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The relevance of comorbidities for heart failure treatment in primary care: A European survey

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Abstract

Aim: To assess the impact of comorbidities on chronic heart failure (CHF) therapy.

Methods: The IMPROVEMENT-HF survey included 11,062 patients from 100 primary care practices in 14 European countries. The influence of patient characteristics on drug regimes was assessed with multinomial logistical regression.

Results: Combined drug regimes were given to 48% of CHF patients, consisting of 2.2 drugs on average. Patient characteristics accounted for 35%, 42% and 10% of the variance in one-, two- and three-drug regimes, respectively. Myocardial infarction (MI), atrial fibrillation (AF), diabetes, hypertension, and lung disease influenced prescribing most. AF made all combinations containing β -blockers more likely. Thus for single drug regimes, MI increased the likelihood for non-recommended β -blocker monotherapy (OR 1.3; 95% CI 1.2–1.4), while for combination therapy recommended regimes were most likely. For both hypertension and diabetes, ACE-inhibitors were the most likely single drug, while the most likely second drugs were β -blockers in hypertension and digoxin in diabetes.

Conclusions: Patient characteristics have a clear impact on prescribing in European primary care. Up to 56% of drug regimes were rational taking patient characteristics into account. Situations of insufficient prescribing, such as patients post MI, need to be addressed specifically.

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Keywords: European survey; Chronic heart failure; Comorbidities; Prescribing; Primary care; IMPROVEMENT programme

1. Introduction

Chronic heart failure (CHF) is a common condition with increasing prevalence in all western countries [1], has a high morbidity and mortality, and accounts for expenditure of around 2% of total healthcare budgets [2]. Therefore, efficient treatment according to the best available evidence is of major importance, not only for individual patients' health outcomes but also for health care spending overall.

At present, evidence-based treatment is not widely implemented in daily practice [3]. This is particularly evident in primary care [4,5], which is where the majority

of heart failure patients are treated in Europe. Moreover, despite internationally available evidence, there are clear differences in prescribing between countries both for inpatient care [6] as well as in primary care [7].

Usually, quality of prescribing is evaluated using a two-dimensional approach, relating a diagnosis to the use of an individual drug. In CHF this equates to the overall use of ACE-inhibitors or β -blockers [6,8]. However, CHF often requires complex poly-drug regimes. CHF patients frequently have multiple comorbidities, which require overlapping therapies. Therefore, patient characteristics are a very important factor when assessing the quality of prescribing for heart failure.

The aim of this study in European primary care was to determine the impact of patient characteristics and comor-

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bidities on CHF management, and to identify areas of prescribing which could be improved.

2. Methods

2.1. Study population

The data used in this study was derived from the IMPROVEMENT-HF program, which was undertaken to evaluate and assess management of CHF [7] in primary care in Europe. The study was an initiative of the working group on HF of the European Society of Cardiology (ESC). Fourteen European countries participated in the survey, each country had 10 regional centers which randomly selected approximately 10 primary care physicians to participate in the survey. The physicians each identified nine patients with a diagnosis of CHF and/or a history of MI during a 2-month period in 1999. This created a study population consisting of 11,062 patients. Data for each patient, including relevant concomitant diseases, diagnostic procedures and pharmaceutical treatment was collected by professional health care workers using patient records. The study design has been described in detail elsewhere [9].

2.2. Drug regimes

Prescribing patterns were assessed based on drug regimes rather than on individual drugs. Drug regimes

Table 1
Prevalence of drug regimes

Drug regime ^a	Included in analysis, n (%)	Not included, n (%)
One-drug regimes	5733 (51.8)	
ACE-inhibitor (recommended)	2463 (22.3)	
BB	1164 (10.5)	
Digoxin	882 (8.0)	
Diuretic monotherapy	604 (5.5)	
No drug	620 (5.6)	
Two-drug regimes	3625 (32.8)	
ACE+BB (recommended)	1629 (14.7)	
ACE+digoxin	1721 (15.6)	
ACE+spironolactone	275 (2.5)	
BB+digoxin		57 (0.5)
Digoxin+spironolactone		198 (1.8)
Three-drug regimes	855 (7.7)	
ACE+BB+digoxin (recommended)	475 (4.3)	
ACE+digoxin+spironolactone	380 (3.4)	
BB+digoxin+spironolactone		49 (0.4)
Total patients (11,062)	10,213 (92.3)	849 (7.7) ^b

Regimes are grouped according to the number of drug classes used, reflecting treatment intensity.

Regimes <2% were not included in analysis.

^a Each regime can contain diuretics.

^b Includes also not mentioned combinations.

Table 2

Prevalence of patient characteristics (determinants for drug regimes) per treatment intensity level

Determinants	One-drug regimes, n=5733 (%)	Two-drug regimes, n=3625 (%)	Three-drug regimes, n=855 (%)
Sex (M)	56	54	53
Severity (NYHA 3/4)	34	45	58
Goal (relief)	9	9	13
Goal (progress)	61	63	58
Echo (abnormal)	61	73	78
Creatinine (abnormal)	16	18	22
MI	35	36	30
AF	15	25	41
Hypertension	44	54	50
Diabetes	16	20	22
Lung disease	23	24	27
Stroke	7	8	8
Peripheral vascular disease	16	17	21

were grouped in levels of comparable treatment intensity to determine the impact of patient characteristics on prescribing. Finally, prescription patterns were reassessed in relation to evidence and recommendations taking the significant patient characteristics into account.

Regimes with a prescribing frequency <2% ($n < 250$) in the total population were excluded from the analysis. Diuretics were not considered as a separate drug category, as they may be added or withdrawn at any stage of disease according to symptoms [10]. Thus all regimes may include diuretics, except for the drug regimes “diuretic monotherapy” and “no treatment”. A diuretic was defined as loop-diuretic, thiazide or a combination of both. “ACE” consisted of either ACE-inhibitor or AII-antagonist.

Three levels of treatment intensity were defined for the drug regimes according to the number of drug groups prescribed (one, two or three drugs). The influence of patient characteristics on prescribing was analyzed within each level separately and against the recommended drug regime (Table 1).

2.3. Patient characteristics (determinants)

Patient characteristics included comorbidities and severity of CHF (Table 2). New York Heart Association (NYHA) classes 1 and 2 were combined into the category “mild” and NYHA 3 and 4 into “severe”. The six therapeutic goals in the questionnaire were combined to make three categories: “relief” of symptoms, slowing down “progress” of disease and the combination of “relief and progress”. The latter was used as reference.

2.4. Statistical analysis

The influence of patient characteristics (determinants) on drug regimes in each therapeutic step was first assessed using univariate logistic regression. Significant determi-

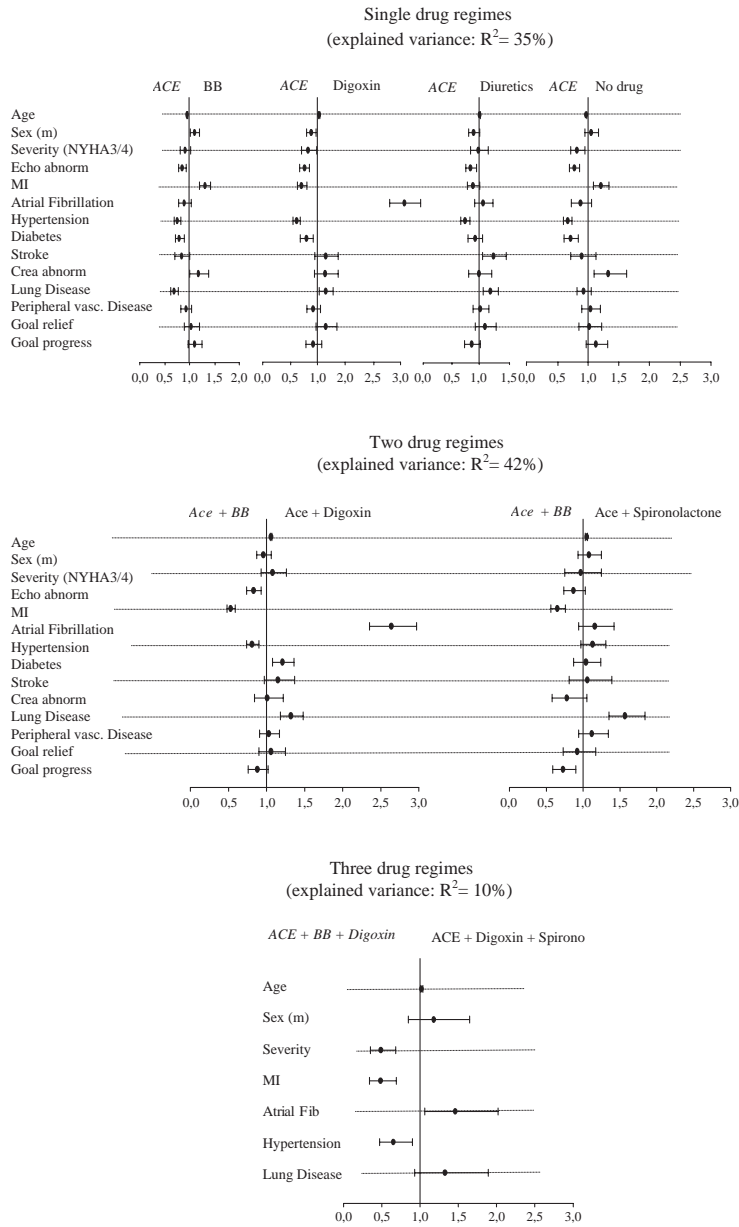


Fig. 1. Determinants for the use of drug regimes (odds ratios, 95% CI). Explained variance includes all patient characteristics in the model including nationality. Bars entirely on the right indicate that patients with this characteristic are significantly less likely to get the recommended drug regime.

nants ($p < 0.10$), with the country as a covariate, were included in the multivariate analysis. A multinomial logistical model was performed with random effects [11] for each therapeutic step.

2.5. Prescribing according to evidence and adjustment to patient characteristics

Prescribing in relation to evidence was evaluated using four degrees of adherence:

- Adherence 1: crude adherence directly derived from guideline recommendations before taking comorbid-

ities into account (=reference drug regimes of each step);

- Adherence 2: comorbidity induced treatment in line with evidence and recommendations taking comorbidity into account;
- Adherence 3: comorbidity induced treatment not in line with evidence;
- Non-adherent: still unexplainable after taking patient characteristics into account.

Patients whose treatment was not adherent at the first level (adherence 1) were reassessed according to their comorbidities, if these made another drug regime signifi-

cantly more likely (conditions resulting in significant $OR > 1$; Fig. 1).

3. Results

Data from 11,062 patients in 14 countries were analyzed. Baseline characteristics of the study population and descriptive results are described in detail elsewhere [7]. Mean age was 69.3 (STD 12.4) years, 45% of the patients were female. Main factors contributing to CHF were: history of myocardial infarction (34%), ischemic heart disease (28%) and hypertension (48%). Patients on average had 2.1 coexisting conditions; only 11% of the patients had none.

On average patients received 1.5 (STD 0.8) drugs for CHF and 2.2 (STD 1.1) drugs if diuretics were included. 51.8% of the patients were treated with a single drug regime (potentially including diuretics). Two-drug regimes were given to about a third and three-drug regimes to 7.7% of the patients (Table 1).

If a one-drug regime was used, ACE-inhibitors were the most commonly used drug (42.9%), followed by β -blockers (20.3%) and digoxin (15.4%). If more than one drug was given, most combinations contained ACE-inhibitors (93.4% in two-drug; 94.6% in three-drug regimes). More than half of the combinations did not include β -blockers (66.3%). For two-drug regimes the combination of ACE-inhibitors and digoxin (44.3%) was slightly more commonly prescribed than ACE-inhibitors combined with β -blockers (42.0%). ACE-inhibitors and β -blockers were more often combined with digoxin than with spironolactone.

3.1. Determinants of drug treatment

Patient characteristics accounted for 35%, 42% and 10% of the variation in each treatment intensity level in the multivariate analysis (Fig. 1).

Age was a determinant in each step of treatment intensity. Younger patients were more likely to receive no therapy rather than single drug regimes (except β -blockers). With each additional year of age, patients had a 3% greater chance (OR: 1.03, 95% CI 1.02–1.04) of being given digoxin rather than an ACE-inhibitor as a single drug regime and a 6% higher chance (OR: 1.06, 95% CI 1.05–1.07) of being given digoxin combined with an ACE-inhibitor rather than the recommended β -blocker combined with an ACE-inhibitor. Age also increased the chance of receiving spironolactone rather than a β -blocker in combination with an ACE-inhibitor plus digoxin by 2% (OR 1.02, 95% CI 1.01–1.04).

Sex was only a significant determinant in the first level where men were 11% more likely (OR: 1.11, 95% CI 1.02–1.21) to be given β -blockers and women 10% more likely (OR: 0.90, 95% CI 0.82–0.98) to be given digoxin than ACE.

Patients with an abnormal echocardiogram were more likely to receive recommended therapy (ACE-inhibitors over all other single drug therapies and in combination with

β -blockers instead of digoxin (OR: 0.83, 95% CI 0.74–0.93)).

Higher NYHA score increased the likelihood of getting ACE-inhibitors rather than no treatment in level one (OR: 1.2, 95% CI: 1.05–1.39) and increased the likelihood of receiving the recommended treatment within level three (OR: 2.04, 95% CI: 1.47–2.85).

Patients with a history of MI had a higher chance of getting β -blockers rather than ACE-inhibitors as single drug regime (OR: 1.32, 95% CI 1.21–1.43) and combinations with β -blockers in the more complex treatment regimes.

Patients with atrial fibrillation had a 2.4-fold increased chance (OR: 2.4, 95% CI 2.2–2.7) of being given digoxin rather than an ACE-inhibitor for single drug regimes, and a 2.6-fold increased chance (OR 2.64 95% CI 2.35–2.97) of being given digoxin rather than β -blockers combined with ACE-inhibitors. β -blockers were more likely to be used than spironolactone as the third drug in combination with ACE-inhibitors and digoxin for these patients (OR: 1.46, 95% CI 1.06–2.02).

Hypertension or diabetes both increased the odds of being given an ACE-inhibitor rather than any other single drug regime. Within two-drug regimes, β -blockers were more likely to be given along with ACE-inhibitors in hypertensive patients (OR 0.81, 95% CI 0.74–0.90), whereas diabetic patients were more likely to be prescribed digoxin as the second drug (OR 1.21, 95% CI 1.08–1.36).

Lung disease decreased the chance of getting β -blockers alone or combined with ACE-inhibitors, but it increased the chance of being given digoxin or diuretic monotherapy instead of an ACE-inhibitor.

Most of the influence of abnormal creatinine levels seen in univariate analysis disappeared when correcting for other patient characteristics, although there was a higher chance in single drug regimes for β -blockers to be prescribed rather than ACE-inhibitors.

3.2. Prescribing according to evidence

Prescription patterns were explained better by taking patient characteristics into account (Table 3). The overall crude adherence rate (adherence 1) was 45%. Including comorbidity-induced prescribing still in line with evidence and recommendation (adherence 2) increased the overall rate to 56%. An additional 14% of prescriptions could be explained by patient characteristics; however, these were usually not in line with evidence (adherence 3). For example, 567 patients with a history of MI were treated only with a β -blocker, 267 patients with lung disease were treated only with digoxin and 194 with diuretics only.

4. Discussion

We aimed to assess the impact of patient characteristics and comorbidities on CHF treatment in European primary

Table 3
Patient characteristic induced treatment in relation to evidence

Drug regime ^a	Adherence			
	Adherence 1 ^b <i>n</i>	Adherence 2 <i>n</i> (determinant)	Adherence 3 <i>n</i> (determinant)	Non-adherent <i>n</i> (determinant)
ACE-inhibitor	2463	0	0	0
BB	0	0	567 (MI)	358 (Male, no MI)
Digoxin	0	0	267 (Lung disease) 341 (AF)	0
Diuretic monotherapy	0	0	194 (Lung disease)	42 (Stroke, no lung disease)
No drug	0	0	0	250 (MI) 53 (Creatinine abnormal)
Total one-drug regimes	2463	0	1369	703
ACE+BB	1629	0	0	0
ACE+digoxin	0	718 (AF) 521 (Lung disease)	166 (Diabetes; no AF or lung disease)	0
ACE+spironolactone	0	100 (Lung disease)	0	0
Total two-drug regimes	1629	1339	166	0
ACE+BB+digoxin	475	0	0	0
ACE+digoxin+spironolactone	0	0	0	175 (AF)
Total three-drug regimes	475	0	0	175
Total patients (11,062)	4567	1339	1535	3114
Adherence (rate ^c)	45%	+11%	+14%	

Patients whose treatment was not adherent at the first level (adherence 1) were reassessed according to their characteristic, if that made the drug regime significantly more likely (see text).

^a Each regime can contain diuretics.

^b Adherence 1: reference drug regimes of each step; adherence 2: patient characteristic induced treatment in line with evidence; adherence 3: patient characteristic induced treatment usually not in line with evidence.

^c Corrected for the number of patients in each treatment intensity step.

care in order to improve the understanding of prescribing not in line with evidence.

Two factors inherent in CHF management considered of major importance for the assessment of prescribing quality are poly-pharmacy and comorbidities [12]. More than 50% of the patients in this study were treated with combined drug regimes and 89% had coexisting diagnoses. Thus physicians not only have to adapt treatment to the individual patient's physical and social situation but also need to take competing therapeutic requirements and drug interactions into account [3].

Our analysis identified several important issues. Firstly and most importantly, comorbidities and other patient characteristics are key factors driving prescribing patterns, whether these are in line with recommendations or not. Secondly, under-prescribing of ACE-inhibitors is limited to single drug regimes. Finally: prescribing in male patients, with atrial fibrillation or a history of myocardial infarction has potential for improvement.

The use of combination therapy as a quality indicator for CHF drug therapy has been suggested [13,14] but is not often applied. Initial analysis of this dataset had already indicated the negative impact of age, concomitant disease and prior hospitalization on the combined use of ACE-inhibitors and β -blockers [7]. Further to a recently published analysis of this population [15], our analysis enables us to predict which drug combinations are most

likely to be given to specific patient subgroups. For instance low use of ACE-inhibitors was restricted to single drug regimes; however, they were almost always included in more intense treatment regimes. Furthermore it was shown that the more complex prescription patterns which were induced by patient characteristics still resulted in effective therapy, while single drug regimes often resulted in insufficient treatment. For example, patients with AF who are treated with digoxin and an ACE-inhibitor are being treated in line with recommendations, while those who are only treated with digoxin have to be considered undertreated.

In primary care, patient demographics are frequently different to those from patients included in randomized clinical trials. Our patient population was about 8 years older and included 20% more women than an average trial [16]. This is often used as an argument to justify the lower uptake of evidence-based treatment in primary care. The influence of age was a significant determinant for treatment, even after correction for other potentially debilitating conditions and the therapeutic goal. The trend to a more "conservative" or symptomatic rather than prognostic treatment (diuretics or digoxin rather than β -blockers) with increasing age is in agreement with other studies [17,18]. One possible explanation is that older patients with long-standing CHF are more likely to be treated with established therapeutic regimes, which are not automatically updated in

response to newer evidence. Furthermore a perceived lack of benefit [19–21] could contribute to the potential lack of awareness of newer evidence including broader study populations [22]. Also, the tendency in single drug regimes against the use of ACE inhibitors and a preference for digoxin or diuretics in women and for β -blockers in men needs attention.

The common comorbidities in patients with CHF are potential hurdles to the implementation of therapy according to guideline recommendations [12,20,23]. Accordingly we found that lung disease, which was present in about 25% of patients, decreased the odds of β -blocker and single ACE-inhibitor therapy significantly.

Moreover, the effect of a given comorbidity could be detected consistently over all treatment levels. Patients with a history of MI and those with atrial fibrillation were both more likely to receive a β -blocker or digoxin rather than an ACE-inhibitor as a single drug treatment. However, when more intensive treatment was required, ACE-inhibitors were the most likely second drug in these patients. This finding is in line with other studies which describe doctors' reluctance to disturb the therapeutic status quo [19], and suggests that physicians tend to add sequentially to an established therapy (which might even have been started for a different primary diagnosis).

Overall crude recommended prescribing (adherence 1) was 45%, which is compatible with common rates of overall ACE- and β -blocker-use found in the literature [6,8,17]. However, this assessment does not take into account coexisting patient conditions from everyday practice, which is a frequent criticism from practicing physicians. Including patient characteristics in the assessment gave substantially higher scores, 56% of prescriptions were in accordance with evidence for specific patients.

On the other hand, although additional 14% of prescriptions were explained by patient characteristics, those treatments often appeared inappropriate and a further 30% of treatments remained unexplained. These provide a target for improving prescribing. Patients with a previous myocardial infarction, who are more likely to be given no drug rather than ACE-inhibitors, are just one example. The fact that older age per se evoked a trend to more symptomatic therapy is another.

4.1. Limitations

All definitions in this study were made in an effort to measure prescribing quality while taking everyday conditions into account. They are all based on a combination of guideline recommendations, accumulated evidence and clinical practice [24].

Drug regimes were defined to make comparisons within levels of similar treatment intensity possible. Therefore diuretics which are considered symptomatic drugs, and are not necessary for maintenance therapy were not defined as a separate drug class. Digoxin in contrast should be con-

tinued, once introduced [10], although the prognostic value of this drug class for a wider population is still under debate [24].

Adherence rates can only give indications rather than absolute measurements and depend on the indicators used. We tried to reflect everyday practice as much as possible in our assessment.

4.2. Conclusions and implications

Patient characteristics explain up to one third of the variation in CHF drug treatment in European primary care. Up to 56% of prescription patterns appeared rational on the basis of this analysis and therefore prescribing might be more rational than generally perceived [25]. On the other hand, specific areas of poor prescribing were detected. Therapy is strongly influenced by age and concomitant conditions, which provide relative contra-indications. Our results provide the opportunity to target interventions to improve evidence-based prescribing, particularly in male patients and those with AF or a history of MI.

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