

# Carvedilol in the treatment of elderly patients with chronic heart failure

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**Abstract:** Chronic heart failure (CHF) is common, and increases in incidence and prevalence with age. There are compelling data demonstrating reduced mortality and hospitalizations with adrenergic blockade in older patients with CHF. Despite this, many older patients remain under-treated. The aim of the present article is to review the potential mechanisms of the benefits of adrenergic blockade in CHF and the clinical data available from the large randomized studies, focusing particularly on older patients.

**Keywords:** beta-blockers, chronic heart failure

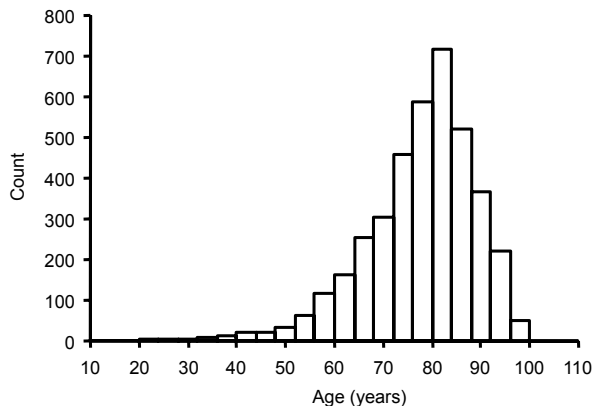
## Introduction

Chronic heart failure (CHF) is common. It affects 2% of people between 50 and 60 years of age (Dargie et al 1992), yet the prevalence increases to approximately 10% of those over 80 years (Cowie et al 1997). The incidence of CHF is rising (Bonneux et al 1994; Brown and Cleland 1998) at the same rate in men as women, although men present at an earlier age (Cowie et al 1999). CHF has a high mortality (30% at one year, and 60%–70% after 5 years), [2] and is one of the leading causes of death in industrialized countries (Braunwald 1997). Patients with CHF also have a high morbidity. Of all UK medical hospital admissions, 5% (120,000 per year (Sutton 1990; McMurray and Dargie 1992)) are due to heart failure, making it the single most common reason for medical admission (Brown and Cleland 1998) and costing around £360 million per year (McMurray et al 1993a). New medical and device treatments have had benefits on symptoms and prognosis (Cleland, Swedberg et al 1998), but high readmission rates (20% of patients needing two or more admissions per year (McMurray et al 1993b) for heart failure and other reasons, including chest pain, arrhythmias and stroke (Brown and Cleland 1998; Cleland et al 2001; Khand et al 2001), and reduced quality of life (Stewart et al 1989) remain features of CHF.

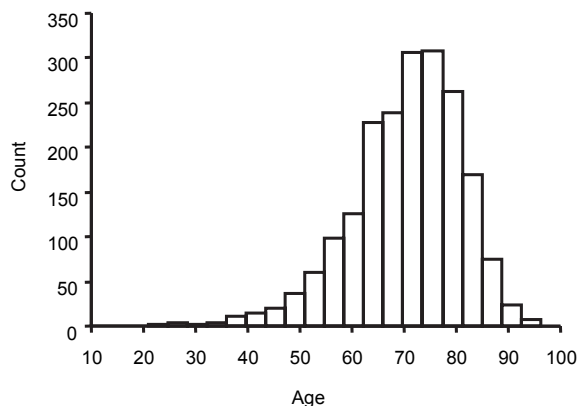
Figure 1a shows the distribution of age in a large community based heart failure clinic in the North of England. Most patients with chronic heart failure are over 70 years of age. Similarly, patients admitted with decompensated heart failure are also most likely to be aged between 70 and 79 years (Figure 1b) (Niemenen et al 2006). Mortality and morbidity in chronic heart failure are directly related to age (Cleland, Massie et al 1999; Dulin et al 2005) with older patients less likely to survive an admission with heart failure than younger individuals (Cleland, Massie, et al 1999), and much more likely to be readmitted in the subsequent 6 months, requiring more bed days (Cleland and Clark 1999). Few randomized studies have examined the effects of treatment specifically in older (>65 years) patients. The mean age of the populations in almost all randomized studies of patients with chronic heart failure is around 60 years (Table 1). However, in those trials with published sub-studies, or where the outcomes have been examined by age group, the relative reduction in mortality in older patients is generally similar to that seen in younger subjects, and as a consequence of their

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- (a) N = 3924  
 Mean (SD) 77.1 (11.2)  
 Median (IQR) 79.0 (71.0–84.5)



- (b) N = 2002  
 Mean (SD) 70.4 (10.6)  
 Median (IQR) 71.8 (64.4–77.9)



**Figure 1** (a) Age distribution of 3924 consecutive patients admitted to hospital as an emergency with a diagnosis of heart failure between 2003 and 2005. (b) Age distribution of 2002 consecutive patients being followed up for a diagnosis of heart failure due to left ventricular systolic dysfunction in a community heart failure clinic.

poorer absolute outcome, the number needed to treat to extend life or prevent hospital admission is much lower in older patients.

Despite these facts, elderly patients with chronic heart failure are frequently under-treated with disease-modifying drugs (Komadja et al 2003). They are less likely to be prescribed an angiotensin converting enzyme inhibitor or a  $\beta$ -blocker (Sin and McAlister 2002; Maggioni et al 2003), and have up-titration of these agents to the recommended doses less frequently (Komadja et al 2003). The aim of the present article is to review the data for disease modifying drugs in elderly patients with

CHF focusing on the effects and mechanisms of action of the adrenoceptor antagonists, specifically carvedilol.

## Non-adrenergic blockade therapy for chronic heart failure

### Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors block the degradation of bradykinin and the formation of angiotensin II, the product of the heightened renin-angiotensin system activity due to heart failure and the diuretics used to treat it. This blockade results in venous and arterial dilatation, a fall in arterial pressure and an increase in renal blood flow. ACE inhibitors improve symptoms and retard the progression of ventricular dysfunction and consequently worsening of symptoms (The SOLVD Investigators 1991; Yusuf, Nicklas et al 1992; Yusuf et al 2000; Jong et al 2003) Treatment of patients with asymptomatic left ventricular dysfunction, either chronic (Yusuf, Nicklas et al 1992) or occurring soon after a myocardial infarction (Pfeffer et al 1992; Ball et al 1993; Flather et al 2000), delays the development of heart failure and reduces mortality (The CONSENSUS Trial Study Group 1987; Cohn et al 1991; Cleland, Freemantle et al 1999), reduces total hospitalizations (Yusuf, Pepine et al 1992; Garg and Yusuf 1995; Packer et al 1999; Torp-Pedersen and Kober 1999), days in hospital (The Solvd investigators 1991; Jong et al 2003), and increases average life expectancy by 6–36 months (The SOLVD investigators 1991; Swedberg et al 1999; Cleland et al 2001). Higher doses appear more effective in reducing morbidity (The NETWORK Investigators 1998; Packer et al 1999).

Overall there seems to be no difference in benefit between older and younger patients in any of the outcomes from ACEi in patients with systolic dysfunction (Garg and Yusuf 1995). The first trial into the effect of ACE inhibitors enrolled 253 patients with a mean age of 70 years (range 36–91). Enalapril 2.5–40 mg per day lead to a 40% reduction in mortality due to progressive heart failure over placebo. The only other ACE inhibitor trial performed in older (>70 years) patients examined outcomes in patients with chronic heart failure with preserved left ventricular systolic function revealing reductions in hospitalisations and improvements in symptoms, along with a trend to reduced total mortality after one year (Cleland, Tendera, et al 2006).

### Aldosterone antagonists

Aldosterone, increased in CHF due to renin-angiotensin system activation and impaired liver function, leads to

Table 1

Study (year)	Setting	Agent	Subject number (active/placebo)	Mean age (range/SD)	Follow-up	Mortality % (BB v placebo) (p-value)(risk reduction%)	Hospitalization % (BB v placebo) (p-value)	Combined death and hospitalization % (or other outcome)
Effect of carvedilol on morbidity and mortality in patients with chronic heart failure (1996)	Moderate chronic heart failure	Carvedilol	696/398	58 (12)	7 months	3 v 8 (p < 0.001) (-65)	14 v 20 (p = 0.038)	16 v 25 (p < 0.0001)
Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure (1996)	Mild chronic heart failure	Carvedilol	232/134	54 (12)	12 months	1 v 4 (p < 0.05)	Not published	Not published
Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure (PRECISE)(1996)	Severe heart failure	Carvedilol	133/145	60 (12)	6 months	Not examined	Not published	Significant improvement in NYHA, symptoms, and walk test
Safety and efficacy of carvedilol in severe heart failure (1997)	Severe heart failure	Carvedilol	70/35	60 (20)	6 months	3 v 6 (p = ns)	Not published	Improvement in symptoms and quality of life in BB treated patients
Cardiac Insufficiency Bisoprolol Study (CIBIS II) (1999)	Chronic heart failure	Bisoprolol	1327/1320	61 (22-80)	1.3 years	12 v 17 (p < 0.0001) (-32)	33 v 39 (p < 0.0001)	29 v 35 (p < 0.001)
Metoprolol randomized intervention trial in congestive heart failure (MERIT-HF) (1999)	Chronic heart failure	Metoprolol (CR/XL)	2001/1990	64 (10)	1 year	2 v 11 (p < 0.0001) (-35)	29 v 33 (ns)	32 v 38 (p < 0.01)
Bucindolol evaluation of survival trial (BEST)(2001)	Chronic heart failure	Bucindolol	1354/1354	60 (12)	2 years	30 v 33 (p = 0.13) (-10)	61 v 65 (0.08)	Not published
Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction (CAPRICORN) (2001)	Post-infarct heart failure	Carvedilol	975/984	63 (29-88)	1.3 years	12 v 15 (p < 0.05) (-33)	Not published	35 v 37 (p = ns)
Carvedilol prospective randomised cumulative survival study (COPERNICUS)(2002)	Severe heart failure	Carvedilol	1156/1133	63 (12)	10.4 months	11 v 19 (p < 0.0001) (-35)	Not published	37 v 45 (p < 0.001)
Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure (COMET)(2003)	Chronic heart failure	Metoprolol v Carvedilol	1518 (M) v 1511 (C)	62 (11)	58 months	40 (M) v 34 (C) (p = 0.0017)	Not published	74 v 76 (p = ns)

potassium wasting and stimulates myocardial and vascular collagen synthesis. ACE inhibitors do not block all aldosterone production; other enzymes, such as chymase, convert angiotensin I to angiotensin II with resultant aldosterone production – known as aldosterone ‘escape’ (Pitt 1995). Adding aldosterone antagonists to ACE inhibitors reduces noradrenaline levels, collagen turnover and ventricular arrhythmias on Holter monitoring and increases heart rate variability (Barr et al 1995; MacFadyen et al 1997). In the post-infarction setting (Pitt et al 2003), aldosterone antagonists reduce hospital admissions with heart failure and mortality, predominantly sudden death, indicating that they may have a role for the management of asymptomatic patients. Aldosterone antagonists seem most effective when added on top of ACE inhibitors and beta-blockers (Pitt et al 1999, 2003). There are no data to indicate whether benefits are dose related but higher doses are more likely to provoke dangerous hyperkalemia (The RALES Investigators 1996). Elderly patients seem to benefit from aldosterone antagonists to the same extent as younger patients (Pitt et al 1999, 2003, 2005).

### Digoxin

Digoxin has modest inotropic and diuretic properties, modulates neuro-endocrine function and slows heart rate and atrio-ventricular conduction (Gheorghiadu et al 1995; Krum et al 1995; Slatton et al 1997). In patients in sinus rhythm, digoxin appears to improve symptoms (Packer et al 1993) but has no overall effect on mortality when added to an ACE inhibitor (The Digitalis Investigation Group 1997). There are no randomized data exploring differential effects of digoxin in elderly subgroups.

### Angiotensin receptor blockers (ARBs)

These agents block the effects of angiotensin II and can be used as an alternative or in addition to ACE inhibitors. They are likely to be as effective as ACE inhibitors (Granger et al 2003). For patients who cannot tolerate ACE inhibitors, for example due to cough or angio-neurotic edema, ARBs may be used as an alternative (Maggioni et al 2002; Granger et al 2003). Adding an ARB to the combination of ACE inhibitors and  $\beta$ -blockers reduces morbidity and mortality in CHF (McMurray et al 2003) despite one study suggesting adverse effects (Cohn et al 2001). In post-infarct patients with clinical evidence of heart failure, either an ACEi or an ARB can be used, but the combination of both increases side effects and offers no additional reduction in mortality (Pfeffer et al 2003).

The CHARM program was a randomized study comparing the ARB, candesartan, with placebo in three different sub-studies. It enrolled more than 700 over the age of 80 (Granger et al 2003; McMurray et al 2003). The mean daily dose of candesartan was lower in the elderly, but overall the relative reduction in mortality was the same as in younger patients. However, since older patients had more events, the number needed to treat to “save” a life was lower in the elderly cohort. Older patients had more hypotension and renal dysfunction than younger patients, but the difference in these side effects between the placebo and active therapy groups was not different across age groups.

### Adrenergic activity in chronic heart failure

In health, the major autonomic influence on the heart at rest is the parasympathetic. The circulation is under the control of resting sympathetic tone resulting from continuous outflow from the vasomotor centre in the brain stem. Major inputs to the vasomotor centre come from the carotid and aortic baroreceptors, central cardiopulmonary receptors, chemoreceptors and muscle derived receptors (metabo- or ergo- receptors), stimulation of which results in sympathetic activation. In response to an increase in blood pressure detected by the baroreceptors, the vasomotor centre reduces constrictor tone and increases parasympathetic outflow. Central cardiopulmonary receptors have a similar effect. When stimulated by stretch, they cause a decrease in sympathetic and increase in parasympathetic outflow (Mohanty et al 1987; Grassi et al 1988). The ergoreceptors are sensitive to work performed by exercising skeletal muscle (Iaria et al 1959; Rowell and O’Leary 1990), and lead to a withdrawal of parasympathetic tone (Rowell and O’Leary 1990) as well as an enhancement of adrenergic activity (Rowell and O’Leary 1990; Iellamo et al 1999).

The heart failure syndrome is associated with adrenergic overactivity (Leimbach et al 1986; Davis et al 1987), which is linked to an adverse prognosis (Cohn et al 1984; Rector et al 1987; Kaye et al 1995). The traditional explanation for adrenergic activation in heart failure centers on the baroreflexes. The generally adopted concept is that reduced cardiac contractility leads to lower blood pressure, and a withdrawal of baroreflex activity, resulting in a reduction in the inhibitory input to adrenergic control (Mancia et al 1990, 1992). The consequent adrenergic activation is the body’s attempt to maintain blood pressure by causing vasoconstriction (Harris 1987). However, the increased peripheral resistance feeds back as an increase in left ventricular afterload, further depressing cardiac function. Blood pressure does not rise

in response to the vasoconstriction in heart failure, and so further adrenergic activation occurs as a consequence of withdrawal of the normal baroreflex inhibition of sympathetic activity. These changes are seen at an early stage in the development of heart failure (Grassi et al 1995a).

In fact, the baroreflexes are blunted in heart failure (Ferguson et al 1984; Ellenbogen et al 1989; Marin-Neto et al 1991; Grassi et al 1995b), and it seems likely that the baroreflexes, rather than being the cause of adrenergic activation, are down-regulated as a consequence of chronic sympathetic overactivity caused by something else.

Enhanced ergoreflex activity may lie with the abnormal skeletal muscle seen in heart failure patients. Muscle bulk (Mancini et al 1992), strength (Buller et al 1991) and endurance (Minotti et al 1992) are reduced; histology is abnormal (Lipkin et al 1988; Mancini et al 1989), as is the biochemical content of skeletal myocytes (Sullivan et al 1990). Experiments in normal subjects suggest that induced changes in muscle metabolism may cause ergoreflex activation (Clark et al 1995). These findings form the basis of the "muscle hypothesis" (Clark et al 1996) which suggests that many of the pathophysiological abnormalities of heart failure result from abnormal skeletal muscle with consequent ergoreflex and adrenergic activation.

## Adrenergic antagonists

### Mechanisms of benefit

The sympathetic nervous system activation in heart failure contributes to vasoconstriction, accelerates adverse remodeling, provokes arrhythmias, may be directly toxic to cardiac myocytes and can stimulate renin-angiotensin system activation and hypokalemia (Cleland et al 1996). These effects are mediated by beta-1, beta-2 and alpha-1 receptors. Agents that block the beta-1 receptor can reduce the effects of sympathetic activation, although agents that block a greater array of receptors may be even more effective (Poole-Wilson et al 2002; Poole-Wilson, Swedberg et al 2003).

### Adverse remodeling

Chronic adrenergic stimulation leads to calcium loading of the cardiomyocytes and thereby to impaired contractility, and cell death (Wynne et al 1996). Not only does adrenergic antagonism prevent further deterioration in left ventricular dysfunction, but over several months can lead to reduction in left ventricular volume and increase in ejection fraction (Hall et al 1995; Bristow et al 1996). This effect is likely to underlie some of the benefit of  $\beta$ -blockers on hospitalization and death due to heart failure and is probably due to a combination of

increased myocardial perfusion (perhaps due to bradycardia (Thackray et al 2006)) and reduced afterload.

### Prevention of cardiomyocytes apoptosis

Chronic sympathetic activation causes cardiomyocyte apoptosis (Communal et al 2003; Goldspink et al 2003) which leads to ongoing contractile loss and fibrosis (Dorn 2002). Blocking these stimuli reduces apoptosis (Patterson et al 2004).

### Reduction of arrhythmia

Cardiac adrenergic stimulation leads to an increase in ventricular dysrhythmia (Meredith et al 1991) by shortening the action potential thereby increasing the potential for ventricular dysrhythmias.  $\beta$ -blockade lengthens the action potential, thereby reducing ventricular ectopy and non-sustained ventricular tachycardia even in patients with severe heart failure (Aronson et al 2002).

### Renin-angiotensin system activation

Sympathetic activation leads to an increase in the activity of the renin-angiotensin system with the consequent vasoconstriction, sodium and water retention and cardiomyocytes apoptosis mediated by angiotensin II and aldosterone. The hypokalemia induced by renin-angiotensin system activation is pro-arrhythmogenic. Renin levels are reduced by carvedilol administration (Cohen-Solal et al 2004).

### Reduction in ischemia

Ischemic but viable myocardium is not contractile, yet some degree of recovery is possible. Hence, in addition to reducing ongoing cell death as discussed above, by lengthening diastole and increasing myocardial perfusion,  $\beta$ -blockers might encourage the regeneration of contractile proteins within hibernating myocardial cells. This hypothesis has been tested in the Christmas study described below (Bellenger et al 2004).

### Vasodilator effect

Increased peripheral vascular resistance is a feature of chronic heart failure. The increased afterload placed on the left ventricle contributes to the adverse remodeling and deterioration in ventricular dysfunction and reduction of afterload has long been seen as an aim in the treatment of CHF (Franciosa et al 1977). Peripheral capacitance vessels have both vasodilating  $\beta_2$  and constricting  $\alpha$ -adrenergic receptors. Cardiac-selective  $\beta_1$ -adrenergic antagonists have little afterload-reducing effect, but non selective  $\beta_1$  and  $\beta_2$  antagonists can cause peripheral vasoconstriction. However,  $\alpha$ -blockade can have beneficial

effects on symptoms, left ventricular function and exercise tolerance probably through afterload reduction (Awan et al 1977). Carvedilol is the only non-selective  $\alpha$  and  $\beta$ -adrenergic antagonist currently used in patients with CHF. Although cardio-selective, nebivolol has a vasodilating effect due to its action on the L-arginine/nitric oxide pathway.

## Beta-blockers in chronic heart failure

$\beta$ -blockers as therapy for heart failure have been investigated in a number of settings. Table 1 summarizes the largest of the randomized-placebo controlled trials and one head-to-head comparison of  $\beta$ -blockers in heart failure.

Several large studies have examined the use of beta-blockers in patients with chronic heart failure.  $\beta$ -blockers seem not improve symptoms in the short-term and they may make them worse (Macmahon et al 1997). In the long-term however, they improve symptoms of breathlessness in many patients (Witte et al 2005) and stop them getting worse in many more (Packer et al 2002).  $\beta$ -blockers reduce the risk of hospitalization, mainly by reducing the risk of worsening heart failure (CIBIS investigators 1999; MERIT-HF study group 1999; Hjalmarson et al 2000; Packer, Coats et al 2001; Packer et al 2002), and they also reduce the overall proportion of time that the patient spends in hospital (CIBIS-II investigators and committee 1999; The MERIT-HF study group 1999; Hjalmarson et al 2000; Packer, Coats et al 2001; Packer et al 2003). These agents may increase average life expectancy by 12–24 months (Packer, Bristow et al 1996; MERIT-HF study group 1999; Hjalmarson et al 2000; Packer, Coats et al 2001; Packer et al 2002), in addition to that offered by ACE inhibitor therapy. Traditionally ACE inhibitors are the first-line agents in such patients, although  $\beta$ -blockers can be initiated as first line safely in patients with stable symptoms (Willenheimer et al 2005).

The Christmas study demonstrated that the improvement in left ventricular function seen with carvedilol was greater in those patients with evidence of hibernating myocardium than in those with no reversibility of perfusion defects (Bellenger et al 2004). Thus, by prolonging diastole and improving perfusion, carvedilol might lead to the recovery of hibernating cells (those with the capacity to recover contractile function). However, since ischemia/reperfusion is a major stimulus to apoptosis, the reduction of ischemia might lead to reduced programmed cell death and a prevention of further deterioration in cardiac function.

Sudden death is a common event in patients with CHF (Poole-Wilson, Uretsky et al 2003), with an annualized incidence up to 11% in those with three of higher brain natriuretic peptide (BNP) levels, poorer left ventricular

function (EF <30% or left ventricular end diastolic diameter >60mm), diabetes or non-sustained ventricular tachycardia (Watanabe et al 2006). By lengthening the action potential, reducing the incidence of ventricular ectopy, reducing ischemia and improving left ventricular function,  $\beta$ -blockers lead to a significant reduction in sudden death (Brodine et al 2005).

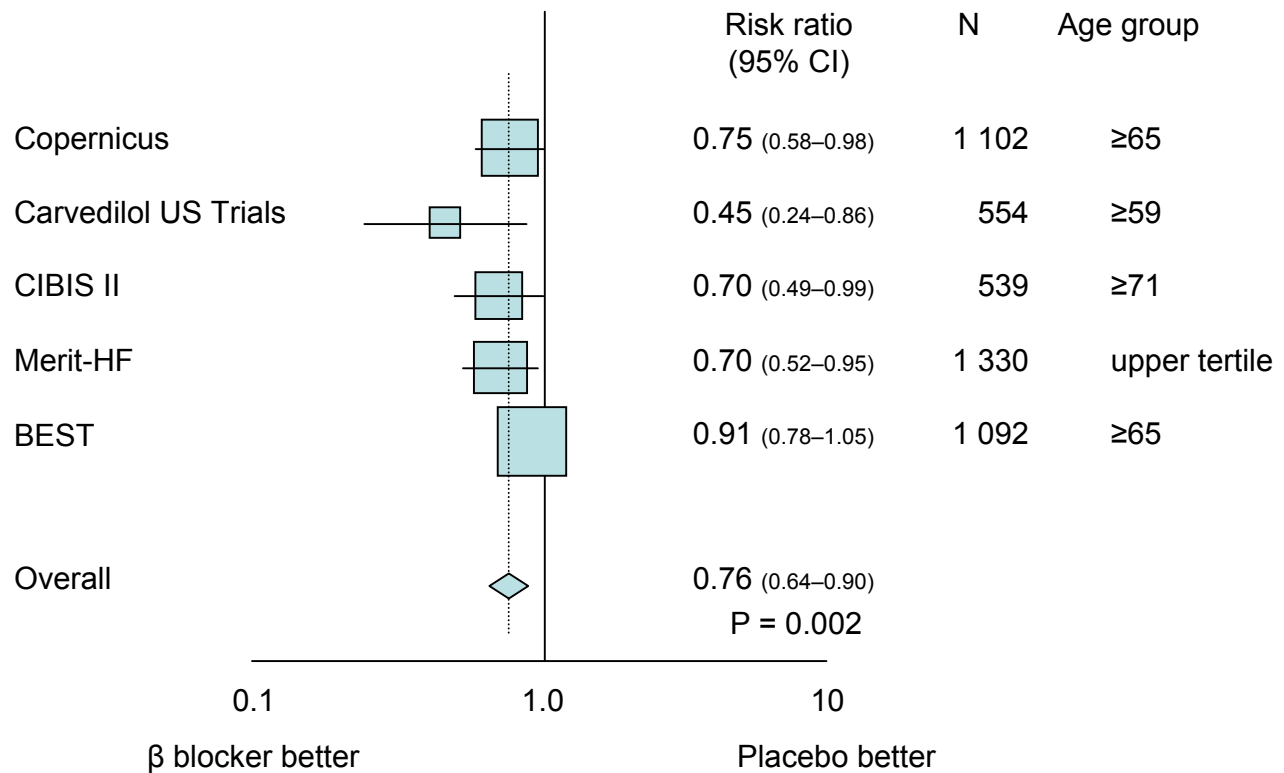
No study has specifically examined the use of  $\beta$ -blockers in elderly patients with chronic heart failure specifically due to left ventricular systolic dysfunction. Nevertheless, most of the trials have included older patients (Table 1) such that more patients with chronic heart failure aged >65 years have been randomized into studies of  $\beta$ -blockers than other agents used for heart failure therapy. In the early US carvedilol trials in which half of the enrolled patients were elderly (defined as >59 years!), there was no difference in the risk reduction with carvedilol between older and younger patients. In the MERIT study with metoprolol, patients older than the median (69.4 years) had the same mortality benefit as those below the median age (Hjalmarson et al 2000; Deedwania et al 2004). CIBIS II (using bisoprolol) enrolled 539 patients over 71 years, in whom the risk reduction of death or hospitalization over the duration of the study period (16 months) was similar to that seen in the younger patient group. Although the BEST study did not confirm the mortality advantage of bucindolol over placebo (Beta-Blocker Evaluation of Survival Trial Investigators 2001), there was once again no difference in outcomes between elderly (>65 years) and younger patients.

Observational studies in older patients (>65 years) have also demonstrated reductions in mortality and hospital admissions (Sin and McAlister 2002) and increases in left ventricular ejection fraction (Krum, Hill et al 2006) similar to those seen in the subgroup analyses. There seems to be no difference between older patients and very elderly patients (>80 years) in terms of increase in LVEF (Krum, Hill et al 2006).

Finally a meta-analysis, combining the effects of all of the major  $\beta$ -blocker studies and using data from 12,729 patients (4,617 elderly) confirms that older patients have the same benefit in all outcomes as younger patients (Figure 2) (Dulin BR et al 2005).

## Beta-blockers in post-infarct heart failure

$\beta$ -blockers reduce mortality after myocardial infarction, predominantly by reducing sudden death and the risk of recurrent infarction (Freemantle et al 1999; Houghton et al 2000). The only placebo-controlled randomized study to examine the benefits of  $\beta$ -blockade in patients with post-myocardial infarction heart failure demonstrated significant



**Figure 2** Box plot of beta-blocker versus placebo for older patients in each of the major randomized studies of beta-blockade in chronic heart failure. Point estimates and 95% confidence intervals next to box plot. (Redrawn from Dulin BR et al (2005) with permission).

reductions in mortality and readmission with carvedilol (Dargie 2001). This study included elderly patients, but no subgroup analysis has been published. Carvedilol therapy was associated with increased ejection fraction and reduced left ventricular volumes at follow-up (Doughty et al 2004) and reduced atrial and ventricular arrhythmias, and caused a reduction in sudden death (McMurray et al 2005).

### Beta-blockers in asymptomatic left ventricular dysfunction

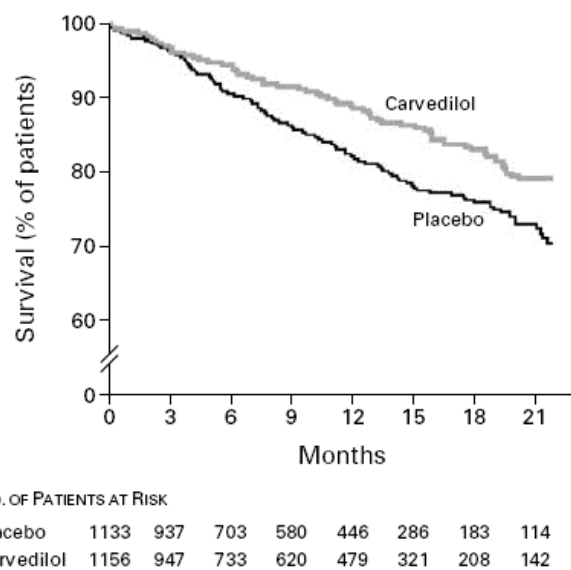
$\beta$ -blockers in combination with ACE inhibitors can reduce the progression of heart failure in patients with asymptomatic left ventricular dysfunction (Remme et al 2004), or mild heart failure (Colucci et al 1996). Furthermore, in mild heart failure, the prescription of a  $\beta$ -blocker as first line does not have an adverse effect and is well tolerated (Komadja et al 2004). There are no published data examining the effect of age in this group of patients.

### Beta-blockers in severe chronic heart failure

There are two placebo-controlled studies in patients with severe heart failure, both with carvedilol. The Precise trial

enrolled patients with severe symptoms of heart failure (mainly NYHA class III) and demonstrated improvements in symptoms, NYHA status and six-minute walk test distance, in those treated with carvedilol, irrespective of the etiology of the heart failure (Packer, Colucci et al 1996). No age-based subgroup analysis has been published. The mortality at six months in the placebo group was 8% at 6 months confirming that these patients had severe heart failure.

The only study selectively to recruit patients with decompensated heart failure was COPERNICUS (Packer, Coats et al 2001; Packer et al 2003). Patients in this study could be on intravenous diuretics, but not positive inotropic agents. However, that they were sick is shown by a 42% one year hospitalization or death rate in the placebo group. The benefits were striking even in this population of very sick patients (Figure 3) and were seen within the first month from randomization (Krum et al 2003). The greatest reduction in mortality was noted in those patients with a recent admission for decompensation of heart failure or very poor left ventricular systolic function (Krum et al 2003). The benefit was seen despite the high level of use of other disease modifying drugs (Krum, Mohacsi et al 2006). There were no differences in the benefit from carvedilol between patients under 65 years and those over 65 years.



**Figure 3** Kaplan-Meier analysis of time to death in the placebo group and the carvedilol group. The 35 percent lower risk in the carvedilol group was significant:  $p = 0.00013$  (unadjusted) and  $p = 0.0014$  (adjusted). (Reprinted from Packer M et al [106] with permission).

## Heart failure and atrial fibrillation

Atrial fibrillation is more frequent in elderly patients with chronic heart failure (Cleland et al 2002). It is an important marker for worse outcome (Middlekauff et al 1991; Dries et al 1998; Swedberg et al 2005).  $\beta$ -blocker therapy leads to similar reductions in mortality and morbidity in patients with atrial fibrillation as in those with sinus rhythm (Joglar et al 2001; Fung et al 2002). Use of carvedilol in elderly patients with atrial fibrillation is as safe and as well-tolerated as in patients with sinus rhythm with similar reduction in hospitalizations (Cioffi et al 2006) and improvement in left ventricular function (Opasich et al 2005).

Patients with heart failure and atrial fibrillation often have poor rate control during exercise. Digoxin has little effect on atrio-ventricular conduction during exercise. The addition of carvedilol in such patients to digoxin leads to superior rate control to either alone (Khand et al 2003).

## Heart failure with preserved left ventricular systolic function

Until recently, there had been little published data on the effects of  $\beta$ -blockade specifically in elderly patients with chronic heart failure. Older patients may represent a slightly different population of patients from those commonly recruited to clinical trials. A greater proportion of older patients with heart failure have apparently preserved left ventricular systolic function; they are more likely to have

atrial fibrillation; they are more likely to be female; and they are much more likely to have co-morbidity.

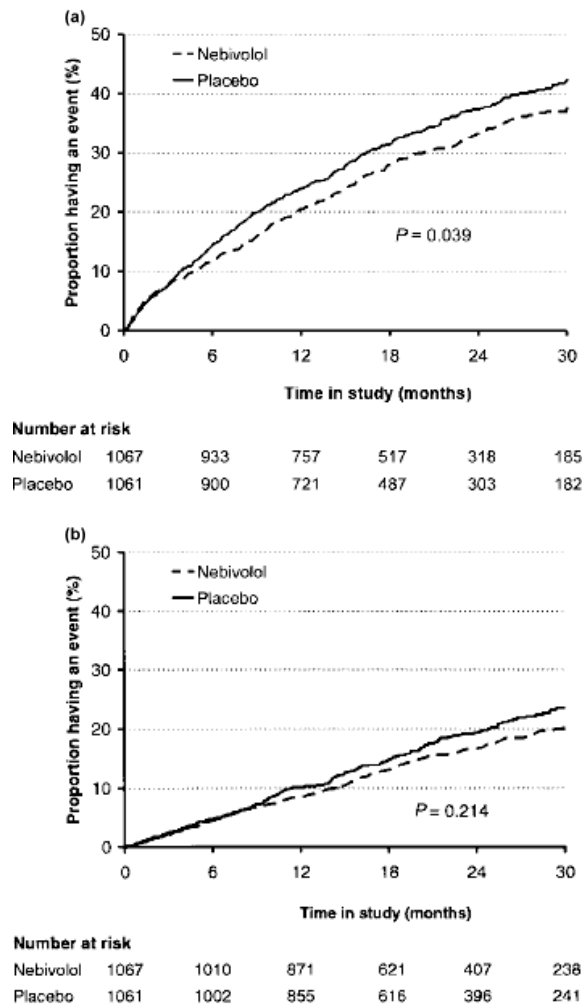
The first randomized study to suggest a potential benefit of  $\beta$ -blockers in a population of 158 older patients (mean age 81 years) with NYHA functional class II or III disease, prior myocardial infarction, and heart failure with left ventricular ejection fractions of 40% or higher used propranolol. All patients were treated with diuretics and ACE inhibitors at baseline and mean ejection fraction was 56%. At the end of the follow-up period, the two end-points of total mortality (RR 0.65) and mortality plus non-fatal myocardial infarction (RR 0.63) were significantly reduced in patients taking the  $\beta$ -blocker (Aronow et al 1997).

The only large randomized placebo-controlled study of  $\beta$ -blockers in elderly patients with chronic heart failure included 2128 patients with clinical evidence of heart failure, or impaired left ventricular systolic function. Nebivolol (mean dose 7.7 mg daily) treatment lead to reductions in the primary composite endpoint of all cause mortality or cardiovascular hospitalization (31% v 35%;  $p = 0.039$ ) but no reduction in all cause mortality as a result of a very low event rate (Figures 4a and 4b) (Flather et al 2005). In patients with impaired ventricular function, (LVEF  $\leq 35\%$ ) ( $n = 684$ ) there was a significant reduction in all-cause mortality (RR 0.62). In this group, LV ejection fraction increased and LV volume decreased (Ghio et al 2006). There was no change in LV variables in those with higher ejection fraction at baseline. There were no differences in the benefit of nebivolol between patients aged 75 and 85 and patients older than 85 years.

## Which beta-blocker?

There are important differences between  $\beta$ -blockers. Sympathomimetic agents with partial agonist activity, such as xamoterol, initially thought to be of potential benefit on exercise capacity in patients with left ventricular dysfunction following myocardial infarction (Persson et al 1995), seem to confer less benefit on long term mortality reduction than those without intrinsic sympathomimetic activity. Xamoterol, in fact, seems harmful to left ventricular function (Persson et al 1996), and its use is associated with a worse outcome than placebo (The Xamoterol in Severe Heart Failure Study Group 1990). Similarly, bucindolol, a partial agonist at beta-1 receptors (Andreka et al 2002), showed no overall benefit on mortality in patients with chronic heart failure in the BEST study (Beta-blocker Evaluation of Survival Trial Investigators 2001).

Clinical trial evidence of benefit is limited to agents without partial agonist or sympathomimetic properties (carvedilol, bisoprolol, metoprolol, and nebivolol).



**Figure 4** Time to (a) first occurrence of events (all cause death or hospital admission for a cardiovascular reason – primary endpoint) and (b) all cause death in patients randomized to nebivolol or placebo. (Reprinted from Flather MD et al [137] with permission).

Carvedilol has the most widespread effects on adrenergic receptors, blocking beta-1, beta-2 and alpha-1 receptors. In addition, it has anti-oxidant effects. The suggestion that non-selective blockade might be of additional benefit compared with  $\beta_1$  selective antagonism using metoprolol was tested in the COMET study (Poole-Wilson, Swedberg et al 2003), which randomized 3029 patients to either carvedilol or twice-daily short-acting metoprolol at doses used in clinical practice which for metoprolol were lower than those used in MERIT (MERIT-HF Study Group 1999). The average age of the randomized patients was 62 (11) years. Patients randomized to carvedilol had a 16% lower mortality than those taking metoprolol despite similar reductions in heart rate (Figure 5). This reduction was exactly the same for older patients ( $\geq 65$  years) as for the younger patients (Poole-Wilson, Swedberg et al 2003). Furthermore, patients with left ventricular dysfunction taking

carvedilol might have a greater increase in ejection fraction (Packer, Antonopoulos et al 2001), a less new-onset diabetes mellitus (Torp-Pedersen et al 2007), and fewer vascular events (Remme et al 2007), than those taking metoprolol, along with reduced hospital admissions for all age groups, including elderly patients (Poole-Wilson, Swedberg et al 2003; Cleland Charlesworth, et al 2006).

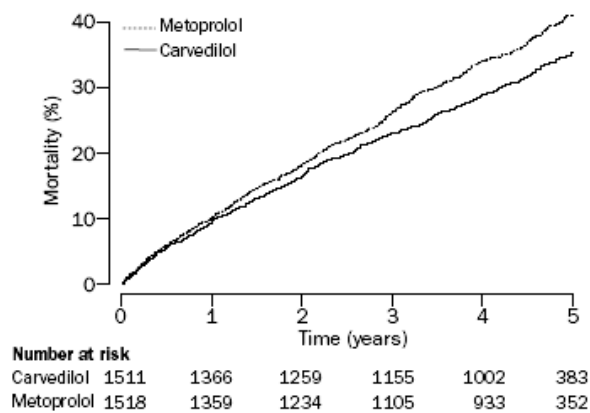
Nebivolol has some vasodilating properties, but despite a reduction in mortality in the subgroup of patients with significant left ventricular dysfunction (LVEF  $< 35\%$ ), the SENIORs study did not show an overall mortality reduction in elderly patients with chronic heart failure (Flather et al 2005). It would be useful to see nebivolol agent tested against another  $\beta$ -blocker. Therefore, despite the controversy created by the COMET study, this remains the only head-to-head trial of beta-blockers in patients with chronic heart failure, and suggests that non-selective adrenergic blockade might be the better option.

## Which dose?

Little is known about which dose of  $\beta$ -blocker is most effective. Much depends on how well tolerated they are by patients. Older patients tolerate higher doses less well than younger patients (Krum et al 2000). Lower doses can, however, lead to an increase in left ventricular ejection fraction and reduction in hospitalisation (Rochon et al 2000; Cioffi et al 2003). Nevertheless, as with studies in younger populations, higher doses of  $\beta$ -blocker are associated with a greater reduction in mortality (Simon et al 2003; Tandon et al 2004) even in very elderly patients (Krum, Hill et al 2006). It is important, though, to bear in mind that intolerance to higher doses might identify a sicker cohort of patients who have an intrinsically worse outcome. The only study to look at the subject of dose closely, compared the effects of three doses of carvedilol (6.25 mg, 12.5 mg, and 25 mg each twice a day) and placebo in 345 CHF patients on mortality, exercise capacity (6-minute walk test), hospitalizations and left ventricular ejection fraction (Bristow et al 1996). There was no effect of the  $\beta$ -blocker on walk distance and there were fewer hospitalization with carvedilol at any dose. However, there was a dose-related increase in left ventricular ejection fraction and reduction in mortality during the six-month follow-up period. Thus, even in elderly patients, it seems prudent to increase the  $\beta$ -blocker to the maximally tolerated dose.

## Side effects and tolerability

Side effects include bradycardia, hypotension, temporary worsening of heart failure and fatigue.  $\beta$ -blockers are



**Figure 5** Kaplan-Meier estimates of all-cause mortality for carvedilol and metoprolol. The hazard ratio was 0.83 (95% CI 0.74–0.93,  $p = 0.0017$ ) in favor of carvedilol. (Reprinted from Poole-Wilson et al [144] with permission).

probably not as well tolerated as ACE inhibitors (Cleland, McGowan et al 1998; Cleland, Gemmell et al 1999). Despite this, most symptoms do not lead to withdrawal of the medication. For example, in the US Carvedilol heart failure study dizziness was seen in 33% of those taking carvedilol and 20% in those taking placebo but was not associated with withdrawal of study medication (Packer, Bristow et al 1996). In the same study, worsening of CHF was the most common reason to stop therapy but was more common in those taking placebo (Packer, Bristow et al 1996). Interestingly, not all studies have confirmed that  $\beta$ -blockers are a major cause of fatigue (Ko et al 2002). In the Copernicus study, performed in patients with severe heart failure, many requiring intravenous diuretics, patients in the carvedilol group were more likely to require a dose reduction than those randomized to placebo, (38.3% v 33.2%;  $p < 0.01$ ), but were less likely to have the drug withdrawn (12.6% v 15.9%, respectively,  $p < 0.03$ ). In addition, even in these patients with severe heart failure, 74% tolerated carvedilol at the target dose. In fact, those with lower systolic blood pressure had a greater absolute benefit from the  $\beta$ -blocker (since they had a greater absolute risk) than those with higher systolic blood pressure (Rouleau et al 2004).

Few studies have specifically addressed tolerability in the elderly. One observational study found that the very elderly (>80 years) tolerated carvedilol less well than their younger peers (70–79 years) (Krum, Hill et al 2006). Nevertheless, in this very elderly group, more than 76% tolerated doses higher than the starting dose of carvedilol. Once the patients were stabilized, discontinuation of the higher dose of carvedilol over the follow-up period was not different between the groups. Older patients (>70 years) tolerate carvedilol as

frequently and to the same doses as patients under 70 years (Nul et al 2005; Lawless et al 2005). Carvedilol seems not to have adverse effects on cognitive function or functional capacity in elderly patients (Leonetti-Luparini et al 1999).

Heart rate and blood pressure reductions for equivalent doses are the same in older as in younger patients despite the fact that older patients are more likely to have a longer duration of CHF, more likely to have ischemic heart disease as the etiology of their CHF, higher NYHA scores, higher noradrenaline levels and overall higher placebo group mortality than their younger counterparts (Aranda et al 2002). Outpatient initiation and uptitration of carvedilol appears to be safe, even in an elderly population (Rickli et al 2004; Opasich et al 2006).

## Co-morbidities and beta-blocker therapy

Elderly patients are more likely to have other chronic conditions in addition to their CHF. This has potential implications for their management. The co-morbidities do not reduce the benefits patients gain from  $\beta$ -blockers, however, and may in some cases have an additional beneficial effect.  $\beta$ -blockers are often reported anecdotally to worsen diabetic control and can blunt the symptoms of hypoglycemia. However, carvedilol is as well tolerated in non-diabetics as in diabetics (Nodari et al 2003), leads to a decrease in insulin resistance (Ferrua et al 2005), and no increase of glycosylated hemoglobin (HbA1c). Metoprolol, on the other hand, had no effect on insulin resistance and was associated with an increase in HbA1c level (Kveiborg et al 2006; Bakris et al 2004). Diabetics with heart failure have a similar reduction in mortality with carvedilol as their non-diabetic counterparts (Bell et al 2006).

Peripheral vascular disease is also often thought to be a contraindication to  $\beta$ -blockade; however, worsening of claudication has not been reported as an adverse event in trials of systolic heart failure. Furthermore, studies of  $\beta$ -blockers in patients with known peripheral vascular disease have demonstrated that neither metoprolol nor propranolol worsened claudication distance or peripheral perfusion (Hiatt et al 1985). Carvedilol has the advantage that it might have some peripheral vasodilating properties, although it is not known if these persist long term (Kubo et al 2001), which might reduce the potential for worsening of claudicant symptoms.

Chronic airways disease is particularly common in patients with chronic heart failure, and the prevalence increases with age. The fear of inducing a deterioration in lung function is a factor in the under-prescribing of  $\beta$ -blockers in CHF patients.

However, most patients with chronic obstructive pulmonary disease (COPD) do not have reactive bronchospasm (Hunt et al 2001), and even if there were a reactive component, the alpha-adrenergic blockade of carvedilol might offset some of the bronchoconstriction induced by  $\beta$ -blockade (Sirak et al 2004). In any case,  $\beta$ -blockers are well tolerated in CHF (Kotlyar et al 2002; Shelton et al 2006) and post-infarct (Chen et al 2001) patients with COPD, with little change in pulmonary function tests (Sirak et al 2004; Witte and Clark 2005).

## Practical issues

Patients with preserved blood pressure or hypertensive patients will generally tolerate initiation of  $\beta$ -blocker and uptitration well. We often prescribe both the starting dose and the first titration dose on the same prescription in such patients, allowing a review at four rather than two weeks. In patients in whom there is a concern about hypotension, the loop diuretic dose should be reduced, or even omitted, on the first day. Alternatively, a slight reduction in the ACE inhibitor or angiotensin antagonist will allow safe uptitration.

Concerns over the consequences of the hemodynamic changes are frequently not realized even in those with systolic blood pressure around 100 mmHg and although early symptoms of postural hypotension often recur at each titration stage, they often settle once the patient is established on the increased dose. Finally, in patients where an increase in only one agent ( $\beta$ -blocker or ACE inhibitor) seems feasible, one should keep in mind that the remodeling effects of  $\beta$ -blockers are dose dependant, and a policy of increasing the  $\beta$ -blocker over the ACE inhibitor leads to a better response in terms of LV function (Sliwa et al 2004).

If a patient is admitted to hospital with an episode of decompensation of their heart failure,  $\beta$ -blocker therapy is commonly stopped in the short term. Once patients have stabilized, we recommend that the  $\beta$ -blocker is restarted prior to discharge, since this improves long term uptake (Gattis et al 2004).

## Conclusions

One of the great joys for physicians working with patients with chronic heart failure is that our practice is strongly informed by compelling evidence from clinical trials, and that evidence demonstrates that we can now have a profound impact on the quantity and quality of life of our patients. There are compelling data supporting the use of  $\beta$ -blockers in patients over 65 years. More patients have been enrolled in clinical trials of  $\beta$ -blockers than in studies of other agents,

and no important differences in outcomes between younger and older patients have been found. Contrary to popular belief,  $\beta$ -blockers are well tolerated, even in the presence of co-morbidities, and can be safely initiated in older patients both in the outpatient setting and before discharge from hospital following an acute exacerbation of heart failure. Although care is needed, physicians treating older patients with chronic heart failure need to be confident in initiating and up-titrating  $\beta$ -blockers in this group of high risk individuals.

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