B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode

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Aims
Whether or not beta-blocker therapy should be stopped during acutely decompensated heart failure (ADHF) is unsure.

Methods and results
In a randomized, controlled, open labelled, non-inferiority trial, we compared beta-blockade continuation vs. discontinuation during ADHF in patients with LVEF below 40% previously receiving stable beta-blocker therapy. 169 patients were included, among which 147 were evaluable. Mean age was 72 ± 12 years, 65% were males. After 3 days, 92.8% of patients pursuing beta-blockade improved for both dyspnoea and general well-being according to a physician blinded for therapy vs. 92.3% of patients stopping beta-blocker. This was the main endpoint and the upper limit for unilateral 95% CI (6.6%) is lower that of the predefined upper limit (12.5%), indicating non-inferiority. Similar findings were obtained at 8 days and when evaluation was made by the patient. Plasma BNP at Day 3, length of hospital stay, re-hospitalization rate, and death rate after 3 months were also similar. Beta-blocker therapy at 3 months was given to 90% of patients vs. 76% (P < 0.05).

Conclusion
In conclusion, during ADHF, continuation of beta-blocker therapy is not associated with delayed or lesser improvement, but with a higher rate of chronic prescription of beta-blocker therapy after 3 months, the benefit of which is well established.

Keywords
Heart failure • Beta-blockade • Acute heart failure • Systolic dysfunction

Introduction
Beta-blockade is a good example of how medical progress can lead us to consider as necessary today what was previously considered as a danger. Because of their acute haemodynamic action, including negative inotropic effect, beta-blockers have been contra-indicated in patients with systolic heart failure for years. However, prospective randomized trials in patients with chronic systolic heart failure have consistently concluded that this therapy actually improves survival, quality of life, decreases hospitalization rate whatever the aetiology, the sex, associated therapy, and age.1–6

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Their initiation remains contra-indicated during acute heart failure with systolic dysfunction because of their acute negative inotropic effect.7 Effectively, cardiac output drops and left ventricular filling pressures increase after introduction of a beta-blocker in a patient with systolic heart failure.8,9 These effects are detrimental at a time when therapy is aiming to increase cardiac output and decrease filling pressure. It therefore appears logical to wonder what would be the best clinical practice in patients receiving a chronic beta-blocker therapy who are hospitalized for an acute heart failure with systolic dysfunction.7 In the absence of random-ized trial, the recommendations from the ESC are not clear cut and recognize that dosage in beta-blocker therapy may have to be decreased or stopped, but that the re-institution of the therapy should be as rapid as possible.

The present study compares the clinical evolution of patients who are hospitalized for an acute heart failure with systolic dysfunction (ejection fraction <40%), receiving a stable beta-blocker therapy for more than 1 month, randomized to pursue or stop the beta-blocker therapy on hospital admission.

Methods

Patients

Eligible patients were men and women aged 18 years or older, having received a beta-blocker therapy at a stable dosage for more than 1 month, hospitalized for acute heart failure with pulmonary oedema, including dyspnoea and pulmonary rales or radiological evidence of oedema. Respiratory rate had to be >24 min⁻¹ at some point during the acute heart failure episode prior to or at the time of inclusion. Left ventricular ejection fraction had to be measured within the preceding 12 months and be lower than 40%.

Exclusion criteria included acute ST elevation myocardial infarction, clinical indications for dobutamine according to the practicing physician within the preceding 12 months and be lower than 40%. Left ventricular ejection fraction had to be measured during the acute heart failure episode prior to or at the time of inclusion. Patients with systolic heart failure.8,9 These effects are detrimental to test differences in evolutions between groups. Death rate, re-hospitalization rate, and the percentage of patients receiving beta-blockers at 3 months were compared using the Fisher exact test.

Statistical analysis

The study aimed at demonstrating the non-inferiority of pursuing beta-blocker therapy compared with stopping beta-blocker therapy with regards to the percentage of patients with both improved general well-being and dyspnoea at 3 days, which was assumed to be of 90% in both treatment groups. As specified in the protocol, pursuing beta-blockers was considered non-inferior if the upper limit of the unilateral 95% confidence interval for the between-group absolute difference was <12.5%. To achieve a power of 80% to show non-inferiority in a per-protocol analysis, with a type-1 error probability of 5% (1-sided), 77 patients were needed in each group. Assuming that 5% of patients would be excluded from the per-protocol analysis, at least 162 patients were to be selected for randomization. The per-protocol sample was defined as all randomized patients, excluding those who would be random-ized to pursue beta-blocker and then stopped it for a reason other than an adverse effect or a worsening of heart failure.

The primary endpoint result is presented as the absolute difference between groups with the upper-limit of the unilateral 95% confidence interval. Deaths occurring within the first three days were treated as failure. The duration of hospital stay was compared using the Mann–Whitney test. Evolutions over time of blood pressure, respiratory rate, heart rate, and plasma BNP levels were studied using a linear mixed-model with a random subject effect and a group-by-time interaction term to test differences in evolutions between groups. Death rate, re-hospitalization rate, and the percentage of patients receiving beta-blockade at 3 months were compared using the Fisher exact test.

Since no patient stopped beta-blocker for a reason other than an adverse effect or a worsening of heart failure the per-protocol sample was identical to the intention-to-treat sample. All analyses were done with the SAS statistical software.

Results

Population

One hundred and sixty-nine patients were randomized. However, some patients could not be used in the statistical study due to: non-administration of the questionnaire (4 patients), questionnaire administered another day than Day 3 (15 patients), withdrawal of consent by the patient (1 patient), and an incomplete data set (2 patients). Therefore the analysis was performed on the remaining 147 patients. These patients were recruited through 28 active
centres of whom 12 included three-fourth of the population. Patients were randomized into two groups: keeping beta-blockade (group keep, n = 69) and stopping beta-blockade (group stop, n = 78) which were well balanced at baseline (Tables 1 and 2).

Mean age was 72.3 ± 11.9 years, 65% of the patients were male, 39.5% diabetics, 64.6% hypertensive. Aetiology of heart failure was reported as ischaemic by the investigator in 60.5% of the patients, either because of a previous myocardial infarction (27%) or a significant stenosis on coronary angiography (73%). Seventy-six percent of the patients had previously been hospitalized for heart failure (median 7 months prior to actual hospitalisation). Thirty-five percent of them have been hospitalized twice or more in the previous year.

Causes and precipitating factors of acute heart failure were lack of adherence to therapy (20%), infection (16%), myocardial ischaemia (14%), arrhythmias (12%), hypertensive crisis (9%), or undetermined (42%). The molecule of beta-blocker used was bisoprolol in 70% of the patients, carvedilol in 11%, and atenolol in 10%.

**Evolution during hospitalization**

**Evolution of therapy**

Beta-blocker therapy was initially pursued in the 69 patients from the ‘group keep’. The dose remained unchanged in all patients but four (in three it was decreased by half and in one it was doubled). Beta-blocker therapy was stopped later during hospitalization in four patients: three at the time of dobutamine introduction (one from Day 1 to Day 4; one from Day 3 to Day 5, one definitively at Day 4), one because of a bronchospasm at Day 2. The dose of beta-blocker therapy was increased during hospitalization in six patients, and decreased by half in one. Beta-blocker therapy was stopped at entry for at least 3 days in the 78 patients from the group stop. In 29%, the beta-blocker was started again before Day 8.

At the time of discharge or Day 8, angiotensin-converting enzyme inhibitors (ACE-I) had been stopped in 11 patients (5 in the ‘group keep’, 6 in the ‘group stop’), introduced in 17 (5 in the ‘group keep’, 12 in the ‘group stop’), and the dosage of ACE-I was increased in 22 patients (12 in the ‘group keep’, 10 in the ‘group stop’). At the time of discharge or Day 8, spironolactone had been stopped in three of the eight patients who received the drug at inclusion and was started in 10 additional patients (five in each group).

**Clinical evolution of the patient**

During hospitalization, clinical features of heart failure (dyspnoea, fatigue, pulmonary rales, lower limb oedema, jugular vein distension, hepatomegaly) decreased similarly in the two groups of patients as did blood pressure and respiratory rate. In contrast, the decrease in heart rate was lesser in the group stop (interaction time-by-group: \( P < 0.001 \); Figure 1). Interestingly, the heart rate at entry was similar in the two groups suggesting similar remaining beta-blockade at Day 0.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients demographics at baseline and therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Keep BB, n = 69</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.6 ± 12.2</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>41 (59)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>30 (43)</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>45 (65)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>32 (46)</td>
</tr>
<tr>
<td>Active, n (%)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Aetiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>39 (56)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>11 (28)</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>21 (30)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32 ± 6.9</td>
</tr>
</tbody>
</table>

| Treatment before decompensation, n (%) | BB, n (%) | 50%, patients receiving the recommended maximal dose of the beta-blocker; 50% < dose < 100%, patients receiving at least 50% but not the maximal dose; dose < 50%, patients receiving <50% of maximal recommended dosage. |
| BB, beta-blocker therapy; HTN, hypertension; MI, myocardial infarction; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; ACE-I, angiotensin converting enzyme inhibitor; Max dose, patients receiving the recommended maximal dose of the beta-blocker; 50% < dose < 100%, patients receiving at least 50% but not the maximal dose; dose < 50%, patients receiving <50% of maximal recommended dosage. |
| Max dose | 14 (20) | 21 (27) | 0.6 |
| 50% < Dose < 100% | 18 (26) | 17 (22) | 0.89 |
| Dose < 50% | 37 (54) | 40 (51) | 0.57 |
| ACE-I, n (%) | 45 (65) | 50 (64) | 0.76 |
| Diuretics, n (%) | 56 (81) | 66 (84) | 1.0 |

| Treatment during decompensation, n (%) | Diuretics | 69 (100) | 77 (99) | 0.11 |
| Nitrates | 35 (51) | 28 (36) |         |
Beta-blocker continuation vs. interruption

Endpoints of the study

After 3 days, improvements in both dyspnoea and general well-being according to a blinded investigator were observed in 92.8% of the patients from the ‘group keep’ vs. 92.3% of the patients from the ‘group stop’; the difference was −0.5% (unilateral 95% CI: −7.6 to 6.6%) in favour of pursuing beta-blockade. The upper limit of the unilateral 95% confidence interval of the difference was 6.6%, i.e. lower than the predefined limit (12.5%), indicating that the percentage of patients improved at 3 days was not decreased when beta-blocker therapy was not stopped. Actually, 12.5% was the upper limit of the 99.7% confidence limit, indicating a 0.3% risk of concluding wrongly at non-inferiority. If patients for whom questionnaire was given at Day 4 or 5 were also included in the analysis, 155 patients were included in the analysis, 80 in the ‘group stop’ of whom 92.5% improved and 75 in the ‘group keep’ of whom 93.3% improved. The difference was −0.8% (unilateral 95% CI: −8.0 to 6.0%) in favour of pursuing beta-blockade. The improvement of patients was not related to dosage of beta-blocker at entry.

Similarly, after 3 days, improvement was observed in 88.4% of the patients from the ‘group keep’ vs. 82.7% of the patients from the ‘group stop’ according to the patient. The upper limit of the unilateral 95% confidence interval was 3.8%, lower than 12.5%, indicating equivalence. After 8 days improvement was observed in 95.2 vs. 95.4% according to the blinded physician (upper limit of unilateral 95% CI 6.3), and 94.8 vs. 95.2% according to the patient (upper limit of unilateral 95% CI 6.9). Therefore continuing with beta-blocker therapy did not appear to induce any worsening of the patient at Day 3 or Day 8 according to both the physician and the patient. (Figure 2).

Plasma BNP levels significantly decreased from 1314 ± 1214 pg/mL at Day 0 to 882 ± 950 pg/mL at Day 3 in the ‘group keep’ and similarly from 1387 ± 1124 pg/mL to 876 ± 1382 pg/mL in the ‘group stop’ (NS between groups). At Day 8, BNP plasma levels were also similar in the two groups (865 ± 949 pg/mL vs. 765 ± 982 pg/mL, NS).

Three deaths occurred during hospitalization, all secondary to heart failure: one in a patient from the ‘group keep’ (Day 26) and two in patients from the ‘group stop’ (Day 1 and Day 3). The length of hospital stay was similar in the two groups (Table 3). After 3 months, death rate and re-hospitalization rate were also similar in the two groups (six deaths in both groups). Hospitalization for heart failure occurred in 22% of the patients from ‘group keep’ and 32% in the ‘group stop’.

The number of patients receiving beta-blockade 3 months after the acute heart failure episode was higher in the group of patients in whom beta-blocker therapy was not systematically stopped during the acute event (90 vs. 76%; P = 0.04). Overall, 19% of patients were receiving maximal dosage (26 vs. 11%, P = 0.04) and 51% (60 vs. 38%, P = 0.03) at least half the maximum recommended dosage.7

Discussion

This randomized study demonstrates that pursuing chronic beta-blocker therapy during acute decompensation in patients with systolic heart failure does not delay clinical improvement when dobutamine is not required. After both 3 and 8 days, the clinical improvement reported by both the physician and the patient was similar whether the beta-blocker therapy was pursued or discontinued.

There is no clear recommendations about management of patients with acutely decompensated heart failure treated with...

### Table 2  Clinical and biological features at baseline

<table>
<thead>
<tr>
<th></th>
<th>Keep BB, n = 69</th>
<th>Stop BB, n = 78</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sBP (mmHg)</td>
<td>127 ± 24</td>
<td>122 ± 20</td>
<td>0.26</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>71 ± 15</td>
<td>73 ± 14</td>
<td>0.51</td>
</tr>
<tr>
<td>HR (b.p.m.)</td>
<td>83 ± 17</td>
<td>81 ± 16</td>
<td>0.48</td>
</tr>
<tr>
<td>RR (b.p.m.)</td>
<td>25 ± 5</td>
<td>24 ± 5</td>
<td>0.17</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>94 ± 5</td>
<td>93 ± 5</td>
<td>0.46</td>
</tr>
<tr>
<td>Dyspnoea, n (%)</td>
<td>64 (93)</td>
<td>72 (92)</td>
<td>0.92</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td>65 (94)</td>
<td>73 (94)</td>
<td>0.88</td>
</tr>
<tr>
<td>Rales, n (%)</td>
<td>66 (96)</td>
<td>72 (92)</td>
<td>0.2</td>
</tr>
<tr>
<td>Oedema, n (%)</td>
<td>33 (48)</td>
<td>44 (56)</td>
<td>0.9</td>
</tr>
<tr>
<td>JVD, n (%)</td>
<td>33 (48)</td>
<td>38 (49)</td>
<td>0.9</td>
</tr>
<tr>
<td>Creatininemia</td>
<td>130 ± 61</td>
<td>134 ± 57</td>
<td>0.36</td>
</tr>
<tr>
<td>BNP (triage, pg/mL)</td>
<td>1387 ± 1124</td>
<td>1250 ± 1269</td>
<td>0.25</td>
</tr>
</tbody>
</table>

BB, beta-blocker therapy; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SaO₂, arterial O₂ saturation; JVD, jugular venous distension.

**Figure 1** Evolution of heart rate (top) and systolic and diastolic blood pressure (bottom) in the two groups. The ‘group keep’ is depicted in green, the ‘group stop’ in red. No difference in blood pressure (bottom) in the two groups. The ‘group keep’ is similarly from 1387 pg/mL at Day 0 to 949 pg/mL at Day 3 in the ‘group keep’ and 1124 pg/mL to 882 pg/mL in the ‘group stop’ (NS between groups). At Day 8, BNP plasma levels were also similar in the two groups (865 ± 949 pg/mL vs. 765 ± 982 pg/mL, NS).

Three deaths occurred during hospitalization, all secondary to heart failure: one in a patient from the ‘group keep’ (Day 26) and two in patients from the ‘group stop’ (Day 1 and Day 3). The length of hospital stay was similar in the two groups (Table 3). After 3 months, death rate and re-hospitalization rate were also similar in the two groups (six deaths in both groups). Hospitalization for heart failure occurred in 22% of the patients from ‘group keep’ and 32% in the ‘group stop’.

The number of patients receiving beta-blockade 3 months after the acute heart failure episode was higher in the group of patients in whom beta-blocker therapy was not systematically stopped during the acute event (90 vs. 76%; P = 0.04). Overall, 19% of patients were receiving maximal dosage (26 vs. 11%, P = 0.04) and 51% (60 vs. 38%, P = 0.03) at least half the maximum recommended dosage.7

**Figure 2**
beta-blocker: the ESC guidelines state that in patients admitted to hospital due to worsening heart failure, a reduction in the dose of beta-blocker may be necessary, and that in severe situations, temporary discontinuation can be considered; these recommendations are based on observational data and questions remain regarding the safety and efficacy of this approach. The negative inotropic action of beta-blocker therapy may be deleterious: cardiac output and blood pressure decrease and BNP plasma levels increase after the first use of beta-blockade. Besides, acute heart failure has been reported as a side effect during beta-blocker therapy initiation or after increases in dosage in patients with systolic heart failure. Finally, when the patient requires positive inotropic therapy, dobutamine effectiveness is altered by beta-blockade. One may therefore have feared that improvement of the patients during acute heart failure would be delayed, and dobutamine infusion ineffective if required in patients with acute heart failure pursuing beta-blockade. The safety issue was thus the first that needed evaluation: our results are clear in this setting as improvement in both dyspnoea and general well-being was similar in the two groups both from the physician and from the patient point of view, both after 3 and 8 days, as were similar the duration of hospital stay, the re-hospitalization rate at 3 months, and the death rate.

Also important is the fact that our population is representative of severe patients seen in clinical practice (age 72 ± 12 years, EF 32 ± 7%, mean plasma BNP at entry above 1200 pg/mL, re-hospitalization rate of 40% at 3 months), because adverse effects of beta-blocker therapy are more likely to occur in severe patients. Actually, re-admission rates similar or lower are reported in registries. This differentiates our population from that used in post hoc analysis of randomized trials of beta-blocker therapy which have included younger patients: as an example, in CIBIS 2 mean age was 61 years, 80% were males. However, a recent retrospective analysis of a large cohort of patients with acute heart failure included older patients and reported results similar to ours.

Once safety of beta-blockade continuation during acute decompensation of heart failure is established, one should prefer continuation of beta-blocker during the acute event. Our study was not powered to demonstrate a long-term clinical benefit of one strategy over the other, but strong indirect evidence already exists supporting this view. First, all published retrospective studies, either with data obtained from randomized trials or from registries, have unanimously indicated a better clinical evolution when beta-blocker therapy has not been stopped during hospitalization for acute heart failure. Limitations associated with non-randomized, retrospective studies are well recognized even when multivariate analyses are being performed to reduce the effect of the confounding prognostic factors, as beta-blocker therapy is usually stopped in the more severe patients with a worse prognosis. However, the positive result of our study supports the validity of these data.

Secondly, in contrast with the benefits of beta-blocker therapy during acute decompensation of heart failure, the benefits of chronic therapy are well established and beta-blockers are a mainstay of medical therapy in all recommendations. Although the prescription rate of beta-blockers is increasing over the successive registries published, it remains under-prescribed. Maintaining beta-blocker therapy during hospitalization is important in this setting, as prescribing a drug when a patient leaves the hospital is a main determinant of its chronic use. In fact, in our study, the number of patients receiving a beta-blocker after 3 months was lower in patients discontinuating beta-blocker therapy during the hospitalization (90 vs. 76%), despite the fact that hospitals participating in this study were all very aware of the importance of such chronic therapy, which is illustrated by the 29% of patients in whom beta-blocker therapy was re-initiated before discharge. Moreover non-stopping the beta-blocker during worsening phase may also improve the patient’s confidence in the drug benefits and will improve the observance of the treatment.

### Table 3 Clinical events

<table>
<thead>
<tr>
<th></th>
<th>Keep BB, n = 69</th>
<th>Stop BB, n = 78</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durations (days)</td>
<td>11.5 ± 8.3</td>
<td>10.4 ± 9.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Median, range</td>
<td>9 (1–50)</td>
<td>8 (1–62)</td>
<td></td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>1 (HF)</td>
<td>2 (HF)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine (n)</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>After 3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>6 (9)</td>
<td>6 (8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Rehospit, n (%)</td>
<td>27 (40)</td>
<td>36 (47)</td>
<td>0.43</td>
</tr>
<tr>
<td>For HF</td>
<td>15 (22)</td>
<td>24 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>For arrhythmia</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>1</td>
</tr>
<tr>
<td>Receiving BB, n (%)</td>
<td>61 (90)</td>
<td>58 (76)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Rehospit, rehospitalization; HF, heart failure; BB, beta-blocker.
Limitations of the study
This study was an open-labelled study, not powered to detect differences in hard endpoints such as death or hospitalization at 3 months which would have needed a much larger population. Also patients with indication of dobutamine infusion in the mind of the investigator were excluded from the study, as combining a beta-agonist with a beta-antagonist is illogical. Most of the patients were not receiving the maximum recommended dosage of beta-blocker (50% were receiving at least 50% of maximal recommended dose), and we did not collect the reason for not giving maximal dosage. Lastly, in the group of patients keeping the beta-blockade, the dosage was decreased by half in three, and had to be stopped during the course of the study in four because of dobutamine initiation or bronchospasm. However, the aim of our study was to validate the attitude consisting of pursuing beta-blocker therapy at entry, and individual adaptation of therapy according to clinical status remains necessary thereafter.

In conclusion, during acute heart failure, beta-blocker therapy should be continued in patients receiving the drug because this attitude is not associated with delayed or lesser improvement, but with a higher rate of prescription of beta-blocker therapy at 3 months, which benefit is well established.

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We want to thank Isabelle Brindel, head of project at the direction de recherche Clinique, Arnaud Keslick and Damien Vanhoye, research assistants from the URC Pitié Salpêtrière, without the enthusiasm of whom this study would not have been possible.

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Conflict of interest: none declared.

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