NHS
County Durham and Darlington
NHS Foundation Trust

CVD risk - micro and macrovascular disease screening and management

Shafie Kamaruddin
Consultant Diabetes & Endocrinology

Disclosures

- Speaker Honoraria
    - Lilly, Boehringer Ingelheim, Sanofi, Novo Nordisk, Astra Zeneca, Takeda, Roche & Medtronic

Background

Headline stats

Infographics available

1 **4.7 million** people in the UK have diabetes.

2 Someone is diagnosed with diabetes every **two minutes.**

Headline stats

Infographics available

3 **At least 10,350** people in the UK have end stage kidney failure because of their diabetes.

4 **More than 1,700** people have their sight seriously affected by their diabetes every year in the UK.

5 **Every week** diabetes leads to more than

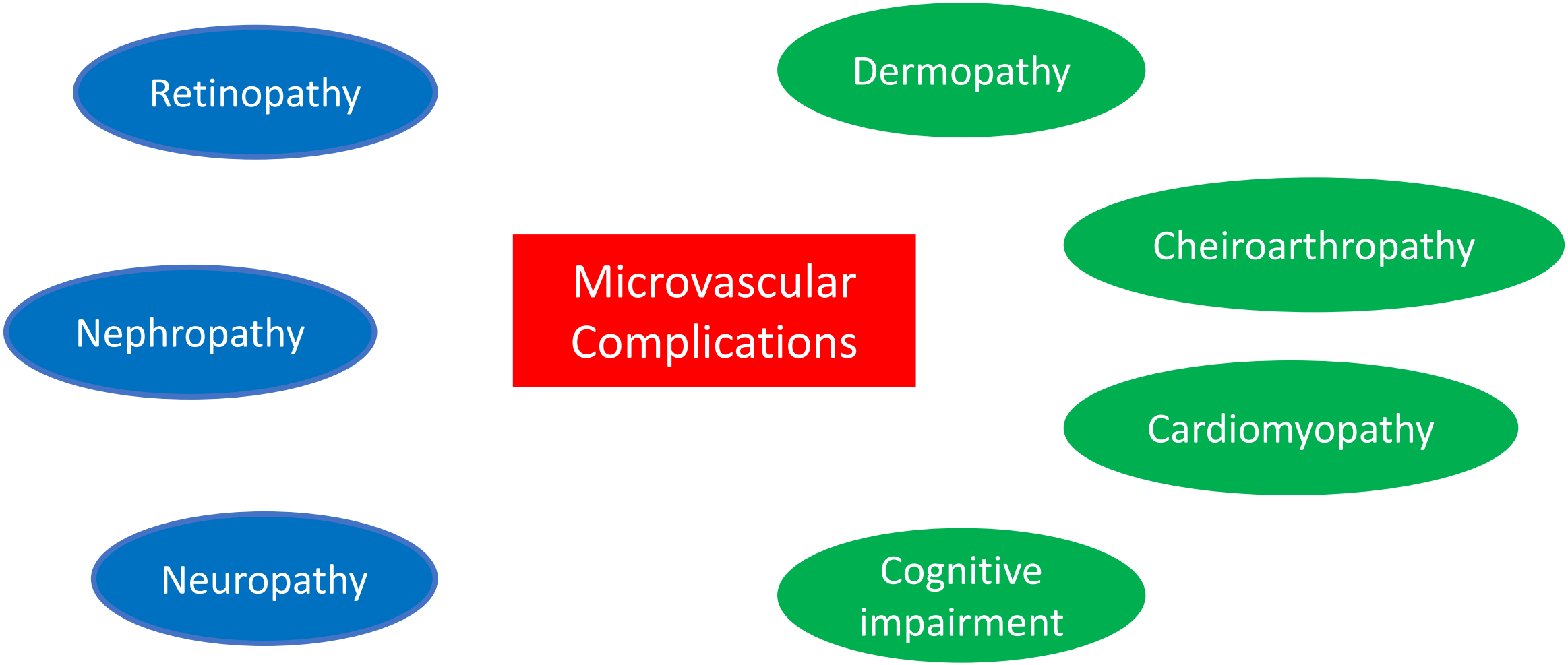
169 amputations

680 strokes

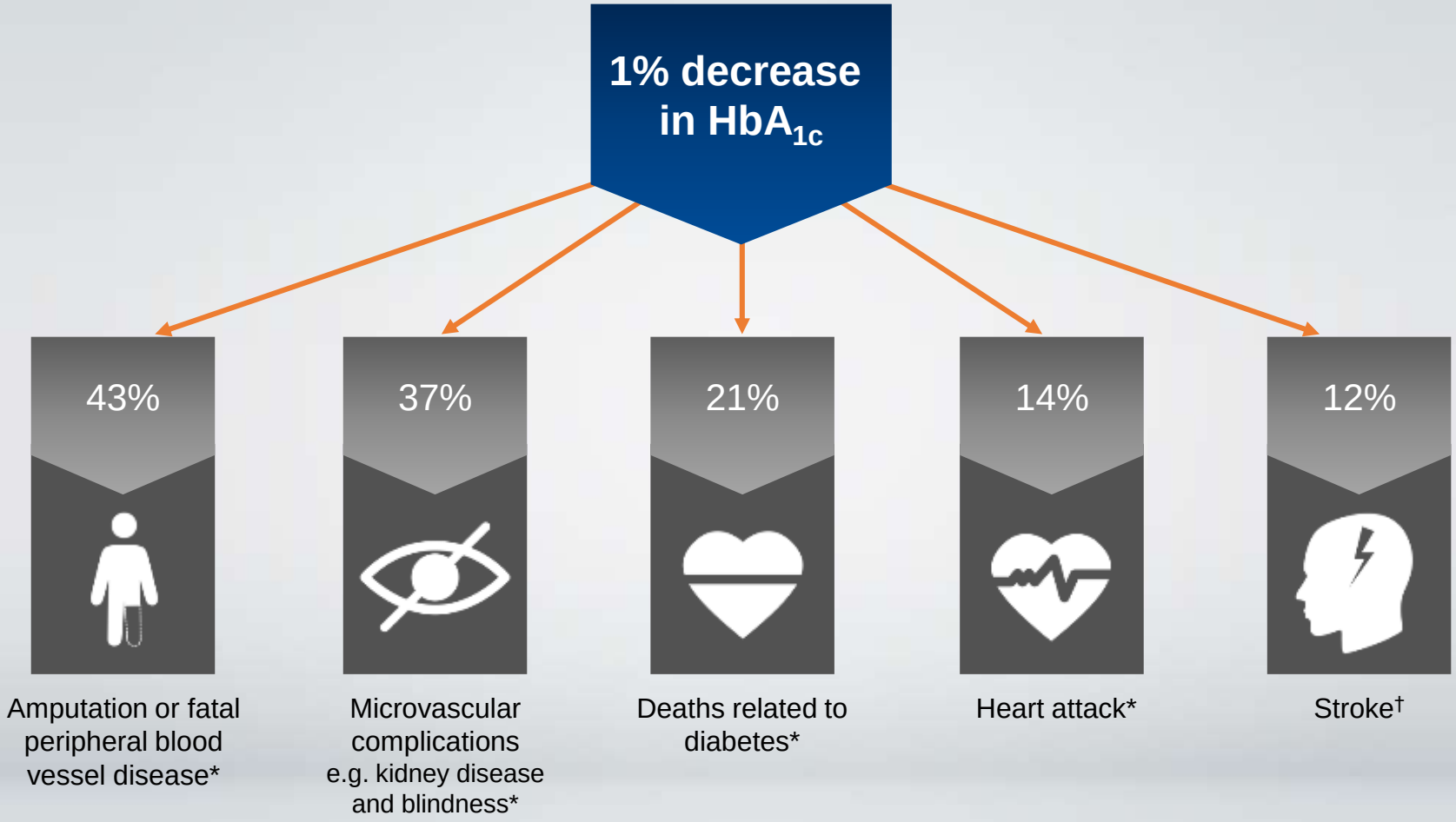
530 heart attacks and almost **2,000** cases of heart failure.

More than **500** people with diabetes die prematurely every week.

Microvascular



UKPDS analysis: 1% (11mmols/mol) decrease in HbA1c is associated with a lower relative risk of complications



*P<0.0001; †P=0.035.
UKPDS=UK Prospective Diabetes Study.

Stratton IM et al (2000) BMJ 321: 405–12

Retinopathy

Why bother screening?

- Leading cause of new onset blindness in the developed world
- Sight threatening microvascular complications
- >90% of vision loss resulting from proliferative retinopathy is preventable
- Majority are asymptomatic even at proliferative stage

Retinopathy

Type 1 Diabetes

- 25% will develop after 5 years
- 60-80% after 10-15 years

Type 2 Diabetes

- Proliferative Retinopathy (DPR) present in 25% after 15 years

Retinopathy

Risk factors:

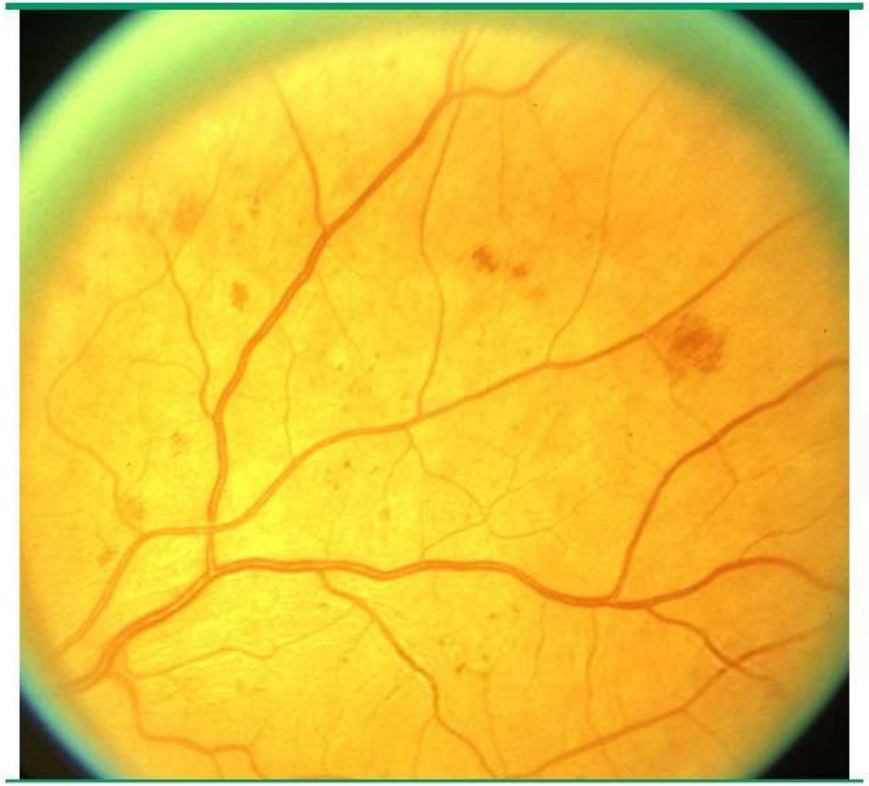
- Long duration of diabetes
- Poor glycaemia
- Hypertension
- Pregnancy*
- Asian or Afro-Caribbean ethnic background

Retinopathy

Stages:

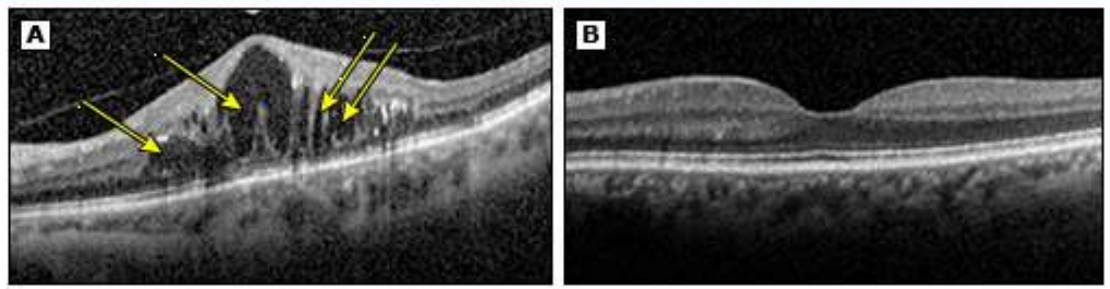
- Background retinopathy (R1)
  - bulge slightly (microaneurysms)
  - leak blood (retinal haemorrhages)
  - leak fluid (exudates)
- Pre-proliferative (R2)
  - R1 + hard exudates, cotton wool spots
  - IRMA
- Proliferative (R3)
  - Neovascularisation
  - Vitreous haemorrhage
  - Retinal detachment
  - S (stable), P (photocoagulation)
- Maculopathy
  - M0 – no macular involvement
  - M1
    - Above + leakage involving the fovea

Standard retinal photograph #2A



Standard photograph from the Early Treatment of Diabetic Retinopathy Study (ETDRS), which is used as the gold standard for grading severity in the clinical and research arena. Photograph #2A shows retinal hemorrhages and microaneurysms.

Diabetic macular edema: Appearance on optical coherence tomography



(A) Optical coherence tomography (OCT) of diabetic macular edema. There are numerous large cysts visible within the macula (arrows), and the retinal thickness is increased.
(B) OCT of normal macula (for comparison) showing typical foveal contour.

Retinopathy

Management:

- Frequency of screening subject to staging and referral to ophthalmology
- Glycaemic control
- Drugs
  - Anti-VEGF & steroid injections
    - reduce macular oedema
    - reduce proliferation
  - ACE inhibitors
    - effect of lowering blood pressure
    - lower levels of vascular endothelial growth factor
  - Aspirin – no contraindication

Nephropathy

Definition:

- Presence of albuminuria with progressive decline in glomerular filtration rate
- Increased urinary albumin excretion is defined as ≥3.4 mg/mmol

Screening:

- Spot urine for albumin creatinine ratio – 2 samples
- Qualitative test –not useful for diagnosis or follow up
- Annual test

Nephropathy

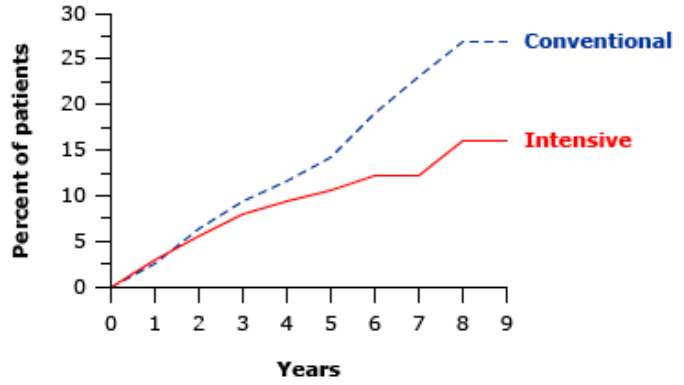
- In Type 1 Diabetes, albuminuria is typically associated with retinopathy
- Rapid decline in eGFR is a greater prognostic importance as albuminuria can be variable and may regress
- However long duration of albuminuria (even after regression) can lead to up to four fold decline in eGFR when compared to patients with normoalbuminuria

Nephropathy

Management:

- Optimise glycaemia
- Optimise blood pressure
- ACE inhibitor /ARB renal protection
- SGLT2 inhibitor
  - CREDENCE Study
    - Type 2 DM + Chronic Kidney Disease (CKD)
    - eGFR 30–90
    - Urine albumin creatinine ratio (ACR) >30 mg/mmol

Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus



Cumulative incidence of moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time ($p<0.04$).

Data from: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977.

UpToDate®

CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

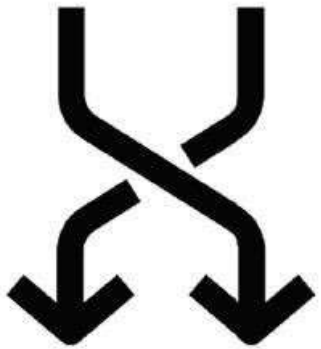
eGFR 57

UACR 927 mg/g

104.7 mg/mmol

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

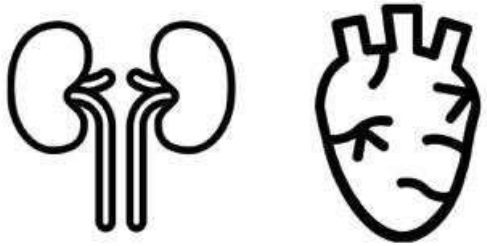


Canagliflozin **Placebo**

Outcomes

Primary outcome

(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

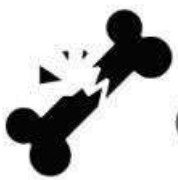
NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

Fractures

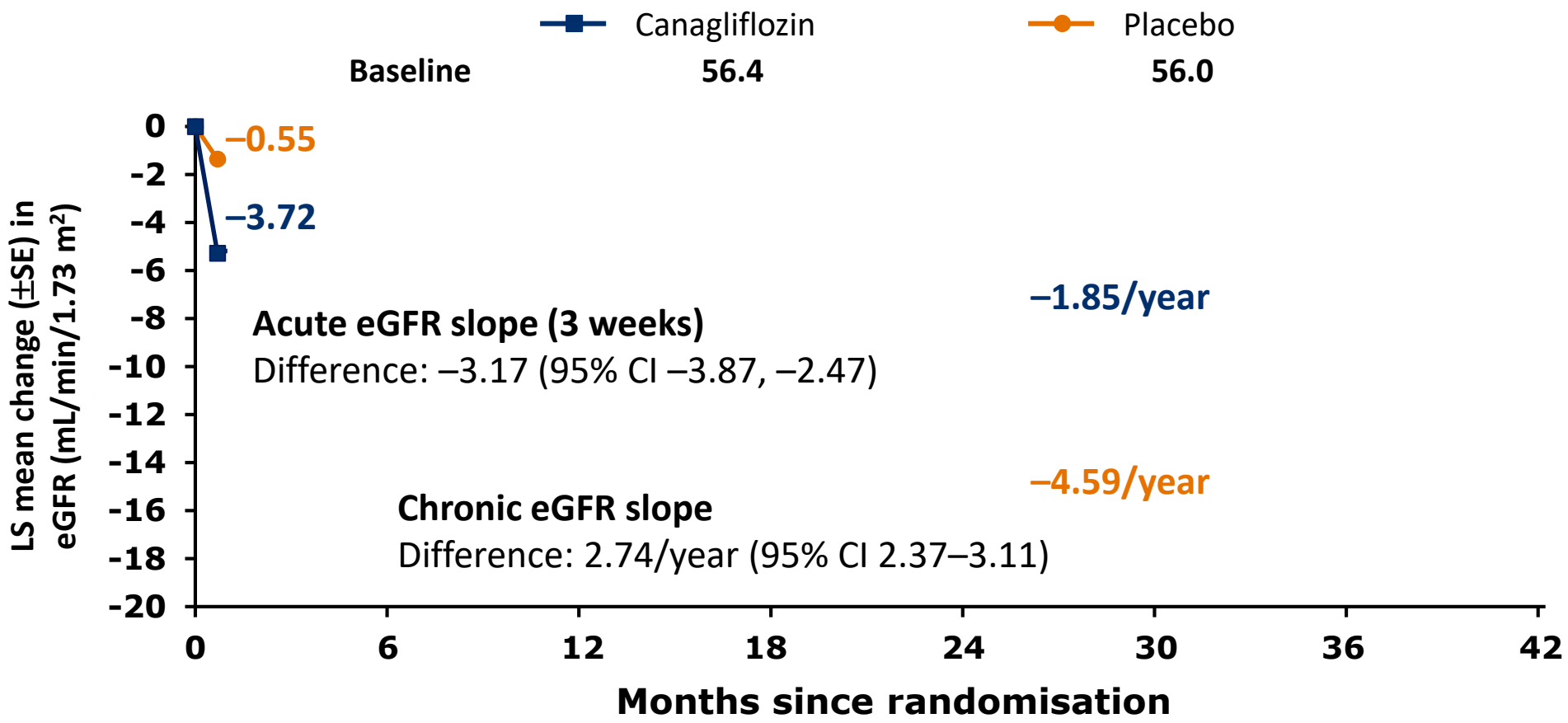


HR 0.98
(95% CI 0.70-1.37)

Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Effects on eGFR in the CREDENCE study



No. of Participants									
Placebo	2,178	2,084	1,985	1,882	1,720	1,536	1,006	583	210
Canagliflozin	2,179	2,074	2,005	1,919	1,782	1,648	1,116	652	241

On treatment

Perkovic et al. N Engl J Med. April 2019. doi:10.1056/NEJMoa1811744.

Neuropathy

- Peripheral & autonomic neuropathy is the commonest form in both type 1 and type 2 diabetes
- Prevalence varies with severity and duration of hyperglycaemia, superimposed upon cardiovascular risk factors
- Approximately 50% of patient with diabetes will develop neuropathy
- Substantial morbidity leading infection, ulcerations & amputations
- Diabetic foot ulcer associated with 2.5 increased risk of mortality

Neuropathy

Classification:

- Distal symmetric polyneuropathy
- Autonomic neuropathy
- Painful diabetic neuropathy
- Individual cranial and peripheral nerve involvement causing focal mononeuropathies, especially affecting the oculomotor nerve (cranial nerve III) and the median nerve
- Asymmetric involvement of multiple peripheral nerves, resulting in a mononeuropathy multiplex

Neuropathy

- Screening
  - 10 gauge monofilament testing
  - pulse / doppler
  - deformity
  - basic foot care
  - moderate to high risk – podiatry led*
  - Always consider other causes
- History
  - Distal symmetrical neuropathy
    - Pin prick & temperature (small fibres)
    - Sensory & vibration (large fibres)
  - Autonomic neuropathy (small fibres)
    - Hypoglycaemia unawareness
    - Orthostatic hypotension
    - Recurrent UTI’s, Sexual dysfunction & ED
    - Resting tachycardia
    - Abnormal sweating
    - Gastroparaesis

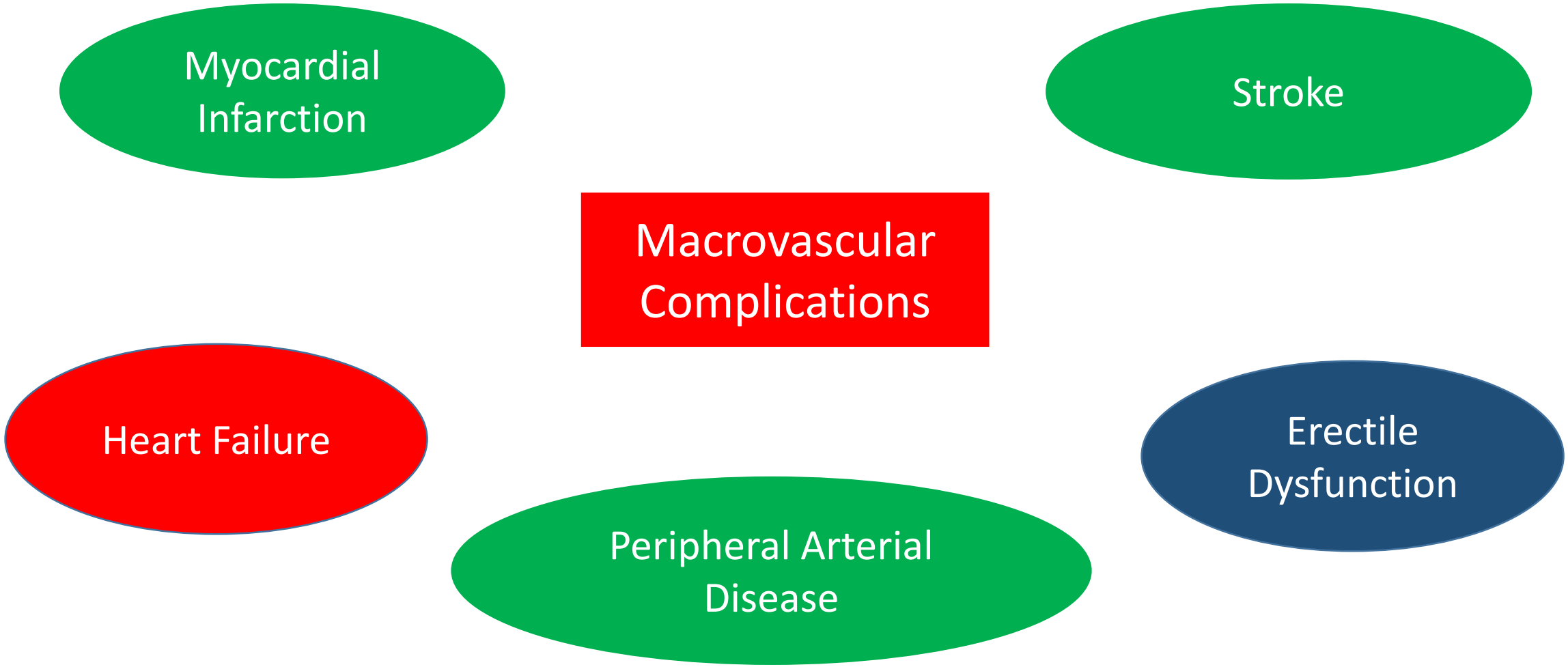
Neuropathy

- Management
  - Glycaemia control
    - Slow down progression, no reversal of neuronal loss
  - Risk assessment & frequency of review
  - Basic foot care
  - Appropriate foot wear
  - Pain management
    - Simple analgesia for mild to moderate then Duloxetine, Amitryptiline, Pregabalin
    - Tapentadol

Neuropathy

- Management of autonomic dysfunction
  - Gastroparaesis
    - Medication review that can affect gut motility – Anticholinergics, GLP-1 RA
    - Prokinetics – Metoclopramide (short term)
      - Domperidone & Erythromycin - tachyphylaxis
    - Insulin Pump Therapy (Type 1 DM)
    - Gastric pacemaker
  - Orthostatic hypotension
    - Medication review
    - Adequate salt & fluid intake
    - Exercise to avoid deconditioning
    - Drugs - Midodrine

Macrovascular

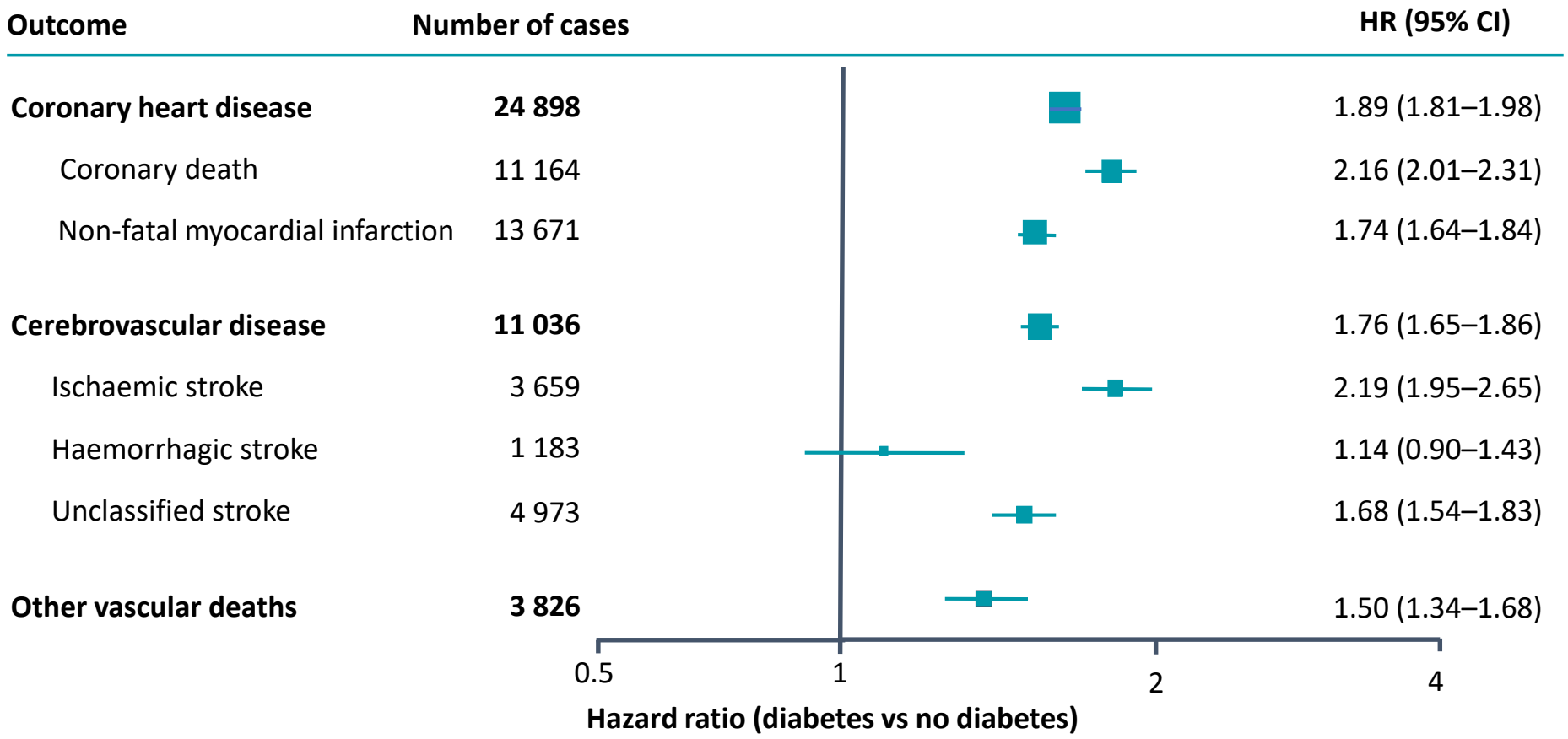


INTERVENTION	NNT OVER 5 YEARS TO PREVENT 1 CV EVENT
Lowering HbA1C by 11mmol/mol (1%)	119
Lowering cholesterol by 1mmol/l	44
Lowering BP by 10/5mmHg	34

Type 2 Diabetes & CVD

- CVD remains the leading cause of death in T2D
    - Overall, CVD risk is around double in those with T2D *(Emerging Risk Factors Collaboration, Lancet 2010)*
- Despite optimal treatment of risk factors, there is still significant residual CV risk in those with diabetes
    - TNT trial *(NEJM 2005),* STENO-2 study 21-year follow-up *(Diabetologia 2016)*

Diabetes and the risk of vascular disease



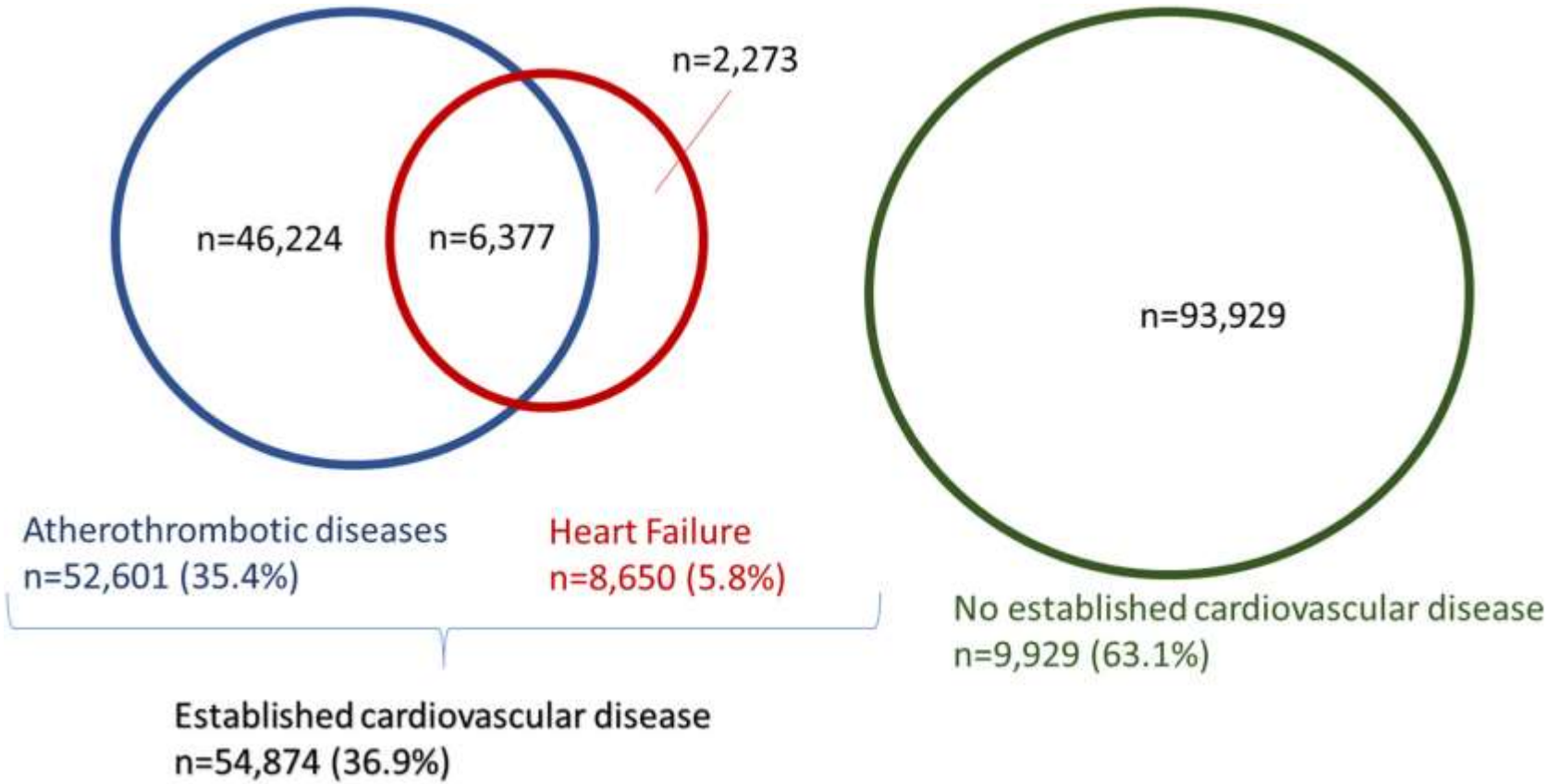
Data from 528,877 participants – adjusted for age, sex, cohort, SBP, smoking, BMI.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; I^2, evolution of heterogeneity; SBP, systolic blood pressure
Emerging Risk Factors Collaboration et al. Lancet 2010;375:2215–22

Diabetes Ther
https://doi.org/10.1007/s13300-019-00698-9

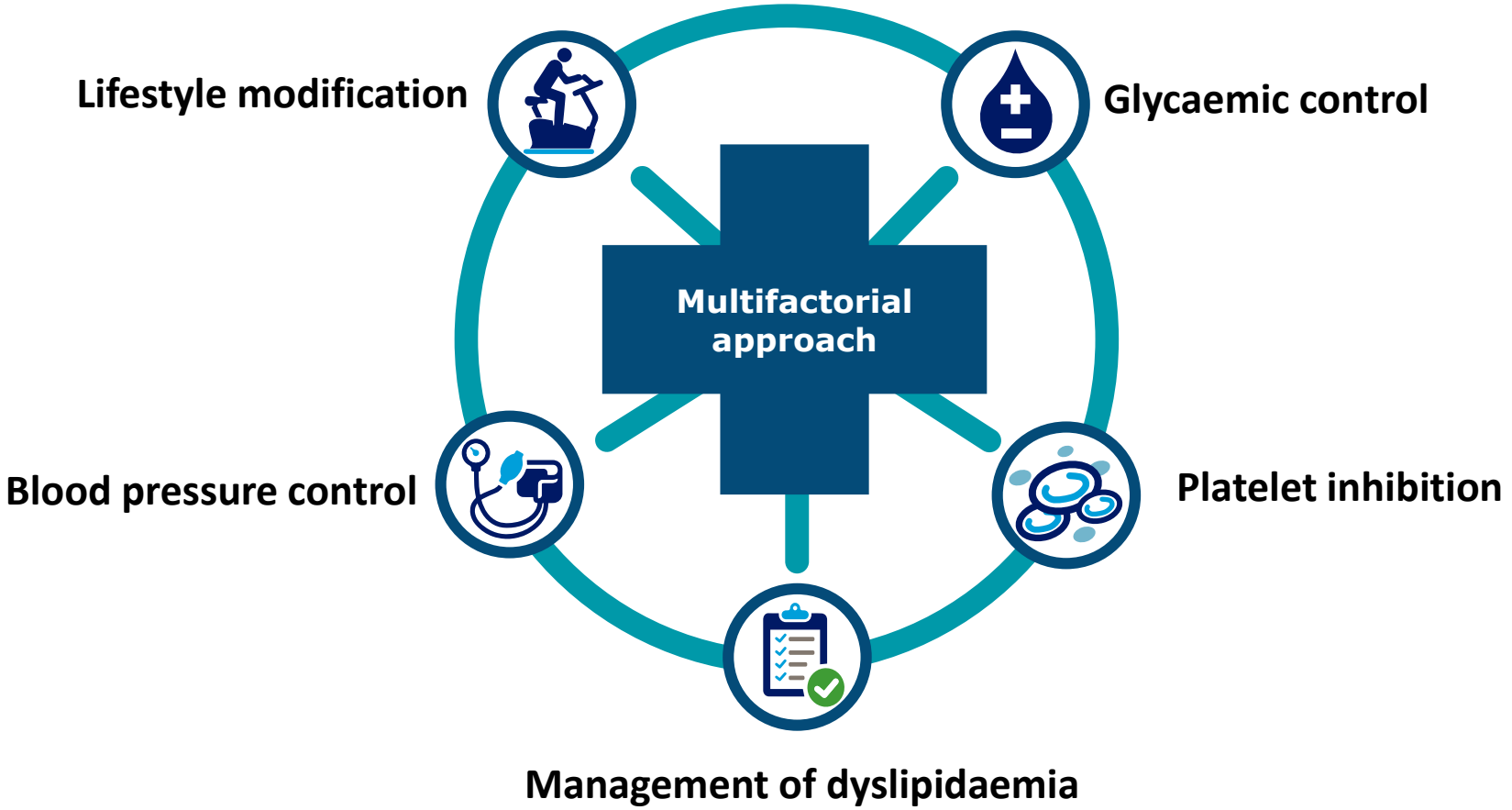
ORIGINAL RESEARCH

Prevalence of Established Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus in the UK

Dominik Lautsch · Tongtong Wang · Lingfeng Yang · Swapnil N. Rajpathak



How do we modify CV risk in T2D?

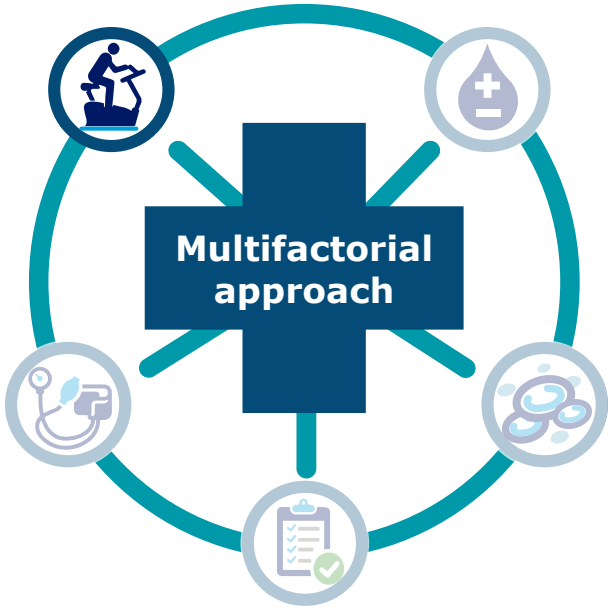


CV, cardiovascular

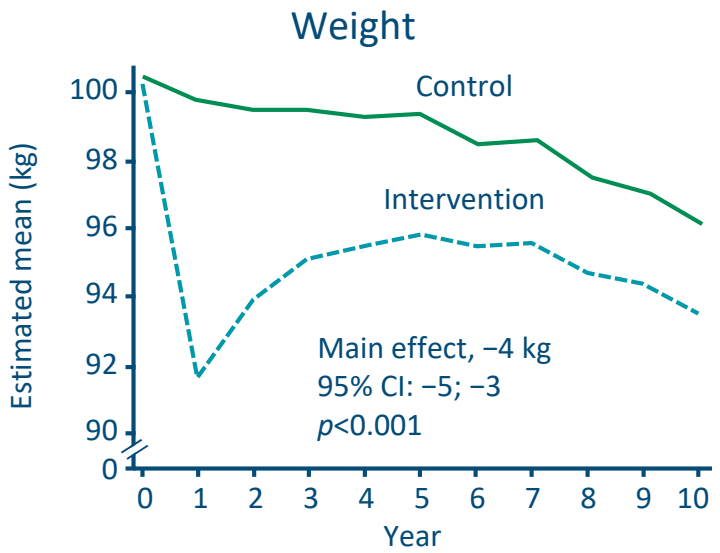
Rydén *et al. Eur Heart J* 2013;34:3035–87; Fox *et al. Diabetes Care* 2015;38:1777–803; Piepoli *et al. Eur Heart J* 2016;37:2315–81

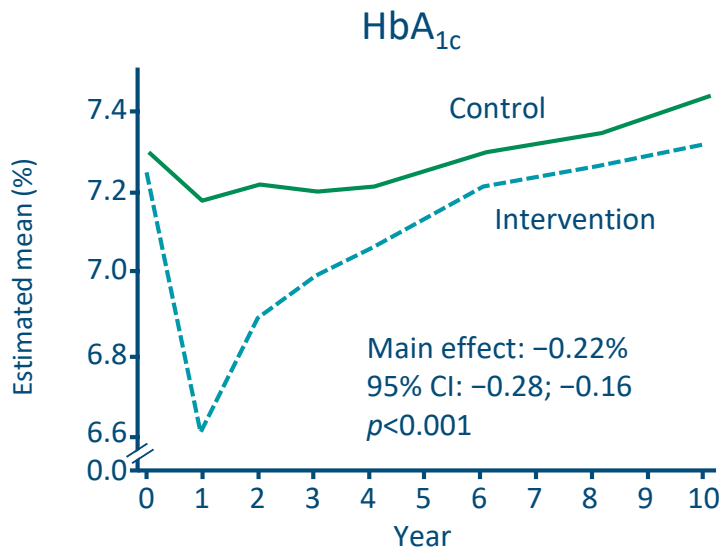
Effects of modifying CV risk factors in diabetes:

Lifestyle modification



Improvements in CV risk factors, and glucose-lowering medications





Look AHEAD, 2013

The Look AHEAD Research Group. *N Engl J Med* 2013;369:145–54

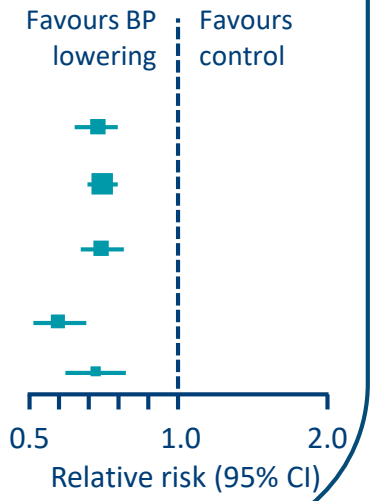
Effects of modifying CV risk factors in diabetes:

Blood pressure control

A 10 mmHg reduction in systolic blood pressure was associated with a significant reduction in macrovascular outcomes

Outcome	No. of studies	BP lowering Events	BP lowering Participa			Relative risk (95% CI)
Mortality	20	2 334	27 693			0.87 (0.78; 0.96)
CV disease	17	3 230	25 756			0.89 (0.83; 0.95)
CHD	17	1 390	26 150		61	0.88 (0.80; 0.98)
Stroke	19	1 350	27 614	1 475	26 447	0.73 (0.64; 0.83)
Heart failure	13	1 235	21 684	1 348	20 791	0.86 (0.74; 1.00)

15 %



Emdin *et al. JAMA* 2015: Meta-analysis

Emdin CA, et al. JAMA. 2015 Feb 10;313(6):603-15

Blood pressure

Age < 80

- Clinic BP < 140/90
- ABPM or HBPM < 135/85
- Type 1 DM < 135/85

Age ≥ 80

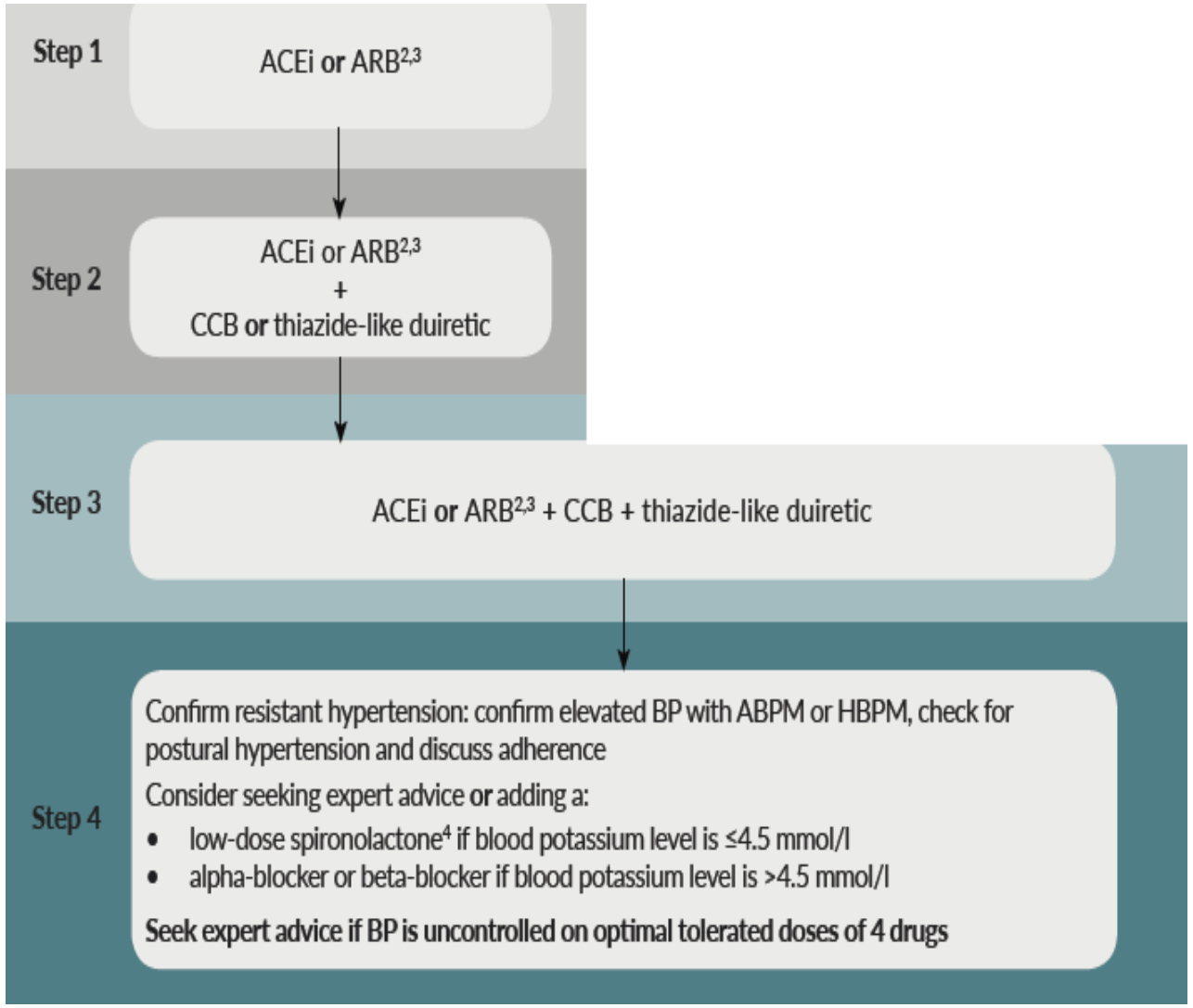
- Clinic BP < 150/90
- ABPM or HBPM < 145/85

Postural Hypotension

- Base target on standing BP

CKD, albuminuria > 70mg/mmol

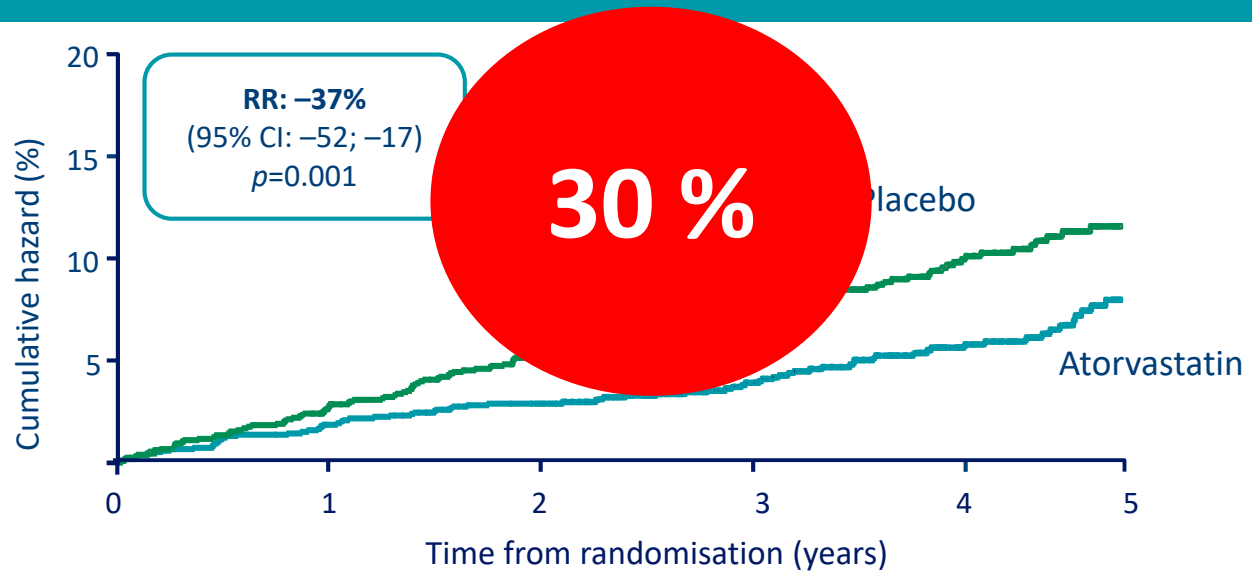
- <130/80 (systolic 120 - 129 mmHg)



Effects of modifying CV risk factors in diabetes:

Management of dyslipidaemia

37% reduction in acute coronary events, coronary revascularisation or stroke



Colhoun *et al. Lancet* 2004

Adapted from Colhoun *et al. Lancet* 2004;364:685–96

Dyslipidaemia

Primary prevention

- Type 1 Diabetes
  - > 40 years
  - diabetes > 10 years
  - established nephropathy
  - CVD risk factors
- Type 2 Diabetes
  - 10% or greater 10-year risk of developing CVD (QRISK2)

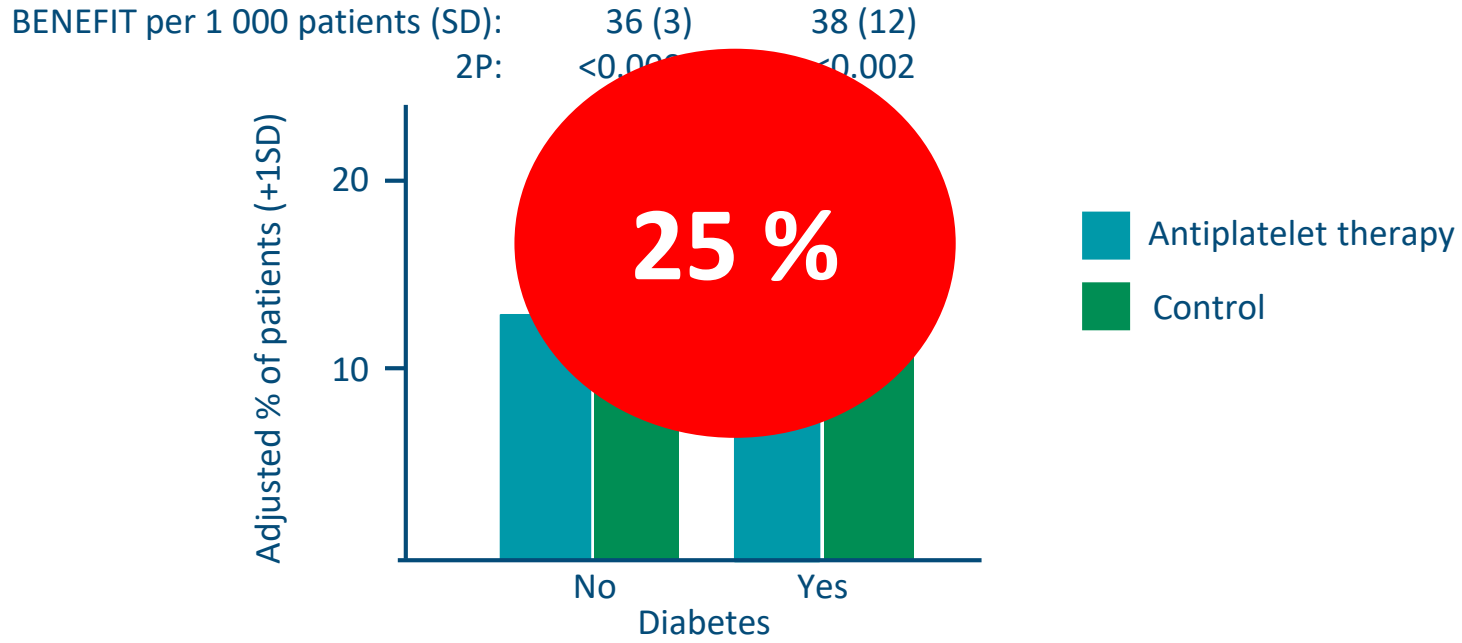
Lipid modification

- Baseline lipid profile
  - non fasting
- Primary prevention
  - Atorvastatin 20 mg
- Secondary prevention
  - Atorvastatin 80 mg
- Target > 40% reduction in non-HDL

Effects of modifying CV risk factors in diabetes:

Platelet inhibition

25% reduction in CV death, non-fatal MI and non-fatal stroke[3]

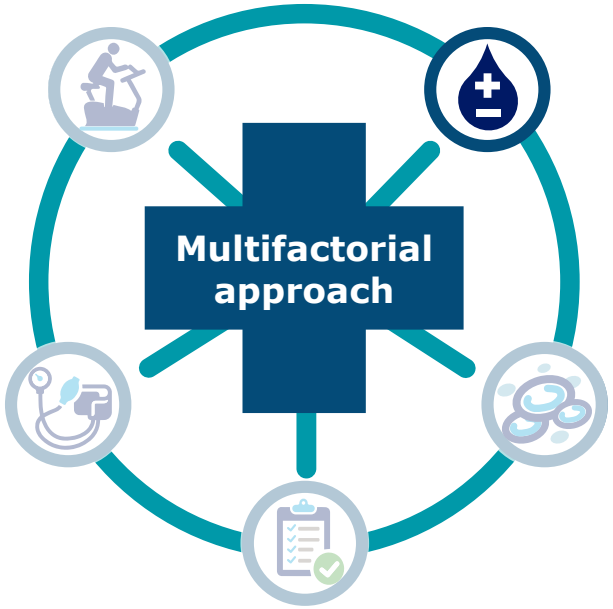


Antiplatelet Trialists' Collaboration, 1994

Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106

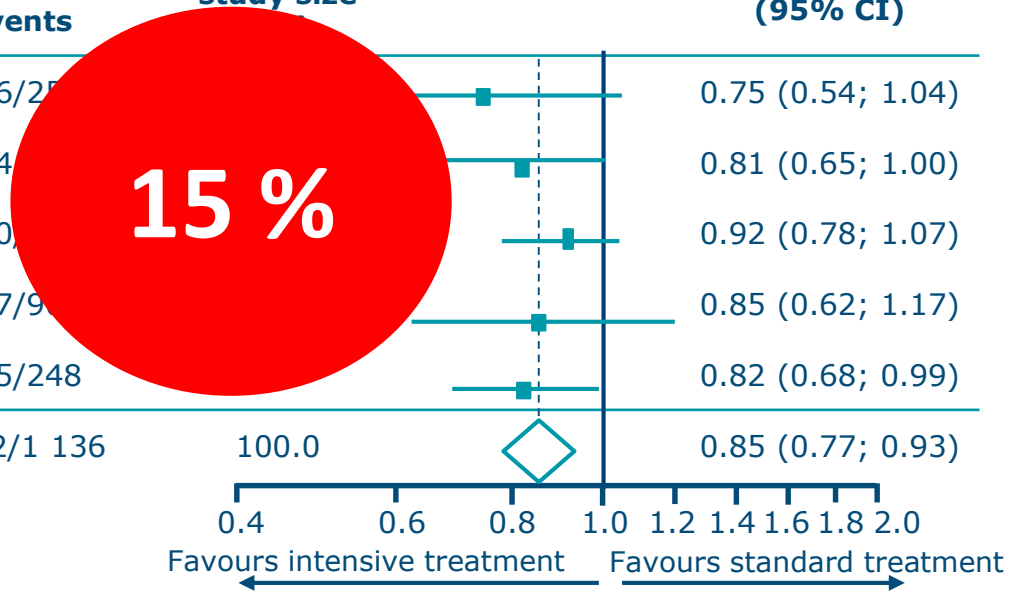
Effects of modifying CV risk factors in diabetes:

Glycaemic control



15% reduction in CHD with intensive glucose control

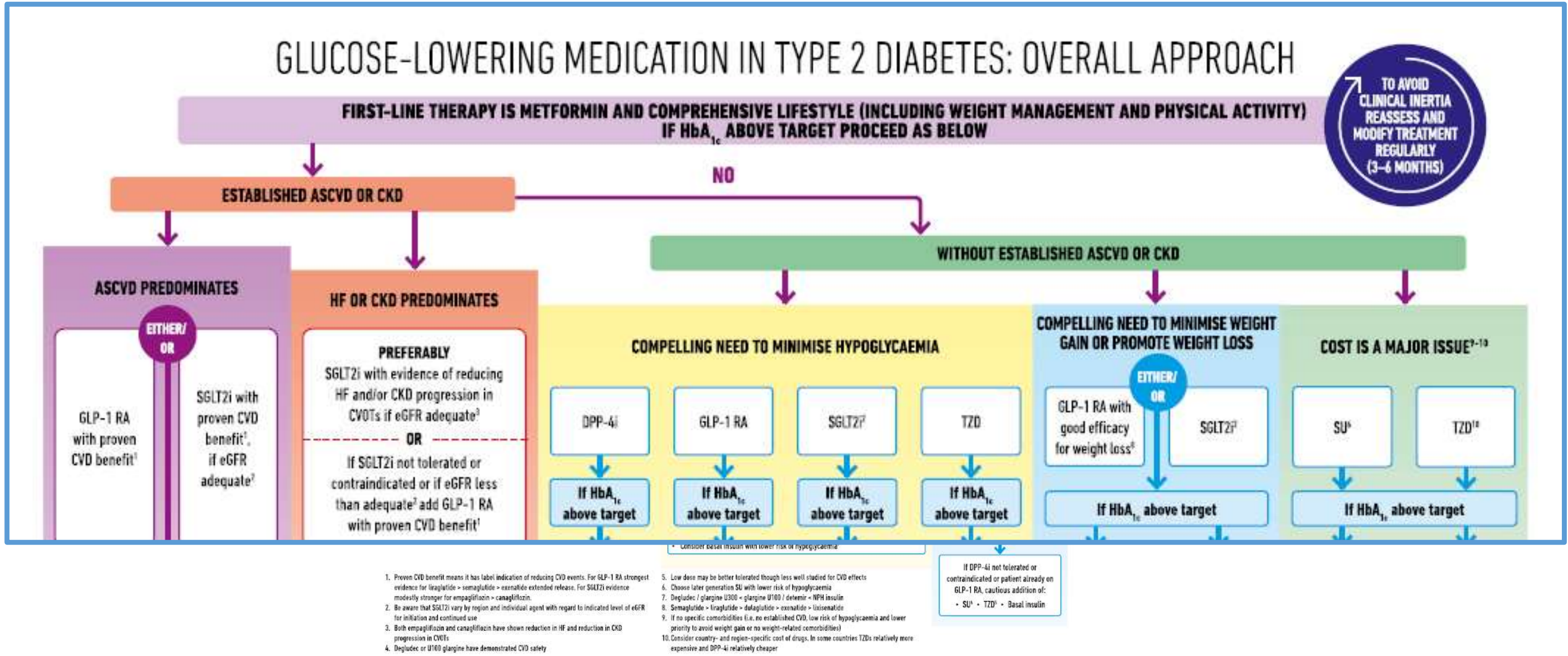
Study	Intensive/standard treatment: Participants	Events	Weight of study size	Odds ratio (95% CI)
UKPDS	3071/1 549	426/2		0.75 (0.54; 1.04)
PROactive	2605/2 633	164		0.81 (0.65; 1.00)
ADVANCE	5571/5 569	310		0.92 (0.78; 1.07)
VADT	892/899	77/9		0.85 (0.62; 1.17)
ACCORD	5128/5123	205/248		0.82 (0.68; 0.99)
Overall	17267/15773	1182/1 136	100.0	0.85 (0.77; 0.93)



Ray *et al. Lancet* 2009

The Look AHEAD Research Group. *N Engl J Med* 2013;369:145–54; 2. ADVANCE Collaborative Group. *Lancet* 2007;370:829–40; 3. Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106; 4. Heart Protection Study Collaborative Group. *Lancet* 2003;361:2005–16; 5. Ray *et al. Lancet* 2009;373:1765–72

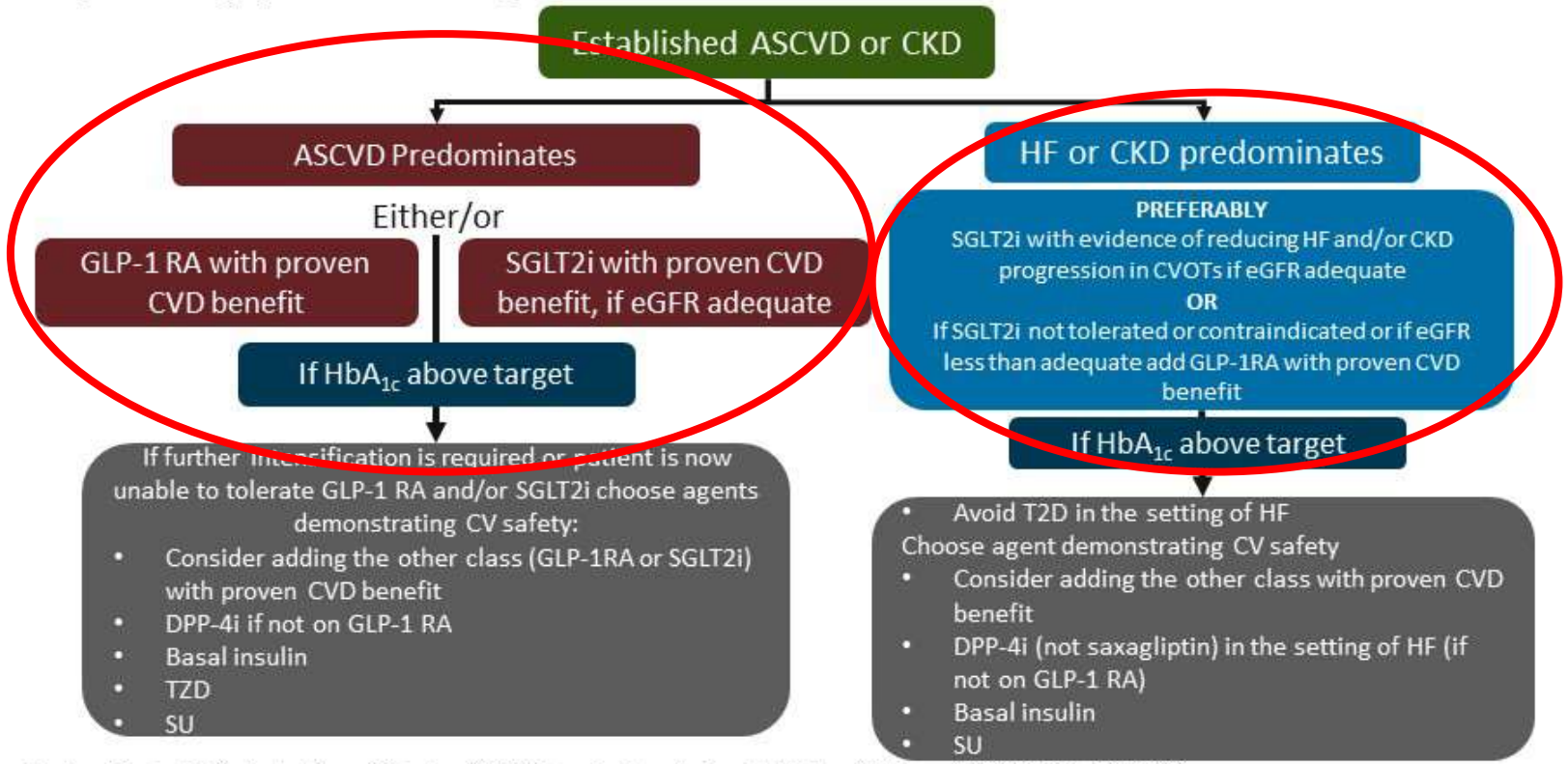
The 2018 EASD/ADA consensus report has incorporated Cardiovascular Outcome Trial Data



The EASD/ADA report is a consensus statement and should not be used as guidance.
ADA = American Diabetes Association; CVOT = cardiovascular outcome trial; EASD = European Association for the Study of Diabetes.
Davies MJ, et al. *Diabetologia* 2018;61:2461–2498.

Pharmacologic Therapy for T2DM: ADA/EASD 2018 Recommendations

Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management



Davies M, et al. *Diabetes Care*. October 2018; [epub ahead of print] https://doi.org/10.2337/dci18-0033.

Conclusion

- Early intensive optimisation of glycaemia is essential in reducing microvascular complications
- Cardiovascular disease remains the leading cause of death in Diabetes
- Optimal management of CV risk factors is essential in reducing macrovascular complications
- SGLT2 inhibitors & GLP-1 receptor agonist have a significant impact on residual CV risk reduction