Diabetes MCN

NHS
Greater Glasgow and Clyde

Dr Kashif Ali

General Practitioner
Primary Care Lead

01

T2DM
CURRENT
SITUATION

02

LIFESTYLE &
SELF-
MANAGEMENT

03

GGC
TYPE 2
MANAGEMENT
GUIDELINES

04

CVOT DATA
+
CASE STUDIES

DIABETES IN SCOTLAND

NEW CASES OF T2DM PER YEAR **17,000**

500,000 AT RISK OF DEVELOPING T2DM

REMAIN UNDIAGNOSED **10%**

WHO IS AT RISK?

87% ARE ABOVE IDEAL WEIGHT

GESTATIONAL DIABETES

ETHNICITY

50% OF WOMEN DIAGNOSED WITH GDM WILL DEVELOP TYPE 2 DIABETES WITHIN 5 YEARS OF GIVING BIRTH

a

b

c

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

TYPE 2 DIABETES
KNOW YOUR RISK

https://qdiabetes.org/

Age (25-84): 50
Sex: (•) Male ( ) Female
Ethnicity: Pakistani

Leave blank if unknown
Postcode:

Clinical information -- check those that apply

Do you smoke at all?	Moderate
Do you have diabetes?	No
Are you on regular steroid tablets?	☐
Do you have high blood pressure requiring treatment?	☐
Have you had a heart attack, angina, stroke or TIA (a mini-stroke with full recovery within 24hrs)?	☐
Has anyone in your immediate family* had angina or a heart attack whilst under 60?	☐
Do immediate family* have diabetes?	☑
Have you been diagnosed with rheumatoid arthritis?	☐
Have you been diagnosed with chronic kidney disease (stage 4 or 5)?	☐
Have you been diagnosed with atrial fibrillation or irregular heartbeat?	☐
Do you have congestive cardiac failure?	☐
Do you have hypothyroidism?	☐
Do you have liver failure?	☐

*mother, father, brothers or sisters

Leave blank if unknown

Cholesterol/HDL ratio: 4.1
Systolic blood pressure (mmHg): 142

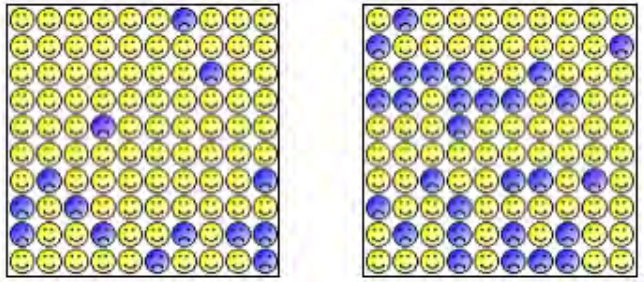
Body mass index

Weight (kg): 79
Height (cm): 175

Your results

Your 10-year QRISK®2 score and QDiabetes® score are: **14.4%** and **27.6%** respectively.

In other words, in a crowd of 100 people like you, 14 will develop heart disease or have a stroke/TIA in the next 10 years. Similarly, 28 will develop diabetes in the next 10 years. This is represented by the smileys below.



QRISK2
Cardiovascular disease

QDiabetes
Type 2 diabetes

Your score has been calculated using estimated or corrected data, as some information was left blank. Your body mass index was calculated as 25.8 kg/m^2.

A healthy person with the same age, sex and ethnicity would have a 7% risk of getting cardiovascular disease and a 9% risk of getting diabetes in the next 10 years.

Your QRISK®2 Heart Age (i.e. the age at which a healthy person of your sex and ethnicity has your 10-year QRISK®2 score), is 60.

What if..? (Scroll down to see the full results)

- I were to go on statins? ☐
- I lose enough weight to bring my body mass index down to 25? ☐
- I stop smoking? ☐
- I get my systolic blood pressure down to 140 mmHg? ☐

Calculate the "What if"s

Intended effects of interventions

With these interventions, a person like you on average would have a 14% risk of getting cardiovascular disease and a 28% risk of getting diabetes in the next 10 years.

Your Heart Age would be 60.

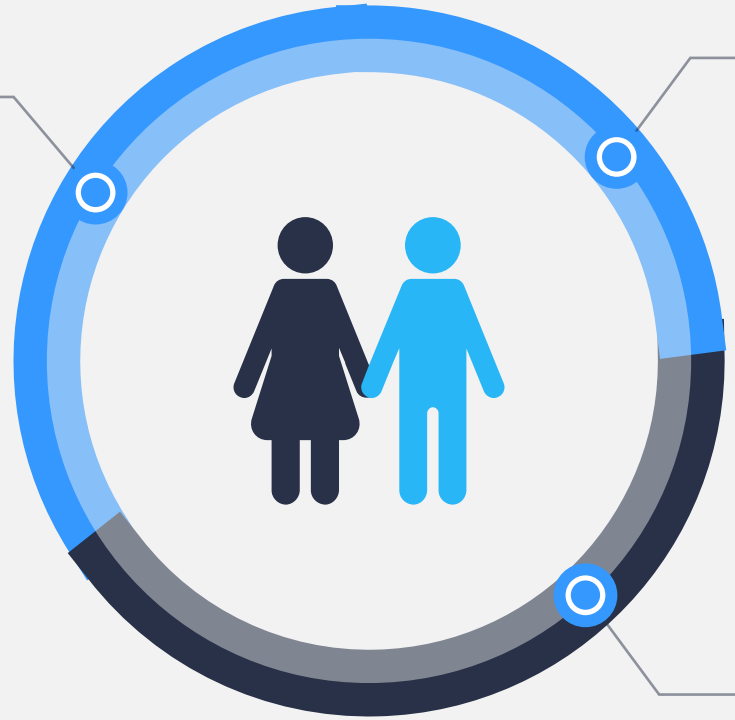
Intended effects of interventions

30%

Type 2 Diabetics in Glasgow 57,952

Patients with HbA1c < 58mmol/l

52 %

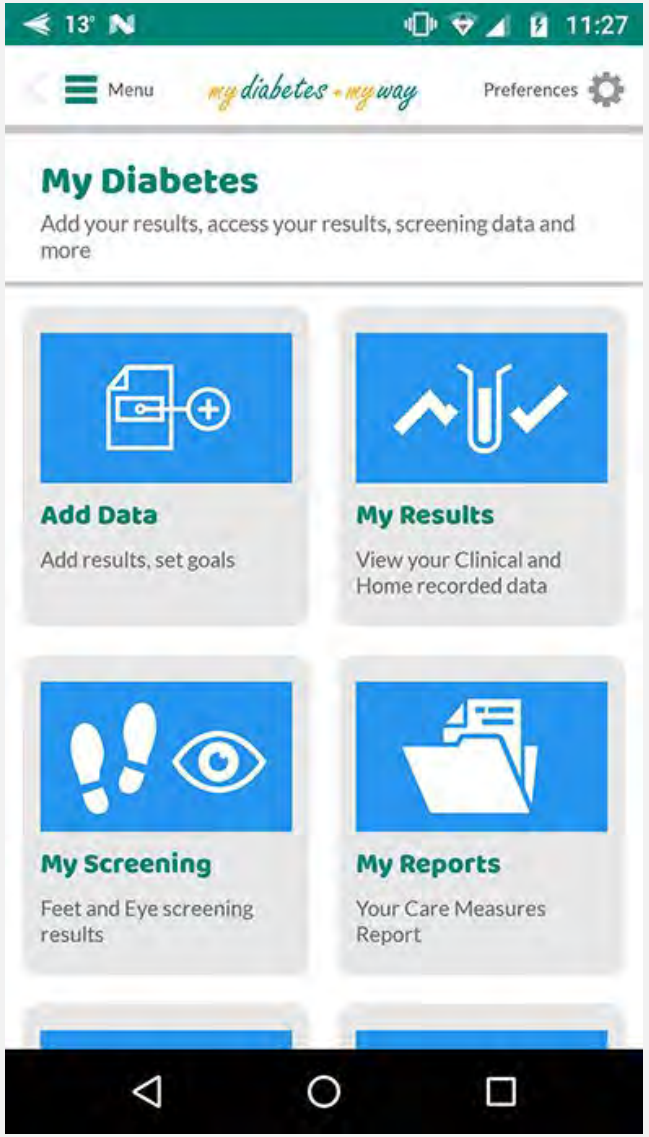


43% Patients receiving all 9 “Processes of Care”

86% Patients with BMI ≥ 30

my diabetes * my way

NHS SCOTLAND



GOAL SETTINGS	DATE:
What do you want to work on? HbA1c and cholesterol	
What do you want to achieve? Lose 5kg by March 2020	
How important is for you? (1 not important, 10 important) 8	

ACTION PLAN	DATE:
What exactly are you going to do? Exercise	
What might stop you and what can you do about it? Takeaways - limit to once a month	
How Confident you feel? (1 not confident, 10 confident) 8	
Review of goal/action plan:	
When:	Where:

DIABETES CARE PLANNING RESULT LETTER

Name: ARCHIBALD MACKIE **CHI No:** 597464119

Your Appointment: _____

Before your appointment take time to:

- Make a note of anything you would like to discuss at the appointment
- Look over your results (page 2-3) and think about what they mean to you
- Think about any goals you want to achieve and how you might achieve them

Please bring this to your appointment so we can use it to help decide how you want to manage your diabetes.

These are some of the things you wish to discuss

, Your mood , Eating the right amount

What aspects of your diabetes would you like to discuss?

Portion size

Mood: How you are coping with things in life can affect your diabetes

During the last month, have you been bothered by feeling down, depressed or hopeless? During the last month, have you had little interest or pleasure in doing things?

Never Never

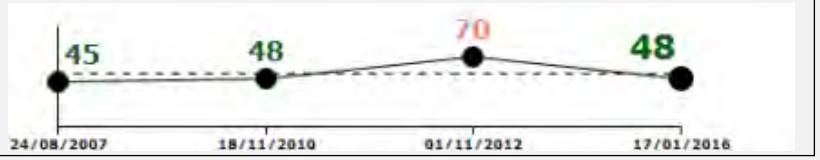
Your results of measurements that affect your future risk of health problems: Low Risk | Medium Risk | High Risk | No results

Blood Sugar Control (HbA1c)

HbA1c is a measure of average blood sugar over the past 8-12 weeks. Its levels are associated with risk of complications.

Your Risk: Low

Target: 53 mmol/mol

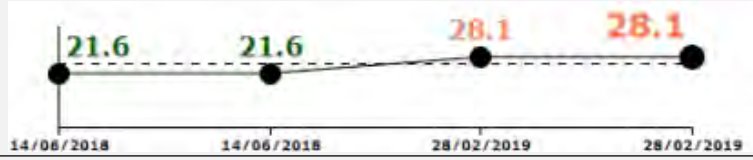


Body Mass Index

Body mass index (BMI) assesses your weight in relation to your height.

Your Risk: Medium

Target: 25 kg/m^2

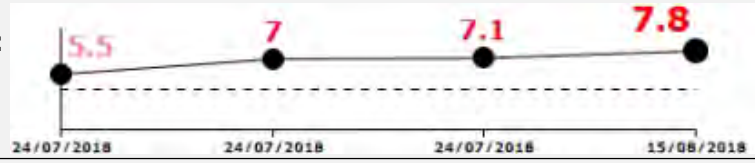


Total Cholesterol

Cholesterol is a measure of bad fats(lipids) in the blood. If raised, it can increase your risk of heart attack and stroke.

Your Risk: High

Target: 4.0 mmol/mol

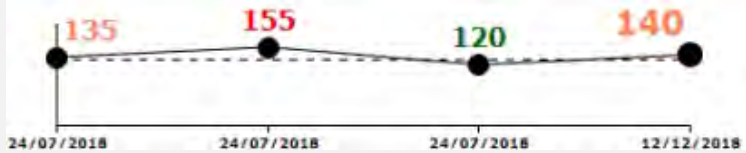


Blood pressure

Blood pressure, if raised can increase the risk of heart attacks, strokes, kidney and eye problems.

Your Risk: Medium

Target: 130 mmHg



Target: 80 mmHg

Smoking

Smoking causes problems with your health in many ways but is particularly damaging in people with diabetes.

Status: Ex

Your risk: Medium

Kidney: Blood (eGFR)

Previous result: 63
Latest result: 68
Target: more than 60
Your Risk: Low
OVERDUE

Kidney: Urine (ACR)

Previous result: 1
Latest result: 2
Target: less than 2.5
Your Risk: Low
OVERDUE

Feet

Last check: 28/10/2005
Result: Active Charcot and Foot Ulcer
OVERDUE

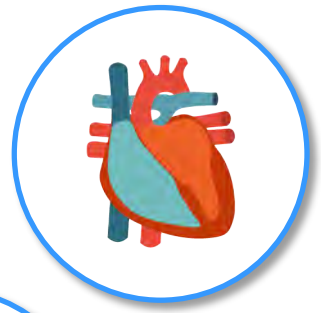
Eyes

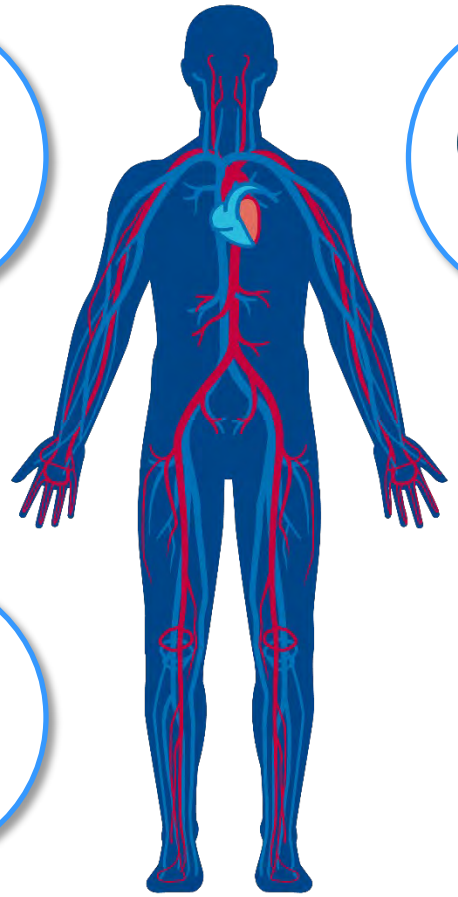
Last check:
Result: No results
Your Risk: No results
OVERDUE

Questions,thoughts or ideas about your annual screening checks:

Diabetes is a leading cause of cardiovascular disease, kidney failure, blindness and lower-limb amputation[1]

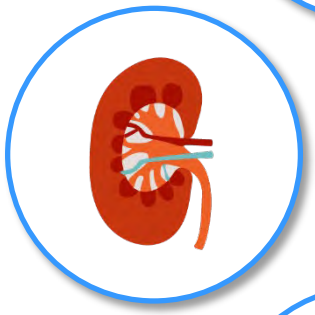
50% of people with diabetes die from cardiovascular disease[2]





16% of people aged >65 years with diabetes die of stroke[4]

44% of new kidney failure cases are caused by diabetes[3]



29% of people with diabetes aged ≥40 years have diabetic retinopathy[3]

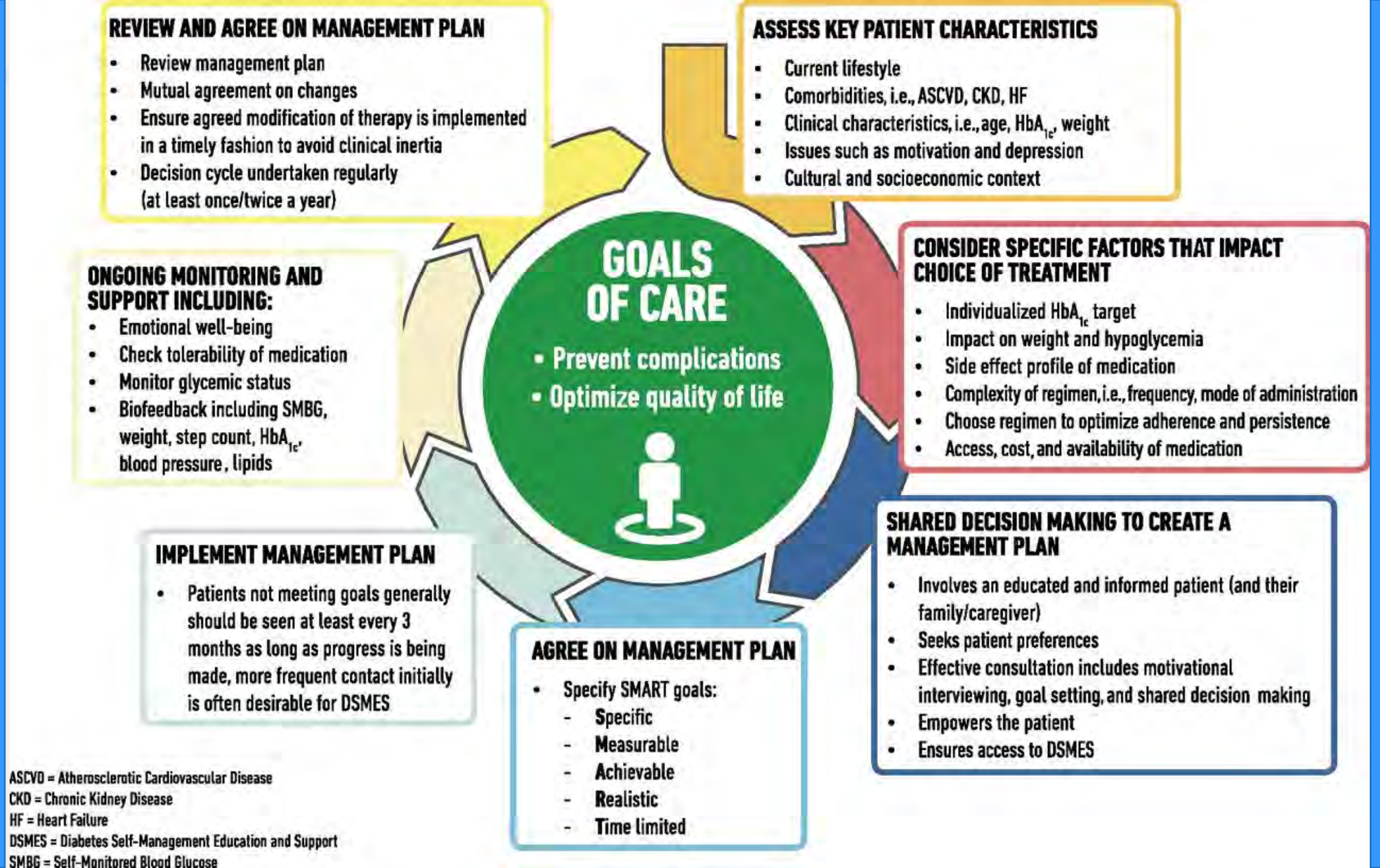
60% of all non-traumatic lower-limb amputations occur in diabetic patients ≥20 years old[3]

A significant unmet need exists to reduce complications of diabetes

1. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. 2017. [Accessed August 2018]. www.idf.org/diabetesatlas
2. World Health Organization. Diabetes: Data and statistics. [Accessed August 2018]. www.euro.who.int/en/health-topics/noncommunicable-diseases/diabetes/data-and-statistics
3. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2011. [Accessed August 2018]. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011pdf
4. American Heart Association. Statistical Fact Sheet, 2014. [Accessed August 2018]. www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_462019.pdf

Patients diagnosed between Jul 17-Jun 18 and have had Anniversary HbA1c

HSCP	Patients Diagnosed	Patients <58 (includes <48)	% <58	Patients <48	% <48
GGC	3365	1500	44.6%	792	23.5%
EAST DUN	232	113	48.7%	63	27.2%
EAST REN	174	67	38.5%	38	21.8%
GLASGOW NE	574	220	38.3%	106	18.5%
GLASGOW NW	530	273	51.5%	144	27.2%
GLASGOW SOUTH	766	320	41.8%	177	23.1%
INVERCLYDE	238	103	43.3%	48	20.2%
RENFREWSHIRE	557	255	45.8%	133	23.9%
WEST DUN	294	149	50.7%	83	28.2%

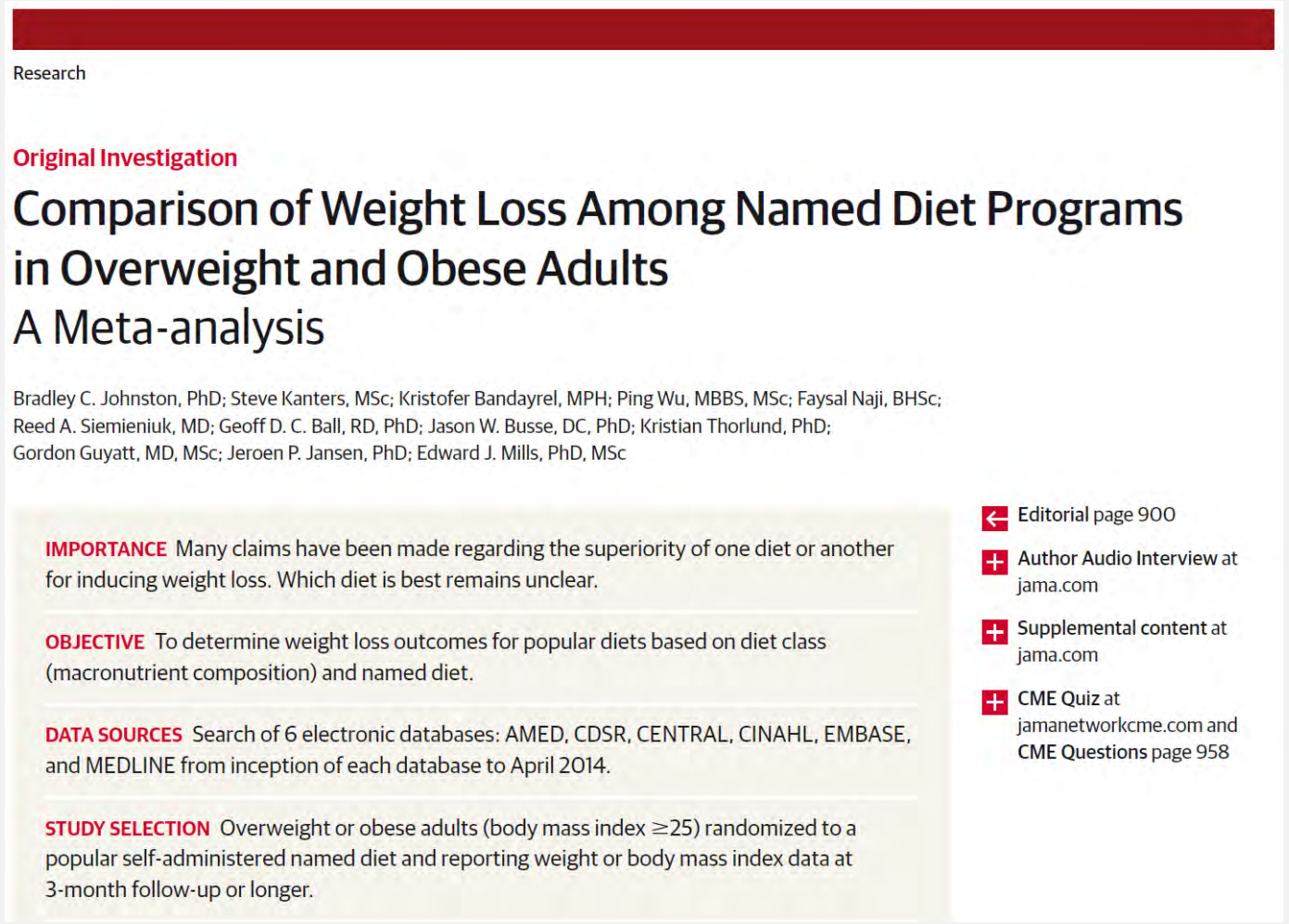


ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Lifestyle Management


ASK for Permission to Discuss Weight
ASSESS obesity related risk and potential 'root causes' of weight gain
ADVISE on obesity risks, discuss benefits & options
AGREE on realistic weight-loss expectations and on a SMART plan to achieve behavioural goals
ASSIST in addressing drivers & barriers, offer education & resources, refer to provider, and arrange follow-up
STEP 1
5As of Obesity Management © 2012 Canadian Obesity Network

It doesn't matter which diet you use



Research

Original Investigation

Comparison of Weight Loss Among Named Diet Programs in Overweight and Obese Adults
A Meta-analysis

Bradley C. Johnston, PhD; Steve Kanters, MSc; Kristofer Bandayrel, MPH; Ping Wu, MBBS, MSc; Faysal Naji, BHSc; Reed A. Siemieniuk, MD; Geoff D. C. Ball, RD, PhD; Jason W. Busse, DC, PhD; Kristian Thorlund, PhD; Gordon Guyatt, MD, MSc; Jeroen P. Jansen, PhD; Edward J. Mills, PhD, MSc

IMPORTANCE Many claims have been made regarding the superiority of one diet or another for inducing weight loss. Which diet is best remains unclear.

OBJECTIVE To determine weight loss outcomes for popular diets based on diet class (macronutrient composition) and named diet.

DATA SOURCES Search of 6 electronic databases: AMED, CDSR, CENTRAL, CINAHL, EMBASE, and MEDLINE from inception of each database to April 2014.

STUDY SELECTION Overweight or obese adults (body mass index ≥25) randomized to a popular self-administered named diet and reporting weight or body mass index data at 3-month follow-up or longer.

Editorial page 900

Author Audio Interview at jama.com

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 958

Johnston et al (2014) JAMA 312:923-933

It doesn't matter which diet you use

Figure 1. Difference in Mean Weight Loss at 6- and 12-Month Follow-up Across All Diet Classes With 95% Credible Intervals

		12-mo Weight Loss, kg			
	No diet (6 mo: 0; 12 mo: 0)[a]	5.16 (2.68 to 7.63)	5.70 (4.14 to 7.35)	7.25 (5.33 to 9.25)	7.27 (5.26 to 9.34)
6-mo Weight Loss, kg	6.07 (4.23 to 7.84)	LEARN (6 mo: 0; 12 mo: 0.02)[a]	0.55 (−1.71 to 2.87)	2.10 (−0.20 to 4.47)	2.12 (−0.33 to 4.59)
	6.78 (5.50 to 8.05)	0.71 (−0.97 to 2.44)	Moderate macronutrients (6 mo: 0; 12 mo: 0)[a]	1.55 (0.13 to 2.95)	1.56 (−0.17 to 3.30)
	8.73 (7.27 to 10.20)	2.66 (0.93 to 4.44)	1.95 (1.13 to 2.79)	Low carbohydrate (6 mo: 0.83; 12 mo: 0.48)[a]	0.02 (−1.78 to 1.79)
	7.99 (6.01 to 9.92)	1.92 (−0.19 to 4.06)	1.20 (−0.42 to 2.79)	−0.74 (−2.31 to 0.78)	Low fat (6 mo: 0.17; 12 mo: 0.50)[a]

The values above the diet classes (blue boxes) correspond to the difference in mean weight lost between the columns and row at 12 months (eg, the difference in average weight lost between moderate macronutrients and no diet at 12 months is 5.70 kg). The values below the diet classes correspond to the difference in mean weight lost between the row and the column at 6 months (eg, the difference in average weight lost between moderate macronutrients and no diet at 6 months is 6.78 kg). LEARN indicates Lifestyle, Exercise, Attitudes, Relationships, and Nutrition.

[a] The values in parentheses represent the estimated probability of that treatment being the best.

CONCLUSIONS AND RELEVANCE Significant weight loss was observed with any low-carbohydrate or low-fat diet. Weight loss differences between individual named diets were small. This supports the practice of recommending any diet that a patient will adhere to in order to lose weight.

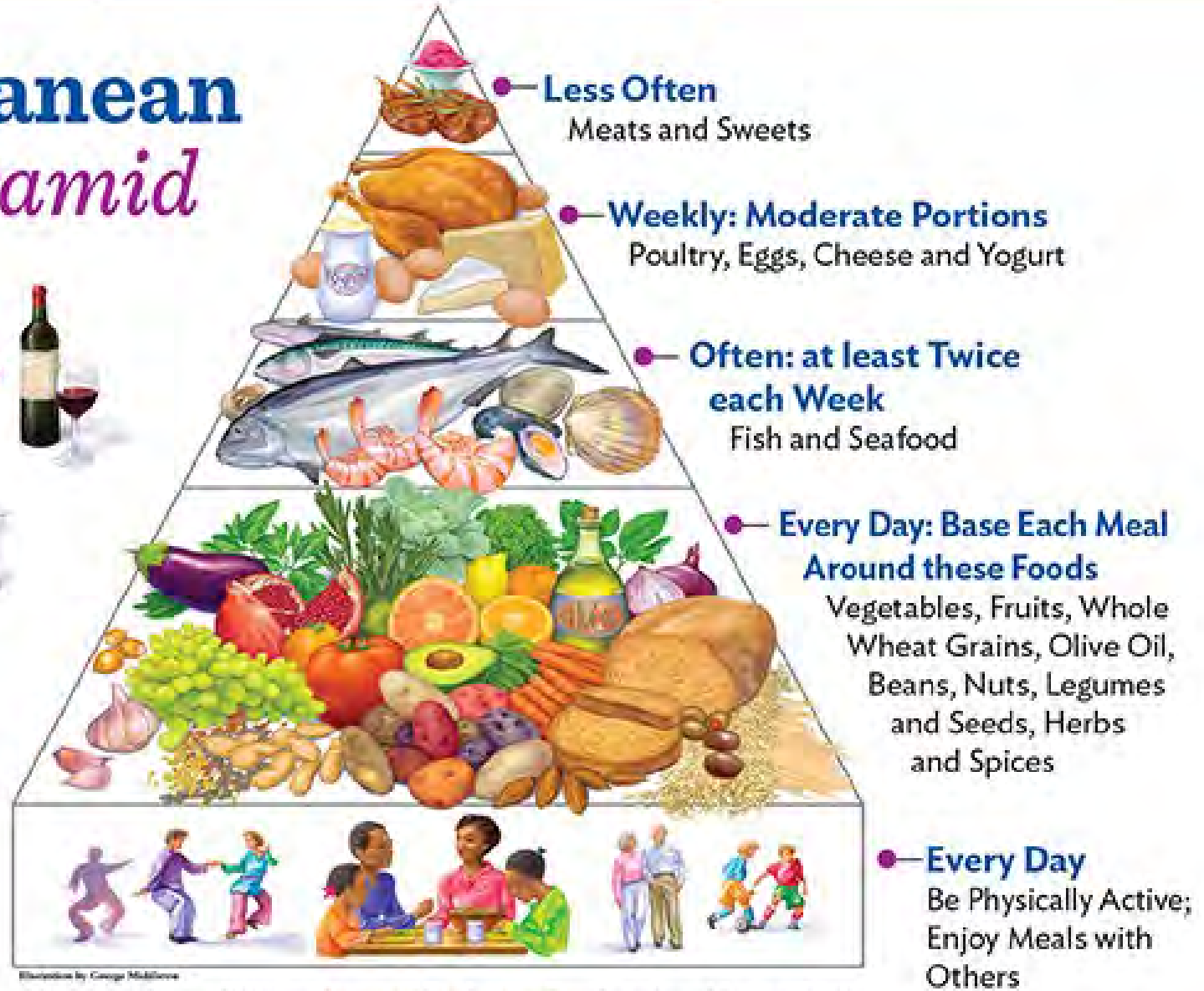
Johnston et al (2014) JAMA 312:923-933

Dietary approaches to the management of type 2 diabetes

Diet type	Change in weight compared to other diets (kg) (mean (95% CI))	Change in HbA1c compared to other diets (%) (mean (95% CI))
Low CHO	-0.69 (-1.77 to 0.39)	-0.12 (-0.24 to -0.00)
Low GI	+1.39 (-1.58 to 4.36)	-0.14 (-0.23 to -0.03)
Mediterranean	-1.84 (-2.54 to 1.15)	-0.47 (-0.64 to -0.30)
High protein	+0.44 (-0.96 to 1.84)	-0.28 (-0.38 to -0.18)

Ajala et al (2013) Am J Clin Nutr 97:505-515

Mediterranean Diet *Pyramid*



Less Often
Meats and Sweets

Weekly: Moderate Portions
Poultry, Eggs, Cheese and Yogurt

Often: at least Twice each Week
Fish and Seafood

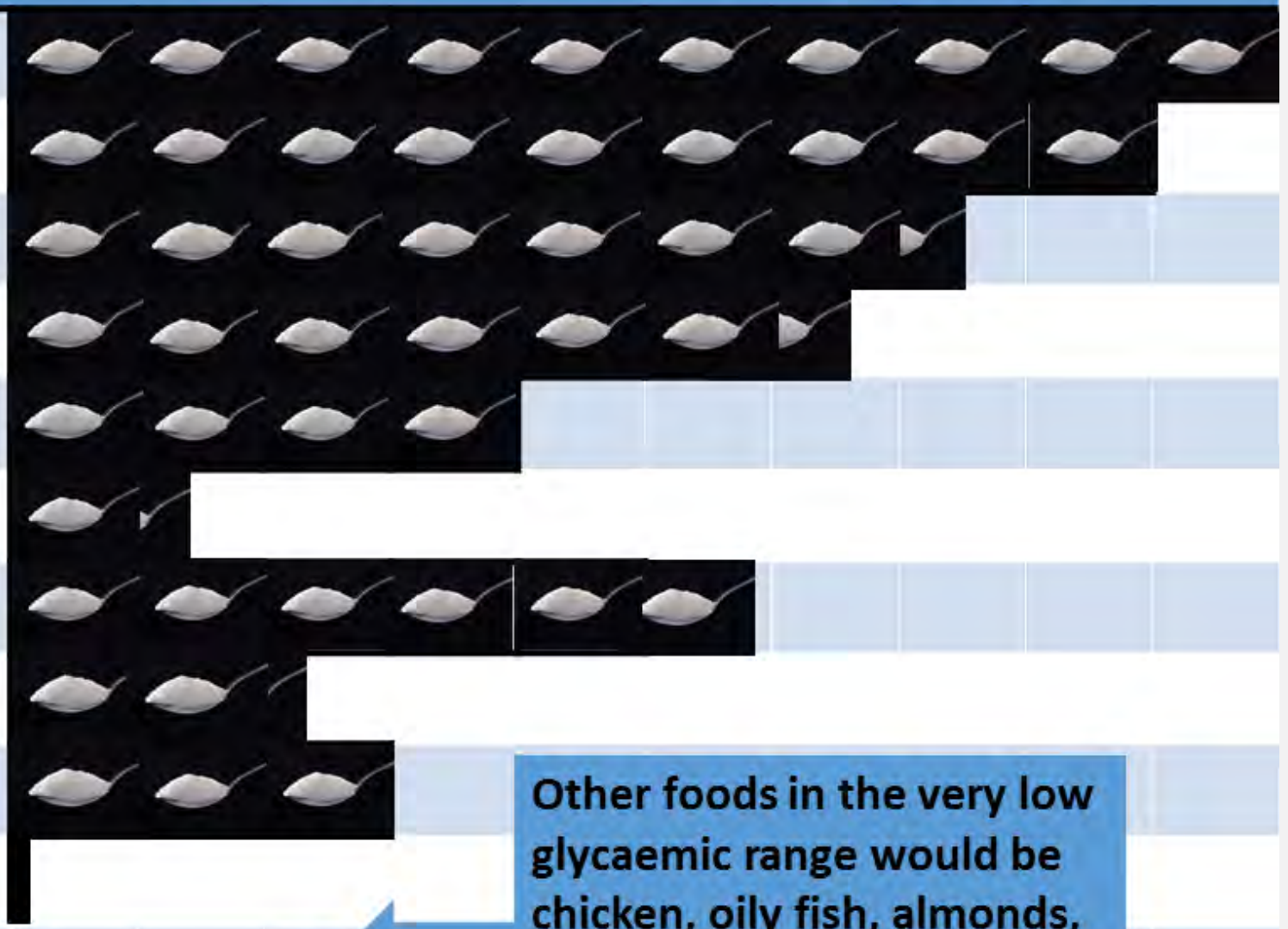
Every Day: Base Each Meal Around these Foods
Vegetables, Fruits, Whole Wheat Grains, Olive Oil, Beans, Nuts, Legumes and Seeds, Herbs and Spices

Every Day
Be Physically Active; Enjoy Meals with Others

In Moderation
Wine

Every Day
Water

Food Item	Glycaemic index	Serve size g	How does each food affect blood glucose compared with one 4g teaspoon of table sugar?
Basmati rice	69	150	**10.1**
Potato, white, boiled	96	150	**9.1**
French Fries baked	64	150	**7.5**
Spaghetti White boiled	39	180	**6.6**
Sweet corn boiled	60	80	**4.0**
Frozen peas, boiled	51	80	**1.3**
Banana	62	120	**5.7**
Apple	39	120	**2.3**
Wholemeal Small slice	74	30	**3.0**
Broccoli	15	80	**0.2**
Eggs	0	60	**0**



Other foods in the very low glycaemic range would be chicken, oily fish, almonds, mushrooms, cheese

The DiRECT study

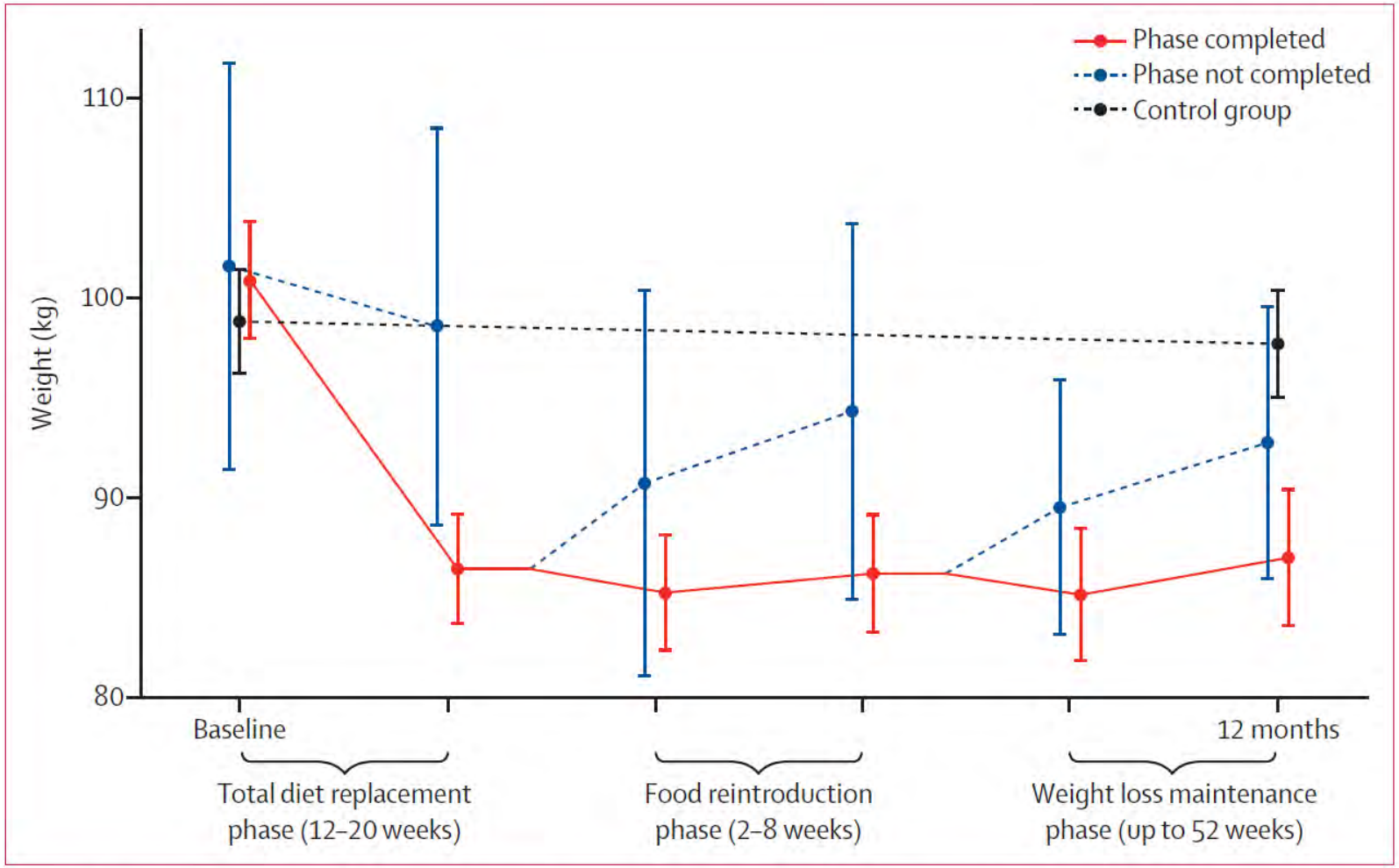
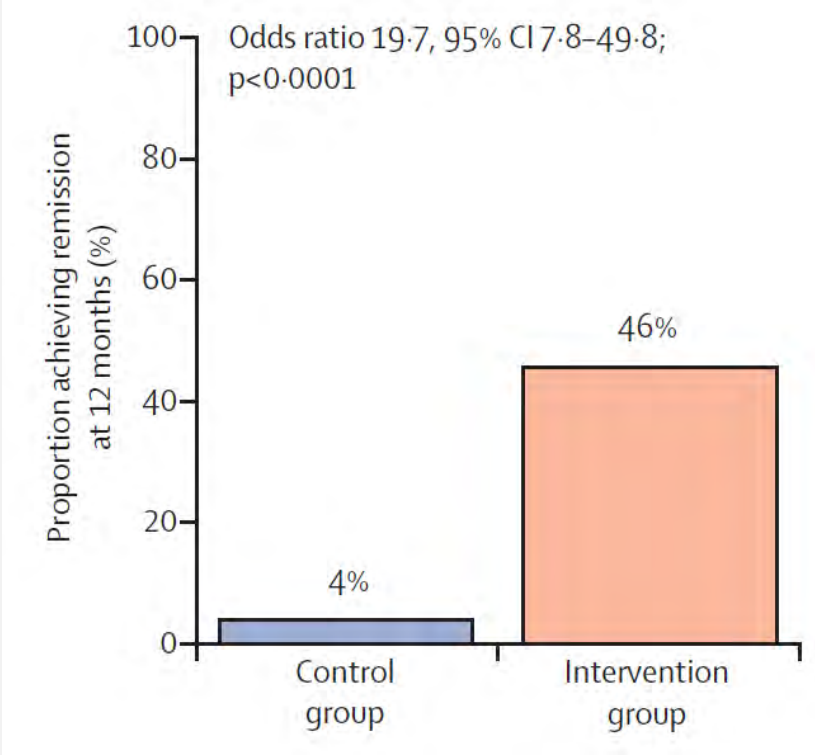
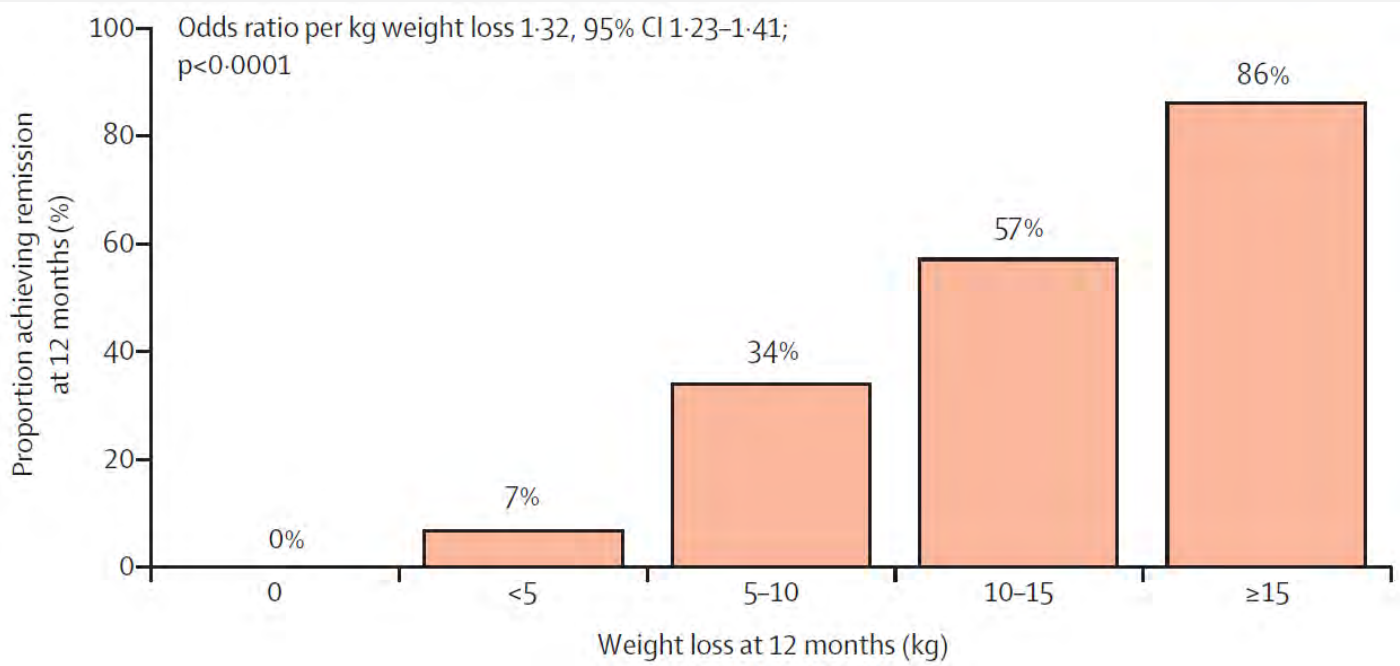


***Figure 3*: Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention**
Error bars represent 95% CIs.

Lean et al (2017) Lancet

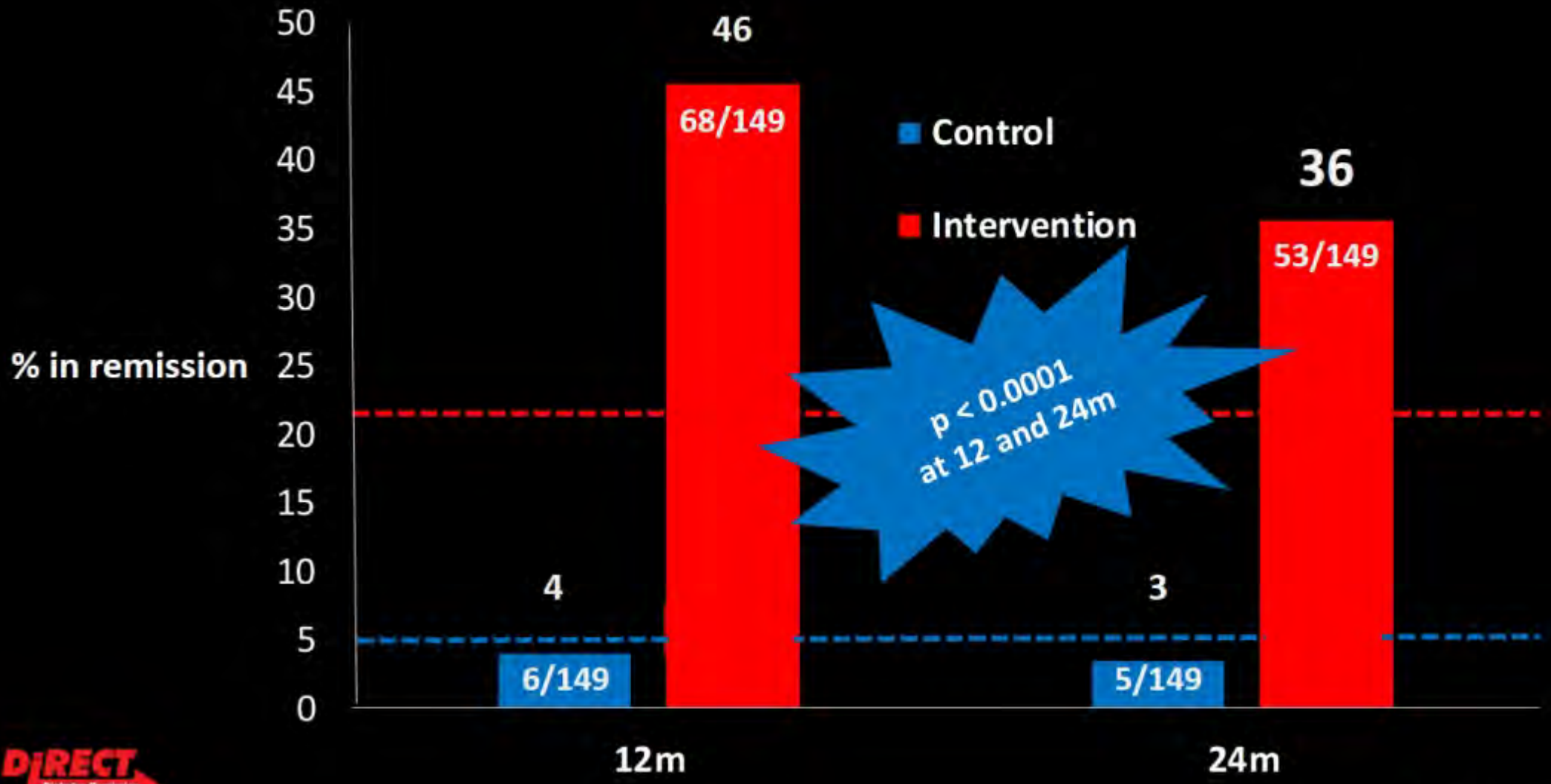
The DiRECT study





Lean et al (2017) Lancet

Remissions at 24 months



DiRECT Diabetes Remission Clinical Trial

Lean ME et al *Lancet Db&End* 2019

Glasgow Weight Management Services

BMI	Condition
Self-referral criteria	
≥25 (22.5*)	Type 2 diabetes
≥30 (27.5*)	Type 1 diabetes
	Heart disease
	Stroke
Health professional referral criteria	
≥25 (22.5*)	Impaired fasting glucose/ Impaired glucose tolerance/ High diabetes risk/ Previous GDM
≥25 (22.5*)	Type 2 diabetes
≥30 (27.5*)	Type 1 diabetes
Bariatric surgery criteria (triaged by servce)	Type 2 diabetes AND
	BMI 35-55 AND
	Age 18-55 AND
	Diabetes diagnosis <10 years

SELF-REFERRAL 0141 211 3379

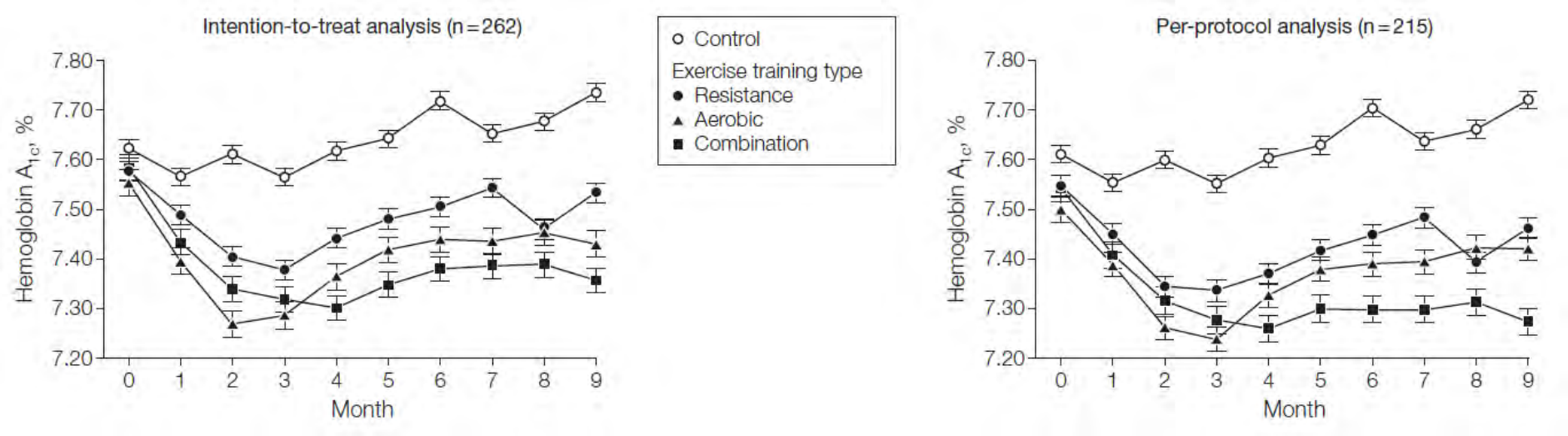
Community Weight Management Service (currently Weight Watchers)		Specialist Weight Management Service	
T2DM	BMI ≥25 (22.5*) (patients who meets surgical criteria will be triaged to specialist service)	T2DM	BMI≥45
T1DM	BMI ≥30 (27.5*)	T1DM	BMI≥45
Impaired fasting glucose/ impaired glucose tolerance/	BMI ≥25 (22.5*)	Potential bariatric surgery patient (as per criteria)	BMI≥35

Aerobic vs Resistance activity

Aerobic

Resistance

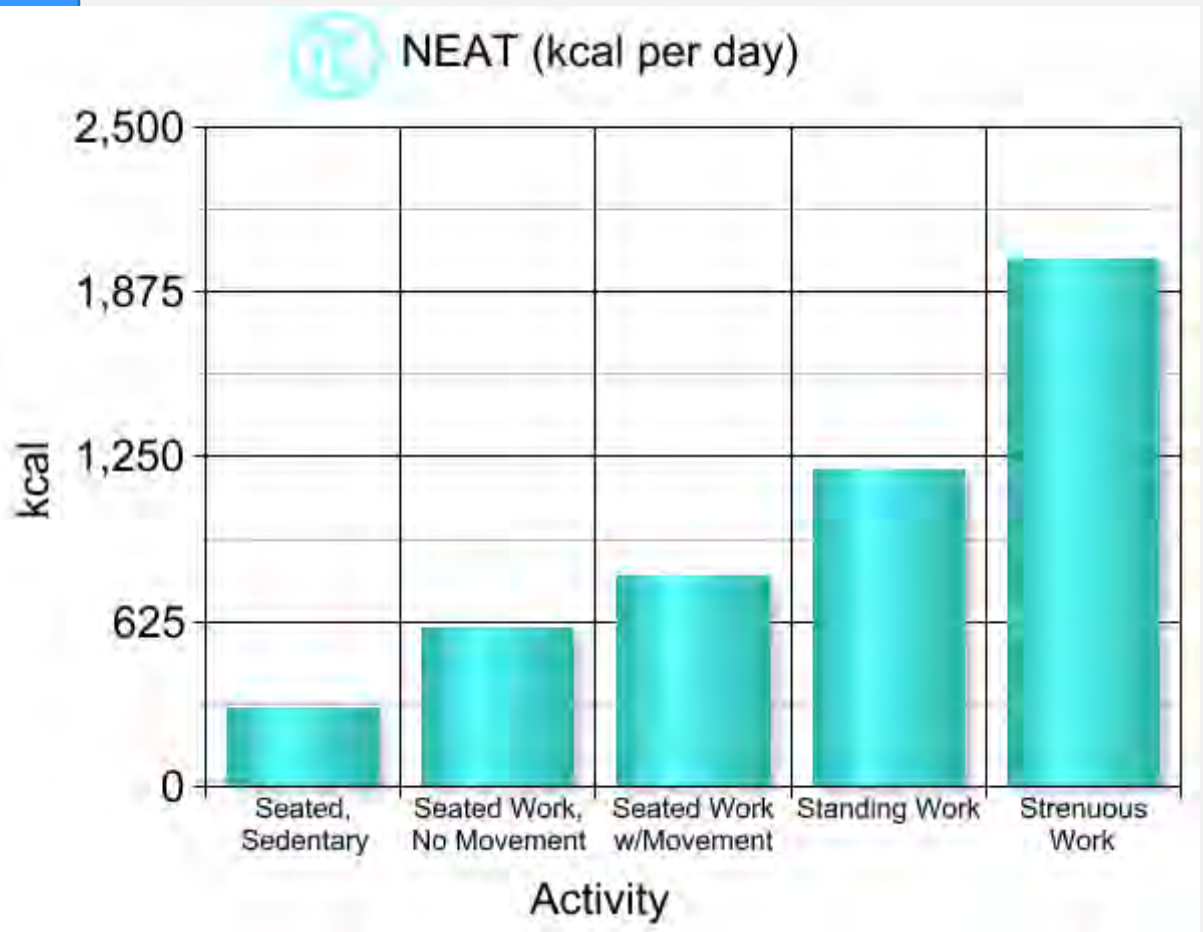
Aerobic training, resistance training or both on glycaemic control in type 2 diabetes



- **Control group** (n = 41) – no exercise
- **Aerobic training group** (n = 72) – 12 kcal/kg/week aerobic exercise over 3 sessions/week
- **Resistance training group** (n = 73) – 2-3 sets of 9 resistance exercises 3 x per week
- **Combined training group** (n = 76) – 12 kcal/kg/week aerobic exercise over 3 sessions/week PLUS 1 set of 9 resistance exercises in each session

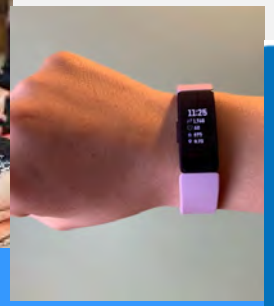
SIMILAR EXERCISE TIME FOR THE 3 INTERVENTION GROUPS (~130-150 MIN/WEEK)

Church et al (2010) JAMA, 304(20):2253-2262


NEAT (kcal per day)
2,500
1,875
1,250
625
0
kcal
Seated, Sedentary
Seated Work, No Movement
Seated Work w/Movement
Standing Work
Strenuous Work
Activity


NEAT Calories Burned per Hour*
100 - 200
Walking, Cleaning Vacuuming, Gardening, Taking the Stairs, Dancing
50 - 100
Standing, Cooking, Stretching, Ironing, Dusting
0 - 50
Sitting Activities
*Estimated calories burned above those burned at rest for a 150 pound person.
Source: The Compendium of Physical Activities Tracking Guide

WHAT LIFESTYLE ADVICE?



a

Aerobic exercise

Or

Combination Aerobic/Resistance

b

Leisure Time Activities

e.g Walking, Swimming, Gardening, Tai Chi, Yoga

c

Supervision of Exercise and motivational strategies

e.g Step Counter / Fitbit / Myfitness Pal

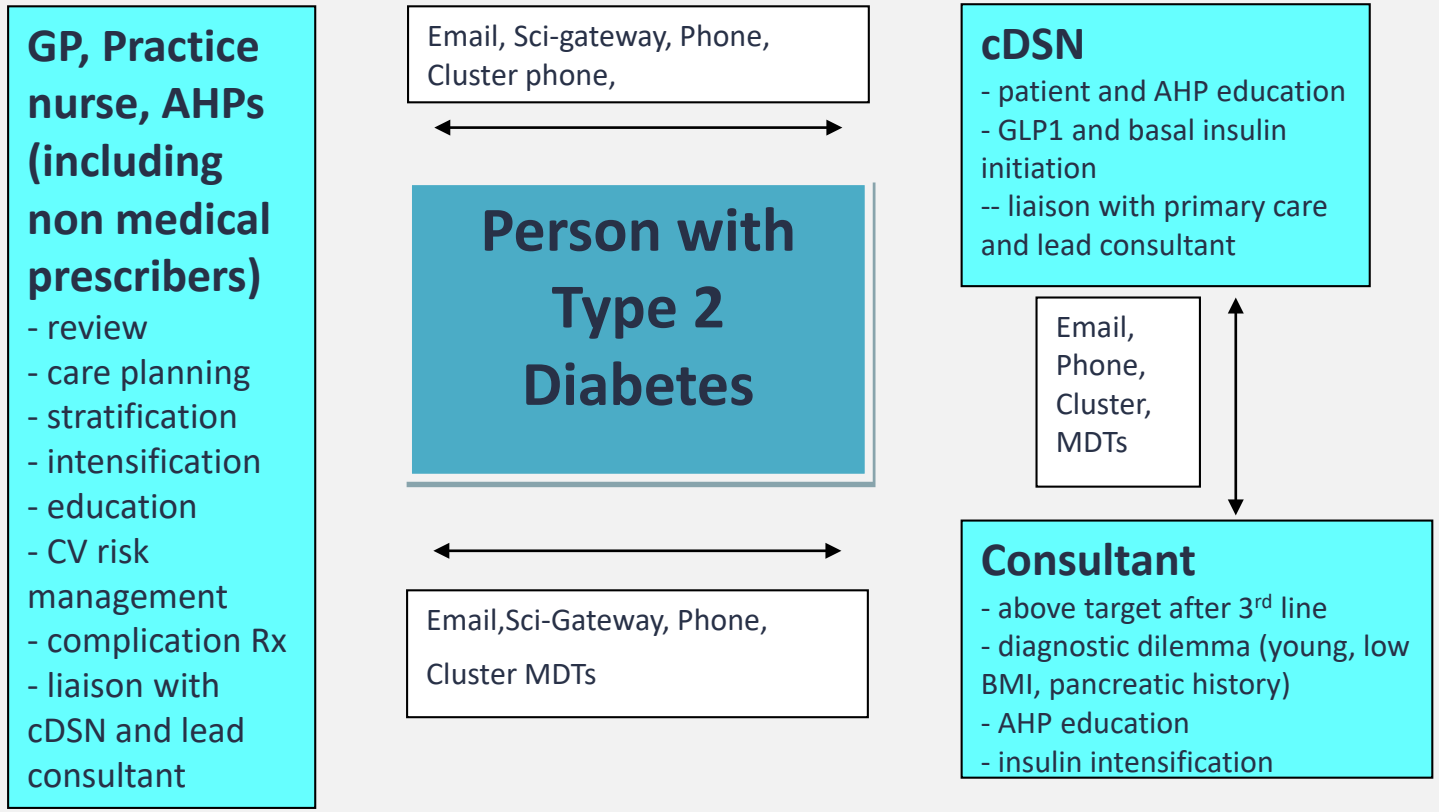
d

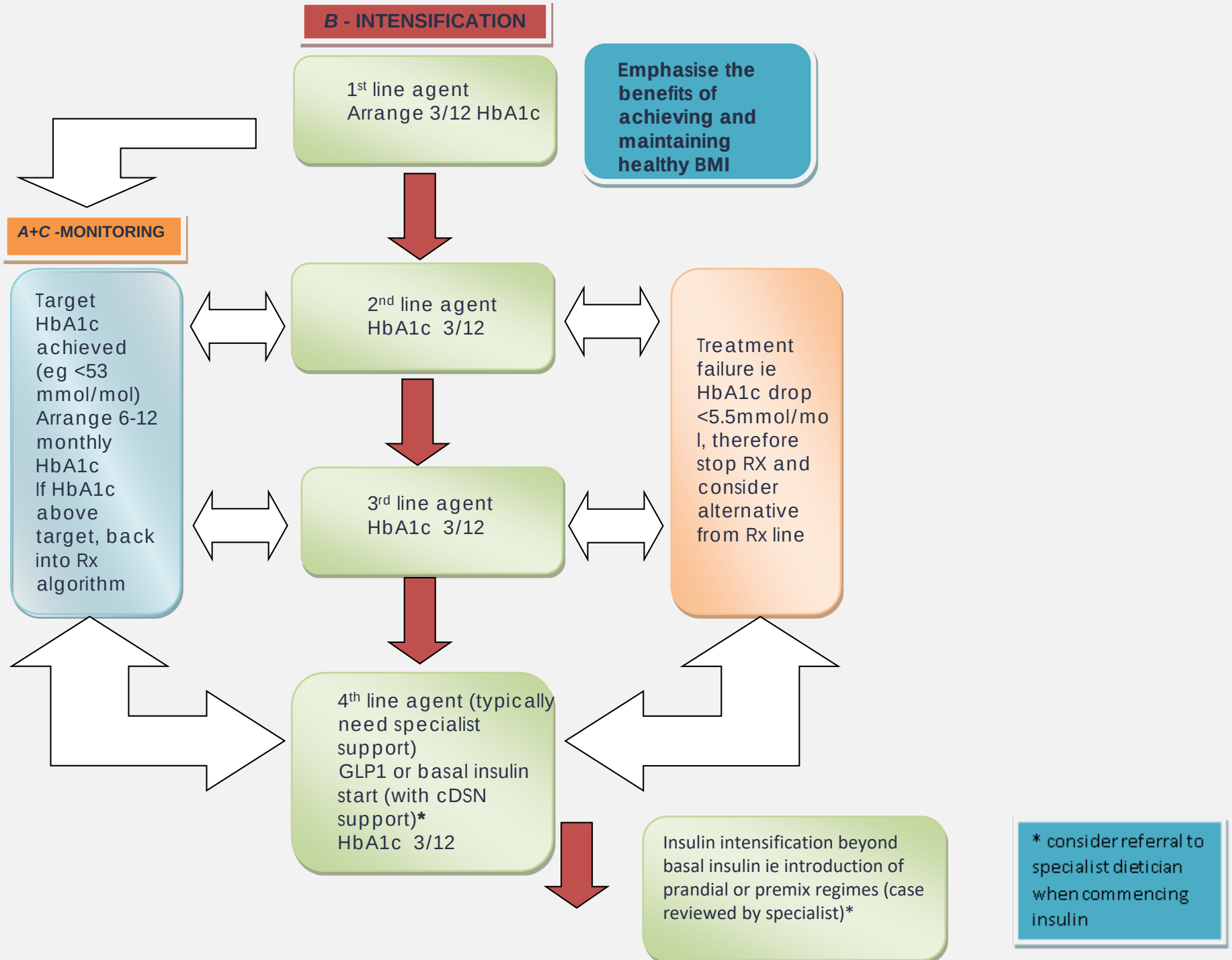
Combination of Dietary change for weight reduction + Physical Exercise better!

Type 2 Guidelines following Current GG&C Priorities

NHS
Greater Glasgow and Clyde

Type 2 Management Team




B - INTENSIFICATION
1st line agent
Arrange 3/12 HbA1c
Emphasise the benefits of achieving and maintaining healthy BMI
A+C -MONITORING
Target HbA1c achieved (eg <53 mmol/mol)
Arrange 6-12 monthly HbA1c
If HbA1c above target, back into Rx algorithm
2nd line agent
HbA1c 3/12
3rd line agent
HbA1c 3/12
Treatment failure ie HbA1c drop <5.5mmol/mol, therefore stop RX and consider alternative from Rx line
4th line agent (typically need specialist support)
GLP1 or basal insulin start (with cDSN support)*
HbA1c 3/12
Insulin intensification beyond basal insulin ie introduction of prandial or premix regimes (case reviewed by specialist)*
* consider referral to specialist dietician when commencing insulin

FIRST LINE	METFORMIN	*SU	*SGLT2i (if BMI>30 or CV disease)
Advantages	Weight CV Low hypo risk	Efficacy	*Weight loss* *CV (and BP)* *Low hypo risk*
Cautions/ side effects	GI	Hypos Weight gain Frailty BGM	*Diuretics* *Thrush* *Ketosis*
Contraindications	CKD 4		*CKD 3a (initiation)* *Frailty*

*Alternative to metformin if contraindicated or not tolerated

SECOND LINE	SGLT2i	SU	DPP4i	Pioglitazone
Advantages	Weight loss CV (and BP) Low hypo risk	Efficacy	Weight Low hypo risk tolerated	Efficacy Low hypo risk
Cautions/ side effects	Diuretics Thrush Ketosis	Hypos Weight gain Frailty BGM	Efficacy CKD (adjustment)	Oedema Central adiposity osteoporosis
Contraindications	CKD 3a (initiation) Frailty		Pancreatic history	CCF Bladder cancer (haematuria)

THIRD LINE	3rd agent from 2nd line	GLP1 RA	O.D. insulin
Advantages	As above	Efficacy Weight loss CV Low hypo risk	Efficacy
Cautions/ side effects	As above	GI Injections	Hypos Weight gain BGM Injections
Contraindications	As above	Pancreatic history CKD 4 (egfr <15 for some)	

FOURTH LINE	Specialist input (cDSN and/or consultant)	If >1 insulin injection required should be offered clinic review until stable

Obesity and /or CV disease

If known CV disease, choose SGLT2i or GLP1 RA with proven CV benefit.
*Alternative to metformin if contraindicated or not tolerated

FIRST LINE	**METFORMIN**	***SU**	***SGLT2i (if BMI>30 or CV disease)***

SECOND LINE	**SGLT2i**	**SU**	**DPP4i**	**Pioglitazone**

THIRD LINE	**GLP1 RA**	**3rd agent from 2nd line**	**O.D. insulin**

Elderly/Frail

Relaxing glycaemic target may be appropriate eg HbA1c 65-75 mmol/mol, and concentrating on treating symptoms whilst minimising risks of potential side effects like hypoglycaemia.

FIRST LINE	**METFORMIN**	***SU**	***SGLT2i (if BMI>30 and or CV disease)***

SECOND LINE	**DPP4i**	**SGLT2i**	**SU**	**Pioglitazone**

THIRD LINE	**3rd agent from 2nd line**	**GLP1 RA**	**O.D. insulin**

The Management of Hyperglycaemia in those with Diabetes & Kidney Disease

GP notebook shortcuts

CKD Stage (ml/min/1.73m2)	Stages G1 & G2 eGFR>60	Stage G3a eGFR 45-59	Stage G3b eGFR 30-44	Stage G4 eGFR 15-30	Stage G5 eGFR<15
Metformin			Reduce dose to 500mg twice daily		
Sulfonylureas	Gliclazide & glipizide preferred as metabolised in the liver	Increased risk of hypoglycaemia if eGFR<60. Consider reducing SU dose			
Repaglinide					
Acarbose					Avoid if eGFR<25
Pioglitazone	Avoid in those on dialysis				
Alogliptin		Reduce to 12.5mg daily		Reduce to 6.25mg daily	
Linagliptin					
Saxagliptin		Reduce to 2.5mg daily. Avoid in those on dialysis			
Sitagliptin			Reduce to 50mg daily	Reduce to 25mg od	
Vildagliptin		Reduce to 50mg once daily if eGFR<50			
Canagliflozin	Do not initiate if eGFR<60	If eGFR later falls <60 reduce dose to 100mg & stop if <45			
Dapagliflozin	Do not initiate if eGFR<60				
Empagliflozin	Do not initiate if eGFR<60	If eGFR later falls <60, reduce dose to 10mg & stop if <45			
Ertugliflozin	Do not initiate if eGFR<60				
Dulaglutide					
Exenatide bid					
Exenatide qw		Not recommended if CrCl<50ml/min			
Liraglutide	No therapeutic experience in those with ESRD and therefore not recommended for use				
Lixisenatide					
Semaglutide					
Insulin		Increased risk of hypoglycaemia as kidney main route of insulin clearance			

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No dose adjustment required

Dose adjustment recommended

Not recommended / contraindicated

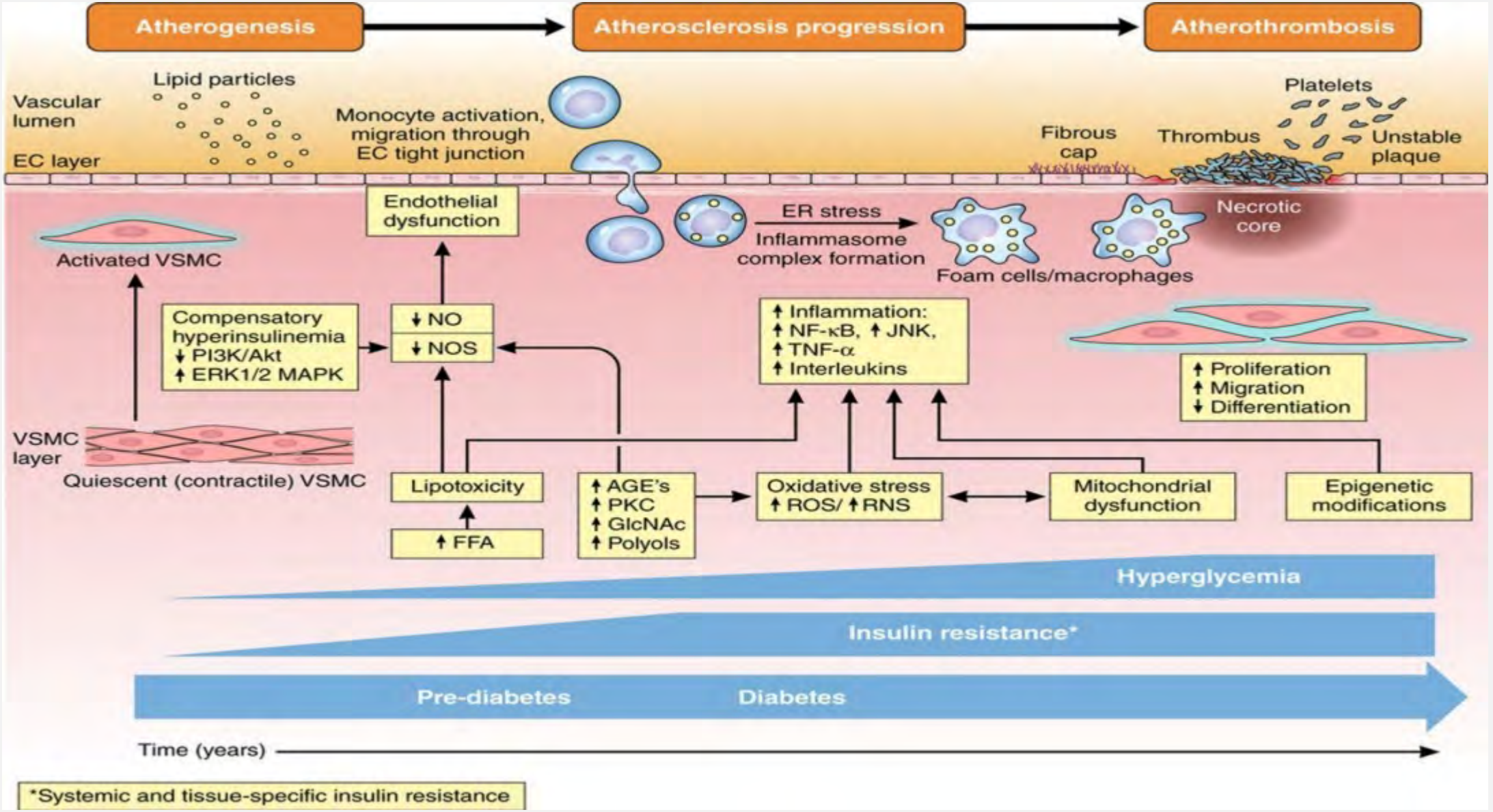
Last Updated November 2019

MOST COMMON CAUSE OF DEATH IN TYPE 2 DIABETES

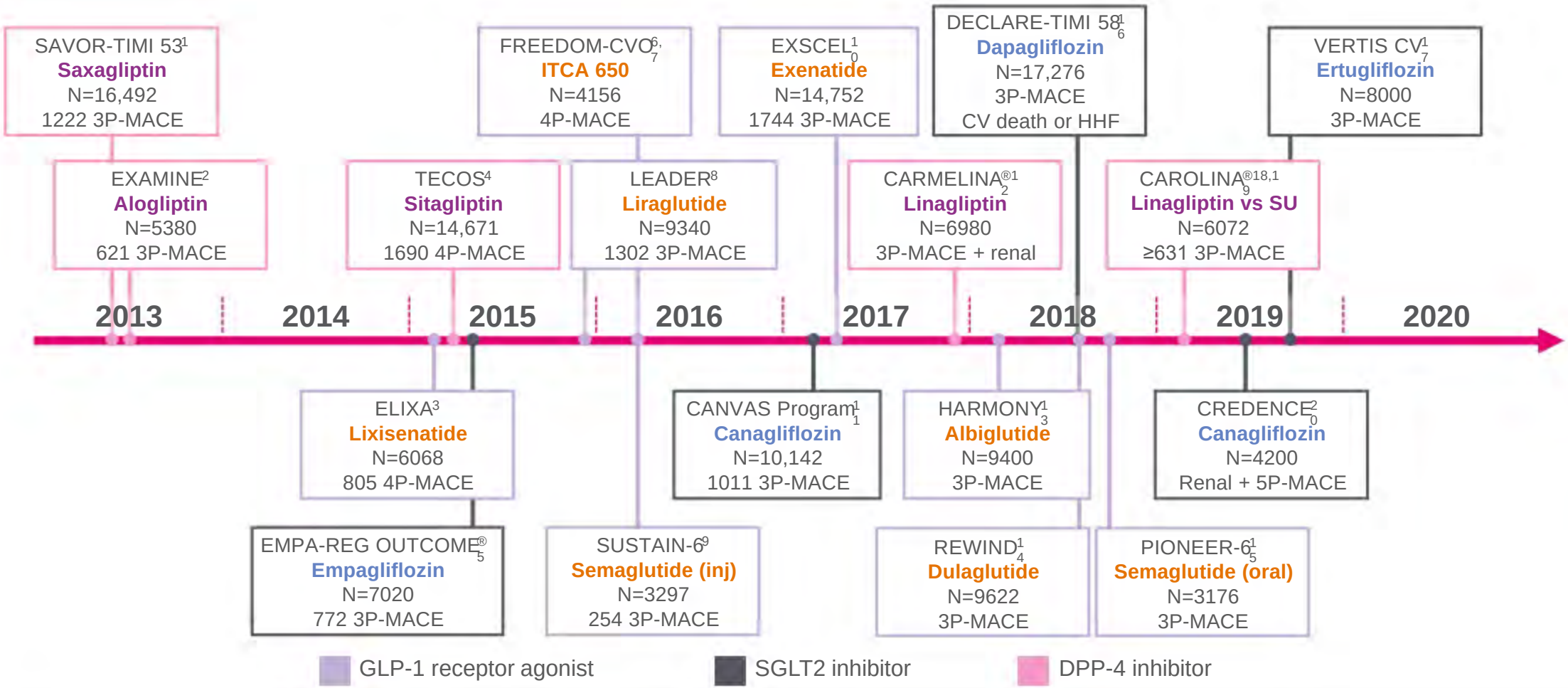
RISK OF CV DEATH 2-6 X HIGHER IN TYPE 2 DIABETES

ON AVERAGE DIABETIC PATIENTS WILL DIE 6 YEARS EARLIER

CVD IS THE LARGEST CONTRIBUTOR TO THE COSTS OF DIABETES


Atherogenesis
Atherosclerosis progression
Atherothrombosis
Lipid particles
Vascular lumen
EC layer
Monocyte activation, migration through EC tight junction
Platelets
Fibrous cap
Thrombus
Unstable plaque
Endothelial dysfunction
ER stress
Inflammasome complex formation
Necrotic core
Activated VSMC
Foam cells/macrophages
Compensatory hyperinsulinemia
↓ PI3K/Akt
↑ ERK1/2 MAPK
↓ NO
↓ NOS
↑ Inflammation:
↑ NF-κB, ↑ JNK,
↑ TNF-α
↑ Interleukins
↑ Proliferation
↑ Migration
↓ Differentiation
VSMC layer
Quiescent (contractile) VSMC
Lipotoxicity
↑ FFA
↑ AGE's
↑ PKC
↑ GlcNAc
↑ Polyols
Oxidative stress
↑ ROS/ ↑ RNS
Mitochondrial dysfunction
Epigenetic modifications
Hyperglycemia
Insulin resistance*
Pre-diabetes
Diabetes
Time (years)
*Systemic and tissue-specific insulin resistance

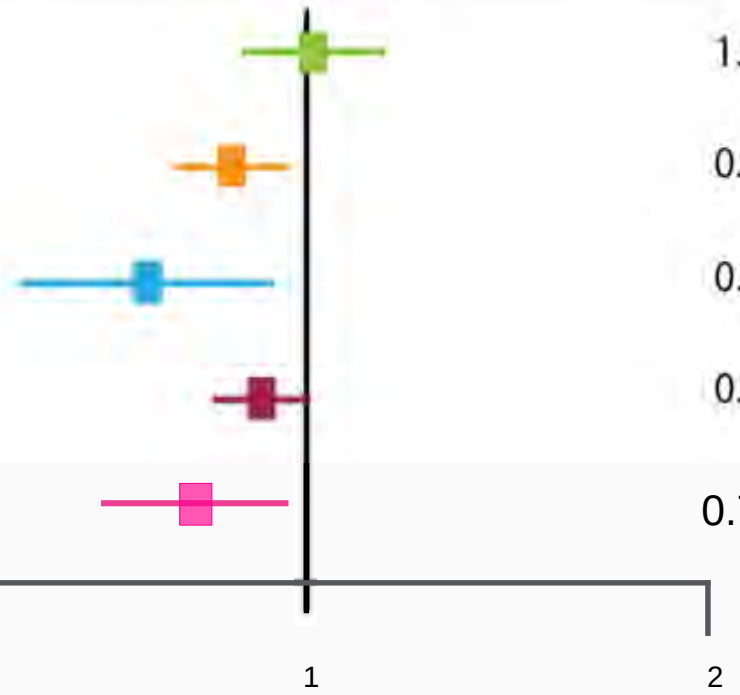
Evolving landscape of CVOT



All trial completion and estimated disclosure dates come from ClinicalTrials.gov
3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major adverse cardiovascular events; 5P-MACE, 5-point major adverse cardiovascular events; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea
Adapted from: Johansen OE. *World J Diabetes* 2015;6:1092.

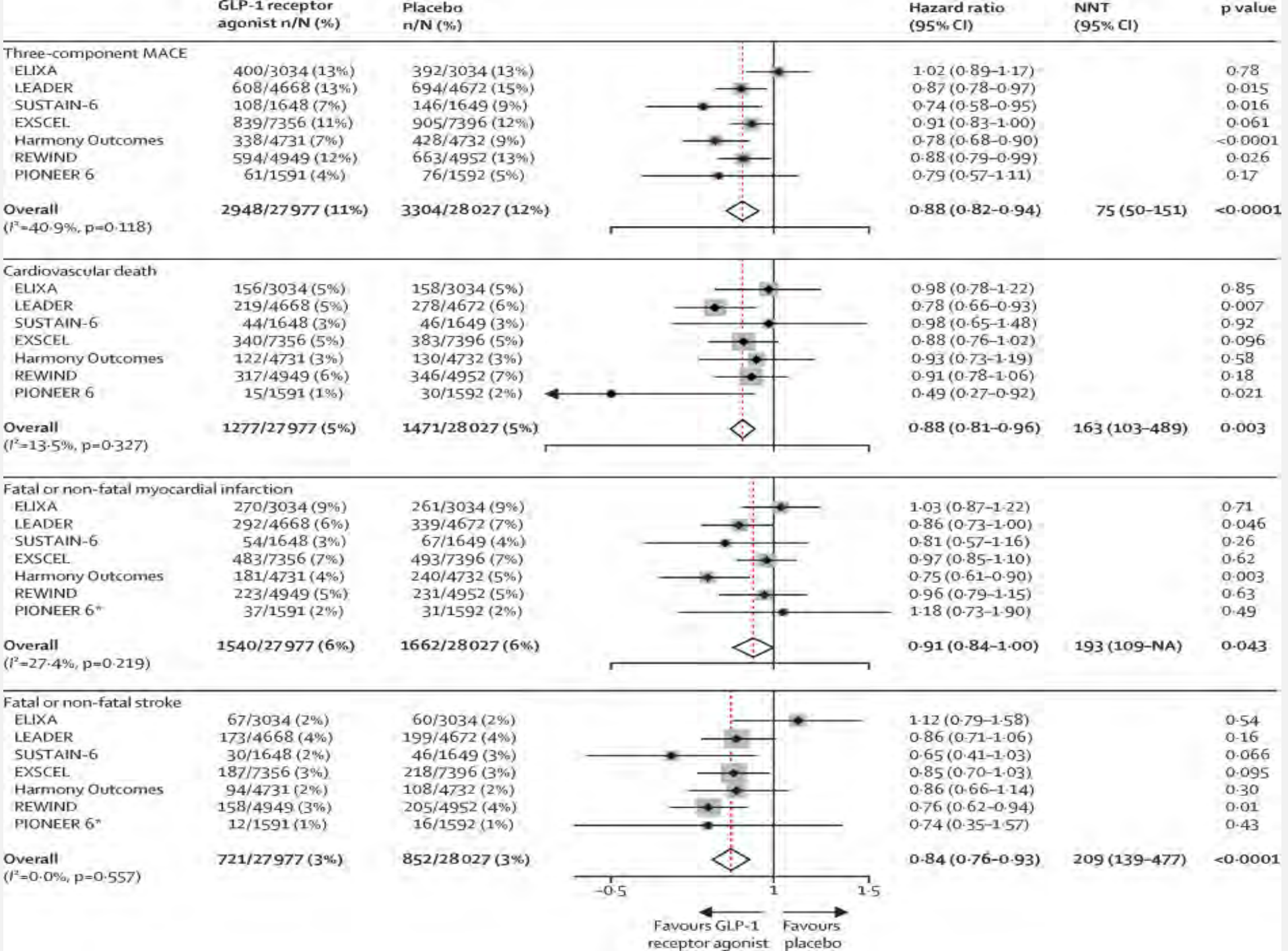
GLP-1 receptor agonists — 3P-MACE outcomes

Study name	GLP-1 Group	Placebo Group	Hazard ratio	Lower limit	Upper limit	p-Value
ELIXA	400/3034 (13.2%)	392/3034 (12.9%)	1.02	0.89	1.17	0.776
LEADER	608/4668 (13.0%)	694/4672 (14.9%)	0.87	0.78	0.97	0.015
SUSTAIN-6	108/1648 (6.6%)	146/1649 (8.9%)	0.74	0.58	0.95	0.016
EXSCEL	839/7356 (11.4%)	905/7396 (12.2%)	0.91	0.83	1.00	0.061
Harmony Outcomes	338 /4731 (7.1%)	428/4732 (9.0%)	0.78	0.68	0.90	0.001



HARMONY investigated an agent that has now been discontinued (albiglutide)

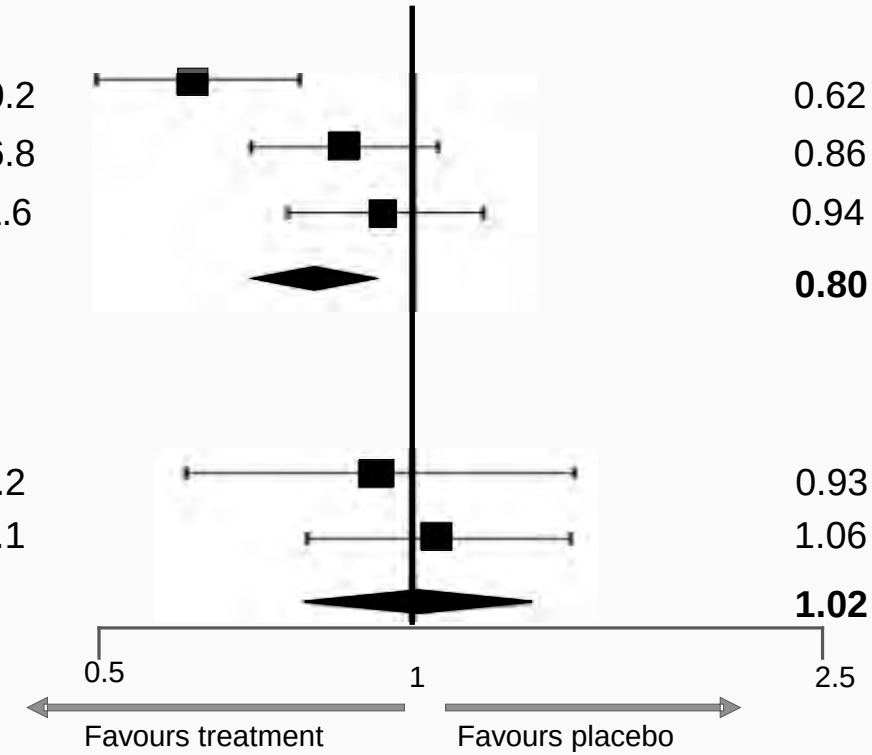
Pfeffer et al. N Engl J Med 2015;373:2247–57. 2. Marso et al. N Engl J Med 2016;375:311–22. 3. Marso et al. N Engl J Med. 2016 Nov 10;375:1834–1844. 4. Holman et al. N Engl J Med 2017;377:1228–39. 5. Hernandez et al. Lancet 2018;392:1519–29.


GLP-1 receptor agonist n/N (%)
Placebo n/N (%)
Hazard ratio (95% CI)
NNT (95% CI)
p value
Three-component MACE
ELIXA 400/3034 (13%) 392/3034 (13%) 1·02 (0·89–1·17) 0·78
LEADER 608/4668 (13%) 694/4672 (15%) 0·87 (0·78–0·97) 0·015
SUSTAIN-6 108/1648 (7%) 146/1649 (9%) 0·74 (0·58–0·95) 0·016
EXSCEL 839/7356 (11%) 905/7396 (12%) 0·91 (0·83–1·00) 0·061
Harmony Outcomes 338/4731 (7%) 428/4732 (9%) 0·78 (0·68–0·90) <0·0001
REWIND 594/4949 (12%) 663/4952 (13%) 0·88 (0·79–0·99) 0·026
PIONEER 6 61/1591 (4%) 76/1592 (5%) 0·79 (0·57–1·11) 0·17
Overall 2948/27977 (11%) 3304/28027 (12%) 0·88 (0·82–0·94) 75 (50–151) <0·0001
(I²=40·9%, p=0·118)
Cardiovascular death
ELIXA 156/3034 (5%) 158/3034 (5%) 0·98 (0·78–1·22) 0·85
LEADER 219/4668 (5%) 278/4672 (6%) 0·78 (0·66–0·93) 0·007
SUSTAIN-6 44/1648 (3%) 46/1649 (3%) 0·98 (0·65–1·48) 0·92
EXSCEL 340/7356 (5%) 383/7396 (5%) 0·88 (0·76–1·02) 0·096
Harmony Outcomes 122/4731 (3%) 130/4732 (3%) 0·93 (0·73–1·19) 0·58
REWIND 317/4949 (6%) 346/4952 (7%) 0·91 (0·78–1·06) 0·18
PIONEER 6 15/1591 (1%) 30/1592 (2%) 0·49 (0·27–0·92) 0·021
Overall 1277/27977 (5%) 1471/28027 (5%) 0·88 (0·81–0·96) 163 (103–489) 0·003
(I²=13·5%, p=0·327)
Fatal or non-fatal myocardial infarction
ELIXA 270/3034 (9%) 261/3034 (9%) 1·03 (0·87–1·22) 0·71
LEADER 292/4668 (6%) 339/4672 (7%) 0·86 (0·73–1·00) 0·046
SUSTAIN-6 54/1648 (3%) 67/1649 (4%) 0·81 (0·57–1·16) 0·26
EXSCEL 483/7356 (7%) 493/7396 (7%) 0·97 (0·85–1·10) 0·62
Harmony Outcomes 181/4731 (4%) 240/4732 (5%) 0·75 (0·61–0·90) 0·003
REWIND 223/4949 (5%) 231/4952 (5%) 0·96 (0·79–1·15) 0·63
PIONEER 6* 37/1591 (2%) 31/1592 (2%) 1·18 (0·73–1·90) 0·49
Overall 1540/27977 (6%) 1662/28027 (6%) 0·91 (0·84–1·00) 193 (109–NA) 0·043
(I²=27·4%, p=0·219)
Fatal or non-fatal stroke
ELIXA 67/3034 (2%) 60/3034 (2%) 1·12 (0·79–1·58) 0·54
LEADER 173/4668 (4%) 199/4672 (4%) 0·86 (0·71–1·06) 0·16
SUSTAIN-6 30/1648 (2%) 46/1649 (3%) 0·65 (0·41–1·03) 0·066
EXSCEL 187/7356 (3%) 218/7396 (3%) 0·85 (0·70–1·03) 0·095
Harmony Outcomes 94/4731 (2%) 108/4732 (2%) 0·86 (0·66–1·14) 0·30
REWIND 158/4949 (3%) 205/4952 (4%) 0·76 (0·62–0·94) 0·01
PIONEER 6* 12/1591 (1%) 16/1592 (1%) 0·74 (0·35–1·57) 0·43
Overall 721/27977 (3%) 852/28027 (3%) 0·84 (0·76–0·93) 209 (139–477) <0·0001
(I²=0·0%, p=0·557)
0·5
1
1·5
Favours GLP-1 receptor agonist
Favours placebo

CV death – comparison between SGLT2-I's

Study name	Events per 1,000 PY: SGLT2 inhibitor	Events per 1,000 PY: Placebo	CV death HR (95% CI)	*P*-value
Patients with ASCVD				
EMPA-REG OUTCOME ®[1,4]	12.4	20.2	0.62 (0.49, 0.77)	
CANVAS Program [2,4]	14.8	16.8	0.86 (0.70, 1.06)	
DECLARE-TIMI 53 [3,4]	10.9	11.6	0.94 (0.76, 1.18)	
Pooled analysis (all SGLT2 inhibitors)			**0.80 (0.71, 0.91)**	**0.0005**
Patients with multiple risk factors				
CANVAS Program [2,4]	6.5	6.2	0.93 (0.60, 1.43)	
DECLARE-TIMI 53 [3,4]	4.4	4.1	1.06 (0.79, 1.42)	
Pooled analysis (all SGLT2 inhibitors)			**1.02 (0.80, 1.30)**	**0.89**

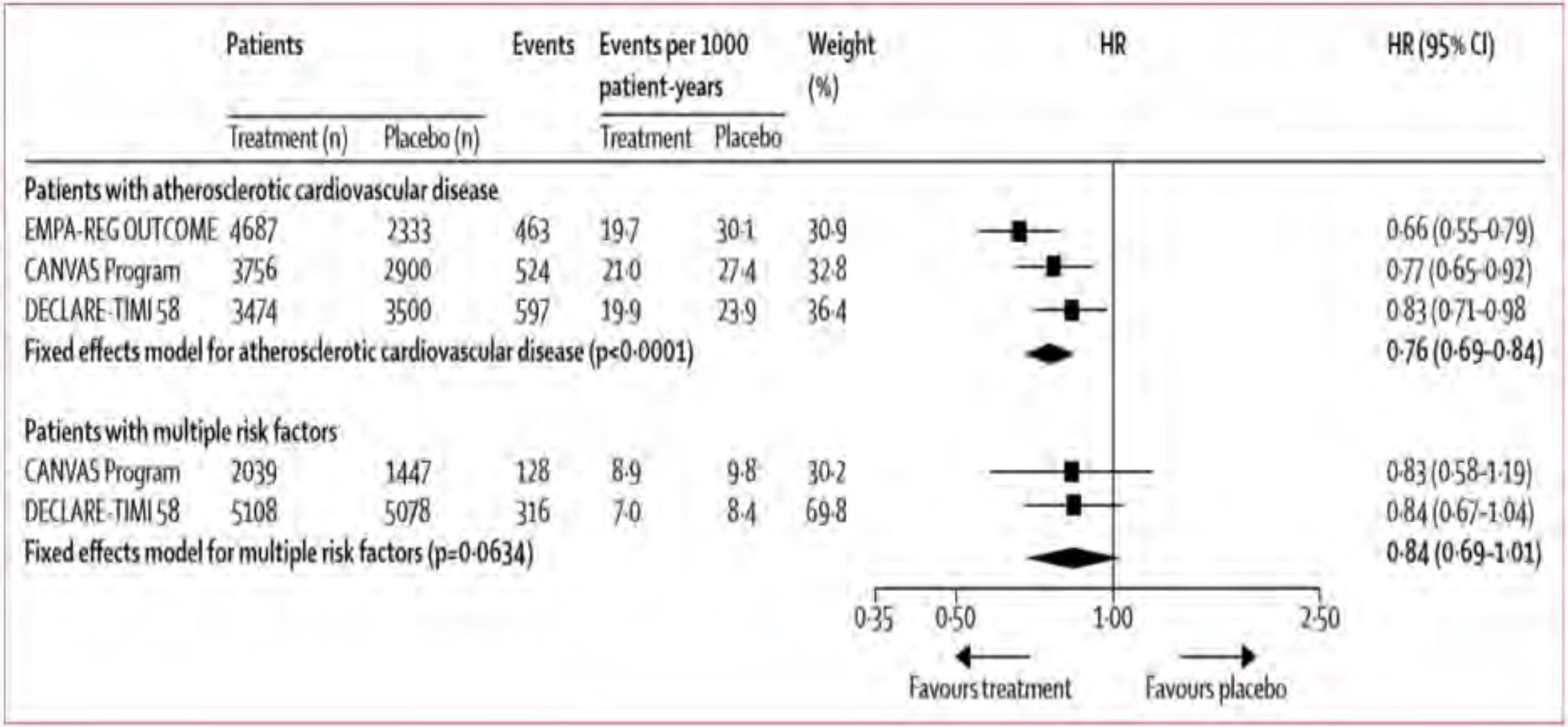
P-value for subgroup differences: 0.31



ASCVD, atherosclerotic CVD, CI, confidence interval; CV, cardiovascular, CVD, CV disease; HR, hazard ratio; PY, patient-year; SGLT2, sodium–glucose transporter 2.

1. Zinman et al. N Engl J Med 2015;373:2117–28. 2. Neal et al. N Engl J Med. 2017;377:644–57. 3. Wiviott et al. N Engl J Med 2018;doi:10.1056/NEJMoa1812389.
4. Zelniker et al. Lancet 2018;doi:10.1016/S0140-6736(18)32590-X.

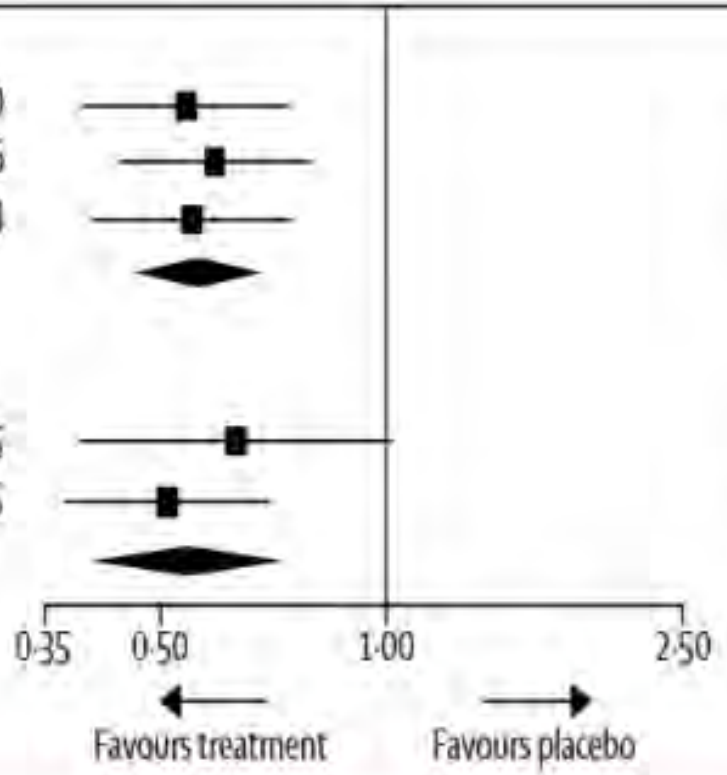
Meta-analysis of SGLT2i trials on hospitalisation for HF and CV death stratified by the presence of established atherosclerotic CVD



*Source: **Zelniker, T et al., Lancet 2019; 393: 31–39***

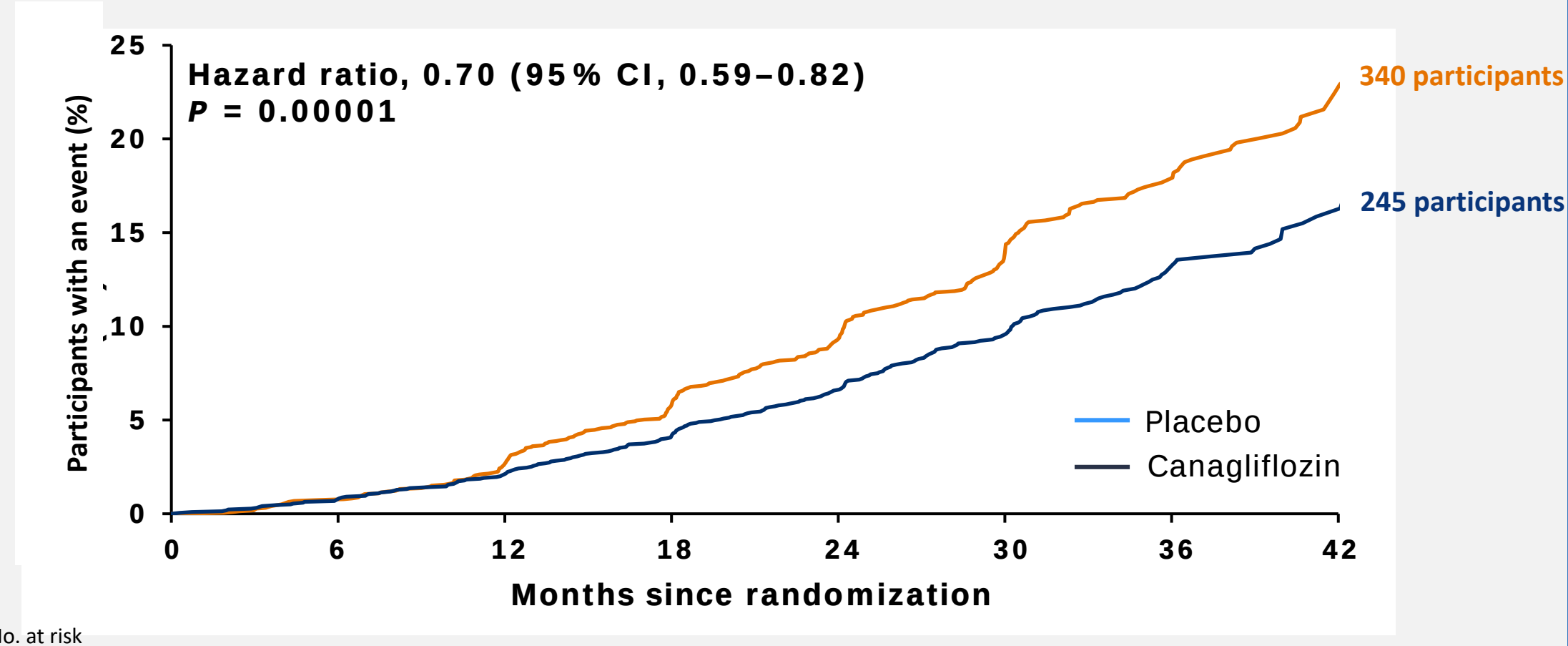
Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic CVD

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



*Source: **Zelniker, T et al., Lancet 2019; 393: 31–39***

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



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

Number needed to treat to prevent **one patient death**

HOPE[1]

Ramipril 10mg
for 4.5 years

32

T2DM + CVD OR HIGH RISK

HPS[2]

Simvastatin 40mg
for 5 years

56

T2DM + CV RISK

EMPA-REG[3]

Empagliflozin
for **2.6** years

39

T2DM with CVD

LEADER[4]

Liraglutide
for **3.8** years

66

T2DM + CVD OR HIGH RISK

SUSTAIN-6[5]

Semaglutide
for **2** years

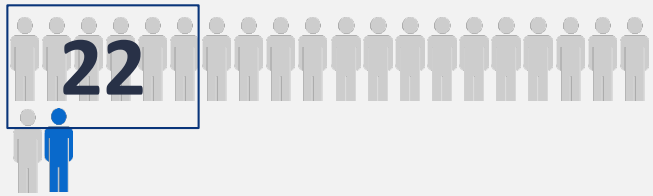
45

T2DM + CVD OR HIGH RISK

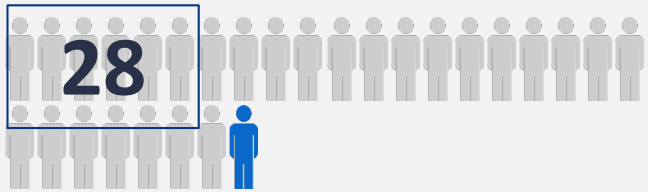
1. Lancet. 2000 Jan 22;355(9200):253-9.2. Collins et al Lancet. 2003 Jun 14;361(9374):2005-16. 3. Zinman et al. N Engl J Med. 2015 Nov 26;373(22):2117-28 4. Marso SP et al. N Engl J Med 2016;375:311
5. Marso SP et al. N Engl J Med 2016;375:1834-44.

CREDENCE NNT for Renal and CV Outcomes Over 2.5 Years

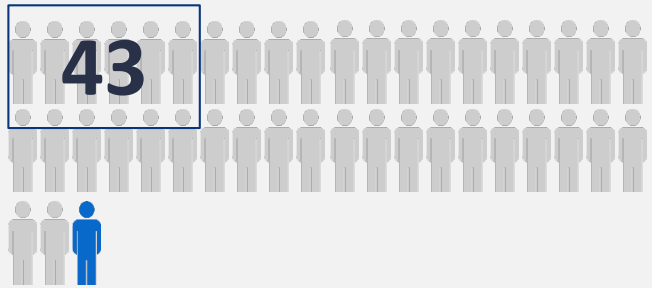
Primary composite outcome



ESKD, doubling of serum creatinine, or renal death

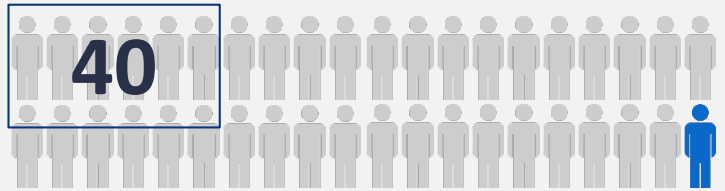


ESKD



Hospitalization for heart failure

CV death, MI, or stroke



Case 1

- 42 year old male with new diagnosis of T2DM
- No osmotic symptoms
- No macrovascular disease
- No retinopathy
- Non-Smoker, BMI 38
- HbA1c 68, BP 158/86, TC 6.2
- eGFR >60, Urine ACR 1.6
- Low risk feet

- Anything else you would like to know?
- What would you do next to manage T2D?

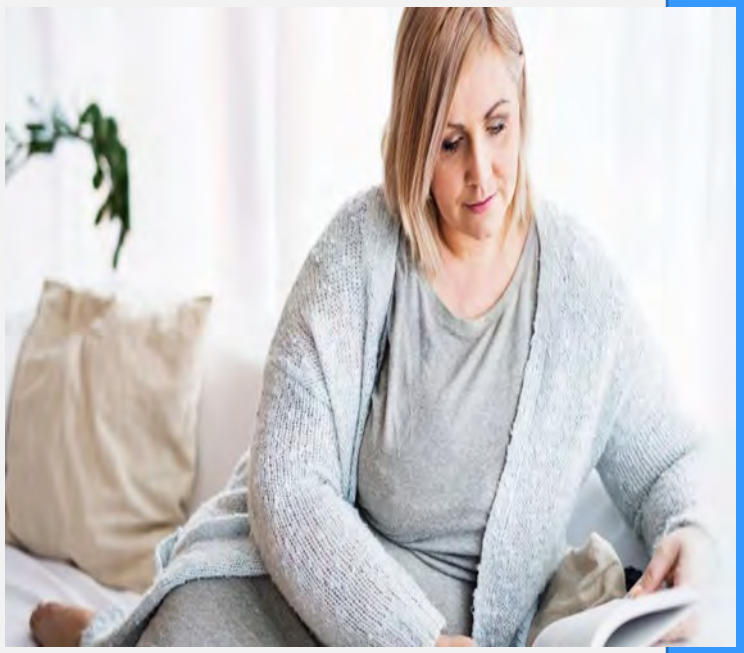
Case 1

- 42 year old male with new diagnosis of T2DM
- No osmotic symptoms
- No macrovascular disease
- No retinopathy
- Non-Smoker, BMI 38
- HbA1c 68, BP 158/86, TC 6.2
- eGFR >60, Urine ACR 1.6
- Low risk feet

- **Consider:** GWMS, Metformin, ?ACE ?Statin

Case 2

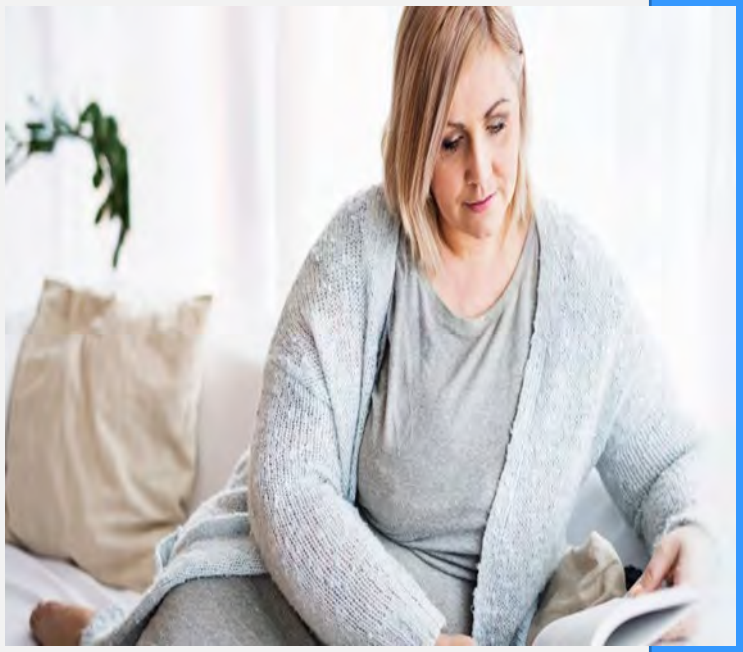
- 52 year old female with 5 year history of T2DM
- Osmotic symptoms
- History of MI
- No history of microvascular disease
- Smoker, BMI 34
- HbA1c 71 (May) to 68 (Nov) after addition of DPP4i
- BP 132/75, TC 4.2, eGFR >60, Urine ACR 2.5
- Low risk feet
- Metformin 1g bd, Alogliptin 25mg, Aspirin 75mg od, Ramipril 5mg od, Atorvastatin 40mg od.



- Anything else you would like to know?
- What would you do next to manage T2D?

Case 2

- 52 year old female with 5 year history of T2DM
- Osmotic symptoms
- History of MI
- No history of microvascular disease
- Smoker, BMI 34
- HbA1c 71 (May) to 68 (Nov) after addition of DPP4i
- BP 132/75, TC 4.2, eGFR >60, Urine ACR 2.5
- Low risk feet
- Metformin 1g bd, Alogliptin 25mg, Aspirin 75mg od, Ramipril 5mg od, Atorvastatin 40mg od.



- **Consider:** GWMS, stop DPP4i, SGLTi
  Smoking cessation services.

Case 3

- 36 year old female with 2 year history of T2DM
- No osmotic symptoms
- No microvascular disease
- No macrovascular disease
- Non-Smoker, BMI 50
- HbA1c 68 (Aug), 53 (Nov) BP 126/85, TC 4.9
- eGFR >60, Urine ACR 1.9
- Low risk feet
- Metformin 1g bd, Dapagliflozin 10mg

- Anything else you would like to know?
- What would you do next to manage T2D?

Case 3

- 36 year old female with 2 year history of T2DM
- No osmotic symptoms
- No microvascular disease
- No macrovascular disease
- Non-Smoker, BMI 50
- HbA1c 68 (Aug), 53 (Nov) BP 126/85, TC 4.9
- eGFR >60, Urine ACR 1.9
- Low risk feet
- Metformin 1g bd, Dapagliflozin 10mg.

- **Consider:** GWMS (Bariatric criteria), pre-pregnancy counselling

Case 4

- 29 year old male with 1 year history of T2DM
- Osmotic symptoms
- No retinopathy
- No macrovascular disease
- Non-Smoker, BMI 47
- HbA1c 60 (78 at diagnosis)
- BP 140/80, TC 7.2
- eGFR >60 , Urine ACR 2.4
- Low risk feet
- Metformin 500mg bd

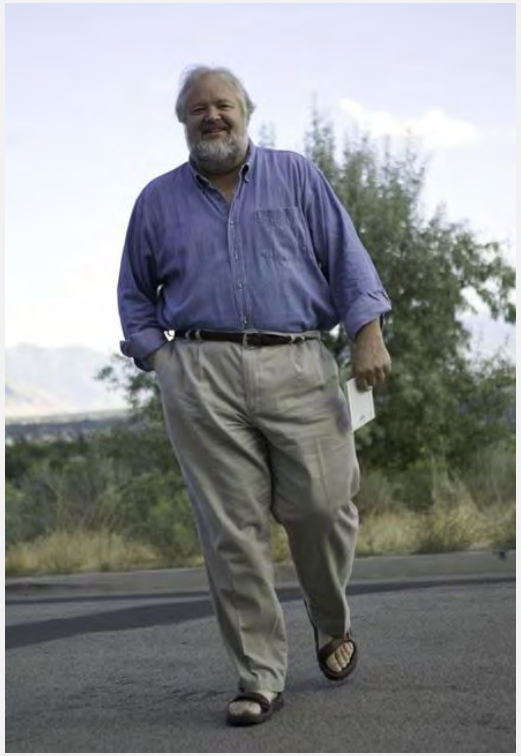
- Anything else you would like to know?
- What would you do next to manage T2D?

Case 4

- 29 year old male with 1 year history of T2DM
- Osmotic symptoms
- No retinopathy
- No macrovascular disease
- Non-Smoker, BMI 47
- HbA1c 59 (72 at diagnosis)
- BP 140/80, TC 7.2
- eGFR >60 , Urine ACR 2.4
- Low risk feet
- Metformin 500mg bd

- **Consider: Increase metformin / GWMS / ?SGLT2-I ?GLP-1**

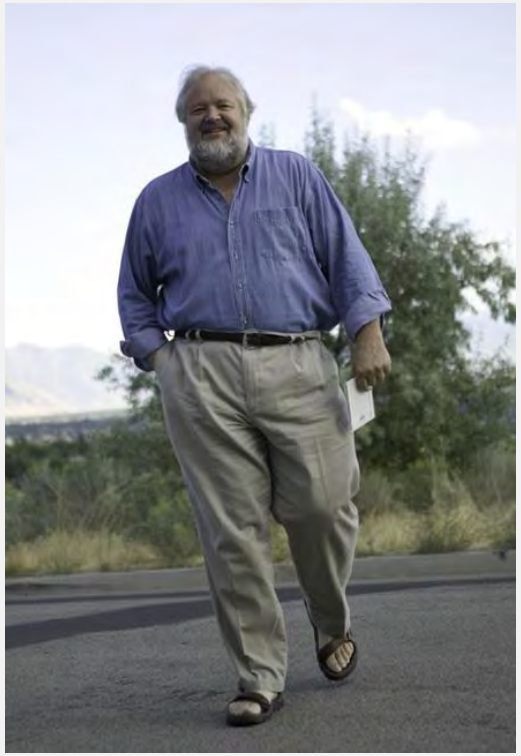
Case 5



- 64 year old male with 20 year history of T2DM
- Osmotic symptoms
- Peripheral neuropathy, Retinopathy
- History of IHD, CVA last year
- Ex-smoker, BMI 40
- HbA1c 75 (Aug), 73 (Nov), BP 112/67, TC 3.2,
- eGFR 40, Urine ACR 2.3
- Active foot ulceration.
- Metformin 1g bd, Empagliflozin 25mg od, Aspirin 75mg od, Ramipril 10mg od, Amlodipine 10mg od, Atorvastatin 80mg od.

- Anything else you would like to know?
- What would you do next to manage T2D?

Case 5



- 64 year old male with 20 year history of T2DM
- Osmotic symptoms
- Peripheral neuropathy, Retinopathy
- History of MI, CVA
- Ex-smoker, BMI 40
- HbA1c 75 (Aug), 73 (Nov) BP 112/67, TC 3.2,
- eGFR 40, Urine ACR 2.3
- Active foot ulceration.
- Metformin 1g bd, Empagliflozin 25mg od, Aspirin 75mg od, Ramipril 10mg od, Amlodipine 10mg od, Atorvastatin 80mg od.

- **Consider:** GWMP, Stop SGLTi, Add GLP (proven benefit)


Summary


WORK IN PARTNERSHIP
LIFESTYLE MANAGEMENT
ESCALATE AS PER GUIDELINES
REVIEW AND STOP