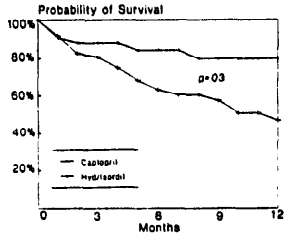
Wednesday, March 6, 1991
2:00PM–3:30PM, Room 264, West Concourse
Controlled Clinical Trials in Heart Failure

2:00

SURVIVAL WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITION VS. DIRECT VASODILATION FOR THE SAME HEMODYNAMIC GOALS IN ADVANCED HEART FAILURE: 106 RANDOMIZED PATIENTS. Gregg Fonarow, Catherine Chelimsky-Fallick, Lynne W. Stevenson, Michael Luu, Michele Hamilton, Jaime Moriguchi, Julie Walden, Elaine Albanese, Jan Tillisch. UCLA Medical Center, Los Angeles, CA.

Both angiotensin-converting-enzyme inhibition (ACEI) and direct vasodilation reduce heart failure mortality, but have not been compared in a randomized trial. We randomized 106 pts evaluated for transplant to captopril (ACEI) or hydralazine/isordil (H/I) titrated to match the hemodynamics achieved on nitroprusside + diuretics to approach SVR 1200 d-sec-cm^{-5} and PCW 15 mm, with oral drug crossover for poor hemodynamics or side effects (46% from ACEI, 28% from H/I). Pts discharged on ACEI had same EF=.20, initial RA=13 mm, PCW=27 mm, CO 3.1-3.2L, and SVR 1830-1920. On discharge regimen, final RAs were 7 mm, SVRs 1150, Na 134 vs 133, final PCWs 16 vs 18 mm (p=.05) and CO 4.3 vs 4.9L (p=.005). By Cox analysis, ACEI predicted survival without transplant (p=.015) independently of Na (.018) and low PCW on therapy (.081). ACEI benefit was most apparent in pts with Na ≤135. This study cannot determine if good hemodynamic response to ACEI is itself a major predictor of survival.



Despite titration to the same hemodynamic goals, ACEI reduced death in advanced heart failure compared to H/I in this randomized trial.

2:15

LONG TERM CLINICAL AND NEUROHORMONAL EFFECTS OF NICARDIPINE IN PATIENTS WITH SEVERE HEART FAILURE ON MAINTENANCE THERAPY WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Mihai Gheorghiade, Veronica Hall, A. David Goldberg, T. Barry Levine, Sidney Goldstein, Heart and Vascular Institute, Henry Ford Hospital, Detroit, Michigan

It has been proposed that the worsening of heart failure (HF) with dihydropyridines such as nicardipine is related to the activation of the neuroendocrine system. To test this, we evaluated 20 pts with severe HF (age 55±14 yrs; Functional Class: NYHA III; left ventricular ejection fraction[EF]:18±8%) on maintenance therapy with captopril 75 mg/day, randomized to nicardipine 60 or 90 mg/day or placebo during a 4 mo. double-blind protocol. The following measurements were obtained at baseline (B) monthly x 4 or last follow-up (F): rest and exercise radionuclide ventriculography (RVG EF), maximal treadmill time (T),and 6-minute walking test distance (W), serum norepinephrine (Nor) and aldosterone (Aldo) concentrations and plasma renin activity. During follow-up, worsening of HF occurred in 6 pts in the nicardipine group and 2 pts on placebo (p=0.06).

	Nor (pg/ml)		Renin (ng/ml/hr)		Aldo (pg/ml)	
	B	F	B	F	B	F
Placebo	678±499	691±524	16±27	11±13	10±7	15±1
Nicardipine	532±247	564±303	7± 6	22±28*	11±9	11±7

*p <0.05 compared to B

In the 6 Nicardipine pts who deteriorated, renin increased from 4±4 to 21±15 ng/ml/hr (p=0.001). The T time, W distance, and exercise RVG EF at the last follow-up did not change in pts who did not deteriorate with HF in the P or N group, compared to baseline. In this group of pts with severe HF receiving captopril, nicardipine caused worsening of HF without an increase in serum Nor and Aldo.

2:30

RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF AMLODIPINE IN PATIENTS WITH MILD-TO-MODERATE HEART FAILURE.

Milton Packer, Pascal Nicod, Bijoy R. Khandheria, Dennis L. Costello, Alan G. Wasserman, Marvin A. Konstam, Robert J. Weiss, Richard R. Moyer, David J. Pinsky, Meyer H. Abittan, Joseph F. Souhrada. Mount Sinai School of Medicine, New York, NY

Previous studies have shown that calcium channel blockers (CCBs) are ineffective and may be deleterious in heart failure (CHF), but these unfavorable responses might not be seen with all CCBs. We conducted a multicenter, double-blind, placebo-controlled trial of a new CCB, amlodipine (AML), in 118 CHF pts. All pts had class II-III symptoms, LV ejection fraction (EF) < 40% and were treated with digoxin and diuretics; 80 pts were also taking converting-enzyme inhibitors. After a single-blind run-in period, pts received either AML (10 mg once daily, n=58) or placebo (PLA, n=60) for 2 months. All pretreatment variables were similar in the two groups. Symptoms and exercise time (ExT) were assessed before randomization and after 4 & 8 weeks of treatment; * = P < 0.05 (8 wks vs baseline); † = P < 0.05 (AML vs PLA).

	4 weeks	8 weeks
Placebo	↑ 12 ± 13 sec	↑ 22 ± 13 sec
Amlodipine	↑ 39 ± 13 sec	↑ 62 ± 17 sec*†

After 8 weeks of therapy, ExT ↑ more with AML than PLA (P = 0.037). In addition, more pts treated with AML experienced improvement in CHF symptoms (AML vs PLA, 55% vs 29%, P < 0.05). Although AML did not affect LVEF in the trial as a whole, LVEF tended to ↑ with AML in pts treated with converting-enzyme inhibitors. Interestingly, plasma norepinephrine decreased in pts treated with AML (344 to 249 pg/ml) but tended to increase on PLA (391 to 421 pg/ml), AML vs PLA, P < 0.05. Eleven pts on AML and 12 on PLA withdrew due to adverse reactions.

In conclusion, unlike other CCBs, AML improves the exercise capacity of pts with mild-to-moderate CHF. The mechanism by which AML exerts this effect is unknown, but it may involve an action of the drug to reduce sympathetic activity in CHF.

2:45

DOUBLE-BLIND, PLACEBO-CONTROLLED (P), COMPARISON OF ENOXIMONE (E) AND DOBUTAMINE (D) INFUSIONS IN MODERATE TO SEVERE CONGESTIVE HEART FAILURE PATIENTS (NYHA III-IV)

Edward Gilbert, M.D., For The Enoximone Working Group, University of Utah, School of Medicine, Salt Lake City, UT

Enoximone is a selective PDE Type III inhibitor that has both inotropic and vasodilatory properties. This study compared the hemodynamic response of E to P for 24 hours and to open-labeled D for 48 hours. 136 patients were enrolled. At baseline treatment groups were comparable. Mean CI (L/min/m²) was 1.79 E, 1.79 D, and 1.88 P. PCWP (mmHg) was 25.6 E, 25.8 D, and 26.0 P. After 48 hours patients were transferred to standard oral therapy. Serial 24-hour Holter recordings were obtained to assess proarrhythmic potential. Statistically significant improvement was found in multiple hemodynamic parameters for both E and D compared to P. Compared to D, E was more effective in reducing PCWP and more patients tolerated switching to oral therapy (E 65% vs D 49%). Adverse events were reported with equal frequency for D and E patients. Both active compounds increased ventricular ectopy compared to P.

	CHANGE FROM BASELINE AT 24 HOURS ± SE		
	ENOXIMONE(n=46)	DOBUTAMINE(n=43)	PLACEBO(n=47)
CI L/min/m²	0.89[a,b] ±0.07	0.55[a] ±0.06	0.09 ±0.08
PCWP mmHg	-6.0[a,b] ±1.0	-2.4 ±1.3	-1.6 ±0.9
SVR d.sec.cm²	-647[a] ± 73	-489[a] ± 70	-78 ± 58
PVR d.sec.cm²	-99[a] ± 23	-106[a] ± 26	18 ± 34
Mean PVC/HR	126[a] ± 32	77[a] ± 25	11 ± 26
Dropouts	4 (8.7%)	9 (20.9%)	5 (10.6%)
Deaths	1 (MI)	1 (MI)	0

a: P<.05, E or D compared to P; b: P<.05, E compared to D CONCLUSION: Enoximone is effective in improving the hemodynamic status in patients with moderate to severe CHF and is tolerated at least as well as dobutamine. Continuous infusion was associated with increased ventricular ectopy with both active compounds.