HEART FAILURE

Treatment strategies for heart failure:
β blockers and antiarrhythmics

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The role of β blockers and antiarrhythmic drugs in the management of patients with heart failure is reviewed.

β Blockers

Although several investigators since the 1970s proposed β adrenergic blocking agents as a possible treatment for patients with heart failure,¹ the simple observation that they can reduce myocardial contractility confined them to being absolutely contraindicated for the treatment of this condition. However, the medical approach to heart failure has changed dramatically over the past 10 years, progressing from a haemodynamic to a neurohormonal pathophysiological paradigm.² Since activation of the sympathetic system is recognised as one of the cardinal pathophysiological abnormalities in patients with chronic heart failure,³ the effects of β adrenergic receptor blockers have been specifically tested in randomised clinical trials. Consequently, over a relatively brief period of time, a treatment that was once contraindicated is now an established, evidence based recommended treatment for heart failure.

Rationale for use

The concentrations of circulating catecholamines are increased in patients with chronic heart failure.³ The adrenergic activation observed in these patients can be useful initially to maintain an acceptable cardiac performance by increasing contractility and heart rate, but ultimately the increase in the adrenergic drive can damage the failing human heart.⁴ In the human cardiac myocyte, there are three adrenergic receptors—β1, β2, and α1—whose activation can lead to cardiac myocyte growth (β1, β2, α1), positive inotropic response (β1, β2), positive chronotropic response (β1, β2), myocyte toxicity (β1, β2), and myocyte apoptosis (β1).⁵ Therefore, the continuously increased activation of the adrenergic system leads to several adverse biological signals to the cardiac myocytes through the adrenergic receptors. The rationale for the use of β adrenergic blocking agents in patients with heart failure is based mainly upon these observations.

Effects on physiologic end points

Left ventricular function and remodelling processes
All available trials testing β blockers versus placebo showed that, apart from short term negative inotropic effect, β blocker treatment given

for at least three months is always associated with an improvement in left ventricular systolic function.^{6,7} Further, after longer treatment periods, normalisation of ventricular shape and regression in myocardial hypertrophy can occur.⁷ These modifications are generally called “reverse remodelling”. This phenomenon has been observed with different β blockers, and, together with the improvement in ventricular function, is unique among all the other “evidence based” recommended treatments for heart failure patients.

Effects on exercise capacity

The long term effect of β blockers on exercise tolerance remains controversial.⁸ Several trials have shown a significant improvement in maximal exercise tolerance, while others report no change⁹ or even a detrimental effect.⁸ A more consistent improvement was seen with metoprolol than with carvedilol or bucindolol.

Effects on neurohormones

There are sparse data on the long term effects of β blockers on neurohormonal activation, the majority of studies suggesting a reduction in the circulating noradrenaline (norepinephrine) concentrations.¹⁰ Recently, the RESOLVD study specifically addressed the issue of neurohormonal modifications induced by long term (23 weeks) metoprolol treatment.⁹ Metoprolol did not modify plasma catecholamine, aldosterone, and endothelin concentrations but decreased significantly renin and angiotensin II concentrations, which is in agreement with other reports. Interestingly, circulating concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) increased significantly in patients allocated to metoprolol treatment. The reasons for this modification are not readily apparent, though an increase in left ventricular filling pressure determined by metoprolol is a possible explanation.

Effects on hospital admissions and quality of life

Hospital admissions are now generally considered in clinical trials as one of the most relevant end points, both for their relation to patient quality of life and for cost implications. In this context, large scale clinical trials testing carvedilol,¹¹ bisoprolol¹² or metoprolol¹³ consistently showed that the hospitalisation rate for heart failure among patients allocated to β blockers was significantly reduced in comparison to that observed in placebo allocated patients. This benefit was not counterbalanced by a significant increase in other causes of hospital admission, resulting in a significant reduction of all cause hospitalisations.

When quality of life was evaluated with specific questionnaires, results obtained with β blocker treatment were conflicting.⁹ While the MDC trial showed an improvement of quality of life, the RESOLVD trial¹⁰ and the US carvedilol studies¹¹ did not show any difference. The Australian–New Zealand study showed a trend toward worsening quality of life scores.

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Table 1 Characteristics of randomised trials testing β blockers in patients with heart failure

Trial	Drug	Number of patients	NYHA class	Mean age (years)	Ejection fraction (%)	Annual mortality placebo group (%)	Primary end point	Mean follow up (months)	Run-in phase
US Carvedilol Program ¹¹	Carvedilol	1094	II-IV	58	≤ 35	12	Total mortality	6.5*	Yes
CIBIS-II ¹²	Bisoprolol	2,647	III-IV	61	≤ 35	11.2	Total mortality	16	No
MERIT-HF ¹³	Metoprolol	3,991	II-IV	64	≤ 40	9.4	Total mortality or hospitalisations	12	No

*Median.

Effects on survival

Over the last five years clear evidence has accumulated to show that β blockers improve the morbidity and mortality of patients with symptomatic heart failure and decreased ejection fraction. As a result, editorials, reviews, and official guidelines now consistently suggest that these drugs should be added to conventional treatment with angiotensin converting enzyme (ACE) inhibitors and diuretics. A meta-analysis of placebo controlled, randomised trials on 3023 patients, recruited in 18 published small scale studies, showed that β blockade reduced the combined risk of death and hospitalisation for heart failure by 37%.¹⁴ These encouraging observations were confirmed by the US Carvedilol Program which showed that in 1094 patients with heart failure carvedilol reduced the risk of total mortality by 65%.¹¹ This very impressive finding led the data and safety monitoring board of the study to recommend the early termination of the trial because of a clear evidence of benefit. On the basis of this study, carvedilol was approved for the clinical use in patients with chronic heart failure in several countries. Carvedilol has pharmacological properties in addition to β adrenergic blockade. It has been claimed that its favourable effects could be due to the peculiar characteristic of the drug and that this favourable evidence could not allow the conclusion that similar effects can be obtained with all the other β blockers.

More recently, two adequately powered, well conducted, large scale clinical trials, testing bisoprolol¹² and metoprolol,¹³ confirmed that β blockade does reduce total and sudden deaths of patients with symptomatic heart failure and impaired ventricular function. Table 1 shows the characteristics of the above trials, and fig 1 summarises the results on total mortality and sudden death. While the US Carvedilol

Program¹¹ pools data from four different studies to provide statistically reliable information on total mortality, CIBIS-2¹² and MERIT-HF¹³ are the only two randomised clinical trials specifically powered to test the effects of β blockers on survival.

CIBIS-2, a multicentred, double blind, placebo controlled trial conducted in eastern and western Europe, enrolled 2647 patients with severely symptomatic (New York Heart Association (NYHA) functional class III and IV) heart failure with an ejection fraction of 35% or less receiving standard treatment with ACE inhibitors and diuretics.¹² Patients allocated to treatment with bisoprolol, a β_1 selective adrenoreceptor blocker, showed a total mortality reduction of nearly 34%. Sudden death—one of the most common types of death in patients with chronic heart failure—was reduced by more than 40%. Hence, β blockers can be considered as complementary to ACE inhibitor treatment, whose effects on sudden death are not established. The trial was stopped after a planned interim analysis which showed a significant difference in all cause mortality between the two treatment groups.

MERIT-HF was a randomised, double blind controlled trial which tested metoprolol (a β_1 adrenoreceptor blocker) versus placebo in 3991 patients enrolled in 14 countries in North America and Europe. Patients must have been symptomatic (NYHA class II-IV) with a left ventricular ejection fraction of 40% or less. The incidence of the most relevant predefined end point was significantly lower in the metoprolol group. Specifically the combined end point of total mortality or heart transplantation was reduced by 32%, and sudden death by nearly 50%. Similarly to the US Carvedilol Program and the CIBIS-2 trial, the MERIT-HF trial was

Figure 1. β Blockers in patients with heart failure: effects on total mortality and sudden death.

Trial acronyms

AVID: Antiarrhythmic Versus Implantable Defibrillator trial
 BEST: β Blocker Evaluation Survival Trial
 CIBIS-2: Cardiac Insufficiency Bisoprolol Study
 COMET: Carvedilol or Metoprolol European Trial
 COPERNICUS: Carvedilol Prospective Randomised Cumulative Survival Trial
 DIAMOND: Danish Investigators of Arrhythmia and Mortality On Dofetilide
 GESICA: Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
 MADIT: Multicenter Automatic Defibrillation Implantation Trial
 MDC: Metoprolol in Dilated Cardiomyopathy
 MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure
 RESOLVD: Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study
 SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial
 STAT-CHF: Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure

prematurely terminated because of a clear evidence of benefit.

Clinical recommendations*Which patients should be treated with β blockers?*

On the basis of the evidence available, all patients with chronic, stable, mild to moderate symptomatic heart failure with depressed left ventricular function should be treated with β blockers. Benefits from β blockers appear to be similar in patients with heart failure caused by ischaemia or dilated cardiomyopathy. β Blocker treatment should be prescribed in addition to the other recommended treatments, such as ACE inhibitors and diuretics.

There is scant information on the effects of β blockers in patients with more severe (NYHA functional class IV) heart failure and in those with preserved left ventricular function. Furthermore, although in existing trials there were generally no age limits, elderly patients are poorly represented. Table 2 summarises the recommendations for β blocker use in patients with heart failure.

Table 2 Summary of the recommendations for β blocker use in patients with heart failure

Indications

Which patients with congestive heart failure are suitable for β blocker treatment?

- Patients with symptomatic heart failure of any cause, with depressed left ventricular function (ejection fraction $\leq 40\%$), in NYHA class II/III, clinically stable, already on treatment with ACE inhibitor, diuretic, and digitalis

Which patients are more likely to benefit?

- History of hypertension
- Heart rate > 90 beats/min

Which patients are less likely to benefit?

- Severe biventricular dysfunction
- Systolic blood pressure < 100 mm Hg
- Heart rate < 60 beats/min

Uncertain indications

For which patients do uncertainties still exist (scarce data from trials)?

- Elderly patients (> 75 years)
- NYHA class IV
- Asymptomatic left ventricular dysfunction
- Heart failure caused by valvar disease or diastolic dysfunction
- Comorbidities (diabetes, mild to moderate obstructive pulmonary disease, renal failure, peripheral vasculopathy)

Contraindications

What are the contraindications?

- Severe chronic obstructive pulmonary disease
- First degree AV block (PQ > 0.28 seconds) and second degree AV block (Mobitz 2 or advanced)
- Heart rate < 50 beats/min
- Systolic blood pressure < 90 mm Hg

AV, atrioventricular.

Which β blocker agent should be used?

Similar results in terms of morbidity and mortality reduction have been obtained with second or third generation β adrenergic blockers. Therefore, carvedilol, metoprolol or bisoprolol are the suggested agents to be used in patients with heart failure. In the absence of studies which directly compare the different compounds, there are no definite reasons to prefer any particular one of these three agents. The COMET trial, which is still ongoing, is comparing the effects of carvedilol versus metoprolol.

Table 3 summarises the pharmacological characteristics and the proposed dosages of the β blocker compounds most frequently studied in patients with heart failure. While for carvedilol, bisoprolol, and metoprolol there is clear evidence of a favourable effect in terms of mortality reduction, up to now bucindolol and nebivolol cannot be considered as evidence based recommended treatments for heart failure patients.

Table 3 Characteristics and proposed dosages of β blocker agents tested in patients with heart failure

Drug	Generation	$\beta 1$ selectivity	Vasodilator	Starting dose	Maximal maintenance dose
Metoprolol	Second	++	No	5 mg twice daily 25 mg once daily**	75 mg twice daily 200 mg once daily**
Bisoprolol	Second	+++	No	1.25 mg once daily	10 mg once daily
Carvedilol	Third	$\pm$	Yes	6.25 mg twice daily	50 mg twice daily
Bucindolol	Third	0	yes	12.5 mg once daily	200 mg once daily
Nebivolol	Third	+++	yes	1.25 mg once daily	10 mg once daily

** CR/XL formulation.

Evidence from β blocker trials

- Long term treatment with different types of β blockers results in normalisation of left ventricular shape, regression in myocardial hypertrophy, and an improvement in ventricular function (“reverse modelling”)
- Effects of β blockers on exercise tolerance remain controversial, with some trials showing a significant improvement in maximal exercise tolerance and others showing no change or even a detrimental effect
- Clinical trials consistently show that the hospitalisation rate for heart failure is significantly reduced by β blocker treatment
- When quality of life for heart failure patients is evaluated using specific questionnaires, results of the effects of β blockers are conflicting
- Adequately powered clinical trials testing different types of β blockers (carvedilol, bisoprolol, metoprolol) clearly demonstrate that total and cardiovascular mortality are significantly improved by each of these agents

Initiation of treatment

Since the adrenergic system is activated to support the reduced contractility of the failing heart, the administration of a β blocker in a patient with heart failure can induce myocardial depression that can be associated with different degrees of symptom manifestations. This possible initial deterioration of the clinical conditions could occur with any β blocking agent, although with non-selective first generation agents, such as propranolol, this phenomenon can be more evident. Second generation, β_1 selective agents, such as metoprolol or bisoprolol—which leave β_2 receptors unblocked and thus capable of supporting myocardial function—are generally better tolerated. Metoprolol or bisoprolol, started at very low dosages (table 3), are associated with a tolerability rate of more than 80%. The third generation compounds (carvedilol, bucindolol, nebivolol) have an acceptable initial tolerability rate, reducing the afterload and thus counteracting the negative inotropic properties of adrenergic blockade. While these vasodilating properties can play a favourable role at the initiation of treatment, it is less likely that vasodilation can give a substantial contribution to the long term effects of third generation compounds. Once treatment is started and the maintenance dosage is reached, the treatment should be continued indefinitely at the maximal tolerated dosage.

Open issues

Subgroups of patients not yet adequately studied

Uncertainties still exist on the effects of β blockers in patients with *advanced heart failure*—that is, those in NYHA functional class

IV. The COPERNICUS trial, which specifically addressed this question, has been prematurely stopped because of an evidence of benefit, but the results have not yet been published. The only study that was terminated early because there was no likelihood of demonstrating a beneficial effect of treatment on mortality is the BEST trial, which tested bucindolol, a potent non-selective β blocker with sympathomimetic activity. This trial included 2708 patients with advanced heart failure. The less favourable effect observed in this trial could be explained by the fact that bucindolol may be less effective than metoprolol, carvedilol or bisoprolol. However, the most likely reason for the differing results is that the BEST trial randomised more patients with advanced heart failure than the other β blocker trials.

Furthermore, the BEST trial enrolled a large number of black patients. Black patients are already known to be poorly responsive to β blockade for the treatment of hypertension. The trend toward a detrimental effect of bucindolol observed in the BEST trial underscores the paucity of information in this population of patients.

There is not yet clear evidence of benefit from β blockers in the treatment of two other very important categories of patients: (a) the patients with overt heart failure but with *preserved left ventricular function*; and (b) *elderly patients*, who are today the largest majority of patients with heart failure as revealed by epidemiological surveys conducted in community settings. For all these categories of patients, further adequately powered studies are necessary.

Transferability of results to clinical practice

Finally, despite the impressive results in terms of morbidity and mortality reduction, and the increasing availability of β blockers in appropriate formulations, the transfer of these results into clinical practice is certainly difficult, mainly because of a distorted perception which clinicians have about the efficacy and tolerability of β blockers in congestive heart failure. International data show that only a minority of patients are treated with β blockers in clinical practice in the “real world”. It is commonly perceived that β blockers are difficult to initiate and uptitrate, and that they have multiple contraindications so that very few patients can be considered eligible and only highly selected patients can tolerate them. The explanation for this discrepancy lies in part in the large differences which exist between the populations of patients with heart failure enrolled in clinical trials and those patients commonly encountered in clinical practice with respect mainly to age, sex distribution, and presence of comorbidities. Methods of implementing the results of trials in clinical practice should be developed to overcome these barriers and to start β blocker treatment in the huge number of patients with heart failure who could benefit from this treatment.¹⁵

β Blockers: summary

- At one time contraindicated in the treatment of heart failure, β blockers have become an established, evidence based, recommended treatment for patients with this condition
- The increased activation of the adrenergic system induced by heart failure—which leads to transmission of several adverse biological signals to the cardiac myocytes through the adrenergic receptors—provides the rationale for the use of β blockers in heart failure
- While the effects of β blockers on exercise capacity, quality of life, and the neurohormonal profile are still controversial, clinical trials clearly show that left ventricular shape and function, and the need for hospitalisation are improved by β blocker treatment
- Three adequately powered trials—US Carvedilol Program, CIBIS-2, and MERIT-HF—testing carvedilol, bisoprolol, and metoprolol, respectively, showed that these β blockers significantly reduce total and sudden mortality in heart failure patients
- On the basis of all available evidence, all patients with chronic, stable, mild to moderate, symptomatic heart failure (NYHA functional class II/III) and with depressed left ventricular function should be treated with β blockers
- Uncertainties still exist about the use of β blockers in heart failure patients in NYHA functional class I or IV, in those patients of advanced age, and/or in those patients with preserved left ventricular function
- β Blocker treatment should be started in stable patients with a very low initial dosage and then uptitrated to the maximal tolerated dosage
- Once treatment is started and the maintenance dosage is reached, treatment should be continued indefinitely and at the maximal dosage tolerated
- Despite the impressive results in terms of morbidity and mortality reduction, and the increasing availability of β blockers in appropriate formulations, the transfer of these benefits to the clinical practice setting in the “real world” is difficult, with international data showing only a minority of patients being treated

Antiarrhythmic drugs

Despite the clear evidence of benefit in terms of mortality reduction obtained with ACE inhibitors and β blockers, the prognosis of heart fail-

ure has remained a major issue. The five year mortality rate has been estimated to be at least 50%, and, besides progressive pump dysfunction, sudden death is the most common reason, being considered responsible for 25–70% of all deaths. The relative rate of sudden death is generally higher in patients with less severe functional status.¹³ The majority of sudden deaths are generally caused by ventricular arrhythmias. In this context, the potential role of antiarrhythmic strategies has been considered of primary relevance for a long period of time. Over the last two decades, antiarrhythmic drugs have been tested by specific clinical trials to evaluate their role in improving survival of patients with congestive heart failure. It must be noted that almost all trials testing antiarrhythmic agents have been conducted when ACE inhibitor treatment was not yet largely adopted in clinical practice and β blockers were still a contraindicated treatment.

The use of antiarrhythmic agents in patients with heart failure has two potential serious adverse consequences: depression of left ventricular function and, in some cases, exacerbation of ventricular arrhythmias. Consistent with these unfavourable effects, several class I antiarrhythmic agents—such as encainide, flecainide, moricizine, and propafenone—have been demonstrated to increase mortality.¹⁰ Apart from β blockers, only amiodarone among all antiarrhythmic drugs seems to have a potentially beneficial effect in terms of total mortality reduction.¹⁶

Amiodarone

In the presence of left ventricular dysfunction, amiodarone appears to be haemodynamically well tolerated even in the cases of more advanced heart failure. For this reason, several trials investigated the role of amiodarone in patients with congestive heart failure. Two of these trials were specifically powered to evaluate the effect of amiodarone on total mortality—the GESICA¹⁷ and the STAT-CHF¹⁸ trials.

The Argentinian GESICA study was an open, randomised trial testing amiodarone (600 mg/day for two weeks followed by a maintenance dose for 300 mg/day) versus placebo in 516 patients with severe heart failure: mean ejection fraction was 20%, and nearly 80% of the total population was in NYHA functional class III or IV. The mean period of follow up was 24 months. Amiodarone treatment was associated with a significant reduction of total and sudden mortality of 28% and 27%, respectively. The benefit appeared after only three months following initiation of treatment, and was consistent across subgroups defined by symptomatic severity.

Less favourable results have been shown by the STAT-CHF trial.¹⁸ This randomised, double blind trial included 674 patients with symptomatic heart failure, with an ejection fraction of 40% or less, cardiac enlargement, and at least 10 premature ventricular beats per hour. During the median follow up period of 45 months, there was no significant difference in terms of either total or sudden deaths. While

survival was not modified, in those patients allocated to treatment with amiodarone the mean ejection fraction increased by 42%, confirming that amiodarone has no negative inotropic effect.

An overview of 6500 patients with heart failure or survivors of myocardial infarction showed a small but significant reduction in total mortality of 13%.¹⁶ The effect was similar among patients with heart failure and those with a previous myocardial infarction.

Although the evidence on efficacy is still controversial, amiodarone is the only antiarrhythmic drug whose use is acceptable to treat symptomatic ventricular arrhythmias in patients with heart failure, particularly if the patients are survivors of myocardial infarction. Furthermore, patients with atrial fibrillation treated with amiodarone were more likely to convert into sinus rhythm and those in sinus rhythm were less likely to go into atrial fibrillation.

New class III agents

While *d*-sotalol, a class III potassium channel blocker, was found to be harmful—being associated with increased mortality in patients with left ventricular dysfunction¹⁹—two new class III antiarrhythmic agents, dofetilide and azimilide, are under evaluation in patients with heart failure.¹⁹ The DIAMOND trial tested dofetilide versus placebo in 1518 patients with congestive heart failure. The investigators concluded that there was no protection but also no harm with the use of this drug in patients with heart failure. The effect of azimilide versus placebo on total mortality is still being tested in nearly 2500 patients with reduced left ventricular function after myocardial infarction. Results will be available in the next couple of years.

Clinical implications and perspectives

Patients with congestive heart failure frequently have ventricular arrhythmias on 24 hour Holter monitoring and, even more importantly, sudden death is one of the most frequent causes of death. Several antiarrhythmics, approved to suppress ventricular arrhythmias, not only failed to improve survival, but have been shown to be harmful. Amiodarone is the only drug which seems potentially beneficial, suppressing atrial and ventricular arrhythmias without depressing left ventricular function. Furthermore, survival appears to be unaffected by the drug; on the contrary, available evidence shows a small reduction in total mortality. Dofetilide was shown to have a neutral effect on mortality. Thus, of the currently available antiarrhythmic treatments, amiodarone appears to have the greatest potential in patients with heart failure, but its use should be limited to patients with symptomatic atrial and/or ventricular arrhythmias already being treated with ACE inhibitors and β blockers.

More recently, several trials have suggested that for patients who have survived cardiac arrest the preferred treatment may be an implantable cardioverter-defibrillator (ICD).²⁰ Although none of these trials was specifically

Antiarrhythmic drugs: summary

- In addition to progressive pump dysfunction, sudden death is the most common cause of death in patients with heart failure, being responsible for 25–70% of all deaths
- Continuous ECG monitoring shows that patients with heart failure have frequent and repetitive ventricular arrhythmias
- Antiarrhythmic agents in patients with heart failure can depress left ventricular function and, in some cases, exacerbate ventricular arrhythmias; accordingly, several class I antiarrhythmic agents—such as encainide, flecainide, moricizine, and propafenone—have been shown to increase mortality
- Of the available antiarrhythmics, amiodarone is the only one which seems to be potentially beneficial in patients with heart failure, suppressing atrial and ventricular arrhythmias, without depressing left ventricular function and affecting survival

focused on heart failure, many of the enrolled patients had some degree of cardiac dysfunction. The two most relevant trials (MADIT and AVID) showed a significant benefit on total survival, and subgroup analysis showed that the greatest benefit was achievable in the higher risk patients, such as those with heart failure. Two ongoing trials (SCD-HeFT and MADIT-2) are now enrolling patients with reduced ejection fraction, in an attempt to demonstrate the beneficial effect of ICDs in patients with congestive heart failure.

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