LECTURE 2: DIABETES MEDICATIONS FOR T2D

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Disclosures:

- Dr. Ehrhardt has received a consulting fee from Novo Nordisk and received investigator initiated grants from Dexcom and Educational Grants from Merck and Novonordisk

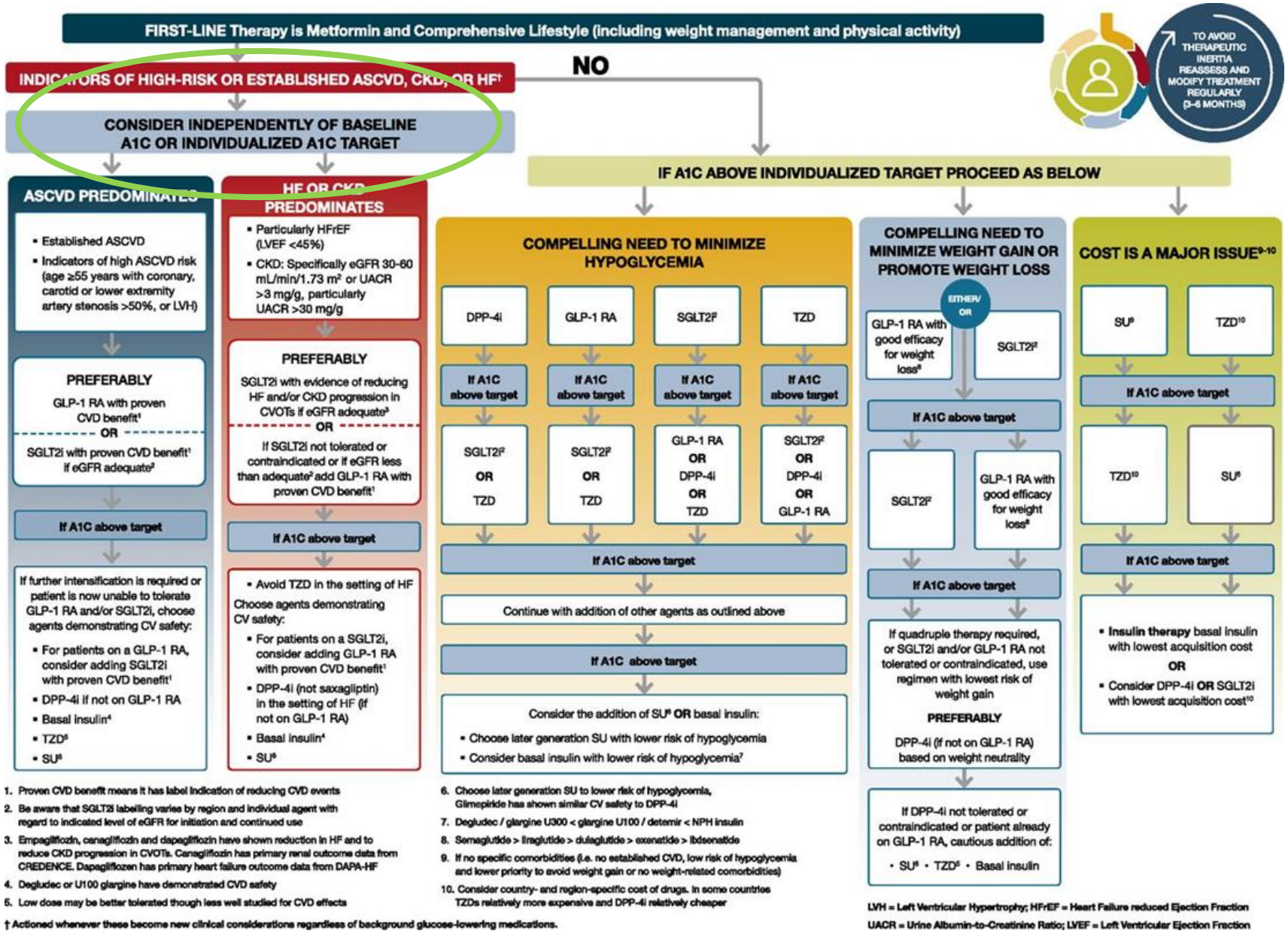
Objectives:

- Understand how to safely prescribe and use “newer” diabetes medications
- Understand physiology and mechanism of action, efficacy, safety, tolerability, managing side effects, dosing and administration of individual drugs
- Understand how to use these medications in CKD
- Assess the cardiac and renal benefits in these newer medications

Diabetes Medications

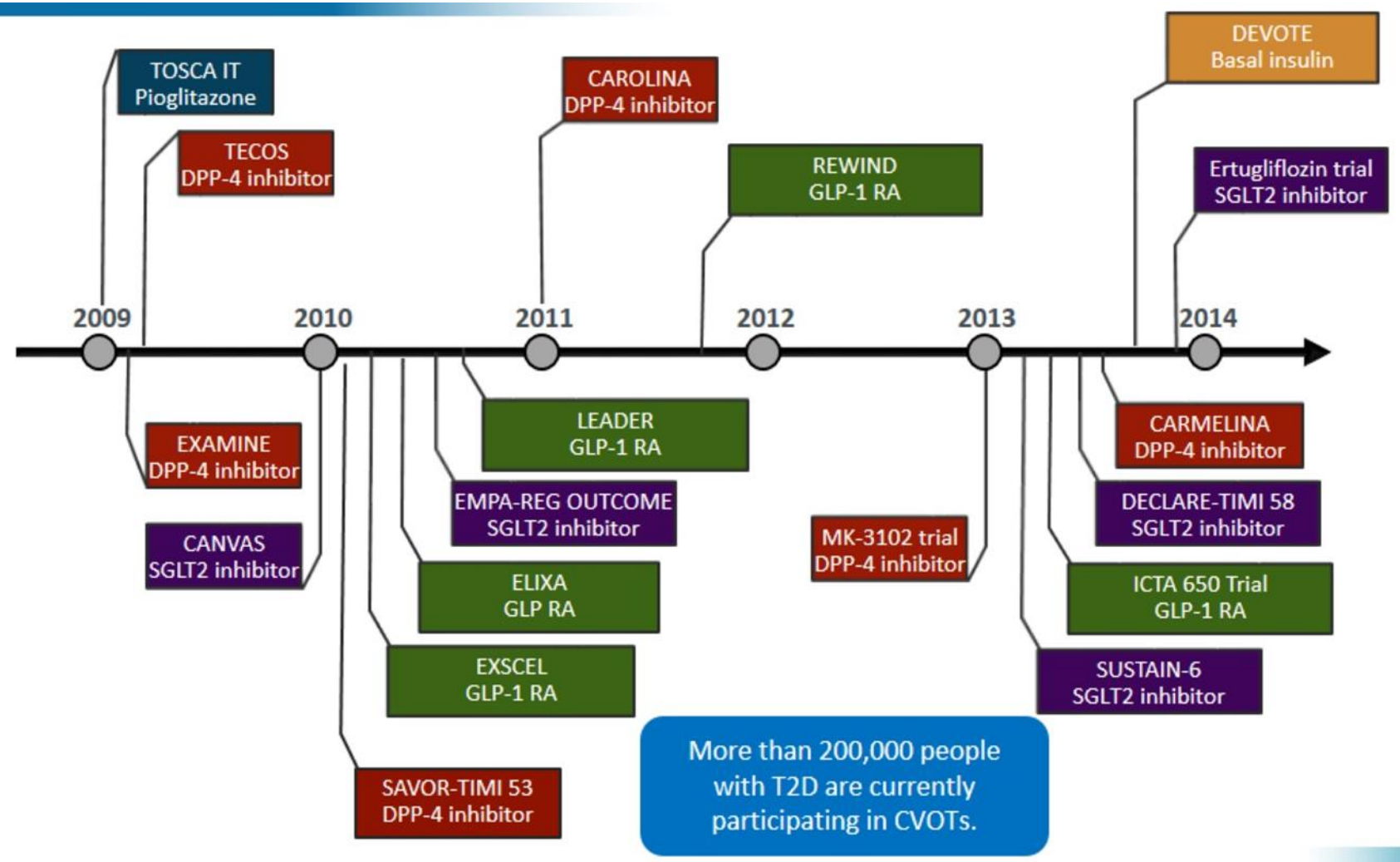
- Mechanism of action
- Efficacy (on average how much does it lower blood sugar)
- Does it cause hypoglycemia yes/no
- Common side-effects
- Serious side-effects
- Weight gain/Weight loss/Weight neutral
- Cardiovascular effects
- Use in CKD and renal protective effect

Glucose-lowering medication in type 2 diabetes: overall approach.



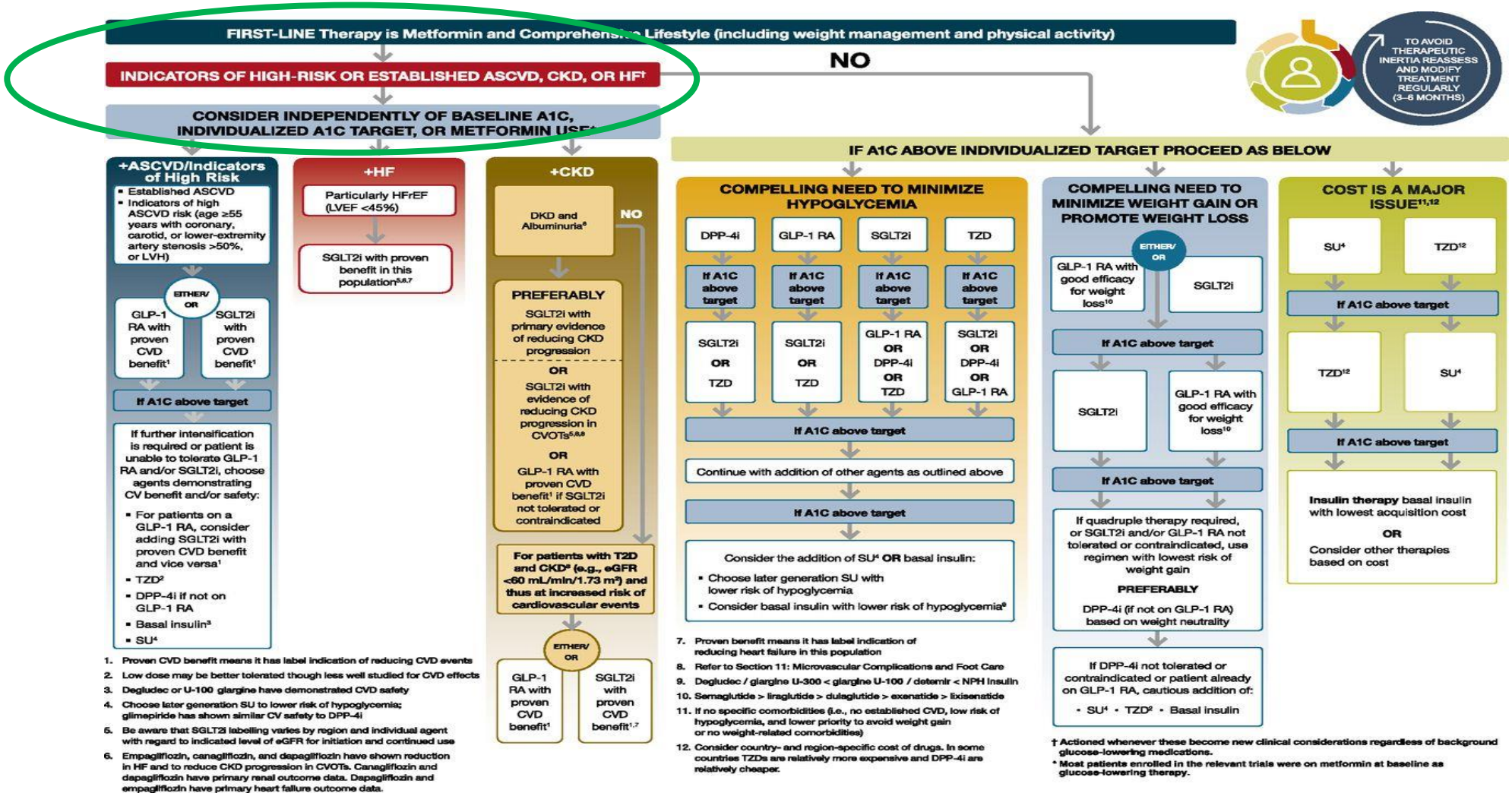
American Diabetes Association.

Timing of CV safety trials with Drugs for Type 2 Diabetes



Standl E, et al. *Lancet Diabetes Endrocrinol*. 2017;5:391-402.

Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.



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.

American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

Thiazolidinediones: “TZDs”

Thiazolidinediones: "TZDs"

Class/Main Action	Name(s)	Daily Dose Range	Considerations
Thiazolidinediones "TZDs" • Increases insulin sensitivity	pioglitazone (Actos) rosiglitazone (Avandia)	15 – 45 mg daily 4 – 8 mg daily	Black Box Warning: TZDs may cause or worsen CHF. Monitor for edema and weight gain. Increased peripheral fracture risk. Actos may increase risk of bladder cancer. Lowers A1c 0.5% – 1.0%

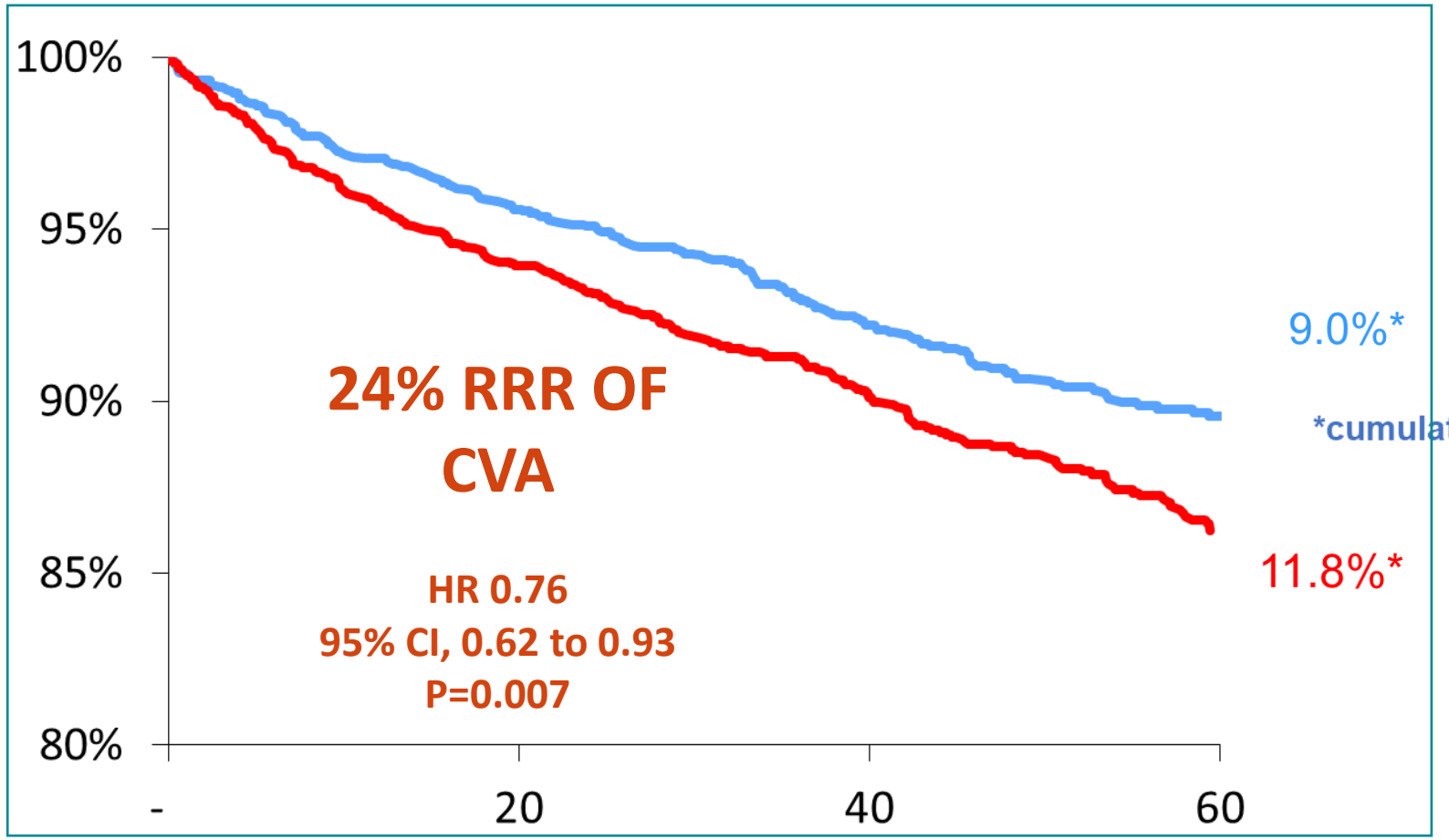
http://diabetesed.net/pocket-cards-insulin-and-diabetes-meds

TZD Adverse Effects

- Weight gain
- Increased risk of edema
- Contraindicated in Class III HF or higher and possible increase risk of HF
- Increased risk of long-bone fractures
- possible increased risk macular edema
- Pioglitazone ?? Bladder cancer risk

Pioglitazone after CVA or TIA

Insulin Resistance Intervention After **Stroke Trial** (**IRIS**) :



*Inclusion Criteria: Insulin resistance (did not need a diagnosis of DM)

Kernan et al. N Engl J Med 2016; 374:1321-1331

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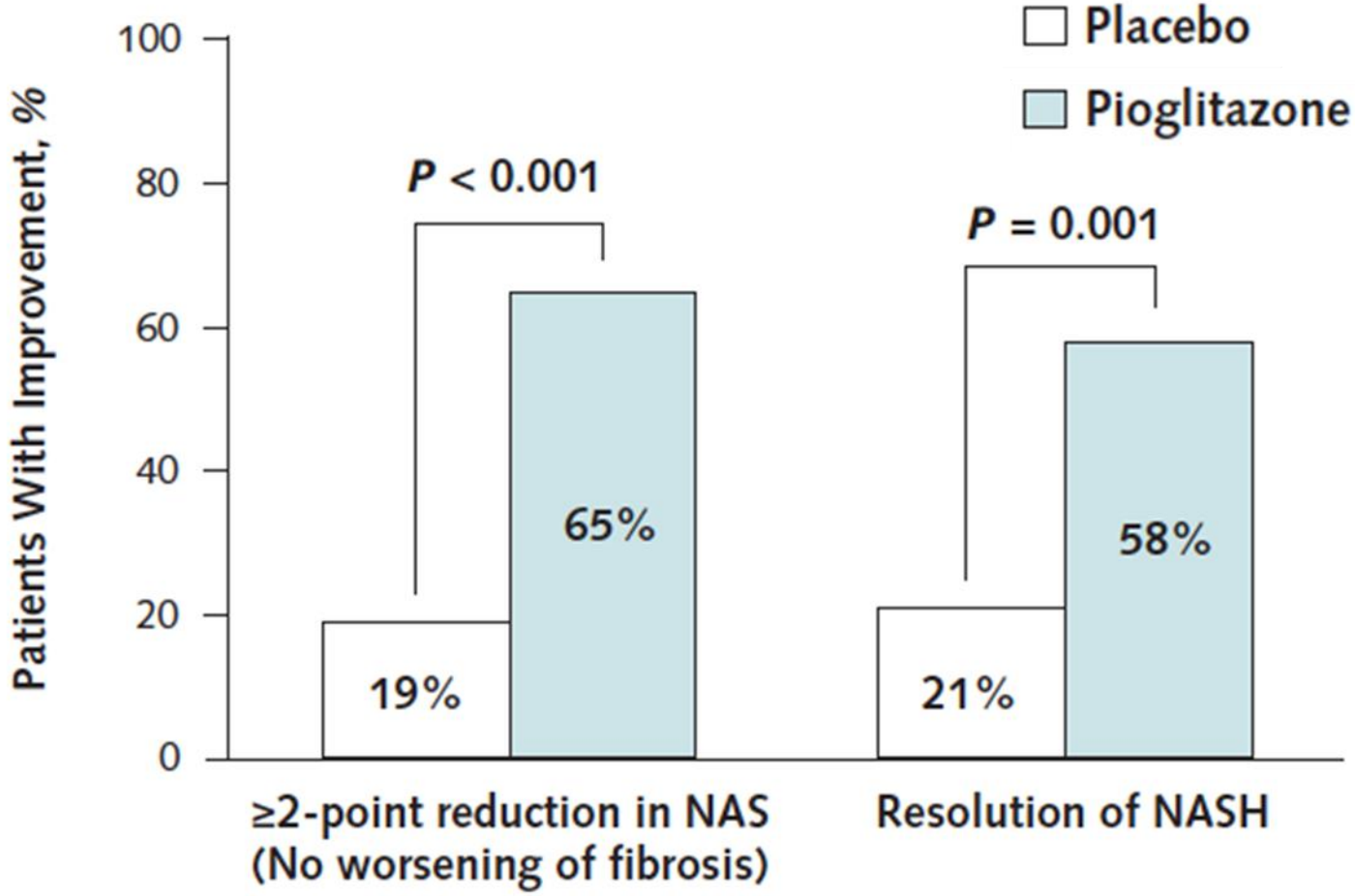
Effect of 18 Months of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes



Resolution of NASH defined as absence of NASH after 18 mo of therapy with definite NASH at baseline

Cusi et al, Ann Intern Med June 21, 2016. [Epub].

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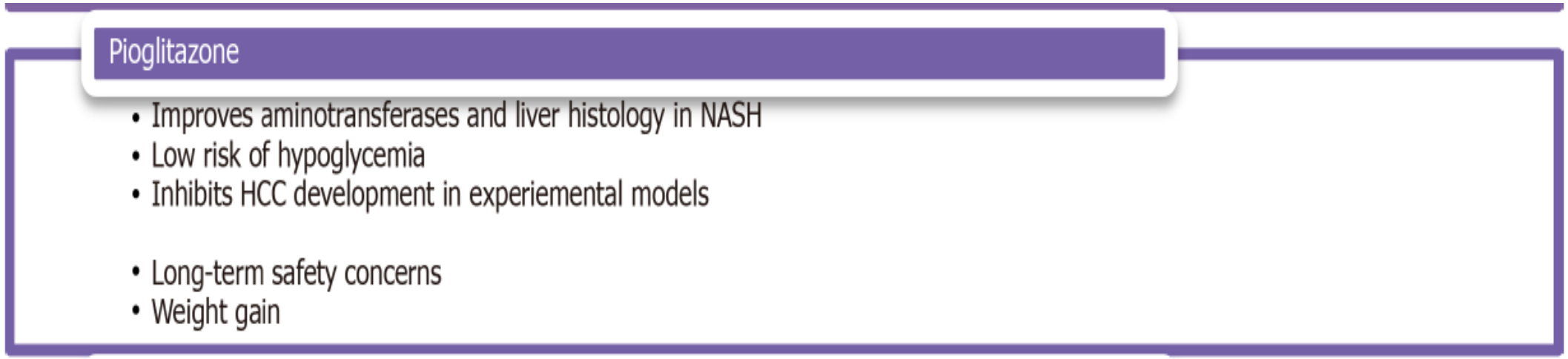
LIVER Disease and TZD



- Small pilot study that showed a reduction in hepatic steatosis on imaging in patients with human immunodeficiency virus (HIV)/HCV coinfection
- Limited data on the use of pioglitazone in other etiologies of CLD
- Data suggesting that pioglitazone may inhibit HCC development but these findings have not been confirmed in human studies

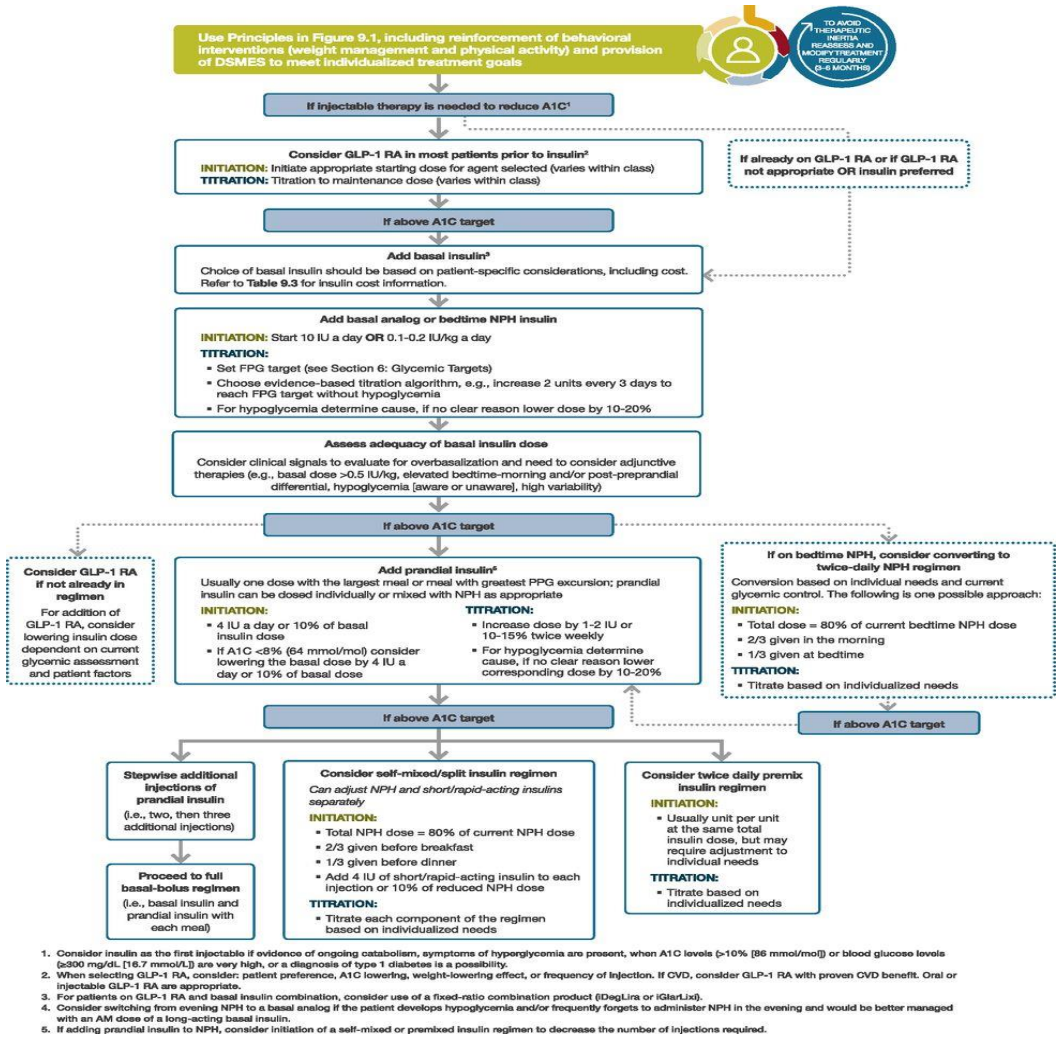
World J Hepatol 2020 September 27; 12(9): 533-692

Summary: Thiazolidinediones (TZDs)

- Helps to target insulin resistance
- May improve dyslipidemia
- NASH (Non-Alcoholic liver disease)
- Established CVA may have some CV benefit
- Weight gain, edema, and fractures
- Risk for worsening HF - *do not use in CHF*
- Use in select population

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA)

Intensifying to injectable therapies.



American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

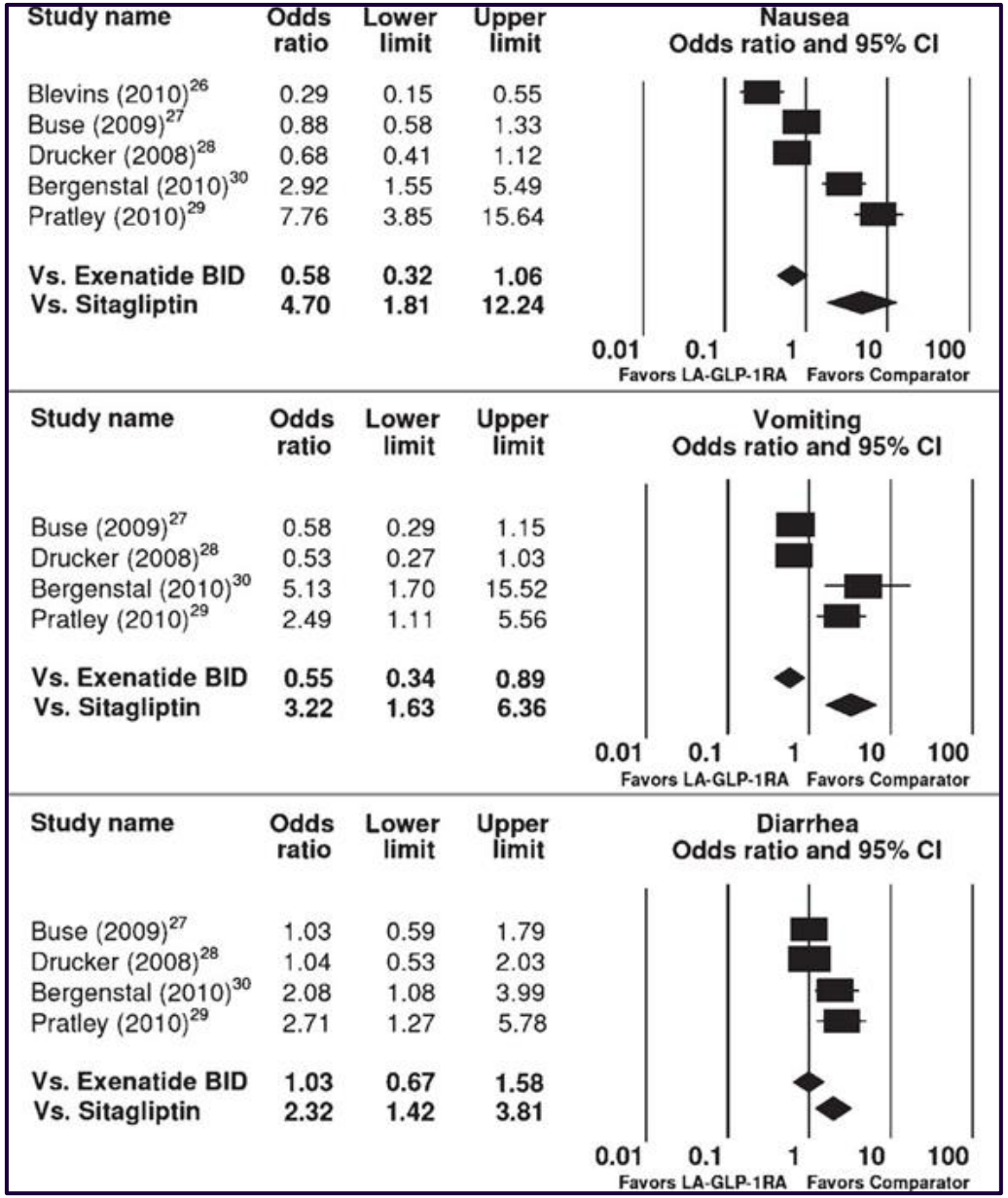
Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA)

Class/Main Action	Name	Dose Range	Considerations
GLP-1 Receptor Agonist (GLP-1 RA) **"Incretin Mimetic"** • Increases insulin release with food • Slows gastric emptying • Promotes satiety • Suppresses glucagon	exenatide (Byetta)	5 and 10 mcg BID	**Side effects for all:** Nausea, vomiting, weight loss, injection site reaction. Report signs of acute pancreatitis (severe abdominal pain, vomiting), stop med. Renally excreted. **Black box warning:** Thyroid C-cell tumor warning for exenatide XR, liraglutide, dulaglutide, and semaglutide (avoid if family history of medullary thyroid tumor). *Significantly reduces risk of CV death, heart attack, and stroke. Lowers A1c 0.5 – 1.6% Weight loss of 1.6 to 6.0kg†
	exenatide XR (Bydureon)	2 mg 1x a week Pen injector - Bydureon BCise	
	liraglutide (Victoza)*	0.6, 1.2 and 1.8 mg daily Approved for pediatrics 10 yrs +	
	dulaglutide (Trulicity)*	0.75, 1.5, 3.0 and 4.5 mg 1x a week pen injector	
	lixisenatide (Adlyxin)	10 mcg 1x a day for 14 days 20 mcg 1x day starting day 15	
	semaglutide (Ozempic)*†	0.5 and 1.0 mg 1x a week pen injector	
	(Rybelsus) Oral tablet	3, 7, and 14 mg daily in a.m. Take on empty stomach w/H2O sip	
Amylin Mimetic • Slows gastric emptying • Supress glucagon	pramlintide (Symlin)	Type 1: 15 - 60 mcg; Type 2: 60 - 120 mcg immediately before major meals	For Type 1 or 2 [illegible]nsulin. Severe hypogly[illegible]ic risk, decrease insulin dose wh[illegible]tarting. **Side effects:** na[illegible]a, weight loss. Lowers A1c 0.5[illegible]%

http://diabetesed.net/pocket-cards-insulin-and-diabetes-meds

GLP-1 RA: Side-Effects /Potential Patient Perceived Barriers

- Nausea / diarrhea/constipation
- Possible risk for Pancreatitis??
- Theoretical risk for medullary thyroid cancer??
  - Induces rodent thyroid C-cell tumors
- Injection



Ann Pharmacother 2011;45:850-860

GLP-1 receptor agonists

GLP-1 receptor agonist/ basal insulin fixed-dose combinations

Pen devices for injection

Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

Nauck MA et al. Eur J Endocrinol. 2019 Dec;181(6):R211-R234

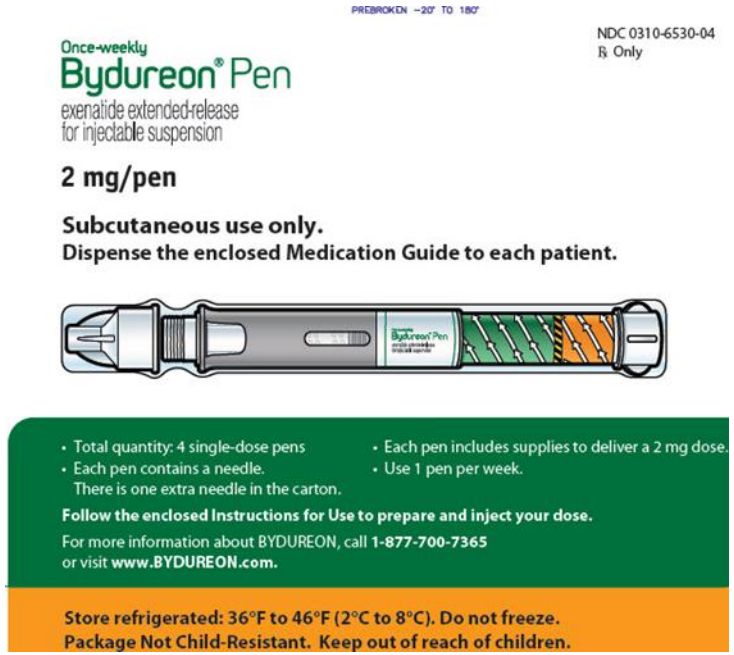

3 ml
Victoza®
6 mg/ml injection
0mg


trulicity
dulaglutide once-weekly injection


OZEMPIC®
(semaglutide) injection
For Single Patient Use Only
-0- mg

How to use Exenatide(Bydureon)

- English: https://www.youtube.com/watch?v=72w756RKawY
- Spanish: https://www.youtube.com/watch?v=Wqn1iKBiQkk



Oral Semaglutide

Take on an empty stomach

Take with a a small amount of water (no more than 4 oz).

Wait 30 minutes after taking it and then eat food

GLP-1 RA in CKD

- In CKD stages 2 and 3: no dose adjustment is required for liraglutide and dulaglutide, semaglutide, extended release exenatide
    - Exenatide: reduce dose to 5mcg bid if 30–50 mL/min
- In CKD stages 4 and 5: GLP-1 RA limited data
- What about Stage 3 CKD GFR < 45??

GLP-1 use in CKD: LIRA-RENAL Study

	Liraglutide 1.8 mg (*n* = 140)	Placebo (*n* = 137)
Sex, *n* (%)		
Female	65 (46.4)	72 (52.6)
Male	75 (53.6)	65 (47.4)
Age, mean (SD), years	68.0 (8.3)	66.3 (8.0)

****Can use/initiate in GFR 30-45**

GFR

30 to < 45	61 (43.6)	59 (43.1)
45–59	78 (55.7)	78 (56.9)
> 59	1 (0.7)	0 (0.0)

Diabetes Care 2016 Feb; 39(2): 222-230

GLP-1 RAs and CV Risk Baseline Characteristics

	ELIXA	LEADER	SUSTAIN 6	REWIND
Drug tested	Lisixenatide	Liraglutide	Semaglutide	Dulaglutide
Dose	20 µg/d	1.8 mg/d	0.5 or 1 mg/wk	1.5 mg/wk
N	6068	9340	3297	9901
Mean age, years	60	64	65	66
Percent women	31	36	39	46
Percent prior CVD	100	81	59	31
Mean BMI, kg/m^2	30	33	31	32
Mean HbA1c, %	7.7	8.7	8.7	7.3
Primary outcome	MACE[a] or unstable angina	MACE[a]	MACE[a]	MACE[a]

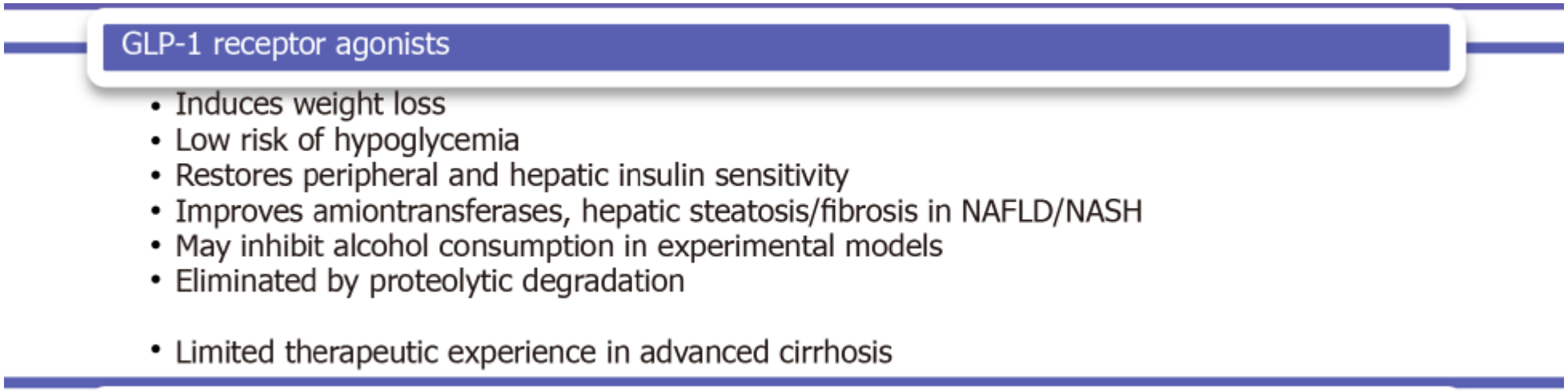
Gerstein et al. Diabetes Obes Metab. 2018 Jan;20(1):42-49

CV and Renal Benefits of GLP-1 RAs

Administration:	subcutaneous						oral	
Compound:	**Exenatide**	**Lixisenatide**	**Liraglutide**	**Exenatide**	**Dulaglutide**	**Semaglutide**	**Semaglutide**	
Frequency:	b.i.d.	q.w.	q.d.	q.w.	q.w.	q.w.	q.d.	
Effects:								
HbA_{1c} reduction:	+	+	++	+	++	+++	++(+)	
Post-prandial glucose	++[a]	++[a]	+	+	+	+	+	
Body weight reduction:	+(+)	+	++	+	+(+)	+++	++(+)	
Injection device:	+	+	++	(+)	+++	++	n.a.	
Conveniance/adherence:	(+)	+	++	+	+++	+++	+++?[b]	YES
CV benefit („MACE"):	not known	±	++	(+)	++	++	(+)	YES
Mortality benefit:	not known	±	++	(+)	±	±	±	YES
Renal benefit:	±	(+)	+	±	+	+	+	
Nausea/vomiting:	- -	-	- (-)	-	- (-)	- (-)	- (-)	
Immunogenicity[c]:	++	++	(+)	++	(+)	(+)	? (not known)	

Nauck MA et al. Eur J Endocrinol. 2019 Dec;181(6):R211-R234

GLP-1 RA and Liver disease



Initial data on NASH and GLP-1 RA encouraging

Fasting serum GLP-1 levels were decreased in patients with chronic HCV, but not those with HBV

Yan J et al *Hepatology* 2019; 69: 2414-2426
Armstrong MJ, et al. . *Lancet* 2016; **387**: 679-690
Chung et al. *World J Hepatol* 2020 September 27; 12(9): 533-692

NASH and GLP-1 RA

The NEW ENGLAND JOURNAL of MEDICINE

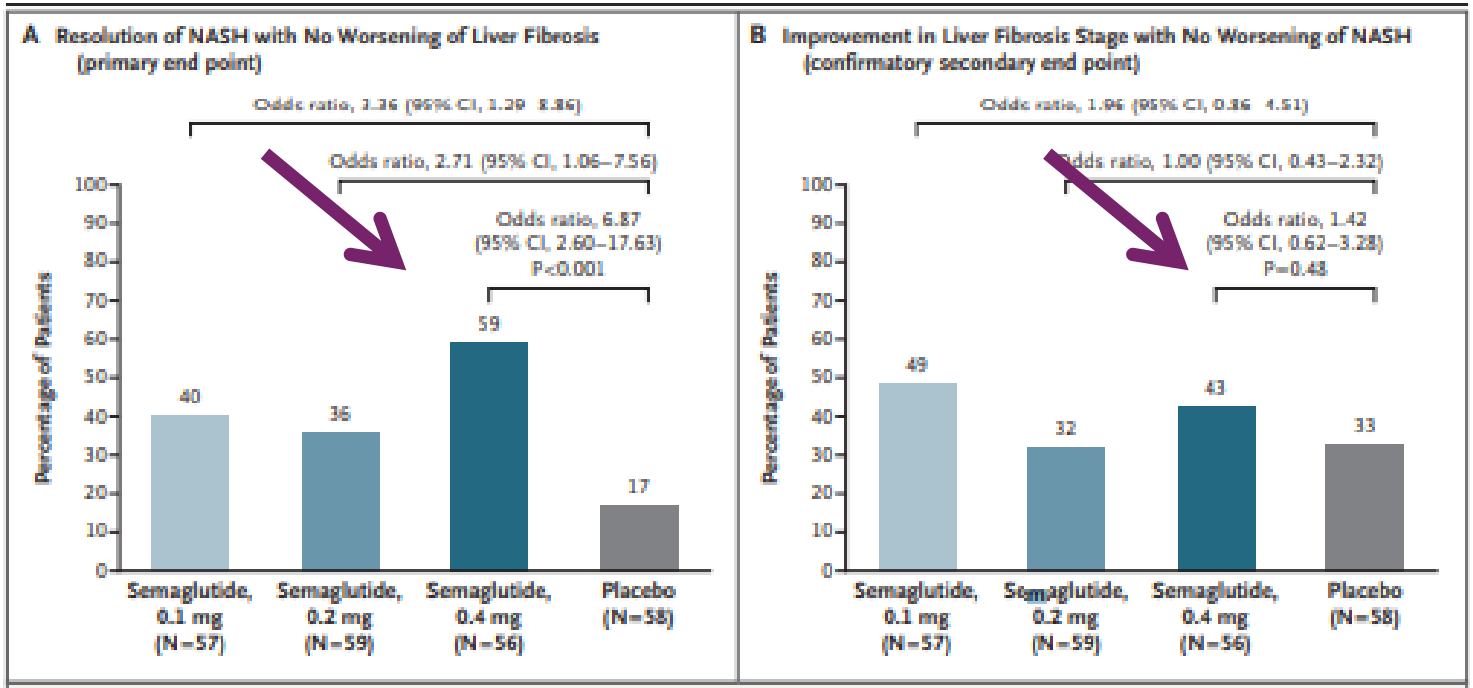


Figure 1. Primary and Secondary Confirmatory End Points.

Panel A shows the observed percentages of patients with stage F2 or F3 fibrosis in whom resolution of nonalcoholic steatohepatitis (NASH) was achieved by week 72 with no worsening of liver fibrosis (with worsening defined as an increase of one stage or more). Resolution was defined by the NASH Clinical Research Network as no more than mild residual inflammatory cells [score of 0 or 1] and no hepatocyte ballooning [score of 0]). Panel B shows the observed percentages of patients with stage F2 or F3 fibrosis who had an improvement of at least one fibrosis stage by week 72 with no worsening of NASH (with worsening defined as an increase of ≥1 point in either the lobular inflammation score or the hepatocyte ballooning score according to the NASH Clinical Research Network criteria). Data were analyzed with the use of a Cochran–Mantel–Haenszel test stratified according to baseline diabetes status and baseline fibrosis stage. Data from the in-trial observation period (from randomization until the last study-related procedure) were included, and missing outcome data were imputed as nonresponse.

N Engl J Med. 2020 Nov 13. doi:

Summary: GLP-1 RAs

- Expensive
- May cause weight loss (8-12 pounds)
- CV benefit and renal benefit
- > 1% HbA1c reduction
- Weekly dosing likely improves compliance
- Low risk for hypoglycemia
- Oral version now available
- Nausea main side-effect

Sodium-Glucose Co-Transporter -2 Inhibitors (SGLT2I)

Sodium-Glucose Co-Transporter Inhibitors (SGLT2I)

Class/Main Action	Name(s)	Daily Dose Range	Considerations
SGLT2 Inhibitors "Glucoretic" • Decreases glucose reabsorption in kidneys	Canagliflozin* (Invokana) Dapagliflozin* (Farxiga) Empagliflozin* (Jardiance) Ertugliflozin (Steglatro)	100 - 300 mg 1x daily Don't start if GFR <45. 5 - 10 mg 1x daily Don't start if GFR<45. 10 - 25 mg 1x daily Don't start if GFR <45. 5 – 15 mg 1x daily Don't start if GFR <60.	**Side effects:** hypotension, UTIs, increased urination, genital infections, ketoacidosis. **Monitor GFR and other considerations:** See package insert for dosing based on GFR. *Empagliflozin, Dapagliflozin, & Canagliflozin: - Reduce risk of CV death, heart failure and preserve long-term kidney function. **Benefits:** no hypo or weight gain. Lowers A1c 0.6%-1.5%. Lowers wt 1-3 lbs.

http://diabetesed.net/pocket-cards-insulin-and-diabetes-meds

Sodium-Glucose Co-Transporter Inhibitors (SGLT2I)

TABLE. A1C REDUCTION VERSUS PLACEBO	
Medication	**Mean A1C Reduction (95% CI)**
Canagliflozin 300 mg	−0.86% (−0.96 to −0.76)
Canagliflozin 100 mg	−0.76% (−0.86 to −0.66)
Dapagliflozin 10 mg	−0.66% (−0.74 to −0.58)
Dapagliflozin 5 mg	−0.56% (−0.67 to −0.44)
Empagliflozin 25 mg	−0.66% (−0.76 to −0.56)
Empagliflozin 10 mg	−0.60% (−0.70 to −0.50)

A1C = glycated hemoglobin.

Zaccardi F et al. *Diabetes Obes Metab*. 2016;18(8):783-794

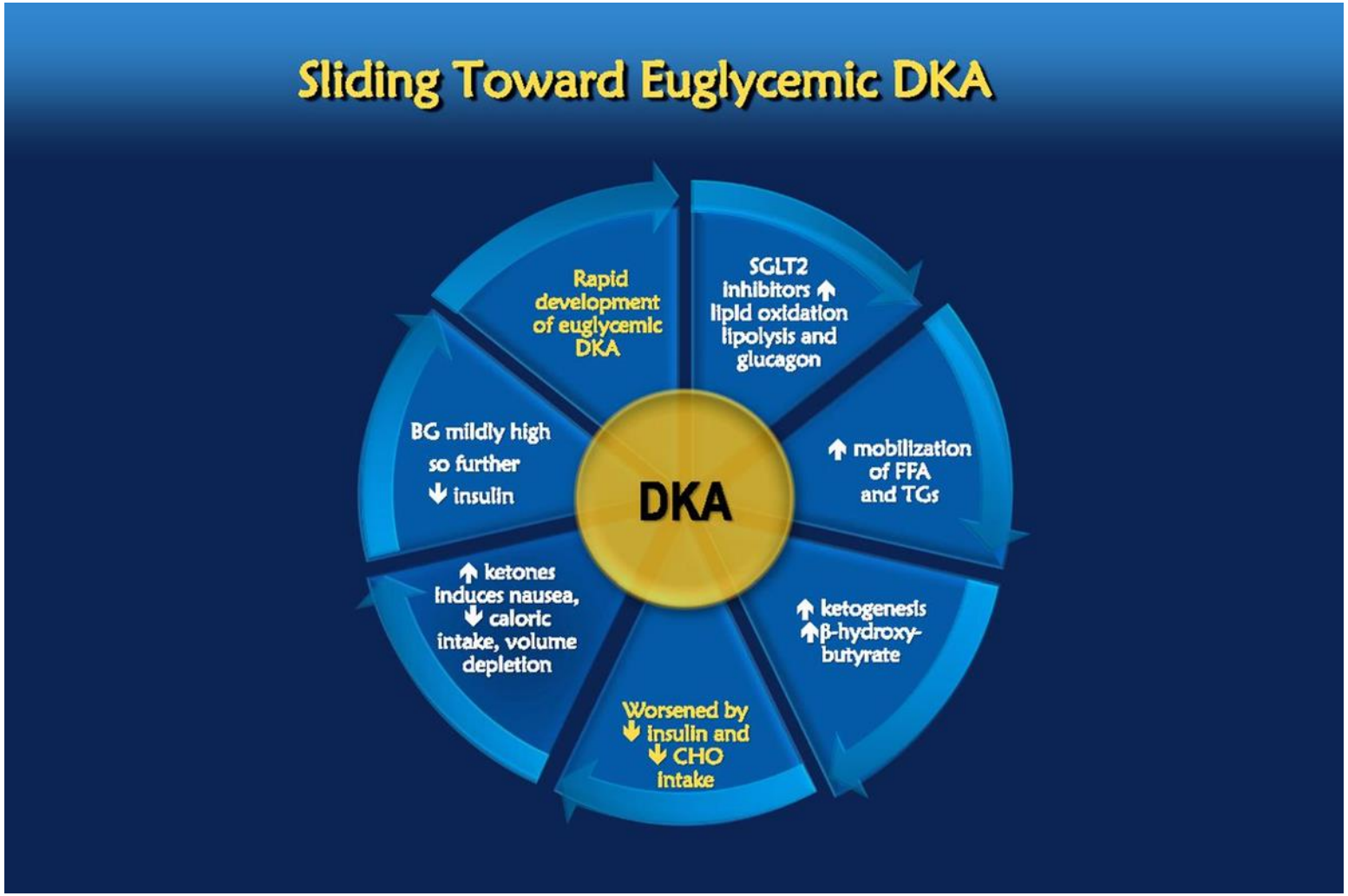
SGLT2 Inhibitors:

Warnings and Precautions - Canagliflozin/Dapagliflozin/Empagliflozin

- Hypoglycemia: risk with secretagogues, insulin
- Genital mycotic infections
- UTI, urosepsis
- Volume depletion/orthostatic changes
- DKA
- Bladder cancer (Dapagliflozin only)
  - removed recently
- Increased fracture risk
- Increased risk for amputation

Diabetes Care 2015;38:1638-1642
Diabetes Therr.. 2020 Jan; 11(1): 7–1
Fralick M et al. *BMJ* 2020; 370 :m2812

Demonstration of the cascade of clinical events and metabolic changes that contribute sequentially to progressive clinical deterioration and development of full-blown episodes of euDKA.



Diabetes Care 2015;38:1638-1642

American Diabetes Association.

Risk for DKA , Genital Infections, Amputation and Fractures

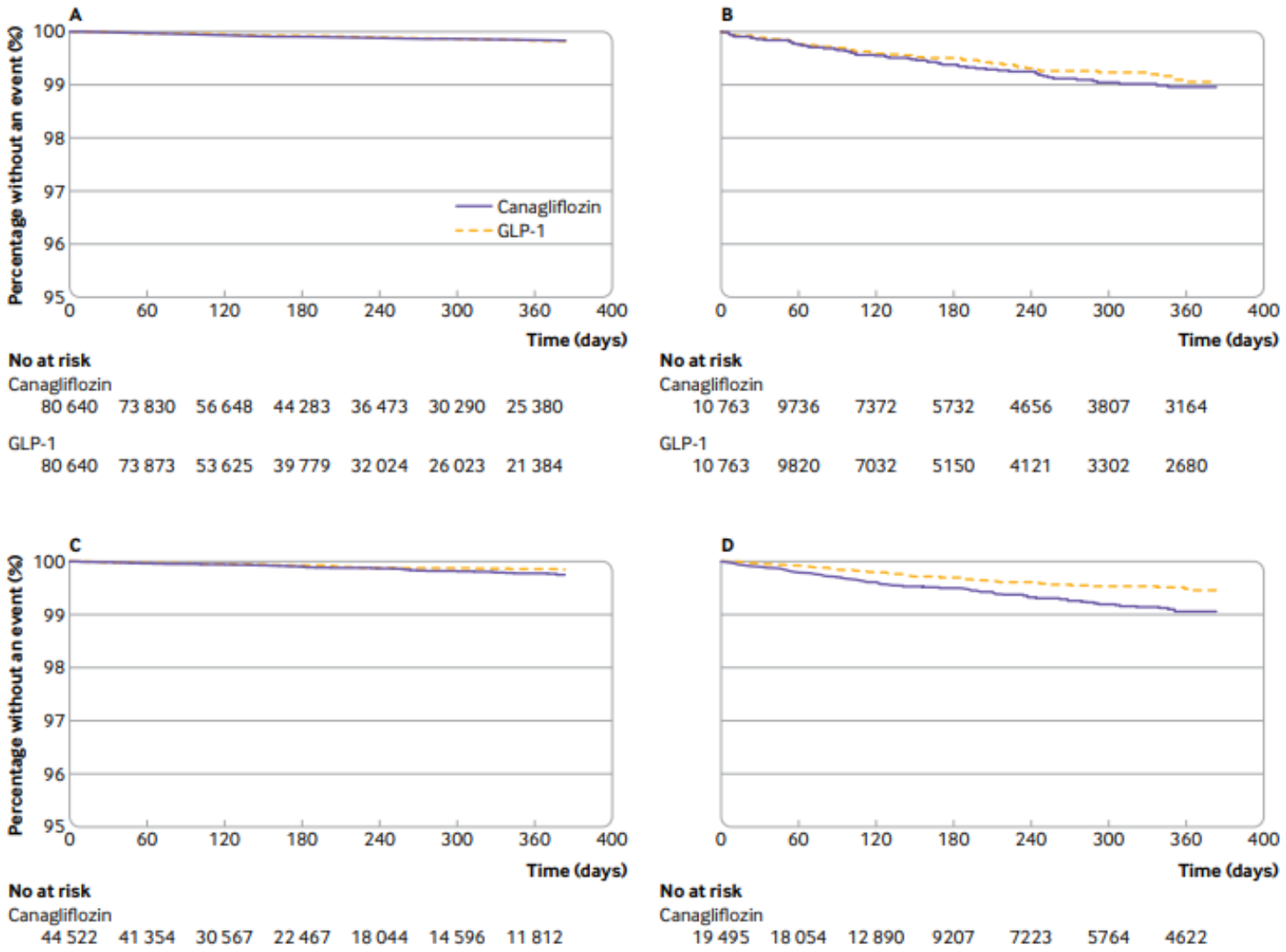
- DECLARE and EMPA-REG: less than 0.1% risk for DKA
- CANVAS: The estimated DKA incidence rates—0.5, 0.8, and 0.2 per 1,000 patient-years
- EMPA-REG OUTCOME: (22 vs 75) had genital infection(53 more in Empa)
- Rare case reports of ARI and risk for orthostatic hypotension
- Fournier's gangrene
- CANVAS increased fracture risk (4% vs.2.6%)but neutral in pooled non-CANVAS studies
- CANVAS Amputation (6.3% vs 3.4%) but neutral and recent 2 large retrospective study

EMPA- REG N Engl J Med 2015; 373:2117-2128
Yu O et al.. Diabetes Care. 2020 Oct;43(10):2444-2452
CANVAS. Lancet Diabetes Endocrinol. 2018 Sep;6(9):691-704
DECLARE. N Engl J Med 2019; 380:347-357

Risk of Amputation with Canagliflozin Across Categories of Age and Cardiovascular Risk

NNT=556 patients at six months

18 more amputations per 10 000



BMJ 2020;370:m2812

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SGLT2 Inhibitor use in CKD -For Glycemic Management

- Invokana (canagliflozin) < 45mL/min- DO Not use
- Jardiance (empagliflozin) < 45ml/min Do Not use
- Farxiga (dapagliflozin) < 60ml/min- Do Not Use
- Example: patient on empagliflozin GFR < 60 mL/min decrease to 10 mg daily when < GFR 45 mL/min stop
- At stage 3b CKD or greater, all SGLT-2 inhibitors are contraindicated, mainly because efficacy may be worst at GFR < 60mL/min

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE)

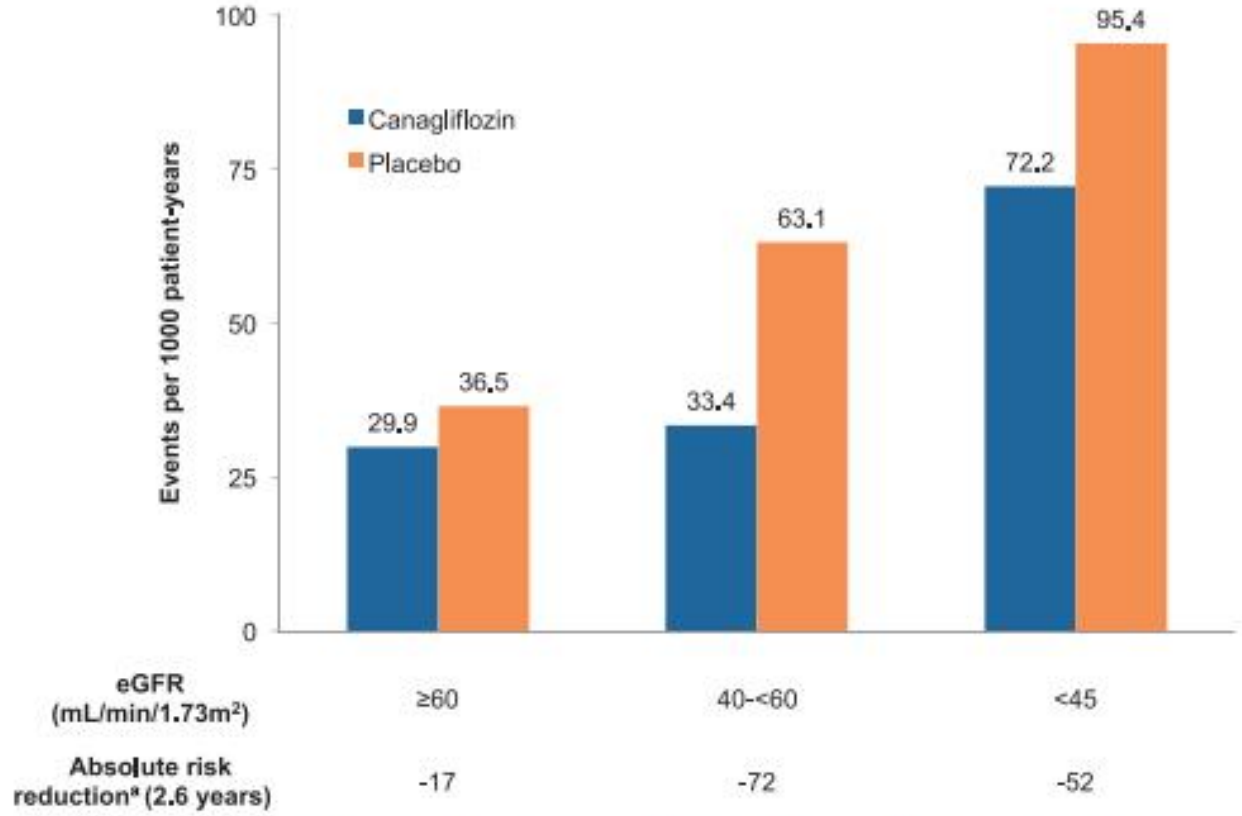


FIGURE 1: Estimated number of primary events (doubling of serum creatinine, ESKD or cardiovascular or kidney-related death) prevented per 1000 patients treated over 2.6 years in the CREDENCE trial by baseline eGFR. *Absolute risk reductions estimated as the number of events prevented per 1000 patients treated over 2.6 years.

ADA guidelines: SGLT2 inhibitors for the prevention of kidney failure, cardiovascular events or both in patients with an eGFR >30 mL/min/1.73 m2

**Especially with severely increased albuminuria

The NNT= 19 (95% CI, 12–40) in the primary
NNT= 26 (95% CI, 15–96) in the secondary prevention

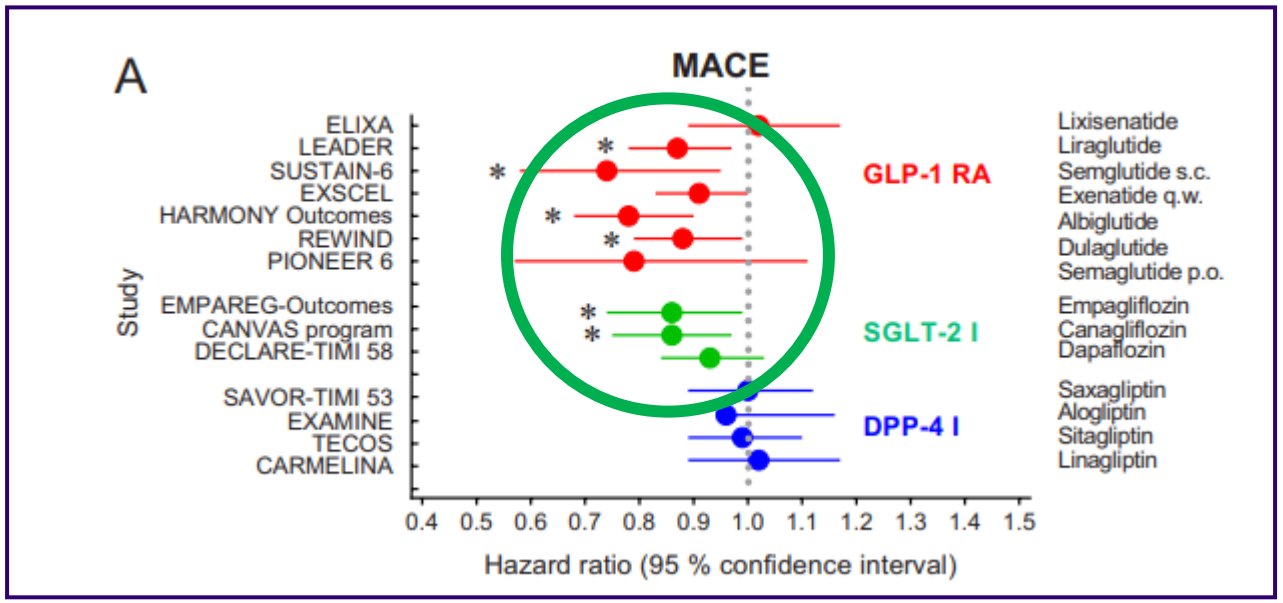
Neuen BL et al. *Nephrol Dial Transplant*. 2020;35(Suppl 1) i48–i55.

Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306

Canagliflozin: SGLT2I : For Renal and CV Benefit

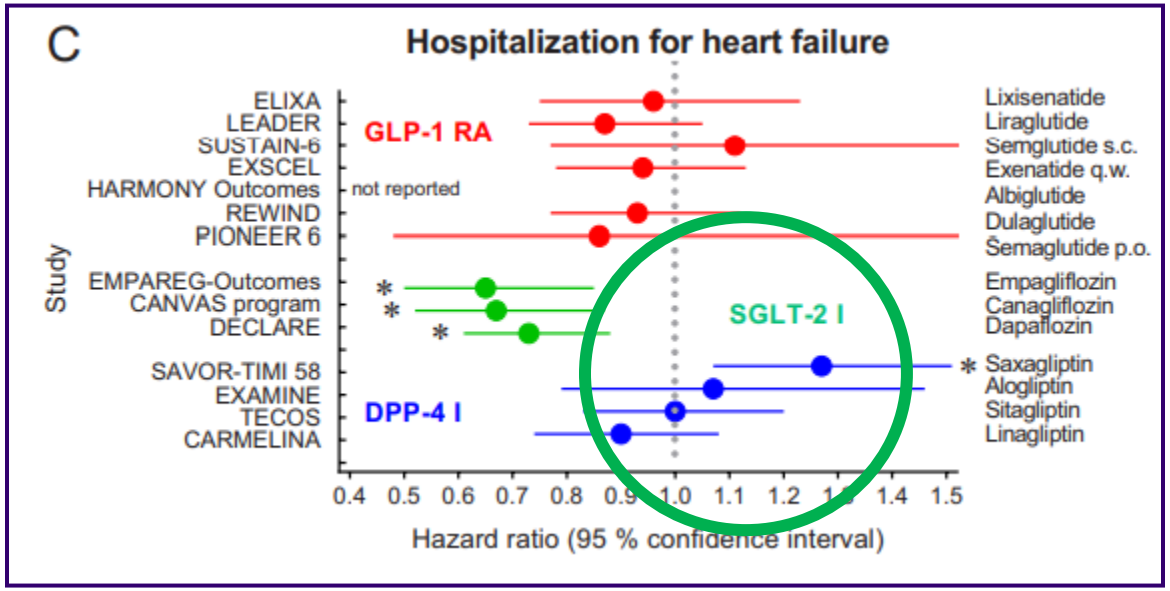
- GFR ≥60 mL/min/1.73 m^2: No **dosage** adjustment necessary.
- eGFR 30 to <60 mL/min/1.73 m^2: 100 mg qDay.
- eGFR <30 mL/min/1.73 m^2 with albuminuria >300 mg/day: 100 mg qDay to reduce risk of end-stage **kidney** disease, doubling of serum creatinine, CV death, and hospitalization for heart **failure**.

CV Outcomes Comparison



CV Benefits and All Cause Mortality Benefit for GLP-1 RA & SGLT-2 I

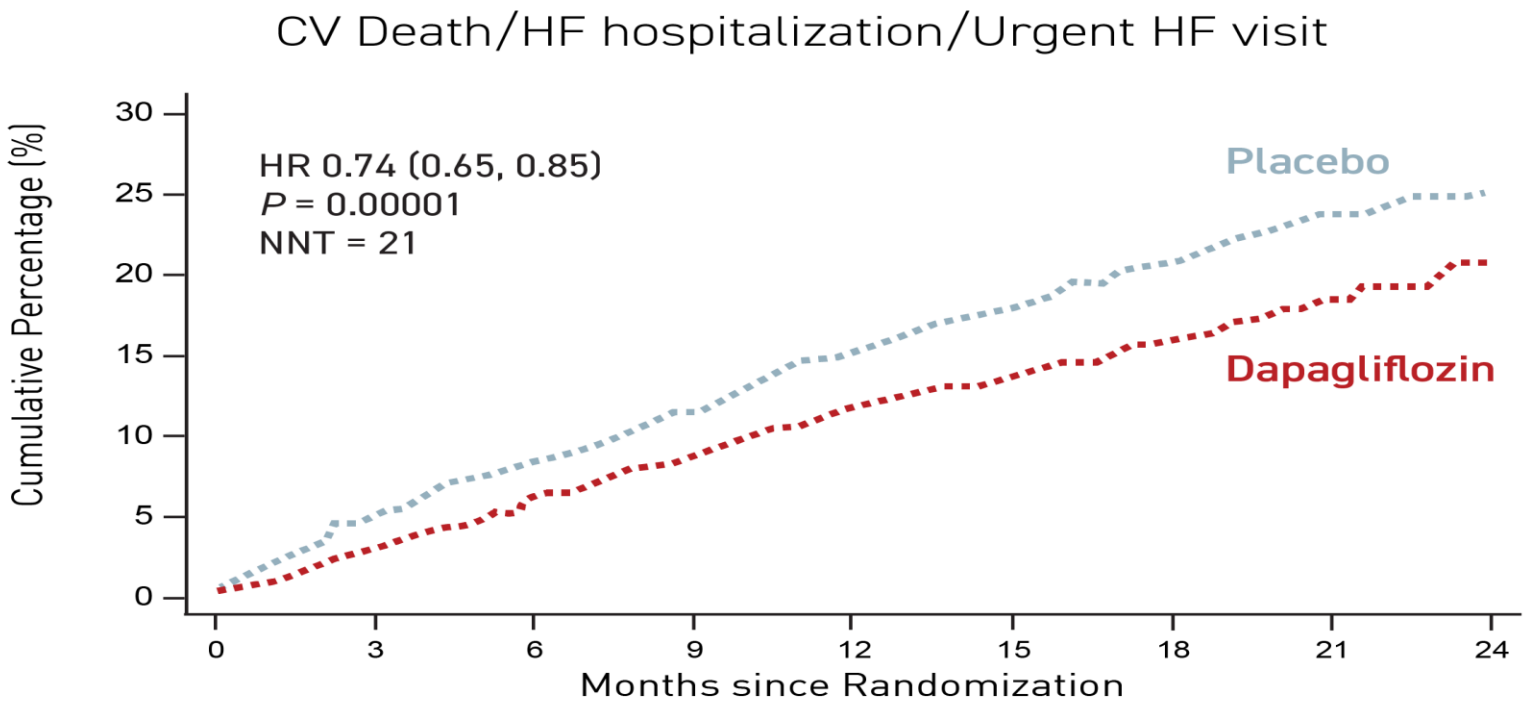
**Heart Failure Benefit only in SGLT-2I



Nauck MA et al. Eur J Endocrinol. 2019 Dec;181(6):R211-R234

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction With and Without DM

Primary Composite Outcome



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Adapted from McMurray JJV et al. As presented during ESC Congress 2019, Hot Line Session 1.

The Medical Xchange

UW Medicine

N Engl J Med 2019; 381:1995-2008

SGLT-2 Inhibitors and Liver Disease

SGLT-2 inhibitors

- Induces weight loss
- Low risk of hypoglycemia
- Improves hepatic steatosis on imaging and hepatic fibrosis markers in NAFLD/NASH

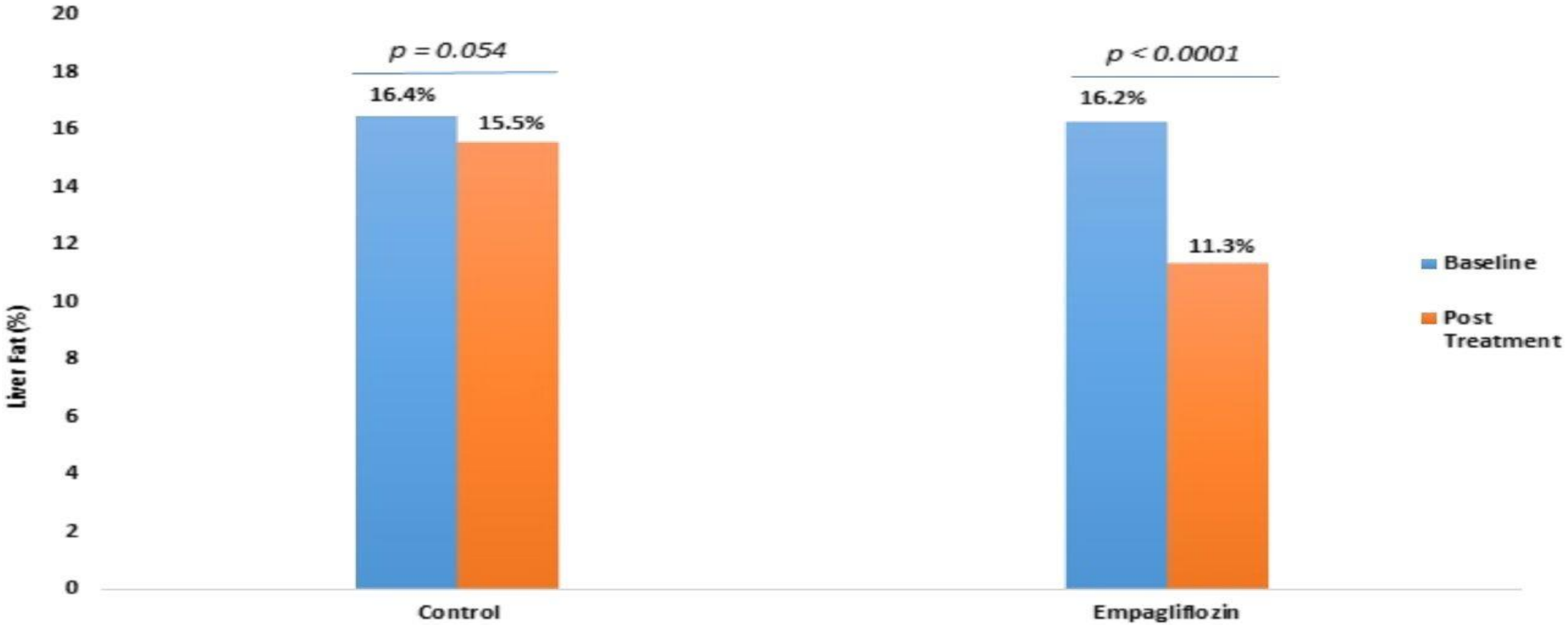
- Increased risk of urinary and genital tract infections
- Limited therapeutic experience in advanced cirrhosis

? Attenuate HCC development

Benefit in NASH

World J Hepatol 2020 September 27; 12(9): 533-692

Baseline and posttreatment changes in liver fat in the empagliflozin and control groups as assessed by MRI-PDFF.



Mohammad Shafi Kuchay et al. Dia Care 2018;41:1801-1808

American Diabetes Association.

Summary: SGLT2 Inhibitors

- CV and renal benefit for patients with DM
- HF benefit pts for with and without DM
- Risk for DKA, UTI, genital infections, amputation, bone loss
- Some weight loss
- Overall can be well tolerated
- NASH benefit and promising potential in liver disease but not well studied
- HbA1c drop is usually < 1.0%
- More expensive: Consider using 150 canagliflozin or 12.5mg empagliflozin (cut tablet in ½)

Comparative Considerations

Drug	Availability	~A1c Reduction	Cost/30 d Varies	Hypoglycemia Risk	Weight Change
SFU/glinides	Generic*	~1.5%	$/$-$$$	Yes	GAIN
Metformin		%	$	No	Neutral
TZD		%	$$		GAIN
AGI	Generic*	0.5 – 1.0%	$$		Neutral
DPP4-Is	Brand	0.5 – 0.8%	$$$$		Neutral
GLP-1 RAs			$$$$	No	LOSS
Colesevelam			$$$	No	Neutral
Cycloset ™	Brand	0.6%	$$$	No	Neutral
SGLT2	Brand	0.9%			LOSS

$5-90 /month
$60-1000/yr

$650-950/month
$6000-8000/yr

$350-450 /month
$4000-5,000/yr

$400-500 /month
$4800-6000/yr

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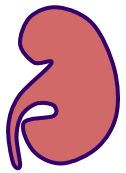
Adapted from D'Allesio DA and Hirsch IB. glycemic Management of Type 2 DM. *Translational Endocrinology & Metabolism. 2011;2(1):75.*

Conclusions

- Some medications for the treatment of T2D have cardiovascular and reno-protective effects in the those with CVD or are high-risk for CVD.
- As well certain medications help initiate weight loss and are less likely to cause hypoglycemia than other agents
- Cost must be a factor in use of these medications


Questions?

COST of a Major CV Event in US

- MI $US 73,300
- Hospitalization for angina $US 36,000
- Non-fatal hemorrhagic stroke $US 71,600

Pharmacoeconomics. 2011 Aug;29(8):693-704

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Your Patient?
HbA1c 10.5%, BMI 35 recent weight loss and polyuria

Case:

- Pt was placed on insulin and metformin at initial visit
- Pt returns for follow-up visit
- Tolerating metformin well on 1000mg XR bid
- Has gained 5 pounds over last month
- Titrated up to 52 units of glargine
- Sugars fasting < 150mg/dL and most sugars in 100-180mg/dL range
- Had recent TIA

WHAT NEXT??

Individualizing DM Medications Based on Patient Characteristics

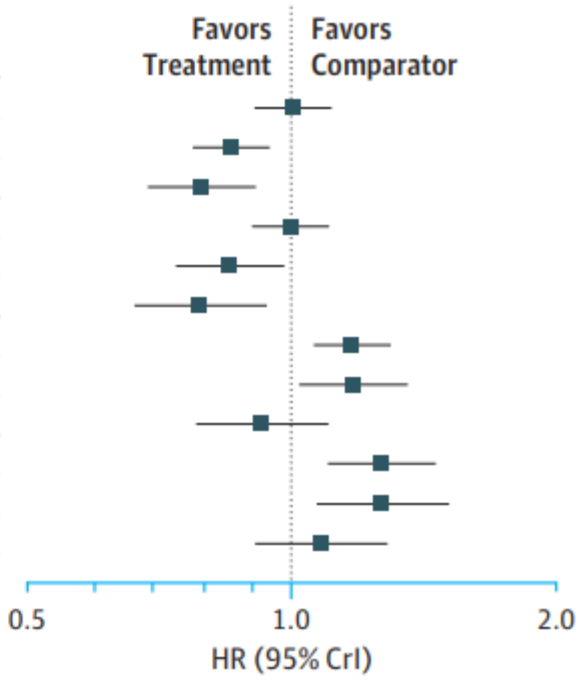
- Important to consider transitioning off insulin/minimizing insulin
- Use of insulin sparing agents
- Given TIA and BMI > 30 would favor GLP-1 RA
- If known CHF then would consider SGLT2I

SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors with all-cause mortality in patients with T2D

B Cardiovascular mortality, 56 trials; $I^2 = 19\%$

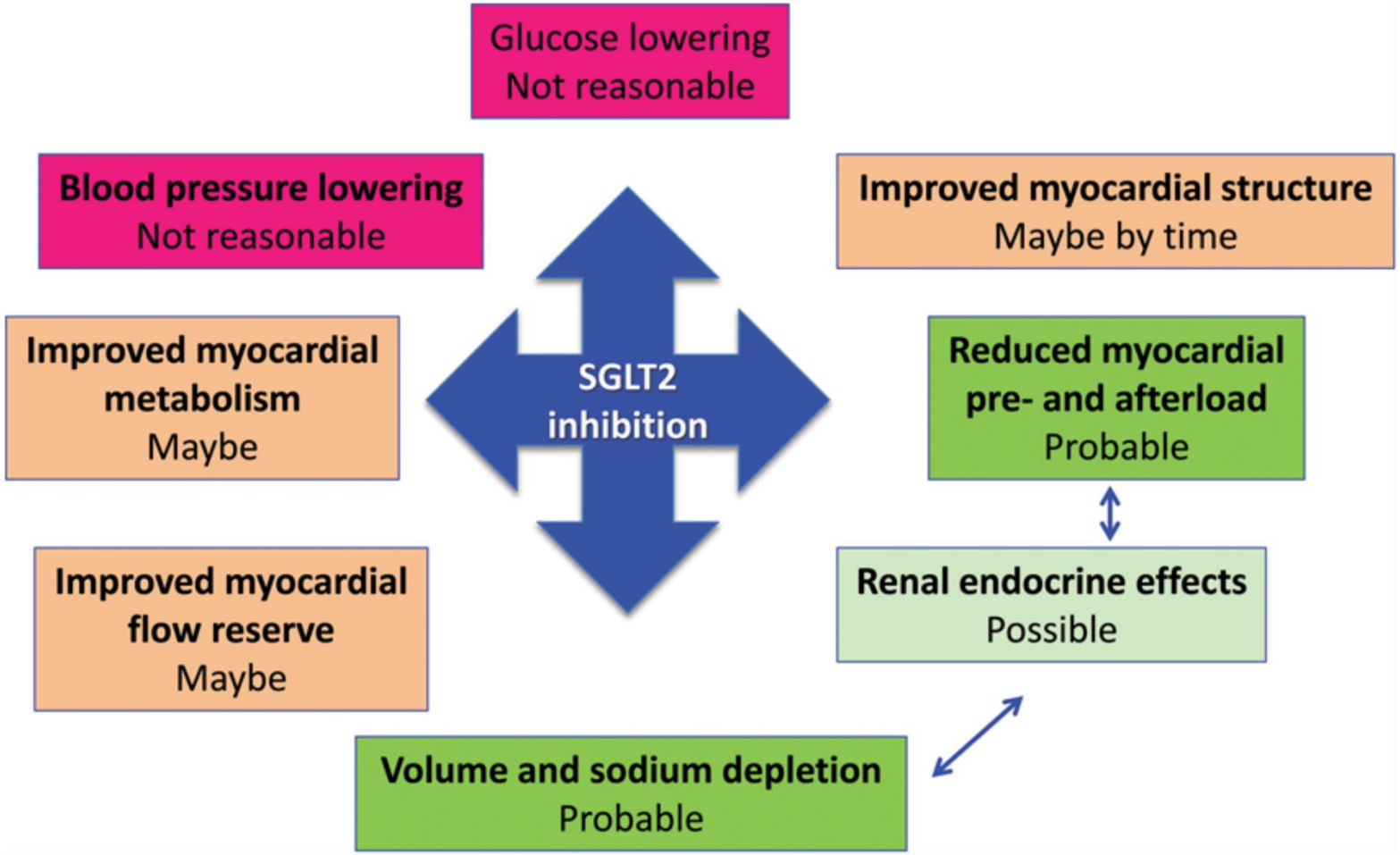
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist	vs Control	-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor	vs Control	-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist	vs DPP-4 inhibitor	-0.5 (-0.8 to -0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor	vs DPP-4 inhibitor	-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor	vs GLP-1 agonist	0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor	vs GLP-1 agonist	-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor	vs SGLT-2 inhibitor	0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist	vs SGLT-2 inhibitor	0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50869
DPP-4 inhibitor	27	763 (3.1)	24519
GLP-1 agonist	19	704 (3.0)	23554
SGLT-2 inhibitor	19	468 (2.5)	18407



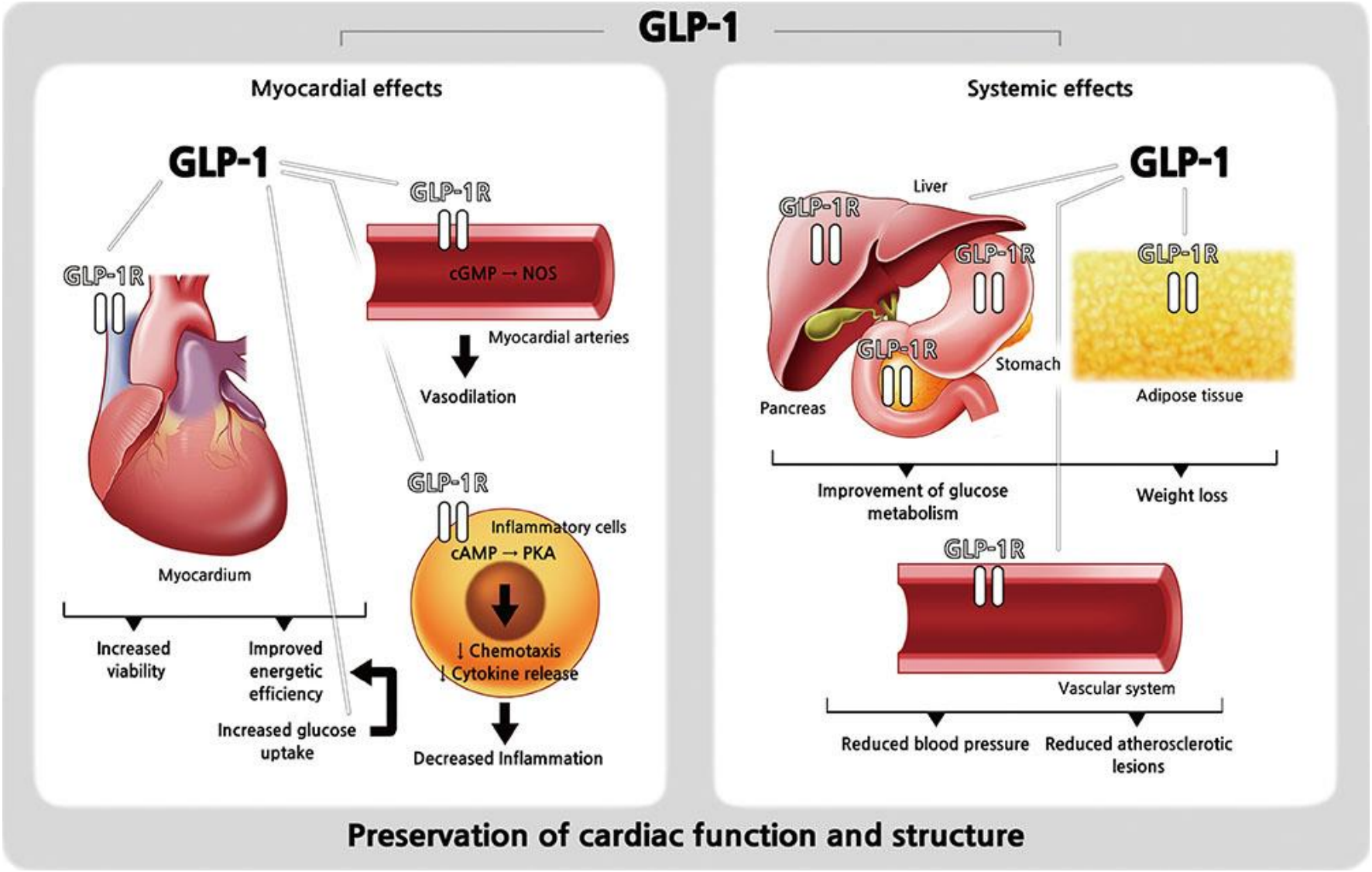
Zheng et al JAMA. 2018 Apr 17;319(15):1580-1591

Effects of SGLT2 Inhibitors



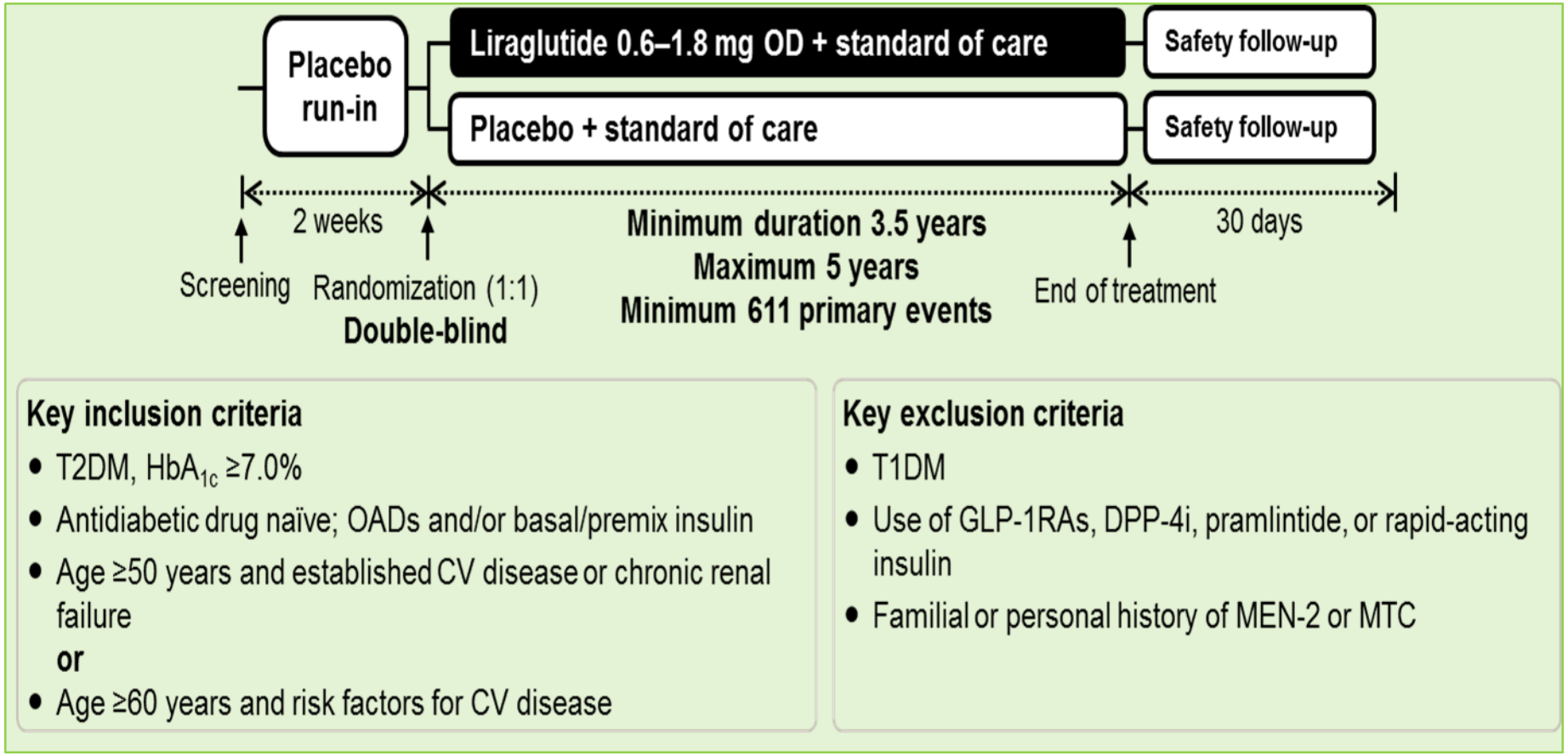
Swedberg et al. Eur Heart J. 2016;37(19):1535-1537.

Effect of GLP-1 Agonists



Kang et Endocrinol Metab. 2016 Jun;31(2):258-274

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

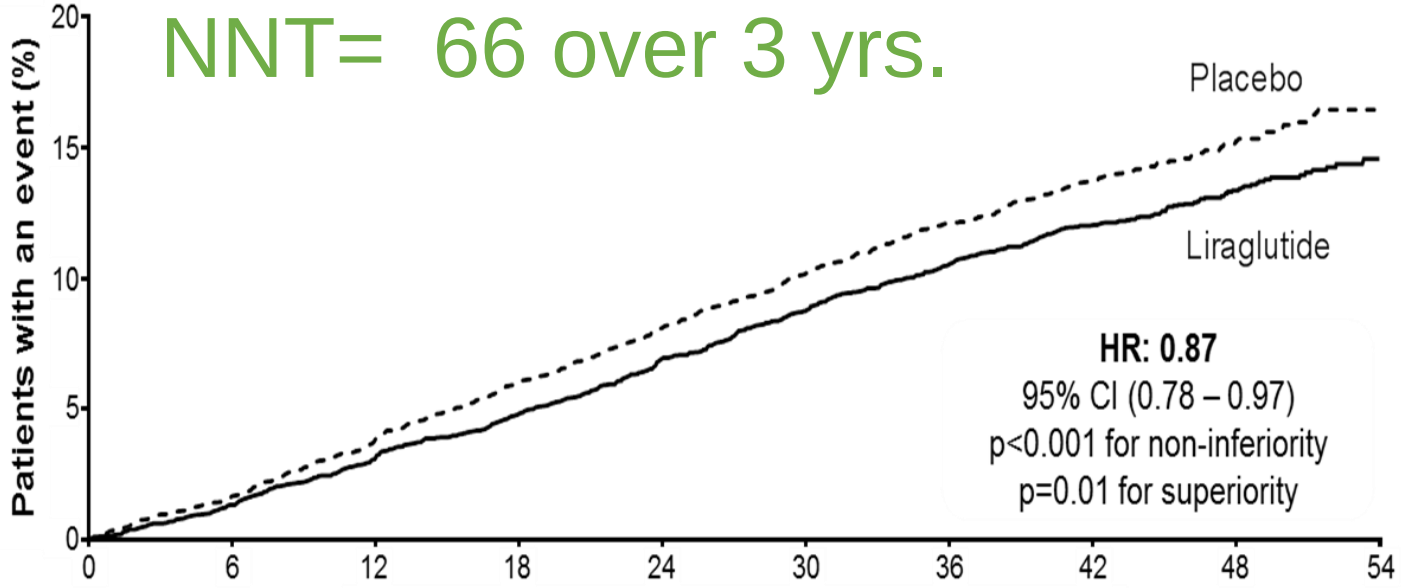
N Engl J Med 2016; 375:311-322

LEADER (Liraglutide CVOT):

- Primary outcome CV death, non-fatal myocardial infarction, or non-fatal stroke

13% RRR in CVOT (*P*=0.01)

NNT= 66 over 3 yrs.



Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

N Engl J Med 2016; 375:311-322

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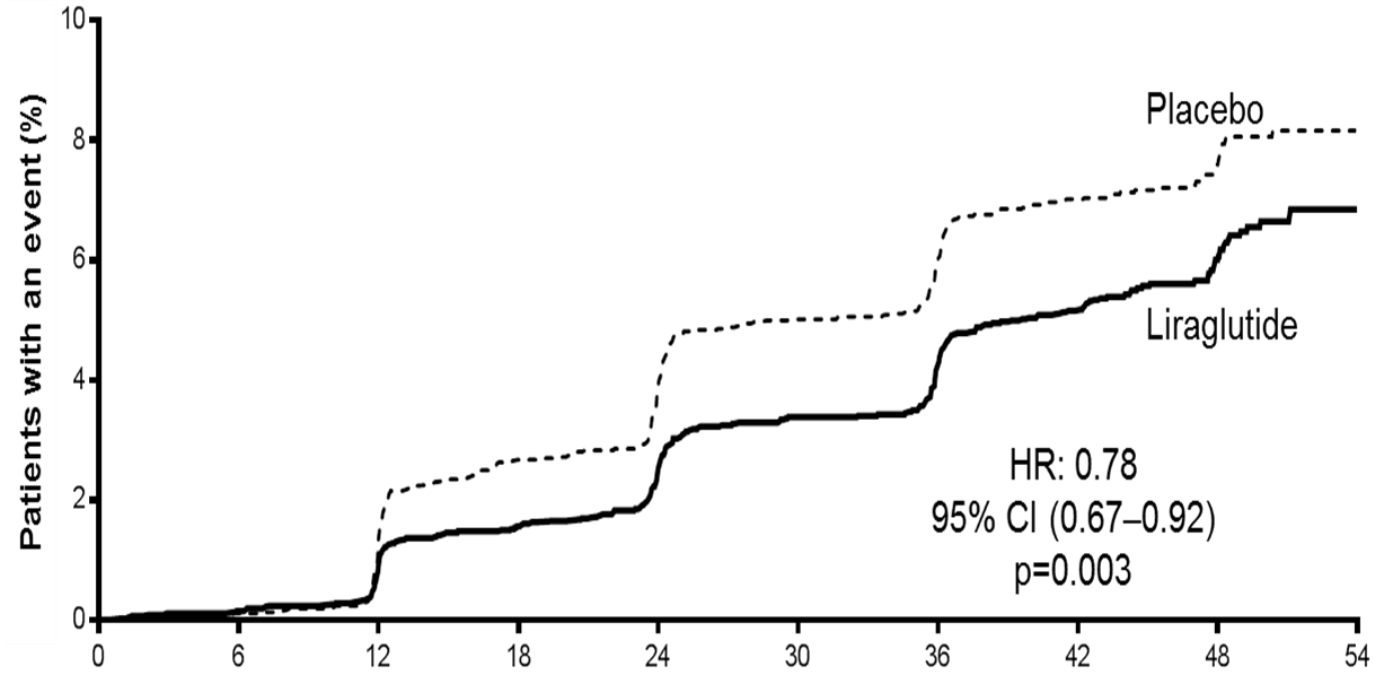
LEADER: Time to first renal event

- Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

N Engl J Med 2016; 375:311-322

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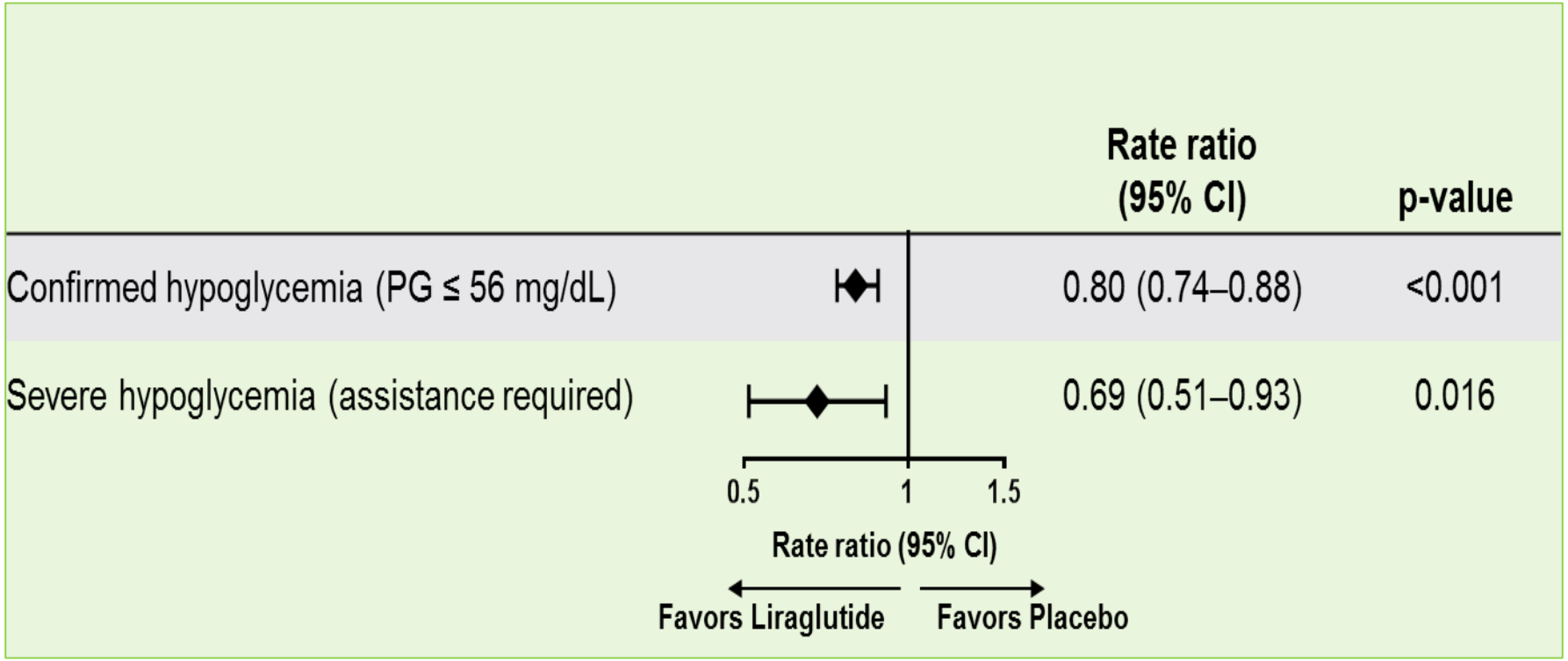
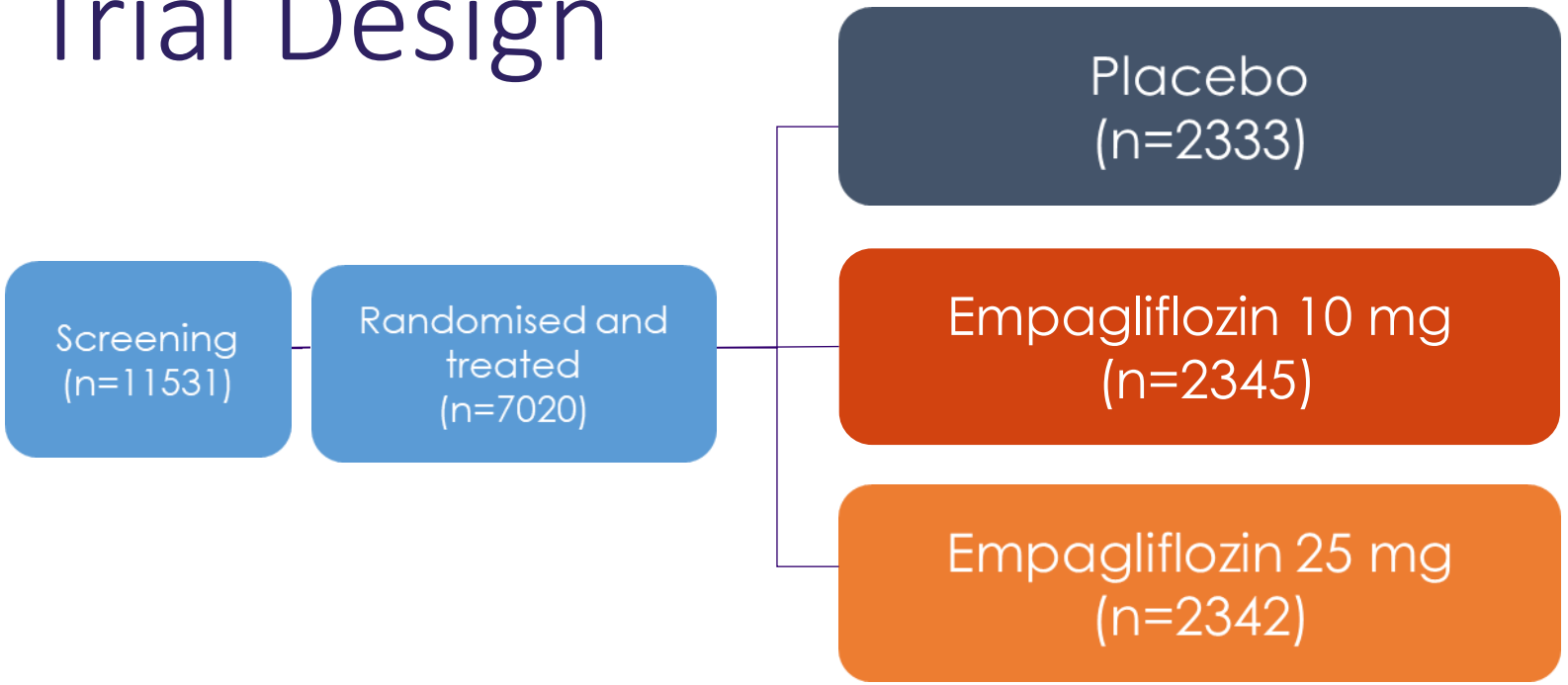
Hypoglycemia



Confirmed hypoglycemia was defined as plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter) or a severe event. Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party. Analyzed using a negative binomial regression model.

EMPA-REG: Trial Design



- All patients had known cardiovascular disease
- Study medication was given in addition to standard of care
- Treatment assignment double masked.
- The trial was to continue until at least 691 patients *experienced an adjudicated primary outcome event*

N Engl J Med 2015; 373:2117-2128

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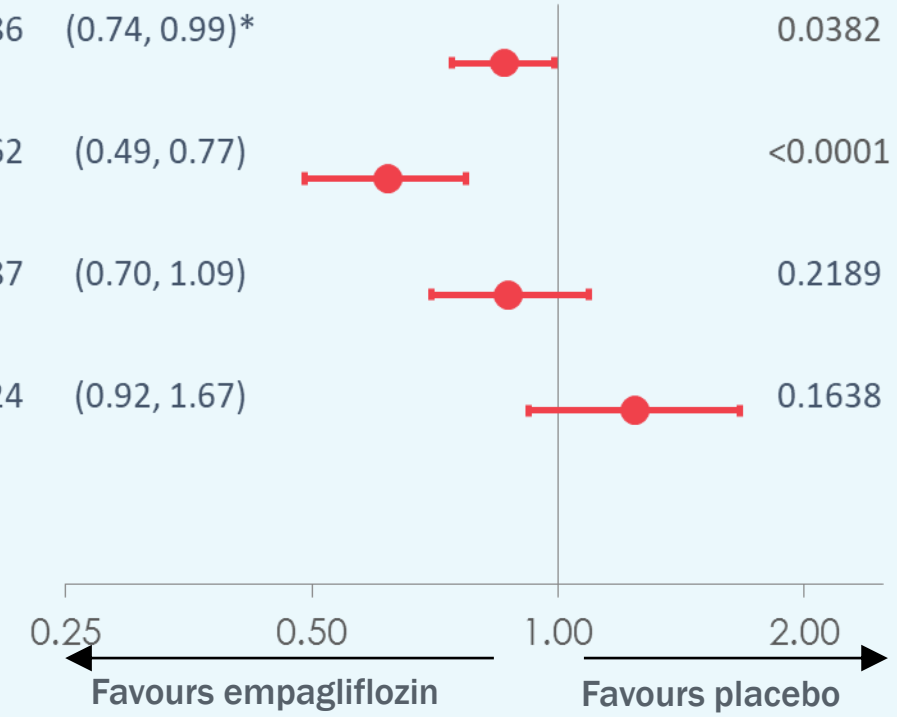
EMPA-REG: CV Death, MI, and Stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



38% RRR
Cardiovascular Mortality:
NNT = 45

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

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

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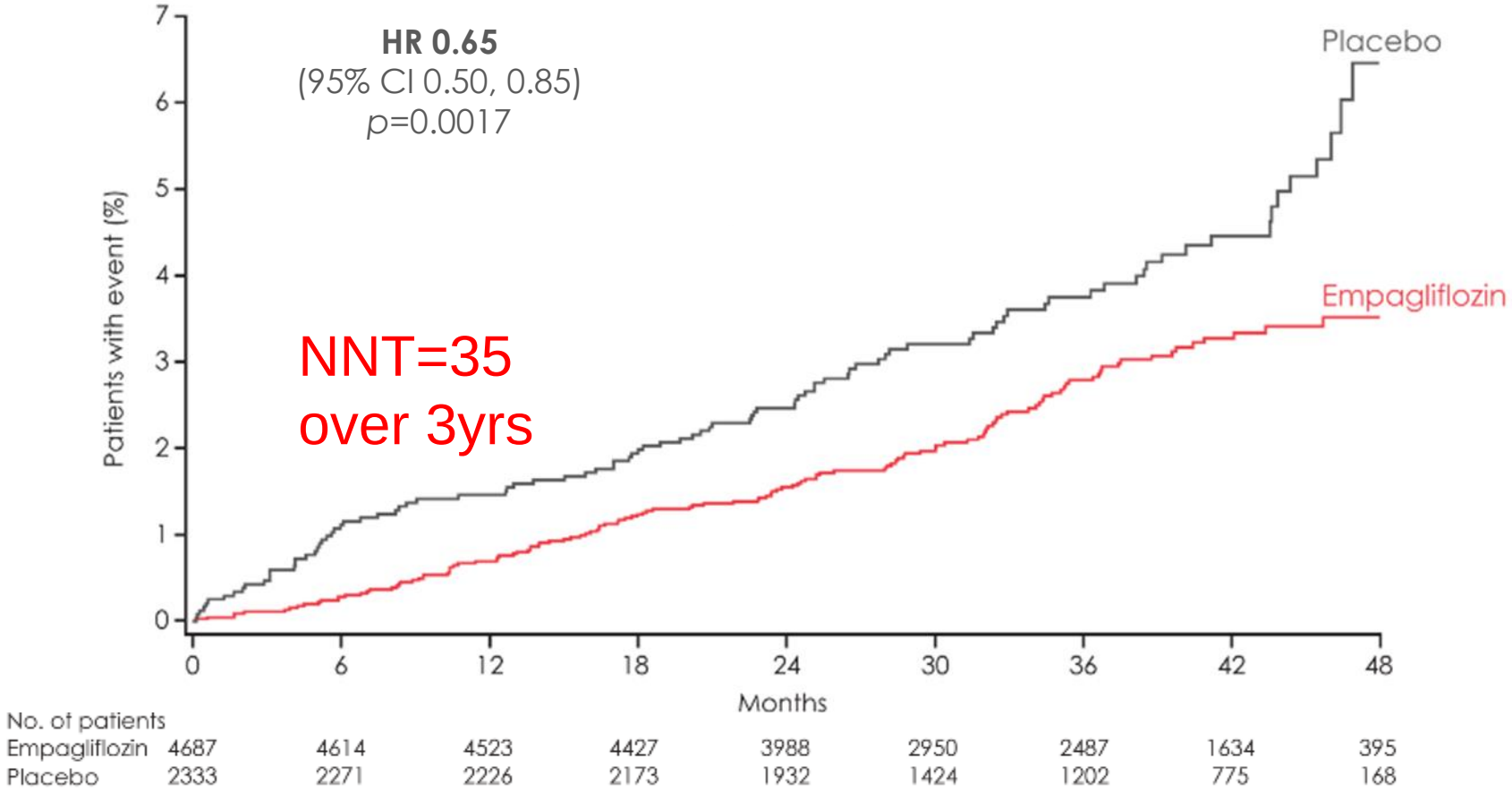
Hospitalization for Heart Failure



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

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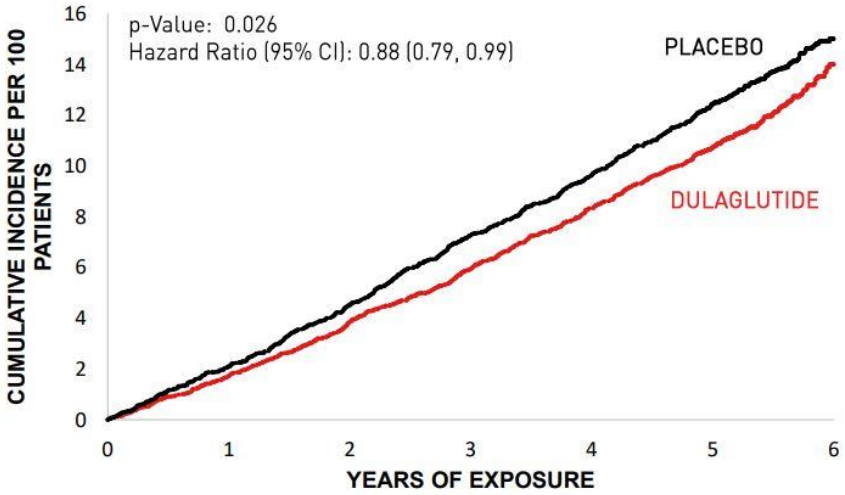
REWIND Study/ Dulaglutide

TRULICITY CV OUTCOME TRIAL

PRIMARY MACE 3 RESULT

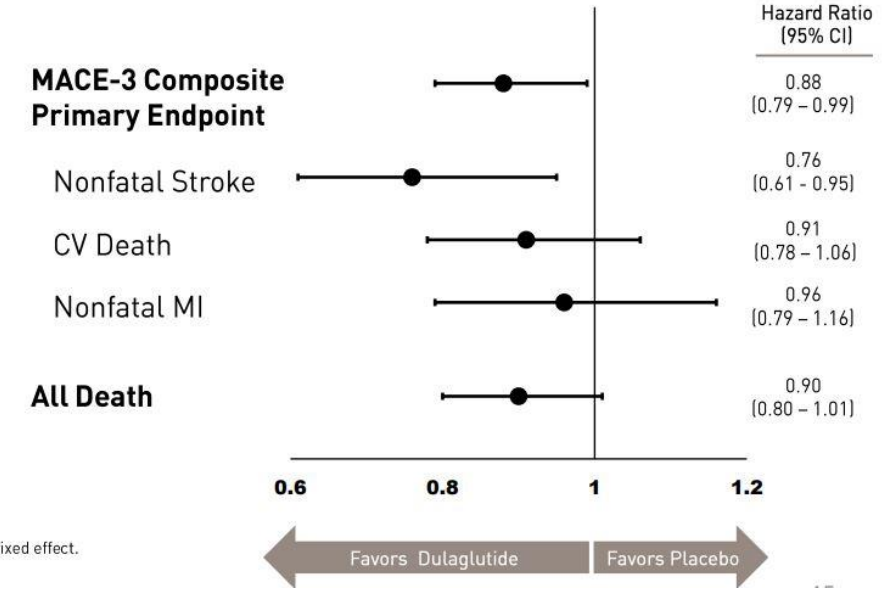
Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) **by 12% vs. placebo**



Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.
Gerstein et al. Lancet 2019.

CV OUTCOMES

Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke



SOURCE

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Credence study

Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)