CONFLICTS OF INTEREST

Research companies  Government / University research
Both have type 2 diabetes
Both have hypertension
Both have normal ejection fractions

Diabetic Heart Disease: A Ticking Time Bomb!
Translational Considerations in Heart Failure Treatment

Preserved EF with heart failure (HF pEF)
≈50% 5 year survival
Introduction
Translational considerations in vascular risk factors
“No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.”

ESC Guidelines 2016

Symptom relief-diuretics
Possible mortality morbidity reduction and symptom relief-- SGLT2 inhibitors

Translational considerations in heart failure: normal ejection fraction
Concluding comments
Type 2 diabetes and inflammation

Immune system are altered in obesity and type 2 diabetes

Most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the cardiovascular system and circulating leukocytes

Altered levels of specific cytokines and chemokines

HEART RELATIONSHIPS WITH LUNG VASCULATURE

Right ventricle
Septum
LV
In 2015 it affected about 40 million people globally.

In the year after diagnosis the risk of death is about 35% after which it decreases to below 10% each year.
Heart failure syndrome: symptoms and signs
Brain natriuretic peptide (BNP) >100 pg/ml or N-terminal pro-BNP >360 pg/ml
Completed trials: historical perspective of diabetes related heart failure
HEART FAILURE PREVALENCE IN SELECTED T2DM TRIALS

Average percent of patients with heart failure in T2DM trials

- **Glucose lowering trials**
  - UKPDS 33: NR
  - ADVANCE: NR
  - ACCORD: 4.3%
  - VADT: NR

- **DPP4 inhibitors**
  - SAVOR: 13%
  - TECOS: 18%
  - EXAMINE: 28%

- **SGLT2 inhibitors**
  - EMP-Reg: 10%
  - CANVAS: 14%

- **GLP-1 agonist**
  - LEADER: 14%
  - ELIXA: 22%
  - EXSCEL: 16%

Chilton-pending publication
**T2DM Prevalence in Selected Heart Failure Trials**

- **Acute HF**
  - RELAX-AHF (2) - 47%
  - ASCEND-HF - 42.6%
  - TRUE-AHF - 39%
  - EVEREST - 39%

- **HF pEF**
  - I-Preserve - 27%
  - PEP-CHF - 21%
  - DIG-PEF - 29%
  - CHARM-Preserved - 28%
  - TOPCAT - 33%

- **HF rEF**
  - PARADIGM-HF - 35%
  - SHIFT - 30%
  - EchoCRT - 41%
  - HF-ACTION - 32%
  - SENIORS - 26%
  - MERIT-HF - 25%
  - CHARM-Added - 29%
  - DIG-REF - 28%

*Chilton-pending publication*
**TREATMENT OPTIONS (HFpEF) (NORMAL EJECTION FRACTION) SYMPTOMATIC**

- **Diuretics**
- **SGLT2 inhibitor**

Lower filling pressure to LV (reduce pulmonary edema)

Reduce BNP

**No treatment** has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF

ESC HF 2016 guideline

**Global risk reduction**

- **Matrix matters**
- **Rhythm**
  - Heart rate
  - Wall stress
- **Metabolics**

Reduce MVO2
Reduce demand

**Quality of life**

- Both?
- CV death / events
Acute treatment options for diabetes patients with heart failure and normal EF
Pulmonary Edema

High filling pressures

Normal (reduced) filling pressures

↑↑ Left atrium pressure
Increased PCW
Post capillary-LV dysfunction

Modified Mayo
Clinical outcome trials for preserved EF with heart failure overview

CHARM-Preserved
- Placebo: 366 (24.3%)
- Candesartan: 333 (22.0%)
- HR 0.89 (95% CI 0.77-1.03), P=0.118
  Adjusted HR 0.86, P=0.051

PEP-CHF
- Treatment Groups
  - Perindopril
  - Placebo
- HR 0.92; 95% CI 0.70 to 1.21; P=0.545

I-PRESERVE
- Placebo
- Irbesartan
- N=4,128
- (Mean follow-up 49.5 months)

TOPCAT
- Placebo
- Spironolactone
- HR = 0.89 (0.77 – 1.04)
  p=0.138

Graphs showing cumulative incidence of primary events over time for various treatments in clinical outcome trials.
In this randomized, double-blind trial, we assigned 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

With a mean follow-up of 3.3 years, the primary outcome occurred in 320 of 1722 patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.77 to 1.04; P=0.14). Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs. 245 patients [14.2%]; hazard ratio, 0.83; 95% CI, 0.69 to 0.99, P=0.04). Neither total deaths nor hospitalizations...
<table>
<thead>
<tr>
<th>Outcome</th>
<th>P-value for interaction term</th>
<th>Enrolled on basis of hospitalization in the past year for which management of heart failure was a major component (N=2464)</th>
<th>Enrolled on basis of natriuretic peptide entry criteria (N=981)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number and % of Participants with Event, and Incidence Rate per 100 person-years</td>
<td>Number and % of Participants with Event, and Incidence Rate per 100 person-years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unadjusted Model (HR(1 vs. 2), 95% CI, p-value)</td>
<td>Unadjusted Model (HR(1 vs. 2), 95% CI, p-value)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.01</td>
<td>242 (19.6%)</td>
<td>78 (15.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0 per 100 person-years</td>
<td>5.5 per 100 person-years</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>235 (19.1%)</td>
<td>116 (23.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0 per 100 person-years</td>
<td>8.5 per 100 person-years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.01 (0.84-1.21)</td>
<td>0.923</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.923 (0.49-0.87)</td>
<td>0.65 (0.49-0.87)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>N = 490</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>N = 491</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Type 2 diabetes: EMPA reg

This was not the primary endpoint.
# All Cause Mortality in Heart Failure Trials: Focus on Type 2 Diabetes

<table>
<thead>
<tr>
<th>HFrEF</th>
<th>Drug</th>
<th>Significant increase adjusted all cause mortality in T2DM</th>
<th>Significant increase in adjusted CV mortality in T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARADIGM-HF</td>
<td>Sacubitril/valsartan</td>
<td>1.4 Hazard ratio</td>
<td>1.54 HR</td>
</tr>
<tr>
<td>Echo-CRT</td>
<td>CRT</td>
<td>2.08 HR</td>
<td>1.79</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Enalapril</td>
<td>1.29 HR</td>
<td>NA</td>
</tr>
</tbody>
</table>

Chilton-pending publication
Canadian study of Ivedip
Translational biology
Structural heart changes

Myocardium

Endocardium
High glucose induced myocardial fibrosis
Diabetes

LVH

Increased matrix

STZ-treated rats
High glucose
Green Massons stain
Collagenous matrix deposition

Control Animal

Circ Res 49:1268–1277
Heart Fail Rev (2014) 19:15–23
Symptoms improve and less pulmonary congestion / SOB

Diuretics ≈ SGLT2 inhibitors
DIASTOLIC DYSFUNCTION: VERY STIFF, NON COMPLIANT LEFT VENTRICLE

LARGER LEFT ATRIAL SIZE HFP EF

End-Diastolic Pressure, mmHg

Indexed End-Diastolic Volume, ml/m²

CON

EDVI_{20} = 61.7 ml/m²

HTN *

EDVI_{20} = 59.7 ml/m²

HFnIEF *

EDVI_{20} = 55.7 ml/m²

LVEDP≈ PCW

BNP

Olmsted County (Minn) residents without cardiovascular disease (n=617)

HEMODYNAMICS CHANGES: ECHOCARDIOGRAM

HUMANS WITH LEFT VENTRICULAR HYPERTROPHY

CASE 1

38 y/o obese woman
SOB / Atypical chest pain
BMI-48
Type 2 DM-metformin
HT

300 NS over 15 minutes-developed SOB
Molecular considerations

Heart fuel sources
- Glucose
- FFA
- Ketones (liver produces)

Human heart horsepower ≈ 0.75 to 1
CHRONIC ELEVATED GLUCOSE

- Oxidative stress
- Reduced ATPs
- Swollen ballooned mitochondria
- Reduced numbers
- Dysfunctional myofibrils

MRI

Normal EF

Severe systolic dysfunction

2-5 watts of mechanical power
Beats about 40 million times a year

Diabetes
Diabetes caused mitochondrial swelling and crista fragmentation (yellow arrow).

Diabetes led to myocyte dissolution, muscular fiber twists and Z line disappearance, the effects of which were reversed by empagliflozin.

Redox Biology 15 (2018) 335–346
POTENTIAL BENEFICIAL EFFECTS OF SGLT2 INHIBITORS

SGLT 2 inhibition / increased excretion of glucose / H2O / Na

Calorie restriction

↑ glucagon: insulin ratio

Reduced glucogenolysis

Increased lipolysis / FFA

Liver

Increase in β-hydroxybutyrate (ketones)

Am J Cardiol. 1997 Aug 4;80(3A):50A-64A

Chilton-pending publication
Left atrium

Left ventricle

Pulmonary artery

Right ventricle

Capillaries

Post capillary

Oxygen saturation=100%

Lungs

Left atrium

Left ventricle
Left atrium (6-10 mm Hg)

Left ventricle (LVEDP 6-10)

Post capillary

Capillaries

Pulmonary artery

Right ventricle

Oxygen saturation=100%

Lungs

Pressures:
- PA Systolic 8-20 mm Hg at rest
- Exercise <30 mmHg

Pre capillary

Matrix matters
Ischemia-reduced LV function

Many diabetes patients have both

RV hypertrophy compensates

RV hypertrophy decompensates

↑↑↑ Pulmonary artery

↑↑ Left atrium (Increased risk for Afib)

Left ventricle dysfunction

PRESSURE increases-fluids alveoli

↑↑↑ Pulmonary artery

Left atrium

PRESSURE increases-fluids alveoli

↑↑ Left atrium (increased risk for Afib)

Lungs

Post capillary

Capillaries

Pulmonary artery

Right ventricle

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Lungs

Post capillary

Capillaries

Pulmonary artery

Right ventricle

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Ischemia-reduced LV function

Many diabetes patients have both
HEART FAILURE WITH NORMAL EJECTION FRACTION (HFpEF) : ANNUAL MORTALITY

% Yearly mortality

Real world studies overestimate True annual mortality

Epidemiology
Mayo
N= 6076
15 years

RCT
PEP-HF
N=852

NEJM 355:251
EHJ 27:2338
Lancet 362:777

0 10 20 30

0 30 60

Yearly
HEART FAILURE WITH NORMAL EF: MORTALITY RATE

In hospital: 3%
1 month: 5.3%
3 months: 9.5%
6 months: 15%
5 years: 50%

Percent mortality

NEJM 355:251
J. Cardiac Failure 9:107
Modes of death in heart failure

60-70% die of CV etiologies

- Sudden death (40-45%)
- Heart failure 25-30%
- Stroke 10-15%
- MI 6-8%
- Other

Eur Heart J. 2017 Mar 7;38(10):742-750
## Treatments for Heart Failure with Normal Ejection Fraction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PAH</th>
<th>HFpEF</th>
<th>Treatment Effects in HFpEF</th>
<th>Under Study</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI</td>
<td>?</td>
<td>+/-</td>
<td>No reduction in TR velocity(^{158})</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>+</td>
<td>+/-</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>+/-</td>
<td>+/-</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Apelin</td>
<td>+</td>
<td>?</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>+</td>
<td>+</td>
<td>Improved pulmonary vascular function(^{157})</td>
<td>NCT02885636</td>
<td>PA vasodilatation</td>
</tr>
<tr>
<td>IASD</td>
<td>?</td>
<td>?</td>
<td>LA pressure, TAP pressure/volume</td>
<td>NCT01913613</td>
<td>Reduction in LA pressures</td>
</tr>
<tr>
<td>PA denervation</td>
<td>?</td>
<td>?</td>
<td>None</td>
<td>NCT02220335</td>
<td>Destruction of pulmonary baroreceptors and sympathetic nervous fibres</td>
</tr>
<tr>
<td>Wireless PAP monitoring</td>
<td>?</td>
<td>+</td>
<td>UHF hospitalizations (^{171,172}), Class IIb-B recommendation in HF to reduce the risk of recurrent HF hospitalization(^{44})</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Aerobic exercise training</td>
<td>++</td>
<td>++</td>
<td>Class Ia recommendation to improve functional capacity and symptoms in HF(^{34})</td>
<td>NCT02435667, NCT02636429</td>
<td>Aerobic training improves exercise capacity and symptoms</td>
</tr>
</tbody>
</table>

Diuretics SGLT2 inhibitor?
Inflammatory cytokines (e.g. IL6, TNF-α)

Non-cardiac comorbidities
- Hypertension
- Obesity
- Diabetes mellitus
- COPD

Endothelium
- ↑RDS
- ↓NO
- TGF-β
  - Fibrosis

LV cardiomyocytes
- ↓sGC
- ↓cGMP
- ↓PKG
- Growth and remodelling
- Oxidative stress
  - Concentric remodelling and stiffening
- ↑PCWP
- Chronic pulmonary congestion
- Muscularization of pulmonary venules
- Haemangiomatosis-like endothelial cell proliferation in pulmonary capillaries
- Pulmonary arterial remodelling

Pulmonary vasculature
- ↑MPAP
- ↑PVR
- Neurohormonal activation
- Cytokine release (IL1, IL6, TNF-α)
- Mechanical-stretch signalling

RV cardiomyocytes
- ↓sGC
- ↓cGMP
- ↓PKG
- Growth and remodelling
- Oxidative stress
- Apoptosis
- Necrosis
  - Eccentric remodelling, dilatation and failure
HF WITH NORMAL EJECTION FRACTION (HFpEF)

Endothelium / glycocalyx

- ↑ ROS & ↓ NO

Growth / remodeling
- Oxidative stress
- TGF-b

Cardiomyocyte

- ↓↓ sGC
- ↓↓ cGMP
- ↓↓ PKG

Increase in PCW / LVEDP

Non cardiac comorbidities
- Diabetes / obesity
- Hypertension
- COPD

Concentric remodeling
- Reduced LV compliance

SOB / pulmonary congestion

Non cardiac comorbidities

- Concentric remodeling
- Reduced LV compliance

Increased risk for Afib

Left atrium dysfunction

Left ventricle dysfunction

Matrix matters
- Ischemia-reduced LV function

Many diabetes patients have both
HF WITH NORMAL EJECTION FRACTION (HFrEF)

Chronic pulmonary congestion

Muscularization of pulmonary vessels
- ↑ SMC
- ↑ EC
- ↑ Matrix
- ↓ PPARγ
- ↓ Adiponectin

Proliferation of pulmonary capillaries

Remodeling of pulmonary artery

Oxygen saturation = 100%

Pulmonary Pharmacology & Therapeutics 26 (2013) 420e426
Circulation 2007:115:1275e84

INCREASED Left ventricle end diastolic pressure
HF WITH NORMAL EJECTION FRACTION (HFrEF)

Normal RVEF is 62% & 65% LV Pulm HT RVEF ≈ 34%

INCREASED Right ventricle dysfunction

Right ventricle view

Pre capillary

↑ Pulmonary artery

Capillaries

Post capillary

Oxygen saturation=100%

INCREASED Left ventricle end diastolic pressure

RV fails

Hypertrophy (compensate)

Circ Res. 2014;115:176-188
HF WITH NORMAL EJECTION FRACTION (HFP EF)

Septum becomes flattened and less convex to the RV at end-diastole

- Oxygen saturation=100%
- Normal left ventricle end diastolic pressure
- Normal post capillary pressure
- Pre capillary pressure

- Pulmonary artery ↑
- ↑ thickness of wall
- ↑ resistance (afterload)

Normally the LV pressure exceeds RV pressure during diastole. Here you see RV pressure higher flattening the septum
Obesity and HFpEF

- **Obese HFpEF** (BMI ≥ 35 kg/m², n=99)
- **Non-obese HFpEF** (BMI < 30 kg/m², n=96)
- **Non-obese controls free of HF** (n=71)

Pulmonary capillary wedge pressure was correlated with body mass and plasma volume in obese HFpEF.

- ↑↑ Heart volume
- ↑↑ PCW
- ↑↑ pericardial restraint
- ↑↑ R & L ventricular pressures
- ↓ exercise capacity (VO2 max)

![Graph showing plasma volume and epicardial fat volume comparisons between obese HF, non-obese HF, and controls.](image)

Circulation. 2017 July 04; 136(1): 6–19
Right ventricular failure has very high mortality

Beta-Blocker Evaluation of Survival Trial (BEST)
N=2008
Systolic dysfunction patients

Int J Cardiol. 2012 February 23; 155(1): 120–125