Diabetic Cardiomyopathy

Ariel COHEN, Paris,

Webinar CNCH

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Disclosures

DISCLOSURE STATEMENT
Ariel COHEN, MD, PhD, FESC, FACC

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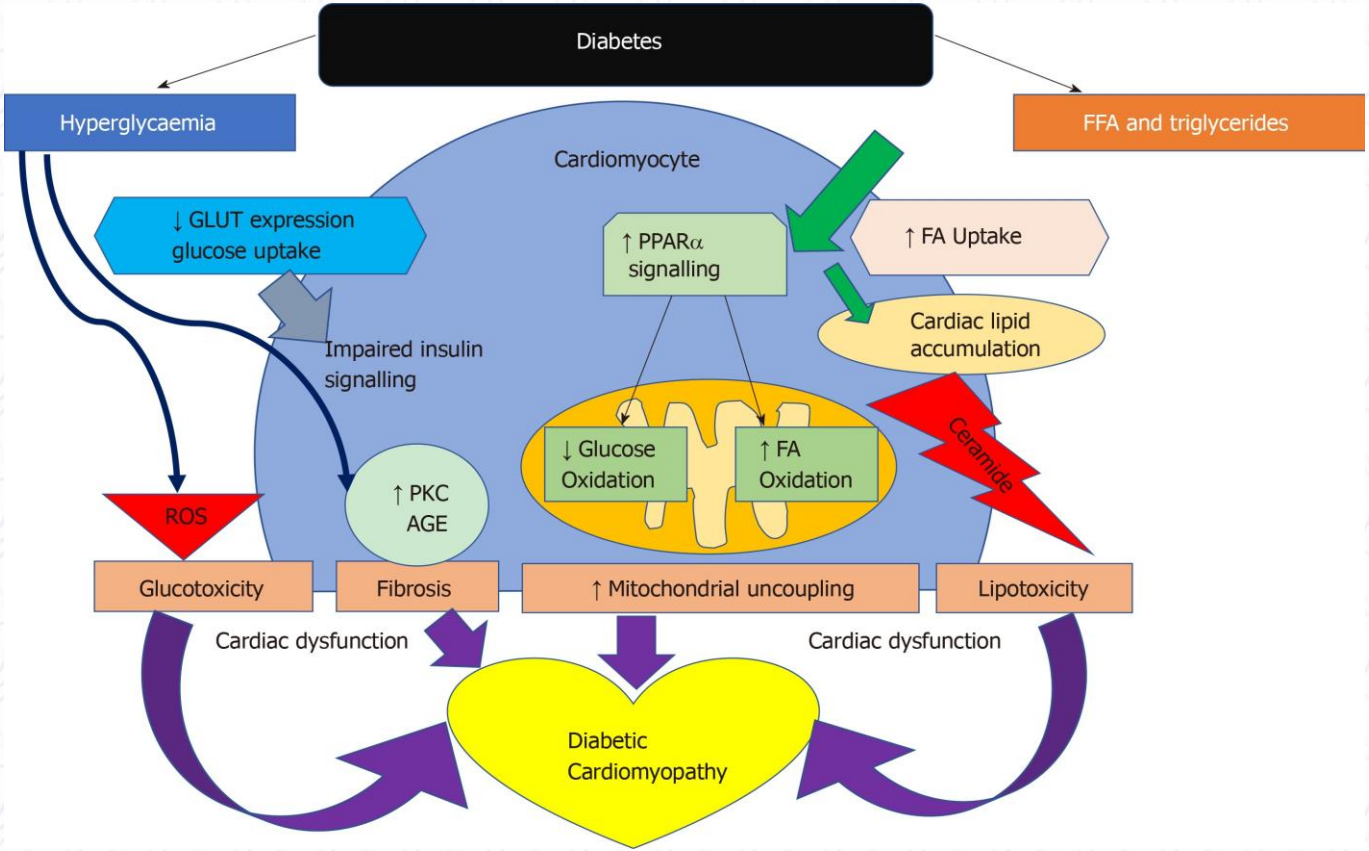
Pathways of cardiac dysfunction leading to diabetic cardiomyopathy



AGE: Advanced glycation end products; FA: Fatty acids; FFA: Free fatty acids; GLUT: Glucose transporters; PKC: Protein kinase C; PPARα: Peroxisome proliferator- activated receptor alpha; ROS: Reactive oxygen specie

Athithan L. World J Diabetes 2019;10: 490-510

Diabetic cardiomyopathy

1- Epidemiology: diabetes in cardiovascular diseases

Epidemiology

LV function / HF	Technique / Event	percentage
Left ventricular dysfunction		
Impaired LV diastolic function	DTI	40%
Impaired LV systolic function	DTI and 2D speckle tracking echocardiography (asymptomatic patient)	43%
Heart failure and diabetes		
	Framingham Study, men/women with diabetes	M: 2.4-fold W: 5-fold
	Diabetes in HF	24–40% (30% in HFPEF)
	Prevalence of HF in diabetes if age > 65 years	22%

Epidemiology: morbi-mortality

LV function / HF	Technique / Event	percentage
Heart failure and diabetes		
	3-year mortality in heart failure with diabetes	40%[1]
	Risk of requiring admission to hospital due to HF Patients with diabetes (vs no diabetes).	30% greater risk
	3-year cardiovascular mortality in diabetes admitted to hospital with HF	23–30%

Prospective randomized treatment trials in patients with type 2 diabetes reporting heart failure as a cardiovascular outcome

Trials comparing intensity of glucose lowering

	UKPDS (n=3 867)	ADVANCE (n=11 140)	ACCORD (n=10 251)	VADT (n=1 791)
Median/mean duration of diabetes (y)	-	8	10	11-5
Median/mean FU (years)	10	5	3,5	5,6
Outcomes				
CV deaths, n (%)	-	542 (5%)	229 (2%)	67 (4%)
All MI, n (%)	573 (15%)	679 (6%)	-	142 (8%)
All stroke, n (%)	203 (5%)	484 (4%)	-	64 (4%)
All HF, n (%)	116 (3%)	-	276 (3%)	158 (9%)

McMurray JJV. Lancet Diabetes Endocrinol 2014; 2: 843–51

Cardiovascular events in diabetic subgroups of patients in clinical trials of patients with chronic arterial disease, hypertension, or acute MI

Diabetic subgroup from trials in patients with chronic arterial disease, HT, or both

	HOPE (MICRO-HOPE ; n = 3577)	EUROPA (PERSUADE n= 1 502)	LIFE (n= 1 195)	VALUE (n=5 250)	ACCOMPLISH (n=6 946)
Participants	Age ≥ 55y with CVD ; or ≥1 CV risk factor	Age > 18y ; CHD	Age 55-80y ; HT ; LVH	Age ≥ 50y ; HT; CVD or CV risk factors	Age ≥ 50y ; HT ; CVD or CV risk factors
Exclusion criteria	Nephropathy, HF or LVEF <40%	HF	HF or LVEF <40%	HF requiring an ACE inhibitors	HF or LVEF <40% requiring an ACE inhibitor
Median/mean FU (years)	4,5	4,3	4,7	4,2	2,5
Outcomes					
CV deaths, n (%)	284 (8%)	107 (7%)	99 (8%)	286 (5%)	136 (2%)
All MI, n (%)	414 (12%)	134 (9%)	91 (8%)	299 (6%)	168 (2%)
All stroke	184 (5%)	41 (3%)	116 (10%)	234 (4%)	134 (2%)
All HF	434 (12%)	39 (3%)	-	412 (8%)	141 (2%)

Diabetic cardiomyopathy

1- Epidemiology: diabetes in cardiovascular diseases

3- Diabetic cardiomyopathy

Definition / Pathophysiology / diagnosis

THE LANCET] ORIGINAL ARTICLES [FEB. 20, 1954

DIABETIC ANGIOPATHY
A SPECIFIC VASCULAR DISEASE

KNUD LUNDBÆK
M.D. Copenhagen
PROFESSOR OF INTERNAL MEDICINE IN THE UNIVERSITY OF AARHUS, DENMARK
From the Second University Clinic of Internal Medicine, Kommunehospitalet, Aarhus

be regarded as "complicating disease"—arteriosclerosis, atherosclerosis, medial sclerosis, diffuse arteriolar sclerosis, or any other more or less well-known and more or less well-defined vascular disease?

Until recently the vascular diseases in diabetes mellitus were usually classified as arteriosclerosis, and the high incidence of these anomalies was usually dealt with only by stating that diabetes mellitus promotes the

Archives of Cardiovascular Disease (2012) 105, 218–225

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Elsevier Masson France EM|consulte www.em-consulte.com/en

REVIEW

Diabetic cardiomyopathy: Myth or reality?

Cardiomyopathie diabétique : mythe ou réalité?

Laura Ernande[a,*,b], Geneviève Derumeaux[a,b]

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Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus

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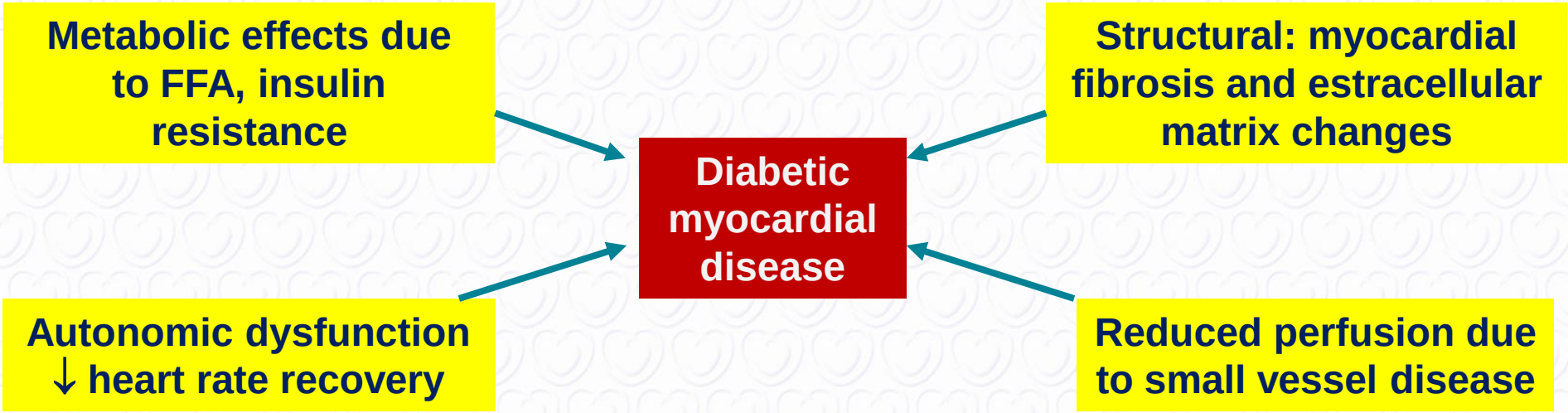
Diabetic cardiomyopathy

Definition and pathophysiology

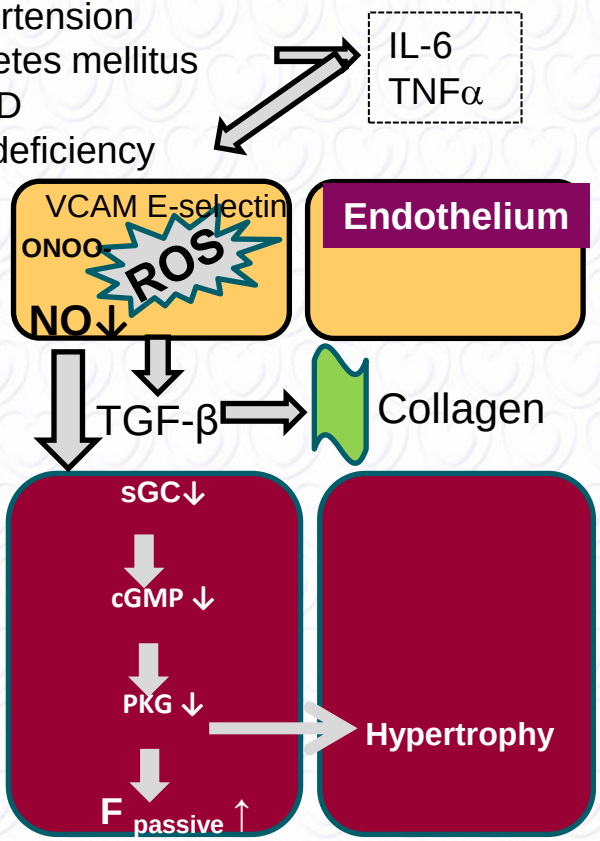
Diabetic heart disease («*Diabetic myocardial disease* ») is defined as myocardial disease in patients with diabetes that cannot be ascribed to hypertension, coronary artery disease, or other known cardiac disease.



Subclinical CAD and LVH excluded

Heart failure with preserved ejection fraction: HFPEF

Overweight/obesity
Hypertension
Diabetes mellitus
COPD
Iron deficiency



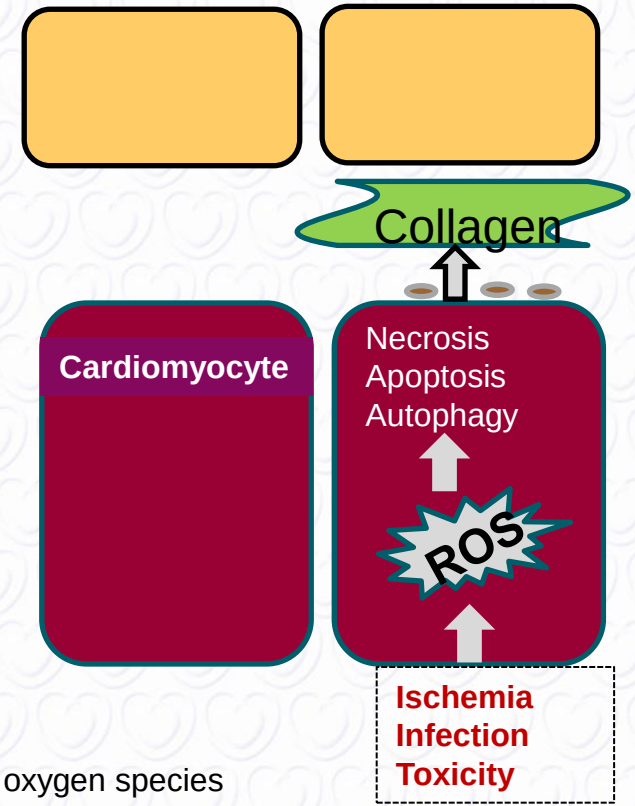
Myocardial dysfunction and remodeling are driven by endothelial inflammation and oxidative stress

PKG: protein kinase G activity

Paulus W. J Am Coll Cardiol 2013;62:263–71

Myocardial Dysfunction and Remodeling in HFPEF, HFREF, and Advanced HFREF

Heart failure with reduced ejection fraction: **HFREF**



Oxidative stress originates in the cardiomyocytes because of ischemia, infection, or toxic agents.

ROS (reactive oxygen species**) trigger cardiomyocyte autophagy, apoptosis, or necrosis.**

Necrosis attracts leukocytes.

Dead cardiomyocytes are replaced by fibrous tissue.

ROS: reactive oxygen species

Paulus W. J Am Coll Cardiol 2013;62:263–71

Diabetic cardiomyopathy

Diagnostic tools

Tool	Parameter
Clinical diagnosis	Asymptomatic patients with diabetes
ECG	Aspecific
2D-echocardiography	**LVEF** (3D > 2D >> M-mode), LV - RV - LA remodelling
Doppler echo	Diastolic dysfunction (E/e', IVRT, LA size..)
Speckle imaging	Strain (longitudinal, radial…)
MRI	**LVMI, LVEF**. LV - RV - LA remodelling
Biomarkers	BNP, NT-pro-BNP…
Exercise capacity	↓peak oxygen consumption (VO_2) and VO_2 at submaximal levels of exercise

Diabetic cardiomyopathy

1- Epidemiology: diabetes in cardiovascular diseases

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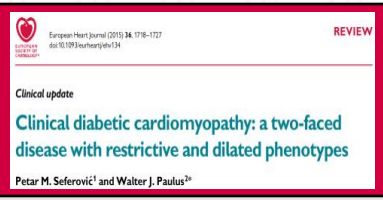
Definition / Pathophysiology / diagnosis

Restrictive *versus* dilated phenotypes

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

	DMCMP with restrictive/HFPEF phenotype	DMCMP with dilated/HFREF phenotype
Hyperglycaemia	+++	+
Lipotoxicity	+++	+
AGEs deposition	+++	+++
Microvascular rarefaction	+++	+++
Autoimmunity	-	+++
Insulin resistance/hyperinsulinaemia	+++	-

AGEs, advanced glycation end-products

Seferovic PM. Eur Heart J 2015; 36: 1718–27

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

Diagnostic criteria for diabetic cardiomyopathy (DMCMP)

DMCMP restrictive / HFPEF phenotype

1- **Presence of DM**
2- Exclusion of CAD, valvular or congenital heart disease
3- Exclusion of hypertensive heart disease (=DBP < 90 mmHg)
4- Exclusion of infiltrative heart disease by endomyocardial biopsy
5- **LVEF > 50%** ; **LVEDVI < 97mL/m²**

6- E/E'> 15 or
8<E/E'<15+LAVI> 40 mL/m² or
8<E/E'<15+BNP > 200 pg/mL or
8<E/E'<15+AF or
8<E/E'<15+LVH (LVMI (women) >122g/m² ; LVMI (men) > 149 g/m²

DMCMP dilated / HFPEF phenotype

1- **Presence of DM**

2- Exclusion of CAD, valvular or congenital heart disease
3- Exclusion of hypertensive heart disease (=DBP < 90 mmHg)

4- Exclusion of myocarditis by endomyocardial biopsy

5- **LVEF <50%** ; **LVEDVI > 97mL/m²**

Seferovic PM. Eur Heart J 2015; 36: 1718–27

Diastolic Dysfunction in Patients with Type 2 Diabetes Mellitus: Is It Really the First Marker of Diabetic Cardiomyopathy?


Diastolic Dysfunction in Patients with Type 2 Diabetes Mellitus: Is It Really the First Marker of Diabetic Cardiomyopathy?

Laura Ernande, MD, Cyrille Bergerot, MD, Ernst R. Rietzschel, MD, PhD, Marc L. De Buyzere, PhD, Hélène Thibault, MD, PhD, Pierre Gautier PignonBlanc, MD, Pierre Croisille, MD, PhD, Michel Ovize, MD, PhD, Laure Groisne, MD, Philippe Moulin, MD, PhD, Thierry C. Gillebert, MD, PhD, and Geneviève Derumeaux, MD, PhD, *Lyon, France; Ghent, Belgium*

Prospective

114 patients with type 2 diabetes mellitus (DM) with controlled BP without overt heart disease were prospectively enrolled

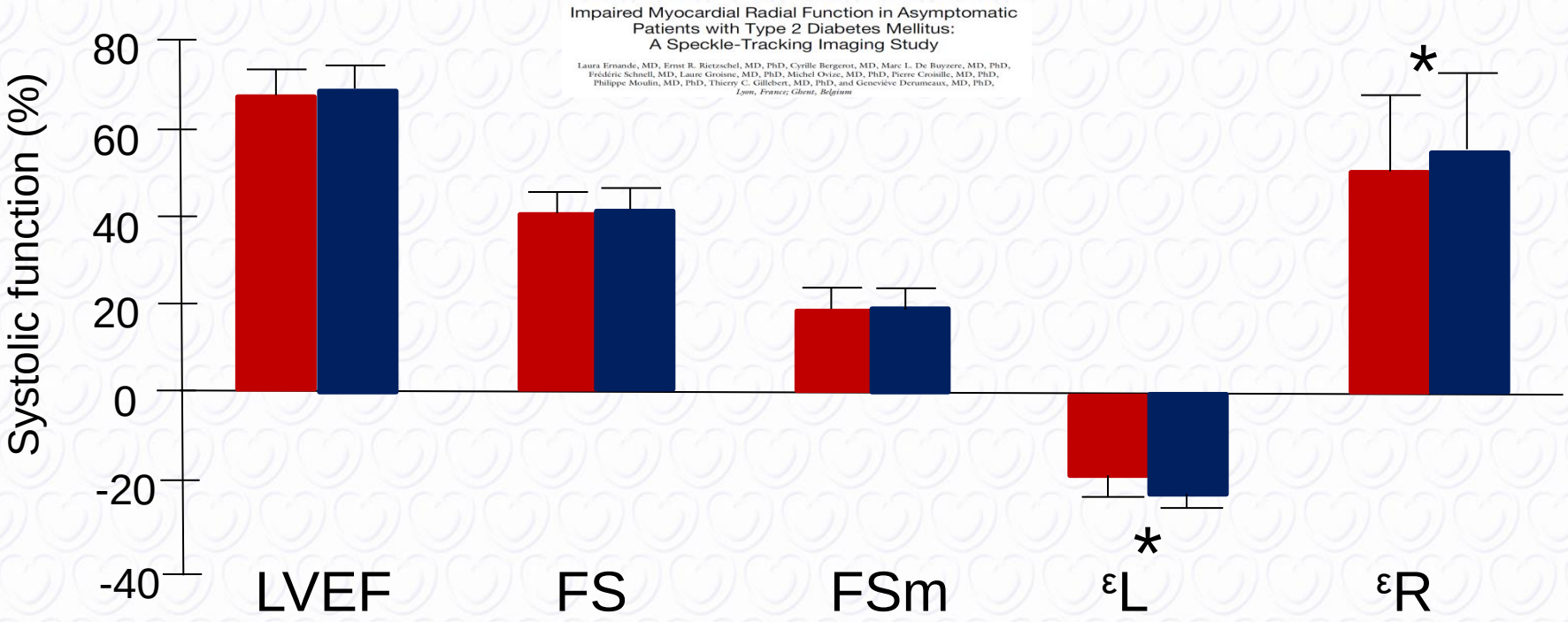
88 age-matched controls

Diastolic dysfunction	**Prevalence in DM**
Overall	47%
Grade I diastolic dysfunction	33%
Grade II diastolic dysfunction	14%
Systolic dysfunction	
Global longitudinal strain ≥ -18%).	32%

Ernande L. J Am Soc Echocardiogr 2011;24:1268-75

Impaired Myocardial Radial Function in Asymptomatic Patients with Type 2 Diabetes Mellitus : A Speckle-Tracking Imaging Study

Systolic function parameters in diabetics (n=114) compared with controls (n=88).



FS, fractional shortening; FSm, midwall fractional shortening; εL, mean longitudinal strain; εR, mean radial strain.
*P < .05 between diabetics and controls

Ernande L. J Am Soc Echocardiogr 2010;23:1266-72

Strain Imaging and Diabetic cardiomyopathy

Studies on left ventricular function and myocardial strain in diabetes

Publication and imaging modality	Group and baseline characteristics	Exclusion criteria	Main findings
Ernande *et al* 2010 **Echocardiography**	T2DM: *n* = 119, 69 males Controls: *n* = 39, 30 males	LVEF < 56%, age < 35 or > 65, signs, symptoms or history of heart disease, no RWMA, valve disease, renal disease, T1DM, poor DM control (HbA1C > 12%)	↓**GLS** (-19.3% ± 3% *vs* -22% ± 2%) and GRS (50% ± 16% *vs* 56% ± 12%, $^{n}P <$ 0.003) in participants with diabetes *vs* participants without diabetes Multivariate analysis showed DM (*t* = 3.9, *P* < 0.001) and gender (*t* = 3.4, *P* = 0.001) independent determinants of GLS, DM only independent determinant of GRS.
Ng *et al*, 2012 **MRI**	*n* = 69 DMs (*n* = 50, 35 T1DM) Mean age 51 ± 10 yr, 54% males. BMI 26.3 ± 3.7 Controls (*n* = 19), matched for age (45 ± 15), sex (63.2% males) an BMI 26.1 ± 4.4	Age < 18 yr, arrhythmia, CAD, MI, RWMA, segmental LGE, EF < 50%, valve disease	↓**GLS DM *vs* controls** (-16.1% ± 1.4% *vs* 20.2% ± 1.0% $^{p}P <$ 0.001) ↓**GLS DM T2DM *vs* T1DM** (-15.3% ± 1.2% *vs* 16.4% ± 1.4%, ^{q}P = 0.009)

CTCA: Computed topography coronary angiogram; GLS: Global longitudinal strain; GRS: Global radial strain; PEDSR: Peak early diastolic strain rate; PSSR: Peak systolic strain rate; RWMA: Regional wall motion abnormality.

Athithan L. World J Diabetes 2019;10: 490-510

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1- Epidemiology: diabetes in cardiovascular diseases

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- Definition / Pathophysiology
- Restrictive *versus* dilated phenotypes
- Prognostic significance

Myocardial dysfunction in the Community

2042 randomly selected residents of Olmsted County, Minnesota, ≥ 45 years
F.U.: 7000 person-years

	Diastolic dysfunction				p
	Normal	Mild	Moderate	Severe	
Diabetes					
No	1211 (73.3)	329 (19.5)	108 (6.5)	11 (0.7)	.001
Yes	66 (52.4)	48 (38.1)	10 (7.9)	2 (1.6)	

Systolic dysfunction					
	LVEF ≤ 50%			LVEF > 50%	
Diabetes	N at risk	N affected	p	N affected	p
No	1885	102 (5.4)	.001	34 (1.8)	.07
Yes	151	21 (13.9)		6 (4.0)	

Redfield M. JAMA 2003 ; 289 : 194-202

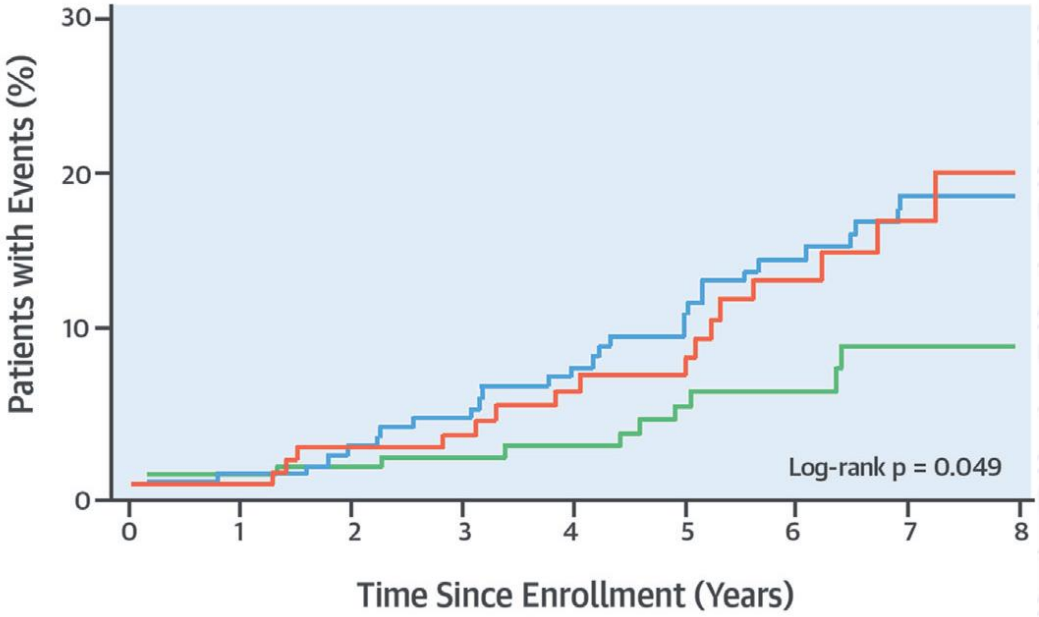
Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus

Cardiac Phenotypes and prognosis

Cluster 1 (low comorbidity)
lowest LVMi
lowest E/e' ratio,
highest LVEF and strain values.
predominantly male patients,
lowest rate of obesity or HTN.

Cluster 2 (elderly, diastolic dysfunction)
highest strain values
lowest e' velocities and? highest E/e' ratio.
Oldest patients, predominantly female
lowest rate of isolated T2DM.
Blood pressure, BMI, and HR the highest

Cluster 3 (hypertrophic systolic dysfunction)
highest LVMi and LV volumes
Lowest LVEF and strain.
Predominantly males, similar age and rate of obesity and HTN as cluster 1



Enande L. J Am Coll Cardiol 2017;70:1704–16

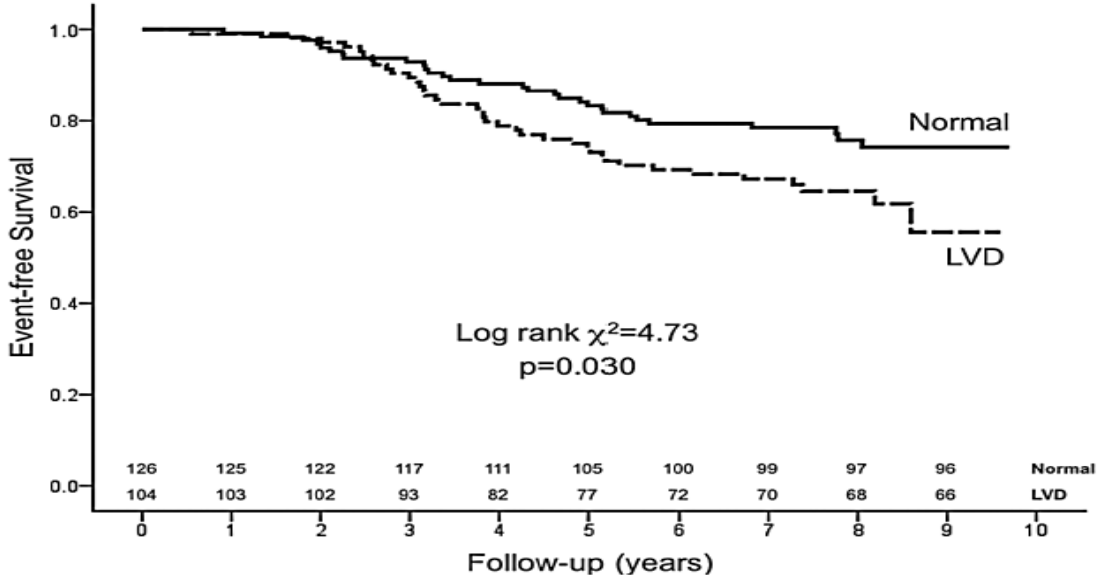
Subclinical LV dysfunction (LVD) in type 2 diabetes and the risk of adverse outcome.

Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus

David J Holland,[1,2,3] Thomas H Marwick,[4] Brian A Haluska,[1] Rodel Leano,[1] Matthew D Hordern,[3] James L Hare,[5,6] Zhi You Fang,[1] Johannes B Prins,[1,7] Tony Stanton[1]

Primary outcome: all-cause mortality and hospitalisation

Prospective cohort study, 230 asymptomatic patients with type 2 DM, LVEF ≥50%),
Measurement of **global longitudinal 2D strain (GLS)**
No evidence of coronary artery disease at recruitment. F.U.: up to 10 years.

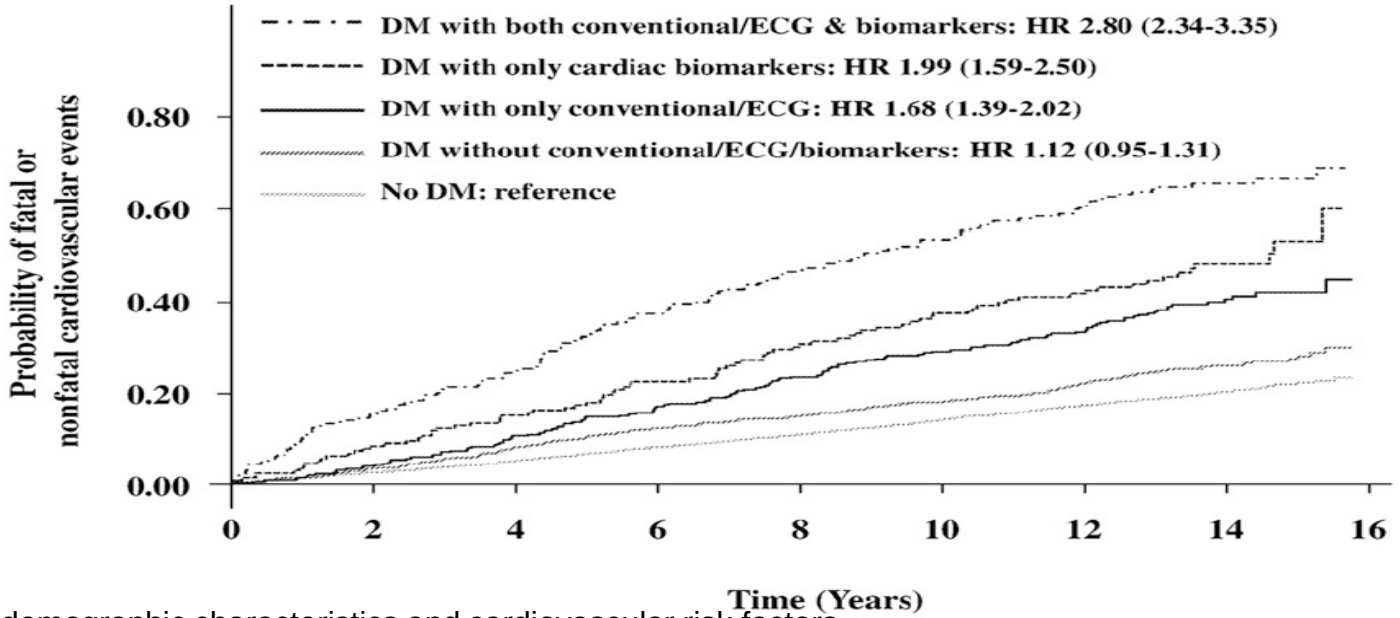


Holland DJ. Heart. 2015;101: 1061-6

Natriuretic Peptide and High- Sensitivity Troponin for Cardiovascular Risk Prediction in Diabetes: The ARIC Study

Kaplan-Meier curves for probability of fatal and nonfatal cardiovascular events.

8,402 participants without prevalent CVD
1,510 subjects with diabetes (mean age 63 years, 52% women, 60% hypertensive).
Median F.U.: 13.1 years, 540 incident fatal/nonfatal CVD events (CHD, heart failure, and stroke)



HRs adjusted for demographic characteristics and cardiovascular risk factors.

Gori M. Diabetes Care. 2016;39:677-85.

Diabetic cardiomyopathy

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- Restrictive *versus* dilated phenotypes
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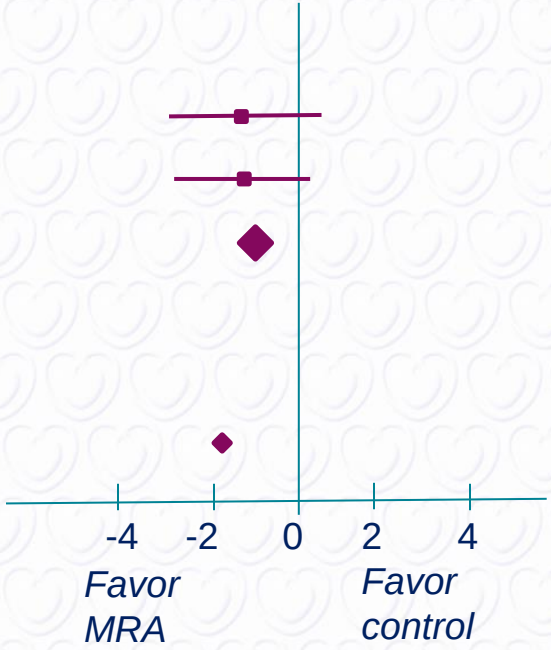
4- Treatment principles in LVD / heart failure

Effect of Mineralocorticoid Receptor Antagonists on Cardiac Structure and Function in Patients With Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: A Meta-Analysis and Systematic Review

Study	weight	Between group diff in outcome change, mean diff (95%CI)
Asymptomatic Diastolic dysfunction		
Kosmala 2011	8,00 %	-0,90 (-2,14-0,34)
Kosmala 2013	10,9%	-1,00 (-2,06-0,06)
Subtotal (95% CI)	18,9 %	-0,96 (-1,77-0,15)
Heterogeneity : Chi² =0,01, df=1 (p=0,90), I²=0%		
Test for overall effect : Z=2,32 (p=0,02)		
Total (95%CI)	100,0%	-1,68 (-2,03- -1,33)
Heterogeneity : Chi² =0,01, df=1 (p=0,90), I²=0%		
Test for overall effect : Z=9,39 (p<0,00001)		
Test for subgroup differences : Chi²=3,80, df=1 (p=0,05), I²=73,7%		

E/E'



Pandey A. J Am Heart Assoc.2015;4:e002137 doi: 10.1161/JAHA.115.002137

Meta-analyses of Heart Failure with Preserved Ejection Fraction treatments in diabetic patients

	ACEi[1]	Betablockers[2]	ARB[3]
All-cause Mortality	NS	RR: 0.91; 95% CI: 0.87 - 0.95; P < 0.001	-
Hospitalization for HF	RR 0.89; 95 % CI 0.82–0.97; p = 0.01	RR, 1.01; 95% CI, 0.66 to 1.53; P=0.97	RR, 0.83; 95% CI, 0.70 to 0.98; p = 0.01

[1]Effects of renin-angiotensin-aldosterone system inhibitors on mortality, hospitalization, and diastolic function in patients with HFpEF. A meta-analysis of 13 randomized controlled trials
[2]Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis.
[3]Effects of mineralocorticoid receptor antagonists in patients with preserved ejection fraction: a meta-analysis of randomized clinical trials.

[1] Zhang Q. Herz 2016;41:76–86
[2]Liu F. PLoS One. 2014;9: e90555
[3]Chen Y. BMC Med. 2015 ;13:10.

Comparison of the event rates for different SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) endpoints between non-diabetic HF patients and all diabetic HF patients, diabetic HF patients on insulin, or diabetic HF patients not on insulin

Endpoint	Adjusted HR (95% CI), p (*vs* non-diabetic)			
		History of diabetes		
	History of diabetes	On insulin	Not on insulin	On insulin vs not on insulin
Primary endpoint[1]	**1,18 (1,07-1,31) 0,001**	1,43 (1,24-1,66) <0,001	1,07 (0,95-1,21) 0,23	**1,33 (1,13-1,58) 0,001**
CV mortality	1,05 (0,91-1,20) 0,53	1,11 (0,89-1,37) 0,35	1,02 (0,87-1,20) 0,83	1,09 (0,85-1,38) 0,497
HF mortality	1,15 (0,88-1,49) 0,31	1,85 (1,32-2,59) <0,001	0,83 (0,59-1,16) 0,28	**2,23 (1,46-3,40) <0,001**
All cause mortality	1,10 (0,96-1,25) 0,17	1,24 (1,02-1,50) 0,031	1,03 (0,89-1,20) 0,68	1,20 (0,96-1,50) 0,108
Hospitalization for worsening HF	**1,28 (1,13-1,44) <0,001**	1,73 (1,47-2,05) < 0,001	1,08 (0,93-1,25) 0,31	**1,61 (1,33-1,95) 0,001**

[1]cardiovascular death or hospitalisation for worsening HF

Komajda M. Eur J Heart Failure 2015; 17: 1294–1301

PARADIGM

Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced EF

Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

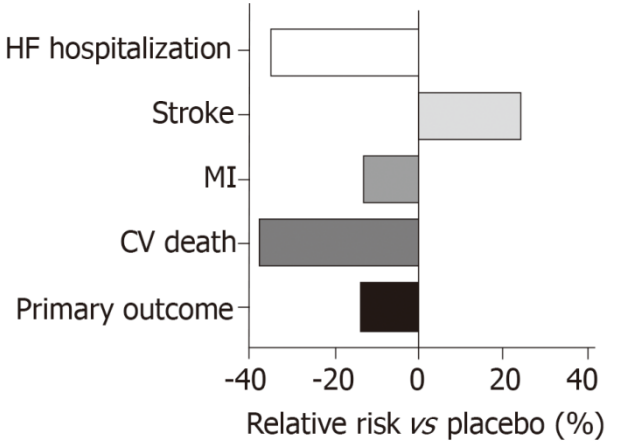
Relationship between ejection fraction (EF) and the primary outcome stratified by history of diabetes mellitus (DM) and glycemic status.

LVEF *vs* DM status	<15% HR (95% CI)	15-20% HR (95% CI)	20-25% HR (95% CI)	25-30% HR (95% CI)	30-35% HR (95% CI)	>35% HR (95% CI)
Normo-glycemia	1,79 (0,95-3,35)	1,86 (1,22-2,86)	1,45 (0,98-2,15)	1,43 (0,99-2,05)	1,19 (0,83-1,72)	1,00 (ref)
Prediabetes	2,78 (1,63-4,73)	2,12 (1,39-3,24)	2,11 (1,44-3,08)	1,77 (1,23-2,54)	1,44 (1,01-2,06)	1,37 (0,92-2,05)
Undiagnosed diabetes	4,01 (2,29-7,01)	3,17 (2,00-5,00)	2,44 (1,63-3,67)	1,93 (1,30-2,86)	1,71 (1,17-2,50)	1,38 (0,85-2,24)
Diabetes	3,37 (2,11-5,39)	2,59 (1,77-3,79)	2,66 (1,87-3,80)	2,49 (1,77-3,50)	2,11 (1,51-2,96)	1,67 (1,15-2,44)

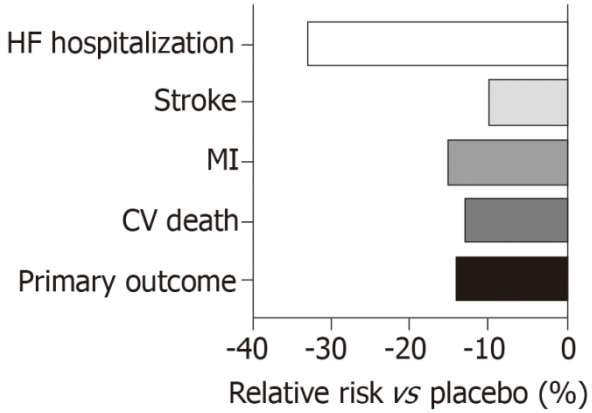
Kristensen SL. Circ Heart Fail. 2016;9:e002560

Major cardiovascular outcome trials examining SGLT2 inhibitors.

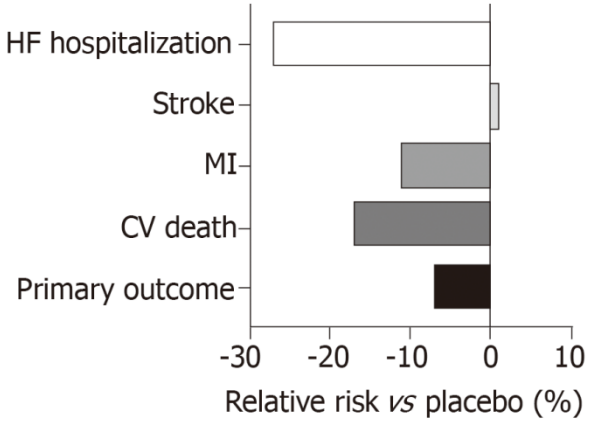
EMPA-REG outcome-Empagliflozin
(*n* = 7020)



Canvas-Canagliflozin
(*n* = 10142)

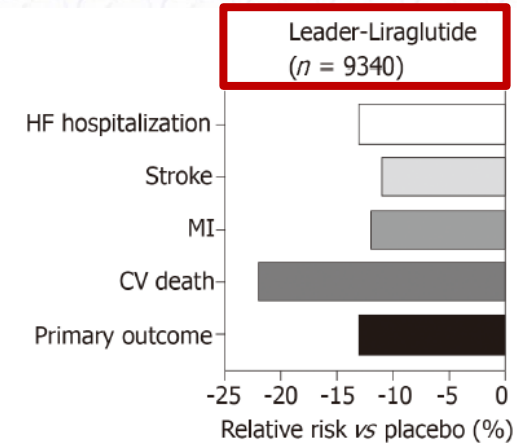


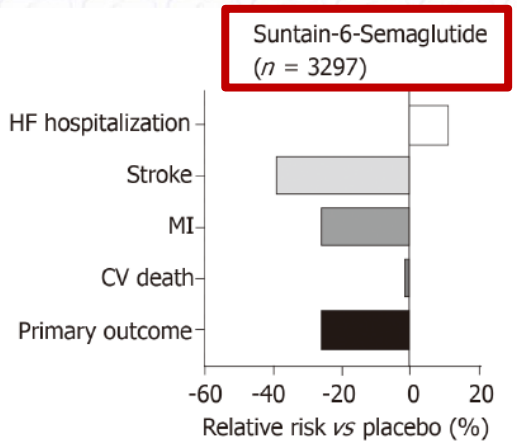
Declare TIMI 58-Dapagliflozin
(*n* = 17160)

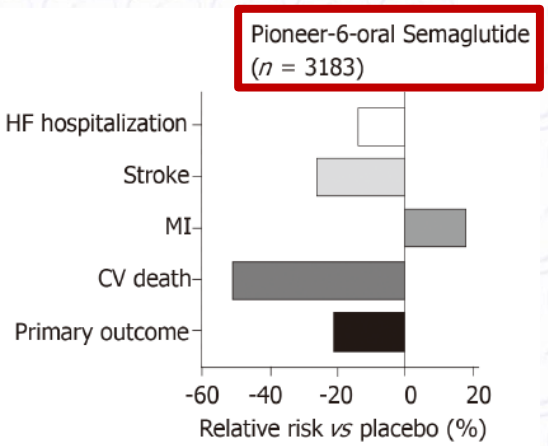


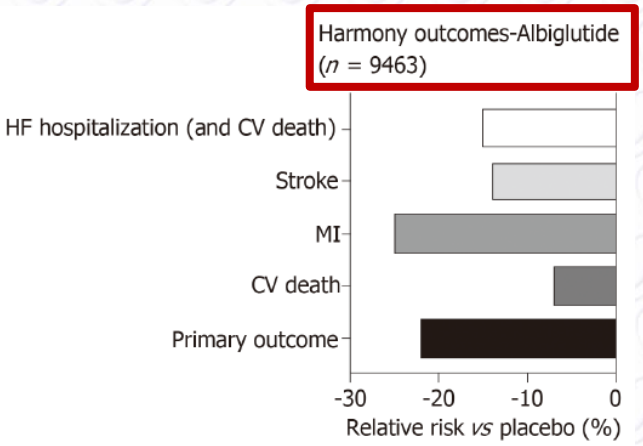
Athithan L. World J Diabetes 2019;10: 490-510

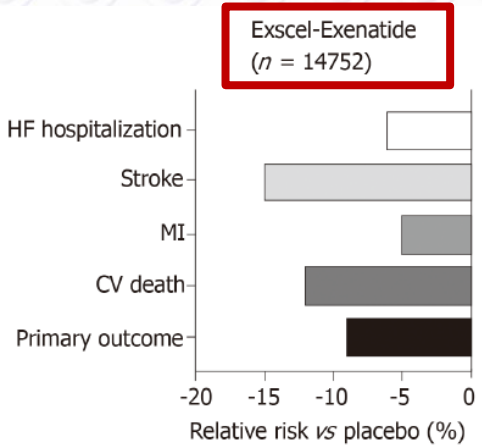
Major cardiovascular outcome trials using GLP1 receptor antagonists











Athithan L. World J Diabetes 2019;10: 490-510

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

	DMCMP with restrictive/HFPEF phenotype	DMCMP with dilated/HFREF phenotype
Diagnosis		
 REVIEW Clinical update Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes Petar M. Seferović[1] and Walter J. Paulus[2]*	**DM (mainly T2DM, obese)** Dyspnoea and signs of congestion, S4 Gallop No coronary, valvular, or congenital cardiac disease No arterial hypertension No infiltrative heart disease in endomyocardial biopsy LVEF ≥ 50% ; LVEDVI ≤ 97 mL/m² Diastolic LV dysfunction	**DM (mainly longstanding T1DM)** Dyspnoea and signs of congestion, S3 Gallop No coronary, valvular, or congenital cardiac disease No arterial hypertension No inflammation or virus in endomyocardial biopsy LVEF < 50% ; LVEDVI > 97 mL/m² Diastolic LV dysfunction
Treatment		
	Diuretics MRA? *Ongoing iSGLT2- studies*	ACEIs, ARBs, β-blockers, ARNIs, mineralocorticoid-receptor antagonists, ivabradine, *iSGLT2-liraglutide?* Resynchronization ….

After and modified from Seferovic PM. Eur Heart J 2015; 36: 1718–27

Circulation

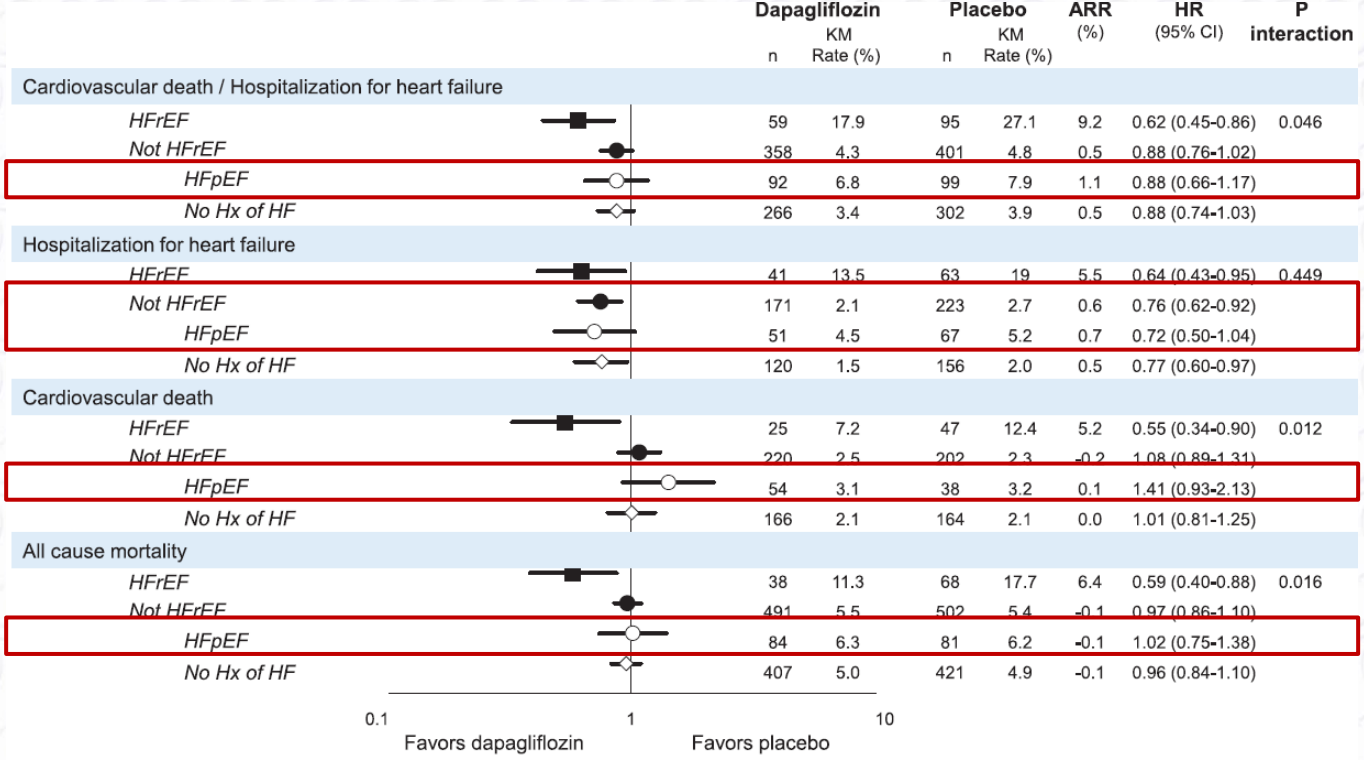
ORIGINAL RESEARCH ARTICLE

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

Kato ET. Circulation. 2019;139:2528–2536

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

Cardiovascular outcomes by heart failure (HF) category



Kato ET. Circulation. 2019;139:2528–2536

Circulation

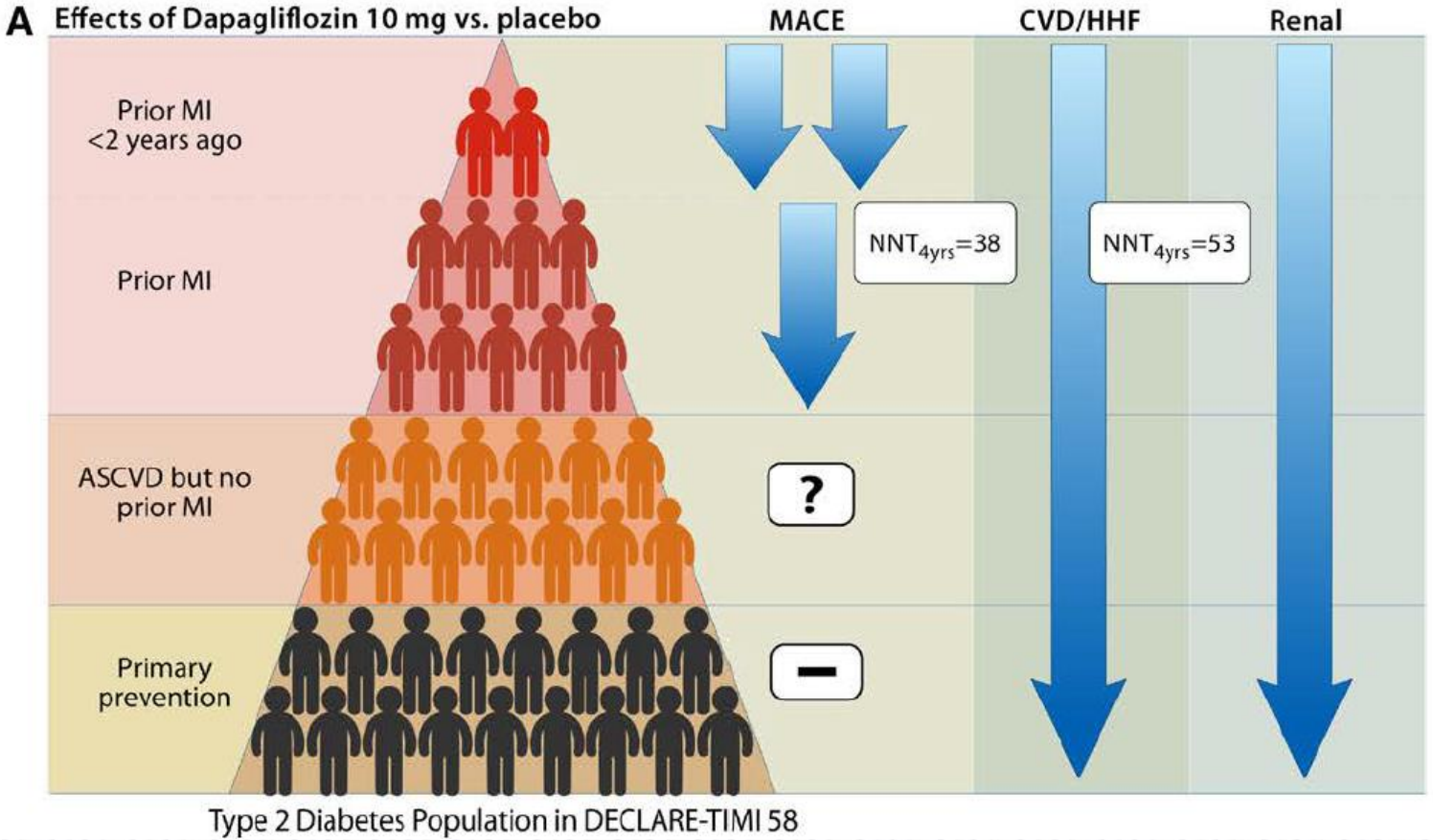
EDITORIAL

The Serendipitous Story of SGLT2 Inhibitors in Heart Failure

New Insights From DECLARE-TIMI 58

Verma S. Circulation. 2019;139:2537–2541

The Serendipitous Story of SGLT2 Inhibitors in Heart Failure
New Insights From DECLARE-TIMI 58



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The Serendipitous Story of SGLT2 Inhibitors in Heart Failure
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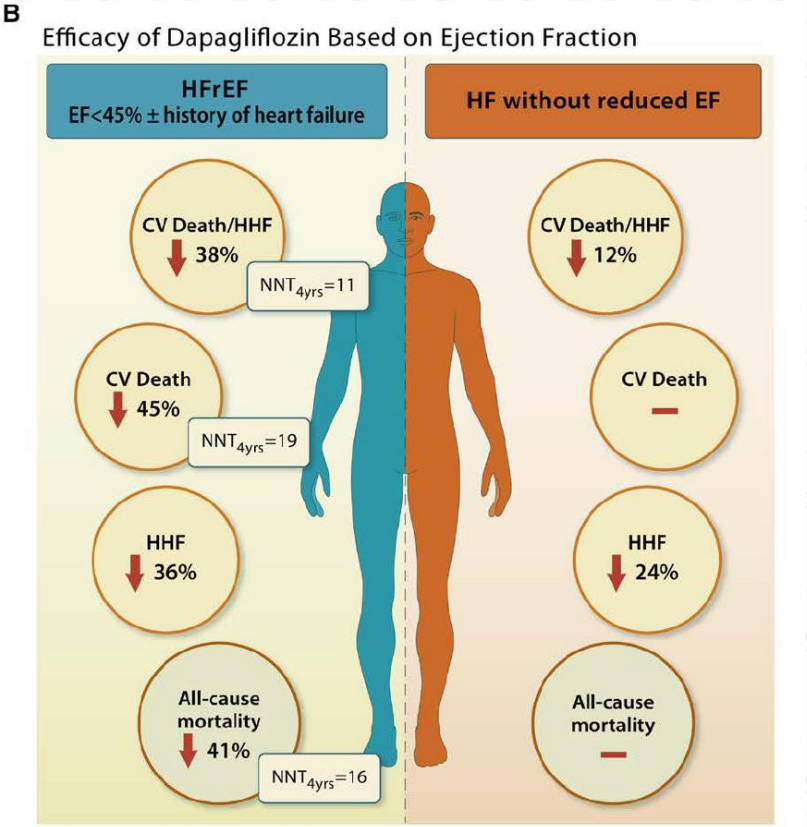


Verma S. Circulation. 2019;139:2537–2541

ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1954

POSITION PAPE

Check for updates

Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1,2*†], Gabriele Fragasso[3], Mark Petrie[4], Wilfried Mullens[5,6], Roberto Ferrari[7], Thomas Thum[8], Johann Bauersachs[9], Stefan D. Anker[10,11], Robin Ray[12], Yuksel Çavuşoğlu[13], Marija Polovina[1,14], Marco Metra[15], Giuseppe Ambrosio[16], Krishna Prasad[17], Jelena Seferović[1,18], Pardeep S. Jhund[19], Giuseppe Dattilo[20], Jelena Čelutkiene[21], Massimo Piepoli[22], Brenda Moura[23], Ovidiu Chioncel[24,25], Tuvia Ben Gal[26], Stefan Heymans[27], Rudolf A. de Boer[28], Tiny Jaarsma[29], Loreena Hill[30], Yuri Lopatin[31], Alexander R. Lyon[32], Piotr Ponikowski[33], Mitja Lainščak[34,35], Ewa Jankowska[33], Christian Mueller[36], Francesco Cosentino[37], Lars Lund[38], Gerasimos S. Filippatos[39], Frank Ruschitzka[40], Andrew J.S. Coats[41], and Giuseppe M.C. Rosano[42†]

Seferovic PM. Eur J Heart Fail 2020; doi:10.1002/ejhf.1954

SGLT2 inhibitors in heart failure: beyond glycaemic control.

The position paper of the Heart Failure Association of the European Society of Cardiology

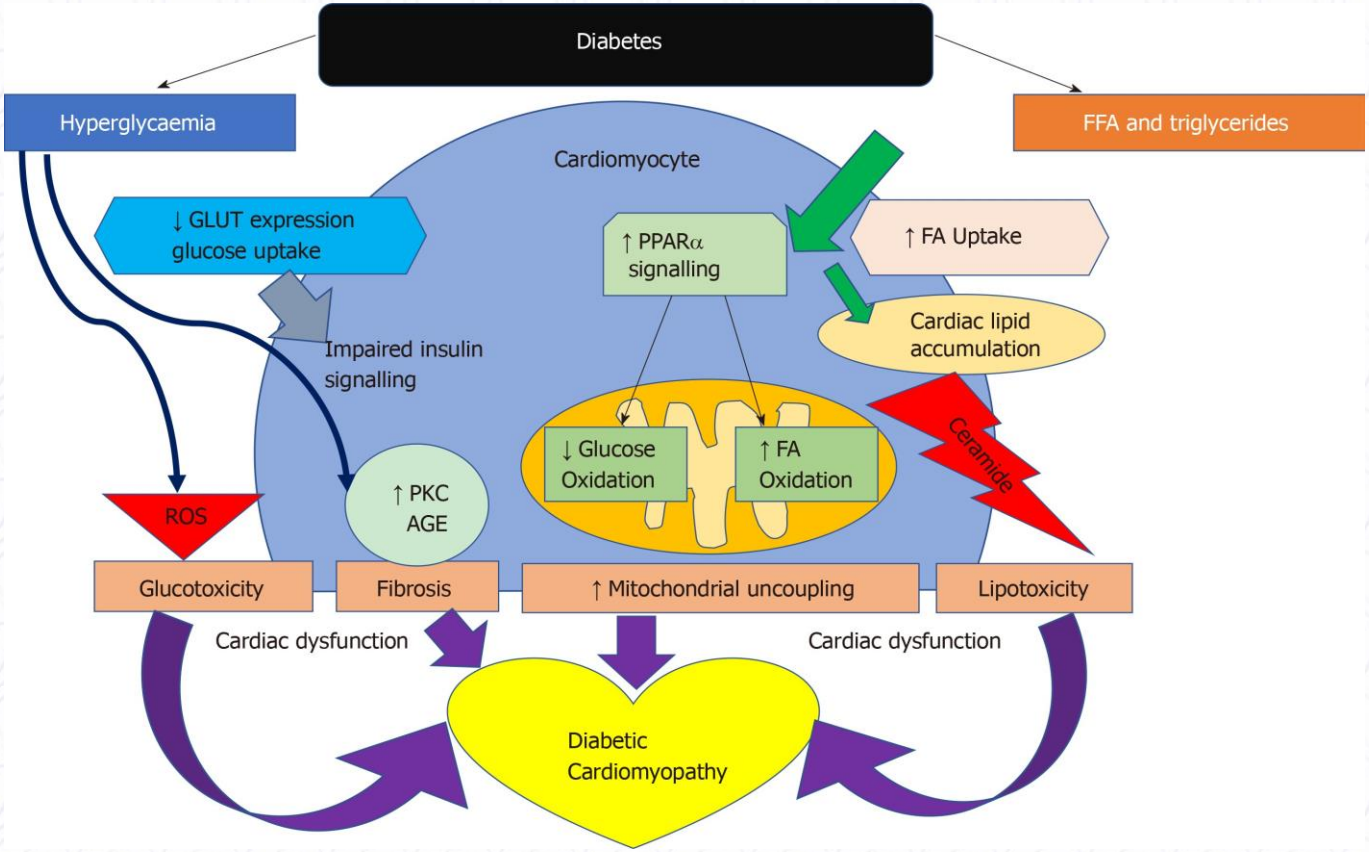
HFPEF: Ongoing clinical trials with sodium–glucose co-transporter 2 inhibitors

		Primary outcome
Cardiovascular outcomes in patients with HFpEF		
EMPEROR-Preserved (NCT03057951)	Empagliflozin in patients with HFpEF with/without T2DM	cardiovascular death or HF hospitalisation
DELIVER (NCT03619213)	Dapagliflozin in patients with HFpEF with/without T2DM	composite of cardiovascular death, hospitalisation for HF or urgent HF visit
Symptoms and functional status		
DETERMINE-Preserved (NCT03877224)	Dapagliflozin in patients with HFpEF with/without T2DM	change from baseline in KCCQ and 6-min walk distance at week16

HFPEF: Ongoing clinical trials with sodium–glucose co-transporter 2 inhibitors

		Primary outcome
Cardiac physiology and metabolism		
EMPA-VISION (NCT03332212)	Empagliflozin in patients with HFrEF or HFpEF with/without T2DM	effect on cardiac physiology and metabolism as assessed by cardiac magnetic resonance spectroscopy
EmDia (NCT02932436)	Empagliflozin in patients with T2DM	effect on left ventricular diastolic function as assessed by echocardiography

Pathways of cardiac dysfunction leading to diabetic cardiomyopathy



AGE: Advanced glycation end products; FA: Fatty acids; FFA: Free fatty acids; GLUT: Glucose transporters; PKC: Protein kinase C; PPARα: Peroxisome proliferator- activated receptor alpha; ROS: Reactive oxygen specie

Athithan L. World J Diabetes 2019;10: 490-510