mmHg and 28±8 mmHg (p=0.528); systolic blood pressure 98±13mmHg and 99±18mmHg (p=0.839); cardiac index 2.2±0.7lt/min/$m^2$ and 2.1±0.6lt/min/$m^2$ (p=0.719). Kaplan-Meier survival analysis showed a 60% reduction in the risk of death from any cause in the group treated with the combination of dobutamine and amiodarone, compared with the group treated with placebo and amiodarone (hazard ratio 0.403; 95% confidence interval 0.164-0.992, p=0.048). The 1- and 2-year survival rates were 69% and 44%, in the dobutamine-treated group, versus 28% and 21%, respectively, in the placebo-treated group (p<0.05 for both comparisons). Median survivals were 574 and 144 days in Groups 2 and 1, respectively. At six months, the NYHA functional class was significantly improved in the surviving patients of both groups. **Conclusion:** Long-term IDI combined with amiodarone, added to conventional treatment, improves survival of patients with severe CHF.

1085-76 **Statin Therapy Is Associated With Improved Survival in Ischemic and Nonischemic Heart Failure**

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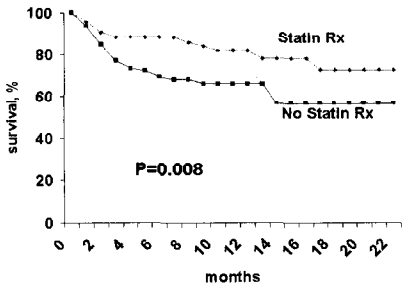
**Background:** Although HMG CoA reductase inhibitors (statins) are known to decrease mortality in CHD, concern has been raised about potential negative effects in patients with heart failure (HF). The impact of statins on the progression of advanced HF has not been studied.
**Methods:** We retrospectively studied a cohort of 251 pts with advanced HF referred for management and transplant evaluation. Pts without adequate documentation of medical regimen (n=33) were excluded from analysis. Survival free from death or urgent transplant was determined.
**Results:** Mean age, EF, and total cholesterol (TC) were 52, 25%, and 165 mg/dl, respectively. Fifty-one % of pts were on statin Rx. CAD was etiology of HF in 52% of patients, 79% of whom were on statin Rx. In non-CAD HF pts, 28% were on statin Rx. Pts on statins were significantly older, and had higher rates of CAD, smoking, HTN, and DM. Treated and non-treated pts were similar in NYHA, LVEF, sex, BMI, TC, and HF medications. Pts on statin Rx had improved survival over a 22 month follow-up (74% vs 56%, p=0.008). In subsets of pts without CAD and with TC <165 mg/dl, statins were similarly associated with improved survival (p=0.006, p=0.04 respectively). Statin Rx was an independent predictor of improved survival after risk-adjustment for age, sex, EF, ACEI Rx, renal function, and serum cardiac troponin I.
**Conclusions:** Statin Rx was associated with improved survival in ischemic and non-ischemic HF. Randomized trials are needed for confirmation of therapeutic benefit in non-ischemic HF.




1085-77 **Does the Magnitude of the Beneficial Effect of Beta-Blockers in Chronic Heart Failure Differ Between Diabetic and Nondiabetic Patients? A Meta-Analysis of All-Cause Mortality Outcomes From Major Chronic Heart Failure Beta-Blocker Trials**

Steven Haas, Theo Vos, Richard Gilbert, Henry Krum, Monash University, Melbourne, Australia

Background: Diabetes mellitus (DM) is a frequent co-morbid association of patients (pts) with chronic heart failure (CHF). Although CHF pts derive benefit from beta-blockers (BBs), these agents are still thought by many to be contraindicated amongst DM pts and definitive data is lacking within this sub-group. We therefore performed a meta-analysis of major BB CHF trials to determine the benefits (or otherwise) of BBs in DM pts with CHF.
Methods: All-cause mortality data concerning DM pts were obtained from all completed CHF trials of >1000 pts randomised to BB or placebo. Trials were identified via MEDLINE literature searches, manual reference checks & reference texts. Results were pooled using the Mantel-Haenszel method.
Results: 24.8% of pts were reported as having DM in the studies analyzed. DM pts had increased mortality overall c.f. non-DM pts (annualised placebo mortality rate: DM 17.0%, non-DM 13.9%; RR: 1.22, 95% CI: 1.07-1.39). The impact of BBs on mortality is summarised in the Table.
BBs for CHF appears to be clinically beneficial in DM as well as non-DM pts. However, the benficial impact of BBs is significantly greater in non-DM pts, by calculation of risk difference (P<0.05).
Discussion: CHF pts with DM appear to derive prognostic benefit from BBs, even though the magnitude of that benefit is signficantly less than that observed in non-DM CHF pts. Therefore, all eligible pts with symptomatic CHF, regardless of their DM status, should receive BBs for their prognostic benefits.

All-Cause Mortality: Diabetic vs Non-Diabetic Patients

| | Diabetics | | | Non-Diabetics | | |
|---|---|---|---|---|---|---|
| Study | N | RR | 95% CI | N | RR | 95% CI |
| BEST | 964 | 0.95 | 0.80, 1.12 | 1744 | 0.89 | 0.77, 1.02 |
| US Carvedilol | 307 | 0.37 | 0.14, 0.93 | 772 | 0.44 | 0.23, 0.86 |
| CIBIS II | 312 | 0.81 | 0.52, 1.27 | 2335 | 0.68 | 0.55, 0.82 |
| COPERNICUS | 589 | 0.68 | 0.46, 0.99 | 1700 | 0.67 | 0.53, 0.85 |
| MERIT-HF | 984 | 0.82 | 0.58, 1.17 | 3007 | 0.58 | 0.46, 0.74 |
| Total | 3156 | 0.85 | 0.74, 0.97 | 9558 | 0.72 | 0.65, 0.79 |

1085-78 **Electrophysiologic Alterations Seen in Patients With Advanced Cardiac Failure After Angiotension Converting Enzyme Inhibitor Therapy**

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Background: Recognizing that mechanical circulatory support induces changes in myocardial contractile function and intraventricular conduction (IVC),we examined whether there are changes in IVC among heart failure patients with medical therapy only. Methods: We studied 85 consecutive patients with New York Heart Association (NYHA) class 2 and 3 heart failure undergoing medical therapy with ACE-Inhibitors and Beta-Blockers. Mean follow-up time was 452 d +/- 186( median 374 d, range 128 to 745 d). Doppler Echocardiograms, ECGs and clinical symptom evaluations (NYHA) were obtained in 3 to 6 months intervalls. Results: OF 85 patients, 79 (92%) showed IVC improvement on surface ECG following medical therapy initiation (p< 0.01). Measured effects included a decrease in QRS duration from 115+/- 8 to 102 +/- 6 ms (p< 0.01) a decrease in absolute QT duration from 398 +/- 12 ms to 348 +/- 7 ms (p< 0.01) and a decrease in heart rate from 100.8 +/- 22.6 to 65 +/-12 ms (p< 0.01). A LBBB pattern observed in 32(37%)patients prior to treatment initiation resolved in 14 (43%) patients after 6 months of medical therapy (p< 0.01). Improved IVC on surface ECG and echocardiographic changes in myocardial structure and contractile function were positively correlated (p< 0.01). All echocardiographic and electrocardiographic findings could be positivly correlated with clinical symptom improvement (NYHA class 1 and 2) in 83 ( 97%) patients (p< 0.01). Conclustions: Electrocardiographic changes seen with medical therapy aimed to improve myocardial contractility in heart failure patients demonstrate that IVC and repolarization are dependent on longterm myocyte contractile function and possibly on altered calcium homeostasis. Improved left ventricular conduction and shortened cardiac action potential seen with ACE-Inhibitors therapy in heart failure seems therefore rather a *longstanding Ion channel dependent process implicating variable gene expression in the* failing heart than a pure mechanical response to hemodynamic loading conditions of the left ventricle.

1085-79 **Sustained Hemodynamic Benefit During Long-Term Positive Inotropic Infusion in Patients With Advanced *Heart Failure***

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**Background:** Long term intravenous inotropic therapy is used as a bridge to cardiac transplantation in patients with end-stage chronic heart failure (CHF). We aimed to determine whether acute hemodynamic benefits were sustained during chronic therapy.
**Methods:**We analyzed serial hemodynamic data from 21patients with advanced CHF (mean age 55 ys, LVEF 21%) listed for cardiac transplantation and treated with continuous home infusions of positive inotropic agents. Rest hemodynamic data before, and at 24 hours and 3-6 months after initiation of positive inotropic therapy were compared. Inotropic agent was dobutamine in 12 subjects (mean dose 4.5 mcg/kg/min, range 2.5-7.5 mcg/kg/min), milrinone in 8 subjects (mean dose 0.44 mcg/kg/min, range 0.375-0.55 mc/kg/min), and dopamine 3 mcg/kg/min in 1 subject. Oral neurohormonal antagonists were given as tolerated. Diuretics were adjusted to maintain a non-edematous state.
**Results:** Inotropic therapy acutely improved rest hemodynamics characterized by decreased PA pressure, PCWP and PVR and increased cardiac index (Table). During chronic therapy, further reductions in PA pressure and PVR were observed without change in PCWP or cardiac index.
**Conclusion:** Acute beneficial hemodynamic effects of positive inotropic therapy were sustained during chronic therapy in patients with advanced CHF awaiting cardiac transplantation. Tachyphylaxis was not a clinically important factor limiting the use of continuous positive inotropic agents in these patients.

Resting hemodynamics before and during positive inotropic infusion

| Right atrial pressure (RA) mm Hg | Pulmonary artey mean (PAM) mm Hg | Pulmonary caplillary wedge pressure (PCWP) | Pulmonary vascualr resistance (PVR) wood units | cardiac Index (CI) l/mn/$m^2$ |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Pre inotrope infusion | 11.4 ± 6 | 35 ± 11 | 22.2 ± 8 | 3.7 ± 2 | 1.85 ± 0.5 |
| 24 hours on inotrope infusion | 7.3 ± 3 | 30.4 ± 9 | 18.5 ± 8 | 2.5 ± 1.7 | 2.8 ± 0.9 |
| 3-6 months on inotrope infusion | 3.9 ± 3 | 27.5 ± 9 | 17.7 ± 5 | 2.0 ± 1.5 | 2.5 ± 0.5 |



1085-80

## The Value of Dobutamine Stress Echo in Predicting Improvement in Left Ventricular Function in Patients With Ischemic and Nonischemic Cardiomyopathy After One Year of Beta-Blocker Therapy

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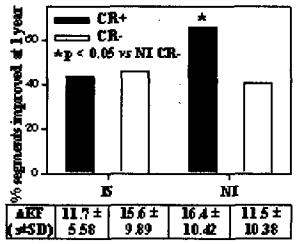
**Background:** Beta-blockers reduce morbidity and mortality in chronic heart failure. However, the value of dobutamine stress echo (DSE) in predicting long-term global and segmental improvement in LV function in ischemic (IS) vs nonischemic (NI) cardiomyopathy is not well defined.
**Methods:** We studied 32 heart failure patients, 18 IS and 14 NI with LVEF< 35%. All were on stable doses of ACE-inhibitors. DSE was obtained prior to initiation of beta-blockers to define contractile reserve (CR). 2D echoes were obtained at baseline and after 12 months of carvedilol (n=29, mean dose 47.0 ±19.0 mg/d), metoprolol XL (n=2, mean dose 62.5 mg/d) or atenolol (n=1, 12.5 mg/d). The left ventricle was divided into 16 segments using the traditional ASE classification scheme. Contractility of each segment was assessed and an echo score (ES) was given. Each segment was classified as CR positive (+) or negative (-) based on presence or absence of improvement in ES ≥ 1 with low dose dobutamine (5mcg/kg/min) compared to baseline. The Δ EF was calculated as the difference in EF between baseline and 12 months.
**Results:** See Fig.
**Conclusion:** After 1 year of beta-blockers, EF and ES improve in both IS and NI patients irrespective of contractile reserve status. However, the magnitude of improvement is greatest in NI patients with CR.




1085-81

## Favorable Effects of Digoxin on Mortality and Morbidity in Patients With Class IV Congestive Heart Failure Due to Systolic Dysfunction: Retrospective Analysis of the DIG Study

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Backgound: Previous small studies have suggested that digoxin exerts beneficial effects in severe symptomatic heart failure (HF), but data specifically in patients (Pts) with NYHA class IV and reduced ejection fraction are lacking. Therapeutic options are limited in NYHA class IV Pts, so effects of digoxin in this subset are of interest.
Methods: The DIG Study, a large-scale prospective trial of the effect of digoxin on morbidity and mortality, included Pts with NYHA class IV. Data from this trial were analyzed to assess the effect of digoxin in Pts with NYHA class IV HF and reduced ejection fractions.
Results: A total of 142 Pts with NYHA class IV symptoms at baseline and LVEF ≤ 45% in the DIG Study were analyzed. As a group, these patients had severe left ventricular dysfunction (mean LVEF 24 ± 9.1%) with 1 year and 3 year survival rates of 68% and 41% respectively. Of these Pts, 76 were randomized to digoxin and 66 to placebo. Unadjusted survival analysis demonstrated a trend toward a lower mortality rate in Pts randomized to digoxin (hazard ratio 0.68 with 95% confidence interval of 0.45 - 1.03, p = 0.068). Multivariate, Cox analysis adjusting for baseline characteristics predictive of survival in this subset (prior digoxin therapy, systolic blood pressure, ischemic etiology, diabetes, and HF score), indicated that digoxin therapy was associated with better survival (hazard ratio 0.47 with 95% confidence interval of 0.30 - 0.74, p = 0.001). Similar adjusted analysis found digoxin reduced the risk of the combined endpoint of mortality and time to first hospitalization for HF (hazard ratio 0.51 with 95% confidence interval 0.34 - 0.76, p = 0.001).
Conclusions. Retrospective analysis of the DIG Study results suggests digoxin is efficacious in Pts with NYHA class IV HF due to systolic dysfunction. Although these results must be treated with caution due to the small number of Pts studied, lack of effective therapies and the high risk of NYHA class IV HF suggests strong consideration for digoxin therapy in this population.

1085-82

## Sildenafil (Viagrafi) Improves Arterial Stiffness and Reduces Left Ventricular Load in Patients With Congestive Heart Failure

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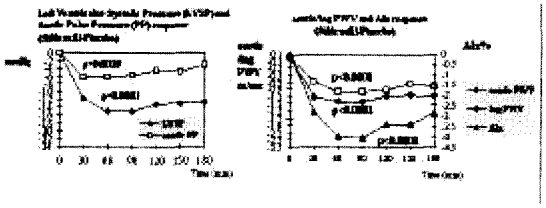
**Background:** Sildenafil (S) is an effective drug for erectile dysfunction affecting the nitric oxide-cGMP pathway. The impairment of this pathway has been implicated in the pathogenesis of congestive heart failure (CHF). Arterial stiffness and wave reflection are important determinants of left ventricular function, while wave reflection has also been inversely associated with exercise capacity.
**Methods:** To investigate the effect of S on arterial stiffness and wave reflection in CHF we studied 20 patients (age 48-88 yrs) in NYHA class II or III (EF<35%), in a randomized, double-blind, placebo-controlled, cross-over design (50 mg of S and placebo). Carotid-femoral (aortic) and leg pulse wave velocity (PWV) were measured as indices of arterial stiffness using a validated device (Complior®). Wave reflection was studied by measuring augmentation index (AIx) using a validated system (SphygmoCor®) that employs high-fidelity arterial tonometry and pulse wave analysis.
**Results:** S was well tolerated with no side effects in any patient. S caused a decrease in left ventricular systolic pressure and on aortic pulse pressure by 13.9 mmHg and 4.8 mmHg respectively (net sildenafil minus placebo effect, graph). Aortic and leg PWV and AIx were also decreased by 0.89 m/sec, 1.14 m/sec, and 3.5% (graph).
**Conclusions:** S leads to an improvement in arterial stiffness and to a reduction in left ventricular load in patients with CHF. This has important implications for cardiac performance and exercise capacity in such patients.



1085-83

## Serum Digoxin Concentration and the Efficacy of Digoxin Therapy in the Treatment of Heart Failure

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**Background:** The association of serum digoxin (DIG) concentrations and all-cause mortality in patients with stable heart failure has not been assessed.
**Methods:** We conducted an analysis of the Digitalis Investigation Group trial to assess variations in serum DIG concentration and their association with mortality. Because of a sex*DIG therapy interaction and the small number of women with measured serum DIG levels, analysis was restricted to male patients with an ejection fraction ≤45% (n=3,782). Patients randomized to DIG were divided into three groups based on their serum DIG concentration (SDC, in ng/mL) at 1 month - SDC ≤0.8 (n=572), SDC 0.9 to 1.1 (n=322), and SDC ≥1.2 (n=277) - and compared with patients randomized to placebo (n=2,611). Multivariable Cox proportional hazards analysis adjusting for age, renal function, LVEF, NYHA class, other patient characteristics, and medical therapy was conducted to assess the association of SDC and all-cause mortality (mean follow-up: 37 months).
**Results:** Mortality rates were similar for patients randomized to placebo and DIG (36.2% vs. 36.6%, P=0.80). However, higher SDCs were associated with increased crude mortality rates (SDC ≤0.8 29.9%; SDC 0.9 to 1.1 38.8%; SDC ≥1.2 48.0%, P<0.001 for trend). Patients with SDC ≤0.8 had a 6.3% (95% CI 2.1%, 10.5%) lower all-cause mortality rate than patients randomized to placebo. DIG was not associated with a reduction in all-cause mortality rates among patients with SDC 0.9 to 1.1 (2.6%, 95% CI -3.0%, 8.3%), while patients with SDC ≥1.2 had an 11.8% (95% CI 5.7%, 18.0%) higher absolute mortality rate than patients randomized to placebo. After multivariable adjustment, all-cause mortality risks were lower among patients with SDC ≤0.8 (hazard ratio [HR] 0.80, 95% CI 0.68, 0.94), statistically comparable among patients with SDC 0.9 to 1.1 (HR 0.89, 95% CI 0.74, 1.08), and trended toward increased harm among patients with SDC ≥1.2 (HR 1.16, 95% CI 0.96, 1.39) compared with patients randomized to placebo.
**Conclusions:** Our findings suggest that the efficacy of digoxin therapy is optimized in the serum DIG concentration range of 0.5 ng/mL to 0.8 ng/mL among stable male heart failure patients with left ventricular dysfunction.