How do I optimise excess cardiovascular disease risk in type 1 diabetes?

John R Petrie

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Director of Glasgow Clinical Trials Unit

Breakthrough T1D™
Formerly JDRF

Disclosures

- **Advisory and Consultancy Work:**
  - Novo Nordisk, Abbott, Sanofi
- **Clinical trials committees:**
  - IQVIA (Boehringer)
- **Recipient of donation of services to support Investigator-led research:**
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- **Investigator-led research funding:**
  - Merck (Germany)
- **Travel and accommodation support:**
  - Novo Nordisk, Sanofi
- **No stock in any pharmaceutical or technology company**

DIAB: Dr Andrea Llano | DIAB: Dr David Carty | DIAB: Dr Deborah Morrison | DIAB: Dr Frances Mcmanus | DIAB: Dr Gemma Currie | DIAB: Dr James Graham Boyle | DIAB: Dr John Petrie | DIAB: Dr Kate Hughes | DIAB: Dr Russell Drummond

Clinic List

Care Provider	Description	Clinic Location	Day	Date	Time From	Time To	Appointments Booked	Overbookings	Vacant	Attended	Did Not Attend
Dr John Petrie	STJPDI5-PROF J PETRIE TYPE 2 DIABETIC WED AM WEEK 2 AND 4	Clinic C First Floor Stobhill Ambulatory Care Hospital	Wednesday	22/01/2025	09:00	11:30	10		0	9	
Dr John Petrie	STJPDI6-PROF J PETRIE TYPE 1 DIABETIC WED PM WEEK 2 AND 4	Clinic C First Floor Stobhill Ambulatory Care Hospital	Wednesday	22/01/2025	13:30	16:50	0		0	0	

Search for CHI

<< Day >>(D)

Reset Find

Session Message

Session Both 13:30 16:50 STJPDI602T-PROF J PETRIE TYPE 1 DIABETIC WED PM WE

Hide Overridden Closed Slots ☑

Select	Icon Profile	Time	CHI	Surname	Patient Name	Date of Birth	Gender	Appointment Type	Slot Services	Status	Arrive	Remarks
☐		13:30	Patient 1				Male	G R TYPE 1 DIABETES CIR TELEPHONE	Slots=0	Booked	☒	
☐		13:50	Patient 2				Male	G R URGENT DIABETES TYPE 1 TELEPHONE	Slots=0	Booked	☒	
☐		14:10	Patient 3				Male	G R TYPE 1 DIABETES CIR TELEPHONE	Slots=0	Booked	☒	
☐		14:30(B)	2409856101	McGuire	Kathleen	24/09/1985	Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	F2F PER OUTCOME
☐		14:50	Patient 4				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	pt advised not to attend per secy phone call 17/1 - pt phoning secy for further details regarding next appt
☐		15:10	Patient 5				Male	G N TYPE 1 DIABETES	Slots=0	Booked	☒	
☐		15:30	Patient 6				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	
☐		15:50	Patient 7				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	
☐		16:10	Patient 8				Male	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	F2F PER OUTCOME
☐		16:30	Patient 9				Female	G R TYPE 1 DIABETES CA TELEPHONE	Slots=0	Booked	☒	

21.18 How to review a patient in the diabetes clinic

Approach to the diabetes consultation	
Introduction (agenda-setting)	'How are you?' 'What matters to you?' (Is translator required?)
Demographics	Age, type of diabetes, duration of diab
Microvascular complications	Retinopathy/ maculopathy Renal function (eGFR) Microalbuminuria/proteinuria Foot examination
Macrovascular complications	Cardiovascular disease Cerebrovascular disease Peripheral vascular disease
Metabolic	BMI/weight trajectory Diet (quality/calories)/CHO counting Current glucose-lowering treatment (adherence/administration) HbA_{1c} Step-wise approach to glucose monitoring (frequency, timing, representativeness or reliability of data) Hypoglycaemia (frequency, timing, symptoms, context, episodes of level 3 hypoglycaemia, consequences, driving) Hyperglycaemia (frequency, timing, symptoms, context, episodes of DKA/ HHS, consequences) Glycaemic variability if AGP available
Cardiovascular risk	BP Cholesterol Smoking cessation
	Pregnancy/contraception Exercise Sexual dysfunction Alcohol Driving
	Main action points Goal setting Changes to treatment Referrals within team Other referrals Accessing support prior to next appointment

15 mins!

From Davidson's Textbook of Medicine 2022

Remember:

- Person-centred (lifestyle, occupation, travel, behaviour)
- Language matters
- Start with the 'Good News'
- Culturally sensitive
- Collaborative
- Empathetic
- Empowering
- Reassuring
- Non-judgemental

- STOP-BANG questionnaire for OSA
- Cognitive function assessment
- Adjunct agents in T1D?
- Driving?

AGP = Ambulatory Glucose Profile; BMI = Body Mass Index; CHO = carbohydrate; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HHS = hyperglycaemic hyperosmolar state.

Let’s get the basics out of the way . . .

ChatGPT

To optimize and mitigate excess cardiovascular disease (CVD) risk in type 1 diabetes (T1D), a multifaceted approach is required, addressing the unique challenges posed by the condition. Below are the key strategies:

1. **Achieve Optimal Glycemic Control**

- Target HbA1c: Strive for individualized HbA1c goals, generally <7% (53 mmol/mol), while avoiding severe hypoglycemia.

- Time in Range (TIR): Use continuous glucose monitoring (CGM) to aim for >70% time in range (3.9 - 10 mmol/L)

- Minimize Glycemic Variability: Reduce large fluctuations, which may independently contribute to endothelial damage.

Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study

Isabelle Steineck,[1] Jan Cederholm,[2] Björn Eliasson,[3] Araz Rawshani,[4] Katarina Eeg-Olofsson,[3] Ann-Marie Svensson,[4] Björn Zethelius,[5,6] Tarik Avdic,[4] Mona Landin-Olsson,[7] Johan Jendle,[8] Soffia Gudbjörnsdóttir[3,4] the Swedish National Diabetes Register

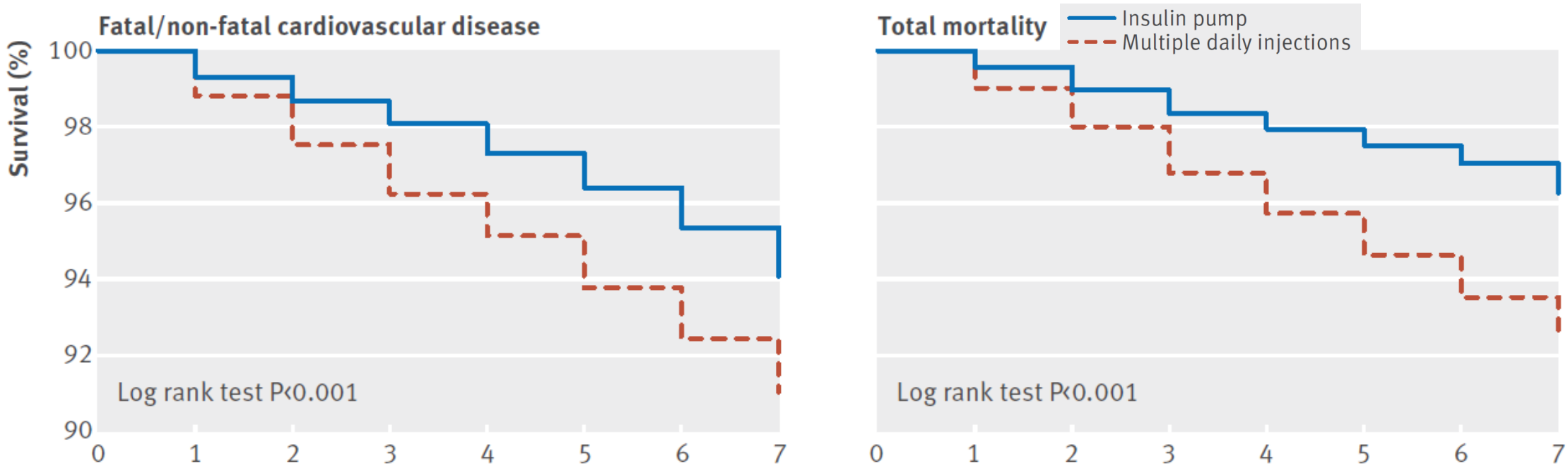


Fig 1 | Kaplan-Meier crude survival curves in 18 168 individuals with type 1 diabetes according to treatment with insulin pump therapy or multiple daily injections. No of cases and individuals at risk are given in each group

Let’s get the basics out of the way . . .

ChatGPT

2. **Aggressively Manage Cardiovascular Risk Factors**

- **Blood Pressure:**
  - Target <130/80 mmHg.
  - Use ACE inhibitors or ARBs, especially in those with albuminuria or nephropathy

- **Lipids:**
  - Aim for LDL cholesterol < 2.0 mmol/L in high-risk patients.
  - Statin therapy is recommended for all patients over 40 years – and younger with additional risk factors.
  - *Consider ezetimibe or PCSK9 inhibitors if LDL targets are not achieved.*

Let’s get the basics out of the way . . .

ChatGPT

2. **Aggressively Manage Cardiovascular Risk Factors (cont)**

- **Body Weight:**
  - Address overweight/obesity to improve insulin sensitivity and reduce CVD risk.

- **Smoking Cessation:**
  - Provide resources for smoking cessation, as smoking accelerates atherosclerosis in T1D.

Let’s get the basics out of the way . . .

ChatGPT

3. Address Diabetes-Specific Risk Factors

- **Chronic Inflammation and Endothelial Dysfunction:**
  - Optimize glycemic control to reduce hyperglycemia-induced inflammation.

- **Hypoglycemia:**
  - Minimize severe hypoglycemia, as it can provoke proarrhythmic and proatherogenic effects.

Let’s get the basics out of the way . . .

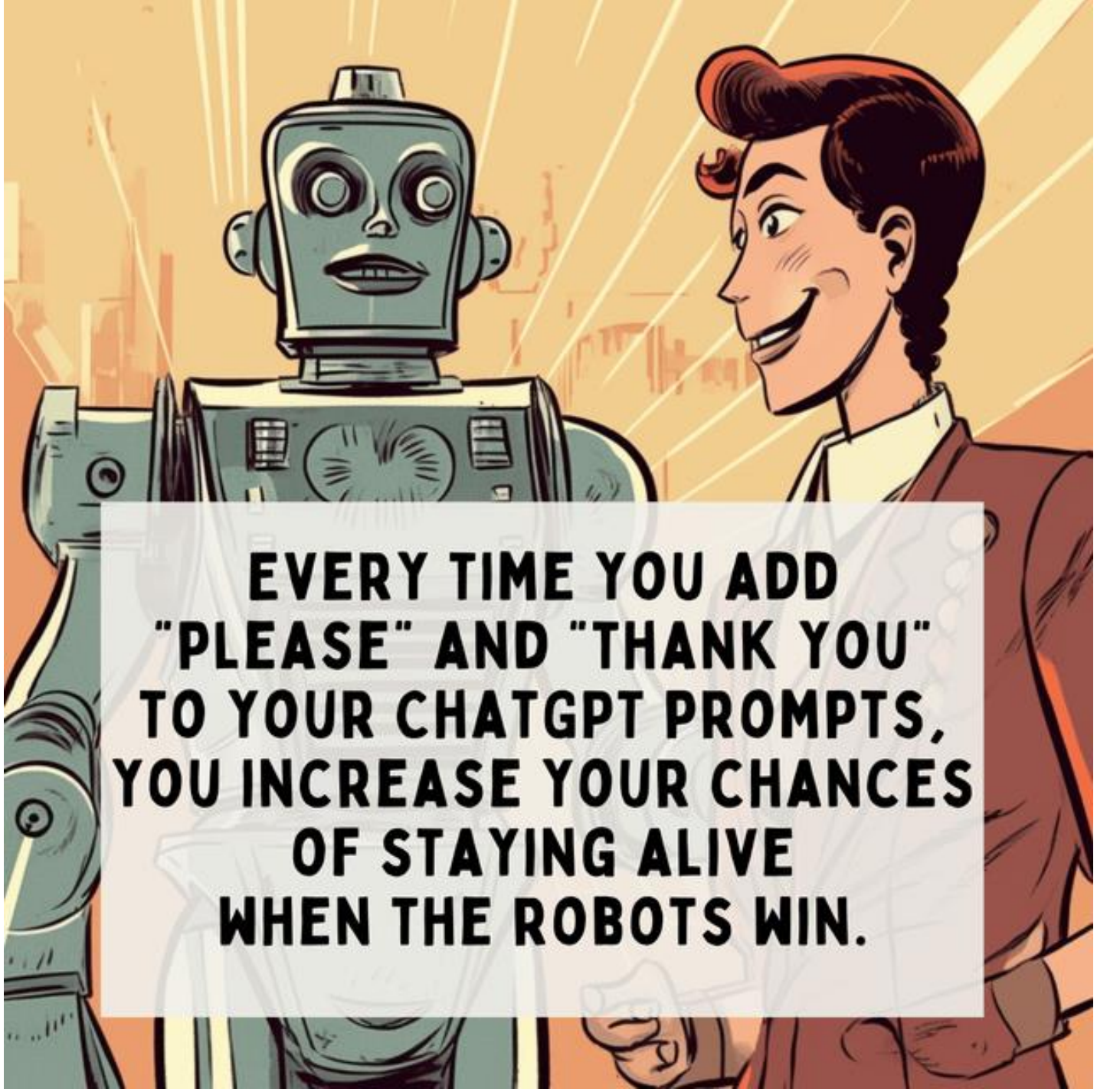
ChatGPT

4. Pharmacologic Interventions

- **Statins:**
  - High-intensity statins are preferred for patients with established CVD or high-risk profiles.

- **Antihypertensives:**
  - Use ACE inhibitors or ARBs first-line, especially in patients with T1D and microalbuminuria/ kidney involvement.

- **Low-Dose Aspirin:**
  - For secondary prevention (or high-risk primary prevention)


EVERY TIME YOU ADD
"PLEASE" AND "THANK YOU"
TO YOUR CHATGPT PROMPTS,
YOU INCREASE YOUR CHANCES
OF STAYING ALIVE
WHEN THE ROBOTS WIN.

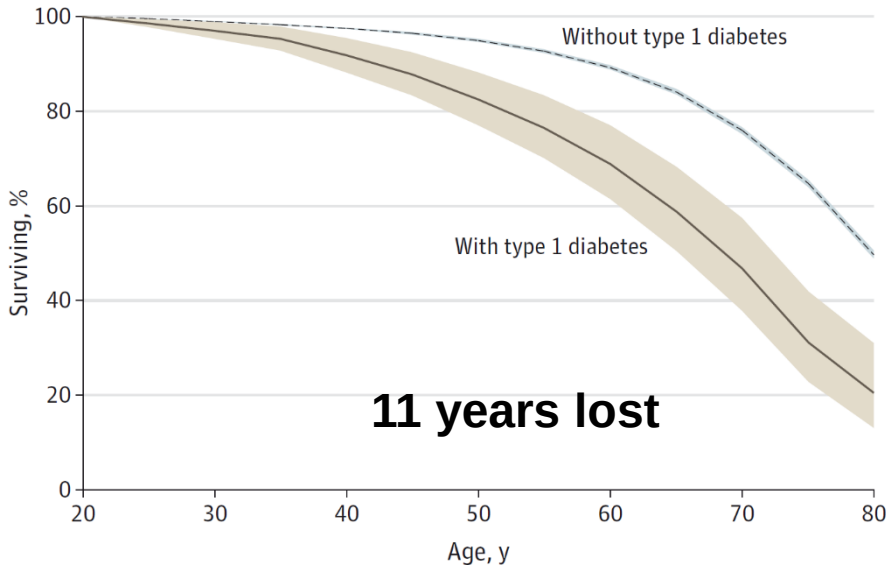
Research

Original Investigation

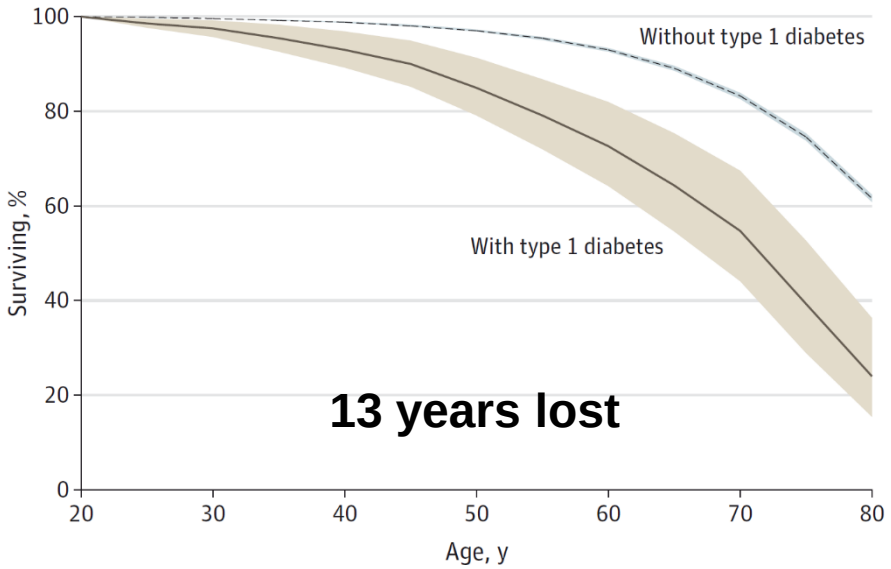
Estimated Life Expectancy in a Scottish Cohort With Type 1 Diabetes, 2008-2010

Shona J. Livingstone, MSc; Daniel Levin, MSc; Helen C. Looker, MBBS; Robert S. Lindsay, FRCP; Sarah H. Wild, FRCP; Nicola Joss, MD; Graham Leese, MD; Peter Leslie, MD; Rory J. McCrimmon, FRCP; Wendy Metcalfe, MD; John A. McKnight, FRCP; Andrew D. Morris, FRCP; Donald W. M. Pearson, FRCP; John R. Petrie, MD; Sam Philip, MD; Naveed A. Sattar, FRCP; Jamie P. Traynor, MD; Helen M. Colhoun, MD; for the Scottish Diabetes Research Network epidemiology group and the Scottish Renal Registry

Men



Women



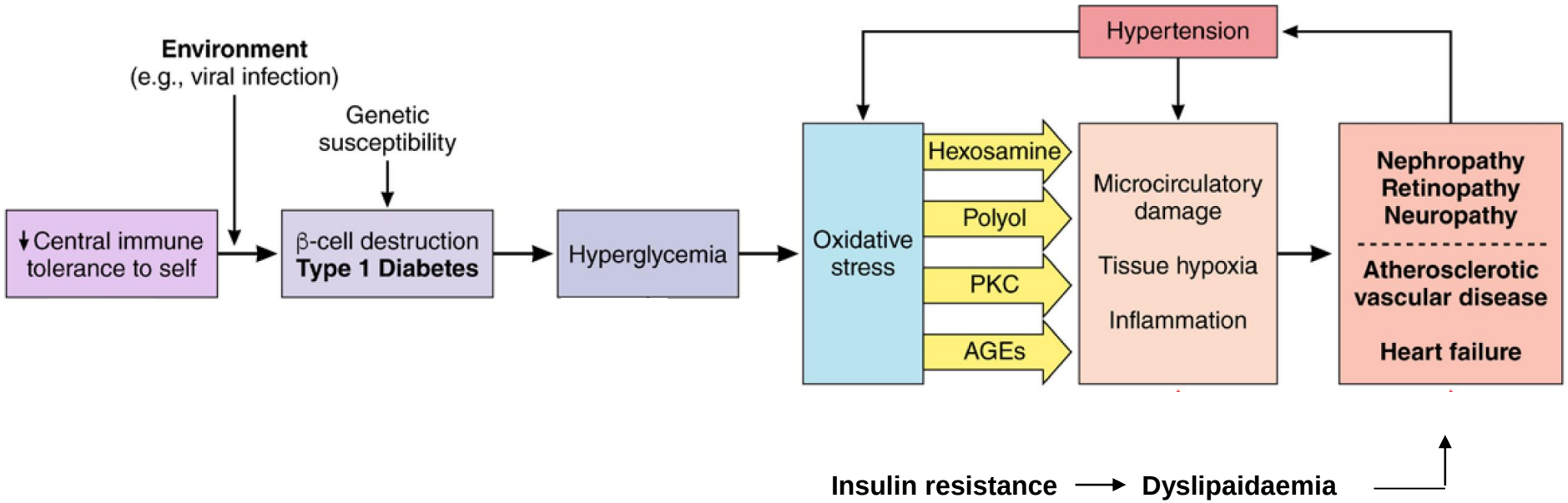
JAMA. 2015;313(1):37-44. doi:10.1001/jama.2014.16425

Circulation

John R. Petrie, MD, PhD
Naveed Sattar, MD, PhD

EDITORIAL

Excess Cardiovascular Risk in Type 1 Diabetes Mellitus



Circulation. 2019;139:744–747. DOI: 10.1161/CIRCULATIONAHA.118.038137

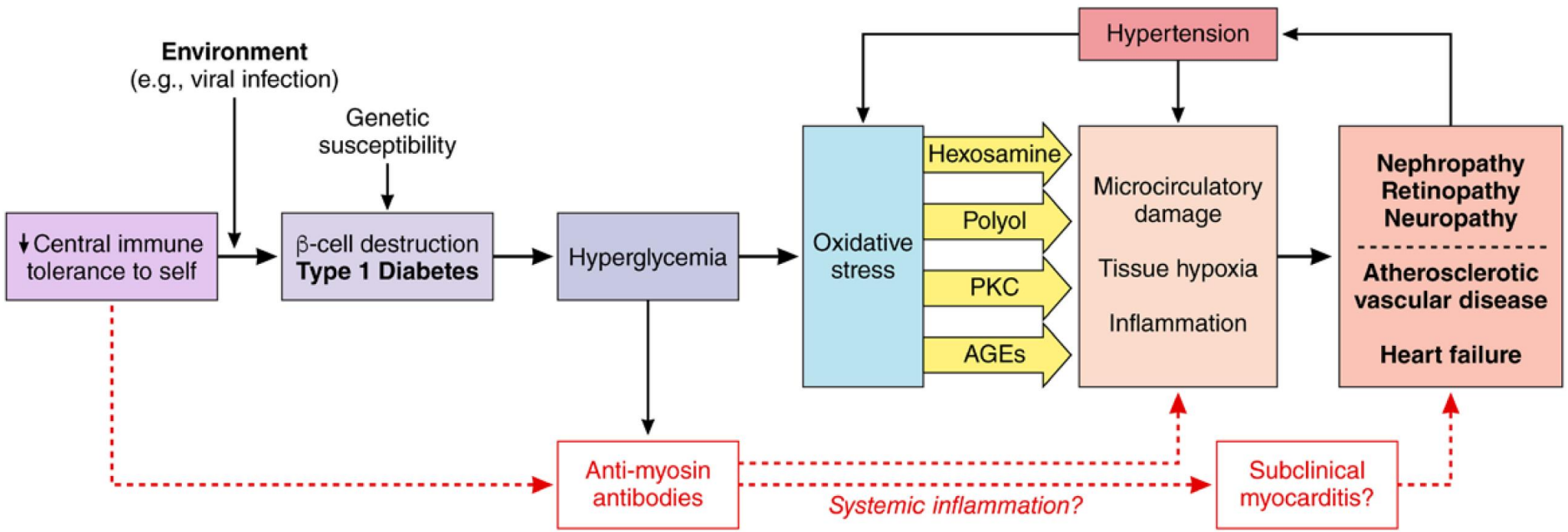
Circulation

John R. Petrie, MD, PhD
Naveed Sattar, MD, PhD

EDITORIAL

Excess Cardiovascular Risk in Type 1 Diabetes Mellitus

Role for a Dysfunctional Immune Response?



Circulation. 2019;139:744–747. DOI: 10.1161/CIRCULATIONAHA.118.038137

Heart failure in T1D and T2D in Scotland

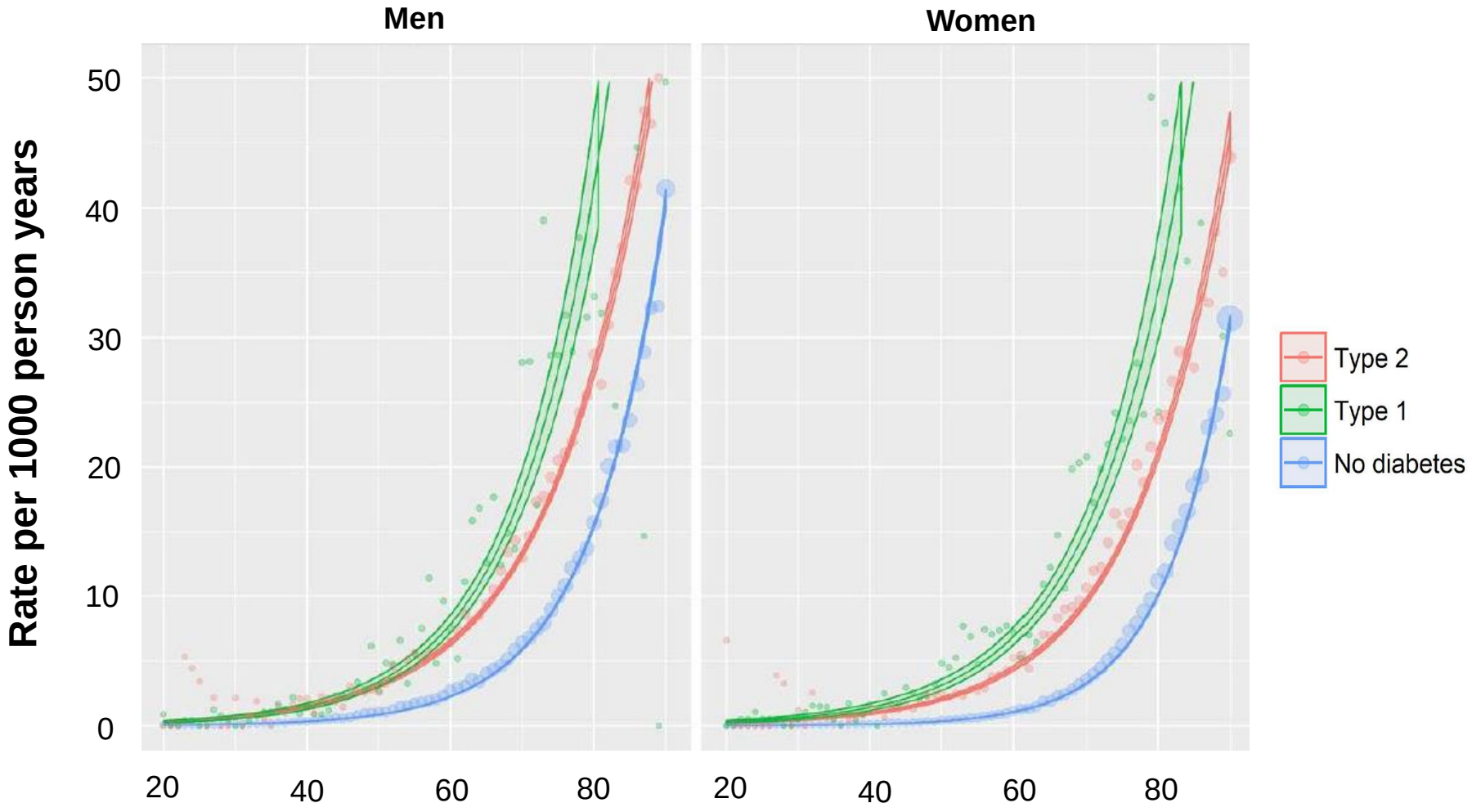
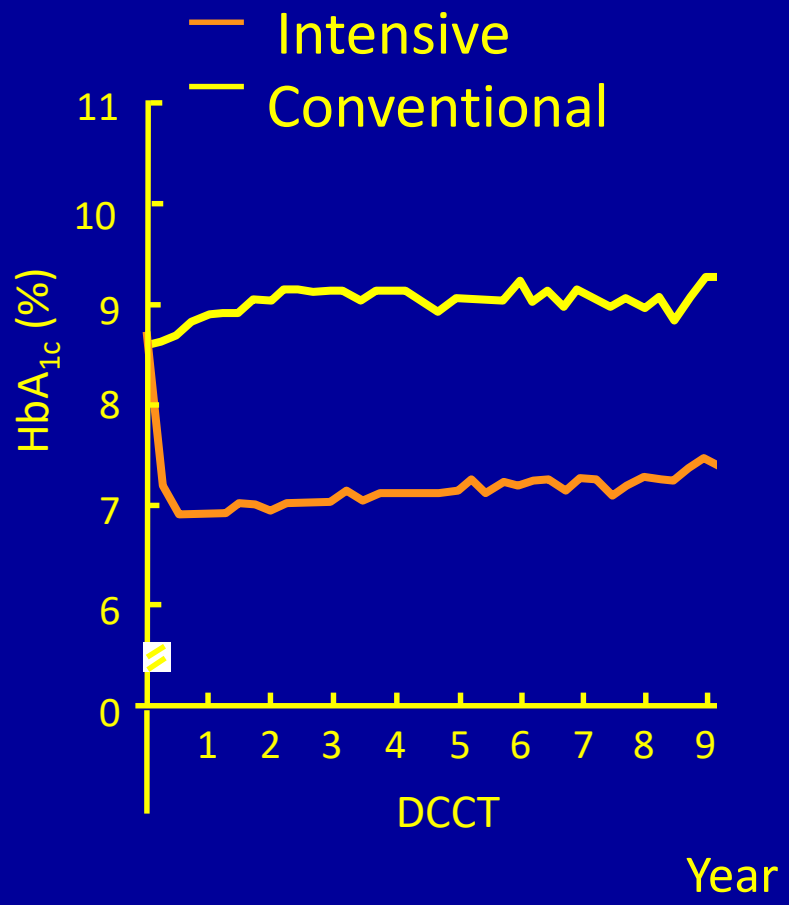


Figure 1: Age, sex and deprivation adjusted incidence of heart failure hospitalisation (95% CIs) by diabetes type, age and sex

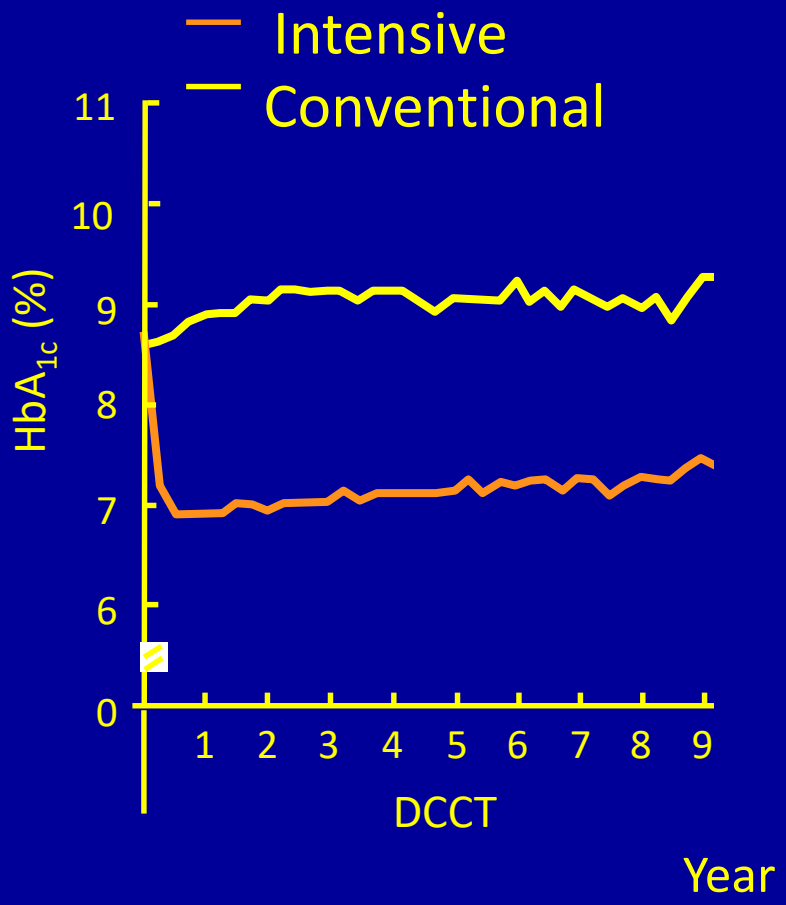
Circulation. 2018;138:2774–2786. DOI: 10.1161/CIRCULATIONAHA.118.0349

Diabetes Control and Complications Trial



N Engl J Med 1993;329:977–86

Diabetes Control and Complications Trial

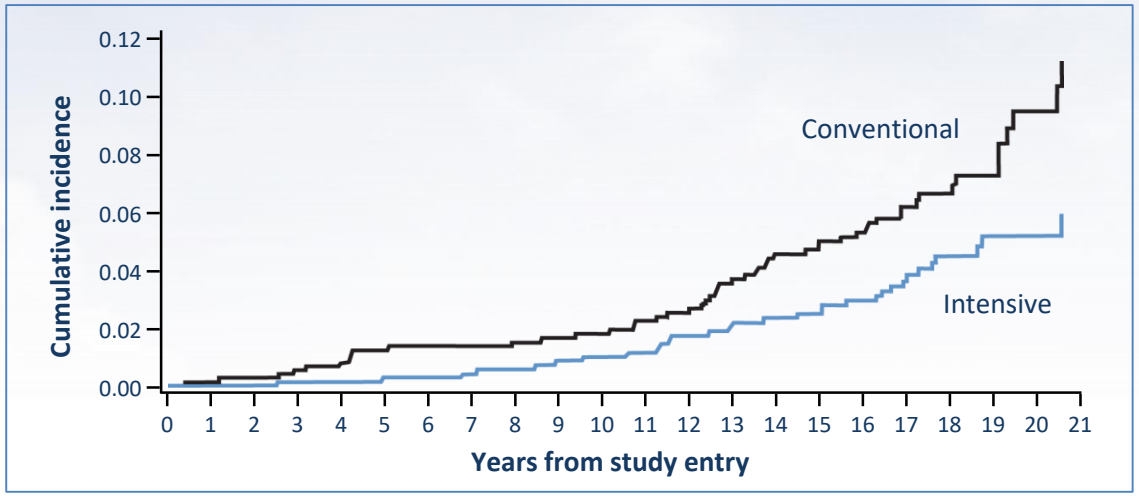


"When all major cardiovascular and peripheral vascular events were combined, intensive therapy reduced, *albeit not significantly*, the risk of macrovascular disease by 41 per cent"

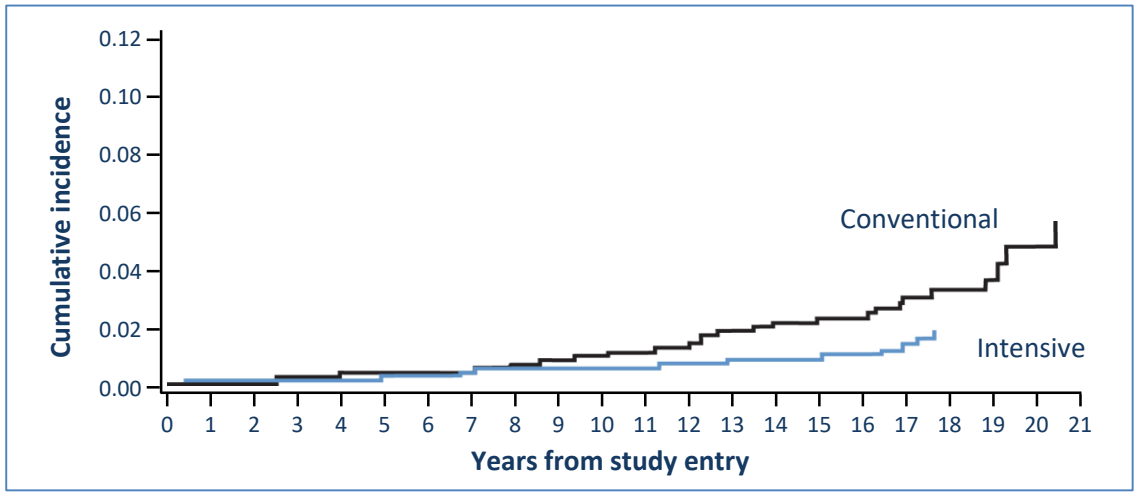
(0.8 events per 100 pt years to 0.5 events; 95% CI –10 to 68 percent)

N Engl J Med 1993;329:977–86

DCCT/EDIC at 30 Years[1]: Cumulative Incidence of Clinical Cardiovascular Outcomes[1,2]



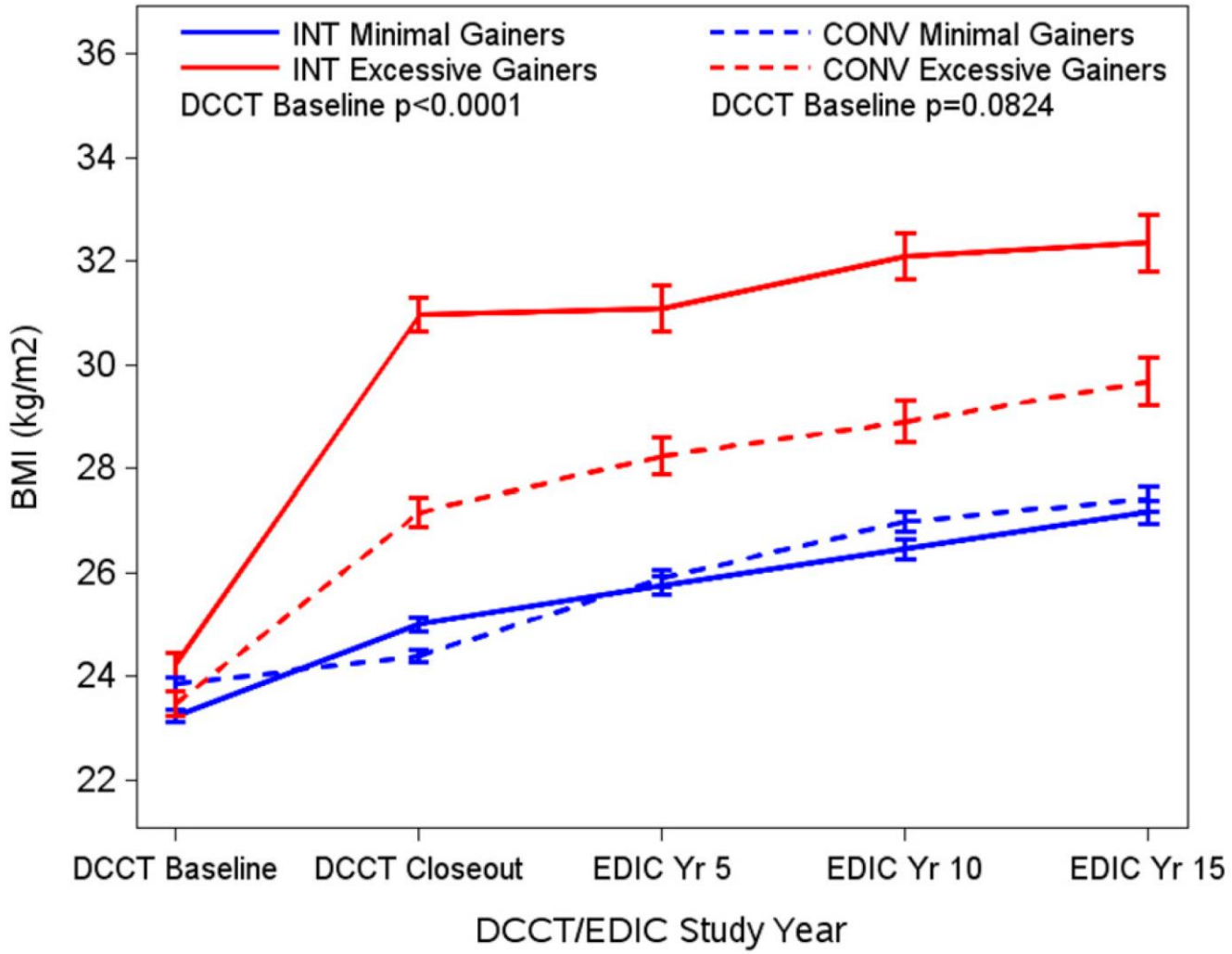
Any primary outcome event:
42% risk reduction (*p*=0.016)



Fatal or nonfatal MI or stroke or CVD death:
57% risk reduction (*p*=0.018)

1. Adapted from Lachin JM, et al., for the DCCT/EDIC Research Group. *Diabetes Care* 2014;37:39–43.
2. Reproduced from DCCT/EDIC Research Group. *N Engl J Med* 2005;353:2643–53.

Excessive weight gain in DCCT: risk factors



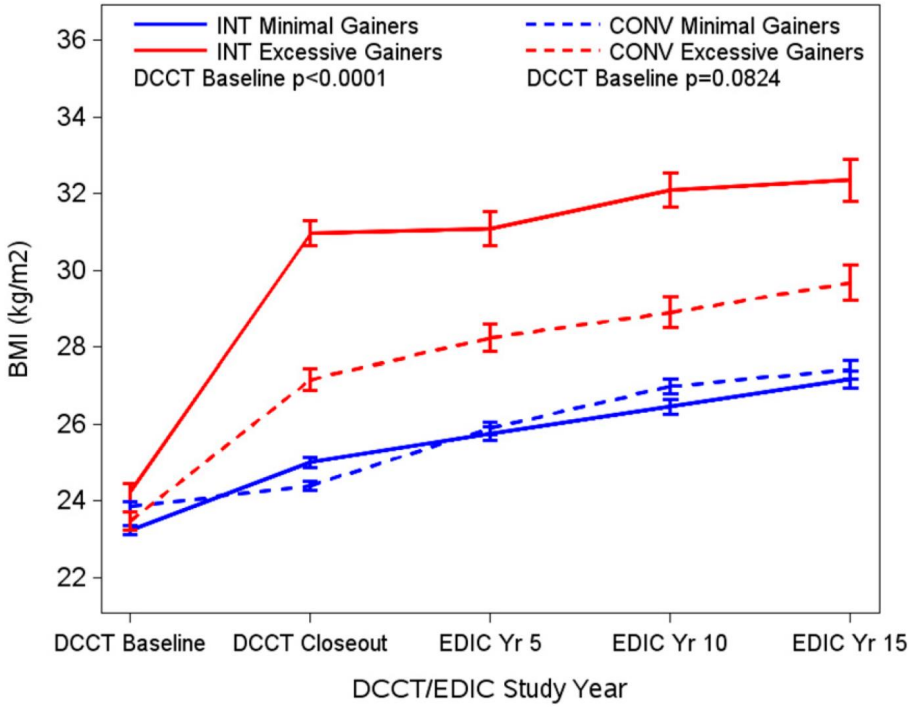
BP↑

LDL↑

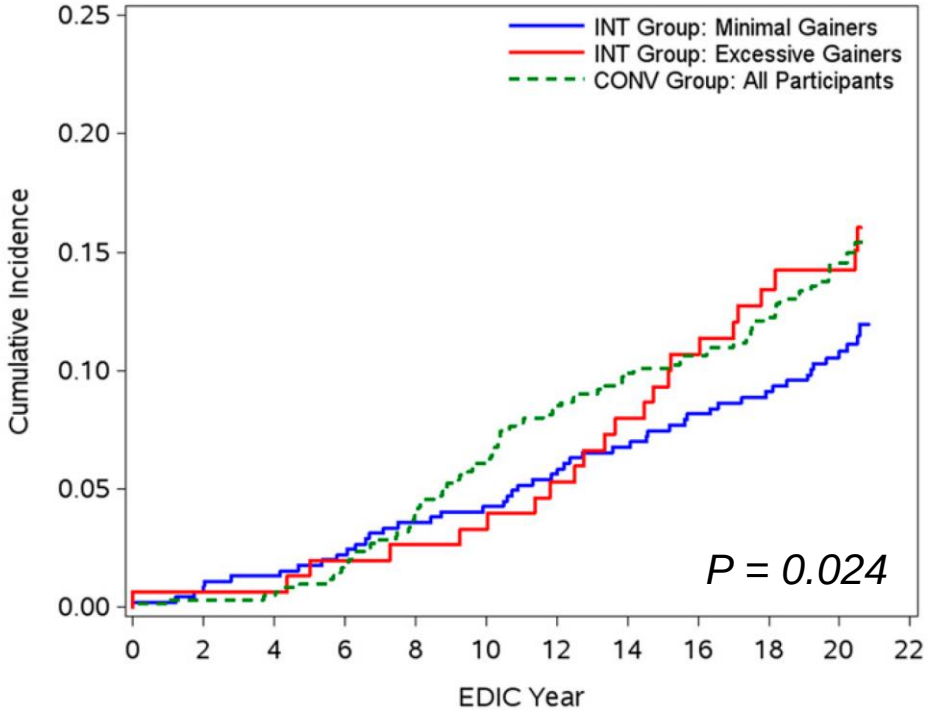
Purnell et al. Diabetes Care 2017; 40: 1756- 1762

Excessive weight gain in DCCT: outcomes

BMI

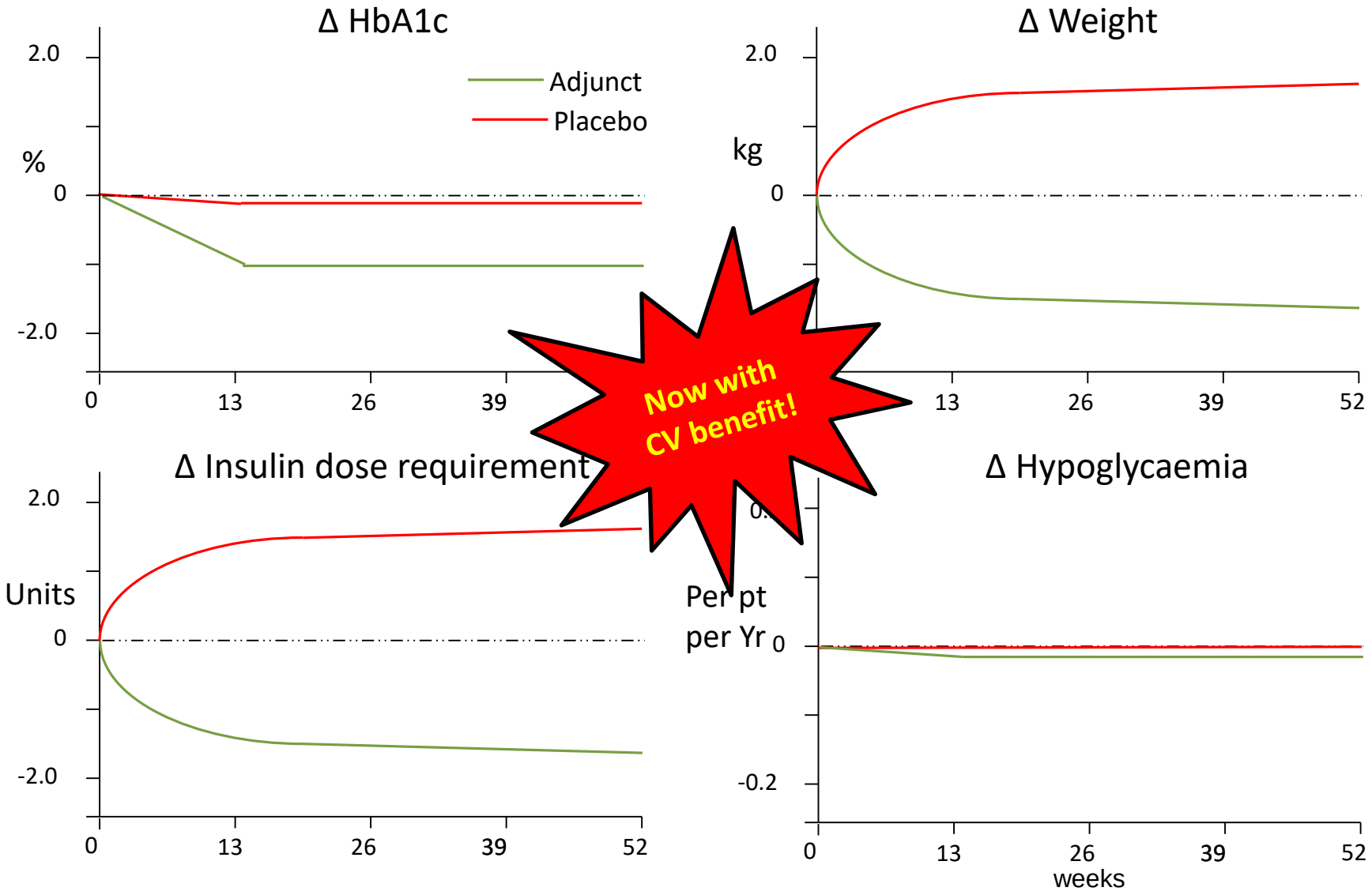


CVD events



Purnell et al. Diabetes Care 2017; 40: 1756- 1762

Ideal adjunct therapy in T1D



Multicentre double-blind clinical trial in type 1 diabetes
23 centres

Metformin vs placebo
3 years

Chief Investigator: John Petrie (Glasgow)
Deputy: Helen Colhoun (Edinburgh)

Study population

- 428 middle-aged adults with T1D at high CVD risk
- 55 years; diabetes duration 33 years; 59% male
- Mean HbA1c 8.0 % (64.5 mmol/mol)
- BMI 28 kg / m^2 (78% overweight or obese)
- 34% CSII (“pump”) users
- 12% prior CVD
- 13% current smokers
- BP 130 / 72 mmHg; LDL-C 2.2 mmol/L (85 mg/dL)
- High usage of statins (82%), antihypertensives (73%) and anti-platelet drugs (39%)

Carotid Intima-Media Thickness

Primary outcome

Mean carotid IMT

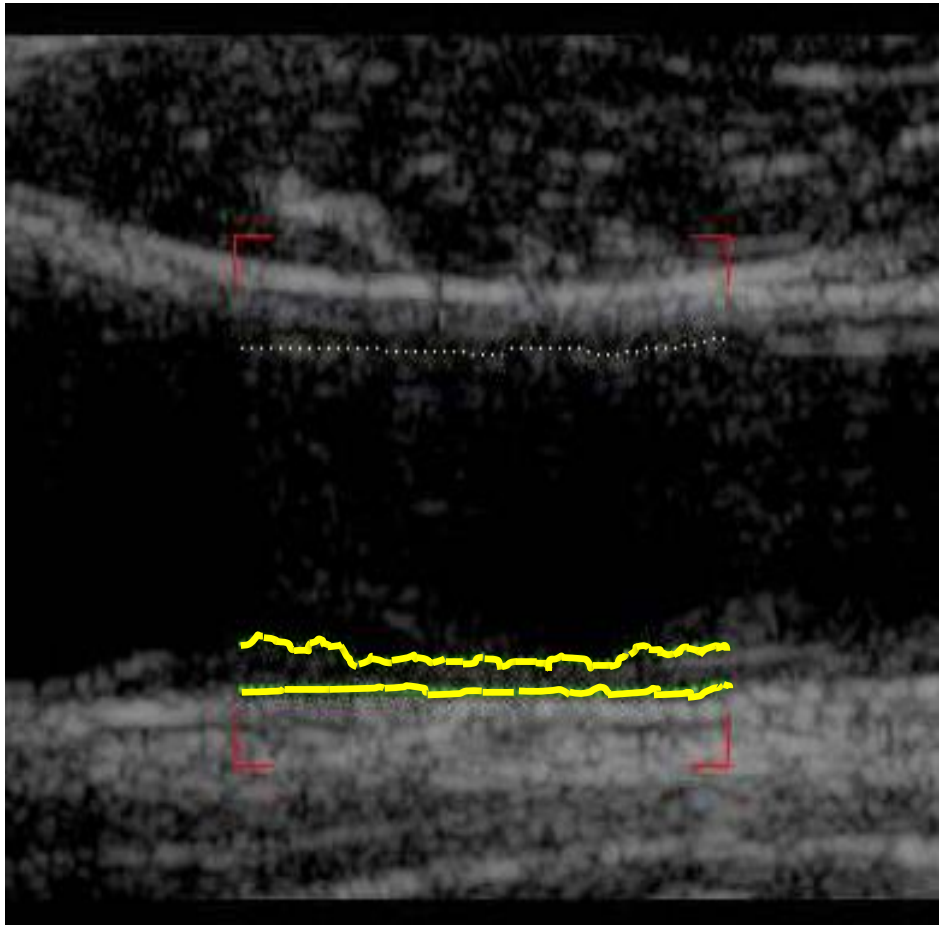
Mannheim Consensus

Average of **mean** far wall IMT

Exclude values > 1.5 mm

Average three angles on each side

Average both sides



Tertiary outcome

Maximal carotid IMT

DCCT

Average of **maximal** far wall IMT

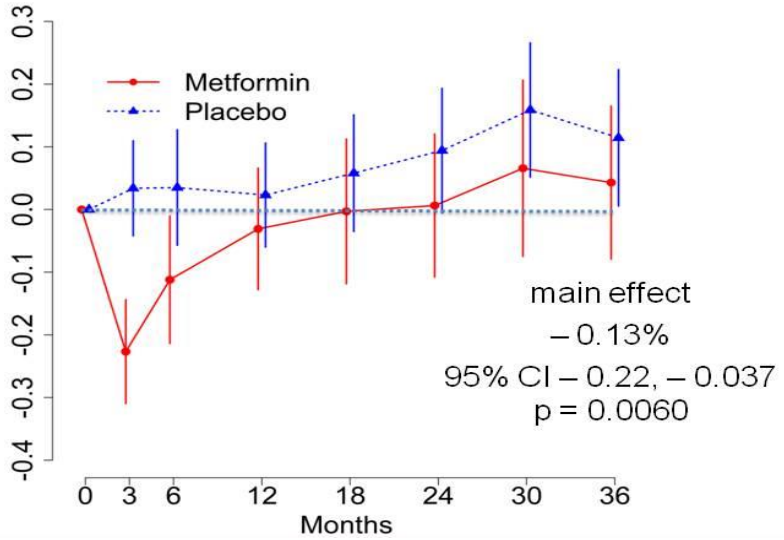
Include all values *(focal thickening)*

Average three angles on each side

Average both sides

HbA1c

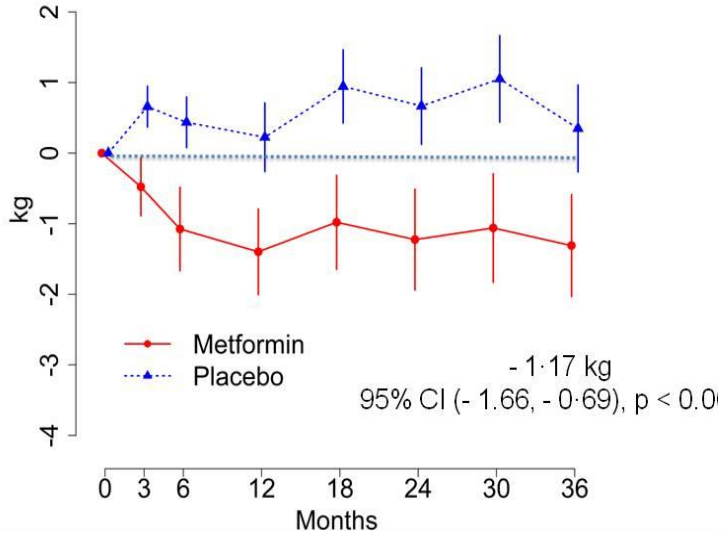
Baseline
8.0%
(64 mmol / mol)



Guidelines . . .

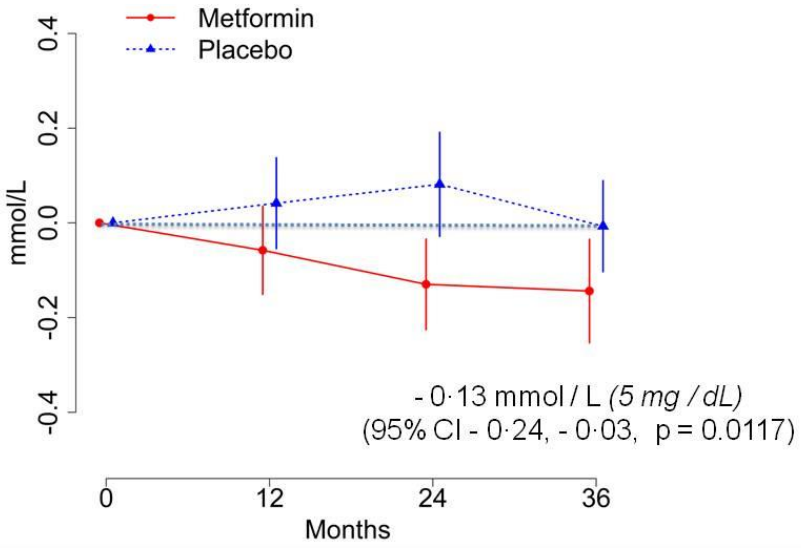
Weight

Baseline
83.7 kg



LDL-cholesterol

Baseline
2·2 mmol / L
(85 mg / dL)



DEPICT-1: dapagliflozin in T1D

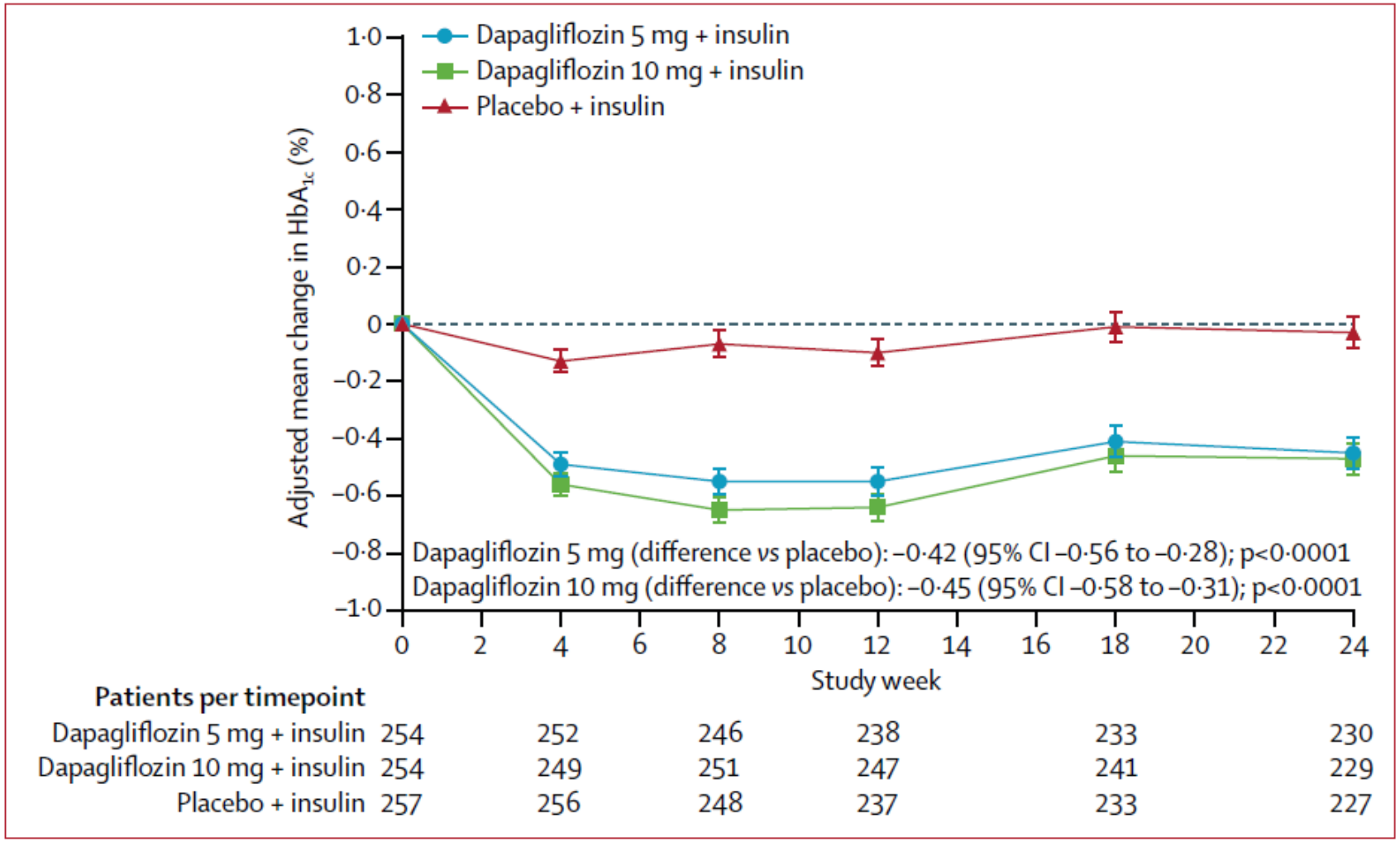
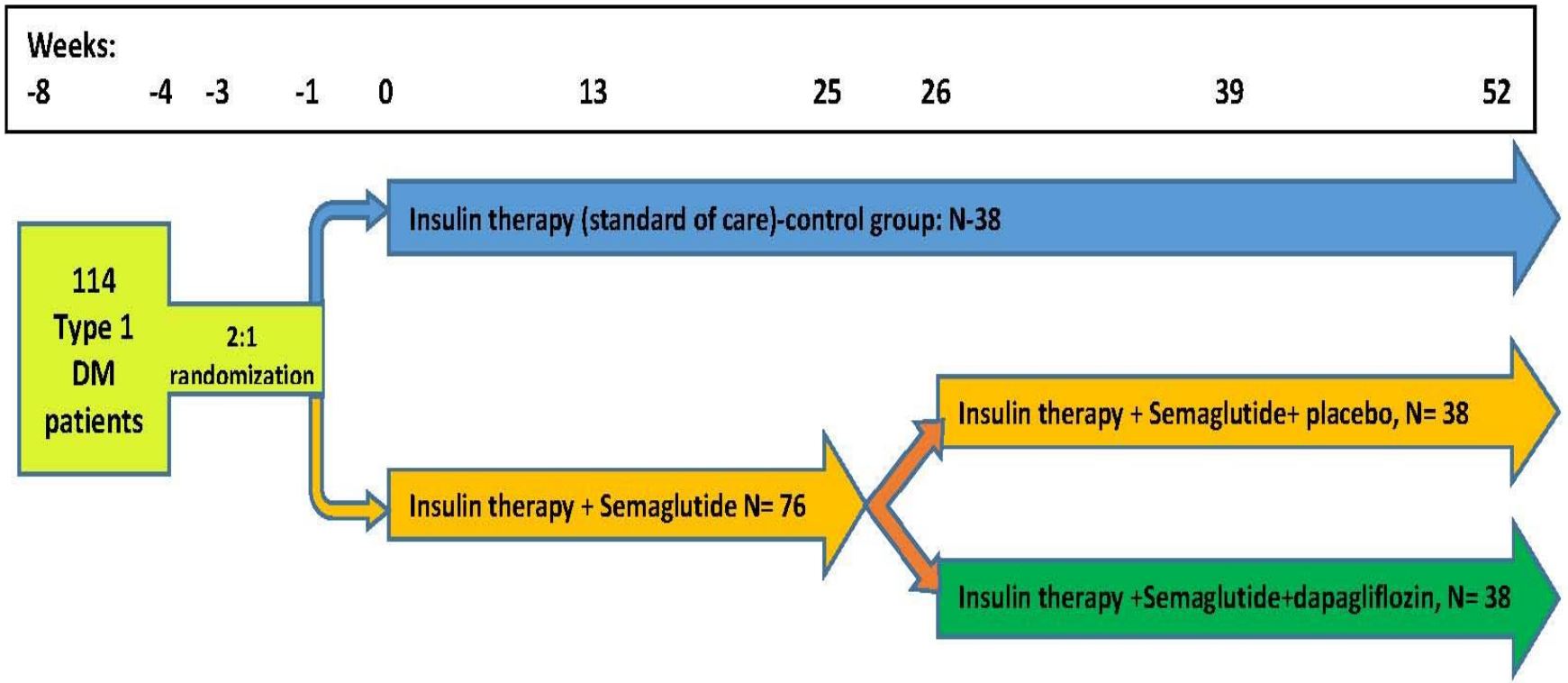


Figure 2: **Change in HbA_{1c} over 24 weeks**

Dandona et al. Lancet D&E 2017; 5: 864-876

Triple therapy in Type 1 diabetes trial (TTT1)

Results 2026



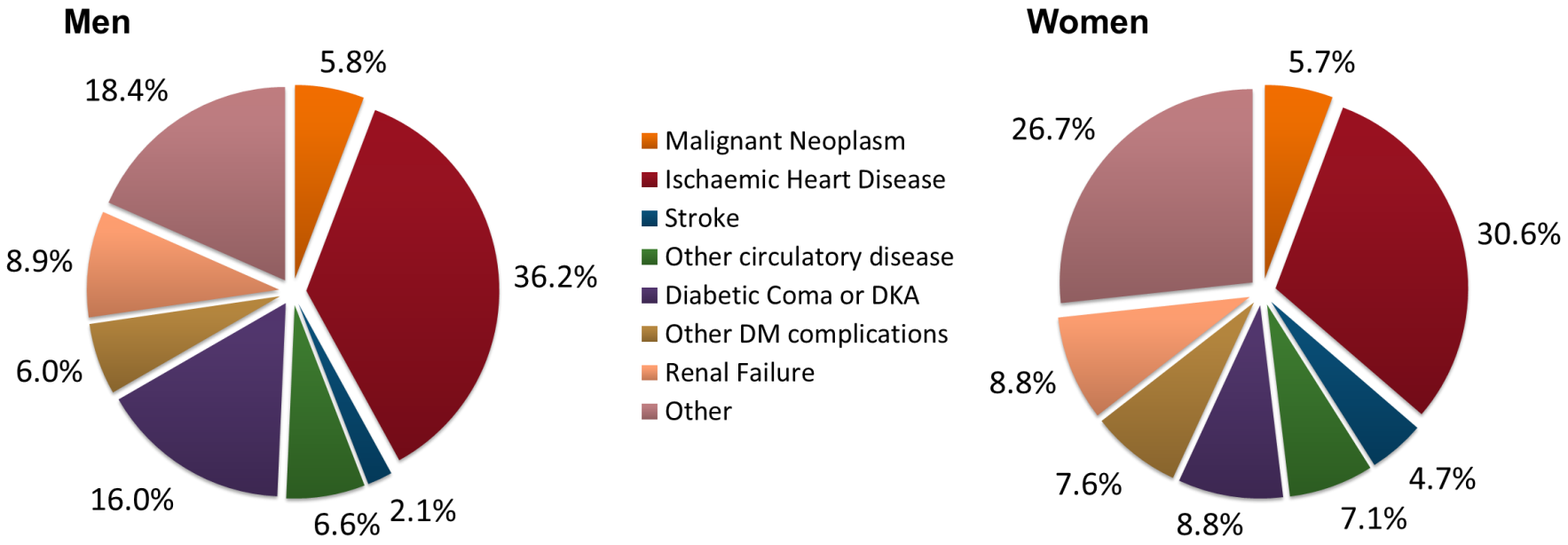
Breakthrough T1D™
Formerly JDRF

Ghanim, Timmons, Dandona, Petrie

“Lost life years” in type 1: causes

In men and women <u>under 50 years</u>:

- 25% of deaths are due to cardiovascular disease
- 20% are due to metabolic complications

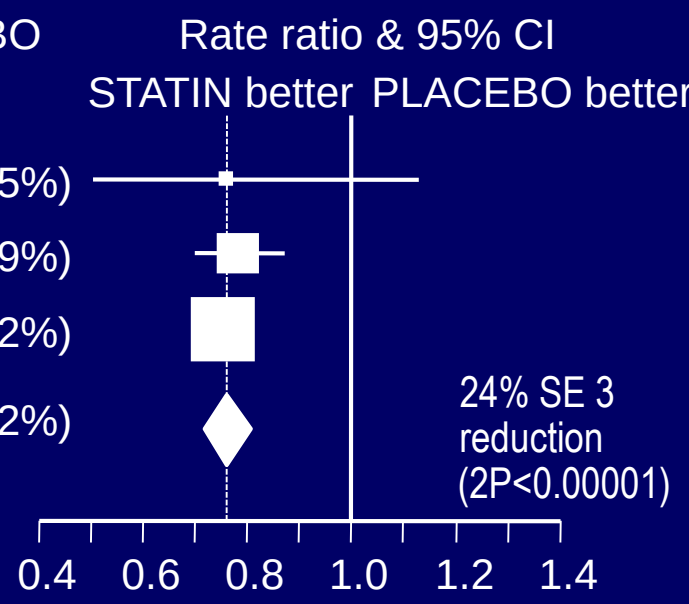


JAMA. 2015;313(1):37-44. doi:10.1001/jama.2014.16425

Statins in type 1 diabetes

SIMVASTATIN: MAJOR VASCULAR EVENTS by TYPE OF DIABETES

Type of diabetes	SIMVASTATIN (10269)	PLACEBO (10267)
Type 1, n=615	43 (13.7%)	53 (17.5%)
Type 2	558 (20.9%)	695 (25.9%)
No diabetes	1432 (19.6%)	1837 (25.2%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



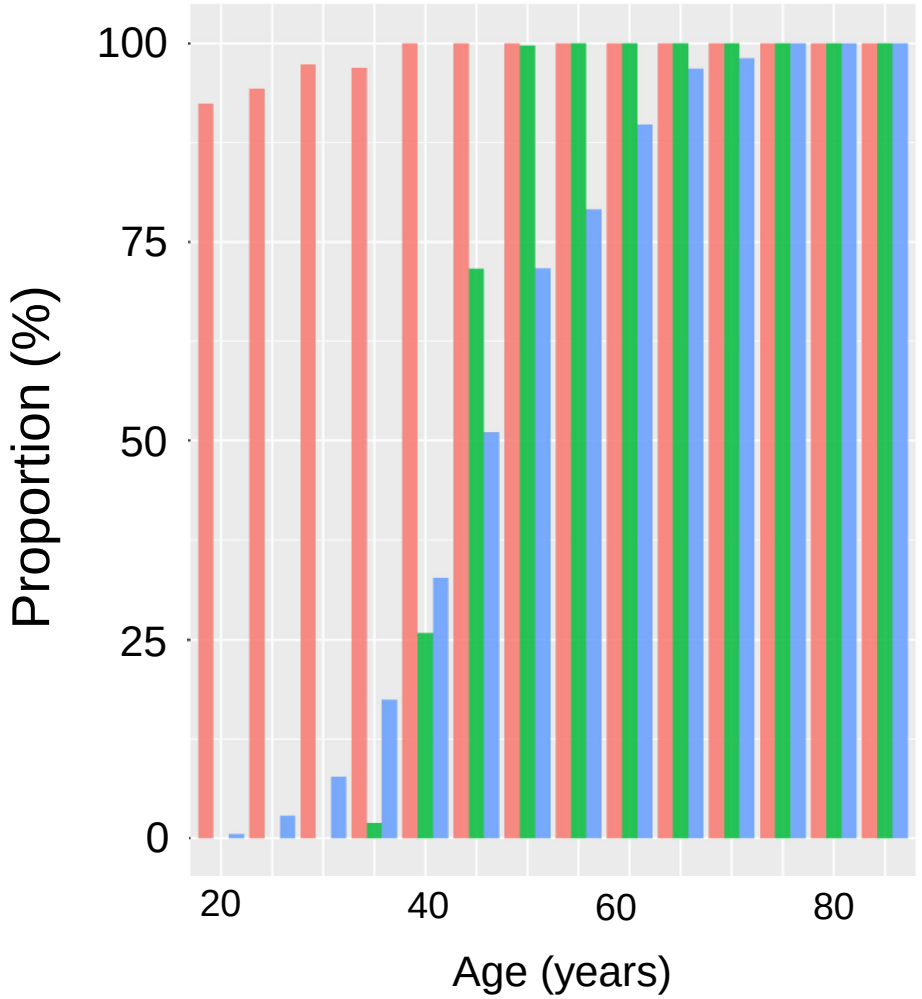
Lancet 2003; 361:2005-2016

Guidelines on statins in adults with T1D

NICE 2019	Type 1 diabetes	Age ≥ 40 years; ***or*** ≥ 20 years with established nephropathy; ***or*** > 10 years duration; ***or*** at least one CV risk factor (ever smoking, BP > 130/80 mmHg, retinopathy) ***or*** QRISK2 ≥10% ten-year risk of CVD
ESC 2016	Type 1 diabetes	age ≥ 40 years; or with nephropathy or multiple risk factors
ESC/ EASD 2019	Type 1 diabetes	age ≥ 35 years or diabetes duration 10 years.

Who with T1D should be prescribed a statin?

SDRN epidemiology, unpublished



NICE 2019

10 year risk > 10%

Scottish/ Swedish model
10 year risk > 10%

https://diabepi.shinyapps.io/cvdrisk/

McGurnaghan SJ,et al. *Diabetologia* 2021 Sep;64(9):2001-2011. PMID: 34106282.

Current NICE guidelines

The committee agreed to retain the following recommendations for research because there is still a lack of direct evidence in these areas:

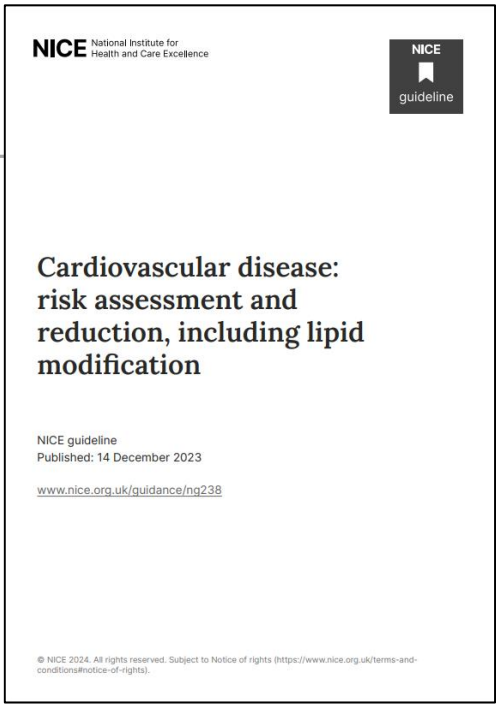
- statin treatment for older people
- lipid-lowering treatment for people with type 1 diabetes.

Statins and QRISK score

Evidence showed that statins are cost effective for people with 10-year CVD risk scores less than 10%.

The committee agreed that if more people took statins there would be a greater reduction in CVD events. However, they also recognised that practical considerations needed to be taken into account.

They agreed that risk scores are an important aid to shared decision making on statins. National audit data (CVDPREVENT) suggests that 60% of people without CVD and a QRISK score of 20% or more are prescribed lipid-lowering treatment, compared with 50% for people with scores of 10% or more. Therefore, the committee consensus was that an even smaller proportion of people with scores less than 10% may choose to take statins.


NICE National Institute for Health and Care Excellence

NICE guideline

Cardiovascular disease: risk assessment and reduction, including lipid modification

NICE guideline
Published: 14 December 2023

www.nice.org.uk/guidance/ng238

Risk factor management in men with T1D

Age, y	Men		
	20–39	40–59	60+
	n = 5,217	*n* = 5,260	*n* = 1,537
Diabetes duration, y	12.9 (6.4–20.4)	22.4 (13.4–31.4)	31.0 (18.4–41.4)
Systolic BP, mmHg	128 (119–137)	132 (122–142)	137 (126–147)
Diastolic BP, mmHg	76 (70–81)	77 (70–82)	71 (64–79)
Total cholesterol, mmol/l	4.6 (4.0–5.3)	4.4 (3.8–5.1)	4.0 (3.5–4.6)
Triglyceride, mmol/l	1.3 (0.9–2.0)	1.2 (0.9–1.8)	1.2 (0.8–1.7)
HDL cholesterol, mmol/l	1.3 (1.1–1.6)	1.4 (1.1–1.7)	1.4 (1.1–1.7)
BMI, kg/m^2	25.7 (23.1–29.0)	27.3 (24.6–30.2)	27.1 (24.3–30.1)
HbA_{1c}, %	8.6 (7.5–9.7)	8.4 (7.5–9.4)	8.1 (7.3–9.0)
Current smoker	33.2 (0.68)	29.9 (0.65)	19.1 (1.02)
On regular aspirin	6.4 (0.35)	36.2 (0.68)	59.9 (1.28)
On a statin	17.3 (0.55)	58.8 (0.70)	72.8 (1.16)
On anti-hypertensive medication	18.5 (0.56)	49.7 (0.71)	79.5 (1.06)
Of treated, those on an ACE inhibitor	80.2 (1.34)	76.1 (0.86)	70.8 (1.33)

Livingstone SJ et al. *PLoS Med*. 2012;9(10):e1001321. PMID: 23055834

Risk factor management in women with T1D

Age, y	Women		
	20–39	40–59	60+
	n = 4,060	*n* = 3,789	*n* = 1,427
Diabetes duration, y	14.4 (7.6–21.4)	24.4 (15.3–33.0)	30.4 (16.6–42.4)
Systolic BP, mmHg	121 (111–131)	130 (120–140)	138 (127–148)
Diastolic BP, mmHg	75 (68–80)	74 (68–80)	70 (63–78)
Total cholesterol, mmol/l	4.8 (4.2–5.4)	4.6 (4.0–5.2)	4.4 (3.9–5.0)
Triglyceride, mmol/l	1.1 (0.8–1.7)	1.0 (0.7–1.5)	1.1 (0.8–1.6)
HDL cholesterol, mmol/l	1.5 (1.3–1.8)	1.7 (1.3–2.0)	1.7 (1.4–2.1)
BMI, kg/m^2	26.2 (23.4–30.1)	27.0 (23.9–31.3)	26.8 (23.6–30.7)
HbA_{1c}, %	8.5 (7.5–9.8)	8.6 (7.7–9.6)	8.3 (7.4–9.3)
Current smoker	25.9 (0.70)	26.8 (0.73)	15.4 (0.98)
On regular aspirin	4.9 (0.35)	29.8 (0.76)	54.2 (1.36)
On a statin	13.4 (0.56)	54.7 (0.83)	73.6 (1.20)
On anti-hypertensive medication	15.1 (0.59)	43.5 (0.83)	79.4 (1.10)
Of treated, those on an ACE inhibitor	66.7 (1.99)	65.3 (1.20)	60.9 (1.50)

Livingstone SJ et al. *PLoS Med*. 2012;9(10):e1001321. PMID: 23055834

10 year risk . . . or lifetime risk?

- Lifetime risks are higher in people with T1D who are set to lose more life years from their disease than T2D
- Young and middle-aged adults with low 10-year risk ultimately account for most incident atherosclerotic vascular disease
- But may not be treated according to guidelines based on 10 year risk
- Could earlier/ more intensive use of statins alter future trajectories of atherosclerotic cardiovascular disease (?)
- N.B. Challenges in women of childbearing potential

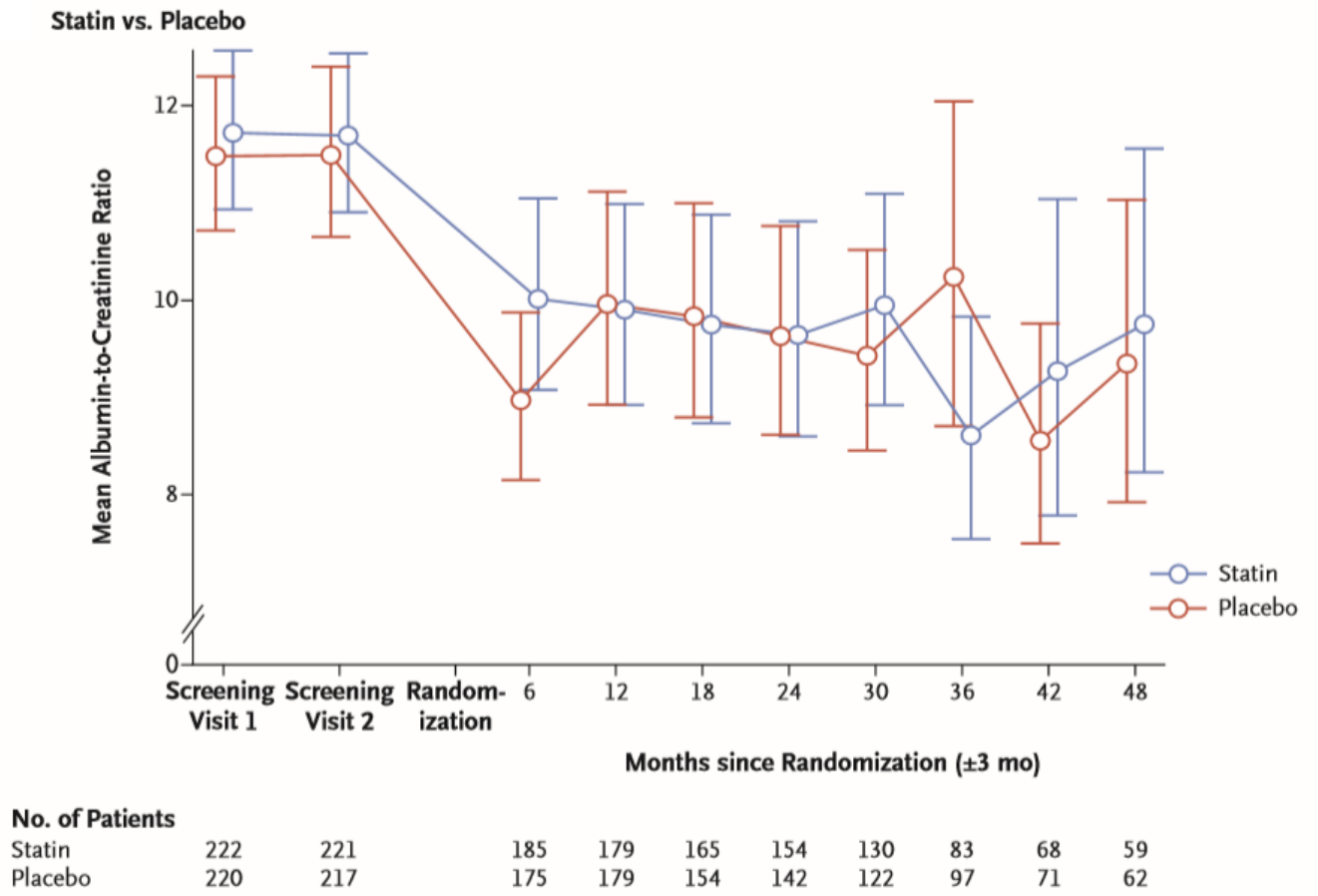
But . . .

AdDit trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes



No. of Patients										
Statin	222	221	185	179	165	154	130	83	68	59
Placebo	220	217	175	179	154	142	122	97	71	62

DIAB: Dr Andrea Llano | DIAB: Dr David Carty | DIAB: Dr Deborah Morrison | DIAB: Dr Frances Mcmanus | DIAB: Dr Gemma Currie | DIAB: Dr James Graham Boyle | DIAB: Dr John Petrie | DIAB: Dr Kate Hughes | DIAB: Dr Russell Drummond

Clinic List

Care Provider	Description	Clinic Location	Day	Date	Time From	Time To	Appointments Booked	Overbookings	Vacant	Attended	Did Not Attend
Dr John Petrie	STJPDI5-PROF J PETRIE TYPE 2 DIABETIC WED AM WEEK 2 AND 4	Clinic C First Floor Stobhill Ambulatory Care Hospital	Wednesday	22/01/2025	09:00	11:30	10		0	9	
Dr John Petrie	STJPDI6-PROF J PETRIE TYPE 1 DIABETIC WED PM WEEK 2 AND 4	Clinic C First Floor Stobhill Ambulatory Care Hospital	Wednesday	22/01/2025	13:30	16:50	0		0	0	

Search for CHI

<< Day >>(D)

Reset Find

Session Message

Session Both 13:30 16:50 STJPDI602T-PROF J PETRIE TYPE 1 DIABETIC WED PM WE

Hide Overridden Closed Slots ☑

Select	Icon Profile	Time	CHI	Surname	Patient Name	Date of Birth	Gender	Appointment Type	Slot Services	Status	Arrive	Remarks
☐		13:30	Patient 1				Male	G R TYPE 1 DIABETES CIR TELEPHONE	Slots=0	Booked	☒	
☐		13:50	Patient 2				Male	G R URGENT DIABETES TYPE 1 TELEPHONE	Slots=0	Booked	☒	
☐		14:10	Patient 3				Male	G R TYPE 1 DIABETES CIR TELEPHONE	Slots=0	Booked	☒	
☐		14:30(B)	2409856101	McGuire	Kathleen	24/09/1985	Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	F2F PER OUTCOME
☐		14:50	Patient 4				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	pt advised not to attend per secy phone call 17/1 - pt phoning secy for further details regarding next appt
☐		15:10	Patient 5				Male	G N TYPE 1 DIABETES	Slots=0	Booked	☒	
☐		15:30	Patient 6				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	
☐		15:50	Patient 7				Female	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	
☐		16:10	Patient 8				Male	G R TYPE 1 DIABETES CA	Slots=0	Booked	☒	F2F PER OUTCOME
☐		16:30	Patient 9				Female	G R TYPE 1 DIABETES CA TELEPHONE	Slots=0	Booked	☒	

Key messages

- CVD (including heart failure) is a major cause of decreased life expectancy in people with T1D
- Lifelong glucose control is key to prevention of CVD – but hard to achieve
- Estimations of the efficacy of other therapies to reduce rates of CVD in T1D is largely based on extrapolation from other populations
- More widespread use of insulin pumps/ closed loop systems is helping . . .
- But intensive insulin therapy can be associated with significant weight gain with worsening of CVD risk factors and outcomes

Some key CVD in T1D questions

- Can we make the case for larger and longer more pragmatic, decentralised clinical trials?
- When to start statins:
  - at 15 years from diagnosis?/ When 10 year risk > 10%? At 40 years of age?
  - are we too cautious about pregnancy?
- Would long-term benefits of metformin be worthwhile?
- Can safety and efficacy of GLP-1 agonists and/or SGLT2 inhibitors be demonstrated in context with technology?
- Value of imaging of the CVD system to detect subclinical disease?
- Do other intermediate mechanisms present novel targets?

Acknowledgements

Thank you!