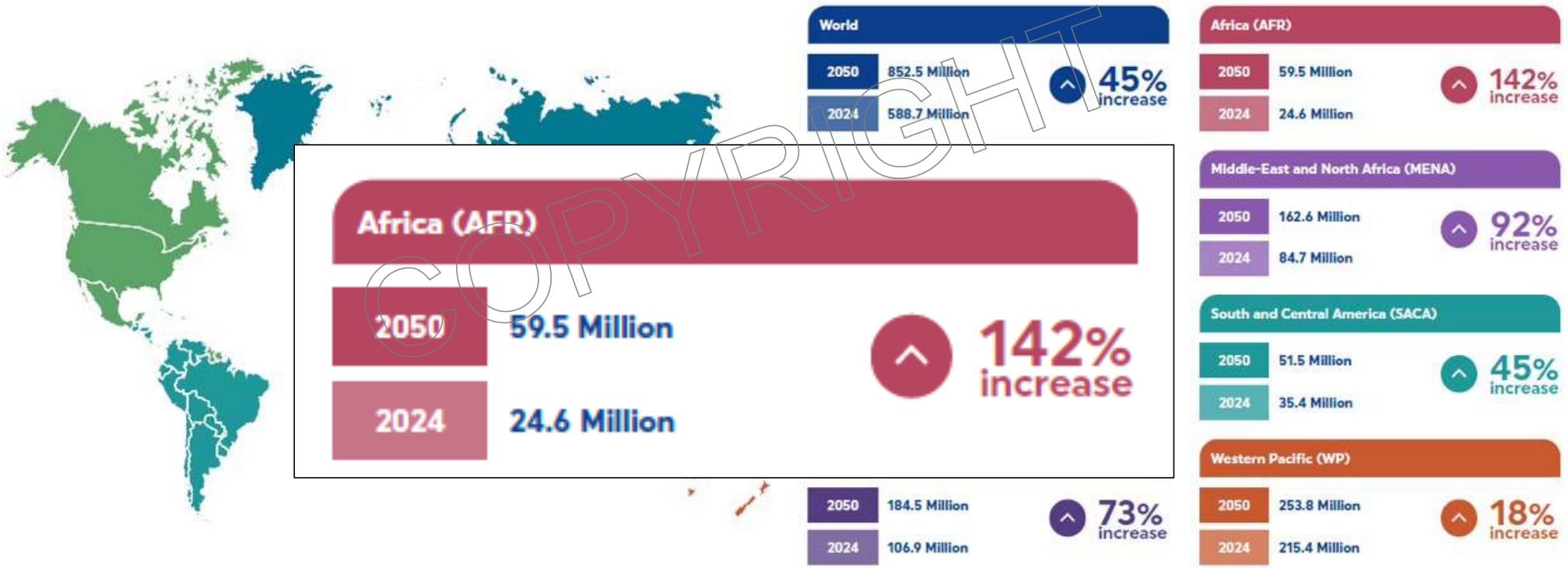
Treatment of Type 2 Diabetes
Cost Effective Management

Joel Dave
Division of Endocrinology
Groote Schuur Hospital/University of Cape Town

Prevalence of Diabetes



IDF Diabetes Atlas 2024 – 11th edition | www.diabetesatlas.org

Cost of diabetes globally

589 million adults

589 million adults (20-79 years) are living with diabetes – 1 in 9. This number is predicted to rise to **853 million by 2050**

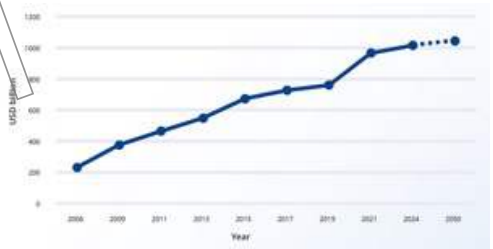
3.4 million deaths

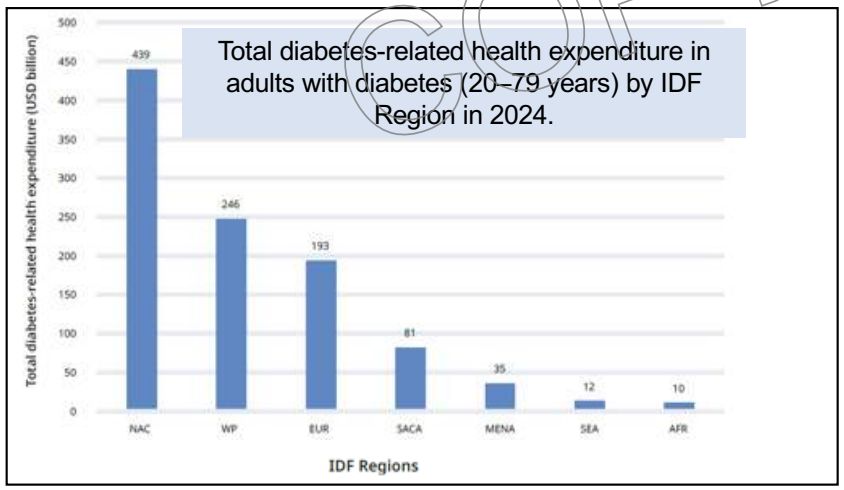
Diabetes was responsible for **3.4 million deaths** in 2024 – 1 every 6 seconds.

1 trillion dollars

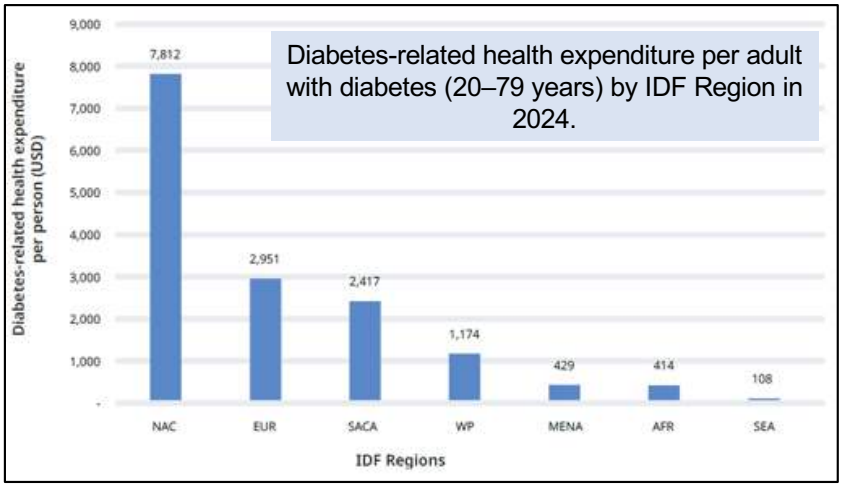
Diabetes caused at least **USD 1 trillion dollars** in health expenditure – a **338% increase** over the last 17 years.

Total diabetes-related health expenditure for adults (20–79 years) with diabetes 2006 to 2050.





Total diabetes-related health expenditure in adults with diabetes (20–79 years) by IDF Region in 2024.



Diabetes-related health expenditure per adult with diabetes (20–79 years) by IDF Region in 2024.

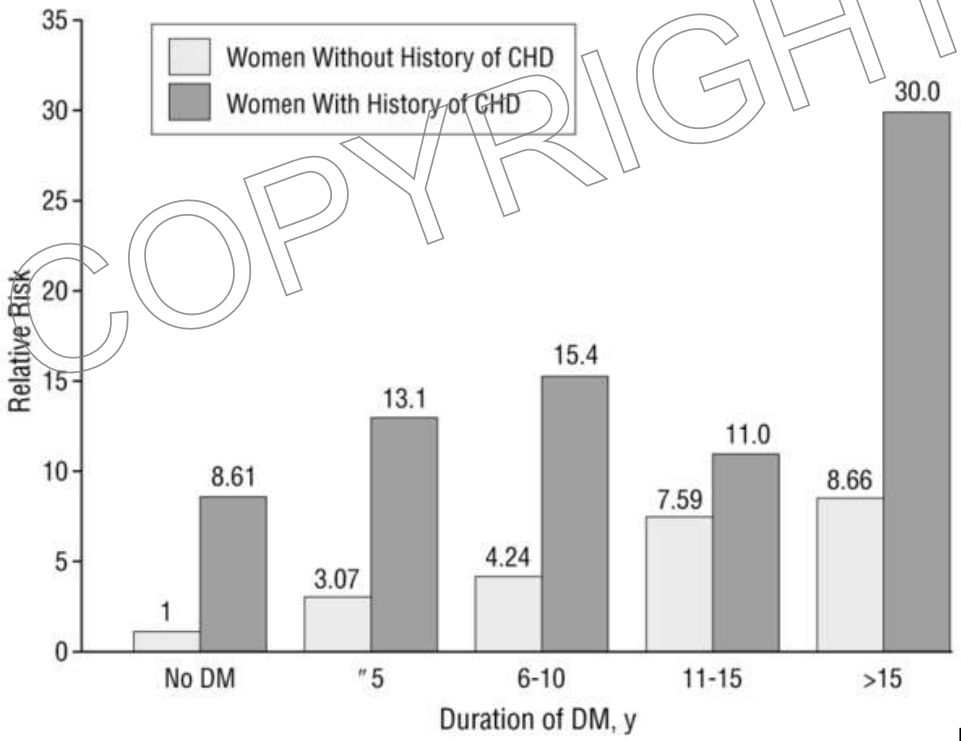
IDF Diabetes Atlas 2024 – 11th edition | www.diabetesatlas.org

Complications of Diabetes

Microvascular	Neuropathy Nephropathy Retinopathy	Glucose
Macrovascular	Ischaemic heart disease Cerebrovascular disease Peripheral vascular disease	
Emergencies	Diabetic ketoacidosis Hyperosmolar non-ketotic coma Hypoglycaemia	

Risk of coronary heart disease in T2DM

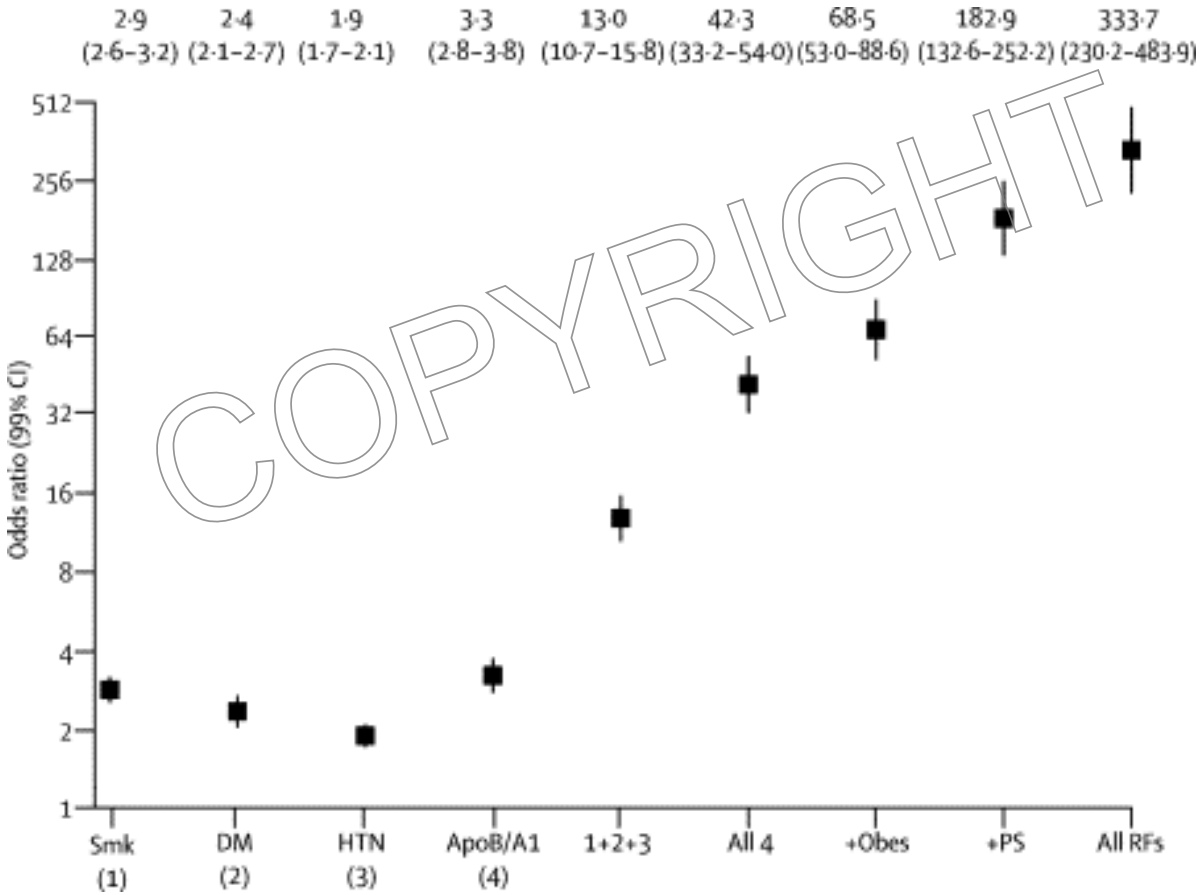
Type 2 Diabetes for >15 Years Duration Confers a Similar Risk of Fatal CHD as Prior CHD and No Diabetes



20-year follow-up of 121,046 women aged 30 to 55 years in Nurses' Health Study

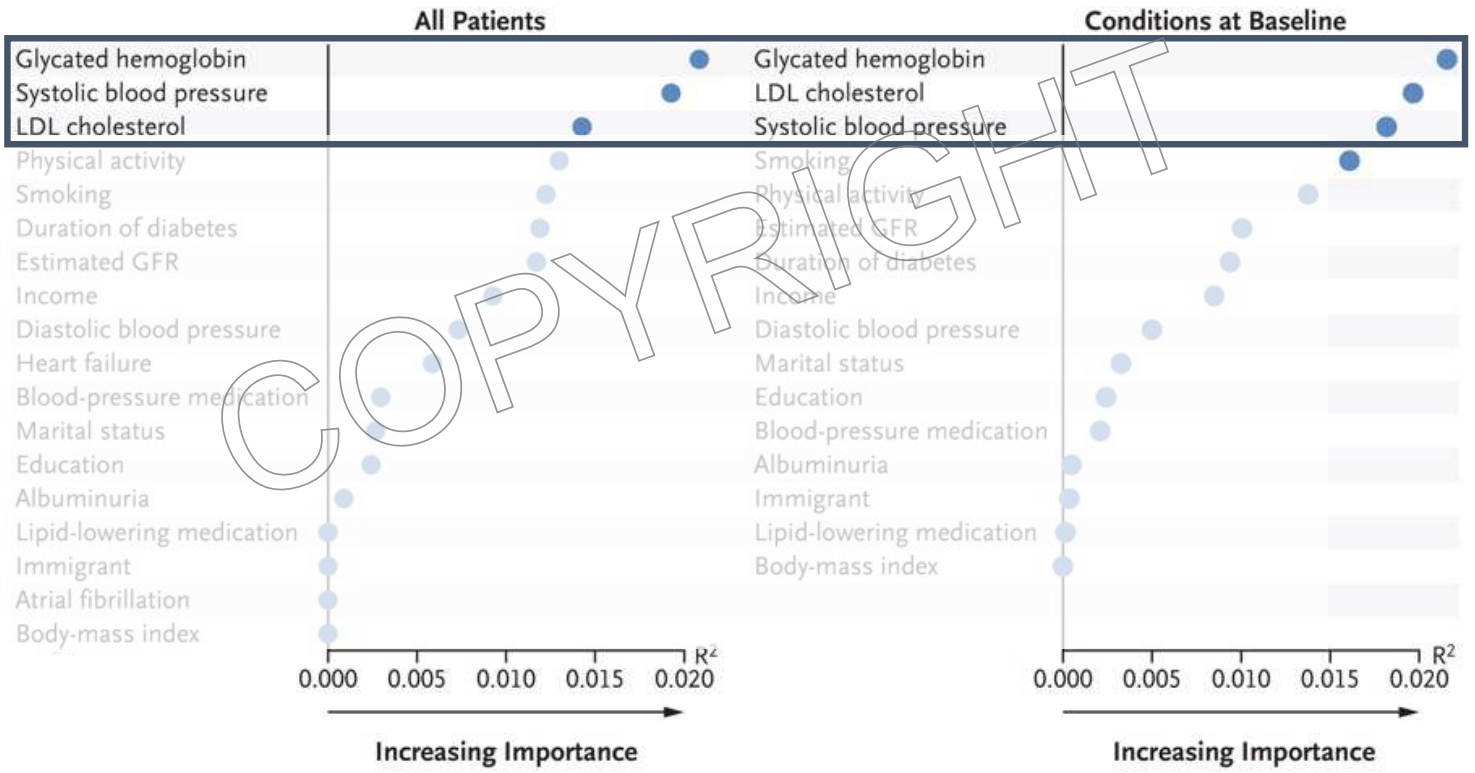
Hu *et al* **(2001)**. Arch Intern Med. 161:1717-1723

The Interheart Study



Lancet 2004; 364: 937–52

Factors predicting acute MI in people with T2DM



Rawshani A et al ***N Engl J Med.*** 2018;379:633-644

Complications of Diabetes

Microvascular
- Neuropathy
- Nephropathy
- Retinopathy

Macrovascular
- Ischaemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease

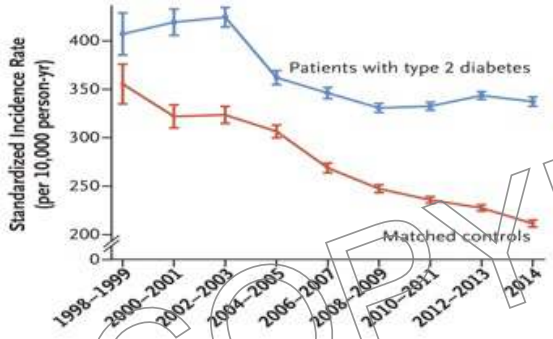
Emergencies
- Diabetic ketoacidosis
- Hyperosmolar non-ketotic coma
- Hypoglycaemia

Glucose

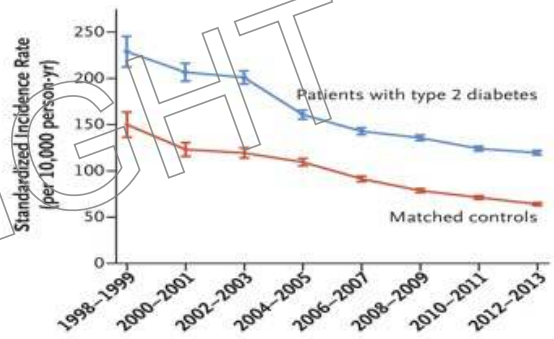
BP
LDL
other

Mortality and CVD in adults with T2DM

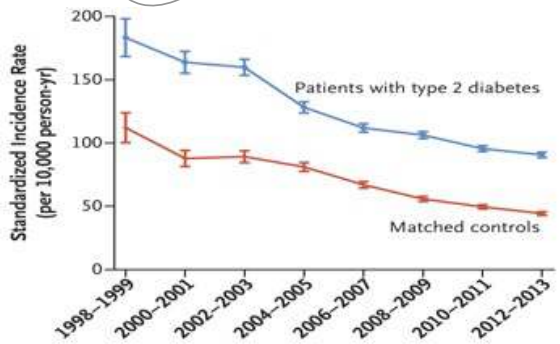
Death from Any Cause



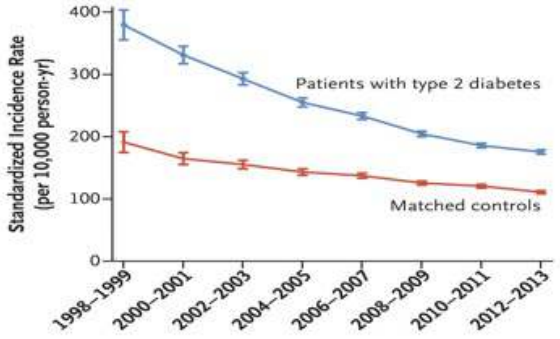
Death from CV Disease



Death from Coronary Artery Disease

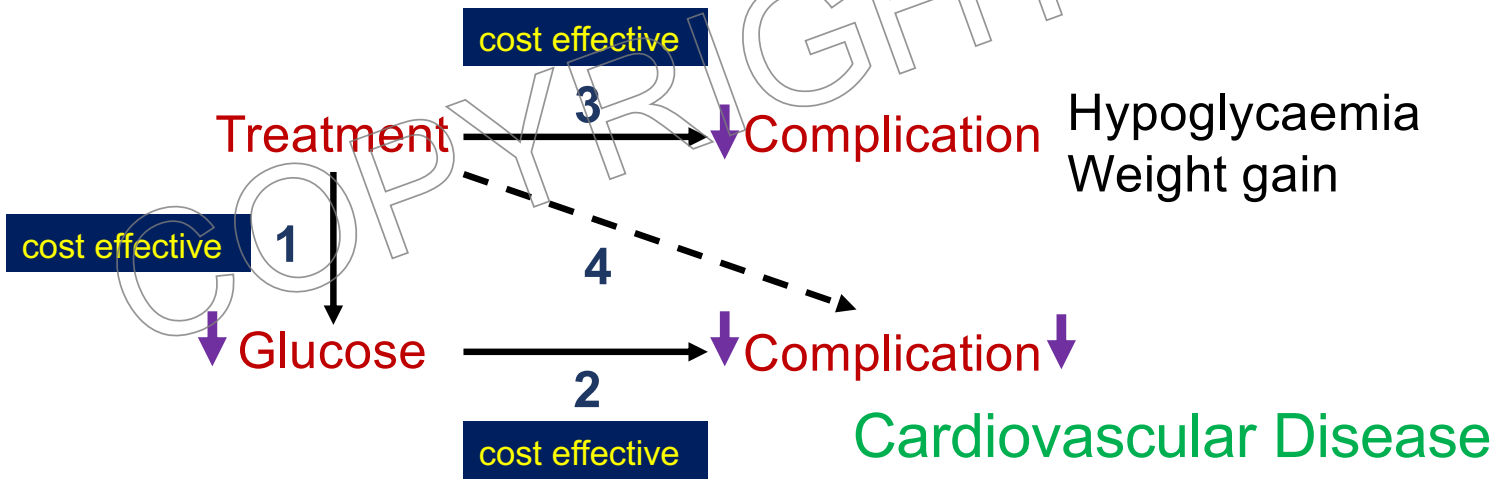


Hospitalization from CV Disease

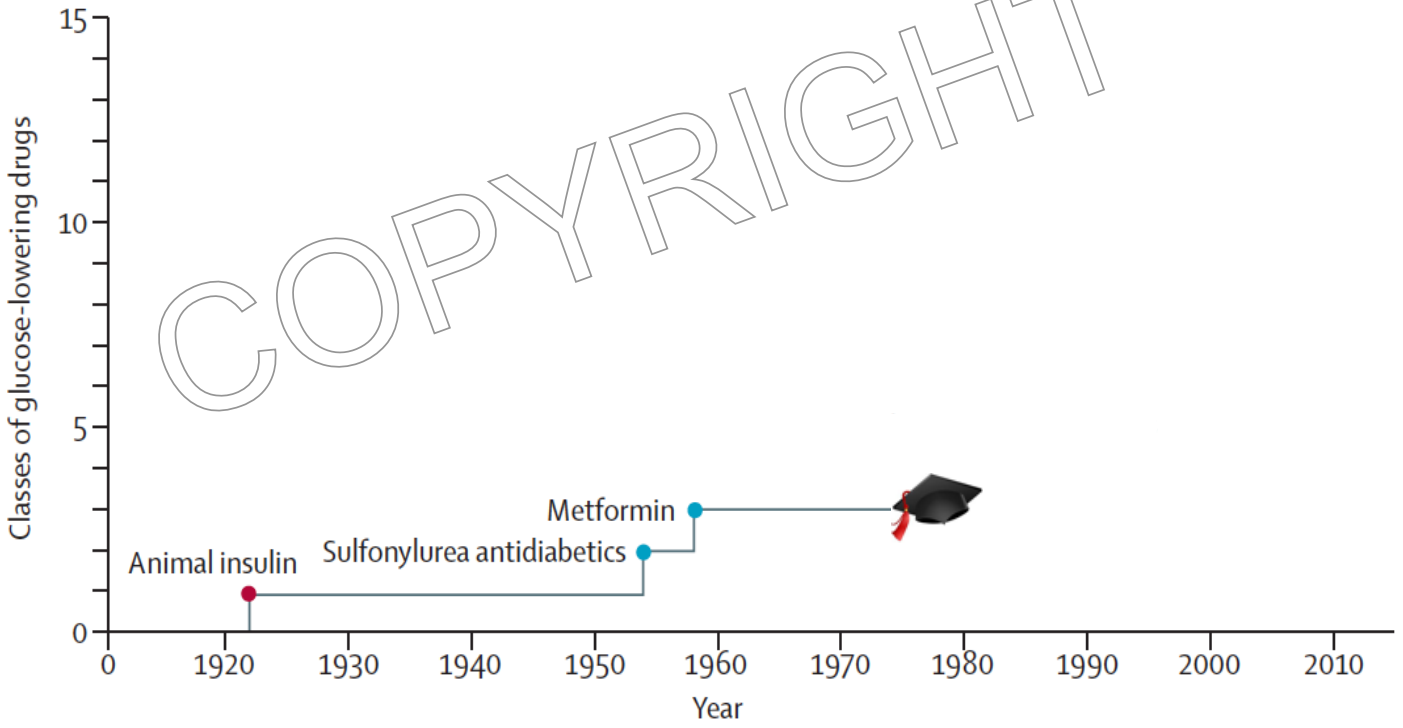


Rawshani A et al ***N Engl J Med*** 2017;376:1407-18.

Treating people with type 2 diabetes

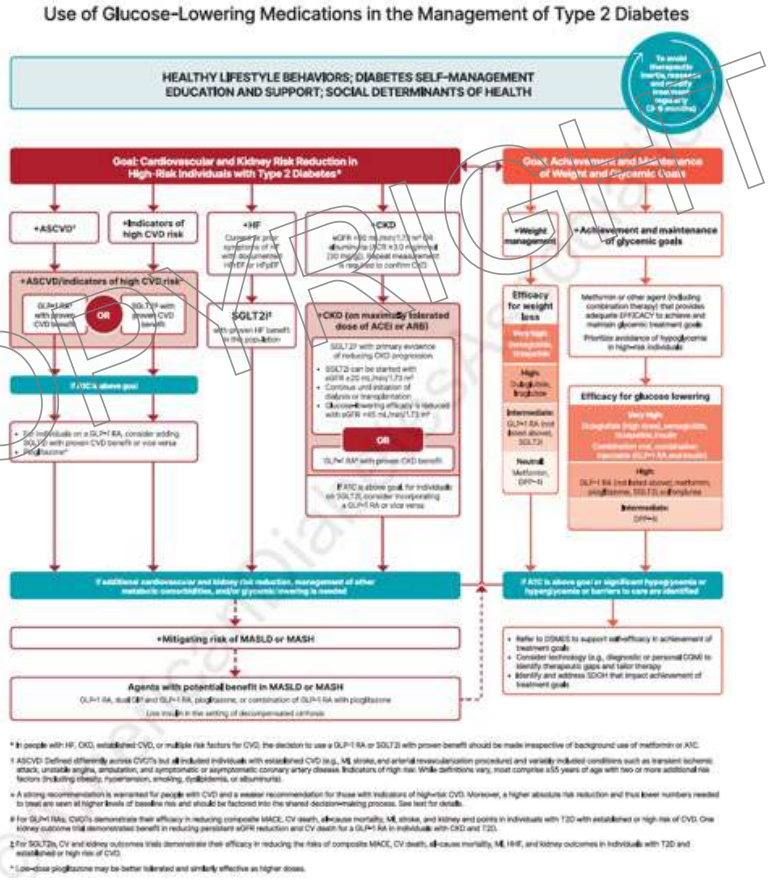


Drugs used to treat people with T2DM



Adapted from Kahn S, Cooper M, Del Prato S. ***Lancet*** 2014; 383: 1068–83

ADA/EASD: Management of people with T2DM



Diabetes Care 2023;46(Suppl.1):S140–S157

The cost of using a GLP-1 receptor analogue

Cardiovascular mortality

Study	NNT [95% CI] 12 months	NNT [95% CI] 24 months	NNT [95% CI] 36 months	NNT [95% CI] 48 months
GLP-1 receptor agonists				
EXSCEL[32]	760 [349 to ∞ to −4279]	327 [151 to ∞ to −1886]	202 [93 to ∞ to −1168]	144 [66 to ∞ to −834]
HARMONY[31]	754 [192 to ∞ to −391]	358 [91 to ∞ to −186]	—	—
LEADER[35]	396 [230 to 1437]	173 [101 to 602]	107 [63 to 370]	77 [45 to 264]
PIONEER 6[33]	138 [76 to 774]	—	—	—
REWIND[30]	1662 [627 to ∞ to −2548]	634 [239 to ∞ to −980]	363 [137 to ∞ to −563]	246 [93 to ∞ to −382]
SUSTAIN 6[34]	1424 [159 to ∞ to −205]	—	—	—

Cost of preventing 1 death from CVD	**R7 603 200**	**R6 643 200**	**R6 163 200**	**R 5 913 600**

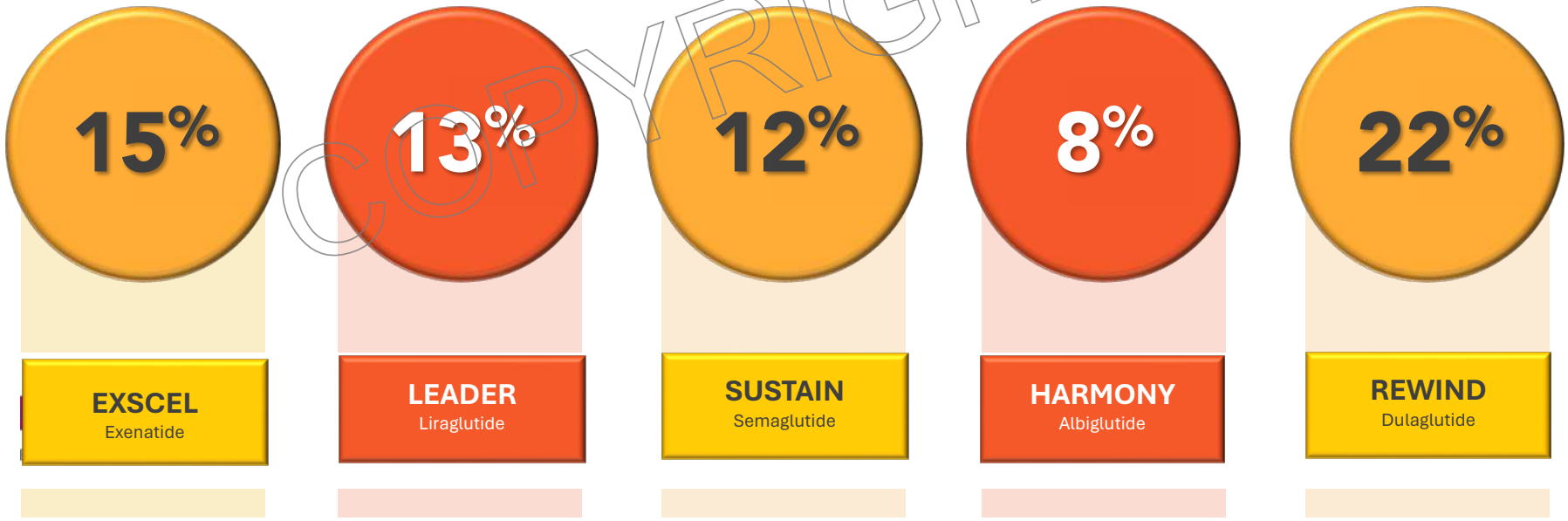
Lancet Diabetes Endocrinol 2020; 8: 418–35

Where does the evidence lie?

Age	Duration DM	No CVD	CVD
<60 years			
	New	UKPDS	
	<10 years		
	>10 years		
≥60 years			
	New		
	<10 years		ELIXA
	≥10 years	REWIND	LEADER SUSTAIN-6 HARMONY EXSCEL REWIND AMPLITUDE-O FREEDOM-CVO

The majority of people with T2DM do not meet the criteria for the GLP-1 RA CVOTs

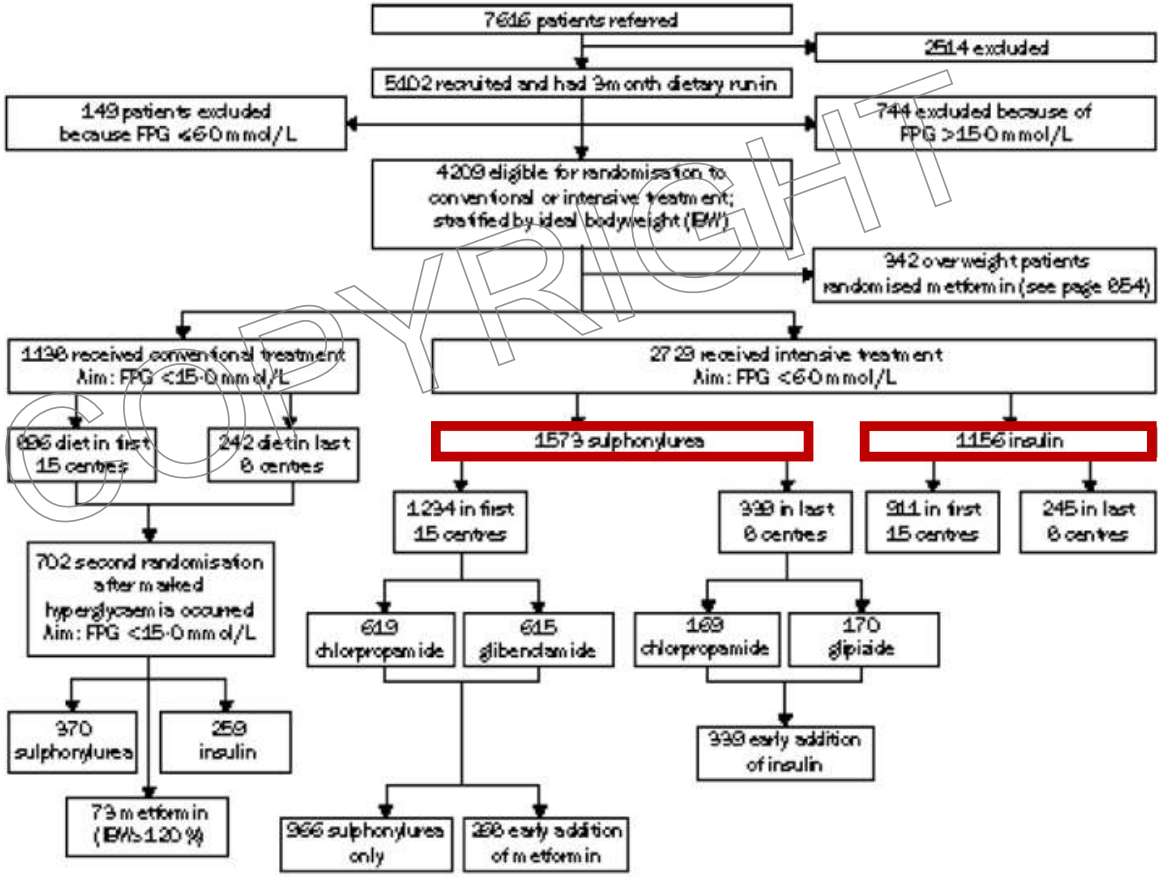
Proportion of patients with T2DM in the US population who would have met eligibility criteria for the following CVOTs



Wittbrodt ET et al. Am J Manag Care. 2018;24:S146-S155; Lage MJ. Am J Manag Care. 2019;25(4):170-171 (Comment)

What we have learnt from the UKPDS

UKPDS

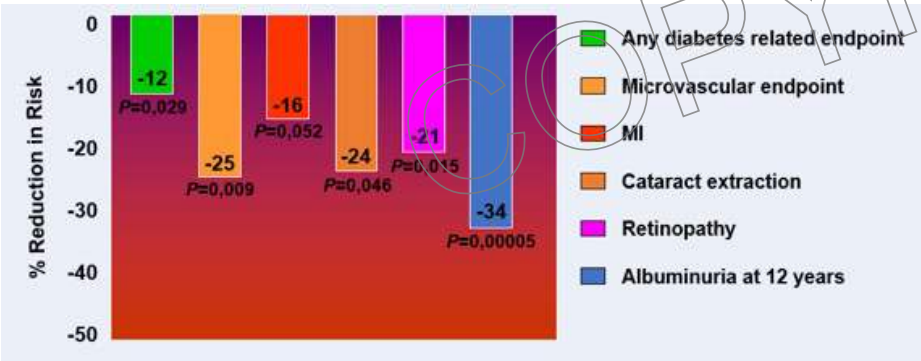


UKPDS Group (UKPDS 33). Lancet 1998;352:837-53

What we have learnt from the UKPDS

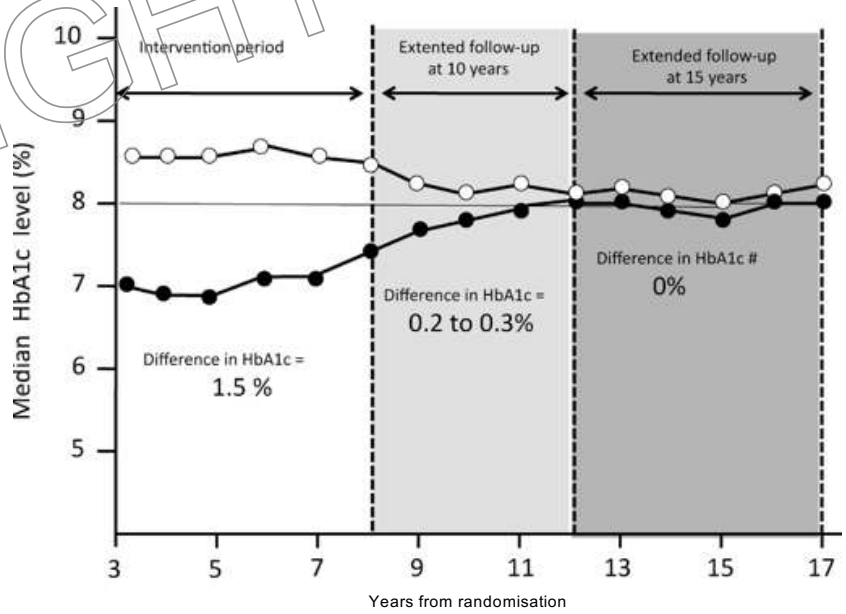
Target HbA1c + < 7%

Benefit with every 1% reduction in HbA1c



Macrovascular benefit at 10 years follow up

The Legacy Effect



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

Diabetes drugs and HbA1c reduction

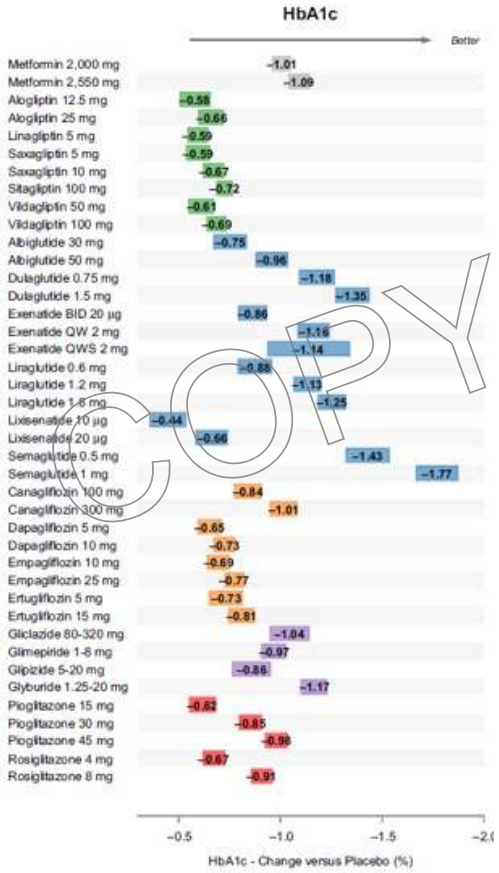
DPPIV inhibitors

GLP-1 RA

SGLT2 inhibitors

Sulphonylureas

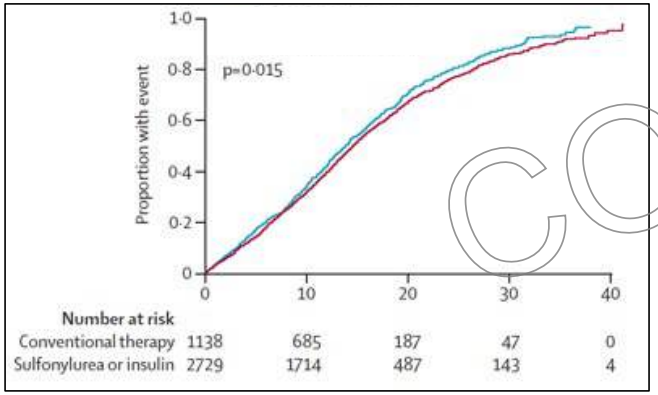
Thiozolidinediones



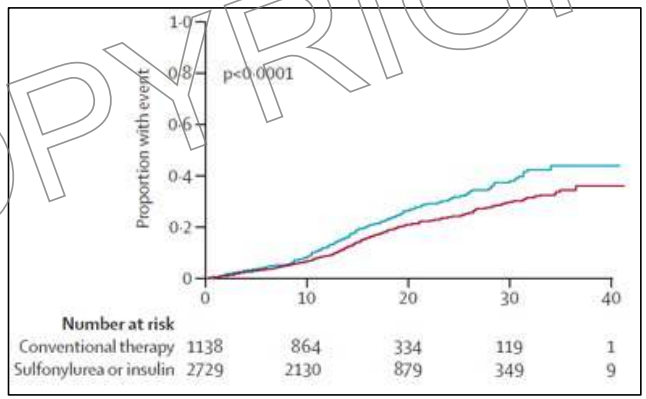
Maloney *et al* (2019). *Clinical Pharmacology & Therapeutics* 105.5: 1213-1223.

UKPDS: 24-year follow-up

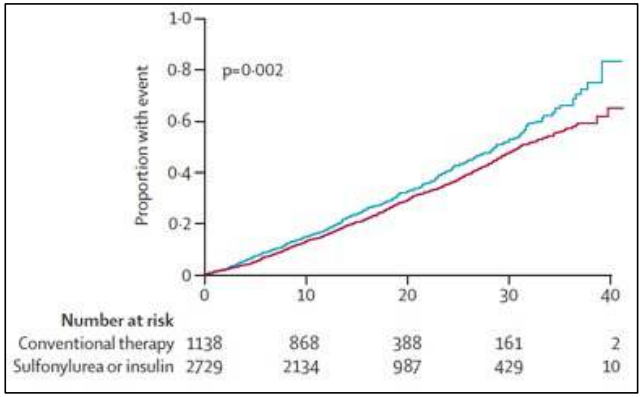
Any diabetes-related end point



Microvascular disease



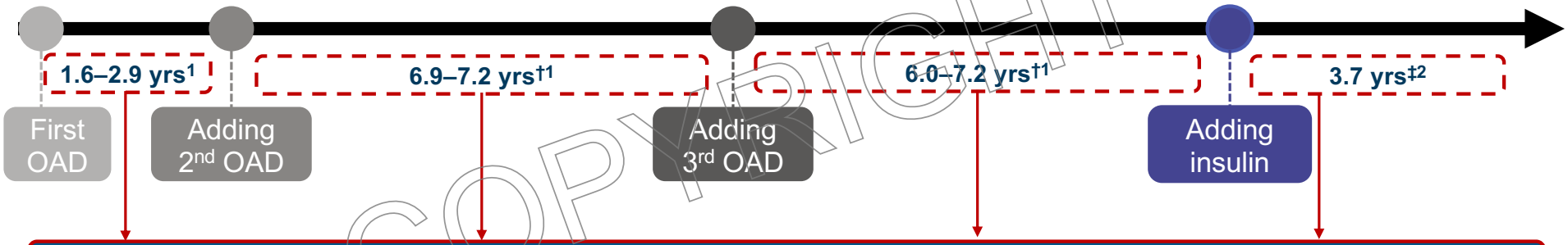
Myocardial infarction



Conventional therapy
Sulfonylurea or insulin

Adler *et al* (2024). Lancet; 404: 145–55

Sequential treatment approach promotes **therapeutic inertia** and delayed achievement of targets



Glycemic burden

Having suboptimal glycaemic control for many years can lead to "dramatic consequences for the individual in terms of quality of life, morbidity and mortality"[3]

Glycaemic burden drives the risk of developing disease-related comorbidities[4]

*Retrospective cohort analyses; †From time when HbA1c was ≥7.0%, ≥7.5% or ≥8.0%;
‡From time when HbA1c was ≥7.5%
GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug

1. Khunti K, et al. Diabetes Care 2013;36:3411–7
2. Khunti K, et al. Diabetes Obes Metab 2016;18:401–9
3. Reach G, et al. Diabetes Metab 2017;43:501–11
4. Del Prato S, et al. Int J Clin Pract 2010;64:295–304

Achieving HbA1c targets

Delayed treatment intensification reduces the likelihood of patients with T2DM achieving target HbA_{1c}

Among people with **T2DM** who intensified therapy after monotherapy failure, the likelihood of achieving glycaemic control was:

22%
LOWER
in **intermediate** intensifiers
(12 to <24 months after monotherapy failure)

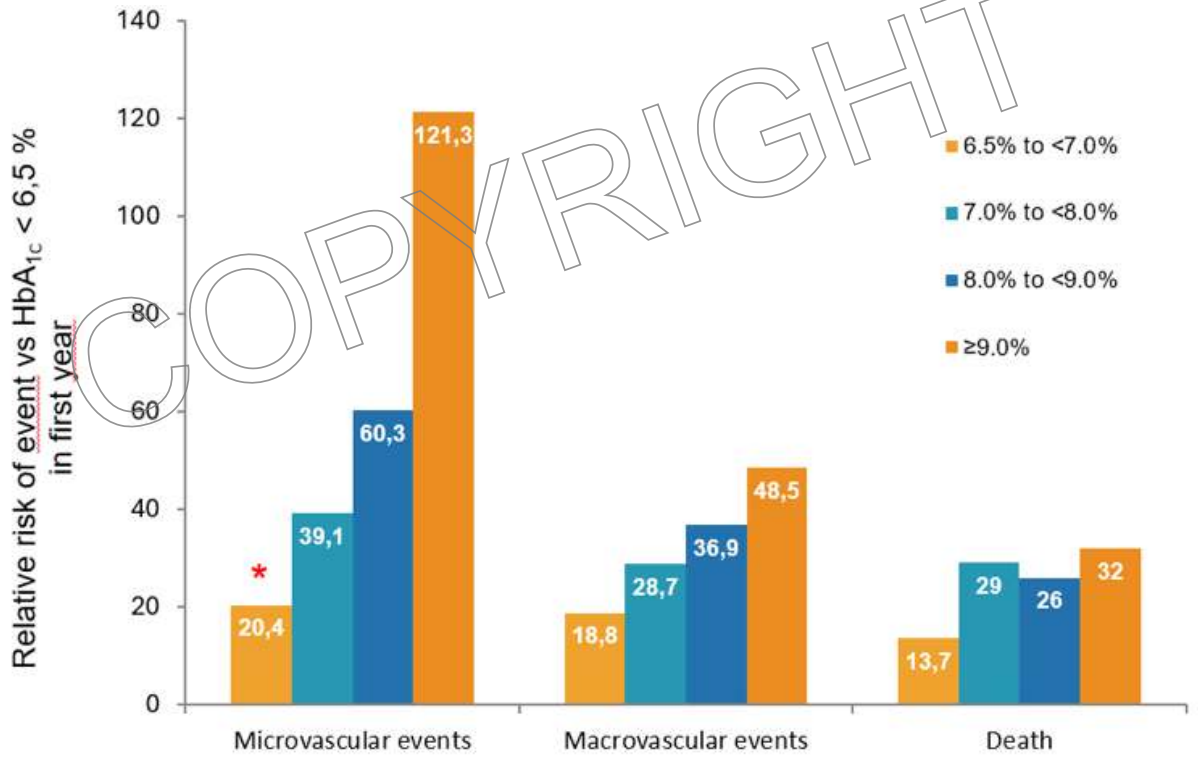
28%
LOWER
in **late** intensifiers
(24 to <36 months after monotherapy failure)

vs early intensifiers
(<12 months after monotherapy failure)

Desai *et al* (2018). Diabetes Care. 41(10):2096-2104; Levin *et al (2016).* Drugs Clin Ther. 38(1):110-121

Early diabetes control is important

Poor glycaemic control in the first year leads to increased risk of micro/macrovascular events and death



Cohort study of managed care patients with newly diagnosed type 2 diabetes and 10 years of survival (1997–2013, average follow-up 13.0 years, N = 34 737)

RR based on HR vs HbA1c < 6.5 % in the first year * significant

Laiteerapong N, et al. Diabetes Care. 2019;42(3):416-426

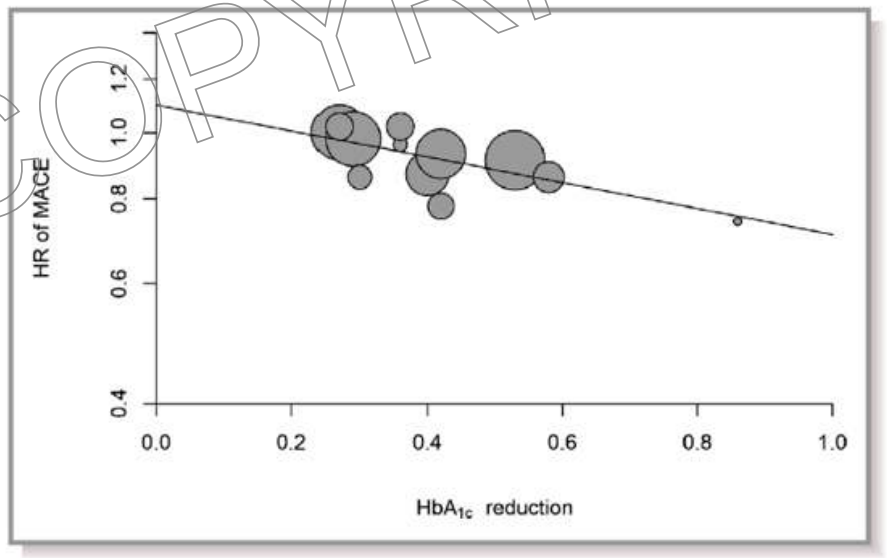
Comparison of CV/death outcomes non-insulin therapies

	MI	CV safety	Death all	Death CV	HF	3-point MACE
Sulphonylureas	UKPDS	ADVANCE	UKPDS			
DPPIV inhibitors		SAVOR EXAMINE TECOS CARMELINA				
GLP-1 receptor agonists	LEADER HARMONY		LEADER PIONEER 6 EXSCEL	LEADER PIONEER 6		LEADER HARMONY SUSTAIN-6 REWIND AMPLITUDE-O
SGLT-2 inhibitors			EMPAREG	EMPAREG CANVAS	EMPAREG CANVAS	
Thiozolidinediones	ProActive					
Insulin	UKPDS	Origin	UKPDS			

HbA1c vs MACE risk in the 12 CVOTs

Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

Dario Giugliano, MD; Maria Ida Maiorino, MD, PhD; Giuseppe Bellastella, MD; Paolo Chiodini, MSc; Katherine Esposito, MD, PhD



J Am Heart Assoc. 2019;8:e012356

Glucose lowering and CVD

Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials

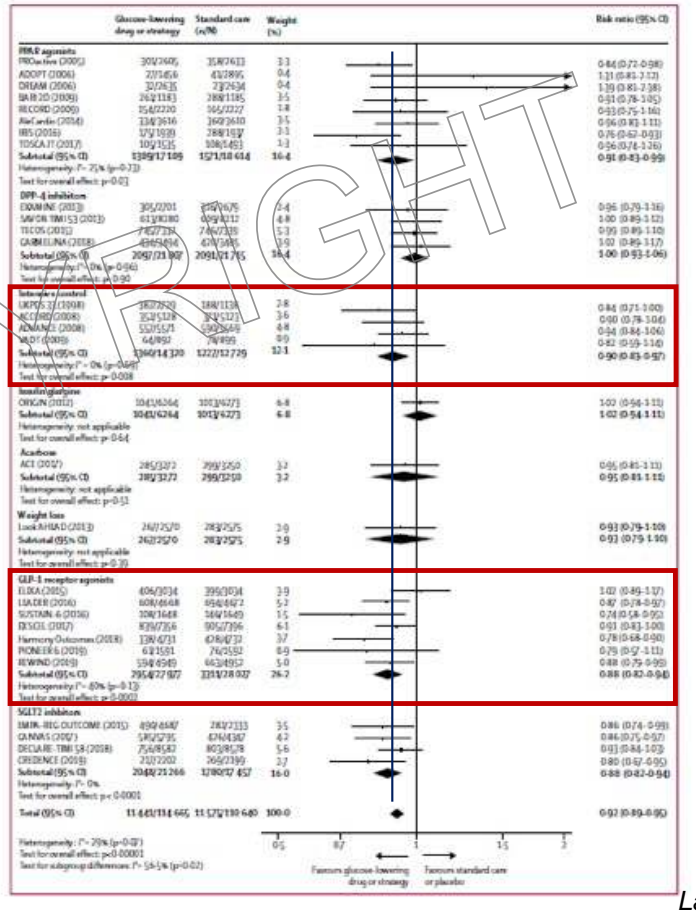
Olivia W Ghosh-Swaby, Shaun G Goodman, Lawrence A Leiter, Alice Cheng, Kim A Connelly, David Fitchett, Peter Jüni, Michael E Farkouh, Jacob A Udell

TZDs

Intensive control

GLP-1 RA

SGLT2 inhibitors



Lancet Diabetes Endocrinol 2020; 8: 418–35

Medical Nutrition Therapy (MNT) and HbA1c reduction

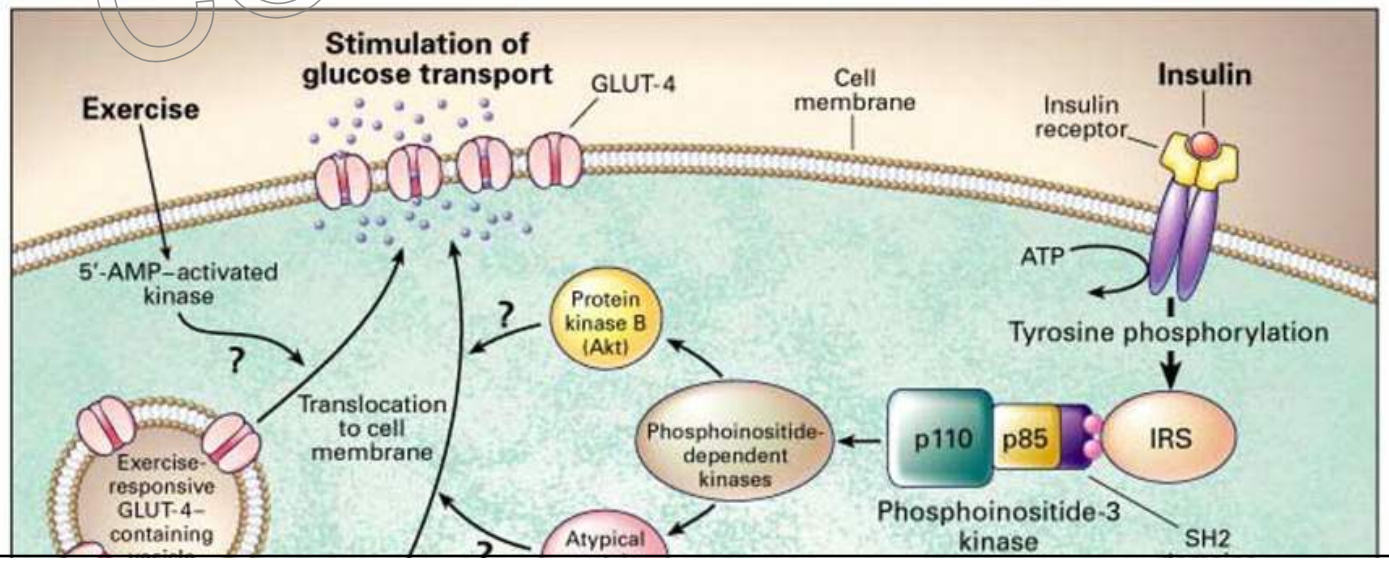
- Variety
- Low carbohydrate, Mediterranean, low fat, low glycaemic index
- Science of medical nutrition therapy continues to evolve
- Can achieve an HbA1c reduction:
  - Type 1 diabetes 1.0-1.9%
  - Type 2 diabetes 0.3-2.0%
- Individualise MNT
- All people with diabetes should be referred or receive education on MNT

Franz *et al* (2010). J Am Diet Assoc. 110(12):1852–89; Franz et al (2017). J Acad Nutr Diet. 117:1659-1679

Exercise and HbA1c reduction

Effects of exercise training and physical activity advice on HbA1c in people with type 2 diabetes: A network *meta*-analysis of randomized controlled trials

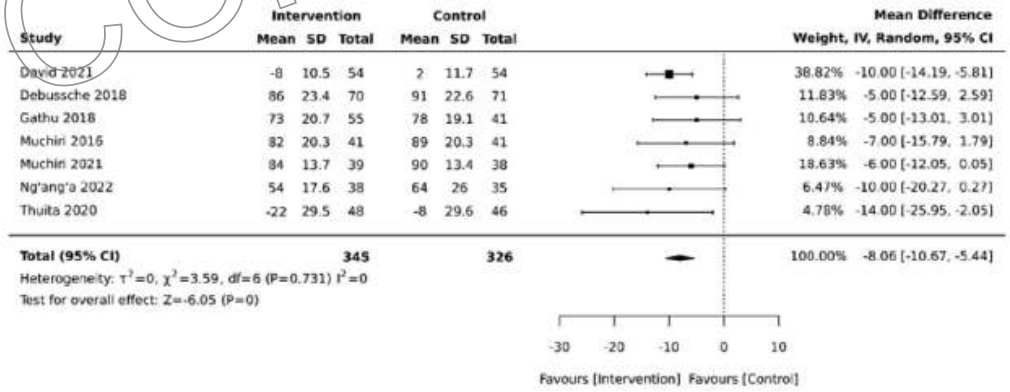
- 12 990 records screened
- 158 RCTs (n=17 059) included



Self-management interventions and HbA1c reduction

Effectiveness and safety of self-management interventions for improving glycemic control and health-related quality of life among adults with type 2 diabetes mellitus in sub-Saharan Africa: a systematic review and meta-analysis

- 2699 records, included 18 RCTs
- broad self-management education programs, peer support, exercise interventions with education, nutrition education, educational text messaging, and blood glucose self-monitoring support



- No HbA1c reduction at 12 months

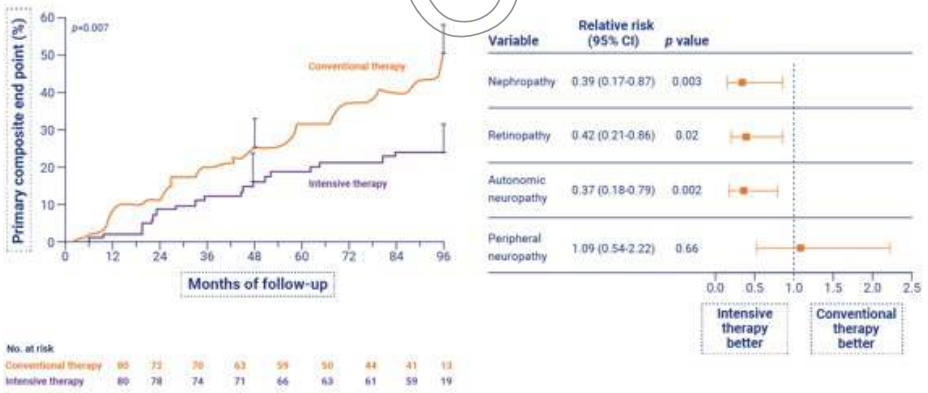
Carter *et al* (2024). JBI Evid Synth. 22(9):1715–1788

STENO-2 Study

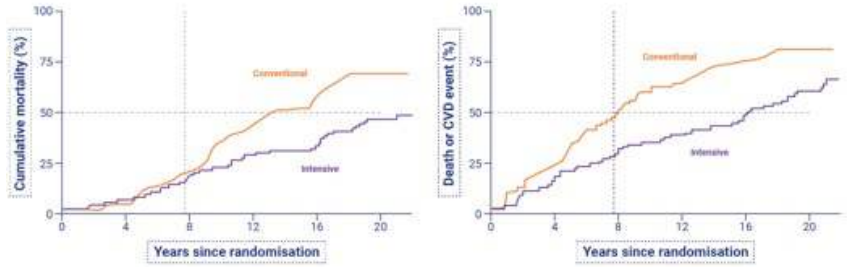
	Conventional	Intensive
Haemoglobin A_{1c} (%)	<7.5	<6.5
F-s-cholesterol (mmol/l)	<6.5	<4.5
F-s-triglycerides (mmol/l)	<2.2	<1.7
Systolic BP (mm Hg)	<160	<130
Diastolic BP (mm Hg)	<95	<80
ACEi irrespective of BP	No	Yes
Aspirin, primary prevention	No	Yes

Reduction in Mortality at 13.3 years

Reduction in complications at 7.8 years



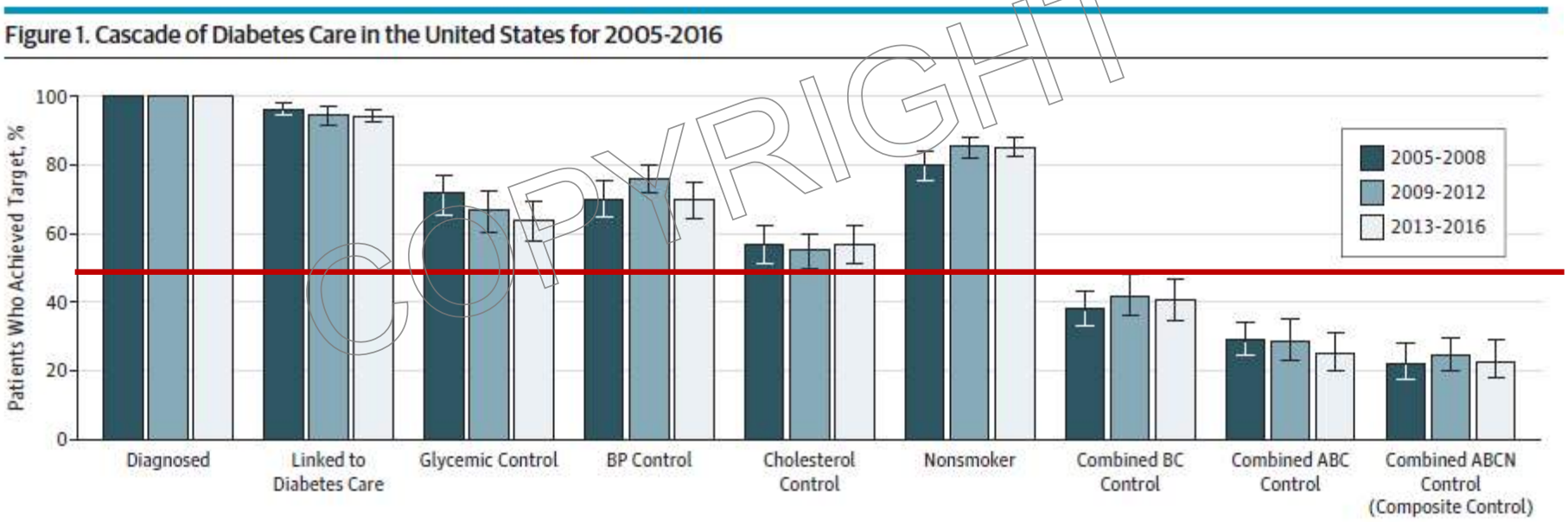
Life years gained at 21 years



N Engl J Med 2003;348:383-93; N Engl J Med 2008;358:580-91; Diabetologia 2016. 59:2298–2307

Many patients with diabetes are NOT at target HbA1c

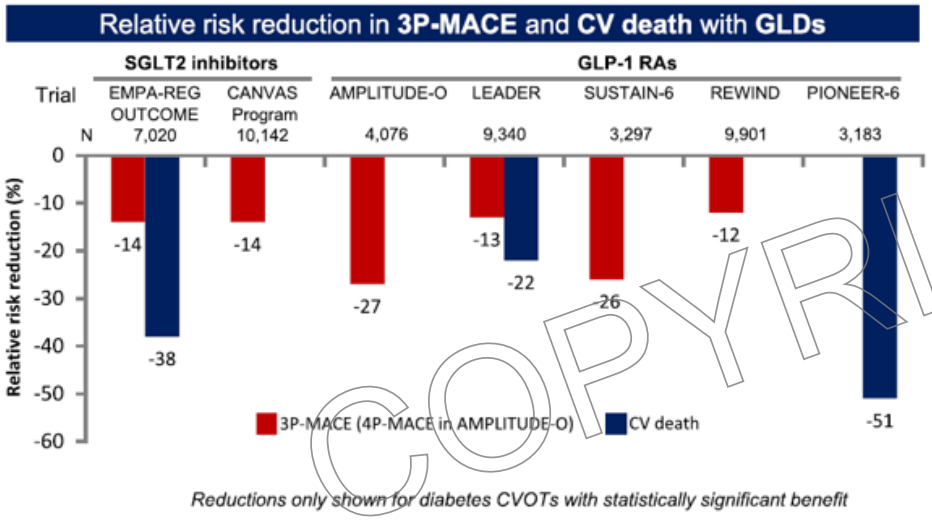
National Health and Nutrition Examination Survey (NHANES) cross-sectional data from 2005 to 2016

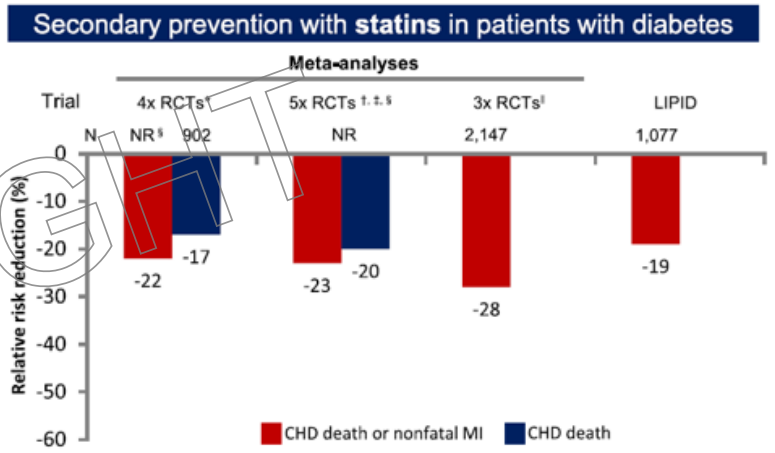


BC= BP and cholestrol
ABC=HbA1c, BP and cholesterol
ABCN= HbA1c, BP, cholesterol and non-smoker

JAMA Intern Med. 2019;179(10):1376-1385

Glucose lowering and CVD





NNT with GLDs

Empagliflozin EMPA-REG OUTCOME	Liraglutide LEADER	Semaglutide SUSTAIN-6	Empagliflozin EMPA-REG OUTCOME
63 NNT in 3.1 years to prevent one 3P-MACE	53 NNT in 3.8 years to prevent one 3P-MACE	44 NNT in 2 years to prevent one 3P-MACE	39 NNT in 3.1 years to prevent one death
R1 235 000	R4 480 750	R2 662 180	R765 000

NNT with cardiorenal therapies

Aspirin in prior MI or stroke	Statins in known CAD or stroke	Antihypertensive therapy
50 NNT in 2 years to prevent one 3P-MACE	83 NNT in 5 years to prevent one death	125 NNT in 5 years to prevent one death
R33 600	R149 400	R855 000

Davies et al (2022). Cardiovascular Diabetology 21:144

Summary

- HbA1c reduction towards an individualized target remains the most important part of managing a person with T2DM – drugs, MNT, exercise
- HbA1c reduction as early and safely as possible
- Multifactorial intervention is important, especially blood pressure and LDL lowering
- Use the cheapest drugs available in your country with proven benefits such as metformin, gliclazide MR, pioglitazone, insulin
- Place for everything - individualise therapy, cost IS important

Thank you for listening