Biological Correlates of Frailty in Older Heart Failure Patients

Dalane W. Kitzman, MD
Professor of Internal Medicine:
Cardiovascular Medicine and Geriatrics
Kermit Glenn Phillips II Chair in Cardiology
Wake Forest School of Medicine
Heart Failure: a disease of the elderly

- Prevalence, incidence rise sharply with age

- Elderly account for up to 88% of HF deaths
- 1 million hospitalizations / year
- $39 Billion in annual health care costs

HF Readmissions: A National Crisis

• Older ADHF patients have high persistently high rate of rehospitalizations
  – despite numerous strategies to reduce
  – nearly all recent large trials (n=11) aim at reducing outcomes in hospitalized acute HF have been negative

• Associated with: reduced quality of life, markedly increased mortality, high costs to health care system

• Key Medicare performance measure

• Large financial penalties to under-performing institutions began in January 2013
- Why are Readmission Rates and Other Outcomes So Poor in Elderly HF patients?

- Why have they not improved with a wide range of disease specific (HF) interventions?

Possible, overlooked clue:

• A majority of re-hospitalizations in older HF patients are non-cardiovascular! (Ather et al JACC 2012)

• < 30% are due to HF!
Under-Appreciated Factors That May Explain the High Rate of Non-cardiovascular Rehospitalizations in Elderly HF Patients

- Multiple comorbidities
- Frailty
Contribution of Non-Cardiac Comorbidities

• In >122,00 Medicare recipients ≥ 65 years:
  – 96% had ≥ 1 non-cardiac co-morbid condition; 39% had ≥ 5 non-cardiac comorbidities
  – Accounted for 81% of rehospitalizations

• 1,077 incident HF cases in Olmsted County (JACC 2009); average age 77; 4.7 yr f/u; 75% mortality
  – 4,359 hospitalizations
  – 83% at least once, median 3
  – 62% due to non-cardiovascular; only 16% were HF
  – > 2/3 never hospitalized for HF after diagnosis
  – Co-morbid disease independent predictors of hospitalization
Contribution of Frailty

- Excess vulnerability to stressors with reduced ability to recover after an event
- Increases with age, co-morbidities, and severity of cardiovascular disease; very high rates in elderly HF patients
- Strong, independent predictor of all-cause mortality and hospitalizations in a wide range of populations: CAD, HF, aortic stenosis

J Cardiovasc Med 2010, 11:739-747
Frailty in Patients with Chronic HF

- Patients with chronic stable HF:
  - 74% met at least one Fried frailty criteria (pre-frail)
  - 19% considered frail (3+)

- Frail patients had:
  - 92% increased risk for ED visits
  - 22% increased risk for Hospitalization – both CV and non-CV causes

Impact of Frailty on Outcomes in HF

Cox regression adjusted survival curve in subjects with CHF ($n = 120$) stratified by frailty *Eur J Clinical Invest* 2005, 35(12): 723–730
Frailty in Acute Decompensated HF

Survival independently associated with SPPB score.

• Compared to a score of 9-12:

<table>
<thead>
<tr>
<th>SPPB Score</th>
<th>HR (95% CI) for Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-8</td>
<td>1.95 (0.67-5.70)</td>
</tr>
<tr>
<td>1-4</td>
<td>4.78 (1.63-14.02)</td>
</tr>
<tr>
<td>0</td>
<td>6.06 (2.19-16.76)</td>
</tr>
</tbody>
</table>

Survival by SPPB score quartiles. Multivariable Cox regression model adjusted for age, gender, study site, NYHA class, comorbidity, pharmacological therapy, and functional status before hospitalization.

Chiarantini et al. J Cardiac Fail 2010;16:390-395
How do Frailty and Multiple Comorbidities Drive Poor Outcomes in Elderly Acute HF Patients?

- Frailty and multiple comorbidities have in common: physical dysfunction
  - HF is a systemic syndrome
    * Involves inflammation and other unidentified circulating factors that affect the whole patient, not just cardiovascular system
  - Skeletal muscle, which is striated, like cardiac muscle, is nearly 50% of body mass.
    * Multiple, severe skeletal muscle abnormalities are present and contribute significantly to disability in HF
      * Reduced capillary density, mitochondrial function, adipose infiltration
      * Not merely deconditioning; present independent of physical activity level
Increased Intermuscular Adipose in Elderly HFpEF

Healthy Control
Skeletal muscle = 81 cm
Intermuscular fat = 14 cm
Subcuataneous fat = 107

Legend
Red = skeletal muscle
Green = intermuscular fat
Blue = subcuataneous fat

HFpEF Patient
Skeletal muscle = 71 cm
Intermuscular fat = 28 cm
Subcuataneous fat = 96 cm
Decreased Capillarity in Skeletal Muscle in Older Patients with HFpEF: Relationship to Exercise Capacity
Kitzman et al, J Appl Physiol 2014

Parallels microvascular rarefaction in myocardium (Mohammed, Circulation 2015)
Central Hypothesis: Contribution of Physical Dysfunction

- Hospitalized older HF patients have severe impairments in physical function and frailty:
  - Baseline physical dysfunction from aging, chronic HF, multiple comorbidities
  - Accelerates as HF decompensation develops
  - Further worsened by the hospital environment and immobility → loss of skeletal muscle → delayed, incomplete recovery; incremental functional loss becomes permanent with new, worsened baseline (Krumholz NEJM 2012: “post-hospitalization syndrome”)
  - Often unrecognized
  - Multiple domains: balance, strength, mobility, endurance
  - May drive poor outcomes

- Suggests potential utility of physical function / rehabilitation interventions
Aging
Chronic HF
Decompensation
Hospitalization
Immobility
Comorbid disease
Aging
Impairments in Physical Function, Cognition, etc.
Frailty
Increased vulnerability to poor outcomes:
Rehospitalization, disability, death
**HF-ACTION: All-Cause Mortality or All-Cause Hospitalization**

![Graph showing event rate over years from randomization for Usual Care and Exercise groups.](image)

*(Primary) HR 0.93 (95% CI: 0.84, 1.02), $P = 0.13$

*Adjusted HR 0.89 (95% CI: 0.81, 0.99), $P = 0.03$

*Adjusted for key prognostic factors*

Whellan et al, *JAMA* 2009
HF-ACTION: Other Outcomes

• Small but significant increase in exercise capacity, quality of life, and HF class
• Better adherence predicted more improvement
HF-ACTION: Key Gaps Remaining

- HF with Preserved EF
- Elderly (mean age 59)
- Patients with recent hospitalization:
  - risk of adverse outcomes highest in the first 30 days after discharge
- Frail, multiple comorbidities, unstable HF
  - May need other than standard cardiac rehab
- 2015 NIH Task Force:
  - HF-ACTION may have excluded the patients at greatest risk, most likely to benefit
  - Urgent need for novel interventions to address
REHAB-HF Study Hypothesis

- In elderly patients with acute HF and multiple comorbidities, a novel, tailored, progressive, multi-domain rehabilitation intervention focused on balance, strength, mobility, and endurance that begins early during hospitalization and continues for 3 months following discharge will improve physical function (SPPB), quality of life, and reduce rehospitalizations.
REHAB-HF Pilot Study

- **Purpose:** To determine the feasibility of a future, definitive REHAB-HF trial and provide preliminary support for the study hypotheses

- **Funded by Wake Forest Aging Center**

- **27 patients enrolled**

- **Demographics:**
  - Mean 72 years (range 60-98 years)
  - 59% women, 56% African-American
  - Mean EF 37%; 41% had preserved EF (≥ 45%)
REHAB-HF Baseline Results

• Severely reduced physical function in all domains
• High rates of frailty (> 50% by Fried criteria)
• Very poor quality-of-life
REHAB-HF Trial Design Overview

- NIA Funding began June 1, 2015
- 3 Lead Clinical Sites (Wake Forest, Duke, Jefferson)
  - Coordinating Center = Wake Forest (Drs. Kitzman, Duncan, Morgan)
  - Each lead center may have up to 3 'satellite' sites
- 360 consenting patients ≥ 60 years old hospitalized with ADHF
- Following baseline testing, randomized to receive a novel, 12-week, progressive, multi-domain rehabilitation intervention or attention control
- Repeat measures of physical function and quality of life at baseline, 1 month, and 3 months
- Clinical events monitored for 6 months following index hospitalization
- First patient enrolled September 17, 2015
REHAB-HF
STRONG BODY – STRONG HEART