ATHEROSCLEROSIS: FUTURE CLINICAL CHALLENGES

1 trillion strong.. (Hum Pathol. 1987;18(3):234)(0.2 pounds)

Nitr¢ oxide

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ACC/AHA 2017 pending
INTRODUCTION

• **WE NEED BETTER TREATMENTS FOR CARDIOMETABOLIC DISEASE**
  Prevention: good place to start

Time
Environmental risk factors
Picked wrong genome

Reduce wall stress (BP)
Reduce plaque erosion

Young
Highest technologies available we still have unacceptable recurrent acute coronary events after treatment with secondary prevention.....10-20% in first 12 months.

Eur Heart J. 2015;36:1163–1170
Hematologic importance in plaque rupture

Macrophages

Angiotensin II

Plaque cap

MMP / PAR 1

Cholesterol / fibroatheroma

Translational biology of atherosclerosis

Nature medicine 2013;19:1094
Austin et al Blood 2013;121:431
Mass Spectrometer

Measures the masses within a sample

Ionizes chemical species and sorts the ions based on their mass to charge ratio

matrix-assisted laser desorption/ionization (MALDI)
TRANSLATIONAL BIOLOGY: HUMAN CORONARY THROMBOSIS

**RAP1β** converts integrin's

**Integrin IIb**

**TSP1** matrix protein

**β Parvin**

**DiDO 1** Pro-apoptosis transcriptional factor expressed in platelets / RBC

**Redox state/apoptosis protein**

- **↑ Platelets activation/formation**
  - CD41 platelet marker

- **↑ Integrin IIb**

- **↑ TSP1** matrix protein

- **Multimerin 1**, also known as *elastin microfibril interfacer 4* (EMILIN-4), is a protein that in humans is encoded by the **MMRN1** gene

- **MMRRI1**-associated with WBC recruitment and eosinophils

- **β Parvin**

- **DiDO 1** Pro-apoptosis transcriptional factor expressed in platelets / RBC

- **Redox state/apoptosis protein**
LIFE EXPECTANCY DECREASED 0.2 YEARS IN US

Diabetes adjusted death rates same period:
- 2014: 20.9 deaths per 100,000 standard population
- 2015: 21.3 deaths per 100,000 standard population

P < 0.05

... increased diabetes deaths

NCHS, National Vital Statistics System, Mortality 2017
GOOD NEWS: REDUCTION IN CV EVENTS IN DIABETES... BAD NEWS ITS STILL VERY HIGH

- **Swedish National Diabetes Register 1998-2014**
- **Matched controls**
- **Type 2 diabetes N=457,473**
- **Reduction in death, CAD, heart failure**
- **Missed opportunity**
  - **Only 37% on statins**

**Baseline characteristics**

- **Controls N=2,287,365**
- **Type 2 DM N=457,473**

**Death from Any Cause**

OVERVIEW

• Clinical Vascular Biology of Atherosclerosis
• 9 Risk factors accounting for 90% of first MI
• A Decade of Clinical CV Event Research
• Global Risk Reduction
• Inside look @ Human Atherosclerosis with Atorvastatin
OUR BEST TREATMENT FOR CAD: LIMA LIFE SAVING

Yearly mortality

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<td>8.2</td>
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J Am Coll Cardiol. 1996;27:964–1047
**PRIMARY OUTCOME – DEATH / STROKE / MI**

Diabetes

- **PCI/DES**: 26.6%
- **CABG with LIMA**: 18.7%

5-Year Event Rates

- **Logrank P=0.005**
- **FREEDOM trial**

Prevention is a better choice

We need better treatments

Our "life saving surgery?" not good enough

ACS-N=697
PCI

Diabetes-N=1900

0.8 ARR/year

1.2 ARR/year

% CV event rates per year

Per year

LookAHEAD

ACS-PROSPECT

CABG-Lima...

CARDS-Plac

CARDS-Statin

EMP-Reg-Cit

EMP-Reg-Tx

Primary Prevention

Treatment of ischemic heart disease: reduce myocardial oxygen consumption

Law of Laplace

Wall tension - $P \times \frac{R}{W}$

Transmural pressure

Wall thickness ($W$)

Radius ($R$)

↓↓ blood pressure

↓↓ preload/afterload (Heart size)

47 y/o Hispanic
Women
3 children
ONLY short of breath
No chest pain
INTRODUCTION HIGHLIGHTS

- **Primary prevention is best choice**

- **Global risk reduction**
  - **Target:** BP reduction 130 systolic
  - **Target:** LDL <55 mg/dL in high risk patients

Identifying patients at risk for acute myocardial infarction
LIPIDS ARE STILL # 1 AND SMOKING # 2

- **Abnormal Lipids**
- **Smoking**
- **Hypertension**
- **Diabetes**
- **Abdominal Obesity**
- **Psychosocial**
- **Physical Activity**
- **Alcohol**
- **Fruits/Vegetables**

9 Modifiable Factors Account for 90% of First MI

PAR = population attributable risk, adjusted for all risk factors

INTERHEART Trial
INTERHEART trial: 9 modifiable risk factors account for 90% of myocardial infarctions

- Smoking
- Diabetes
- HT
- ApoB/apoA1
- All 4 & obesity

Odds ratio (99% CI)
All significant

Adapted from Lancet 2004; 364: 937–52
PATIENTS PRESENTING TO CATH LAB WITH ANGINA

Heart failure
Heart failure

- Normal ejection fraction
- Low ejection fraction

......not your friend

60 y/o male
No diabetes

Framingham 40 year follow-up, N=5070
Diastolic heart failure-young diabetes patient

Ejection fraction-55%
>80% OF PATIENTS IN RECENT LARGE DIABETES TRIALS HAVE HYPERTENSION
PATIENTS WITH HEART FAILURE

- Diabetes
- Cardiometabolic
- Ischemic heart disease
- Left ventricular hypertrophy
- Hypertension
- Diastolic dysfunction
- Ischemic (endstage)
- Cardiomyopathy (endstage)
Impact of diabetes on death in patients with heart failure

**Acute heart failure**
DIAMOND study - **YES** - HR 1.5 (1.3-1.6)
EPHESUS - NO – HR 1.12 (0.93-1.37)

**Diabetes** was a independent risk factor for **CV death** in patients with heart failure

**Chronic heart failure**

**EF (26-39%)**
COMET – **YES** - HR 1.20 (1.05-1.34)
CHARM – **YES** - HR 1.69 (1.43-1.97)
CORONA – **YES** - HR 1.31 (1.13-1.51)
SENIORS – **YES** - HR 1.36 (1.15-1.6)
EVEREST – **YES** - HR 1.16 (1.0-1.34)

**EF (59%)**
I-PRESERVE - **YES** - HR 1.48 (1.29-1.6)

Only randomized controlled trials

Chilton pending 2017
REDUCED RISK FOR HOSPITALIZATION FOR **HEART FAILURE: EMPA REG OUTCOME**

van de Borne P et al. ESC-HF 2016. Poster P2231

*Splits in 1 month*

**Hospitalization for Heart Failure**

- Hazard ratio, 0.79 (95% CI, 0.71–0.89)
- P<0.001

**No. of patients**
- Empagliflozin
  - 4687, 4614, 4523, 4427, 3988, 2950
- Placebo
  - 2333, 2271, 2226, 2173, 1932, 1424

**Days since Randomization**

- 0, 180, 360, 540, 720, 900, 1080, 1260
- Enalapril
- LCZ696


PARADIGM-HF
ONLY for RESEARCH CONSIDERATIONS
RESEARCH only….not proven
……not for human use………..
New emerging research DPP 4 inhibitors...NOT FOR HUMANS
Increasing prevalence of **calcific aortic disease** with increase ATP III metabolic syndrome (MetS) risk factors

<table>
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<th>MetS Risk Factors</th>
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<tr>
<td>Four</td>
<td>20</td>
</tr>
<tr>
<td>Five</td>
<td>25</td>
</tr>
</tbody>
</table>

**Females**
- 0: 3
- 1: 7
- 2: 11
- 3: 12
- 4: 15
- 5: 17

**Males**
- 0: 9
- 1: 15
- 2: 17
- 3: 22
- 4: 23
- 5: 30

MESA (Multiethnic Study of Atherosclerosis) study

Adapted from Katz et al
REDUCTION OF AORTIC STENOSIS WITH DPP-4 INHIBITION: RABBITS @ 12 WEEKS

Choi et al 10.1161/CIRCULATIONAHA.116.024270
Inhibiting DPP-4 prevents VIC osteogenic differentiation allows IGF-1 to bind to the IGFR and promote IGFR signaling.

DPP-4 cleaves IGF-1, inducing VIC osteogenic differentiation via the inhibition of IGF-1-IGFR signaling.

VIC = Valvular interstitial cell

Choi et al. 10.1161/CIRCULATIONAHA.116.024270
Closing comments
VENTRICULAR-ARTERIAL COUPLING RELATIONSHIPS

Pressure (mmHg)

Diastolic dysfunction

120

Diastole 0.15 sec

Relaxation

Systole

Cellular

0.25 second

0.05 second Power development

0.55 sec

Volume (cc)

50

125

Metabolics of Diabetes

Ketones “Super fuels”? Hyperglycemia Metabolic inflexibility

Chilton May 2017
Answers to long life are in here
Pulse

Thank you