1.069]	0.496	1.016 [0.966; 1.068]	0.534
Left ventricular ejection fraction (%)	0.998 [0.977; 1.019]	0.823	1.000 [0.983; 1.018]	0.970	1.000 [0.983; 1.018]	0.971
Female	0.967 [0.689; 1.357]	0.845	1.000 [0.748; 1.336]	1.000	1.000 [0.748; 1.337]	1.000
Systolic blood pressure (mmHg)	0.999 [0.992; 1.007]	0.852	1.000 [0.994; 1.006]	1.000	1.000 [0.993; 1.007]	1.000
Time since heart failure diagnosis (years)	1.023 [0.998; 1.049]	0.075	1.000 [0.972; 1.029]	1.000	1.000 [0.971; 1.030]	1.000
New York Heart Association classification						
II vs. I	1.361 [0.872; 2.125]	0.175	1.000 [0.672; 1.488]	1.000	1.000 [0.672; 1.488]	1.000
III vs. I	1.378 [0.859; 2.212]	0.184	1.023 [0.671; 1.561]	0.915	1.023 [0.668; 1.568]	0.916
IV vs. I	1.109 [0.527; 2.334]	0.785	0.981 [0.557; 1.730]	0.948	0.981 [0.555; 1.735]	0.948
Atrial fibrillation	1.509 [1.132; 2.013]	0.005	1.083 [0.830; 1.413]	0.558	1.083 [0.822; 1.427]	0.572
Ivabradine (n = 198)						
Age (years)	1.006 [0.991; 1.020]	0.436	1.006 [0.992; 1.021]	0.407	1.007 [0.992; 1.022]	0.387
Asthma	2.437 [2.060; 2.884]	<0.001	1.630 [0.719; 3.693]	0.242	1.611 [0.664; 3.906]	0.292
Body mass index (kg/m^2)	1.013 [0.982; 1.043]	0.419	1.014 [0.983; 1.045]	0.382	NA [NA; NA]	NA
Chronic kidney disease	0.924 [0.573; 1.489]	0.744	0.926 [0.574; 1.494]	0.754	0.899 [0.556; 1.454]	0.664
Chronic obstructive pulmonary disease	0.853 [0.492; 1.480]	0.572	0.839 [0.482; 1.463]	0.537	0.823 [0.472; 1.433]	0.490
Coronary artery disease	1.187 [0.840; 1.678]	0.330	1.187 [0.840; 1.677]	0.331	1.161 [0.816; 1.653]	0.407
Diabetes mellitus	1.340 [0.966; 1.858]	0.079	1.339 [0.966; 1.856]	0.080	1.330 [0.959; 1.844]	0.088
Resting heart rate (bpm)	1.022 [1.009; 1.034]	<0.001	1.022 [1.009; 1.035]	<0.001	1.021 [1.009; 1.035]	0.001
Hypertension	1.067 [0.753; 1.513]	0.714	1.072 [0.756; 1.521]	0.695	1.026 [0.712; 1.480]	0.890
Time since last hospitalization (months)	0.980 [0.922; 1.041]	0.514	0.980 [0.923; 1.040]	0.504	0.978 [0.920; 1.040]	0.476
Left ventricular ejection fraction (%)	0.981 [0.959; 1.003]	0.085	0.981 [0.959; 1.003]	0.092	0.979 [0.957; 1.002]	0.067
Female	0.981 [0.666; 1.445]	0.922	0.986 [0.669; 1.454]	0.945	0.949 [0.638; 1.410]	0.794
Systolic blood pressure (mmHg)	0.984 [0.981; 0.987]	<0.001	NA [NA; NA]	NA	NA [NA; NA]	NA
Time since heart failure diagnosis (years)	0.970 [0.929; 1.012]	0.162	0.970 [0.929; 1.013]	0.172	0.962 [0.921; 1.006]	0.092
New York Heart Association classification						
II vs. I	1.042 [0.537; 2.022]	0.904	1.089 [0.547; 2.168]	0.808	1.054 [0.533; 2.084]	0.879
III vs. I	0.933 [0.470; 1.853]	0.844	0.972 [0.478; 1.973]	0.937	0.931 [0.462; 1.877]	0.842
IV vs. I	1.667 [0.797; 3.485]	0.175	1.740 [0.812; 3.729]	0.154	1.764 [0.818; 3.803]	0.147
Atrial fibrillation	0.865 [0.485; 1.544]	0.623	0.860 [0.482; 1.536]	0.611	0.797 [0.440; 1.443]	0.454

Model I is unadjusted, Model II is adjusted for dosage level at baseline, Model III is adjusted for age, sex and dosage level at baseline. Patients on target dose of drug at baseline are not included in the analyses.

only a modest increase in the proportion of patients on target dose at follow-up for either class. Uptitration was more likely in younger patients, those with a higher blood pressure, and in those without the co-morbidities of T2DM or CKD—suggesting either clinical caution or clinical inertia.

Under-dosing at all time points was particularly apparent with BBs although uptitration was again more common in younger patients and also in those with a higher BMI or resting heart rate or lower LVEF. Perhaps surprisingly, those with underlying CAD (as classified by the study doctor) were less likely to be uptitrated, possibly due to their older age and higher LVEF (data not shown).

For MRAs, more patients were on target dose at enrolment than for other drug groups, but the proportion did not change during follow-up, again suggesting little attention to drug uptitration.

Similarly, few patients were on the target dose of ivabradine at baseline, with little change during follow-up. A higher resting heart rate was associated with a higher probability of uptitration, which is clinically unsurprising as the drug's initiation and uptitration should be modified by the resting heart rate.[16]

By providing baseline and 18 month follow-up data on uptitration of recommended HFrEF disease-modifying medications from a global population, these data extend our understanding of dosing patterns reported in previous studies, which tended to be regional rather than global.

In the BIOSTAT-CHF registry of patients with HFrEF suboptimally treated at baseline, recruited in Europe from December 2010–December 2012, only 22% achieved target dose of a renin-angiotensin system (RAS) inhibitor at a median 21 months' follow-up, and 12% target BB dose—lower proportions than in our study.[6] Similarly to our data, the registry not only showed an association between lack of RAS inhibitor uptitration and lower BMI and eGFR but also reported less uptitration in women. For BB, older age, lower heart rate, and lower blood pressure were associated with less uptitration, similarly to our data.

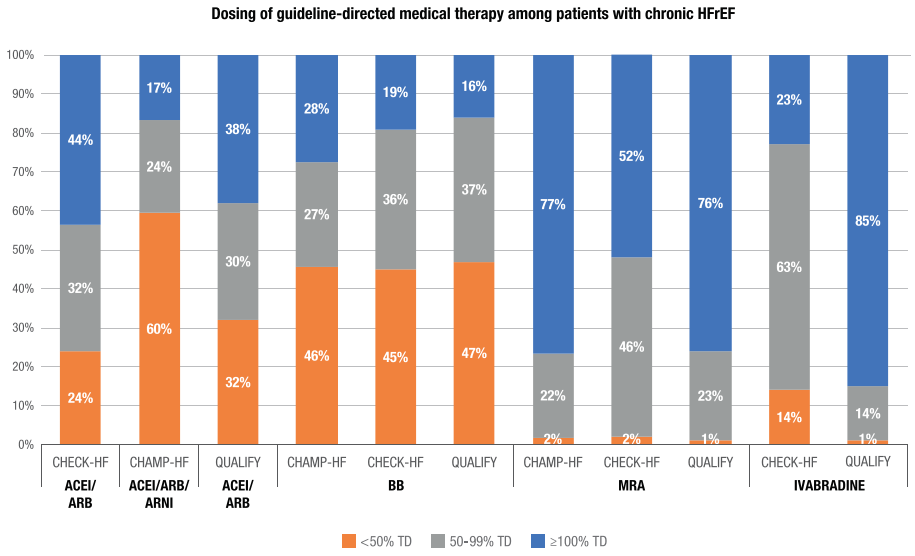
The ESC Heart Failure Long-Term Registry of patients, recruited with acute and chronic HF from May 2011–April 2013, showed similar levels of drug usage to QUALIFY for RAS blockers, BBs, and MRAs, with somewhat lower proportions at target dose. However, many physicians were still uptitrating their patients.[9] No clear reason for failing to reach target dose was recorded for 29% of patients prescribed ACEIs, ARBs, or BBs and 47% of those prescribed MRAs.

A comparison of QUALIFY dosing data with those from two other recently published registries, CHECK-HF[17,18] and CHAMP,[8,19] is presented in *Figure 3*.

Baseline data from the Dutch CHECK-HF registry (2013–2106) showed relatively high use of evidence-based treatment in HFrEF, especially in younger patients. However, only half of eligible patients achieved ≥100% of target doses for ACEI/ARB and MRAs and 19% for BBs,[17] similar to our data. Older age, lower BMI, and lower blood pressure were associated with lower dosage across drug classes, similar to our data.[18]

Baseline prescribing levels of ACEI/ARB, BB, and MRA in the CHAMP-HF (Change the Management of Patients with Heart Failure) registry in the USA (December 2015–March 2017) were lower than in QUALIFY.[8,19] During 12 months'

Figure 3 A comparison of dosing of guideline-recommended medical therapy among patients with chronic HFrEF: QUALIFY, CHECK-HF, and CHAMP (CHECK HF[17] reported prescription rates for all patients, whereas CHAMP[8] and QUALIFY reported prescriptions in eligible patients with no documented contraindication or intolerance).



follow-up, initiation and uptitration only occurred in a small minority of patients, with associated factors similar to those we report: for ACEI/ARBs—higher systolic blood pressure; for BB—younger age, higher systolic blood pressure, or higher heart rate. The presence of CAD was associated with a higher likelihood of BB dose decrease or medication discontinuation.

Evidence of sub-optimal dosing is not limited to European and US studies. In the ASIAN-HF registry (October 2012–December 2015), guideline-recommended target doses were achieved in only 17% of patients treated with ACEI/ARB, 13% for BB, and 29% for MRAs.[7] This was lower than European or US data, although there were marked differences between countries. Similar factors were associated with target dosage as in our study: younger age and no CKD for ACEI/ARBs; younger age, higher BMI and hypertension history for BBs; and older age, higher systolic blood pressure and hypertension history for MRAs. Similar to BIOSTAT-CHF,[6] ASIAN-HF reported a clear association between dosage of ACEI/ARB or BB achieved and subsequent risk of all-cause mortality or HF hospitalization,[7] as has also been reported in the large multiyear national registry of HF in the UK.[20]

The results of our study, and those mentioned earlier, contrast with those from randomized controlled trials in which at least 50–60% of patients achieved target doses.[21–25] Patients in clinical practice are generally older and with more co-morbidities than those in clinical trials, and this is likely to affect prescribing decisions and the perception of risk and benefit of these therapies. Additionally, some trials have a run-in period prior to randomization, which is likely to lead to an overestimation of drug tolerability in real-world practice.[26]

The QUALIFY data show that clinical factors, including age, lower blood pressure, and lower BMI, along with co-morbidities such as CAD, DM, and CKD are associated with lower likelihood of appropriate uptitration of drug therapy, even when under the supervision of a specialist. This translates into an inability to achieve target doses of medication, a target that has consistently been shown to be associated with better outcomes.[6,8,12,19] Such patients are at higher absolute risk and are therefore missing out on the potential to gain important clinical benefits.

The lack of appropriate drug optimisation for patients with HFrEF has been reported before,[27] and many initiatives have attempted to improve the quality of care, including the Get With The Guidelines programme.[28] Disease management programmes have been introduced, often including early review after hospital discharge, HF nurse specialists, or pharmacists to support patient education and medication optimization. Financial incentives may encourage hospitals or general practitioners to achieve better process and outcome measures (e.g. 30 day readmission penalties and best practice tariffs).[29,30] Some clinical features associated with inability to achieve target doses may be physiological and clinically appropriate, but the wide variation in achievement within studies[6–8,20] suggests that there are potentially many patients who could tolerate more appropriate drug doses, given the opportunity.

A recent review highlighted the practical considerations that might extend maximal medical therapy for patients with HFrEF[26] including better education, more clinical time for patients (either face-to-face or remotely), adjustment of concomitant medication to allow better use of HF drugs, management of side-effects, and optimized timing of drug dosages.

Collection of data from routine practice, and benchmarking against standards, will allow poor performance to be identified, but the responsibility to improve performance is likely to lie locally, and local champions are required to drive improvement. Improved clinical decision support, coupled with healthcare professional and patient/family education, and benchmarking of key process and outcome measures, are likely to be front and centre of any solution.

Strengths and limitations

Strengths of this study include the large number of patients recruited and followed up for 18 months from many centres in 36 countries.

The relatively young age of the QUALIFY population may not be typical of that seen in clinical practice in Western countries but reflects the international nature of the registry. QUALIFY centres were selected by national coordinators, on a voluntary basis, and selection bias cannot be excluded.

A large majority of QUALIFY patients (90%) were treated by cardiologists, which does not reflect routine practice in some countries. The failure to uptitrate HF medicines and reach target doses may be even more apparent in patients treated by a non-cardiologist workforce.

At the time the QUALIFY registry was initiated, international HF guidelines did not include a recommendation for neprilysin inhibitor therapy, and this drug was not available.[10] As a result, data on its use were not collected.

We did not have complete follow-up data on all patients enrolled in the QUALIFY registry and had to limit our analyses to those who did. There were no major differences in clinical and demographic characteristics between those for whom we did, or did not, have such data, but we cannot exclude unmeasured confounding.

Conclusions

In this international HFrEF patient cohort, despite good adherence to the use of guideline-directed therapy, few

patients attain target doses of drug classes, with little evidence of drug uptitration over time for any individual patient. Optimization of drug therapy in HFrEF remains a global challenge. This problem is not likely to reduce unless more specifically targeted and incentivized by healthcare systems and quality improvement initiatives.

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Conflict of interest

M. C. reports consultancy and speaker fees from AstraZeneca, Boehringer-Ingelheim, Lilly, RestMed, Servier, Novartis, Pfizer, Bayer, Medtronic, Boston Scientific, Abbott, Amgen, and MSD. J. S. reports no conflicts of interest. M. B. and S. W. are supported by the Deutsche Forschungsgemeinschaft (SFB TTR 219, S-01). M. B. reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Servier, Medtronic, Vifor, Novartis, RECor, and Abbott outside the submitted work. S. W. reports grants from Servier Affaires Medicales during the conduct of the study. L. T. reports trial committee member and member of speakers bureau for Servier (within the submitted work) and trial committee member for CVIE Therapeutics (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, Novartis, Berlin Chemie, Bayer, Vifor Pharma, Boehringer Ingelheim, AstraZeneca, Cibiem, Respicardia, Abbott Vascular, and Renal Guard Solutions outside the submitted work. S. D. A. reports personal fees from Servier during the conduct of the study; personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, Cardiac Dimension, Impulse Dynamics, and Novartis outside the submitted work, and grant support from Abbott Vascular and Vifor Pharm outside the submitted work. G. S. F. reports that he was a committee member of trials and registries sponsored by Boehringer Ingelheim, Medtronic, Bayer, Novartis, Servier, and Vifor. M. K. reports consulting/invited speaker fees from Servier, Novartis, AstraZeneca, Torrent, Sanofi, and Bayer.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of patients with complete data for analysis (study cohort), patients with incomplete data (excluded) and comparison with the total QUALIFY cohort.
Table S2. Patient characteristics by % target dosing groups by medication class, at baseline.
Table S3. Patient characteristics and % target dosing groups by medication class, at 18 months.
Table S4. Achievement of target dosing for multiple drugs

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