The cardiovascular challenge of diabetes for primary care?

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Competing interests

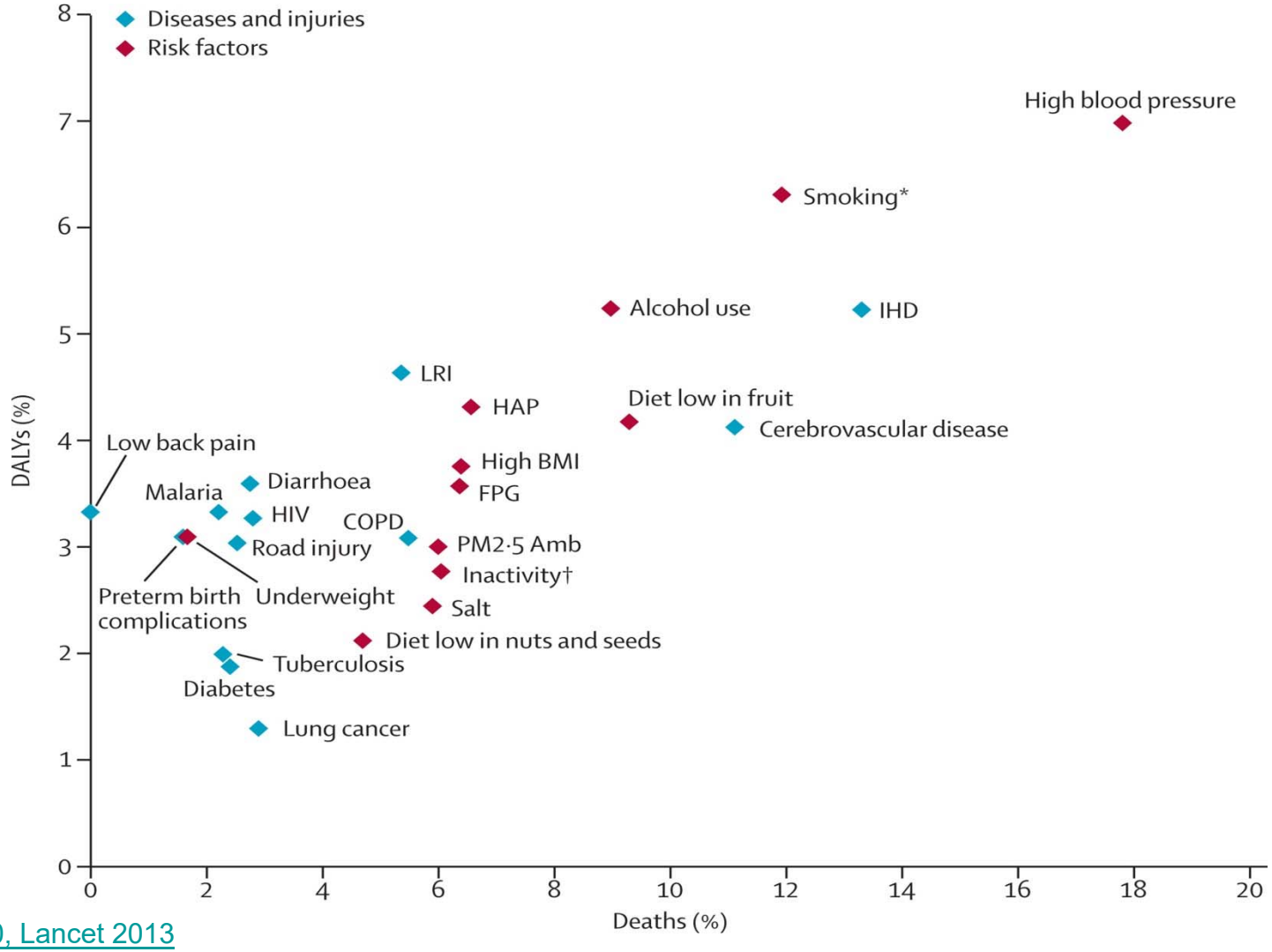
Speaker or congress sponsorship disclosures in past 5 years:
Amgen, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer

Presentation outline

- Epidemiology of T2DM and CVD
- Modifying CVD risk in T2DM

Is targeting cardiovascular disease prevention in general important?

Comparison of 10 leading diseases/injuries & leading risk factors on % deaths/DALYs



GBD 2010, Lancet 2013

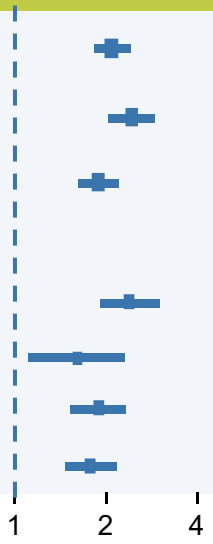
Why is targeting cardiovascular disease prevention in diabetes so important?

Type 2 diabetes significantly increases the risk of cardiovascular events

Data from 102 prospective studies, 530,083 participants (adjusted for age sex, cohort, SBP, smoking, BMI)

Hazard ratios* for vascular outcomes in people with versus without diabetes at baseline (n=530,083)

	Number of cases	Hazard ratio (95% CI)	I^2 (95% CI)
Coronary heart disease*	26,505	2.00 (1.83, 2.19)	64 (54, 71)
Coronary death	11,556	2.31 (2.05, 2.60)	41 (24, 54)
Non-fatal myocardial infarction	14,741	1.82 (1.64, 2.03)	37 (19, 51)
Stroke subtypes†			
Ischaemic stroke	3799	2.27 (1.95, 2.65)	1 (0, 20)
Haemorrhagic stroke	1183	1.56 (1.19, 2.05)	0 (0, 26)
Unclassified stroke	4973	1.84 (1.59, 2.13)	33 (12, 48)
Other vascular deaths	3826	1.73 (1.51, 1.98)	0 (0, 26)



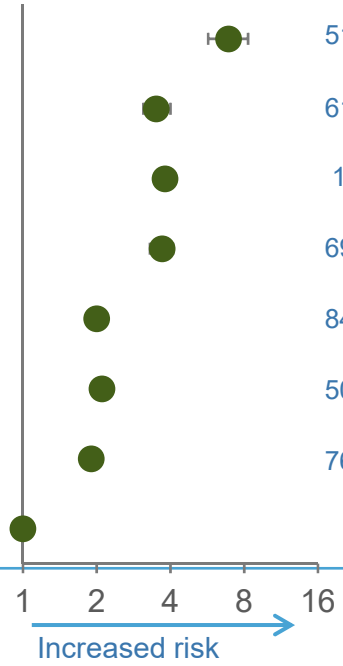
*Adjusted for age, smoking status, BMI, systolic blood pressure, and where appropriate stratified by sex and trial arm;
†Includes both fatal and non-fatal events. BMI, body mass index; CI, confidence interval.

Adapted from: Emerging Risk Factors Collaboration. *Lancet* 2010;**375**:2215–22

Cardiometabolic morbidity in DM with CVD

All-cause mortality for the Emerging Risk Factors Collaboration by disease status of participants at baseline (N=689,300)

Disease status at baseline	No. of participants	No. of deaths	Person-years	HR (95% CI)	I^2 (95% CI)
Diabetes, stroke and MI	541	379	3584	6.9 (5.7,8.3)	51 (38, 62)
Stroke and MI	1836	1174	14,210	3.5 (3.1, 4.0)	61 (52, 69)
Diabetes and stroke	1321	778	10,234	3.8 (3.5, 4.2)	18 (0, 38)
Diabetes and MI	3233	1794	25,321	3.7 (3.3, 4.1)	69 (62, 75)
MI	21,591	9636	216,081	2.0 (1.9, 2.2)	84 (80, 86)
Stroke	8583	3814	82,208	2.1 (2.0, 2.2)	50 (36, 61)
Diabetes	24,677	8087	254,608	1.9 (1.8, 2.0)	76 (70, 80)
None	627,518	103,181	8,772,977	1 [reference]	

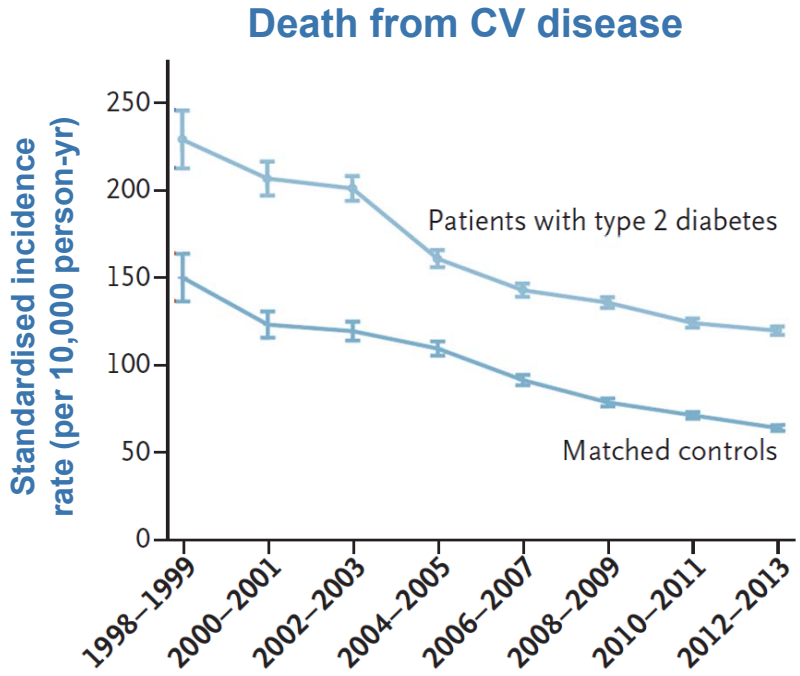


HRs calculated using a cox proportional hazards regression model, stratified by sex and adjusted by age at baseline.
Analyses based on participants from 91 studiesMI, myocardial infarction

The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

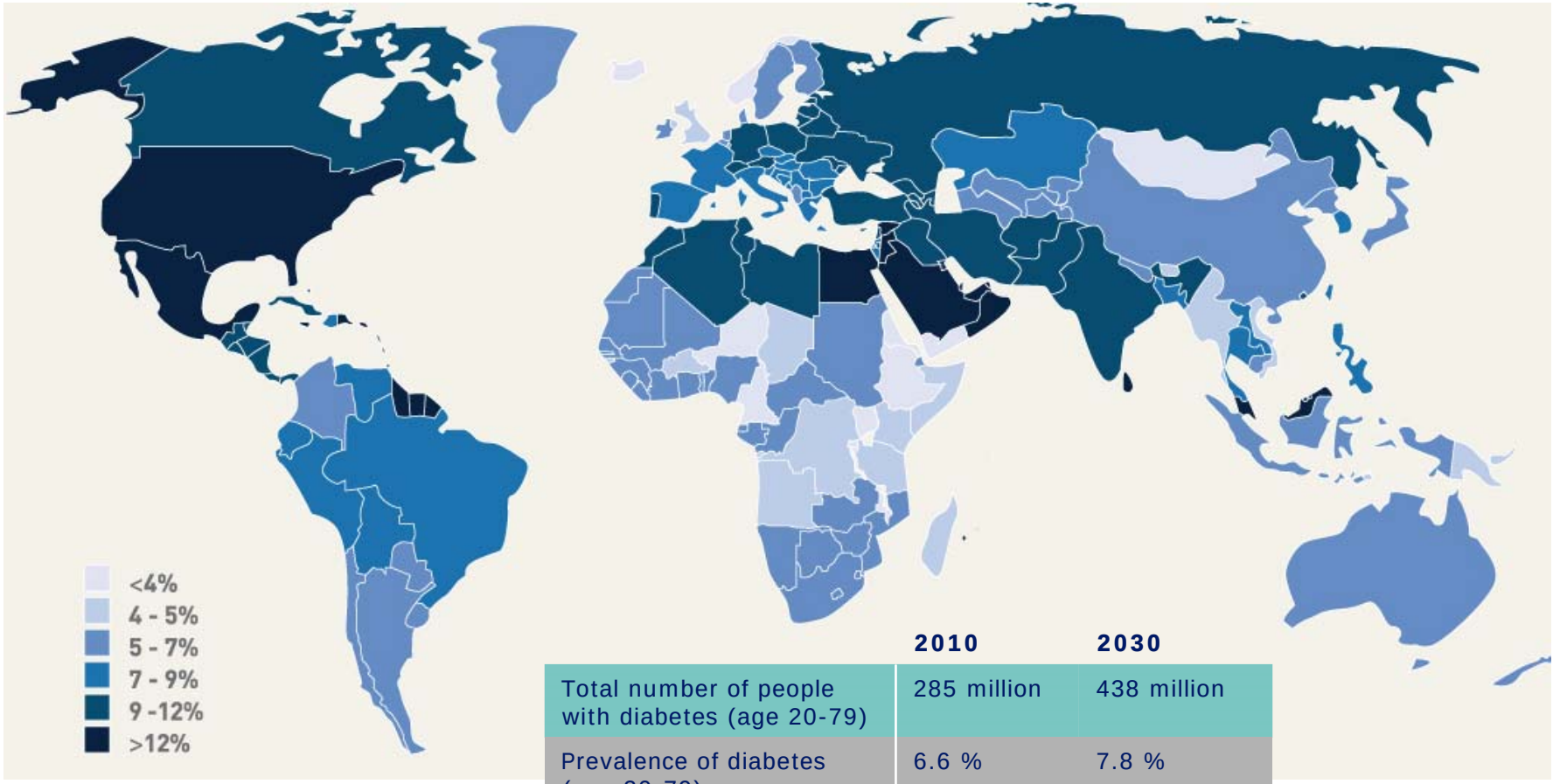
Despite improvements in survival, patients with T2D remain at greater risk of CV mortality

Data from 457,473 patients with T2D from the Swedish National Diabetes Register



CV, cardiovascular; T2D, type 2 diabetes Rawshani A *et al. N Engl J Med* 2017;376:1407

Prevalence of diabetes in 2030

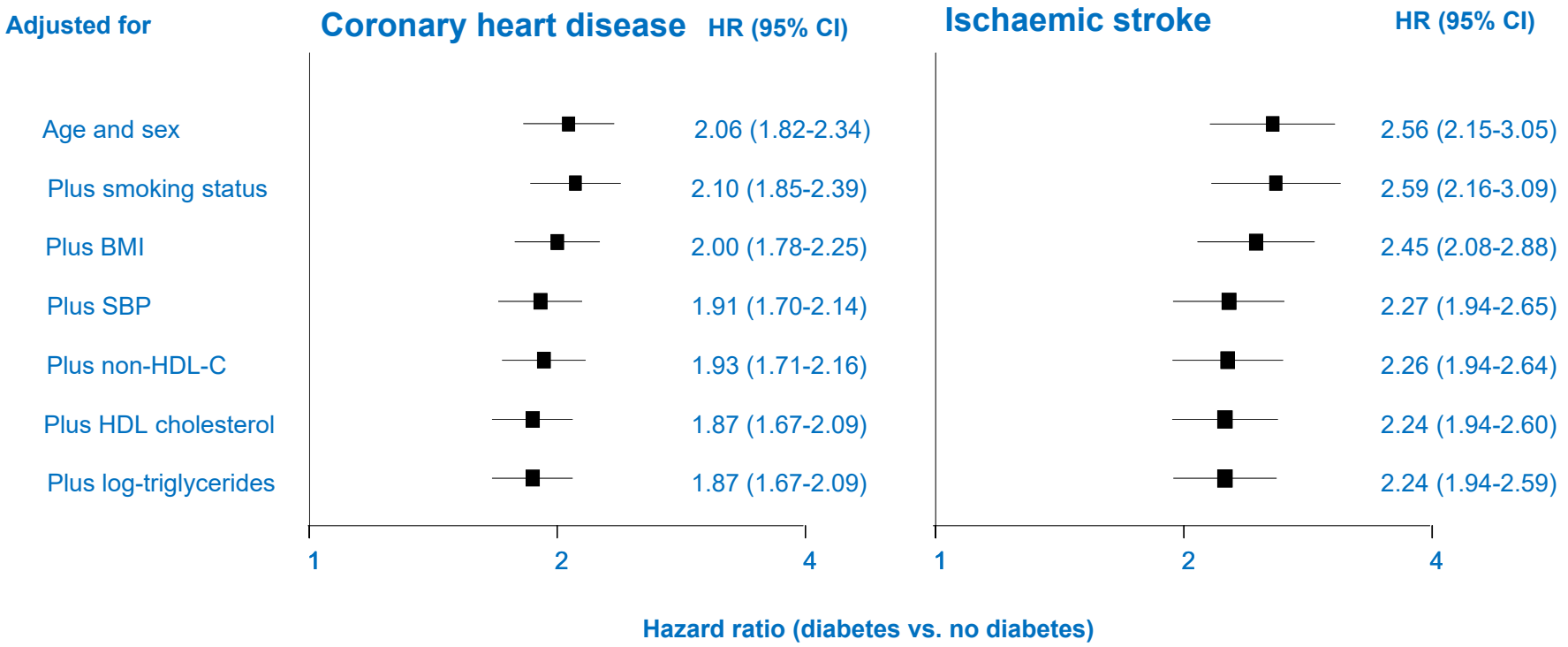


	2010	2030
Total number of people with diabetes (age 20-79)	285 million	438 million
Prevalence of diabetes (age 20-79)	6.6 %	7.8 %

IDF diabetes atlas, 4th edition, 2009

What drives increased cardiovascular disease in diabetes?

Diabetes risk is not fully explained by CV conventional risk factors



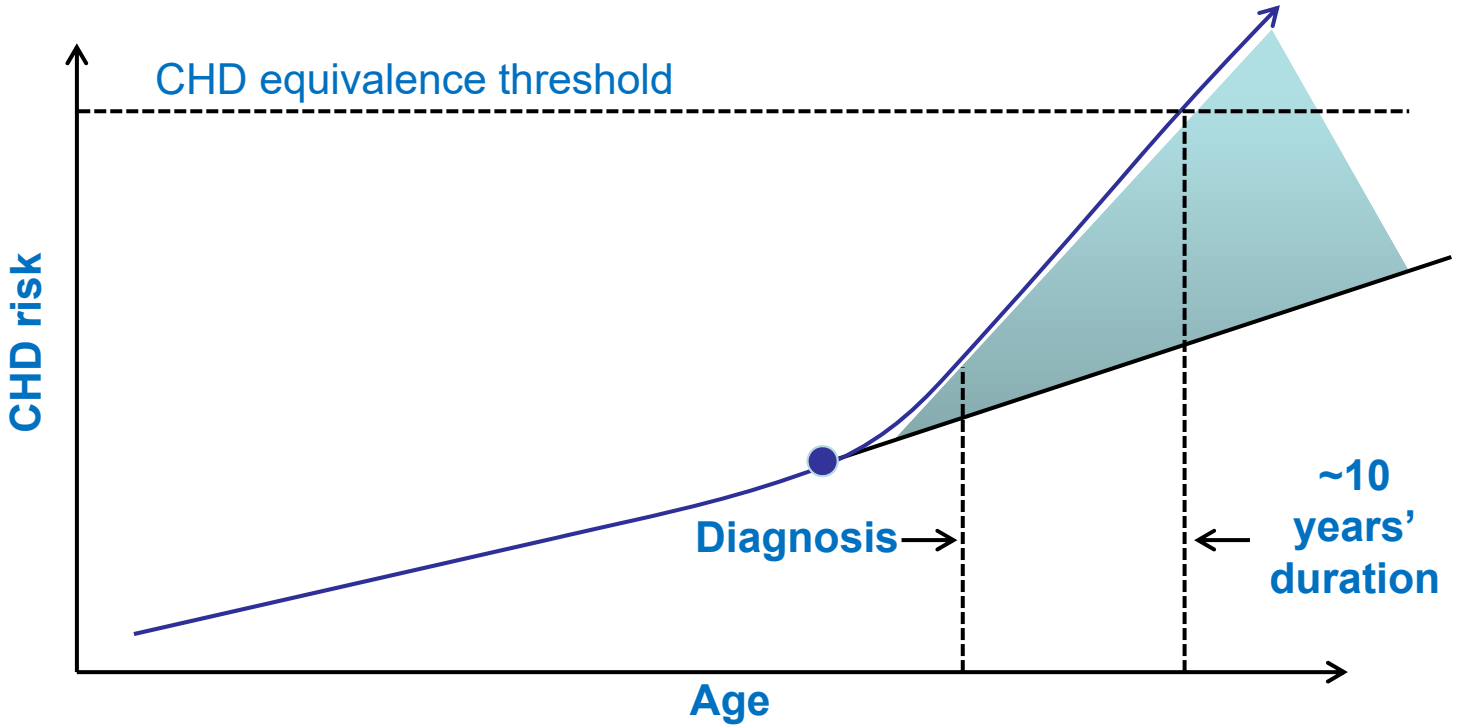
Lancet. 2010 Jun 26;375(9733):2215-22

DM duration matters to CVD

		Men with diabetes without MI		Men with MI
	None N=3197	Late onset N=307 **Mean duration 1.7 years**	Early onset N=107 **Mean duration 16 years**	Without diabetes N=368
CVD events (n=534)				
Age	1.00	1.59 (1.19,2.12)	2.61 (1.73,3.96)	2.35 (1.88,2.95)
Adj	1.00	1.53 (1.15,2.06)	2.52 (1.65,3.84)	2.23 (1.76,2.83)

Wannamethee, Shaper, Whincup, Lennon, Sattar. Br Reg Heart Survey.Arch Intern Med. 2011,14;171(5):404-10

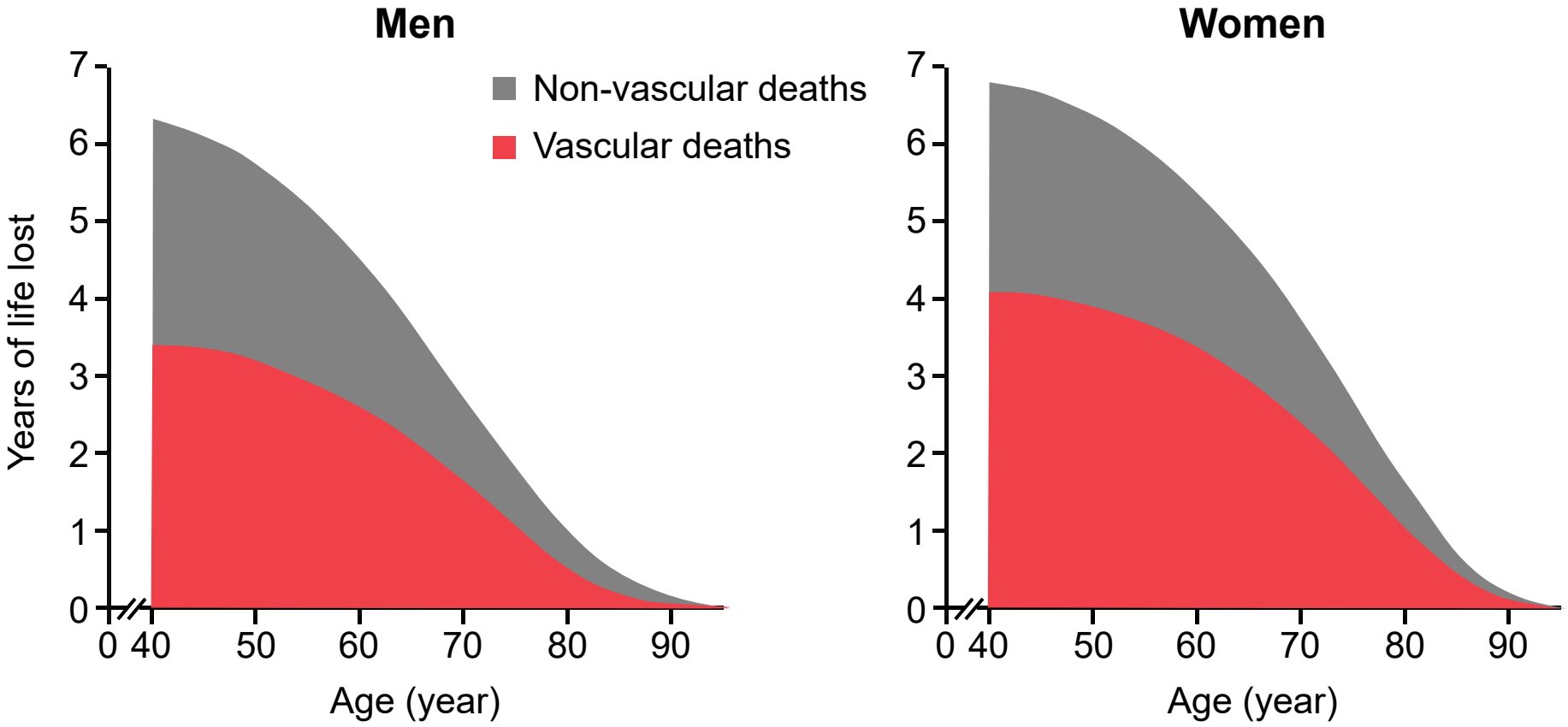
Type 2 diabetes increases CVD risk over time



- CVD/CHD risk at or prior to diagnosis is determined by conventional CHD risk factors
- Hyperglycaemia in the diabetic range increases CHD risk over time
- After a diabetes duration of >10 years CHD risk equivalence is reached

Sattar N. Diabetologia 2013;56:686-695.

Diabetes associated with significant loss of life years

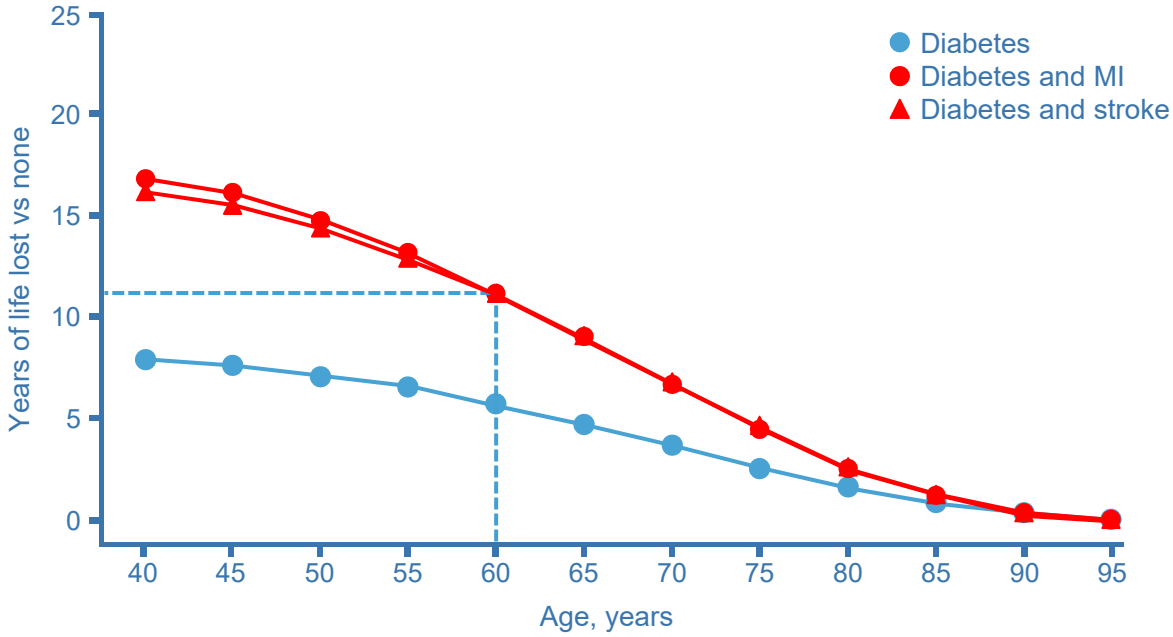


On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes

Seshasai et al. N Engl J Med 2011;364:829-41.

Life expectancy reduced by ~12 years in diabetes patients with previous CVD*

Modelling of years of life lost by disease status of participants at baseline compared with those free of diabetes, stroke and MI



*Male, 60 years of age with history of MI or stroke
CVD, cardiovascular disease; MI, myocardial infarction

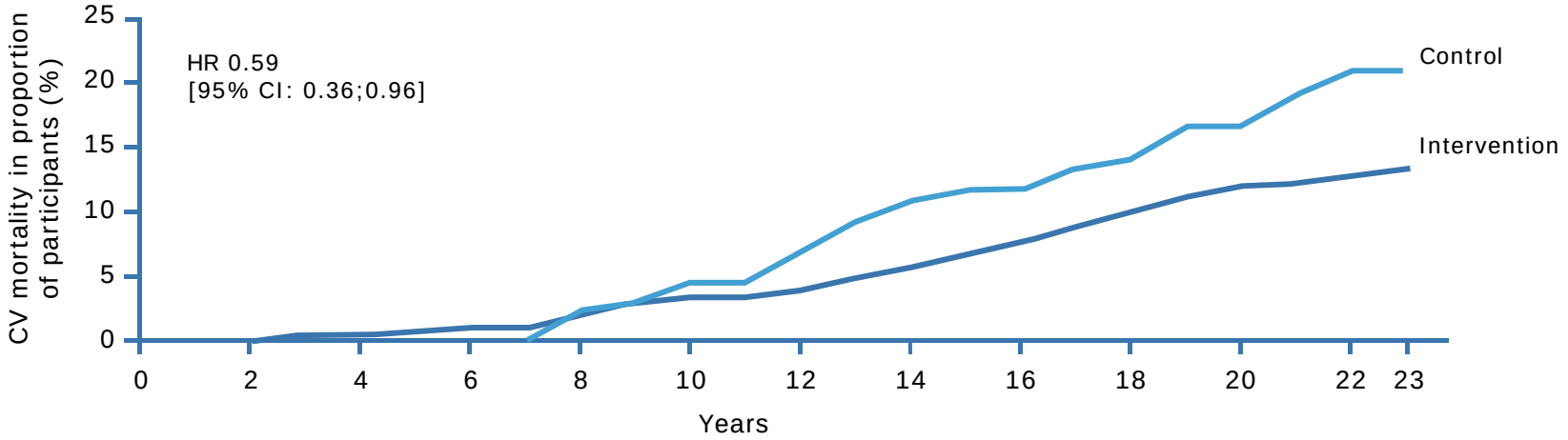
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52–60

Does managing CV risks in diabetes work?

Lifestyle intervention* associated with reduced CV mortality

DA QING DIABETES PREVENTION STUDY:

6-year lifestyle intervention programme for Chinese people with impaired glucose tolerance



Cumulative death incidence % [95% CI]	Intervention (n=430)	Control (n=138)	Hazard ratio [95% CI]	p value
All-cause mortality	28.1 (23.9;32.4)	38.4 (30.0;46.5)	0.71 (0.51;0.99)	0.049

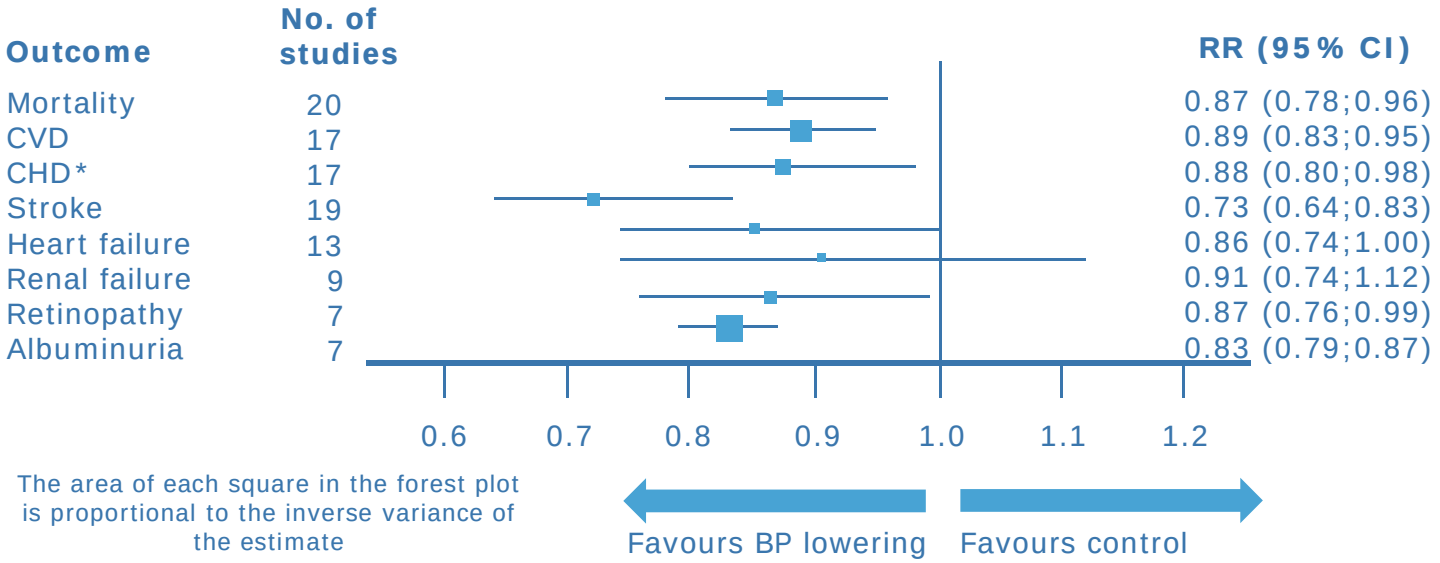
*Intervention was split across three categories: diet, exercise and both diet and exercise. Data are n (%) unless stated otherwise
CI, confidence interval; CV, cardiovascular; HR, hazard ratios adjusted by clinic

Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–480

CVD risk benefit of BP lowering in a T2D population

META-ANALYSIS OF 40 RCTs PUBLISHED 1966–2014 (N=100,354 PATIENTS WITH T2D)

Standard associations between 10 mmHg lower SBP and all-cause mortality and macrovascular and microvascular outcomes in patients with T2D

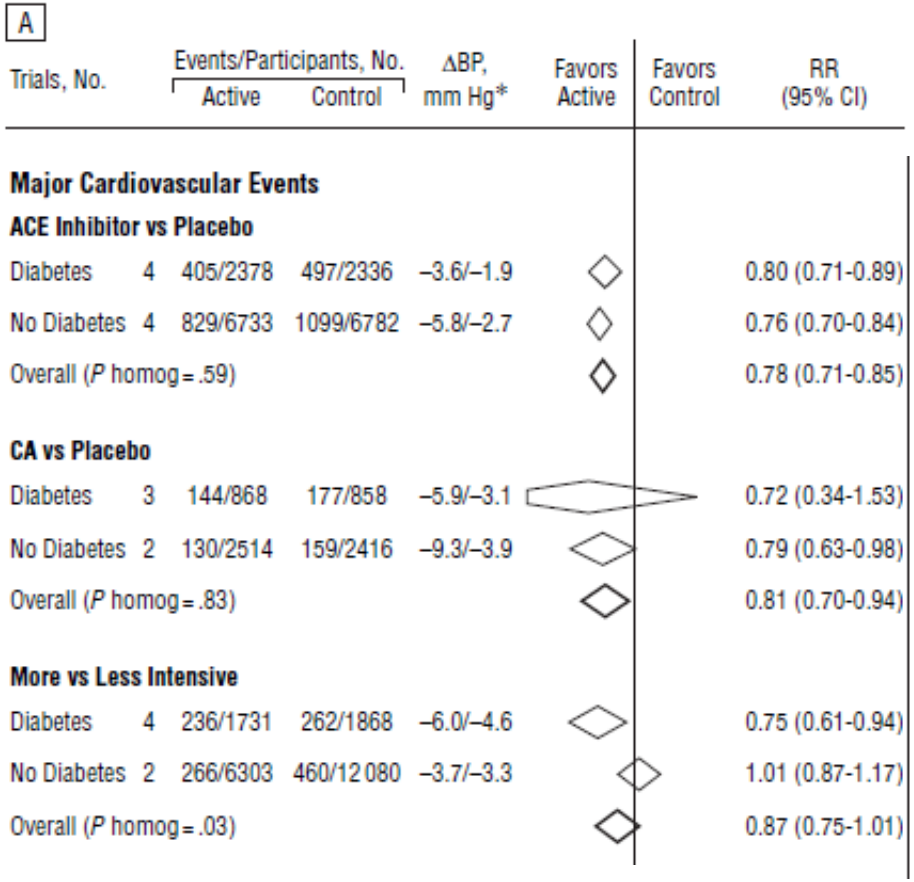


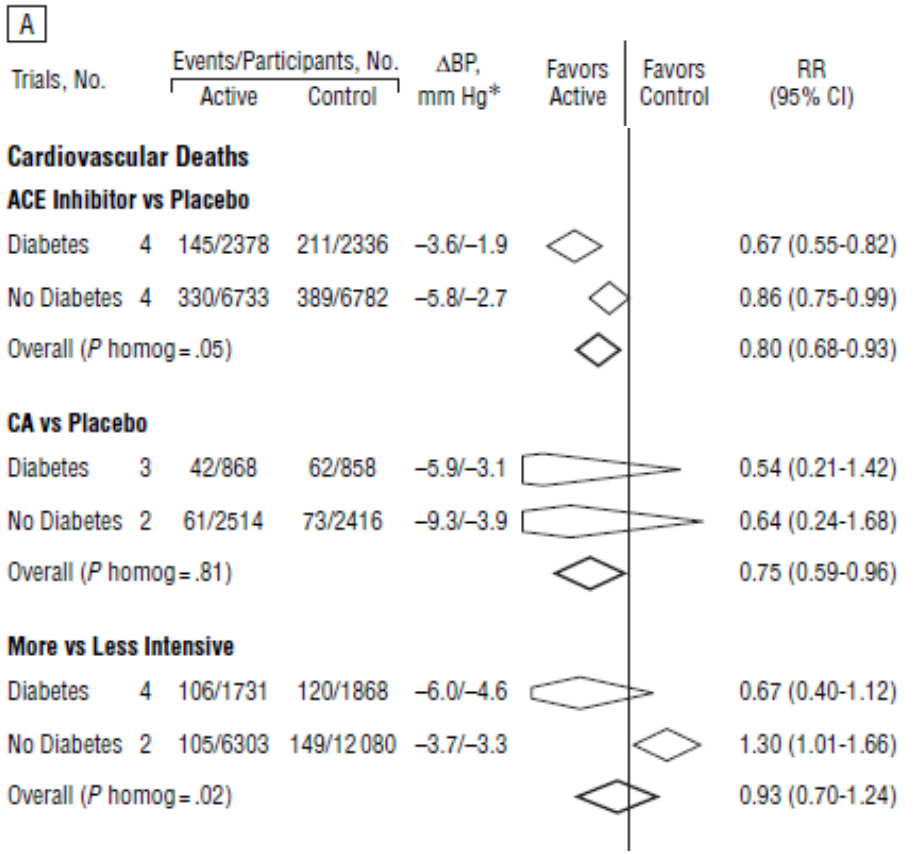
*Defined as fatal and non-fatal MI (excluding silent MI) and sudden cardiac death

BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; RCT, randomised controlled trial; RR, relative risk; SBP, systolic blood pressure

Emdin CA et al. *JAMA* 2015;313:603–615

Similar proportional reductions in risk with BP lowering in diabetes as non-diabetes



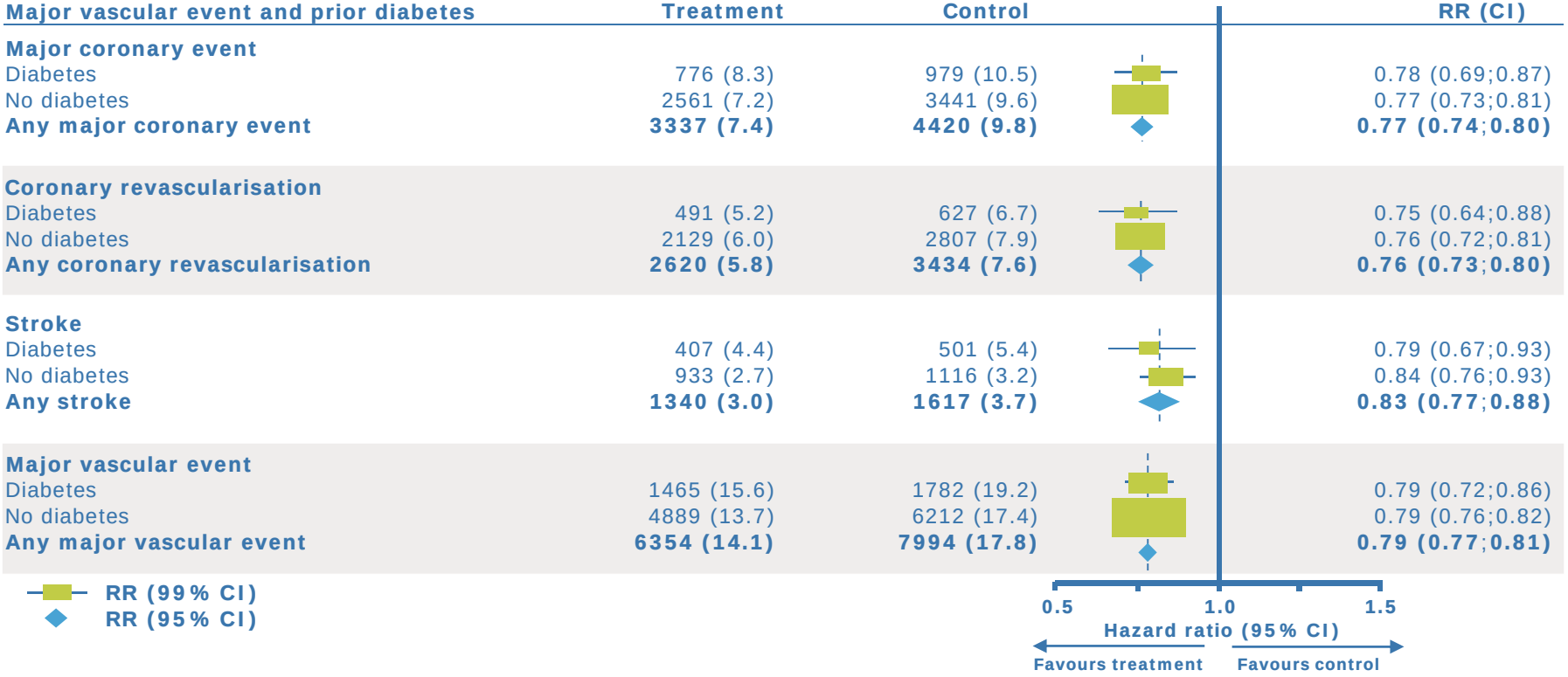


BP treatment Trialists. Arch Int Med 2005, 165, 1410-1419

Effects of 1 mmol/L reduction in LDL-C on vascular events

PATIENTS WITH AND WITHOUT DIABETES FROM 14 RCTS

Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8.3)	979 (10.5)	0.78 (0.69;0.87)
No diabetes	2561 (7.2)	3441 (9.6)	0.77 (0.73;0.81)
Any major coronary event	**3337 (7.4)**	**4420 (9.8)**	**0.77 (0.74;0.80)**
Coronary revascularisation			
Diabetes	491 (5.2)	627 (6.7)	0.75 (0.64;0.88)
No diabetes	2129 (6.0)	2807 (7.9)	0.76 (0.72;0.81)
Any coronary revascularisation	**2620 (5.8)**	**3434 (7.6)**	**0.76 (0.73;0.80)**
Stroke			
Diabetes	407 (4.4)	501 (5.4)	0.79 (0.67;0.93)
No diabetes	933 (2.7)	1116 (3.2)	0.84 (0.76;0.93)
Any stroke	**1340 (3.0)**	**1617 (3.7)**	**0.83 (0.77;0.88)**
Major vascular event			
Diabetes	1465 (15.6)	1782 (19.2)	0.79 (0.72;0.86)
No diabetes	4889 (13.7)	6212 (17.4)	0.79 (0.76;0.82)
Any major vascular event	**6354 (14.1)**	**7994 (17.8)**	**0.79 (0.77;0.81)**

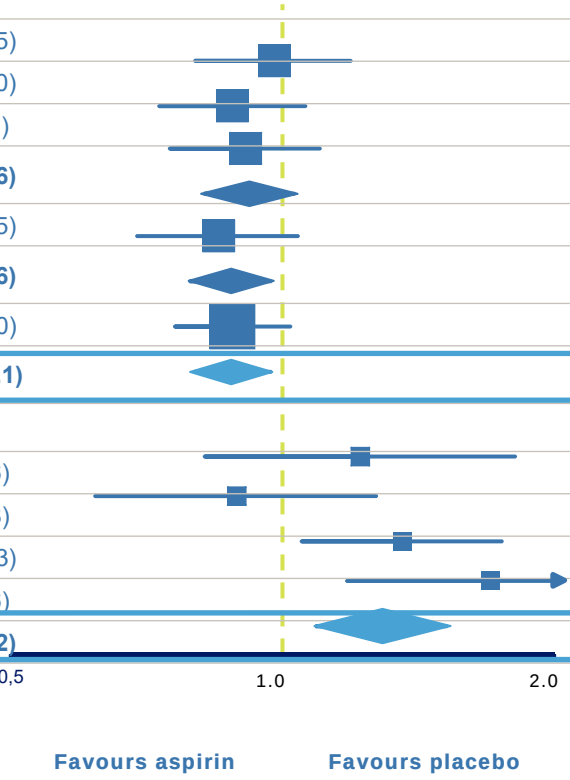


CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; RCT, randomised controlled trial; RR, relative risk

CTT Collaboration. *Lancet* 2008;371:117–125

ASCEND: Impact of aspirin on the primary safety outcome and other bleeding

Type of event	Aspirin (N=7740)	Placebo (N=7740)	Rate ratio (95% CI)	*p*-value
Vascular outcomes	*no. of participants with event (%)*			
Non-fatal MI	191 (2.5)	195 (2.5)	0.98 (0.80;1.19)	
Non-fatal presumed IS	202 (2.6)	229 (3.0)	0.88 (0.73;1.06)	
Vascular death excluding IH	197 (2.5)	217 (2.8)	0.91 (0.75;1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82;1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69;1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79;0.97)**	**0.01**
Any arterial revascularisation	340 (4.4)	384 (5.0)	0.88 (0.76;1.02)	
Any serious vascular event or revascularisation	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80;0.97)**	
Major bleeding				
Intracranial haemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82;1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62;1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05;1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18;2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09;1.52)**	**0.003**

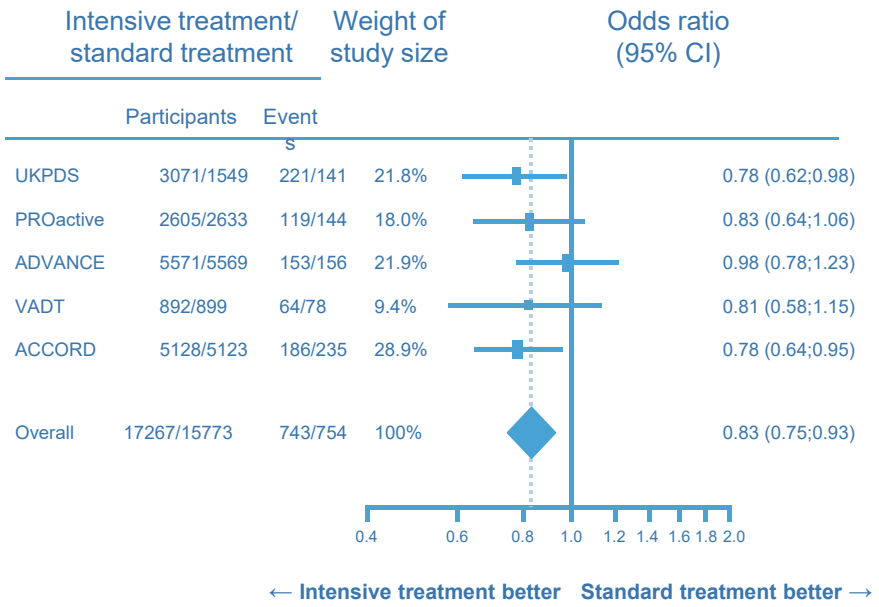


CI, confidence interval; IH, intracranial haemorrhage; IS, ischaemic stroke; MI, myocardial infarction; TIA, transient ischaemic attack

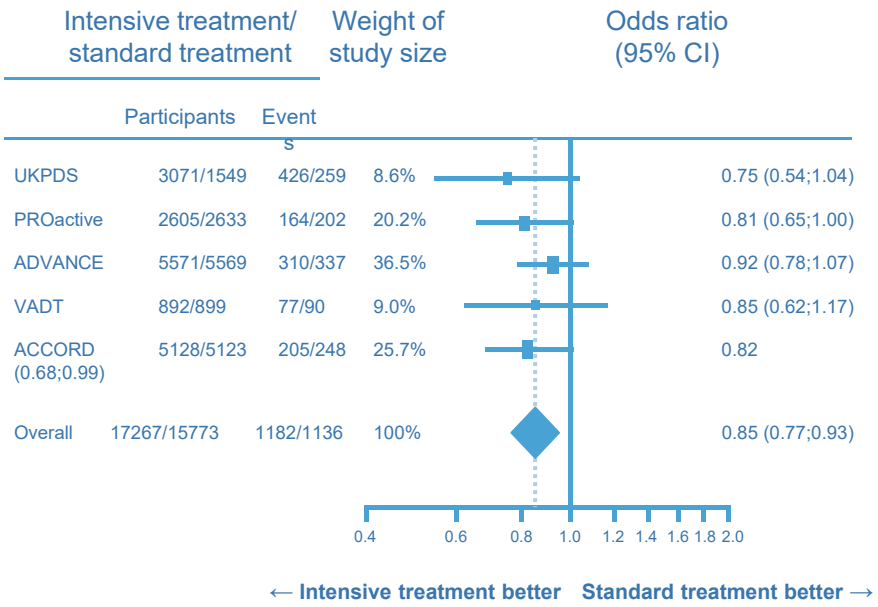
Bowman L et al. *N Engl J Med* 2018;379:1529–1539

Probability of events with intensive glucose lowering versus standard treatment

Non-fatal myocardial infarction



Coronary heart disease

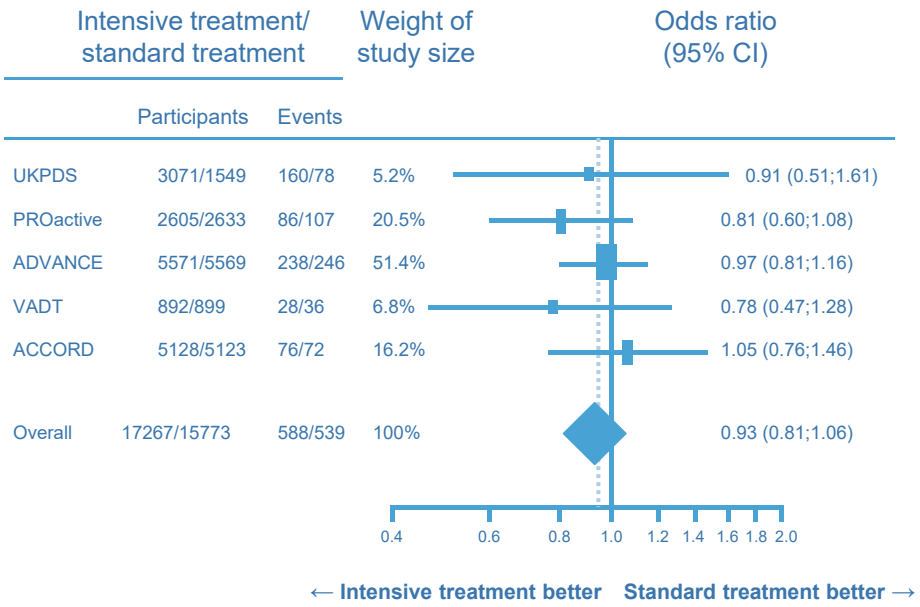


CI, confidence interval

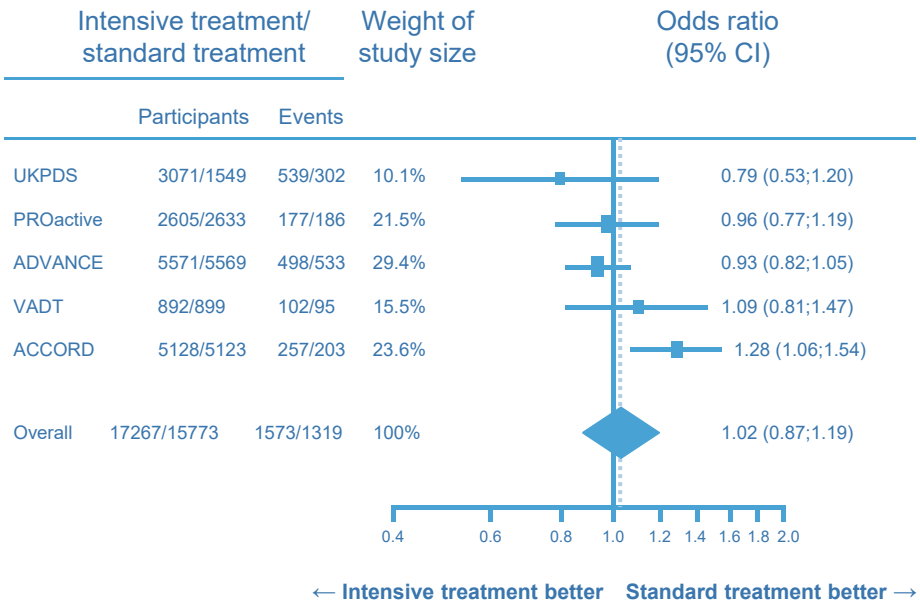
Ray KK et al. *Lancet* 2009;9677:1765–1772

Probability of events with intensive glucose-lowering versus standard treatment

Stroke events

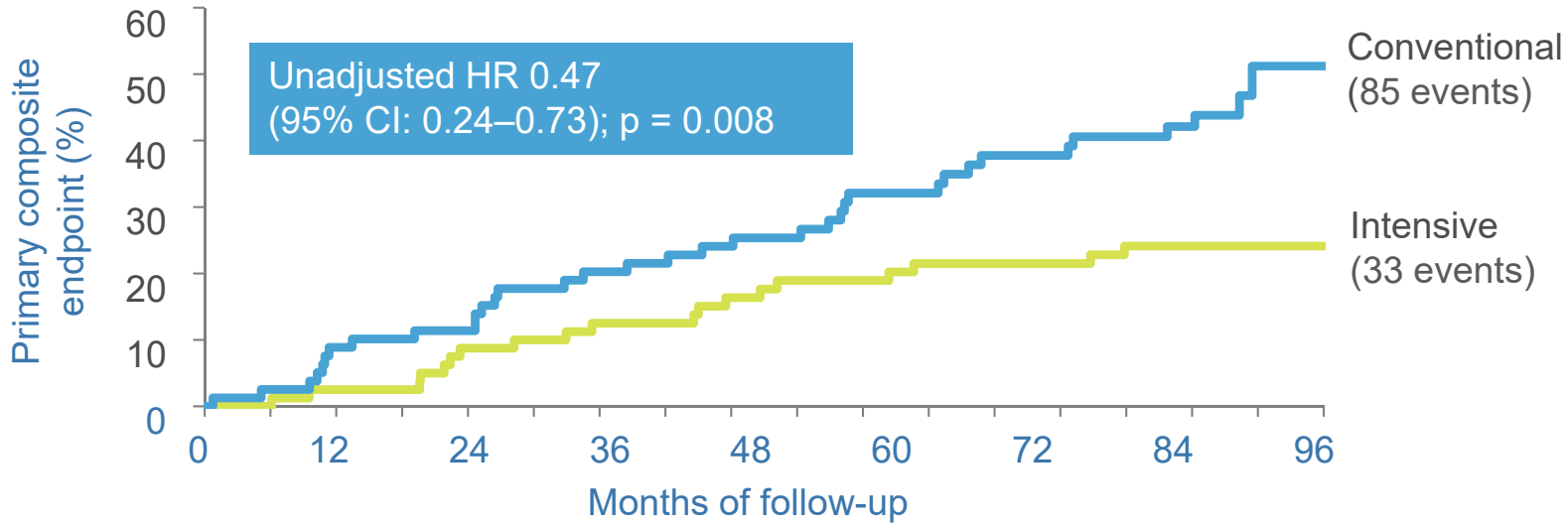


All-cause mortality



CI, confidence interval
Ray KK et al. *Lancet* 2009;9677:1765–1772

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



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

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

Conclusions

- Diabetes represents a state of accelerated CVD risk
- Challenges for primary care
  - Recognise and maximise traditional CV risk reduction
  - Use interventions proven to improve diabetes CV risk
    - especially in those with established disease
  - Teamwork and organized care
- Prevention of diabetes strategies are needed
    - reduce obesity
    - early diagnosis of diabetes (role of screening?)