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Reduced costs with bisoprolol treatment for heart failure

An economic analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II)

CIBIS-II Investigators and Health Economics Group*

Background Beta-blockers, used as an adjunctive to diuretics, digoxin and angiotensin converting enzyme inhibitors, improve survival in chronic heart failure. We report a prospectively planned economic analysis of the cost of adjunctive beta-blocker therapy in the second Cardiac Insufficiency BIsoprolol Study (CIBIS II).

Methods Resource utilization data (drug therapy, number of hospital admissions, length of hospital stay, ward type) were collected prospectively in all patients in CIBIS II. These data were used to determine the additional direct costs incurred, and savings made, with bisoprolol therapy. As well as the cost of the drug, additional costs related to bisoprolol therapy were added to cover the supervision of treatment initiation and titration (four outpatient clinic/office visits). Per diem (hospital bed day) costings were carried out for France, Germany and the U.K. Diagnosis related group costings were performed for France and the U.K. Our analyses took the perspective of a third party payer in France and Germany and the National Health Service in the U.K.

Results Overall, fewer patients were hospitalized in the bisoprolol group, there were fewer hospital admissions per patient hospitalized, fewer hospital admissions overall, fewer days spent in hospital and fewer days spent in the most expensive type of ward. As a consequence the cost of care in the bisoprolol group was 5–10% less in all three countries, in the per diem analysis, even taking into account the cost of bisoprolol and the extra initiation/up-titration visits. The cost per patient treated in the placebo and bisoprolol groups was FF35 009 vs FF31 762 in France, DM11 563 vs DM10 784 in Germany and £4987 vs £4722 in the U.K. The diagnosis related group analysis gave similar results.

Interpretation Not only did bisoprolol increase survival and reduce hospital admissions in CIBIS II, it also cut the cost of care in so doing. This 'win–win' situation of positive health benefits associated with cost savings is favourable from the point of view of both the patient and health care systems. These findings add further support for the use of beta-blockers in chronic heart failure.
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Introduction

Worldwide, chronic heart failure is recognized as a large and growing public health problem[1,2]. In particular, the number of hospitalizations for heart failure have increased substantially over the past two decades in all countries studied[3–7]. Primarily as a result of this trend, the economic burden of heart failure is also believed to have risen substantially[1,2]. This is because hospital admissions account for up to 70% of the total direct health care costs of heart failure to society[8]. It is hoped that new therapies for heart failure will not only improve symptoms and reduce mortality but also further decrease hospitalizations and, in so doing, cut costs[8]. Given the relationship between hospitalization costs and the overall cost of heart failure, any treatment that substantially reduces admission rates is likely to be cost effective[9].

Beta-blockers have been clearly shown to reduce the morbidity and mortality related to heart failure. A pooled analysis of several small studies with carvedilol in the U.S.A. demonstrated that short-term (median follow-up 6·5 months) mortality was

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reduced[10]. Cardiovascular hospitalizations were also decreased by active therapy. The second Cardiac Insufficiency BIsoprolol Study (CIBIS-II) was a single, prospective, randomized, controlled trial comparing the effects of bisoprolol to those of placebo, when added to conventional therapy, in patients with chronic heart failure[11]. Both mortality and all-cause hospitalization were significantly reduced after a mean follow-up of 1·3 years. Subsequently, the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) study has reported a mortality reduction of similar magnitude to that seen in CIBIS-II, over a comparable period of follow-up[12].

The present study examines the cost of bisoprolol, as an adjunctive treatment for chronic heart failure, using prospectively collected resource utilization data in a planned health economic analysis of CIBIS-II[13].

Methods

This analysis is based on a comparison of conventional therapy for heart failure (diuretic, digoxin and ACE inhibitor) to conventional therapy plus adjunctive bisoprolol. We have examined the effect of adding bisoprolol to conventional therapy on resource utilization in all 2647 patients randomized in all 18 countries taking part in CIBIS II. We have also performed a detailed costing of medical care in all patients randomized in France (n=231), Germany (n=215) and the U.K. (n=226). Our analysis takes the perspective of a third party payer in France and Germany and the National Health Service in the U.K. For all CIBIS II patients, information was collected, prospectively, on drug therapy, patients admitted to hospital (proportion admitted, number of admissions per patient, number of hospital days per patient), admissions (number, duration, ward type). These data were used to determine the additional direct costs incurred, and savings made, with bisoprolol therapy. Indirect costs were not considered, although a major one of these, loss of productivity due to unemployment, was unlikely to be significant as 72% of patients were retired. The average follow-up of the main trial was 1·3 years and the present analysis relates to that same time period.

Effectiveness is expressed as patients alive and extra years of life gained, on the basis of mortality rates and Kaplan–Meier survival estimates[11].

Costs of health care

The costs of drug therapy were obtained from standard tariffs for the financial year 1997/98 (Vidal, France; Rote Liste, Germany; British National Formulary; U.K.)[14–16].

Additional costs related to the use of bisoprolol

Based on the average daily bisoprolol dose prescribed in CIBIS II, the cost per day of treatment used in the analysis was French Francs (FF) 1·77 for France (considering a reimbursement rate of only 65%), Deutschemarks (DM) 1·17 for Germany and British Pounds (£) 0·69 for the U.K. Because, at the time of the analysis, the precise tablet formulations and doses used in CIBIS II to treat patients with heart failure were not available, these drug costs are estimates which over- rather than under-estimate real bisoprolol costs.

We also assumed that all patients treated with bisoprolol will require four additional outpatient clinic/office visits for the initiation and up-titration of bisoprolol. Information on the cost of these visits was obtained from the Nomenclature Générale in France, Einheitlicher Bewertungs—Massstab (EBM) in Germany and unit costs of health and social care in the U.K.[17–19].

Some adverse events, which were reported by a greater proportion of bisoprolol treated patients, including dizziness (13·3% vs 9·5%), bradycardia (15·2% vs 4·5%), hypotension (11·4% vs 7·3%) and fatigue (9·3% vs 7·1%), all recognized side-effects of beta-blocker therapy. The differences in severe adverse effects, such as bradycardia (placebo 0·5% vs bisoprolol 1·4%) and hypotension (placebo 0·7% vs bisoprolol 1·1%), are assumed to be reflected in the hospitalization data.

Differences in milder adverse events are extremely difficult to value in economic terms. Any medication related to them is accounted for in this analysis. However, it is also possible that additional clinic visits may have been needed. It is also important to note that other adverse effects were less common in the bisoprolol group (cardiac failure, dyspnoea and tachycardia). Given the difficulties in costing all of these milder adverse effects, we have assumed that the cost of the adverse effects that are less frequent with bisoprolol cancel out those that are more frequent with this therapy.

Discounting was not performed because of the relatively short follow-up of patients in CIBIS II and because no long-term projection of results was undertaken.

Analyses and statistics

Two separate cost analyses were performed for hospital admissions:

(i) a per diem (per hospital bed day) costing using data obtained from standard sources[20]. The costs used in the present analysis are summarized in Table 1,

and

(ii) a diagnosis related group costing using data obtained from the Programme Médicalisé des Systèmes d'Information (PMSI) in France (1998) and The New National Health Service Reference Costs (1998) in the U.K.; diagnosis related group costs are not available for Germany[23,24]

Table 1 Costs used in the economic analysis of CIBIS-II

Diagnosis related costs	France (FF)	UK (£)
Cardiovascular hospital admissions		
Worsening CHF	24 693	1362
Angina	14 180	829
Supraventricular tachycardia	15 879	925
Ventricular tachycardia/fibrillation	15 879	925
Stroke	25 373	1994
PTCA/CABG	87 105	4389
Myocardial infarction	28 371	1396
Hypotension	14 604	838
Cardiogenic shock	24 693	1362
Cardiac transplantation	176 006	31 442
Bradycardia	15 879	925
Other cardiac surgery	49 021	6007
Other cardiovascular	14 082	1231
Non-cardiovascular admissions	10 598	817
Per diem costs		
Intensive/Coronary Care Unit	6371	1294
Cardiology ward	2535	354
General Medical ward	1912	164
Other ward	1912	164

CHF=chronic heart failure; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting. For Germany these costs were (in DM): Intensive/Coronary Care Unit 1837, Cardiology ward 547, General Medical ward 424 and other ward 424.

Categorical variables, expressed as number and percentages, were analysed using the chi-square test or Fisher's exact test. Continuous variables, expressed as mean, standard deviation, median and range, have been analysed using one-way ANOVA. Bootstrap confidence intervals were calculated for cost differences between the bisoprolol and the conventional-therapy group.

A sensitivity analysis was performed, examining the effect of adjusting the length of hospital stay, a major driver of the cost of heart failure, by +30% and the number of physician visits for initiation/titration of bisoprolol therapy (3 or 5 vs 4 in the base-case).

Discounting was not performed because of the relatively short follow-up of patients in CIBIS II and because no long-term projection of results was undertaken. This analysis was supervised by an independent 'Health Economics' committee (Appendix 1) and written up independently of the sponsor, whose main role was the provision of data from the main CIBIS-II trial for the analysis.

Results

Bisoprolol was taken by 99% of randomized patients (n=1327) for 462·3 days on average; the comparable figures for placebo were 99% (n=1320) and 446 days. The average dose of bisoprolol taken was 6·2 mg.

Effects of bisoprolol: hospital admissions in overall CIBIS II population

The principal effects of bisoprolol on morbidity related to heart failure are shown in Table 2. The types of hospital admission and hospital beds occupied are shown in Tables 3 and 4. Cumulative hospital admissions are shown in Fig. 1.

Overall, fewer patients were hospitalized in the bisoprolol group, there were fewer hospital admissions per hospitalized patient, fewer hospital admissions overall, fewer days spent in hospital and fewer days spent in the most expensive types of ward (e.g. Intensive Care Units). There was no reduction in the average length of hospital stay.

Forty percent of patients in the conventional therapy group were hospitalized compared to 34% in the bisoprolol group (a 15% relative risk reduction). The number of admissions per patient hospitalized in the conventional therapy group was 1·9 and this figure was 1·6 in the bisoprolol group. Overall there were 0·8 hospitalization per patient in the conventional therapy group compared to 0·6 in the bisoprolol group. This resulted in fewer total hospital admissions (739 vs 1013) and days in hospital (10 085 vs 12 144) in the bisoprolol

Table 2 Hospital admissions and patients hospitalized in CIBIS-II

	Placebo (n=1320)	Bisoprolol (n=1327)	Difference of mean (95% CI)
All patients			
Number of hospital admissions	1013	739	
Number of days in hospital per admission	12·1	13·7	1·6 (0·2; 2·9)
Number of hospital admissions per patient	0·8	0·6	−0·2 (−0·3; −0·1)
Number of days in hospital per patient	9·3	7·6	−1·7 (−3·0; −0·3)
Patients hospitalized			
Number of patients hospitalized**	530 (40%)	454 (34%)	0·78 (0·66; 0·91)*
Number of admissions per patient hospitalized	1·9	1·6	−0·3 (−0·5; −0·1)
Number of days in hospital per patient hospitalized	23·1	22·2	−0·9 (−3·9; 2·2)

*Odds ratio

**The numbers of patients hospitalized differ slightly from the main CIBIS II publication[11]. That analysis only considered hospital admissions constituting an 'approved clinical event' whereas the present analysis takes account of all hospitalizations.

Table 3 Numbers of hospital admissions by cause in CIBIS-II

	Number of admissions		N (%) of patients		*P* value#
	Placebo (n=1320)*	Bisoprolol (n=1327)*	Placebo (n=1320)*	Bisoprolol (n=1327)*	
Cardiovascular					
Worsening CHF	393	211	232 (17·6%)	159 (12·0%)	<0·001
Angina	54	46	44 (3·3%)	41 (3·1%)	0·72
Supraventricular tachycardia	44	26	33 (2·5%)	23 (1·7%)	0·17
Ventricular tachycardia/fibrillation	25	7	20 (1 5%)	6 (0·5%)	<0·01
Stroke	17	31	16 (1·2%)	31 (2·3%)	0·03
PTCA/CABG	13	12	12 (0·9%)	11 (0·8%)	0·82
Myocardial infarction	11	16	11 (0·8%)	16 (1·2%)	0·34
Hypotension	11	4	11 (0·8%)	3 (0·2%)	0·03
Cardiogenic shock	7	7	7 (0·5%)	7 (0·5%)	0·99
Cardiac transplantation	5	6	5 (0·4%)	6 (0·5%)	0·77
Bradycardia	2	14	2 (0·2%)	14 (1·1%)	<0·01
Other cardiac surgery	1	1			
Other cardiovascular	81	84	76 (5·8%)	77 (5·8%)	0·96
Non-cardiovascular	258	199	186 (14·1%)	153 (11·5%)	0·05
Unknown	35	23	30 (2·3%)	19 (1·4%)	0·11
Total**	957	687	530 (40·2%)	454 (34·2%)	<0·01

CHF=chronic heart failure; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting (surgery).
*530 placebo and 454 bisoprolol treated patients were hospitalized.
**The data taken from the critical event forms differ slightly from those in Table 2, which were directly drawn from the clinical case report forms. For example, planned inpatient stays for investigation or diagnosis were not documented in the critical event forms.
#Chi-square test.

Table 4 Types of hospital bed utilized in CIBIS-II. Number of days of bed occupancy*

	Placebo (n=1320)**	Bisoprolol (n=1327)**	*P* value#
Intensive/Coronary Care Unit	1056	796	0·15
Cardiology ward	5280	4379	0·11
General Medical ward	3300	2787	<0·01
Other	2508	2123	0·23
Total	12 144	10 085	<0·01

*Taken directly from case report forms (average length of stay multiplied by the number of patients).
**530 placebo and 454 bisoprolol treated patients were hospitalized.
#Wilcoxon Rank sum test for the comparison of duration per service per patient between groups.

group than the conventional therapy group. Fewer days were spent in intensive/coronary care units in the bisoprolol group (796 vs 1056) although the average length of stay in hospital was similar in the two treatment groups (22·2 vs 23·1 days per patient hospitalized in the bisoprolol and conventional therapy groups, respectively).

Effects of bisoprolol: hospital admissions in different countries

We examined whether or not the beneficial effects of bisoprolol on these major contributors to health care costs were also seen in France, Germany and the U.K. (Figs 2–4). The proportion of patients hospitalized, number of admissions per patient randomized and average length of admission varied between countries (Figs 2–4). There was, however, a clear reduction in the percentage of patients hospitalized and number of admissions per patient randomized in the bisoprolol group, in all three countries, consistent with the overall analysis of the whole CIBIS II population. Curiously, in France, bisoprolol also appeared to reduce length of hospital stay.

Drug use in overall CIBIS II population

The four major categories of drug prescription were angiotensin converting enzyme (ACE) inhibitors, loop diuretics, other vasodilators and digitalis glycosides. The

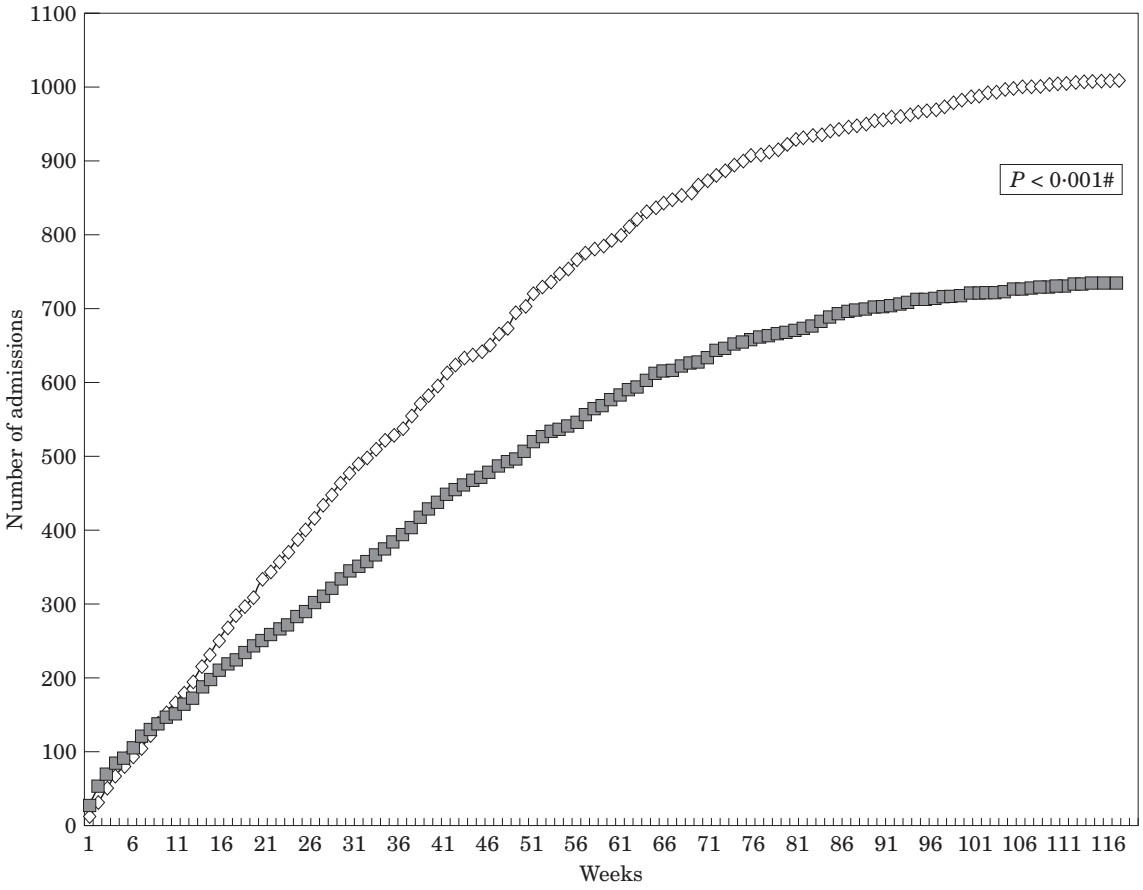

Figure 1 **Cumulative number of hospital admissions in the placebo and bisoprolol groups in CIBIS II. ◇=placebo; □=bisoprolol. #Wilcoxon Rank sum test on the comparison of the number of admissions between groups.**

average number of days of prescription per patient in the placebo and bisoprolol groups, respectively, were: ACE inhibitors (475 vs 495), loop diuretics (480 vs 456), other vasodilators (435 vs 469) and digitalis glycosides (446 vs 468). There was no significant difference between treatment groups in the use of these or other medications.

Costs of adjunctive bisoprolol vs conventional therapy in France, Germany and the U.K.: per diem analysis

The costs of conventional care vs conventional care plus adjunctive bisoprolol therapy, based on the analysis using per diem costs, are shown in Table 5.

In all three countries the cost of care in the bisoprolol group was 5 to 10% less, even taking into account the cost of bisoprolol and the extra initiation/up-titration visits. The estimated costs per patient treated in the bisoprolol group was FF31 762, DM10 784 and £4722 in France, Germany and the U.K., respectively (Fig. 5).

Costs of adjunctive bisoprolol vs conventional therapy in France and the U.K.: diagnosis related group analysis

The costs of conventional care vs conventional care plus adjunctive bisoprolol therapy, based on the analysis using diagnosis related group costs for the overall trial, is shown in Table 6. Whereas the diagnosis-related groups' costs for 'other cardiovascular hospitalizations' were included in this analysis ('other cardiovascular disorder' in France or 'other cardiac diagnosis' in the U.K.), we could not take into account the costs of 'unknown' hospitalizations which contributed 4% of all admissions in the conventional therapy group and 3% of all hospitalizations in the bisoprolol group. This analysis is, therefore, 'conservative' as fewer 'unknown' hospitalizations occurred in the bisoprolol group.

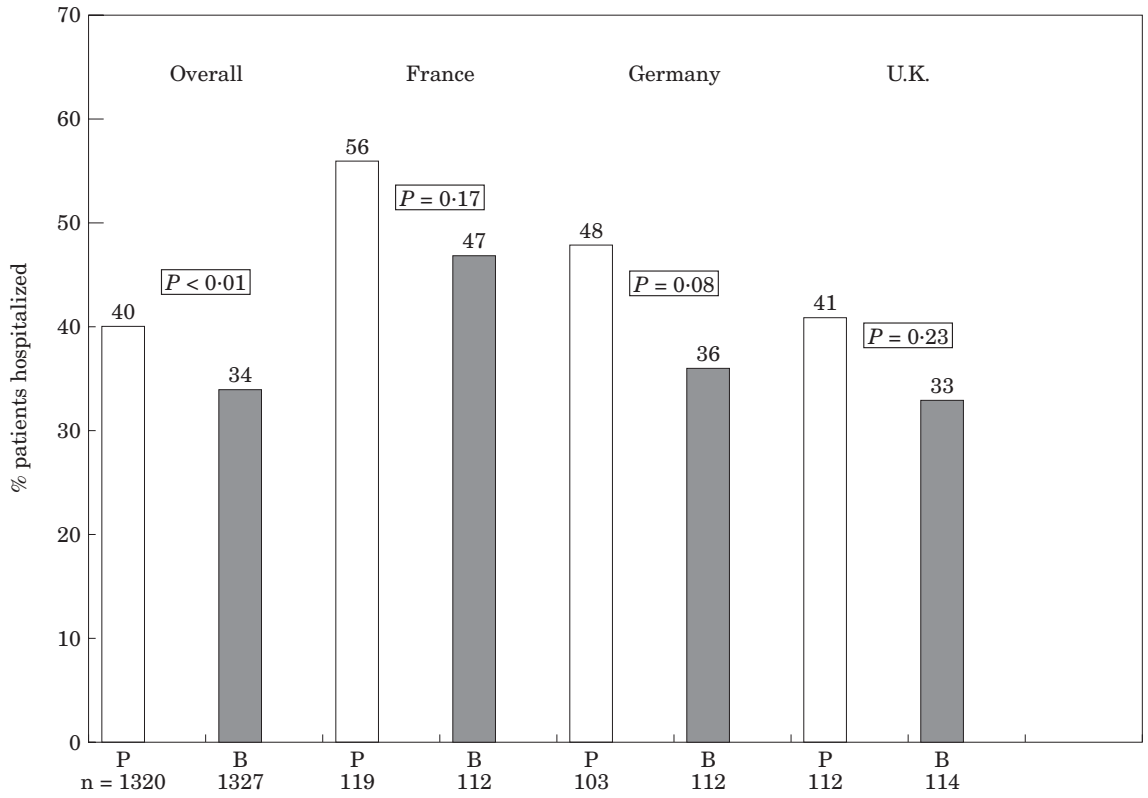

Figure 2 **Proportion (percentage) of patients hospitalized in the two treatment groups of CIBIS II by country. *P*-values derived from chi-square tests. P=placebo; B=bisoprolol.**

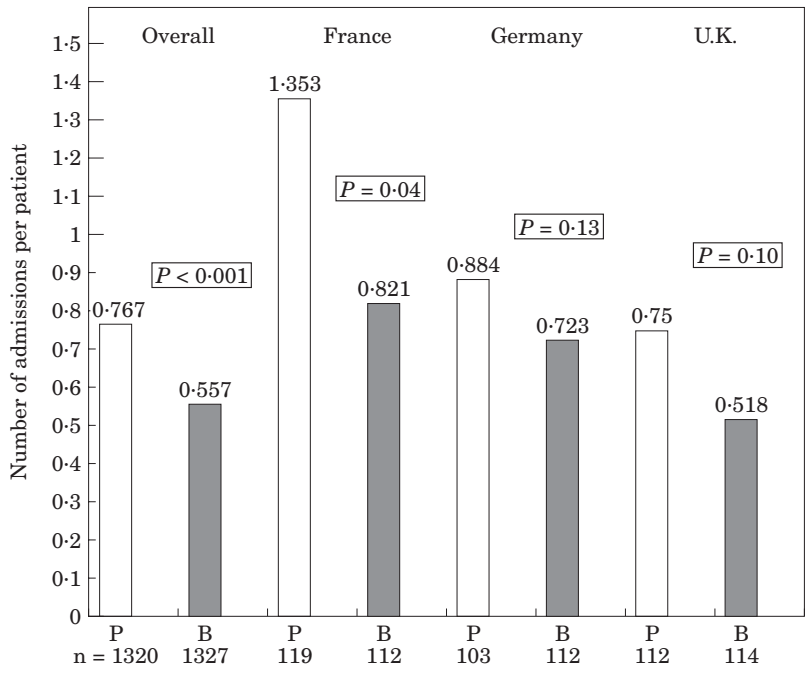

Figure 3 **Number of admissions per patient randomized in the two treatment groups of CIBIS II according to country. *P*-values derived from Wilcoxon Rank sum test. P=placebo; B=bisoprolol.**

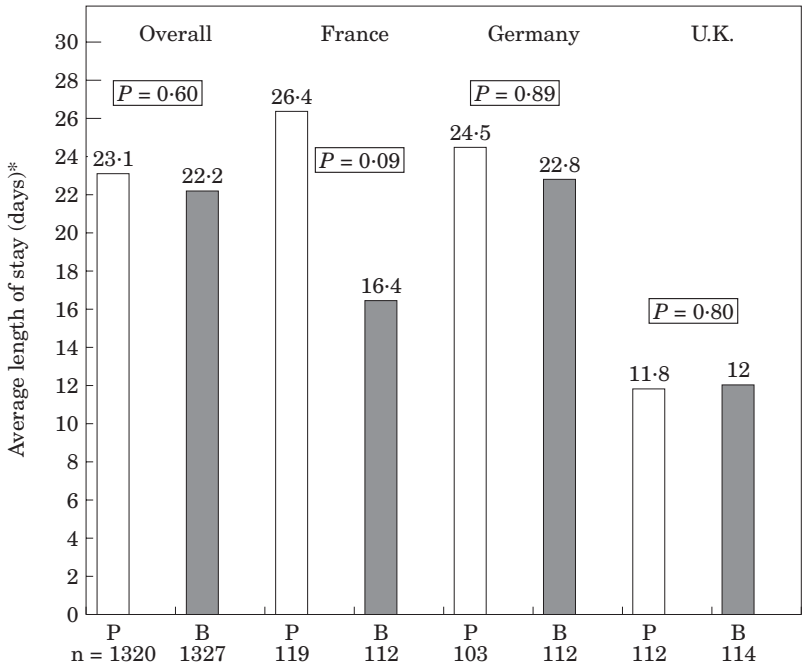

Figure 4 **Average length of hospital admission in the two treatment groups of CIBIS II by country. *Per patient hospitalized. *P*-values derived from Wilcoxon Rank sum tests. P = placebo; B = bisoprolol.**

Table 5 ***Overall cost of treatment in CIBIS-II — per diem analysis***

	France (FF)		Germany (DM)		U.K. (£)	
	Placebo	Bisoprolol	Placebo	Bisoprolol	Placebo	Bisoprolol
Ward in-patient care†						
ITU/CCU	6·73	5·07	1·94	1·37	1·37	1·03
Cardiology ward	13·38	11·10	2·89	2·39	1·87	1·55
General medical ward	6·31	5·33	1·40	1·18	0·54	0·46
Other	4·80	4·06	1·06	0·90	0·41	0·35
Total hospital inpatient	31·22	25·56	7·29	5·94	4·19	3·39
Medication†						
Other medication	14·99	14·99	7·98	7·88	2·39	2·39
Bisoprolol	0·00	1·07	0·00	0·065	0·00	0·42
Total medication	14·99	16·07	7·98	7·94	2·39	2·81
Outpatient/office consultations†	0·00	0·52	0·00	0·434	0·00	0·07
Total†	46·21	42·15	15·26	14·31	6·58	6·27
Total per patient*	35 009	31 762	11 563	10 784	4987	4722

†Millions, *Thousands.

In France the overall cost of care per patient treated was lower in the bisoprolol group (FF25 459 in the conventional care group vs FF22 689 in the bisoprolol group) but in the U.K. costs were estimated to be slightly higher in the bisoprolol group (£2756 in the conventional care group vs £2908 in the bisoprolol group).

Effectiveness of adjunctive bisoprolol vs conventional therapy

As the primary analysis demonstrated net savings with bisoprolol for France and Germany, the calculation of incremental cost-effectiveness ratios was not appropriate in these two countries. In the U.K., however, the diagnosis related group analysis suggested additional costs of about £2·2 million in the bisoprolol group or about £150 per patient treated with bisoprolol.

Based on the differences in mortality (all-cause mortality 17% in the placebo group vs 12% with bisoprolol) and the Kaplan–Meier survival estimates, the number of additional patients alive with bisoprolol was 74, and the number of life years gained was 39·81, at week 65[11]. This translates into a cost-effectiveness ratio of about £3000 per additional patient alive or £5500 per life year gained for bisoprolol treatment in the U.K.

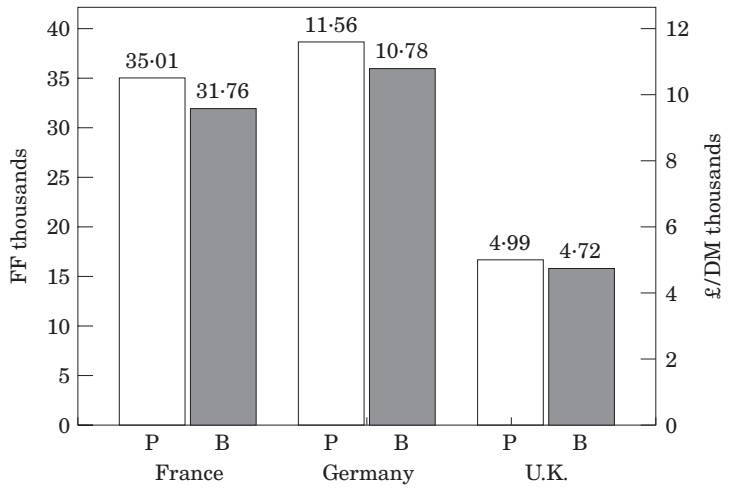

Figure 5 **Total cost per patient treated, in the two treatment groups in CIBIS II, according to country (per diem analysis). P=placebo; B=bisoprolol.**

Table 6 Overall cost of treatment in CIBIS-II — diagnosis related analysis

	France (FF)		U.K. (£)	
	Placebo	Bisoprolol	Placebo	Bisoprolol
Ward inpatient care				
Cardiovascular hospitalizations				
Worsening CHF	9·70	5·21	0·54	0·29
Angina	0·77	0·65	0·04	0·038
Supraventricular arrhythmia	0·70	0·42	0·04	0·024
Ventricular tachycardia/fibrillation	0·40	0·11	0·02	0·006
Stroke	0·43	0·79	0·03	0·062
PTCA/CABG	1·13	1·05	0·06	0·053
Myocardial infarction	0·31	0·45	0·02	0·022
Hypotension	0·16	0·06	0·009	0·003
Cardiogenic shock	0·17	0·17	0·009	0·009
Cardiac transplantation	0·88	1·06	0·16	0·18
Bradycardia	0·03	0·22	0·002	0·013
Other cardiac surgery	0·05	0·05	0·006	0·06
Other cardiovascular	1·14	1·18	0·099	0·06
Non-cardiovascular hospitalizations	2·73	2·11	0·21	0·16
Total hospital inpatient	18·61	13·52	1·24	0·98
Medication†				
Other medication	14·99	14·99	2·39	2·39
Bisoprolol	0·00	1·07	0·00	0·42
Total medication	14·99	16·07	2·39	2·81
Outpatient/office consultations†	0·00	0·52	0·00	0·07
Total†	33·61	30·11	3·64	3·86
Total per patient*	25 459	22 690	2756	2908

†Millions, *Thousands.

Sensitivity analysis

The length of hospital admission increased by 30%, increasing the cost difference per patient treated in the per diem analysis from − £265 in to − £454 in the U.K., − FF4567 in France and − DM779 to − DM1095 in Germany. Reducing the length of stay by 30% changed the differential to − £81, − FF1934 and − DM468.

These differentials were changed to − £280/ − 255, − FF3348/ − 3153 and − DM863/ − 700 by reducing/increasing the number of initiation/titration physician visits to 3/5. In the diagnosis related group analysis the

differentials were changed from +£152 to −£32/+162 in the U.K. and from −FF2769/−2674 in France.

Discussion

In addition to improving survival in CIBIS-II, bisoprolol substantially reduced hospital admission rates[11]. The overall number of hospitalizations was decreased by 28% and the number of cardiovascular hospitalizations by 30%. Non-cardiovascular admissions were also reduced, by 23%. Amongst cardiovascular hospitalizations, there was a striking 46% reduction in admissions related to worsening heart failure[11]. The costs avoided related to this reduction in hospital admissions more than offset the extra costs of bisoprolol therapy and the extra hospital outpatient or office visits we added to cover the initiation and up-titration of the dose of bisoprolol. Indeed, the per diem analysis showed that the overall cost of care was between 5 and 10% lower in the bisoprolol group in all three countries studied. The diagnosis related group based analysis for France and the U.K. was broadly consistent with the per diem analysis. In France the absolute cost per patient treated in both groups was similar to that in the per diem analysis i.e. the diagnosis related group cost was about 71% of the per diem one. The reduction in cost per patient treated in the bisoprolol group in the diagnosis related group analysis was 10·8% compared to a reduction of 9·3% in the per diem analysis. In the U.K. the per diem analysis gave higher absolute costs (60 to 80% higher) per patient treated than the diagnosis related group analysis. Although there was a 5·3% reduction in cost per patient treated in the bisoprolol group in the per diem analysis, the cost per patient treated in this group in the diagnosis related group analysis in the U.K. increased by 5·5%. Given the uncertainty surrounding the costing of health care these results can still be regarded as consistent.

Even if the diagnosis related group analysis for the U.K. is correct, the 'worst case scenario' is that bisoprolol costs £3000 per additional patient alive or £5500 per life year gained over the duration of the study.

Few treatments in cardiology or any other medical or surgical speciality can be shown to be cost neutral or cost saving, making these findings all the more remarkable[25–27].

Our findings are also consistent with economic analyses of the much smaller CIBIS-I trial carried out in Germany, France and the U.K.[19,28,29]. Conversely, an economic analysis of the U.S. carvedilol studies did not show a net cost saving[10,30]. This may reflect the shorter average treatment duration (median 6·5 months), greater unit cost of treatment and data modelling carried out in that analysis.

As no major published beta-blocker trial in chronic heart failure has a greater average follow-up than CIBIS II (1·3 years), the longer term benefits and risks of this form of therapy are unknown. This is an important limitation in our understanding of the value of beta-blocker treatment in heart failure.

Another potential limitation is the generalizability of our findings to all patients with heart failure and to other countries. Our results can really only be said to apply to patients like those randomized in CIBIS II and when bisoprolol is used as it was in the trial. We do believe, however, that out findings are more generalizable in a geographical sense. Beta-blockers seem to reduce morbidity and mortality in all countries and continents studied and hospital admissions are the main driver of the cost of heart failure globally[1,2,31]. Consequently, it is likely that beta-blockers are cost effective in CIBIS II-like patients in most countries.

These results have clear implications for the management of patients. Not only does bisoprolol increase survival and reduce hospital admission rates in CIBIS-II, it also cut the cost of care of heart failure in so doing. In addition, adverse effects are uncommon and generally mild. Collectively, these findings argue persuasively for routine use of beta-blockers as a treatment for heart failure. It seems very unlikely that many patients would prefer the outcomes expected without beta-blocker therapy to those anticipated with this type of treatment. The 'win–win' situation of positive health benefits associated with cost-savings is also favourable from the point of view of health care systems as there is no trade-off between the interest of individual patients and the whole population of patients served by the health care system[26].

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Appendix 1

CIBIS II Health Economics Group

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