Is There Evidence Favoring the Use of Beta-Blockers and Dobutamine in Acute Heart Failure?

Luiz Carlos Santana Passos, Andréa Cristina Costa Barbosa, Márcio Galvão Oliveira, Edval Gomes Santos Jr.
Programa de Pós-Graduação em Medicina e Saúde da Universidade Federal da Bahia, Salvador, BA – Brazil

Abstract

Several studies have reported the benefits of beta-blockers (BB) for patients presenting with systolic heart failure. however, many patients hospitalized as a result of acute heart failure are already using BB and require dobutamine for arterial hypotension and low cardiac output. Therefore, a decision must be made regarding whether BB should be maintained or even started in such cases. The aim of this study was to establish whether there is evidence supporting the safety andyeffectiveness of BB together with dobutamine for patients presenting with acute decompensated heart failure (ADHF). We conducted a search of the English-language literature in the databases MEDLINE, ISI Web of Science, Virtual Health Library, Cochrane Library and the CAPES Portal of Scientific Journals to identify related studies. Additional literature was obtained through the review of relevant references in the identified articles. The expected outcomes included information on the prognosis (in-hospital and on follow-up mortality, number of days of hospitalization and readmission),yeffectiveness and safety (worsening of symptoms, shock, intolerance) of the concomitant use of these drugs in hospitalized patients with ADHF and low cardiac output. This review included nine studies. however, no randomized clinical trials on this subject were found. Most studies include a low number of patients, and no studies addressing the safety of the concomitant use of these drugs were found. The resulting data suggest that a careful literature review did not supply evidence for the systematic use of BB in patients with low cardiac output syndrome who require dobutamine for inotropic support.

Introduction

Acute Heart Failure (AHF) is one of the main causes of hospitalization in adult[1,2]. Despite advancements in modern treatment, many patients progress to a potentially terminal phase of the disease, namely heart failure (HF) stage D, which comprises symptoms refractory to conventional treatmen[3,4]. In large case-series studies, approximately 20 - 30% of hospitalized patients required an intravenous inotropic agen[5-7]. In several Western countries, dobutamine is the most frequently used agen[8].

After several decades of clinical research resulted in conflicting data on the effectivenesy of beta-blockers (BB) in heart failur[9-13], clinical trials on the use of carvedilol, metoprolol and bisoprolol showed a remarkable reduction in mortality and hospitalization in patients with systolic H [14-18]. BBs are negative inotropic and chronotropic agents, whereas dobutamine is a positive inotropic drug with agonistic effects on the β1, β2 and (partially) α1 receptors in the hear[19]. Although they are physiologically incompatible, these agents have been used concomitantly in clinical practic[20-24]. Some studies suggest that carvedilol mightgdecrease the response to intravenous infusion of dobutamine. This interaction necessitates dosage increases to achieve significant effects in patients with chronic HF and continuing use of carvedilo[25, 26].

The first studies on BB in HF were restricted to compensated patients, who did not require additional or intravenous doses of diuretics. Recently, however, observational studies have suggested that the early introduction of BB might be safe in the short term and beneficial in the long ter[20, 24, 27-29].

In clinical practice, many patients admitted for AHF are already using BB. Under these circumstances, clinicians must decide whether to maintain or start BB in patients who still require an inotropic catecholamine agent to maintain an appropriate cardiac output.

The international guidelines regarding the use of BB in acute decompensation are conservative. They recommend discontinuation in cases requiring inotropic suppor[2, 30, 31]. Alternatively, the guidelines recommend against discontinuing BB whenever possible and favor dosage reductions even during the use of inotropic agents, especially dobutamin[8].

In this study, we performed a literature review to establish whether evidence supports the safety andyeffectiveness of the joint use of BB and dobutamine in this clinical setting.

Methods

The relevant studies were found by searching for original articles, clinical trials and observational studies in the following databases: MEDLINE, ISI Web of Science, Virtual Health Library (Biblioteca Virtual em Saúde – BVS; Brazilian Ministry of Health – MS), Cochrane Library and CAPES journals (Portal

Keywords

Heart Failure; cardiac output, low; adrenergic beta-agonists, therapeutic use; Dobutamine, therapeutic use.

Mailing Address: Luiz Carlos Passos •
Rua Waldemar Falcão, 870, 601 B, Candeal, Postal Code 40296-710, Salvador, BA – Brazil
E-mail: lcpassos@ufba.br
Manuscript received May 03, 2012; manuscript revised July 30, 2012; accepted July 30, 2012.

DOI: 10.5935/abc.20130034

periódicos CAPES). The latter is a database developed by the Brazilian government for researchers in Brazilian universities.

The following textual and MeSH search terms were used in different combinations: heart failure, beta-blocker, beta-blockade, adrenergic beta antagonist, carvedilol, inotropic agent, and dobutamine. The search was designed to select original clinical trials assessing the use of BB in patients with severe HF being treated with dobutamine. Expected outcomes included information on the prognosis (in-hospital and follow-up mortality, number of days of hospitalization and rehospitalization) and theyeffectiveness and safety (worsening of symptoms, shock or intolerance) of the concomitant use of these agents in hospitalized patients diagnosed with acute decompensated HF and low cardiac output.

The references in the located articles were searched manually to find further studies on this subject. Four independent researchers performed the review and subsequently selected the relevant articles. Data extraction was performed by two authors.

Inclusion criteria: Qualifying original studies were defined as clinical trials or observational studies on patients hospitalized for AHF and treated with dobutamine and BB and that contained information on the outcomes of interest.

Exclusion criteria: Studies that did not include information on the frequency of dobutamine and BB use and studies in languages other than English were not included.

Results

Selection and assessment of studies:

From 1173 citations identified in databases for inclusion in this systematic review, 54 were eligible (Figure 1). Of these, 13 were excluded because they were reviews, editorials or expert opinions. Two studies were excluded because milrinone was used together with BB; four studies were excluded because they performed echo stress test with dobutamine to assess viability in outpatients using BB; two studies were excluded because they were published only as abstracts in proceedings. Finally, one study was excluded because it addressed the use of medication in patients with postoperative low cardiac output syndrome. In a second round, thirty-two full-text articles were assessed for eligibility. Seven were excluded because they did not report on the frequency of BB and dobutamine use; and 15 were excluded because they did not describe the outcomes of interest. One study was excluded because it was written in French.

Nine studies were included in this review. The data in the included studies are summarized in Tables 1 and 2.

Overall summary of the main results:

• There is a small number of studies addressing the topic of interest;

• Most studies had a small n;

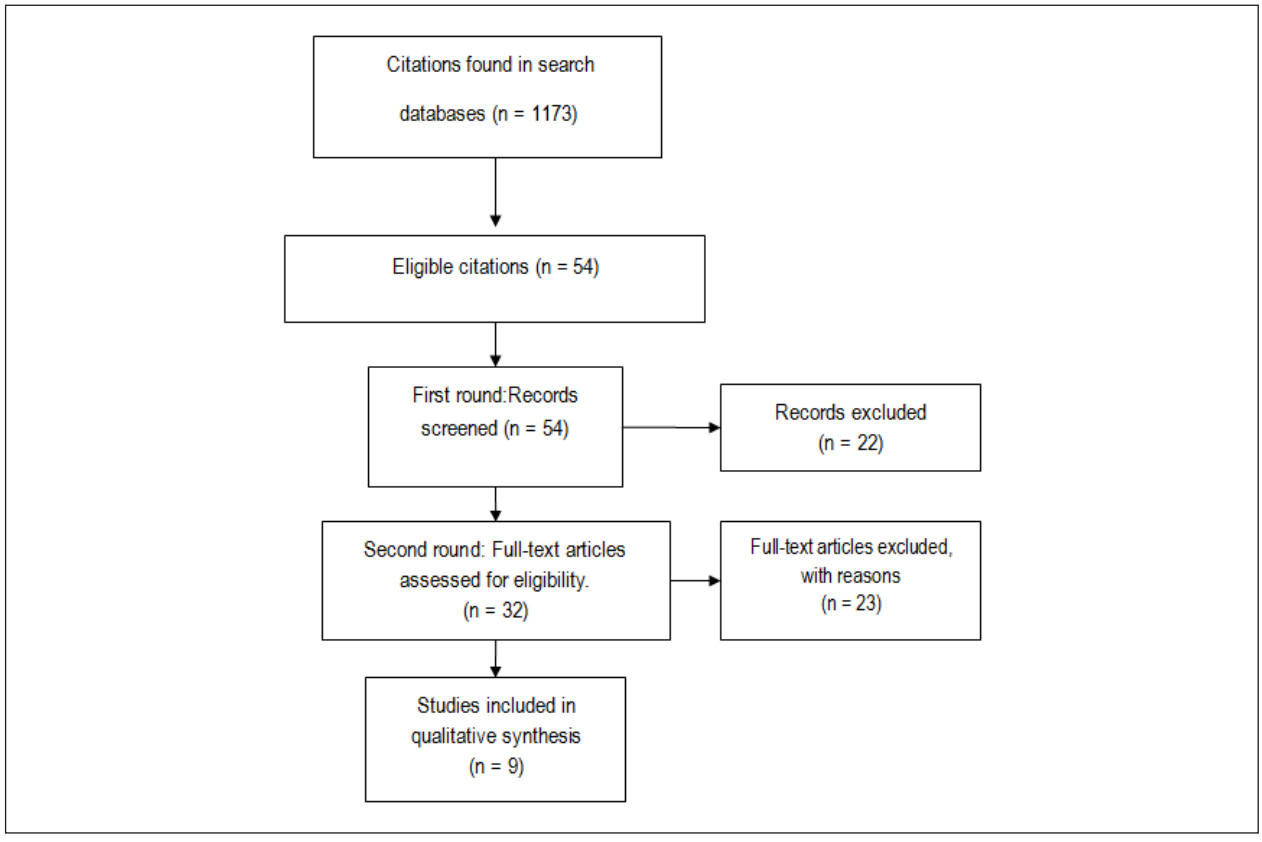

Figure 1 - *Flowchart of study.*

• No clinical trial was specifically designed to answer to the questions of interest (indirect data);

• No studies were found addressing the safety of the concomitant use of these drugs;

• Very heterogeneous population in regard to the inclusion criteria, nonrandomized selection of BB use, and few clinical outcomes of interest to perform summary-measures.

Discussion

None of the clinical studies on theyeffectiveness of BB in acute HF included patients with low cardiac output (SAP < 90 mmHg). Thus, IMPACT H[32], B-CONVINCE[33], COMET[34] and OPTIMIZE HF[35] were not included in this analysis.

Of 49 studies potentially eligible for analysis, only 9 included data on the use of BB and dobutamine, allowing assessing the outcomes of interest.

None of the nine studies assessed used an adequate approach to assess the safety and effectiveness of BB in patients using dobutamine. The direct assessment of this question requires a randomized, double-blind, controlled study comparing a group in which the use of BB is maintained while positive inotropic support is provided with a group in which BB is discontinued. Further assessments include the division of patients who require dobutamine and have no previous use of BB into two randomized groups, one in which BB is started, and a control group maintained without these drugs. Studies should focus on the following outcomes of interest: time of hospitalization, need to discontinue or reduce the dose of BB throughout the study, adverse events and mortality between groups and death or rehospitalization on follow-up.

Among the nine assessed studies, those by Lowes et al[25], Metra et al[36], Duygu et al[37], Bergh et al[38] and Triposkiadis et al[39] primarily assess short-term hemodynamic improvements by means of invasive or noninvasive measurements in patients who were using BB as well as dobutamine or another intravenous inotropic agent. Despite the small number of cases, these studies did not use controls (patients not using BB) to assess the hemodynamic effectiveness of the inotropic agents. Moreover, none included the group of major clinical interest, namely patients with formal indications for inotropic agents.

In the study LIDO[26], patients used dobutamine or levosimendan; 39% of patients in the dobutamine group used BB versus 37% of patients in the levosimendan group. The effects of dobutamine were attenuated by the use of BB. The hemodynamic improvement among BB users was greater in the levosimendan group than in the dobutamine group. Death occurred within 31 days in 8% of patients in the levosimendan group versus 17% of patients in the dobutamine group, and the three in-hospital deaths occurred in the dobutamine group. In general, these findings suggest that there are stronger interactions between BB and dobutamine than between BB and levosimendan. A discussion of the safety and adverse effects associated with the use of BB in the in-hospital phase is not possible because the low number of patients precludes a stratified analysis.

The study by Lima et al[40] more directly approaches the topic of this study. These authors report results in patients who did or did not use BB and who patently exhibited low cardiac output requiring the use of vasoactive amines. After performing a stratified analysis of BB use in each group, the authors conclude that continued use of BB did not result in worse progression of the disease. The main limitations of the Lima et al[40] study are that it comprises an observational cohort of surviving patients who were discharged from the hospital and that the choice to use BB or not was not based on explicit criteria, which probably allowed for the use of BB in less severely affected patients.

Triposkiadis et al.'s study[39] also addresses more directly the aim of this review; however, their assessment was restricted to patients in whom carvedilol exacerbated HF, while excluding patients using any other BB. Although all included patients used low doses of carvedilol, the study showed that the use of dobutamine was associated with a small increase in the left ventricular ejection fraction (1.5%) without alterations of the heart rate, arterial pressure, cardiac output or systemic vascular resistance. This study has severe limitations: the number of patients was small [31], randomization was not performed and the control group and the patients were not assessed blindly.

Mebazaa et al[41] and Bohm et al[42] performed randomized studies to compare two inotropic agents: levosimendan and dobutamine. It is worth noting that one of the limitations of the use of levosimendan is the hypotension occurring in patients with low cardiac output. Therefore, severely affected patients requiring a catecholamine inotropic agent were excluded from the study. In Mebazaa et al[41], 48% of patients were using BB at the time of randomization. These authors indicate a possible advantage of levosimendan over dobutamine regarding short-term mortality by all causes in patients with acute decompensated HF and previous HF who were treated with oral BB. This finding suggests that in patients with AHF and previous history of HF who use oral BB and in whom vasoactive amines are not formally indicated, levosimendan is preferable to dobutamine as an inotropic agent. This conclusion may be related to the potential for an undesirable interaction between BB and dobutamine.

Bohm et al study[42] is a secondary analysis of SURVIVE data with patients stratified by BB use. The patients were randomized for levosimendan or dobutamine use; thus, previous, in-hospital and post-discharge use of BB was not randomized. Moreover, patients who died during hospitalization, were hospitalized for more than 30 days or lost contact before follow-up (16.8% of the sample) were excluded from the analysis. These authors divided their population into four groups by BB use at admission and upon discharge. They concluded that patients who used BB at admission and continued this use after discharge exhibited higher survival rates at 31 and 180 days compared to the group that used BB neither at admission nor at discharge. These findings reinforce the idea that the patients who tolerate the use of BB, including during acute decompensation, potentially have better prognoses compared to patients that do not tolerate BB neither before nor during hospitalization (study groups no/no and yes/no).

Table 1 – Summary of studies that included patients using dobutamine and BB: Main question, study design, population and number of patients

Study (year) (reference)	Principal aim	Study design	Population	N (number of patients)
Lowes et al, 2001[25]	To compare the hemodynamic responses to milrinone and dobutamine in patients with HF FC II to IV who receive long-term treatment with carvedilol	2 prospective cohorts	Adults, FC II to IV, LVEF < 40%. All using carvedilol at a minimum dose of 25 mg/day for at least 3 months	11 milrinone cohort 9 dobutamine cohort
Follath et al, 2002 (LIDO Trial)[26]	To compare the hemodynamic and clinical responses to levosimendan or dobutamine in patients with low output HF	Multicenter, double-blind, randomized clinical trial. Post-hoc analysis.	Low-output HF in which hemodynamic monitoring and treatment with IV inotropic agent were needed. LVEF < 35%, CI < 2.5, PCWP > 15 mmHg ,> 21 a	203
Metra et al, 2002[36]	To compare the hemodynamic effects of dobutamine and enoximone before and after long-term treatment with metoprolol or carvedilol in patients with chronic HF	Prospective cohort	Patients in FC II to IV, LVEF ≤ 35%.	29
Duygu et al, 2008[37]	To compare the effects of dobutamine and levosimendan on the LV systolic and diastolic function in patients who receive long-term treatment with carvedilol	Randomized clinical trial	All patients with ischemic heart disease (CAD to heart catheterization), FC III-IV, presenting with symptoms despite treatment with diuretics IV and/or vasodilators, LVEF<40%, treatment with ACEI, furosemide and carvedilol maintained.	40
Triposkiadis et al, 2008[39]	To assess the hemodynamic effects of dobutamine in hospitalized patients in whom chronic HF is exacerbated and who had been using carvedilol	Quasi-experimental study	Patients with exacerbation of HF, ventricular ejection fraction ≤ 0.5 and systolic pressure between 85 and 110 mmHg	31
Mebazaa et al, 2009[41] (SURVIVE)	To assess the response to treatment (dobutamine vs. levosimendan) in patients in the SURVIVE study who have previously used BB	Multicenter, randomized, blind clinical trial. Post-hoc analysis	Hospitalized patients with acute HF who need inotropic support (unsatisfactory response to diuretics IV or vasodilators plus one of the following criteria: oliguria, dyspnea at rest or need of MV, Swan-Ganz hemodynamic parameters PCWP ≥ 18 and/or CI≤ 2.2)	1327
Bergh et al, 2010[38] (BEAT CHF trial)	To compare the effects of 24-hour infusion of levosimendan and 48-hour infusion of dobutamine on invasive hemodynamic variables between patients with acute HF who are receiving optimized treatment that includes BB.	Multicenter, double-blind clinical trial.	Age > 18, acute HF, in FC III-IV despite optimized clinical treatment including BB, on a stable regime for at least 3 months, on optimized doses of oral medication, might benefit from positive inotropic agents. LVEF ≤ 35%, with CI < 2.5 and PCWP > 15.FEVE ≤ 35%, com IC <2,5 e PCP> 15.	60
Lima et al, 2010[40]	To analyze prospectively whether the course of disease in patients using BB and dobutamine concomitantly differed from that in decompensated patients not using BB and patients who discontinued BB in favor of dobutamine.	Prospective cohort study (observational)	>18 years old, in FC IV, hospitalized due to acute HF, LVEF < 45%, using dobutamine (with signs of low cardiac output)	44
Böhm et al, 2011[42] (SURVIVE)	To assess whether starting or maintaining BB therapy during hospitalization influenced survival 31 or 180 days post-discharge.	Multicenter, randomized, double-blind clinical trial with active control. Post-hoc analysis of the group using BB.	Critical patients hospitalized for decompensated acute HF with signs of severe disease characterized by an unsatisfactory response to diuretics IV or to vasodilators plus one of the following signs: oliguria, dyspnea at rest or need of MV, hemodynamic decline in Swan-Ganz measurements (CI ≤ 2.2 and/or PCWP ≥ 18) with available information on the use of BB at admission and hospital discharge.	1104

HF: Heart failure; FC: Functional class; LV: Left ventricle; BB: Beta-blocker; LVEF: Left ventricular ejection fraction, ACEI: Angiotensin-converting enzyme inhibitor; MV: Mechanical ventilation; PCWP: Pulmonary capillary wedge pressure; CI: Cardiac index; CAD: Coronary artery disease.

Table 2 – Summary of studies that included patients who used dobutamine and BB: outcomes, main results and limitations of the studies

Study (year) (reference)	Outcomes	Main results	Study limitations
Lowes et al, 2001[25]	PO: Comparison of hemodynamic measurement (Swan-Ganz)	Improvement in cardiac output in both groups. The dobutamine group required high doses (20 µg/kg/min) to induce significant effects.	Use of inotropic drugs probably not indicated (FC II) Patients with SAP < 90 mmHg excluded Follow-up comprised 4 serial measurements during hospitalization.
Follath et al, 2002[26] (LIDO Trial)	PO: Proportion of patients showing hemodynamic improvement [CO (↑30%), PCWP (↓25%) in 24 h] Safety outcomes: spontaneous reports of adverse reactions, laboratory safety tests (blood and urine) and all-cause mortality at 31 and 180 days after randomization	A higher proportion of patients in the levosimendan group achieved hemodynamic improvement (28% vs. 15%) within 24 h (HR=1.9; 95%CI=1.1-3.3) In the BB users subgroup, hemodynamic improvement was observed in 10/33 (30.3%) of patients in the levosimendan group and in 3/29 (10.3%) of patients in the dobutamine group; p=0.056 The serum levels of creatinine and markers of liver dysfunction were lower in the levosimendan group. Adverse effects occurred in 47% of patients in the levosimendan group vs. 42% of patients in the dobutamine group. In-hospital deaths 3/203 (all in the dobutamine group) Deaths in the levosimendan group: 8% vs. 17% in the dobutamine group within 31 d	Death within 180 d was not assessed post-hoc, which is characteristic of short-term follow-up. Patients with SAP < 85 mmHg were excluded.
Metra M et al, 2002[36]	PO: hemodynamic variables (Swan-Ganz).	Long-term treatment with metoprolol or carvedilol was associated with significant improvements in symptoms, LV function and hemodynamic parameters. The type of BB used influenced the hemodynamic response to the investigated inotropic agents. The response to dobutamine was slightly affected by metoprolol and deeply depressed by carvedilol. The response to enoximone was not affected; in some cases, it improved with the use of both BBs. Hospital mortality: 5/34 (14.7%), from which 3 were sudden deaths (2 in metoprolol group and 1 in carvedilol group).	Use of inotropic drugs probably not indicated (FC II) All other cardiovascular medication was stopped at least 12 h before each hemodynamic study. No information is available on the management of or tolerance to BB throughout the study. Patients with advanced HF and unstable clinical conditions were excluded.
Duygu et al, 2008[37]	PO: echocardiographic variables at baseline and 24 h later (at the end of infusion). SO: clinical and hemodynamic variables 30-day follow-up.	In the dobutamine group, the echocardiographic parameters of systolic and diastolic function and of SPAP did not change. This group exhibited increases in heart rate, SAP and DAP. In the levosimendan group, LVEF and other parameters of systolic and diastolic function exhibited significant increases. No adverse effects were reported with the use of levosimendan or dobutamine. Patients using levosimendan exhibited significant improvement in FC (NYHA) after the end of infusion. The rate of death within 30 days was similar between groups (5% levosimendan vs. 10% dobutamine).	Patients with SAP < 85 mmHg were excluded. In-hospital mortality was not recorded. Noninvasive method for hemodynamic assessment. Small N.
Triposkiadis et al, 2008[39]	Hemodynamic measurements: ventricular ejection fraction, heart rate and cardiac output.	Dobutamine associated with increase of the ventricular ejection fraction (26.3±4.3% to 27.8±4.3%; P=0.05). Heart rate and cardiac output did not exhibit significant increases.	Patients using BB other than carvedilol were excluded. Small N. Assessment of intermediate outcomes. Lacking control group for comparison.
Mebazaa et al, 2009[41] (SURVIVE)	PO: all-cause mortality in 31 days.	664 randomized for levosimendan and 663 randomized for dobutamine. 669 using BB. 333 concomitantly using BB and dobutamine. The most frequently used BB was carvedilol (21%), followed by metoprolol (15%) and bisoprolol (12%). Patients using BB exhibited fewer adverse events in both treatment groups. In the subgroup with previous history of HF, all-cause mortality within 14 d was lower in the levosimendan group compared to the dobutamine group, with tendencies toward improvement at 5 and 31 d. Upon stratifying the population by use or nonuse of BB, BB users exhibited lower mortality in 5 days in the levosimendan group, but this benefit was not maintained at 14 or 31 d. In the levosimendan group, all-cause mortality was lower in patients with previous histories of HF and BB users compared to patients with previous histories of only HF or only BB at 5, 14 and 31 days Previous use of BB did not affect the HR, SAP or DAP response to any of the randomized drugs (levosimendan/dobutamine) in 5 days. There was no difference between BB users and nonusers in the dose and duration of treatment with levosimendan or dobutamine. A later study reported that at 180 days of follow-up, there were 173 (26%) deaths in the levosimendan group and 185 (28%) in the dobutamine group. This difference was not significant.	Post-hoc analysis at 5 and 14 days. Analysis of the SURVIVE subgroup. Previous use of BB was defined as the use of one dose of the drug within 24 h before IV infusion. Randomization was applied to levosimendan vs. dobutamine, but not to BB. Analysis of subgroup BB was performed later. In-hospital mortality was not reported (only data on sudden death and CPA). Small N to analyze sudden death among dobutamine users who used BB (2/233) or did not use BB (4/327). There is overlap between the groups with previous history of HF and previous use of BB. Nonuse of BB in this study might be associated with a more severely affected subgroup that did not tolerate the use of the drug. Onset or change in the dose of BB was not monitored after discharge. Whenever patients were rehospitalized due to decompensation, it was not required that they use the same randomized drug as in the first hospitalization. Users of BB exhibited a higher frequency of treatment with ACEI and more frequent non-ischemic etiology.

Continuation of Table 2

Bergh et al, 2010[38] (BEAT CHF trial)	PO: changes in hemodynamic variables (Swan-Ganz) CI, PCWP between baseline and 24 h after the onset of the drug infusion and comparison of changes between the treatment groups. SO: not directly reported – FC NYHA baseline and 1 month classified by the physician and the patient (7-point scale between markedly better and markedly worse), rehospitalization in 1 month, changes in the treatment with BB, and need of use of rescue medication or other interventions, measurement of BNP at baseline, 24 h, 48 h and 1 month. Randomization was stratified for treatment with carvedilol. One-month follow-up.	31 patients were using dobutamine. All patients were using BB. Both levosimendan and dobutamine induced hemodynamic improvement. Levosimendan induced significant improvement of CI and PCWP in 48 hours compared to dobutamine group, with tendency to improve in 24 h. There was no difference in the change in FC at 48-h and 1-month follow-up between groups. The improvement in symptoms reported by patients was similar in both groups. The improvement in fatigue and dyspnea reported by doctors was higher in the dobutamine group at 24 h and 48 h. There was no difference between groups regarding use of BB on follow-up, survival, rehospitalization, discontinuation of treatment or need to administer other drugs due to lack of effectiveness. 14 patients were rehospitalized (6 in the levosimendan group and 8 in the dobutamine group). The average percentage of change in the dose of BB between baseline and 1 month follow-up was 9.5% in the levosimendan group and 21.5% in the dobutamine group. This difference was not significant. There was significant reduction of BNP between baseline and 48 h in the levosimendan group. The profile of adverse events was similar in both groups except for hypotension and nausea, which were more frequent in the levosimendan group. SAP exhibited significant reduction in the levosimendan group during the first hours of infusion, but there was no significant difference compared to dobutamine at 48 h. Hospital mortality was 2/60 = 3% (1 in each group levosimendan vs. dobutamine). 1 patient in the levosimendan group died 3 days after the end of the study. 4 patients discontinued treatment in each group; the reason was adverse effects in 3 patients in the levosimendan group and 2 patients in the dobutamine group.	Subjective admission criteria (optimized doses of oral medication, according to the researcher's opinion, that might benefit from positive inotropic agents). Patients with SAP ≤ 85 mmHg were excluded. The dose of BB administered at the beginning of the study ought to be maintained as much as possible until the end of the study. The reasons to change the dose of BB were not informed. The study ended before the established number of participants was recruited. Patients were not randomized to receive or not receive BB. Despite stratification of randomization regarding treatment with carvedilol, there is no direct reference to the effects of stratification. Secondary outcomes not directly reported.
Lima et al, 2010[40]	Time of use of inotropic agent, number of hospitalization days, carvedilol dose upon discharge.	Division into 3 groups: A = 8 (did not use BB), B = 25 (BB was discontinued when starting dobutamine), C = 11 (used BB together with dobutamine). 81% of patients previously used BB (seemingly all used carvedilol). There was no difference between the baseline characteristics of groups. The time of hospitalization was high, however, without significant difference among the 3 groups. Mean among groups was 23 days (Group A 28 days, Group B 23 days, and Group C 20 days). Patients not using BB at admission required inotropic agent longer than patients in previous use of BB (Group A 15.4, Group B 8.4, and Group C 7.9 days). Dose of carvedilol upon discharge was higher in Group C compared to patients that discontinued or did not use BB.	Outcomes not clearly defined. The criteria used for nonuse or discontinuation of BB are not reported. Only 1 death is reported among a high risk population (not reported in the article but in an answer to a letter to the editor) – probable cohort of survivors Nonuse or discontinuation of BB might have been due to the severity of symptoms, and thus, patients who maintained BB might be a subgroup with better prognosis. Small N. The blood pressure levels are not reported. There was no statistically significant difference among groups for any outcome of interest (p-values > 0.05).
Böhm et al, 2011[42] (SURVIVE)	PO: all-cause mortality 180 days after treatment with levosimendan or dobutamine. SO: all-cause mortality in 31 days.	Division into 4 groups: yes/yes = 549 (using BB at admission and discharge), yes/no = 40 (received BB at admission but not upon discharge), no/yes = 256 (did not receive BB at admission but did upon discharge), and no/no (did not use BB at admission and discharge). In the group yes/yes, 270 used dobutamine (49.2%). Patients in the group yes/yes (use of BB at admission and discharge) had shorter hospitalizations (data not shown) and significantly higher odds of survival compared to the group no/no at 31 and 180 days. The mortality risk was higher in the group yes/no compared to the group yes/yes. The paired comparison showed that the non-adjusted mortality risk decreased by 77.4% in 31 days and by 53% in 180 days in the group yes/yes compared to the group no/no. When the mortality data were adjusted for age and comorbidities, this benefit was maintained (70% reduction in 31 d and 46% in 180 d). Patients in the group yes/no had higher mortality risks at 31 and 180 days compared to the group yes/yes in a non-adjusted analysis; however, an adjusted analysis showed no significant difference. The mortality risk in the group no/no was similar to that in the group yes/no. Group yes/yes exhibited lower mortality risk at 1 and 6 months compared to groups not using BB upon discharge (groups yes/no and no/no). When BB was introduced before discharge (no/yes), patients did not show survival benefits compared to patients who were not using BB upon discharge (groups yes/no and no/no). Hospital mortality was 142/1,327 (10.7%) – patients excluded from analysis.	Patients with the worst prognosis were excluded (patients hospitalized more than 30 days, died at initial hospitalization, lost for follow-up, or who retracted informed consent to SURVIVE study, 223/1,327 = 16.8%). Retrospective analysis of the subgroup of patients using BB. Patients with SAP < 85 mmHg were excluded. According to the clinical practice of the centers, BB were started, maintained, transiently interrupted or not interrupted, or reinstituted during hospitalization or upon discharge. The reasons were not recorded. Data on management of BB during hospitalization were not recorded (dose, treatment duration, use during hospitalization and changes in treatment between admission and discharge). Beta-blockers are described as a whole (whereas response might vary among BB). The author concludes that there was an association between BB discontinuation and worse prognosis; however, the group yes/no did not exhibit higher mortality risk in adjusted analysis compared to the group yes/yes.

PO: Primary outcome; SO: Secondary outcome; CO: Cardiac output; PCWP: Pulmonary capillary wedge pressure; BB: Beta-blocker; FC: Functional class; SAP: Systolic arterial pressure; SPAP: Systolic pulmonary artery pressure; CI: Cardiac index; NYHA: New York Heart Association; d: days; HR: Hazard ratio; DAP: Diastolic arterial pressure; CPA: Cardiopulmonary arrest; BNP: B-type natriuretic peptide.

The data described in the present study suggest that a careful literature review did not provide evidence supporting the systematic use of BB in patients with low cardiac output syndrome who require inotropic support in the form of dobutamine. The secondary results of SURVIVE[42] suggest that patients who have previously used BB and who may continue to use it during decompensation probably have less severe cases. Thus, they will potentially exhibit longer short-term survival. Concomitantly with the findings in LIDO, it might be inferred that patients who require inotropic agents but do not exhibit severe hypotension will benefit more from levosimendan than from dobutamine if they are using BB agents. Currently, very little may be concluded about the safety and effectiveness of starting BB therapy in patients with low cardiac output and arterial hypotension. This question represents a gap in knowledge about AHF management that should be filled soon by studies using the appropriate methods.

Conclusion

There are no conclusive evidence supporting the concomitant use of dobutamine and BB in patients with decompensated HF and low cardiac output.

Author contributions

Conception and design of the research: Passos LCS, Oliveira MG, Barbosa ACC; Acquisition of data, analysis and interpretation of the data and writing of the manuscript: Passos LCS, Oliveira MG, Barbosa ACC, Santos Jr. EG; Statistical analysis: Passos LCS, Barbosa ACC, Santos Jr. EG; Critical revision of the manuscript for intellectual content: Passos LCS, Barbosa ACC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Andréa Cristina Costa Barbosa, from Universidade Federal da Bahia.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De SG, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010;121(7):e46-e215.
2. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update: ACCFf/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.
3. Gheorghiade M, Filippatos GS, Felker GM. Diagnosis and management of acute heart failure syndromes. In: Bonow RO, Mann DL, Zipes DB, Libby P. (editors). Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders/Elsevier;2011. p. 517-39.
4. Bocchi EA, Marcondes-Braga FG, Ayub-Ferreira SM, Rohde LE, Oliveira WA, Almeida DR, et al.; Sociedade Brasileira de Cardiologia. III Diretriz brasileira de insuficiência cardíaca crônica. Arq Bras Cardiol. 2009;93(1 supl.1):1-71.
5. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol. 2005;46(1):57-64.
6. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725-36.
7. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, et al. Nationwide survey on acute heart failure in cardiology ward services in italy. Eur Heart J. 2006;27(10):1207-15.
8. Montera MW, Almeida RA, Tinoco EM, Rocha RM, Moura LZ, Réa-Neto A, et al.; Sociedade Brasileira de Cardiologia. II Diretriz brasileira de insuficiência cardíaca aguda. Arq Bras Cardiol. 2009;93(3 supl.3):1-65.
9. A randomized trial of beta-blockade in heart failure. The cardiac insufficiency bisoprolol study (CIBIS). CIBIS investigators and committees. Circulation. 1994;90(4):1765-73.
10. SoRelle R. Beta-blocker trials seem to be in conflict. Circulation. 2001;103(23):E9049-50.
11. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J. 1975;37(10):1022-36.
12. Talwar KK, Bhargava B, Upasani PT, Verma S, Kamlakar T, Chopra P. Hemodynamic predictors of early intolerance and long-term effects of propranolol in dilated cardiomyopathy. J Card Fail. 1996;2(4):273-7.
13. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659-67.
14. Effect of metoprolol cr/xl in chronic heart failure: Metoprolol cr/xl randomised intervention trial in congestive heart failure (merit-hf). Lancet. 1999;353(9169):2001-7.
15. Packer M, Bristow M, Cohn J, Colucci W, Fowler M, Gilbert E, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol heart failure study group. N Engl J Med. 1996;334(21):1349-55.
16. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194-9.
17. Packer M, Coats A, Fowler M, Katus H, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8.
18. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
19. Mann DL. Management of heart failure patients with reduced ejection fraction. In: Bonow RO, Mann DL, Zipes DB, Libby P, (editors). Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders/ Elsevier; 2011. p. 543-68.
20. Keller D, Carballo D, Garin N, Carballo S. [Beta-blocker therapy during acutely decompensated heart failure]. Rev Med Suisse. 2011;7(313):2035-6.

21. Yilmaz MB, Cohen-Solal A, Mebazaa A. Very early management of acute heart failure syndromes. Turk Kardiyol Dern Ars. 2011;39(5):427-32.

22. Salem R, Sibellas F, Socrates T, Arenja N, Yilmaz MB, Mueller C, et al. Novelties in the early management of acute heart failure syndromes. Swiss Med Wkly. 2010;140:w13031.

23. Omerovic E, Waagstein F, Swedberg K. Is levosimendan better than dobutamine in acute heart failure in patients on beta-blockade treatment? What is the evidence? Eur J Heart Fail. 2010;12(4):313-4.

24. Marcondes-Braga FG, Mangini S, Ayub-Ferreira SM, Bocchi EA, Bacal F. How to treat acute decompensated heart failure in the 'beta-blocker era'? Eur J Heart Fail. 2010;12(8):893-4.

25. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. Int J Cardiol. 2001;81(2-3):141-9.

26. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the lido study): A randomised double-blind trial. Lancet. 2002;360(9328):196-202.

27. Fares WH, Aneja A. Should beta-blockers be discontinued when a patient is admitted to the hospital with acutely decompensated heart failure? Cleve Clin J Med. 2006;73(6):557-9.

28. Bristow MR, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: is there a need for new guidelines? J Card Fail. 2001;7(2 Suppl. 1):8-12.

29. Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. Clin Cardiol. 2000;23(3 Suppl):III11-6.

30. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, 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 J Heart Fail. 2008;10(10):933-89.

31. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):e1-194.

32. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the initiation management predischarge: Process for assessment of carvedilol therapy in heart failure (impact-hf) trial. J Am Coll Cardiol. 2004;43(9):1534-41.

33. Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, et al. B-convinced: Beta-blocker continuation vs. Interruption in patients with congestive heart failure hospitalized for a decompensation episode. Eur Heart J. 2009;30(18):2186-92.

34. Metra M, Torp-Pedersen C, Cleland JG, Di LA, Komajda M, Remme WJ, et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. Eur J Heart Fail. 2007;9(9):901-9.

35. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, 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(3):190-9.

36. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol. 2002;40(7):1248-58.

37. Duygu H, Turk U, Ozdogan O, Akyuz S, Kirilmaz B, Alioglu E, et al. Levosimendan versus dobutamine in heart failure patients treated chronically with carvedilol. Cardiovasc Ther. 2008;26(3):182-8.

38. Bergh CH, Andersson B, Dahlstrom U, Forfang K, Kivikko M, Sarapohja T, et al. Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers. Eur J Heart Fail. 2010;12(4):404-10.

39. Triposkiadis F, Dalampiras P, Kelepeshis G, Skoularigis J, Sitafidis G. Hemodynamic effects of dobutamine in patients with an exacerbation of chronic systolic heart failure treated with low doses of carvedilol. Int J Clin Pharmacol Ther. 2008;46(3):136-9.

40. Lima MV, Cardoso JN, Ochiai ME, Grativvol KM, Grativvol PS, Brancalhao EC, et al. [Is it necessary to suspend betablockers in decompensated heart failure with low output?]. Arq Bras Cardiol. 2010;95(4):530-5.

41. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. Eur J Heart Fail. 2009;11(3):304-11.

42. Bohm M, Link A, Cai D, Nieminen MS, Filippatos GS, Salem R, et al. Beneficial association of beta-blocker therapy on recovery from severe acute heart failure treatment: data from the survival of patients with acute heart failure in need of intravenous inotropic support trial. Crit Care Med. 2011;39(5):940-4.