Heart Failure Awareness Week

Lunch & Learn
Monday, February 14th, 2022
Preventing Heart Failure Among the Expanding Population of Older Adults
Preventing HF Among the Expanding Population Of Older Adults

Daniel E. Forman, M.D.
Professor of Medicine, University of Pittsburgh
Chair, Section of Geriatric Cardiology, Divisions of Geriatrics and Cardiology, University of Pittsburgh Medical Center
Director of Translational Research, Geriatric Research, Education, and Clinical Center, VA Pittsburgh Healthcare System
Associate Director for Clinical Translation and Director of Emerging Therapeutics, Aging Institute, University of Pittsburgh
Director, Transitional Care (Cardiac Rehabilitation, GeroFit, C-TraC, COMPASS), VA Pittsburgh Healthcare System
• No disclosures
• As the population is getting older, the concept of risk factors for heart failure is undergoing changes
Average US Life Expectancy at Birth


↑ CVD with Aging

Percentage of Population

Men
Women

20-24 25-34 35-44 45-54 55-64 65-74 75+

NHANES III
↑ CVD with Age: Driven by Biological Changes

Genomic instability
Telomere attrition
Epigenetic alterations
Loss of proteostasis
Deregulated nutrient sensing
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Altered intercellular communication

Primary hallmarks
Causes of damage

Antagonistic hallmarks
Responses to damage

Integrative hallmarks
Culprits of the phenotype

Age: CVD with Cumulative Disease and Vulnerability

Lakatta EG, J Mol Cell Cardiol. 2015;83:1-13
Age: CVD with Cumulative Disease and Vulnerability

Disease

CVD in a context of multimorbidity
Age: CVD with Cumulative Disease and Vulnerability

CVD in a context of multimorbidity and frailty

Frailty

Disease

Lakatta EG, J Mol Cell Cardiol. 2015;83:1-13
CVD risks and typical aging...
CVD Risk: Drivers of Frailty and CVD Overlap

Environment

Genetics
Epigenetics
Telomeres
Proteostasis

Physiological Drivers of Frailty
- Stress-response system
- Musculoskeletal system
- Metabolic system

Cellular/Molecular Drivers of Frailty
- Cellular senescence
- Mitochondrial dysfunction
- Poor DNA repair
- Central adiposity

Physiological Drivers of CVD
- Inflammation
- Metabolic dysfunction
- Coagulopathy

Cellular/Molecular Drivers of CVD
- Oxidative stress
- Mitochondrial dysfunction
- Apoptosis
- Insulin resistance

Sarcopenia: Skeletal Muscle Weakening and Atrophy

Inflammation
- ↑ infiltrating adipose
- ↓ type 2 fibers
- ↓ Microvascular perfusion
- ↑ Mitochondrial dysfunction
- ↑ Apoptosis
- ↑ Motor neuron loss
Adipose Tissue

Fat Cells

Macrophage

Ectopic Lipids

Liposomes

↑ Insulin Resistance

↑ Inflammation

↑ RAAS Activity

↑ Insulin

↑ Mechanical Load

↑ SNS Activation

Dyslipidemia

Lipotoxicity

CAD

Diabetes

OSA

HTN

Gadde KM, J Am Coll Cardiol. 2018;71:69-84
Distinctive Age-Related Vulnerabilities to HF Pathophysiology

Cardiac Dysfunction
Body Composition Changes
Multiorgan Dysfunction

- Sarcopenia
- Mitochondrial Dysfunction
- Capillary Rarefication
- Endothelial Dysfunction

Comorbidities
Aging
Obesity
Physical inactivity

Impaired QOL
Hospitalization Death
Nursing Home Placement
Excess Healthcare Costs
Functional Impairment

HFpEF

Pandey A…Kitzman DW. J Am Coll Cardiol. 2021;78:1166-87
Modifying Risk Factors to Incident HF

• Traditional CVD risk factors:
  – ↓Hypertension
  – ↓Cholesterol
  – ↓Sedentariness

• New Risk factors
  – Caloric Restriction
  – Caloric Restriction Mimetics
Systolic Blood Pressure Intervention Trial (SPRINT): Lower is better...

Composite of MI, ACS, stroke, HF, or death from cardiovascular causes

**Primary Outcome**

Hazard ratio with intensive treatment

0.75 (95% CI, 0.64–0.89)

**All-Cause Mortality**

Hazard ratio with intensive treatment

0.73 (95% CI, 0.60–0.90)
Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP)

• 60-80 yo
• N=8511
• olmesartan, amlodipine, and HCTZ
• BP systolic target: 110-130 mmHg

1° Outcome:
Composite of stroke, acute coronary syndrome (MI and UA), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or CVD death

HF declines 28%

Increased adverse events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intensive BP control</th>
<th>Standard BP control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>133,900</td>
<td>77,800</td>
</tr>
<tr>
<td>Syncope</td>
<td>128,500</td>
<td>94,100</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>172,000</td>
<td>128,500</td>
</tr>
<tr>
<td>Acute kidney injury or acute renal failure</td>
<td>228,100</td>
<td>139,400</td>
</tr>
</tbody>
</table>

HR 1.67

HR 1.33

HR 1.35

HR 1.66

Data combined from Jupiter and HOPE-3:

- Adults ≥70 years: 26% relative risk reduction for the endpoint nonfatal MI, nonfatal stroke, or CV death

**New Statin Use in US Veterans Over Age 75**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude rate/1000 person-years</th>
<th>Weighted incidence rate difference/1000 person-years (95% CI)a</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (n = 206 902)</td>
<td>78.7</td>
<td>98.2 (-19.45 (-20.38 to -18.52))</td>
<td>0.75 (0.74 to 0.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All CV death (n = 53 296)</td>
<td>22.6</td>
<td>25.7 (-3.09 (-3.63 to -2.55))</td>
<td>0.80 (0.78 to 0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD composite (n = 123 379)b</td>
<td>66.3</td>
<td>70.4 (-4.05 (-5.09 to -3.02))</td>
<td>0.92 (0.91 to 0.94)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

N=57,178,  
Mean age 81.4 yrs

Orkaby AR, et al. JAMA. 2020;324:68-78
### Atherosclerotic cardiovascular disease composite

#### Sex

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of events/No. at risk</th>
<th>Weighted incidence rate difference/1000 person-years (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin user</td>
<td>Statin nonuser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>21111/55622, 99098/318244</td>
<td>-4.20 (-5.25 to -3.15)</td>
<td>0.92 (0.91-0.94)</td>
</tr>
<tr>
<td>Women</td>
<td>593/1556, 2584/8737</td>
<td>1.49 (-4.57 to 7.56)</td>
<td>0.99 (0.90-1.08)</td>
</tr>
</tbody>
</table>

#### Race

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of events/No. at risk</th>
<th>Weighted incidence rate difference/1000 person-years (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin user</td>
<td>Statin nonuser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18961/51570, 88680/296617</td>
<td>-3.63 (-4.69 to -2.56)</td>
<td>0.93 (0.91-0.94)</td>
</tr>
<tr>
<td>Black</td>
<td>2341/4530, 11320/24641</td>
<td>-10.88 (-15.49 to -6.27)</td>
<td>0.89 (0.85-0.93)</td>
</tr>
<tr>
<td>Other</td>
<td>402/1078, 1567/4645</td>
<td>1.44 (-5.62 to 8.51)</td>
<td>0.97 (0.86-1.08)</td>
</tr>
</tbody>
</table>

#### Age group, y

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of events/No. at risk</th>
<th>Weighted incidence rate difference/1000 person-years (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin user</td>
<td>Statin nonuser</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>9161/24092, 50538/163178</td>
<td>-2.95 (-4.31 to -1.59)</td>
<td>0.92 (0.90-0.95)</td>
</tr>
<tr>
<td>80-84</td>
<td>9279/24295, 36084/115062</td>
<td>-4.94 (-6.68 to -3.20)</td>
<td>0.93 (0.90-0.95)</td>
</tr>
<tr>
<td>85-89</td>
<td>2901/7826, 12269/40186</td>
<td>-3.40 (-7.16 to 0.36)</td>
<td>0.96 (0.92-1.00)</td>
</tr>
<tr>
<td>≥90</td>
<td>363/965, 2791/8555</td>
<td>-12.99 (-26.36 to 0.39)</td>
<td>0.90 (0.80-1.01)</td>
</tr>
</tbody>
</table>

---

N=57,178,
Mean age 81.4 yrs

Orkaby AR, et al. JAMA. 2020;324:68-78
DM and HF: More than glucose control

Commonly Used Current Pharmacological Therapies to Lower Hyperglycemia
- Biguanides
- SU
- TZDs
- GLP-1 RA
- DPP4-i
- SGLT2
- Insulin

Potential Pathways that Could be Targeted to Modulate Specific Pathophysiologic Mechanisms that Contribute to Diabetes-Associated Heart Failure
- Altered Myocardial Substrate Metabolism
- Mitochondrial Bioenergetics
- Oxidative Stress
- Lipotoxicity
- Inflammation
- ER Stress
- Insulin Signaling
- β2Adrenergic Receptor Signaling
- GRK2 Signaling
- Renin Angiotensin Aldosterone Signaling
- Autophagy
- AGEs

Kenny HC, Abel ED. Circ Res. 2019;124:121-141
Age-Specific Shifts in CVD Risk Factors

Implications of Lifestyle Risk Factors in Older Adults

- Physical Activity
- Caloric Restriction
- Caloric Restriction Mimetics
  - Rapamycin
  - Resveratrol
  - Metformin
  - Canakinumab
Physical Activity and Heart Failure

## Exercise as Medicine

### Mitochondrial
- ↑ mitochondrial DNA deletions and mutations
- Electron transport chain abnormalities
- ↑ mitochondrial fission
- ↓ mitochondrial content
- ↓ respiration

### Skeletal Muscle
- ↑ IL-6 and CRP
- Activation of proteolytic systems
- Inactivation of the PI3K/Akt/mTOR pathway
- ↓ lean muscle mass
- Greater proportion of hybrid fibers possibly due to dysregulation in MHC isoform expression

### Cardiac Muscle
- ↑ AGE accumulation indicative of collagen cross-linking
- ↑ Left ventricular stiffness
- β-adrenergic receptor desensitization resulting in impaired inotropic and chronotropic responses to adrenergic stimulation
- ↓ SERCA2a contributes to prolonged calcium transients

### Conduit Arteries
- ↓ sympathetic baroreflex sensitivity and sympathetic activation
- ↑ NOS uncoupling, ↓ NO bioavailability, thereby ↑ oxidative stress
- Extracellular matrix remodeling through elastin degradation by MMPs and formation of AGEs
- Endothelial dysfunction

### Sedentary
- ↑ mitochondrial protein turnover through degradation of damaged proteins and de novo synthesis of new functional proteins
- ↑ expression of PGC-1α
- ↑ SIRT3 content
- ↑ mitochondrial volume

### Physical Activity
- ↑ metabolic enzymes profile: citrate synthase, β-HAD, glycogen phosphorylase
- ↓ catabolic mRNA expression (FOXO3a, MuRF-1, Atrogin-1, myostatin)
- ↑ capillary-to-fiber ratio
- ↑ insulin sensitivity
- ↑ SERCA2a mRNA & protein expression
- ↑ phosphorylation of threonine-17 residue of phospholamban allowing for faster reuptake of cytoplasmic calcium
- ↑ contractility and relaxation due to faster systolic rise and diastolic decay time of calcium
- ↓ Left ventricular stiffness

### Conduit Arteries
- Lower expression of the transcription factor p53 which is associated with senescence compared to sedentary counterparts
- Lower markers of senescence (p21 and p16)
- ↓ expression of nitrotyrosine and NADPH oxidase (prooxidant)
- ↑ expression of manganese SOD (antioxidant)

---

Calorie Restriction

Insulin/IGF-1

Sirtuins

TOR

AMPK

LKB1

Autophagy

Mitochondrial Biogenesis

Genome Integrity

Stress Resistance

Metabolic Disease

Cardiovascular Disease

Neurological Disease

Longevity

Sarcopenia, Multimorbidity, Sedentary Lifestyle

- Normal Aging
- Vulnerable Aging
- Pre-Frail
- Frail
- Disability

Time (Allostatic Load)

Inflammaging

- Diet
- Exercise
- Novel anti-inflammatory therapeutics (Canakinumab)

Ferrucci L, Fabbri E. Nat Rev. 2018; 15:505-22
Targeting Aging with Metformin (TAME)

Metformin
• Most widely prescribed oral medication for type 2 DM worldwide

Barzilai N, Cell Metab. 2016;23:1060-5
Summary

• The rapidly growing population of older adults is intrinsically vulnerable to incident CVD

• Traditional risk factors have sustained and even increased benefit to moderate risks of HF amidst high susceptibility to CVD

• Novel risk factors associated with aging are now being recognized and provide new targets for risk modification
Heart Failure Awareness Week

Lunch & Learn
Monday, February 14th, 2022
Prevention and Early Detection of Heart Failure Patients
Heart Failure Awareness Week!

• Welcome!
• Daily Newsletters via email
• Lunch & Learns Monday - Friday 12om CST/ 1pm EST
• Join HFSA and other heart failure-focused organizations on Twitter at 11:00 AM CT on Wednesday, February 17 for a lively discussion on heart failure. The purpose of the chat is to provide healthcare providers and heart failure patients with an overview on the status of heart failure and to discuss ways to improve quality of care and expand heart failure awareness. Follow hashtag #HFChat2022
• Recordings
• Slides & Attachments
• Submit questions through the question panel
Prevention and Early Detection of Heart Failure Patients

Jennifer Maning, DO
Heart Failure Burden

Prevalence of HF is projected to increase by 46% from 2012 to 2030, affecting >8 million people 18 years of age or older.

NHANES indicates National Health and Nutrition Examination Survey.
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.31

Heart Failure Risk Factors

Coronary heart disease
PAR 20%

Hypertension
PAR 30%

Diabetes
PAR 12%

Obesity
PAR 12%

Smoking
PAR 14%

PAR, population attributable risk

Data from NHANES show that one-third of US adults have at least 1 HF risk factor

Sex Differences in Risk Factors

- *Hypertension* is the most common risk factor in women while *coronary artery disease* is the most common risk factor among men.

Hypertension

- Long term treatment of hypertension reduces the risk of HF by ~50% and is associated with lower HF mortality

Most effective anti-hypertensive medication classes in reducing the incidence of HF

- Diuretics: OR 0.59
- ACEI: OR 0.70
- ARB: OR 0.76

• For patients with diabetes, **SGLT2 inhibitors** have been shown to reduce incident heart failure (*even without a history of a prior MI or ASCVD*)
Dyslipidemia

Relations of Lipid Concentrations to Heart Failure Incidence
The Framingham Heart Study

Ragha S. Velagaleti, MD, Joseph Massaro, PhD, Ramachandran S. Vasan, MD, Sander J. Robins, MD, William B. Kannel, MD, and Daniel Levy, MD

Figure 1. Kaplan-Meier curves of unadjusted survival free of HF in each HDL-C category.

Tobacco use dependence is a without a history of a prior MI or ASCVD but with multiple risk factors,

For former smokers, the risk of HF is comparable to that of never smokers after >15 years of tobacco cessation.
Meta-analysis of 10 cohort studies comprised of 282,889 patients who were followed for up to 30 years. RR for HF among patients with regular exercise pattern was 28% lower (RR: 0.72; 95% CI: 0.67 to 0.79)

Figure 2. Meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure. Forest plot showing the overall estimate of the association of physical activity and heart failure. CI indicates confidence interval.
Key Preventative Strategy

• Promote a **healthy lifestyle** throughout life
Social Determinants of Health

Table 2. Example Considerations for Addressing Social Determinants of Health to Help Prevent ASCVD Events

<table>
<thead>
<tr>
<th>Topic/Domain</th>
<th>Example Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk</td>
<td>Adults should be routinely assessed for psychosocial stressors and provided with appropriate counseling.</td>
</tr>
<tr>
<td></td>
<td>Health literacy should be assessed every 4 to 6 y to maximize recommendation effectiveness.</td>
</tr>
<tr>
<td>Diet</td>
<td>In addition to the prescription of diet modifications, body size perception, as well as social and cultural influences, should be assessed.</td>
</tr>
<tr>
<td></td>
<td>Potential barriers to adhering to a heart-healthy diet should be assessed, including food access and economic factors; these factors may be particularly relevant to persons from vulnerable populations, such as individuals residing in either inner-city or rural environments, those at socioeconomic disadvantage, and those of advanced age.</td>
</tr>
<tr>
<td>Exercise and physical activity</td>
<td>In addition to the prescription of exercise, neighborhood environment and access to facilities for physical activity should be assessed.</td>
</tr>
<tr>
<td>Obesity and weight loss</td>
<td>Lifestyle counseling for weight loss should include assessment of and interventional recommendations for psychosocial stressors, sleep hygiene, and other individualized barriers.</td>
</tr>
<tr>
<td></td>
<td>Weight maintenance should be promoted in patients with overweight/obesity who are unable to achieve recommended weight loss.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>In addition to the prescription of type 2 diabetes mellitus interventions, environmental and psychosocial factors, including depression, stress, self-efficacy, and social support, should be assessed to improve achievement of glycemic control and adherence to treatment.</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Short sleep duration (&lt;6 h) and poor-quality sleep are associated with high blood pressure and should be considered.</td>
</tr>
<tr>
<td></td>
<td>Because other lifestyle habits can impact blood pressure, access to a healthy, low-sodium diet and viable exercise options should also be considered.</td>
</tr>
<tr>
<td>Tobacco treatment</td>
<td>Social support is another potential determinant of tobacco use. Therefore, in adults who use tobacco, assistance and arrangement for individualized and group social support counseling are recommended.</td>
</tr>
</tbody>
</table>

Detecting Heart Failure: symptoms and/or signs

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Reduced exercise capacity
- Ankle swelling

- Elevated jugular venous pressure
- Positive abdominojugular reflux
- S3 gallop
- Laterally displaced apical impulse

- Cough
- Abdominal distension
- Wheeze
- Abdominal bloating
- Early satiety
- Bendopnea

- Weight gain
- Lung rales
- Peripheral edema
- Ascites
- Cool and/or mottled extremities
- Narrow pulse pressure
- Weight loss and cachexia
Detecting Heart Failure

- Diagnostic tools

**Diagnostic imaging**
- Chest x-ray
- Transthoracic echocardiogram
- Coronary angiogram
- Cardiac MRI

**Labs**
- NT-proBNP
- Complete blood count
- Basic metabolic panel
- Liver function tests
- Iron studies
- Thyroid function tests
- Hemoglobin A1c
- Lipid panel
- Electrocardiogram
- Right heart catheterization
- Endomyocardial biopsy

Disparities in Detection of Heart Failure

Critical disparities in diagnosis of HF: female sex, black race, and low net worth were associated with higher rates of diagnosis in the acute care setting.
THANK YOU!

For questions or more information: please contact your local AHA Quality Improvement Manager OR reach out via the below link:
https://www.heart.org/en/professional/quality-improvement/contact-your-local-get-with-the-guidelines-representative

Registration for tomorrow’s Lunch & Learn on Health Equity in Heart Failure can be completed by clicking here.