Tolerability of beta-blockers in heart failure: reassurance needed, reassurance provided

Henry Krum

NHMRC Centre of Clinical Research Excellence in Therapeutics, Departments of Medicine, Epidemiology and Preventive Medicine, Monash University Central and Eastern Clinical School, Alfred Hospital, Melbourne, Victoria, Australia

(Ital Heart J 2003; 4 (4): 225-227)

Received March 14, 2003;
accepted March 25, 2003.

Address:

Prof. Henry Krum,
MBBS, PhD, FRACP

*NHMRC CCRE in Therapeutics
Departments of Medicine, Epidemiology and Preventive Medicine
Monash University
Alfred Hospital
Commercial Road
Melbourne, Victoria 3004
Australia
E-mail: henry.krum@med.monash.edu.au*

Introduction

Beta-blockers are now well established agents of proven benefit in the treatment of systolic chronic heart failure (CHF). This is based on at least 5 major (> 1000 patients) placebo-controlled, double-blind trials of drugs within the beta-blocker class[1-5]. Meta-analysis of these trials, together with smaller trials (not necessarily powered individually for mortality) confirm the large and generally concordant mortality benefit observed within this class[6].

In addition to the mortality benefit observed with beta-blockers, there is also considerable evidence that these agents reduce all-cause hospitalization, hospitalization for heart failure and progression of heart failure as assessed by key surrogate markers of disease progression such as ventricular remodeling and neurohormonal profiling[7,8]. Based on the above, all current national CHF guidelines recommend the use of beta-blockers in patients with symptomatic systolic heart failure unless contraindicated or otherwise not tolerated.

Despite the above, there remains, even in 2003, considerable underutilization of these agents. This has been observed in a number of surveys including the CASE study[9] in Australia, EPICAL[10] in France and the most recent IMPROVEMENT[11] survey. These reports record utilization rates between 5-58% of eligible patients.

Perceptions regarding tolerability of beta-blockade in heart failure

The major cause for avoidance of commencement of beta-blockers relates to misconceptions regarding the tolerability of these agents. These concerns are understandable given traditional teaching of the importance of increased sympathetic drive in attempting to overcome systolic ventricular dysfunction in the setting of CHF. It is of course this sympathetic activation that is blocked by these agents.

Concerns regarding these agents in heart failure include perceived complexity in initiation and uptitration, risk of intolerance and worsening of heart failure symptom status with initiation, and perceived delay in beneficial effects on outcomes. All of the above are thought to be especially true in patients with advanced disease.

The reluctant physician in turn performs a number of manipulations to avoid the introduction of beta-blockers. These may include spending considerable time in "maximizing" the dose of ACE-inhibitors, adding an alternative therapy such as spironolactone and/or angiotensin receptor blocker (perceived to be easier to introduce) and/or "optimizing" patient volume status in order to best permit introduction of beta-blockers. Although these actions are all well intentioned, the net result is either a delay in the patient receiving beta-blockers or indeed the patient not receiving these agents at all.

In order to dispel these misconceptions, a large database of tolerability of beta-blockers within heart failure can be drawn on from a variety of sources. These include placebo-controlled clinical trials across a broad spectrum of heart failure severity, a large open-label registry experience from everyday clinical practice and, most recently, comprehensive analysis of the initiation process of beta-blockers within major trials.

Markers of tolerability of drug therapy

There are a number of generic markers of how well a patient is able to tolerate the introduction and maintenance of a prescribed drug. These include the adverse event profile, permanent treatment discontinuation rates, mean achieved dose in relation to the target dose of the drug, and the percent of patients reaching target dose.

Data from clinical trials

Tolerability in clinical trials based on percent drug discontinuation can be observed to be generally more favorable with the beta-blocking agent than with placebo in all of the major trials conducted[1-5]. Risk ratios ranged from 0.73-1.0 (Table I).

With regard to mean achieved dose in these trials, these have been found to be of the order of 80% or higher in relation to the target dose (Table II). To put this in perspective, the mean achieved dose in the ACE-inhibitor trials was of a lower percentage than this in relation to target dose; we must also remember that the beta-blocker trials were conducted on top of background ACE-inhibitor therapy.

Open-label experience

There also exists a large open-label experience, particularly with the agent carvedilol. In this experience, tolerability (defined as percent of patients remaining on therapy at the time of evaluation, and having been on therapy for at least 3 months) was between 69 and 95%[12,13]. Furthermore, the mean achieved dose amongst these patients was relatively high, being between 31 and 43 mg/day.

Whilst these data are not controlled, they are important because these represent the experiences of prescribers in everyday clinical practice, as distinct from the highly motivated investigators involved in clinical trial research programs.

Tolerability during initiation of therapy

The early initiation experience of two major trials has recently been reported.

Table II. Tolerability in clinical trials: mean achieved doses (mg/day).

Study	Drug	Target dose	Achieved dose
COPERNICUS[1]	Carvedilol	50	43
MERIT-HF[2]	Metoprolol	200	159
CIBIS-II[3]	Bisoprolol	10	8.6
BEST[4]	Bucindolol	100*	152
US Carvedilol[5]	Carvedilol	50**	45

* 200 mg in patients > 75 kg; ** 100 mg in patients > 85 kg.

In the MERIT-HF trial, there was a slight excess of discontinuations with metoprolol compared with placebo over the first 3 months of therapy, in contrast to slight fewer withdrawals with metoprolol by the end of the study[14]. This early excess of discontinuations was particularly prominent amongst the more advanced NYHA functional class III-IV patients. Therefore, these data supported the historical paradigm that there may be poorer tolerability during the initial phase of introduction of beta-blockers.

In contrast there was no early excess of permanent withdrawals with carvedilol within the COPERNICUS study, an overall more advanced group of heart failure patients[5]. Furthermore, this remained true even when a high-risk subset of 624 patients (with frequent or recurrent hospitalization, very low ejection fraction and/or need for intravenous therapy) were studied.

Further analysis has been made of the very early time points of uptitration of drug therapy, i.e. the first 8 weeks, within both trials[15,16].

In the MERIT-HF study there was a slight excess of permanent drug discontinuations, hospitalizations and deaths in the metoprolol group compared to placebo[15]. This excess began early and persisted through the 8-week period.

In contrast, there were overall fewer of these events in the carvedilol group, compared to placebo, in the COPERNICUS study during the first 8 weeks[16]. Kaplan-Meier plots reveal a divergence beginning around 2-4 weeks with fewer events on carvedilol therapy. Interestingly, this was particularly observed amongst the highest risk subset of patients. The point estimate for the relative risk of these early events, was similar to that observed for the overall study, suggesting that the well

Table I. Tolerability in clinical trials: percent drug discontinuation.

Study	No. patients	Average duration (months)	Discontinuation rate		
			Placebo	Beta-blocker	Risk ratio
COPERNICUS[1]	2289	10.4	11.3	9.5	0.84
MERIT-HF[2]	3991	12	15.3	13.9	0.90
CIBIS-II[3]	2647	15	15.0	15.0	1.0
BEST[4]	2708	24	25.0	23.0	0.92
US Carvedilol[5]	1094	6	7.8	5.7	0.73

demonstrated efficacy and safety of carvedilol over the entirety of the COPERNICUS study was similar to that of the first 8 weeks of therapy. Indeed, it could be argued that much of the benefit of beta-blocker therapy occurred early, which challenges the paradigm that there is a delay in benefit of beta-blocker therapy in advanced heart failure patients.

In support of this excellent tolerability during initiation of therapy, there were fewer adverse events and serious adverse events with carvedilol compared to placebo during the first 8 weeks, even amongst the highest risk subgroup of patients.

It is worth noting in particular, one such serious adverse event, that of worsening heart failure. This is perhaps the most feared of adverse events associated with introduction of beta-blockers in heart failure and was the only event to occur in more than 5% of patients. However, during the first 8 weeks of the COPERNICUS study, there were fewer rather than more worsening heart failure adverse events with carvedilol than placebo.

Summary

In contrast to widely held perceptions regarding tolerability of beta-blockers in heart failure, it is clear that initiation and uptitration is not as complex as perceived. In particular, there is no increased risk of intolerance and/or worsening of heart failure symptoms with initiation of beta-blocker therapy (at least as demonstrated by carvedilol in COPERNICUS). Furthermore, the perceived delay in beneficial effects on outcomes is perhaps challenged by the COPERNICUS study. Interestingly, all of the above observations appear to hold true in patients with advanced disease.

Because of the unique history of beta-blockers in systolic heart failure, physicians have needed particular reassurance regarding the tolerability of these agents. Reassurance regarding tolerability has now been definitively provided.

References

1. Packer M, Coats AJ, Fowler MB, et al, for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-8.
2. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA 2000; 283: 1295-302.
3. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9-13.
4. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344: 1659-67.
5. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334: 1349-55.
6. Meyer FP. Meta-analysis of beta-blockers in heart failure. Int J Clin Pharmacol Ther 2001; 39: 561-3.
7. Lee CR, Adams KF Jr, Patterson JH. Surrogate end points in heart failure. Ann Pharmacother 2002; 36: 479-88.
8. Massie B. Neurohormonal blockade in chronic heart failure. How much is enough? Can there be too much? J Am Coll Cardiol 2002; 39: 79-82.
9. Krum H, Tonkin AM, Currie R, Djundjek R, Johnston CI. Chronic heart failure in Australian general practice. The Cardiac Awareness Survey and Evaluation (CASE) Study. Med J Aust 2001; 174: 439-44.
10. Zannad F, Briancon S, Juilliere Y, et al. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL Study. Epidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine. J Am Coll Cardiol 1999; 33: 734-42.
11. Cleland JG, Cohen-Solal A, Aguilar JC, et al, for the IMPROVEMENT of Heart Failure Programme Committees and Investigators. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002; 360: 1631-9.
12. Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. Heart 2000; 84: 615-9.
13. Maggioni AP, Sinagra G, Opasich C, et al, for the Beta Blockers in Patients with Congestive Heart Failure: Guided Use in Clinical Practice Investigators. Treatment of chronic heart failure with beta adrenergic blockade beyond controlled clinical trials: the BRING-UP experience. Heart 2003; 89: 299-305.
14. Gottlieb SS, Fisher ML, Kjekshus J, et al, for the MERIT-HF Investigators. Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Circulation 2002; 105: 1182-8.
15. Gottlieb SS, Fisher ML, Kjekshus J, et al. MERIT-HF: tolerability of beta-blocker initiation NYHA II, III, and IV CHF. (abstr) Circulation 2000; 102 (Suppl II): II-778.
16. Krum H, Roecker EB, Mohacsi P, et al, for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS study. JAMA 2003; 289: 712-8.