Biological Correlates of Frailty in Older Heart Failure Patients

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Heart Failure: a disease of the elderly

- Prevalence, incidence rise sharply with age

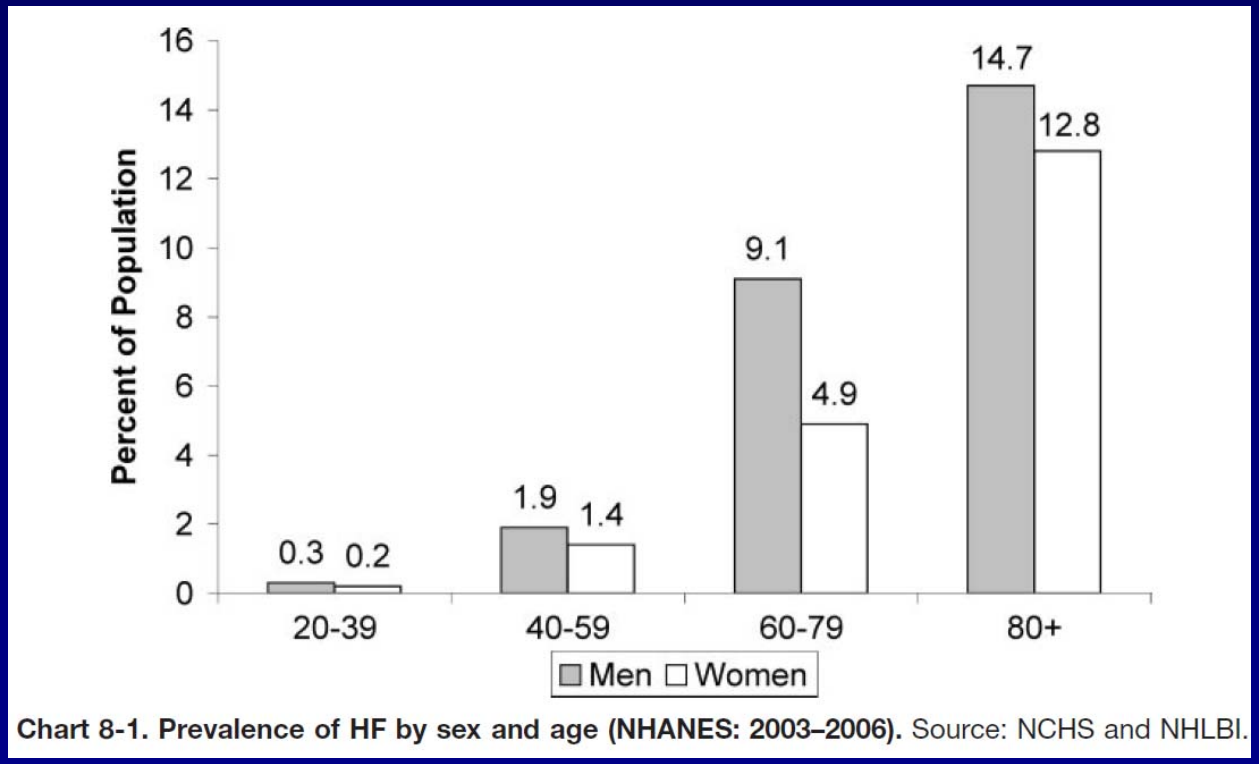


Chart 8-1. Prevalence of HF by sex and age (NHANES: 2003–2006). Source: NCHS and NHLBI.

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

Natl Health Stat Report. 2010 Oct 26;(29):1-20, 24
Vital Health Stat 13 1992;113:1–225.

Circulation 2010;121;e46-e215

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

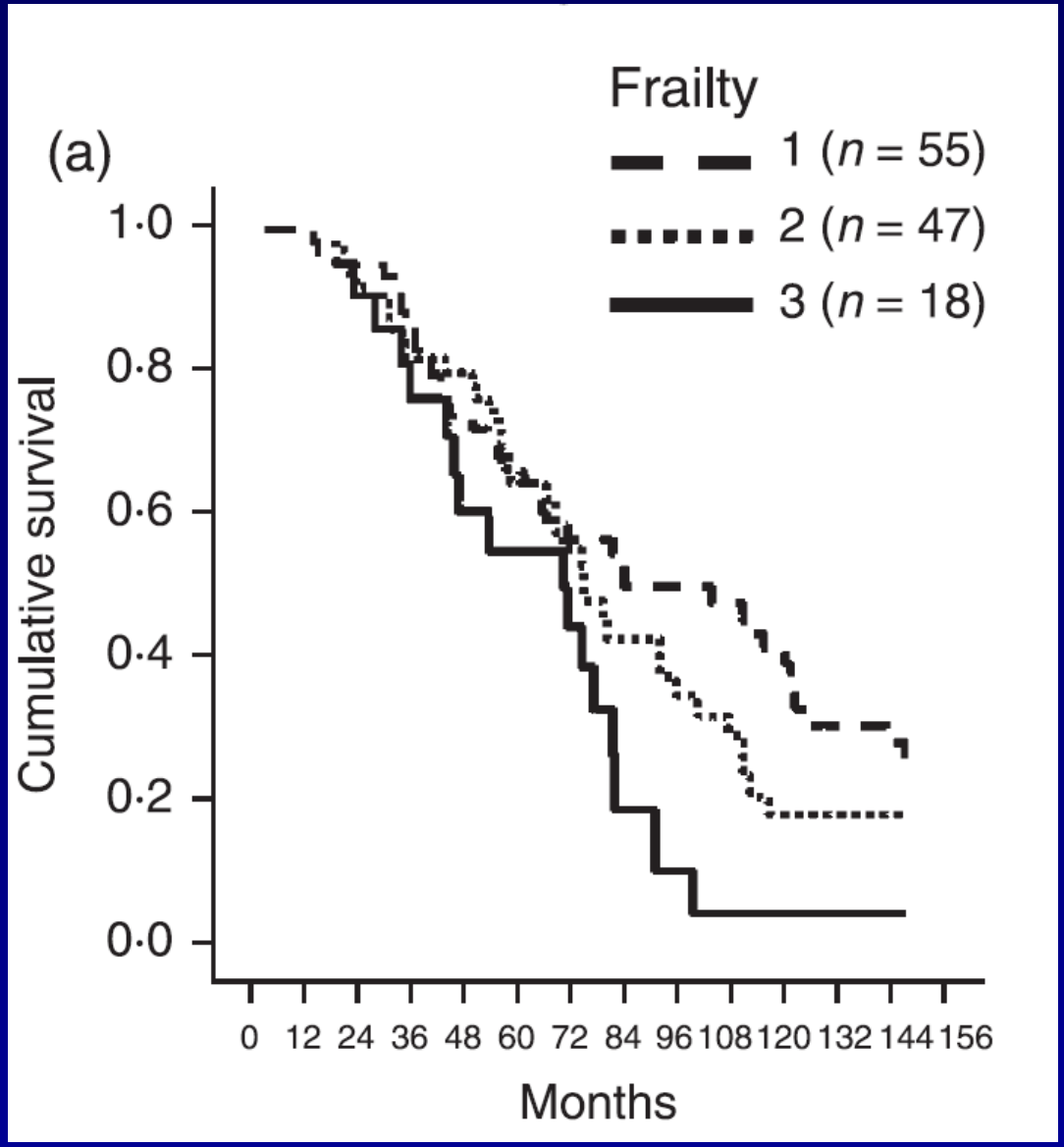
J Cardiovasc Med 2010, 11:739-747
Rev Esp Cardiol. 2008;61(8):835-42

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

McNallan et al. J Am Coll Cardiol HF 2013;1:135–41

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

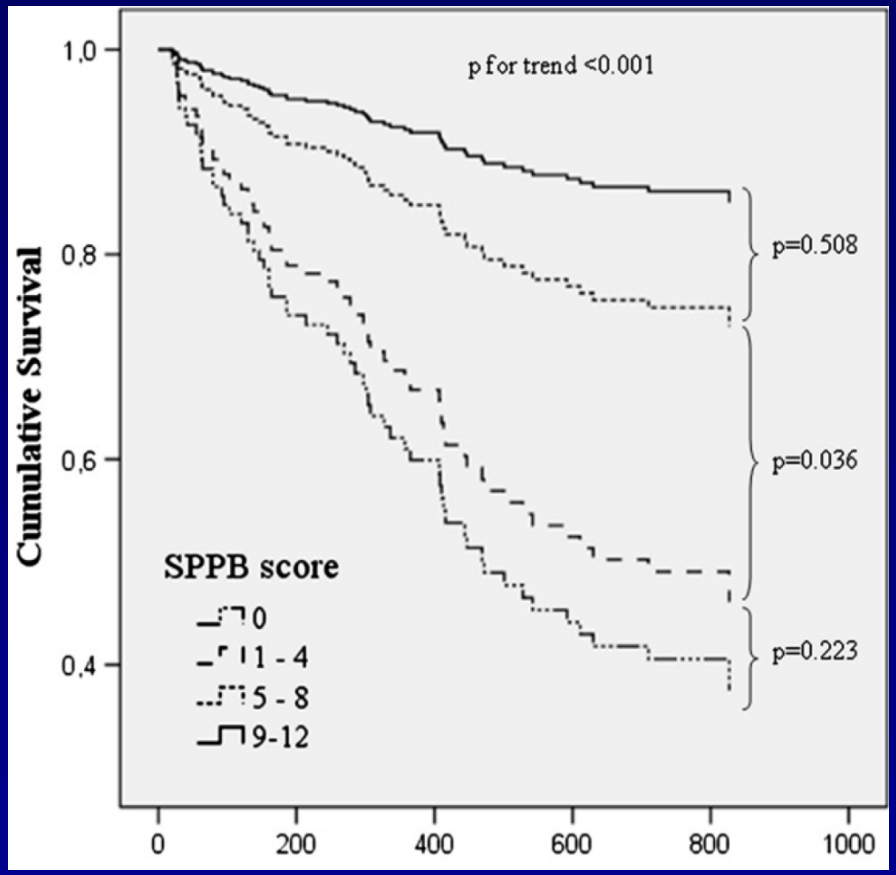
Frailty in Acute Decompensated HF

Survival independently associated with SPPB score.

- Compared to a score of 9-12:

SPPB Score	HR (95% CI) for Mortality
5-8	1.95 (0.67-5.70)
1-4	4.78 (1.63-14.02)
0	6.06 (2.19-16.76)

Chiarantini et al. J Cardiac Fail 2010;16:390-395



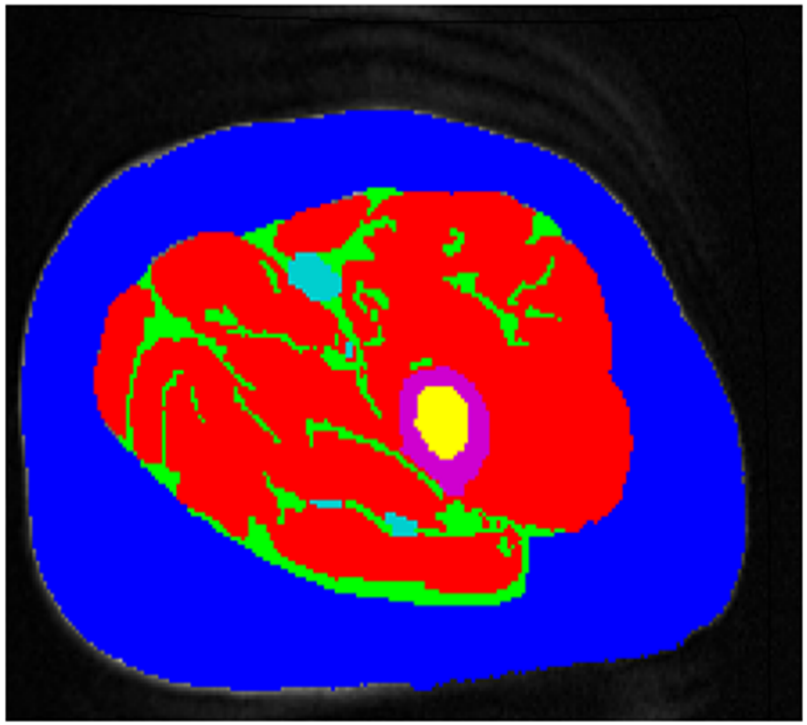
Survival by SPPB score quartiles. Multivariable Cox regression model adjusted for age, gender, study site, NYHA class, comorbidity, pharmacological therapy, and functional status before hospitalization.

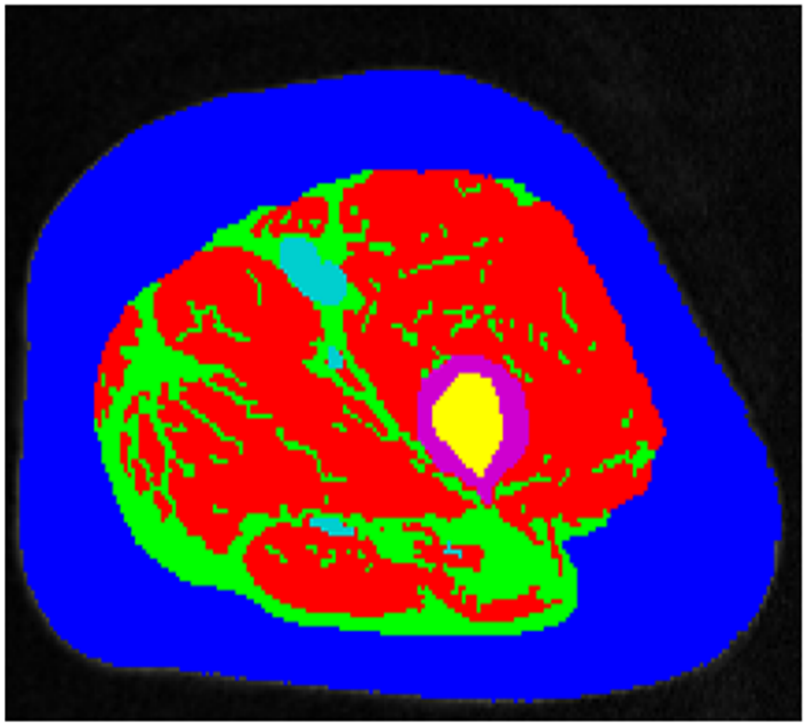
How do Frailty and Multiple Comorbidities Drive Poor Outcomes in Elderly Acute HF Patients?

- 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

Haykowsky, Kitzman, et al, Am J Cardiology, 2014





Healthy Control

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

Legend

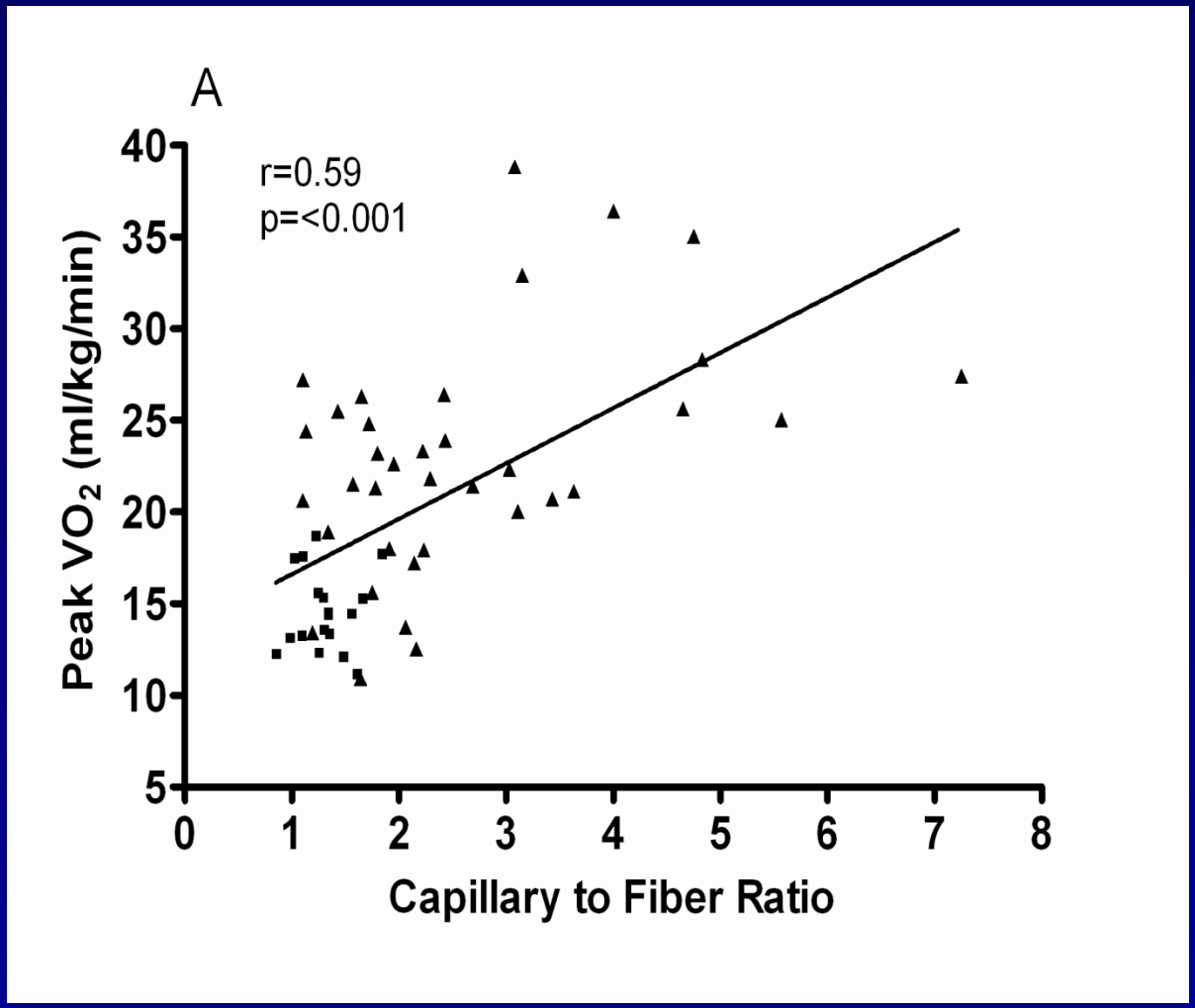
Red = skeletal muscle
Green = intermuscular fat
Blue = subcuataneous fat

HFpEF Patient

Skeletal muscle = 71 cm
Intermuscular fat = 28
Subcuataneous fat = 96

Decreased Capillarity in Skeletal Muscle in Older Patients with HFpEF:Relationship to Exercise Capacity

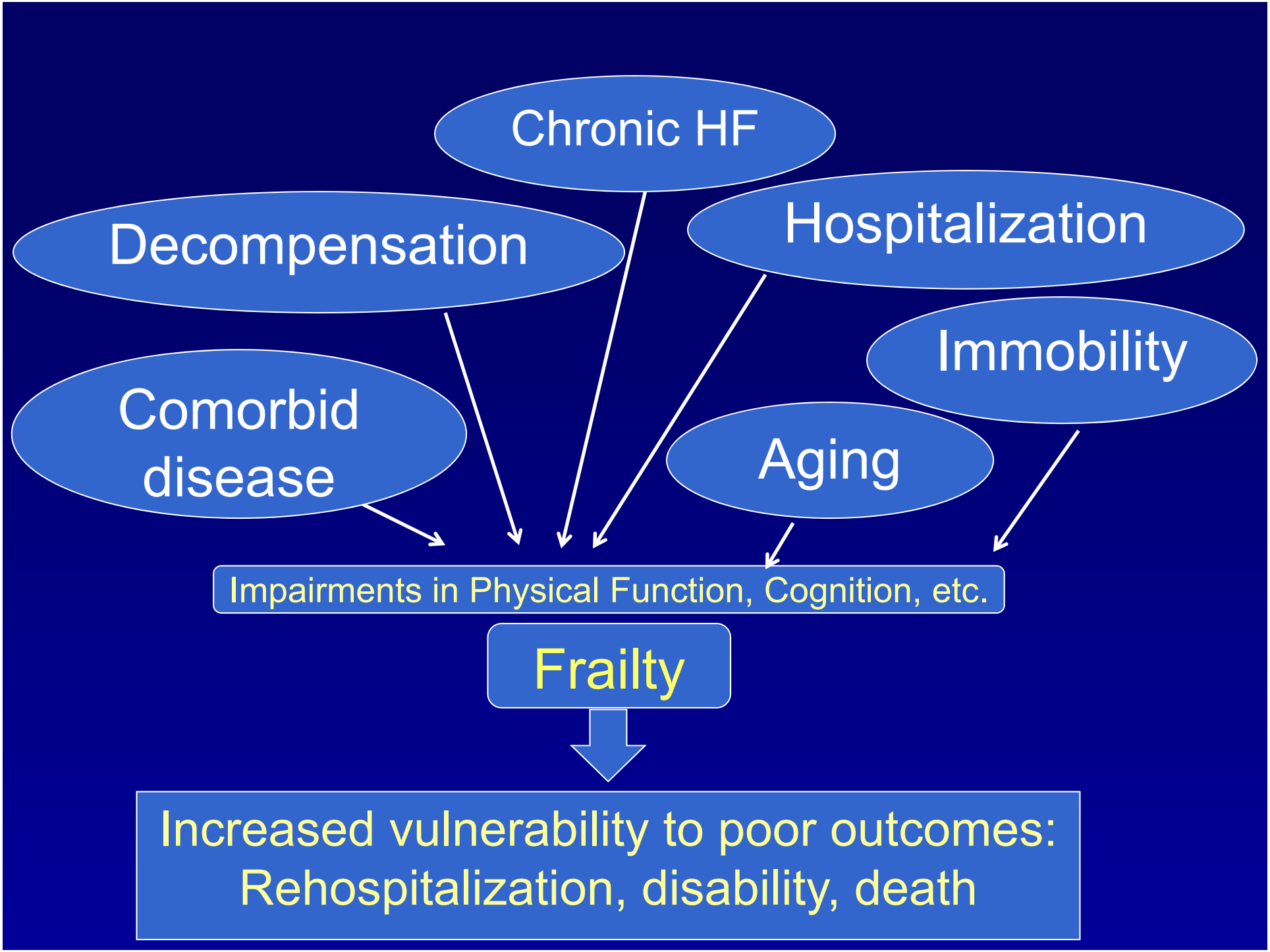
Kitzman et al, J Appl Physiol 2014



Parallels microvascular rarefaction in myocardium (Mohammed,Circulation2015)

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


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

* 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 ($\geq$ 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 hospitalization
- Trial registered: http://clinicaltrials.gov/ct2/show/NCT02196038
- First patient enrolled September 17, 2015

REHAB-HF

STRONG BODY – STRONG HEART