g/kg intravenous glucose tolerance test (IVGTT), and Si was calculated according to Bergman's Minimal Model.

**Results:** At baseline, we observed an inverse correlation between Si and fasting plasma insulin ($r = -0.44$, $p < 0.001$), BMI ($r = -0.42$, $P = 0.002$), plasma urate ($r = -0.42$, $P = 0.002$), plasma triglycerides ($r = -0.34$, $p = 0.01$) and fasting plasma glucose levels ($r = -0.29$, $P = 0.03$). Furthermore, a positive correlation between Si and plasma HDL cholesterol levels ($r = 0.39$, $P = 0.03$) and maximal oxygen uptake ($r = 0.35$, $P = 0.009$) was found. The Si did not correlate with NYHA class, W/H ratio, age, EF, or plasma catecholamine levels. A trend towards an inverse correlation between insulin sensitivity and plasma endothelin was seen ($r = -0.26$, $P = 0.056$). Si was unchanged both within the carvedilol group from $2.63 \pm 1.45$ to $2.38 \pm 1.64$ * 10−4 * min−1/mU * L−1 (NS) and compared with the placebo group (−0.25 vs. −0.33 * 10−4 * min−1/mU * L−1, NS).

**Conclusion:** Additional treatment with carvedilol to patients with mild to moderate CHF is neutral with regard to influence insulin sensitivity. Further prospective studies may show how selective beta-blockers affect the insulin sensitivity in patients with CHF.

## P51/10063 Beneficial neuroendocrine modulation of spironolactone in severe congestive heart failure

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In the Randomized ALdactone Evaluation Study (RALES), spironolactone, an aldosterone-receptor antagonist, decreased mortality and morbidity in patients with severe congestive heart failure. To clarify the mechanism of action, the effects of spironolactone (25 mg daily) on the plasma concentration of N-terminal proatrial natriuretic factor (N-proANF) and of brain natriuretic peptide (BNP), a neurohormonal marker of left ventricular function, were assessed in a subset of 107 patients (NYHA III–IV, mean EF:25%) at entry (T0) into study, at 3 months (T3) and at 6 months (T6) and compared the changes to the placebo group. 54 patients were included in the spironolactone group and 53 in the placebo group. Data were compared using a Student t-test on a logtransformed scale and the natriuretic peptides changes from baseline are expressed by the ratios T3/T0 and T6/T0. Compared to the placebo group, a significant decrease of 19% in N-proANF was observed at 3 months in the spironolactone group (1.0 vs 0.81, $p = 0.03$). Moreover, we evidenced overtime, compared to the placebo group, a significant 23% reduction of BNP plasma concentration in the spironolactone group (0.99 vs 0.77, $p = 0.004$ and 0.96 vs 0.77, $p = 0.05$, respectively at 3 and 6 months). In conclusion, spironolactone significantly decreased the plasma levels of N-proANF and more importantly of BNP. The reduction of BNP plasma levels during the follow-up period reflects the beneficial effects of spironolactone on the left ventricular remodeling through the reduction of myocardial stretching. Spironolactone can influence the progression of left ventricular remodeling by several mechanisms: reduction in wall stress, reduction in interstitial fibrosis, and reorganization of the collagen matrix. This neuroendocrine modulation and cardioprotection may contribute to limit the progression of heart failure and to explain the decreased mortality and morbidity observed with spironolactone.

## P52/10423 Vitamin C acutely improves ejection duration in chronic heart failure (CHF) patients in a heart rate independent fashion

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**Background:** Shortened ejection duration (ED) is a feature of chronic heart failure (CHF) and correlates with stroke work index and fractional shortening and is inversely related to pulmonary capillary wedge pressure. ED is determined both by intrinsic myocardial function and also by the effects of the reflected aortic pressure wave. Increased pulse wave velocity (PWV) due to increased large artery stiffness results in earlier return of the pressure wave and may contribute to early aortic valve closure. We hypothesized that by improving endothelial function and reducing PWV, vitamin C would prolong ED in patients with CHF.

**Methods:** 40 CHF patients with an ejection fraction (EF) of less than 35% (21 NYHA II and 19 NYHA III) were studied. Pulse wave analysis (PWA) was performed with the SphygmoCor® (PWV Medical) device which uses a high fidelity tonometer to record a radial pressure trace from which central aortic pressures and ED can be accurately estimated applying a generalized transfer factor. ED measurements have been validated against invasive recordings. Baseline recordings were performed after 10 minutes of supine rest. 30 patients were randomised in a double blind parallel group fashion to receive either 2 g vitamin C or N-Saline i.v. PWA was performed 30 minutes later.

**Results:** Data are expressed as mean ± SEM. ED was 282 ± 5 msec at baseline and was shorter in NYHA III vs NYHA II patients (ED 271 ± 8 msec vs 290 ± 4 msec; $p = 0.03$). Vitamin C prolonged ejection duration from 284 ± 5 msec to 298 ± 6 msec; $p = 0.0005$ vs baseline, $p = 0.018$ vs placebo. When ED was corrected for heart rate (HR) these changes remained very significant; $p = 0.008$ vs baseline, $p = 0.007$ vs placebo.

**Conclusions:** 1. In CHF ejection duration is reduced in parallel with the reduction in functional capacity (NYHA class). Vitamin C given intravenously prolongs ED. This might theoretically be due to either a myocardial effect or a delay in wave reflection as a result of improved large artery endothelial function. 3. PWA can be used to determine accurately the effects of pharmacological interventions on ventricular-vascular coupling.

## P53/10514 Effects of HMG-COA reductase inhibitors (statins) in patients with heart failure

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HMG-CoA Reductase Inhibitors (statins) are used infrequently in patients with heart failure and systolic left ventricular dysfunction in part due to concerns about ubiquinone (co-enzyme Q) inhibition, mitochondrial dysfunction, and associated myopathy. We examined the effects of statins on clinical outcomes (mortality) in the Losartan Heart Failure Survival Study, ELITE II, a multinational, double-blind, randomized study of patients ≥ 60 years with symptomatic heart failure which showed that the AII blocker losartan had no significant difference in mortality compared to the ACE inhibitor, captopril.

**Methods:** A retrospective analysis of outcomes from the ELITE II study was performed to compare the effects of statins on mortality (Cox regression with $\beta$-blocker use at randomization as stratification factor, and region as covariate).

**Results:** Of the 3,152 patients enrolled in ELITE II, 359 (11%) patients were on statins at the time of randomization and 617 (19.6%) administered concomitantly with study therapy. Baseline demographics were generally similar between patients on statins compared to those not on statins except for distribution in NYHA class (62% *vs* 50% class II respectively), history of ischemic heart disease (91% *vs* 77%) and myocardial infarction (78% *vs* 56%). Regardless of treatment with losartan or captopril there was a significantly lower mortality rate for patients on statins at randomization, and similarly, for patients on statins after randomization. No significant difference was seen in this effect between losartan and captopril.

| | With Statins* | | Without Statins | |
|---|---|---|---|---|
| | N | Crude Rate (%) | N | Crude Rate (%) |
| Totals | 359 | 38 (10.6) | 2793 | 492 (17.6) |
| Losartan | 176 | 20 (11.4) | 1402 | 260 (18.5) |
| Captopril | 183 | 18 (9.8) | 1391 | 232 (16.7) |
| Los./Cap. Δ (95% CI) | | 1.19 (0.63, 2.26) | | 1.12 (0.94, 1.34) |

*p = 0.003 for statin effect on reducing mortality across treatment groups (Cox regression)

**Conclusion:** In this study patients with symptomatic heart failure and left ventricular dysfunction, patients who took statins had significantly lower mortality; losartan was not different from captopril in reducing mortality either with or without statins as concomitant therapy. Prospective evaluation of statin use in patients with heart failure is warranted.

## P54/10590 Reduction of cough as a complication of ACE inhibitors

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**Introduction:** ACE inhibitors are using progressively as antihypertensive drugs and also in the management of patients with congestive Heart failure.