Diabetes Drugs and Cardiovascular Outcomes

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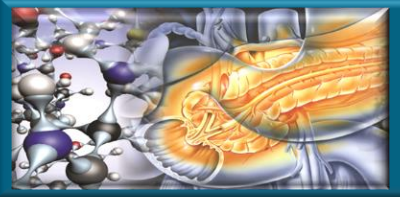
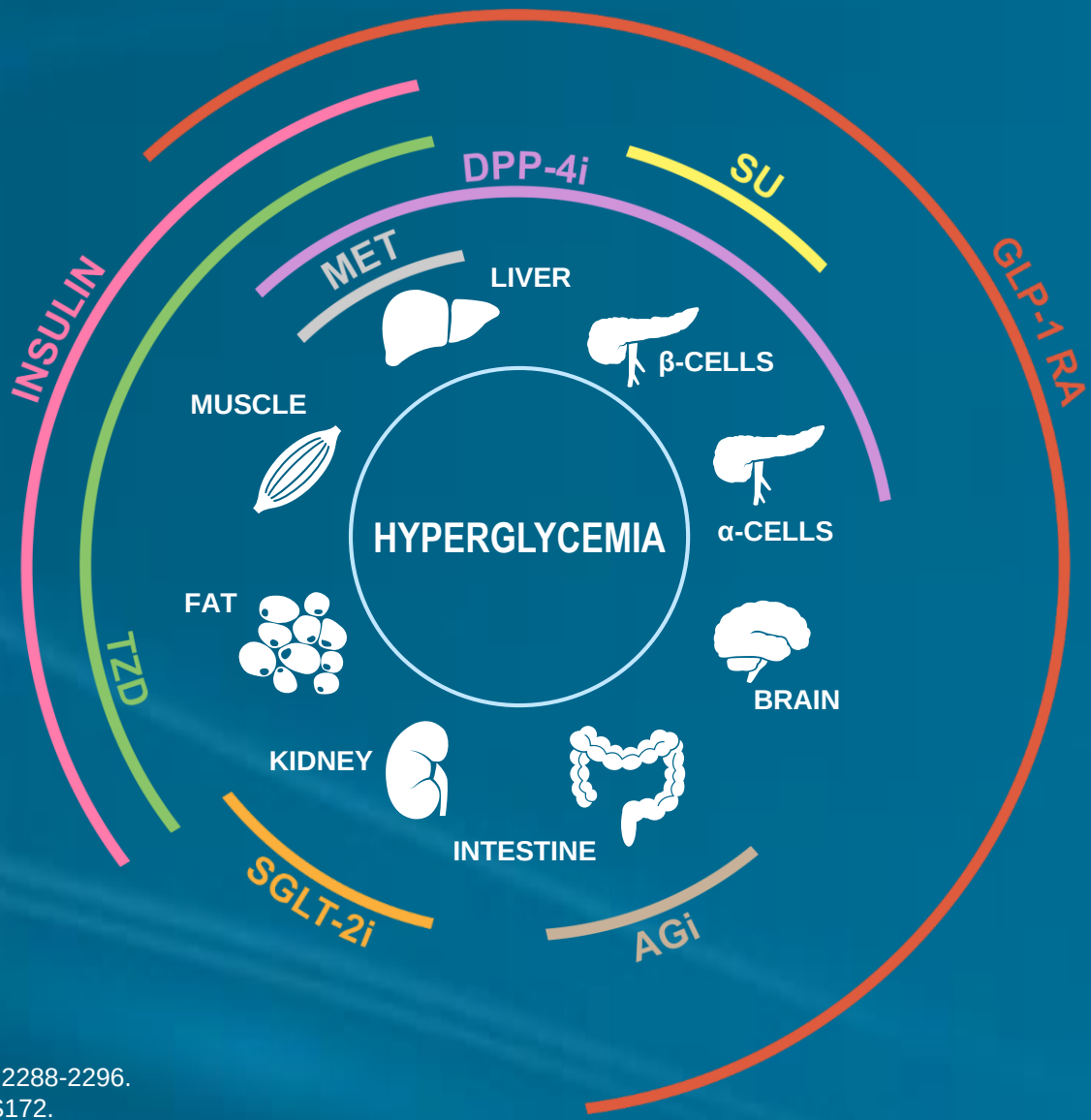
Duality of Interest

Consultant: Novo Nordisk, Sanofi and Merck Pharmaceuticals
Speakers' Bureau: Janssen, Novo Nordisk, Sanofi, Merck and AstraZeneca



Therapies to Address the Multiple Defects Leading to Hyperglycemia in Type 2 Diabetes



AGi, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

1. Ferrannini E et al. *Eur Heart J*. 2015;36(34):2288-2296.
2. ADA. *Diabetes Care*. 2018;41(suppl 1):S1-S172.

A decade of learning on the effects of glucose lowering therapies and ASCVD

1- Targeting multiple risk factors to reduce CV risk in patients with T2DM

2- A turning point: the 2008 FDA Guidance

3- Summary of Current CVOT Findings

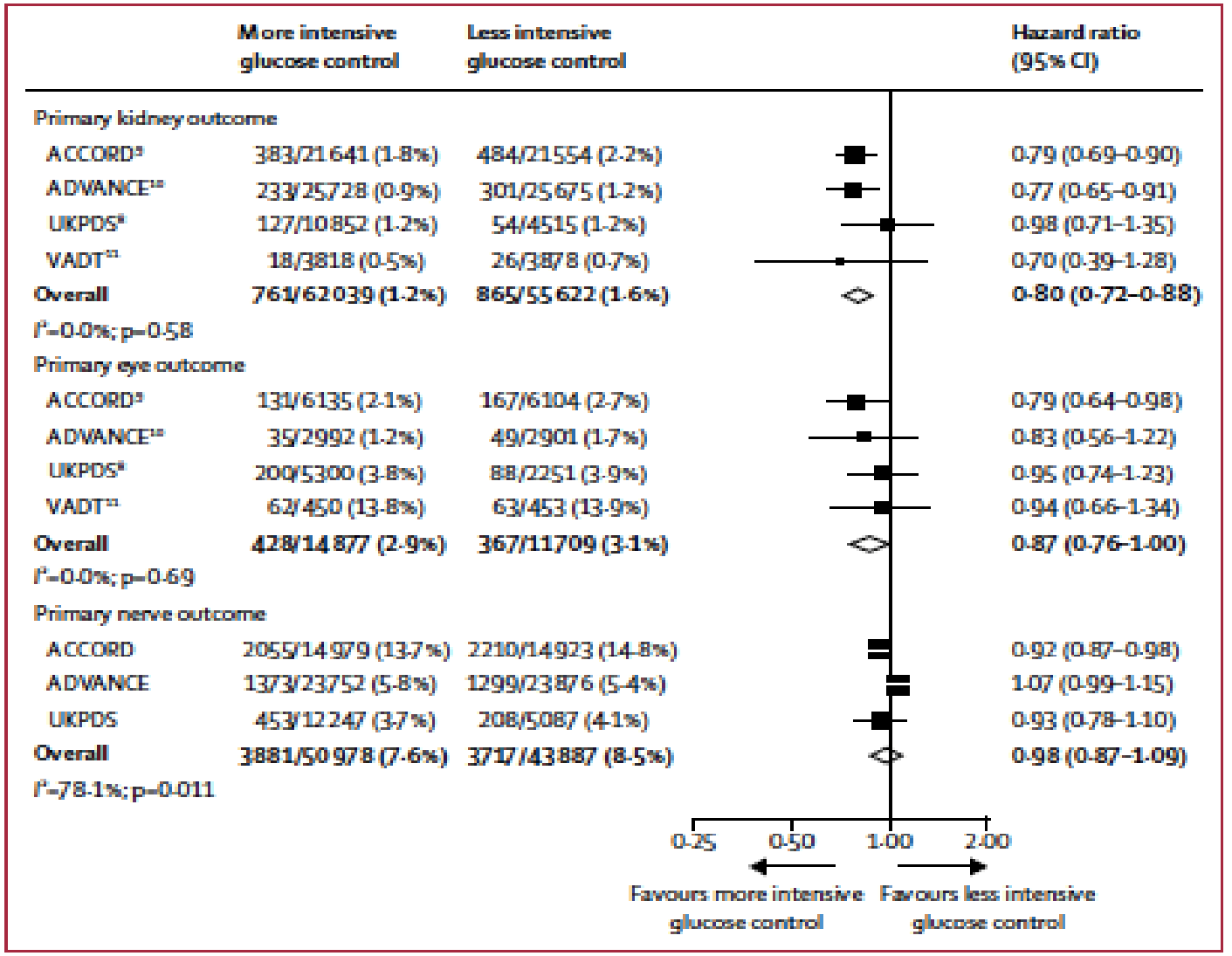
- DDP4 *inhibitors*
- SGLT2 *inhibitors*
- GLP-1 *RA*

4- Proposed Mechanisms of CV Protection

5- Impact on Regulatory Agencies and Professional Society Guidelines/Recommendations

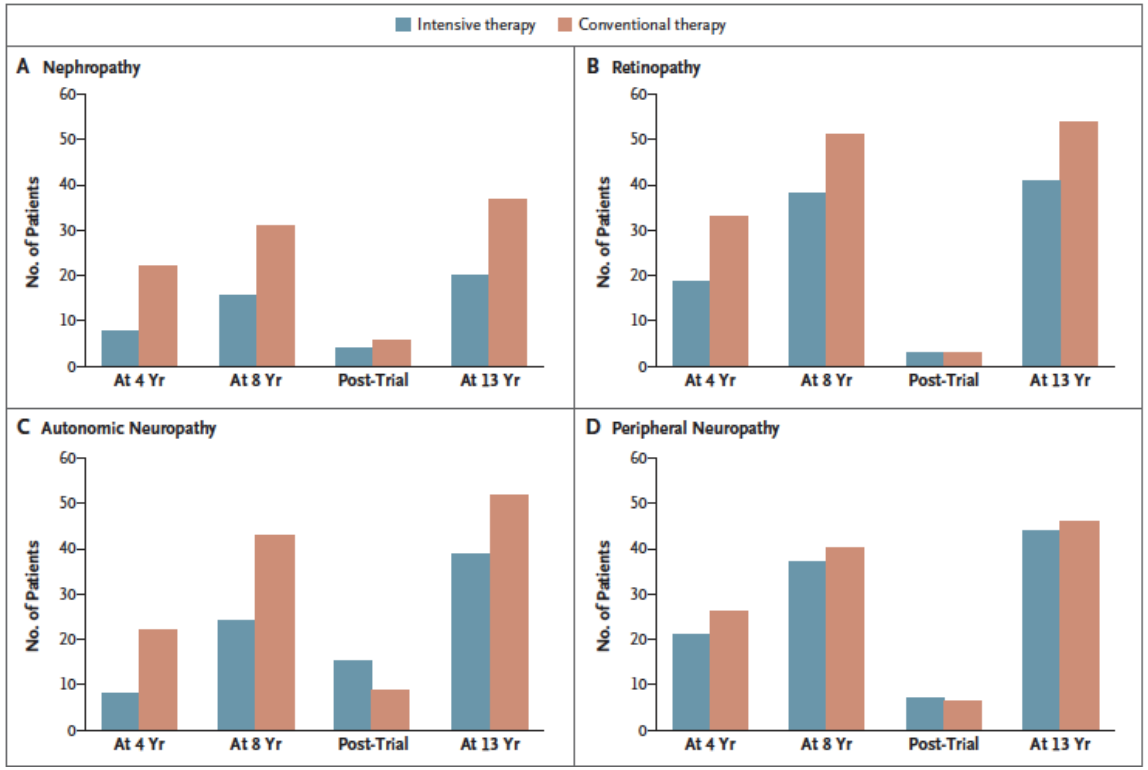
6- Lessons learned from other Disease States or Study Designs

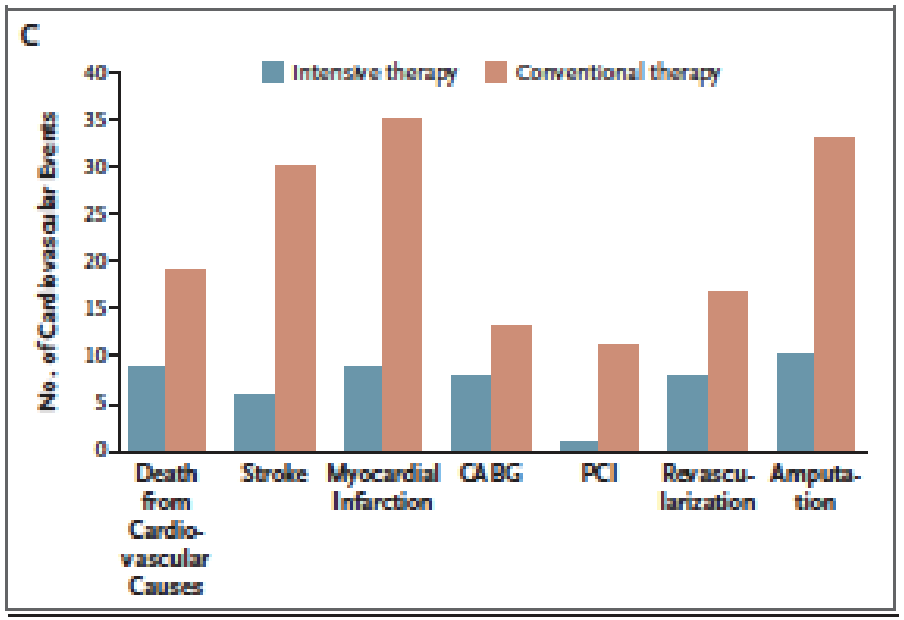
7- SUMMARY/CONCLUSIONS


More intensive glucose control
Less intensive glucose control
Hazard ratio (95% CI)
Primary kidney outcome
ACCORD[9] 383/21 641 (1·8%) 484/21 554 (2·2%) 0·79 (0·69–0·90)
ADVANCE[10] 233/25 728 (0·9%) 301/25 675 (1·2%) 0·77 (0·65–0·91)
UKPDS[8] 127/10 852 (1·2%) 54/4515 (1·2%) 0·98 (0·71–1·35)
VADT[11] 18/3818 (0·5%) 26/3878 (0·7%) 0·70 (0·39–1·28)
Overall 761/62 039 (1·2%) 865/55 622 (1·6%) 0·80 (0·72–0·88)
I²=0·0%; p=0·58
Primary eye outcome
ACCORD[9] 131/6135 (2·1%) 167/6104 (2·7%) 0·79 (0·64–0·98)
ADVANCE[10] 35/2992 (1·2%) 49/2901 (1·7%) 0·83 (0·56–1·22)
UKPDS[8] 200/5300 (3·8%) 88/2251 (3·9%) 0·95 (0·74–1·23)
VADT[11] 62/450 (13·8%) 63/453 (13·9%) 0·94 (0·66–1·34)
Overall 428/14 877 (2·9%) 367/11 709 (3·1%) 0·87 (0·76–1·00)
I²=0·0%; p=0·69
Primary nerve outcome
ACCORD 2055/14 979 (13·7%) 2210/14 923 (14·8%) 0·92 (0·87–0·98)
ADVANCE 1373/23 752 (5·8%) 1299/23 876 (5·4%) 1·07 (0·99–1·15)
UKPDS 453/12 247 (3·7%) 208/5087 (4·1%) 0·93 (0·78–1·10)
Overall 3881/50 978 (7·6%) 3717/43 887 (8·5%) 0·98 (0·87–1·09)
I²=78·1%; p=0·011
0·25
0·50
1·00
2·00
Favours more intensive glucose control
Favours less intensive glucose control

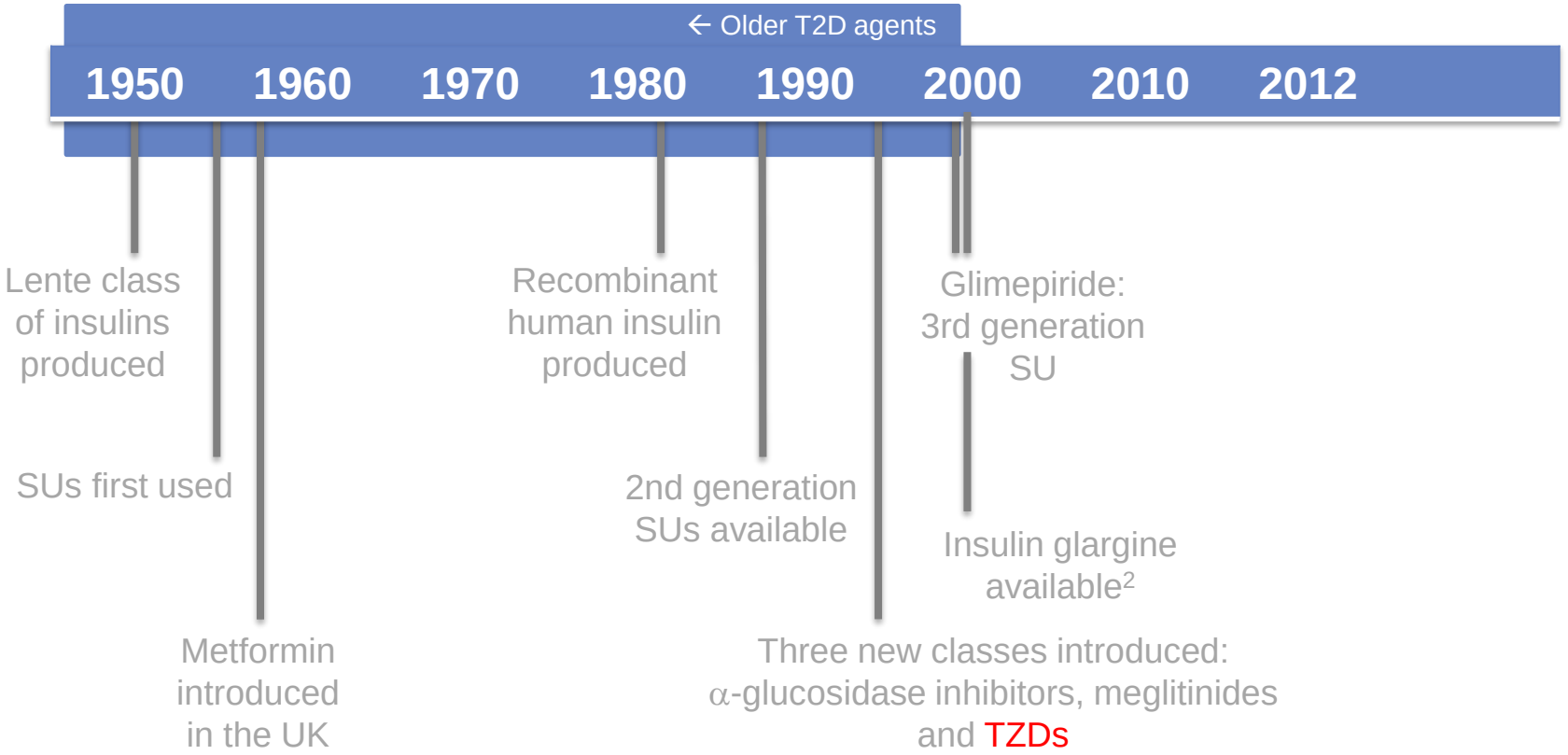
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

STENO-2





T2D agents before 2008



Adapted from 1. Kirby. Br J Diabetes Vasc Dis 2012;12:315–20. 2. Lantus® SPC. FDA 2015.

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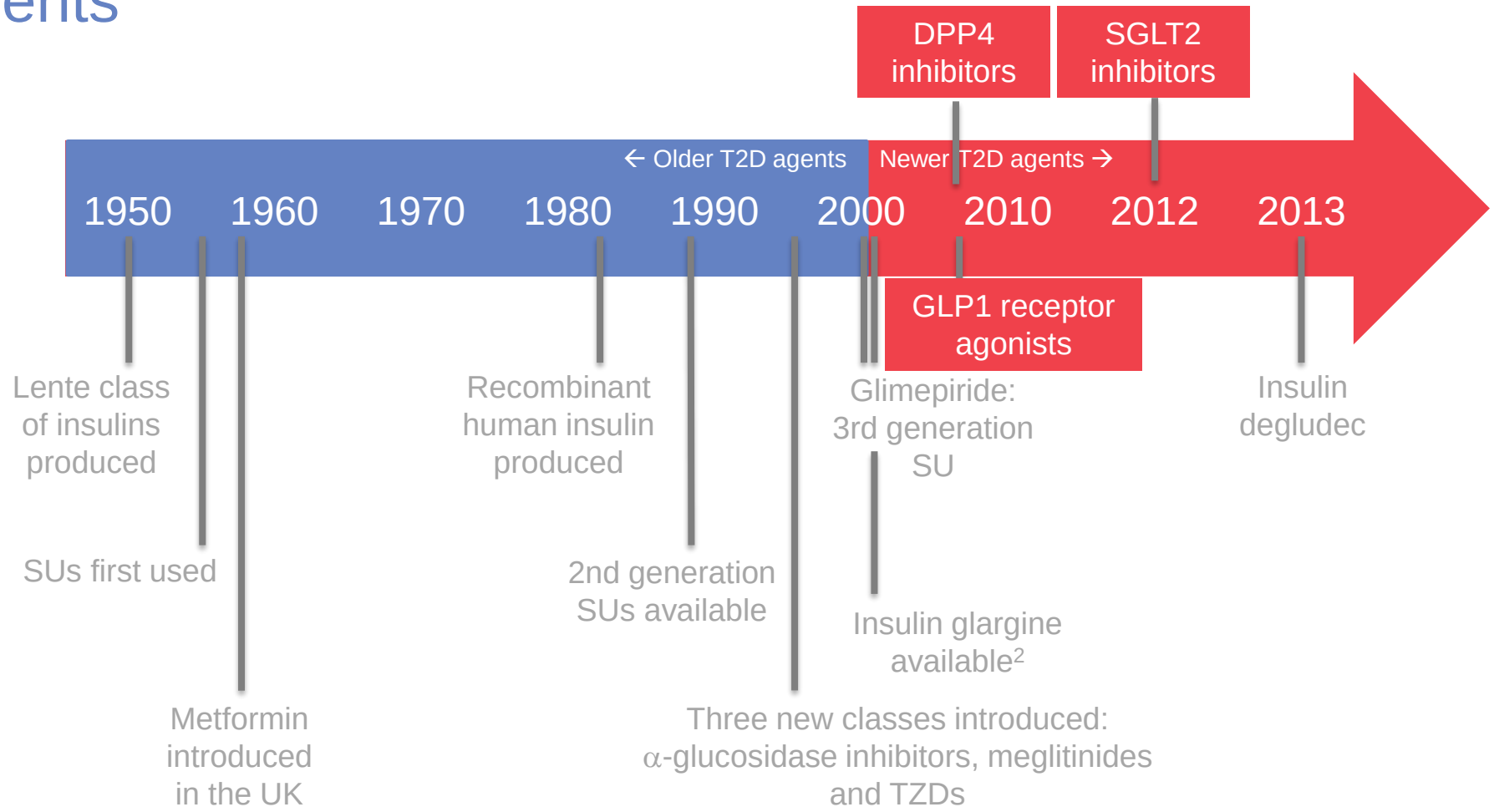
A closer look at CV effects of 21st century T2D agents



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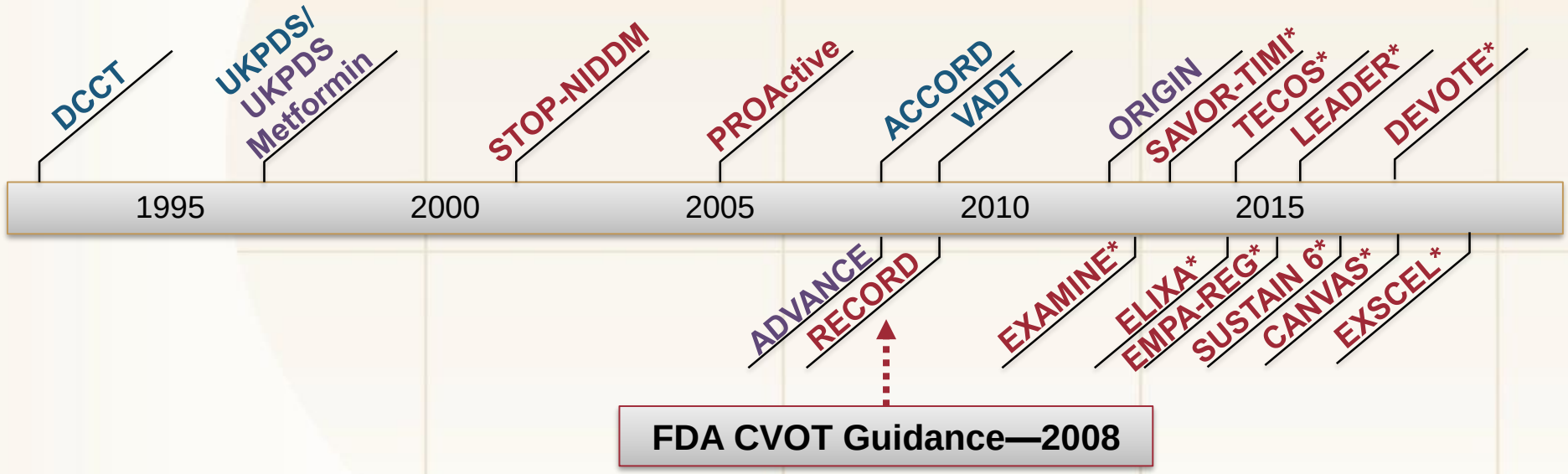
Cardiovascular Outcomes Trials (COVTs) with Antihyperglycemic Agents



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
***** = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

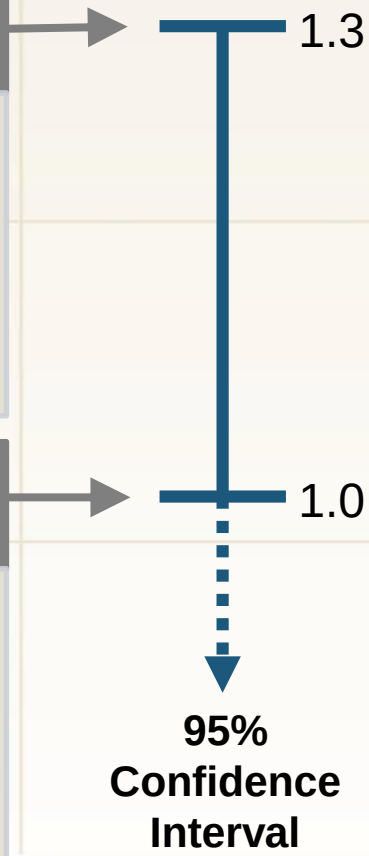
Noninferiority and Superiority Criteria in CVOTs

Noninferiority

- Upper bound of the confidence interval for the primary endpoint is less than a prespecified threshold (often 1.3, but criteria vary with study design)
- **Means study drug performed no worse than comparator and is <u>safe</u>**

Superiority

- Upper bound of confidence interval for the primary endpoint is typically less than 1 (criteria may vary with study design)
- Tested after noninferiority criteria are met
- **Means study drug reduced CV outcomes relative to comparator**

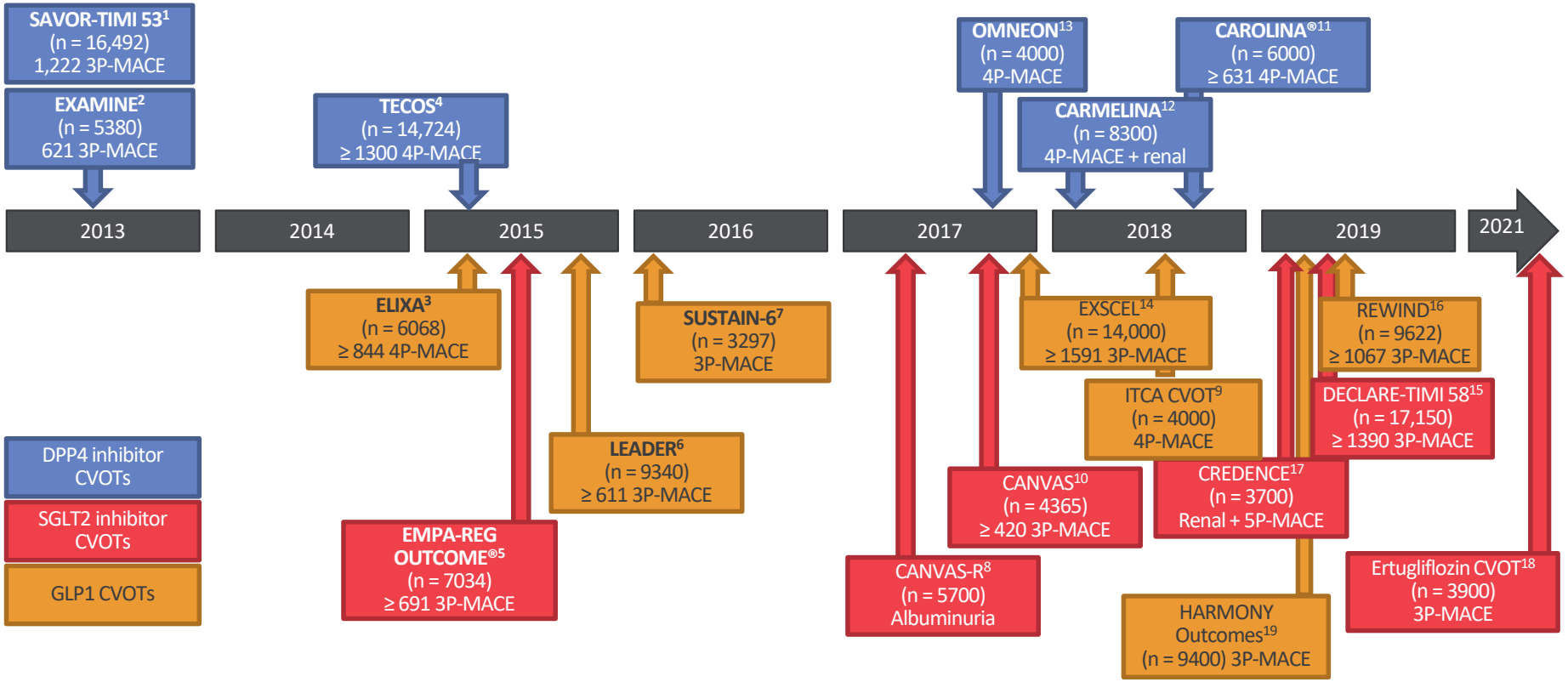


Agents Shown to Have CV Safety:
All antihyperglycemic agents evaluated in CVOTs to date

Agents Shown to Reduce CV Outcomes:
Canagliflozin
Empagliflozin
Liraglutide

FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

CV safety trials are being conducted for each compound within the newer classes



Timings represent estimated completion dates as per ClinicalTrials.gov.

Adapted from Johansen. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)

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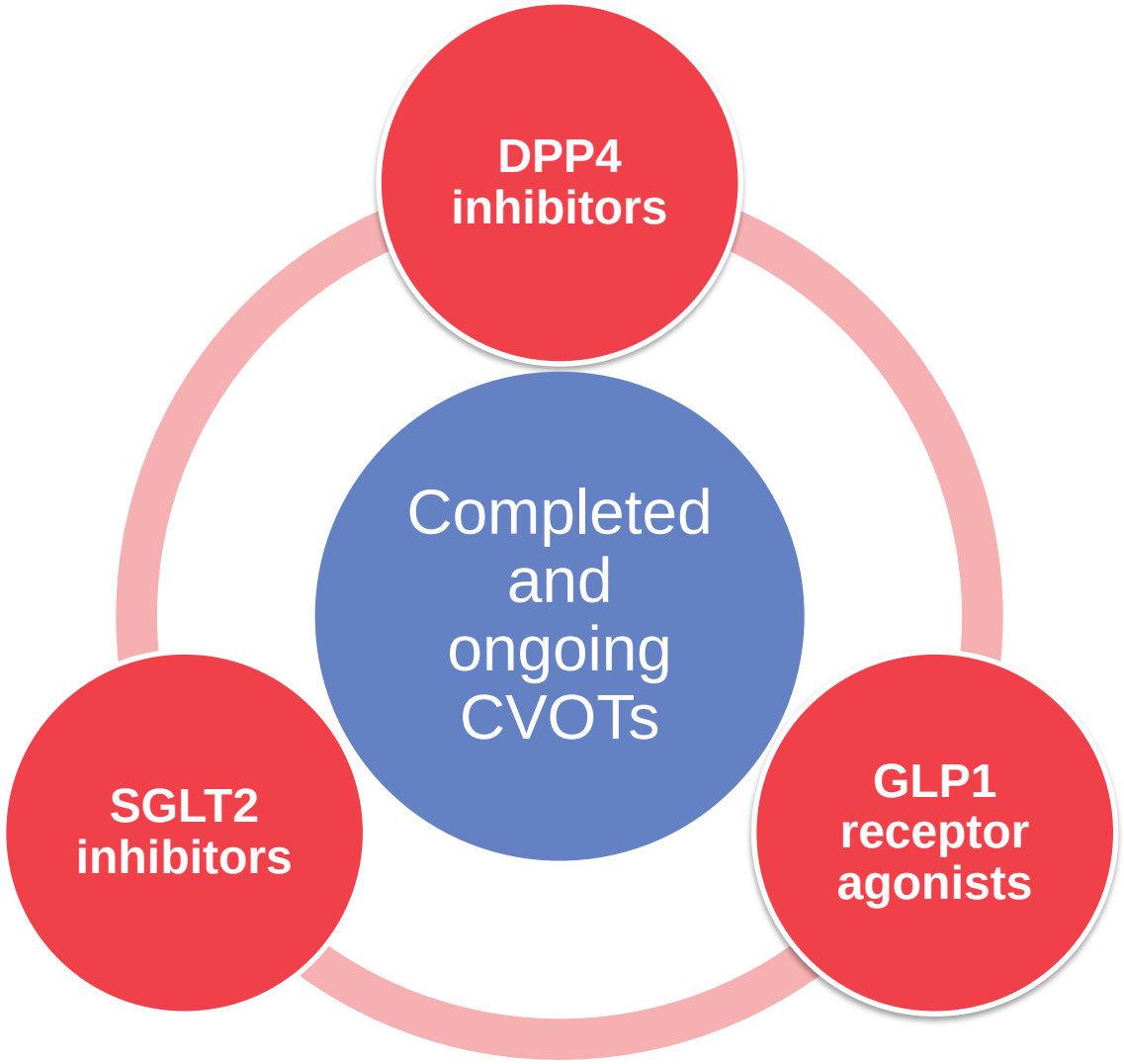
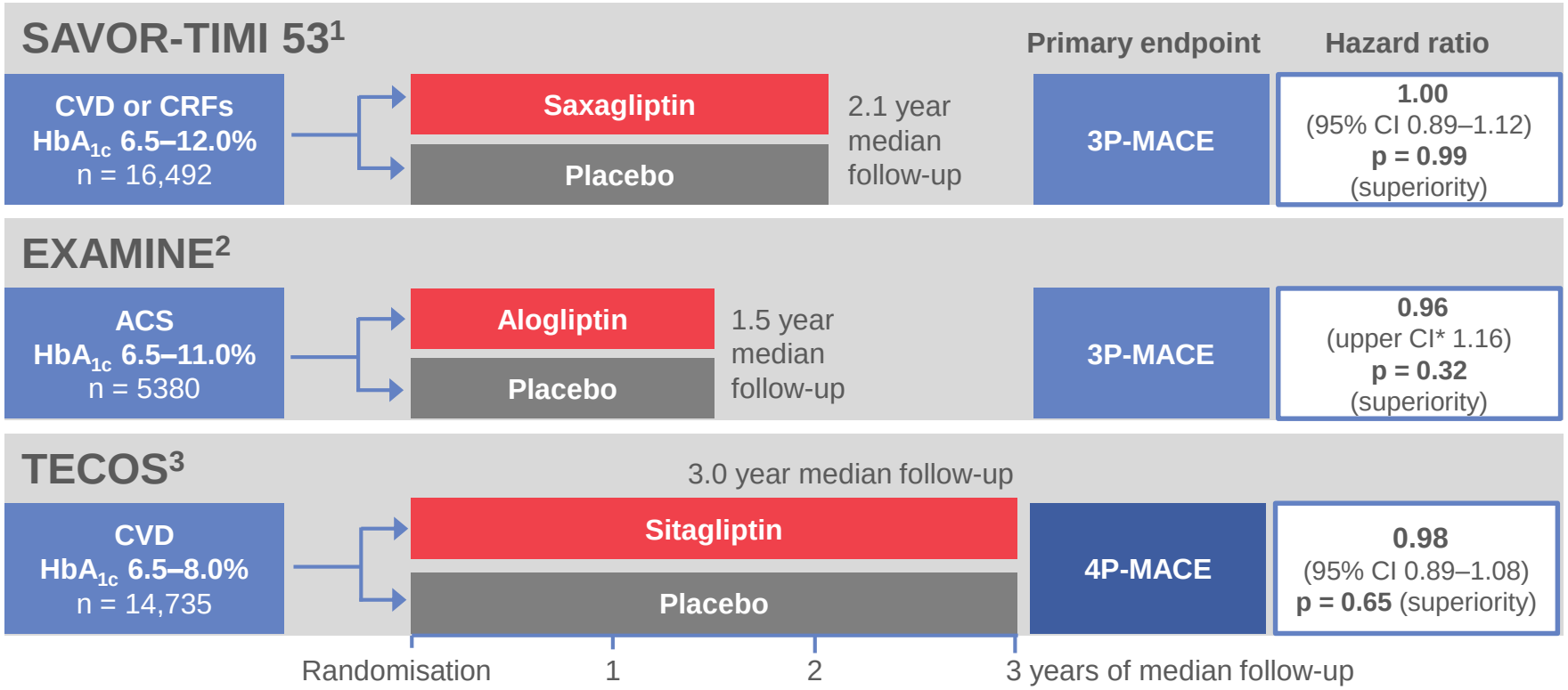


Summary of completed DPP4 inhibitor CVOTS



*Upper boundary of 1-sided repeated CI.

1. Scirica et al. N Engl J Med 2013;369:1317–26. 2. White et al. N Engl J Med 2013;369:1327–35.
3. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501352.

ACROSS T2D The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

Summary of Published DPP4i Cardiovascular Outcomes Trials

	EXAMINE**	SAVOR-TIMI 53	TECOS	CARMELINA
Primary outcome, HR (95% CI)	0.96 (≤1.16)‡	1.00 (0.89-1.12)	0.98 (0.88-1.09)	1.02 (0.89-1.17)
CV death, HR (95% CI)	0.79 (0.60-1.04)	1.03 (0.87-1.22)	1.03 (0.89-1.19)	0.96 (0.81-1.14)
Fatal or nonfatal MI, HR (95% CI)	1.08 (0.88-1.33)	0.95 (0.80-1.12)	0.95 (0.81-1.11)	1.12 (0.90-1.40)
Fatal or nonfatal stroke, HR (95% CI)	0.91 (0.55-1.50)	1.11 (0.88-1.39)	0.97 (0.79-1.19)	0.91 (0.67-1.23)
All-cause mortality, HR (95% CI)	0.88 (0.71-1.09)	1.11 (0.96-1.27)	1.01 (0.90-1.14)	0.98 (0.84-1.13)
HF hospitalization, HR (95% CI)		1.27 (1.07-1.51)	1.00 (0.83-1.20)	0.90 (0.74-1.08)

‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01. * Numerical imbalance (not statistically significant) with increased hospitalizations for heart failure with alogliptin.

CI, confidence interval; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CV, cardiovascular; DPP4i, dipeptidyl peptidase-4 inhibitors; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin

1. White WB, et al. *N Engl J Med*. 2013 Oct 3;369(14):1327-35.

2. Scirica BM, et al. *N Engl J Med.* 2013 Oct 3;369(14):1317-26.

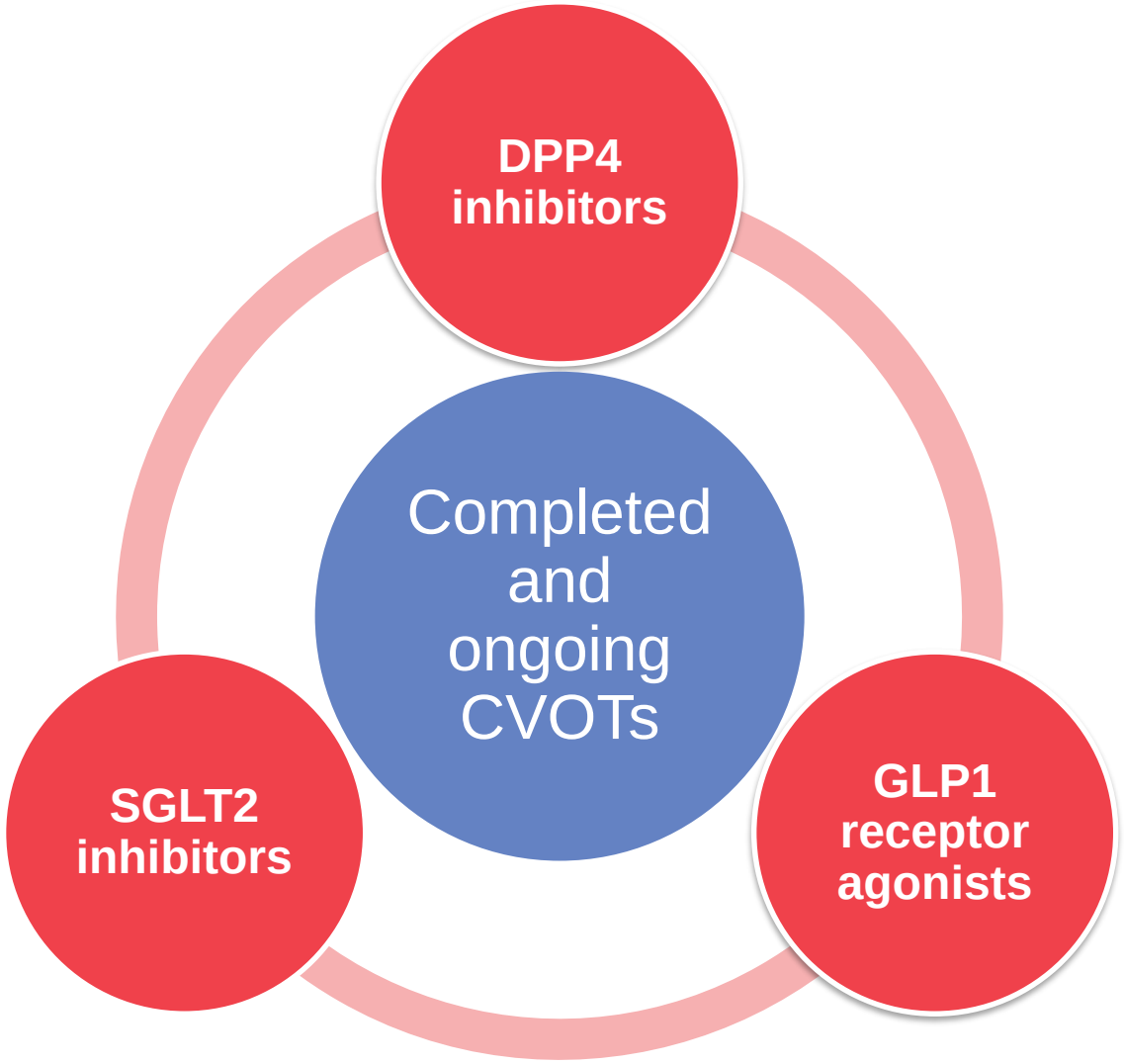
3. Green JB, et al. *N Engl J Med.* 2015 Jul 16;373(3):232-42.

4. Rosenstock J, et al. *JAMA.* 2019 Jan 1;321(1):69-79.

Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes

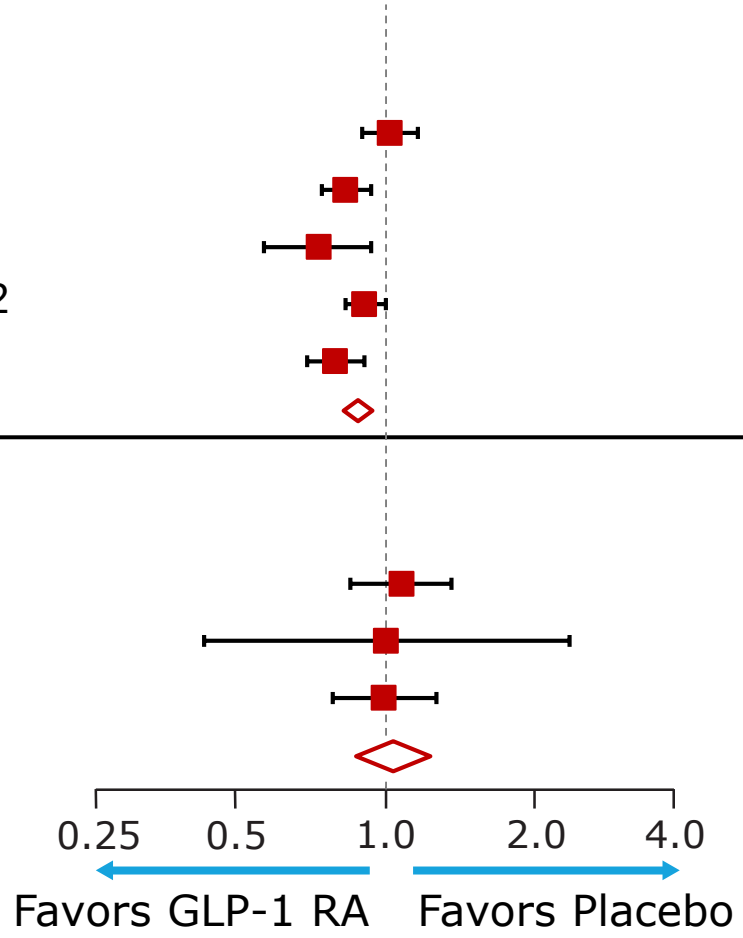
The CAROLINA Randomized Clinical Trial

Outcome	Linagliptin (n = 3023) No. (%)	Linagliptin (n = 3023) Rate/100 Patient-Years	Glimepiride (n = 3010) No. (%)	Glimepiride (n = 3010) Rate/100 Patient-Years	Incidence Rate/ 100 Patient-Years Difference, Linagliptin – Glimepiride (95% CI)	HR[a]/Odds Ratio[b] (95% CI)
Primary End Point						
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3P-MACE)	356 (11.8)	2.1	362 (12.0)	2.1	0.0 (−0.4 to 0.3)	0.98 (0.84 to 1.14)[a,c,d]
Cardiovascular death[c]	129 (4.3)		125 (4.2)			
Nonfatal myocardial infarction	141 (4.7)		138 (4.6)			
Nonfatal stroke[c]	86 (2.8)		101 (3.4)			
Key Secondary End Points						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina pectoris (4P-MACE)	398 (13.2)	2.3	401 (13.3)	2.4	0.0 (−0.4 to 0.3)	0.99 (0.86 to 1.14)[a]
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication, without any moderate/severe hypoglycemic episodes, and without >2% weight gain[c]	481 (16.0)		305 (10.2)			1.68 (1.44 to 1.96)[b]
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication and without >2% weight gain[c]	524 (17.4)		422 (14.1)			1.29 (1.12 to 1.48)[b]



CV Death, MI, or Stroke by CV Disease History in GLP-1 Receptor Agonist CVOTs

	Events/Patients	Hazard ratio (95% CI)
Patients with atherosclerotic CV disease (secondary prevention)		
ELIXA	805/6068	1.02 (0.89–1.17)
LEADER	1051/6775	0.82 (0.73–0.93)
SUSTAIN-6	235/2735	0.72 (0.55–0.93)
EXSCEL	1508/10,782	0.90 (0.82–1.00)
HARMONY	766/9463	0.78 (0.68–0.90)
Overall (*P* <0.001)		0.87 (0.82–0.92)
Patients with multiple risk factors (primary prevention)		
LEADER	251/2565	1.08 (0.84–1.38)
SUSTAIN-6	19/562	1.00 (0.41–2.46)
EXSCEL	236/3970	0.99 (0.77–1.28)
Overall (*P* = 0.71)		1.03 (0.87–1.23)



Zelnicker TA, et al. *Circulation*. 2019;139(17):2022-2031.

Summary of Published GLP-1 RA Cardiovascular Outcomes Trials

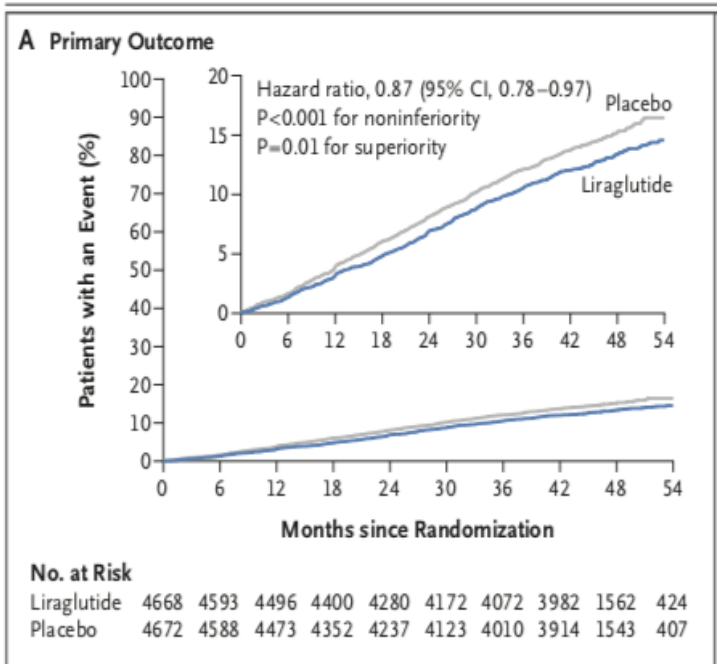
	LEADER	SUSTAIN-6	EXSCEL	ELIXA	HARMONY	REWIND
Primary outcome, HR (95% CI)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.91 (0.83-1.00)	1.02 (0.89-1.17)	0.78 (0.68-0.90)	0·88 (0.79-0.99)
CV death, HR (95% CI)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.98 (0.78-1.22)	0.93 (0.73-1.19)	0·91 (0.78-1.06)
Fatal or nonfatal MI, HR (95% CI)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.97 (0.85-1.10)	1.03 (0.87-1.22)	0.75 (0.61-0.90)	0·96 (0.79-1.15)
Fatal or nonfatal stroke, HR (95% CI)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.85 (0.70-1.03)	1.12 (0.79-1.58)	0.86 (0.66-1.14)	0·76 (0.62-0.94)
All-cause mortality, HR (95% CI)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.94 (0.78-1.13)	0.95 (0.79-1.16)	0.90 (0.80-1.01)
HF hospitalization, HR (95% CI)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0.96 (0.75-1.23)		0·93 (0.77-1.12)

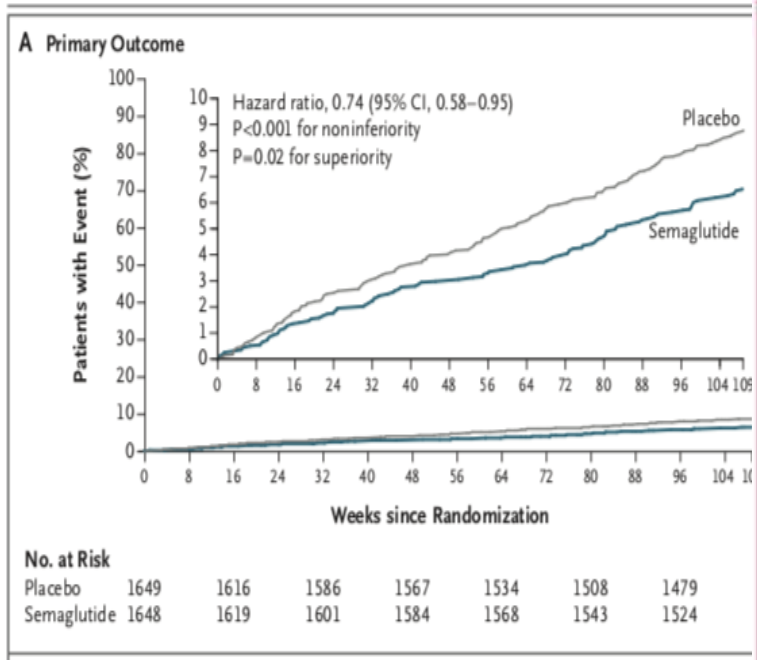
CV, cardiovascular; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, Harmony Outcomes (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus); HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

1. Adapted from Das SR, et al. J Am Coll Cardiol. 2018;72:3200-3223.

2. Gerstein HC, et al. Lancet. 2019;http://dx.doi.org/10.1016/S0140-6736(19)31149-3; e-pub ahead of print.

GLP-1 RA with HR significant for superiority versus SOC





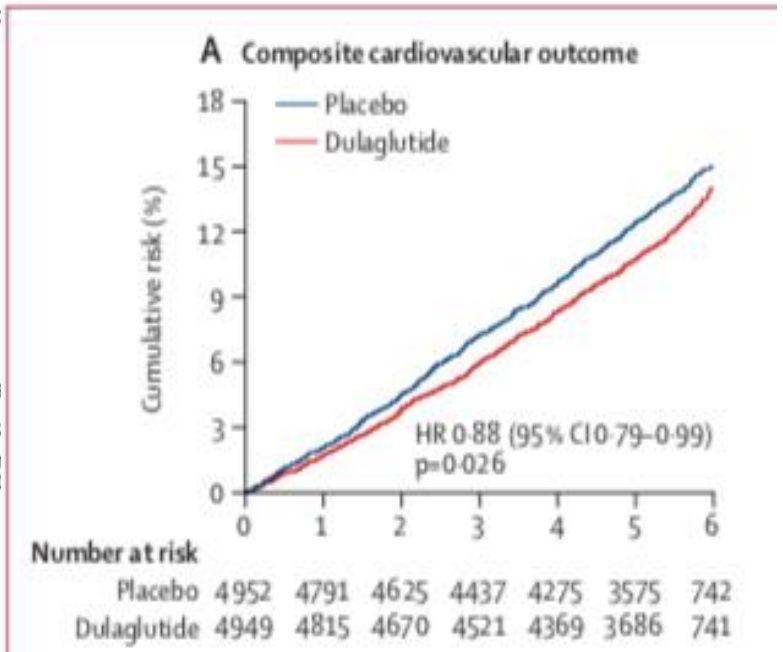


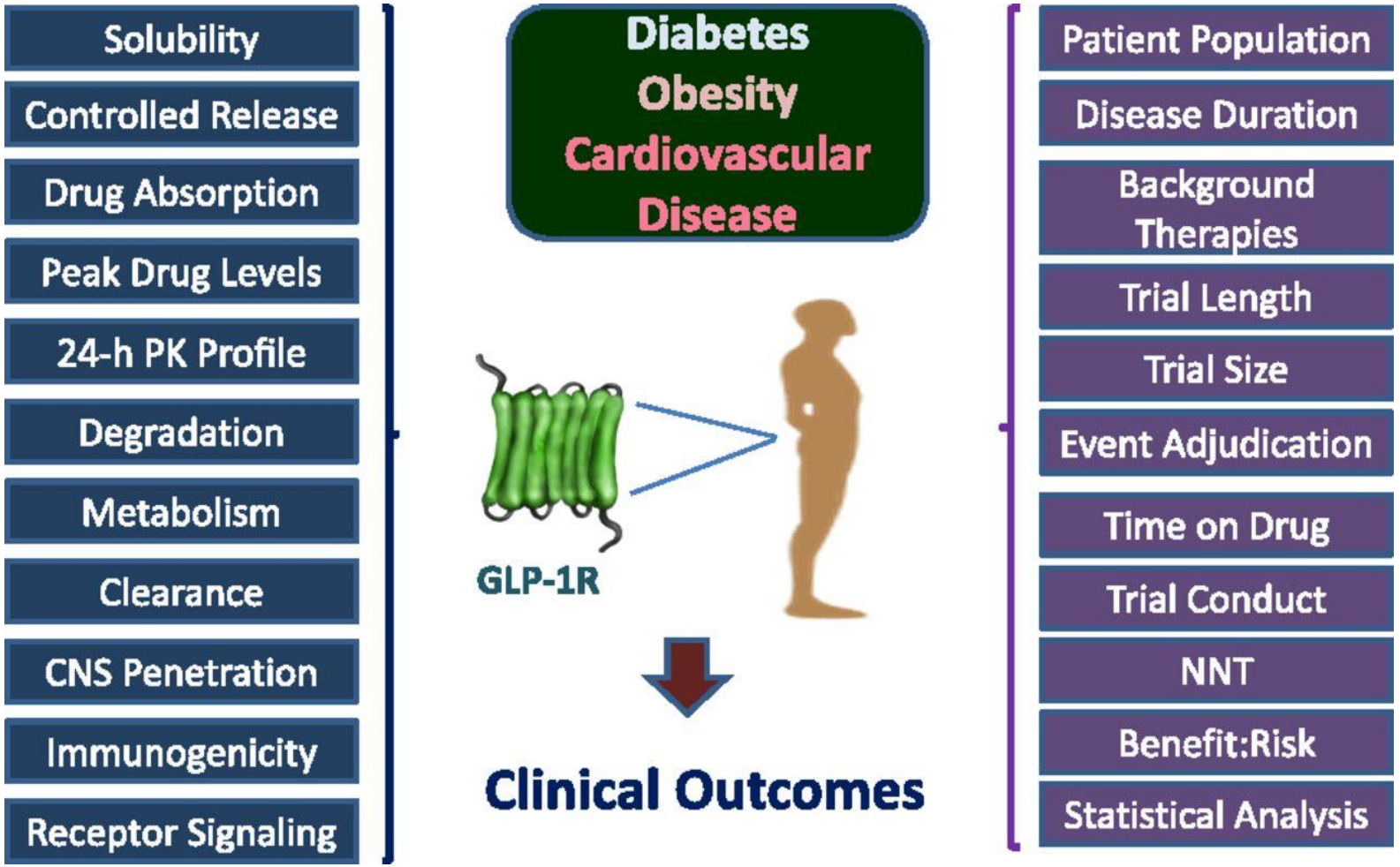
Table 1b Completed Incretin-Based COVT's

	Agent/trial	Number of subjects	Men%	Age	Duration of DM	Primary Outcome	Duration of follow-up years	Established (%) CVD/CKD	HR(95%CI)
No effect	ELIXA lixisenatide	6068	69.1	59.9	9.2	4pMACE	2.1	100/22	1.02(0.89,1.17)
No effect	EXSCEL Exenatide	14752		61.0	13.1	3-MACE	3.2	73/21.3	0.91(0.83,1.00)
Positive effect	LEADER liraglutide	9340	64.3	64.3	12.8	3pMACE	3.8	81/24	0.87(0.78,0.97)
Positive effect	HARMONY albiglutide	9463	70	64.1	14.1	3pMACE	1.6	70.5/22.6	0.78(0.68,0.90)
Positive effect	SUSTAIN-6 semaglutide	3297		64.6	13.9	3pMACE	2.1	83/28.5	0.74(0.58,0.95)
Positive effect	REWIND dulaglutide	9901	53	66.2	10.0	3pMACE	5.4	31.4/22.2	0.88(0.79,0.99)
No effect	PIONEER-6 Oral Semaglutide	3176	NK	>50	NK	3pMACE	1.3	84.7/27.2	0.79(0.55,1.11)

(Fernandez, et al., 2018) (Gerstein, et al., 2019) (Holman, et al.) (Husain, et al., 2019) (Marso, et al., 2016) (Marso, et al., 2016) (Pfeffer, et al., 2015)

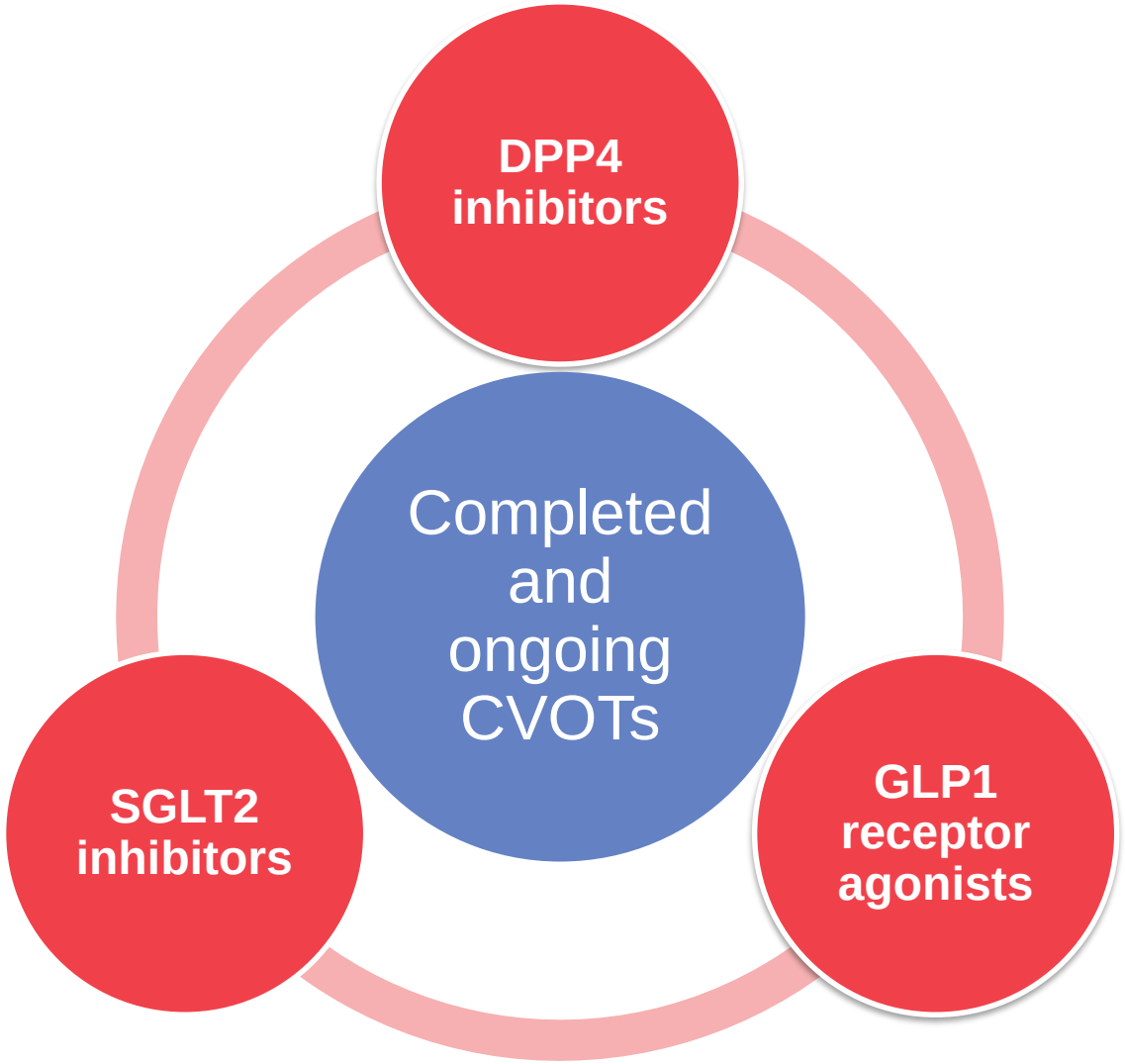
The Ascending GLP-1 Road From Clinical Safety to Reduction of Cardiovascular Complications

Parameters determining the efficacy of GLP-1R agonists and corresponding clinical trial results.



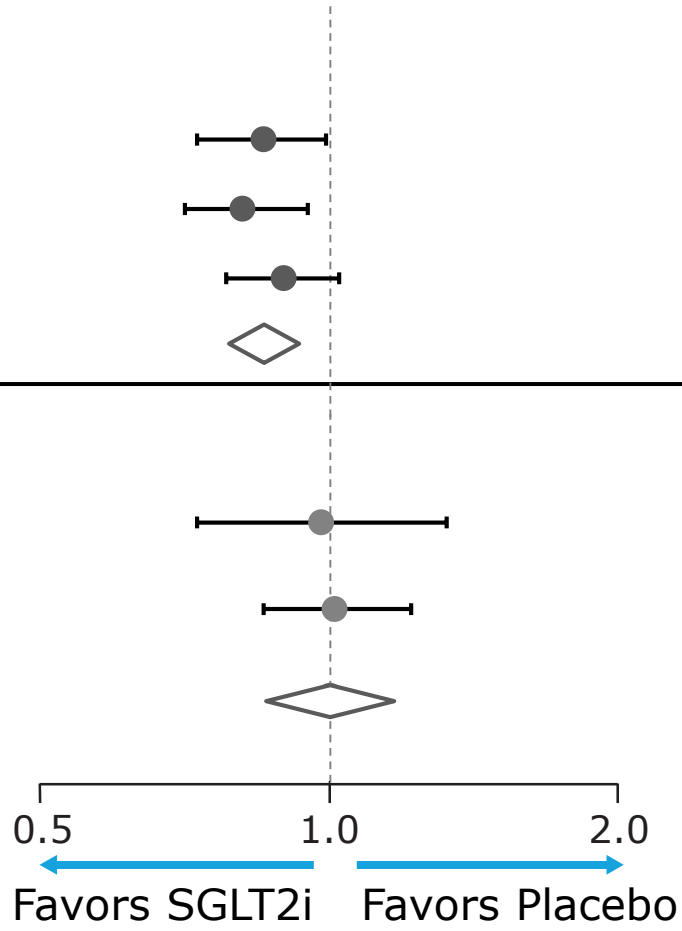
Daniel J. Drucker Diabetes 2018;67:1710-1719

American Diabetes Association.



CV Death, MI, or Stroke by CV Disease History in SGLT2 Inhibitor CVOTs

	Events/Patients	Hazard ratio (95% CI)
Patients with atherosclerotic CV disease (secondary prevention)		
EMPA-REG OUTCOME	772/7020	0.86 (0.74–0.99)
CANVAS Program	796/6656	0.82 (0.72–0.95)
DECLARE-TIMI 58	1020/6974	0.90 (0.79–1.02)
Overall (*P* = 0.0002)		0.86 (0.80–0.93)
Patients with multiple risk factors (primary prevention)		
CANVAS Program	215/3486	0.98 (0.74–1.30)
DECLARE-TIMI 58	539/10,186	1.01 (0.86–1.20)
Overall (*P* = 0.98)		1.00 (0.87–1.16)



Zelnicker TA, et al. *Lancet*. 2019;393(10166):31-39.

Summary of Published SGLT-2i Cardiovascular Outcomes Trials

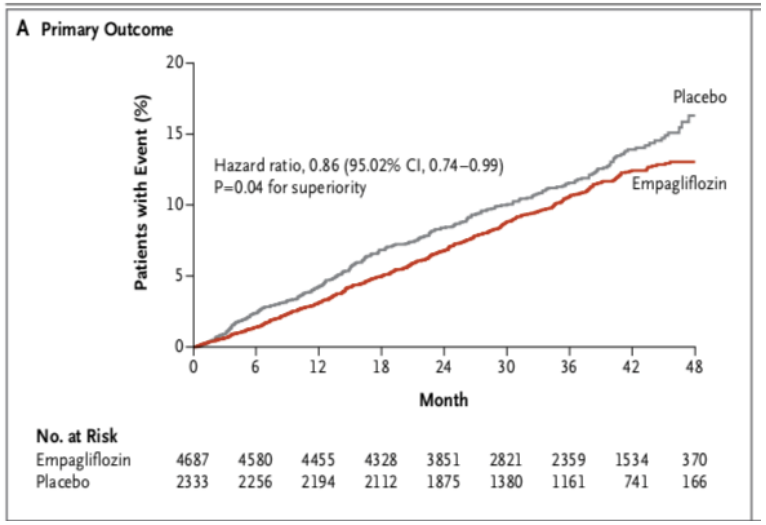
	EMPA-REG OUTCOME	CANVAS/CANVAS-R	DECLARE - TIMI 58	CREDENCE‡
MACE outcome (HR [95% CI])*	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)**	0.80 (0.67-0.95)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	
Fatal or nonfatal stroke	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	
All-cause mortality	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68–1.02)
Heart failure hospitalization	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47–0.80)

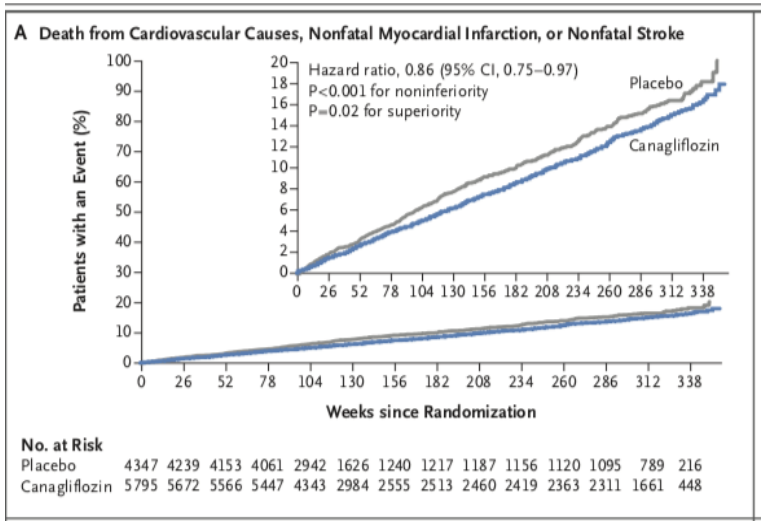
*MACE outcome: cardiovascular death, non-fatal MI, non-fatal stroke (primary outcome in EMPA-REG, CANVAS/CANVAS-R, and DECLARE-TIMI 58, secondary outcome in CREDENCE). **Additional primary outcome in DECLARE-TIMI 58: CV death and hospitalization for heart failure, HR= 0.83 (0.73–0.95). ‡ CREDENCE enrolled patients with diabetic kidney disease. Primary outcome included composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days), doubling of the serum creatinine level, or death from renal or cardiovascular disease. The primary outcome was lower in those receiving canagliflozin HR= 0.7 (0.59-0.82).

CANVAS, Canagliflozin Cardiovascular Assessment Study; CANVAS-R, A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; MI, myocardial infarction; SLGT2, sodium-glucose cotransporter 2. CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation.

Adapted from Das SR, et al. *J Am Coll Cardiol.* 2018;72:3200-3223.

SGLT-2i with HR significant for superiority versus SOC (Dapa for one of the two primary outcomes)





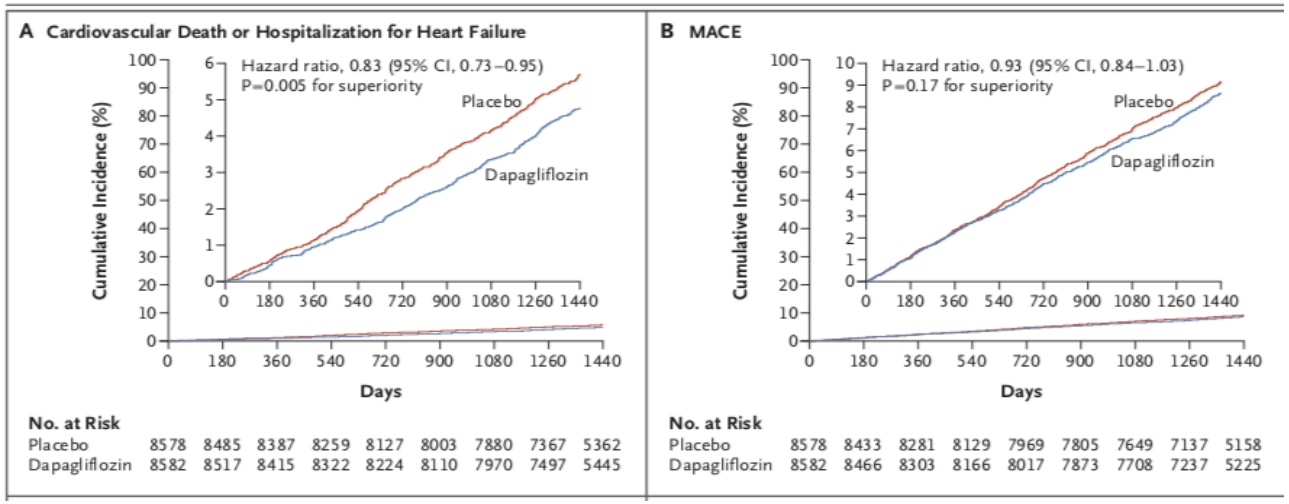


Table 2 SGLT2 inhibitors COVT's

	Agent/trial	Number of subjects	Men %	Age	Duration of DM	Primary Outcome	Duration of follow-up years	Established (%) CVD/CKD	HR(CI)
Reported	CANVAS canagliflozin	10142	64.2	63.3	13.5	3pMACE	3.6	65.6	0.86(0.75,0.97)
	EMPA-REG empagliflozin	7034	72	63.1	57% over 10 years	3pMACE	3.1	99	0.86(0.74,0.99)
	DECLARE saxagliflozin	17160	62.6	63.8	11.8	DUAL	4.2	40.6	MACE 0.93(0.84,1.03) CV/HFH 0.83(0.73,0.95)
On Going	VERTIS-CV ertugliflozin	8237	70	64.4	12.9	3pMACE	NA	99/21.6	NA
	SCORED Sotagliflozin*	Estimated 10500	NA	NA	NA	DUAL	NA	NA	NA

- A dual SGLT1/SGLT2 inhibitor

(Cannon, et al., 2018) (NCT03315143, n.d.) (Neal, et al., 2017) (Wiviott, et al., 2019) (Zinman, et al., 2015)

A decade of learning on the effects of glucose lowering therapies and ASCVD

1- Targeting multiple risk factors to reduce CV risk in patients with T2DM
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- SGLT2 *inhibitors*
- GLP-1 *RA*

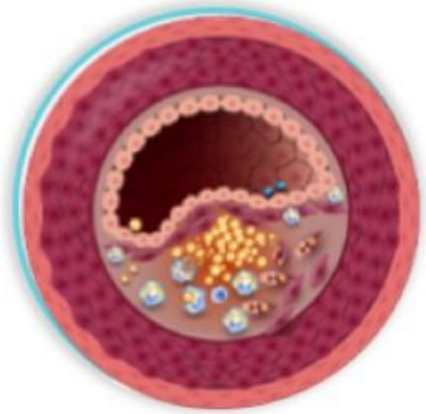
4- Proposed Mechanisms of CV Protection

5- Impact on Regulatory Agencies and Professional Society Guidelines/Recommendations
6- Lessons learned from other Disease States or Study Designs
7- SUMMARY/CONCLUSIONS

Characteristics Associated With Atherothrombosis in Patients With CAD and T2D

Pathophysiology of Thrombotic Risk in Patients With CAD and T2D Can Be Distilled Into 3 Main Characteristics…

Endothelial dysfunction

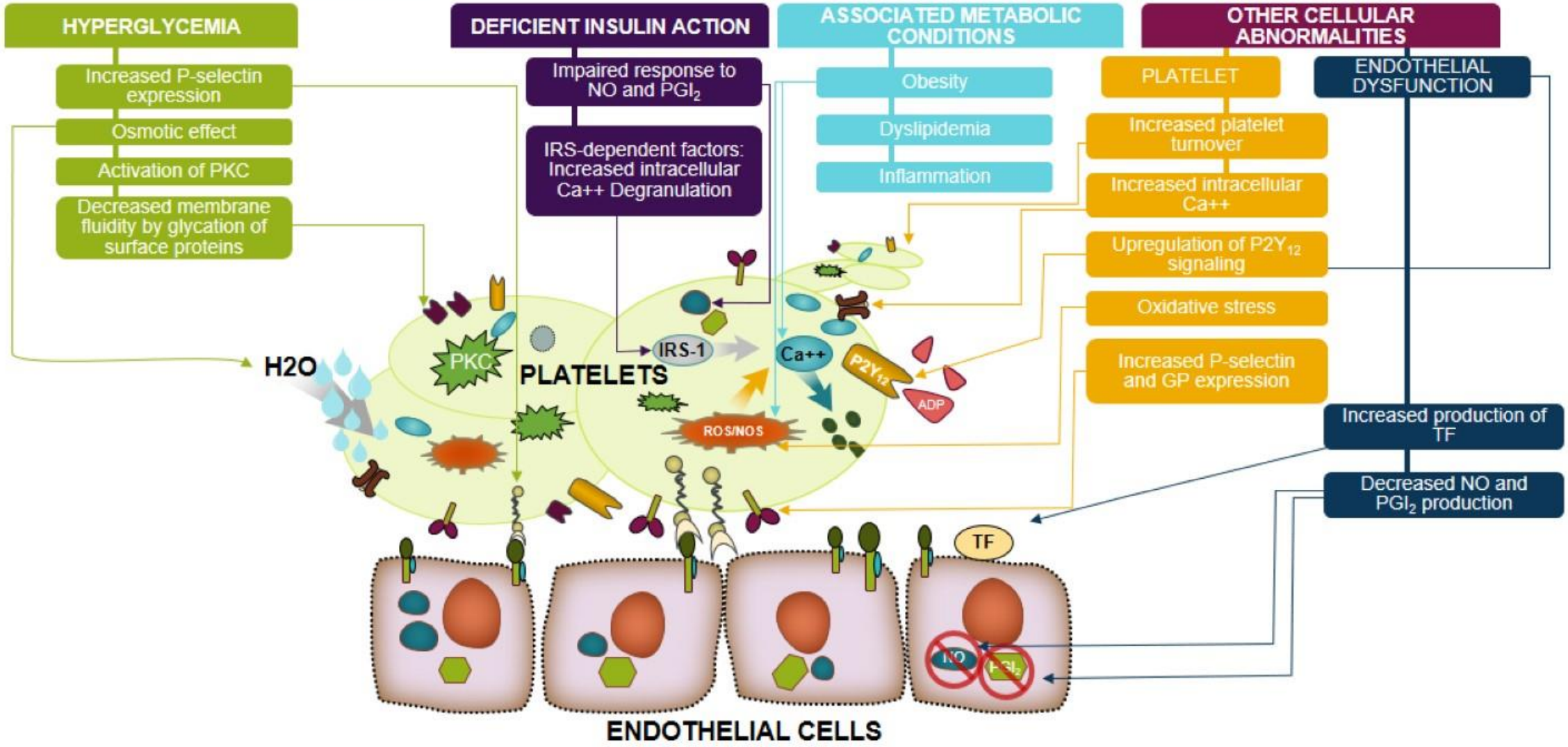


High platelet turnover and reactivity

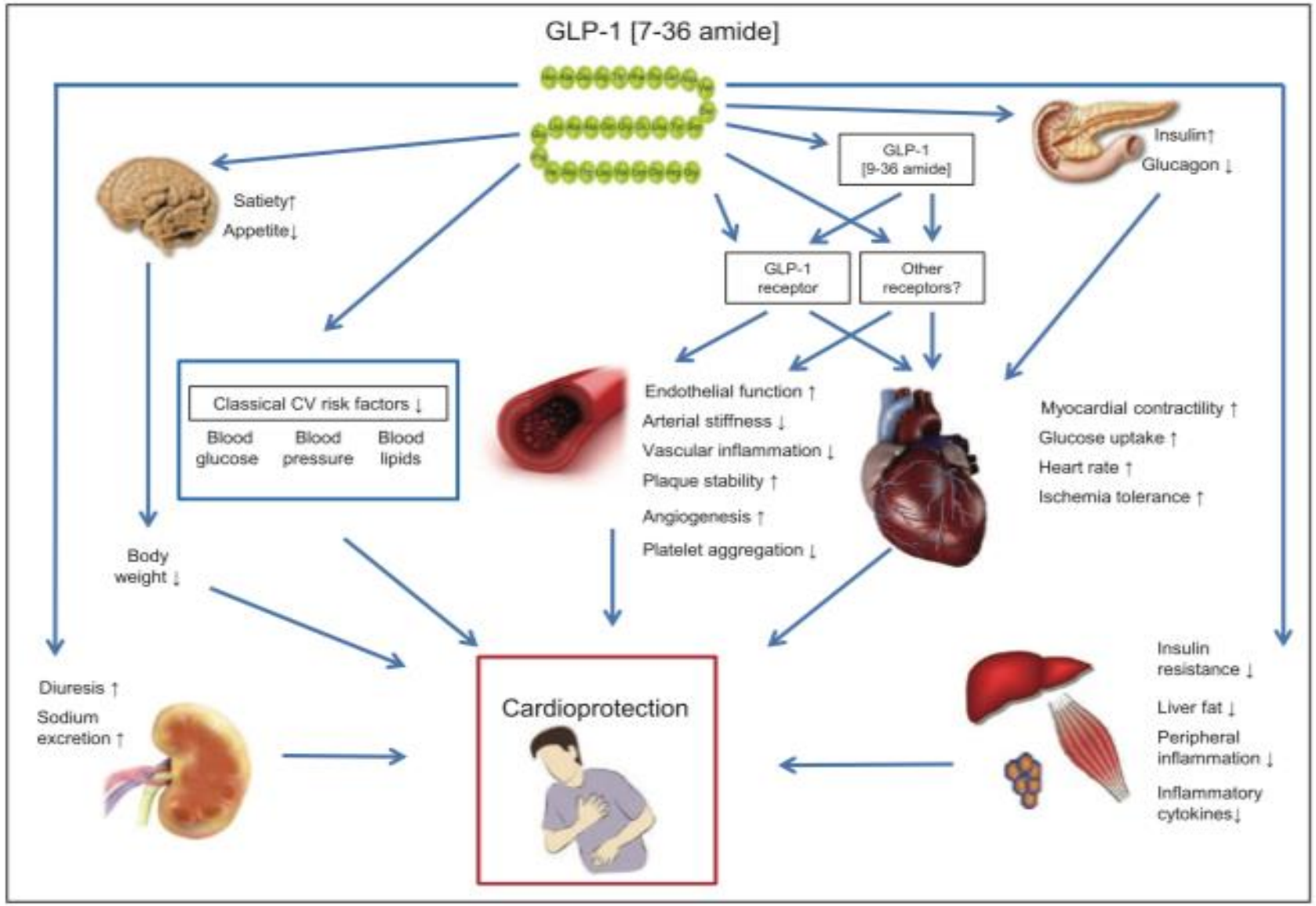
Inflammation

Ferreiro JL, Angiolillo DJ. *Circulation*. 2011;123(7):798-813.

Numerous Mechanisms Are Involved in Altered Platelet Function in Patients With CAD and T2D (cont'd)

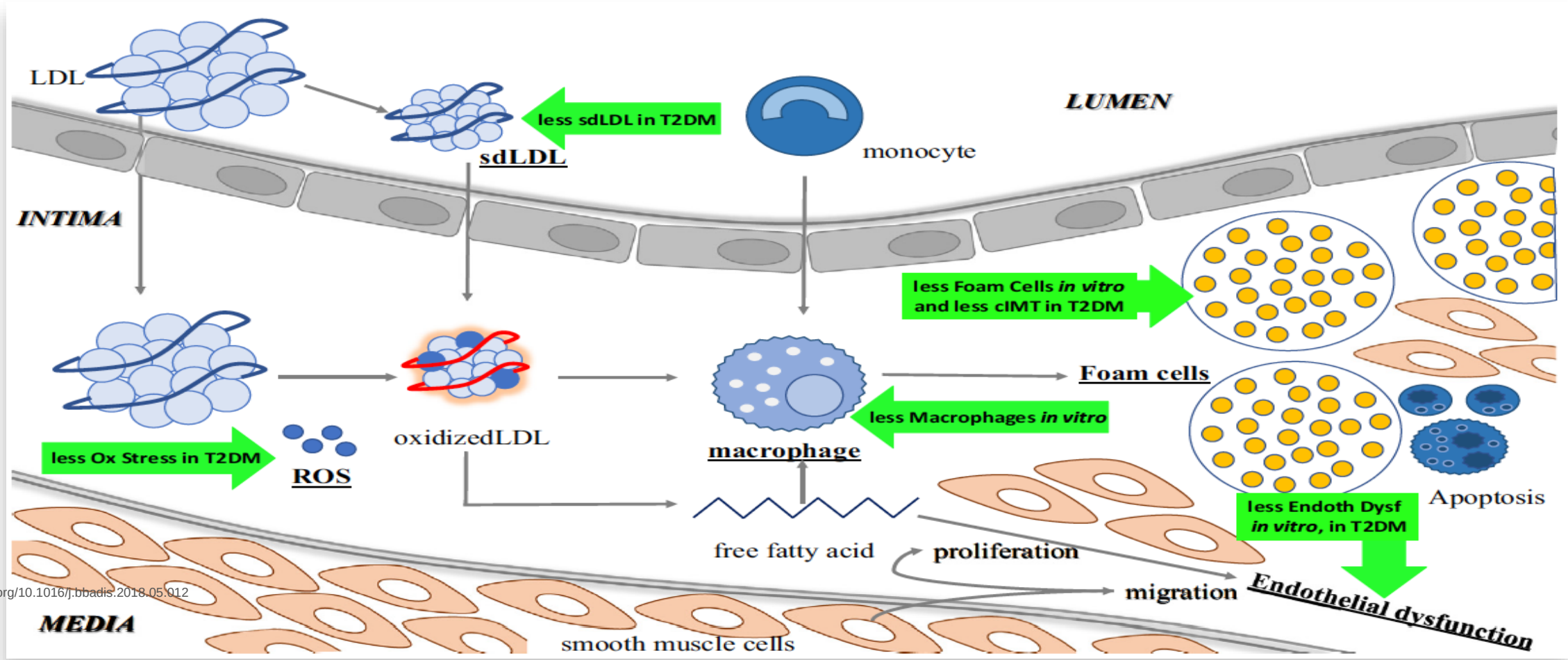


Ferreiro JL, Angiolillo DJ. *Circulation*. 2011;123(7):798-813.



Circulation. 2017;136:849–870. DOI: 10.1161/CIRCULATIONAHA.117.028136

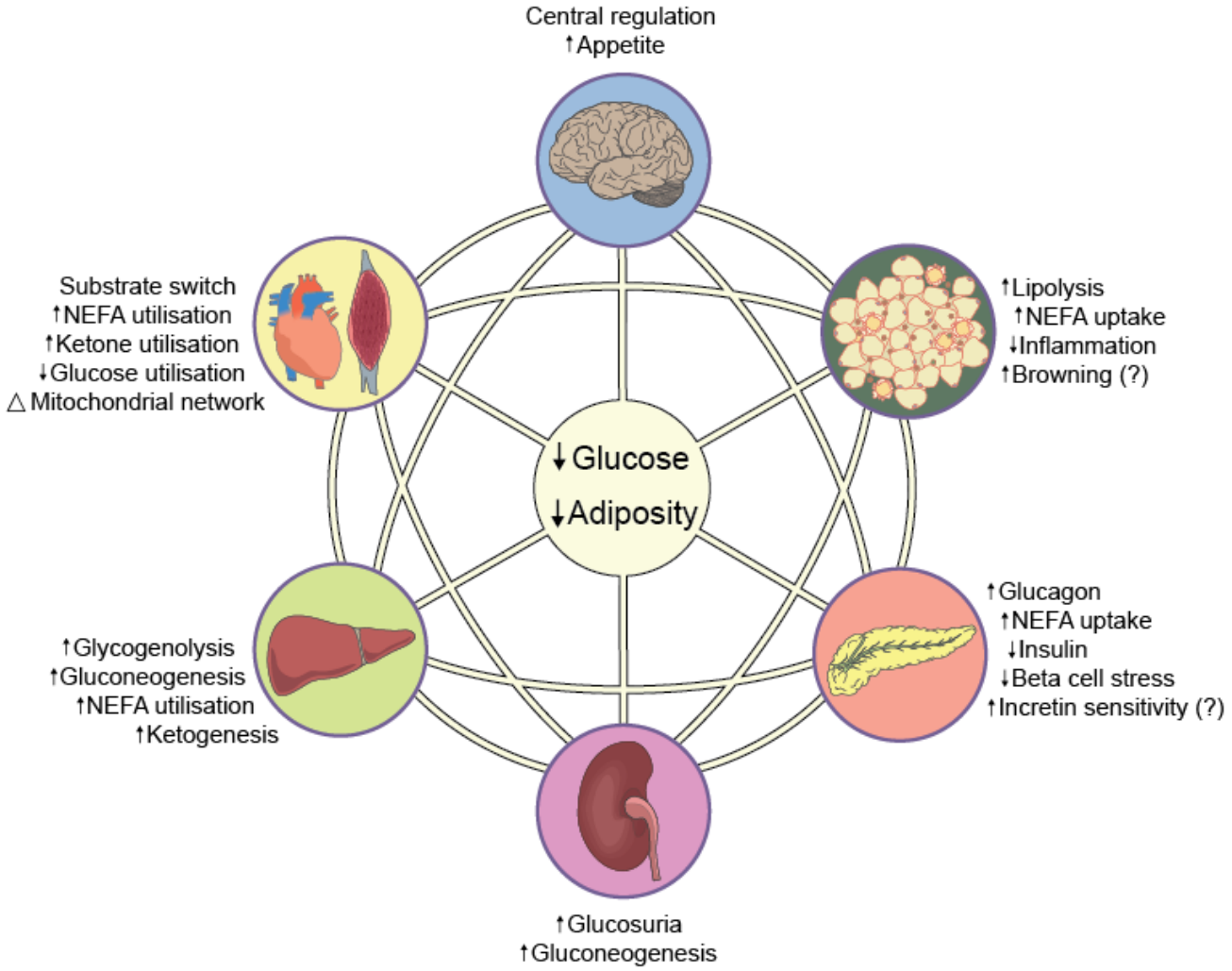
Potential Underlying Mechanisms of GLP-1



https://doi.org/10.1016/j.bbadis.2018.05.012

Rakipovski et al, JACC, Volume 3, Issue 6, December 2018

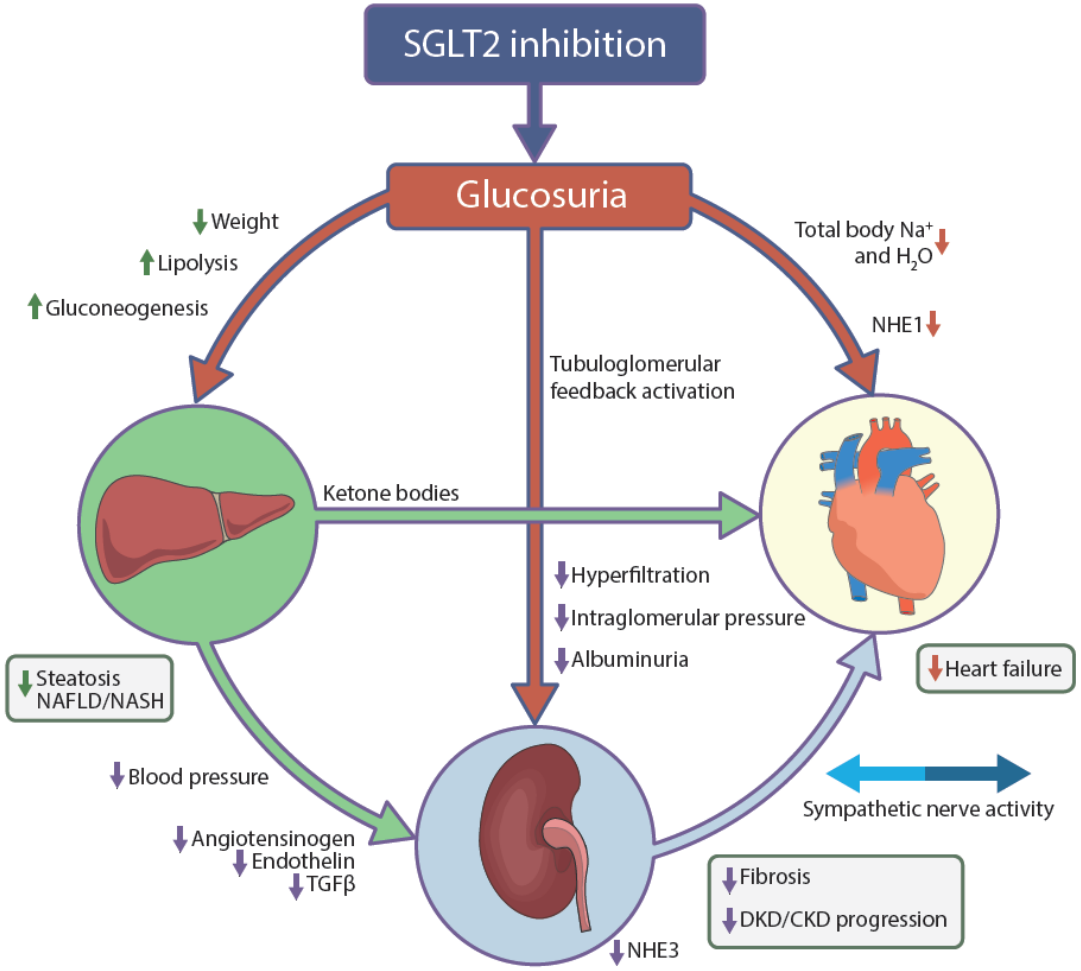
The nexus of metabolic changes contributing to reduced plasma glucose and adiposity following inhibition of SGLT2



Thomas and Cherney (2018) Diabetologia DOI 10.1007/s00125-018-4669-0

Diabetologia

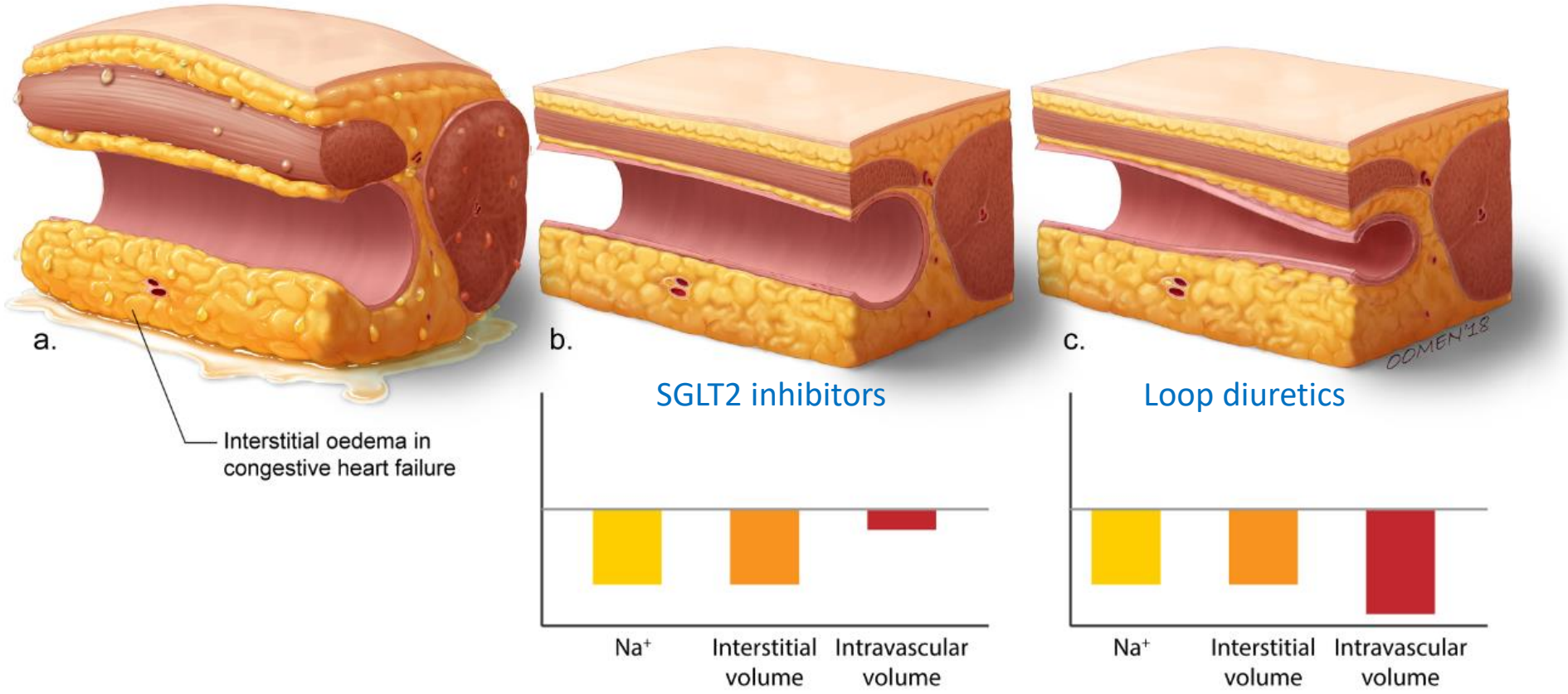
Consequences of inhibition of SGLT2 on glucose, salt and water excretion, as well as its potential metabolic impact on kidney, liver and heart function



Wanner and Marx (2018) Diabetologia DOI 10.1007/s00125-018-4678-z

Diabetologia

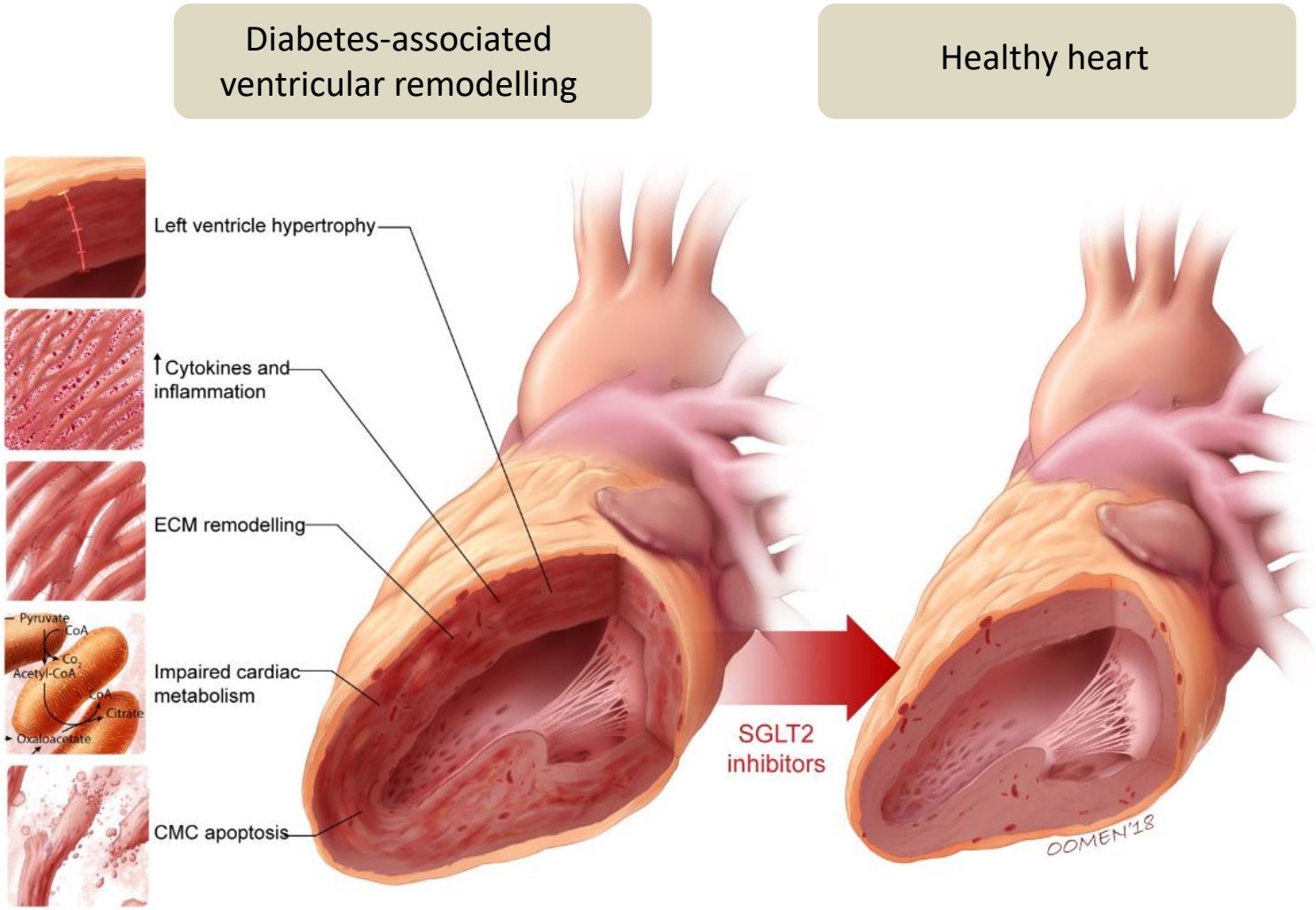
SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

Cardiovascular protection by SGLT2 inhibitors



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2

a Natriuresis

Tubuloglomerular feedback

- ↓ P_G
- ↑ P_{BOW}
- ↓ Proteinuria

Contraction of plasma volume

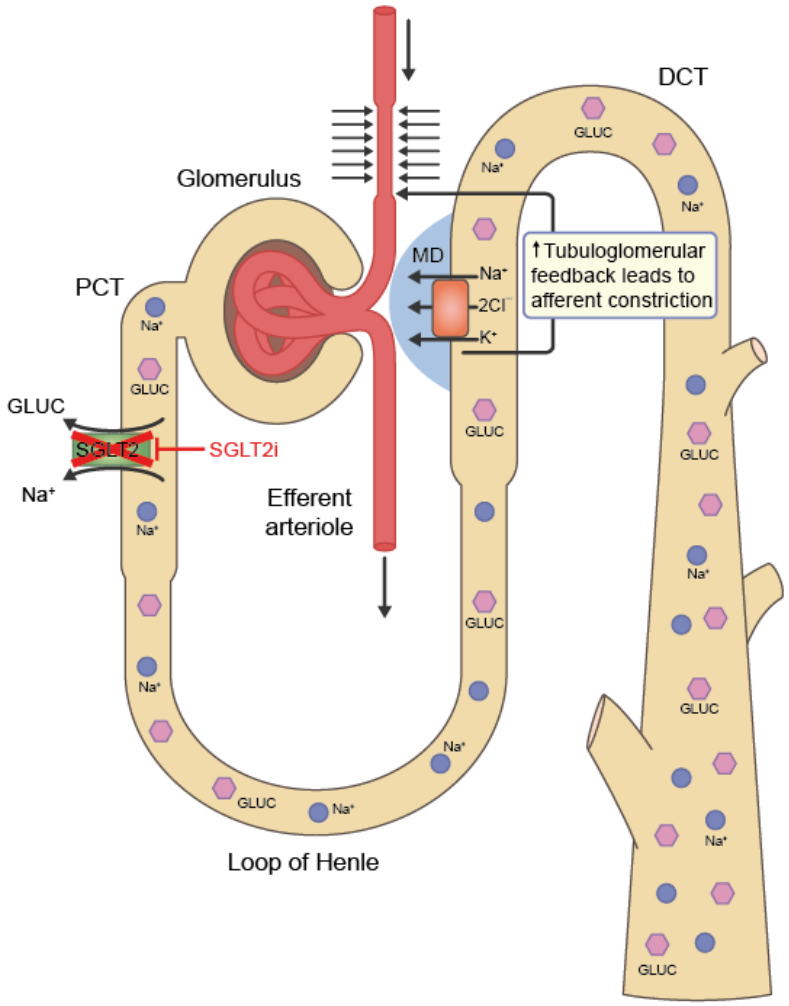
- ↓ Blood pressure
- ↓ Heart failure
- ? Direct/indirect effect on vascular function (e.g. endothelial function)
- ↓ Use of diuretic agents
- ↓ NHE3 activity – additional natriuresis?
- ↑ Erythropoeitin leading to ↑ haematocrit
- ↓ Tubular ischaemia/injury/fibrosis
- ↓ Markers of inflammation
- ↓ Oxidative stress

b Glycosuria

↓ HbA_{1c}, ↓ Body weight → ↓ Metabolic risk and microvascular complication risk

c Natriuresis + Glycosuria

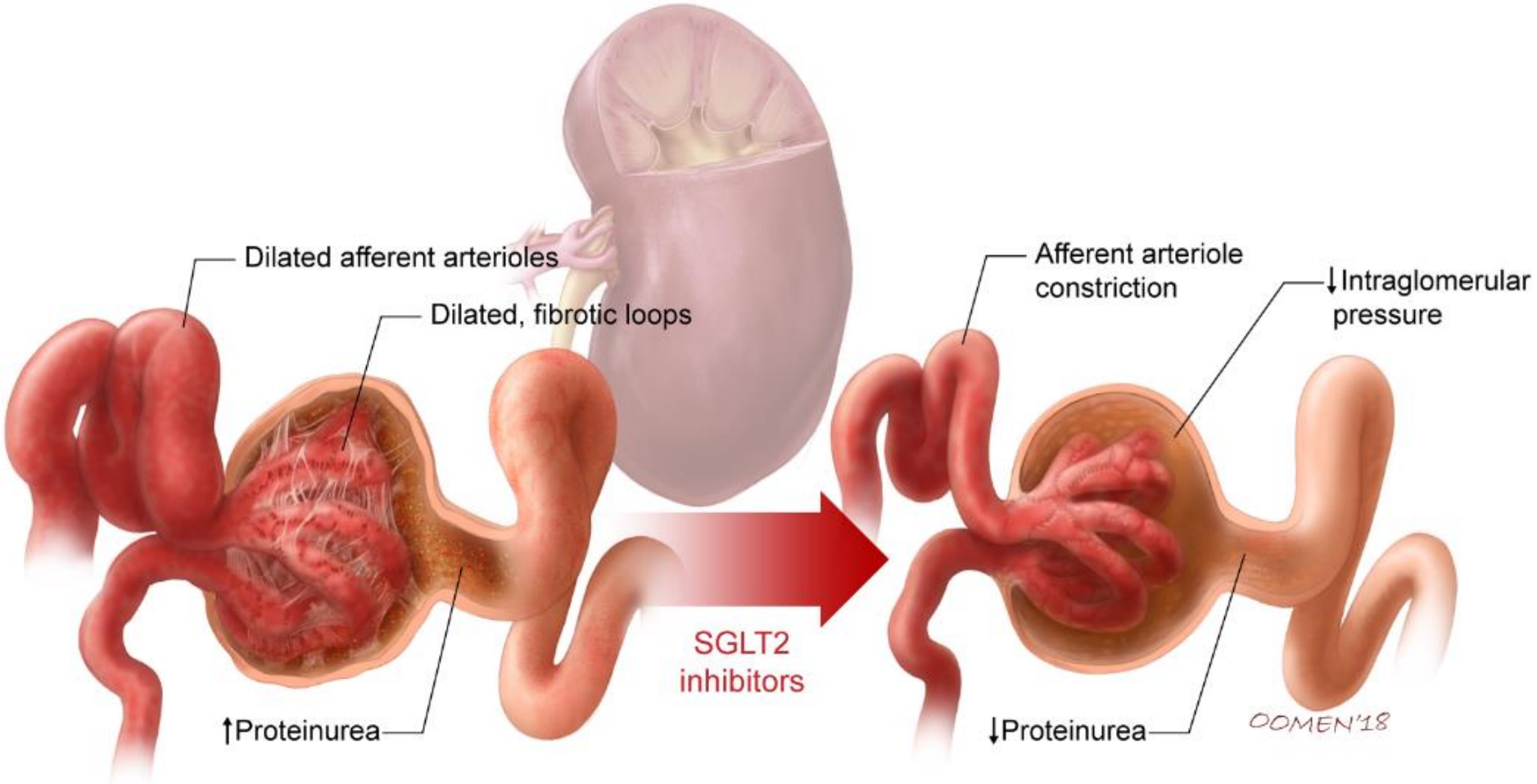
- ↓ Proximal solute reabsorption
- ↓ Energy requirement/utilisation
- ↓ Hypoxia in the kidney



Thomas and Cherney (2018) Diabetologia DOI 10.1007/s00125-018-4669-0

Diabetologia

SGLT2 inhibitors improve ventricular loading conditions



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

A decade of learning on the effects of glucose lowering therapies and ASCVD

1- Targeting multiple risk factors to reduce CV risk in patients with T2DM
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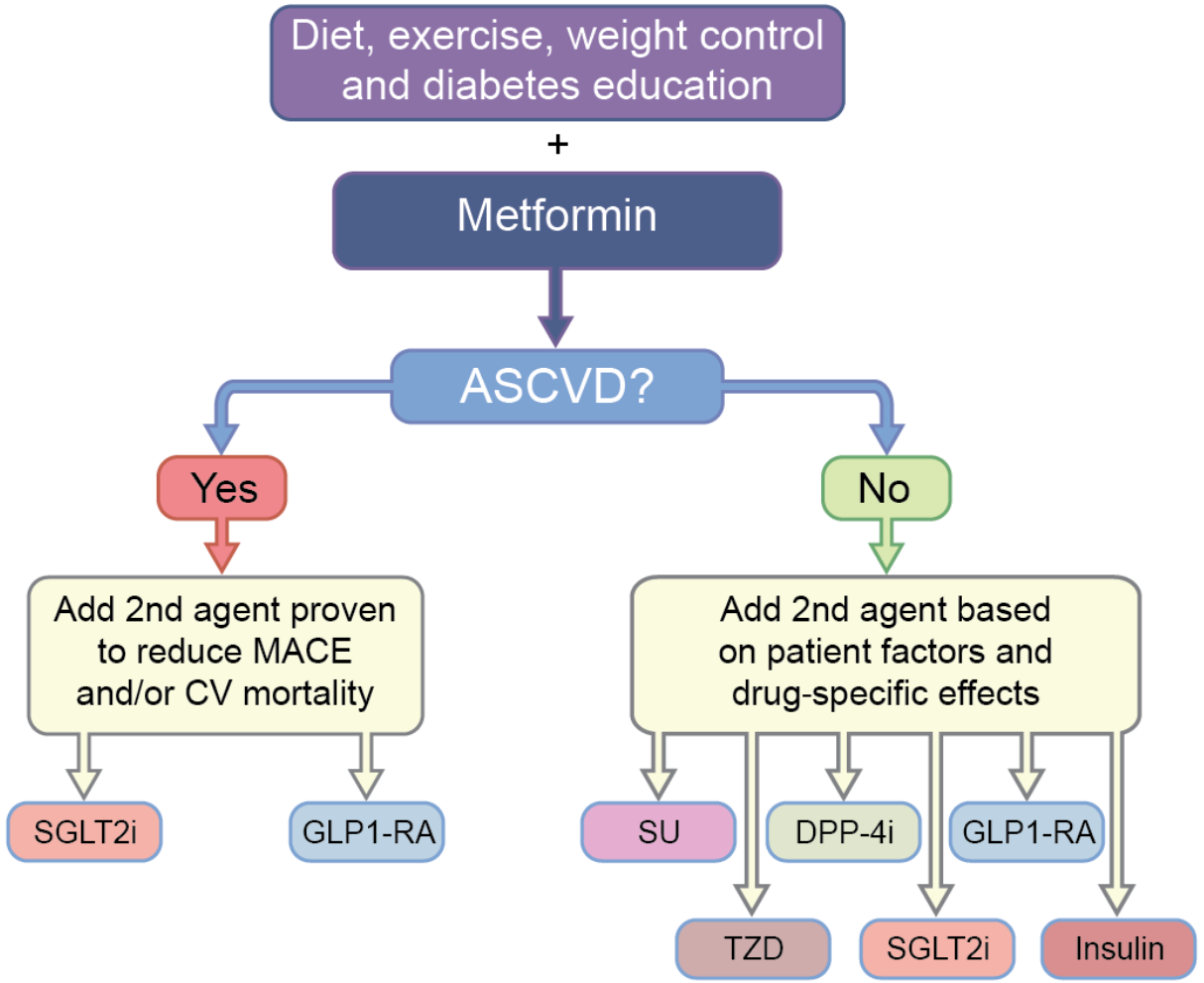
Standards of Medical Care in Diabetes – 2019

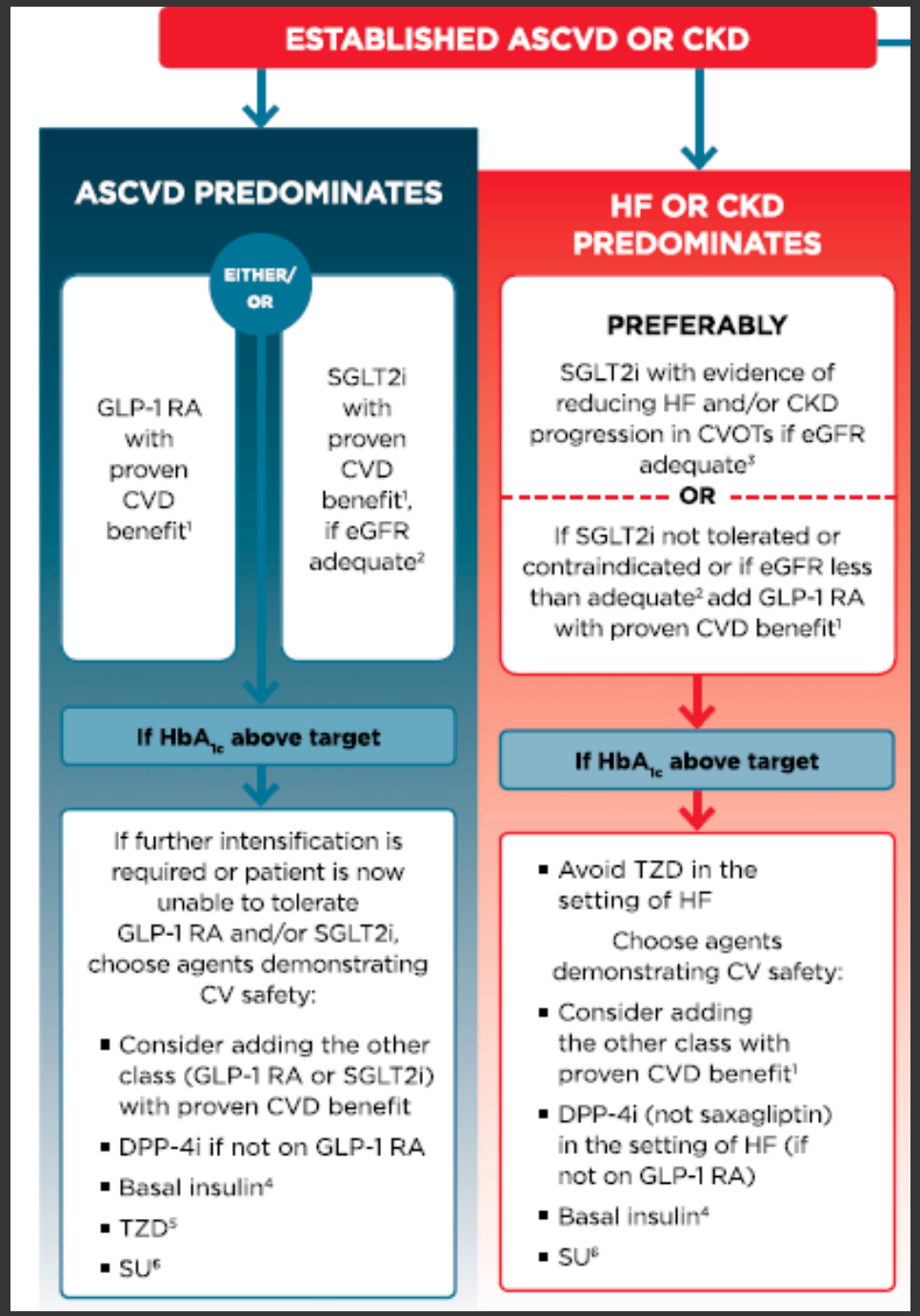
American Diabetes Association®

Summary of latest ADA guidelines for the use of glucose-lowering drugs in individuals with type 2 diabetes in monotherapy and dual combination therapy



Lupsa and Inzucchi (2018) Diabetologia DOI 10.1007/s00125-018-4663-6

Diabetologia



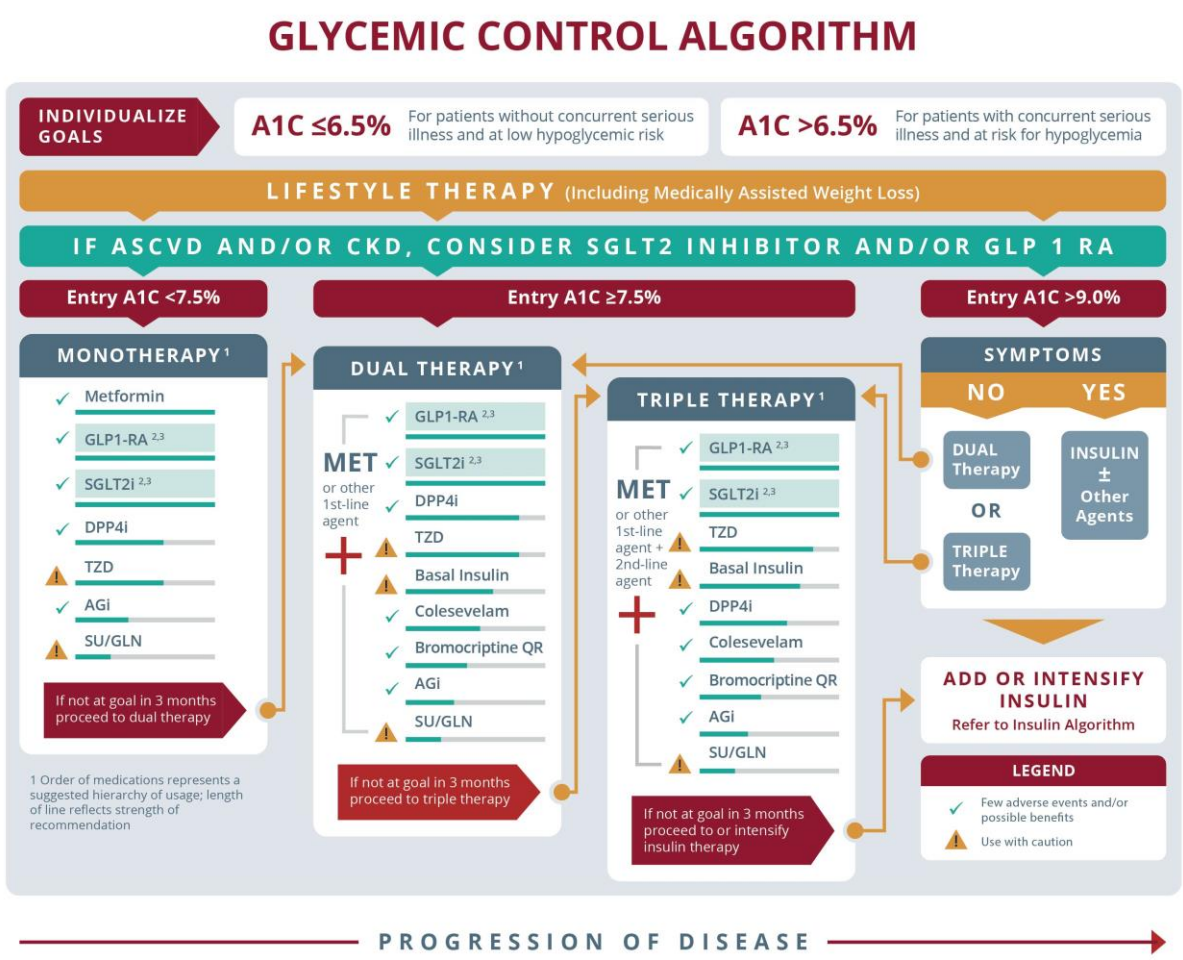
- If A1C is above target despite recommended first-line treatment and the patient has ASCVD or CKD:
  - **ASCVD Predominates:**
    - Add GLP-1 RA with proven CVD benefit, OR
    - Add SGLT-2 inhibitor with proven CVD benefit (if eGFR adequate)
  - **If HF or CKD Predominates:**
    - Add SGLT-2 inhibitor with evidence of benefit
    - If can't take an SGLT-2 inhibitor, use a GLP-1 RA with proven CVD benefit

American Diabetes Association®

2019 AACE Glycemic Control Algorithm

Key principles include:

- Individualized goals
- Inclusion of lifestyle therapy
- Prompt initiation of mono-, dual, or triple therapy (including insulin), based on A1C targets



A1C, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; AGi, alpha-glucosidase inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; GLN, glinides; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SLGT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylureas; TZD, thiazolidinediones.

Garber AJ, et al. *Endocr Pract*. 2019;25:69-90.

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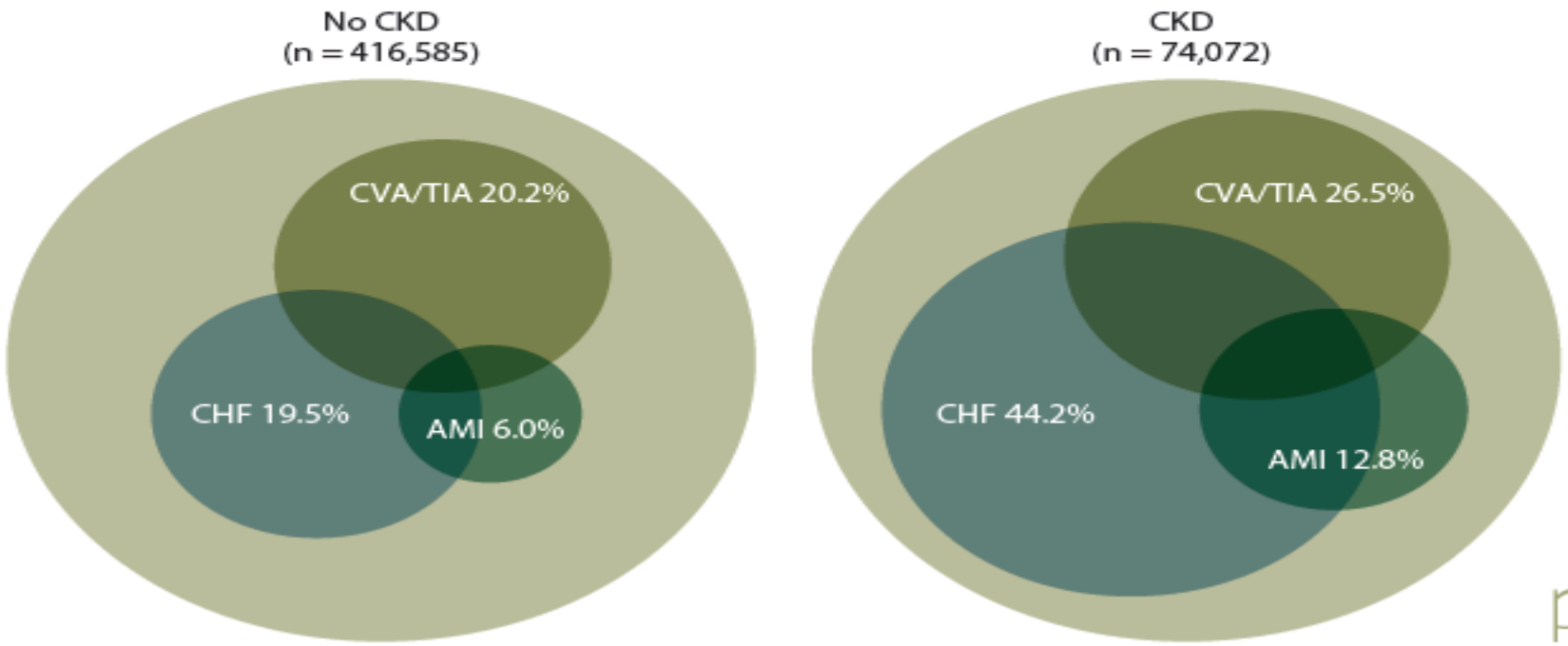
7- SUMMARY/CONCLUSIONS

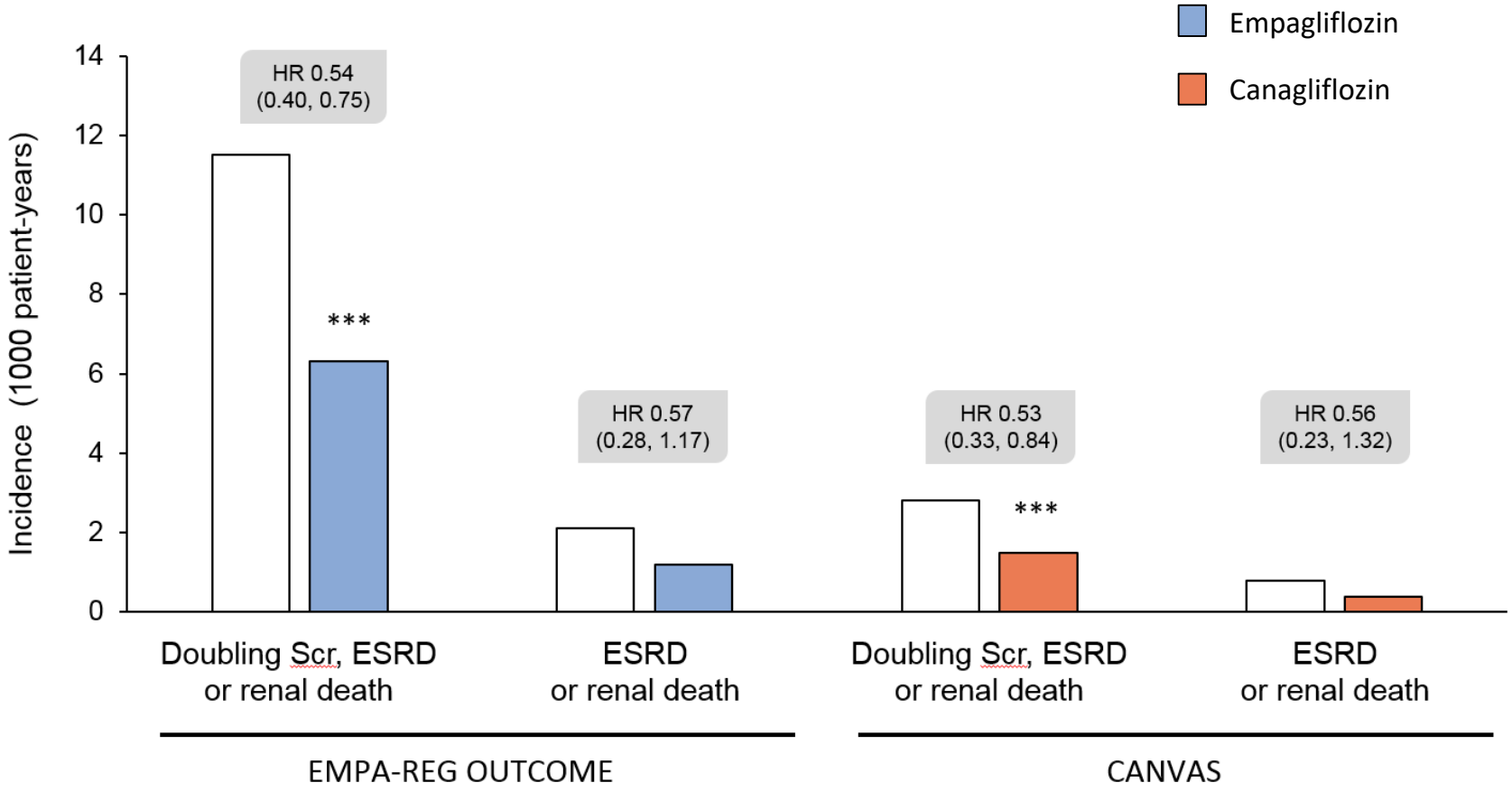
Relative Burden of CVD in General and CKD Populations

>> **Figure 4.1**; see page 125 for analytical methods. *December 31 point prevalent Medicare enrollees age 66 & older, with fee-for-service coverage for all of 2009.*

4.1i Cardiovascular disease in patients with or without chronic kidney disease, 2009



Renal outcomes in the EMPA-REG OUTCOME trial and CANVAS

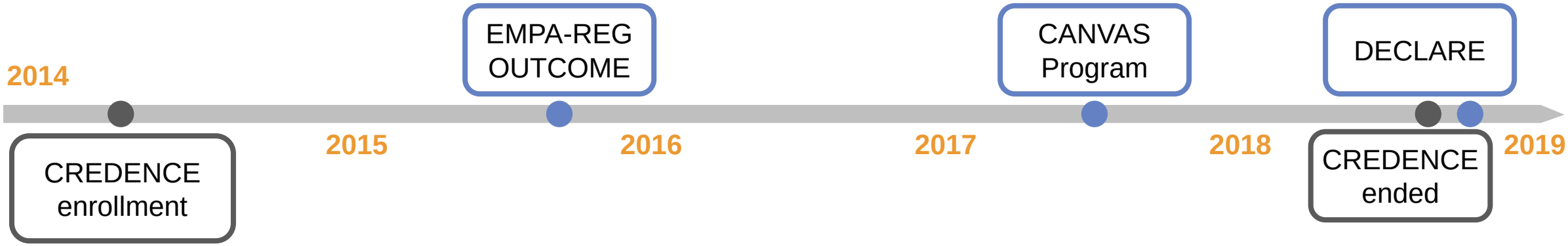


Thomas and Cherney (2018) Diabetologia DOI 10.1007/s00125-018-4669-0

Diabetologia

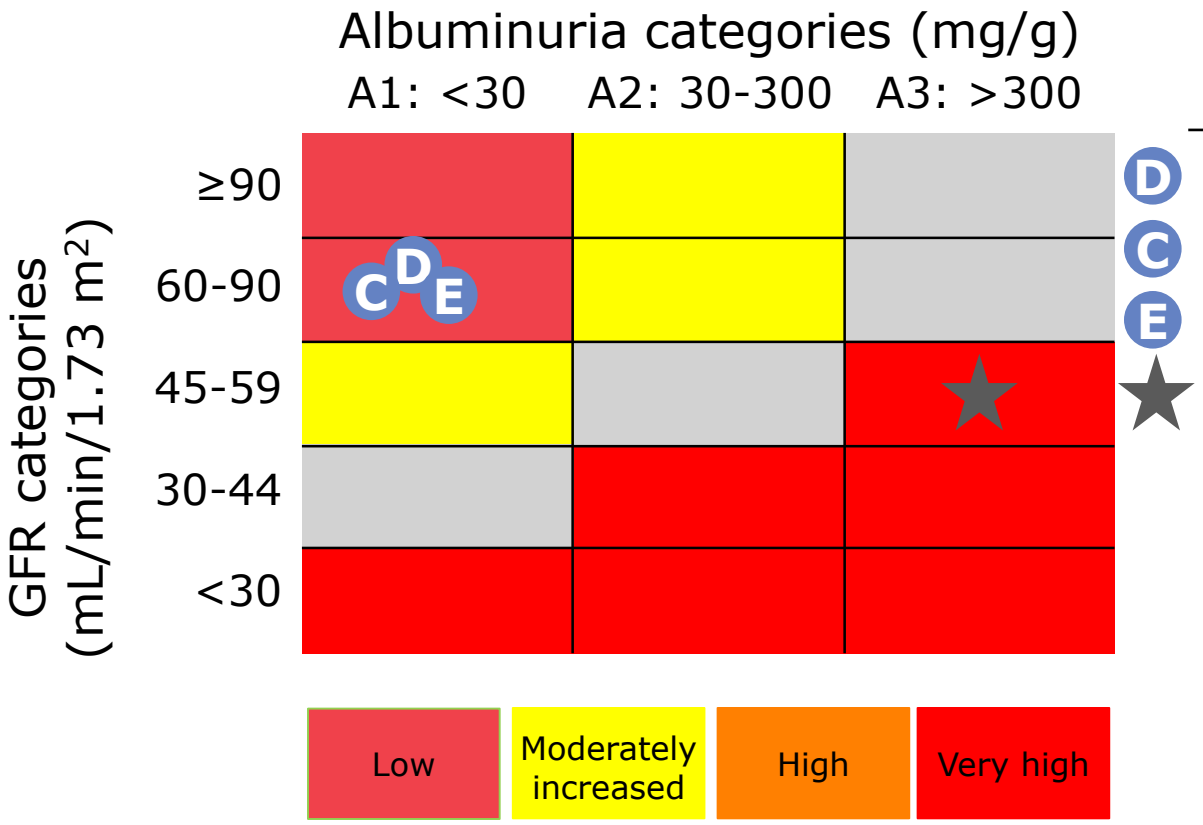
Timeline of Major SGLT2 Inhibitor Trials

- CREDENCE began while SGLT2 inhibitor CV outcomes trials were ongoing



- Renal effects were not the primary focus of the CV outcomes trials

Higher Renal Risk Population in CREDENCE



	Mean eGFR (mL/min/1.73 m²)	MedianU ACR (mg/g)
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18

Sustained RRT Events

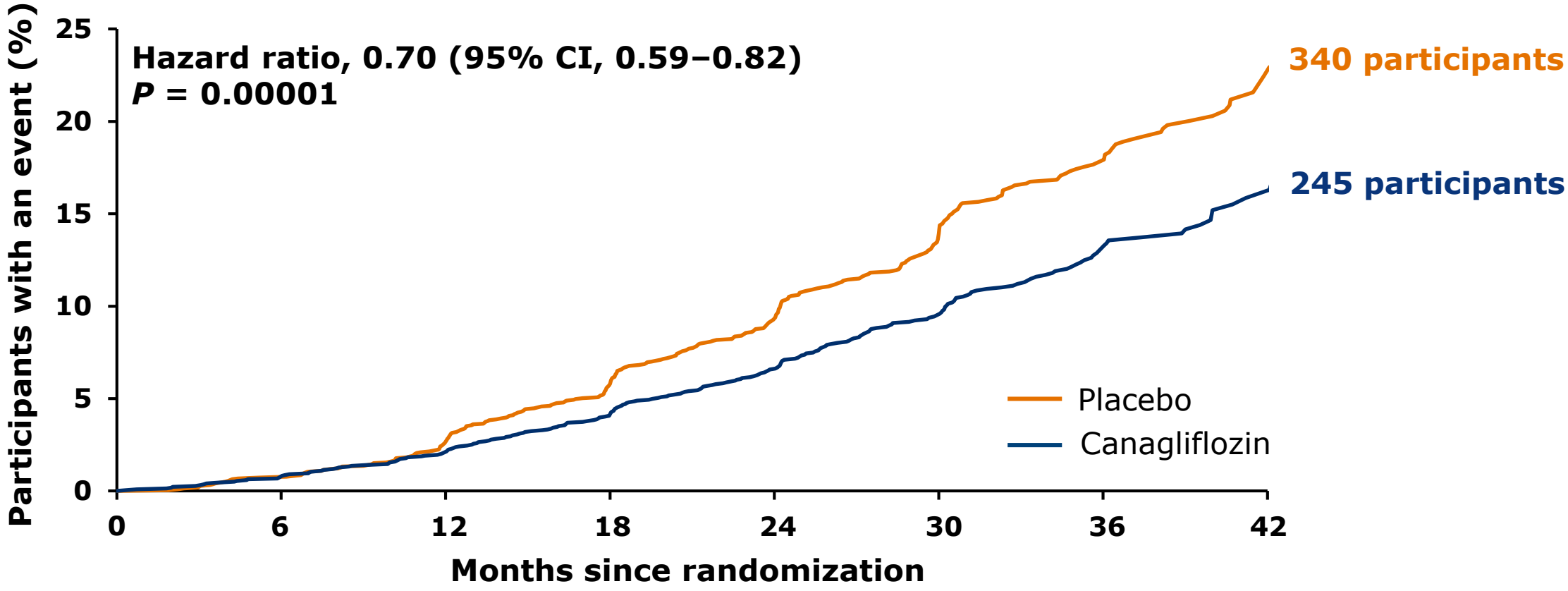
DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

RRT, renal replacement therapy.

Primary Endpoint Definitions

- **ESKD**
  - Chronic dialysis for ≥30 days
  - Kidney transplantation
  - eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment
- **Doubling of serum creatinine**
  - Doubling from the baseline average sustained for ≥30 days by central laboratory assessment
- **Renal death**
  - Deaths in patients who have reached ESKD who die prior to initiating renal replacement therapy and no other cause of death is adjudicated
- **CV death**
  - Death due to MI, stroke, heart failure, sudden death, death during a CV procedure or as a result of procedure-related complications, presumed sudden CV death, death of unknown cause, or death resulting from a documented CV cause other than those listed

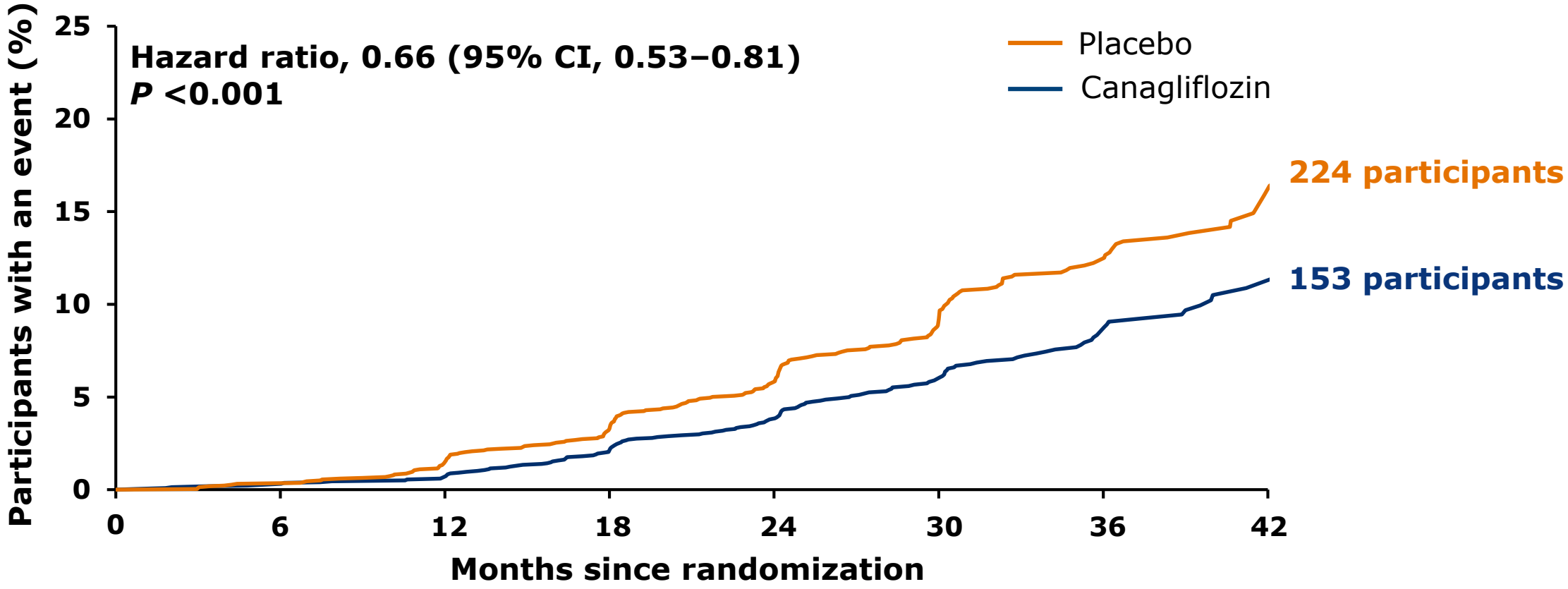
Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

ESKD, Doubling of Serum Creatinine, or Renal Death



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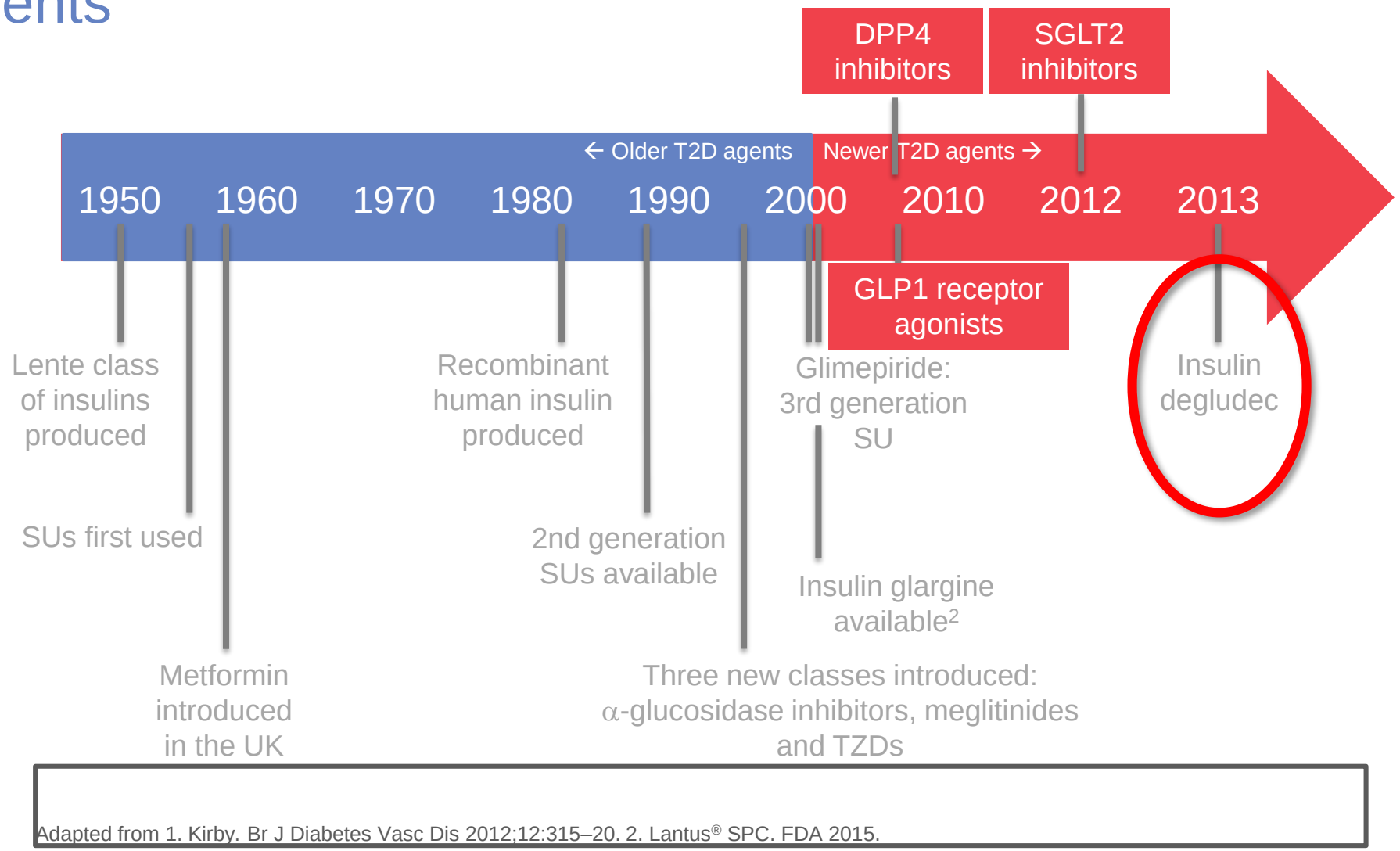
Perkovic V, et al. *N Engl J Med*. 2019. doi: 10.1056/NEJMoa1811744.

Presented at the 79th Scientific Sessions of the American Diabetes Association; June 11, 2019; San Francisco, CA.

CREDENCE

A closer look at CV effects of 21st century T2D agents

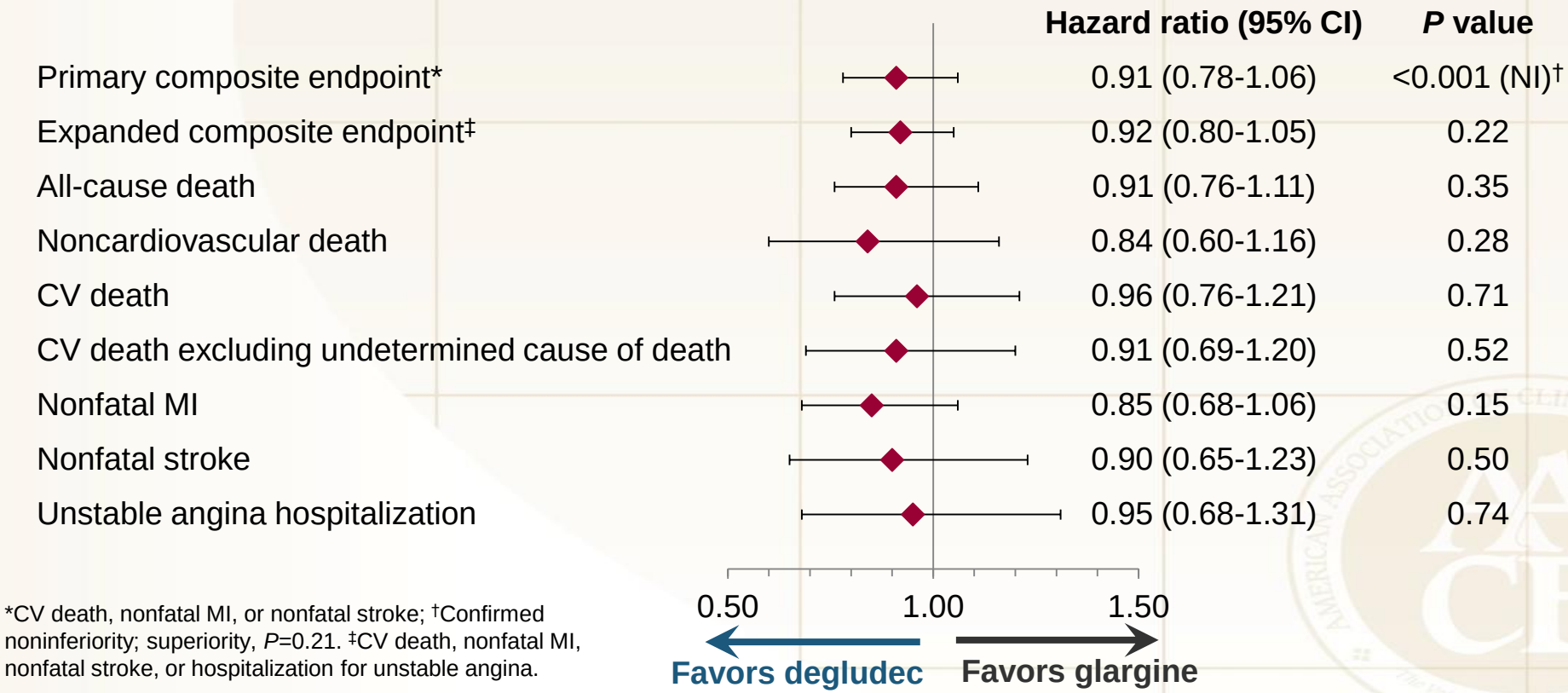


Adapted from 1. Kirby. Br J Diabetes Vasc Dis 2012;12:315–20. 2. Lantus® SPC. FDA 2015.

Clinical Outcomes with Insulin Degludec and Glargine

DEVOTE CV Outcomes (N=7637)

Median follow-up: 1.99 years



*CV death, nonfatal MI, or nonfatal stroke; †Confirmed noninferiority; superiority, *P*=0.21. ‡CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

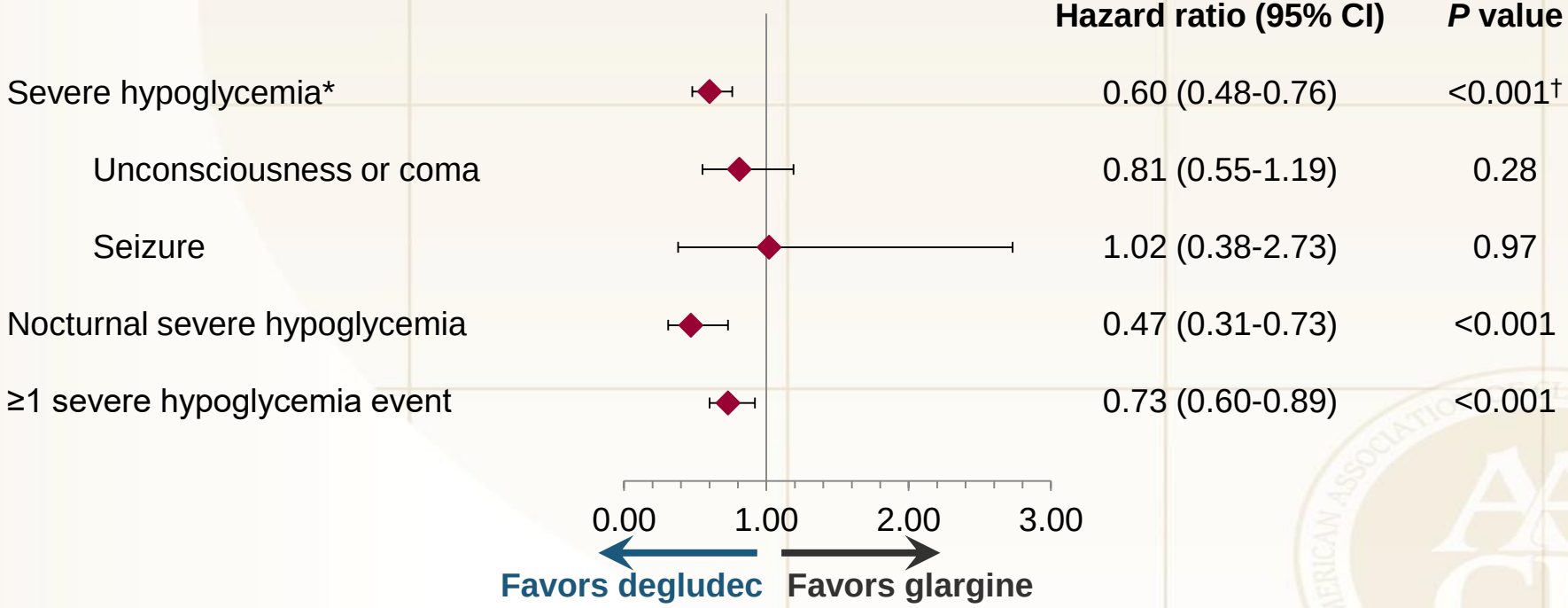
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NI, noninferiority.

Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

Clinical Outcomes with Insulin Degludec and Glargine

DEVOTE Safety Outcomes (N=7637)

Median follow-up: 1.99 years



*Episode requiring assistance from another person to actively administer carbohydrate or glucagon or take other corrective actions.

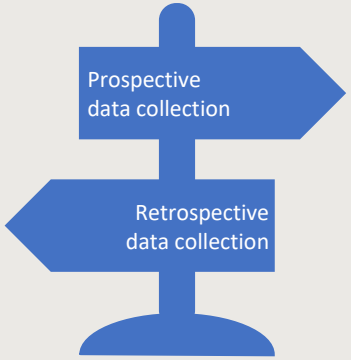
CI, confidence interval.

Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

Randomized Controlled Trials or Real World Evidence?

Real World Data can come from a variety of sources

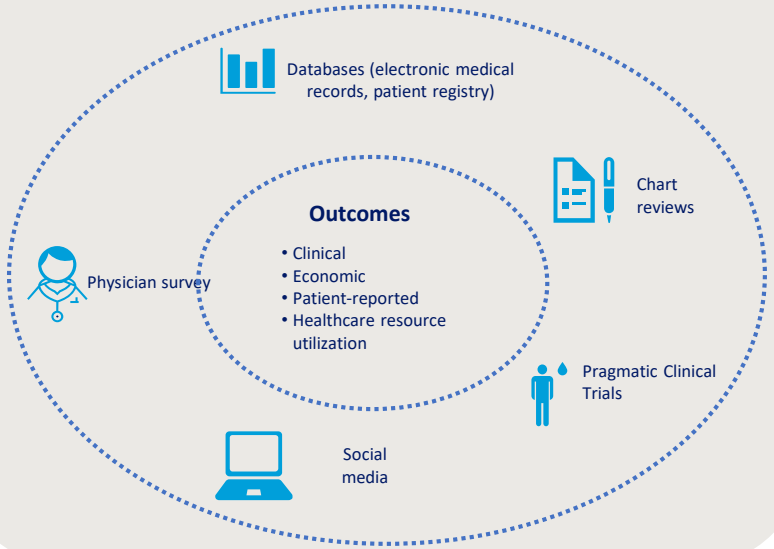
Data collection



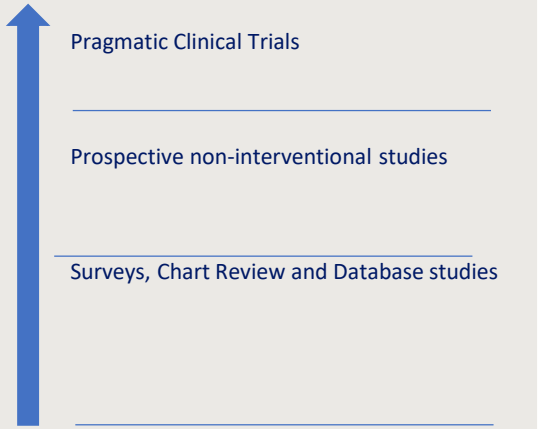
Research purposes:

- Primary data collection
- Secondary use of data

Outcomes and RWD sources



RWE study designs



HCRU, Healthcare resource utilization, PCT, Pragmatic Clinical Trial;
RWD, Real World Data; RWE, Real World Evidence

Observational research on sodium glucose co-transporter-2 inhibitors: A real breakthrough?

TABLE 2 Incidence rates and NNTB/NNTH of the different CV outcomes (exposure to SGLT2-Is), including risk of amputations

	MACE		All-cause mortality		HHF		BKAs	
Study	Incidence rate[a]	NNTB	Incidence rate[a]	NNTB	Incidence rate[a]	NNTB	Incidence rate[a]	NNTH
UK cohort (dapagliflozin vs. non-SGLT2-Is)[16]	1.338[b]	NC	0.527[b]	259	/	/	/	/
Swedish cohort (dapagliflozin only vs. insulin)[17]	1.68	95	0.98	66	/	/	/	/
US cohort (canagliflozin vs. DPP4-Is)[15]	0.99	2523	0.07	5889	0.89	535	/	/
EASEL (SGLT2-Is vs. non-SGLT2-Is)[14]	2.31	55	1.29	62	0.51	158	0.17	743
CVD-REAL (SGLT2-Is vs. non-SGLT2-Is)[10]	0.89	166	0.52	211	0.36	681	/	/
CVD-REAL Nordic (SGLT2-Is vs. non-SGLT2-is)[11]	1.64	206	1.05	76	0.98	220	/	/
CVD-REAL Nordic (dapagliflozin vs. DDP4-Is)[12]	1.86	187	1.03	108	0.99	169	/	/
CVD-REAL 2 (SGLT2-Is vs. non-SGLT2-Is)[13]	1.91	151	0.80	173	1.23	333	/	/
OBSERVE-4D (canagliflozin vs. select non-SGLT2-Is)[24]	/	/	/	/	1.18	58	0.45	NC
OBSERVE-4D (SGLT2-Is vs. select non-SGLT2-Is)[24]	/	/	/	/	0.96	104	0.42	NC

BKAs, atraumatic below-knee lower extremity amputations; DPP4-Is, dipeptidyl peptidase-4 inhibitors; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm. /: not available. NC: not calculated because no statistically significant difference emerged between exposed and unexposed group.

[a] Data expressed × 100 person-years.

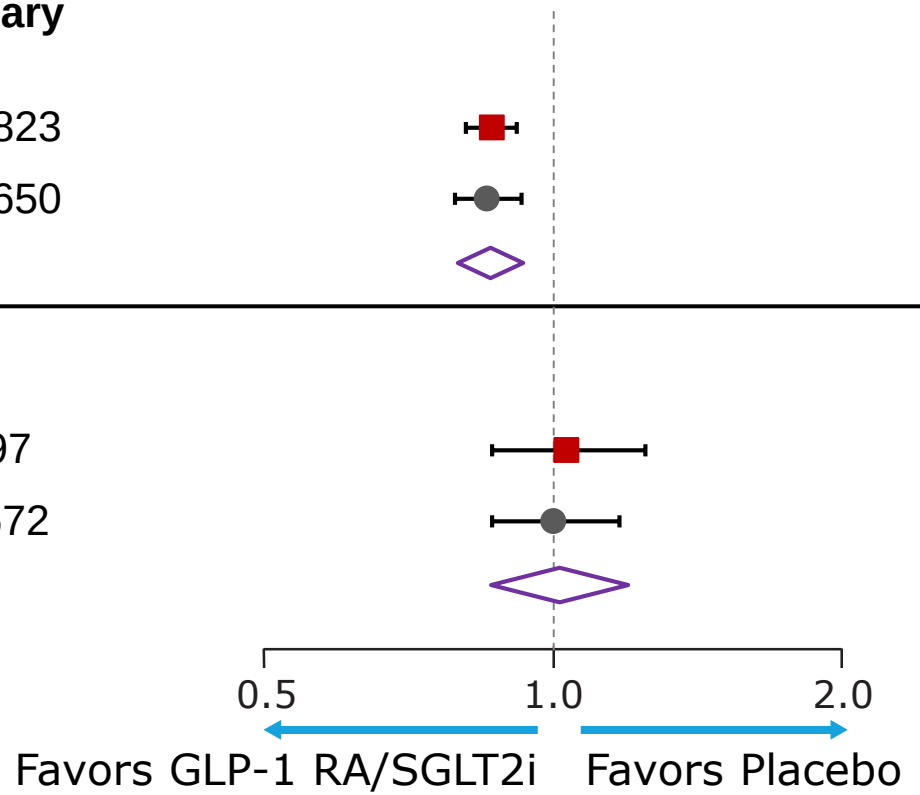
[b] Data for low-risk population (see Table 1 for the definition of MACE, which in this case was defined as incident cardiovascular disease).

A decade of learning on the effects of glucose lowering therapies and ASCVD

1- Targeting multiple risk factors to reduce CV risk in patients with T2DM
2- A turning point: the 2008 FDA Guidance
3- Summary of Current CVOT Findings
- DDP4 *inhibitors*
- SGLT2 *inhibitors*
- GLP-1 *RA*
4- Proposed Mechanisms of CV Protection
5- Impact on Regulatory Agencies and Professional Society Guidelines/Recommendations
6- Lessons learned from other Disease States or Study Designs
7- SUMMARY/CONCLUSIONS

CV Death, MI, or Stroke by CV Disease History in SGLT2 Inhibitor and GLP-1 Receptor Agonist CVOTs

	Events/Patients	Hazard ratio (95% CI)
Patients with atherosclerotic CV disease (secondary prevention)		
GLP-1 receptor agonists	4365/35,823	0.87 (0.82–0.92)
SGLT2 inhibitors	2558/20,650	0.86 (0.80–0.93)
Overall (*P* = 0.002)		0.86 (0.80–0.93)
Patients with multiple risk factors (primary prevention)		
GLP-1 receptor agonists	506/7097	1.03 (0.87–1.23)
SGLT2 inhibitors	754/13,672	1.00 (0.87–1.16)
Overall (*P* = 0.81)		1.01 (0.87–1.19)

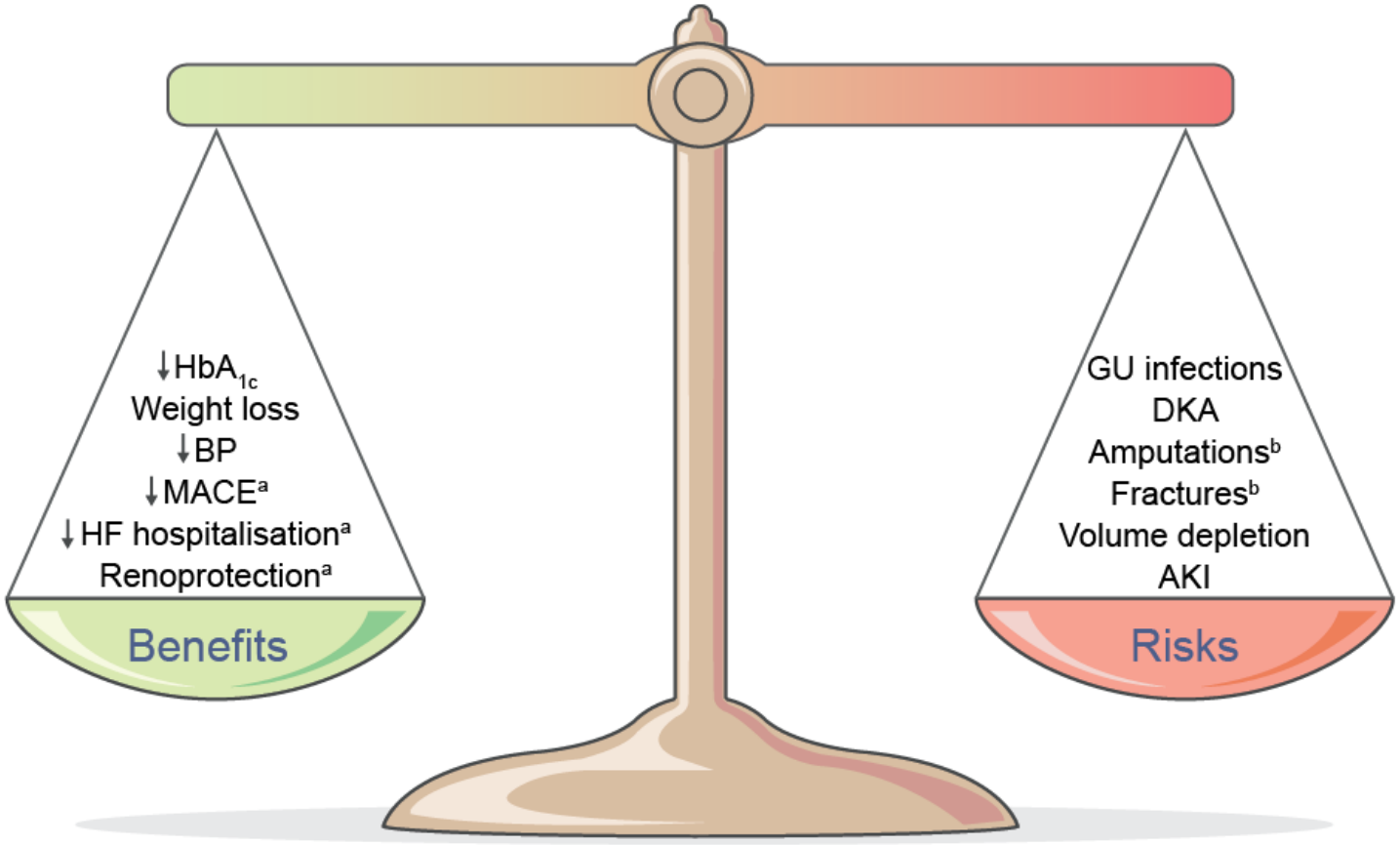


- To date, trials of antihyperglycemic agents for the treatment for T2DM have not shown a CV benefit in participants with CV risk factors (primary prevention)

Zelnicker TA, et al. *Lancet*. 2019; 393(10166):31-39.
Zelnicker TA, et al. *Circulation*. 2019;139(17):2022–2031.

Recognised major risks and benefits of SGLT2 inhibitors

[a]Empagliflozin, canagliflozin
[b]Canagliflozin



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Muchas gracias por su atencion!

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