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Superior Performance of Intrathoracic Impedance-Derived fluid Index versus Daily Weight monitoring in Heart Failure Patients: Results of the Fluid Accumulation Status Trial (FAST)

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Background: Self-monitoring of daily weight is recommended for the management of heart failure (HF). Diagnostic parameters, such as intrathoracic impedance assessment, derived from implantable devices may offer an adjunctive tool for remote monitoring. We compared the relative sensitivity and unexplained detection rate of changes in daily weights versus intrathoracic impedance changes.

Methods: The FAST study prospectively followed 156 subjects (77% Male, 69 ± 11 yrs) from 18 enrolling centers with previously implanted ICDs (n = 13) or CRT-D devices(n = 143) for 537 ± 312 days. Each device was modified to record daily changes in intrathoracic impedance in a blinded fashion. Daily impedance changes were used to calculate a reference impedance and a fluid index that could be compared to a pre-specified threshold. Sensitivity was defined as the percentage of adjudicated HF events, including hospitalizations, emergency room visits, urgent care or unscheduled office visits occurring within 30 days of a super threshold fluid index value or an acute gain in weight, respectively. Unexplained detections were defined as threshold crossings or acute weight gains not associated with an HF event.

Results: Impedance measurements were performed on >99% of follow-up days used for sensitivity analysis. However, weight measurements were provided by the subjects for only 75.7% of days during that same period. A total of 65 adjudicated HF events occurred during the follow-up period (0.32 pt^{-1}yr^{-1}). A total of 40 HF events were detected by impedance but not weight, whereas only 5 were detected by weight but not impedance. The sensitivity was significantly greater (76.4 [60.8, 87.1] vs. 22.5[12.5, 37.1]; GEE[95% CI]; p < 0.0001) and unexplained detection rate was lower (1.9[1.7, 2.1] vs. 4.3[3.2, 5.8]; p < 0.0001) for intrathoracic impedance monitoring at the nominal threshold of 60 ohm-days compared to acute weight increases of 3 lbs overnight or 5 lbs in three days. Sensitivity and unexplained detection rates were also superior for the fluid index over a wide range of weight (range 2lbs overnight or 3 lbs in 3 days−5lbs overnight or 9 lbs in 3 days) and fluid index (range: 30-180 ohm days) thresholds (figure).

Conclusions: The sensitivity and unexplained detection rate of an intrathoracic fluid index were superior to those for acute weight changes in heart failure patients with implantable devices. Intrathoracic impedance monitoring represents a positive addition to our armamentarium for managing HF and should be considered for routine use in patients with implanted devices with this feature in addition to daily weight monitoring.
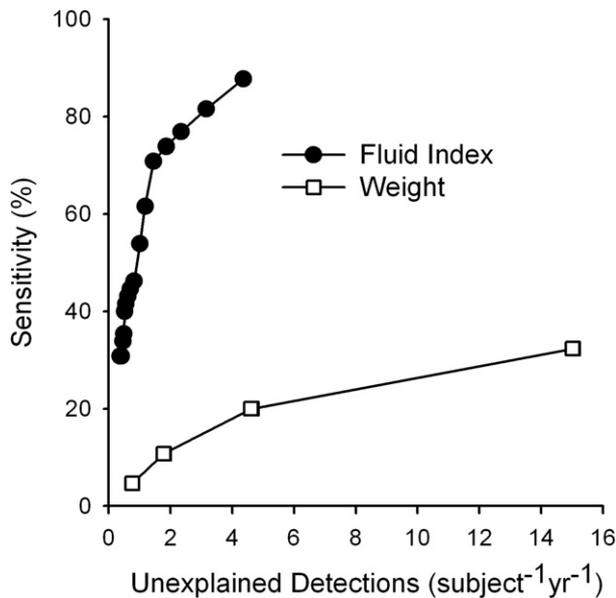
Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices: Primary Results of IMPROVE HF

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Introduction: A well-documented treatment gap exists between national heart failure (HF) guidelines and the clinical care of patients with HF. IMPROVE HF prospectively tested the effect of a practice-specific performance improvement intervention on quality measures in patients with HF in outpatient cardiology practices.

Hypothesis: The IMPROVE HF practice-specific performance improvement intervention would improve use of guideline-recommended therapy for HF at 24 months compared to baseline.

Methods: Performance data were collected longitudinally at baseline, 12 months, and 24 months from 167 US outpatient cardiology practices in patients with chronic systolic HF or post-MI and LVEF ≤35%. To quantify guideline adherence, 7 individual quality measures (use of ACEIs/ARBs, β-blockers, aldosterone antagonists, anticoagulation for atrial fibrillation, ICD, and CRT in indicated patients and HF education) were assessed. Performance improvement tools (clinical decision support, patient education materials, and benchmarked quality reports) were provided to all practices. Treatment differences were evaluated by normal approximations to the binomial distributions.

Results: This study included 15,177 patients. Mean age was 69 years with 29% women, 65% ischemic etiology, and LVEF 25% ± 7%. Practices were 65% non-teaching. The performance intervention resulted in significant improvements in 6 of 7 quality measures at 24 months (each P < 0.001) (Table). No significant improvement resulted in anticoagulation for atrial fibrillation. Sensitivity analyses of practice level improvements and assessment confined to patients with both baseline and 24-month quality measure data yielded similar results.

Conclusions: The IMPROVE HF initiative resulted in substantial improvements in use of evidence-based therapies in eligible patients with systolic HF in outpatient cardiology practices. Implementation of a defined and scalable practice-specific intervention enhances use of guideline-recommended HF therapies demonstrated to improve outcomes.

Use of Guideline-Recommended Therapies at Baseline and 24 Months

Quality Measure	Baseline (95% CI) N = 15,177	24 Months (95% CI) N = 7605	Absolute Improvement (95% CI)	Relative Improvement (95% CI)	P-value[*]
ACEI/ARB	79.8% (79.2-80.5)	86.5% (85.6-87.3)	+ 6.7% (5.6-7.8)	+ 8.4% (7.0-9.7)	<0.001
Beta-Blocker	86.2% (85.6-86.8)	93.6% (93.0-94.2)	+ 7.4% (6.6-8.2)	+ 8.6% (7.7-9.6)	<0.001
Aldosterone Antagonist	34.4% (32.7-36.1)	61.8% (59.2-64.5)	+ 27.4% (24.3-30.6)	+ 79.7% (70.5-89.0)	<0.001
Anticoagulation for Atrial Fib	68.6% (67.2-70.0)	69.3% (67.5-71.0)	0.7% (-1.5-2.9)	1.0% (-2.2-4.2)	0.546
CRT-P/CRT-D	37.7% (35.2-40.1)	68.5% (65.8-71.3)	+ 30.9% (27.2-34.5)	+ 81.9% (72.2-91.7)	<0.001
ICD/CRT-D	48.8% (47.8-49.8)	79.1% (78.0-80.2)	+ 30.3% (28.8-31.8)	+ 62.1% (59.1-65.1)	<0.001
HF Education	61.8% (61.0-62.5)	70.8% (69.8-71.9)	+ 9.1% (7.8-10.4)	+ 14.7% (12.6-16.8)	<0.001

*P-value is for relative improvement comparison. Pre-specified primary endpoint: 20% or more relative improvement in at least 2 measures from baseline to 24 months.

Reduction in the Risk of Heart Failure with Preventive Cardiac Resynchronization Therapy: MADIT-CRT Trial

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Introduction: The randomized Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) was designed to determine if prophylactic cardiac resynchronization therapy with defibrillator (CRT-D) would reduce the primary end point (all cause mortality or heart failure events [iv diuretic Rx or hospitalization Rx for HF], whichever occurred first, when compared to patients receiving only an implanted cardiac defibrillator (ICD-only). The study population involved patients with ischemic (NYHA I & II) and non-ischemic (NYHA II) cardiomyopathy with ejection fraction ≤0.30 and QRS ≥ 130ms.

Methods: The trial enrolled 1820 patients from 110 centers in Europe, Canada, and the United States with 3:2 randomization of CRT-D to ICD-only between Dec. 22, 2004 and April 23, 2008. The Independent Data & Safety Monitoring Board recommended trial termination on June 22, 2009 when the difference in the primary end point between the two treatment groups reached the prespecified efficacy boundary. All patients received optimal medical therapy for heart failure during the clinical trial (99% ACE/ARBs, 93% beta-blockers, 73% diuretics). Analyses involved Kaplan-Meier and Cox proportional hazard regression methods.

Results: The baseline characteristics of patients in the two treatment arms were similar with mean age 65 years, 75% male, 15:85% NYHA I:II, and 55:45% with ischemic:non-ischemic cardiomyopathy. Follow-up averaged 2.4 years per patient.

Kaplan-Meier analyses revealed a significant difference between the two treatment arms (p < 0.001), with a 27% reduction in the cumulative 4-year primary end point between ICD-only (37%) and CRT-D (27%). The time course of overall mortality was almost identical in the two treatment arms, with benefit from CRT-D therapy driven by a 41% reduction in first heart-failure events (p < 0.0001). The CRT-D:ICD-only hazard ratio (HR) for the primary end point was 0.66, 95% CI 0.52-0.84, p = 0.001. Superiority of CRT-D to ICD-only was also present in patients with ischemic (HR = 0.67, p = 0.003) and non-ischemic (HR = 0.62, p = 0.01) cardiomyopathy.

Conclusion: Preventive cardiac resynchronization therapy in asymptomatic or mildly symptomatic cardiac patients with a reduced ejection fraction and wide QRS complex is associated with a significant 34% decrease in the risk of death or heart failure, with the CRT-D benefit dominated by a reduction in heart-failure events.

Effect of Rolofylline, a Selective Adenosine A$_1$ Receptor Antagonist, in Patients Hospitalized for Acute Decompensated Heart Failure and Renal Impairment: Findings from the PROTECT Study

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Context: Patients with acute heart failure (AHF) often present with or develop worsening renal function (WRF) and diuretic resistance during treatment (often termed "cardiorenal syndrome"), with poorer subsequent in-hospital and post-discharge outcomes. Experimental and clinical studies suggest that counter- regulatory responses mediated by adenosine are mechanistically involved.

Objective: Therefore, we conducted the PROTECT trial to test the hypothesis that rolofylline, a selective A$_1$ receptor antagonist (A$_1$RA), administered in conjunction with loop diuretics, would improve dyspnea and reduce the risk of WRF, leading to a more favorable clinical course and improved outcomes.

Methods: PROTECT was a multicenter, randomized, double-blind, placebo-controlled trial in patients hospitalized for AHF with dyspnea at rest, volume overload requiring IV loop diuretic therapy, and impaired renal function. Patients were randomized within 24 hours of admission, and rolofylline 30 mg/day IV or matching placebo was infused daily for up to 3 days. The primary endpoint was a 3 category ordered outcome of treatment success, failure, or lack of change. Secondary endpoints included time to death or rehospitalization for cardiovascular or renal causes through Day 60 and the proportion of patients with persistent renal impairment.

Results: 2,033 patients were randomized in a 2:1 ratio to rolofylline or placebo at 173 sites in North America, Europe, Israel and Argentina. Rolofylline did not improve the primary trichotomous endpoint (odds ratio versus placebo 0.92, 95%CI 0.78, 1.09, p = 0.35). More rolofylline patients met the criteria for treatment success, but also for treatment failure. Rolofylline also did not achieve either of the prespecified secondary endpoints. Death or cardiovascular or renal hospitalization through day 60 occurred in 30.7% and 31.9% of rolofylline and placebo patients, respectively (hazard ratio 0.98, 95%CI 0.83, 1.17, p = 0.86). Persistent renal impairment occurred 15.0% of rolofylline patients placebo group, respectively (odds ratio 1.11, 95%CI 0.85, 1.46; p = 0.44). The number of patients experiencing adverse events was similar overall; however, more rolofylline patients experienced adverse neurological events.

Conclusions: The PROTECT trial did not confirm earlier favorable studies with rolofylline and other investigational A$_1$RAs.

Clinical and Prognostic Value of Galectin-3, a Novel Fibrosis-Associated biomarker, in Patients with Chronic Heart Failure

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Background: Biomarkers are increasingly being used in the management of patients with heart failure (HF). Galectin-3 (Gal-3) is a recently developed, novel biomarker that is related to fibrosis underlying cardiac adverse remodelling.

Methods: We examined 592 patients with mild to moderate/severe HF, who were part of a multicenter study in the Netherlands (COACH), and studied them during 18 months follow-up. Gal-3 was measured in EDTA plasma using an optimized enzyme-linked immunosorbent assay (ELISA) (Galectin-3 Assay™; BG Medicine, Inc., Waltham, MA). The primary endpoint of the study was a composite of all-cause mortality and HF hospitalization. The prognostic value of Gal-3 was investigated using univariate and multivariate analyses.

Results: The mean age of the patients was 72 ± 12 yrs and 65% of patients was male. Half of the patients were in NYHA class II, and 50% in NYHA class III-IV, mean LVEF was 33 ± 15%, and mean eGFR was 55 mL/min/1.73 m^2. Median BNP was 448 pg/ml and patients were on optimal medication for HF. During follow-up, 248 patients reached the primary endpoint (and 164 patients died).

Baseline Gal-3 showed a significant association with several clinical parameters, including age, and BNP. On univariate analysis, Gal-3 showed a powerful association with outcome, and the HR of the highest quartile was 3.34 (2.23-5.01, p < 0.0001). When adjusted for age, gender, and BNP this HR was still 2.67 (1.74-4.09, p <.00001) (see figure).

Relationship between quartiles of Galectin 3 and outcome
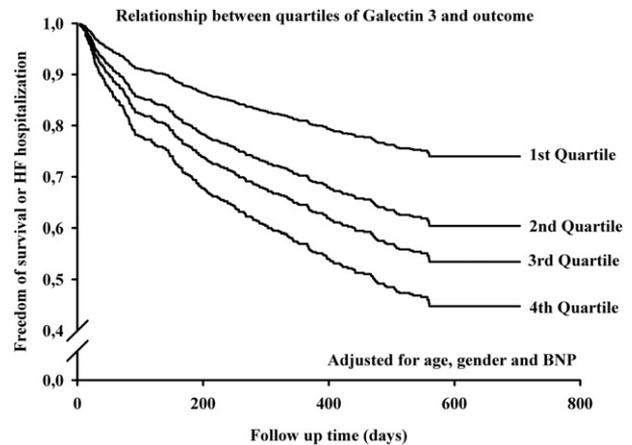
Conclusion: GAL-3 is a powerful novel marker with incremental value for outcome stratification in patients with chronic HF, which is independent of the severity of HF, as reflected by plasma BNP levels. Because of its role in fibrosis forming, further studies are warranted to elucidate the role of Galectin-3 in the process of remodelling and disease progression in HF.

Relationship of Baseline Gated Rest SPECT Myocardial Perfusion Imaging to Death and Hospitalization in Heart Failure Patients: Results from the Nuclear Substudy of the HF-ACTION Trial

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Background: There are currently limited data from large, prospective studies regarding the ability of single photon emission tomography (SPECT) myocardial perfusion imaging (MPI) variables to predict adverse outcomes in patients with heart failure (HF) and reduced left ventricular (LV) ejection fraction (EF). We hypothesize that the severity of resting perfusion defects ("myocardial scarring") as measured by the summed rest score (SRS) by SPECT MPI will be associated with higher rates of adverse outcomes as defined by a composite primary endpoint of all-cause mortality and cardiovascular hospitalization in patients enrolled in the HF-ACTION trial.

Methods: HF-ACTION was a multi-center, randomized controlled trial of exercise training vs. usual care in 2331 stable patients with LVEF ≤35% and NYHA class II-IV heart failure symptoms treated with optimal medical therapy. 240 subjects were enrolled in the HF-ACTION nuclear substudy and underwent resting Tc^{99m} tetrofosmin gSPECT MPI. Images were evaluated for extent and severity of perfusion abnormalities using a 17-segment model and a 5-degree gradation severity score (SRS). LV function and volumes were assessed using validated available commercial software.

Results: The average age of patients enrolled was 59, 69% were male, 63% were white, and 33% were African-American. Of the 240 participants, 129 (54%) were ischemic and 111 (46%) were non-ischemic in etiology. The median LV EF by gSPECT for the entire cohort was 26%. In the multivariate model, ischemic etiology was a powerful predictor of the primary outcome with a HR 1.77 (95% CI 1.09-2.89, χ^2 = 5.23). LV EF and SRS were also predictors of adverse events with HR 0.967 (95% CI 0.95-0.99, χ^2 = 8.32) and HR 0.984 (95% CI 0.97-0.99, χ^2 = 4.24), respectively. The interaction between SRS and the primary outcome was confounded by the high number of events, primarily hospitalizations, in ischemic patients with a low SRS. Nuclear variables provided incrementally more prognostic information for the primary outcome when added to background clinical information (p = 0.006). Phase SD was not predictive of the primary outcome (p = 0.23) nor did it provide incremental prognostic value when added to other nuclear variables (p = 0.72).

Conclusions: SPECT MPI provides important and powerful information in patients with HF and reduced LV EF. 1) Ischemic etiology of HF is a predictor of adverse events compared with non-ischemic etiology, 2) SRS and LV EF are predictors of increased mortality and hospitalization, 3) Patients with ischemic HF should undergo stress testing to ascertain the degree of underlying ischemia as the SRS alone likely underestimates their risk for adverse events, 4) Nuclear variables including SRS, LV EF, and LV volumes provide powerful prognostic information in addition to background clinical variables.