中國醫藥大學附設醫院
China Medical University Hospital

Adapt 2018 Diabetes Guidelines into Clinical Practice – The Perspective of a Cardiologist

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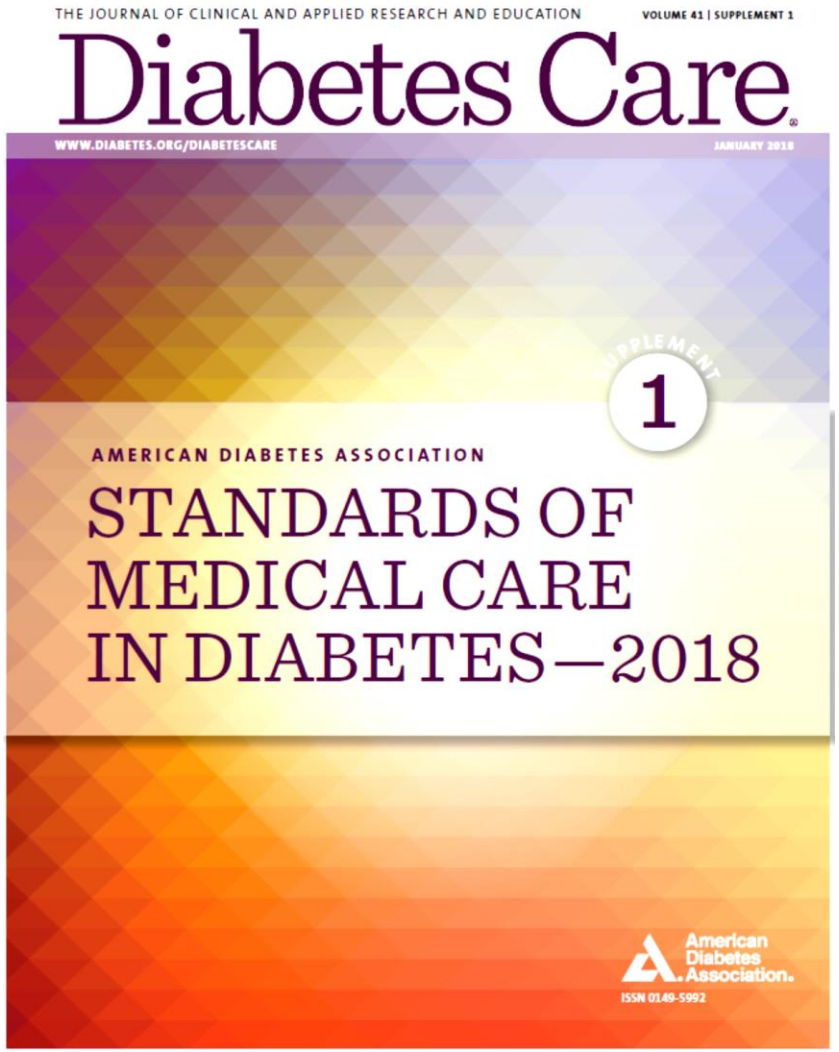
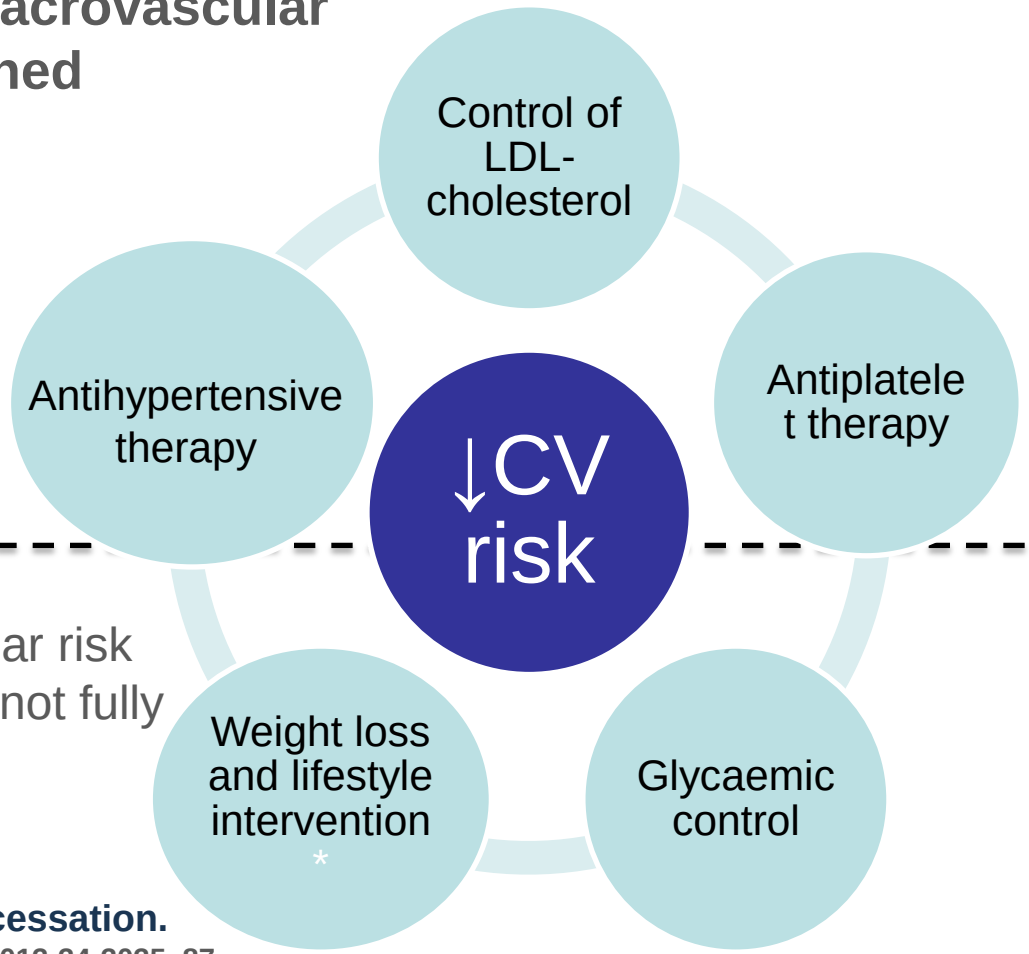
Implementation of ADA Guideline 2018 - “Standards of care!”



Approaches to managing CV risk in patients with T2D

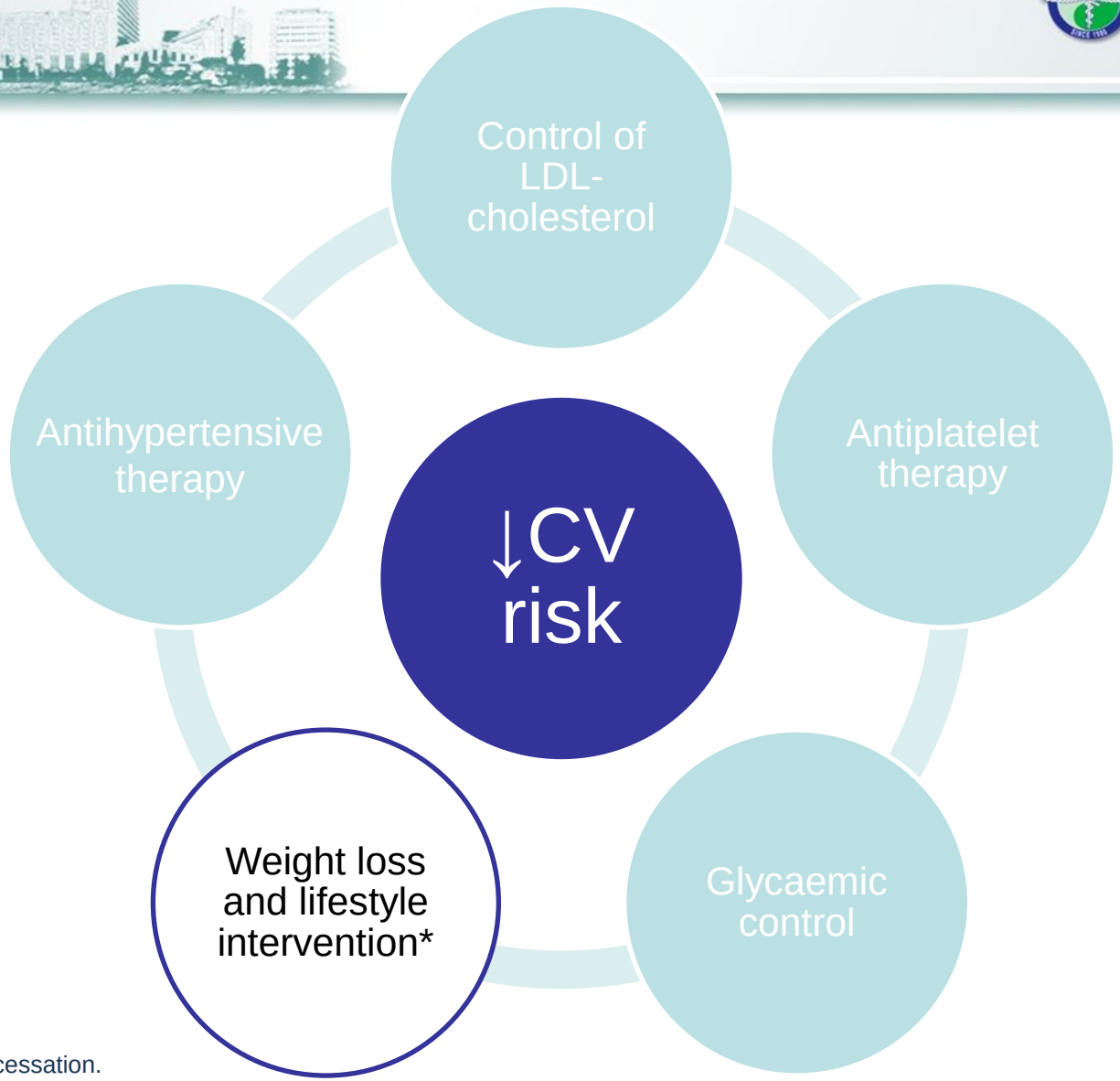
Effects on macrovascular risk established



Effects on macrovascular risk uncertain or not fully established

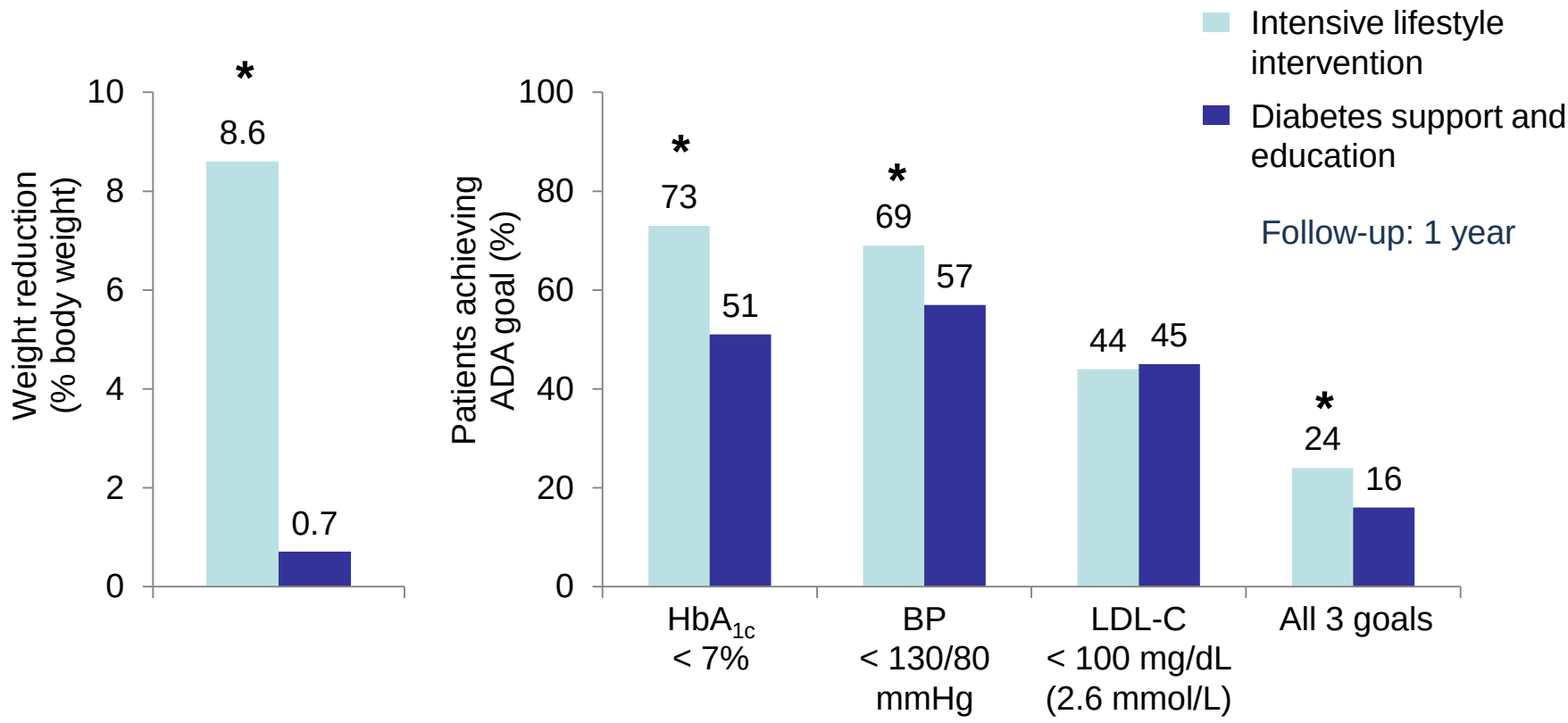
***Includes smoking cessation.**

Rydén et al. Eur Heart J 2013;34:3035–87.



*Includes smoking cessation.

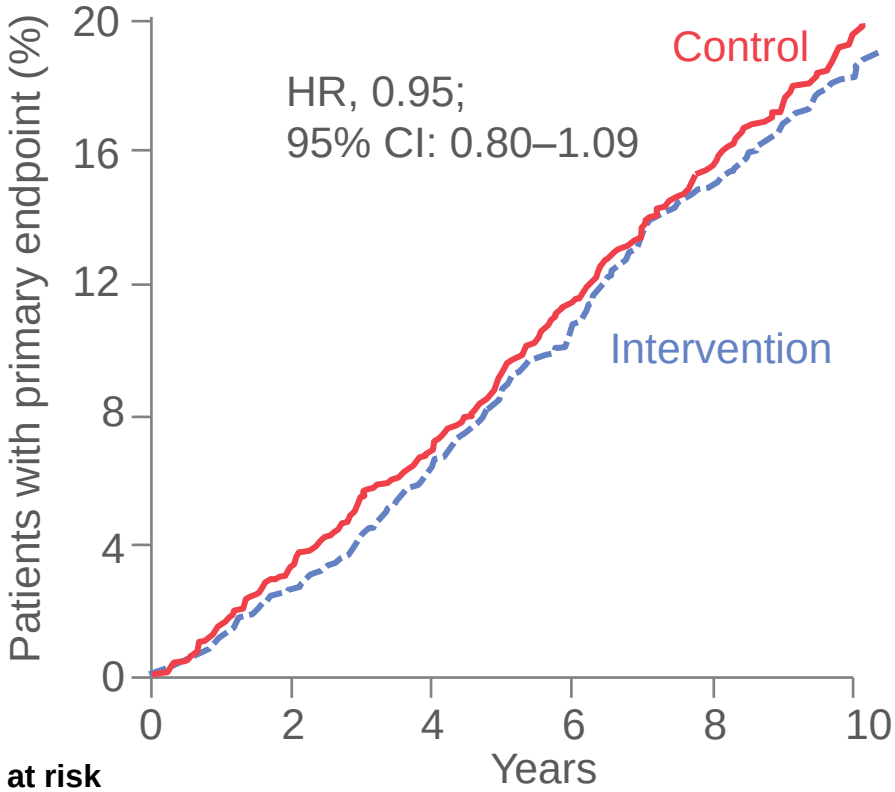
Intensive lifestyle intervention, focused on weight loss, improved CV risk factors in T2D in the short term

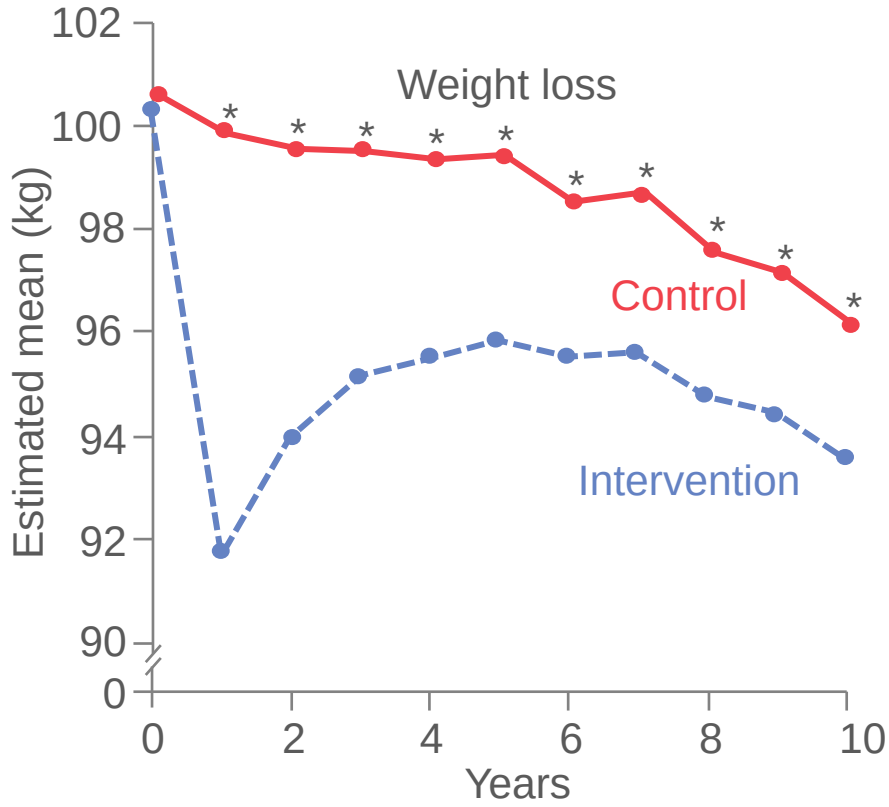


*p < 0.001 vs diabetes support and education.

Look AHEAD Research Group. Diabetes Care 2007;30:1374–83.

Intensive lifestyle intervention, focused on weight loss, did not improve CV risk in T2D in the long term





No. at risk

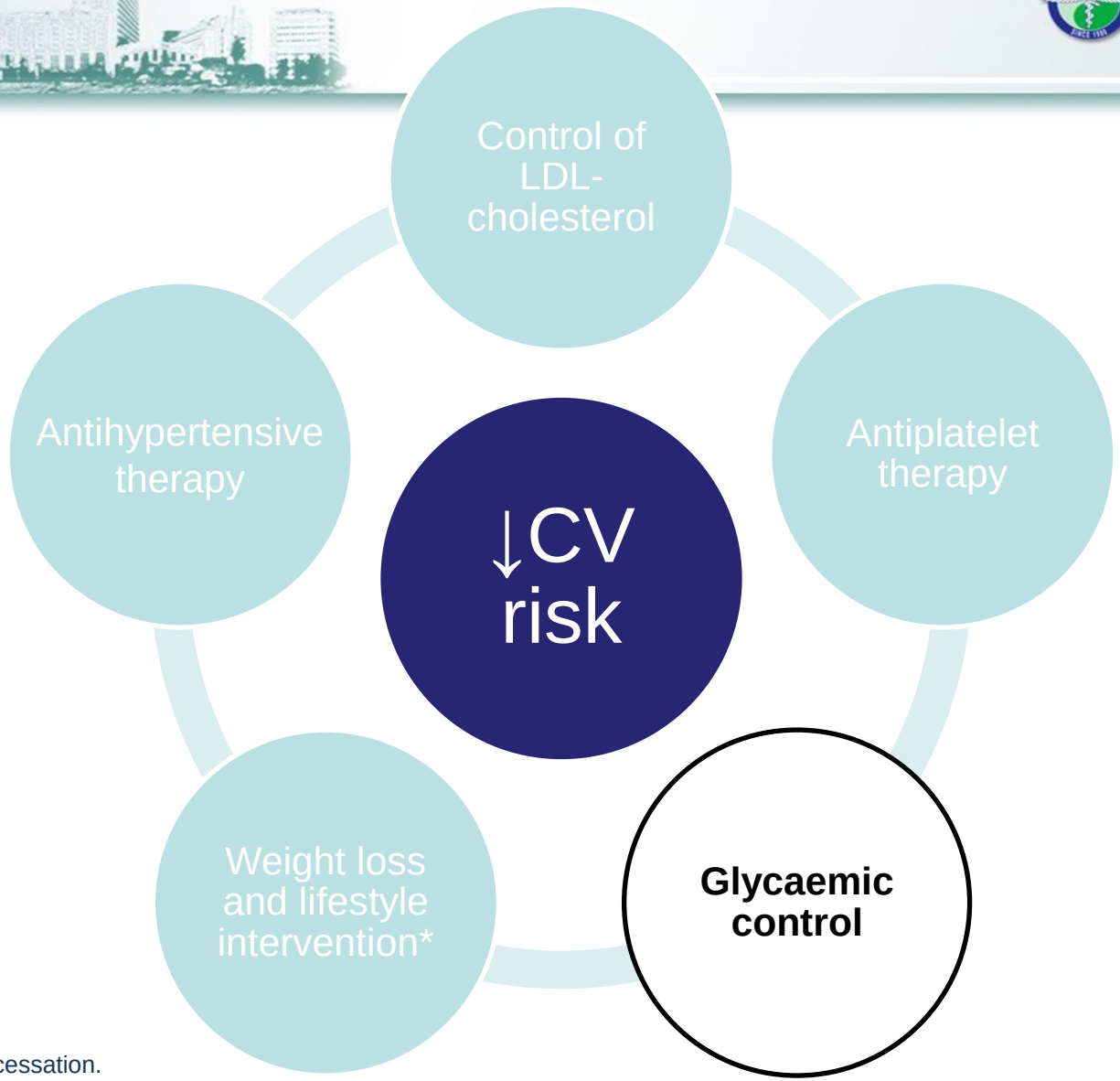
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Main effect: -4 (95% CI: -5 to -3)

* $p < 0.001$

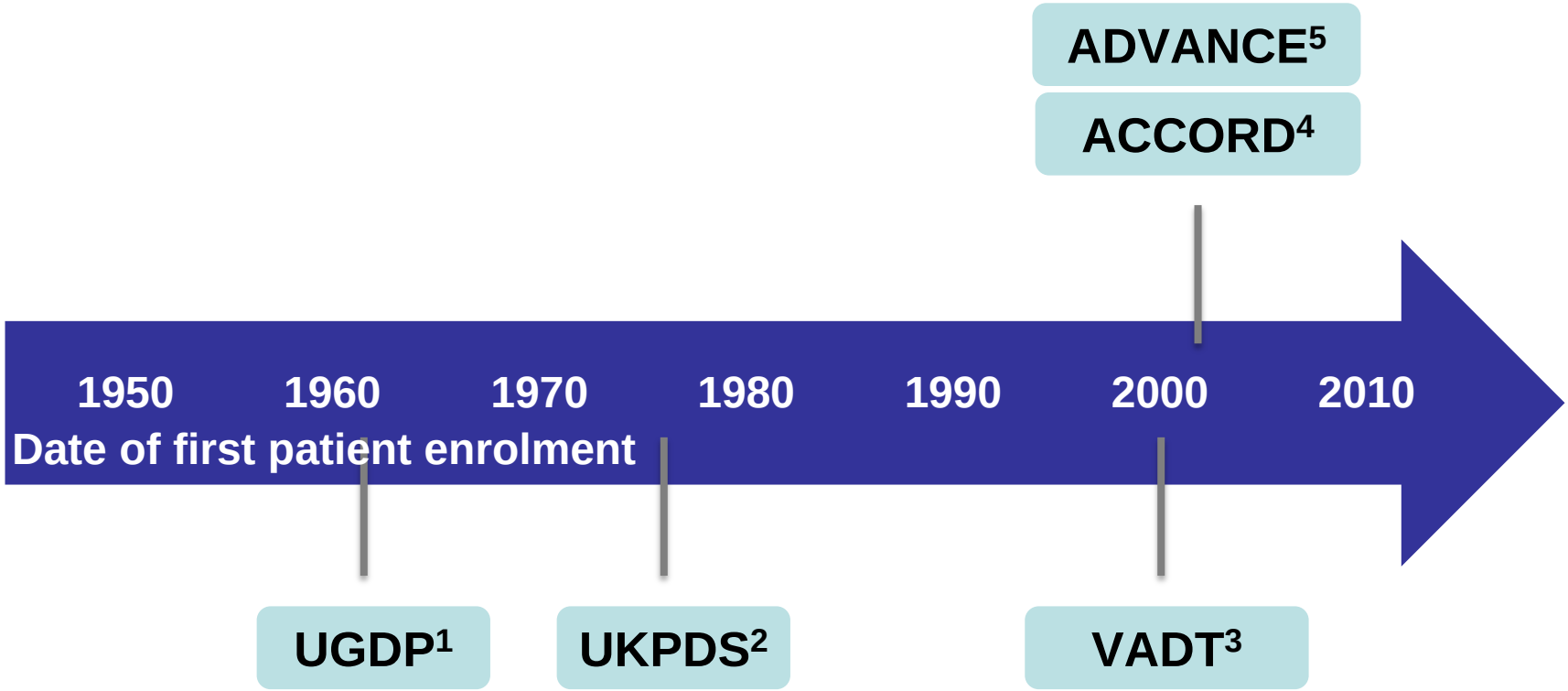
Endpoint: Composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for angina.

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



*Includes smoking cessation.

Major historic T2D CV outcomes trials focused on intensive vs conventional glycaemic control



1. Meinert et al. Diabetes 1970;19(suppl):789–830. 2. UKPDS 33. Lancet 1998;352:837–53.
3. Duckworth et al. N Engl J Med 2009;360:129–39. 4. Gerstein et al. N Engl J Med 2008;358:2545–59.
5. Patel et al. N Engl J Med 2008;358:2560–72.

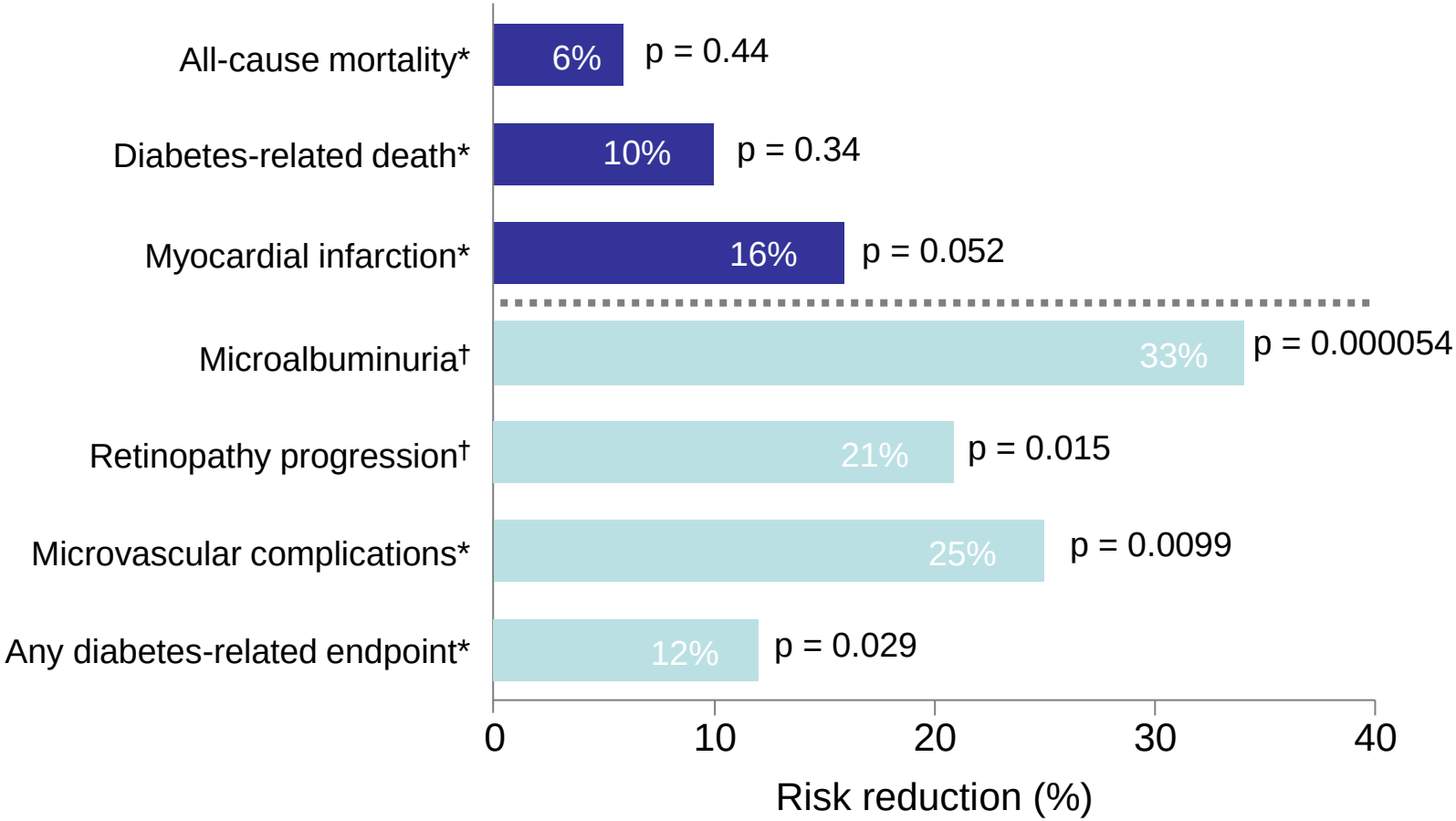
Major historic T2D CV outcomes trials had different durations and baseline CV risk

Trial	N	Duration of follow-up (years)	Glycaemic target		Main inclusion criteria
			Intensive treatment	Standard treatment	
UKPDS[1]	3,867	10.0*	FPG < 6 mmol/L	FPG < 15 mmol/L	T2D newly diagnosed
ADVANCE[2]	11,140	4.3*	HbA_{1c} ≤ 6.5%	per local guidelines	T2D and macrovascular or microvascular disease, or ≥ 1 CV risk factor
ACCORD[3]	10,251	3.5†	HbA_{1c} < 6.0%	HbA_{1c} 7.0–7.9%	T2D and CVD or ≥ 2 CV risk factors
VADT[4]	1,791	5.6*	HbA_{1c} ≤ 6%	HbA_{1c} 8–9%	Long-standing, poorly controlled T2D

*Median; †Mean.

1. UKPDS 33. Lancet 1998;352:837–53. 2. Patel et al. N Engl J Med 2008;358:2560–72.
3. Gerstein et al. N Engl J Med 2008;358:2545–59. 4. Duckworth et al. N Engl J Med 2009;360:129–39.

UKPDS: Intensive glycaemic control reduced microvascular but not macrovascular outcomes

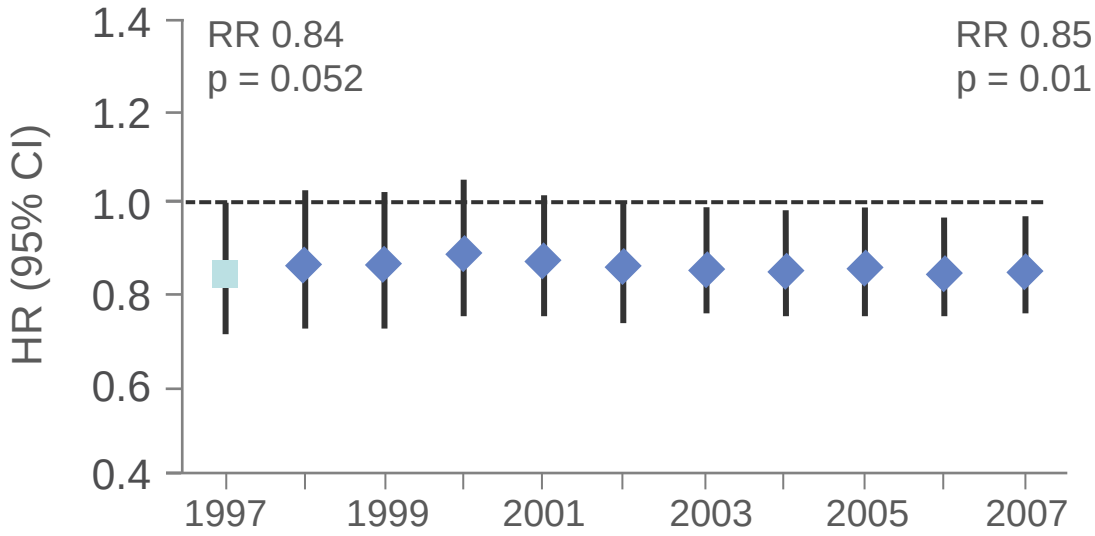


*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.

UKPDS 33. Lancet 1998;352:837–53.

UKPDS: Long-term follow-up revealed significant reduction in MI associated with previous intensive glycaemic control

Fatal or non-fatal MI: Intensive treatment

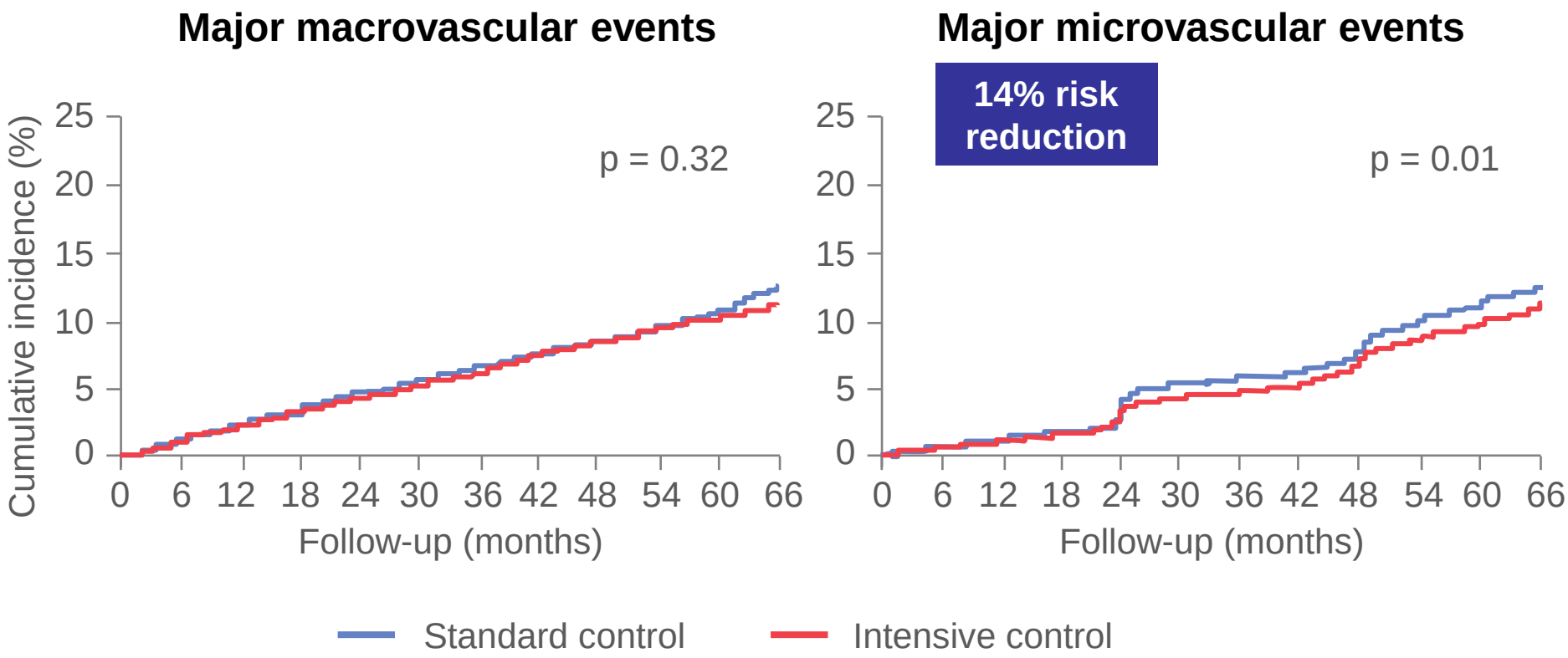


No. of events						
Conventional therapy	186	212	239	271	296	319
Sulphonylurea–insulin	387	450	513	573	636	678

■ Overall values at the end of the study in 1997
◆ Annual values during the 10-year post-trial monitoring period

Holman et al. N Engl J Med 2008;359:1577–89.

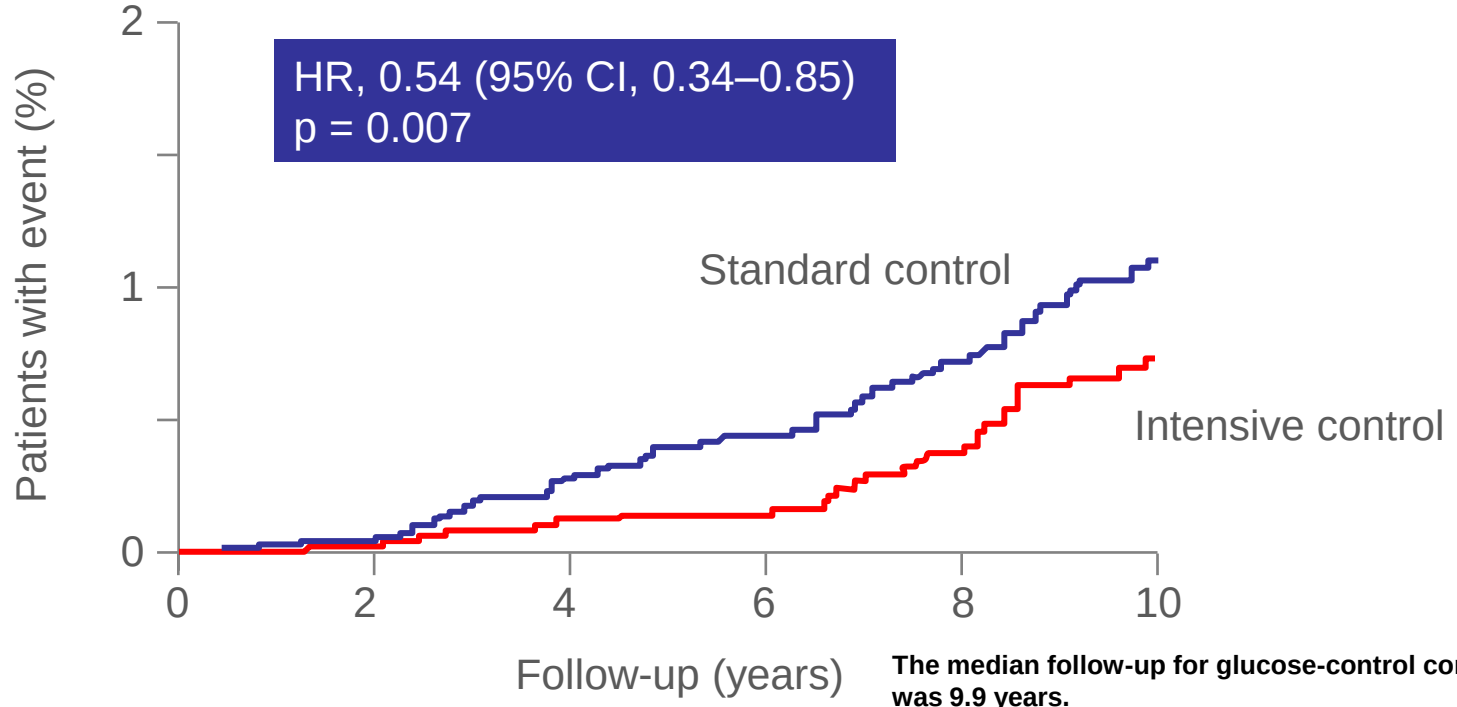
ADVANCE: intensive glycaemic control reduced microvascular but not macrovascular events



Patel et al. N Engl J Med 2008;358:2560–72.

ADVANCE-ON: intensive glycaemic control had significant benefit for end-stage renal disease

End-stage renal disease



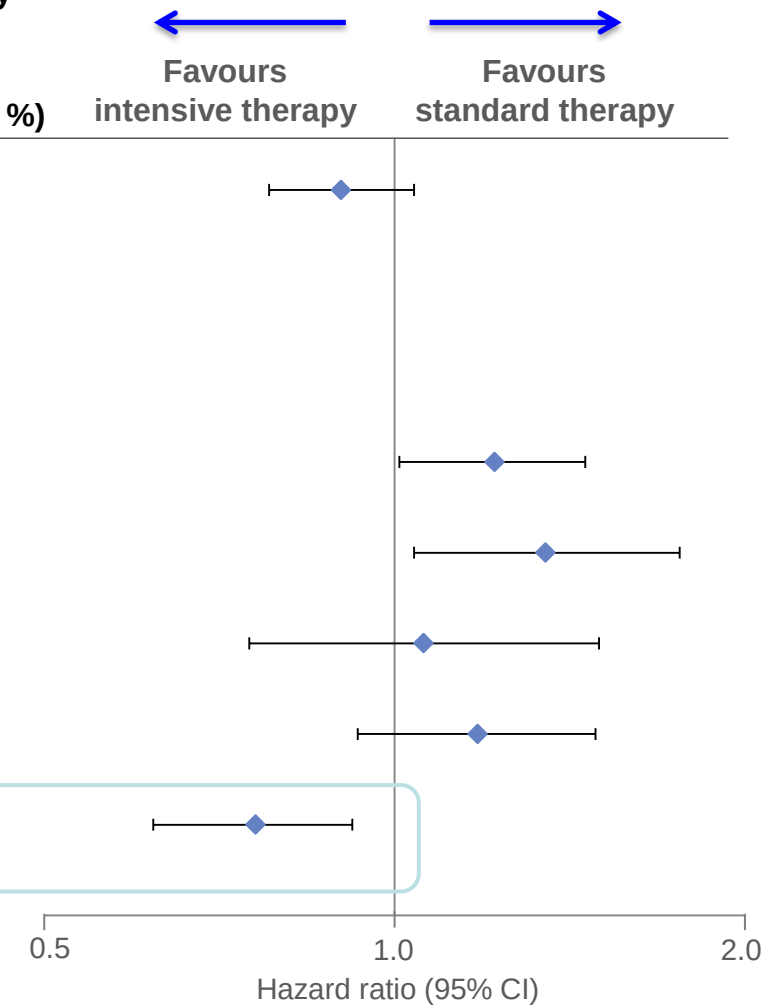
The median follow-up for glucose-control comparison was 9.9 years.

No. at risk						
Intensive	5571	5402	5186	4124	3764	2811
Standard	5569	5400	5173	4041	3681	2683

Zoungas et al. N Engl J Med 2014;371:1392-406.

ACCORD: Intensive glucose-lowering arm terminated early (after 3.5 years) because of higher mortality

Outcome	Intensive therapy (n = 5128) No. of patients (annual event rate, %)	Standard therapy (n = 5123) No. of patients (annual event rate, %)
Primary outcome*	**352 (2.11)**	**371 (2.29)**
Secondary outcome		
Death		
Any cause	**257 (1.41)**	**203 (1.14)**
CV cause	**135 (0.79)**	**94 (0.56)**
Non-fatal stroke	**67 (0.39)**	**61 (0.37)**
Fatal or non-fatal CHF	**152 (0.90)**	**124 (0.75)**
Non-fatal MI	186 (1.11)	2 3 5 (1.45)

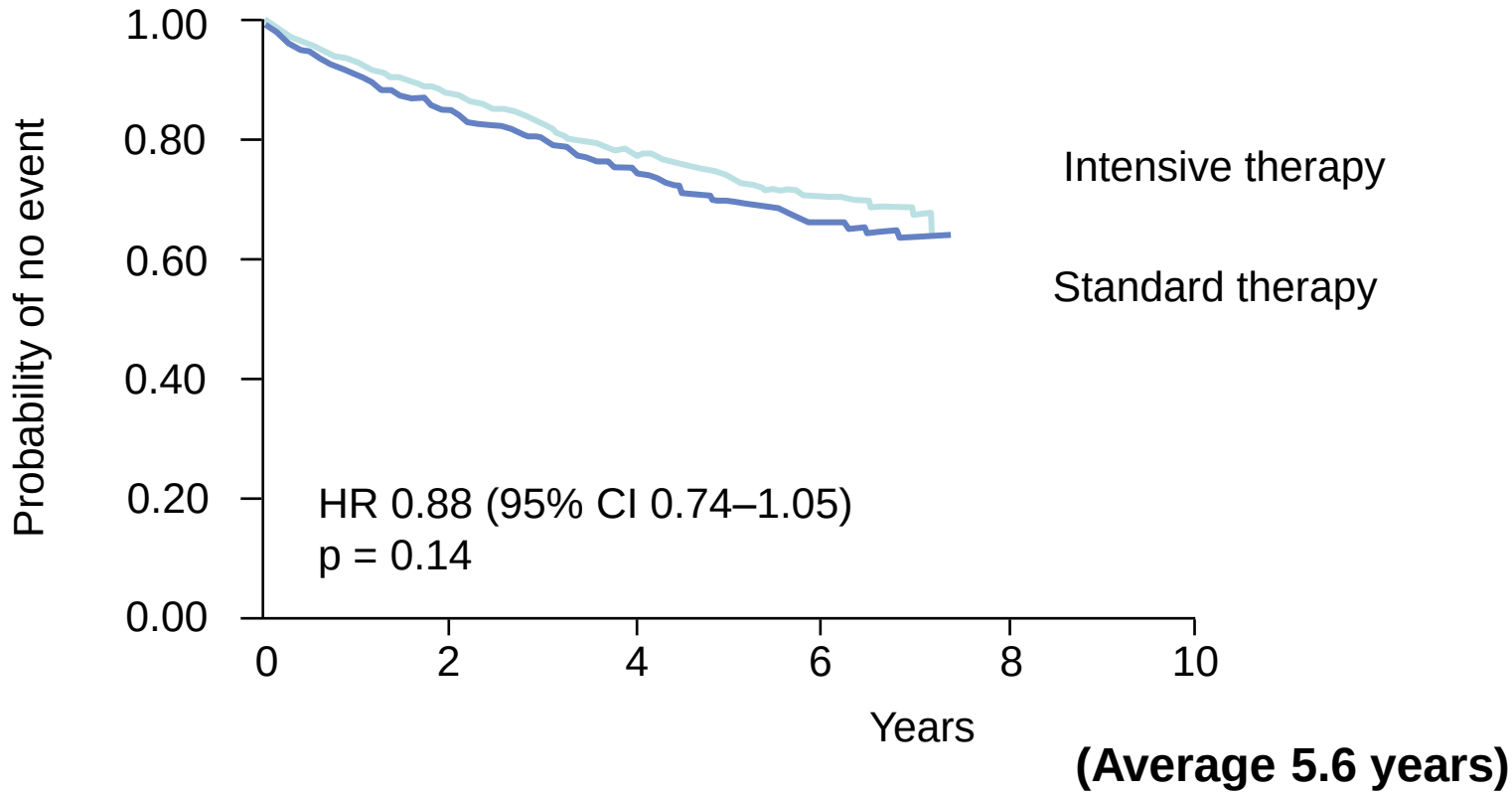


*First occurrence of non-fatal MI or non-fatal stroke or death from CV causes.

Gerstein et al. N Engl J Med 2008;358:2545–59.

VADT: No difference in primary endpoint between intensive and standard glucose-lowering therapy

Primary outcome*



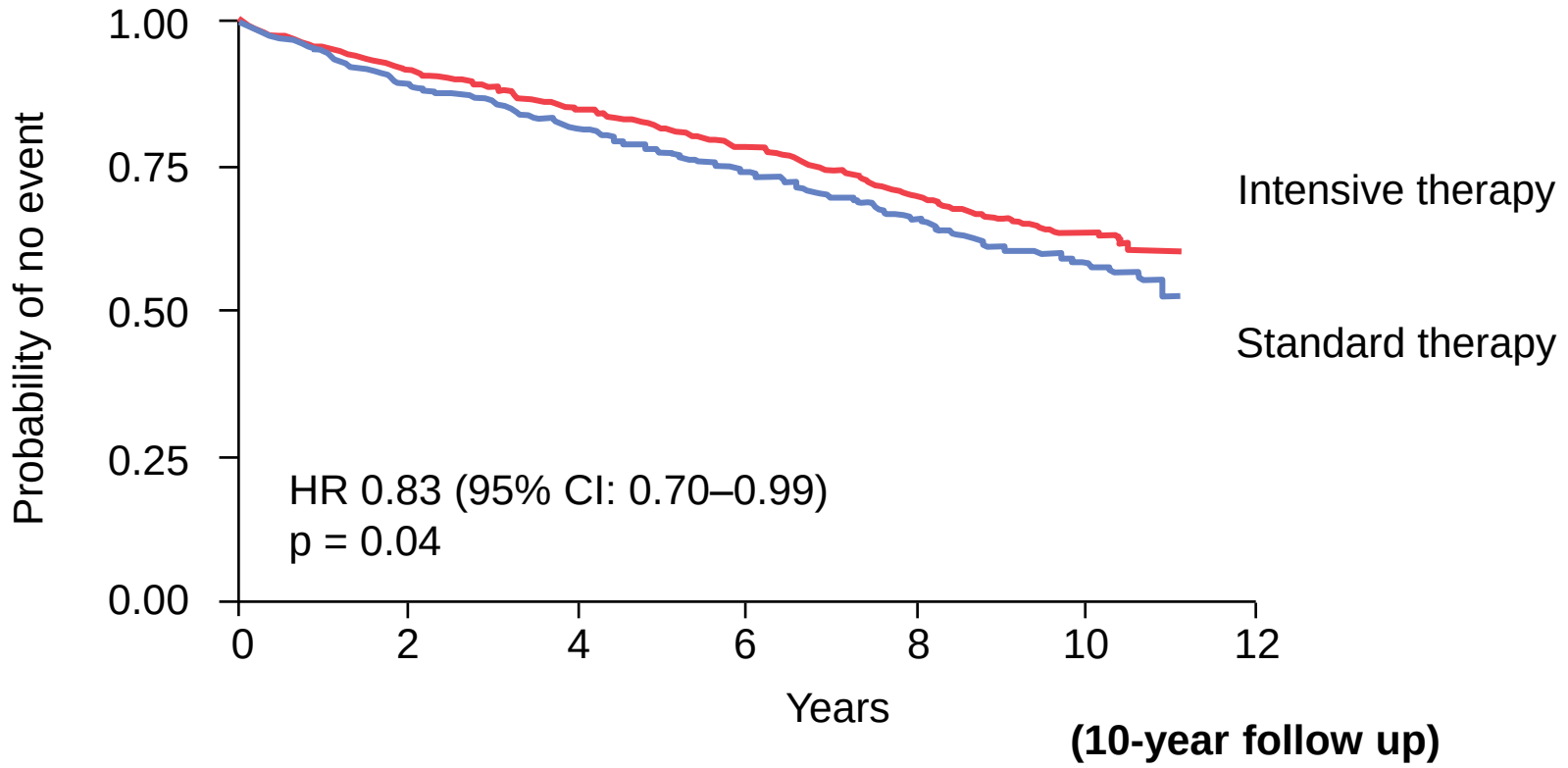
(Average 5.6 years)

***composite of MI, stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischaemic gangrene**

Duckworth et al. N Engl J Med 2009;360:129–39.

VADT: Significant benefit of intensive vs. standard glucose-lowering therapy in primary endpoint

Primary outcome*



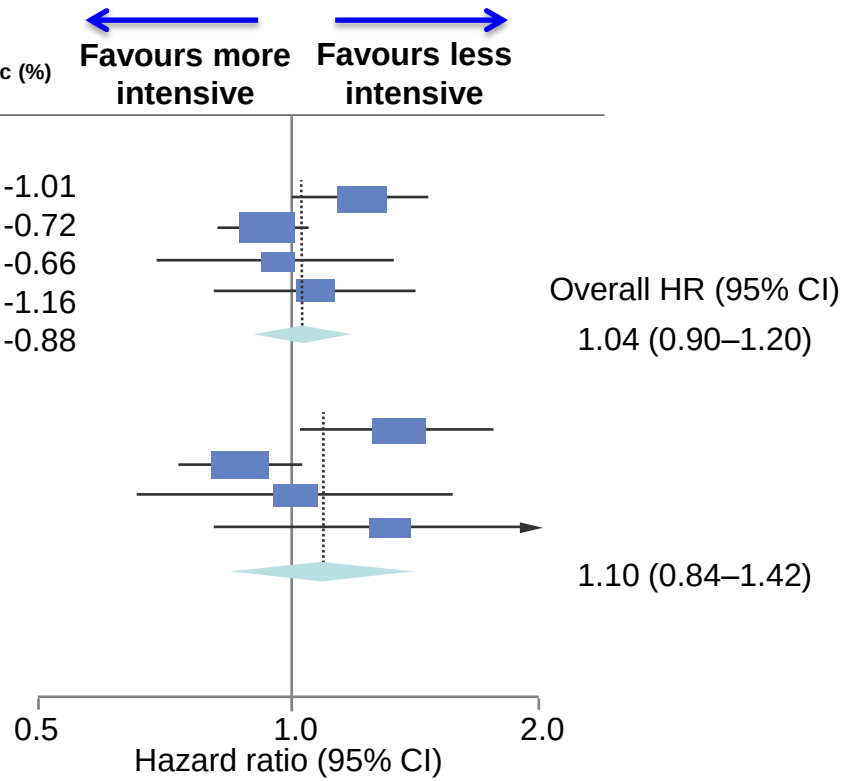
***composite of heart attack, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes**

Hayward et al. N Engl J Med 2015;372:2197-206.

No evidence from prospective trials demonstrate intensive glycaemic control reduces mortality

Meta-analysis including 27,049 participants and 2370 major vascular events

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA$_{1c}$ (%)
All-cause mortality			
ACCORD	257 (1.41)	203 (1.14)	-1.01
ADVANCE	498 (1.86)	533 (1.99)	-0.72
UKPDS	123 (0.13)	53 (0.25)	-0.66
VADT	102 (2.22)	95 (2.06)	-1.16
Overall	980	884	-0.88
Cardiovascular death			
ACCORD	137 (0.79)	94 (0.56)	-1.01
ADVANCE	253 (0.95)	289 (1.08)	-0.72
UKPDS	71 (0.53)	29 (0.52)	-0.66
VADT	38 (0.83)	29 (0.63)	-1.16
Overall	497	441	-0.88

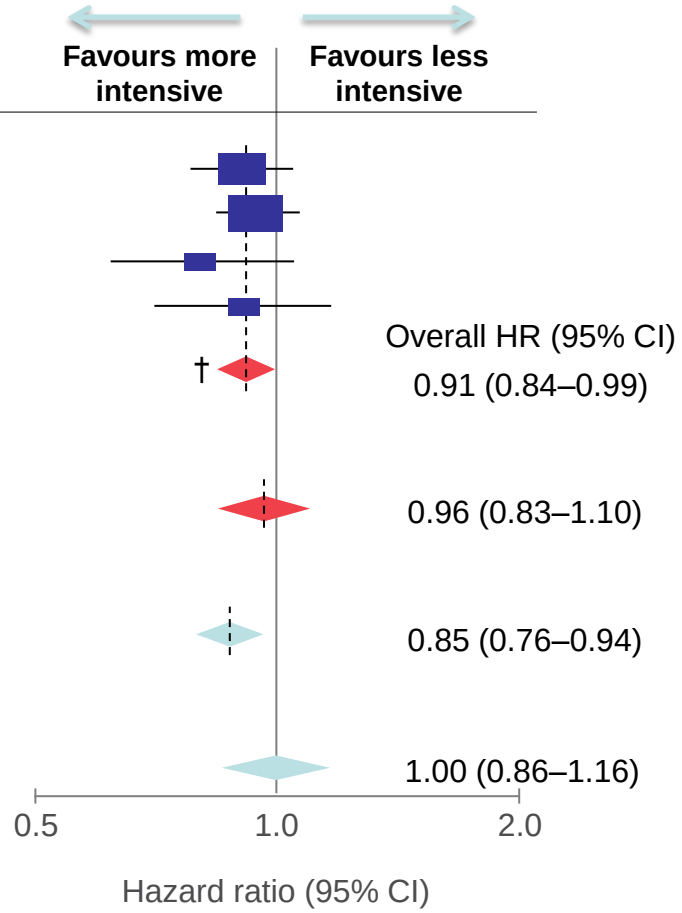


Turnbull et al. Diabetologia 2009;52:2288–98.

Meta-analysis shows modest benefit of intensive glycaemic control on macrovascular risk

Meta-analysis including 27,049 participants and 2370 major vascular events

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA_{1c} (%)
Major cardiovascular events*			
ACCORD	352 (2.11)	371 (2.29)	-1.01
ADVANCE	557 (2.15)	590 (2.28)	-0.72
UKPDS	169 (1.30)	87 (1.60)	-0.66
VADT	116 (2.68)	128 (2.98)	-1.16
Overall	1194	1176	-0.88
Stroke			
Overall	378	370	-0.88
Myocardial infarction			
Overall	730	745	-0.88
Hospitalised/fatal heart failure			
Overall	459	446	-0.88



*Major CV events = CV death or non-fatal stroke or non-fatal MI.

†Diamonds incorporate point estimate (vertical dashed line) and encompass 95% CI of overall effect for each outcome.

Turnbull et al. Diabetologia 2009;52:2288–98.

Glucose-lowering studies confirmed benefit on microvascular complications but mixed results on macrovascular outcomes

Study[1]	Baseline HbA_{1c} Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS	9%→ 7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[1–3]	8.3%→ 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE	7.5 %→ 7.3% vs 6.5%	8.0	↓	↔**	↔	↔	↔	↔
VADT	9.4 %→ 8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]

**No change in major clinical microvascular events but significant reduction in ESRD (p = 0.007)[5]

1. Table adapted from Bergenstal et al. Am J Med 2010;123:374.e9–e18. 2. Genuth et al. Clin Endocrinol Metab 2012;97:41–8.
3. Ismail-Beigi et al. Lancet 2010;376:419–30. 4. Hayward et al. N Engl J Med 2015;372:2197-206 (VADT). 5. Zoungas et al. N Engl J Med 2014;371:1392-406.

Does hypoglycaemia impact CV risk?

- Hypoglycaemia may be associated with co-morbidities that impact CVD
- A UK cohort study showed **hypoglycaemia was associated with increased CV risk and mortality**[1]
- In **ACCOR**D, severe hypoglycaemia was more frequent in the intensive glucose-lowering than in the standard arm[2]
  - Severe hypoglycaemia associated with increased risk of death in both arms but in patients who experienced hypoglycaemia, risk of death was lower in the intensive than in the standard arm[3]

1. Khunti et al. Diabetes Care 2015;38:316–22. 2. Gerstein et al. N Engl J Med 2008;358:2545–59.
3. Bonds et al. BMJ 2010;340:b4909. 4. Turnbull et al. Diabetologia 2009;52:2288–98. 5. Goto et al. BMJ. 2013;347:f4533.

Does hypoglycaemia impact CV risk?

- Meta-analysis of major glycaemic control trials associated **intensive glucose control with increased risk of severe hypoglycaemia, but with no increase in CV events[4]**
- Systematic review of prospective and retrospective datasets suggested **severe hypoglycaemia associated with 2-fold increase in CVD[5]**
  - **Co-morbidities alone could not account for this association**

1. Khunti et al. Diabetes Care 2015;38:316–22. 2. Gerstein et al. N Engl J Med 2008;358:2545–59. 3. Bonds et al. BMJ 2010;340:b4909. 4. Turnbull et al. Diabetologia 2009;52:2288–98. 5. Goto et al. BMJ. 2013;347:f4533.

ADA 2018 : CVD management

Antihyperglycemic Therapies and Cardiovascular Outcome

	SGLT2 inhibitors		
	EMPA-REG OUTCOME (133) (*n* = 7,020)	CANVAS (135) (*n* = 4,330)	CANVAS-R (135) (*n* = 5,812)
Cardiovascular death§	0.62 (0.49–0.77)	0.96 (0.77–1.18)¶ 0.87 (0.72–1.06)#	
MI§	0.87 (0.70–1.09)	0.85 (0.65–1.11)	0.85 (0.61–1.19)
Stroke§	1.18 (0.89–1.56)	0.97 (0.70–1.35)	0.82 (0.57–1.18)
HF hospitalization§	0.65 (0.50–0.85)	0.77 (0.55–1.08)	HR 0.56 (0.38–0.83)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)‡‡ 0.90 (0.76–1.07)##	
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	

What is Different with 2017 ?

2017

Pharmacologic Therapy For T2DM

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Metformin** **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy **Metformin +** **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

New: "For patients with ASCVD, add a second agent with evidence of cardiovascular risk reduction after consideration of drug-specific and patient factors"

2018

Pharmacologic Therapy For T2DM

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy **Lifestyle Management + Metformin**

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy **Lifestyle Management + Metformin + Additional Agent**

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

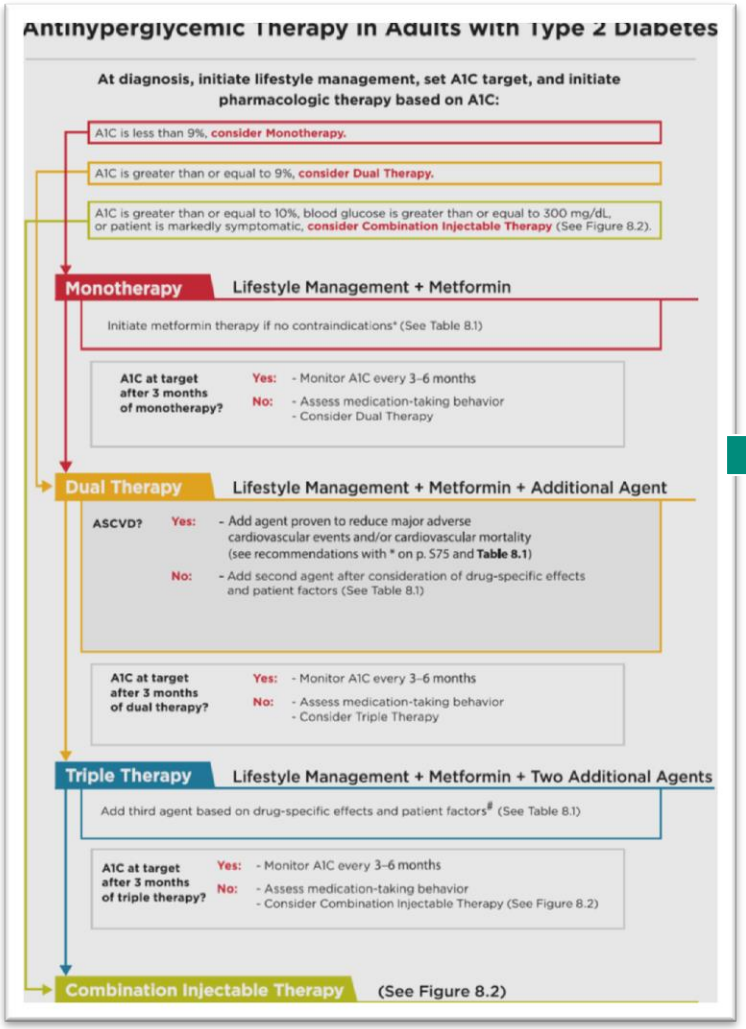
No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Pharmacologic Therapy For T2DM



"For patients with **ASCVD**, **add a second agent with evidence of cardiovascular risk reduction** after consideration of drug-specific and patient factors"

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: – Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Atherosclerotic cardiovascular disease (ASCVD)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

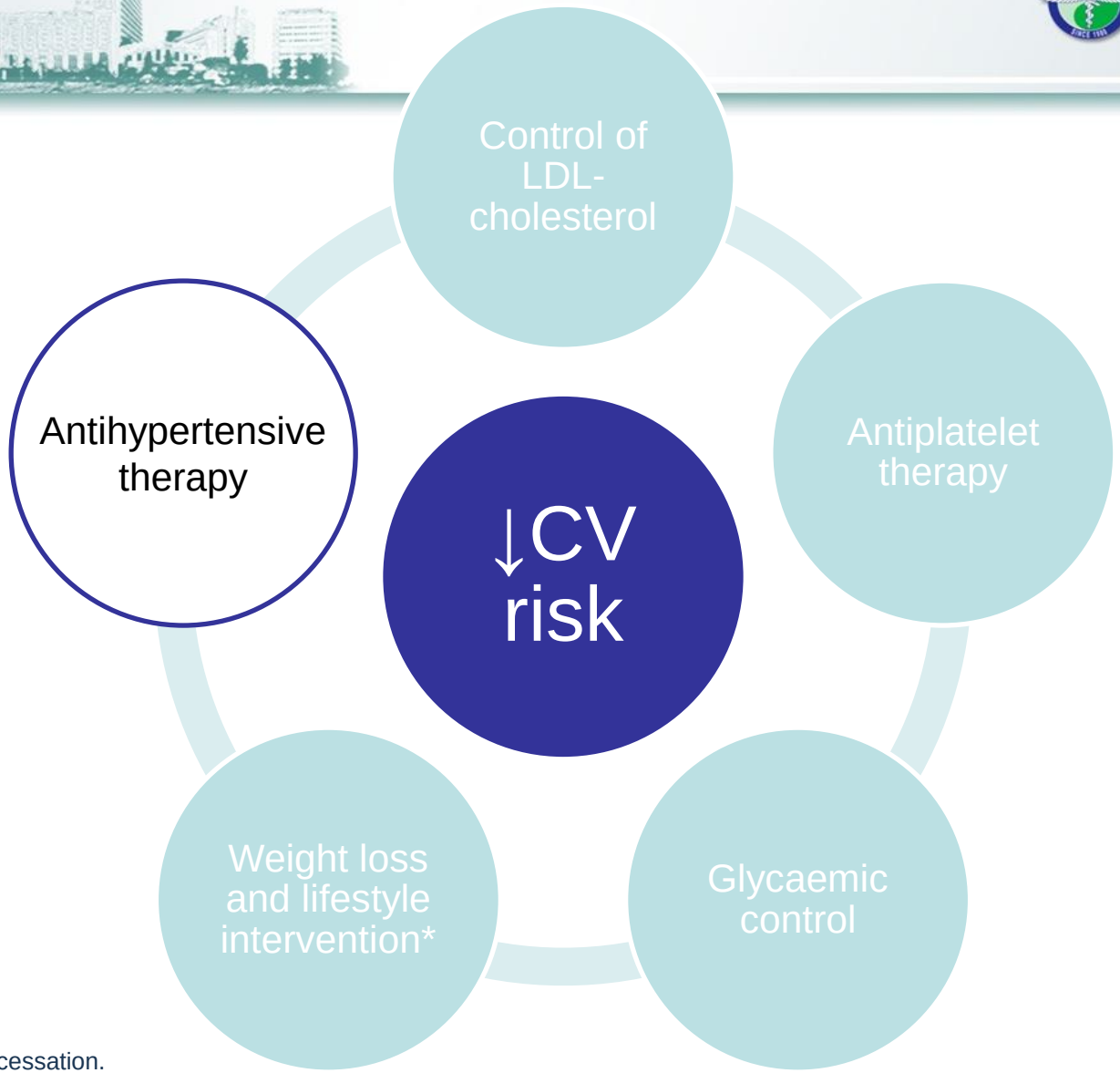
ADA 2018 : Standard of Medical Care in T2DM

8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2018

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

- For patients with ASCVD, add a second agent with evidence of cardiovascular risk reduction after consideration of drug-specific and patient factors"

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, Antihyperglycemic therapy should begin with **lifestyle management** and **metformin** and **subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality** (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. A"



*Includes smoking cessation.

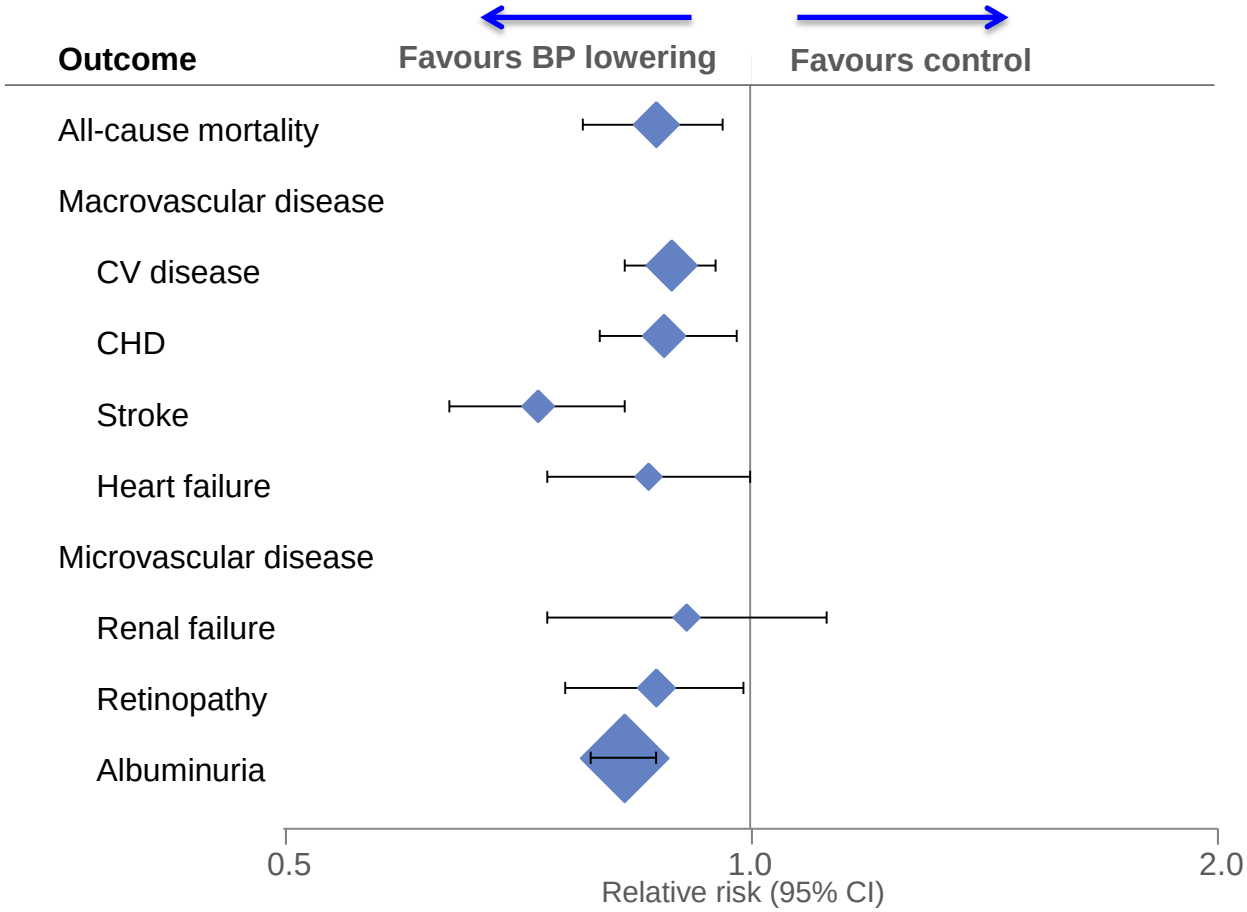
Recent updates to blood pressure goals reflect limited evidence of benefit <140/90 mmHg

Guidelines	Goal BP (mmHg)		
	General	Diabetes	Elderly (≥80 years)
ESC/EASD 2013[1]		<140/85†	
ESH/ESC 2013[2]	<140/90	<140/85	<150/90
NICE 2011[3,4]	<140/90	<140/80*	<150/90
ASH/ISH 2013[5]	<140/90	<140/90*	<150/90
JNC 8 2014[6]	<140/90	<140/90*	<150/90 (Aged ≥60 years)
ADA 2015[7]		<140/90	
CHEP[8]	<140/90	<130/80	<150/90
ADA 2018		?	

*<130/80 mmHg in chronic kidney disease and albuminuria; †SBP < 130 mmHg in nephropathy.

1. Rydén et al. Eur Heart J 2013;34:3035–87. 2. Mancia et al. J Hypertens 2013;31:1281–357.. 3. http://guidance.nice.org.uk/CG127;
4. http://www.nice.org.uk/guidance/cg87; 5. Weber. J Hypertens 2014;32:3–15; 6. James. JAMA 2014;5;311:507–20.
7. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94. 8. Daskalopoulou et al. Can J Cardiol 2015;31:549–68.

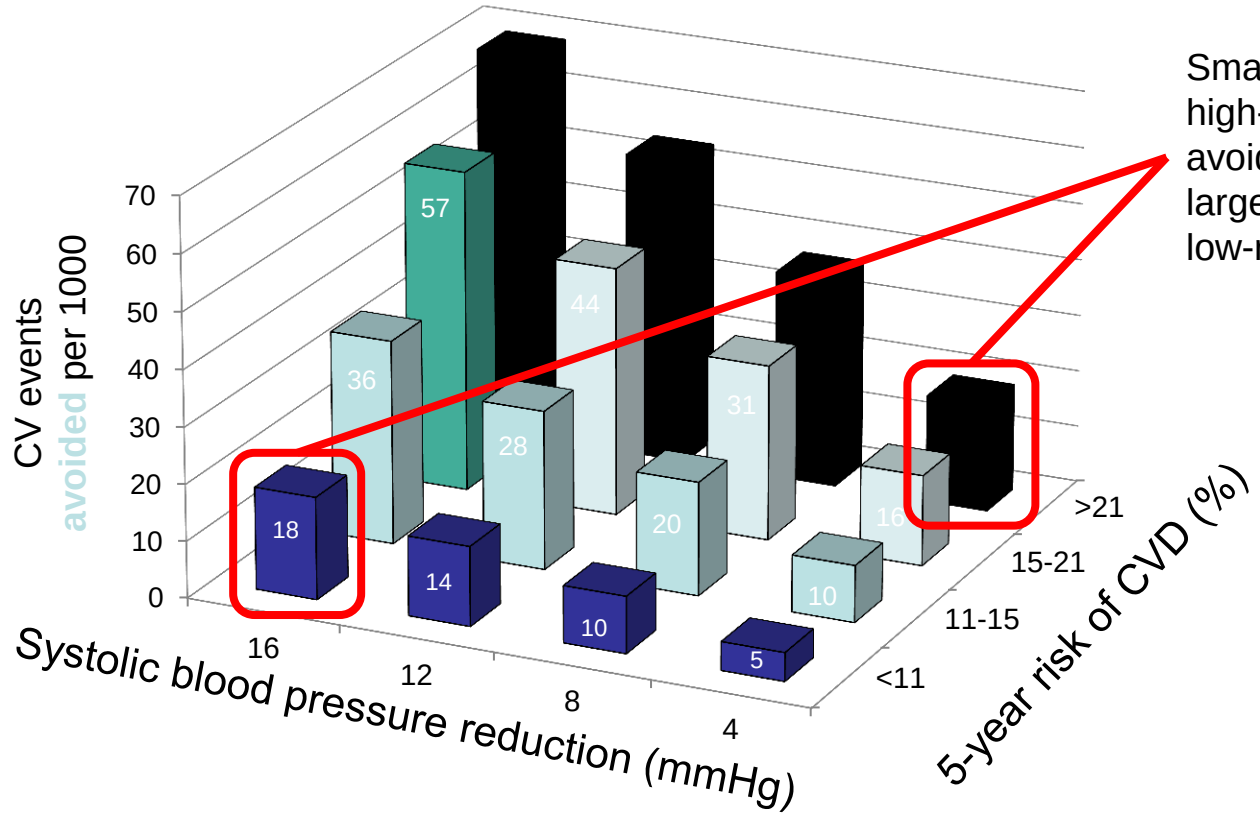
10 mmHg reduction in SBP reduces all-cause mortality, macrovascular and microvascular outcomes in T2D



Meta-analysis of 40 large scale, randomised, controlled trials of BP-lowering treatment including patients with diabetes (n=100,354 participants).

Emdin et al. JAMA 2015;313:603–15.

Even small reductions in BP can reduce risk in high CV risk patients

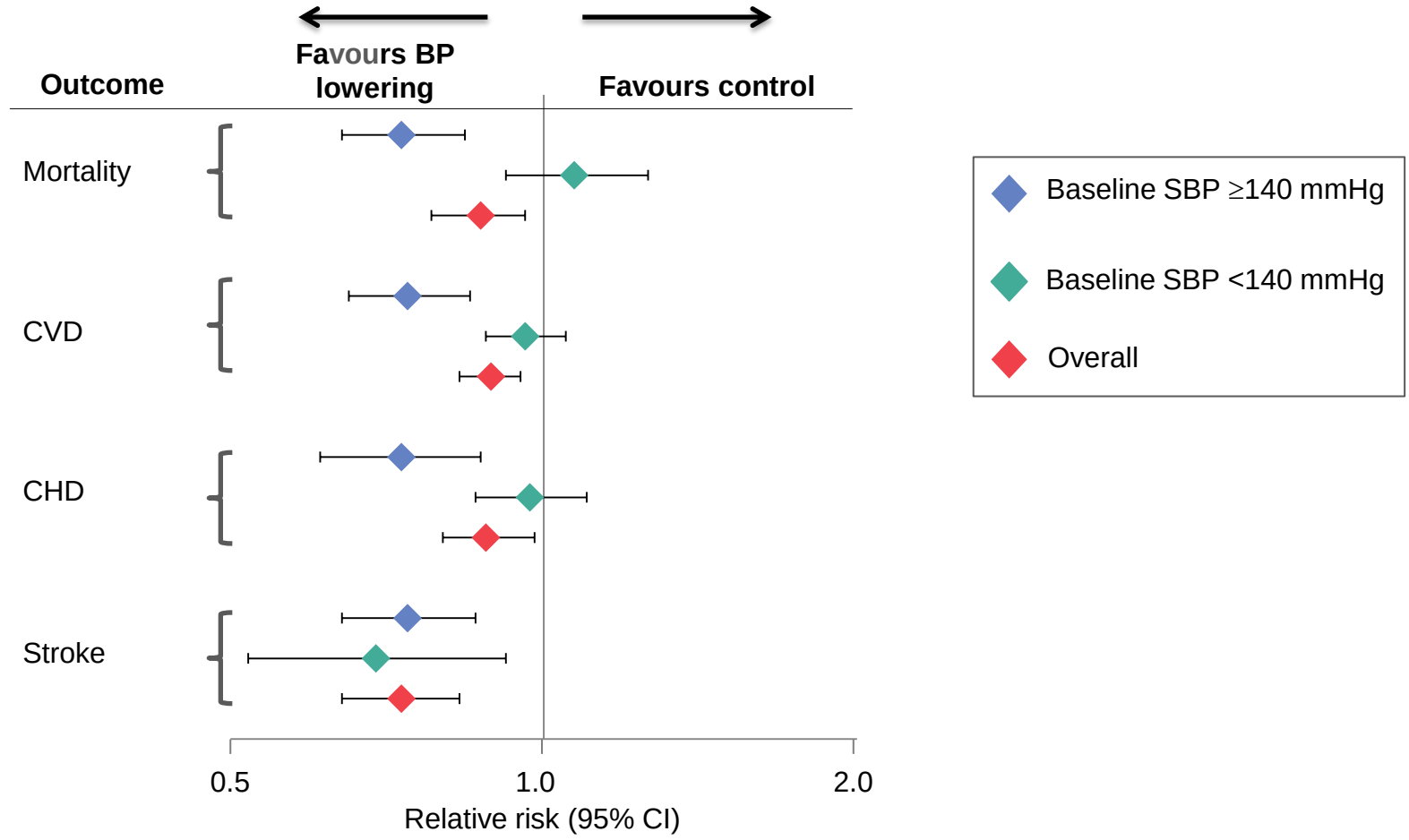


Small BP reductions in high-risk individuals avoid as many events as large BP reductions in low-risk individuals

Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2014;384:591–8.

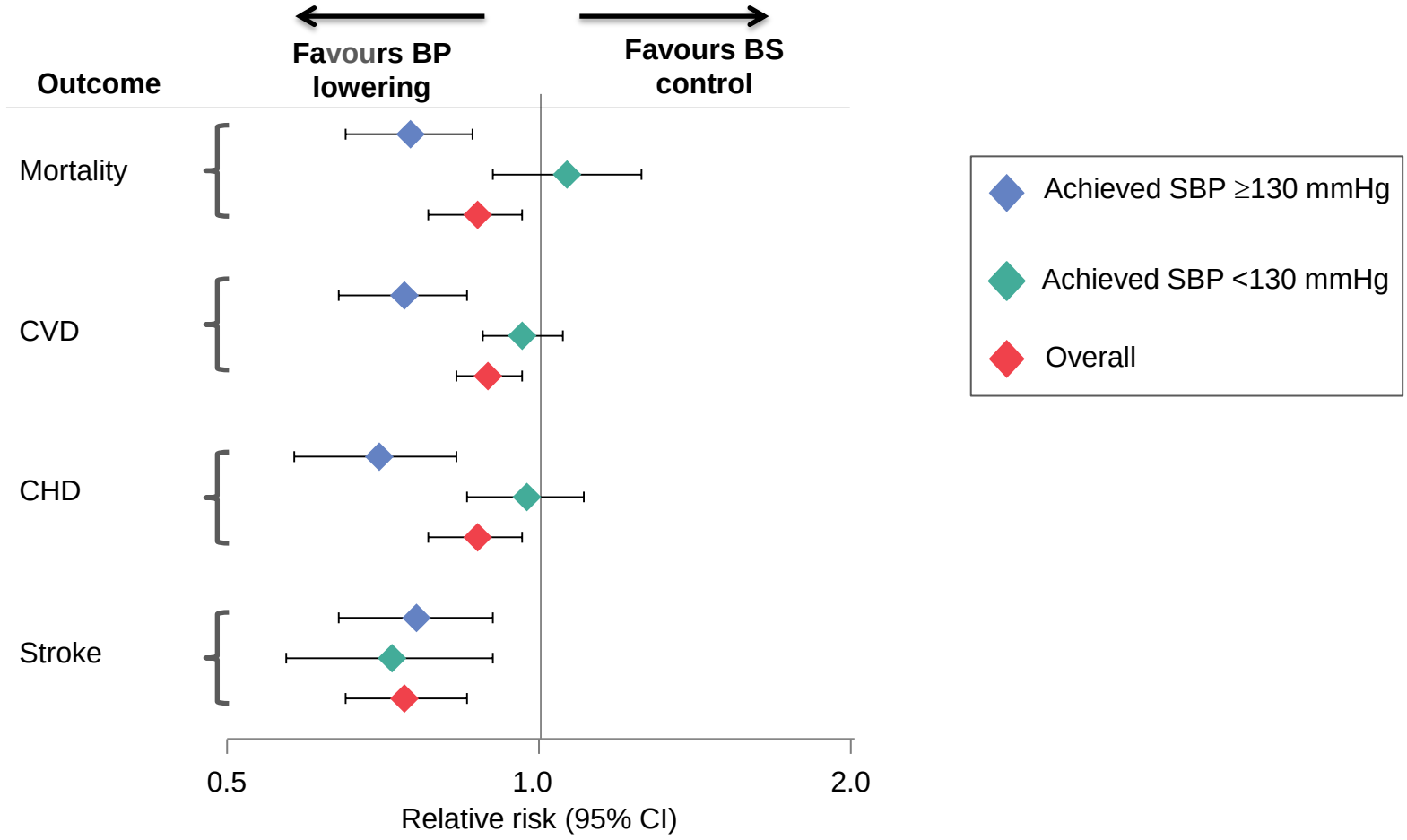
29

Effect of 10 mmHg reduction in SBP on CV outcomes by baseline ≥ 140 or < 140 mmHg



Meta-analysis of 40 trials of BP-lowering treatment including patients with diabetes (n=100,354 participants). Emdin et al. JAMA 2015;313:603–15.

CV outcomes based on mean SBP achieved (≥ 130 or < 130 mmHg)



Meta-analysis of 40 trials of BP-lowering treatment including patients with diabetes (n=100,354 participants). Emdin et al. JAMA 2015;313:603–15.

Systematic review with meta-analysis

Blood pressure lowering in patients with type 2 diabetes improves cardiovascular events including mortality, but more intensive lowering to systolic blood pressure less than 130 mm Hg is associated with further reduction in stroke and albuminuria without further reduction in cardiac events

10.1136/ebmed-2015-110197

Bora Toklu, Sripal Bangalore

European Heart Journal Advance Access published June 8, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Societies: [1]European Society of Cardiology (ESC); [2]European Association for the Study of Diabetes (EASD); [3]European Atherosclerosis Society (EAS); [4]European Heart Network (EHN); [5]European Society of Hypertension (ESH); [6]European Stroke Organisation (ESO); [7]International Diabetes Federation European Region (IDF Europe); [8]International Federation of Sport Medicine (FIMS); [9]International Society of Behavioural Medicine (ISBM); [10]WONCA Europe.

European Heart Journal doi:10.1093/eurheartj/ehw106

Recommendations for management of hypertension

Recommendations	Class[a]	Level[b]	Ref[c]
Lifestyle measures (weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fruits, vegetables, and low-fat dairy products) are recommended in all patients with hypertension and in individuals with high normal BP.	I	A	337, 428-430
All major BP lowering drug classes (i.e. diuretics, ACE-I, calcium antagonists, ARBs, and ß-blockers) do not differ significantly in their BP-lowering efficacy and thus are recommended as BP lowering treatment.	I	A	431, 432
In asymptomatic subjects with hypertension but free of CVD, CKD, and DM, total CV risk stratification using the SCORE model is recommended.	I	B	30
Drug treatment is recommended in patients with grade 3 hypertension irrespective of CV risk, as well as in patients with grade 1 or 2 hypertension who are at very high CV risk.	I	B	433
Drug treatment should be considered in patients with grade 1 or 2 hypertension who are at high CV risk.	IIa	B	433
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, lifestyle measures are recommended.	I	B	433
In patients at low to moderate total CV risk and with grade 1 or 2 hypertension, if lifestyle measures fail to reduce BP, drug treatment may be considered.	IIb	B	433

Recommendations for management of hypertension

SBP <140 mmHg and DBP <90 mmHg are recommended in all treated hypertensive patients <60 years old.	I	B	433
In patients >60 years old with SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg.	I	B	434
In fit patients <80 years old, a target SBP <140 mmHg may be considered if treatment is well tolerated. In some of these patients a target SBP <120 mmHg may be considered if at (very) high-risk and tolerate multiple BP lowering drugs.	IIb	B	434, 435
In individuals >80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B	434
In frail elderly patients, a careful treatment intensity (e.g. number of BP lowering drugs) and BP targets should be considered, and clinical effects of treatment should be carefully monitored.	IIa	B	436
Initiation of BP lowering therapy with a two-drug combination may be considered in patients with markedly elevated baseline BP or at high CV risk. Combination of two drugs at fixed doses in a single pill may be considered because of improved adherence.	IIb	C	437
ß-blockers and thiazide diuretics are not recommended in hypertensive patients with multiple metabolic risk factors,[d] due to the increased risk of DM.	III	B	438

2016 European Guidelines on cardiovascular disease prevention

Key messages

✓**Elevated BP is a major risk factor for CAD, HF, cerebrovascular disease, PAD, CKD and AF.**

✓**The decision to start BP-lowering treatment depends on the BP level and total CV risk.**

✓**Benefits of treatment are mainly driven by BP reduction per se, not by drug type.**

✓**Combination treatment is needed to control BP in most patients.**

European Heart Journal doi:10.1093/eurheartj/ehw106

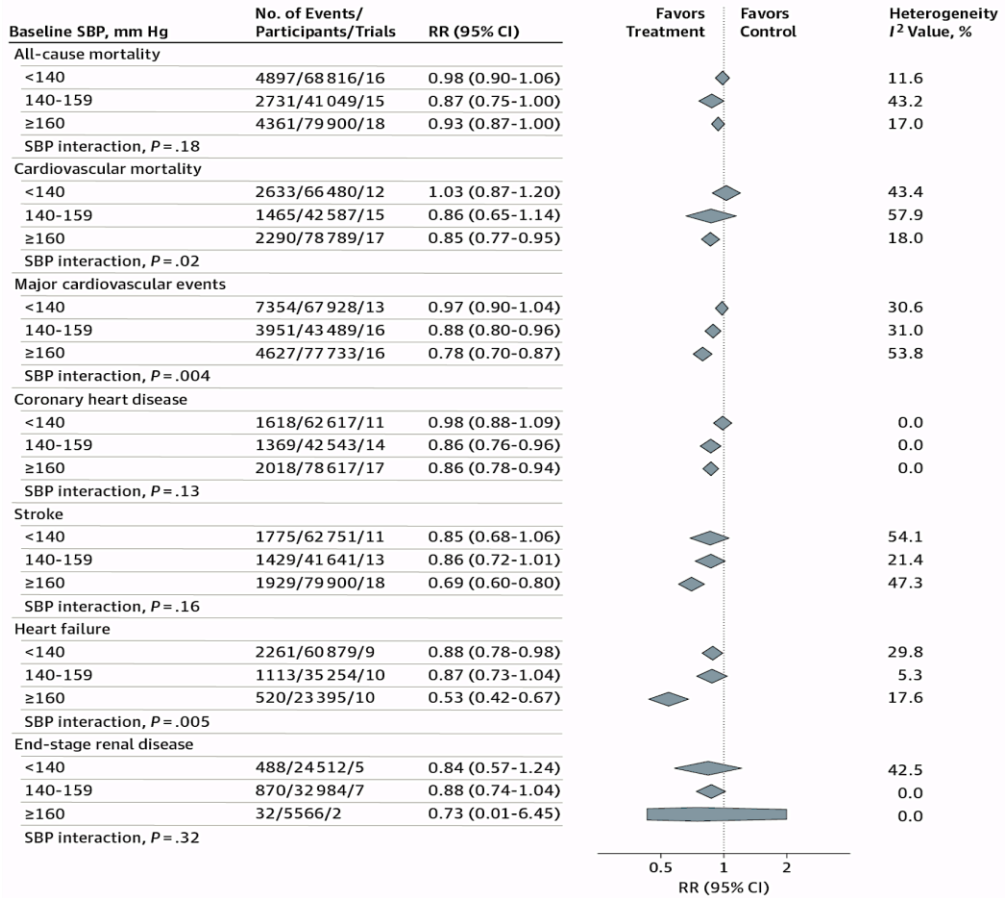
Table 9.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (16)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Systolic blood pressure target: <120 mmHg Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg	Systolic blood pressure target: 130–140 mmHg Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP (17)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (142)
HOT (143)	18,790 participants, including 1,501 with diabetes	Diastolic blood pressure target: ≤80 mmHg	Diastolic blood pressure target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (144)	9,361 participants without diabetes	Systolic blood pressure target: <120 mmHg Achieved (mean): 121.4 mmHg	Systolic blood pressure target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI

CVD, cardiovascular disease; T2D, type 2 diabetes. Data from this table can also be found in the ADA position statement "Diabetes and Hypertension" (5).

From: **Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels A Systematic Review and Meta-analysis**

JAMA Intern Med. 2018;178(1):28-36. doi:10.1001/jamainternmed.2017.6015



Baseline SBP, mm Hg	No. of Events/ Participants/Trials	RR (95% CI)	Heterogeneity I^2 Value, %
All-cause mortality			
<140	4897/68 816/16	0.98 (0.90-1.06)	11.6
140-159	2731/41 049/15	0.87 (0.75-1.00)	43.2
≥160	4361/79 900/18	0.93 (0.87-1.00)	17.0
SBP interaction, $P = .18$			
Cardiovascular mortality			
<140	2633/66 480/12	1.03 (0.87-1.20)	43.4
140-159	1465/42 587/15	0.86 (0.65-1.14)	57.9
≥160	2290/78 789/17	0.85 (0.77-0.95)	18.0
SBP interaction, $P = .02$			
Major cardiovascular events			
<140	7354/67 928/13	0.97 (0.90-1.04)	30.6
140-159	3951/43 489/16	0.88 (0.80-0.96)	31.0
≥160	4627/77 733/16	0.78 (0.70-0.87)	53.8
SBP interaction, $P = .004$			
Coronary heart disease			
<140	1618/62 617/11	0.98 (0.88-1.09)	0.0
140-159	1369/42 543/14	0.86 (0.76-0.96)	0.0
≥160	2018/78 617/17	0.86 (0.78-0.94)	0.0
SBP interaction, $P = .13$			
Stroke			
<140	1775/62 751/11	0.85 (0.68-1.06)	54.1
140-159	1429/41 641/13	0.86 (0.72-1.01)	21.4
≥160	1929/79 900/18	0.69 (0.60-0.80)	47.3
SBP interaction, $P = .16$			
Heart failure			
<140	2261/60 879/9	0.88 (0.78-0.98)	29.8
140-159	1113/35 254/10	0.87 (0.73-1.04)	5.3
≥160	520/23 395/10	0.53 (0.42-0.67)	17.6
SBP interaction, $P = .005$			
End-stage renal disease			
<140	488/24 512/5	0.84 (0.57-1.24)	42.5
140-159	870/32 984/7	0.88 (0.74-1.04)	0.0
≥160	32/5566/2	0.73 (0.01-6.45)	0.0
SBP interaction, $P = .32$			

Effect of Treatment to Lower Blood Pressure (BP) at Different BP Levels in Primary Prevention

RR indicates relative risk; SBP, systolic BP. Different size markers indicate weight. Studies included in the analyses are given in eTable 7 in the Supplement.

From: **Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels A Systematic Review and Meta-analysis**

JAMA Intern Med. 2018;178(1):28-36. doi:10.1001/jamainternmed.2017.6015

Outcome	No. of Events/ Participants/Trials	RR (95% CI)	Heterogeneity I^2 Value, %
All-cause mortality	7061/77562/12	0.98 (0.89-1.07)	49.1
CV mortality	4156/76737/11	0.95 (0.84-1.09)	55.3
MACE	13075/77562/12	0.90 (0.84-0.97)	65.1
Coronary heart disease	4112/68305/10	0.88 (0.77-1.00)	55.8
Stroke	2412/75812/11	0.83 (0.73-0.96)	31.8
Heart failure	2905/74385/9	0.83 (0.72-0.96)	38.4

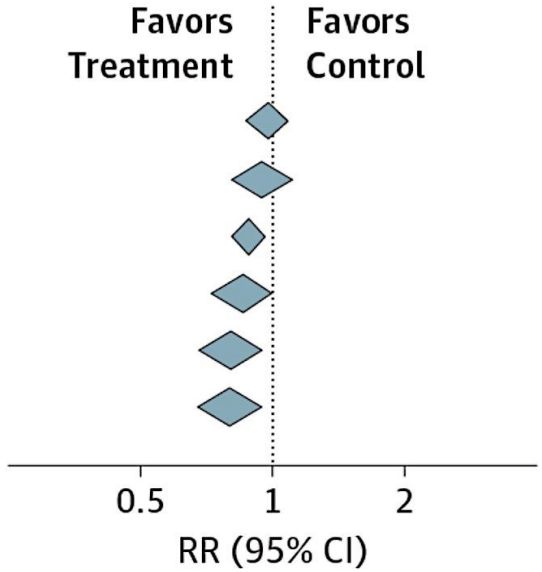


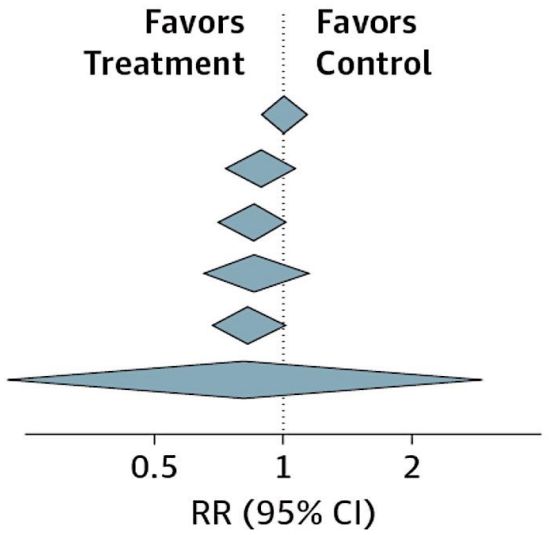
Figure Legend:

Effect of Treatment to Lower Blood Pressure (BP) in Coronary Heart Disease TrialsCV indicates cardiovascular; MACE, major cardiovascular events; and RR, relative risk. The following trials were included in the analysis: Poole-Wilson et al,[19] Nissen et al,[20] Fox and the EUROPA Investigators,[21] Yusuf et al,[22] Rouleau et al,[85] the MACB Study Group (all outcomes except coronary heart disease and heart failure),[86] Yusuf et al,[23] Braunwald et al (all outcomes except coronary heart disease),[24] Pitt et al (all outcomes except CV mortality),[25] Pitt et al (all outcomes except stroke and heart failure),[87] Teo et al (all outcomes except heart failure),[26] and Yusuf et al.[27]

From: **Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels A Systematic Review and Meta-analysis**

JAMA Intern Med. 2018;178(1):28-36. doi:10.1001/jamainternmed.2017.6015

Outcome	No. of Events/ Participants/Trials	RR (95% CI)	Heterogeneity I^2 Value, %
All-cause mortality	2610/32 102/6	1.00 (0.91-1.10)	0.0
CV mortality	1179/32 102/6	0.91 (0.78-1.05)	0.0
MACE	4731/32 102/6	0.88 (0.76-1.01)	62.1
Coronary heart disease	844/32 102/6	0.89 (0.72-1.11)	1.7
Stroke	3167/32 102/6	0.86 (0.74-1.01)	53.5
Heart failure	508/26 889/3	0.85 (0.32-2.29)	68.1



Effect of Treatment to Lower Blood Pressure (BP) in Poststroke Trials. CV indicates cardiovascular; MACE, major cardiovascular events; and RR, relative risk. The following trials were included in all the analyses except for heart failure: the Dutch TIA Trial Study Group, Hypertension-Stroke Cooperative Study Group, Yusuf et al, MacMahon et al, Benavente et al, and Eriksson et al. The following trials were included in the heart failure analysis: Hypertension-Stroke Cooperative Study Group, Yusuf et al, and MacMahon et al.

Recent updates to blood pressure goals reflect limited evidence of benefit <140/90 mmHg

Guidelines	Goal BP (mmHg)		
	General	Diabetes	Elderly (≥80 years)
ESC/EASD 2013[1]		<140/85[†]	
ESH/ESC 2013[2]	<140/90	<140/85	<150/90
NICE 2011[3,4]	<140/90	<140/80*	<150/90
ASH/ISH 2013[5]	<140/90	<140/90*	<150/90
JNC 8 2014[6]	<140/90	<140/90*	<150/90 (Aged ≥60 years)
ADA 2015[7]		<140/90	
CHEP[8]	<140/90	<130/80	<150/90
ADA 2018		<140/90	

*<130/80 mmHg in chronic kidney disease and albuminuria; [†]SBP < 130 mmHg in nephropathy.

1. Rydén et al. Eur Heart J 2013;34:3035–87. 2. Mancia et al. J Hypertens 2013;31:1281–357.. 3. http://guidance.nice.org.uk/CG127;
4. http://www.nice.org.uk/guidance/cg87; 5. Weber. J Hypertens 2014;32:3–15; 6. James. JAMA 2014;5;311:507–20.
7. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94. 8. Daskalopoulou et al. Can J Cardiol 2015;31:549–68.

Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes 2018

- **….. patients with type 1 or type 2 diabetes who have hypertension should, at a minimum, be treated to blood pressure targets of <140/90 mmHg.**
- **Intensification of antihypertensive therapy to target blood pressures lower than 140/90 mmHg (e.g. <130/80 or 120/80 mmHg) may be beneficial for selected patients with diabetes such as those with a high risk of cardiovascular disease.**
- **…..meta-analyses consistently show that treating patients with baseline blood pressure ≥140 mmHg to targets <140 mmHg is beneficial, while more intensive targets may offer additional, though probably less robust, benefits.**

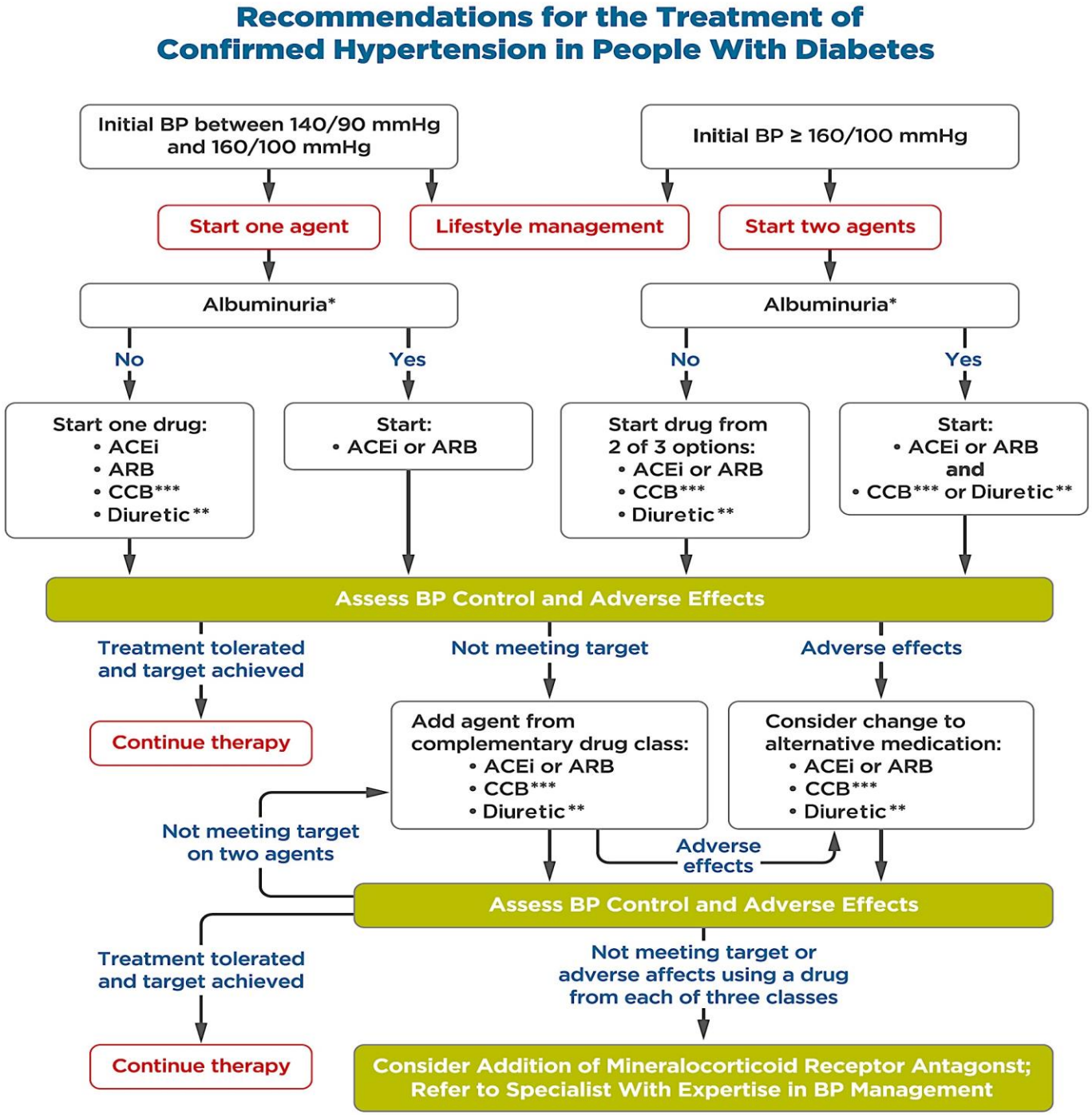
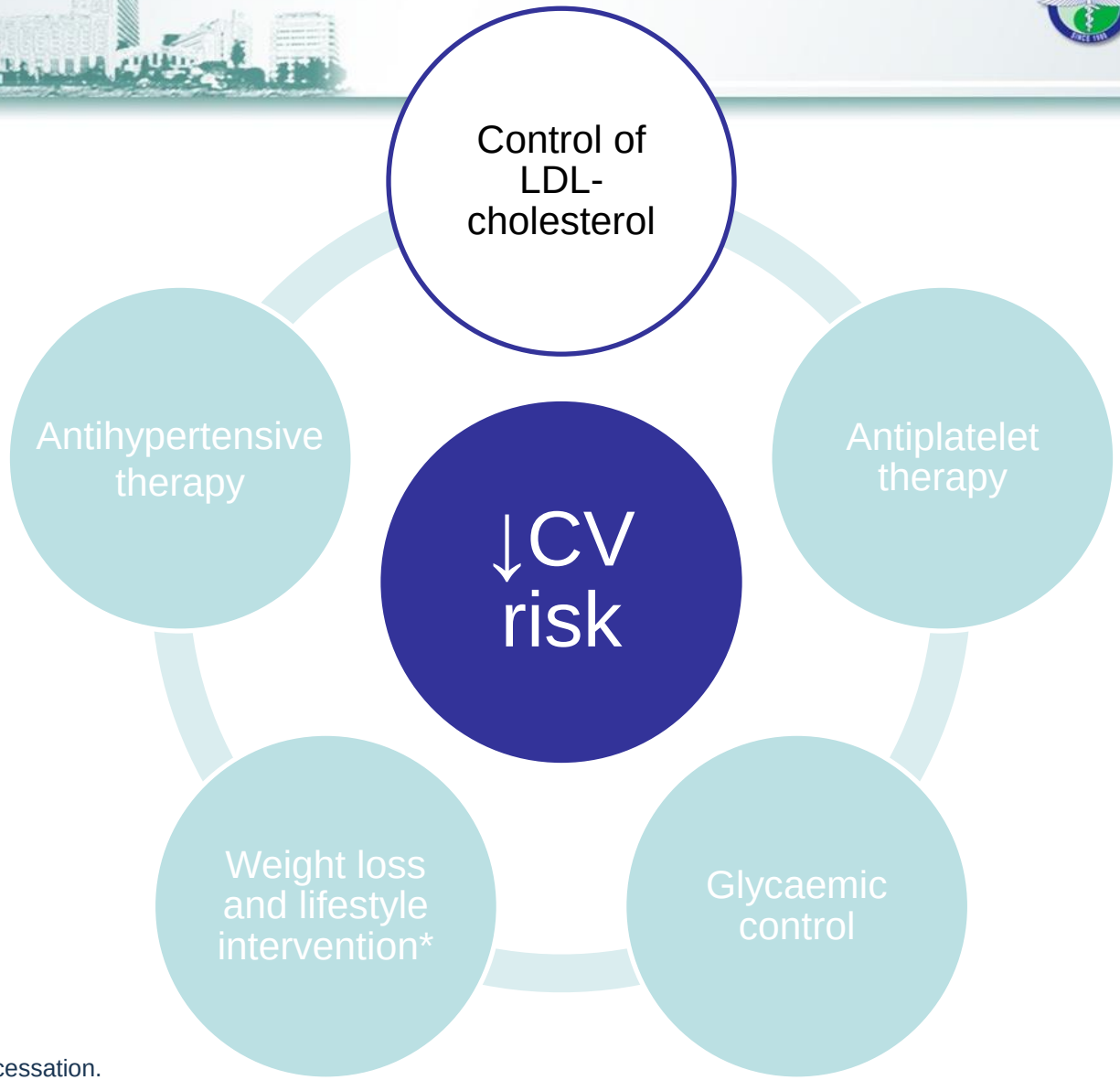


Figure 9.1 Recommendations for the treatment of confirmed hypertension in people with diabetes.

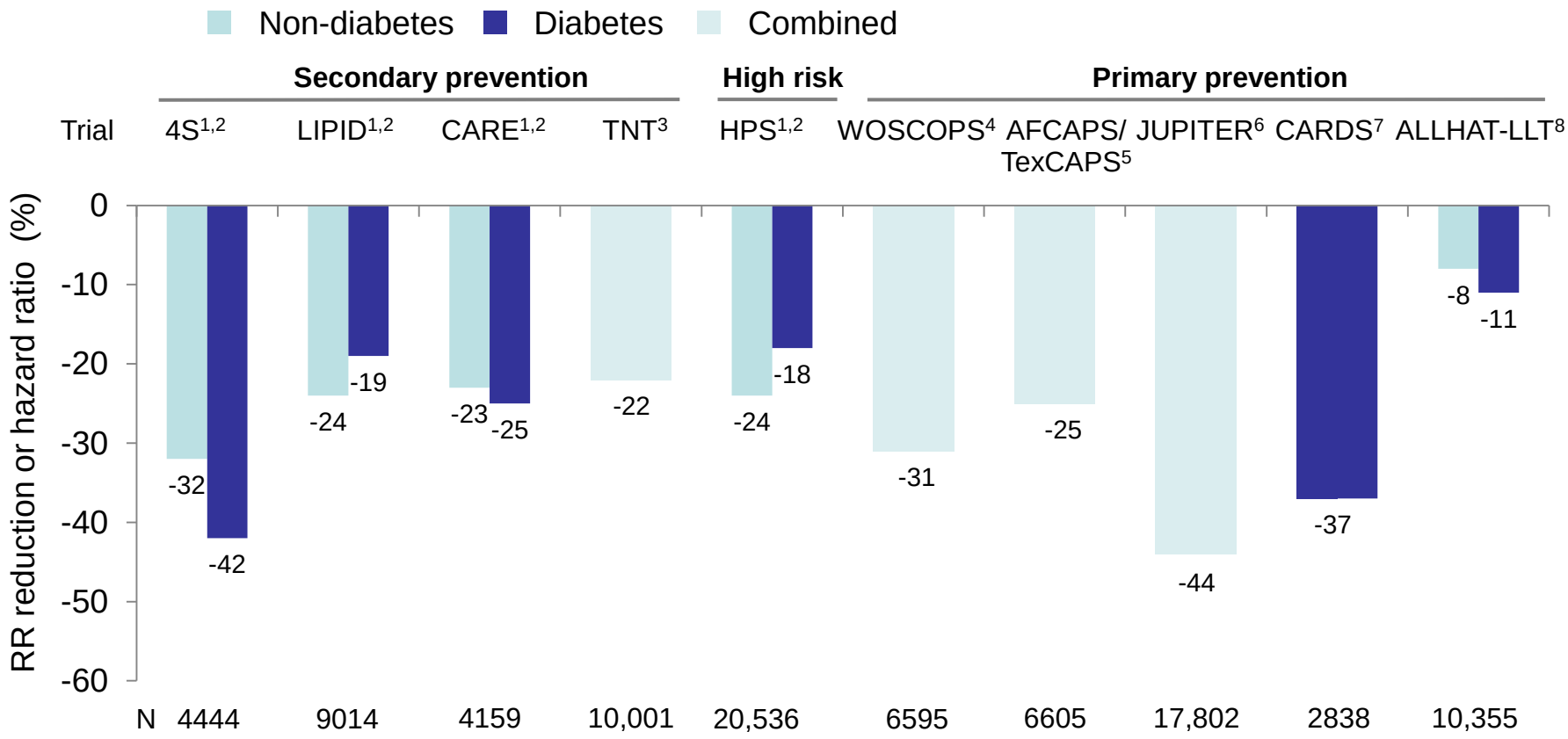
***An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR>300 mg/g creatinine.**

****Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.**



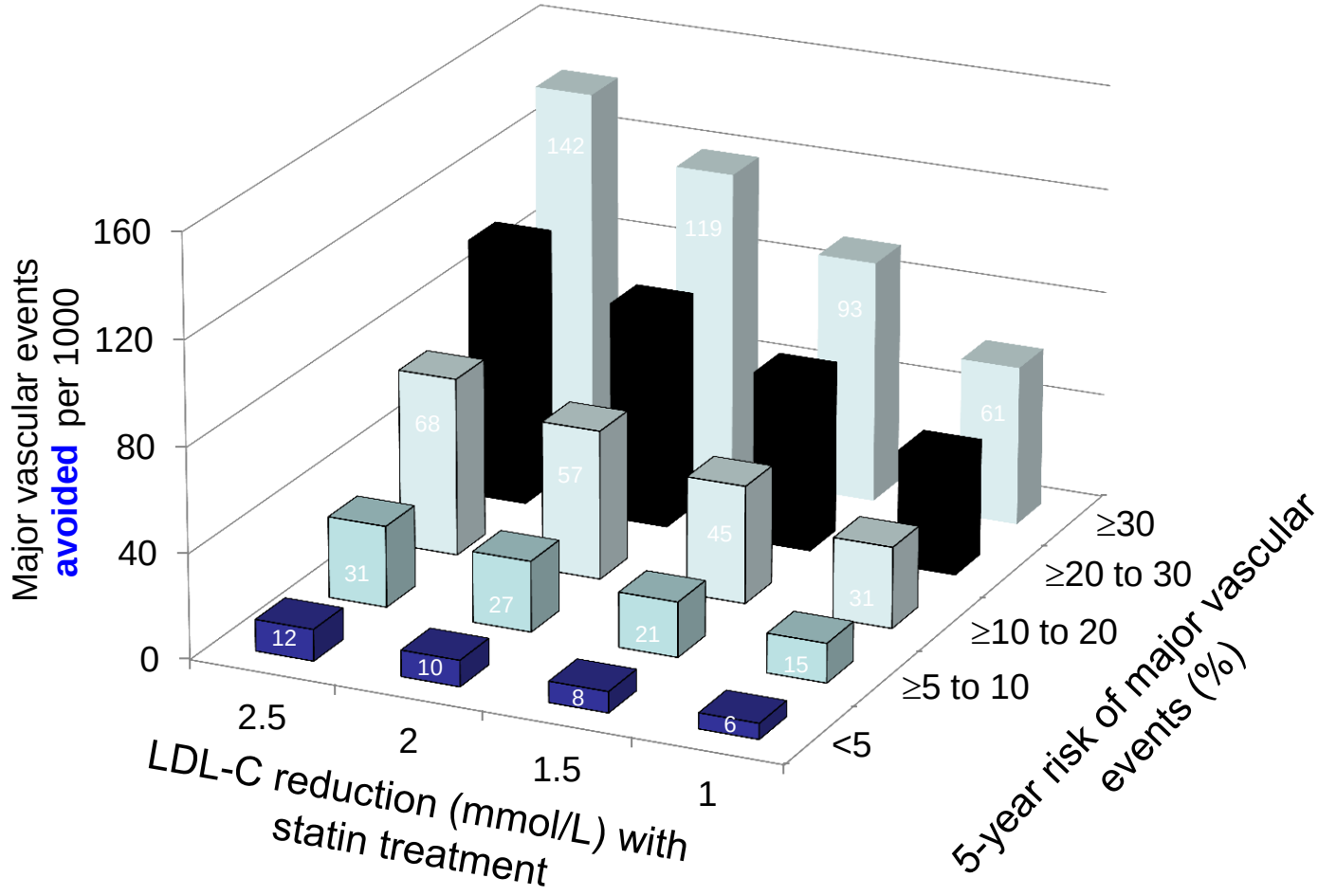
*Includes smoking cessation.

Statin therapy has a pivotal role in reducing CV risk



1. Ryden et al. Eur Heart J 2007;28:88–136. 2. Libby. J Am Coll Cardiol 2005;46:1225–8. 3. LaRosa et al. N Engl J Med 2005;352:1425–35.
4. Shepherd et al. N Engl J Med 1995;333:1301–8. 5. Downs et al. JAMA 1998;279:1615–22. 6. Ridker et al. N Engl J Med 2008;359:2195.
7. Colhoun et al. Lancet 2004;364:685–96. 8. ALLHAT-LLT. JAMA 2002;288:2998–3007.

CV risk reduction with statins is proportional to LDL cholesterol decrease

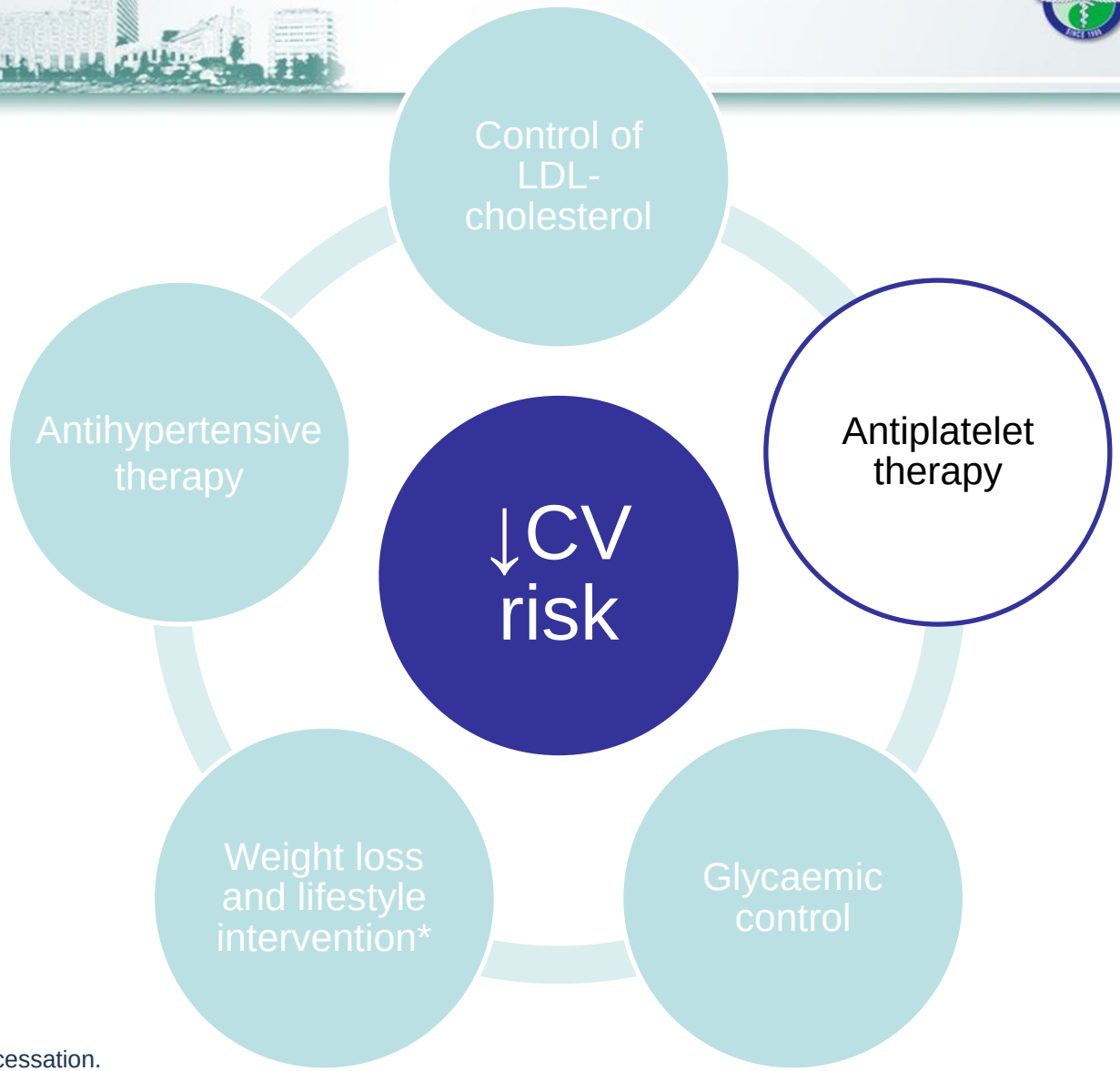


Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2012;380:581–90.

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

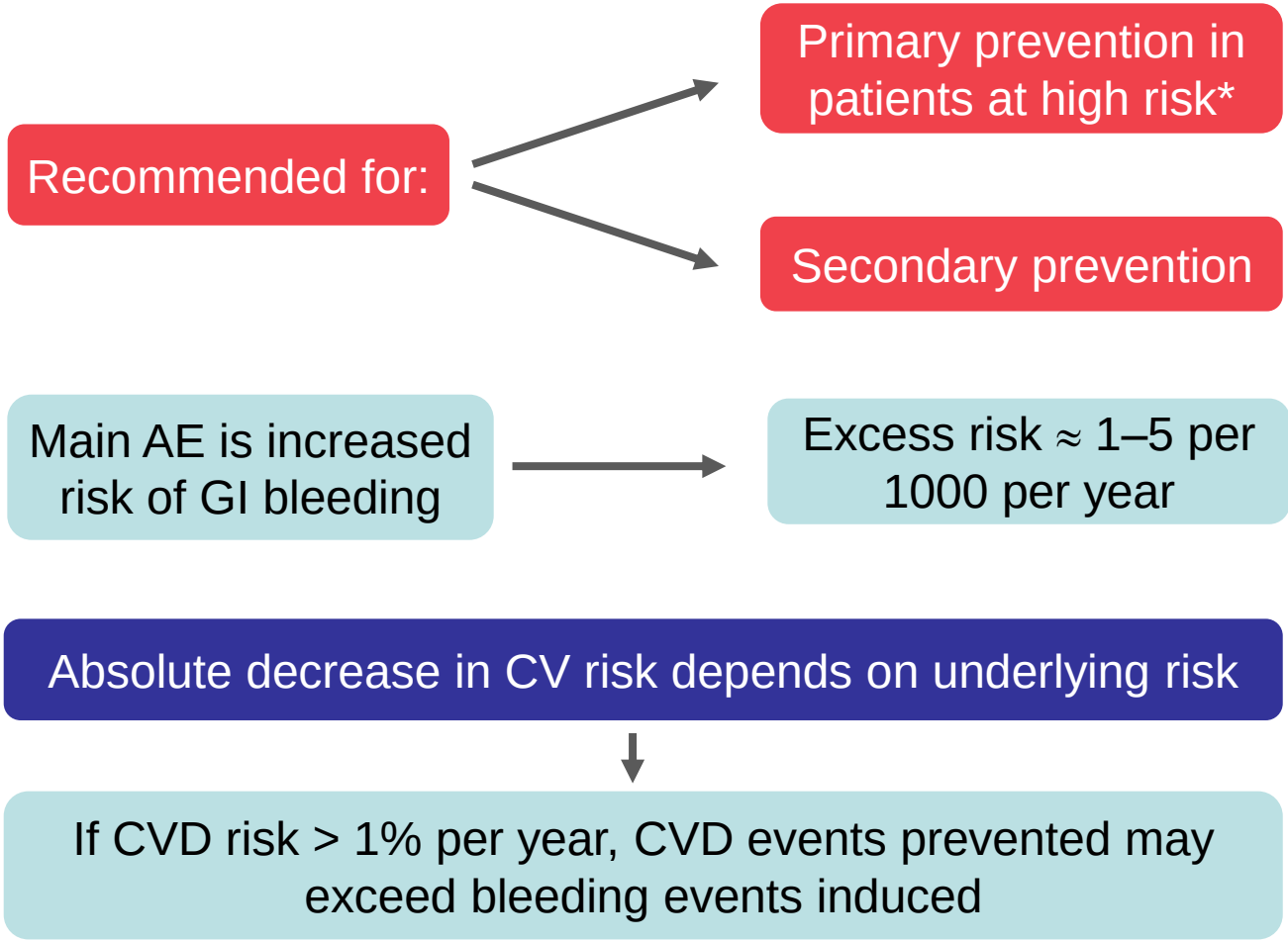
Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

In addition to lifestyle therapy. For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol >100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged<40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.



*Includes smoking cessation.

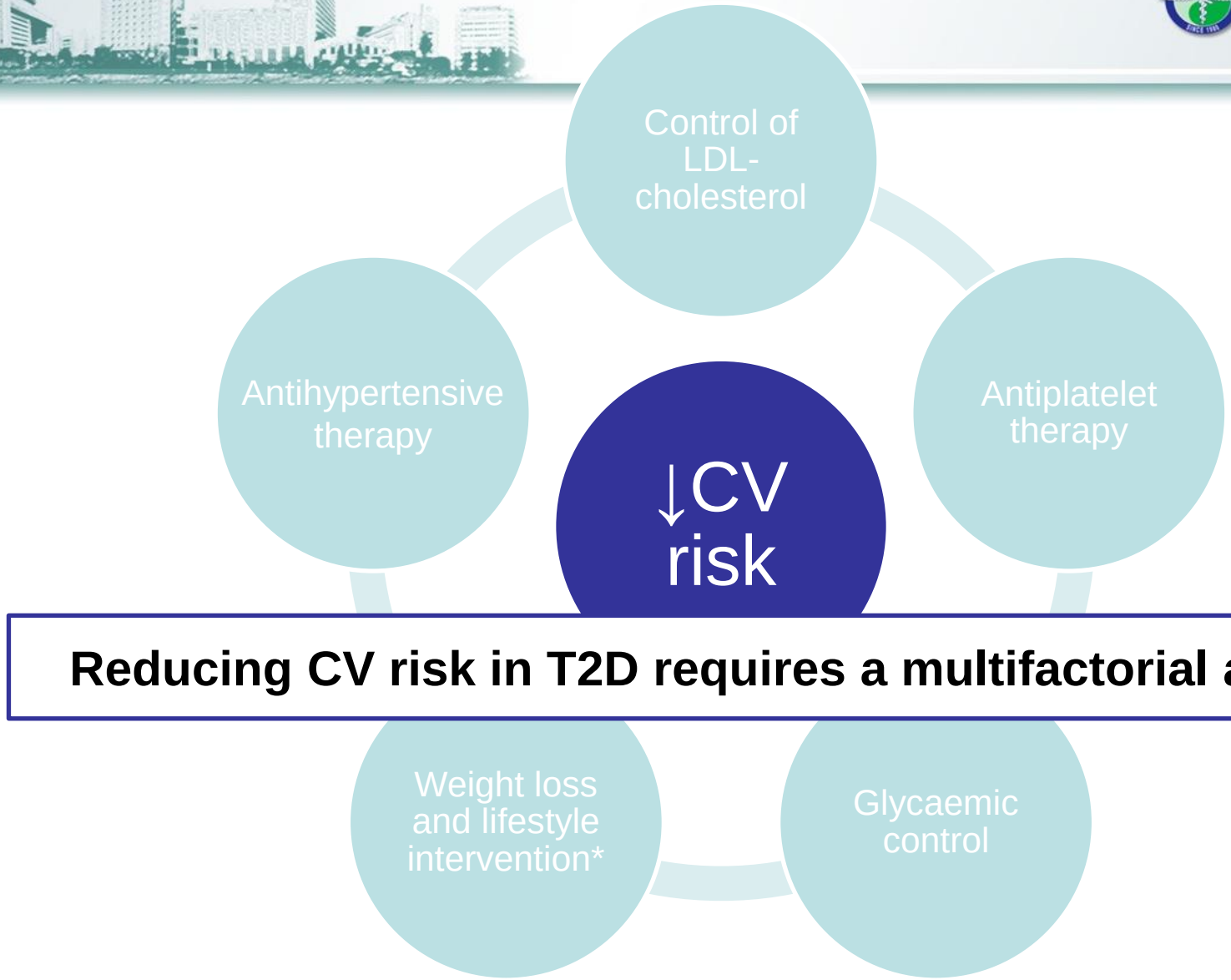
ASA reduces CV risk in patients post-primary event



American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94.

*10-year CV risk >10%.

49

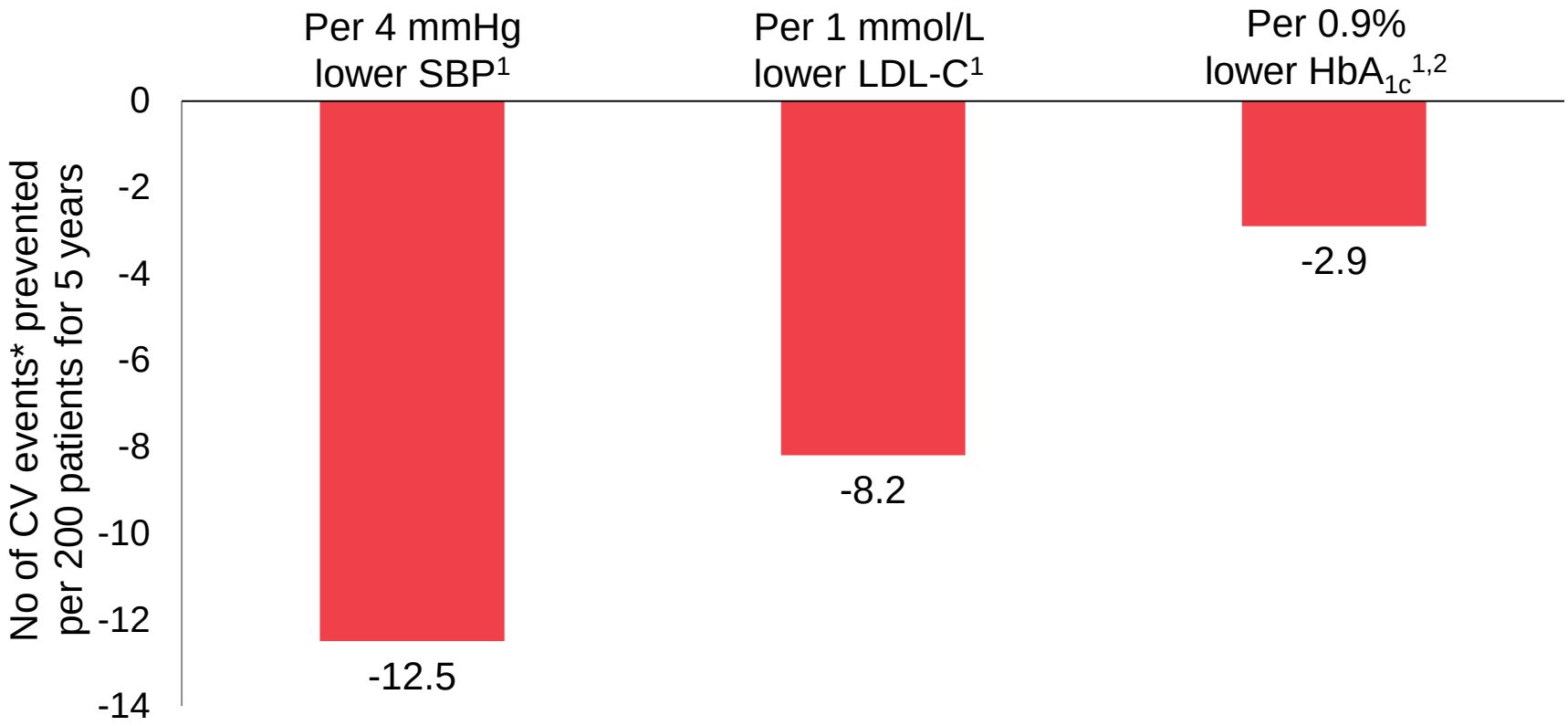


Reducing CV risk in T2D requires a multifactorial approach

***Includes smoking cessation.**

Rydén et al. Eur Heart J 2013;34:3035–87.

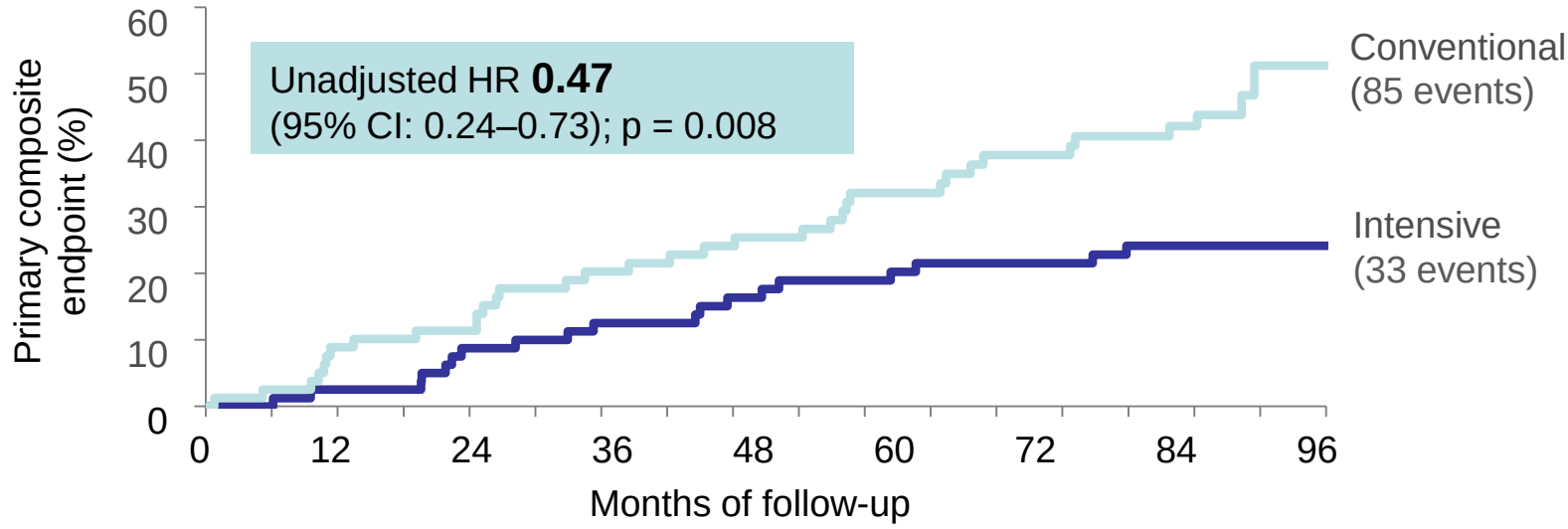
CV risk reduction in T2D may require multiple interventions including BP and lipid management



*Non-fatal MI, CHD, stroke and all-cause mortality.

1. Sattar. Diabetologia 2013;56:686–95.
2. Ray et al. Lancet 2009;373:1765–72.

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



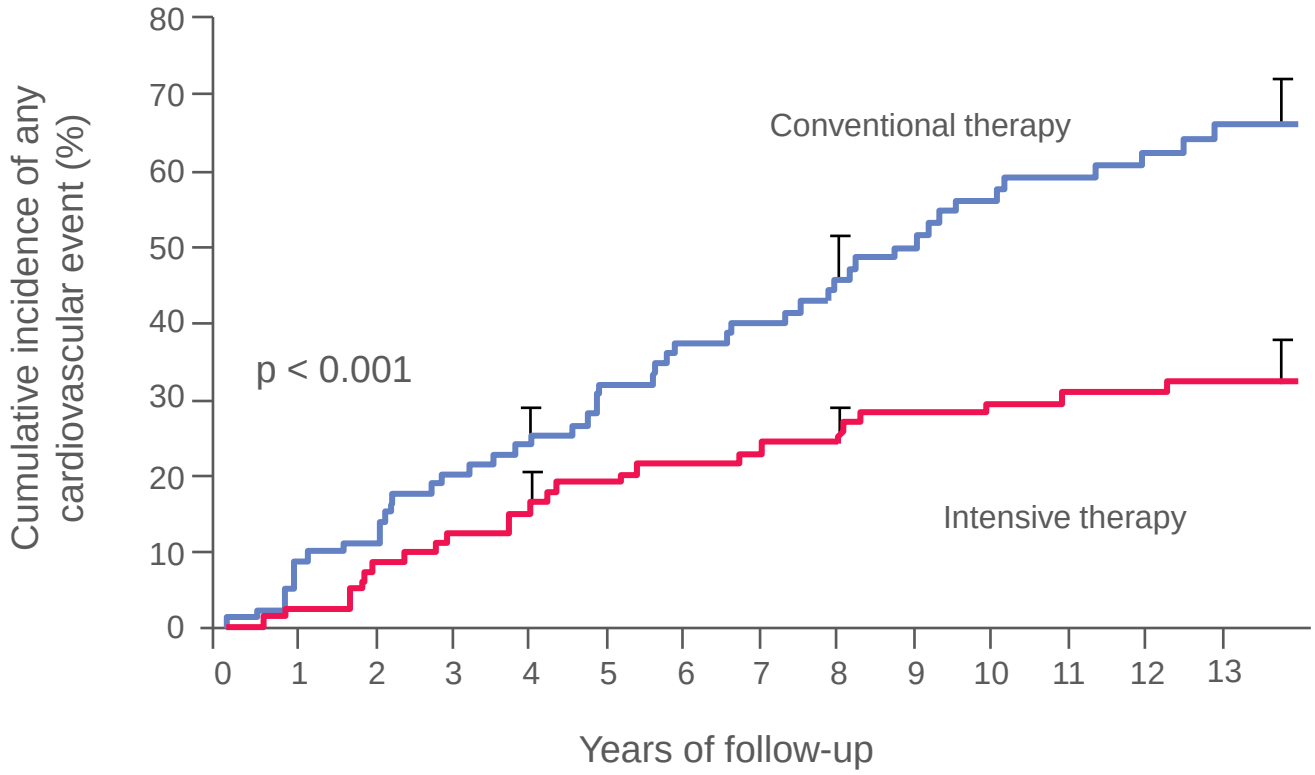
The Steno-2 trial was a single-centre study that enrolled a high-risk population of patients with T2D (n = 160)

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

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

52

Steno-2: Intensive multifactorial control of CV risk factors continues to reduce CV risk over long-term follow-up



Gaede et al. N Engl J Med 2008;358:580–91.

SCORE risk assessment

Very high Risk:	Subjects v • CVD • Type 2 • Patients • SCORE
High Risk:	Subjects v • Marked - Fam - Seve • SCORE
Moderate Risk:	SCORE is • family h • abdomi • physical
Low Risk:	SCORE les

WHAT ARE THE TARGETS?

Smoking	No exposure to tobacco in any form
Diet	Healthy diet- low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish*
Physical Activity	2.5 to 5 hours moderately vigorous physical activity per week or 30-60 minutes most days
Body weight	BMI 20-25. Waist circumference <94 cm (men) or <80 cm (women)
Blood pressure	BP <140/90
Lipids	Very high risk: LDL <1.8 mmol/L or >50% reduction High risk: LDL <2.5 mmol/L Low to moderate risk: LDL <3 mmol/L HDL cholesterol: No target but >1.0 mmol/L in men and >1.2 mmol/L in women indicates lower risk Triglycerides: No target but <1.7 mmol/L indicates lower risk and higher levels indicate a need to look for other risk factors
Diabetes	HbA1C <7%, BP <140/80

A multifactorial approach is recommended for control of CV risk in patients with T2D

Risk factor	Goal[1]	Recommendation[1]
Raised blood pressure	< 140/90 mmHg*	ACE inhibitor or ARB
Abnormal blood lipids	LDL cholesterol < 100 mg/dL (< 2.6 mmol/L)	Lifestyle modification and statin therapy
Tobacco use	Smoking cessation	Counselling and pharmacological therapy
Hyperglycaemia	HbA_{1c} < 7%† (< 53 mmol/mol)	Lifestyle modification and then metformin as initial monotherapy
Raised CV risk: 10-year risk > 10%	Antiplatelet use	ASA (75–162 mg/day)‡

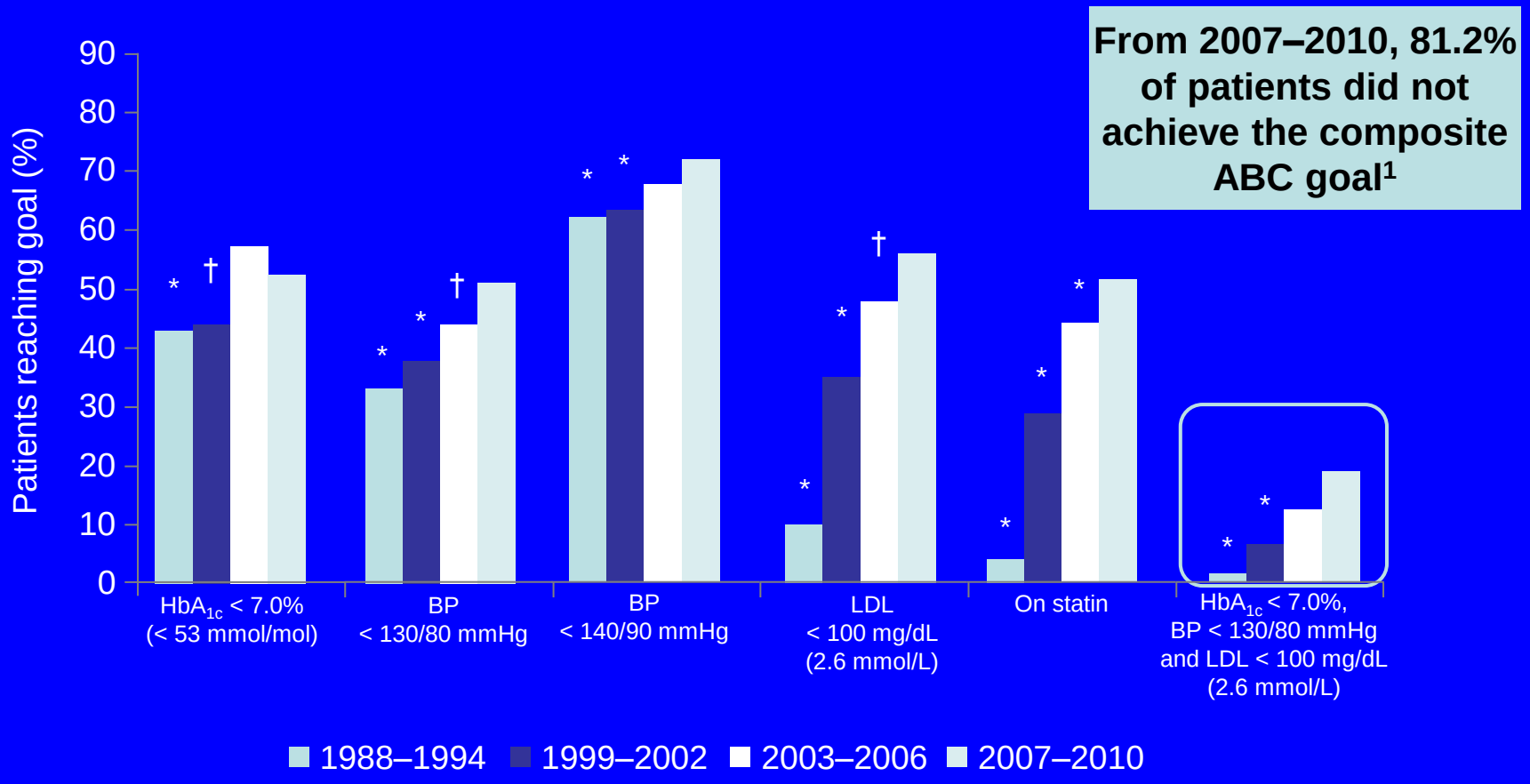
- American[1] and European[2] recommendations on CV risk factor management are similar

***Lower targets (e.g., <130/80 mmHg) may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. †More or less stringent goals may be appropriate for individuals. ‡Not recommended for those at low CV risk.**

1. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94. 2. Rydén et al. Eur Heart J 2013;34:3035–87.

5

Despite improvement over 2 decades, many patients with diabetes are still not reaching CV goals



*p < 0.01, †p < 0.05, each vs 2007–2010.

NHANES 1988–2010. Casagrande et al. Diabetes Care 2013;36:2271–9.

Conclusions

- Among patients at high risk for cardiovascular events but **without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, <u>resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause</u>, although significantly higher rates of some adverse events were observed in the intensive-treatment group.**

Summary

- **Beneficial effect of glycaemic control on macrovascular risk has not been established in prospective, long-term CV outcome trials**
- **Beneficial effects of LDL-cholesterol lowering[1], antihypertensive[2] and antiplatelet[3] therapy on CV risk are well established**
- **Multifactorial approach recommended for control of CV and microvascular risk[1,4]**
  - **recommended treatment goals with regard to glucose, blood pressure and lipids**
  - **lifestyle interventions**
  - **Provide antiplatelet therapy if indicated**
- **However, many patients fail to achieve CV risk factor goals[5]**

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2012;380:581–90. 2. Emdin et al. JAMA 2015;313:603–15.
3. American Diabetes Association. Diabetes Care 2015;38(suppl. 1):S1–S94. 4. Rydén et al. Eur Heart J 2013;34:3035–87.
5. NHANES 1988–2010. Casagrande et al. Diabetes Care 2013;36:2271–9.

Take Home messages

- **Most countries in the East Asia, stroke surpassed coronary heart disease in causing premature death so that TSOC/THS disagreed with**
  - **What ESC/ESH joint hypertension guidelines have suggested to loosen BP targets to <140/90 mmHg for all patients.**
  - **The suggestion by the 2014 JNC report to raise BP target to <150/90 mmHg for patients aged 60 – 80 years.**
- **To assist hypertensive patients reach BP goals, the ATGOALs algorithm can be executed, for example,**
  - **Greater dose is also considering, especially for organ protection to patients needed**
  - **Single-pill combination (SPC) can improve patients' adherence and may reduce more CV events**
- **The most effective approach to preventing stroke is to use BP-lowering drugs that reduce both mean BP and BPV, and to avoid drugs that increase BPV even if they reduce mean BP**

Take Home messages

- **In 2018, ADA statements**
  - cardiovascular risk factors should be **systematically assessed at least annually** in all patients with diabetes. These risk factors include **hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria**.
  - For patients with type 2 diabetes who have ASCVD, on lifestyle and metformin therapy, it is recommended to **incorporate an agent with strong evidence for cardiovascular risk reduction,** especially those with proven benefit on both major adverse cardiovascular events and cardiovascular death

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blood pressure to goal levels of less than 120 mm Hg was associated with a lower incidence of cardiovascular diseases, cardiovascular-related mortality, and even overall mortality as compared with reduction to a goal level of less than 140 mm Hg. Treatment was relatively well tolerated, but there were some potentially worrisome complications, including syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure. The lower average diastolic blood

120 mm Hg be advocated for most people with hypertension? I would take a more conservative view at present, particularly since in many participants in the intensive-treatment group, the target blood pressure was probably not reached. In my opinion, the results from SPRINT warrant reducing the treatment goal for systolic blood pressure to less than 130 mm Hg in most people with hypertension who are over 50 years of age and do not have diabetes or a history of stroke.

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Achieving stricter blood-pressure goals will probably require more careful titration of medications, greater use of combination drug preparations, more monitoring for adverse effects, and more frequent patient visits than currently occur.

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