Diabetes and Hypertension Project ECHO* Clinic

*ECHO: Extension of Community Healthcare Outcomes

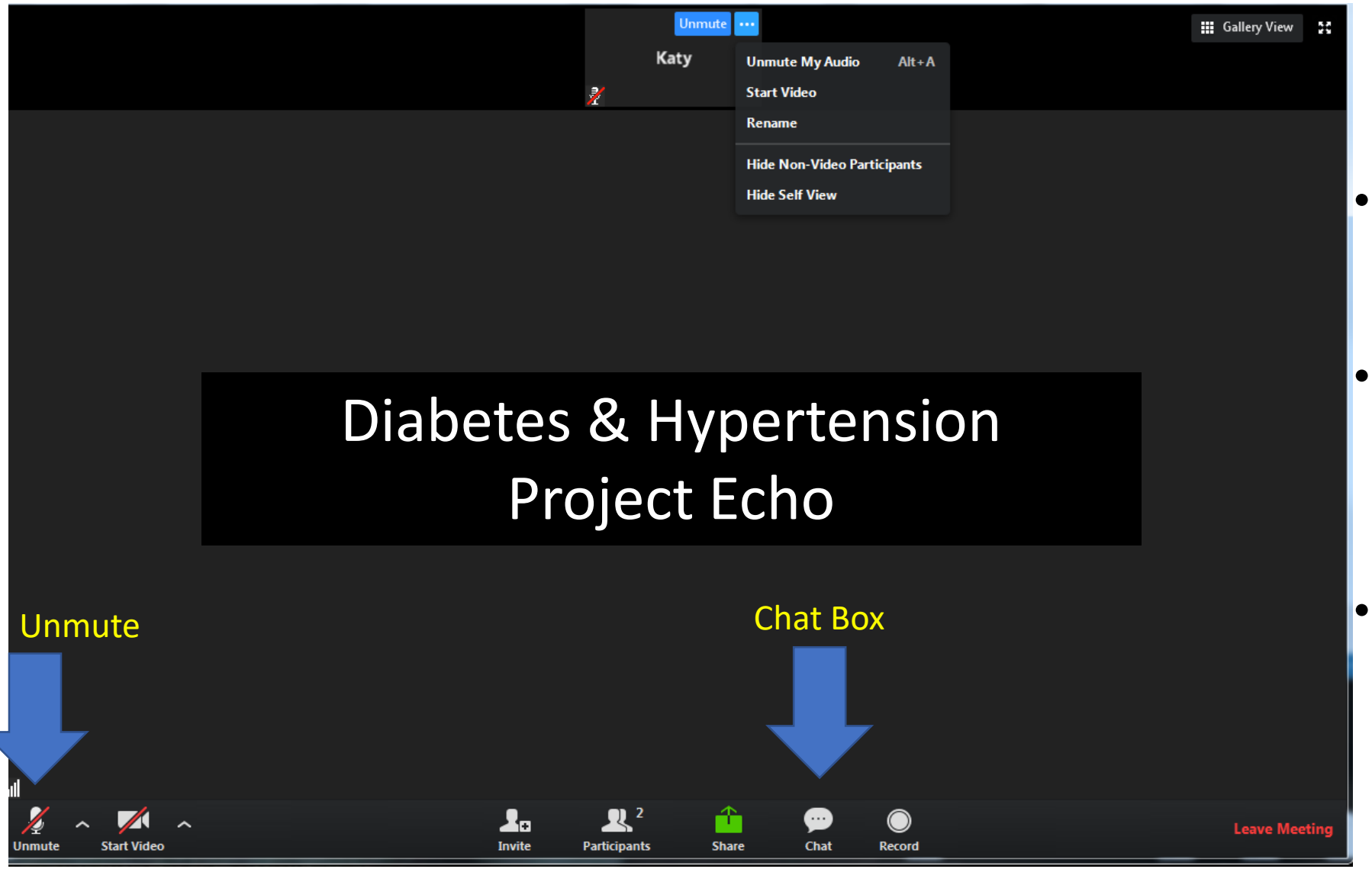
Sept. 9, 2021

Before we begin:

- Rename your Zoom screen with your name and organization
- Claim CE: text 19179-18817 to 804-625-4041
  - Go to **vcuhealth.org/echodmhtn** for instructions on creating your account

The Diabetes and Hypertension ECHO is made possible by funding through CDC Cooperative Agreement NU58DP006620-InnoVAte.

Zoom Reminders



- You are all on mute. Please unmute to talk.
- If joining by telephone audio only, press *6 to mute and unmute.
- Use the chat function to speak with our team or ask questions.

Helpful Reminders

- Please feel free to eat your lunch or step away briefly if needed
- We are recording and can share sessions upon request
  - Each session's slides are available on www.vcuhealth.org/echodmhtn
- Please **do not share any protected health information** in your discussion or the chat box
- Project ECHO operates on the "All Teach, All Learn" model
  - Feel free to ask questions in the chat or unmute to ask questions at designated times
  - We're all here to learn from each other and value each person's input and expertise!

VCU Health Diabetes & Hypertension ECHO Clinics

VCU Hub Team	
Principal Investigator	Dave Dixon, PharmD
Administrative Medical Director ECHO Hub	Vimal Mishra, MD, MMCi
Clinical Experts	Niraj Kothari, MD Trang Le, MD
Project Coordinator/IT Support	Madeleine Wagner

- **NEW: *1-hour*** ECHO clinics on 2nd and 4th Thursdays
- Every ECHO clinic includes a didactic presentation followed by case discussions
- Website: www.vcuhealth.org/echodmhtn
  - Directions for claiming CE can be found here
  - You have up to six days after our session to claim CE by texting **19179-18817** to **804-625-4041**

Disclosures

Salvatore Carbone, Ph.D., has no financial conflicts of interest to disclose.

Trang Le, M.D., has no financial conflicts of interest to disclose.

Niraj Kothari, M.D., has no financial conflicts of interest to disclose.

There is no commercial or in-kind support for this activity.

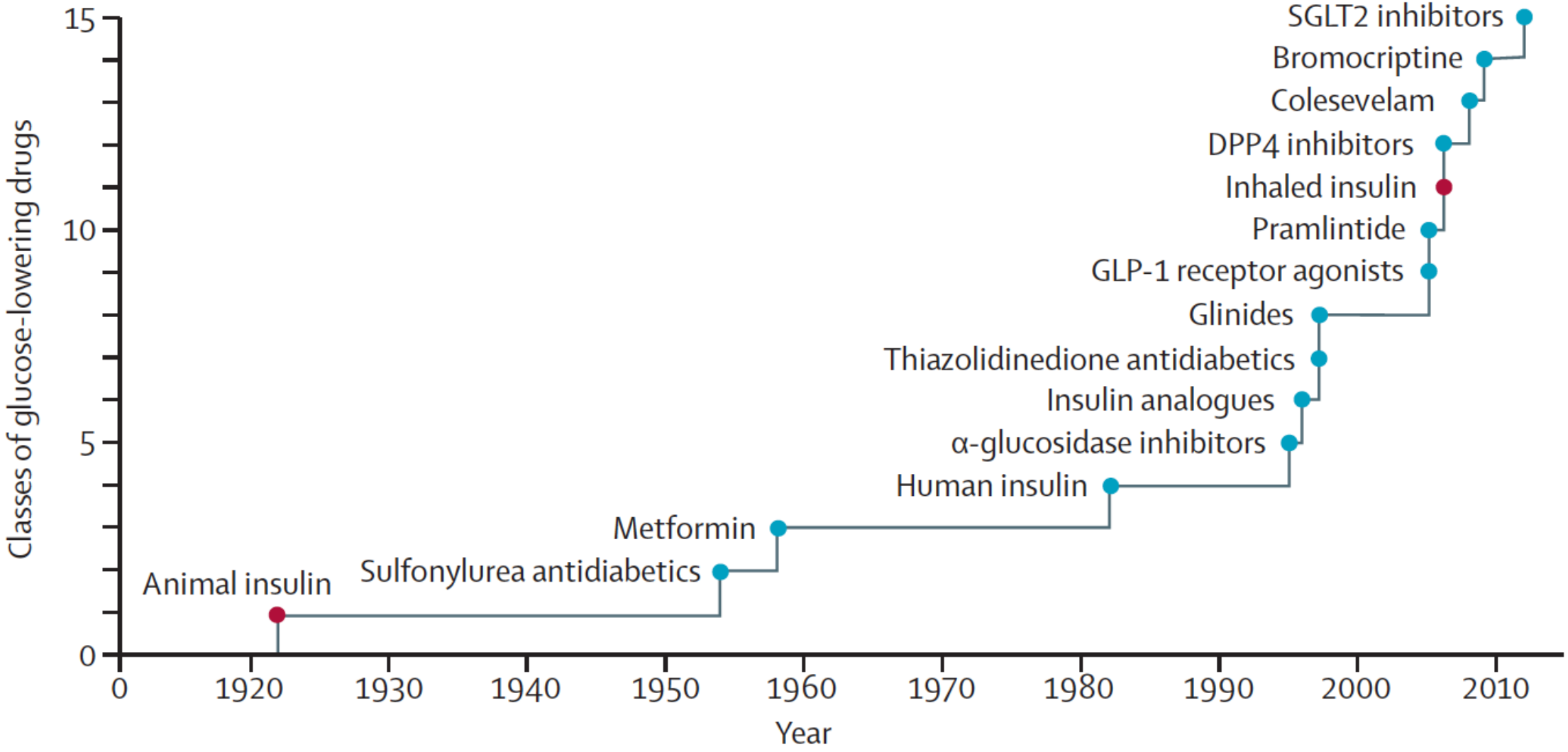
SGLT2 Inhibitors and GLP1 Receptor Agonist for Cardiovascular Disease Prevention

Salvatore Carbone, PhD
Assistant Professor
Department of Kinesiology & Health Sciences
College of Humanities & Science
Virginia Commonwealth University
Email: *scarbone@vcu.edu*
@totocarbone

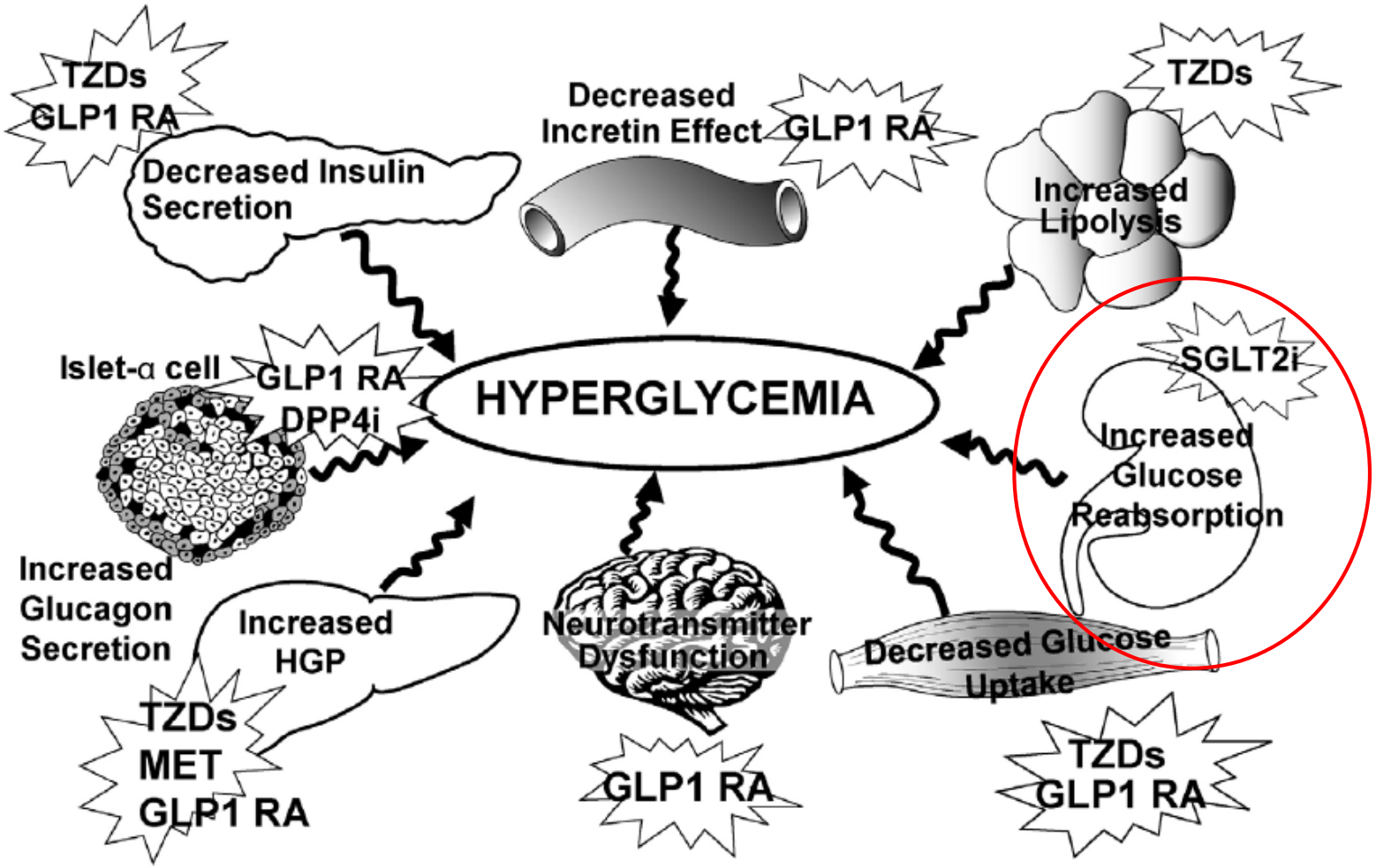
Objectives

- Understand the new classes of glucose-lowering drugs and their mechanism of action focusing on SGLT2i and GLP1RA
- Recognize the SGLT2i and GLP1RA associated with a reduction in cardiovascular events
- Briefly review the guidelines for CVD risk reduction in patients with T2DM
- Identify the patients that may benefit the most from SGLT2i and/or GLP1RA to reduce CV risk

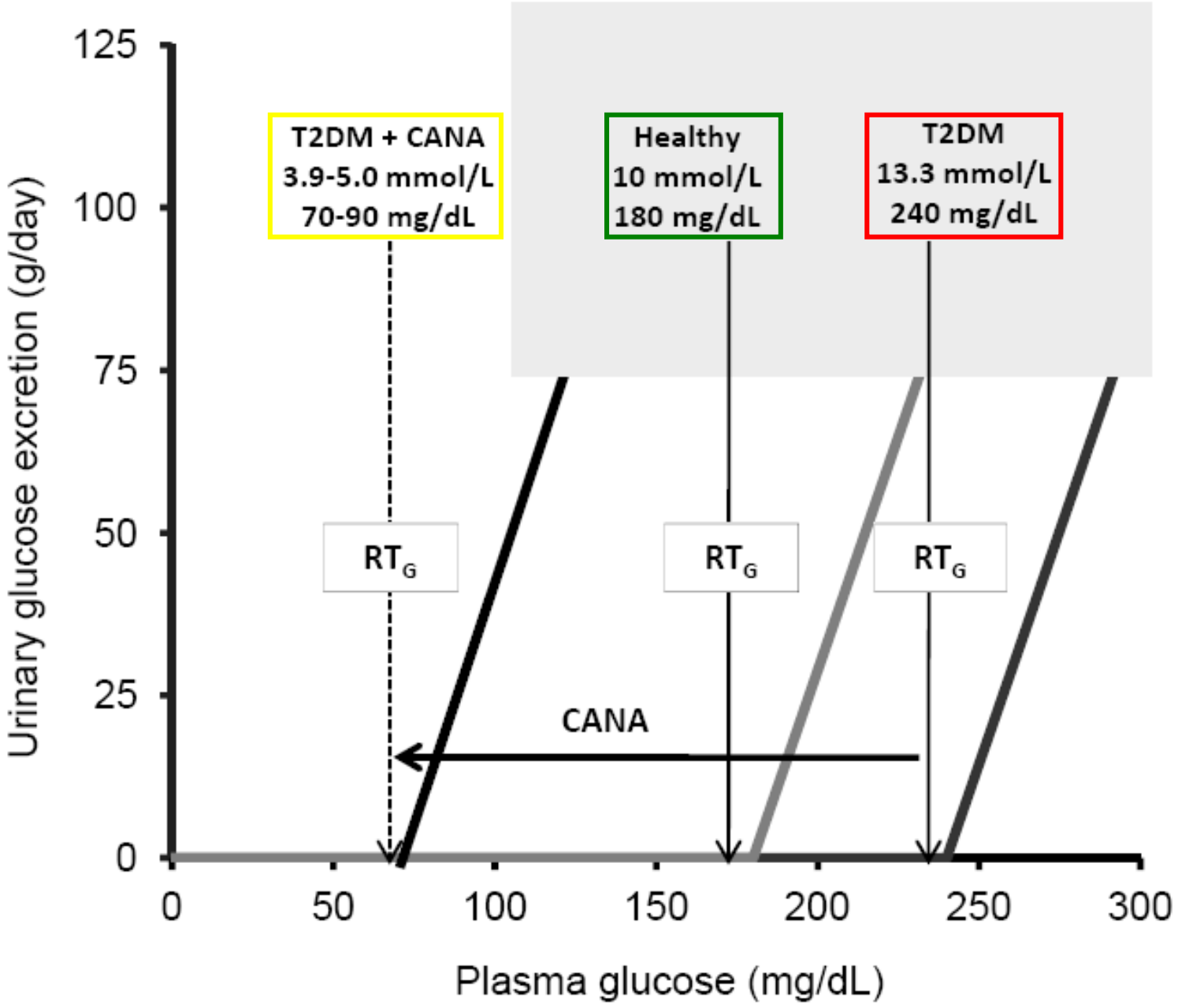
Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future



Kahn SE et al. *Lancet* 2014;383(9922):1068-83
Defronzo RA. Diabetes 2009;58(4):773-95

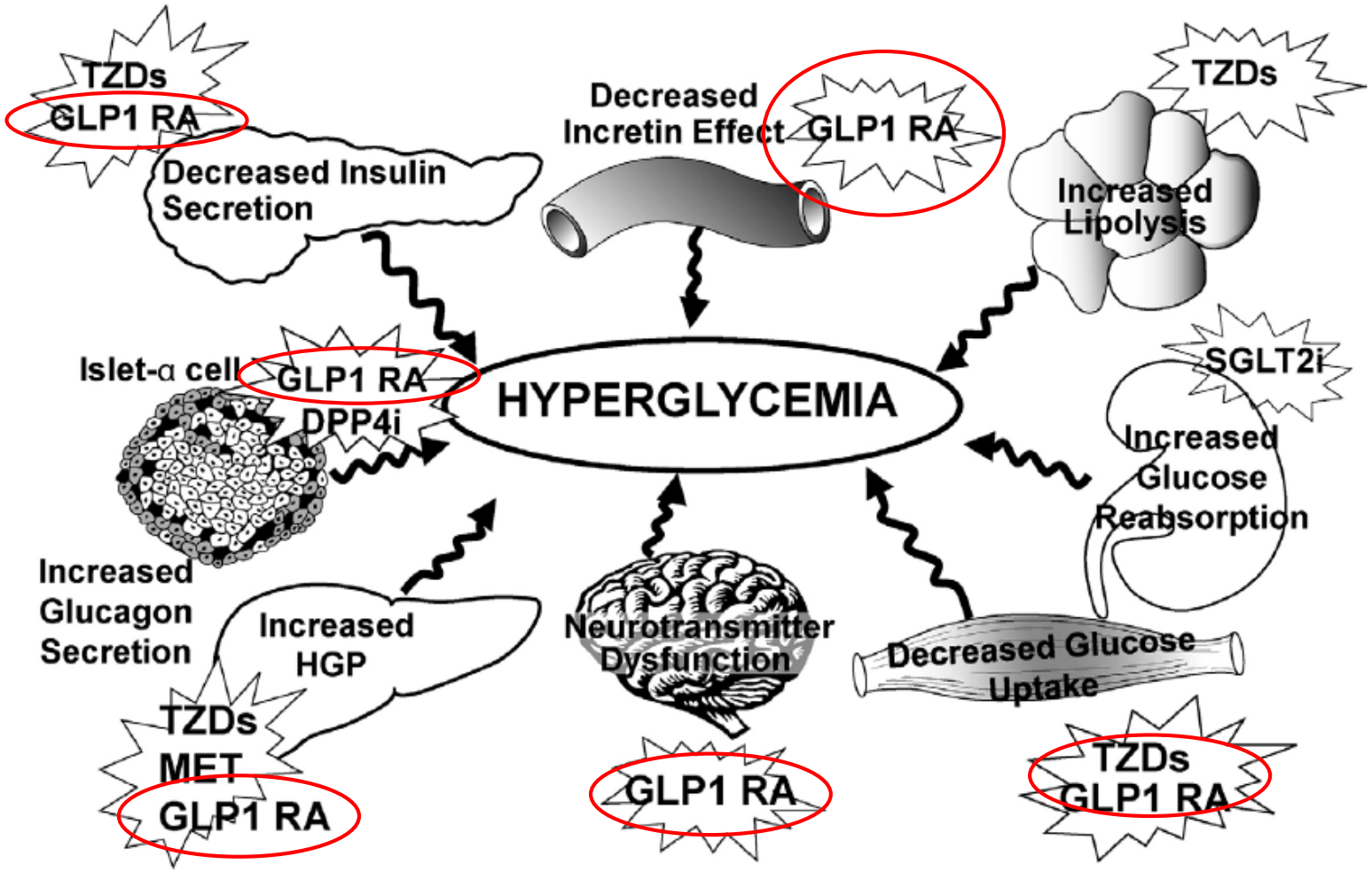


DeFronzo RA et al. *Diabetes Spectr* 2014;27(2):100-12



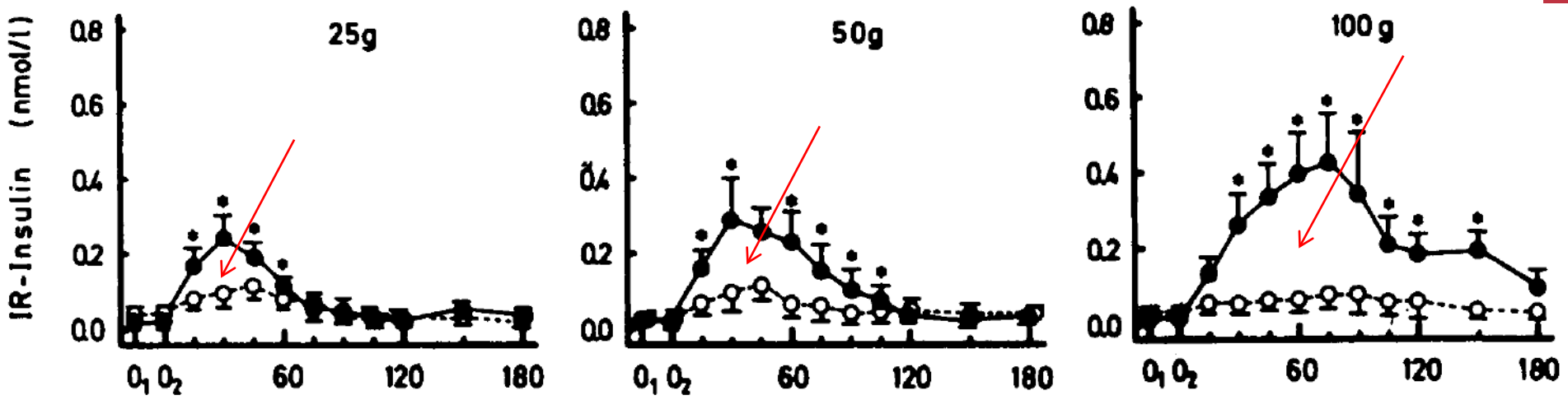
Carbone S and Dixon DL. *Cardiovasc Diabetol* 2019;18(1):64

The Ominous Octet

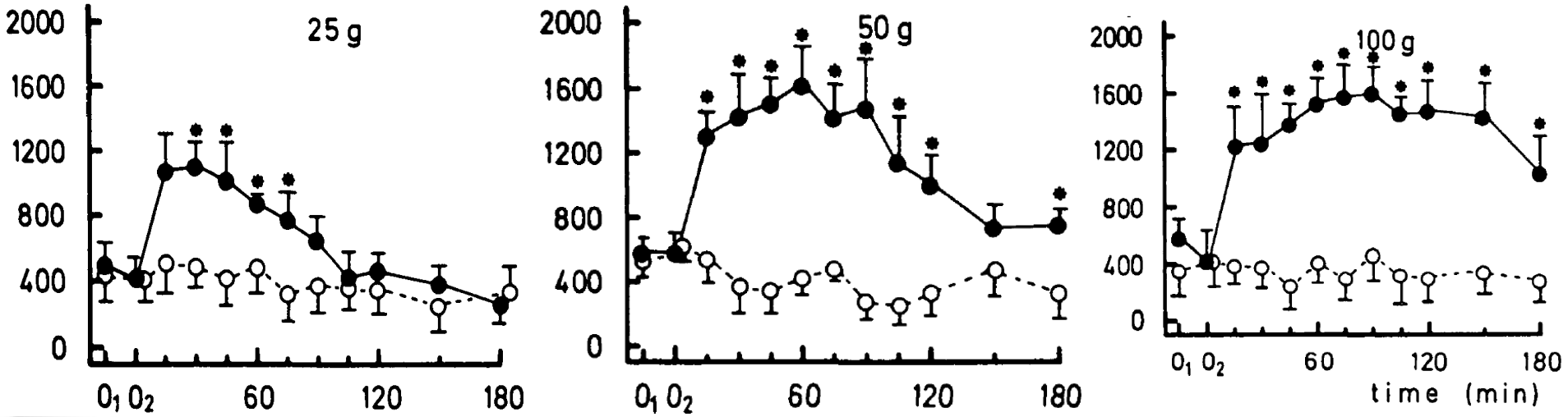


DeFronzo RA et al. *Diabetes Spectr* 2014;27(2):100-12

Incretin Effect → Incretin (Intestin – Secretion – Insulin)



Glucose-dependent insulinotropic peptide (GIP) and Glucagon Like Peptide-1



Nauck MA et al. *J Clin Endocrinol Metab* 1986;63:492-498

Risk of Hypoglycemia

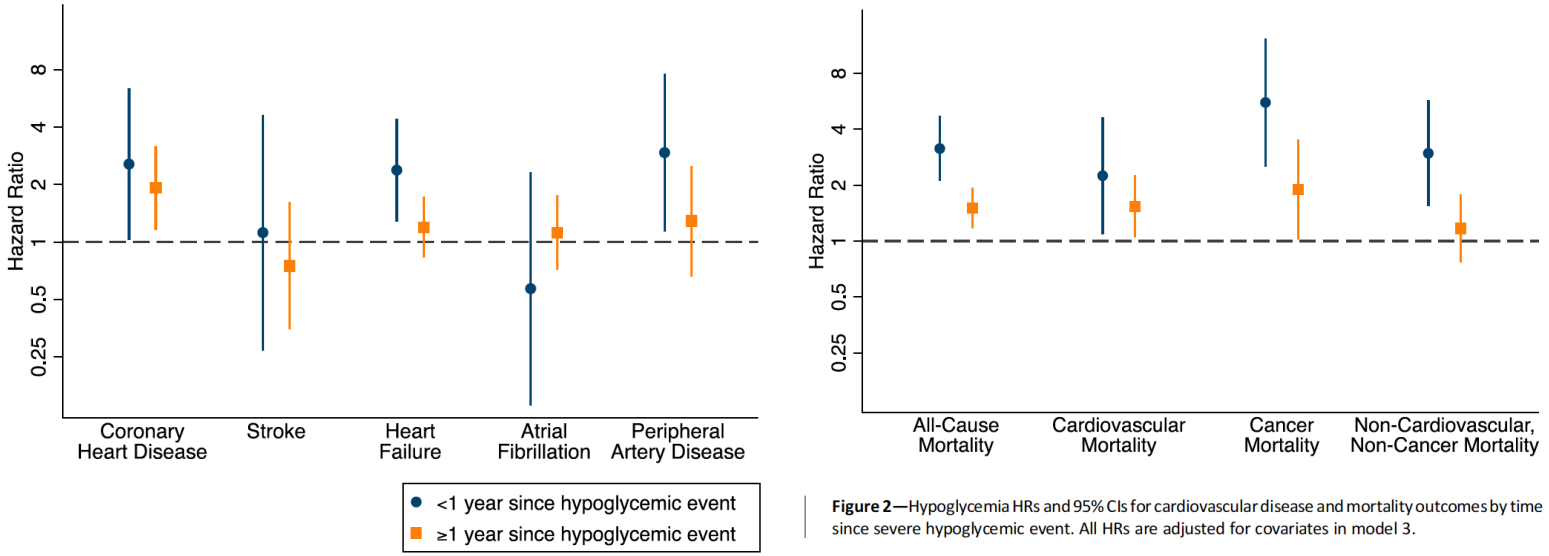
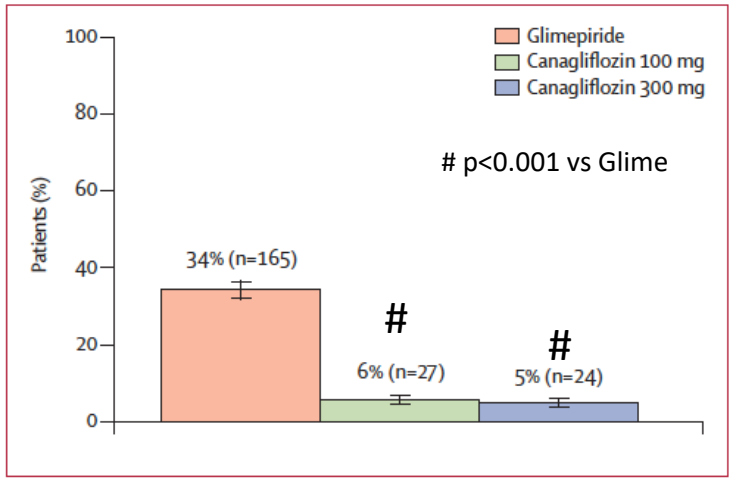
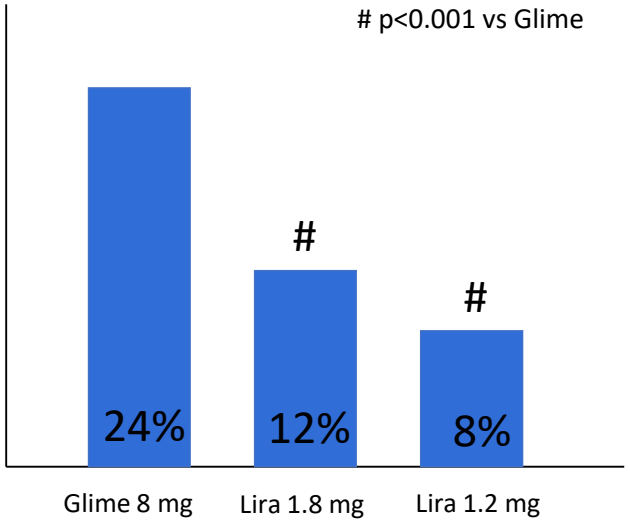


Figure 2—Hypoglycemia HRs and 95% CIs for cardiovascular disease and mortality outcomes by time since severe hypoglycemic event. All HRs are adjusted for covariates in model 3.



Cefalu WT. *Lancet* 2013(9896):941-50

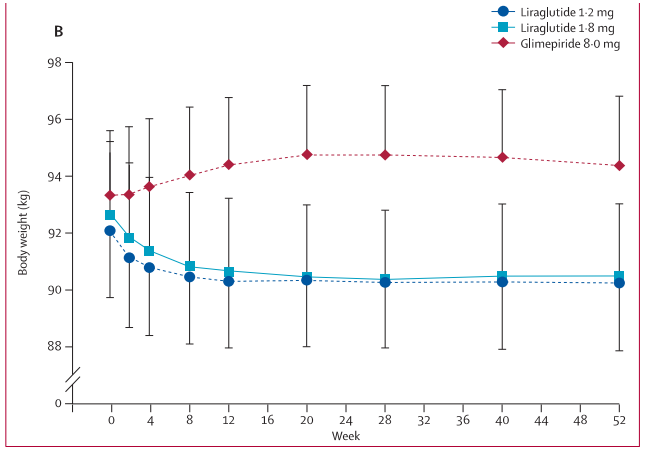


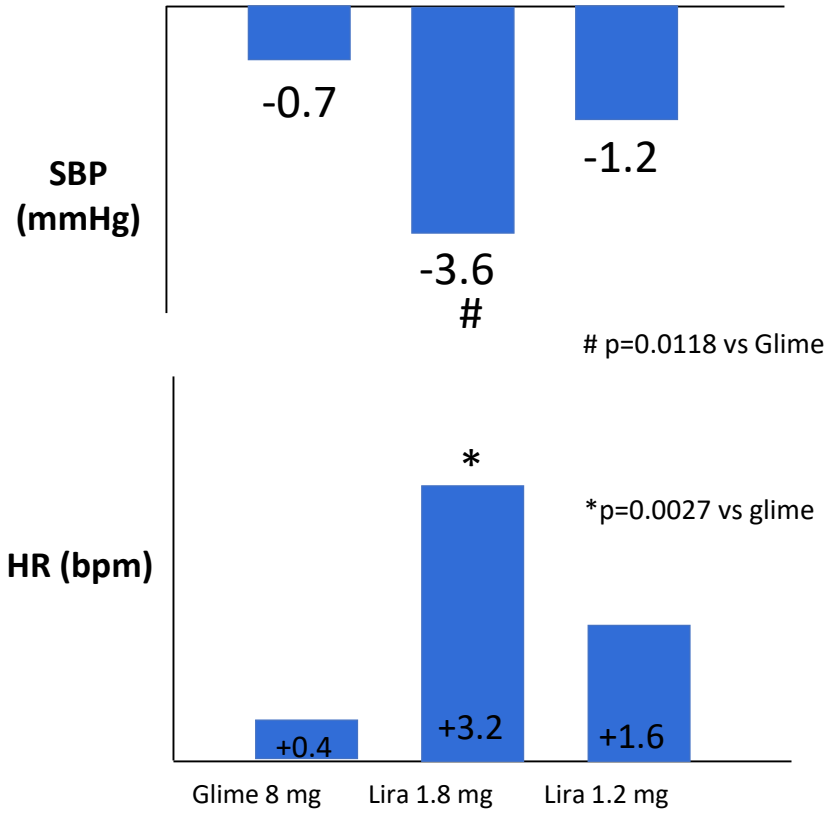
Garber A et al. *Lancet* 2009;373(9662):473-81

	Glimepiride	Canagliflozin 100 mg	Canagliflozin 300 mg
Overall population			
Bodyweight (n)	478	479	480
Mean (SD) baseline (kg)	86·6 (19·8)	86·8 (20·0)	86·6 (19·3)
LS mean (SE) change	0·7 (0·2)	−3·7 (0·2)	−4·0 (0·2)
Difference (95% CI) *vs* glimepiride	..	−4·4 (−4·8 to −3·9)	−4·7 (−5·2 to −4·3)
LS mean (SE) percentage change	1·0% (0·2)	−4·2% (0·2)	−4·7% (0·2)
Difference (95% CI) *vs* glimepiride	..	−5·2 (−5·7 to −4·7)*	−5·7 (−6·2 to −5·1)*
Systolic blood pressure (n)	480	479	480
Mean (SD) baseline (mm Hg)	129·5 (13·5)	130·0 (12·4)	130·0 (13·8)
LS mean (SE) change	0·2 (0·6)	−3·3 (0·6)	−4·6 (0·6)
Difference (95% CI) *vs* glimepiride	..	−3·5 (−4·9 to −2·1)	−4·8 (−6·2 to −3·4)
Diastolic blood pressure (n)	480	479	480
Mean (SD) baseline (mm Hg)	79·0 (8·4)	78·7 (8·0)	79·2 (8·4)
LS mean (SE) change	−0·1 (0·4)	−1·8 (0·4)	−2·5 (0·4)
Difference (95% CI) *vs* glimepiride		−1·7 (−2·6 to −0·8)	−2·4 (−3·3 to −1·5)
Pulse rate (n)	346	365	357
Mean baseline (beats per min)	73·5	74·2	74·6
Mean (SD) change	0·5 (8·3)	−1·1 (8·5)	−1·2 (8·7)

*p<0·0001 *vs* glimepiride.

Cefalu WT. *Lancet* 2013(9896):941-50





Garber A et al. *Lancet* 2009;373(9662):473-81

Why focusing not only on HbA1c reduction?

Outcome	Relative Risk Reduction	Source
Retinopathy*	29% per 0.9% ↓ A1c	UKPDS[27]
Neuropathy†	19% per 0.9% ↓ A1c	UKPDS[27]
Microalbuminuria‡	33% per 0.9% ↓ A1c	UKPDS[27]

*Surrogate outcome defined as ≥1 microaneurysm in 1 eye or worse retinopathy, and progression of retinopathy as a 2-step change in Early Treatment of Diabetic Retinopathy Study grade.

† Surrogate outcome defined as loss of both ankle reflexes or both knee reflexes, or mean biothesiometer reading from both toes >25 V.

‡ Surrogate outcome defined as urinary albumin concentration >50 mg/L.

UKPDS group. *Lancet* 1998;352(9131):837-53
Makam AN et al. *Circulation* 2017;135(2):180-195

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

	Clinical trial of intensive *v* conventional policy[1]		
	No of events	Decrease in risk (%) seen for 0.9% difference in HbA_{1c} (95% CI)	P value
Aggregate end points			
Any end point related to diabetes	1401	12 (1 to 21)	0.029
Deaths related to diabetes	414	10 (–11 to 27)	0.34
All cause mortality	702	6 (–10 to 20)	0.44
Myocardial infarction	573	16 (0 to 29)	0.052
Stroke	203	–11 (–49 to 19)	0.52
Peripheral vascular disease*	47	35 (–18 to 64)	0.15
Microvascular disease	346	25 (7 to 40)	0.0099
Single end points			
Heart failure	116	9 (–35 to 39)	0.63
Cataract extraction	229	24 (0 to 42)	0.046

*Lower extremity amputation or fatal peripheral vascular disease.

Stratton IM et al. *BMJ* 2000;321:405-12

Guidance for Industry

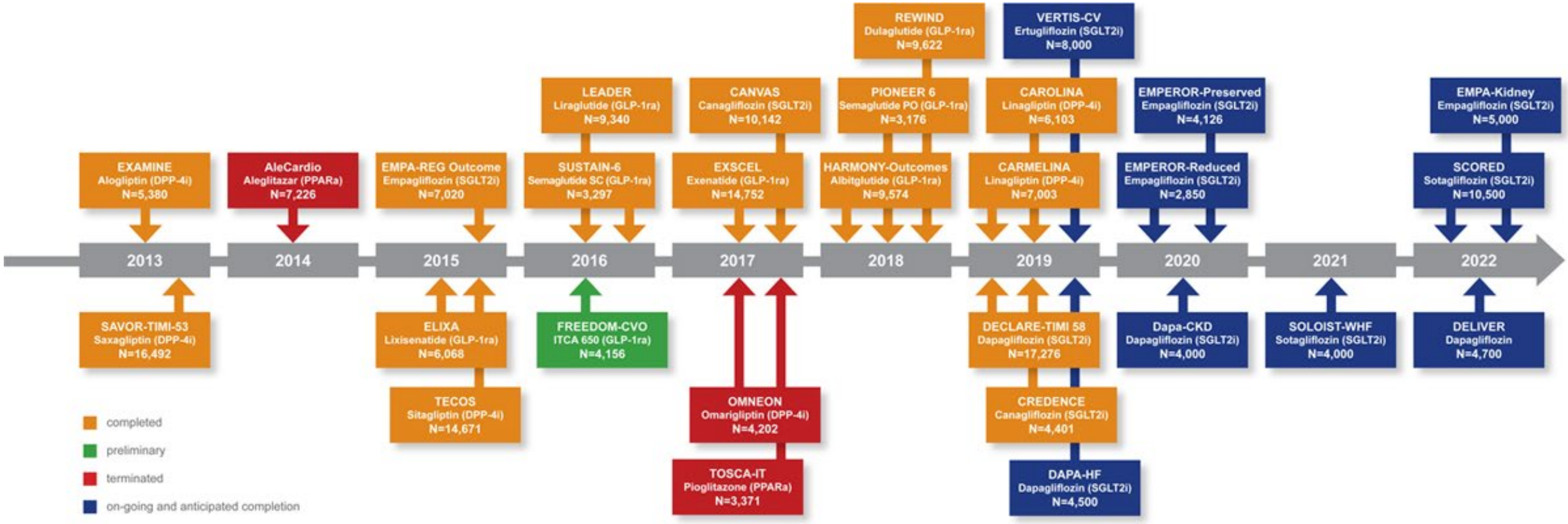
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

post marketing trials
to provide definitive evidence of a CV RR <1.3
(vs Placebo)

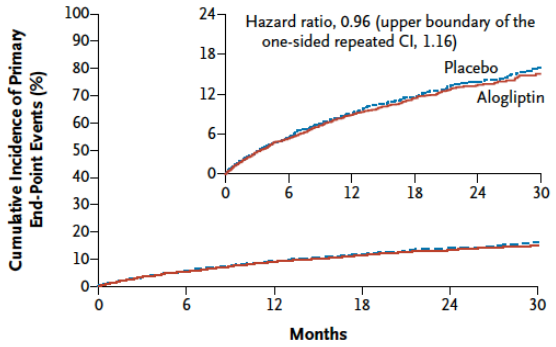
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Timeline of CV "Safety" Trials per FDA Guidance on New Diabetes Therapies

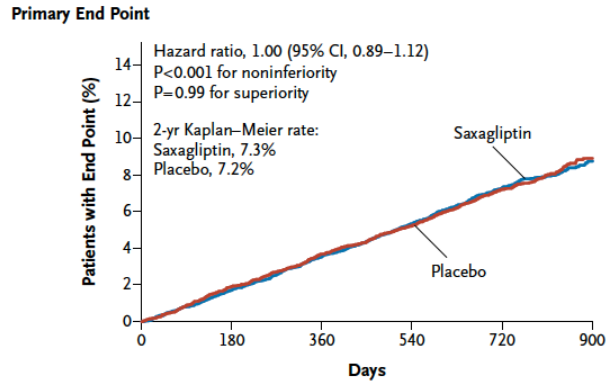


EXAMINE[1]



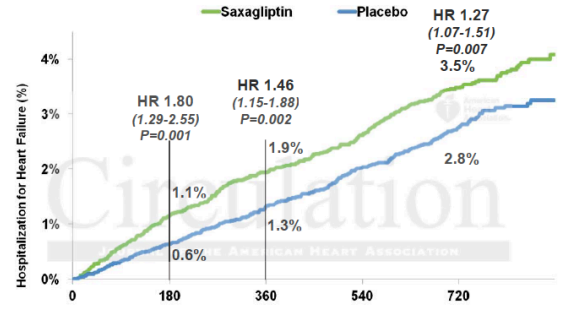
No. at Risk						
Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

SAVOR-TIMI 53[2]



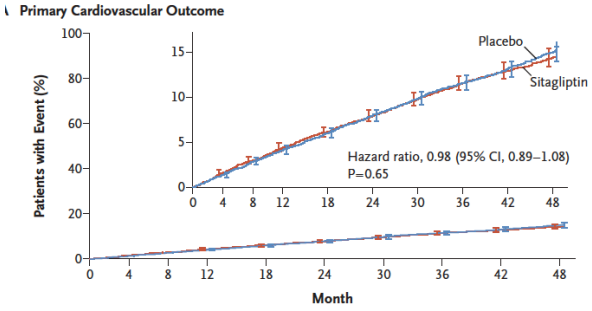
No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

SAVOR-TIMI 53[3] - Heart Failure



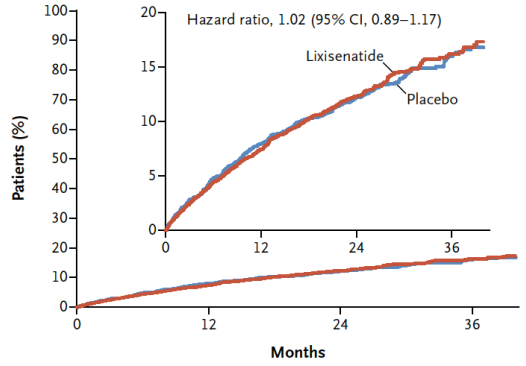
Placebo	8212	8036	7856	7389	4959
Saxagliptin	8280	8064	7867	7375	4978

TECOS[4]



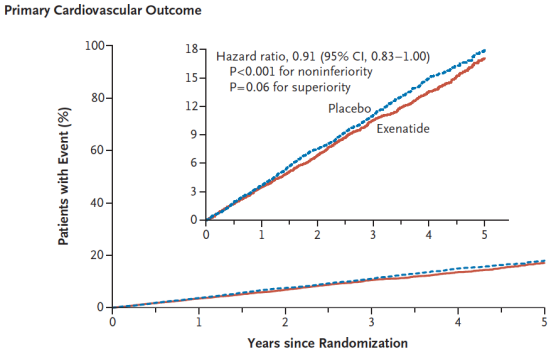
No. at Risk										
Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

ELIXA[5]



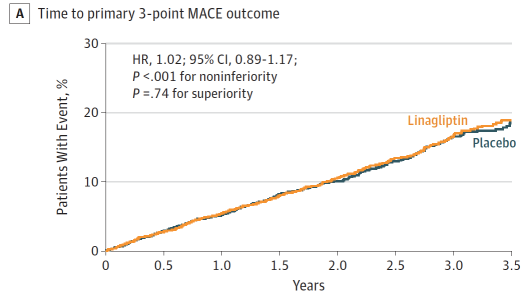
No. at Risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

EXSCEL[6]



No. at Risk											
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727

CARMELINA[7]



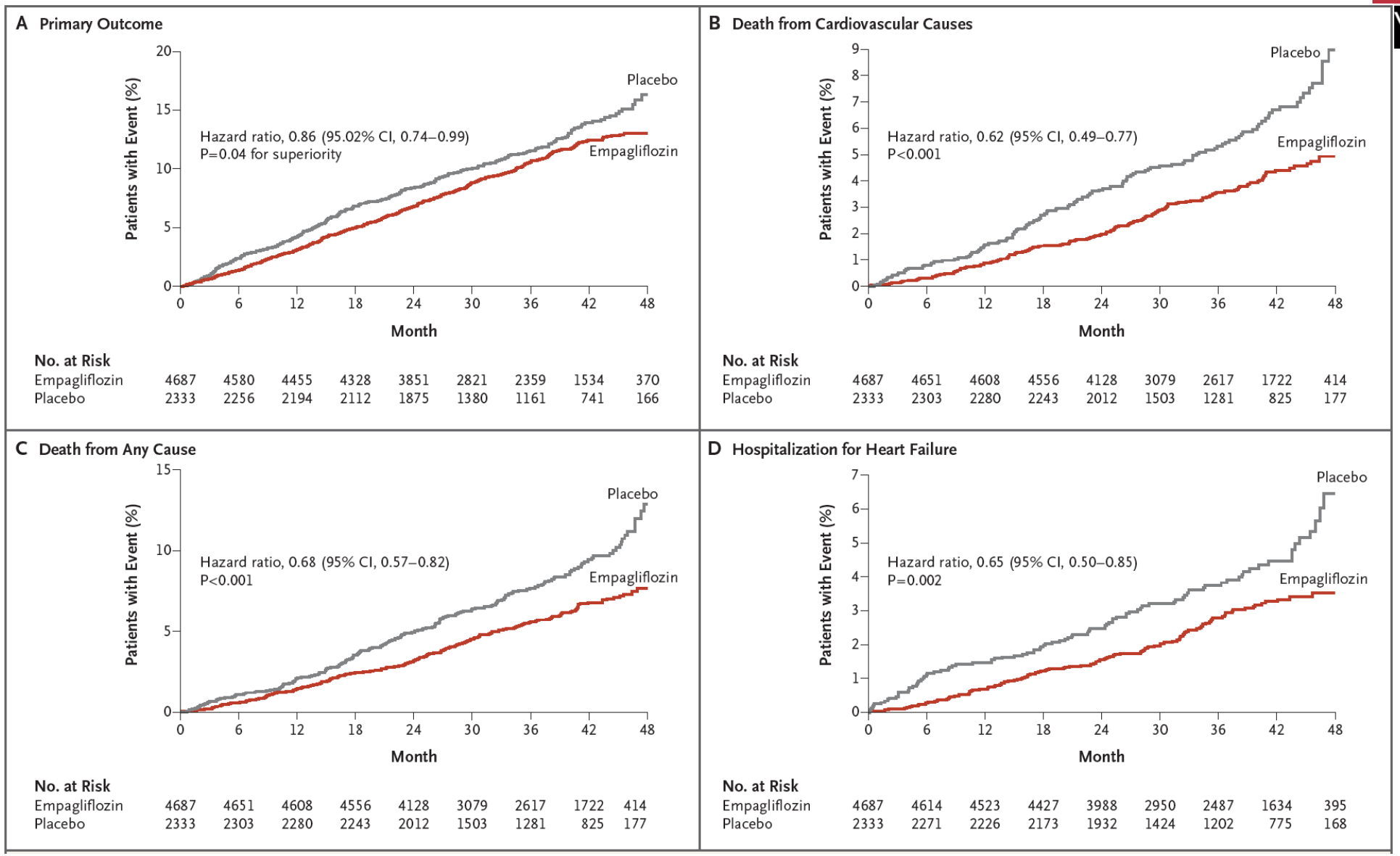
No. of patients								
Placebo	3485	3353	3243	2625	1931	1285	758	251
Linagliptin	3494	3373	3254	2634	1972	1306	778	269

[1]White WB et al. *N Engl J Med* 2013;369(14):1327-35
[2]Scirica BM et al. *N Engl J Med* 2013;369(14):1317-26
[3]Scirica BM et al. *Circulation* 2015;132(15):e198
[4]Green JB et al. *N Engl J Med* 2015;373(3):232-42
[5]White WB et al. *N Engl J Med* 2015;373(23):2247-57
[6]Holman RR et al. *N Engl J Med* 2017;377(13):1228-1239
[7]Rosenstock J et al. *JAMA* 2019;321(1):69-79

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Secondary prevention study
Type 2 Diabetes Mellitus
Approximately 7,000 patients followed for a median of 2.5 years, up to 4 years

Project ECHO®
Virginia Commonwealth University



VCU

Zinman B et al. *N Engl J Med* 2015;373(22):2117-28

December 2, 2016

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm

Less AE
Less SAE

Less UTI in women

Less renal failure

More genital (fungal) infections

Table 2. Adverse Events.*

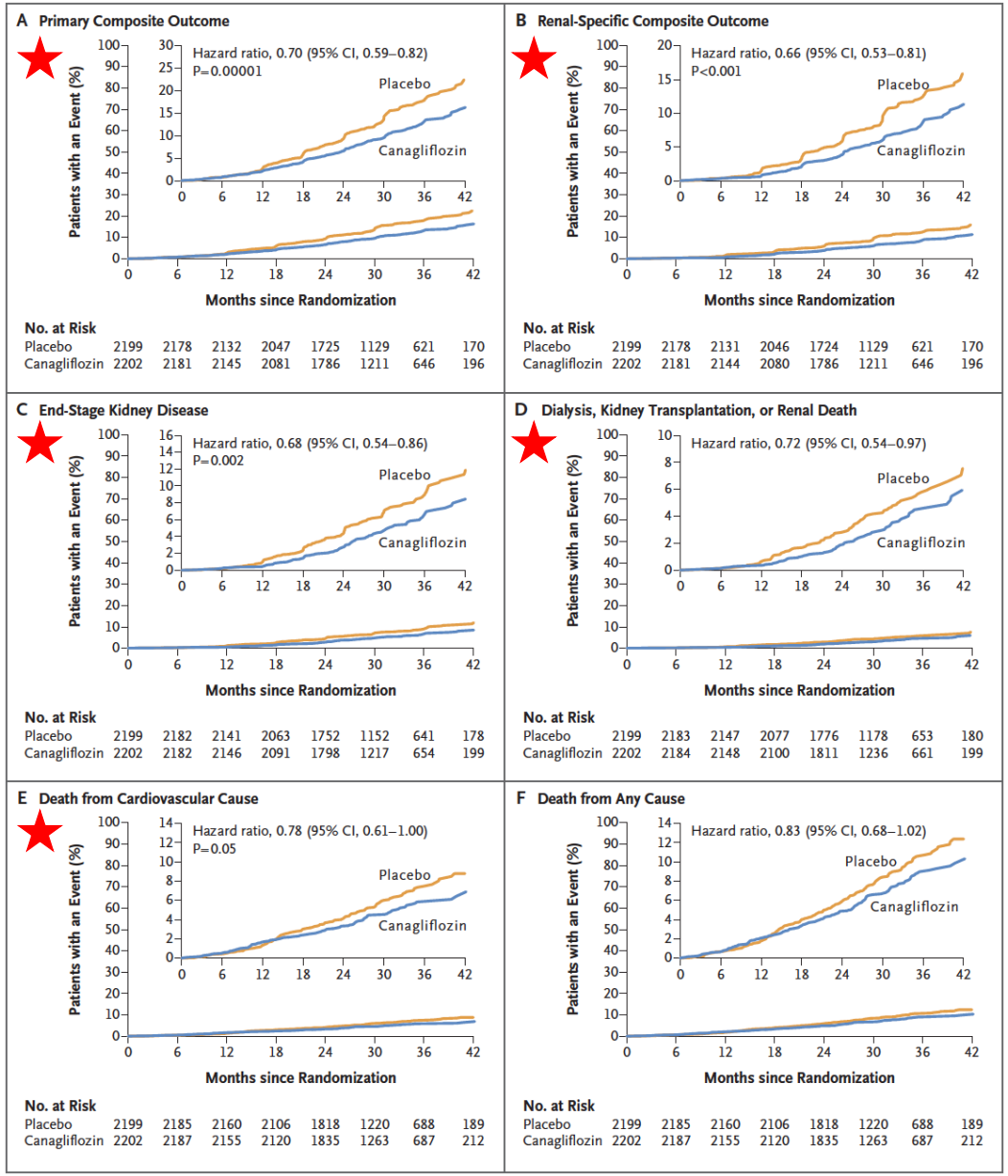
Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)‡
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

* Data are for patients who had one or more event and who had received at least one dose of a study drug. All events occurred within 7 days after the last receipt of the study drug.
† P<0.001 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.01 for the comparison with placebo.

Zinman B et al. *N Engl J Med* 2015;373(22):2117-28

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

Primary and Secondary (mainly) Prevention study
Type 2 Diabetes Mellitus with albuminuric CKD
Approximately 4,400 followed for a median 2.6 years, but up to 4.5 years
On top of ACE/ARB therapy!



Perkovic V et al. *N Engl J Med* 2019 Apr 14. [Epub ahead of print]

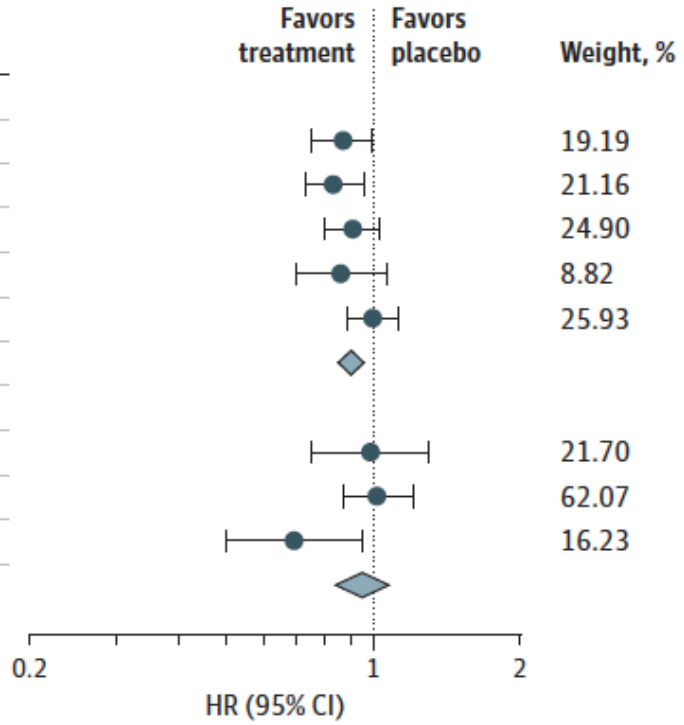
Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes

A Meta-analysis

Project ECHO® Virginia Commonwealth University

B MACEs by ASCVD status

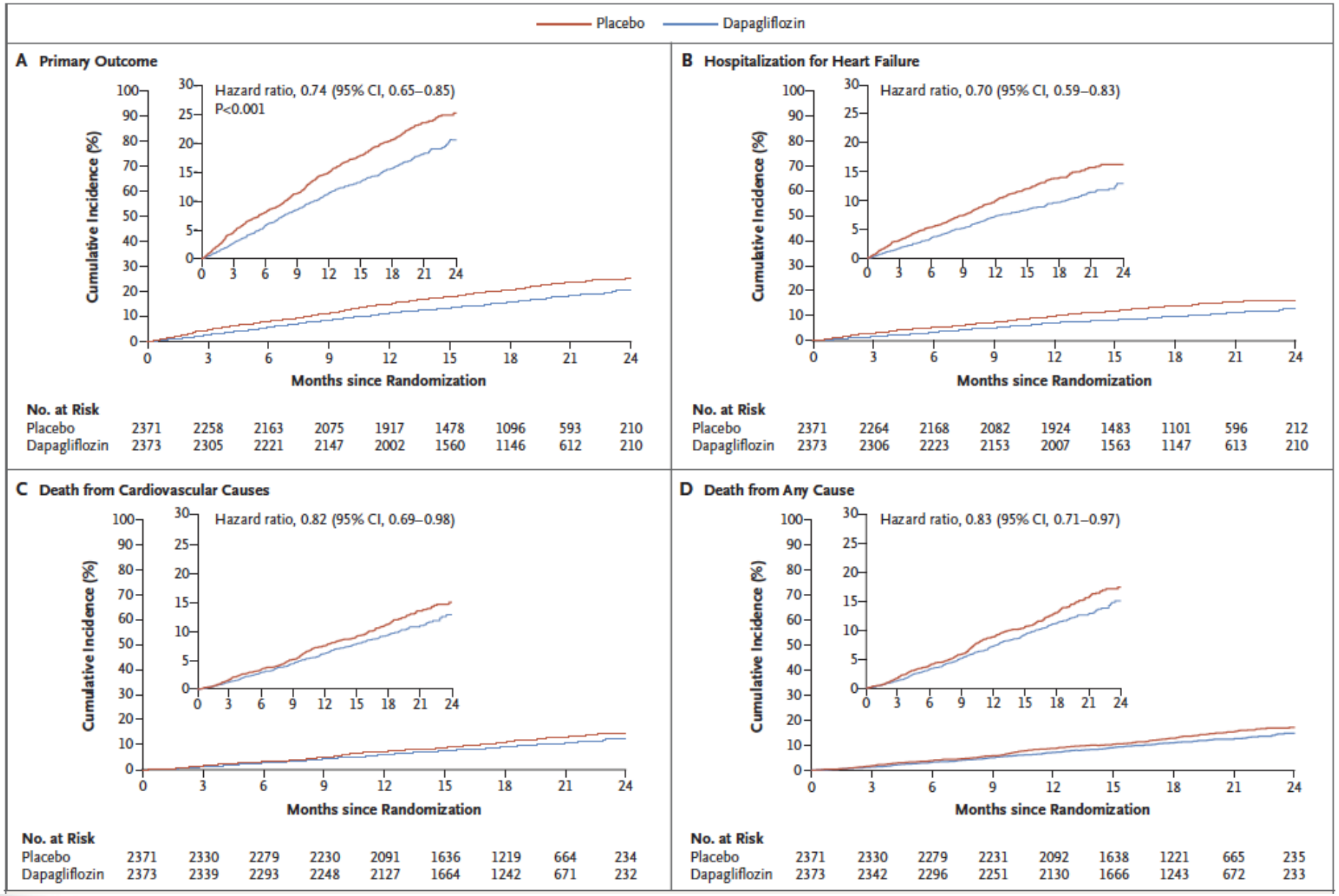
	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MACEs, major adverse cardiovascular events; NA, not available; VERTIS CV, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease.

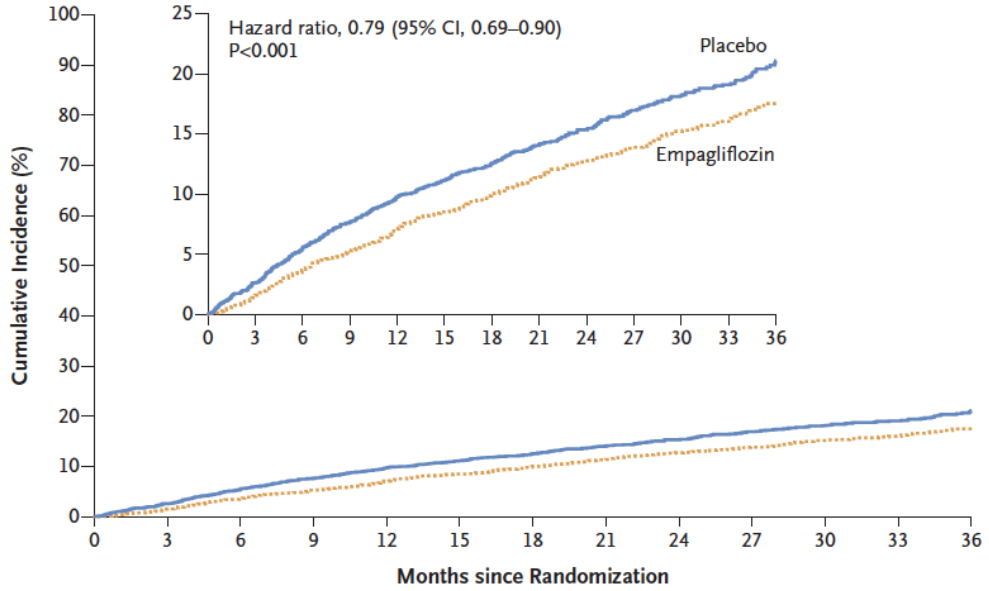
McGuire DK et al. *JAMA Cardiol* 2020 Oct 7:e20451

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

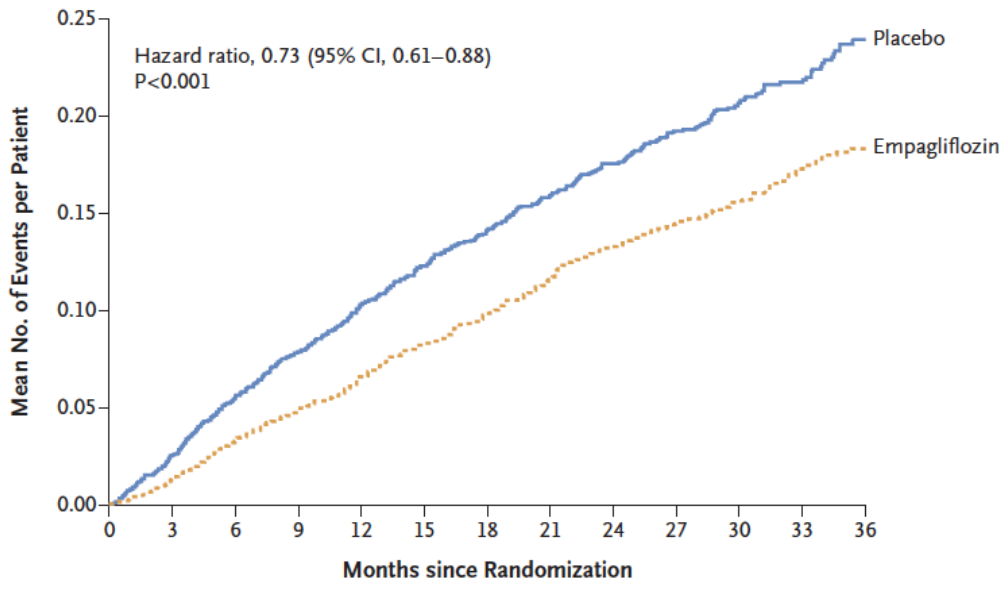


McMurray JJV et al. *N Engl J Med* 2019;381(21):1995-2008

Empagliflozin in Heart Failure with a Preserved Ejection Fraction



No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402



No. at Risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Anker SD et al. *N Engl J Med* 2021

Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)

Randomized within 24 h from admission

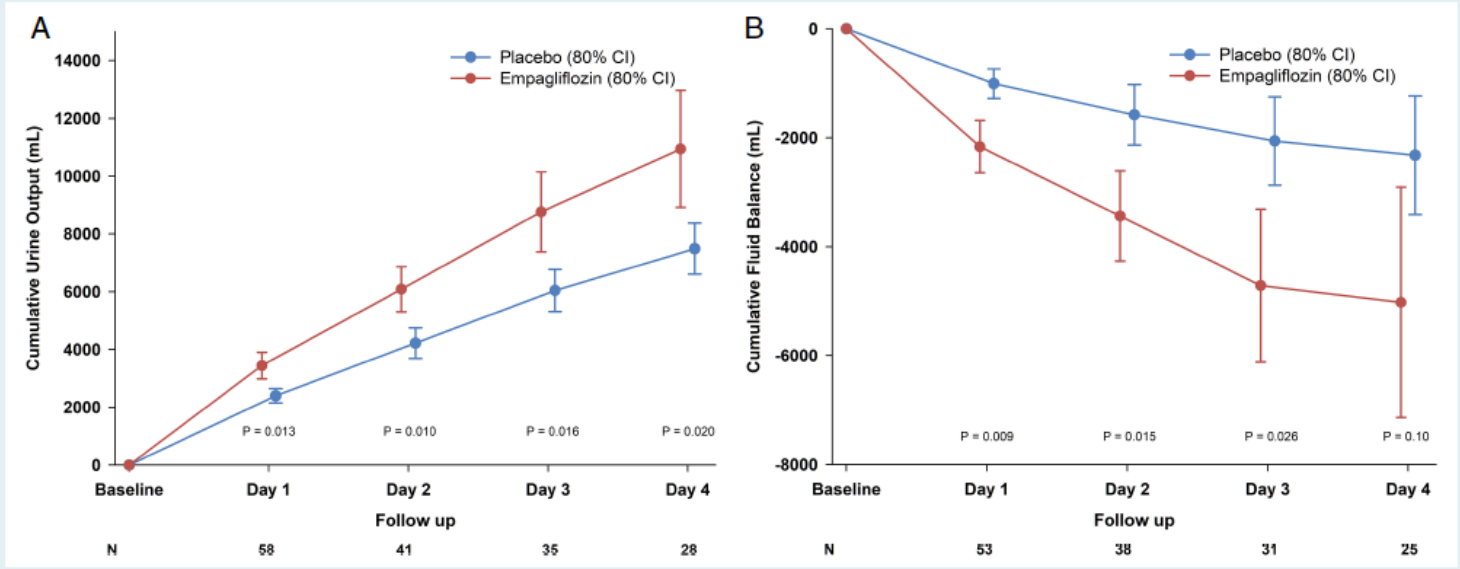
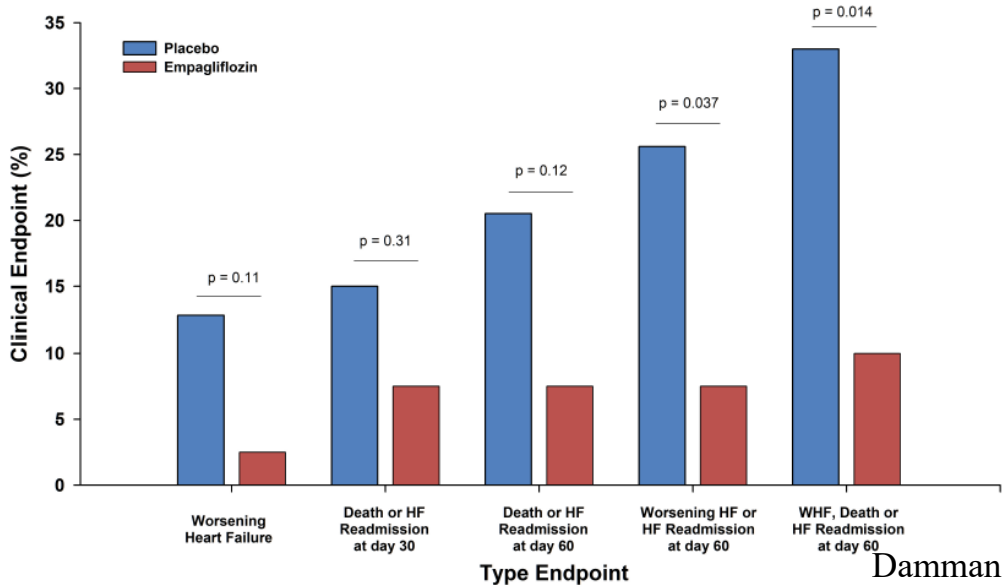


Figure 5 Urinary output and net fluid balance through day 4. (*A*) Cumulative urine output. (*B*) Cumulative net fluid balance. CI, confidence interval.



Damman K et al. *Eur J Heart Fail* 2020;22(4):713-722

Randomized Trial of Empagliflozin in Non-Diabetic Patients with Heart Failure and Reduced Ejection Fraction

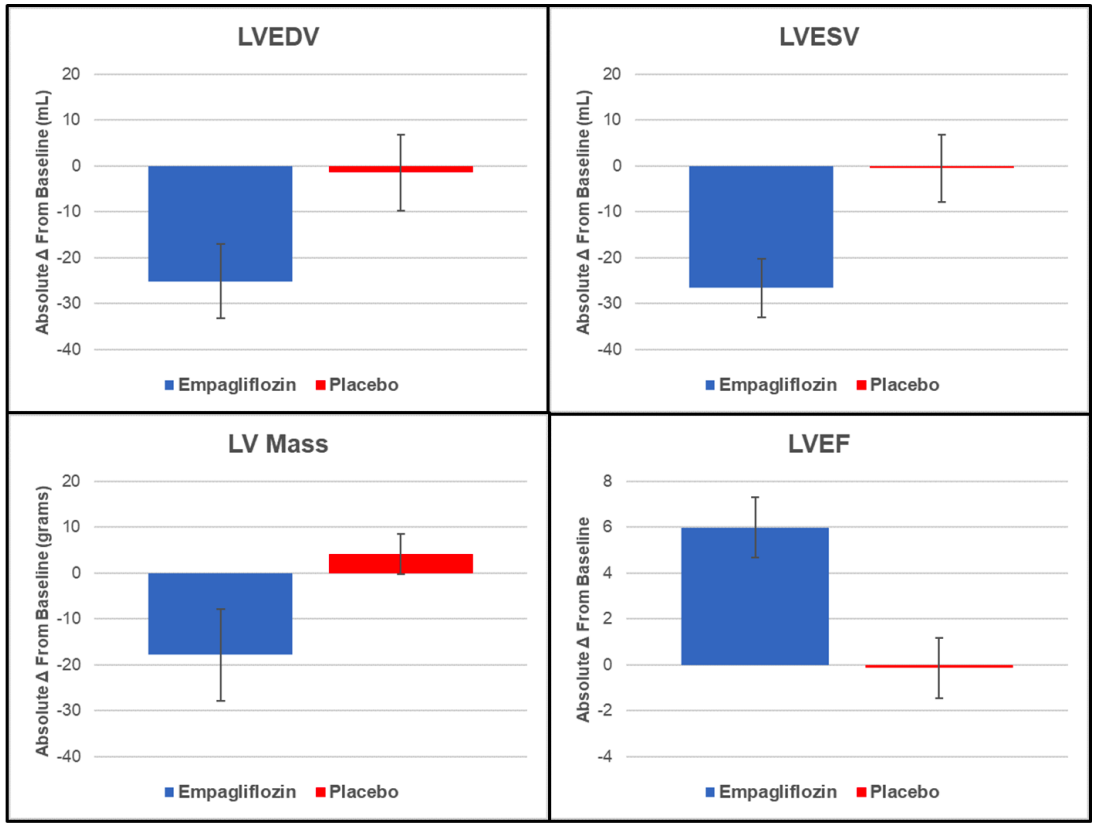
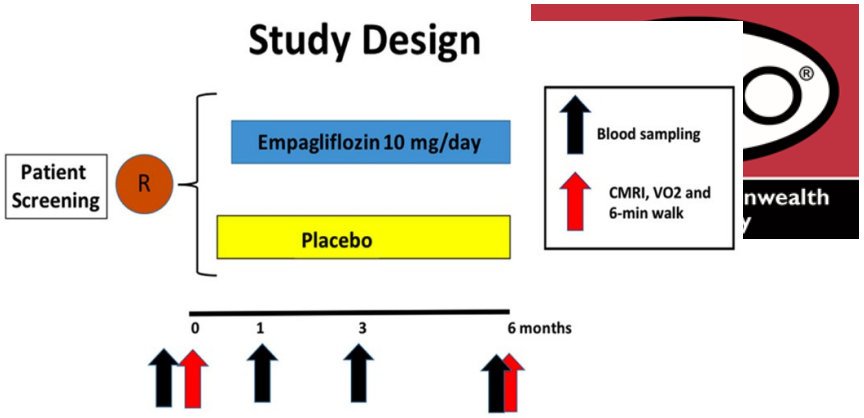


Figure 3



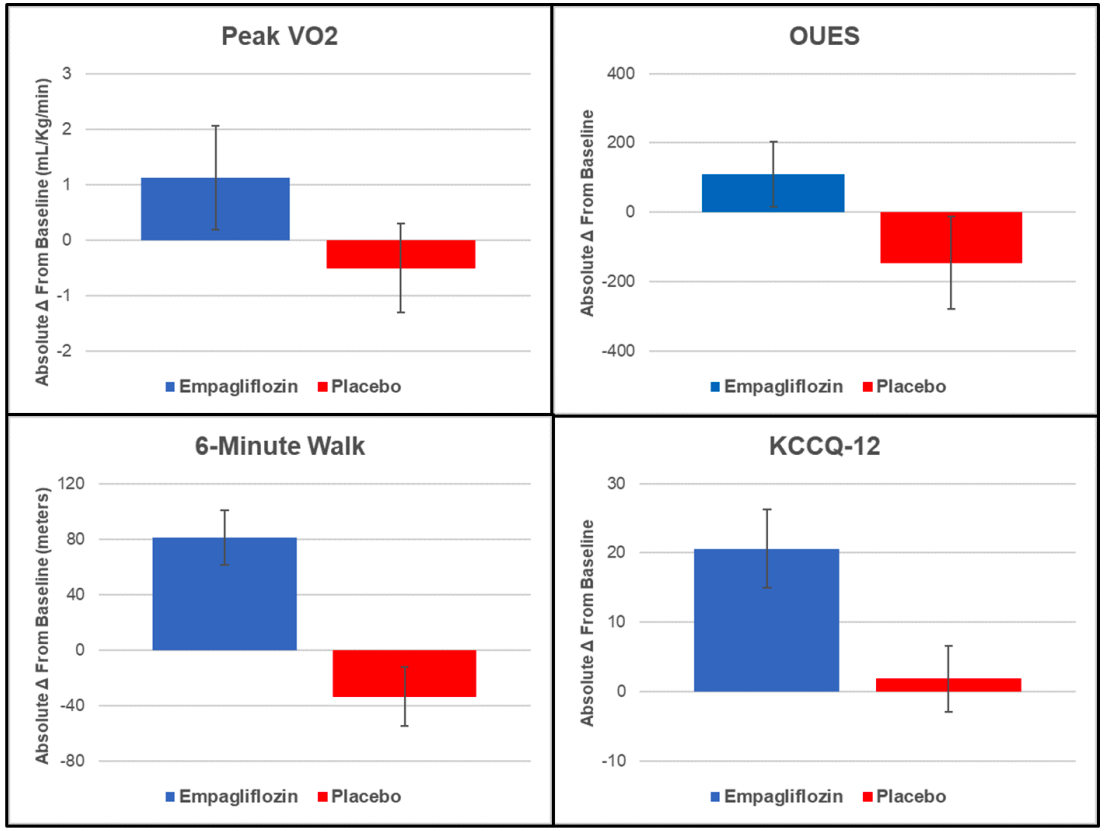
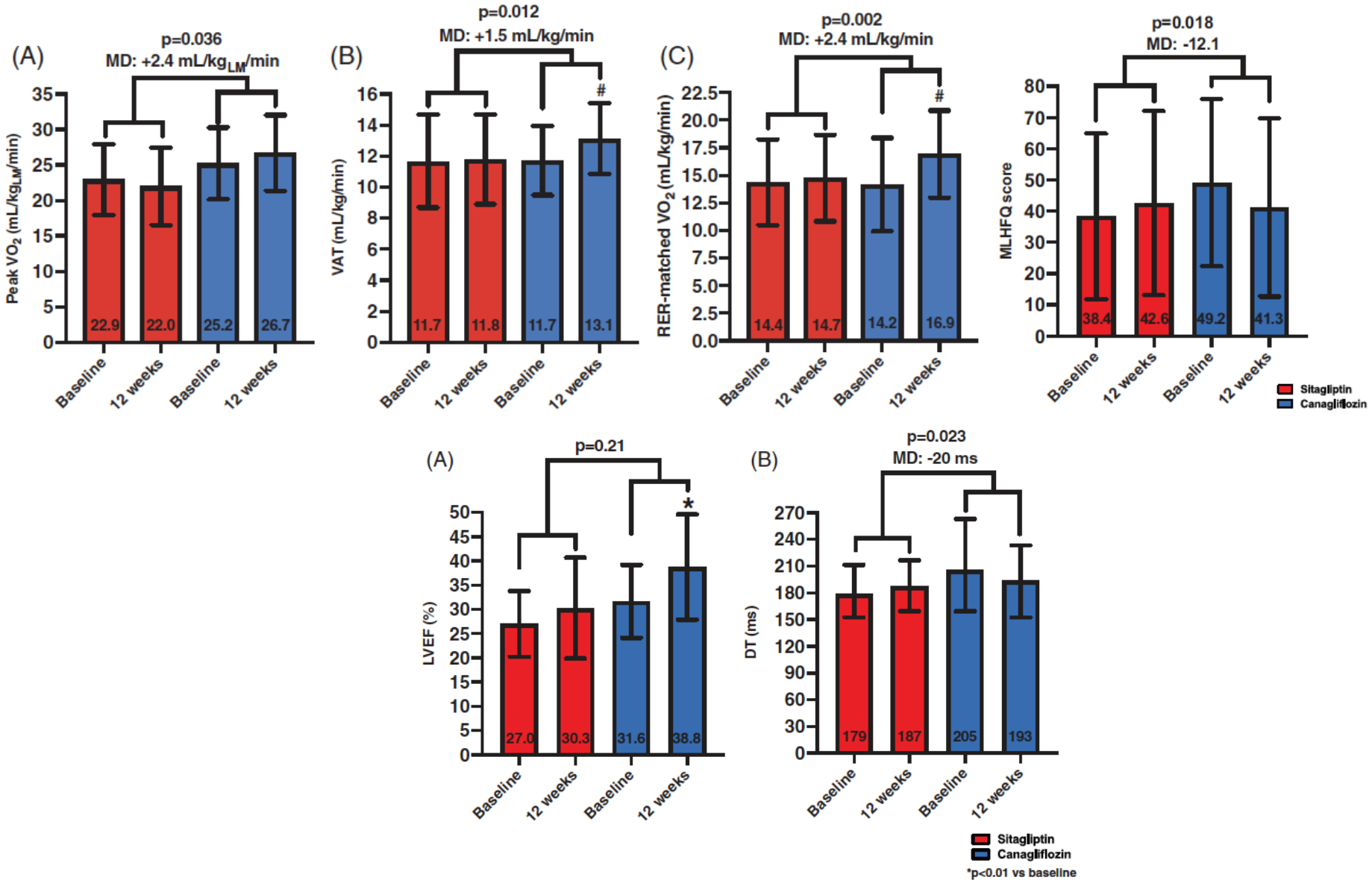


Figure 4 ~430-440 m baseline 6MWTD

Santos-Gallego CG et al. *J Am Coll Cardiol* 2020. Online ahead of print

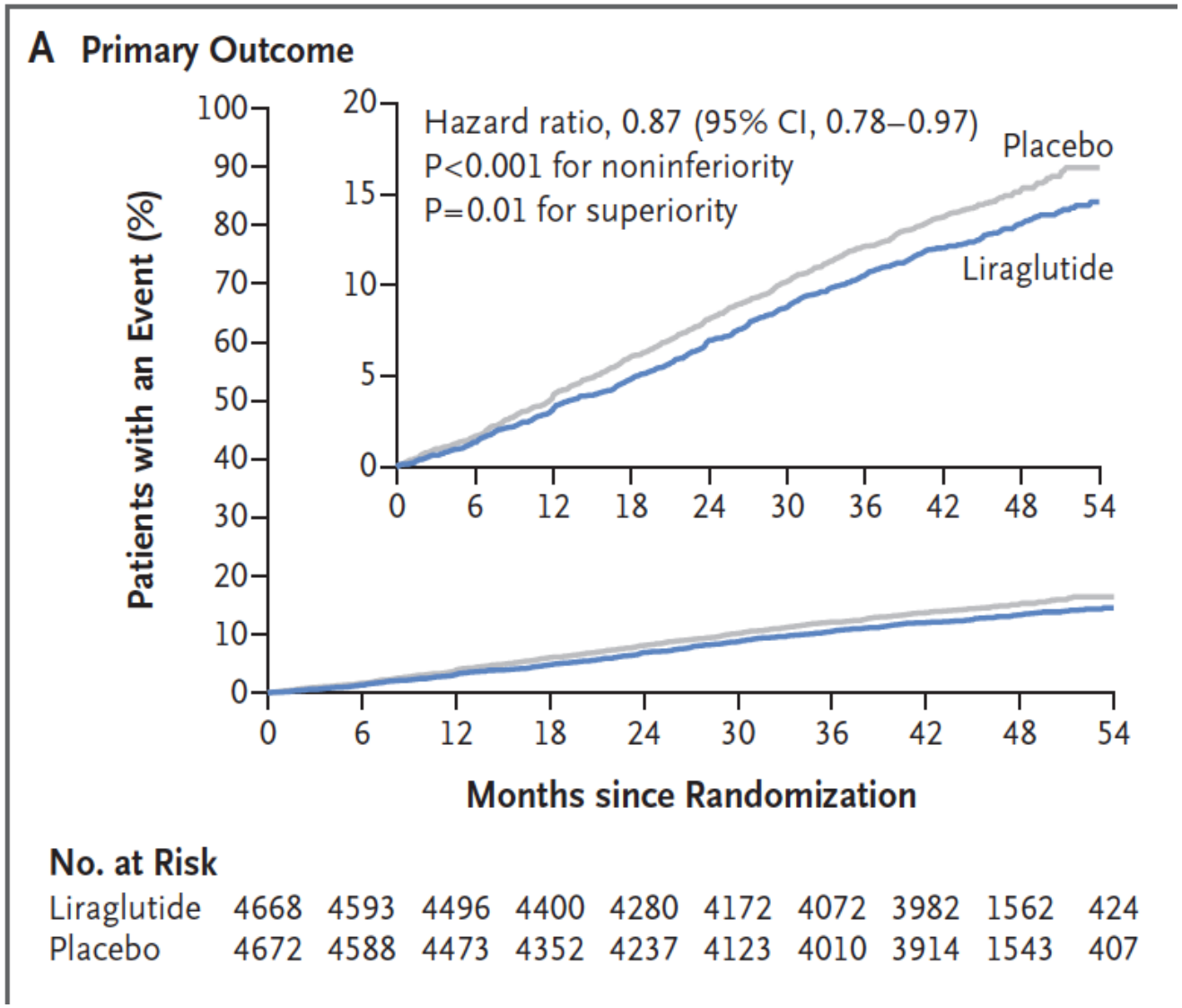
The effects of canagliflozin compared to sitagliptin on cardiorespiratory fitness in type 2 diabetes mellitus and heart failure with reduced ejection fraction: The CANA-HF study



Carbone S et al. *Diabetes Metab Res Rev* 2020;36(8):e3335

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Mostly secondary prevention study
Type 2 Diabetes Mellitus
Approx 9,300 patients
Followed for a median of 4 years



Marso SP et al. *N Engl J Med* 2016 Jul 28;375(4):311-22

FDA Grants Liraglutide(Victoza) Cardiovascular Events Indication

Miriam E. Tucker

DISCLOSURES

August 25, 2017

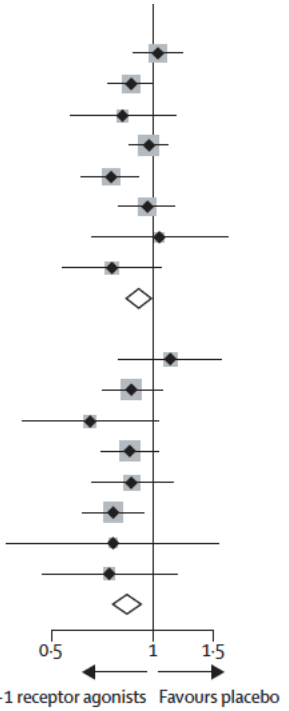
9Read Comments

The US Food and Drug Administration (FDA) has approved a new indication for liraglutide (*Victoza*, Novo Nordisk), for reducing the risk for myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes who have established cardiovascular disease.

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Project ECHO®
Virginia Commonwealth University

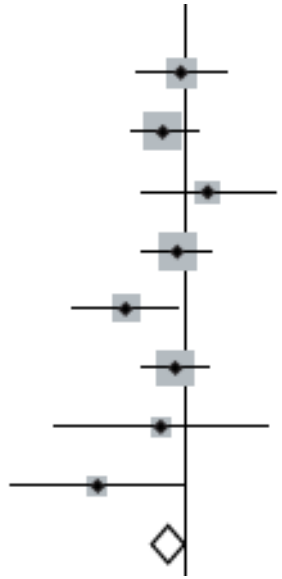
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**



Sattar N et al. *Lancet Diabetes Endocrinol* 2021

VCU

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

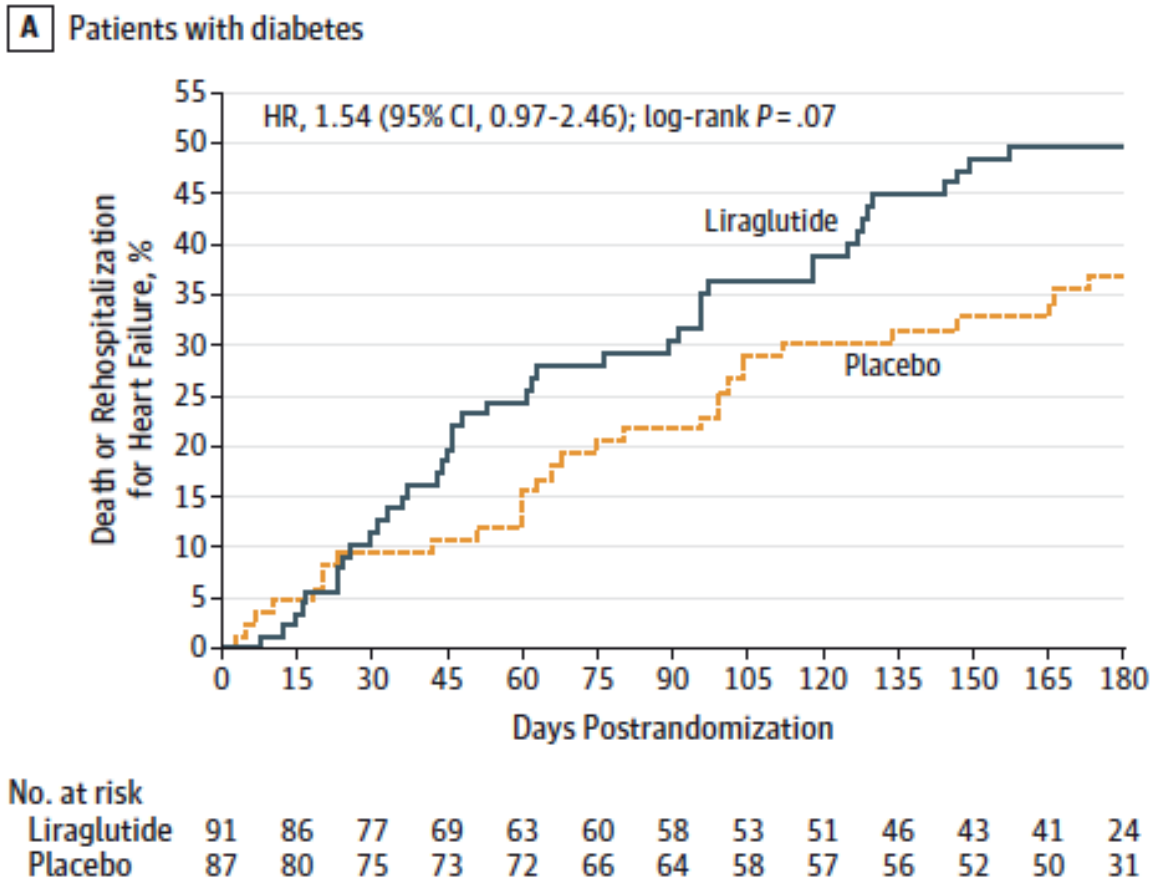


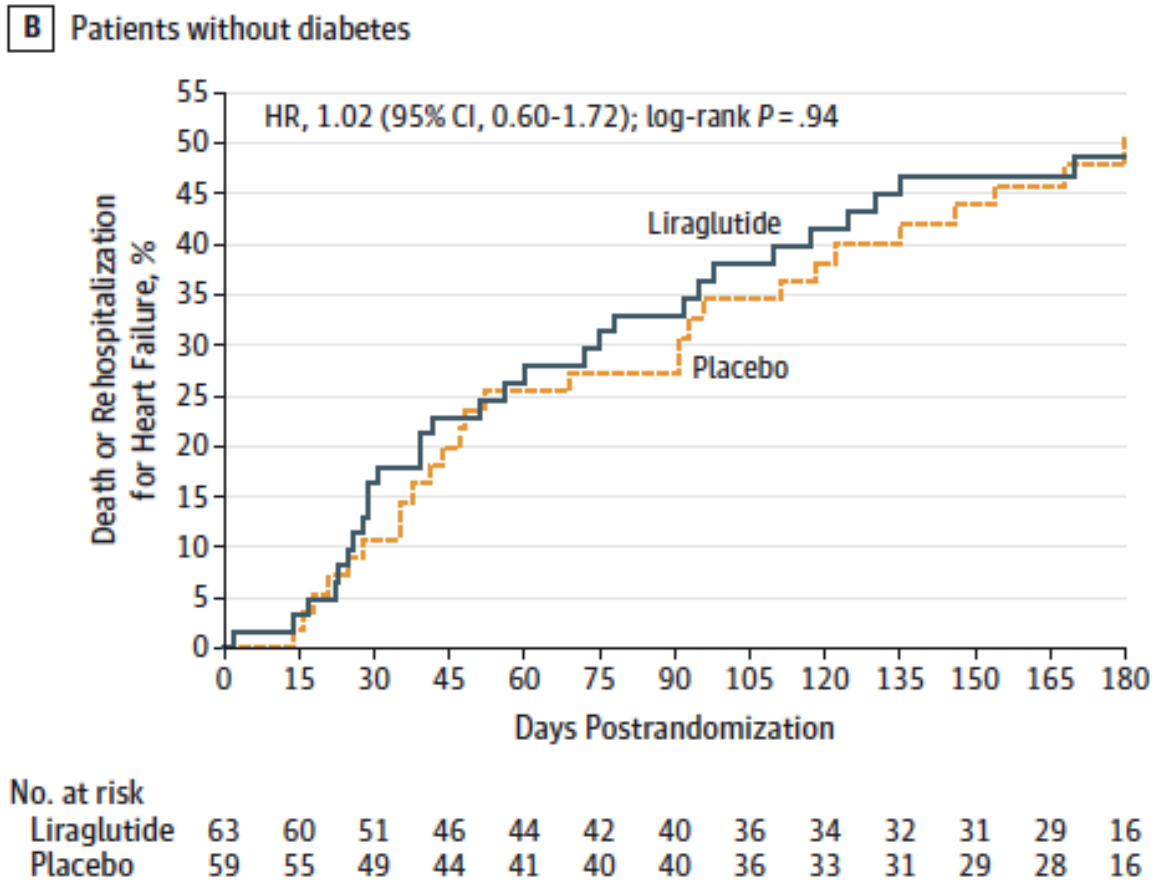
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**

Sattar N et al. *Lancet Diabetes Endocrinol* 2021

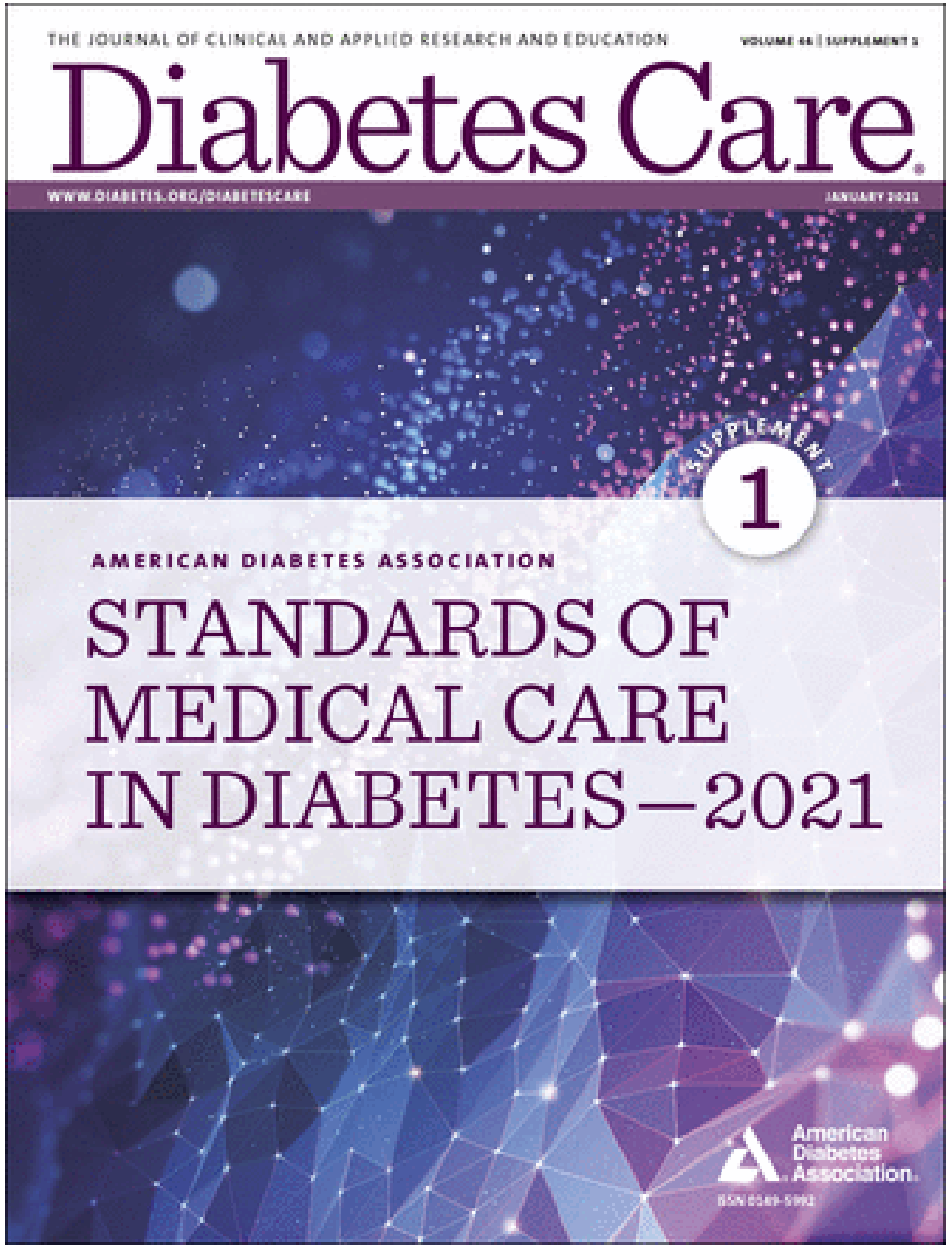
Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction

A Randomized Clinical Trial



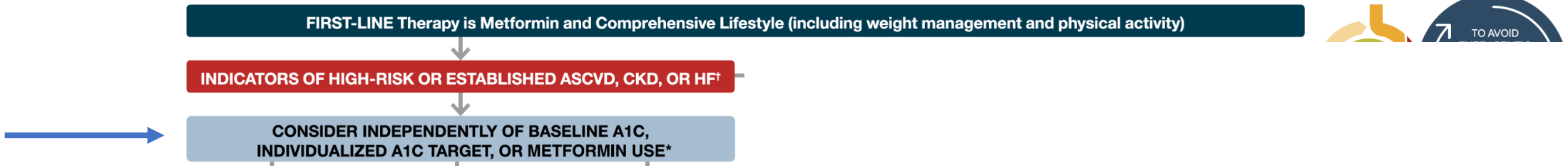


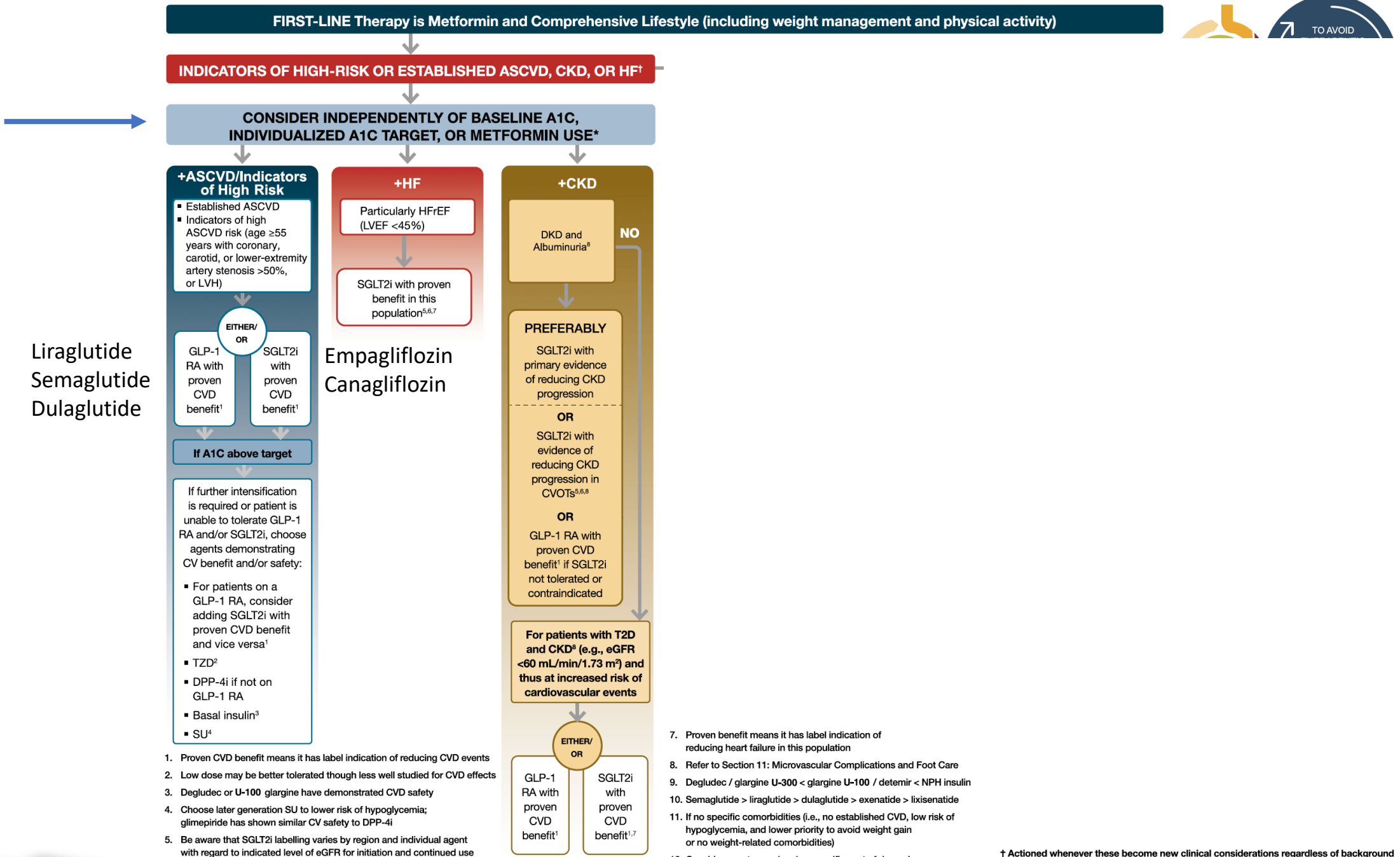
Margulies KB et al. *JAMA* 2016 Aug 2;316(5):500-8



Project ECHO®
Virginia Commonwealth University

VCU


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*



Liraglutide
Semaglutide
Dulaglutide

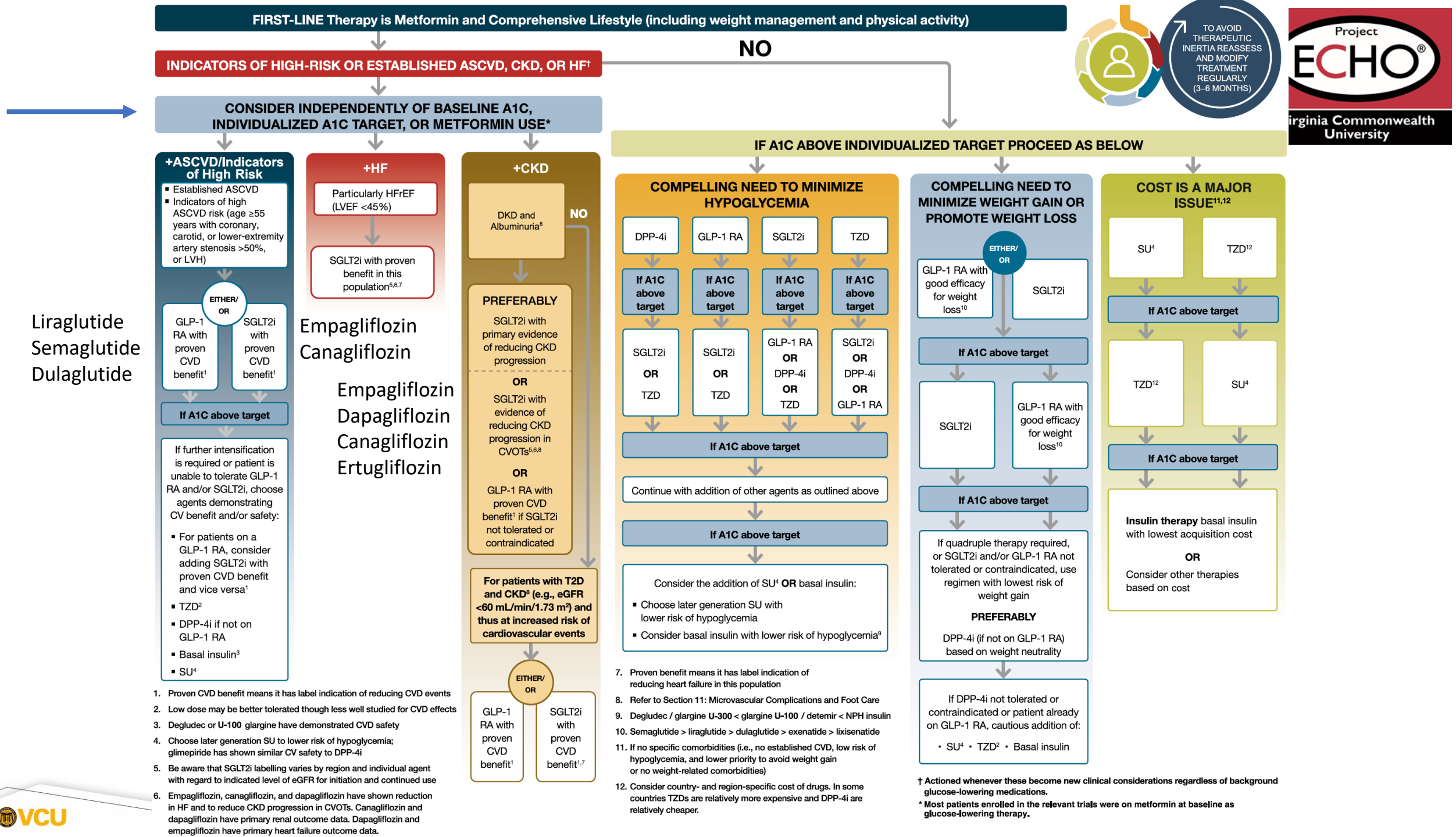
Empagliflozin
Canagliflozin

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

*** Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

TO AVOID
Project ECHO®
Virginia Commonwealth University
VCU



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† **Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.**

* **Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

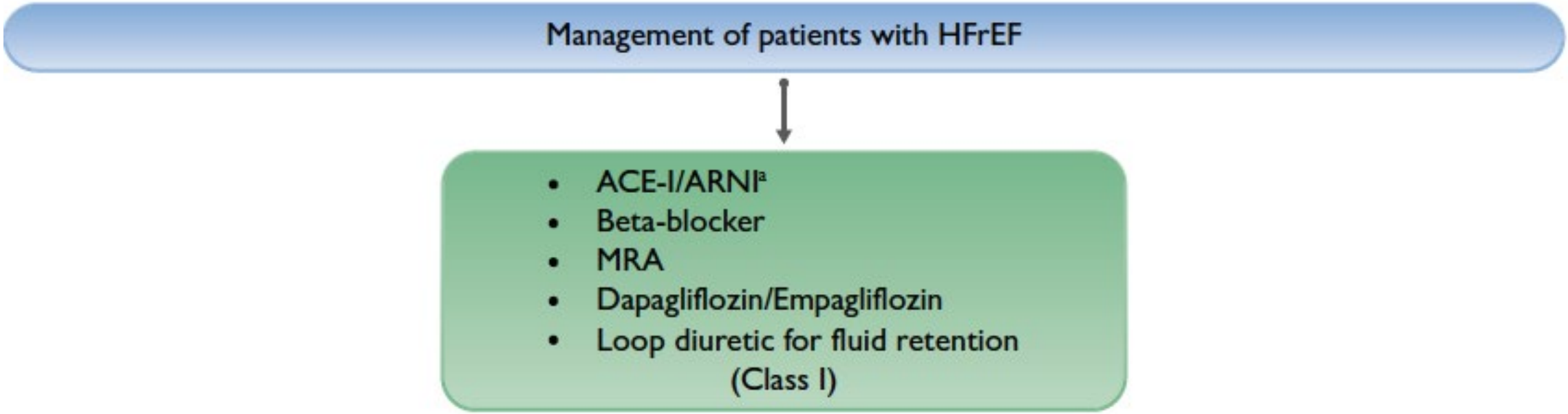
VCU

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – Analogs						High	SQ			

Project ECHO®
Virginia Commonwealth University

VCU

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



McDonagh TA, et al. *Eur Heart J* 2021

Conclusions

- GLP1RA (particularly liraglutide, semaglutide and dulaglutide) and SGLT2i (particularly empagliflozin and canagliflozin) reduce MACE in patients with T2DM.
- SGLT2i and GLP1RA are associated with lower risk for HF, however, in patients with established HF, especially advanced HFrEF (with and without T2DM), SGLT2i empagliflozin and dapagliflozin should be preferred and empagliflozin in HFpEF.
- CV benefits, especially in patients with HF, occur very early (within a month), therefore delaying the use of these agents may be preventing significant clinical benefits.

Case Study #1:

HPI: 50 year old lady with T2DM, Hyperlipidemia, anxiety, BMI 30.3, weight 82.5kg, presenting to establish care for diabetes

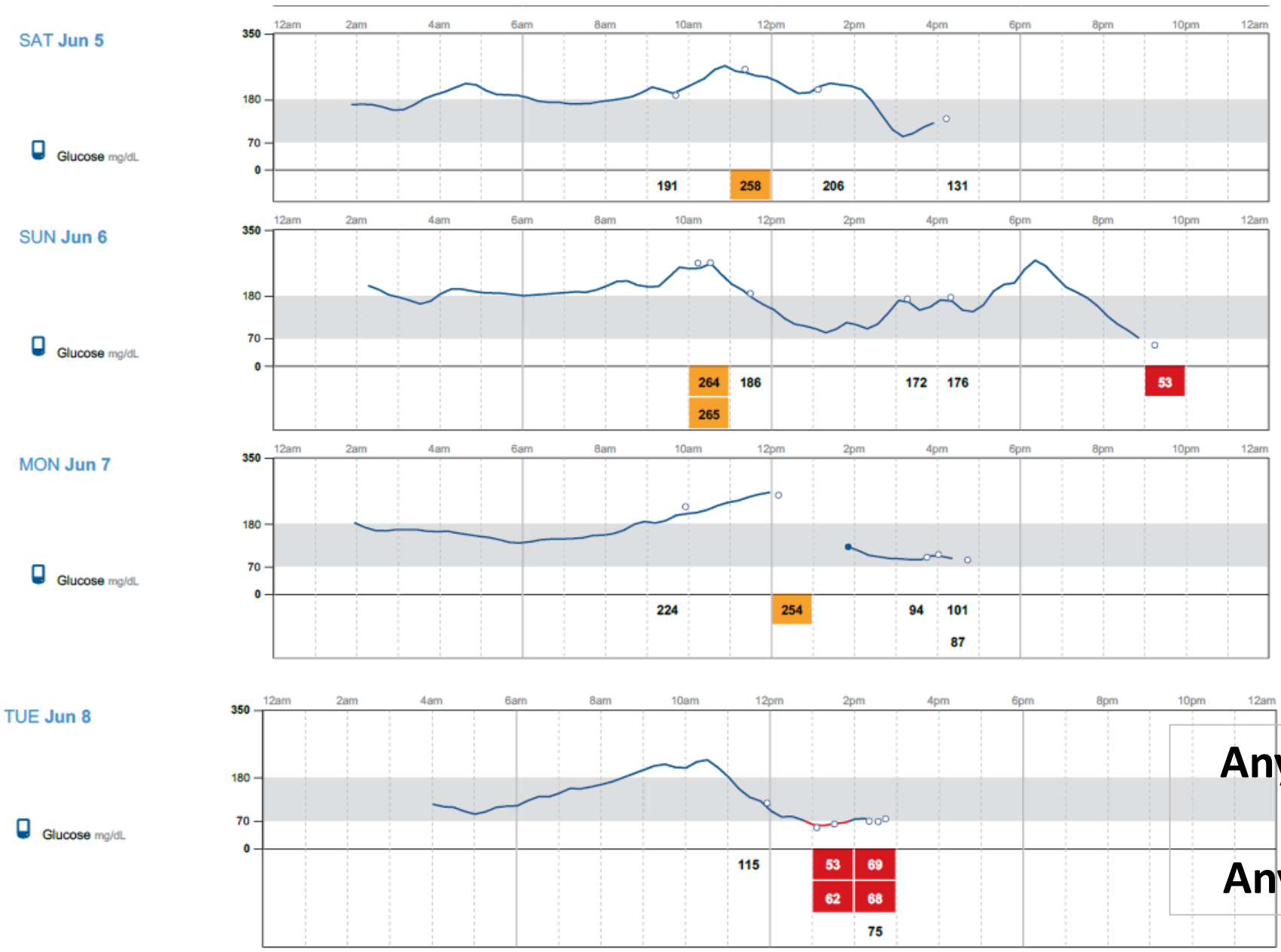
Diabetes for 3 years, diagnosed on screening annual A1c 9%, progressed to 11% and started on insulin

Medications:

- Victoza 1.8mg SQ daily--> discontinued, when patient started Humulin R 20 units ac TID
- Glimeperide 4mg daily,
- Januvia 100mg daily,
- Jardiance 25mg daily,
- Metformin 1000mg BID

Any clarifying questions?

Any proposed solutions?



Any clarifying questions?

Any proposed solutions?

Case Study #2:

HPI: 54 year old man with sarcoidosis (primarily pulmonary involvement), T2DM, osteoporosis, hyperlipidemia, hypertension, re-establishing care with diabetes clinic.

Diabetes dx 2013, concerning for progression over past year from A1c 8%→ 10.2%. Attributes this progression solely to dietary indiscretions. BMI 25, weight 81.4kg

Medications:

- NPH 8 units with breakfast and dinner, prefers to obtain without a prescription at Wal-Mart due to cost concerns,
- Metformin 1500mg daily (2 in AM, 1 at night)
- Prednisone 5mg daily in AM
- Glucose checks: BID, Range: Per patient recall, range 100s-190s

Any clarifying questions?
Any proposed solutions?

Case Study #2:

- No changes made at 1st visit due to patient preferences to focus on nutrition changes first
- At follow up visit 6 months later, A1c 8.1%
- NPH 7 units with breakfast and dinner, metformin 2000mg daily
- Glucose monitoring; BID, every day , Range: Per patient recall, range 140s fasting AM, bedtime 170s- 180s

Any clarifying questions?
Any proposed solutions?

Case Studies

- Anyone can submit cases: www.vcuhealth.org/echodmhtn
- Receive feedback from participants and content experts
- Earn **$150** for submitting and presenting

Provide Feedback

www.vcuhealth.org/echodmhtn

- Feedback
  - Overall feedback related to session content and flow?
  - Ideas for guest speakers?

Access Your Evaluation

vcuhealth.org/services/telehealth/for-providers/education/diabetes-and-hypertension-project-echo

For Providers

- Education
  - **Diabetes and Hypertension Project ECHO**
    - Our Team
    - Curriculum
    - Claiming CE Credit
    - Contact Us
  - VCU Nursing Home ECHO
  - VCU Health Palliative Care ECHO
  - Virginia Opioid Addiction ECHO
  - Virginia Sickle Cell Disease ECHO

Diabetes and Hypertension Project ECHO

Welcome to the Diabetes and Hypertension Extension for Community Health Outcomes or ECHO, a virtual network of multidisciplinary diabetes and hypertension experts. An ECHO model connects professionals with each other in real-time collaborative virtual sessions on Zoom. Participants present de-identified cases to one another, share resources, connect to each other, and grow in their expertise. This ECHO will address practice level issues and solutions related to managing complex patients with difficult to control diabetes and hypertension. Register now for an ECHO Session!

Network, Participate and Present

- Engage in a collaborative community with your peers.
- Listen, learn and discuss informational and case presentations in real-time.
- Take the opportunity to submit your de-identified case study for feedback from a team of specialists for diabetes and hypertension.
- Provide valuable feedback.
- Claim CE credit by texting in attendance.

Benefits

VCU Diabetes & Hypertension Project ECHO Clinics

2nd and 4th Thursdays — ***NEW: 12 p.m. to 1 p.m.***

Mark Your Calendars — Upcoming Sessions

Sept. 23: Diabetic Neuropathy

Oct. 14: Primary and Secondary Aldosteronism

Please register at www.vcuhealth.org/echodmhtn

Thank you for coming!

Text **19179-18817** to **804-625-4041** for CE credit

Reminder: Mute and Unmute to talk
Press *6 for phone audio
Use chat function for questions