



Programme to improve the use of beta-blockers for heart failure in the elderly and in those with severe symptoms: Results of the BRING-UP 2 Study

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Abstract

Background: Beta-blockers are underused in HF patients, thus strategies to implement their use are needed.

Objectives: To improve beta-blocker use in elderly and/or patients with severe heart failure (HF) and to evaluate safety and outcome.

Methods: Patients with symptomatic HF and age ≥ 70 years or left ventricular EF $< 25\%$ and symptoms at rest were enrolled, including those already on beta-blocker treatment. Patients who were not receiving a beta-blocker were considered for carvedilol treatment. All patients were followed up for 1-year.

Results: Of the 1518 elderly patients, 505 were already on beta-blockers, and carvedilol was newly prescribed in 419 patients. At 1-year, patients treated with carvedilol had a lower incidence of death [10.8% vs. 18.0% in already treated (adjusted RR 0.68; 95%CI 0.49–0.96) and 11.2% in newly treated patients (adjusted RR 0.68; 95%CI 0.48–0.97)].

Of the 709 patients with severe HF, 38.4% were already on beta-blockers, and carvedilol was newly prescribed in 189 patients. Patients not treated with carvedilol showed the worst clinical outcome. Total rate of discontinuation (including adverse reaction and non-compliance) was 14% and 9%, respectively, in elderly and severe patients.

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¹ See the Appendix for a complete list of participating Centers and Investigators. The study was supported in part by Roche Spa Italy.

Conclusions: In a real world setting, beta-blocker treatment was not associated with an increased risk of adverse events in elderly and severe HF patients.

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Keywords: beta-blockers; Heart failure; Elderly

1. Introduction

Although several randomised, placebo-controlled trials have demonstrated the efficacy of beta-blocker treatment in patients with chronic heart failure (CHF) this life-saving therapy is still underused [1–6]. Changing clinical practice represents a major challenge, and an effective strategy to implement clinical guidelines is required.

Over the last few years, a strategy for introducing and guiding beta-blocker treatment into clinical practice has been developed by the Italian Association of Hospital Cardiologists (ANMCO). Its effects were recently tested in an observational study of consecutive CHF patients, the BRING-UP study (*beta-blockers in patients with congestive heart failure: guided use in clinical practice*) [7]. The results showed that the overall rate of beta-blocker use increased from 25% to 50% during the study period. It was concluded that a controlled cooperative national research programme could safely accelerate the implementation of beta-blocker therapy in clinical practice.

The favourable results of clinical trials like COPERNICUS, CIBIS II, and MERIT-HF [3,8,9] have expanded the recommendation for beta-blockers to patients with more severe/advanced CHF.

In addition, the recently published SENIORS trial showed that a beta-blocker with vasodilating properties is an effective and well-tolerated treatment for heart failure in the elderly [10]. There is very little data on feasibility, safety and efficacy profiles for beta-blocker use in elderly patients in a real life situation, among whom these agents are considerably underused [5–7,11,12]. The major reasons for poor adherence to treatment guidelines in these patients are related to the perceived complexity of up-titration, and to the fear of adverse events and/or of unfavourable effects on other co-existing conditions, such as diabetes or chronic obstructive pulmonary disease [13–14].

Thus, the BRING-UP 2 study was designed to address these issues using the same strategy as the BRING-UP study, but focusing on improving beta-blocker use in the routine care of these more complex patients. The main objective of the study was to evaluate the feasibility, safety profile and associated outcomes of carvedilol use in elderly patients and those with severe CHF (LVEF < 25% and symptoms at rest or during minimal exercise), subgroups of patients who are generally under treated with beta-blockers.

2. Methods

The strategy adopted for the BRING-UP 2 study was the same as that for BRING-UP [7]. Regional meetings were organized to present the study design, to review clinical guidelines regarding the management of beta-blocker implementation, and to promote patient education and discuss clinical cases with the physicians.

Consecutive out-patients fulfilling the inclusion criteria, whether or not they were already on beta-blocker therapy, were considered eligible for the study and were followed up for 1 year.

The inclusion criteria were:

1. symptomatic chronic heart failure *and* age ≥ 70 years. If left ventricular ejection fraction was $>40\%$, at least one hospitalisation for heart failure in the previous year was also required (Group 1—elderly),
2. left ventricular ejection fraction $<25\%$ *and* symptoms at rest or during minimal exercise, irrespective of age (Group 2—severe CHF). This group intentionally had the same clinical profile as patients enrolled in the COPERNICUS trial [4].

The protocol clearly stated the contraindications to beta-blocker treatment, as follows: bronchial asthma, chronic obstructive airway disease despite therapy with β_2 agonists and/or steroids, II–III degree COPD (such as patients with $FEV_1 < 50\%$), severe vasospastic peripheral disorders, severe peripheral artery disease characterised by rest pain and/or non-healing lesions, long P–R interval ($PR > 0.28$ s) or second degree AV block, heart rate < 50 bpm, and systolic blood pressure ≤ 85 mm Hg. Patients enrolled in randomised clinical trials were excluded from the study. Patients with comorbid conditions could be admitted to the study according to clinical judgement of the responsible cardiologist.

Patients fulfilling the eligibility criteria and not currently being treated with a beta-blocker were considered for carvedilol treatment. Carvedilol prescription was at the discretion of the individual physician; reasons for the physician's choice had to be reported in the study record form. If carvedilol was prescribed, it was after at least 2 weeks of clinical stability and at a dosage of 3.125–6.25 mg b.i.d., up-titrated every 1–2 weeks to the maximal dosage tolerated. At the time of the study carvedilol was the only beta-blocker approved for clinical use in heart failure patients in Italy.

The frequency of the follow-up visits depended on whether or not carvedilol treatment was initiated. Patients

who were started on carvedilol at study entry or during the follow up period were seen at one and three months after treatment onset. Thereafter, all these patients—as well as those not treated or already treated with carvedilol—had clinical follow up visits at six and 12 months, in which data on their clinical status and hospital admissions were collected. All deaths were documented, and the cause of death was determined by the responsible clinician from the clinical records for patients who died in the hospital, or by collecting information from the relatives and from the death certificate when death occurred outside the hospital.

The primary end point of the study was to measure: 1) the number of patients with CHF aged ≥ 70 years (Group 1—elderly) and the number of patients with severe CHF (Group 2—severe CHF), who started carvedilol treatment and were still on treatment after 12 months, 2) the number of discontinuations from carvedilol treatment, and the associated reasons.

The secondary end point was to measure the number of patients, treated or not with carvedilol, who died or were admitted to hospital during the course of the follow-up.

The study was coordinated by the Research Centre of the Italian Association of Hospital Cardiologists (ANMCO). Ninety-four centres (75 cardiology centres and 19 internal medicine departments) participated in the study. The enrolment period lasted from March 2001 to January 2002 with a follow up of one year for all the included patients.

2.1. Statistical analysis

Separate analyses were performed on Group 1—elderly and Group 2—severe CHF patients. The stratification of these two cohorts of patients was predefined as follows: 1) patients already on beta-blocker treatment at entry, 2) patients started on carvedilol, 3) patients not considered for beta-blocker therapy. Clinical and demographic data, rate of hospitalisation, total mortality and cause of death were compared by χ^2 tests. Differences in continuous variables were tested by one way analysis of variance. Multivariate analysis was used to evaluate the independent predictors of initiation of carvedilol (logistic regression model) and all-cause total mortality during the one year follow up (Cox model). The variables considered were age, heart rate and systolic blood pressure (as continuous variables), sex, atrial fibrillation, aetiology (ischaemic vs. no ischaemic disease) and beta-blocker therapy (on treatment vs. not treated and started vs. not treated). Furthermore, LVEF ($<30\%$ vs. $\geq 30\%$) and NYHA class (III–IV vs. II–I) were considered in the analysis relative to elderly patients. A p value <0.05 was considered statistically significant.

2.2. Ethical considerations

The study complied with the principles of the “Declaration of Helsinki”. Each local independent Institutional

Review Board was informed of the existence of the Registry. Informed consent was obtained from each patient prior to study enrolment.

3. Results

Between March 2001 and January 2002, 2018 patients entered the study. One thousand five hundred and eighteen patients were aged ≥ 70 years (Group 1—elderly) and 709 patients had severe heart failure defined according to the inclusion criteria (Group 2—severe CHF). Two hundred and nine elderly patients also had severe heart failure.

3.1. Group 1—elderly

The clinical characteristics of the elderly patients according to beta-blocker treatment are shown in Table 1. Of the 1518 elderly patients, 505 (33.3%) were already on beta-blocker treatment. Carvedilol was newly prescribed in 419 (27.6%) patients. Among the 594 (39.1%) patients who did not start carvedilol at the beginning of the study, 378 were reported as having one or more clinical contraindications (severe COPD in 220, severe peripheral disease in 47, a P–R interval longer than 0.28 s in 38). Forty-five patients started carvedilol later during the follow-up. Thus, 464 new patients (30.6% of all the elderly patients) started carvedilol during the study period. The number of patients who were not prescribed beta-blockers in the absence of contraindications was 171, 11.3% of the total population of elderly patients included in the study, which can be regarded as the true rate of under treatment (Fig. 1).

Follow-up data were available in 1495 patients (98.5%), of whom 1290 (86%) were still alive after one year. At 1 year, 58.7% of survivors were still on beta-blocker treatment at a mean dose of 24 ± 21 mg/daily. Six- and 12-month compliance was lower in patients who started carvedilol within the study period than in patients already treated with beta-blockers (respectively: 82% vs. 89%, $p=0.003$ and 75% vs. 83%, $p=0.005$). Forty-six percent of discontinuations occurred within the first month of therapy, and were due to worsening heart failure in 34% of the cases, hypotension in 20%, bradycardia or atrio-ventricular block in 10%. Withdrawals caused by exacerbations of comorbidities were rare (15%).

At the end of the year of the study, the overall proportion of patients on beta-blocker treatment increased from 33.3% to 58.7% ($p<0.001$).

The independent predictors of beta-blocker treatment in elderly heart failure patients, from the logistic regression analysis are presented in Table 2.

During 1-year follow up (data available in 501 already treated, 412 newly started and 582 not treated patients) there were no differences in the rate of worsening heart failure (15% in already treated vs. 18% in newly treated patients vs. 18% in not treated patients), all-cause hospitalization (26%

Table 1
Baseline clinical characteristics in the 1518 elderly patients (Group 1)

Baseline	Already on beta-blockers n. 505 (33.3%)	Newly started carvedilol n. 419 (27.6%)	No beta-blockers n. 594 (39.1%)	p value
Age (yr) mean±SD	75±5	76±5	77±5	<0.0001
Male, %	62	56	67	0.002
HR (bpm) mean±SD	71±13	81±14	76±16	<0.0001
SBP (mm Hg) mean±SD	133±21	133±22	128±22	0.0002
Hypertension, %	68	65	61	0.045
Diabetes, %	27	26	26	0.916
LVEF (%) mean±SD	33±10	35±9	34±12	0.220
NYHA class III–IV, %	44	56	55	<0.0001
Symptom duration (mth) mean±SD	39±46	35±40	46±61	0.0009
HF hospitalisation in the last year, %	60	71	72	<0.0001
Principal aetiology				<0.0001
Ischaemic, %	54	47	44	
Idiopathic, %	19	16	16	
Hypertensive, %	18	23	23	
Valvular, %	5	8	12	
Other/unknown, %	3	7	5	
Concomitant treatment				
ACE-I, %	76	80	74	0.040
Diuretics, %	92	93	93	0.908
Digitalis, %	40	48	52	0.0002
Amiodarone, %	9	16	25	<0.0001

HR=heart rate, SBP=systolic blood pressure, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, HF=heart failure.

vs. 26% vs. 31%, respectively) and myocardial infarction (2% vs. 2% vs. 1%, respectively), but patients not treated with carvedilol had the highest incidence of death (18.0% vs. 10.8% in already treated and 11.2% in newly treated patients; $p=0.0005$), mainly occurring during the first six months of follow up.

3.2. Group 2—severe CHF

Baseline characteristics of the 709 patients with LVEF<25% and symptoms at rest or during minimal

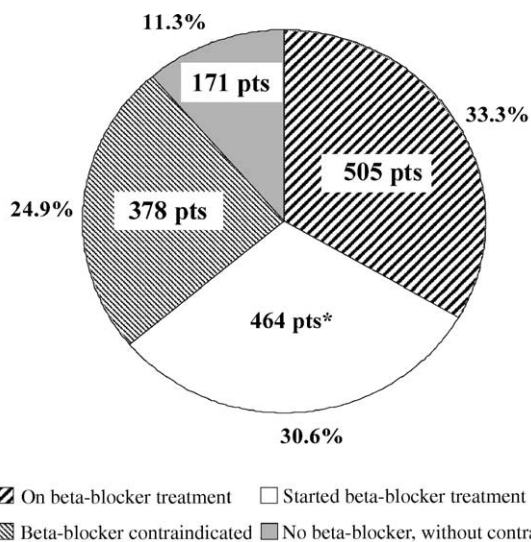


Fig. 1. Summary of beta-blocker usage in 1518 elderly patients in the BRING-UP 2 study. *419 patients initiated beta-blocker treatment at the start of the study and 45 patients initiated treatment during the follow-up.

exercise are shown in Table 3. Of these 709 patients, 38.4% were already on beta-blocker treatment and carvedilol was newly prescribed in 189 patients (26.7%). Among the 248 patients who did not start carvedilol, 163 were judged by their clinicians as having one or more clinical contraindications (intravenous inotropic treatment in 58, severe COPD in 59, severe peripheral vascular disease in 22). Thirty-one patients started carvedilol later during the follow-up. Thus, 220 patients (31.0% of the severe CHF patients) started carvedilol during the study period. A possible under utilization of carvedilol was reported for 54 patients (7.6% of the total population) who were never started on carvedilol despite the absence of contraindications to beta-blocker therapy (Fig. 2).

Only 4 patients (0.6%) were lost to follow-up, and 122 (17.3%) died. After 1 year, 65.2% of survivors were still on beta-blocker treatment at a mean dose of 32 ± 27 mg/

Table 2
Significant predictors of beta-blocker treatment (logistic regression)

Variables	OR	95%CI	p
<i>In elderly patients</i>			
Heart rate (as a continuous variable)	1.04	1.03–1.05	<0.0001
Sex (females vs. males)	1.38	1.08–1.76	0.0108
LVEF (<30% vs. ≥30%)	0.75	0.57–0.98	0.0340
<i>In severe HF patients</i>			
Systolic blood pressure (as a continuous variable)	1.01	1.01–1.02	0.0012
Heart rate (as a continuous variable)	1.01	1.01–1.02	0.0303

LVEF=left ventricular ejection fraction.

Table 3
Baseline clinical characteristics in 709 severe HF patients (Group 2)

Baseline	Already on beta-blockers n. 272 (38.4%)	Newly started carvedilol n. 189 (26.7%)	No beta-blockers n. 248 (35.0%)	p
Age (yr) mean±SD	61±12	64±10	67±12	<0.0001
Male, %	74	71	76	0.505
HR (bpm) mean±SD	75±15	82±16	82±19	<0.0001
SBP (mm Hg) mean±SD	118±20	126±22	118±23	<0.0001
Hypertension, %	35	48	44	0.009
Diabetes, %	28	28	25	0.657
LVEF (%) mean±SD	21±3	21±3	21±3	0.086
NYHA class III–IV, %	100	100	100	/
Symptom duration (mth) mean±SD	48±55	38±52	58±64	0.002
HF hospitalisation in the last year, %	73	76	76	0.697
Principal aetiology				0.028
Ischaemic, %	49	48	42	
Idiopathic, %	32	37	33	
Hypertensive, %	7	9	9	
Valvular, %	4	2	10	
Other/unknown, %	7	5	7	
Concomitant treatment				
ACE-I, %	82	82	73	0.024
Diuretics, %	94	95	96	0.656
Digitalis, %	53	59	62	0.094
Amiodarone, %	16	19	32	<0.0001

HR=heart rate, SBP=systolic blood pressure, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, HF=heart failure.

daily, with similar compliance rates among newly started and already treated patients (81% vs. 84% at 6 months, $p=0.396$, and 77% vs. 77% at 12 months, $p=0.916$, respectively). Among the newly started patients, 16 (8.6%) stopped carvedilol therapy, of these, 10 were within the first month of therapy. Reasons for stopping carvedilol were: hypotension ($n=4$), worsening heart failure ($n=3$), bradycardia ($n=1$); withdrawals caused by exacerbations of the comorbid condition were rare ($n=3$), and non-medical reasons were recorded in 5 patients.

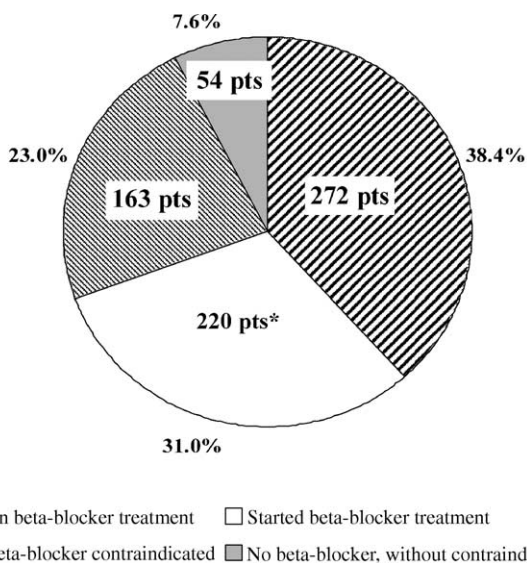


Fig. 2. Summary of beta-blocker usage in 709 severe CHF patients in the BRING-UP 2 study. *189 patients started beta-blocker treatment at the start of the study and 31 patients initiated treatment during the follow-up.

At the end of the year of the study, the overall proportion of patients on beta-blocker treatment increased from 38.4% to 65.2% ($p<0.001$).

The independent predictors of beta-blocker treatment in severe heart failure patients, from the logistic regression analysis, are shown in Table 2.

During 1-year follow up (data available in 271 already treated, 187 newly started and 247 not treated patients), patients not treated with carvedilol showed the highest rate of worsening heart failure (29% vs. 19% in newly treated vs. 19% in already treated patients; $p=0.012$), all-cause hospitalizations (41% vs. 26% in newly treated vs. 32% in

Table 4
Significant predictors of all-cause mortality at 12 months

Variables	RR	95%CI	p
<i>In elderly patients</i>			
NYHA class (III–IV vs. I–II)	2.14	1.56–2.93	<0.0001
Systolic blood pressure (as a continuous variable)	0.98	0.98–0.99	<0.0001
Age (as a continuous variable)	1.04	1.01–1.06	0.0127
Beta-blockers (on treatment/not treated)	0.68	0.49–0.96	0.0297
Beta-blockers (started/not treated)	0.68	0.48–0.97	0.0335
LVEF (<30% vs. ≥30%)	1.34	1.01–1.80	0.0472
<i>In severe HF patients</i>			
Systolic blood pressure (as a continuous variable)	0.97	0.96–0.98	<0.0001
Age (as a continuous variable)	1.03	1.01–1.05	0.0016
Beta-blockers (on treatment/not treated)	0.66	0.43–1.01	0.0576
Beta-blockers (started/not treated)	0.68	0.42–1.10	0.1164

NYHA=New York Heart Association, LVEF=left ventricular ejection fraction.

already treated patients; $p=0.006$), and death (25% vs. 13% in newly treated vs. 14% in already treated patients; $p=0.0007$). Death mainly occurred during the first six months of follow-up.

Table 4 shows the significant predictors of 12 month all cause mortality from the Cox model analysis and the results concerning the beta-blocker treatment. In elderly patients, use of beta-blockers was independently associated with a better prognosis, with a relative risk reduction (RR) of 0.68 (95%CI 0.49–0.96) in already treated and 0.48–0.97 in newly treated patients. The result was similar in severe HF patients although the difference was not significant, probably due to the small number of patients and events.

4. Discussion

Over the one year BRING-UP 2 study the overall rate of beta-blocker treatment doubled, rising from 33% to 64% and from 38% to 69% in elderly and severe CHF patients, respectively.

Physicians started carvedilol more frequently in elderly patients with a mildly compromised ejection fraction, a higher heart rate and, surprisingly, in female patients. Sixty-four percent of the patients who did not start carvedilol had clear contraindications, among them severe chronic obstructive pulmonary disease was highly prevalent.

Overall, 37% of the 1013 elderly patients not treated with a beta-blocker at the start of the study showed a contraindication to carvedilol. Thus, during the BRING-UP 2 study, 73% of the elderly patients without clearly defined contraindications, who were not being treated with a beta-blocker were started on carvedilol, while 27% remained untreated. It is possible that even this low rate of under treatment could be further reduced by an individual reconsideration of the strength and of the persistence of the beta-blocker contraindications.

In patients with severe CHF, only higher heart rate and a high systolic blood pressure predicted the non-prescription of carvedilol. While the finding on systolic blood pressure is understandable, one could speculate that severe patients with increased sympathetic stimulation and lower vagal tone are more dependent upon the inotropic effects of circulating norepinephrine and more prone to carvedilol intolerance. Thirty-seven percent of the 437 patients with severe CHF who were not treated with carvedilol at the start of the study had a contraindication, the majority due to a low output state. During the course of BRING-UP 2, 80% of the untreated severe HF patients without a contraindication started beta-blocker therapy, while 20% remained untreated.

Interestingly, among comorbid conditions possibly limiting carvedilol prescribing, chronic obstructive pulmonary disease had a relevant role while diabetes mellitus did not. Physicians need to be convinced that cardioselective beta-blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive

airway disease and chronic airway obstruction. Therefore patients with these conditions should not be deprived of the beneficial effects of beta blockade [16]. In diabetic patients beta-blockers may provide additional benefits because they may improve insulin sensitivity, even if the extension of the cardiovascular benefit seems to be less effective in comparison with non-diabetic patients [17–19].

We did not observe any increase in death or hospitalisation rates in patients starting carvedilol treatment. Permanent withdrawals due to serious adverse reactions (worsening heart failure, hypotension, bradycardia) occurred rarely even in patients with advanced disease, and generally occurred during the first month of treatment. This good tolerability may be due to the recommendations included in the BRING-UP 2 strategy: the careful up-titration program and the relative stability of the patients. It should be noted, however, that the target dosage of carvedilol was relatively low in both groups. The carvedilol withdrawal rate was close to that observed in trials, with 75% and 77% of the elderly and the severe CHF patients, respectively, still on treatment after one year.

When data from patients with severe HF in COPERNICUS, CIBIS II and MERIT-HF were pooled (more than 3800 patients in NYHA III/IV and $EF < 25\%$), the reduction in total mortality was greater than 30% [9,20]. In the BRING-UP 2 study, the patients with severe CHF had a high rate of events, with the highest number occurring in those who were not considered eligible for carvedilol. This finding may be explained by the relatively greater disease severity in these patients when compared to patients treated with beta-blockers, as shown by their high rate of cardiovascular contraindications to beta-blocker treatment, longer disease duration, and lower blood pressure values, which is also likely to limit ACE-inhibitor therapy. Adjusted analysis showed that carvedilol treatment was associated with a 33% reduction in all-cause death, however, due to the relatively small sample size, the conventional level of significance was not reached. In any case, we did not observe a long-term increase in cardiac events in patients with severe CHF treated with beta-blockers in routine clinical practice.

Data on the effects of beta blockade in elderly patients came from the recently published SENIORS trial [10] showed that the primary outcome (all-cause mortality or cardiovascular hospitalisation) occurred in 31% of patients on nebivolol compared with 35% on placebo (hazard ratio 0.86, 95% CI 0.74–0.99; $p=0.039$). Moreover, in an observational study conducted in patients older than 65 years, beta-blocker use was associated with a lower rate of all-cause mortality (–28%), mortality due to heart failure (–45%), and hospitalisations for heart failure (–18%) [15]. In a pre-specified subgroup analysis of the MERIT-HF trial, beta-blocker treatment in patients aged over 69 years was associated with a significant reduction in the combined endpoint (total mortality+hospitalisations), but not of total mortality alone [21]. In the elderly population of the

BRING-UP 2 study, beta-blocker treatment was associated with a significantly lower one-year total mortality.

Due to the observational nature of this study, the improvement in survival of patients treated with beta-blockers could be related to the fact that treated patients are less severe and/or supervised better than untreated patients. However, after adjustment for the confounding variables the lower mortality rate observed in treated patients broadly corresponds to the mortality reduction obtained with beta-blockers in clinical trials.

Methods to improve guideline implementation could focus on changing physician behaviour or on the organizational support and environment of the providers. Recently Ansari et al. published the results of a randomised trial evaluating three different strategies to increase beta-blocker use in patients with CHF [22]. Among the strategies tested, the involvement of a HF nurse to facilitate and supervise the initiation and titration of beta-blockers was successful, producing a 67% increase in beta-blocker prescribing; moreover, 43% of treated patients maintained the target dose at 12 months. It is possible that careful monitoring by a nurse facilitator was successful in overcoming time consuming barriers (i.e., frequent visits). This strategy could improve the implementation of beta-blocker use in elderly patients once they have been considered eligible for treatment, while for the patients with severe CHF the implementation efforts should be focused primarily on the physicians. The recent IMPACT-HF trial [23] examined the benefits of starting aggressive carvedilol therapy prior to hospital discharge. Pre-discharge initiation was not associated with an increased risk of serious adverse events or length of stay. The early initiation of beta-blocker therapy removes the burden of prescribing from the primary care physician, and ensures that the patient not only receives therapy, but also that dose titration is performed. The results showed that after 2 months 91% of patients randomised to pre-discharge carvedilol initiation were still on the beta-blocker, compared with 73% of those randomised to post-discharge initiation. Thus, a combined intervention that initiates treatment before hospital discharge, continues during the follow up with dose-titration in the outpatient setting, seems to be feasible in many patients. However, as the BRING-UP 2 study shows, more effort should be concentrated on up titration of the beta-blocker dose as far as possible, to achieve maximum benefit. The BRING-UP 2 results confirm that an active intervention rather than a passive dissemination of guidelines is a more successful strategy in changing the processes of care.

5. Contributors

C. Opasich, L. Tavazzi and A.P. Maggioni contributed to the conception and design of the study, analysis and interpretation of data, drafting of the manuscript, and obtaining funding.

D. Lucci contributed to the acquisition of data, analysis and interpretation of data, critical revision of the manuscript, and statistical analysis.

A. Boccanelli, M. Cafiero, V. Cirrincione, D. Del Sindaco, A. Di Lenarda, S. Di Luzio, P. Faggiano, M. Frigerio, M. Porcu, G. Pulignano, M. Scherillo, contributed to the conception and design of the study, and critical revision of the manuscript.

6. Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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The Steering Committee of the study had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A

Steering committee

Cristina Opasich (Chairperson), Alessandro Boccanelli, Massimo Cafiero, Vincenzo Cirrincione, Donatella Del Sindaco, Andrea Di Lenarda, Pompilio Faggiano, Maria Frigerio, Maurizio Porcu, Giovanni Pulignano, Marino Scherillo, Luigi Tavazzi.

Executive committee

Aldo P. Maggioni, Cristina Opasich, Luigi Tavazzi.

Data management, revision and analysis

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