Calcitonin: A Novel Therapy to Lower FGF23 in X-linked Hypophosphatemia

Alice Abraham, M.D., Karl Insogna, M.D.

**Background:** XLH is the most common inherited form of rickets/osteomalacia in the United States. Its defining biochemical features are normocalcemia, hypophosphatemia due to reduced renal phosphate reabsorption and paradoxically normal to low-normal circulating levels of 1,25 (OH)_{2} vitamin D. Patients with XLH have rickets as children and osteomalacia as adults. Short stature, very frequent tooth root abscesses and enthesopathy (ligamentous and periarticular calcifications) in adults are common complications. The genetic basis for XLH is loss of function mutations in the neutral endopeptidase, PHEX. By currently unknown mechanisms, the absence of a functional PHEX protein leads to increased production of FGF23. FGF23, which is produced by osteocytes in bone, inhibits renal tubular phosphate reabsorption and suppresses renal production of 1,25 (OH)_{2} vitamin D. Conventional therapy for XLH consists of an oral regimen of phosphate and 1,25(OH)_{2} vitamin D. This therapy is associated with nephrocalcinosis and hyperparathyroidism. Furthermore, conventional therapy does not lower circulating levels of FGF23. Indeed, it has been shown that 1,25(OH)_{2} vitamin D and phosphate supplementation can both stimulate FGF23 production in vivo. Indeed patients with XLH treated with this regimen have higher serum FGF23 levels than untreated patients. Osteocytes express the calcitonin receptor and we have recently shown that a single subcutaneous dose of salmon calcitonin lowers FGF23 levels in XLH.

**Specific Aim:** We wish to determine if daily administration of nasal calcitonin can suppress FGF23 levels and increase both serum phosphorus and 1,25(OH)_{2} vitamin D, in a sustained manner in XLH.

**Hypothesis:** We hypothesize that giving nasal calcitonin to patients with XLH will suppress serum levels of FGF23, resulting in increased renal phosphate absorption as well as an increase in levels of 1,25(OH)_{2} vitamin D.

**Methods:** This is a double-blind randomized placebo controlled trial. The principal outcome variable for this trial will be area under the curve for FGF23 at three months. Twenty adult volunteers (≥ 18 years of age) with confirmed XLH will be recruited for the study. Study drug administration will consist of a nasal spray bottle (calcitonin or placebo) sufficient for 1 month. Study volunteers will be admitted to our Hospital Research Unit for 24 hours. Blood samples will be obtained every 4-6 hrs and assayed for serum PTH, calcium, phosphorus, creatinine, 1,25(OH)_{2} vitamin D, CTX, P1NP, alkaline phosphatase, FGF23 and Klotho. Serum 25-OH vitamin D will be measured once at baseline. Fasting urine specimens will be collected to calculate the renal phosphate threshold and 24 hr urines collected for calcium and phosphorus excretion. This inpatient analysis will be repeated for every study subject at the end of three months of treatment. At the end of Months 1 and 2, study participants will return for fasting blood work and spot fasting urine collection.

**Results:** Our data from an earlier study show that injectable calcitonin in XLH patients decreased FGF23 levels and increased 1,25(OH)_{2} vitamin D. For the present study, we await results from our enrolled patients. Our first enrolled study subject is half-way through the study and tolerating it well.

**Conclusions:** We have demonstrated in a previous study that calcitonin administration resulted in decreased FGF23 levels and increased 1,25(OH)_{2} vitamin D. We would like to determine whether this effect can be sustained over three months using a nasal preparation.
Association of Experience with Illness and End-of-life Care with Advance Care Planning

Halima Amjad, M.D., M.P.H., Terri Fried, M.D.

**Background:** Advance care planning (ACP) remains an underused tool in medical care, and identifying factors associated with increased participation in ACP is important for the promotion of this health behavior. One factor that would likely be a driver for participation in ACP is personal experience with serious illness or end-of-life care. Research regarding the possible relationship between previous experiences and readiness to take part in ACP is limited, however, and shows mixed results.

**Specific Aim:** Examine the relationship between previous experiences with illness and end-of-life care and decision-making with advance care planning.

**Hypothesis:** A substantial proportion of community-dwelling older persons have had experience with serious illness and end-of-life care, either personally or through loved ones, and this experience is associated with increased readiness to participate in ACP.

**Methods:** 304 individuals aged 65 and older were recruited from physician practices and a senior center. Participants were asked whether they had ever faced a life-threatening illness or surgery. They were also asked whether they had ever made a medical decision for someone who was dying, whether they knew someone who they believe had a bad death due to receiving too much or too little medical care, and whether they had experienced the death of a loved one who made his or her wishes about end-of-life known. Stages of change were assessed for six ACP behaviors: completion of a living will and healthcare proxy, communication with loved ones regarding use of life-sustaining treatments and quantity versus quality of life, and communication with physicians about these same topics. Mantel-Haenszel chi-square analysis was used to examine the association between each life experience and stages of change for each ACP behavior.

**Results:** 84% of participants had experiences with their own illness or end-of-life care for a loved one. Personal experience with life-threatening illness was not associated with increased readiness to participate in ACP behaviors except for discussing life-sustaining treatments with loved ones (p<0.03). In contrast, participants who reported end-of-life experiences with loved ones or acquaintances were in later stages of change for multiple ACP behaviors. Having one or more of these experiences was associated with increased readiness to complete a living will and/or healthcare proxy, discuss life-sustaining treatment and quantity versus quality of life with loved ones, and discuss quantity versus quality of life with clinicians (p<0.05).

**Conclusions:** Older individuals who have had experience with end-of-life care and decision-making for others demonstrate increased readiness to participate in ACP. Discussions with older patients regarding their previous experiences may be a useful tool for clinicians in promoting participation in ACP.
Diagnostic Accuracy of Systemic Inflammatory Response Syndrome Criteria for Predicting Life-Threatening Infections in Cirrhotic Patients Admitted to a Medical Intensive Care Unit

Stephen R. Baldassarri, M.D., Mark D. Siegel, M.D.

Background: Liver cirrhosis is a major independent risk factor for the development of sepsis and sepsis-related mortality. Patients with cirrhosis have been noted to have infections more frequently than the general population. While the systemic inflammatory response syndrome (SIRS) criteria are helpful in the diagnosis of sepsis in non-cirrhotic patients, the use of SIRS criteria may be problematic in diagnosing life-threatening infections in patients with cirrhosis. Liver cirrhosis causes physiologic abnormalities that alter temperature, heart rate, respiratory rate, and white blood cell count. Consequently, cirrhotic patients may develop life-threatening infections without fulfilling SIRS criteria and potentially elude detection. Further, cirrhotic patients frequently present with acute conditions that cause abnormal vital signs and labs that can lead to SIRS without infection. Recognizing and treating infections in patients with cirrhosis early in the course of their illness could reduce morbidity, mortality, and treatment costs. Consequently, it is helpful to know what features characterize the presentation of serious infections in patients with cirrhosis. The purpose of this study was to determine the diagnostic accuracy of SIRS criteria as a screening tool for intensive care unit (ICU) patients with cirrhosis at risk for infection.

Specific Aim: Determine the sensitivity and specificity of SIRS criteria in identifying cirrhotic patients with bacteremia or SBP.

Hypothesis: A significant number of patients with cirrhosis who have life-threatening infections present to the ICU without fulfilling SIRS criteria.

Methods: We performed a retrospective chart review of patients with cirrhosis admitted to our MICU from December 2010 until August 2011. Patients were included if they were ≥ 18 years old, had cirrhosis, and were not already receiving antibiotics on admission to treat an active infection. Patients were categorized as infected if they received ≥ 7 days of antibiotics after admission in conjunction with a high clinical suspicion of infection based on laboratory, microbiologic, and radiographic data. For patients who had multiple ICU admissions during the designated time period, only the most recent admission was included. We collected data on vital signs to determine the sensitivity and specificity of SIRS criteria in identifying patients with severe infections. We compared mortality and hospital length-of-stay among the groups.

Results: Of 85 patients, the median age was 53 years (IQR range 48-61); 67% were men. 58% had alcoholic cirrhosis and 34% Hepatitis C. 40% were infected. 24% died, with no difference in mortality between the infected and non-infected groups. Mortality was higher in infected patients with positive blood cultures (71% vs. 19%; p = 0.014). Hospital length-of-stay was longer for infected patients (median 11 days; IQR = 6, 17 vs. 7 days; IQR = 4, 13; p = 0.043). Abnormal temperature and WBC counts occurred in a minority of infected patients (32% and 47% respectively). As a diagnostic tool to help predict infection, having ≥ 2 SIRS criteria was insensitive (50%) and relatively nonspecific (65%). Having ≥ 3 SIRS criteria was more specific (94%) but too insensitive (21%) to be used as a screening tool for life threatening infection.

Conclusions: SIRS criteria are insufficiently sensitive and specific to serve as a diagnostic screening tool for severe infection in patients with cirrhosis. Further investigation is needed to determine more accurate ways to identify critically ill patients with life-threatening infections.
Contribution of TLR3 Stimulation by Poly (I:C) to the Pathogenesis of COPD in Cigarette Smoke-exposed Mice

Whitney Besse, MD, and Erica L. Herzog, MD, PhD

Background: The combination of cigarette smoke and simulated viral infection with double stranded RNA [Polyinosinic:polycytidylic acid, Poly (I:C)] causes enhanced alveolar destruction in a mouse model of chronic obstructive pulmonary disease (COPD). While it is known that Toll-Like Receptor 3 (TLR) does not mediate the aggravated lung destruction seen in this model, less is known about whether TLR3 participates in repair responses. Delineation of such an effect could have important ramifications for human COPD, where the combination of viral infections and cigarette smoke synergize to cause worsened clinical outcomes.

Specific Aim: Determine the role of TLR3 in the impeded repair responses seen in mice exposed to cigarette smoke and Poly (I:C)

Hypothesis: TLR3 participates in epithelial repair responses induced by exposure to cigarette smoke and Poly (I:C)

Methods: Wild type and TLR3null mice were exposed to cigarette smoke (CS) and 1,2,3 or 4 doses of Poly (I:C), while a control group received no exposure. A group of mice was sacrificed after each dose, and the left lung was inflated and fixed for my analysis. Immunofluorescence techniques were used to label Ki67 (a marker of active cell proliferation) as well as either Clara Cells in small-airway epithelium or AT2 cells in alveoli. In addition, H&E stained lung sections underwent morphometric analysis of alveolar size using chord length calculations. TUNEL staining for labeling apoptotic cells was attempted, but immunoflourescent double-labeling with this technique was not feasible.

Results: We detected a trend towards increased Ki67 staining in AT2 cells (3% vs. 11%, p=0.175) and a significant increase in Ki67+ airway epithelial cells (1% vs. 12%, p=0.038) in WT mice relative to TLR3null mice after 2 doses of Poly(I:C), but at no other timepoint. While we initially found no difference in alveolar size in these samples, further investigation determined that the samples had not been inflated properly and thus could not be analyzed in this manner.

Conclusions: These data lend important insights into the effect of TLR3 signaling in the response to Poly (I:C). The fact that TLR3null mice seemed to have lower levels of proliferation than did the WT mice, suggests that stimulation of TLR3 leads to time-dependent repair responses in our model and that the repair response is time-dependent. TLR3 may importantly regulate epithelial repair responses. Limitations of my study were the small numbers and significant variability between mice of the same background assigned to the same exposures. We suspect that this may represent a limitation in our ability to deliver consistent doses of CS and Poly(I:C) among the mice. However, as well, there was variability among unexposed mice suggesting possible variation of results depending on the level of airway and location imaged. In addition, our inability to quantify cell death and alveolar size is another problem. Nevertheless, ours are the first data to suggest a role for TLR3 in the regulation of epithelial repair in this model and they will almost certainly lead to further mechanistic studies in this area.
Title: Prevention of Ventilator-Associated Pneumonia Using Components of a Ventilator Bundle: A Retrospective Study

Joseph Canterino, M.D., Vincent Quagliarello, M.D.

**Background:** Ventilator-associated pneumonia (VAP) is an infection of the lung that develops more than 48-72 hours after endotracheal intubation. Studies show that VAP occurs in 9.3% of patients receiving mechanical ventilation for >24 hours and in 10-20% of patients receiving mechanical ventilation for >48 hours. Patients with VAP also have an average of 9.6 additional days of ventilation and 6.1 additional days in the intensive care unit than their non-VAP counterparts leading to an average of >$40,000 increase in hospital bills. Therefore many hospitals have begun devising measures to minimize their rates of VAP. “Ventilator bundles” utilize multiple strategies in the prevention of VAP and include interventions such as elevation of the head of the bed, oral antiseptic use, and daily sedation interruption. However, many of the studies evaluating the efficacy these strategies are limited by the great inconsistency in diagnosing VAP, which translates into mixed results for the preventative power of ventilator bundles. As a result, there is no consensus on what strategies should comprise a ventilator bundle. This provides the opportunity to study whether these components when used alone or in combination improve the risk for pneumonia among mechanically ventilated patients.

**Specific Aim:** To determine if the use of components of a ventilator bundle, either individually or in combination, are protective against the development of ventilator-associated pneumonia, or improve secondary outcomes of hospital and ICU length of stay and mortality.

**Hypothesis:** The individual or combined use of components of a ventilator bundle in mechanically ventilated patients in the intensive care unit reduces the incidence of ventilator-associated pneumonia as well as secondary outcomes.

**Methods:** A retrospective review at Yale-New Haven Hospital of adults ≥ age 18 years old admitted to the intensive care unit who were mechanically ventilated for > 48 hours from June 2010 to January 2011. Patient records were analyzed for up to 2 weeks after initial intubation to determine whether a ventilator-associated pneumonia developed. Ventilator-associated pneumonia was defined according to an algorithm from the Centers for Disease Control (CDC). Subjects’ records were analyzed to determine if the following interventions were used during the time of mechanical ventilation: 1) oral antiseptic use, 2) daily ventilator weaning trials, 3) testing of a cuff leak, 4) stress ulcer prophylaxis, and 5) daily interruption of sedation. Multivariable analysis was used to determine if the previously mentioned interventions either individually or collectively provide a statistically significant reduction in incidence of ventilator-associated pneumonia or secondary outcomes, defined as hospital and ICU length of stay and in-hospital mortality.

**Results:** The records of 98 patients intubated for >48hrs were screened. 58 of these were eligible for inclusion in the study. Of these 58 ventilated patient’s, 18 met the CDC criteria for VAP. This is a VAP rate of 31%. Of the bundle components, the combination of documented weaning trial, stress ulcer prophylaxis, and oral antiseptic use were associated with protection from VAP (p=0.003); daily interruption of sedation was associated with VAP (p<0.001).

**Conclusions:** The VAP rate of the sample collected is higher than that quoted in the literature, suggesting that the rate of VAP is higher at Yale-New Haven Hospital. Ventilator bundle components have competing impact on VAP risk among ventilated ICU patients.
An Evaluation of Capacity-Building Outcomes in Ugandan Junior Medical Faculty Members following Clinical Training at Yale

Cassidy Claassen, M.D., M.P.H., Asghar Rastegar, M.D.

**Background:** Cross-cultural training and overseas experiences have been demonstrated to have lasting effects on American medical students and residents. However, little evidence exists to demonstrate a similar benefit for medical personnel trained through short-term rotation in institutions in developed countries. Yale University Medical School (YSM) and its affiliated hospitals have a unique partnership with Makerere College of Health Sciences (MakCHS) to enhance bidirectional capacity building at various academic levels. To date, it appears that short-term training of Ugandan junior medical faculty at YSM has direct, lasting, and measurable benefits in enhancing Ugandan medical capacity and ultimately strengthening the educational and care missions of MakCHS.

**Specific Aim:** To assess the impact of medical training at YSM on Ugandan medical faculty from MakCHS, to assess the achievements and contributions of Ugandan medical faculty upon returning to Uganda, and to analyze the impact of training in resource-rich settings on work in resource-limited settings.

**Hypothesis:** MakCHS faculty that have trained at YSM have improved clinical skills that manifest in improved patient care and better medical education, as well as a higher degree of medical professionalism; they are also more likely to demonstrate leadership by starting novel clinical projects and taking on administrative duties.

**Methods:** Current junior faculty members were invited to participate in an online self-assessment survey that assessed demographic data and then asked a series of questions pertaining to medical professionalism, such as importance of informed consent or teaching of interns. The survey was designed to assess the impact of the exposure of training abroad. Since not all faculty members have been abroad, the groups were standardized to answering questions based on when they finished their residency training (pre-exposure) and at the current time (post-exposure).

**Results:** 35 persons were eligible for the survey; 9 of 13 MUYU participants completed the survey and 9 of 23 non-MUYU participants completed the survey. The groups were similar in terms of age, gender, and medical education. MUYU participants felt like they obtained substantial clinical (100%) and teaching skills (78%) at Yale, while finances proved to be the major obstacle (33%). All survey participants noted that patient care and medical education at Mulago Hospital had improved due to clinical training and knowledge of MUYU participants. There was no difference between groups in the difference between pre- and post-exposure measures of medical professionalism. The MUYU participants had the highest pre and post mean values (4.66, 4.72 respectively) as compared to the other groups. Other markers of impact were difficult to quantify, but MUYU participants appeared more likely to have clinical projects (p=0.07) and teaching responsibilities (p=0.04) than those who did not participate.

**Conclusions:** Bilateral international medical collaborations can offer substantial benefit to participants. Physicians from developing countries who participate in clinical training in developed countries obtain clinical skills and knowledge as well as aptitude in medical education. This appears to improve patient care and medical education at their home institution, as viewed by both the participants and their colleagues who did not participate. Participants believe they are better patient advocates, and also seem to be leaders as they start clinical projects and take on administrative duties.
Effect of estrogen replacement therapy on soluble colony-stimulating factor 1 and rate of bone loss in post-menopausal women

Elaine Cong, M.D., Karl Insogna, M.D.

**Background:** Soluble colony-stimulating factor-1 (sCSF-1) is a cytokine essential for osteoclastogenesis. Mice with a spontaneous frameshift mutation of sCSF-1 result in osteopetrosis phenotype, reversed by transgenic reconstitution with sCSF-1. Patients with erosive psoriatic arthritis have higher levels of sCSF-1 versus healthy controls and non-erosive psoriatic patients. In mice models of inflammatory arthritis, monoclonal antibody to CSF-1 receptor blunts bone resorption markers and arrests osteolysis. Estrogen inhibits osteoclasts indirectly by decreasing osteoblast sCSF-1 expression and inhibiting TNF-alpha and IL-1 which mediate expression of sCSF-1. In ovariectomized animals, increases in sCSF-1 levels correlate directly with that of osteoclast production, while neutralizing antibody to sCSF-1 prevents ovariectomy-induced osteoclastogenesis and bone loss. In humans, sCSF-1 levels is negatively correlated with that of estrogen and sCSF-1 rises in late menopause.

**Specific Aim:** Compare levels of sCSF-1 in women treated with estrogen replacement therapy versus placebo and correlate sCSF-1 levels with bone mineral density.

**Hypothesis:** Higher levels of sCSF-1 will correlate with higher rates of bone loss and treatment with estrogen will blunt the rate of bone loss via lowering sCSF-1 levels.

**Methods:** This study is an ancillary study to the KEEPS study. The KEEPS study is a multi-center randomized double-blinded, placebo-controlled study approved by HIC (#27022). Of the volunteers enrolled in KEEPS, 245 women met criteria for the ancillary study by participating at a study site performing DXA scan. The women were randomized to four years of placebo/placebo, oral estrogen (Premarin 0.45mg/d)/prometrium (200mg/d) or transdermal estrogen (Climera 50 mcg/wk)/prometrium (200mg/d). sCSF-1 was measured via sensitive and specific ELISA for human CSF-1 (R&D Systems) and was collected from blood drawn as part of KEEPS study at baseline, 12, 36 and 48 months after treatment. Bone density scan was done at baseline, 24, 36 and 48 months to assess for bone mineral density at lumbar spine, femoral neck and total hip, and was read by a certified technician.

**Results:** At the time of abstract submission, the study had been completed but randomization status had not been revealed. In addition, sCSF-1 data had returned for only the Yale study site (n=64). Therefore, analysis of sCSF-1 level by randomization status will be deferred and only analysis of sCSF-1 data from Yale study site with regards to bone mineral density will be presented. Baseline sCSF-1 levels did not correlate significantly with bone mineral density at any site at any time-point, nor did baseline sCSF-1 level or change in sCSF-1 from baseline to 48 months correlate significantly with change in bone density at any site from baseline to 48 months. However, when baseline sCSF-1 was divided into quartiles, there was a statistically significant difference by one-way ANOVA in the baseline femoral neck bone mineral density raw and T-score (F=3.3, p=0.02). Post-hoc comparisons using the Tukey test revealed significance between the 25-50th and 50-75th quartiles (M=-0.39, SD=0.45 for 25-50th quartile vs M=-1.08, SD 0.58 for 50-75th quartile).

**Conclusion:** Analysis of the Yale study site data suggest an overall correlation between higher sCSF-1 levels and lower bone mineral density, a finding we hope to delineate in further detail when sCSF-1 data from all study sites become available.
Title: Predicting disease behavior in Crohn’s disease patients based on NOD2 allele genetic polymorphisms

Aaron Dickstein, MD, Deborah Proctor, MD

Background: Twin and familial studies have established a clear role for genetic factors in the development of Crohn’s disease (CD). Moreover, genome wide association studies have identified over 100 genetic loci that are associated with disease. Despite this success, however, the precise causal alleles and their functional consequences have not been clearly defined. Previous studies have identified NOD2 polymorphism carriers as being more likely to have fibrostenosis, ileal disease, and increased need for surgery. The theory behind these associations has its basis in the innate immune response role in CD. The key feature of active CD is pronounced infiltration into the lamina propria of innate immune cells. Increased numbers and activation of these cells in the intestinal mucosa leads to local elevation of TNFα and various other interleukins to stimulate inflammation. The NOD2 allele (16q12) encodes an intracellular sensor of peptidoglycan—a component of bacterial cell walls and activates cell signaling through a complex pathway leading to inflammation. Several common alterations in the coding region of the NOD2 gene, including R702W (rs2066844), G908R (rs2066845), Leu1007fsX1008 (rs5743293) have been implicated in the development of Crohn’s disease. Unfortunately, however, because of heterogeneity in individual clinical presentation previous studies have produced discordant results with regard to affect on phenotypic expression.

Specific Aims: 1) To investigate the prognostic power of three NOD2 SNPs (single nucleotide polymorphisms) on disease behavior—specifically, the risk of strictureing/penetrating disease and need for surgery. 2) To study the association between these three NOD2 SNPs and disease location.

Hypothesis: In CD patients, increasing numbers of NOD2 allele mutations leads to more severe disease behavior. Further, having one of the three studied mutant alleles will portend an increased risk of ileal disease and need for resection.

Methods: We constructed a gene-association study from a Crohns cohort using three NOD2 SNPs (rs2066844, rs2066845, and rs5743293). The patients studied were enrolled in the multi-centered NIDDK IBD Genetics Consortium database. We extracted 1153 samples with documented CD along with data on sex, family history, smoking, disease location (jejunal, ileal, colorectal, perianal), surgery, disease duration, disease behavior (divided into B1, B2, B3 by Montreal classification) as well as genotype data for the three NOD2 SNPs. We built an ordinal logistic regression model with all 3 SNPs as predictors and disease behavior as the response and carried out step backward model selection while controlling for independent risk factors. We also built a logistic regression with the 3 SNPs to assess for associations with disease location.

Results: From the summary statistics, smoking, ileal disease location, and increasing duration of disease proved significant predictors for more severe disease behavior. Of the three SNPs, only rs5743293 was significantly associated with this worse outcome. The ordinal logistic regression model showed the rs5743293 SNP minor allele to be associated with increased risk of having B2 or B3 disease with an odds ratio (OR) of 1.66 (p<0.01). Our second logistic regression found all three minor alleles to be associated with ileal disease location (OR of 1.75, 3.94 and 3.86 respectively). Interestingly, rs5743293 was noted to be protective against perianal disease with an OR 0.56 (p 0.01). In addition, this SNP was associated with surgical intervention with OR 1.83 (p <0.01).

Conclusions: In sum, we found that carrying the frame shift insertion SNP rs5743293 was significantly associated with more severe disease behavior as well as need for surgery. Moreover, this SNP seems to be protective against perianal disease, a novel finding. All three chosen SNPs were associated with an increased risk of having ileal disease, a predictor of worse disease outcome. However, as in prior studies, there are likely to be unaccounted for environmental factors playing a role in phenotypic expression. Indeed, our particular SNP may simply be a marker for more severe CD rather than causative. Yet, our findings do suggest that a positive test for the rs5743293 NOD2 SNP at diagnosis might justify the use of more aggressive therapy early on to prevent strictureing or fistulizing complications.
Unchanged Prescription of Dual Anti-Platelet Therapy Following CHARISMA


Background: CHARISMA was a landmark randomized clinical trial that failed to demonstrate a benefit of dual anti-platelet therapy (DAPT) with aspirin and clopidogrel over aspirin alone for preventing cardiovascular events. However, subgroup analyses of the trial found benefit for patients with established cardiovascular disease (CVD) but harm for patients with multiple cardiovascular risk factors without established CVD.

Specific Aim: Our objective was to examine DAPT use in contemporary clinical practice following the publication of CHARISMA.

Hypothesis: We hypothesized that the CHARISMA subgroup analyses caused increased prescription of DAPT to patients with established CVD but decreased prescription of DAPT to patients with multiple cardiovascular risk factors without established CVD.

Methods: We queried the NCDR® PINNACLE Registry® of outpatient cardiovascular visits to over 1000 physicians for patients meeting inclusion criteria of CHARISMA: CVD defined as coronary artery disease, unstable or stable angina, prior stroke or TIA, or peripheral arterial disease; or multiple cardiovascular risk factors defined as 3 of diabetes, hypertension, hyperlipidemia, smoking, male ≥65 or female ≥70 without established CVD; patients with PCI within 12 months or atrial fibrillation were excluded. Clinical characteristics and prescription rates of DAPT were compared for patients with established CVD and for patients with multiple cardiovascular risk factors only by quarter from 9/2008 to 12/2009. A Poisson regression model was established for DAPT prescription by patient-quarter, adjusting for age, sex, and history of co-morbidities.

Results: Using the CHARISMA inclusion criteria, we identified 41,131 patients with established CVD and 5100 patients with multiple cardiovascular risk factors but no CVD. Prescription of DAPT to patients with CVD increased during the study period from 18.95% to 25.04%. Prescription of DAPT to patients with multiple cardiovascular risk factors but no CVD increased from 4.23% to 5.06%. In the Poisson model, after adjustment for age, sex, and history of co-morbidities, the prescription rate ratios were 1.03 (95% CI 0.98-1.09) for patients with CVD and 1.03 (95% CI 0.92-1.15) for patients with multiple cardiovascular risk factors but no CVD.

Conclusions: Use of DAPT is modest in patients with established CVD, for whom CHARISMA subgroup analyses suggested benefit, and prescription rates have remained stable over time. Use of DAPT in patients with multiple cardiovascular risk factors only, for whom CHARISMA suggested that DAPT may lead to harm, has remained stably low but not zero. Two principal factors likely contribute to these findings: clinicians are slow to incorporate new evidence into their practice; and clinicians found the controversial CHARISMA subgroup analyses inadequate to inform their DAPT prescription decisions.
Title: Circulating fibrocyte and pro-inflammatory mediators are similar in outpatients with systemic sclerosis-related interstitial lung disease and IPF

Colin Ligon, MD and Erica Herzog, MD, PhD

**Background:** Systemic sclerosis-related interstitial lung disease (SSc-ILD) and idiopathic pulmonary fibrosis (IPF) are two poorly understood conditions characterized by excessive accumulation of lung collagen. Substantial differences exist between the two in the population affected, histologic pattern, and the clinical responsiveness to immunosuppression. However, in both SSc-ILD and pulmonary fibrosis, increased levels of collagen-producing fibrocytes are found in the peripheral blood compared to normal controls, and in IPF higher levels of fibrocytes have been demonstrated to correlate with disease flares and poor prognosis. Comparisons of levels of circulating fibrocytes between these two conditions have not been performed, and would be of interest as SSc-ILD generally portends a better prognosis than even histologically similar cases of IPF. In addition, while circulating proinflammatory mediators are increased in both of these diseases, direct comparison of IPF and SSc-ILD subjects has not been performed.

**Specific Aim:** Compare levels of circulating fibrocytes and proinflammatory mediators in patients with SSc-ILD and IPF, and explore the contributions of differing age, sex, and smoking status between these two populations.

**Hypothesis:** Circulating levels of peripheral fibrocytes are higher in IPF than in SSc-ILD and may mediate some of the worsened prognosis classically attributed to the former. Profibrotic cytokines are similar in the two conditions and dependent upon the extent of disease.

**Methods:** Peripheral blood samples were obtained from a convenience sample of patients with IPF or SSc-ILD at the Winchester Chest Clinic. Peripheral blood fibrocytes were enumerated via flow cytometry as we have previously described. Multianalyte ELISA was performed using Luminex Technology as we have previously described. Comparisons between SSc-ILD and IPF were made using nonparametric Wilcoxon tests. Multivariate analysis was performed using linear regression for continuous variables and logistic regression for categorical ones. Statistical analysis was performed using SAS, with p values <0.05 considered significant.

**Results:** Peripheral fibrocytes were analyzed in 18 patients with SSc-ILD and 34 with IPF; protein data were available for 11 patients with SSc-ILD and 34 patients with IPF. Patients with IPF, as compared to SSc-ILD, were older (mean 67.8 vs 50.7 yr, p<0.0001), more male (88% vs 27%, p<0.001), more overweight (mean BMI 29 vs 24.3, p=0.007), more ever smokers (79% vs 36%, p=0.02), and had lower mean DLCO (46% vs 62%, p=0.01). Quantities of circulating fibrocytes did not differ between IPF or SSc-ILD (proportions 15.9% vs 8.4%, p=0.4; numbers 1.8x10^6 vs 4.0x10^6, p=0.3). Older patients had a significantly lower fraction of circulating fibrocytes (12.8% vs 14.3%, p=0.01) and a trend toward a lower number of circulating fibrocytes (1.5x10^6 vs 4.4x10^6, p=0.05); neither age nor lung disease was a significant predictor of fibrocyte fraction in multivariate regression. Fibrocyte number and fraction did not differ by other demographic, smoking, or pulmonary function. IL-10 concentrations were lower in IPF compared to SSc-ILD (7.8 vs 15.2 pg/mL, p=0.002), but this effect was mediated by smoking history in regression (OR 5.7 for higher IL-10 in never smokers, p = 0.03). Plasma levels of adiponectin were higher in IPF vs SSc-ILD (3.8 vs 2.8 µg/mL, p=0.03), and did not correlate with BMI (p=0.8). We did not detect a difference in levels of CRP, endothelin-1, ICAM-1, IL-1ra, IL-2, IL-6, IL-16, IL-18, MMP-2, MMP-3, MPO, RANTES, TNF-a, TNFR-2, VCAM-1, or VEGF (p > 0.05 for all comparisons).

**Conclusions:** Quantities of circulating fibrocytes do not differ substantially between IPF and SSc patients, and do not vary by smoking status, pulmonary function, or sex, but did appear to be higher in younger patients in this sample. Adiponectin levels were lower in SSc-ILD than IPF despite similar indices of inflammation, and levels were not related to BMI or lung function in this study. These data suggest that adiponectin may mediate or reflect some of the phenotypic differences between patients with SSc-ILD and IPF.
Is Weight Gain Beneficial for Individuals Initiating Combination Antiretroviral Treatment Regardless of Initial Body Mass Index?

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**Background:** Since the advent of highly active antiretroviral therapy (HAART), HIV-associated wasting is less common. Many individuals are now normal weight or overweight at the time of HAART initiation. Some experts now advocate for weight gain restrictions among HIV infected individuals initiating HAART, however, existing studies investigating weight trends are small, and the long-term consequences of weight gain remain unclear. **Aim:** To compare 12-month weight trends among uninfected and HIV infected individuals initiating HAART and investigate whether the associated mortality outcomes of weight gain depend on weight status at HAART initiation. **Hypothesis:** We hypothesize that weight gain after HAART initiation among those who are overweight or obese is associated with worse survival given the recognized health consequences of obesity. **Methods:** We analyzed data from the Veterans Aging Cohort Study (VACS) Virtual Cohort, a longitudinal prospective multi-site observational study of HIV-infected and uninfected veterans across 128 nation-wide Veterans Administration sites. We identified 4,732 HAART initiators between the years of 2000 and 2008 who were HAART naive at baseline and were alive and in follow-up at one year, as well as 18,769 HIV negative comparators. Changes in weight were examined over a 12-month period. Patients were stratified by initial weight category (overweight vs. not overweight) and by change in weight (gained >5 lbs, lost >5 lbs or stayed within 5 lbs). Our outcomes were the VACS Risk Index (a validated prognostic index comprising age, CD4, viral load, hemoglobin, FIB4, GFR and hepatitis infection) and all cause mortality. **Results:** Overall, mean one-year weight change was 6.6 lbs greater in HIV infected compared to uninfected veterans (p<0.05). Among the 43% HIV+ who started out overweight (BMI>25), 72% gained >10 pounds and 36% gained >20 pounds. HIV positive patients who gained weight had lower baseline CD4 counts, higher viral loads, and experienced greater improvements in their VACS index (a measure of disease burden). Among HIV positive veterans, weight gain after HAART initiation was not associated with increased mortality, regardless of starting BMI category. There was no threshold of weight gain that was associated with increased mortality. Further, those who gained weight were more likely to achieve viral suppression (HIV RNA<500) (p=0.001), and weight gain was associated with decreased mortality among those with detectable viral loads at one year (p=0.002). **Conclusions:** In the first year after HAART initiation, HIV infected individuals gain weight well beyond that observed among demographically and behaviorally similar uninfected veterans. Compared to HIV infected individuals who maintain weight, weight gain is associated with greater improvements in clinical biomarkers and comparable survival regardless of baseline weight. Further, weight gain is associated with improved survival among patients who do not achieve viral suppression, suggesting that weight gain is not only a marker of immune response, but may be protective against progression of disease in the setting of underlying immunodeficiency and inflammation. Despite significant weight gain after HAART initiation among normal and overweight individuals, we find no support for weight gain restrictions in this population.
Moving towards a Better Understanding of the Relationship Between Gastroesophageal Reflux Disease and Asthma
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Background: The prevalence of gastroesophageal reflux disease (GERD) is markedly increased amongst asthmatics relative to the general population. Despite the known co-existence of these two clinical entities, little is known about the relationship between GERD and asthma severity. This is in stark contrast to another airway disease, bronchiolitis obliterans, where the impact of GERD in post-lung transplant patients is well established and surgical fundoplication has become standard-of-care. Major limitations in studying the relationship between GERD and asthma have been invasive and costly research methods, such as 24-hour pH manometry, as well as the overlap of GERD and asthma symptoms. Therefore, additional clinical studies characterizing the overlap between asthma and GERD, complimented by non-invasive methods, such as sputum and serum biomarkers, are needed.

Specific Aims: Evaluate asthma severity amongst patients with GERD relative to patients without GERD and pilot a new quantitative sputum marker for GERD.

Hypothesis: Asthmatics with GERD have poorly controlled asthma symptoms.

Methods: The Yale Center for Asthma and Airway Disease (YCAAD) has established a translational research platform to collect information on asthma characteristics, symptoms, comorbidities and treatments. During every visit PFTs and induced sputum are collected. Biologic samples are available for further analysis. The Asthma Control Test (ACT) is a validated questionnaire that assesses control of asthma symptoms; scores less than 19 suggest poorly controlled symptoms. YKL-40 is a chitinase-like protein whose serum levels have been shown to directly correlate with asthma severity and airway remodeling in asthmatics. Pepsin is a proteolytic enzyme secreted by the chief cells in stomach, but is not expressed in the lungs. In this cross-sectional analysis of patients in the YCAAD database, we used the Mann-Whitney test to make comparisons between ACT scores, Forced Expiratory Volume in 1 second percent predicted (FEV1%) and serum YKL-40 levels between patients with and without GERD. Finally, we piloted an enzyme-linked immunosorbent assay (ELISA) on induced sputum samples from 4 patients to quantify the degree of GERD in asthmatics.

Results: Data was available for 172 patients. Relative to patients who did not report having a history of GERD (n=57), patients with GERD (n=116) had lower ACT scores [16 [9-21]* vs. 21 [16-23], p<0.01], lower FEV1% [0.83L [0.63-0.96] vs. 0.89 [0.77-1.02], p=0.03] and higher YKL-40 levels [40 [11.4-91.7] vs. 26.6 [13.9-48.3] (ng/mL), p =0.02]. A subgroup analysis of patients for whom pH manometry was available (n=110) showed that patients with evidence of GERD during testing had lower ACT scores relative to those without evidence of GERD [11 [9-15] vs. 16 [10-20], p=0.02]. Comparisons of FEV1% and YKL-40 in this small subset did not achieve statistical significance. A pepsin ELISA was optimized to be used with induced sputum. Measured pepsin levels have ranged from 0 to 20.29 ng/uL. (*median [IQR])

Conclusions: Individuals with asthma and GERD have higher symptom burden, based on ACT scores as well as lower values on FEV1% and higher levels of serum YKL-40. In fact, ACT scores of patients with GERD, either by self-reported history or as confirmed by pH manometry, suggests that most patients with GERD have poorly controlled asthma symptoms. The inability of the subgroup analysis to identify differences in FEV1% and serum YKL-40 amongst patients for whom pH manometry was available may be due to the small sample size, however further systematic characterization of GERD in this particular population is needed. To further such research efforts, we have also successfully optimized an assay for quantifying pepsin in induced sputum samples and will extend its application to a larger number of subjects to validate this minimally invasive and potentially useful biomarker. In conclusion, asthma and GERD coexist in a large number of patients, however the relationship between symptom burden, decline in lung function and biomarkers deserve further characterization.
Discharge Summary Quality and Effect on Readmission Rates in Patients Hospitalized with Congestive Heart Failure

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**Background:** Thirty day hospital readmissions incur significant cost to the US healthcare system, accounting for nearly $17 billion annually by estimates in 2009 and occurring in nearly 20% of Medicare beneficiaries. For this reason, avoiding hospital readmission has become the focus of quality improvement measures in recent years. Discharge summaries play a critical role in the transition of care from the inpatient to outpatient setting, serving as a way to communicate a patient’s care plan to outpatient providers. The Joint Commission mandates that six components be included in all discharge summaries (reason for hospitalization, significant findings, procedure and treatment provided, patient’s discharge condition, patient and family instructions, and attending physician signature). However, despite these standardized requirements, many discharge summaries fail to include important information that results in suboptimal post-hospitalization care, resulting in readmission.

**Specific Aim:** To assess the quality of discharge summaries based on predefined, objective parameters in patients admitted with congestive heart failure and determine if the inclusion or exclusion of these parameters affects readmission rates.

**Hypothesis:** Hospital discharge summaries often do not contain critical information about a patient’s hospitalization. This information is needed by outpatient healthcare providers to better care for patients and prevent readmission for congestive heart failure.

**Methods:** An abstraction tool was constructed including parameters deemed important to convey to outpatient providers of patients admitted specifically with congestive heart failure. Data to be abstracted included type of discharge summary (outline, narrative, dictation, produced from electronic medical record, handwritten), summary length in pages, and inclusion of reason for admission, baseline patient weight and weight at discharge, documentation of left ventricular ejection fraction, clinical condition at discharge, hospital course, admission and discharge medication reconciliation, name and contact information for attending physician during hospitalization, and whether follow up arrangements were made. The discharge summaries from which this data will be abstracted come from a collection of 1585 discharge summaries used previously to determine the effect of telemonitoring on heart failure outcomes (N Engl J Med 2010; 363:2301-2309). Unforeseen delay was experienced in gaining access to these discharge summaries, and much of the data abstraction has yet to be done.

**Results:** Preliminary review of data from initial abstraction shows that discharge summaries vary widely in quality and content. Though only a small number of the summaries have been reviewed to date, it has been noted that a very small percentage of the reviewed summaries contain a detailed follow up plan. None of the reviewed summaries thus far have included a discharge weight. Discharge medications have been lacking from approximately half of the reviewed summaries. All reviewed discharge summaries have included a reason for admission, hospital course, and attending physician name.

**Conclusions:** The vast disparities in the quality and content of hospital discharge summaries can result in a tenuous discharge plan whereby the events of a patient’s hospitalization and follow up plan is unrealistically communicated with outpatient providers. This break in communication can result in increased readmission rates. Having a standardized format for discharge summaries may be a better way to make sure that necessary information is passed along to outpatient providers.
Identification of Potential Candidates for Implantable Cardioverter-Defibrillators (ICDs) for Primary Prevention via Echocardiography Screening

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**Background:** ICDs have consistently been shown to be more efficacious than optimal medical therapy in preventing sudden cardiac death in patients with ischemic and nonischemic cardiomyopathy. Following publication of MADIT-II and SCD-HeFT, ICDs for primary prevention became standard of care. However, under-utilization of ICDs is well-documented. Less than 40% of potentially eligible patients hospitalized for heart failure receive ICD therapy.

The potential benefit of identifying appropriate candidates via echocardiography laboratory-based screening is unknown.

**Specific Aims:** To quantify the underutilization of ICDs for primary prevention of sudden cardiac death among eligible patients in a large academic center that can be identified by echo screening.

**Methods:** We sought to determine whether individuals who were identified as having a depressed EF on echo reports, and who were otherwise eligible, were receiving primary-prevention ICDs. We performed a retrospective review of charts of patients who had LVEF \( \leq 35\% \) on echos done between October 2009 and March 2010 to determine appropriateness for ICD and whether implantation was performed within the following 6 months. Patients with prior ICDs were excluded, as were patients with contraindications, including major comorbidities suggesting limited life-expectancy, or major psychiatric illness such as schizophrenia, or dementia. Other information collected included age, if they are within 40-days post-MI, follow-up echo, medical/cardiology follow-up, and if and when they received an ICD.

**Results:** Four hundred and five patients with LVEF \( \leq 35\% \) were identified. Of these, 160 (39.5%) already had ICDs. 140 patients (34.57%) had either contraindications, LVEF improved on follow-up echo, or expired. 2 patients (0.49%) had insufficient records. The remaining 103 patients were considered eligible for primary-prevention ICD (25% of low-EF echos). Of these, 39 (38%) received an ICD and 64 (62%) did not.

**Conclusions:** Echocardiography screening identified many patients with low EF who will potentially benefit from primary-prevention ICD implantation. Less than half of these patients receive ICDs. Identifying the reasons for nonreferral and whether an echo-based reminder system can improve appropriate ICD referral are important avenues of future research.

References:

Project Title: Non-surgical versus surgical management of distal radius fractures in patients greater than 55 years of age.

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Background: There is uncertainty regarding optimal treatment for distal radius fractures in patients greater than 55 years of age, despite many trials that compare various methods of fixation. While conservative management is known to correlate with poorer final anatomical alignment, it is not clear that older patients require better anatomical alignment in order to have good functional outcomes.

Specific Aim: The aim of this study was to compare surgical (i.e., pinning, external fixation, or open reduction and internal fixation) versus conservative (i.e., casting) management of distal radius fractures in patients greater than 55 years of age using a decision analysis model.

Hypothesis: Casting of distal radius fractures in adults over age 55 will offer greater quality of life than surgical management.

Methods: We created a Markov state transition model to estimate total quality-adjusted life years (QALYs) achieved using surgical versus non-surgical management of distal radius fractures in patients greater than 55 years of age. We considered patient cohorts aged 55, 65, 75 and 85 years of age. Input assumptions were drawn from published literature. Mortality data were derived from Centers for Disease Control data. The model was run as a Monte Carlo simulation and estimated the experiences of 10,000 hypothetical patients suffering from distal radius fracture. We performed one-way sensitivity analyses of all model variables across their plausible ranges to quantify the impact of data uncertainty on model output. We also performed a probabilistic sensitivity analysis to estimate the proportion of simulations favoring surgical versus non-surgical treatment for each age cohort.

Results: In the base analyses, surgery produced higher total quality-adjusted life expectancy than non-surgical treatment in all but the 85 year-old cohorts. This finding was supported by the probabilistic sensitivity analysis, which found that surgery was favored in 64% of simulations when all variables in the model were simultaneously ranged across their plausible values. However, the benefit of surgery was on average only one additional quality-adjusted week greater than that of non-surgical treatment over the patient’s remaining lifespan among 55 year-olds. Among 85 year-olds, casting offered 11 additional quality-adjusted days over surgery. This effect persisted across one-way sensitivity analyses. Among 55 year-olds, surgery produced higher lifetime QALYs than casting when each variable in the model was independently ranged across its clinically plausible spectrum of values. Similarly, casting was uniformly favored over surgery among 85 year-olds in one-way sensitivity analyses.

Conclusions: Overall clinical outcomes are similar between conservative and surgical management of distal radius fractures in adults older than 55 years of age. However, surgery is less favored among older patients. Decisions regarding management should be based on individual patient and fracture characteristics and patient preferences.
The Therapeutic Potential of Statins in Hepatitis C: A Systematic Review

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Background: Chronic hepatitis C infection is frequently associated with metabolic abnormalities including hepatic steatosis, insulin resistance and dyslipidemia. Despite the cardiovascular benefits of statins and the potential for increased cardiovascular risk in hepatitis C, statin use in chronic liver disease has been limited. Current data indicates that statins can be used safely in chronic, stable hepatitis C. Pre-clinical studies have shown that the hepatitis C virus (HCV) relies heavily on host lipid metabolism and that statins can inhibit viral replication. Given the pleotropic effects of statins, there may also be a clinical role for statins as antiviral agents in HCV.

Specific Aims: To systematically examine existing evidence to determine the clinical impact of statins on hepatitis C viral load and sustained viral response (SVR) rates, in order to provide guidance for therapeutic interventions and help identify areas for future research.

Hypothesis: The use of statins as adjunctive therapy in HCV may positively impact treatment outcomes.

Methods: We searched MEDLINE, ISI Web of Science, SCOPUS and Cochrane databases. The combinations of key words used were limited to “hepatitis C”, “hydroxymethylglutaryl-CoA reductase inhibitors”, “anticholesterol agent”, and “statin”, along with generic and trade names of individual statins. Meeting abstracts from 2009-2011, published in four major journals (Gastroenterology, Hepatology, American Journal of Gastroenterology and Journal of Hepatology) were searched manually. Bibliographies of the included studies were also searched.

Results: Our search revealed 344 citations. A total of 11 papers plus 7 published abstracts met selection criteria. There were 5 retrospective and 13 prospective studies, 8 of which were randomized controlled trials. Studies were generally small and heterogeneous in statin selection and dosing. Only 2 of the 7 studies assessing statins as monotherapy for HCV demonstrated significant effects on viral RNA titers. All 11 studies evaluating statin use with peg-interferon plus ribavirin showed either a trend to or a significant reduction in viral load, with pooled data from 475 subjects in 6 prospective trials demonstrating a significant improvement in SVR in the statin versus no statin group (60.2% vs. 42.8%, RR 1.4, 95% CI = 1.17-1.68, p < 0.001). Fluvastatin, rosvastatin and pitavastatin showed positive results in prospective trials. Atorvastatin and simvastatin were the most commonly used statins in 2 retrospective studies that identified statins as independent predictors of SVR. None of the studies had adequate power to detect differences in potency between statins. There was no increase in statin-related adverse events.

Conclusions: When used as an adjunctive therapy to peg-IFN plus RBV, statins appear to be safe and may enhance HCV treatment response. Adequately powered randomized clinical trials are needed to further clarify the role, optimal dosing, and timing of statin use in the era of directly acting antiviral agents (DAAs) such as recently approved protease inhibitors telaprevir and boceprevir.
Recognition of Cognitive Impairment in Older Adults Admitted for Heart Failure

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Background: Heart failure is largely a disease of older adults; 80% of heart failure patients are at least sixty-five years of age (1,2). It constitutes the largest common diagnosis-related group of inpatients (3) and is associated with great cost, $37.2 billion in 2009 alone (4). Due to the aging cohort of “Baby Boomers,” the adult population in the United States aged ≥ 65 year of age will more than double in the next 40 years, from 40.2 million in 2010 to 88.5 million in 2050 (5). While cognitive impairment is common in heart failure (6), and is an important independent predictor of heart failure outcomes including mortality, it has received minimal attention because it falls outside of the traditional disease model used in heart failure research and clinical care (7-10). This study seeks to evaluate physicians’ recognition of cognitive impairment in older adults hospitalized for heart failure.

Specific Aims: To assess physicians’ recognition of cognitive impairments in older patients admitted with heart failure at the time of discharge, and examine differences between patients whose cognitive impairment was recognized and those whose impairment was not recognized.

Hypothesis: We hypothesized that the proportion of patient with cognitive impairment recognized by physicians as documented by discharge documentation is less than fifty percent.

Methods: This study utilized data previously collected as part of an ongoing, prospective, cross-sectional cohort study - the Co-morbidity in Older Patients with Heart Failure (COPing with HF) – in which older adults were enrolled if they met the following criteria: 1- with an admission diagnosis of HF, 2- radiographic evidence of HF, 3- admitted to a medical service, and 4- medical records evidence meeting the widely used HF criteria. Cognitive status was defined using the Mini-Mental State Examination (MMSE). An MMSE score of 21-24 was used to indicate mild cognitive impairment and a score of ≤20 indicated moderate to severe impairment. To evaluate physicians’ recognition of cognitive impairment, we used a standardized form with targeted keyword strategy to review hospital discharge summaries. With research nurses’ MMSE assessment of cognitive impairment as the “gold standard,” we calculated the percentage of cognitively impaired patients recognized as such by physicians, and compared the characteristics of patients with and without recognized cognitive impairment.

Results: 282 patients were included in this study. Their mean age was 80, 18.8% were nonwhite, and 53.2% were female. Cognitive impairment was present in 132/282 patients (46.8% overall; 25.2% mild, 21.6% moderate-severe). Amongst those with cognitive impairment, 30/132 (22.7%) was recognized by physicians. Compared with patients whose cognitive impairment was recognized by physicians, those with unrecognized impairment were younger (81.3 years vs. 85.2 years, P<0.05), and had impairment that was less severe (median MMSE score 22.0 vs. 18.0, P<0.01).

Conclusions: Cognitive impairment is common in older adults hospitalized for heart failure and it is under-recognized by physicians. Even in patients with moderate to severe impairment, less than half were recognized. Future studies should assess whether improving recognition of cognitive impairment improves outcomes in these patients.