Type 2 Diabetes: Beyond A1c

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Disclosures

1. Champion 2020 VA/DoD CPG Screening and Management of Obesity and Overweight.

2. Research funding NovoNordisk (Sub-PI SELECT), study site withdrawn 3/2020.

→OFF FDA label prescribing practices to consider may be discussed.

Objectives

- Review therapeutic strategies to improve glycemic control in a case-based format.
- Discuss key concepts from the 2020 American Diabetes Association Standards of Care.
- Identify critical comorbidities that influence treatment decisions.

Case 1

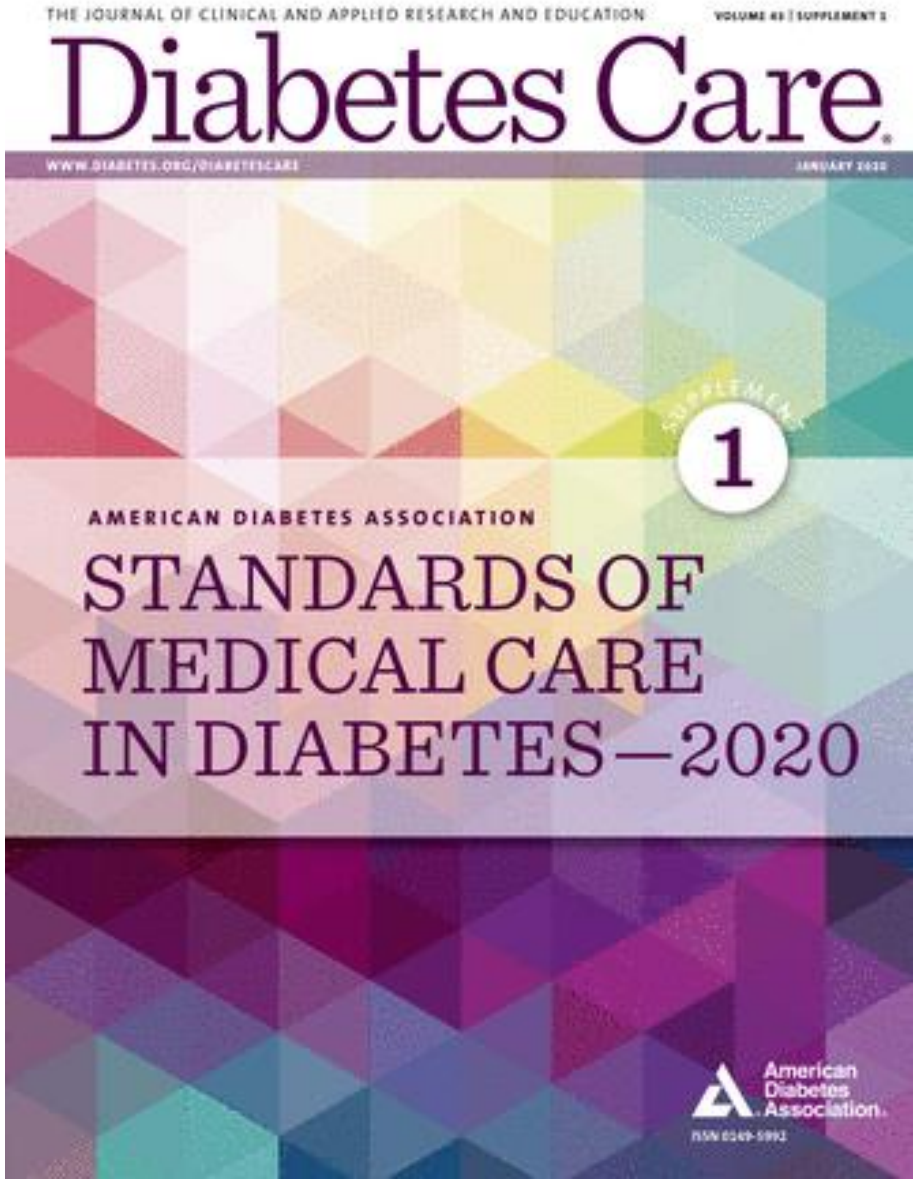
65 y.o. female lawyer with hx of HTN and hyperlipidemia complicated by coronary stent placed in 2017 for an NSTEMI. BMI of 36 kg/m2. A1c of 8.4%. eGFR of 42 ml/min/1.73m2. She has + microalbuminuria 120 mg/g Cr.

In addition to Lifestyle changes what would you start? What options would you consider and why, or why not?

A) Metformin alone
B) Metformin + second agent (dipeptidyl peptidase type 4 inhibitor (DPP4i), or sulfonylurea, or glucagon-like peptide 1 agonist (GLP-1), or sodium-glucose cotransporter type 2 inhibitor (SGLT2i)
C) Sulfonylurea alone
D) DPP4i alone
E) GLP-1 agonist injection alone
F) SGLT2i alone

Therapeutic Objectives of T2DM

- Achieve glycemic control
- Resolve symptoms of hyperglycemia
- Prevent microvascular complications
- Prevent macrovascular complications



https://care.diabetesjournals.org/content/43/Supplement_1

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

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

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY

GLP-1 RA with proven CVD benefit[1]

OR

SGLT2i with proven CVD benefit[1] if eGFR adequate[2]

If A1C above target

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

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY

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

OR

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

If A1C above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

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

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

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[8] **EITHER/OR** SGLT2i[2]

If A1C above target

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

If A1C above target

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

PREFERABLY

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

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

• SU[6] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6] | TZD[10]

If A1C above target

TZD[10] | SU[6]

If A1C above target

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

OR

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

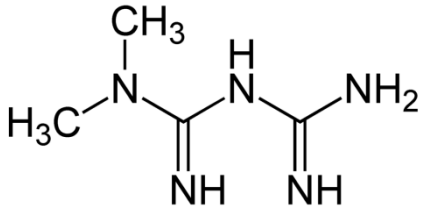
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Gilmepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

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

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction

UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

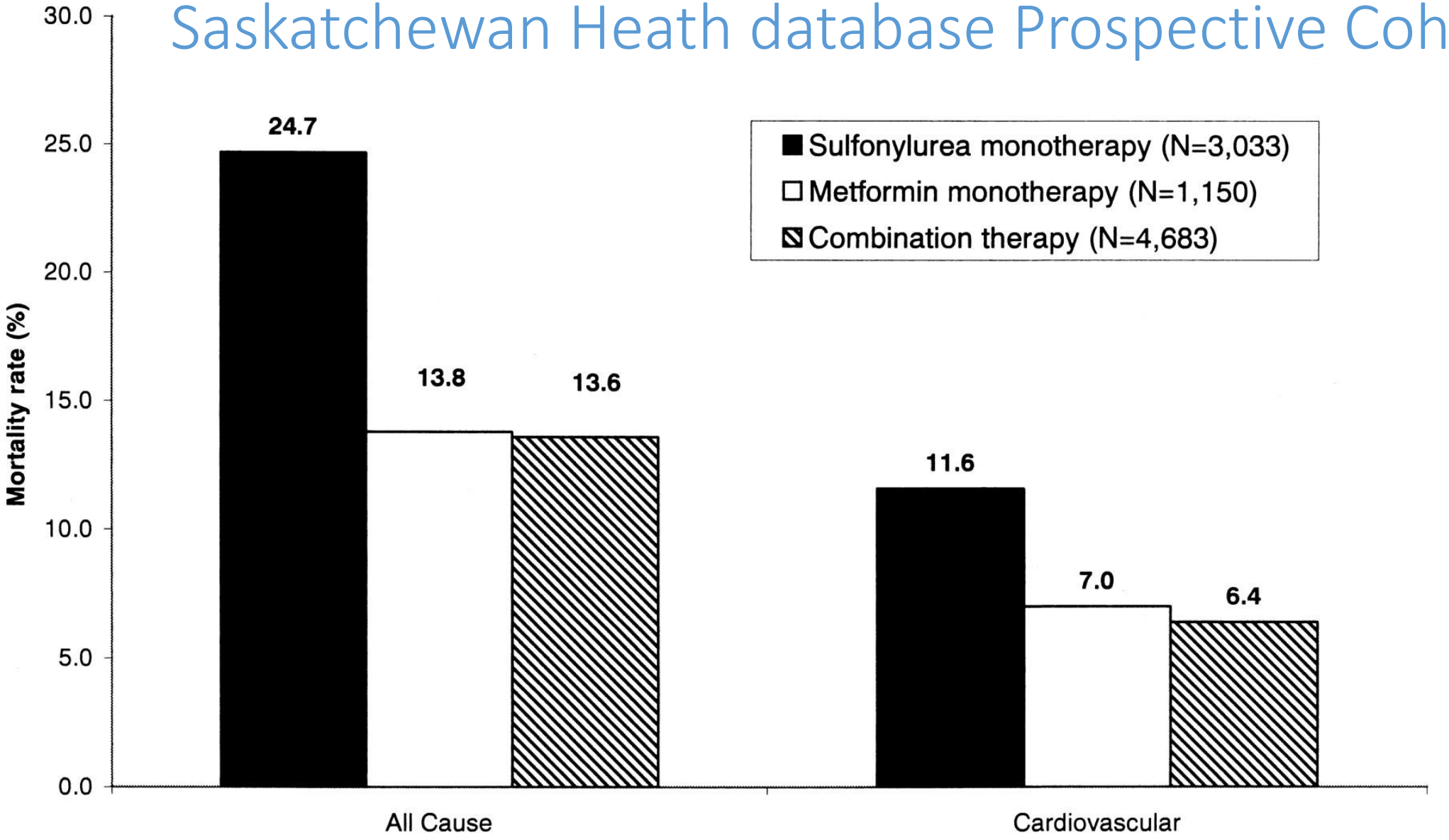
Biguanides
i.e. Metformin



- MOA: (pleiotropic)
- Via AMP-Kinase activation (among other proposed mechanisms) results in:
  a) reduce hepatic gluconeogenesis
  b) increasing GLUT 4 translocation and transport activity
  c) increase insulin receptor tyrosine kinase activity
  d) enhance muscle uptake of glucose
  e) suppress appetite (protein kinase signaling in brown adipocytes)

  - UKPDS trial: reduced all-cause mortality and any DM-related endpoint in patients with DM2 and obesity

Saskatchewan Heath database Prospective Cohort



Johnson et al. Diabetes Care 2002

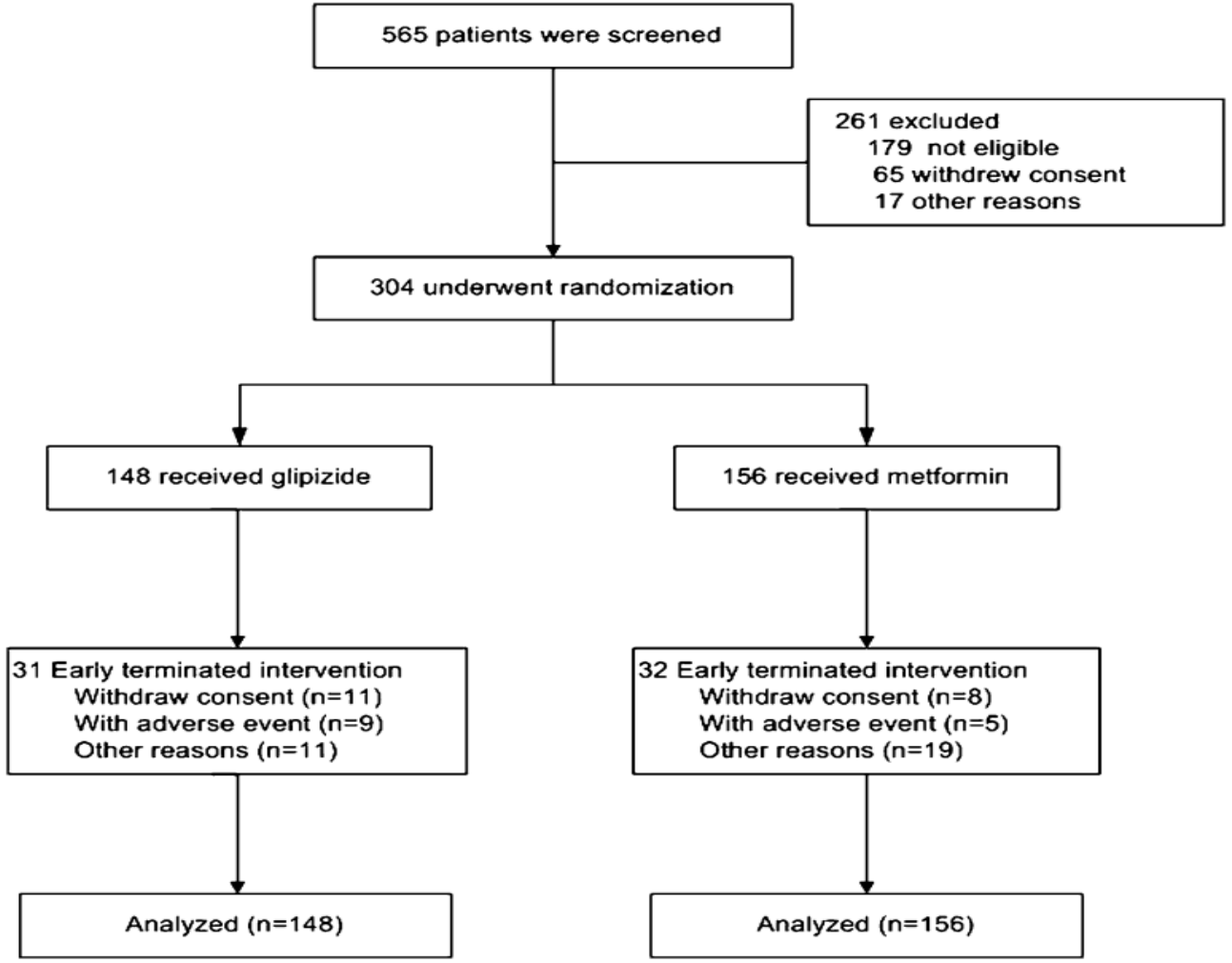
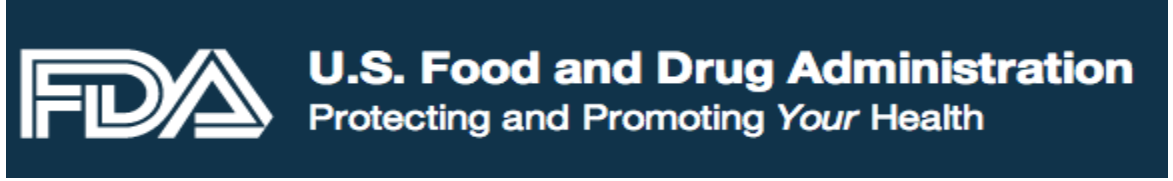


Figure 1—*SPREAD-DIMCAD trial profile.*

Primary (CV event, death from CV or any cause)→25% in metformin group and 35.1% in glipizide group (adjusted HR 0.54; 95% CI, 0.30- 0.90)

Hong J et al. Diabetes Care. 2013;36(5):1304-1311.



FDA label update 4/8/2016: Metformin

Contraindicated with eGFR <30 mL/minute/1.73 m2

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf

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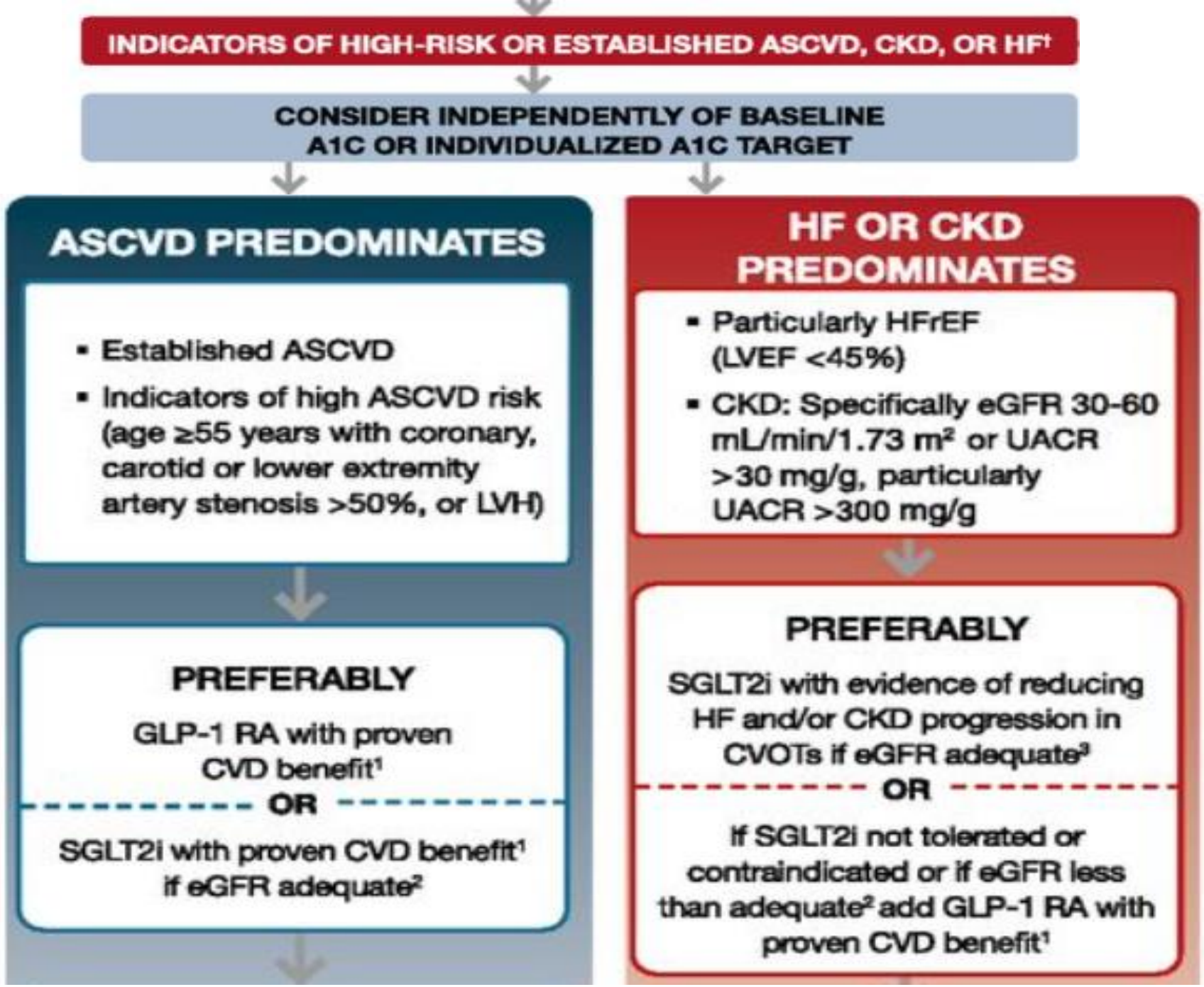
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SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

Glucagon-like Peptide 1 analogues

- Effect: ~1% A1c reduction

- MOA: Incretins, including GLP-1, are peptide hormones secreted by L-cells in the small intestine in response to food –>bind to GLP-1 receptors in many tissues (β cells and brain).

a) enhance glucose-dependent insulin secretion

b) slowed gastric emptying

c) reduce postprandial glucagon release

d) reduce food intake (appetite centers in brain)

*in rats stimulates beta cell regeneration and proliferation

Glucagon-like Peptide 1 analogues

- Side effects: nausea (40-50%), constipation or diarrhea, headaches, dizziness
- Caution: gastroparesis, ? hx pancreatitis
- Contraindication: medullary thyroid cancer in pt or family, MEN2A or B

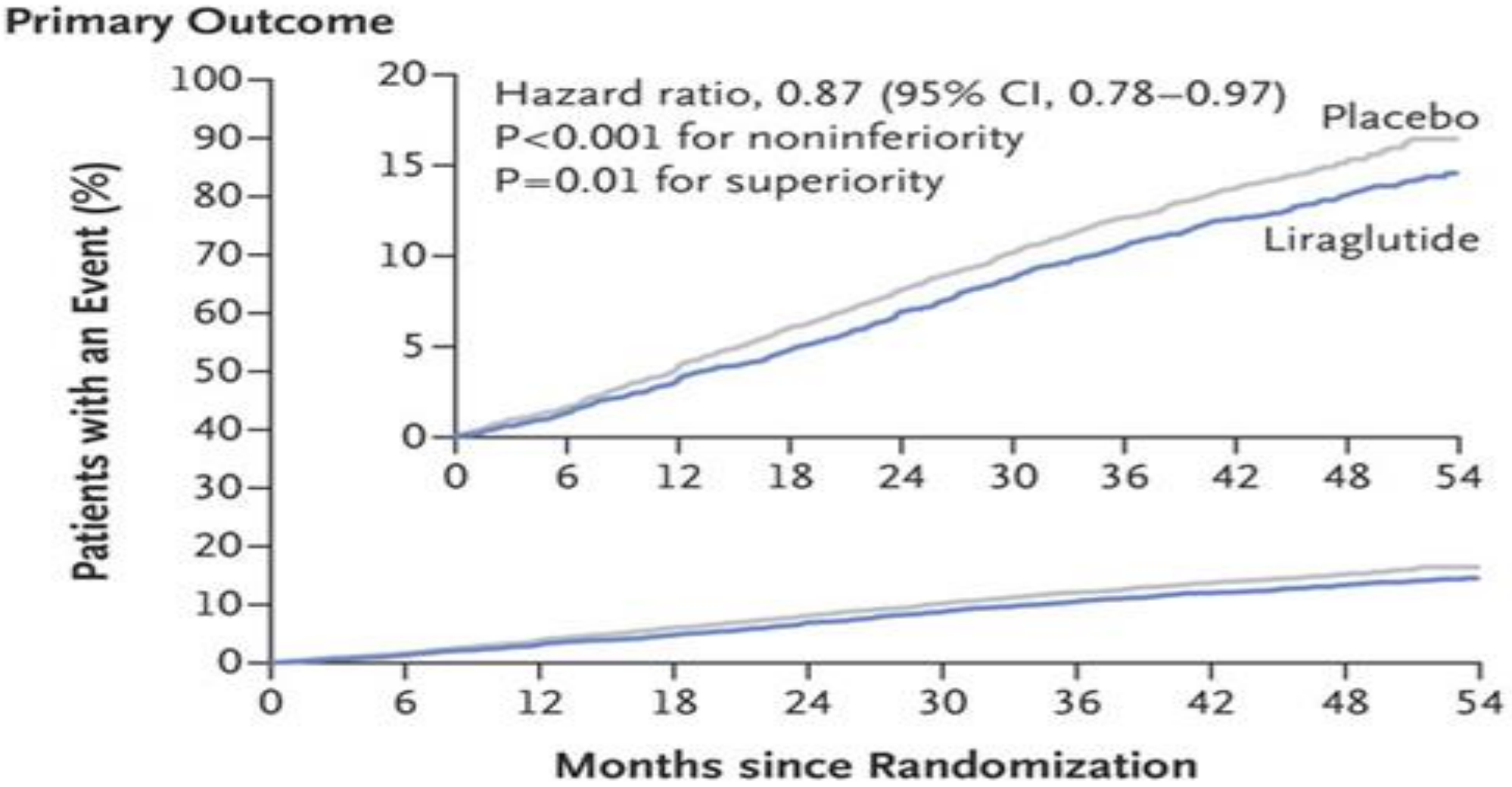
- Examples: semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide

Glucagon-like Peptide 1 analogues

- Benefits: weight loss! Does not require renal dosing!
- rare to cause hypOglycemia as monotherapy

- long-term CV effects reassuring and beneficial in most:
  - Liraglutide +benefit CVOT
  - Albiglutide + benefit CVOT
  - Inj Semaglutide collective + primary outcome benefit
  - Dulaglutide + benefit CVOT
  - but Lixisenatide, Exenatide and oral Semagluide: no harm but no benefit, non-inferior
- Drawbacks: injection (daily or weekly), COST

LEADER Trial – Liraglutide, N=9,340



New Engl J Med 2016; 375:311-322 July 28, 2016

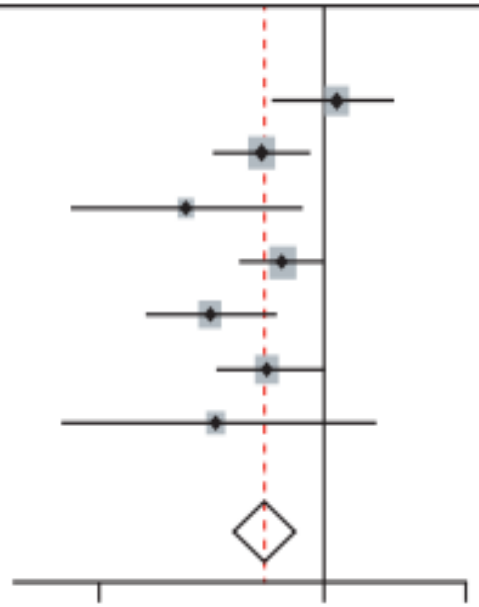
FDA label update 8/25/2017: Liraglutide

- The U.S. Food and Drug Administration approved a new indication for Liraglutide (Victoza®, Novo Nordisk) to reduce the risk of myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes mellitus who have established cardiovascular disease.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

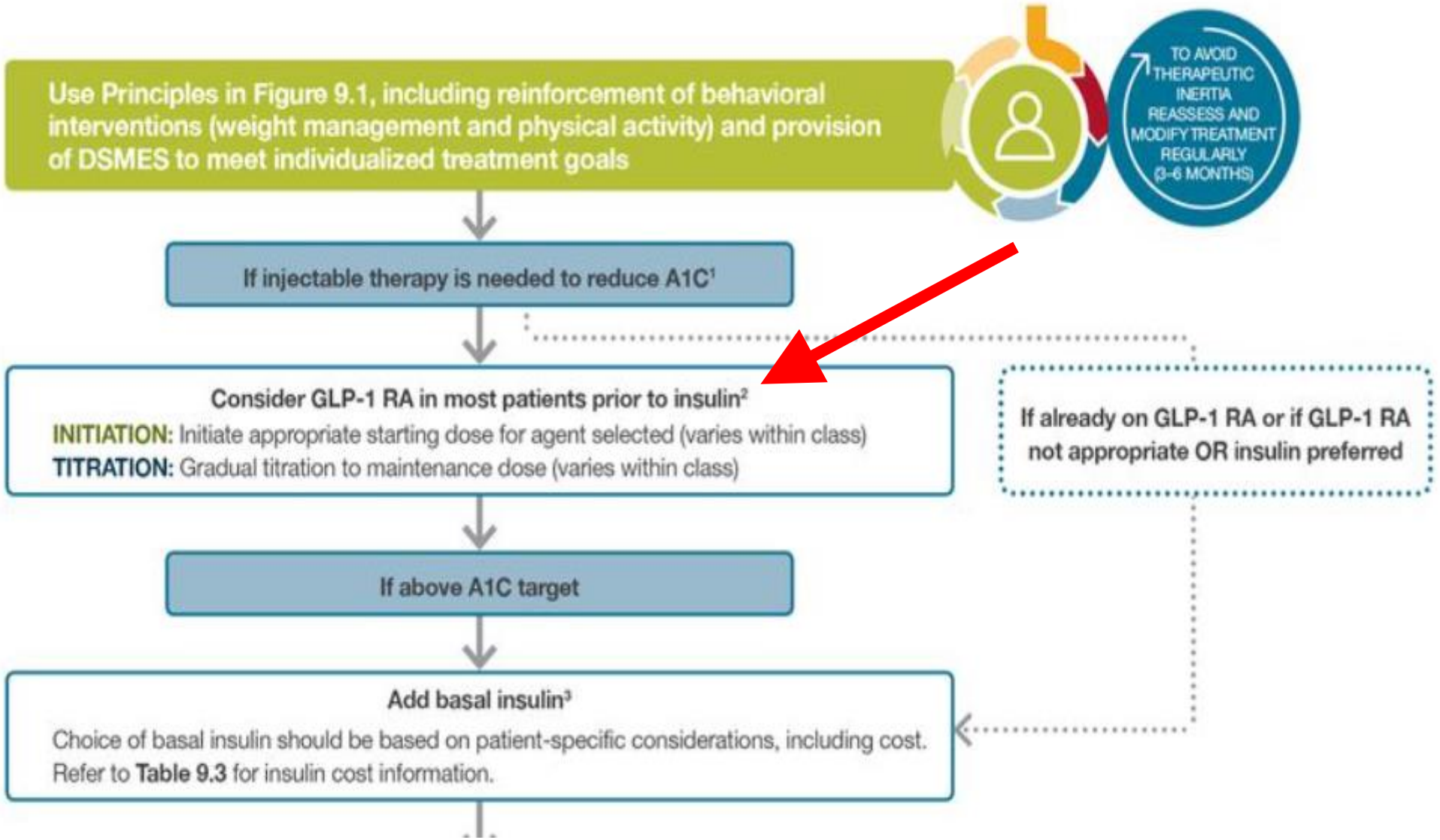
Systematic Review + Meta-Analysis GLP-1 in DM2 CVOT

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component 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)		0·015
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)		<0·001
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
Overall (I^2=40·9%, p=0·118)	**2948/27977 (11%)**	**3304/28027 (12%)**	**0·88 (0·82–0·94)**	**75 (50–151)**	**<0·001**

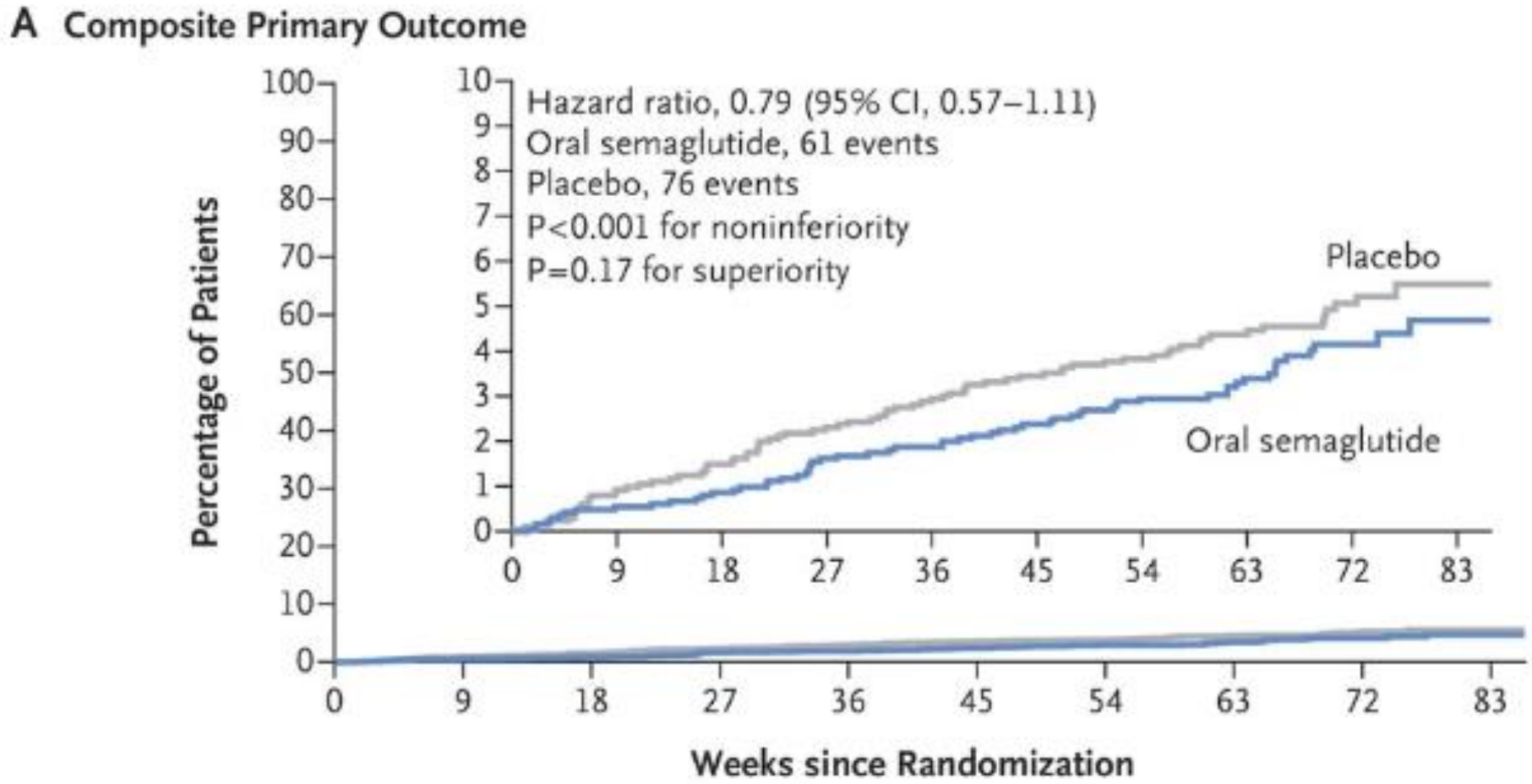


Kristensen SL et al. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776-785.

ADA Standards of Care – Role of GLP-1 RA



Oral Semaglutide – PIONEER 6



Husain et al. N Engl J Med 2019

Practical Considerations for GLP-1 Selection

1) Insurance coverage – (favor + CVOT data agents)
2) Health literacy – if lower health literacy dulaglutide lock/unlock
3) Needle phobia – dulaglutide pen
4) BMI – more weight to lose, semaglutide weekly (O'Neil 2018 Lancet)
5) Prefer daily to weekly?
6) Send tutorial video via health portal, ask them to watch x 3

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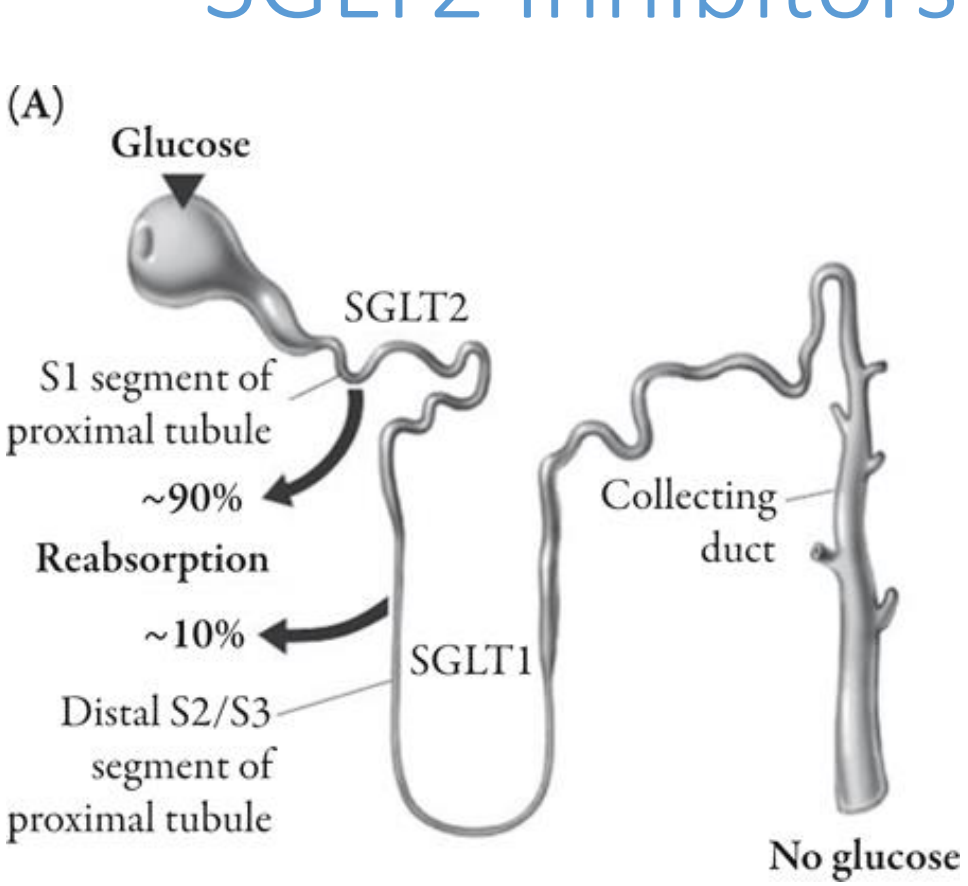
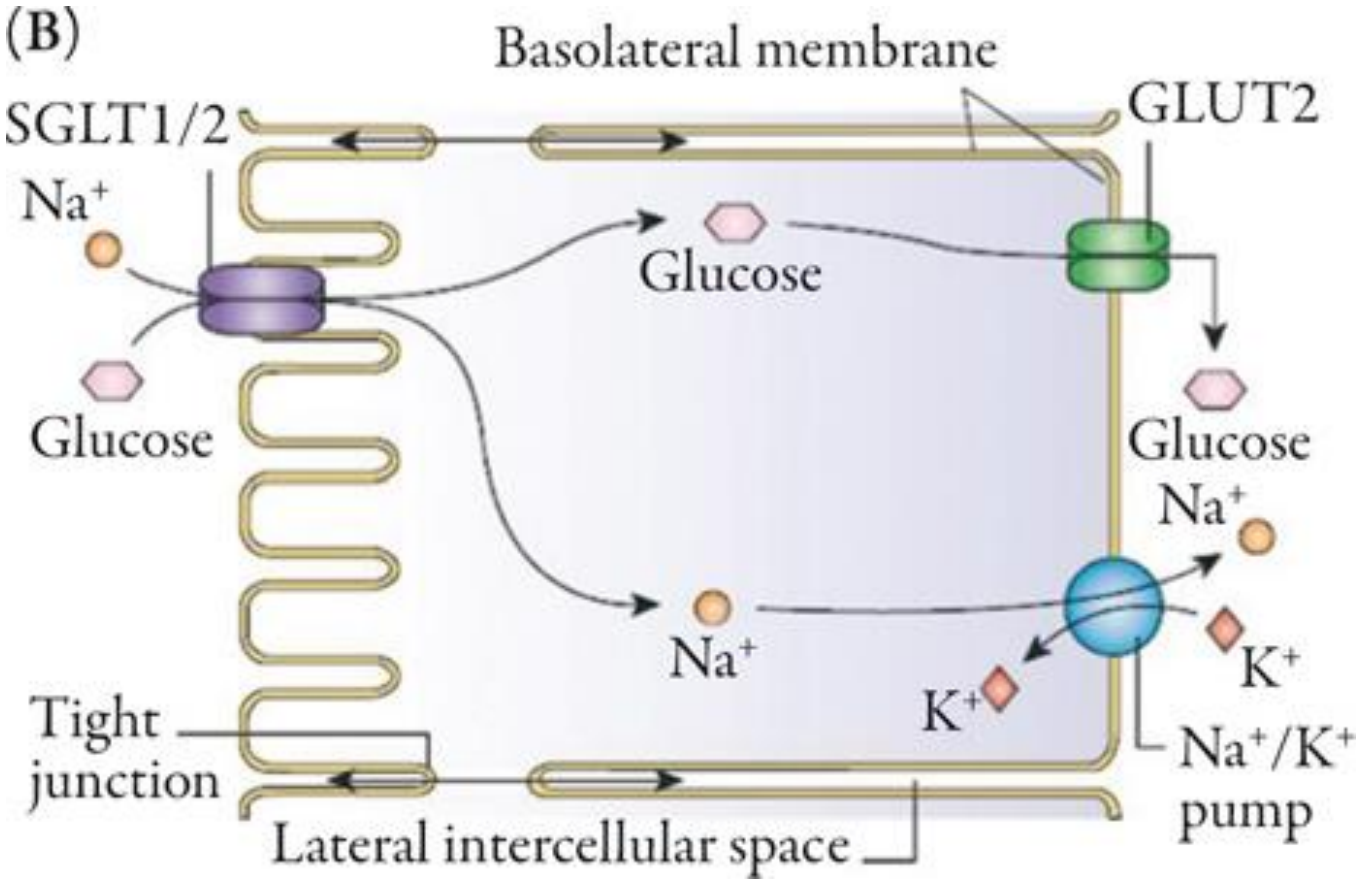
SGLT2 Inhibitors





- MOA: by inhibiting the SGLT2 cotransporter expressed in proximal tubules, reduces reabsorption of filtered glucose load→increases urinary excretion of glucose

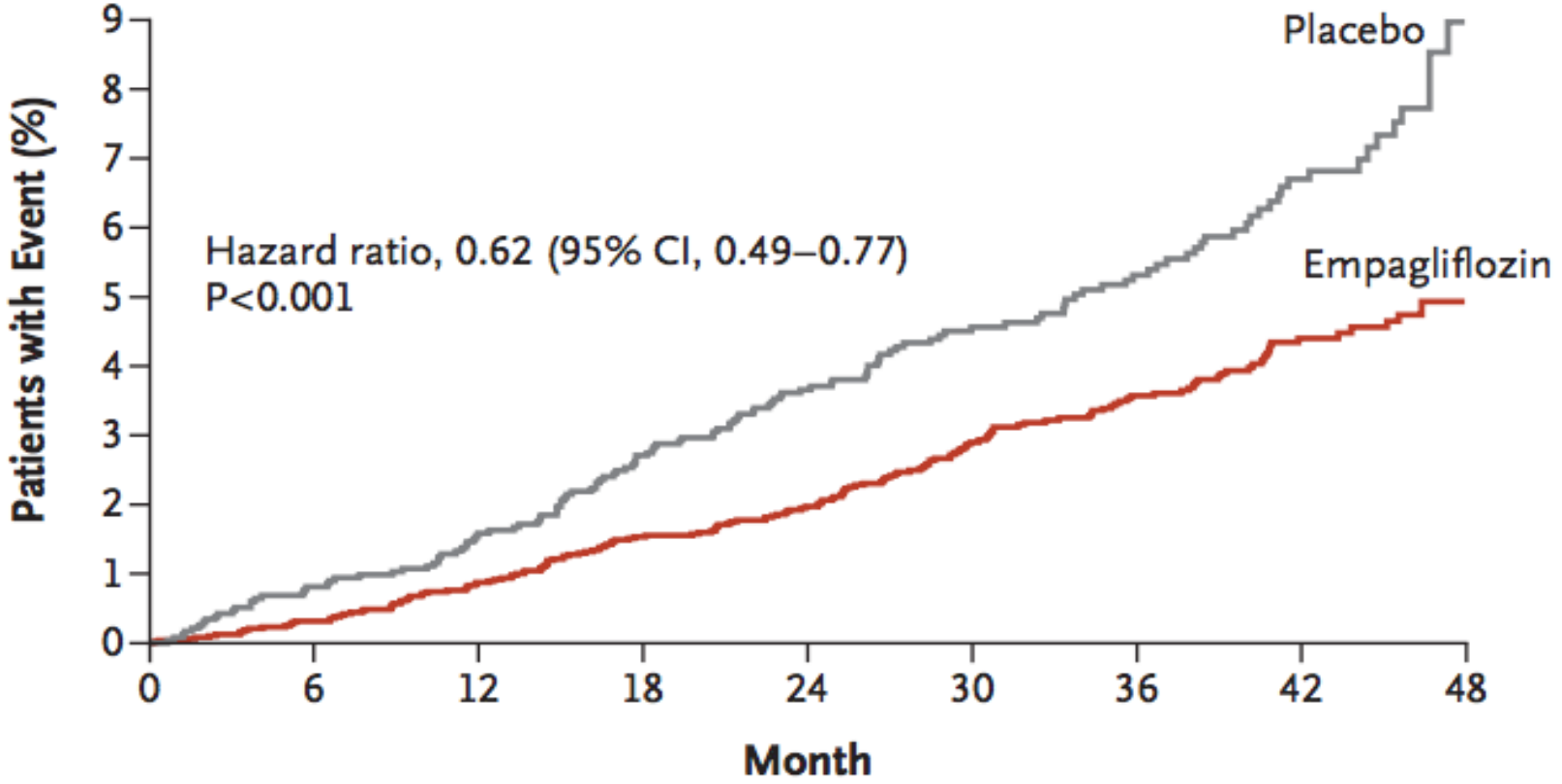
Tahrani et al. Diabetes Ther. 2010 Dec;1 (2):45-56

SGLT2 Inhibitors

- Effect: 0.5-0.7% A1c reduction
- Side effects: vulvovaginal mycotic infections (10-15%), renal insufficiency (2-4%), hypOtension, decreased BMD
- Contraindication: DKA (can cause 'euglycemic DKA'), eGFR <25 ml/min/1.73m² (evolving data, formulation dependent), recurrent UTIs or yeast infections
- Examples: empagliflozin, canagliflozin, dapagliflozin, ertugliflozin

EMPA-REG-OUTCOME study N=7,020

B Death from Cardiovascular Causes



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

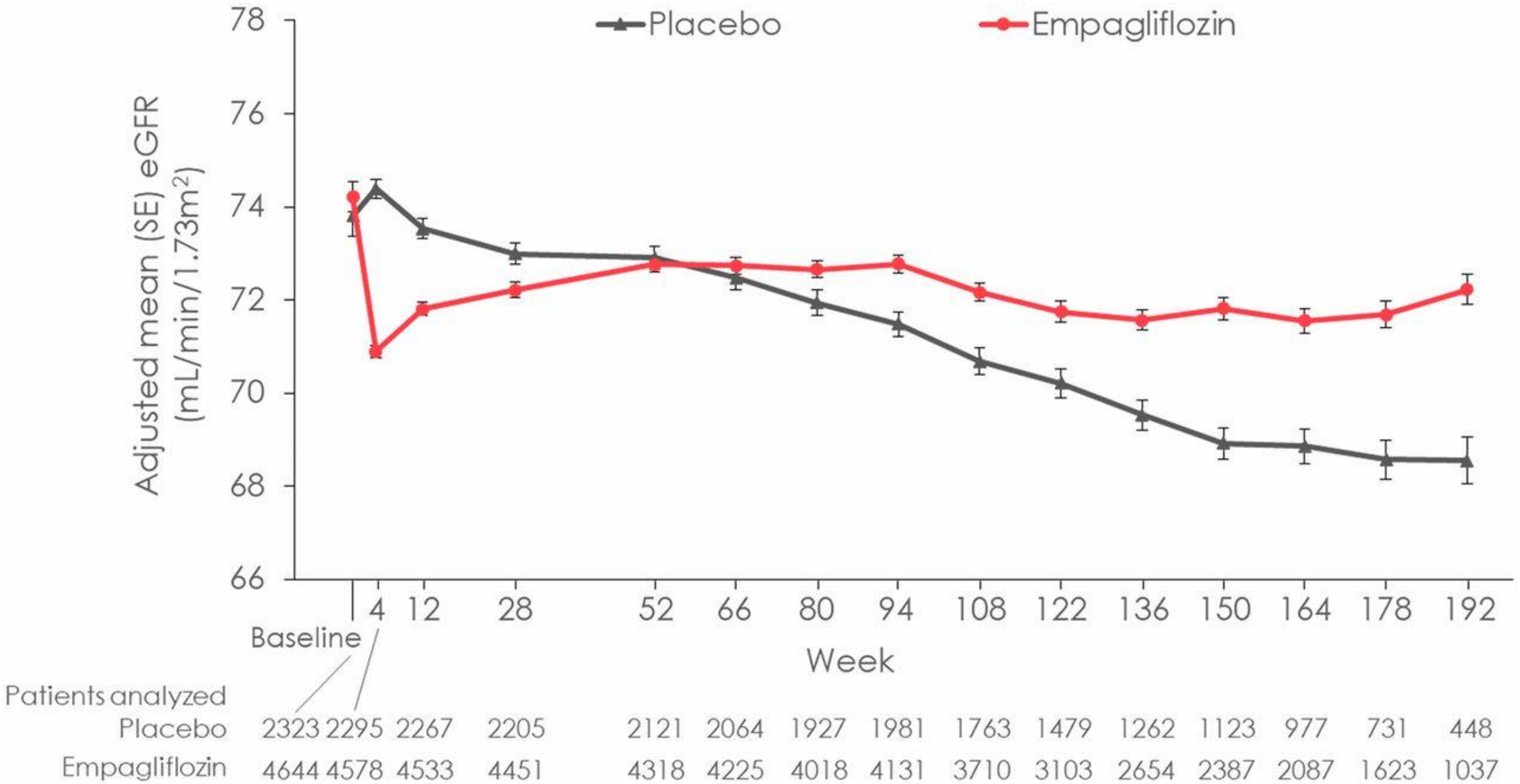
Zinman et al. N Engl J Med 2015. 373; 22.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA label update 12/2/2016: Empagliflozin

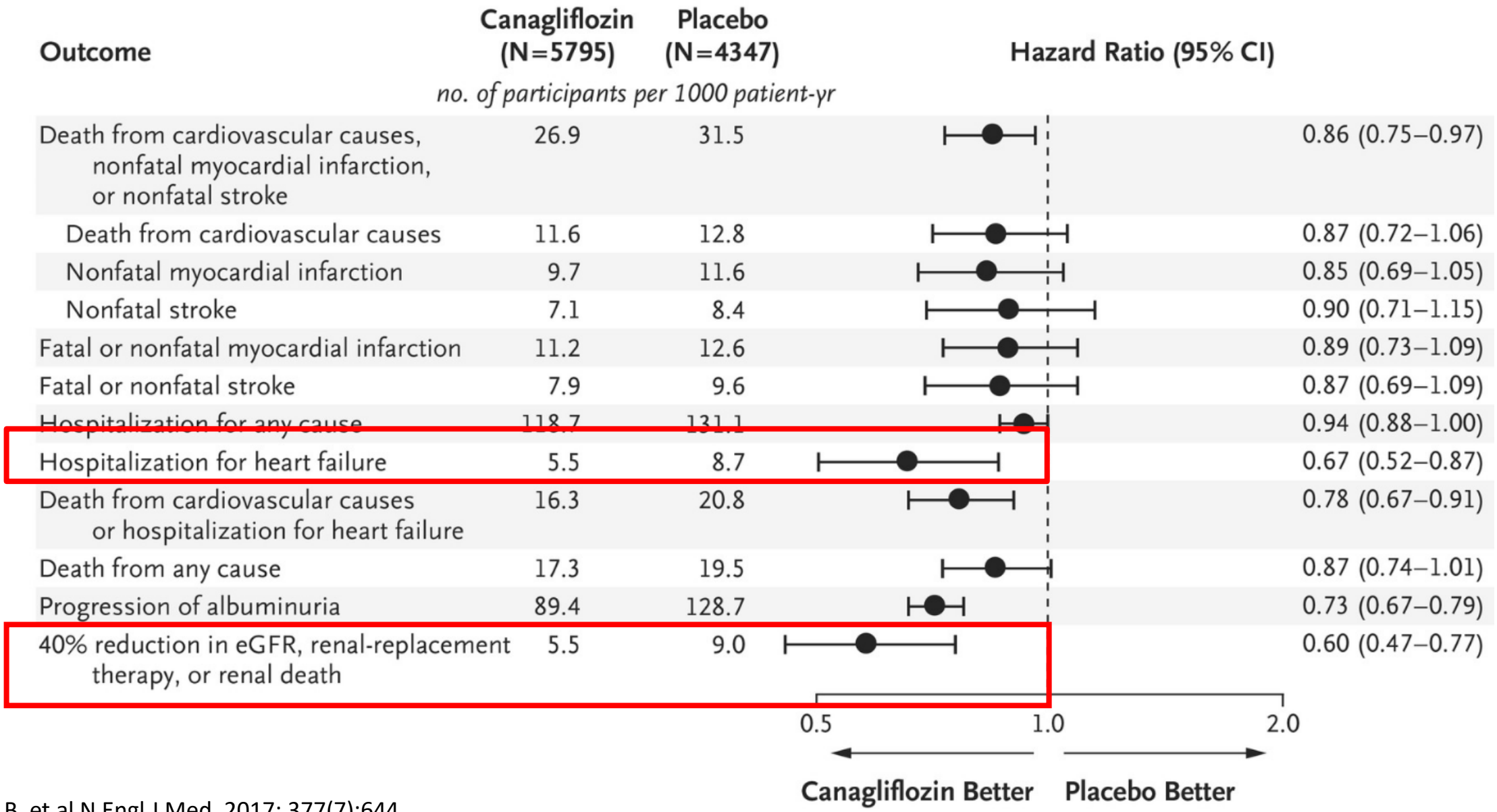
- The U.S. Food and Drug Administration approved a new indication for Empagliflozin (Jardiance®, Eli Lilly) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery



Wanner et al. JASN November 2018

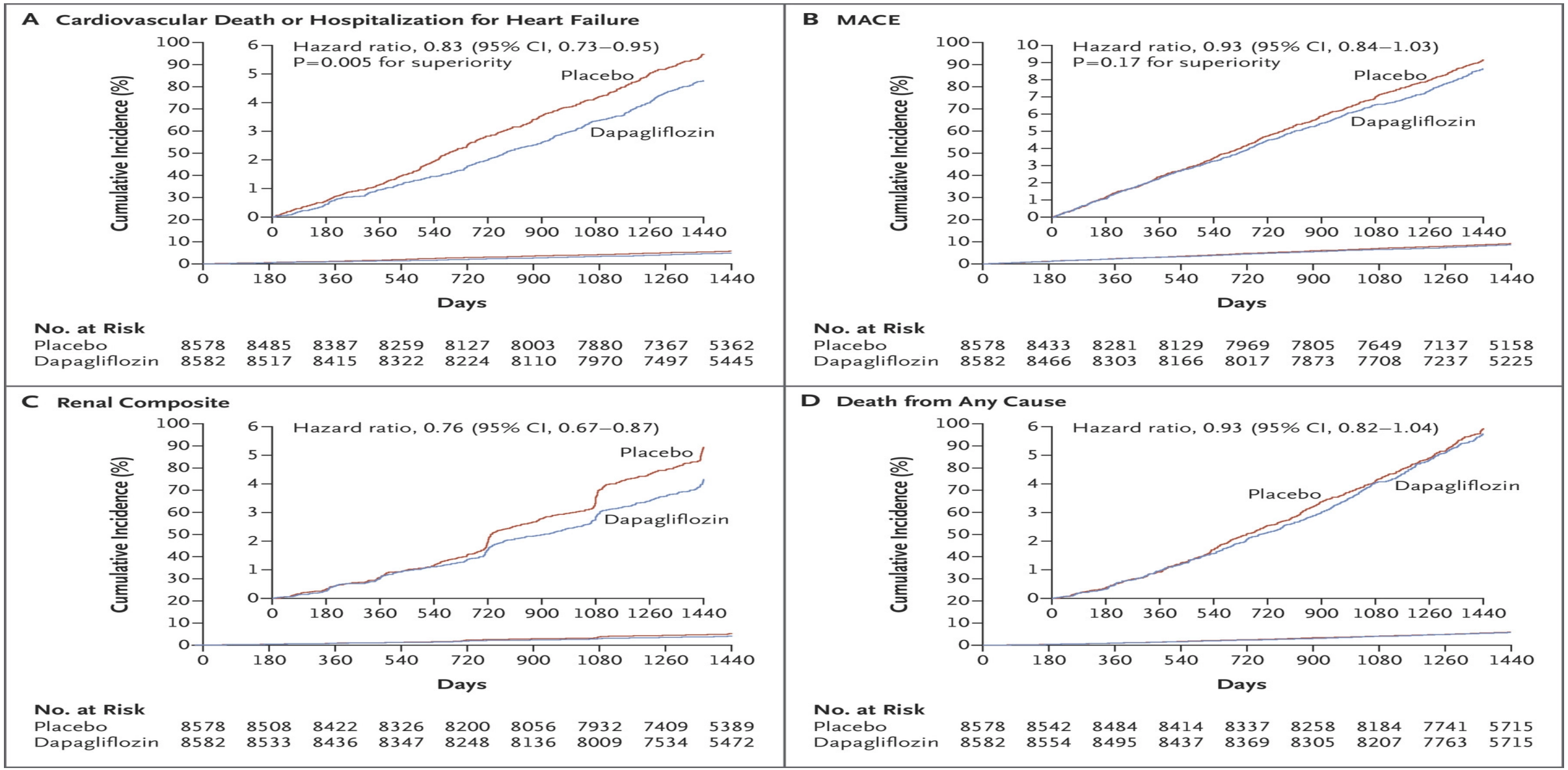
CANVAS Trials 2 RCTs N=10,142 (35% women)



Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

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

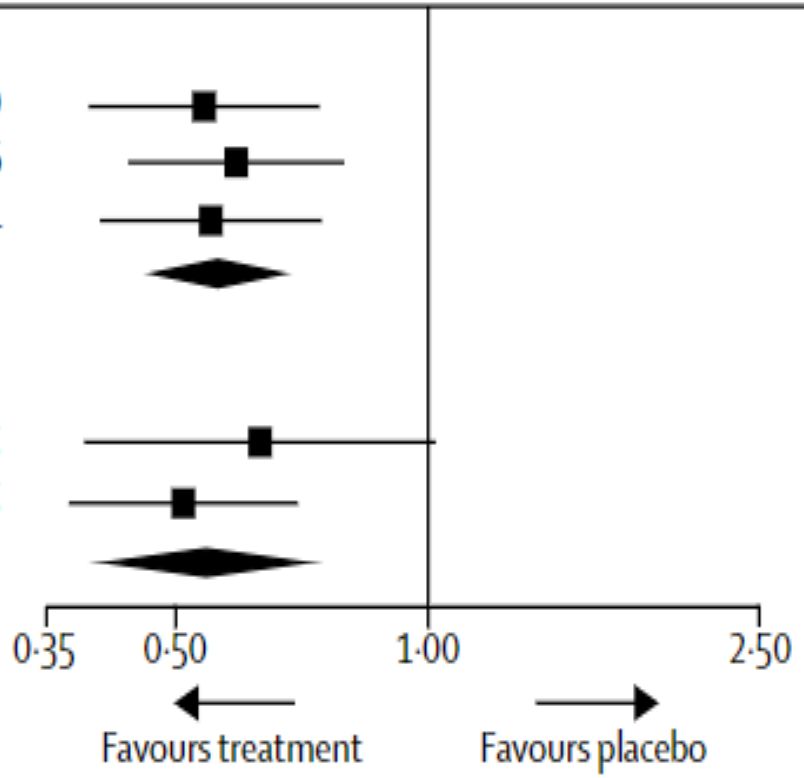
DECLARE–TIMI 58 – Dapagliflozin N=17,160



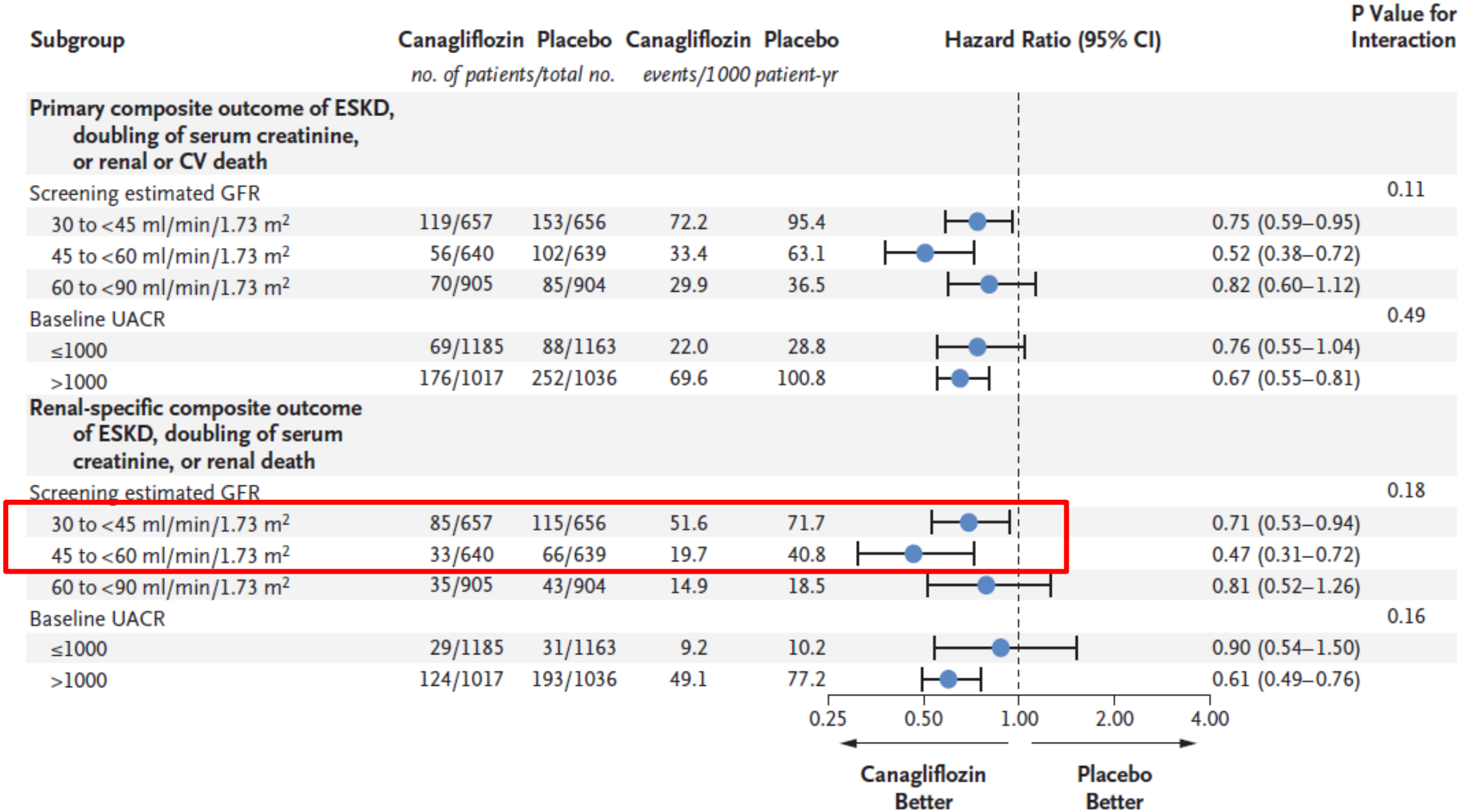
Wiviott et al. NEJM 2019

Meta-analysis on Composite of Renal Worsening, ESRD, or Renal Death

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645	2323	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756	2900	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474	3500	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108	5078	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**

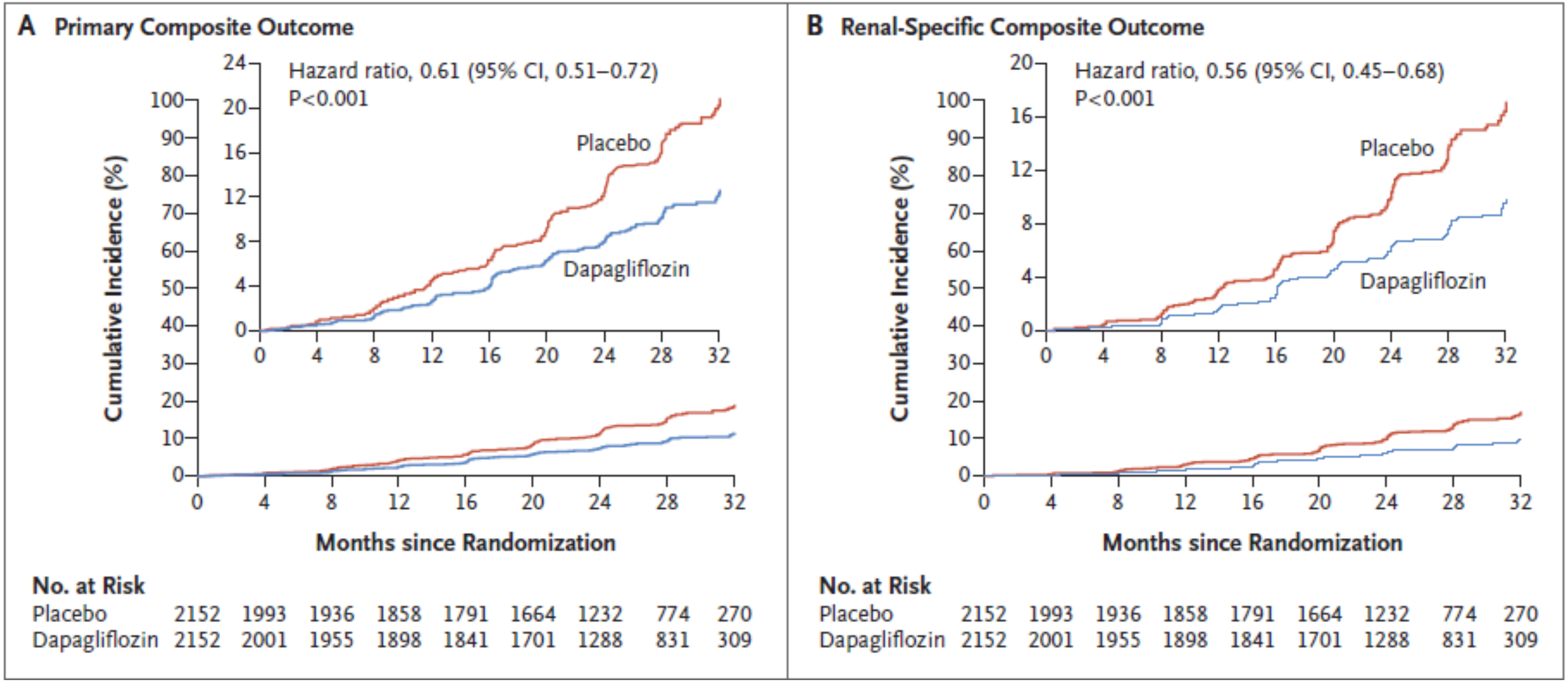


Zelniker et al. Lancet Jan. 2019

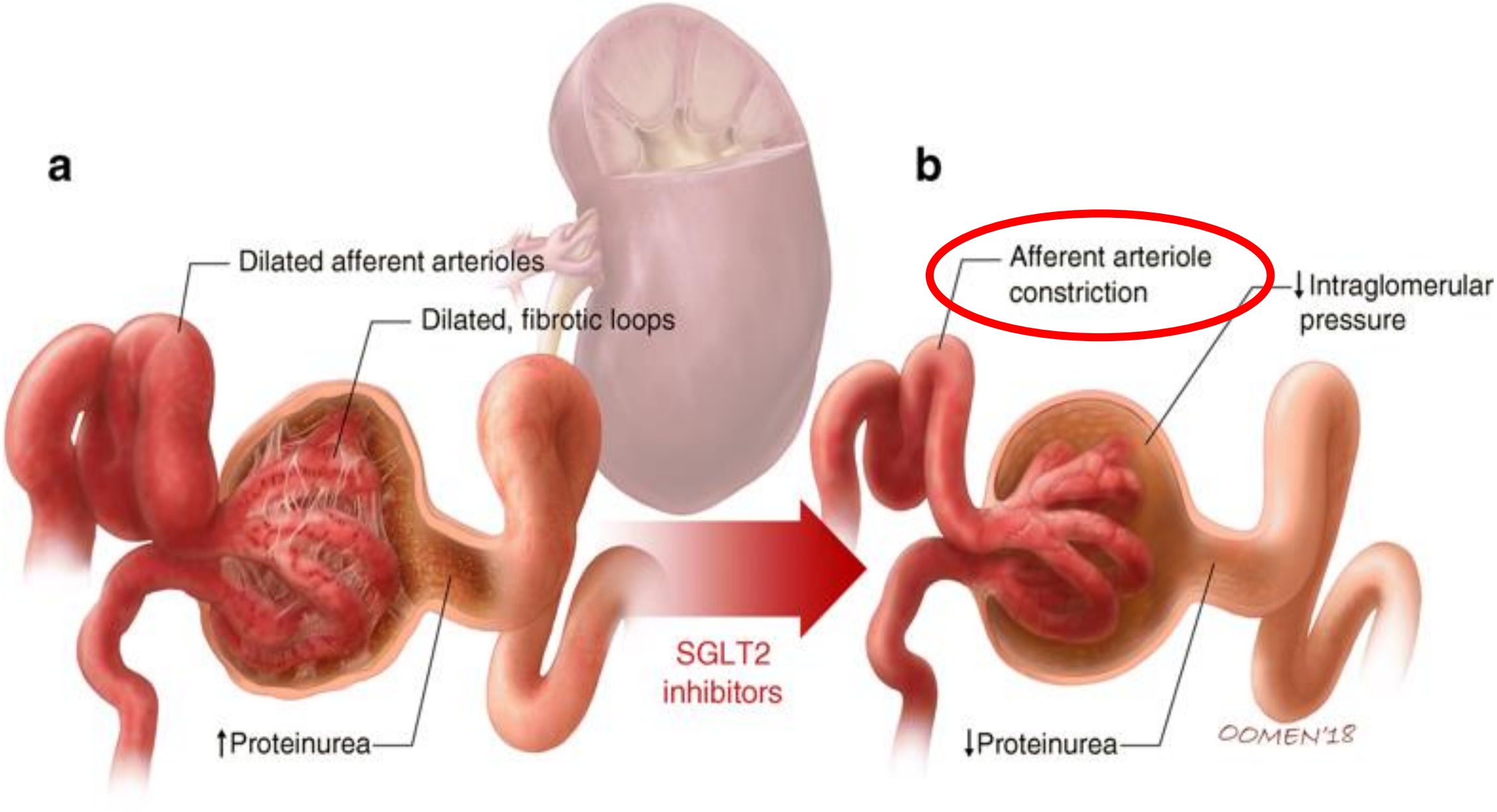


Perkovic et al. Credence Group. NEJM April 2019.

DAPA-CKD eGFR 25-75 ml/min/1.73m² N= 4,304



Heerspink et al. N Engl J Med. September 24th 2020

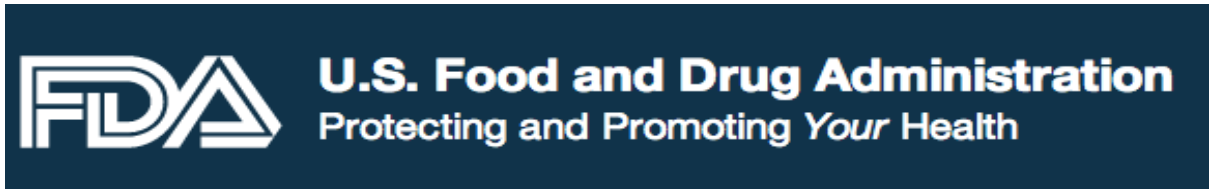


Verma and McMurray. Diebetologia 2018

Warning/Precaution	EMPA	CANA	DAPA	ERTU
Hypotension	✓	✓	✓	✓
Ketoacidosis	✓	✓	✓	✓
AKI and renal impairment	✓	✓	✓	✓
Urosepsis/pyelonephritis	✓	✓	✓	✓
Hypoglycemia[a]	✓	✓	✓	✓
Genital mycotic infections	✓	✓	✓	✓
Necrotizing Fasciitis	✓	✓	✓	✓
Increased LDL-C (3-8%)	✓	✓	✓	✓
Bone fractures		✓[b]		
Amputations		✓[c]		✓
Bladder cancer			✓[d]	

[a]May consider reducing dose of insulin or insulin secretagogue
[b]Mostly fractures of the upper extremities due to low trauma
[c]Black box warning
[d]Avoid in patients with active, or a history of, bladder cancer

Invokana (canagliflozin). Package Insert.
Jardiance (empagliflozin). Package Insert.
Farxiga (dapagliflozin). Package Insert.
Steglaro (ertugliflozin). Package Insert.



- FDA safety labeling recommends temporary discontinuation of SGLT2 inhibitors before any scheduled surgery to avoid potential risk for diabetic ketoacidosis.

U.S. Food and Drug Administration. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. 19 March 2020 update [FDA Drug Safety Communication]

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

- 05/16/2017 FDA Safety Alert : canagliflozin causes an increased risk of leg and foot amputations

- 8-26-2020 FDA Drug Safety Communication:

Based on (FDA) review of new data we have removed the Boxed Warning about amputation risk from the diabetes medicine canagliflozin

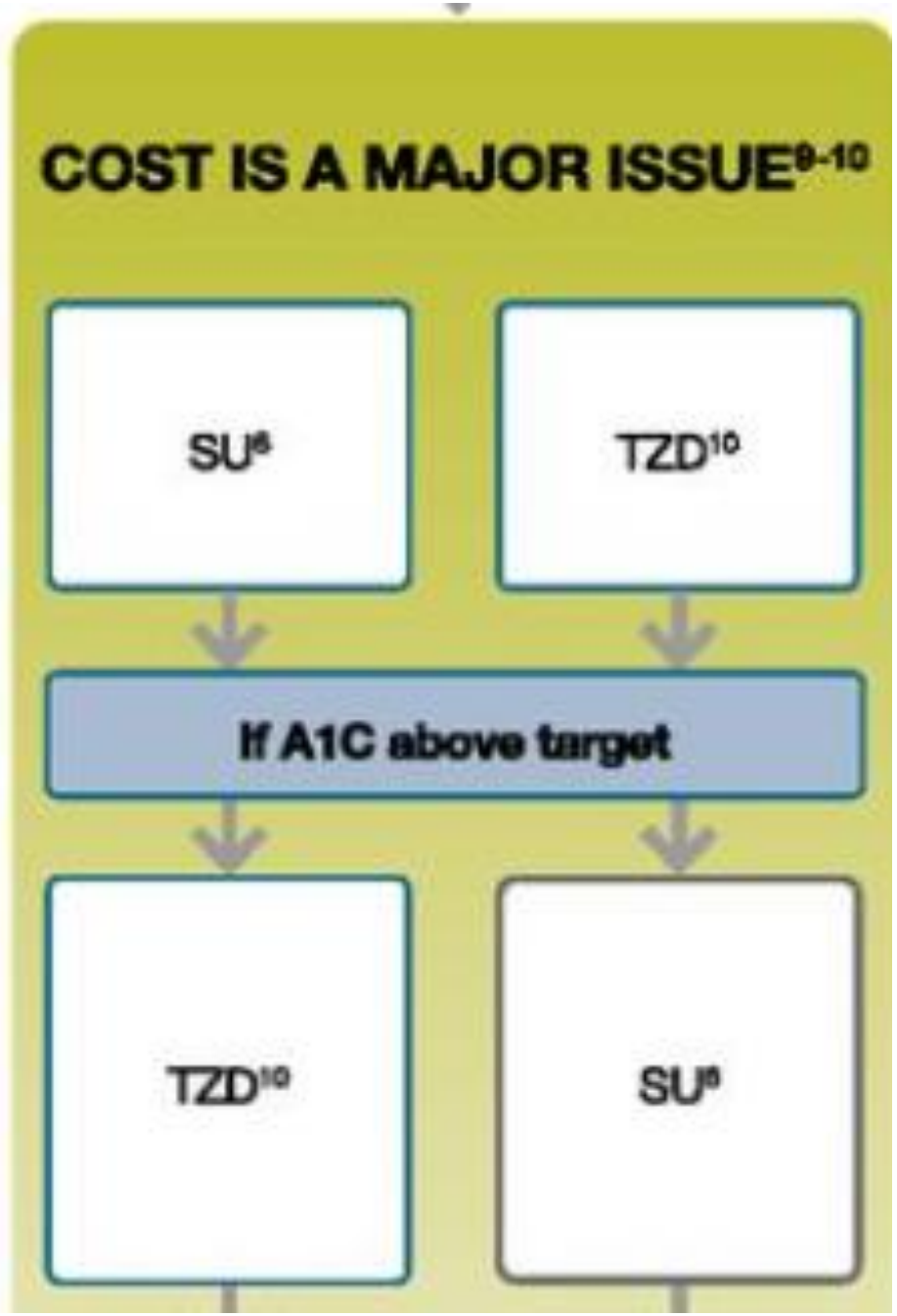
https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin#:~:text=8%2D26%2D2020%20FDA%20Drug,%2C%20Invokamet%20XR)%20prescribing%20information.

Case 2

45 y.o. female truck driver with hx of HTN and hyperlipidemia, BMI of 31 kg/m2. No known cardiac disease. A1c of 8.1%. eGFR 45 ml/min/1.73m2. She wants to avoid needles “at all cost.” Financially difficult social situation.

In addition to Lifestyle changes what would you start?

A) Metformin
B) Thiazolidinedione
C) Sulfonylurea alone
D) Meglitinide alone
E) SGLT2i (sodium-glucose co-transporter type 2 inhibitor)
F) GLP-1 agonist


COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If A1C above target
TZD[10]
SU[6]

Sulfonylureas (SU)

- Effect: 1%-2% HbA1c reduction
- Side effects: hypOglycemia (4 to 20%), increased serum ALT (2%), +*weight gain*
- Caution: hepatic or renal impairment, Glucose 6 phosphate dehydrogenase deficiency (G6PD)
- Contraindication: sulfonamide allergy
- Examples: 1st generation: chlorpropamide, tolbutamide, 2nd gen: glipizide, glimeperide, glyburide* (*glyburide specifically has been implicated for impairing ischemic preconditioning)

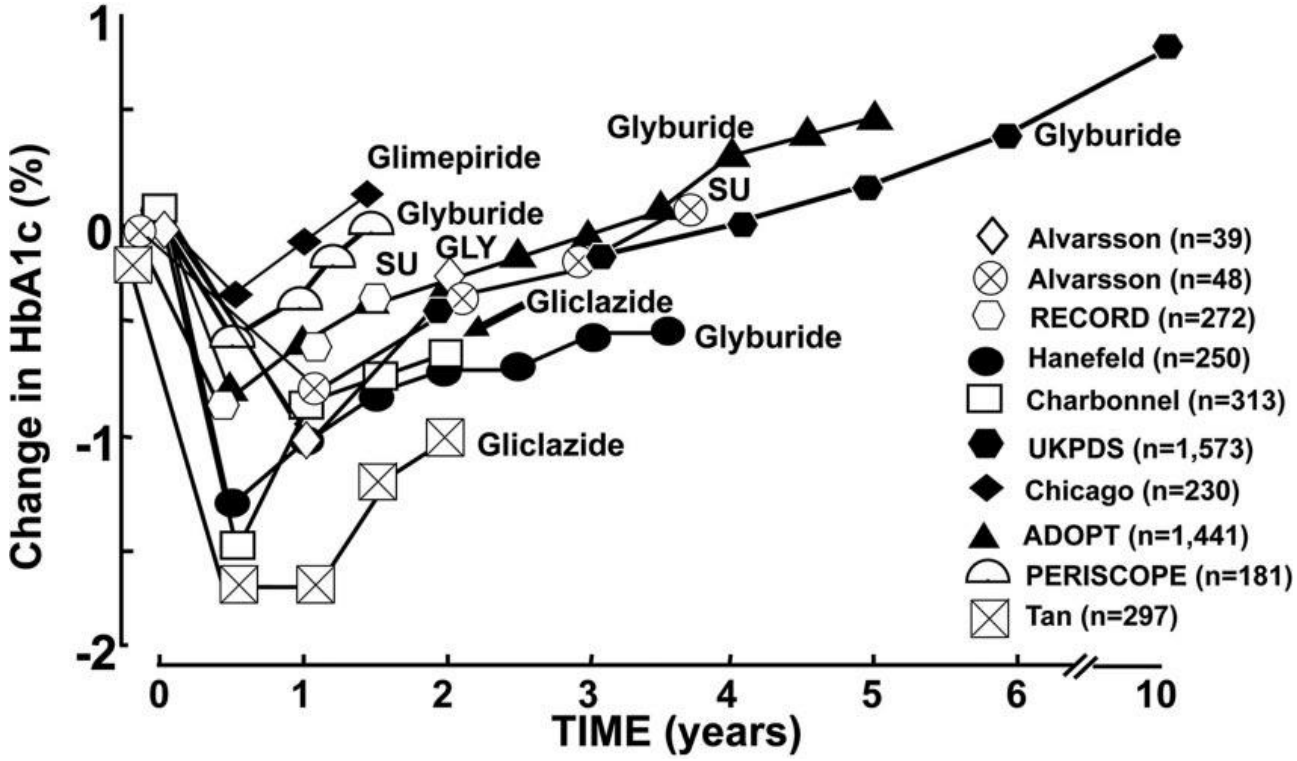
* Riddle MC. J Clin Endocrinol Metab 2003

Sulfonylureas (SU)

- Benefits: once daily available, promotes release of endogenous insulin (portal effects on hepatic gluconeogenesis), generic

- Drawbacks: weight gain, hypOglycemia (especially with renal dz)
  - *controversial*: some data suggests increased rate of β cell failure vs. natural progression

Summary of studies examining the effect of SU treatment vs. placebo or active comparator on A1c in DM2



DeFronzo, R. Banting Lecture, *Diabetes* vol. 58 2009

Thiazolidinediones

- Effect: 0.5 – 2% A1c reduction
- MOA:
  - a) binds peroxisome proliferator-activated receptor-γ (PPAR-γ) (family of nuclear transcription factors) in insulin target tissues muscle and fat, agonist effect →enhance sensitivity to insulin in peripheral tissues →reduce hepatic gluconeogenesis
- Side effects: +*weight gain*, edema (by activating sodium channels in the distal nephron), osteoporosis and fracture in postmenopausal women
- Contraindication: NYHA class III or IV CHF, active hepatocellular disease, ALT >2.5x ULN
- Examples: pioglitazone, rosiglitazone

Thiazolidinediones

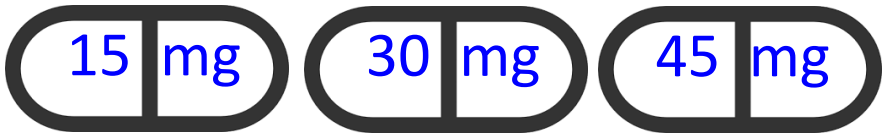
- Benefits: oral, once daily dosing (prior interest for PCOS treatment due to improved insulin sensitivity, largely fallen out of favor due to weight gain)

- Drawbacks: +*weight gain*, fluid retention, bone loss, and signal for increase risk bladder cancer with pioglitazone > 1 year use in post marketing surveillance (<1%)

Thiazolidinediones (TZDs)

Effect seen in 8-12 weeks

	Pioglitazone (Actos®)	Rosiglitazone (Avandia®)
Dosing	15-45 mg once daily	4-8 mg in 1-2 divided doses
Hepatic impairment	Hepatic impairment during therapy – interrupt therapy, measure LFTs. Do not **reinitiate** if ALT > 3x ULN	Do not **initiate** if ALT > 2.5 x ULN
Contraindications	**NYHA Class III-IV Heart Failure**	
Adverse Reactions	Weight gain, edema, **HF exacerbation**, fractures, bladder cancer (avoid pioglitazone)	



Actos ® Package Insert 2017

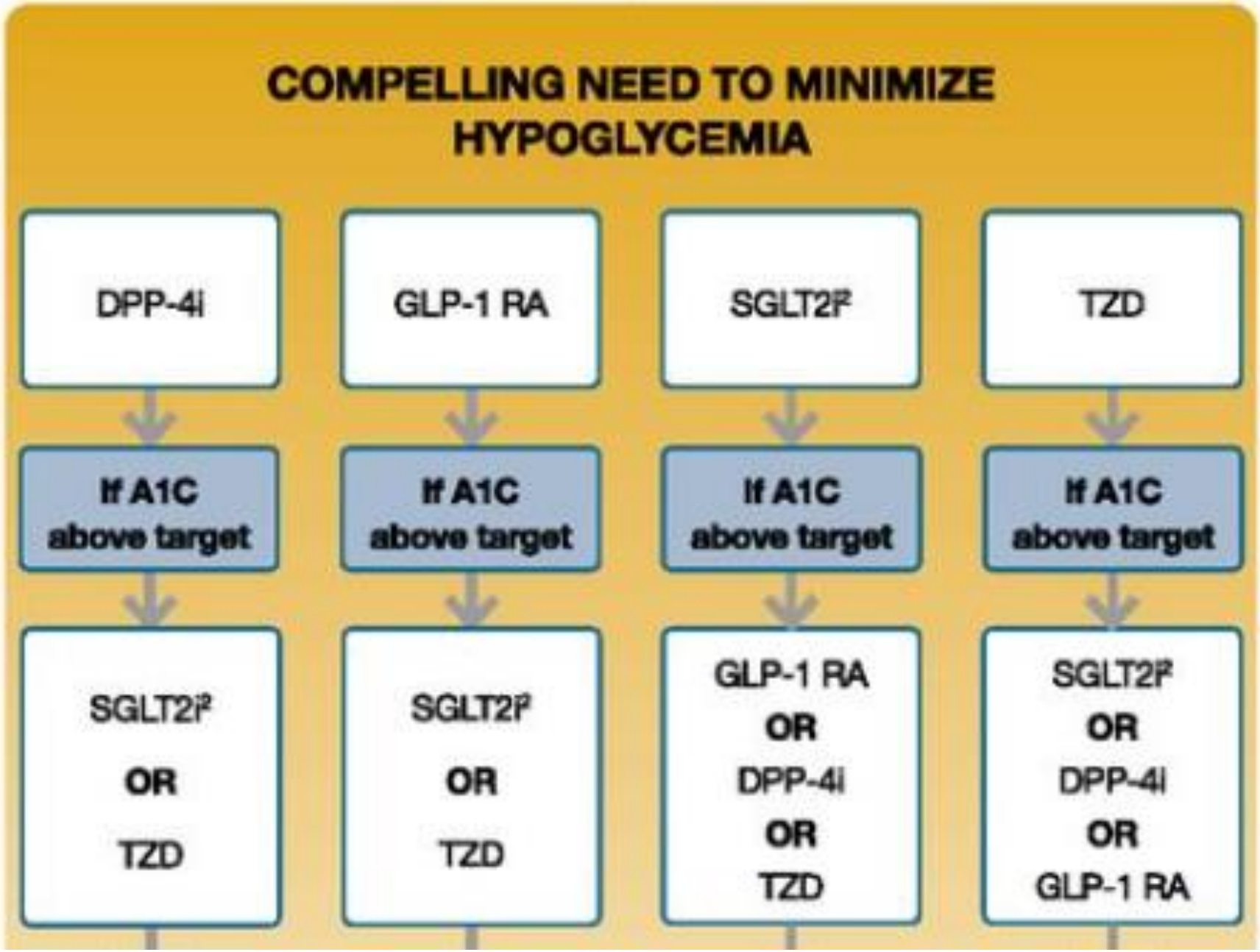
Avandia ® Package Insert 2016

Case 3

85 y.o. retired mechanic who lives alone. He had a second TIA two months ago presents for follow-up. A1c is 9.2%.

Which of the following classes of agents INCREASE the risk of hypoglycemia the most?

A) Metformin
B) Sulfonylurea and Meglitinides
C) DPP4i and GLP-1 agonists
D) SGLT2i
E) α-glucosidase inhibitors
F) Thiazolidinediones


COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i*
TZD
If A1C above target
If A1C above target
If A1C above target
If A1C above target
SGLT2i*
OR
TZD
SGLT2i*
OR
TZD
GLP-1 RA
OR
DPP-4i
OR
TZD
SGLT2i*
OR
DPP-4i
OR
GLP-1 RA

Dipeptidyl Peptidase-IV Inhibitors (DPP-IVi)

- Effects: 0.5-0.7% A1c reduction

- MOA: Dipeptidyl peptidase-IV is an enzyme that degrades the gut peptide hormones GLP-1 and GIP within minutes. DPP-IV inhibitors allow endogenous incretins to have longer effect.
- Side effects: rare edema, nausea, rare hypOglycemia (1%)
- Contraindication: none
- Examples: sitagliptin, saxagliptin, linagliptin, aloglitptin

Dipeptidyl Peptidase-IV Inhibitors (DPP-IV)

- Benefits: can be renally dosed (even for CrCl <30ml/min), very rare to ever cause hypOglycemia as monotherapy

- Drawbacks: cost, only very modestly effective

DPP4 Inhibitors and Heart Failure = Mixed Results

	Saxagliptin *no.* (2-yr KM%)	Placebo *no.* (2-yr KM%)	Hazard Ratio (95% CI)	P-value for superiority
Efficacy Endpoints				
Number of Patients	(N =8240)	(N =8173)		
CV death, MI, or stroke	512 (6.8)	487 (6.4)	1.03 (0.91-1.17)	0.60
CV death, MI, stroke, or hospitalization for unstable angina, heart failure, or coronary revascularization	943 (12.5)	898 (11.8)	1.04 (0.95-1.14)	0.41
CV death	203 (2.7)	174 (2.2)	1.15 (0.94-1.41)	0.18
MI	234 (3.1)	236 (3.1)	0.98 (0.81-1.17)	0.79
Ischemic stroke	135 (1.8)	120 (1.6)	1.11 (0.87-1.42)	0.40
Hospitalization for unstable angina	89 (1.2)	75 (1.0)	1.17 (0.86-1.60)	0.30
Hospitalization for heart failure	256 (3.4)	194 (2.6)	1.31 (1.09-1.58)	0.004
Hospitalization for coronary revascularization	395 (5.3)	422 (5.6)	0.92 (0.81-1.06)	0.26
All-cause mortality	278 (3.6)	234 (3.0)	1.17 (0.98-1.39)	0.083
Non-cardiovascular death	75 (0.9)	60 (0.8)	1.22 (0.87-1.72)	0.25

Event rates are Kaplan-Meier failure rates during 24 months.

Scirica BM et al. SAVOR-TIMI 53. N Engl J Med 2013; 369: 1317-1326

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FDA Safety Alert Alogliptin and Saxagliptin

Based on new data from two large clinical trials (EXAMINE and SAVOR-TIMI 53), the FDA has added additional cautions for both alogliptin and saxagliptin to use with caution in patients with heart failure and monitor for signs and symptoms of worsening heart failure.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-adds-warnings-about-heart-failure-risk-labels-type-2-diabetes

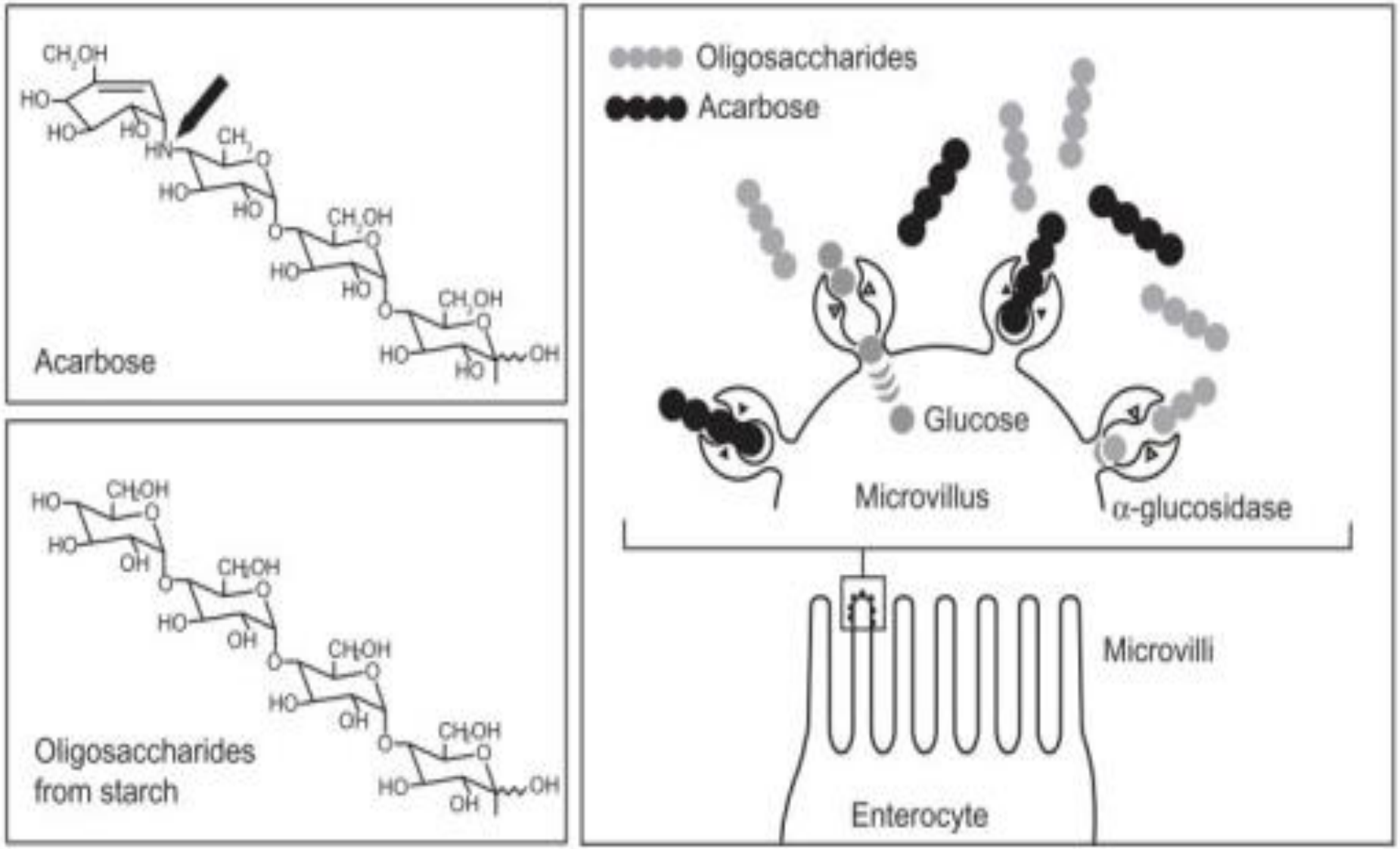
α-Glucosidase Inhibitors

- Effect: 0.5-1% A1c reduction

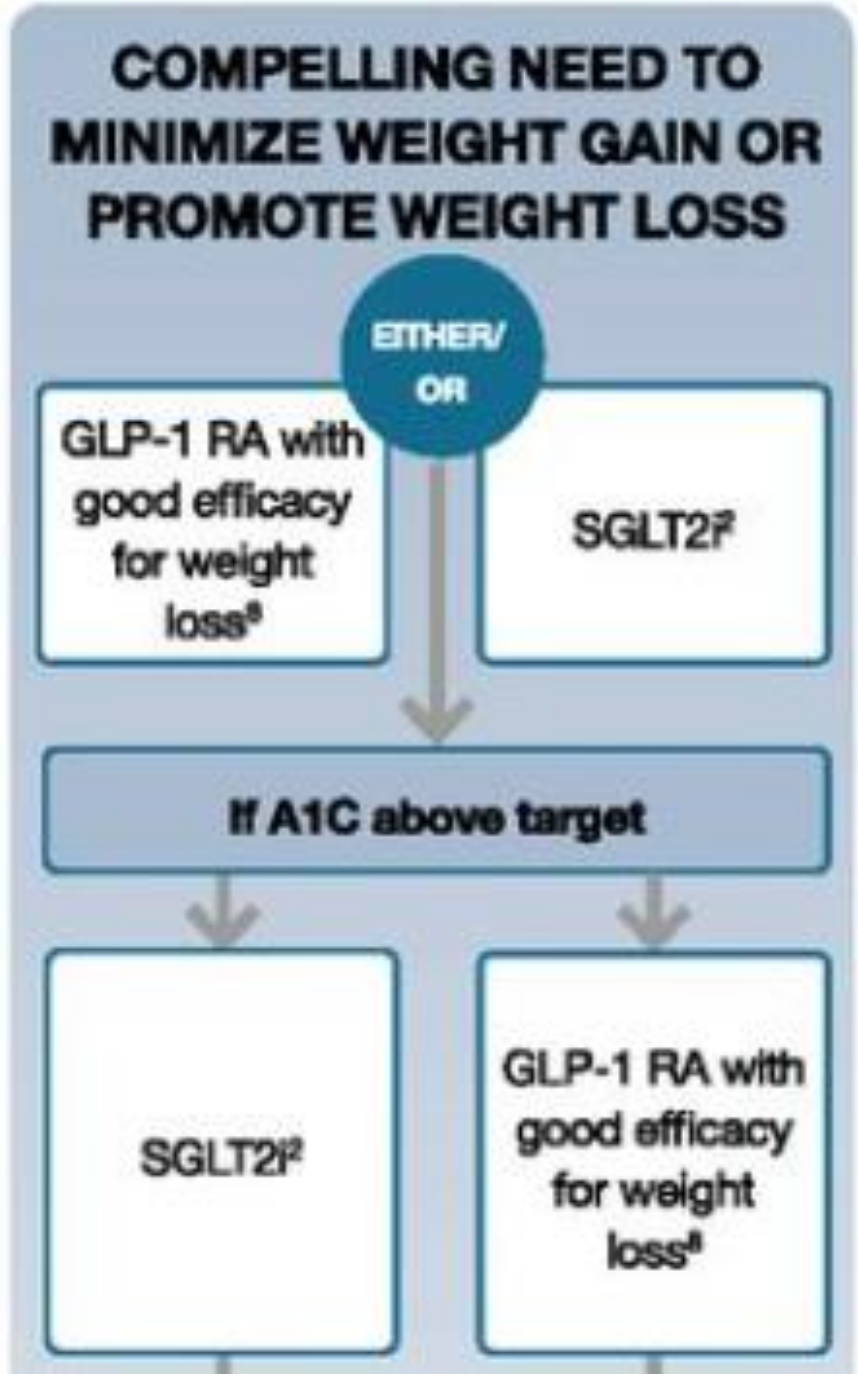
- MOA: competitively inhibits intestinal glucosidase enzymes that break down complex carbohydrates →reduces intestinal glucose resorption

- Side effects: GI: flatulence, and diarrhea
- Contraindication: IBD, chronic intestinal disease
- Examples: acarbose, miglitol, and voglibose

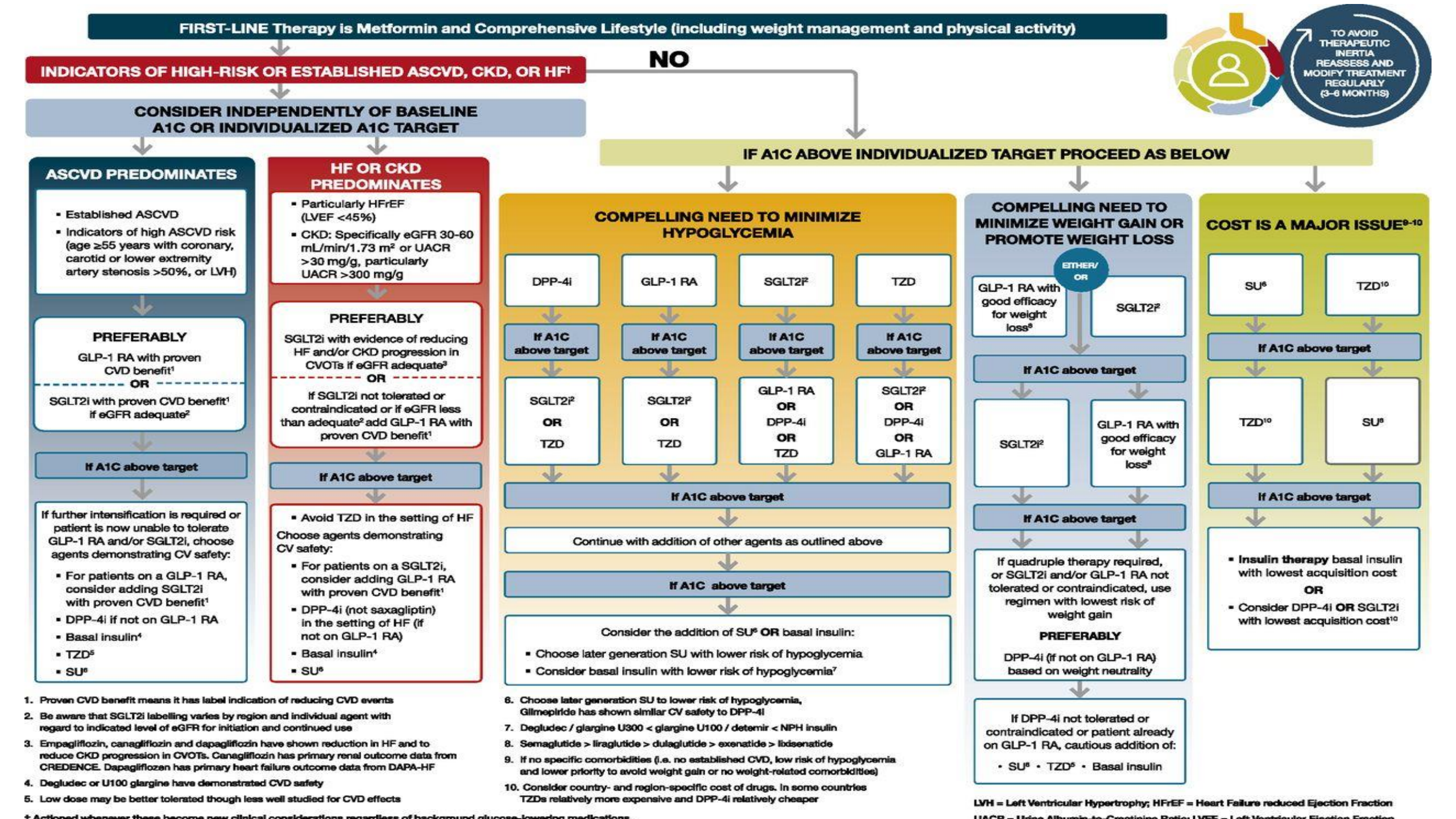
α-Glucosidase Inhibitors MOA



Bischoff H. “Effect of acarbose on diabetic late complications and risk factors – new animal experimental results”. *Akt Endokr Stoffw*. 1991;12:25–32.


COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If A1C above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]

Category	OBESOGENIC – CAUSE WEIGHT GAIN	Alternative to Consider
Antidepressants	TCAs (amitriptyline, nortriptyline, clomipramine, imipramine, doxepin, protriptyline*); Mirtazipine SSRIs (paroxetine, sertraline, citalopram*, escitalopram*, fluoxetine*) ; MAOIs (phenelzine)	Bupropion Desvenlafaxine Venlafaxine Duloxetine
Antipsychotics	Olanzipine; Quetiapine; Risperidone; Clozapine; Thioridazine	Aripiprazole; Haloperidol; Ziprasidone
Antiepileptics/ Mood Stabilizing	Gabapentin; Pregabalin; Divalproex; Valproic acid; Vigabatrin; Lithium; Carbamazepine	Topiramate; Lamotrigine; Zonisamide
Antiglycemics	Insulin Sulfonylureas (glipizide, glimepiride, glyburide etc) Thiazoledinediones (pioglitazone, rosiglitazone) Meglitinides (nateglinide, repaglinide)	Biguanides (metformin) SGLT2i (empagliflozin, canagliflozin, dapagliflozin etc.) GLP-1 (semaglutide, liraglutide, dulaglutide etc.) DPP4i (sitagliptin, saxagliptin, alogliptin etc.) alpha glucosidase inhibitors (acarbose or miglitol) Amylin analogs (pramlintide)
Antihypertensives	α Adrenergic Blocker (terazosin) β Adrenergic Blockers (especially nonselective metoprolol, propranolol, atenolol)	ACEi (lisinopril, ramipril etc) ARB (losartan, valsartan etc) CCB (amlodipine, verapamil, diltiazem) Diuretics
Steroid Hormones	Glucocorticoids (prednisone, hydrocortisone, methylpred) Contraceptives injectables >oral; any Progesterone based	NSAIDs; biologics; non-traditional therapies Copper IUD
Antihistamines	Cyproheptadine, Cetirizine, Fexofenadine	Decongestants, inhalers (aim for less sedation)



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Gilmepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

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

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction


Merci
de tout
Coeur