

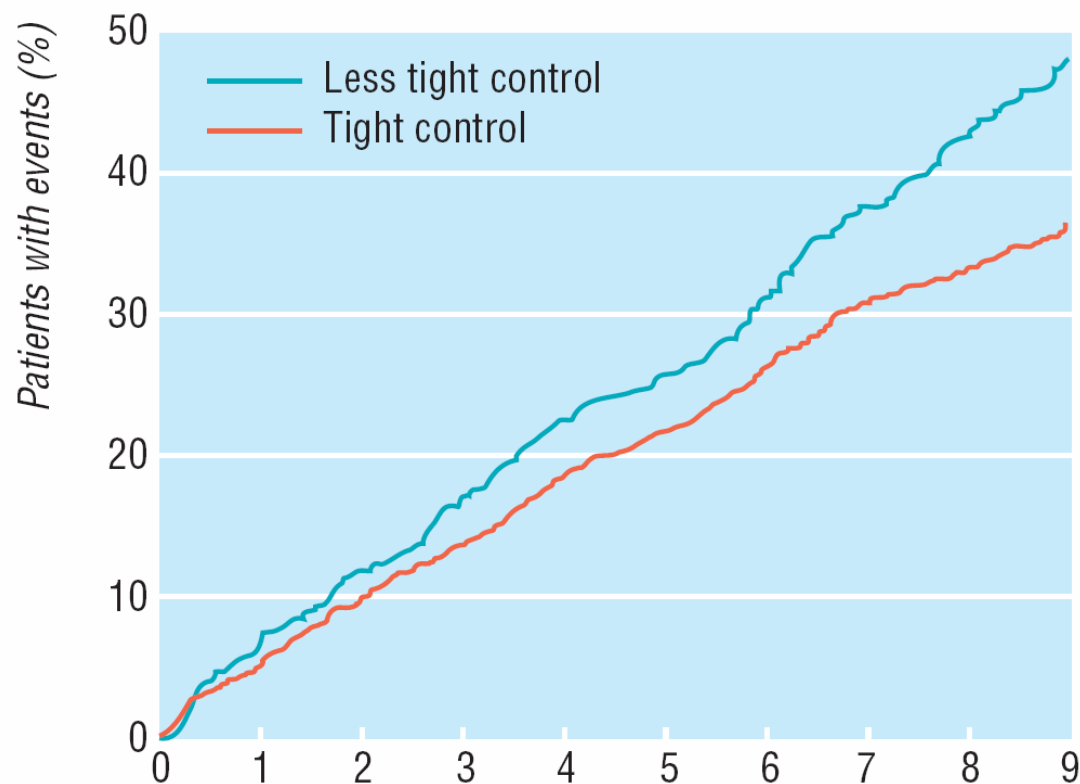
ADVANCE: a factorial randomised trial of blood pressure lowering and intensive glucose control in 11,140 patients with type 2 diabetes

Effects of a fixed combination of the ACE inhibitor, perindopril, and the diuretic, indapamide on major vascular events

ADVANCE
Collaborative Group

Blood pressure and vascular risk in diabetes

Best evidence: 2000

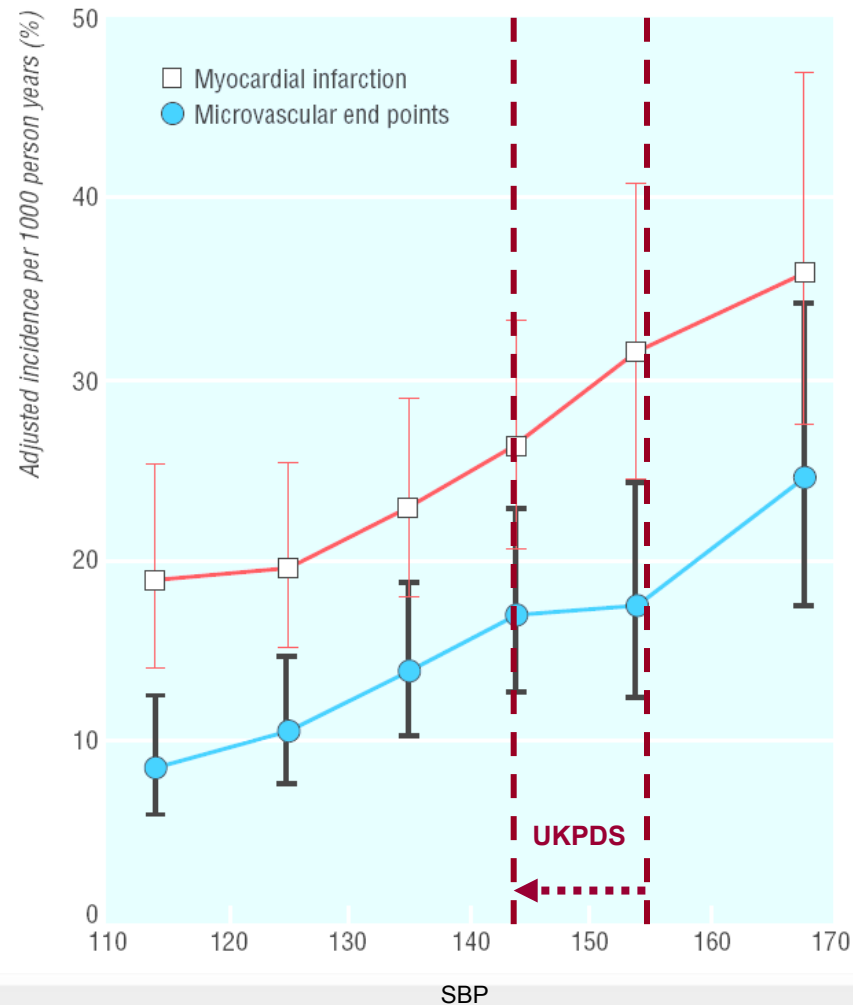


Reduction in risk with tight control 24% (95% CI 8% to 38%)(P = 0.0046)

Fig 5 Kaplan-Meier plots of proportions of patients with any clinical end point, fatal or non-fatal, related to diabetes

Blood pressure and vascular risk in diabetes

Best evidence: 2000



BMJ VOLUME 317 12 SEPTEMBER 1998

Blood pressure lowering in diabetes: *Unresolved issues 2000*

Among patients with diabetes, does blood pressure lowering therapy:

- Produce additional benefits when systolic pressure is lowered **below 145 mmHg**?
- Produce similar benefits for hypertensive and **non-hypertensive** patients?
- Add to the benefits produced by other cardiovascular preventive therapies including **ACE inhibitors**?



ADVANCE study hypotheses

Perindopril-indapamide arm

Among patients with diabetes, does blood pressure lowering therapy:

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Inclusion criteria

- **Type 2 diabetes mellitus**
- **Age 55 years or older**
- **Additional risk of vascular event**
 - **Age \geq 65 years**
 - **History of major macrovascular disease**
 - **History of major microvascular disease**
 - **First diagnosis of diabetes >10 years prior to entry**
 - **Other major risk factor**
- **Hypertensive or normotensive**



Randomised study treatments

- **Blood pressure lowering**
 - **Double-blind perindopril-indapamide *versus* matching placebo**
 - 2.0 / 0.625mg or placebo for first 3 months
 - 4.0 / 1.25mg or placebo thereafter
- **Blood glucose lowering (ongoing)**
 - **Open-label gliclazide MR-based intensive therapy targeting an HbA1c of 6.5% *versus* usual guideline-based care**



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Ancillary drug treatment

- **Blood pressure lowering therapy**
 - At discretion of treating physician
 - Only thiazide diuretic contraindicated
- **ACE inhibitor**
 - Open-label perindopril (up to 4 mg daily), if indicated
- **All other treatment**
 - At discretion of treating physician
 - Except glucose control for those assigned intensive therapy



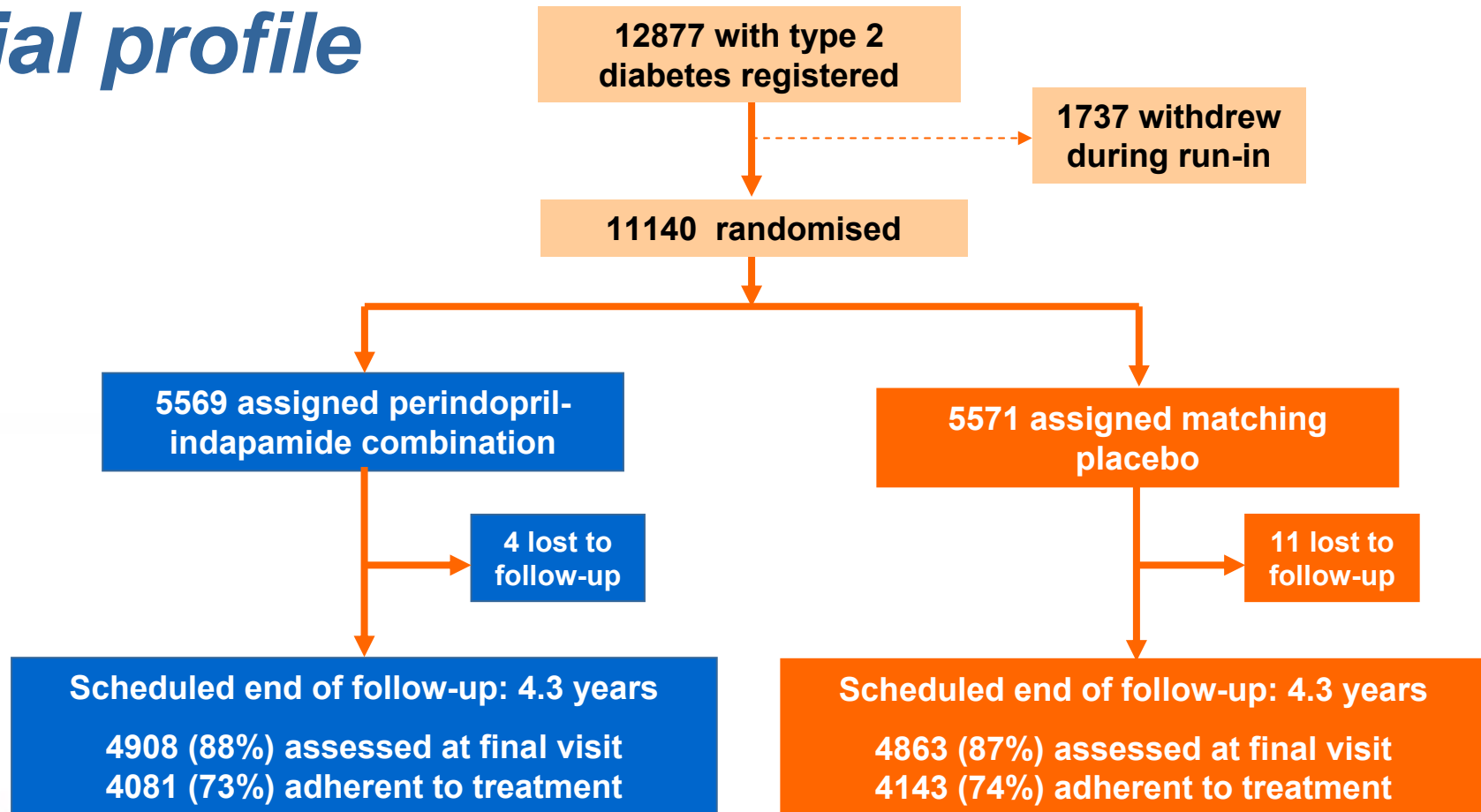
Primary study outcomes

- **Macrovascular**
 - Non-fatal stroke, non-fatal myocardial infarction or death from any cardiovascular cause (including sudden death)
- **Microvascular**
 - New or worsening nephropathy or diabetic eye disease
- **Prespecified analyses:**
 - Macrovascular and microvascular jointly
 - Macrovascular and microvascular separately



ADVANCE

Trial profile



Baseline characteristics

	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Age (years)	66	66
Systolic blood pressure (mmHg)	145	145
Diastolic blood pressure (mmHg)	81	81
Haemoglobin A1c (%)	7.5	7.5
History of macrovascular disease	32%	32%
History of microvascular disease	10%	10%
Microalbuminuria	26%	26%



Baseline characteristics

Cardiovascular and diabetes drugs

	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Any blood pressure lowering drug	75%	75%
ACE inhibitor*	43%	43%
Oral hypoglycaemic drugs	91%	91%
Statin	28%	29%
Other lipid modifying drug	9%	8%
Aspirin	44%	44%
Other antiplatelet drugs	4%	5%

*By end of run-in period: 47% were receiving open label perindopril



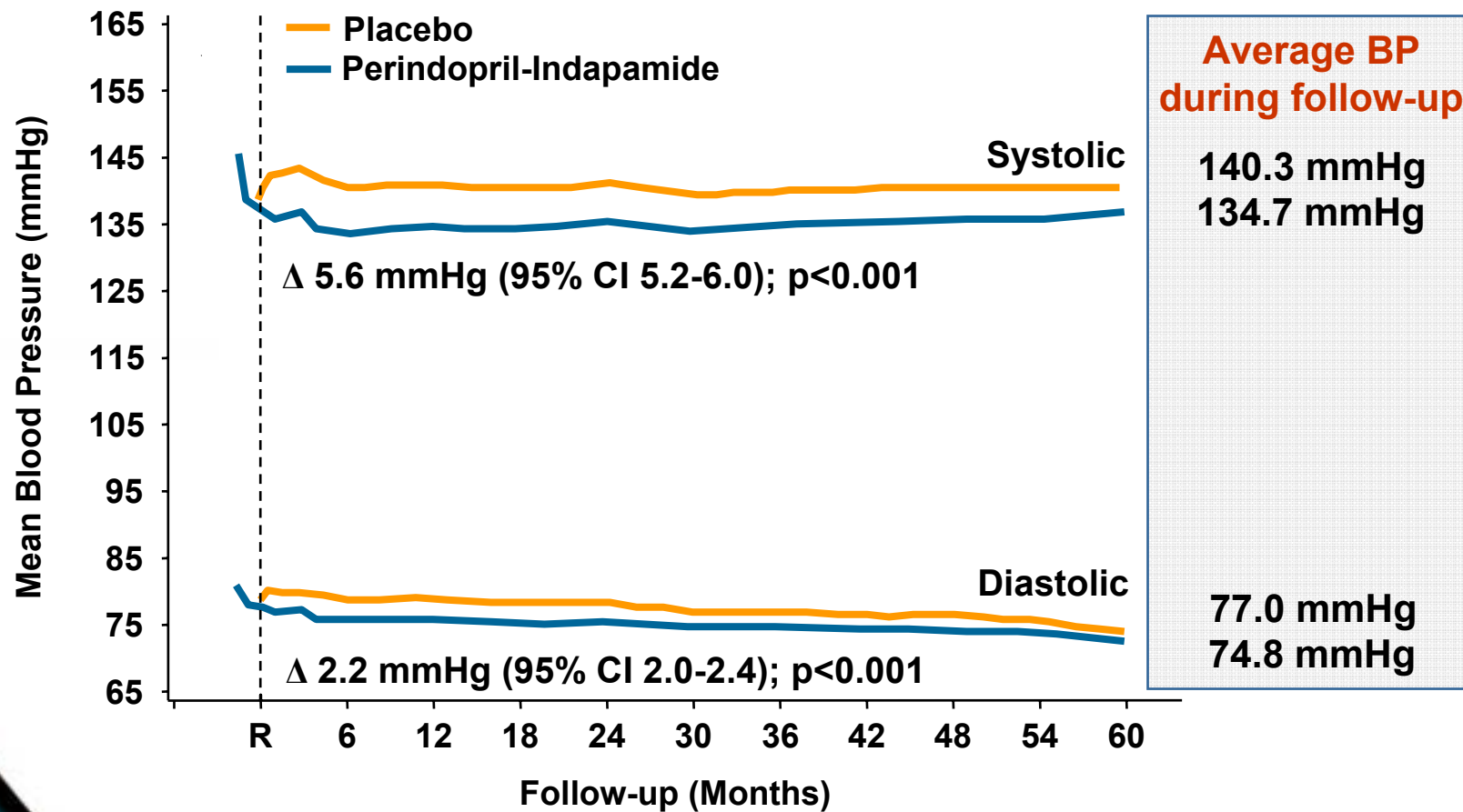
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Main results

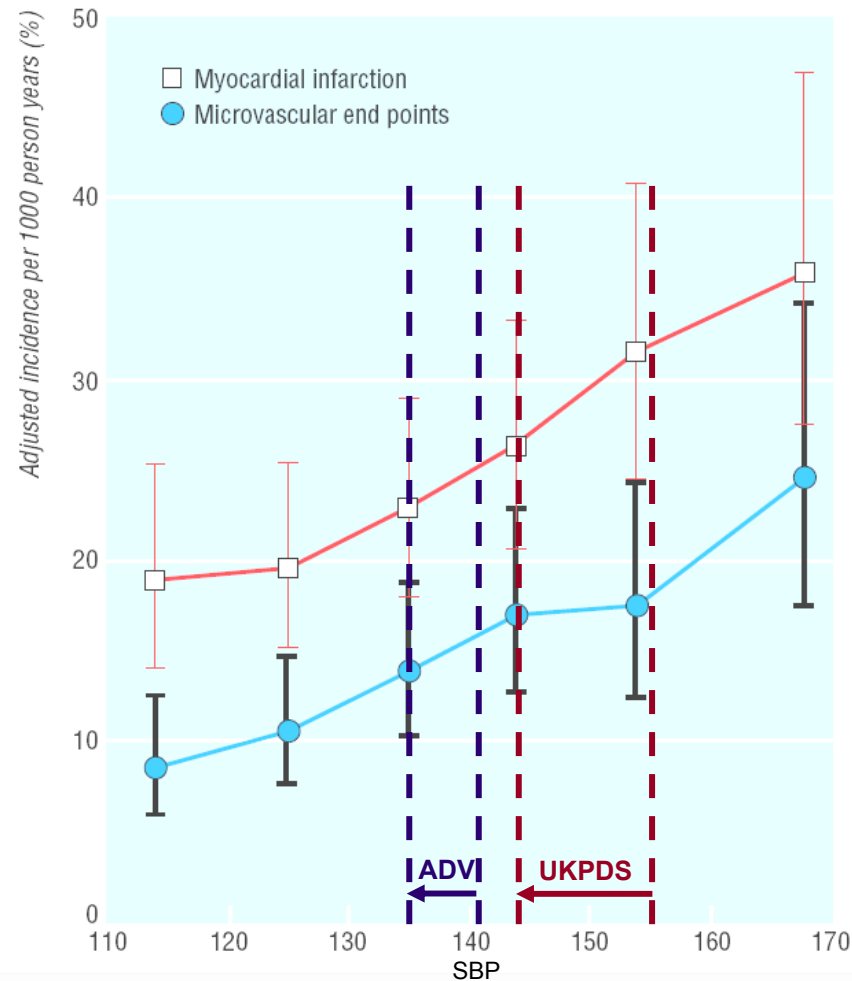
Blood pressure



Blood pressure reduction



ADVANCE BP reduction in context: UK Prospective Diabetes Study



BMJ VOLUME 321 12 AUGUST 2000

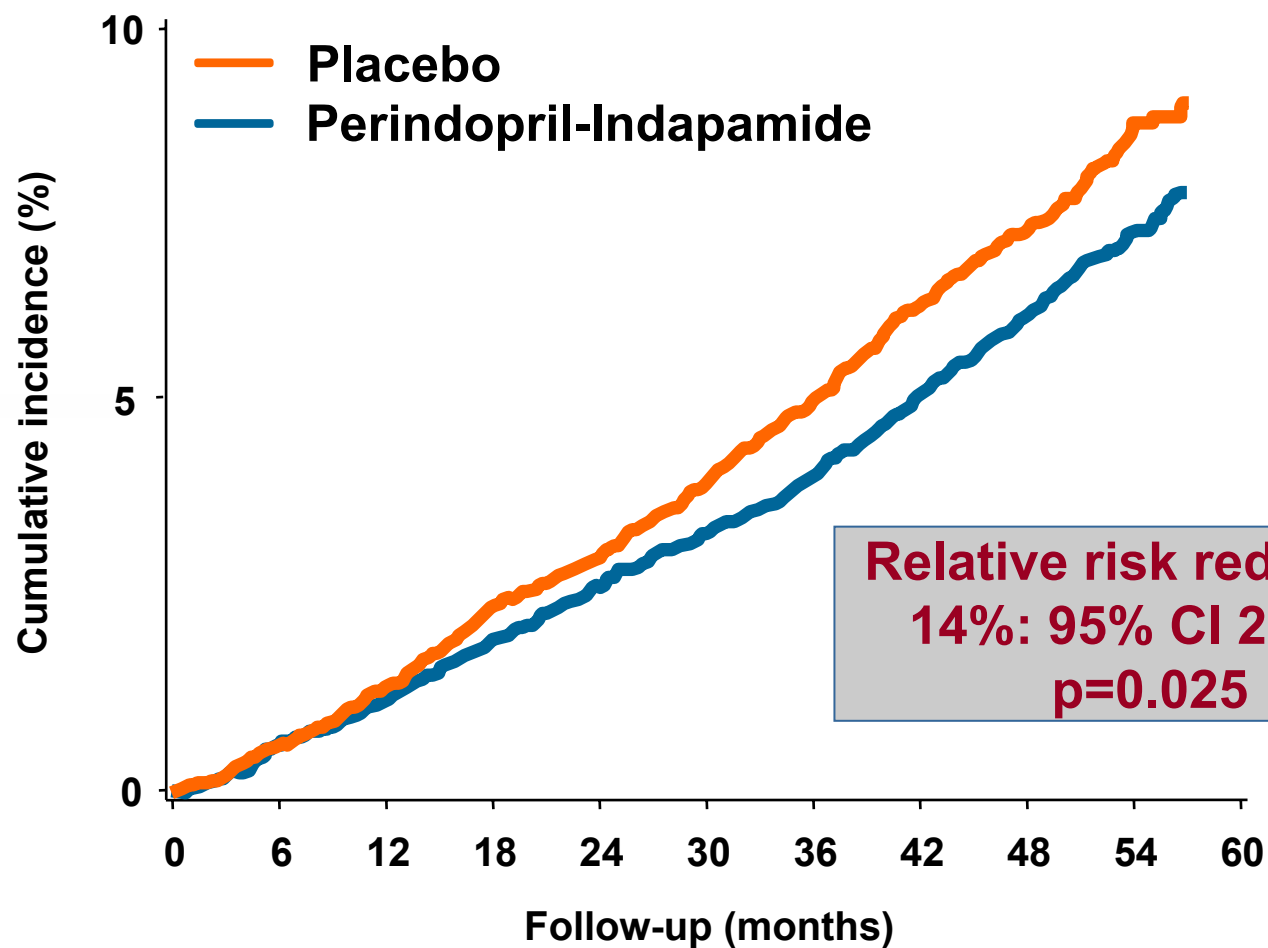
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Main results

Mortality and morbidity

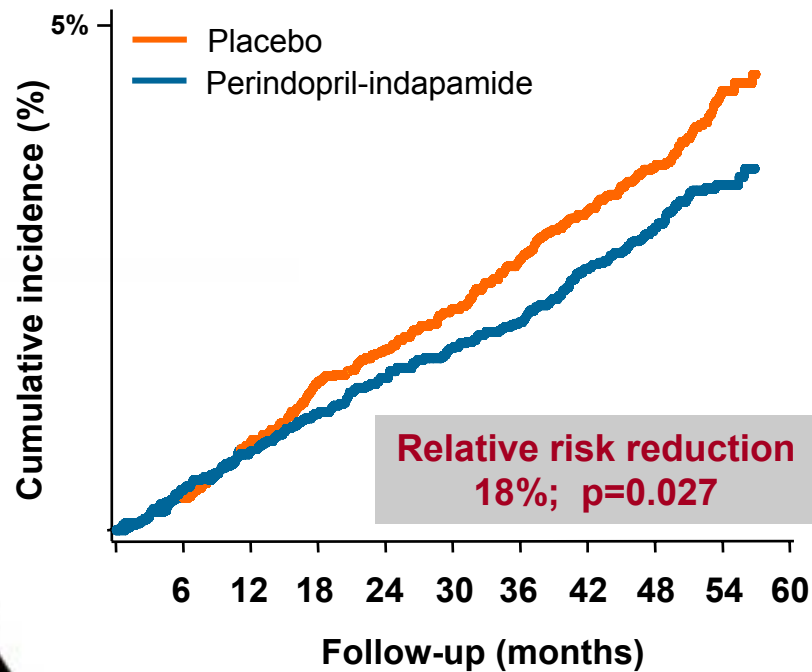


All-cause mortality

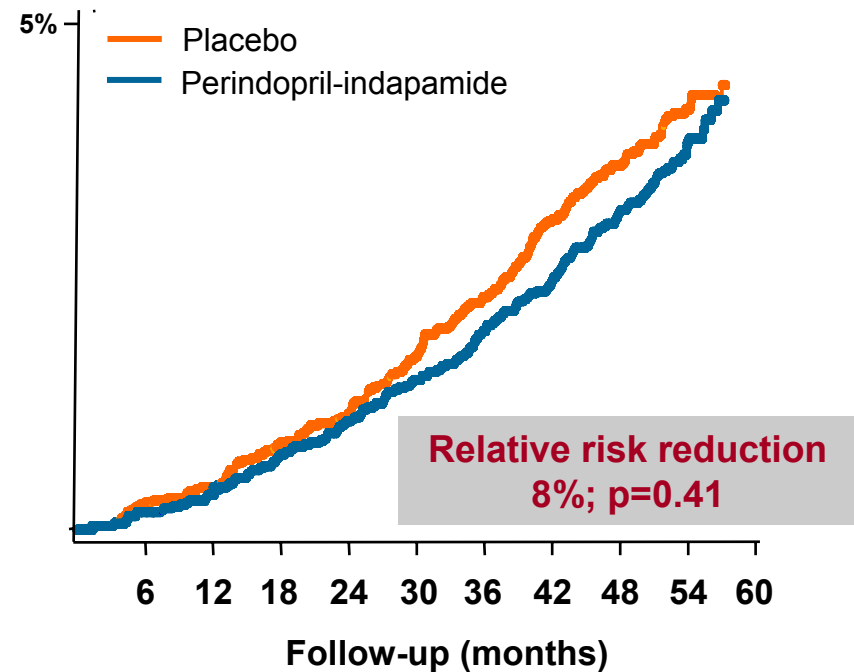


Deaths

Cardiovascular

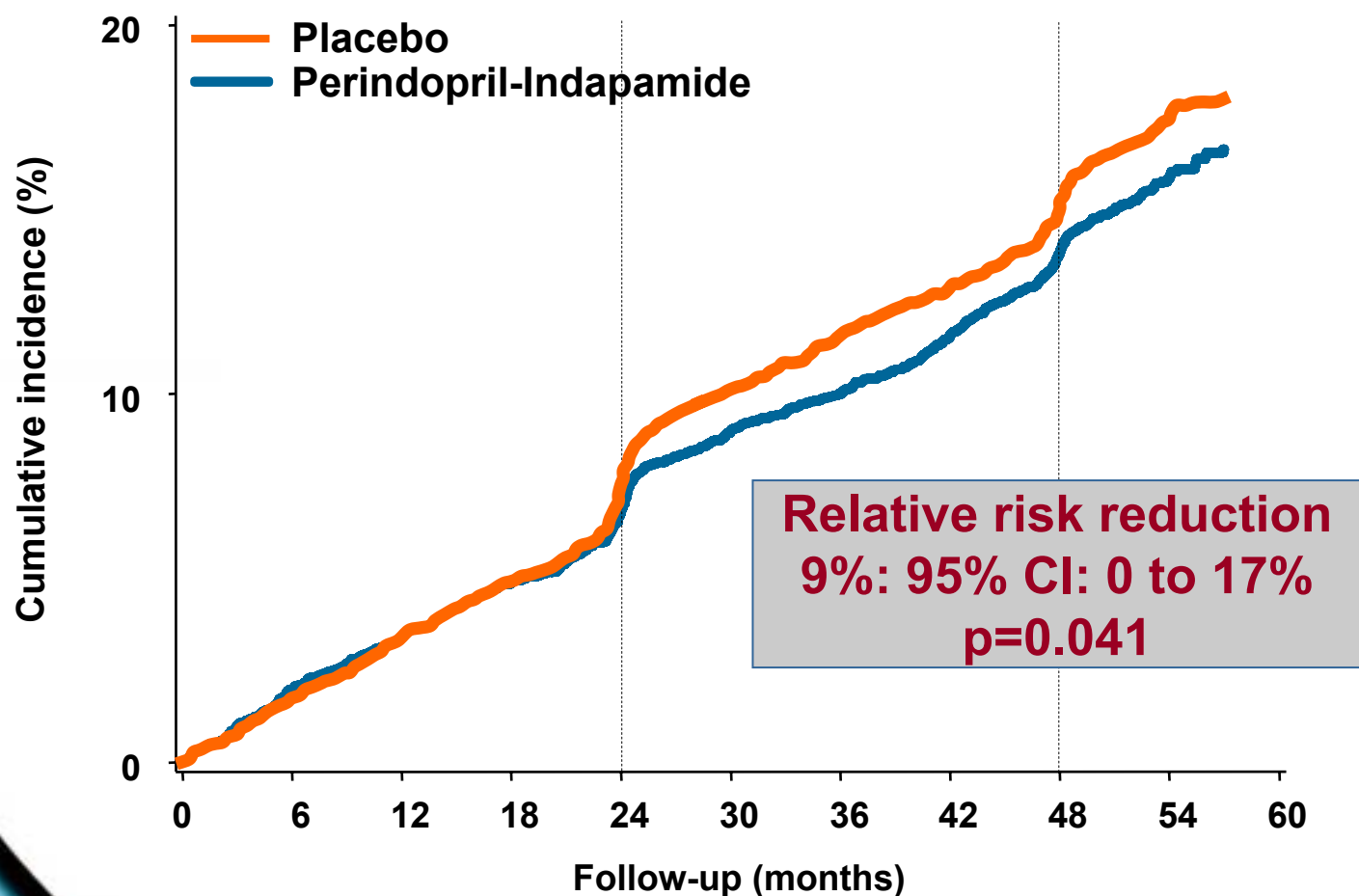


Non-cardiovascular



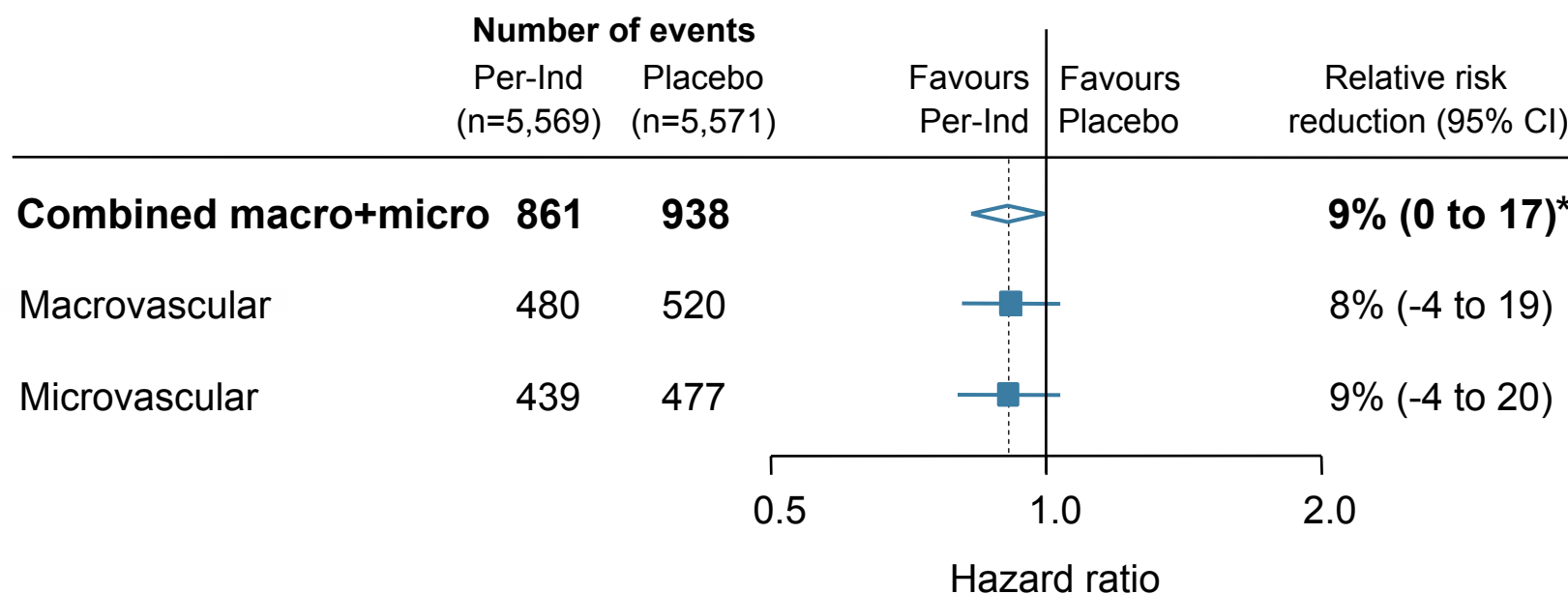
Combined primary outcomes

Major macro or microvascular event



Primary outcomes

Major macro or microvascular event

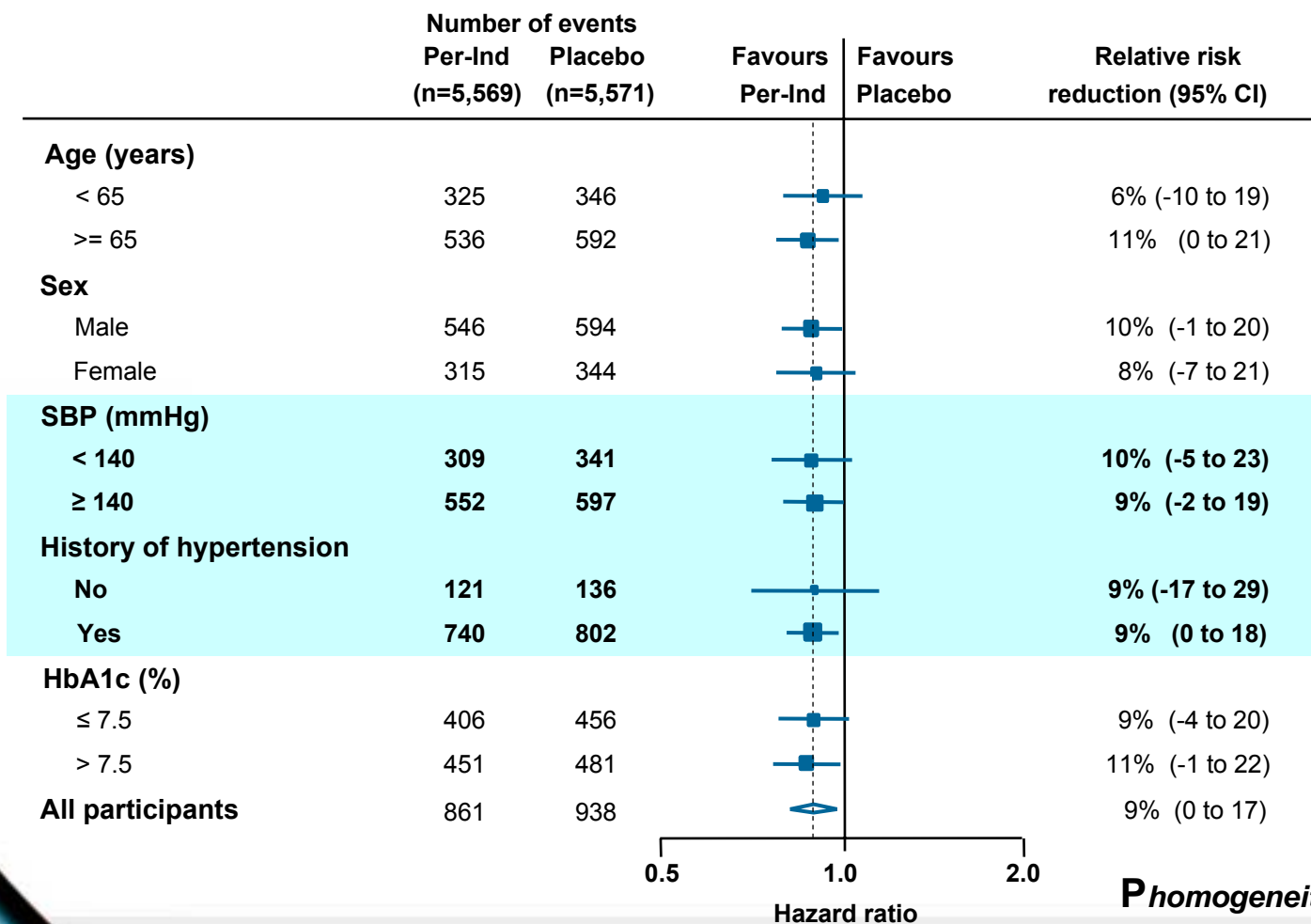


***2P=0.04**



Effects by age, sex, BP and HbA1c

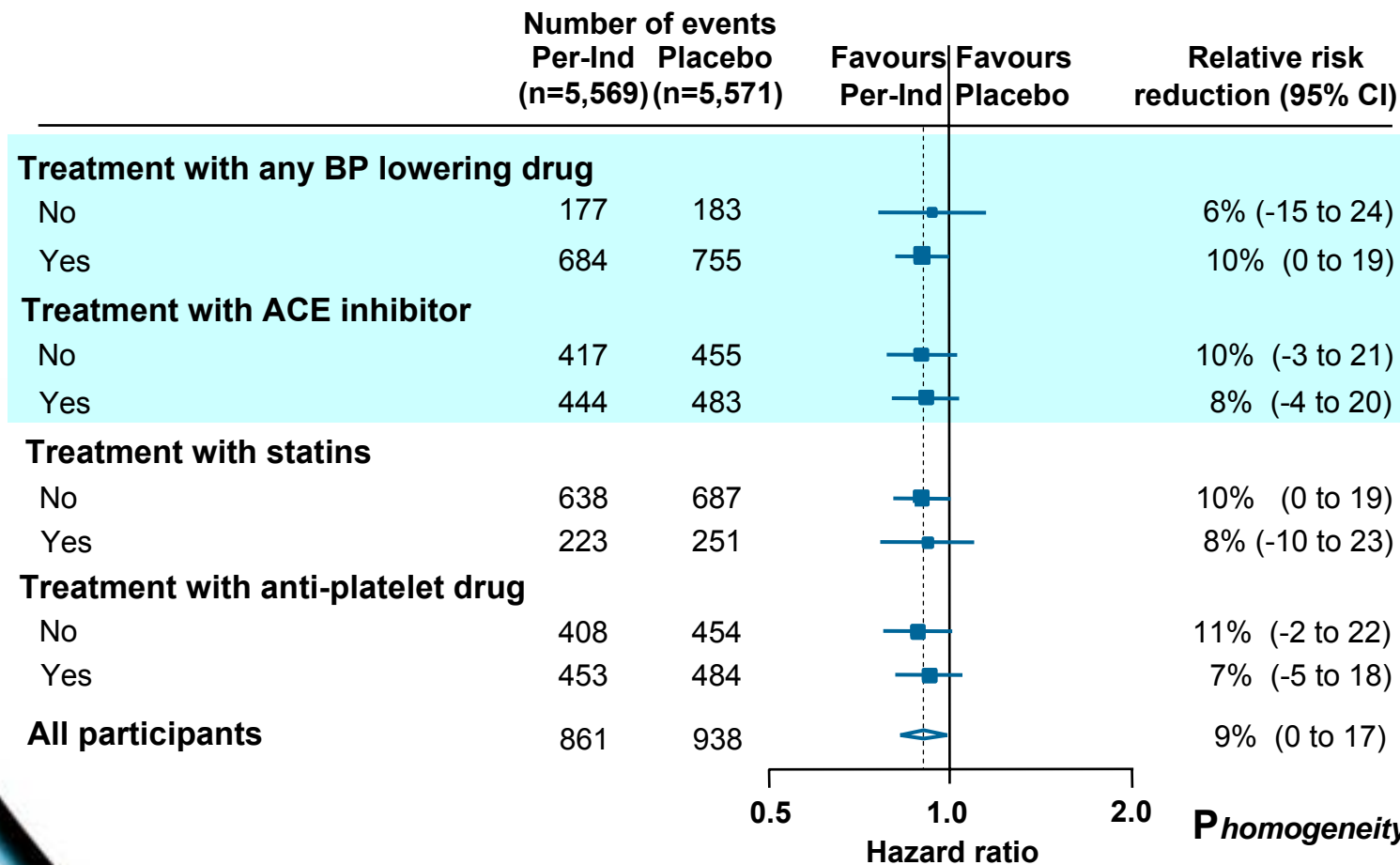
Combined primary endpoint



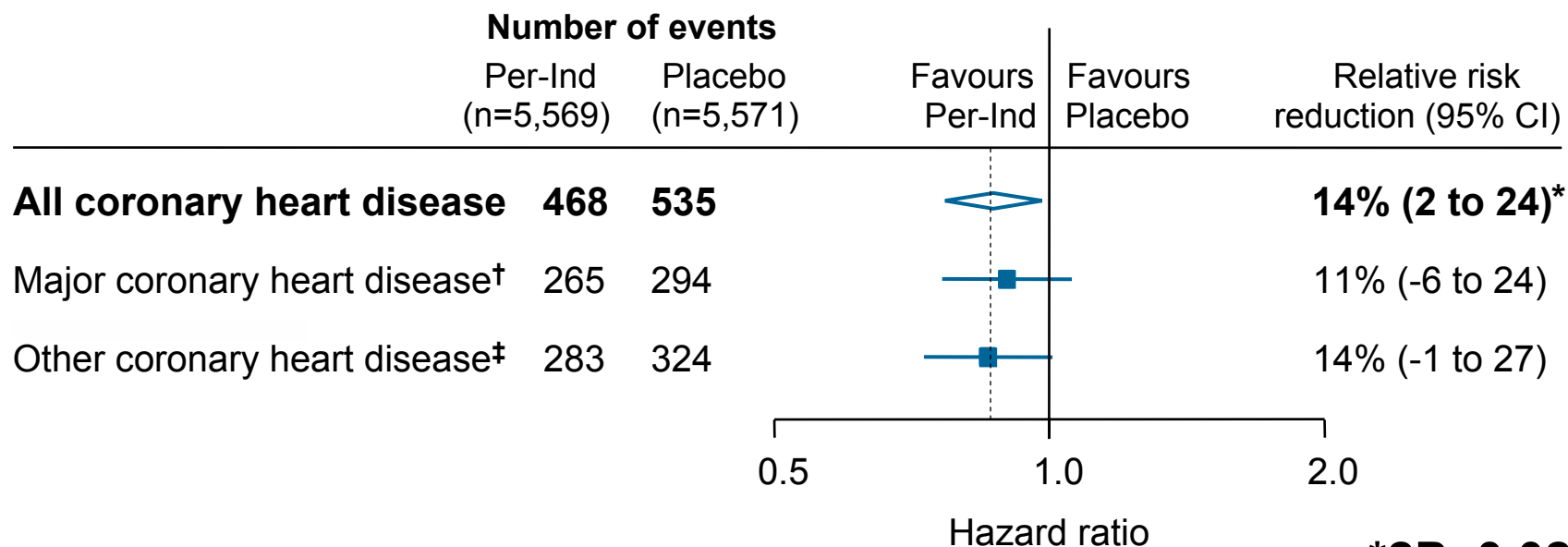
Phomogeneity all >0.1

Effects by ancillary treatment

Combined primary endpoint



Coronary events



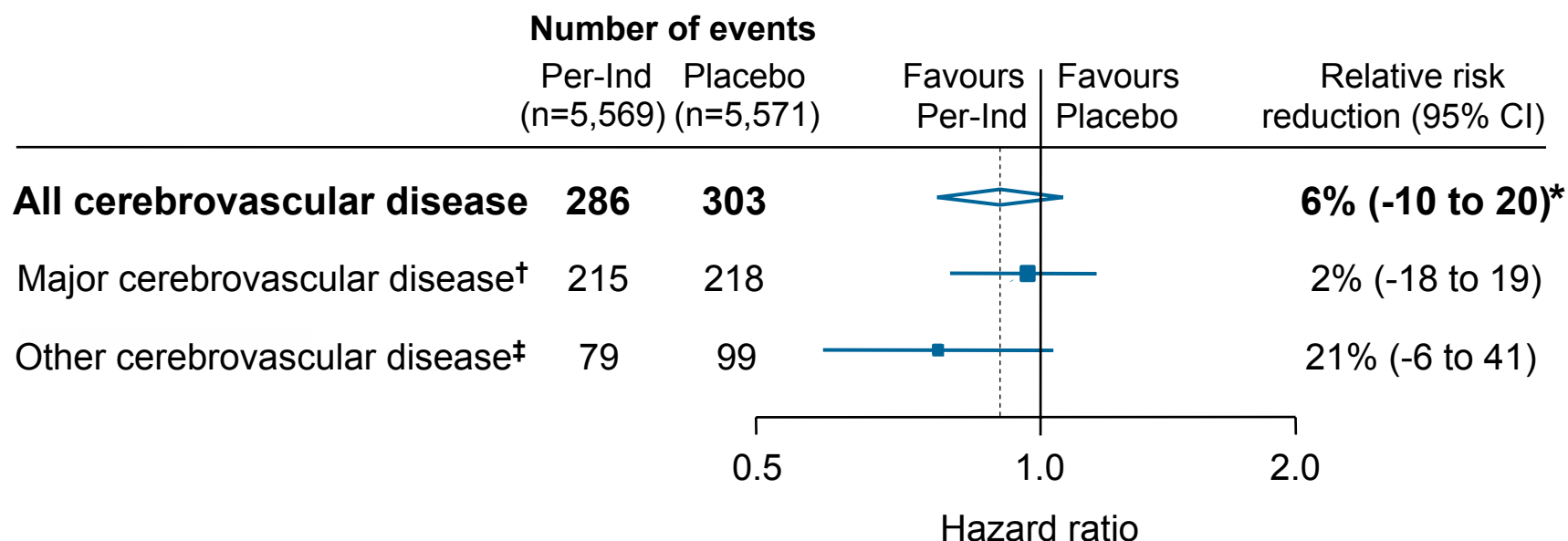
***2P=0.02**

[†]Non-fatal MI or death from coronary heart disease

[‡]Unstable angina requiring hospitalisation, coronary revascularisation or silent MI



Cerebrovascular events



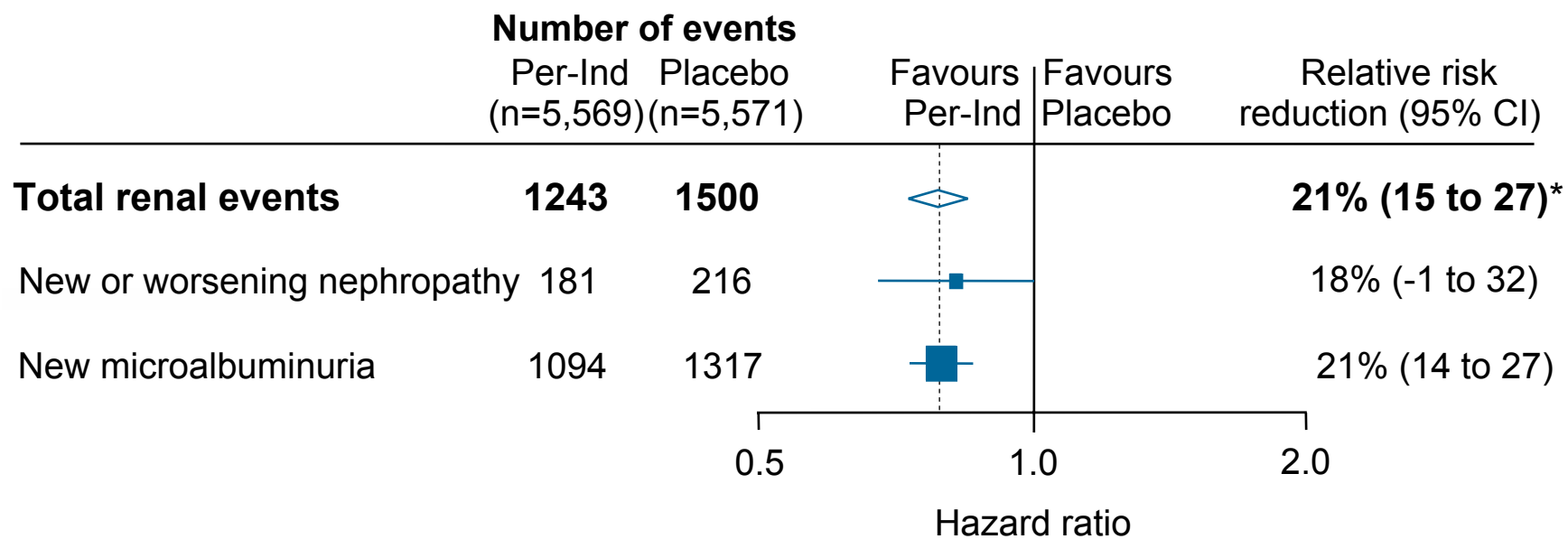
***2P=0.40**

†Non-fatal stroke or death from cerebrovascular disease

‡Transient ischaemic attack or subarachnoid haemorrhage



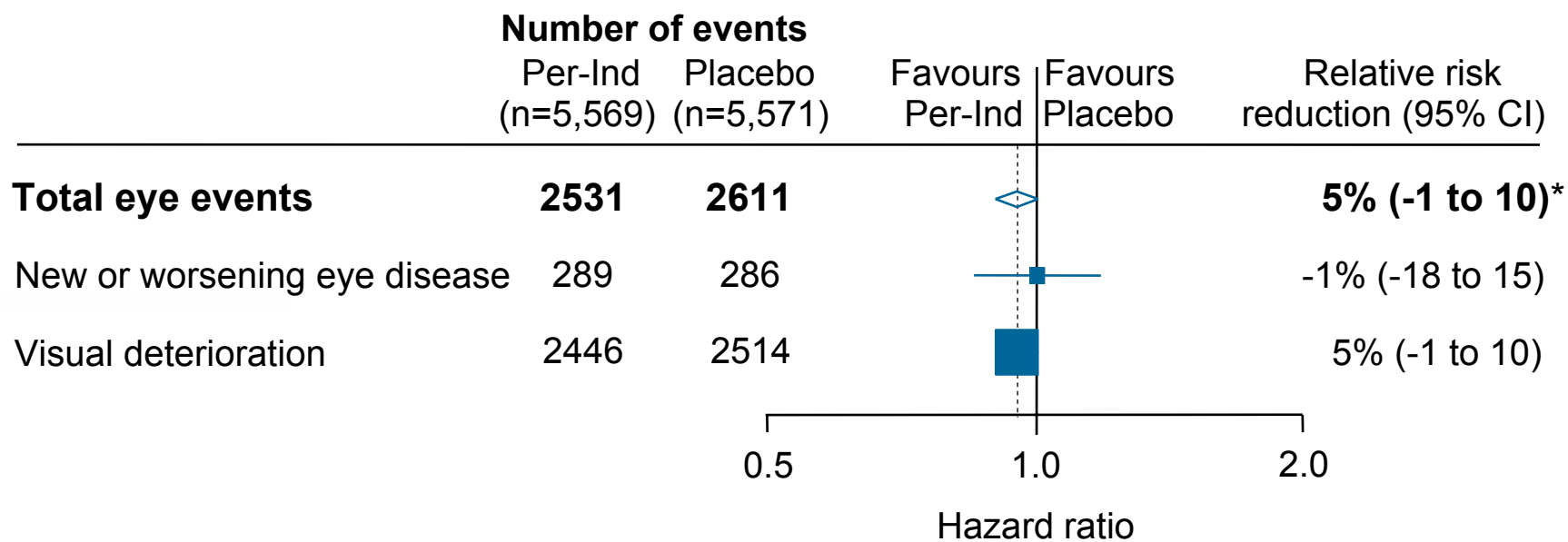
Renal events



***2P=<0.01**



Eye events



***2P=0.09**

Absolute benefits of routine treatment with perindopril and indapamide

After 5 years, treatment would prevent:	Among every
One major vascular event	66 patients
One death	79 patients
One coronary event	75 patients
One renal event*	20 patients

**mostly new onset microalbuminuria*



Risk factors levels

At end of follow-up

Parameter	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Systolic BP (mmHg)	135.6	139.9
Diastolic BP (mmHg)	73.6	75.1
Haemoglobin A1c (%)	6.9	6.9
Total cholesterol (mmol/L) *	4.7	4.6
HDL cholesterol (mmol/L) *	1.3	1.3
LDL cholesterol (mmol/L) *	2.7	2.6
Triglycerides (mmol/L) *	1.8	1.7



Ancillary drug therapy

At end of follow-up

	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Any BP lowering drug	74%	83%
ACE inhibitor	50%	60%
Oral hypoglycaemic drugs	90%	91%
Insulin	33%	30%
Statin	44%	45%
Other lipid modifying drug	8%	7%
Aspirin	56%	55%
Other antiplatelet drugs	6%	6%



Summary

Routine treatment of type 2 diabetic patients with perindopril-indapamide resulted in:

- > 14% reduction in total mortality**
- > 18% reduction in cardiovascular death**
- > 9% reduction in major vascular events**
- > 14% reduction in total coronary events**
- > 21% reduction in total renal events**

Benefits appeared to be similar in all major subgroups. Treatment was very well tolerated, with few side effects and adherence similar to that with placebo.



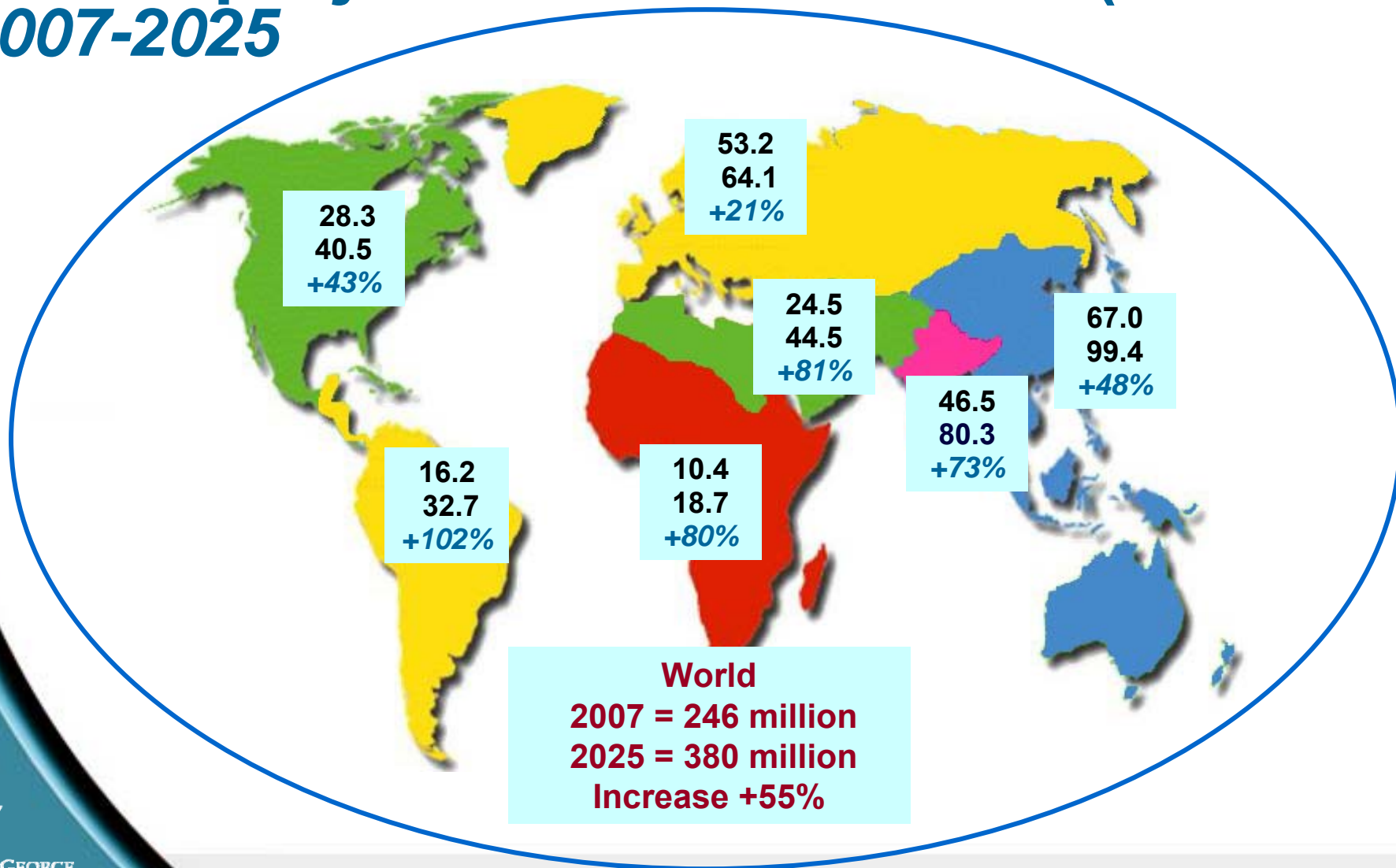
Blood pressure lowering in diabetes: *Unresolved issues 2000*

Among patients with diabetes, does blood pressure lowering therapy:

- Produce additional benefits when systolic pressure is lowered **below 145 mmHg**? **YES**
- Produce similar benefits for hypertensive and **non-hypertensive** patients? **YES**
- Add to the benefits produced by other cardiovascular preventive therapies including **ACE inhibitors**? **YES**



Global projections for diabetes (millions) 2007-2025



Potential global benefits of treatment 2010-2015

A world map with various regions highlighted in different colors: North America (green), South America (yellow), Europe (light green), Africa (orange), Asia (pink), and Australia (light blue).

**If the benefits observed in
ADVANCE were applied to just half
the world's diabetic population**

**Approximately 1.5 million deaths
could be avoided over this period**



ADVANCE *Collaborative Group*



Australian Government

National Health and Medical Research Council



The University of Sydney



SERVIER



**THE GEORGE
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for International Health