Beta-Blockers in Congestive Heart Failure: the Evolution of a New Treatment Concept - Mechanisms of Action and Clinical Implications

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For a long time beta-blockers were considered contraindicated for use in heart failure although some experimental and clinical data already in the 1960s and 1970s suggested a beneficial role for beta-blockers in heart failure. Observations of good tolerability of i.v. beta-blockers in acute myocardial infarction and acute heart failure encouraged us to test beta-blockers also in chronic congestive heart failure. The accumulating knowledge of harmful effects from activated neurohormones and negative long-term effects by inotropic drugs eventually rendered the concept of beta-blocker treatment in heart failure more attractive. Beta-blockers are antiischaemic, antiproliferative, antiapoptotic, attenuate inflammatory cytokine, stabilise electrically unstable myocardium and reverse ventricular remodelling. Recent multicentre trials have definitely proved that beta-blockers reduce mortality and morbidity, are well tolerated and improve quality of life. Even in a subset of severe compensated heart failure beta-blockers have been shown to be safe and to reduce mortality and hospitalisation by 35–50% in addition to conventional heart failure treatment with diuretics, digitalis and ACE-inhibitors.

All patients with stable compensated systolic heart failure should therefore be challenged with a beta-blocker. Once stabilised on the beta-blocker most primary physicians would be able to be responsible for the long-term follow-up of these patients.

Key words: beta-blockers, congestive heart failure

In the early 1970s there were only few alternatives for the treatment of chronic congestive heart failure. Diuretics and digoxin were the only drugs available but worked only as symptomatic relief for the disease (Tab. 1). Spontaneous improvement was seldom seen except in acute onset of heart failure and the inevitable progression of disease was considered to be due to irreversible damage of the myocardium. The clinical presentation of heart failure was mostly regarded as a condition with fluid retention and therefore the aspect of sudden cardiac death was not acknowledged until later. Today we know from intervention studies that sudden cardiac death is the most common cause of death in mild and moderate heart failure NYHA classes II and III (Fig. 1) [1].

The fated conception regarding the inevitable poor prognosis in heart failure could be challenged already at that time due to the fact that several patients with severe congestive heart failure, mimicking dilated cardiomyopathy, after severe drinking, severe thiamine deficiency or during long-lasting tachycardia could undergo complete restitution after refrainment from alcohol, by vitamin B1-supplementation or ablation of the focus of arrhythmia.

Pacing induced heart failure in dogs was shown already by Whipple in 1962 [2]. In 1974 our group showed that chronic administration of noradrenaline could produce a cardiomyopathic condition in rats [3] (Fig. 2). These two findings linked high heart rate and high catecholamine levels to heart failure. During the 1960s there has been a debate whether high catecholamine levels in heart failure was 1.) a compensatory phenomenon necessary to maintain the haemodynamic homeostasis in the failing heart [4, 5] or 2.) a potentially harmful condition which could increase the metabolic burden.
The Clinical Background for the Use of Beta-Blockade in Congestive Heart Failure in Man

In 1971, when we introduced intravenous treatment with beta-blockers in the acute phase of transmural myocardial infarction with severe chest pain three important phenomena were observed. 1.) The chest pain score was markedly reduced almost equipotent with morphine, 2.) ST-segment elevation was significantly reduced which was not seen by saline or morphine, and later confirmed in a bigger study [8–11], 3.) approximately 20% of the patients had basal lung rales indicating pulmonary congestion suggestive of acute heart failure and tolerated beta-blockade well clinically [12]. The excellent tolerability was later confirmed by invasive haemodynamic monitoring in a placebo controlled study with intravenous metoprolol to patients with acute myocardial infarction [13, 14]. A tentative explanation why acute i.v. beta-blockade was well tolerated is illustrated in Figure 4. Thus beta-blockade reduced the amount of ischaemic myocardium in the acute phase of acute myocardial infarction by reducing rate-pressure product and prolonging diastole. Despite the negative inotropic effect of beta-blockade the net effect was a maintained left ventricular filling pressure.

Table 2. Development of the inotropic concept for heart failure – the haemodynamic approach

<table>
<thead>
<tr>
<th>Alterations in the failing heart</th>
<th>Use of inotropic drugs</th>
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Table 3. Energy imbalance as a cause of heart failure – focus on myocardial energy balance 1966–73

1. There is a biochemical defect in the failing heart due to impairment of oxidative phosphorylation. Chidsey et al. J Clin Invest 1966; 45: 40 [6]
2. Positive inotropy can increase the amount of ischaemic damage and negative inotropy reduces the extent of necrosis.

One year later, in late 1972, a patient with chronic congestive heart failure secondary to previous myocardial infarction was admitted with severe pulmonary oedema and sinus tachycardia of 120 beats/min but with no electrocardiographic signs of ongoing new infarction. He was unresponsive to treatment for pulmonary oedema available at that time such as furosemide i.v. tourniquets on legs and arms to reduce venous return. He responded within 10 minutes to an i.v. injection of practolol 20 mg, a β1-selective beta-blocker with moderate intrinsic stimulatory effect, by reducing heart rate to 70 beats/min and underwent a fast dramatic reduction of pulmonary congestion.

This observation leads us to try a similar approach in patients with chronic heart failure and tachycardia. We chose to concentrate our treatment on patients with dilated cardiomyopathy for two reasons: 1.) We thought that diffuse reduction of systolic function seen in these patients, rather than localized akinesia or dyskinesia, might have a greater potential for recovery in contrast to patients with an obvious big loss of myocardium secondary to myocardial infarction. The idea was based on the observed effect on heart function after refraining from alcohol in drinkers and abolition of tachycardia in arrhythmia patients. 2.) We were a referral centre for patients with dilated cardiomyopathy which gave us access to a study population.

Figure 3. Two competing concepts for treating chronic heart failure 1975

Figure 4. Effects of acute beta-blockade in acute transmural myocardial infarction
We anticipated that the high sympathetic stimulation should be withdrawn slowly to avoid sudden haemodynamic deterioration as observed earlier in experimental studies to allow a smoother adaptation to a lower inotropic support concomitantly with a metabolic unloading secondary to reduction of the high heart rate hoping for some restoration of function to counterbalance the negative inotropic effect. The hypothesis was simple: We wanted to restore an anticipated imbalance between high energy requirement and low energy supply, primarily by reducing heart rate. As we shall see later the explanation for improvement seems to be much more complicated.

In the first series of 7 patients we found a uniform response. Before there were obvious signs of increase in ejection fraction there was symptomatic improvement predominantly relief of resting and exertional dyspnoea. An early bedside finding was disappearance of third heart sound and normalisation of apex cardiogram where decrease of the relative size of early filling e-wave corresponded to disappearance of third heart sound. This change was later shown to correlate well with change in left ventricular filling pressure [15] and we therefore postulated that the earliest improvement seen after initiating beta-blockade was improvement of early ventricular filling. This has later been confirmed by us and others [16, 17]. We may hypothesise that improved calcium reuptake by sarcoplasmatic reticulum may be an early step in the process of improvement with beta-blockers. When beta-blockers are withdrawn the earliest signs of deterioration appear in the diastolic function and may occur as early as a few days after withdrawal in some patients [15, 18] (Fig. 5). Slow increment in beta-blocker dose was important particularly in patients with the most compromised function, eg, low blood pressure and high filling pressure, whereas in less sick patients titration in most instances went smoothly. Reactions from colleagues were however mostly sceptic, in some instances even hostile. At best they recommended to wait and see. This was expressed both orally at meetings and in letters to the editor. One misinterpretation by these colleagues was the initiate treatment with an abrupt increase in the beta-blocker dose which obviously had led to a disaster including death of the patient. These observations in combination with the lack of improvement after short-term improvement may have added to a general sceptical attitude. This scepticism was also fuelled by results from two short-term placebo-controlled trials showing no objective improvement in function or exercise tolerance [19, 20]. The authors commented however that treatment was surprisingly well tolerated. In general, European cardiologists, with exception of the Italians, were more reluctant than Americans of the beta-blocker concept. The first support for the beta-blocker concept was a 6-month placebo-controlled study clearly showing improvement in left ventricular function and exercise capacity [21, 22] and led later to a close cooperation with American colleagues finally resulting in the first big placebo-controlled multicentre trial with "hard" endpoints, the MDC trial [23]. Due to the fact that most of the participating centres were strong believers in the beta-blocker concept and had their own heart transplant program and we aimed exclusively at relatively young patients with dilated cardiomyopathy, we all found it unethically to use death as the single primary endpoint. We therefore, for the first time in the history of controlled heart failure trials, constructed the combined endpoint "death + need for heart transplant". The need for heart transplant was based on strict objective criteria [23]. We thereby made it almost impossible to achieve an effect on death alone, except for sudden death, since severe deterioration of cardiac function would inevitably lead to listing for heart transplantation. Recruitment to the study was relatively slow due to poor funding. Most grants and pharmaceutical investments went to finance trials with inotropic drugs and angiotensin converting enzyme drugs in the late 1980s. The study was underpowered because we had to limit the number of included patients to less than half of the calculated number needed to show an effect. Nevertheless, for the first time it was clearly shown that beta-blockers showed improvement of both functional and clinical parameters including exercise tolerance, hospitalisation for heart failure and need for heart transplantation, whereas no effect was seen on mortality alone. Although per definition a negative study, it was considered a landmark study and had a marked impact on the cardiology community and gave impulse to the pharmaceutical industry to perform well powered controlled trials. The most obvious immediate effect was to reduce the need for heart transplantation in dilated cardiomyopathy making a somewhat better balance between supply and demand of donor hearts [24].

The big question after completion of the MDC trial was if beta-blockers had any effect on heart failure of ischaemic aetiology. The CIBIS I trial with bisoprolol versus placebo, included both ischaemic and non-ischaemic patients and was also underpowered [25]. In this study, a subgroup analysis showed no effect in the ischaemic group, whereas a significant effect was seen in the non-ischaemic group much like in the MDC trial. There was, however, a small controlled study which also showed functional improvement in heart failure patients of ischaemic aetiology [26]. It was shown that metoprolol caused recovery from left ventricular asynergy [27].
Moreover, retrospective analysis of post-infarction trials indicated that the most marked effect on mortality was seen in patients showing signs of poor left ventricular function [28, 29]. Therefore the US carvedilol trial [30], consisting of 4 separate smaller trials, with the majority of patients of ischaemic origin, showed both functional improvement and increased survival for the ischaemic patients. This was a very important observation, since the majority of heart failure patients have an ischaemic background.

Most of the beta-blocker trials have studied the effect of a beta-blocker added to an ACE-inhibitor. A great majority of the patients were also digitalised. Early studies showed that beta-blockers by themselves without ACE-inhibition have a beneficial effect. It is however most likely that ACE-inhibitors and beta-blockers, which have different modes of action, could have additive or maybe even synergistic effects. Moreover, many patients with heart failure may not be adequately stabilised on diuretics alone and are therefore not in optimal condition for titration of a beta-blocker. In the future it may be possible to treat mild heart failure with beta-blockers alone. This must however first be evaluated in controlled trials. The question whether we need to give digoxin also cannot be answered by present trials. It may make sense to add digoxin to ACE-inhibitors in case the patients cannot be stabilised on diuretics and ACE-inhibitors alone.

**Mechanism of Beta-Blockers in Heart Failure**

A number of mechanisms have been suggested for beta-blockers in heart failure (Tab. 4, Fig. 4). It is shown that beta-blockers increase myocardial efficiency since the left ventricle can improve stroke work index without increasing oxygen uptake. A more efficient aerobic metabolism is achieved after long term beta-blockade indicated by a switch from myocardial release to uptake of lactate [31]. Our hypothesis that insufficient turnover of high energy phosphate may be compromised in heart failure is suggested both from human studies [32] and our own experimental data. Normalisation of the phosphocreatine/ATP ratio (Pc/ATP) after one month treatment with metoprolol in rats with post-myocardial infarction heart failure, which parallels improved ejection fraction, suggests that this is an important mechanism for the improvement of restoration of energy balance [34].

The observed marked reduction in sudden cardiac death in all three beta-blocker trials could be explained by a combination of central and peripheral effects. Reduction in ventricular volume and wall stress will reduce the stretch which can provoke arrhythmias whereas improved subendocardial flow will reduce the ischaemia, another important trigger for arrhythmias. Moreover, the long-term central nervous effect of beta-blockers will reduce sympathetic outflow to the heart and increase vagal tone and this will by itself reduce the risk of ventricular fibrillation, the most important cause of sudden death [1] (Fig. 1).

Recently, strong interaction between the sympathetic nerve system with other neurohormones and cytokines has been demonstrated and which are favourably affected by beta-blockers (Tab. 5, Fig. 6). An interesting hypothesis is that beta-blockers could block a possible interaction between sympathetic nerve system and immune system.

**Myocardial Function and Remodelling**

**Ejection Fraction**

A great number of studies have shown improvement of ejection fraction with different beta-blockers indicating a class effect [15, 23, 26–28, 60–67] but only a few have studied the time dependent effect [63, 68]. As a rule the onset of the effect on systolic function is markedly delayed compared to the effect of ACE-inhibitors, vasodilators and digoxin.

Improvement is not present until after 2–3 months of treatment [68]. Improvement may continue for as long as 12 months with a significant number of patients continuing to improve between 6 and 12 months of treatment [23]. The increase in ejection fraction averaging 5–10 units [23], depending on duration of treatment, is more impressive than the effect by ACE-inhibitors and digoxin. One has to consider that this effect is additive to the effect of ACE-inhibitors. It is therefore evident that beta-blockers have effect on systolic function in addition to ACE-inhibitors.

**Table 4. Possible mechanisms for beneficial effects of beta-blockers in congestive heart failure**

- Reduce subendocardial ischemia [31, 33]
- Normalize high phosphorus energetic imbalance [34]
- Improve myocardial work/oxygen consumption ratio [31, 35, 36]
- Increase heart rate variability [44, 45]
- Reduce QT-dispersion [46]
- Reduce endothelin production and release [39]
- Reduce sympathetic tone [40, 41]
- Increase norepinephrine re-uptake [42]
- Increase vagal tone [43]
- Reduce renin release [38]
- Reverse of deteriorated fractal behaviour of heart rate variability [47]
- Uro-regulate beta-adrenergic receptors [15, 48, 49*]
- Increase heart rate variability [44, 45]
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* Not for carvedilol and bucindolol [49]

**Table 5. How can beta-blockers improve myocardial energy balance in heart failure?**

- Heart rate
- Diastolic flow time
- Relaxation
- Myocardial restriction
- Perfusion pressure
- Filling pressure
- Hypertrophy
- Free fatty acids
- Remodelling

**Figure 6. Proven mechanism for beta-blockers in heart failure**
Beta-Blockers in Congestive Heart Failure

Conductility
Load independent indices of LV-function clearly demonstrated that beta-blockers have a true effect on conductility [15, 35, 36]. The effect on ejection fraction was not secondary to heart rate reduction because pacing to baseline heart rate before long-term beta-blockade did not affect ejection fraction [53] and was also seen in patients with small reduction in heart rate.

Diastolic Function
Beta-blockers improve diastolic function after i. v. administration [36, 68]. Diastolic improvement was observed as early as after 2 weeks [15], much earlier than systolic improvement, reaching its maximum already after 3 months [16, 17] in contrast to maximal improvement in systolic function after 12 months [14].

Mitral Regurgitation
After 6 months treatment there was a significant reduction in grade and volume of mitral regurgitation [17, 69].

Remodelling
In 6-month studies with beta-blockers given in addition to ACE-inhibitors there was a reversal of remodelling of left ventricle due to continuously increased left ventricular systolic and diastolic volumes in the placebo-treated patients and reduction in beta-blocker-treated patients [70].

Whether this beneficial effect of beta-blockers on remodelling will remain during longer follow-up or will exhibit escape as seen with long-term treatment with ACE-inhibitors is not known.

Effects on Exercise Tolerance
Data are not conclusive because the effect on exercise tolerance will depend on 1) how sick the patient is at baseline, 2) the serum concentration of the beta-blocker and 3) at what time-point the exercise test is performed, at peak or at trough concentration.

In the MDC trial, in which there was a significant increase in exercise tolerance by metoprolol compared to no change in the placebo group after 12 months [23], the exercise fraction was very low (22 %) and an immediate release metoprolol formulation was used which may have given a low serum concentration of metoprolol at the time the exercise test was performed. In contrast, there was no difference in a substudy to the MERIT-HF trial [71]. The baseline exercise fraction was higher (26 %) and an extended release formulation was used which gives an almost constant serum concentration of metoprol over 24 hours. A clinical expression is however that the reason for stopping exercise is fatigue rather than dyspnoea which may be explained by the fact that there is less increase in exercise pulmonary wedge pressure after long-term treatment with metoprolol [33].

Effects on NYHA Class and Quality of Life Scores
In the MERIT-HF trial effects on NYHA class and MacMaster Overall Treatment Evaluation (OTE) score improved significantly whereas the total Living with Heart Failure Score in a subset of 17 % of the patients did not change significantly although decreased (improved) with metoprolol and increased (deteriorated) with placebo [72].

Effects on Mortality – Results from Mega-Trials in Heart Failure with Beta-Blockers
At present, there are four major placebo-controlled trials with beta-blockers given in the combination with ACE-inhibitors or AT-II blockers with mortality and morbidity as predefined endpoints [1, 72, 73] (Figs. 7–12). The Cardiac Insufficiency Bisoprolol Study I (CIBIS II) [73] included clinically stable patients in NYHA classes III and IV with ejection fraction ≤ 0.35. The Metoprolol CR/XL Randomized
Intervention Trial in Heart Failure (MERIT-HF) [72] included stable patients in NYHA classes II–IV [1] and the COPERNICUS trial [74] included patients in euvolemia with EF ≤ 0.25 without notion about the clinical severity described as NYHA classification. However, judged from the ejection fraction value and the placebo mortality these patients seemed to have somewhat more advanced heart failure compared to the patients in CIBIS-II and MERIT-HF trials. The effect on mortality in these three trials was however very similar with a reduction in total mortality of 34%, 34% and 35%, respectively [1, 72–74]. When a post-hoc analysis on data from the CIBIS II and MERIT-HF trials on patients in NYHA classes III–IV and EF ≤ 0.25 was performed baseline characteristics were similar and the outcome very similar to the COPERNICUS trial [75]. This suggested that the important common property for the three beta-blockers bisoprolol, metoprolol and carvedilol used in these three studies is the beta1-adrenergic receptor blockade, whereas properties such as beta2-adrenergic and α-adrenergic receptor blockade do not seem to have any additional effects.
on mortality and morbidity. There was a strong consistency for the results for gender, aetiology of heart failure, heart rate, blood pressure, NYHA class, ejection fraction and concomitant disease like hypertension and diabetes [72, 76].

A fourth study with beta-blocker in heart failure, Bucindolol Evaluation of Survival Trial (BEST) [77], showed a not significant reduction in mortality of 10%. There was however a significant reduction in cardiovascular morbidity, which was a secondary endpoint, and a borderline significant reduction in total mortality in NYHA class IV.

One reason for this study to differ from the three other studies may be the high placebo mortality of 33% indicating that the patients in the BEST trial were much sicker. Another explanation may be too marked adrenergic blockade due to a too strong beta2-adrenergic blockade. A third explanation may be that the negative chronotrope and inotropy effects of bucindolol are lower compared to the other three beta-blockers because of its intrinsic stimulatory effects [78] which also may explain why there was less reduction in heart rate compared to the other beta-blockers without intrinsic stimulatory effect. It could therefore be concluded that there is excellent consistency in the effect between the three beta-blockers bisoprolol, metoprolol and carvedilol which all lack intrinsic stimulatory effect. Since relatively few patients in these three trials were in class IV, some caution should be recommended in these patients. More patients in NYHA class IV are expected not to tolerate beta-blockade. However, both hospitalisation due to heart failure and withdrawal rate are lower for metoprolol CR/XL compared to placebo [72]. Only experienced cardiologists should therefore initiate beta-blockers in these patients. Once they are stable on a beta-blocker, continued follow-up could be performed by a less experienced physician.

Effects on Morbidity and Tolerability

All four beta-blocker trials showed a significant reduction in morbidity as reflected by number of hospitalisations and days in hospital [72–74, 77] (Fig. 13). The main reasons for reduction were less admissions for worsening heart failure. Also withdrawal rate, especially for cardiovascular reasons, tended to be lower in all trials reflecting that the beta-blockers were well tolerated [73, 74, 77, 79].

Can We Predict Tolerability to a Beta-Blocker in the Individual Patient?

There is a paradox when beta-blockers are used in severe heart failure. The sicker the patient the more likely tolerability problem could arise when a beta-blocker is added. On the other hand, the more likely a stronger effect on mortality in absolute number of saved life is expected among those tolerating the drug. In the MERIT-HF trial, treatment with metoprolol for one year in 100 patients saved 1.8 lives in NYHA class II, 5.1 lives in NYHA class III, and 8.2 lives in NYHA class IV [1]. Therefore, one should not avoid to attempt beta-blocker treatment in stabilised severely failing patients. Baseline predictors for not tolerating carvedilol could not be defined in an open-labelled study except for NYHA class. Carvedilol was withdrawn in 9% in NYHA class II, 13% in class III, 22% in NYHA class IV patients which is in accordance with figures from placebo-controlled trials with metoprolol (13.9%) [72] and bisoprolol (15%) [73]. It must be stressed that patients with unstable heart failure, reversible airway disease, bradycardia (HR < 60 bpm [73]) or HR < 68 bpm [1] first degree AV-block or higher, and systolic hypotension < 100 mmHg [1, 73, 74] were excluded.

Which Beta-Blocker Dose Should be Given?

Only one trial has studied effect of different beta-blocker doses prospectively [65]. In that study there was a dose-dependent effect on ejection fraction [65]. Other studies aimed at a target dose [1, 73, 74, 77] but final dose was defined on discretion of the physician based on clinical judgment weighing factors as heart rate, blood pressure and possible side-effects. In a retrospective analysis of MERIT-HF [81] trial the effect on mortality and morbidity was the same among those who received a low dose as in those receiving a high dose when the beta-blocker was titrated on behalf of the physician to what the patient could tolerate. The final heart rate was 67 bpm, i.e., the same in the low-dose group (76 mg) as in the high-dose group (192 mg), indicating that a similar degree of beta-blockade was achieved [81]. The conclusion should be that one should aim at the recommended target dose as long as this dose is well tolerated, but accept a dose which is lower than target dose when appropriate reduction of heart rate is achieved with a lower dose or a higher dose is not tolerated due to symptomatic bradycardia, hypotension or fatigue.

Which Beta-Blocker Should be Preferred?

Since there are still no data from the head-to-head trial COMET [82], comparing the non-selective beta-blocker carvedilol with the beta1-selective beta-blocker metoprolol and the effect on mortality and morbidity is of the same order in the three positive survival trials with predefined primary endpoints [1, 73, 74], one should be free to choose between the three approved beta-blockers carvedilol, bisoprolol and metoprolol. Side-effects could differ among the three beta-blockers and therefore a switch between the drugs should be possible in case of problems tolerating one of them. Recently it was shown that increase in ejection fraction was significantly higher with carvedilol compared to metoprolol and decrease in left ventricular filling pressure was more pronounced with carvedilol compared to metoprolol [83]. Whether this difference in the effect on left ventricular filling pressure and increase in ejection fraction is due to an unload-
ing effect of α-adrenergic blockade is not clear. Neither of these findings seems however to have any impact on survival, morbidity or well-being and could therefore only be considered as surrogate endpoints without any clinical relevance.

## Summary and Conclusion

Beta-blockers inhibit disease progression in congestive heart failure, improve contractility and to some extent reverse defects in ventricular geometry and size. In contrast to ACE-inhibitors they reduce sudden death markedly. They have now been approved for stable symptomatic heart failure in NYHA classes II and III and ejection fraction below 0.40. NYHA class IV patients who also may benefit should be treated with caution and require experienced cardiologists to initiate beta-blockade. Provided patients are stabilised on diuretics and ACE-inhibitors and carefully titrated from low beta-blocker doses to target dose or to the highest tolerated dose there is an excellent tolerability and pronounced effect on mortality and cardiovascular morbidity.

Improvement in the individual patient cannot be predicted from the above variables, so attempts should be undertaken to treat every patient with heart failure or asymptomatic left ventricular dysfunction with the combination of ACE-inhibitors and beta-blockers. Provided patients are stabilised on diuretics and ACE-inhibitors and carefully titrated from low beta-blocker doses to target dose or to the highest tolerated dose there is an excellent tolerability and pronounced effect on mortality and cardiovascular morbidity.

## References

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