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Regional Comparison of Baseline Therapy in Patients Hospitalized for Acute Heart Failure with Systolic Dysfunction

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Background: In clinical trials, regional variations in treatment could impact outcomes. **Methods:** EVEREST was a multi-center, double-blind study which randomized patients with acute heart failure (HF) and systolic dysfunction on standard therapy to tolvaptan and placebo. A total of 4,133 patients were randomized at 359 centers in 20 countries, and divided among four regions: 1,251 in North America (NA), 699 in South America (SA), 564 in Western Europe (WE), and 1,619 in Eastern Europe (EE). The baseline therapy was recorded and assessed by region. **Results:** SA and EE, when compared to NA and WE, had significantly higher rates of spironolactone use and lower rates of revascularization and electrophysiologic devices (Table). **Conclusion:** Baseline therapy for patients hospitalized for acute HF differed based on region. Testing for possible interaction between region and the effect of the study drug should be pre-specified in multi-center international studies.

	NA n = 1249	SA n = 699	WE n = 563	EE n = 1619	p-value
THERAPY (%)					
Diuretics	96	99	99	96	0.001
ACE Inhibitors	58	80	69	85	<0.0001
Angiotensin II Receptor Blockers	21	10	18	3	<0.0001
Beta-Blockers	77	47	61	71	<0.0001
Spironolactone	38	71	43	68	<0.0001
Digoxin	47	55	34	48	<0.0001
Amiodarone	19	18	24	11	<0.0001
Calcium Channel Blockers	11	5	7	8	<0.0001
Prior PCI	33	12	25	7	<0.0001
Prior CABG	41	13	25	7	<0.0001
Pacemaker	33	11	20	7	<0.0001
ICD	34	3	13	5	<0.0001

p-values are for the overall comparison of the four regions
ACE indicates angiotensin-converting enzyme; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator

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Who Escaped Randomization To Receive a Pulmonary Artery Catheter? The ESCAPE Registry

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Background: The ESCAPE trial demonstrated equivalent 6-month heart failure (HF) hospitalization and mortality in patients (pts) randomized to therapy guided by pulmonary artery catheter (PAC) plus clinical assessment versus clinical assessment alone. However, it is unknown to what extent HF pts receiving PAC outside the trial differ from pts randomized using inclusion criteria designed to select for PAC equipoise. **Methods:** The ESCAPE registry was a concomitant repository of advanced HF pts receiving a PAC who did not fulfill trial entry criteria or were thought by HF specialists to require PAC-guided therapy. Survival was determined from the National Death Index and Alberta Registry. **Results:** From 23 ESCAPE sites, the registry enrolled 439 pts. Compared to trial pts, registry pts had lower blood pressure, less use of neurohormonal antagonists, more inotrope use, greater degree of renal dysfunction, longer hospital stay, and higher 6-month mortality (see table). Initial filling pressures were similar in both groups but registry pts had higher cardiac output. **Conclusions:** Clinical assessment and trial exclusion criteria identified a HF population with greater baseline severity of disease and higher risk for adverse clinical outcomes during and after hospitalization. It is not known if hemodynamic information in these sicker pts changed selection of therapies or outcomes. However, the registry population on average had unexpectedly similar hemodynamics to the randomized pts in whom PAC had no impact on outcome.

Characteristic	Registry (N = 439)	Trial (N = 433)
Age, years	61 (51−69)	56 (47−66)
Systolic BP, mmHg	103 (92−117)	109 (97−119)
Creatinine, mg/dL	1.6 (1.2−2.4)	1.4 (1.1−1.8)
ACE inhibitor, %	45.8	78.5
Inotrope, %	35.3	15.5
PCWP, mmHg	24 (18−29)	24 (19−30)*
Cardiac output, L/min	4.1 (3.2−5.2)	3.8 (2.9−4.6)*
Length of stay	13 (7-26)	6 (3-8)
6 month mortality	33.5%	19.7%

Continuous results in medians (interquartile range); *N = 201.

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Effects of 5′phosphodiesterase Chronic Inhibition with Sildenafil on Exercise Capacity, Ventilatory Efficiency, Oxygen Uptake Kinetics and Reactive Pulmonary Hypertension in Patients with Chronic Heart Failure: A Double-Blinded Placebo-Controlled Clinical Trial

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Background: Acute inhibition of 5′phosphodiesterase with sildenafil improves both functional capacity and pulmonary hypertension in patients with heart failure. The objectives of this prospective study were to assess whether continued administration of sildenafil could improve functional capacity, ventilatory efficiency, oxygen uptake kinetics and reactive pulmonary hypertension in chronic heart failure patients (CHF). **Methods:** We conducted a randomized, double-blinded, placebo-controlled clinical trial to assess acute (1 hour after 50mg PO) and chronic effects (four weeks after 50mg TID PO) of sildenafil in CHF outpatients. Study outcomes were cardiopulmonary exercise testing parameters (chronic effect) and echocardiographic-derived pulmonary artery systolic pressure (PASP) (acute and chronic effects). **Results:** Nineteen patients, with a mean age of 48 ± 12 years and left ventricular ejection fraction of 28 ± 6% were studied. Patients receiving sildenafil (n = 11) increased VO_2 peak after four weeks of administration from 16.4 ± 3 to 18.5 ± 3 mL/Kg/min (relative increment of 13%), compared to a decrease in the placebo group (n = 8) from 17.2 ± 2 to 16.5 ± 3 mL/Kg/min (relative decrement of 4%; P = 0.004), increased ventilatory efficiency (VE/VCO_2 slope, relative decrease of 24%, p = 0.002) and oxygen uptake kinetics ($T_{1/2}$ VO_2, relative decrease of 35%, p < 0.001). Sildenafil administration also significantly decreased PASP levels at 60 min (mean difference of 10 mmHg from baseline) and at four weeks (mean difference of 18 mmHg from baseline) compared to no meaningful changes after placebo (p = 0.004 for group and time interaction). Finally, we observed a moderate positive association between improvements on ventilatory efficiency (VE/VCO_2 slope) and pulmonary hypertension (r = 0.62, p = 0.03). **Conclusions:** Acute beneficial effects of sildenafil are maintained after 4 weeks of administration in stable CHF outpatients, with significant improvements on functional capacity, ventilatory efficiency, oxygen uptake kinetics and reactive pulmonary hypertension.

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Heart Failure Improvement after Autologous Bone Marrow Mononuclear Cells (ABMMC) Transplantation

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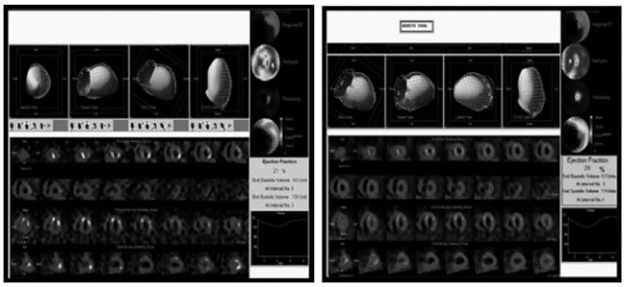
Background: Pilot studies suggest that intracoronary transplantation of unselected ABMMC cells may improve Left Ventricular Ejection Fraction (LVEF) in heart failure (HF) patients. **Methods:** Eighteen patients were enrolled and completed 1 year follow up. Patients underwent SPECT evaluation, all had ejection fraction < 35%, 6 patients were randomly allocated to the control group and 12 in Bone Marrow Cells (BMC) group, median age 65 years old, male/female ratio 17/1; all with ischemic cardiomyopathy. All of cohort had NYHA class of III with maximal medical therapy and median basal LEVF was 29,8%. Median number of mononuclear and CD34+ cells infused were $8.1*10^8$ and $1.2*10^7$ respectively in a 50 cc delivered retrograde via coronary sinus approach using balloon occlusion "over wire" for 8 to 10 minutes. No study related adverse events were observed. **Results:** After a median time of 21 days, patients in the BMC group had relief of dyspnea symptoms and improvement in

functional class. At 1 year, NYHA class improved in 92% of the patients in the BMC group by at least 1 class and no improvement in the control group. Mean improvements of LVEF post BMC transplantation were 5.0% and 7.4% at rest and stress SPECT respectively. Either rest and stress LVEF differences at one-year follow up and baseline between the BMC and control groups demonstrated significant difference; with rest LVEF was 4.8% vs 1.1% (p = 0.016) and with stress LVEF was 7.4% vs 0.08% (p = 0.001). **Conclusions:** Infusion of progenitor cells into the coronary sinus is safe and feasible in the ischemic HF patients. It is associated with significant improvement in symptoms, functional capacity and LVEF. Larger randomized studies are in progress.



Gated Spect Stress EF. Note the increased of 8% in the EF at 1 year evaluation.

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Atrial Fibrillation and Mortality in Patients Enrolled in the African American Heart Failure Trial

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Background: Atrial fibrillation (AF) is common in patients (pts) with heart failure (HF) and portends a worsened prognosis. African American (AA) pts with HF have a higher morbidity and mortality than the general HF population. Because of the low enrollment of AA in randomized HF trials, not much is known of AF in HF in this cohort. We sought to evaluate morbidity and mortality in pts enrolled in the African American Heart Failure Trial (A-HeFT). **Methods:** 1050 AA pts with NYHA class III/IV systolic HF, well treated (87% beta-blockers, 93% ACEI and/or ARB), were randomized to added fixed-dose combination of isosorbide dinitrate/hydralazine (FDC I/H) or placebo. **Results:** AF recorded in 174 (16.6%) pts at baseline and 183 (17.4%) combined baseline plus new development of AF during mean 12.8-month follow-up. Comparison of pts with AF vs. no AF revealed: mean age 61 ± 12 vs. 56 ± 13 yr (p < 0.001); systolic BP 124 ± 18 vs. 127 ± 18 mmHg (p = 0.044), diastolic BP 74 ± 11 vs. 77 ± 10 (p = 0.002); creatinine 1.4 ± 0.5 vs. 1.2 ± 0.5 (p < 0.001) and BNP 431 ± 443 vs. 283 ± 396 (p < 0.001). No significant difference was observed in ejection fraction, left ventricular end diastolic diameter or Quality of Life scores. However, survival differed significantly between AA pts with and without AF, (Fig 1A) and the use of FDC I/H influenced that survival (Fig 1B). **Conclusion:** AA with HF and AF (vs. no AF) were older, had lower BP and higher creatinine and BNP levels. They also had lower survival. The use of FDC I/H significantly improved survival in these high-risk HF patients.

Fig. 1A. Effect of Atrial Fibrillation at Baseline or During Trial on Survival

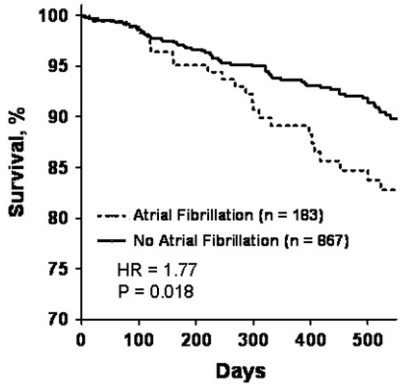
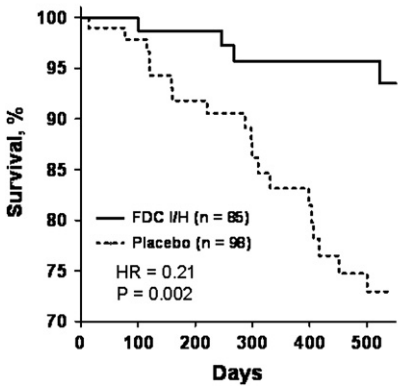


Fig. 1B. Effect of FDC I/H on Survival in Patients with Atrial Fibrillation



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Compliance with Once Daily Controlled Release vs Twice Daily Immediate Release Carvedilol in Patients with Heart Failure: The CASPER Trial

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Background: Once daily (QD) vs twice daily (BID) dosing may increase compliance, thereby increasing effective daily dosage. The CASPER Trial was designed to measure differential compliance, quality of life (QOL) and satisfaction with medication in chronic heart failure (HF) patients taking BID carvedilol immediate release (Carv IR) vs bioequivalent QD Carv controlled release (CR). **Methods:** HF pts with LV EF < 40% on > 2 mos stable Carv IR BID were randomized to either group A: staying on Carv IR BID double blind, group B: switched to equivalent dose carv CR in AM and placebo in PM, double blind, or Group C: switched to open label equivalent dose carv CR QD. Compliance was measured by medication event monitoring system caps, and QOL by KCCQ and other instruments (including TSQM - satisfaction wth treatment) over 5 months. Sample size assumed 75% BID compliance and 90% QD compliance. Primary endpoint was ''taking compliance'' (% correct doses/doses prescribed). 405 pts were randomized at 55 US sites (62% HF specialists). Mean age was 65 yrs, mean LVEF 29%, 64% NYHA class II, with > 90% taking ACEi/ARB and 100% on Carv IR BID. **Results:** see Table. There were also no differences in change in NYHA class. Adverse events were reported in 56% of pts staying on their Carv IR BID and in 58% of pts switched to Carv CR (p = NS). There was no difference in serious adverse events between groups. **Conclusions:** Switching from Carv IR BID to Carv CR QD in this trial setting was not associated with better drug taking compliance, in part due to higher than anticipated compliance in the BID cohort. Switching from Carv IR to Carv CR was well tolerated, with no adverse events or safety issues associated with switching.

Results

Group	A (Carv IR BID)	B (Carv CR/Plac)	C (Carv CR QD	
	n = 133	n = 136	n = 136	p
Taking compliance (%)	89 +/− 21	87 +/− 25	88 +/−24	NS
Correct dosing days (%)	86 +/− 20	85 +/− 25	87 +/− 25	NS
KCCQ Δ >= 5 (% of pts)	34	23	28	NS
Δ median BNP (IQR) (pg/ml)	− 4 (−337, 418)	− 1 (−855, 1556)	0 (−632, 1828)	NS
Δ TSQM score	−3 +/− 18	−4 +/− 20	−1 +/− 21	NS

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Withdrawn

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Sildenafil Improves Exercise Capacity and Quality of Life in Patients with Systolic Heart Failure and Secondary Pulmonary Hypertension

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Background: Patients with systolic heart failure (HF) who develop secondary pulmonary hypertension (PH) have reduced exercise capacity and increased mortality