Congresso Regionale **SID-AMD**

Veneto-Trentino Alto Adige

NOVITÀ E CONTROVERSIE NELLA GESTIONE DEL DIABETE TIPO 1 E DEL DIABETE TIPO 2

Padova, 23 Novembre 2024

NH Padova

Programma

Il rischio cardiovascolare: focus sull'insufficienza cardiaca e suo trattamento con farmaci anti- iperglicemizzanti

Sandro Inchiostro

Direzione Percorso Aziendale
di Cura del Diabete
APSS – Trento

DICHIARAZIONE CONFLITTO DI INTERESSI

Il sottoscritto_____Inchiostro Sandro_____

In ottemperanza alla normativa ECM ed al principio trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, il ***docente deve "rilasciare al provider o all'organizzatore la dichiarazione di conflitto d'interessi (ultimi 2 anni rapporti diretti con aziende) e che successivamente debba informare l'aula all'atto della sua presentazione o comunque prima della lezione/relazione dichiarandolo ai discenti".***

Dichiara che negli ultimi due anni sono stato relatore o membro di board scientifico per eventi scientifici ECM, aventi il supporto incondizionato delle seguenti aziende:

Astra Zeneca

Bayer

Boehringer Ingelheim

Eli Lilly

Guidotti

Novo Nordisk

Sanofi Aventis

Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

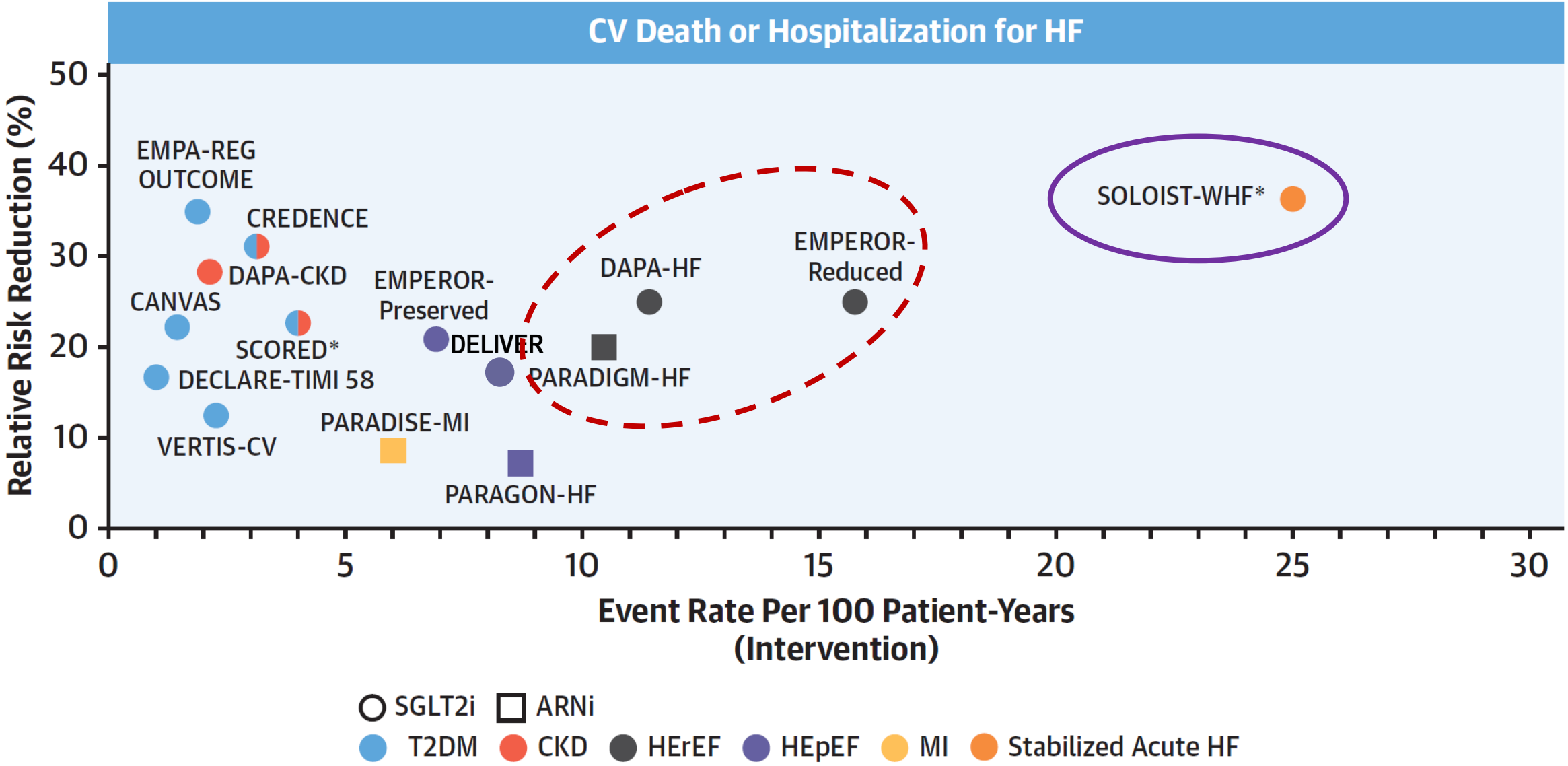
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

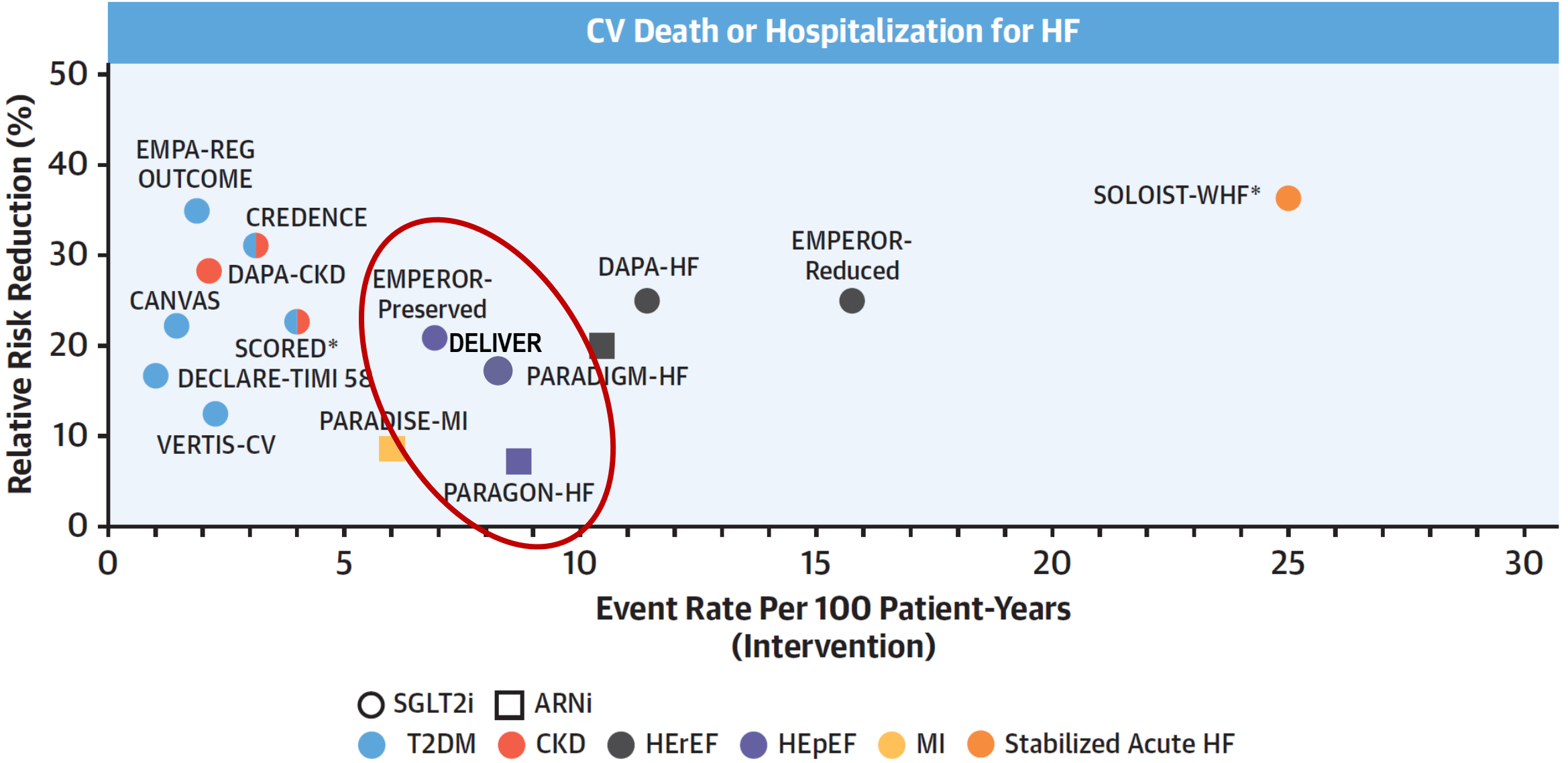
- ✓ The prevalence of HF appears to be 1- 2% of adults
- ✓ The prevalence increases with age:
  from around 1% for those aged <55 years to >10% in those aged 70 years or over
- ✓ About 50% have HFrEF, and 50% have HFpEF/HFmrEF
- ✓ In Western-type and developed countries, coronary artery disease and hypertension are predominant aetiologic factors
- ✓ With regard to ischaemic aetiology, HFmrEF resembles HFrEF, with a higher frequency of underlying CAD compared to those with HFpEF

ESC
European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)


CV Death or Hospitalization for HF
Relative Risk Reduction (%)
50
40
30
20
10
0
0
5
10
15
20
25
30
Event Rate Per 100 Patient-Years (Intervention)
EMPA-REG OUTCOME
CREDENCE
DAPA-CKD
CANVAS
SCORED*
DECLARE-TIMI 58
VERTIS-CV
EMPEROR-Preserved
DELIVER
PARADIGM-HF
PARADISE-MI
PARAGON-HF
DAPA-HF
EMPEROR-Reduced
SOLOIST-WHF*
SGLT2i
ARNi
T2DM
CKD
HErEF
HEpEF
MI
Stabilized Acute HF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DAPA-HF
EMPEROR-Reduced
SOLOIST-WHF*
SGLT2i
ARNi
T2DM
CKD
HErEF
HEpEF
MI
Stabilized Acute HF

SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Muthiah Vaduganathan, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*

SGLT2 inhibitors reduction of the risk of cardiovascular death and hospitalisations for heart failure independently from:

- ✓ Left Ventricular Ejection Fraction
- ✓ Age
- ✓ Sex
- ✓ Race
- ✓ Region
- ✓ NYHA functional class
- ✓ KCCQ—TSS
- ✓ NT-proBNP concentration
- ✓ KCCQ—TSS
- ✓ Diabetes status
- ✓ Body-mass index
- ✓ Kidney function
- ✓ Hospitalisation for heart failure in previous 12 months
- ✓ MRA
- ✓ ARNI

Lancet 2022; 400: 757–67

SGLT2 inhibitors as the bedrock of therapy for heart failure

The evolution of SGLT2 inhibitors from glucose-lowering agents to heart failure therapies is a rare story of serendipity. It began with a requirement by the US Food and Drug Administration in 2008 to show cardiovascular safety of new glucose-lowering agents after their regulatory approval for treatment of hyperglycaemia.[1] Although the initial focus was on cardiovascular safety, it became quickly apparent that SGLT2 inhibitors were not only safe, but they were also effective for reducing cardiovascular risk in type 2 diabetes. Important gains included substantially improving clinical outcomes for heart failure and chronic kidney disease.[2,3]

Research moved quickly to dedicated outcome trials for heart failure and chronic kidney disease in patients

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https://doi.org/10.1016/
S0140-6736(22)01584-7

See Articles page 757

Heart failure with preserved ejection fraction

Definition of HFpEF is: clinical diagnosis of HF and LVEF >50% due to a cardiac aetiology that is not attributable to an alternative underlying cause such as an infiltrative cardiomyopathy, hypertrophic cardio-myopathy, valvular disease, pericardial disease or high-output HF.

- Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of all cases of heart failure[26]
- HFpEF prevalence increases with age[29]
- HFpEF prevalence is greater in women than in men[31]
- Lifetime risk of HFpEF is 24% in the USA[38]
- 5-year mortality is 53–74% for hospitalized patients with HFpEF[5,41,63,64]
- Patients with HFpEF have a lower risk of all-cause death than patients with heart failure with reduced ejection fraction (HFrEF)[23,67–69]
- HFpEF accounts for a higher proportion of non-cardiovascular-related deaths than HFrEF[64,70–72]
- Among cardiovascular-related deaths: 43% sudden cardiac death and 20–30% heart failure death[71]
- HFpEF has a higher or equal rate of hospitalization compared with HFrEF[41,78–80]

Obesity has a prevalence of ~ 80% among individuals with HFpeEF.

Nature Reviews Disease Primers | (2024) 10:55

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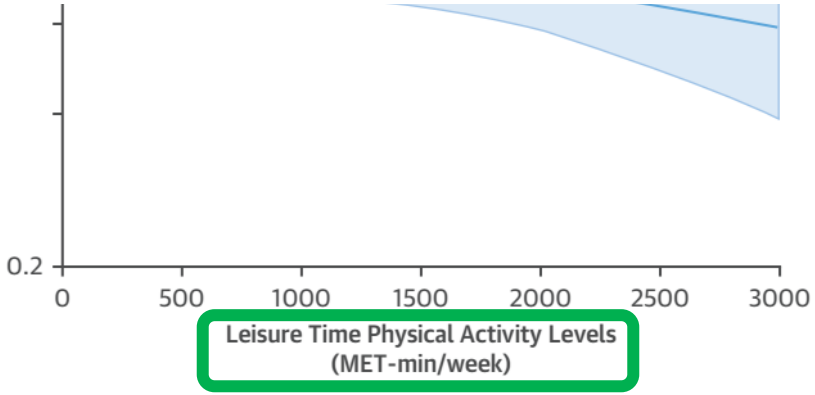
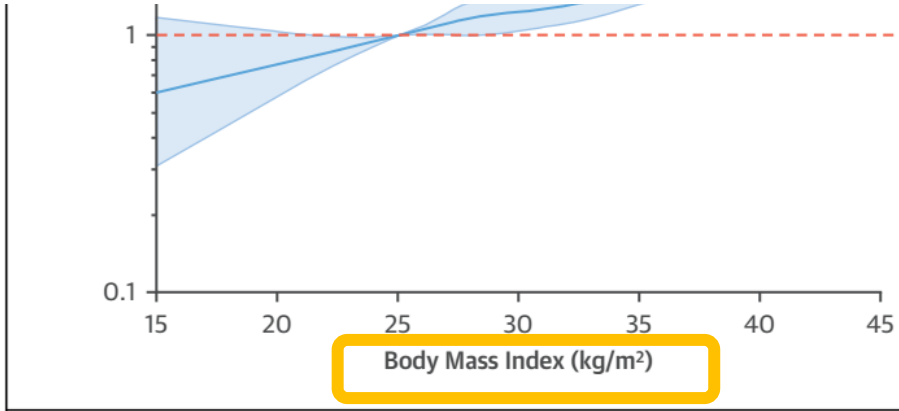
SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure

Ambarish Pandey, MD,[a] Michael LaMonte, PhD, MPH,[b] Liviu Klein, MD, MS,[c] Colby Ayers, MS,[a,d] Bruce M. Psaty, MD, PhD,[e] Charles B. Eaton, MD, MS,[f] Norrina B. Allen, PhD,[g] James A. de Lemos, MD,[a] Mercedes Carnethon, PhD,[g] Philip Greenland, MD,[g] Jarett D. Berry, MD, MS[a,d]



J Am Coll Cardiol 2017;69:1129–42



The NEW ENGLAND JOURNAL of MEDICINE

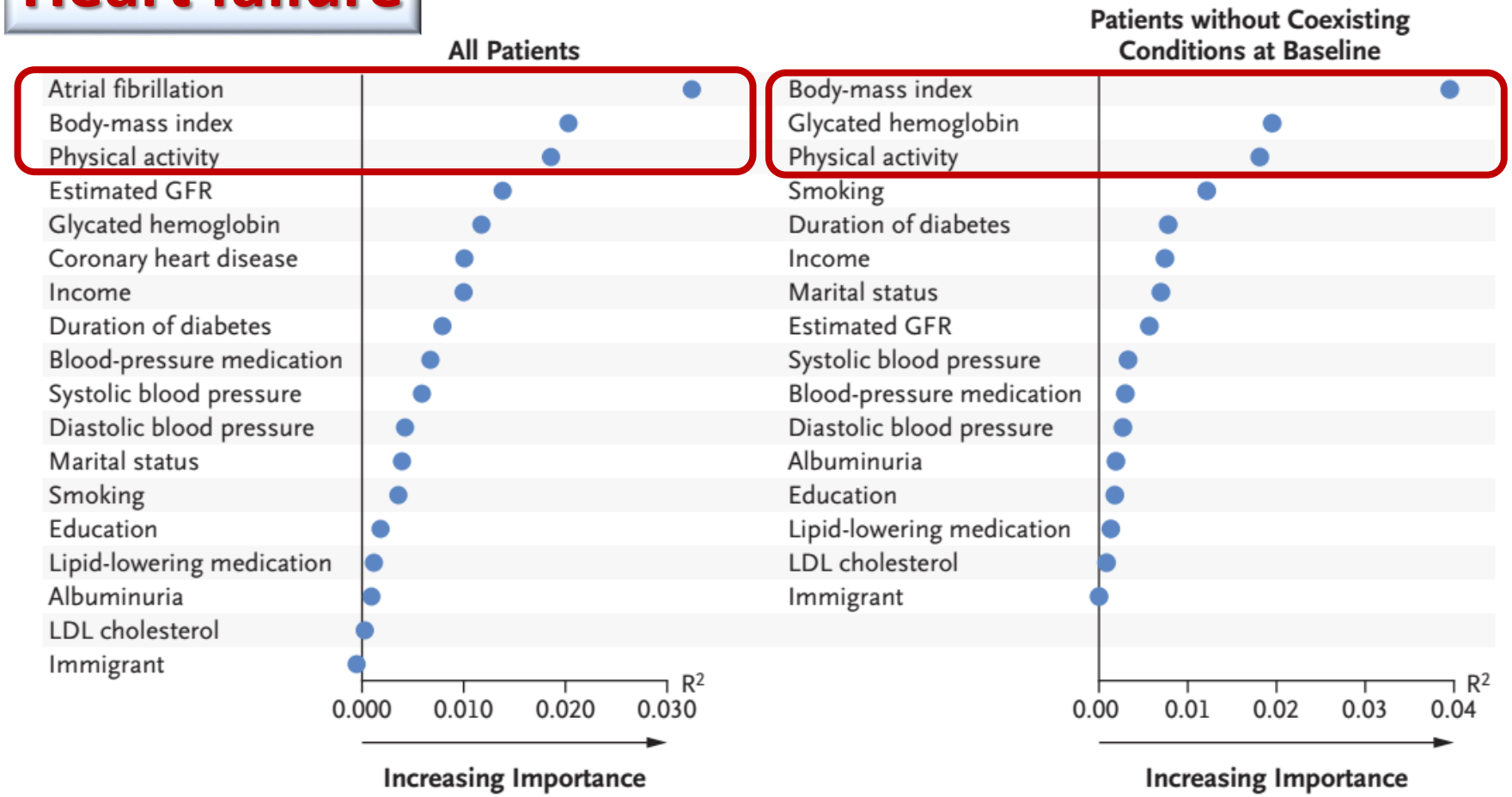
N Engl J Med 2018;379:633-44.

ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

Heart failure



Excess adiposity (especially visceral)

INFLAMMATION

→ systemic, epicardial, perivascular
→ fibrosis
→ stiffness
→ reduced capillary density
→ reduced NO
→ reduced vasodilatation
→ ischemia
→ impaired relaxation, stiffness

HAEMODINAMIC

→ vasodilation
→ neurohormonal activation
→ volume expansion
→ ventricular hypertrophy

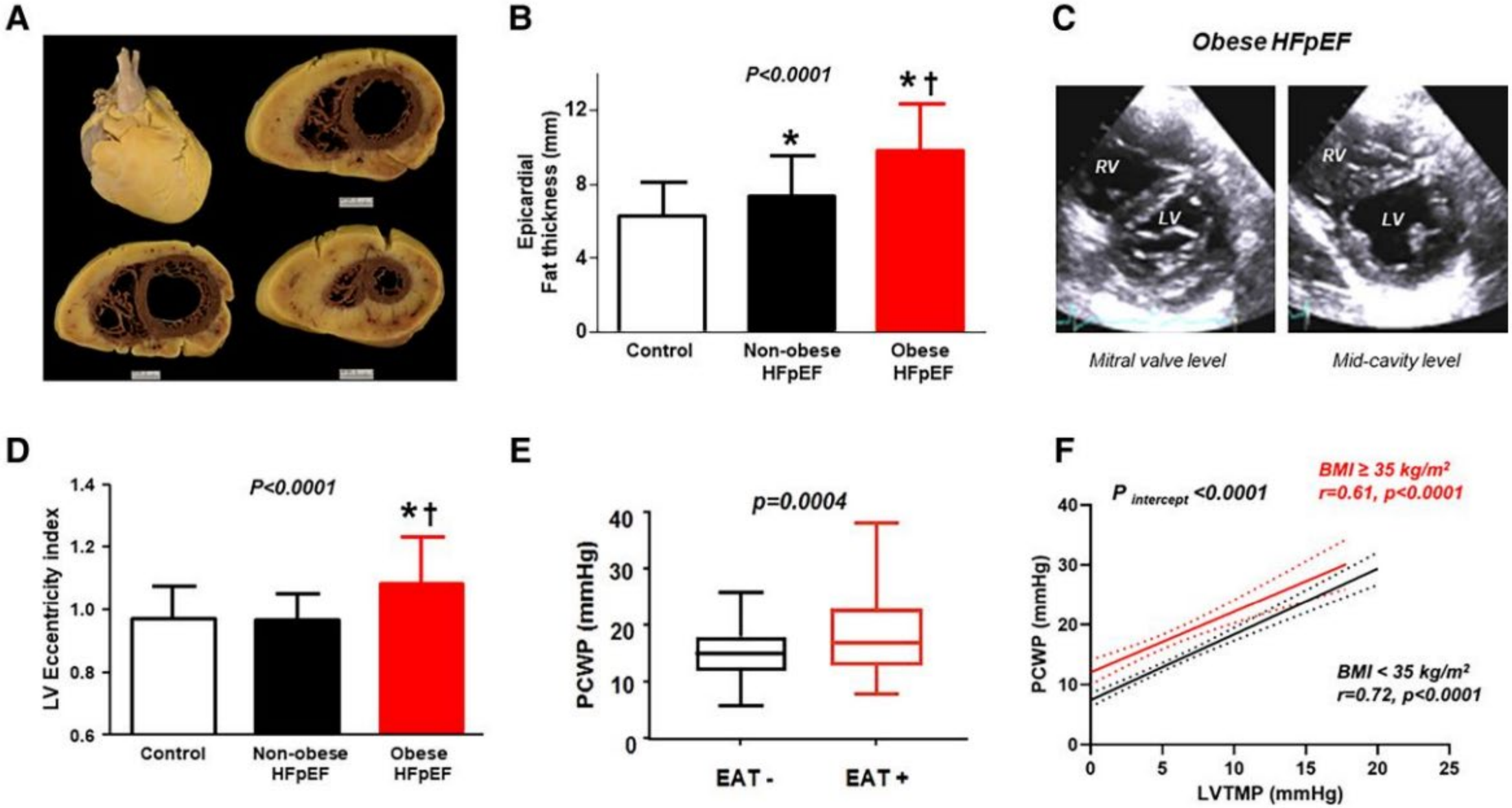
MECHANICAL CONSTRAINT

→ increased epicardial and chest wall fat
→ increased external pressure
→ ventricular interdipendence
→ increased ventricular pressure

HEART FAILURE WITH PRESERVED EJECTION FRACTION

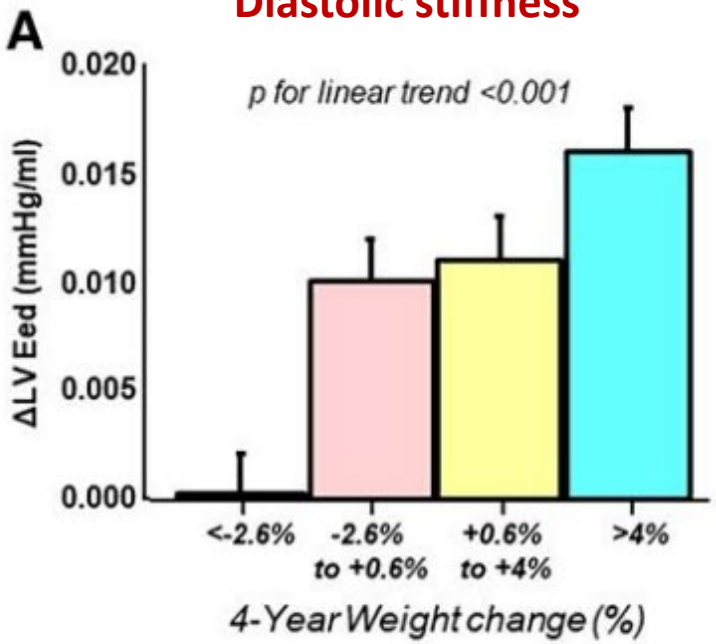
REDUCED ENERGETIC EFFICIENCY

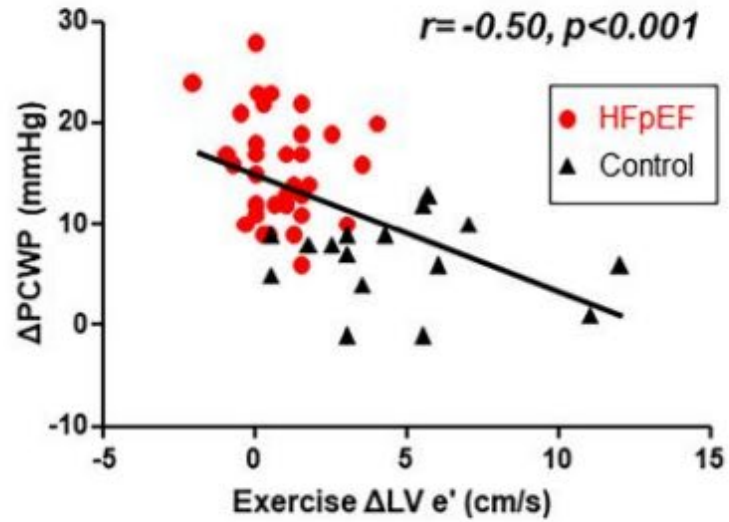
→ metabolic shift
→ mitochondrial and metabolic defect
→ reduced ATP production
→ sarcomere disfunction
→ Altered diastolic (and subclinical sistolic) function

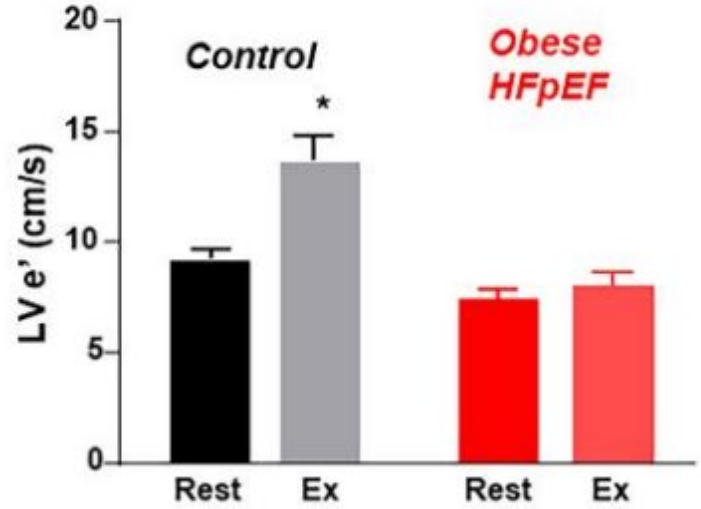

A
B
P<0.0001
*†
*
Epicardial Fat thickness (mm)
12
8
4
0
Control
Non-obese HFpEF
Obese HFpEF
C
Obese HFpEF
RV
LV
RV
LV
Mitral valve level
Mid-cavity level
D
P<0.0001
*†
LV Eccentricity index
1.4
1.2
1.0
0.8
0.6
Control
Non-obese HFpEF
Obese HFpEF
E
p=0.0004
PCWP (mmHg)
40
30
20
10
0
EAT -
EAT +
F
P intercept <0.0001
BMI ≥ 35 kg/m²
r=0.61, p<0.0001
BMI < 35 kg/m²
r=0.72, p<0.0001
PCWP (mmHg)
40
30
20
10
0
0
5
10
15
20
25
LVTMP (mmHg)

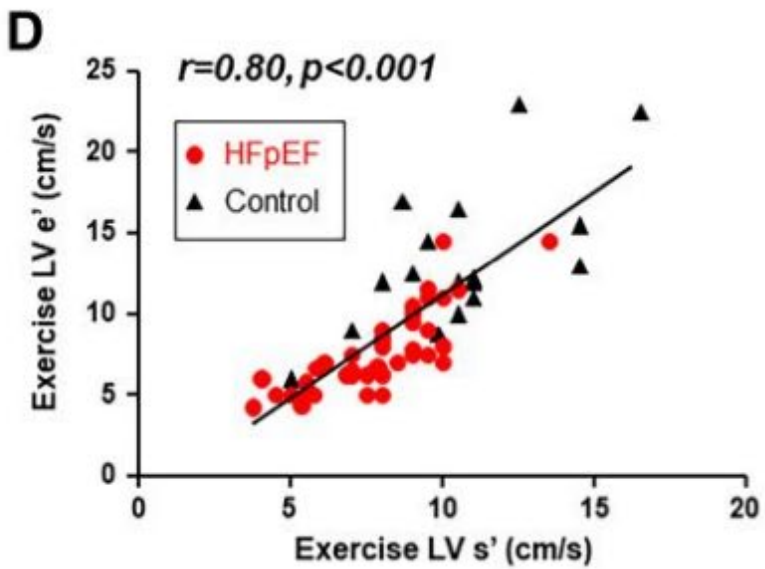
Diastolic stiffness

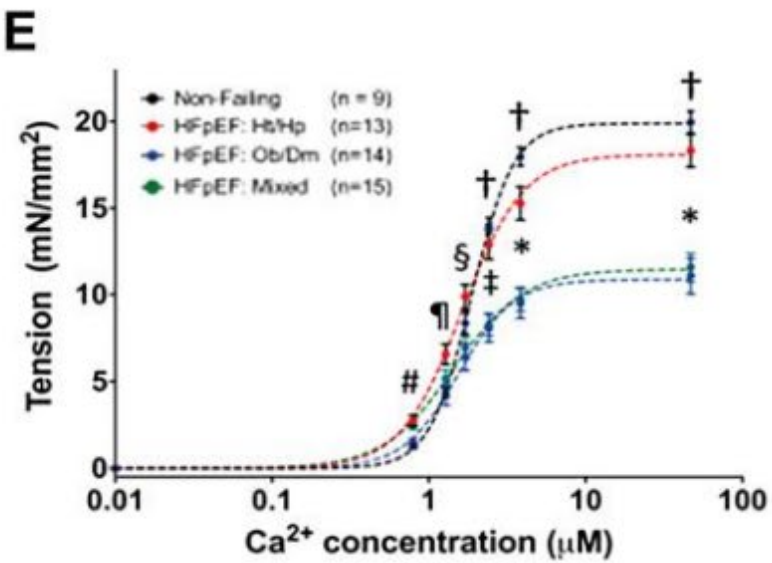
LV early diastolic relaxation velocity vs pulmonary capillary wedge pressure (PCWP)

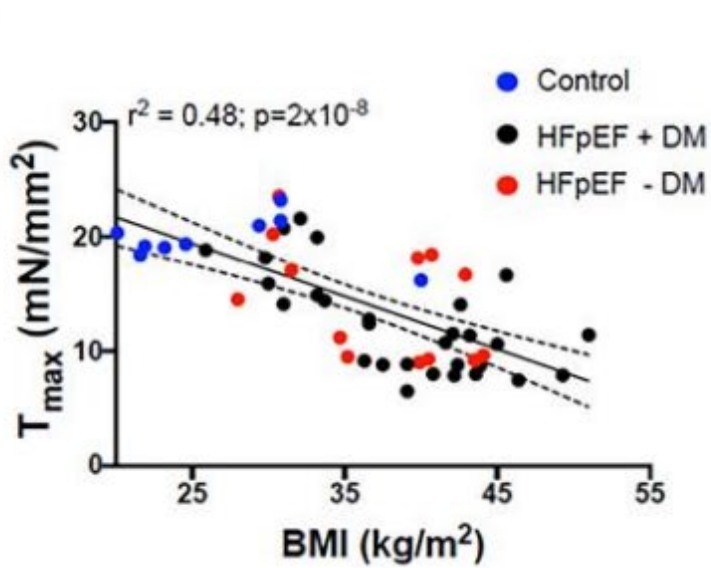




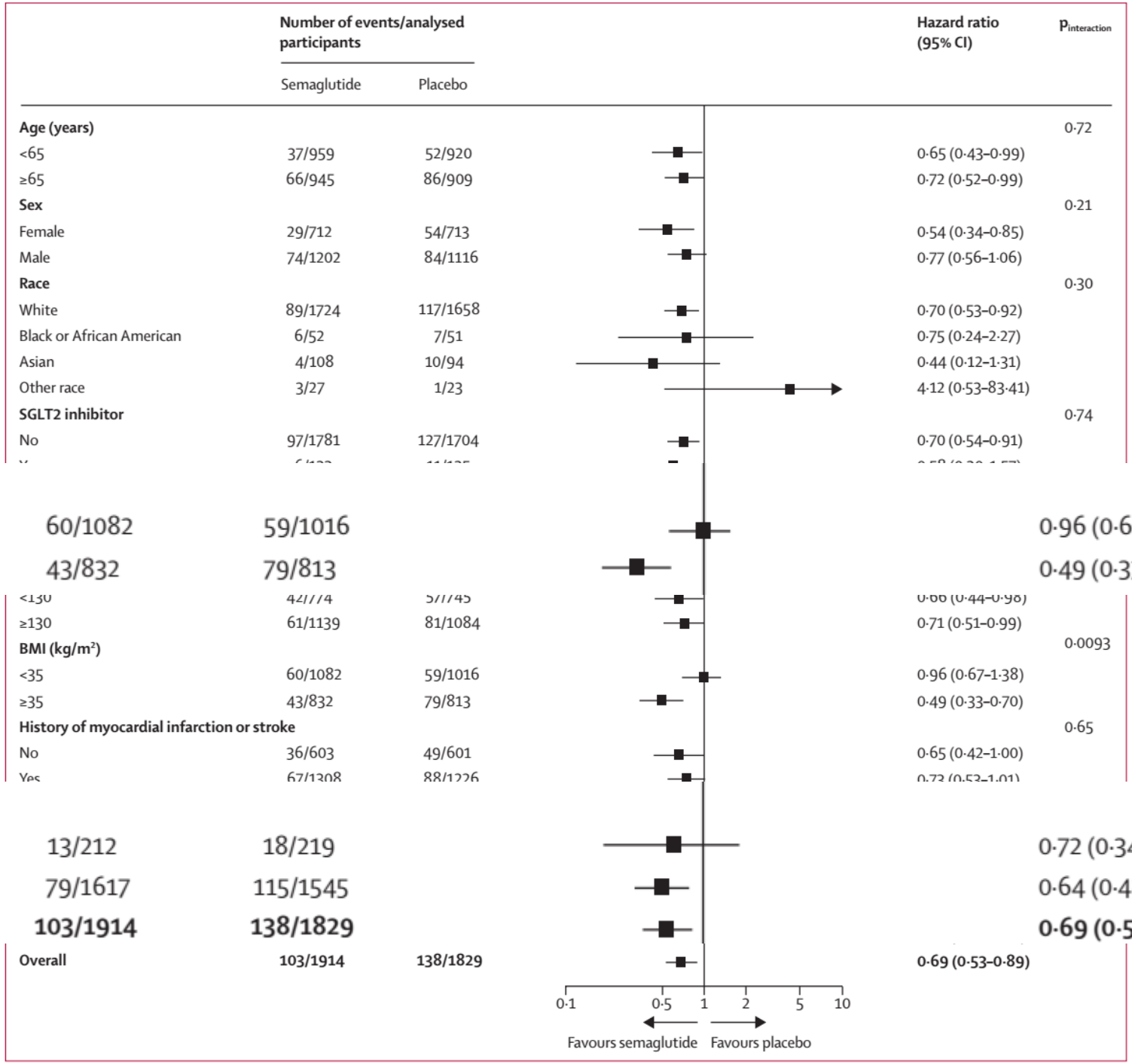








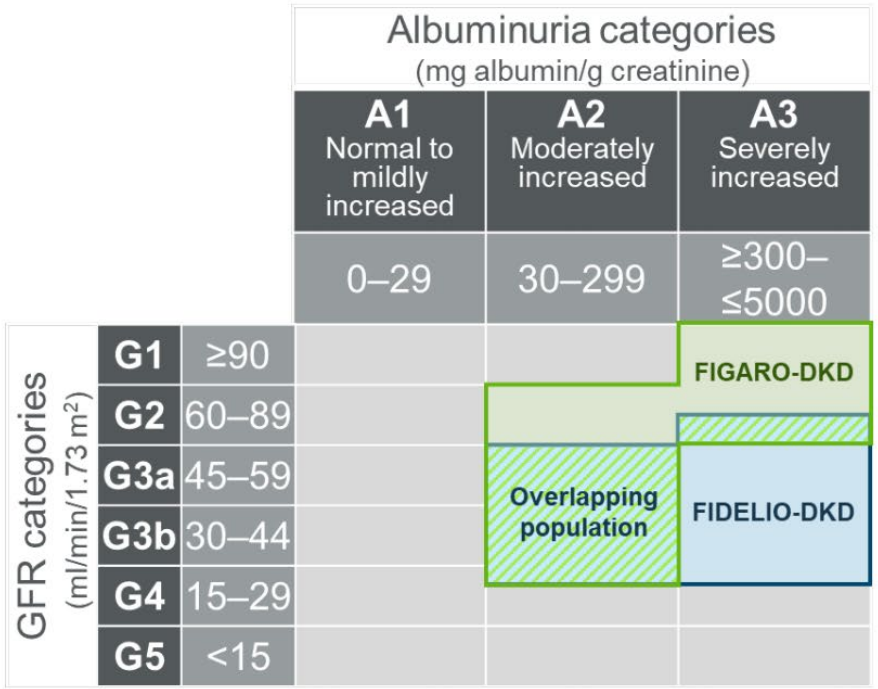
Lancet 2024; 404: 949–61



ESC European Society of Cardiology
European Heart Journal (2022) **43**, 474–484
https://doi.org/10.1093/eurheartj/ehab777

European Heart Journal (2022) 43, 474–484

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



FIGARO-DKD

- UACR ≥30–<300 mg/g and eGFR ≥25–≤90 ml/min/1.73 m²*
- UACR ≥300–≤5000 mg/g) and eGFR ≥60 ml/min/1.73 m²

FIDELIO-DKD

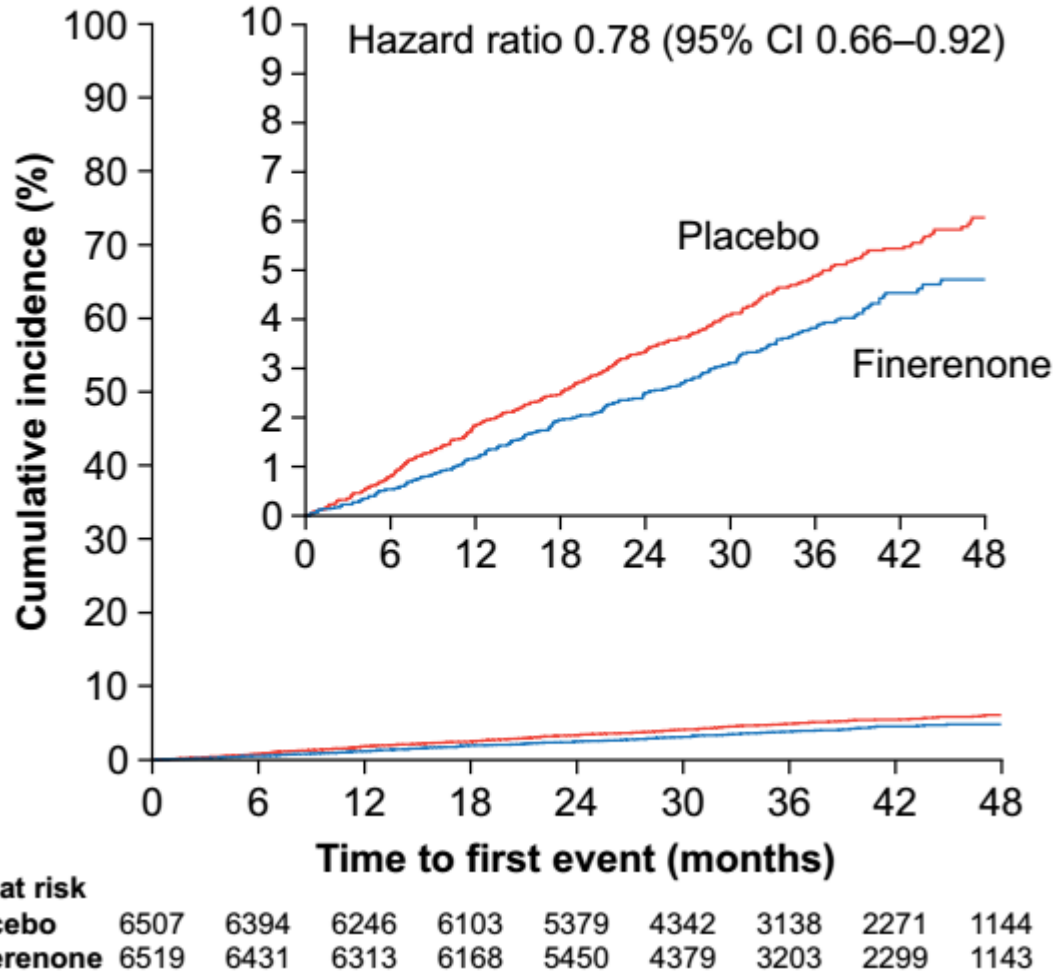
- UACR ≥30–<300 mg/g and eGFR ≥25–<60 ml/min/1.73 m² and history of diabetic retinopathy§
- UACR ≥300–≤5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m²†

ESC European Society of Cardiology
European Heart Journal (2022) 43, 474–484
https://doi.org/10.1093/eurheartj/ehab777
FASTTRACK CLINICAL RESEARCH
Diabetes and metabolic disorders

European Heart Journal (2022) 43, 474–484

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

D Hospitalization for heart failure



2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

FINEARTS-HF

- ✓ **Patients with heart failure and a left ventricular ejection fraction of 40% or greater, in a 1:1 ratio, to receive finerenone (at a maximum dose of 20 mg or 40 mg once daily) or matching placebo, in addition to usual therapy.**
- ✓ **Primary outcome was a composite of total worsening heart failure events (with an event defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure) and death from cardiovascular causes.**
- ✓ **6001 patients were included in the efficacy analysis; 2439 were diabetics (40.6%).**
- ✓ **Follow-up of 32 months**

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 3627–3639
https://doi.org/10.1093/eurheartj/ehad195

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Grazie per l'attenzione!

Circulation

Circulation. 2024;149:450–462.

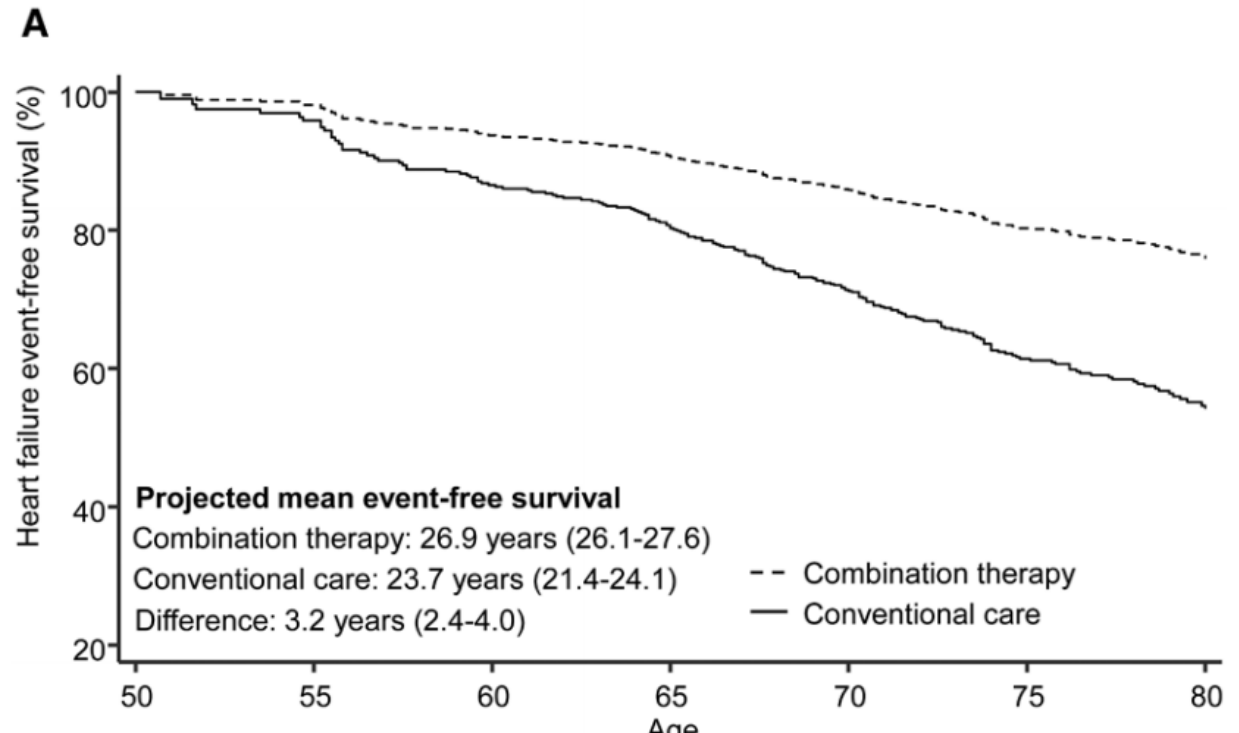
ORIGINAL RESEARCH ARTICLE

Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria

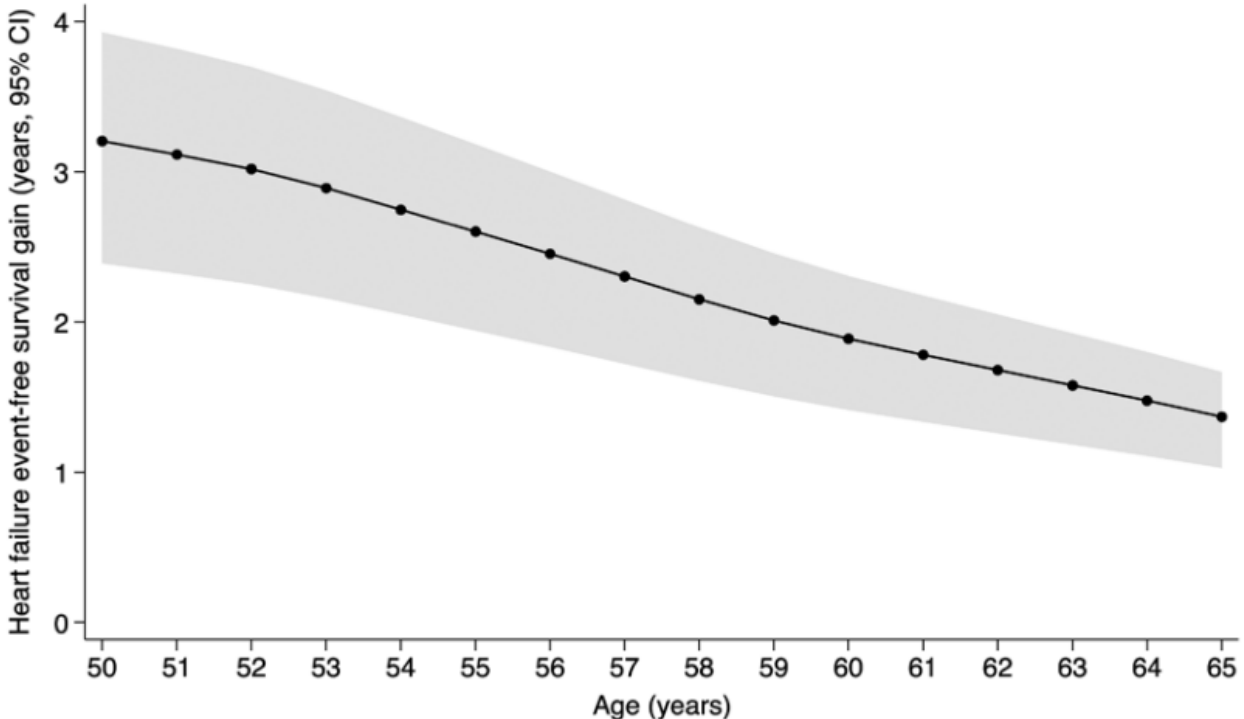
Brendon L. Neuen, MBBS, MSc, PhD; Hiddo J.L. Heerspink, PhD; Priya Vart, PhD; Brian L. Claggett, PhD; Robert A. Fletcher, MSc; Clare Arnott, MBBS, PhD; Julianna de Oliveira Costa, PhD; Michael O. Falster, PhD; Sallie-Anne Pearson, PhD; Kenneth W. Mahaffey, MD; Bruce Neal, MB ChB, PhD; Rajiv Agarwal, MD; George Bakris, MD; Vlado Perkovic, MBBS, PhD; Scott D. Solomon, MD; Muthiah Vaduganathan, MD, MPH

Survival free from from hospitalization for heart failure

Event-free survival among people 50 years of age at baseline



Gains in event-free survival by for every age between 50 and 65 years.



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 68, NO. 1, 2016

ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.03.597

Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes

Eylem Levelt, MBBS, DPhil,[a,b] Michael Pavlides, MBBS,[a,c] Rajarshi Banerjee, BMBCh, DPhil,[d] Masliza Mahmod, DPhil,[a] Catherine Kelly, PhD,[d] Joanna Sellwood, BSc,[a] Rina Ariga, MBBS, BSc,[a] Sheena Thomas, PgC, BsC, BA,[e] Jane Francis, DCR(R), DNM,[a] Christopher Rodgers, MChem, DPhil,[a] William Clarke, MChem,[a] Nikant Sabharwal, BSc, BM, BCh, DM,[f] Charalambos Antoniades, MD, PhD,[e] Jurgen Schneider, PhD,[a] Matthew Robson, PhD,[a] Kieran Clarke, PhD,[b] Theodoros Karamitsos, MD, PhD,[a] Oliver Rider, BMBCh, DPhil,[a] Stefan Neubauer, MD[a,d]

BACKGROUND Type 2 diabetes (T2D) and obesity are associated with nonalcoholic fatty liver disease, cardiomyopathy, and cardiovascular mortality. Both show stronger links between ectopic and visceral fat deposition, and an increased cardiometabolic risk compared with subcutaneous fat.

OBJECTIVES This study investigated whether lean patients (Ln) with T2D exhibit increased ectopic and visceral fat deposition and whether these are linked to cardiac and hepatic changes.

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Ectopic and Visceral Fat Deposition in Lean and Obese Patients With Type 2 Diabetes

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TABLE 1 Clinical and Biochemical Characteristics

	Normal Control Subjects (n = 12)	Lean T2D Patients (n = 15)	Obese T2D Patients (n = 27)	p Value
Age, yrs	50 ± 10	56 ± 9	56 ± 8	0.163
BMI, kg/m^2	23 ± 3	23 ± 2	33 ± 3*	<0.001
Male	58	60	40	0.35
Diabetes duration, yrs	–	6.1 ± 4.7	6.6 ± 6.5	0.78
Heart rate, beats/min	66 ± 10	65 ± 7	69 ± 7	0.34
Systolic blood pressure, mm Hg	118 ± 14	131 ± 7†	130 ± 9†	0.002
Diastolic blood pressure, mm Hg	70 ± 8	76 ± 7	76 ± 7	0.05
Plasma fasting glucose, mmol/l	5.0 ± 0.5	8.1 ± 3.0†	9.5 ± 3.3†	0.001
Glycated hemoglobin, %	–	7.4 ± 0.9	7.7 ± 1.4	0.22

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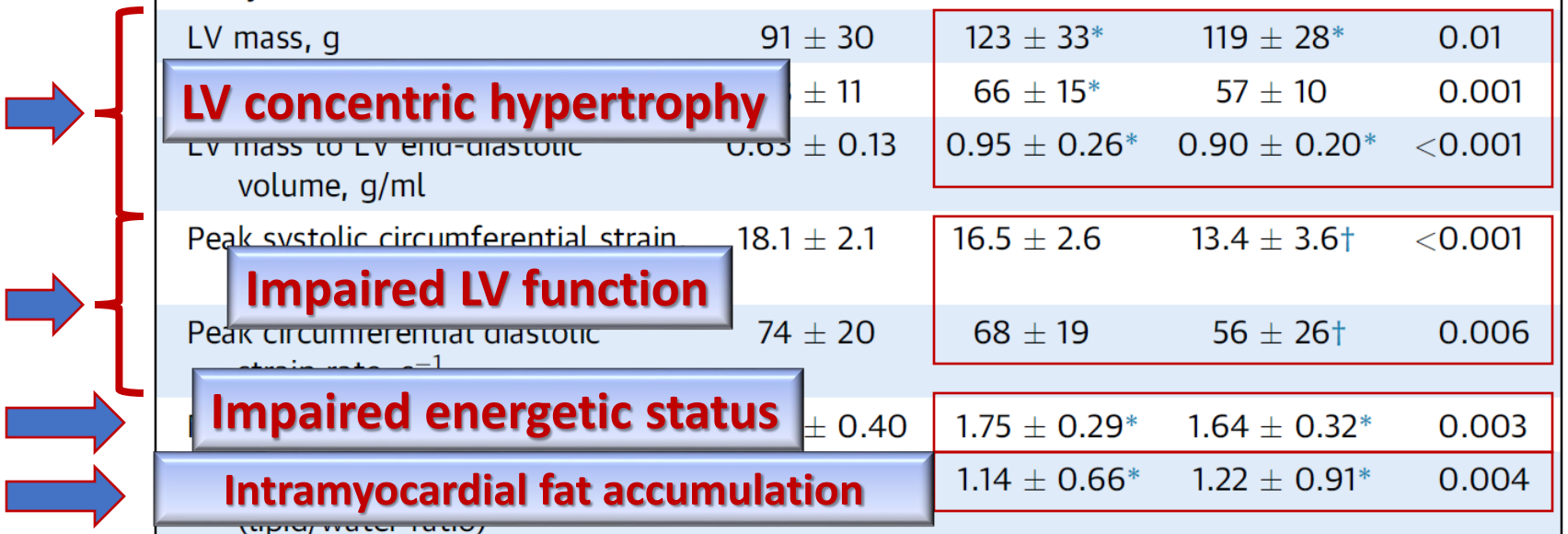
TABLE 2 CMR and Cardiac MRS Findings

	Control Subjects (n = 12)	Lean T2D Patients (n = 15)	Obese T2D Patients (n = 27)	p Value
LV end-diastolic volume, ml	145 ± 40	124 ± 33	126 ± 25	0.15
LV ejection fraction, %	68 ± 5	73 ± 7	68 ± 8	0.11
LV mass, g	91 ± 30	123 ± 33*	119 ± 28*	0.01
	± 11	66 ± 15*	57 ± 10	0.001
LV mass to LV end-diastolic volume, g/ml	0.63 ± 0.13	0.95 ± 0.26*	0.90 ± 0.20*	<0.001
Peak systolic circumferential strain	18.1 ± 2.1	16.5 ± 2.6	13.4 ± 3.6†	<0.001
Peak circumferential diastolic strain rate, s⁻¹	74 ± 20	68 ± 19	56 ± 26†	0.006
	± 0.40	1.75 ± 0.29*	1.64 ± 0.32*	0.003
(lipid/water ratio)		1.14 ± 0.66*	1.22 ± 0.91*	0.004

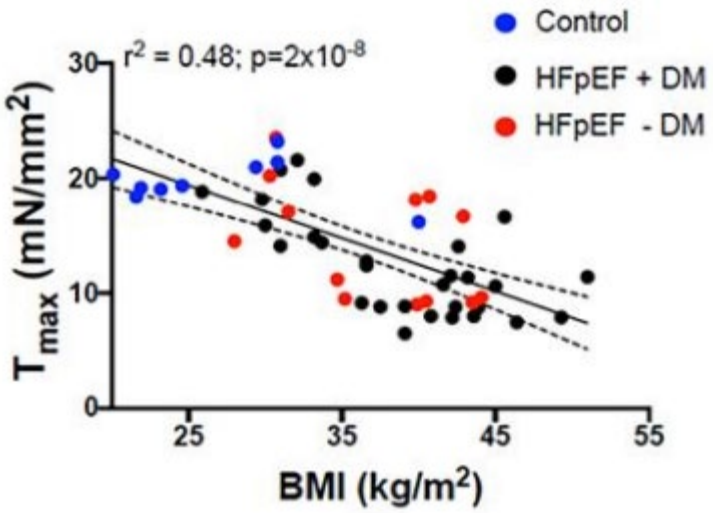
Values are mean ± SD. *p < 0.05 versus control subjects with Bonferroni correction. †p < 0.05 versus lean patients with T2D and control subjects with Bonferroni correction.

CMR = cardiac magnetic resonance; LV = left ventricular; MRS = magnetic resonance spectroscopy; PCr/ATP = phosphocreatine to adenosine triphosphate concentration ratio; T2D = type 2 diabetes.



LV hypertrophic remodelling,
increases in chamber stiffness,
prolonged myocardial relaxation,
altered substrate utilization,
reduced myocardial ATP availability,
mild systolic ventricular dysfunction.
Obesity is also associated with
volume expansion,
neurohormonal activation,
systemic inflammation,
dysfunction of multiple extra-cardiac organ systems of relevance to HFpEF, including skeletal muscle, liver, and kidney.

maximal tension development (Tmax) at the level of the sarcomere



higher cardiac output and total blood volume
(TBV) resulting from increased fat mass that accompanies obesity leads to LV cavity dilatation and subsequent hypertrophy secondary to increased wall stress. Although this accounts for an eccentric hypertrophic pattern, it is evident that concentric remodelling occurs commonly in obesity.
LV diastolic function assessed using echocardiography is impaired in patients with obesity, and weight gain is strongly correlated with increasing diastolic chamber stiffness over time

Haemodinamic → **vasodilation, volume expansion, neurohormonal activation,** → **ventricular hypertrophy,**

Excess adiposity (especially visceral) → **systemic , epicardial, perivascular inflammation** (fat) –>
proinflammatory citokines → fibrosis, reduced capillary density;
reduced NO → reduced vasodilatation → ischemia → i

Epicardial, intratoracic fat fat → Mechanical constraint → Ventricular interdipendence

Biochemical alteration → reduced energetic efficiency, reduced ATP production

Altered sarcomeric action → left ventricular increased pressure—> increased atrial pressure, increased pulmonar capillary pressure, increased artery pulmonar and RV pressure → sign and symptoms of Heart failure

INSUFFICIENZA CARDIACA A FRAZIONE D'EIEZIONE RIDOTTA