

# Beta Blocker Therapy, Decompensated Heart Failure, and Inotropic Interactions: Current Perspectives

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**ABSTRACT:** Beta blockers are a fundamental treatment in chronic heart failure (HF), yet concern and disagreement regarding their role in the treatment of decompensated HF and during hospitalization are common in clinical practice. This review summarizes the literature on various aspects of beta blocker treatment during acute and chronic decompensated HF. In recent years evidence has accumulated concerning the efficacy and tolerability of beta blockers in decompensated HF. Clinical analyses show that withdrawal of chronic beta blockade should be avoided when possible during hospitalization and that beta blocker therapy be initiated as soon as hemodynamic stability and a euvoletic state are achieved. This strategy may increase adherence to beta blockers after discharge and lower rehospitalization and mortality rates. We also discuss the various positive inotrope regimens (phosphodiesterase inhibitors, levosimendan, dobutamine) and their interactions with beta blockers in decompensated HF.

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**KEY WORDS:** beta blockers, decompensated heart failure, inotropic therapy, hospitalization

In the past decade beta blocker drugs became the standard of care in the treatment of chronic heart failure. Various studies demonstrated major benefits of beta blockers for patients with stable chronic systolic HF; these include amelioration of symptoms, reverse remodeling, improvement in left ventricular systolic function, fewer hospitalizations and lower mortality rates – even in patients taking angiotensin-converting enzyme inhibitors [1-4]. Less information is available on the appropriateness of beta blockers for HF patients with preserved ejection fraction, since the evidence was based on small trials with inconclusive results and was not supported by multiple randomized controlled studies [5-9]. Currently, the American College of Cardiology and the

**Beta blockers should be initiated or continued in hospitalized acute systolic HF patients following hemodynamic stabilization, with adequate target organ perfusion and no contraindications such as shock, bradycardia, asthma or hypotension**

American Heart Association HF guidelines provide a class IIb indication (weak supportive evidence) for the use of beta blockers in the treatment of patients with HF and preserved systolic function [4].

In contrast to chronic HF, there are limited data on the efficacy and tolerability of beta blockers in severely symptomatic patients during hospitalization due to decompensation or acute HF. The dilemma whether to decrease or discontinue long-term beta blocker therapy, which has negative inotropic activity, during exacerbation of HF is a common clinical scenario. Furthermore, despite improvements in the treatment of HF, many patients deteriorate during decompensation and eventually require treatment with inotropic agents. The concomitant administration of inotropes and beta blockers may attenuate the desirable hemodynamic response to inotropic agents and this is also an issue in dispute [10].

The European Society of Cardiology/European Society of Intensive Care Medicine 2008 HF guidelines [Figure 1] referred to this topic when selecting common HF issues that suffered from a lack of evidence and warrant future clinical research [11]. Among them was the question “How should beta blocker treatment be managed in patients with acute decompensation of HF?” We review here the updated data on the management of beta blockers in acute and chronic decompensated HF and provide current perspectives on this issue.

## BETA BLOCKERS IN SEVERE HF

The heart in severe HF is adrenergically driven, increasing cardiac output in the short term but in the long term ultimately damaging the failing heart and resulting in reduced adrenergic signal transduction. Because of this dependence on adrenergic support, there was genuine concern that beta blockers may exert potential adverse effects in the short term and may not be tolerated in severe HF.

Macdonald and colleagues in 1999 [12] retrospectively assessed the tolerability and efficacy of carvedilol in patients with New York Heart Association functional class IV symptoms.

HF = heart failure

**Figure 1.** Current guidelines for beta blocker treatment in HF

**ACCF/AHA 2009 focused update for the management of heart failure**

- Beta blockers (bisoprolol, carvedilol and sustained-release metoprolol succinate) are recommended for stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (class I, level A)
- For patients with reduced ejection fraction experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with beta blocker therapy, it is recommended that these therapies be continued in the absence of hemodynamic instability or contraindications (class I, level C)
- For hospitalized HF patients with reduced ejection fraction not treated with beta blocker therapy, initiation of this therapy is recommended in stable patients prior to hospital discharge (class I, level B)
- Initiation of beta blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators and inotropic agents. Beta blockers should be started at a low dose and only in stable patients. Particular caution should be exerted when initiating beta blockers in patients who required inotropes during their hospital course (class I, level B)

**ESC/ESCIM 2008 guidelines for the diagnosis and treatment of acute and chronic heart failure**

- Beta blockers should be used in all patients with symptomatic HF and LVEF < 40%, unless contraindicated or not tolerated (class I, level A)
- For hospitalized patients, when possible, treatment with a beta blocker should be initiated cautiously before discharge (class I, level A)
- For patients admitted to hospital due to worsening HF, a reduction in the beta blocker dose may be necessary. In severe situations, temporary discontinuation can be considered. Low dose therapy should be reinstated and up-titrated as soon as the patient's clinical condition permits, preferably prior to discharge (class I, level A)

ACCF/AHA = American College of Cardiology Foundation/American Heart Association, LVEF = left ventricular ejection fraction, ESC/ESCIM = European Society of Cardiology/European Society of Intensive Care Medicine

In this study, NYHA class IV HF patients were more likely to develop adverse events during initiation and dose titration of carvedilol when compared with less symptomatic patients, but more likely to show symptomatic improvement in the long term. The authors concluded that carvedilol is useful in NYHA IV patients but requires close observation during initiation and dose titration of the drug. Of note, patients with cardiogenic shock and patients who required intravenous inotropic support were excluded from the study. There were similar findings in a sub-analysis of the FIRST study, which evaluated intravenous epoprostenol therapy versus conventional therapy alone in patients with advanced HF [13]. In that

**Routine withdrawal of beta blocker therapy in patients hospitalized for worsening HF due to left ventricular dysfunction should be avoided; if necessary, it should be resumed after euvoemia is attained and before discharge**

observational analysis, patients with NYHA class IIIb-IV who received beta blocker therapy had lower rates of hospitalization and were less likely to experience HF or death at 6 months follow-up than patients who were not treated with beta blockers.

Bouzamondo and co-authors [14] examined the potential relationship between the severity of HF and the benefits of beta blockers (bisoprolol, metoprolol, carvedilol). In their meta-analysis presented in 2003 they showed a similar reduction in mortality according to the severity of HF, evaluated in terms of NYHA class or left ventricular ejection fraction [14]. No heterogeneity in beta blocker benefit was observed according to the severity of HF. In 2003 Gardner and colleagues [15] presented a retrospective study on the effect of baseline beta blocker use in patients with advanced HF (85% NYHA III-IV) who were candidates for cardiac transplantation [15]. Patients not treated with beta blockers were five times more likely to die. The best prognostic predictors in this analysis were N terminal pro-B type natriuretic peptide serum levels, and lack of beta blocker treatment. Patients treated with a beta blocker had significantly lower NT-proBNP levels. The 2003 COPERNICUS study group assessed the effects of carvedilol in 2289 patients with symptomatic severe systolic HF who were clinically euvolemic [16]. Patients were randomly assigned to receive carvedilol, starting at a low dosage with gradual up-titration, or placebo. Patients on positive inotropic agents or those with low systolic blood pressure were excluded. Patients treated with carvedilol as compared to placebo had no cardiogenic shock, increase in pulmonary edema, or risk of worsening HF, and had lower death rates and fewer hospitalizations, as early as 2 to 3 weeks following initiation of treatment.

Thus, evidence from research conducted in the last decade demonstrates lower rehospitalization and mortality rates, not only in stable mild and moderate HF patients but also in symptomatic severe NYHA IV patients. However, it should be remembered that most of these trials excluded patients requiring inotropic therapy and those in cardiogenic shock, and that some of those patients with such advanced HF may not tolerate the initiation and up-titration of beta blockers.

**BETA BLOCKERS IN ACUTE DECOMPENSATED HF**

Despite the numerous benefits of beta blockade in the treatment of various severity levels of HF, for many years these drugs were under-prescribed in patients after HF hospitalizations. The under-use of beta blockers among HF patients was demonstrated in the ADHERE registry presented in 2004, suggesting that beta blockers were

NYHA = New York Heart Association

NT-proBNP = N terminal pro-B type natriuretic peptide

prescribed in only 47% of eligible patients at admission and 58% at discharge from hospital [17]. Similar results were observed in the national HF survey in Israel (HFSIS) [18]. Moreover, there is evidence that adherence to guidelines may improve clinical outcomes in patients with acute decompensated HF [19].

In recent years, as the evidence of efficacy accumulated, beta blocker therapy for HF became more widespread, and thus more patients hospitalized with exacerbation of HF are being admitted while receiving chronic beta blocker treatment. Therefore, the issue of how to handle beta blocker drugs during and after HF hospitalization is of increasing importance in current clinical practice.

The IMPACT-HF trial published in 2004 was a prospective study evaluating pre-discharge carvedilol initiation in stabilized patients hospitalized for HF, versus post-discharge (> 2 weeks) initiation at the physician's discretion [20]. Pre-discharge initiation of carvedilol enhanced the utilization of beta blockers at 60 days post-hospitalization (91% vs. 73%,  $P < 0.0001$ ), without increasing side effects or length of hospital stay. Thus, initiating therapy before hospital discharge may be an effective strategy to raise the adherence to beta blocker therapy.

Of note, patients presenting with low cardiac output states requiring inotropic support were excluded from this trial.

The OPTIME-CHF trial evaluated milrinone versus placebo in patients hospitalized for exacerbation of HF [21]. From their database, a non-randomized analysis was conducted in 2003 to determine clinical outcomes in patients treated with beta blockers at the time of hospital admission versus those who were not [21]. There was no difference in clinical events between the two groups. However, patients whose beta blocker treatment was discontinued had a higher risk of adverse outcome, suggesting that continuation of preexisting beta blocker treatment is not associated with increased risk of adverse clinical events during 2 months of follow-up, and that caution should be taken when withdrawing beta blockade in this population. The increase in mortality in patients discontinuing beta blocker treatment might have been related to a more severely ill population, but the baseline characteristics of the patients did not reflect a higher risk population. The authors suggested that the potential of adrenergic surge after beta blocker withdrawal is likely to be harmful in patients with decompensated HF.

Following the ESCAPE trial, which examined pulmonary artery catheter use among patients admitted with decompensated HF, the same investigators used the data in a retrospective sub-study published in 2006 in which they investigated the differences in clinical characteristics and outcomes of patients admitted to hospital with decompensated HF in whom beta blocker therapy was continued compared with those in whom it

was not [22]. Beta blockers were prescribed before admission to 268 of 432 patients (68%) in the ESCAPE trial, and 209 (79%) of them were discharged on beta blockers. Patients who were on beta blockers before admission had significantly shorter length of stay in hospital and a lower 6 month mortality rate (16% vs. 25%,  $P = 0.03$ ). Continuation of beta blocker therapy during hospitalization, even after adjusting for potential confounders, was associated with a lower mortality and rehospitalization rate 6 months after discharge (odds ratio 0.27, 95% confidence interval 0.1–0.71,  $P < 0.01$ ). The authors state that discontinuation of beta blocker therapy may be related to worsening HF or other medical conditions that may be responsible in part for their poor outcome. Patients in whom beta blockers were discontinued were more tachycardiac and tachypneic on admission, had lower ejection fraction, and were more likely to develop hypotension during hospitalization.

In a sub-study of the COMET trial published in 2007, the investigators examined the effect of changes in beta blocker dosage at the visit following hospitalization due to HF exacerbation compared to that administered before, and the subsequent outcomes [23]. Of the 752 patients taking beta blockers, the treatment was withdrawn in 8%, 22% had a

dose reduction, and 70% were maintained on the same dose. One and 2 year mortality rates were significantly lower in the group maintaining beta blocker dosage (hazard ratio 1.59, 95% CI 1.28–1.98,  $P < 0.001$ ) than the other two groups, and remained significant even after adjustment for baseline variables. Even reduction in the beta blocker dose was associated with an increase in mortality.

In OPTIMIZE-HF, the investigators conducted a sub-study using data from their large hospital-based registry; they examined the relationship between continuation or withdrawal of beta blockers and clinical outcomes in patients hospitalized due to new or worsening systolic HF [24]. Among the 2373 patients who were eligible for beta blockers at discharge, 57% were receiving beta blockers before admission and continued on therapy, 26.6% newly started during hospitalization, in 3.3% the therapy was withdrawn, and 12.8% were eligible for beta blockers but not treated. Continuation of beta blockers was associated with significantly lower adjusted post-discharge death (HR 0.6, 95% CI 0.37–0.99,  $P = 0.04$ ) and death or rehospitalization (OR 0.69, 95% CI 0.52–0.92,  $P = 0.01$ ) compared with lack of beta blockers. In contrast, withdrawal of beta blocker therapy was associated with worse adjusted risk for mortality. In addition, continuation of beta blockers was well tolerated after discharge, and the patients in whom the treatment was withdrawn during hospitalization were less likely to

### **Clinical evidence shows that these strategies increase adherence to beta blockers after discharge and reduce rehospitalization and mortality rates**

CI = confidence interval  
HR = hazard ratio  
OR = odds ratio

receive beta blockers after discharge. The authors stress that their results deal with “real world” patients in a usual care setting, different from prior analyses on selected patients enrolled in randomized clinical trials.

B-CONVINCED was the first prospective randomized trial to examine non-inferiority of the strategy of continuing versus discontinuing chronic beta blocker therapy during acute decompensation of systolic HF. In that 2009 study, Jondeau and colleagues [25] randomized 147 patients with acute decompensated HF to two arms of continuing versus stopping beta blockers. Inclusion criteria included hospitalization for acute HF with pulmonary edema and left ventricular ejection fraction less than 40% in the preceding year. It is important to note that patients with clinical indication for dobutamine were excluded (use of phosphodiesterase inhibitors was not a contraindication). After 3 and 8 days there was a nearly equal percentage (93% in the continuing group versus 92% in the discontinuing group) of patients with attenuated dyspnea and general well-being according to a physician blinded to therapy, indicating non-inferiority for continuation of beta blockers. Plasma B-type natriuretic peptide levels, length of hospital stay, rehospitalization rates and death rate after 3 months were also similar between the two groups. At 3 months after discharge beta blocker therapy was given to considerably more patients in the group who continued with beta blockers during hospitalization (90% vs. 76%,  $P < 0.05$ ). The authors concluded that during acute decompensated HF, continuation of beta blocker therapy is not associated with delayed or lesser improvement when dobutamine is not required, but with more chronic prescriptions of beta blockers after 3 months. The study population represented severe HF patients, with a mean age of 72 years, ejection fraction  $32\pm 7\%$ , mean BNP at entry  $> 1200$  pg/ml and rehospitalization rate of 40% at 3 months. However, patients requiring dobutamine were excluded from the study. Concerns were raised by other authors regarding the potential of selection bias in a non-inferiority trial, the small population size, the less severe clinical features of the study population, the relatively lower dosage of beta blockers used, and the under-representation of other populations with acute decompensated heart failure (hospitalization with pulmonary edema represents only 25% of this population) [26].

Overall, the accumulating aforementioned data indicate that continuation of beta blocker treatment during decompensation of HF is well tolerated at the time of hospitalization, increases drug adherence after discharge, and thus may prevent future adverse clinical events. Nevertheless, as mentioned above, caution should be exerted when up-titrating beta blocker dosage at the time of hemodynamic instability and

during concomitant dobutamine inotrope therapy, conditions that were an exclusion criterion in the above-cited literature.

### BETA BLOCKERS IN DECOMPENSATED HF PATIENTS ON INOTROPIC THERAPY

Decompensated states of HF may require short-term therapy with positive inotropic agents. These drugs may improve cardiac function in the acute phase and thereby stabilize the patient, but concomitantly may increase oxygen consumption, myocardial ischemia and cardiac arrhythmias. As pointed out earlier, as the number of patients with chronic HF increases so does the number of chronic HF patients receiving beta blocker therapy during episodes of hospitalization due to decompensated or acute HF. In those patients, the response to treatment with a positive inotropic agent may be blunted or unpredictable, and the action of beta agonists such as dobutamine and beta receptor-blocking agents may antagonize each other [27].

### DOBUTAMINE IN HF PATIENTS TREATED WITH BETA BLOCKERS

Dobutamine is an agonist for beta-1, beta-2 and alpha-1 receptors, enhancing production of cyclic adenosine monophosphate, and resulting in improvement in cardiac output and possibly slight reduction in systemic vascular resistance. High doses of beta blockers may inhibit the pharmacologic response to dobutamine. Non-selective beta adreno-receptor blockers (carvedilol) or beta-1 selective blockers (metoprolol) may respond differently to dobutamine. Metoprolol may be

**Patients treated with beta blockers before admission and requiring concomitant inotropic therapy should be preferably treated with a PDE III inhibitor or levosimendan rather than a beta adrenergic agonist such as dobutamine**

counteracted by dobutamine, whereas with carvedilol, a non-selective beta adrenoreceptor blocker, a low dose of dobutamine increases cardiac output slightly, and a higher dose causes a vasopressor effect without increasing cardiac output or stroke volume further, causing the hemodynamic effects of dobutamine to be less beneficial [28]. Accordingly, Triposkiadis et al. [29] demonstrated that in patients with exacerbation of systolic HF treated with low doses of carvedilol, the favorable hemodynamic effects of dobutamine are blunted, suggesting that alternative inotropic agents be used.

### PHOSPHODIESTERASE INHIBITORS VS. DOBUTAMINE IN HF PATIENTS RECEIVING BETA BLOCKERS

Milrinone and enoximone raise cyclic adenosine monophosphate through inhibition of phosphodiesterase III in the myocardium and vascular smooth muscle, thereby mediating positive inotropic and vasodilatoric activity. The rationale of combining these agents with beta blockers is that their site of action is beyond the beta-adrenergic receptor, such that PDE

BNP = B-type natriuretic peptide

PDE = phosphodiesterase

III inhibitors can retain their hemodynamic action in the presence of beta blockade. Moreover, beta blockers may reduce the adverse events of PDE III inhibitors by lowering heart rate and reducing their pro-arrhythmic effects.

Lowes and team [30] compared the efficacy of milrinone and dobutamine in patients chronically treated with carvedilol. In their small study population, the two intravenous agents exerted different hemodynamic effects. Milrinone increased cardiac index and decreased pulmonary capillary wedge pressure and arterial blood pressure, without altering heart rate. Dobutamine, in comparison, increased cardiac index only at high doses (15–20  $\mu$ /kg/min), resulting in increased heart rate, systemic pressure and mean pulmonary artery pressure. Metra et al. [31] compared the hemodynamic effects of dobutamine and enoximone before and after long-term beta blocker therapy with metoprolol or carvedilol in patients with chronic HF. Carvedilol, and to a lesser extent metoprolol, significantly inhibited the favorable hemodynamic response to dobutamine, while no such beta blocker-related amelioration of hemodynamic effects occurred with enoximone. Overall, these cumulative data support the use of PDE III inhibitors over dobutamine when an inotropic agent is needed for patients receiving beta blockers, especially carvedilol. It appears that combination therapy with a beta blocker and PDE III inhibitor in patients with advanced HF is well tolerated [32] and may attenuate the negative inotropic side effects of beta blockers on the one hand, and the long-term adverse effects of PDE inhibitors such as pro-arrhythmia on the other [33].

#### LEVOSIMENDAN VS. DOBUTAMINE IN HF PATIENTS RECEIVING BETA BLOCKERS

Intravenous levosimendan is increasingly used short term for acute decompensated HF states. It increases myocardial contractility via sensitization of cardiac troponin C to calcium, produces vasodilatation by opening ATP-sensitive potassium channels, and inhibits PDE III *in vitro*. Accordingly, it may increase cardiac output and decrease PCWP. The site of action of levosimendan is beyond the beta adrenergic receptor and is independent of the occupancy of the beta adrenergic receptors. Thus, there is potential benefit of combined therapy with beta blockers and levosimendan.

In the LIDO study, presented in 2002, the clinical effects of levosimendan were compared with those of dobutamine in severe low output HF. In a small subgroup analysis of this trial, the use of beta blockers lessened the effect of dobutamine on cardiac output and PCWP but did not reduce those hemodynamic effects when combined with levosimendan [34]. In 2009 the SURVIVE trial investigators presented a sub-hoc analysis assessing outcomes in 669 patients with acute decompensated HF who were treated with beta blocker therapy before receiving infusion of levosimendan or dobutamine [35]. Mortality

was significantly lower in the levosimendan group at day 5 (1.5% vs. 5.1% deaths, HR 0.29, CI 0.11–0.78,  $P = 0.01$ ), suggesting that levosimendan rather than dobutamine be considered as an appropriate treatment for acute decompensated HF in patients receiving chronic beta blockade therapy.

Bergh and co-researchers [36] recently compared the effects of levosimendan 24 hour infusion compared with 48 hours of dobutamine in acute decompensation of advanced NYHA III-IV HF patients receiving beta blocker therapy. Sixty patients were randomly allocated to each drug. Both drugs increased cardiac index and decreased PCWP. Similar hemodynamic improvement was seen during 24 hours, but at 48 hours levosimendan achieved significantly greater hemodynamic improvement (increased cardiac index and decreased PCWP) and neuro-hormonal improvement (reduction in BNP levels) than dobutamine. The authors noted that concomitant beta blocker may have diminished the effect of dobutamine therapy. Moreover, the formation of an active metabolite of levosimendan may probably account for the extended influence of this drug. Other small trials presented similar beneficial hemodynamic effects of levosimendan in comparison to dobutamine in patients with acute decompensated HF treated with beta blockers [37,38].

These trials on the effects of various inotropes and beta blocker combinations on decompensated HF were small-scale studies, most of them post-hoc analyses, and usually excluded patients with unstable clinical and hemodynamic conditions. Nevertheless, the evidence in the literature supports the use of intravenous PDE inhibitors or levosimendan over dobutamine treatment when considering inotropic therapy in decompensated HF patients treated concomitantly with beta blocker drugs.

#### SUMMARY

Beta blocking agents are well established in the treatment of advanced systolic HF. They have a proven role in severe stable HF and during hospitalization for decompensated HF. Evidence shows that withdrawal of chronic beta blockade should be avoided when possible during hospitalization in the absence of contraindications such as cardiogenic shock or symptomatic bradycardia. The initiation of beta blockers should be sought as soon as hemodynamic stability and euvolemic states are achieved, preferably before the patient leaves the hospital. Patients receiving beta blockers who need inotropic therapy should be preferably treated with PDE inhibitors or levosimendan, which do not interact directly with beta adrenergic receptors.

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PCWP = pulmonary capillary wedge pressure

References

1. 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.
2. CIBIS investigators and committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II). A randomised trial. *Lancet* 1999; 353: 9-13.
3. Packer M, Coats AJ, Fowler MB, et al. 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.
4. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119 (14): 1977-2016.
5. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction  $\geq$  40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol* 1997; 80: 207-9.
6. Dobre D, Van Veldhuisen DJ, DeJongste MJL, et al. Prescription of beta-blockers in patients with advanced heart failure and preserved ejection fraction. Clinical implications and survival. *Eur J Heart Fail* 2007; 9: 280-6.
7. Massie BM, Nelson JJ, Lukas MA, et al.; the COHERE Participant Physicians. Comparison of outcomes and usefulness of carvedilol across a spectrum of left ventricular ejection fractions in patients with heart failure in clinical practice. *Am J Cardiol* 2007; 99: 1263-8.
8. Flather MD, Shibata MC, Coats AJ, et al.; SENIORS investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; 26 (3): 215-25.
9. Paulus WJ. Novel strategies in diastolic heart failure. *Heart* 2010; 96: 1147-53.
10. Bristow MR, Shakar SF, Linseman JV, Lwes BD. Inotropes and beta-blockers: is there a need for new guidelines? *J Card Fail* 2001; 7 (2 Suppl 1): 8-12.
11. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29 (19): 2388-442.
12. Macdonald PS, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffery DJ. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J Am Coll Cardiol* 1999; 33: 924-31.
13. O'Connor CM, Gattis WA, Zannad F, et al. Beta-blocker therapy in advanced heart failure: clinical characteristics and long-term outcomes. *Eur J Heart Fail* 1999; 1: 81-8.
14. Bouzamondo A, Hulot JS, Sanchez P, Lechat P. Beta-blocker benefit according to severity of heart failure. *Eur J Heart Fail* 2003; 5: 281-9.
15. Gardner RS, Martin W, Carter R, McDonagh TA. Importance of beta blockade in the treatment of advanced heart failure. *Heart* 2003; 89: 1442-4.
16. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS study. *JAMA* 2003; 289: 712-18.
17. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 149 (2): 209-16.
18. Garty M, Shotan A, Gottlieb S, et al. The management, early and 1-year outcome in hospitalized patients with heart failure: a national heart failure survey in Israel - HFSIS. *IMAJ Isr Med Assoc J* 2007; 9: 227-33.
19. Braun E, Landsman K, Zuckerman R, Berger G, Meilik A, Azzam ZS. Adherence to guidelines improves the clinical outcome of patients with acutely decompensated heart failure. *IMAJ Isr Med Assoc J* 2009; 11: 348-53.
20. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghade M; the IMPACT-HF investigators and coordinators. Pre-discharge initiation of carvedilol in patients hospitalized for decompensated heart failure. *J Am Coll Cardiol* 2004; 43: 1534-41.
21. Gattis WA, O'Connor CM, Leimberger JD, Felker M, Adams KF, Gheorghade M. Clinical outcomes in patients on beta blocker therapy admitted with worsening chronic heart failure. *Am J Cardiol* 2003; 91: 169-74.
22. Butler J, Young JB, Abraham WT, et al. For the ESCAPE Investigators. Beta-blocker use and outcomes among hospitalized heart failure patients. *J Am Coll Cardiol* 2006; 47: 2462-9.
23. Metra M, Torp-Pedersen C, Cleland JGF, et al; the COMET investigators. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail* 2007; 9: 901-9.
24. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure. Findings from the OPTIMIZE-HF program. *J Am Coll Cardiol* 2008; 52: 190-9.
25. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker continuation vs. interruption in patients with congestive heart failure hospitalized for decompensation episode. *Eur Heart J* 2009; 30: 2186-92.
26. Swedberg K.  $\beta$ -Blockers in worsening heart failure: good or bad? *Eur Heart J* 2009; 30: 2177-9.
27. Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000; 23 (3 Suppl): 11-16.
28. Bollano E, Scharin TM, Hjalmarson A, Waagstein F, Andersson B. Different responses to dobutamine in the presence of carvedilol or metoprolol in patients with chronic heart failure. *Heart* 2003; 89: 621-4.
29. Triposkiadis F, Dalampiras P, Kelepeshis G, Skoularigis J, Sitafidis G. Hemodynamic effects of dobutamine in patients with exacerbation of chronic systolic heart failure treated with low doses of carvedilol. *Int J Clin Pharmacol Ther* 2008; 46: 136-9.
30. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone vs. dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001; 81: 141-9.
31. Metra M, Nodari S, D'Alòia S, et al. Beta blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoxamine before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002; 40: 1248-8.
32. Jennings DL, Thompson ML. Use of combination therapy with a beta-blocker and milrinone in patients with advanced heart failure. *Ann Pharmacother* 2009; 43 (11): 1872-6.
33. Shakar SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol* 1998; 31: 1336-40.
34. Follath F, Cleland JG, Just H, et al. Steering committee and investigators of the LIDO study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double-blind trial. *Lancet* 2002; 360: 196-202.
35. Mebazza A, Nieminen MS, Filippatos GS, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on  $\beta$ -blockers in SURVIVE. *Eur J Heart Fail* 2009; 11: 304-11.
36. Bergh CH, Andersson B, Dahlstrom U, et al. Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers. *Eur J Heart Fail* 2010; 12: 404-10.
37. Kirlidis TT, Skoularigis KT, Karayiannis G, Tsaknakis TK, Triposkiadis F. The influence of  $\beta$ -blockade on the hemodynamic effects of levosimendan in elderly ( $\geq$ 70 years) patients with acutely decompensated systolic heart failure. *Int J Clin Pharmacol Ther* 2009; 47: 454-9.
38. Duygu H, Turk U, Ozdogan O, et al. Levosimendan versus dobutamine in heart failure patients treated chronically with carvedilol. *Cardiovasc Ther* 2008; 26: 182-8.