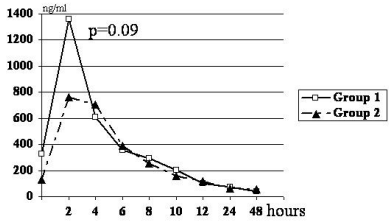

Figure 1. Serial measurements of plasma myoglobin levels

POSTER SESSION

1012 Heart Failure: Chronic Treatment

Sunday, March 07, 2004, 9:00 a.m.-11:00 a.m.
Morial Convention Center, Hall G
Presentation Hour: 10:00 a.m.-11:00 a.m.

1012-103 Blood Pressure Changes Do Not Influence the Beneficial Effects of Carvedilol Compared to Metoprolol in the Patients With Heart Failure: Results From COMET (Carvedilol or Metoprolol European Trial)

Marco Metra, Andrea Di Lenarda, Peter Hanrath, Michel Komajda, Beatrix Lutiger, John G. Cleland, Willem J. Remme, Armin Scherhag, Andrew Charlesworth, Karl Swedberg, Christian Torp-Pedersen, For the COMET investigators, University of Brescia, Brescia, Italy, National Heart and Lung Institute, London, United Kingdom

Background: The Carvedilol or Metoprolol European Trial (COMET) has shown a reduction in all-cause mortality with carvedilol, compared with metoprolol, in 3029 patients with chronic heart failure (RR 0.83, 95%CI, 0.74-0.93, p=0.0017). The potenital influence on this difference of effects on blood pressure (BP) is unknown.
Methods: We have related the effects on long-term mortality of baseline BP and its early changes (Δ) in COMET. Baseline analyses are presented for the intent to treat population. ΔBP analyses are on treatment.
Results: At the end of the uptitration phase, 4 months after randomization, mean systolic BP (SBP) declined from baseline by 3.8 ± 17.4 mm Hg in the carvedilol group and 2.0 ± 17.7 mm Hg in the metoprolol group (p = 0.01). Patients on carvedilol maintained a significantly lower mean SBP at most visits and also had a lower mean diastolic BP (DBP) at 4, 8, 16, 32, 44 and 52 months. Among the 2589 patients reassessed at 4 months, ΔSBP ≤ -3 mm Hg (median value) was found in 685/1291 (53%) patients on carvedilol and in 617/1298 (48%) on metoprolol. Compared with the others, the patients with a ≥ -3 mm Hg ΔSBP had a higher baseline SBP (133±19 versus 121±17 mm Hg, p<0.001) and DBP (79±11 versus 76±10 mm Hg, p<0.001) with an higher prevalence of ischemic heart disease (54% versus 48%, p=0.002) and a lower prevalence of idiopathic cardiomyopathy (43% versus 49%; p=0.001) and diabetes (21% versus 26%; p=0.002). There were 409/1302 deaths (31%) in the patients with a ΔSBP ≥ -3 mm Hg and 400/1287 (31%) in the others. Mortality was reduced with carvedilol, compared to metoprolol, both in the patients with ΔSBP ≥ -3 mm Hg (28% versus 36%; RR, 0.76, 95% CI, 0.62-0.92; p=0.0049) and in the others (28% versus 34%; RR, 0.79; 95% CI, 0.65-0.97; p=0.0229). No interaction between the effect on mortality of carvedilol, compared to metoprolol, and the ΔSBP was found (RR 1.05; 95% CI, 0.80-1.39). By multivariate analysis, a SBP >120 mmHg at baseline was associated with a lower mortality (RR, 0.72; 95% CI, 0.63-0.83; p<0.0001) while ΔSBP was not significant.
Conclusion: Carvedilol reduces mortality compared to metoprolol irrespective of BP lowering. A higher baseline SBP is associated with a lower mortality risk.

1012-104 Safety of Beta-Blockers in Patients With Heart Failure and Renal Insufficiency: Data From IMPACT-HF

Adrian F. Hernandez, Wendy A. Gattis, Jyotsna Garg, Alan Chu, A. Bleakley Chandler, Mihai Gheorghiade, Christopher M. O'Connor, Duke Clinical Research Institute, Durham, NC

Background: Renal insufficiency is a significant predictor of poor outcomes in heart failure (HF) patients. To date, little is known about the safety of beta-blockers (BB) in heart failure patients with renal insufficiency because clinical trials of BB excluded patients with significant renal disease.
Methods: The IMPACT-HF study was conducted in patients with systolic dysfunction admitted for worsening chronic HF symptoms. The trial randomized patients to in-hospital initiation of carvedilol compared to the standard practice of post discharge (>2 weeks) BB initiation. A registry was conducted concurrently with the main trial to collect data on all HF hospitalizations. The IMPACT-HF trial and registry databases were combined and retrospectively analyzed to determine if the use of BB in HF patients with moderate (estimated GFR 30-60 mL/min per 1.73 m2) or severe (<30 mL/min per 1.73 m2) renal insufficiency had a higher rate of death or rehospitalization within 60 days than patients without beta-blockers. An unadjusted analysis was performed, as well as a model adjusted for age, systolic blood pressure at baseline and nitrates prescribed at admission and prior HF hospitalizations.
Results: Overall, 908 pts were enrolled in the IMPACT-HF trial and registry. In the total population, 270 (29.7%) pts had severe renal insufficiency and 308 (33.9%) pts had moderate renal insufficiency. Degree of renal insufficiency significantly correlated with 60-day death and rehospitalization- severe 37.4%; moderate 33.4%; normal 18.2% (p <0.01). There were 531 pts with BB and 377 pts without a BB on discharge. In a risk-adjusted model, there was no adverse effect of BB use in patients with moderate or severe renal insufficiency (wald chi-sqr =0.0748; p= 0.7845).
Conclusions: Beta-blockers may be safely used in HF patients with renal insufficiency. Beta-blocker use does not appear to cause early worsening HF requiring rehospitalization even in patients with moderate or severe renal insufficiency.

1012-121 Lack of Heart Rate Effects on the Mortality Benefits of Carvedilol Compared to Metoprolol in the Patients With Heart Failure: Results From the Carvedilol or Metoprolol European Trial (COMET)

Marco Metra, John G. Cleland, Andrea Di Lenarda, Peter Hanrath, Michel Komajda, Beatrix Lutiger, Philip A. Poole-Wilson, Willem J. Remme, Armin Scherhag, Andrew Charlesworth, Karl Swedberg, Christian Torp-Pedersen, For the COMET investigators, University of Brescia, Brescia, Italy, National Heart and Lung Institute, London, United Kingdom

Background: The Carvedilol or Metoprolol European Trial (COMET) has shown a reduction in all-cause mortality with carvedilol, compared with metoprolol, in 3029 patients with chronic heart failure (RR 0.83, 95%CI, 0.74-0.93, p=0.0017). The potential influence on this difference of effects on heart rate (HR) are unknown.
Methods: We related the effects on long-term mortality of baseline HR and early changes (Δ) of HR in COMET. Baseline analyses are presented for the intent to treat population, ΔHR analyses are on treatment.
Results: At the end of uptitration, 4 months after randomization, mean HR declined from baseline by 13.3 beats per minute (bpm) in the carvedilol group and 11.7 bpm in the metoprolol group (difference -1.6 bpm; 95%CI, -2.7 to -0.6). Patients on carvedilol maintained a significantly lower mean HR only at two more visits (8, 16 months). Among the 2579 patients reassessed at 4 months, Δ HR ≥ -12 bpm (median value) was found in 714/1289 (55%) patients on carvedilol and in 640/1290 (50%) patients on metoprolol (p=0.0033). Compared with the others, the patients with a ≥ -12 bpm ΔHR had a higher baseline HR (87±13 versus 75±11 bpm, p<0.001) and a lower LVEF (25.6±7 versus 26.7±7% p<0.001) with a lower percentage of males (78% versus 82%, p=0.0082) and of patients with a pacemaker (2.6% versus 9.1%; p<0.001) and a higher percentage in sinus rhythm (78.5% versus 73.2%; p=0.0017). Within each subgroup, the HR profiles were the same for carvedilol and metoprolol. Mortality was the same (31%) in the patients with a ΔHR ≥ or < -12 bpm. Mortality was reduced with carvedilol, compared to metoprolol, both in the patients with ΔHR ≥ -12 bpm (28% versus 35%; RR 0.77, 95% CI, 0.64-0.94; p=0.0086) and in the others (28% versus 34%; RR 0.79; 95% CI, 0.65-0.97; p=0.0229). No interaction between the effect on mortality of carvedilol, compared to metoprolol, and the ΔHR was found (RR 1.021; 95% CI, 0.77-1.35). By multivariate analysis, neither the baseline HR nor ΔHR were associated with mortality.
Conclusion: Outcome is not directly or simply related to baseline HR or its early changes in COMET.

1012-122 Chronic Treatment With Carvedilol Improves Left Ventricular Pump Performance by Increasing Intrinsic Myocardial Contractility in Patients With Heart Failure

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Background: Chronic treatment with β-blockers improves LV pump performance in patients with heart failure (HF); however, it is not known whether this improvement is related to changes in LV remodeling, LV loading conditions or intrinsic myocardial contractility. Accordingly, the **purpose** of this study was to study mechanisms of improvement in LV pump performance following β-blocker treatment in HF patients. **Methods:** 32 patients with HF, LVEF<35 %, NYHA Class II-IV, on ACE inhibitors but not on β-blockers were studied at baseline and at 6 months after treatment with carvedilol. Cardiac output (CO), LV fractional shortening (FS), velocity of circumferential fiber shortening (VCF)- relatively afterload dependent measures of contractility, LV end systolic stress (LVESS),VCF:LVESS relation –an afterload corrected measure of contractility, LV end diastolic volume (LVol), and LV mass (LVM) were measured by echocardiography and LVEF by MUGA. **Results:** Carvedilol treatment resulted in significant (p 0.01-0.04) improvements in load independent (VCF:LVESS ratio), and load dependent indices of contractility (FS,VCF, LVEF), as well as a decrease in LV end-diastolic volume.(Table) There were no significant changes in LV end-systolic stress or in LV mass. **Conclusions:** Taken together these studies suggest that the improvements in LV pump performance after chronic treatment with carvedilol are multifactorial and are related to changes in intrinsic myocardial contractility as well as changes in LV preload.

Table

	LVol (ml)	LVMass (gm)	C.O.(L/min)	FS (%)	VCF (circ/sec)	LVESS(gm/cm^2)	VCF:LVESS ratio	LVEF (%)by MUGA
Baseline	221 ± 68	168 ± 73	3.0 ± 0.9	17.1± 6.3	0.63 ± 0.24	234 ± 87	0.0032 ± 0.0021	28.2 ± 8.4
6 Months	197 ± 70 *	163 ± 63	2.9 ± 0.8	23.4 ± 8.0 *	0.78 ±0.22 *	191± 67	0.0048 ±0.0017 *	35.8± 12.9 *

1012-123 Safety and Tolerability of Fast Up-Titration of Carvedilol in Patients With Heart Failure

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Background: Although beta-blockers (BB) are now the cornerstone in the treatment of congestive heart failure (CHF), many patients are still receiving inadequate doses, probably due to cautious prescription. We designed this study to evaluated the safety and tolerability of a fast up-titration of carvedilol soon after compensation.
Methods: After compensation, 31 consecutive hospitalized patients (pts) with left ventricular ejection fraction (LVEF) <= 0.45 who had never used BB to treat CHF and with no contraindication to BB were selected. Mean age was 55.5 years; 21 were men, and in 54.8% (n=17) inotropic support was needed for compensation. Mean LVEF was 0.29±0.07; mean left ventricular diastolic diameter was 7.0±0.7 cm. The initial dose of 3.125 mg bid was doubled each 2 days until day 8 (target dose of 25 mg bid). Criteria for increment were HR >= 55 bpm, systolic blood pressure (SBP) >= 90 mmHg and no worsening of CHF. A 6-minute walk test was performed on day zero, day 5, day 8 and day 30; 24 hours blood pressure continuous monitoring was performed on day zero and day 8.
Results: It was possible to reach the daily dose of 25 mg in 23/31 (74.2%) and 50 mg in 19/31 (61,2%) pts. The dose reached on day 8 was not different between pts who did or did not required inotropic support for compensation. In the patients who reached the dose of 25 mg/day the distance walked did not differ between days zero, 5, 8 and 30 (373.6±86.5 vs. 408.7±108.8 vs. 396.3±145.5 vs. 420.0±153.8 meters – p=0.18, 0.48 and 0.22). Mean weight gain was 2.1 kg (p=0.52), and SBP tended to be lower on day 8 (98.5±15.2 vs. 93.2±17.4 mmHg – p=0.06). The same tolerability was observed on day 30. The dose could not be increased in 9 patients, had to be reduced in 1, and had to be withdrawn in 2.
Conclusion: Introduction and the fast up-titration of carvedilol can be done even after inotropic support. Rapid up-titration was safe and can be done on lower intervals than currently recommended.

1012-124 Carvedilol Improves Myocardial Perfusion in Conscious Dogs With Pacing Induced Dilated Cardiomyopathy

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Background: Both combined (β1, β2, α1, Carvedilol) and selective (β1, Metoprolol succinate) adrenergic blockade have been associated with improved survival and clinical outcomes in DCM. Whether there are important differences between the subclasses remains controversial. Little is known with respect to differences in regional myocardial perfusion between agents, especially in non-ischemic DCM. We have shown previously that DCM in conscious dogs is associated with reduced subendocardial perfusion in the absence of CAD.
Methods: We studied 15 conscious, chronically instrumented dogs with severe DCM induced by 29 days of rapid pacing (240 min-1). We measured regional (subendocardium: ENDO, subepicardium: EPI) myocardial perfusion in the LV and RV using neutron activated microspheres before and after treatment with carvedilol (CARV: 25 mg po BID) or metoprolol (MET: 100 mg po QD) for 3 days. Measurements of coronary perfusion pressure (CPP=MAP-LVEDP-RA) and heart rate (HR) were recorded simultaneously to insure comparable flow determinants.
Results: Both treatments were associated with significant ($p \leq 0.01$) decreases in HR (CARV: - 49±6 from 126±26 min-1; MET: -42±3 from 124±6 min-1) and LVEDP (CARD: -17±4 from 35±2 mmHg; MET: -14±3 from 36±2 mmHg) and significant increases in CPP (CARV: +12±3 from 44±4 mmHg; MET: +14±3 from 41±3 mmHg).
CARV treatment increased LV ENDO (1.26±0.15 to 1.49±0.22 ml/min/g) but not LV EPI flow (1.06±0.15 to 1.05±0.11 ml/min/g). In contrast, MET decreased LV ENDO (1.17±0.12 to 1.05±0.13 ml/min/g, $p \leq 0.05$ compared to CARV) but did not change LV EPI (0.96±0.18 to 0.95±0.11 ml/min/g). CARV also increased RV ENDO (0.98±0.15 to 1.56±0.14 ml/min/g) while MET had no effect (1.18±0.19 to 1.12±0.25 ml/min/g, $p \leq 0.05$ compared to CARV).
Conclusion: Despite comparable effects on HR and CPP, CARV improves LV and RV ENDO perfusion compared to MET. These differences are likely explained by α1 adrenergic blocking effects and may help to explain differences in clinical outcomes between CARV and MET.

1012-125 Monotherapy With Extended Release Metoprolol Succinate Normalizes Exppression of Type-1 Protein Phosphatase in Left Ventricular Myocardium of Dogs With Chronic Heart Failure

Ramesh C. Gupta, Sudhish Mishra, Hideaki Morita, Sidney Goldstein, Hani N. Sabbah, Henry Ford Health System, Detroit, MI

Background: We previously showed that in dogs with chronic heart failure (HF) type-1 protein phosphatase (PP1) activity is increased and that this increase is due, in part, to increased protein level of the alpha catalytic subunit of PP1 (PP1Calpha), an enzyme considered to be a negative regulator of cardiac function. Increased PP1 activity in HF can lead to dephosphorylation of phospholamban and consequently to abnormalities of calcium cycling within the sarcoplasmic reticulum (SR) ultimately leading to LV systolic and diastolic dysfucnction. In the same canine model of coronary microembolization-induced HF, we showed that chronic monotherapy with extended release metoprolol succinate (ER-MET), a selective beta-1 adrenoceptor blocker, improves left ventricular (LV) ejection fraction, reduces end-diastolic wall stress and improves myocardial relaxation. In this study, we examined whether the improvement in LV systolic and diastolic function following chronic ER-MET therapy is associated with reduced PP1Calpha protein expression. **Methods:** Protein expression of PP1Calpha and calsequestrin (CSQ), an SR protein not altered in HF, were measured in LV tissue of 6 dogs with HF treated long-term (3 months) with ER-MET (100 mg once daily), 6 dogs with HF that were untreated and 6 normal dogs. In all instances, protein expression was measured in LV homogenate using Western blots. Bands were quantified in densitometric units. **Results:** Protein expression of PP1Calpha normalized to total tissue levels of CSQ increased significantly in untreated HF dogs compared to normal dogs (0.99 ± 0.05 vs. 0.47 ± 0.02, P<0.05). In dogs with HF treated with ER-MET, PP1Calpha protein expression decreased significantly compared to untreated HF dogs (0.63 ± 0.05 vs. 0.99 ± 0.05, P<0.05), but remained higher than that measured in normal dogs (0.63 ± 0.05 vs. 0.47 ± 0.02, P < 0.05). **Conclusions:** In dogs with chronic HF, PP1Calpha protein expression is increased. Long-term therapy with ER-MET partially restores protein expression of PP1Calpha to near normal levels. Normalization of PP1Calpha expression in HF can explain, in part, the improvement of LV systolic and diastolic function seen with long-term ER MET therapy.

1012-126 Contemporary Dosing of Angiotensin Converting Enzyme Inhibitors and Beta Blockers in Chronic Heart Failure: Report From the STAMINA:HFP (Study of Anemia in a Heart Failure Population) Registry

Javed Butler, Alan Miller, Ron M. Oren, Jalal K. Ghali, Biljana Pavlovic-Surjancev, Carla A. Sueta, Christopher M. O'Connor, Kathy Hebert, Mihai Gheorghiade, Douglas Schocken, William Cotts, Todd A. Schwartz, Kirkwood F. Adams, Jr., The STAMINA-HFP Investigators, University of North Carolina - Chapel Hill, Chapel Hill, NC

Background. Optimal utilization of angiotensin converting enzyme inhibitors (ACEI) and beta blockers (BB) in heart failure requires treatment of eligible patients and use of doses proven effective in clinical trials. However, doses commonly given patients with heart failure are not well studied.
Methods. The STAMINA-HFP Registry enrolled randomly selected patients with heart failure from 6/24/02 to 5/15/03 in 12 specialty clinics and 45 community cardiology clinics. Data on 656 return patients with EF < 40 who were taking either ACEI or BB and had information available on doses of these drugs and use of angiotensin receptor blockers (ARB) were analyzed. Doses were converted to milligram equivalents of enalapril or metoprolol CR/XL. Extent of titration in each patient was evaluated as 1) % of the clinical trial target dose in ACEI and BB mortality trials (%CTTD), (20 mg/d for enalapril and 200 mg/d of metoprolol CR/XL) and 2) % of the mean doses actually achieved in these trials (%MDA) (16.6 mg/d for enalapril and 159 mg/d for metoprolol CR/XL).
Results. No patients were taking ACEI + ARB and no BB. Only 2.6% of patients were taking BB + ACEI + ARB. The percentage of patients reaching at least CTTD or MDA and the mean±SD dose equivalents achieved in the other patient groups are shown.

Drug(s) (N)	ACEI CTTD ≥100%	ACEI MDA ≥100%	Enalmg (mg/d)	BB CTTD ≥100%	BB MDA ≥100%	Metocrmg (mg/d)	ACEI + BB CTTD ≥100%	ACEI + BB MDA ≥100%
ACEI (43)	42	42	17±16	--	--	--	--	--
BB (156)	--	--	--	32	33	113±82	--	--
BB+ARB (96)	--	--	--	48	49	161±114¶	--	--
BB+ACEI (344)	54	54	19±15†	39	42	136±116*,§	25	27

*Enalmg=milligram equivalents of enalapril, Metocrmg=milligram equivalents of metoprolol CR/XL, -- = not applicable.
†p=0.408 BB + ACEI versus ACEI alone, *p=0.012 BB alone versus BB + ACEI,
¶p=0.001 BB alone versus BB + ARB,
§p=0.080 BB + ACEI versus BB + ARB

Conclusions. Registry patients with documented systolic dysfunction were commonly treated with doses of ACEI and BB below MDA. Whether dose titration is limited by clinical characteristics or other factors is under investigation.

1012-127 Neutral Endopeptidase Inhibition Augments the Vascular Actions of Bradykinin in Patients With Heart Failure on Chronic Angiotensin-Converting Enzyme Inhibitor Therapy

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Background Angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) degrade kinins. ACE inhibition potentiates bradykinin mediated vasodilatation and endothelial release of the pro-lytic factor, tissue plasminogen activator (t-PA) in patients with chronic heart failure (CHF). We investigated whether additional NEP inhibition with thior-