Differences in drug treatment of chronic heart failure between European countries

D. J. van Veldhuisen*, A. Charlesworth†, H. J. G. M. Crijns*, K. I. Lie‡ and J. R. Hampton§

Aims A large number of drugs are currently used for the treatment of chronic heart failure. Treatment for other cardiovascular disorders has been shown to differ between countries. In this study we examined whether this would also be true in heart failure.

Methods and Results We studied patients with moderate to severe heart failure, who were enrolled in an international survival study, and compared patterns of drug use between the nine countries that each included >50 patients in the study. The results were analysed to determine whether observed differences between countries could be explained by differences in the patients recruited. 1825 patients were studied (range 81–427 per country). By trial protocol, most patients were treated with angiotensin converting enzyme (ACE) inhibitors (92%) and all with diuretics, but the proportion of patients taking high doses of these drugs was markedly different between countries. Large differences were also observed in the use of digoxin (overall 64%, 39% in the U.K. to 87% in Germany) and antiarrhythmics (overall 25%, with the highest use 44% in France). The use of beta-blockers and calcium antagonists was low (overall 6% and 8%, respectively), but also different between countries. Anticoagulants (overall 43%) were used in many patients in the Netherlands and Switzerland (around 70%), while antiplatelets (overall use 30%) were most often prescribed in Denmark (51%).

Conclusions Large differences in drug use and dosing for patients with advanced heart failure are observed between (European) countries. None of these differences could be explained by differences in patient characteristics, and whether they are related to factors such as tradition, economic circumstances and national guidelines, etc. is unknown.

Key Words: Heart failure, treatment, international differences.

See page 637 for the Editorial comment on this article

Introduction

Chronic heart failure is a growing medical and epidemiological problem, characterized by a high morbidity and mortality. Although a large number of drugs are prescribed in heart failure, the use of these various agents is not uniform, and treatment is often less than optimal[1,2]. In the past, most heart failure patients were treated with digoxin and diuretics, but whereas the use of diuretics remains widespread, the value of digoxin has become controversial in patients with heart failure and sinus rhythm. Angiotensin converting enzyme (ACE) inhibitors have become the most important drugs in heart failure, since they reduce morbidity and mortality, although in most trials with ACE inhibitors, high-doses of these drugs were used, in clinical practice the doses are often much lower[3]. In two recent large heart failure trials, one showed a therapeutic advantage of a high- over a low-dose ACE inhibitor regimen in slowing the progression of the disease[4], but in the other, no relationship between dose and outcome could be demonstrated[5]. In addition to diuretics and ACE inhibitors (with or without digoxin), many other drugs have been tested in heart failure[6], and are often


Presented in part at the 47th Annual Scientific Sessions of the American College of Cardiology, March 1998, Atlanta GA, U.S.A.

Dr van Veldhuisen is a Clinical Scientific Investigator of the Dutch Heart Foundation.

Correspondence: Dr Dirk J. van Veldhuisen, Department of Cardiology/Thoraxcentre, University Hospital Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
used in these patients, but the value of most of these agents in heart failure is unclear, with the exception of beta-blockers, which have recently been shown to prolong survival[7]. This category includes antiarrhythmic drugs (in particular amiodarone), calcium channel antagonists, long-acting nitrates, anticoagulants and antiplatelets[8].

Previous studies have shown that therapeutic strategies vary markedly between countries with respect to myocardial infarction[9]. The aim of our study was to examine whether such differences exist in heart failure. We therefore examined drug treatment between nine different European countries in a large population of patients with moderate to severe heart failure, who were part of a recently published study[10].

**Methods**

**Study population**

All patients in this study were part of the PRIME-II Trial (Prospective Randomized study of ibopamine on Mortality and Efficacy), of which the inclusion and exclusion criteria have previously been described in detail[8]. In short, patients aged 18–80 years, were eligible for PRIME-II if they had signs and symptoms of moderate to severe chronic heart failure (New York Heart Association [NYHA] functional class III–IV). They were required to have had symptoms at rest, or a hospital admission for heart failure within the previous 2 months, but those who could not be discharged from the hospital were not eligible. All patients had to be on optimal medical treatment, including ACE inhibitors (unless intolerant), diuretics (in a dose of furosemide ≥80 mg [or equivalent] if ACE inhibitors were not prescribed, or ≥40 mg, when combined with an ACE inhibitor), and, if indicated, digoxin and vasodilators. Evidence of heart disease had to be proved by a left ventricular ejection fraction <0·35, or by an echocardiography-determined left ventricular end-diastolic diameter >60 mm or fractional shortening <20%, or by a cardiothoracic ratio on a chest X-ray >0·50. Standard exclusion criteria were used, which have been described in detail elsewhere[8].

**Data analysis**

The primary objective was to compare the use of drugs for heart failure (in % of patients) between the European countries that participated in PRIME-II. Also, dose of ACE inhibitors and diuretics was compared, and we prospectively defined high-, medium-, and low-dose ACE inhibition per day as follows:

‘high-dose’: 75–150 mg captopril, 21–40 mg enalapril or lisinopril, or equivalent;
‘medium-dose’: 25–50 mg captopril, 10–20 mg enalapril or lisinopril, or equivalent;
‘low-dose’: <25 mg captopril, <10 mg enalapril or lisinopril, or equivalent.

With regard to diuretics, we defined high-dose as >120 mg furosemide or equivalent daily, and low-dose as ≤120 mg.

In the analysis presented, data from all 13 countries are included in the overall rates. In order to avoid bias from countries that included only a few patients, we chose to analyse only countries recruiting >50 patients in the study. Differences between the use of drugs between countries were assessed using a logistic regression analysis. Pairwise comparisons between the individual countries were made using the parameter estimates from the fitted model. To examine the impact of the presenting baseline characteristics on any difference observed, further logistic regression models were fitted including the baseline variables (such as age, sex, left ventricular ejection fraction, NYHA class, underlying aetiology, rhythm, heart rate and blood pressure, etc).

**Results**

**Patient population**

Of the 13 European countries that participated in PRIME-II, nine countries included >50 patients, giving a patient population of 1825 patients (Table 1). Patients from Hungary (n=37), Portugal (n=16), Luxembourg (n=15), and Austria (n=13) were not analysed in this study. All patients were randomized between September 1992 and August 1995, and all 155 participating centres were cardiological practices. Baseline demographics and 1-year mortality in the nine countries are presented in Table 1. There were no significant differences in heart rate (mean 81 ± 15 beats . min⁻¹) and blood pressure (systolic 122 ± 20 mmHg, diastolic 75 ± 11 mmHg).

**Use of drugs**

Digoxin (Fig. 1) was used by 64% of the overall population, but this varied from 39% in the U.K. to 87% in Germany. The most pronounced finding was the low use of digoxin in the U.K., which was significantly lower than in the rest of the countries (P <0·001). The use of digoxin was independent of any baseline variable, and in particular, could not be explained by differences in severity of heart failure, or presence of atrial fibrillation.

Diuretics were, by definition, used by all patients and the overall median diuretic dose (furosemide or equivalent) was 80 mg (mean 117 mg, range 40–1600 mg). The mean dose varied from 64 mg in Belgium to 173 mg in Denmark. Use of high-dose diuretics varied from 2% and 4% in Spain and Belgium to 34% in the U.K. and 56% in Denmark (Fig. 2). These differences between countries were highly significant (P <0·001), but could not be explained by the recorded severity of heart failure, or by any index of left ventricular dysfunction.
<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Number of centres</th>
<th>Age (years)</th>
<th>% male</th>
<th>LVEF (%)</th>
<th>NYHA§ (% III)</th>
<th>Aetiology % IHD*</th>
<th>Aetiology hypertension</th>
<th>Diabetes (present)</th>
<th>Rhythm (% SR/AF)</th>
<th>Duration CHF (months)</th>
<th>1-year mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands (NL)</td>
<td>427</td>
<td>25</td>
<td>67</td>
<td>77</td>
<td>23</td>
<td>70</td>
<td>77</td>
<td>5</td>
<td>22</td>
<td>76/20</td>
<td>36</td>
</tr>
<tr>
<td>United Kingdom (GB)</td>
<td>337</td>
<td>23</td>
<td>65</td>
<td>82</td>
<td>30</td>
<td>57</td>
<td>77</td>
<td>3</td>
<td>18</td>
<td>67/25</td>
<td>41</td>
</tr>
<tr>
<td>Germany (DE)</td>
<td>223</td>
<td>17</td>
<td>61</td>
<td>82</td>
<td>27</td>
<td>55</td>
<td>46</td>
<td>4</td>
<td>27</td>
<td>62/31</td>
<td>54</td>
</tr>
<tr>
<td>Italy (IT)</td>
<td>220</td>
<td>27</td>
<td>64</td>
<td>78</td>
<td>28</td>
<td>64</td>
<td>39</td>
<td>13</td>
<td>18</td>
<td>71/23</td>
<td>42</td>
</tr>
<tr>
<td>France (FR)</td>
<td>208</td>
<td>30</td>
<td>67</td>
<td>78</td>
<td>27</td>
<td>61</td>
<td>40</td>
<td>4</td>
<td>18</td>
<td>70/23</td>
<td>53</td>
</tr>
<tr>
<td>Belgium (BE)</td>
<td>124</td>
<td>12</td>
<td>68</td>
<td>75</td>
<td>25</td>
<td>43</td>
<td>65</td>
<td>5</td>
<td>23</td>
<td>65/23</td>
<td>44</td>
</tr>
<tr>
<td>Spain (ES)</td>
<td>123</td>
<td>10</td>
<td>64</td>
<td>82</td>
<td>27</td>
<td>47</td>
<td>54</td>
<td>6</td>
<td>29</td>
<td>63/29</td>
<td>53</td>
</tr>
<tr>
<td>Switzerland (CH)</td>
<td>82</td>
<td>5</td>
<td>61</td>
<td>87</td>
<td>24</td>
<td>63</td>
<td>51</td>
<td>5</td>
<td>15</td>
<td>73/17</td>
<td>40</td>
</tr>
<tr>
<td>Denmark (DK)</td>
<td>81</td>
<td>6</td>
<td>65</td>
<td>89</td>
<td>25</td>
<td>61</td>
<td>58</td>
<td>6</td>
<td>14</td>
<td>65/28</td>
<td>39</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; CHF = chronic heart failure; IHD = ischaemic heart disease; LVEF = left ventricular ejection fraction; SR = sinus rhythm.

*Aetiology listed as primary underlying aetiology for CHF.

§At baseline, patients were classified as NYHA III, III/IV (see 10).
ACE inhibitors were used by 92% of the population (according to protocol, patients were required to be treated with, or to have known intolerance to them), and there were no significant differences between countries. High-dose ACE inhibitors, however, were only given in 25% of patients overall, varying from 35% in the U.K. to 17% in Belgium (Fig. 3). There was no relationship between the use of high-dose ACE inhibitors and any of the clinical parameters, including severity of heart failure.

Antiarrhythmic drugs were used in 25% of all patients (Fig. 4), and in the majority this was amiodarone (87% of antiarrhythmics, used in 22% of total population). Class I drugs were used in the other 13% of patients given antiarrhythmics. Prescription of antiarrhythmic drugs was markedly more common in France (44%) than in other countries (P <0.001), except for Switzerland (P =0.05). Class I antiarrhythmic drugs were used in 0–6% of all patients (3% of the total population). The high use of antiarrhythmic drugs could not be explained by the presence of atrial fibrillation, or by any other difference in baseline characteristics.

Beta-blockers were used in 6% of all patients, ranging from 2% in the U.K., to 11% in the Netherlands (difference P <0.001 between these two countries) (Fig. 5). Use of beta-blockers was not related to differences in severity of heart failure.

Calcium antagonists were used in 8% of all patients. Only 1% of patients were using these drugs in Switzerland, compared to 15% of patients in France (Fig. 6). These differences were not related to any of the baseline clinical characteristics, such as the presence of hypertension or angina pectoris.

Long-acting nitrates were used in 46% in the total population (Fig. 7), but only slight differences were observed between countries, which were of borderline significance, and not related to baseline demographics.

Anticoagulant use (overall 43%) (Fig. 8) was markedly different between the countries, varying from 19% of the patients in France, to 68% of the patients in Switzerland, and 70% of the patients in the Netherlands. This use in the Netherlands and
Switzerland was significantly higher ($P < 0.01$) than in all other countries. Prescription of these drugs was not related to any of the baseline conditions, in particular atrial fibrillation or left ventricular dimensions.

Antiplatelets were used in 30% of all patients (Fig. 9), and ranged from 18% in the Netherlands (and 23% in Switzerland), to 51% in Denmark. In these countries with a higher use of anticoagulants, the use of antiplatelets was low.

**Discussion**

The therapeutic approach to chronic heart failure is complex and drug treatment plays an important part in it, since it may improve quality of life and prognosis. A vast number of large-scale trials have been conducted in heart failure[6], and there are well-defined guidelines for its treatment[11,12]. Therefore, although in individual patients, differences in treatment strategy may always be justified given the variety of underlying diseases, one would expect to find certain treatment patterns among most of the countries in such a large-scale trial. The present study shows, however, that significant differences of treatment regimens exist between individual European countries, not only in the use of drugs, but also regarding the dose. These results cannot be explained by differences in baseline demographics and...
severity of disease, and therefore it appears that there are true differences in the pharmacological treatment of heart failure.

ACE inhibitors and diuretics have become widely established as being the cornerstone in the treatment of heart failure. Although there are many theoretical considerations why high-dose ACE inhibition would be more beneficial than low-dose, recent studies have neither shown conclusive results, nor a significant reduction in mortality[4,5]. In the present study, substantial differences in the dose of ACE inhibitors used were observed. For diuretics, the proportion of patients who were on high doses varied even more, and there was no relationship with the dose of ACE inhibitors. The precise value of most, if not all, other adjunctive drugs is less defined. Traditionally, digitalis was also part of the standard treatment of heart failure, and it still is in the majority of patients who are in atrial fibrillation. However, its value in patients with sinus rhythm is questioned, and a recent survival trial in almost 8000 patients did not show a favourable effect on mortality, although the number of hospitalizations decreased[13]. The low use of digitalis in the U.K. in the present study confirms previous observations, and it has been suggested that this goes back to the beginning of this century[14].

The use of antiarrhythmic drugs (mostly amiodarone) was markedly different between countries, and the most striking finding was the high use in France (44% of all patients). Although it is possible that more patients in France had an unrecorded history of sustained ventricular arrhythmias or cardiac arrest, this is unlikely, since other baseline characteristics were similar. The use of amiodarone in heart failure has long been controversial, particularly because of its high incidence of toxicity, and in current European guidelines for chronic heart failure routine use of this drug is not recommended[12]. However, in a recent meta-analysis, use of amiodarone was associated with a 13% reduction of all-cause mortality, and it was concluded that prophylactic use of this agent should be considered in high-risk patients[15]. Overall, 22% of patients in the present study were on amiodarone, which is higher than in the U.S.A. (7%)[16], although the use of this drug has been shown to increase in recent years[17]. Only 3% of the present patients were using class I agents, and in contrast to amiodarone, their use appears to have declined in recent years[17]. According to European guidelines for heart failure, these drugs should in general be avoided, since they may have an adverse effect on prognosis[12].

The use of both beta-blockers and calcium antagonists in the present study was overall rather low, and conclusions regarding differences between countries should be drawn with caution. Furthermore, many patients may have previously been started on these drugs because of hypertension or angina pectoris, rather than heart failure. In some countries as many as 15% of these patients with advanced disease were taking calcium antagonists, drugs that have not been licensed for chronic heart failure, and for which the available data so far do not support their use[6,12]. With regard to beta-blockers the situation is markedly different, since recent large-scale data suggest that these drugs may reduce mortality in heart failure[27]. Most if not all of the positive data on beta-blockers, however, were published in the last few years, and particularly in advanced heart failure, many physicians may be reluctant to use these drugs. This may explain their low use in the present study, although the observed differences between countries also suggest that other factors such as ‘belief in the concept of beta-blockade in heart failure’ (at that time) might have played a role. This latter aspect is supported by data from another study in a similar patient population, in which as many as 25% of all patients were using beta-blockers in Scandinavia[16], where these drugs were first advocated for heart failure 20 years ago[18]. The use of (long-acting) nitrates was remarkably similar between countries in this study and almost 50% overall, which confirms their place in the treatment of heart failure[1,16].

Anticoagulants and antiplatelets were used in a substantial proportion of all patients, with large differences between countries, despite the fact that current guidelines do not advocate routine use of these drugs in heart failure[11,12]. In recent substudies from the Studies of Left Ventricular Dysfunction (SOLVD), however, both anticoagulant and antiplatelet (monotherapy) were associated with a significant reduction in mortality[19,20]. Patients with atrial fibrillation may particularly benefit from anticoagulants, but a large proportion of these patients are not treated with these drugs[21]. In the present study, the use of anticoagulants was high in The Netherlands and Switzerland, two countries that have experienced and qualified thrombosis services. The use of antiplatelets obviously does not require such services, but may be associated with a reduction of the beneficial effect of ACE inhibitors[8].

Clinical implications and limitations of the study

Although the present study clearly suggests that there are differences between countries in the treatment of heart failure, the most important issue is to determine whether these findings are true, and not due to baseline differences in patient populations. In PRIME-II a very large number of baseline parameters was recorded, and although at baseline the populations were certainly not uniform, none of the parameters could explain the differences between countries. Further, it is well-known, that there are significant differences in the treatment of heart failure between general practitioners and hospital-based specialists[22], and between internists and cardiologists within one hospital[23]. Thus, only experienced cardiologists were asked to participate in PRIME-I[10]. As observed in previous, somewhat similar studies comparing prescription patterns between countries[16,24], it is difficult to see why there should be so much variation. Tradition may play a role, particularly with the use of
digoxin. The cost of treatment may also have some influence, although in general heart failure drugs are not particularly expensive. National guidelines may differ, although one might have expected adherence to the guidelines of the European Society. Locally conducted trials may also affect prescription of drugs. Another factor may be the availability of facilities, which may lower the threshold for some drugs, such as anticoagulants. Finally, an important factor may be the promotion of certain drugs by local pharmaceutical companies. Whatever the reasons, the present data indicate that factors other than scientific evidence guide drug prescriptions for heart failure. This observation needs further study since the implications may be significant.

We thank all investigators of the original PRIM E-II Study, for the careful collection of the data. A complete list of these investigators has been published in[20].

References


