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

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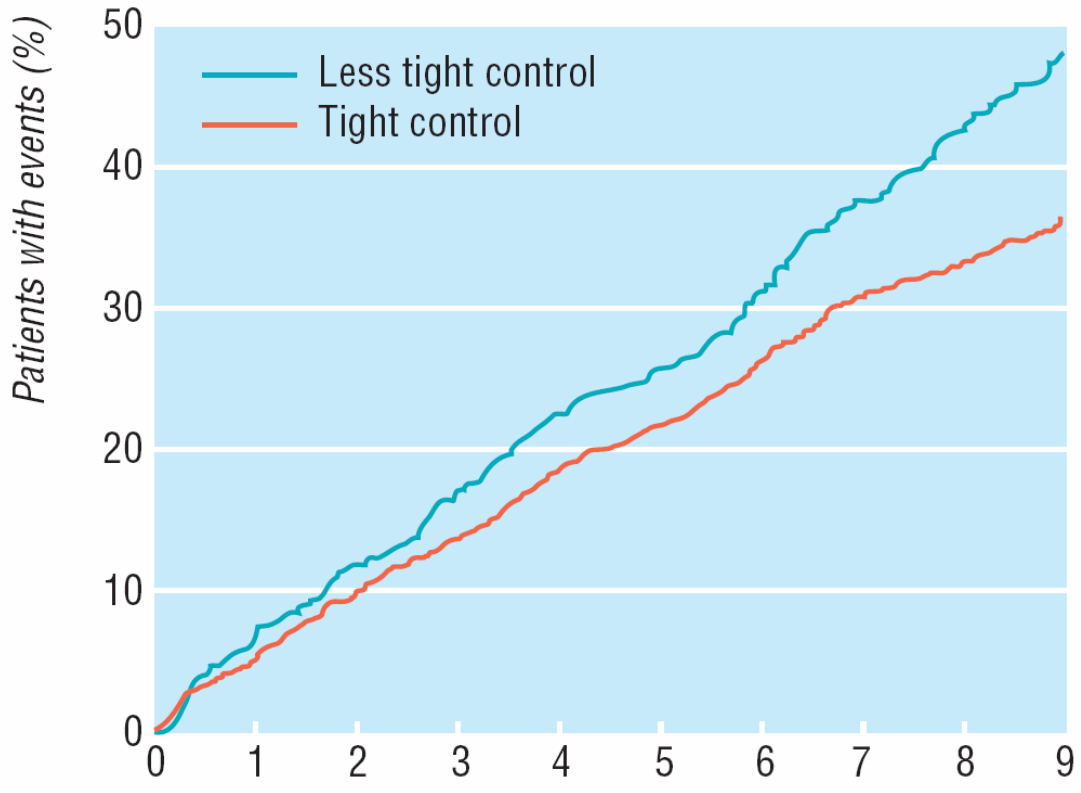
Blood pressure and vascular risk in diabetes
Best evidence: 2000



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

BMJ VOLUME 317 12 SEPTEMBER 1998

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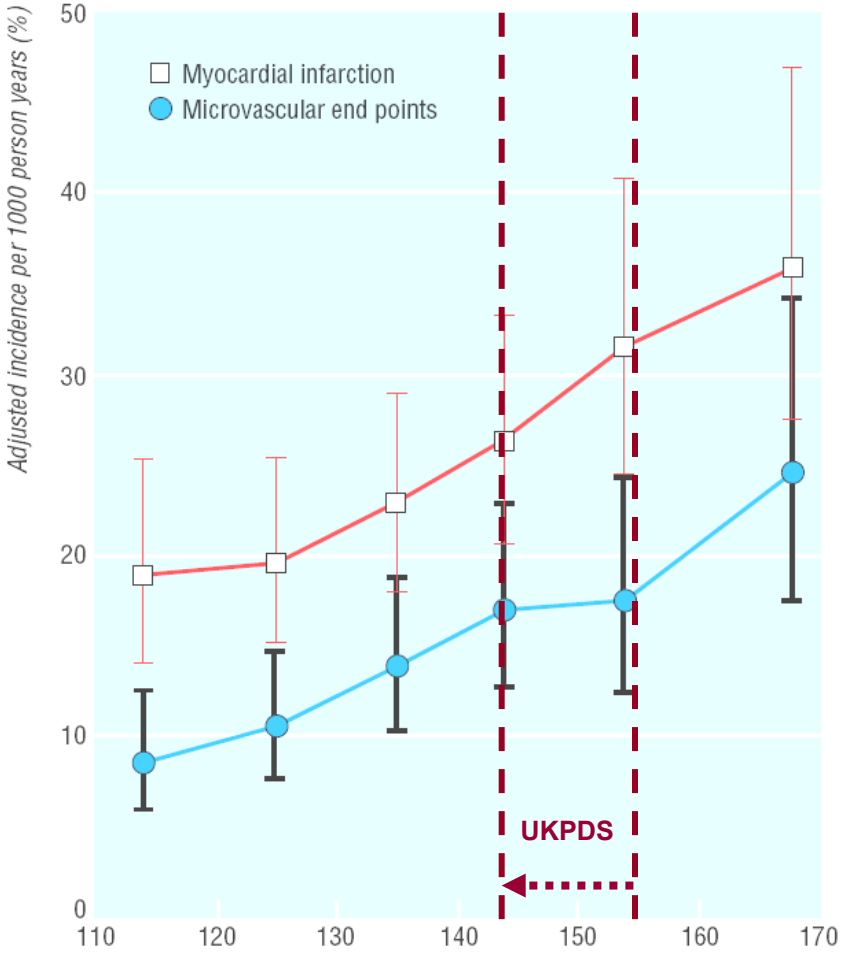

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UK Prospective Diabetes Study

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:

- **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?**

Inclusion criteria

- Type 2 diabetes mellitus
- Age 55 years or older
- Additional risk of vascular event
  - Age ≥ 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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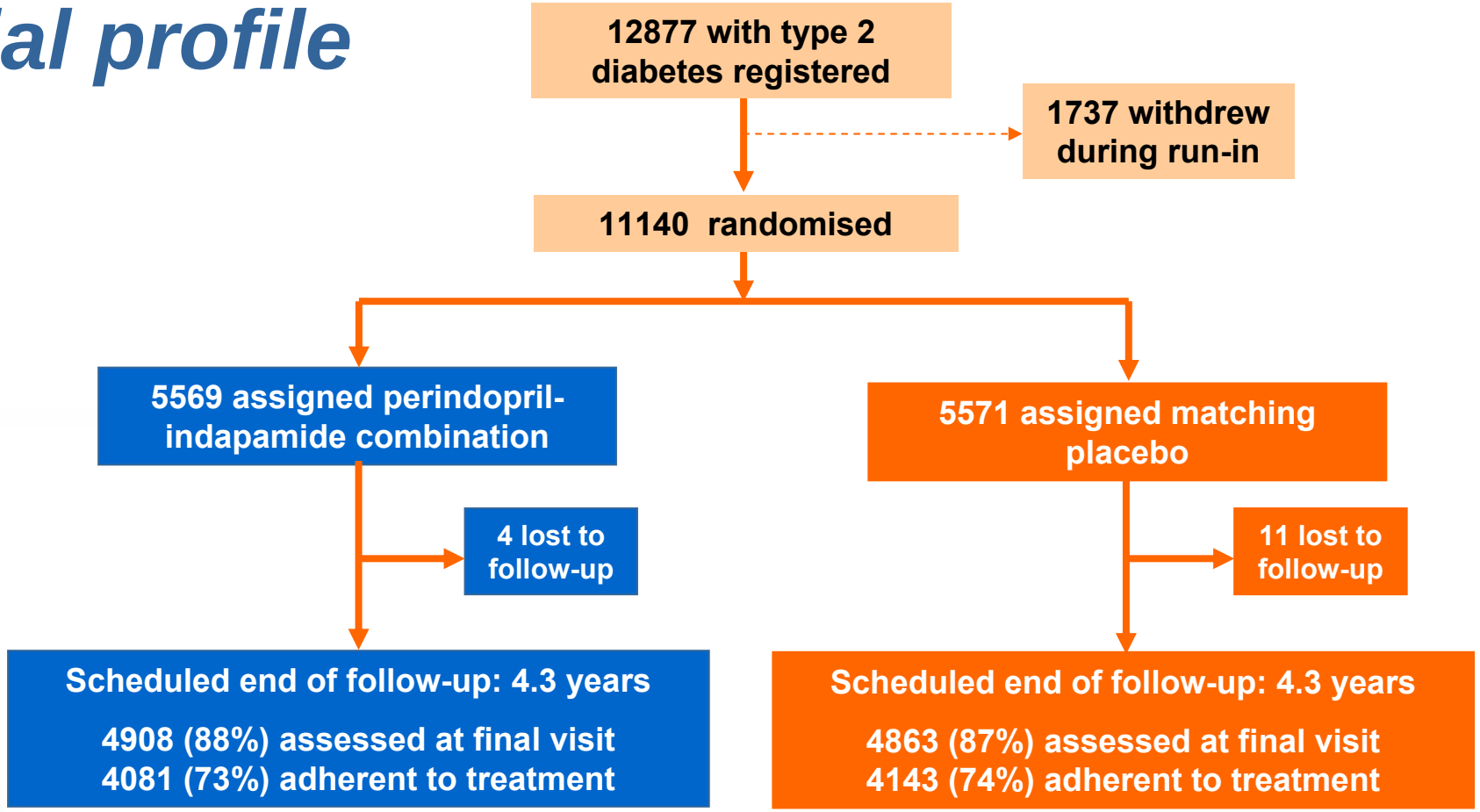
Ancillary drug treatment

- 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 of 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

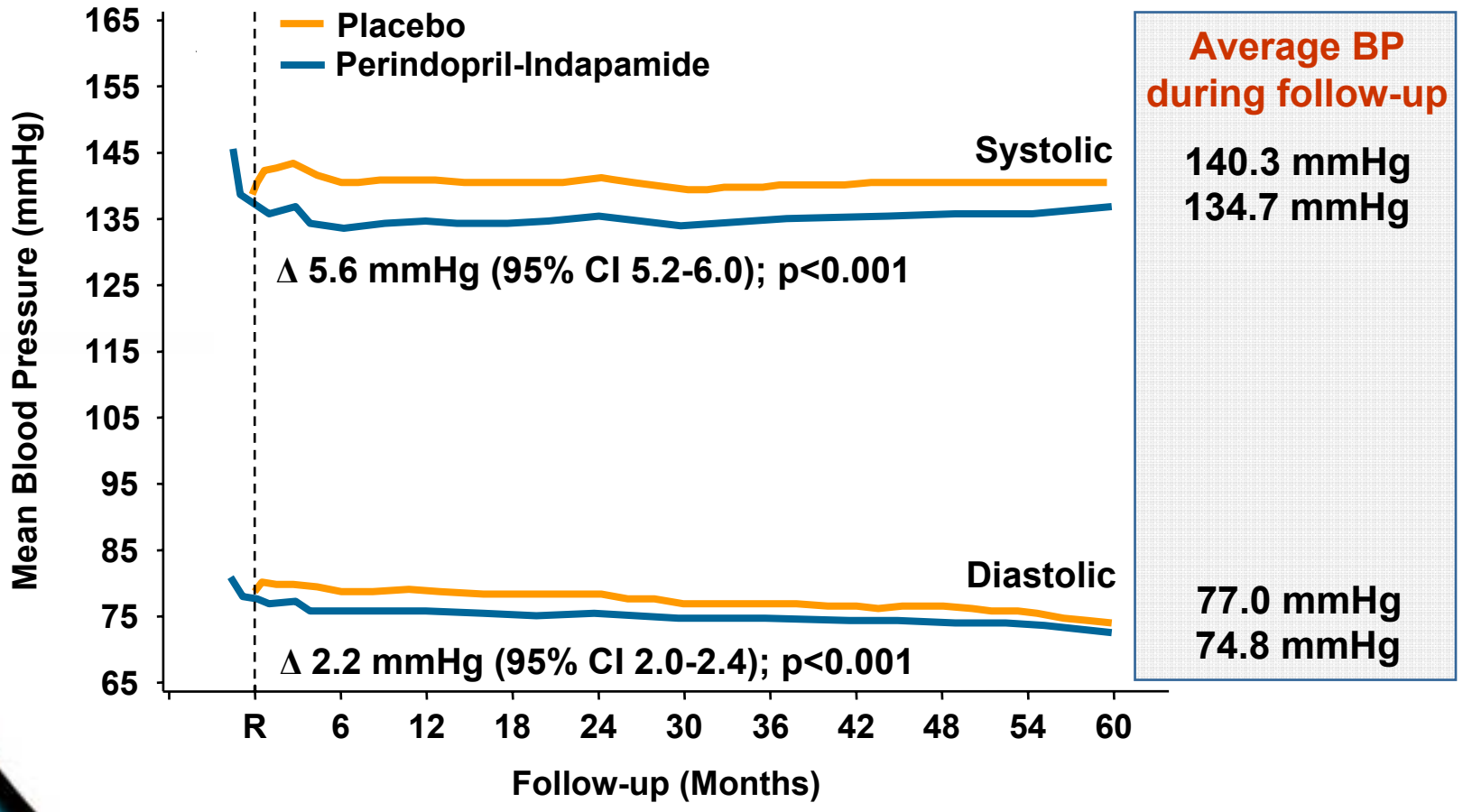
	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Any blood pressure lowering drug	75%	75%
ACE inhibitor*	43%	43%
Oral hypoglycaemic drugs	91%	91%
Statin	28%	29%
Other lipid modifying drug	9%	8%
Aspirin	44%	44%
Other antiplatelet drugs	4%	5%

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

Main results

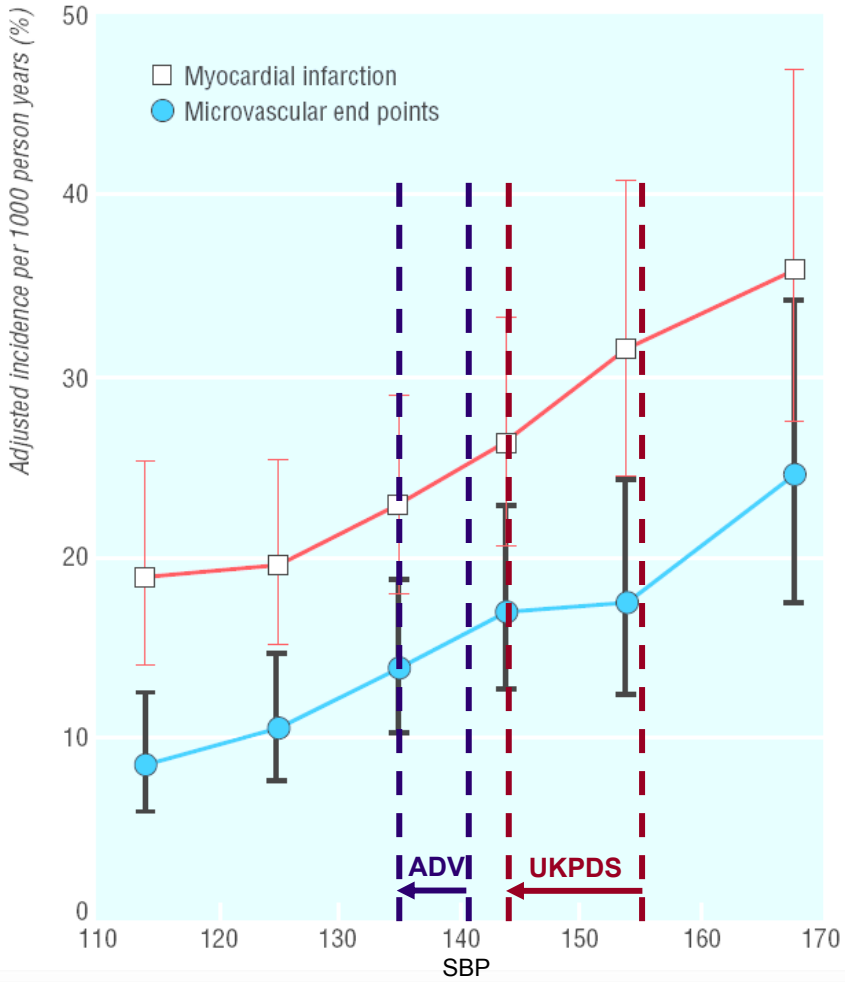
Blood pressure

Blood pressure reduction



ADVANCE BP reduction in context:

UK Prospective Diabetes Study



BMJ VOLUME 321 12 AUGUST 2000

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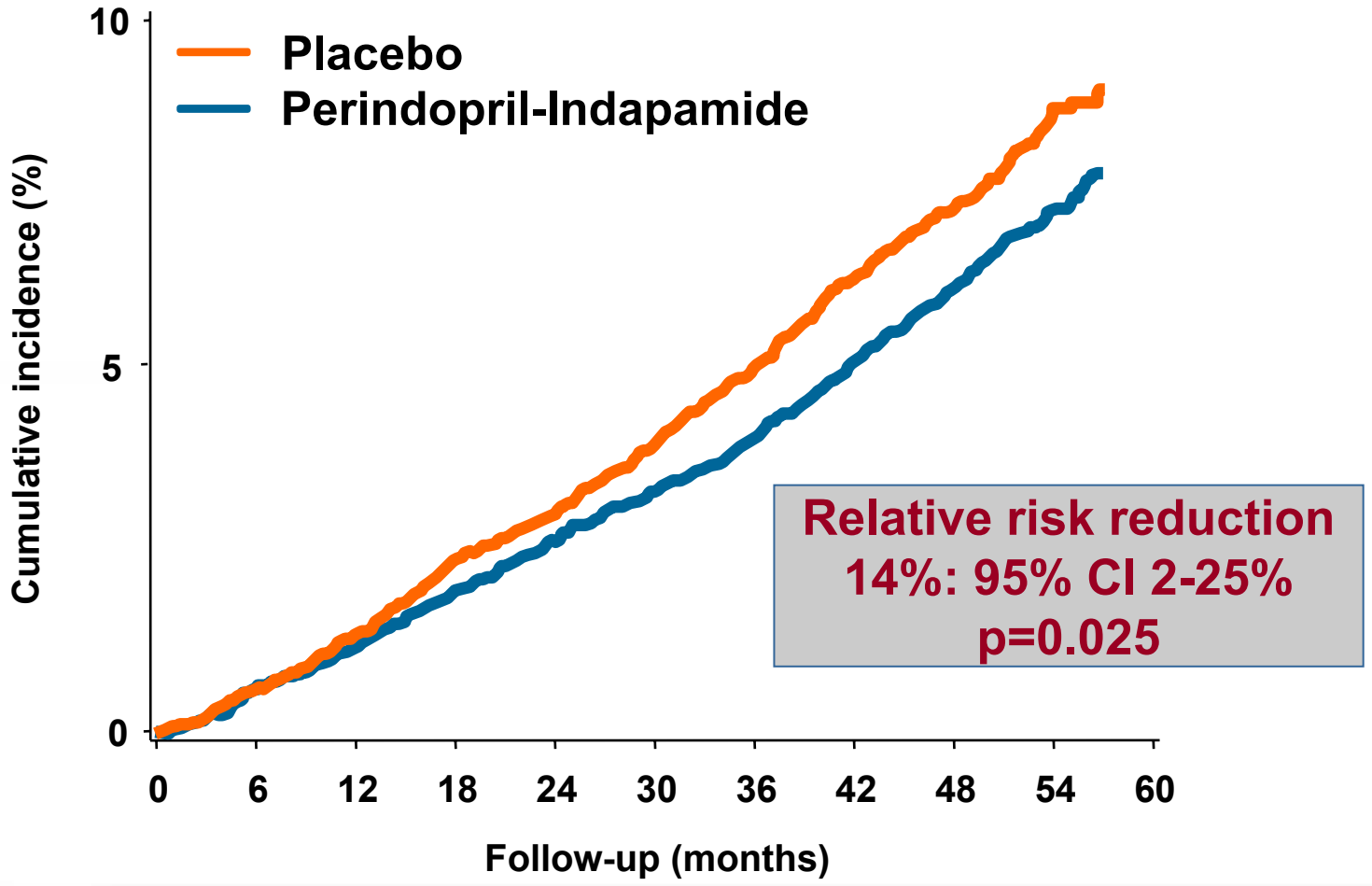
Main results

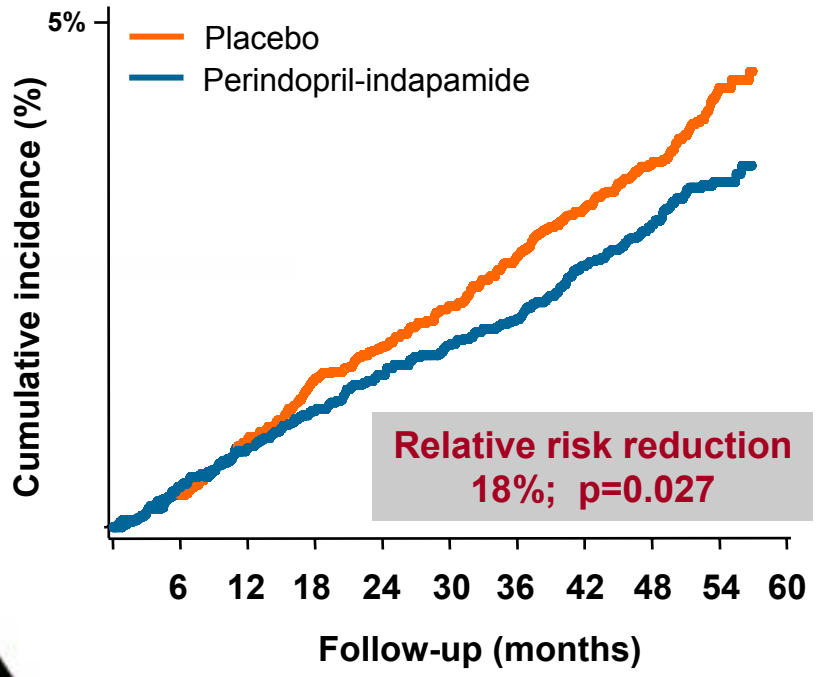
Mortality and morbidity

All-cause mortality

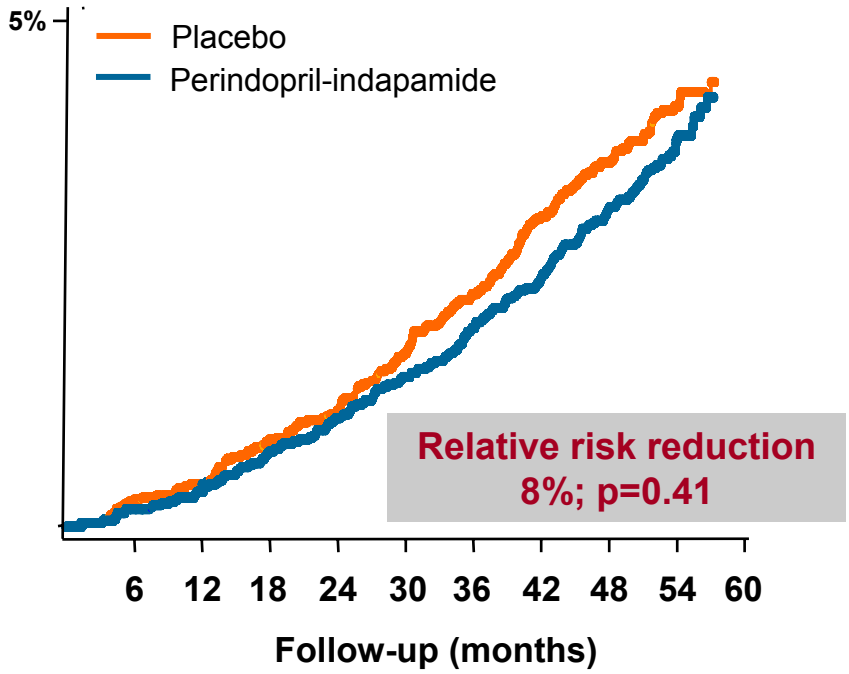


Deaths

Cardiovascular

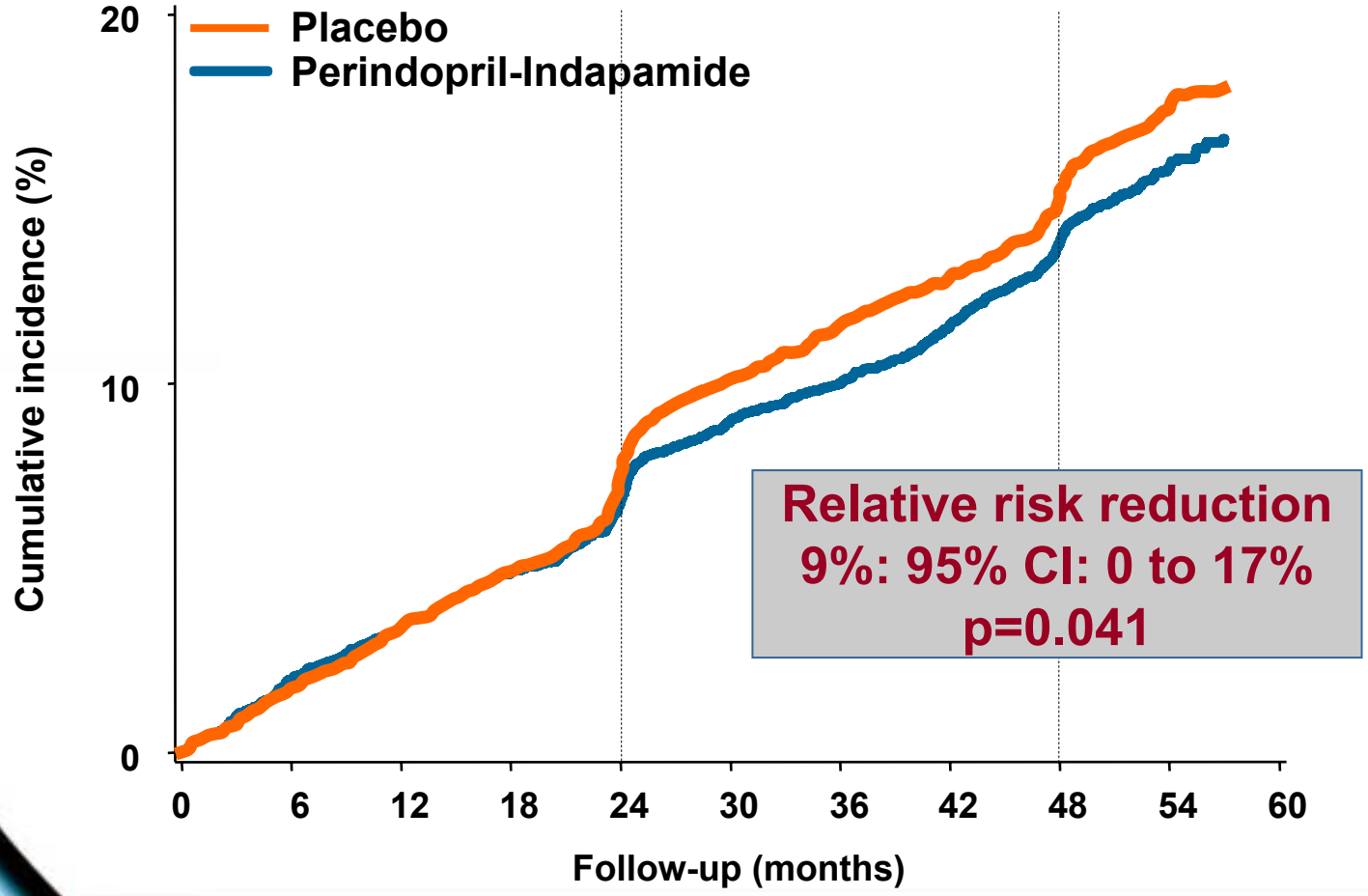


Non-cardiovascular



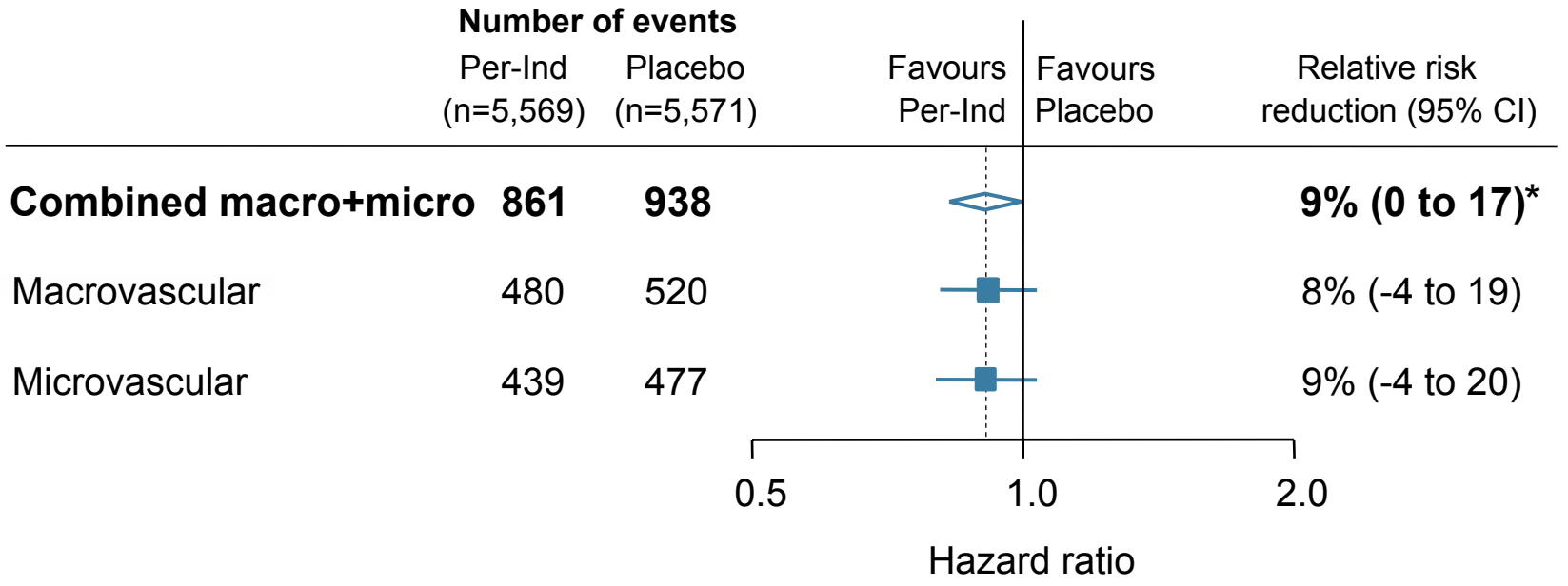
Combined primary outcomes

Major macro or microvascular event



Primary outcomes

Major macro or microvascular event



*2P=0.04

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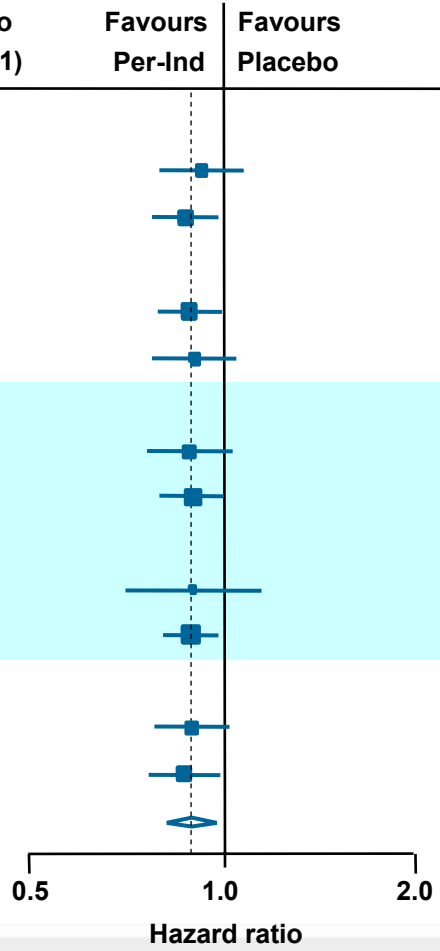
Effects by age, sex, BP and HbA1c

Combined primary endpoint

	Number of events Per-Ind (n=5,569)	Placebo (n=5,571)	Relative risk reduction (95% CI)
Age (years)			
< 65	325	346	6% (-10 to 19)
>= 65	536	592	11% (0 to 21)
Sex			
Male	546	594	10% (-1 to 20)
Female	315	344	8% (-7 to 21)
SBP (mmHg)			
< 140	**309**	**341**	**10% (-5 to 23)**
≥ 140	**552**	**597**	**9% (-2 to 19)**
History of hypertension			
No	**121**	**136**	**9% (-17 to 29)**
Yes	**740**	**802**	**9% (0 to 18)**
HbA1c (%)			
≤ 7.5	406	456	9% (-4 to 20)
> 7.5	451	481	11% (-1 to 22)
All participants	861	938	9% (0 to 17)



P*homogeneity* all >0.1

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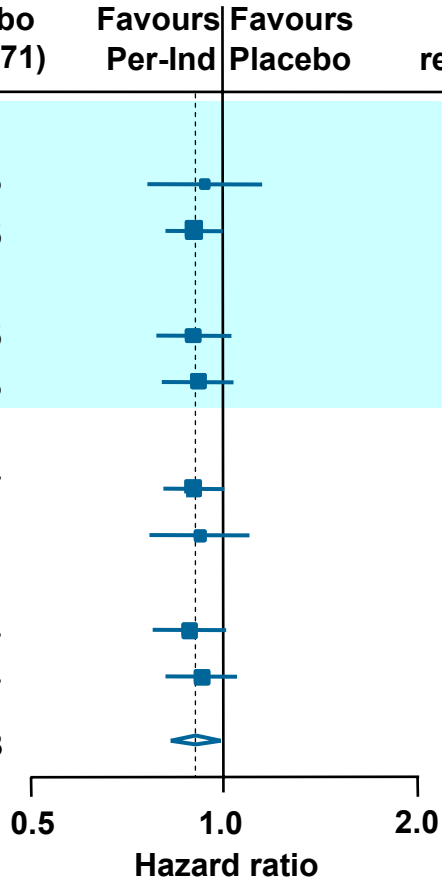
Effects by ancillary treatment

Combined primary endpoint

	Number of events Per-Ind (n=5,569)	Placebo (n=5,571)	Relative risk reduction (95% CI)
Treatment with any BP lowering drug			
No	177	183	6% (-15 to 24)
Yes	684	755	10% (0 to 19)
Treatment with ACE inhibitor			
No	417	455	10% (-3 to 21)
Yes	444	483	8% (-4 to 20)
Treatment with statins			
No	638	687	10% (0 to 19)
Yes	223	251	8% (-10 to 23)
Treatment with anti-platelet drug			
No	408	454	11% (-2 to 22)
Yes	453	484	7% (-5 to 18)
All participants	861	938	9% (0 to 17)



P*homogeneity* all >0.1

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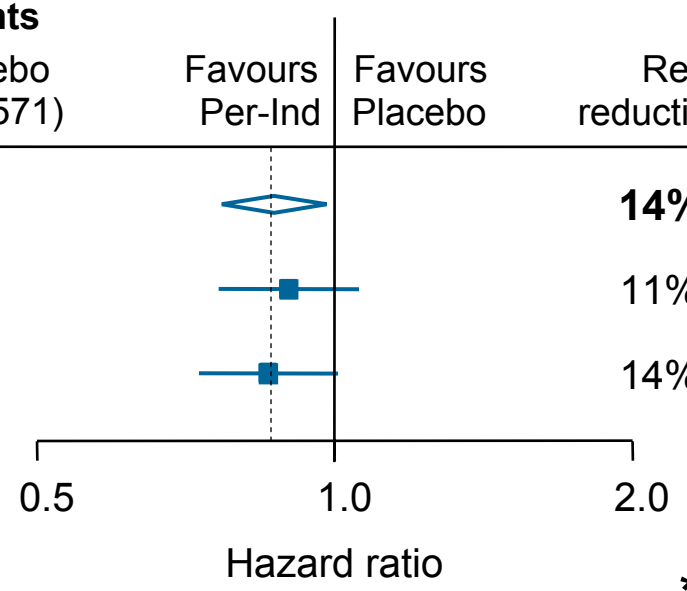
Coronary events

	Number of events: Per-Ind (n=5,569)	Placebo (n=5,571)	Relative risk reduction (95% CI)
All coronary heart disease	**468**	**535**	**14% (2 to 24)***
Major coronary heart disease†	265	294	11% (-6 to 24)
Other coronary heart disease‡	283	324	14% (-1 to 27)

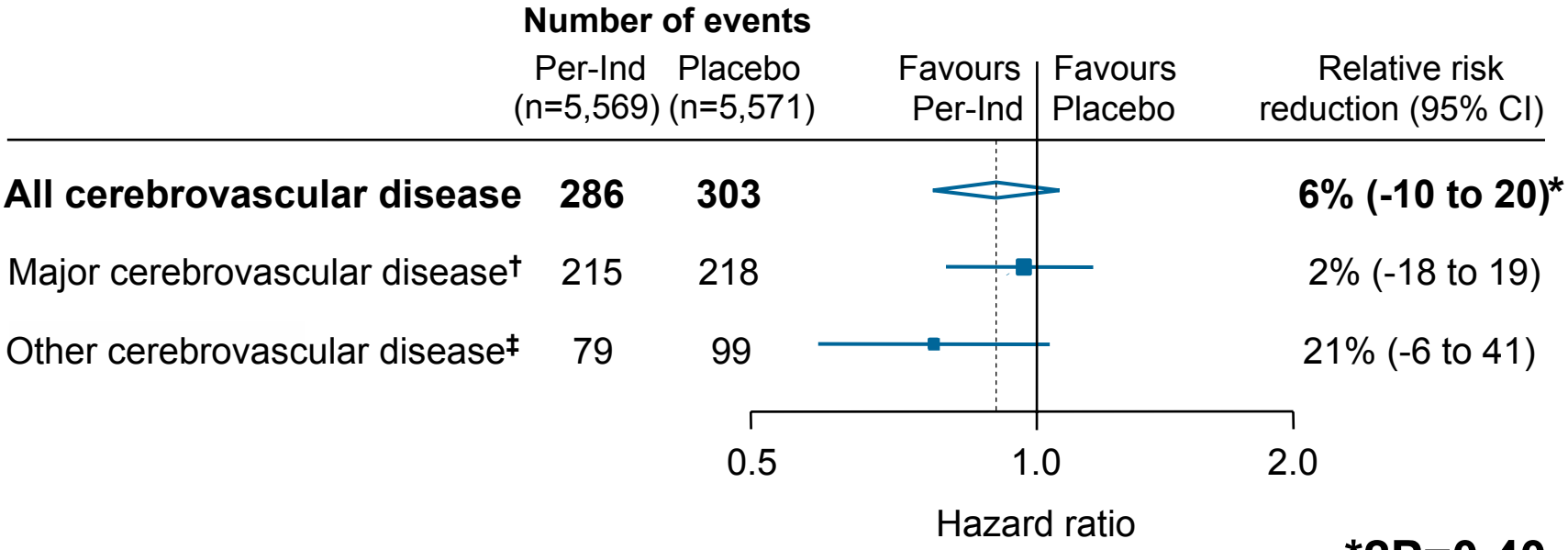


***2P=0.02**

†Non-fatal MI or death from coronary heart disease

‡Unstable angina requiring hospitalisation, coronary revascularisation or silent MI

Cerebrovascular events

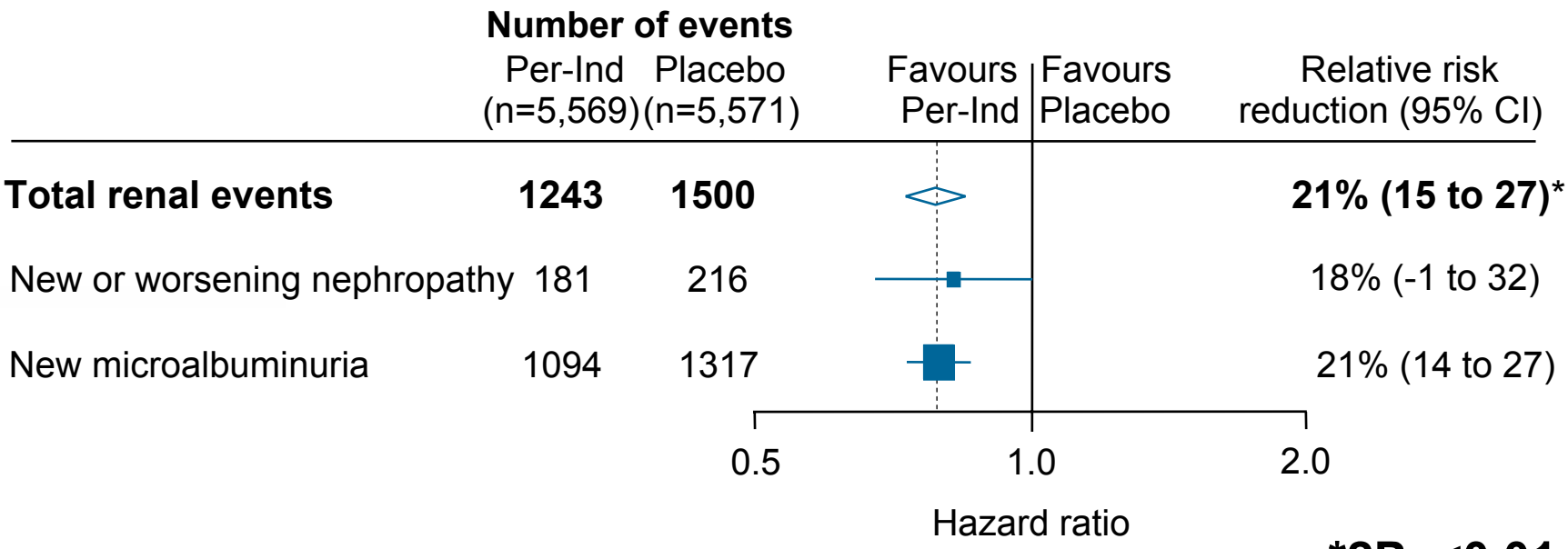


*2P=0.40

†Non-fatal stroke or death from cerebrovascular disease

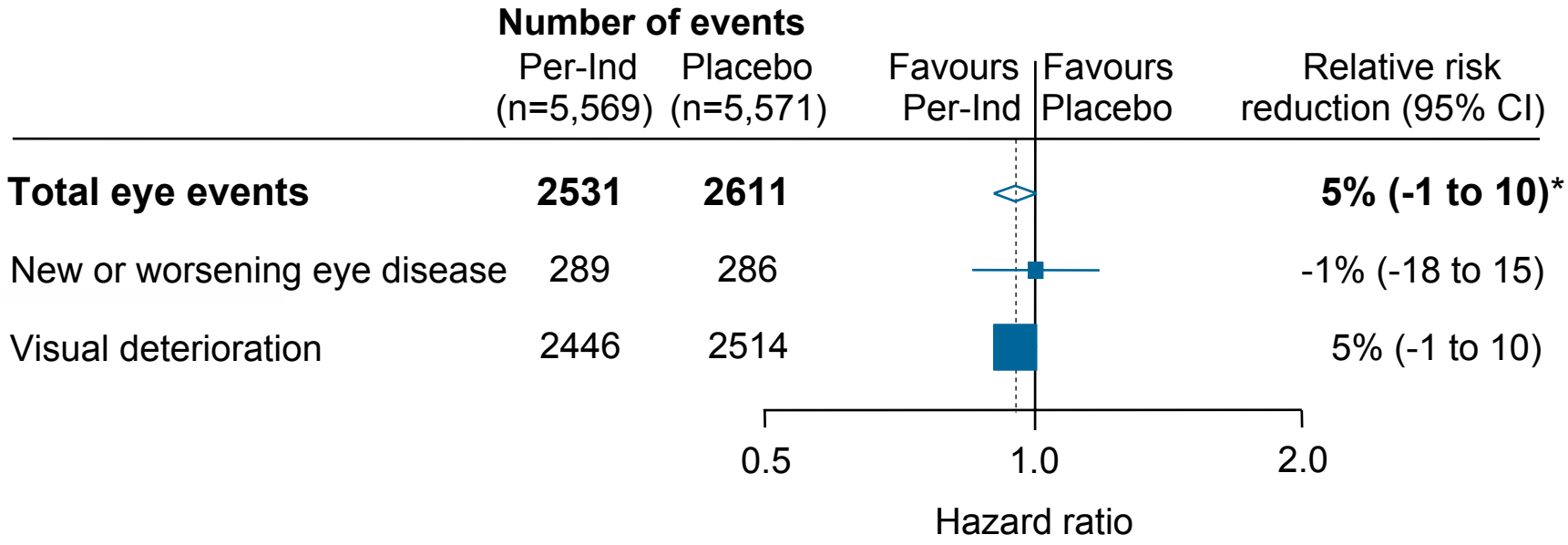
‡Transient ischaemic attack or subarachnoid haemorrhage

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

* Measurements taken at month 48

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.

ADVANCE

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**

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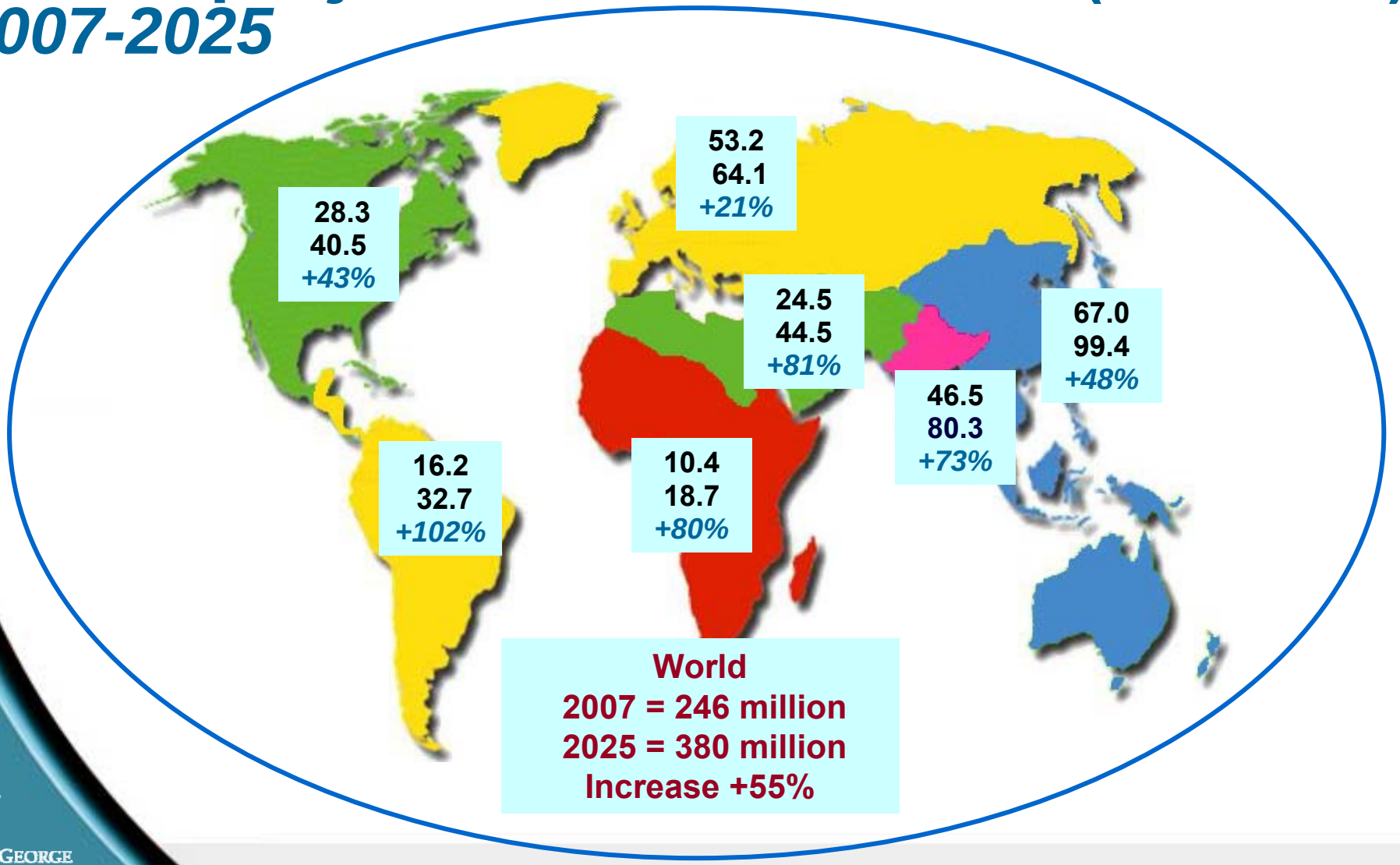
Global projections for diabetes (millions)
2007-2025



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Diabetes Atlas, 3rd edition, IDF 2006

Potential global benefits of treatment
2010-2015

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

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Diabetes Atlas, 3rd edition, IDF 2006

ADVANCE Collaborative Group

Australian Government

National Health and Medical Research Council

SERVIER

The University of Sydney

The George Institute for International Health