Original articles

Cost-effectiveness analysis of bisoprolol treatment for heart failure

Francesca Di Stasi*, Luciana Scalone*, Simona De Portu§, Enrica Menditto§, Lorenzo Giovanni Mantovani*§

*Center of Pharmacoeconomics, Faculty of Pharmacy, University of Milan, Milan, §CIRF, Faculty of Pharmacy, "Federico II" University, Naples, Italy

Key words:
Bisoprolol;
Congestive heart failure;
Cost-effectiveness.

Background. **Beta-blockers have provided evidence of improving survival in chronic heart failure patients. Specifically, the Cardiac Insufficiency Bisoprolol Study II has shown a significant reduction in mortality and morbidity among patients with moderate to severe chronic heart failure treated with bisoprolol. Our aim was to investigate the economic consequence of bisoprolol therapy in chronic heart failure patients in Italy.**

Methods. **Data were derived from the Cardiac Insufficiency Bisoprolol Study II trial. We conducted a cost-effectiveness analysis, comparing standard care with bisoprolol vs standard care with placebo in the perspective of the Italian National Health Service. We identified and quantified medical costs: drug costs according to the Italian National Therapeutic Formulary; specialist visits for initiation and up-titration of bisoprolol therapy and hospitalizations were quantified based on the Italian National Health Service tariffs (2005). Effects were measured in terms of mortality and morbidity reduction (number of deaths, life-years gained and frequency of hospitalizations). We considered an observational period of 1.3 years, i.e. the average follow-up recorded in the trial. Discounting was not performed because of the relatively short follow-up of patients. We conducted one- and multiway sensitivity analyses on unit cost and effectiveness. We also conducted a threshold analysis.**

Results. **The overall cost of care per 1000 patients treated for 1.3 years was estimated in €2,075,548 in the bisoprolol group and in €2,396,265 in the placebo group, resulting in a net saving of €320,718. The number of additional patients alive with bisoprolol was 55 per 1000 patients, the number of life-years gained was 36 at 1.3 year.**

Conclusions. **Bisoprolol therapy is dominant since it is both less costly and more effective than standard care. Results of sensitivity analysis showed that bisoprolol therapy remains dominant even to changes in unit cost of drug and hospitalizations.**

(Ital Heart J 2005; 6 (12): 950-955)

This study was made possible thanks to an unrestricted educational grant from Bracco, Bayer and Merck Pharma.

Received May 3, 2005; revision received July 26, 2005; accepted August 1, 2005.

Address:

Dr. Lorenzo Giovanni Mantovani

CIRF
Facoltà di Farmacia
Università degli Studi
"Federico II"
Via Domenico Montesano, 49
80131 Napoli
E-mail:
lorenzo.mantovani@unimi.it

Introduction

The European Society of Cardiology, representing countries with a total population of > 900 million, suggests that there are at least 10 million patients with heart failure (HF) in those countries[1]. In western countries the incidence of HF ranges between 1 to 5 individuals per 1000 patient-years in the general population each year, increasing steeply with age to > 30 cases per 1000 patient-years among those aged ≥ 75 years[2]. Findings from the Framingham Heart Study report an increasing annual rate of HF in men from 2 per 1000 at age 45-54 years to 32 per 1000 at age 85-94 years, and from 1 per 1000 at age 45-54 years to 26 per 1000 at age 85-94 years in women[3,4]. No studies estimating prevalence and incidence in Italy have been published so far. Anyway, according to data published by Rengo and Acanfora[5], the prevalence of HF in consecutive patients admitted to geriatric departments has been estimated to be 43% in those aged 65-74 years and 58% in those > 85 years.

The incidence and prevalence of HF have been increasing in the last years, because of several reasons: one of the major driving factors is the increasing proportion of the elderly in developed countries. Moreover, improvement in the treatment of coronary artery disease, by decreasing mortality, is keeping more people alive and, therefore, at higher risk of developing HF[6].

It has been shown that incidence and prevalence trends of HF have a strong economic impact on health care systems: cost-of-illness studies conducted in the 1990s suggested that approximately 1-2% of the total health care budget in developed countries is spent for HF management[7]. Accord-

ing to a prevalence-based study conducted in the UK[8], in 1995 the management of HF accounted for 1.83% of the total healthcare cost provided by the National Health Service (NHS) in the UK. The main contributor to the overall cost was hospitalization, accounting for 69%, the second largest component of cost was drug treatment, corresponding to 18% of total expenditure. Another cost-of-illness study was conducted in 1996 in Sweden[9], and similarly it was found that 74% of costs for managing HF were attributable to institutional care (hospitals and nursing homes), whereas the cost for pharmaceuticals accounted for 11%. Other evaluations have been conducted in countries like France, the Netherlands and the United States[7] and they all agree that hospital care is the most important component of expenditure for managing chronic HF.

Regarding Italy, HF associated with shock is one of the most common reasons of hospital admissions: in 2002 it was the second most common reason, accounting for 2.1% of all hospital discharges. With more than 186 000 discharges hospital costs for HF in 2002 amounted to €576 million for the NHS[10]. The number of hospitalizations has been increasing in the last years: in the United States hospital discharges for HF rose from 377 000 in 1979 to 995 000 in 2001, corresponding to an increase of 2.6 times[6]. In Italy, hospital admissions for HF and shock increased by 32% in the last 6 years, with 127 000 hospital discharges in 1996 up to 186 000 in 2002[10].

Beta-blockers have become an established therapy for HF in combination with diuretics, cardiac glycosides and angiotensin-converting enzyme inhibitors. The relatively recent introduction of beta-blockers in the treatment of HF is due to their efficacy in terms of mortality and morbidity, as demonstrated in a number of large randomized clinical trials[11-16]. Results of these trials reported a positive effect of beta-blockers in reducing the number of hospitalizations in patients treated with these drugs compared to those treated with placebo.

In particular, the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial evaluated the effect of adding bisoprolol to conventional therapy in patients with a diagnosis of HF. It was a double-blind placebo-controlled randomized trial that enrolled 2647 patients (81% men, mean age 61 years) in 18 countries of western and eastern Europe. Eligible patients were aged 18-80 years, and had a left ventricular ejection fraction of ≤ 35%. Their symptoms had to correspond to New York Heart Association (NYHA) class III or IV. The cardiovascular therapy had to include a diuretic and an angiotensin-converting enzyme inhibitor. Patients were randomly assigned to bisoprolol (n = 1327) or placebo (n = 1320) treatment. Daily dose was titrated up to 10 mg. The primary endpoint was all-cause mortality. Secondary endpoints were cardiovascular mortality, all-cause hospital admissions and cardiovascular hospital admissions. The average follow-up of the main trial was 1.3 years as the trial was stopped early, because all-cause mortality was significantly less in the bisoprolol group than in the placebo group. According to the CIBIS-II trial, bisoprolol added to standard therapy is effective, significantly reducing mortality and morbidity. A total of 156 (11.8%) patients died for all cause in the bisoprolol group compared with 228 (17.3%) in the placebo group. Cardiovascular deaths were 9 and 12% in the bisoprolol and placebo groups respectively. Even hospital admissions were significantly lower in the bisoprolol group: 33% compared with 39% of patients hospitalized for all causes in the bisoprolol and in the placebo group, respectively. With bisoprolol therapy all-cause hospital admissions were reduced by 28%, and cardiovascular hospitalizations were reduced by 30%.

Therefore it would seem that an effective treatment of patients with HF, reducing morbidity and consequently hospital admissions, may potentially provide financial savings[17].

Our objective was to evaluate the economic consequences in Italy of treatment of chronic HF with the beta-blocker bisoprolol.

Methods

Study design. In order to reach our objective we used the CIBIS-II trial as data source. We conducted a cost-effectiveness analysis[18,19] comparing conventional therapy of HF with conventional therapy plus bisoprolol in Italy. The technique and the alternatives were determined by the choice to use the CIBIS-II trial as a data source of our study.

The analysis was applied to a time horizon of 1.3 years, in order to be adherent to the mean follow-up period of the CIBIS-II trial.

In this study the Italian NHS perspective was adopted as in Italy the NHS provides health care services for patients affected by HF[20]. All the analyses were referred to a hypothetical cohort of 1000 subjects with the characteristics of those included in CIBIS-II trial.

Costs. The analysis regarded direct medical costs: specifically we estimated the cost of pharmacological therapy, cost of hospitalizations and cost of additional visits for beginning and up-titration of therapy with bisoprolol. Costs were quantified according to tariffs[21] and to the National Therapeutic Formulary[22] of the year 2005; in that year €1 corresponded to US$1,29. Unit costs are shown in tables I[23] and II.

As conventional therapy was comparable between the two groups, we estimated only costs of bisoprolol adjunctive therapy. Drug costs were computed according to the dosage established in the treatment protocol: patients started on 1.25 mg/day of bisoprolol or placebo, the drug being increased successively to 2.50, 3.75, 5.00, 7.50 and 10.00 mg, according to tol-

Table I. Unit cost.

Variable	DRG	Unit cost (€)
Worsening chronic HF	127	3,091.51
Angina	140	2,179.45
Supraventricular tachycardia	138	3,231.99
Ventricular tachycardia/ fibrillation	138	3,231.99
Stroke	14	3,926.62
PTCA/CABG	106, 107, 112*	8.060.61
Myocardial infarction	121, 123*	4,554.82
Hypotension	141	2,416.50
Cardiogenic shock	127	3,091.51
Cardiac transplantation	103	49,967.20
Bradycardia	138	3,231.99
Other cardiac surgery	104, 105, 108, 110, 115, 116, 118*	10,404.16
Other cardiovascular	113, 114, 117, 119, 120,124, 126, 128, 129, 130, 132, 134, 135, 143, 144, 478	3,099.31
Non-cardiovascular admissions	–	3,122.56
Up-titration visit	–	20.66

CABG = coronary artery bypass grafting; DRG = diagnosis-related group; HF = heart failure; PTCA = percutaneous transluminal coronary angioplasty. * a weighted average unit cost was computed according to the frequency of hospital discharges occurred in Italy in 2002[23].

Table II. Drug unit cost.

Bisoprolol dose (mg)	Cost/tablet (€)
1.25	0.262
2.50	0.285
3.75	0.309
5.00	0.346
7.50	0.368
10.00	0.389

erance. Patients received the first three concentrations of each dose for 1 week, and the higher concentrations for 4 weeks. The unit tablet cost of bisoprolol (in Italy, tablets of bisoprolol are marketed with every dosages above reported) was multiplied with the total number of tablets used by the patients during the follow-up. Actually, not all patients reached the maximum prescribed dosage: in particular, the most common dose of bisoprolol during the maintenance phase was 10.0 mg/day in 564 patients (41%), 7.5 mg/day in 152 patients (11%), and 5.0 mg/day in 176 patients (13%). According to data published by the CIBIS-II investigators[16], some patients withdrew prematurely from the study and some other patients died in the course of the trial. We had no information about time when patients stopped to take bisoprolol therapy. So, in order to evaluate costs of therapy for these subjects, we assumed they underwent bisoprolol treatment till half of the time horizon considered (227 days). To avoid double counting, drug cost during hospital stay was subtracted from the overall therapy cost since in Italy pharmacological therapy during hospitalization is included in the diagnosis-related group (DRG)-based reimbursement for cost provided to hospitals by the NHS.

For the beginning and up-titration of bisoprolol therapy we assumed that all patients required four additional specialist visits, according to what reported by the investigators of the CIBIS-II Health Economic Evaluation[16]. In order to quantify visit costs we multiplied the total number of visits by their unit costs.

Hospital cost was quantified for cardiovascular and non-cardiovascular admissions as well. As unit cost we used the DRG reimbursement tariffs[23].

Regarding hospitalizations occurring during the follow-up for cardiovascular reasons, we used DRG tariffs as follows: when both tariffs for discharges with and without complications exist, costs were computed by taking into account only those referred to discharges with complications. In fact, inclusion criteria were to be severely affected by HF (NYHA class III or IV, with left ventricular ejection fraction ≤ 35%) and this condition leads to increasing hospital costs for other cardiovascular reasons. When more than one DRG tariff exists for a given diagnosis or event and no more detailed information was available from our data source, we used the arithmetic mean cost of all hospitalizations of interest.

As no detailed information on non-cardiovascular hospitalizations was available, costs for their occurrence were computed as the average of all possible hospital admissions, excluding cardiovascular ones. We computed a mean unit cost by weighting each tariff with frequency of admission occurred in the most recent Italian hospital discharge records available and then we obtained a unit cost for "non-cardiovascular hospitalizations"[10].

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

Effectiveness. In order to evaluate effects of using bisoprolol against placebo we used results on all-cause mortality, cardiovascular mortality and all-cause hospitalizations. Furthermore we calculated life-years gained due to all-cause mortality reduction as the difference in the area between survival curves reported in the trial. In adherence with the trial, the intention-to-treat results were used in our estimate.

Furthermore, as admissions to hospital gave rise to costs for the NHS, their occurrence was quantified in monetary terms as described before.

Sensitivity analysis. To examine the impact of change in one or more of key variables on the results of the analysis, we performed a one-way sensitivity analysis. Unit cost of bisoprolol, unit cost of hospitalizations and the number of hospitalizations were changed of ± 10%.

In order to identify the best and the worst possible scenarios, we also conducted a multiway sensitivity analysis, by contemporarily changing all clinical and economic parameters included in our evaluation. Moreover a threshold analysis was performed, in order to obtain the bisoprolol price which would determine the same cost for the two treatment alternatives under study[24].

Results

Based on Kaplan-Meier survival curves we estimated that bisoprolol therapy saved 36 life-years per 1000 patients per 1.3 years against placebo.

Results are shown in table III. The total cost of bisoprolol drug was estimated in €146,979 per 1000 patients for 1.3 years. According to data published by the CIBIS-II investigators and health economics group[25], globally 7629 days per 1000 patients were spent in hospital: so we subtracted €2,362.5 for bisoprolol given during hospital days from the cost of drug. We estimated a net cost of drug therapy of €144,622. Cost of specialist visits for the beginning and up-titration of bisoprolol therapy was € 82,640 per 1000 patients. Hence, the total cost of pharmacological therapy with bisoprolol corresponded to €227,261 per 1000 patients per 1.3 years.

Hospitalization costs for cardiovascular events were €1,787,366 and €1,379,902 for placebo and bisoprolol group respectively. Costs for non-cardiovascular events were €608,899 for patients treated with placebo and €468,384 for patients treated with bisoprolol. The overall hospital cost was estimated of €1.8 million in bisoprolol group and of €2.4 million in the placebo group.

Hence, the overall cost of care per 1000 patients treated for 1.3 years with bisoprolol was estimated in €2,075,548 vs €2,396,265 in the placebo group, resulting in a net saving of €320,718. Treating HF patients with bisoprolol therapy reducing hospital admissions corresponded to a reduction of 22.9% in total hospital costs.

Results are shown in tables III and IV. These results show that bisoprolol therapy is both less costly and more effective than standard care. On this basis, adjunctive bisoprolol is to be considered a dominant treatment.

Estimates are stable under different sensitivity analyses: bisoprolol therapy remains dominant, unless its price is more than tripled, when hospitalizations for all causes are considered, or more than doubled, when only cardiovascular hospitalizations are taken into account. Results are shown in table V.

Discussion

HF is a clinical condition whose prevalence and incidence is dramatically increasing. As the management

Table III. Cost analysis.

Variable	Bisoprolol		Placebo		Cost difference (€)
	Expected number/1000 patients over 1.3 years	Total cost (€)	Expected number/1000 patients over 1.3 years	Total cost (€)	
Worsening chronic HF	159	491,550.09	298	921,269.98	-429,719.89
Angina	35	76,280.75	41	89,357.45	-13,076.73
Supraventricular tachycardia	20	64,639.80	33	106,655.67	-42,015.87
Ventricular tachycardia/ fibrillation	5	16,159.95	19	61,407.81	-45,247.86
Stroke	23	90,312.26	13	51,046.06	39,266.20
PTCA/CABG	9	72,545.40	10	80,606.09	-8,060.61
Myocardial infarction	12	54,657.86	8	36,438.57	18,219.29
Hypotension	3	7,249.50	8	19,332.00	-12,082.50
Cardiogenic shock	5	15,457.55	5	15,457.55	0
Cardiac transplantation	5	249,836.00	4	199,868.80	49,967.20
Bradycardia	11	35,551.89	2	6,463.98	29,087.91
Other cardiac surgery	1	10,404.16	1	10,404.16	0.00
Other cardiovascular	63	195,256.77	61	189,058.14	6,198.63
Non-cardiovascular admissions	150	468,384.00	195	608,899.20	-140,515.20
Up-titration visit	1000	82,640.00	0	0	82,640.00
Bisoprolol	1000	144,621.63	1000	0	144,621.63
Total	–	2,075,547.69	–	2,396,265.46	-320,717.78

CABG = coronary artery bypass grafting; HF = heart failure; PTCA = percutaneous transluminal coronary angioplasty.

Table IV. Cost differences.

Variable	Bisoprolol		Placebo		Cost difference (€)	
	Observed number/1000 patients over 1.3 years	Total cost (€)	Observed number/1000 patients over 1.3 years	Total cost (€)	Total	Cardiovascular
Total admission costs		1,848,286.06		2,396,365.46	-548,079.40	
Non-cardiovascular admissions	150	468,384.00	195	608,899.20	-140,515.20	
Cardiovascular admissions	351	1,379,902.06	503	1,787,366.26	-407,464.20	-407,464.20
Up-titration visit	1000	82,640.00	0	0	82,640.00	82,640.00
Bisoprolol	1000	144,621.63	0	0	144,621.63	144,621.63
Total		2,075,547.69		2,396,265.46	-320,717.78	-180,202.57

Table V. Sensitivity analysis.

Description	Variation (%)
Saving from ranging bisoprolol price within ± 10%	± 4.5
Saving from ranging cost of events within ± 10%	± 10.0
Worst-case scenarios evaluated	28.8

of HF requires long-term therapies and frequent hospitalizations, with considerable economic input, it is necessary to consider new therapeutic measures to prevent worsening HF and consequent admissions to hospital.

This is the first Italian pharmacoeconomic study aimed at assessing the economic consequences related to treatment with the beta-blocker bisoprolol in patients with HF whose severity corresponds to NYHA class III and IV and with a left ventricular ejection fraction ≤ 35%.

According to the CIBIS-II trial, treating these patients with bisoprolol for an average of 1.3 years significantly reduces mortality and morbidity. The overall number of hospitalizations was reduced by 28% and cardiovascular hospitalizations were reduced by 30%. In our pharmacoeconomic evaluation these benefits turn out in cost savings estimated as €320,718 per 1000 patients treated for a mean of 1.3 years in the Italian NHS perspective, corresponding to a reduction of 13% in total cost. The additional costs of bisoprolol and medical visits, estimated as €227,262 per 1000 patients, are more than offset by the cost saving attributable to the reduction in hospital admissions, which is the major component of health care cost for HF[11]. Although the present economic evaluation is focused on bisoprolol, it would also be interesting to consider treatment of chronic HF patients with other beta-blockers, including carvedilol, metoprolol and nebivolol, characterized by different acquisition costs. Unfortunately this was not possible in the framework of our analysis.

Sensitivity analyses show that therapy with bisoprolol is dominant even in the most unfavorable scenarios we considered. The threshold analysis shows that bisoprolol therapy remains dominant although the drug price is doubled, when cardiovascular hospitalizations only, or all causes for hospitalization, are considered; it is still dominant when its price is more than tripled, when all causes for hospitalization are considered.

Our study has some potential limitations. The CIBIS-II trial involved eastern and western European countries, including Italy. We could not extract specific Italian data, so we applied our estimate to the overall sample enrolled in the study, assuming that they can be generalized to the Italian context. Our results are consistent with those of studies conducted in France and Germany, in that bisoprolol therapy resulted to be dominant, and in the UK and Sweden, in that it was found a favorable cost-effectiveness ratio per additional patient alive and per life-year gained[25,26-28].

We did not consider indirect costs, since data on working time lost or inability to do usual activities were not collected during the trial. Actually, 72% of the enrolled patients were retired[25], hence loss of productivity is unlikely to deeply influence our estimate. Anyway, patients in the bisoprolol group, reporting more clinical benefits, probably would have reported lower productivity loss, because of the lower frequency of hospitalizations and hospital stay. It is likely that the evaluation of indirect costs would have increased the economic benefit deriving from bisoprolol therapy in patients with HF. Our estimate is likely to be conservative.

Moreover, it should be considered that, in order to adhere with the original clinical study, this analysis is limited to 1.3 years of follow-up, while it would be interesting to take into account the economic consequences of a longer follow-up, which may result in lower or higher overall cost.

In conclusion, bisoprolol added to standard drug therapy for HF is dominant, as the reduction in mortality and morbidity takes to a net cost saving for the NHS, which provides almost completely for costs of managing HF in Italy. The results of the present study should anyway be put into the perspective of the current epidemiology of chronic HF: whereas the CIBIS-II reports

on a relatively young (61 years of age, on average) and mainly male population (81%), in clinical practice the disease occurs in older patients (75-80 years of age) with a male to female ratio of 1:1[29].

Results of this study can be a useful contribution for an optimal allocation of healthcare and should be considered by policy and decision makers in their attempt to appropriately allocate healthcare resources.

References

1. Remme WJ, Swedberg K, on behalf of the Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001; 22: 1527-60.
2. Sharpe N, Doughty R. Epidemiology of heart failure and ventricular dysfunction. Lancet 1998; 352 (Suppl I): SI3-SI7.
3. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev 2000; 5: 167-73.
4. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993; 22 (Suppl A): 6A-13A.
5. Rengo F, Acanfora D. Lo scompenso cardiaco nell'anziano. G Ital Cardiol 1994; 24: 1423-34.
6. http://www.americanheart.org
7. Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. Eur J Heart Fail 2001; 3: 283-91.
8. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. Eur J Heart Fail 2002; 4: 361-71.
9. Ryden-Bergesten T, Andersson F. The health care costs of heart failure in Sweden. J Intern Med 1999; 246: 275-84.
10. http://www.ministerosalute.it/programmazione/sdo/sdo.jsp
11. Cowper PA, DeLong ER, Whellan DJ, Allen LaPointe NM, Califf RM. Economic effect of beta-blocker therapy in patients with heart failure. Am J Med 2004; 116: 104-11.
12. Maggioni AP. Heart failure: treatment strategies for heart failure. Beta-blockers and antiarrhythmics. Heart 2001; 85: 97-103.
13. Bouzamondo A, Hulot JS, Sanchez P, Lechat P. Beta-blocker benefit according to severity of heart failure. Eur J Heart Fail 2003; 5: 281-9.
14. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001-7.
15. Packer M, Coats AJ, Fowler MB, et al, for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-8.
16. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9-13.
17. Scalone L, Mantovani LG. Valutazione economica della terapia con lisinopril ad alto verso basso dosaggio nel trattamento dei soggetti con scompenso cardiaco cronico. Pharmacoeconomics - Italian Research Articles 2002; 4: 45-55.
18. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977; 296: 716-21.
19. Drummond MF, Stoddart GL, Torrance GW. Methods for economic evaluation of health care programmes. Oxford: Oxford University Press, 1997.
20. Szucs TD, Mantovani LG. The perspective of a pharmacoeconomic study: targeting for audiences. Pharmacol Res 1997; 35: 471-5.
21. Ministry Decree July 22, 1996. Prestazioni di assistenza specialistica ambulatoriale erogabili nell'ambito del Servizio Sanitario Nazionale e relative tariffe. Supplement to Gazzetta Ufficiale n. 216, September 14, 1996.
22. Informatore Farmaceutico 2005. 64th edition. Milano: Edimed, 2005.
23. Ministry Decree December 14, 1994. Tariffe delle prestazioni di assistenza ospedaliera. Supplement to Gazzetta Ufficiale n. 209, September 8, 1997.
24. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. Health Econ 1994; 3: 95-104.
25. Reduced costs with bisoprolol treatment for heart failure: an economic analysis of the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II). Eur Heart J 2001; 22: 1021-31.
26. Schadlich PK, Paschen B, Brecht JG. Economic evaluation of the Cardiac Insufficiency Bisoprolol Study for the Federal Republic of Germany. Pharmacoeconomics 1998; 13 (Part 2): 147-55.
27. Varney S. A cost-effectiveness analysis of bisoprolol for heart failure. Eur J Heart Fail 2001; 3: 365-71.
28. Ekman M, Zethraeus N, Jonsson B. Cost effectiveness of bisoprolol in the treatment of chronic congestive heart failure in Sweden: analysis using data from the Cardiac Insufficiency Bisoprolol Study II trial. Pharmacoeconomics 2001; 19: 901-16.
29. Tavazzi L. Ventricular pacing: a promising new therapeutic strategy in heart failure. For whom? Eur Heart J 2000; 21: 1211-4.