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REVIEW

Bucindolol: A Pharmacogenomic Perspective on Its Use in Chronic Heart Failure

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Abstract: Bucindolol is a non-selective β-adrenergic receptor blocker with α-1 blocker properties and mild intrinsic sympatholytic activity. The Beta-Blocker Evaluation of Survival Trial (BEST), which is the largest clinical trial of bucindolol in patients with heart failure, was terminated prematurely and failed to show an overall mortality benefit. However, benefits on cardiac mortality and re-hospitalization rates were observed in the BEST trial. Bucindolol has not shown benefits in African Americans, those with significantly low ejection fraction and those in NYHA class IV heart failure. These observations could be due to the exaggerated sympatholytic response to bucindolol in these sub-groups that may be mediated by genetic polymorphisms or changes in gene regulation due to advanced heart failure. This paper provides a timely clinical update on the use of bucindolol in chronic heart failure.

Keywords: bucindolol, chronic heart failure, beta-blocker, therapy

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Introduction

Despite initial misgivings, the beneficial role of beta (β)-blocker therapy in chronic heart failure (CHF) has been well proven in clinical trials.[1] However there remains debate regarding the use of specific β-blockers for individual New York Heart Association (NYHA) heart failure categories.[2] Adrenergic drive is enhanced as a compensatory mechanism in heart failure and this has prognostic implications. Counteracting the adrenergic drive with β-blocker therapy seems to offer long-term symptomatic and prognostic benefits in heart failure patients.[3,4] Bucindolol is a non-selective β-antagonist that may offer benefit to certain groups of patients with heart failure in NYHA class I-III,[5] but not other patient groups, such as African Americans.[6] This review will describe the mechanism of action of bucindolol, review evidence from relevant clinical trials, and evaluate efficacy and safety in the use of bucindolol in the different sub groups of heart failure patients.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Compensatory neurohormonal activation is a primary adaptive response in CHF, employed to maintain cardiac output and preserve the perfusion of vital organs. However, short-term cardiovascular support afforded by sympathetic hyperactivation is clinically negated by the poor long-term prognosis associated with altered β-adrenergic receptor sensitivity, which may lead to decompensation and increased susceptibility to ventricular tachy-arrhythmias.[7] β-adrenergic receptor blockade has been effectively employed in patients with CHF to counter the enhanced sympathetic activity and improve mortality, cardiovascular function and clinical status.[8] Bucindolol is a third-generation, non-selective β-adrenergic receptor blocker, that acts on both β-1 and β-2 receptors. Bucindolol's additional α-1 antagonistic activity contributes to its mild vasodilator effect.[7] Bucindolol's neurohormonal activity profile is similar to that of carvedilol but different in some respect to older agents.[9]

An important attribute in the classification of β-adrenergic agents is the presence or absence of intrinsic sympathomimetic activity (ISA). Early studies trialing bucindolol reported no ISA in human myocardium,[10,11] however, a later study measuring intracellular cyclic AMP observed bucindolol to have partial agonist activity at the β-adrenergic receptor.[12] At present, the effect of bucindolol on ISA appears to be unresolved. Bucindolol is a lipophilic compound with a high hepatic first-pass metabolism through the hepatic cytochrome P450 pathway.[7] Increased plasma concentrations may occur in patients with hepatic impairment necessitating caution and possible dose decrement.

Early Mechanistic Studies of Bucindolol

Due to the conflicting results and inconclusive data from research carried out thus far, the precise role of bucindolol in the management of CHF remains debatable. Several trials have examined the effect of bucindolol on hemodynamic responses and/or ventricular function[10,13–15] with the drug consistently demonstrating improvement in left ventricular ejection fraction and cardiac index while reducing left ventricular filling pressures, pulmonary artery pressures, and heart rate in CHF. In addition, bucindolol has been shown to increase stroke volume and minute work without increasing myocardial oxygen demand.[13] The latter fact suggests some increase in myocardial efficiency, although comparisons did not reach statistical significance in the trial by Eichhorn and colleagues.[13] The improved ventricular performance may be predominantly due to the enhanced cardiac contractility and not due to the modest vasodilator effect.[13] This improvement in contractility has been confirmed by relatively load-independent methods (end-systolic elastance and the maximum dP/dt and end-diastolic volume relations).[13] Bucindolol reduces isovolumic relaxation times despite having little effect on chamber stiffness (over a 3-month trial period).[13]

The improvement in cardiac performance with bucindolol appears to be greatest in patients with idiopathic dilated cardiomyopathy compared with patients with ischemic heart disease, although there does appear to be benefits in these patients also.[15] Underlying mechanisms of this variation in treatment benefits is unclear, and some proposed reasons include: (1) increased adrenergic down-regulation that exists in idiopathic dilated cardiomyopathy compared to ischemic cardiomyopathy; (2) β-adrenergic receptors in left and right ventricles of patients with ischemic heart failure demonstrate a moderate degree of

uncoupling from pharmacologic response compared with idiopathic dilated cardiomyopathy;[15,16] (3) The patterns of connective tissue scar formation may be different in idiopathic versus ischemic groups;[17] and (4) ongoing ischemia may exist in the ischemic group preventing efficient substrate utilization.[10,18] Several studies examining the effect upon NYHA class have demonstrated improvement with bucindolol,[10,13–15] however this improvement has not translated to increases in exercise tolerance or increased maximal oxygen consumption. However, all β-blockers (including bucindolol), have been shown to blunt exercise tolerance even in patients without objective evidence of heart failure,[19] probably by limitation of cardiac output (heart rate).

Bucindolol Clinical Trials

Early bucindolol trials were small and of short duration and focused on softer end points rather than hard endpoints such as mortality and hospitalization. These trials showed conclusive improvements in cardiac function, control of hypertension and quality of life (QOL), but equivocal data for peak oxygen consumption (peak VO_2). Table 1 summarizes the published trials of bucindolol to date.

The first clinical trial to test bucindolol was carried out amongst asthmatics (without heart failure) to assess its bronchoconstrictor effect. This study showed a 25% incidence of bronchoconstriction with bucindolol use.[20] In addition, the remainder of patients demonstrated an impaired bronchodilator response to salbutamol, independent of baseline pulmonary function and consistent with a traditional dose-response relationship.[20] The early bucindolol heart failure trials were carried out in small and heterogeneous populations. Eichorn et al conducted a cohort analysis in 15 patients with heart failure. In this trial, cardiac contractility was improved, despite unchanged chamber stiffness or efficiency, without reducing myocardial oxygen consumption in post-myocardial infarction patients with left ventricular dysfunction.[13] Bristow also found exercise tolerance to be preserved or increased with three different doses of bucindolol in patients with left ventricular dysfunction, but left ventricular ejection fraction only improved at the highest (200 mg) dose.[21] Small studies by Gilbert[10] (idiopathic etiology) and Pollock[14] (mixed etiology), also showed improved left ventricular ejection fraction and symptoms at a dose of 200 mg in patients with cardiomyopathies of various etiology. Anderson[16] reported 23 month follow up data from the same patient group as Gilbert[10] and showed improved left ventricular ejection fraction, NYHA functional class and stable maximal oxygen uptake. Perhaps the most important finding of Anderson's work was that all 20 patients survived the full duration of follow up leading to the recommendation of a larger trial. Contemporaneously, this same group reported isolated improvements in left ventricular ejection fraction, left ventricular chamber dimensions, filling

Table 1. Clinical trials of bucindolol to date.

Study	Patients	Subjects	Dose(s) mg · d^{-1}	Duration
Ruffin[20]	COPD/asthma	16	50, 100, 200	Acute
Eichorn[13,#]	NYHA I (7%), II (47%), III (33%), IV (13%)	15	150–200	12 weeks
Bristow[21]	NYHA class II (43%) and III (57%)	141	12.5, 50, 200	12 weeks
Gilbert[10,‡]	NYHA II (43%), III (57%)	23	200	12 weeks
Pollock[14]	NYHA II (5%), III (74%), IV (21%)	19	200	12 weeks
Anderson[16,‡]	NYHA II (50%), III (50%)	20	25–200	2 years
Woodley[15,‡]	NYHA II (37%), III (67%)	49	170–200	12 weeks
Bristow[22]	NYHA I (1%), II (43%), (55%), IV (1%)	139	12.5, 50, 200	12 weeks
Heesch[23,∞]	27/30 non-ischemic NYHA I–IV (% n/a)	30	200	12 weeks
BEST[25,*]	NYHA III (92%) IV (8%)	2708	100 (<75 kg), 200 (>75 kg)	2 years*
Torp-Pederson[26]	NYHA I (45%), II (43%), III (10%), IV (2%)	343	100 (<75 kg), 200 (>75 kg)	Ongoing*
BEAT*				

Notes: #Study not a randomized, controlled trial; ‡Some duplication of subjects between these studies; ∞Comparator was Metoprolol; *Study stopped prematurely.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; NYHA, New York Heart Association Functional Class; BEST, Beta Blocker Evaluation of Survival Trial.

pressures and circulating norepinephrine levels, after bucindolol therapy in heart failure due to idiopathic dilated cardiomyopathy, although this observation was not seen in, patients with ischemic heart failure.[15] A dose-response analysis reported a larger improvement in left ventricular ejection fraction at higher doses.[22] A head to head comparison of bucindolol and the β-1 selective controlled-release metoprolol in heart failure patients concluded that the former produced more favorable improvements in resting cardiac index and end-diastolic pressure. The latter agent was observed to reduce coronary blood flow and myocardial oxygen consumption.[23]

The positive observations in smaller trials proved the need for a well structured large randomized, controlled trial to gather more conclusive outcomes data on bucindolol therapy in heart failure. As a result, in 1995 the Beta-Blocker Evaluation of Survival Trial (BEST) study protocol was published.[24] BEST was designed to study whether bucindolol, would reduce all cause mortality in patients with advanced heart failure as the primary end point and to assess its effect in various subgroups of heart failure patients as defined by ethnic background and demographic criteria. Secondary end points were total cardiovascular mortality, mortality due to worsening heart failure, sudden death, quality of life, hospitalization and its cost, left ventricular ejection fraction after 3 and 12 months of therapy, and myocardial infarction. Further analysis was carried out to study the effect of heart failure etiology, ethnicity and gender on the outcome measures.[24,25] The BEST study failed to show significant reductions in mortality at the seventh interim analysis in mid-1999, after a mean (final) follow up period of 2 years.[25] Subject withdrawal was very low and compliance to therapy was 81% in both arms of the study. However, the secondary endpoints of cardiovascular death and hospitalization were significantly lower in the bucindolol group. The bucindolol group also showed greater improvement in left ventricular ejection fraction, which was also significant (bucindolol 5.5% ± 7.8% versus placebo 2.1 ± 13.4, $P < 0.001$).

The BEST study group and the control group were well matched for NYHA class, left ventricular ejection fraction and optimal background therapy, nevertheless, the protocol administration may have varied between the 90 administering sites. A total of 449 patients in the placebo group (33%), and 411 in the bucindolol group died during the study and follow up period (30%); (hazard ratio [HR] = 0.90; 95% confidence interval (CI) = 0.78 to 1.02; unadjusted $P = 0.10$; adjusted $P = 0.13$), a non significant trend. The annual mortality in the placebo group was 17% and 15% in the bucindolol group. The rate of death from cardiovascular causes was significantly lower in the bucindolol group (HR = 0.86; 95% CI = 0.74–0.99; $P = 0.04$). The rates of death due to pump failure and sudden death showed trend to the lower; these results are comparable to the overall effect on the rate of death from cardiovascular causes.[25] Table 2 compares BEST mortality data with those of the other placebo controlled trials of β-blocker therapy in heart failure.

Bucindolol significantly reduced the heart failure related hospital readmission rates (HR = 0.78; 95% CI = 0.69 to 0.88; $P < 0.001$) but there was a

Table 2. Placebo-controlled heart-failure trials involving β-blockers—all cause mortality.

	Study	B-blocker	ISA	NYHA class	Number of patients	All-cause mortality	*P* value
Positive trials	CIBIS II[3]	Bisoprolol (high β-1 selective)	No	III–IV	2649	↓34%	<0.0001
	MERIT[65]	Metoprolol succinate (mod β-1 selective)	No	II–IV	3991	↓34%	<0.0001
	COPERNICUS[78]	Carvedilol (non-selective + α-blocker)	No	IV	2289	↓35%	<0.0014
Negative trials	BEST[25]	Bucindolol (weak α-blocker + non selective)	25% ISA	III–IV	2708	↓10%	<0.10
	SENIORS[79]	Nebivolol (β-1 selective)	Both β-2 and β-3 ISA	II–IV	2128	↓12%	<0.21

Abbreviations: NYHA, New York Heart Association; ISA, Intrinsic Sympathomimetic Activity.

non-significant reduction in all-cause hospitalization rates (HR = 0.92; 95% CI = 0.84 to 1.01; $P = 0.08$). Bucindolol reduced the average number of hospitalizations and the average number of inpatient days per patient. The combined end point of death or heart transplantation during the trial occurred in 32% of the patients in the bucindolol group and 35% in the placebo group (HR = 0.87; 95% CI = 0.77–0.99; $P = 0.04$).[25] Left ventricular ejection fraction was improved with bucindolol therapy at 3 months compared with placebo (5.5% ± 7.8% vs. 2.1% ± 6.9% in the placebo group; $P < 0.001$) and at 12 months (7.3% ± 10.0% vs. 3.3% ± 8.7% for placebo; $P < 0.001$). Authors also found a trend toward improved survival with bucindolol among patients in NYHA class III, but not in class IV, with a HR of 0.87 (95% CI = 0.75 to 1.01; $P = 0.06$); for those with a left ventricular ejection fraction greater than 20 percent, the HR was 0.83 (95% CI = 0.69 to 1.00; $P = 0.05$).

The BEST study is the largest trial of bucindolol in heart failure patients to date and the decision to prematurely terminate BEST had an effect on the implementation of the 2000-patient Bucindolol Evaluation in Acute myocardial infarction Trials (BEAT).[26] BEAT studied bucindolol's effects on the mortality in post-myocardial infarction (MI) heart failure patients, but only 343 patients were recruited before BEAT was also terminated prematurely. The analysis of the outcomes data in the recruited subjects in BEAT showed a non-significant trend towards a mortality benefit in the bucindolol group.[26]

Several other subsequent sub-analyses of BEST data suggest certain heart failure patients groups are less likely to benefit from bucindolol therapy, these studies are summarized in Table 3. O'Connor et al[27] reported a 52% ($P = 0.001$) reduction in non-fatal MI in those receiving bucindolol, but in those that were suspected of having MI, the 2 year mortality rate was higher (56% versus 30%; $P = 0.01$). The benefit of bucindolol therapy was not proven in heart failure patients with NYHA class IV symptoms, African Americans or those with a left ventricular ejection fraction <20%, although these observations are not without dispute.[2] Various reasons have been examined to explain the reduced effects of bucindolol in certain heart failure sub-groups. One such explanation involves the existence of several different polymorphisms of the β-1 adrenergenic receptor gene (ADRB1) and variants of the pre-junctional adrenergenic receptor that may affect the clinical response to bucindolol therapy. Others have attributed bucindolol's failure to produce significant reductions in all-cause mortality to its ISA.[28]

Table 4 summarizes the gene polymorphisms relevant to the individual's response to therapy with β-blockers. Both the variant 389Gly and 49Gly alleles

Table 3. BEST sub-analyses.

Study	N	Finding(s)
Anderson[5]	226	Class IV patients were high risk for early risk of death or heart failure hospitalization were not reduced.
Domanski[37]	1668	Different heart failure sub-groups respond differently to β-blocker therapy.
Ghali[53]	2708	Prognostic predictive values of some variables vary between women and men. Survival advantage of women is confined to patients with non-ischemic etiology.
Eichorn[64]	79	Patients without contractile reserve have higher resting adrenergic drive, (higher) plasma norepinephrine, and may experience greater ISA effects from bucindolol.
Bristow[80]	2126	Likelihood ratios indicated 18% of bucindolol group but only 1% of placebo group had an increased risk of death related to reduction in norepinephrine at 3 months due to sympatholysis, which compromised bucindolol efficacy.
O'Connor[27]	2708	Bucindolol appears to attenuate the risk of non-fatal MI.
Liggett[36]	1040	Beta-1 Arg-389 polymorphism affects (amplifies) therapeutic response to bucindolol in heart failure.
Tate[77]	2708	Bucindolol improves quality of life.
Frantz[73]	206	Lack of effect of bucindolol on natriuretic peptides appears consistent with lack of overall efficacy.
Bristow[42]	1040	Patients who were α_{2c} Del carriers (heterozygous or homozygous) were more likely to exhibit an ISA response to bucindolol which did not translate into a survival benefit as it did (by 30%) in α_{2c} wild type carriers.

Table 4. Relevant gene polymorphsims to β-blockers.

Gene	Polymorphisms studied	Type of alteration*
ADRB1	Arg389Gly; Ser49Gly	Pharmacodynamic
ADRB2	Arg16Gly; Glu27Gln	Pharmacodynamic
CYP2D6 (eg, metoprolol, carvedilol)		Pharmacokinetic

Notes: *Pharmaco-kinetics is defined as what the body does to the drug; pharmaco-dynamics is defined as what the drug does to the body.

of the ADRB1 gene occur more frequently in African Americans than Caucasians.[29] The distribution of the Arg389 allele of the β-1 adrenergenic receptor also appears to vary based on ethnicity; Chinese (74%), Caucasians (72%), Hispanics (67%) and African-Americans (58%).[30] In vitro, these polymorphisms have been shown to affect the function of the receptor as well as its cell signaling.[31,32] Specifically, data demonstrated that the wild type 389Arg and 49Ser alleles to be associated with increased in-vitro activity. These observations suggest that patients with certain allelic variants of the β-1 adrenergic receptor (ADRB1) would have a superior help prevent adverse cardiac remodeling, but possibly harmful to patients with extremely severe cardiac dysfunction that are likely to be dependent on adrenergic support.[2]

ADRB1 polymorphisms

In both animal models[33] and healthy African American subjects[34] with the 389Arg phenotype showed a greater reduction in left ventricular diameter and improvement in left ventricular ejection fraction. Heart failure subjects with the 49Ser genotype have a higher mortality rate as compared to the 49Gly genotype; however, the use of β-blocker therapy has shown to mitigate this difference.[35] Retrospective analysis of BEST data identified that patients with the arginine, rather than glycine, phenotype of β-1-Arg-389 exhibit a superior norepinephrine lowering response to bucindolol therapy.[36] Large reductions in norepinephrine have been associated with increased mortality rates probably due to those with worst cardiac function being most reliant on adrenergic drive for the maintenance of cardiac pump function and hemodynamics.[2] Moreover the arginine phenotype has been reported to be less prevalent in non-Caucasian patients and may therefore explain why a sub-analysis of BEST data, with 100% Caucasian patients, produced a significant all-cause mortality benefit with a HR of 0.77 (95% CI = 0.65 to 0.92; $P = 0.004$).[37] Cruikshank[2] argues racial differences in polymorphisms do not explain the non-significant mortality data from BEST as a sub-study of the MERIT-HF trial found no association between heart failure outcome or response to β-blocker therapy (metoprolol) and the Arg389 genotype.[38] However, Domanski's (2003) comparison of a sub-analysis of 1668 BEST patients, together with the results from three other β-blocker trials, showed an all-cause mortality benefit with bucindolol therapy when African Americans were removed from the analysis.[37] This latter study is difficult to interpret because statistical analysis of interaction between ADRB1 genotype and treatment and their association with the outcome was not included in the publication. Another study of 637 patients with heart failure enrolled in registries found no association between β-receptor genotypes and survival in heart failure with sustained-release metoprolol and carvedilol therapy.[39]

Pre-junctional adrenergenic receptor variants

The regulation of cardiac adrenergic activity is complex and involves mechanisms modulating central sympathetic outflow, norepinephrine neuronal synthesis, pre-junctional norepinephrine release, and neuronal reuptake of norepinephrine.[40] Adrenergic activity is also likely to be influenced by genetic variation, particularly in adrenergic receptors (ARs) that regulate norepinephrine release, such as the α2C-AR, which is present in the pre-junctional adrenergic nerve terminals where it provides tonic inhibition of norepinephrine release.[41] Recent work on pre-junctional adrenergenic receptors reported that patients who were 2C Del322-325 carriers (heterozygotes or homozygotes) exhibited a much greater ISA response to bucindolol.[42] The same authors also showed decreased norepinephrine activity at 3 months compared with placebo patients of 2C wild type (standard or common type).[42] A genetic sub-study of BEST (n = 1040) evaluated the association between the

ADRB1 Arg-389Gly and α2c Del322-325 polymorphisms and the effect on mortality with bucindolol therapy.[43] Subjects who were 389Arg homozygous had a statistically higher rate of overall survival, with bucindolol. They also showed, reduced heart failure severity and cardiovascular re-hospitalization with bucindolol therapy. Conversely, subjects possessing the 389Gly allele had no response to bucindolol therapy, but nothing remarkable was attributed to the α2c Del322-325 polymorphism.[43] Prevalence of the α2c Del322-325 genetic variant is enriched in African-American populations, where it has an allele frequency of ~0.40 compared with ~0.04 in whites.[44] Based on animal observations that norepinephrine release by isolated atria is increased[41,45] it has been predicted that α2C Del322-325 variant in humans would be associated with increased systemic norepinephrine levels, particularly in situations such as heart failure where central sympathetic outflow is increased.[46] Indeed, there is evidence that the α2C Del322-325 polymorphism leads to an increased adrenergic activity in normal subjects,[34] however, there is conflicting experimental evidence that β-2-adrenoceptor polymorphisms significantly influence the relationship between heart rate and cardiac adrenergic drive in heart failure[39,47] and also whether this affects the rate of norepinephrine release from sympathetic nerve terminals.[48] As a result, norepinephrine levels may fall to levels below that which can support cardiac function, predisposing the patient to adverse events that neutralize the beneficial effects of β-blockade. On the other hand, when the major "wild type" allele is present in the homozygous state, bucindolol is likely to produce only mild and clinically beneficial degrees of norepinephrine lowering.

Safety

COPD patients

The use of β-blocker therapy in patients with chronic obstructive pulmonary disease (COPD) remains contentious. In a Cochrane systematic review, Salpeter et al found no evidence to suggest cardioselective β-blockers, given as a single dose or for longer duration, produced any change in forced expiratory volume over one second (FEV_1) or change in respiratory symptoms compared to placebo.[49] Furthermore the FEV_1 treatment response to β-2 agonist was not affected.[49] Moreover subgroup analysis revealed no change in results for those participants with severe COPD or for those with a reversible obstructive component. However the same author later suggested that the demonstrated benefit in heart failure, coronary artery disease and hypertension dictates that cardioselective β-blockers should not be routinely withheld from patients with COPD.[50] However β-2 agonist use in patients with COPD increases the risk for adverse cardiovascular events.[50] It is well known that β-2 agonists can induce tachycardia and hypokalemia. The benefits of β-blockade in COPD patients appear to outweigh any potential risk of side effects according to the available evidence.[51] It is reasonable to avoid bucindolol in elderly COPD patients due to the higher prevalence of CHF in these older patients.[52]

Gender

Data from BEST reports that prognostic predictive values of some variables differ in magnitude between women and men. The survival benefit in women is limited to those with heart failure due to a non-ischemic etiology.[53] However hormone replacement therapy is associated with a marked improvement in survival in postmenopausal women with advanced heart failure.[54]

Diabetes

There appears little direct evidence to suggest bucindolol blocks β-3 adrenergic receptors. It has been suggested that non-selective β-blockers may have a role in weight gain and metabolic changes that may adversely impact on heart failure in patients with diabetes.[2,55] A sub-analysis of BEST data reported that diabetes worsens the prognosis in advanced heart failure, an observation limited to those with ischemic cardiomyopathy.[56] Bucindolol may mask tachycardia and thus mask the symptoms of therapy induced hypoglycemia.[57] Evidence exists that carvedilol, may promote a better metabolic profile in those with diabetes compared to metoprolol.[58] Meta-analysis has shown that renin-angiotensin axis inhibitor agents may be preferable to β-Blockade in diabetics.[59] Although those with diabetes mellitus and heart failure appear to derive prognostic benefit from β-blocker therapy, the magnitude of that benefit is blunted compared to the non-diabetics.[60] Available evidence indicates that bucindolol is best avoided in the diabetics with heart failure due to ischemic etiology.

African Americans

Carvedilol should be preferred over bucindolol for the treatment of heart failure in African Americans based on the data from CAPRICORN[61] and BEST,[25] where the former showed benefit with the latter showing none.

NYHA class IV and elderly patients

Previous work has shown that only a small proportion of patients with decompensated heart failure are able to tolerate β-blocker therapy,[62] especially NYHA class IV.[63] Heart failure patients with contractile reserve tend to demonstrate lower baseline norepinephrine levels.[64] Those patients without a reasonable contractile reserve may not tolerate the significant fall in norepinephrine brought on by bucindolol. This fact may contribute to the higher mortality rates observed in the patient sub-set with extremely low ejection fraction and decompensation.[62,64] Combined data on NYHA class IV patients from MERIT-HF,[65] CIBIS-II[3] and CIBIS[66] show overall mortality benefits with β-blocker therapy.[67] These analyses also suggest the findings for bucindolol in class IV patients should not be generalized to all β-blockers and that an alternative β-blocker, should probably chosen for elderly heart failure patients.[68]

Heart failure with preserved ejection fraction

Up to half of all heart failure presentations have normal left ventricular ejection fraction (HFpEF).[69] Whilst β-blockade has been trialed in this patient subgroup, no randomized, controlled trial has demonstrated treatment benefits on mortality.[70] However, as patients with HFpEF are often older, improving symptoms (such as exercise tolerance) may present more appropriate and realistic outcomes. In a recent meta-analysis of therapy in HFpEF, β-blockade increased exercise capacity despite no improvement in diastolic function.[70] However, there have been no trials to date investigating the effects of bucindolol in HFpEF.

Drug metabolism and interactions

Bucindolol metabolism predominantly involves hepatic cytochrome P450 pathways.[7] Hence plasma levels of this drug may be affected by the concomitant use of other drugs that are metabolised by the same pathways. Bucindolol may blunt the response to other β- or α-adrenergic agonists.[71] Patients with severe renal impairment or hepatic dysfunction may need dose alteration.[71]

Dosing

In lieu of the risk of acute decompensation upon initiation of β-blocker therapy, bucindolol was titrated in the BEST study from an initial dose of 3 mg b.d.; up to a mean dose of about 75 mg b.d.[25] These doses were well tolerated in BEST and doses as high as 200 mg have been trialed with no adverse effects and low (circa 9%) dropout rates.[22] It has been suggested that if bucindolol were approved for use in heart failure a target dose of approximately 75 mg b.d. (the average value achieved in BEST) would be recommended.[57]

Adverse reactions

Significant adverse effects observed with bucindolol therapy include dizziness, diarrhea, hyperglycemia, bradycardia and intermittent claudication ($P < 0.05$). It is reasonable to assume that adverse effect profile of bucindolol to be similar to that of other β-blockers.

Efficacy

Bucindolol's suggested effects on ISA may present a likely explanation for the observed negative outcome in BEST.[28,72] A recent review suggested that the larger falls in norepinephrine were associated with higher mortality risk that is explained by the sympatholytic effect.[2] A neurohormonal sub-study of 206 BEST patients reported no change in serum brain natriuretic peptide levels following bucindolol therapy and this observation is consistent with the overall negative results in BEST.[73]

It should be noted that, in the BEST trial, a nominally significant interaction effect of therapy was found only for race (African American vs. Caucasian) ($\chi^2 = 5.06$; $P = 0.02$). The apparent effect of race and treatment is the lack of benefit observed in African Americans (HR for death with bucindolol versus placebo = 1.17; 95% CI = 0.89 to 1.53; $P = 0.27$), compared to the significant survival benefit seen in non-African Americans (HR = 0.82; 95% CI = 0.70 to 0.96; $P = 0.01$). The BEST trial demonstrated that bucindolol may not be beneficial to heart failure patients who are African Americans, with severe impairment of systolic function and who are decompensated.[2]

Place in therapy

The retrospective analyses of BEST data looked into the genetic factors that determined the response to bucindolol therapy. Currently genetic testing is being examined as a useful means whereby theraputic decisions could be made in relation to bucindolol. Bucindolol was reviewed by the Federal Drug Administration for the treatment of heart failure in 2009 and subsequently rejected.[74] Nevertheless a European regulatory authorisation was issued in October 2010 to ARCA biopharma, Inc., that allowed bucindolol therapy in heart failure, but only following genetic testing.[75] It is interesting to note that ADRB1 genotype is associated with varying response to bucindolol therapy in CHF, but not in metoprolol or carvedilol therapy. More work is required to further explore the genetic associations of the response to bucindolol therapy in heart failure. It is also important to examine the healthcare economic implications related to genetic testing prior to therapy if relevant.

Patient tolerence

Studies showed that bucindolol therapy was associated with an improvement in NYHA class with no corresponding improvement in exercise tolerance or oxygen utilization.[71] While peak VO_2 is considered a strong predictor of mortality in those with cardiomyopathy,[76] self-reported quality of life (QOL) measures have also been shown to predict mortality in BEST patients.[77] Two of the four QOL questionnaires used in the BEST analysis reported bucindolol treated patients had improved QOL at 12 months.[77] Patients treated with bucindolol experienced significantly less angina, tachycardia, insomnia, depression, palpitations and atrial fibrillation compared to those receiving placebo.[25] However, side-effects were more common, with significantly more dizziness, diarrhea, hyperglycemia, bradycardia, and intermittent claudication in the bucindolol arm.[57]

Conclusions

Bucindolol is a non-selective β-adrenergic receptor blocker, with α-1 blocker properties and mild ISA. The BEST study, which is the largest clinical trial of bucindolol in patients with CHF, was terminated prematurely and failed to show an overall mortality benefit. There were, however, observed benefits in cardiac mortality and re-hospitalization rates in the BEST trial. Bucindolol has not shown benefits in African Americans, those with significantly low ejection fraction and those in NYHA class IV heart failure. These observations could be due to the exaggerated sympatholytic response to bucindolol in these subgroups that may be mediated by genetic polymorphisms. In Europe bucindolol therapy is approved for heart failure therapy but only upon genetic testing. In light of this the healthcare economics implications of therapy with bucindolol remains yet to be studied. Given the mixed results from the various studies published hitherto, the precise role and the use of bucindolol in the management of heart failure remains ill defined, especially considering the effectiveness of current β-blockade and other therapies. Further studies and clinical trials based upon genetic testing are needed before we can clearly define the safety and efficacy of bucindolol in the management heart failure.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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