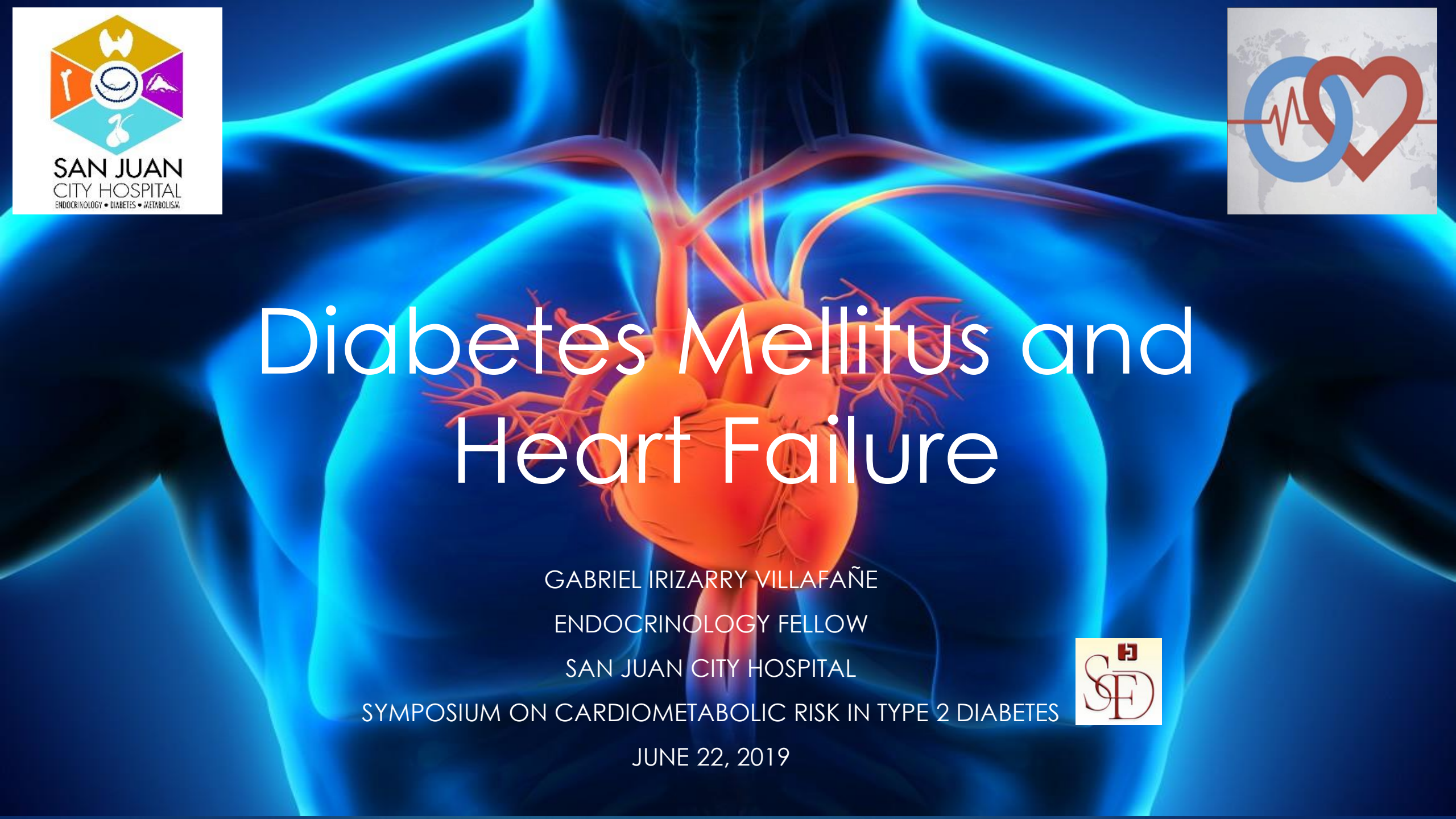

Diabetes Mellitus and Heart Failure

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SYMPOSIUM ON CARDIOMETABOLIC RISK IN TYPE 2 DIABETES

JUNE 22, 2019

Objectives

- Discuss the association between diabetes and heart failure
- The possible mechanisms for heart failure in diabetic patients
- Establish the relationship between glycemic control and heart failure
- Discuss the phenotypes of heart failure in patients with diabetes
- Discuss the relationship between cardiovascular markers and the risk for heart failure in patients with diabetes
- Antihyperglycemic agent evidence for use in this population

The Framingham heart study

Patients with T2DM are more than 2X more likely to develop HF than people without diabetes

TABLE IV

Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	Incidence: Crude Annual per 10,000	Incidence: Age-Adjusted* per 10,000	Relative Risk
Men Aged 45 to 74 years				
Nondiabetic	26,988	31.87	32.14	2.36†
Diabetic	1,226	89.72	75.98	
Women Aged 45 to 74 years				
Nondiabetic	35,322	19.53	19.75	5.14‡
Diabetic	1,190	142.85	101.60	

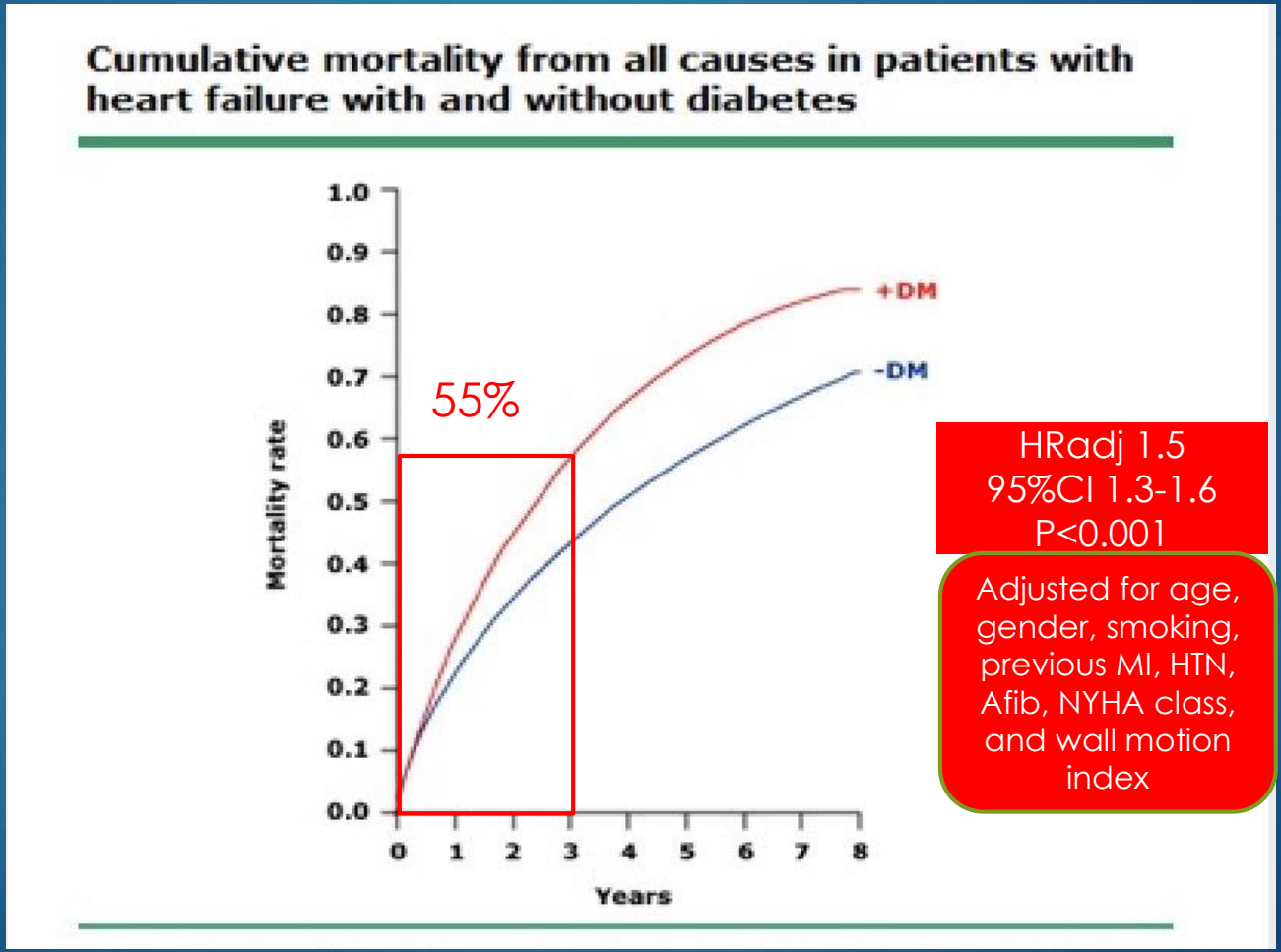
* Indirect method.
† Significant at $P < 0.05$ (chi square = 6.50).
‡ Significant at $P < 0.01$ (chi square = 12.53).

Risk remains high even after adjusting for CV risk factors

1. Kenny HC, et al. Heart Failure in Type 2 Diabetes: Impact of Glucose-Lowering Agents, Heart Failure Therapies, and Novel Therapeutic Strategies. Circulation Research. Jan 2019; 124: 121-141. 2. Kannel ET AL. Role of Diabetes in Congestive Heart Failure: The Framingham Study. The American Journal of Cardiology. Vol 34. July 1974. 29-34.

Risk of Death High in Patients with Heart Failure and Diabetes

N: 5,491 pts Diamond Trial

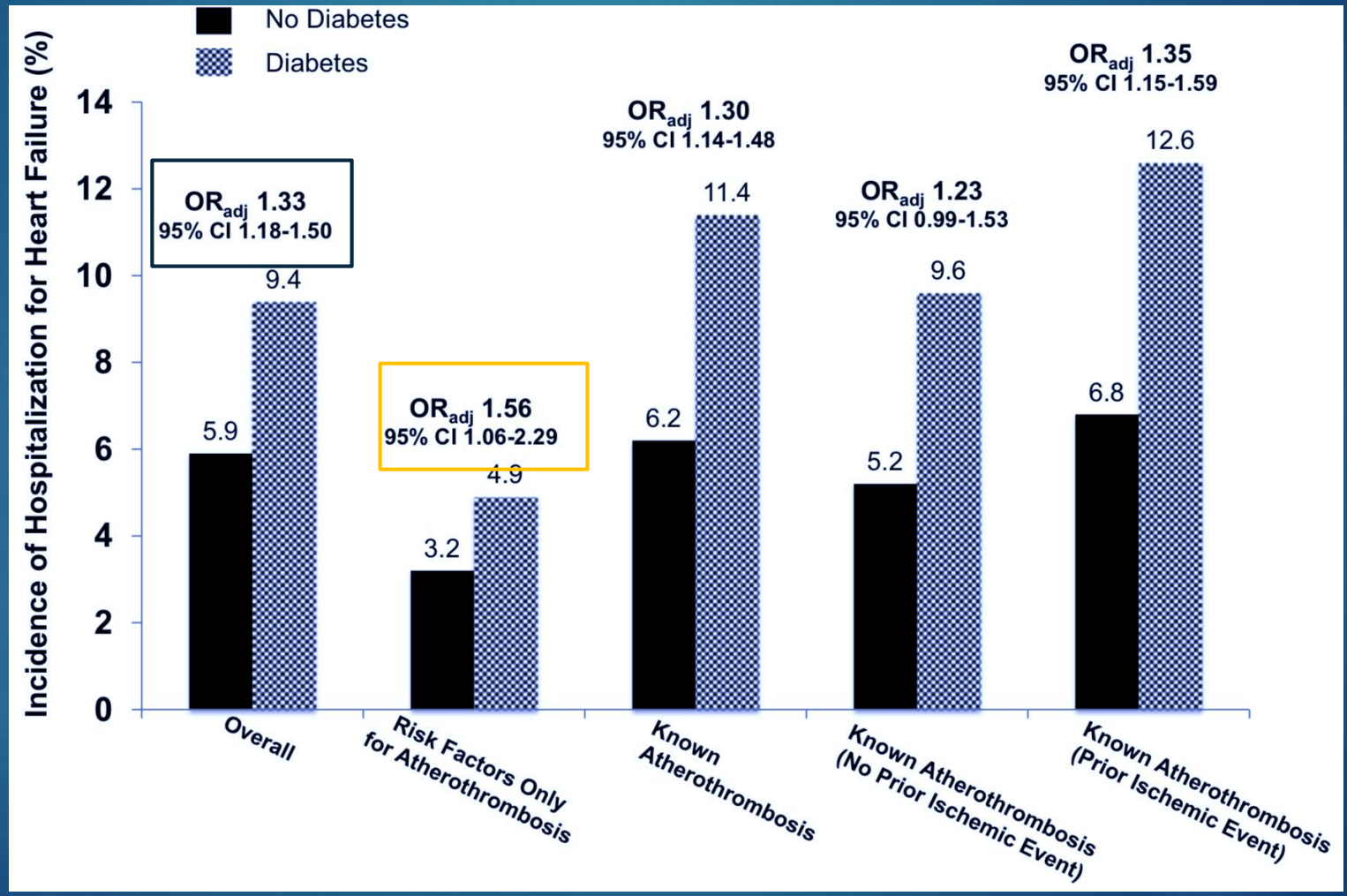


J Am Coll Cardiol 2004;43:771-7

Heart Failure Risk Increased in Diabetes

n: 19,699 pts in Reach Registry Study with DM

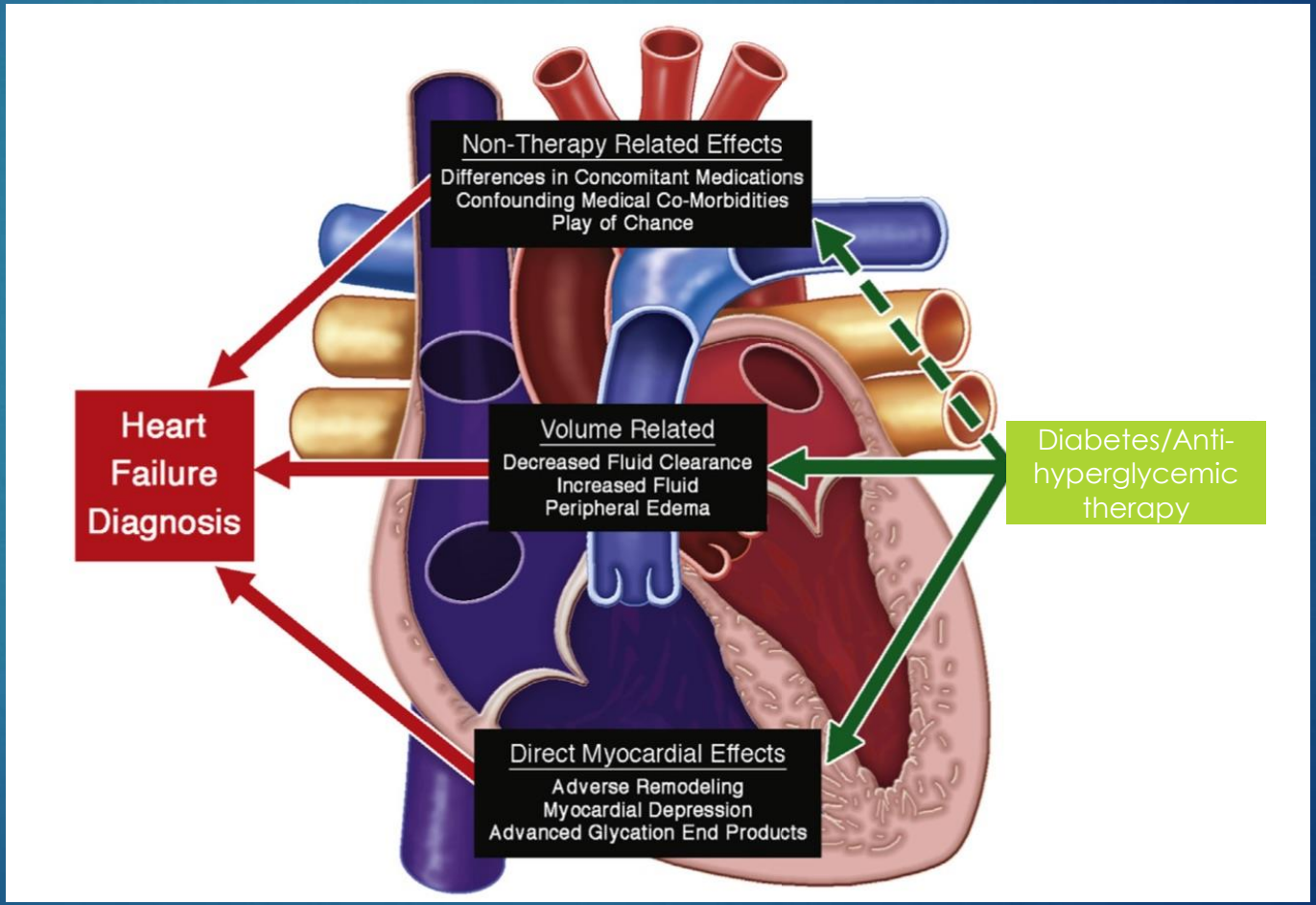
4 year F/U



Circulation.2015;132:923-931.

Potential mechanisms for heart failure in diabetic patients

Complex entity associated with multiple contributing mechanisms



1. Marwick, TH et al. J Am Coll Cardiol. 2018;71:339-351.
2. Bhatt DL. Cavender MA. 2014; JACC: Heart Failure 2(6): 583.

Diabetic Cardiomyopathy

Defined as the existence of abnormal cardiac structure and performance in the absence of other cardiac risk factors, such CAD, hypertension, and significant valvular disease

Term introduced by Rubler et al. 1972

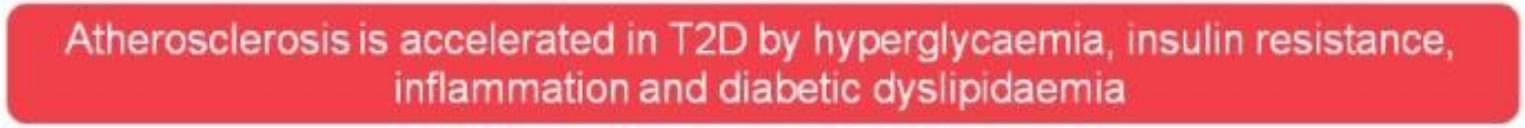


Figure adapted from Libby. Circulation 2001;104:365–72.
Zeadin et al. Can J Diabetes 2013;37:345e350.

Diabetes Affects the heart in different ways

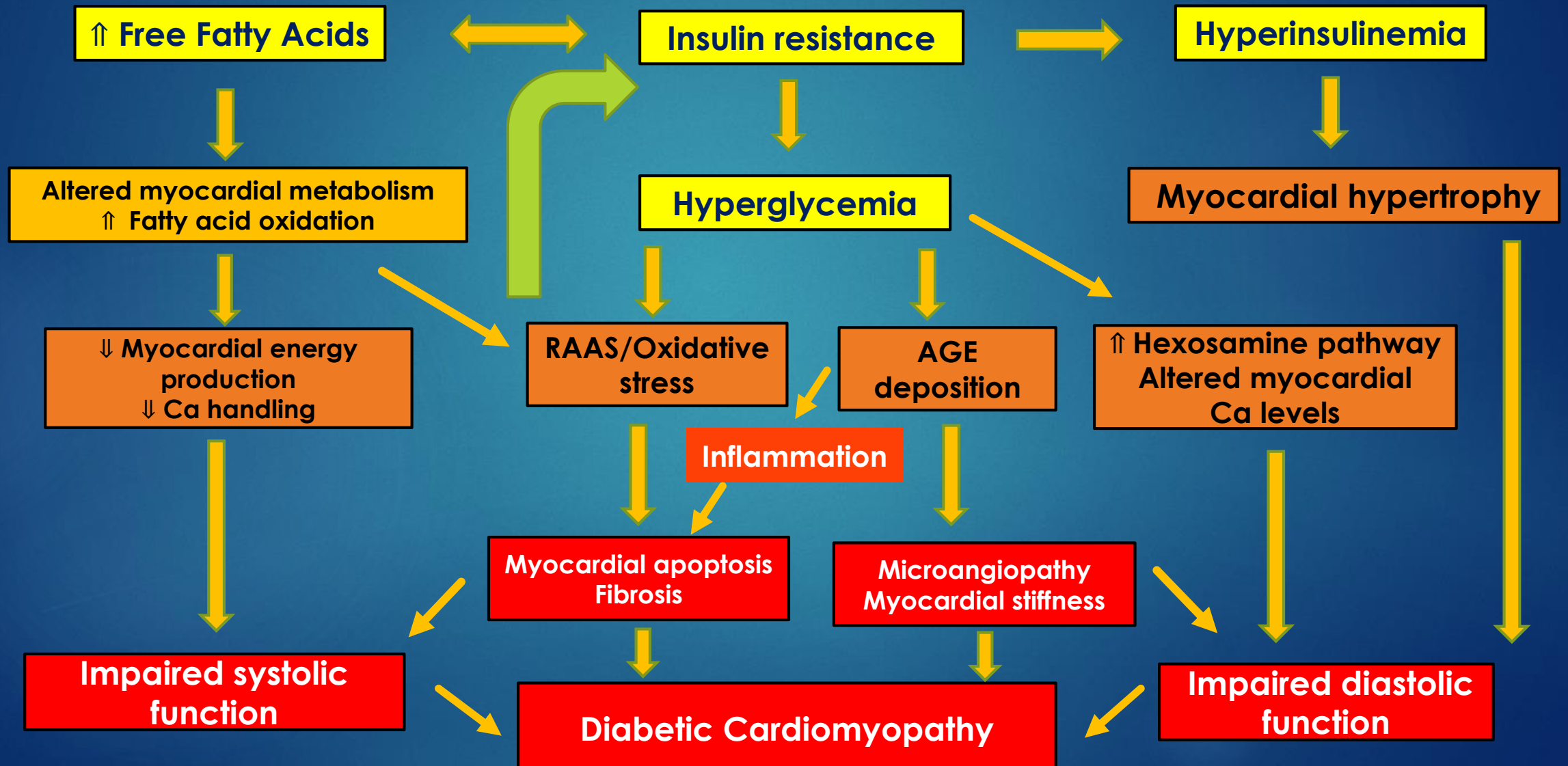
- Atherosclerosis and hypertension are often present in diabetic patients and contribute to coronary artery disease (CAD)
- Mayor drivers of myocardial dysfunction in T2DM:
  - Hyperglycemia
  - Insulin resistance/Hyperinsulinemia
  - Metabolic changes
  - Accumulation of AGEs
  - Oxidative stress
  - Inflammation

Heart failure is a multifactorial disease in diabetic patients.

Clinically the diabetic heart is characterized by diastolic dysfunction with preserved Ejection fraction by pathologic remodeling of the heart

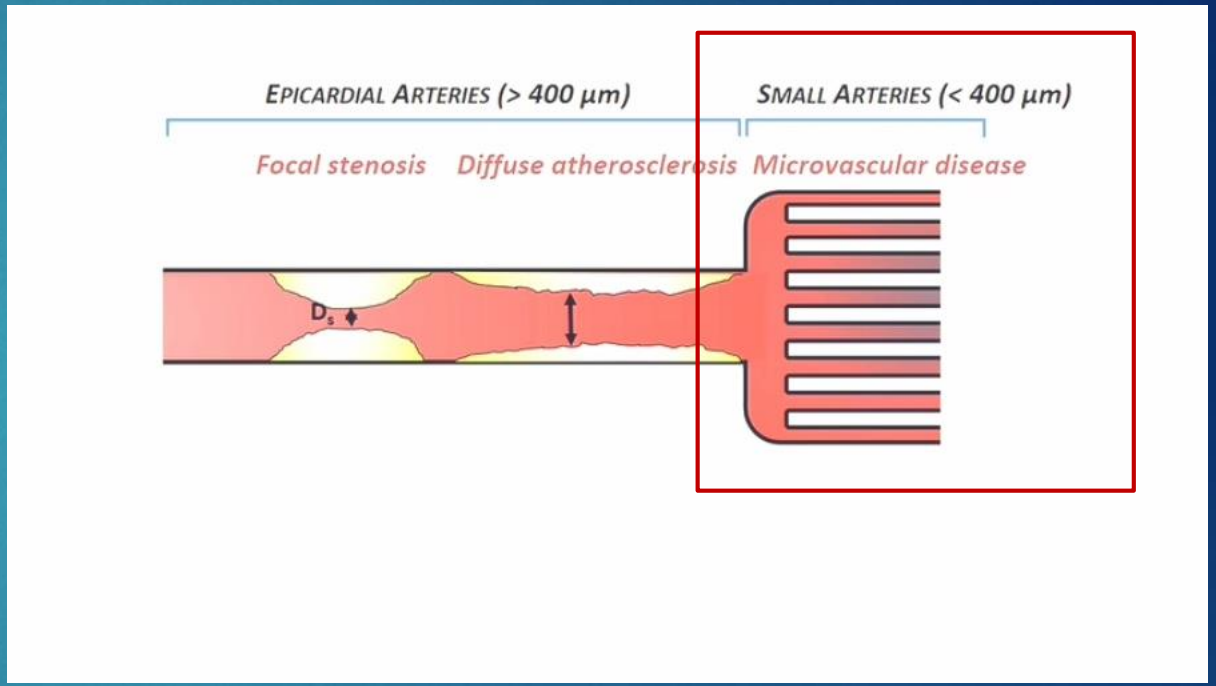
Front Physiol. 2018 Oct 30;9:1514.

Pathophysiology Diabetic Cardiomyopathy



Coronary Microvascular Dysfunction (CMD)

- Heart disease affecting the structure and function of small coronary arteries
- Most influential mechanism:
  - Advanced glycocylated end products (AGEs)
  - Coronary Autonomic Neuropathy (CAN)



Reduced coronary microvascular density assoc w Fibrosis in HFpEF → Tissue Hypoxia

Circulation Research. Jan 2019; 124: 121-141

8% increase in Heart failure for every 1% rise in HgbA1C

n= 48858 pts in the Kaiser Diabetes Registry

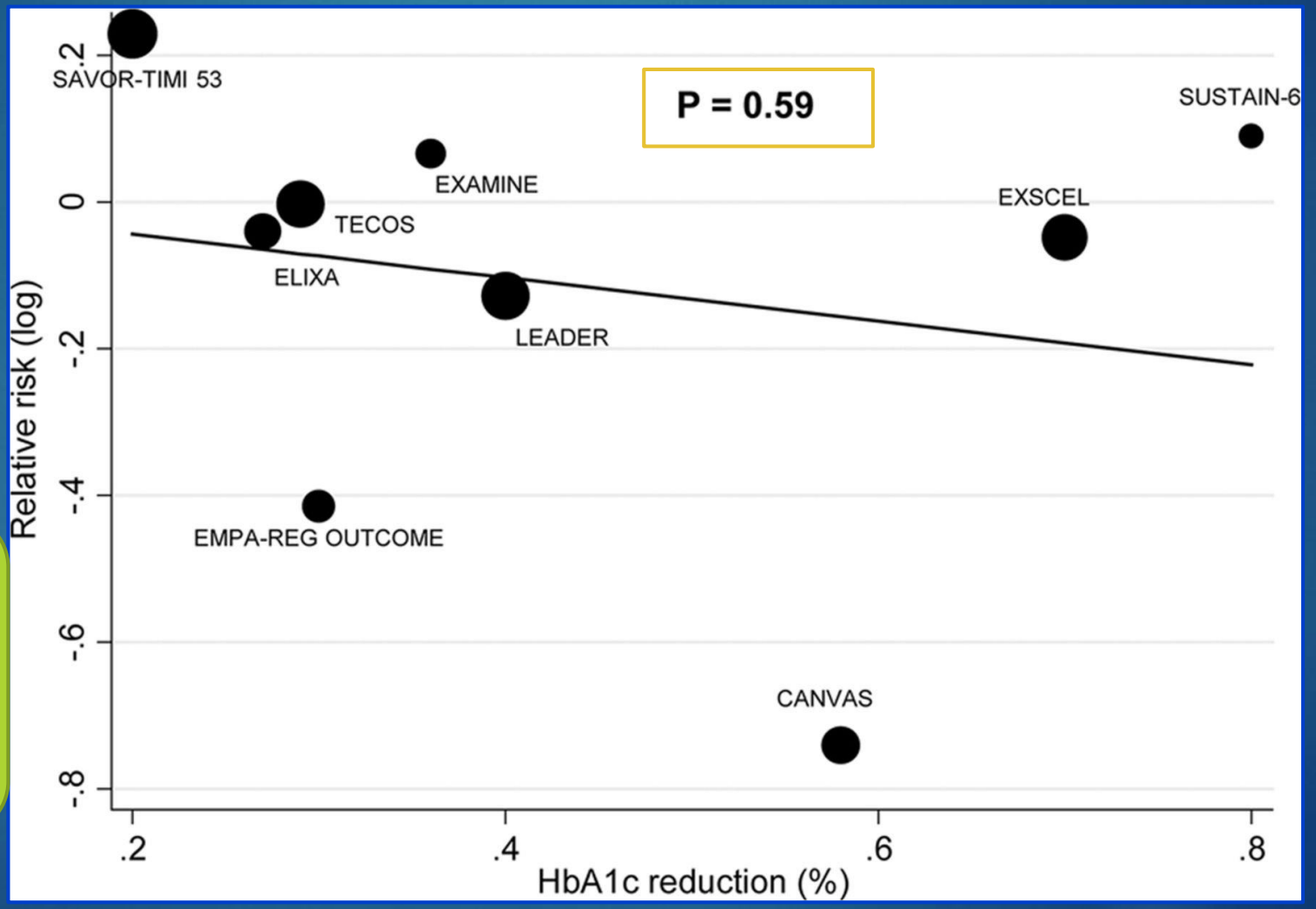
Hemoglobin A_{1c}, %	Model 1	Model 2	Model 3	Model 4
All (n=48 858; 935 events)				
<7	1	1	1	1
7 to <8	1.20 (0.97–1.48)	1.21 (0.98–1.50)	1.15 (0.92–1.42)	1.15 (0.93–1.43)
8 to <9	1.25 (1.01–1.56)	1.26 (1.01–1.57)	1.12 (0.89–1.39)	1.10 (0.88–1.38)
9 to <10	1.64 (1.31–2.04)	1.62 (1.30–2.03)	1.42 (1.13–1.78)	1.39 (1.11–1.74)
≥10	1.83 (1.48–2.25)	1.80 (1.45–2.22)	1.57 (1.27–1.95)	1.56 (1.26–1.93)
Per 1% difference	1.12 (1.08–1.16)	1.11 (1.07–1.15)	1.09 (1.05–1.13)	1.08 (1.05–1.12)

Circulation. 2001; 103:2668-2673

No relationship between glycemic control and HHF
N: 87,162 pts/ 9 trials

All 9 placebo controlled RCTS studies reported hospital admission for HF as a secondary outcome

Data suggests that glycemic control is not likely a mechanistic basis for the diverse effects of these antidiabetic medication classes on HF risk



Kramer et al. J Am Coll Cardiol HF 2018

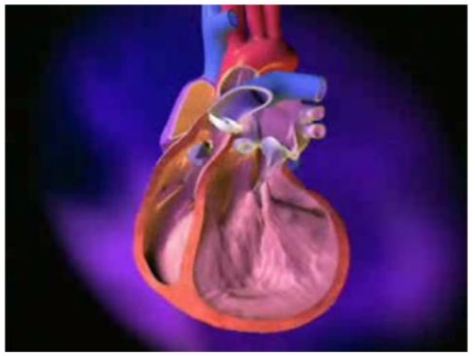
Phenotypes of heart failure in diabetic patients

HFrEF

- CAD mayor cause in T2DM
- CAD in T2DM is usually diffuse, multi-vessel and may lead to silent MI
- HFrEF with non ischemic etiology- (Early EF can be normal)

Systolic heart failure:

- reduced contractile function



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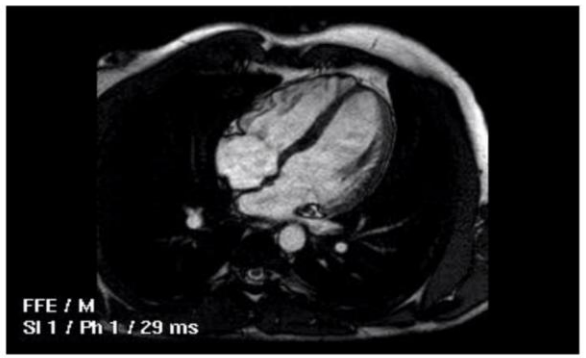
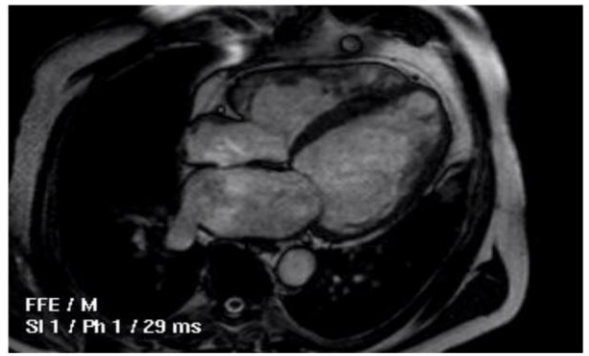




Abnormal global longitudinal strain (GLS)= sensitive marker for early systolic dysfunction (normal EF)

Adapted from PACE CME Lecture: Heart Failure: The next frontier for SGLT2 inhibitors

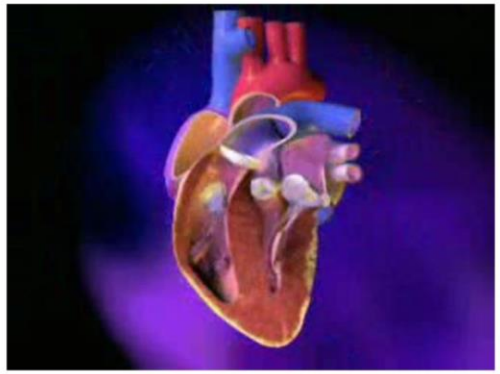
Phenotypes of heart failure in diabetic patients

HFpEF

- Detected in 75% of T2DM patients and develops early in T2DM course
- Degree of glucose dysregulation correlates with left ventricular diastolic dysfunction severity, ⇑ risk of incident HF and CV mortality

Diastolic heart failure:

- reduced relaxation
- impaired ventricular filling



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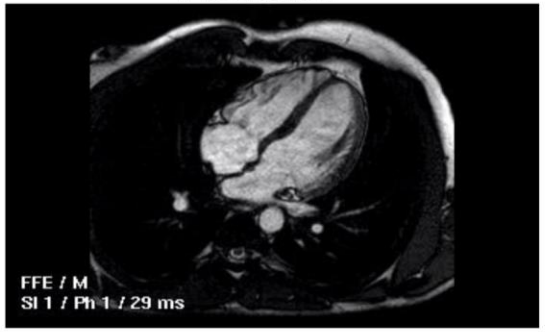
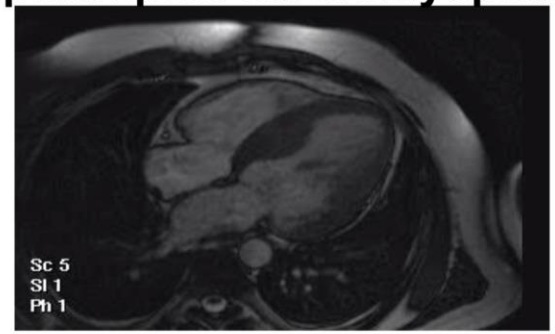


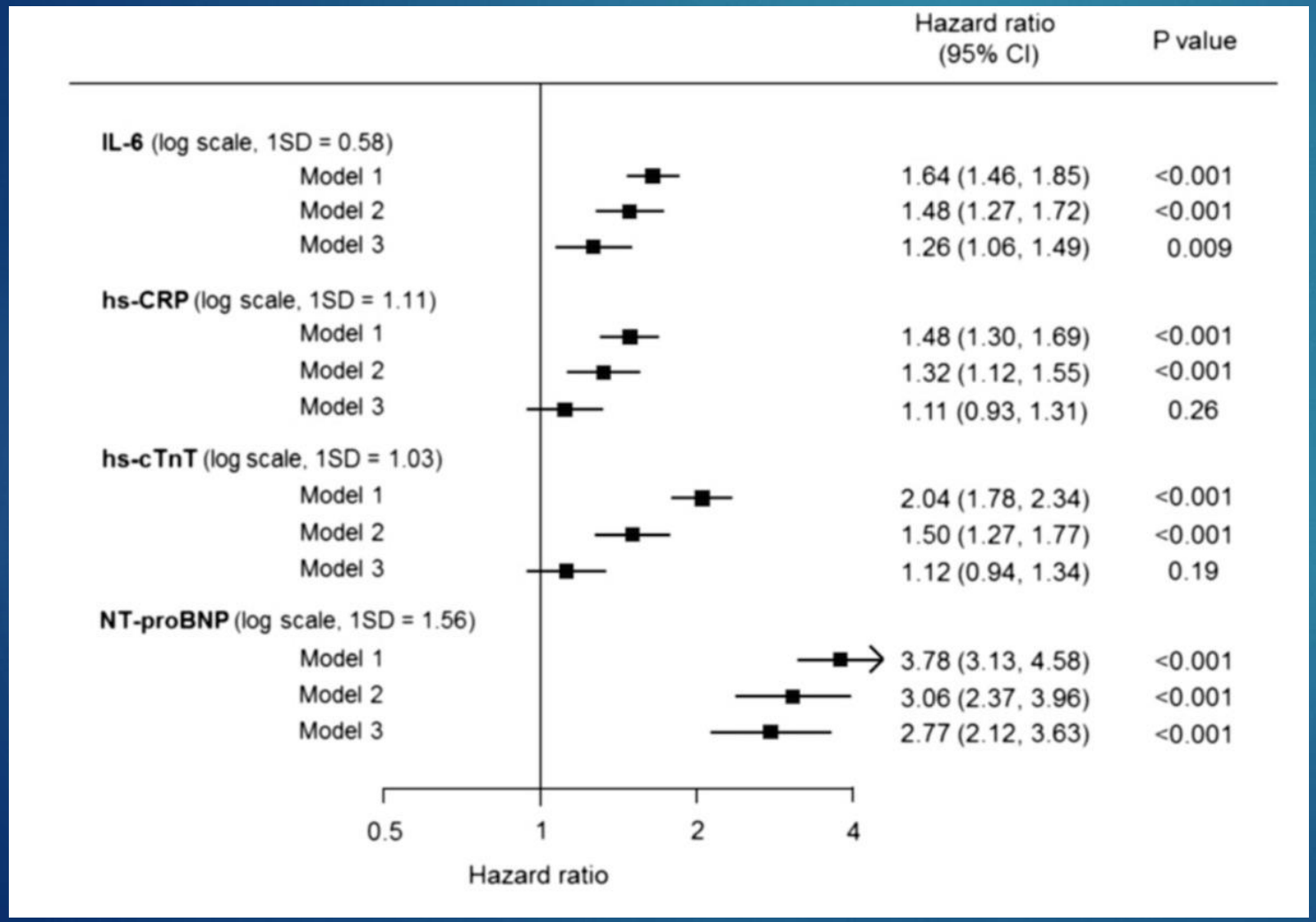
Hypertrophic cardiomyopathy



Detection of coronary microvascular dysfunction (CMD) helps reclassify these patients to higher risk

Adapted from PACE CME Lecture: Heart Failure: The next frontier for SGLT2 inhibitors

Cardiovascular Biomarkers and Risk of Heart Failure



Diabetes Care Volume 40, September 2017

Cardiac Stress and Inflammatory Markers as Predictors of Heart Failure in Patients With Type 2 Diabetes: The ADVANCE Trial

Diabetes Care 2017;40:1203–1209 | https://doi.org/10.2337/dc17-0509

Diabetes Care 2017; 40:1203-1209

Cardiovascular Biomarkers

- The use of biomarkers for the identification of LV dysfunction remains controversial.
- Nonetheless, a natriuretic peptide–based screening strategy, based on low cutoff levels, is effective for detecting moderate diastolic dysfunction

No clear consensus has been reached on clinical role of these biomarkers

1. Marwick, TH et al. J Am Coll Cardiol. 2018;71:339-351.
2. Am Heart J 2006;152:941-8.

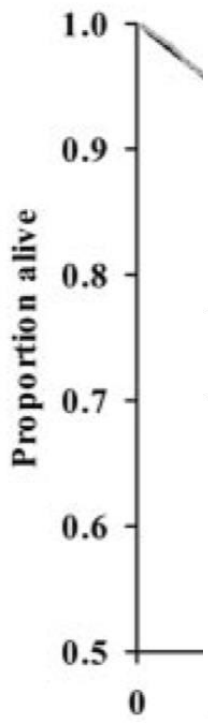
Glucose Lowering Agents and HF Outcome

- Metformin
- Thiazolidinediones (TZD)
- DPP-IV inhibitors
- GLP-1 Agonists
- SGLT2 Inhibitors

Metformin Associated with Improved Outcomes in Medicare Patients Discharged After HHF

udy

Original Article



Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure

Systematic Review of Observational Studies Involving 34 000 Patients

Dean T. Eurich, PhD; Daniala L. Weir, BSc; Sumit R. Majumdar, MD, MPH; Ross T. Tsuyuki, PharmD, MSc; Jeffrey A. Johnson, PhD; Lisa Tjosvold, MLIS; Saskia E. Vanderloo, MSc; Finlay A. McAlister, MD, MSc

Background—There is an ongoing controversy regarding the safety and effectiveness of metformin in the setting of heart failure (HF). Therefore, we undertook a systematic review of the trial and nontrial evidence for metformin in patients with diabetes mellitus and HF.

Methods and Results—We conducted a comprehensive search for controlled studies, evaluating the association between metformin and morbidity and mortality in people with diabetes mellitus and HF. Two reviewers independently identified citations, extracted data, and evaluated quality. Risk estimates were abstracted and pooled where appropriate. As measures of overall safety, we examined all-cause mortality and all-cause hospitalizations. Nine cohort studies were included; no randomized controlled trials were identified. Most (5 of 9) studies were published in 2010 and were of good quality. Metformin was associated with reduced mortality compared with controls (mostly sulfonylurea therapy): 23% versus 37% (pooled adjusted risk estimates: 0.80; 0.74–0.87; I^2=15%; P<0.001). No increased risk was observed for metformin in those with reduced left ventricular ejection fraction (mortality pooled adjusted risk estimate: 0.91; 0.72–1.14; I^2=0%; P=0.34), nor in those with HF and chronic kidney disease (pooled adjusted risk estimate: 0.81; 0.64–1.02; P=0.08). Metformin was associated with a small reduction in all-cause hospitalizations (pooled adjusted risk estimate: 0.93; 0.89–0.98; I^2=0%; P=0.01). Metformin was not associated with increased risk of lactic acidosis.

Conclusions—The totality of evidence indicates that metformin is at least as safe as other glucose-lowering treatments in patients with diabetes mellitus and HF and even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease. Until trial data become available, metformin should be considered the treatment of choice for patients with diabetes mellitus and HF. **(*Circ Heart Fail.* 2013;6:395-402.)**

- Metformin significantly lowers risk of death compared to non-sensitizing agents after HHF

***Circulation*. 2005;111:583-590**

Metformin as first line treatment for T2DM

- Recent analysis support the case for metformin having a survival benefit in diabetic patients with HF compared with alternative glucose-lowering regimens

Potential cardioprotective mechanisms:

- ✓ mTOR inhibition suppressing cardiac hypertrophy
- ✓ Increased myocardial glucose utilization by activating AMPK or increasing myocardial insulin sensitivity.

1. Circulation Research. Jan 2019; 124: 121-141
2. *Circ Heart Fail.* 2013;6:395-402.

Sulfonylureas and Heart Failure Risk

- The UGDP study raised concern with Tolbutamide (excess cardiac deaths vs placebo).
- UKPDS 33 demonstrated no deleterious effect of Sus on CV safety compared with insulin or conventional management.
- Advance trial, Gliclazide not associated with negative outcomes.
- Currently, **Carolina trial** demonstrated Glimepiride non-inferiority vs linagliptin on cardiovascular outcomes.

European Journal of Heart Failure (2018) **20**, 853–872

TZDs

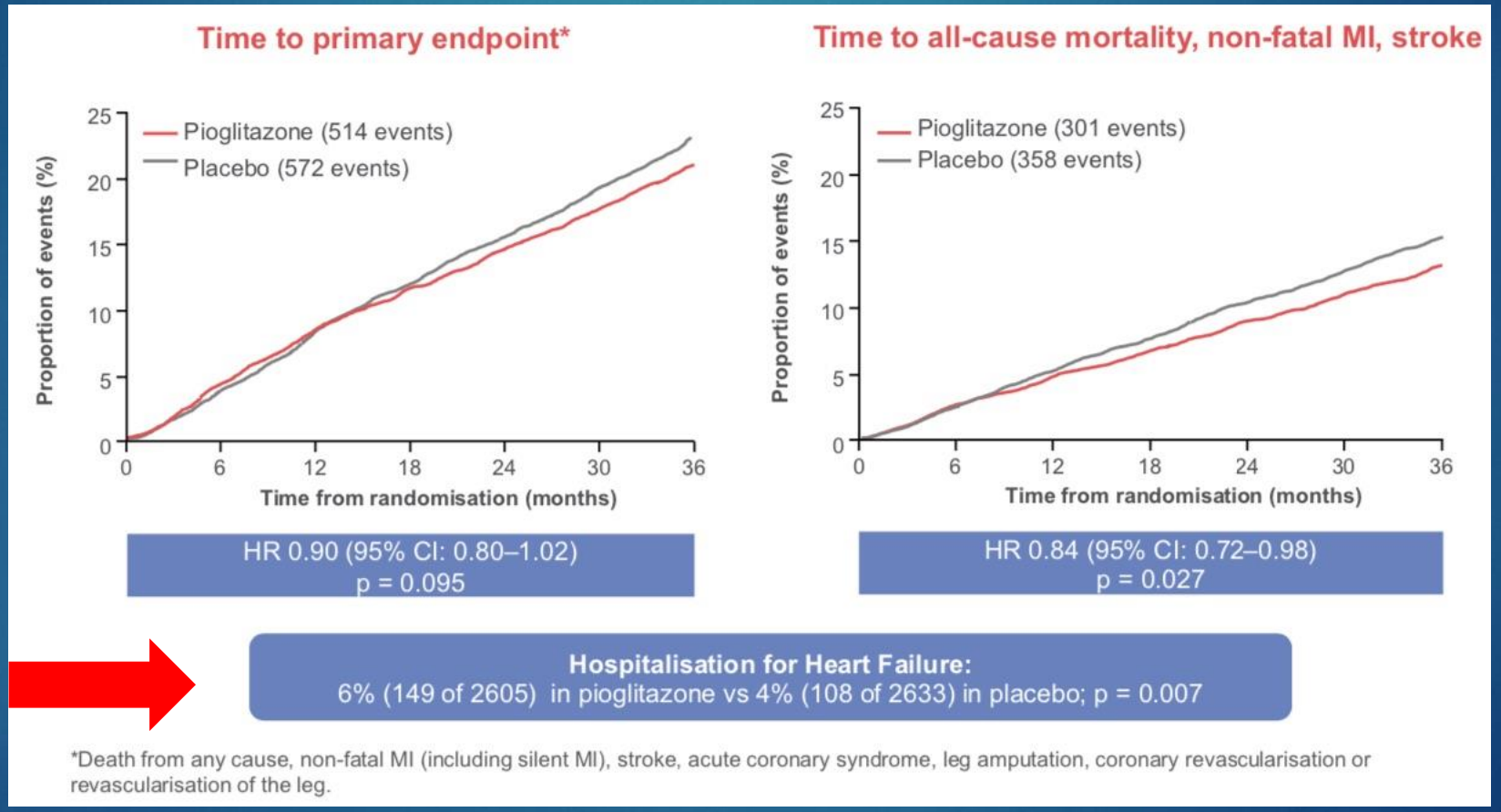
AHA SCIENTIFIC STATEMENT 2019

TZDs are not recommended in patients with established HF and may increase the risk of HF events in individuals with DM w/o HF

Table 2. Select Therapeutic Effects of Various Glucose-Lowering Therapies on Cardiovascular and HF Outcomes

Improves Overall Cardiovascular and HF Outcomes	Improves Overall Cardiovascular Outcomes but Not HF outcomes	No Effect on Overall Cardiovascular or HF Outcomes	No Effect on Overall Cardiovascular Outcomes But Potential HF Harm
Empagliflozin (EMPA-REG OUTCOME[92])	Liraglutide (LEADER[70])	Insulin glargine (ORIGIN[30])	Pioglitazone (PROactive[56])
Canagliflozin (CANVAS/ CANVAS-R[95])	Semaglutide (SUSTAIN-6[73])	Acarbose (ACE[29])	Rosiglitazone (RECORD[58]) 0.4% HF baseline
		Lixisenatide (ELIXA[69])	Saxagliptin (SAVOR-TIMI 53[83])
		Exenatide (EXSCEL[79])	
		Alogliptin (EXAMINE[82])	
		Sitagliptin (TECOS[85])	

Pioglitazone: Proactive trial



Dormandy et al. Lancet 2005;366:1279-89

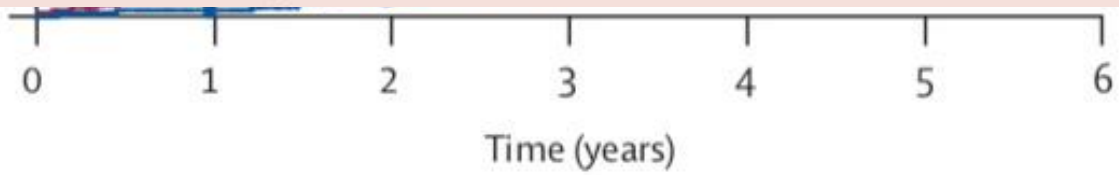
Rosiglitazone increased Hospitalizations for Heart Failure RECORD Trial

F Heart failure

	Rosiglitazone (N=2220)	Active control (N=2227)	HR	Rate difference per 1000 person-years	p
CV death or CV hospitalisation	321	323	0·99 (0·85 to 1·16)	−0·2 (−4·5 to 4·1)	0·93
All-cause death	136	157	0·86 (0·68 to 1·08)	−1·7 (−4·3 to 0·9)	0·19
CV death	60	71	0·84 (0·59 to 1·18)	−0·9 (−2·7 to 0·9)	0·32
Myocardial infarction*	64	56	1·14 (0·80 to 1·63)	0·6 (−1·1 to 2·4)	0·47
Stroke*	46	63	0·72 (0·49 to 1·06)	−1·4 (−3·1 to 0·2)	0·10
CV death, MI, or stroke	154	165	0·93 (0·74 to 1·15)	−1·0 (−3·9 to 1·9)	0·50
Heart failure*	61	29	2·10 (1·35 to 3·27)	2·6 (1·1 to 4·1)	0·0010

Data are numbers, HR (95% CI), or rate differences (95% CI). CV=cardiovascular. MI=myocardial infarction. *Fatal and non-fatal.

Table 4: Deaths and hospitalisations from cardiovascular causes



TZDS

- In the RECORD and the PROactive trials, patients randomized to TZDs, rosiglitazone and piogliazone, respectively, had more HF events than those on placebo.
- Pioglitazine was associated with significant 16% reduction in 3P-MACE (as secondary endopoint) vs placebo in PROactive
- Rosiglitazone open-label RECORD data showed no increase in CV death.

11. AVANDIA US Prescribing information. 2. Dormandy et al. Lancet 2005;366:1279–89. 3. FDA Safety Information. 4. Rosenson et al. Am Heart J. 2012;164:672–80.

Glucose Lowering Agents and HF Outcomes

- **In clinical trials of T2DM patients, the prevalence of HF at baseline has varied between approximately 10% and 30%**

Table 1 Prevalence of heart failure in selected trials of type 2 antidiabetic drugs

Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS 33[11]	NR (severe concurrent illness excluded)
ADVANCE[12,13]	NR
ACCORD[14]	4.3%
VADT[15]	NR
DPP4 inhibitor trials	
SAVOR-TIMI 53[16,17]	13%
TECOS[18]	18%
EXAMINE[19]	28%
SGLT2 inhibitor trials	
EMPA-REG OUTCOME[20]	10%
CANVAS[21]	14–15%
GLP-1 receptor agonist trials	
LEADER[22]	14%
ELIXA[23]	22%
EXSCEL[24]	16%

Carmelina 26%

Declare 14%

Harmony 20 %
Rewind 8 %

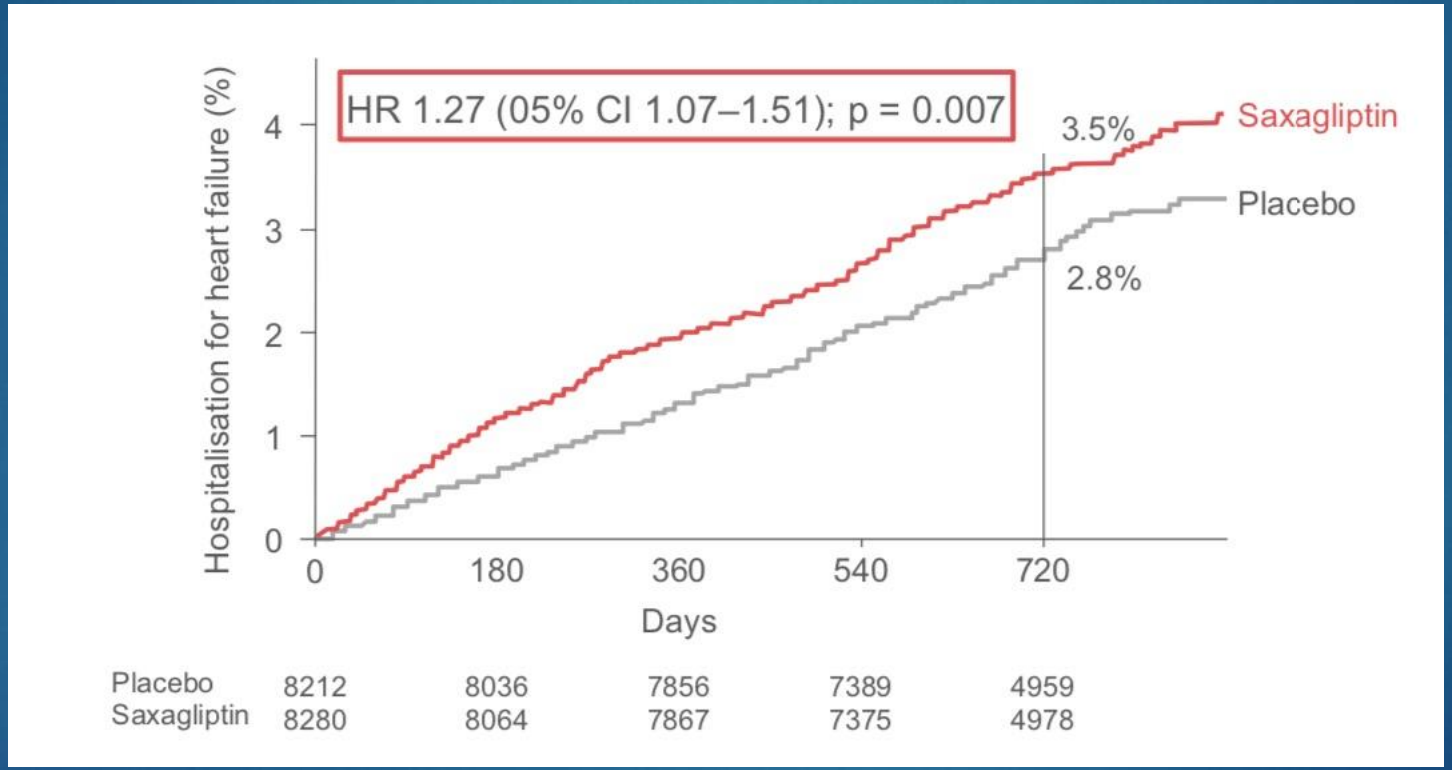
DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; NR, not reported; SGLT2, sodium–glucose co-transporter type 2.

Front Physiol. 2018 Oct 30;9:1514.

DPP-4 Inhibitors

Is worsening heart failure a class effect of DPP-4 inhibitors?

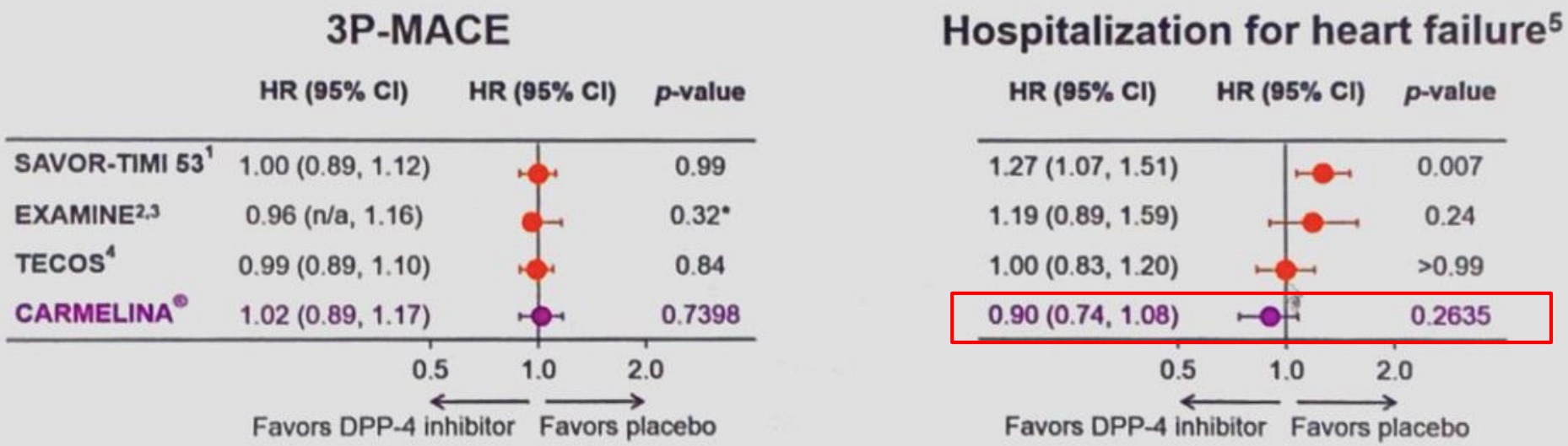
SAVOR-TIMI 53: Increased Risk of Hospitalization for Heart Failure-Saxagliptin arm



Scirica et al. Circulation 2014; 130-1579-88

DPP-4 Inhibitor effects on risk of HHF in large scale cardiovascular outcome trials in T2DM patients

DPP-4 inhibitor CVOT overview



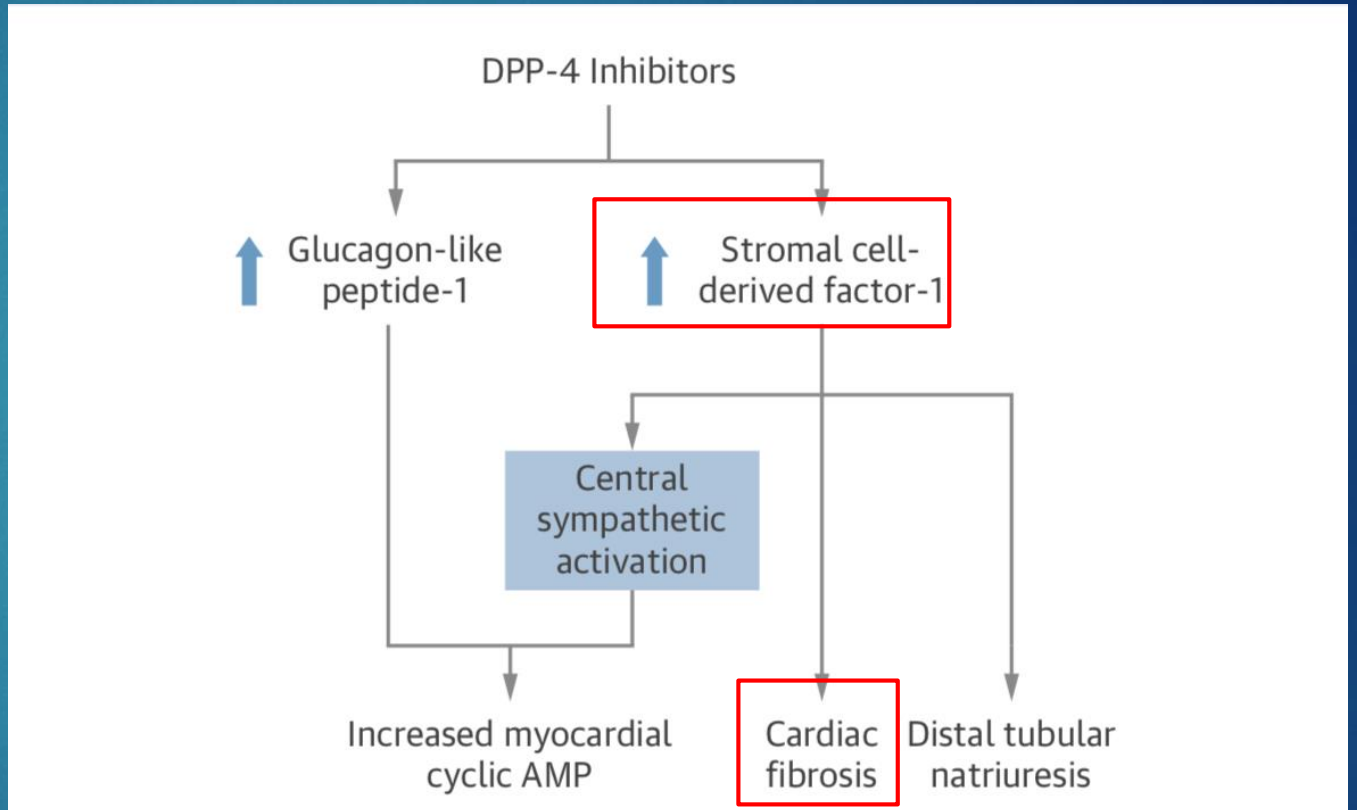
Linagliptin proves CV safety without a signal for heart failure

Alogliptin: FDA warning on patients with HF

J Am Coll Cardiol HF 2018;6:445–51

Pathophysiological Mechanisms for DPP4- Inhibitor Heart Failure Risk

- Potentiation of several endogenous peptides that can exert deleterious cardiovascular effects.
- SDF-1 (potentially)
  - Mesenchymal cell promote inflammation
  - Suppress myocardial force
  - Also may lead to fibrosis



Packer, M. J Am Coll Cardiol HF. 2018;6(6):445-51.

AMP = adenosine monophosphate; DPP = dipeptidyl peptidase.

Is it a class effect?

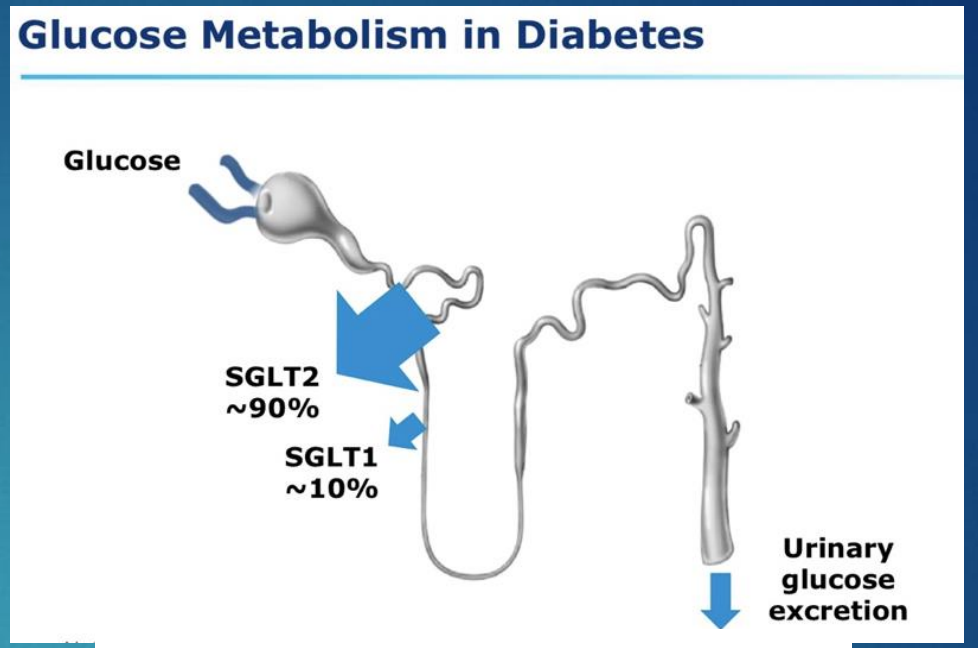
- Metanalysis suggests that DPP-4 inhibitor increase in HHF risk is a class effect
- Overall, the DPP-4 inhibitors have established MACE safety.
- The risk-benefit balance for most DPP-4 inhibitors does not justify their use in patients with established HF or those at high risk for HF

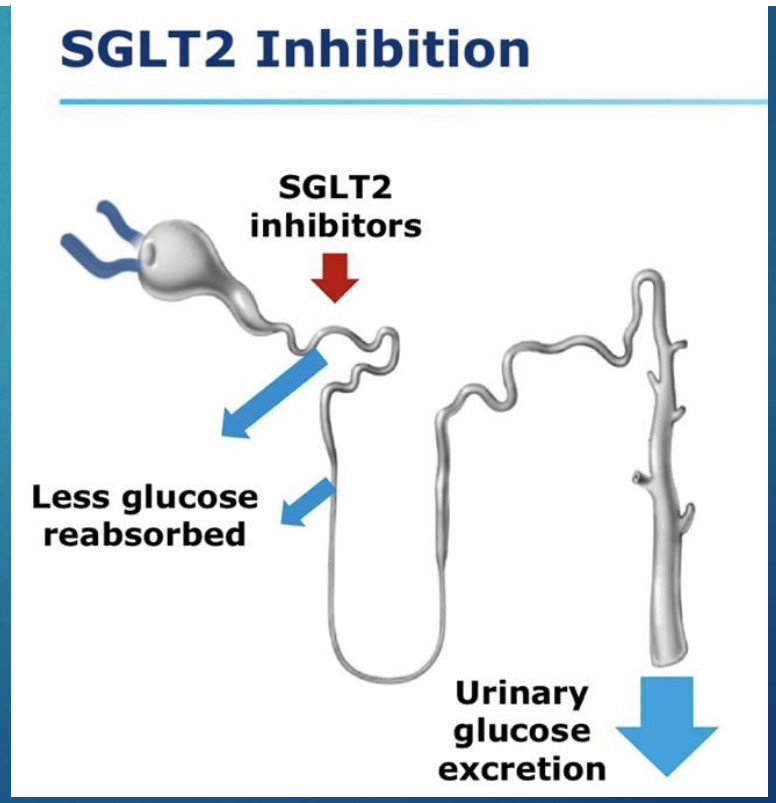
American Diabetes Association®

AHA Statement 2019

Measure-HF trial will provide additional data for T2DM pts with HFrEF

SGLT2-Inhibitors





CVOTs with SGLT2 inhibitors

Baseline characteristics

Baseline Variables	EMPA REG Outcome (Empaglifozin)	Integrated CANVAS Program (Canaglifozin)	DECLARE (Dapagliflozin)
Participants (n)	7,034	10,142	17,160
Age (y)	63	63	64
Diabetes Duration (y)	57% > 10 y	13.5 y	10 y
BMI (kg/m^2)	31	32.0	32
A1C (%)	8.1	8.2	8.3
Prior CVD (%)	99	64.8	40
Prior HF	10	14	10
Comparator	Placebo	Placebo	Placebo

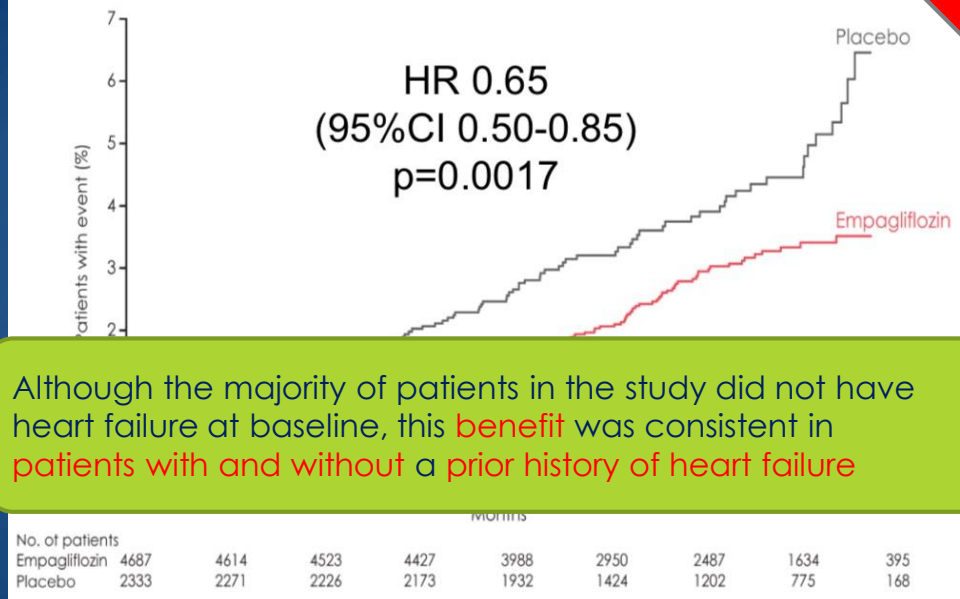
Adapted from PACE-CME Lecture: Heart Failure: The next frontier SGLT2 inhibitors

Reduction of heart failure hospitalizations in diabetes/SGLt2 Inhibitors

100% CVD

EMPA-REG Outcome

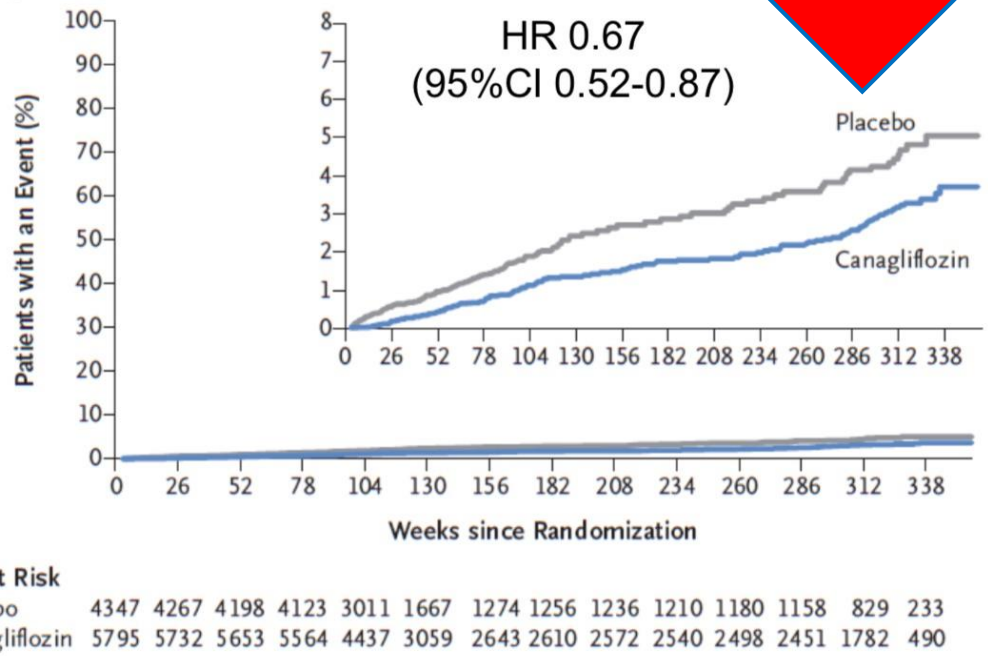
35% RR



Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a prior history of heart failure

Canvas Program

33% RR



1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128;
2. Eur Heart J 2017;39:363–370

Neal B et al. N Engl J Med. 2017 Aug 17;377(7):644-657

Reduction of heart failure hospitalizations in diabetes/SGLt2 Inhibitors

DECLARE TIMI 58

	Dapagliflozin rate/1000 patient-yr	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P value
CV death/HHF	12.2	14.7	0.83 (0.73-0.95)	0.005*
MACE	22.6	24.2	0.93 (0.84-1.03)	<0.001** 0.17*
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death	10.8	14.1	0.76 (0.67-0.87)	
All-cause death	15.1	16.4	0.93 (0.82-1.04)	
HHF	6.2	8.5	0.73 (0.61-0.88)	
Myocardial infarction	11.7	13.2	0.89 (0.77-1.01)	
Ischemic Stroke	6.9	6.8	1.01 (0.84-1.21)	
CV death	7.0	7.1	0.98 (0.82-1.17)	
Non-CV death	6.0	6.8	0.88 (0.73-1.06)	
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal death	3.7	7.0	0.53 (0.43-0.66)	

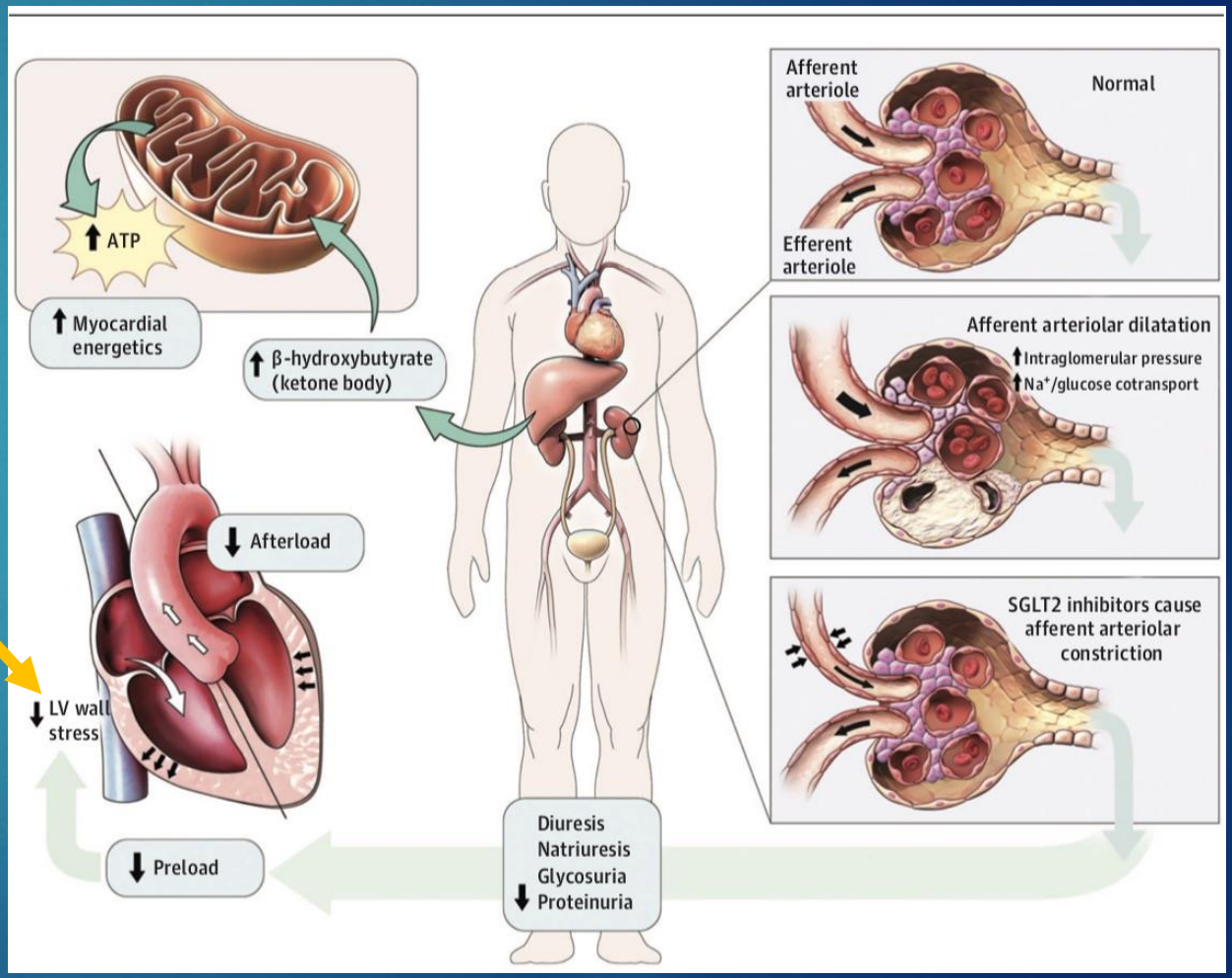
- Significant Reduction of co-primary endopoint CV death or HHF driven by significant reduction for HHF
- Greater HHF Risk reduction in HFrEF and Non HFrEF group (more studies needed)
- Reduced CV death in HFrEF group

1. N Engl J Med 2019; 380:347-3571.
2. 2. Circulation 2019 May 28;139(22):2528-2536.

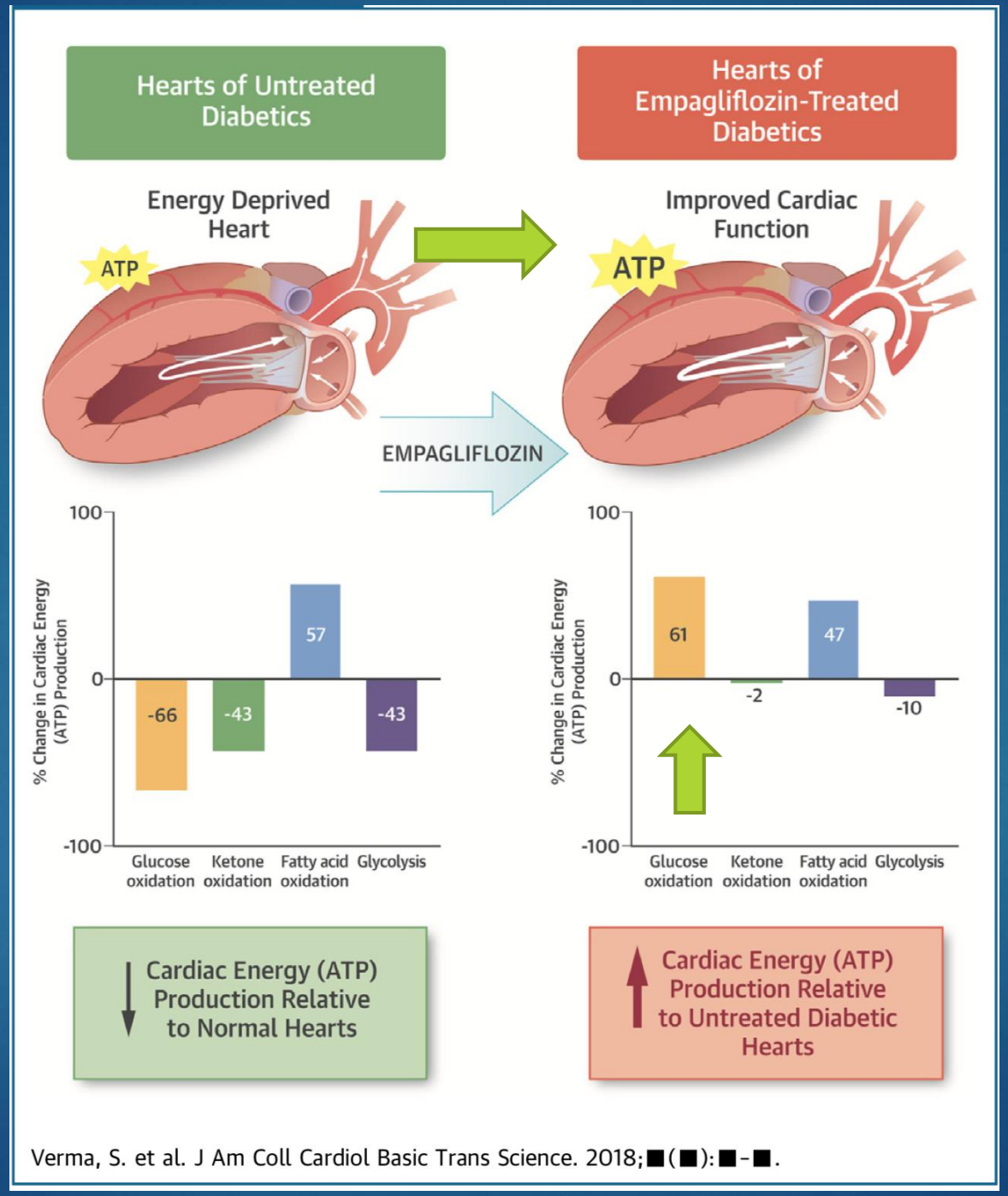
SGLT2i reduce Hospitalizations for Heart Failure

POTENTIAL MECHANISMS

- Natriuretic + Glucosuria
  - ⇓ in preload and afterload (BP) -> optimizes ventricle filling conditions
- Effect on myocardial metabolism (mostly ketone or BCAA utilization)
- Direct effect on myocardium LV mass reduction
- Renal protective effect



Diabetes Care. 2016;39(12):e212-e213. JAMA Cardiol. 2017. E1-E2.

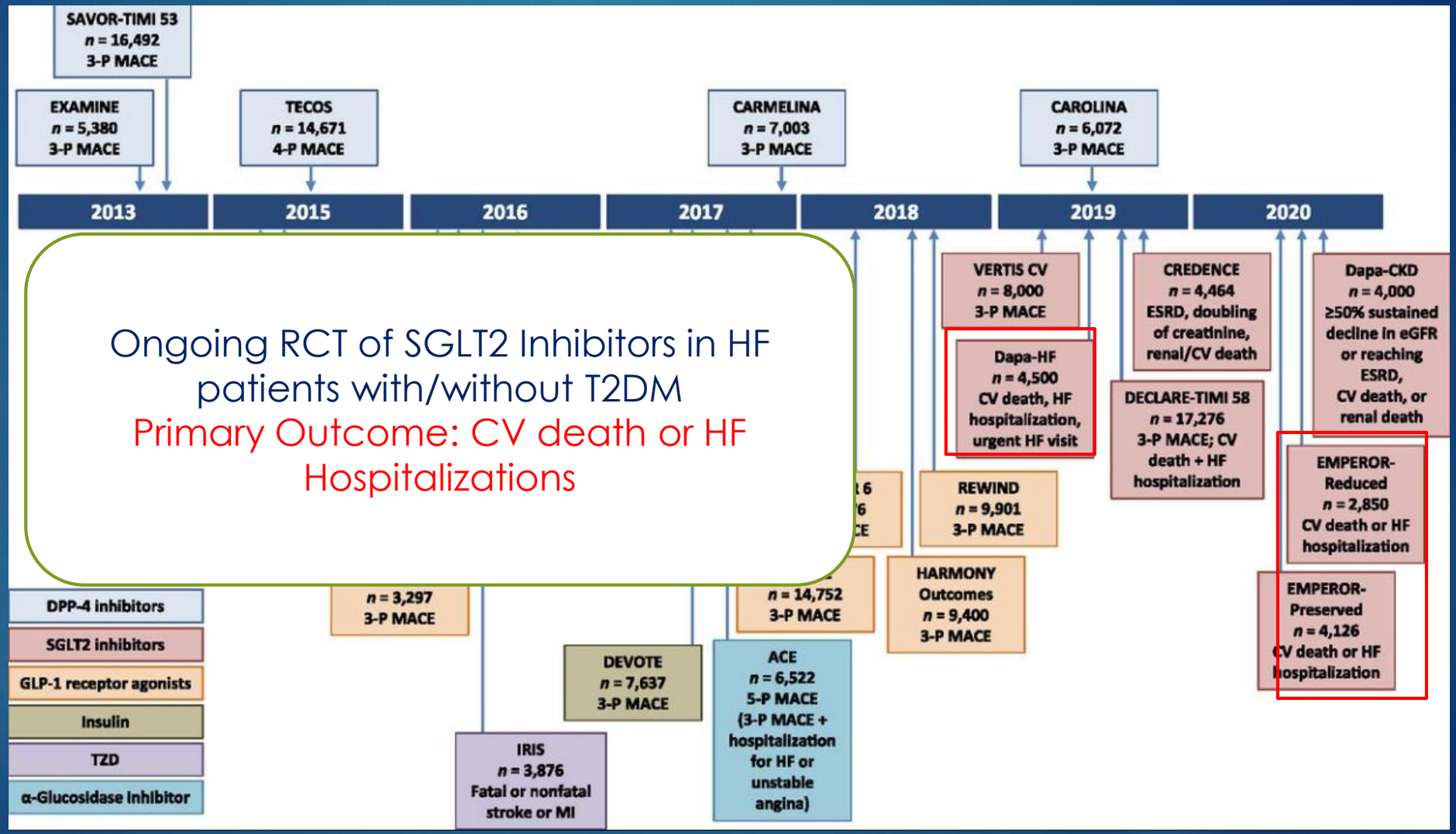


Verma, S. et al. J Am Coll Cardiol Basic Trans Science. 2018;■(■):■-■.

Beta-hydroxybutyratye theory Stimulate antihypertrophic mechanism

↓ Fibrosis

Future Studies



GLP-1 Agonisits

GLP-1 Agonists Various Potential Mechanisms on CV Event Reduction

- Improved endothelial function/vasodilation
- Improved contractility in human and dog subjects
- Anti-inflammatory/Anti-atherogenic effects

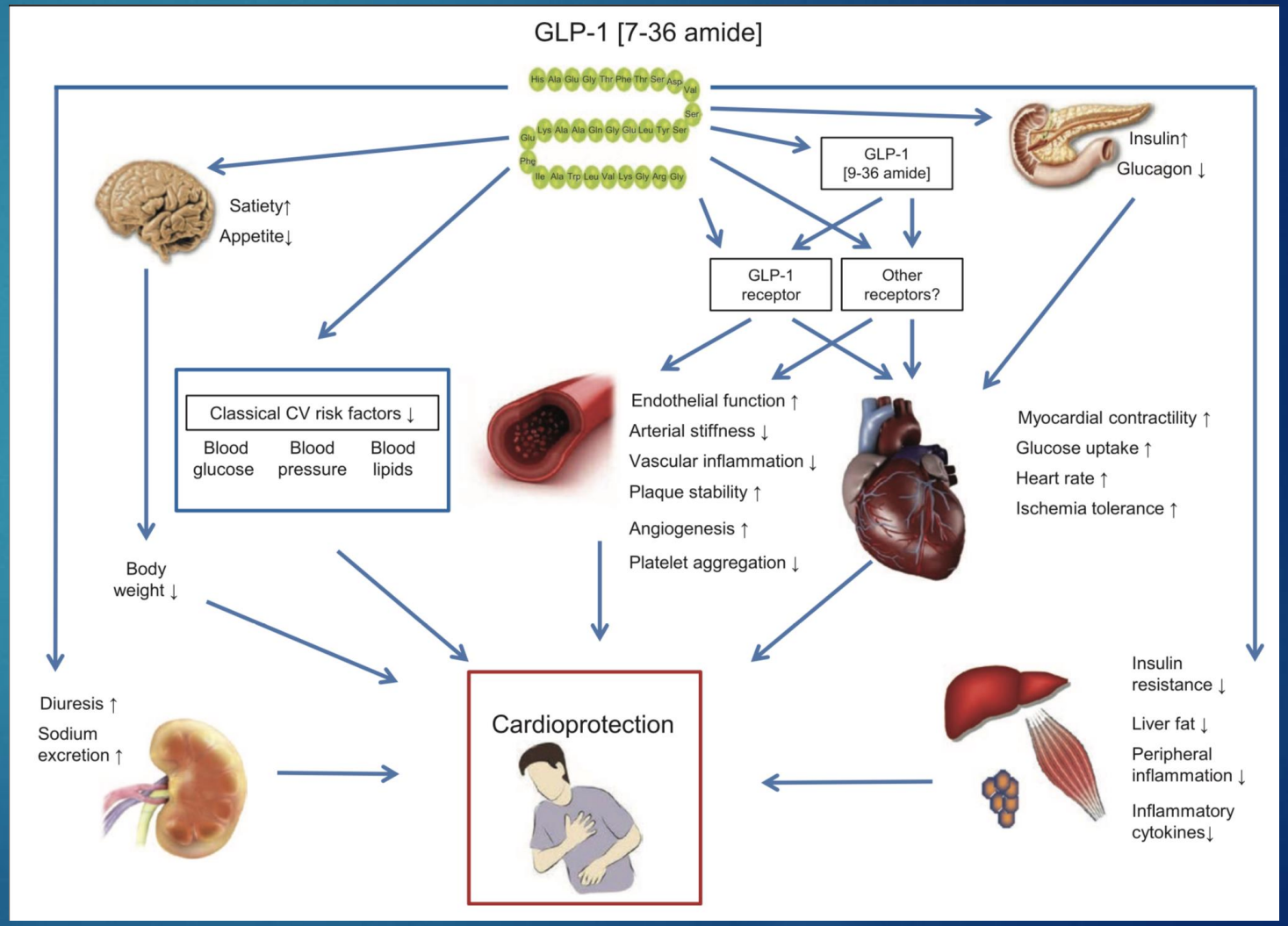
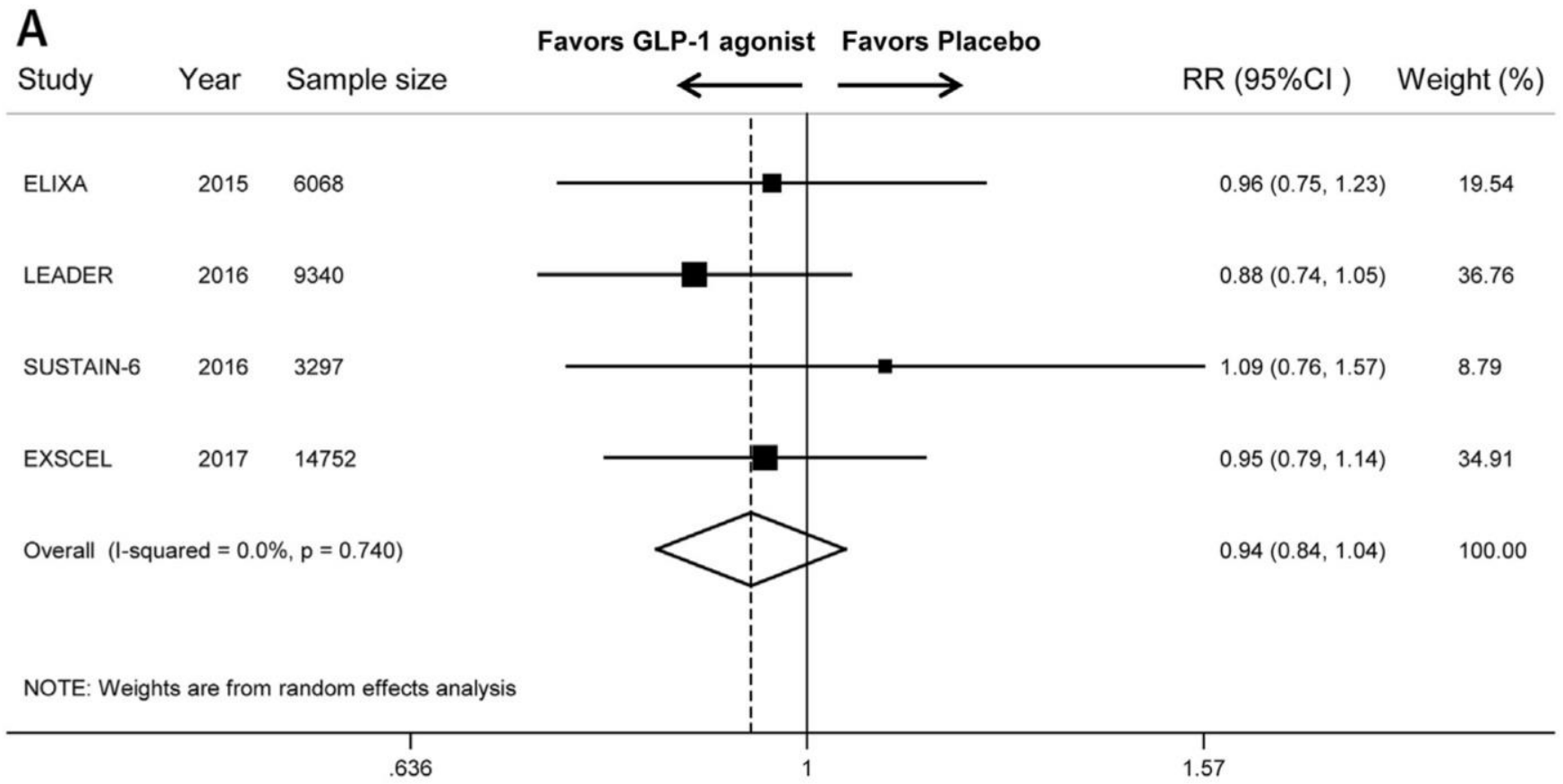


FIGURE 2 Meta-Analyses of the Impact of the Following Classes of Glucose-Lowering Medication on Hospitalization for Heart Failure Compared With Placebo



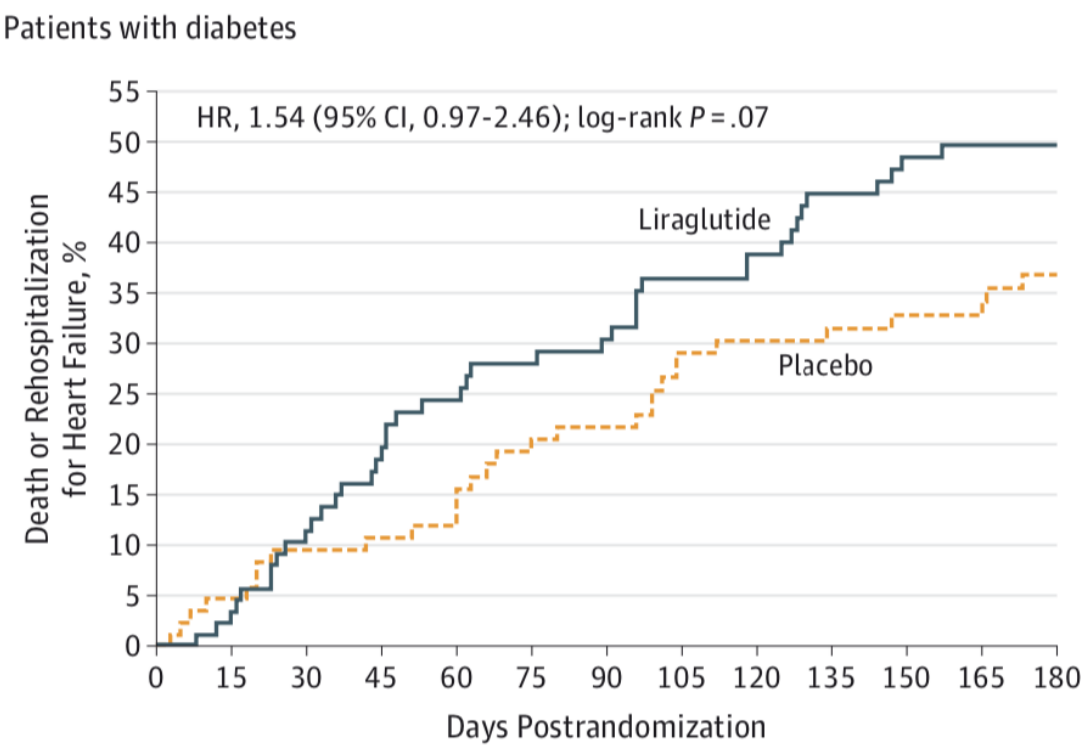
- In the pooled analysis of the 4 trials involving GLP-1 agonists, this class of medications was not associated with reduction in hospitalization for HF (RR: 0.94; 95% CI: 0.84 to 1.04)

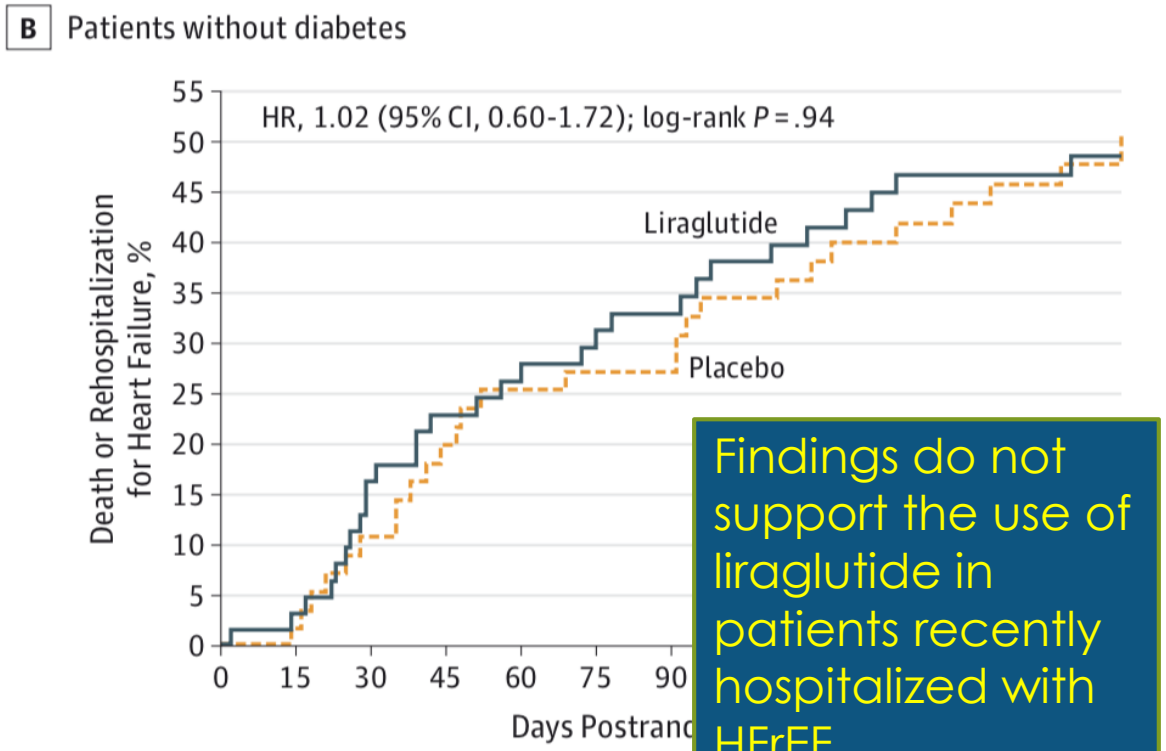
Kramer et al. J Am Coll Cardiol HF 2018

Outcomes with Liraglutide in heart failure

N= 300 patients acute heart failure and LVEF <40% (w/w/o DM) in FIGHT study

Figure 3. Prespecified Subgroup Analysis of Patients Who Died or Experienced Rehospitalization for Heart Failure by Type 2 Diabetes Status





Findings do not support the use of liraglutide in patients recently hospitalized with HFrEF

- Liraglutie did not improve post hospital clinical stability in Advanced HF with Low EF
  - Trend for harm by death and hospitalization owing to HF in this complicated population

JAMA. 2016;316(5):500-508.

Rewind Trial: CVOT Dulaglutide

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome	594 (12·0%)	2·35	663 (13·4%)	2·66	0·88 (0·79–0·99)*	0·026
Myocardial infarction	223 (4·5%)	0·87	231 (4·7%)	0·91	0·96 (0·79–1·15)	0·63
Non-fatal myocardial infarction	205 (4·1%)	0·80	212 (4·3%)	0·84	0·96 (0·79–1·16)	0·65
Fatal myocardial infarction	26 (0·5%)	0·10	20 (0·4%)	0·08	1·29 (0·72–2·30)	0·40
Stroke	158 (3·2%)	0·61	205 (4·1%)	0·81	0·76 (0·62–0·94)	0·010
Non-fatal stroke	135 (2·7%)	0·52	175 (3·5%)	0·69	0·76 (0·61–0·95)	0·017
Fatal stroke	26 (0·5%)	0·10	33 (0·7%)	0·13	0·78 (0·47–1·30)	0·34
Cardiovascular death†	317 (6·4%)	1·22	346 (7·0%)	1·34	0·91 (0·78–1·06)	0·21
Non-cardiovascular death	219 (4·4%)	0·84	246 (5·0%)	0·95	0·88 (0·73–1·06)	0·18
All-cause death	536 (10·8%)	2·06	592 (12·0%)	2·29	0·90 (0·80–1·01)	0·067
Hospital admission for heart failure or urgent visit	213 (4·3%)	0·83	226 (4·6%)	0·89	0·93 (0·77–1·12)	0·46
Hospital admission for unstable angina	88 (1·8%)	0·34	77 (1·6%)	0·30	1·14 (0·84–1·54)	0·41
Composite microvascular outcome (eye or renal outcome)	910 (18·4%)	3·76	1019 (20·6%)	4·31	0·87 (0·79–0·95)	0·0020
Eye outcome‡	95 (1·9%)	0·37	76 (1·5%)	0·30	1·24 (0·92–1·68)	0·16
Renal outcome§	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004

All hazard ratios (HRs) were estimated with Cox proportional hazards models and p values are two-sided. *After accounting for α=0·009 spent on the primary outcome for the interim analysis, the α for the final analysis is 0·0467, and the HR is 0·88 (95·33% CI 0·79–0·99). †Includes deaths of unknown cause. ‡Photocoagulation, anti-vascular endothelial growth factor therapy, or vitrectomy. §New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy.

Table 2: **Primary and secondary outcomes**

Lancet 2019

Pioneer 6: CVOT oral semaglutide

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Outcome	Oral Semaglutide (N=1591)		Placebo (N=1592)		Hazard Ratio (95% CI)
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*	
Primary outcome†	61 (3.8)	2.9	76 (4.8)	3.7	0.79 (0.57–1.11)‡
Expanded composite outcome§	83 (5.2)	4.0	100 (6.3)	4.9	0.82 (0.61–1.10)
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	69 (4.3)	3.3	89 (5.6)	4.4	0.77 (0.56–1.05)
Death from any cause	23 (1.4)	1.1	45 (2.8)	2.2	0.51 (0.31–0.84)
Death from cardiovascular causes	15 (0.9)	0.7	30 (1.9)	1.4	0.49 (0.27–0.92)
Nonfatal myocardial infarction	37 (2.3)	1.8	31 (1.9)	1.5	1.18 (0.73–1.90)
Nonfatal stroke	12 (0.8)	0.6	16 (1.0)	0.8	0.74 (0.35–1.57)
Unstable angina resulting in hospitalization	11 (0.7)	0.5	7 (0.4)	0.3	1.56 (0.60–4.01)
Heart failure resulting in hospitalization	21 (1.3)	1.0	24 (1.5)	1.2	0.86 (0.48–1.55)

Lancet 2019

GLP-1 agonists

- GLP-1 receptor agonists have had NO impact on the risk of HF hospitalizations in large RCTs-> safe to use/not beneficial for HF prevention

- In patients with established HFrEF and recent decompensation, GLP-1 receptor agonists should be used with caution, given no evidence of benefit and a trend toward worse outcomes in 2 small RCTs.

American Diabetes Association®

AHA Statement 2019

1. Diabetes Care 2019;42 (Suppl. 1):S103-S123; 2. Diabetes Care 2018;41:2669–2701

Treatment for HF in diabetic patients

- Cornerstone treatment similar to treatment for HF in non-diabetic patients
- SGLT2 inhibitors have been shown to reduce CV events, particularly heart failure. They are the preferred therapy for T2DM patients at risk for heart failure
- In order to provide optimal treatment for this patients, a multidisciplinary team is needed composed of primary care physicians, cardiologists, endocrinologists, nursing staff and community resources.

In patients with T2DM and Heart Failure
Metformin and SGLT2 i are the drugs of choice

American Diabetes Association®

EASD

European Association for the Study of Diabetes

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

EITHER/ OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

NO

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target			
SGLT2i[2] OR TZD	SGLT2i[2] OR TZD	GLP-1 RA OR DPP-4i OR TZD	SGLT2i[2] OR DPP-4i OR GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6]	TZD[10]
If HbA_{1c} above target	
TZD[10]	SU[6]

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

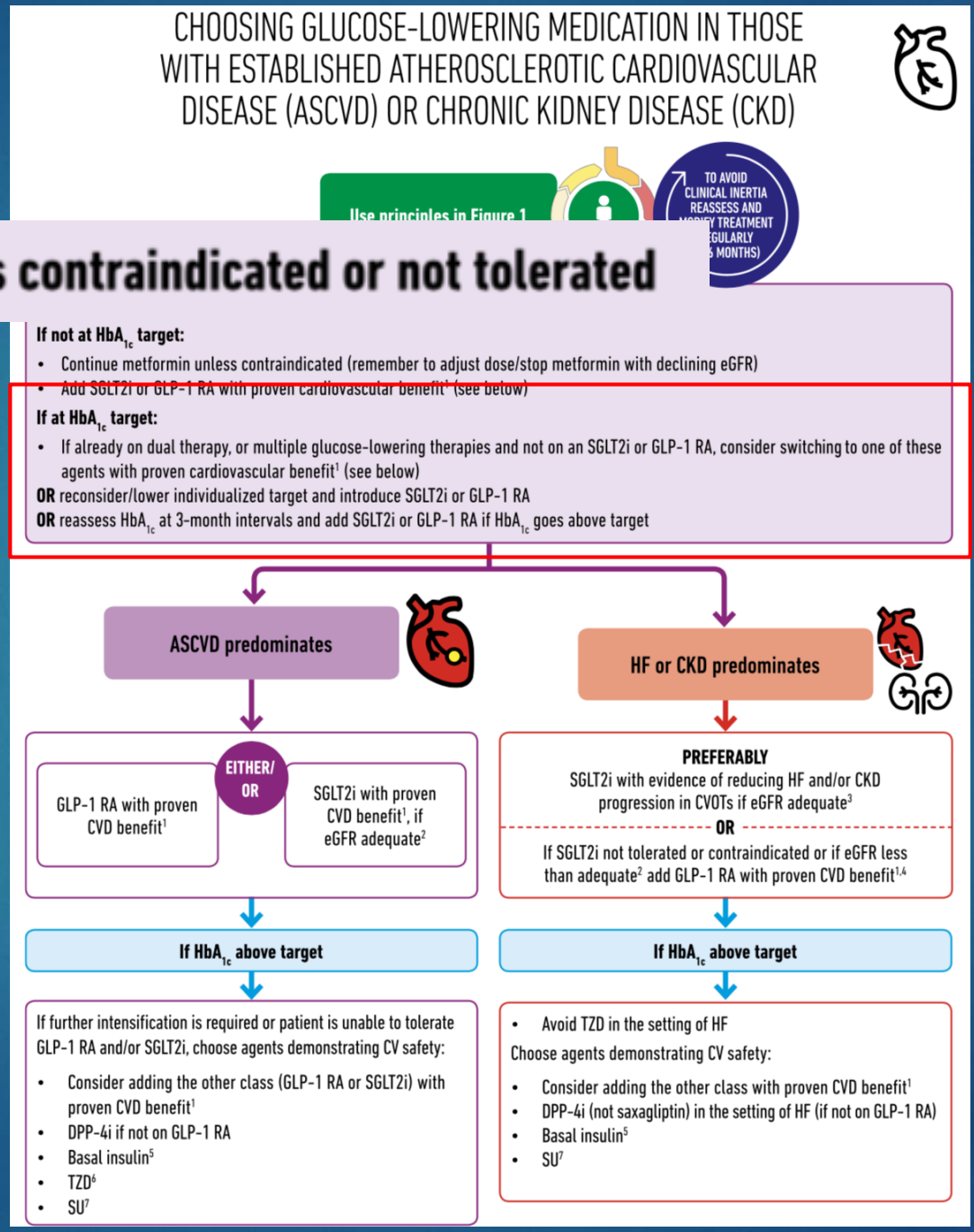
OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Diabetes Care 2018;41:2669–2701

Use metformin unless contraindicated or not tolerated



T2DM with HF

Consensus recommendation

- Among patients with ASCVD in whom HF coexists or is of special concern, SGLT2 inhibitors are recommended (Figs. 2 and 3).

Diabetes Care 2018;41:2669–2701

ANY QUESTIONS?

TABLE 1 Characteristics of Included Studies

Study, Year	Study Drug	N	Population	Age (yrs)	Male (%)	Statin (%)	Aspirin (%)	ACEI (%)	Duration of Diabetes (yrs)	Median Follow-Up Duration (months)	Baseline HbA_{1c} (%)	HbA_{1c} Lowering (Mean)*	Change in Weight (kg)*
EXAMINE, 2013	Alogliptin	5,380	T2DM on antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome within 15 to 90 days before randomization	61	68	90.4	90.7	82	7.2	18	8.0	0.36	0.06
SAVOR-TIMI 53, 2013	Saxagliptin	16,492	T2DM and history of CVD or multiple risk factors for CVD	65	70	78.4	75.3	54.2	10.3	25.2	8.0	0.2	−0.1
ELIXA, 2015	Lixisenatide	6,068	T2DM and acute coronary event 180 days before screening	60.3	69	92.7	97.5 (antiplatelet)	85	9.3	25	7.6	0.27	−0.7
EMPA-REG OUTCOME, 2015	Empagliflozin	7,020	T2DM and established CVD	63.2	71.6	77	82.7	81	NA	37.2	8.0	0.3	−1
TECOS, 2015	Sitagliptin	14,671	T2DM and established CVD	65.5	70.7	79.9	78.5	78.8	11.6	36	7.2	0.29	NA
LEADER, 2016	Liraglutide	9,340	T2DM and CV condition (if >50 yrs of age) or CV risk factors (if >60 yrs of age)	64.3	64.3	71.5	63.3	51	12.8	45.6	8.7	0.4	−2.3
SUSTAIN-6, 2016	Semaglutide	3,297	T2DM and established CVD or CKD or age >60 yrs with CV risk factors	64.6	60.7	72.8	63.9	33.7	13.9	26	8.7	0.8	−3.6
CANVAS, 2017	Canagliflozin	10,142	T2DM and asymptomatic CV condition (if >30 yrs of age) or CV risk factors (if >50 yrs of age)	63.3	64.2	74.9	73.6 (antiplatelet)	80	13.5	47.05	8.2	0.58	−1.6
EXSCEL, 2017	Once-weekly Exenatide	14,752	T2DM with (70%) and without (30%) previous CVD	62.0	62	73.5	63.5	48.7	12.0	38.5	8.0	0.70	−1.27