VIEW

Management of heart failure in clinical practice – breaks, solutions

Alain Cohen-Solal

Cardiology Department, Lariboisière Hospital, Paris, France

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REVIEW

The value of nebivolol in chronic heart failure management

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Management of heart failure in clinical practice – breaks, solutions

The increase in prevalence of chronic heart failure (CHF) as shown by various epidemiological studies[1] is partly related to increased life expectancy. While its incidence and prevalence seem to plateau in the young, they increase year by year in the elderly. It is also in part due to considerable improvements in the treatment of coronary artery disease (CAD) and hypertension leading to a reduction in CHF-related mortality of almost 50% over the last twenty years. Treatments now include angiotensin-converting enzyme inhibitors (ACE-Is), beta-blockers (BBs), aldosterone antagonists and, more recently, cardiac resynchronisation therapy and the intracardiac defibrillator. Among these, BBs represent a major improvement, at least as important as the emergence of ACE-Is. Various studies have shown their effectiveness on symptoms, disease course and prognosis. The guidelines of the scientific Societies[2] attribute a major role to them in the long-term treatment of the disease.

However, analysis of the registries of hospitalised or community-managed CHF patients have shown that in reality very few patients, and in particular the elderly, actually receive BBs. Whereas in the most recent clinical trials almost one CHF patient out of two receives a BB (rising to almost 2 out of 3 in trials including HF patients with an LVEF <45%), figures are much lower in real practice: less than 30% of patients receive a BB and generally at a lower dose than recommended. Various studies have shown that poor adherence to BB therapy is associated with a worse outcome.[3,4] In the SENIORS study, patients intolerant to BBs had the worst prognosis (**fig. 1**).[5] Another reason for non-implementation of beta-blockade in the real world is that most of the BB trials were done in relatively young patients (mean age of 65 years) and exclusively in patients with a low LVEF (<40%) (**tab. 1**). However, today there are more patients over 70 with CHF and preserved LVEF (>50%)

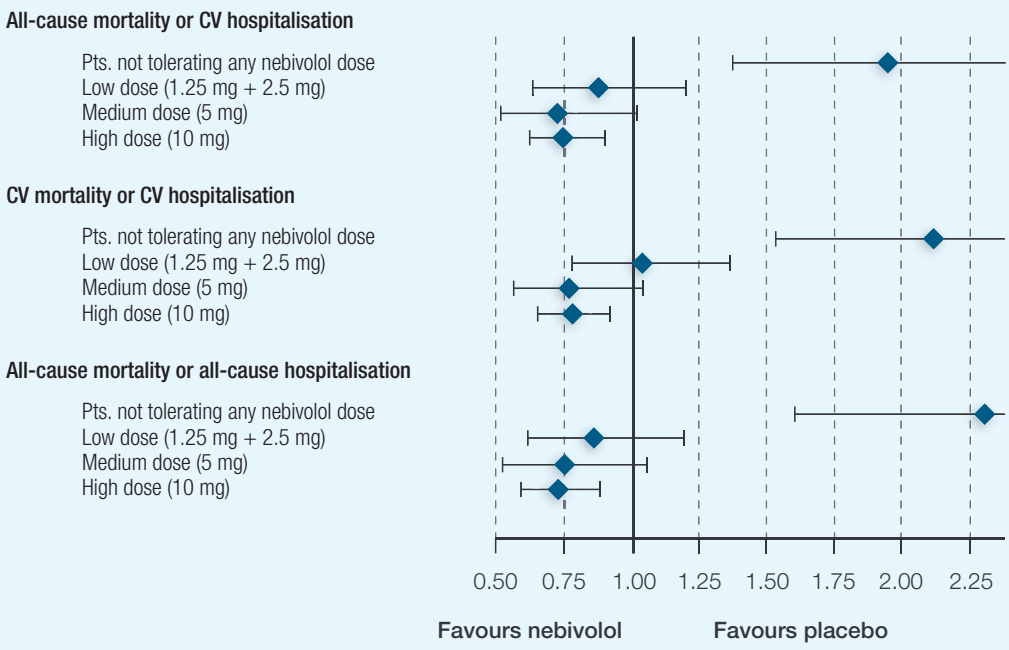

Figure 1.
Interaction between nebivolol and outcome in SENIORS.[5]

Trial	B-blocker	*n*	Mean age
BEST	Bucindolol	2708	60
CIBIS-I	Bisoprolol	641	60
CIBIS-II	Bisoprolol	2647	61
COPERNICUS	Carvedilol	2289	63
MERIT-HF	Metoprolol CR/XL	3991	64
US Carvedilol	Carvedilol	1094	58
COMET	Carvedilol/metoprolol CR	3029	62
Mean			**61**

Table 1.
Age of patients in major beta-blockers trials in heart failure.

than those with systolic dysfunction, especially women (**fig. 2**). Therefore, guidelines for BBs in the treatment of CHF with preserved LVEF are relatively elusive.

While it must be said that BBs do have contra-indications, the reluctance to prescribe them is usually related to a poor knowledge of the benefit/risk ratio of BB in CHF. This deserves to be improved.

Reasons of low BB prescriptions rates in CHF

The reasons why BBs are under-prescribed are multiple.

1. **Age.** Age is a major explanation for the under-use of BBs in CHF. The EuroHeart Failure Survey[6] (**fig. 3**) conducted in European hospitals in 2000-2001, found that prescription rates of BBs was only 37%. The odds ratio of BB treatment was only 0.55 for patients ≥70 (compared to 0.35 for those with respiratory disease). In the BRING-UP study,[7] the main reasons for non-initiation of a BB treatment were age, NYHA functional class, low BP, and bradycardia. In IMPACT-RECO,[8] age (odds ratio 0.54), also coupled with either asthma or chronic obstructive pulmonary disease (COPD) (odds ratio 0.31),

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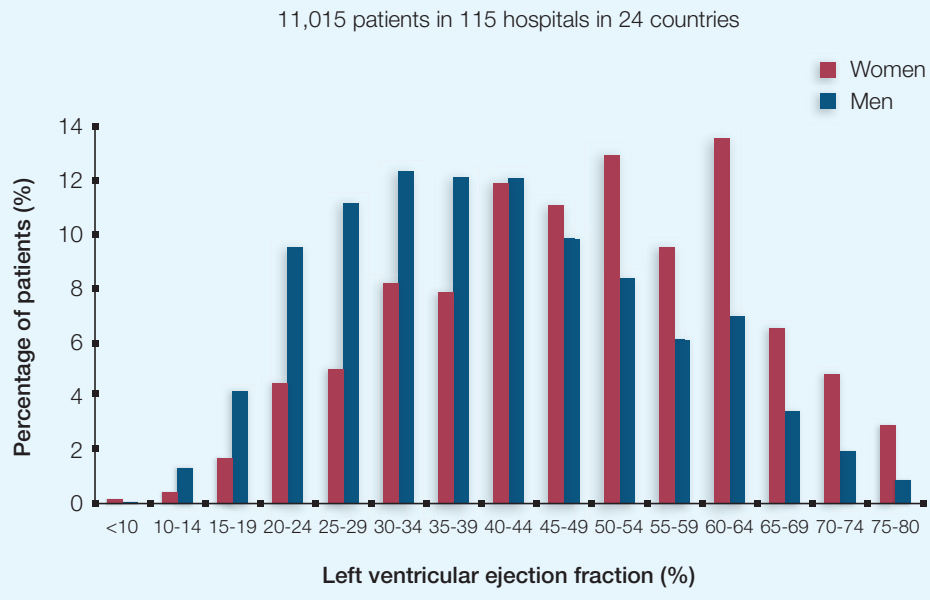

Cleland, et al. Eur Heart J, 2003; 24(5):442-63

Figure 2.
Distribution of ejection fraction by age and sex in EuroHeart Failure Survey.[1]

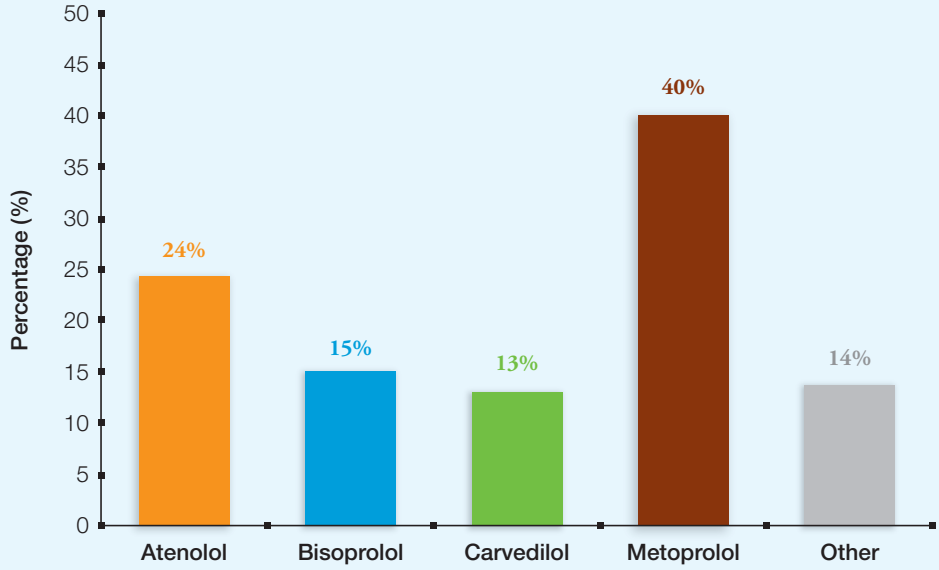

Figure 3.
Use of beta-blockers in the EuroHeart Failure Survey.[6]

Komajda, et al. Eur Heart J 2003; 24(5):464-74

was the most often quoted factor for not prescribing a BB. Elderly patients often have latent sinus node dysfunction, renal dysfunction, orthostatic hypotension and numerous associated comorbidities and treatments. And until SENIORS, all the BB trials were done in young patients.

2. **Heart failure.** HF is no longer a contra-indication to BB when it is stabilised and the treatment initiated at distance from an episode of acute congestive decompensated HF in a patient on a long-term treatment with ACE-I and diuretics. It is however undisputable that it is sometimes difficult to maintain BB treatment with time, especially when the patient has experienced multiple episodes of cardiac decompensation, leading to the reduction or interruption of the treatment. In COMET,[9] only half of the survivors were still on BB after 5 years of follow-up.
3. **Bradycardia.** Bradycardia, generally taken to be a heart rate of <50/min, remains a contra-indication for BB treatment. In the event of it occurring in a patient under BB therapy, an attempt should be made to discontinue other treatments possibly linked to heart rate lowering and which have not been demonstrated to be effective in HF, before stopping BBs. These treatments include digoxin and amiodarone (calcium antagonists with bradycardiac action are in theory contra-indicated in HF). It is now possible to implant a cardiac pacemaker to increase BB dose, especially a triple chamber pace-maker in the event of left bundle branch block and an LVEF <35%. However, while there is a dose/effect relationship of BBs on LVEF, the relation is less obvious on reduction in mortality.[10] In MERIT-HF,[11] patients in whom it was not possible to increase beta-blockade up to the target doses derived the same prognostic benefit from BB than those patients who had reached the target dose. Therefore, it has not yet been clearly demonstrated that patients in whom bradycardia limits titration of BB treatment benefit from a cardiac pacemaker.
4. **Asthma and chronic obstructive pulmonary disease (COPD).** Although asthma remains a contra-indication for beta-blockers, things are different for COPD. COPD is widely perceived as the most common cause of BB intolerability or even contra-indication in HF, due to the common belief that beta-blockade may significantly deteriorate pulmonary function. Therefore, long-term BB therapy is under-used in these patients. However, there is strong evidence that the majority of patients with HF and COPD can safely tolerate low-dose initiation and gradual up-titration of BB and that benefits from beta-blockade by far exceed the potential risks. Mild deterioration in pulmonary function and symptoms should not

be a reason for sudden discontinuation. The association of HF and COPD is frequent, and these patients should in theory derive at least the same benefit from BBs as the others. Meta-analyses[12] have shown that BBs, especially cardio-selective ones, do not worsen the respiratory function of those patients. Other associated properties such as beta-2 stimulation may be another factor of tolerability. In practice, these patients should undergo a test of bronchial reactiveness and BBs should only be contra-indicated if significant bronchial hyper-reactiveness is present.

5. **Sexual side-effects.** The sexual side-effects of BBs, mainly relevant in younger patients, are well known. One first has to differentiate between the sexual limitation related to the disease *per se* (diabetes, severe hypogastric arteries atherosclerosis) and that related to BB treatment (or to combined therapy with diuretics). Recently found solutions lie in the use of PDE5 inhibitors, such as sildenafil, or of specific BBs such as nebivolol. While sildenafil has been used for a long time in the treatment of erectile dysfunction, it has long been contra-indicated in patients with CHF because of the fear of hypotension. However, in CHF-patients without symptomatic hypotension, it is no longer contra-indicated unless HF is related to CAD in patients with angina pectoris and in need of nitrates. Moreover, sildenafil seems to be effective in decreasing pulmonary hypotension in patients with severe HF.[13]
6. **Diabetes mellitus.** Diabetes mellitus has also often been a cause of non-prescription of BB therapy. Diabetes has been found to be associated with HF in 30% of all studies and registries. Beta-blockade reduces insulin sensitivity and tends to increase plasma glucose. Moreover, BBs alter the sympathetic reaction to hypoglycaemia the harmful role of which has been recently emphasised in studies like ACCORD or VADT. However, in a recent meta-analysis, compared with placebo, BB therapy for CHF was beneficial both in patients with diabetes (RR 0.84, p=0.011) and in those without (RR 0.72, p<0.001).[14] Here also, the use of selective BBs especially when combined with other properties such as beta-2 stimulation (celiprolol)[15] or nitric oxide synthase stimulation (nebivolol) which do not cause this detrimental action on glucose metabolism may be a solution.
7. **Renal dysfunction.** Renal dysfunction is also a limitation to various drugs in the treatment of CHF, especially those acting on the renin-angiotensin-aldosterone system (RAAS). Renal dysfunction is also often associated with aging. It should be noted though that patients with advanced renal dysfunction have not been included in clinical trials with BBs in CHF and therefore the safety and the effectiveness of BBs in this category of patients is not known. However, recent data suggest that BBs can be used safely in those patients.

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The value of nebivolol in chronic heart failure management

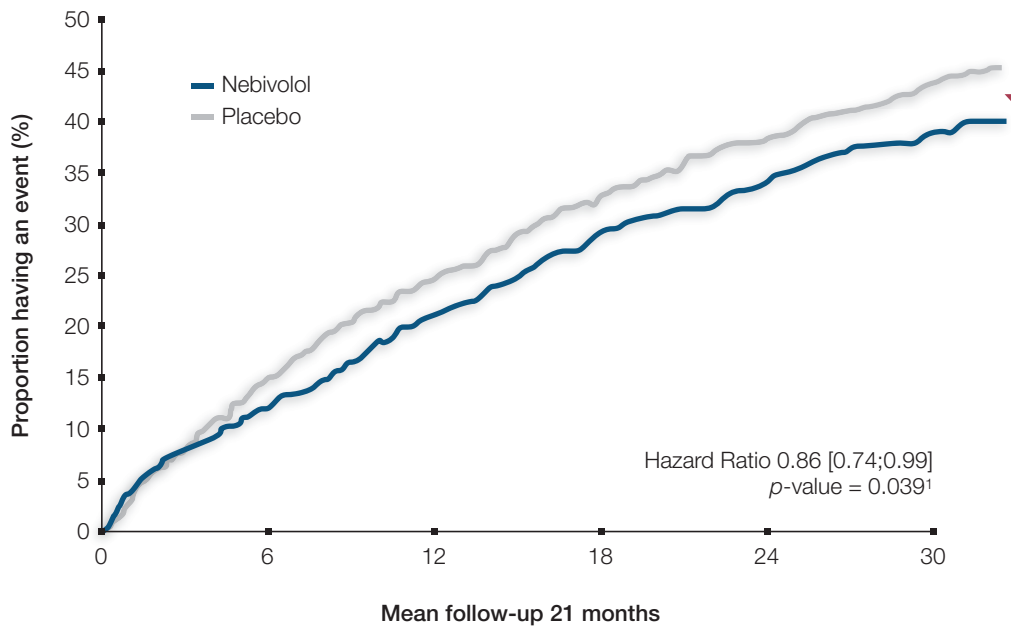
Nebivolol is a BB that has been used for years in the treatment of systemic hypertension in Europe and that has been recently evaluated in CHF,[1,2] especially with the SENIORS trial.[3] Nebivolol has one of the highest beta-1 selectivities, studies having shown a greater affinity for beta-1 receptors than drugs such as atenolol or bisoprolol.[4,5] It also has vasodilatory properties, mainly related to stimulation of NO production by the vascular wall.[6-10] This action is partly due to activation of the beta-3 adrenergic receptors[11] conveying a greater vasodilatory action and a better sexual and bronchial tolerability compared with other BBs. In HF, nebivolol reduces heart rate but less so than bisoprolol, atenolol or carvedilol. However, it increases similarly LVEF and decreases left and right filling pressures more than other beta-blockers.[1,10] Nebivolol therapy has also been shown, like other BBs, to reduce LV remodelling in systolic HF as shown in the SENIORS trial.[12]

Age

Nebivolol provides answers to the issue of BB therapy:

1. in elderly patients with HF (age ≥70 years);
2. in CHF patients with preserved LVEF (≥40%).

In SENIORS,[3] nebivolol was tested against a placebo (optimal standard therapy) in a large international multicenter trial that included patients over 70 years old whatever their baseline LVEF (provided that patients with preserved LVEF had been hospitalised for HF at least once in the previous year). Titration



Number of events: nebivolol 332 (31.1%); placebo 375 (35.3%)

[1] Adjusted by sex, age and baseline LVEF; unadjusted HR = 0.85 [0.74; 0.99] *p*-value = 0.034

Flather, et al. Eur Heart J 2005; 26(3):215-25

Figure 1.
SENIORS primary end-point.[3]

was progressive for 16 weeks with a target dose of 10 mg per day. 2128 patients were included. More than one third of them were women and average LVEF was 36%.

Patients able to reach a dose ≥5 mg/day at the end of the titration phase were 76.4% and 68% of the patients received the target dose of 10 mg/day. 2,135 patients were included. The primary endpoint was a composite one, all-cause mortality or hospitalisation for a cardiovascular reason (**fig. 1**). Nebivolol reduced this risk by 14% (p=0.039) compared to placebo. All-cause mortality was reduced by 12% (p=0.2) but the study was not powered to analyse the effect of mortality. Sudden death was reduced by 35%. There was no interaction between nebivolol effectiveness and age, sex or LVEF.

Safety was remarkable and nebivolol was well tolerated: only 2.2% of the patients had to stop nebivolol for side effects compared to 0.8% in the placebo group. 4.4% of the patients in the nebivolol group developed a contra-indication to BB compared to 2.7% on placebo. In patients with LVEF <35% and age ≤75 years, the primary endpoint was reduced by 27%, (95% CI 0.56-0.96), and total mortality by 38% (95% CI 0.43-0.89). This post-hoc analysis suggests that the reduction in mortality in the less elderly patients with systolic dysfunction – close to those included in the previous trials with BB in CHF - is comparable to that observed previously with carvedilol, metoprolol or bisoprolol.[13-15]

Finally, cost-analysis showed that nebivolol appears to be a cost-effective treatment for elderly patients with HF compared with standard care.[16]

Bradycardia

In SENIORS (**tab. 1**), there was more bradycardia with nebivolol than with placebo, as expected. However, when taking into account the age of the patients in this trial, the incidence was low whatever the dose used with a maximum of 4% with the 10 mg dose.

Renal dysfunction

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Safety of nebivolol for renal function was also evaluated in SENIORS. In patients with altered renal function (defined by an eGFR <60 ml/min), nebivolol was not only well tolerated, but is effectiveness compared to placebo was also maintained.[17]

Heart failure with preserved LVEF

Until recently, there have been few studies in patients with CHF and preserved LVEF. Moreover, the results of these studies have been somewhat disappointing: absence of efficacy of irbesartan in I-PRESERVE,[18] modest or disputable effects of candesartan and perindopril in CHRAM-PRESERVED[19] and PEP-CHF respectively. In SENIORS, there was no interaction between the benefit of nebivolol and LVEF <35%, between 35 and 45% and above 45%.[10]

Sexual problems

Various studies (conducted in patients without HF) have found a good tolerability of nebivolol compared to other BBs or to comparators regarding erectile dysfunction.[20-22] Interestingly, the interaction between sildenafil

Table 1.
Incidence of bradycardia as an adverse event in SENIORS.[3]

	No. of patients	Incidence
Placebo	28	2.6%
Nebivolol 1.25 mg	25	2.3%
Nebivolol 2.5 mg	21	2.0%
Nebivolol 5 mg	26	2.4%
Nebivolol 10 mg	38	3.6%

and NO-donors/organic nitrates does not apply to the NO-liberating properties of nebivolol, suggesting that sildenafil may be used safely in patients treated with nebivolol.[23] In patients with sexual problems appearing under BB therapy, nebivolol may be a good solution.

Diabetes

Nebivolol is better tolerated than other BBs (atenolol) in terms of glucose metabolism with an effect on plasma glucose close to that observed with placebo. Other BBs with ancillary properties such as carvedilol or celiprolol share this advantage. These BBs should thus be first choice for patients with diabetes mellitus. Diabetics who have NO dysfunction may specifically benefit from nebivolol.[24]

COPD

It has been shown that selective beta-1-blockade and combined beta- and alpha-adrenergic blockade do not induce bronchoconstriction in COPD patients. In patients with CHF and COPD with reversible airway obstruction, selective beta-1-blockade remains the preferred approach in the absence of safety data on agents combining non-selective beta- with alpha-adrenergic blockade.[25] Recent data with nebivolol also suggest that nebivolol is well tolerated in COPD patients.[26-27]

In summary, BB therapy represents a major improvement in the management of patients with CHF, an increasingly large population with a stationary outcome grid. The poor implementation in the real world of the scientifc Societies guidelines for BB therapy may largely be explained by doctors' reluctance to use a drug that has previously been contraindicated in this disease in routine practice as well as the fear of poor tolerability, especially in the elderly and when there are associated comorbidities. Moreover, a lot of these patients have preserved LVEF, a situation for which few scientific data are available regarding drug efficacy. Recent studies with nebivolol suggest that this drug is as effective as the other BBs when comparable subpopulations are considered and is better tolerated. Furthermore, its effectiveness has been demonstrated in an elderly population previously unevaluated. Knowledge of these results should allow broader use of beta-blockers – and especially of nebivolol – in elderly patients with HF whatever their LVEF and whatever the associated comorbidities.

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