

Hypertension and diabetes: Case based management

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Clinical case

Name: T. L.

Age: 54 years old

Occupation: truck driver

His father was hypertensive with abdominal aorta aneurisma. He died when he was 83 for colon cancer.

His mother was hypertensive and diabetic. She died when she was 61 years old for acute myocardial infarction.

Negative family history for other chronic or degenerative diseases. Blood pressure: 165/100 mm Hg

He states to be a normal eater. Moderate assumption of alcoholic beverages. Smoker (15-20 cigarettes/day). Very low level of physical activity.

Clinical case

Hypertension since 8 years

Diabetes since 3 years

Current treatment:

Fixed combination: ramipril 2.5 mg + hydrochlorothiazide (HCTZ) 12.5 mg

Metformin 500 mg bid

Blood pressure:	155/95 mmHg
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Fasting plasma glucose	92 mg/dl (= 5.1 mmol/l)
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A1c	6.6%
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Not at BP goal on current therapy and therefore referred to an hypertensive center

Case study: clinical examination

Weight: 86 kg

Height: 1.74 m

Waist circumference: 104 cm

BMI: 28.4

BP: 165/100 mm Hg

Heart rate: 72 bpm

Heart sounds and chest auscultation: normal

Abdominal examination: normal

Fundoscopic examination: normal

Peripheral examination: normal

Case study: investigations

Fasting plasma glucose	92 mg/dl	=	5.1 mmol/l
A1C	6.1%		
Serum potassium	4.2 mEq/l		
Serum creatinine	1.2 mg/dl		
Estimated GFR (MDRD formula)	94 ml/min		

Total cholesterol	252 mg/dl	=	6.5 mmol/l
High-density lipoprotein	32 mg/dl	=	0.8 mmol/l
Low-density lipoprotein	183 mg/dl	=	4.7 mmol/l
Triglycerides	184 mg/dl	=	2.1 mmol/l

Urinalysis	Normal
Dipstik microalbuminuria	Absent

Electrocardiogram	Normal
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CV risk assessment

What is the CV risk for this patient?

1) Low risk

2) Moderate risk

3) High risk

4) Very high risk

Stratification of CV Risk in four categories. The dashed line indicates how definition of hypertension may be variable, depending on the level of total CV risk.

Other risk factors, OD or disease	Blood pressure (mmHg)				
	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

CV risk assessment

CV risk factors

Hypertension

Diabetes

Smoking

Dyslipidemia

Family history of premature CV disease

Stratification of CV Risk in four categories. The dashed line indicates how definition of hypertension may be variable, depending on the level of total CV risk.

Other risk factors, OD or disease	Blood pressure (mmHg)				
	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

CV risk assessment

Are you satisfied with this CV risk determination or do you believe it is important to perform adjunctive tests?

1) Yes, I am satisfied

2) No, it is necessary to perform an echocardiogram

3) No, it is necessary to perform an ultrasound

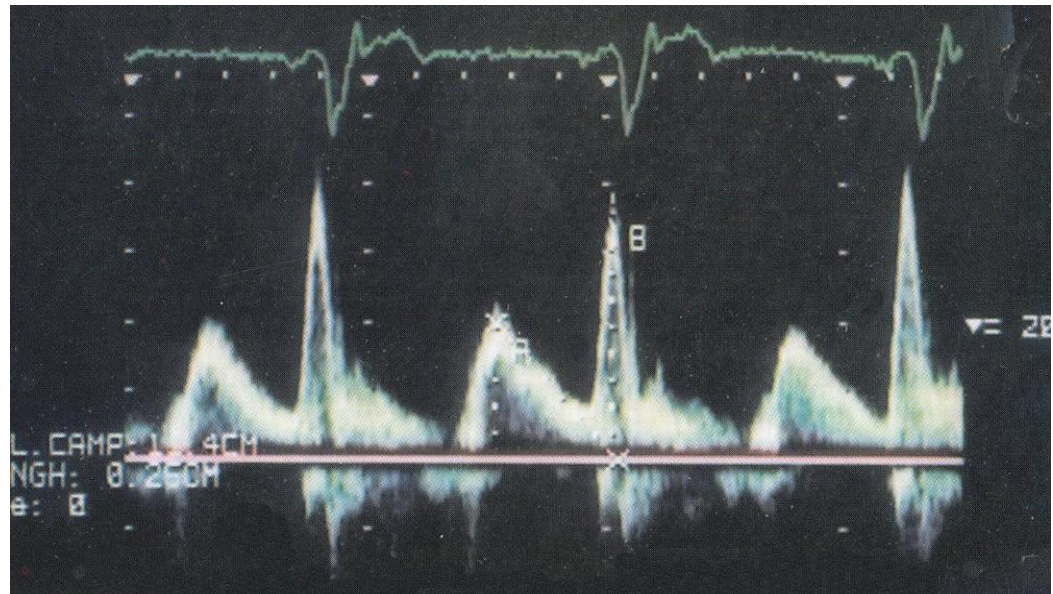
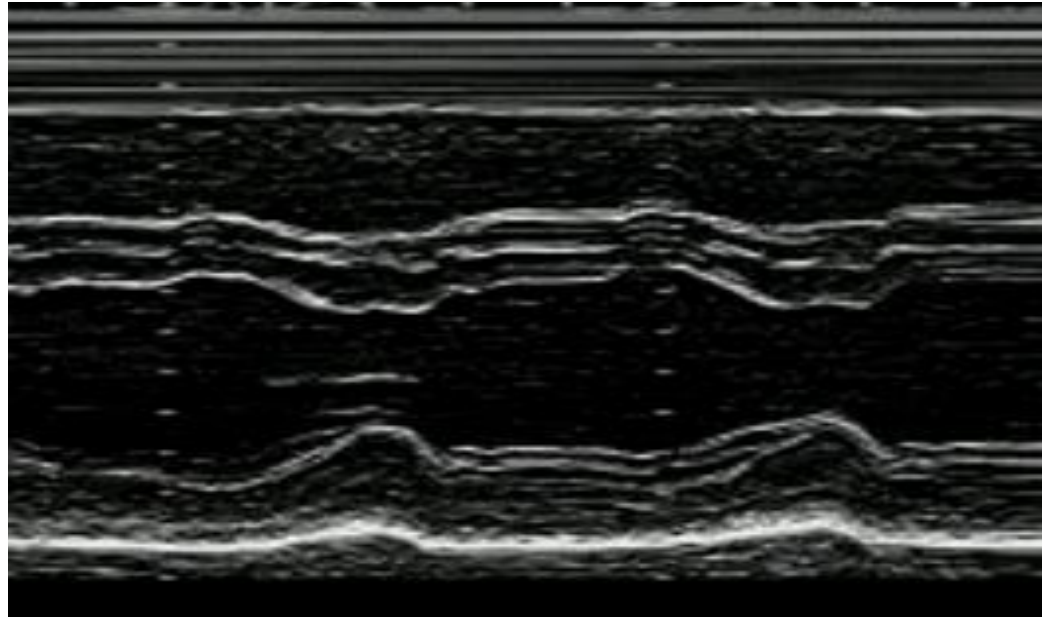
4) No, it is necessary to perform an ABPM

Clinical case

This patients could be managed without adjunctive tests.
However, expecially in a specialistic center, it is convenient to better characterize the CV risk profile.

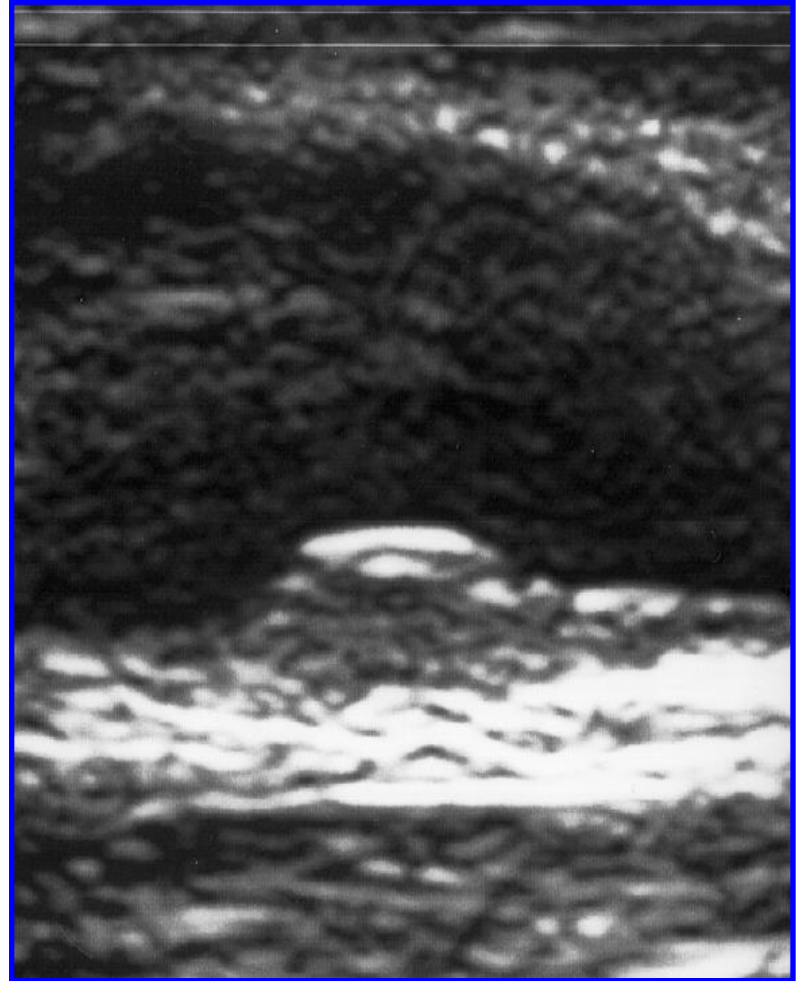
Echocardiogram

- Concentric LVH (LMVS 58 g/m².7; LVMI: 148 g/mq; RWT: 0.47).
- Increased left atrial (44 mm)
- Normal contractility (EF 56%)
- Diastolic dysfunction (E/A= 0.6)
- Mild mitral failure lieve (+)
- Mild tricuspidal failure (+)



Carotid ultrasound

- 30% stenosis of left bifurcation
- diffuse intima-media thickening



Clinical case

Tests confirm that this patient is at high CVrisk.

CV risk assessment

In this patient would you perform an abdomen echography and/or a renal artery doppler?

- 1) No
- 2) Only an abdomen echography
- 3) Only a renal artery doppler
- 4) Both

Indications for abdominal echography

High risk for abdominal aorta aneurysm (male, smoker, hypertensive, positive family history).

Indications for renal arteries doppler

High risk for renal artery stenosis (smoking and diabetes)

Abdominal echography

Mild-moderate hepatic hypertrophic steatosis. Normal adrenals and kidneys. Atherosclerotic plaques at the level of abdominal aorta.

Renal arteries doppler

No renal artery stenosis, normal renal perfusion, increased vascular resistance indices

Diagnosis

- Essential arterial hypertension with high CV risk
- Global cardiovascular risk: family history for CV disease, smoking habitus, diabetes, hypercholesterolemia, sedentary life
- Target organ damage: LVH, carotid artery IMT and plaque

Treatment

- Life style modifications: low calories and low cholesterol diet; dynamic exercise; smoking cessation
- Antihypertensive treatment: any compelling evidence?
- Need for accompanying non-antihypertensive treatment:
 - Statins?*
 - Antiplatelet therapy?*

Treatment

What is BP target for this patient?

1) < 140-90 mmHg

2) < 135-85 mmHg

3) < 130-80 mmHg

4) < 125-75 mmHg

Box 8 Position statement: Goals of treatment

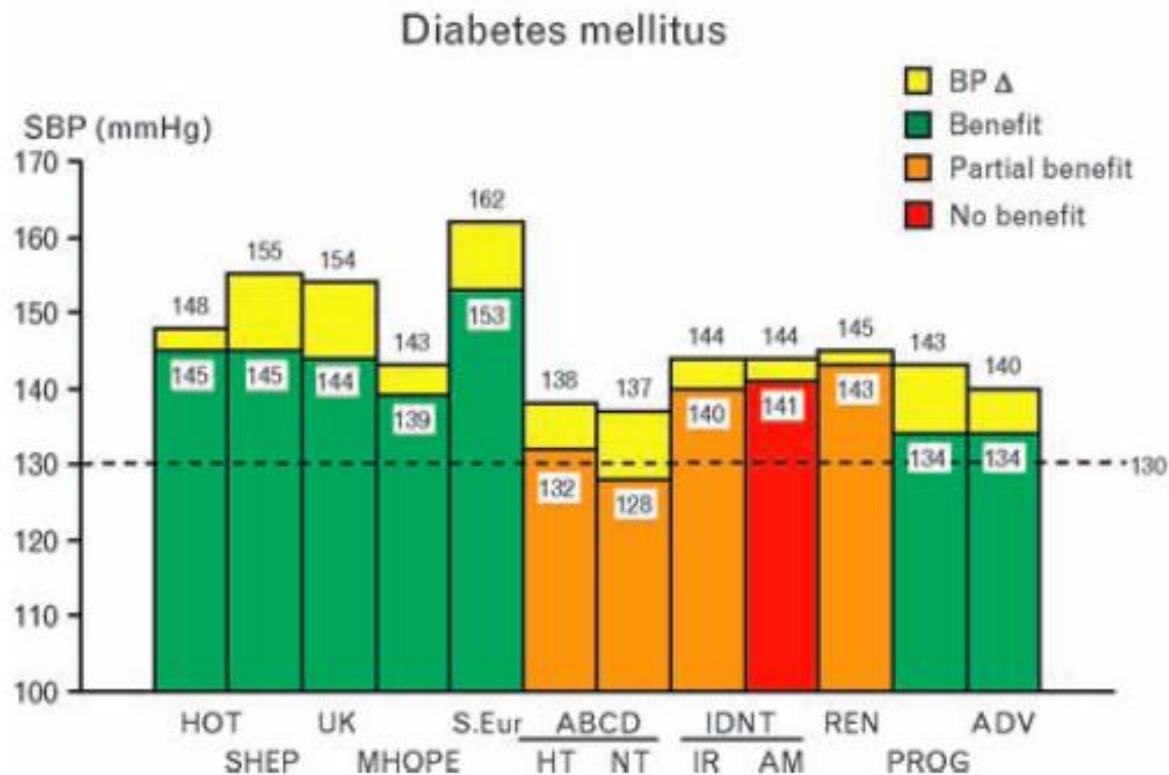
- In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular disease.
- This requires treatment of the raised BP per se as well as of all associated reversible risk factors.
- BP should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients.
- Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).
- Despite use of combination treatment, reducing systolic BP to < 140 mmHg may be difficult and more so if the target is a reduction to < 130 mmHg. Additional difficulties should be expected in elderly and diabetic patients, and, in general, in patients with cardiovascular damage.
- In order to more easily achieve goal BP, antihypertensive treatment should be initiated before significant cardiovascular damage develops.

BP target in diabetic hypertensive patients according to different Guidelines

- < 130/80 mmHg (JNC 7, 2003)
- < 130/80 mmHg (ESH-ESC, 2007)
- < 130/80 mmHg (American Diabetes Association, 2002)

Reappraisal of the European Society of Hypertension Guidelines for the Management of Hypertension

Blood pressure goals



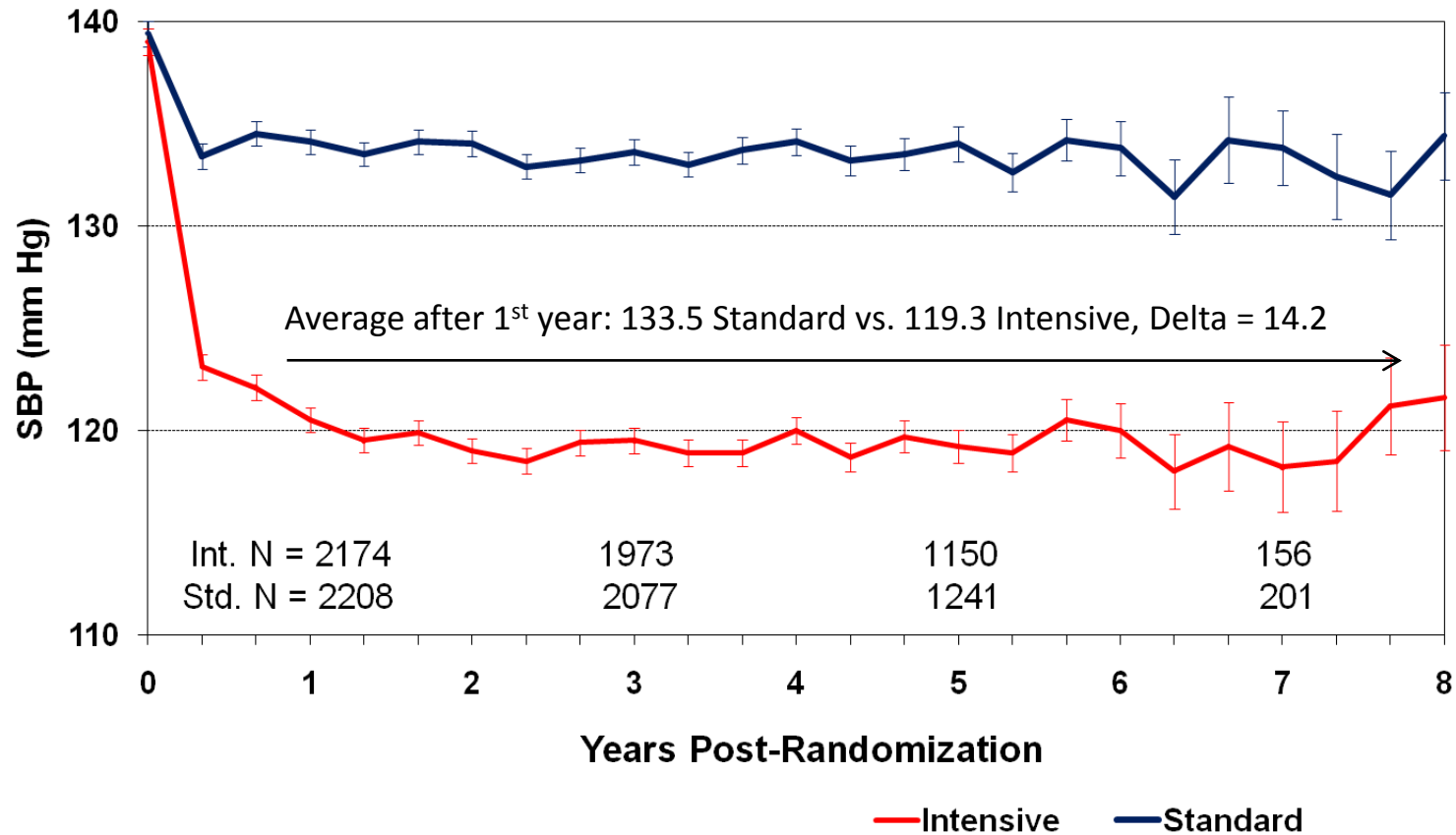
Recommendation to lower BP less than 130/80mmHg in patients with diabetes is not supported by incontrovertible trial evidence.

Achieved SBP in patients randomized to a more active (lower part of histograms) or less active (upper part of histograms) treatment

The ACCORD Study

Mean # Meds

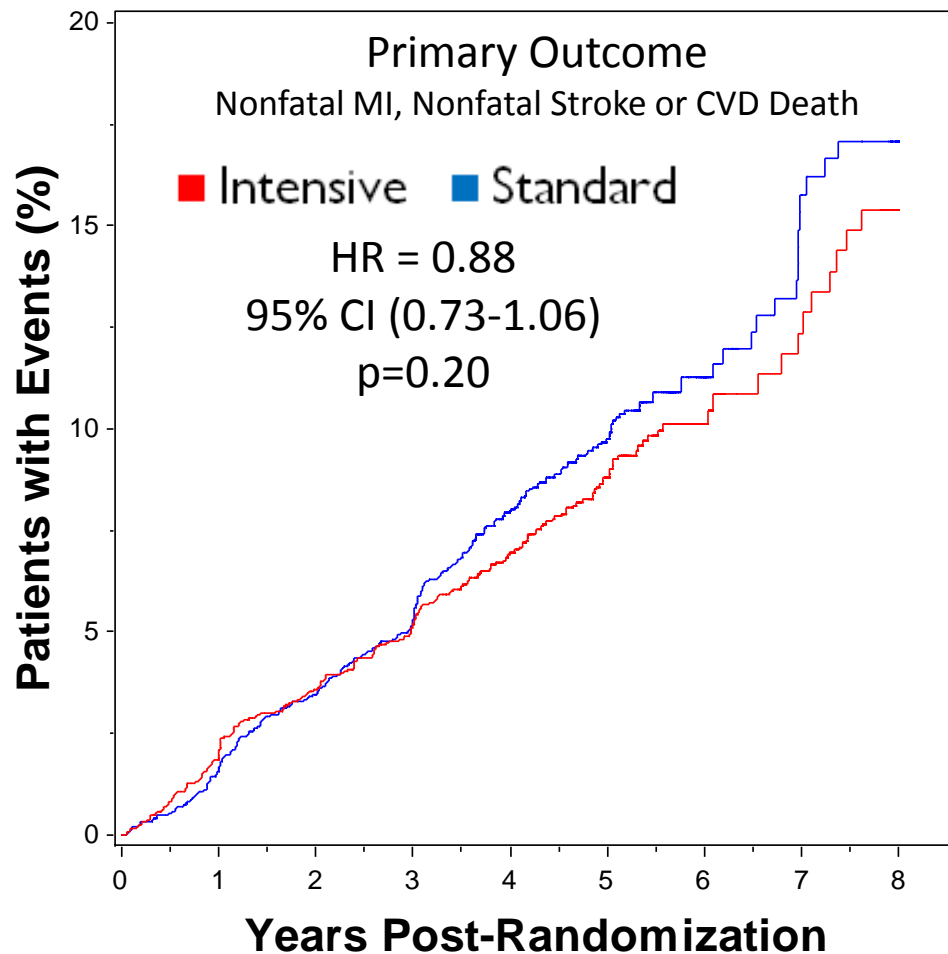
Intensive:	3.2	3.4	3.5	3.4
Standard:	1.9	2.1	2.2	2.3



The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. The New England Journal of Medicine (2010)

The ACCORD Study

Primary End-point

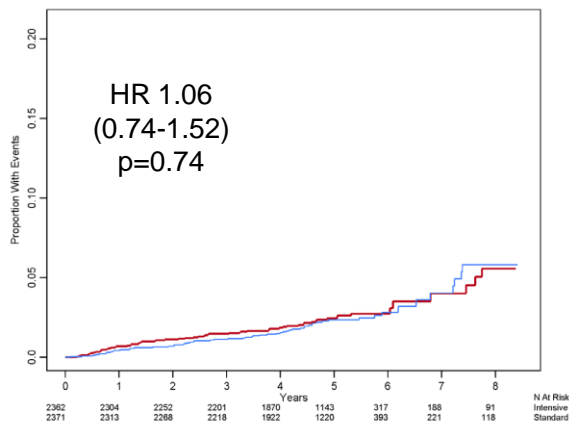


The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. The New England Journal of Medicine (2010)

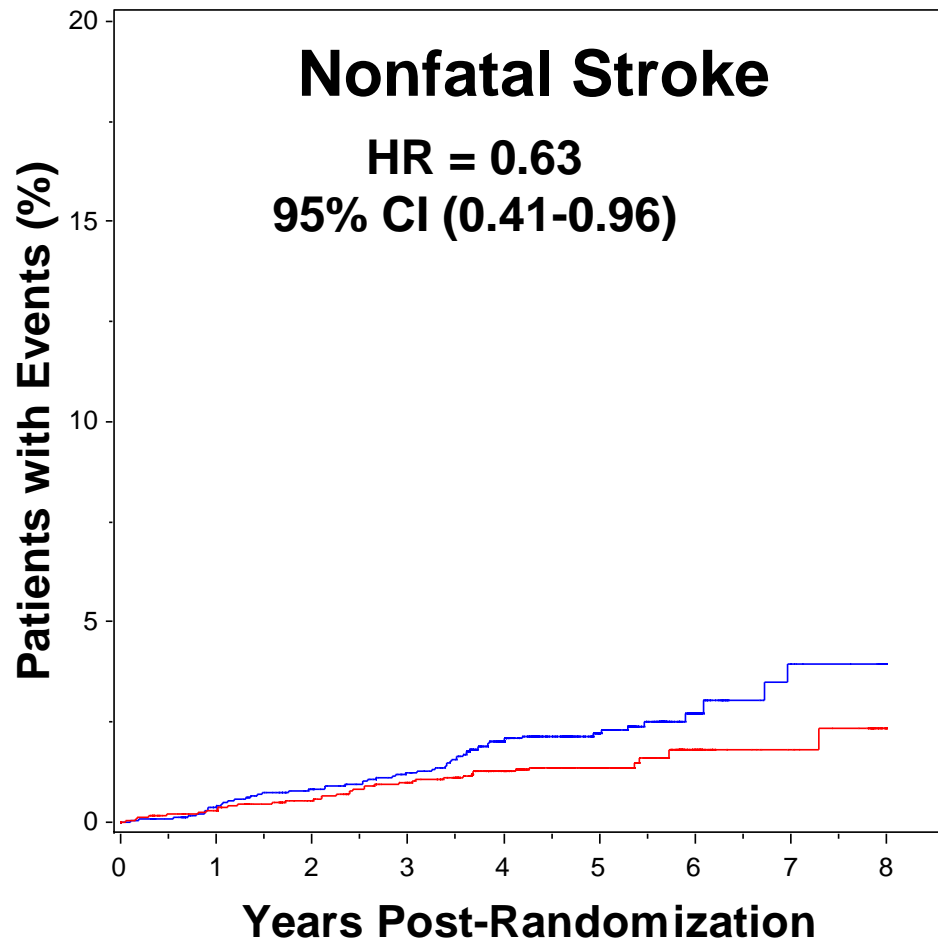
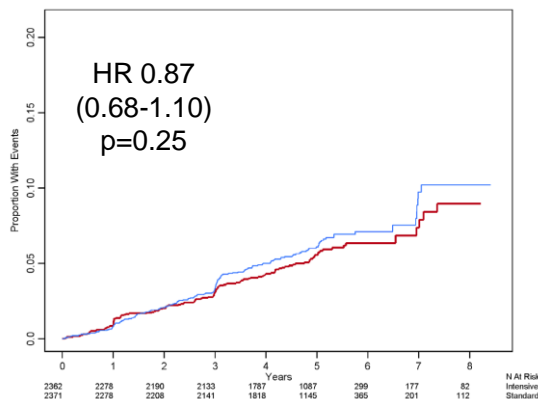
The ACCORD Study

Secondary End-points

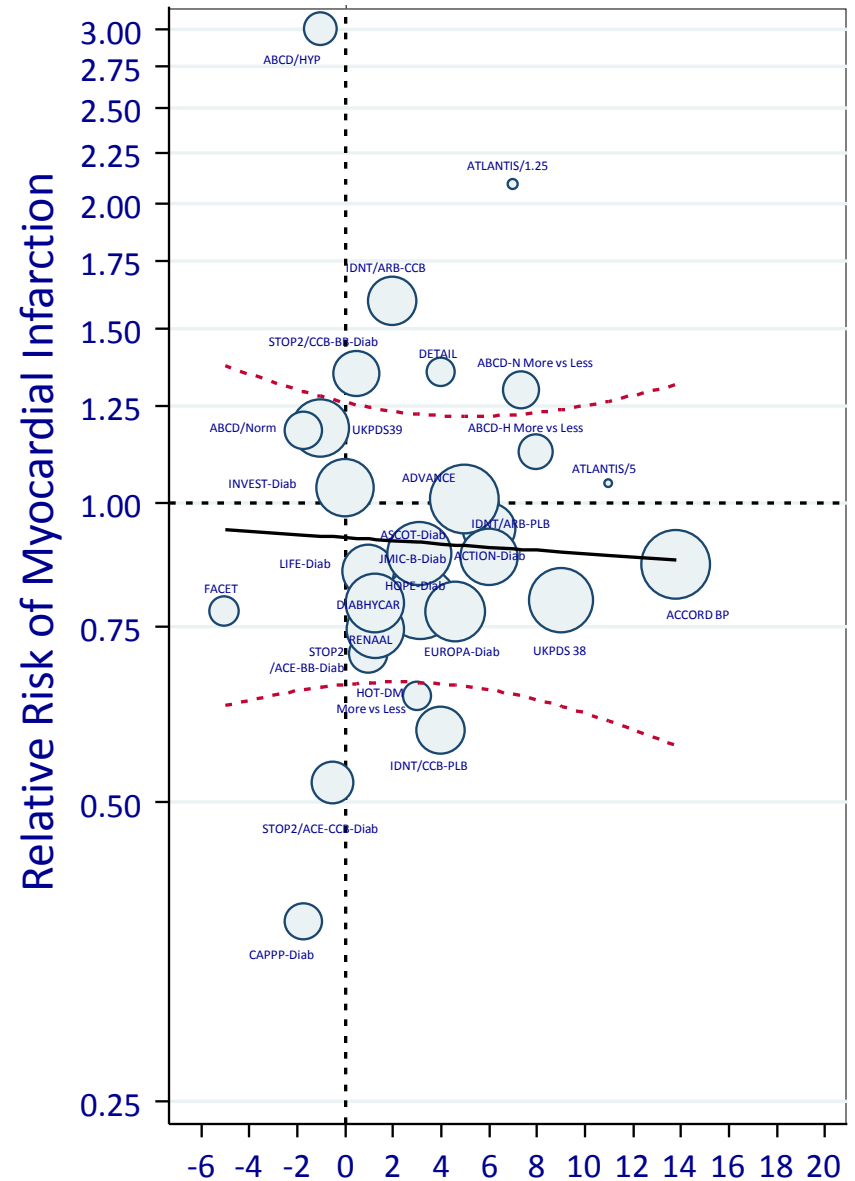
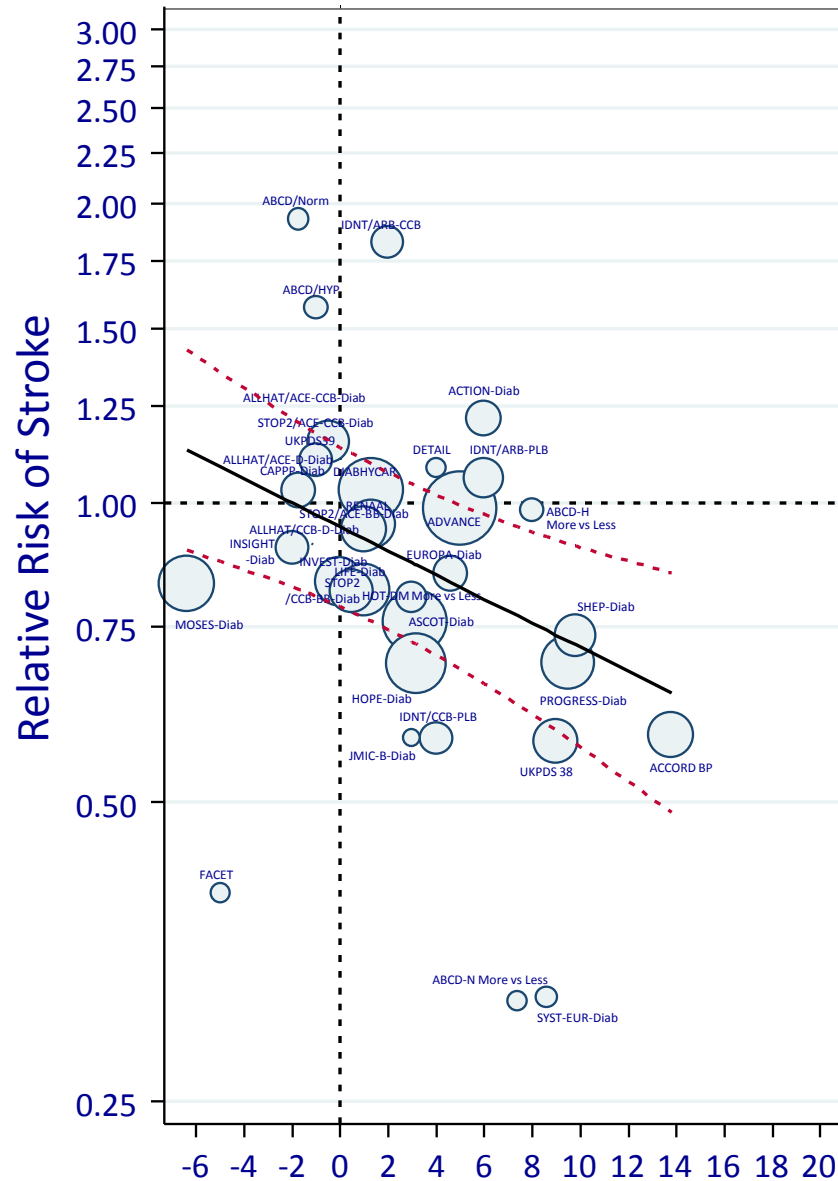
CV Mortality



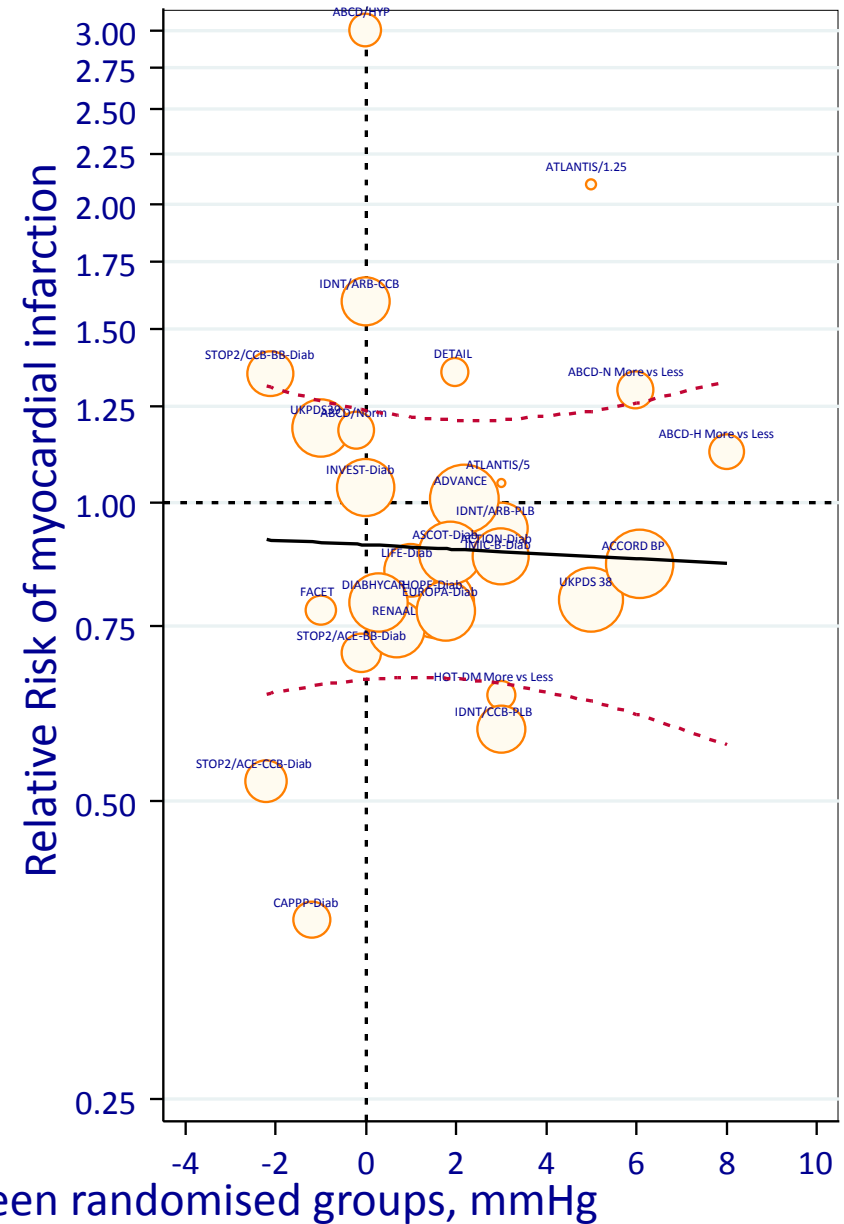
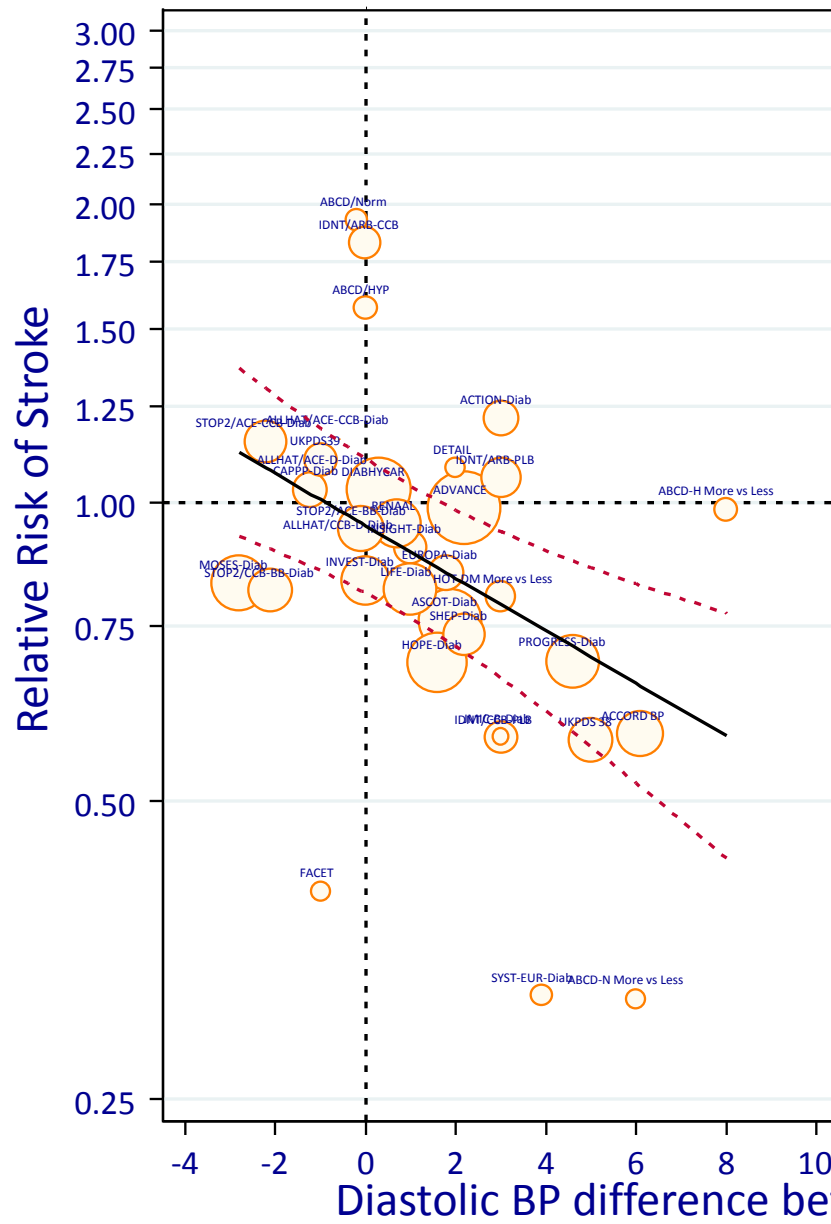
Nonfatal MI



Outcome trials comparing the effect of systolic blood pressure reduction on the risk of stroke or myocardial infarction in diabetic patients



Outcome trials comparing the effect of diastolic blood pressure reduction on the risk of stroke or myocardial infarction in diabetic patients



BP target

In a patient with hypertension and diabetes it should be mandatory to lower BP values well below 140-90 mmHg.

The more aggressive target of less than 130-80 mmHg should be individually considered.

Treatment

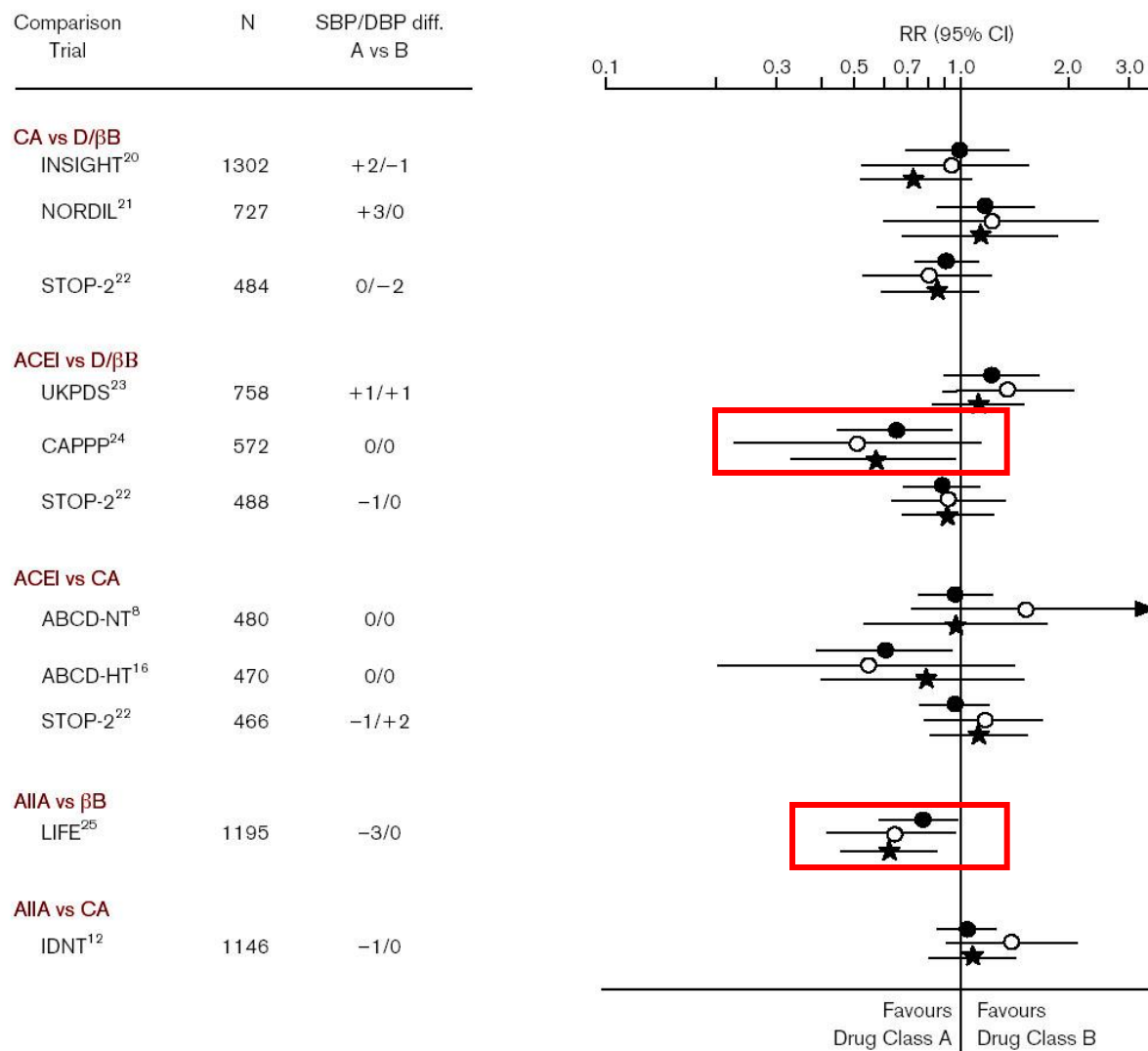
What is the first choice drug for this patient?

- 1) ACE-inhibitor
- 2) AT-1 antagonist
- 3) Calcium antagonist
- 4) Beta-blocker
- 5) Diuretic

Box 14 Antihypertensive treatment in diabetics

- Where applicable, intense non-pharmacological measures should be encouraged in all diabetic patients, with particular attention to weight loss and reduction of salt intake in type 2 diabetes.
- Goal BP should be <130/80 mmHg and antihypertensive drug treatment may be started already when BP is in the high normal range.
- To lower BP, all effective and well tolerated drugs can be used. A combination of two or more drugs is frequently needed.
- Available evidence indicates that lowering BP also exerts a protective effect on appearance and progression of renal damage. Some additional protection can be obtained by the use of a blocker of the renin-angiotensin system (either an angiotensin receptor antagonist or an ACE inhibitor).
- A blocker of the renin-angiotensin system should be a regular component of combination treatment and the one preferred when monotherapy is sufficient.
- Microalbuminuria should prompt the use of antihypertensive drug treatment also when initial BP is in the high normal range. Blockers of the renin-angiotensin system have a pronounced antiproteinuric effect and their use should be preferred.
- Treatment strategies should consider an intervention against all cardiovascular risk factors, including a statin.
- Because of the greater chance of postural hypotension, BP should also be measured in the erect posture.

Trials Comparing Regimens Based on Different Drug Classes in diabetic patients



Effects of Different Blood Pressure–Lowering Regimens on Major Cardiovascular Events in Individuals With and Without Diabetes Mellitus

Results of Prospectively Designed Overviews of Randomized Trials

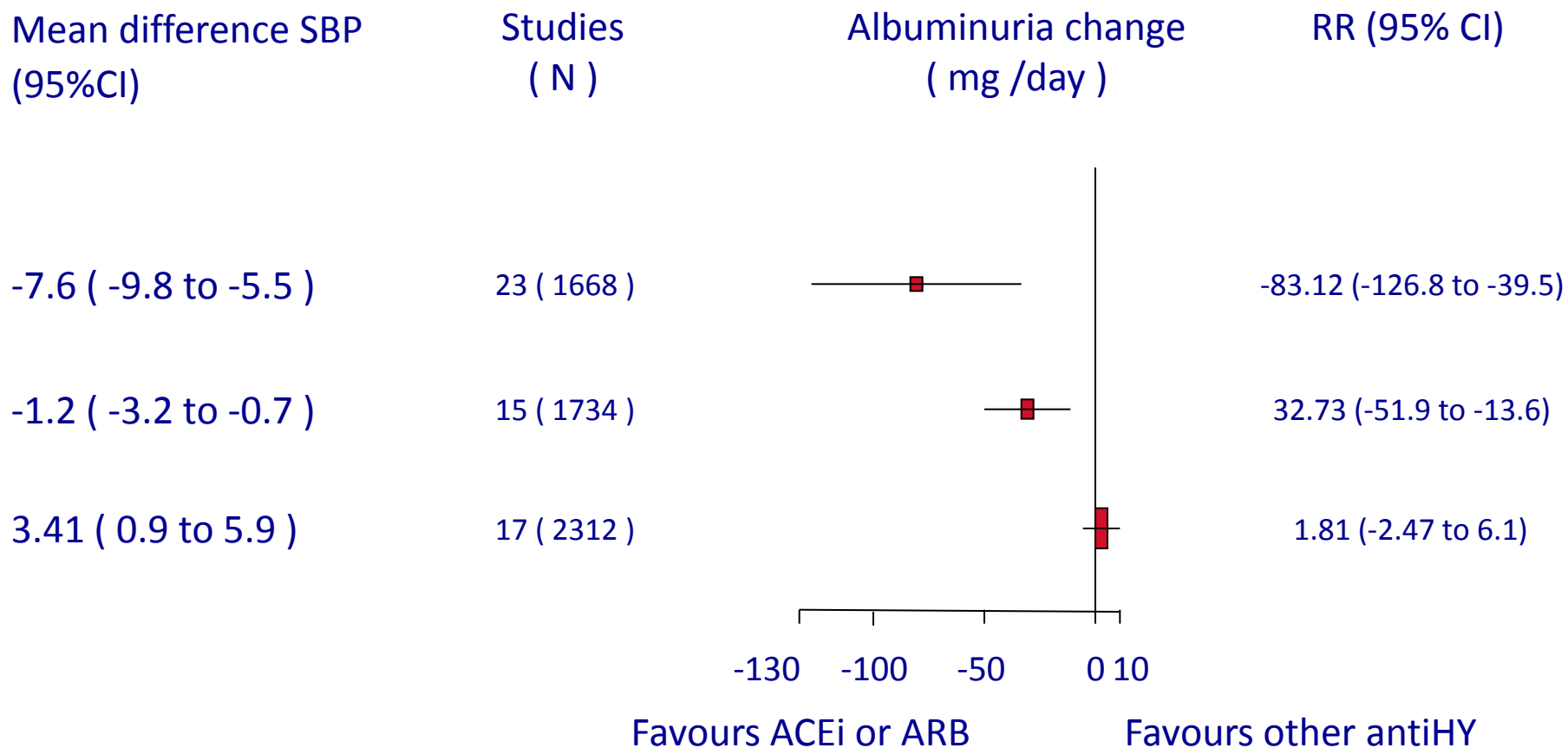
*Blood Pressure Lowering Treatment Trialists' Collaboration**

Conclusions: These overviews showed that the short- to-medium-term effects on major cardiovascular events of the BP-lowering regimens studied were broadly comparable for patients with and without diabetes. Different effects of regimens on intermediate renal outcomes not evaluated in these overviews may still provide a rationale for using specific drug classes in patients with diabetes.

Arch Intern Med. 2005;165:1410-1419

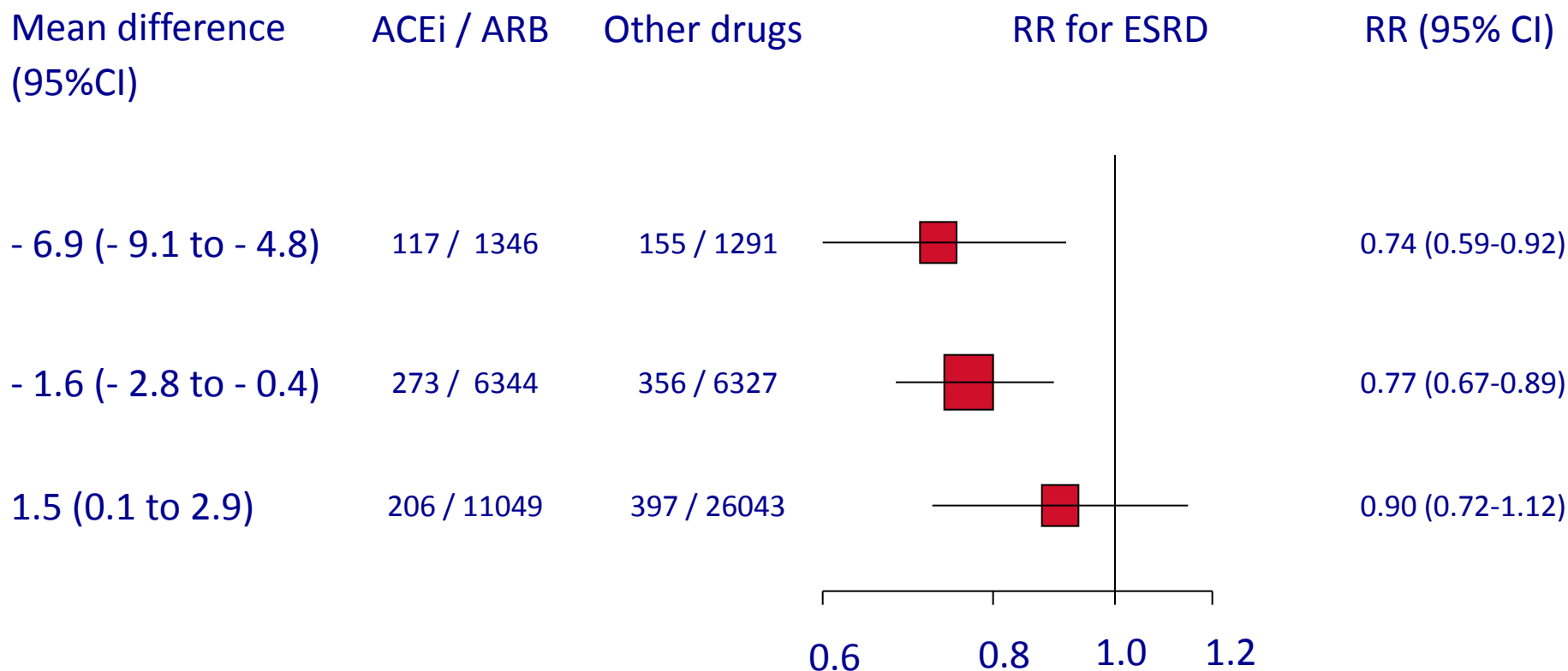
Effect of ACEi or ARBs on renal outcomes: systematic review and meta-analysis

Degree of change of SBP and proteinuria reduction



Effect of ACEi or ARBs on renal outcomes: systematic review and meta-analysis

Degree of change of SBP and RR for ESRD



Treatment

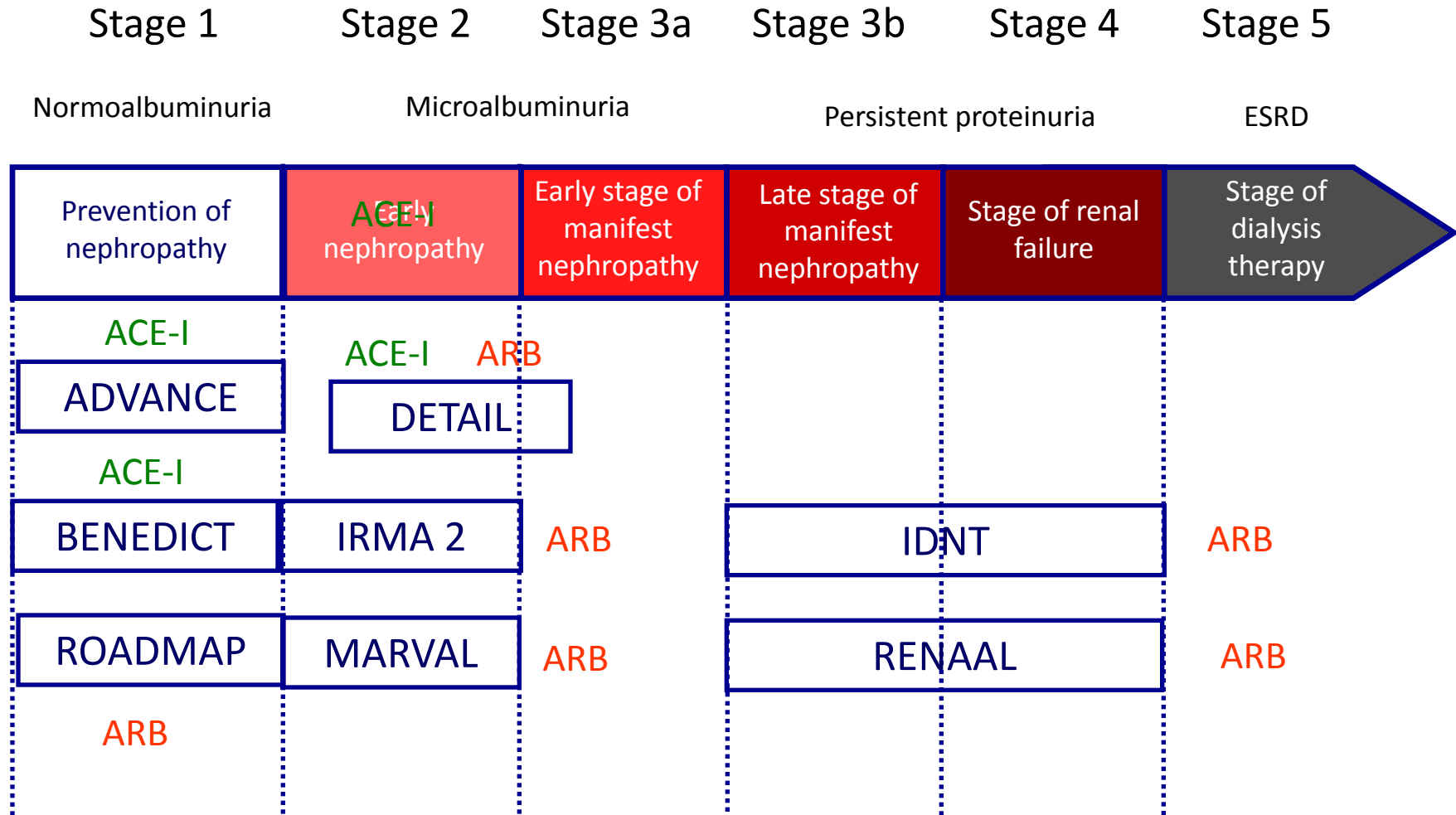
It is better to use an ACE-I or an ARB for the renal protection?

1) ACE-I

2) ARB

3) No difference

Diabetic Nephropathy and Outcome Studies



Treatment

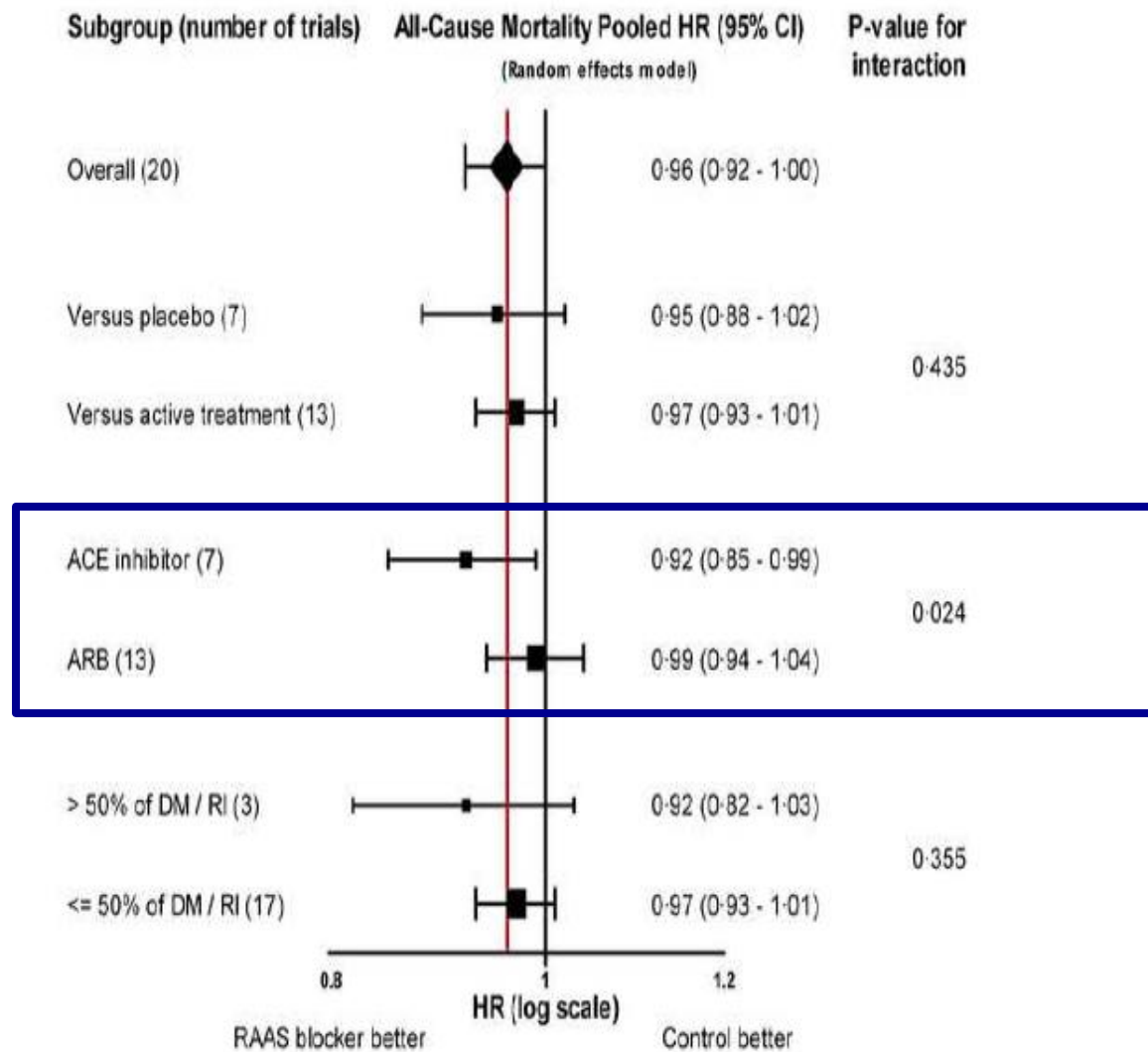
It is better to use an ACE-I or an ARB for global protection?

1) ACE-I

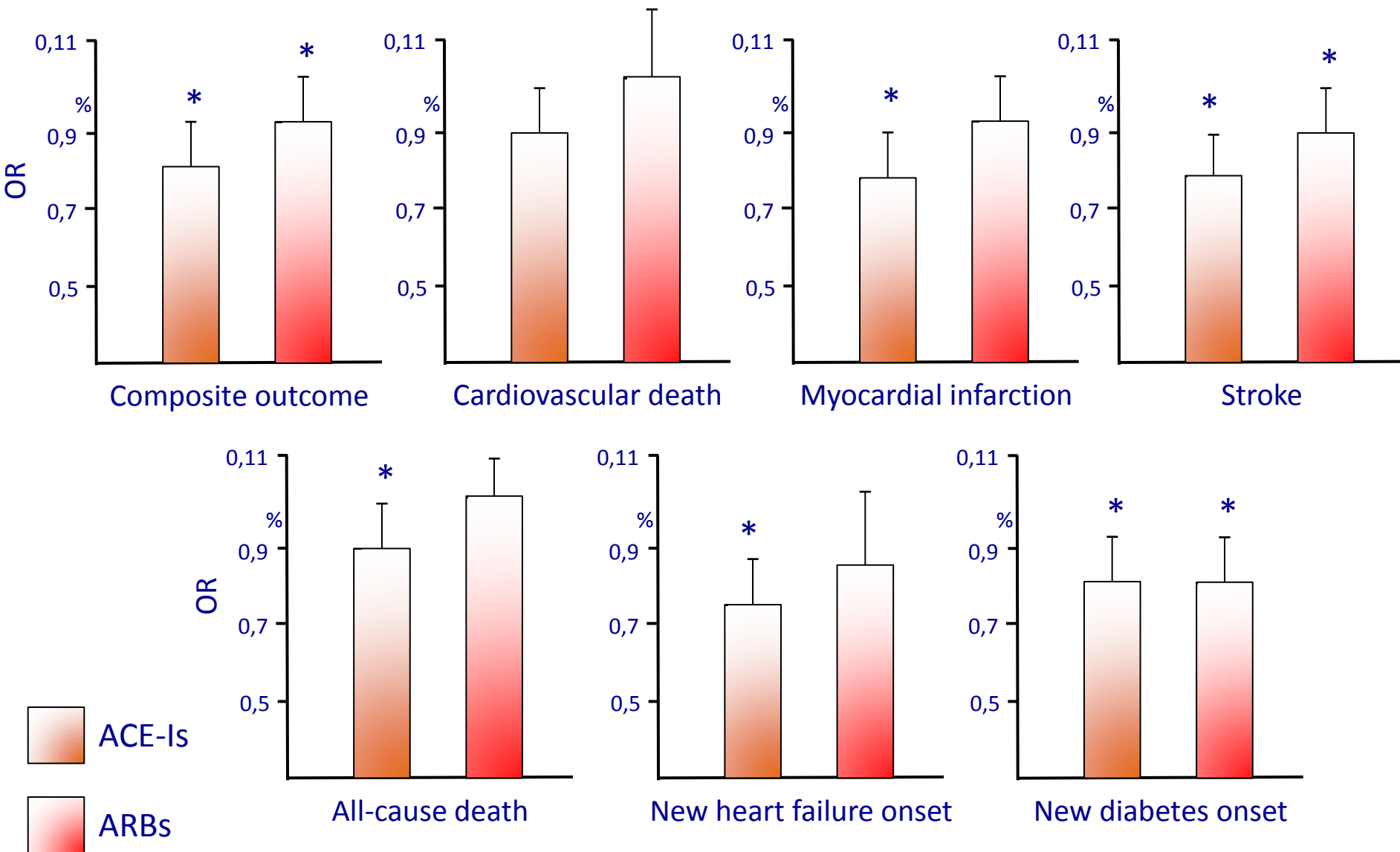
2) ARB

3) No difference

Effect of ACE-I and ARBs on total mortality

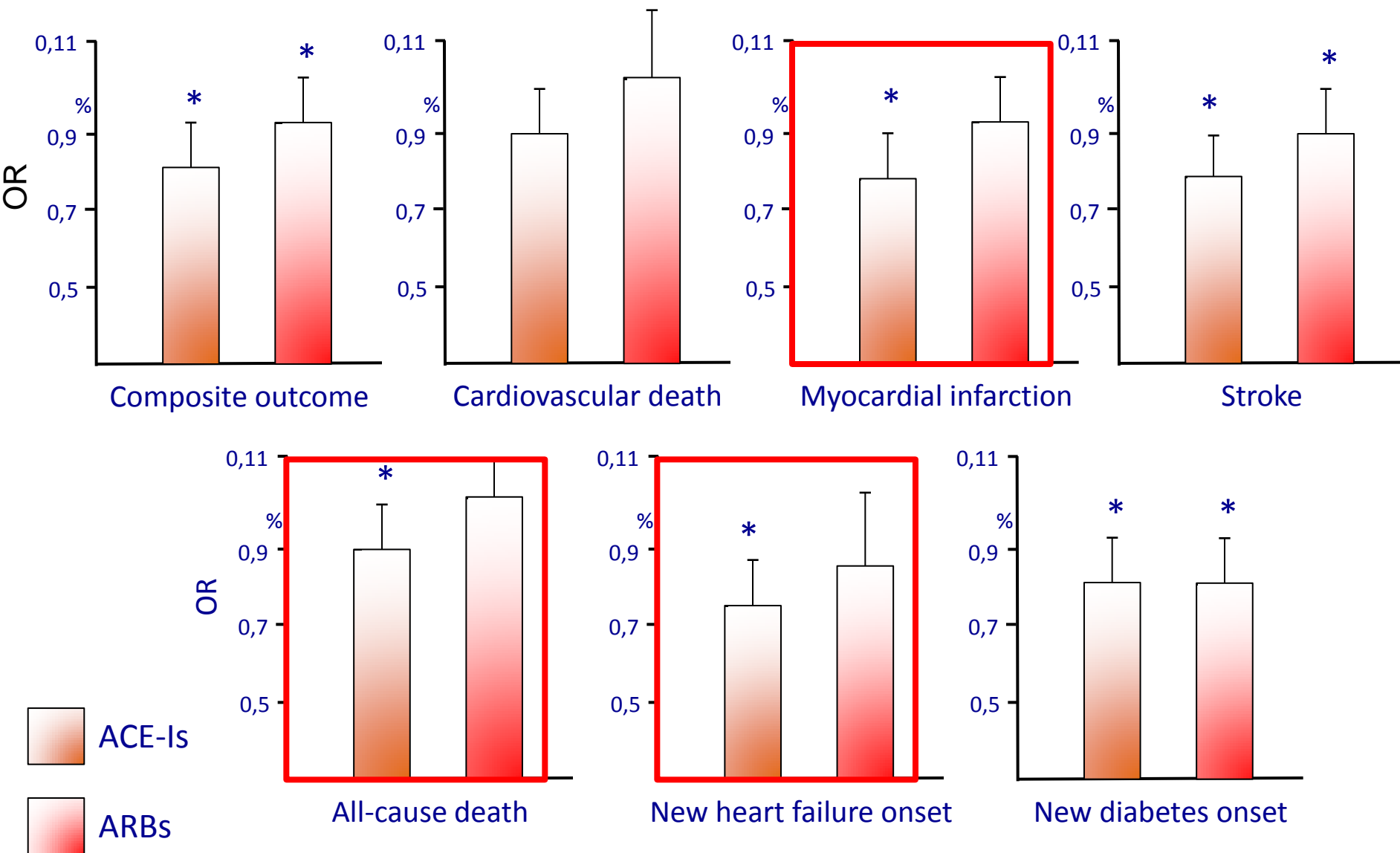


Effect of ACE-Is or ARBs on outcomes



* outcome significantly reduced as compared to placebo

Effect of ACE-Is or ARBs on outcomes

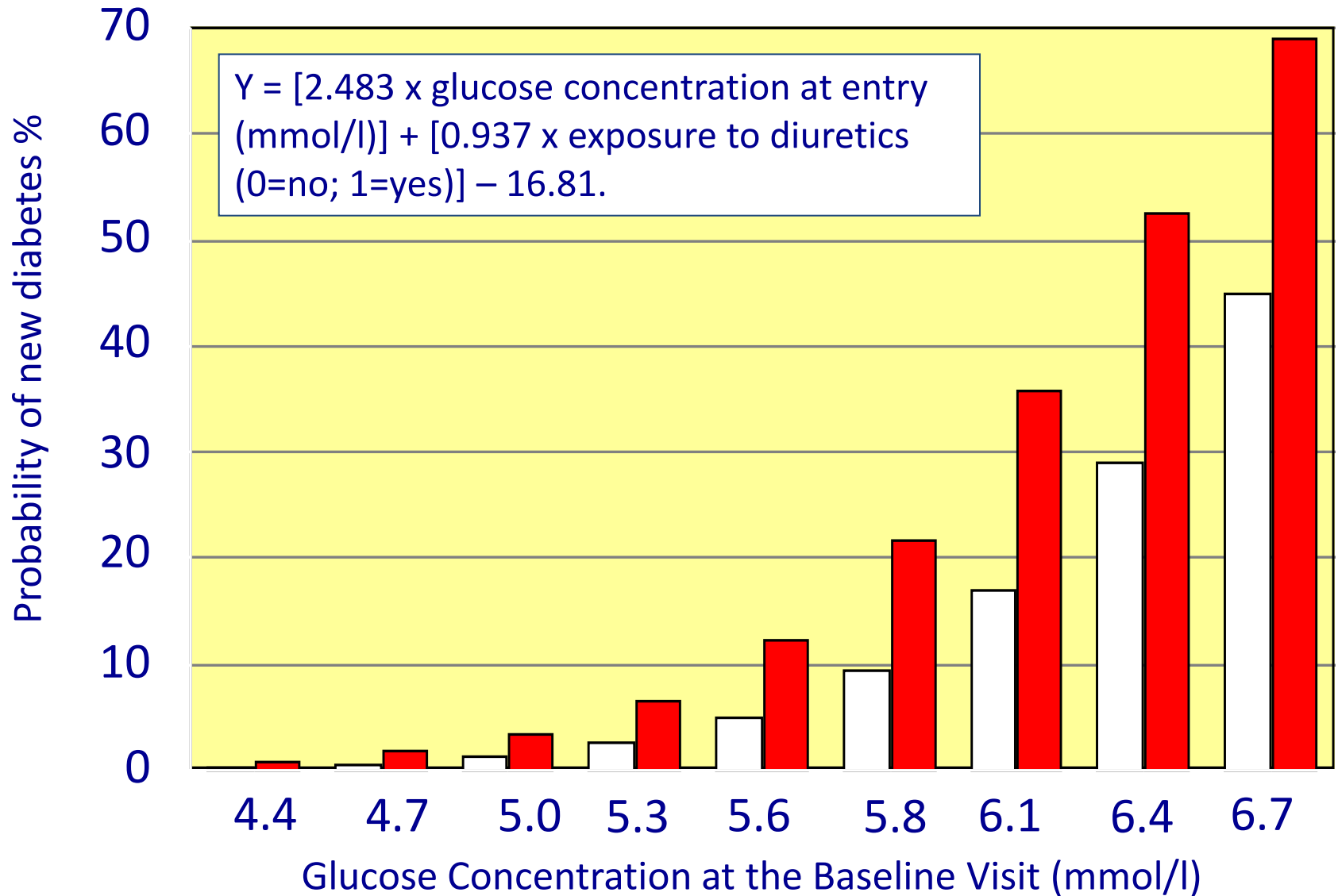


* outcome significantly reduced as compared to placebo

Which drugs should be avoided in hypertensive diabetic patients?

□ Not Receiving diuretics

■ Receiving diuretics



Incidence of New Diabetes Among 12 550 Adults The Atherosclerosis Risk in Communities (ARIC) Study

Antihypertensive Medication	Hazard Ratio* (95% Confidence Intervals)
None	1.0
ACE-Inhibitors	0.98 (0.72-1.34)
Beta-blockers	1.28 (1.04-1.57) †
Calcium channel blockers	1.17 (0.83-1.66)
Thiazide diuretics	0.91 (0.73-1.13)

* After adjustment for age, sex, race, use of other drugs, BMI, waist-to-hip ratio, level of education, smoking, alcohol use, level of physical activity, SBP, DBP, fasting insulin, hypercholesterolemia, previous CD disease, previous pulmonary disease, family history of diabetes.

† = $p < 0.05$

How to improve blood pressure control in this patient?

Clinical case

Current treatment:

Fixed combination: ramipril 2.5 mg + hydrochlorothiazide (HCTZ) 12.5 mg

Metformin 500 mg bid

Blood pressure:	155-95 mmHg
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Fasting plasma glucose	92 mg/dl
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A1C	6.6%
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Treatment

Which strategy do you suggest to improve the efficacy of antihypertensive treatment?

- 1) Increase the dose of the ACE-inhibitor
- 2) Increase the dose of the diuretic
- 3) Increase the dose of both
- 4) Combination with a calcium antagonist

Dosing of antihypertensive drugs

For some drugs:

Low dose

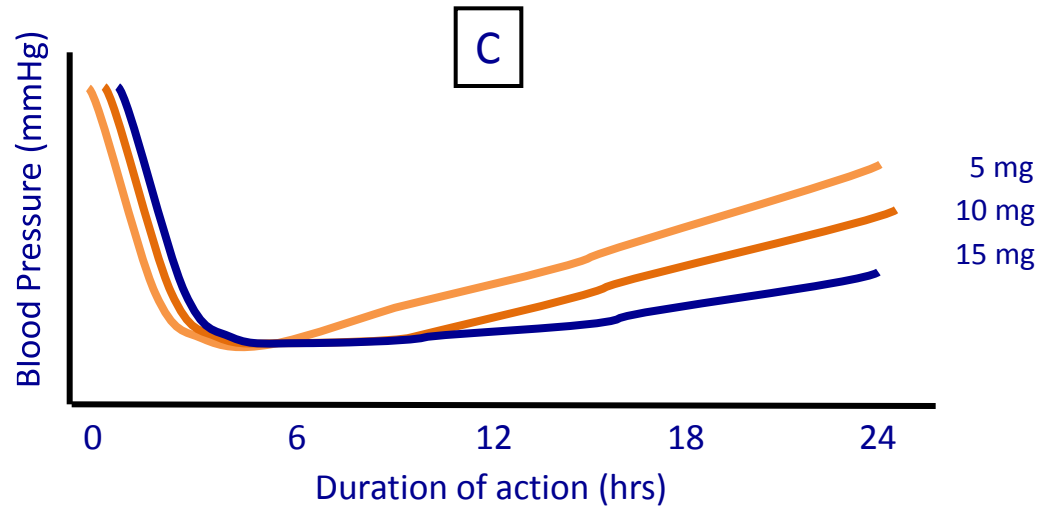
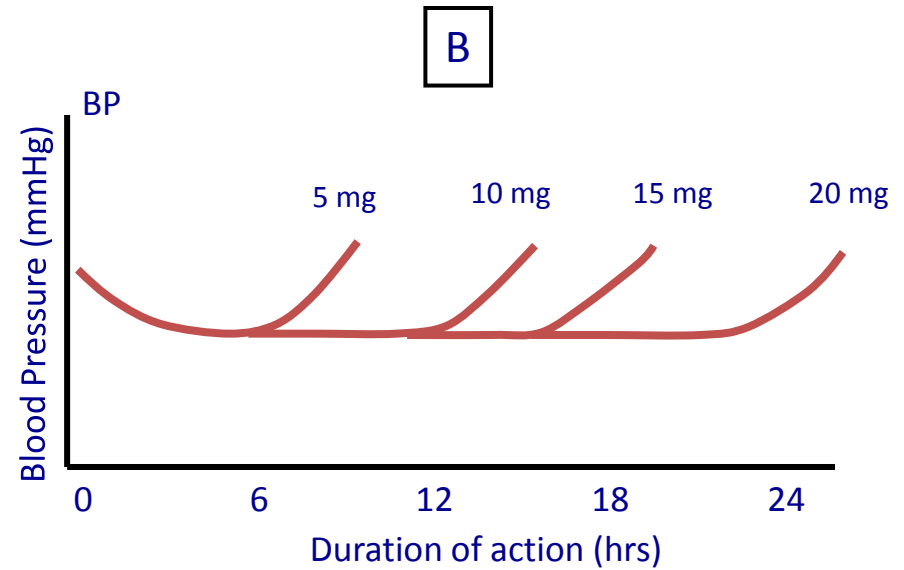
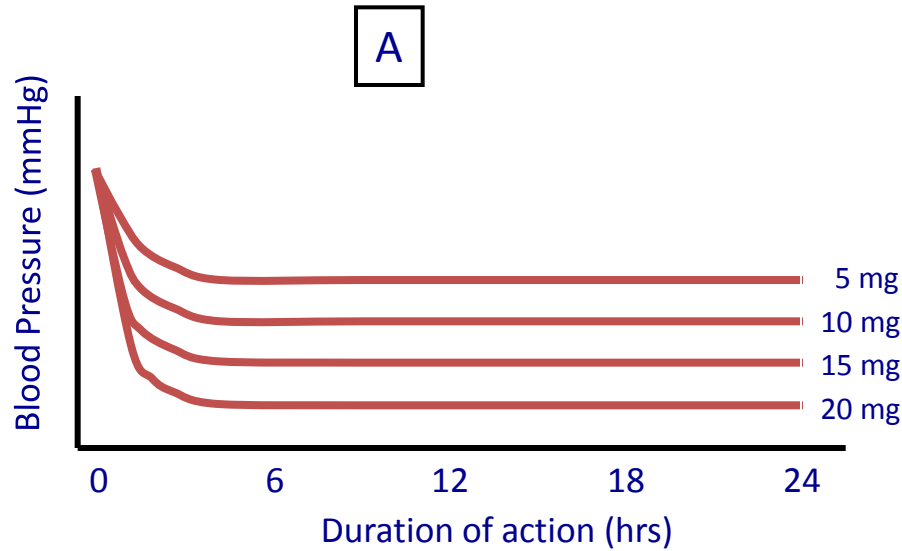
Intermediate dose

High dose

For other drugs:

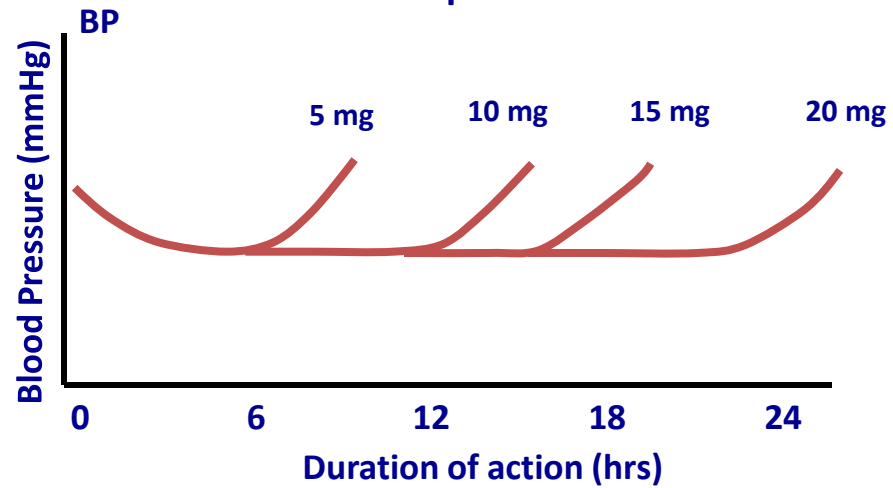
Single correct dose

Dose-response curves of antihypertensive drugs

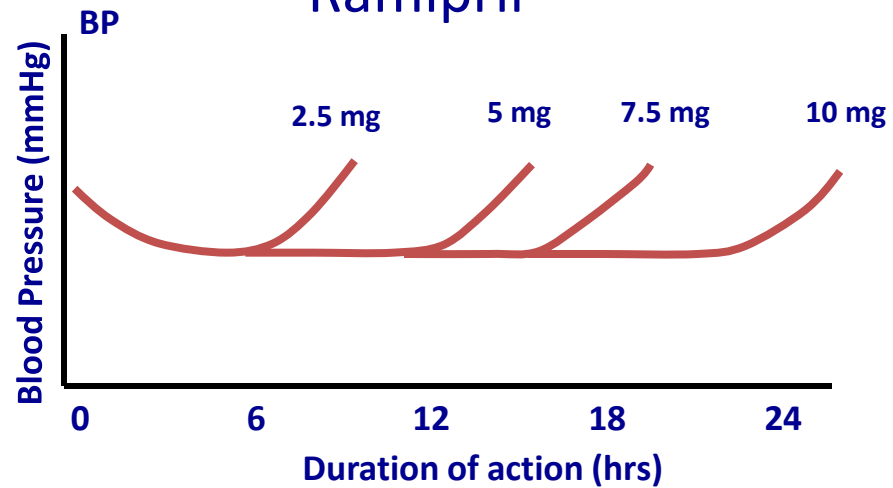


ACE-inhibitors

Enalapril

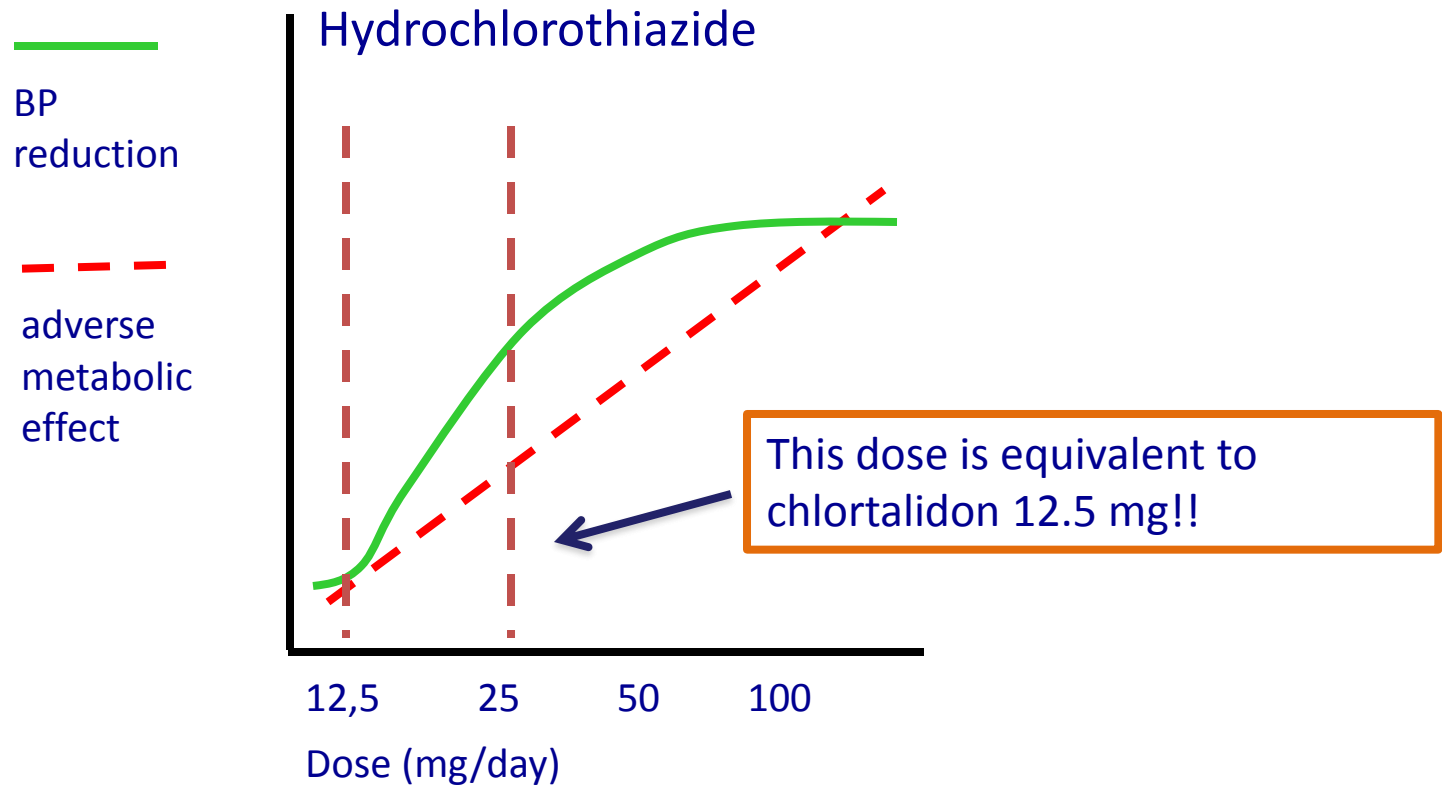


Ramipril



BP reduction and side effects* of thiazide diuretics

*hypokalemia, increase in total cholesterol and glycaemia



adapted from Carter BL et al. Hypertension 2004

“homeopathic” combination!

Ramipril 2.5 mg / HTCZ 12.5 mg

Treatment

Which strategy do you suggest to improve the efficacy of antihypertensive treatment?

Proposal:

- Combination of an ACE-inhibitor at full dose with a DHP calcium antagonist

Rational:

- The most effective combination in hypertensive patients with no negative metabolic effects

Case study: follow-up management

Following the administration of ramipril 10 mg plus amlodipine 5 mg for 4 weeks patient's BP is now 140/90 mm Hg

Question

What action do you now take?

1. Nothing, the BP reduction is good enough
2. Increase the dose of amlodipine
3. Add a third drug

Antiplatelet therapy

Antiplatelet therapy should be given to patients:

With a history of CV events

>50-year-old with any elevation of serum creatinine
or a 10-year CV risk of $\geq 20\%$

In hypertensive patients, good BP control should be achieved before commencing antiplatelet therapy

Summary

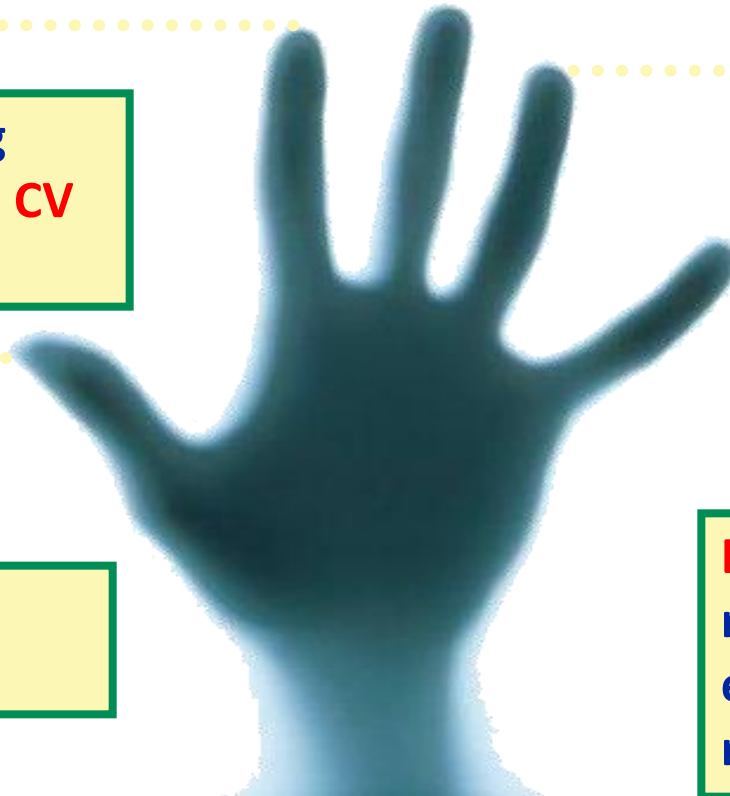
Create a supportive **alliance**
between the patient and the
physician

Accurate and ongoing
assessment of **overall CV**
risk

Select, **achieve**
and maintain
ambitious BP
goals

Detect and prevent end
organ damage

Empower the patient to
reduce their CV risk –
encourage lifestyle
modification



Summary

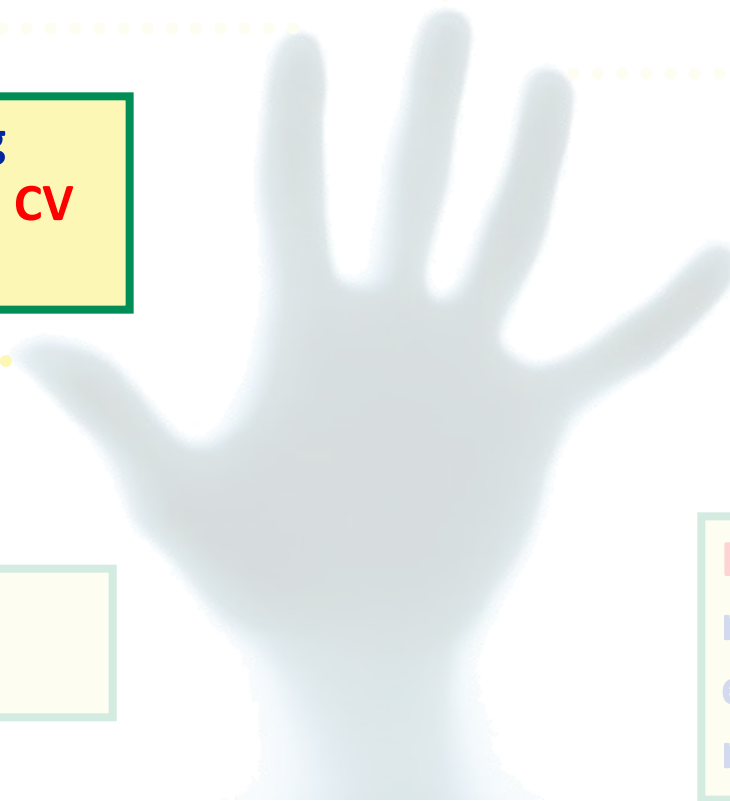
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Empower the patient to
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modification



Case study: investigations

Fasting plasma glucose	92 mg/dl	=	5.1 mmol/l
A1C	6.1%		
Serum potassium	4.2 mEq/l		
Serum creatinine	1.2 mg/dl		
Estimated GFR (MDRD formula)	94 ml/min		

Total cholesterol	252 mg/dl	=	6.5 mmol/l
High-density lipoprotein	32 mg/dl	=	0.8 mmol/l
Low-density lipoprotein	183 mg/dl	=	4.7 mmol/l
Triglycerides	184 mg/dl	=	2.1 mmol/l

Urinalysis	Normal
Dipstick microalbuminuria	Absent

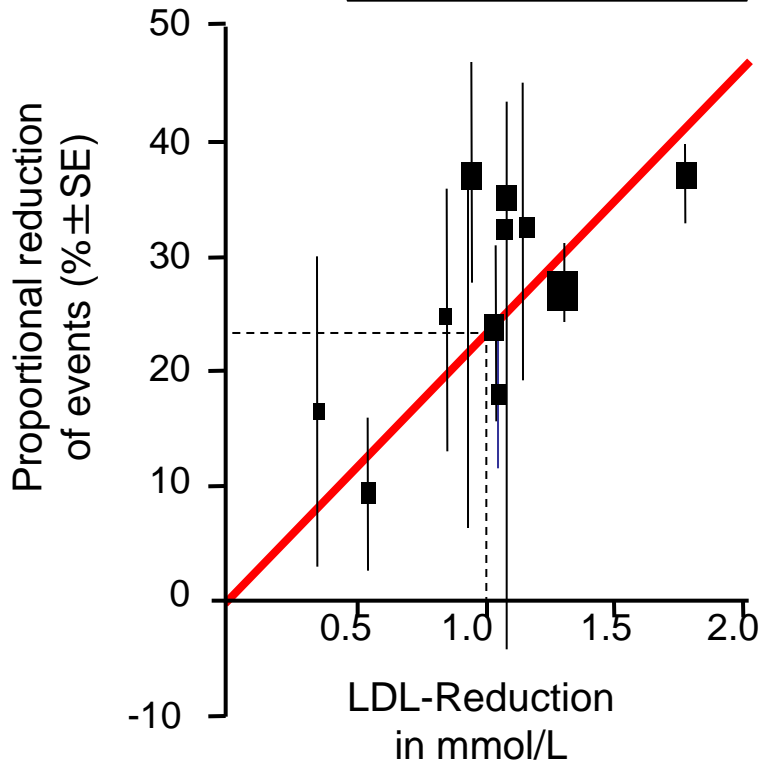
Electrocardiogram	Normal
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LDL-Reduction with statins and vascular events

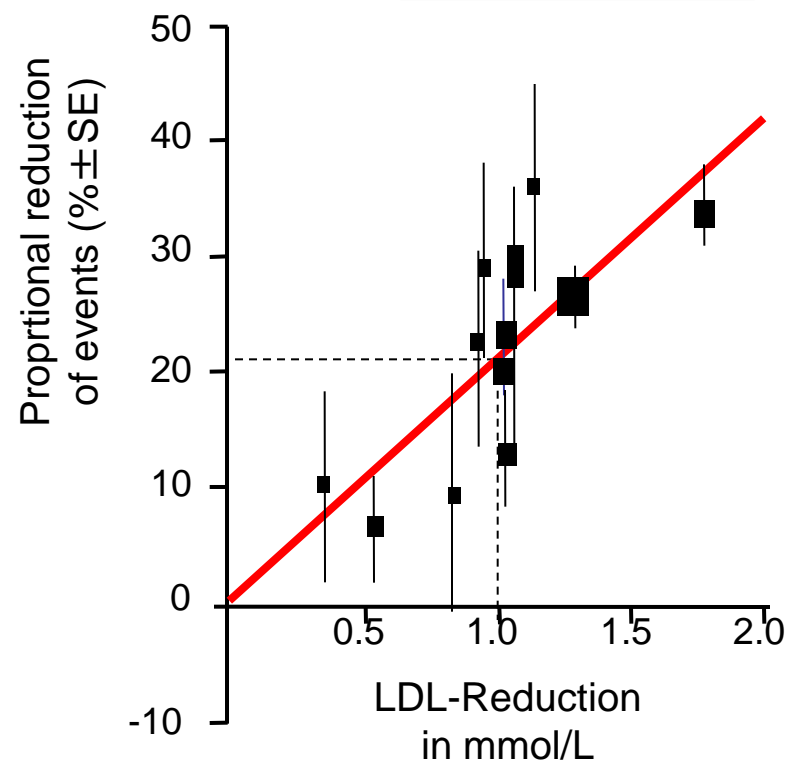
Prospective metaanalysis of 90,056 patients from 14 studies¹

1 mmol/L LDL-Reduction is associated with.....

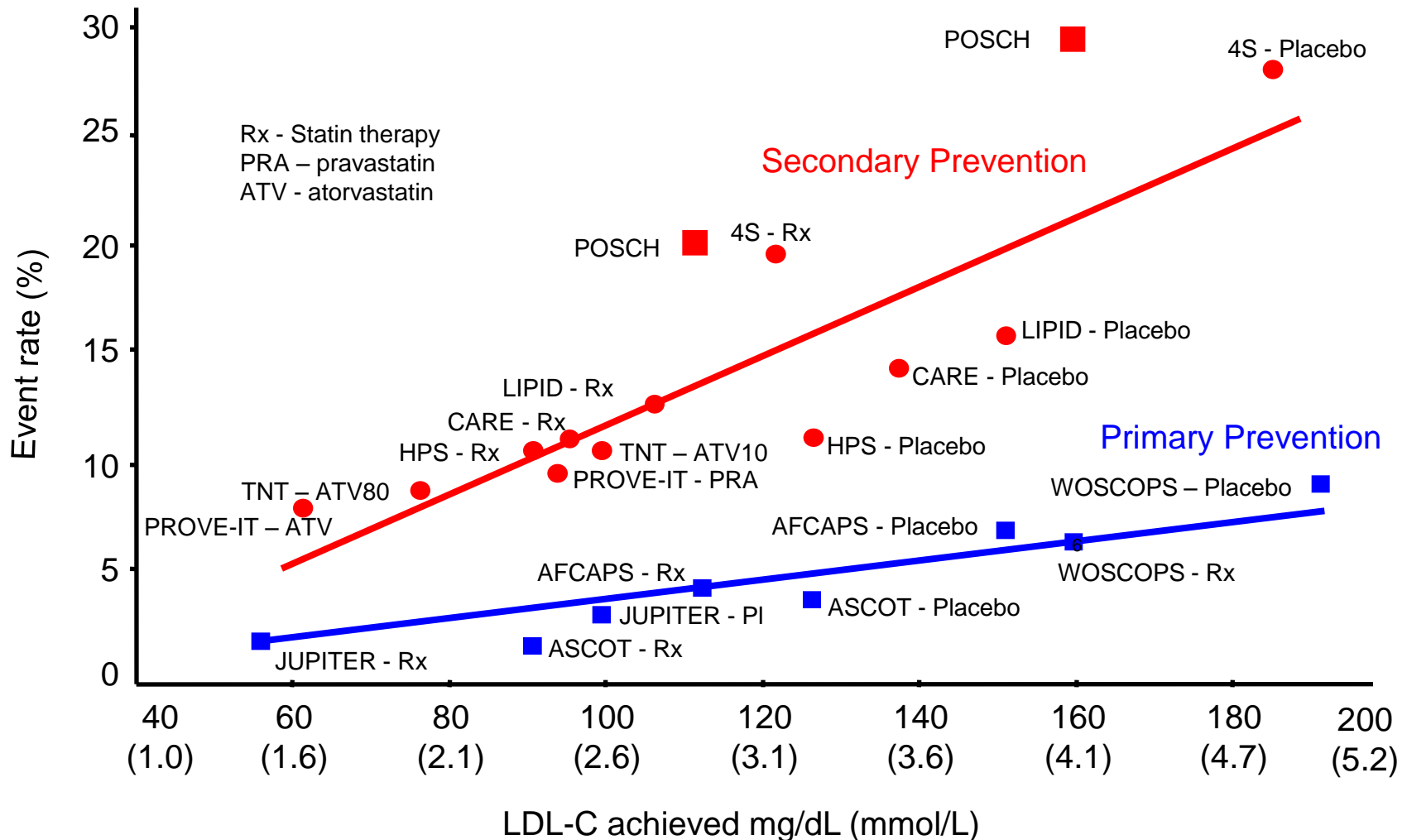
.... 23% Reduction of
coronary events



.... 21% Reduction
of vascular events



The lower the better!



EuroASPIRE Surveys

	n	Participation rate (%)	Age years	Women (%)	PTCA (%)
EuroASPIRE I 1995-1996	3180	77.2	47.8	24.9	25.6
EuroASPIRE II 1999-2000	2975	76.5	48.1	25.2	27.8
EuroASPIRE III 2006-2007	2392	68.4	40.6	23.1	49.8

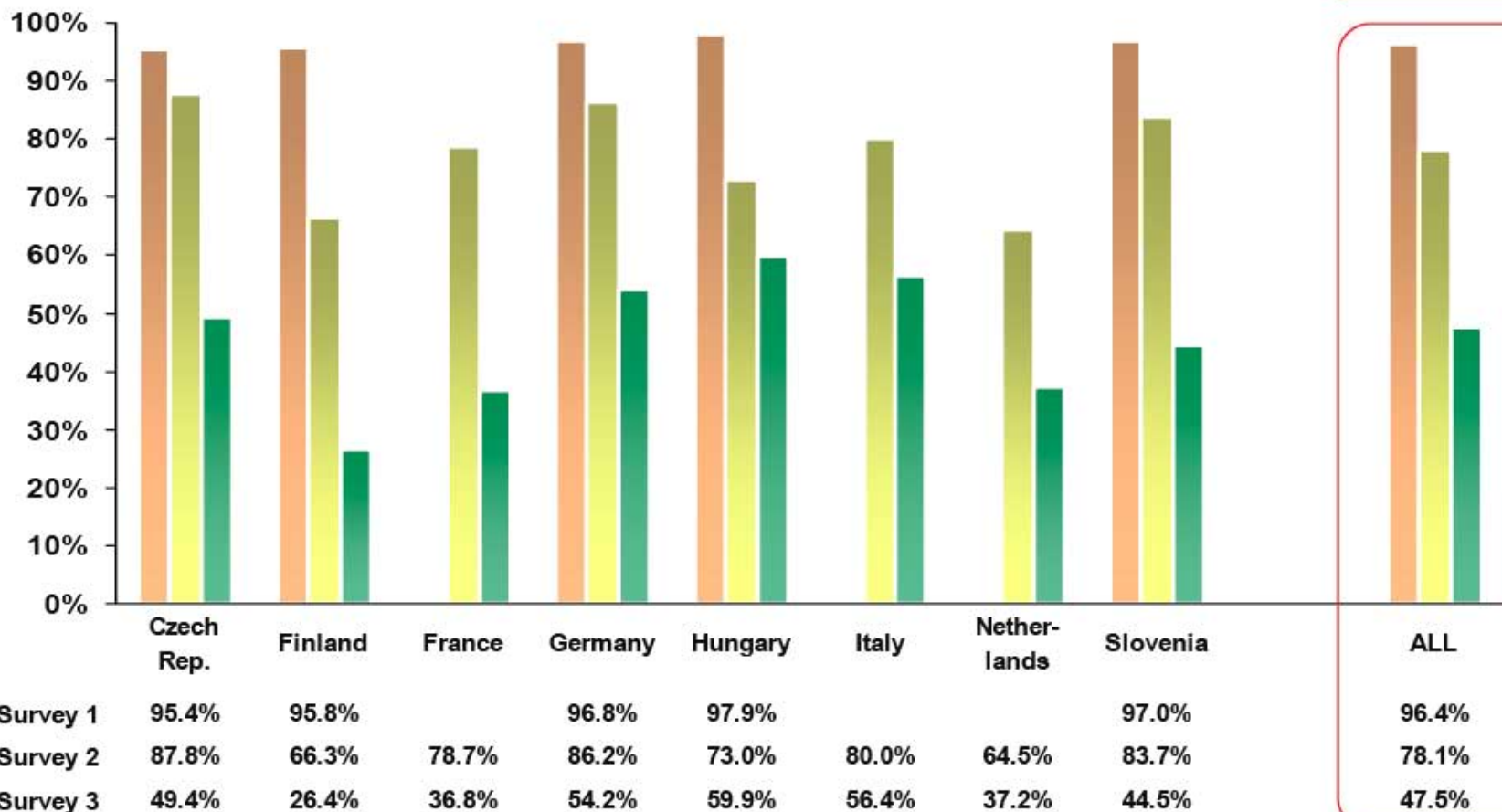
Consecutive patients, ≤ 70 years at time of index event



Prevalence of Raised LDL Cholesterol (2)*



$P < 0.0001$



*LDL C ≥ 2.5 mmol/L for patients fasting for at least 6 hours
(calculated according to Friedewald formula)

S2 vs. S1 : $P = 0.001$

S3 vs. S2 : $P < 0.0001$

S3 vs. S1 : $P < 0.0001$

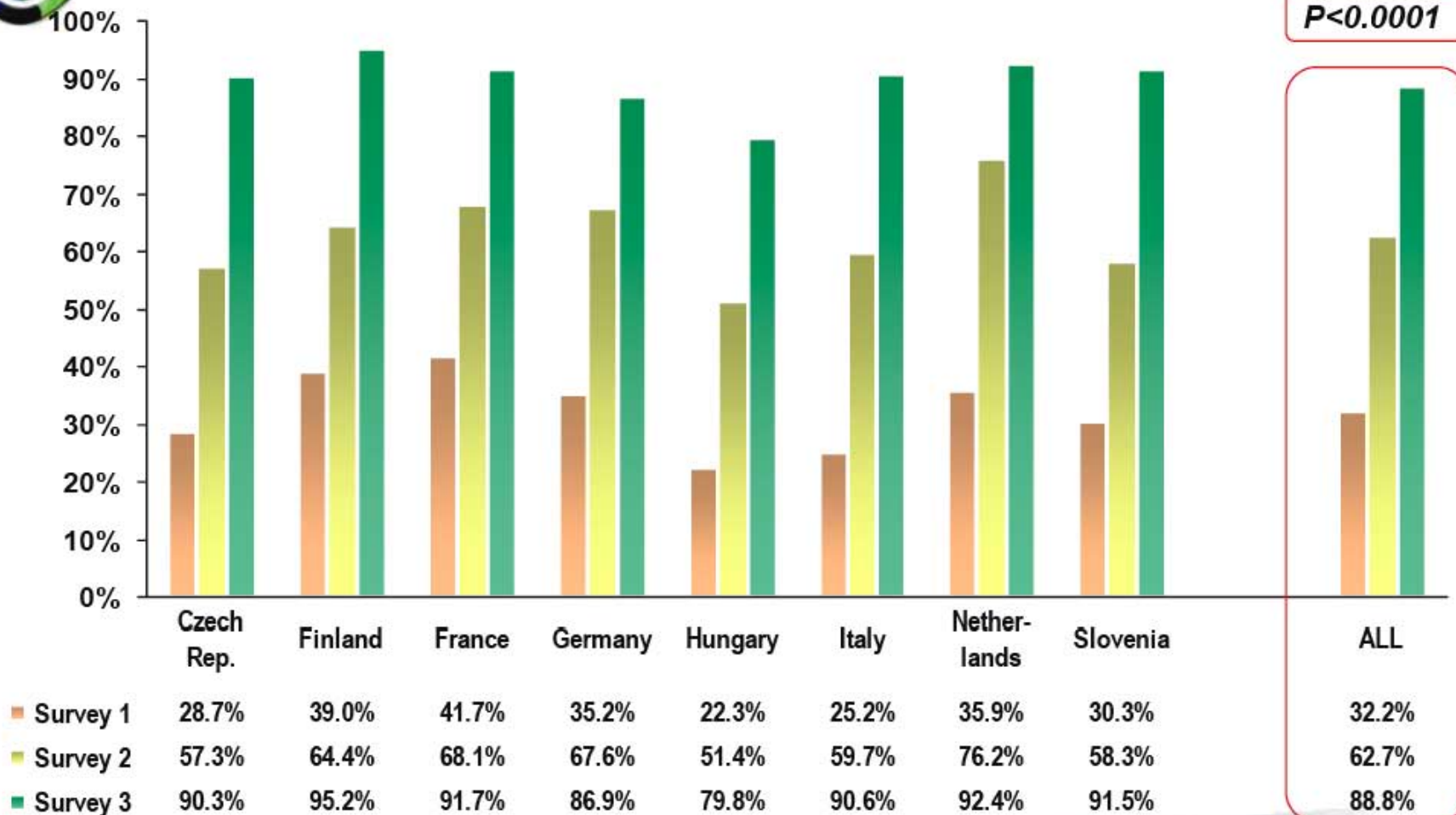




Medication Use: Lipid Lowering Drugs



$P < 0.0001$



S2 vs. S1 : $P < 0.0001$

S3 vs. S2 : $P < 0.0001$

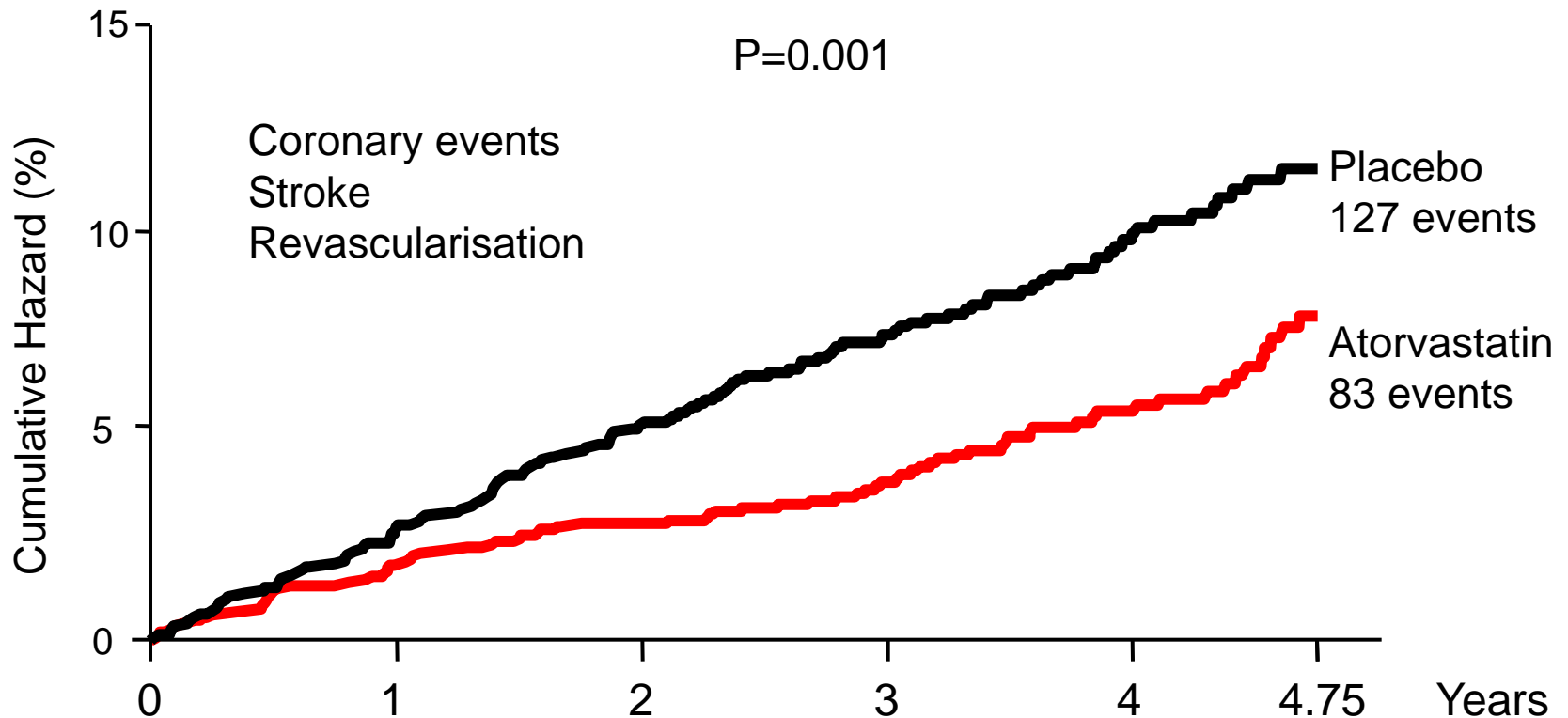
S3 vs. S1 : $P < 0.0001$



CARDS: Primary endpoint

Relative Risk Reduction 37% (95% CI: 17-52)

P=0.001



Placebo	1410	1351	1306	1022	651	305
Atorva	1428	1392	1361	1074	694	328

Clinical case

Hypertension for 8 years

Diabetes for 3 years

Fasting plasma glucose	92 mg/dl	=	5.1 mmol/l
A1C	6.1%		
Serum potassium	4.2 mEq/l		
Serum creatinine	1.2 mg/dl		
Estimated GFR (MDRD formula)	94 ml/min		

Total cholesterol	252 mg/dl	=	6.5 mmol/l
High-density lipoprotein	32 mg/dl	=	0.8 mmol/l
Low-density lipoprotein	183 mg/dl	=	4.7 mmol/l
Triglycerides	184 mg/dl	=	2.1 mmol/l

Cardiovascular risk stratification

Is there a need to calculate the risk score?

1) Yes

2) No

ESC/EAS Guidelines for the management of dyslipidaemias



European Heart Journal (2011) **32**, 1769–1818
doi:10.1093/eurheartj/ehr158

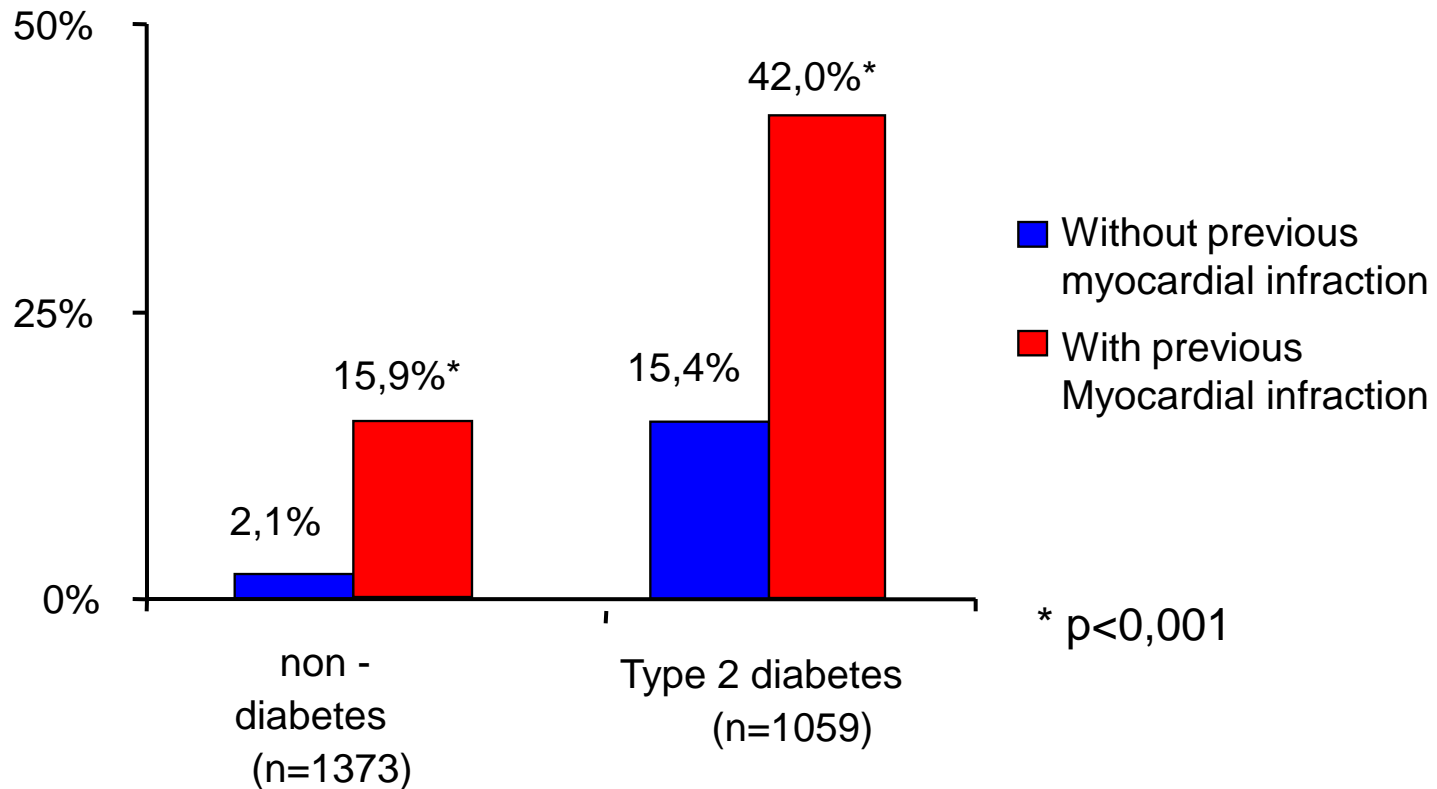
Those with :

- 1) Documented CVD (invasive or non-invasive testing)
- 2) Type 1 or 2 diabetes with target organ damage (e. g. microalbuminuria)
- 3) A calculated 10 years risk SCORE > 10 %
- 4) Chronic kidney disease (GFR < 60 ml/min)

are automatically at **VERY HIGH TOTAL CARDIOVASCULAR RISK**

Patients with type 2 diabetes are at very high risk for CAD

7 years follow-up: Incidence for cardiovascular death



What are the treatment goals for cholesterol in type 2 diabetes ?

1) LDL-Cholesterol < 1.8 mmol/l

2) LDL-Cholesterol < 2.5 mmol/l

3) LDL-Cholesterol < 3.0 mmol/l

4) Consider others (HDL-Cholesterol, triglycerids ?)

Table 8 Recommendations for treatment targets for LDL-C

Recommendations	Class ^a	Level ^b	Ref ^c
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level $\geq 10\%$) the LDL-C goal is <1.8 mmol/L (less than ~ 70 mg/dL) and/or $\geq 50\%$ LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥ 5 to $<10\%$) an LDL-C goal <2.5 mmol/L (less than ~ 100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to $\leq 5\%$) an LDL-C goal <3.0 mmol/L (less than ~ 115 mg/dL) should be considered.	IIa	C	-

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol.

Table 25 Recommendations for treatment of dyslipidaemia in diabetes

Recommendations	Class ^a	Level ^b	Ref ^c
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.	I	C	
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (less than ~ 70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL.	I	B	15, 16
In all people with type 2 diabetes LDL-C <2.5 mmol/L (less than ~ 100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets.	I	B	15, 16

^aClass of recommendation.

^bLevel of evidence.

^cReferences.

apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol.

How to treat hypercholesterinemia ?

Table 14 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class ^a	Level ^b	Ref ^c
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

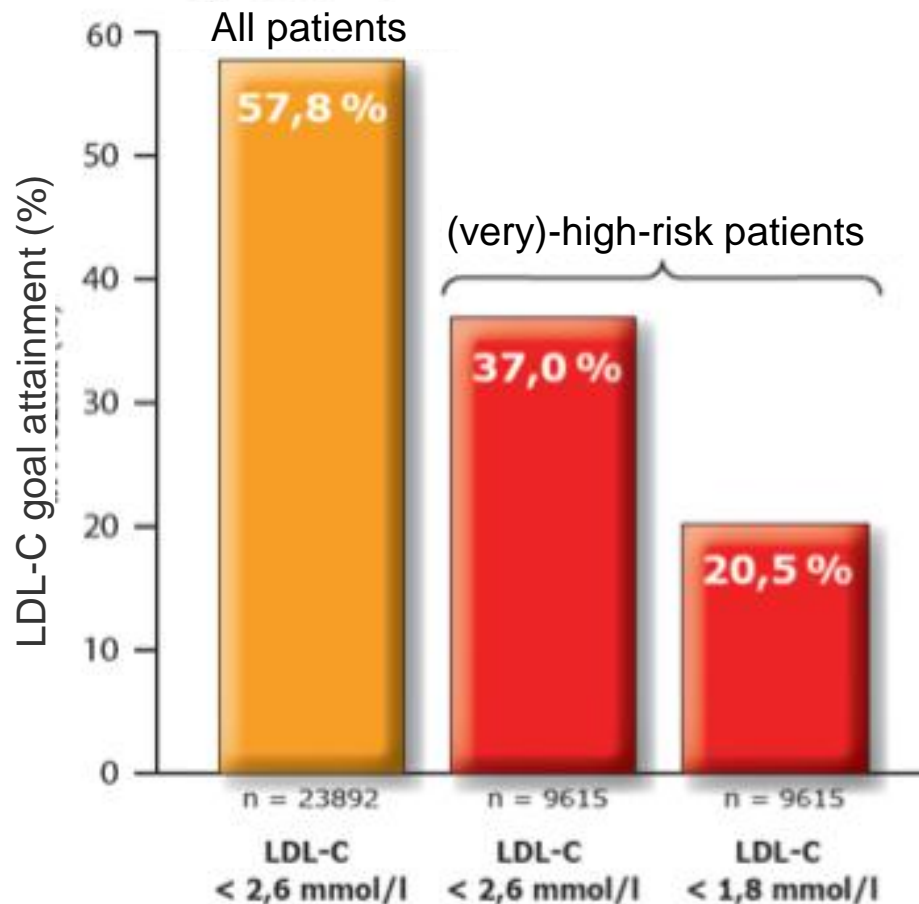
^aClass of recommendation.

^bLevel of evidence.

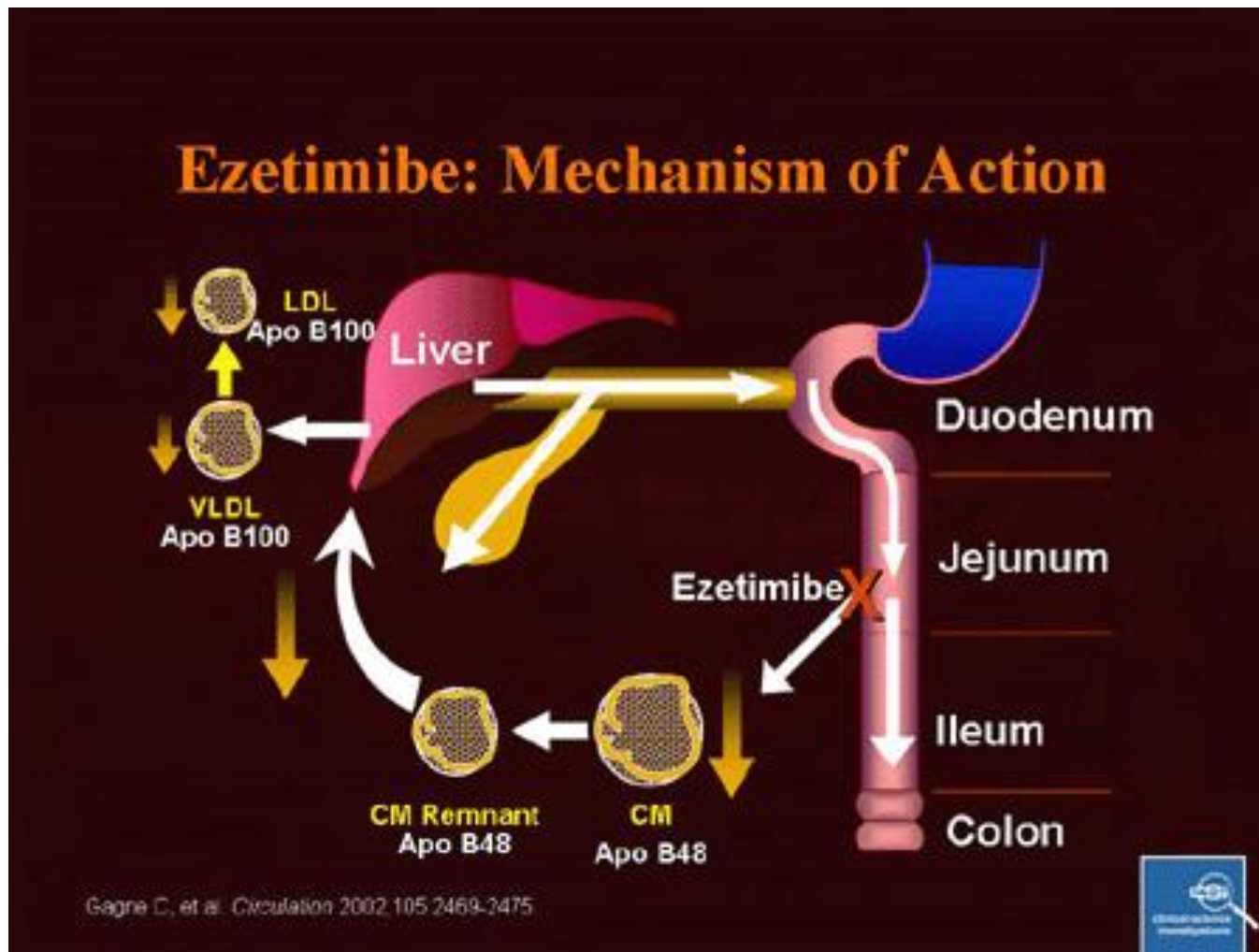
^cReferences.

New LDL-C goal < 1.8 mmol/l : how to reach target?

Less than 40% of 24,000 Swiss high-risk patients reach the LDL-C target <2.6 mmol/l



Drug combination - Ezetimibe



The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial



Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David C Wheeler, Charles Tomson, Christoph Wanner, Vera Krane, Alan Cass, Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawrence Agodoa, Mike Gaziano, Bertram Kasiske, Robert Walker, Ziad A Massy, Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Bengt Fellström, Hallvard Holdaas, Vladimir Tesar, Andrzej Wiecek, Diederick Grobbee, Dick de Zeeuw, Carola Grönhagen-Riska, Tanaji Dasgupta, David Lewis, William Herrington, Marion Mafham, William Majoni, Karl Wallendzus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Armitage, Alex Baxter, Christopher Bray, Yiping Chen, Zhengming Chen, Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Young, Rory Collins, on behalf of the SHARP Investigators*

SHARP: Rationale/ background

- patients with CKD: high risk of vascular events
- Pattern of vascular disease atypical -> large proportion non-atherosclerotic
- high statin doses : increased risk of myopathy, especially in patients with impaired renal function
- Previous trials : **inconclusive**
(Atorvastatin 20 mg (4D) , Rosuvastatin 10 mg (AURORA):
nonsignificant relative risk reduction of 8% and 4% respectively)

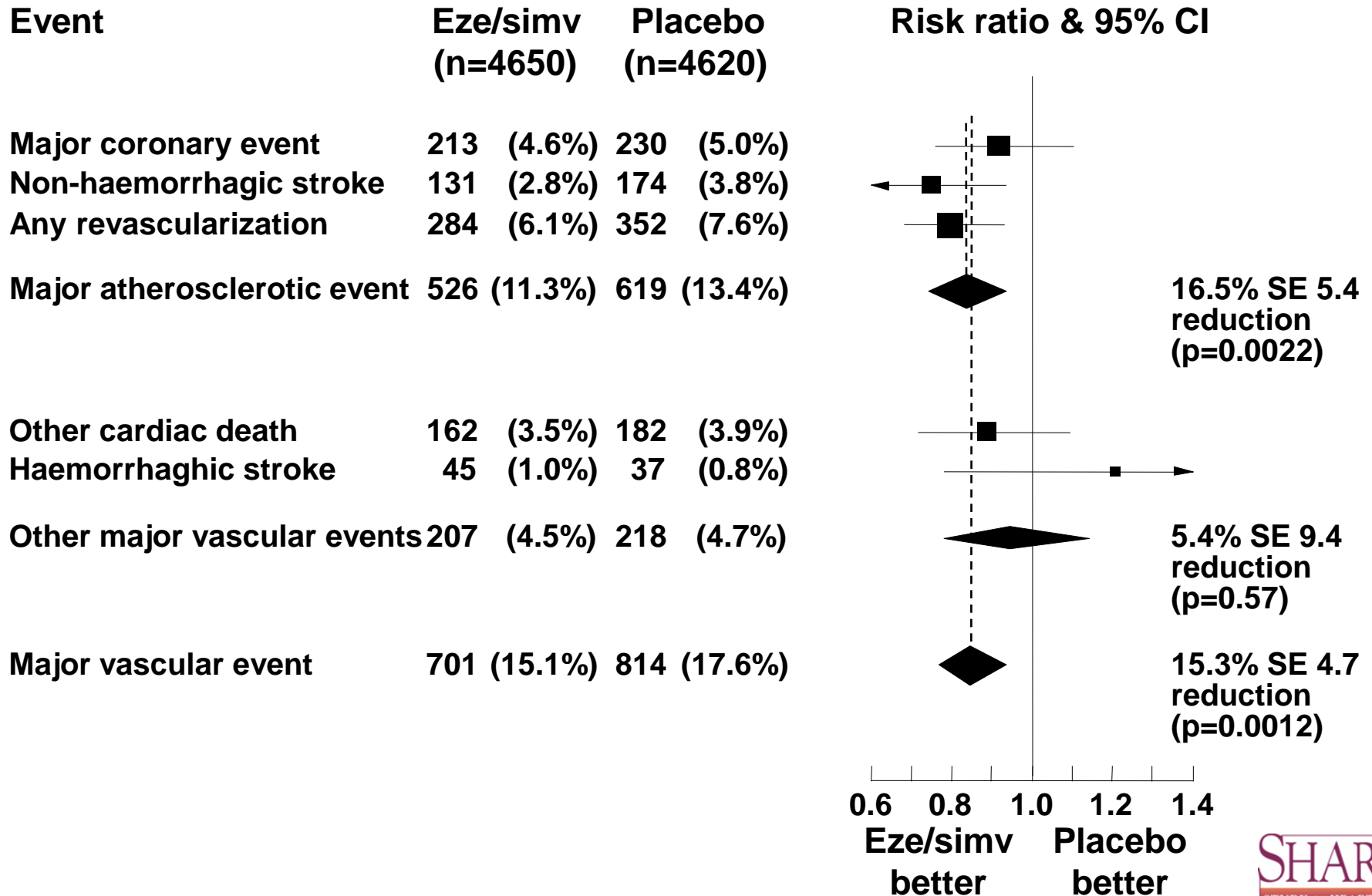
SHARP: Eligibility

- History of chronic kidney disease
- Not on dialysis → elevated creatinine on 2 occasions:
 - Men: ≥ 1.7 mg/dL (150 $\mu\text{mol/L}$)
Women: ≥ 1.5 mg/dL (130 $\mu\text{mol/L}$)
- On dialysis → haemodialysis or peritoneal dialysis
- Age ≥ 40 years
- No history of myocardial infarction or coronary revascularization
- Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated

SHARP: Baseline characteristics

Characteristic	Mean (SD) or %
Age	62 (\pm 12)
Men	63 %
Systolic BP (mm Hg)	139 (\pm 22)
Diastolic BP (mm Hg)	79 (\pm 13)
Body mass index	27 (\pm 6)
Current smoker	13 %
Vascular disease	15 %
Diabetes mellitus	23 %
Non-dialysis patients only	(n=6247, 67 %)
eGFR (ml/min/1.73m ²)	27 (\pm 13)
Albuminuria	80 %

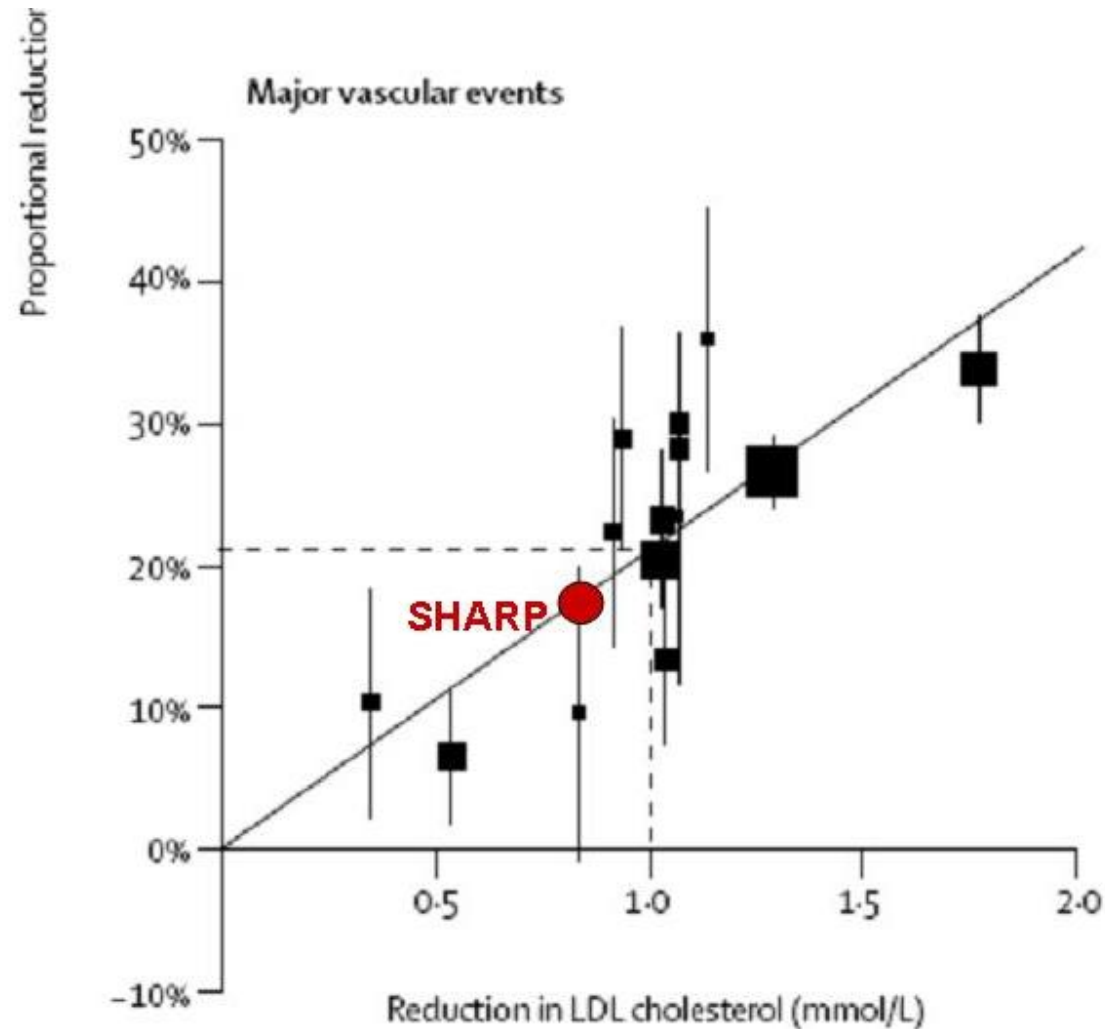
SHARP: Major Atherosclerotic Events



SHARP: Major Atherosclerotic Events

significant 17% reduction in major atherosclerotic events with 0.85 mmol/L LDL-C reduction

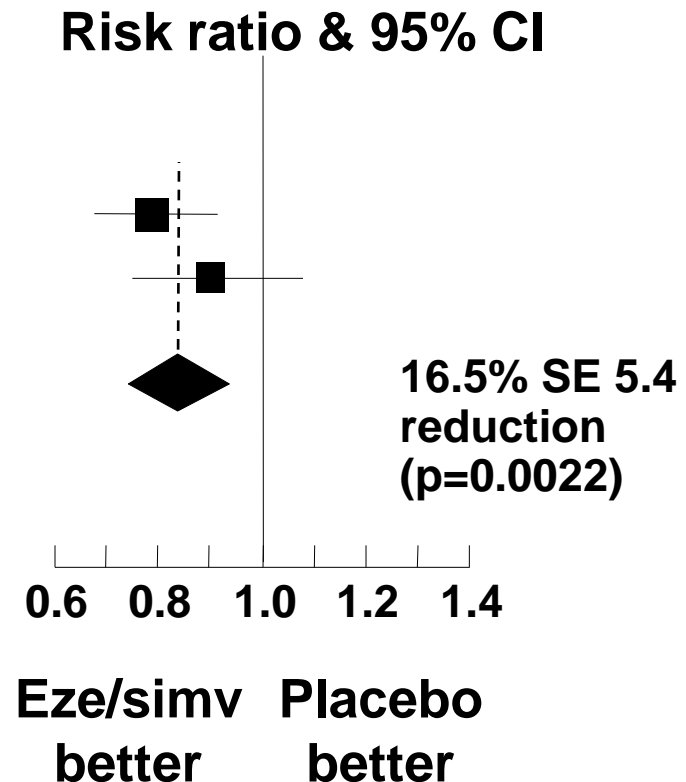
-> similar to the effects seen in the CTT with statin regimens of equivalent LDL lowering efficacy



SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	526 (11.3%)	619 (13.4%)

**No significant heterogeneity between
non-dialysis and dialysis patients
(p=0.25)**



- **Diabetic dyslipidemia is a cluster of lipid abnormalities**
- **In 50 % in patients suffering from type 2 diabetes:**
 - **High triglycerids**
 - **Low HDL-Cholesterol**

Table 24 Summary of dyslipidaemia in MetS and in type 2 diabetes

- | |
|---|
| <ul style="list-style-type: none"> • Dyslipidaemia in MetS represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial TGs, apo B, and small dense LDL, and low HDL-C and apo A I. |
| <ul style="list-style-type: none"> • Non-HDL-C or apo B are good surrogate markers of TRLs and remnants and are a secondary objective of therapy.
Non-HDL-C <3.3 mmol/L (less than ~130 mg/dL) or apo B <100 mg/dL is desirable. |
| <ul style="list-style-type: none"> • Increased waist circumference and elevation of TGs seems to be a simple tool to capture the high risk subjects with MetS. |
| <ul style="list-style-type: none"> • Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes. |

apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein; MetS = metabolic syndrome; TG = triglyceride; TRLs = triglyceride-rich lipoproteins.

Triglycerids

FIELD trial: No effect on primary endpoint (CAD death or non-fatal MI), but significantly reduced CVD events by 11%

ACCORD trial: Patients with high TG and low HDL-Cholesterol benefit from adding fenofibrate

HDL-Cholesterol

If lower than < 1.0 mmol/L and TG elevated > 1.8 mmol/l
→ According to **4S trial**: Increased risk for major coronary events (not on mortality)