Early-Stage Investigator Lecture

# Type 2 Diabetes and Cardiovascular Disease: A Focus on Heart Failure

Presented by:

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**NIH** National Institutes of Health
*Office of Disease Prevention*

# Disclosure

My work is supported by the National Institute of Health

# Outline

- Burden of diabetes-related heart failure

- Extent of the risk of heart failure associated with diabetes

- Diabetes-specific drivers of progression of cardiac dysfunction

- Biomarkers of diabetes-related heart failure

- Strategies to prevent and manage heart failure in diabetes

# Underappreciated Complication of Diabetes

## Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association

Rodica Pop-Busui,[1] James L. Januzzi,[2]
Dennis Bruemmer,[3] Sonia Butalia,[4]
Jennifer B. Green,[5] William B. Horton,[6]
Colette Knight,[7] Moshe Levi,[8]
Neda Rasouli,[9] and
Caroline R. Richardson[10]

# Burden of Heart Failure Associated with Diabetes

# Most Common Diabetes-related Cardiovascular Conditions

- CALIBER Study- English Primary Care

- 1,921,260 individuals aged ≥ 30 years; 34,198 with diabetes, median follow-up: 5.5 years

- initial cardiovascular complication:
  - peripheral artery disease: 16.2%
  - heart failure : 14.1%
  - stable angina: 11.9%
  - non-fatal myocardial infarction : 11.5%
  - stroke: 10.3%



Shah AD et al. *Lancet Diabetes Endocrinol*. 2015;3(2):105-13.
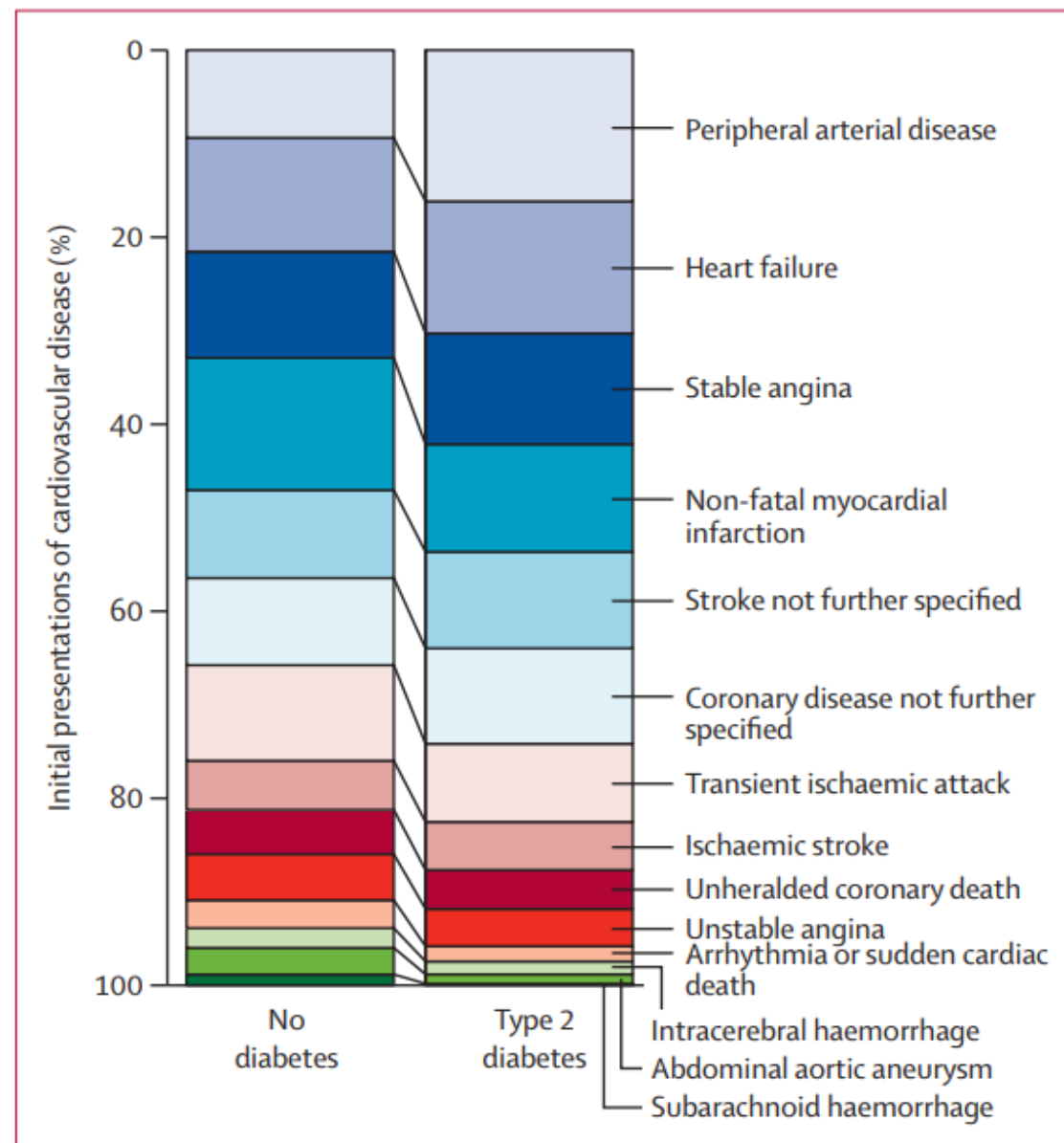
# Diabetes & Heart Failure – Common comorbid conditions

364,480 heart failure patients from 462 hospitals in the US
44% of individuals admitted with heart failure also have diabetes
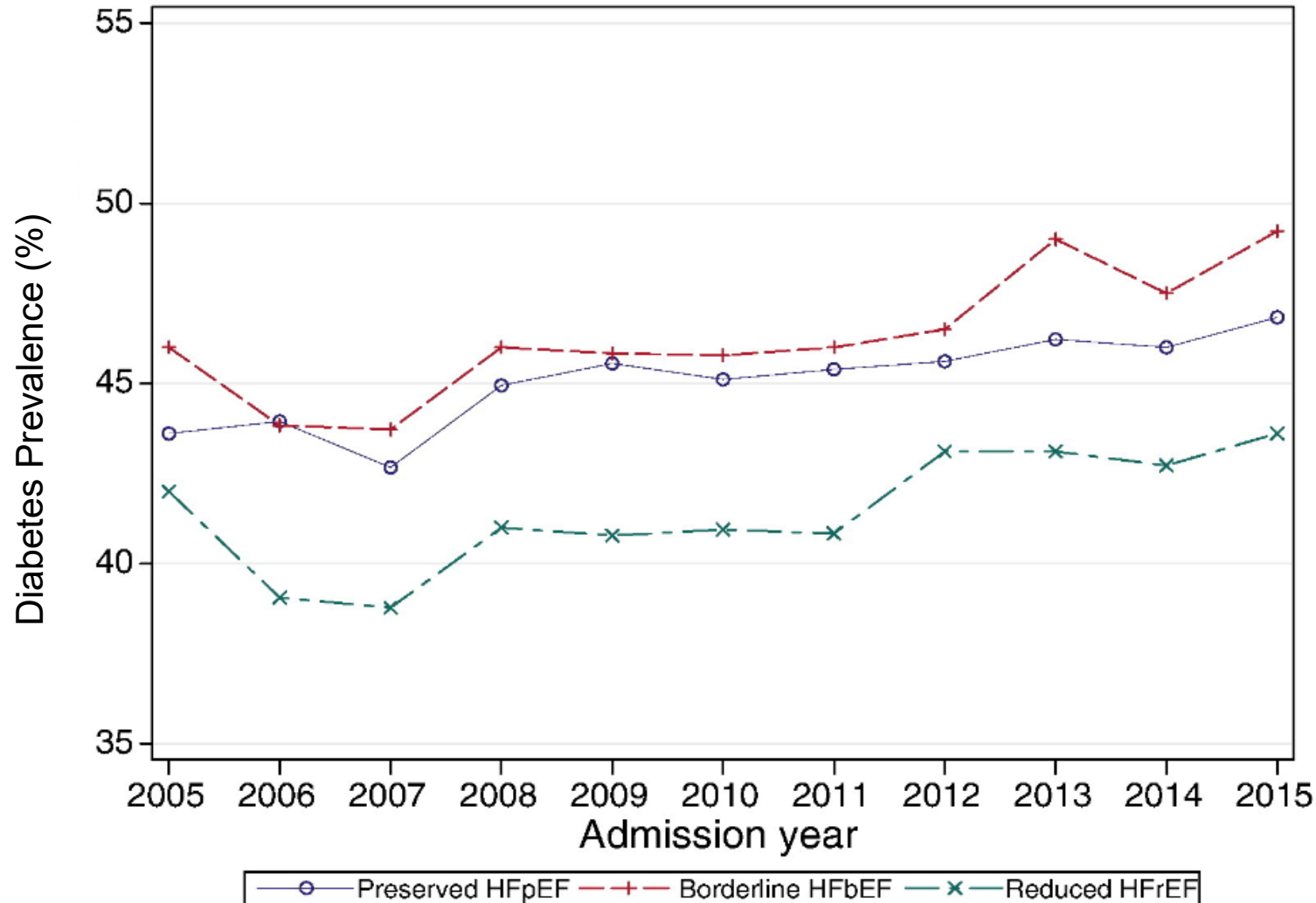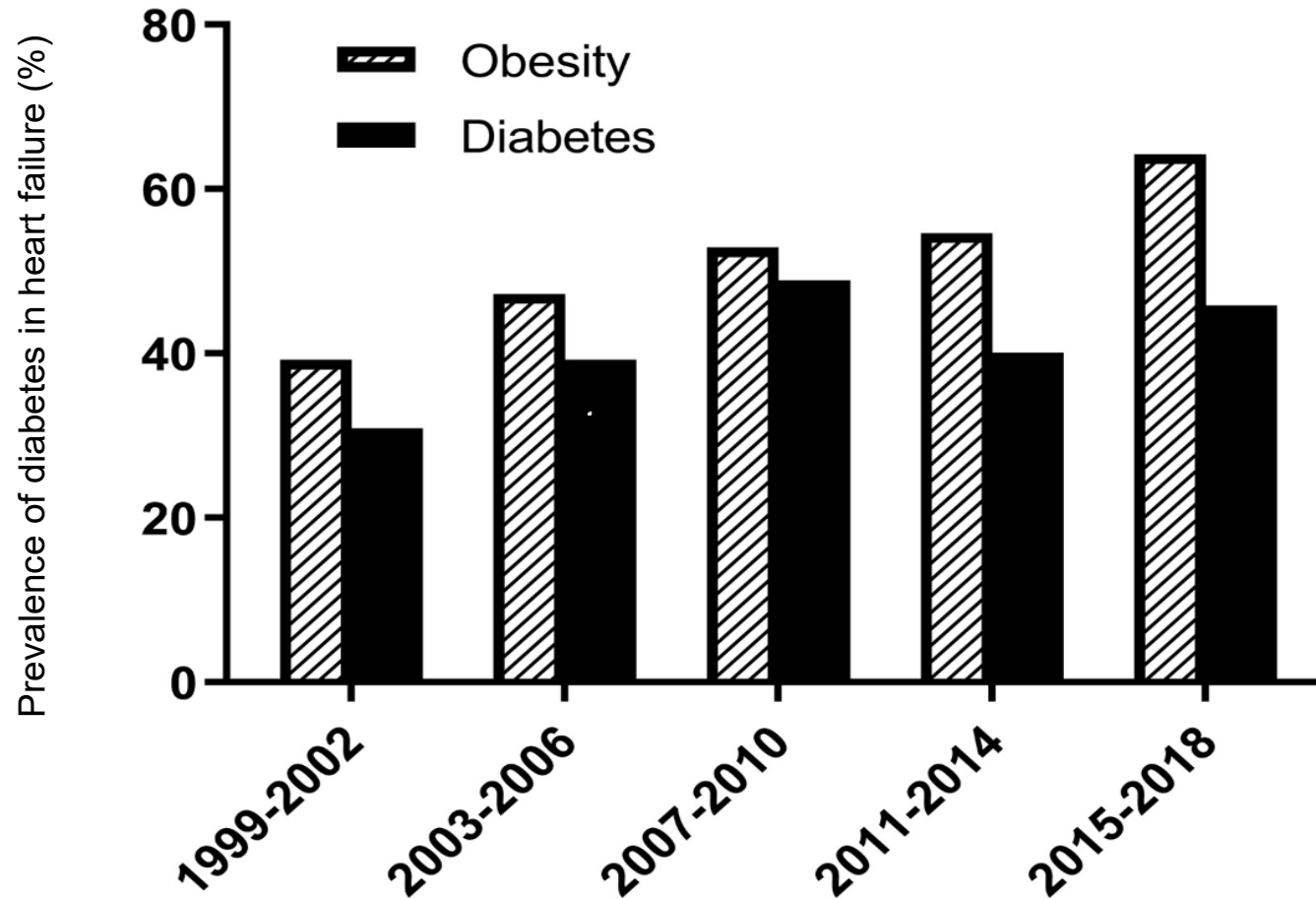


**41.8% in HFrEF**

**46.7% in HFbEF**

**45.5% in HFpEF**

**Echouffo-Tcheugui JB, et al.** *Am Heart J*. 2016;182:9-20.

# U.S. National Data - Diabetes & Heart Failure Combination

NHANES 1999- 2018: 40 to 49% of those with self-reported heart failure had diabetes
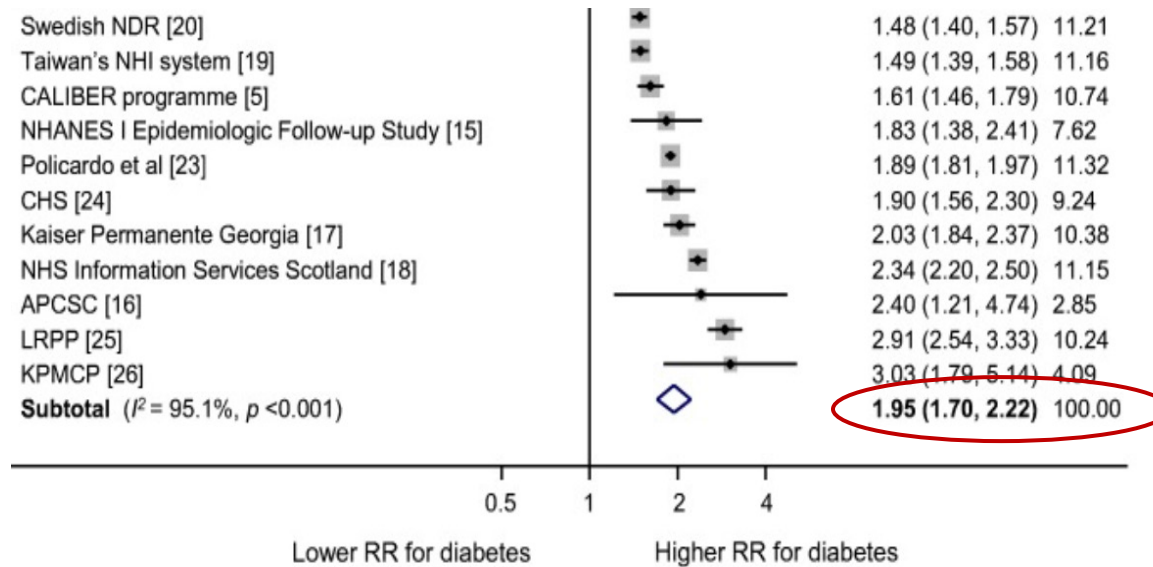


Heart failure assessment is suboptimal – self-report only and no objective evaluation
Diabetes assessment based on self-report and biochemical assessment

Ciardullo S, et al. Int J Cardiol. 2022;362:104-109.

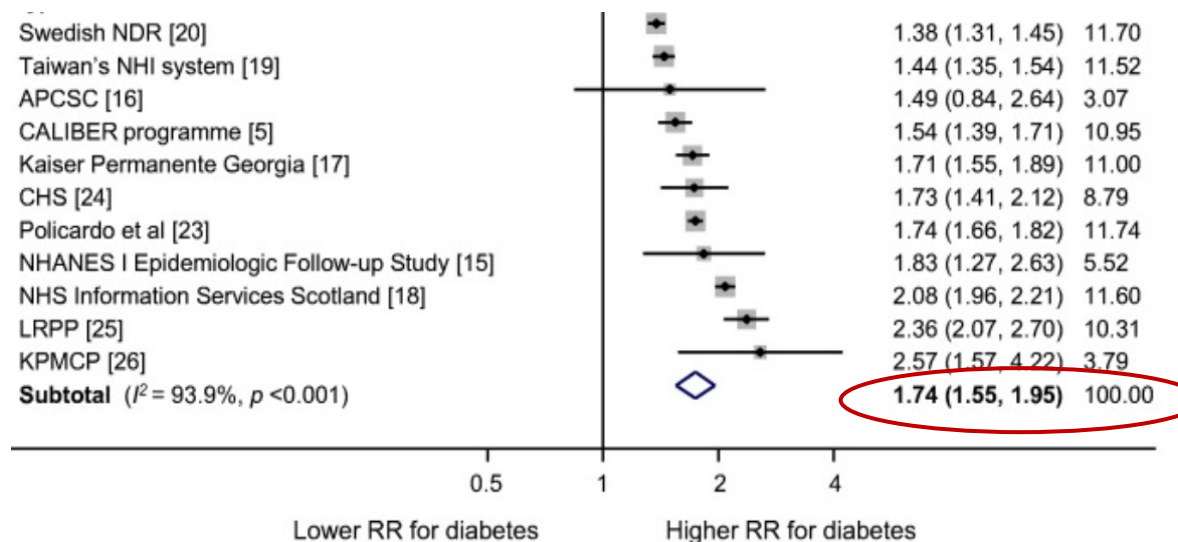# Extent of Heart Failure Risk Associated with Diabetes

# Relative Risk of Heart Failure Associated with Diabetes

Systematic review – including a total of 12,142,998 individuals and 253,260 heart failure events
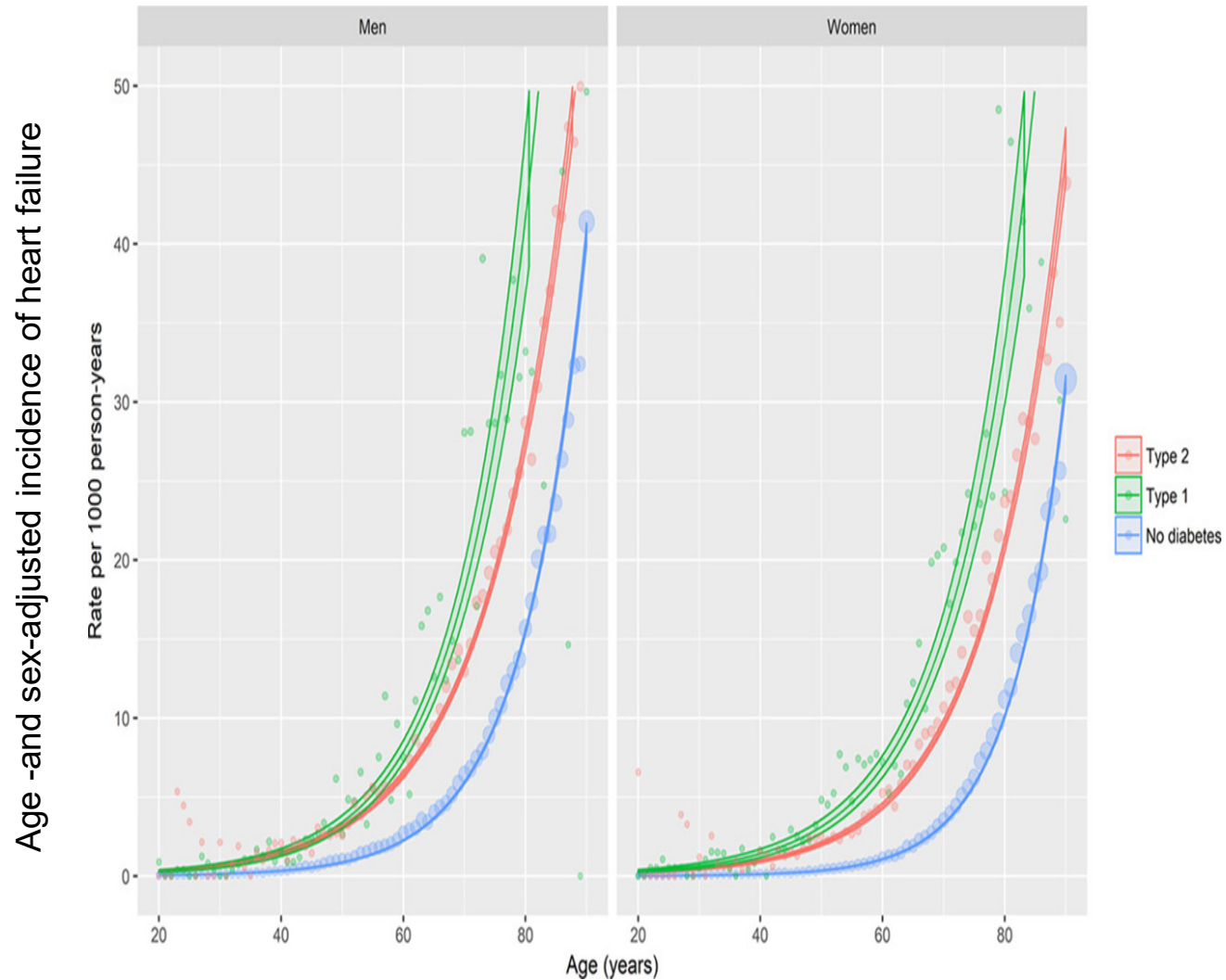


**Women**

| Study | RR (95% CI) | Weight |
|---|---|---|
| Swedish NDR [20] | 1.48 (1.40, 1.57) | 11.21 |
| Taiwan's NHI system [19] | 1.49 (1.39, 1.58) | 11.16 |
| CALIBER programme [5] | 1.61 (1.46, 1.79) | 10.74 |
| NHANES I Epidemiologic Follow-up Study [15] | 1.83 (1.38, 2.41) | 7.62 |
| Policardo et al [23] | 1.89 (1.81, 1.97) | 11.32 |
| CHS [24] | 1.90 (1.56, 2.30) | 9.24 |
| Kaiser Permanente Georgia [17] | 2.03 (1.84, 2.37) | 10.38 |
| NHS Information Services Scotland [18] | 2.34 (2.20, 2.50) | 11.15 |
| APCSC [16] | 2.40 (1.21, 4.74) | 2.85 |
| LRPP [25] | 2.91 (2.54, 3.33) | 10.24 |
| KPMCP [26] | 3.03 (1.79, 5.14) | 4.09 |
| **Subtotal** ($I^2$ = 95.1%, $p$ <0.001) | **1.95 (1.70, 2.22)** | 100.00 |

0.5    1    2    4

Lower RR for diabetes         Higher RR for diabetes

**Men**

| Study | RR (95% CI) | Weight |
|---|---|---|
| Swedish NDR [20] | 1.38 (1.31, 1.45) | 11.70 |
| Taiwan's NHI system [19] | 1.44 (1.35, 1.54) | 11.52 |
| APCSC [16] | 1.49 (0.84, 2.64) | 3.07 |
| CALIBER programme [5] | 1.54 (1.39, 1.71) | 10.95 |
| Kaiser Permanente Georgia [17] | 1.71 (1.55, 1.89) | 11.00 |
| CHS [24] | 1.73 (1.41, 2.12) | 8.79 |
| Policardo et al [23] | 1.74 (1.66, 1.82) | 11.74 |
| NHANES I Epidemiologic Follow-up Study [15] | 1.83 (1.27, 2.63) | 5.52 |
| NHS Information Services Scotland [18] | 2.08 (1.96, 2.21) | 11.60 |
| LRPP [25] | 2.36 (2.07, 2.70) | 10.31 |
| KPMCP [26] | 2.57 (1.57, 4.22) | 3.79 |
| **Subtotal** ($I^2$ = 93.9%, $p$ <0.001) | **1.74 (1.55, 1.95)** | 100.00 |

0.5    1    2    4

Lower RR for diabetes         Higher RR for diabetes

**~ 2-fold higher risk of heart failure among individuals with diabetes vs. those without diabetes**
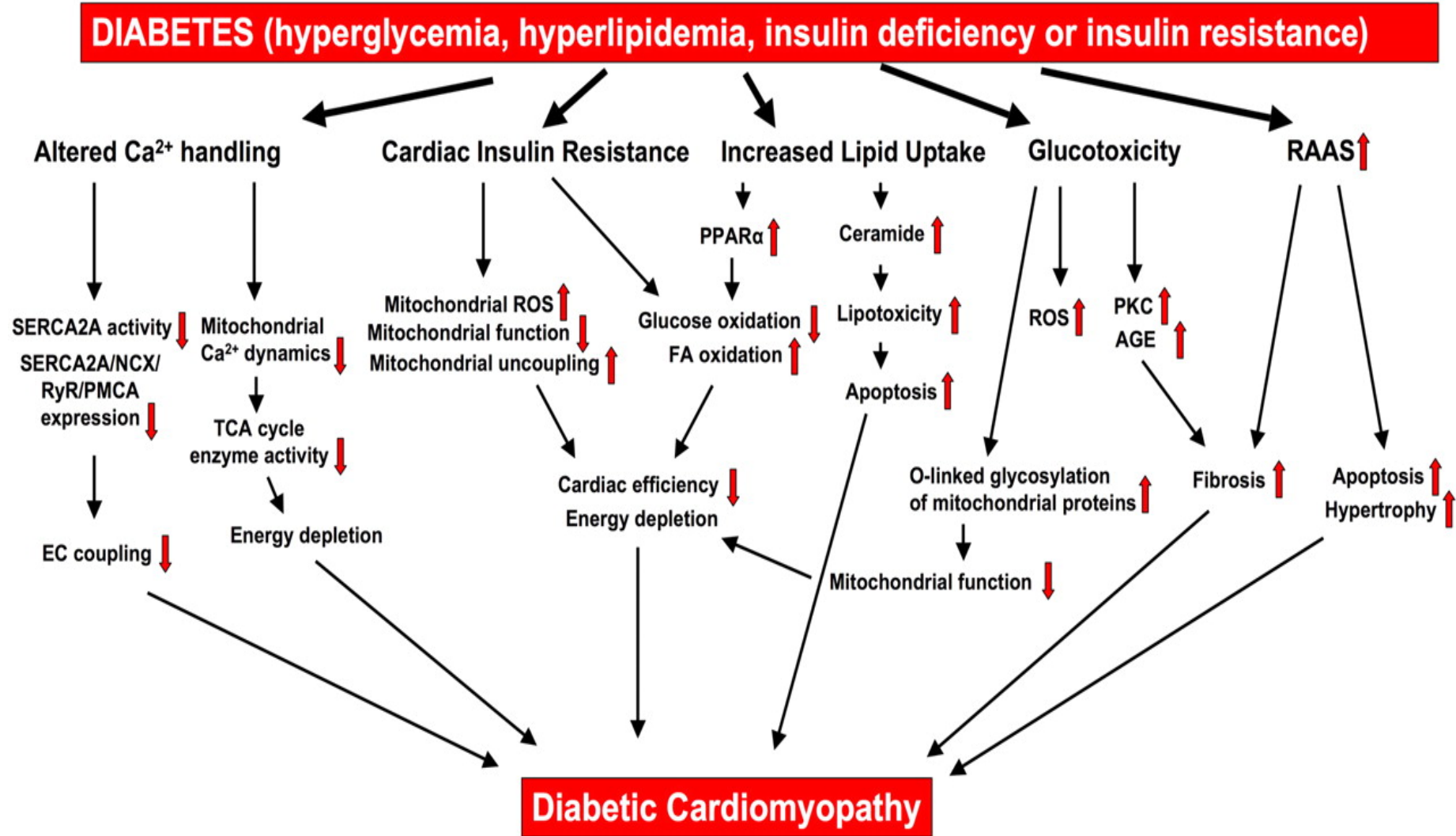
Ohkuma T et al. *Diabetologia*. 2019;62(9):1550-1560.

# Absolute Risk of Heart Failure Associated with Diabetes

3.25 million people – Scotland primary care – (51% women, age ≥30years ) – follow-up over a 10-year period



**Higher absolute risk (IR) among older individuals & men**
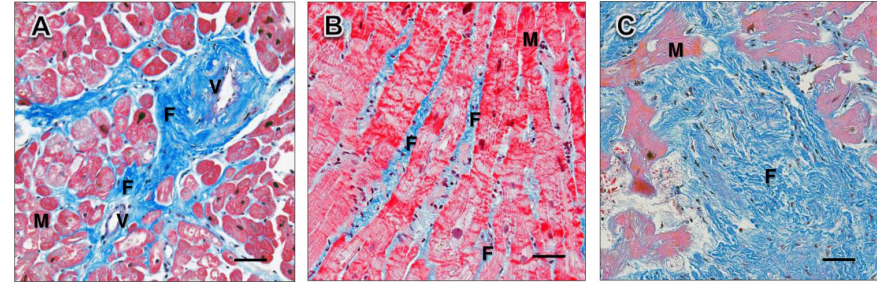**Higher relative risks (RR) in younger individuals & women**

McAllister DA,  et al. *Circulation*. 2018;138(24):2774-2786.

# Diabetes Cardiomyopathy – Biological Underpinning



Heiko Bugger, E. Dale Abel. *Dis. Model. Mech.* 2009;2:454-466

# Morphological & Structural Phenotypes - Diabetic Heart

- ## Cardiac Fibrosis
  - Histology: autopsies studies
  - Imaging: cardiac MRI /Echocardiography

- ## Cardiac Hypertrophy
  - Histology: cardiomyocyte hypertrophy
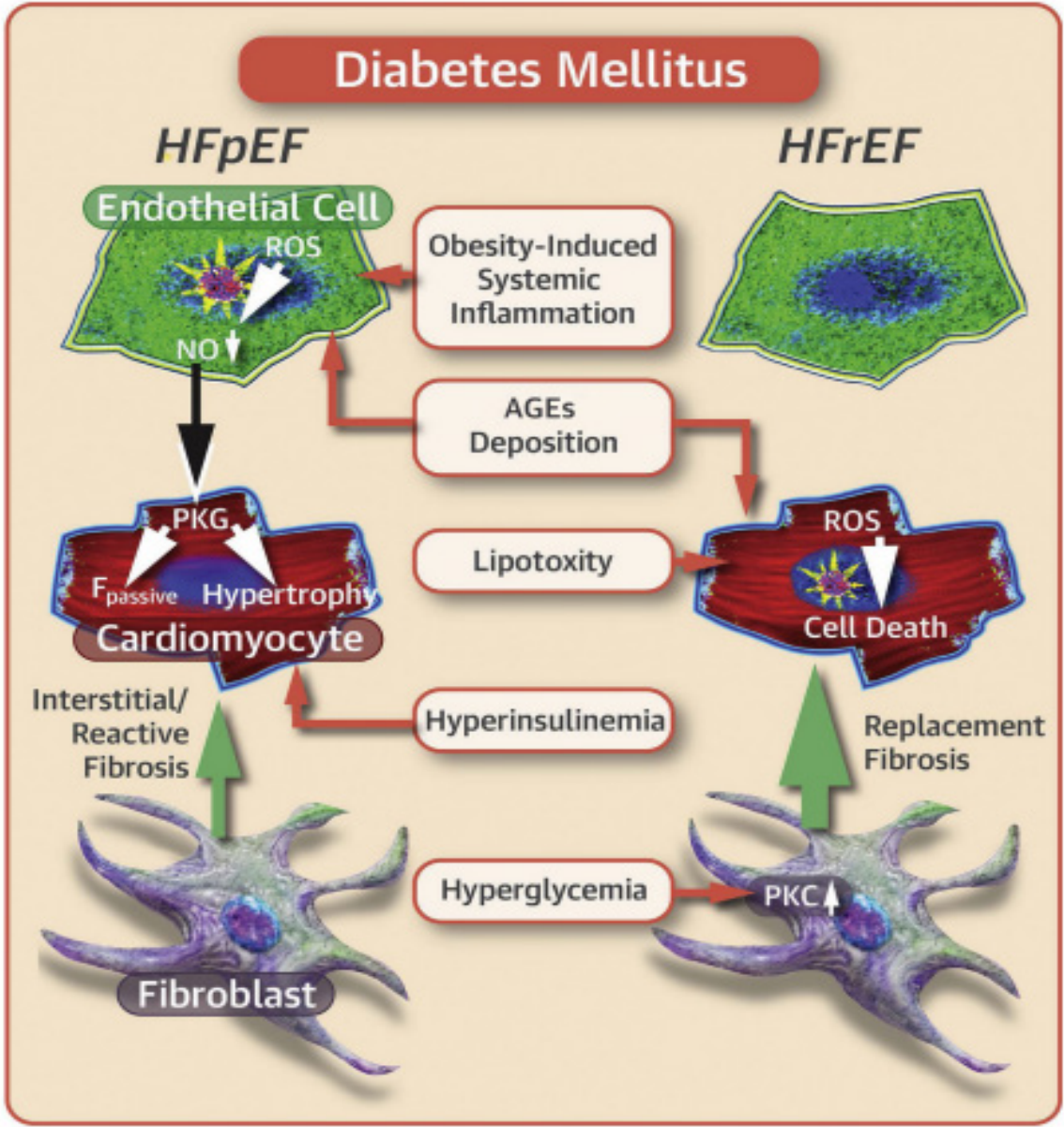  - Imaging:   increased LV mass
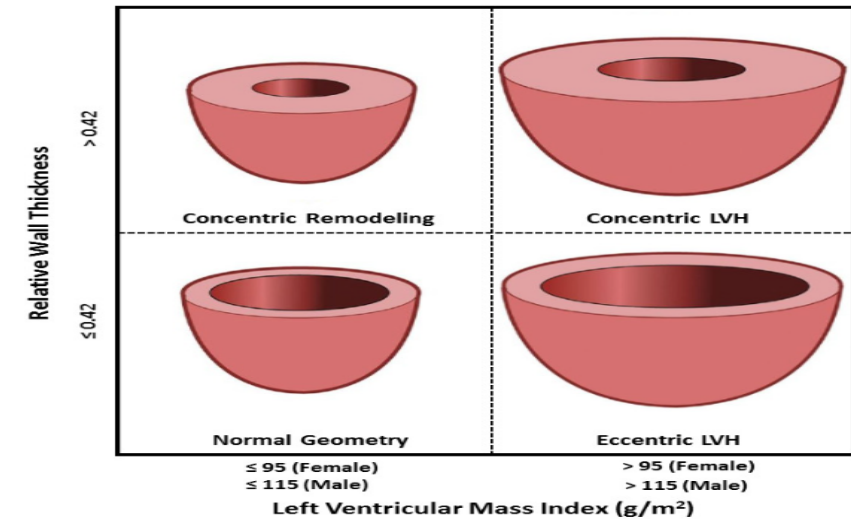
- ## Impaired Coronary Microvascular Perfusion
  - Histology: decreased myocardial capillary density
  - PET scan : impairment in coronary flow reserve



Ritchie RH, Abel ED. *Circ Res.* 2020;126(11):1501-1525
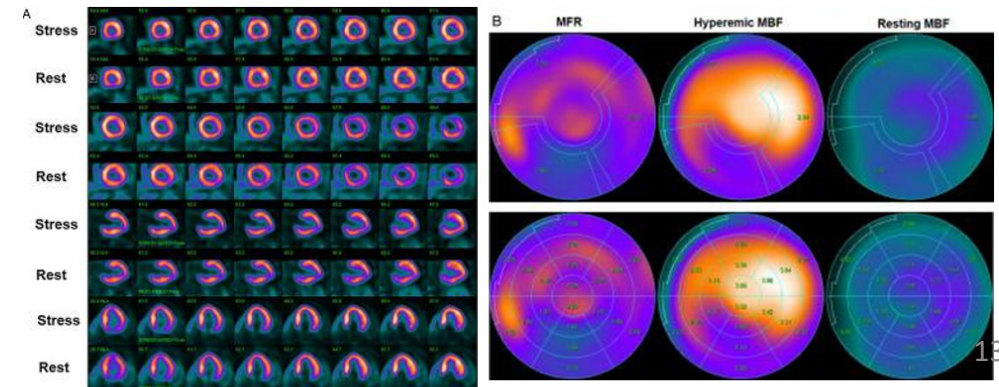
# Distinct Pathways : Diabetes-related HF Preserved vs. Reduced Ejection Fraction

**HF with preserved EF:**
Hyperinsulinemia
Microvascular/endothelial inflammation
Hypertrophy & stiffness

**HF with reduced EF:**
Lipotoxicity/glycation
Myocardial injury/wall stress
Myocyte cell death
Replacement fibrosis



Paulus WJ, Dal Canto E. *JACC Heart Fail*. 2018;6(1):1-7.

# Diabetes and Heart Failure Subtypes

6,668 individuals (mean age: 62 years, 53% women, 39% White, 28% Black,12% Chinese, 22% Hispanic)
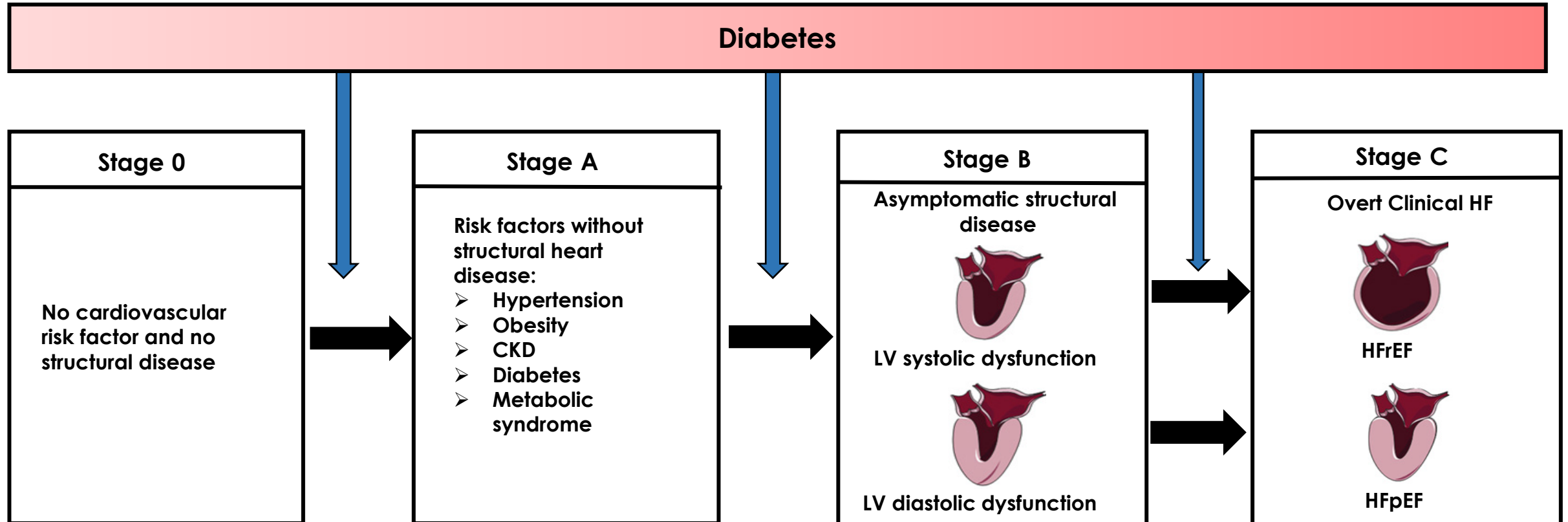average follow-up:15 years
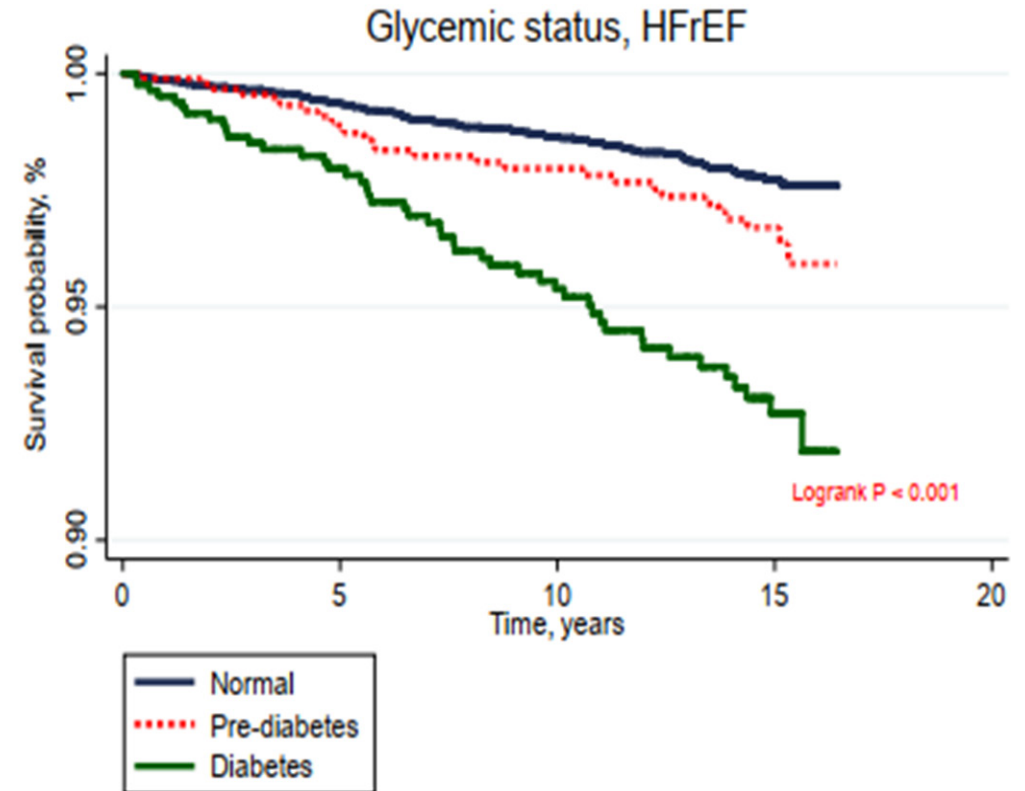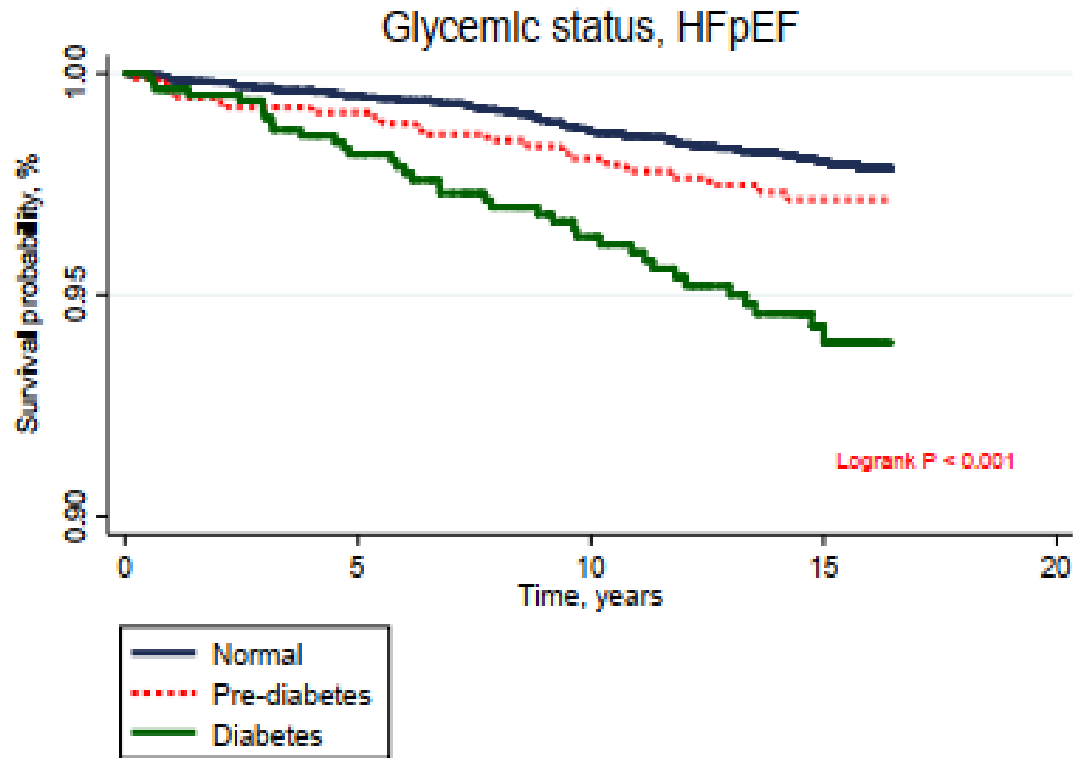


**Adjusted hazard ratio for HFpEF : 1.85 (95% CI: 1.57, 2.68)**

**Adjusted hazard ratio for HFrEF : 2.02 (95% CI: 1.38, 2.97)**

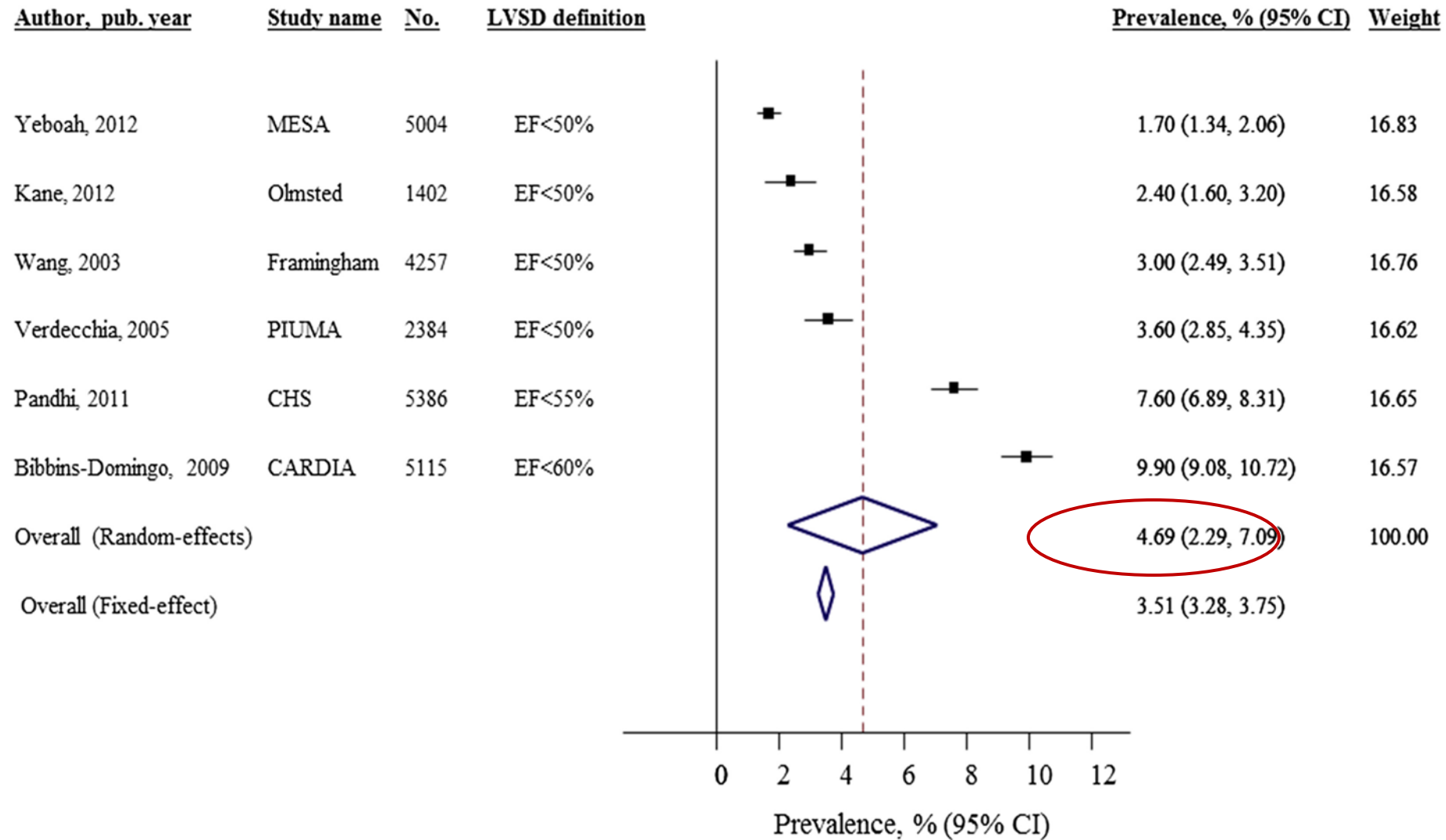Echouffo-Tcheugui JB, al. *J Card Fail.* 2022:S1071-9164(22)00036-7.

# Diabetes, Hyperglycemia & Progression of Cardiac Dysfunction

# Diabetes Influence – Natural History of Heart Failure

**Diabetes and transition across heart failure stages**

**Diabetes**

### Stage 0

No cardiovascular risk factor and no structural disease

### Stage A

Risk factors without structural heart disease:
- Hypertension
- Obesity
- CKD
- Diabetes
- Metabolic syndrome

### Stage B

Asymptomatic structural disease

LV systolic dysfunction

LV diastolic dysfunction

### Stage C

Overt Clinical HF

HFrEF

HFpEF

# Burden of Preclinical Heart Failure – Asymptomatic LV dysfunction

| Author, pub. year | Study name | No. | LVSD definition | Prevalence, % (95% CI) | Weight |
|---|---|---|---|---|---|
| Yeboah, 2012 | MESA | 5004 | EF<50% | 1.70 (1.34, 2.06) | 16.83 |
| Kane, 2012 | Olmsted | 1402 | EF<50% | 2.40 (1.60, 3.20) | 16.58 |
| Wang, 2003 | Framingham | 4257 | EF<50% | 3.00 (2.49, 3.51) | 16.76 |
| Verdecchia, 2005 | PIUMA | 2384 | EF<50% | 3.60 (2.85, 4.35) | 16.62 |
| Pandhi, 2011 | CHS | 5386 | EF<55% | 7.60 (6.89, 8.31) | 16.65 |
| Bibbins-Domingo, 2009 | CARDIA | 5115 | EF<60% | 9.90 (9.08, 10.72) | 16.57 |
| Overall (Random-effects) | | | | 4.69 (2.29, 7.09) | 100.00 |
| Overall (Fixed-effect) | | | | 3.51 (3.28, 3.75) | |

Prevalence, % (95% CI)

Underestimation of prevalence of stage B of the heart failure process – based on ejection fraction only

# Asymptomatic Stages in Natural History of Heart Failure



Stage 0 — 5%
Stage A — 52%
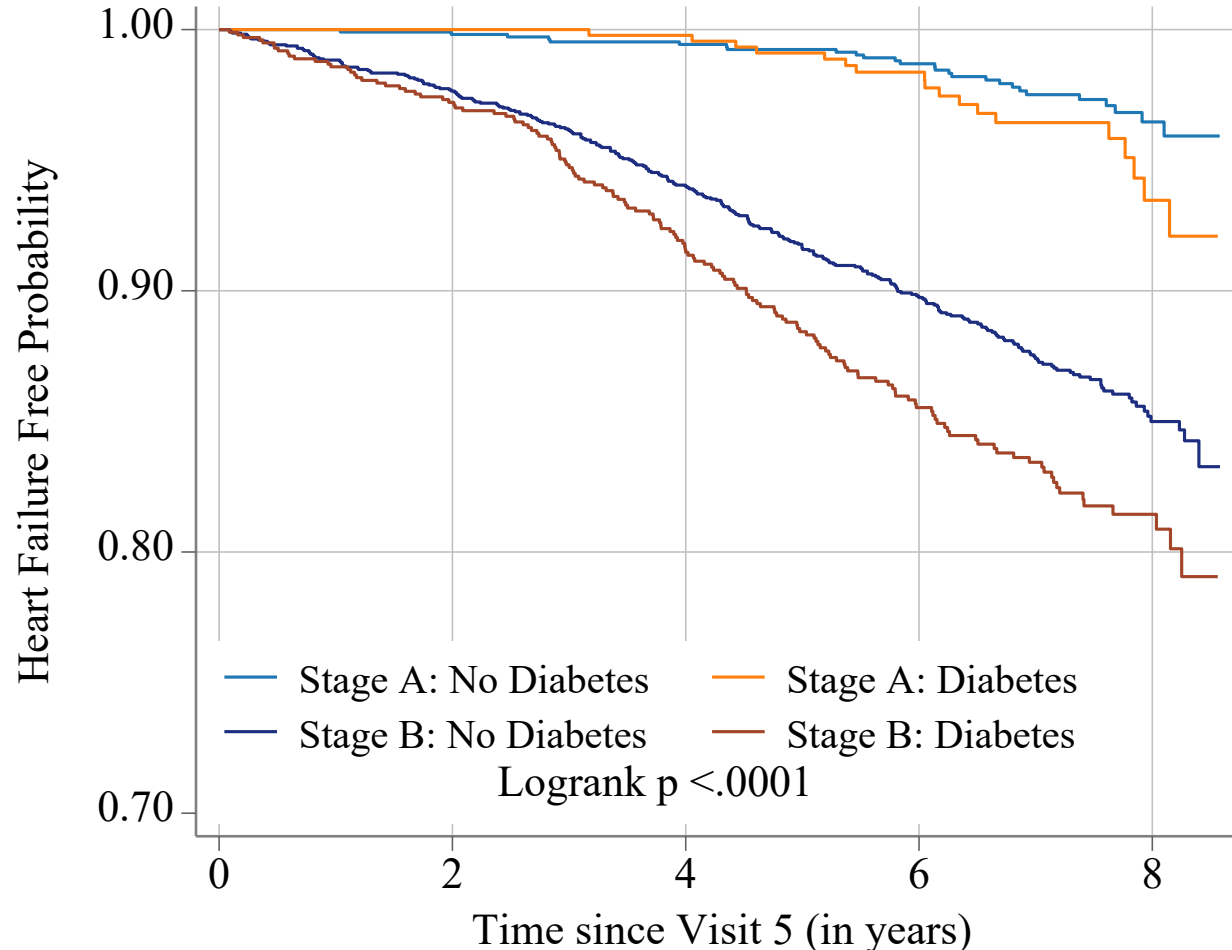Stage B — 30%
Stage C1 — 7%
Stage C2 — 6%
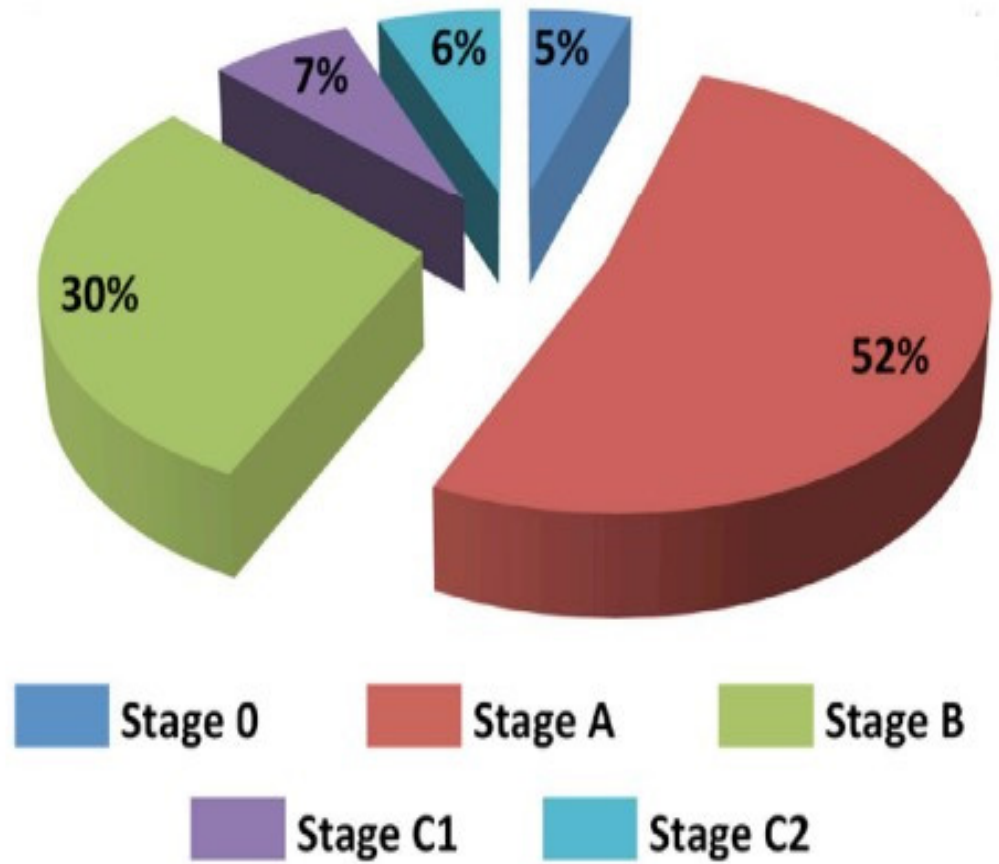
Heart failure process staging – comprehensive :

- ≥ 1 of : abnormal LVEF, RWM abnormality, LV enlargement (based on LVEDV), LVH, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis

- N-terminal pro–B-type natriuretic peptide [NT-proBNP] ≥125 pg/mL) and/or high-sensitivity cardiac troponin T >14 ng/L

# Diabetes and Progression of Cardiac Dysfunction

4,474 individuals (mean age: 75 years, 58% women, 20% Blacks, 18 % with diabetes)
average follow-up: 7.5 years



Reference: no DM & stage A :
- Stage B & DM: **HR: 3.35 (95% CI: 2.53, 4.44)**

- Stage B & no-DM: **HR: 2.47 (95% CI:1.96, 3.12)**

- Stage A & DM: **HR: 1.52 (95% CI: 0.53, 4.58)**

Development of HF in stage B & DM :
- 3 years earlier than those in stage B & no-DM
- 5 to 6 years earlier than those in stage A

Echouffo-Tcheugui  JB, al. *J Am Coll Cardiol.* 2022;79(23):2285-2293

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# Glycemic Control & Progression of Cardiac Dysfunction
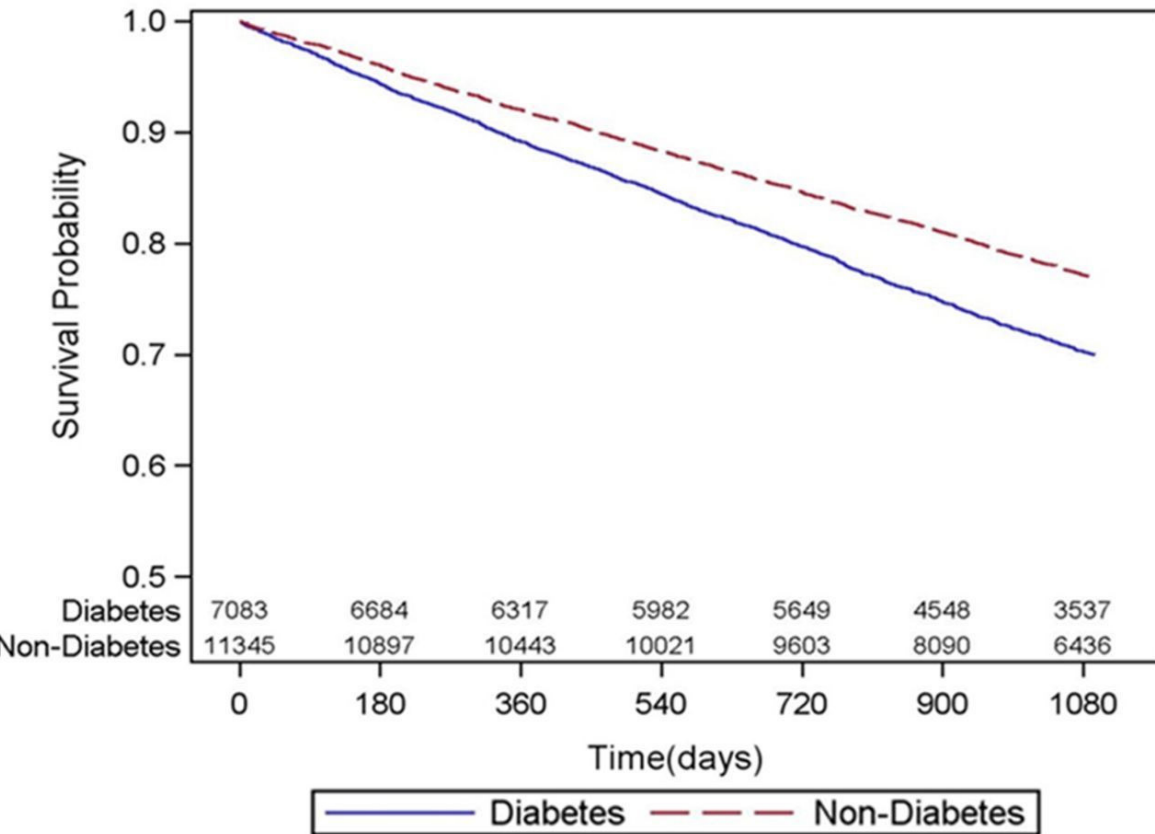


(A)

(B)
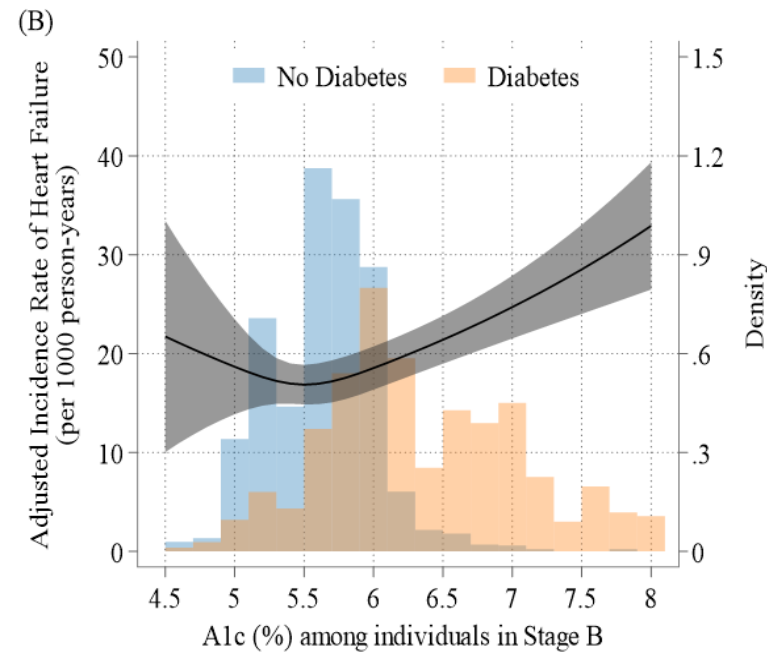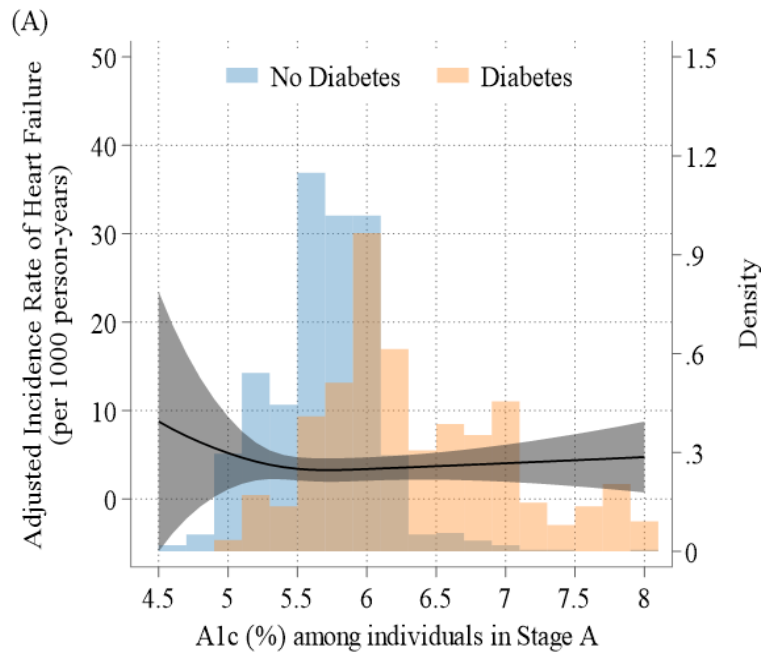
A1C ≥7% association with HF
Reference: no DM & stage A

- **Stage A: HR: 1.52 (95% CI: 0.53, 4.38)**

- **Stage B: HR: 1.83 (95% CI: 1.33, 2.51**

- *P*_interaction=0.04

**Echouffo-Tcheugui JB, al. *J Am Coll Cardiol*. 2022;79(23):2285-2293**

# Diabetes and Outcomes of Cardiac Resynchronization Therapy

18,428 subjects receiving CRT-D (mean age:75 years, 32% Women, 89% Whites, 38% with T2DM), 3-year follow-up



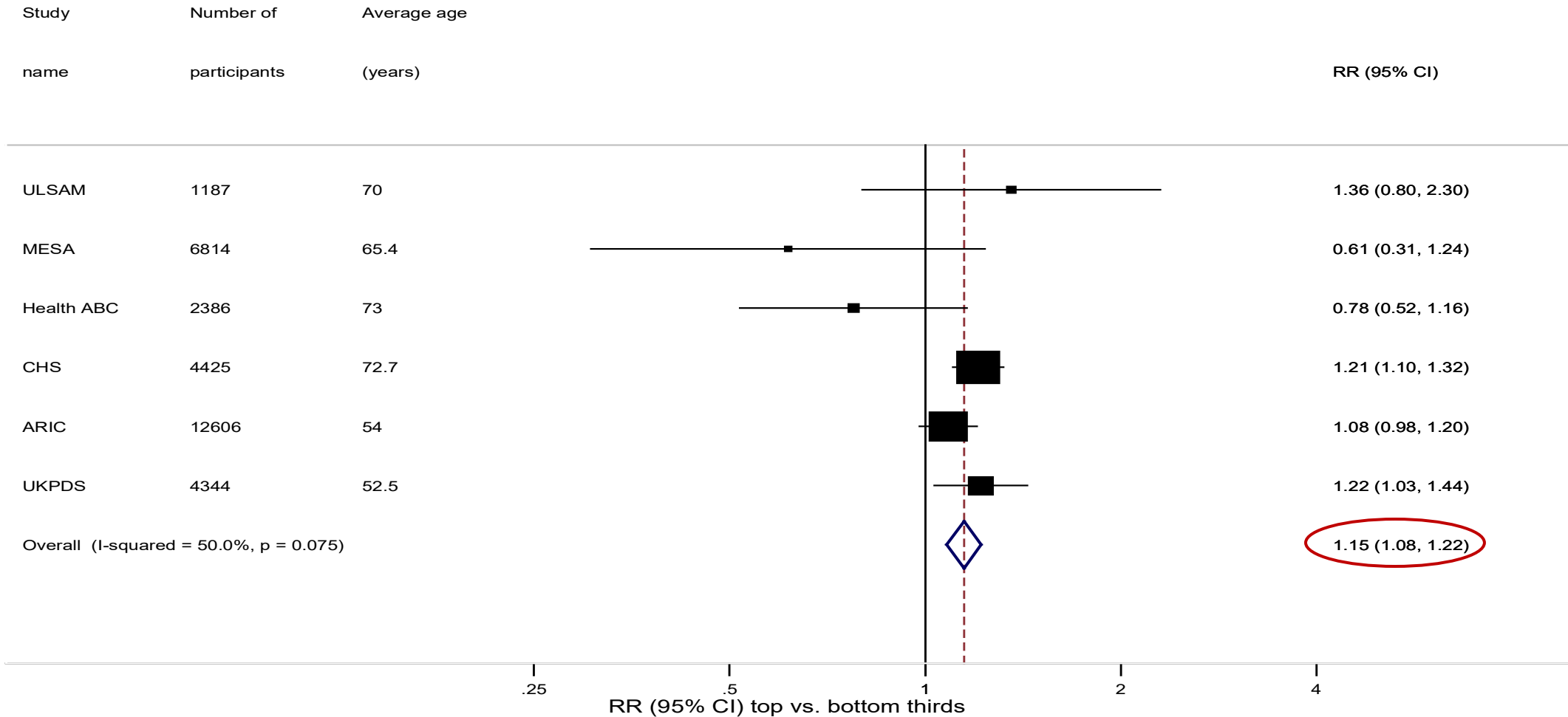**Hazard Ratio for mortality: 1.16 (95% CI: 1.01, 1.29**
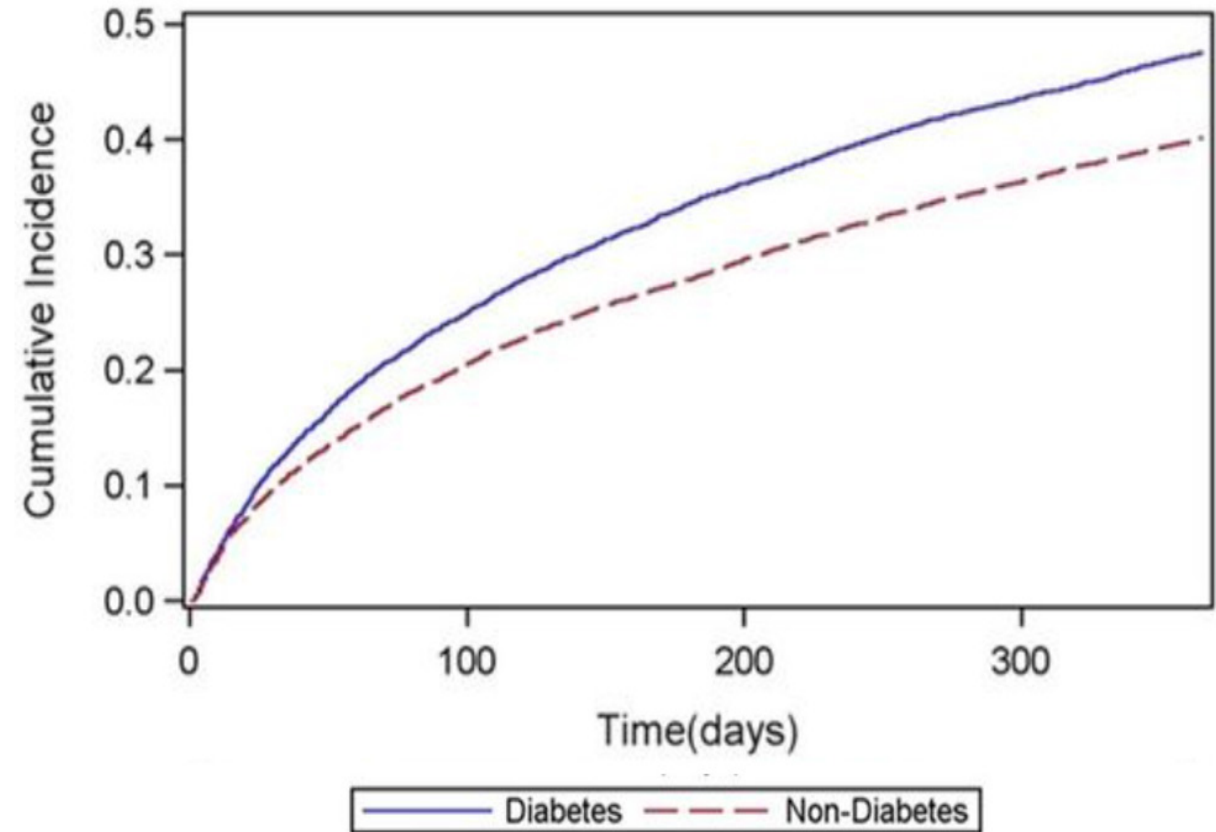
**Hazard Ratio for readmissions: 1.16 (95% CI: 1.01, 1.29**

Echouffo-Tcheugui JB, et al. *Circ Arrhythm Electrophysiol.* 2016;9(8):e004132

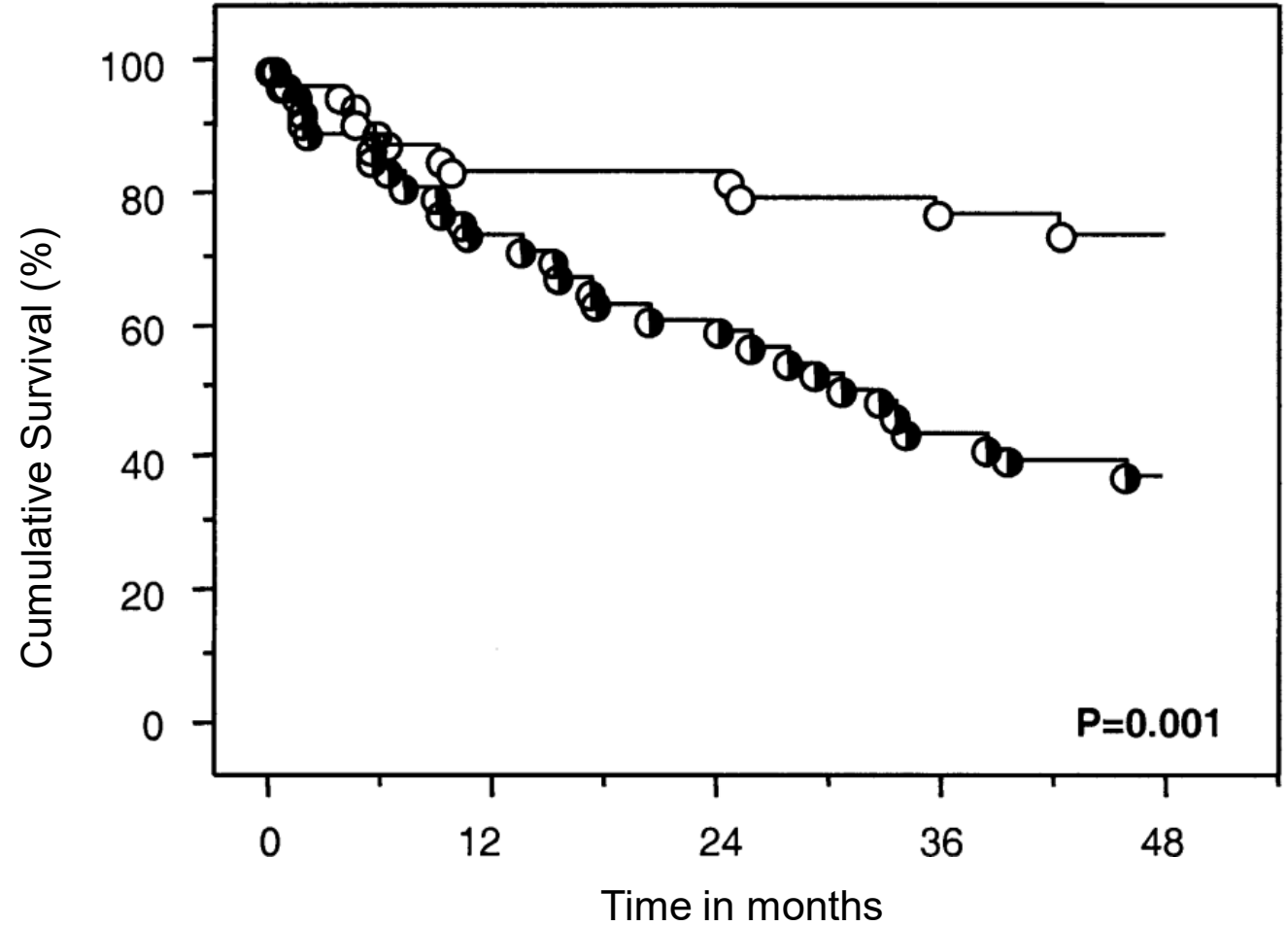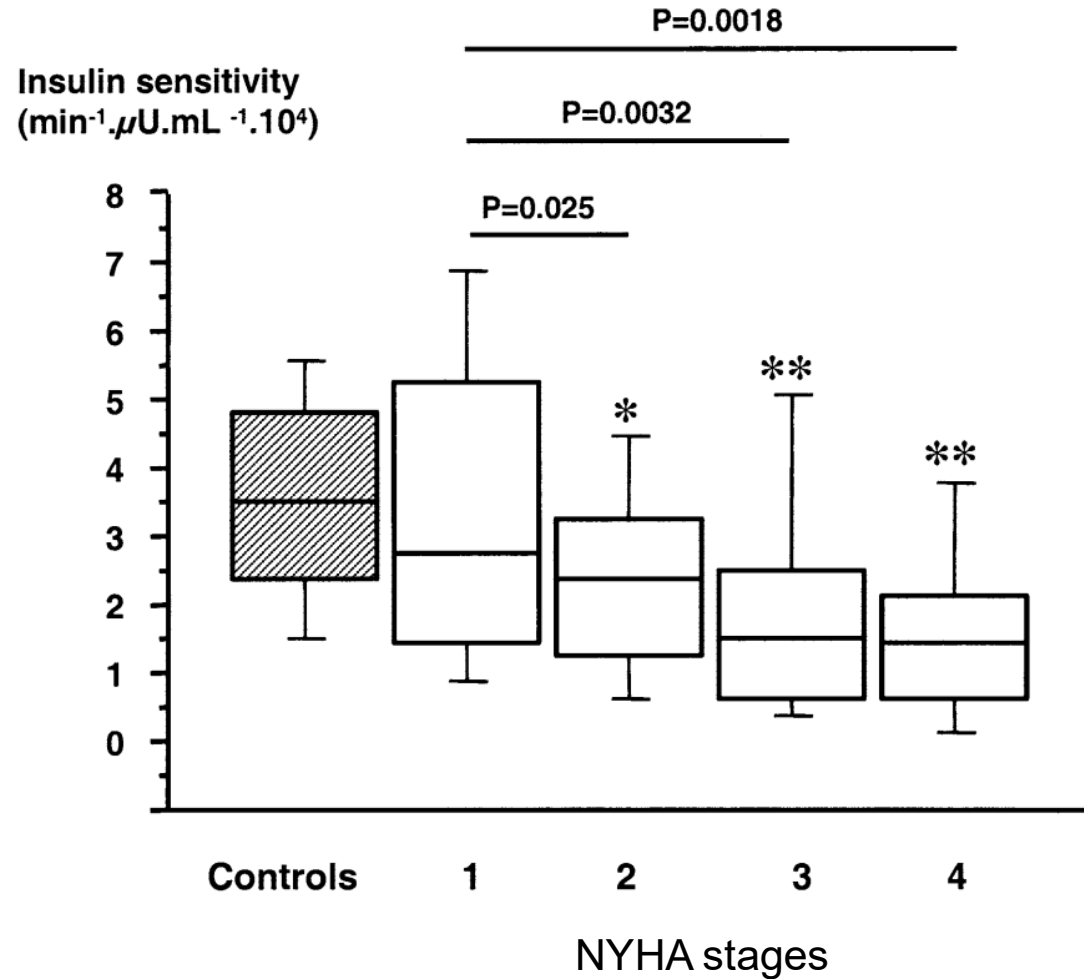# Diabetes-specific Drivers of Heart Failure Risk

# Insulin Resistance and Incident Heart Failure

Systematic review and meta-analysis including 31,762 participants and 3,247 incident HF events

Relative risk of HF comparing top vs. bottom thirds of HOMA-IR



| Study name | Number of participants | Average age (years) | RR (95% CI) |
|---|---|---|---|
| ULSAM | 1187 | 70 | 1.36 (0.80, 2.30) |
| MESA | 6814 | 65.4 | 0.61 (0.31, 1.24) |
| Health ABC | 2386 | 73 | 0.78 (0.52, 1.16) |
| CHS | 4425 | 72.7 | 1.21 (1.10, 1.32) |
| ARIC | 12606 | 54 | 1.08 (0.98, 1.20) |
| UKPDS | 4344 | 52.5 | 1.22 (1.03, 1.44) |
| Overall (I-squared = 50.0%, p = 0.075) | | | 1.15 (1.08, 1.22) |

RR (95% CI) top vs. bottom thirds

Erqou S, Adler AI, Challa AA, Fonarow GC, Echouffo-Tcheugui JB. *Eur J Heart Fail*. 2022;24(6):1139-1141.

# Insulin Sensitivity and Outcomes in Chronic Heart Failure
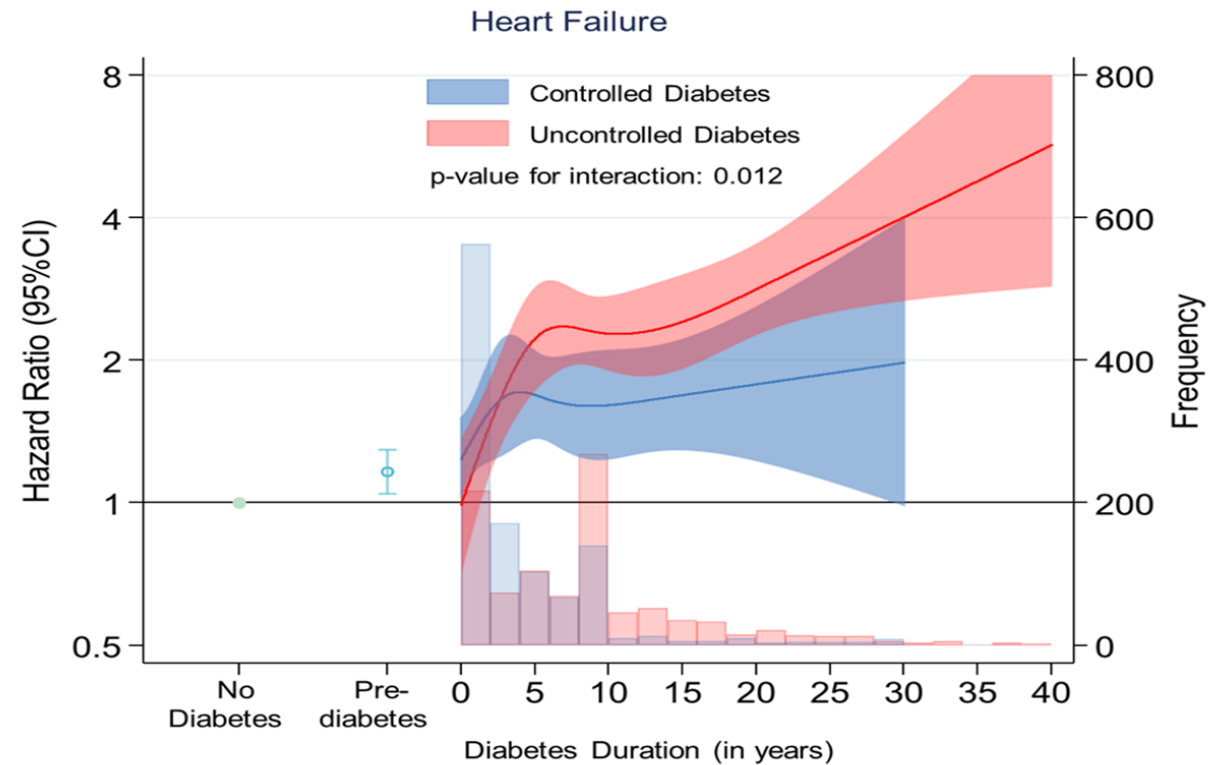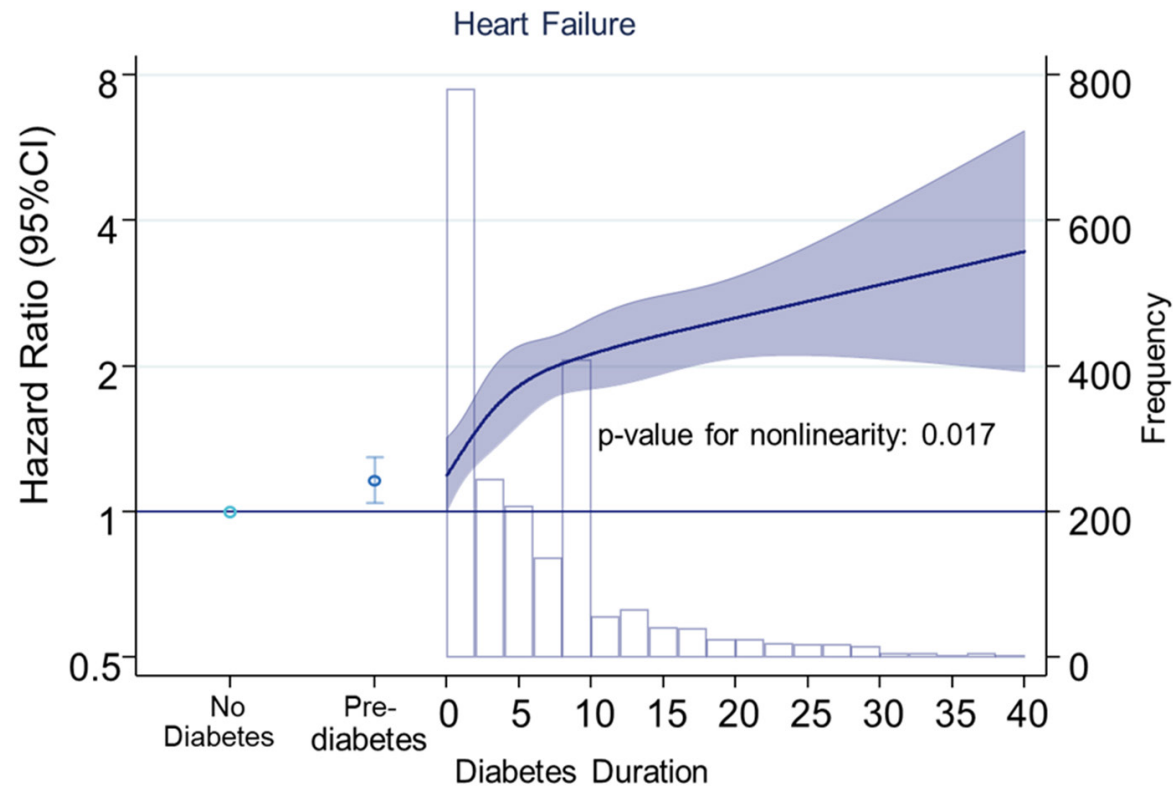


Doehner W, et al. J Am Coll Cardiol. 2005;46(6):1019-26.

Insulin sensitivity is associated with better:
- survival – Hazard ratio for unit change in IS: 0.38 (0.21, 0.67)
- functional capacity – VO2 max

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# Diabetes Duration and Risk of Incident Heart Failure

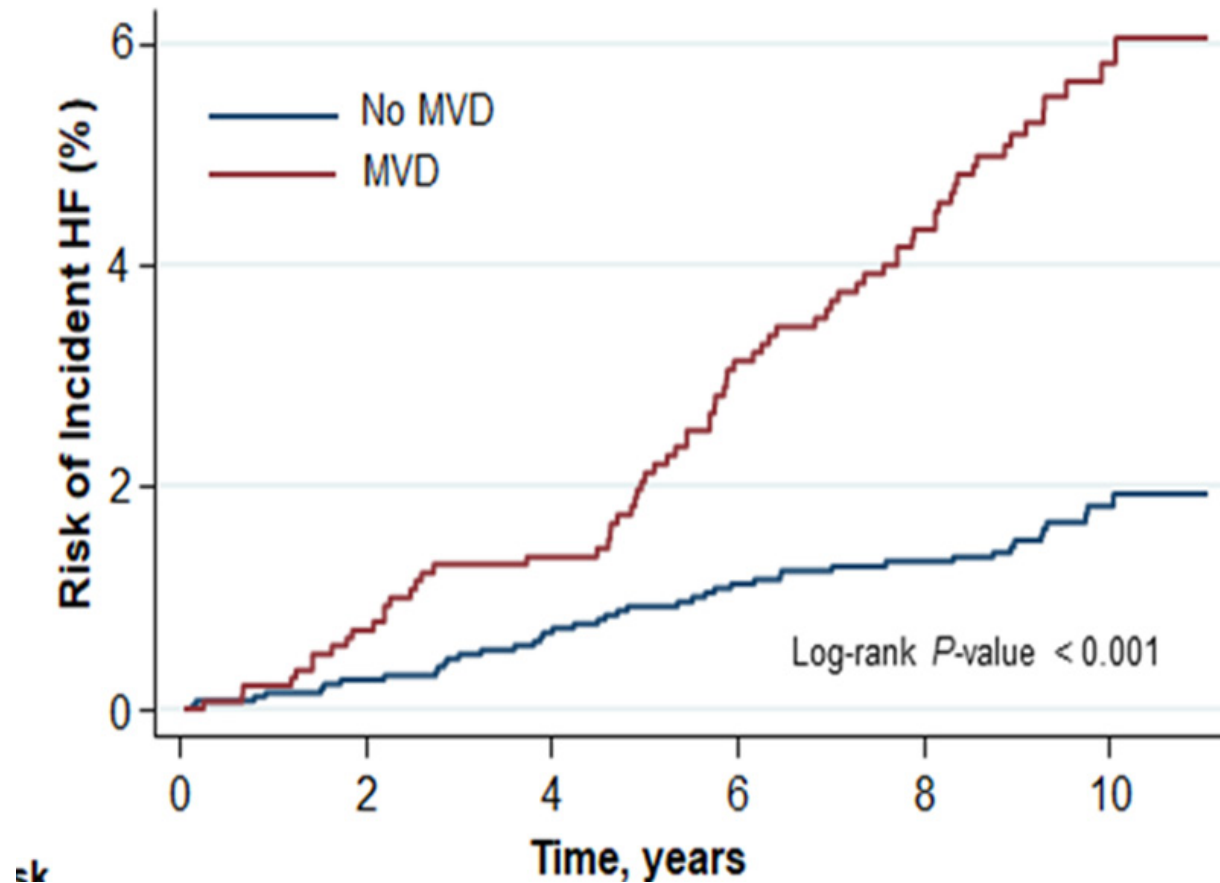9,734 individuals (mean age 63 years, 58% Women, 22% Blacks, 19% with diabetes), average follow-up : 22.5 years



**Each 5-year longer diabetes - 17% (95% CI: 1.11, 1.22) higher risk**

**Duration ≥15 years & A1C ≥ 7% : HR: 2.66 ( 95% CI: 1.93, 3.66)**

**Duration ≥15 years & A1C <7%:  HR 1.91 (95% CI: 1.19, 3.07)**

Echouffo-Tcheugui JB, et al. *JACC Heart Fail.* 2021;9(8):594-603.

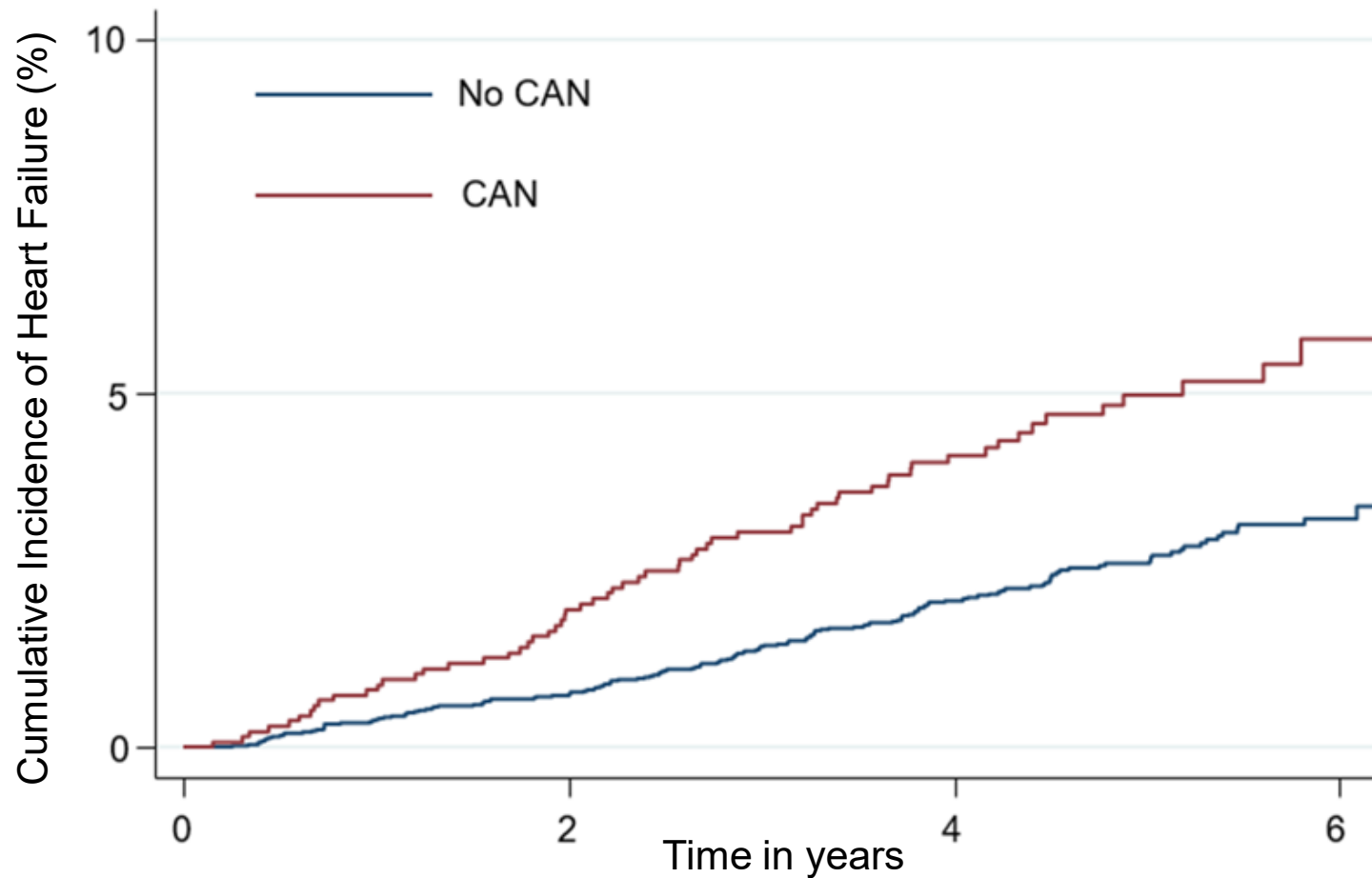# Microvascular Disease and Heart Failure in Type 2 diabetes

4,098 individuals with T2DM (mean age 58 years, 62% Women, 65% Whites, 17% non-Hispanic Blacks, 155 Blacks)
1424 with microvascular disease (MVD - nephropathy, retinopathy, or neuropathy), average follow-up: 9.7 years



**Hazard ratio for MVD vs . no MVD : 2.42  (95% CI: 1.64, 3.57)**

*Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni A, Echouffo-Tcheugui JB. J Am Heart Assoc. 2021;10(12):e018998.*
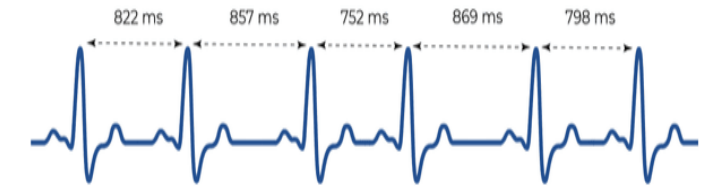
# Cardiac Autonomic Dysfunction & Heart Failure in Type 2 diabetes

7,160 individuals with T2DM (mean age: 62 years, 41% women, 62% Whites)
19.5% with cardiac autonomic neuropathy (CAN), average follow-up: 5 years



**CAN conferred a 2.7-fold greater risk of heart failure - HR 2.65 (95% CI 1.57, 4.48)**

*Kaze AD, Yuyun MF, Erqou S, Fonarow GC, Echouffo-Tcheugui JB.  Eur J Heart Fail. 2022;24(4):634-64.*

# Biomarkers of Diabetes-Related Heart Failure

# Proteomic Analyses: Novel Biomarkers/Pathways

- Data on pathogenesis of diabetes-related heart failure mainly stems from preclinical models

- Proteomics could yield additional insights in humans

- Paucity of human & population-based data linking proteomic markers to diabetes-related cardiac dysfunction .

**Ritchie RH, Abel ED.** *Circ Res.* **2020;126(11):1501-1525**
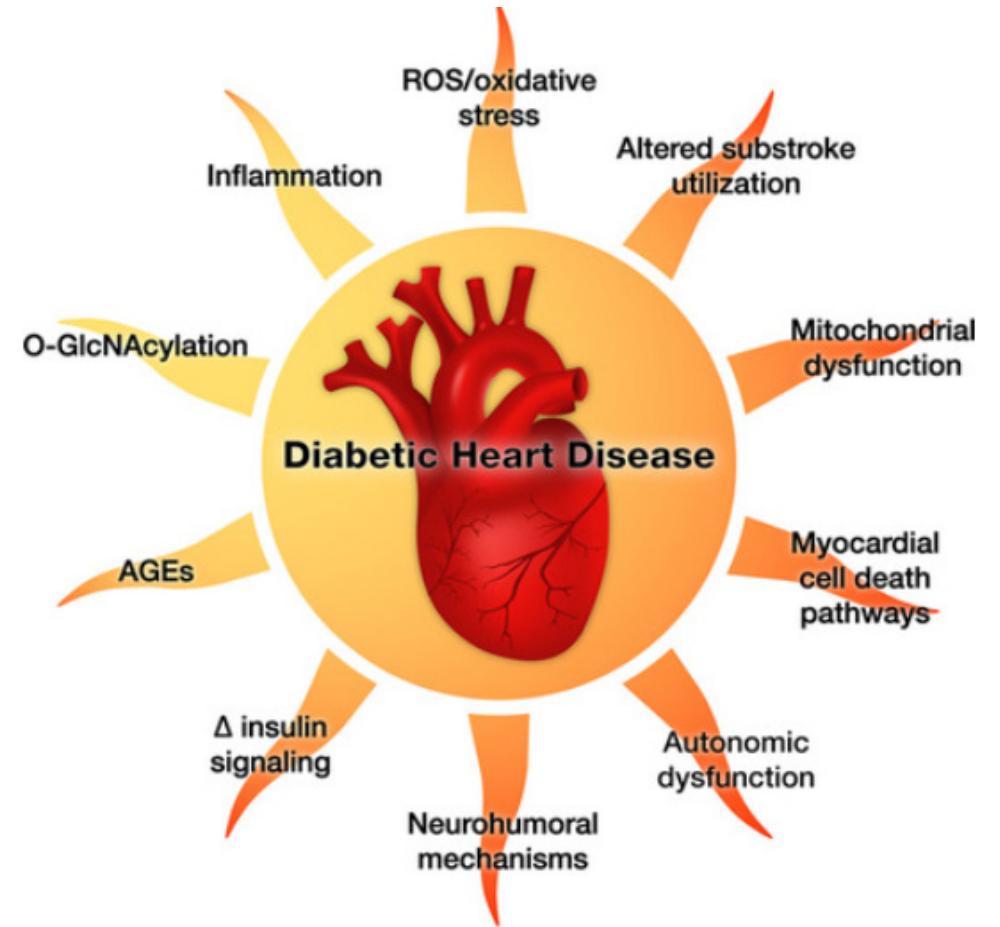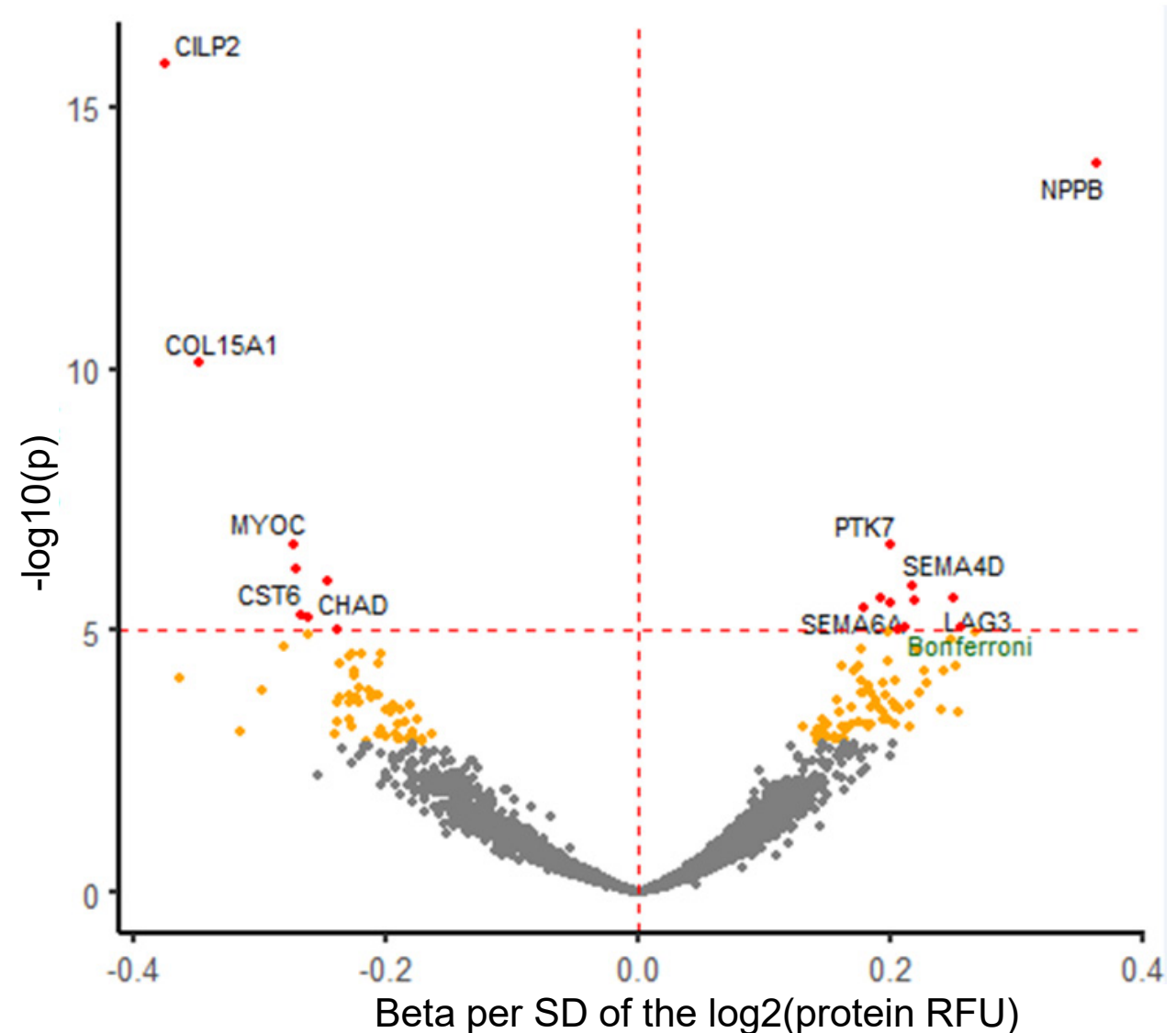
# Design of Analyses

- Cohort: 10,189 individuals, mean age 57 years, 78% Whites, 22% Blacks; 14.5% with diabetes

- Split sample validation:  2/3 Discovery (n= 6854)  & 1/3 validation (n= 3335

- Exposure : **4,955 proteins** assessed using the SOMAScan platform

- Incident heart failure over a median follow-up of 24 years  (2417 events overall, 605 among those with diabetes)

# Novel Proteins associated with Heart Failure in Diabetes

**ARIC**™

- Discovery (N with T2DM = 993)
  - **19 proteins identified**

- Validation (N with T2DM = 484)
  - **12 proteins validated internally**
  - Consistency with discovery sample

Volcano plot for incident heart failure

# Nine of the 12 HF-related Proteins linked to Prevalent Diabetes

| Protein Symbol | Protein Name | Association with Prevalent diabetes | Beta coefficient of association with diabetes | P Value |
|---|---|---|---|---|
| CILP2 | *Cartilage intermediate layer protein 2* | **Yes** | - 0.60 | 8.8E-36 |
| NPPB | *N-terminal pro-BNP* | No | - | - |
| COL15A1 | *Collagen alpha-1(XV) chain* | **Yes** | 0.58 | 6.6E-26 |
| PTK7 | *Inactive tyrosine-protein kinase 7* | **Yes** | 0.61 | 1.8E-37 |
| CHAD | *Chondroadherin* | **Yes** | -0.45 | 2.6E-22 |
| SEMA4D | *Semaphorin-4D* | **Yes** | 0.56 | 9.6E-30 |
| SEMA6A | *Semaphorin-6A* | **Yes** | 0.82 | 9.7E-58 |
| SEMA6B | *Semaphorin-6B* | **Yes** | 0.69 | 6.4E-46 |
| LINGO1 | *Leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 1* | **Yes** | 0.23 | 1.8E-11 |
| TNFRSF11B | *Tumor necrosis factor receptor superfamily member 11B* | **Yes** | 0.29 | 7.9E-11 |
| TXNDC5 | *Thioredoxin domain-containing protein 5* | No | - | - |
| FBLN5 | *Fibulin-5* | No | - | 6 |

# Preventing Heart Failure in Diabetes

# Stepwise Approach to Screening for Heart Failure in Diabetes

Pop-Busui R, et al. *Diabetes Care*. 2022;45(7):1670-1690.
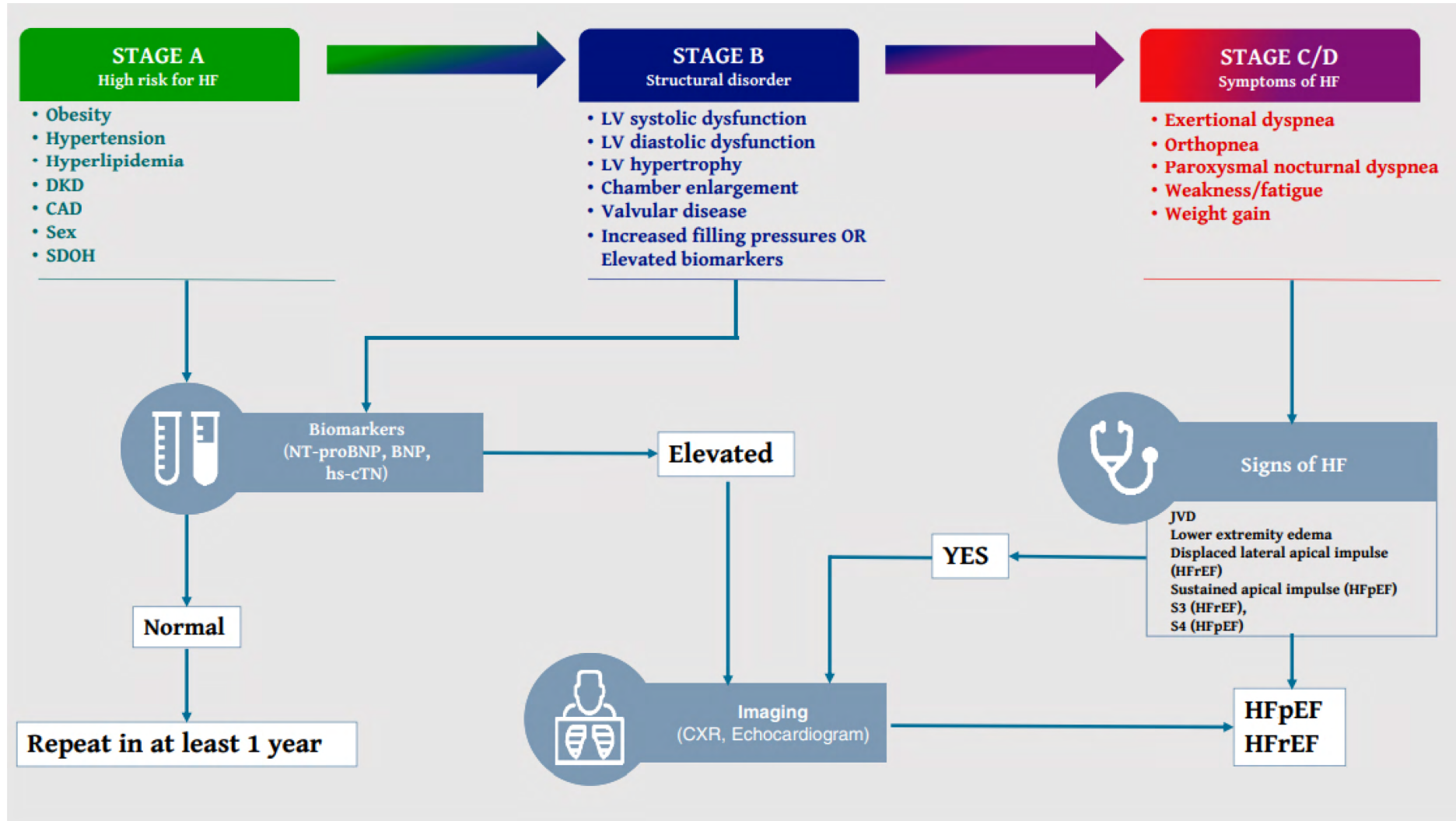
# Prevention of Heart Failure in Diabetes - Potential Challenges

- No trial of screening
  - evidence on the efficacy of detection and early treatment is indirect
  - most appropriate screening strategy unclear
  - no guarantee that implementation would lead to an improvement of outcomes

- Lack of trial data on strategies to treat early stages of heart failure- stage B
  - no approved  strategy to treat early stage of heart failure process
  - Potential therapies: RAAS inhibitors, β-blockers, SGLT2 inhibitors.

- Cost-effectiveness unexplored
  - Health system: delivers suboptimal diabetes and heart failure care
  - Need to strength health care system to enhance the value of screening
  - Resources needed to provide preventive interventions including lifestyle modification

# THANK YOU !

# Early-Stage Investigator Lecture (ESIL)

## Thank you for attending!

Our final 2023 lecture will be **June 7 at 11:00 a.m. ET:**

*Cardiometabolic Health and Cardiovascular Prevention in Latino Population*
Rodrigo M. Carrillo-Larco, M.D., Ph.D.

Register at prevention.nih.gov/ESIL

National Institutes of Health
Office of Disease Prevention