TYPE 2 DM: "GLYCEMIC CONTROL: WHAT THE HEART'S GOT TO DO WITH IT"

Dr Andrian Dreyer
FCP(SA), MMED(WITS), MBChB(UFS), DipHIVMan (SA)

DISCLOSURES

1. I received financial support from Servier for the time spent in preparation for this talk.

DIABETES:
A MAJOR MODIFIABLE CVD RISK

Dr. Andrian Dreyer
Specialist Physician / Internis

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

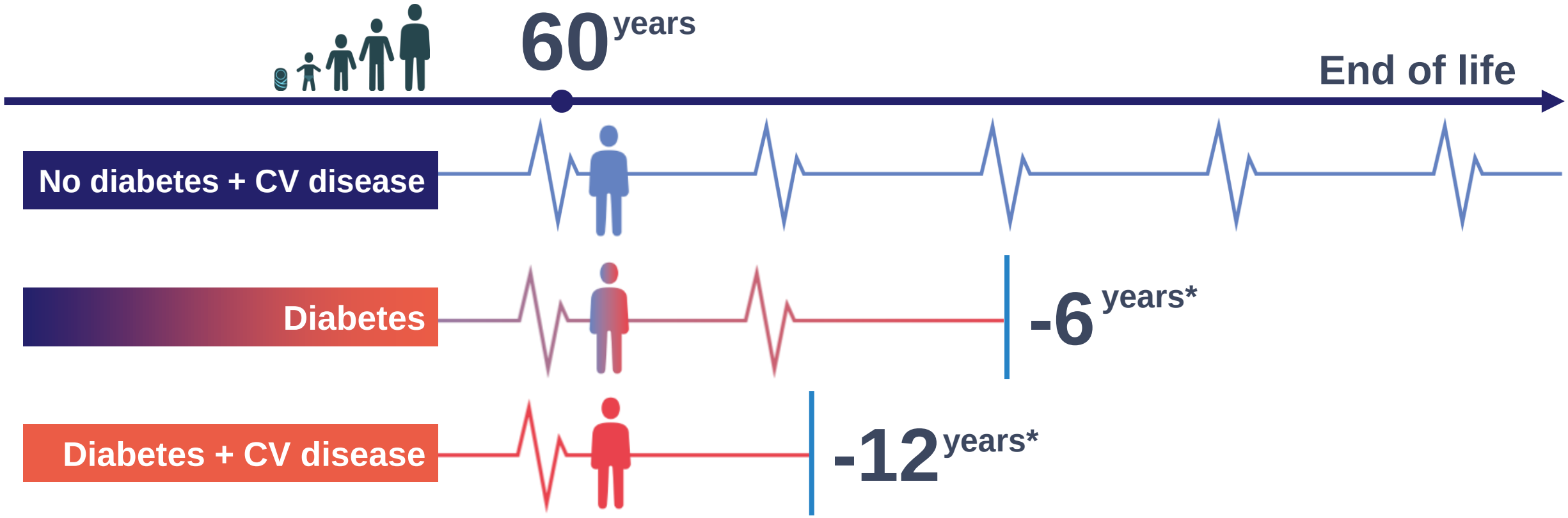
die from CV disease[2]

CV, cardiovascular; T2D, type 2 diabetes

1. Booth 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

AT THE HEART OF DIABETES

Diabetes & Heart Disease By The #s

U.S. DIABETES PATIENTS HAVE:

2-3x

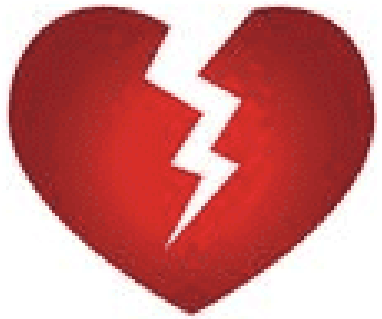
increased risk for heart disease

30%

of coronary stents implanted in 2011

280,000

heart attacks annually



2-4x

higher heart disease morbidity and mortality rates

60%

chance of dying from heart disease

The Death toll is enormous…

- 4,2 Million deaths due to DM annually age 20-79
- 1/9 deaths amongst 20-79 = DM
- 46,2% of deaths due to DM = <60 year olds
- Africa contributes 73,1% of the diabetics deaths in the <60 year olds

Practically:

- 31 536 000 / 4 200 000 = 7,5 secs = DM death

- 2/3 due to CVD

Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, Unwin N, Wild SH, Williams R. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2020 Apr;162:108086. doi: 10.1016/j.diabres.2020.108086. Epub 2020 Feb 15. PMID: 32068099.

CVD PREVENTION – THE BASICS

- 2021 ESC guidelines* offer an excellent framework for considering risk stratification and CVD prevention at an individual and population level
- Tries to individualize CVD prevention into broad patient groups
  - Apparently heathy
  - Established ASCVD
  - CKD
  - Familial hypercholesterolemia
  - **Diabetes Mellitus**

* https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/2021-ESC-Guidelines-on-cardiovascular-disease-prevention-in-clinical-practice

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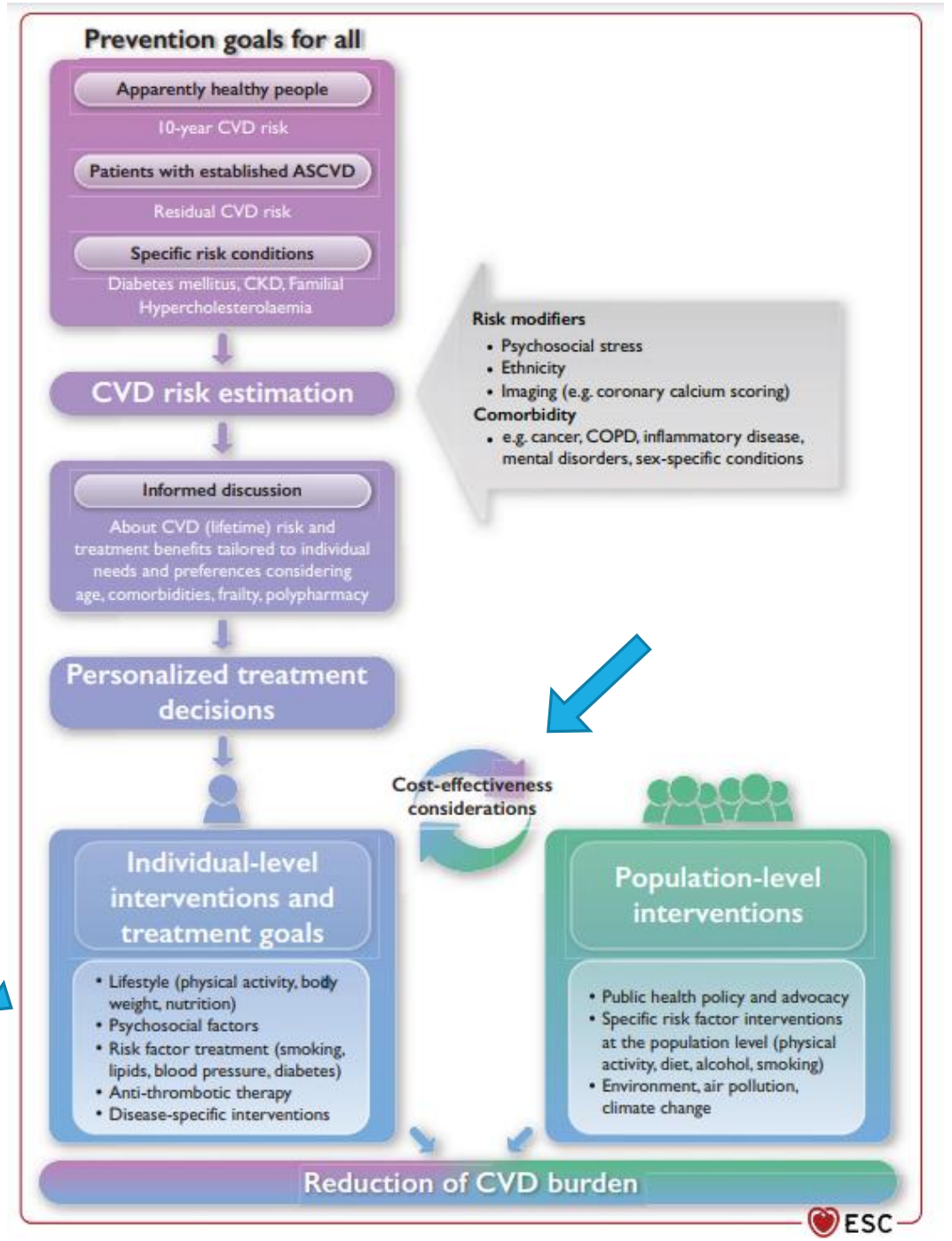
Multifactorial risk augmentation



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CVD PREVENTION IN PATIENTS WITH T2D

AS FEW AS 10% OF DIABETICS REACH 3 TARGETS*

- Modifiable factors driving ASCVD
  - Blood apolipoprotein-B-containing lipoproteins (RRR 23% in 5 years)
  - High blood pressure (20-25% RRR)
  - Cigarette smoking (50% RRR within 1 year)
  - **HBA1c**

*Menon, A. S., & Ahluwalia, A. I. (2015). The ABC of diabetes. How many patients are able to achieve the goal laid down by American Diabetes Association?. *Medical journal, Armed Forces India*, *71*(2), 132–134. https://doi.org/10.1016/j.mjafi.2014.10.008

Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291:335-342

American Diabetes Association. Standards of medical care in diabetes -- 2008. Diabetes Care 2008;31:Suppl 1:S12-S54

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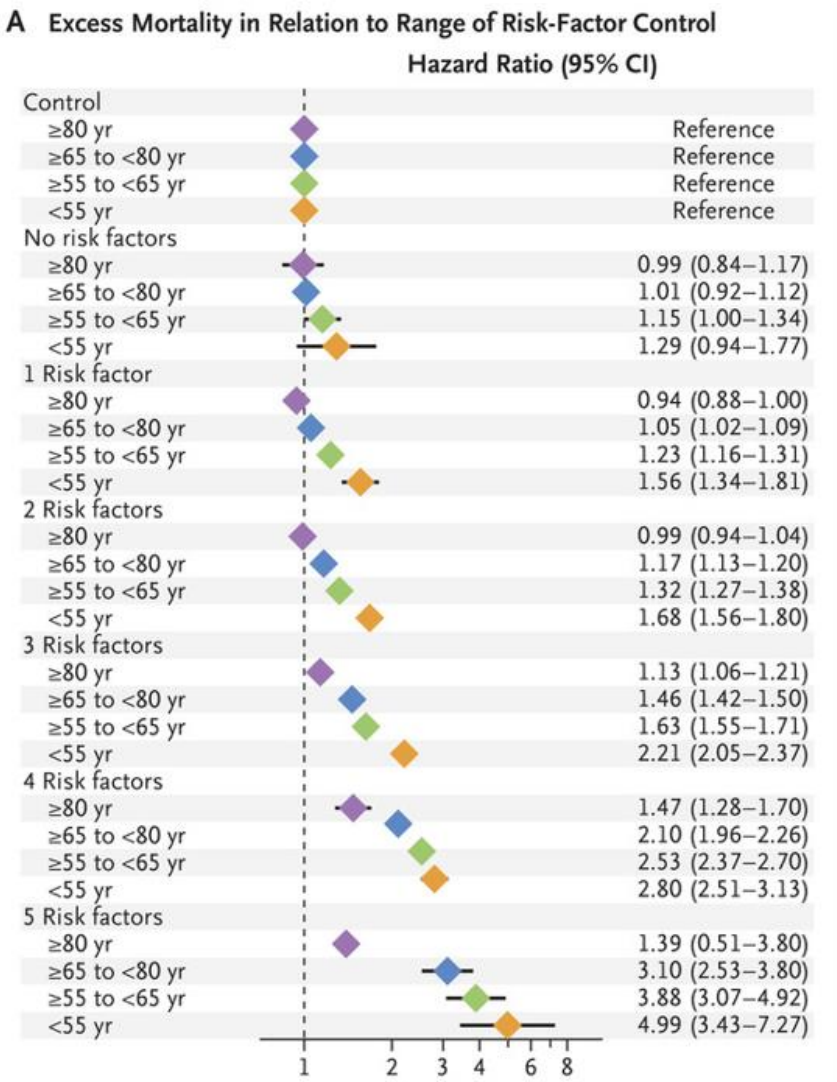
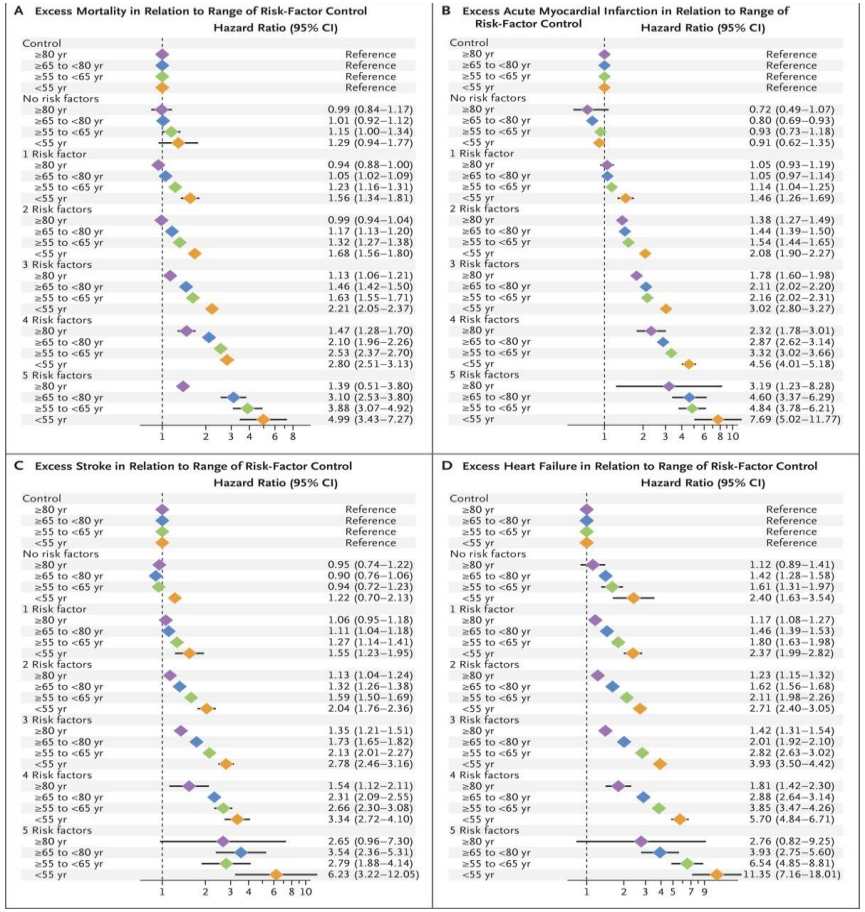
ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.





Definition of control:

1. HBA1c <7,0%
2. Systolic BP <140 mmHg
3. Nil macroproteinuria
4. Smoking - stop
5. LDL <2,5mmol/L

In conclusion, patients with type 2 diabetes who had five risk-factor variables within target ranges appeared to have little or no excess risks of death, myocardial infarction, and stroke as compared with the general population.

LIFE'S ESSENTIAL 8 – AHA

PRIMARY CARE PARADIGM FOR POPULATION BASED CVD PREVENTION

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LIFE'S ESSENTIAL 8 – A PARADIGM FOR CVD RISK MANAGEMENT FOR DAILY USE

1. Stop smoking
2. Limit alcohol to 100g per week
3. Screen for and treat hypertension
    1. First goal SBP 130-140mmHg
        1. Using SPC
            1. Molecules with proven efficacy and as close to 24 hours duration of action as possible
    2. Then intensification <130mmHg if tolerated
4. Lifestyle modification and exercise recommendations
5. Weight loss and dietary advice
6. Lipid management
    1. Initial target <2,6mmol/L and lower in very high risk groups
    2. Target 1,4-1,8mmol/L in established ASCVD groups
7. Sleep hygiene and rest

https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

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HBA1C – THE VIRAL LOAD OF DIABETES

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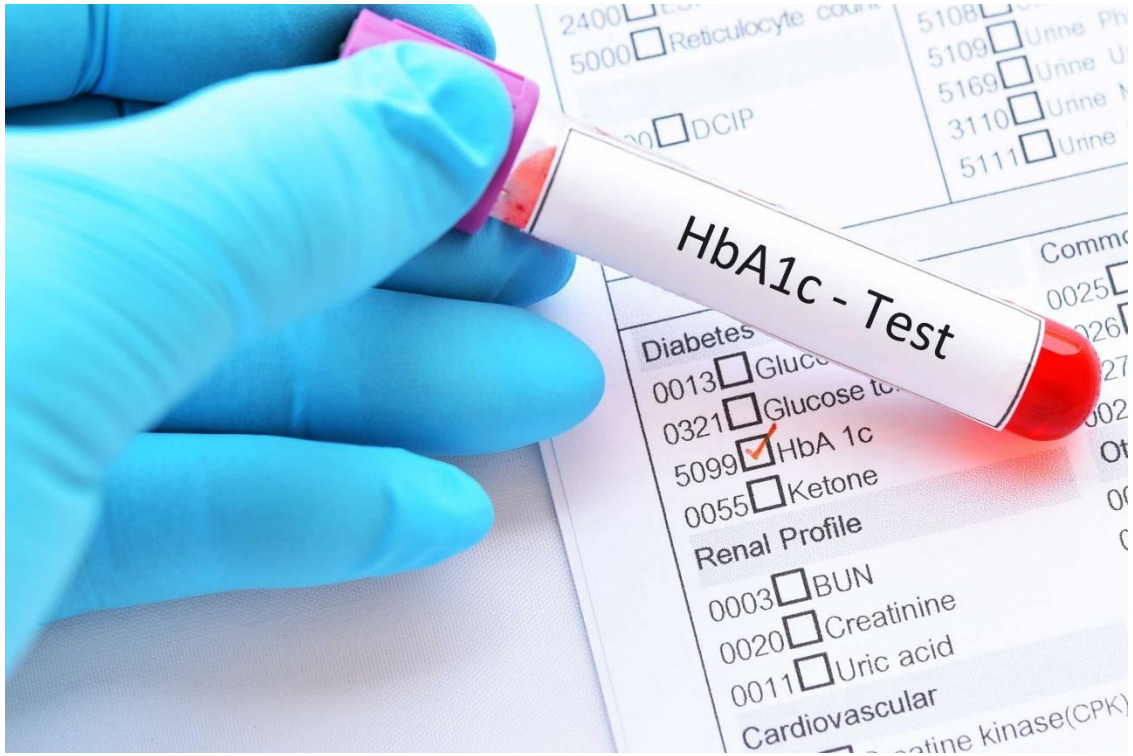
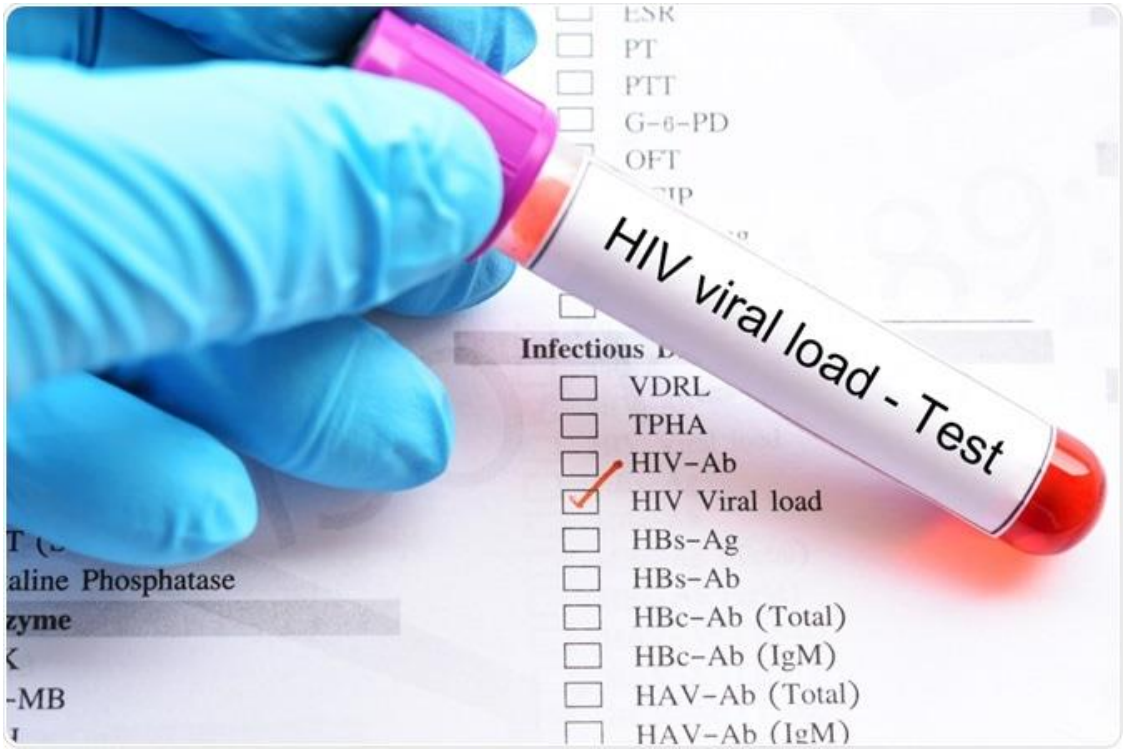
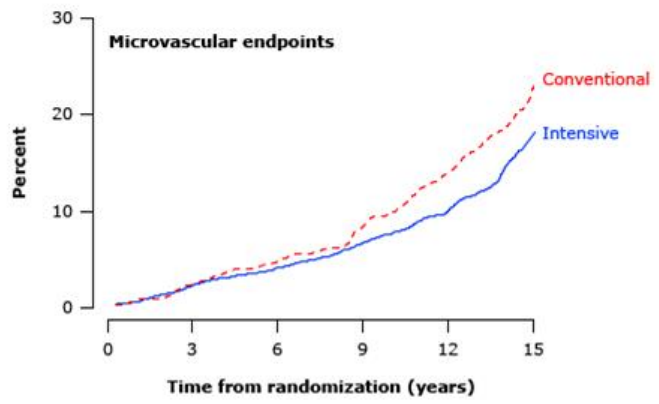
WHY ARE YOU NOT WORRIED?





HBA1C AND MICROVASCULAR DISEASE IN T2D

Intensive glycemic control prevents severe microvascular disease in patients with type 2 diabetes



Kaplan-Meier plots of aggregate endpoints of microvascular disease in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to receive either intensive therapy with a sulfonylurea or insulin, or to conventional treatment with diet; drugs were added if the patients had hyperglycemic symptoms or fasting blood glucose concentrations greater than 270 mg/dL (15 mmol/L). Intensive therapy was associated with a 25% reduction (p = 0.01) in the development of microvascular disease, which was defined as renal failure, death from renal failure, retinal photocoagulation, or vitreous hemorrhage.

Data from: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

UpToDate®

Benefit well established Cumulatively 34 912 pts

Early HBA1c goal achieved

Lower HBA1c

Sustained

=

Fever long term microvascular complications

Effect of intensive versus standard blood glucose control on major microvascular outcomes in type 2 diabetes

Study	Kumamoto study	UKPDS 33	UKPDS 80 (post-UKPDS 33)	ACCORD	ADVANCE	VADT
Population	110	4209	3277	10,251	11,140	1791
Age (years)	47-52	53		62	66	60
BMI (kg/m^2)	19-21	28		32	28	31
Complications	−/+	−/+		++	++	++
Disease duration (years)	6-10	0		10	8	11.5
Baseline A1C (%)	8.9-9.4	7.1		8.3	7.5	9.4
Post-trial A1C (intensive versus standard; %)	7.1 versus 9.4	7.0 versus 7.9		6.3 versus 7.5	6.5 versus 7.3	7.0 versus 8.5
Microvascular endpoints						
Retinopathy	0.31 (0.13-0.76) ≥2-step cumulative change	0.75 (0.60-0.98) Any microvascular outcome	0.76 (0.64-0.89) Any microvascular outcome	0.67 (0.51-0.87)* 3-step progression	0.72 (0.44-1.17)* 3-step progression	0.77 (0.58-1.02) 2-step progression
Nephropathy	0.30 (0.11-0.86) New or worsening nephropathy			0.72 (0.61-0.84) Incident macroalbuminuria	0.79 (0.66-0.93) New or worsening nephropathy	0.65 (0.49-0.89) Any increase in albuminuria
Neuropathy				0.92 (0.86-0.99) Neuropathy (MNSI>2)		0.99 (0.87-1.14) Any new neuropathy

UKPDS: United Kingdom Prospective Diabetes Study; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease; VADT: Veterans Affairs Diabetes Trial; BMI: body mass index; A1C: glycated hemoglobin; MNSI: Michigan Neuropathy Screening Instrument.

* Data are relative risk (95% confidence interval) or odds ratio.

HBA1C AND MACROVASCULAR DISEASE IN T2D

VADT
ADVANCE
ACCORD*

=

No benefit in Macrovascular disease based on intensive HBA1c reductions

VS

UKPDS

=

Significant benefit for MACE after INTENSIVE reduction in HBA1c reduction
Sustained after trial period

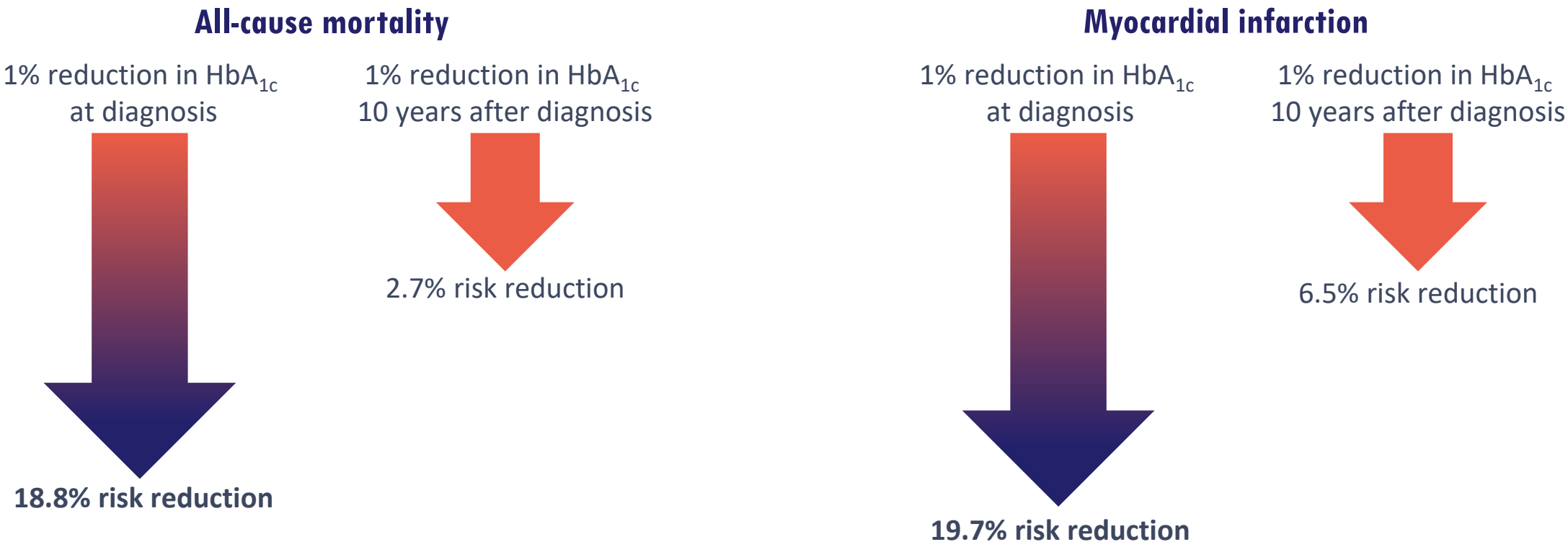
- Patients with longstanding DM
- *Thiazolidinediones and insulin (weight gain ? Fluid retention)
- *Shorter trial duration – terminated
- *No increase in mortality if no ASCVD

Newly diagnosed DM

Prolonged follow up (reached significance after 10 years)

Dr. Andrian Dreyer
Specialist Physician / Internis

DOES "LEGACY EFFECT" AND "METABOLIC MEMORY" EXIST? EVIDENCE FROM UKPDS 88

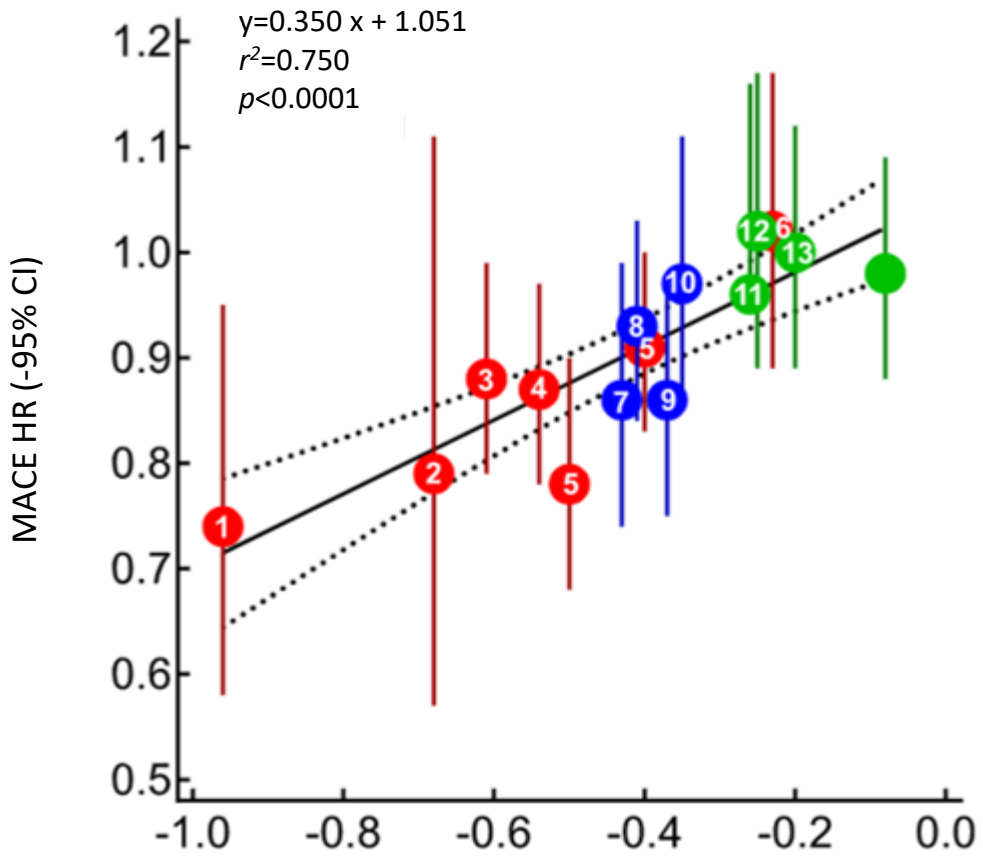


Detection of prediabetes and T2DM (screening) with early glycaemic optimisation (tight control) will contribute to effectively preventing long-term complications

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

CVOTS SHOWED HBA_{1C} REDUCTION LEADS TO SIGNIFICANT RISK REDUCTION OF MACE

Regression analysis of differences achieved in HbA_{1c} concentrations between patients treated with placebo and active drug vs. HRs for MACE



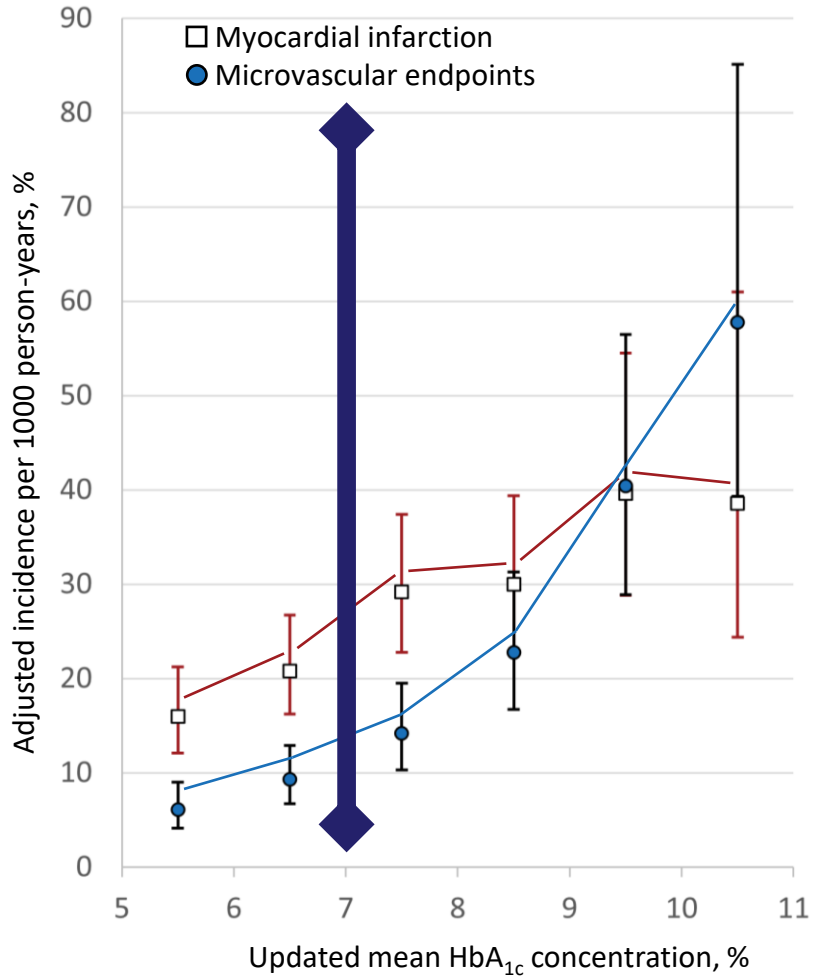
1: SUSTAIN-6 (subcutaneous semaglutide)
2: PIONEER-6 (oral semaglutide)
3: REWIND (dulaglutide)
4: LEADER (liraglutide)
5: EXCSEL (once-weekly exenatide)
6: ELIXA (lixisenatide)
7: EMPA-REG Outcomes (empagliflozin)
8: DECLARE-TIMI-58 (dapagliflozin)
9: CANVAS program (canagliflozin)
10: VERTIS-CV (ertugliflozin)
11: EXAMINE (alogliptin)
12 CARMELINA (linagliptin)
13: SAVOR-TIMI-53 (saxagliptin)
14: TECOS (sitagliptin)

Δ, change; CI, confidence interval; CVOT, cardiovascular outcome trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1C}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT-2i, sodium-glucose transport protein 2 inhibitor. Nauck MA, et al. *Mol Metab*. 2021;46:101102.

INTENSIVE GLUCOSE CONTROL LOWERS BOTH MICRO- AND MACROVASCULAR COMPLICATIONS

- There is a direct relation between the risk of complications of diabetes and glycaemia over time
- The rate of increase of risk for microvascular disease with hyperglycaemia is greater than that for macrovascular disease
- The lower the glycaemia, the lower the risk of complications

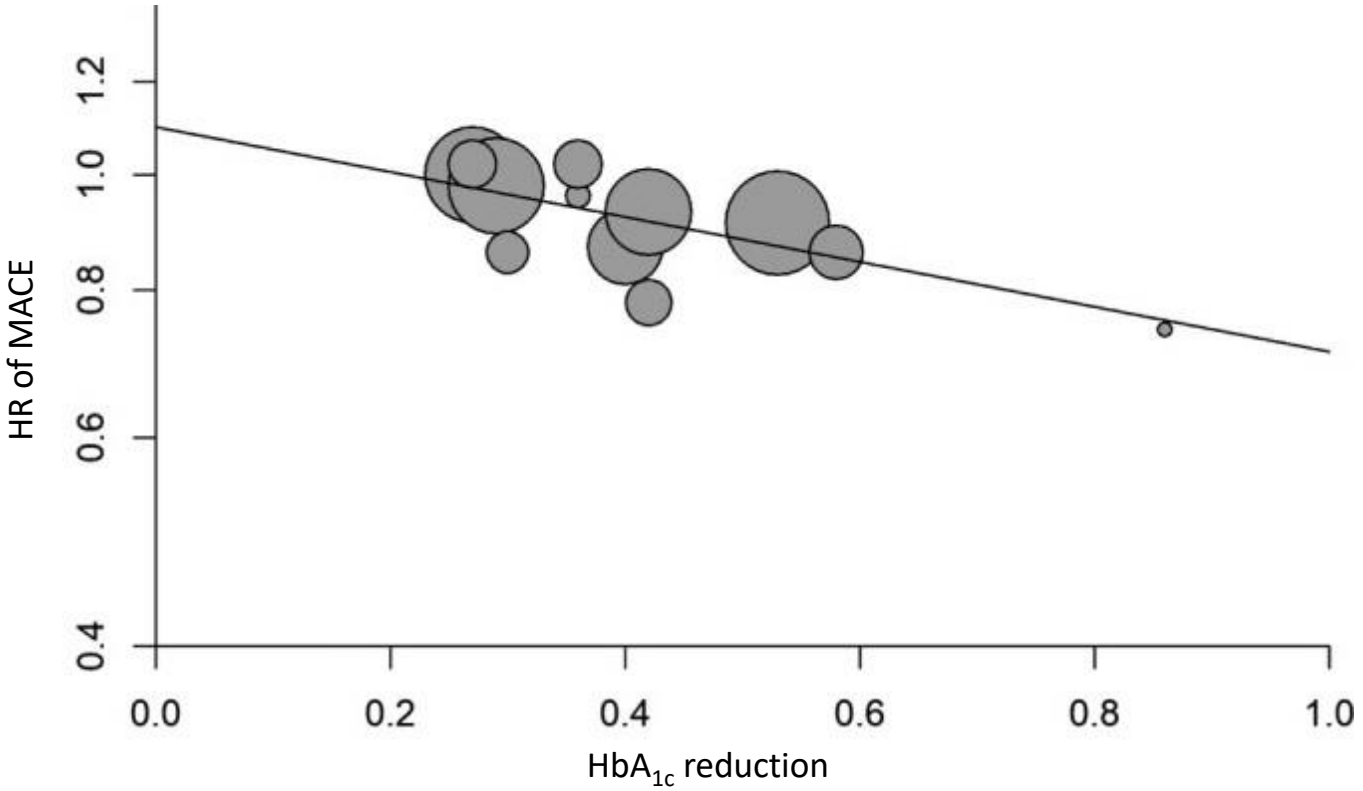
Incidence of complications in patients with type 2 diabetes (n=4585)



Incidence rate and 95% CI for any endpoint related to diabetes by category of updated mean HbA_{1c}, adjusted for age, sex and ethnic group, expressed for white men aged 50–54 years at diagnosis and with mean duration of diabetes of 10 years. HbA_{1c}, glycated haemoglobin.
Stratton IM, et al. *BMJ.* 2000;321(7258):405-12.

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)
- Reduction of MACE expected if all CVOTs had achieved a **0.9% HbA_{1c} reduction would have been 33%** (expected β=0.67, 95% CI 0.49–0.93)

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.

CONCEPTUALIZE BENEFIT OF HBA1C REDUCTION:

1. Intensive Glycemic control significantly reduces the risk of microvascular disease – regardless of duration of T2D

2. Intensive Glycemic control early in the disease process offers significant and sustained long term benefit – legacy effect

3. Intensive Glycemic control early in the disease process offers protection against macrovascular complications in the absence of established ASCVD

4. Benefit is seen especially as part of a holistic approach to managing ASCVD:
Smoking, diet, exercise, hypertension, lipids

5. Drug independent concept

Dr. Andrian Dreyer
Specialist Physician / Internis

HBA1C – INDIVIDUALISING PATIENT TARGETS

Dr. Andrian Dreyer
Specialist Physician / Internis

HBA1C TARGET IS PATIENT DEPENDENT: BALANCE INTENSIVE CONTROL WITH HYPOGLYCEMIA RISK

Figure I: Selection of HbA_{1c} Targets according to risk (adapted from Ismail-Beigi et al[33])

Patient features	< 6.5 %	< 7 %	7 - 8 %
Risks of hypoglycaemia / drug interactions	Low	⟷	High
Disease duration	Newly diagnosed	⟷	Long Standing
Life expectancy	Long	⟷	Short
Major comorbidities	Absent	⟷	Severe
Established macrovascular disease	Absent	⟷	Severe
Patient attitude	Highly motivated Adherent Good self-care capacity	⟷	Not motivated Non-adherent Poor self-care capability
Resources and support	Readily available	⟷	Limited

SEMDSA Type 2 Diabetes Guidelines Expert Committee. JEMDSA 2017; 22(1)(Supplement 1): S1-S196

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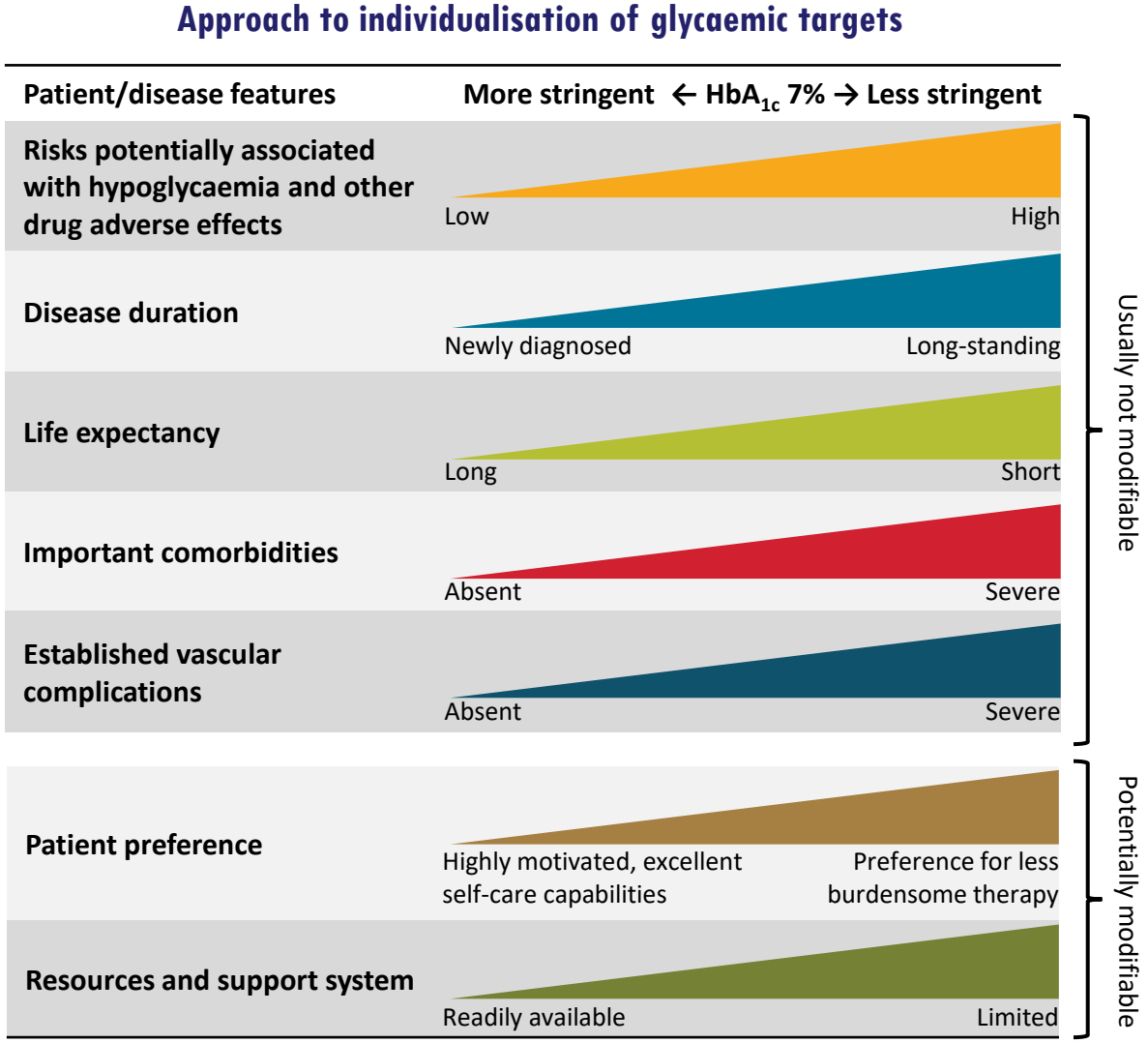
PATIENT-CENTERED APPROACH TO TREATMENT INITIATION: WHAT TO CONSIDER

- Efficacy in achieving glycaemic control
- Risk of macrovascular and/or microvascular complications
- Comorbid conditions
- Cost
- Access/availability
- Patient adherence: Oral drugs and fixed-dose combination pills are preferable



ADA/EASD 2019 Update (Buse, et al. 2020) and ADA Guidelines 2021 recommend shared decision-making around initial combination therapy in new-onset cases of type 2 diabetes

T2D TREATMENT

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METFORMIN – THE UNDISPUTED KING T2D

I. MOA:
   I. primary mechanism is to impair hepatic gluconeogenesis
   II. Increases insulin-mediated glucose utilization in peripheral tissues
   III. Anti-lipolytic effect that lowers serum FFA – main substrate for gluconeogenesis

II. Metformin is considered the cornerstone of therapy in T2D
   I. No weight gain
   II. No hypoglycemia
   III. Tolerable (aside for GIT – transient, consider MR formulation 2000mg at night)
   IV. Safe
   V. Low cost

I. Cx:
   I. eGFR less than 30ml/min/1,73m2
      I. eGFR 30-45ml/min/1,73m2 = max 1g dly
   II. Active or progressive liver disease
   III. Active alcohol use
   IV. Unstable or acute heart failure – risk of hypoperfusion
   V. Previous lactic acidosis

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Specialist Physician / Internis

METFORMIN AND CARDIOVASCULAR EFFECTS

1. No adverse effects
2. Decrease cardiovascular events:
    1. UKPDS = T2D with obesity Metformin rather than SU or insulin = sustained reduction in macro and microvascular complications

    2. 390 pts, Insulin therapy, placebo controlled (metformin vs placebo added to insulin). No weight gain, improved glycemic control and after 4,3 years of follow up = reduced macrovascular risk*

    3. 304 pts, T2D with established CAD, randomized double blind, Metformin vs glipizide, 5 year follow up, reduced macrovascular disease**

*Kooy A, de Jager J, Lehert P, Bets D, WulffeléMG, Donker AJ, Stehouwer CD, Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus, Arch Intern Med. 2009;169(6):616.
**Hong J, et al, Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease, Diabetes Care. 2013 May;36(5):1304-11. Epub 2012 Dec 10

T2DM TREATMENT GUIDE

Address the components of life's essential 8

Step 1: Unless contra-indicated all patients start on Metformin

T2DM TREATMENT GUIDE

Address the components of life's essential 8

Step 1: Unless contra-indicated all patients start on Metformin

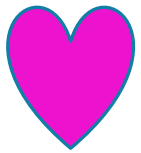
Step 2: is there an Indication for insulin therapy → Yes

No

Step 3: Is there ESTABLISHED ASCVD risk or a compelling indication for SGLT2 (HF or CKD)

No

Yes



1. Metabolic decompensation
2. HBA1c >10%
3. Symptomatic with glucose 16,7mmol/L
4. DKA or HHS

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RISK STRATIFICATION OF THE T2D

Patients with type 2 diabetes mellitus			
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate-risk	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria	High-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
	Patients with DM with established ASCVD and/or severe TOD:[87, 93-95] • eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m^2 and microalbuminuria (ACR 30 -300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

T2DM TREATMENT GUIDE

Address the components of life's essential 8

Step 1: Unless contra-indicated all patients start on Metformin

Step 2: Indication for insulin therapy

Yes

1. Metabolic decompensation
2. HBA1c >10%
3. DKA or HHS

No

Step 3: Is there ESTABLISHED ASCVD risk or a compelling indication for SGLT2 (HF or CKD)

No

Gliclazide

1. SUs are bad, not good, old!!
2. The patient will gain weight?
3. Hypoglycemia galore?
4. Cheap

Yes

SGLT2i

1. Patient will lose weight!
2. Its what all the guidelines are saying!
3. It's a superior drug
4. Superior HBA1c reduction
5. Everyone should be on one

T2DM TREATMENT GUIDE

Address the components of life's essential 8

Step 1: Unless contra-indicated all patients start on Metformin

Step 2: Indication for insulin therapy

Yes

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LET US SEE…

SULPHONYL UREAS

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Specialist Physician / Internis

SULPHONYL UREAS:
WELL REPRESENTED IN CVOT TRIAL DATA

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Specialist Physician / Internis

Table 1. Differences between the ACCORD and ADVANCE Studies.

Characteristic	ACCORD	ADVANCE
Baseline data		
No. of participants	10,251	11,140
Mean age (yr)	62	66
Duration of diabetes (yr)*	10	8
Median glycated hemoglobin at baseline (%)	8.1	7.2
History of macrovascular disease (%)	35	32
Intervention		
Target glycated hemoglobin value (%)	<6.0	≤6.5
Median duration (yr)	3.4	5.0
Medical treatment at study completion (intensive vs. standard) (%)		
Insulin	77 vs. 55	41 vs. 24
Metformin	95 vs. 87	74 vs. 67
Secretagogue (sulfonylurea or glinide)	87 vs. 74	94 vs. 62
Thiazolidinedione	92 vs. 58	17 vs. 11
Incretin	18 vs. 5	Not reported
Statin	88 vs. 88	46 vs. 48
Any antihypertensive drug	91 vs. 92	89 vs. 88
Angiotensin-converting–enzyme inhibitor	70 vs. 72	Not reported
Aspirin	76 vs. 76	57 vs. 55
Outcome (intensive vs. standard)		
Median glycated hemoglobin at study end (%)	6.4 vs. 7.5†	6.4 vs. 7.0†
Death		
From any cause (%)	5.0 vs. 4.0†	8.9 vs. 9.6
From cardiovascular causes (%)	2.6 vs. 1.8†	4.5 vs. 5.2
Nonfatal myocardial infarction (%)	3.6 vs. 4.6†	2.7 vs. 2.8
Nonfatal stroke (%)	1.3 vs. 1.2	3.8 vs. 3.8
Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%/yr)	3.1 vs. 1.0†	0.7 vs. 0.4
Weight gain (kg)	3.5 vs. 0.4	0.0 vs. −1.0†
Current smoking (%)	10 vs. 10	8 vs. 8

* Duration of diabetes is the median for the ACCORD trial and the mean for the ADVANCE trial.
† The comparison of the intervention with the standard therapy was significant.

THE NUMBER OF PATIENTS ON SU INITIAL LANDMARK DIABETIC TRIALS

THE NUMBER OF PATIENTS ON SU IN CVOT

Name of the CVOT	Number of patients on SU in control group (% of patients)	Number of patients on SU in treatment group
LEADER [28]	2363 (50.6)	2370 (50.8)
ELIXA [29]	1016 (33.5)	988 (32.6)
HARMONY [30]	1379 (29)	1346 (28)
ORIGIN [31]	1810 (28.9)	1901 (30.3)
DECLARE-TIMI 58[25]	3707 (43.2)	3615 (42.1)
EMPA-REG [24]	220 (39.1)	440 (37.4)
TECOS [26]	3299 (45.0)	3346 (45.6)
EXAMINE [27]	1237 (46.2)	1266 (46.9)
CARMELINA[33,34]	1140 (32.7)	1102 (31.5)

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Trials; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; HARMONY: Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; ORIGIN: Outcome Reduction with Initial Glargine Intervention; DECLARE-TIMI 58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Event; ESRD: End-stage renal disease; EMPA-REG: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus; TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; EXAMINE: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus.

Kalra, S., Ghosh, S., Das, A. K., Nair, T., Bajaj, S., Priya, G., Mehrotra, R. N., Das, S., Shah, P., Deshmukh, V., Chawla, M., Sanyal, D., Chandrasekaran, S., Khandelwal, D., Joshi, A., Eliana, F., Permana, H., Fariduddin, M. D., Shrestha, P. K., Shrestha, D., … Shaikh, K. (2020). Unravelling the utility of modern sulfonylureas from cardiovascular outcome trials and landmark trials: expert opinion from an international panel. *Indian heart journal*, *72*(1), 7–13. https://doi.org/10.1016/j.ihj.2020.01.001

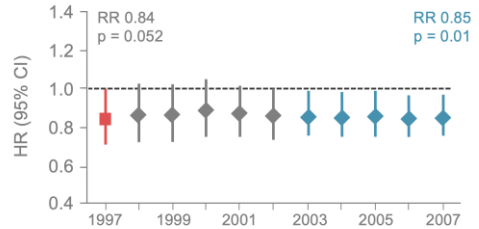
SULPHONYL UREAS:
CV SAFE

Dr. Andrian Dreyer
Specialist Physician / Internis

THERE HAS BEEN NO SIGNAL OF ADVERSE CV OUTCOMES IN TRIALS OF INTENSIVE GLUCOSE CONTROL (WITH SU)

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

Fatal or non-fatal MI: Intensive treatment



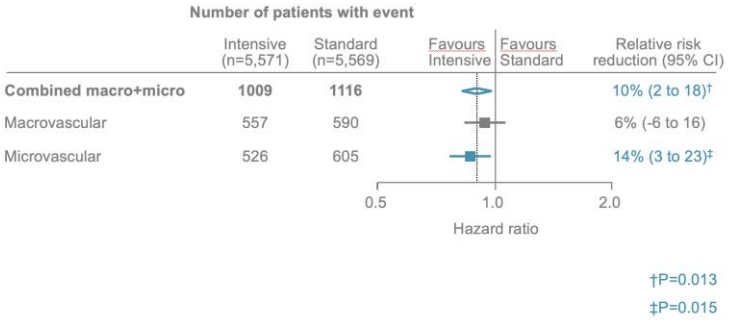
No. of events						
Conventional therapy	186	212	239	271	296	319
Sulphonylurea–insulin	387	450	513	573	636	678

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



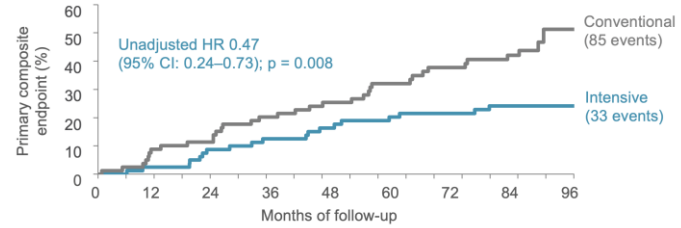
Patel et al. N Engl J Med 2008;358:2560–72.

ADVANCE

gliclazide MR

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

Composite CV endpoint
CV death, non-fatal MI, non-fatal stroke revascularisation and amputation.



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

STENO

gliclazide

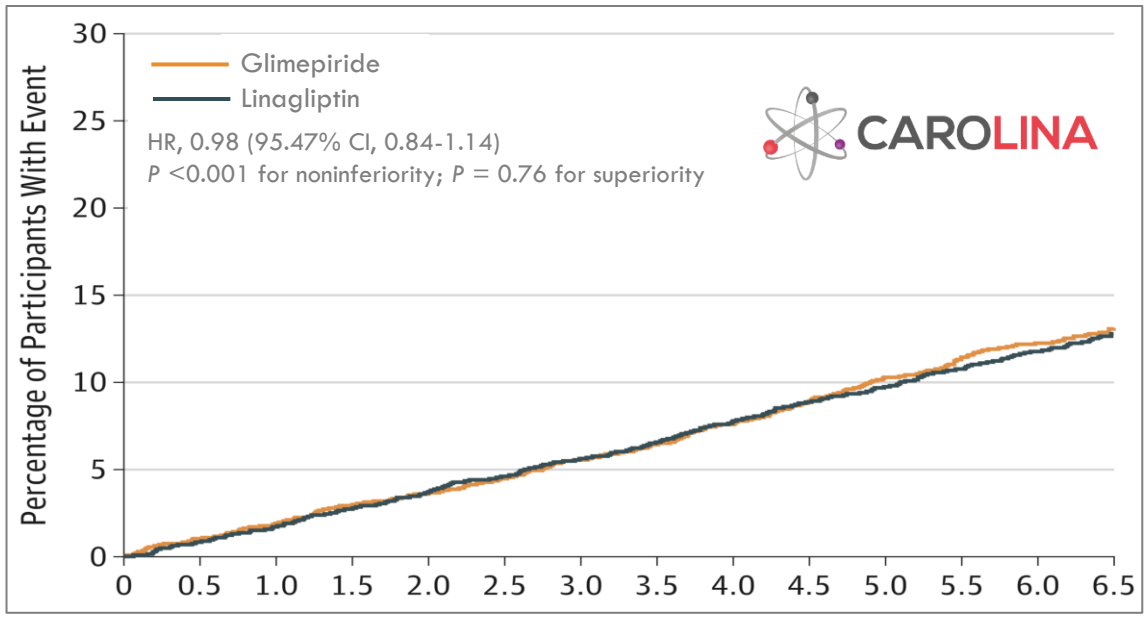
NOT BAD…

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

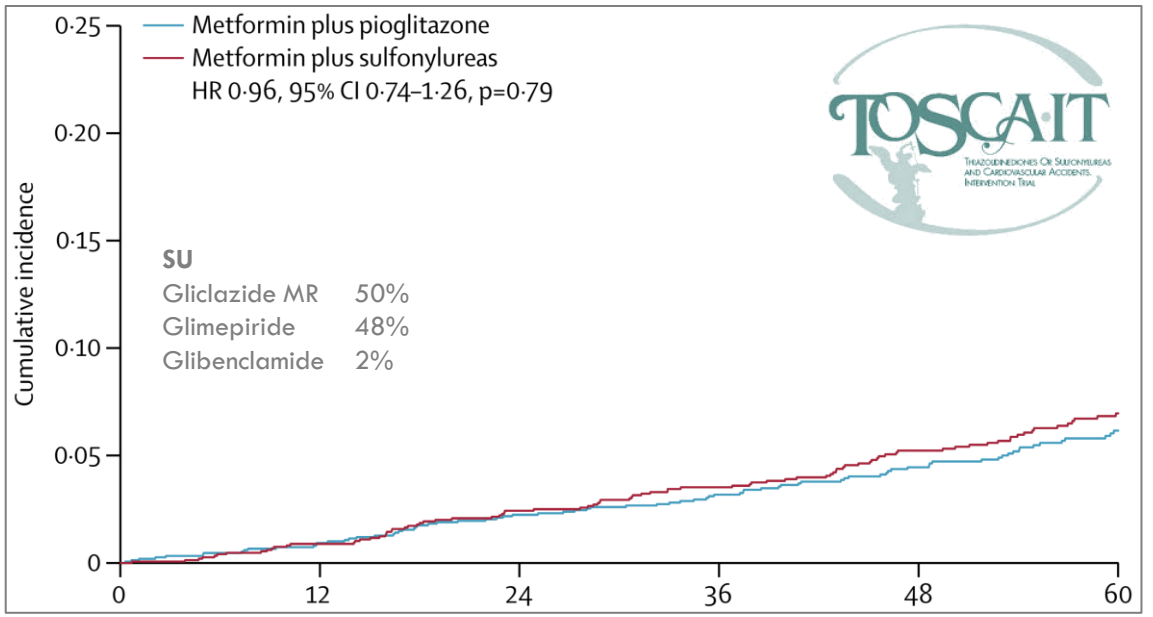


3P-MACE: Composite end point of cardiovascular death, first nonfatal myocardial infarction, or first nonfatal stroke

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.

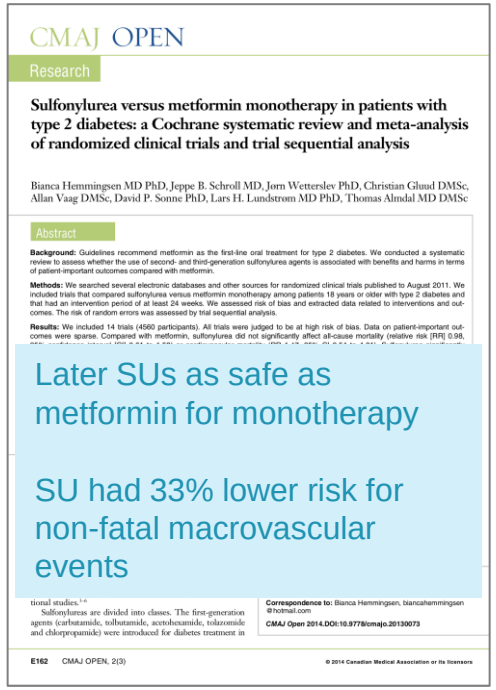
Vaccaro O et al. Lancet Diabetes Endocrinol. Sep 2017: 11:887-897

NOT BAD…

SYSTEMATIC REVIEWS AND META-ANALYSES OF RCTS – SAFE AND EFFECTIVE

Systematic reviews and meta-analyses of RCTs

NOT BAD…


CMAJ OPEN

Research

Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis

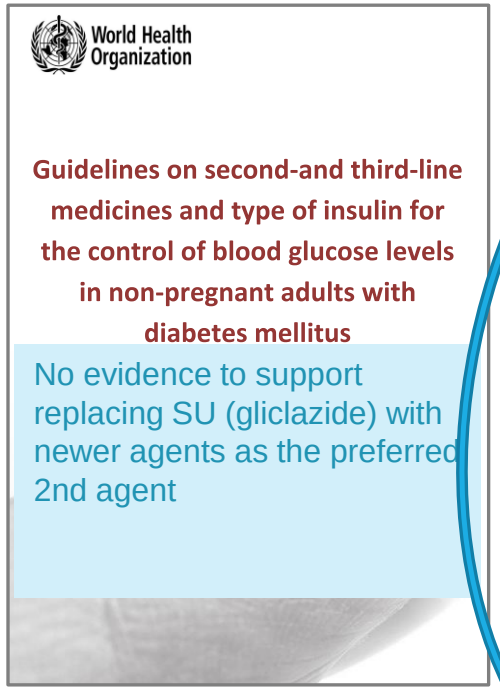
Bianca Hemmingsen MD PhD, Jeppe B. Schroll MD, Jørn Wetterslev PhD, Christian Gluud DMSc, Allan Vaag DMSc, David P. Sonne PhD, Lars H. Lundstrom MD PhD, Thomas Almdal MD DMSc

Abstract

Later SUs as safe as metformin for monotherapy

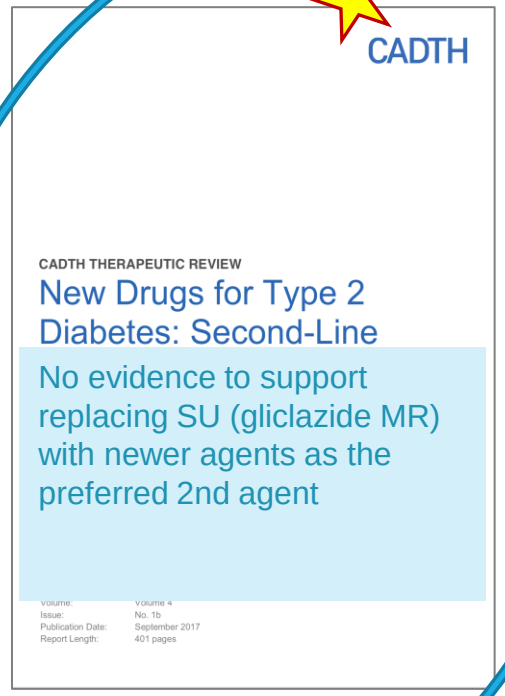
SU had 33% lower risk for non-fatal macrovascular events

AS GOOD…


World Health Organization

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

No evidence to support replacing SU (gliclazide) with newer agents as the preferred 2nd agent

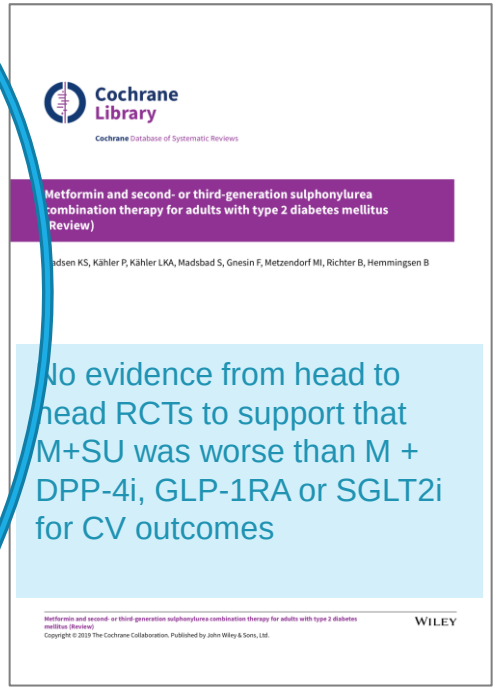

CADTH

CADTH THERAPEUTIC REVIEW

New Drugs for Type 2 Diabetes: Second-Line

No evidence to support replacing SU (gliclazide MR) with newer agents as the preferred 2nd agent

SAFE…


Cochrane Library

Cochrane Database of Systematic Reviews

Metformin and second- or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus (Review)

No evidence from head to head RCTs to support that M+SU was worse than M + DPP-4i, GLP-1RA or SGLT2i for CV outcomes

CMAJ Open. 2014 Jul 22;2(3):E162-75

WHO, Geneva, 2018

CADTH Therapeutic Review, No. 4.1b. Canadian Agency for Drugs and Technologies in Health; 2017

Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD012368

SULPHONYL UREAS:
STILL PROVEN EFFECTIVE IN THE CVOT ERA

Dr. Andrian Dreyer
Specialist Physician / Internis

GRADE TRIAL:

NOT OLD…

1. Published 2022
2. Patients metformin treated T2D, <10 years diagnosis
3. Comparison
   1. Insulin glargine – Insulin
   2. Liraglutide – GLP1a
   3. Glimeperide – SU
   4. Sitagliptin – DPP4

AS GOOD…

4. All 4 effective at reducing HBA1c

NOT BAD…

5. All 4 safe
   1. Infrequent hypoglyecemia
   2. Liraglutide – weight loss over 4 years
   3. Conclusion – no significant increase in weight insulin or SU

NOT FAT..

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Glycemia Reduction in Type 2 Diabetes — Glycemic Outcomes

The GRADE Study Research Group DOI: 10.1056/NEJMoa2200433

CLINICAL PROBLEM

Metformin is the primary glucose-lowering medication prescribed in persons with type 2 diabetes, but a second medication is often needed to achieve or maintain a glycated hemoglobin level below 7.0%. However, data are sparse on the relative effectiveness of second glucose-lowering medications.

CLINICAL TRIAL

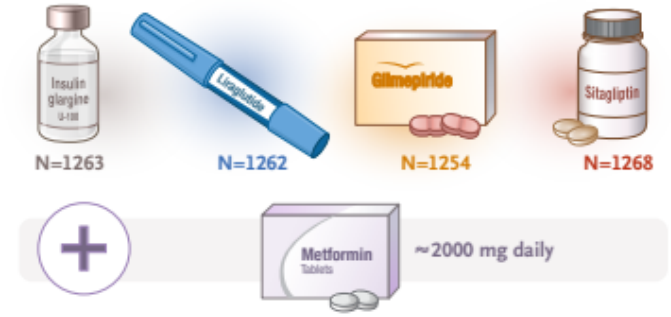
Design: A multicenter, parallel-group, comparative-effectiveness, randomized clinical trial assessed the efficacy and safety of four commonly used glucose-lowering medications in achieving and maintaining target glycated hemoglobin levels in participants with metformin-treated type 2 diabetes.

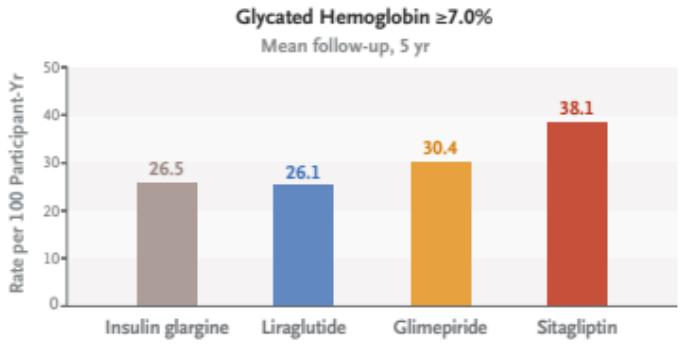
Intervention: 5047 participants with type 2 diabetes of less than 10 years' duration who were receiving metformin without other glucose-lowering medications and who had a baseline glycated hemoglobin level of 6.8 to 8.5% were randomly assigned to receive insulin glargine U-100, the sulfonylurea glimepiride, the glucagon-like peptide-1 receptor agonist liraglutide, or the dipeptidyl peptidase 4 inhibitor sitagliptin, in addition to metformin (at a target dose of 2000 mg per day). The primary outcome was metabolic failure, defined as a glycated hemoglobin level of 7.0% or higher.

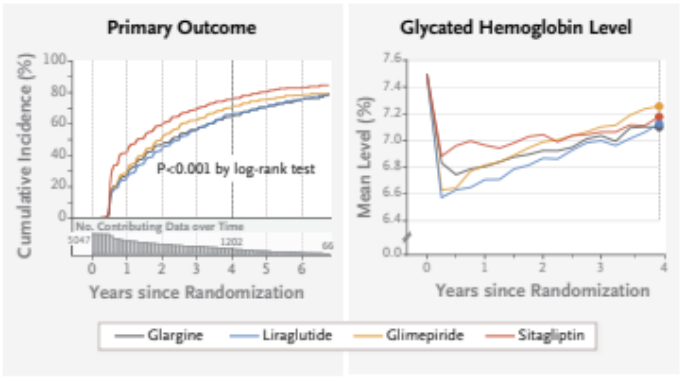
RESULTS

Efficacy: During a mean follow-up of 5 years, the cumulative incidence of a glycated hemoglobin level of 7.0% or higher differed significantly among the four groups; the rates with glargine and liraglutide were similar and lower than those with glimepiride and sitagliptin.

Safety: Severe hypoglycemia was uncommon but occurred more often in the glimepiride group than in the other groups.







SULPHONYL UREAS:
HYPOGLYCEMIA?

Dr. Andrian Dreyer
Specialist Physician / Internis

WHAT ARE THE ABSOLUTE RATES OF SEVERE HYPOGLYCAEMIA

Real-world observational studies

TRIAL	DIA-RAMADAN	UK CPRD
Strategy	Gliclazide MR based	Gliclazide MR
Comparator	None	Sitagliptin
N (SU)	(1 244)	1 986 (993)
Duration	3.5 months	±3 years
Baseline HbA1c	7.5%	8.5
HbA_{1c} (end)	7.2%	51% more likely to reach <6.5%
Severe hypoglycaemia: additional episodes	0 / 100 person-years	0.13 vs 0.03 0.1 / 100 person years

Rx 1244 for 3,5 months = 1 severe hypoglycemia

Rx 993 patients 1 year for 1 severe hypoglycemia

Hassanein m et al. Diabetes Res Clin Pract.https://doi.org/10.1016/j.diabres.2020.108154.

Zaccardi F et al. Diabetes Obes Metab. 2020;22(12):2417-2426

WHAT ARE THE ABSOLUTE RATES OF SEVERE HYPOGLYCAEMIA

Meta-analysis of randomised controlled trials

219 RCTs	24 non-insulin therapies		121 914 patients
Severe hypoglycaemia	**Any hypoglycaemia**	**RR vs placebo**	**The relative risk with gliclazide was more similar to metformin than other SUs**
	Metformin	**2.1**	
Too few episodes for comparison	**GLP-1RA**	**2.0**	**"Thus, although class is important, drugs within the same class may exhibit real and important differences"**
	Gliclazide	**3.6**	
	Glimepiride	8.9	
	Glibenclamide	10.4	
	Glipizide	13.9	

Not all SU are created equal

Maloney A, Rosenstock J and Fonseca V. *Clinical Pharmacology & Therapeutics* 2019; 105 (5): 1213-1223

SULPHONYL UREAS:
EFFICACY IN HBA1C REDUCTION?

Dr. Andrian Dreyer
Specialist Physician / Internis

ON AVERAGE EXPECTED HBA1C REDUCTIONS ARE COMPARABLE ACROSS THE CLASSES

Figure I: Some of the factors to consider when choosing glucose lowering drug therapy at various stages of type 2 diabetes

	Gliclazide modified release	Pioglitazone	DPP-4 inhibitor	GLP-1 receptor agonist	SGLT2 inhibitor	Basal insulin
Mean HbA_{1C} reduction	-0.8 to -1.0%	-0.8 to -1.0%	-0.7%	-0.8 to -1.2%	-0.8 to -1.0%	-0.8 to -1.2%
Hypoglycaemia (monotherapy)	Yes	Rare	Rare	Rare	Rare	Yes
Hypoglycaemia (added to SU)	-	++	+	+	+	++
Weight change	+0.0 to 1.5kg	+3.0 to 5.0 kg	Neutral	-3.0 kg	-3.0kg	+3-5kg
Adverse events*	None	Fluid retention (oedema, CHF)	Heart failure with saxagliptin	Common – GI upset	Common - GU infection Dehydration	Local skin reactions
Rare SAEs	None	Fractures, ?bladder cancer	Pancreatitis, pancreatic cancer	Pancreatitis, pancreatic cancer	Fractures Amputation DKA	None
Treatment complexity	Low	High	Low	Intermediate	High	High
Cardiovascular benefit	None	Yes, 1° and 2° prevention	None	Yes (2° prevention)	Yes (2° prevention)	None
Cost#	<R100	R120-180	R250-350	R650-2150	Unknown	R200 to >1000§
Initiate at	1st or 2nd Line	1st or 2nd Line	1st or 2nd Line	3rd Line	2nd Line	3rd Line

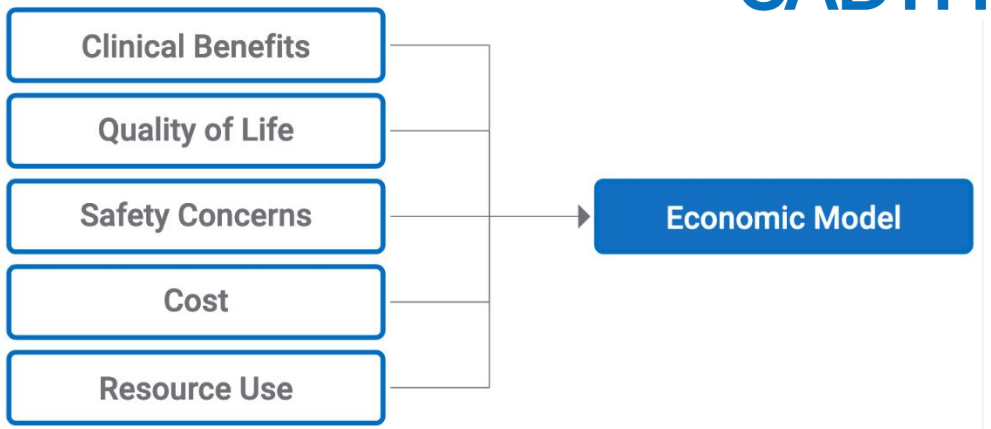
*Side effects other than weigh gain and hypoglycaemia; GI=gastrointestinal; GU= genitourinary; SU = sulphonylurea; SAEs= serious adverse events

SULPHONYL UREAS: COST EFFECTIVE AND INEXPENSIVE

Dr. Andrian Dreyer
Specialist Physician / Internis

2018: WHICH CLASS OF DIABETES DRUGS IS THE BEST CHOICE FOR SECOND-LINE THERAPY **IN PATIENTS WITHOUT ASCVD?**

CADTH



Key Messages

- **For adults with type 2 diabetes without established cardiovascular disease, add a sulfonylurea drug to metformin once metformin, diet, and exercise are not enough to control blood glucose levels.**
- **For adults with type 2 diabetes with established cardiovascular disease, refer to the CADTH Common Drug Review (CDR) recommendations on individual drugs[a] that have been reviewed for this indication.**

[a] As of August 2017, the only drug reviewed by CDR for this indication is empagliflozin (Jardiance). The recommendation is to reimburse empagliflozin for patients with type 2 diabetes as a second-line therapy after metformin if these patients have established cardiovascular disease, as defined by the EMPA-REG OUTCOME trial that looks at empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes.

Canadian Agency for Drugs and Technologies in Health

- This was not a “which is cheapest” model:
  - Considered many different scenarios and factors
- In all cases, sulfonylureas ranked #1
- Other drugs had no clinically meaningful additional benefits to offset the higher cost
  - DPP-4i and SGLT-2i – 10x higher
  - Exenatide – 15x higher
  - Insulin – 8 to 16 x higher
  - Reference used by CADTH: gliclazide modified-release
- Key Message

CADTH June 2018 from https://www.cadth.ca/sites/default/files/pdf/diabetes_cost_comparison_infographic.pdf;

SEMDSA 2017 Recommendations for sulphonylureas	
The sulphonylurea of choice should be gliclazide modified-release because: ◦ It has equivalent efficacy compared to other sulphonylureas. ◦ It is consistently associated with lower rates of hypoglycaemia and better cardiovascular and renal safety relative to other sulphonylureas. ◦ It has proven benefits for long-term microvascular disease outcomes.	A
Glibenclamide must not be used at primary care level.	A
Consider gliclazide modified-release as initial monotherapy when metformin is not tolerated or is contraindicated.	B
Consider gliclazide modified-release as add-on (dual therapy) to metformin (or other initial drug therapy) in most patients not achieving or maintaining their glycaemic targets.	A
If not already in use, consider gliclazide modified-release as a third glucose lowering drug.	A
To convert treatment from another sulphonylurea to gliclazide modified-release, use the following dose conversion: ◦ Glibenclamide 5 mg ≈ Gliclazide modified-release 30 mg ◦ Glimepiride 1-2 mg ≈ Gliclazide modified-release 30 mg	C
Only continue gliclazide modified-release beyond stage 3 chronic kidney disease (when the eGFR is less 30 ml/min/m^2) with specialist supervision.	C
Circumstances where gliclazide MR may be preferred to other treatment options: ◦ Gliclazide MR should be the preferred second drug for the majority of patients with type 2 diabetes. ◦ At diagnosis when rapid control of hyperglycaemic symptoms is required.	C
Circumstances where gliclazide MR may not be the preferred option: ◦ The individualised glycaemic target is ≤ 6.5% (as the risk of hypoglycaemia may be unacceptably high with this target). ◦ There is a history of severe hypoglycaemia or hypoglycaemia unawareness. ◦ There is a history of recurrent hypoglycaemia (any degree) despite dose adjustments. ◦ The risk of hypoglycaemia is high and/or its consequences are severe. ◦ The patient has advanced liver disease.	

T2DM TREATMENT GUIDE

Step 1: Unless contra-indicated all patients start on Metformin

Step 2: Indication for insulin therapy

Yes

1. Metabolic decompensation
2. HBA1c >10%
3. DKA or HHS

No

Step 3: Is there ESTABLISHED ASCVD risk or a compelling indication for SGLT2 (HF or CKD)

No

Gliclazide

1. SUs not bad, safe, comparably effective
2. Weight gain marginal, less insulin
3. Few severe hypoglycemic events with Gliclazide MR
4. Cost effective

Yes

SGLT2i

1. Its what all the guidelines are saying!
2. All patients should be on SGLT2i
3. It's a superior drug
4. Superior HBA1c reduction

Dr. Andrian Dreyer
Specialist Physician / Internis

SGLT2I

Dr. Andrian Dreyer
Specialist Physician / Internis

SGLT2I: WHY THESE DRUGS STOLE THE SPOTLIGHT

Dr. Andrian Dreyer
Specialist Physician / Internis

Review Article

Gliflozins in the Management of Cardiovascular Disease

Eugene Braunwald, M.D.

N Engl J Med
Volume 386(21):2024-2034
May 26, 2022

The NEW ENGLAND JOURNAL of MEDICINE

HOW THE SGLT2S STOLE THE SPOTLIGHT?

- 1835 Phlorizin isolated from an apple tree – Petersen
- 50 years later – found to cause glycosuria – von Mering
- 1980s discovered to target the proximal tubules
- 1990s develop first synthetic SGLT2 – Tanabe Seiuaku
- 1999 - ??could this be used in DM – increased attention to SGLT2i – HBA1c reduction 0,5 to 1,1%
- 2008 – rosiglitazone raised concerns for CV safety due to heart failure – FDA all new or recently approved diabetic agents needed to :"demonstrate the therapy will not result in an unacceptable increase in CV risk" = era of the CVOT
- EMPA-REG OUTCOME trial – 1st = Empaglifozin safe and suggested cardioprotective
  - Decreased: CV death 38%, hospitalization for HF 35%, all cause mortality 32%

Dr. Andrian Dreyer
Specialist Physician / Internis

HOW THE SGLT2S STOLE THE SPOTLIGHT?

- Fantastic!
  - CANVAS program
  - CREDENCE

- Fizzle…
  - DECLARE TIMI 58
    - At risk individuals
    - Lowest prevalent rate of CVD
    - Dapaglifozin NO reduction in CVD events
  - VERTIS
    - No effect on CV death
    - Reduced risk of HF admissions

- **Of these 5 initial CVOT trials = 31 116/46 969 patient had established ASCVD = Very High Risk CVD Group (66%)**

Dr. Andrian Dreyer
Specialist Physician / Internis

SGLT2S STOLE OUR HEARTS!

- DAPA – HF
  - Enrolled patients with HFreF (below 40%)
  - 55% of patients DID NOT HAVE DM – IT BRIDGED THE GAP
  - **SIMILAR CARDIOVASCULAR EFFECTS IN DM AND NON-DM = CVD PROTECTION INDEPENDENT OF HBA1C REDUCTION**

- EMPEROR-REDUCED
  - EVEN WORSE LV FUNCTION than DAPA-HF
  - **DM AND NON-DM EQUALLY WELL SERVED**

- BUT MORE THAN 50% OF PATIENTS WITH HEART FAILURE HAVE PRESERVED EJECTION FRACTION…

- SOLOIST-WHF
  - Trial of a non-specific SGLT2 and 1 inhibitor = 250 patients with HFpEF received sotaglifozin – showed improved primary outcome
- EMPEROR-PRESERVED
  - 5988 patient with HFmrEF and HFpEF
  - **BENEFIT: DM AND NON-DM**

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Specialist Physician / Internis

SGLT2S ARE LIQUID GOLD!

- But wait there's more! Renoprotective

- EMPA-REG OUTCOME
  - Reduction in worsening kidney function and increase in albuminuria, initiation or RRT and death due to kidney disease
  - Also seen in EMPEROR REDUCE

- DECLARE TIMI 58
  - In the group with renal impairment – renoprotective

- DAPA-CKD – bridged the gap
  - CKD stage 3B with albuminuria
  - 1/3 = NON DM
  - BENEFIT!

- EMPA-KIDNEY – stopped early 16/03/2022 = "clear positive efficacy"

Dr. Andrian Dreyer
Specialist Physician / Internis

SGLT2I:

MECHANISM OF ACTION – UNDERSTANDING HOW THE NON-DM BENEFITS

Dr. Andrian Dreyer
Specialist Physician / Internis

HOW DO THEY DO IT?

Cardioprotective mechanisms are bit unclear

1. Changes cardiomyocyte energy metabolism
    1. Improves ATP production – in heart failure cardiomyocyte ATP production decreased
    2. Increased ketones – improve mitochondrial function – improves ventricular contraction

2. Changes cardiomyocyte sodium concentration
    1. In heart failure – intracellular sodium increased – poor contraction and arrhythmias

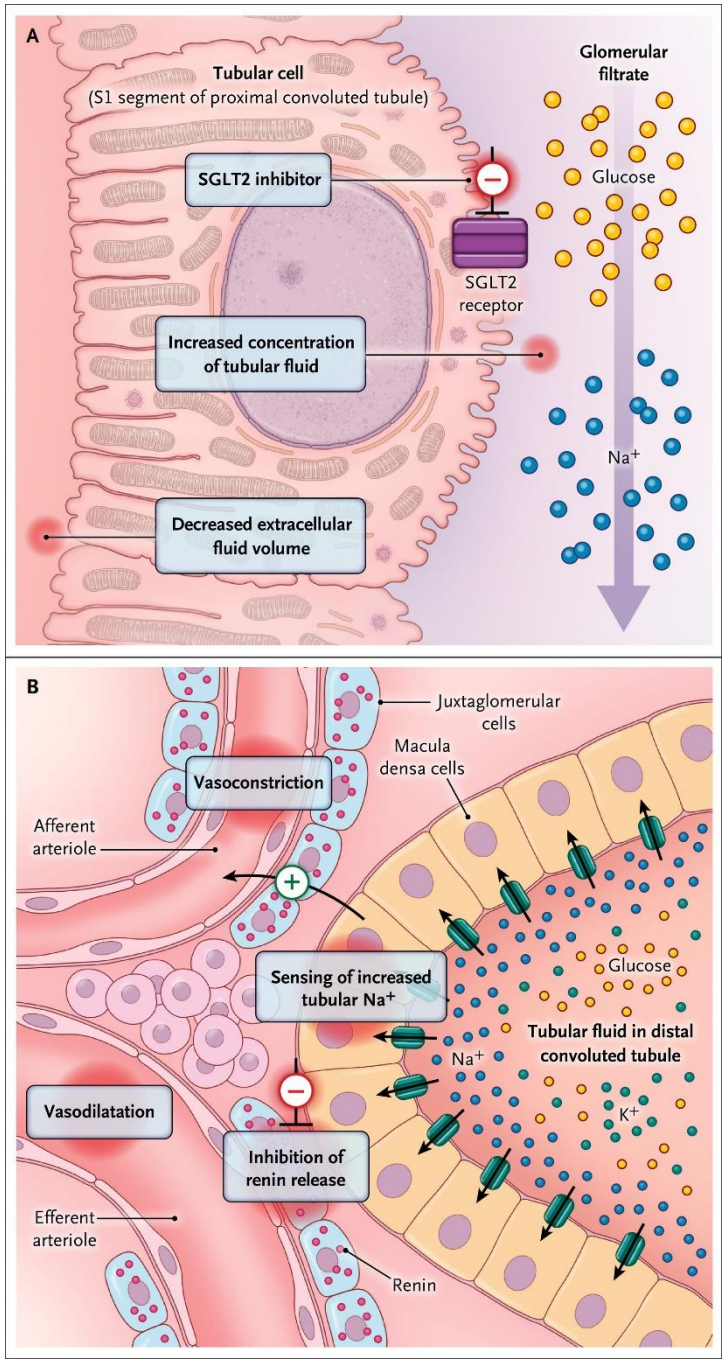
3. Decreases inflammation
    1. Reduced inflammation in carotid-artery plaques in patients with SGLT2i evaluated post artherectomy
    2. Reduce free radicals in human cardiomyocytes improving systolic and diastolic function
4. Improves coronary endothelial function
5. Improves flow mediated vasodilation

Dr. Andrian Dreyer
Specialist Physician / Internis

HOW DO THEY DO IT?

Renal protection:

1. Inhibit proximal tubule sodium and glucose absorption
   1. Increased solute delivery in the distal tubule – macula densa
   2. Decreased tubular oxygen consumption and workload
2. Macula densa
   1. Senses more sodium
   2. Inhibits RAAS by limiting renin release
   3. Vasodilates the afferent arteriole – reduces intraglomerular pressure
3. Net effect
   1. Decreased metabolic demand – protective against ischemic tubules
   2. Decreased hyperfiltration



THE RESULT OF THESE TRIALS

1. Are these diabetic drugs?
    1. I think they need to be reclassified…
    2. It is a class of medication with cardio-renal benefit in high risk ASCVD and established CKD patients irrespective of diabetic status
    3. With the side effect of reducing HBA1c

2. What do the guidelines say:
    1. ADA recommends SGLT2 or GLP1a for reduction in MACE in high risk individuals – T2D with multiple risk factors, CKD or ASCVD
    2. Current ESC and AHA guidelines recommend SGLT2i for management of heart failure

3. Future:
    1. 20 ongoing phase 3 trials for SGLT2…

Dr. Andrian Dreyer
Specialist Physician / Internis

SOUNDS LIKE EVERYONE SHOULD BE ON A SGLT2?

NO…DON'T COMPARE APPLES AND PEARS

Dr. Andrian Dreyer
Specialist Physician / Internis

BASELINE CHARACTERISTICS IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D

	EMPA-REG OUTCOME[1] (N=7020)	CANVAS Program[2] (N=10,142)	DECLARE-TIMI 58[3] (N=17,160)	VERTIS CV[4] (N=8246)¶	CREDENCE[5] (N=4401)
Age (years), mean	63.1	63.3	64.0	64.4	63.0
Male (%)	71.5	64.2	62.6	70.0	66.1
Duration of diabetes, years	NR	13.5	11.0	13.0	15.8
HbA_{1c} (%), mean	8.1*	8.2	8.3	8.2	8.3
BMI (kg/m^2), mean	30.6	32.0	32.1	31.9	31.3
ASCVD	**100**	**65.6**	**40.7**	**100**	**50.4**
Heart failure (known)	10.1	14.4	10.1	23.7	14.8

DEFINITIONS OF BASELINE CHARACTERISTICS VARY ACROSS TRIALS

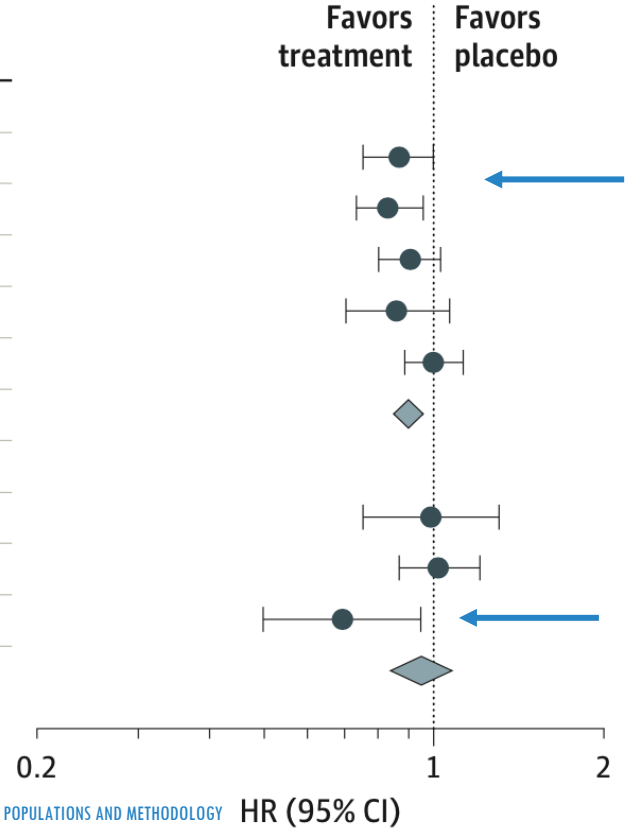
*DATA AVAILABLE FOR 7018 PATIENTS; †CONVERSION FACTOR: 1 MG/DL =0.02586 MMOL/L FOR CHOLESTEROL; ‡DATA AVAILABLE FOR 6935 PATIENTS; §DATA AVAILABLE FOR 6932 PATIENTS. ¶DATA AVAILABLE FOR 8238 PATIENTS. SEE SLIDE NOTES FOR ABBREVIATIONS

1. ZINMAN B *ET AL. N ENGL J MED* 2015;373:2117; 2. NEAL B *ET AL. N ENGL J MED* 2017;377:644; 3. WIVIOTT SD *ET AL. N ENGL J MED* 2019;380:347; 4. CANNON CP *ET AL. AM HEART J* 2018;206:11; 5. PERKOVIC V *ET AL. N ENGL J MED* 2019;380:2295

MACE IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D

B MACEs by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



COMPARISON OF TRIALS SHOULD BE INTERPRETED WITH CAUTION DUE TO DIFFERENCES IN STUDY DESIGN, POPULATIONS AND METHODOLOGY

*FDA-MANDATED UPPER 95% CI OF THE HR FOR CV SAFETY IS A MARGIN OF 1.3 FOR POST-APPROVAL;[2,3] †COCHRANE Q TEST STATISTIC AND HIGGINS AND THOMPSONS' I^2 WERE USED TO ASSESS HETEROGENEITY. HETEROGENEITY WAS CONSIDERED TO BE LOW IF I^2=25%, MODERATE IF I^2=25–75%, OR HIGH IF I^2=75%.[1]

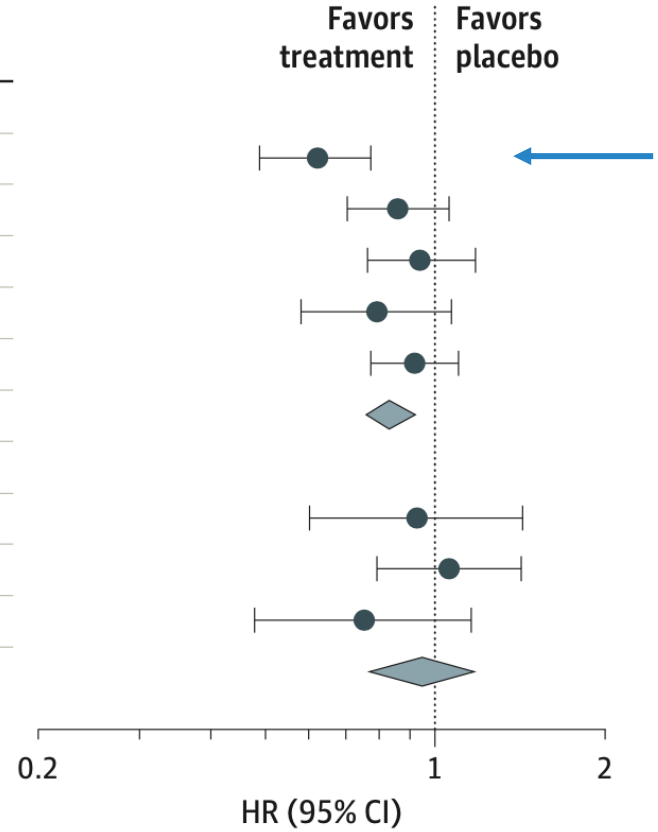
DF, DEGREES OF FREEDOM; NA, NOT REPORTED; SEE NOTES PAGE FOR CLINICAL TRIAL ABBREVIATIONS

1. MCGUIRE D *ET AL. JAMA CARDIOL* 2021;6:148

CV DEATH IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D

B CV death by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/3756	14.8	NA/2900	16.8	0.86 (0.70-1.06)
DECLARE-TIMI 58	153/3474	10.9	163/3500	11.6	0.94 (0.76-1.18)
CREDENCE	75/1113	25.7	93/1107	32.4	0.79 (0.58-1.07)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model (Q = 9.10; *df* = 4; *P* = .06; I^2 = 56.1%)					0.83 (0.76-0.92)
Patients without ASCVD					
CANVAS program	NA/2039	6.5	NA/1447	6.2	0.93 (0.60-1.43)
DECLARE-TIMI 58	92/5108	4.4	86/5078	4.1	1.06 (0.79-1.42)
CREDENCE	35/1089	12.2	47/1092	16.4	0.75 (0.48-1.16)
Fixed-effects model (Q = 1.65; *df* = 2; *P* = .44; I^2 = 0.0%)					0.95 (0.77-1.17)

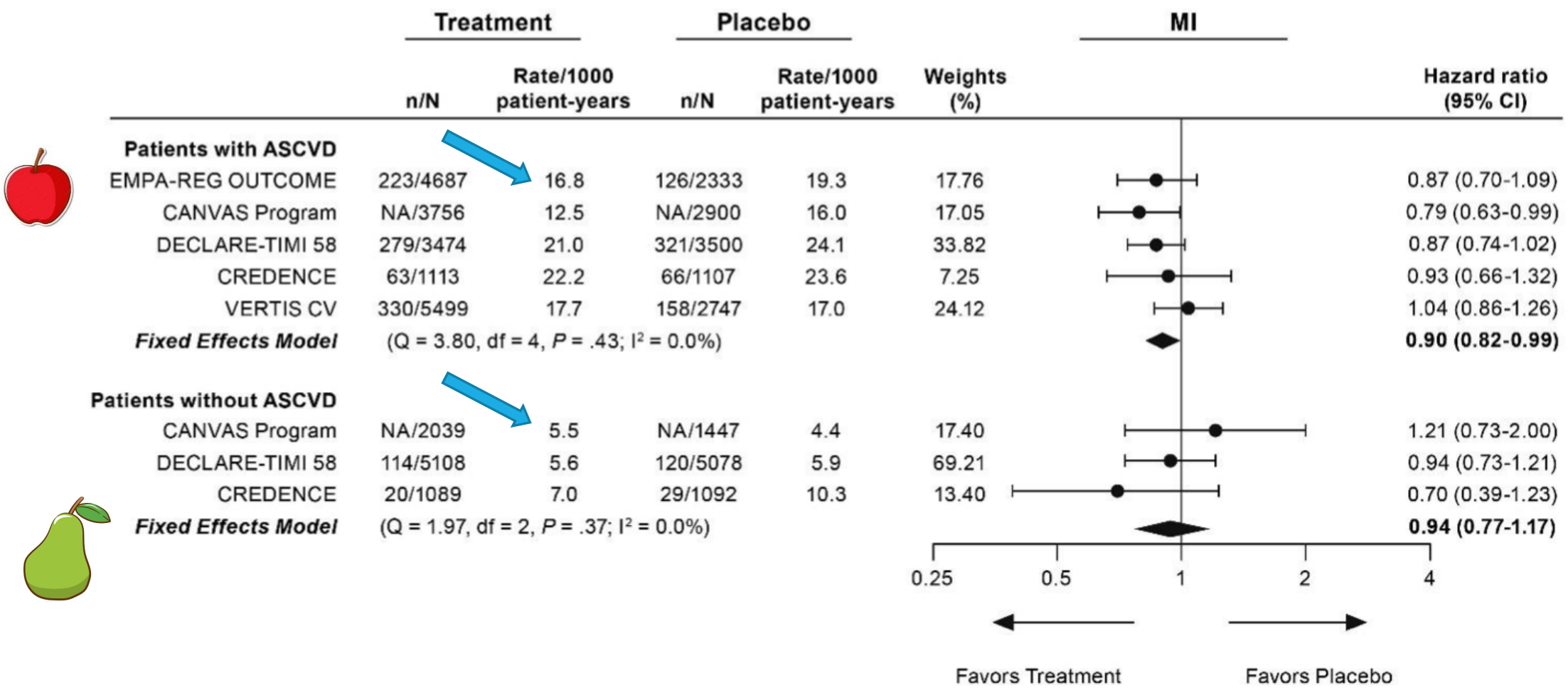


THOMPSONS *P* WERE USED TO ASSESS HETEROGENEITY. HETEROGENEITY WAS CONSIDERED TO BE LOW IF *P*=25%, MODERATE IF *P*=25–75%, OR HIGH IF *P*=75%.

DF, DEGREES OF FREEDOM; NA, NOT REPORTED; SEE NOTES PAGE FOR CLINICAL TRIAL ABBREVIATIONS

1. MCGUIRE D *ET AL. JAMA CARDIOL* 2021;6:148

MI IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D



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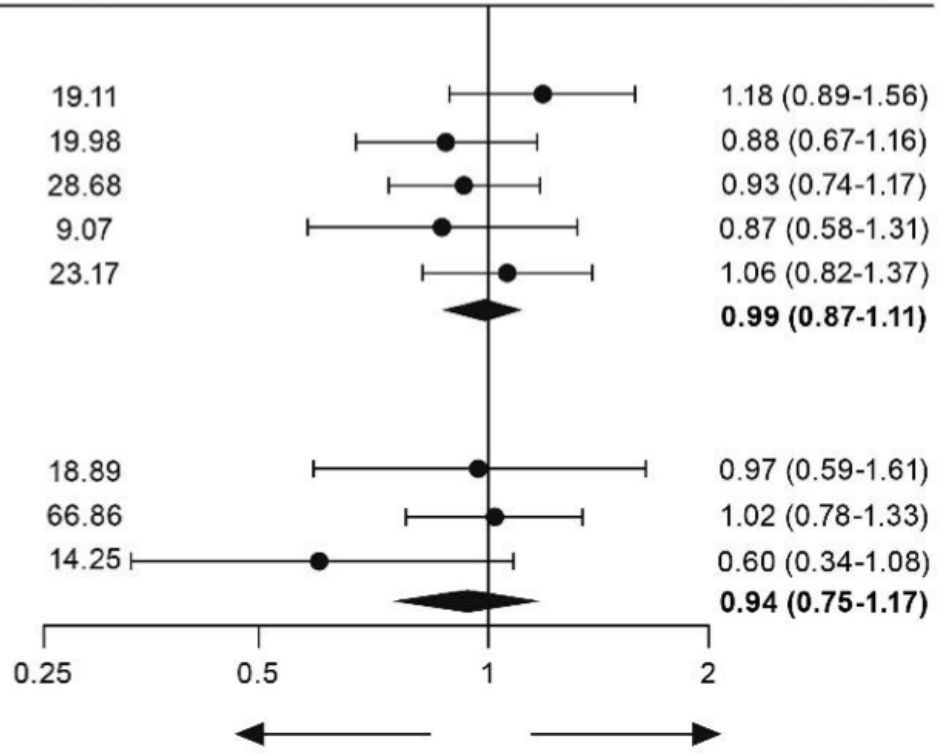
DF, DEGREES OF FREEDOM; NA, NOT REPORTED; SEE NOTES PAGE FOR CLINICAL TRIAL ABBREVIATIONS

1. MCGUIRE D *ET AL. JAMA CARDIOL* 2021;6:148

STROKE IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D

	Treatment n/N	Treatment Rate/1000 patient-years	Placebo n/N	Placebo Rate/1000 patient-years	Weights (%)	Hazard ratio (95% CI)
Patients with ASCVD						
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	19.11	1.18 (0.89-1.56)
CANVAS Program	NA/3756	8.8	NA/2900	10.4	19.98	0.88 (0.67-1.16)
DECLARE-TIMI 58	NA/3474	10.9	NA/3500	11.7	28.68	0.93 (0.74-1.17)
CREDENCE	44/1113	15.4	50/1107	17.7	9.07	0.87 (0.58-1.31)
VERTIS CV	185/5499	9.8	87/2747	9.3	23.17	1.06 (0.82-1.37)
Fixed Effects Model	(Q = 3.16, df = 4, *P* = .53; I^2 = 0.0%)					**0.99 (0.87-1.11)**
Patients without ASCVD						
CANVAS Program	NA/2039	4.5	NA/1447	5.0	18.89	0.97 (0.59-1.61)
DECLARE-TIMI 58	NA/5108	5.2	NA/5078	5.1	66.86	1.02 (0.78-1.33)
CREDENCE	18/1089	6.3	30/1092	10.7	14.25	0.60 (0.34-1.08)
Fixed Effects Model	(Q = 2.69, df = 2, *P* = .26; I^2 = 25.7%)					**0.94 (0.75-1.17)**



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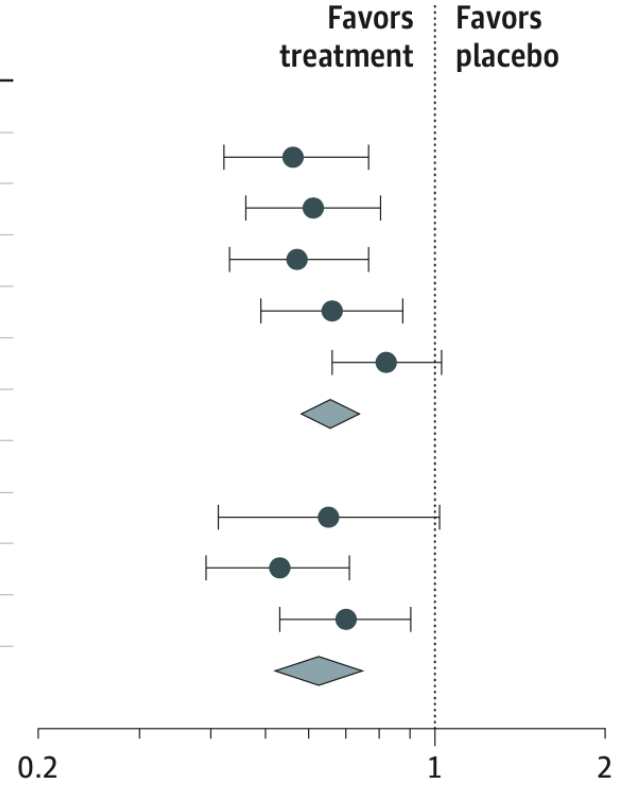
DF, DEGREES OF FREEDOM; NA, NOT REPORTED; SEE NOTES PAGE FOR CLINICAL TRIAL ABBREVIATIONS

1. MCGUIRE D *ET AL. JAMA CARDIOL* 2021;6:148

KIDNEY OUTCOMES IN COMPLETED SGLT2 INHIBITOR OUTCOMES TRIALS IN PATIENTS WITH T2D

B Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)



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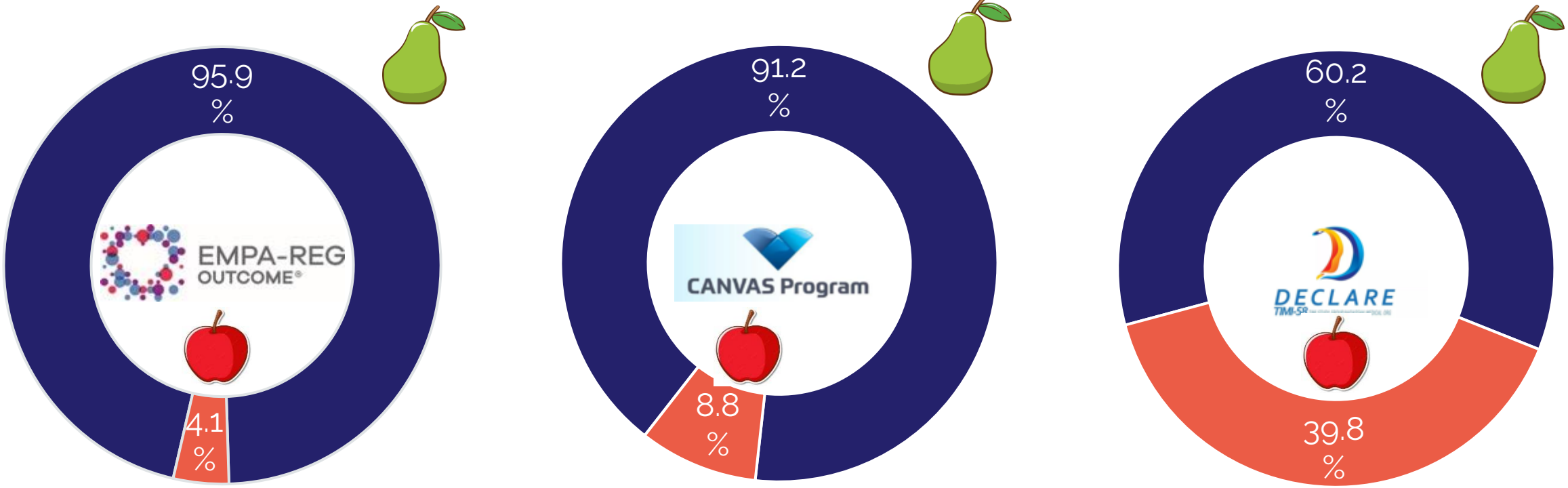
DF, DEGREES OF FREEDOM; NA, NOT REPORTED; SEE NOTES PAGE FOR CLINICAL TRIAL ABBREVIATIONS

1. MCGUIRE D *ET AL. JAMA CARDIOL* 2021;6:148

THE MAJORITY OF T2D PATIENTS DO NOT HAVE CVD / VERY HIGH RISK

NHANES population of 23,941,512 US adults from data on key inclusion criteria for SGLT2i Trials



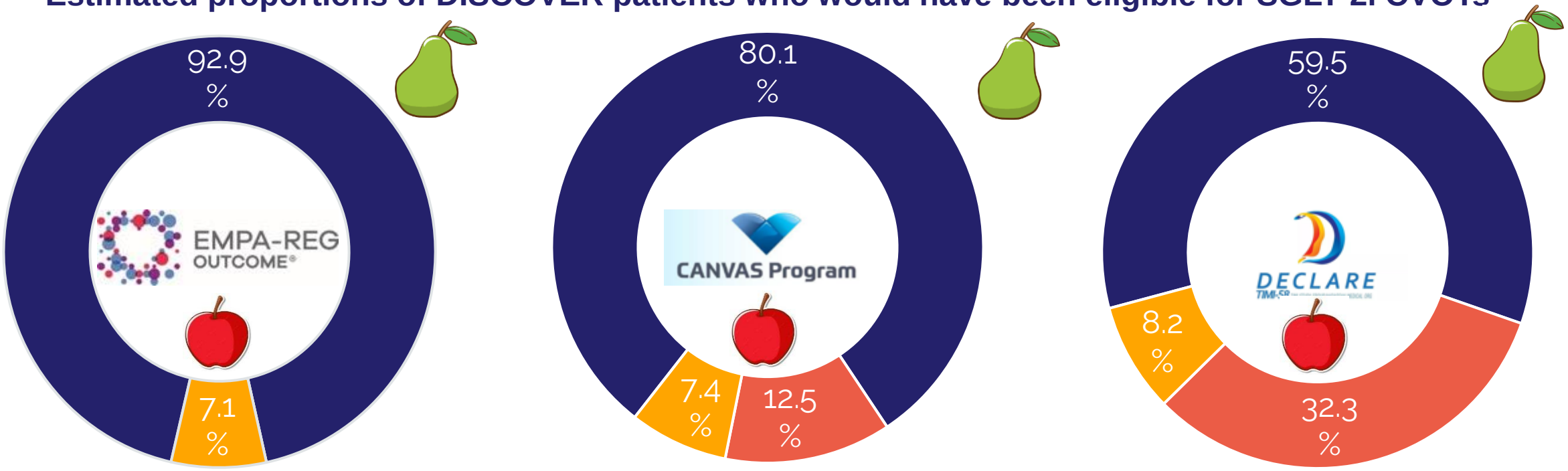
- Not Eligible for enrollment
- Eligible for enrollment

No MACE / mortality benefit

Wittbrot ET et al. Am J Manag Care. 2018;24:S138-S145

THE MAJORITY OF T2D PATIENTS DO NOT HAVE CVD / VERY HIGH RISK

Estimated proportions of DISCOVER patients who would have been eligible for SGLT-2i CVOTs

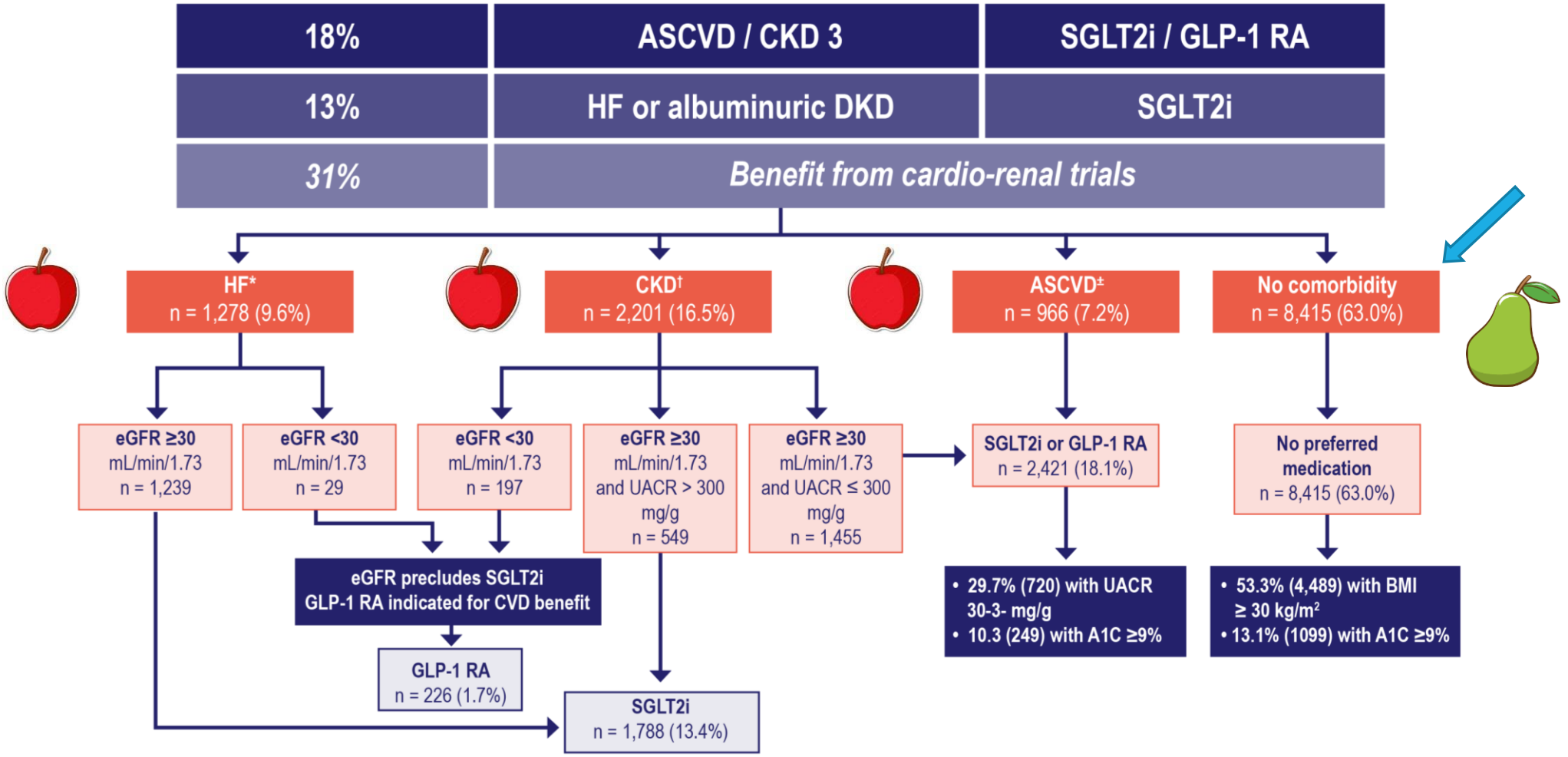


- Not Eligible for enrollment
- Eligible with CVD
- Eligible with Multiple Risk Factors

No MACE / mortality benefit

Pintat S et al BMJ Open Diab Res Care 2019;7:e000627

WHAT IS THE APPLICABILITY OF CVOTS/HF/RENAL OUTCOMES TRIALS AND GUIDELINES TO PRIMARY CARE? (USING 2021 ADA RECOMMENDATIONS)



Colling C, Atlas SJ and Wexler DJ. Diabetes Care 2021;44:1–4

Research

Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

BMJ 2021 ; 372 doi: https://doi.org/10.1136/bmj.m4573 (Published 13 January 2021)
Cite this as: *BMJ* 2021;372:m4573

T2D PATIENTS WITH FEWER THAN 3 RISK FACTORS

"WE SUGGEST NOT USING SGLT-2 INHIBITORS OR GLP-1 RECEPTOR AGONISTS"

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	20 per 1000	**3 fewer**	**2 fewer**
	certainty →	High	High
Cardiovascular mortality 5 years	13 per 1000	**2 fewer**	**2 fewer**
	certainty →	High	High
Non-fatal myocardial infarction 5 years	30 per 1000	**4 fewer**	**2 fewer**
	certainty →	High	High
Non-fatal stroke 5 years	30 per 1000	**No important difference**	**5 fewer**
	certainty →	High	High
Heart failure 5 years	5 per 1000	**2 fewer**	**No important difference**
	certainty →	High	High
End stage kidney disease 5 years	2 per 1000	**1 fewer**	**No important difference**
	certainty →	High	High

> 3 RISK FACTORS

"WE SUGGEST SGLT-2 INHIBITORS. WE SUGGEST NOT USING GLP-1 RECEPTOR AGONISTS"

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	70 per 1000	**10 fewer**	**8 fewer**
	certainty →	Moderate	Moderate due to serious imprecision
Cardiovascular mortality 5 years	46 per 1000	**8 fewer**	**5 fewer**
	certainty →	Moderate due to serious imprecision	High
Non fatal myocardial infarction 5 years	58 per 1000	**7 fewer**	**4 fewer**
	certainty →	Moderate due to serious imprecision	High
Non fatal stroke 5 years	58 per 1000	**1 more**	**9 fewer**
	certainty →	High	Moderate due to serious imprecision
Heart failure 5 years	30 per 1000	**9 fewer**	**2 fewer**
	certainty →	Moderate due to serious imprecision	High
End stage kidney disease 5 years	10 per 1000	**3 fewer**	**2 fewer**
	certainty →	High	High

WITH ASCVD

WE SUGGEST SGLT-2 INHIBITORS OR GLP-1 RECEPTOR AGONISTS

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	120 per 1000	**16 fewer**	**13 fewer**
	certainty →	Moderate	Moderate due to serious imprecision
Cardiovascular mortality 5 years	79 per 1000	**13 fewer**	**9 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Non fatal myocardial infarction 5 years	108 per 1000	**13 fewer**	**8 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Non fatal stroke 5 years	108 per 1000	**1 more**	**16 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Heart failure 5 years	80 per 1000	**23 fewer**	**5 fewer**
	certainty →	High	Moderate due to serious imprecision
End stage kidney disease 5 years	20 per 1000	**6 fewer**	**4 fewer**
	certainty →	High	High

WITH CKD

WE SUGGEST SGLT-2 INHIBITORS OR GLP-1 RECEPTOR AGONISTS

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	170 per 1000	**22 fewer**	**17 fewer**
	certainty →	High	Moderate due to serious imprecision
Cardiovascular mortality 5 years	112 per 1000	**17 fewer**	**12 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Non fatal myocardial infarction 5 years	120 per 1000	**14 fewer**	**9 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Non fatal stroke 5 years	120 per 1000	**1 more**	**17 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Heart failure 5 years	105 per 1000	**30 fewer**	**7 fewer**
	certainty →	High	Moderate due to serious imprecision
End stage kidney disease 5 years	92 per 1000	**26 fewer**	**19 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision

WITH ASCVD AND CKD

WE RECOMMEND SGLT-2 INHIBITORS.
WE SUGGEST GLP-1 RECEPTOR AGONISTS AS AN ALTERNATIVE

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	265 per 1000	**30 fewer**	**24 fewer**
	certainty →	High	High
Cardiovascular mortality 5 years	175 per 1000	**25 fewer**	**18 fewer**
	certainty →	High	Moderate due to serious imprecision
Non fatal myocardial infarction 5 years	190 per 1000	**21 fewer**	**13 fewer**
	certainty →	Moderate due to serious imprecision	Moderate due to serious imprecision
Non fatal stroke 5 years	190 per 1000	**2 more**	**25 fewer**
	certainty →	Moderate due to serious imprecision	High
Heart failure 5 years	235 per 1000	**60 fewer**	**13 fewer**
	certainty →	High	Moderate due to serious imprecision
End stage kidney disease 5 years	148 per 1000	**40 fewer**	**29 fewer**
	certainty →	High	High

UpToDate diabetes cardiovascular Andrian Dreyer CME 500+ Log Out Menu

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Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus

Topic Graphics (1)

Outline

Patient selection — SGLT2 inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes. Initial therapy in most patients with type 2 diabetes should begin with diet, body weight reduction, exercise, and metformin (in the absence of contraindications). (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

In patients with comorbid cardiovascular or kidney disease, many SGLT2 inhibitors have demonstrated benefit for cardiovascular and kidney outcomes (see 'Cardiovascular effects' below and 'Kidney outcomes' below). However, SGLT2 inhibitors confer only modest improvement in glycemia and are costly, and long-term safety data on the effects of prolonged glucosuria are lacking. In addition, there are insufficient data on cardiovascular outcomes in individuals with diabetes but without overt cardiovascular or kidney disease. All of these factors must be recognized when considering combination therapy for monotherapy failure. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Our approach'.)

T2DM TREATMENT GUIDE

Address the components of lifes essential 8

Step 1: Unless contra-indicated all patients start on Metformin

Step 2: Indication for insulin therapy

Yes

1. Metabolic decompensation
2. HBA1c >10%
3. HGT >16,7 mmol/L
4. DKA or HHS

No

Step 3: Is there ESTABLISHED ASCVD risk or a compelling indication for SGLT2 (HF or CKD)

No

Gliclazide

1. SUs not bad, safe, comparably effective
2. Weight gain marginal, less insulin
3. Few severe hypoglycemic events with Gliclazide MR
4. Cost effective

Yes

SGLT2i

1. Most guidelines advocate for their use in certain individuals
2. Established ASCVD or CKD
3. Superior in high risk groups – cost effective in select cases
4. Comparable HBA1c reduction
5. Not cost effective alternative for primary prevention in low risk patients

TYPE 2 DM: "GLYCEMIC CONTROL: WHAT THE HEART'S GOT TO DO WITH IT"

Dr. Andrian Dreyer
Specialist Physician / Internis

CVD RISK STRATIFICATION OF THE T2D IS FUNDAMENTAL IN GUIDING TREATMENT CHOICES

Patients with type 2 diabetes mellitus			
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	**Moderate-risk**	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria	**High-risk**	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
	Patients with DM with established ASCVD and/or severe TOD:[87, 93-95] • eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m^2 and microalbuminuria (ACR 30 -300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	**Very high-risk**	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

T2DM TREATMENT GUIDE

Address the components of lifes essential 8

3 monthly HBA1c till individual target? If no escalate

Step 1: Unless contra-indicated all patients start on Metformin

Step 2: Indication for insulin therapy

Yes

1. Metabolic decompensation
2. HBA1c >10%
3. HGT >16,7 mmol/L
4. DKA or HHS

No

Step 3: Is there ESTABLISHED ASCVD risk or a compelling indication for SGLT2 (HF or CKD)

No

Gliclazide MR

\+ ♥ -

Yes

SGLT2i

Step 4: HBA1c still above target, add SGLT2i if ASCVD/CKD manifest

DPP4i

TZD

GLP1a

Insulin

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment — Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer
- Metformin
- Or if GI disturbance
- Metformin MR

Consider
- DPP-4 inhibitor ('gliptin') or
- Pioglitazone or
- Sulfonylurea

An SGLT2 inhibitor ('flozin') for some people:
- TA 390 Canagliflozin
- TA 390 Dapagliflozin
- TA 390 Empagliflozin
- TA 572 Ertugliflozin

If metformin contraindicated

Offer
- SGLT2 inhibitor alone

If metformin contraindicated

Chronic heart failure or established atherosclerotic CVD

Offer
- Metformin
- or if GI disturbance
- Metformin MR
- and as soon as metfomin tolerability is confirmed, offer
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk

Offer
- Metformin
- or if GI disturbance
- Metformin MR
- and as soon as metfomin tolerability is confirmed, consider
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Consider
- SGLT2 inhibitor alone

If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

Published date: February 2022. Last updated: August 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

How to choose medicines for further treatment

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

Treatment options if further interventions are needed

At any point

HBA1c not controlled below individually agreed threshold

Switching or adding treatments

Consider:

- DPP-4 inhibitor or Pioglitazone
- or Sulfonylurea

SGLT2 inhibitors may also be an option in dual therapy:

- TA 315 Canagliflozin
- TA 288 Dapagliflozin
- TA 336 Empagliflozin
- TA 572 Ertugliflozin

Or in triple therapy:

- TA 315 Canagliflozin
- TA 418 Dapagliflozin
- TA 336 Empagliflozin
- TA 583 Ertugliflozin

At any point

Cardiovascular risk or status change

- If the person has or develops chronic heart failure or established atherosclerotic CVD → **Switching or adding treatments** → **Offer** An SGLT2 inhibitor (if not already prescribed)
- If the person has or develops a high risk of CVD (QRISK2 of 10% or higher, or elevated lifetime risk) → **Switching or adding treatments** → **Consider** An SGLT2 inhibitor (if not already prescribed)

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

At each point follow the prescribing guidance.
Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated).
In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

Insulin therapy

When dual therapy has not continued to control HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other drugs).

- TA 288 Dapagliflozin
- TA 336 Empagliflozin
- TA 315 Canagliflozin

GLP-1 mimetic treatments

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m² or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m² **and**:
  - for whom insulin therapy would have significant occupational implications **or**
  - weight loss would benefit other significant obesity related comorbidities.

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IN CONCLUSION: WHAT DOES THE HEART HAVE TO DO WITH IT

1. DM is a major modifiable risk factor for CVD: The majority of patients with T2D die of cardiovascular disease
2. A multifactorial approach addressing the big 5 (Rawshani) can eliminate excess cardiovascular risk (drug independent)(AHA life essential 8)
3. HBA1c reductions targeting individual goals protect against microvascular and macrovascular disease, earlier = better
4. Get HBA1c down, the viral load of DM
    1. HBA1c every 3 months and escalate therapy
    2. Not at HBA1c target at 12 months – refer to physician
5. CVD "status" assists on deciding if add on therapy with a novel agent is indicated (for non-HBA1c effect)
    1. Established ASCVD, heart failure, CKD or albuminuria – SGLT2i (+/- 1/3 patients – likely need referred to physician for annual review in addition to primary care)
6. No ASCVD, HF, CKD or albuminuria – add SU – Gliclazide reasonable, safe and most cost effective therapy (2/3 of patients)
7. Still not at target – 3 months later
    1. Multifactorial approach to CVD reduction (AHA life's essential 8)
    2. Up-titrate dosing
    3. +/- add DDP4i, Combination SU and SGLT2
8. Still not at target and on 3 oral agents at maximal doses
    1. Multifactorial approach to CVD reduction (AHA life's essential 8)
    2. GLP1a
    3. Insulin therapy
9. Re-evaluate indication for SGLT2i = re-evaluate the patients CVD risk Status
10. Obliged to consider the person in front of you during the consulation, population as a whole when you try and sleep at night
    1. Don't be the reason the person that needs the GLP1a cannot get one (off label use for weight loss)

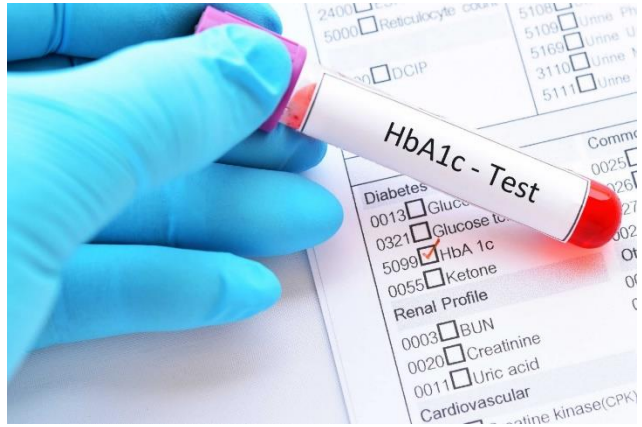
WHY ARE WE OBSESSED WITH NEW DRUGS? BECAUSE THE RIGHT WAY TO DO IT IS HARD.

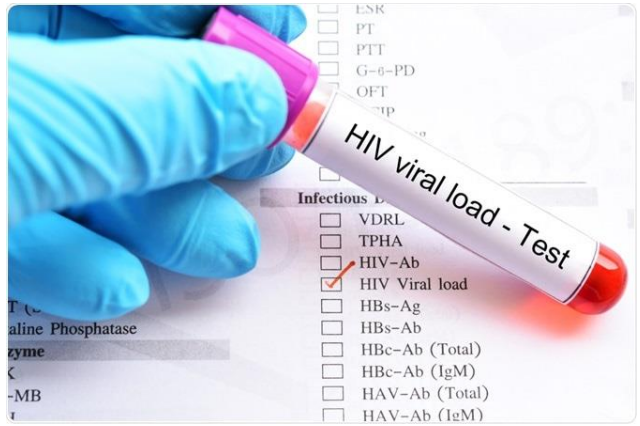
CVD prevention in **the majority of** T2D combines a HBA1c-centric approach with multifactorial risk reduction by addressing major CVD risks.

The more risks that are controlled the better. For maximal benefit HBA1c targets need to be attained early and sustained.

Drug independent.

Should be cost effective.





CVD prevention in **the majority of** T2D Not a result of a miracle drug. Not bought with expensive medicines. The 'miraculous' effects of SGLT2i are independent of their glucose lowering effect as is evidenced by efficacy **Non DM** individuals.