Slowing the Progression of Heart Failure in Patients with Diabetes Mellitus

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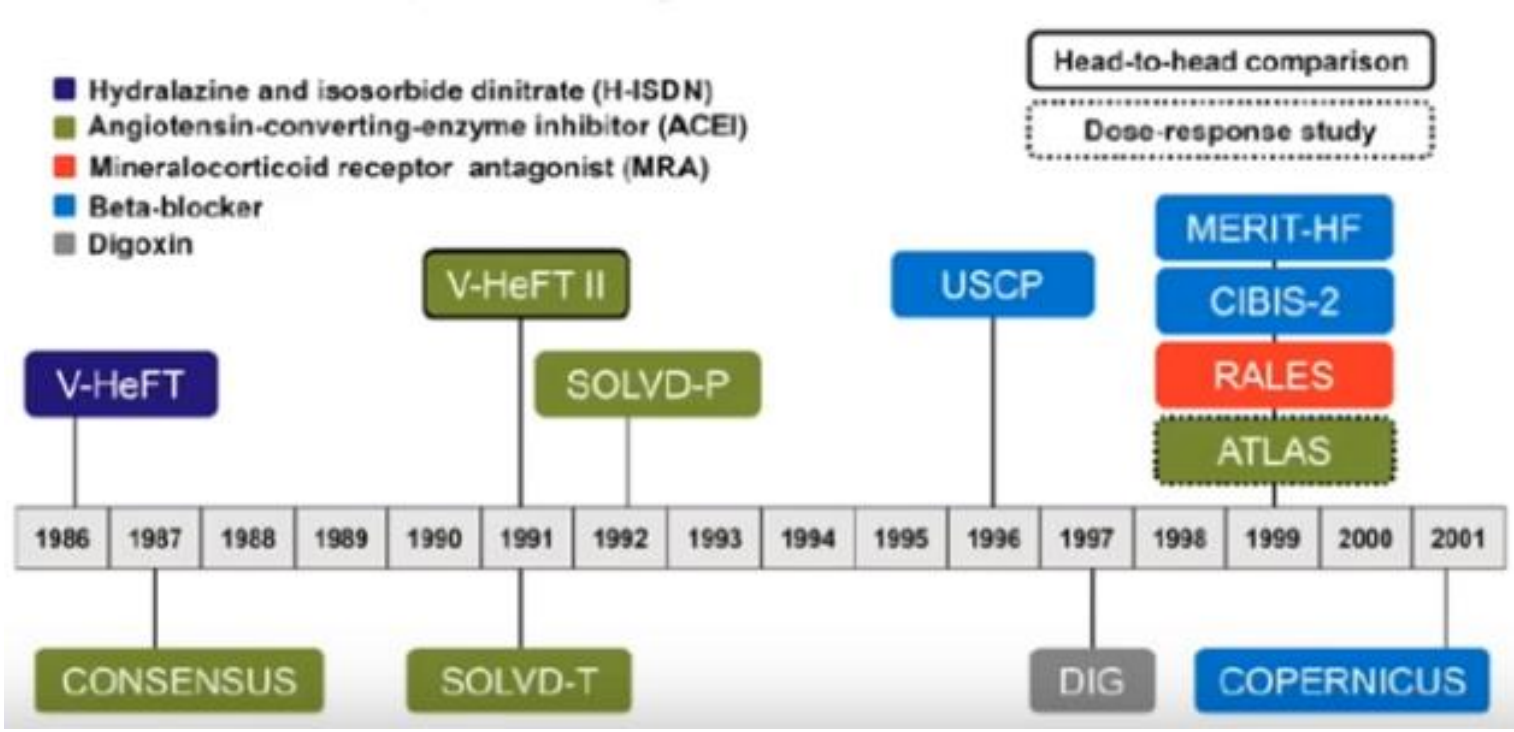
Financial Disclosures

- Lecture Fees:
  - Boehringer Ingelheim
  - Merck
  - Sanofi
  - Amgen
  - Janssen
  - Pfizer

HF reduced EF
30 Years of
Progress
Positive
HF Trials
1986-2001



John Mc Murray. European Heart Journal.36.10.1093

HF reduced EF
30 Years of
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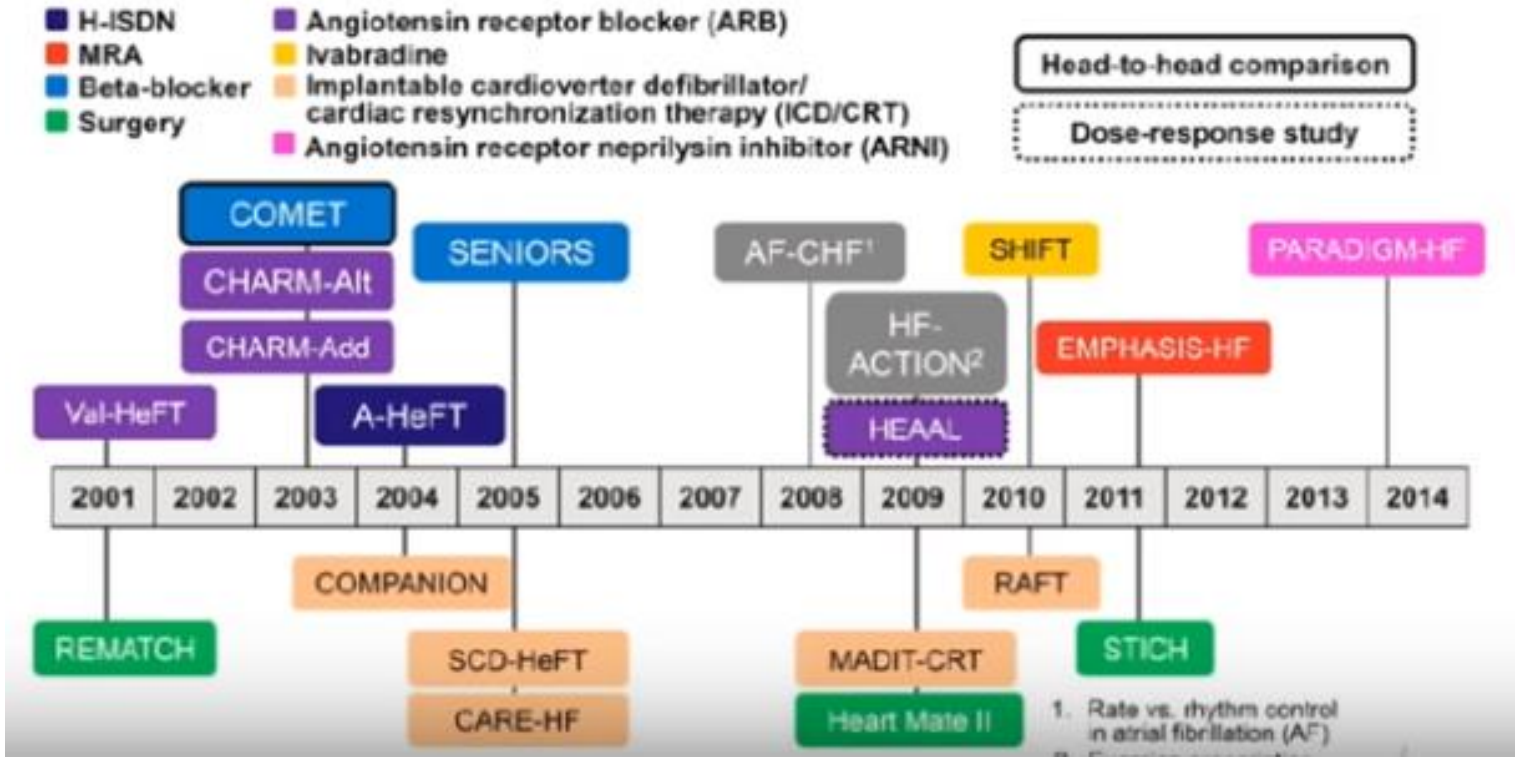

John Mc Murray. European Heart Journal.36.10.1093

The NEW ENGLAND JOURNAL of MEDICINE

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Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

Objectives

- Review the association between diabetes and heart failure
- Glycemic control and heart failure
- Associations of glycemic medications with risks of cardiovascular events and heart failure hospitalization
- Cardiovascular therapy for the patient with diabetes and heart failure

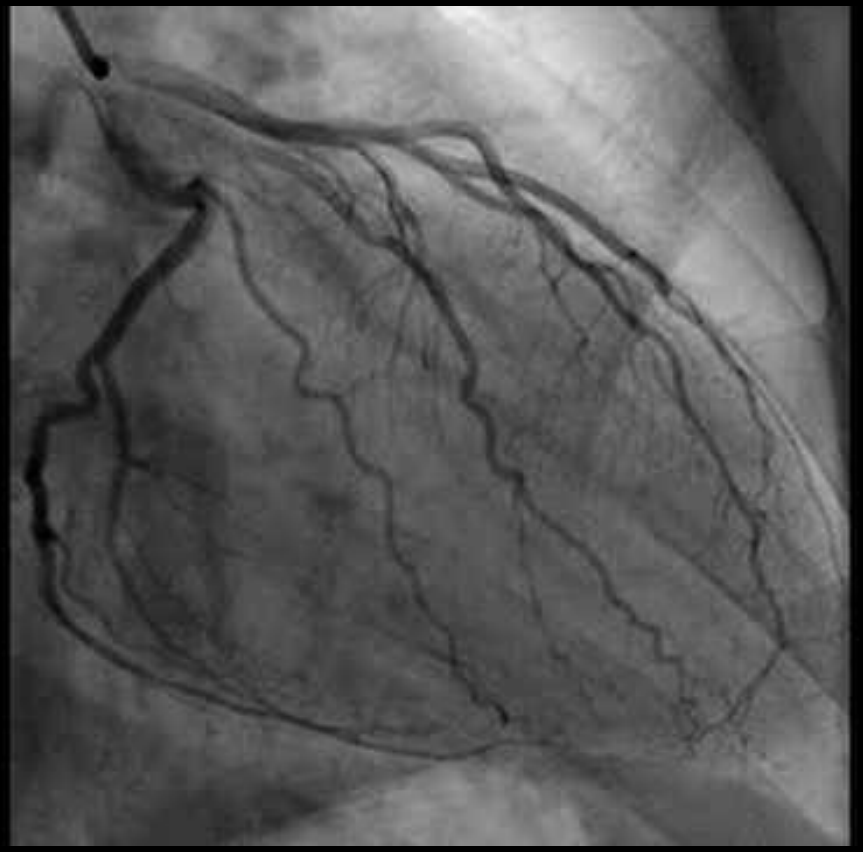
Type 2 Diabetes and Risk of Heart Failure

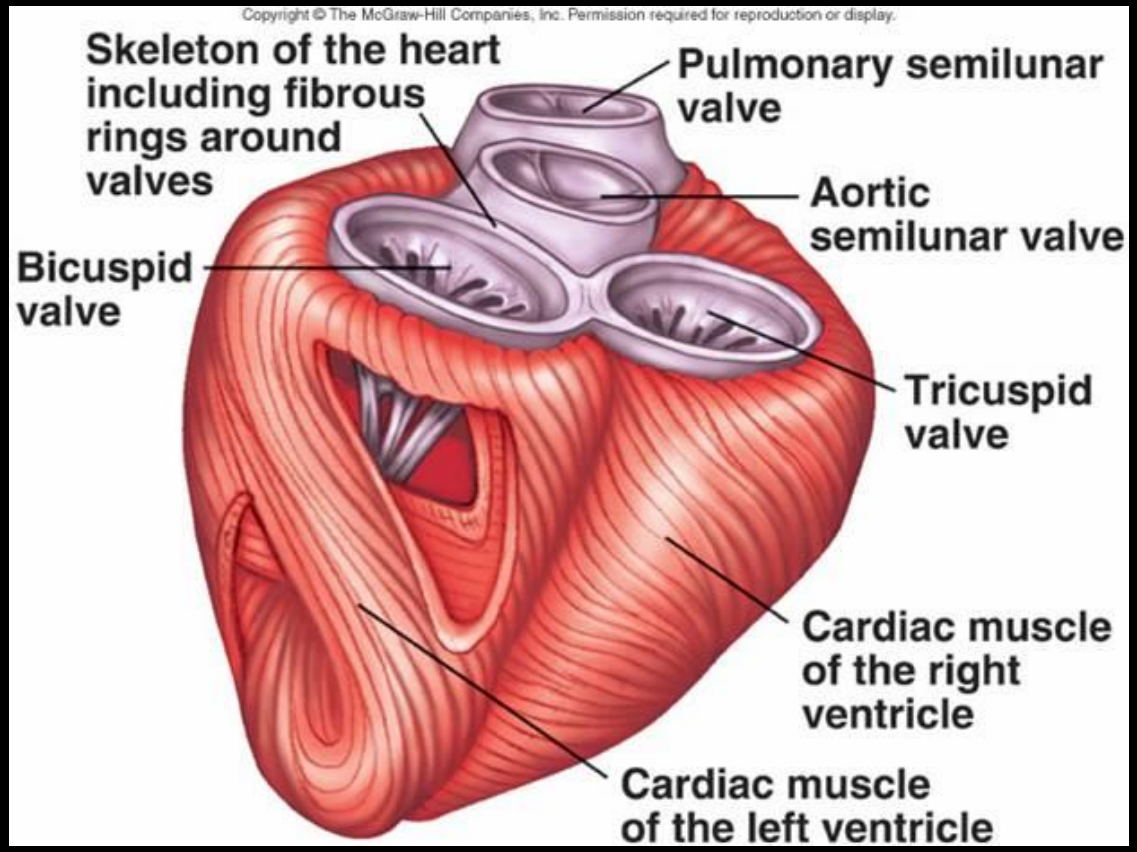
NYHA Class	Level of Clinical Impairment
I 	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
II 	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
III 	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
IV 	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Up to 50% people with T2D may develop heart failure

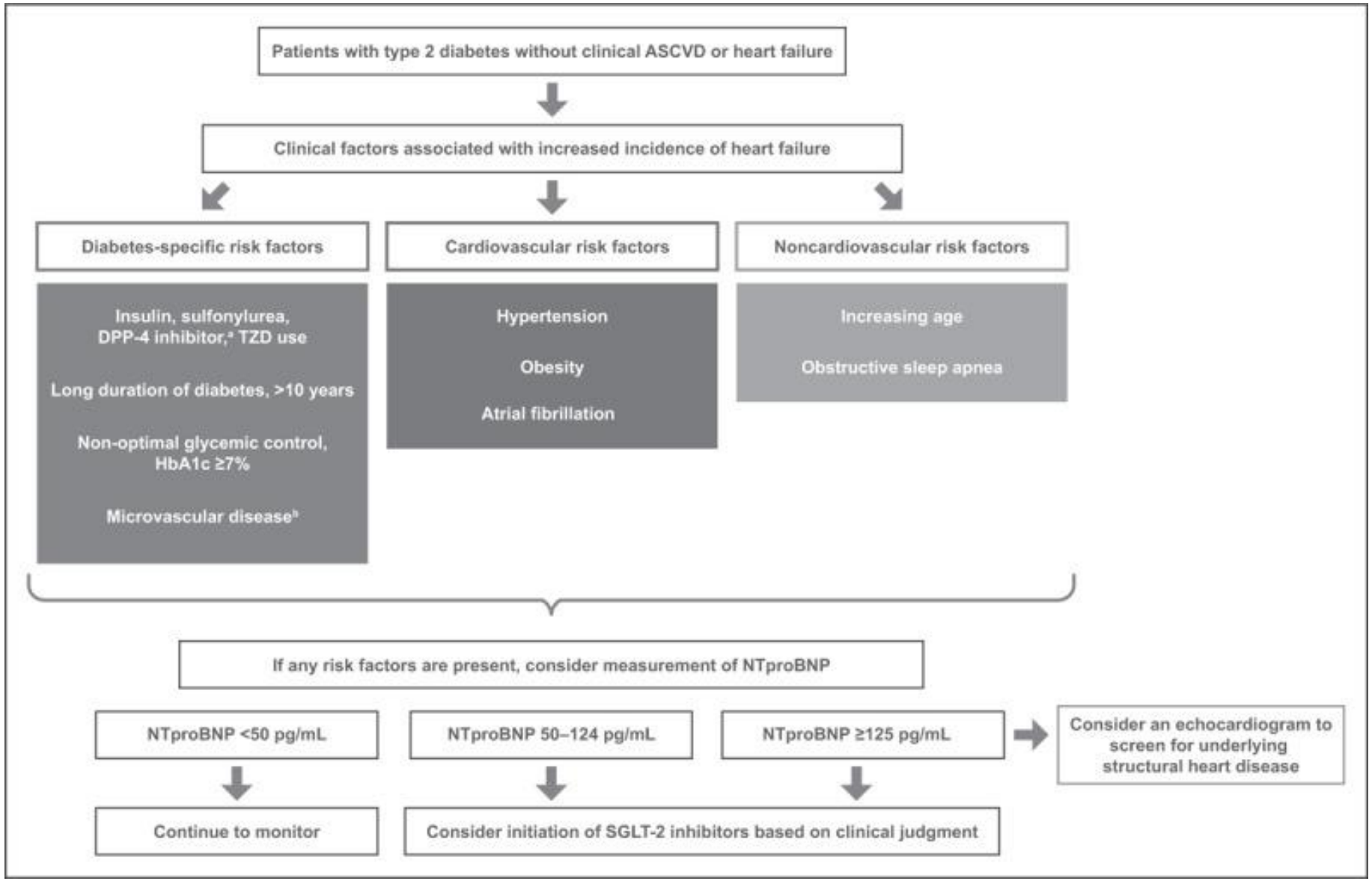
5-year mortality rate after hospitalization for HF id 40 %

ADA Diabetes Care 2019 . 2019;42: S1-S 193, Lohehr LR. Et al.
New York Heart Association (NYHA) Heart Failure Symptom Classification System
Am J Cardiol.2008; 101 (7): 1016-1022





DM as cause of HF: Coronaries vs. Muscle



VERMA S ET AL CURR OPIN CARDIOLOGY 2019;34 (5): 578-583 PREDICTING THE RISK IN PATIENTS WITH TYPE 2 DM W/O ESTABLISHED CARDIOVASCULAR DISEASE OR HEART FAILURE

New Type of Cardiomyopathy Associated With Diabetic Glomerulosclerosis

FIGURE 6. Case 2. Microscopic section of myocardium. Note diffuse areas of fibrosis throughout. (Masson trichrome stain ×125, reduced by 3 percent.)

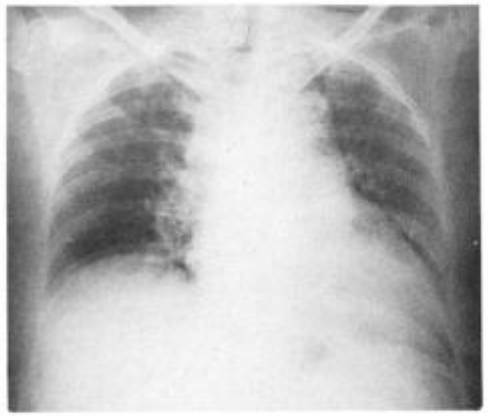


FIGURE 8. Case 3. Chest roentgenogram demonstrating left ventricular hypertrophy and right pleural effusion.

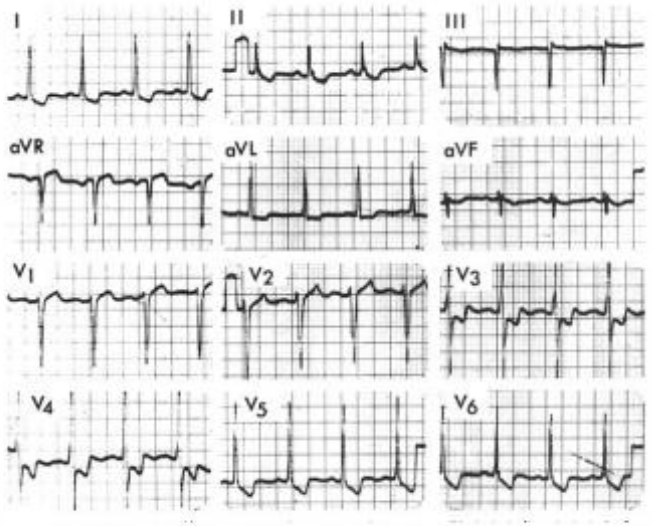


FIGURE 9. Case 3. Electrocardiogram demonstrating left ventricular hypertrophy and diminutive Q wave in lead V_6.

demonstrated nodular hyalinization of the glomeruli with thickening of Bowman's capsule. The arterioles were hyalinized and showed marked thickening of the intima (Fig. 3).

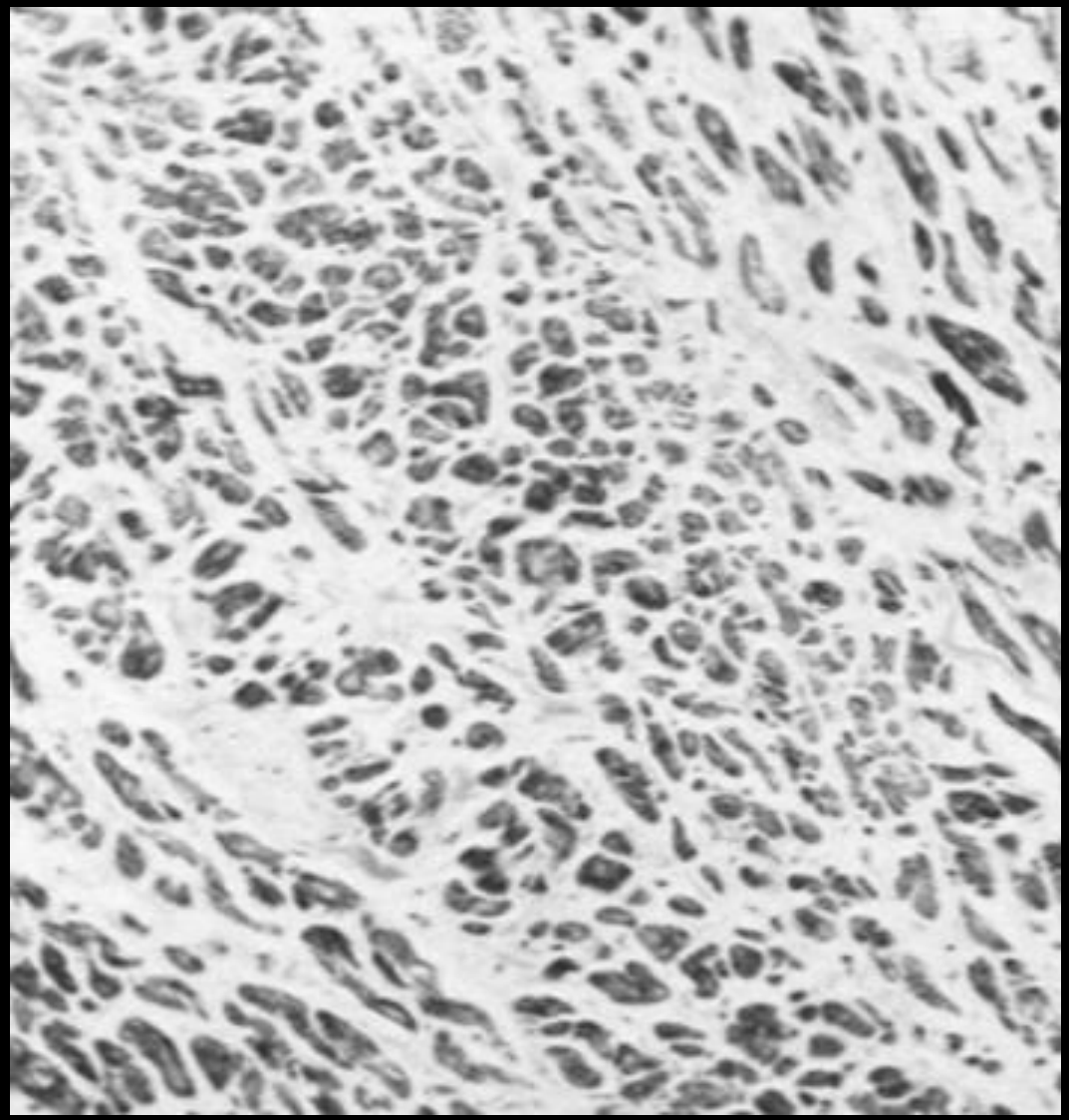
Case 2: A 49 year old Puerto Rican woman with diabetes of 16 years' duration was admitted with vomiting and recent onset of generalized edema. The blood pressure on admission was 100/60 mm Hg. Gross edema of the face and limbs and severe neck vein distension were present as well as cardiomegaly and evidence of bilateral pleural effusion. Pertinent laboratory data are indicated in Table I.

The electrocardiogram (Fig. 4) revealed nonspecific ST–T wave changes and the chest roentgenogram (Fig. 5) confirmed the presence of bilateral pleural effusions and cardiomegaly. The patient's blood urea nitrogen increased gradually from 58 to 150 mg/100 ml, and she was treated with repeated peritoneal dialysis; her condition continued to deteriorate and she died.

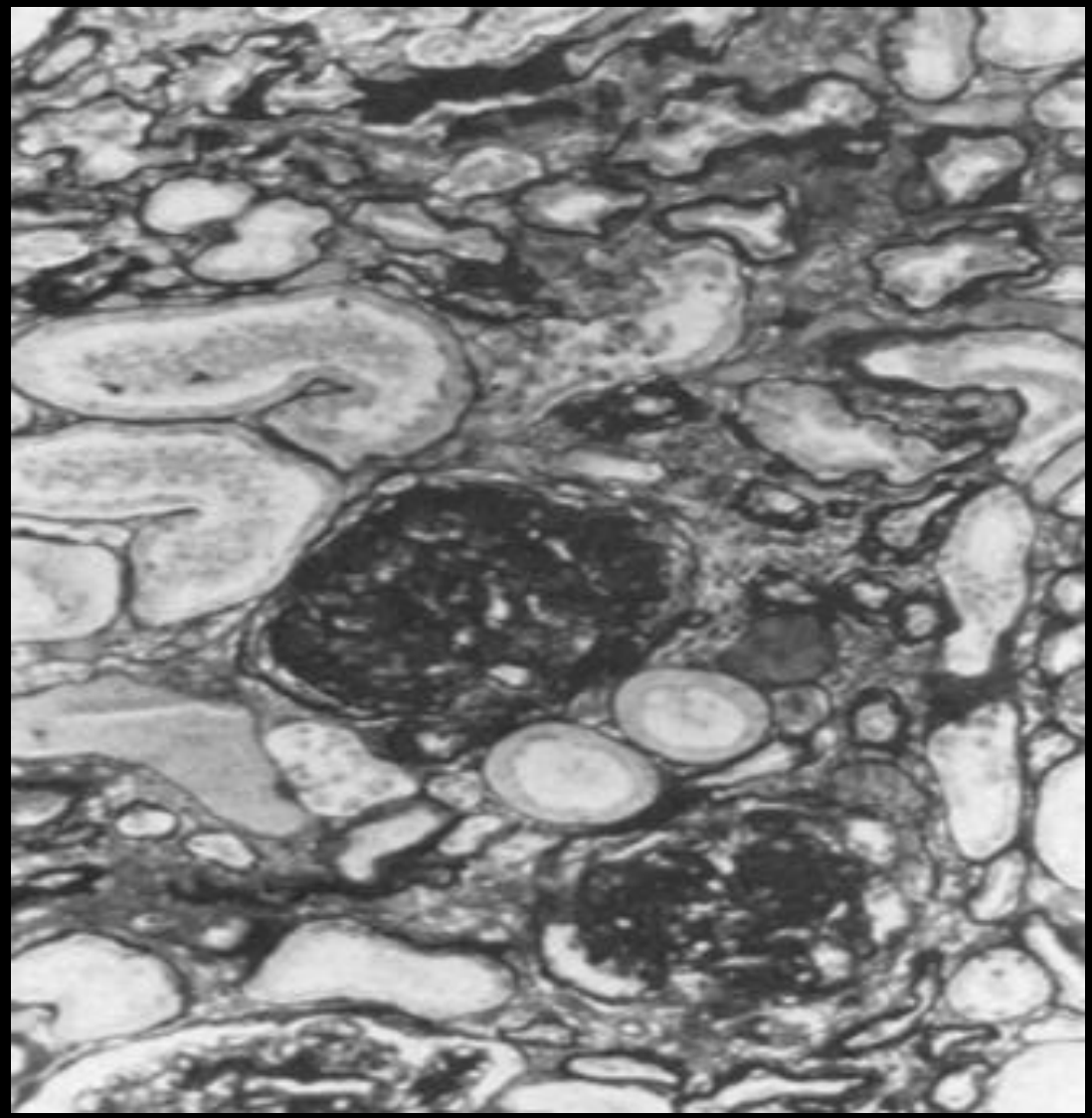
On postmortem examination, the heart weighed 550 g. The right ventricular wall measured 0.4 cm and the left

Am J Cardiol.1972 Nov 8;30(6):595-602.

Myocardium



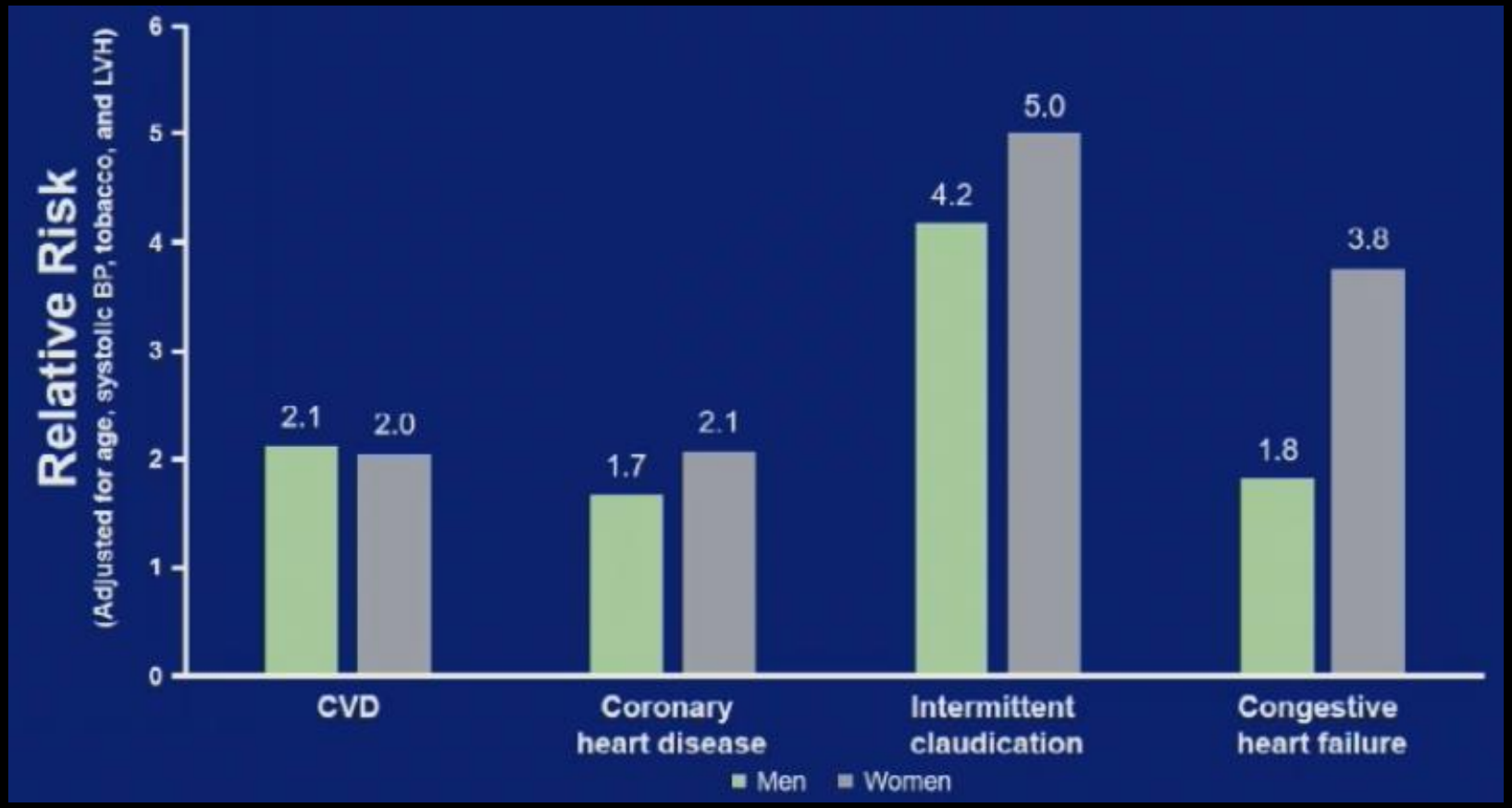
Glomerulus



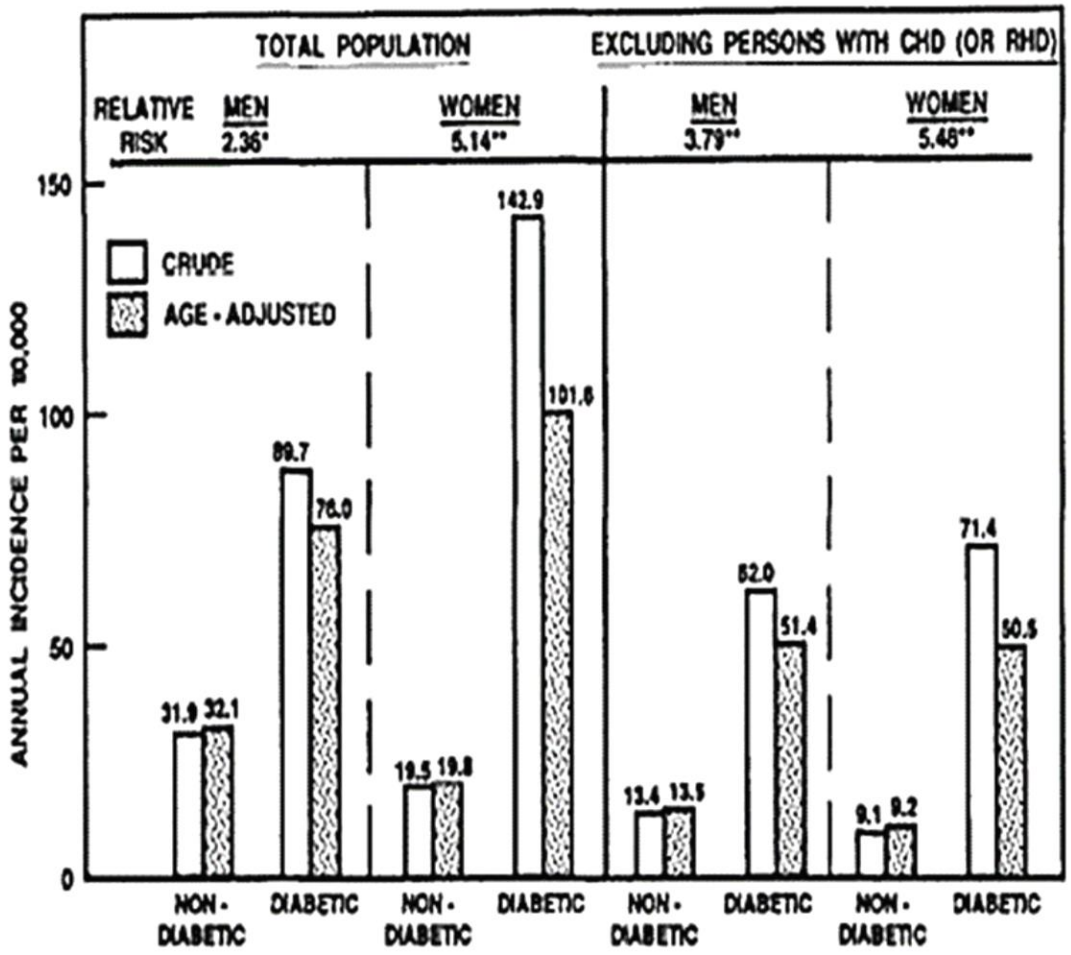
Am J Cardiol.1972 Nov 8;30(6):595-602.

Diabetes Increases Risk of CV Events in Stable Patients 20-year F/U in Framingham Heart Study

Kannel Mc Gee , JAMA. 1979 241: 2035 241: 20135



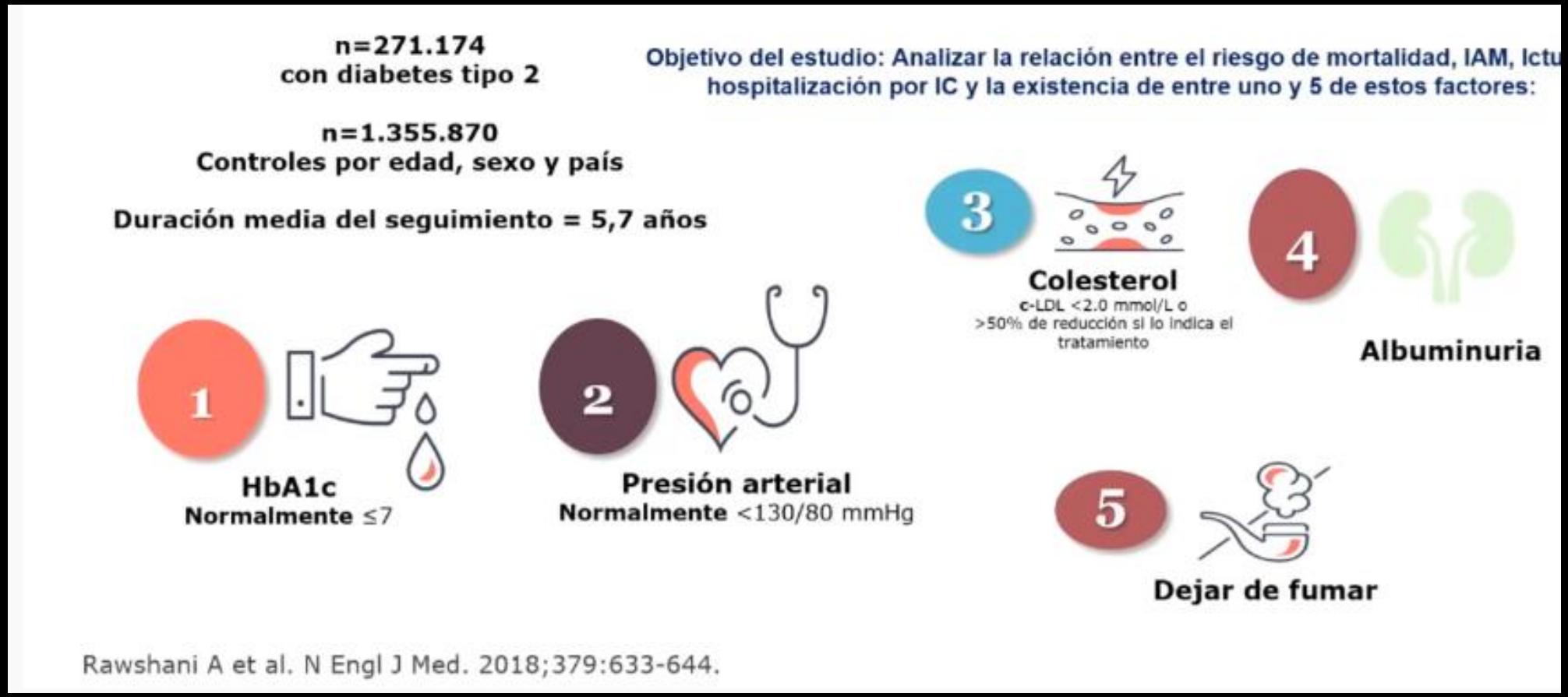
Diabetes Increases Risk of CHF Framingham Heart Study



Risk of congestive heart failure according to diabetic status. Men and women 45 to 74 years old. Framingham Study: 18-year follow-up. *Significantly different, $p < 0.05$; **significantly different, $p < 0.01$. From Zoneraich S. Diabetes and the heart. Springfield, Ill: Charles C Thomas, Publisher, 1978

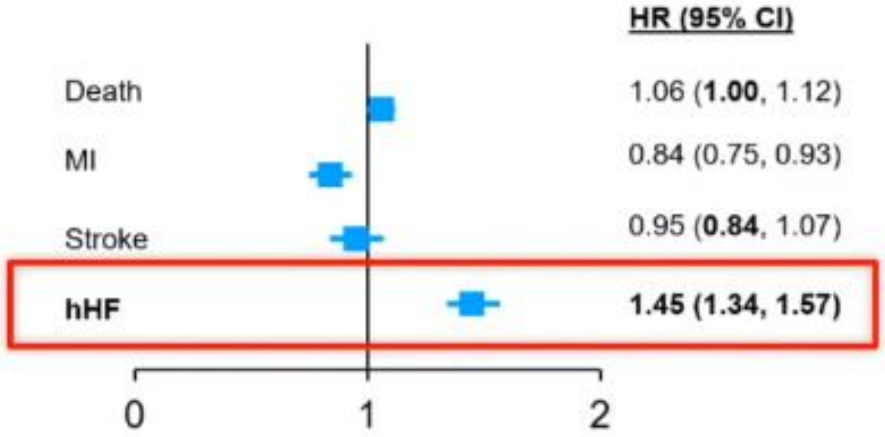
Swedish National Diabetes Registry

Unlike with MI, Residual HF Risk Remains Despite Optimal Control of Traditional CV Risk Factors



Rawshani A et al. N Engl J Med. 2018;379:633-644.

Swedish National Diabetes Registry



On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent

Rawshani A et al. N Engl J Med. 2018;379:633-644.

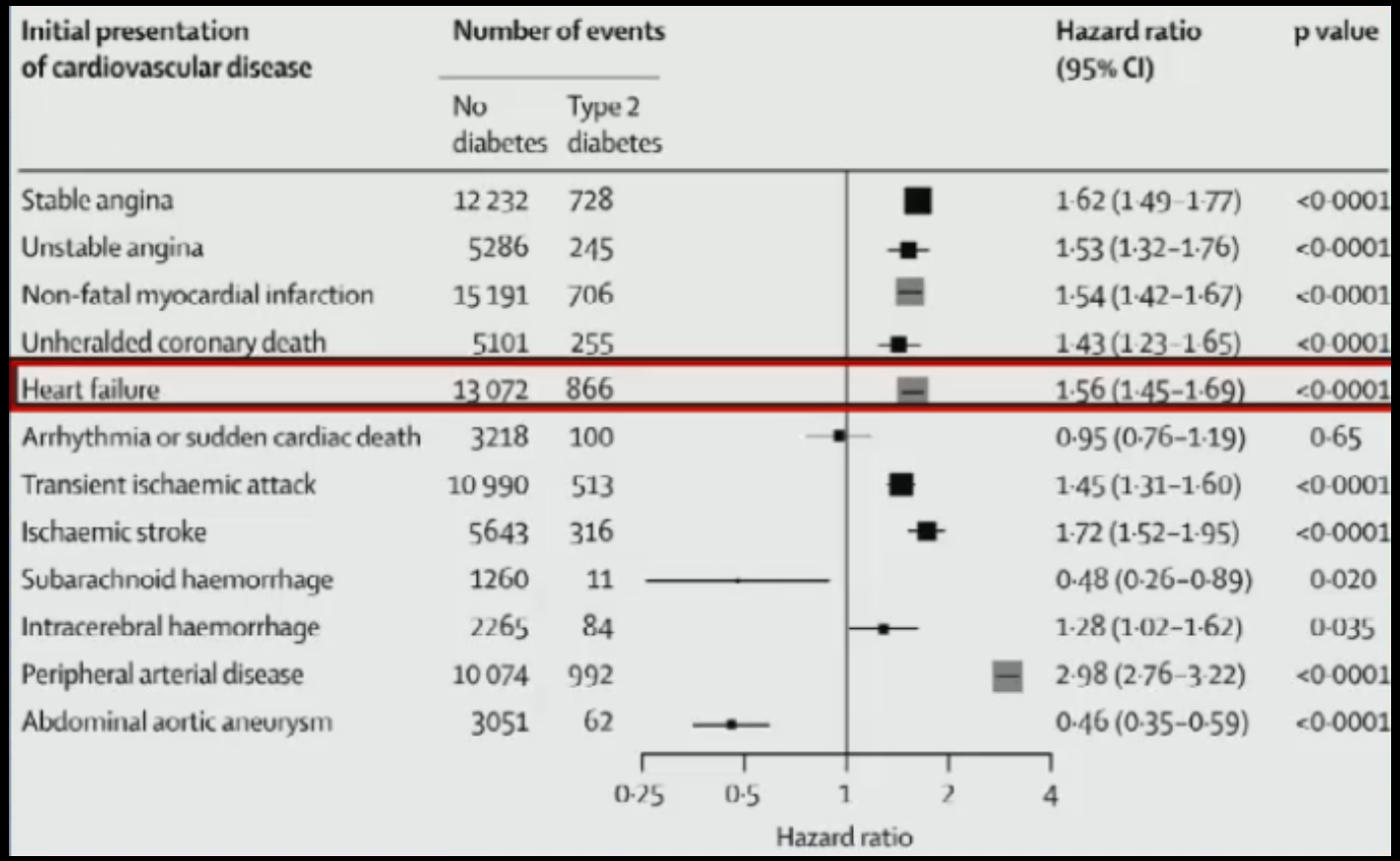
Table 1. Incidence of HF in Individuals With and Without DM in Selected US Observational Studies

Study	Cohort	N	Follow-Up, y	Incidence of HF	Adjusted Risk of HF With vs Without DM	Population-Attributable Fraction
Framingham[21] (study sample included ages 45–74 y)	45–74 y	5209	Up to 20	Age-adjusted rates (person-years): DM (men): 7.6/1000 No DM (men): 3.5/1000 DM (women): 11.4/1000 No DM (women): 2.2/1000	RR (men): 1.82 RR (women): 3.75	Men: 7.7% Women: 18.0%
Cardiovascular Health Study[22]	>65 y	5888	Mean 5.5	Rates (person-years): DM (men): 44.6/1000 No DM (men): 22.9/100 DM (women): 32.5/1000 No DM (women): 12.1/1000	RR: 1.74 (95% CI, 1.38–2.19)	8.3%
Heart and Soul Study[23]	Stable CAD	839	Mean 4.1	Rates (person-years): DM: 36.6/1000 No DM: 17.9/1000	HR, 3.34 (95% CI, 1.65–6.76)	…
MESA[24]	4–84 y	6814	Median 4	…	HR, 1.99 (95% CI, 1.08–3.68)	DM-attributable risk: 19 per 1000
NHANES[25]	25–74 y	13643	Mean 19	Cumulative incidence at age 85 y: DM (men): 65.5% No DM (men): 36.9% DM (women): 61.8% No DM (women): 28.9%	RR, 1.85 (95% CI, 1.51–2.28) Similar in men and women	…

Heart Failure is a Common Presentation of CV disease in Patients With Diabetes

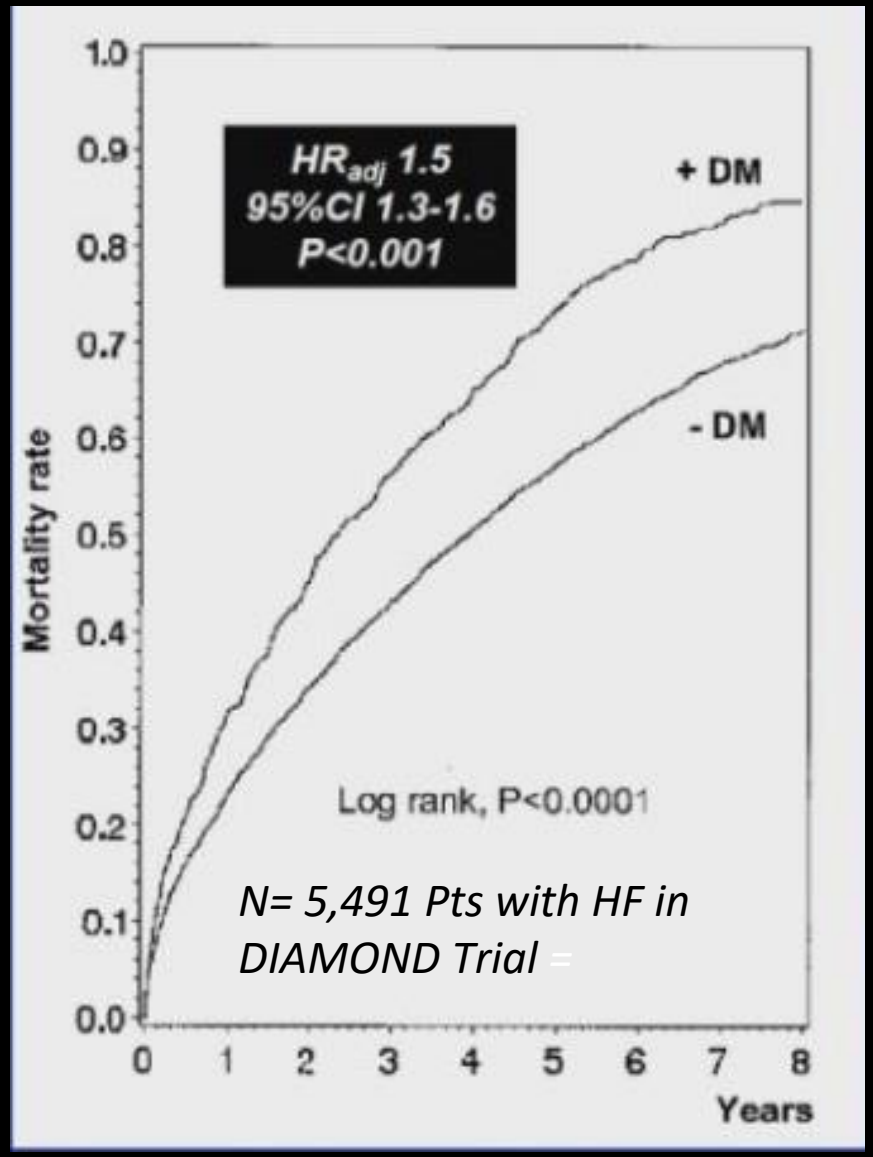
Lancet Diabetes Endocrinology 2015; 3: 105 -13

Initial presentation of cardiovascular disease	Number of events		Hazard ratio (95% CI)	p value
	No diabetes	Type 2 diabetes		
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001

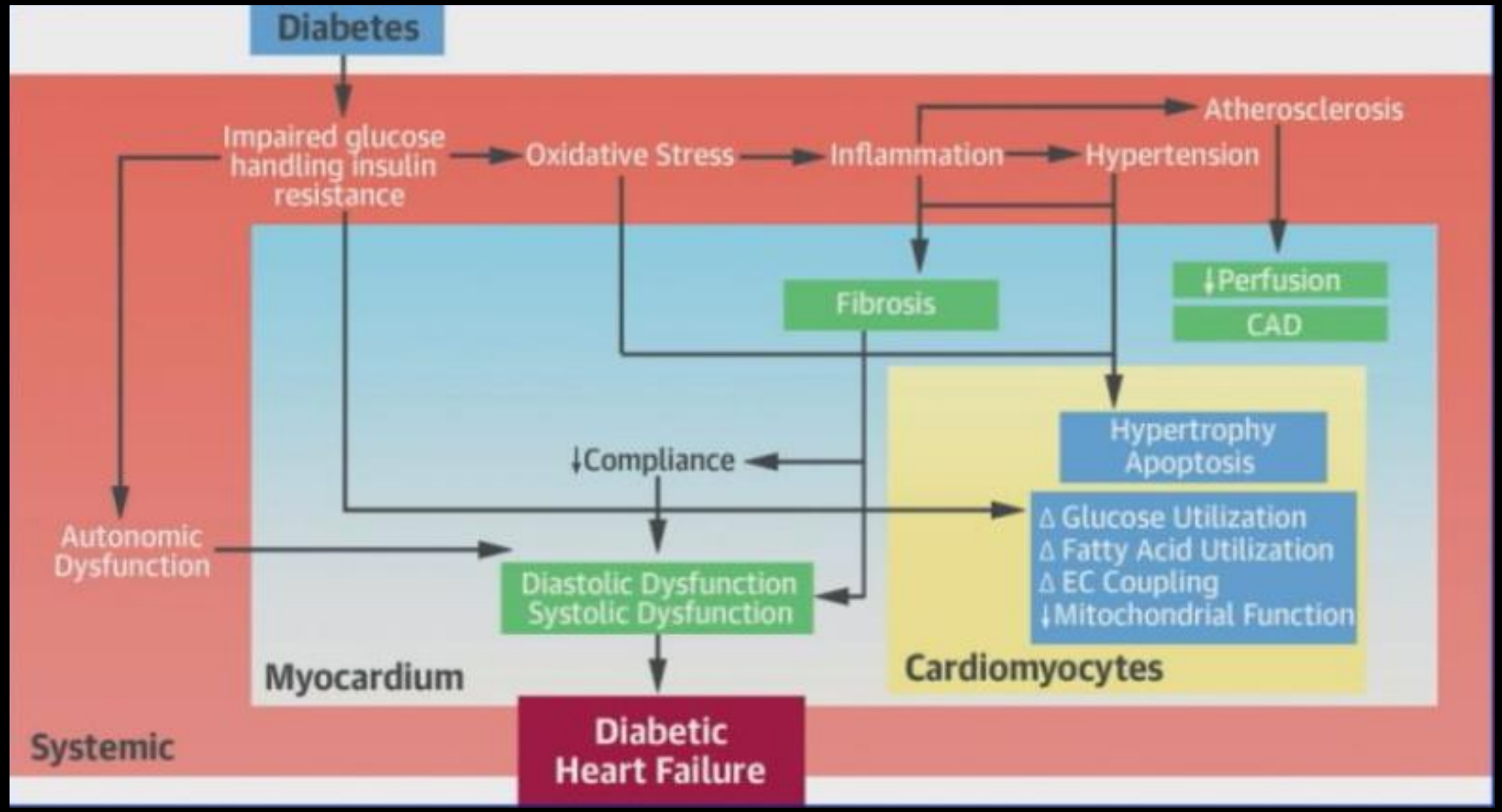


Risk of Death is High in Patients with Heart Failure and Diabetes

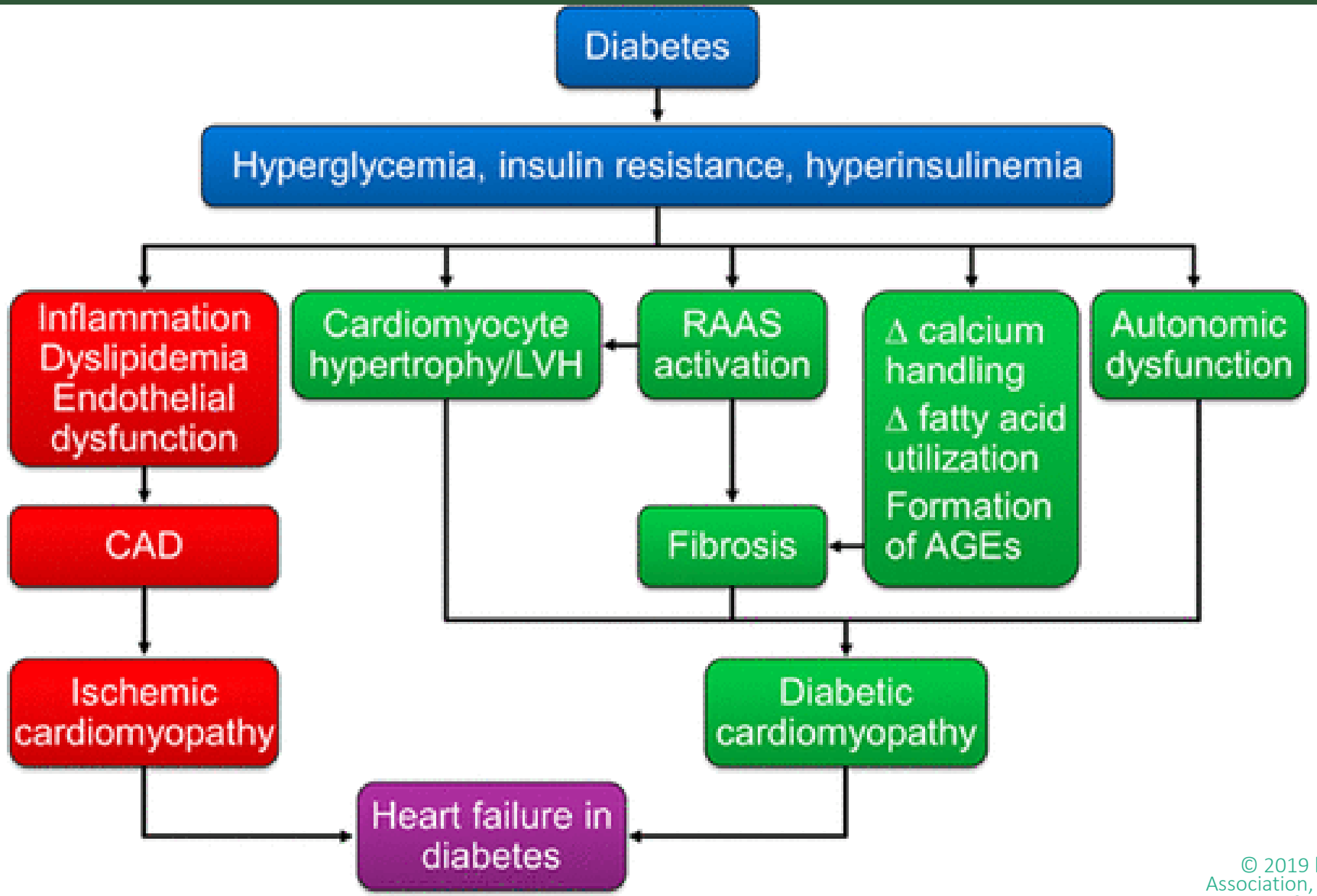
J Am Coll Cardiol 2004; 43; 771- 7



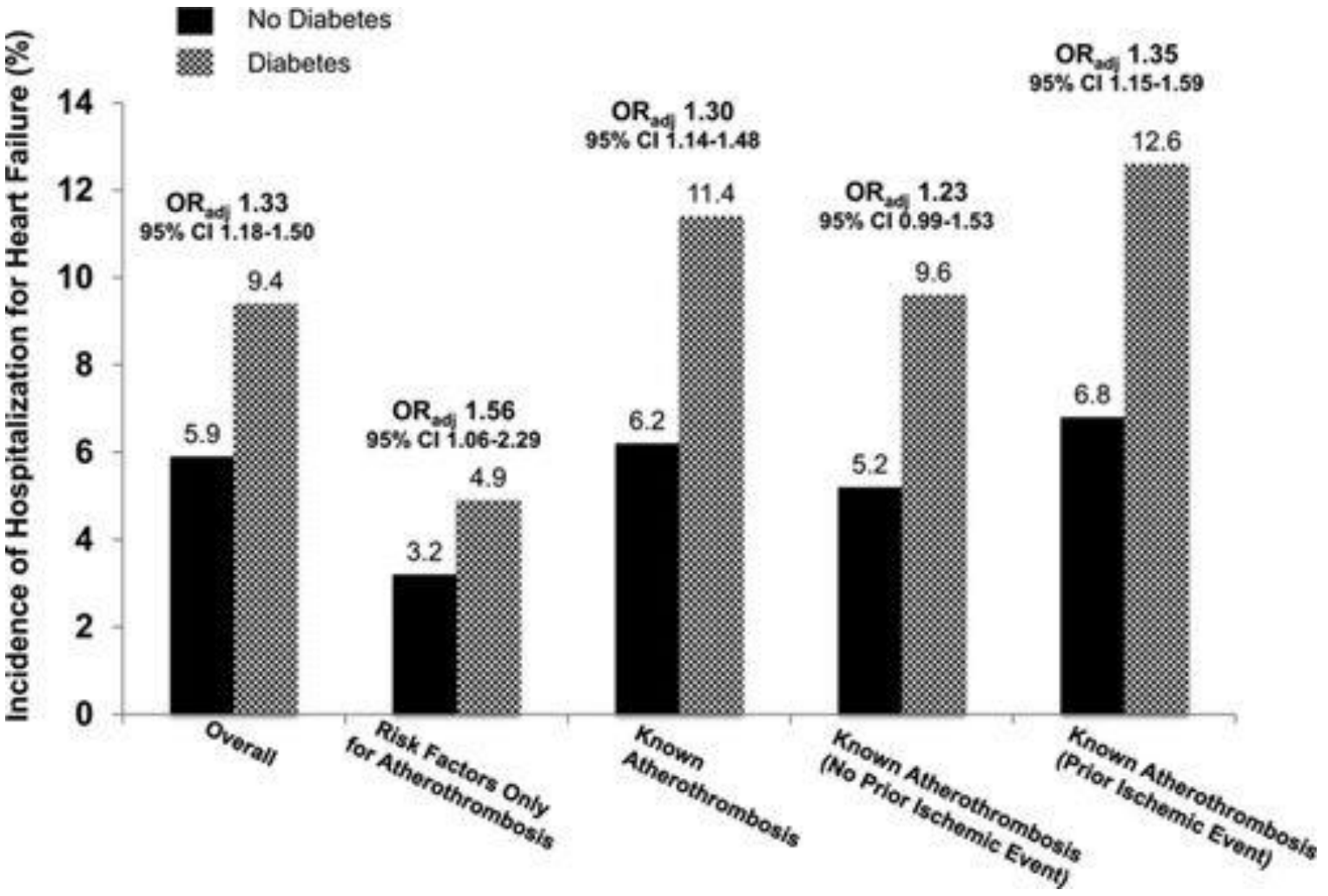
Potential Mechanisms for Heart Failure in Patients With Diabetes



Marwick, T.H.et al. J AM Coll Cardiol.2018;71:339



Diabetes Substantially Increases Risk of Heart Failure REACH Study

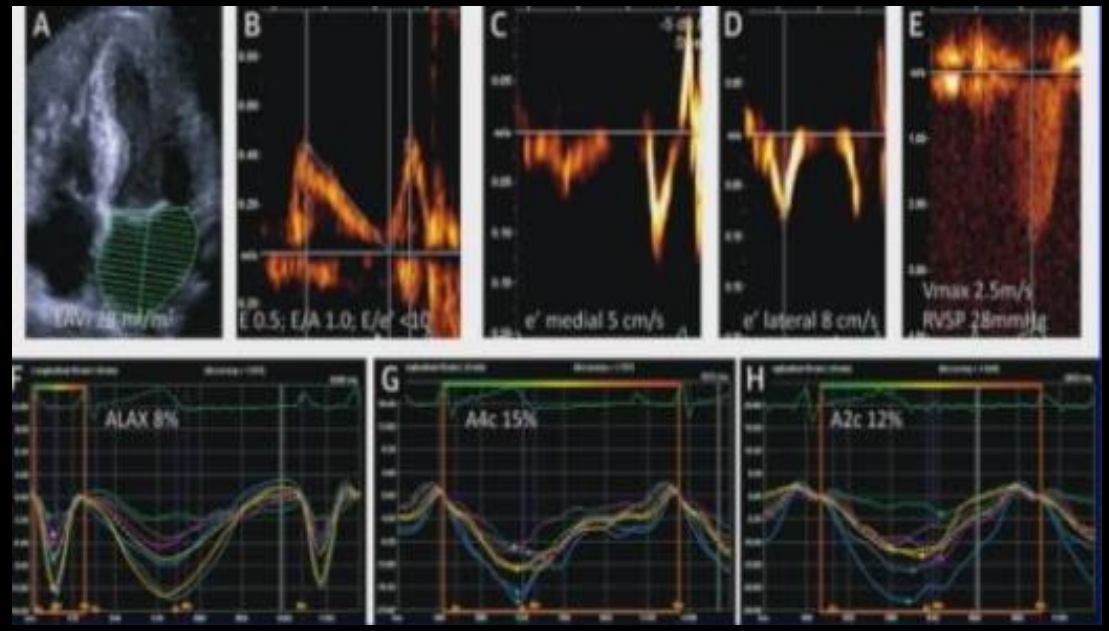


45,227 had follow-up at 4 years
43.6% (n=19 699) had diabetes mellitus at baseline

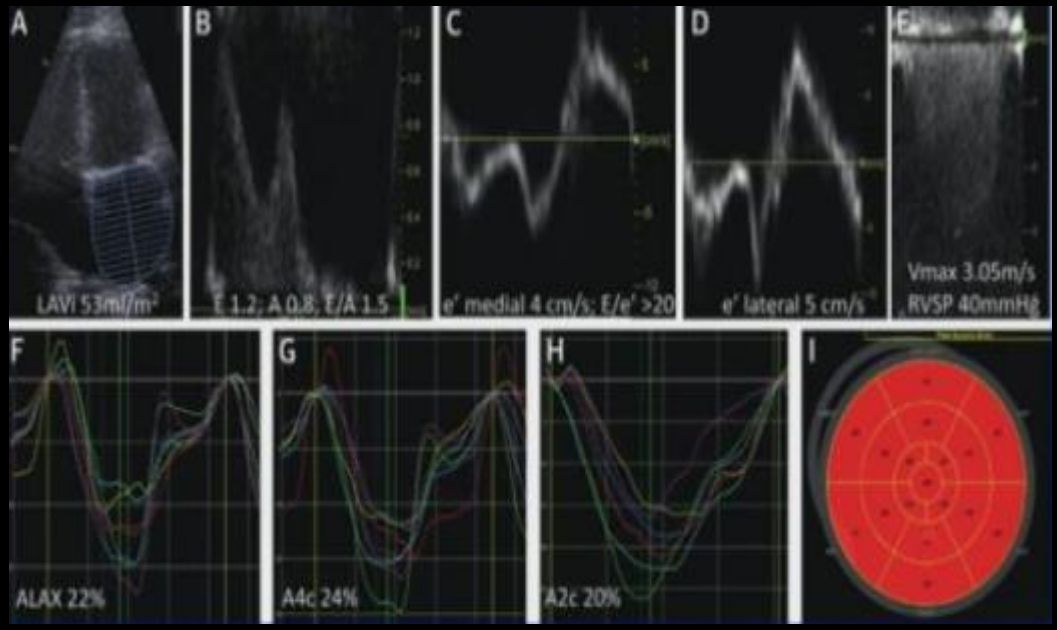
Cavender et al. Circulation. 2015; 132: 923

Phenotypes of Heart Failure in Patients with Diabetes

Systolic Dysfunction with Preserved EF



Diastolic Disfunction



Marwick, T.H.et al. J AM Coll Cardiol.2018;71:339

Objectives

- Review the association between diabetes and heart failure
- Glycemic control and heart failure
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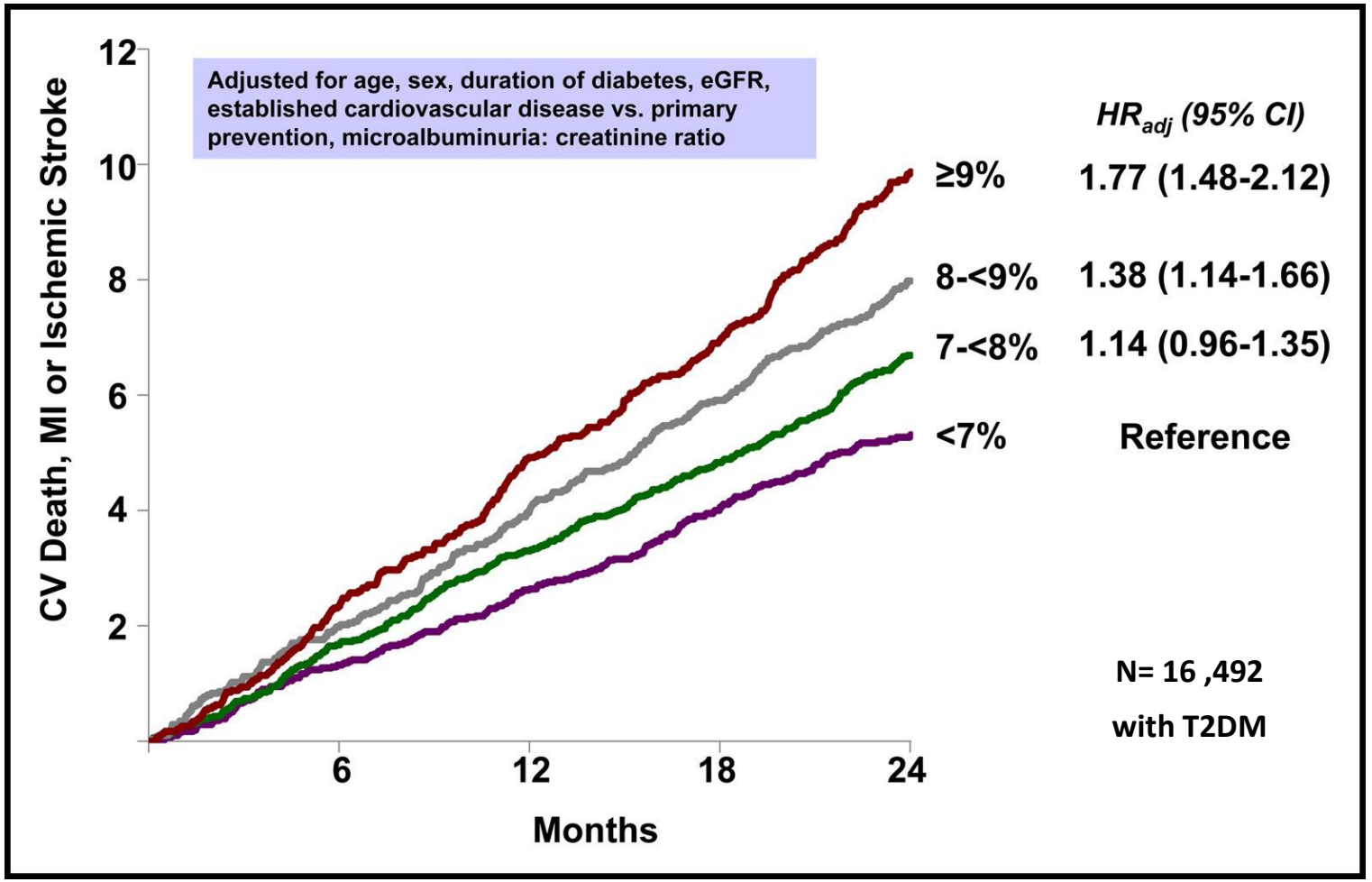
- Cardiovascular therapy for the patient with diabetes and heart failure

Relationship between CV Events and HbA1c



Cavender MA, The American Journal of Medicine 2016 129, 340.e1-340

Kaiser Diabetes Register
N = 48, 858

Each 1 % increase in Hgb A1C was associated with an 8 % increased risk of heart failure

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Clinical Investigation and Reports

Glycemic Control and Heart Failure Among Adult Patients With Diabetes

Carlos Iribarren, MD, MPH, PhD; Andrew J. Karter, PhD;
Alan S. Go, MD; Assiamira Ferrara, MD, PhD; Jennifer Y. Liu, MPH;
Stephen Sidney, MD, MPH; Joseph V. Selby, MD, MPH

Background—Glycemic control is associated with microvascular events, but its effect on the risk of heart failure is not well understood. We examined the association between hemoglobin (Hb) A_{1c} and the risk of heart failure hospitalization and/or death in a population-based sample of adult patients with diabetes and assessed whether this association differed by patient sex, heart failure pathogenesis, and hypertension status.

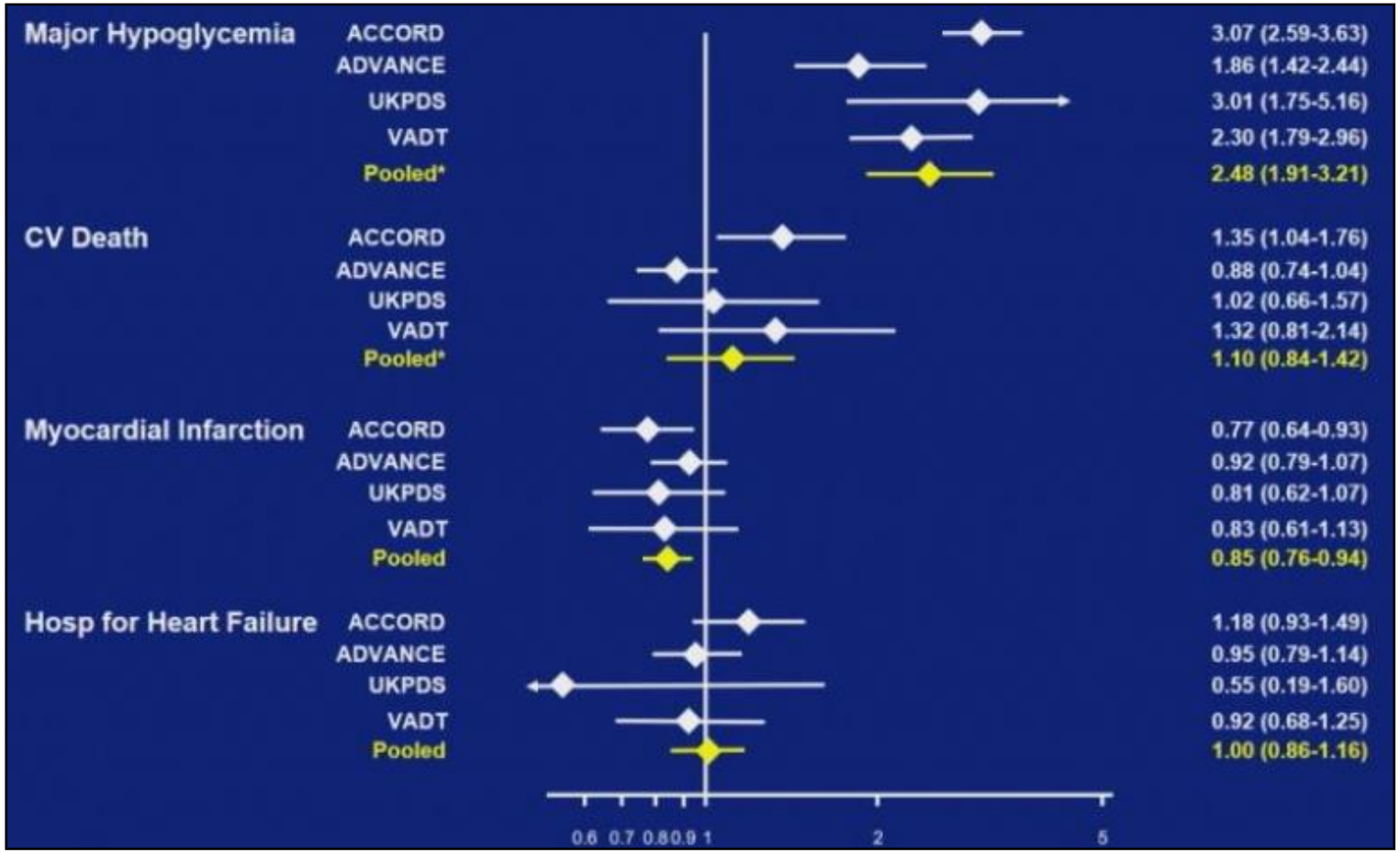
Methods and Results—A cohort design was used with baseline between January 1, 1995, and June 30, 1996, and follow-up through December 31, 1997 (median 2.2 years). Participants were 25 958 men and 22 900 women with (predominantly type 2) diabetes, ≥19 years old, with no known history of heart failure. There were a total of 935 events (516 among men; 419 among women). After adjustment for age, sex, race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, use of β-blockers and ACE inhibitors, type and duration of diabetes, and incidence of interim myocardial infarction, each 1% increase in Hb A_{1c} was associated with an 8% increased risk of heart failure (95% CI 5% to 12%). An Hb A_{1c} ≥10, relative to Hb A_{1c} <7, was associated with 1.56-fold (95% CI 1.26 to 1.93) greater risk of heart failure. Although the association was stronger in men than in women, no differences existed by heart failure pathogenesis or hypertension status.

Conclusions—These results confirm previous evidence that poor glycemic control may be associated with an increased risk of heart failure among adult patients with diabetes. **(*Circulation*. 2001;103:2668-2673.)**

Key Words: heart failure ■ diabetes mellitus ■ glycemia ■ hemoglobin

Circulation. 2001;103:2668-2673

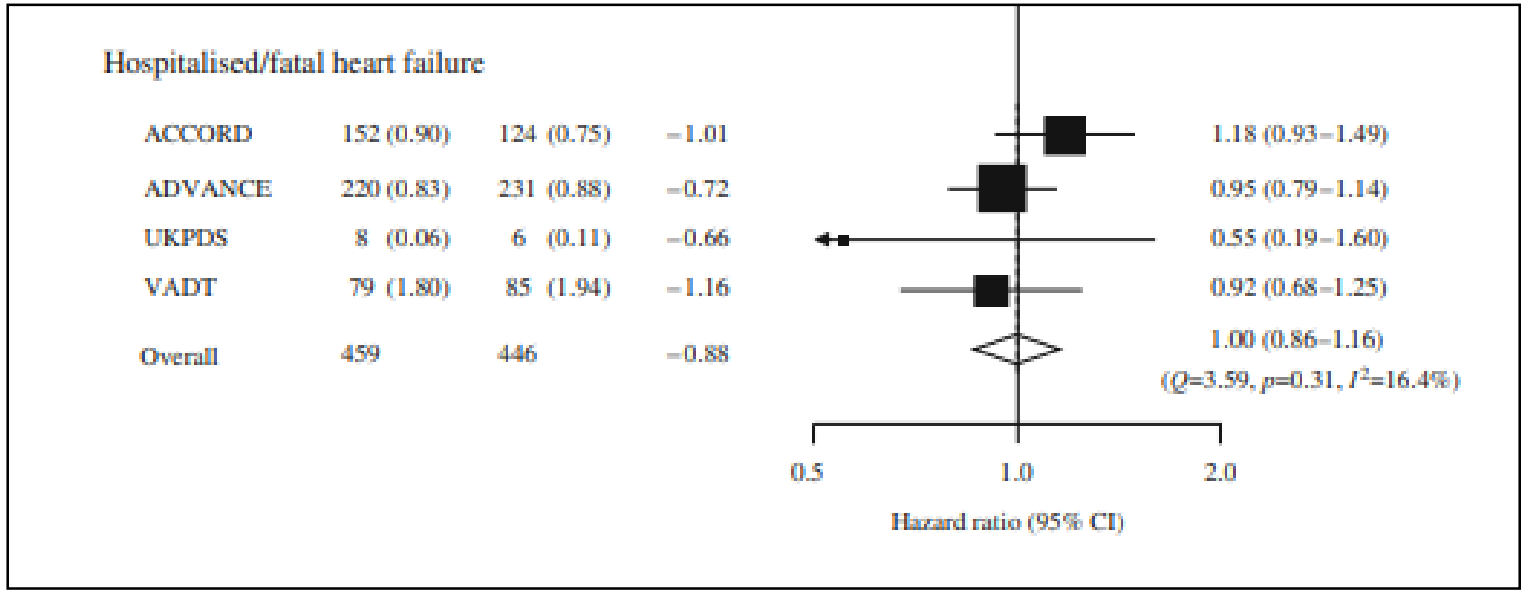
Intensive Glucose Control and Outcomes- Metanalysis n=27,049



Turnbull et al, Diabetologia 2009

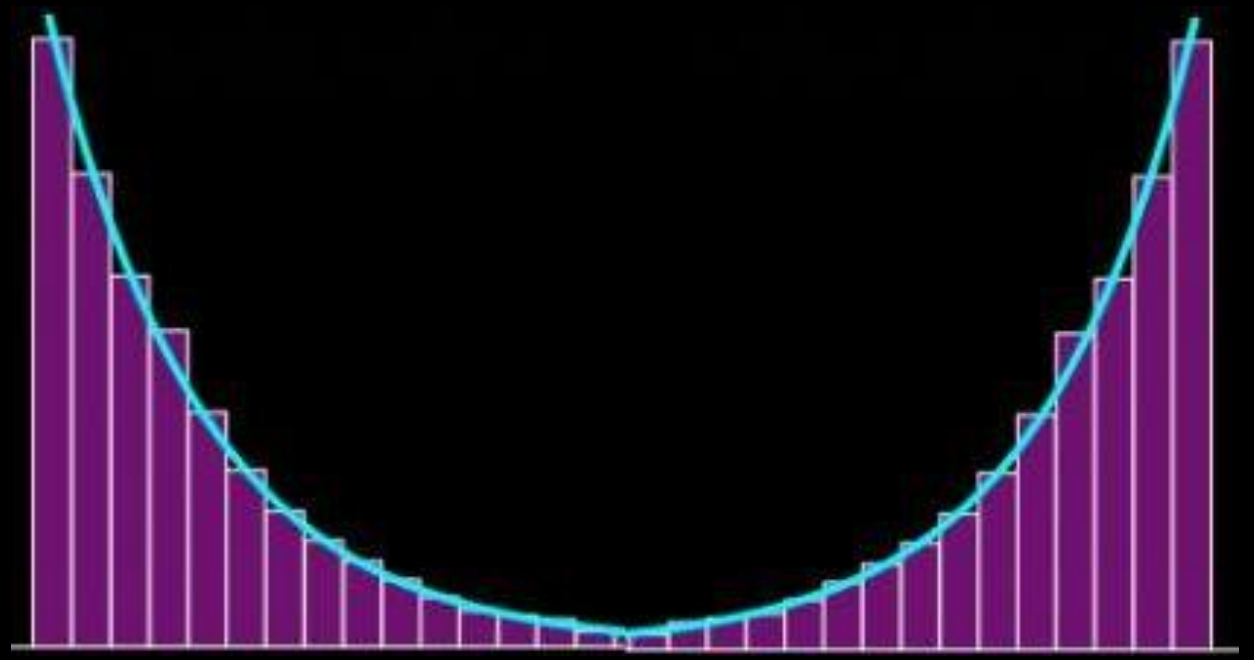
Intensive Glucose Control and Outcomes

While Glucose Control Is Fundamental to Management of T2D,
It Does Not Reduce the Risk of HF Outcomes



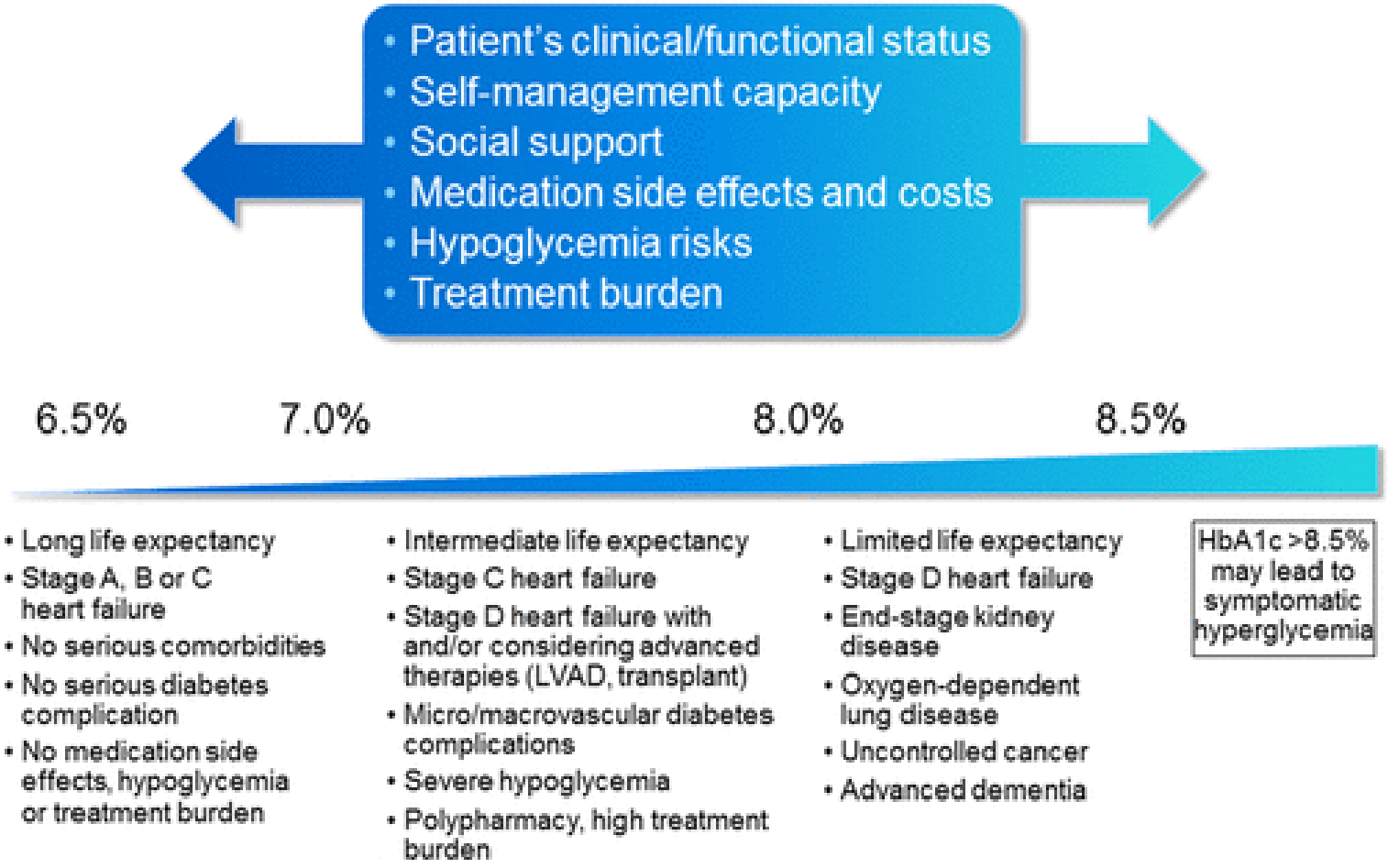
Turnbull et. Al, Diabetology 2009

A1c and HF in a Nutshell



The association between HbA1c and mortality among patients with HF is consistently U shaped, with the lowest mortality in patients with HbA_1C 7% to 8%

Glycemic Control and Heart Failure



More recent trials…..

- More recent RCTs have focused on the cardiovascular safety of glucose-lowering drugs as mandated by FDA (2008) rather than the potential benefits of lower HbA_{1c} targets or more intensive therapies.

- These trials focused on the conventional 3-point MACE but sometimes included HF as a secondary end point

- HF benefits did not correlate with the degree of HbA_{1c} reduction between (0.3% and 0.6%) and were thus largely independent of glycemic control

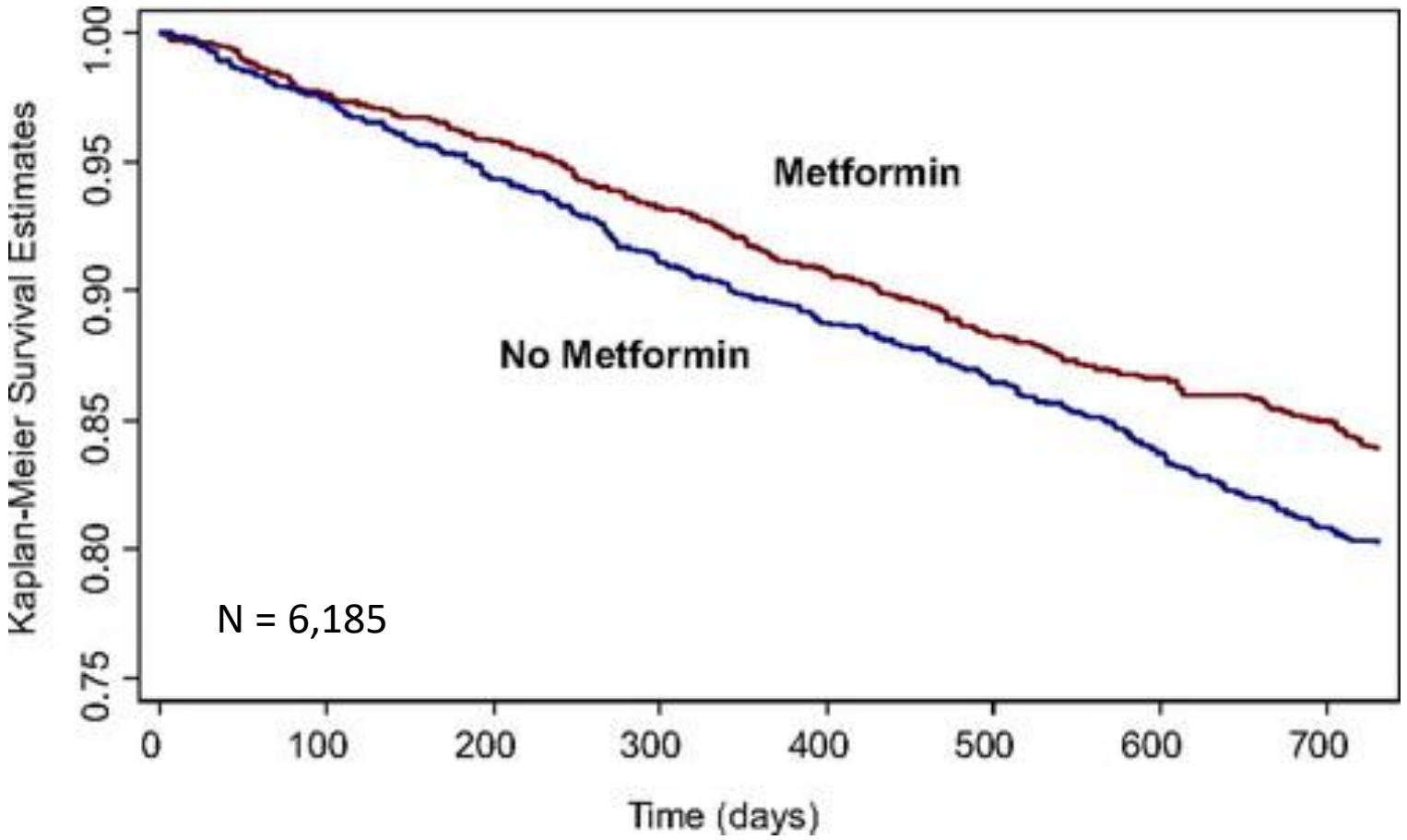
Objectives

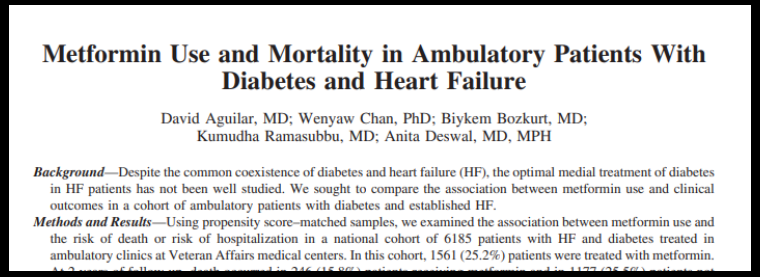
- Review the association between diabetes and heart failure
- Glycemic control and heart failure
- Associations of glycemic medications with risks of cardiovascular events and heart failure hospitalization
- Cardiovascular therapy for the patient with diabetes and heart failure

DM drugs and HF clinical considerations

- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

Metformin Use and Mortality in Ambulatory Patients with Diabetes and Heart Failure





Metformin Use and Mortality in Ambulatory Patients With Diabetes and Heart Failure

David Aguilar, MD; Wenyaw Chan, PhD; Biykem Bozkurt, MD; Kumudha Ramasubbu, MD; Anita Deswal, MD, MPH

Background—Despite the common coexistence of diabetes and heart failure (HF), the optimal medial treatment of diabetes in HF patients has not been well studied. We sought to compare the association between metformin use and clinical outcomes in a cohort of ambulatory patients with diabetes and established HF.

Methods and Results—Using propensity score–matched samples, we examined the association between metformin use and the risk of death or risk of hospitalization in a national cohort of 6185 patients with HF and diabetes treated in ambulatory clinics at Veteran Affairs medical centers. In this cohort, 1561 (25.2%) patients were treated with metformin.

ELSEVIER

International Journal of Cardiology

Volume 166, Issue 2, 20 June 2013, Pages 404-412

Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community

Sotero P. Romero, Jose L. Andrey, Antonio Garcia-Egido, Miguel A. Escobar, Virginia Perez, Ramón Corzo, Gloria J.

Clinical Care/Education/Nutrition

ORIGINAL ARTICLE

Improved Clinical Outcomes Associated With Metformin in Patients With Diabetes and Heart Failure

Dean T. Eurich, BSP, MSC[1,2] Sumit R. Majumdar, MD, MPH[1,3] Finlay A. McAlister, MD, MSC[1,3] Ross T. Tsuyuki, BSC(PHARM), PHARMD, MSC[1,2,4] Jeffrey A. Johnson, PHD[1,2]

OBJECTIVE — Metformin is considered contraindicated in patients with heart failure be-

on the part of patients and providers. Moreover, insulin therapy has also been associated with an increased risk of heart failure (7,8). It is not surprising, therefore, that 10% of Medicare patients with heart failure and diabetes use metformin

Metformin

- Multiple observational studies suggest a survival benefit
- FDA removed HF as a contraindication to metformin use in 2006

Metformin

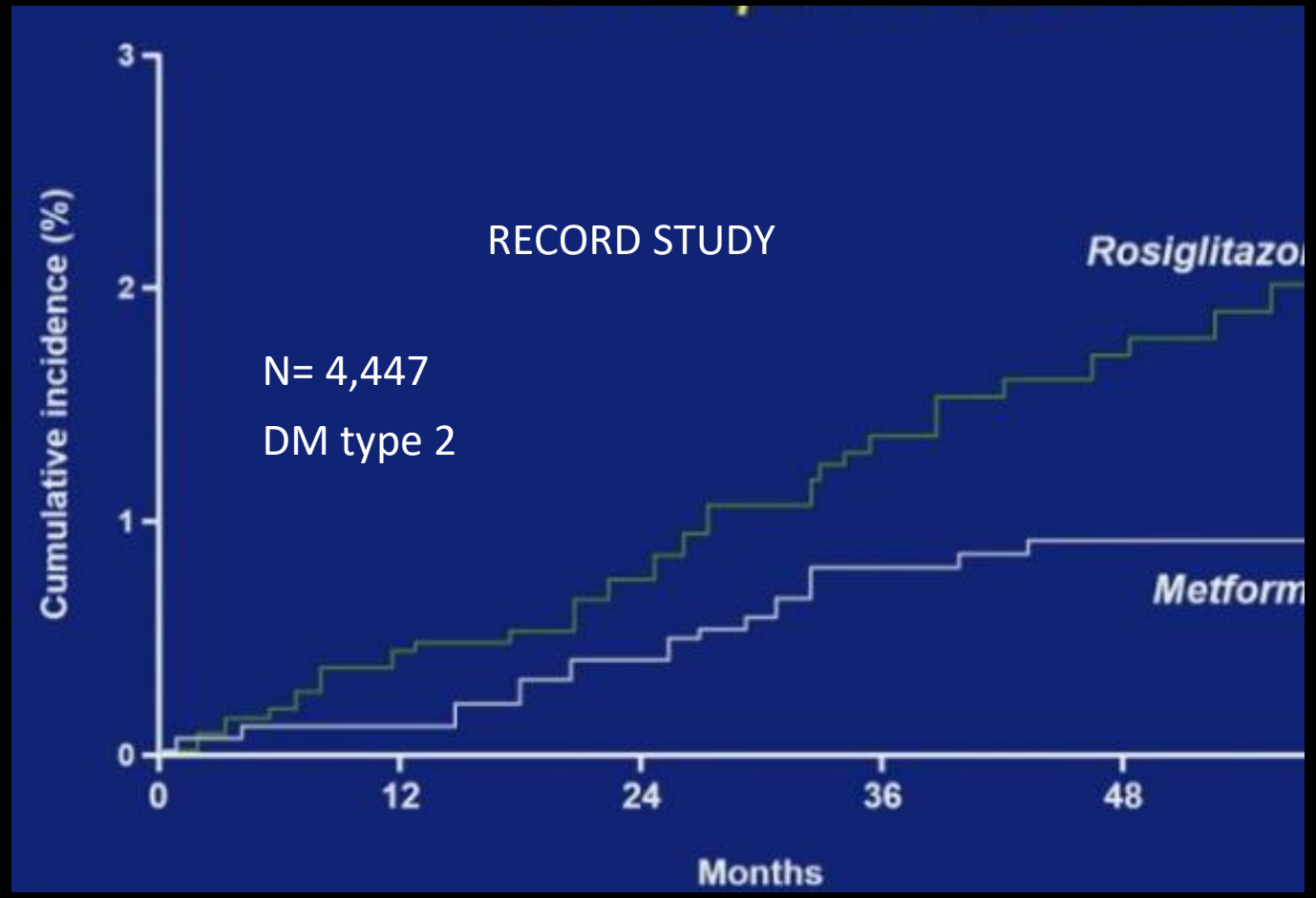
- In a large (n 30,000), propensity-matched observational study, initiation of metformin was associated with lower risk of HF hospitalization than sulfonylurea drugs (Roumey et al 2017)
- It is *reasonable* to use metformin in patients with DM at risk of or with established HF
- Metformin should be discontinued in patients presenting with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock

DM drugs and HF clinical considerations

- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

Rosiglatazone and HF

TZDs are not recommended in patients with established HF and may increase the risk of HF events in individuals with DM without HF



Home PD et al. Lancet 2009; 2125-35 373

DM drugs and HF clinical considerations

- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

Insulin

- The only RCT to specifically assess the cardiovascular safety of insulin was the ORIGIN N= 12 537 to insulin glargine or standard care and found no difference in any cardiovascular outcomes, including hospitalization for HF
- In contrast, observational studies suggested an increase in HF with insulin therapy.
- Insulin is sometimes required to achieve adequate glycemic control in individuals with DM and HF. Insulin use is associated with weight gain and risk of hypoglycemia and should be used with caution
- Metformin and SGLT-2 inhibitors, are preferred if adequate glycemic control can be achieved without insulin

Sulfonylureas

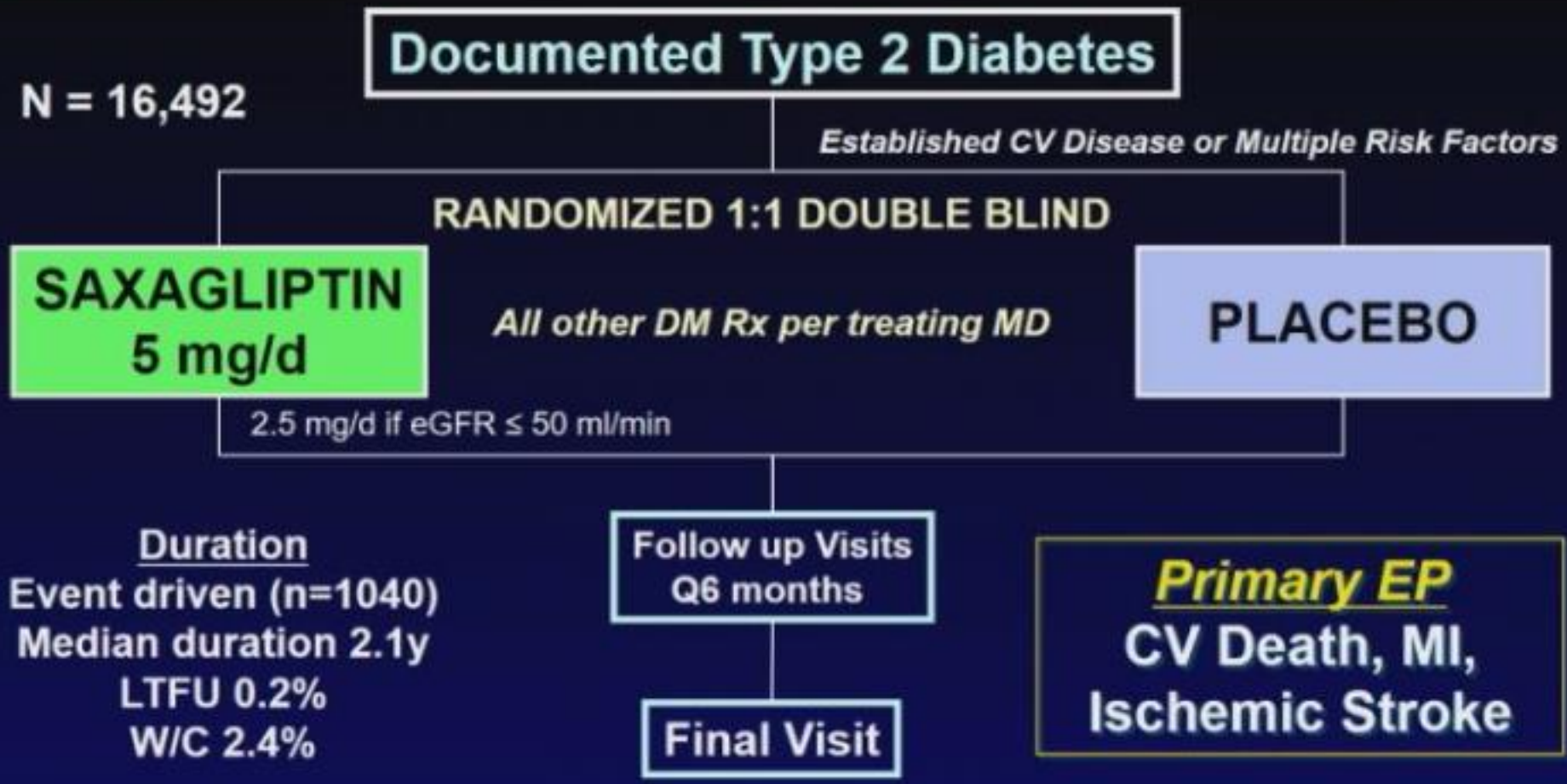
- CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) - No inferiority MACE no data for HF
- In observational studies of patients with DM and HF, sulfonylurea therapy was associated with greater risk of death than metformin
- Use of other agents, such as metformin and SGLT-2 (sodium glucose cotransporter type 2) inhibitors (see SGLT2 Inhibitors), is preferable to use of sulfonylurea drugs in patients at high risk for HF and those with established HF

DM drugs and HF clinical considerations

- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM - TIMI 53

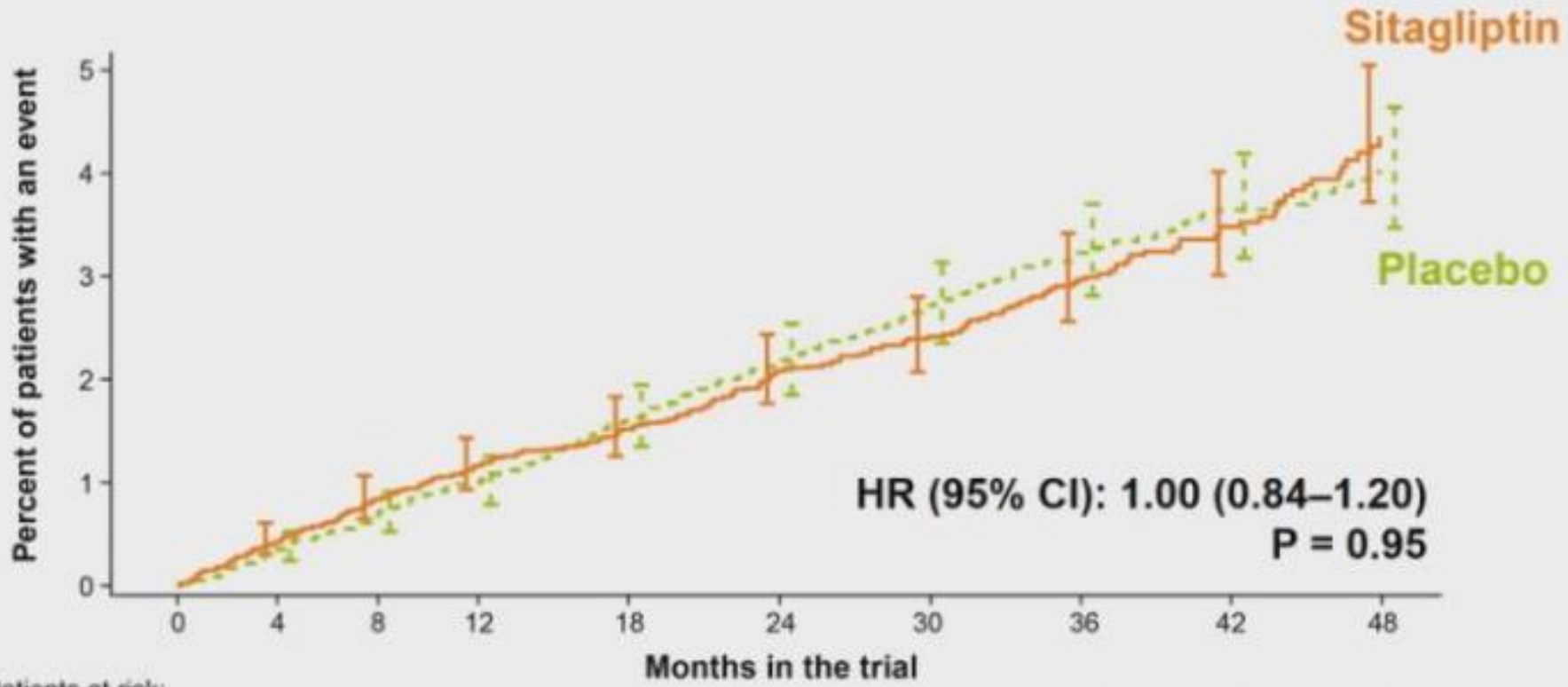
savor TIMI 53



Major Secondary EP: CV death, MI, ischemic stroke, or hosp. for heart failure, unstable angina, or coronary revascularization

Scirica BM et al. *N Engl J Med* 2013; 369:1317-1326

Time to First Hospitalization for Heart Failure*

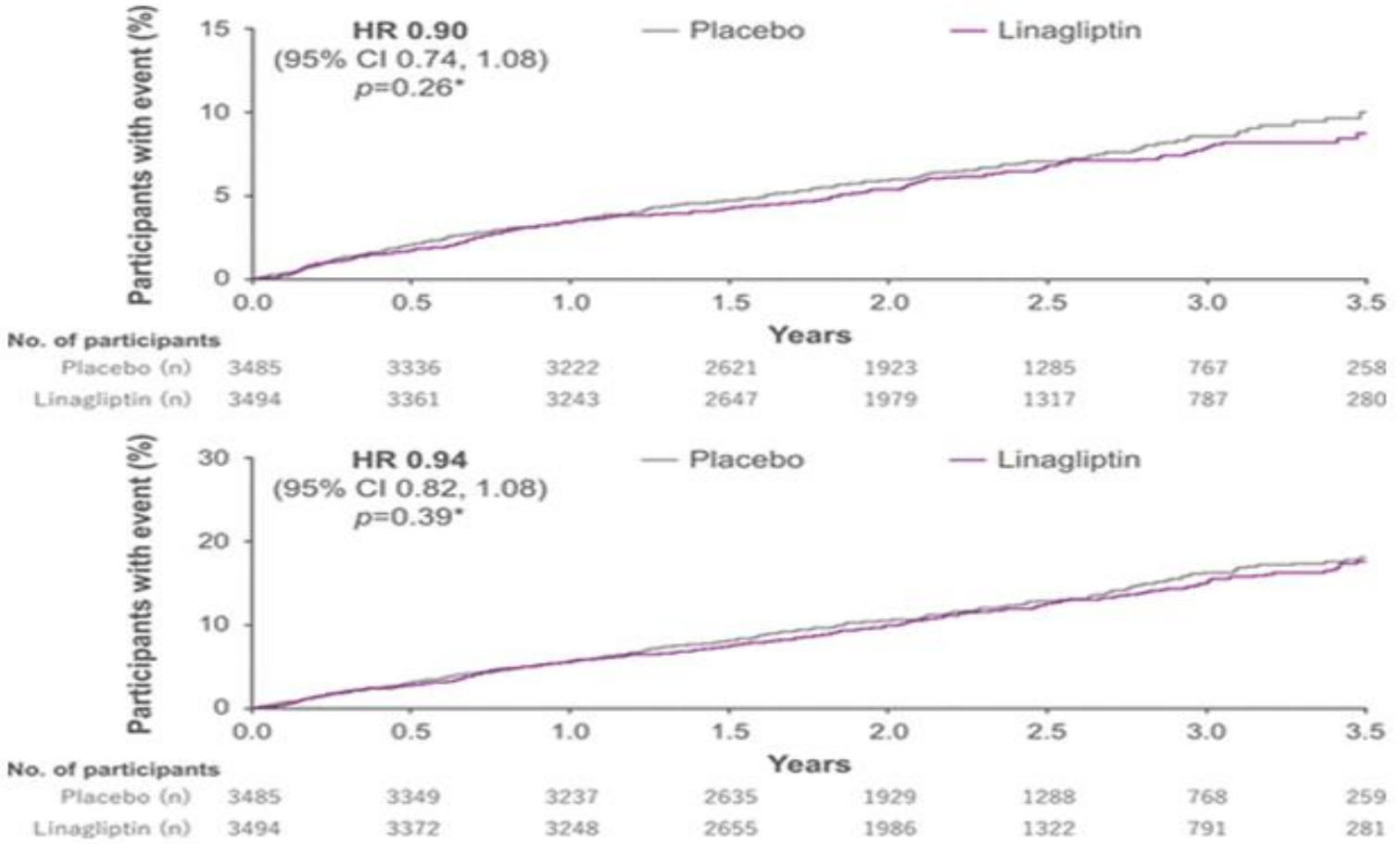


Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

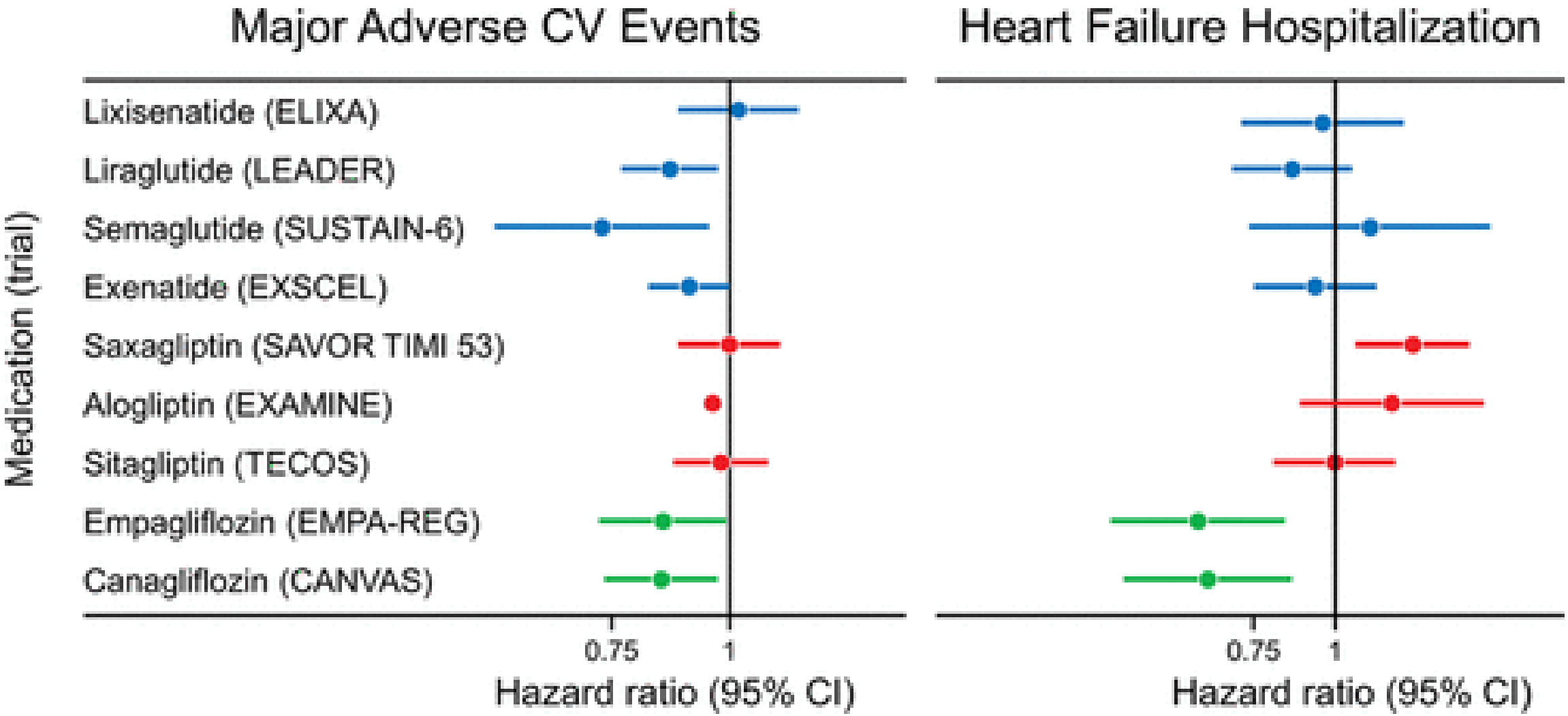
** ITT population*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Linagliptin Effects on HF (CARMELINA)



Darren K. McGuire. Circulation. Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA



Shannon M. Dunlay. Circulation. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update, Volume: 140, Issue: 7, Pages: e294-e324

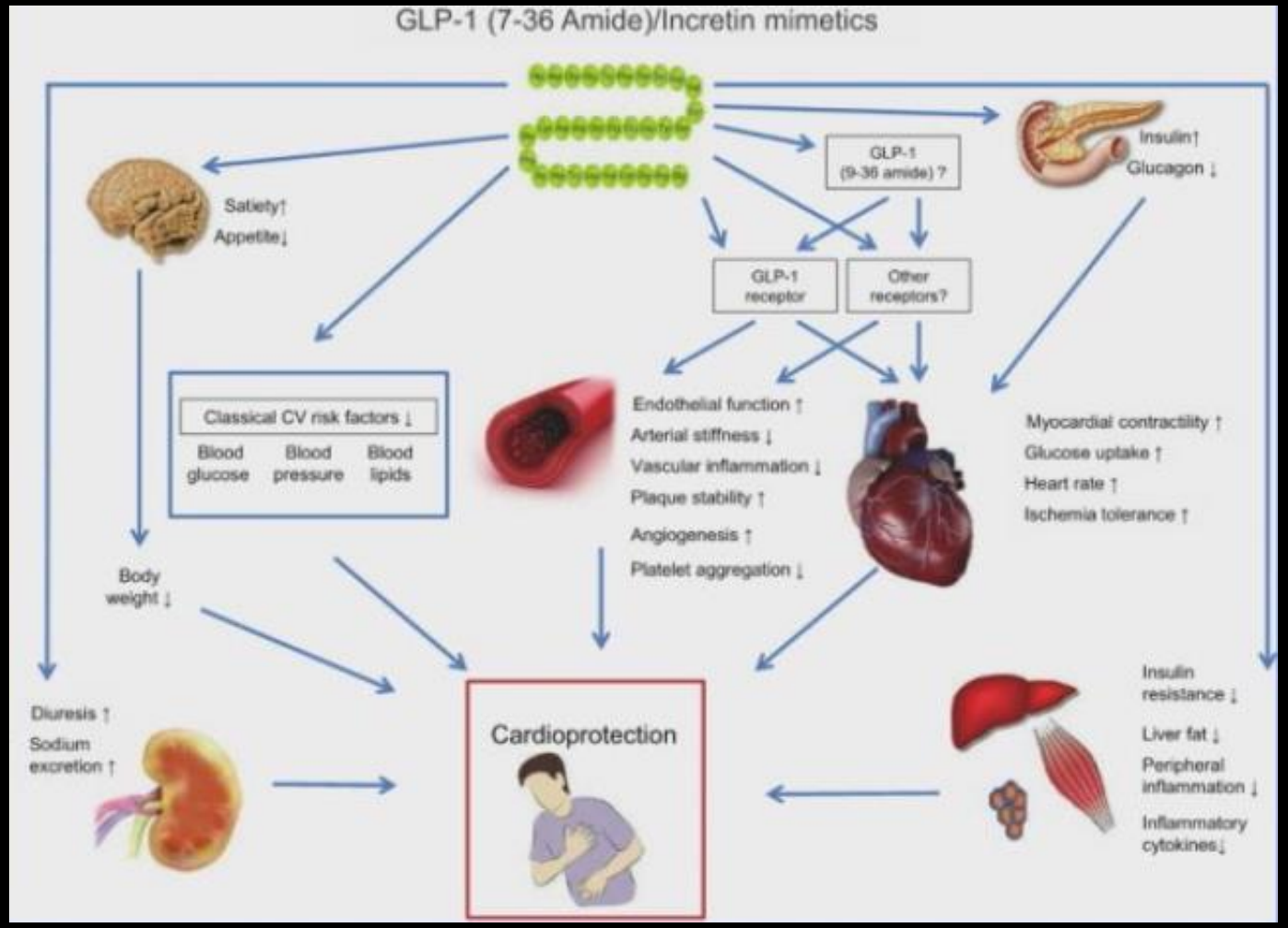
Drug Safety Communications

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin

DM drugs and HF clinical considerations

- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

Potential Mechanisms of CV Benefit with GLP-1 Agonists



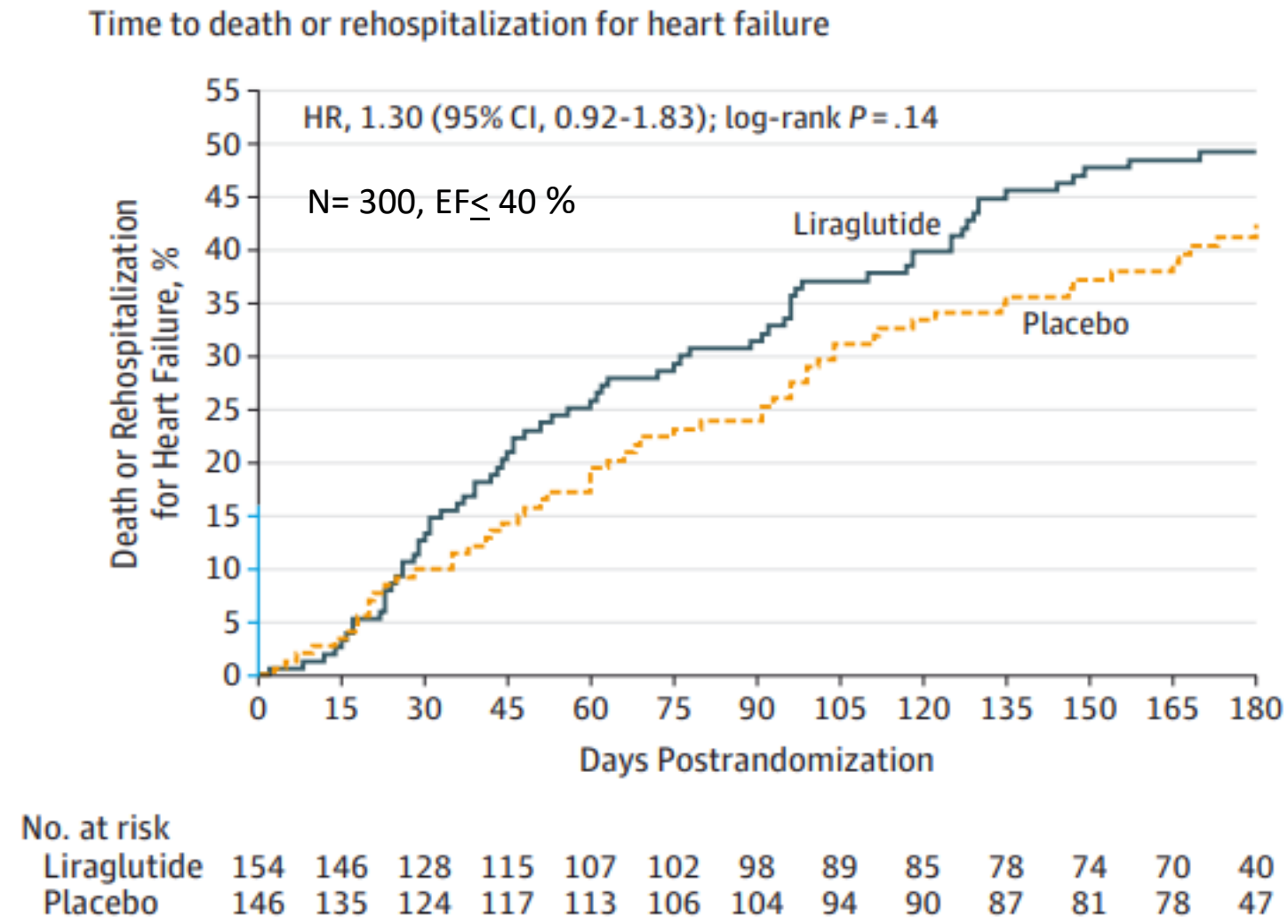
Circulation. 2017 Aug 29;136(9):849-870

Impact of GLP-1 Agonists on Cardiovascular End Points in Cardiovascular Outcomes Trials

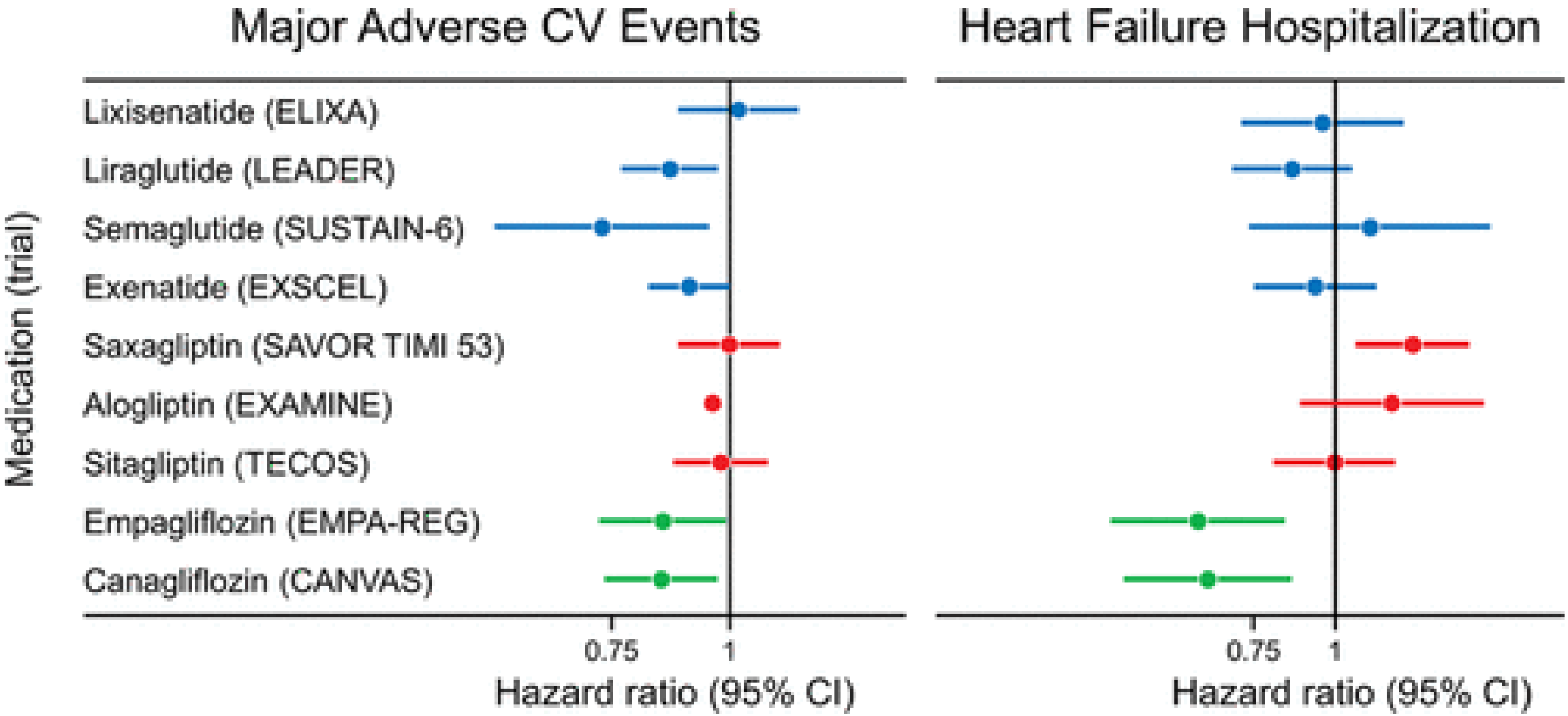
MedicationTrial (Year)	Population	N	% HF	Median Follow-Up, y	Primary Outcome	Impact on Primary Cardiovascular End Point	Impact on HF Hospitalization
Lixisenatide - ELIXA (2015)[93]	Recent ACS	6068	22	2.1	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 1.02 [95% CI, 0.89–1.17])	No difference in risk (HR, 0.96 [95% CI, 0.75–1.23])
Liraglutide - LEADER (2016)[91]	CVD or high risk	9340	14	3.8	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.87 [95% CI, 0.78–0.97])	No difference in risk (HR, 0.87 [95% CI, 0.73–1.05])
Semaglutide - SUSTAIN-6 (2017)[92]	CVD or high risk	3297	24	2.1	Cardiovascular death, MI stroke	Decreased risk (HR, 0.74 [95% CI, 0.58–0.95])	No difference in risk (HR, 1.11 [95% CI, 0.77–1.61])
Exenatide - EXSCEL (2017)[109]	+/− CVD	14 752	16	3.2	Cardiovascular death, MI, stroke	No significant difference* (HR, 0.91 [95% CI, 0.83–1.00])	No difference in risk (HR, 0.94 [95% CI, 0.78–1.13])

Circulation 2019 Aug 13;140(7):e294-e324

Effects of Liraglutide on Clinical Stability Among Patients With Advanced HF and Reduced EF



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

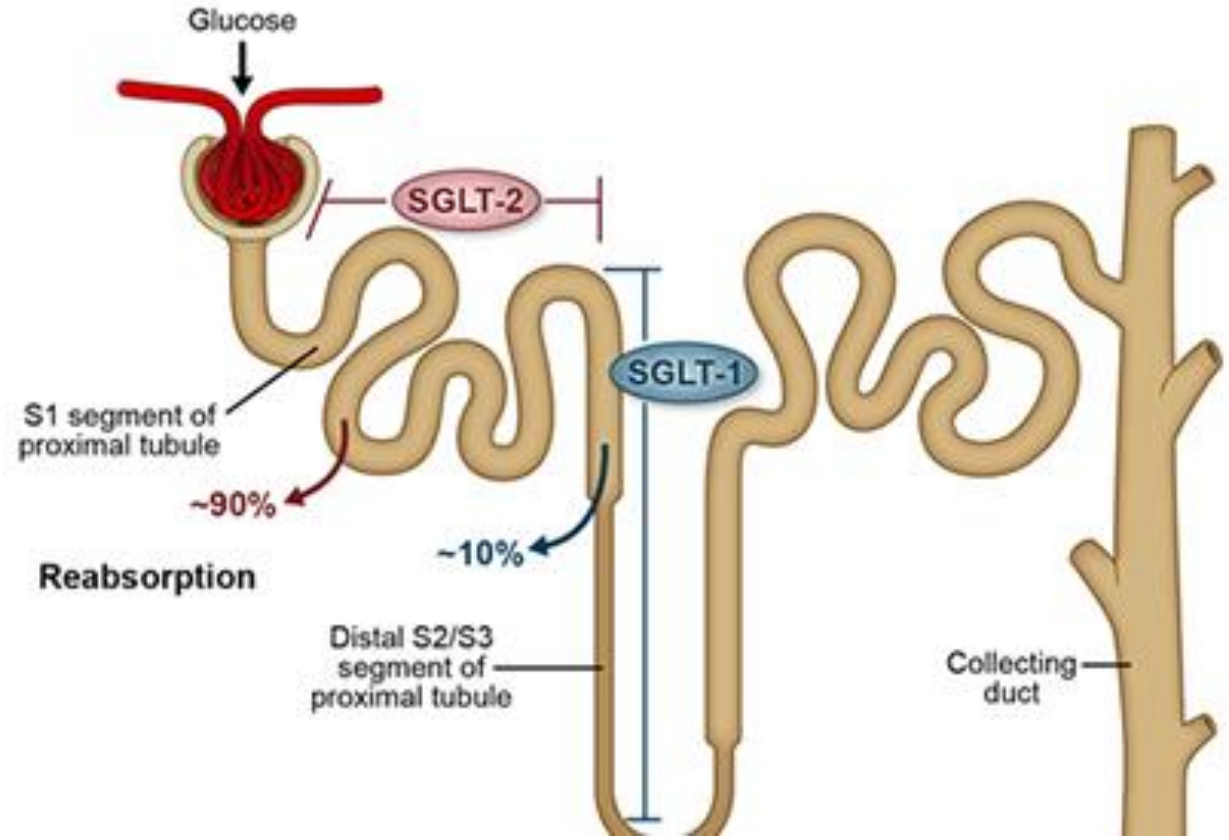


Shannon M. Dunlay. Circulation. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update, Volume: 140, Issue: 7, Pages: e294-e324

DM drugs and HF clinical considerations

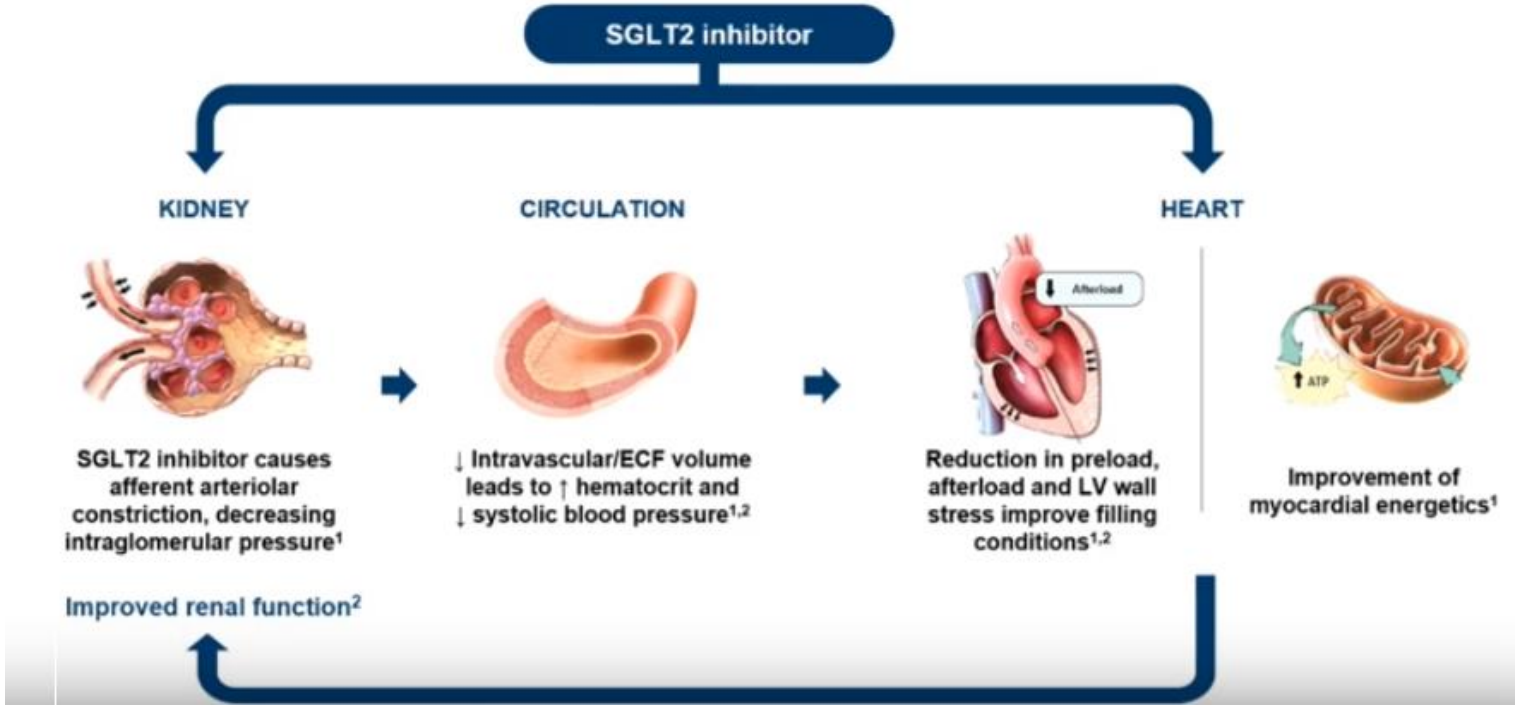
- Metformin
- Thiazolidinedione (TZD)
- Insulin and sulfonylureas
- DPP-IV Inhibitors
- GLP-1 agonist
- SGLT2 Inhibitors

SGLT 2 Inhibitors



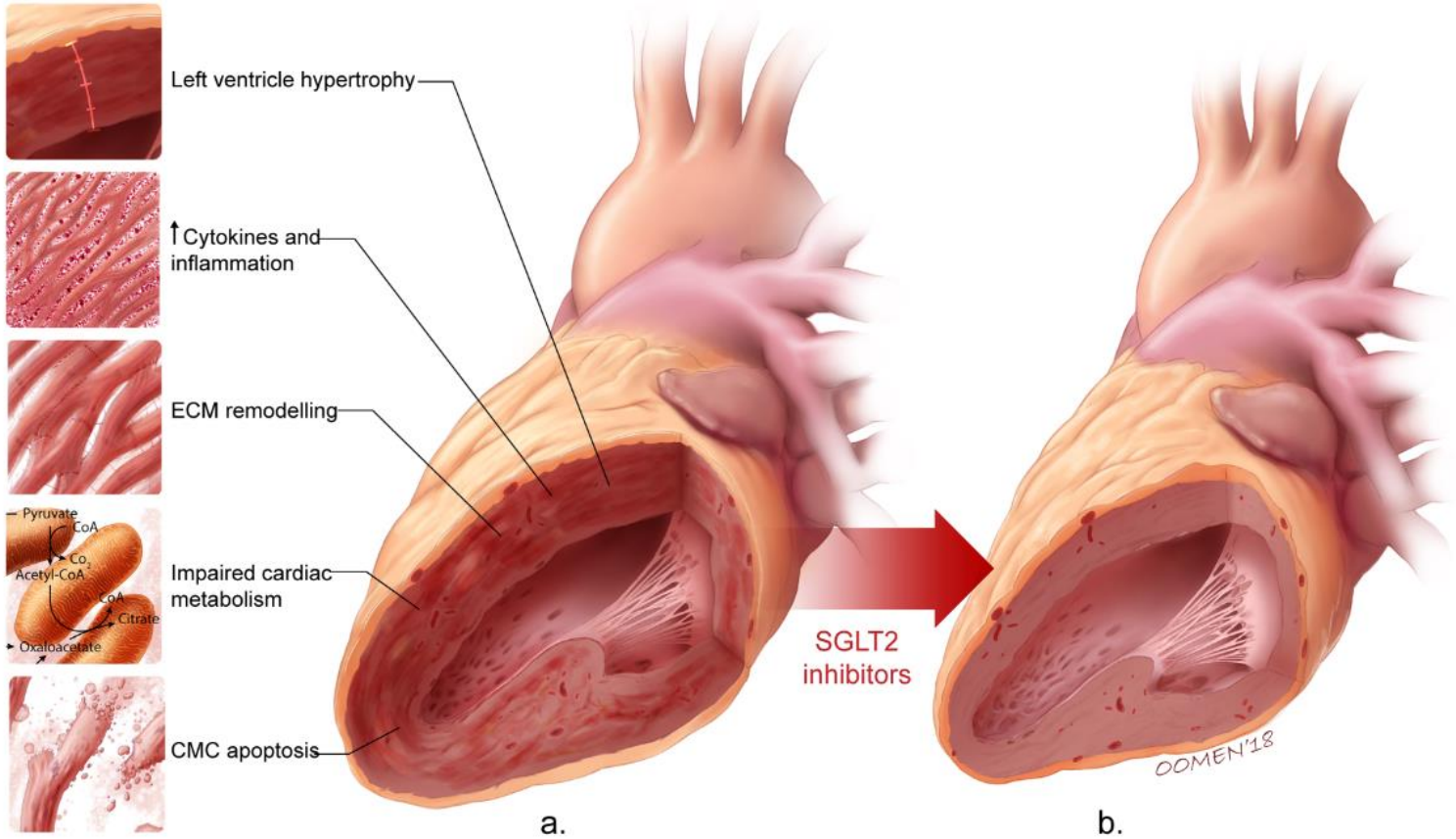
Wright , EM. Am J Physiol Renal Physiol. 2001;280 F 10

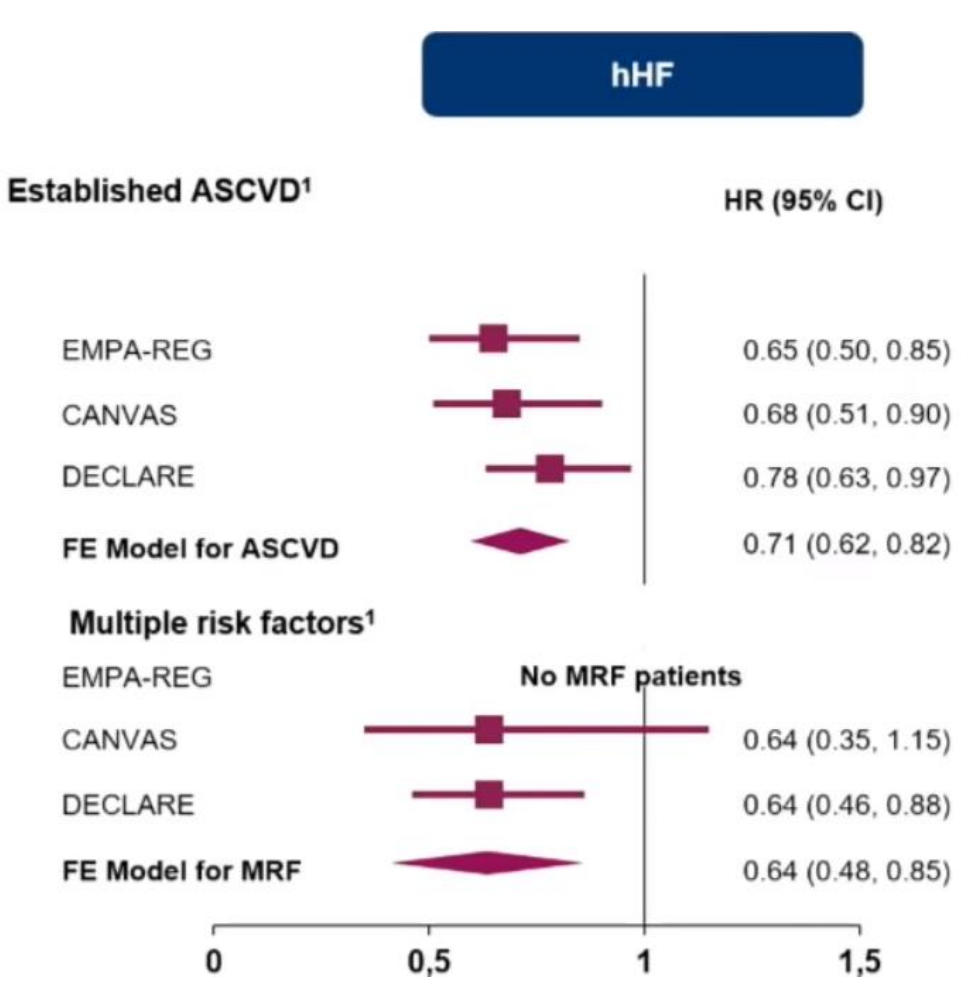
SGLT 2 Inhibitors

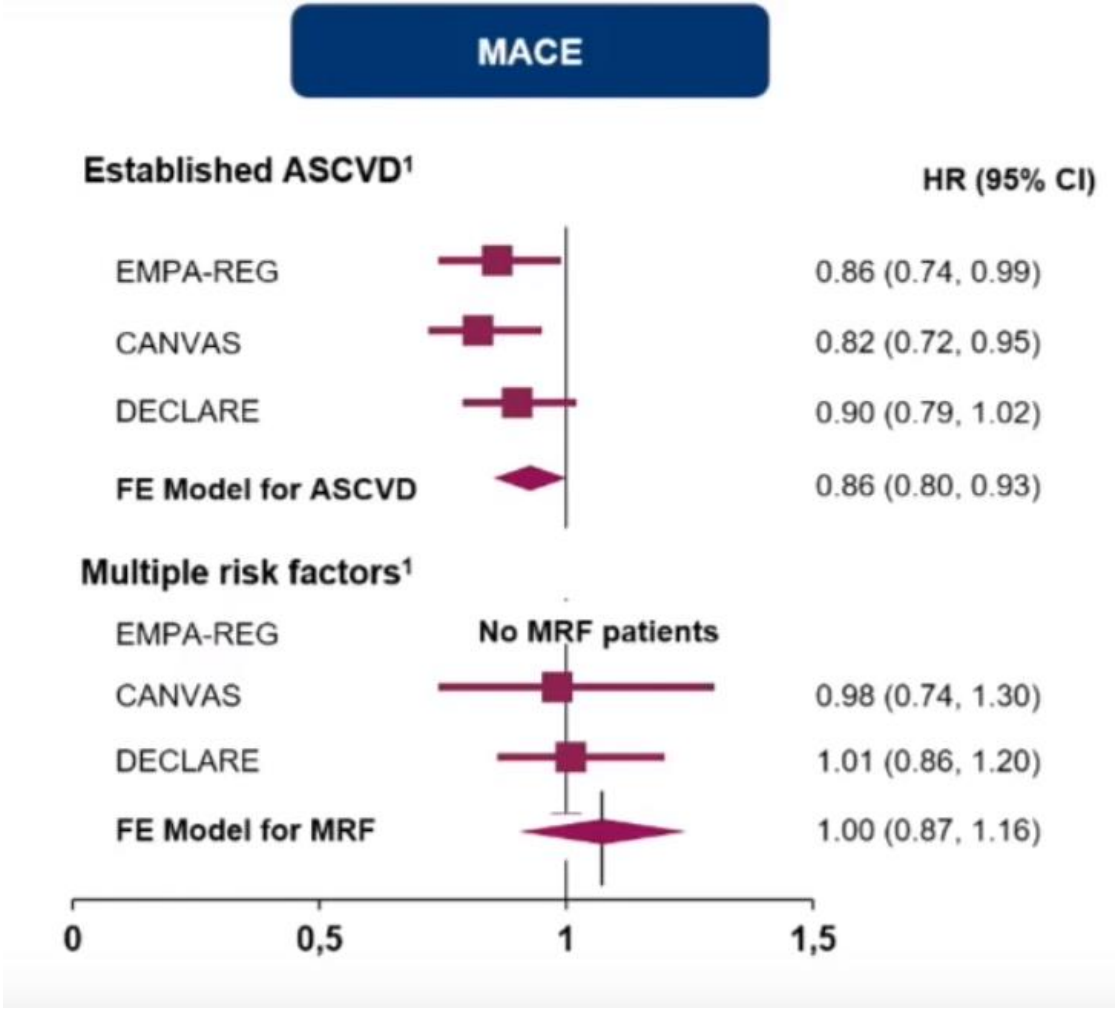


Verma S et al JAMA Cardiology. 2017;2: 939-940

SGLT 2 Inhibitors

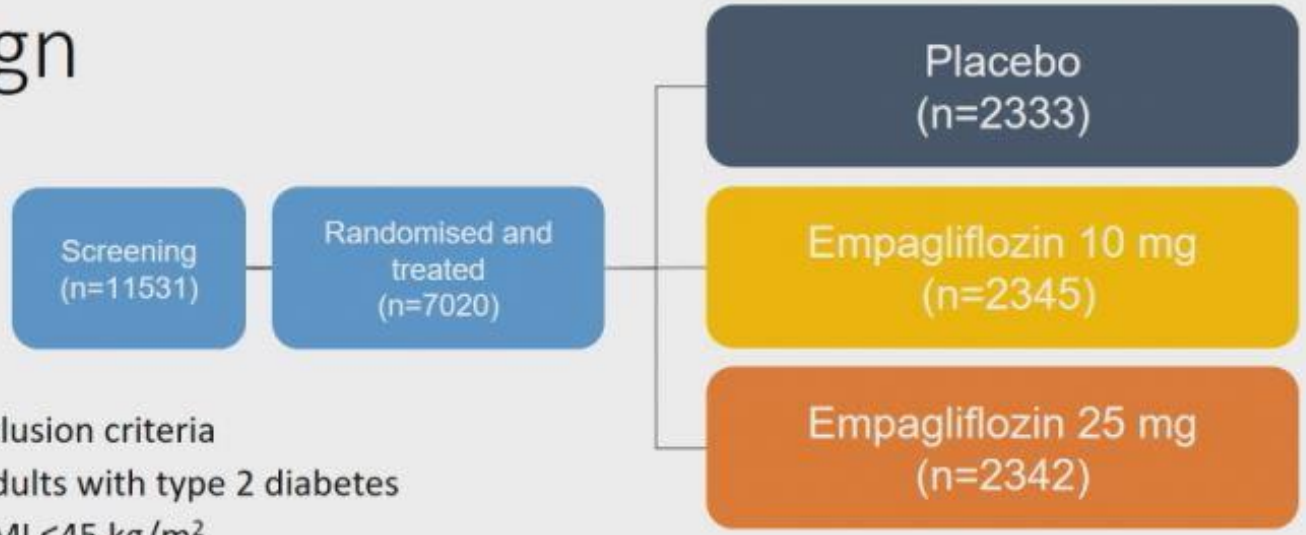






Zelniker ET AL. Lancet.2019; 393: 31-39

Trial design

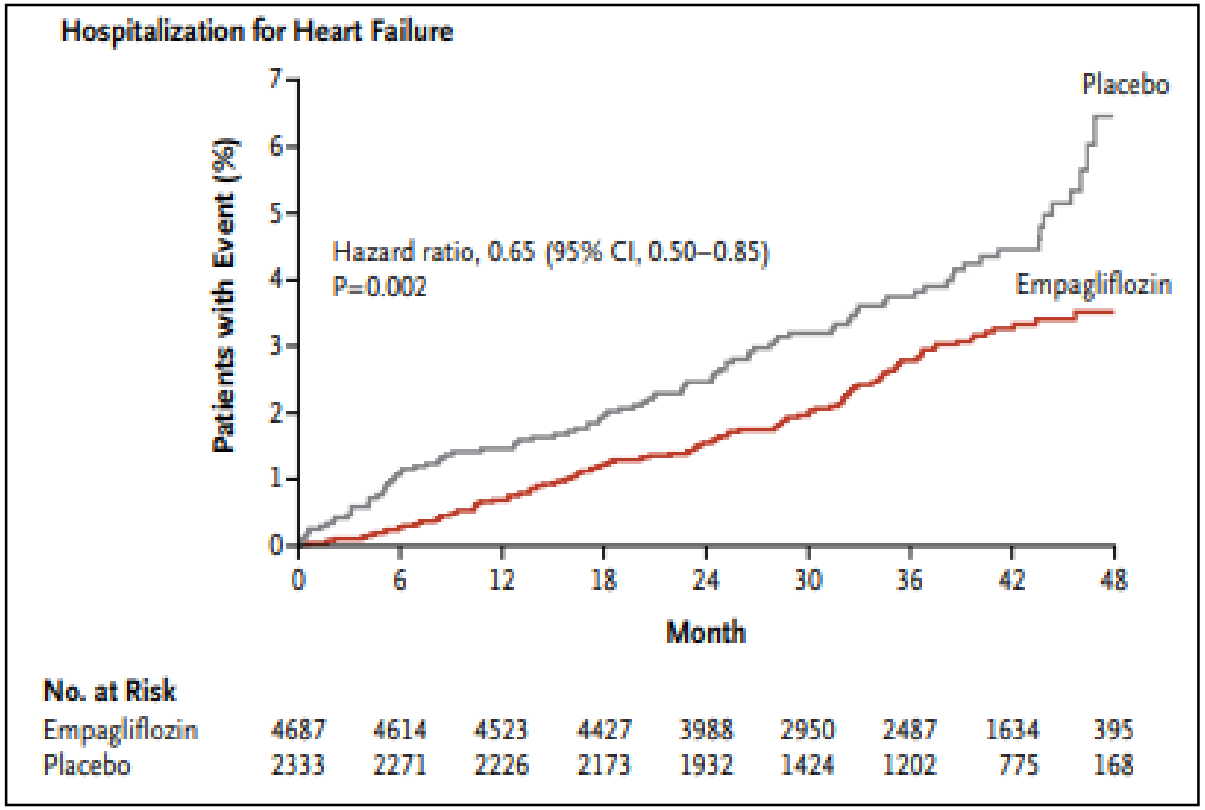


- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m²
  - HbA1c 7–10%*
  - Established cardiovascular disease
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Event driven trial

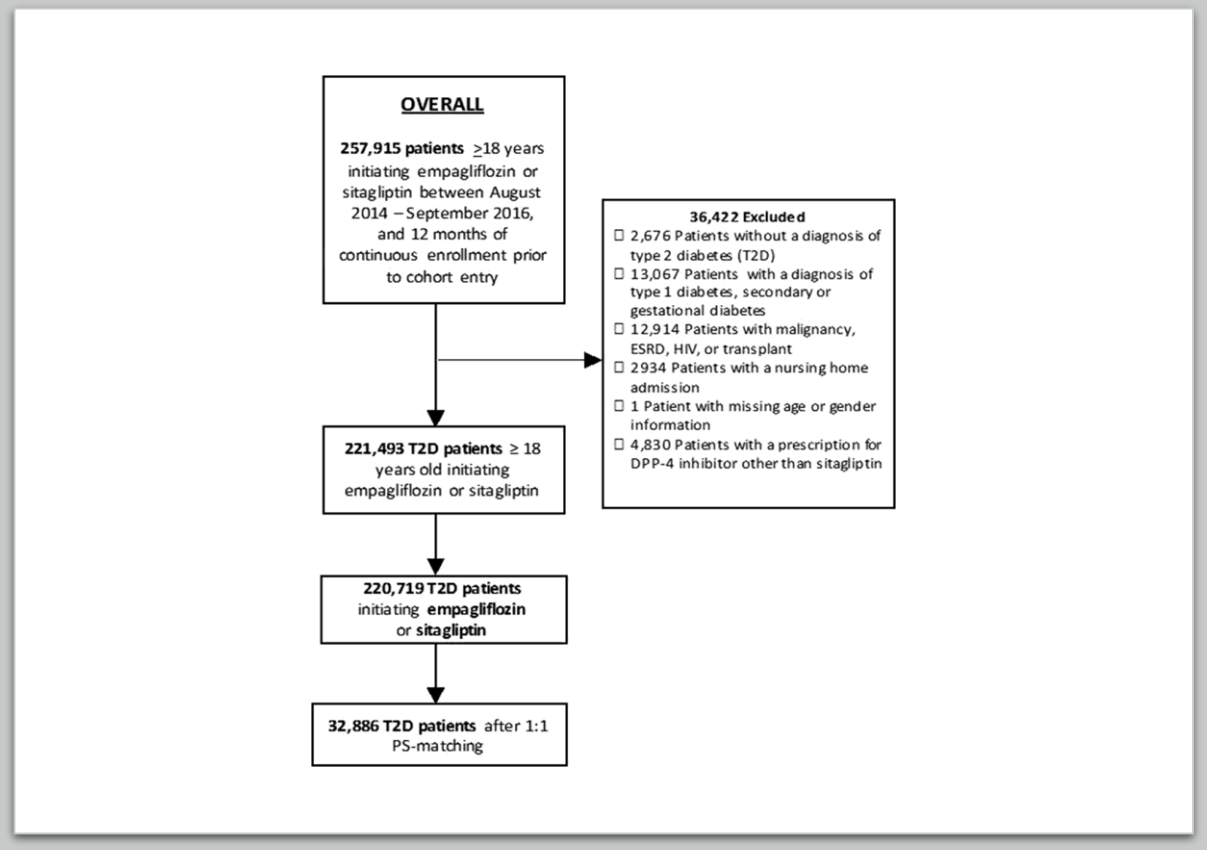
EMPA-REG OUTCOME®

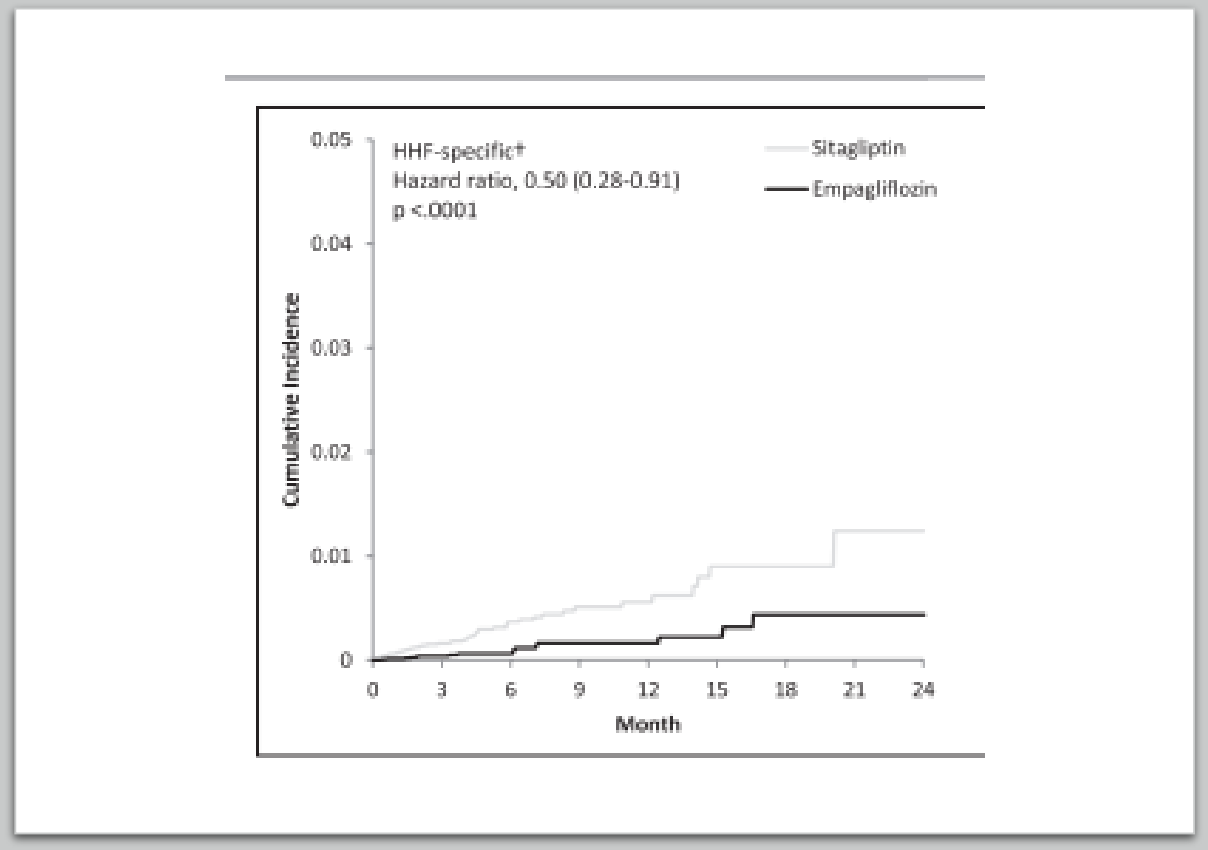
Hospitalization for Heart Failure EMPA-REG OUTCOME trial

- ✓ 35% reduction in HF hospitalizations, an effect that was observed within weeks of randomization
- ✓ 10% of patients had HF at baseline
- ✓ 14% relative decrease in the risk of major cardiovascular events
- ✓ 38% reduction in cardiovascular death



Zinman et al, N Engl J Med 2015; 373:2117-2128



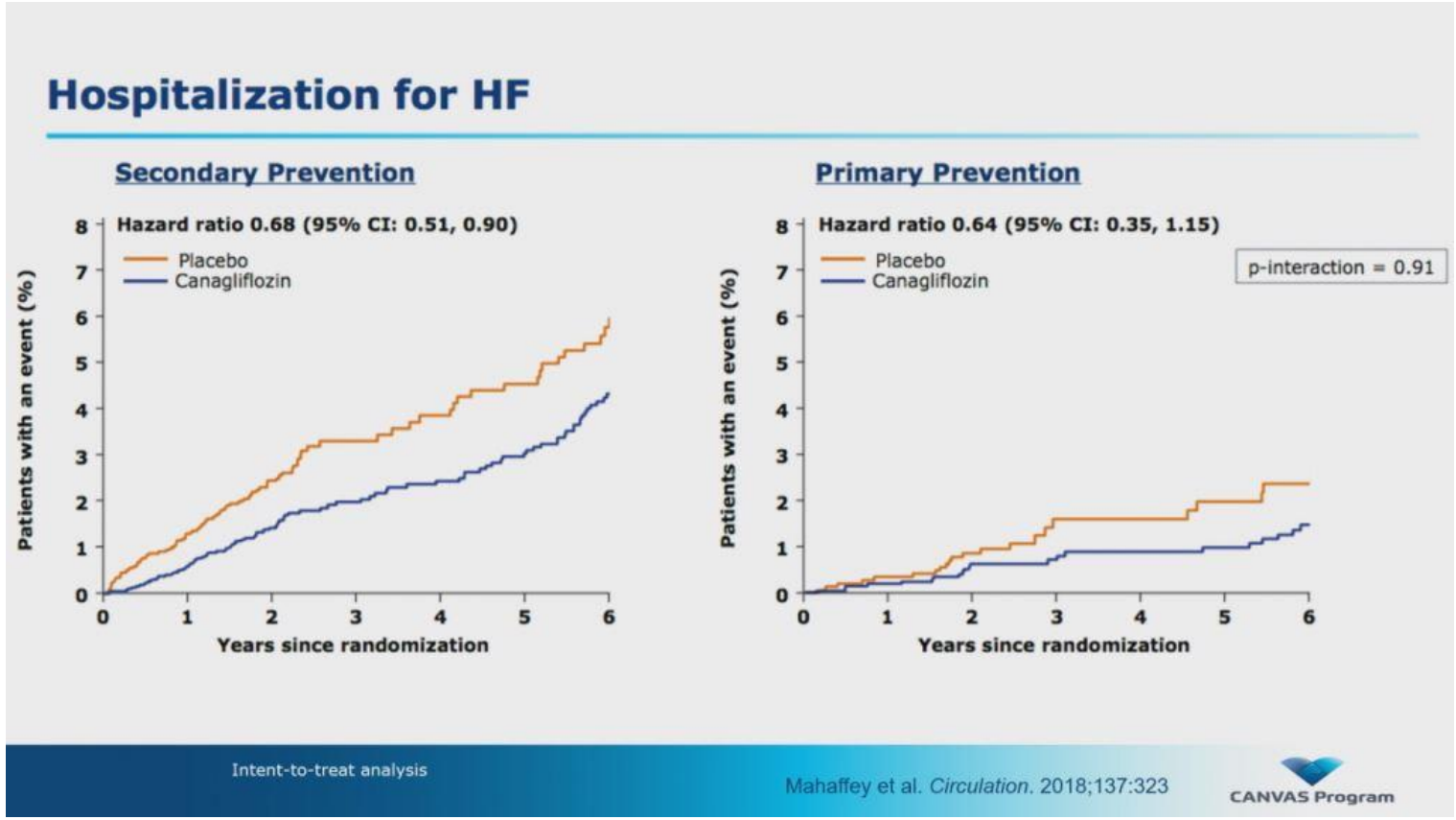


A First Analysis From the EMPRISE Study

Elisabetta Patorno. Circulation. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care,

Volume: 139, Issue: 25, Pages: 2822-2830, DOI: (10.1161/CIRCULATIONAHA.118.039177)

CANVAS TRIAL



14 % reduction in the risk of major cardiovascular events and a 33% relative reduction in the risk of HF hospitalization

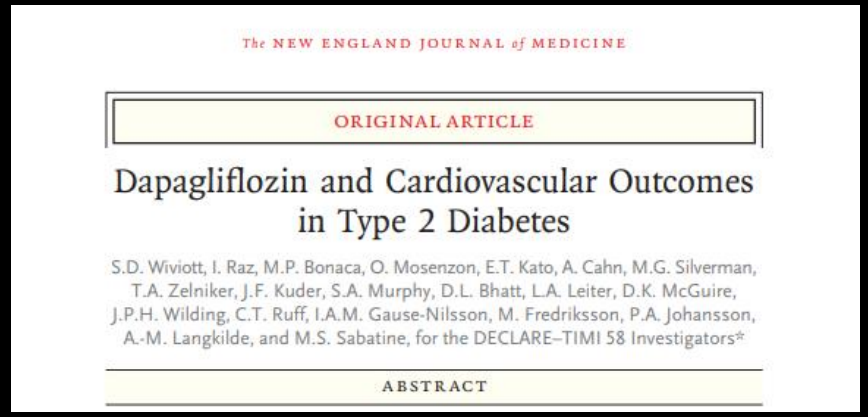
CREDENCE CLINICAL TRIAL
N = 4,401

- On September 30, the FDA granted Invokana® (canagliflozin) an indication to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure nephropathy with albuminuria >300 mg/d adults with T2DM
- Canagliflozin 100 mg a day with placebo
- Adults ≥30 years of age with T2DM and chronic kidney disease—defined by an GFR of 30 to <90 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio <300 to 5,000 mg/g—who were receiving a stable dose of an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker
- 30% Primary Endpoint, 39% Hospitalizations for Heart Failure

DECLARE

- Multiple CV RF N = 10,186
- Established CV = 6,974
- CD and HFH 27 % RR reduction

New England Journal of Medicine 2019
January 24; 380 (4): 347-357



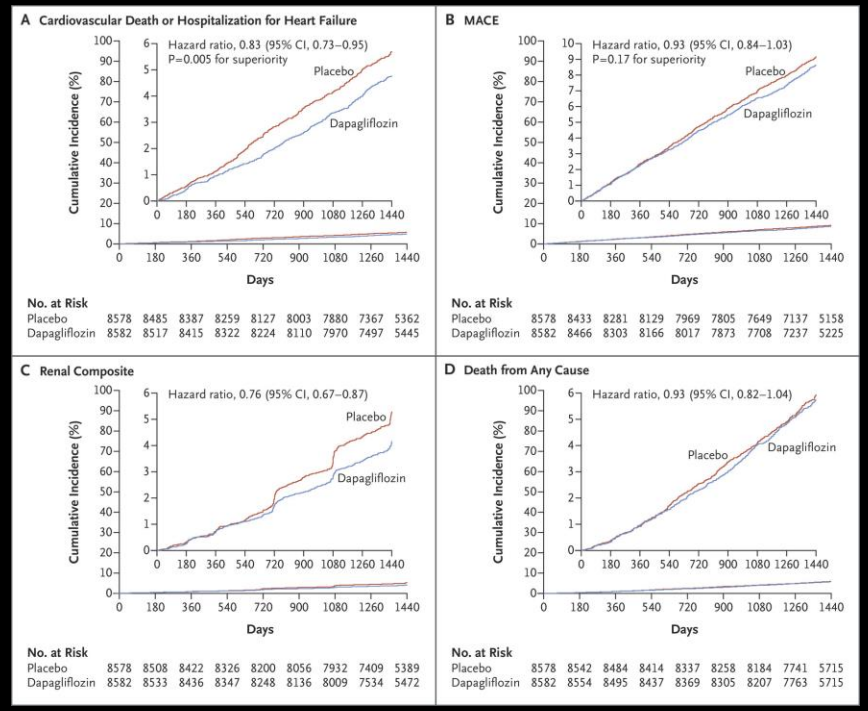
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

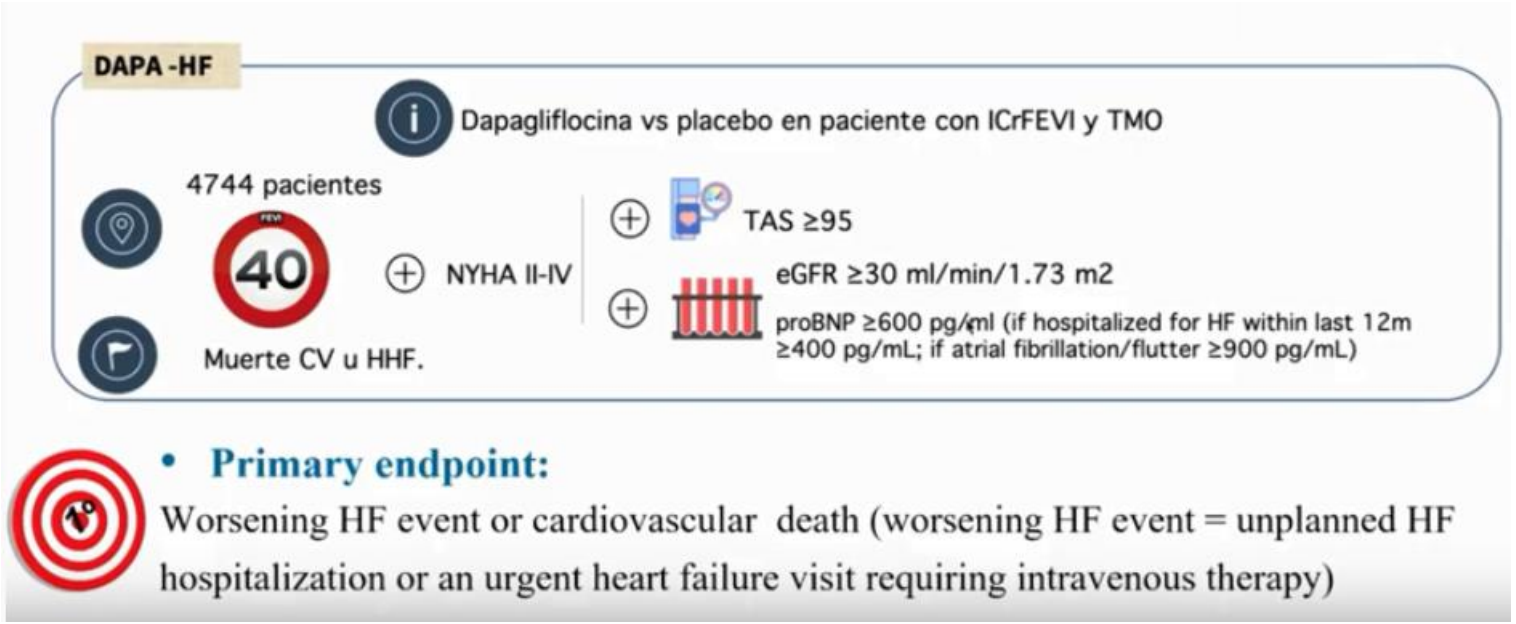
ABSTRACT



DECLARE

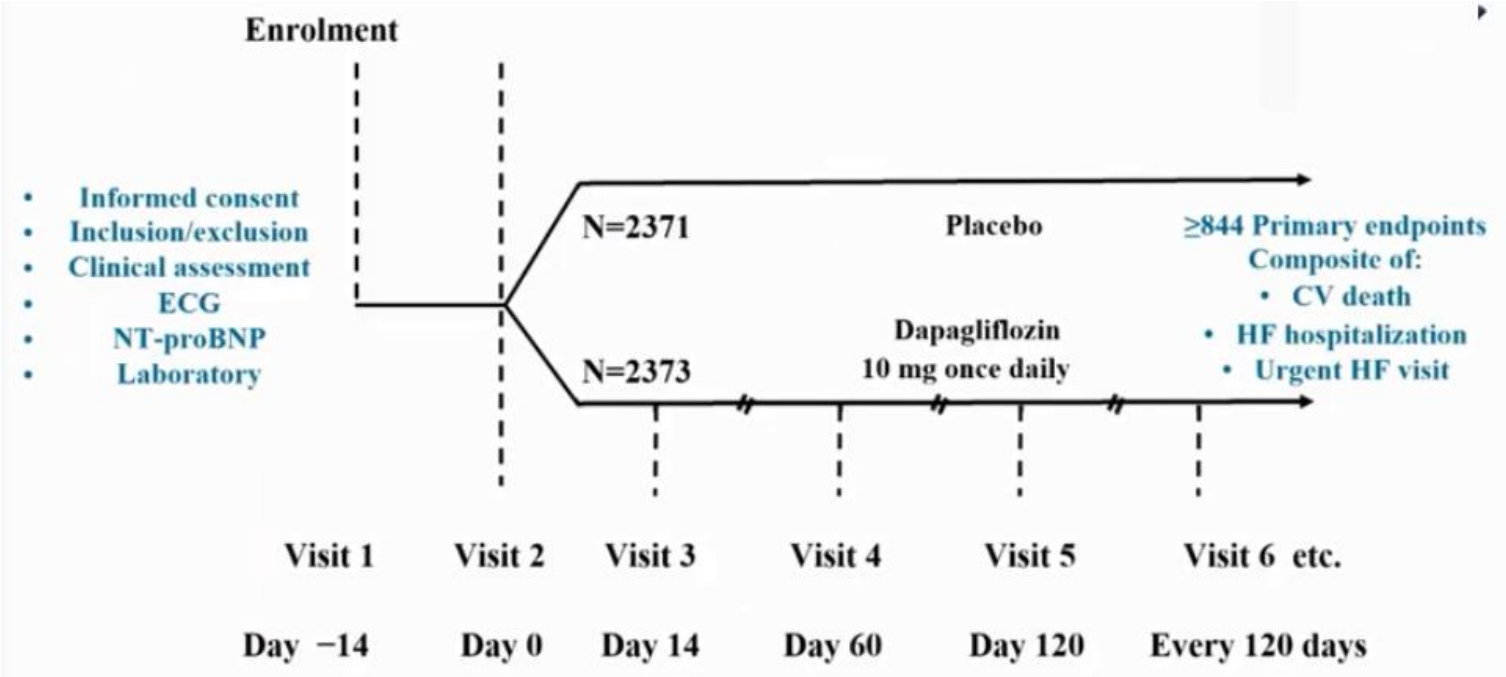
- October 21, 2019 – The U.S. Food and Drug Administration (FDA) has granted market clearance for AstraZeneca's dapagliflozin)to reduce the risk of hospitalization for heart failure (HF) in adults with type 2 diabetes (T2D) and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

DAPA HF



Mc Murrray Presentation ESC 2019

DAPA HF



Murrray Presentation ESC 2019.

DAPA HF

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

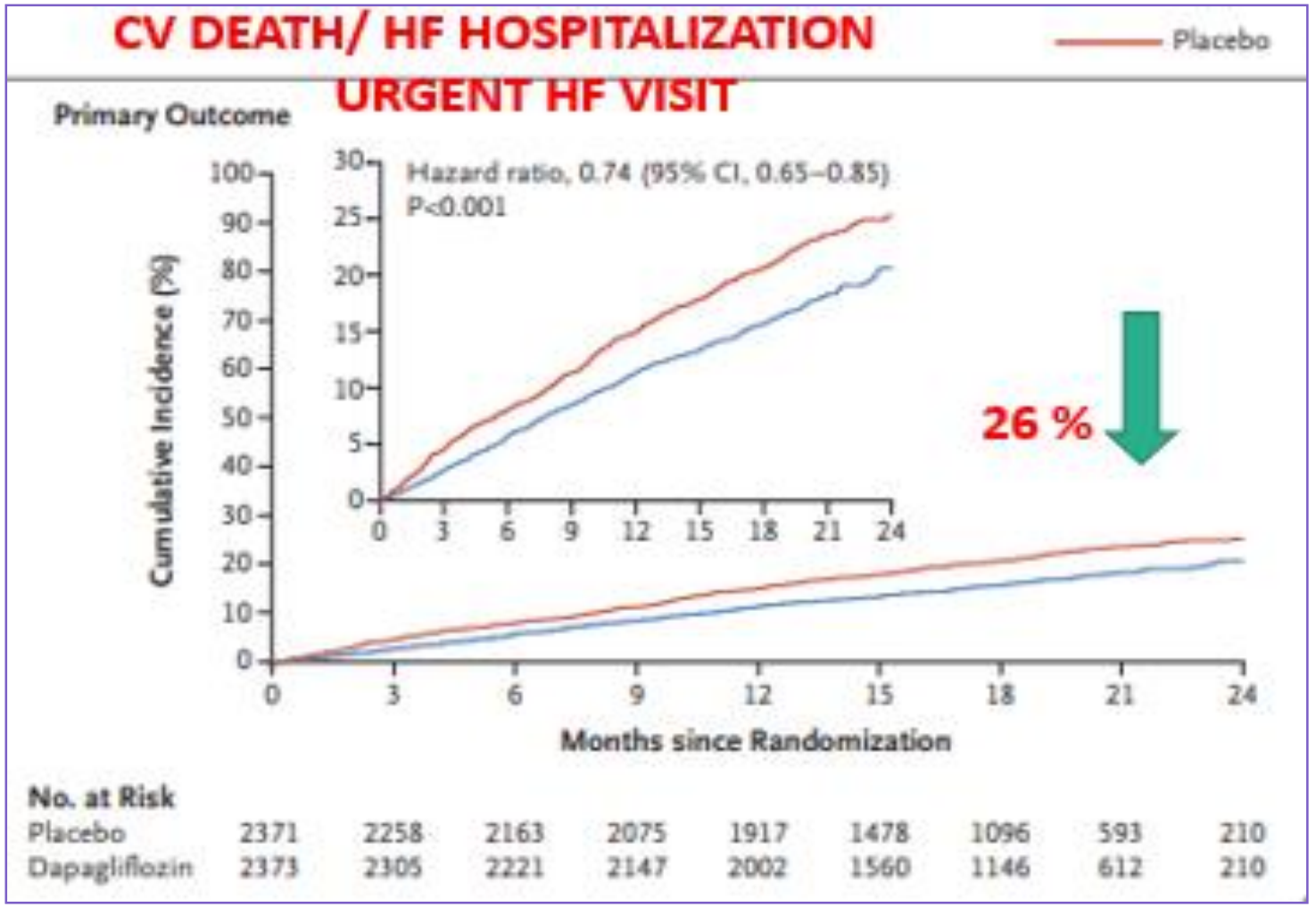
Mc Murrray Presentation ESC 2019.

DAPA HF

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI+	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

Mc Murrray Presentation ESC 2019.

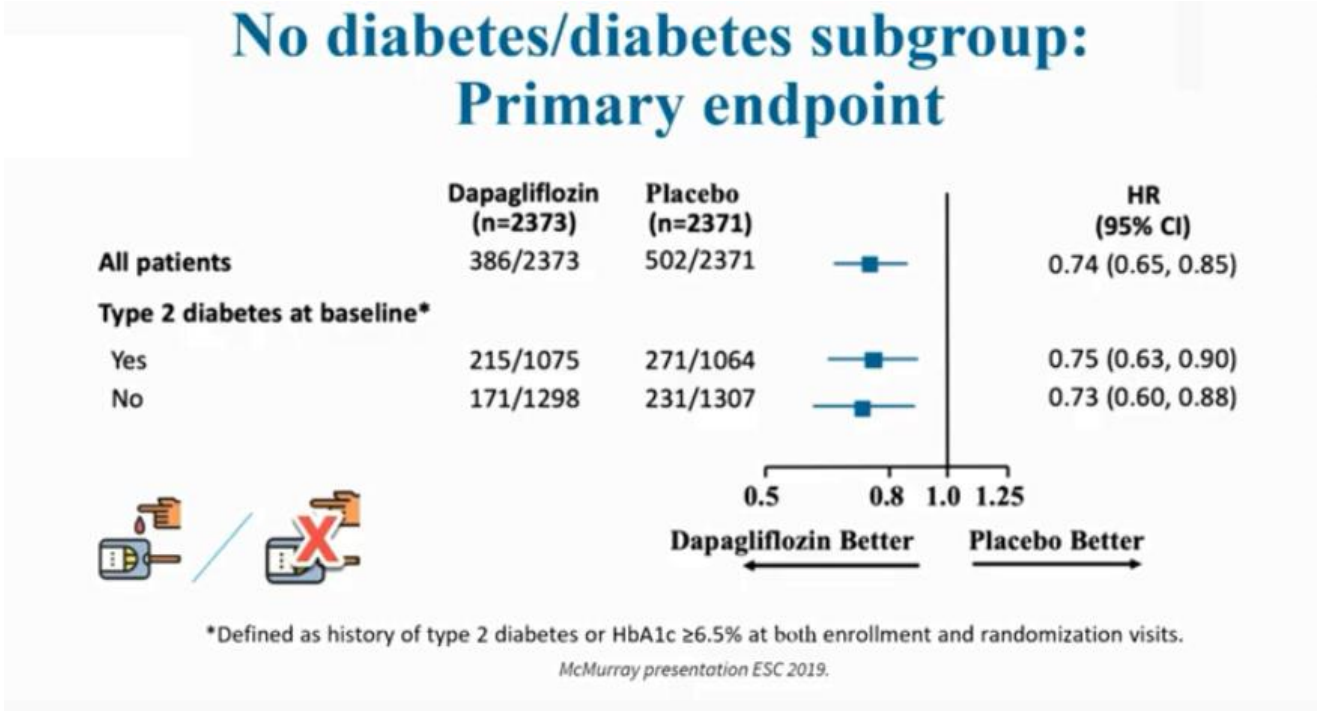
DAPA HF



Murrray Presentation ESC 2019.

DAPA HF

- NNT 21
- Worsening HF 30 % reduction with dapagliflozin
- CD 18 % reduction with dapagliflozin



Mc Murrray Presentation ESC 2019.

DAPA HF

Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion+	7.5	6.8	0.40
Renal AE‡	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

Secondary Points

- Time to the first occurrence of either of the components of the composite: 18 % CV death or 30 % hospitalization for HF.
- Improvement Kansas City cardiomyopathy Questionnaire – Quality of Life
- Decrease time to death from any cause 17 %
- End Point Renal- No difference

The DEFINE-HF Trial September 2019

Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction N = 247

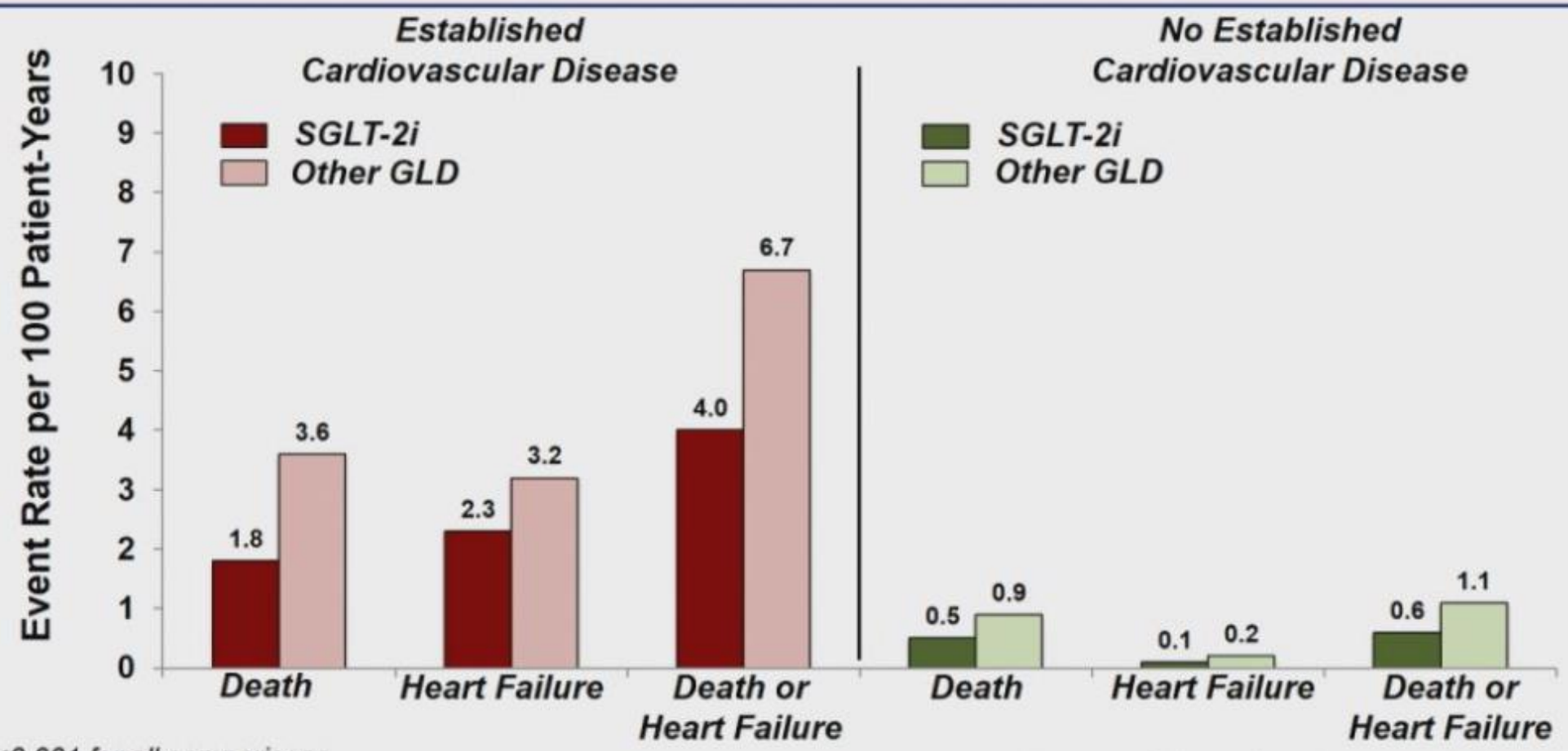
12 weeks did not affect mean NT-proBNP but increased the proportion of patients experiencing clinically meaningful improvements in HF-related health status

Características
Edad ≈ 61 años
FEVI ≈ 27%
CI ≈ 53%
DM2 ≈60%
NYHA III ≈ 33%
NTproBNP ≈1160 pg/ml
ARNI: 30%

Endpoint primario
1. Cambios en NT-proBNP
2. Incrementos en >5 puntos del cuestionario Kansas City o descenso del 20% en NT-proBNP

Absolute Event Rates in Patients Treated With SGLT-2i and Other GLD

CVDREAL



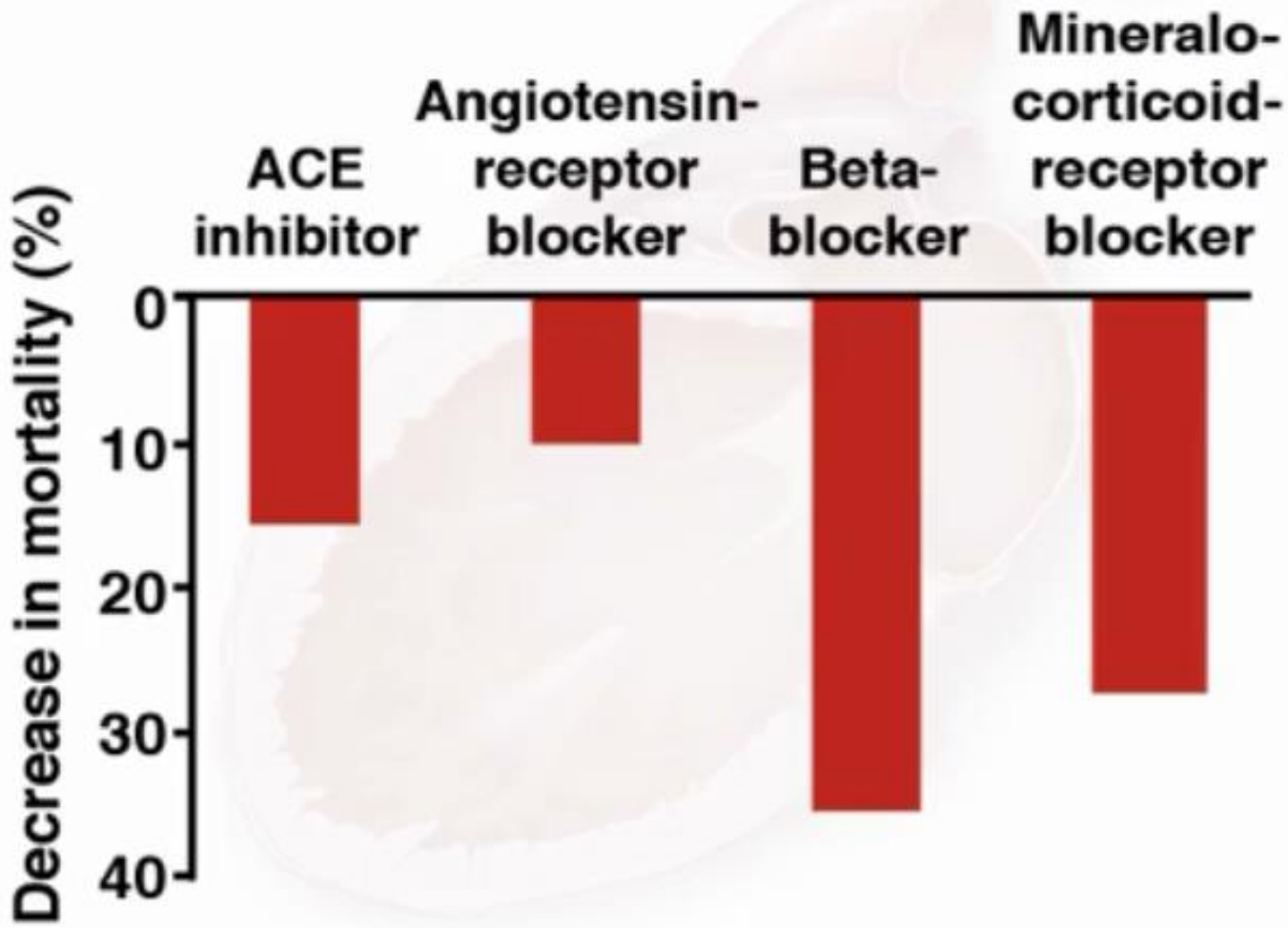
p<0.001 for all comparisons

Cavender MA et al. *J Am Coll Cardiol*. 2018 (In Press)

Objectives

- Review the association between diabetes and heart failure
- Glycemic control and heart failure
- Choice of glucose-lowering pharmacotherapy in patients with DM at high risk for HF or with established HF
- Cardiovascular therapy for the patient with diabetes and heart failure

Guideline-Directed Medical Therapy




The NEW ENGLAND JOURNAL of MEDICINE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

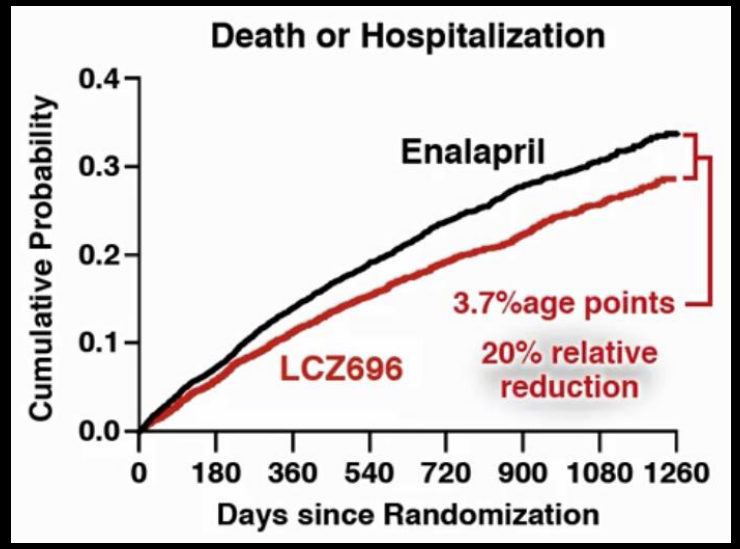
PARADIGM-HF

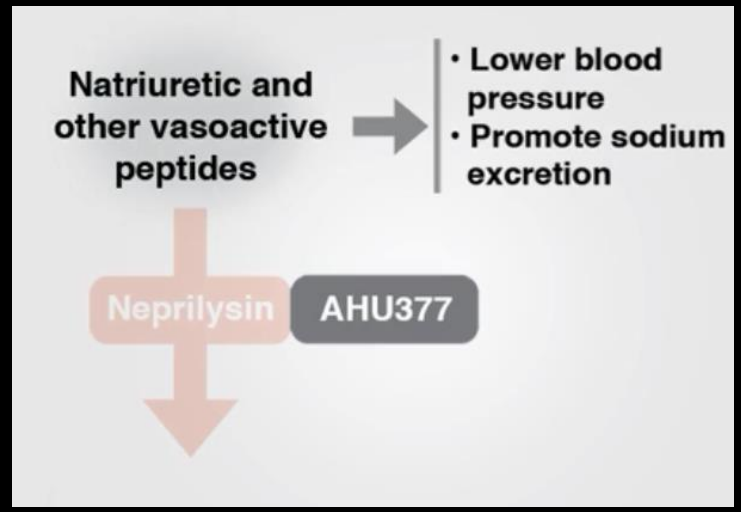
BACKGROUND

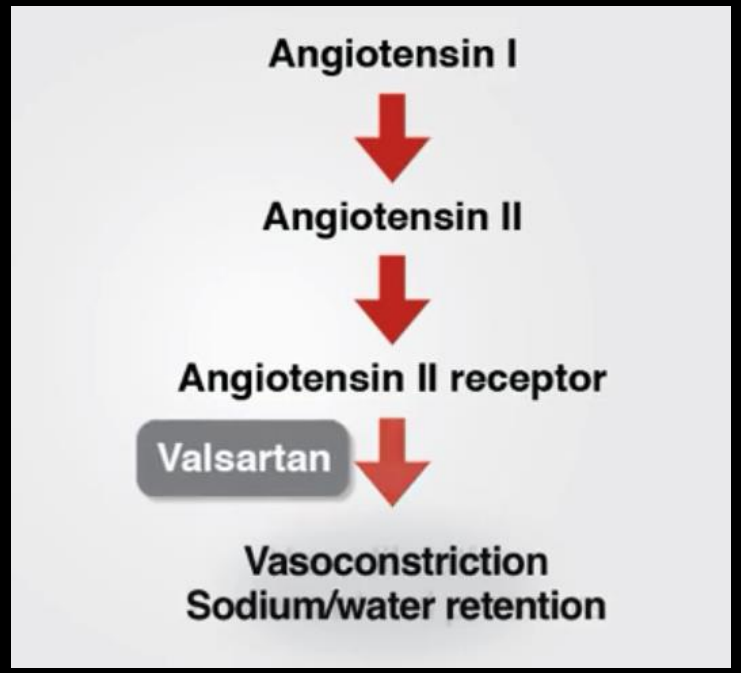
We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or

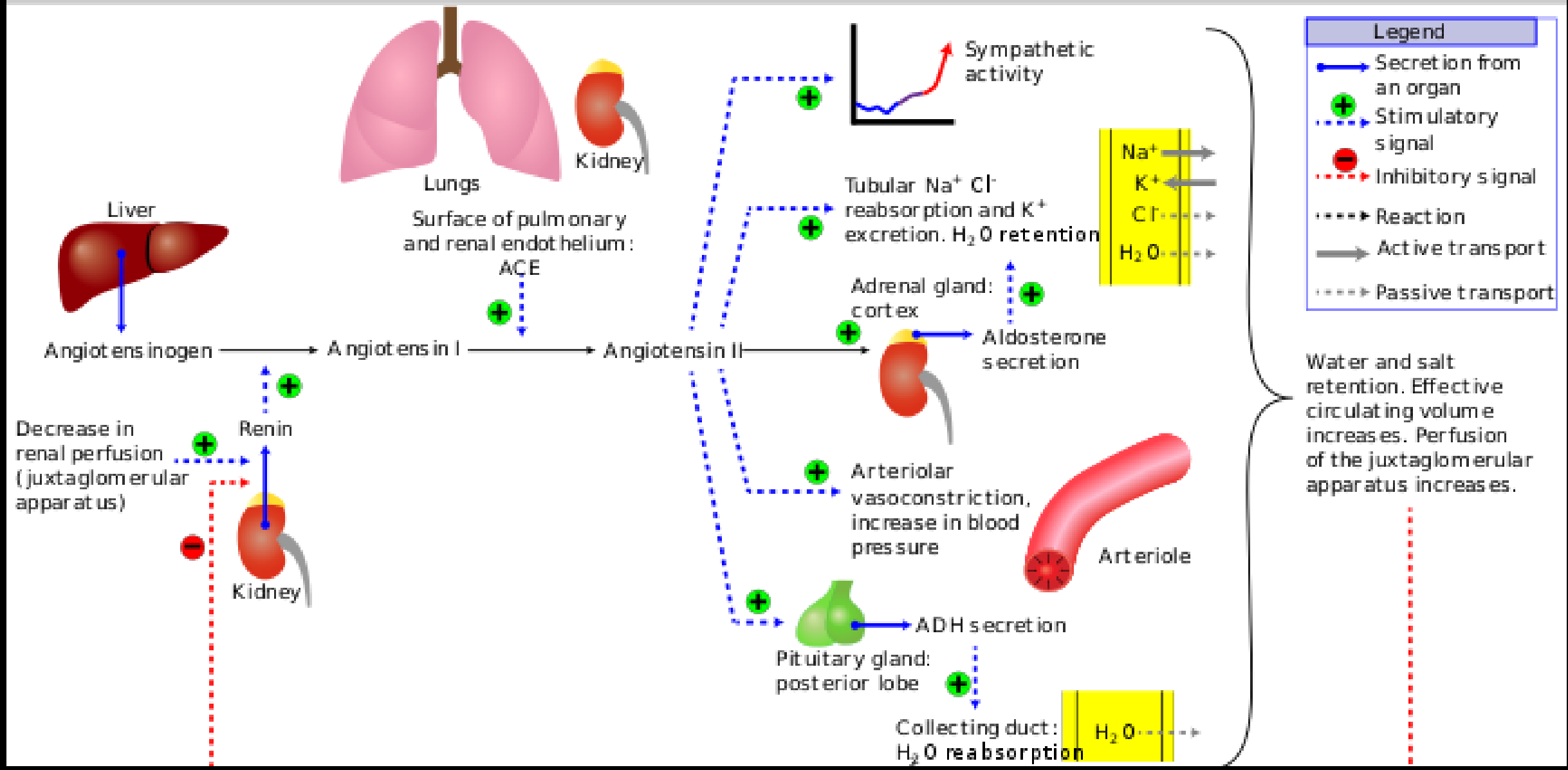






1:1 Neprilysin/Valsartan vs. Enalapril

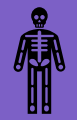
Renin-angiotensin-aldosterone system



Cardiovascular therapy for the patient with diabetes and heart failure

Management of HF in patients with DM is largely the same as treatment of HF in patients without DM

HFrEF and HFpEF includes exercise training



HFrEF and HFpEF Management includes diuretic (for volume control, with careful use to avoid volume depletion)

Secondary pharmacologic agents including mineralocorticoid receptor antagonist, ivabradine, hydralazine plus nitrate, dapagliflozin and digoxin are used as indicated.

Standard indications for implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) apply to patients with DM and HF.

Glucose Control Remains the Foundation of Type 2 Diabetes Management However, Reducing HF Risk is of Utmost Importance

AMERICAN COLLEGE of CARDIOLOGY

"RCTs have shown a significant reduction in heart failure with use of an SGLT-2 inhibitor… the reduction in heart failure has been shown to extend to primary prevention populations."

In patients with T2D with CVD risk factors who need additional glycemic control after metformin, consider an SGLT-2i[1]

[1]Arnett DK, et al, Circulation. 2019 Sep 10;140(11):e563-e595

American Diabetes Association®

"In RCTs, SGLT-2 inhibitors reduced hospitalization for HF…Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, SGLT-2 inhibitors are preferred."

In patients with T2D where HF predominates, SGLT-2i preferred as a second agent after metformin[2]

[2] American Diabetes Association. Diabetes Care. 2019;42(suppl1):S90-S102

DAPA-HF. *Subgroup analysis*

NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)

PARADIGM-HF. *Subgroup analysis*

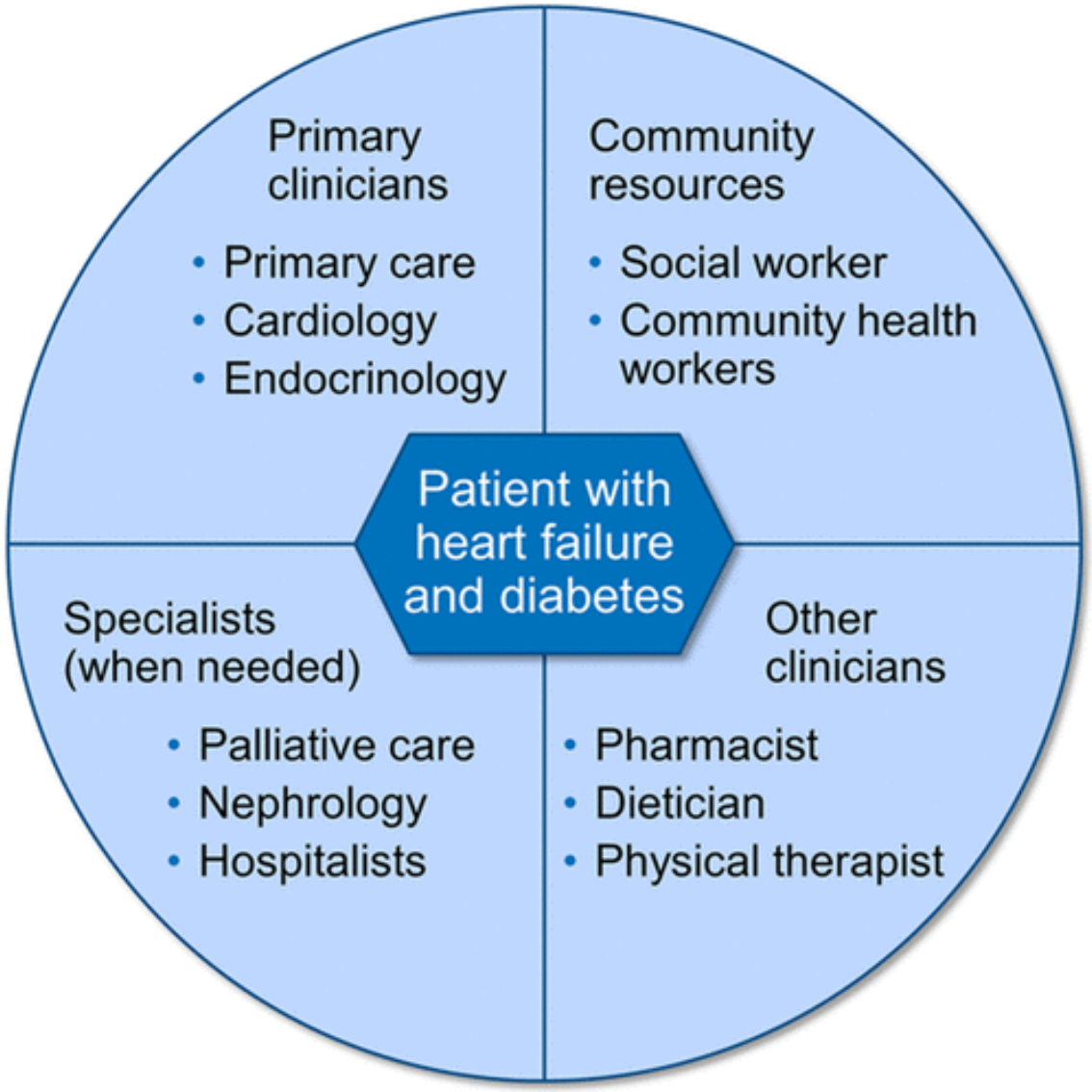
NYHA class			0.03‡
I or II	3,178	3,130	
III or IV	1,002	1,076	0.91

Summary

- Diabetes is associated with an increased risk of heart failure that is present in patients with and without established cardiovascular disease
- Subclinical volume overload is common in patients with diabetes and associated with an increased risk of death
- Glycemic control clearly reduces microvascular events; it is likely (although not definitely proven) that glycemic control reduces myocardial infarction with no effect on cardiovascular death or heart failure

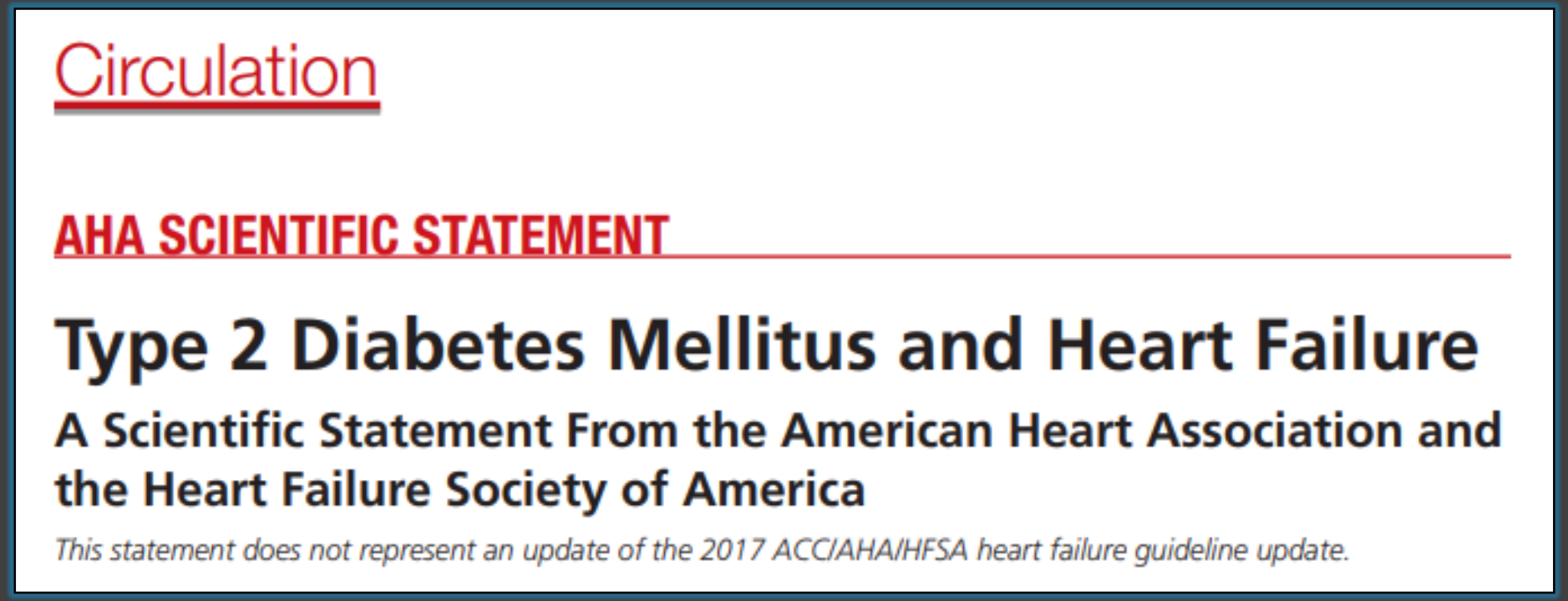
Summary

- SGLT-2i lower glucose and reduce CV events, particularly HF, and are the preferred therapy for patients with DM at risk for heart failure
- Collaborative care between internal medicine/primary care physicians, endocrinologists, cardiologists, and nursing is needed to optimize the care of patients with diabetes



Summary

- SGLT-2 inhibitors have demonstrated benefit in reducing the risk of hHF among patients with T2D and stablished cardiovascular disease or multiple cardiovascular risk factors.
- Routine clinical factors among patients with T2D may identify individuals at higher risk of the *di novo* heart failure.
- Using these clinical risk factors in combination with natriuretic peptide may identify patients who may benefit from initiation of SGLT-2 inhibitors.



- New ACC/AHF Hear Failure Guidelines due on 2021 - Pending new studies
- Last AHA/ HFS statement was published before the DAPA HF Results – Summer 2019
- Use your endocrinology ART before treating patients

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Thank You!