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EDITORIAL COMMENT

# Beta-Blockers in Acute Heart Failure

## Do They Cause Harm?*

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Within the last 40 years beta-blocker therapy status in chronic heart failure has changed from being the most hazardous drug to the most effective therapy. This has been a long journey, because it has been a long time from the first publication of Waagstein et al. (1) to the demonstration of benefit on mortality in double-blind randomized clinical trials (2-7). Moreover the prescription of beta-blockers in daily practice remains an issue because it is known from registries that beta-blockers are still the last drug introduced, the drug for which an increase in dosage is the most difficult so that dosage remains lower than recommended in daily practice (8,9).

This shift in paradigm was simultaneous with progress in the understanding of chronic heart failure. Initially viewed as a purely hemodynamic disease, it is now understood to be a disease in which activation of the deleterious neurohormonal systems and possibly inflammatory processes are responsible for a vicious circle leading to the progressive autoaggravation of the disease (10,11). In contrast, hemodynamic parameters remain the drivers during an acute event and it is in the acute setting that positive inotropic agents are still being used, whereas they have been abandoned in the chronic setting (the only exception is digoxin, the rate of prescription of which is slowly decreasing) (12). However, the benefit of the available positive inotropic agents is more and more questionable even in the setting of acute heart failure, whereas the deleterious side effects are becoming more convincingly demonstrated (13,14). The acute cessation of beta-blockers is physiologically close to inotropic support.

Acute heart failure may be responsible for various clinical presentations varying from cardiogenic shock to hypertensive pulmonary edema (15,16). Here we are speaking of patients with systolic dysfunction already established (and not "de novo" acute heart failure), who usually develop progressive worsening and global fluid overload, in contrast to patients with preserved ejection fraction and abrupt onset of dyspnea. Patients with heart failure related to systolic heart failure progress with repeated episodes of acute heart failure with inter-periods during which symptoms are more limited (17). Each episode of acute heart failure is associated with additional myocardial loss reflected by troponin release and alteration of the systolic function, and the role of beta-blockers is to prevent these events. The decrease in systolic function associated with the acute event is expected to be worsened by the use of positive inotropic agents, which increase oxygen demand of the myocardium. Furthermore, the acute arrhythmogenic risk is also to be integrated into the choice. Only in very severe patients, at the end of the evolution spectrum, may a positive inotropic agent really be required because of severe hypoperfusion related to altered inotropy.

The ACCF/AHA guidelines about management of heart failure accordingly consider that inotropic agents should be used (Class I or IIa) only in patients with cardiogenic shock until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, to maintain systemic perfusion and preserve end organ performance (Class I). Continuous intravenous inotropic support is said to be "reasonable" as "bridge therapy" in

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patients with stage D heart failure refractory to guideline-directed medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation (Class IIa) (17). Available inotropic agents have to be considered as the "last chance" drugs, to be used only when no alternative exists, when one agrees to pay the price of some myocardial loss, which probably impacts long-term survival.

Nevertheless, because inotropic state of the left ventricle is perceived as an important parameter in acute heart failure related to systolic dysfunction, pursuing beta-blocker therapy during the acute event may be suspected to be deleterious. This is especially true in severe patients, who actually most benefit from beta-blocker therapy (18). From a pharmacological point of view, stopping beta-blocker therapy during an acute heart failure episode in a patient who has been receiving this drug for a long period of time is not sound in most instances for several reasons beyond that already developed.

First, only if beta-blocker therapy has just been started or its dosage increased can the drug be held responsible for an acute event. However, if the beta-blocker is taken at a steady dosage for months, it cannot be held responsible for any acute heart failure episode, and it would be more effective and logical to focus on the event triggering the acute heart failure episode (e.g., infection, rhythm disturbance). Second, the beta-blockade remains for some time after drug withdrawal; the expected putative benefit of lessening the negative inotropic agent does not appear for a few hours (e.g., bisoprolol has a half-life of 11 h; carvedilol 6 to 10 h), and these first few hours are often the most critical in these patients.

Finally, after abruptly stopping beta-blocker therapy, a rebound may be observed after several days (i.e., a paradoxical activation of the sympathetic nervous system may occur) (19,20). Abrupt discontinuation of beta-blockade after long-term treatment can exacerbate angina and may increase the risk of sudden death (21-24). It is well established that there is enhanced sensitivity to beta-adrenergic agonists in patients who have undergone long-term treatment with certain beta-blockers after the blocker is withdrawn abruptly. For example, such enhanced sensitivity is evident several days after stopping propranolol and may persist for at least 1 week (25). It can be attenuated by tapering the dose of the beta-blocker before discontinuation (26). This has not been specifically studied in patients with heart failure but should also occur in this population. It would lead to increased sympathetic drive after a few days. The positive inotropic, chronotropic, and bathmotropic effects of the sympathetic drive at this time are probably deleterious, while not justified because the initial possibly critical period is usually over. Moreover, the more severe the patient is, the more benefit is expected from beta-blocker therapy and the more risk there probably is to stopping chronic beta-blocker therapy in this setting.

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The results of the meta-analysis reported by Prins et al. (27) in this issue of *JACC: Heart Failure* confirm the reality of these concepts. They report that, in case of hospitalization for acute heart failure, in-hospital mortality, short-term mortality, and combined mortality and hospitalization are lower when beta-blockers are maintained. These results are very important because the clinical problem is a frequent one. As the authors indicate in their discussion, the data available are not very rich with only 1 randomized study and 4 observational reports. Retrospective, observational reports should be considered with caution, and the randomized trial is of limited size. However, the strength of this report comes from the fact that all the studies indicate the same trend, suggesting lower mortality, in keeping with the pathophysiological concepts developed.

From a practical clinical point of view, stopping beta-blocker therapy in a patient with an altered ejection fraction also significantly complicates the care of the patient. There is no dispute that reintroducing a beta-blocker is necessary (17,28); however, the modality of this reintroduction would probably follow recommendations (i.e., it is unlikely that the full dosage would be obtained before the patient leaves the hospital); it is even probable that the drug will not be started during the same hospitalization in some patients. All registries repeatedly show that once the patient is out of the hospital, it is very difficult to start or increase the dosage of beta-blocker therapy (8,9). As an expected result, patients receive less beta-blocker at 3 months, which is deleterious for the patient (29).

Considering the available evidence, one could propose a practical scheme: When a positive inotropic agent is required (according to guidelines) during acute heart failure it is usually very early on, at a time when withdrawal of beta-blocker therapy is of no effect. In those patients not receiving an inotropic support, it is not founded to stop or decrease the protective drug, (i.e., beta-blocker therapy) because

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there is indication that this attitude is associated with increased mortality. This shift in practice is much less revolutionary than was that of introducing beta-blocker therapy in patients with chronic heart failure years ago.

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