Παθοφυσιολογικοι μηχανισμοί που συνδέουν ΣΔ με καρδιακή ανεπάρκεια. Υπάρχει πρόληψη;

Χριστίνα Χρυσοχόου

Καρδιολόγος, Δ/ντρια ΕΣΥ

Α Πανεπιστημιακή Καρδιολογική Κλινική, ΙΓΝΑ

Cardiovascular diseases (CVDs), especially heart failure (HF), in T2D impose substantial and growing burden on patients, society, and healthcare systems

a	Diabetes is a disease of epidemic proportions with a projected increase in worldwide prevalence from 463 million in 2019 to 693 million by 2045
b	T2D patients are at high risk of developing CVD, up to 46% of diabetic patients will develop CVD in their lifetime, and CVD is responsible for ~50% of mortality in T2D
c	HF is one of the earliest, most common and serious CV complications in T2D, affecting ~30% of T2D patients, and leads to striking deterioration in patients' clinical course marked by frequent hospitalizations
d	In the past, myocardial infarction and stroke were the primary focus of clinicians; however, the paradigm is now shifting as the growing burden of HF among T2D patients requires urgent action
e	CV complications are costly, accounting for 20%-49% of total T2D treatment costs worldwide, and increasing the average cost of treatment by up to $9,705 compared to patients with T2D alone
f	HF-related costs are substantial and contribute to the growing economic burden of T2D management

- Each 1% increase in HbA1c was associated with an 8% increased risk of HF
- In the EuroHeart Failure survey, the prevalence of diabetes was 16–26% in Northern, 18–35% in Western, 12–46% in Central European, and 14–37% in Mediterranean countries

Table 2 Associations of cardiac and non-cardiac co-morbidities with heart failure

Co-morbidity	Risk factor for HF	Negative effect on LV structure/ function	Worsening of HF outcomes	Improvement of HF symptoms/outcomes with specific treatment
Hypertension	+++	+++	HFpEF (+++) HFrEF (–/+)	+++
Myocardial infarction	+++	+++	+++	+++
Atrial fibrillation	+++	+++	+++	+/–
Chronic obstructive pulmonary disease	++	++	++	+/–
Anaemia/iron deficiency	+	++	++	+
Diabetes	++	++	++	+/–
Renal dysfunction	+++	++	++	+/–
Sleep-disordered breathing	+	++	++	+/–
Obesity	++	++	+/–	+/–
Depression	+	+	++	+/–

+++: definite; ++: probable; +: possible; +/– doubtful.
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

EUROPEAN SOCIETY OF CARDIOLOGY®
European Journal of Heart Failure (2016) **18**, 744–758
doi:10.1002/ejhf.600

REVIEW

Reframing the association and significance of co-morbidities in heart failure

Filippos Triposkiadis[1]*, Gregory Giamouzis[1], John Parissis[2], Randall C. Starling[3], Harisios Boudoulas[4], John Skoularigis[1], Javed Butler[5], and Gerasimos Filippatos[2]

Table 5 Type 2 diabetes mellitus and all-cause mortality in clinical trials of heart failure

Clinical trial	Year of publication	Treatment	Total patients, *n*	Patients with T2DM, *n*	Adjusted all-cause mortality risk of T2DM*	Adjusted CV mortality risk of T2DM*
HFrEF trials						
PARADIGM-HF[31,69]	2016	Sacubitril/ valsartan	8399	2907	1.46 (1.26–1.70)	1.54 (1.30–1.83)
SHIFT[32]	2010	Ivabradine	6505	1979	1.10 (0.96–1.25)	1.05 (0.91–1.20) Mortality due to HF: 1.15 (0.88–1.49)
EchoCRT[33]	2013	CRT	809	328	2.08 (1.29–3.36)	1.79 (1.06, 3.03) Mortality due to HF: 2.45 (1.03–5.78)
HF-ACTION[34]	2016	Exercise	2331	748	0.97 (0.78–1.2)	NA
SENIORS[35]	2010	Nebivolol	2128	555	1.25 (0.99–1.58)	NA
SOLVD[88]	1996	Enalapril	4223	647	1.29 (1.1–1.5)	NA
MERIT-HF[37]	2005	Metoprolol	3991	985	1.08 (0.80–1.47)	NA
CHARM[1]	2008	Candesartan	4576	1306	1.55	1.54
HFpEF trials						
DIG-Preserved[42,89]	2010	Digoxin	987		1.48 (1.10–1.99)	NA
I-Preserve[40,90]	2017	Irbesartan	4128	1134	1.59 (1.33–1.91)	1.59 (1.28–1.96)
CHARM[1,91]	2008	Candesartan	3023	857	1.84	1.93
TOPCAT[44]	2017	Spironolactone	3385	1109	Without microvascular complications: 1.51 (1.14–1.99) With microvascular complications: 1.35 (1.04–1.75)	NA
Acute HF trials						
EVEREST[45,92]	2013	Tolvaptan	4133	1657	1.16 (1.00–1.34)	NA

Patients with heart failure have similar pathophysiological features as patients with diabetes

Heart failure

Impaired contractility

Cardiomyocyte apoptosis/fibrosis

Neurohormonal activation

LV remodelling

Shared pathological features

Endothelial dysfunction

Insulin resistance

Mitochondrial dysfunction

RAAS activation

Inflammation

Diabetes

Hyperglycaemia

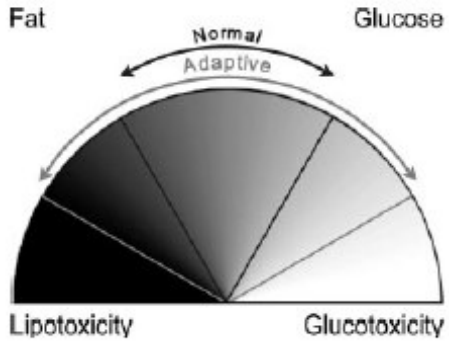
↓ Pancreatic beta-cell function

Advanced glycated end-product toxicity

Neuronal degeneration/ demyelination

Diabetes and vessel wall remodeling

- Αύξηση πάχους έσω μέσου χιτώνα και αυξημένη εναπόθεση κολλαγόνου
- Μειωμένη διατασιμότητα αρτηριών
- Διαστολική δυσλειτουργία αριστερή κοιλίας (ΣΔ τύπου ΙΙ)
- Ο έλεγχος της Hba1c βελτιώνει την μικροαγγειοπάθεια αλλά όχι την μακροαγγειοπάθεια



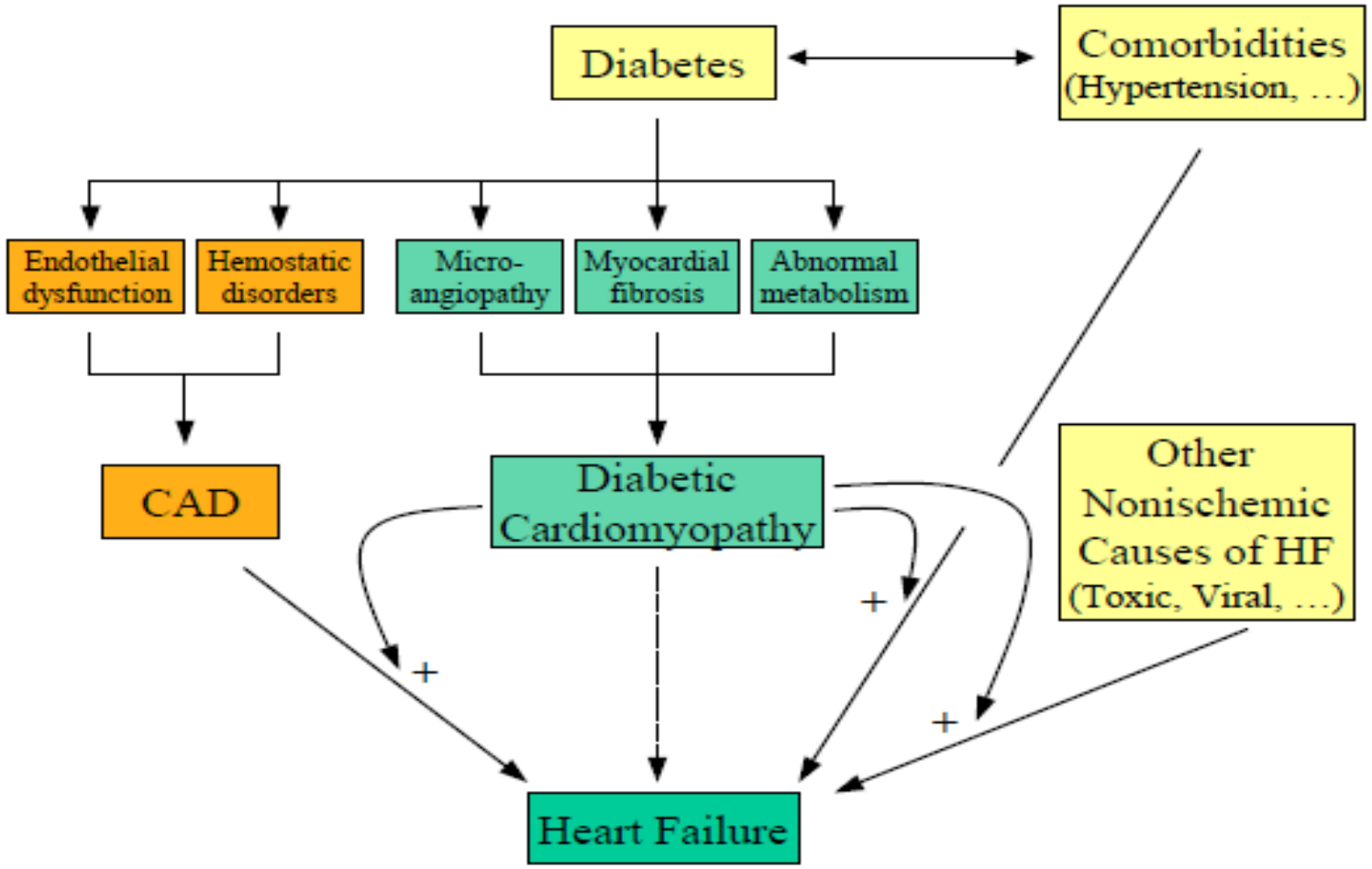
Διαταραχή στη γλυκόλυση και οξείδωση γλυκόζης, οδηγεί σε μειωμένη μεταφορά γλυκόζης στο μυοκαρδιακό κύτταρο (έλλειψη υποδοχέων GLUTs), μειωμένη παραγωγή ATP (αναστολή από την β οξείδωση λόγω υψηλών FFA)

Η διαταραχή στην οξείδωση της γλυκόζης από τα υψηλά επίπεδα FFA είναι η κύρια αιτία της διαβητικής καρδιοπάθειας

Η συστολική εφεδρεία της αριστερής κοιλίας είναι μειωμένη

Cardiovasc Res. 2008 May 1; 78(2): 265

Μηχανισμοί πρόκλησης καρδιακής ανεπάρκειας



Cardiovasc Res. 2008 May 1; 78(2): 265

Diabetic cardiomyopathy

- The existence of a diabetic cardiomyopathy was first recognized by Rubler *et al. at 1972*

- Regan *et al (1977) described* modestly increased LV enddiastolic pressure, normal LV end-diastolic volume, and decreased LV compliance.

- Friedman *et al.(1982), demonstrated that diabetic patients had an* increased end-systolic diameter and volume, a diminished ejection fraction, and a decreased minor axis shortening and velocity of circumferential fiber shortening

J Clin Invest 1977; 60:884–899
Am J Cardiol 1972; 30:595–602
Am J Med 1982;3:846–850

Στάδια διαβητικής μυοκαρδιοπάθειας

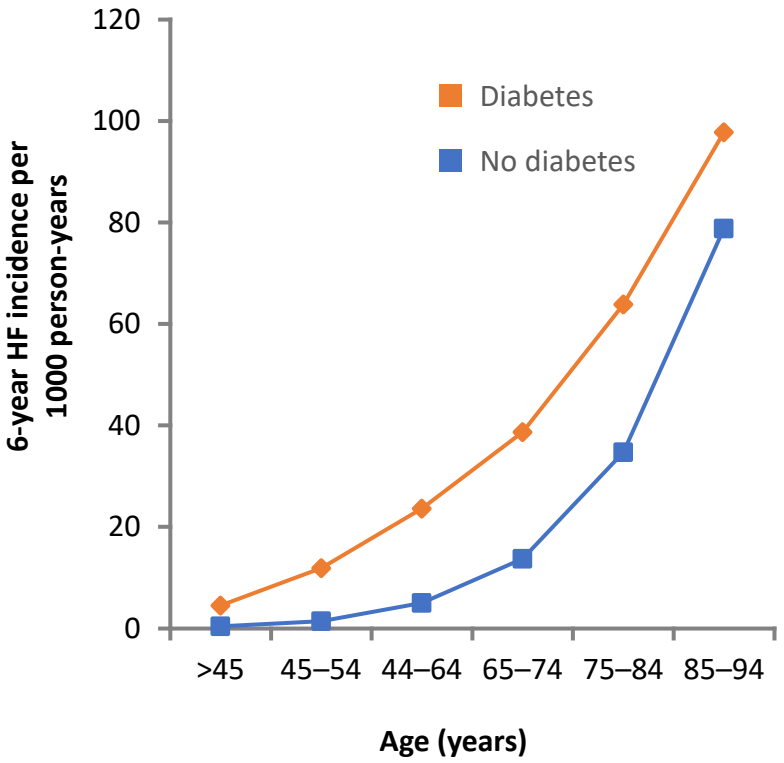
Stages	Characteristics	Functional features	Structural features	Study methods
Early stage	Depletion of GLUT4 Increased FFA Carnitine deficiency Ca^{2+} homeostasis changes Insulin resistance	No overt functional abnormalities or possible overt diastolic dysfunction but normal ejection fraction	Normal LV size, wall thickness, and mass	Sensitive methods such as strain, strain rate, and myocardial tissue velocity
Middle stage	Apoptosis and necrosis Increased AT II Reduced IGF-I Increased TGF-β1 Mild CAN	Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction	Slightly increased LV mass, wall thickness, or size	Conventional echocardiography or sensitive methods such as strain, strain rate, and myocardial tissue velocity
Late stage	Microvascular changes Hypertension CAD Severe CAN	Abnormal diastolic dysfunction and ejection fraction	Significantly increased LV size, wall thickness, and mass	Conventional echocardiography

AT II, Angiotensin II; CAD, coronary artery disease.

Endocrine Reviews,2004, 25(4):543–567
Chrysohoou et al *utrients* **2023**, *15*(6), 1384; **https://doi.org/10.3390/nu15061384**

Age-associated incidence of heart failure increases in patients with diabetes

HF incidence by age group



- Patients with diabetes develop HF at 2.5× the rate of patients without diabetes
  - Overall, the 6-year HF incidence was 30.9 versus 12.4 cases per 1000 person-years (p=0.001)
- Absolute incidence rate of HF increased steadily with age for both groups
- Difference in rates of HF incidence between patients with and without diabetes was greater in younger age groups

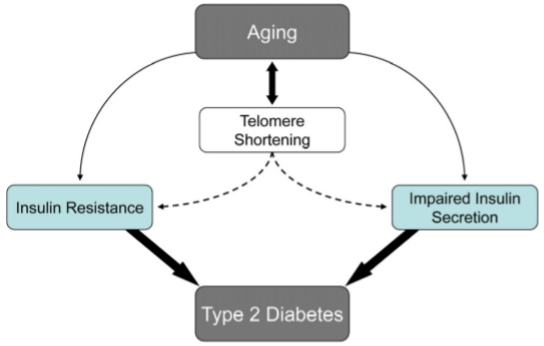


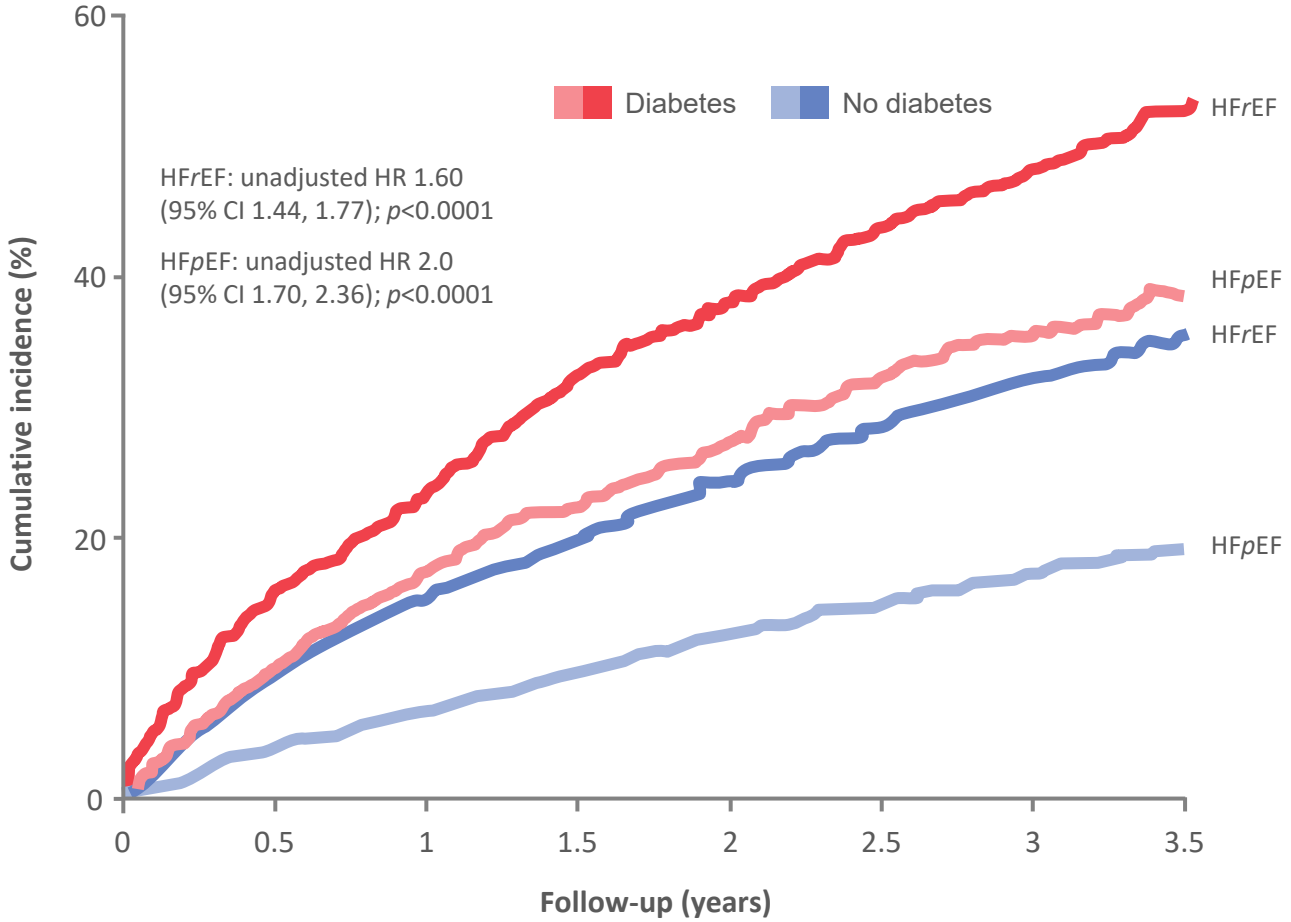
Figure 1. Aging is a well-established risk factor for Type 2 Diabetes. Both insulin secretion and insulin sensitivity, the major pathogenetic processes in Type 2 Diabetes, become impaired with increasing age. Telomere shortening occurs with aging. Studies suggest that this process may be linked with impairments of both insulin secretion and insulin sensitivity.

Nichols GA *et al. Diabetes Care* 2004;27:1879

AGING, October 2010, Vol. 2 No 10

Diabetes is associated with a worse prognosis in patients with heart failure

CV death or HHF in patients with or without diabetes based on ejection fraction category



*HRs refer to the risk of CV death or HHF in patients with diabetes versus non-diabetes

MacDonald MR *et al. Eur Heart J* 2008;29:1377

Pharmacotherapies recommended for heart failure

Class of agent[1]	Mode of action[1]	Effects[1]
ACE inhibitors	Vasodilation, decreased afterload; improved LVEF[1]	Reduce risk of death and hospitalisation in HFrEF; prevent symptomatic HF and reduce mortality
ARBs	Interfere with renin-angiotensin system without inhibition of kininase to inhibit angiotensin[1]	Haemodynamic and neurohormonal effects leading to reduced hospitalisation and mortality
Mineralocorticoid receptor antagonists	Inhibit potassium excretion	Reduce morbidity and mortality, including after an acute MI in patients with LVEF ≤40% who develop HF symptoms or who have a history of diabetes mellitus
Beta blockers: bisoprolol, metoprolol succinate SR, carvedilol	Bisoprolol and metoprolol block beta-1 receptors; carvedilol blocks alpha-1, beta-1 and beta-2 receptors	Reduce the risk of death in patients with chronic HFrEF
Hydralazine plus isosorbide dinitrate	Hydralazine inhibits oxidase and isosorbide dinitrate increases NOS, leading to reduced systemic vascular resistance and resulting in vasodilation[2]	Reduces morbidity and mortality
Valsartan/sacubitril	Valsartan blocks the angiotensin II type-1 (AT_1) receptor; sacubitril is a prodrug that, via its active metabolite LBQ657, inhibits neprilysin, a neutral endopeptidase that degrades vasoactive peptides[3]	Reduces the risk of CV death and HHF in patients with CHF (NYHA Class II-IV) and reduced EF[3]
Diuretics*	Inhibit reabsorption of sodium or chloride at specific sites in renal tubules[1]	Cause transient natriuresis and increased urine volume, leading to reductions in plasma volume; lower serum potassium; activate the sympathetic nervous system
Digoxin	Cardiac glycoside that binds to and inhibits sarcolemma-bound (Na^+/K^+) Mg^+-ATPase[4]	Improves symptoms, HRQoL and exercise tolerance in patients with mild-to-moderate HF

Pharmacotherapies contraindicated in heart failure

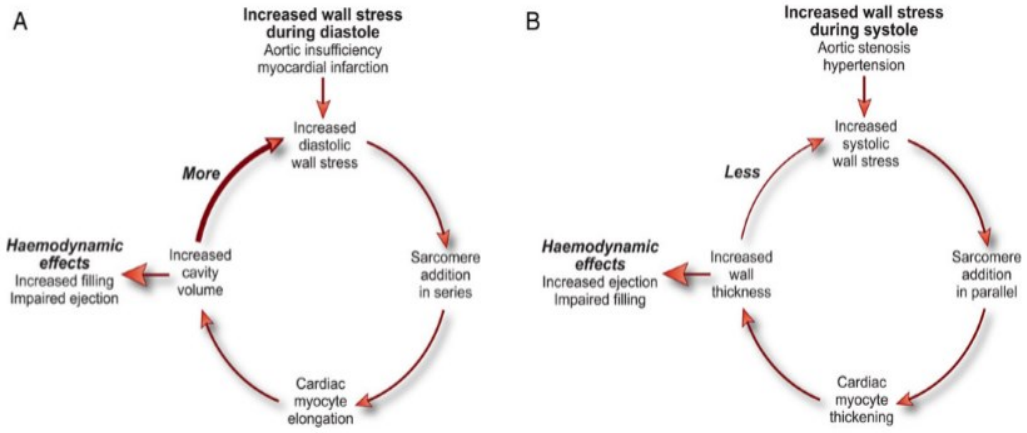
Class of agent	Mode of action	Effects
NSAIDs	Inhibit renal prostaglandin synthesis, which mediates renal vasodilation and directly inhibits sodium resorption	Can cause sodium and water retention, and block the effects of diuretics; may precipitate acute HF
Anti-arrhythmic agents	Interfere with the sodium (Na^+) channel. Most anti-arrhythmics have some negative inotropic effect and some, particularly class I and class III anti-arrhythmic drugs, also have pro-arrhythmic effects	May precipitate acute HF
TZDs (pioglitazone, rosiglitazone)	Activate PPARs, which increase insulin sensitivity and regulate Na^+ reabsorption in renal collecting ducts	Associated with fluid retention in patients with HF; should be avoided in patients with NYHA class II–IV HF; may precipitate acute HF
Calcium-channel blockers (verapamil, diltiazem)	Block calcium channels to reduce peripheral vasoconstriction and LV afterload, but also have myocardial depressant activity	Non-dihydropyridine calcium-channel blockers are contraindicated in patients with HF*r*EF owing to their negative inotropic effect; may precipitate acute HF

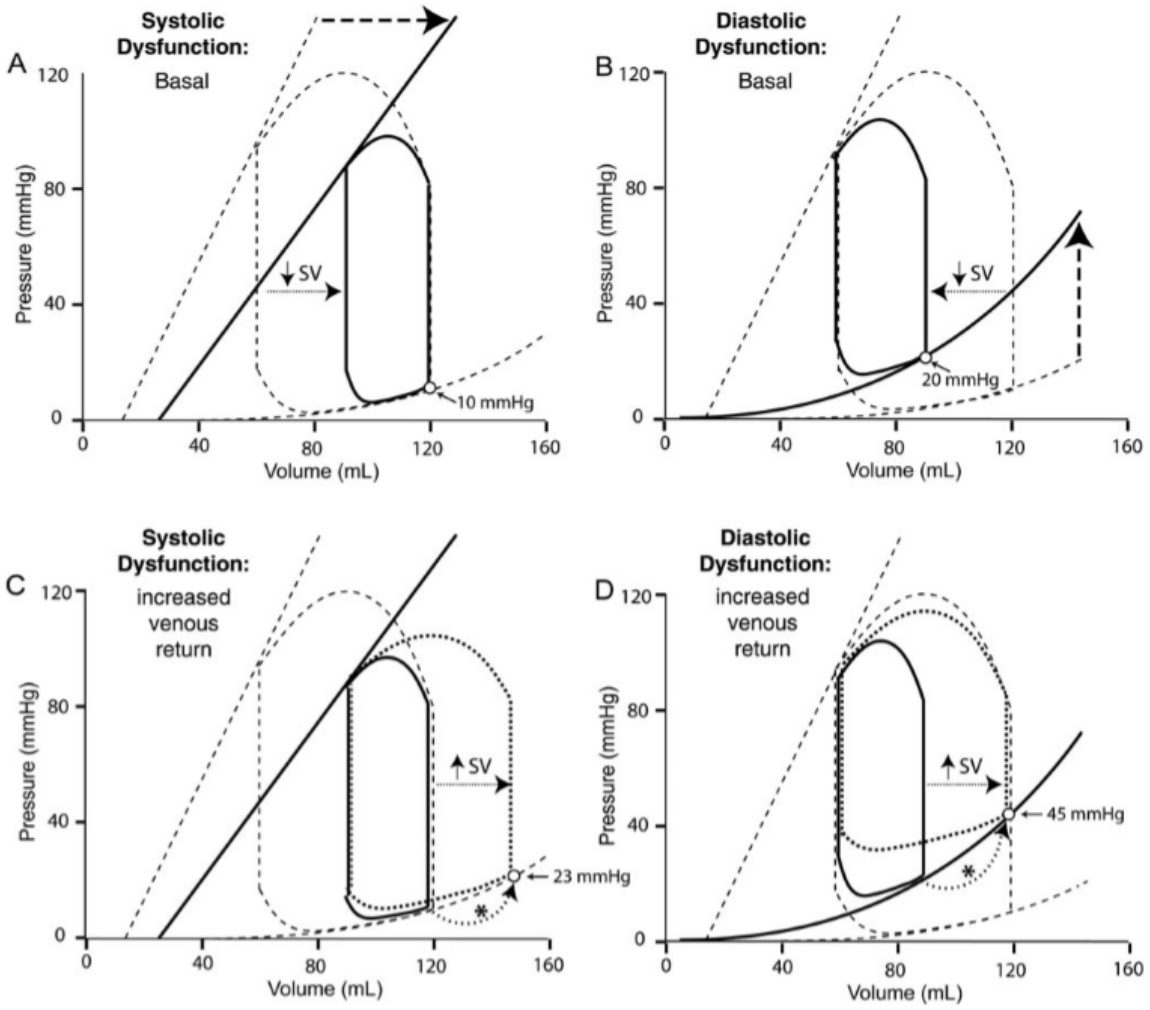
Pharmacotherapies not specifically recommended in heart failure treatment

Class of agent[1]	Mode of action	Recommendations[1]
Statins	Inhibit cholesterol biosynthesis[2]	May not be beneficial as adjunctive therapy when prescribed solely for HF; may be used to prevent symptomatic HF and CV events in patients with history of MI or ACS*
Calcium-channel blockers (dihydropyridines)	Inhibit calcium influx into vascular smooth muscle cells[1,3]	Not recommended as routine treatment in HF*r*EF; amlodipine may be considered in the management of hypertension or ischaemic heart disease in patients with HF
Omega-3 fatty acids	Multiple[4]	Reasonable to use as adjunctive therapy in patients with HF*r*EF or HF*p*EF
Hormonal therapies	Multiple[5]	Not recommended in HF*r*EF, other than to correct deficiencies

Heart failure: when form fails to follow function

- Deformation imaging (strain and strain rate) using speckle-tracking echocardiography has been shown to be more sensitive than EF in detecting myocardial contractility
- Dichotomising function using LV ejection fraction is a major oversimplification, as those with small cavity size (due to hypertrophy), or significantly impaired long axis function may also develop low flow.
- Heart failure with normal or reduced EDV and heart failure with increased EDV



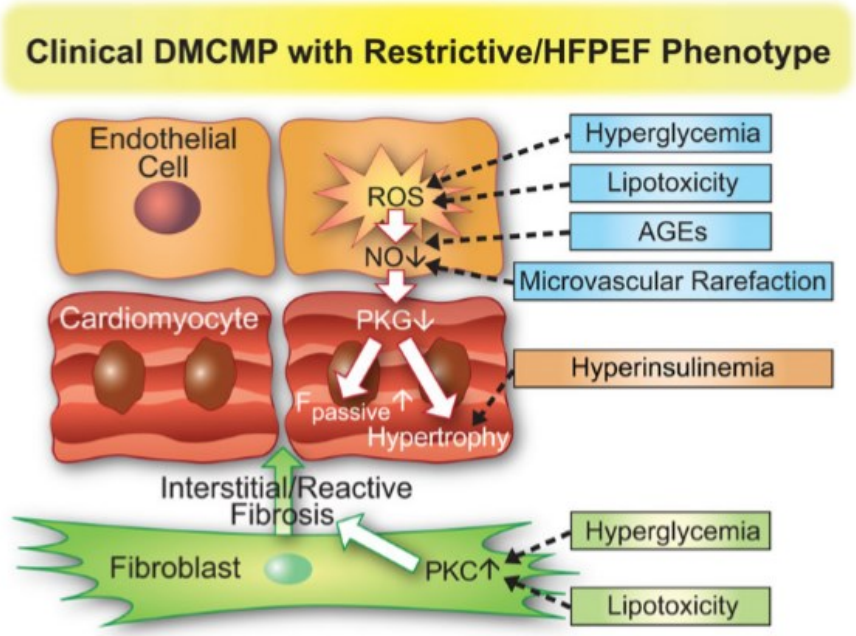


European Heart Journal (2016) 37, 449–454
HJC 2016

Table 1. Pathogenesis of heart failure associated with diabetes.

1.	Coronary artery disease
2.	Ischemia due to capillary disorders (abnormal microcoronary circulation)
3.	Increased myocardial fibrosis and myocardial hypertrophy
4.	Increased activity of the renin–angiotensin–aldosterone system (RAAS)
5.	Impaired myocardial energy metabolism and lipotoxicity
	a. Decrease in myocardial glucose utilization due to absolute and relative insulin deficiency
	b. Increased uptake of fatty acids, increased intermediate products and lipotoxicity
6.	Increased oxidative stress due to advanced glycation end products (AGEs), increased activity of RAAS and mitochondrial dysfunction
7.	Mitochondrial dysfunction
8.	Inflammation
9.	Abnormal myocardial calcium handling
10.	Autonomic dysregulation in the heart
11.	Sodium retention due to hyperinsulinemia

Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes



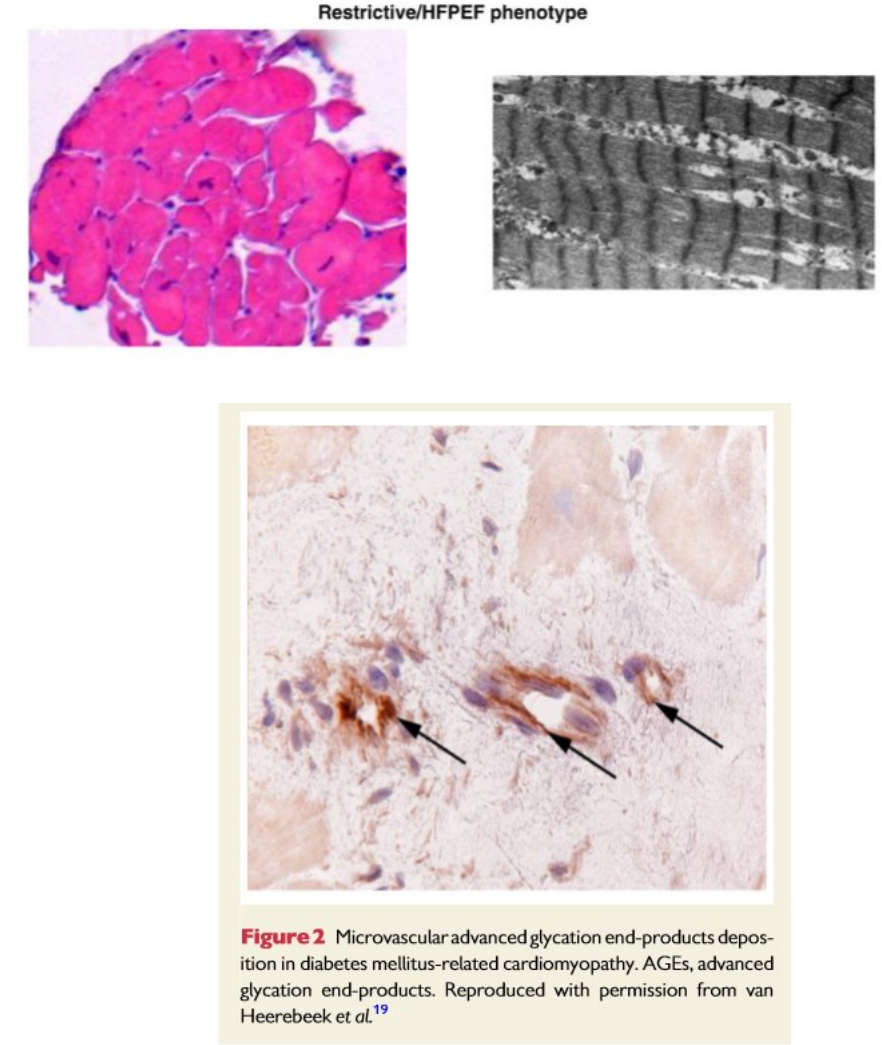
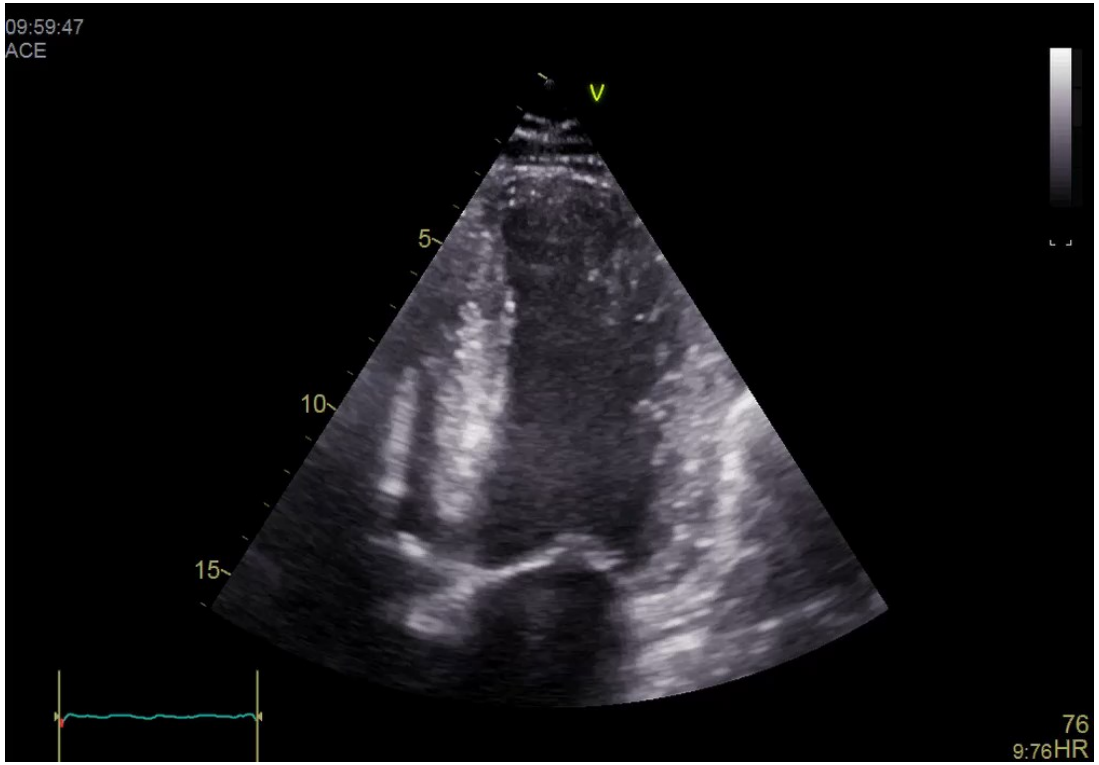
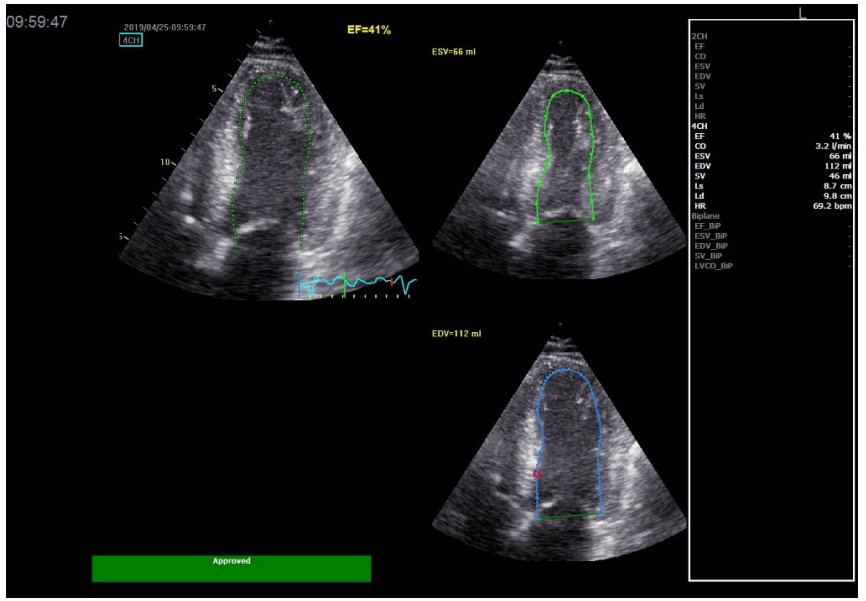


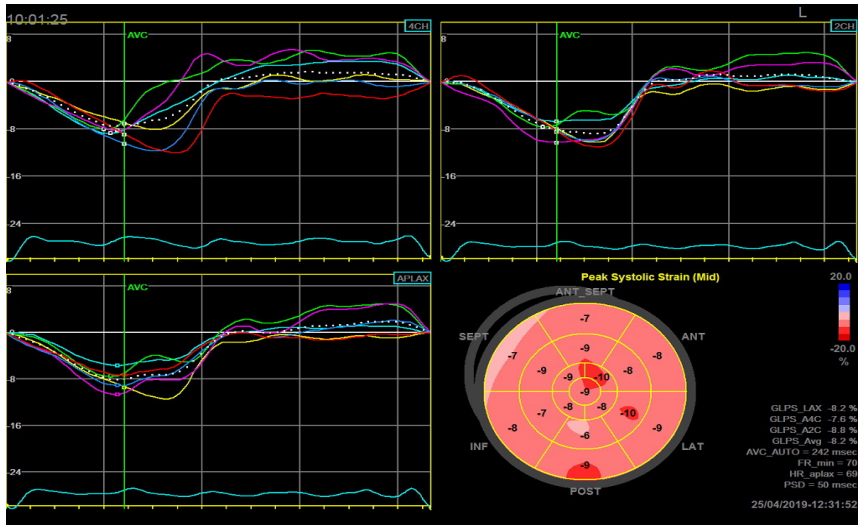
Figure 2 Microvascular advanced glycation end-products deposition in diabetes mellitus-related cardiomyopathy. AGEs, advanced glycation end-products. Reproduced with permission from van Heerebeek *et al.*[19]

European Heart Journal (2015) 36, 1718–1727

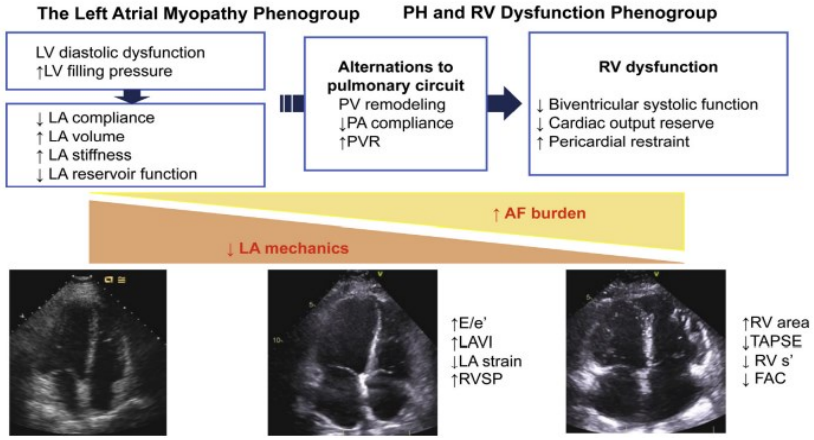
Περιστατικό: 70χρονη γυναίκα με ΣΔ

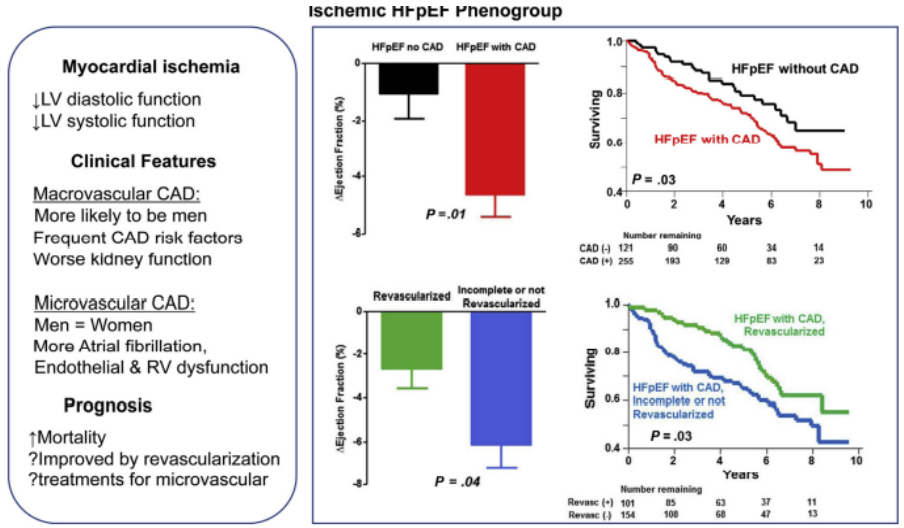


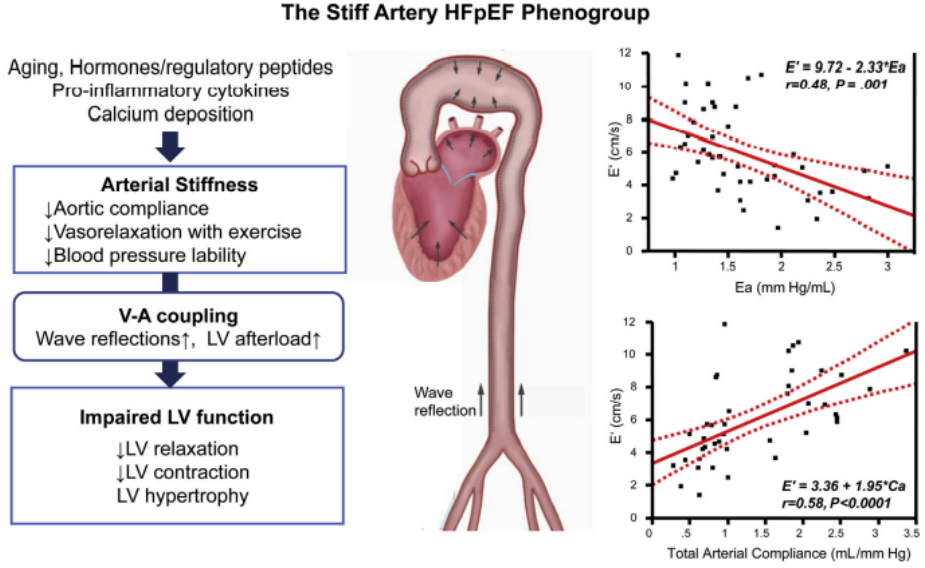


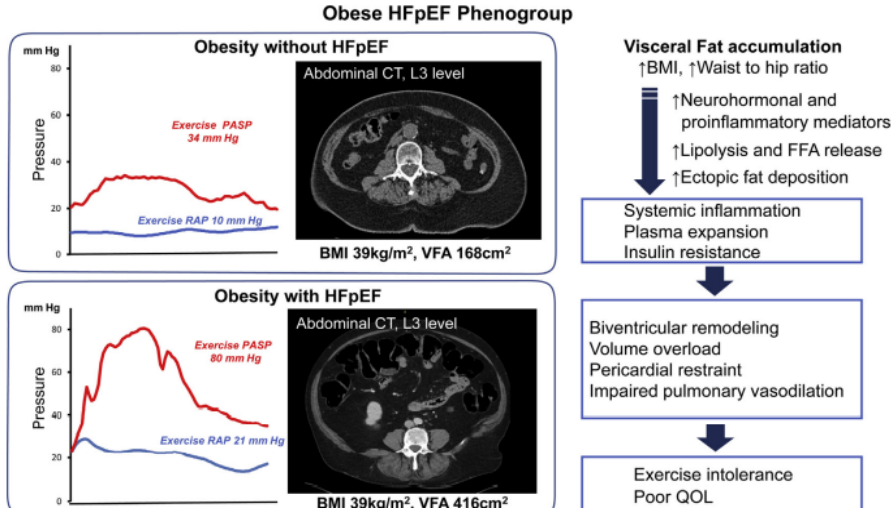


HFpEF Phenotypes







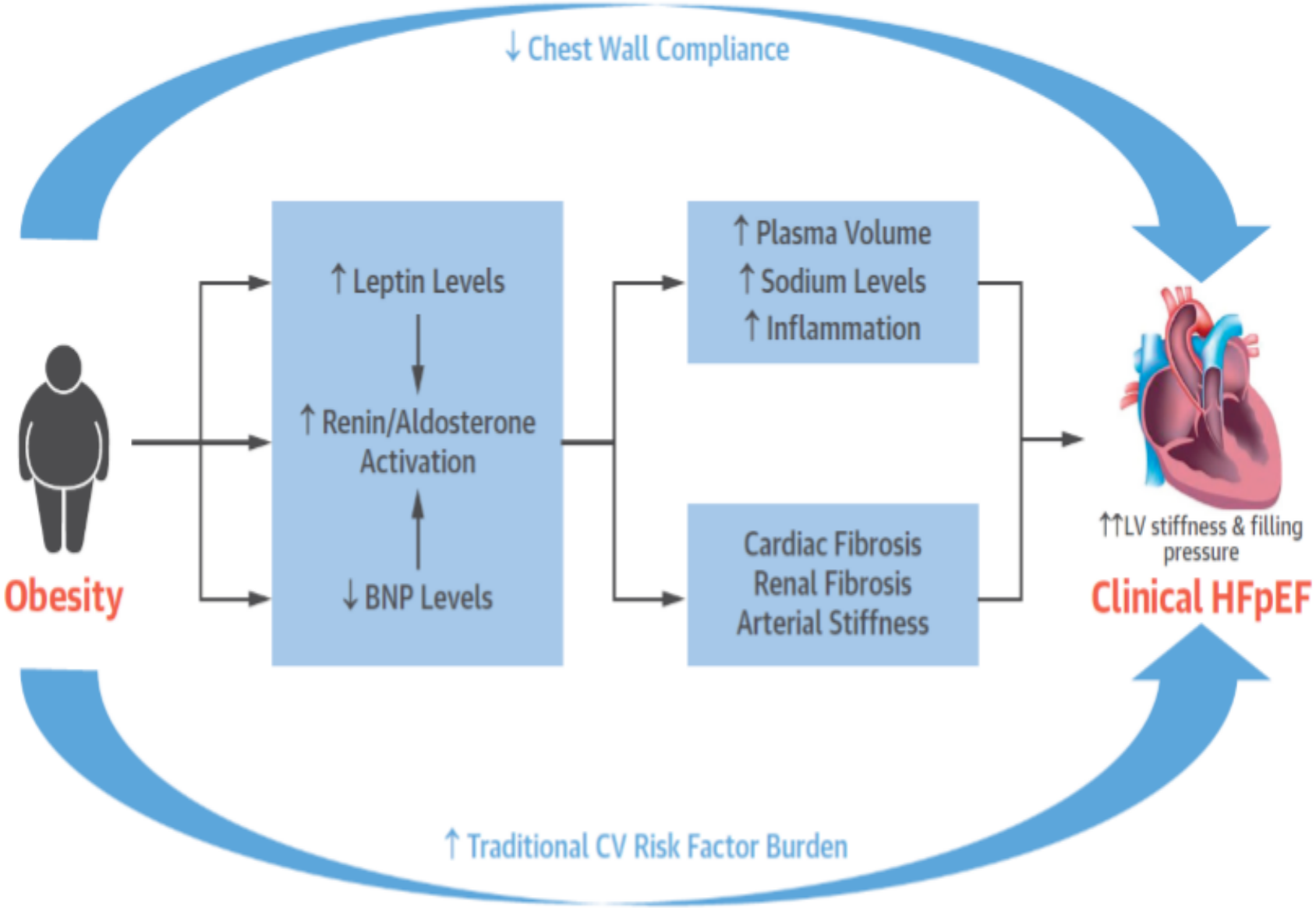


Heart Failure Clin 17 (2021) 483–49

Clinical phenotypes

- How easy to interpret?
- There is abundant data to support the concept of different phenotypes, but the optimal phenotypic nosology is not yet resolved and represents an important knowledge gap in the field

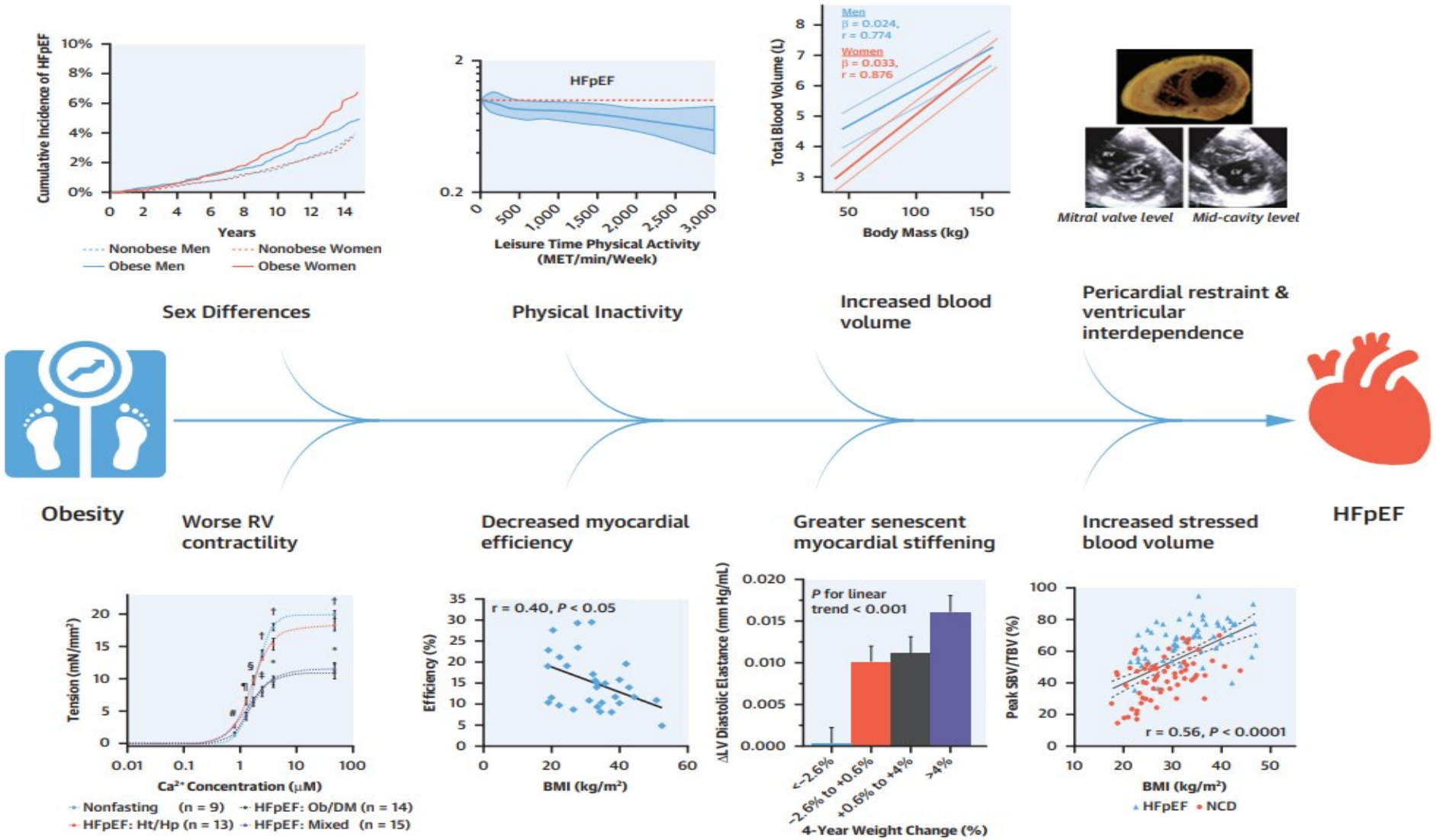
Obesity and HFpEF



Pandey, A. et al. J Am Coll Cardiol HF. 2018;6(12):975-82.

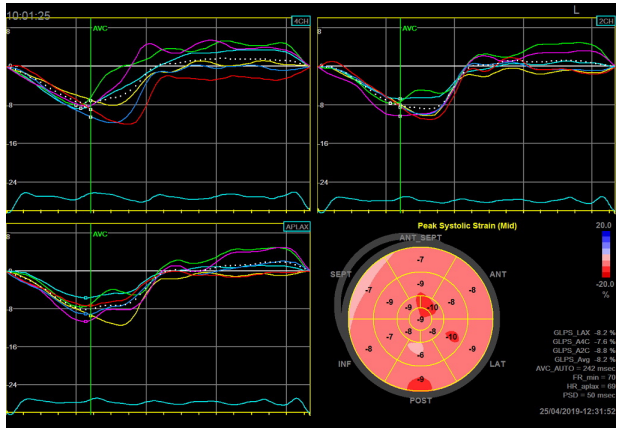
Pathophysiology of obesity HFpEF

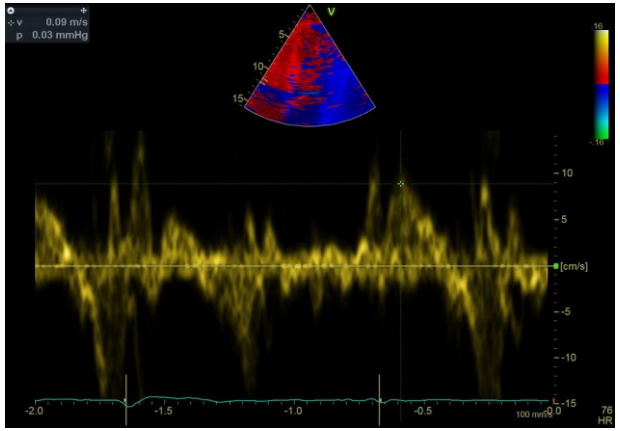
Borlaug et al. JACC 2023

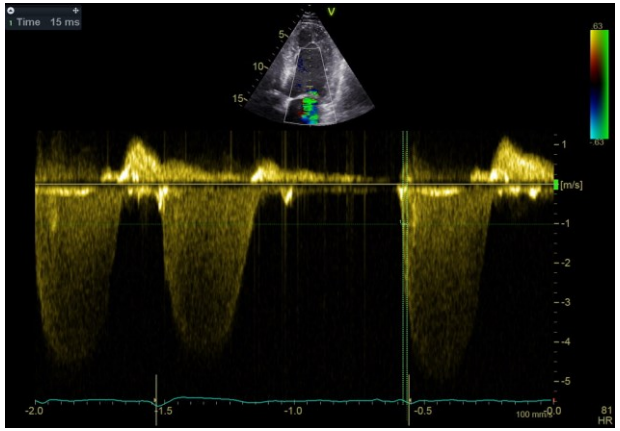


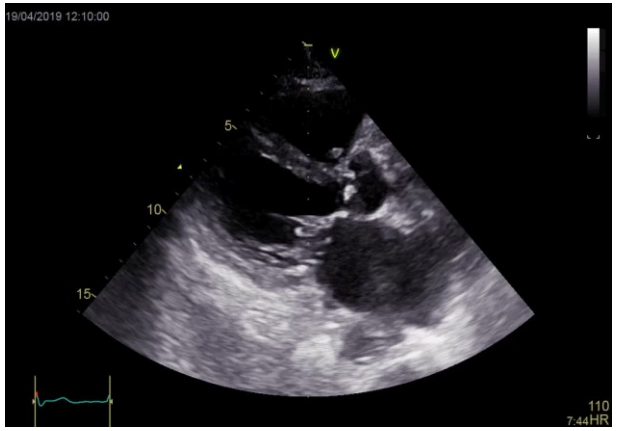
Case

- Woman 65 yrs old (BMI=31kg/m2)
- DM II (metformin 850 mg bid)
- HTN (valsartan 160mg / amlodipine 10mg)
- CrCl=50ml/min
- NtproBNP=350pg/dl
- Complains of exertional shortness of breath

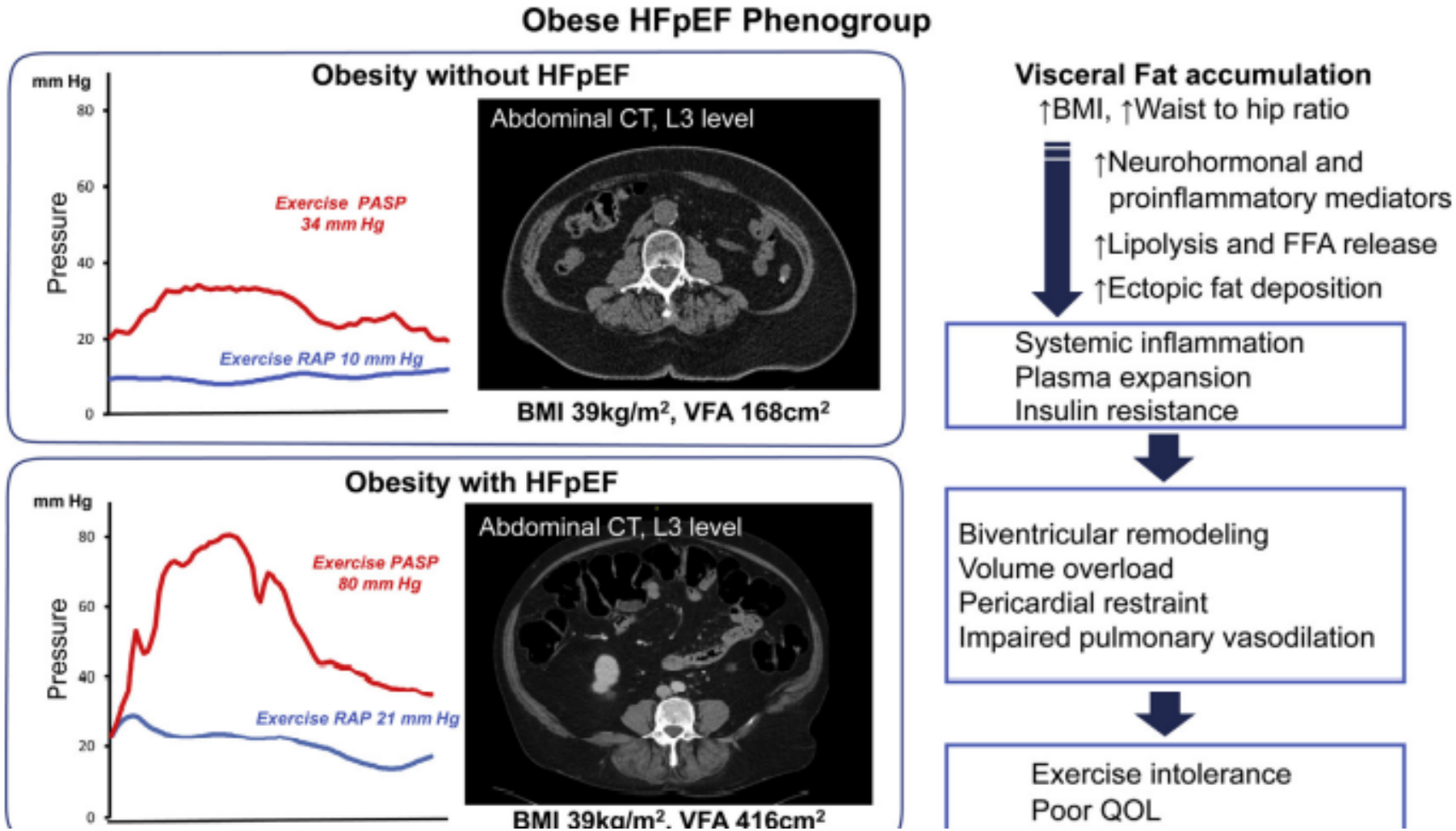






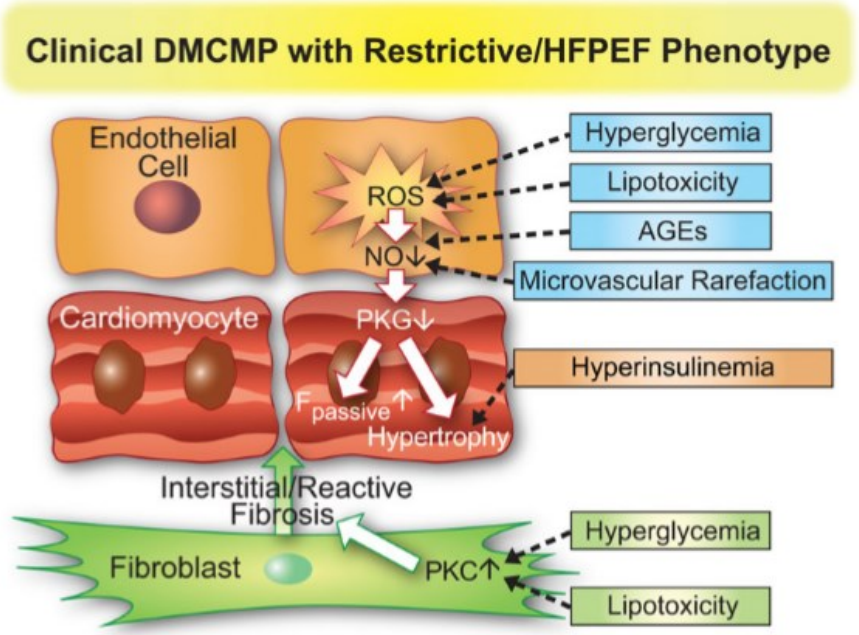


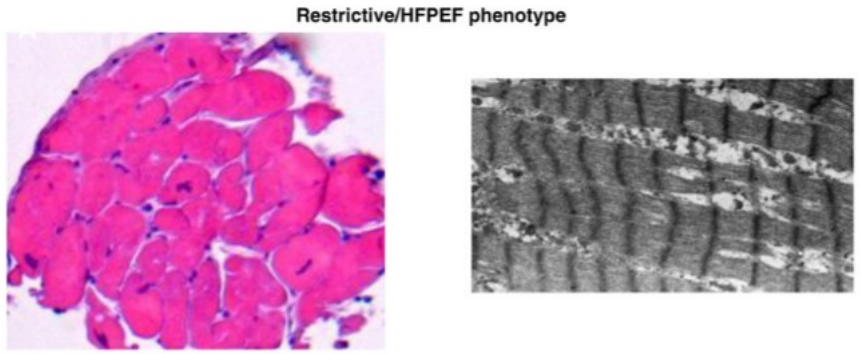
Obese phenotype- not always the case!



Heart Failure Clin 17 (2021) 483–49

Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes





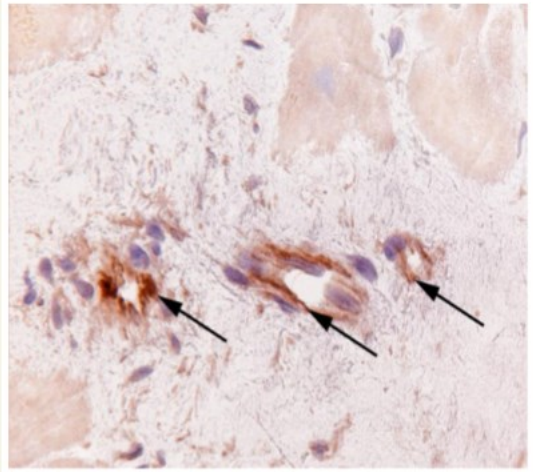


Figure 2 Microvascular advanced glycation end-products deposition in diabetes mellitus-related cardiomyopathy. AGEs, advanced glycation end-products. Reproduced with permission from van Heerebeek *et al.*[19]

European Heart Journal (2015) 36, 1718–1727

Ischemic phenotype

Heart Failure Clin 17 (2021) 483–49

Myocardial ischemia

↓LV diastolic function
↓LV systolic function

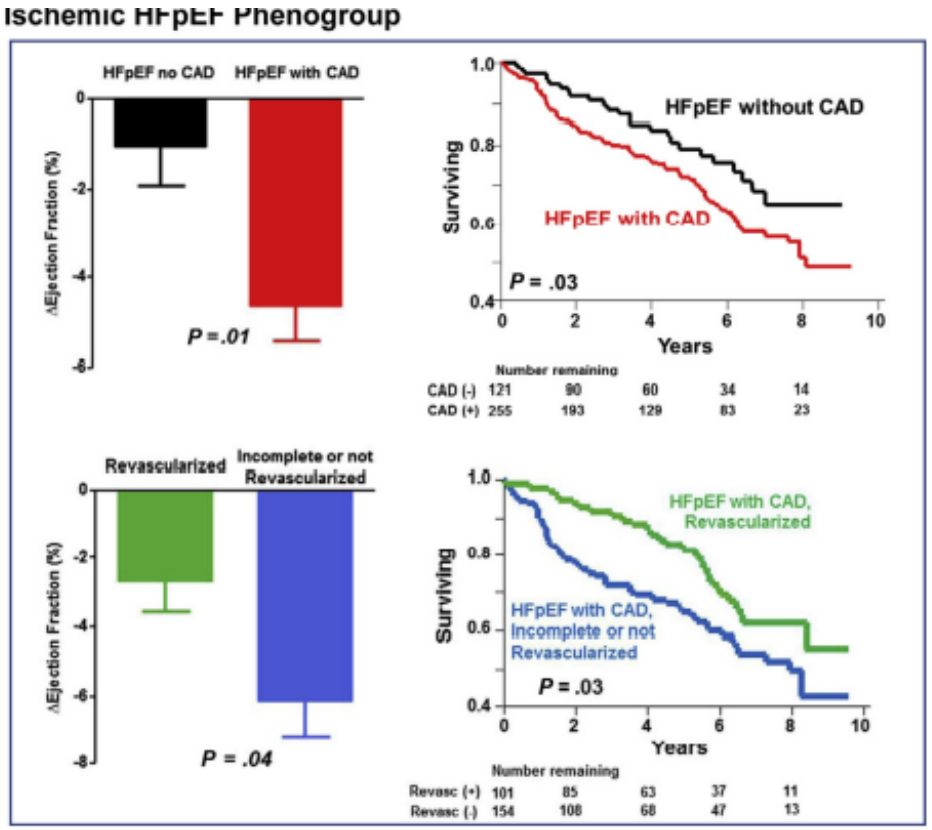
Clinical Features

Macrovascular CAD:
More likely to be men
Frequent CAD risk factors
Worse kidney function

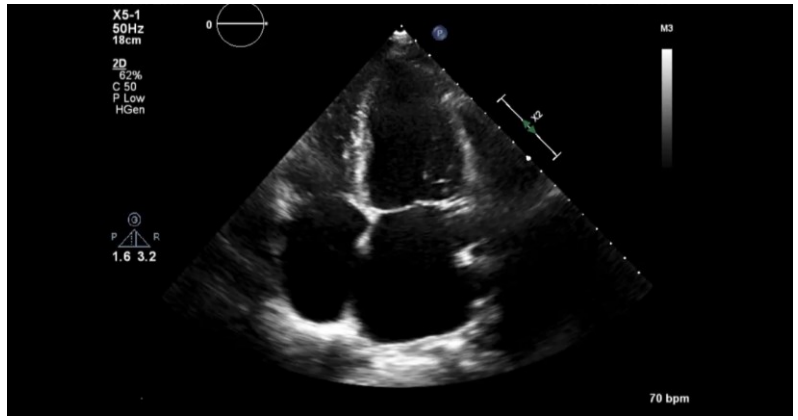
Microvascular CAD:
Men = Women
More Atrial fibrillation,
Endothelial & RV dysfunction

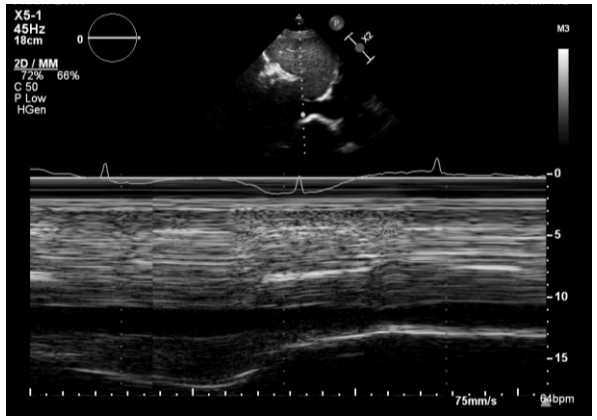
Prognosis

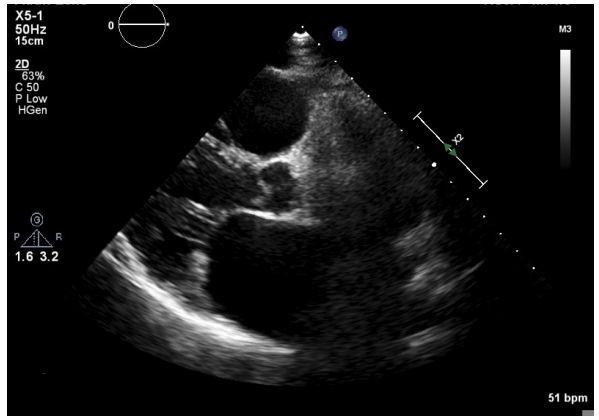
↑Mortality
?Improved by revascularization
?treatments for microvascular

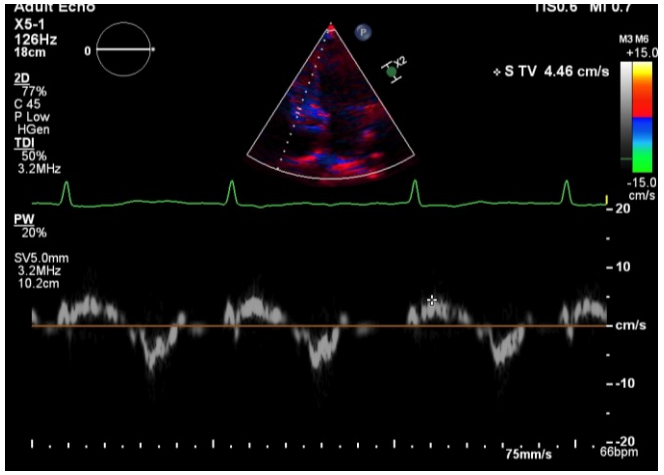


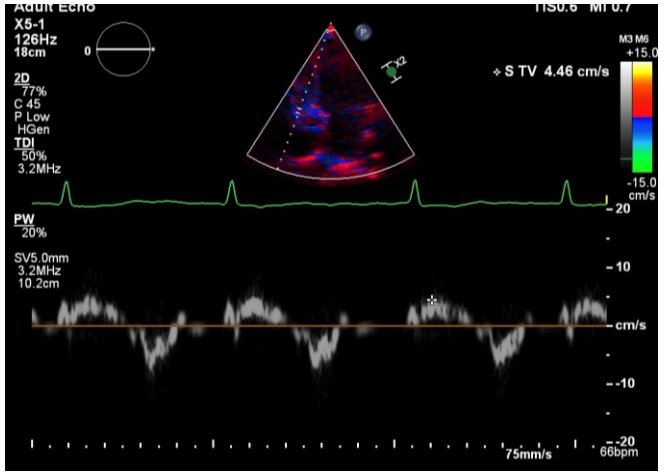
72 yrs old woman with exertional dyspoea/ AF

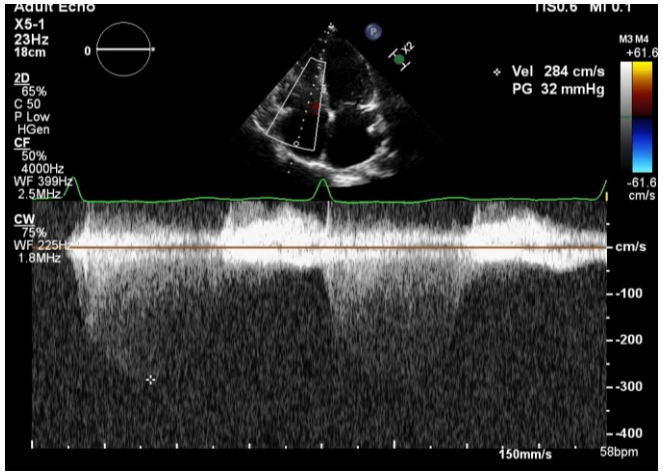












The Left Atrial Myopathy Phenogroup

LV diastolic dysfunction
↑LV filling pressure

↓ LA compliance
↑ LA volume
↑ LA stiffness
↓ LA reservoir function

PH and RV Dysfunction Phenogroup

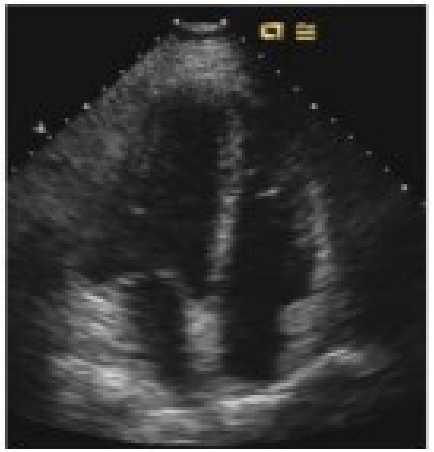
Alternations to pulmonary circuit
PV remodeling
↓PA compliance
↑PVR

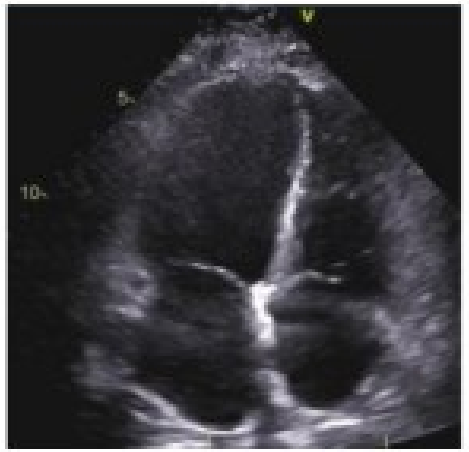
RV dysfunction

↓ Biventricular systolic function
↓ Cardiac output reserve
↑ Pericardial restraint

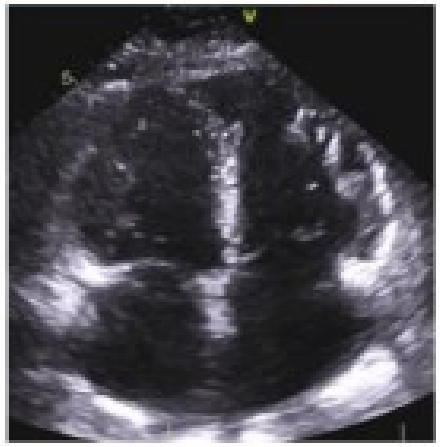
↑ AF burden

↓ LA mechanics





↑E/e'
↑LAVI
↓LA strain
↑RVSP



↑RV area
↓TAPSE
↓ RV s'
↓ FAC

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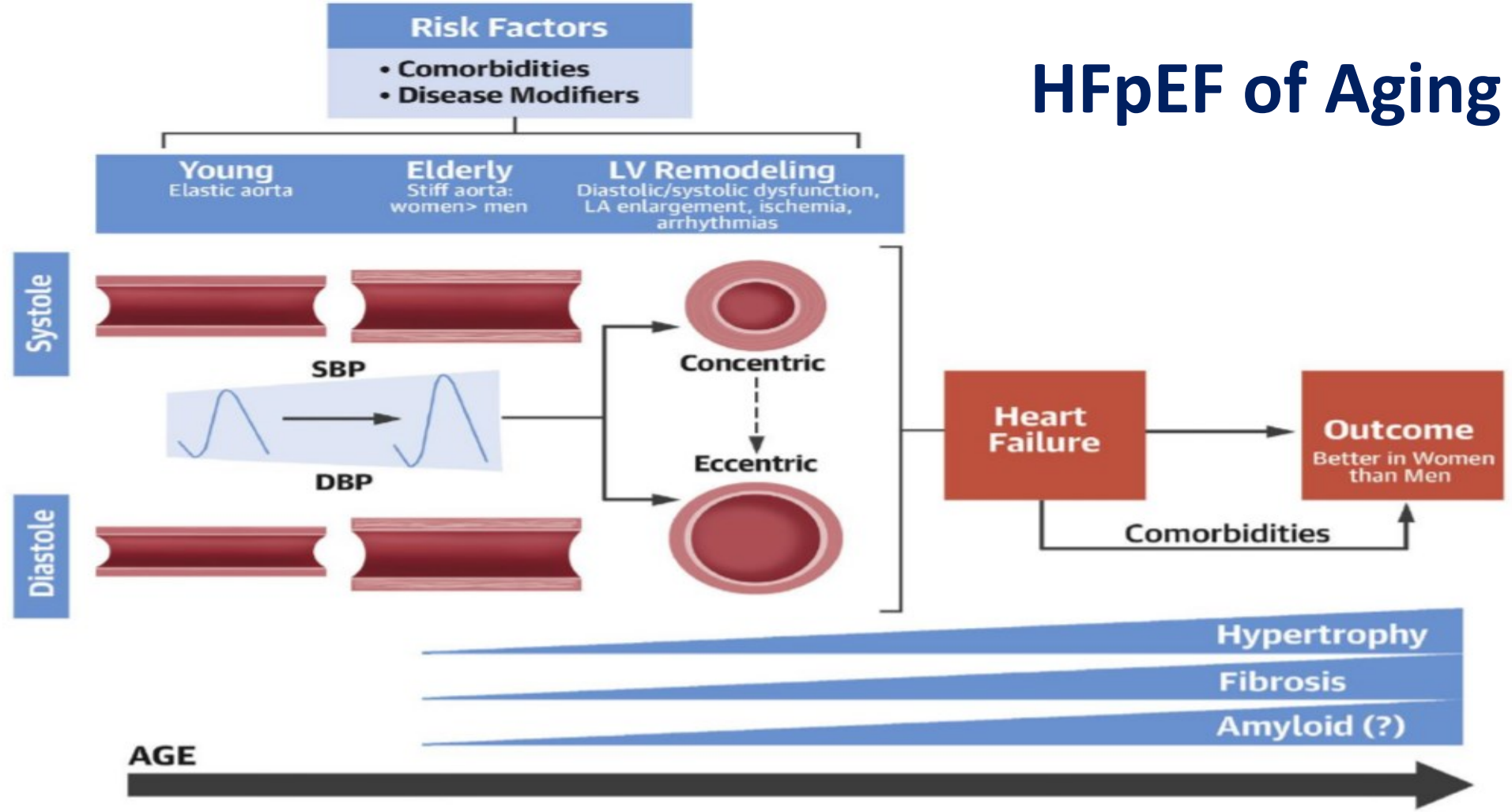
HFpEF of Aging



Triposkiadis, F. et al. J Am Coll Cardiol. 2019;74(6):804–13.

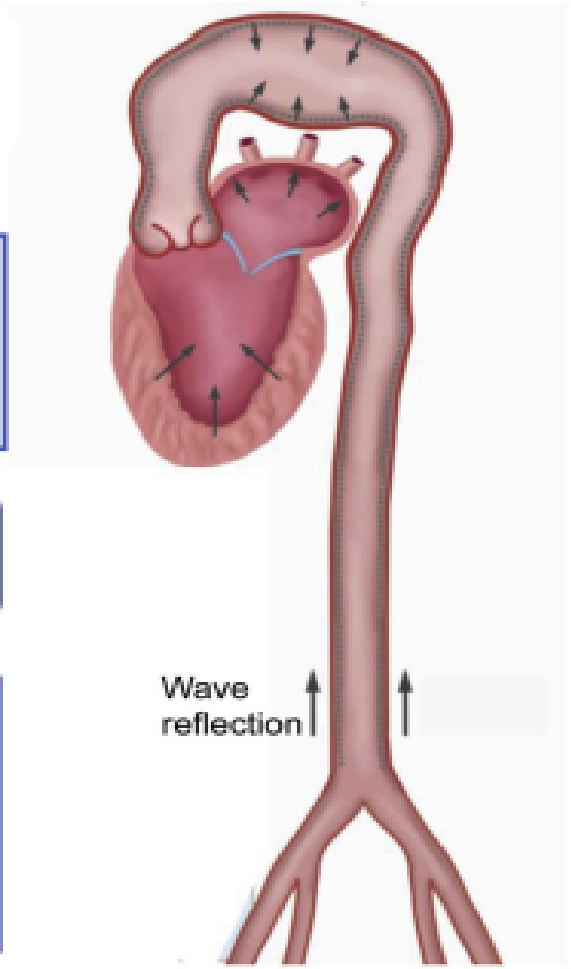
The Stiff Artery HFpEF Phenogroup

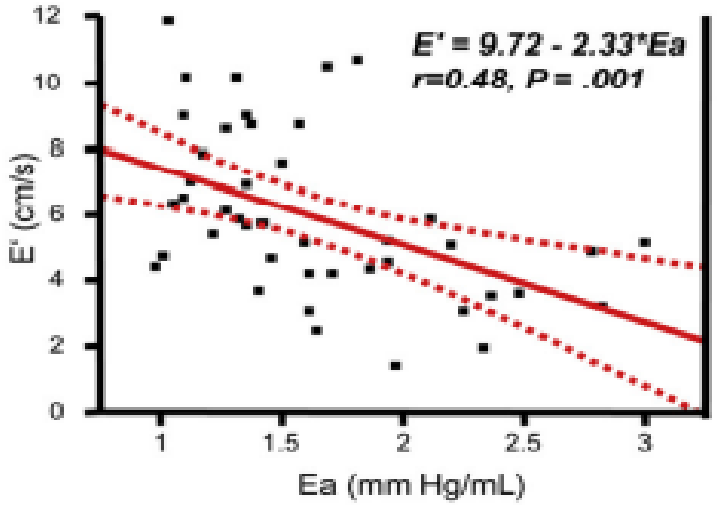
Aging, Hormones/regulatory peptides
Pro-inflammatory cytokines
Calcium deposition

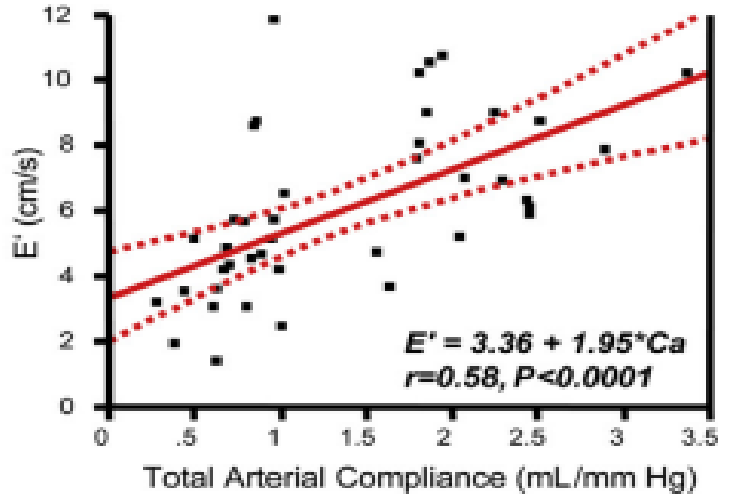
Arterial Stiffness
↓Aortic compliance
↓Vasorelaxation with exercise
↓Blood pressure lability

V-A coupling
Wave reflections↑, LV afterload↑

Impaired LV function
↓LV relaxation
↓LV contraction
LV hypertrophy







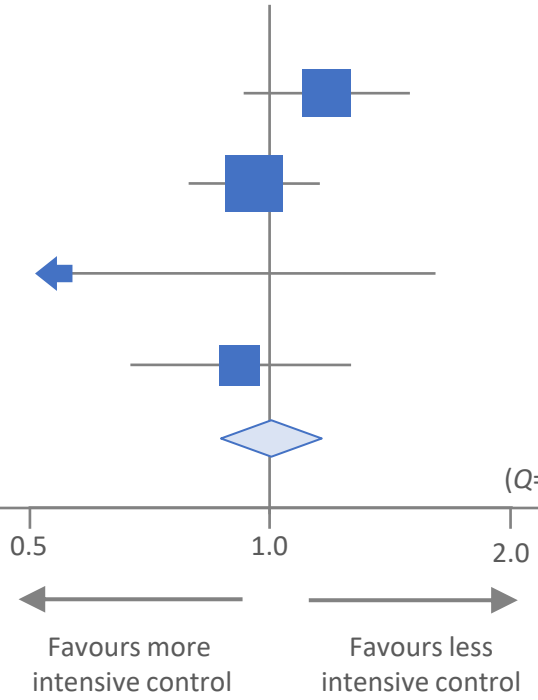
Πως προλαμβάνεται η διαβητική μυοκαρδιοπάθεια?

CVDs in T2D patients are often detected and managed late, resulting in increasing clinical and economic burden, which could be avoided or delayed

a	With the increasing prevalence of T2D, there is an urgent need for early identification and prioritization of CVD prevention measures among T2D patients at high-risk of HF
b	T2D is a heterogenous disease and the individual risk of HF varies widely – 30% of diabetic patients will develop HF in their lifetime, whereas the rest will not - there is a need to identify and distinguish between the two groups
c	T2D patients asymptomatic for HF are often undertreated with medications known to reduce CVD morbidity and mortality resulting in preventable adverse outcomes
d	Identifying T2D patients at high risk for HF is crucial, as delay in initiation of appropriate cardioprotective measures significantly increases the risk of HF

Intensive glycaemic control* has not been shown to significantly impact the risk of HF

	Number of events (yearly rate, %)		ΔHbA1c (%)	Hazard ratio (95% CI)
	More intensive	Less intensive		
Admission to hospital/fatal HF				
ACCORD	152 (0.90)	124 (0.75)	–1.01	1.18 (0.93, 1.49)
ADVANCE	220 (0.83)	231 (0.88)	–0.72	0.95 (0.79, 1.14)
UKPDS	8 (0.06)	6 (0.11)	–0.66	0.55 (0.19, 1.60)
VADT	79 (1.80)	85 (1.94)	–1.16	0.92 (0.68, 1.25)
Overall	**459**	**446**	**–0.88**	1.00 (0.86, 1.16)
				(Q=3.59, p=0.31, I^2=16.4%)



*Versus less-intensive glycaemic control
HbA1c, glycated haemoglobin; HF, heart failure
Turnbull FM *et al. Diabetologia* 2009;52:2288

Currently, there is no consensus on CV risk assessment among diabetic patients, risk assessment is often initiated based on clinician's judgement

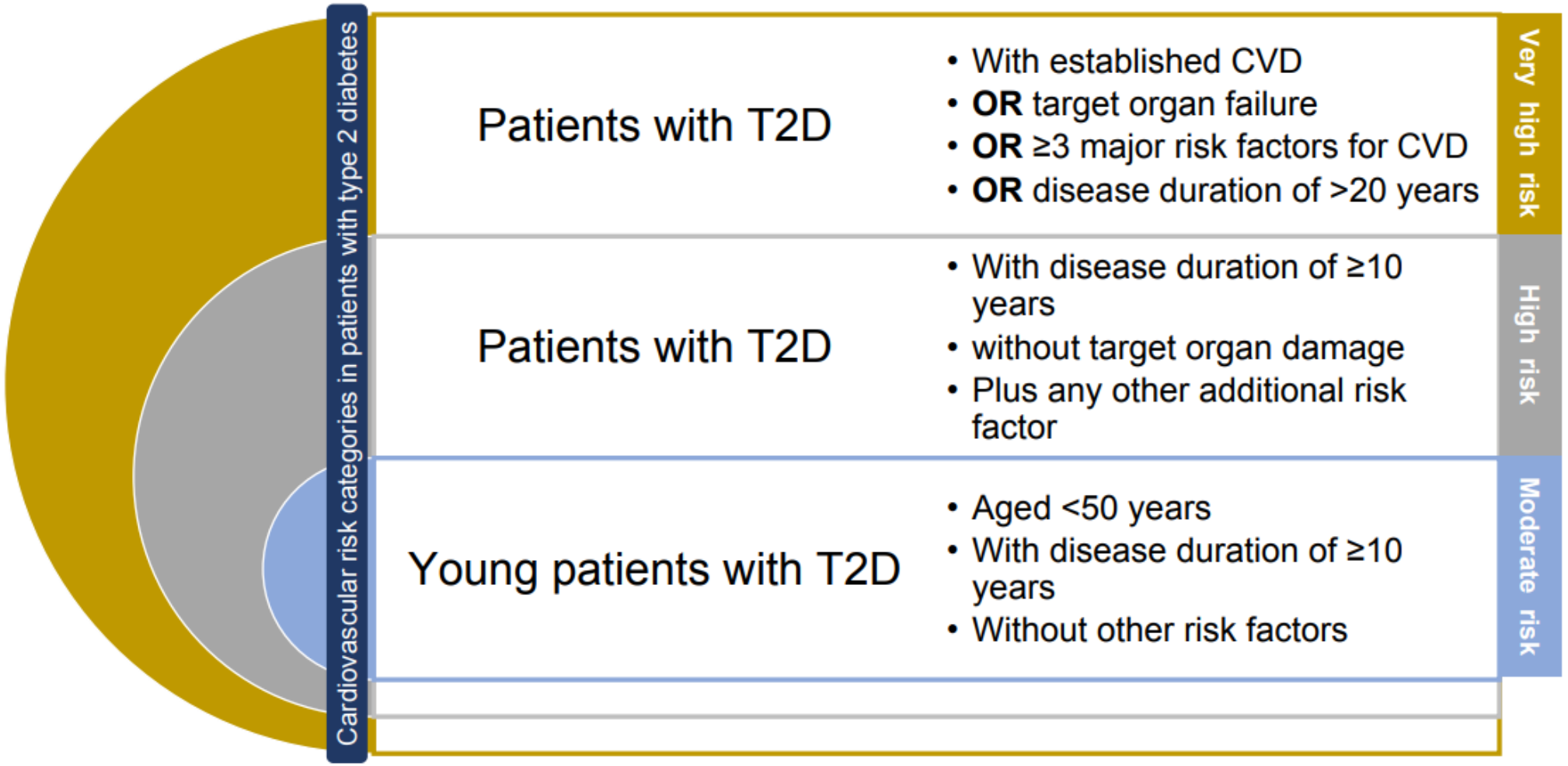
Guideline recommendations on CV risk assessment in T2D patients

	Guideline	CV risk assessment in the guideline
International Diabetes Federation	2012 IDF Global Guideline for Type 2 Diabetes[1]	• Risk factors to be evaluated during annual risk assessment visits include general CV risk factors: • Current or previous CVD; Age and BMI; Smoking status; BP; Serum lipid profile; Family history of premature CVD; Renal damage (particularly albuminuria) • Although CV risk assessment based on risk equations developed for diabetes patients is recommended, no specific model/equation is highlighted or recommended
ESC European Society of Cardiology	2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular disease[2]	• Risk factors to be evaluated include: • BP; HbA1c; Lipid profile; Platelet inhibition; Smoking status; Physical activity; Weight; Dietary habits • Routine assessment of microalbuminuria is indicated to identify patients at high risk of future CVD • Although the value of NT-proBNP in identifying T2D patients who will benefit from intensified control of CV risk factors is noted in the guideline, routine assessment of circulating biomarkers is not recommended for CV risk stratification • Risk scores developed for the general population are not recommended for CV risk assessment in T2D patients
American Diabetes Association®	2020 ADA Standards of Medical Care in Diabetes[3]	• Risk factors to be assessed during annual visits include: • Obesity; Hypertension; Dyspilidemia; Smoking; Family history of premature CVD; Kidney disease (albuminuria) • ASCVD risk calculator (Risk Estimator Plus) is recommended as a CV risk assessment tool

Abbreviations: ADA: American Diabetes Association; BMI: Body Mass Index; BP: Blood Pressure; CV: Cardiovascular; ESC: European Society of Cardiology; GP: General Practitioner; HF: Heart Failure; IDF: International Diabetes Federation; MI: Myocardial Infarction; T2D: Type 2 Diabetes

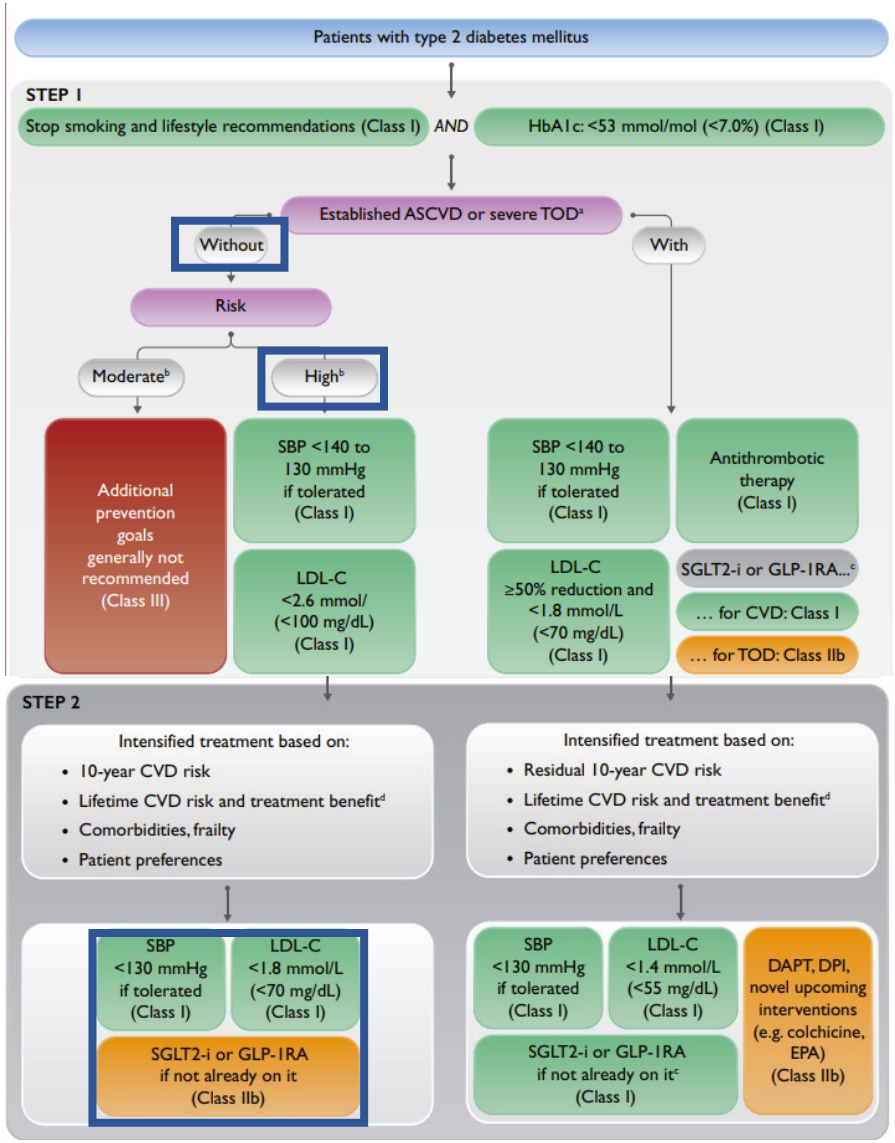
References: **1.** IDF Guideline for Type-2 Diabetes, 2012; **2.** Cosentino, F. et al., *European Heart Journal,* 2020; Vol. 41, pp. 255-323; **3.** ADA Standards of Medical Care in Diabetes, *Diabetes Care,* 2020

Cardiovascular risk stratification in people with type 2 diabetes



Consentino et al. Eur Heart J. 2020;41:255-323

CV risk assessment – An holistic approach



2021 ESC Guidelines on cardiovascular disease prevention in clinical practice (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific comorbidities.	I
In treated patients aged 18—69 years, it is recommended that SBP should ultimately be lowered to a target range of 120—130 mmHg in most patients.	I
In treated patients aged ≥70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.	I
In all treated patients, DBP is recommended to be lowered to <80 mmHg.	I

Recommendations	Class
Risk factors and interventions at the individual level (continued)	
In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes.	I
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.	I
In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.	I
Participation in a medically supervised, structured, comprehensive, multidisciplinary EBCR and prevention programme for patients after ASCVD events and/or revascularization, and for patients with HF (mainly HFrEF), is recommended to improve patient outcomes.	I

In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.	IIb	A
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.	IIa	A

DM treatment to reduce HF risk

SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) are recommended to lower risk of HF hospitalization

Metformin should be considered in patients with DM and HF if eGFR >30 mL/min/1.73 m^2

GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF and may be considered

Insulin treatment in HF may be considered

DPP4 inhibitor saxagliptin in HF is not recommended

Thiazolidinediones (pioglitazone and rosiglitazone) in HF are not recommended

Management of arrhythmias

Attempts to diagnose structural heart disease should be considered in patients with DM with frequent premature ventricular contractions

Hypoglycaemia should be avoided as it can trigger arrhythmias

Diagnosis and management of PAD

Low-dose rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg o.d. may be considered in patients with DM and symptomatic LEAD

Management of CKD

SGLT2 inhibitors are recommended to reduce progression of diabetic kidney disease

Ia	IIa	IIb	III

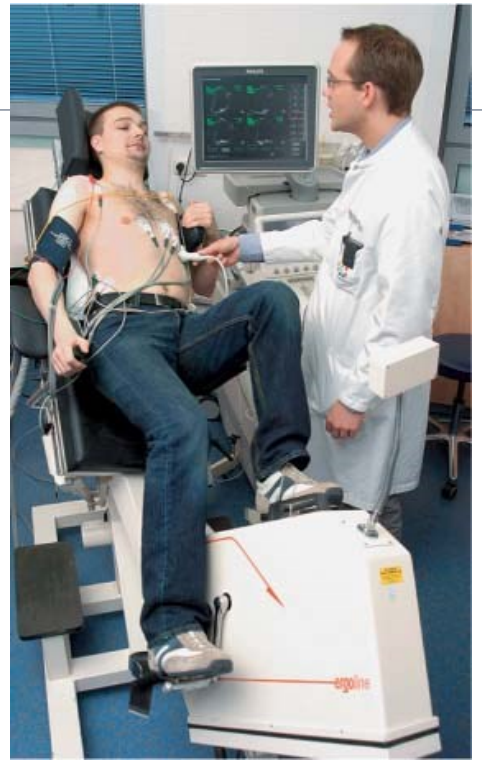
6.3 Blood pressure

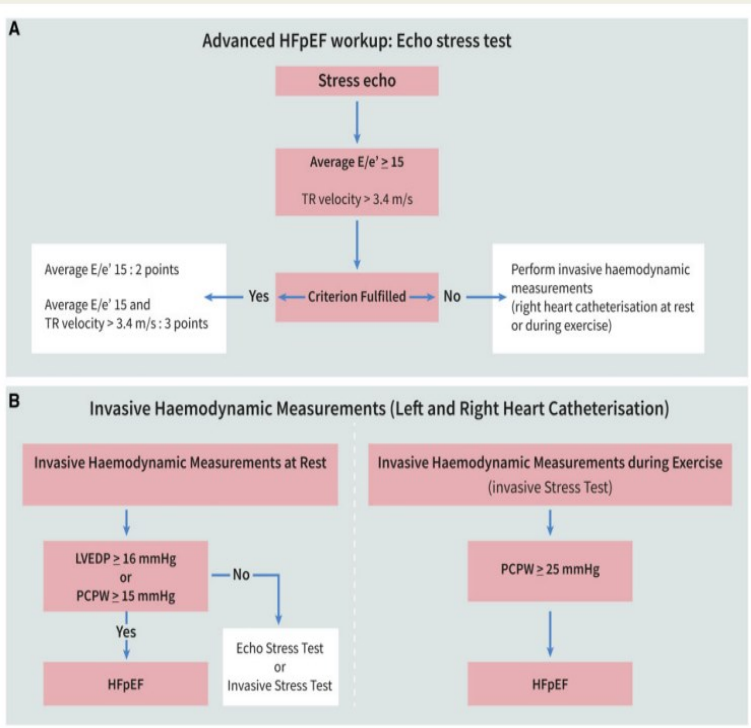
Key messages

- The BP goal is to target systolic BP (SBP) to 130 mmHg in patients with DM and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.
- The diastolic BP (DBP) target is <80 mmHg, but not <70 mmHg.
- Optimal BP control reduces the risk of micro- and macrovascular complications.
- Guidance on lifestyle changes must be provided for patients with DM and hypertension.
- Evidence strongly supports the inclusion of an angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin receptor blocker (ARB) in patients who are intolerant to ACEI.
- BP control often requires multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium channel blocker or diuretic. Dual therapy is recommended as first-line treatment.
- The combination of an ACEI and an ARB is not recommended.
- In pre-DM, the risk of new-onset DM is lower with RAAS blockers than with beta-blockers or diuretics.
- Patients with DM on combined antihypertensive treatments should be encouraged to self-monitor BP.

Recommendations for lifestyle modifications in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM.[27,117]	I	A
Lifestyle intervention is recommended to delay or prevent the conversion of pre-DM states, such as IGT, to T2DM.[85,86]	I	A
Reduced calorie intake is recommended for lowering excessive body weight in individuals with pre-DM and DM.[c] [82,83,89,90]	I	A
Moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise, for ≥150 min/week is recommended for the prevention and control of DM, unless contraindicated, such as when there are severe comorbidities or a limited life expectancy.[d] [110,111–113,119]	I	A
A Mediterranean diet, rich in polyunsaturated and monounsaturated fats, should be considered to reduce CV events.[96,97]	IIa	B
Vitamin or micronutrient supplementation to reduce the risk of DM, or CVD in patients with DM, is not recommended.[79,120]	III	B





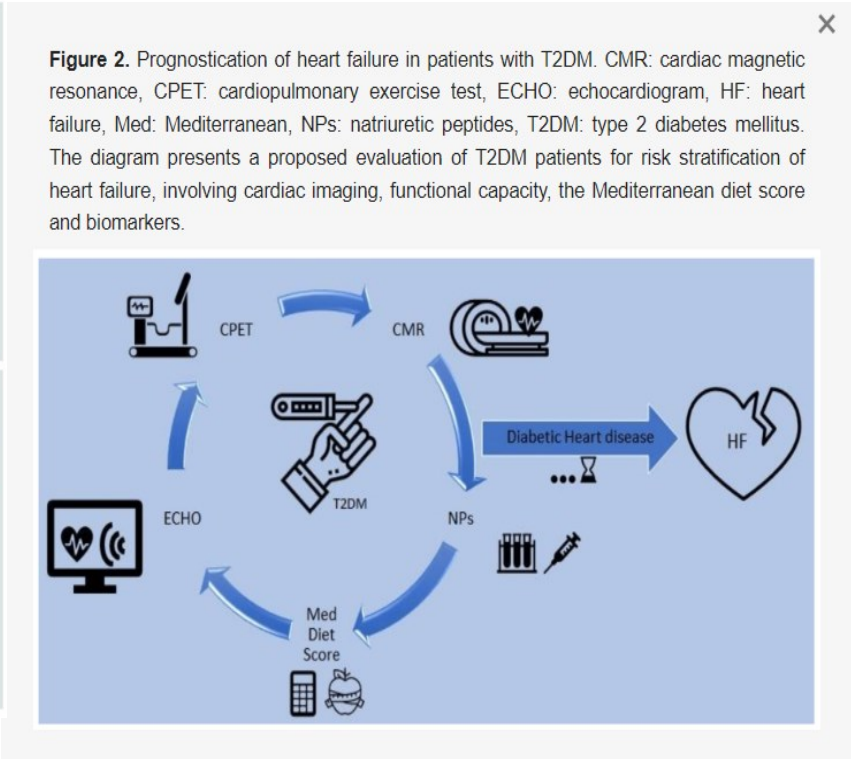


Figure 2. Prognostication of heart failure in patients with T2DM. CMR: cardiac magnetic resonance, CPET: cardiopulmonary exercise test, ECHO: echocardiogram, HF: heart failure, Med: Mediterranean, NPs: natriuretic peptides, T2DM: type 2 diabetes mellitus. The diagram presents a proposed evaluation of T2DM patients for risk stratification of heart failure, involving cardiac imaging, functional capacity, the Mediterranean diet score and biomarkers.

Recognition of HF in DM patients

EMPEROR-Preserved in the Context of Other Studies

Trial	Treatment arms	Primary endpoint	Results (HR and 95% CI)	Risk reduction	P-value
EMPEROR-Preserved (2021)	**Empagliflozin vs placebo**	**CV death + HHF**	**0.79 (0.69–0.90)**	**-21%**	**0.0003**
PARAGON-HF (2019)	Sacubitril/valsartan vs valsartan	CV death + total (first and recurrent) HHF	0.87 (0.75–1.01)	-13%	0.06
TOPCAT (2014)	Spironolactone vs placebo	CV death + HHF + aborted cardiac arrest	0.89 (0.77–1.04)	-11%	0.14
I-PRESERVE (2008)	Irbesartan vs placebo	All-cause mortality + CV Hospitalization	0.95 (0.86–1.05)	-5%	0.35
PEP-CHF (2006)	Perindopril vs placebo	All-cause mortality + HHF	0.92 (0.70–1.21)	-8%	0.55
CHARM-Preserved (2003)	Candesartan vs placebo	CV death + HHF	0.86 (0.74–1.00)	-14%	0.05

Focusing on HFpEF: Optimizing treatment

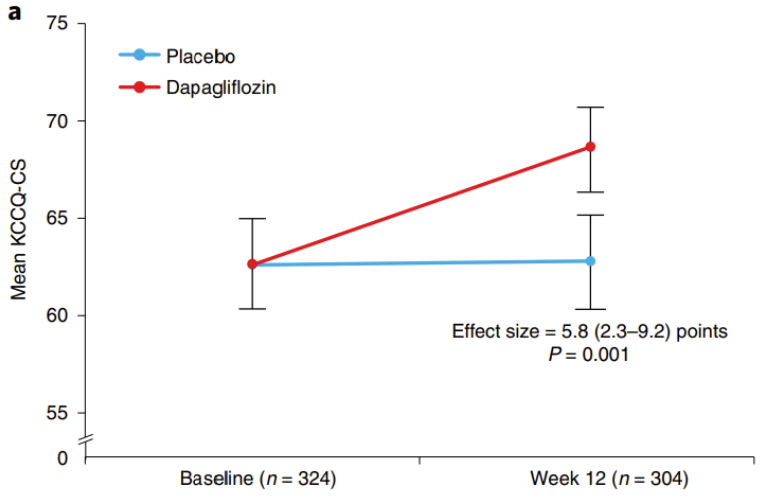
ARTICLES
https://doi.org/10.1038/s41591-021-01536-x
nature medicine
Check for updates

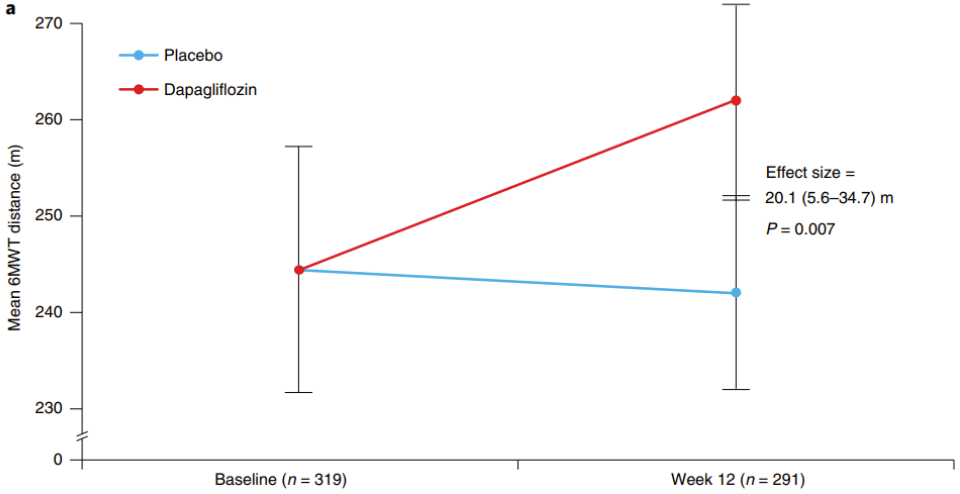
OPEN

The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial

Michael E. Nassif[1,2], Sheryl L. Windsor[1], Barry A. Borlaug[3], Dalane W. Kitzman[4], Sanjiv J. Shah[5], Fengming Tang[1], Yevgeniy Khariton[1,2], Ali O. Malik[1,2], Taiyeb Khumri[1], Guillermo Umpierrez[6], Sumant Lamba[7], Kavita Sharma[8], Sadiya S. Khan[5], Lokesh Chandra[9], Robert A. Gordon[10], John J. Ryan[11], Sunit-Preet Chaudhry[12], Susan M. Joseph[13], Chen H. Chow[14], Manreet K. Kanwar[15], Michael Pursley[16], Elias S. Siraj[17], Gregory D. Lewis[18], Barry S. Clemson[19], Michael Fong[20] and Mikhail N. Kosiborod[1,2,21,22] ✉

- Dapagliflozin significantly improved **symptoms**, **physical limitations** and objectively measured **exercise function** in HFpEF pts.
- Consistent across all prespecified subgroups.

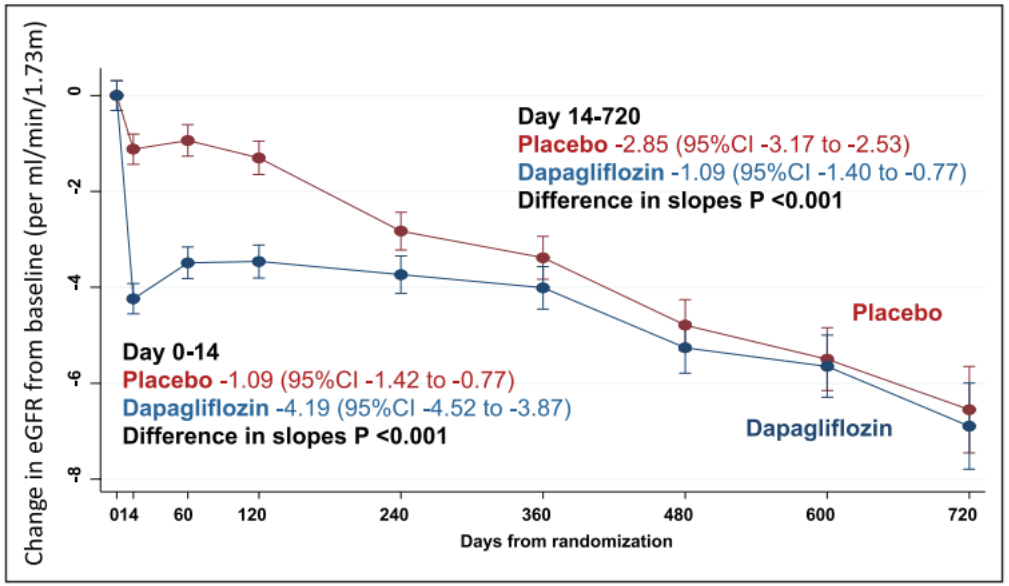




Focusing on HFpEF: Optimizing treatment

- Slower decline in eGFR in pts treated with SGLT2 (HFrEF)

DAPA-HF



Jhund P, McMurray JV. Circulation. 2021;143:298–309

EMPEROR-Reduced

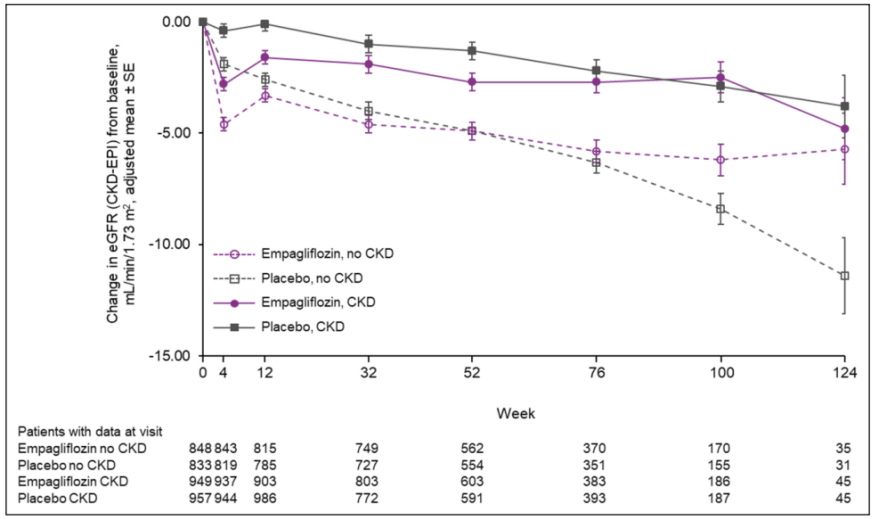
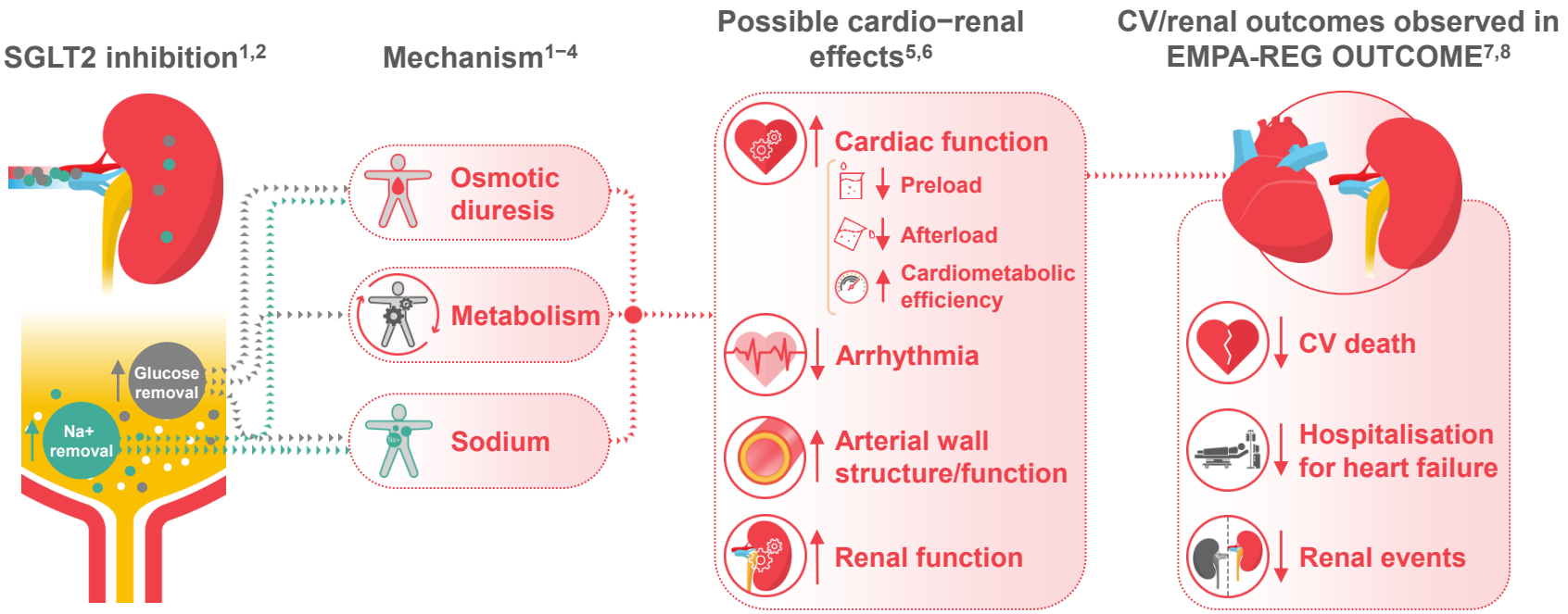


Figure 2. eGFR over time by CKD status at baseline.
Data for treated patients from a mixed model for repeated measures based on on-treatment data. Prevalent CKD defined as eGFR (CKD-EPI) <60 ml/min/1.73 m² or UACR >300 mg/g. CKD indicates chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; and UACR, urinary albumin-to-creatinine ratio.

Zannad F, et al. Circulation. 2021;143:310–321

Focusing on HFpEF: Optimizing treatment

Potential CV and renal function preservation mechanisms of empagliflozin that may benefit heart failure



Empagliflozin is not indicated in all countries for CV risk reduction and is not indicated for the treatment of heart failure

The pathways shown represent not yet proven hypotheses and may not apply to individual patients. The effects shown for renal function are based on the long-term results of empagliflozin versus placebo in EMPA-REG OUTCOME

1. Heise T *et al. Diabetes Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Zinman B *et al. N Engl J Med* 2015;373:2117; 8. Wanner C *et al. N Engl J Med* 2016;375:323

Dapaglifozin acutely improves endothelial dysfunction, reduces aortic stifness and renal resistive index [(PSV-PDV)/PSV] in type 2 diabetic patients: a pilot study

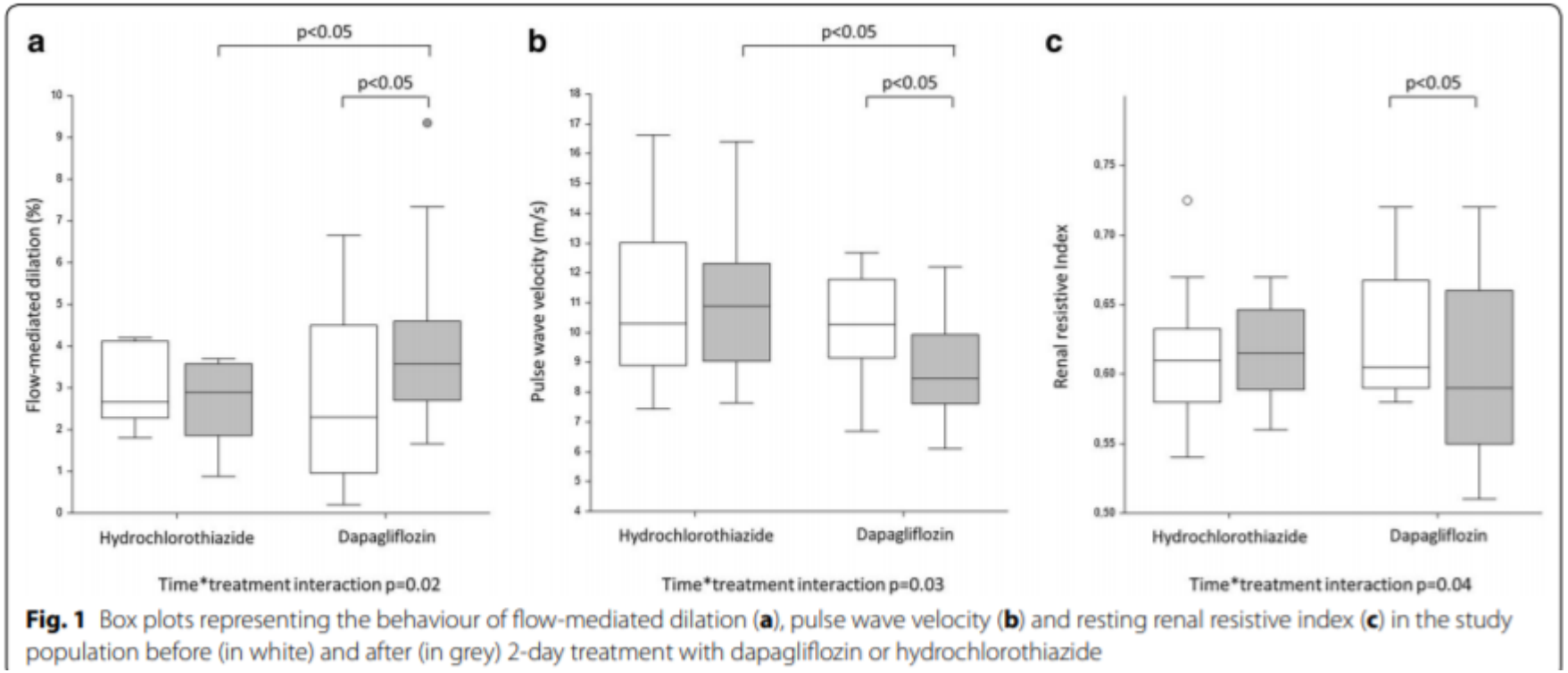


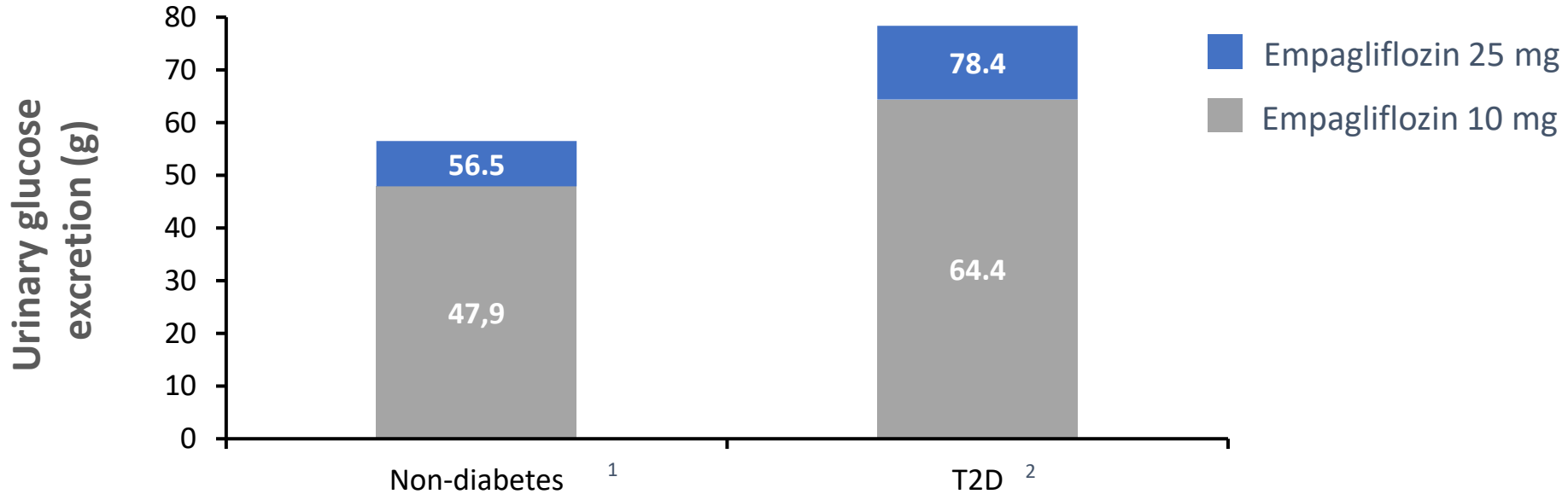
Fig. 1 Box plots representing the behaviour of flow-mediated dilation (**a**), pulse wave velocity (**b**) and resting renal resistive index (**c**) in the study population before (in white) and after (in grey) 2-day treatment with dapagliflozin or hydrochlorothiazide

- beside glycosuria, it increases free water excretion without modifying the urinary electrolyte profile.
- The lack of variation in natriuresis, even after a 2-day treatment, supports the hypothesis of an increased expression and/or functional activity of other sodium transporters that might account for an immediately increased distal Na reabsorption

Solini et al. Cardiovasc Diabetol (2017) 16:138

Empagliflozin-induced glucosuria occurs in diabetes and non-diabetes – both doses provide a similar amount of glucosuria

Glucose excreted within 24 hours after single dose

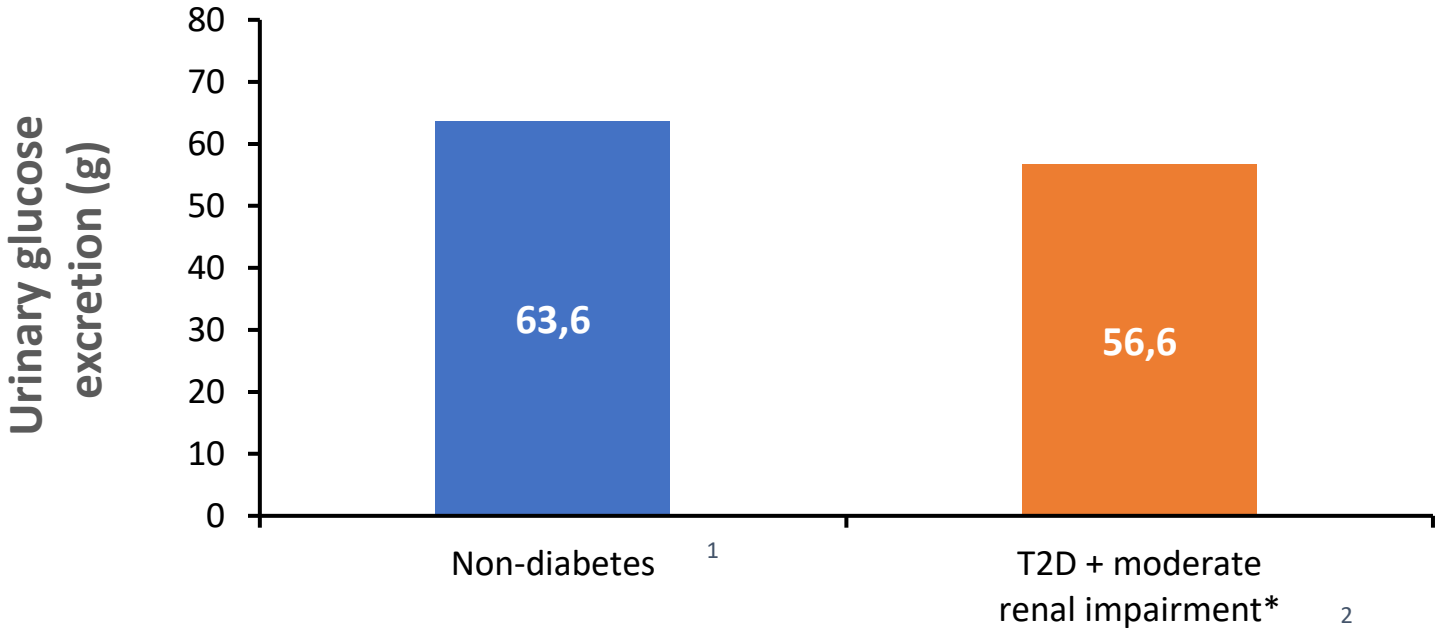


- In EMPA-REG OUTCOME, the reduction in CV outcomes was consistent between 10 mg and 25 mg doses of empagliflozin[3]
- A difference in the magnitude of glucosuria seen between 10 mg and 25 mg doses (and diabetes vs non-diabetes) may be unlikely to impact the risk of CV outcomes with empagliflozin[46]

Therefore, any potential association between empagliflozin-induced glucosuria and CV risk reduction may also be seen in T2D and non-diabetes

Glucosuria in non-diabetes is similar to that observed in T2D with moderate renal impairment

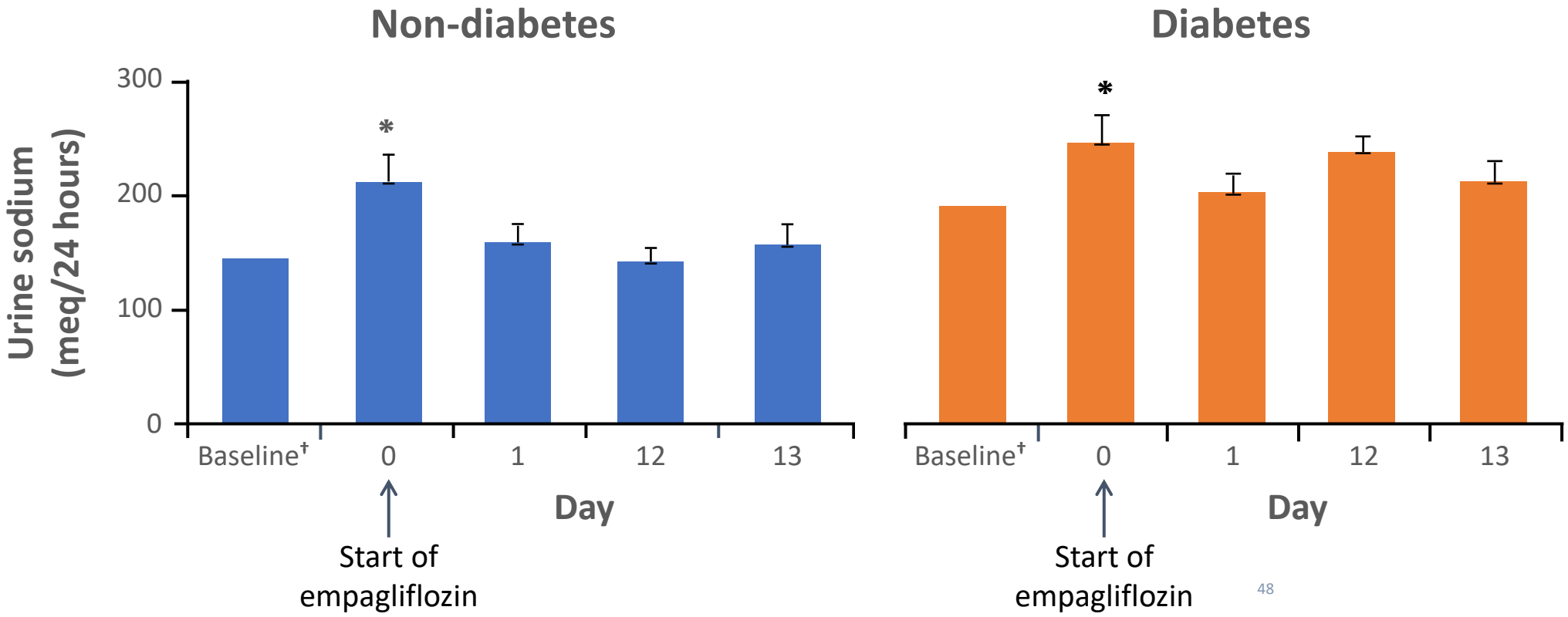
Glucose excreted within 24 hours after 50 mg single dose of empagliflozin



- In EMPA-REG OUTCOME, reduction in CV outcomes was consistent in patients with varying degrees of renal impairment[3]

Therefore, any potential association between empagliflozin-induced glucosuria and CV risk reduction may be independent of renal function

Transient urinary sodium excretion with empagliflozin is observed in non-diabetes, and in patients with T2D and preserved renal function



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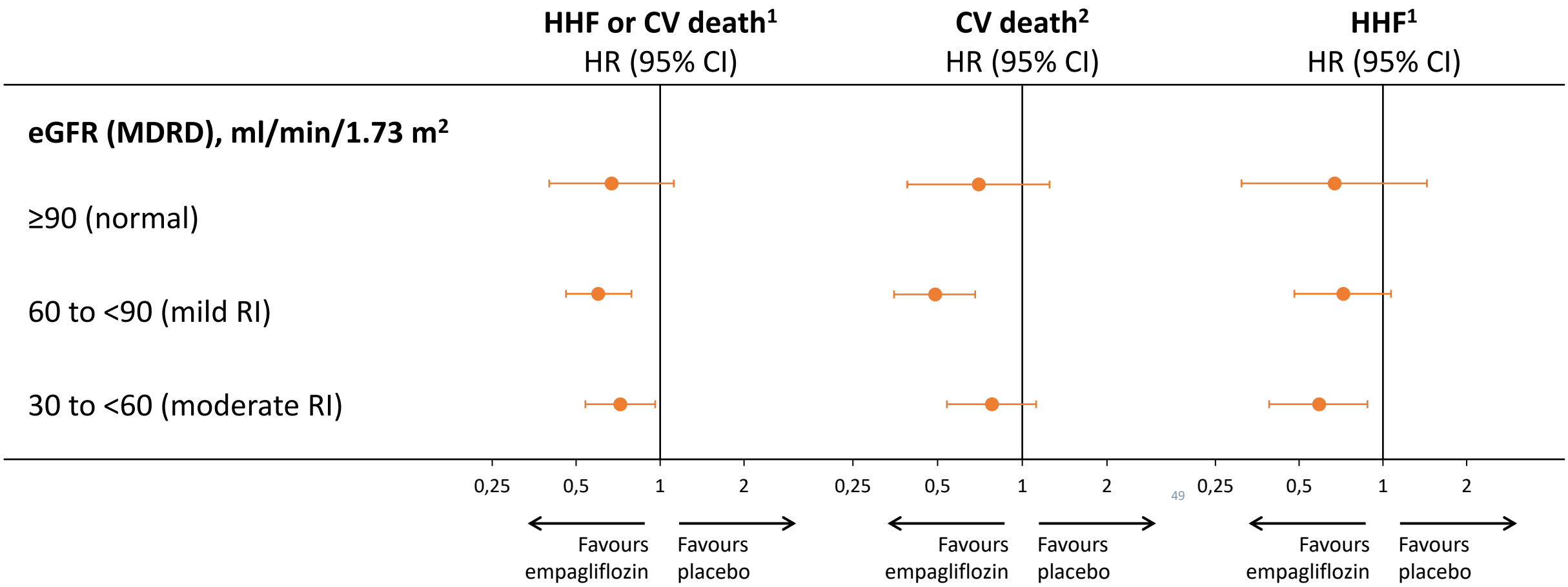
Therefore, any potential association between empagliflozin-induced natriuresis and CV risk reduction may also be seen in non-diabetes

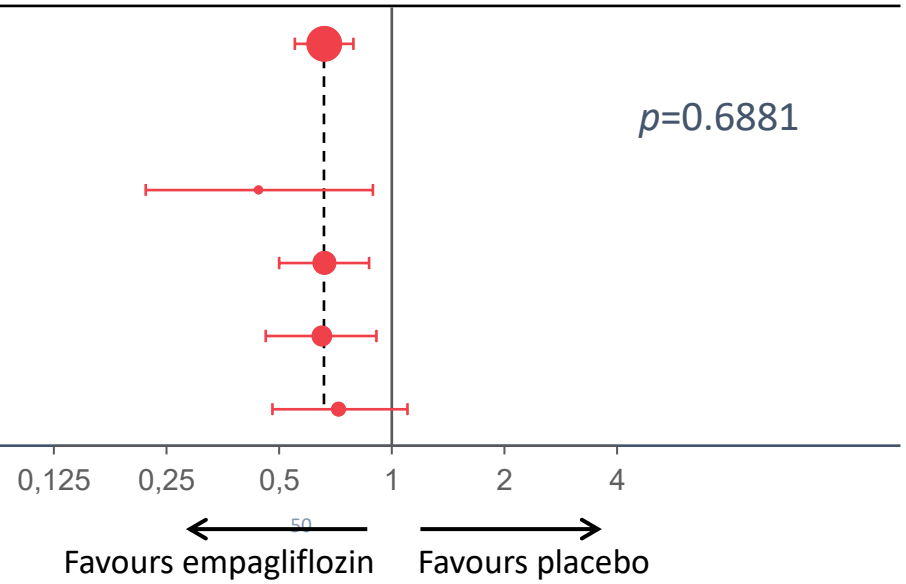
Renal impairment did not affect the CV benefits observed in EMPA-REG OUTCOME



Reduction in risk of HHF or CV death was consistent across subgroups by baseline HbA1c

HHF or CV death by HbA1c at baseline; *post hoc* analysis

	n with event/analysed (%)			Treatment by subgroup interaction
	Empagliflozin	Placebo	HR (95% CI)	
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)	
HbA1c at baseline				*p*=0.6881
<7.0%	16/297 (5.4)	15/127 (11.8)	0.44 (0.22, 0.89)	
7.0% to <8.0%	114/2042 (5.6)	86/1029 (8.4)	0.66 (0.50, 0.87)	
8.0% to <9.0%	77/1534 (5.0)	60/795 (7.5)	0.65 (0.46, 0.91)	
≥9.0%	57/812 (7.0)	37/382 (9.7)	0.72 (0.48, 1.10)	



Indirect evidence suggests non-diabetes patients with heart failure may benefit from empagliflozin

Metabolic principles of empagliflozin are similar in non-diabetes and T2D individuals

	Non-diabetes (N=25)		T2D (N=66)	
	Baseline	Chronic (28 days)	Baseline	Chronic (28 days)
Fasting UGE (AUC, g/h)	0.02	5.4	0.02	9.2
Plasma glucose, mmol/l	7.1	7.0	11.1	9.7
Plasma insulin, pmol/l	520	379	309	253
Plasma glucagon, pmol/l	19	18	18	19
Plasma βHB, mmol/l	145	267	246	561

The magnitude of metabolic changes **are discernable** in non-diabetes compared with those observed in patients with T2D

AUC, area under the curve; βHB, β-hydroxybutyrate; UGE, urinary glucose excretion

Adapted from: Ferrannini E *et al. Diabetes* 2016;65:1190 & supplementary appendix

Myocardial energy supply

- the use of SGLT2i through an increased metabolism of free fatty acid and an increased production of ketone bodies may provide a more efficient source of energy for the myocardium
- reduction of serum uric acid levels , hemoconcentration , improving endothelial function and aortic stiffness and may induce vasodilatation through activation of protein kinase G and the voltage-dependent K^+ channel
- GLT2inhibitors have been associated with increased circulating levels of β-hydroxybutyrate, a ketone body, likely due to glucagon-mediated ketogenesis. Ketones are freely taken up by myocardial cells and, compared with fatty acids, may potentially be a more efficient source of adenosine triphosphate for the failing heart.
- Thirdly, an emerging hypothesis is that SGLT2inhibitors can directly inhibit the myocardial sodium-hydrogen (Na+/H+) exchanger, which leads to increased mitochondrial calcium levels, improved mitochondrial function, reduced oxidative stress, and potentially reduced arrhythmias.

ESC HEART FAILUREESC Heart Failure(2019

Treating Disease Mechanisms in Patients With Heart Failure and Diabetes Mellitus

- SGLT2 inhibitors have been associated with an increase in erythropoietin, which in itself may have cardio-protective effects, and an increase in haemoglobin, which may result in enhanced oxygen delivery to the myocardium.
- The underlying mechanism for the increase in erythropoietin is thought to be due to favourable renal haemodynamic effects such as a reduced intra-glomerular pressure rather than haemoconcentration from diuresis.
- In comparison with placebo or hydrochlorothiazide, treatment with dapagliflozin is associated with a 7% decrease in plasma volume over a 12-week period
- Hematocrit was increased in EMPA-REG OUTCOME when compared with placebo, consistent with volume depletion in the absence of direct SGLT2 inhibitor effect on erythropoiesis

Curr Heart Fail Rep (2017) 14:445–453

Dapaglifozin acutely improves endothelial dysfunction, reduces aortic stifness and renal resistive index [(PSV-PDV)/PSV] in type 2 diabetic patients: a pilot study

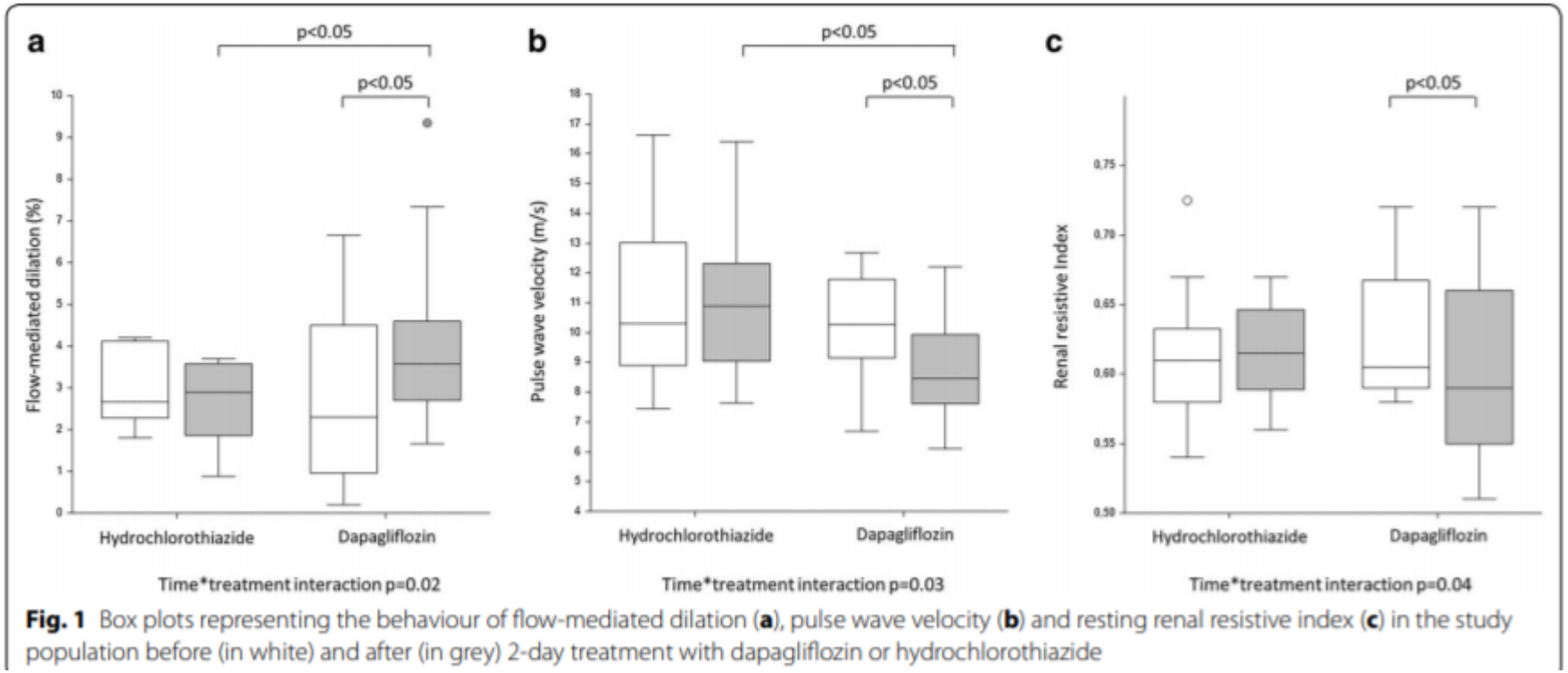
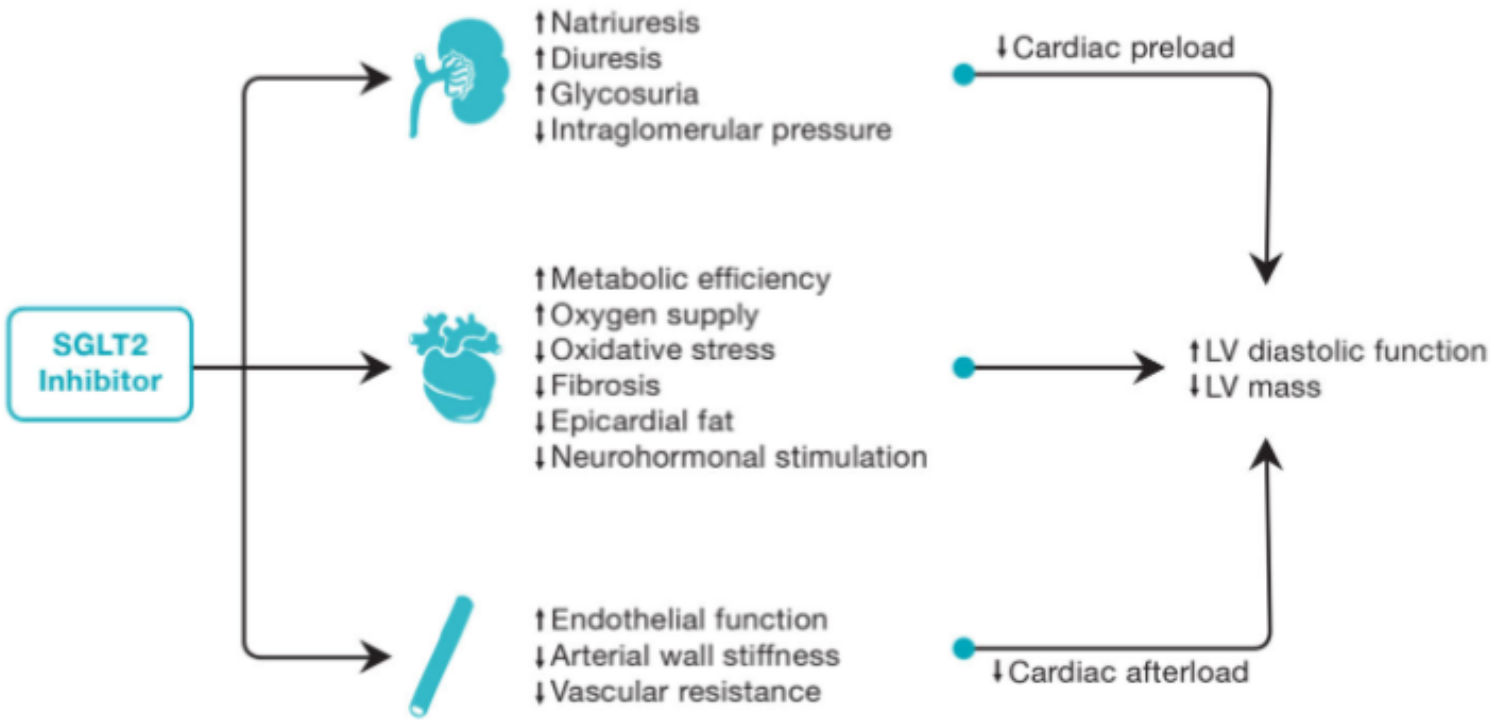


Fig. 1 Box plots representing the behaviour of flow-mediated dilation (**a**), pulse wave velocity (**b**) and resting renal resistive index (**c**) in the study population before (in white) and after (in grey) 2-day treatment with dapagliflozin or hydrochlorothiazide

- beside glycosuria, it increases free water excretion without modifying the urinary electrolyte profile.
- The lack of variation in natriuresis, even after a 2-day treatment, supports the hypothesis of an increased expression and/or functional activity of other sodium transporters that might account for an immediately increased distal Na reabsorption

Solini et al. Cardiovasc Diabetol (2017) 16:138

Figure 1 Potential mechanisms for improved left ventricular diastolic function and reduced left ventricular mass with sodium-glucose cotransporter 2 inhibitors. LV, left ventricular; SGLT2, sodium-glucose cotransporter 2.



ESC Heart Failure (2019)
DOI: 10.1002/ehf2.12505

The effects of sodium-glucose cotransporter2inhibitors on left ventricular function: current evidence and future directions

Table 1 Review of previous studies on SGLT2 inhibitors and LV function

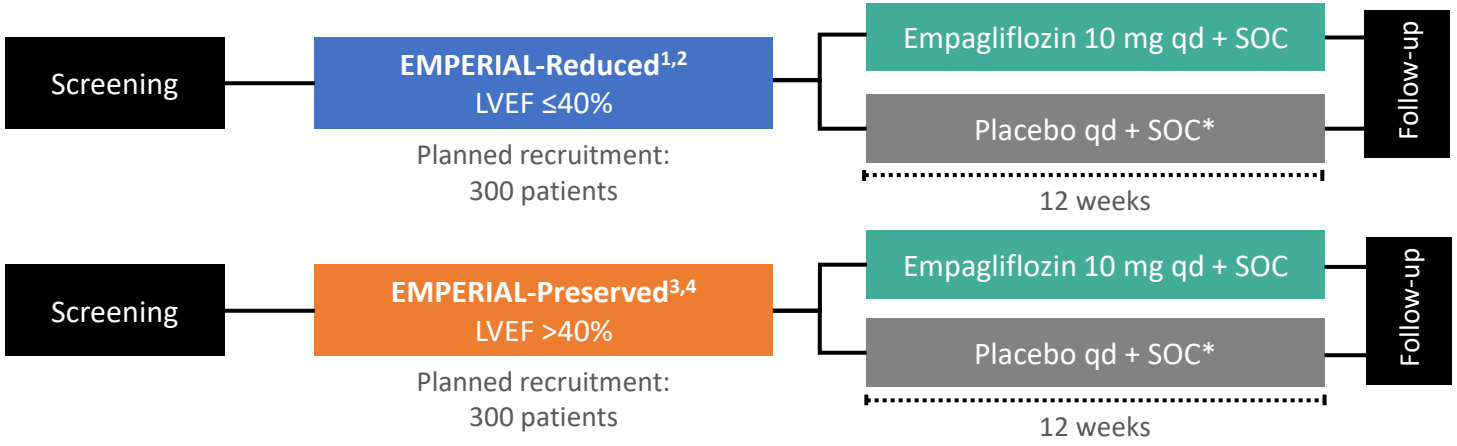
Author	SGLT2 inhibitor	Cohort	Imaging modality	Imaging findings
Verma S., *et al.*	Empagliflozin	10 people with T2DM and CVD	TTE before and 3 months after	• Improved LV diastolic function according to early lateral e' • Reduced LV mass index • No difference in LV volumes and LV EF
Matsutani D., *et al.*	Canagliflozin	37 people with T2DM and ≥2 CVD risk factors or CVD	TTE before and 3 months after	• Improved LV diastolic function according to the E/e' ratio • Reduced LV mass index • No difference in LV diameters, LV EF, and left atrial diameter
Soga F., *et al.*	Dapagliflozin	53 people with T2DM and stable HFrEF or HFpEF	TTE before and 6 months after	• Improved LV diastolic function according to the E/e' ratio • Reduced LV mass index and left atrial volume index • No difference in LV volumes • Improved LV EF
Sakai T., *et al.*[a]	Empagliflozin Luseogliflozin Tofogliflozin	59 people with T2DM and HFpEF 63 people with T2DM and HFpEF 62 people with T2DM and HFpEF	TTE before and 3 months after	• Improved LV diastolic function according to the E/A and E/e' ratios
Verma S., *et al.*[a]	Empagliflozin vs. placebo	97 people with T2DM and CVD (49 drug and 48 placebo)	Cardiac MRI before and 6 months after	• Improved LV mass index • No difference in LV EF and LV end-systolic volume
Cohen N., *et al.*	Empagliflozin vs. placebo	25 people with T2DM (17 drug and 8 placebo)	Cardiac MRI before and 6 months after	• Reduced LV end-diastolic volume • No difference in LV mass, LV EF, atrial volumes, and markers of cardiac fibrosis

EMPERIAL-Reduced and EMPERIAL-Preserved studies

International phase III randomised double-blind placebo-controlled studies

Aim: To evaluate the effect of empagliflozin 10 mg versus placebo on exercise ability using the 6MWT in patients with HF with **reduced** or **preserved** ejection fraction

Population: Chronic HF (HFrEF or HFpEF), with/without T2D



*Guideline-directed medical therapy

6MWT, 6-minute walk test; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction

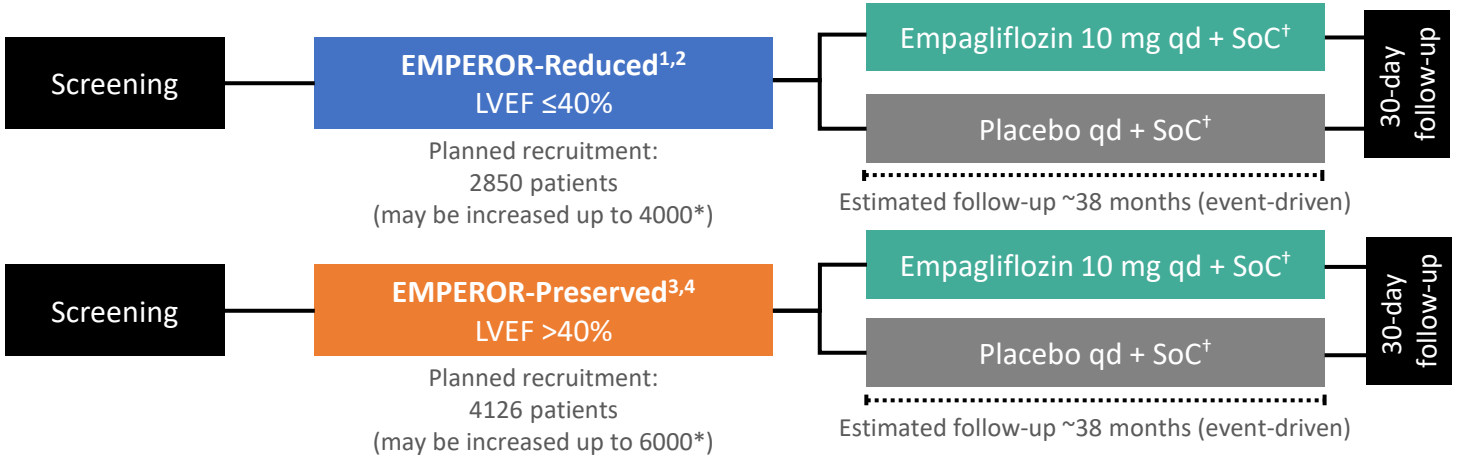
1. ClinicalTrials.gov. NCT03448419; 2. Abraham WT *et al. ESC-HF* 2018; poster P303; 3. ClinicalTrials.gov. NCT03448406;
4. Ponikowski P *et al. ESC-HF* 2018; poster P302

EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials

Phase III randomised double-blind placebo-controlled studies

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with **reduced** or **preserved ejection fraction**

Population: T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)



*Based on blinded assessment of event rate; †Guideline-directed medical therapy

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SoC, standard of care

1. ClinicalTrials.gov. NCT03057977; 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951; 4. Butler J *et al. ESC-HF* 2018; poster P972

European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1170

HFA POSITION PAPER

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1]*, Mark C. Petrie[2], Gerasimos S. Filippatos[3], Stefan D. Anker[4],

Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization
GLP-1 receptor agonists			
ELIXA[23]	Lixisenatide	Placebo	No effect on HF hospitalization
LEADER[22]	Liraglutide	Placebo	No effect on HF hospitalization
SUSTAIN-6[186]	Semaglutide	Placebo	No effect on HF hospitalization
EXSCEL[24]	Exenatide	Placebo	No effect on HF hospitalization
SGLT2 inhibitors			
EMPA-REG OUTCOME[20]	Empagliflozin	Placebo	Reduced HF hospitalization
CANVAS[21]	Canagliflozin	Placebo	Reduced HF hospitalization

Class of drug	Evidence
SGLT2 inhibitors (e.g. empagliflozin, canagliflozin)	No RCTs in HF. Large RCTs in patients with HF with an without T2DM are underway
Metformin	No RCTs in HF. In observational studies in HF, metformin is associated with lower mortality rates than sulphonylureas or insulin.[179] Benefit/risk ratio unknown.
GLP-1 receptor antagonists (e.g. liraglutide, albiglutide)	No large RCTs. Liraglutide - two small RCTs reported no effect on (i) LV function,[180] (ii) hierarchical composite of death/HF hospitalization/BNP change.[181] Benefit/risk ratio unknown.
Sulphonylureas	No RCTs in HF. Data equivocal. Some observational data suggest an increased mortality risk with sulphonylureas compared with metformin.[179,182]
Insulin	No RCTs in HF. In observational studies in HF, insulin was associated with higher mortality rates than metformin.[179] Benefit/risk ratio unknown.
DPP4 inhibitors	No RCTs in HF (saxagliptin contraindicated in HF[16,17]). Benefit/risk ratio unknown.

BNP, B-type natriuretic peptide; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; LV, left ventricular; RCT, randomized clinical trial; SGLT2, sodium–glucose co-transporter type 2; T2DM, type 2 diabetes mellitus.

Table 2 Ongoing studies on SGLT2 inhibitors and LV function

Study name	SGLT2 inhibitor	Anticipated cohort	Imaging modality	Imaging outcome	Estimated end date
Research Into the Effect of SGLT2 Inhibition on Left Ventricular Remodeling in Patients With Heart Failure and Diabetes Mellitus (REFORM) (*NCT02397421*)	Dapagliflozin vs. placebo	56 people with T2DM and HFrEF	Cardiac MRI before and 12 months after	Primary: Change in LV end-systolic and end-diastolic volumes Secondary: Change in LV mass and EF, RV volumes and EF, atrial size, and LV remodelling index	August 2017 (not reported)
Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes? (DAPA-LVH) (*NCT02956811*)	Dapagliflozin vs. placebo	64 people with T2DM and LV hypertrophy	Cardiac MRI before and 12 months after	Primary: Change in LV mass Secondary: Change in LV diastolic function and global longitudinal strain	March 2019
Effects of Empagliflozin on Left Ventricular Diastolic Function Compared to Usual Care in Type 2 Diabetics (EmDia) (*NCT02932436*)	Empagliflozin vs. placebo	158 people with T2DM and LV diastolic dysfunction (E/e' ratio $\geq$ 8)	TTE before and 3 months after	Primary: Change in E/e' ratio Secondary: Change in LV EF and end-diastolic volume	June 2019
EMPA-HEART trial[a]	Empagliflozin vs. sitagliptin	75 people with T2DM and subclinical LV dysfunction	TTE before and at 1 month and 6 months after	Primary: Change in global longitudinal strain Secondary: Change in EF, left atrial volume, and E/e' by 3-D TTE	July 2019
Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? (ATRU-4) (EMPA-TROPISM) (*NCT03485222*)	Empagliflozin vs. placebo	80 people with T2DM and HFrEF	Cardiac MRI before and 6 months after	Primary: Change in LV end-systolic and end-diastolic volumes Secondary: Change in LV EF	December 2020
ERtugliflozin triAl in DIabetes With Preserved or Reduced ejeCtion FrAcTion mEchanistic Evaluation in Heart Failure (ERADICATE-HF) (*NCT03416270*)	Ertugliflozin vs. placebo	36 people with T2DM and HF	TTE before and at 1 week and 3 months after	Primary: N/A Secondary: Change in systolic and diastolic function	March 2021

HF-related costs are substantial and contribute to the growing economic burden of T2D management

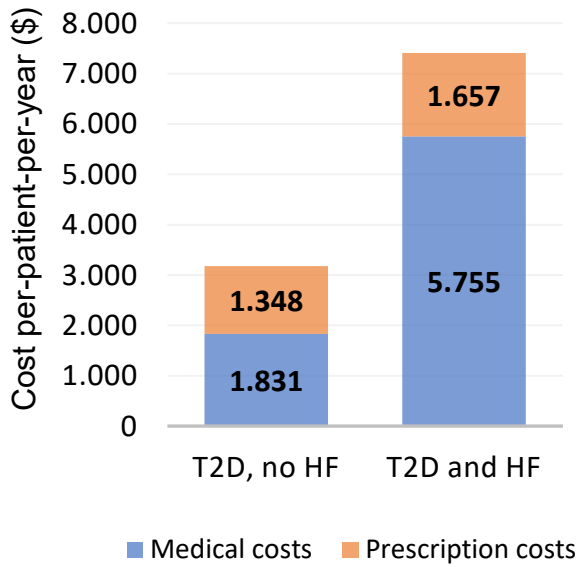
Treatment of HF in T2D patients is associated with a **substantial additional cost of care**[1–4]

Annual cost of treating HF in T2D patients

Country	Annual cost (per-patient-per-year)
USA[1]	$10,630
UK[2]	£3,191
Germany[3]	€6,930
Spain[4]	€6,866

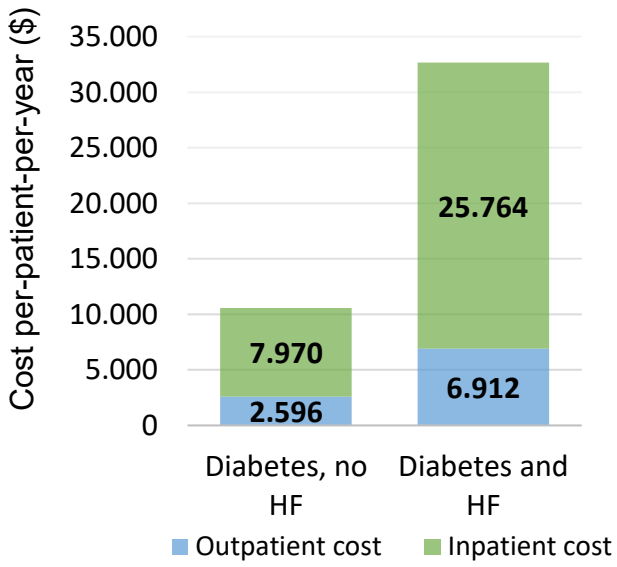
In the US, **T2D patients with HF face higher** per-patient-per year diabetes-related **medical costs and prescription costs** than T2D patients without HF[5]

Annual cost of care for T2D patients with and without HF[5]



In the US, **among elderly** (>65 years of age) **diabetic patients**, both **outpatient and inpatient costs are** significantly **higher for those with HF**, compared to those without HF[6]

Annual unadjusted cost of care for elderly diabetic patients with and without HF[6]



Abbreviations: HF: Heart Failure; T2D: Type 2 Diabetes

References: **1.** Li, R. et al., *Am J Manag Care,* 2013; Vol. 5, pp. 421-430; **2.** Alva, M.L. et al., *Diabet Med*., 2015; Vol. 32, pp. 459-466; **3.** Kähm, K. et al., *Diabetes Care,* 2018; Vol. 41, pp. 971-978; **4.** Mata-Cases, M. et al., *Eur J Health Econ.,* 2016; Vol. 17, pp. 1001-1010; **5.** Lin, D. et al., *Value in Health,* ISPOR poster PDB63, 2019; **6.** Bogner, H.R. et al., *J Card Fail.,* 2010; Vol. 16, pp. 454-460

Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial

Jelena P Seferovic, Brian Claggett, Sara B Seidelmann, Ellen W Seely, Milton Packer, Michael R Zile, Jean L Rouleau, Karl Swedberg, Martin Lefkowitz, Victor C Shi, Akshay S Desai, John J V McMurray, Scott D Solomon

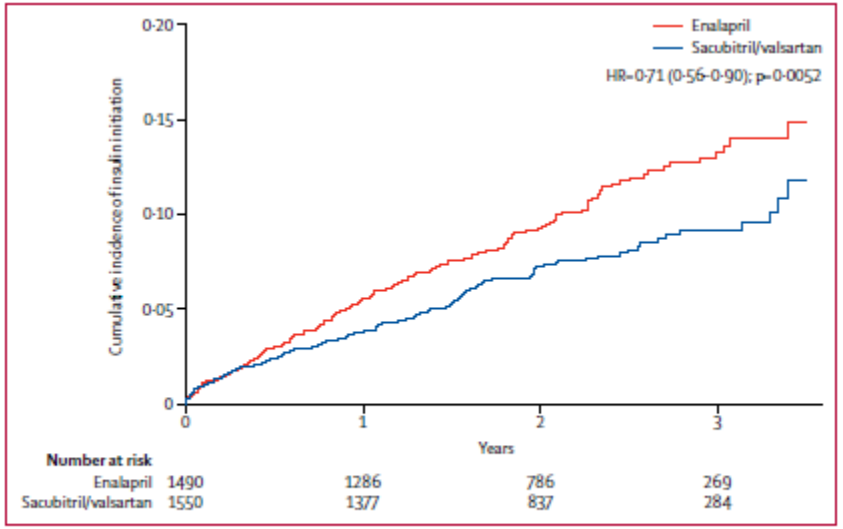


Figure 2: Kaplan-Meier curve showing time to insulin initiation in the sacubitril/valsartan and enalapril groups, in patients previously not treated with insulin

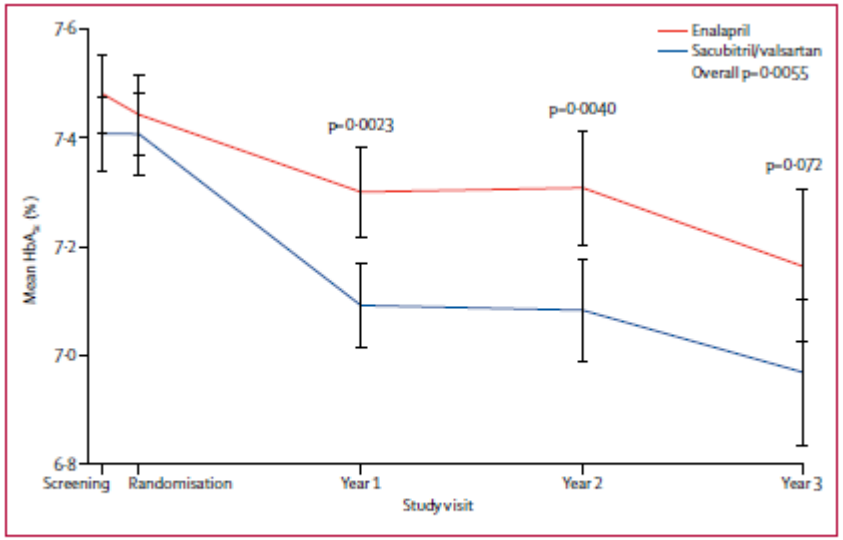


Figure 1: Changes in mean HbA_{1c} and confidence intervals by treatment group at screening, randomisation, 1-year, 2-year, and 3-year visits

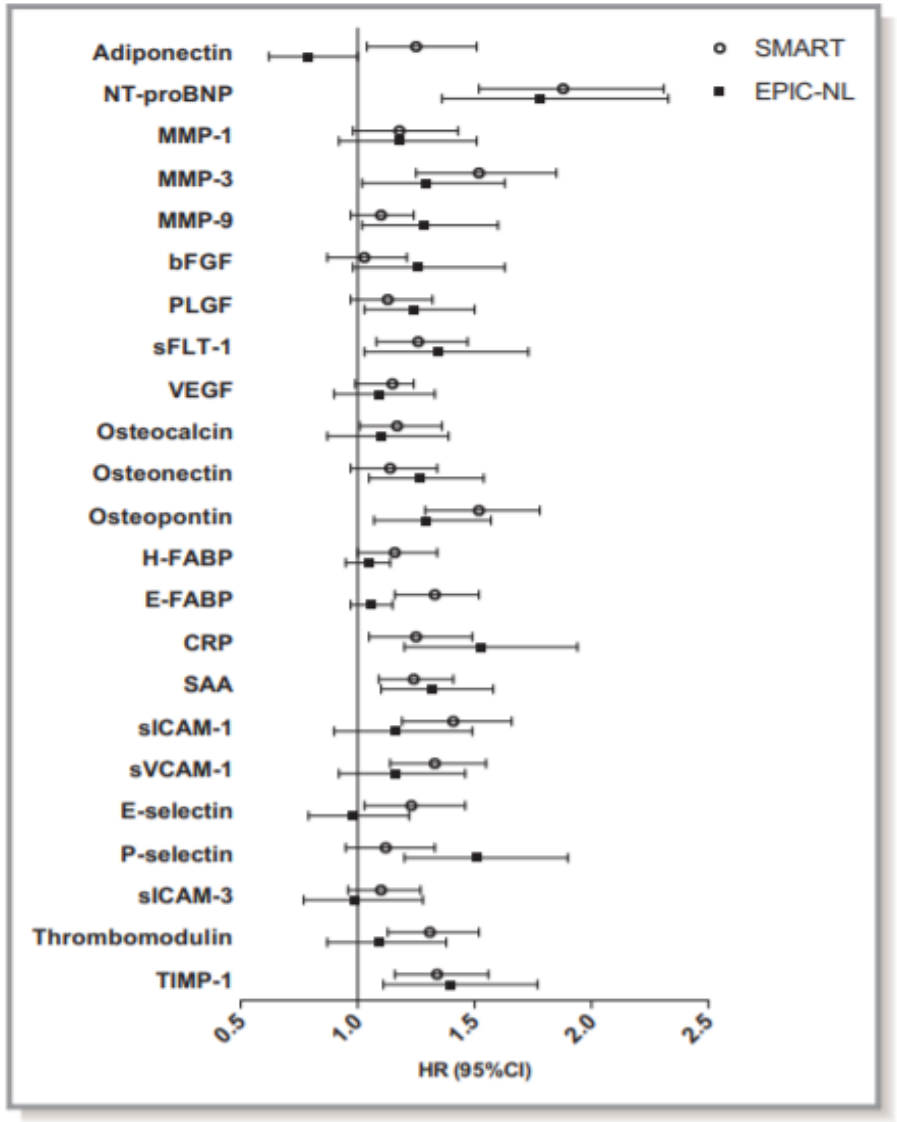
In this post-hoc analysis of patients with mostly type 2 diabetes and HFrEF from the PARADIGM-HF study, we found that treatment with sacubitril/valsartan was associated with greater reductions in HbA1c concentrations than treatment with enalapril.

Lancet Diabetes Endocrinol 2017

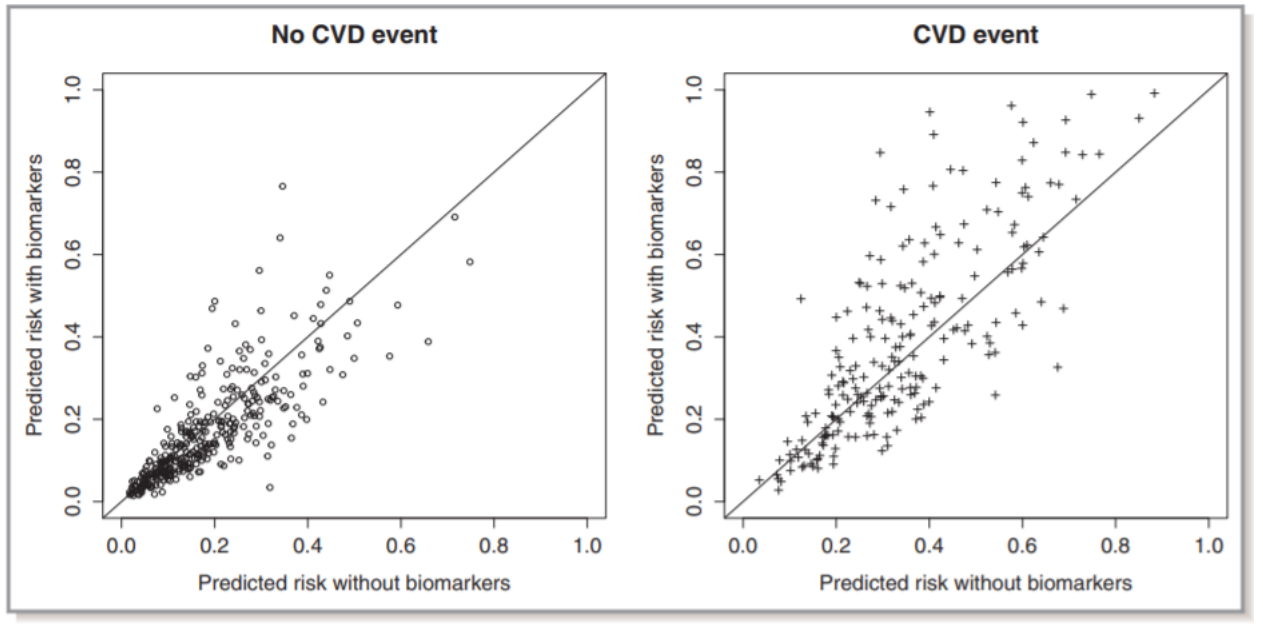
Role of biomarkers for outpatient management (monitoring, risk stratification, therapy switch)

Novel Biomarkers to Improve the Prediction of Cardiovascular Event Risk in Type 2 Diabetes Mellitus

Journal of the American Heart Association
OPEN ACCESS
American Heart Association | American Stroke Association

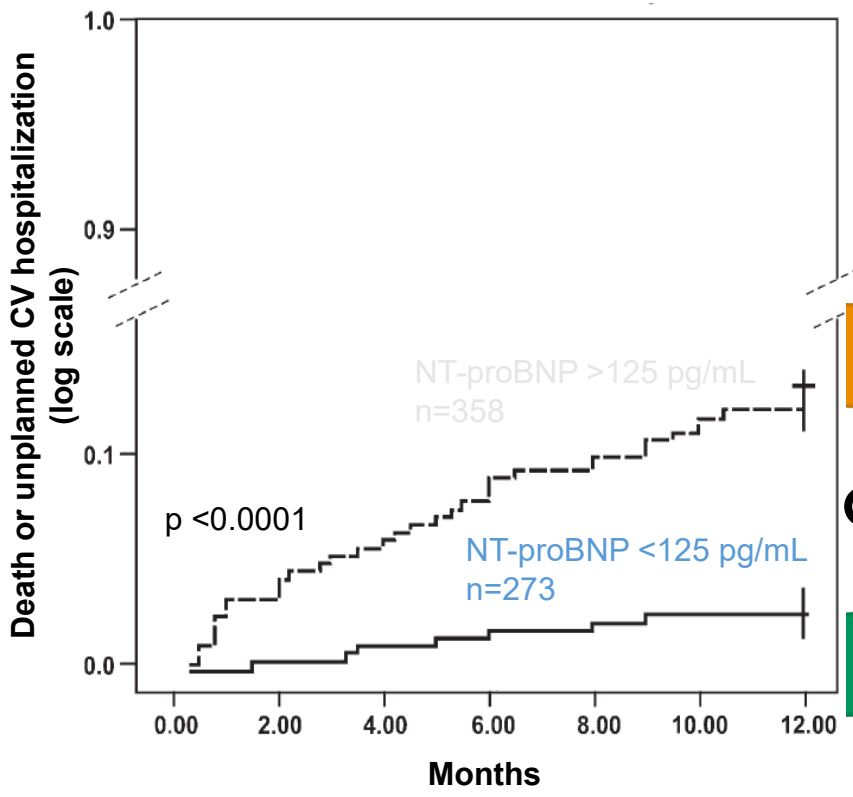


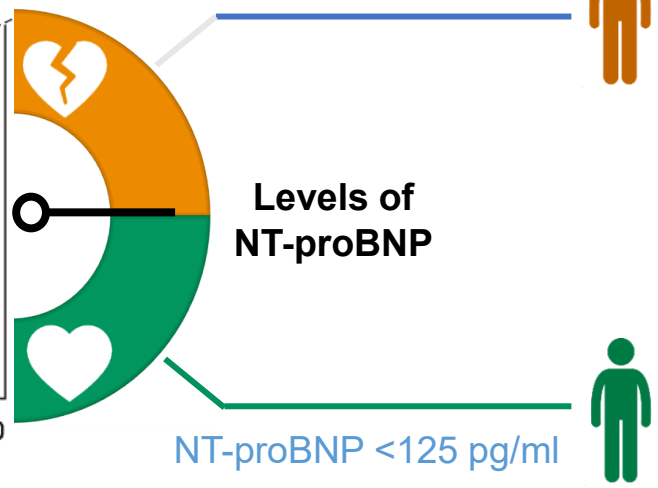
- Of 23 biomarkers evaluated, NT-proBNP, osteopontin, and MMP-3 and their combination resulted in the largest improvement in predictive performance beyond traditional risk factors.
- NT-proBNP is a polypeptide secreted by cardiomyocytes in response to increased ventricular stretch and wall tension



NT-proBNP levels help to identify T2D patients asymptomatic for HF who are at high [*low*] risk of CV complication, especially HF, and who would [*not*] benefit from further assessment

Kaplan–Meier curves of all-cause mortality or unplanned CV hospitalization according to initial NT-proBNP concentration[1]





Action required

Patients with high NT-proBNP have a 2.96 times higher risk of experiencing unplanned hospitalization for CV events or death than patients with low NT-proBNP, within the observation period of 12 months

No action required for one year

Patients with low NT-proBNP have a 2.96 times lower risk of experiencing unplanned hospitalization for CV events or death than patients with high NT-proBNP, within the next 12 months

Abbreviations: CV: Cardiovascular; HF: Heart Failure; T2D: Type 2 Diabetes
For more information, please see Huelsmann 2008 publication summary slides
References: **1.** Huelsmann, M. et al., *Eur Heart J*., 2008; Vol. 29, pp. 2259-2264

Key points

- Many people with diabetes have stage B HF, defined as asymptomatic with at least one of the following: 1) evidence of structural heart disease, 2) abnormal cardiac function, or 3) elevated natriuretic peptide levels or elevated cardiac troponin levels. •
- Early diagnosis of HF could enable targeted treatment to prevent adverse outcomes. •
- Measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify the presence of stage B HF and to determine risk for progression to symptomatic HF.
- Optimal medical treatment and close clinical assessment can reduce risk.