Heart Failure in Diabetes

Frank Riddick Diabetes Symposium

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4/24/21

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Disclosures

- Novo Nordisk

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Introduction

- 30.3 million people (9.4%) have diabetes in US
  - 7.2 million are undiagnosed
- Diabetes is considered to be a coronary heart disease equivalent
- DM 2 patients
  - DM 2 without MI History (20.2%) had equivalent MI risk as pt with out DM 2 that had a previous MI (18.8%)
  - Pt with DM 2 with history of MI- 45% over 7 years

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Haffner et al. NEJM 1998; 339(4):229

Diabetes and Heart Disease

- TAMI trial- Angiography data post acute MI in 148 (DM) vs 923 (Non DM) patients
  - 66% (DM) vs 46% (Non DM) had multivessel disease
  - Pt with diabetes had higher mortality rate- 11% vs 6%
    - Mortality for Female w/ DM- 21%
  - Patients with diabetes had higher incidence of Pulm Edema- 11% vs 4%

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Granger et al. Journ Amer Coll Card, 1993 Mar 15; 21(4): 920-925

Heart Disease Risk factors

- HTN
- Hyperlipidemia
- Glucose control
  - Database search on Type 1 and Type 2 diabetes
  - RR of CV events increased 1.18 for every 1 point increase in A1c
- Microalbuminuria
  - Odds ratio of 2.4 for CV death
  - Odds ratio 2.0 for CV morbidity and mortality
  - Also a risk factor for HF

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-Selvin et al. Ann Intern Med 2004 Sep 21;141(6):421-31.
-Dinneen et al. *Arch Intern Med* **157**: 1413–1418, 1997

Diabetes and Heart Failure

- HFrEF- HF with reduced EF
  - LVEF < 40%
- HFpEF- HF with preserved EF
  - LVEF ≥ 50%
- 6.5 million adults in US have HF
- Prevalence- approx 40% hospitalized with HF
- Patients with Diabetes- 9-22% have HF
- Diabetes = RF for HF (2-4x risk)
- HF= RF for Diabetes

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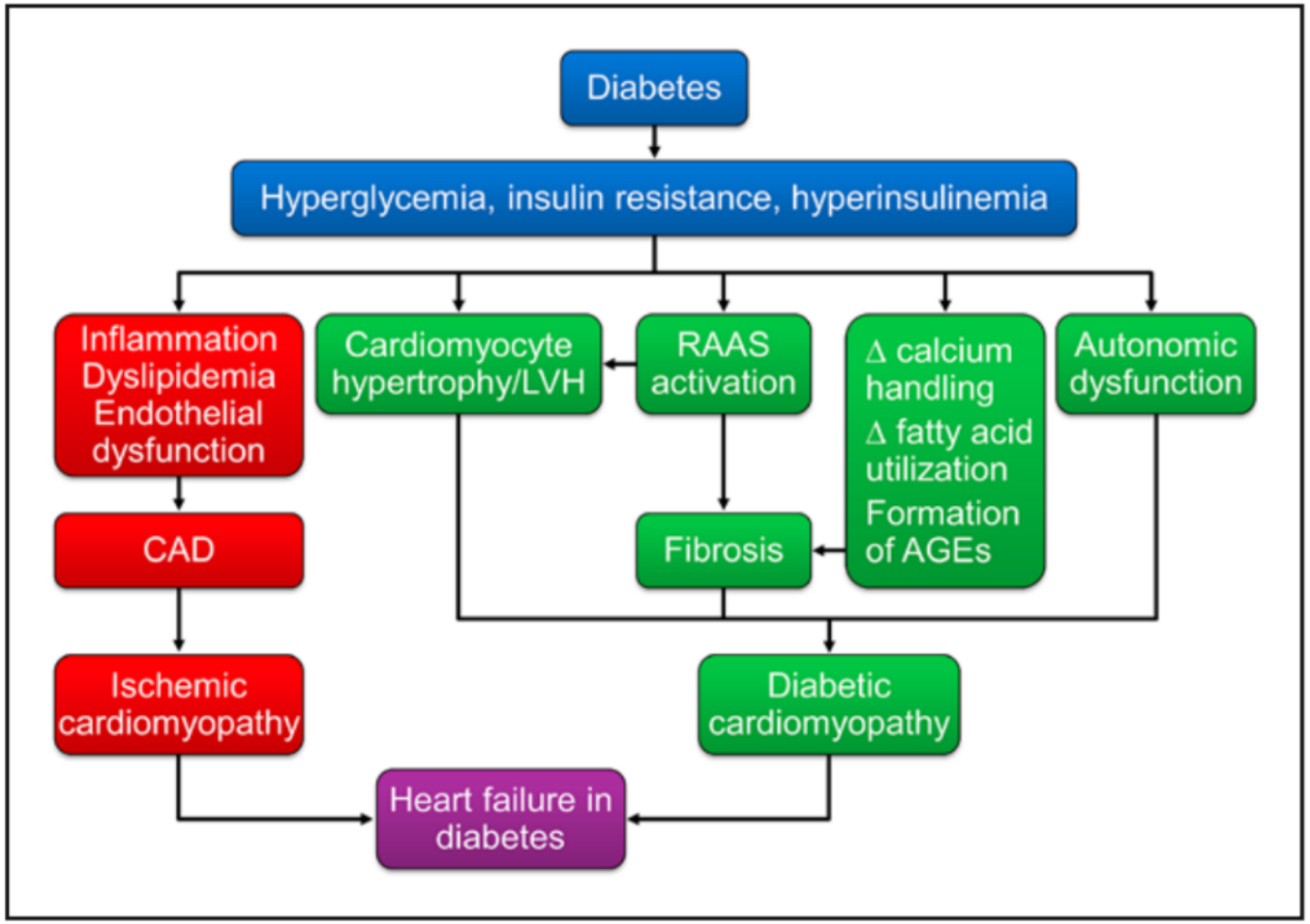
AHA Scientific Statement. Circulation. 2019;140:e294–e324

Diabetes and Heart Failure

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	…
Retrospective cohort of Kaiser Permanente Northwest Database[17]		8231 +DM, 8845 no DM	Up to 6	Rates (person-years): DM: 30.9/1000 No DM: 12.4/1000 Rate ratio, 2.5 (95% CI, 2.3–2.7)	…	…

AHA Scientific Statement. Circulation. 2019;140:e294–e324

Pathophysiology



AHA Scientific Statement. Circulation. 2019;140:e294–e324

Diabetic cardiomyopathy

- Initially described in 1972
- Definition- Ventricular dysfunction in the absence atherosclerosis and HTN in patients with DM.
  - Systolic or diastolic dysfunction
- Initial stages may be asymptomatic- LV hypertrophy and diastolic dysfunction.
- Cardiomyocyte stiffness

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Guanghong et al. Circulation research, Volume 122, Issue 4, 16 February 2018, Pages 624-638

Diabetic cardiomyopathy

- Cardiovascular Health Study
  - 5200 patients
  - Age > 65
  - Patients with Diabetes had increased left post wall and septal thickness.
  - Increased with duration of diabetes,
  - Diabetes a predictor of increased LV mass.

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Guanghong et al. Circulation Volume 122, Issue 4, 16 February 2018, Pages 624-638
Lee et al. Am Heart J1997 Jan;133(1):36-43.

Diabetes Medications and Heart Failure

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Thiazolidinediones

- Rosiglitazone and pioglitazone associated with HF events
- FDA: Do not initiate in Class III-IV HF.
- PROactive Trial
  - Pioglitazone in Type 2 patients with history of macrovascular disease
  - 5238 patients in 19 countries followed a mean of 9.5 years

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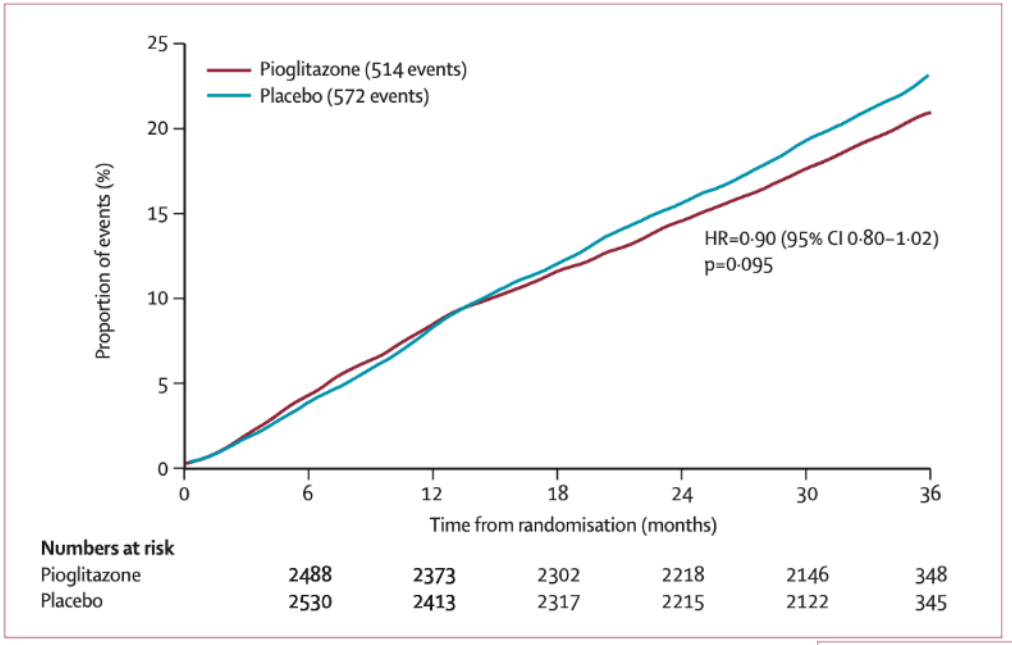
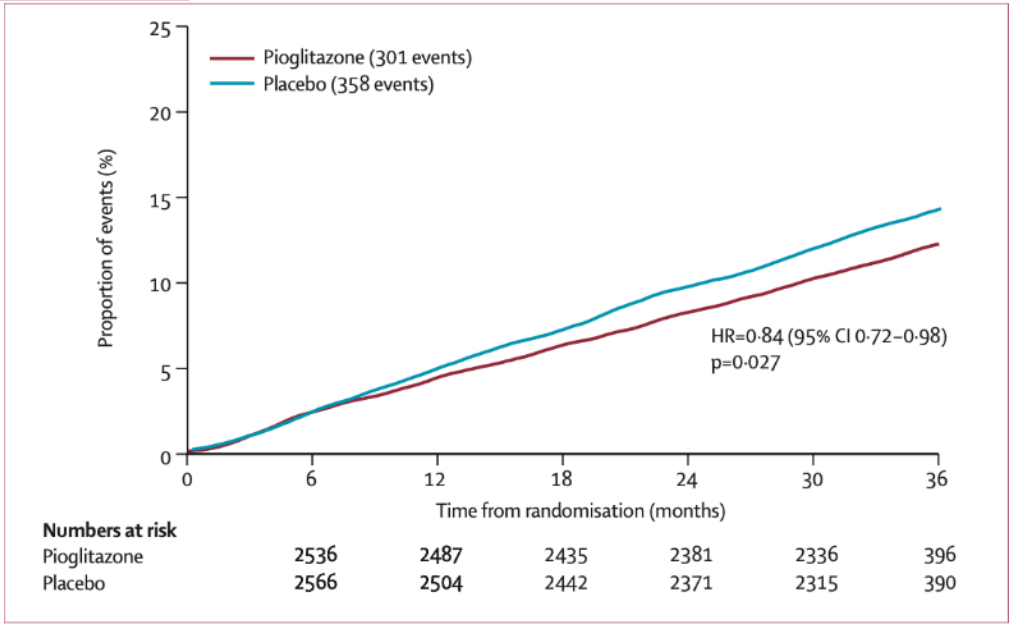
Charbonnel et al. Lancet VOLUME 366. TYPE 2
P1279-1289, OCTOBER 08, 200



Prim Outcome: Comp all cause Mortality, nonfatal MI, Stroke, ACS, PVD intervention, amputation

Sec outcome: Comp All cause mortality, nonfatal MI and Stroke



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Charbonnel et al. Lancet VOLUME 366. TYPE 2 P1279-1289, OCTOBER 08, 200

PROactive Trial

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any report of heart failure*	417	281 (11%)	302	198 (8%)	<0·0001
Heart failure not needing hospital admission*	160	132 (5%)	117	90 (3%)	0·003
Heart failure needing hospital admission*	209	149 (6%)	153	108 (4%)	0·007
Fatal heart failure†	25	25 (1%)	22	22 (1%)	0·634

*Not adjudicated. †Adjudicated cause of death.

***Table 9:* Reports of heart failure**

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Charbonnel et al. Lancet VOLUME 366. TYPE 2 P1279-1289, OCTOBER 08, 200

DPP 4 Inhibitors

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SAVOR TIMI 53

- Saxagliptin
- History of CVD or at risk
  - 78% with CVD/CHF
- Median f/u 2.1 years and 16,492 patient randomized
- 3 point MACE
- Statin use 78%
  - 13% with CHF
- 613 events (Saxa) vs 609 (Placebo): 7.3% vs 7.2%
  - HR 1.00
- HF Hospitalization: 3.5% (Saxa) vs 2.8% (Placebo)
  - HR 1.27
  - P= 0.007
- Similar rates of acute and chronic pancreatitis

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Scirica et a. NEJM, Oct 2013, 369; 14: 1317-26

EXAMINE

- Alogliptin
- Patients with CVD
  - With MI or unstable angina requiring hospitalization within previous 15-90 days
  - 100% with CVD (28% with CHF)
- 5,380 patients with median f/u 1.5 years
- 3 point MACE
- Statin use 91%
- 305 Events (Alog) vs 316 (Placebo): 11.3% vs 11.8%
  - HR 0.96
- Hospitalization for HF: HR 1.19

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White et al. NEJM 2013; 369: 1327-35

TECOS

- Sitagliptin
- Patients with established CVD
- 14,671 patients with median f/u 3.0 years
- Statin use 80%
- 18% with CHF
- 4 point MACE
- 839 events (Sita) vs 851 (placebo): 11.4% vs 11.6%
- Hospitalization for HF: HR 1.00

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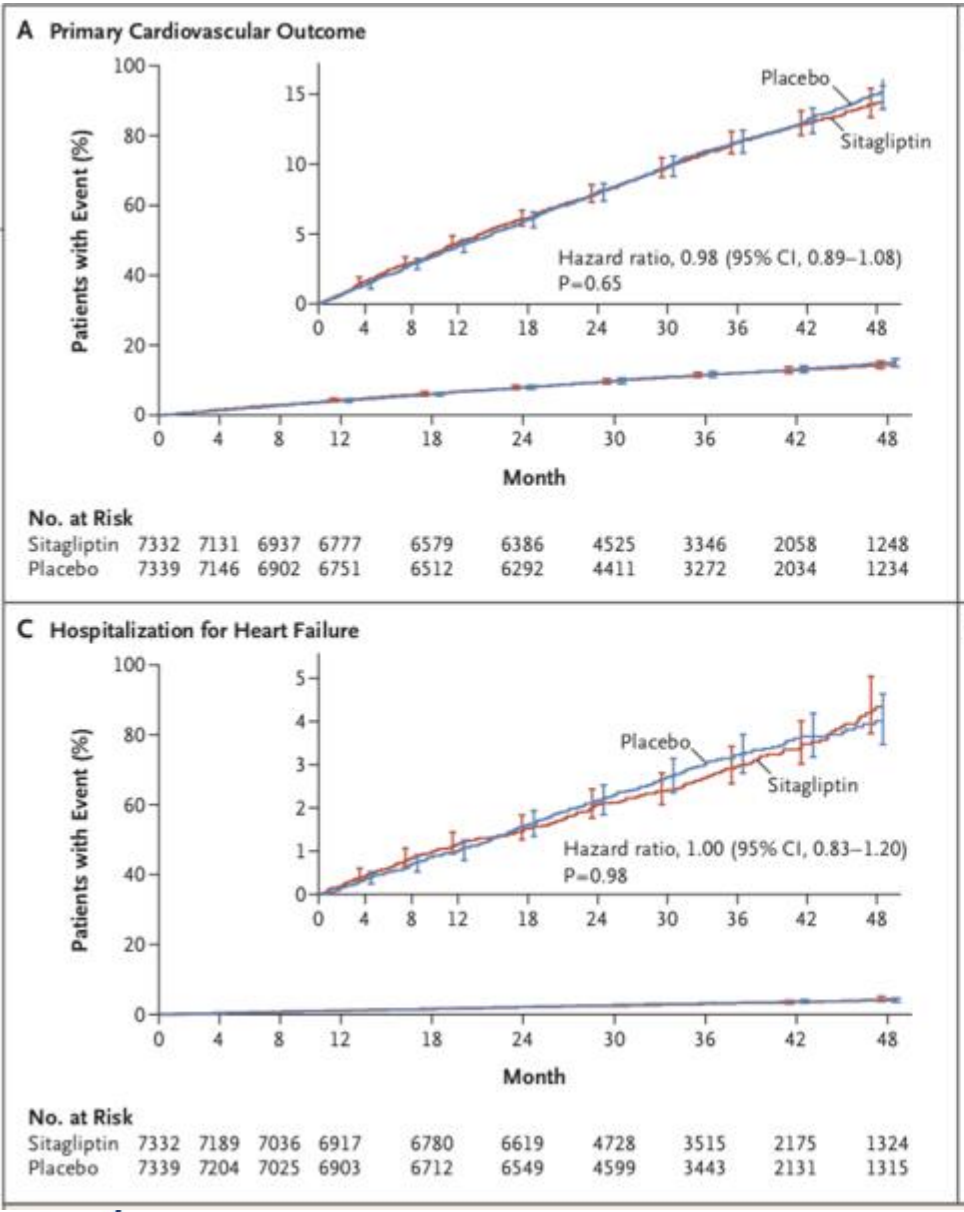
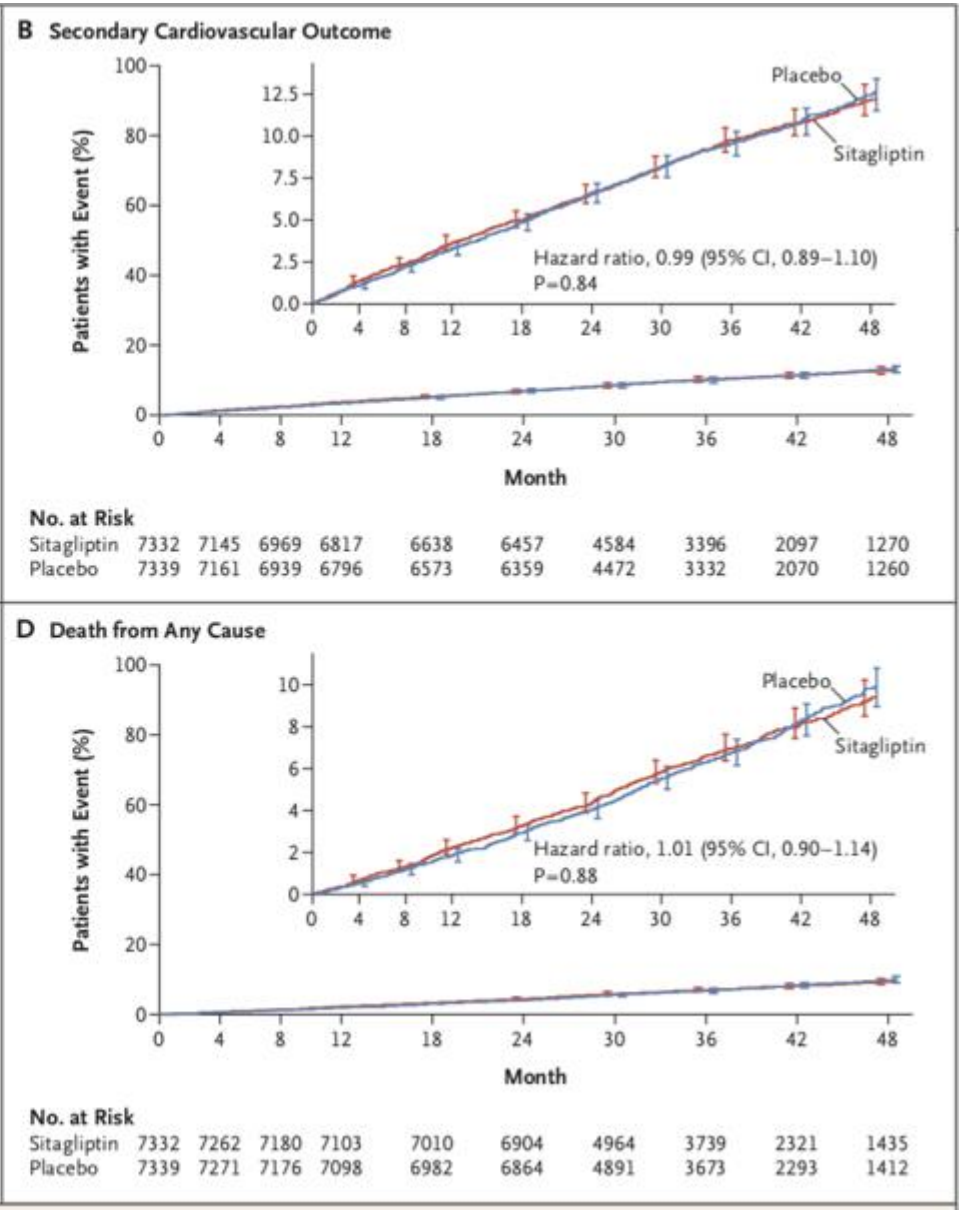
Green et al. NEJM 2015; 373: 232-42





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Green et al. NEJM 2015; 373: 232-42

DPP 4 and Heart Failure

Table 1—Data from randomized placebo-controlled trials of DPP-4 inhibitors and the risk of HF

Study	Year	DPP-4 inhibitor	Population	Sample size	Median follow-up (years)	Hospitalization for HF		
						Rate (no. per 100 PYs)		
						DPP-4 inhibitor	Placebo	HR (95% CI)
SAVOR-TIMI 53 (5,6)	2013, 2014	Saxagliptin	CVD or multiple CVD risk factors	16,492	2.1	1.71*	1.36*	1.27 (1.07–1.51)
EXAMINE (7,8)	2013, 2015	Alogliptin	Post-ACS	5,380	1.5	2.69†	2.28†	1.19 (0.90–1.58)
			With history of HF	1,533		5.60†	5.85†	1.00 (0.71–1.42)
			With no history of HF	3,847		1.53†	0.86†	1.76 (1.07–2.90)
TECOS (9)	2015	Sitagliptin	CVD	14,671	3.0	1.07	1.09	1.00 (0.83–1.20)‡

ACS, acute coronary syndrome; PYs, person-years. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial. ‡Adjusted for baseline history of HF.

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Filion et al. Diabetes Care 2016; 39:735-737

DPP 4 and Heart Failure

- SAVOR TIMI 53- increased risk seen in 1st year- HR 1.27
- Conflicting results in meta-analysis and observational studies
- Claims based observational study- retrospective
  - 3 years
  - 112,888 patients- Saxagliptin vs Sitagliptin
  - HR 0.95 w/ CVD
  - HR 0.99 w/o CVD
  - No difference between Saxa and Sita
  - Also looked at DPP 4 vs SU- no difference

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Filion et al. Diabetes Care 2016; 39:735-737
Fu, ete al Diabetes Care 2016 May; 39: 726-734

GLP-1 and Heart Failure

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Live Trial

- Liraglutide effect with HFrEF
- With and without DM
- N=241 for 24 weeks
- Effect on LVF in stable CHF
- DM 2- 32% in Lira arm and 29% in Placebo arm
- Ischemic Heart Disease- approx 28%

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Jorsal et al. European Journal of Heart Failure (2017) 19, 69–77

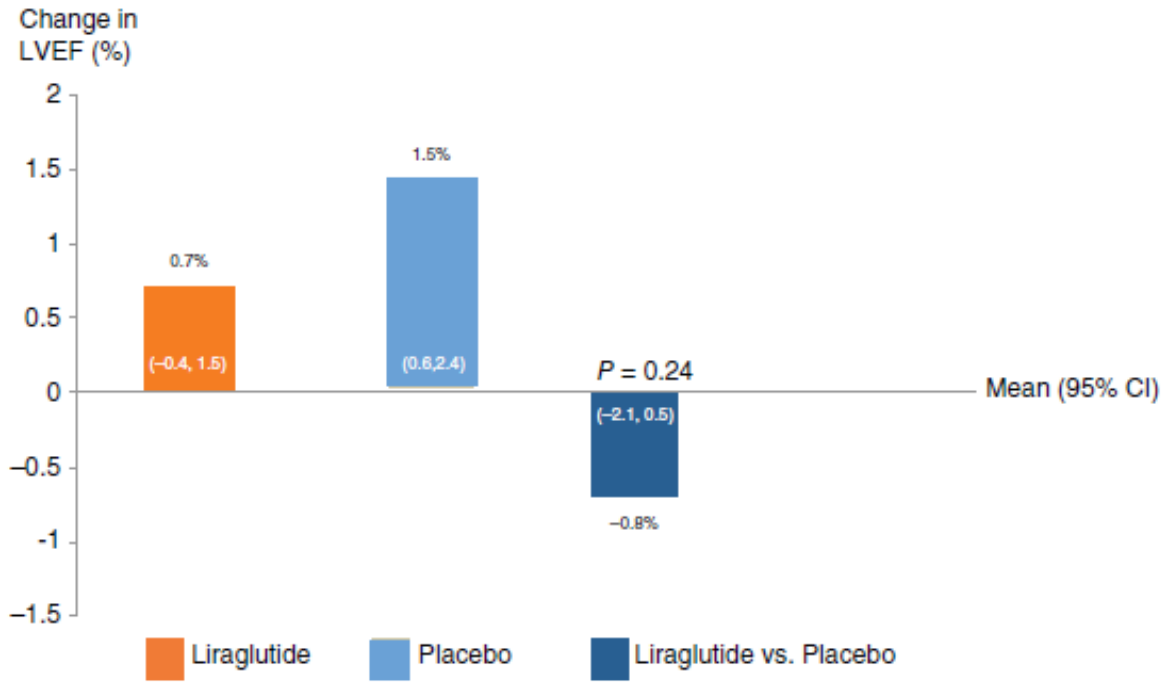

Figure 2 Change in primary endpoint. CI, confidence interval; LVEF, left ventricular ejection fraction.

P Value 0.24

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Jorsal et al. European Journal of Heart Failure (2017) 19, 69–77

Live Trial

- Increase in HR: Diff 7 BPM (P< 0.0001)

	Liraglutide *n* (%)	Placebo *n* (%)
Cardiac		
Death due to ventricular tachycardia	1	0
Ventricular tachycardia	3	1
Atrial fibrillation (DC-converted)	4	2
Acute coronary syndrome	3	0
Worsening of CHF	1	0
Subtotal	12 (10)*	3 (3)

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Jorsal et al. European Journal of Heart Failure (2017) 19, 69–77

Table 3. GLP-1 RAs in Patients With Heart Failure and Reduced Ejection Fraction

Outcomes	LIVE[40]	FIGHT[41]	Lepore et al[42]
Year	2016	2016	2016
N	241	300	82
Follow-up, mo	6	6	3
Primary outcome	LVEF	Global rank (death, HF hospitalization, and N-terminal pro-brain-type natriuretic peptide change)	LVEF
HF hospitalization	NR	HR 1.3 (0.89 to 1.88)	NR
LVEF change, %	–0.8 (2.1 to 0.5), *P*=0.24	–0.1 (–2.3 to 2.1), *P*=0.95	–2.0±1.6 (*P*=0.22)
LVEDV change, mL	3.4 (–2.3 to 9.2), *P*=0.24	6.7 (–2.6 to 16.0), *P*=0.16*	–0.2±6.5 (*P*=0.98)
LVESV change, mL	2.6 (1.2 to 6.4), *P*=0.19	5.0 (–2.6 to 12.7), *P*=0.19*	0.4±6 (*P*=0.95)
6MWD, m	24 (2 to 47), *P*=0.04†	5 (–29 to 39), *P*=0.79	9±16 (*P*=0.58)

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Kahn et al. *Circulation.* 2020;142:1205–1218

SGLT 2 and HF

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EMPA-REG

- Empagliflozin
- Patients with pre-existing CVD
- 10% with HF
- 7,020 patients with median f/u 3.1 years
- 3 point MACE
- 490 events (Empa) vs 282 events (Placebo): **10.5% vs 12.1%**
  - HR 0.86: P= 0.04 for superiority
- **Hospitalization for HF: 2.7% (Empa) vs 4.1% (placebo)**

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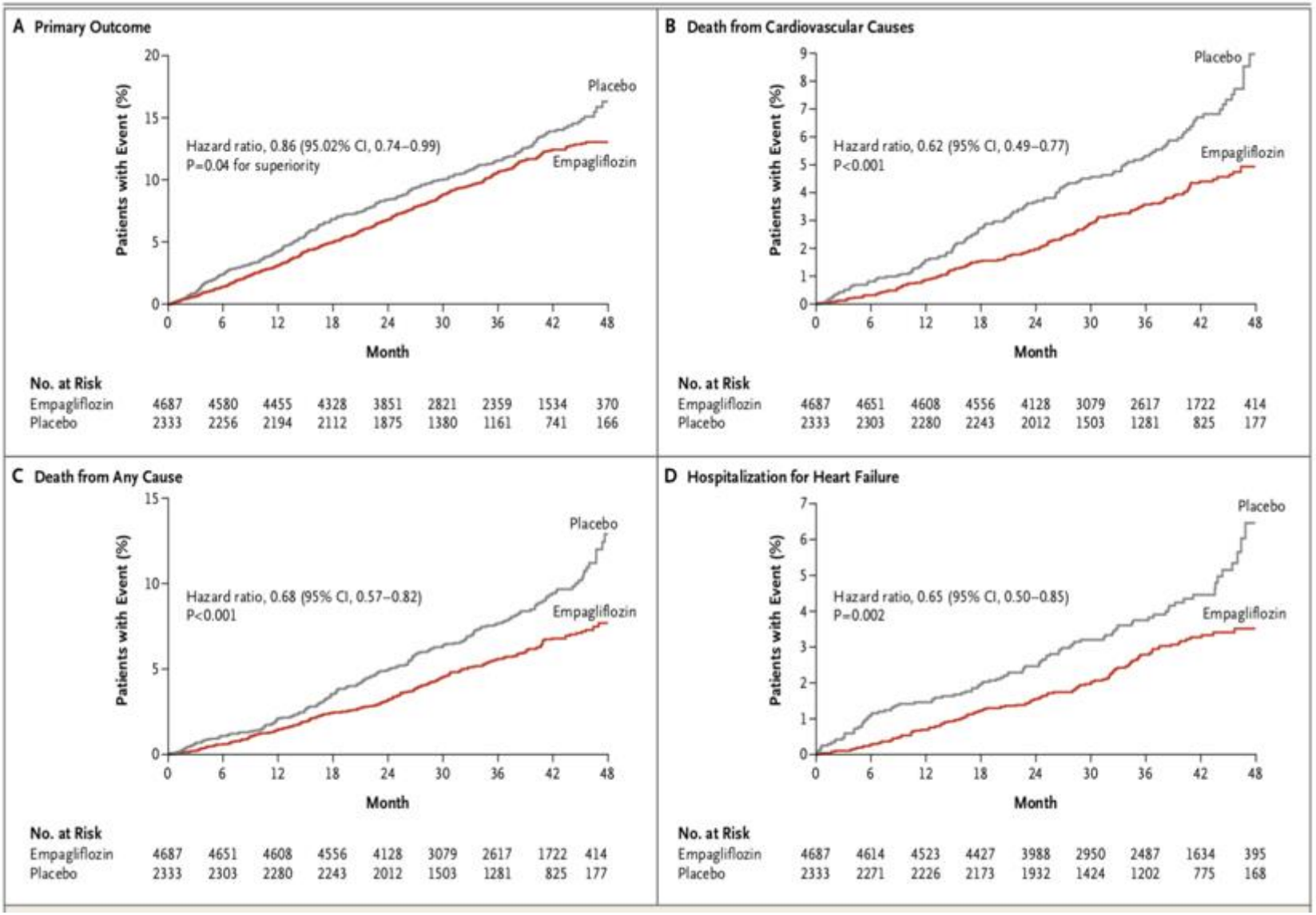
Zinman et al. NEJM 2015;373:2117-28



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Zinman et al. NEJM 2015;373:2117-28

CANVAS Program

- Pooled data of CANVAS and CANVAS-R
- Patients with CVD or age ≥50 with CV risk factors
  - 65.6% with CVD
  - 14.4% with HF
- CANVAS
  - 4,330 patients with median f/u 5.7 years
- CANVAS-R
  - 5,812 patients with median f/u 2.1 years
- 3 point MACE

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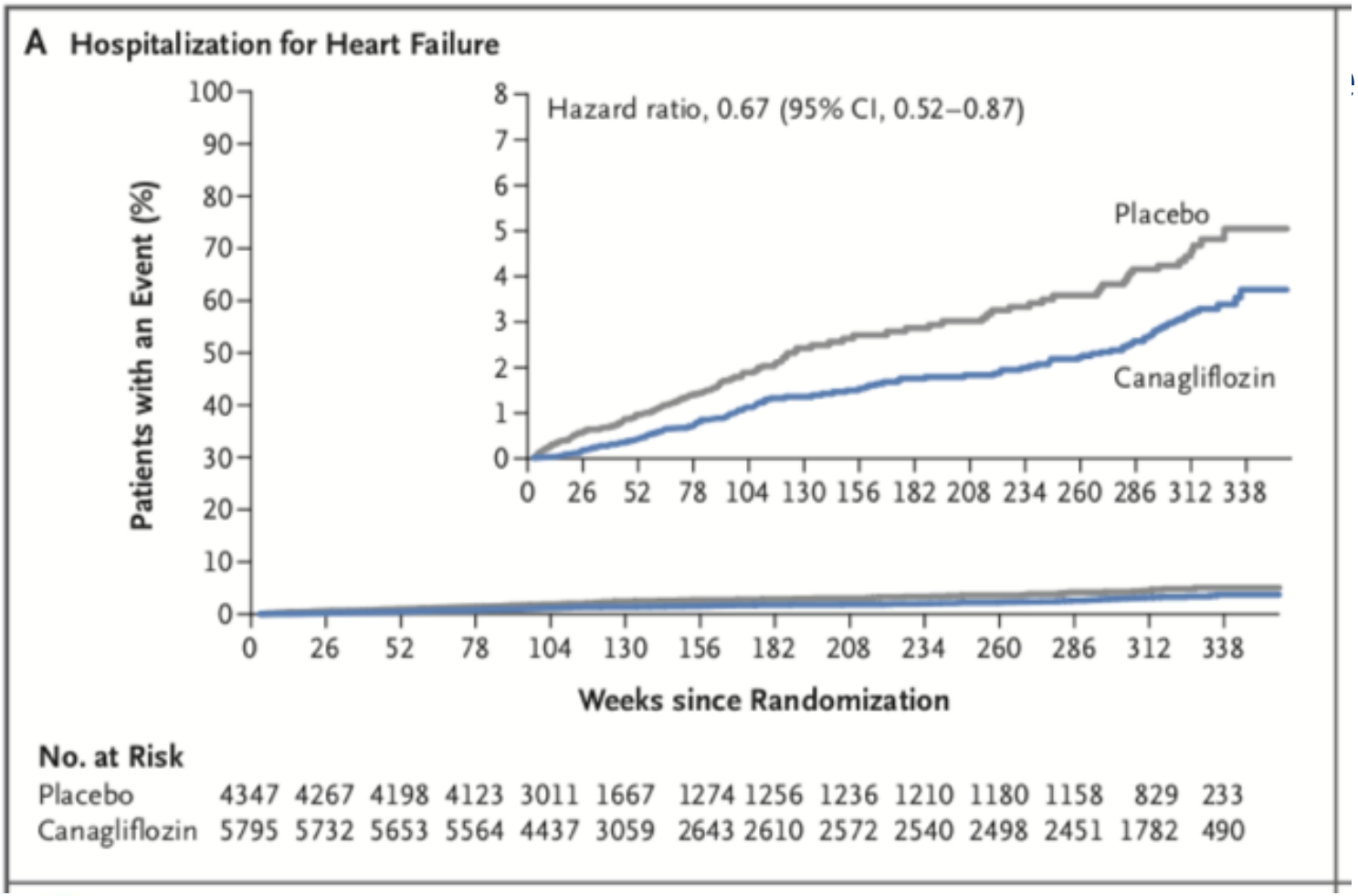
NEAL et al. NEJM 2017; 377:644-57

CANVAS Program



NEAL et al. NEJM 2017; 377:644-57

DECLARE Trial

- Dapagliflozin CVOT
- 17,160 patients with DM 2 with CVD or at risk
- MACE (CV Death, MI, Stroke) and composite of CV death or hospitalization for heart Failure
- Median F/U 4.2 years
- Approx 10% had HF
- CV Death and Hospitalization for HF
  - 4.9% (Dapa) vs 5.8% (Placebo)
  - Hospitalization for HF Alone: HR 0.73

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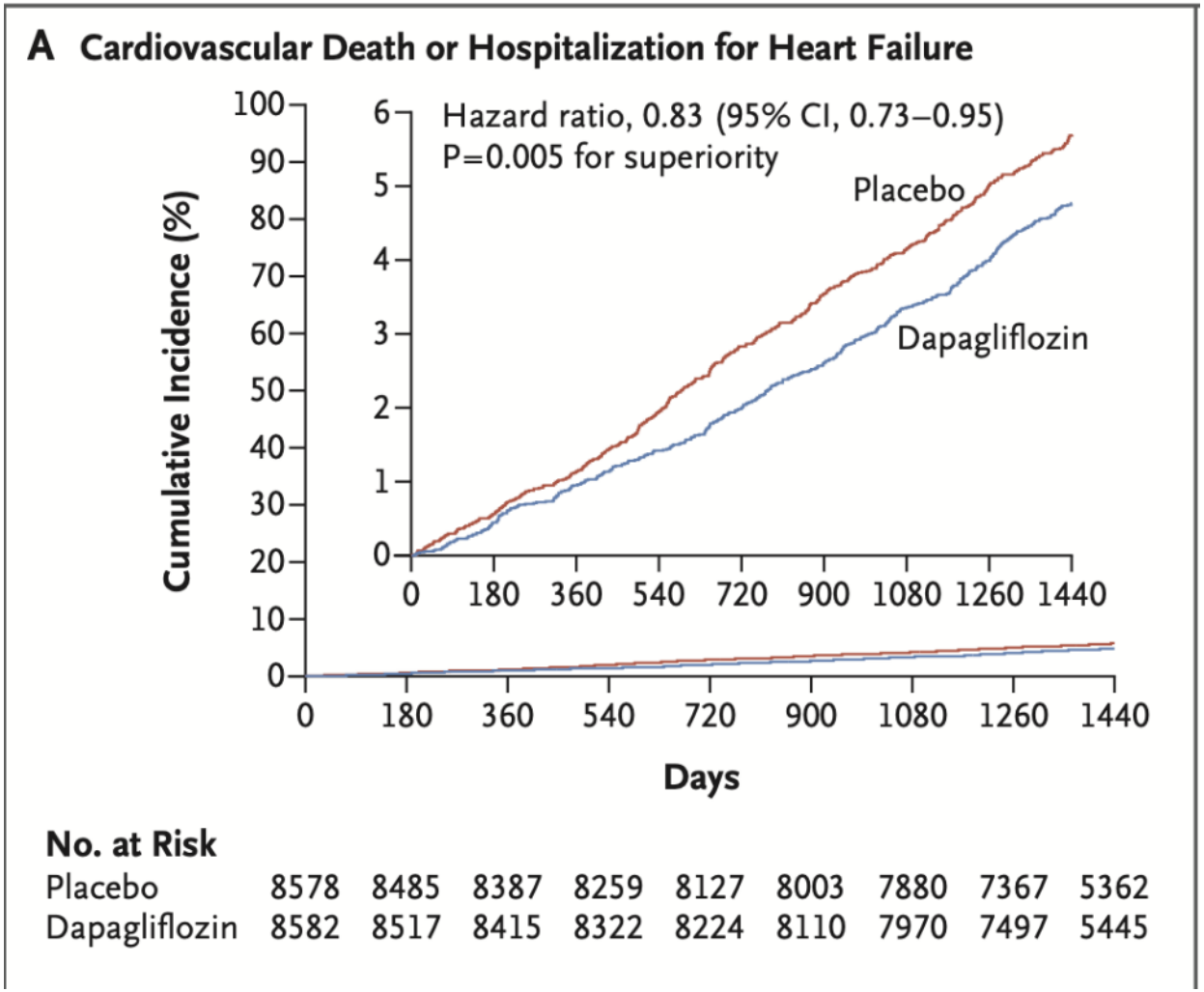
Wiviott et al. N Engl J Med 2019;380:347-57

DECLARE Trial



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Wiviott et al. N Engl J Med 2019;380:347-57

CVD REAL

- Multinational observation study
  - 6 countries
- Data: claims, EHR and registry data (309,056 patients)
- Looked at all SGLT 2 inhibitors
  - Canagliflozin: 53%
  - Dapagliflozin: 42%
  - Empagliflozin: 5%
- HF and death on newly initiated SGLT 2

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Kosiborod et al. Circulation 2017; 136:249-259

CVD REAL

- Hospitalization for HF: HR 0.61 (P= <0.001)
- All Cause Mortality: HR 0.49 (P= <0.001)
- No heterogeneity by country

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Kosiborod et al. Circulation 2017; 136:249-259

CREDENCE Trial

- Double Blind Randomized Trial
  - Cana 100 mg vs placebo
- Type 2 Diabetes in patients with albuminuric chronic kidney disease
- Patient Eligibility
  - Age > 30
  - A1c 6.5%-12%
  - CKD
    - eGFR 30 to < 90 ml/min
    - And Albuminuria- urine albumin/cr > 300 to 5000
    - 60% of participants had eGFR 30-60 ml/min
  - Stable dose of ACE or ARB x 4 weeks

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Perkovic et al. n engl j med 380;24

CREDENCE Trial

- 4401 patients randomized
- Median f/u 2.62 years
- 14.8% had CHF
- DM Duration 15.8 years
- 50.4% had CV disease
- Avg A1c 8.3%
- Avg eGFR 56.2 mL/min
- Median urine alb/cr ratio 927
- Trial stopped early at interim analysis due to positive results

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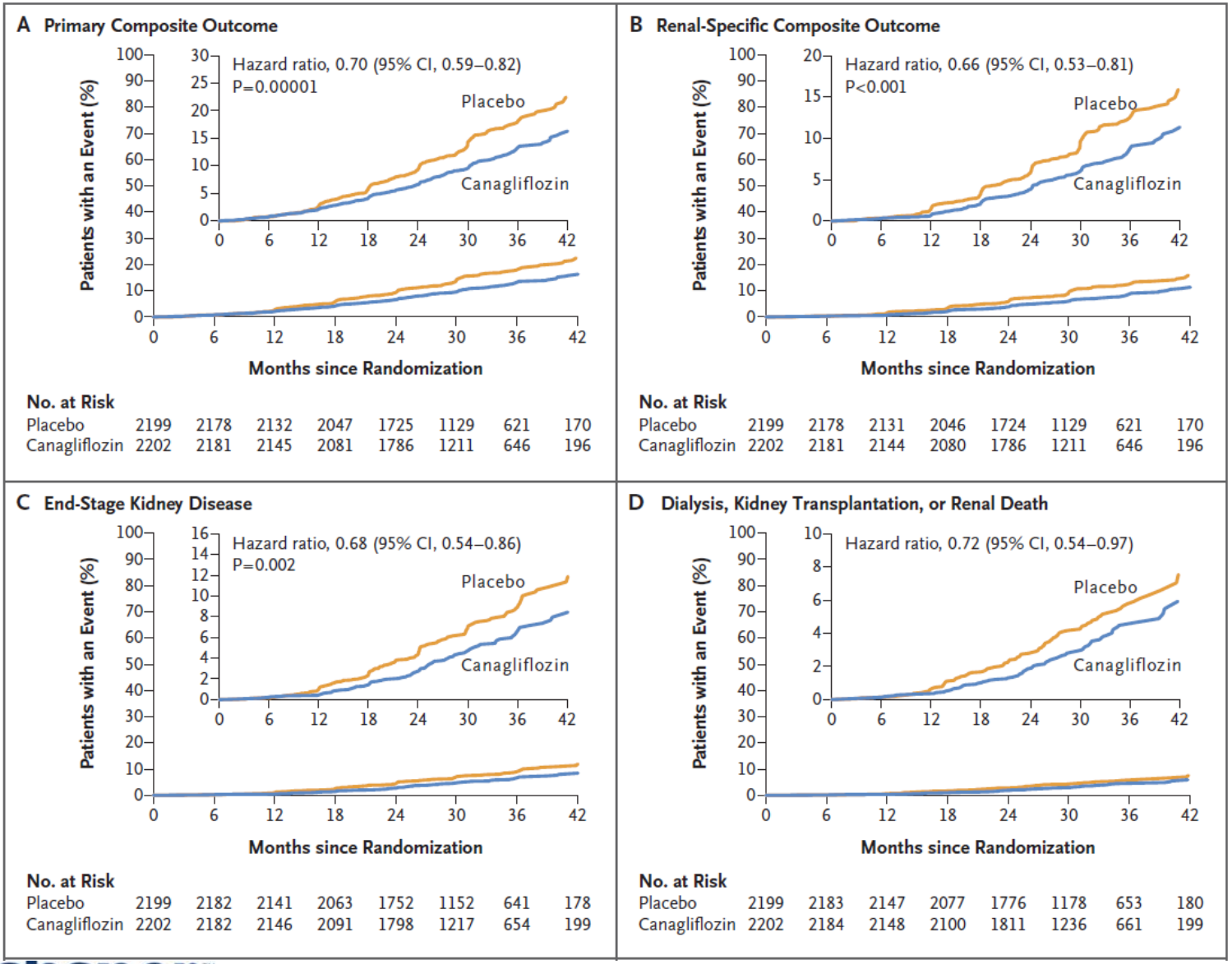
Perkovic et al. n engl j med 380;24



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Perkovic et al. n engl j med 380;24

CREDENCE Trial

- Hosp Heart Failure HR 0.61- P value < 0.001
- NNT- 1000 pt for 2.5 yrs.
  - 22: Prim Composite outcome (ESKD, DBL Cr, Renal or CV Death)
  - 28: Composite of ESKD, DBL Cr, or Renal Death
  - 46: Hosp for Heart Failure

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Perkovic et al. n engl j med 380;24

EMPEROR Reduced Trial

- Empagliflozin in Class II, III, or IV HF
- HFrEF (EF < 40%)
- Patients= 3730
- Primary Outcome- Composite of CV Death or Hospitalization for HF.
- Median F/U 16 months
- All patients on standard HF treatment
- Patients
  - Ischemic HF- Approx 52%
  - Nonischemic HF- Approx 47%
  - DM- Approx 50%

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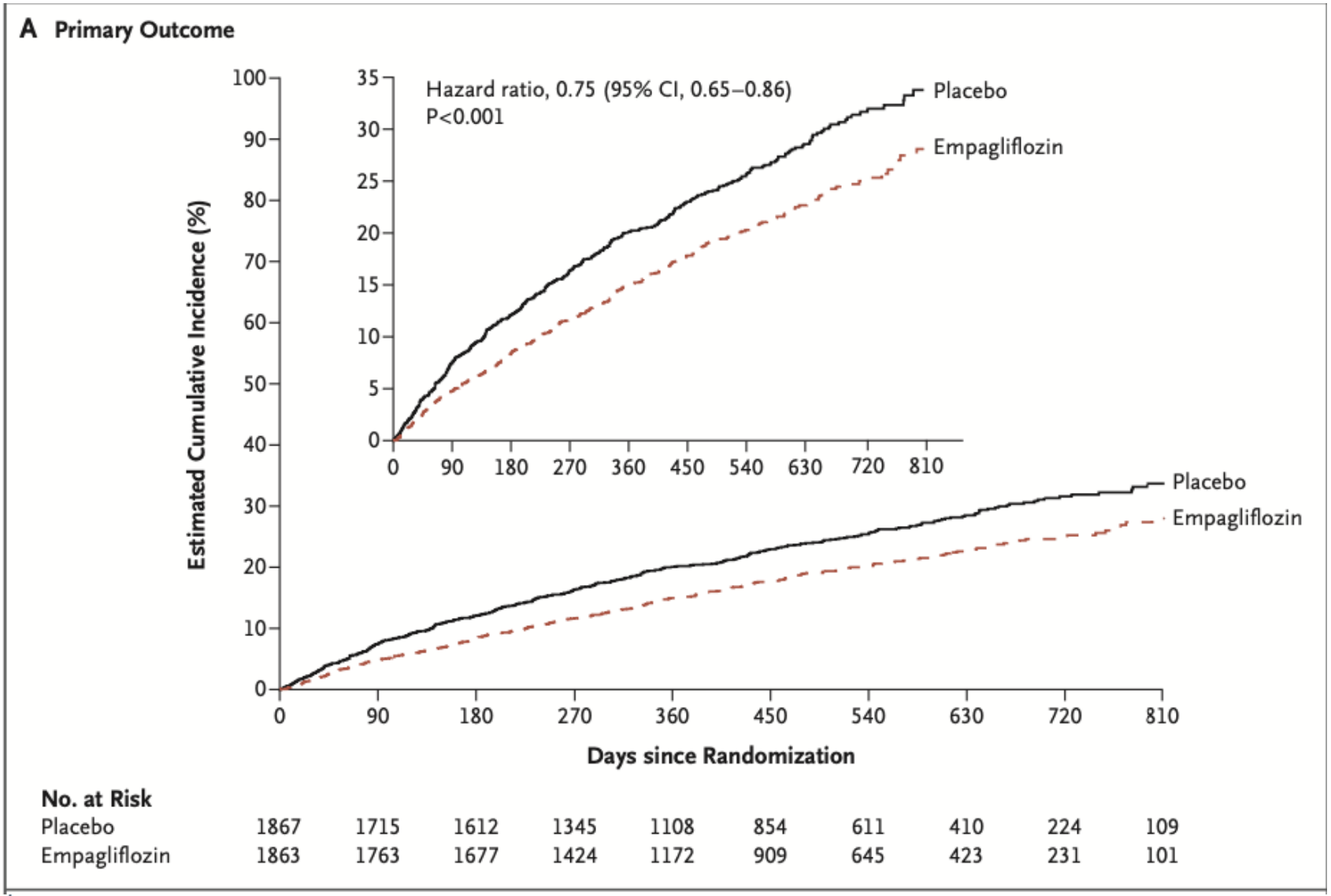
Packer et al. N Engl J Med 2020;383:1413-24



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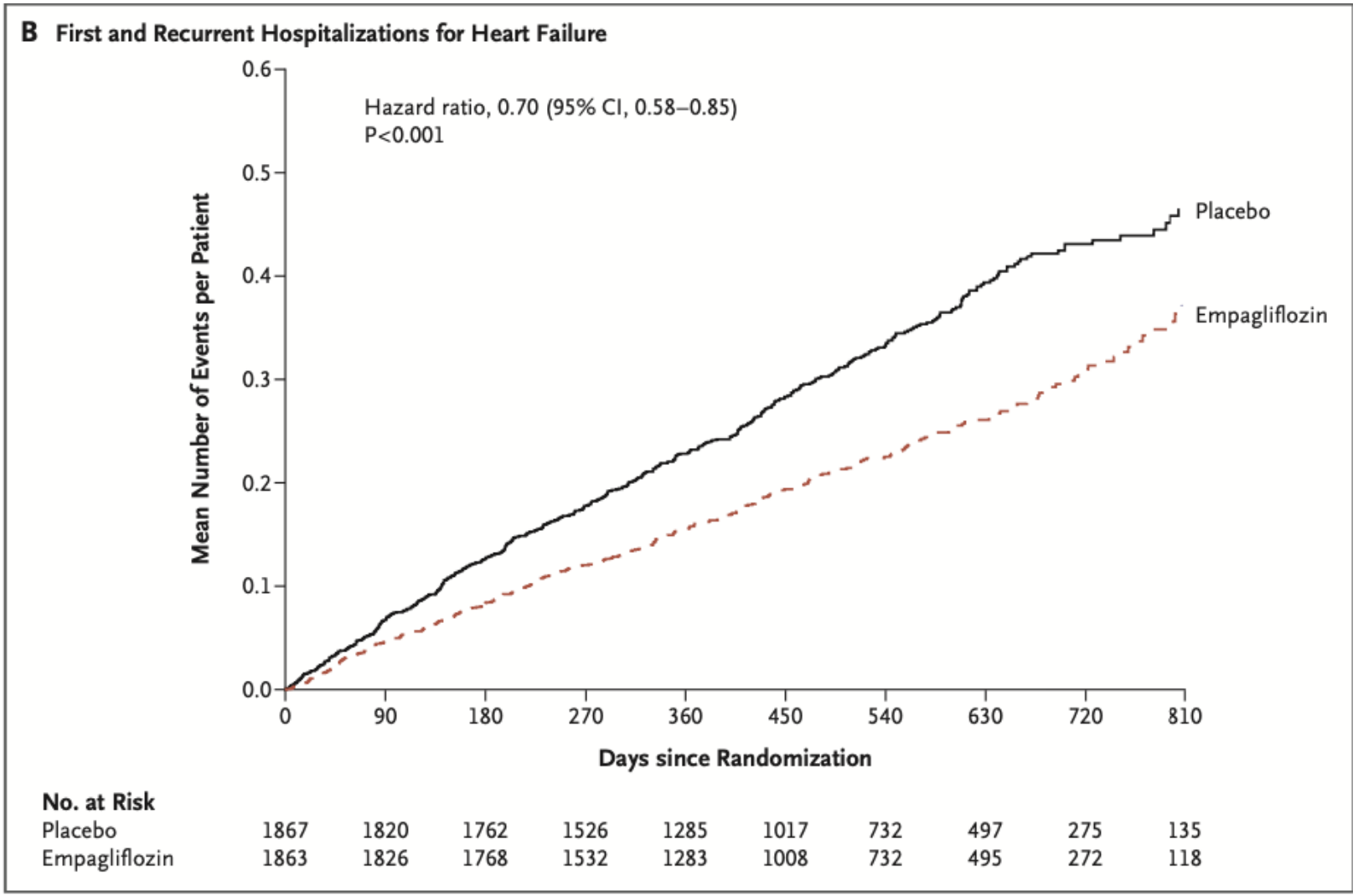
Packer et al. N Engl J Med 2020;383:1413-24



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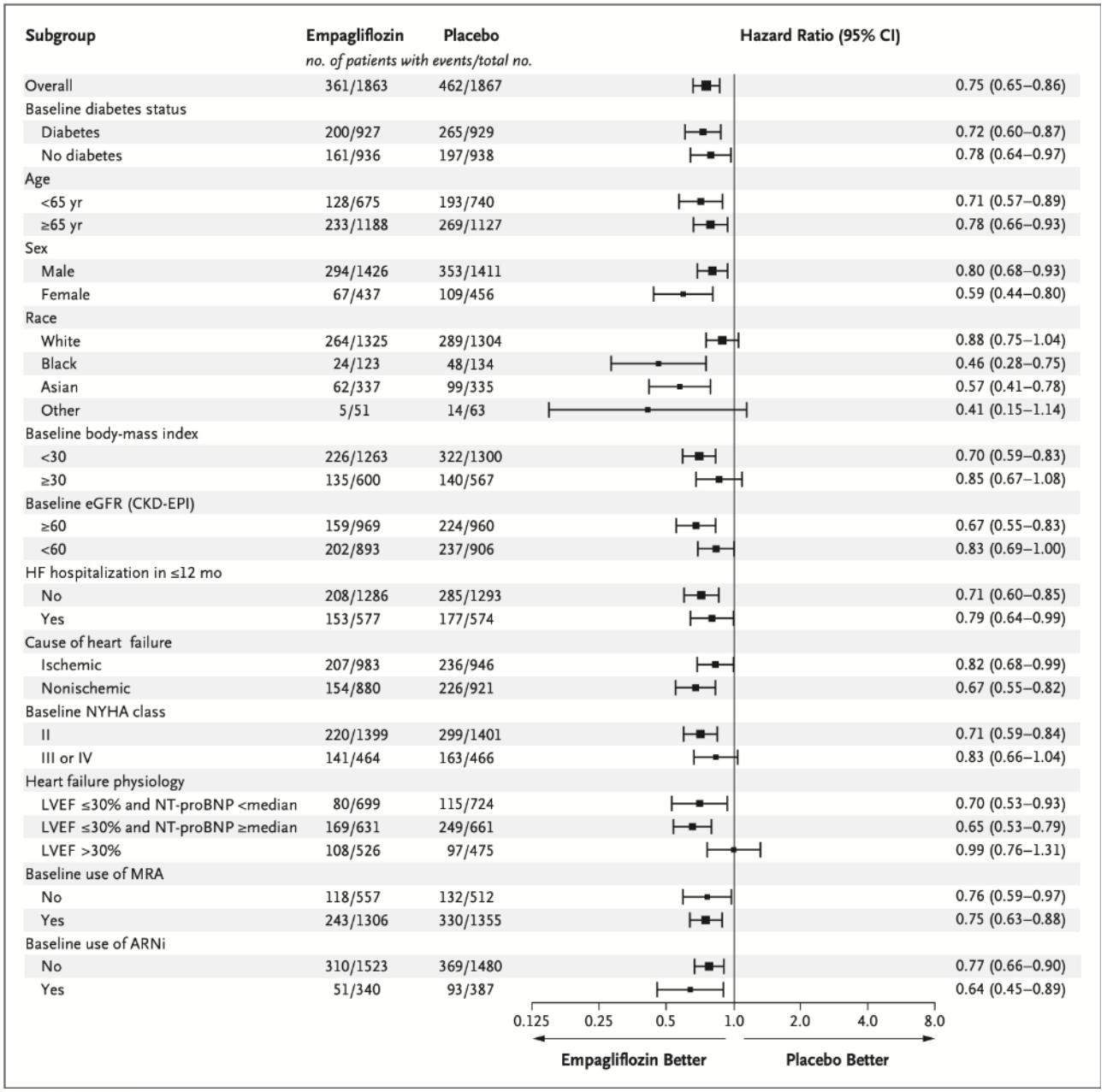
Packer et al. N Engl J Med 2020;383:1413-24



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Packer et al. N Engl J Med 2020;383:1413-24

DAPA-HF

- Dapagliflozin in Class II, III, IV HF
- HFrEF (EF < 40%)
- Patients= 4744
- Primary Outcome- Composite of CV Death or worsening HF
  - Worsening HF= Hospitalization of IV therapy
- Median F/U 18.2 months
- Patients
  - Ischemic HF- approx 55%
  - Nonischemic- approx 36%
  - Diabetes- Approx 42%

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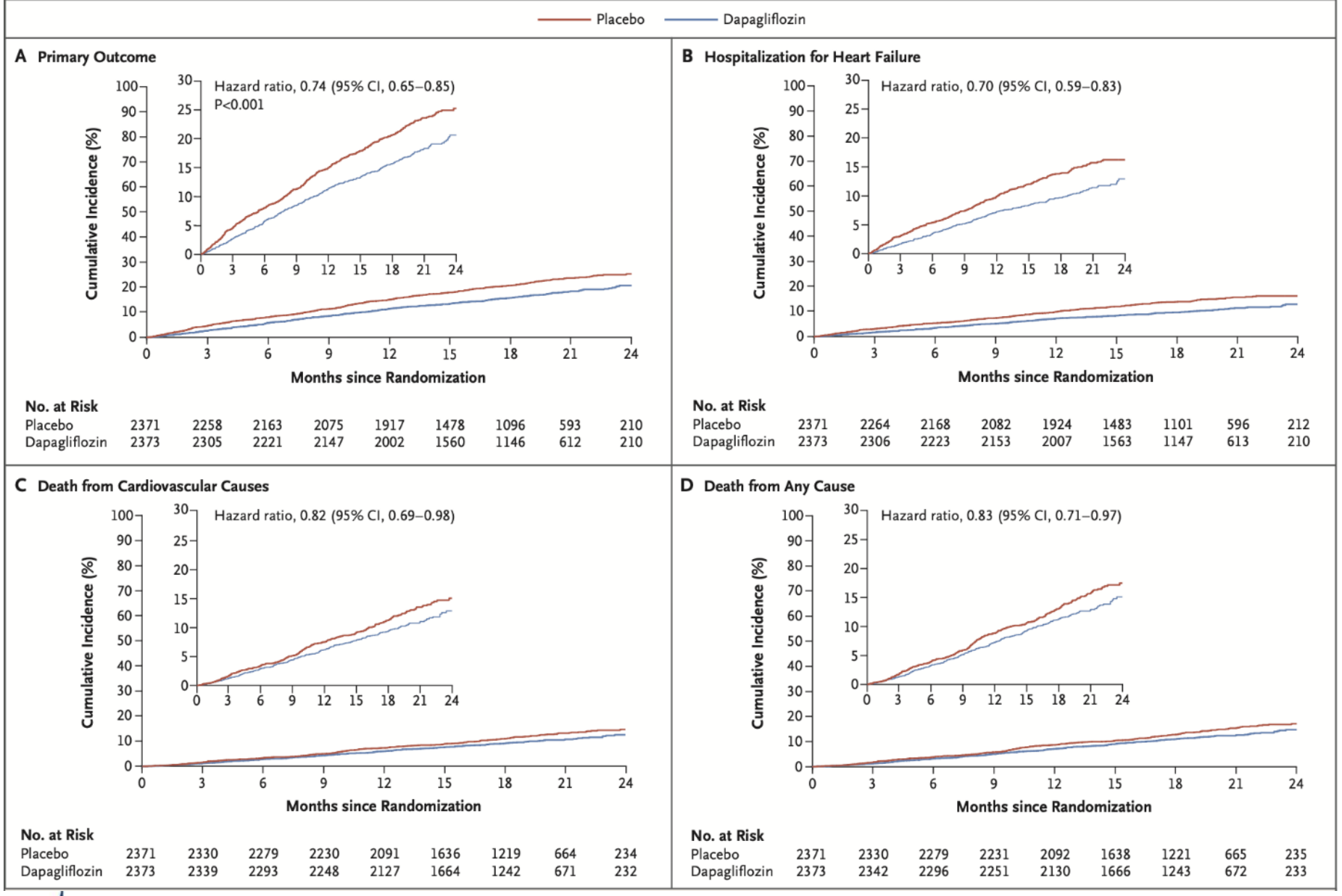
McMurray et al. N Engl J Med 2019;381:1995-2008.



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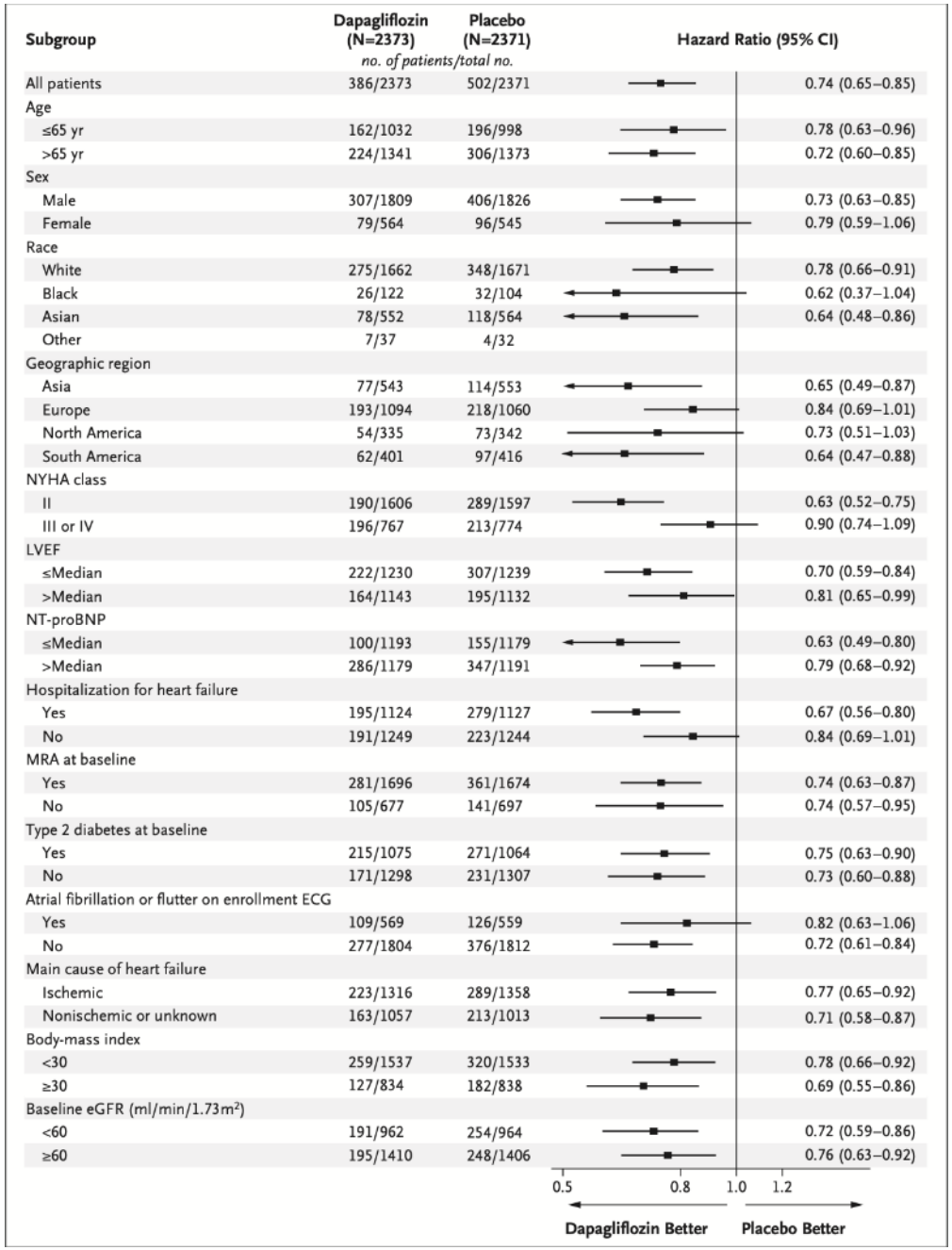
McMurray et al. N Engl J Med 2019;381:1995-2008



McMurray et al. N Engl J Med 2019;381:1995-2008

Current FDA Indications

- Dapagliflozin
  - to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors
  - to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV).
- Canagliflozin
  - to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
  - to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria
- Empagliflozin
  - to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease

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- https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204629s023lbl.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204042s036lbl.pdf

Questions

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