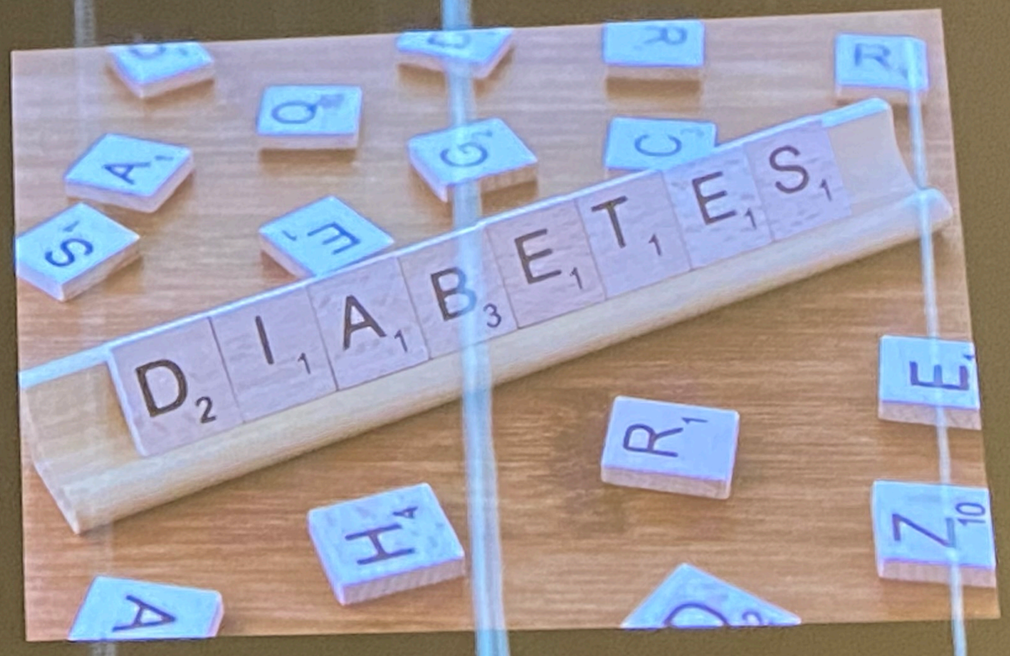
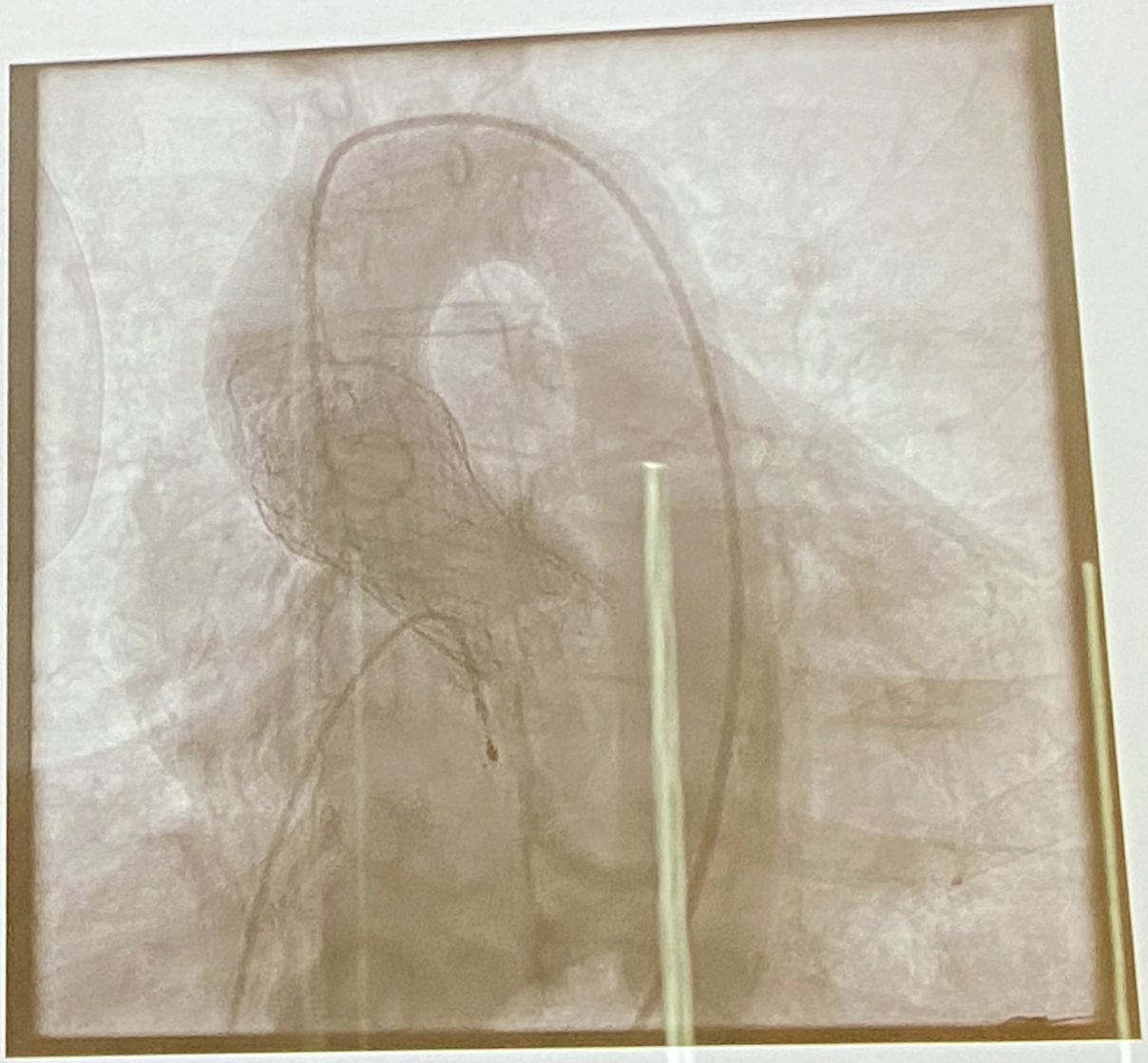
Approach to a patient with Diabetes and Cardiovascular disease. A delicate balancing act

Dr WK Muller
Specialist Physician and Interventional Cardiologist
Life St Georges Hospital
Professional Associate Nelson Mandela University
MBCHB (UCT) FCP (SA) MMED (Int. Med) Cert. Cardiology (SA)



Structural Heart Interventions

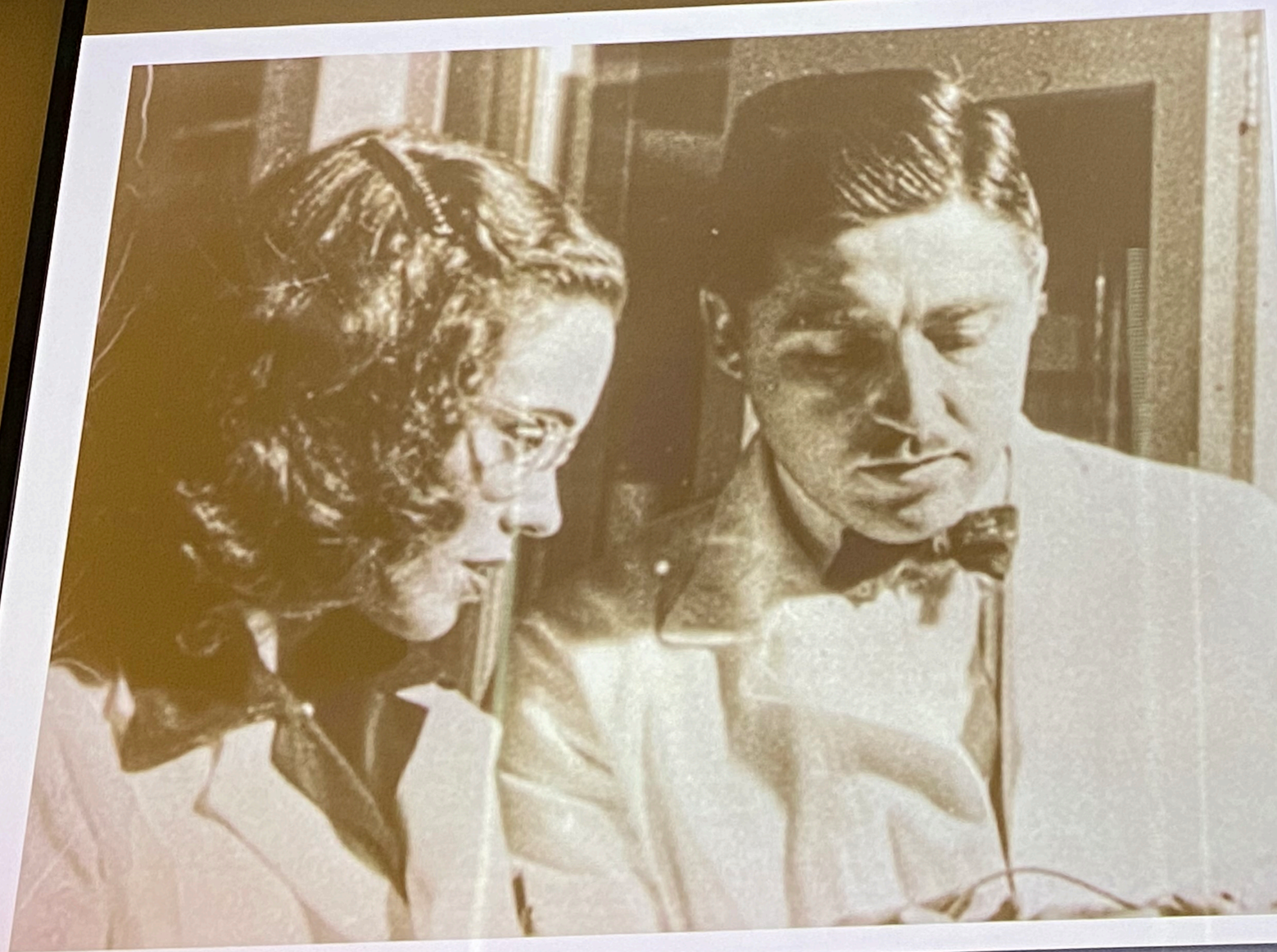
- Aortic Valve Interventions: TAVI (Transcatheter Aortic Valve Implantation
- Stroke Prevention (LAA occlusion, ASD, PFO closure)
- Hypertension (Aortic coarctation interventions, renal denervation)
- CTO's
- Pulmonary Interventions (PE aspiration, angioplasty, pulmonary valve replacements, AVM plugging)





History of Diabetes

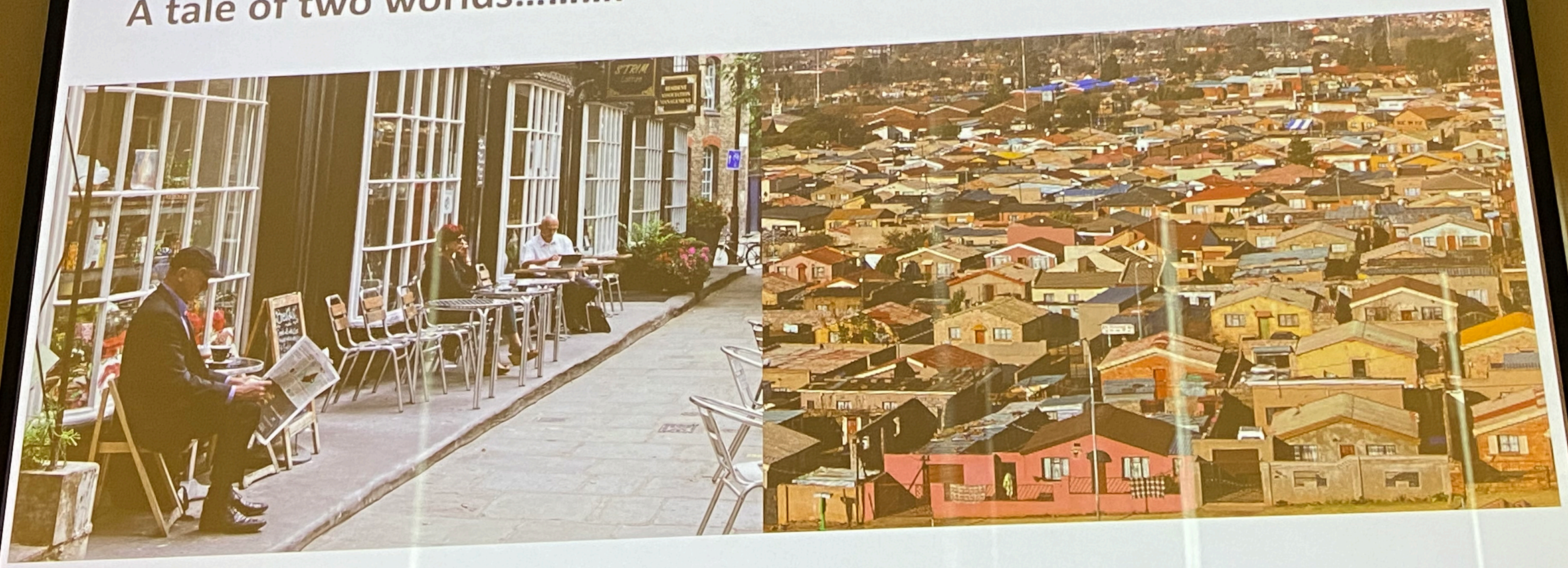
- First described 3000 years ago by ancient Egyptians
- Diabetes coined by Araetus Cappodocia 81-133 AD
- Thomas Willis (1675) -Mellitus (sweet Honey)



- Helen M. Free and Alfred Free

- Inventors of the urine dipsticks

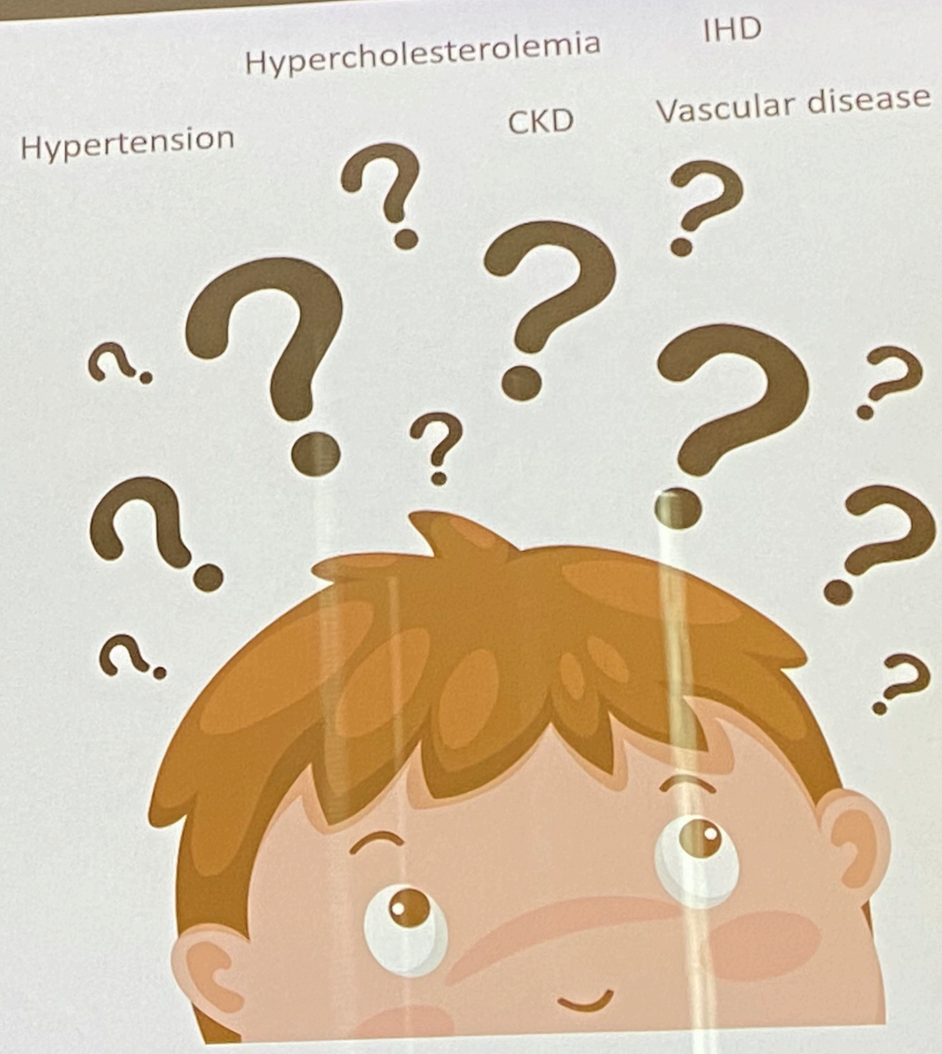
A tale of two worlds.....



Unequal access to healthcare

Questions?

- Which agents to choose?
- Managing cardiovascular targets in diabetes/ classifying risk
- Is HBA1C the bee all and end all in diabetes





Diabetic Patients

- Private vs state funded patients
- Identify residual risk factors contributing to cardiovascular disease
- Multidisciplinary team to control diabetes
- Barriers to healthcare

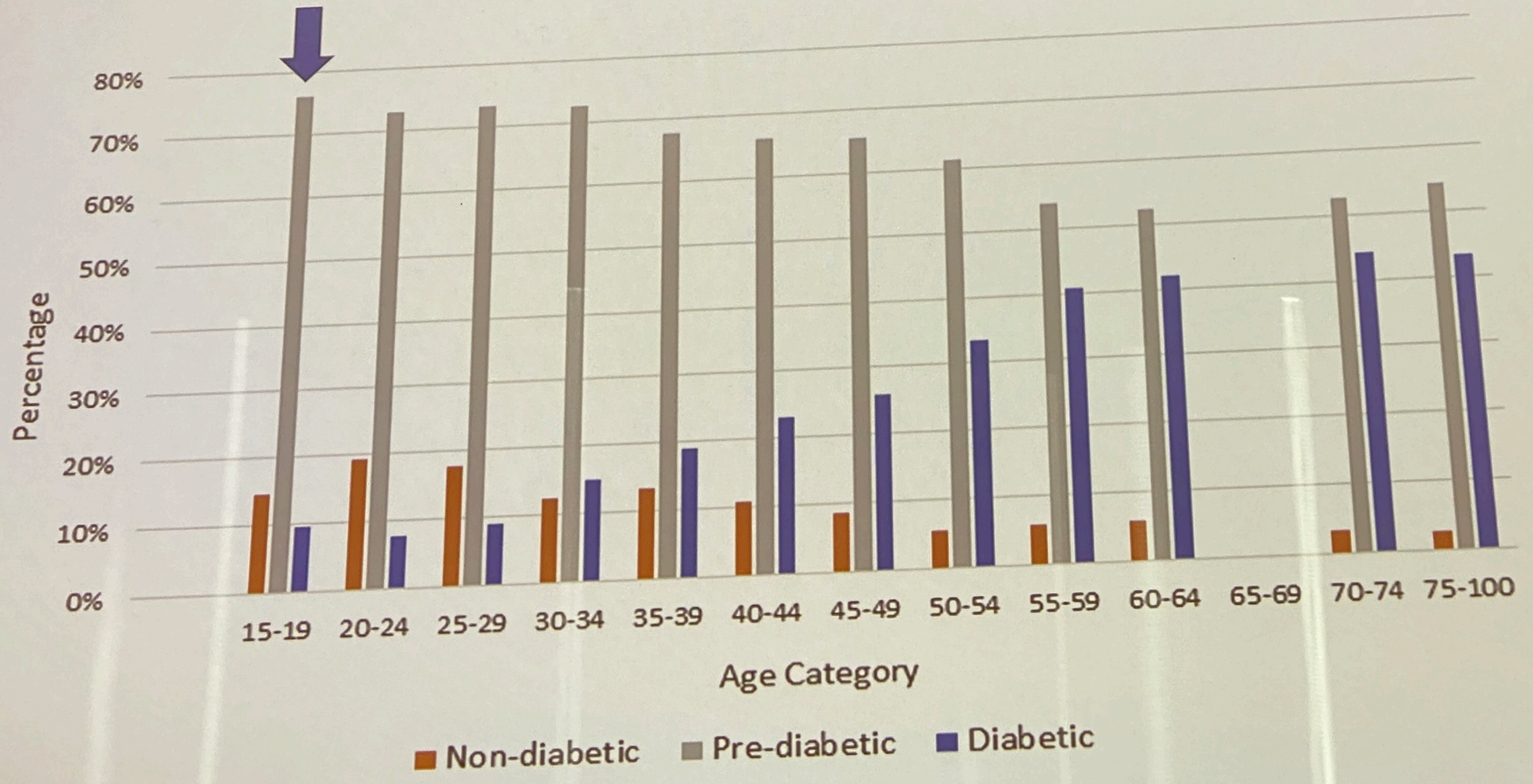
Mentimeter Code

- Menti.com
- 52918851

Diabetic Medications

- Metformin
- Sulphonylureas
- DPP4 inhibitors
- GLP1 agonist
- SGLT 2 inhibitors

Prevalence of Diabetes in South Africa



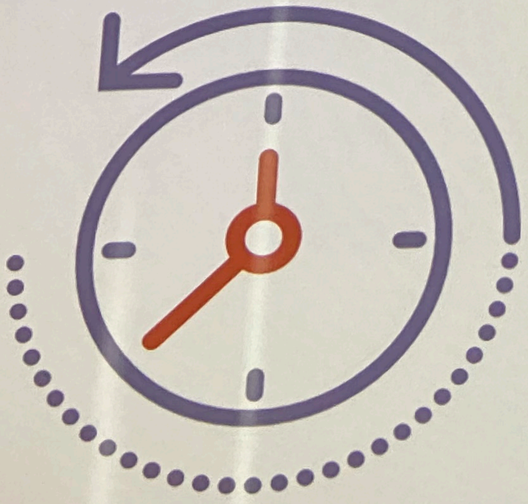
Grundlingh, N., Zewotir, T.T., Roberts, D.J. *et al.* Assessment of prevalence and risk factors of diabetes and pre-diabetes in South Africa. *J Health Popul Nutr* **41**, 7 (2022). https://doi.org/10.1186/s41043-022-00281-2

CV disease occurs early and is the leading cause of mortality in patients with T2D

CV disease can occur

10–15 years earlier

in patients with diabetes compared with those without diabetes[1]



Despite advances in standard of care, most patients with T2D

die from CV disease[2]

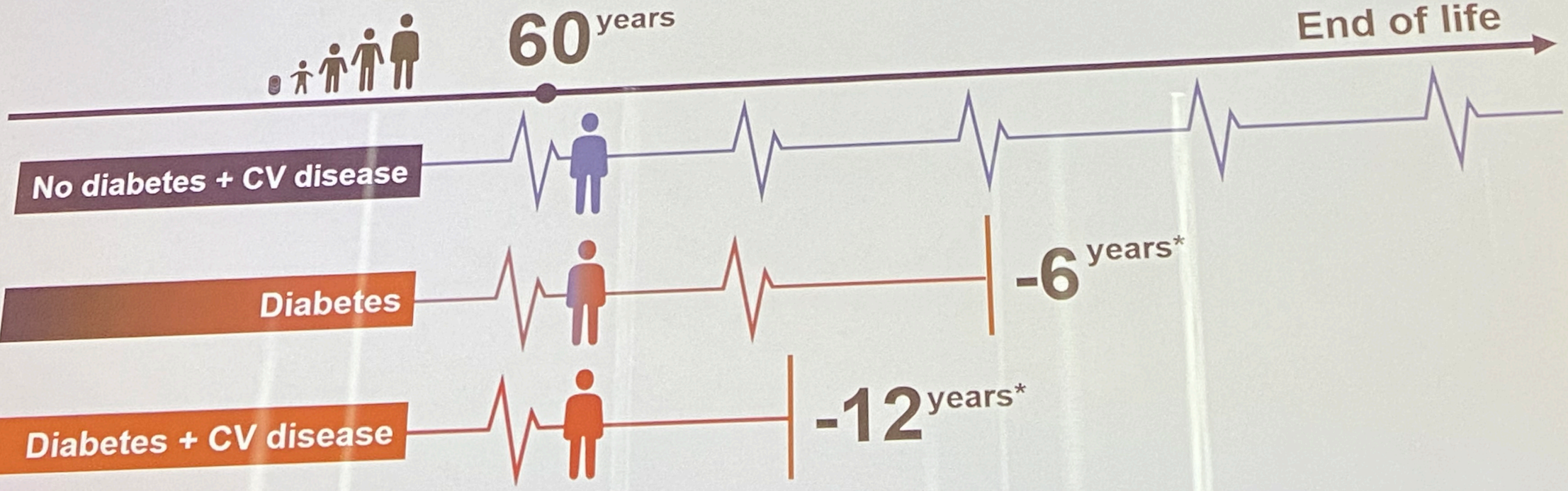


ovascular; T2D, type 2 diabetes

GL *et al. Lancet* 2006;368:29; 2. Morrish NJ *et al. Diabetologia* 2001;44(Suppl 2):S14

Life expectancy is reduced by ~12 years in patients with diabetes and CV disease

A 60-year-old patient with diabetes and CV disease dies, on average, 12 years earlier than a person without diabetes and CV disease



In this case, CV disease is represented by MI or stroke
**Average for men and women*
CV, cardiovascular; MI, myocardial infarction
The Emerging Risk Factors Collaboration. JAMA 2015;314:52

T2D is a CV risk factor that determines the need for cardioprotection



*Patients with **diabetes and at least one other CV risk factor or target organ damage**, should be **considered at very high CV risk**…*

2016 European Guidelines on cardiovascular disease prevention in clinical practice
– *European Society of Cardiology*

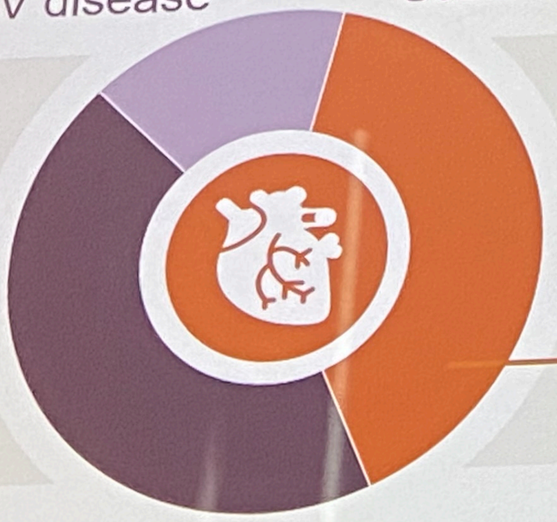
EUROPEAN SOCIETY OF CARDIOLOGY®

CV, cardiovascular; T2D, type 2 diabetes
Piepoli MF *et al. Eur Heart J* 2016;37:2315

CV disease is frequently asymptomatic and unrecognised

16%
No CV disease

44%
Subclinical CV disease



40%
Clinical CV disease

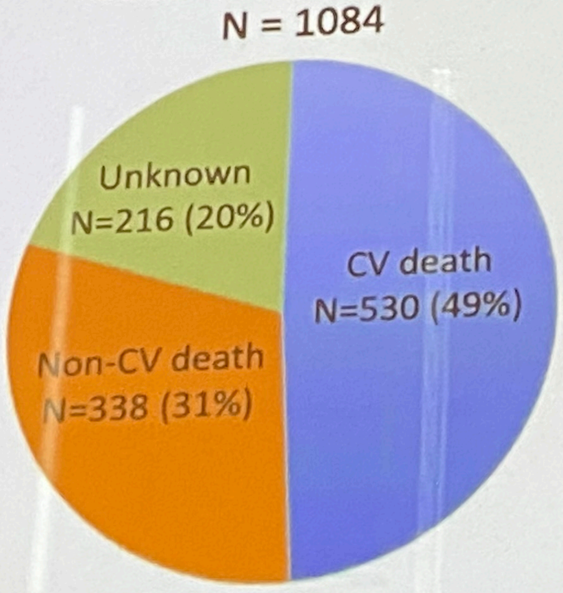
Almost half of patients with diabetes have **subclinical CV disease***

Prevalence of subclinical CV disease across 1343 patients with diabetes aged ≥65 years in the US
**Absence of prevalent clinical disease at baseline: ankle–brachial index ≤0.9, internal carotid artery wall thickness >80th percentile, common carotid artery wall thickness >80th percentile, carotid stenosis >25%, major electrocardiogram abnormalities (based on the Minnesota code), and a Rose Questionnaire positive for claudication or angina pectoris in the absence of clinical diagnosis of angina pectons or claudication*
CV, cardiovascular
***Kuller LH et al. Arterioscler Thromb Vasc Biol* 2000;20:823**

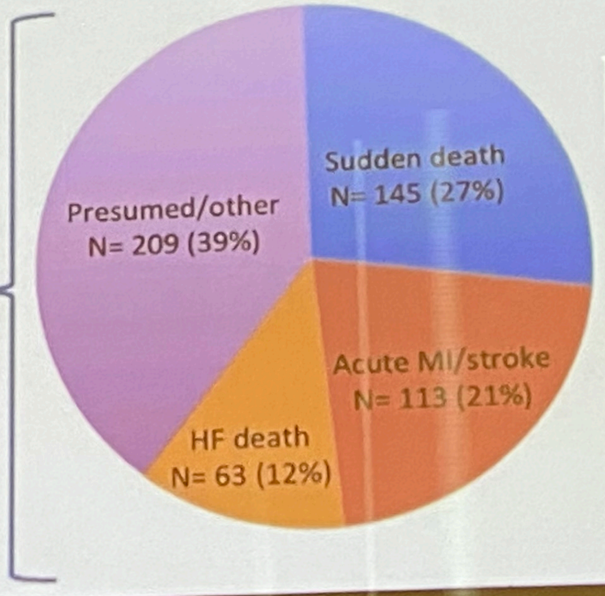
Causes of Death in Type 2 Diabetes

Distribution of Causes of Mortality

Overall causes of death
N = 1084

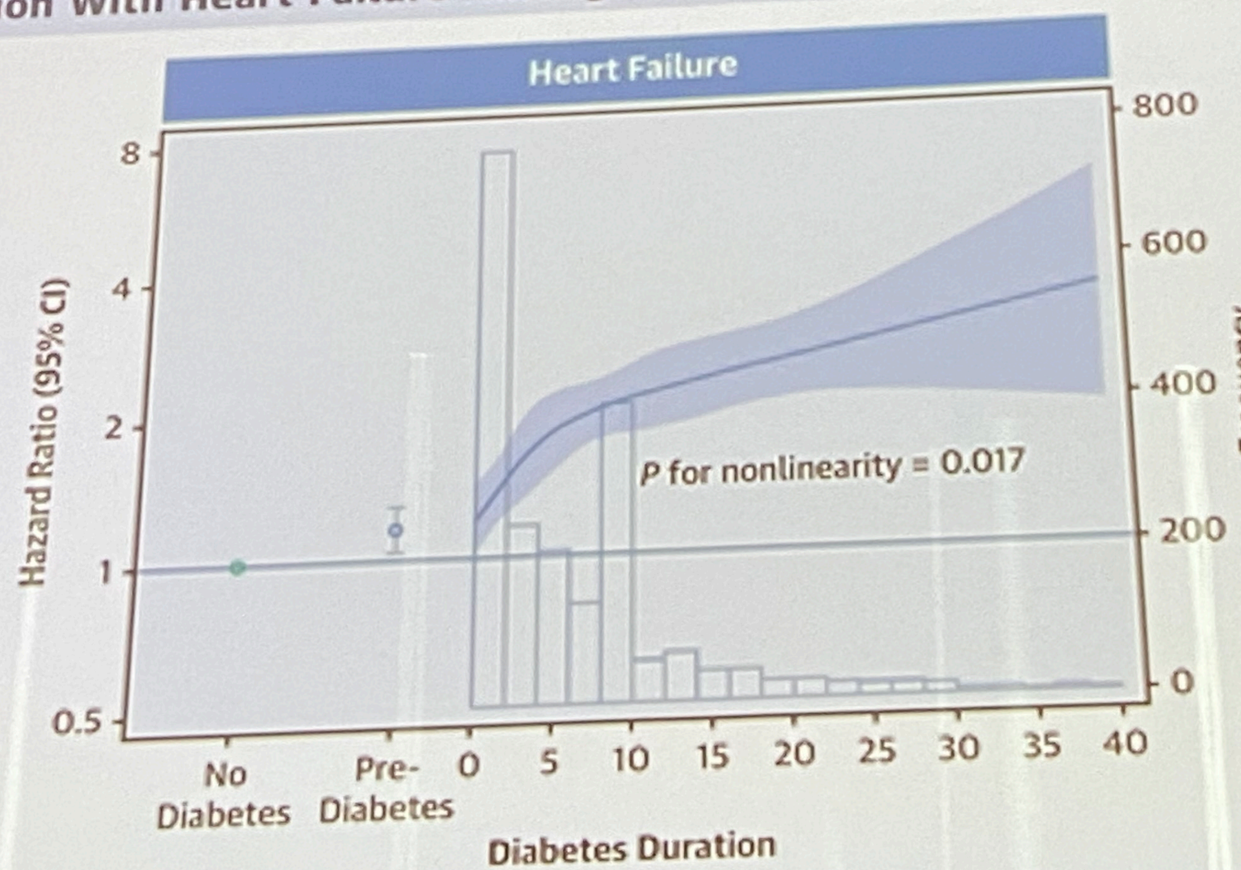


Cardiovascular death
N = 530



Data from the TECO study

CENTRAL ILLUSTRATION: Restricted Cubic Splines of the Diabetes Duration Association With Heart Failure Among Individuals With Diabetes



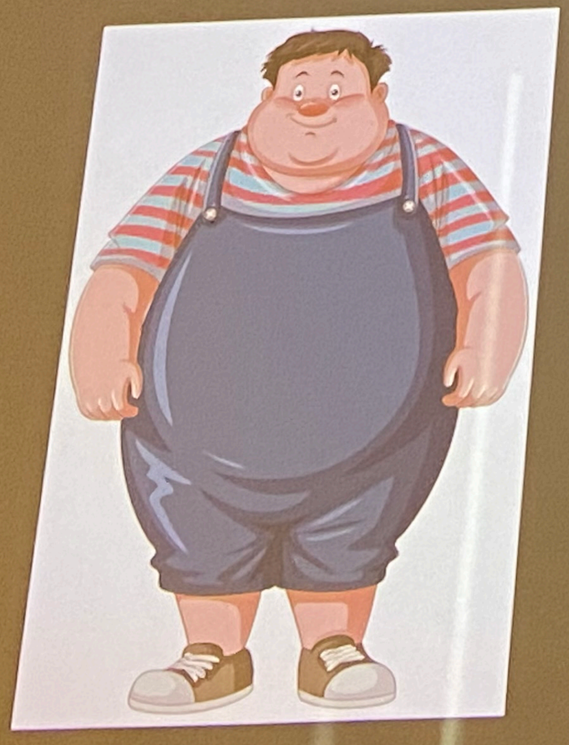
Echouffo-Tcheugui, J.B. et al. J Am Coll Cardiol HF. 2021;9(8):594-603.

Guess the price?

Metformin:	R68
Gliclazide	R85
Dapagliflozin	R302
Semaglutide	R2563



Clinical Case



- 46-year-old-gentlemen, presents with a stable angina

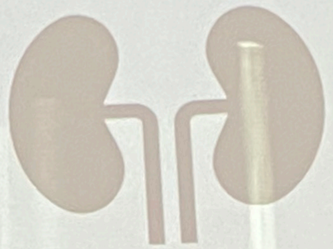
- **CVRF**
  - Hypertension
  - Type 2 Diabetes
  - Hypercholesterolemia

- **Chronic Medications**
  - Metformin 500 mg po bd
  - Gliclazide MR 60 mg po daily
  - Aspirin 100 mg po daily
  - Atorvastatin 10 mg po nocte

- HBA1C 8.5%
- LDL 4.9 mmol/l

1st Step





Risk Stratify all cardiac patients

Co-morbidities

Risk Stratification

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

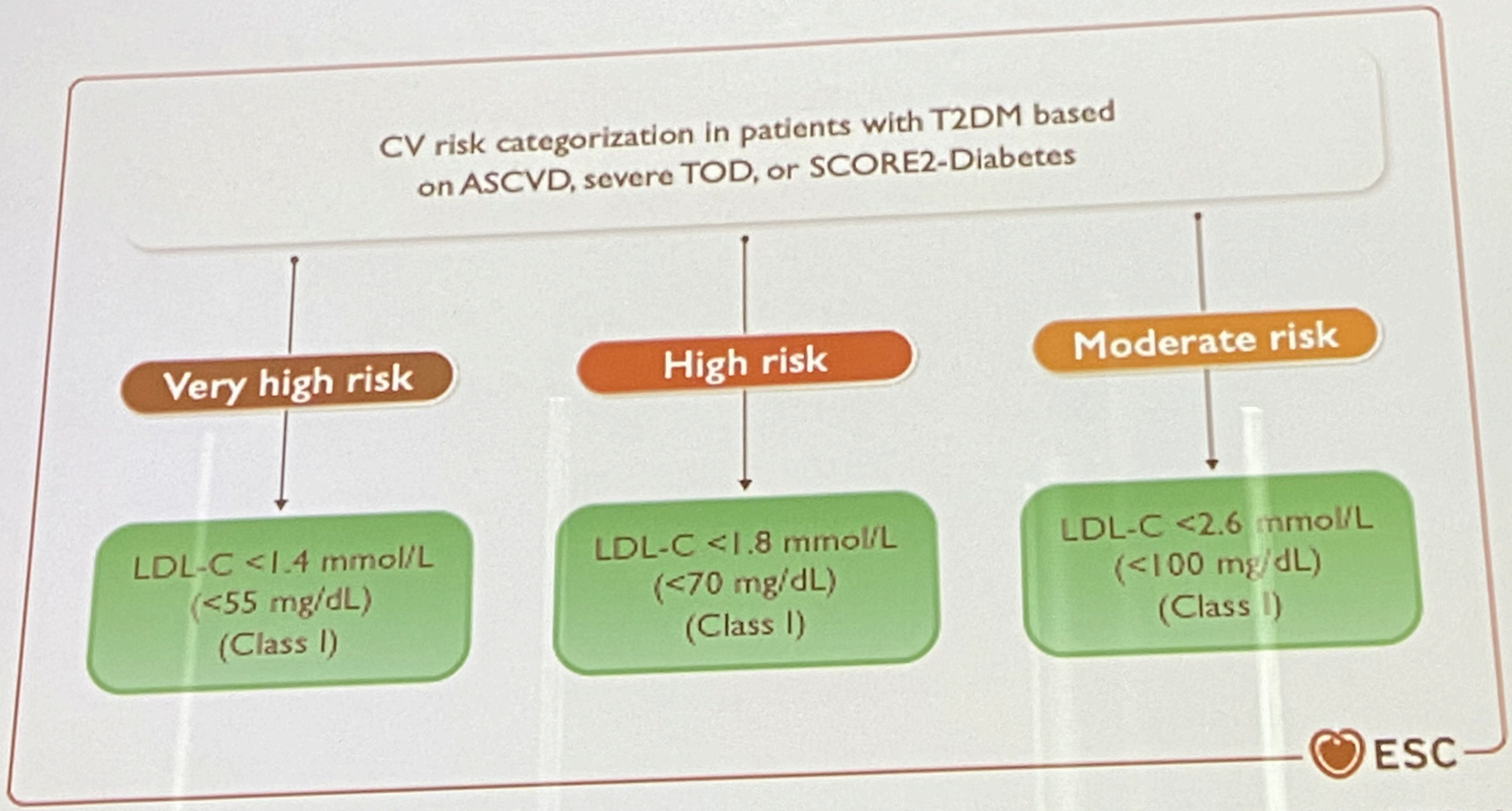


Figure 10 *Recommended low-density lipoprotein-cholesterol targets by cardiovascular risk categories in patients with type 2 diabetes. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol; TOD, target-organ damage; T2DM, type 2 diabetes mellitus.*

Diabetes and the Heart

- Extensive coronary atherosclerosis/calcification
- Multiple co-morbidities (hypercholesterolemia)
- Heart failure (1% increased in HBA1C, 8% increase in HF)
- Higher risk of no-reflow phenomenon
- Higher rate of stent thrombosis



Heart Failure Classification 2021

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

© ESC 2021

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

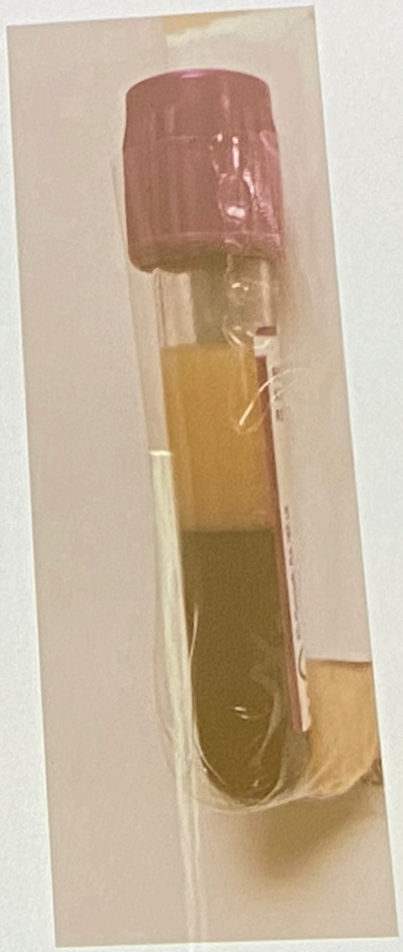
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

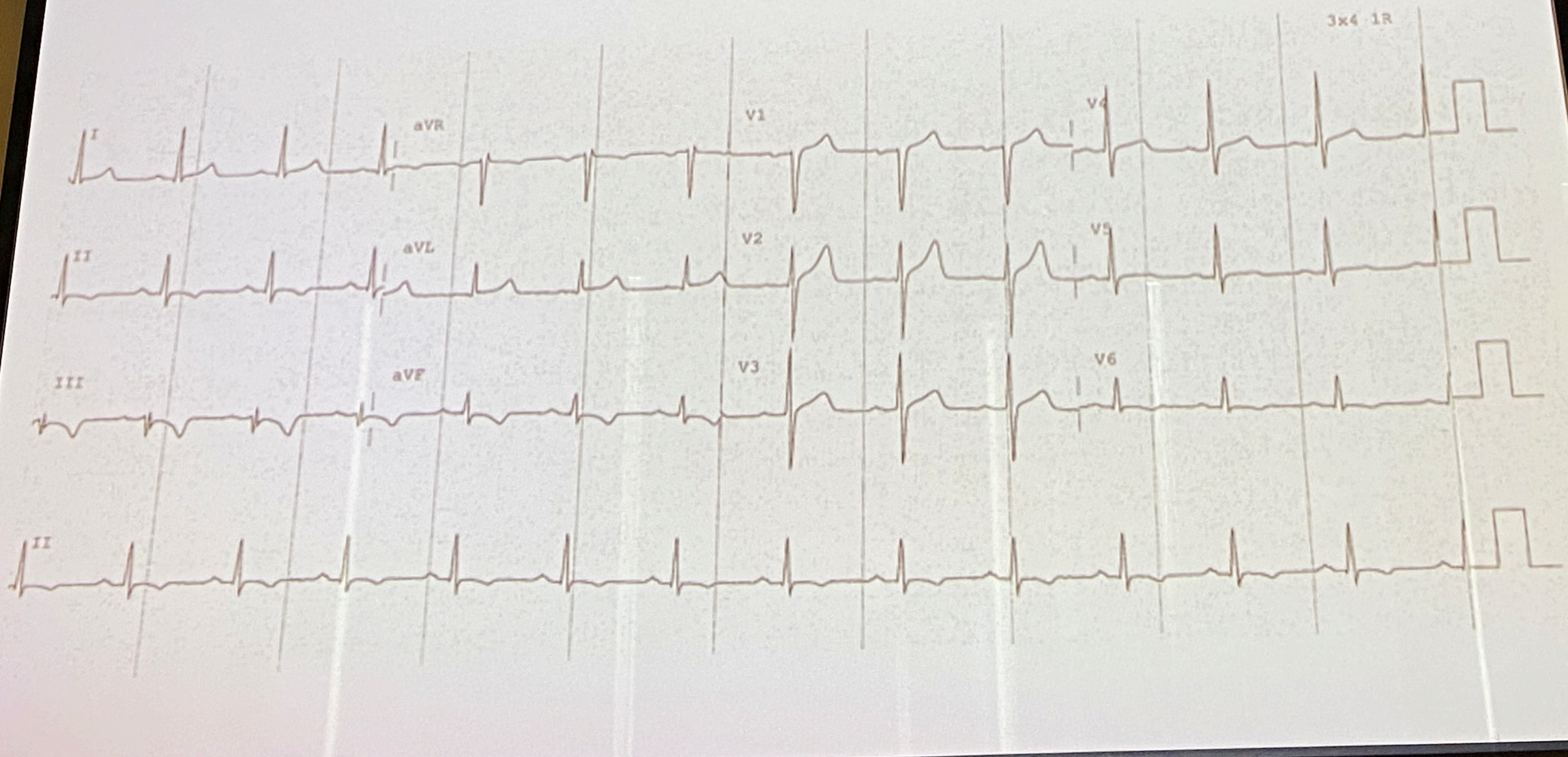
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Clinical Scenario

- 52-year-old-gentlemen, presents with a chest pain
- Type 2 diabetes (HBA1C 9%)
- Hypertension
- Smoker




3x4 1R
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Blood Results

LIPOGRAM				
Cholesterol Total	*H	17.5	2.8-4.9	mmol/l
Triglycerides	*H	24.9	0.5-1.6	mmol/l

HBA1C = 9%

? How would we choose a drug to improve

- Reduce MACE (death, myocardial infarction, stroke



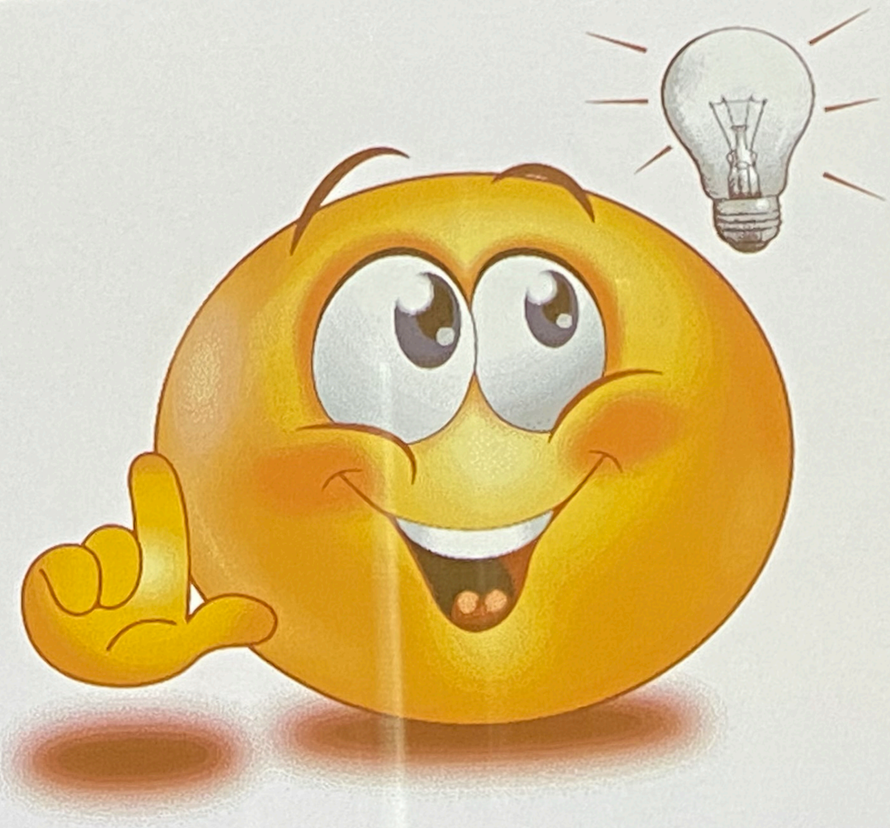
Question

- When choosing diabetic agents in patients with CVD, what are the important targets?

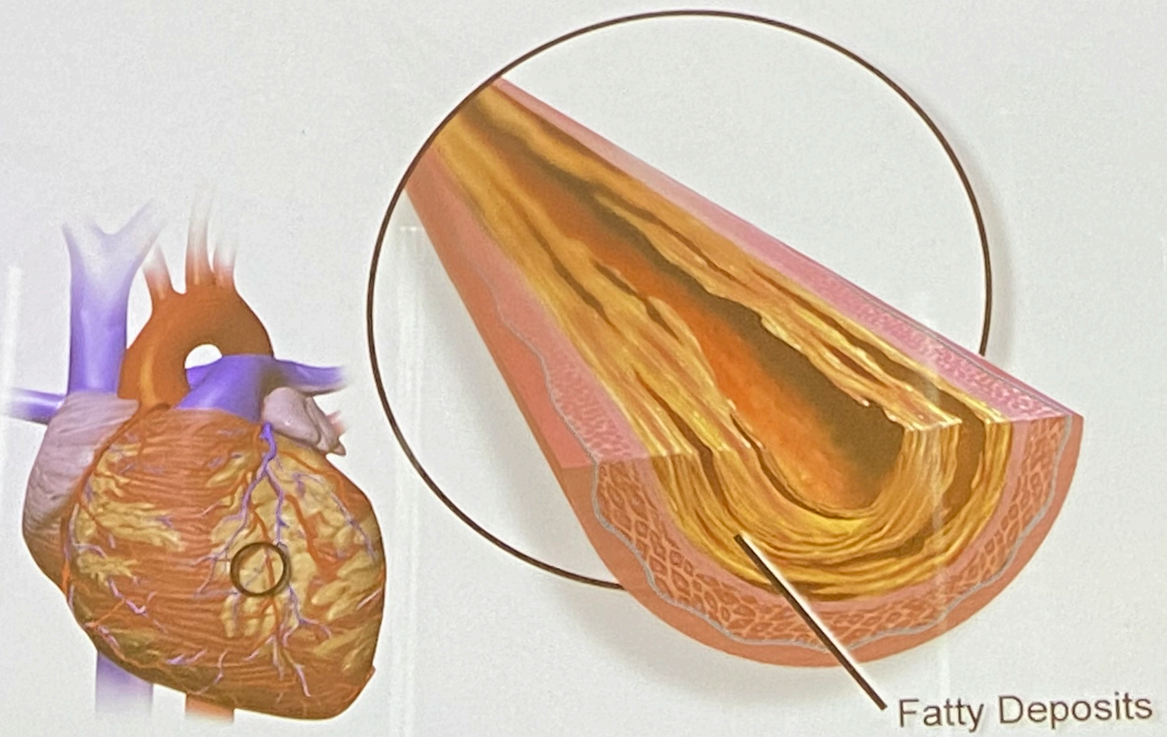
- A: Reducing HBA1C <7%
- B: Reducing MACE (major adverse cardiovascular events)
- C: Reducing MACE and an HBA1C <7%



First must understand diabetes role inside the vessel



Diabetes and plaque modification



ATHEROSCLEROTIC PLAQUE HEALING

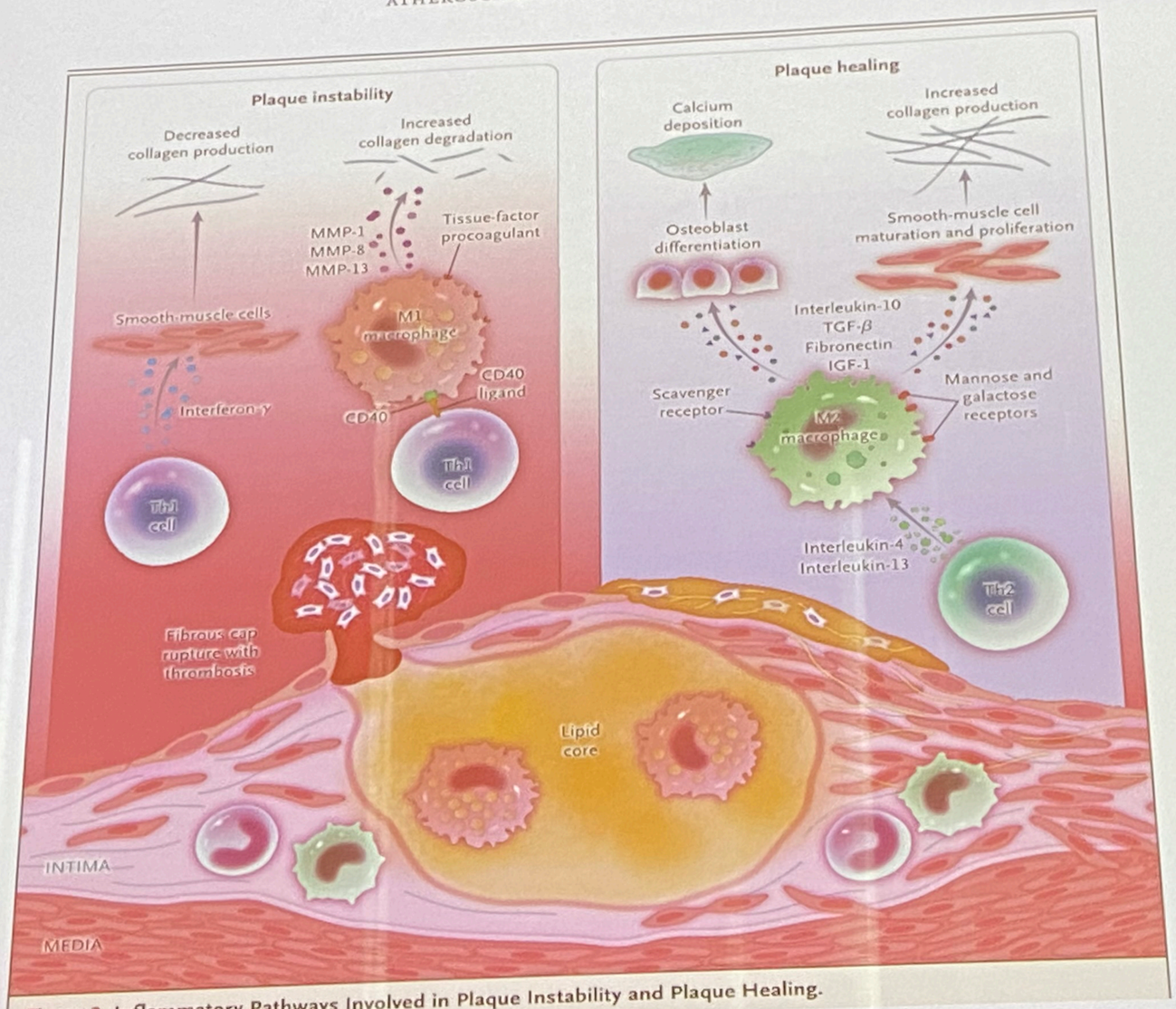
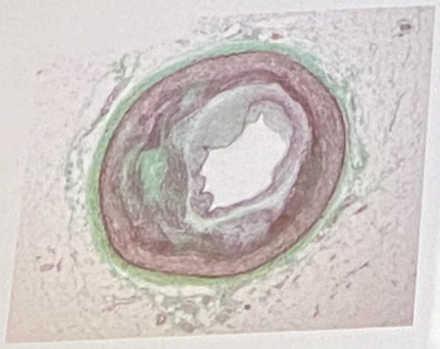


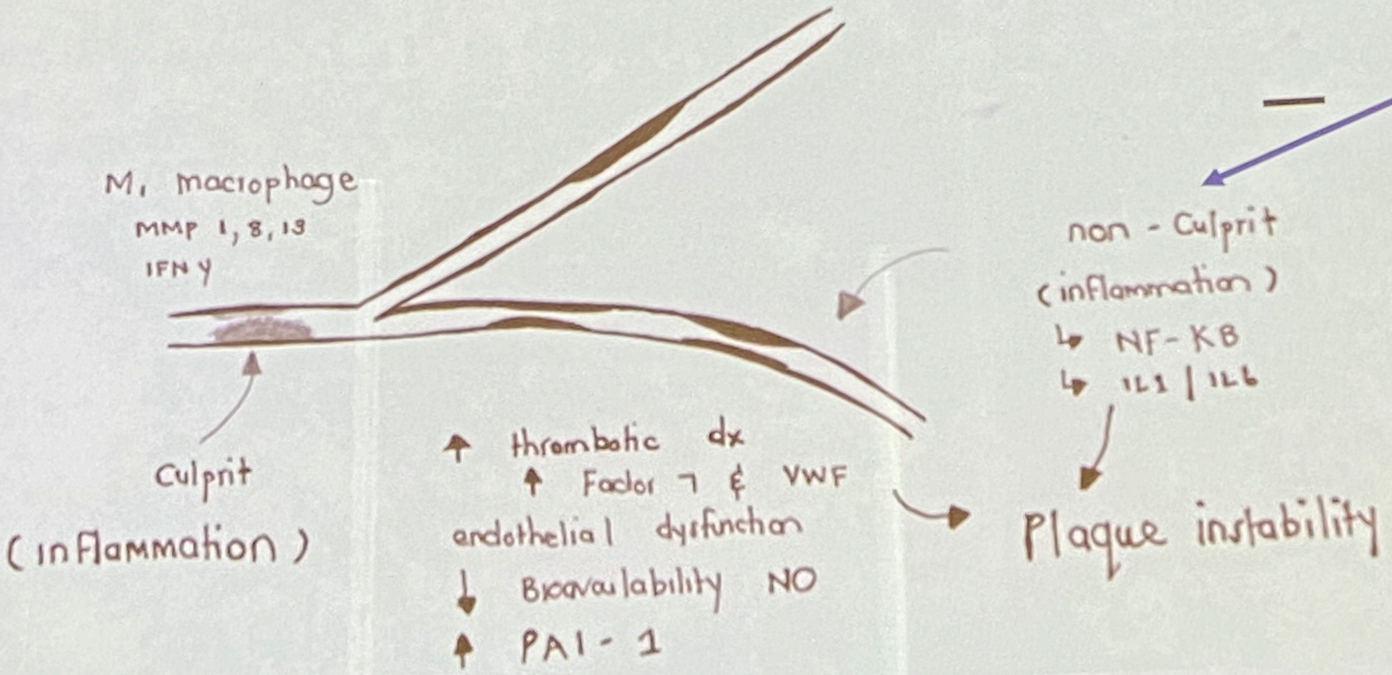
Figure 3. Inflammatory Pathways Involved in Plaque Instability and Plaque Healing.

Plaque Rupture

Atherosclerotic Plaque

Plaque Healing





SGLT 2

GLP-RA

- SIRT6

Ample evidence that inflammation contributes significantly to atherosclerosis: Jean Claude Tardif

ATHEROSCLEROTIC PLAQUE HEALING

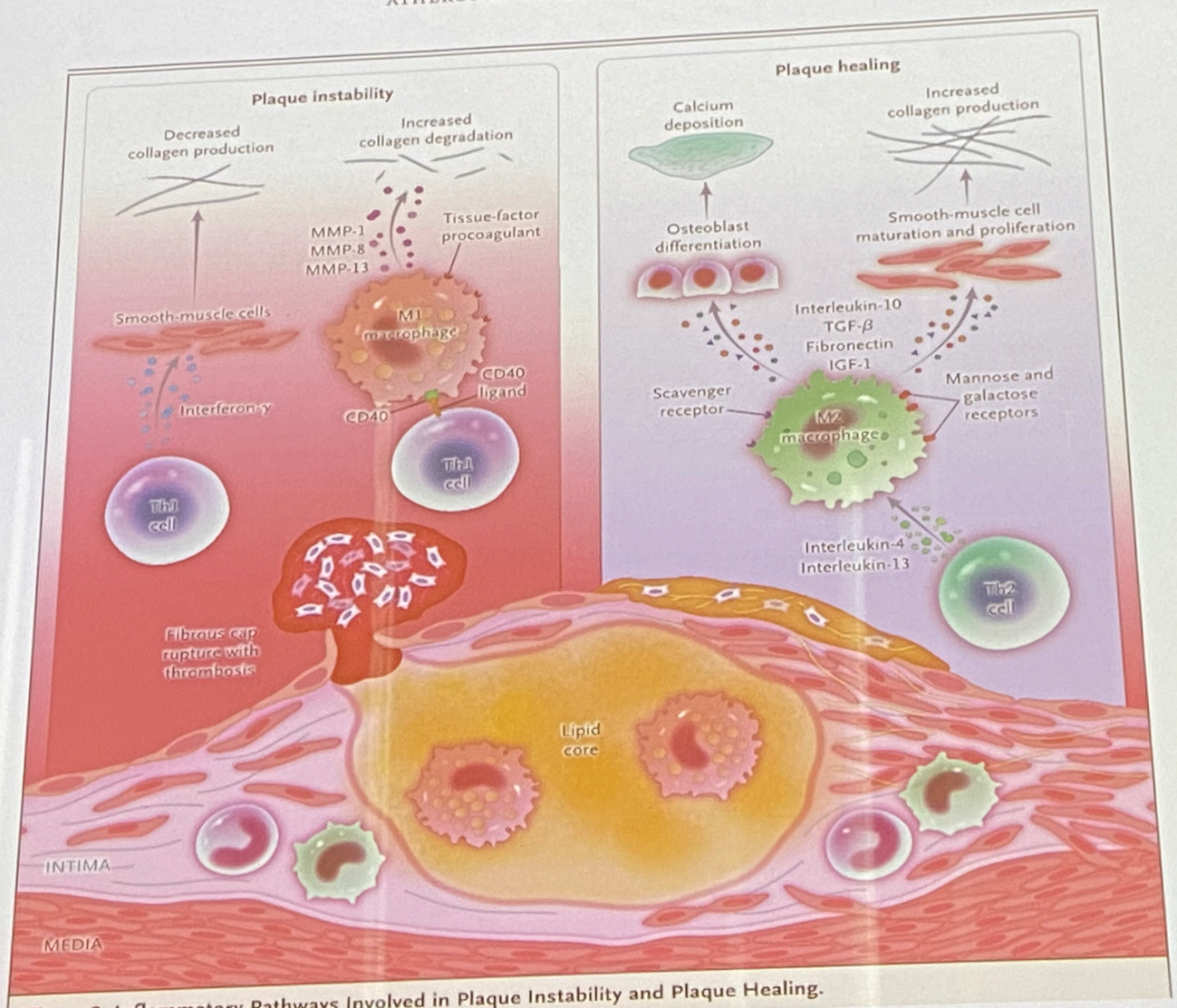
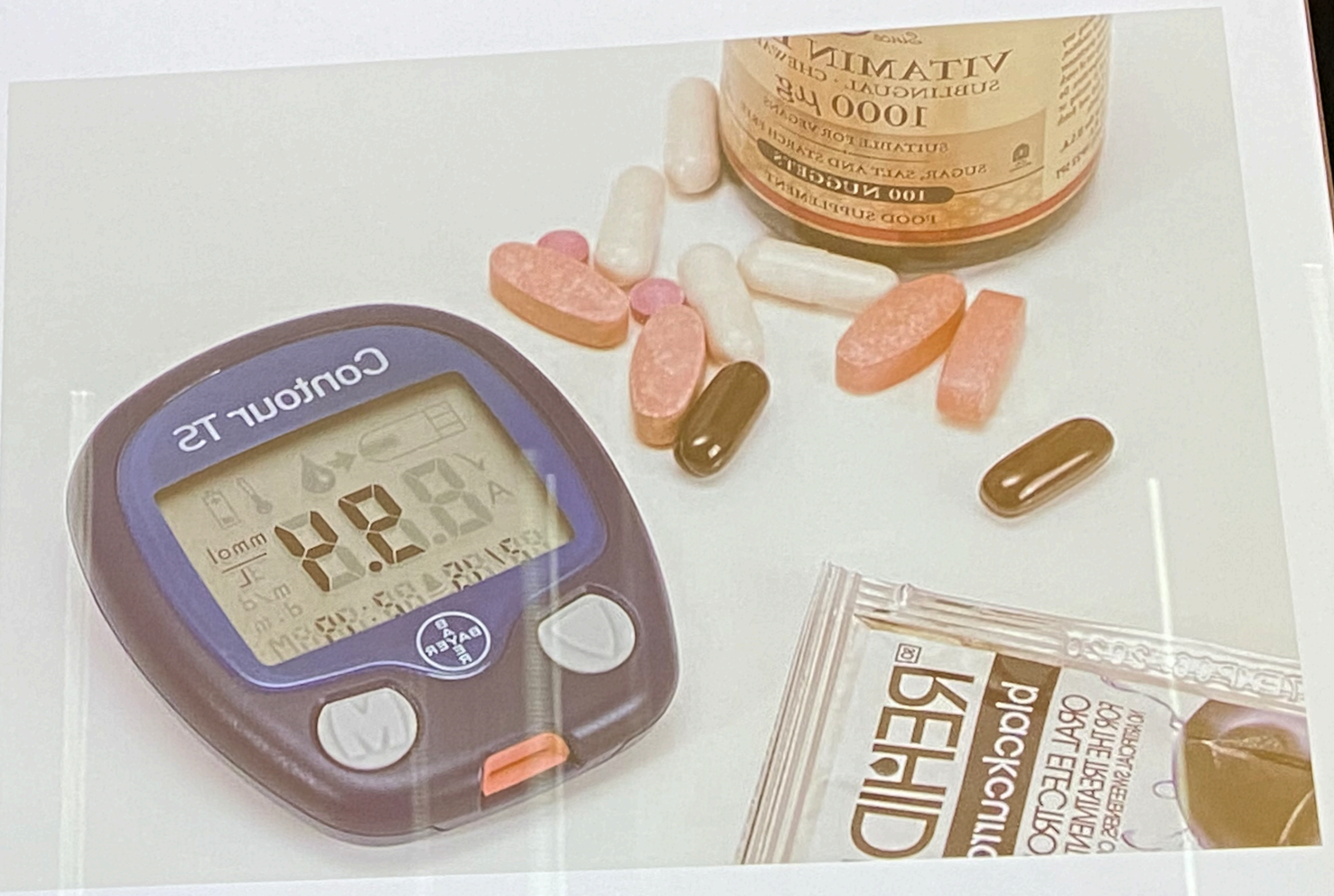


Figure 3. Inflammatory Pathways Involved in Plaque Instability and Plaque Healing.

HBA1C



Establishing a balanced approach to treatment starts with individualised HbA_{1c} targets

ESC/EASD (2019)[1]

Target HbA_{1c} <7%
Individualise targets

Consider more stringent goals *(6.0 to 6.5%) in younger patients with a short duration of T2DM and no evidence of CVD, if achieved without significant hypoglycaemia*

Consider less stringent goals *(e.g., <8% or ≤9%) for elderly patients with long-standing T2DM and limited life expectancy, and frailty with multiple comorbidities, including hypoglycaemic episodes*

ADA/EASD (2019)[2]

Target HbA_{1c} ≤7%
Individualise targets, assessing for:

- Age
- Disease duration
- Comorbidities
- Severity of diabetic complications
- Life expectancy
- Resources
- Patient preferences

ADA, American Diabetes Association; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; HbA_{1c}, glycated haemoglobin; T2DM, type 2 diabetes mellitus.

1. Cosentino F, et al. *Eur Heart J*. 2020;41(2):255-323. 2. Buse JB, et al. *Diabetes Care*. 2020;43(2):487-93.

Does "legacy effect" and "metabolic memory" exist? Evidence from UKPDS 88

All-cause mortality

HbA_{1c}, glycated haemoglobin; T2DM, type 2. 2021;dc202439. diabetes mellitus.
Lind M, et al. *Diabetes Care*

Does "legacy effect" and "metabolic memory" exist? Evidence from UKPDS 88

All-cause mortality

1% reduction in HbA_{1c} at diagnosis

18.8% risk reduction

1% reduction in HbA_{1c} 10 years after diagnosis

2.7% risk reduction

Myocardial infarction

1% reduction in HbA_{1c} at diagnosis

19.7% risk reduction

HbA_{1c}, glycated haemoglobin; T2DM, type 2. 2021;dc202439. diabetes mellitus.
Lind M, et al. *Diabetes Care*

Does "legacy effect" and "metabolic memory" exist? Evidence from UKPDS 88

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1% reduction in HbA_{1c} at diagnosis

19.7% risk reduction

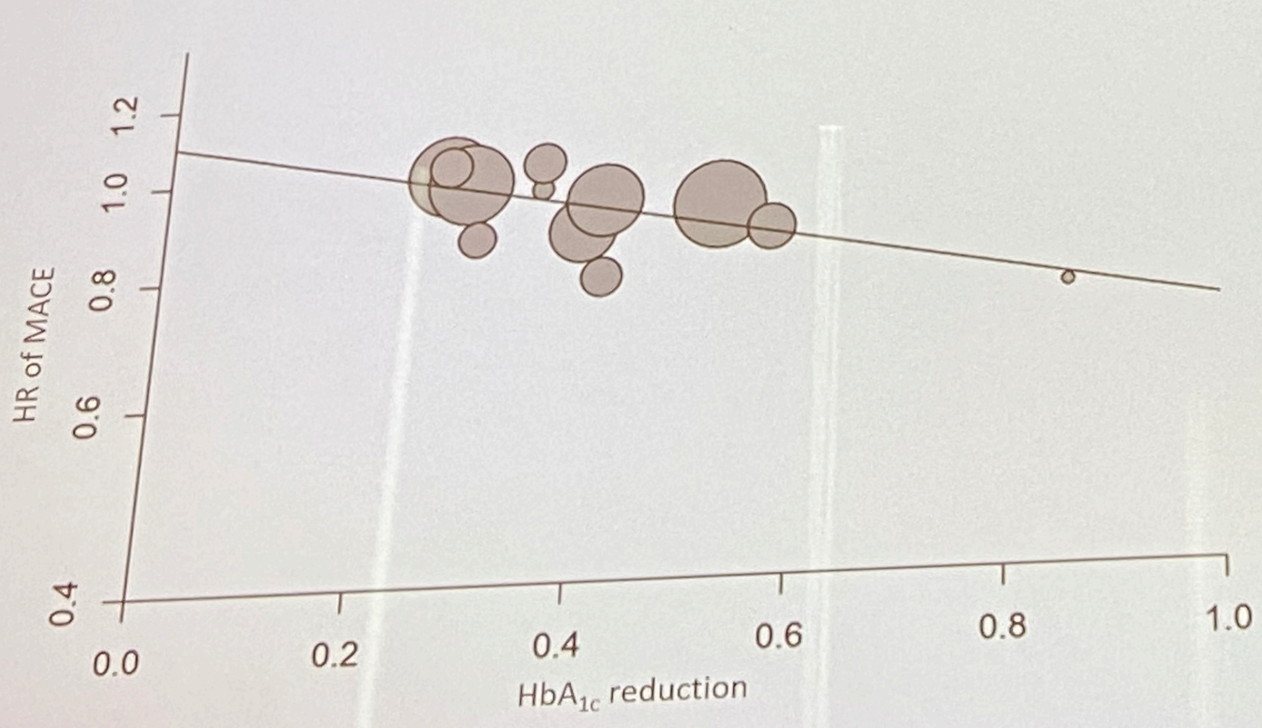
1% reduction in HbA_{1c} 10 years after diagnosis

6.5% risk reduction

HbA_{1c} glycated haemoglobin; T2DM, type 2. 2021;dc202439. diabetes mellitus.
Lind M, et al. *Diabetes Care*

CVOT with the greatest HbA_{1c} reduction had the lowest HR of MACE

Meta-regression analysis between reduction of HbA_{1c} and MACE risk in 12 CVOTs

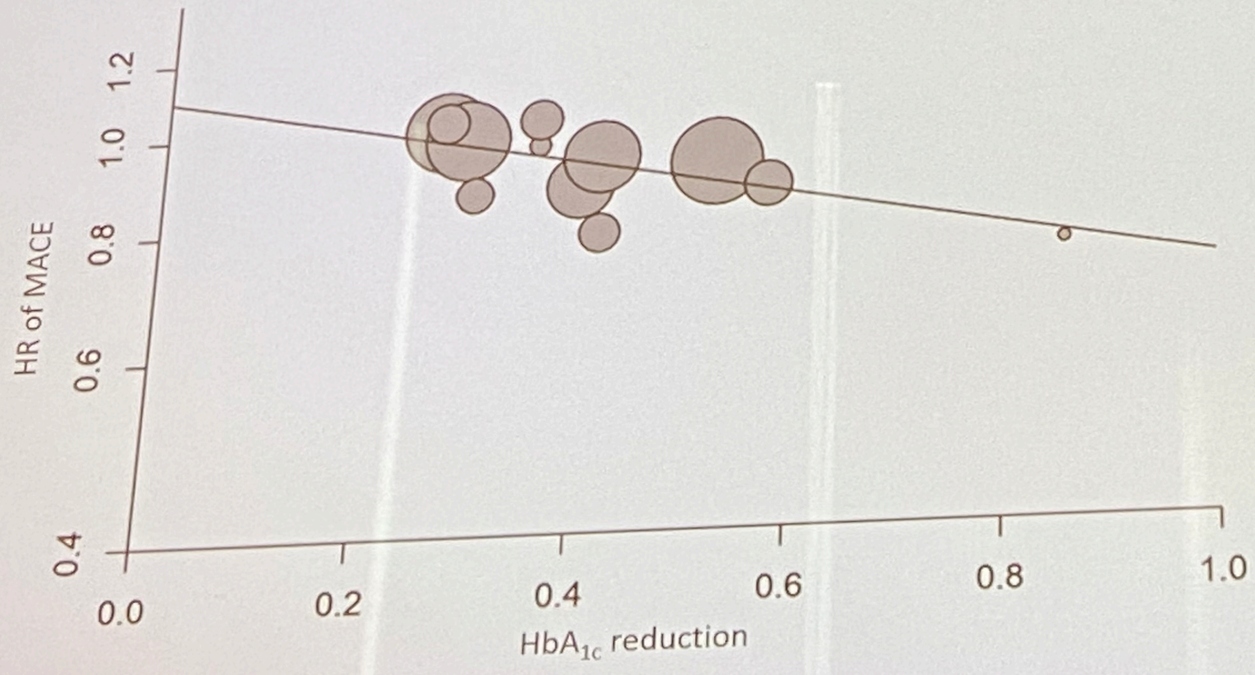


- Significant association between reductions of HbA_{1c} and risk of MACE (p=0.002)

CI, confidence interval; CVOT, cardiovascular outcome trial; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events.
Giugliano D, et al. J Am Heart Assoc. 2019;8(12):e012356.

CVOT with the greatest HbA_{1c} reduction had the lowest HR of MACE

Meta-regression analysis between reduction of HbA_{1c} and MACE risk in 12 CVOTs



- Significant association between reductions of HbA_{1c} and risk of MACE (p=0.002)

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Giugliano D, et al. *J Am Heart Assoc*. 2019;8(12):e012356.

HBA1C Reduction

- ACCORD/ ADVANCE/VADT – 1% reduction in HBA1C had a 15% relative risk reduction in non-fatal MI, no difference in stroke or all cause mortality.

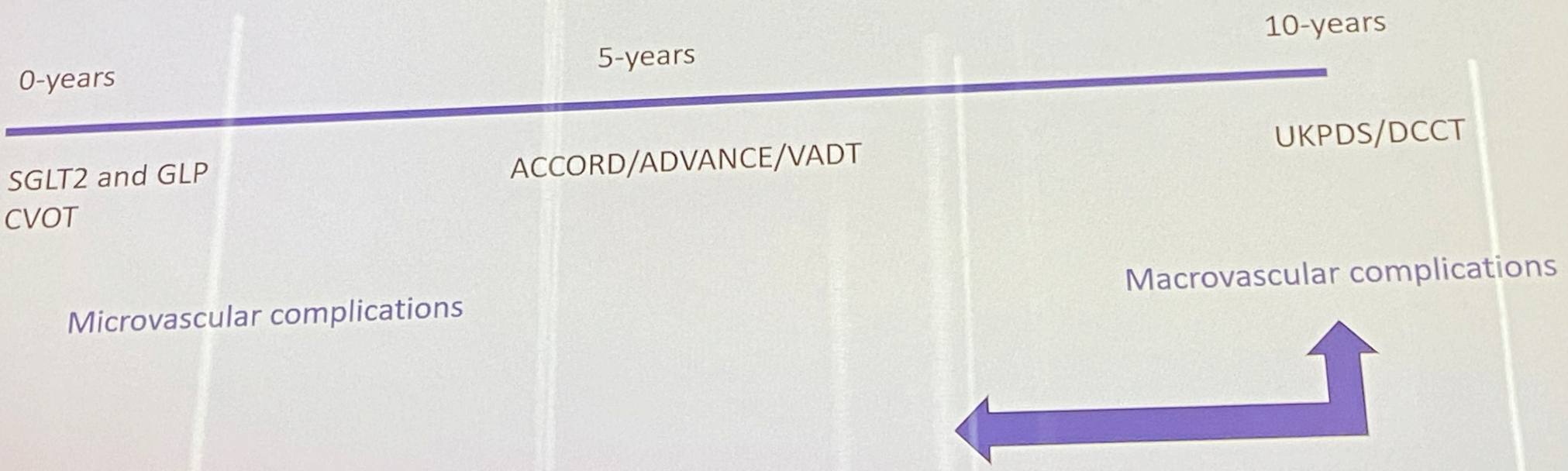
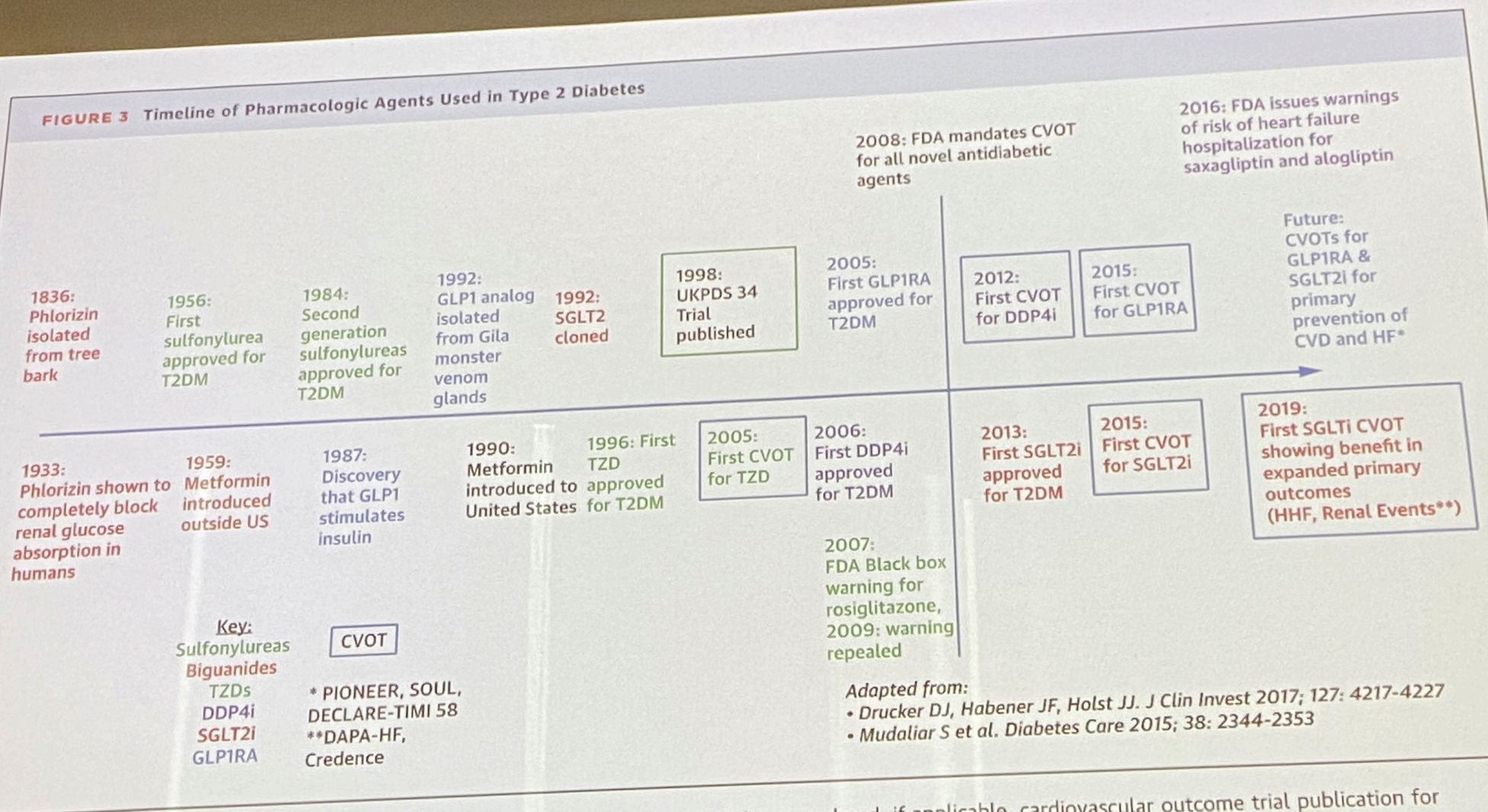


FIGURE 3 Timeline of Pharmacologic Agents Used in Type 2 Diabetes



Timeline delineating the dates of discovery, U.S. Food and Drug Administration (FDA) approval and, if applicable, cardiovascular outcome trial publication for biguanides, sulfonylureas, TZDs, DPP4is, GLP1RAs, and SGLTis. Adapted with permission from Mudaliar et al. (72) and Drucker et al. (102). HHF = hospitalization for heart failure; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study; other abbreviations as in **Figures 1 and 2**.

Metformin and UKPDS

- Reduction in MACE's
- 39% reduction in MI
- 50% reduction in coronary deaths
- 41% reduction in stroke
- All cause mortality reduced by 36% at 10.7 years follow up

ESC
European Society of Cardiology

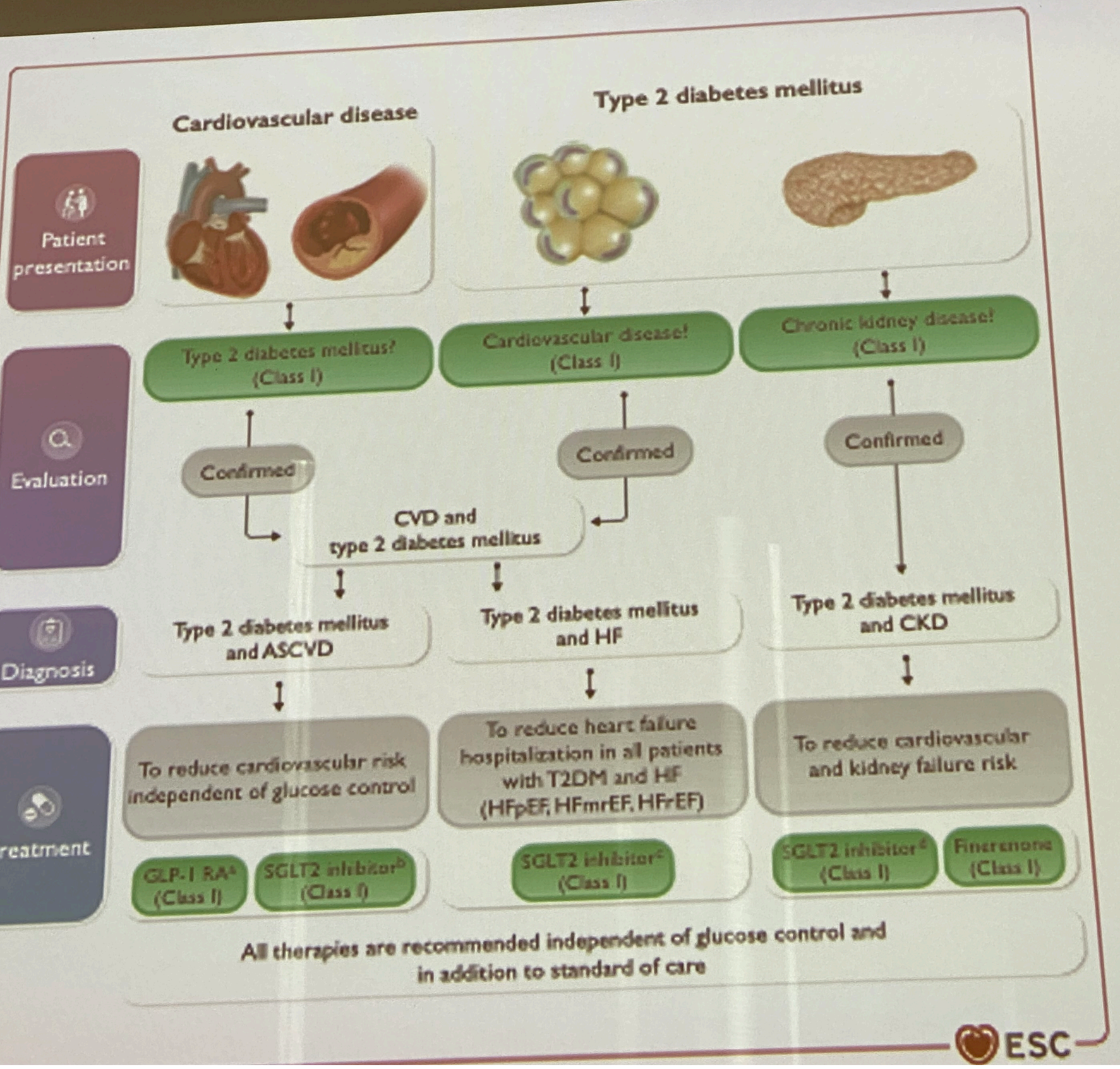
European Heart Journal (2023) **44**, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

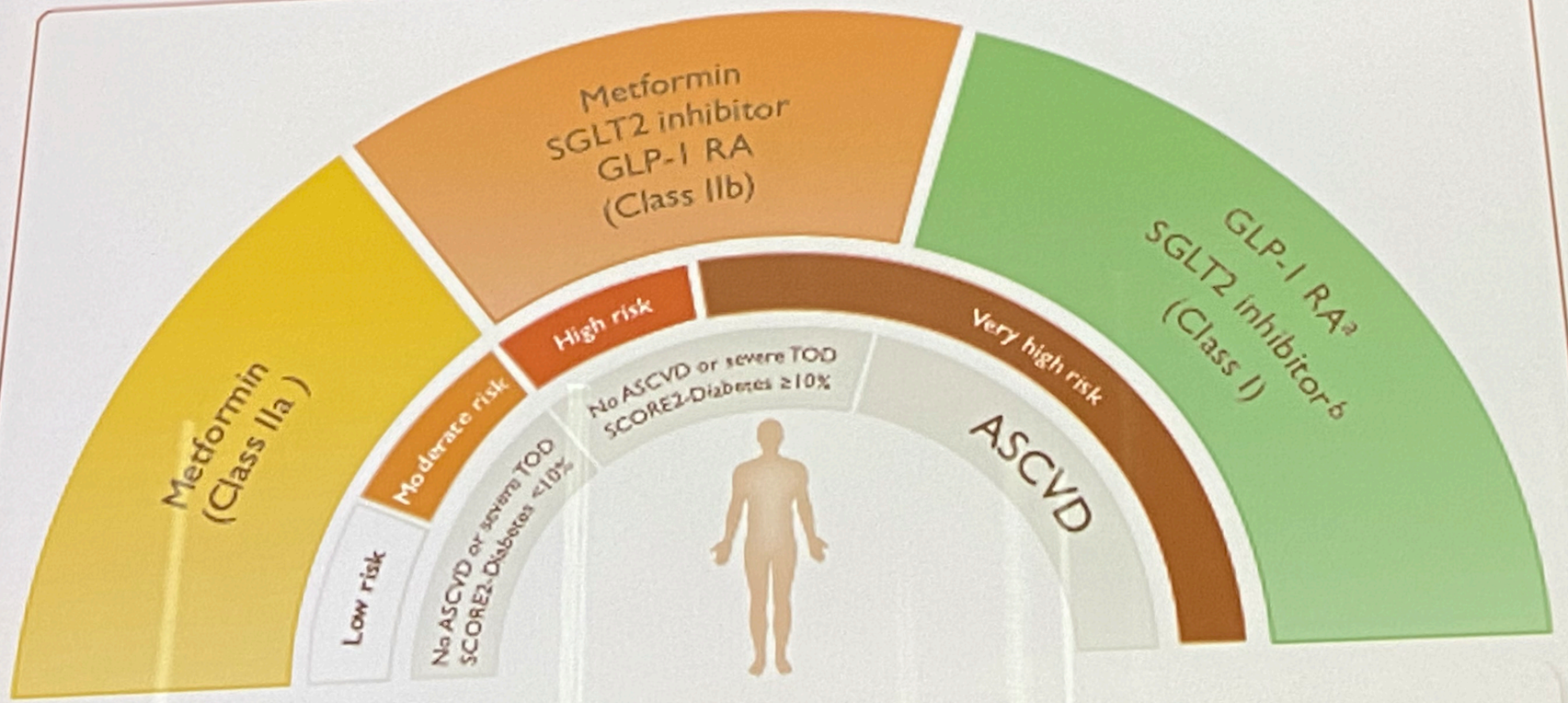
ESC GUIDELINES

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group


Cardiovascular disease
Type 2 diabetes mellitus
Patient presentation
Type 2 diabetes mellitus? (Class I)
Cardiovascular disease! (Class I)
Chronic kidney disease! (Class I)
Evaluation
Confirmed
Confirmed
Confirmed
CVD and type 2 diabetes mellitus
Diagnosis
Type 2 diabetes mellitus and ASCVD
Type 2 diabetes mellitus and HF
Type 2 diabetes mellitus and CKD
Treatment
To reduce cardiovascular risk independent of glucose control
To reduce heart failure hospitalization in all patients with T2DM and HF (HFpEF, HFmrEF, HFrEF)
To reduce cardiovascular and kidney failure risk
GLP-1 RA[a] (Class I)
SGLT2 inhibitor[b] (Class I)
SGLT2 inhibitor[c] (Class I)
SGLT2 inhibitor[d] (Class I)
Finerenone (Class I)
All therapies are recommended independent of glucose control and in addition to standard of care
ESC



Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes

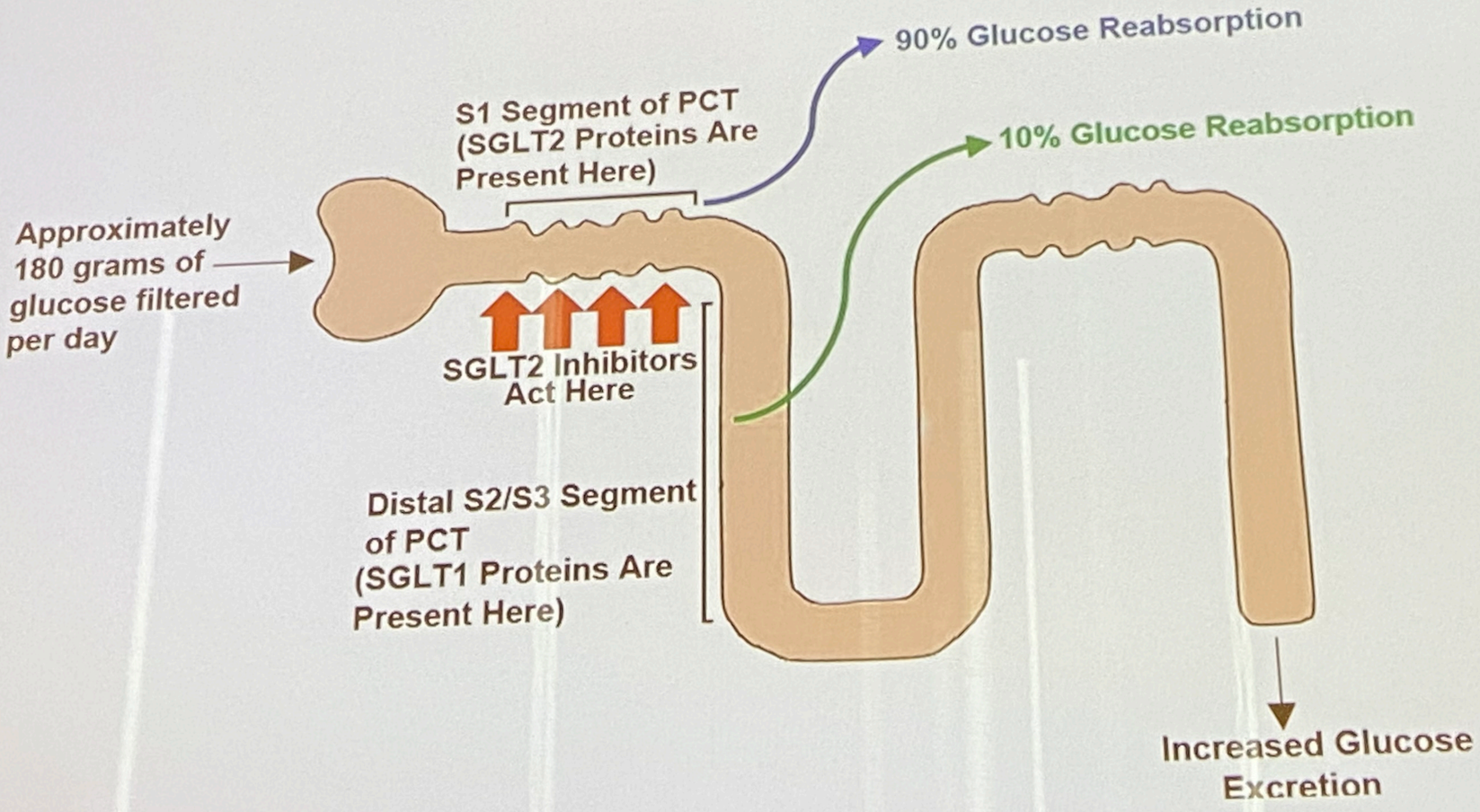
ESC

- When choosing diabetic agents in patients with CVD, what are the important targets?

- A: Reducing HBA1C <7%
- B: Reducing MACE (major adverse cardiovascular events)
- C: Reducing MACE and an HBA1C <7



SGLT 2 Inhibitors



Novel mechanisms of benefit in heart failure with SGLT2 inhibition

Altered adipokine regulation

Suppression of leptin secretion by adipocytes

Reduced serum leptin

Reduced epicardial fat

Autophagy Induction

Increased glucagon vs insulin ratio due to increased urinary glucose excretion

Activation of SIRT1 and AMPK, HIF1,2alfa

Autophagic clearance of damaged organelles

Reduced oxidative stress and inflammation

Improved cardiac ionic homeostasis

NHE-1 inhibition

SGLT1 inhibition

Reduced intracellular sodium and restored sodium-calcium exchanger function

Improved intracellular calcium transients and cardiac contraction

Improved myocardial energetics

Increased catabolism mimicking a state of fasting due to increased urinary glucose excretion

Increased ketone body production

Alternate fuel instead of fatty acids and glucose

Increased ATP production

Improved cardiac work efficiency

Improved cardiovascular health

Improved cardiovascular outcomes

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TABLE 1 SGLT2i Cardiovascular Outcome Trials

	EMPA-REG Empagliflozin (n = 7,020)	CANVAS Program Canagliflozin (n = 10,142)	DECLARE Dapagliflozin (n = 17,160)	CREDENCE Canagliflozin (n = 4,401)	DAPA-HF Dapagliflozin (n = 4744)
Median follow-up, yrs	3.1	2.4	4.2	2.6	1.5
Mean age, yrs	63	63	64	63	66
Female, %	29	36	37	34	23
Mean BMI, kg/m^2	30.6	32.0	32.1	31.3	28.2
HbA1c, %	8.1	8.3	8.3	8.3	NR
Baseline metformin, %*	73	77	82	66	73
Baseline eGFR†	74	77	85	56	65
eGFR† <60 ml/min/1.73 m^2, %	26	20	7	59	40
Prior CVD, %	99	66	41	50	
Prior HF, %	10	14	10	15	
3P-MACE	**0.86 (0.74–0.99)**	**0.86 (0.67–0.91)**	0.93 (0.84–1.03)	**0.80 (0.67–0.95)**	NR
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)	0.82 (0.69–0.98)
MI	0.87 (0.70–1.09)‖	0.89 (0.73–1.09)‖	0.89 (0.77–1.01)	NR	NR
Stroke	1.18 (0.89–1.56)‖	0.87 (0.69–1.09)‖	1.01 (0.84–1.21)	NR	NR
CV death or HHF	**0.66 (0.55–0.79)**	**0.78 (0.67–0.91)**	**0.83 (0.73–0.95)**	**0.69 (0.57–0.83)**	**0.75 (0.65–0.85)**
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)	0.83 (0.71–0.85)
HHF	**0.65 (0.50–0.85)**	**0.67 (0.52–0.87)**	0.73 (0.61–0.88)	**0.61 (0.47–0.80)**	0.70 (0.59–0.83)
Renal events‡	**0.61 (0.53–0.70)** (103)	**0.60 (0.47–0.77)**	0.53 (0.43–0.66)	0.66 (0.53–0.81)	0.71 (0.44–1.16)
Other primary outcome§	NR	NR	NR	**0.70 (0.59–0.82)**	**0.74 (0.65–0.85)**

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

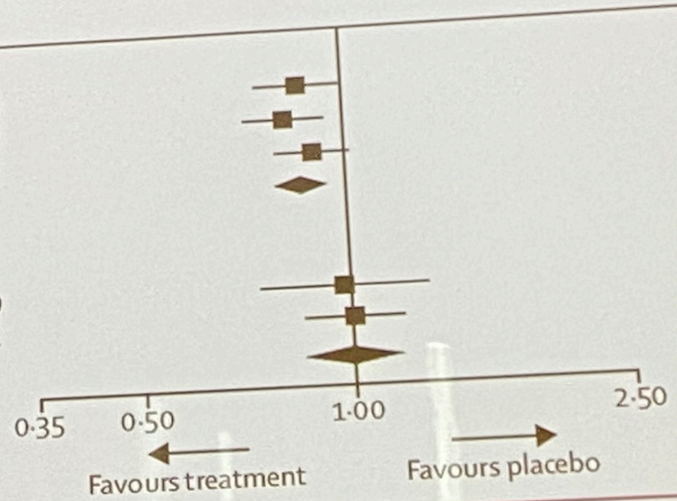


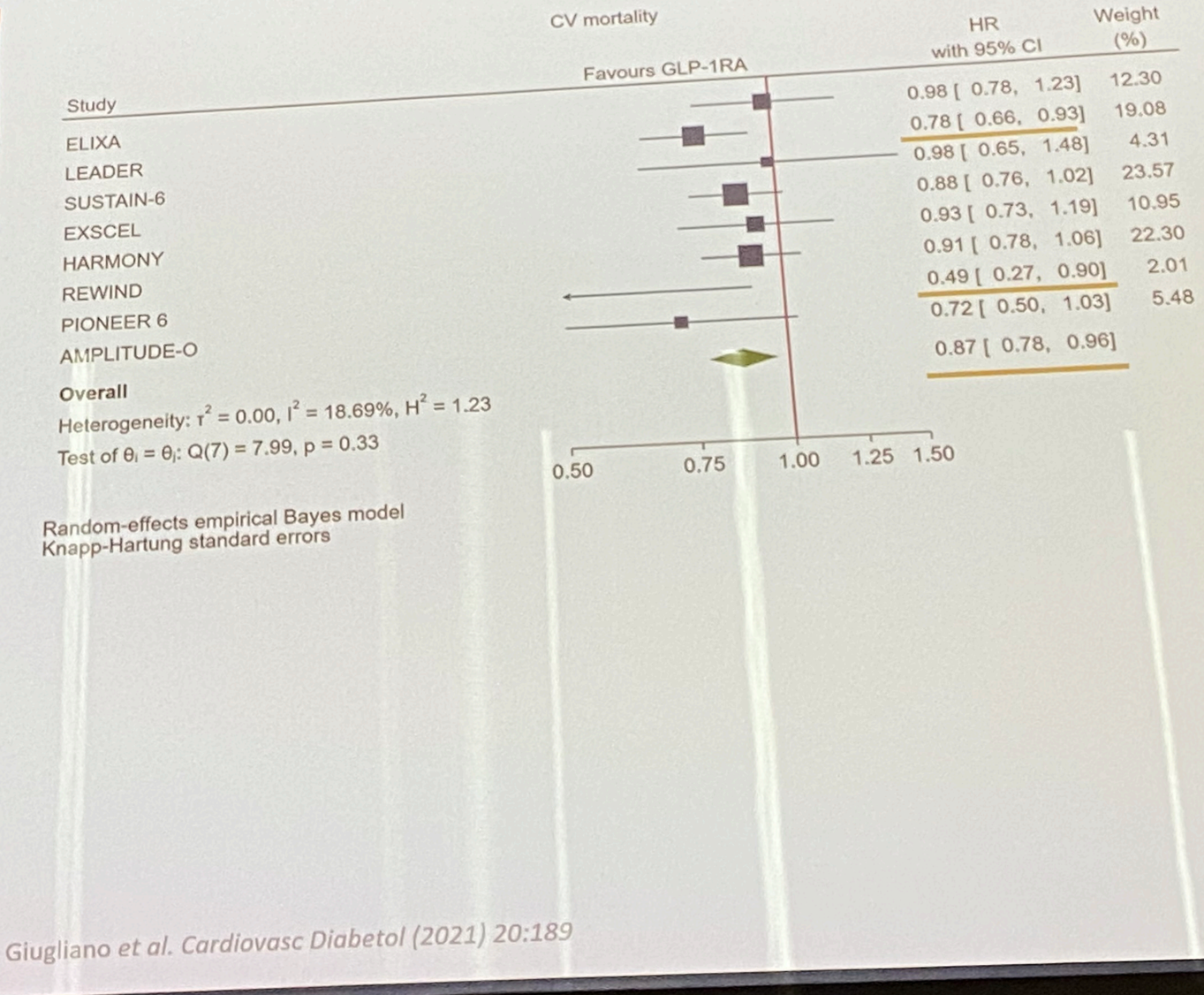
Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

Zelniker, et al"SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials." *The Lancet* 393 (2019): 31-39.

CVOT data update –
GLP-1 RA

GLP-1RA Trials

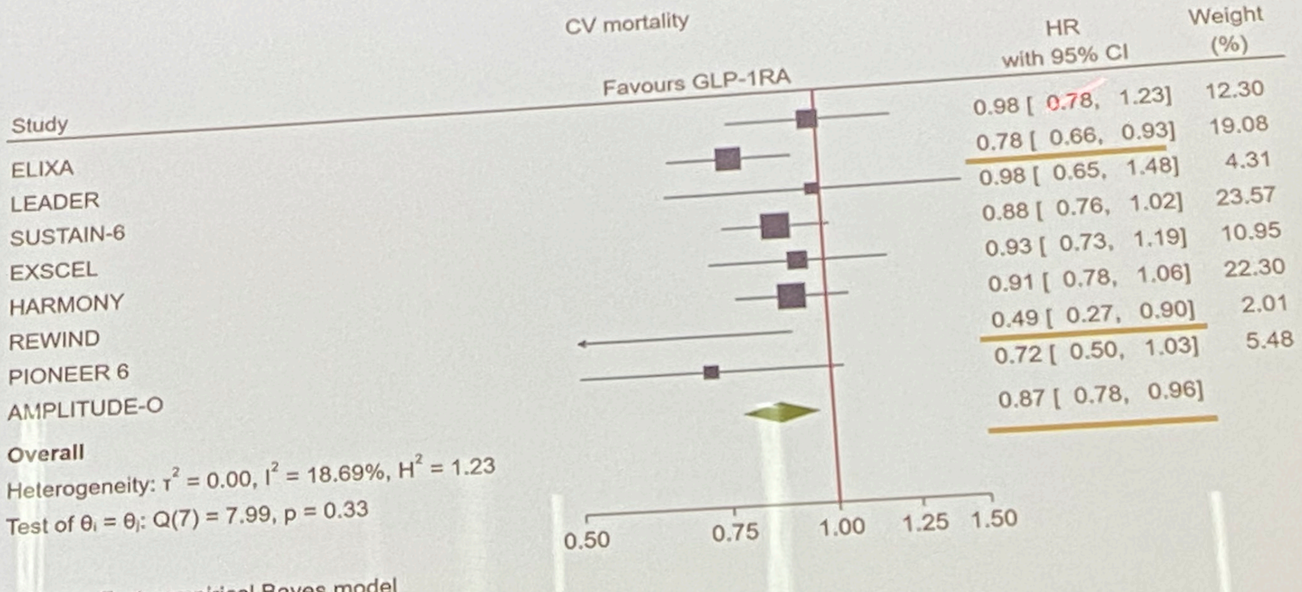
CV Mortality



Giugliano *et al. Cardiovasc Diabetol (2021) 20:189*

GLP-1RA Trials

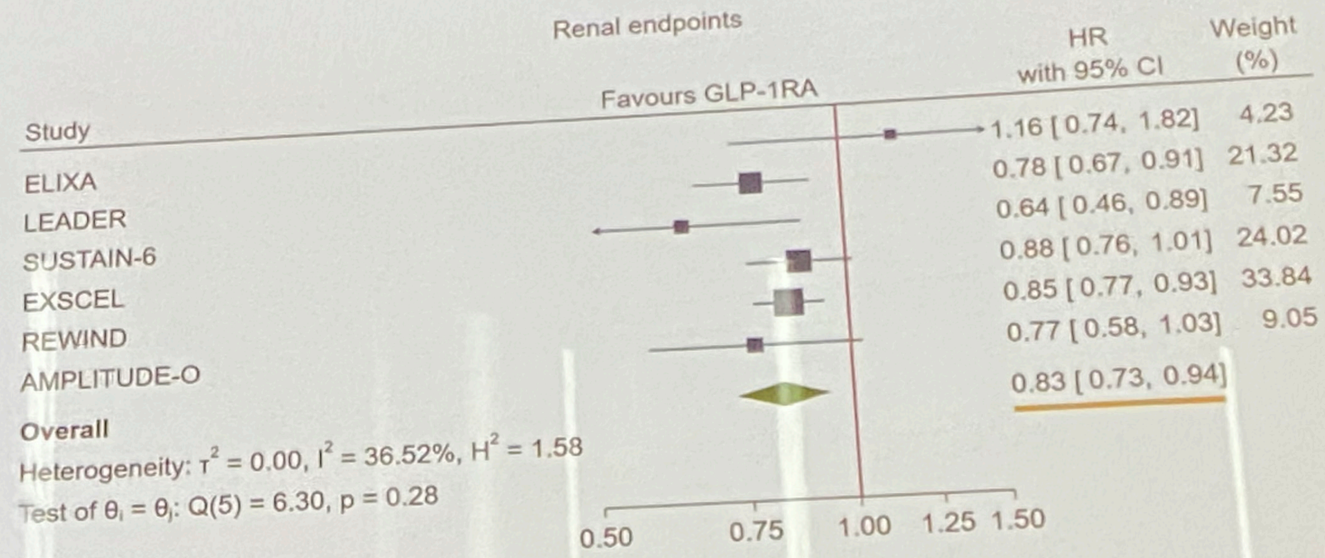
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GLP-1RA Trials

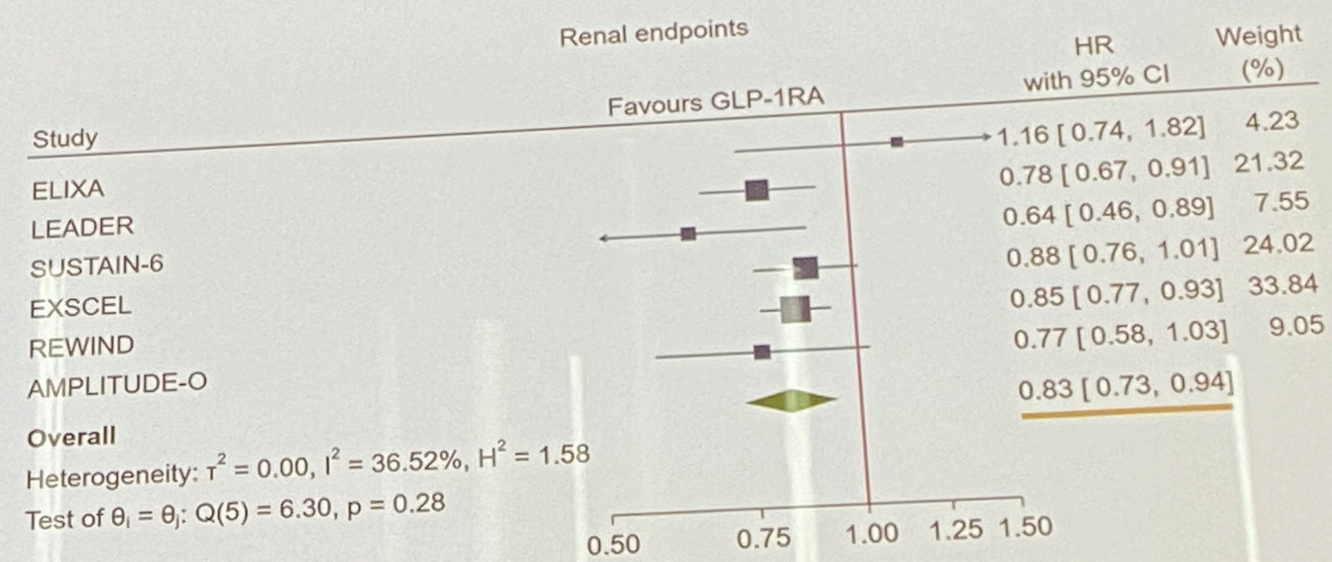
Renal Endpoints



Giugliano *et al. Cardiovasc Diabetol (2021) 20:189*

GLP-1RA Trials

Renal Endpoints



Giugliano *et al. Cardiovasc Diabetol (2021) 20:189*

DPP4 Inhibitors

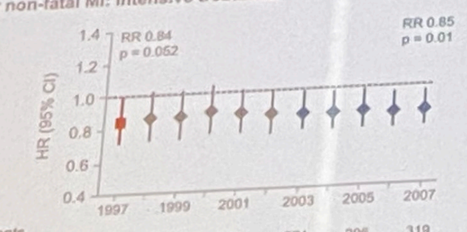
TABLE 2 DPP4i Cardiovascular Outcome Trials

	SAVOR-TIMI 53 Saxagliptin (n = 16,492)	EXAMINE Alogliptin (n = 5,380)	TECOS Sitagliptin (n = 14,523)	CARMELINA Linagliptin (n = 6,979)	CAROLINA Linagliptin vs. Glimepiride (n = 6,033)
Median follow-up, yrs	2.1	1.5	3.0	2.2	5.9
Mean age, yrs	65	61	65	66	64
Female, %	33	32	29	37	40
Mean BMI, kg/m^2	31.2	28.7	30.2	31.4	30.1
HbA1c, %	8.0	8.0	7.2	8.0	7.2
Baseline metformin,* %	69	NA	81	54	83
Baseline eGFR†	73	71	75	55	77
eGFR† <60 ml/min/1.73 m^2, %	<50 ml/min: 16	29	NR	62	19
Prior CVD, %	78	100	100	57	42
Prior HF, %	13	28	18	27	4
3P-MACE	1.00 (0.89-1.12)	0.96 (≤1.16)	0.98 (0.89-1.08)	1.02 (0.89-1.17)	0.98 (0.84-1.13)
CV death	1.03 (0.87-1.22)	0.85 (0.66-1.10)	1.03 (0.89-1.19)	0.96 (0.81-1.14)	1.00 (0.81-1.24)
MI	0.95 (0.80-1.12)	1.08 (0.88-1.33)‖	0.95 (0.81-1.11)	1.12 (0.90-1.40)§	1.03 (0.82-1.29)§
Stroke	1.11 (0.88-1.39)	0.91 (0.55-1.50)‖	0.97 (0.79-1.19)	0.91 (0.67-1.23)§	0.86 (0.66-1.12)§
CV death or HHF	NR	1.00 (0.82-1.20)	1.02 (0.90-1.15)	NR	1.00 (0.84-1.20)
All-cause mortality	1.11 (0.96-1.27)	0.88 (0.71-1.09)	1.01 (0.90-1.14)	0.98 (0.84-1.13)	0.91 (0.78-1.06)
HHF	1.27 (1.07-1.51)	1.07 (0.79-1.46)	1.00 (0.83-1.20)	0.90 (0.74-1.08)	1.21 (0.92-1.59)
Renal events‡	1.08 (0.88-1.3)	NR	NR	1.04 (0.89-1.22)	NR

There has been no signal of adverse CV outcomes in trials of intensive glucose control (with SU)

SU-based RCTs of intensive glucose control (not ACCORD and VADT)

UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycaemic control

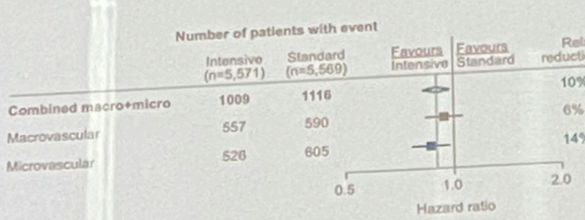


Holman et al. N Engl J Med 2008;359:1577–89.

ukpds-ptm

glibenclamide, chlorpropamide

ADVANCE: intensive glycaemic control reduced microvascular but not macrovascular events



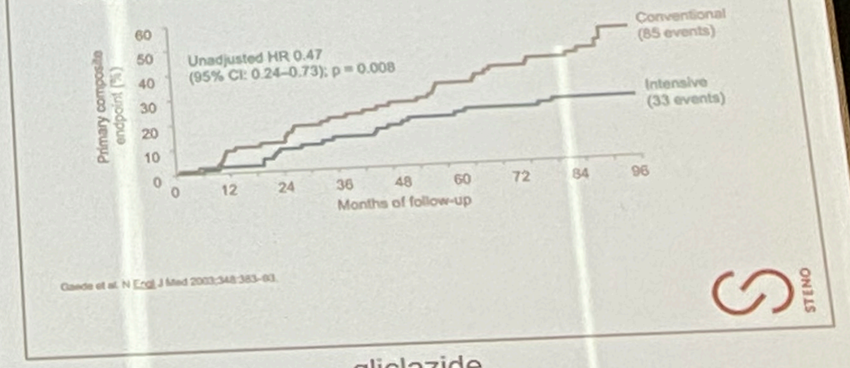
†P=0.013
‡P=0.015

Patel et al. N Engl J Med 2008;358:2560–72.

ADVANCE

gliclazide MR

Steno-2: Intensive multifactorial control of CV risk factors reduces CV risk in patients with T2D and microalbuminuria



Gaede et al. N Engl J Med 2003;348:383–93.

STENO

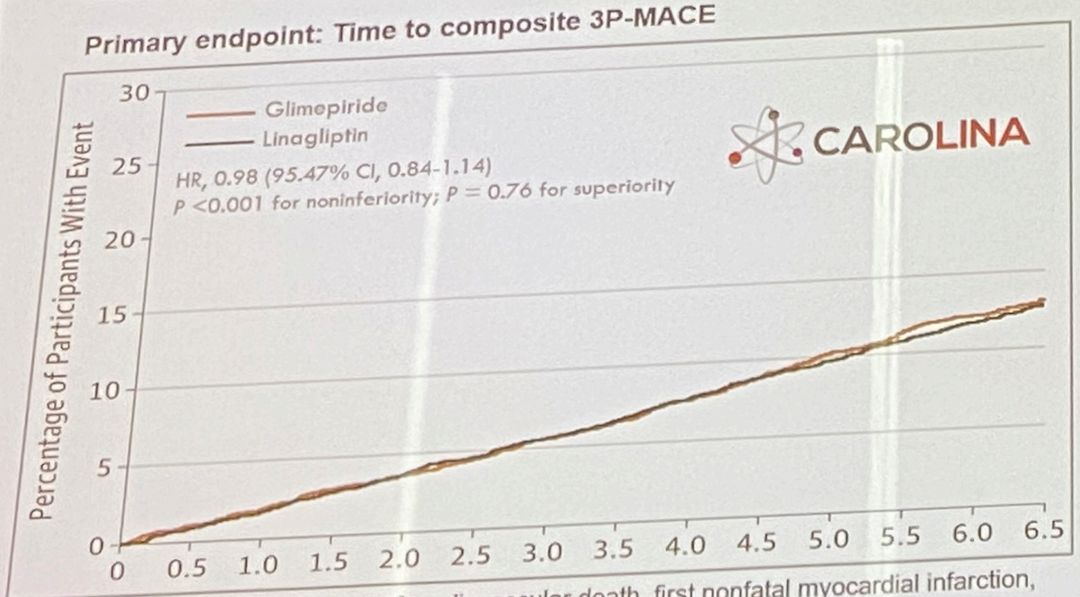
gliclazide

Randomised controlled cardiovascular outcomes trials show no adverse CV outcomes with later SUs

Randomised controlled CV safety trials – head-to-head

Linagliptin: proven CV safety vs standard of care in CARMELINA

Primary endpoint: Time to composite 3P-MACE

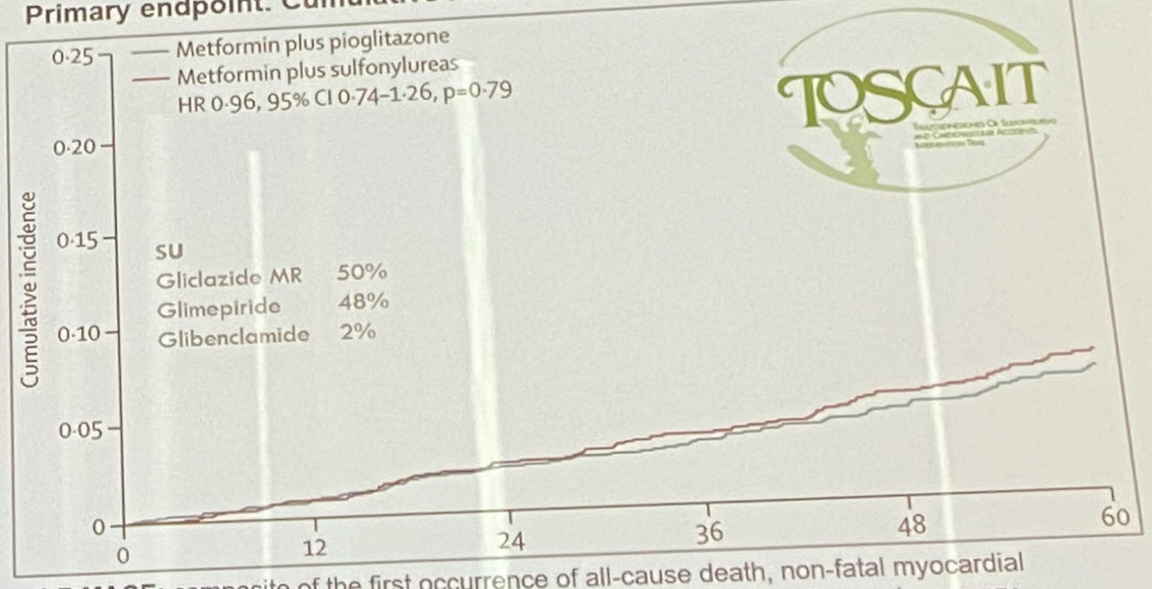


3P-MACE: Composite end point of cardiovascular death, first nonfatal myocardial infarction, or first nonfatal stroke

Rosenstock J et al. *JAMA*. 2019;322(12):1155-1166

Pioglitazone: proven benefit in atherosclerotic cardiovascular disease (PRO-Active, IRIS and PERISCOPE)

Primary endpoint: Cumulative incidence of the composite 4-P-MACE

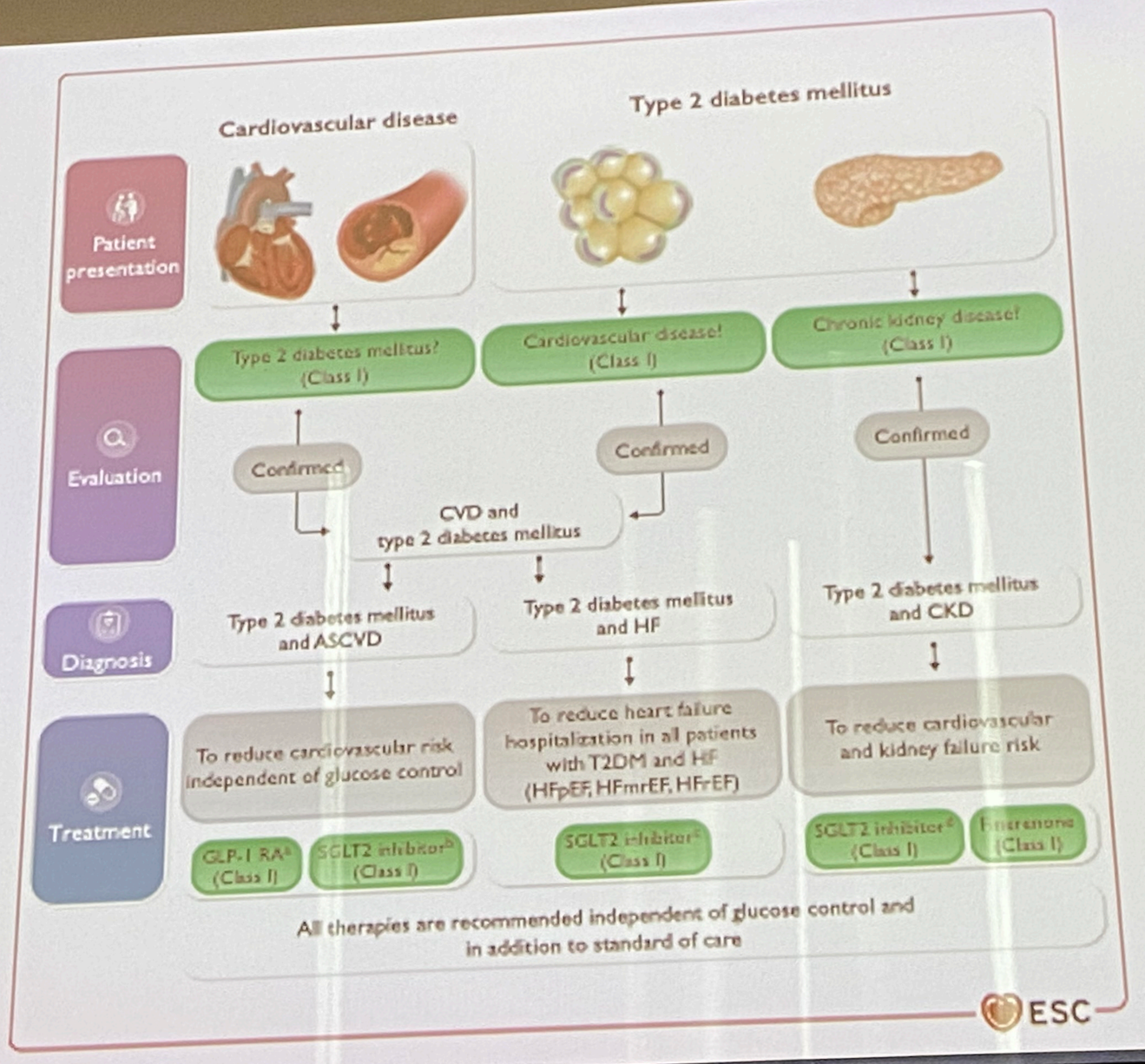


4-P MACE: composite of the first occurrence of all-cause death, non-fatal myocardial infarction (including silent myocardial infarction), non-fatal stroke, or urgent coronary revascularisation. HR=hazard ratio.

Vaccaro O et al. Lancet Diabetes Endocrinol. Sep 2017; 11:887-897

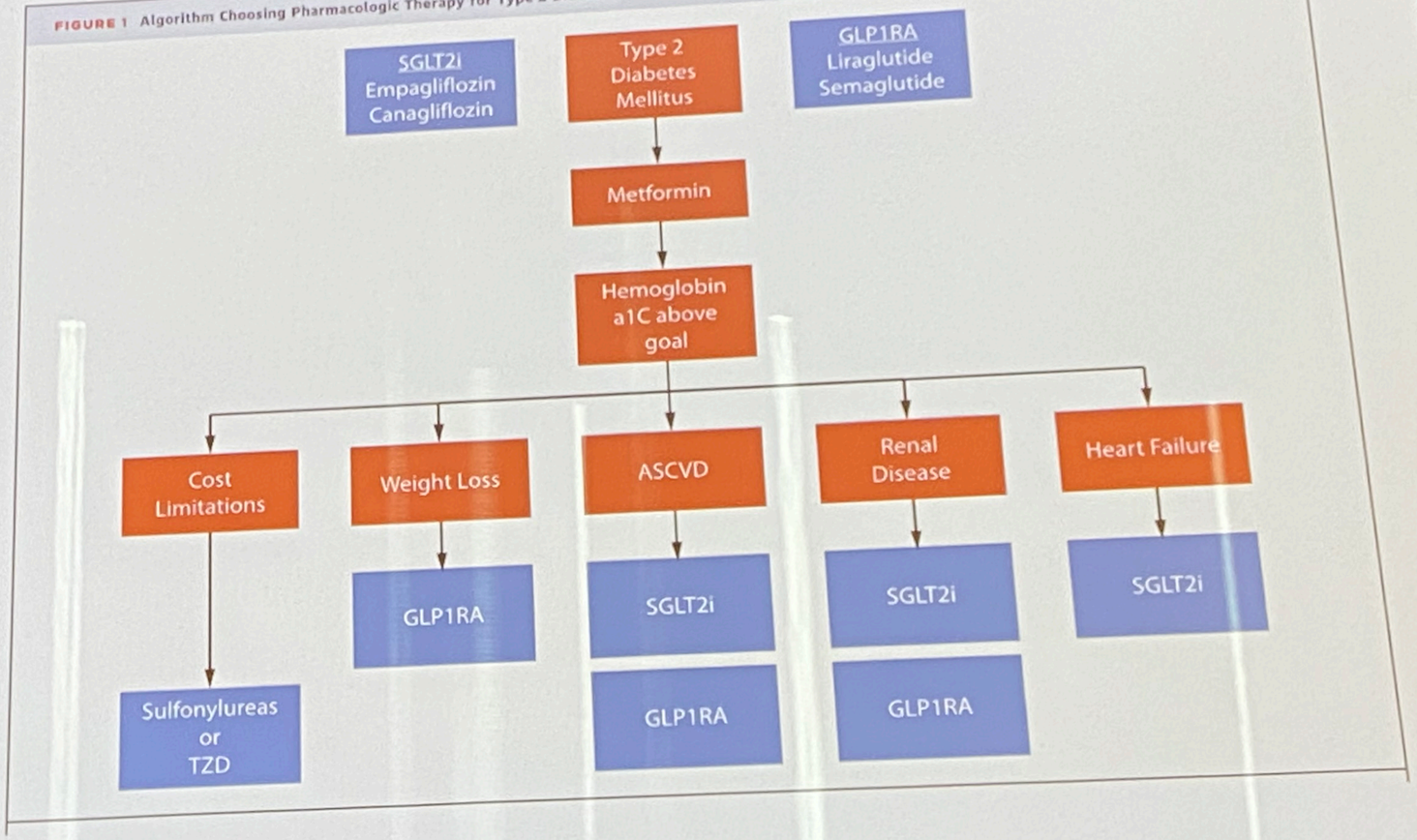
How to choose a successful diabetic drug

- Depends on co-morbidities
- Want something with an anti-inflammatory and effective glucose lowering effect


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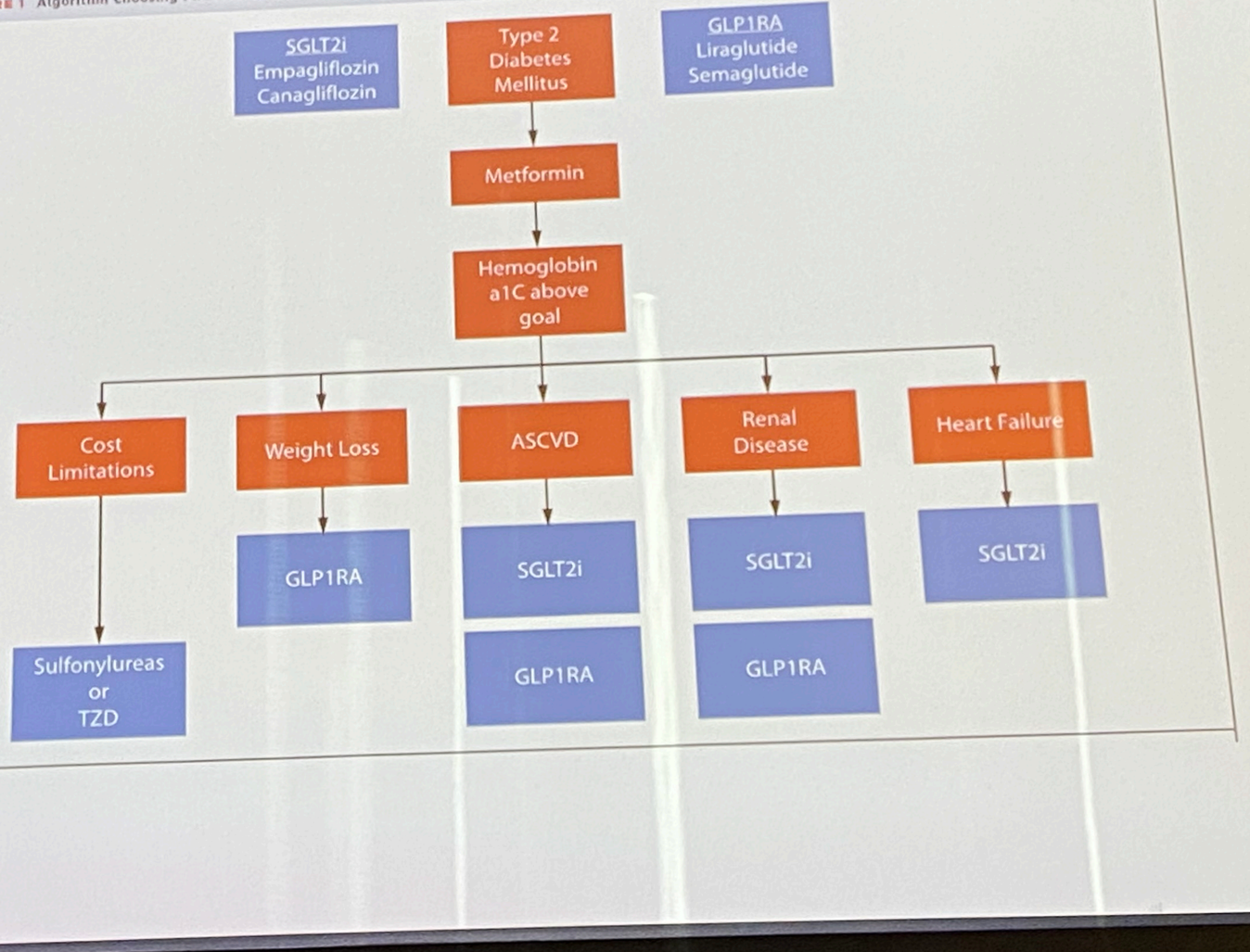
Algorithm for type 2 Diabetes

FIGURE 1 Algorithm Choosing Pharmacologic Therapy for Type 2 Diabetes



Algorithm for type 2 Diabetes

FIGURE 1 Algorithm Choosing Pharmacologic Therapy for Type 2 Diabetes



Clinical Scenario

- 80-year-old gentlemen, known with a background history of type 2 diabetes, metabolic phenotype currently on metformin 1g po bd. Now presents with an HBA1C of 7.5%.

- A: Do nothing, reassure and focus on dietary measures
- B: Add gliclazide MR 30 mg po daily
- C: Add dapagliflozin 10 mg po daily
- D: Refer to a physician for further titration

Clinical Scenario

- 65-year-old gentlemen, known with a background history of type 2 diabetes, ischemic heart disease, metabolic phenotype currently on metformin 1g po bd. Now presents with an HBA1C of 8.5%.

- A: Do nothing, reassure and focus on dietary measures
- B: Add gliclazide MR 30 mg po daily plus dapagliflozin 10mg
- C: Add empagliflozin 10 mg po daily
- D: Refer to someone who cares

Clinical Scenario

- 65-year-old gentlemen, known with a background history of type 2 diabetes, IHD, weight 140 kilograms, metabolic phenotype currently on metformin 1g po bd. Now presents with an HBA1C of 8.5%.

- A: Do nothing, reassure and focus on dietary measures
- B: Add gliclazide MR 30 mg po daily
- C: Add dapagliflozin 10 mg po daily
- D: add empagliflozin plus semaglutide

Practical considerations

- Look at the patient and co-morbidities

- HBA1C
- HBA1C <9 with no cardiovascular disease (Metformin and Gliclazide +/- a DPP4 inhibitor

- HBA1C <9 with cardiovascular disease (Metformin, SGLT 2 inhibitor +/- GLP1 RA +/- gliclazide)

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin.

Practical considerations

- Look at the patient and co-morbidities

- HBA1C
- HBA1C <9 with no cardiovascular disease (Metformin and Gliclazide +/- a DPP4 inhibitor

- HBA1C <9 with cardiovascular disease (Metformin, SGLT 2 inhibitor +/- GLP1 RA +/- gliclazide)

- Regular review of HBA1C's and cardiovascular symptoms

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin.