SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
67° CONGRESSO NAZIONALE SIGG
LA LONGEVITÀ DECLINATA AL FEMMINILE

«IPERGLICEMIA E DIABETE: IMPATTO SUL RISCHIO CARDIOVASCOLARE NELL'ANZIANO»

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Relevant Financial Discloures :

As Speaker, Advisory Board or Consultant in the last 3 years

- AMARIN

DIABETES & CVD
A GLOBAL ANALYSIS
THE SURVEY

THE REALITY

425 million people worldwide have diabetes

People with diabetes are 2 to 3 times more likely to have CVD

50% are unaware of their disease

84% of people aged 65 or older with diabetes die from heart disease and stroke

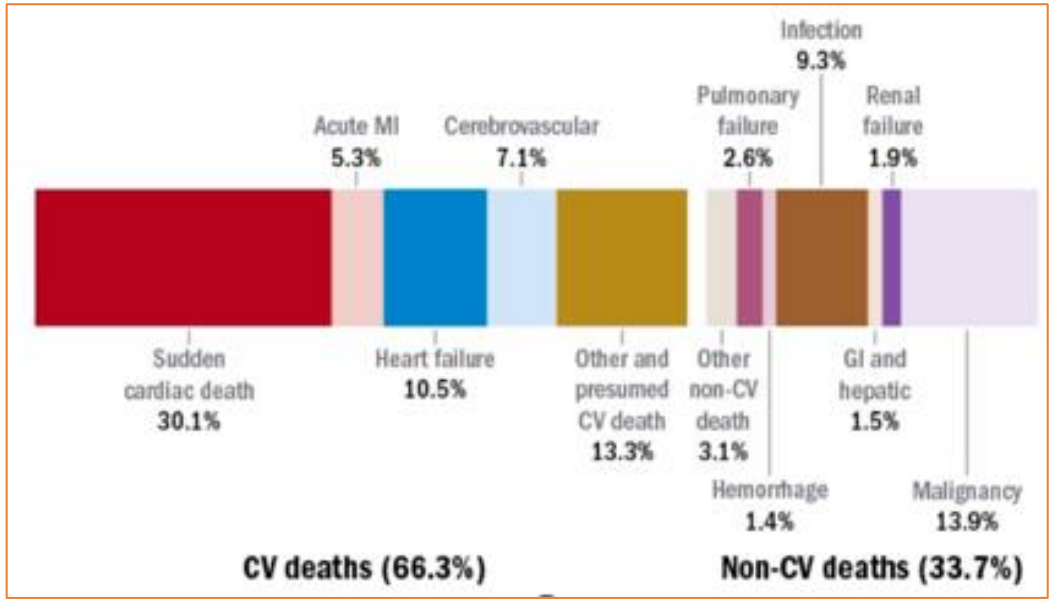
Table 1 Prevalence of cardiovascular disease in T2DM

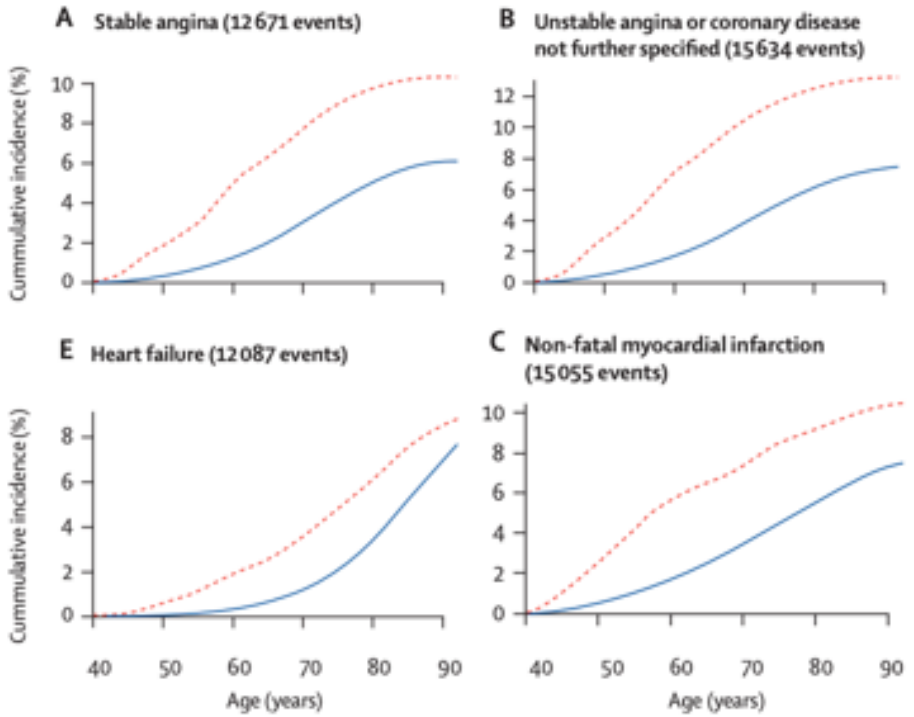
Outcome	Before 2016 [11]	2007–2017 [4]	2019 [12]
All CVDs	14.3–46.9%	32%	34.8%
Coronary artery disease	1.8–25.6%	21%	10.9%
Heart attack	3.3–17.8%	10%	4.6%
Stroke	1.7–17.7%	7.6%	5%
Heart failure		14.9%	2.4%
Peripheral artery disease			2.6%

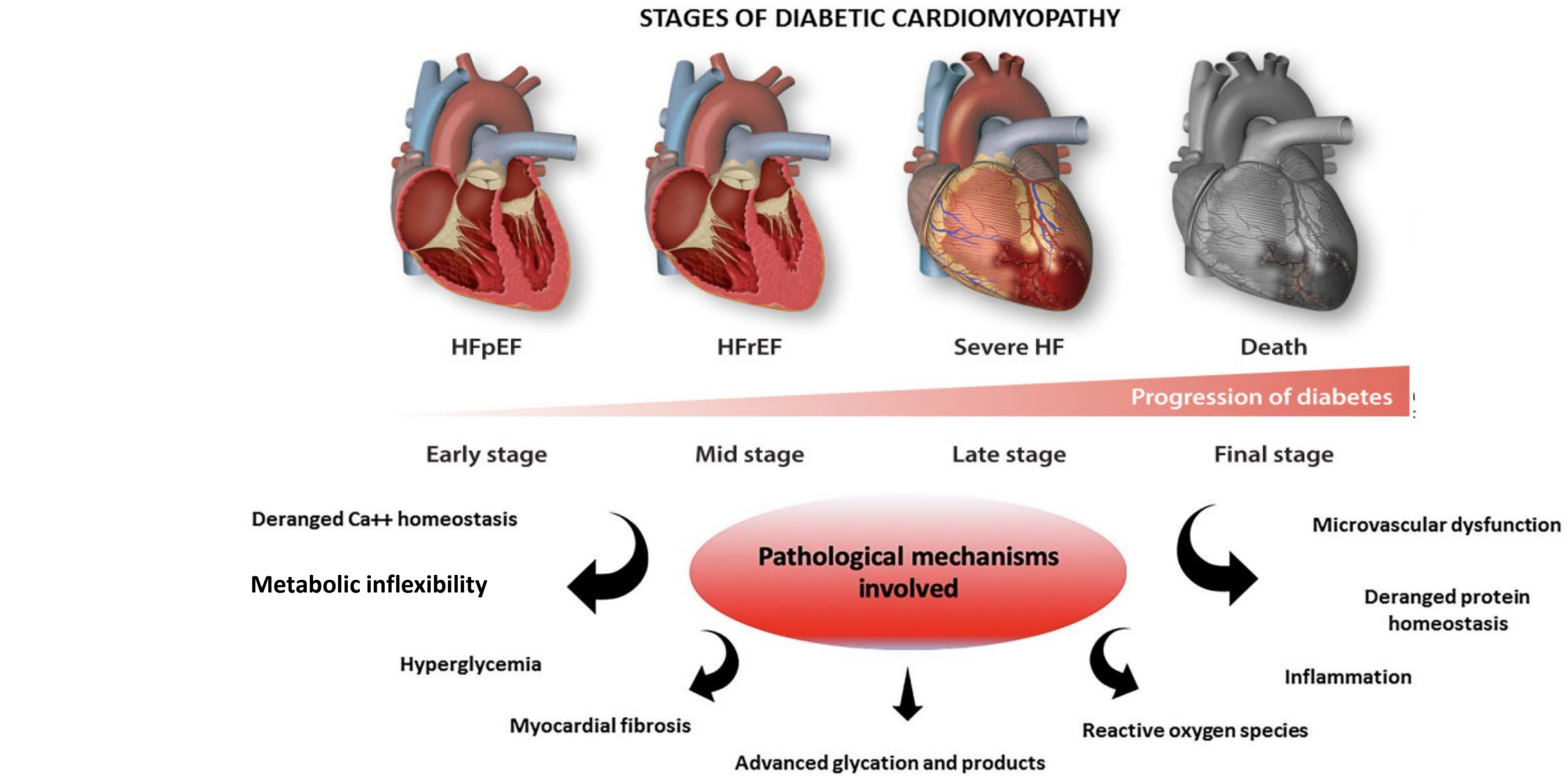
CVD cardiovascular disease

Ma et al. Cardiovascular Diabetology (2022) 21:74

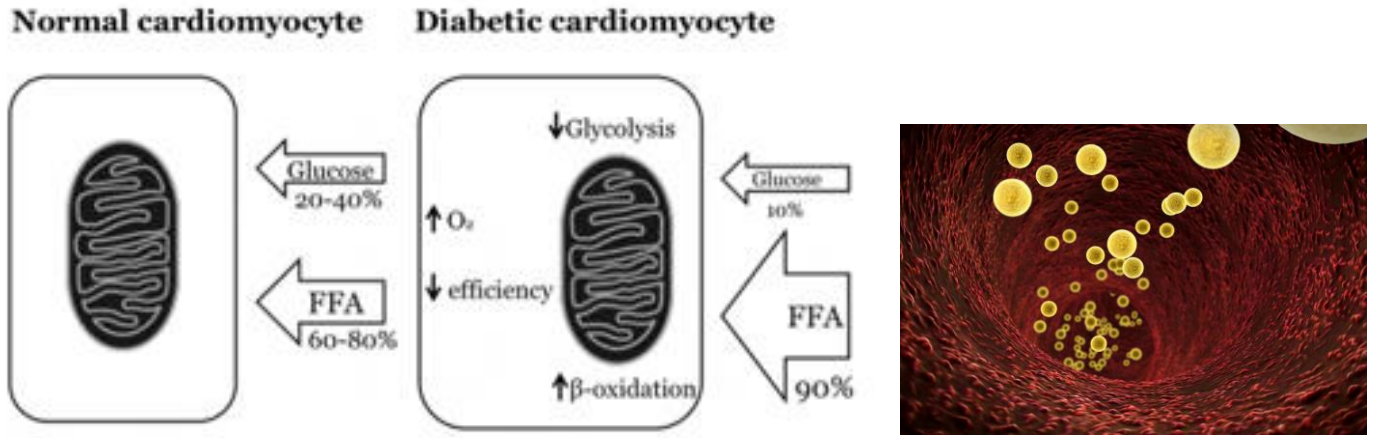
Source: J Am Coll Cardiol. 2021 Apr 13;77[14]:1837-40



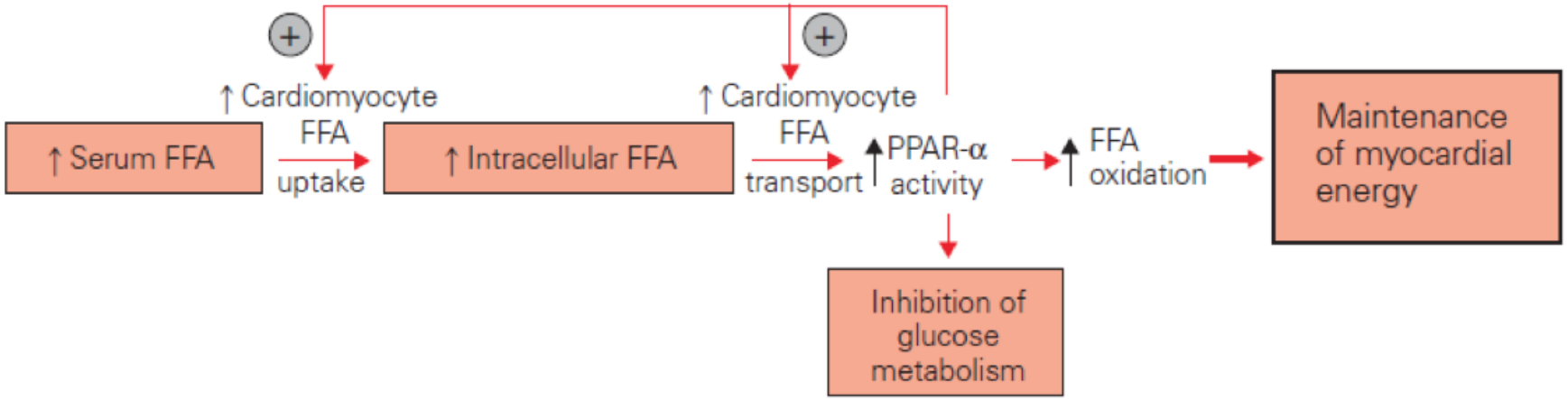



STAGES OF DIABETIC CARDIOMYOPATHY
HFpEF
HFrEF
Severe HF
Death
Progression of diabetes
Early stage
Mid stage
Late stage
Final stage
Deranged Ca++ homeostasis
Metabolic inflexibility
Pathological mechanisms involved
Microvascular dysfunction
Deranged protein homeostasis
Inflammation
Hyperglycemia
Myocardial fibrosis
Advanced glycation and products
Reactive oxygen species

DIABETES AND MYOCARDIAL METABOLISM: Loss of Myocardial Metabolic Flexibility



Early diabetes

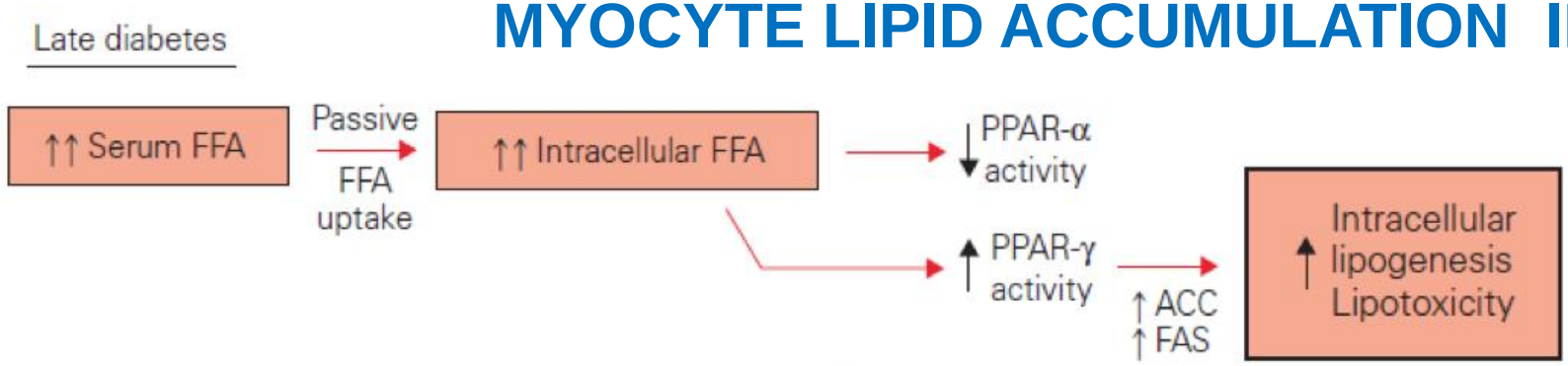


↑ **consumo di ossigeno miocardico**

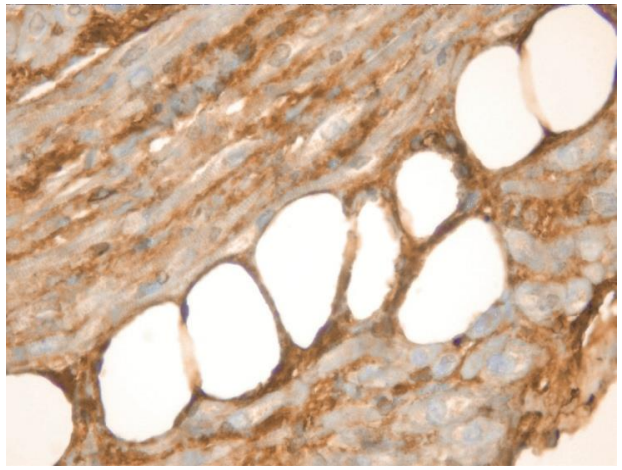
↓

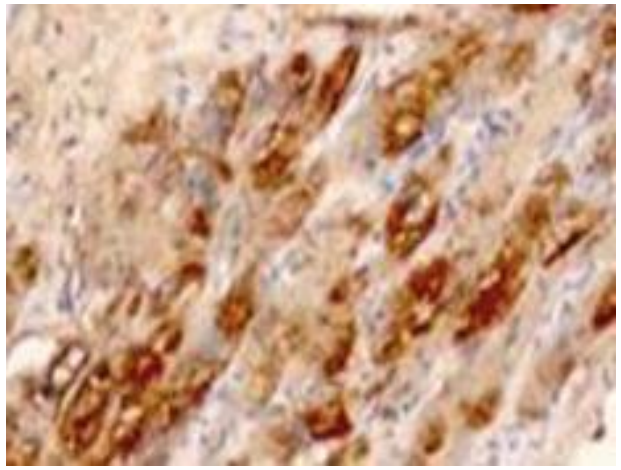
Miocardio più suscettibile a ipossia con danni più diffusi durante gli eventi ischemici

MYOCYTE LIPID ACCUMULATION IN TYPE 2 DIABETIC PATIENTS



Journal of Lipid Research Volume 50, 2009





Pazienti con diabete tipo 2

Pazienti senza diabete

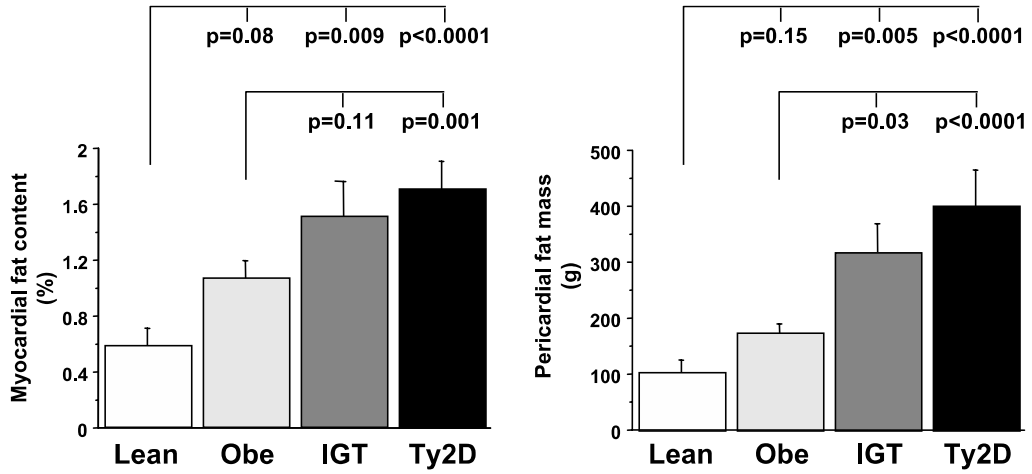
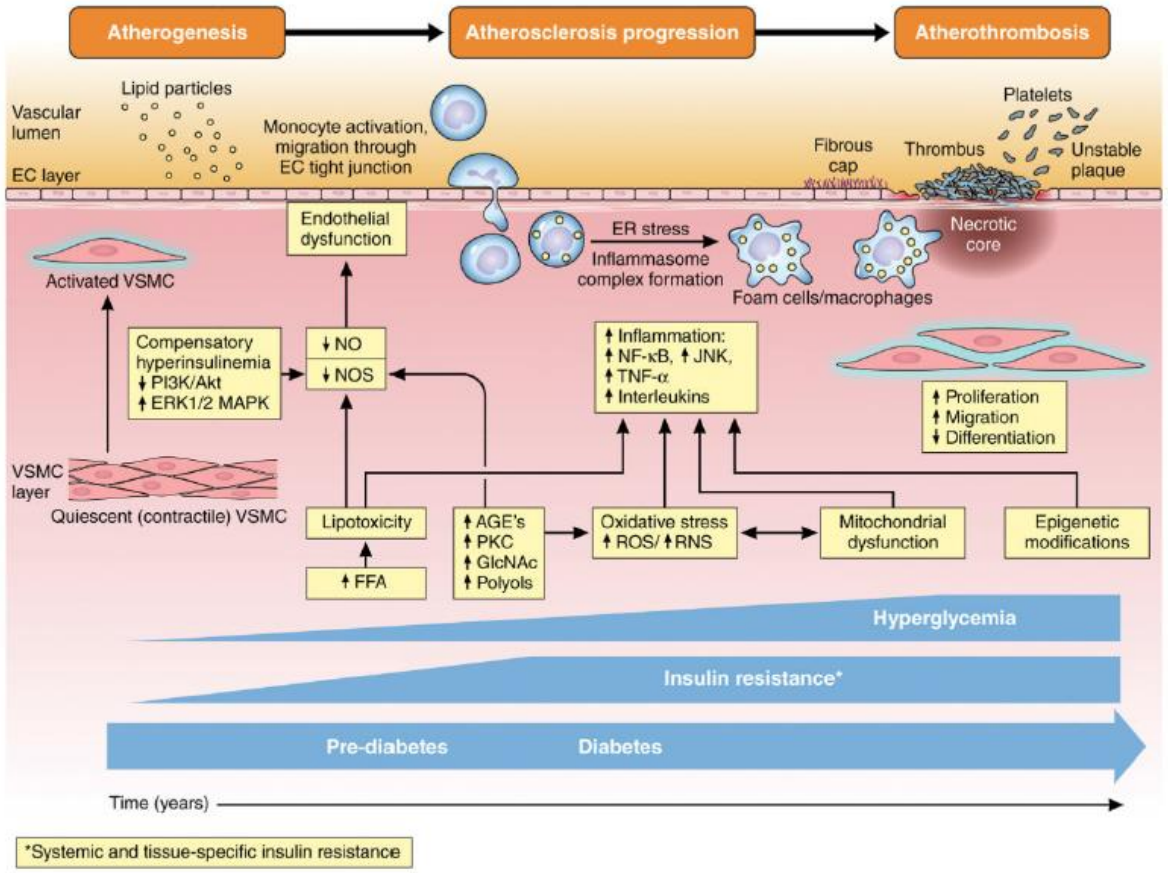
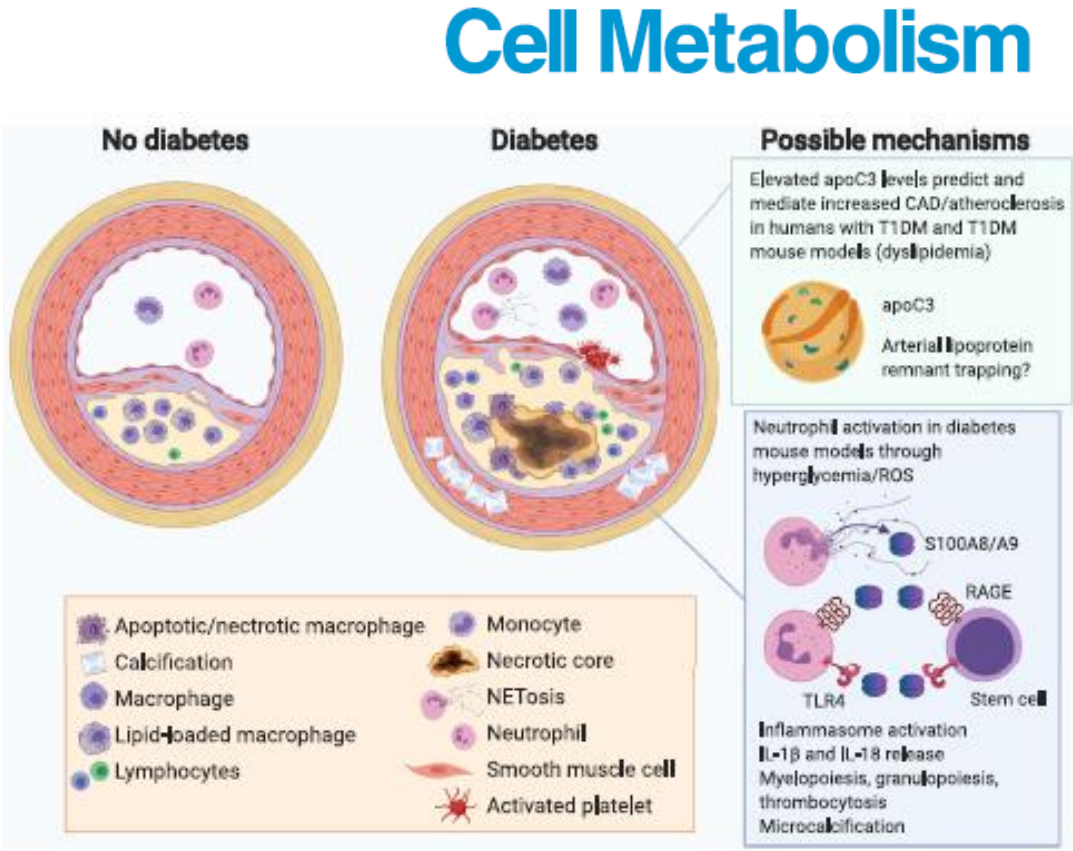


FIG. 1. Myocardial triglyceride content (*left*) and pericardial fat mass (*right*) in the study population, showing a progressive increase from lean to obese individuals and an additional BMI-independent contribution of IGT and Ty2D.

J Clin Endocrinol Metab, November 2009, 94(11):4472–4482

VASCULAR PATHOLOGY IN PATIENTS WITH T2DM





Cell Metabolism 33, August 3, 2021

EVOLUZIONE DELLA TERAPIA DEL DIABETE MELLITO TIPO 2

Cambio Del Paradigma Terapeutico

I° Linea — **METFORMINA**

Prima del 2000	Dal 2000 al 2014	Dopo il 2014
II° Linea		
EFFICACIA	**SICUREZZA**	**PERSONALIZZAZIONE**
HbA_{1c}	**HbA_{1c}**	**HbA_{1c}**
The lower is better !	*The lower is better* !	*The lower is better* !
	Non per tutti, evitare ipoglicemie !!	*Evitare ipoglicemie* !
		Valutare i benefici CV e renali !!

Adverse CV events led the FDA to require demonstration of CV safety for new glucose-lowering drugs

1961 — UGDP trial: tolbutamide discontinued due to increased CV mortality vs other treatment groups[1]

2005 — Muraglitazar found to potentially increase CV risk during FDA assessment[2]
→ Sponsor withdrew application[1]

2007 — Rosiglitazone associated with increased risk for MI and CV-related death[3]
→ Withdrawn in the EU[1]
→ Use restricted in US[1]*

*In 2013, FDA panel voted to reduce safety restrictions on rosiglitazone[7]

2008 — ACCORD trial: intensive glucose lowering was associated with increased all-cause mortality[4]
HR 1.22 (95% CI 1.01–1.46); p = 0.04

2008 — **New FDA requirements[5]**

2012 — **New EMA requirements[6]**

New diabetes drugs should demonstrate CV safety with meta-analysis and a CV outcome trial (CVOT)

EMA 2012 Guideline[2]

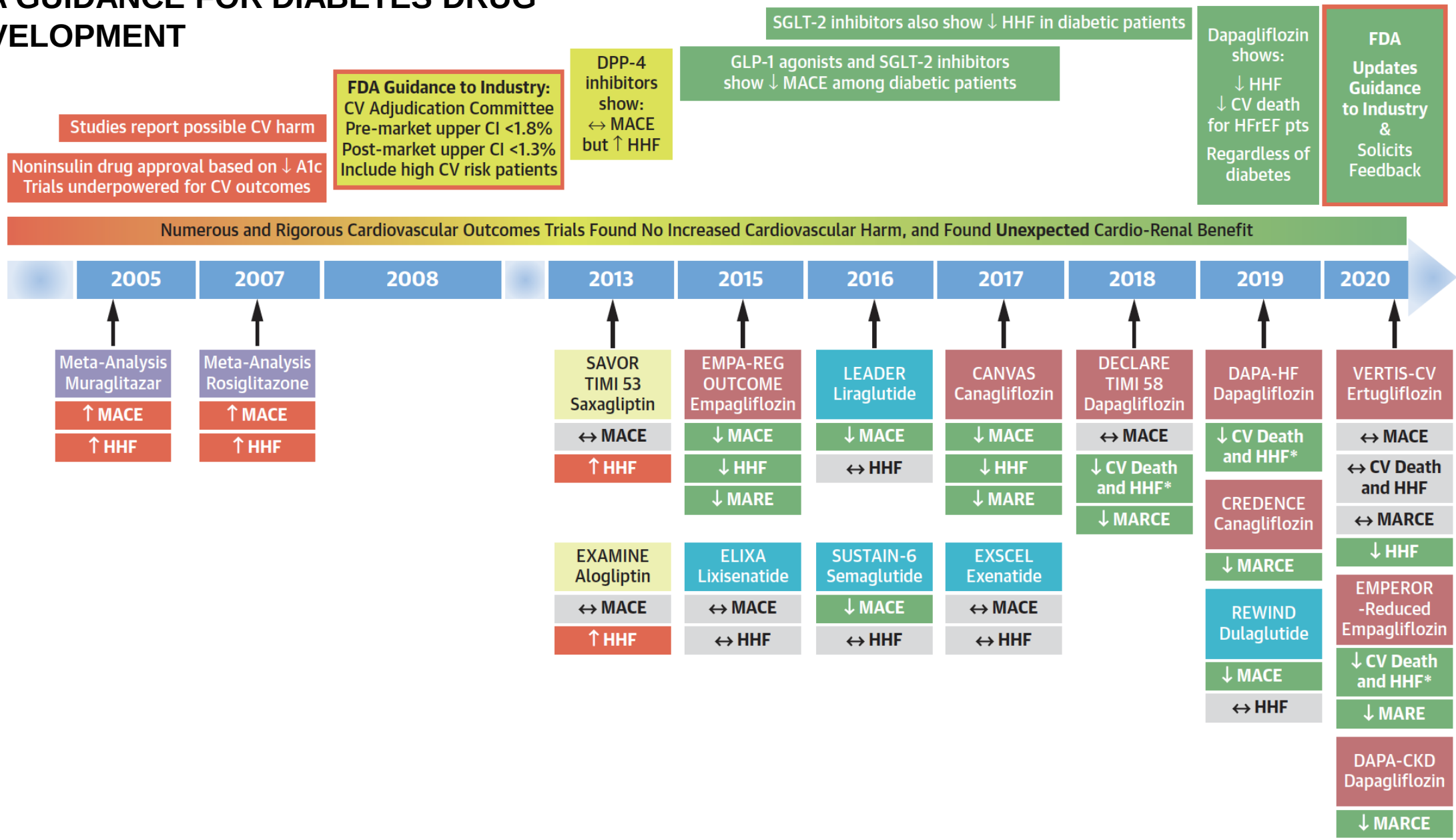
'A fully powered CV safety assessment, e.g., based on a dedicated CV outcome study, should be submitted before marketing authorisation whenever a safety concern is intrinsic in the molecule/MOA or has emerged from pre-clinical/clinical registration studies.'

Two approaches are recommended:

- Meta-analysis of safety events
- Specific long-term controlled outcome study with at least 18–24 months' follow-up

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf.

FDA GUIDANCE FOR DIABETES DRUG DEVELOPMENT



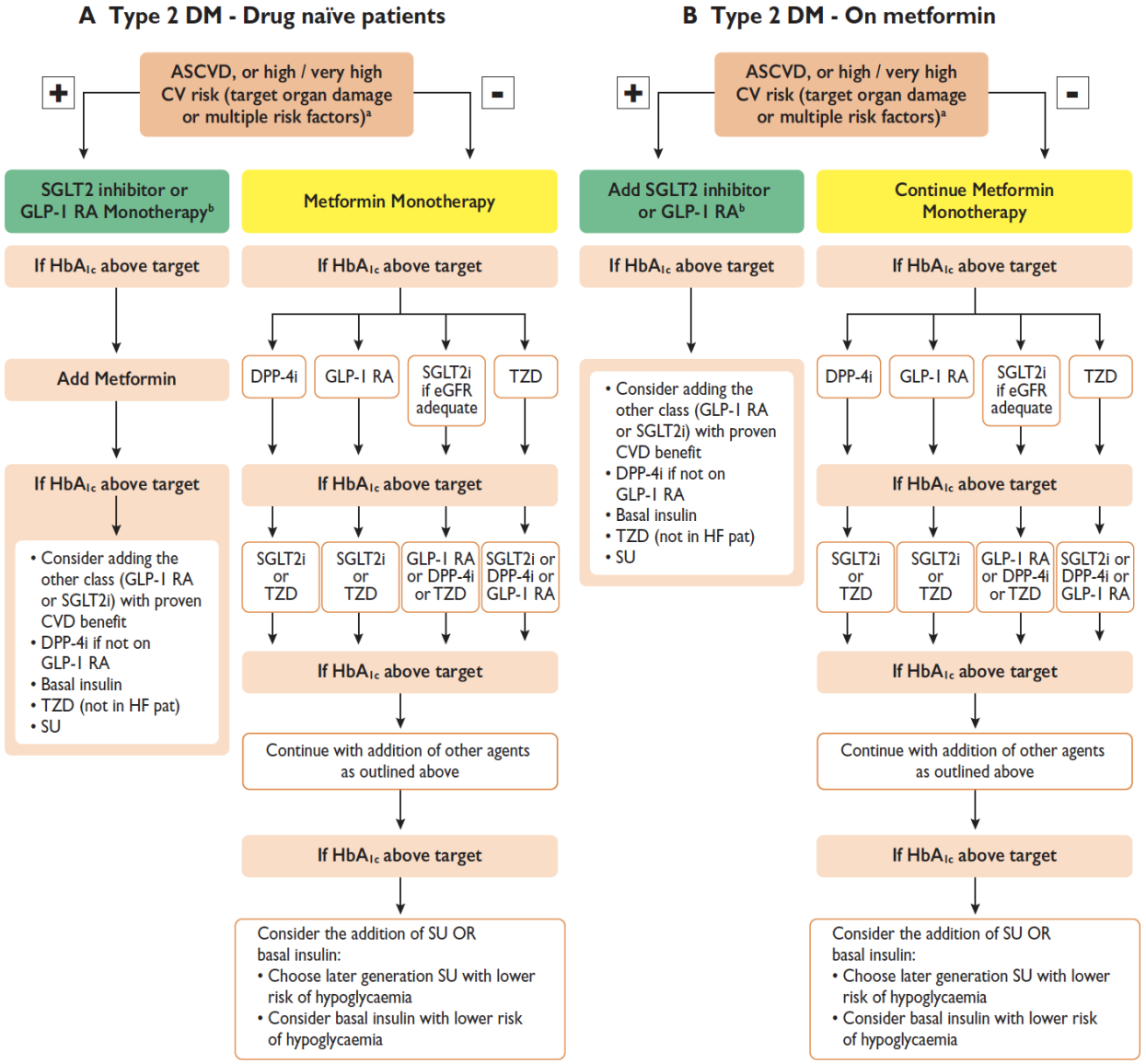
JACC, VOL.76,NO.21,2020

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 255–323
doi:10.1093/eurheartj/ehz486

Prevenzione primaria → **Prevenzione secondaria**

Table 7 Cardiovascular risk categories in patients with diabetes[a]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors



TRIALS

REAL LIFE

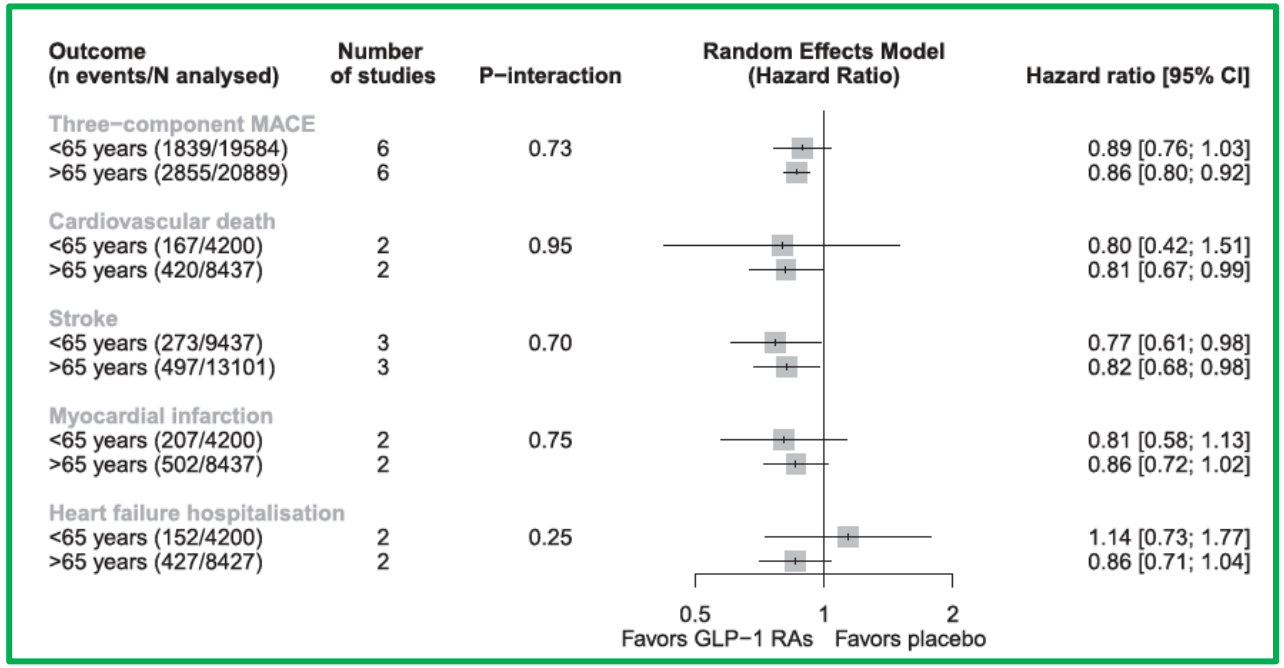
- Comorbidità
- Politerapia
- Insufficienza Renale
- Fragilità

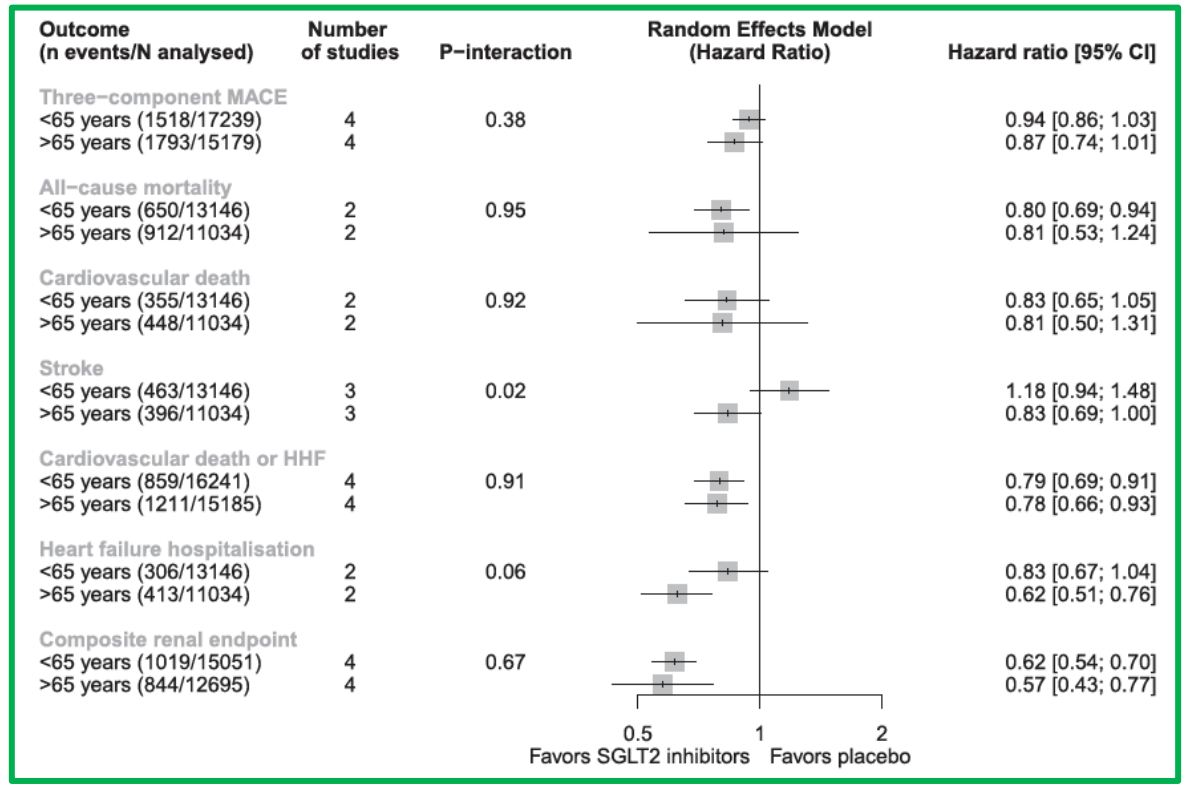
EVIDENCE GAP

Davies et al. Cardiovascular Diabetology (2022) 21:144

GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS FOR OLDER PEOPLE WITH TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

International Diabetes Federation





Diabetes Research And Clinical Practice 174 (2021) 108737

META-ANALYSIS RESULTS VERSUS PLACEBO FOR PATIENTS 75 YEARS OR OLDER AND PATIENTS YOUNGER THAN 75 YEARS.

International Diabetes Federation

Outcome	Number of trials	Age categories (n events/N analyzed)[a]	HR	95% CI	P-interaction	I^2
GLP-1 receptor agonists versus placebo						
3-p MACE	2	All patients	0.87	0.79 to 0.97	0.07	40%
		<75 years (2598/22,006)	0.92	0.85 to 0.99		
		≥75 years (448/2086)	0.75	0.61 to 0.92		
SGLT2 inhibitors versus placebo						
3-p MACE	2	All patients	0.91	0.83 to 0.99	0.16	4%
		<75 years (2075/22,432)	0.93	0.85 to 1.02		
		≥75 years (256/1748)	0.77	0.60 to 0.99		
CVD	2	All patients	0.78	0.58 to 1.06	0.94	71%
		<75 years (691/22,432)	0.79	0.52 to 1.20		
		≥75 years (112/1748)	0.77	0.40 to 1.46		
CVDHHF	2	All patients	0.75	0.62 to 0.90	0.83	52%
		<75 years (1089/22,432)	0.76	0.63 to 0.91		
		≥75 years (187/1748)	0.71	0.40 to 1.27		
HHF	2	All patients	0.71	0.61 to 0.83	0.70	0%
		<75 years (607/22,432)	0.72	0.61 to 0.84		
		≥75 years (102/1748)	0.64	0.36 to 1.12		
Renal composite outcome	2	All patients	0.59	0.52 to 0.65	0.49	0%
		<75 years (1147/21,667)	0.59	0.51 to 0.68		
		≥75 years (133/1668)	0.51	0.36 to 0.65		

Abbreviations: HR, hazard ratio; CI, confidence interval; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2; 3-p MACE, 3-point composite of major adverse cardiovascular events; CVD, cardiovascular death; CVDHHF, cardiovascular death or hospitalization for heart failure; HHF, hospitalization for heart failure. [a]Number of events (n) and patients analyzed (N) are both for intervention and placebo arms.

Diabetes Research And Clinical Practice 174 (2021) 108737

SGLT2-INHIBITORS ARE EFFECTIVE AND SAFE IN THE ELDERLY: THE SOLD STUDY

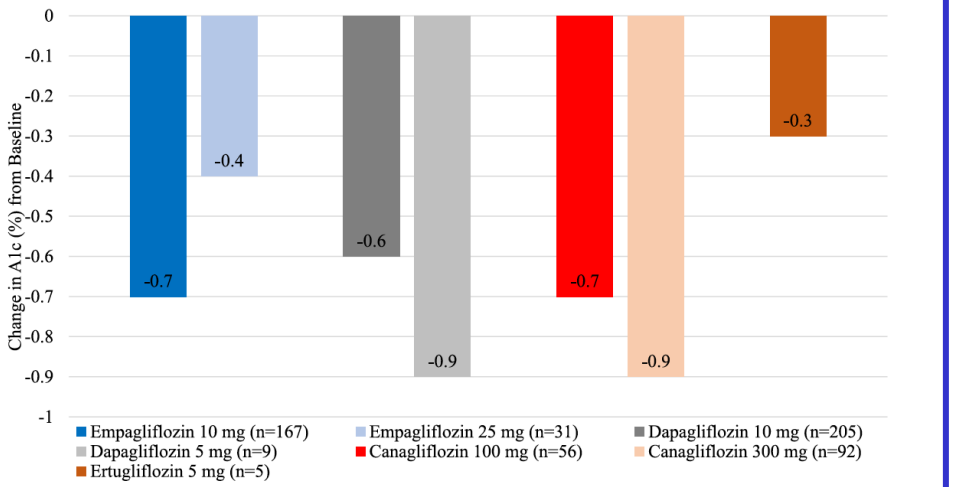


Fig. 2. Changes in A1c (%) values from baseline accordingly to different molecules.

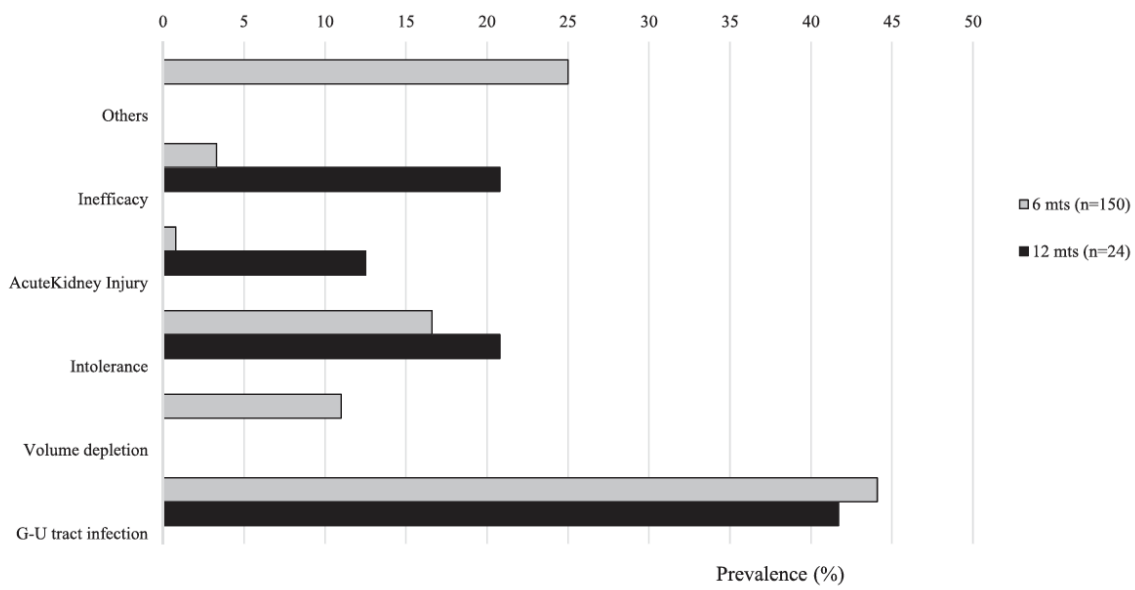
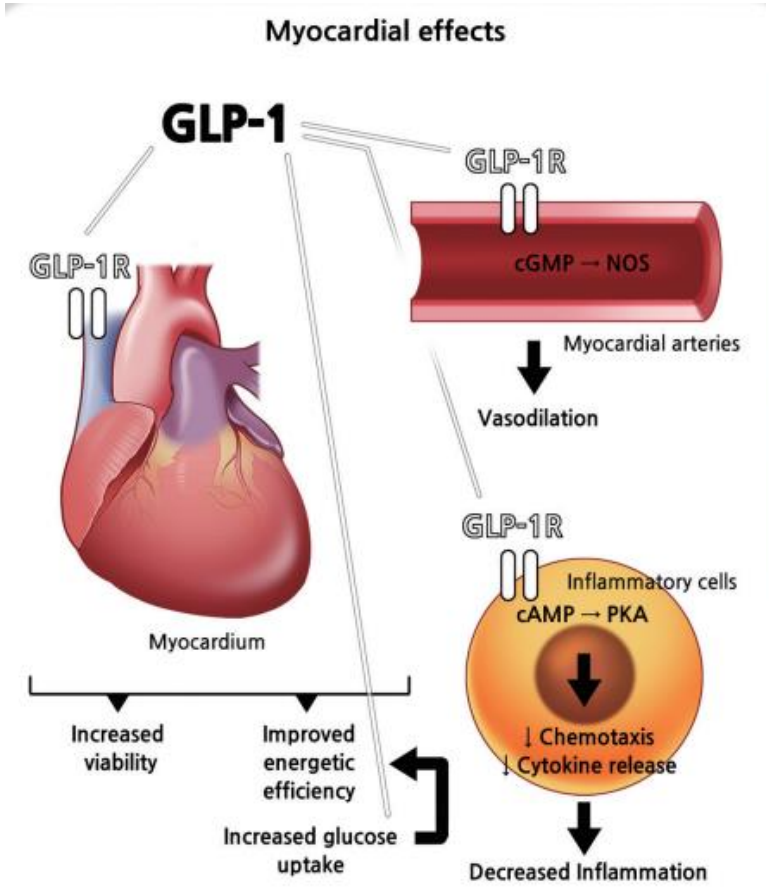


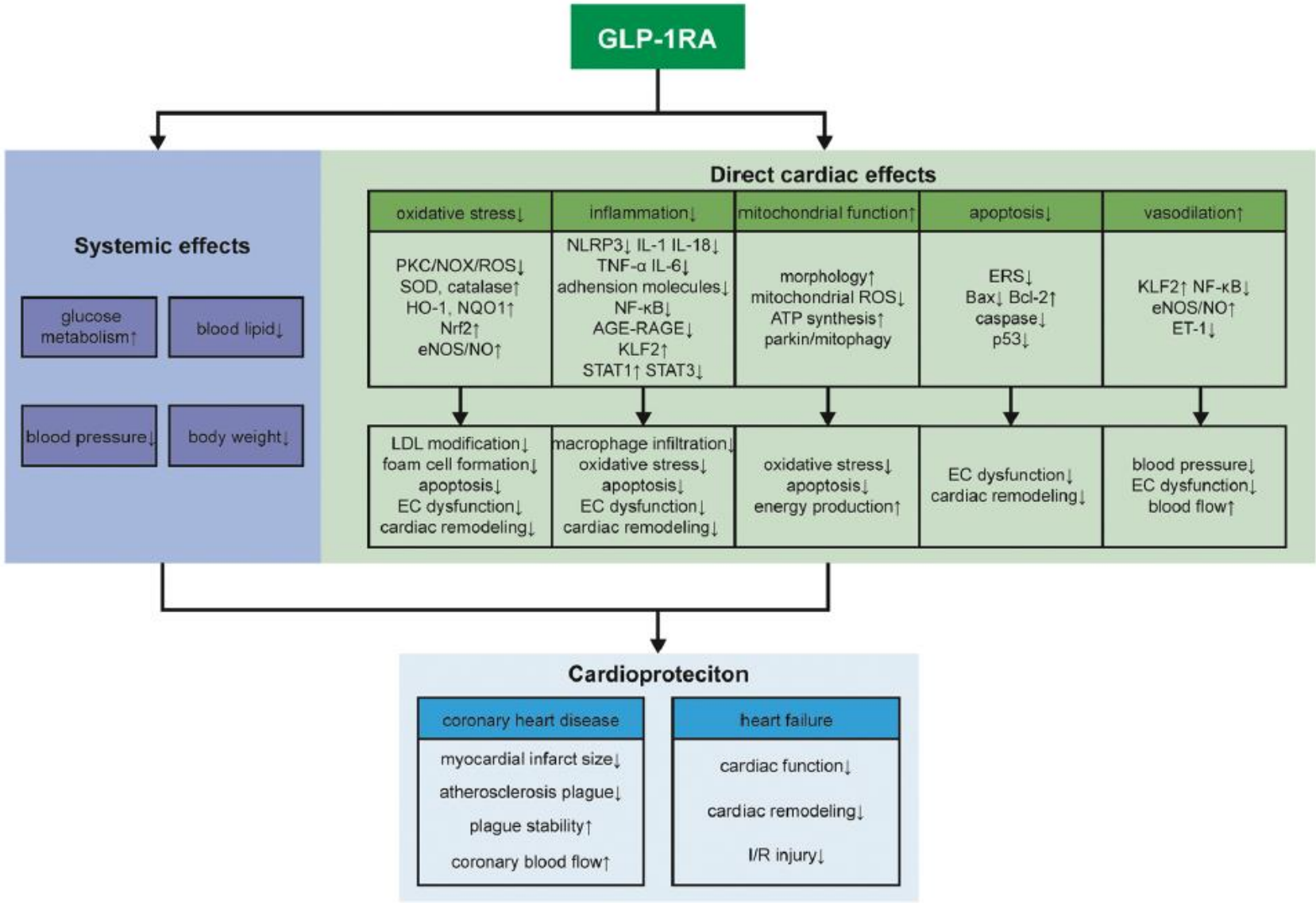
Fig. 3. Causes of treatment discontinuation at 6 and 12 months.

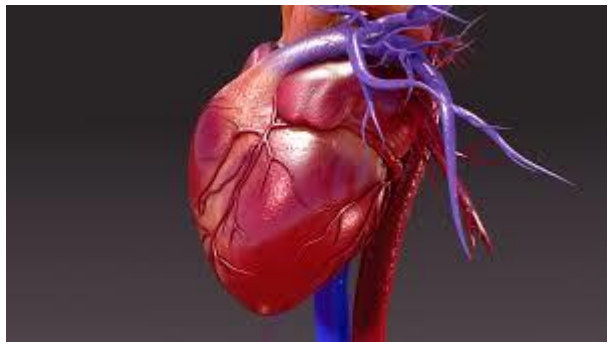
"SGLT2i are well-tolerated and safe in the elderly and appear as an effective therapeutic option, though some caution is also suggested, especially in more fragile subjects"

Pharmacological Research 183 (2022) 106396

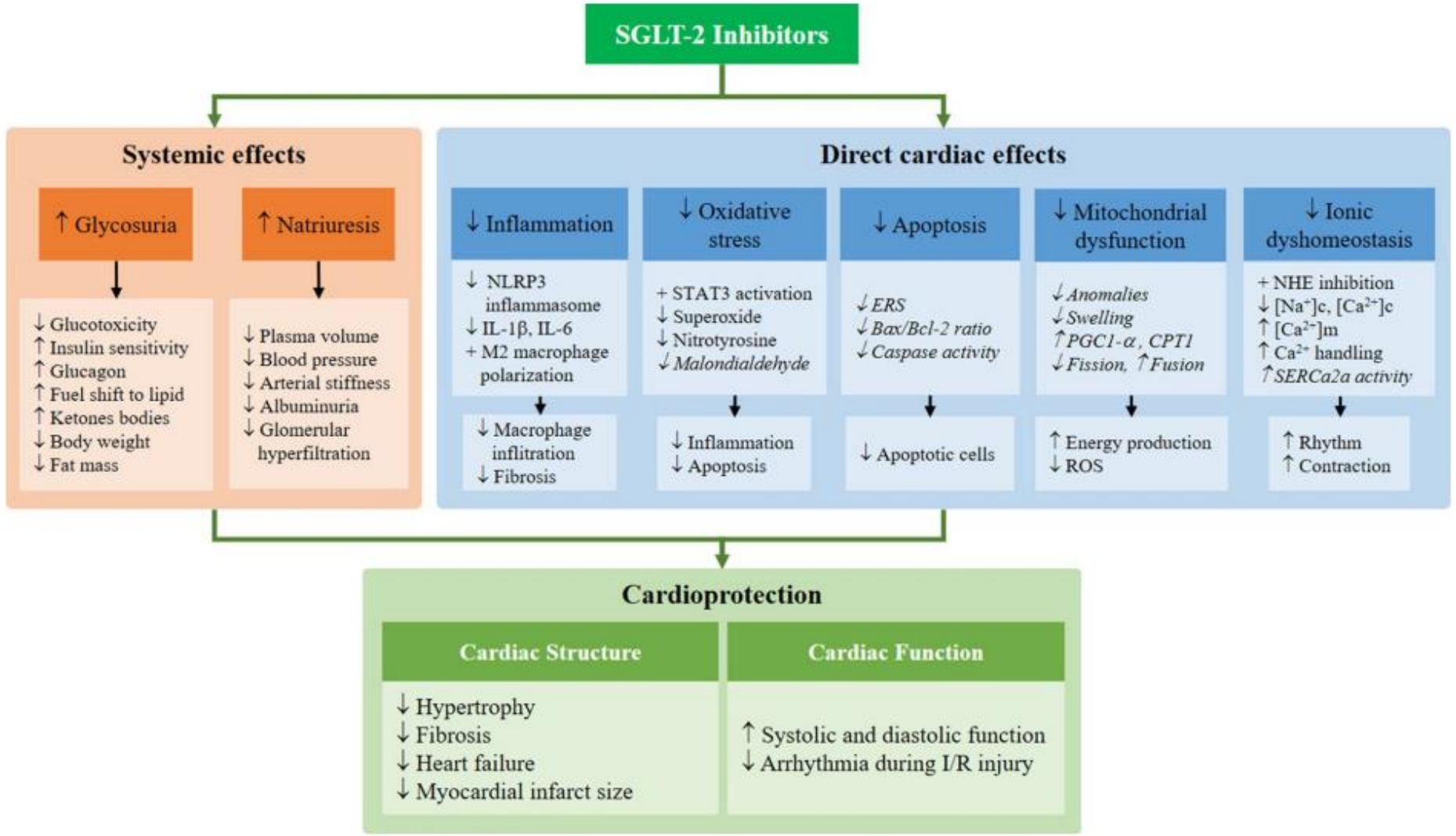
Mechanims of cardiovascular benefits: evidence for extra-glycemic effects


Myocardial effects
GLP-1
GLP-1R
cGMP → NOS
Myocardial arteries
Vasodilation
GLP-1R
GLP-1R
Myocardium
Inflammatory cells
cAMP → PKA
↓ Chemotaxis
↓ Cytokine release
Increased viability
Improved energetic efficiency
Increased glucose uptake
Decreased Inflammation


GLP-1RA
Systemic effects
glucose metabolism↑
blood lipid↓
blood pressure↓
body weight↓
Direct cardiac effects
oxidative stress↓
inflammation↓
mitochondrial function↑
apoptosis↓
vasodilation↑
PKC/NOX/ROS↓ SOD, catalase↑ HO-1, NQO1↑ Nrf2↑ eNOS/NO↑
NLRP3↓ IL-1 IL-18↓ TNF-α IL-6↓ adhension molecules↓ NF-κB↓ AGE-RAGE↓ KLF2↑ STAT1↑ STAT3↓
morphology↑ mitochondrial ROS↓ ATP synthesis↑ parkin/mitophagy
ERS↓ Bax↓ Bcl-2↑ caspase↓ p53↓
KLF2↑ NF-κB↓ eNOS/NO↑ ET-1↓
LDL modification↓ foam cell formation↓ apoptosis↓ EC dysfunction↓ cardiac remodeling↓
macrophage infiltration↓ oxidative stress↓ apoptosis↓ EC dysfunction↓ cardiac remodeling↓
oxidative stress↓ apoptosis↓ energy production↑
EC dysfunction↓ cardiac remodeling↓
blood pressure↓ EC dysfunction↓ blood flow↑
Cardioproteciton
coronary heart disease
myocardial infarct size↓
atherosclerosis plague↓
plague stability↑
coronary blood flow↑
heart failure
cardiac function↓
cardiac remodeling↓
I/R injury↓

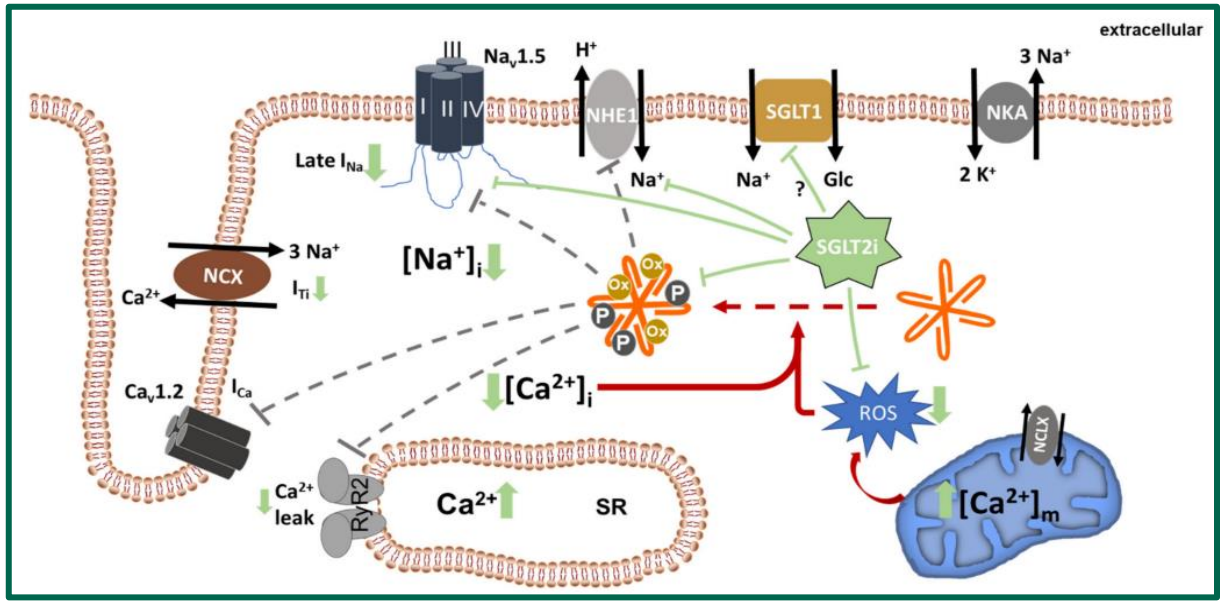


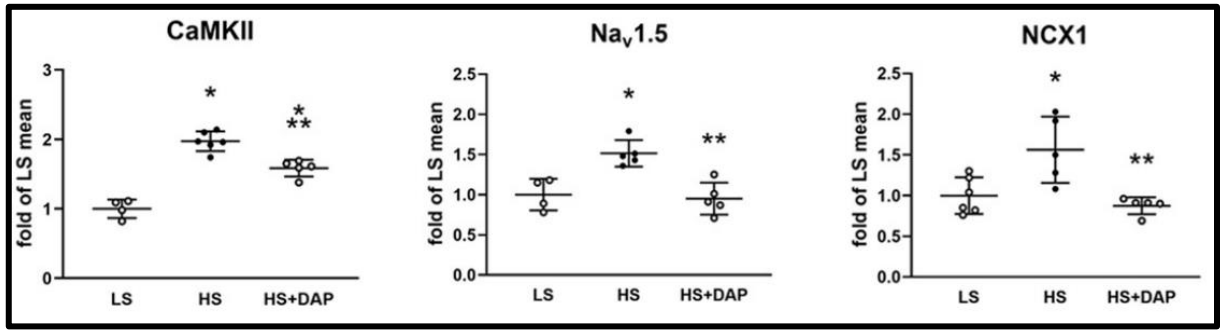
Target
or off target effects ?

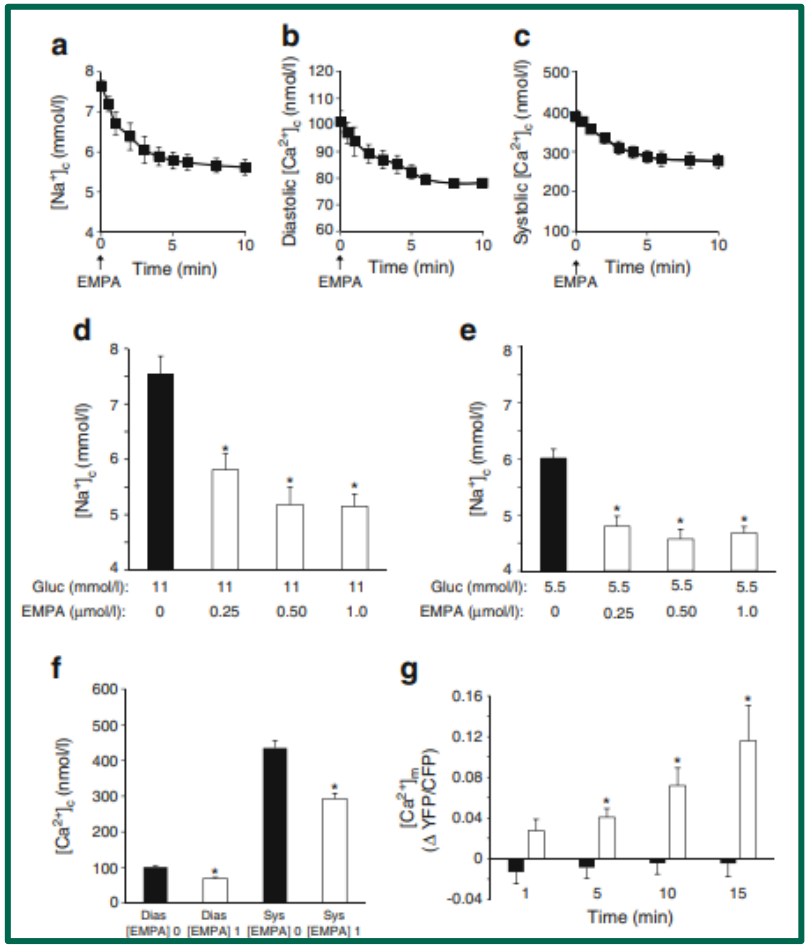


Lahnwong et al. Cardiovasc Diabetol (2018) 17:101

Cardiac off-target effects: NHE-1 and Nav1.5 binding

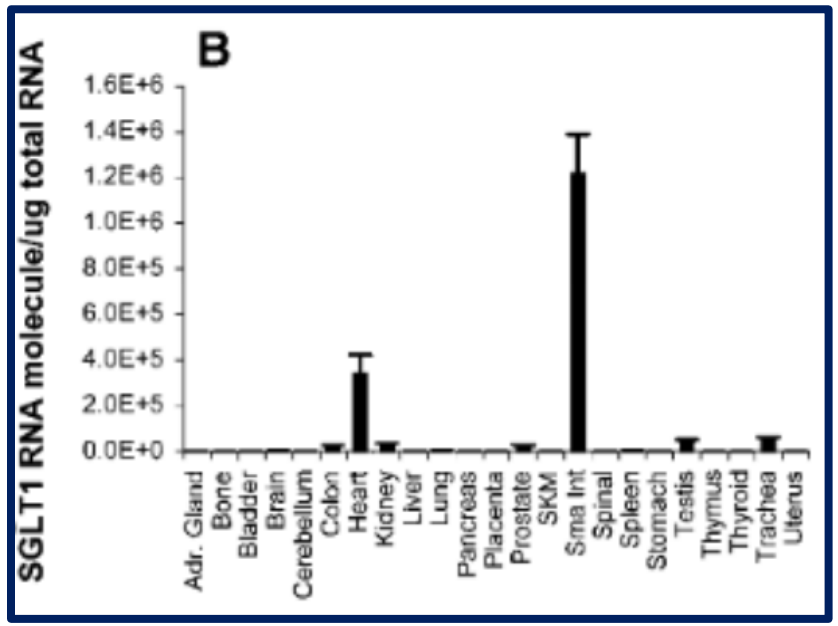


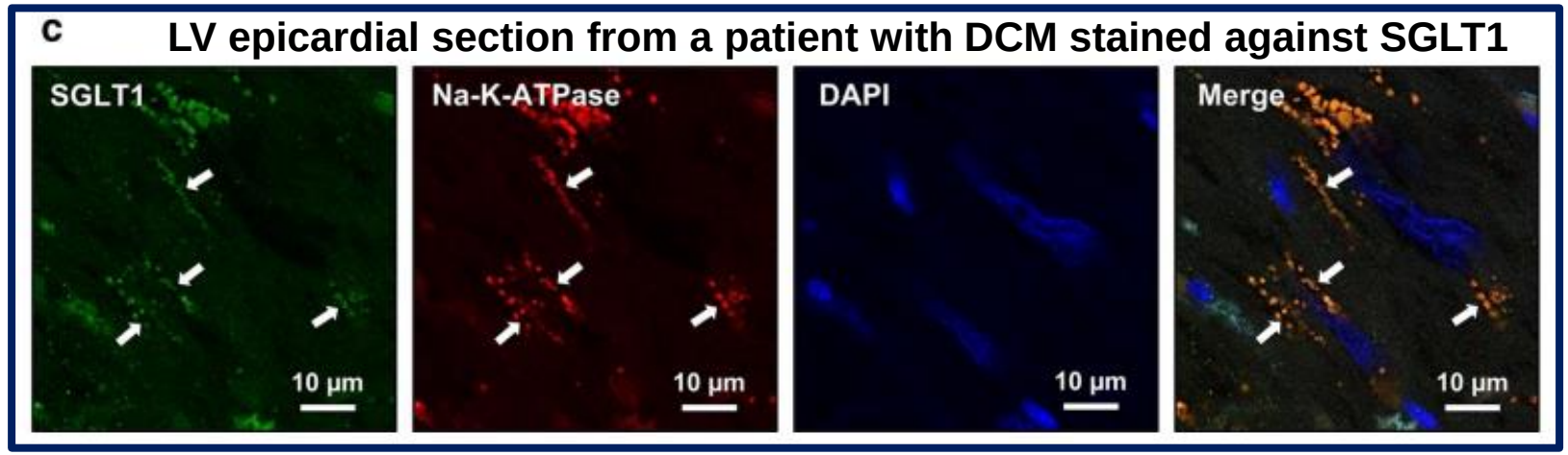




Maximilian Trum et al, Int. J. Mol. Sci. 2021, 22, 7976

EXPRESSION OF MYOCARDIAL SGLT1 IN VARIOUS PATHOLOGICAL CONDITIONS COMPARED WITH HEALTHY CONTROLS





		SGLT1 Expression				
Condition	**Subtype**	**Ref: [41]**	**Ref: [39]**	**Ref: [51]**	**Ref: [54]**	**Ref: [40]**
HF	hypertrophic CM	~	↑		(↑)	
HF	ischemic CM	↑	↑	↑	(↑)	~
HF	dilated CM	↑		~	(↑)	~
HF	metabolic syndrome/T2DM	↑		↑	↑	
HF	post-LVAD			↑		

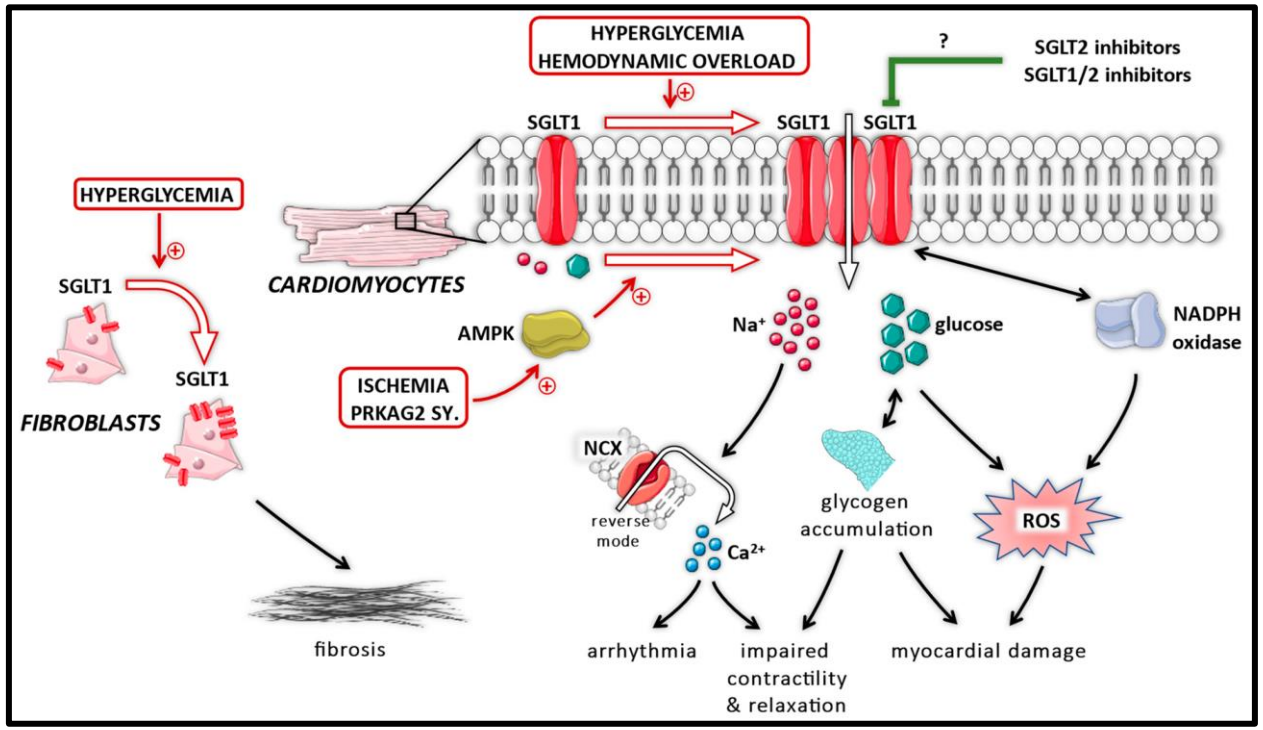
Alex Ali Sayour et al, Int. J. Mol. Sci. 2021, 22, 9852.

Cardiac off-target effects: SGLT-1 binding

Table 1 SGLT2/SGLT1 selectivity of main SGLT inhibitors[33–37]

Molecule	SGLT2 (IC50 nM)	SGLT1 (IC50 nM)	SGLT2 selectivity over SGLT1
Empagliflozin	3.1	8,300	~2,500-fold
Ertugliflozin	0.87	1,960	~2,000-fold
Dapagliflozin	1.2	1,400	~1,200-fold
Canagliflozin	2.7	710	~250-fold
Sotagliflozin	1.8	36	~20-fold
Phlorizin	2,800	4,200	~1.5-fold

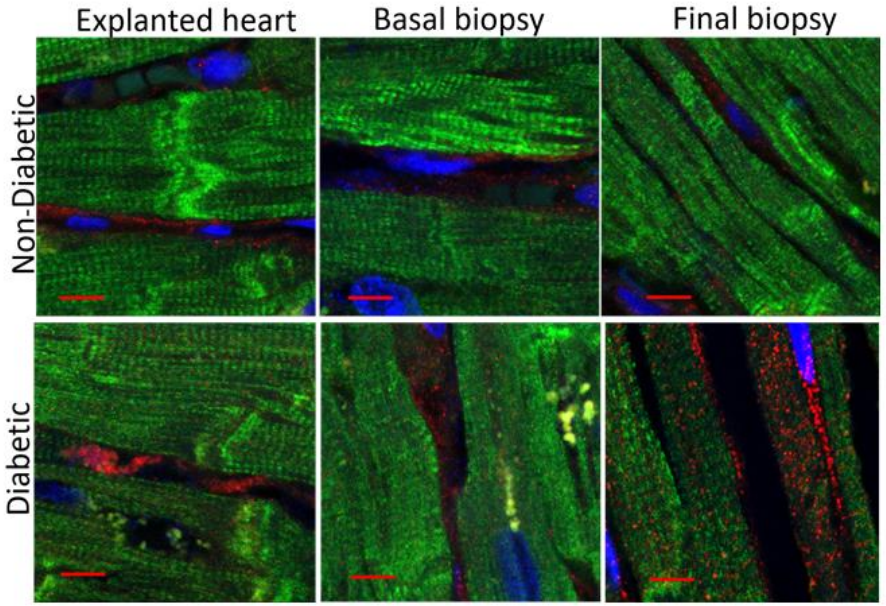
Abbreviations: IC50, half-maximal inhibitory concentration; SGLT, sodium-glucose cotransporter.

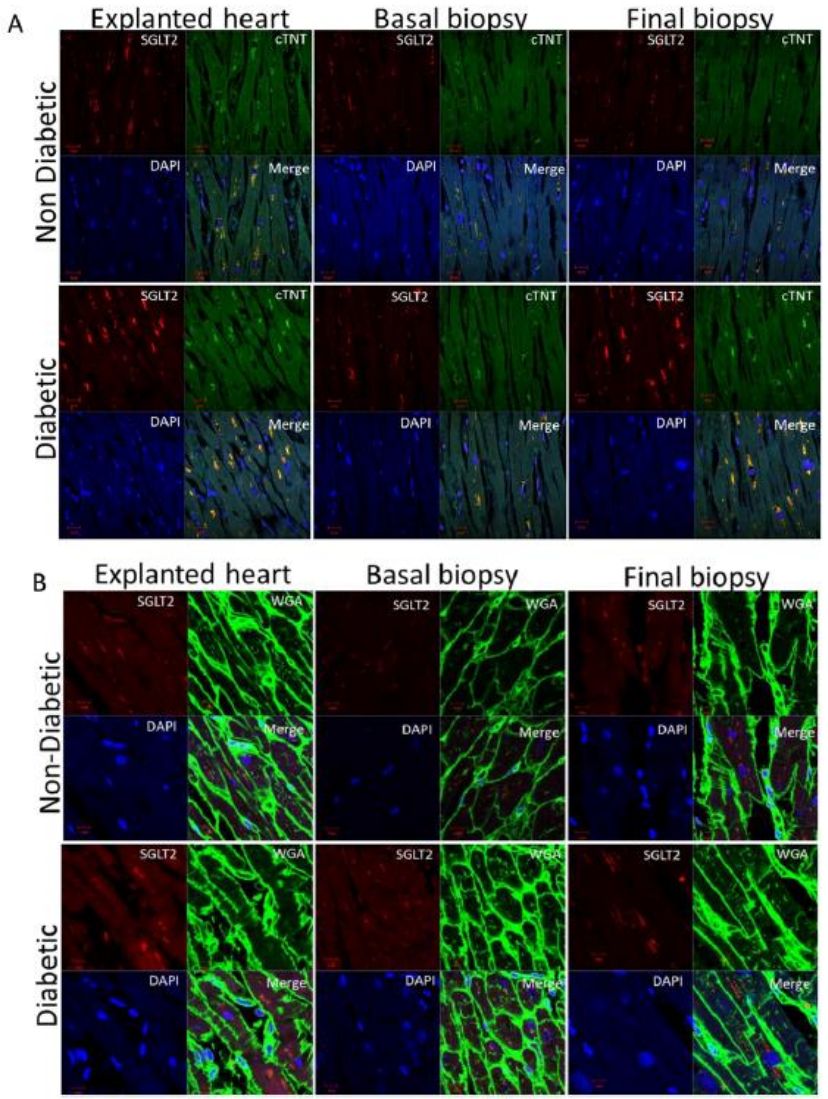


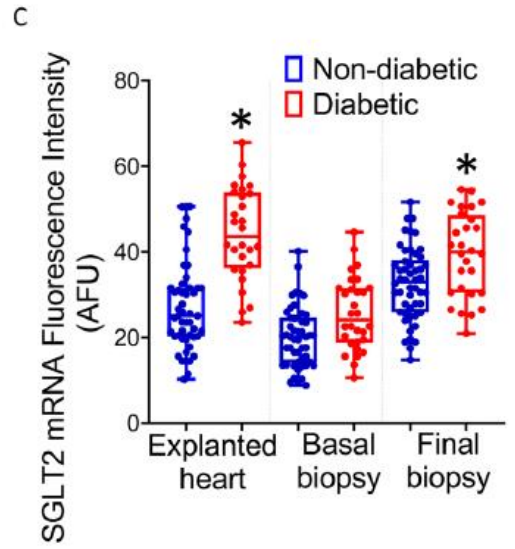
Drug Design, Development and Therapy 2017:11

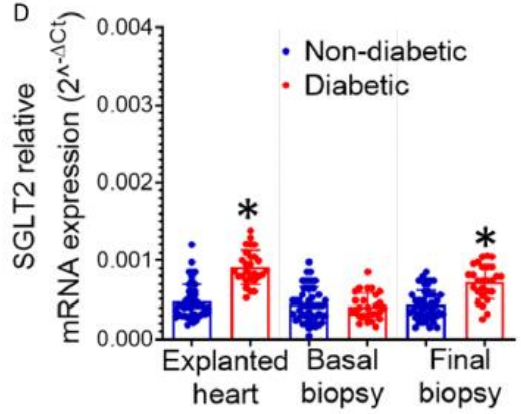
Alex Ali Sayour et al, Int. J. Mol. Sci. 2021, 22, 9852.

SGLT2 protein localization in human cardiomyocyte



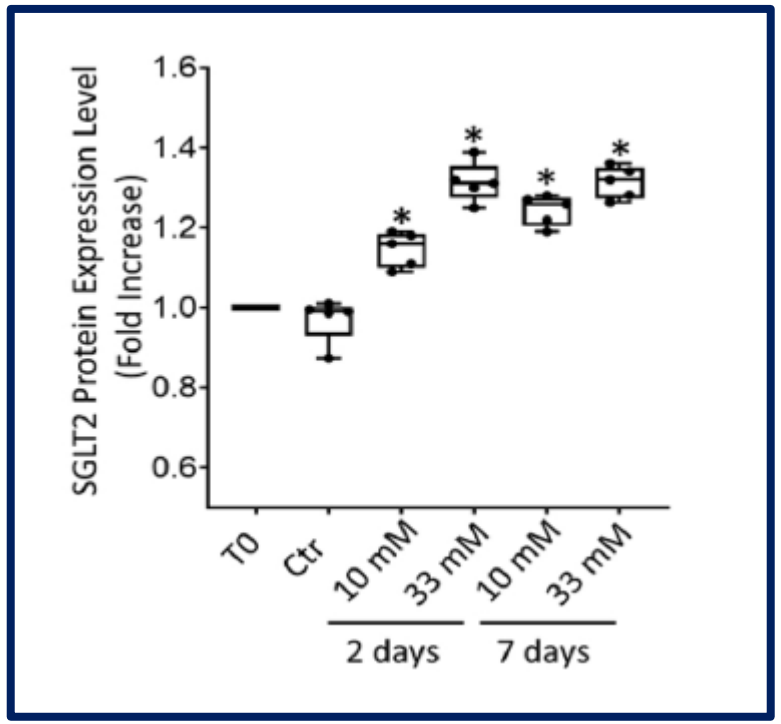


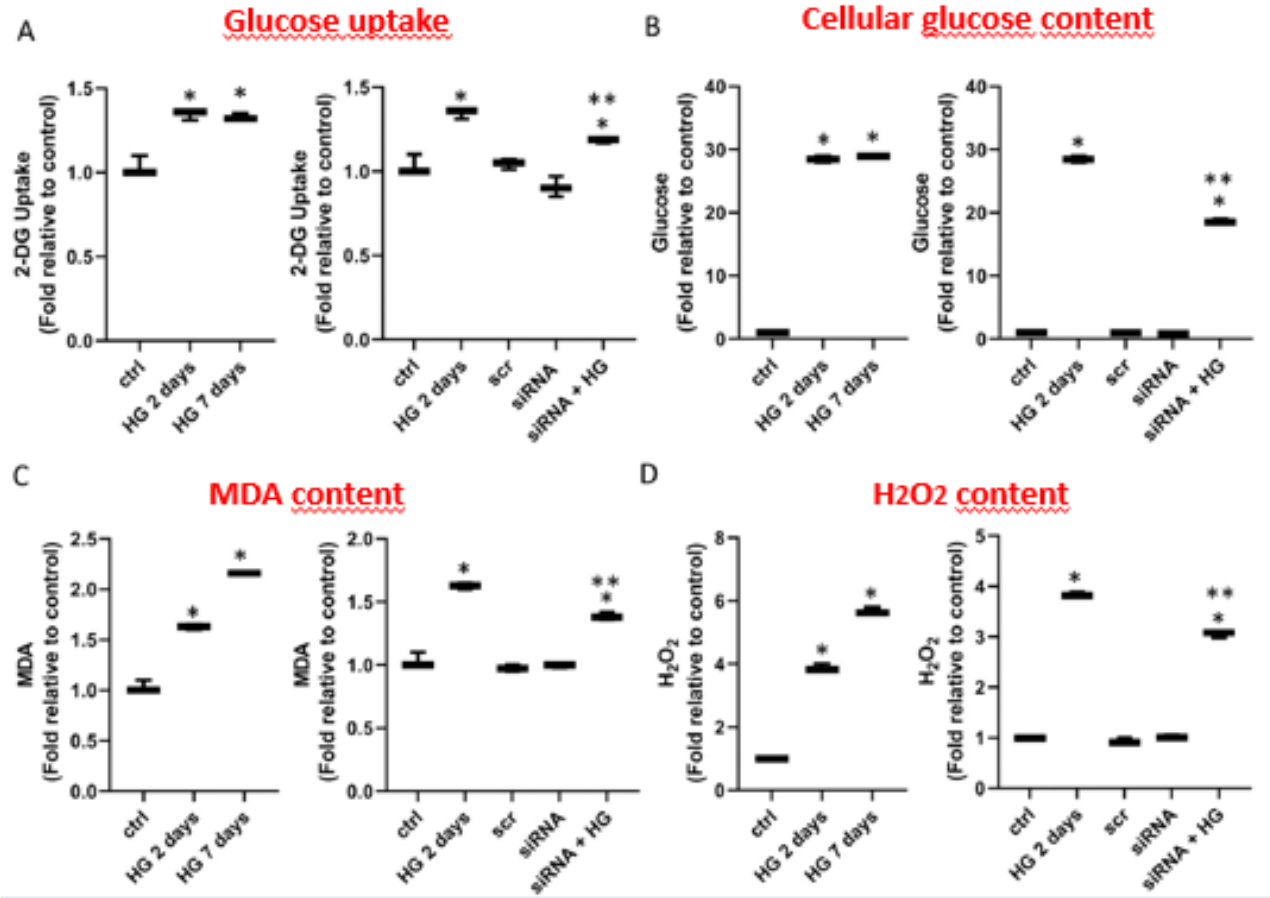




Marfella R et al, Pharmacological Research 184 (2022) 106448

SGLT2 PROTEIN EXPRESSION IN HUMAN CARDIOMYOCYTE CELL LINE EXPOSED TO HIGH GLUCOSE CONCENTRATION

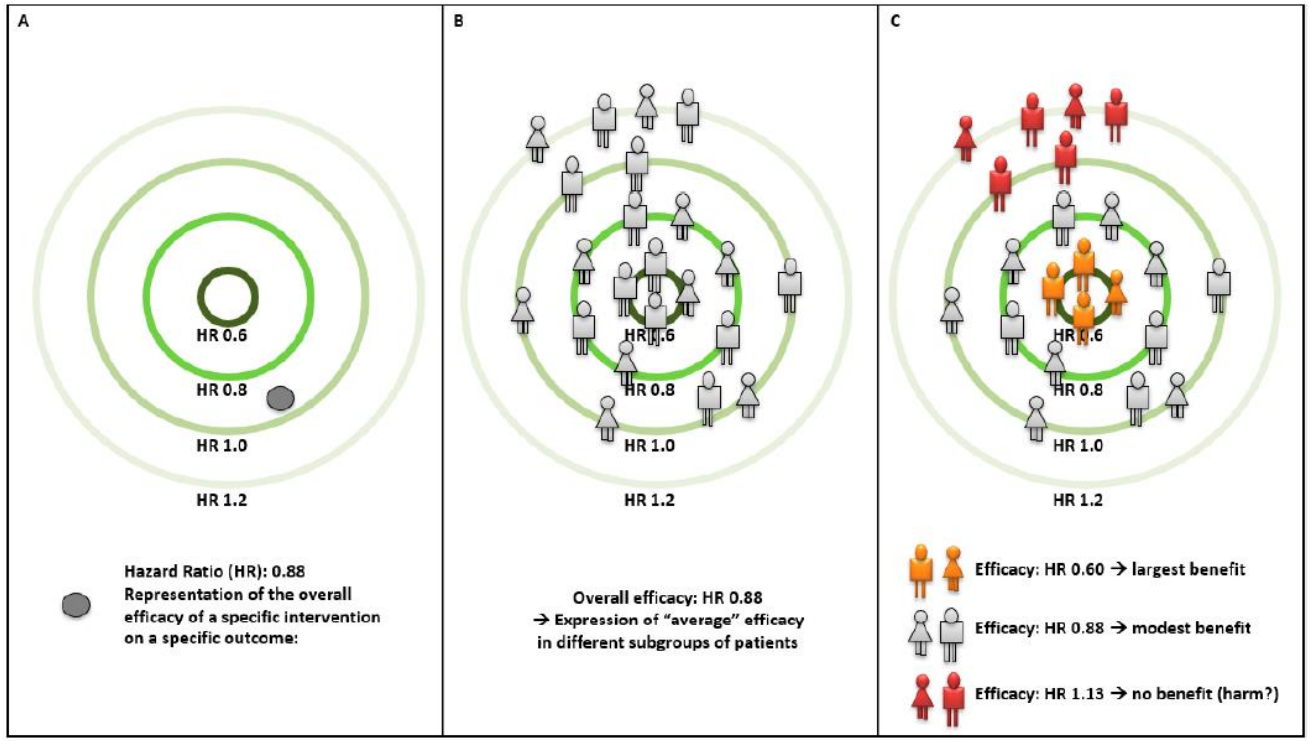


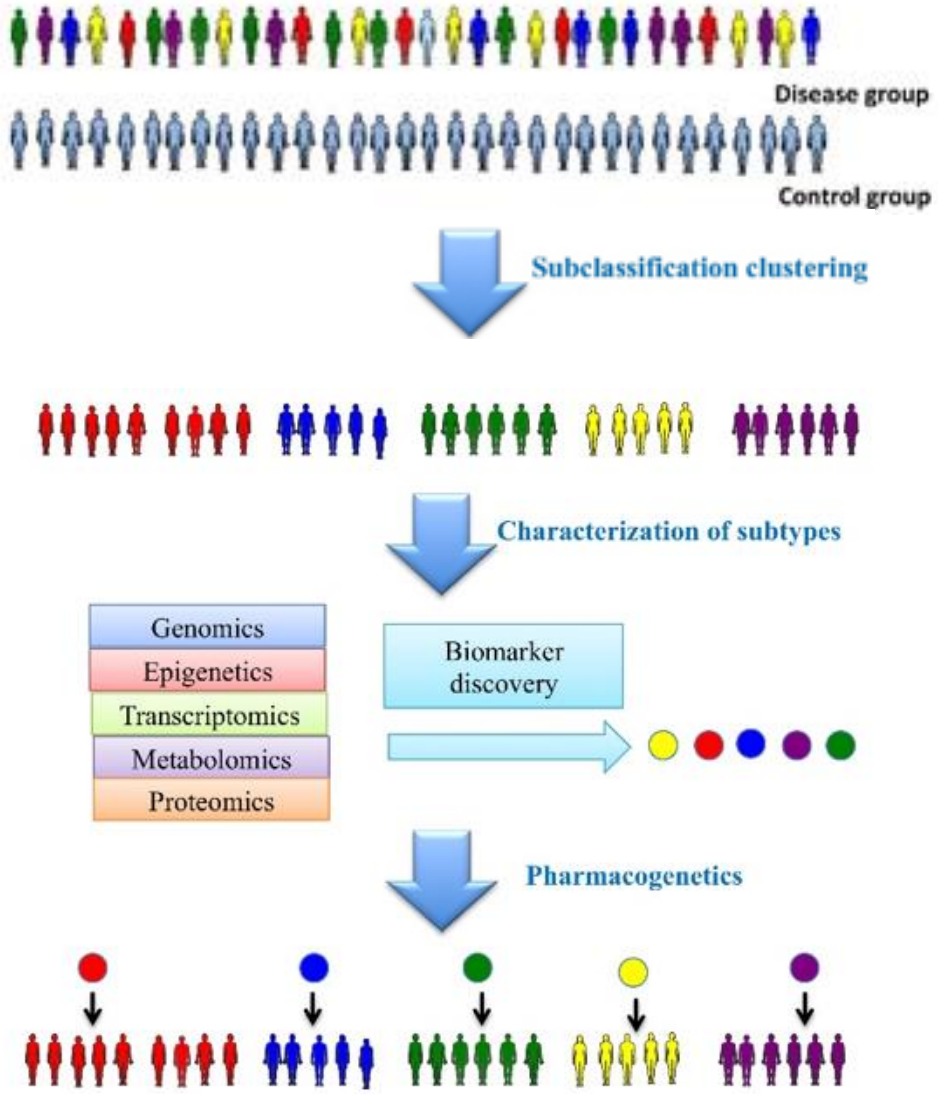


Marfella R et al., Pharmacological Research 184 (2022) 106448

Do we need a Precision Medicine approach to improve diabetic cardiovascular complications?

PRECISION MEDICINE IN TYPE 2 DIABETES

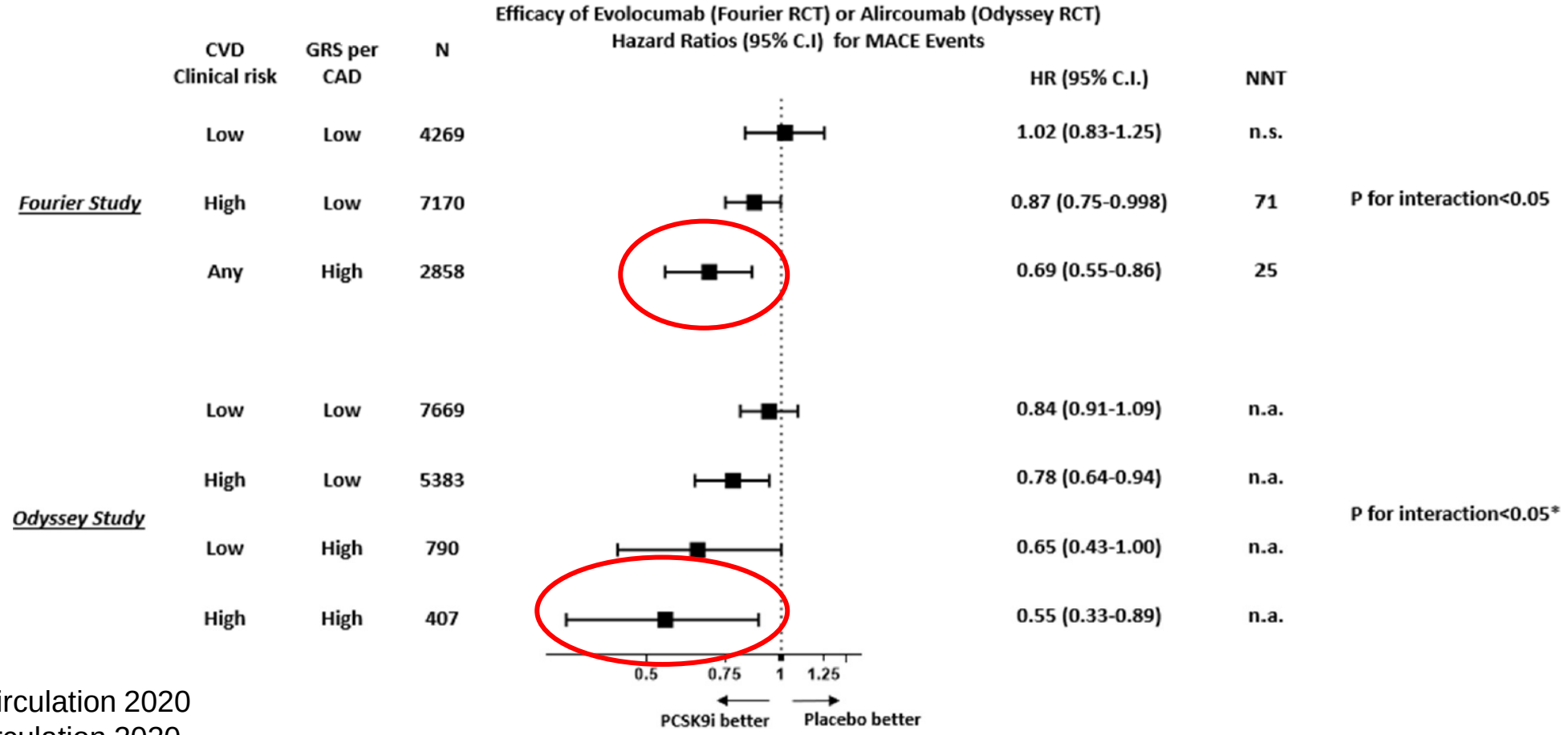




JIM Journal of Internal Medicine Founded in 1863

Journal of Internal Medicine, Volume: 285, Issue: 1, Pages: 40-48, First published: 07 November 2018, DOI: (10.1111/joim.12859)

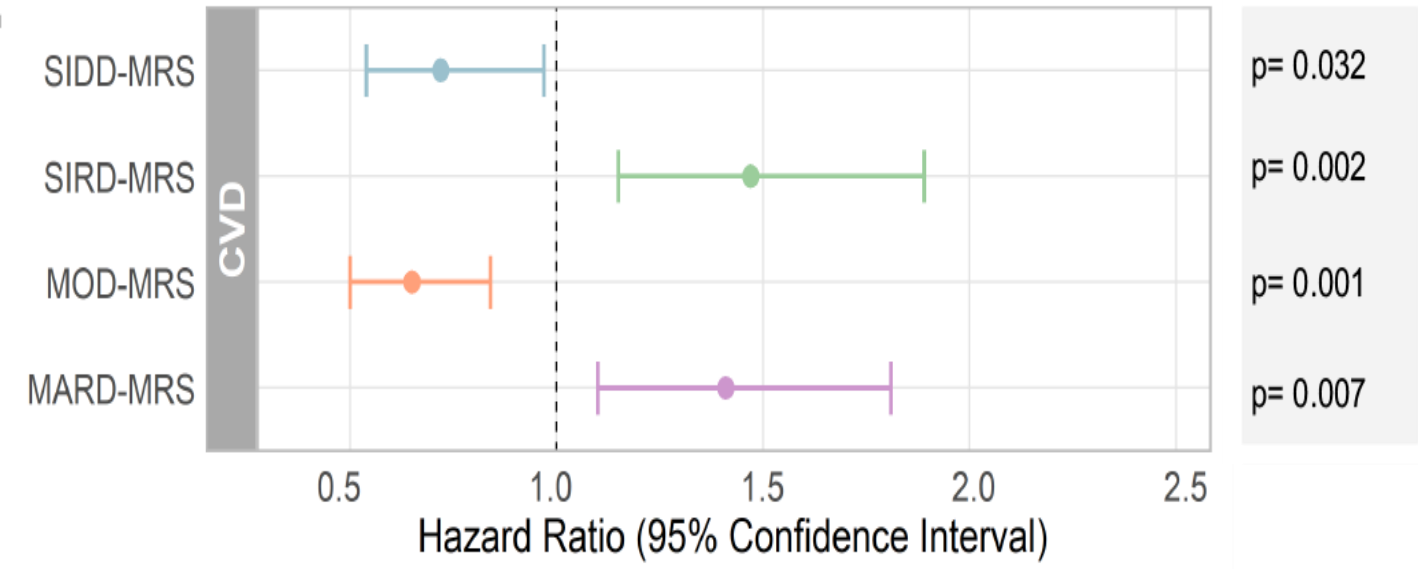
Efficacy of the PCSK9 inhibitors evolocumab and alirocumab in the FOURIER and ODYSSEY studies (patients in secondary cardiovascular prevention) stratified by the combination of clinical and genetic CVD risk (CAD-PGRS) information



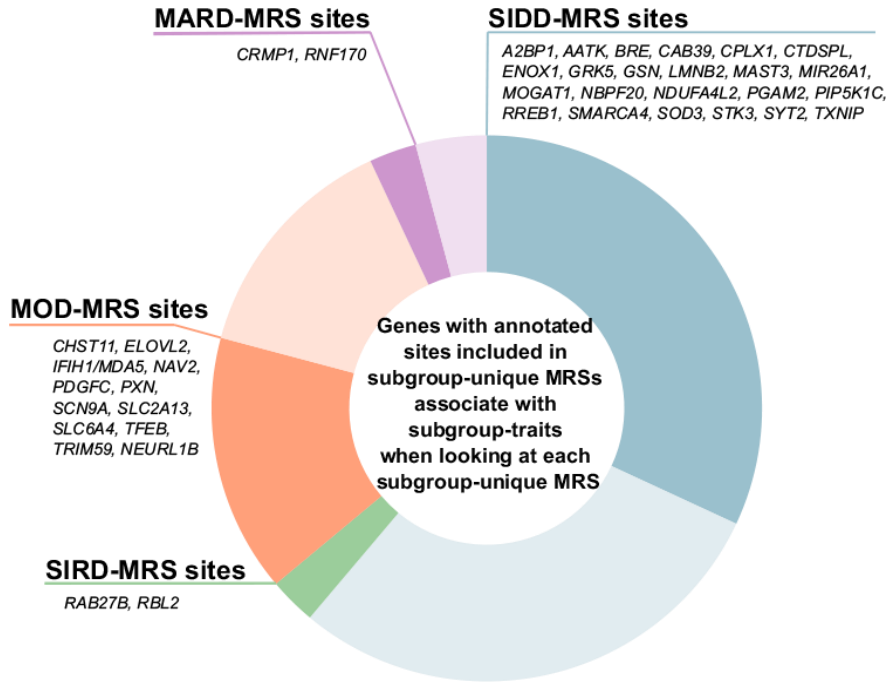
Damask et al., Circulation 2020
Marston et al. Circulation 2020

NOVEL SUBGROUPS OF TYPE 2 DIABETES DISPLAY DIFFERENT EPIGENETIC PATTERNS THAT ASSOCIATE WITH FUTURE CARDIOVASCULAR DIABETIC COMPLICATIONS

American Diabetes Association.

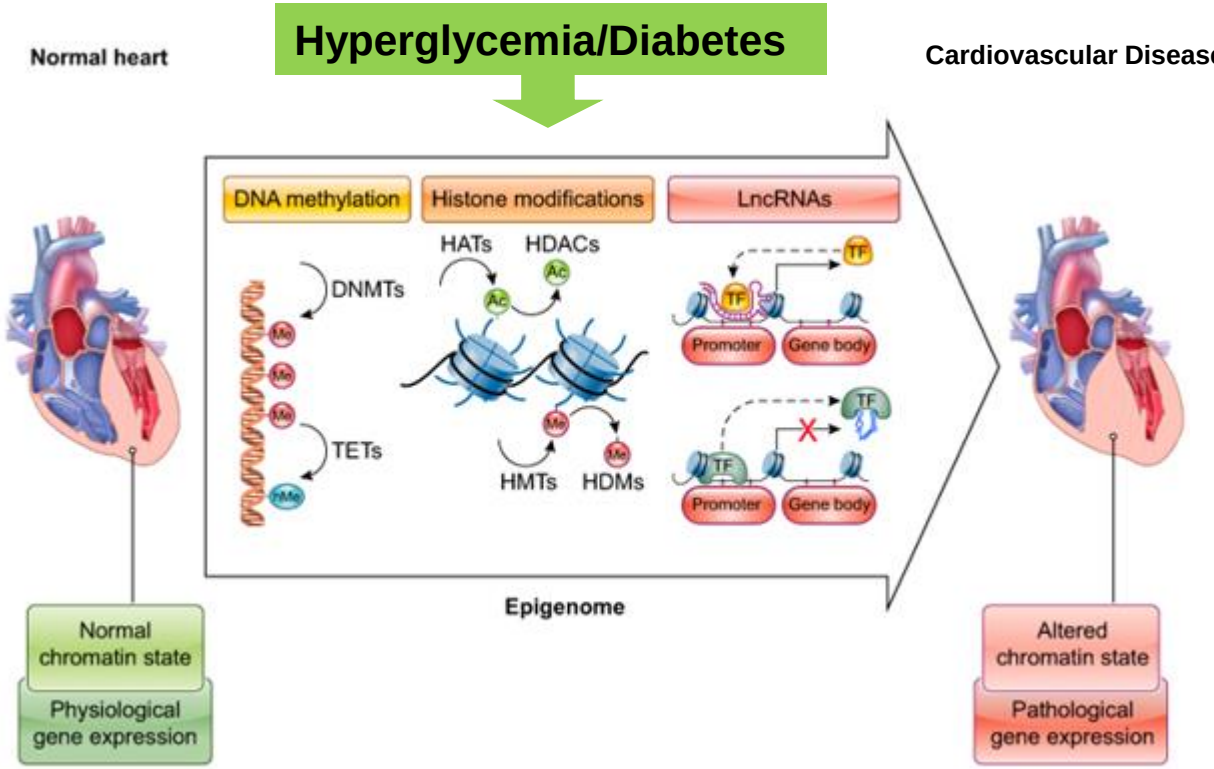


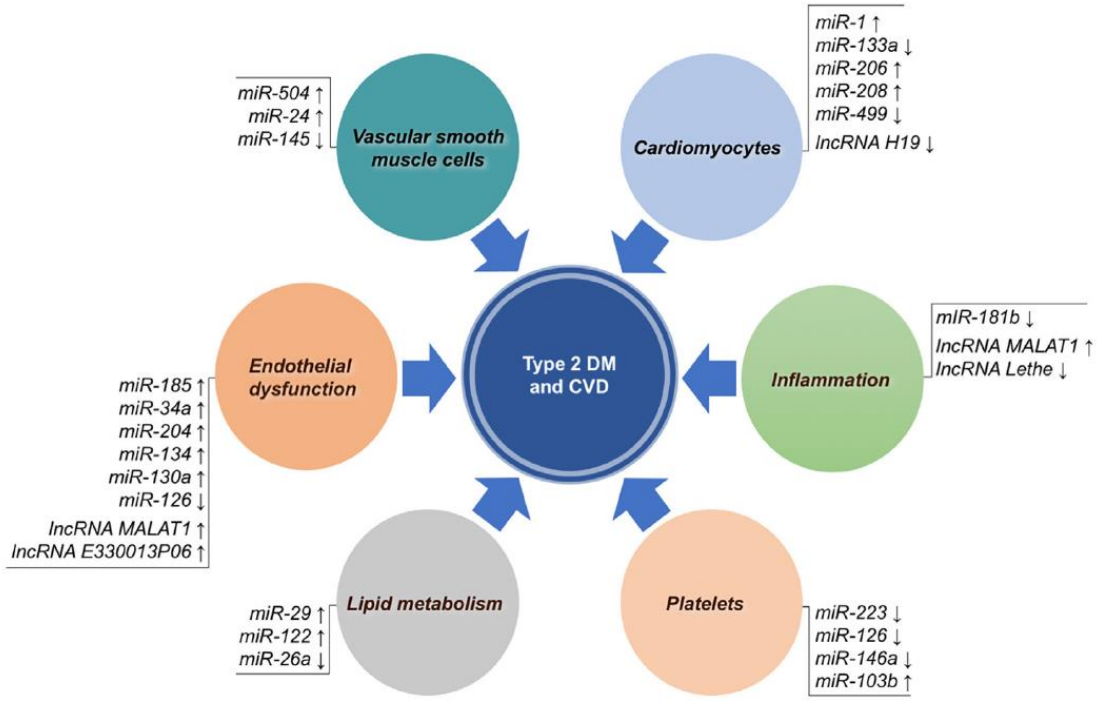
Associations between subgroup-unique MRSs and the risk of developing CVD complications during 8 years of follow-up (mean 4.5 years) in the combined ANDIS discovery, ANDIS replication, and ANDiU replication cohort



Diabetes Care. 2022 Jul 7;45(7):1621-1630. doi: 10.2337/dc21-2489.

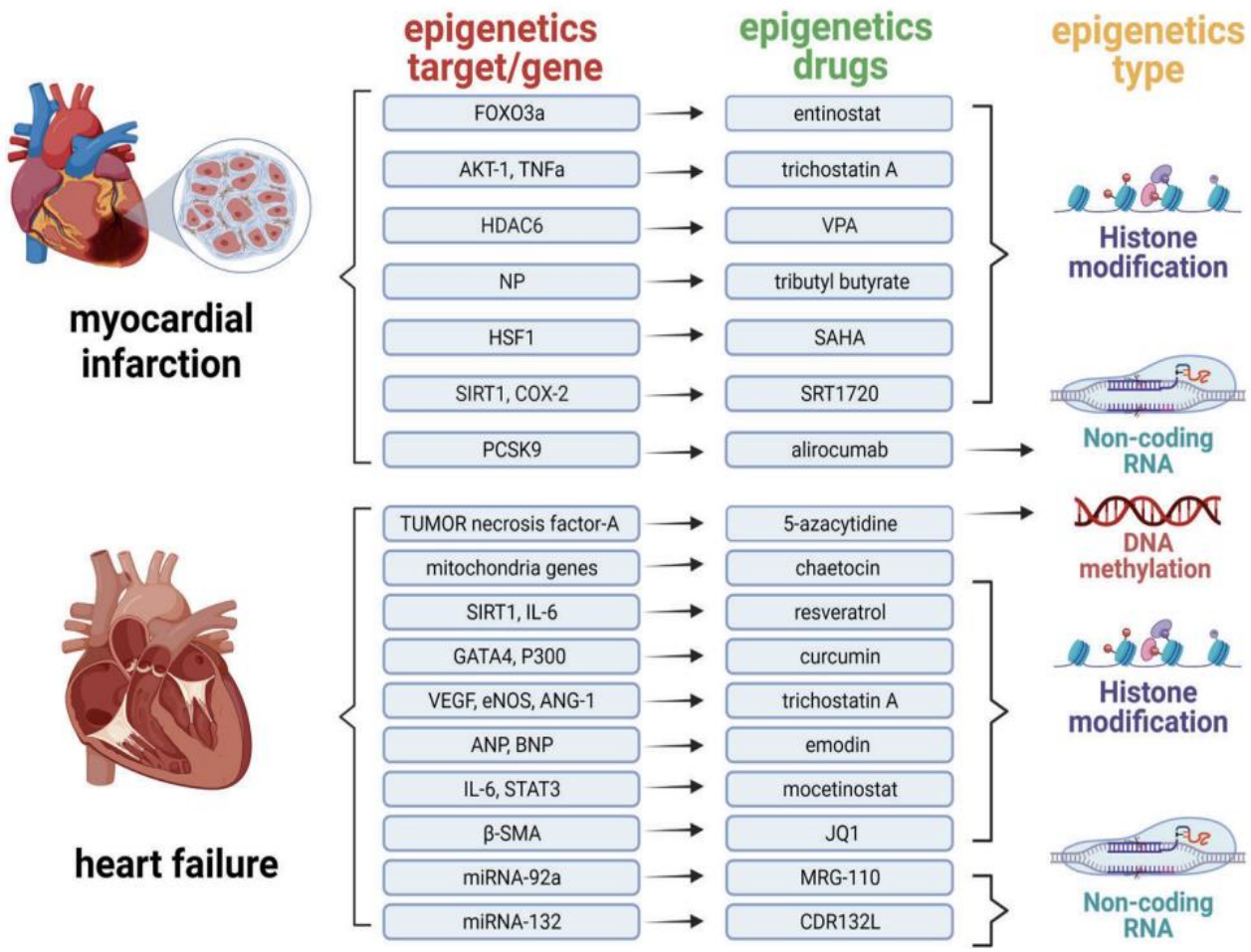
HYPERGLYCEMIA-INDUCED EPIGENETIC MODIFICATIONS

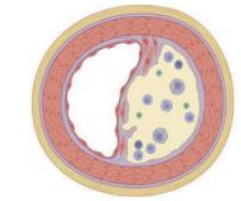


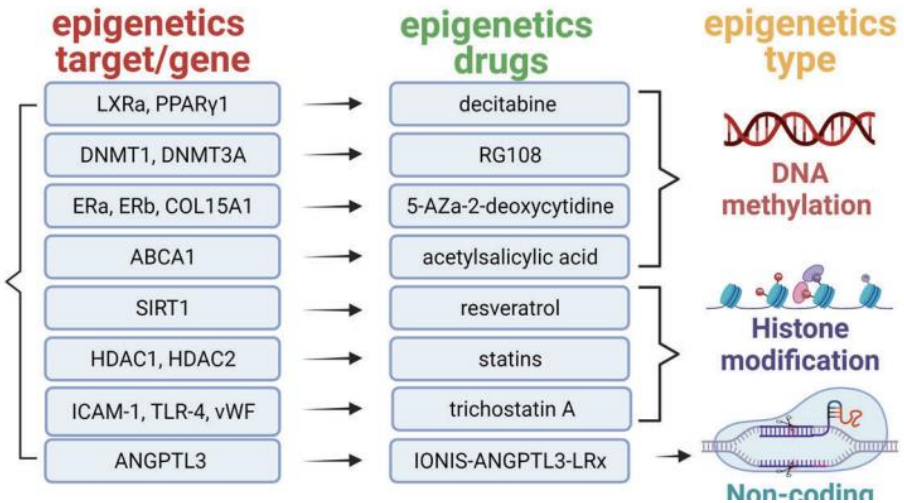


De Rosa et al Front. Endocrinol. 9:2. doi: 10.3389/fendo.2018.00002

EPIGENETIC REGULATION IN CARDIOVASCULAR DISEASE: MECHANISMS AND ADVANCES IN CLINICAL TRIALS







Signal Transduct Target Ther . 2022 Jun 25;7(1):200. doi: 10.1038/s41392-022-01055-2

EPIGENETICS AND VASCULAR EFFECTS OF DAPAGLIFLOZIN

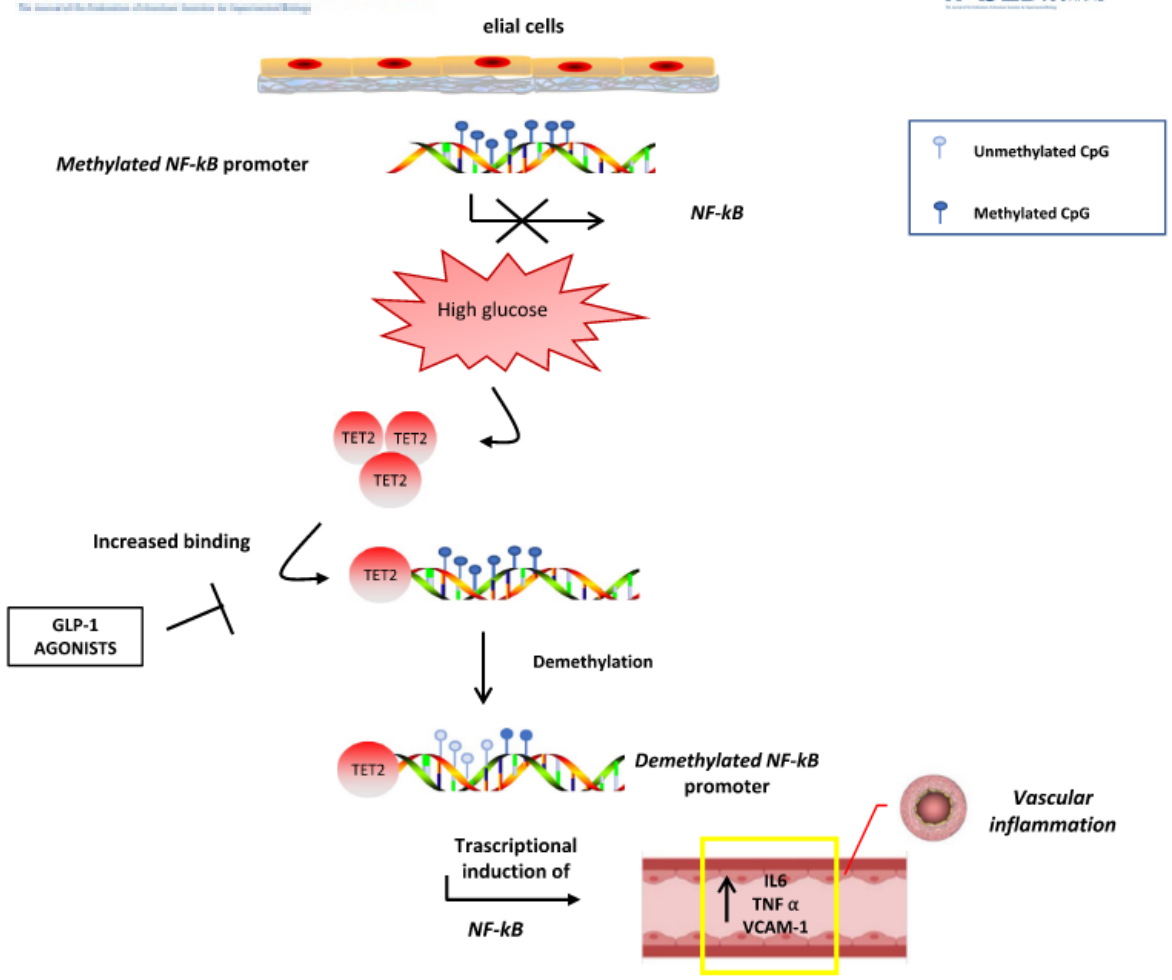
Table 5. Baseline and Posttreatment Expression of Circulating miRs in Patients Receiving Dapagliflozin and HCT

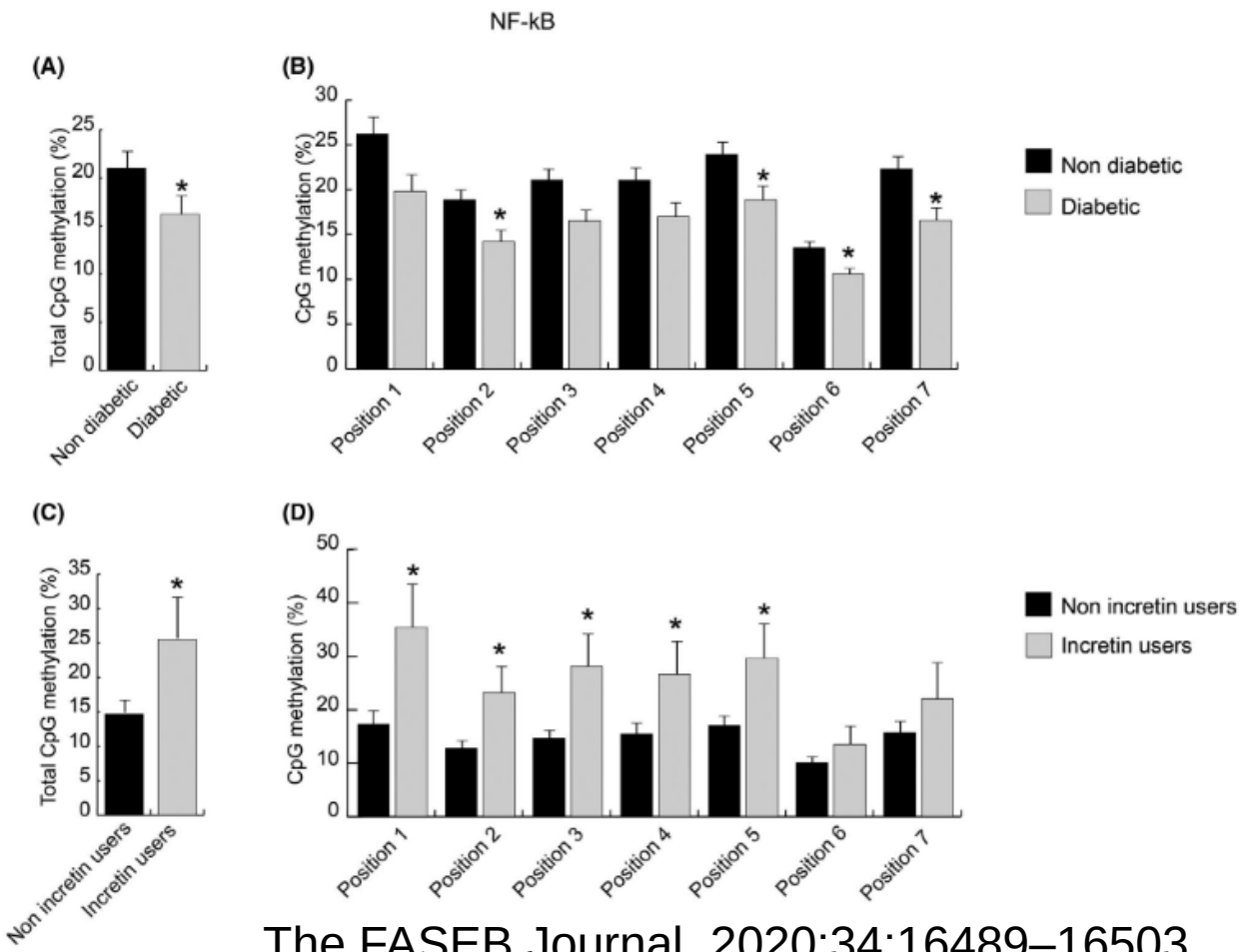
	Dapagliflozin		HCT		
	V0	V1	V0	V1	*P* Value (Time × Group)[a]
miR-21-5p	1.596 (2.088)	1.772 (1.395)	1.443 (1.835)	1.292 (3.206)	0.611
miR-200b	0.379 (0.580)	2.802 (4.179)[b]	0.375 (0.453)	2.105 (2.318)[b]	0.629
miR-30e-5p	1.195 (3.134)	4.004 (3.563)[b]	1.405 (2.062)	2.615 (1.867)[c]	**0.012**
miR-199a-3p	0.353 (0.480)	0.171 (0.181)[b]	0.293 (0.314)	0.418 (0.725)[c]	**0.017**
miR-27b	0.072 (0.050)	0.172 (0.209)[b]	0.063 (0.050)	0.184 (0.305)[b]	0.343
miR-130b-3p	0.074 (0.083)	0.155 (0.200)[b]	0.044 (0.046)	0.096 (0.190)[b]	0.800
miR-27a-3p	0.753 (1.105)	2.039 (2.302)[b]	0.615 (0.619)	2.606 (3.132)[b]	0.297

Solini et al J Clin Endocrinol Metab, October 2019, 104(10):4253–4263

INCRETIN DRUGS EFFECT ON EPIGENETIC MACHINERY: NEW POTENTIAL THERAPEUTIC IMPLICATIONS IN PREVENTING VASCULAR DIABETIC COMPLICATIONS

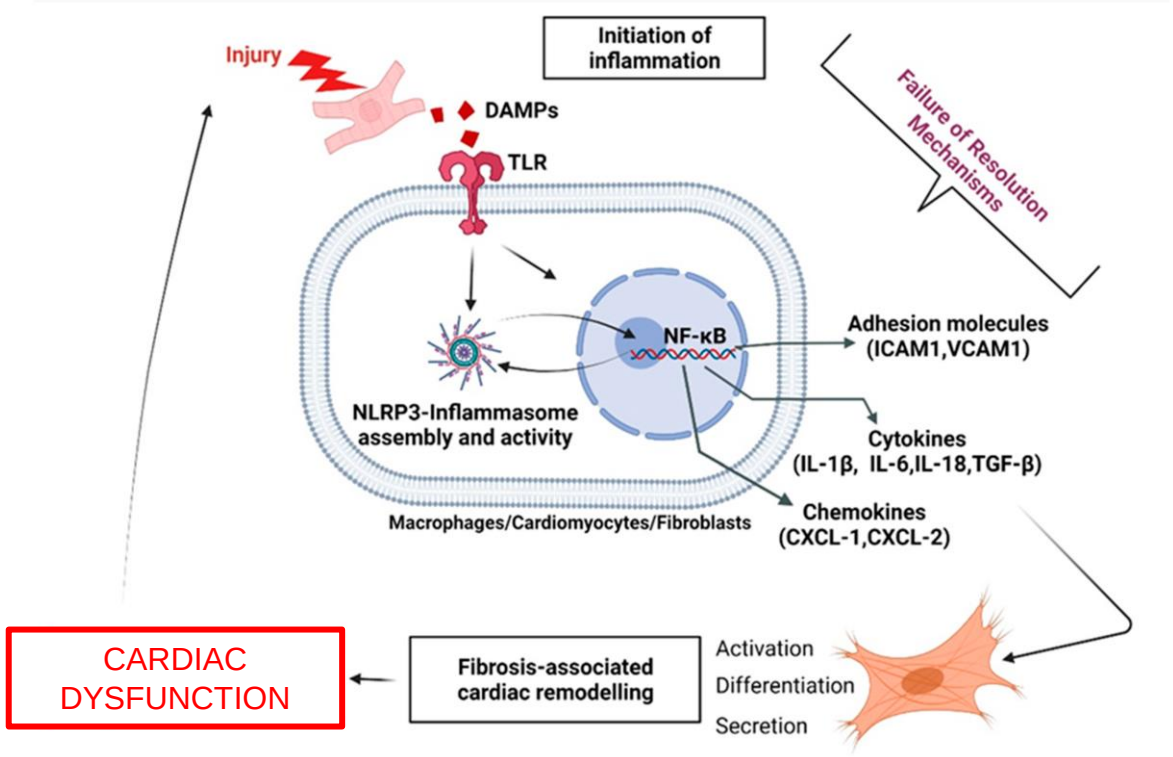
THE FASEB JOURNAL

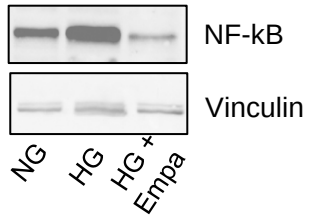


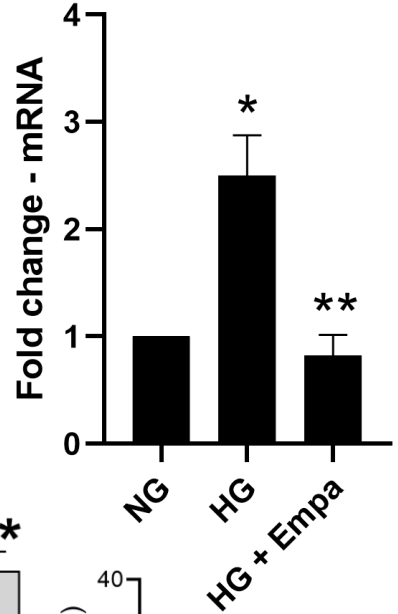


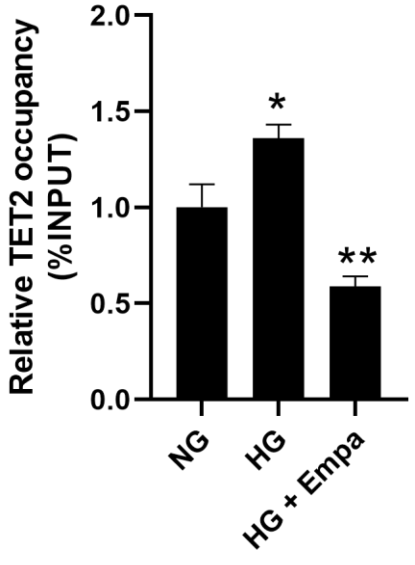
The FASEB Journal. 2020;34:16489–16503.

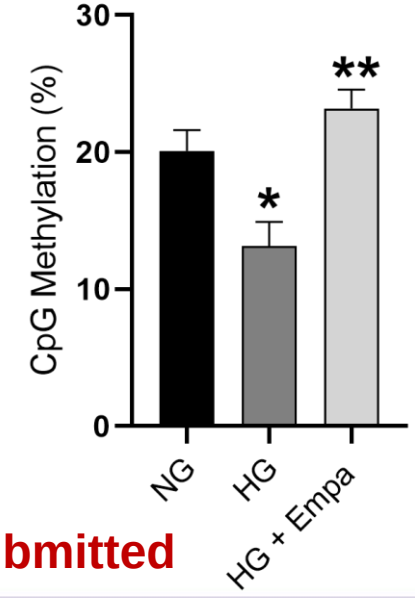
Targeting NFκB in the Failing Heart: the Role of SGLT-2 inhibitors

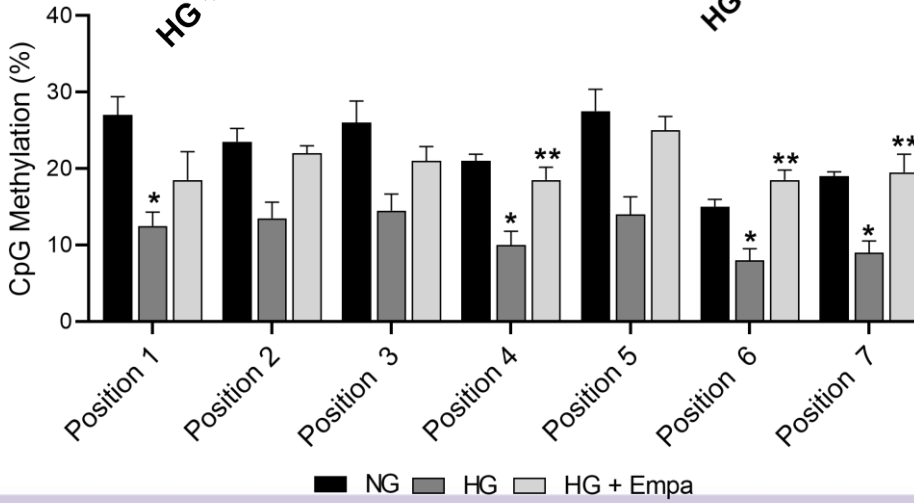












Barbieri et al, Cardiovascular Diabetology 2022, submitted

CONCLUSIONS 1

1. Type 2 DM patients still have an excess of cardiovascular mortality

2. HbA1c goals and treatments need to be individualized

3. Type of treatment in elderly diabetic patients with HF must be drawn on the clinical patients' condition, their degree of autonomy, with respect to the dignity and quality of life.

CONCLUSION 2

1. Separately, and independent of glycaemic control, SGLT2 inhibitor and GLP-1RA class have been shown to reduce CV risk in elderly patients with high CVD risk

2. Precision medicine approach , combining epi-drugs based on epigenotypes and conventional therapies may help enhance the clinical management of vascular complications in elderly patients