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## Beta-Blockers for Treatment of Heart Failure in the Elderly

Hendrik Zimmet, Henry Krum

### ABSTRACT

Pharmacotherapy for heart failure focuses on neurohormonal blocking strategies using predominantly angiotensin converting enzyme inhibitors and beta-blockers, both conferring improved outcomes in patients with systolic chronic heart failure. Despite this, there is ongoing underutilisation of beta-blockers in this context in clinical practice. Advanced age is cited as a common reason for non-prescription of beta-blockers. The concerns are usually perceived reduced efficacy and tolerability of the drug class. However, beta-blockers are an efficacious and well-tolerated treatment in most heart failure patients and recent studies suggest that these benefits extend to the elderly patient population. It is critical to ensure that these findings are translated into practice and that all appropriate patients receive these drugs.

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### INTRODUCTION

Chronic heart failure continues to be a major public health problem. Pharmacotherapy focuses on neurohormonal blocking strategies using predominantly angiotensin converting enzyme (ACE) inhibitors and beta-blockers, both conferring improved outcomes in patients with systolic chronic heart failure. Despite this, there is ongoing underutilisation of beta-blockers in this context in clinical practice.<sup>1,2</sup> Advanced age is cited as a common reason for non-prescription of beta-blockers.<sup>3</sup> The concerns are usually perceived reduced efficacy and tolerability of the drug class. However, to date there is little evidence to support such concerns.

### HISTORICAL PERSPECTIVE

Beta-blockers are well established as vital therapy in systolic heart failure unless not tolerated or contraindicated. Historically, this is somewhat of an 'about face'. Beta-blockers had long been contraindicated in the treatment of patients with systolic heart failure. This view prevailed until it was challenged in the late 70s and early 80s by a group of Swedish researchers. These researchers hypothesised that blockade of chronic sympathetic activation in heart failure patients may be beneficial. Thus began the momentum that ultimately resulted in an extensive clinical trials database demonstrating mortality and morbidity benefits with beta-blocker therapy in heart failure patients.<sup>4-7</sup> This database is now more extensive than that for ACE inhibitors.

The strength of the evidence base for beta-blocker treatment in heart failure is reflected in current international heart failure guidelines which mandate beta-blocker therapy, if tolerated, in patients with all degrees of severity of heart failure symptoms provided the patient is clinically stable and euvolaemic.

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### PATHOPHYSIOLOGICAL CONSIDERATIONS

Heart failure is typified by activation of several neurohormonal vasoconstrictor systems including the sympathetic nervous system, renin-angiotensin system, vasopressin and peptide systems such as endothelin and urotensin-II. The activation of these systems is widely regarded as a compensatory response.

The generalised sympathetic activation seen in heart failure is an important compensatory response in the short-term, however, in the long-term, it appears to be detrimental. Evidence from both mechanistic and clinical outcome studies supports this. Mechanistically, long-term catecholamine excess appears to have direct myocardial toxicity and a number of other adverse effects.<sup>8-11</sup> In terms of clinical outcome, patients with disorders involving chronic catecholamine excess, such as pheochromocytoma, develop myocardial disease phenotypically indistinguishable from dilated cardiomyopathy.<sup>12</sup> Furthermore, drugs which augment the effects of catecholamines on the myocardium, such as beta-agonists (excluding inhaled preparations) are associated with adverse survival outcomes.<sup>13</sup> Additionally, several studies have demonstrated a close correlation between measures of sympathetic activation with markers of disease severity and subsequent mortality.<sup>14,15</sup>

The rationale for adrenergic blockade as a therapy for heart failure is based on this preceding mechanistic and clinical observation data.

### BETA-BLOCKER PHARMACOLOGY

Stimulation of beta-adrenoceptors, on the cardiac myocyte, causes activation of cell membrane regulatory G proteins which increase intracellular cyclic adenosine monophosphate levels via adenylate cyclase stimulation.<sup>10</sup> Increased intracellular cyclic adenosine monophosphate activates downstream protein kinases which in turn phosphorylate calcium channels resulting in influx of intracellular calcium. This influx enhances coupling of actin and myosin filaments ultimately producing cardiac muscle inotropy.

Beta-blockers act by antagonising the beta-adrenoceptor, inhibiting the abovementioned cascade of intracellular events and thus have a negative inotropic effect. The pharmacological properties of beta-blockers vary both from a pharmacokinetic and pharmacodynamic point of view (Table 1). Carvedilol possesses several ancillary properties namely anti-oxidant, anti-proliferative and anti-endothelin activity. Metoprolol is available in both an immediate-release and extended-release formulation, allowing once-daily dosing. Nebivolol's vasodilator properties are mediated via nitric oxide donation. Finally, intrinsic sympathomimetic activity is associated with adverse outcomes.<sup>13</sup>

### BETA-BLOCKER EFFICACY

In early studies, short term use of beta-blockers, for the treatment of heart failure, was found to result in neutral or adverse clinical outcomes.<sup>16,17</sup> Subsequently, it was established that studies of at least three months duration were required to

**Table 1. Pharmacological properties of beta-blockers studied in heart failure**

Beta-blockers	Selectivity as beta-antagonist	Direct vasodilator activity	Activity as alpha-antagonist	ISA	Ancillary properties	Plasma half-life (hours)	Elimination
Bisoprolol	$\beta_1 \gg \beta_2$	-	-	-	-	10-12	hepatic and renal
Bucindolol	$\beta_1 = \beta_2$	+	-	-	-	3-4	hepatic
Carvedilol	$\beta_1 = \beta_2$	+	+	-	++	6-10	hepatic
Metoprolol	$\beta_1 \gg \beta_2$	-	-	-	-	3-5	hepatic
Nebivolol	$\beta_1 \gg \beta_2$	+	-	-	+	27-100	hepatic and renal
Propranolol	$\beta_1 = \beta_2$	-	-	-	-	3-6	hepatic
Xamoterol	$\beta_1 \gg \beta_2$	-	-	++	-	16-27	hepatic

ISA = intrinsic sympathomimetic activity

demonstrate consistent clinical benefit. Additionally, it was observed that beta-blocker therapy, in the context of heart failure, needed to be commenced at extremely low doses to avoid sudden interference with inotropic support.

Later, long-term, double blind, placebo controlled studies of beta-blocker use in chronic heart failure revealed consistent improvements in ejection fraction and patient wellbeing but variable effects on exercise tolerance.<sup>18-21</sup> These were generally single-centre studies.

Multicentre studies have achieved more widespread evaluation of beta-blocker treatment in heart failure. Improvements in left ventricular function were found to be dose-dependent.<sup>4</sup> Retardation of progression of disease was noted.<sup>22</sup> Beneficial effects on mortality and hospitalisation were demonstrated.<sup>4,7</sup> The advantage was seen to be similar in patients across the spectrum of severity of heart failure, whether of idiopathic, dilated or ischaemic aetiology.<sup>4</sup> A number of studies were terminated early by their respective data safety monitoring boards due to significant decreases in mortality, of magnitudes of around 35%, in the beta-blocker study arms.<sup>6,7</sup>

Analyses examining subgroups according to race, gender, age and presence of diabetes have generally noted similar mortality benefits with beta-blocker use in heart failure.<sup>23-26</sup>

### BETA-BLOCKER TOLERABILITY

Generic markers of drug tolerability include adverse event profile, permanent treatment discontinuation rates, mean achieved dose in relation to target dose and proportion of patients reaching target dose. Open-label experience of heart failure treatment with beta-blockers has shown tolerability (defined as per cent of patients remaining on therapy at the time of evaluation, and having been on therapy for at least three months) between 69 to 95%.<sup>27</sup> While uncontrolled, these data are still important as they reflect everyday clinical practice as distinct from the often highly selected patients involved in clinical trials.

Tolerability, in the initial phase of beta-blocker introduction, has also been examined in the more rigorous clinical trial setting. In Metoprolol-CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), there was a minor excess of discontinuations with beta-blocker compared with placebo, over the first three months of therapy, particularly in patients with New York Heart Association (NYHA) Class III-IV chronic heart failure.<sup>28</sup> However, in Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), a more advanced group of heart failure patients overall, there was no excess of early permanent withdrawals with beta-blocker treatment.<sup>29</sup> This study also challenged the paradigm that there was a delay in benefit of therapy in advanced heart failure patients by showing reduced mortality, in the beta-blocker arm, during the first eight weeks of treatment.

The Carvedilol Open Label Assessment (COLA) I study sought to identify baseline predictors of tolerability to carvedilol in patients with chronic heart failure.<sup>30</sup> Low systolic blood pressure, high plasma urea and advanced age were found to be independent predictors of tolerability. Thus patients with borderline hypotension, renal impairment or the extreme elderly require close supervision during initiation of therapy.

### BETA-BLOCKER USE IN THE ELDERLY

High rates of disease in older people encourage high use of medications in this group. Polypharmacy, defined as the use of five or more medications, occurs in 20 to 40% of the elderly.<sup>31-33</sup> The consequences of this may be detrimental and associated with adverse outcomes. Notably, polypharmacy is considered to be the most important factor consistently associated with adverse drug reactions.<sup>34</sup>

A number of studies have also documented that increase in adverse drug reactions correlates with age.<sup>35-39</sup> In a survey of 1268 patients admitted to a general hospital, it was found that the rate of adverse reactions was more than tripled in the elderly.<sup>35</sup> On the contrary, other research groups have found this correlation of adverse drug reactions with age, not to be the case once additional factors, such as number of drugs and renal impairment, were controlled for.<sup>40</sup>

Adverse drug reactions in the elderly are often more severe and less likely to be recognised or reported by the patient.<sup>34,40-42</sup> Furthermore, they are costly and estimated to be the fourth to sixth greatest cause of death in this patient group. In terms of morbidity, 5 to 10% of hospital admissions of elderly patient are linked to drug-related toxicity.<sup>42-46</sup> This figure appears to be even higher in Australian studies with 15 to 20% of elderly unplanned hospital admissions being drug-related.<sup>47,48</sup>

Ironically, despite elderly patients receiving the most medications, they may not derive the greatest benefit. This is partly related to the prescribing of medications to the elderly on the basis of extrapolation of findings from clinical trials performed in younger age groups.<sup>49</sup> Alternatively, the elderly may be denied useful pharmacotherapy because of ageist attitudes and concerns about adverse drug reactions that may not have any strong evidence base.

The elderly are insufficiently represented in clinical trials with near 35% of published trials excluding patients on the basis of age despite no justification.<sup>50</sup> According to Nair et al. in 2000, less than 4% of 8945 randomised controlled trials and 1.2% of 706 meta-analyses were for patients over 65 years old.<sup>51</sup> Clearly, this situation must be addressed, in order for treatments in the elderly to be founded on a solid evidence base.

There are some specific age-related changes in beta-blocker pharmacodynamics in the elderly. Beta<sub>1</sub>-adrenoceptors are down-regulated, plasma noradrenaline levels elevated and

the cyclic adenosine monophosphate response to beta-adrenergic stimulation reduced.<sup>52,53</sup> Additionally, the cardiovascular response to beta-agonists is reduced. The dose of isoprenaline needed to increase heart rate by 25 beats/min is substantially higher in older people.<sup>54</sup> Furthermore, the systolic contractile response of ventricular muscle to isoprenaline is diminished by 46%.<sup>55</sup> Even with this knowledge, the association between age and heart failure-related changes in the beta-adrenergic system and the clinical effects of beta-blockers in the elderly with heart failure, is not well understood.<sup>56</sup>

Interestingly, despite the abovementioned physiological observations in the elderly, there is minimal decrease in efficacy or tolerability of beta-blockers in this age group. From a practical point of view, dosing of beta-blockers in the elderly should be individualised with careful dose titration. The phrase 'start low and go slow' applies well here.

### Meta-Analysis

Despite the overwhelming data supporting the benefits of beta-blocker treatment in heart failure patients, no study published up until 2005 had directly investigated the effect of beta-blocker therapy in the elderly versus the non-elderly. Dulin et al. have published a meta-analysis of all-cause mortality data involving elderly and non-elderly chronic heart failure patients from five completed beta-blocker trials.<sup>25</sup> The trials were all published, randomised, double blind, placebo controlled and included over 1000 patients using beta-blockers for heart failure—Beta Blocker Evaluation of Survival Trial (BEST), Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), COPERNICUS and MERIT-HF.<sup>4,7,57</sup>

The meta-analysis involved a total of 12 729 patients with chronic heart failure of which 4617 (36.3%) were classified as 'elderly'. The results showed that elderly patients had reduced survival compared with non-elderly patients. However, a significant survival benefit was seen in elderly and non-elderly patients receiving beta-blockers. Importantly, there was no statistically significant difference in the relative risk reduction in mortality between the elderly and non-elderly (Figure 1).

It should be noted that meta-analyses are hypothesis generating and therefore not definitive in their conclusions. Additionally, this meta-analysis was limited by heterogeneity between the various trials in terms of their widely varying age range definitions of the 'elderly'.

### SENIORS

The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors (SENIORS) investigated the efficacy of the beta<sub>1</sub>-selective vasodilator nebivolol in 2128 patients over 70 years of age with systolic and diastolic heart failure.<sup>58</sup> The study showed that nebivolol treatment was associated with a significant reduction in the primary endpoint of death and cardiovascular hospitalisation with a hazard ratio (HR) of 0.86. This finding though significant was less impressive than the HR of 0.70 to 0.75 seen in the majority of large beta-blocker trials investigating relatively younger heart failure patients. Notably, in the pre-defined subgroup of patients aged above the median study value of 75.2 years, the effect of nebivolol on the primary outcome was not statistically significant. However, SENIORS was not powered to detect a difference with regard to such pre-defined subgroup analyses.

### COLA II Study

The COLA II study demonstrated for the first time, the tolerability of beta-blockers in an elderly systolic heart failure cohort in everyday clinical practice.<sup>59</sup> It was a prospective, multinational, six-month, observational study of the tolerability of carvedilol introduction in 1030 heart failure patients, evaluated according to age (70-75, over 76-80, over 80 years). Tolerability was defined as being on carvedilol 6.25 mg or greater twice daily at six months having received a total of three months or more of therapy.

All age groups demonstrated significant reductions in heart rate and NHYA class and an increase in left ventricular ejection fraction. Tolerability overall was 80%, with 84.3% for 70-75 years, 76.8% for 76-80 years, and 76.8% for over 80 years. In multivariate analysis, predictors of poor tolerability were:

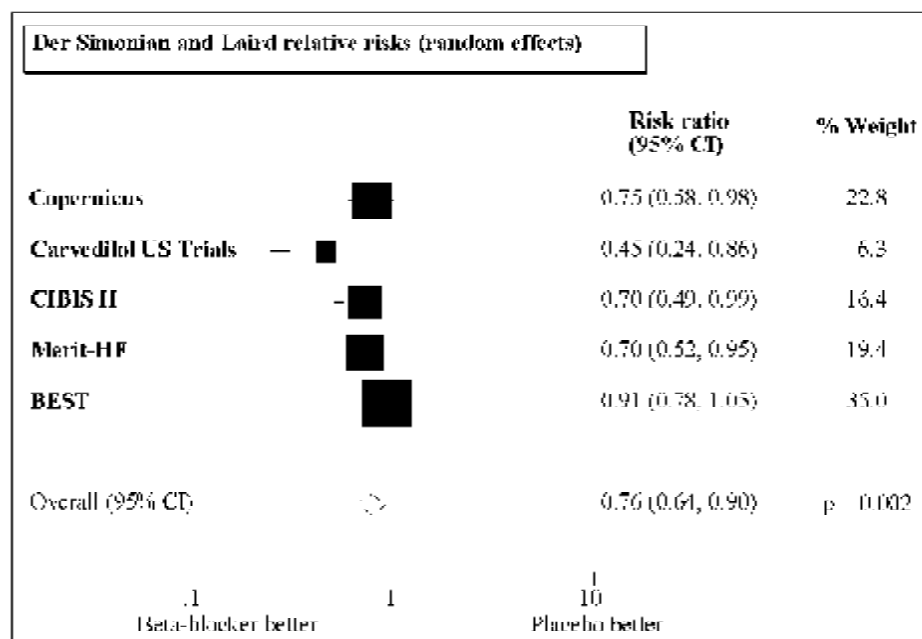


Figure 1. Der Simonian and Laird relative risks (random effects) plot of beta-blocker versus placebo for elderly patients with congestive heart failure<sup>25</sup>

Point estimates and 95% CIs represented next to box plot. BEST = Beta-Blocker Evaluation Survival Trial; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.

advanced age, low diastolic blood pressure, obstructive airways disease and low left ventricular ejection fraction.

Generally, this study showed there was little decrease in tolerability even in the extreme elderly (over 80 years). The pharmacodynamic and functional effects of carvedilol appeared to be preserved within the elderly systolic heart failure group. An achieved dose of carvedilol 29 to 33 mg per day demonstrated that therapeutic doses of carvedilol could be achieved in elderly heart failure patients. Interestingly, it was found that low-dose carvedilol was associated with the poorest tolerability and greatest mortality, indicating that patients who were only able to tolerate lower doses comprised a sicker group. This was consistent with findings in previous studies.<sup>60,61</sup> Despite being well designed the COLA II study did have some limitations. It was an observational study, there was no comparator group and no data were collected on excluded patients.

Overall, the COLA II study showed that physicians, outside of major teaching hospitals and clinical trials settings, were able to successfully commence and maintain carvedilol therapy at clinically efficacious doses, in four out of five elderly heart failure patients thought appropriate for this therapy. Furthermore, elderly patients with co-morbid conditions in which beta-blockers may be considered relatively contraindicated also appeared to tolerate carvedilol well.

In contrast to the COLA II study, a study by Baxter et al. showed poorer tolerability with the rate of withdrawal from bisoprolol being twice as high in elderly compared to younger heart failure patients.<sup>62</sup> However, this study was substantially less robust than the COLA II study as it was retrospective and compromised of only 51 patients compared to the 1030 patients in the COLA II study.

#### PRACTICAL ISSUES IN THE ELDERLY

Use of beta-blockers that possess a vasodilator activity seems to be better tolerated during initiation.<sup>63</sup> This may be due to the vasodilatory effects helping overcome the initial negative inotropic effect of beta-blockers. Generally, commencement of beta-blocker therapy for heart failure should start at very low doses and then be up-titrated on a fortnightly basis. Postural hypotension, if it occurs, can often be effectively managed with temporary reduction of concomitant ACE inhibitor or diuretic dosage. In the authors' experience, separating the beta-blocker and ACE inhibitor dosage time by three hours or more is also frequently helpful.

In some instances, worsening of heart failure may occur at the time of initiation of beta-blocker therapy. Increasing the patient's diuretic dose usually provides stabilisation in this setting. Delay of the next scheduled up-titration of the beta-blocker may also be required. Despite outpatient commencement of beta-blocker therapy for heart failure having been shown to be efficacious and feasible, inpatient commencement, after the patient is clinically stabilised, is also safe and leads to lower withdrawal rates.<sup>64</sup>

It is worthwhile to note that patients who experience difficulties during up-titration are eventually conferred long-term clinical benefits similar to those seen in patients who had no problems during beta-blocker initiation.<sup>65</sup>

Unfortunately, polypharmacy is common in elderly heart failure patients and in some instances very difficult to avoid. Nevertheless, the benefits of multiple heart failure drugs, including beta-blockers, likely outweigh the risks. In any case, such patients should have their entire medication list regularly reviewed by their pharmacist and general practitioner.

#### UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

It remains to be seen whether elderly patients with asymptomatic left ventricular dysfunction respond to beta-blockers similarly to symptomatic patients. Formal prospective trial data is needed in this respect.

Elderly heart failure patients with preserved left ventricular dysfunction (diastolic heart failure) are another group with a paucity of large-scale prospective clinical trial data with regard to the efficacy of beta-blocker therapy. Mechanistically, one would expect beta-blockers to significantly benefit diastolic heart failure patients. SENIORS demonstrated a trend towards reduced mortality and morbidity in elderly heart failure patients with left ventricular ejection fractions both above and below 35%.<sup>58</sup>

Another key question is the order in which life-saving heart failure drugs should be prescribed. Conventionally, ACE inhibitors have been initiated before beta-blockers. This has been the result of ACE inhibitors historically being proven to be a beneficial first even though mechanistically beta-blockers may seem preferred. CIBIS-III showed that it may be as safe and as efficacious to initiate heart failure treatment with a beta-blocker, as with an ACE inhibitor, particularly in patients over 72 years of age.<sup>66</sup>

Finally, the role of pharmacogenomics in patient selection for beta-blocker therapy is likely to emerge in the not too distant future. Equally, the interface of beta-blocker treatment in the elderly, with novel heart failure device and cell-based therapies, is yet to be defined.

#### CONCLUSION

Major advances in our understanding of the pathophysiology of heart failure and the role of beta-blocker therapy have resulted in a sea change of long-held views. Beta-blockers are a pivotal, efficacious and well-tolerated treatment in most heart failure patients. Recent studies suggest that these benefits extend to the elderly patient population. Our greatest challenge now is to ensure that these findings are translated into practice and that all appropriate patients receive these drugs.

**Competing interests:** Professor Henry Krum has served on beta-blocker advisory boards for Roche, GSK, Astra-Zeneca and Alphapharm.

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