Diabetes

new challenges, new agents, new order

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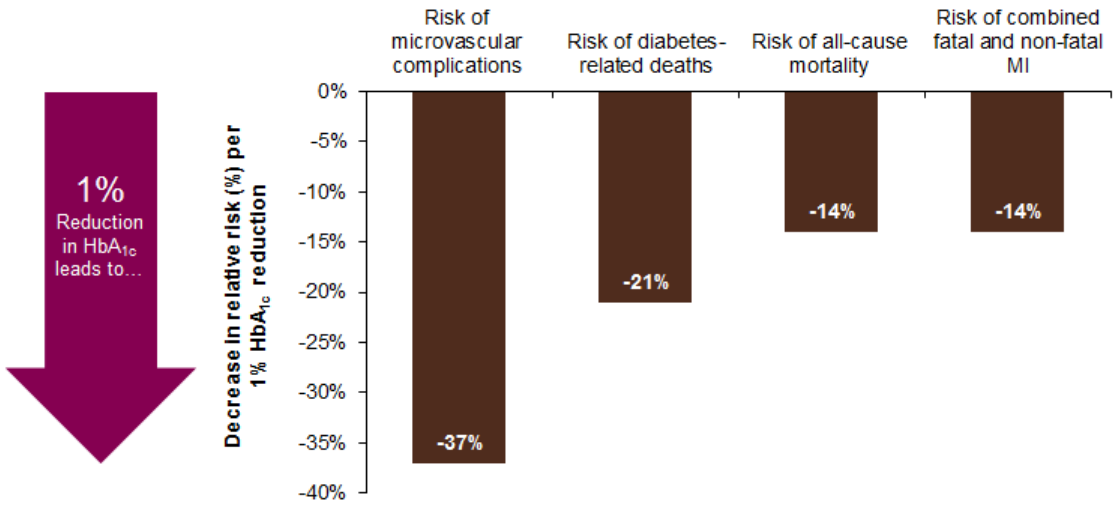
Overview

- Cardiovascular disease – unmet needs
- Treating evident and residual risk
- Integrating care
- Improving outcomes


TODAY
340
people will lose their lives to CVD
...more than
90
people will be younger than
75
5.9 MILLION
people fight their daily battles with CVD
430
people will go to hospital due to a heart attack
145
people will die from a heart attack
12
babies
will be diagnosed with a heart defect

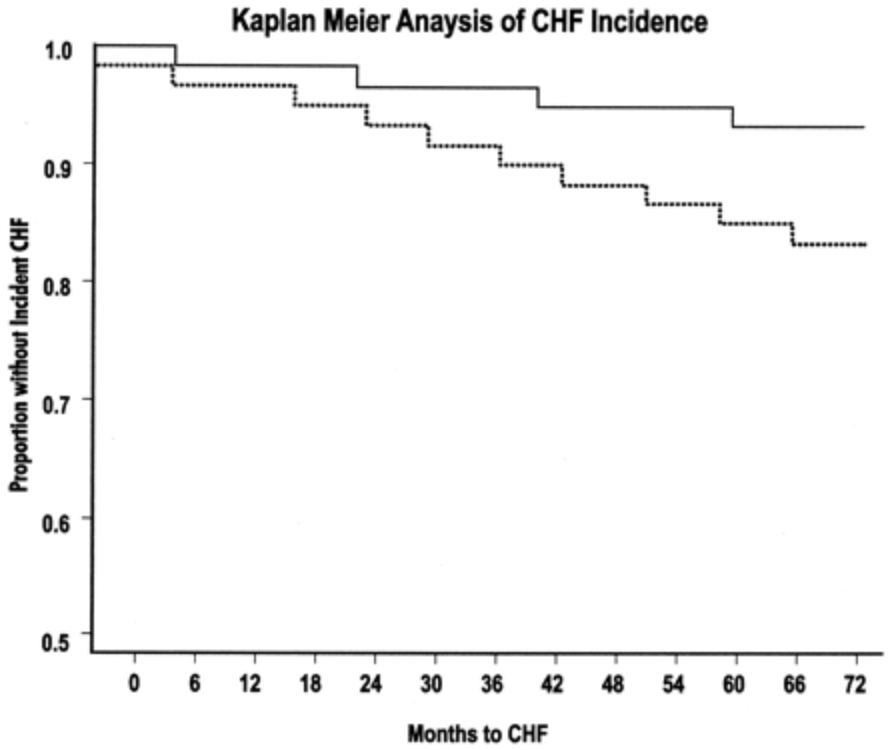
Observational analysis of UKPDS data: Reduction in HbA_{1c} leads to improvements in complications [1]



Adapted from Stratton IM et al (2000) *BMJ* **321**: 405–12.

Observational analysis of relation between glycaemic exposure and complications of diabetes as estimated by decrease in risk for 1% reduction in HbA_{1c} concentration, measured at baseline and as updated mean, controlled for age at diagnosis of diabetes, sex, ethnic group, smoking, albuminuria, systolic blood pressure, HDL and LDL cholesterol, and triglycerides: 3,642 white, Asian Indian and Afro-Caribbean UKPDS patients were included in analyses of relative risk.

The Incidence of Congestive Heart Failure in Type 2 Diabetes



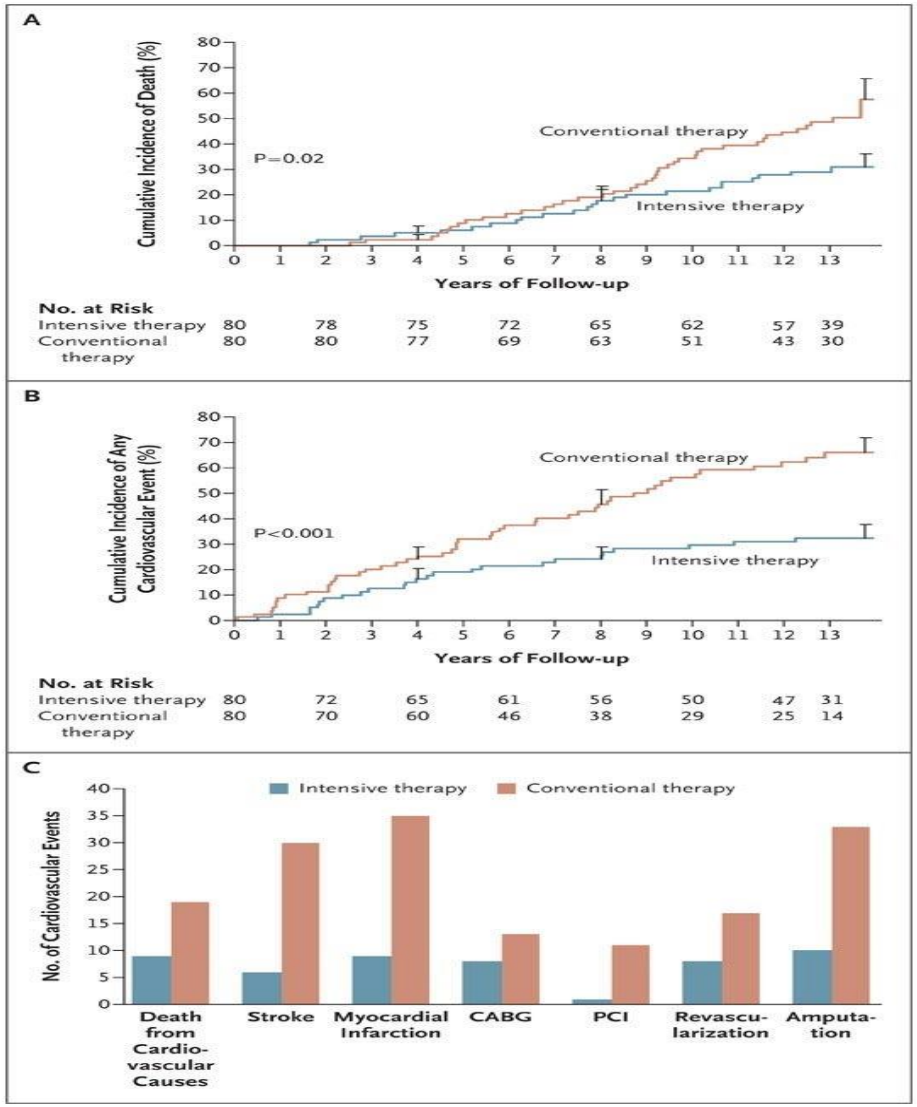
Nichols GA Diabetes Care 2004

Cardiovascular Disease in Type 2 Diabetes

- Cardiovascular disease (CVD) accounts for 80% of the premature morbidity and mortality for individuals with diabetes
- Controlling individual/multiple CVD risk factors may prevent its development.
- Probability for developing coronary heart disease has decreased in the last decade
- Approx 50% of patients do not meet goals*

* Ali MK et al NEJM 2013

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes



Steno-2 NEJM 2008

Intensive therapy: micro- and macrovascular outcomes

Study	Microvascular		Macrovascular		Mortality	
UKPDS[1,2]	↓	↓	↔	↓	↔	↓
ACCORD[3–5]	↓	NR	↔	↔	↑	↑
ADVANCE[6,7]	↓	↓*	↔	↔	↔	↔
VADT[8,9]	↓	NR	↔	↓	↔	↔

Initial trial Long-term follow-up

*End-stage renal disease.

ACCORD=Action to Control Cardiovascular Risk in Diabetes; ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; NR=not reported; UKPDS=UK Prospective Diabetes Study; VADT=Veterans Affairs Diabetes Trial.

2545–59; 4. ACCORD Study Group (2011) *N Engl J Med* **364**: 818–28; 5. Ismail-Beigi F et al (2010) *Lancet* **376**: 419–30; 6. Patel A et al (2008) *N Engl J Med* **358**: 2560–72; 7. Zoungas S et al (2014) *N Engl J Med* **371**: 1392–406; 8. Duckworth W et al (2009) *N Engl J Med* **360**: 129–39; 9. Hayward RA et al (2015) *N Engl J Med* **372**: 2197–206

Hypoglycaemia and treatment intensification

	ACCORD	ADVANCE	VADT
Mean Age (yrs)	62	66	60
Median HbA1c %	8.1	7.2	9.4
Achieved HbA1c %	6.4 v 7.5	6.3 v 7.0	6.9 v 8.5
Hypoglycaemia %	16.2 v 5.1	2.7 v 1.5	21.2 v 9.9

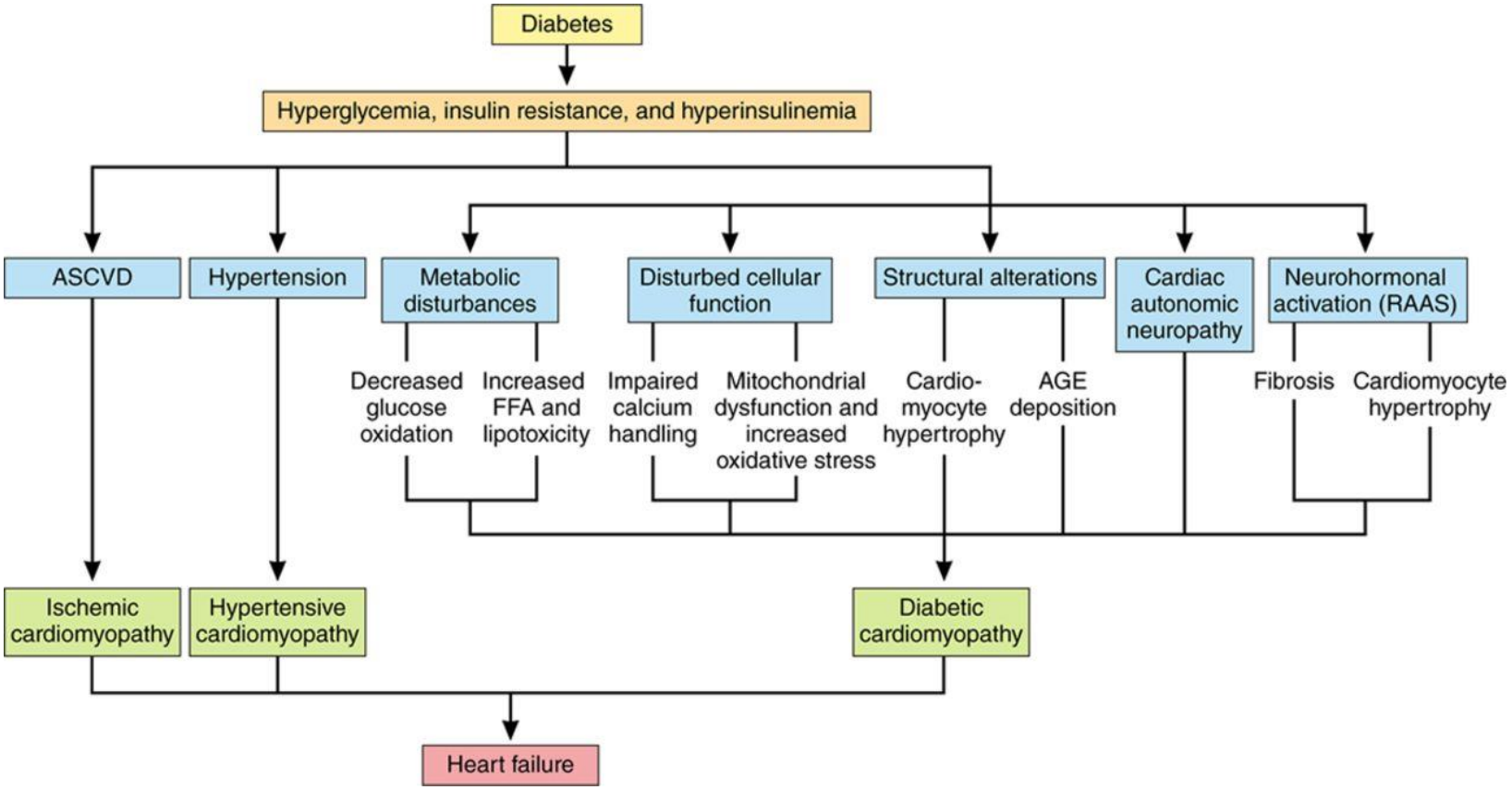
Antihyperglycemic Agents in Type 2 Diabetes

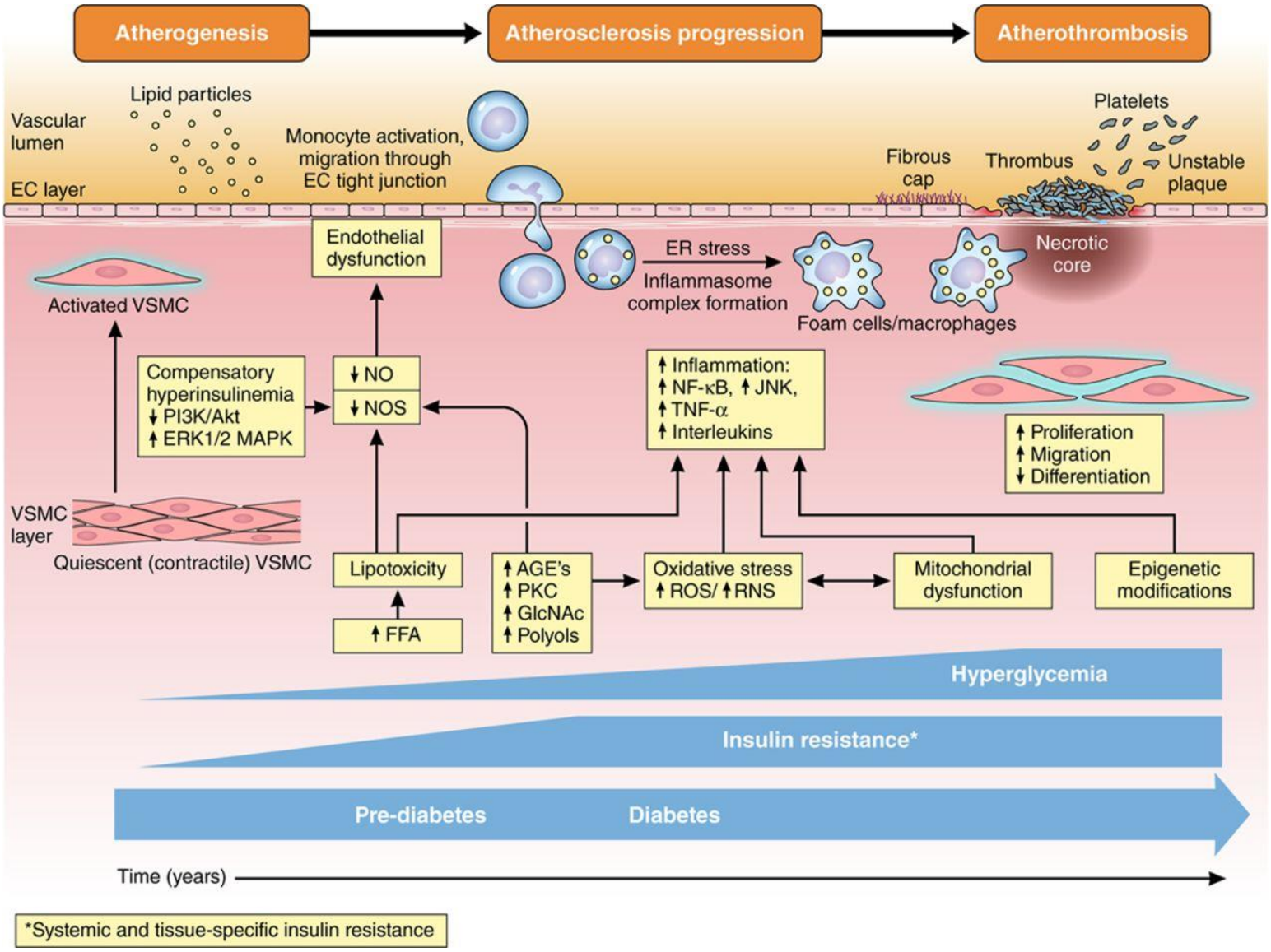
Class	A1C Reduction	Hypo-Glycemia	Weight Change	CVD Risk Factors	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	2	Kidney, liver
Insulin, Long-acting	1.5 - 2.5	Yes	Gain	TG	1, Injected	None
Insulin, Rapid-acting	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Sulfonylureas	1.5	Yes	Gain	None	1	Essentially none
Thiazolidinediones	0.5 - 1.4	No	Gain	Variable	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	Essentially none
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	Essentially none
Alpha-glucosidase Inhibitors	0.5 - 0.8	No	Neutral	Minimal	3	Essentially none
Amylin-mimetics	0.5 - 1.0	No	Loss	With weight loss	3, Injected	None
GLP-1R Agonist	0.5 - 1.0	No	Loss	With weight loss	2, Injected	Kidney
DPP-4 Inhibitor	0.6 - 0.8	No	Neutral	None	1	None
Bile acid sequestrant	0.5	No	Neutral	LDL	1-2	Severe TGs
Bromocriptine	0.7	No	Neutral	Minimal	1	Essentially none

Cardiovascular Disease in Type 2 Diabetes

- 10 years post intensive-glucose control in UKPDS - 15% and 13% relative risk reduction in CVD and all cause mortality*
- Safety concerns raised with glucose lowering strategies and use of peroxisome proliferator-activated receptor agonists
- Tight glycaemic control and weight gain may increase risk of heart failure 7% (95% CI 1.0 -13.6)%**

- Holman RR et al NEJM 2008*
- Udell JA et al Lancet Diabetes Endocrinology 2015**


Diabetes
Hyperglycemia, insulin resistance, and hyperinsulinemia
ASCVD
Hypertension
Metabolic disturbances
Disturbed cellular function
Structural alterations
Cardiac autonomic neuropathy
Neurohormonal activation (RAAS)
Decreased glucose oxidation
Increased FFA and lipotoxicity
Impaired calcium handling
Mitochondrial dysfunction and increased oxidative stress
Cardio-myocyte hypertrophy
AGE deposition
Fibrosis
Cardiomyocyte hypertrophy
Ischemic cardiomyopathy
Hypertensive cardiomyopathy
Diabetic cardiomyopathy
Heart failure

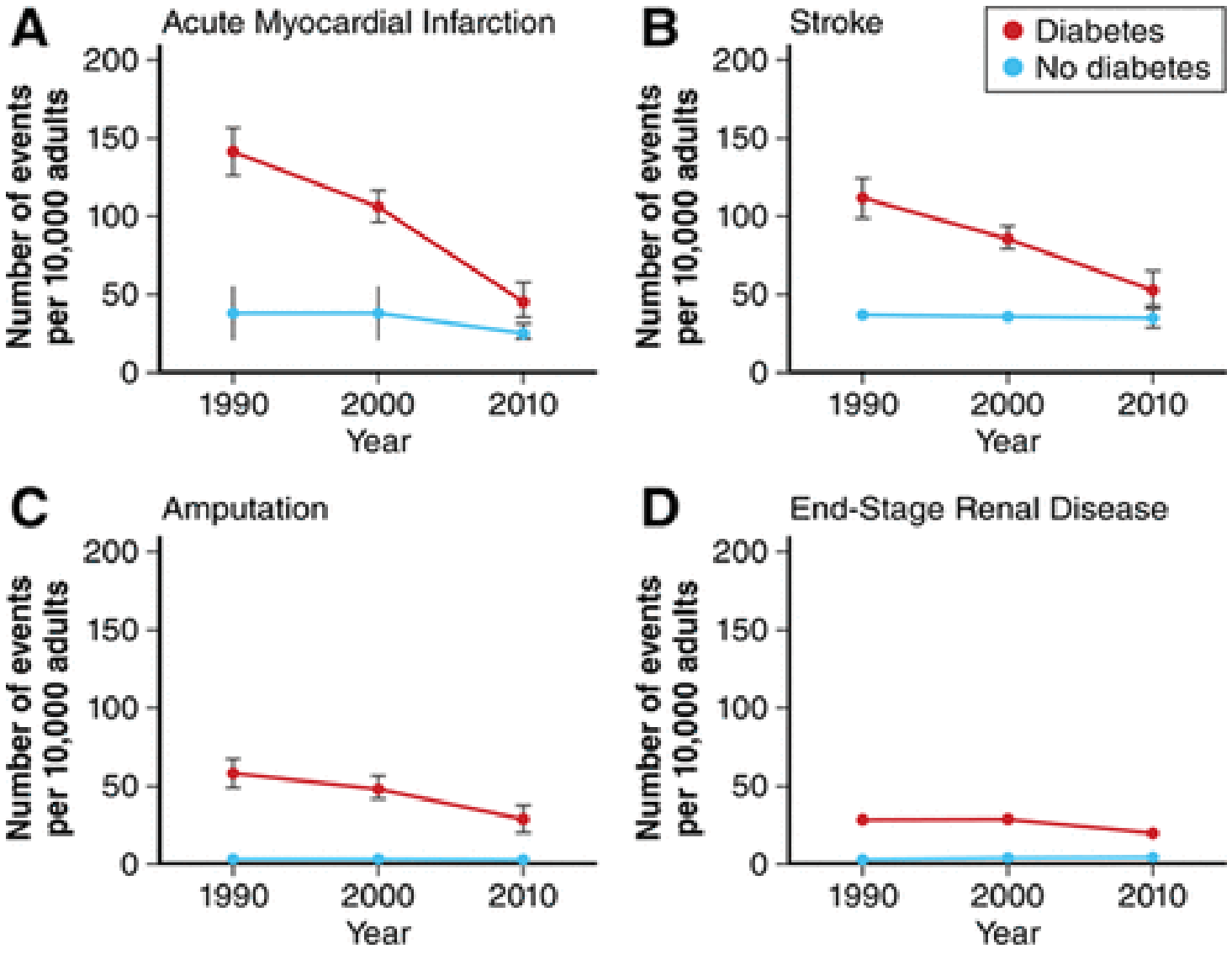

Atherogenesis
Atherosclerosis progression
Atherothrombosis
Lipid particles
Vascular lumen
EC layer
Monocyte activation, migration through EC tight junction
Platelets
Fibrous cap
Thrombus
Unstable plaque
Endothelial dysfunction
ER stress
Inflammasome complex formation
Necrotic core
Foam cells/macrophages
Activated VSMC
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

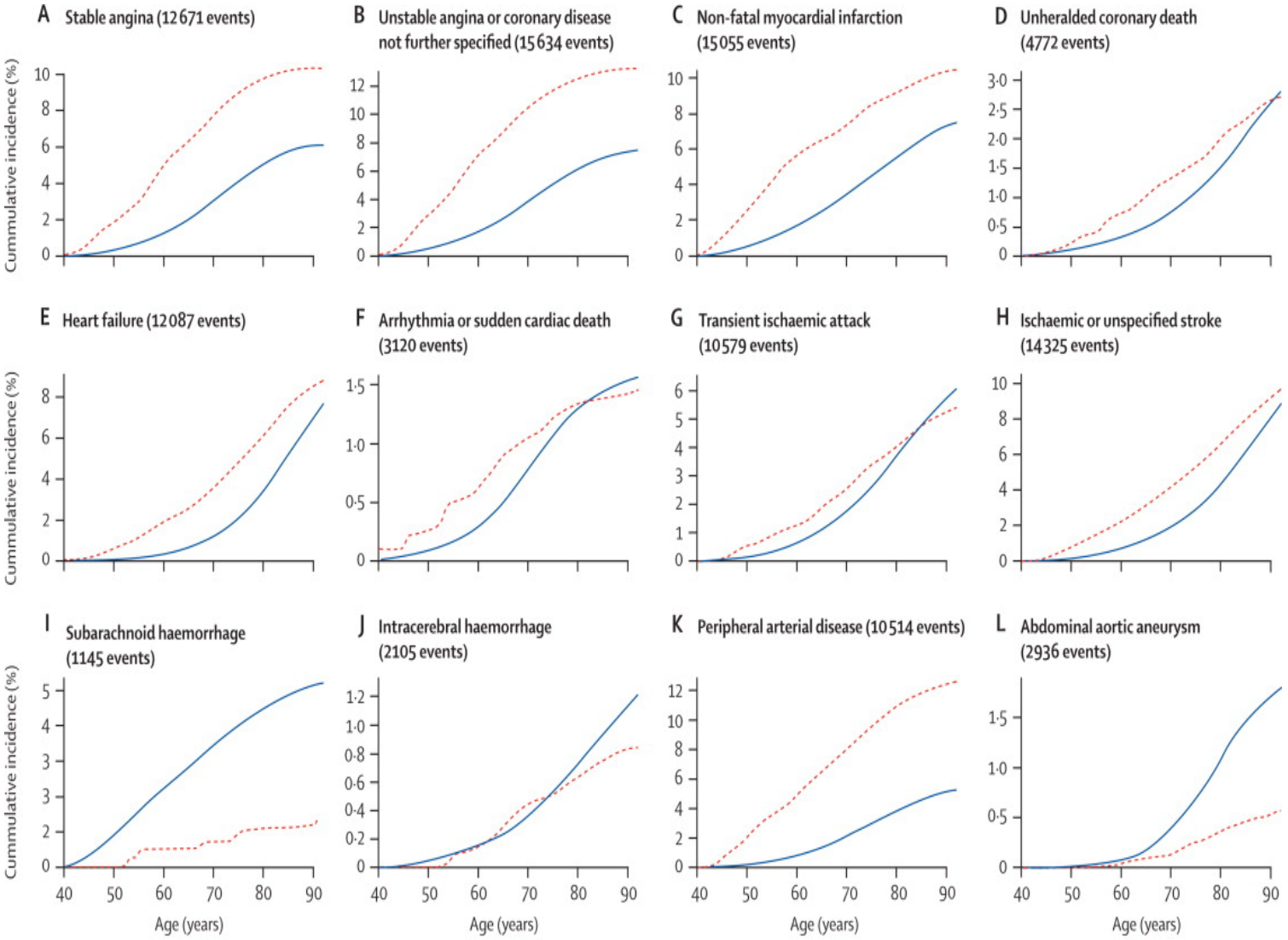
CALIBER

(CArdiovascular disease research
using LInked Bespoke studies and Electronic health Records)

- Primary care electronic health data
- 1.9 M individuals – 35,000 with T2DM
- Aged 30 years between Jan 1, 1998, and March 25, 2010 without CVD

Shah AD Lancet Diabetes & Endocrinology 2015


A
Acute Myocardial Infarction
Number of events per 10,000 adults
200
150
100
50
0
1990
2000
2010
Year
B
Stroke
Diabetes
No diabetes
Number of events per 10,000 adults
200
150
100
50
0
1990
2000
2010
Year
C
Amputation
Number of events per 10,000 adults
200
150
100
50
0
1990
2000
2010
Year
D
End-Stage Renal Disease
Number of events per 10,000 adults
200
150
100
50
0
1990
2000
2010
Year


A Stable angina (12671 events)
B Unstable angina or coronary disease not further specified (15634 events)
C Non-fatal myocardial infarction (15055 events)
D Unheralded coronary death (4772 events)
E Heart failure (12087 events)
F Arrhythmia or sudden cardiac death (3120 events)
G Transient ischaemic attack (10579 events)
H Ischaemic or unspecified stroke (14325 events)
I Subarachnoid haemorrhage (1145 events)
J Intracerebral haemorrhage (2105 events)
K Peripheral arterial disease (10514 events)
L Abdominal aortic aneurysm (2936 events)
Cummulative incidence (%)
Age (years)
Number of patients 40 years 50 years 60 years 70 years 80 years 90 years
No diabetes 297335 265580 224060 133605 76384 20679
Type 2 diabetes 924 2330 4226 4962 3229 717

CALIBER

(CArdiovascular disease research
using LInked Bespoke studies and Electronic health Records)

Risk of developing CVD by age 80 years

- 30·7 vs 58.2% for women without vs with diabetes
- 44·3% vs 68% for men without vs with diabetes

CALIBER

(CArdiovascular disease research
using LInked Bespoke studies and Electronic health Records)

- Over 5 years 6137[17·9%] with CVD

  Peripheral arterial disease in 992 [16·2%]

  Heart failure in 866 [14·1%]

- No association with arrhythmia or sudden cardiac death (0·95 [0·76–1·19])


In 2015, IDF estimates that:
One in 11 adults has diabetes
One in two adults with diabetes is undiagnosed
12% of global health expenditure is spent on diabetes
One in seven births is affected by gestational diabetes
542,000 children have type 1 diabetes


There are three main types of diabetes:
Type 1 diabetes, type 2 diabetes and gestational diabetes
Poorly managed diabetes leads to serious complications and early death
With good self-management and health professional support, people with diabetes can live a long, healthy life

National Diabetes Audit:

helping to improve diabetes care

NHS Digital

Important Patient Information

This GP practice is taking part in an important national project about diabetes care and treatment in the NHS. The project is called the National Diabetes Audit (NDA).

To take part, your GP practice will share information about your diabetes care and treatment with the NDA. The type of information, and how it is shared, is controlled by law and enforced by strict rules of confidentiality and security.

For further information about how your information is used please see the NDA patient information leaflet.

Taking part in the NDA shows that this GP practice is committed to improving care for people with diabetes.

If you do not want your information to be used, please inform the receptionist, your GP or nurse. This will not affect your care.

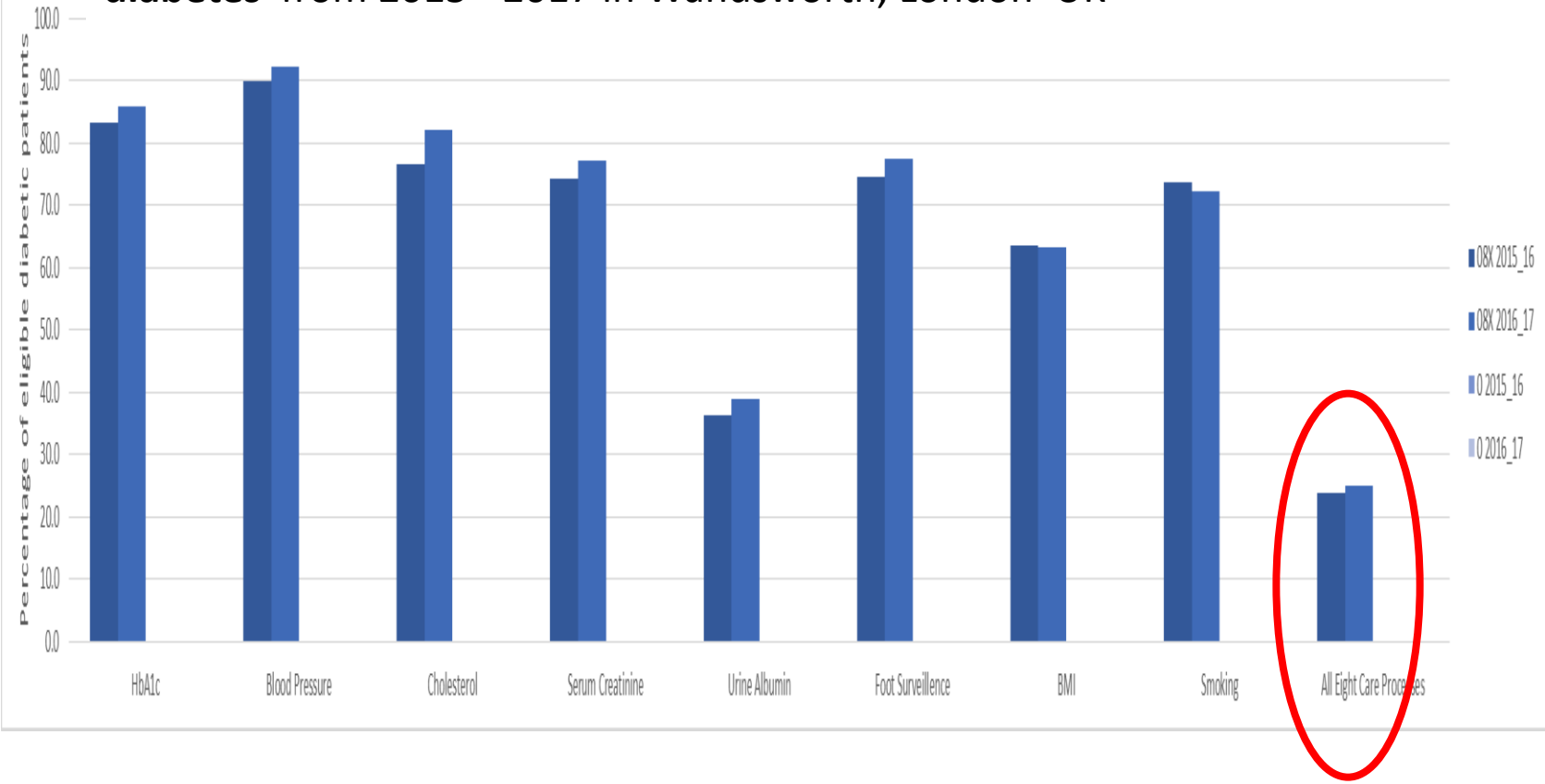
More information is available – please ask a member of staff for a patient information leaflet.

Public Health England

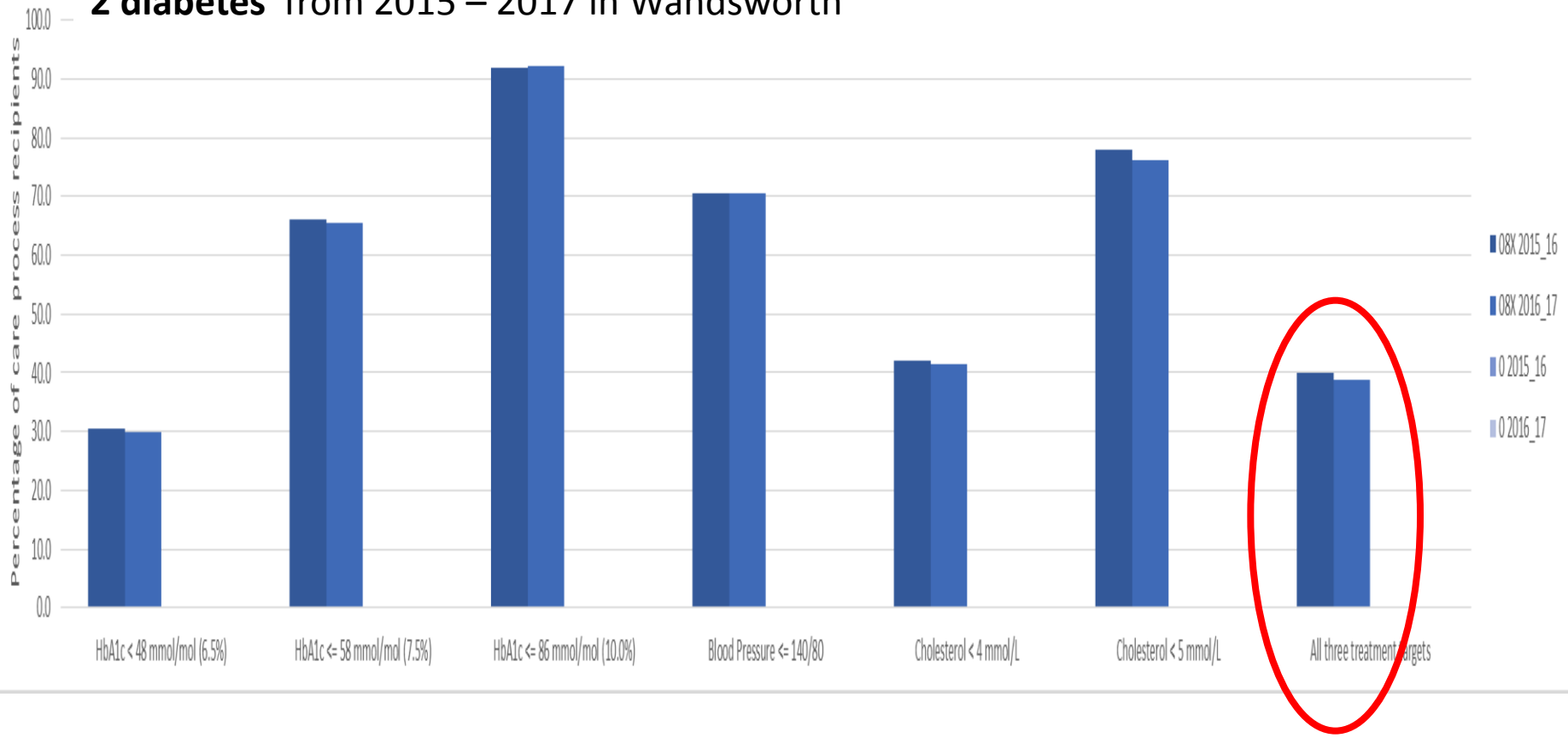
DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

HQIP

The percentage of Processes of Care achieved for patients with **type 1 diabetes** from 2015 - 2017 in Wandsworth, London UK



The percentage of outcomes achieved for processes of care for patients with **type 2 diabetes** from 2015 – 2017 in Wandsworth



Key findings from the audit

- **Diabetes is responsible for relatively greater risk of ill health in younger people**
- **Under the age of 80, attention to heart protection is important and beneficial**
- **Reducing the proportion of people with diabetes and heart problems in hospital from approximately 20-25% needs to be addressed**
- **Patients adhering to process had much better outcomes**

Do No Harm

Novel treatments to demonstrate CV safety and benefits of glucose-lowering medications using combined primary CV endpoints are evaluated, which include CV mortality, non-fatal myocardial infarction (MI) and non-fatal stroke (3-point-MACE).

Cardiovascular Outcome Trials (CVOT)

- FDA and National Institute for Health and Care Excellence (NICE) are demanding an increased inclusion and implementation of real world data to complement results of CVOTs
- Mechanisms?
- Hypoglycaemia?

Empagliflozin and CVD outcomes in T2DM*

- SGLT-2 inhibitor as mono- or add-on therapy
- CVD morbidity & mortality in high risk patients with >1 of the following :-
  - Previous MI
  - multi-vessel CHD + unstable angina
  - Positive non-invasive test for CHD
  - History of stroke
  - Occlusive peripheral artery disease

* Zinman B et al NEJM 2015

EMPA Outcomes

- Primary: composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke.
- Secondary: composite of the primary outcome plus hospitalization for unstable angina
- Intention-to-treat analysis approach
- 7020 (3yr observation) in primary analysis

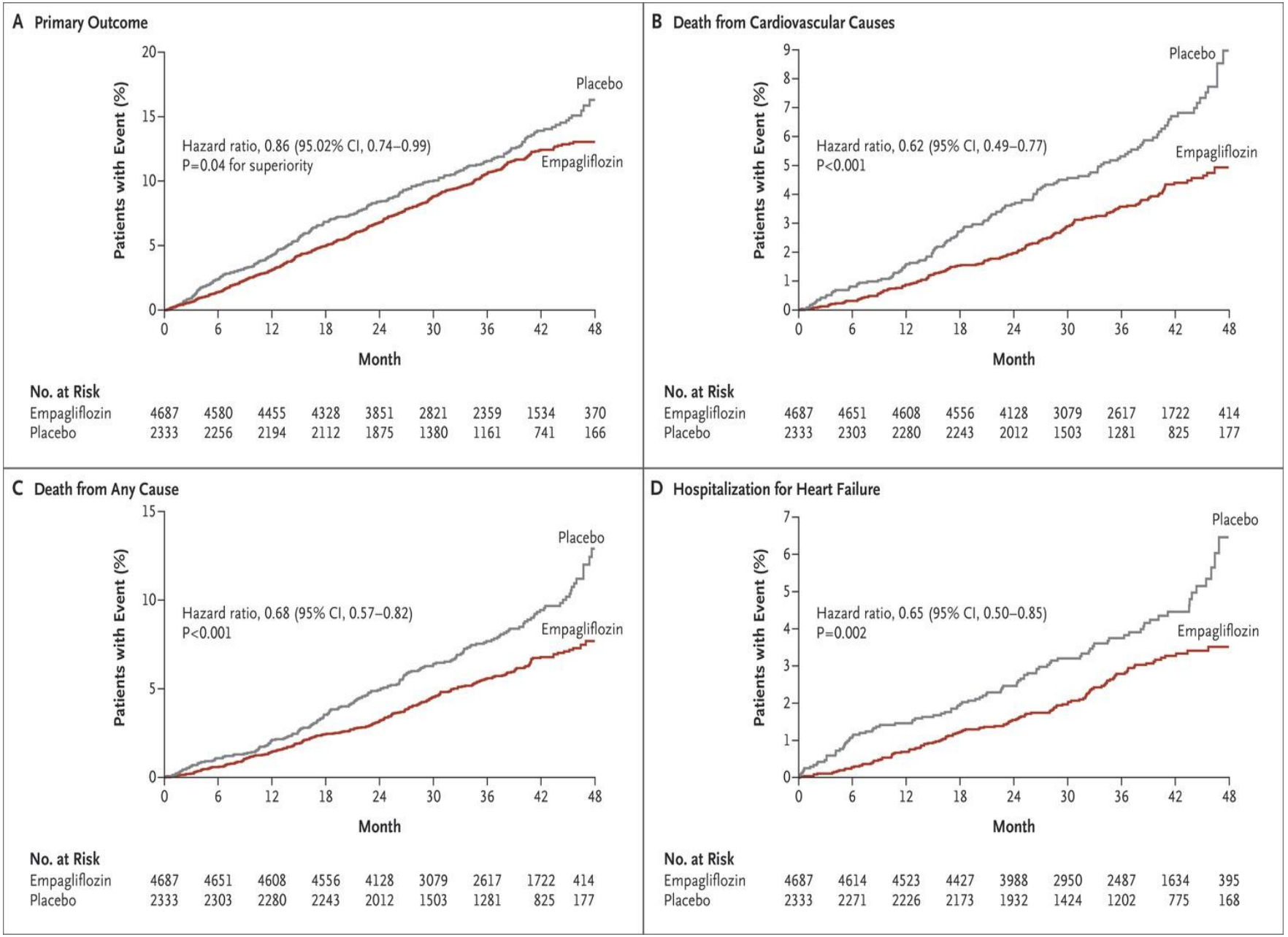
EMPAGLIFLOZIN study criteria

- Patients meeting the inclusion criteria randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily.

- stratified according to: -
  - glycated haemoglobin (<8.5% or ≥8.5%),
  - body-mass index (<30 or ≥30),
  - renal function at screening (eGFR, 30 to 59 ml, 60 to 89 ml, or ≥90 ml per minute per 1.73 m2)
  - geographic region

EMPA vs Placebo Outcome

- Primary outcome : 10.5% vs 12.1%
  - HR 0.86 (95% CI - 0.74 to 0.99; P<0.001)
- Secondary outcome : 12.8% vs 14.3%
  - HR 0.89 (95% CI – 0.78 to 1.01;p=0.08)


A Primary Outcome
Patients with Event (%)
Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
B Death from Cardiovascular Causes
Patients with Event (%)
Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
C Death from Any Cause
Patients with Event (%)
Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
D Hospitalization for Heart Failure
Patients with Event (%)
Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
Placebo
Empagliflozin
Month
No. at Risk
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634 395
Placebo 2333 2271 2226 2173 1932 1424 1202 775 168

- Heterogeneity in the primary outcome
- Benefit in the full population may be limited to sub-groups of age >65 years and HbA1c < 8.5%

Empagliflozin Risk Reduction

- Absolute risk reduction of CV events is 6·5%
- Number needed to treat over 10 years is **15 to prevent one event**

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes*

- 1:1Randomisation Liraglutide and Placebo
- T2DM: untreated, on one or more oral agents with HbA1c >7%

*Marso SP et al NEJM 2016

LEADER inclusion

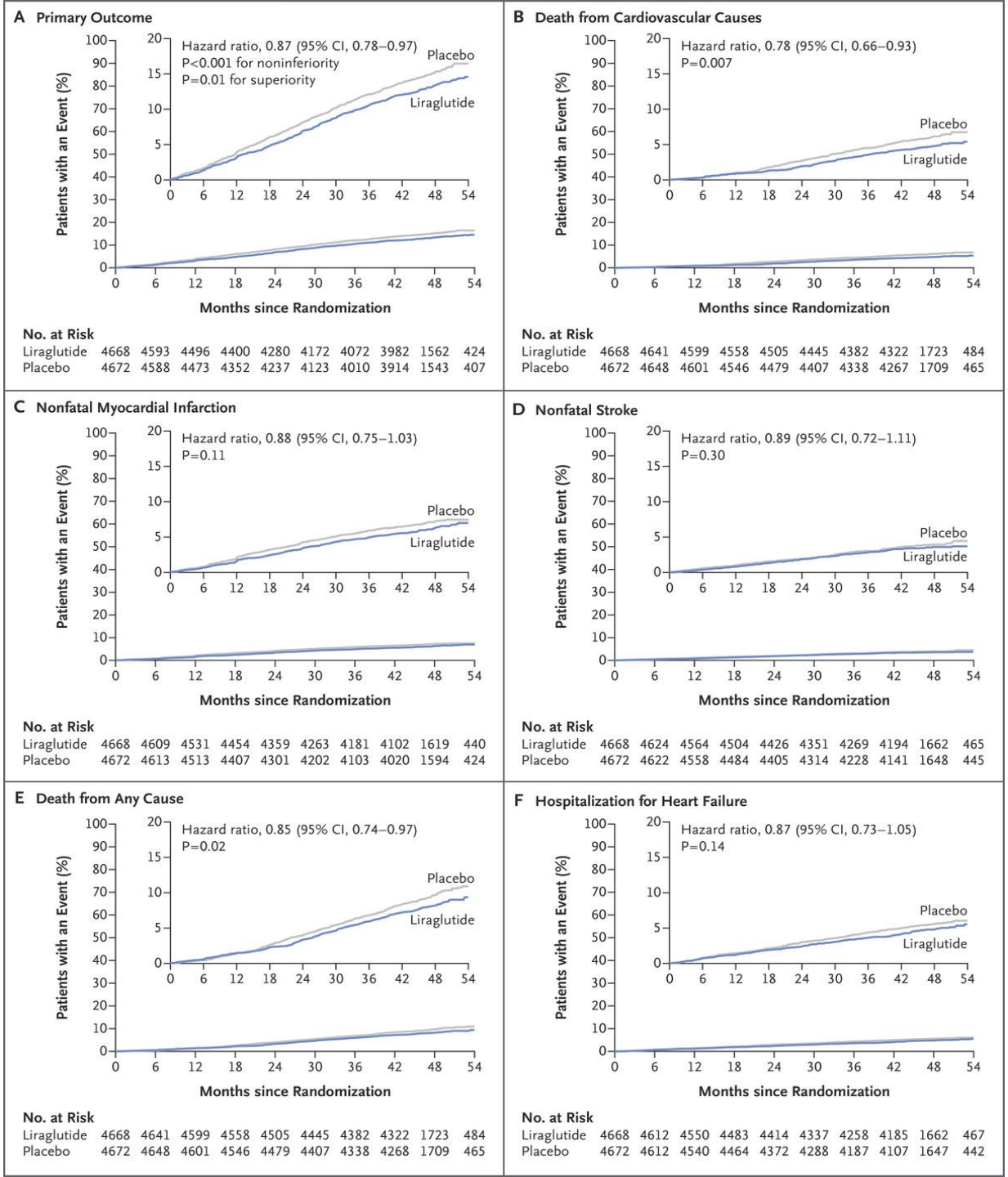
- coronary heart disease, cerebrovascular disease, peripheral vascular disease
- chronic kidney disease of stage 3 or greater,
- chronic heart failure of New York Heart Association class II or III
- microalbuminuria or proteinuria,
- hypertension and left ventricular hypertrophy,
- left ventricular systolic or diastolic dysfunction,
- ankle–brachial index of less than 0.9

LEADER Outcomes

- **Primary composite:** death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

LEADER Outcomes

- 9340 patients followed for 3.8 years
- Primary outcome in treated vs placebo group 13% vs 14.9% p <0.001 (non-inferiority) and p=0.01 (superiority)
- Death from any cause was (381 [8.2%] vs 447 [9.6%]) HR 0.85 (0.74-0.97);p=0.02


A Primary Outcome
Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4593 4496 4400 4280 4172 4072 3982 1562 424
Placebo 4672 4588 4473 4352 4237 4123 4010 3914 1543 407
B Death from Cardiovascular Causes
Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4641 4599 4558 4505 4445 4382 4322 1723 484
Placebo 4672 4648 4601 4546 4479 4407 4338 4267 1709 465
C Nonfatal Myocardial Infarction
Hazard ratio, 0.88 (95% CI, 0.75–1.03)
P=0.11
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4609 4531 4454 4359 4263 4181 4102 1619 440
Placebo 4672 4613 4513 4407 4301 4202 4103 4020 1594 424
D Nonfatal Stroke
Hazard ratio, 0.89 (95% CI, 0.72–1.11)
P=0.30
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4624 4564 4504 4426 4351 4269 4194 1662 465
Placebo 4672 4622 4558 4484 4405 4314 4228 4141 1648 445
E Death from Any Cause
Hazard ratio, 0.85 (95% CI, 0.74–0.97)
P=0.02
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4641 4599 4558 4505 4445 4382 4322 1723 484
Placebo 4672 4648 4601 4546 4479 4407 4338 4268 1709 465
F Hospitalization for Heart Failure
Hazard ratio, 0.87 (95% CI, 0.73–1.05)
P=0.14
Placebo
Liraglutide
Patients with an Event (%)
Months since Randomization
No. at Risk
Liraglutide 4668 4612 4550 4483 4414 4337 4258 4185 1662 467
Placebo 4672 4612 4540 4464 4372 4288 4187 4107 1647 442

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)	
Sex					0.84
Female	3337	183/1657 (11.0)	209/1680 (12.4)	0.88 (0.72–1.08)	
Male	6003	425/3011 (14.1)	485/2992 (16.2)	0.86 (0.75–0.98)	
Age					0.27
<60 yr	2321	140/1197 (11.7)	166/1124 (14.8)	0.78 (0.62–0.97)	
≥60 yr	7019	468/3471 (13.5)	528/3548 (14.9)	0.90 (0.79–1.02)	
Geographic region					0.20
Europe	3296	207/1639 (12.6)	252/1657 (15.2)	0.82 (0.68–0.98)	
North America	2847	212/1401 (15.1)	216/1446 (14.9)	1.01 (0.84–1.22)	
Asia	711	24/360 (6.7)	37/351 (10.5)	0.62 (0.37–1.04)	
Rest of the world	2486	165/1268 (13.0)	189/1218 (15.5)	0.83 (0.68–1.03)	
Race					0.32
White	7238	494/3616 (13.7)	543/3622 (15.0)	0.90 (0.80–1.02)	
Black	777	47/370 (12.7)	59/407 (14.5)	0.87 (0.59–1.27)	
Asian	936	40/471 (8.5)	56/465 (12.0)	0.70 (0.46–1.04)	
Other	389	27/211 (12.8)	36/178 (20.2)	0.61 (0.37–1.00)	
Ethnic group					0.30
Hispanic	1134	68/580 (11.7)	86/554 (15.5)	0.74 (0.54–1.02)	
Non-Hispanic	8206	540/4088 (13.2)	608/4118 (14.8)	0.89 (0.79–1.00)	
Body-mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	
Duration of diabetes					0.42
≤11 yr	4429	265/2216 (12.0)	316/2213 (14.3)	0.82 (0.70–0.97)	
>11 yr	4892	340/2441 (13.9)	376/2451 (15.3)	0.90 (0.78–1.04)	
Risk of CVD					0.04
≥50 yr of age and established CVD	7598	536/3831 (14.0)	629/3767 (16.7)	0.83 (0.74–0.93)	
≥60 yr of age and risk factors for CVD	1742	72/837 (8.6)	65/905 (7.2)	1.20 (0.86–1.67)	
Chronic heart failure					0.53
Yes	1305	112/653 (17.2)	119/652 (18.3)	0.94 (0.72–1.21)	
No	8035	496/4015 (12.4)	575/4020 (14.3)	0.85 (0.76–0.96)	
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	

LEADER Outcomes

- Rates for non-fatal MI and stroke and heart failure were non-significantly lower
- The number needed to treat to prevent one event of the primary composite in 3 years is 66

Mechanism?

- **Empagliflozin** effects more immediate suggesting haemodynamic effect and/or activation of RAS
- **Liraglutide** effects slower suggesting mechanism alters plaque development
- Trials of other GLP, DPP-IV and TZD with similar glucose lowering have not shown similar CVD outcomes

SGLT-2 inhibitors

- CANVAS involved 10,142 participants with type 2 diabetes mellitus (T2DM) at high CV risk.
- Patients treated with the SGLT-2 inhibitor Canagliflozin had a lower risk of CV events and a significant reduction of hospitalisation for Heart Failure.
- The *risk for amputation* was increased compared to the control group

GLP-1 receptor agonists

- EXSCEL demonstrated CV safety in high risk subjects with T2DM who were treated with long-acting exenatide once weekly.
- 14% reduction in all-cause mortality with exenatide once weekly versus placebo (hazard ratio 0.86, 95% CI 0.77–0.97) - not rated as significant due to the protocol-defined hierarchical order of statistical testing.

Basal insulin

DEVOTE - the ultra-long-acting, once-daily basal Insulin degludec is as safe in CV terms as Insulin glargine and associated with much lower rates of severe hypoglycaemia.

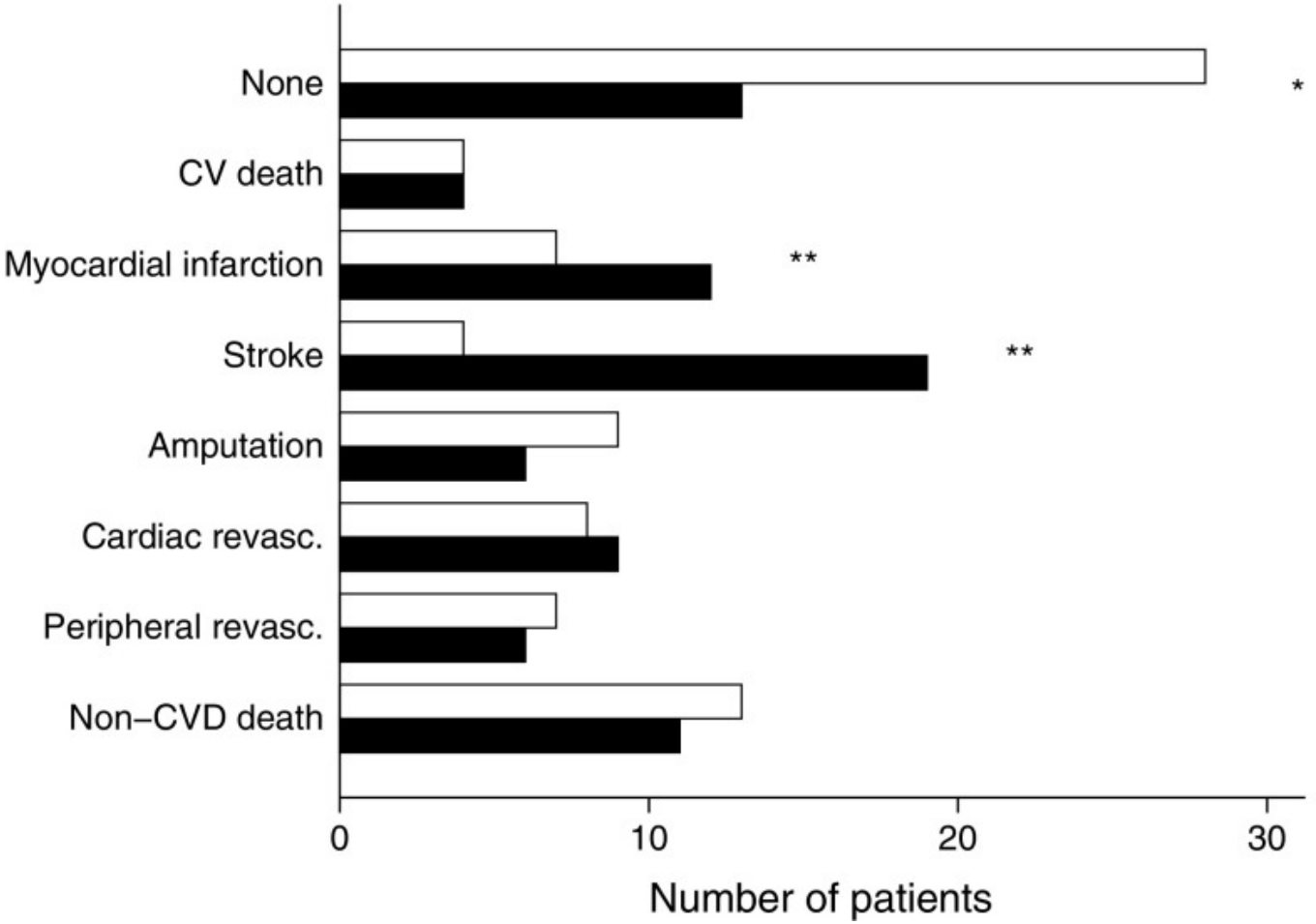
Real-world data

- CVD-REAL - 300,000 T2DM patients across six countries, 87% of whom did not have a history of CVD.
- SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) was significantly associated with a reduced overall rate of hospitalisation for HF by 39% and death from any cause by 51%

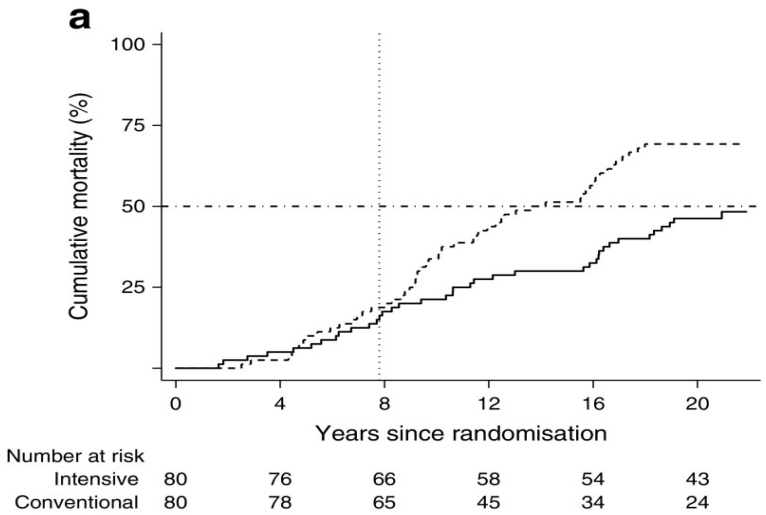
Real-world data

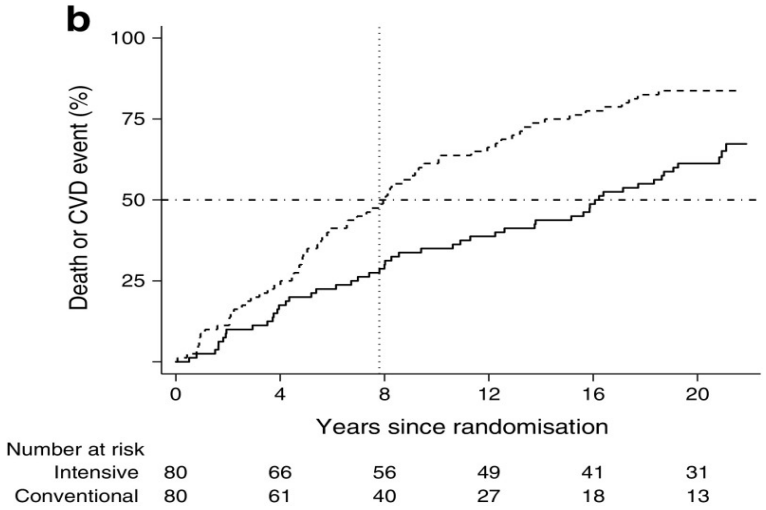
- Swedish RiksSvikt Heart Failure registry from 2003 in the Uppsala Clinical Research Centre. Diabetes compromises survival in HF irrespective of sex, HF aetiology or type and increases mortality by 30–70%
- The prognosis is comparable between male and female diabetes patients and worst in those with systolic dysfunction.

Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

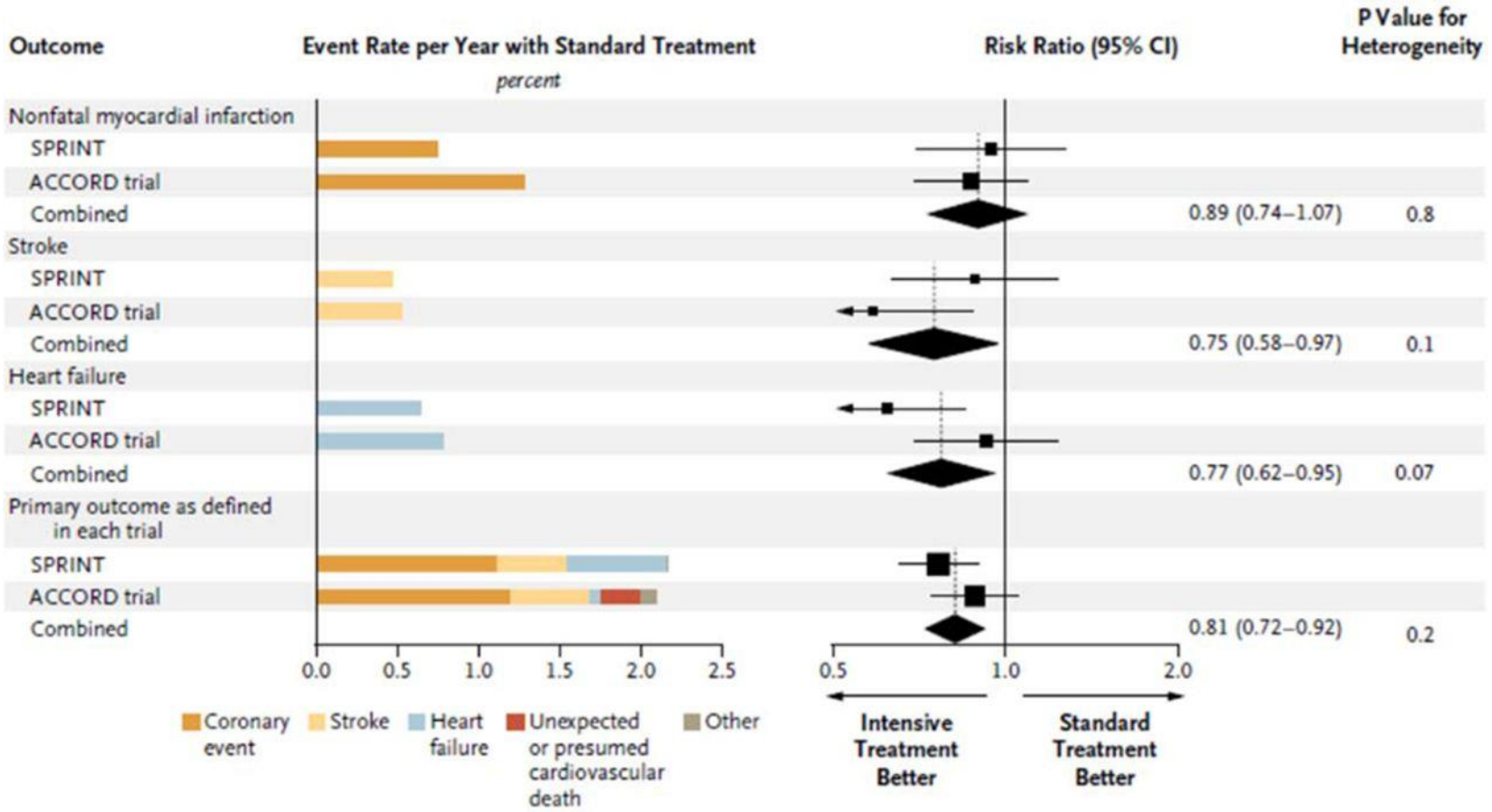


Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

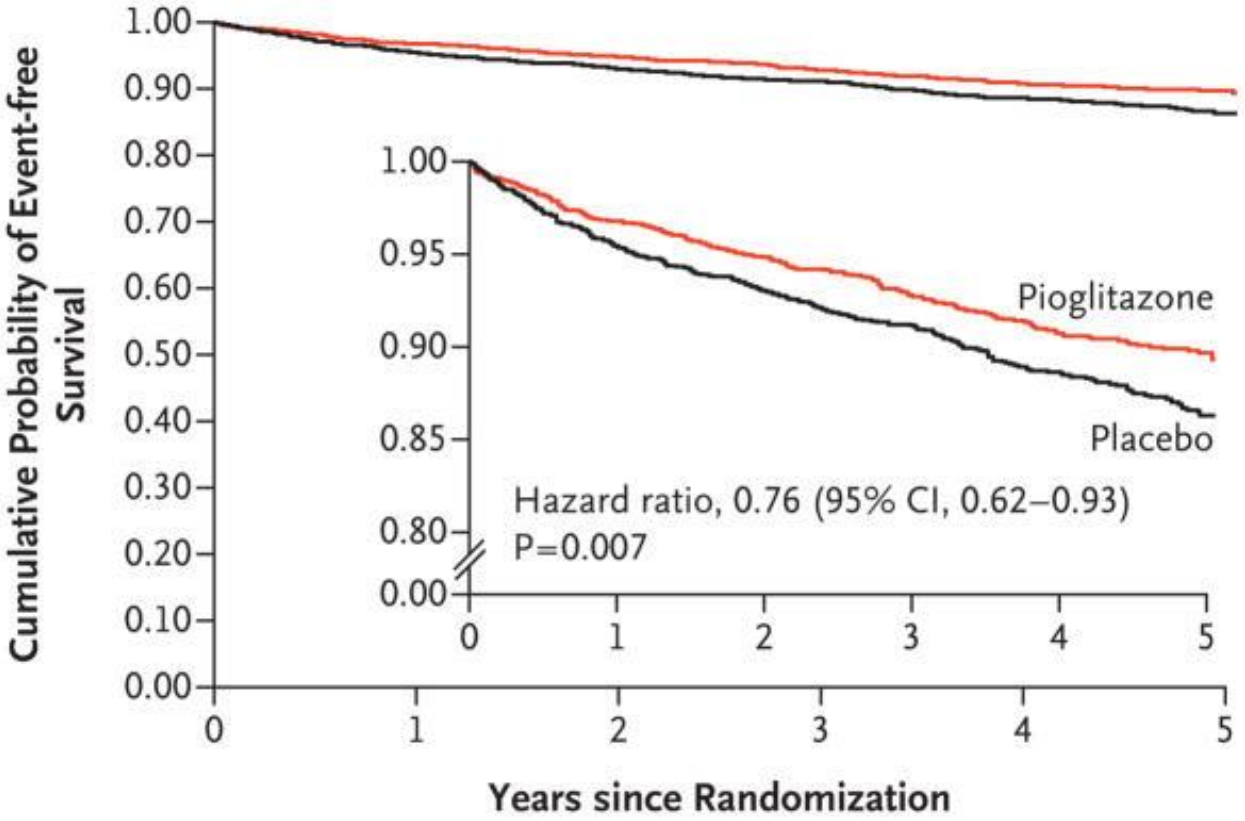




Cardiovascular outcomes in 2 recent blood pressure–lowering trials in patients with and without baseline diabetes mellitus.

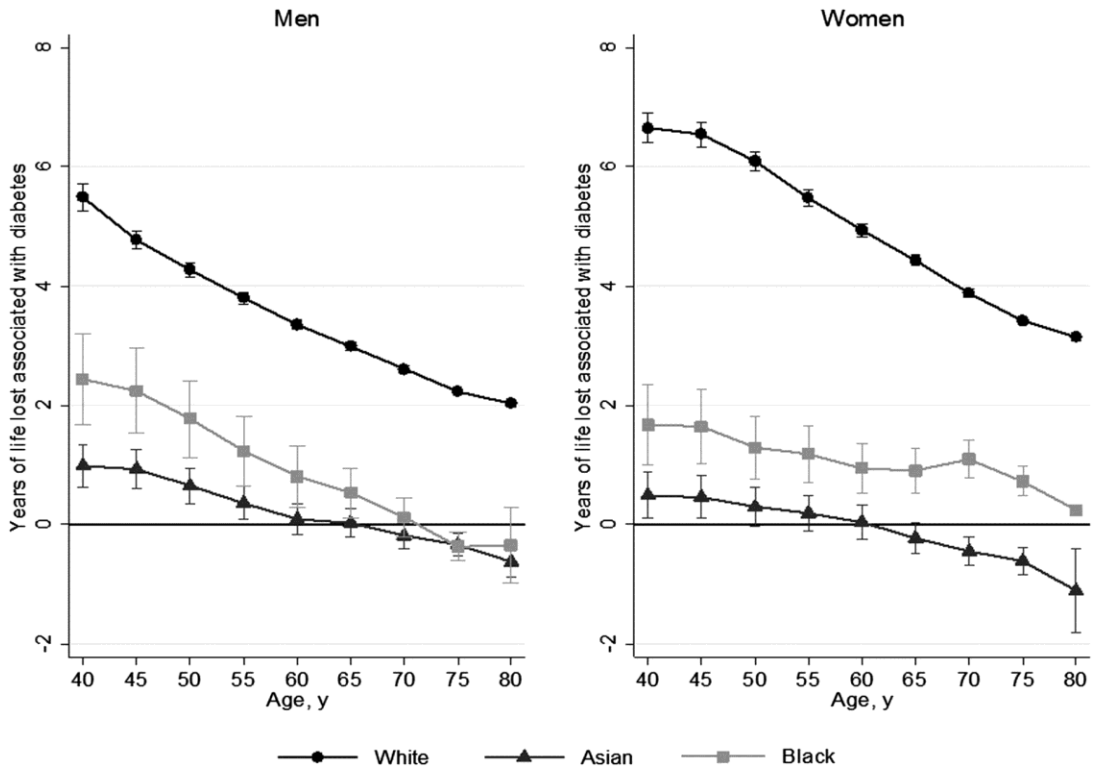


Cecilia C. Low Wang et al. Circulation. 2016;133:2459-2502



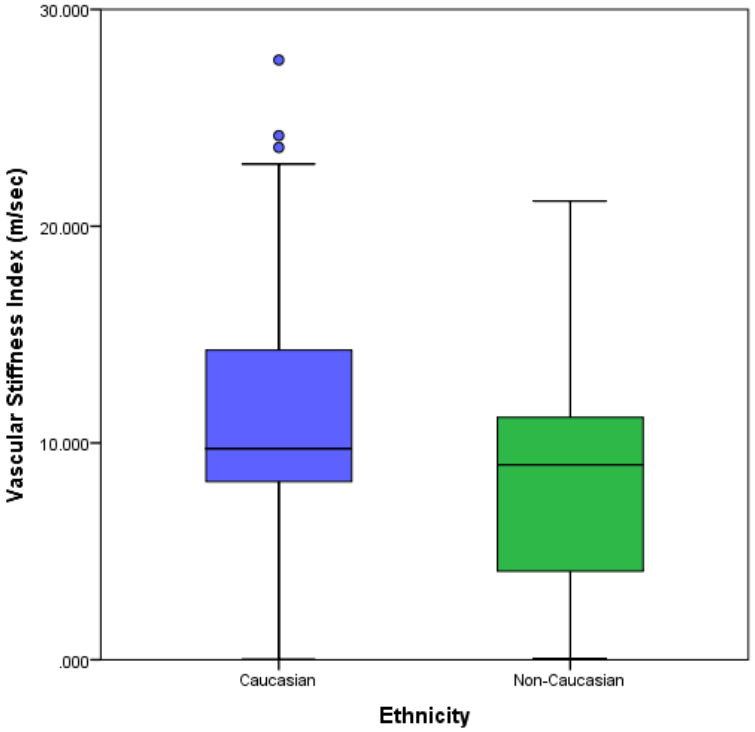
No. at Risk

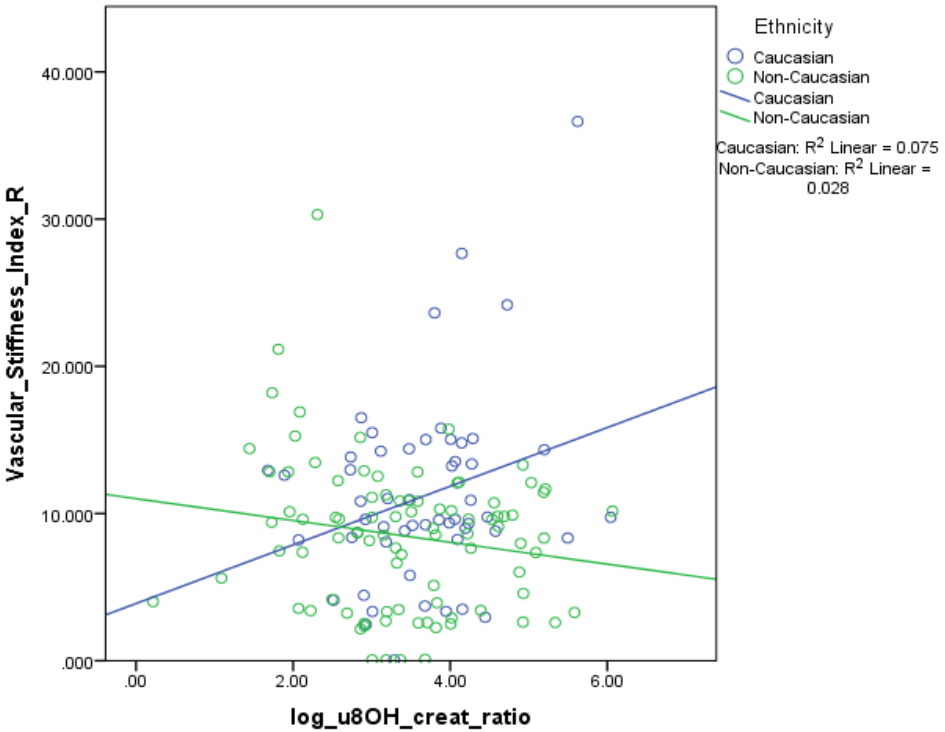
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459



Wright et al Diabetes Care 2016

Differences in urinary 8-OH deoxyguanosine in patients with T2DM at high risk of renal disease without CVD



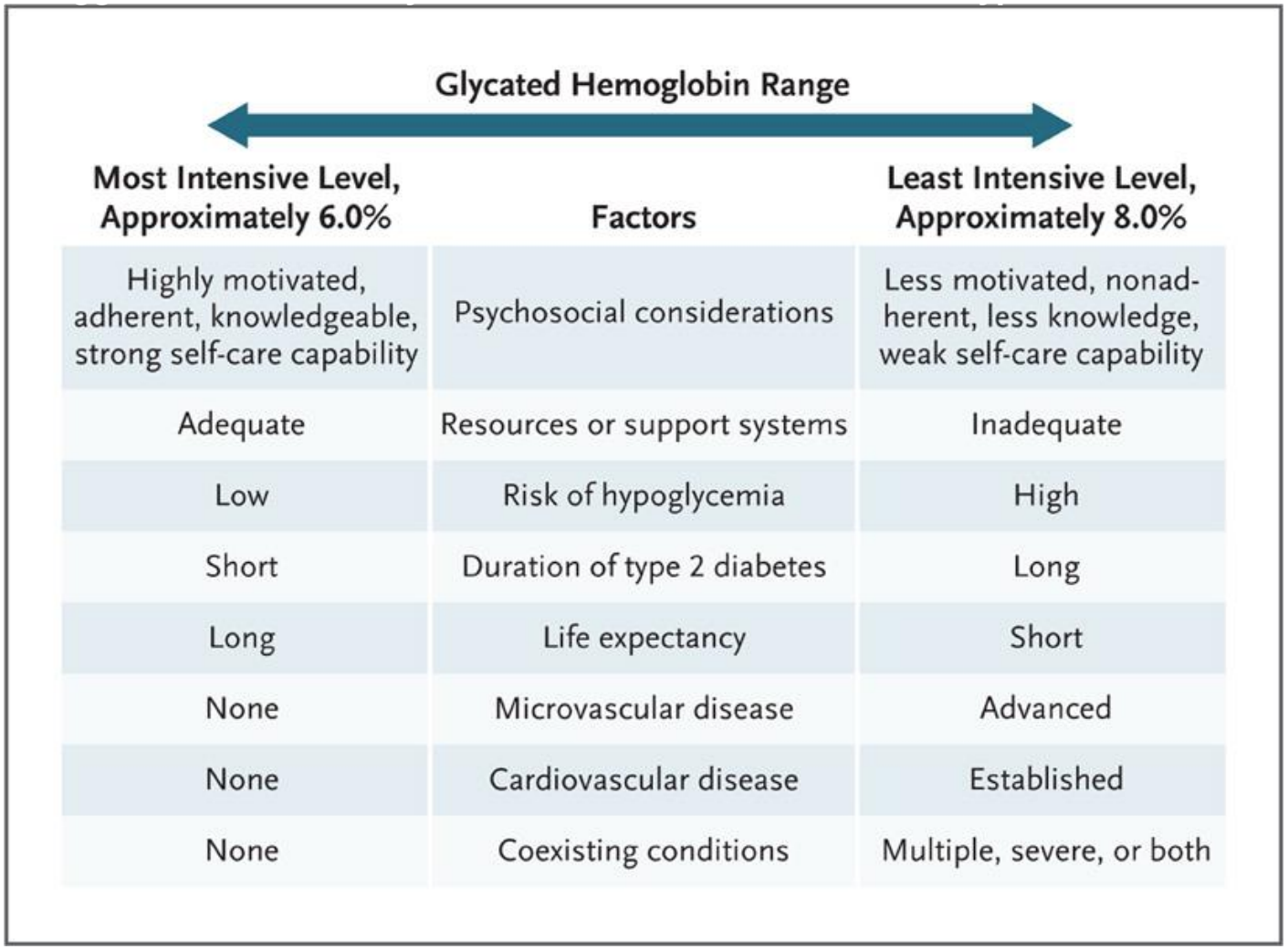


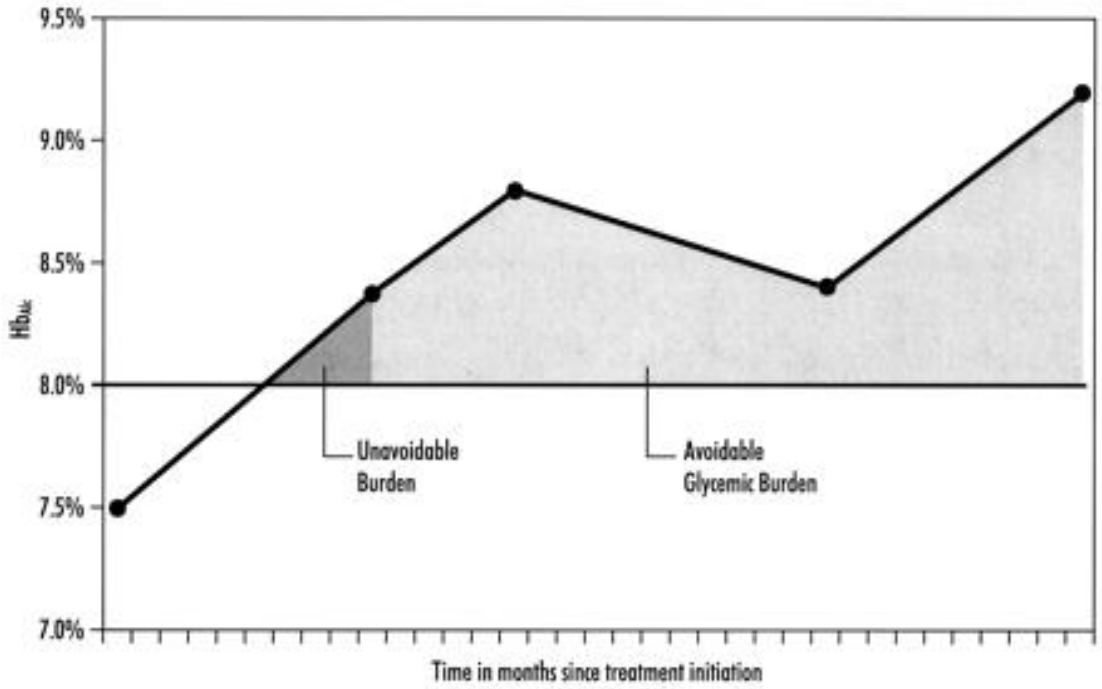
Clinical Relevance

- Beneficial effects of early aggressive glucose lowering agent on CVD morbidity and mortality
- Impact of modulating non-glucose lowering pathways to be determined
- EMPA and LEADER trials suggest heart failure is not an adverse outcome
- Potential benefit of GLP-1 in CKD patients
- Organisation of care and non-glucose targets in the wider at risk population

Treatment choices

- Specificity of effect
- Cost, compliance and control
- CVD Risk and NNT
- Heart failure risk
- Renal disease
- Weight management


Glycated Hemoglobin Range
Most Intensive Level, Approximately 6.0%
Factors
Least Intensive Level, Approximately 8.0%
Highly motivated, adherent, knowledgeable, strong self-care capability
Psychosocial considerations
Less motivated, nonadherent, less knowledge, weak self-care capability
Adequate
Resources or support systems
Inadequate
Low
Risk of hypoglycemia
High
Short
Duration of type 2 diabetes
Long
Long
Life expectancy
Short
None
Microvascular disease
Advanced
None
Cardiovascular disease
Established
None
Coexisting conditions
Multiple, severe, or both



Total Burden $= \sum_{i=1}^{T}(G_i - K)$, where t indicates the number of months elapsed since diagnosis or treatment initiation; T is the number of months elapsed when a successor treatment in initiated; G_t is the actual or interpolated value of Hb_{A1c} in month t; and K is the base from which burden is calculated (in this example, $K = 8.0$).

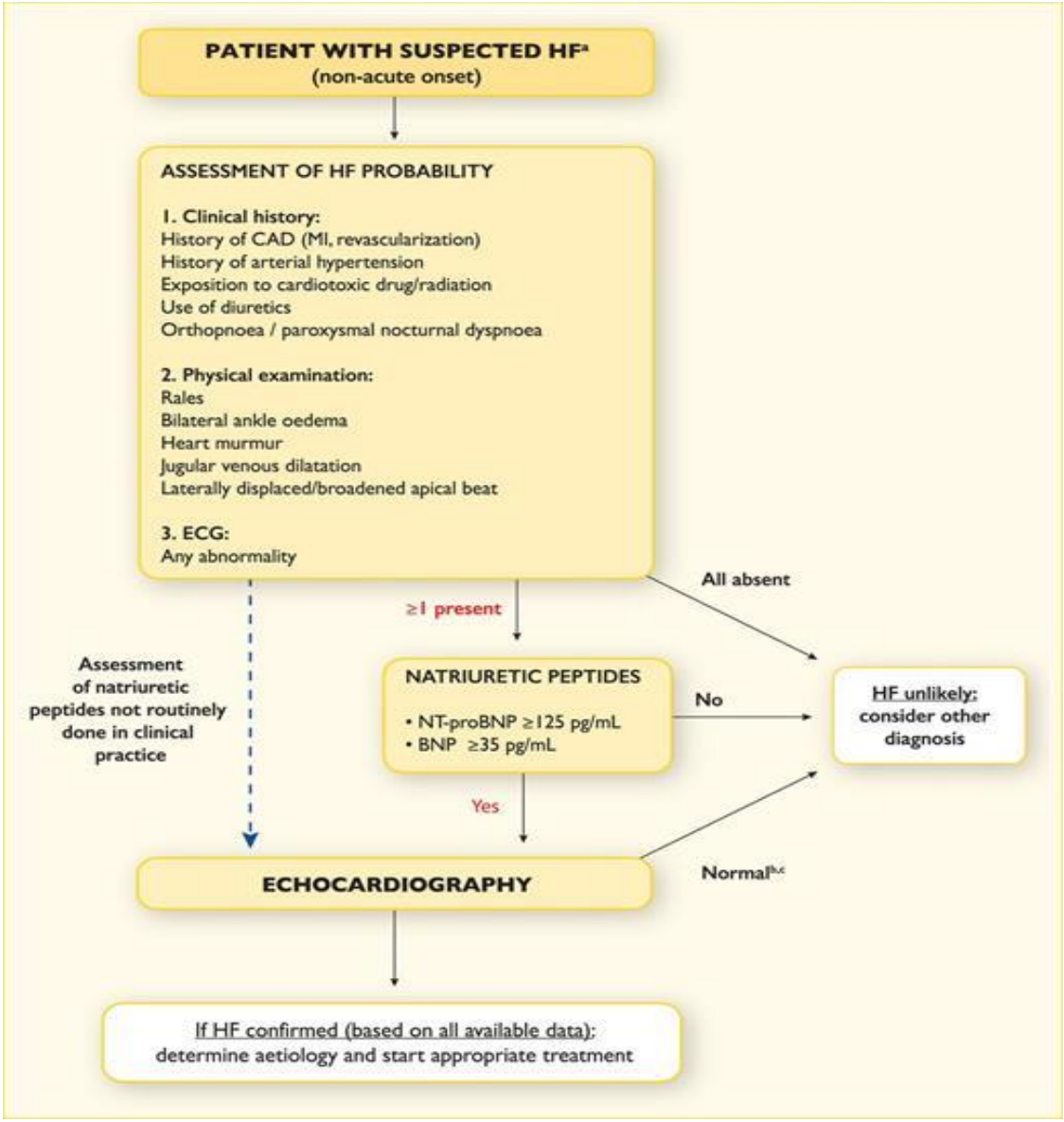
AN ACTION POINT AT 7.0% OR LOWER IS MORE LIKELY TO PREVENT ADDITIONAL DETERIORATION THAN THE TRADITIONAL ACTION POINT OF 8.0%.

The Burden of Treatment Failure in Type 2 Diabetes Brown et al 2004

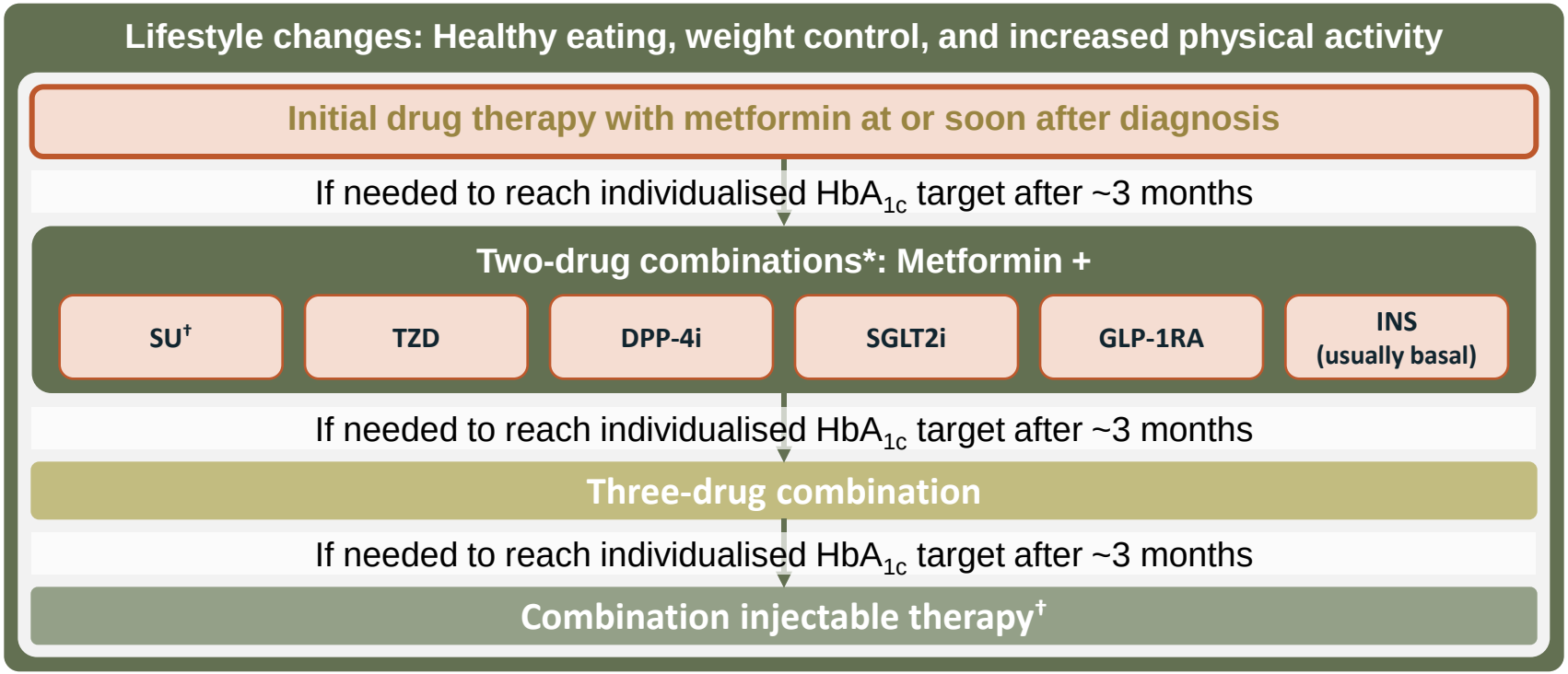
A REALISTIC GOAL?

Fed up with how her diet is going, Charlene takes a more serious aim at her target weight.

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[53]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure


PATIENT WITH SUSPECTED HF[a]
(non-acute onset)
ASSESSMENT OF HF PROBABILITY
1. Clinical history:
History of CAD (MI, revascularization)
History of arterial hypertension
Exposition to cardiotoxic drug/radiation
Use of diuretics
Orthopnoea / paroxysmal nocturnal dyspnoea
2. Physical examination:
Rales
Bilateral ankle oedema
Heart murmur
Jugular venous dilatation
Laterally displaced/broadened apical beat
3. ECG:
Any abnormality
All absent
≥1 present
Assessment of natriuretic peptides not routinely done in clinical practice
NATRIURETIC PEPTIDES
• NT-proBNP ≥125 pg/mL
• BNP ≥35 pg/mL
No
HF unlikely: consider other diagnosis
Yes
ECHOCARDIOGRAPHY
Normal[b,c]
If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

2015 ADA/EASD general recommendations for antihyperglycaemic therapy[1]

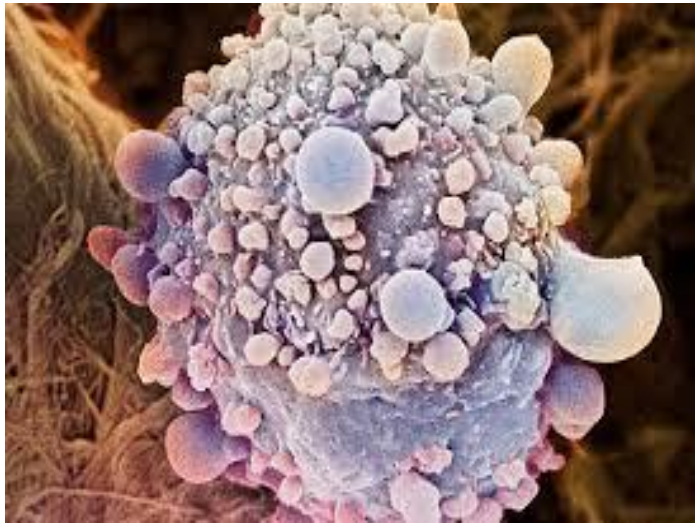


When choosing treatment options, consider comorbidities, efficacy, safety, hypoglycaemia risk, weight, patient preferences, and cost

Consider beginning at this stage in patients with very high A_{1c} (eg, ≥9%). Order does not denote any specific preference.
†Consider initiating combination injectable therapy when blood glucose is ≥300 mg/dL–350 mg/dL and/or A_{1c} is ≥10%–12%†.

ADA=American Diabetes Association; DPP-4i=dipeptidyl peptidase-4 inhibitor; EASD=European Association for the Study of Diabetes; GLP-1RA=glucagon-like peptide-1 receptor agonist; INS=insulin; SU=sulphonylurea; TZD=thiazolidinedione.

1. Adapted from ADA (2015) *Diabetes Care* **38**: S1–94



What's most effective? Is it timely? Is it safe?

Connect for greater effect

Specialist Care

Neuropathy

Renal disease

Vasculopathy

Retinopathy

Self-care

Podiatry

Renal services

Cardiovascular services

Ophthalmology

Education/Dietetics/Behavioural Therapy

Primary Care

Diabetes Care - (ABL-FREE-SUCCEED)

A1c

BP

Lipids

Feet

Retina

estimatedGFR

Support from specialists

Continuing Care

Emotional support

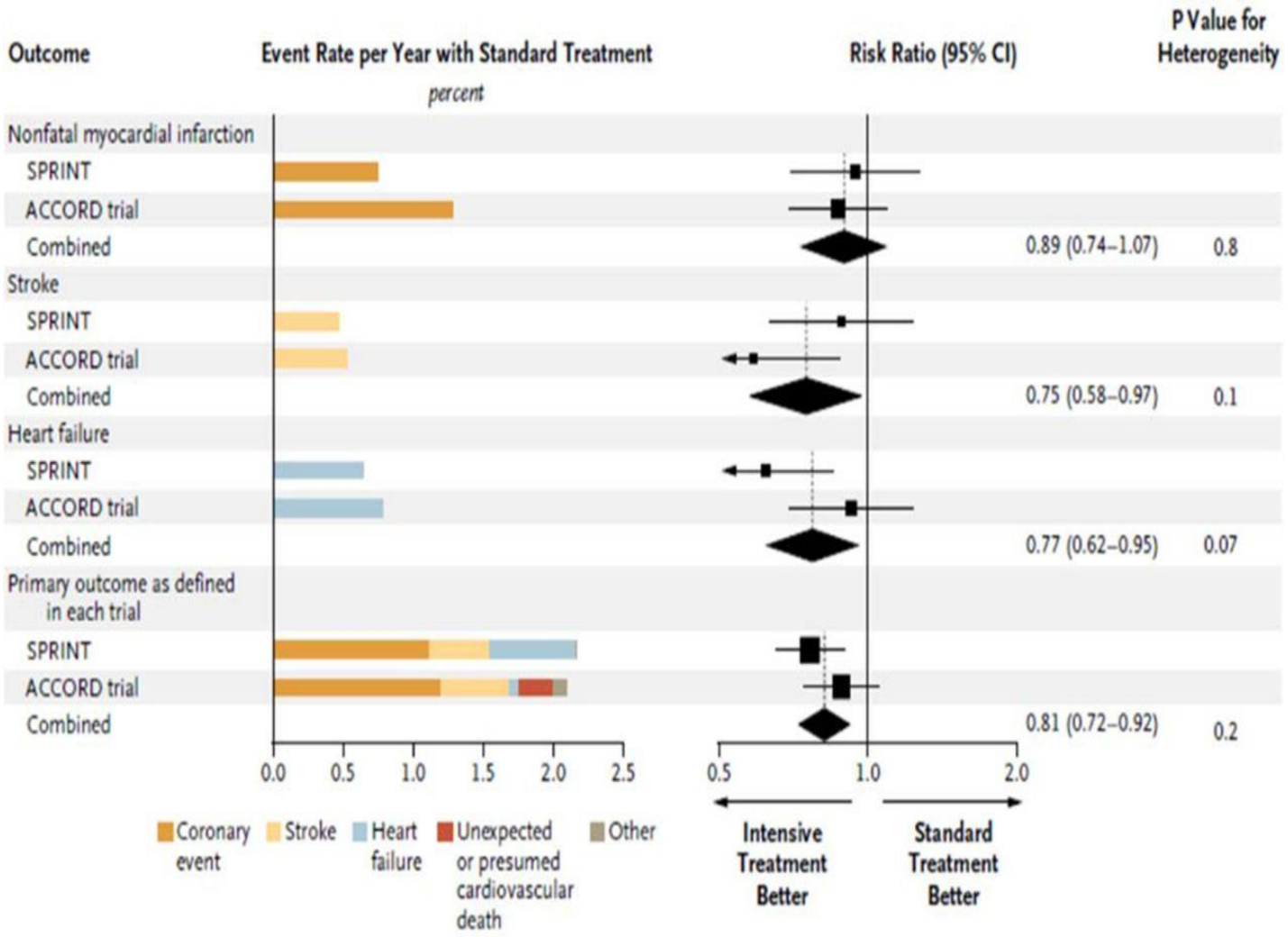
Education

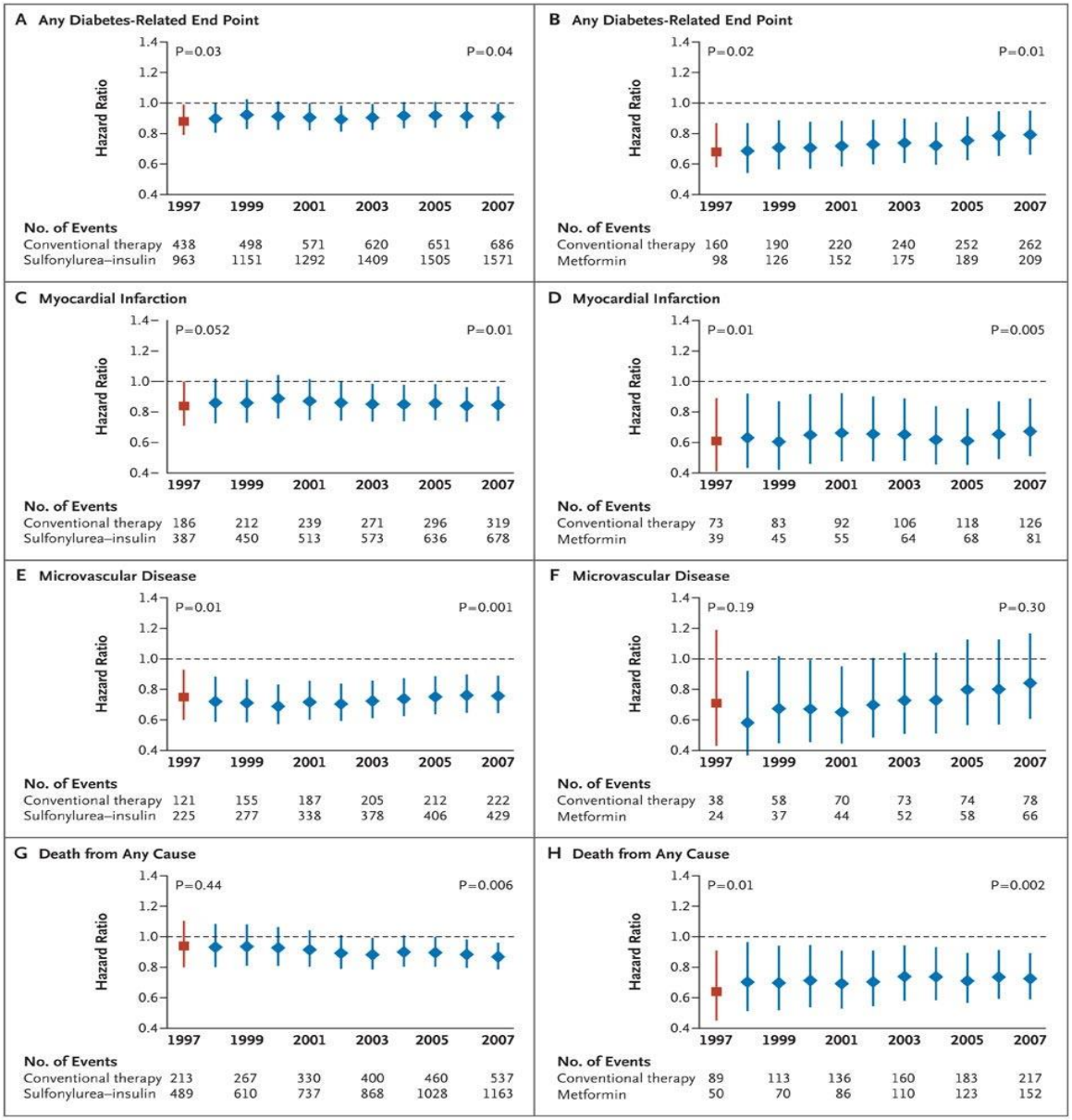
Dietary advice

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

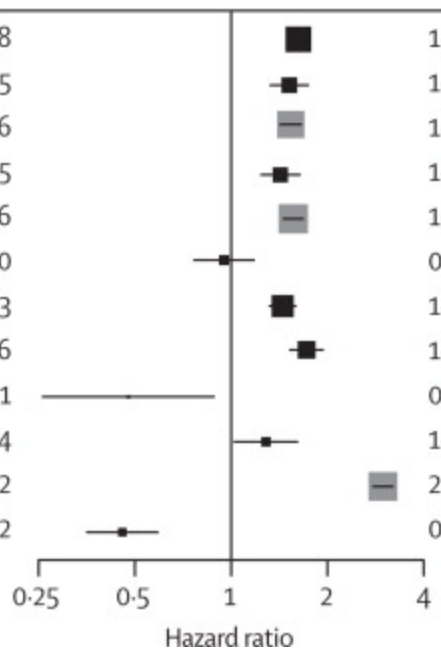
Change in CV risk factors

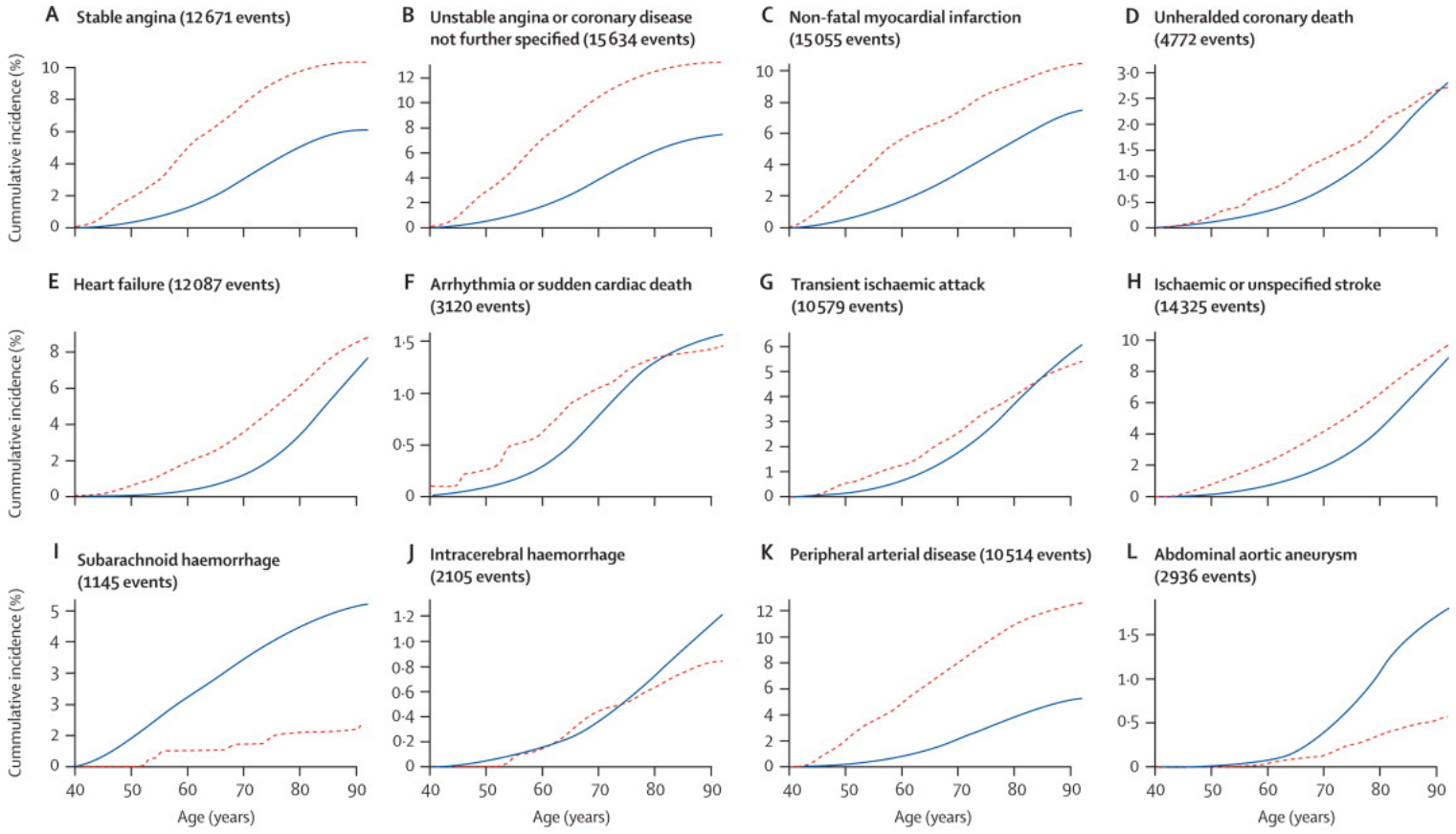
- Reduced weight
- Reduced waist circumference
- Reduced uric acid
- Reduced systolic and diastolic BP
- Raised LDL-cholesterol
- Raised HDL-cholesterol
- Raised haematocrit
- No changes in heart rate

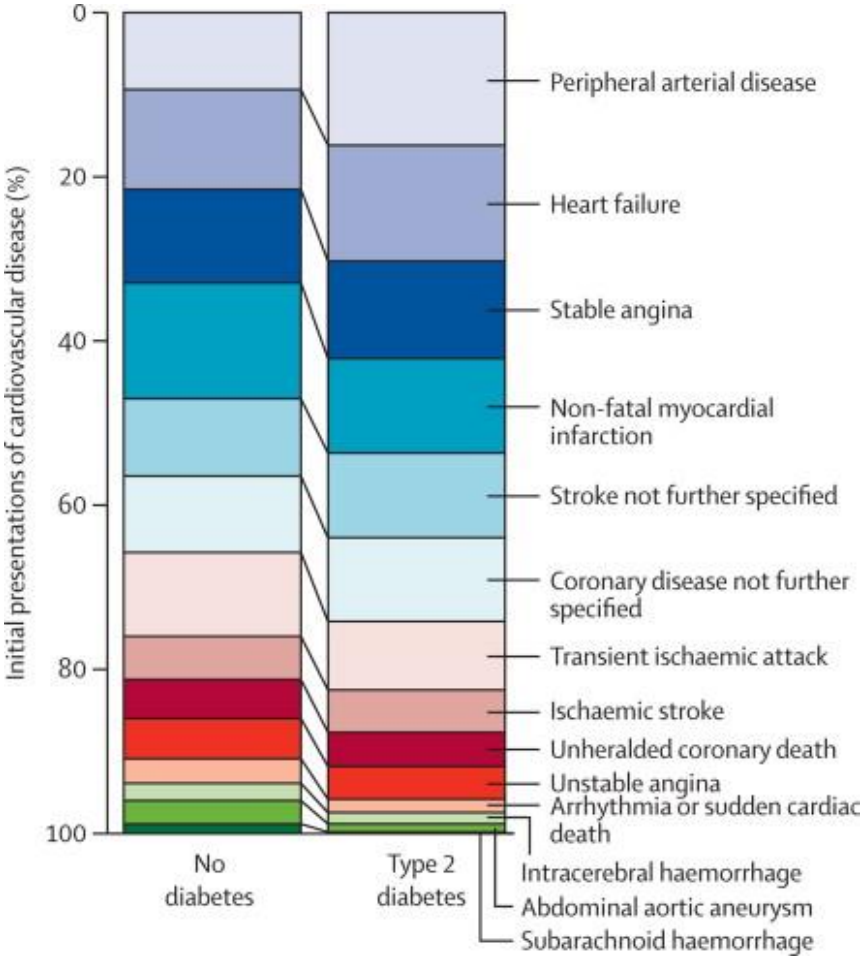

Outcome
Event Rate per Year with Standard Treatment
percent
Risk Ratio (95% CI)
P Value for Heterogeneity
Nonfatal myocardial infarction
SPRINT
ACCORD trial
Combined
0.89 (0.74–1.07)
0.8
Stroke
SPRINT
ACCORD trial
Combined
0.75 (0.58–0.97)
0.1
Heart failure
SPRINT
ACCORD trial
Combined
0.77 (0.62–0.95)
0.07
Primary outcome as defined in each trial
SPRINT
ACCORD trial
Combined
0.81 (0.72–0.92)
0.2
0.0
0.5
1.0
1.5
2.0
2.5
0.5
1.0
2.0
Coronary event
Stroke
Heart failure
Unexpected or presumed cardiovascular death
Other
Intensive Treatment Better
Standard Treatment Better


A Any Diabetes-Related End Point
P=0.03
P=0.04
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 438 498 571 620 651 686
Sulfonylurea–insulin 963 1151 1292 1409 1505 1571
B Any Diabetes-Related End Point
P=0.02
P=0.01
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 160 190 220 240 252 262
Metformin 98 126 152 175 189 209
C Myocardial Infarction
P=0.052
P=0.01
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 186 212 239 271 296 319
Sulfonylurea–insulin 387 450 513 573 636 678
D Myocardial Infarction
P=0.01
P=0.005
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 73 83 92 106 118 126
Metformin 39 45 55 64 68 81
E Microvascular Disease
P=0.01
P=0.001
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 121 155 187 205 212 222
Sulfonylurea–insulin 225 277 338 378 406 429
F Microvascular Disease
P=0.19
P=0.30
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 38 58 70 73 74 78
Metformin 24 37 44 52 58 66
G Death from Any Cause
P=0.44
P=0.006
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 213 267 330 400 460 537
Sulfonylurea–insulin 489 610 737 868 1028 1163
H Death from Any Cause
P=0.01
P=0.002
Hazard Ratio
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 89 113 136 160 183 217
Metformin 50 70 86 110 123 152

Initial presentation of cardiovascular disease	Number of events		Hazard ratio (95% CI)	p value
	No diabetes	Type 2 diabetes		
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001



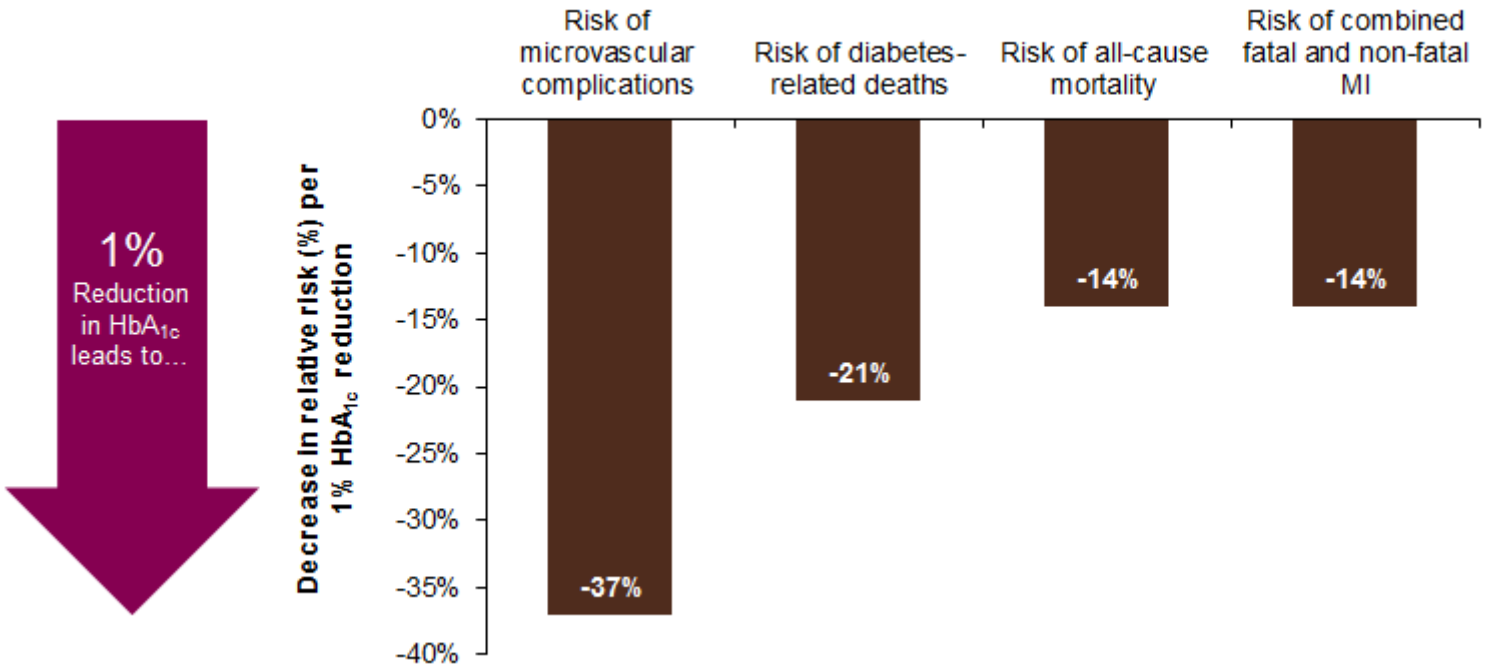

A Stable angina (12 671 events)
B Unstable angina or coronary disease not further specified (15 634 events)
C Non-fatal myocardial infarction (15 055 events)
D Unheralded coronary death (4772 events)
E Heart failure (12 087 events)
F Arrhythmia or sudden cardiac death (3120 events)
G Transient ischaemic attack (10 579 events)
H Ischaemic or unspecified stroke (14 325 events)
I Subarachnoid haemorrhage (1145 events)
J Intracerebral haemorrhage (2105 events)
K Peripheral arterial disease (10 514 events)
L Abdominal aortic aneurysm (2936 events)
Cummulative incidence (%)
Age (years)
Number of patients 40 years 50 years 60 years 70 years 80 years 90 years
No diabetes 297 335 265 580 224 060 133 605 76 384 20 679
Type 2 diabetes 924 2330 4226 4962 3229 717


Initial presentations of cardiovascular disease (%)
0
20
40
60
80
100
No diabetes
Type 2 diabetes
Peripheral arterial disease
Heart failure
Stable angina
Non-fatal myocardial infarction
Stroke not further specified
Coronary disease not further specified
Transient ischaemic attack
Ischaemic stroke
Unheralded coronary death
Unstable angina
Arrhythmia or sudden cardiac death
Intracerebral haemorrhage
Abdominal aortic aneurysm
Subarachnoid haemorrhage

Key findings from the audit

- **Diabetes is responsible for relatively greater risk of ill health in younger people**
- **Under the age of 80, attention to heart protection is important and beneficial**
- **Reducing the proportion of people with diabetes and heart problems in hospital from approximately 20-25% needs to be addressed**
- **Patients adhering to process had much better outcomes**

Observational analysis of UKPDS data: Reduction in HbA_{1c} leads to improvements in microvascular and macrovascular risk[1]



Adapted from Stratton IM et al (2000) *BMJ* **321**: 405–12.

Observational analysis of relation between glycaemic exposure and complications of diabetes as estimated by decrease in risk for 1% reduction in HbA_{1c} concentration, measured at baseline and as updated mean, controlled for age at diagnosis of diabetes, sex, ethnic group, smoking, albuminuria, systolic blood pressure, HDL and LDL cholesterol, and triglycerides: 3,642 white, Asian Indian and Afro-Caribbean UKPDS patients were included in analyses of relative risk.

UKPDS=UK Prospective Diabetes Study.

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

CV event prevention in 2000 T2DM patients over 5 years