Heart Failure and Ischemic Heart Disease

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Outline

- Challenging focus
- Prevalence of CAD in HF
- Managing IHD in HF
CAD and HF: An Increasing Burden

- 5 million Americans have heart failure
  - ~ 550,000 new cases each year in the United States
  - ~ 300,000 attributable deaths yearly

- *Hospital discharges* ↑ 159.4% (1979–1998)
- ~ 60% of heart failure cases have prior CAD
- CAD is the only HF etiology increasing

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Heart Failure and Ischemic Heart Disease: A Challenging Population

Blood Pressure

Heart Failure

Ischemic Heart Disease

Diabetes

Troponin+ ACS STEMI

NYHA I

Congestion

NYHA IV

Age

HF & IHD

Ischemia
CAD and HF: Difficult to Disentangle

- The presence/extent of CAD is associated with the progression of *ventricular remodeling* and HF
  - neurohormonal activation via multiple mechanisms

- *Myocardial necrosis* is common and associated with worse outcomes in HF

- Acute ischemia and *diastolic dysfunction* are closely intertwined
  - ~ 50-60% of HF normal EF associated with CAD

- Ischemic events lead to *sudden cardiac death* among HF patients
CAD and HF: A Dangerous Intersection

- Acute MI
- Recurrent Ischemia
- Progressive Remodeling
- Fibrosis/ Diastolic Dysfunction

- Valvular Dysfunction
- Stunning/ Hibernation
- Neurohormonal Activation
- Endothelial Dysfunction

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Velazquez & Pfeffer. Circ 2004
Gheorghiade et al, Circ 2006
Ischemia and HF: Chicken or Egg?

- Ischemia and subsequent reperfusion lead to impaired followed by improved LV relaxation/filling/stiffness

- Subendocardial and subepicardial longitudinal myocardial fibers are particularly sensitive to ischemia with increasing LVEDP

- DD is associated with systemic endothelial dysfunction/ platelet activation/ thrombogenicity → ischemia

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Bach AHJ 1996; Nagueh JACC 1997; Lee AHJ 2005
Ischemia and HF: Chicken or Egg?

- Acute/transient reduction in regional function
- Acute/transient mitral regurgitation
- Increase filling pressures
- Increased diastolic stiffness
- Promoting myocyte hypertrophy and fibrosis in response to NE, dopamine and endothelin, Ang II release

.... HF (ischemia)
Outline

- Challenging focus
- Prevalence of CAD and HF
  - Troponin release data
  - Epidemiology
- Managing IHD in HF
Myocardial necrosis and AHF

- Acute HF is associated with elevated cardiac troponin on admission
  - Gattis et al. (RITZ 4 cTnl subgroup: n=133)
    91 (69%) with cTnl $> 1.0$ ng/ml
    cTnl $> 1.0$ ng/ml associated with HR $= 1.15^*$
  - Gheorghiade et al. (PRESERVD-HF: n=51)
    79% Tnl $> .01$ mcg/L, 44% TnT $> 0.03$ mcg/L

Gattis et al. AJC 2004; Gheorghiade et al AJC 2005;
Serial Troponin T and 1 year Outcome

- N=62 hospitalized for worsening HF
- 2 cTnT samples: cTnT1 within 4 hours of admission, cTnT2 7 days later
- Primary Endpoint: Relationship between serial cTnT and Death or Rehosp at 1 year
- cTnT measured with 3rd generation immunoassay, LLD 0.01 ng/mL

% Death or Rehosp at 1 year

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/-</td>
<td>13</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>7</td>
<td>71.4</td>
<td>0.007</td>
</tr>
<tr>
<td>-/+</td>
<td>7</td>
<td>85.7</td>
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</tr>
<tr>
<td>+/-</td>
<td>35</td>
<td>91.4</td>
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</table>
## Relationship of Troponin to Clinical Events

<table>
<thead>
<tr>
<th></th>
<th>Death or Worsening HF (n=6)</th>
<th>No Event (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline TnT</strong></td>
<td>0.12 (0.04, 0.16)</td>
<td>0.01 (0.01, 0.02)</td>
<td>0.0069</td>
</tr>
<tr>
<td><strong>Peak TnT</strong></td>
<td>0.17 (0.12, 0.69)</td>
<td>0.01 (0.01, 0.03)</td>
<td>0.0027</td>
</tr>
<tr>
<td><strong>Change TnT</strong></td>
<td>0.02 (0.01, 0.64)</td>
<td>0 (0, 0.003)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Baseline TnI</strong></td>
<td>0.15 (0.08, 0.25)</td>
<td>0.04 (0.02, 0.06)</td>
<td>0.0344</td>
</tr>
<tr>
<td><strong>Peak TnI</strong></td>
<td>0.22 (0.1, 4.26)</td>
<td>0.04 (0.03, 0.06)</td>
<td>0.0094</td>
</tr>
<tr>
<td><strong>Change TnI</strong></td>
<td>0.03 (-0.008, 4.1)</td>
<td>0 (-0.01, 0.01)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
cTnT in Ambulatory HF Patients

- N=136 stable HF
- LVEF <35%
- NYHA II-IV
- cTnT at baseline
  - 3rd generation Elecys STAT immunoassay
  - LLD 0.01 ng/ml
- F/U for survival and CV events ~ 14 months
- N=33 (24%) had elevated baseline cTnT

Cumulative Freedom from Death or HF Hospitalization

Days from Enrollment

Prevalence of Systolic and Diastolic Dysfunction in HF

% With CHF Diagnosis

Ejection Fraction

- ≤50% (n=123)
- ≤40% (n=40)

Systolic Function

Diastolic Function

Validated CHF Diagnosis

Any CHF Diagnosis

Decreasing prevalence of known CAD by DD severity

42% 35% 18%

Redfield et al. JAMA 2003
Acute HF and CAD: HFP EF vs HFr EF

- **STRONG Heart Study:** LVEF known (N=3184)
  - ~ 20% LVEF 40 – 54%; CAD 32%
  - ~ 52% LVEF > 54%; CAD 20%

- **ADHERE Registry** (N=105,388)
  - N=52187 thru Jan 2004 with known LVEF
  - 50.4% LVEF > 40%
  - Lower In Hosp Mortality – 2.8% vs 3.9%
  - Lower MI Hx - 24% vs 36%
  - Lower CAD Hx – 50% vs 59%

- **OPTIMIZE HF Registry:** LVEF known (N=41267)
  - ~ 51% LVEF > 40%; CAD 38%
  - ~ 24% LVEF > 50%; CAD 32%

Devereux et al AJC 2000; Yancy et al. JACC 2006; Fonorow et al JACC 2007;
Silent (?) CAD in DHF

- Arques et al. (n=18) – 39% prevalence of angiographic CAD (22% severe) in DHF patients presenting without overt ischemia
- East et al. (n=3303) – 30% had obstructive CAD (75%) in 1 or more arteries
  - Differing by race, less in AAs (39% v 57%)
Unstable angina after AHF: Unrecognized IHD?

![Graph showing hospitalization due to unstable angina pectoris over time for different LVEF categories.](image)

- **LVEF > 55%**
- **LVEF ≤ 35%**
- **LVEF 35-55%**

Log rank test $p = 0.001$
ACS and HF: Deadly Intersection
VALIANT Registry In-Hospital Clinical Events

- Death: 2.3% (HF/LVSD) vs. 2.5% (No HF/LVSD)
- Reinfarction: 1.4% (HF/LVSD) vs. 2.2% (No HF/LVSD)
- AF: 16.3% (HF/LVSD) vs. 7.1% (No HF/LVSD)
- Stroke: 0.9% (HF/LVSD) vs. 2.2% (No HF/LVSD)
- LOS: 8% (HF/LVSD) vs. 6% (No HF/LVSD)

Velazquez et al. Eur Heart J 2004
New HF Among Stable MI Survivors

Figure 3

Proportion of patients with HF

Time from randomization (Days)

0 <= Age <= 40
40 < Age <= 50
50 < Age <= 60
60 < Age <= 70
70 < Age <= 80
Age > 80

Lewis et al EHJ 2008
Acute Coronary Findings Common in HF SCD

![Bar graph showing acute coronary findings (%)

- CAD + SD
- CAD + HF
- CAD - HF
- CAD - SD

P = 0.0001

## DHF - Mode of Death

### I-Preserve

<table>
<thead>
<tr>
<th>Mode</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Cardiac Death</td>
<td>26</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>14</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
</tr>
<tr>
<td>Other CV Cause</td>
<td>7</td>
</tr>
<tr>
<td>Non-CV Cause</td>
<td>30</td>
</tr>
</tbody>
</table>
Outline

- Challenging focus
- Prevalence of CAD in HF
- Managing IHD in HF
  - STICH
# Acute HF or ACS with HF

## Table 1

<p>| Characteristics of Patients With AHFS and CAD Versus Patients With ACS Complicated by HF |</p>
<table>
<thead>
<tr>
<th>AHFS and CAD</th>
<th>ACS Complicated by HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Common</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Prior HF</td>
<td>Common</td>
</tr>
<tr>
<td>BNP/N-terminal proBNP</td>
<td>Elevated</td>
</tr>
<tr>
<td>Troponin</td>
<td>Normal or elevated*</td>
</tr>
<tr>
<td>Left ventricular systolic function</td>
<td>Normal or depressed</td>
</tr>
<tr>
<td>Diagnostic testing for CAD† (ischemia/viability/angiography)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>Uncommon†</td>
</tr>
<tr>
<td>Secondary prevention for CAD</td>
<td>Underused</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>Relatively low</td>
</tr>
<tr>
<td>Early after-discharge death or rehospitalization</td>
<td>High</td>
</tr>
</tbody>
</table>

*Denotes infants to young adults.
†Diagnostic testing for CAD is often not performed in young adults due to the nonspecific nature of the test and the low likelihood of CAD.

Flaherty et al. JACC 2009
Presence, Extent, and Severity of CAD by CCTA Tightly Linked to Survival

Survival Probability

Survival Time (Years)

- Normal
- Non-Obstructive  $p<0.0001$
- 1-Vessel CAD  $p<0.0001$
- 2-Vessel CAD  $p<0.0001$
- 3-Vessel CAD  $p<0.0001$

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Min JK et al. JACC. 2011
CAD Extent Predicts Survival in LVSD Patients

- 0 - 1 vessels (N = 990)
- 2 vessels (N = 315)
- 3 vessels (N = 616)

Felker GM et al. J Am Coll Cardiol. 2002
Surgical Treatment for Ischemic Heart Failure Trial (STICH)

Surgical Revascularization Hypothesis

In patients with HF, LVD and CAD amenable to surgical revascularization, CABG added to intensive MED will decrease all-cause mortality compared to MED alone.

Velazquez EJ et al. JTCVS 2007
Important Inclusion Criteria

- LVEF ≤ 0.35 within 3 months of trial entry
- CAD suitable for CABG
- MED eligible
  - Absence of left main CAD as defined by an intraluminal stenosis of ≥ 50%
  - Absence of CCS III angina or greater (angina markedly limiting ordinary activity)

Velazquez EJ et al. JTCVS 2007
STICH Revascularization Hypothesis

- 99 clinical sites in 22 countries
- Enrollment: July 2002 – May 2007
- 99.6% Follow-up at Last Visit
- Overall duration of follow-up: 56 months

Velazquez EJ et al. NEJM 2011
## Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MED (N=602)</th>
<th>CABG (N=610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), yrs</td>
<td>59 (53, 67)</td>
<td>60 (54, 68)</td>
</tr>
<tr>
<td>Female, %</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Prior Myocardial infarction, %</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>Prior Heart Failure within 3 months, %</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>Prior PCI or CABG, %</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>LVEF (%) — median</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Multi-vessel disease (&gt;50%), %</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>Proximal LAD stenosis (&gt;75%), %</td>
<td>69</td>
<td>67</td>
</tr>
</tbody>
</table>
# Medical Therapy

<table>
<thead>
<tr>
<th>Medication, %</th>
<th>MED (N=602)</th>
<th></th>
<th>CABG (N=610)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Latest Follow-up</td>
<td>Baseline</td>
<td>Latest Follow-up</td>
</tr>
<tr>
<td>Aspirin</td>
<td>85</td>
<td>84</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Aspirin or warfarin</td>
<td>91</td>
<td>93</td>
<td>84</td>
<td>92</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>88</td>
<td>89</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>88</td>
<td>90</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>Statin</td>
<td>83</td>
<td>87</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>K+ sparing diuretic</td>
<td>46</td>
<td>53</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>ICD</td>
<td>2</td>
<td>19</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>
All-Cause Mortality — As Randomized

HR 0.86 (0.72, 1.04)
P = 0.123
Adjusted HR 0.82 (0.68, 0.99)
Adjusted P = 0.039
Secondary Endpoints – As Randomized

**Cardiovascular Mortality – As Randomized**

- **HR:** 0.81 (0.66, 1.00)
- **P:** 0.050
- **Adjusted HR:** 0.77 (0.62, 0.94)
- **Adjusted P:** 0.012

**Death or Cardiovascular Hospitalization – As Randomized**

- **HR:** 0.74 (0.64, 0.85)
- **P:** < 0.001
- **Adjusted HR:** 0.70 (0.61, 0.81)
- **Adjusted P:** < 0.001

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Velazquez EJ et al. NEJM 2011
STICH Revascularization Hypothesis
Treatment As Received

At 1 year*

Randomized MED only

602

11%

537

Received MED only

55

65

Received CABG

610

9%

555

Randomized CABG

As treated MED (592) vs. CABG (620)

*(Overall 17% vs. 9%)

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All-Cause Mortality
— As Treated within Year 1

HR 0.70 (0.58 – 0.84)
P < 0.001

Velazquez EJ et al. NEJM 2011
What do we know about CABG in HF?

- Modest effect when added to contemporary medical management
- Cautious optimism from STICH
- Longer-term follow-up pending
What do we know about PCI in HF/LVSD?

- No RCTS of PCI in chronic HF or LVSD
- Very few patients with HF or LVSD in CABG vs PCI RCTs
  - SYNTAX included ~5% with HF and ~2% with an LVEF < 30%
  - FREEDOM included 2.6% with LVEF < 40%
- Very few patients with HF or LVSD in RCTs of PCI vs. MED
  - COURAGE excluded patients with LVEF < 30%
## CABG compared to PCI with Stenting – 3 VD

<table>
<thead>
<tr>
<th>Disease of nonproximal LAD artery</th>
<th>All patients</th>
<th>Patients with EF &lt; 40%</th>
<th>Patients with EF ≥ 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting group</td>
<td>2166</td>
<td>342</td>
<td>1824</td>
</tr>
<tr>
<td>CABG group</td>
<td>4946</td>
<td>1196</td>
<td>3750</td>
</tr>
<tr>
<td>Unadj. hazard ratio (95% CI)</td>
<td>0.89 (0.74-1.06)</td>
<td>0.61 (0.46-0.81)</td>
<td>0.94 (0.75-1.17)</td>
</tr>
<tr>
<td>Adj. hazard ratio (95% CI)</td>
<td>0.74 (0.62-0.90)</td>
<td>0.64 (0.48-0.87)</td>
<td>0.76 (0.60-0.96)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease of proximal LAD artery</th>
<th>All patients</th>
<th>Patients with EF &lt; 40%</th>
<th>Patients with EF ≥ 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting group</td>
<td>2165</td>
<td>399</td>
<td>1766</td>
</tr>
<tr>
<td>CABG group</td>
<td>20857</td>
<td>5597</td>
<td>15260</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>0.67 (0.59-0.77)</td>
<td>0.55 (0.44-0.69)</td>
<td>0.64 (0.50-0.72)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.64 (0.56-0.74)</td>
<td>0.68 (0.54-0.85)</td>
<td>0.60 (0.50-0.72)</td>
</tr>
</tbody>
</table>

• Does inducible ischemia modify the relationship between CAD severity, treatment and outcomes in HF?

• Should inducible ischemia guide revascularization decision-making in HF?
Residual Ischemia Associated with Death or MI: COURAGE MPS Substudy

![Graph showing the relationship between residual ischemia and death or MI rate.]

- 0% (n=23)
- 1%-4.9% (n=141)
- 5%-9.9% (n=88)
- ≥10% (n=62)

Death or MI Rate (%)

- 0% (n=23)
- 1%-4.9% (n=141) p=0.023
- 5%-9.9% (n=88) p=0.063
- ≥10% (n=62) p=0.002

Shaw L et al. Circulation 2008
STICH Ischemia Substudy

1212

RN n=219

DE n=205

194

25

180

813

Patients with no usable myocardial ischemia test

399

33% of STICH H1 patients

With Ischemia (64%)

256

Without Ischemia (36%)

143

Patients included in the STICH ischemia study

Panza et al. AHA 2012
All-Cause Mortality With and Without Ischemia

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia : No Ischemia</td>
<td>1.08</td>
<td>0.77, 1.50</td>
<td>0.657</td>
</tr>
</tbody>
</table>

Patients at Risk:
- No Ischemia: 143
- Ischemia: 256

Years Following Randomization

Panza et al. JACC 2013

STICH
Interaction Between Ischemia and Treatment All-Cause Mortality

Top panel: Two line graphs showing mortality rates over years following randomization, with different line colors and styles for MED and CABG groups, differentiated by ischemia status.

Bottom panel: Table showing subgroup analysis with hazard ratios and 95% confidence intervals, and 5-year event rates for MED and CABG groups.

Interaction with Treatment P-value = 0.643

Panza et al. JACC 2013
ACC/AHA 2005 HF Guidelines – CAD

Class I
- Coronary arteriography for HF pts with angina or significant ischemia (C)

Class IIA
- Coronary arteriography reasonable for HF pts with known or suspected CAD without angina (C)
- Non-invasive imaging reasonable to detect myocardial ischemia and viability in HF patients with known CAD and no angina (C)

Class IIB
- Non-invasive imaging reasonable to detect myocardial ischemia and viability in HF patients with known CAD and no angina (C)
## 2011 ACC/AHA Guidelines

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Revascularization Method</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>LVEF 35 - 50 %</td>
<td>CABG</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>LVEF &lt; 35%</td>
<td>PCI</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Insufficient data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insufficient data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Levine G et al. J Am Coll Cardiol 2011*

*Hillis D et al. J Am Coll Cardiol 2011*
Management of Ischemia in HF in 2013

- Medical therapy should always be optimized
- Among low EF HF patients with CAD, CABG leads to a modest improvement relative to MED
- ...data for PCI relative to MED limited, CABG more effective than PCI?
- Ischemia, viability testing in HF should not determine who should or should not receive revascularization
- Iterative, team-based, patient-centered decision making critical
  - Future trials need to focus on PCI, decision support
Final words...

- Troponin release data, rates of UA and angiographic studies to date suggest underdiagnosis of IHD in HF
- HF complicating MI is common and deadly
- MI precedes HF in many; link to SCD?
- STICH data suggests that revascularization should be considered regardless of ischemia (or viability) for low EF patients
- Since current evidence to guide treatment for DHF is slim … unlike CAD… for the foreseeable future a critical means to improve patient outcomes for DHF will be to seek out and treat CAD