Influencing physician prescribing in an international context
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Prescribing for chronic heart failure in Europe: does the country make the difference? A European survey.

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Abstract

**Purpose** International differences in prescribing patterns for chronic heart failure (CHF) have been demonstrated repeatedly. It is not clear whether these differences arise entirely from patient characteristics or factors related to the country itself, such as health care systems or culture. We aim to assess the role of countries in this international variation, aside from the role of patient characteristics.

**Methods** In this European primary care practice survey (from 1999/2000) 11062 CHF patients from 14 countries were included. The influence of country (corrected for patient characteristics) on prescribed drug regimes was assessed by multinomial logistical regression.

**Results** Prescribing of guideline-recommended drug regimes ranged from 28.1% in Turkey to 61.8% in Hungary. Including additional regimes justifiable by patients’ co-morbidities, increased overall “rational” prescribing by 11%, but differences among countries remained similar. Multivariate analysis for one-drug and two-drug regimes explained between 35% and 42% of the total variance, country contributed 7-8% (p<0.005). Countries determined the number of drugs used and the likelihood of individual drug regimes. E.g. in Czech Republic digoxin alone was more likely to be given than the recommended ACE-inhibitors (OR: 3.45; 95%CI: 2.56-4.64), while the combination of digoxin with ACE-inhibitors was not different to the recommended combination of ACE-inhibitors and β-blockers (OR: 1.17; 95%CI: 0.88-1.55).

**Conclusion** Country of residence clearly influenced prescribed drug volume and choice of drug regimes. Therefore, optimal CHF management cannot be achieved without considering country specific factors. It remains to be established which factors within health-care systems are responsible for these effects.

**Keywords:** Chronic heart failure; Europe; quality of care; prescribing; primary care; delivery of health care; European survey
Prescribing for CHF: Does the country make the difference?

Introduction

Heart failure poses a major burden on Western societies; treatment consumes between 1-2% of health care resources.1 Therapeutic options have improved significantly over the last decades. While new evidence is published widely in scientific literature and disseminated by guidelines, application of these guidelines lags behind expectations2, especially in primary care, where most of the patients with CHF are treated in Europe.3 Prescribing for ACE-inhibitors ranges from 48-76%, for β-blockers even lower.4 Marked international differences in cardiovascular therapy have been found5. Various studies6-8,4,7 and trials5,6-11 have described such variation for CHF prescribing, for hospitalized patients6 and primary care4 alike. Explanations for variation in treatment have focused on patient characteristics and concomitant diseases4,12,13, while the influence of health care settings and culture on such variation has remained unclear. This study aims to assess the overall influence of a patient’s country on heart failure prescribing while taking patient characteristics into account.

Methods

Data of 11062 patients from about 100 primary care practices in 14 European countries were included in the Improvement-HF survey from 1999/2000. Details about data collection and main results have been published.4 In each country, participating physicians were randomly chosen from 10 regional centers, urban and rural. Patients seeing their primary care physician with a diagnosis of CHF and/or myocardial infarction (MI) were included over a six week period in 1999. Information about patient characteristics such as age, gender, co-morbidities and diagnostic procedures was abstracted from patient charts.

Drug use was assessed using drug regimes rather than individual drug classes. All regimes found in more than 2% of the cases were included. Diuretics were not considered a separate drug class as they may be part of all regimes for symptomatic use. Diuretics were defined as loop-diuretic, thiazide or a combination thereof; AII-antagonists were grouped with ACE-inhibitors.

Quality of prescribing was classified into three degrees: "Crude adherence" refers to the frequency of recommended drug regimes according to the ESC guidelines published at the time of the study 14 irrespective of patient characteristics. "Adjusted adherence" includes drug regimes that were in line with recommendations taking comorbidity into account. All remaining cases were grouped in the category "Non-Adherent"13.
Statistical analysis
Drug regimes were grouped according to the number of drug classes used, reflecting comparable treatment intensity (table 1). For each group of drug regimes the influence of country, adjusted for patient characteristics, was analyzed separately. Accordingly, three multinomial logistical models were developed. An additional model was calculated to assess determinants for the number of drugs used. The country with the highest use of the guideline-recommended drug regime was used as the reference. Patient characteristics included in the models (significant at the 5% level in univariate analysis) were: age and sex, severity of disease (according to NYHA classes), availability of an abnormal echocardiogram, as well as history of myocardial infarction or stroke, atrial fibrillation, hypertension, diabetes, lung disease, peripheral artery disease, renal dysfunction.

Role of the funding source
Design and data collection of the IMPROVEMENT-HF survey was the responsibility of a steering group of the European Society of Cardiology working group on heart failure (WHG is a member). Design, analysis, interpretation, and writing of the study presented here was the complete responsibility of the authors and was financed by University funds of the University Medical Centre Groningen. The corresponding author had full access to all the data of the survey and had final responsibility for the decision to submit for publication.

Results
In each country between 599 and 1227 patients were included. Characteristics of the populations have been described in detail. Mean age was 69.3 years ranging from 64 in Russia to 76 years in Sweden. Between 40% and 53 % were female patients. Patients had an average of 2.1 coexisting diagnoses; hypertension (48%), myocardial infarction (34%), and ischemic heart disease (28%) were the most frequent ones. Age, sex, severity, myocardial infarction, atrial fibrillation, hypertension, and lung disease were significant determinants for all three intensity levels, while diabetes, stroke, peripheral vascular disease or abnormal creatinine were significant only for one- and two-drug regimes.

Frequencies of prescribed drug regimes are shown in table 1. In all but two countries (Hungary and Italy), single drug regimes were the most common, used in 50% or more of the patients. Between 29% of patients in Sweden and 58% in Belgium were treated with single ACE-inhibitor. In most countries, β-blockers were used less than ACE-inhibitors but more
than digoxin, while digoxin was preferred in three countries, and use of digoxin was equal to β-blockers in one country. Within regimes of two drugs, there was a clear preference for combinations containing ACE-inhibitors with β-blockers or digoxin; spironolactone combined with ACE-inhibitors was used much less everywhere (table 1). While 7.7% of the prescriptions consisted of three drugs, similar variation was found.

Prescribing according to first line recommendations (crude adherence) averaged 44.7% with a range from 28.0% in Turkey to 61.9% in Hungary (figure 1). When including treatment regimes adapted to comorbidities, another 11% were in line with recommendations (adjusted adherence). The difference between crude and adjusted adherence varied between 7.2% (Sweden) to 15.5% (Italy); nevertheless the rank of the two highest and two lowest adhering countries remained unchanged.

Multivariate analysis showed that country and patient characteristics together could explain 42%, 35% and 10% of the variation in prescribing for one- two- and three-drug regimes respectively. Country as determinant contributed 7% to the explanation of one-drug regimes (p<0.005), 8% to two-drug regimes (p<0.005) and 2% to three drug regimes (ns).

Country was also a significant determinant for the distinction between treatment intensity levels (numbers of drugs used). In France (OR 0.69; 95%CI 0.5-0.9), Spain (OR 0.53; 95%CI 0.4-0.6), Switzerland (OR 0.72; 95%CI 0.6-0.9) and the UK (OR 0.70; 95%CI 0.6-0.8), patients were more likely to be treated with fewer drugs than in Hungary, while in Italy (OR 1.54; 95%CI 1.3-1.8) and Poland (OR 2.02; 95%CI 1.6-2.6), combined drug regimes were more likely (figure 2).
### Table 1: Drug regimes and prescribing in line with recommendations (adherence) per country (%)

<table>
<thead>
<tr>
<th>Drug Regime</th>
<th>Belg</th>
<th>Cz/Slo</th>
<th>Fr</th>
<th>Germ</th>
<th>H</th>
<th>I</th>
<th>NL</th>
<th>Po</th>
<th>Ru</th>
<th>Spain</th>
<th>Swe</th>
<th>Swit</th>
<th>Tu</th>
<th>UK</th>
<th>total</th>
</tr>
</thead>
</table>
| **One-drug regimes (51.8%)** | (total n) | 621 | 849 | 1227 | 873 | 778 | 769 | 681 | 900 | 705 | 660 | 876 | 599 | 11062
| One-drug regimes (51.8%) | (total n) | 301 | 409 | 585 | 445 | 320 | 327 | 422 | 331 | 441 | 472 | 366 | 404 | 518 | 392 | 5733
| ACE-inhibitors (recommended) | **57.8†** | 32.3 | 45.1 | 46.1 | 48.8 | 53.8 | 36.7 | 42.9 | 47.2 | 36.4 | 29.2 | 45.3 | 38.8 | 48.0 | 43.0 |
| β-blockers | 19.3 | 30.8 | 25.5 | 16.2 | 26.9 | 14.7 | 26.3 | 23.0 | 12.9 | 16.1 | 31.7 | 20.8 | 6.2 | 18.6 | 20.3 |
| Digoxin | 10.0 | 22.5 | 9.9 | 16.2 | 8.4 | 11.3 | 8.5 | 18.1 | 22.4 | 19.7 | 12.0 | 10.6 | 32.6 | 5.6 | 15.4 |
| Diuretics | 5.6 | 5.9 | 10.3 | 10.6 | 7.2 | 9.8 | 14.9 | 4.5 | 9.5 | 11.0 | 18.0 | 13.9 | 9.5 | 14.8 | 10.5 |
| No therapy | 7.3 | 8.6 | 9.2 | 11.0 | 8.8 | 10.4 | 13.5 | 11.5 | 7.9 | 16.7 | 9.0 | 9.4 | 12.9 | 13.0 | 10.8 |
| **Two-drug regimes (32.8%)** | (total n) | 203 | 335 | 436 | 293 | 358 | 313 | 213 | 288 | 169 | 178 | 182 | 260 | 166 | 3625
| Two-drug regimes (32.8%) | (total n) | 203 | 335 | 436 | 293 | 358 | 313 | 213 | 288 | 169 | 178 | 182 | 260 | 166 | 3625
| ACE-inhibitors + β-blockers (recommended) | **67.3†** | 33.2 | 48.1 | 48.4 | 56.3 | 22.5 | 65.7 | 47.8 | 4.6 | 34.9 | 44.9 |
| ACE-inhibitors + digoxin | 30.0 | 47.2 | 49.1 | 49.8 | 27.9 | 61.7 | 37.2 | 39.0 | 37.5 | 71.0 | 29.2 | 41.8 | 89.2 | 55.4 | 47.5 |
| ACE-inhibitors + spironolactone | 14.8 | 3.0 | 9.6 | 3.4 | 4.7 | 5.1 | 14.7 | 12.7 | 6.3 | 6.5 | 5.1 | 10.4 | 6.2 | 9.6 | 7.6 |
| **Three-drug regimes (7.7%)** | (total n) | 54 | 59 | 71 | 82 | 114 | 90 | 49 | 73 | 88 | 33 | 52 | 35 | 36 | 19 | 855
| Three-drug regimes (7.7%) | (total n) | 54 | 59 | 71 | 82 | 114 | 90 | 49 | 73 | 88 | 33 | 52 | 35 | 36 | 19 | 855
| ACE-inhibitors + β-blockers + Digoxin (recommended) | **85.4†** | 81.6 | 56.7 | 57.1 | 30.1 | 45.5 | 24.2 | 78.8 | 54.3 | 41.7 | 47.4 | 55.6 |
| ACE-inhibitors + digoxin + Spironolactone | 50.0 | 40.7 | 50.7 | 14.6 | 18.4 | 63.3 | 42.9 | 69.9 | 54.5 | 75.8 | 21.2 | 45.7 | 58.3 | 52.6 | 44.4 |
| Other# | (total n) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | 849 |
| Avg. number of drugs used | 2.2 | 2.15 | 2.16 | 2.23 | 2.49 | 2.36 | 2.08 | 2.12 | 2.34 | 1.81 | 2.17 | 1.99 | 1.88 | 1.96 | 2.16 |

*each regime can contain diuretics, † reference country with the highest recommended prescribing
#most frequent regimes not included in analysis: β-blocker + digoxin: n=57 (0.5%); digoxin + spironolactone: n=198 (1.8%); β-blocker + digoxin + spironolactone: n=49 (0.4%); n.a. not applicable.
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**Figure 1: Quality of prescribing**

- % crude adherence
- % adjusted adherence (95% CI intervals) includes patients treated with ACE + digoxin who have atrial fibrillation (n=718) or lung disease (n=521); ACE + spironolactone and lung disease (n=100).

* Confidence intervals refer to the difference to the crude adherence.

**Figure 2: Treatment intensity (frequency of one-, two- or three-drug regimes)**

- correct odds ratios (p<0.005) indicate the likelihood of two or three-drug regimes as compared to single-drug regime use; compared to Hungary.
Figure 3a: Countries as determinant: one-drug regimes (OR, 95% CI. Reference country: Belgium)

Figure 3b: Countries as determinant: two-drug regimes (OR, 95% CI. Reference country: Hungary)

OR corrected for patient characteristics (see text)
Belgium had the highest rate of the recommended one-drug regimes (ACE-inhibitors) and therefore was the reference country (table 1). However, when taking patient characteristics into account, in nine countries ACE-inhibitors were more likely than in Belgium (in five countries compared to digoxin, in four compared to β-blockers; figure 3a). The preference for one drug in one level does not imply consistent preferences in the other levels. For instance, while in one-drug regimes in Italy and Turkey β-blockers were less likely than in the reference country, β-blockers were consistently avoided in all combinations only in Turkey. Of the five countries favoring digoxin in one-drug regimes, only two also preferred the combination of ACE-inhibitors with digoxin over β-blockers (figure 3).

For two-drug regimes, Hungary was the reference country as it had the highest prescribing rate of ACE-inhibitors combined with β-blockers (table 1). Despite the marked differences in absolute prescribing, in only three countries a therapy other than the first line recommendation was significantly more likely than Hungary. By contrast, in eight countries the recommended regime was more likely than in Hungary when taking patient characteristics into account (figure 3b).

With 85.4 % of the patients in Germany receiving the recommended three-drug regime, this was the reference country. Correcting for patient characteristics did not have a major impact: patients in all countries were less likely to being treated with the recommended drug regime than in Germany and therefore three-drug regimes were not presented in figure 3.

Discussion

While the consistent international variation in drug prescribing has raised concerns about implicit underuse of medication,1 the role of the country has hardly ever been directly addressed. This study provides clear evidence that the country strongly influences the treatment irrespective of differences in patient populations.

The performance of countries varied significantly when analyzing prescribing in relation to recommendations and evidence. While in most of the countries overall recommended prescribing ranged from 40 to 50%, there were clear outlier countries on both extremes.

While in countries with a low level of crude adherence, drug regimes that are in line with recommendations only when taking concomitant diseases into account tended to be relatively more frequent, the overall pattern still persisted (figure 1).
In our data, country influenced the choice of specific drug regimes. In some countries there was a consistent trend for or against one specific drug class. For instance in Turkey all drug combinations containing β-blockers were highly unlikely, which is also reflected in the very low absolute β-blocker-use. In other countries different drugs were used at different treatment levels. For instance doctors in the UK prescribed digoxin less likely than an ACE-inhibitor or a β-blocker as single-drug, but digoxin in combination with ACE-inhibitors was not less likely than in the reference country.

In line with other studies, country also influenced the number of drugs prescribed. For example it has been shown that overall prescriptions at consultations were fewer in Sweden than in Poland15 and heart failure drugs were given less in the UK than in Czech Republic.16

Our results indicate that European variation in prescribing for CHF partly is attributable to country-specific organizational or structural features. However, the effect of specific factors is not well understood. It has been suggested, that healthcare systems with unlimited access and/or a large supply of doctors and pharmacies, such as in Italy, Germany, Belgium promote an attitude of “a pill for every ill”, while in countries with gatekeeping and limited numbers of providers, drug use is expected to be lower.17 Also the effect of culture has been discussed.18

In practice, access, financial incentives for patients19,20 and prescribers21 are tools for policy makers to influence doctors prescribing habits.22 Considering the importance of heart failure for Western societies, it is especially relevant to provide clear evidence about effective methods to improve CHF therapy.

**Limitations:**

Drug regimes and adherence were defined based on a combination of guideline recommendations, accumulated evidence and clinical practice23 in an effort to explain prescribing under every day conditions. However, as results depend on the indicators used, they can only give indications rather than absolute measurements.

Some overestimation of prescribing quality might have been present due to the voluntary participation of physicians; however this should not have influenced the relation among countries, since recruitment was uniform everywhere. We did not address differences between physicians’ age and sex. However in earlier analysis4, where physicians’ perceptions about their prescribing influenced β-blocker and ACE-inhibitor use, other physician characteristics have not played a role.24
Some of the evidence regarding β-blocker and spironolactone was fairly new and uptake thereof might have varied between countries. National guidelines available at the time of the study on the other hand have not shown major differences. At that time also the role of spironolactone in relation to diuretics was also disputable. This, along with low frequencies of three-drug regimes, might clarify why the multivariate model explained only 10% of the variation and country was not a significant determinant for three-drug regimes.

This study did not relate specific health care settings to prescribing but merely assessed the effect of country as a global variable while correcting for clinical differences in patient populations. Therefore no conclusions about the role of specific regulations or structures can be made.

**Conclusion:**

Drug regimes in line with evidence varied between roughly 30% and 60%. This could not be sufficiently explained by differences in patient characteristics: Country was a significant determinant of the number of drugs used as well as prescribing of individual drug regimes.

Our findings demonstrate the central role of national factors within a health-care system. Considering the importance of heart failure for Western societies, these results underline that efforts aiming at improving CHF outcomes cannot be limited to interventions focusing on patient care, but need to take other system and culture inherent factors into account. More research is needed to understand the wider set of underlying mechanisms influencing (heart failure) prescribing in European primary care. Our data provide a basis to analyze the influence of specific health care system factors on drug treatment in more detail.

**Acknowledgements:**

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**Conflict of interest statement for authors:**

We declare that we have no conflict of interest. All researchers have been independent of outside funding sources for this study.

Ethics approval not required for that analysis.

This manuscript has been earlier submitted for publication to the BMJ and the Lancet (special series) and been rejected.
References

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Key Notes

- Recommended drugs for heart failure appear not to be prescribed to the degree expected. This is especially true for primary care.
- There is a wide variation of prescribing between countries, which has mostly been explained based on patient characteristics.
- This study focuses on the role of the country.

Findings

- Country as such has a clear influence on prescribing for chronic heart failure in European primary care: Prescribing in line with evidence varies between countries. When taking patient characteristics (and concomitant diseases) into account country is a significant determinant of individual drug regimes and the number of drugs used.
- The distinct role of the patients’ country underlines the need to improve the understanding of how health care systems and culture affect management of CHF.