Beta-Blockers for Heart Failure: An Evidence based Review Answering Practical Therapeutic Questions

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SUMMARY

Beta-blockers are underutilised in heart failure because clinicians may be unsure whether all beta-blockers are useful, how therapy should be initiated and whether beta-blockers are contraindicated in some patients. Bisoprolol, carvedilol and metoprolol succinate have been clearly proven to reduce mortality and hospitalisation in patients with Class II to IV heart failure; limited evidence also support short-acting metoprolol tartrate and nebivolol. Initiating dose should be very low (1.25 mg bisoprolol, 3.125 mg carvedilol, 12.5 mg metoprolol succinate) and increased gradually over weeks. Treatment benefit appears proportional to magnitude of heart rate reduction and thus target dose should be the maximum tolerated for adequate bradycardia. Even in decompensated heart failure or those with coexisting bronchospasm, beta-blockers are not contraindicated although the dose may have to be reduced or withheld temporarily. The consistent trial data should reassure clinicians and encourage them to confidently initiate beta blockers in patients with systolic heart failure.

KEY WORDS:
Systolic heart failure, beta-blockers, practical therapeutics

INTRODUCTION

Although beta-blockers are recommended for treatment of systolic heart failure, many clinicians remain concerned about its use fearing clinical deterioration and worsening of heart failure from its negative inotrophic effect [1]. The aim of this review article is to analyse the trial data to answer practical question clinicians may face in using beta-blockers for heart failure.

MATERIALS AND METHODS

A PubMed Search was made of human studies, in English using the key words ("heart failure"[All Fields] OR "cardiac failure"[All Fields]) AND ("adrenergic beta-antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta-antagonists"[All Fields]) OR "adrenergic beta-antagonists"[All Fields] OR ("beta"[All Fields] AND "blocker"[All Fields]) OR "beta blocker"[All Fields] OR "adrenergic beta-antagonists"[Pharmacological Action]) AND (Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]). The search produces 287 abstracts, which were reviewed together with references from the guidelines on heart failure management of the American and European cardiovascular organisations. The methodology of major trials showing benefit from beta-blockers in heart failure were scrutinised to seek practical pointers on how beta-blockers were initiated, increased and maintained amongst their patients. We seek to answer three important questions based on a careful review of these landmark trials, namely i) which beta-blockers are useful in heart failure, ii) how should beta-blockers be initiated and iii) whether beta-blocker therapy is contraindicated in any particular patient group.

Which beta-blockers are useful in heart failure?

CIBIS-II showed that after a mean of 1.3 years, amongst 2647 patients with New York Heart Association (NYHA Class) III or IV heart failure and ejection fraction (EF) 35% or less, bisoprolol 1.25 - 10 mg daily reduced the primary end-point of all-cause mortality (HR 0.66, 95%CI 0.54-0.81, p<0.0001). Cardiovascular mortality (HR 0.71, 0.56-0.90, p=0.0049) and hospitalisation (HR 0.80, 0.71-0.91, p=0.0006) were also significantly reduced. In COPERNICUS, after 10.4 months amongst 2289 patients with EF under 25%, carvedilol 3.125 mg bd to 25 mg bd significantly reduced total death (HR 0.65, 0.52-0.81, p=0.0014). In MERIT-HF, after a year in 3991 patients with NYHA II to IV and EF 40% or less, metoprolol succinate 12.5 mg to 200 mg daily reduced total mortality or all-cause hospitalisation (HR 0.81, 0.73-0.90, p<0.001). Thus, these three beta-blockers, bisoprolol, carvedilol and metoprolol succinate, have been conclusively shown to reduce mortality and morbidity in patients with systolic heart failure [2,3,4].

However, it is clear that not all beta-blockers are equally effective in heart failure. In BEST, amongst 2708 patients in NYHA Class III or IV and EF 35% or lower, after an average of 2 years, there was no difference in total mortality between bucindolol and placebo (HR 0.90, 0.78-1.02, p=0.10) [5]. In the SENIORS trial, amongst 2128 patients above 70 years with prior heart failure hospitalisation or EF 35% and less, nebivolol 1.25 – 10 mg daily reduced the composite primary end-point of all cause mortality and cardiovascular hospitalisation (HR 0.86, 0.74-0.99; P=0.039)[6]. However despite a median follow up of 21 months, nebivolol did not successfully reduced total mortality amongst these elderly patients, unlike the impressive mortality reduction achieved by bisoprolol, carvedilol or metoprolol. Some retrospective analyses have suggested that heart failure patients on atenolol do as well as on metoprolol or carvedilol but in the absence

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of randomised controlled trials proving the efficacy of atenolol, it cannot be amongst the beta-blockers recommended for treatment of heart failure [7,8]. Based on the available evidence clinicians should presently only be using bisoprolol, carvedilol or metoprolol succinate in treating systolic heart failure.

Although carvedilol and metoprolol produces similar haemodynamic and heart rate effects, COMET suggests that carvedilol may be superior to metoprolol tartrate in extending survival [9,10]. In COMET, 3029 patients with NYHA II to IV and EF below 35% were randomised to carvedilol (targeting 25 mg bd) or metoprolol tartrate (targeting 50 mg bd). After 58 months, total mortality was significantly lower in the carvedilol arm (HR 0.83, 0.74-0.93, p=0.0017). Although metoprolol tartrate has been proven in randomised trials to exert a favourable effect on EF and haemodynamic data, there have been no randomised trials proving its value in reducing mortality and morbidity in heart failure [11,12]. Taken together with the results of COMET, presently only metroprolol succinate and not metoprolol tartrate is recommended for heart failure treatment by the professional guidelines committees [13, 14]. Debate has however erupted whether the dose of metoprolol tartrate chosen in COMET was inadequate since the heart rate of patients on metoprolol tartrate was significantly higher than those on carvedilol in the first 16 months of the trial [15,16]. The recent SHIFT study supports this contention that inadequate heart rate reduction with metorpolol tartrate explains the inferiority of metoprolol in COMET. In SHIFT, amongst 6558 patients with EF 35% or lower, after a median of 22.9 months, treatment with the heart rate reducing agent ivabradine reduced the composite of cardiovascular death and hospitalisation from heart failure (HR 0.82, 0.75-0.90, p<0.0001) [17]. An analysis of the SHIFT data confirms the importance of heart rate in deciding heart failure outcome with the primary outcome increasing by 16% for every 5 beat increase in the heart rate [18]. Since ivabradine has no neuro-hormonal effects, SHIFT raises a very interesting question whether the efficacy of beta-blockers in heart failure is due to its hormonal properties or negative chronotrophic effects [19]. It is thus important to seek the maximum tolerated dose of beta-blockers so as to achieve adequate heart rate reduction. In the major trials, bisoprolol was used up to 10 mg daily, carvedilol up to 25 mg bd, metoprolol succinate up to 200 mg daily, nebivolol up to 10 mg daily and metoprolol tartrate up to 150 mg daily in divided doses.

Since bisoprolol, carvedilol and metoprolol are now all available in the generic form, it is pertinent to ask whether generics are equivalent to the originals. In a comprehensive review of cardiovascular therapeutics, in all 9 randomised controlled trials where a generic beta-blocker was compared to its original, therapeutic clinical equivalence was demonstrated [20]. Thus, commercial claims that originals are better actually have little scientific justification [21].

How should beta-blockers be initiated?

In CIBIS II bisoprolol was initiated at 1.25 mg daily for a week then increased by 1.25 mg daily over a 4 week period to the highest tolerated dose. Although the maintenance daily dose of bisoprolol reached the targeted 10 mg in 43% of patients, fully a third (33%) was on less than 5 mg. In COPERNICUS carvedilol was initiated at 3.125 mg bd for 2 weeks, progressing every 2 weeks to 6.25 mg bd, then 12.5 mg bd before seeking the target dose of 25 mg bd. Mean daily dose of carvedilol was 37 mg, with 78% receiving the targeted dose. In MERIT-HF, metoprolol succinate was initiated at 12.5 mg daily and increased every 2 weeks to the target 200 mg daily. The target dose was reached in 64% of patients, and the mean maintenance dose was 159 mg daily. In COMET, carvedilol initiation regime followed that of COPERNICUS, while metoprolol tartrate was started at 5mg bd, and increased every 2 weeks to 12.5 mg bd, then 25 mg bd before targeting 50 mg bd. Only 75% of patients reached the targeted carvedilol dose, and 78% reached the targeted metoprolol dose. It is clear from the trials that initiation of beta-blockers in heart failure should follow the dictum 'start low, and go slow'. Patients must thus be carefully advised how to correctly divide the commercially available tablets which come in higher dose denominations.

Although evidence suggests that increasing beta-blockade is associated with increasing benefit, a significant number of heart failure patients will not be able to tolerate beta-blockers, at least on the first attempt [22]. In CIBIS II, 15% of patients randomised to bisoprolol had therapy withdrawn, in COPERNICUS the withdrawal rate from carvedilol after 1 year was 14.8%, and in MERIT-HF 9.8% of metoprolol patients experienced an adverse event leading to drug withdrawal [2,3,4]. These withdrawal rates are not higher than in the placebo arm but it is a reminder that even under the cautious setting of a clinical trial 10-15% of heart failure patients cannot be successfully put on beta-blockers. However, in a heart failure clinic beta-blocker non-tolerance is much higher with almost 40% of patients reportedly unable to tolerate either bisoprolol or carvedilol [23]. Since data is convincing that betablockers are useful in all classes of heart failure ranging from asymptomatic left ventricular dysfunction to decompensated heart failure, it is imperative that clinicians overcome their fear of betablocker use and strive to achieve the usage reported in the clinical trials [24-27]. Beta-blockers are not contraindicated even for patients with decompensated heart failure although treatment should be initiated after stabilisation of the patient, optimization of volume status and successful discontinuation of intravenous diuretics as well as inotropic support [28,29]. It is important to remember that whenever possible, beta-blockers should be initiated at a low dose prior to discharge of heart failure patients. Ultimately persistence, patience and confidence from the physician may be the key for successful initiation of betablockade in heart failure treatment.

The evidence on the importance of angiotensin-converting enzyme inhibitors (ACEI) in heart failure is overwhelming and in fact predates the more recently acquired data on beta-blockers [30]. Thus the question arises whether beta-blockers or ACEI should be started first in heart failure. CIBIS III randomised 1010 patients in NYHA Class II and III heart failure with EF 35% and below to initial monotherapy for 6 months with either bisoprolol (1.25 mg to 10 mg daily) or enalapril (2.5 mg bd to 10 mg bd), followed by combination therapy for 6 to 24 months with the primary end-point of all cause mortality or hospitalisation [31]. At the end of study

Table I: Practice recommendations

Bisoprolol, carvedilol and metoprolol have been proven to reduce mortality and hospitalisation in patients with Class II to IV systolic heart failure:	CLASS A
Beta blockers must be initiated in low doses- bisoprolol 1.25 mg daily, carvedilol 3.125 mg bd, metoprolol succinate 12.5 mg daily, navedilol 1.25 mg daily and metoprolol tartrate 5 mg bd. Dose should be increased gradually every fortnight to target a maximum of bisoprolol 10 mg daily, carvedilol 25 mg bd, metoprolol succinate 200 mg daily, navedilol 10 mg daily and metoprolol tartrate 150 mg in divided doses:	CLASS A
Benefit of treatment is proportional to degree of heart rate reduction:	CLASS A
Beta blockers are not contraindicated in patients with coexisting obstructive pulmonary disease or in decompensated acute heart failure:	CLASS A

Table II: Betablocker dosage regimen from the heart failure trials

Trial	Betablocker Used	Dose		
		Initial dose	Interval between dose increase	Maximum dose
CIBIS II	bisoprolol	1.25 mg dly	1 wk	10 mg dly
COPERNICUS	carvedilol	3.125 mg bd	2 wk	25 mg bd
MERIT-HF	metoprolol succinate	12.5 mg dly	2 wk	200 mg dly
MDC	metoprolol tartrate	5 mg bd	1 wk	75 mg
SENIORS	nebivolol	1.25 mg dly	1 wk	10 mg dly

Mg: milligram
Dly: once daily
Bd: twice daily
Wk: weeks

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period, similar outcomes were seen with either treatment for primary end-point (178 bisoprolol-first vs 186 enalapril-first, HR 0.94, 95%CI 0.77-1.16), all cause mortality (65 vs 73, HR 0.88, 0.63-1.22) and hospitalisation (151 vs 157, HR 0.95, 0.76-1.19). At the end of the initial 6 month period of monotherapy, there was also no difference between treatment groups in primary end-point (109 bisoprolol-first vs 108 enalapril-first, HR 1.02, 0.78-1.33, p=0.90), all-cause mortality (23 bisoprolol-first vs 32 enalapril-first, 0.72, 0.42-1.24, p=0.24) or hospitalisation (99 bisoprolol-first vs 92 enalapril-first, 1.08, 0.81-1.43, p=0.59). Although the methodology and results of CIBIS III have been the subject of robust debate, its overall message for practicing clinicians is that there is minimal difference in the benefit of ACEI and beta-blockers in heart failure; both should probably be started together in seeking maximum benefit for the patient [32-35].

Is beta-blocker therapy contraindicated in any patient group?

Given the bradyarrhythmic and hypotensive effects of beta-blockers, patients with heart rate less than 50-68 per min or systolic blood pressure (BP) less than 80-100 mm Hg were excluded from the major heart failure trials of beta-blockade [2-6]. In the light of recent evidence that mortality reduction in heart failure is directly proportional to heart rate reduction, clinicians should now be accepting of and aiming to reach lower heart rates with beta-blocker treatment [18,36]. However, the development of symptomatic bradycardia, second or third degree AV block and heart rate under 50 per min suggest the need to reduce or withhold beta-blockade [13,14]. It is being increasingly realised that BP continues to change throughout the day, with a single clinic measurement giving only an impression of the clinical state and risk for disease [37]. Just as hypertension management does not depend on a single measured BP level, clinical decisions on beta-blocker therapy in heart failure should not be held hostage to a single BP reading. Beta-blockers, diuretics and ACEI all reduce BP and as the BP drops, the clinician should be alert for clinical evidence of hypoperfusion such as postural dizziness or decreasing urine output. In practice, clinicians should look out for clinical hypoperfusion when systolic BP approaches 80-90 mm Hg in patients with heart failure. Dose adjustment, increasing interval between drugs or even stopping treatment may be necessary.

Patients with heart failure can have coexisting chronic obstructive pulmonary disease, and heart failure itself can present clinically with bronchospasm. Beta-blockers can worsen and precipitate bronchospasm and were once thought to be contraindicated in patients with chronic airway disease and asthma. However recent evidence suggest that betablockers are tolerated by these patients and so can be used in patients with heart failure and obstructive pulmonary disease [38,39,40]. In fact, there is reason to believe that

bronchospasm is worsened with excessive stimulation and sensitisation of the beta-2 receptor, and blocking these bronchial beta receptors may even be of therapeutic value [41]. Thus, like the situation with heart failure, beta-blockers which were initially contraindicated may in future have a therapeutic role in treating bronchial obstructive disease [42]. Nevertheless, the danger of worsening bronchospasm with a non-selective beta-blocker such as carvedilol is real, and is more worrying in patients with asthma who tend to have a higher degree of bronchial sensitivity and reactivity [43]. The practical clinical message is that beta-blockers are not contraindicated in patients with pulmonary airway obstructive disease, but must be used cautiously [44,45].

Betablocker treatment is associated with metabolic changes that adversely impact cardiovascular risk profile, and this has led to suggestions that beta-blockers should not be drugs of choice in hypertension since the metabolic adverse effects will cancel out the benefit of BP reduction [46,47,48]. Whatever theoretical debate academics may have on the effect of the adverse metabolic changes induced by betablockers, the fact remains that clinical trials have clearly established that beta-blockers reduce mortality and hospitalisation in patients with systolic heart failure. Thus, there can be no justification to fear betablocker use for these patients. Some clinicians are also under the impression that beta-blockers adversely impact quality of life, causing fatigue, sexual dysfunction and depression. Yet a formal review of data involving over 35,000 patients in 15 trials showed no significant increase in depression, with only small increases in fatigue (1 case per 57 patients treated per year) and sexual dysfunction (1 case per 199 patients treated per year) [49]. When quality of life has been formally assessed in heart failure trials, beta-blocker treatment was in fact shown to improve patient well-being [3, 50,51,52]. There is thus no reason to fear an adverse impact on quality of life amongst heart failure patients from beta-blocker treatment.

Clinicians frequently face the practical question whether patients with acute decompensated heart failure should have beta-blocker treatment stopped or deferred since its negative inotropic effect may worsen the acute state. The answer has now been conclusively obtained from the results of 4 studies [53-56]. B-CONVINCED showed that symptoms, length of hospitalisation and rehospitalisation rates were similar amongst those continuing with beta-blockers compared to those stopping treatment. Continuation of beta-blockers was also shown to result in lower mortality in OPTIMIZE-HF, COMET and in the Italian survey of Heart Failure Investigators. Thus beta blocker therapy should be continued in most patients experiencing a symptomatic exacerbation of heart failure although a temporary reduction of dose (generally by one half) may have to be considered. Abrupt discontinuation in patients with symptomatic exacerbation should be avoided, unless the situation is life-threatening with cardiogenic shock, refractory volume overload, or symptomatic bradycardia. If discontinued or reduced, beta blockers should be reinstated before the patient is discharged [29].

CONCLUSION

The objective of treatment is to reduce adverse clinical events, and recently we had to reassess treatment strategy when clinical trials showed that outcomes were not improved with more aggressive reduction of glucose, cholesterol or BP levels [57,58,59]. However, in the case of betablockers in systolic heart failure, trials have consistently shown that a reduction of mortality and hospitalisation. Yet actual utilisation rate lags far behind the tolerance rates in clinical trials. This review of the trial evidence seeks to answer practical therapeutic questions hindering the utilisation of beta-blockers. Beta-blockers should be initiated in low doses, and increased gradually over weeks. There is no dispute on the benefit of bisoprolol, carvedilol and metoprolol succinate. If short acting metoprolol tartrate is used, adequate doses up to 150 mg daily should be aimed for since treatment benefit appears proportional to heart rate reduction. Acute decompensated heart failure and bronchospasm do not automatically contraindicate beta-blockade, although caution and dose adjustment will be necessary. Beta-blockers should now be considered as important as ACEI in heart failure treatment. A confident approach amongst clinicians to beta-blocker use will see more patients benefit from this proven and inexpensive treatment strategy.

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