P1651 Fluid retention during the initiation of beta-blockade: increased risk in advanced disease and long-term implications

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Introduction: Patients who experience fluid retention (FR) during the initiation of β-blockade respond well to continued therapy over a period of several months. However, the risk factors for FR are poorly defined, and the implications of this side effect of therapy on long-term outcomes have not been investigated. **Methods:** We evaluated 178 consecutive patients (pts) with NYHA class I-IV HF treated with CV starting at 3.125 or 6.25 mg BID and increased to 25-50 mg BID at weekly intervals. Pts were evaluated clinically, and in many cases had neurohormonal (n=105) or hemodynamic (n=51) assessments. Average follow-up was 766 days. **Results:** Fluid retention (FR) sufficient to require increased diuretic therapy occurred in 78 patients (48%). Pts with FR had more advanced HF as reflected by neurohormonal, hemodynamic and clinical factors. Significant risks for FR included low EF, low systolic BP, high PCW & worse NYHA class. Kaplan-Meier analysis revealed no difference in survival between pts with and without early FR, but the endpoints of death + CV hospitalization ($p = 0.12$) and death + HF hospitalization ($p < 0.006$) indicated higher long-term risk for pts who had early FR.

Differences between patients with and without early FR

Group	NYHA	Walk	EF	Aldo	NE	PCW	RA
FR	2.8*	354*	18*	37*	731*	28*	12*
NoFR	2.3	423	21	17	447	20	7

Conclusions: These data demonstrate that pts with more advanced disease are at increased risk of developing FR during the initiation of carvedilol. Despite good response to CV over the first several months, the development of early FR identifies a subset of pts at higher risk of clinical events during long-term follow-up.

P1652 Atenolol, a β1 selective adrenergic antagonist, inhibits progression of heart failure in patients with low (<25%) ejection fraction treated with high dose enalapril

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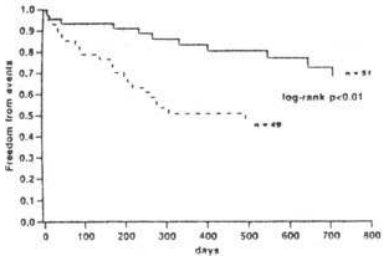
Information on the use of β-blockers in patients with advanced LV dysfunction is limited. A prospective double-blind placebo-controlled trial was performed to investigate the effects of up to 100 mg atenolol added on 40 mg enalapril in heart failure patients with EF < 25%. Endpoints were 1) combined worsening heart failure or death and 2) hospitalization for cardiac events within 2 yrs. 100 patients (88 m, 12 f, 51 ± 1 yrs, 28 isch./72 idiopath. dil. CMP) who passed a challenge dose of 12.5 mg atenolol were included. After 395 ± 26 SEM days interim analysis revealed a significant difference between the atenolol (—) and placebo (- - -) group in regard to worsening heart failure or death (log rank $p < 0.01$) in favour of atenolol and the trial was concluded. Mortality was 13% with 5 deaths (sudden 3, heart failure 1, noncardiac 1) on atenolol vs 8 deaths on placebo (sudden 6, heart failure 1, noncardiac 1) and 27% developed worsening heart failure (8 on atenolol vs 19 on placebo). 17 hospitalizations were due to worsening heart failure (5 on atenolol vs 12 on placebo, $p < 0.05$) and 10 due to arrhythmias (1 on atenolol vs 9 on placebo, $p < 0.01$).



Thus, for optimization of neurohumoral therapy in pts with advanced LV dysfunction efforts should be made to add β-blockers to maximal ACE-inhibitor therapy.

P1653 Differential effects of intravenous inotropes in patients on long-term beta-blocker therapy

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Patients with heart failure on long-term beta-blocker (BB) therapy may need i.v. inotropes during episodes of worsening heart failure. However, the hemodynamic effects of these agents may be influenced by concomitant BB therapy. The hemodynamic response to i.v. dobutamine (dob) (up to 20 mcg/kg/min) and to i.v. enoximone (enox) (up to 2 mg/kg) was studied in 19 patients with heart failure (NYHA class, 2.8 ± 0.5; LV EF, 19 ± 7%; peak VO2, 13 ± 4 ml/kg/min) both before and after long-term (> 9 months) therapy with metoprolol (met) (14 patients, mean dose, 129 ± 38 mg daily) or carvedilol (carv) (15 patients, mean dose, 43 ± 12 mg daily). No significant difference was present at baseline between the two groups. Both treatments caused a significant improvement in the clinical conditions and LV function with an increase in the LVEF from 20 ± 8% to 30 ± 14% and from 17 ± 6% to 28 ± 11% in the met and the carv group, respectively. Significant differences were found in the hemodynamic responses to inotropic agents (see table).

Hemodynamic responses to i.v. inotropes

	Dob, before BB	Dob, after BB	Enox, before BB	Enox, after BB
CI, met pts	1.55 ± 0.74	1.77 ± 0.83	0.97 ± 0.68	1.55 ± 1.44
CI, carv pts	1.73 ± 0.87	0.52 ± 0.57 (*)	1.43 ± 0.86	1.78 ± 0.95
SVR, met pts	-465 ± 312	-389 ± 292	-423 ± 335	-429 ±258
SVR, carv pts	-536 ± 305	+33 ± 357 (*)	-547 ±255	-821 ± 642
PWP, met pts	-7 ± 7	-3 ± 5	-7 ± 4	-5 ± 5
PWP, carv pts	-6 ± 4	+3 ± 6 (*)	-7 ± 5	-6 ±6
PVR, met pts	-53 ± 93	-29 ± 52	-77 ±68	-39 ± 85
PVR, carv pts	-67 ± 63	+41 ± 93 (*)	-79 ± 9	-73 ± 105

Absolute changes versus baseline are shown. Pts=patients; CI= cardiac index, L/min/m2; SVR= systemic vascular resistance, dyn*s*cm-5; PWP= pulmonary wedge pressure, mmHg; PVR = pulmonary vascular resistance;(*) = $p<0.05$ versus before BB and versus met group

In conclusion, long-term carv therapy, differently from met, may inhibit the hemodynamic response to dob whereas the response to enox is not significantly changed. These results are likely related to the greater antiadrenergic effects of carv and indicate the lack of efficacy of agents active on adrenergic receptors to improve the hemodynamics in the patients treated with this drug.

P1654 Haemodynamic effects on the left ventricle during β-blockade with metoprolol in the treatment of chronic heart failure

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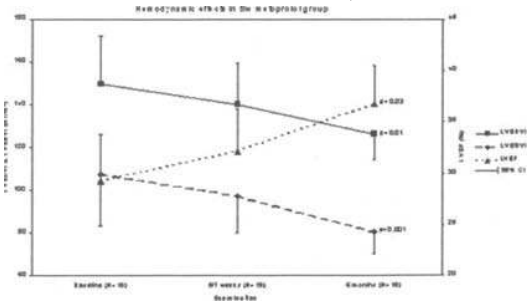
The purpose of the study was to investigate the effects on the left ventricle when treating chronic heart failure with the β1-selective receptor antagonist metoprolol. The mechanism behind the mortality benefit from treatment of chronic heart failure with β-blockers remains yet to be fully elucidated and previous studies have presented insignificant or conflicting results regarding anti-remodelling effects on the left ventricle.

Methods: In a substudy to the randomised, placebo-controlled and double-blind Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF), 41 patients were examined with magnetic resonance imaging at baseline, after 5 weeks and after 6 months of treatment with metoprolol (n=19) or placebo (n=22) assessing left ventricular dimensions and function.

Results: Decreases in both left ventricular end-diastolic volume index (150 ml/m^2 at baseline to 126 ml/m^2 at 6 months, P=0.01) and left ventricular end-systolic volume index (107 ml/m^2 - 81 ml/m^2, P=0.001) were found, whereas left ventricular ejection fraction increased in the metoprolol group (29% - 37%, P=0.03). No significant changes were seen in the placebo group regarding these variables. Left ventricular stroke volume index remained unchanged, whereas left ventricular mass index decreased in both groups (175 g/m^2 - 160 g/m^2 in the placebo group (P=0.005) and 179 g/m^2 - 164 g/m^2 in the metoprolol group (P=0.01)).



Hemodynamics in the metoprolol group

Conclusions: The current study is the first randomised trial to demonstrate that metoprolol has anti-remodelling effects on left ventricular dimensions and function in patients with chronic heart failure and consequently provides an explanation for the highly significant decrease in mortality from worsening heart failure found in the MERIT-HF trial.