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Use and Risk Management of Carvedilol for the Treatment of Heart Failure in the Community in England

Results from a Modified Prescription-Event Monitoring Study

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Abstract

Background: In the UK, the licence for carvedilol was extended in 1998 to include symptomatic heart failure (New York Heart Association [NYHA] class II and III heart failure) with the recommendation that initiation and up-titration should be under the supervision of a hospital physician. A post-marketing surveillance study was conducted to address the UK regulatory authority's request for monitoring the use and safety of carvedilol prescribed for heart failure in clinical practice.

Aim: To investigate adherence to risk management recommendations for the use of carvedilol for heart failure, monitor how patients' subsequent care was managed and collect event data to evaluate the safety profile of carvedilol used for the treatment of heart failure.

Methods: An observational cohort study using a modified prescription-event monitoring technique identified patients from dispensed primary care prescriptions in England (August 1999 to June 2001). An eligibility questionnaire was used to identify patients who had been prescribed carvedilol for heart failure for the first time after 31 July 1999. Up to three follow-up questionnaires were sent to the prescribers of eligible patients, requesting demographic information, dosage, supervision of treatment, status of cardiac failure and event information.

Results: 2311 patients met the eligibility criteria. For 1666 patients, one or more valid follow-up questionnaires were returned: 68.5% were male; male median age 66 years; female median age 72 years; the observation period was up to 3 years. Hospital physicians supervised initiation of treatment and first up-titration in 85.6% and 61.4% of patients, respectively. 49.2% of patients were prescribed the recommended starting dosage of carvedilol (6.25 mg/day). Approximately 25% of patients started on a lower dose than recommended, and the same proportion were prescribed a higher dose. NYHA status of cardiac failure between starting treatment and the third questionnaire improved for 39.5% of patients, deteriorated for 10.9%,

and 11.7% of those for whom NYHA status was given died. Adverse drug reactions (ADRs) were reported for 2.4% of patients; the most commonly reported ADR was malaise/lassitude. Overall, 27.1% of patients stopped taking carvedilol. None of the 163 deaths were attributed to carvedilol.

Conclusions: Regulatory guidelines for the use and risk management of carvedilol in heart failure were mostly followed, and most patients appeared to benefit from treatment with carvedilol for heart failure. Malaise/lassitude was the main reason for discontinuing treatment. Further investigations may be warranted to examine the prescribing of carvedilol at lower than recommended doses.

Background

The benefit of treatment with β-adrenergic receptor antagonists (β-blockers) for patients with heart failure is now well established. Several trials have shown that the treatment of heart failure with β-blockers reduces morbidity and mortality in patients with all stages of heart failure.[1] However, there are concerns that the condition of patients with heart failure may be worsened by the use of β-blockers and/or that their renal function may deteriorate. Signs and symptoms may be difficult to distinguish from the underlying disease and concomitant medications and co-morbidities can make the treatment of these patients complex.

Although the use of β-blockers for the treatment of heart failure has increased in recent years from about 11% in the early 1990s to approximately 32% in 2002, they remain underused in many of these patients.[2-5]

In the UK, the licence for carvedilol, a non-selective β-adrenergic receptor blocking drug with α_1 receptor-blocking activity was extended in 1998 for the treatment of symptomatic New York Heart Association (NYHA) class II and III heart failure (in addition to the original indications of hypertension and angina), with the recommendation by the regulatory authority that initiation of therapy and up-titration should be supervised by a hospital physician. The *British National Formulary* currently specifies that carvedilol may be used as an adjunct to diuretics, digoxin and ACE inhibitors in patients with chronic heart failure.[6] In 2002 the UK National Institute for Clinical Excellence (NICE) published a guideline for the treatment of heart failure in which it recommends adding β-blockers after the introduction of a diuretic and an ACE inhibitor, regardless of whether the patient is symptomatic or not.[7] NICE further advises a "start slow, go slow" method of introducing β-blockers to patients with heart failure. For carvedilol, NICE recommended an initial dosage of 6.25 mg/day, that doses should not be doubled in less than 2 weeks and that patients should be treated with the highest tolerated dose. The target dosage of carvedilol should be 50 mg/day for patients with a bodyweight ≤85 kg and 100 mg/day for those weighing more than 85 kg.

At the time of recruitment for this study, between August 1999 and July 2001, only carvedilol and bisoprolol had been licensed for the treatment of heart failure in the UK.[6]

The Drug Safety Research Unit (DSRU) conducted this post-marketing surveillance study to investigate whether the guidelines issued by the regulatory authority, which were aimed at effective and safe prescribing, would be implemented in everyday clinical practice in England. Further objectives included monitoring how supervision of care and heart failure status changed over time and whether patients experienced any serious adverse drug reactions (ADRs). Furthermore, these data would address the UK regulatory authority's request for further information on the use and safety of carvedilol prescribed for heart failure in clinical practice.

Methods

An observational cohort study was conducted using a modification of the standard prescription-event monitoring (PEM) technique, which has been described previously.[8] This study differed from the standard PEM study technique in the following aspects: carvedilol was not a newly licensed drug (although the addition of the indication for the treatment of heart failure was new); multiple questionnaires, including an eligibility questionnaire (to identify patients with the indication of heart failure) were sent; and the main focus of the study was the assessment of the implementation of the recommendations issued by the regulatory authority in day-to-day clinical practice in the community. Outcome was assessed by collecting data on the NYHA status of patients in addition to examining safety through the collection of adverse event data.

As in standard PEM studies, patients were identified from dispensed UK National Health Service (NHS) prescriptions issued by general practitioners (GPs) in primary care in England, irrespective of the indication for carvedilol, and the outcome data were obtained from follow-up questionnaires sent to the prescribing GP. For this study, patients were identified from prescriptions for carvedilol issued between August 1999 and June 2001.

As the indication for a medicine cannot be determined from the prescription, each GP was initially sent an eligibility questionnaire to ascertain the clinical condition for which carvedilol had been prescribed. A patient had to meet the following four inclusion criteria to be eligible for the study: (i) prescription of carvedilol was for cardiac failure (with or without other cardiovascular conditions); (ii) the prescription was the first issued by the GP for carvedilol; (iii) the patient was on the permanent list of the practice; and (iv) the GP wished to participate in the study. Patients were excluded if they had been prescribed carvedilol prior to 1 August 1999, either by their GP or a hospital physician.

GPs of eligible patients were subsequently sent up to three follow-up questionnaires for each individual patient at intervals, ranging from 12 to 34 months from the date of the first prescription for carvedilol issued in general practice. Final follow-up questionnaires were sent to the GPs of all living eligible patients, irrespective of whether previous questionnaires had been returned. The questionnaires requested information on who initiated treatment, who supervised the patients' care and investigations carried out prior to initiating treatment.

To reduce measurement bias, GPs were asked to assess cardiac failure status based on guidelines by the NYHA at the start of treatment and at the time each follow-up questionnaire was completed.[9] The GP's overall clinical impression of the progress of the patient was captured by asking whether the patient had improved, not changed significantly or deteriorated since starting carvedilol. In addition, the date of starting carvedilol, the initial dose and changes in dose over time, concomitant medications, relevant medical history, reason for discontinuing treatment and date of stopping, if applicable, and any events reported since the start of treatment, were requested. In PEM studies, an event is defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was of sufficient importance to enter in the patient's notes. Deaths for which the cause of death was not specified, were followed up by writing to the prescribing physician for further information.

All events reported were coded onto the DSRU database using a dictionary similar to the *Medical Dictionary for Regulatory Activities* (MedDRA). This hierarchical dictionary, which is arranged in a system-organ classification (SOC), groups associated terminology used by the prescribing physician under 'lower level' event terms (LLTs) and related LLTs under a broader 'higher level' event term (HLT) within the SOCs. More than one adverse event may be entered for the same patient.

For eligible patients, GPs were offered payment of £19, in recognition of the time involved

in completing each of the three follow-up questionnaires. No payment was offered for completing the initial eligibility questionnaire.

The data were analysed by using descriptive statistics. In addition, the incidence rates of first occurrence of each event (HLT) during treatment, expressed as incidence densities (ID) per 1000 person-months of treatment were calculated, ranked and the difference between the ID of each event in the first month (ID_1) and the subsequent 5 months of exposure ($ID_{2–6}$) was computed with 99% confidence intervals.

To examine whether regulatory guidelines for starting treatment and 'up-titration' by a hospital physician had been followed, we analysed factors that may predict initiation of treatment and up-titration by a hospital physician, using Mantel-Haenszel odds ratios (ORs), followed by stepwise logistic regression with entry level of significance of $p=0.05$ and removal of $p=0.1$ (analysis package: Stata, version 9.2, College Station, TX, USA).

Variables included in the analysis for predicting initiation of treatment by a hospital physician were: sex, age (categorized into <65 years and ≥65 years), NYHA class (categorized into I–III vs IV), history of hypertension, history of angina and change in the UK Summary of Product Characteristics (SPC) on 1 April 2000. The recommendation in the SPC relating to initiation of treatment and up-titration of treatment changed from "a hospital physician" to "a professional experienced in the management of chronic heart failure patients".[10] The same variables were included in the analysis of factors that may have influenced who had responsibility for 'up-titration', but with the inclusion of specifying who initiated the drug and the exclusion of the change in the SPC.

This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organizations of Medical Science in collaboration with the WHO.[11] The method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians and the Multicentre Research Ethics Guidance notes.[12,13]

Results

Of the 18 354 eligibility questionnaires posted for all first prescriptions for carvedilol (regardless of indication), 8561 (46.6%) were returned. From these returned eligibility questionnaires, 2311 patients met the eligibility criteria and first follow-up questionnaires were sent to the prescribing GP. 1694 (73.3%) of these first follow-up questionnaires were returned, of which 1454 (62.9%) contained clinical information and were classified as valid. Overall, one or more follow-up questionnaires were returned for 1666 patients (72.1% of the 2311 patients who met the eligibility criteria) but all three follow-up questionnaires were returned for only 603 (36.2%) of these 1666 patients (figure 1). Not all questionnaires were filled out completely; thus, total numbers for different parameters varied. The maximum observation period for this study was up to approximately 3 years (34 months).

Demographic Information

The majority of the patients were male (1142/1666; 68.5%), with a median age of 66 years (1st quartile 57 years; 3rd quartile 74 years). The female patients (498/1666; 29.9%) were older, with a median age of 72 years (1st quartile 63 years; 3rd quartile 79 years). For 26 patients the sex was not specified.

Indication

Nearly half of the patients (788/1666; 47.3%) were treated with carvedilol for cardiac failure alone and a similar number (803 patients; 48.2%) were treated for cardiac failure and at least one other condition, including angina, hypertension or other cardiovascular conditions. For the remaining 75 patients (4.5%) it was not specified by the GP whether carvedilol was given for cardiac failure alone or for cardiac failure and other conditions.

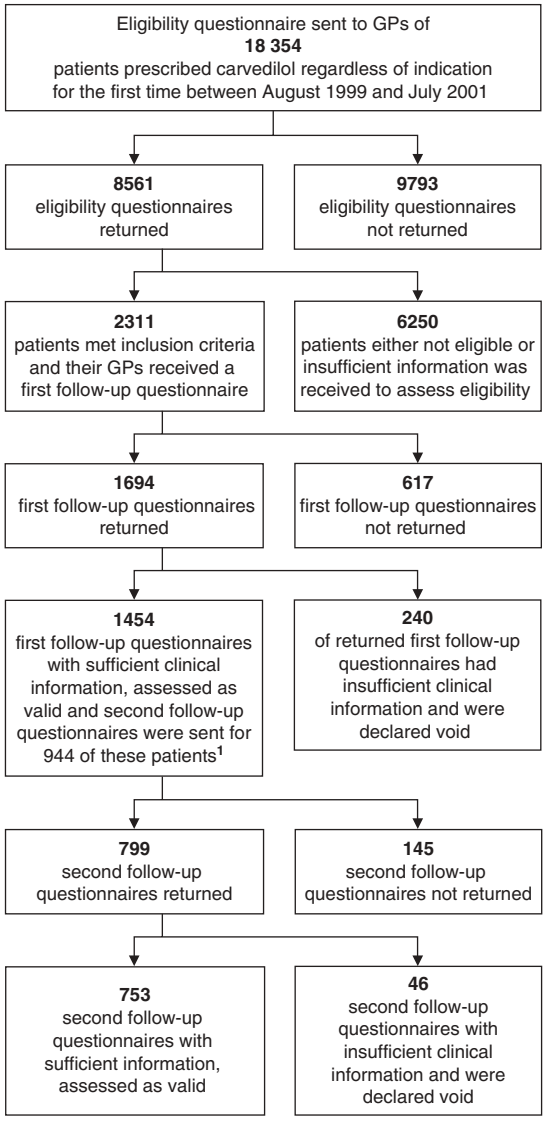

Fig. 1. Patients in carvedilol prescription-event monitoring study. **1** Second follow-up questionnaires were sent for 944 of the 1454 patients for whom a valid first follow-up questionnaire was returned due to delays in receipt of first follow-up questionnaires and the timelines for sending the final follow-up questionnaire. A final follow-up questionnaire was sent for 1916 patients who had not died, regardless of whether first or second follow-up questionnaires had been returned. 1419 questionnaires were returned, 497 were not returned, 1286 had sufficient clinical information and were assessed as valid and 133 had insufficient clinical information and were declared void. Overall, at least one follow-up questionnaire was returned for 1666 patients.

Treatment

At the time this study was conducted, it was recommended that initiation of carvedilol treatment and its subsequent titration should be under the supervision of a hospital physician. This recommendation was mostly followed, as the majority of patients (85.6% [1244] of the 1454 patients for whom the first follow-up questionnaire was returned) had their therapy initiated by a hospital physician and supervision of their care continued on a shared care basis (71.2% [1035] of 1454 patients). Only 12.6% of patients (183/1454) had their treatment initiated by their GP alone. This was reflected by a similar percentage of patients being exclusively cared for by their GP at the time of the first follow-up questionnaire (180/1454; 12.4%). Over time the pattern of care changed. For those for whom the third follow-up questionnaire was returned, it was reported that 48.3% patients (621/1286) had supervision of care on a shared basis, whilst GPs and hospital specialists each managed independently 24.9% (320/1286) and 20.3% (261/1286), respectively. For the remainder, supervision of care was not specified (84 of 1286; 6.5%).

Multivariate analysis showed that male sex (OR 2.0, 95% CI 1.3, 2.9; $p < 0.001$), age <65 years (OR 2.5, 95% CI 1.6, 3.9; $p < 0.001$), no history of hypertension (OR 2.2, 95% CI 1.5, 3.2; $p < 0.001$) and NYHA class IV (OR 1.8, 95% CI 1.0, 3.2; $p = 0.042$) were predictive factors for initiation of treatment by a hospital physician, rather than by the GP (table I).

Information on dose at the start of treatment and at the time of each questionnaire, if the patients were still receiving carvedilol, was requested (table II). Almost half of all patients started treatment at the recommended dosage of 6.25 mg/day, although for one-quarter of patients the initial dose was reported as below this and almost another quarter were started on an initial dose that was higher than the recommended initial dose. At the time of the first follow-up questionnaire 62.9% of patients (914/1454) had increased their dose, 34.2% (497/1454) remained on the same dose and for 3.0% (43/1454) the GP

Table I. Factors predicting initiation of treatment by hospital physician rather than by a general practitioner

Factor	Univariate analysis			Multivariate analysis (no. of patients = 1015)	
	no. of patients	crude OR (95% CI)	p-value	adjusted OR (95% CI)	p-value
Male sex	1404	2.3 (1.7, 3.2)	<0.001	2.0 (1.3, 2.9)	<0.001
Age <65 y	1405	3.3 (2.2, 4.9)	<0.001	2.5 (1.6, 3.9)	<0.001
NYHA class IV	1257	1.7 (1.02, 2.9)	0.039	1.8 (1.0, 3.20)	0.042
No history of hypertension	1181	2.3 (1.6, 3.3)	<0.001	2.2 (1.5, 3.2)	<0.001
No history of angina[a]	1225	1.4 (0.95, 1.9)	0.090		
Pre-SPC change in recommendations[b]	1427	1.6 (1.1, 2.3)	0.019	1.5 (0.98, 2.4)	0.06

a Excluded from multivariate analysis because the stepwise entry level of significance of p = 0.05 was not met.

b Prescribed prior to 1 April 2000 when recommendations for initiation/up-titration of treatment changed from "a hospital physician" to "a professional experienced in the management of chronic heart failure patients".[10]

NYHA = New York Heart Association; **OR** = odds ratio; **SPC** = Summary of Product Characteristics.

did not report whether carvedilol had been increased or not. Up-titration was supervised by a hospital specialist for 61.4% of those who had their dose increased (561/914), by GPs for 302 patients (33.0%) and for the remaining 38 patients (4.2%), it was reported to be on a shared care basis. The proportion of patients reported to be treated with a lower than recommended dosage (6.25 mg/day) fell to 6.3% at the time of the third follow-up questionnaire.

Multivariate analysis showed that initiation of carvedilol by a hospital physician (OR 79.3, 95% CI 24.5, 257.1; p < 0.001), age <65 years (OR 1.6, 95% CI 1.1, 2.4; p = 0.023) and NYHA class IV (OR 2.9, 95% CI 1.5, 5.8; p = 0.002) were predictive factors for 'up-titration' of carvedilol by a hospital physician (table III).

Cardiac Failure Status

Of the patients with a NYHA status reported at the beginning of treatment, 993 patients also had information either on NYHA status on the third follow-up questionnaire or had died. Of the patients who were still alive at the end of the study, the majority of were assessed at the start of treatment as NYHA class III (339/877; 38.7%), followed by NYHA class II (322; 36.7%), NYHA class IV (118; 13.5%) and NYHA class I (98; 11.1%). Of these patients, the NYHA class had improved for 39.5% (392/993) by the time the final follow-up questionnaire was returned. For 38.0% (377/993), no change in NYHA class was observed, for 10.9% (108/993) it had deteriorated and 11.7% (116/993) died; 74 of these patients

Table II. Reported doses of carvedilol

Dose reported (mg/day)	At start of treatment[a] [no. (%)] (n = 1454)	At time of first follow-up questionnaire [no. (%)] (n = 1096)[b]	At time of second follow-up questionnaire [no. (%)] (n = 512)[c]	At time of third follow-up questionnaire [no. (%)] (n = 888)[d]
<6.25	369 (25.4)	60 (5.5)	31 (6.1)	56 (6.3)
6.25	715 (49.2)	200 (18.3)	102 (19.9)	131 (14.8)
≥6.25 to <50	276 (19.0)	586 (53.5)	261 (51.0)	457 (51.5)
50	13 (5.6)	201 (18.3)	107 (20.9)	209 (23.5)
≥50	0 (0)	18 (1.6)	9 (1.8)	28 (3.2)
Unspecified	81 (5.6)	31 (2.8)	2 (0.4)	7 (0.8)
Total	**1454 (100.0)**	**1096 (100.0)**	**512 (100.0)**	**888 (100.0)**

a Information requested in first follow-up questionnaire.

b Number of patients reported as continuing carvedilol therapy at the time the first follow-up questionnaire was returned.

c Number of patients reported as continuing carvedilol therapy at the time the second follow-up questionnaire was returned.

d Number of patients reported as continuing carvedilol therapy at the time the third follow-up questionnaire was returned.

Table III. Factors predicting up-titration of carvedilol

Factor	Univariate analysis			Multivariate analysis (no. of patients = 624)	
	no. of patients	crude OR (95% CI)	p-value	adjusted OR (95% CI)	p-value
Drug initiated by hospital physician	849	103.8 (27.1, 398.0)	<0.001	79.3 (24.5, 257.1)	<0.001
Male sex[a]	850	1.4 (1.1, 1.9)	0.013		
Age <65 y	849	1.9 (1.4, 2.6)	<0.001	1.6 (1.1, 2.4)	0.023
NYHA stage IV	773	2.9 (1.7, 5.1)	<0.001	2.9 (1.5, 5.8)	0.002
No history of hypertension[a]	720	1.5 (1.1, 2.2)	0.016		
No history of angina[a]	741	1.2 (0.9, 1.7)	0.18		

a Excluded from multivariate analysis because the stepwise entry level of siginificance of p = 0.05 was not met.

NYHA = New York Heart Association; **OR** = odds ratio.

died of cardiovascular causes. An additional 24 patients with unknown NYHA class on the first follow-up questionnaire died by the end of the study; 13 of these patients died of cardiovascular causes. A further 23 patients died for whom no first questionnaire was returned; 13 of these patients died as a result of cardiovascular causes.

In addition, GPs were asked to make a subjective assessment of whether the patient's heart failure status had changed since starting carvedilol. For nearly half (618) of the 1286 patients for whom the third questionnaire was returned, the GPs reported that there had been an improvement in the patients cardiac failure, which is a higher proportion than that shown by the changes reported in the NYHA class. Only a small percentage of GPs reported that the cardiac failure had deteriorated (5.4%; n = 70), whereas deterioration in NYHA class was reported for 108 patients (10.0%) [tables IV and V].

Events Reported

The most frequently reported clinical events in the first month of treatment were malaise/lassitude followed by dizziness, dyspnoea, cardiac failure and hypotension. Only malaise/lassitude (ID_1–ID_{2-6} 14.18, 95% CI 3.88, 24.48) and dizziness (ID_1–ID_{2-6} 9.22, 95% CI 1.15, 17.29) were reported significantly more frequently in the first month of treatment than in the subsequent 5 months, indicating that these events may have been associated with the start of treatment with carvedilol. Malaise/lassitude were also the events most frequently reported as ADRs to carvedilol and as reasons for stopping treatment with this drug (table VI). Overall, 53 events in 40 patients (2.4% of 1666 patients) were reported as suspected ADRs to carvedilol. During the study period, 451 patients (27.1% of 1666 patients) were reported to have discontinued treatment. A total of 769 reasons for stopping were reported for 364 of these patients, with lack of effectiveness reported as a reason for stopping treatment for 13.2% of patients (48/364).

Over a quarter of the reasons for stopping were reported during the first 2 months of treatment (242/769; 31.5%). During the entire study period, 26.7% of the patients (97/364) with at least one reason for stopping carvedilol reported events as reasons for stopping that may have been associated with worsening heart failure (including reported adverse event terms of dyspnoea, oedema and cardiac failure *per se*). Furthermore, 21.7% (n = 79) patients stopped treatment as a result of events that may have been associated with hypotension (including reported adverse event terms of dizziness, confusion and hypotension *per se*). In the first month of treatment, 14 events that may have been associated with worsening heart failure and 21 events that may have been due to hypotension were reported as reasons for stopping.

Deaths

There were 163 deaths (9.8% of 1666 patients) reported during this study. The cause of death was reported by GPs for 135 (82.8%) of these 163 patients; no cause of death was ascertained for 28 (17.2%). Thirty-nine patients (23.9% of 163 patients) were known to have taken carvedilol until

Table IV. Change of New York Heart Association (NYHA) class between start of treatment and third questionnaire

NYHA class at start	Number of patients (% of total)	NYHA/death status[a,b] at third questionnaire	Number of patients (% of individual NYHA at start)
I	100 (10.1)	I (no change)	54 (54.0)
		II (deteriorated)	34 (34.0)
		III (deteriorated)	7 (7.0)
		IV (deteriorated)	3 (3.0)
		Died	2 (2.0)
			Cardiovascular deaths: 0
II	348 (35.1)	I (improved)	78 (22.4)
		II (no change)	194 (55.8)
		III (deteriorated)	44 (12.6)
		IV (deteriorated)	6 (1.7)
		Died	26 (7.5)
			Cardiovascular deaths: 16
III	399 (40.2)	I (improved)	57 (14.3)
		II (improved)	160 (40.1)
		III (no change)	108 (27.1)
		IV (deteriorated)	14 (3.5)
		Died	60 (15.0)
			Cardiovascular deaths: 41
IV	146 (14.7)	I (improved)	12 (8.2)
		II (improved)	55 (37.7)
		III (improved)	30 (20.6)
		IV (no change)	21 (14.4)
		Died	28 (19.2)
			Cardiovascular deaths: 17
Total	993 (100.0)		993

a Death took priority over NYHA status.

b 24 patients with unknown NYHA status on the first questionnaire died by the end of the study period (13 cardiovascular deaths). For a further 23 patients, no first questionnaire was returned but they are known to have died during the study period (13 cardiovascular deaths).

their death or within 1 month of their death while 17 patients (10.4% of 163 patients) had stopped taking carvedilol more than 1 month before their death. For the remaining 107 patients (65.6% of 163 patients) it was not specified whether they were continuing treatment with carvedilol at the time of their death.

For the 39 patients who were still being prescribed carvedilol at the time of or shortly before their death, the most frequently reported cause of death was ischaemic heart disease (18 patients), followed by cardiac failure (4 patients). Most of these patients (33 of 39) were elderly (≥65 years; median age 75 years, age range 53–91 years), with only two patients being in their fifties, one of whom died from cardiomyopathy and the other following vascular surgery. Of the four who died from cardiac failure, all were aged over 75 years, had co-morbidities and three were classified as NYHA class IV at the start of treatment.

For the 17 patients who had discontinued carvedilol more than 1 month before their death, the most frequent cause of death was ischaemic heart disease.

Discussion

With this modified PEM study we have demonstrated that the guidelines issued by the regulatory authority for the use of carvedilol in patients with heart failure appeared to have been well implemented in clinical practice in England. Studying how medicines are used in the reality of clinical practice is an essential part of risk management: modification of PEM methodology enables such studies to be conducted and contributes to the risk management of medicines.

The methodology of PEM has been described previously.[8] The strengths of this methodology include that it is observational and, as the patients were identified from dispensed primary care prescriptions, there can be no interference with the prescribing doctors' decision as to the most appropriate treatment for the patient. The participation of GPs in the study was voluntary. A limitation of the study is that questionnaires were returned for 72% of the eligible patients, which may conceal biases if the GPs who did not return questionnaires differed in their adherence to the guidelines or if GPs were selective in the patients for whom they returned questionnaires. It is possible that patients not treated according to the guidelines may have experienced a less favourable or even an adverse clinical outcome. However, inclusion of patients not treated according to treatment guidelines and reporting of

Table V. Change in status of heart failure symptoms based on general practitioner assessment at the time of the third questionnaire

Change in heart failure status	Number	%
Improved	618	48.1
Not changed significantly	420	32.7
Deteriorated	70	5.4
Not specified	178	13.8
Total	**1286**	**100.0**

a Patients who died were excluded.

unfavourable outcomes in this study suggest there may have been little selection bias. Another possible bias is under-reporting by patients and/or GPs, including of adverse events. Furthermore, patients who would have been eligible for inclusion may have not been included if they were only seen by a hospital consultant who also issued repeat prescriptions. However, this is not common clinical practice in the UK and these would have probably been patients with more severe disease and/or more complex medical conditions. Furthermore, patients may have died between leaving hospital and seeing their GP for a repeat prescription, thus possibly introducing a survival bias of patients included into this study. It is likely that the majority of these patients would have been those with NYHA class IV heart failure, for which the drug was contraindicated at the start of this study. This was changed in 2000 when the drug was contraindicated only for patients with uncompensated heart failure.

This study reflected the management of patients in day-to-day clinical practice, where the risk-benefit profile of a treatment is likely to be influenced by many different factors (i.e. compliance), not all related to the prescribed medicine itself. It gives an insight into the management of these patients in the community and how regulatory recommendations impact on day-to-day care in the community. Furthermore, PEM studies in general have a higher reporting rate of ADRs than spontaneous reporting; thus, PEM studies may detect potential drug safety signals which none of the prescribing GPs had suspected previously.[14,15]

Comparing the results of this observational cohort study with those from clinical trials needs to be done with care as methods and results may not easily be transferred from PEM studies into clinical trial settings and *vice versa*. For example, patient cohorts are usually more selective in clinical trials than in PEM studies, where even patients who are treated off-label maybe included. An example is the off-label use of carvedilol in patients with NYHA class IV heart failure in this study. A more detailed discussion of the differences between PEM and clinical trials can be found elsewhere.[8]

Table VI. Most frequently reported events, adverse drug reactions (ADRs) and reasons for stopping treatment

Event term	N_1	N_{2-6}	ID_1	ID_{2-6}	ID_1–ID_{2-6} (99% CI)	No. reported as ADRs	No. given as reason for stopping
Malaise, lassitude[a]	**34**	**57**	**22.44**	**8.26**	**14.18 (3.88, 24.48)**	11	91
Dizziness[a]	**21**	**32**	**13.86**	**4.64**	**9.22 (1.15, 17.29)**	1	34
Dyspnoea	21	63	13.86	9.13	4.73 (–3.61, 13.06)	1	61
Cardiac failure	18	40	11.88	5.80	6.08 (–1.51, 13.67)	2	29
Hypotension	15	30	9.90	4.35	5.55 (–1.34, 12.44)	2	44
Oedema	4	9	2.64	2.03	0.61 (–3.06, 4.29)	1	7
Confusion	0	3	0.00	0.43	–0.43 (–1.08, 0.21)	0	1
Bradycardia[b]	1	8	NA	NA	NA	0	11

a Events in bold are those for which ID_1 is significantly greater than ID_{2-6}.

b This event term was grouped under a broader event term of disorder of rhythm, which also included arrhythmia and tachycardia. This broader event term was not reported significantly more often in the first month of treatment than in months 2–6 of treatment.

c Incidence density is expressed as number of first reports of each event per 1000 patient-months of treatment within the relevant time period.

ID_1 = incidence density for each event during the first month of treatment; **ID_{2-6}** = incidence density for each event during treatment months 2–6; **ID_1–ID_{2-6}** = arithmetic difference between ID_1 and ID_{2-6}; **N_1** = number of first reports of each event during the first month of treatment; **N_{2-6}** = number of first reports of each event during treatment in months 2–6; **NA** = not applicable.

As recommended by the UK regulatory authority, most patients' treatment was initiated by a hospital physician. It is notable that the initial dosage was reported to be lower than recommended (6.25 mg/day) for one-quarter of patients, and by the time of the third questionnaire 26.7% of patients received a daily dosage of 50 mg or above. We were unable to clarify whether the dose specified in the third questionnaire was the highest tolerated dose or whether more patients could have tolerated higher doses. It is possible that clinical benefits may have been even more pronounced if patients would have been titrated up to the recommended target dosage (50 mg/day for patients weighing ≤85 kg; 100 mg/day for those >85 kg) for carvedilol as suggested by the MUCHA (Multicenter Carvedilol Heart Failure Dose Assessment) trial.[16] A study by Tandon et al.[17] noted that only 18% of patients treated with β-blockers in a tertiary care heart failure clinic received dosages used in clinical trials. However, we were concerned that almost a quarter of patients started treatment on a higher than the recommended initial dose. This may have exposed patients to a higher risk of possible ADRs.

Only 30% of patients were female. Whether this was a true reflection of clinical needs or whether women were less likely to be offered treatment with a β-blockers after being diagnosed with heart failure was not clear. Hood et al.[18] reported that women were disproportionally affected by age differences in the management of heart failure. Similar observations were made by Majeed and colleagues.[19]

Patients with all NYHA classes of cardiac failure, including class I and IV, improved clinically during the observation period of this modified PEM study. At the start of this study, carvedilol was licensed for the treatment of symptomatic NHYA class II and III heart failure, and its use in patients with NYHA status IV was contraindicated because of lack of experience.[6] Over 80% of patients with NYHA class IV at the beginning of treatment had improved at the time of the third questionnaire. This confirmed the findings of several large clinical trials suggesting a reduction in morbidity and mortality in patients with heart failure. The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) study found that patients with severe heart failure, including those with a low pre-treatment systolic blood pressure, experienced a reduction in morbidity and mortality of 40% and 34%, respectively, during an average follow-up period of 10.4 months.[20] In 2000, the UK SPC was changed and the contraindication for NHYA class IV heart failure was removed, although physicians were advised not to use the drug in patients with uncompensated heart failure.

Beneficial effects of carvedilol treatment have also been demonstrated in the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial for patients with a recent myocardial infarction and in the CARMEN (Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure EvaluatioN) trial for those taking concomitant ACE inhibitors.[21,22]

In the current study, it was observed that GPs felt that fewer patients had deteriorated compared to changes specified when patients were assessed by NYHA class (5% vs 13%). The reasons for this discrepancy of assessment were unclear. As heart failure is a chronically progressive disease and treatment can only slow disease progression, a certain percentage of patients would be expected to worsen clinically or even die.

Only a small proportion of patients experienced ADRs attributed by the GPs to carvedilol and this was lower than reported in the literature.[23] The most frequently specified clinical event was malaise/lassitude, which was also the most common reason for stopping carvedilol and had the highest ID in the first month of treatment. No serious ADRs were identified, indicating that carvedilol was well tolerated by most patients in this study.

During our study, 27.1% of patients stopped carvedilol. 26.7% of the patients with at least one reason for stopping treatment reported events that may have been associated with worsening heart failure. NICE guidelines recommend doubling the dose of the diuretic as a first measure to treat worsening heart failure and halving the dose of β-blockers if the patient does not respond.[7] Furthermore, 21.7% of patients stopped treatment as a

result of events that may have been associated with hypotension. It is recognized that carvedilol may increase the patient's sensitivity to nitrates.[24,25] Guidelines from NICE suggest that hypotension in these patients should be treated by stopping concomitant vasodilating drugs and reducing the dose of the diuretic, as long as the patient has no signs of cardiac congestion, before reducing or stopping the β-blockers.[7] The literature reported 13.6–30.0% of patients stopping carvedilol treatment, and differences in the setting, i.e. general practice versus clinical trial, have to be taken into account.[21,26]

None of the deaths were attributed to carvedilol by the reporting GPs. The overall proportion of patients who died whilst on treatment or who died shortly after the last prescription for carvedilol was similar to that reported in clinical trials, where between 1.6% and 4.5% of patients treated with carvedilol were reported to have died.[26-28] However, a comparison of these death rates has to be done with care as this is influenced by the NYHA class at the start of treatment and may also be influenced by the maintenance dose and length of follow-up.[16,29]

Of 988 chronic heart failure patients (recruited between 1991 and 1993) with NYHA class II, II and IV, all-cause mortality was reported to be 21.1%, 35.9% and 58.3%, respectively, during a median follow-up period of 38.5 months. Compared with NHYA class I, the adjusted hazard ratio of all-cause mortality in patients with NYHA class II, III and IV was reported as 1.54 (95% CI 1.02, 2.32; $p = 0.042$), 2.56 (95% CI 1.64, 24.01; $p < 0.001$) and 8.46 (95% CI 3.57, 20.03; $p < 0.001$), respectively.[29]

Conclusions

Methodologically, our study demonstrated that modification of PEM methodology can contribute to the risk management of medicines by improving the understanding of usage, effectiveness and adherence to guidelines, as well as the relationship between usage and the safety of the drug. Our study showed that carvedilol was introduced to patients with heart failure mostly according to the recommendations by the regulatory authority and that continuing care for approximately half of the patients was on a shared basis between the hospital specialist and the GP. The condition of most patients improved clinically during treatment, which was well tolerated with no serious ADRs being reported. It was reassuring to observe that most patients with NYHA class IV at the start of treatment seemed to improve during carvedilol therapy and in 2000 the contraindication for the use in patients with stable NYHA class IV was removed. The observation that only a small number of patients with NYHA class I were included in the study cohort, as well as the number of patients stopping treatment in association with events that may have indicated hypotension or worsening heart failure, may indicate areas in day-to-day care that may benefit from further education and discussion. The reasons for prescribing lower than recommended doses of carvedilol may also merit further investigation. Similarly further investigation may be warranted to clarify the lower percentage of women who were prescribed carvedilol.

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