LIPID Cohort

Long-term Safety and Effectiveness of Cholesterol Lowering with Pravastatin Treatment over 11 Years: the LIPID Trial Extension.

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LIPID Cohort

Background

- **The effectiveness and safety of statin therapy has been well established in patients with prior CHD, such as in LIPID[1] and in a broad cross-section of patients at high risk of CVD events[2]**
- **Evidence is based on many randomised trials of statin therapy over 5 years[2]**
- **Little randomised evidence of long term effects of statin therapy for 10+ years**

[1]The LIPID Study. NEJM 1998; 339: 1349-57.

[2]CTT Collaboration. Lancet 2005; 366: 1267-78.

Cause-specific mortality per mmol/L LDL cholesterol reduction

Cause of death	Events (%) Treatment	Events (%) Control	Rate Ratio (CI)
Vascular causes:			
CHD	**1548 (3·4)**	**1960 (4·4)**	**0·81 (0·76 - 0·85)**
Stroke	265 (0·6)	291 (0·6)	0·91 (0·74 – 1·11)
Other vascular	289 (0·6)	302 (0·7)	0·95 (0·78 – 1·16)
Any non-CHD vascular	**554 (1·2)**	**593 (1·3)**	**0·93 (0·83 – 1·03)**
Any vascular	**2102 (4·7)**	**2553 (5·7)**	**0·83 (0·79 – 0·87)**
Non-vascular causes:			
Cancer	1094 (2·4)	1069 (2·4)	1·01 (0·91 – 1·12)
Respiratory	98 (0·2)	125 (0·3)	0·82 (0·62 – 1·08)
Trauma	51 (0·1)	57 (0·1)	0·89 (0·59 – 1·34)
Other/unknown	487 (1·1)	550 (1·2)	0·87 (0·73 – 1·03)
Any non-vascular	**1730 (3·8)**	**1801 (4·0)**	**0·95 (0·90 – 1·01)**
ANY DEATH	**3832 (8·5)**	**4354 (9·7)**	**0·88 (0·84 – 0·91)**

RR & CI (Treatment : Control)

p < 0·00001

0·5 Treatment better

1·0

1·5 Control better

CTT Collaboration. Lancet 2005; 366: 1267-78.

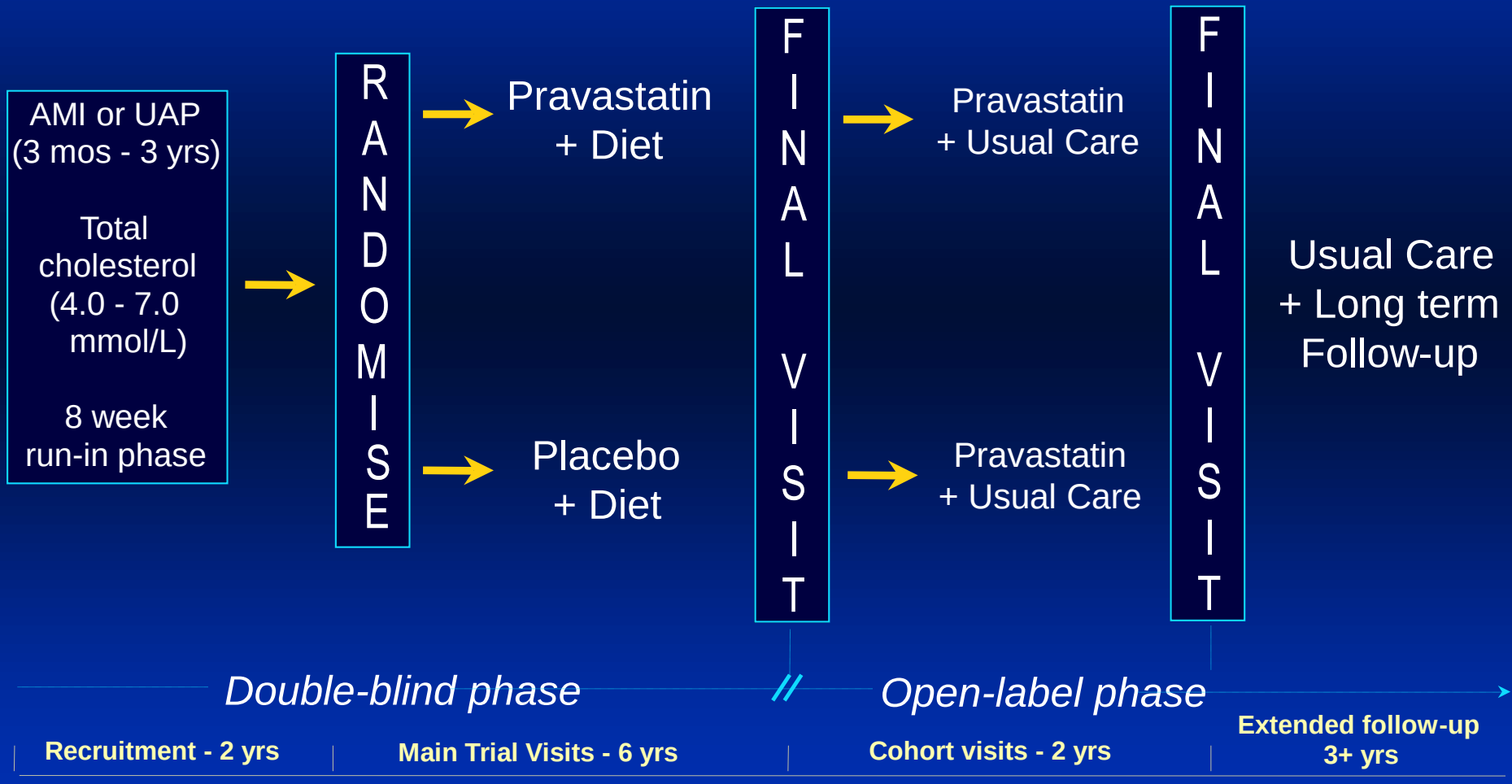
LIPID Cohort

Background
LIPID Cohort

- The LIPID Study evaluated pravastatin versus placebo in 9014 patients with prior AMI or unstable angina and total cholesterol 4–7 mmol/L (155–271 mg/dL)
- The trial closed early with clear evidence that pravastatin had reduced total mortality. All patients were offered pravastatin, with the plan to follow everyone for at least 5 more years.
- 85% of patients decided to receive Rx followed up in clinic visits for 2 years.
- Additional indirect long-term follow-up now obtained for 3+ years

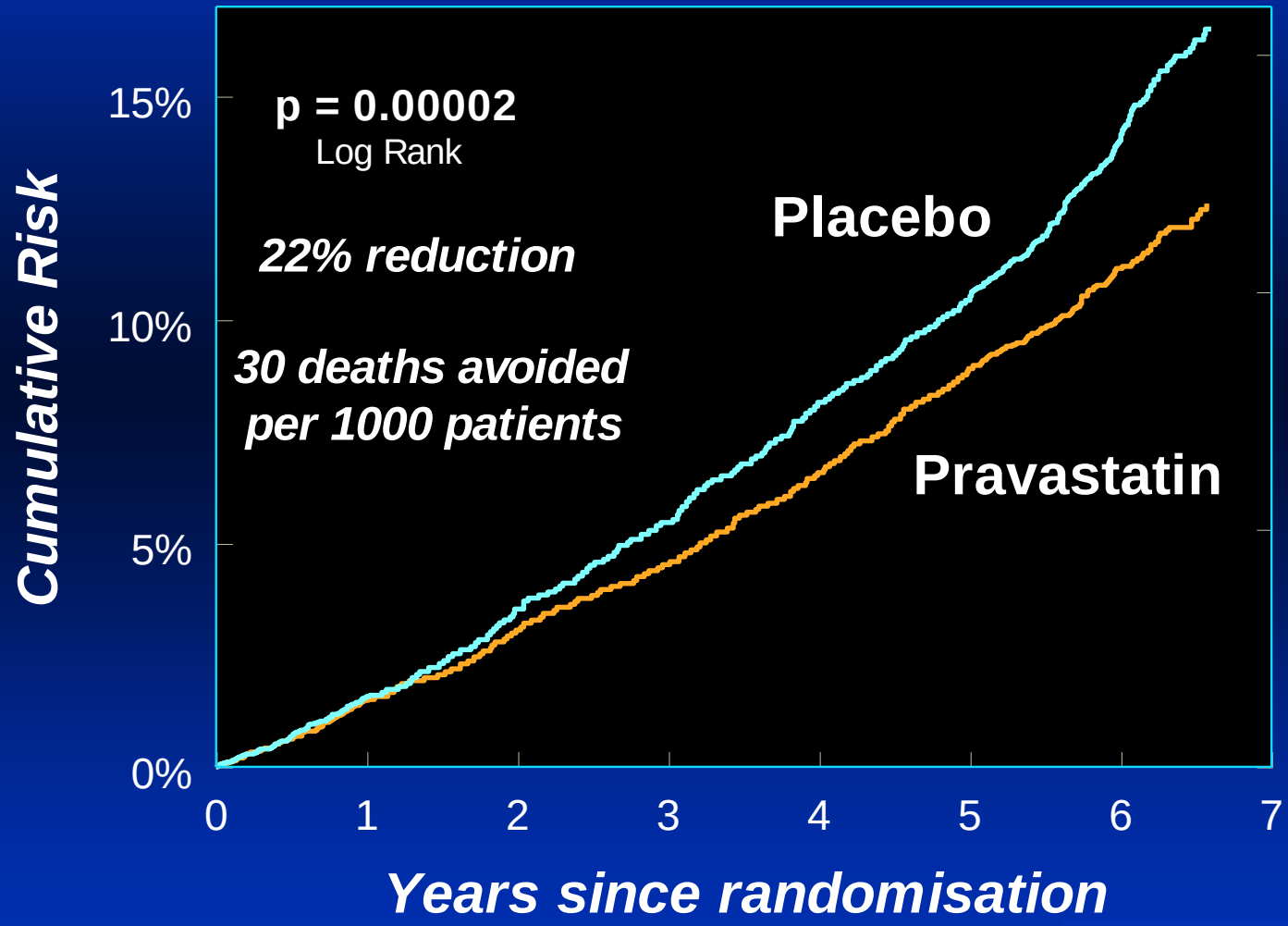
LIPID Cohort

LIPID Extended Follow-up Design



LIPID Cohort

Total Mortality



No. at Risk 9014 8876 8712 8560 8350 7639

NEJM 1998; 339: 1349–57

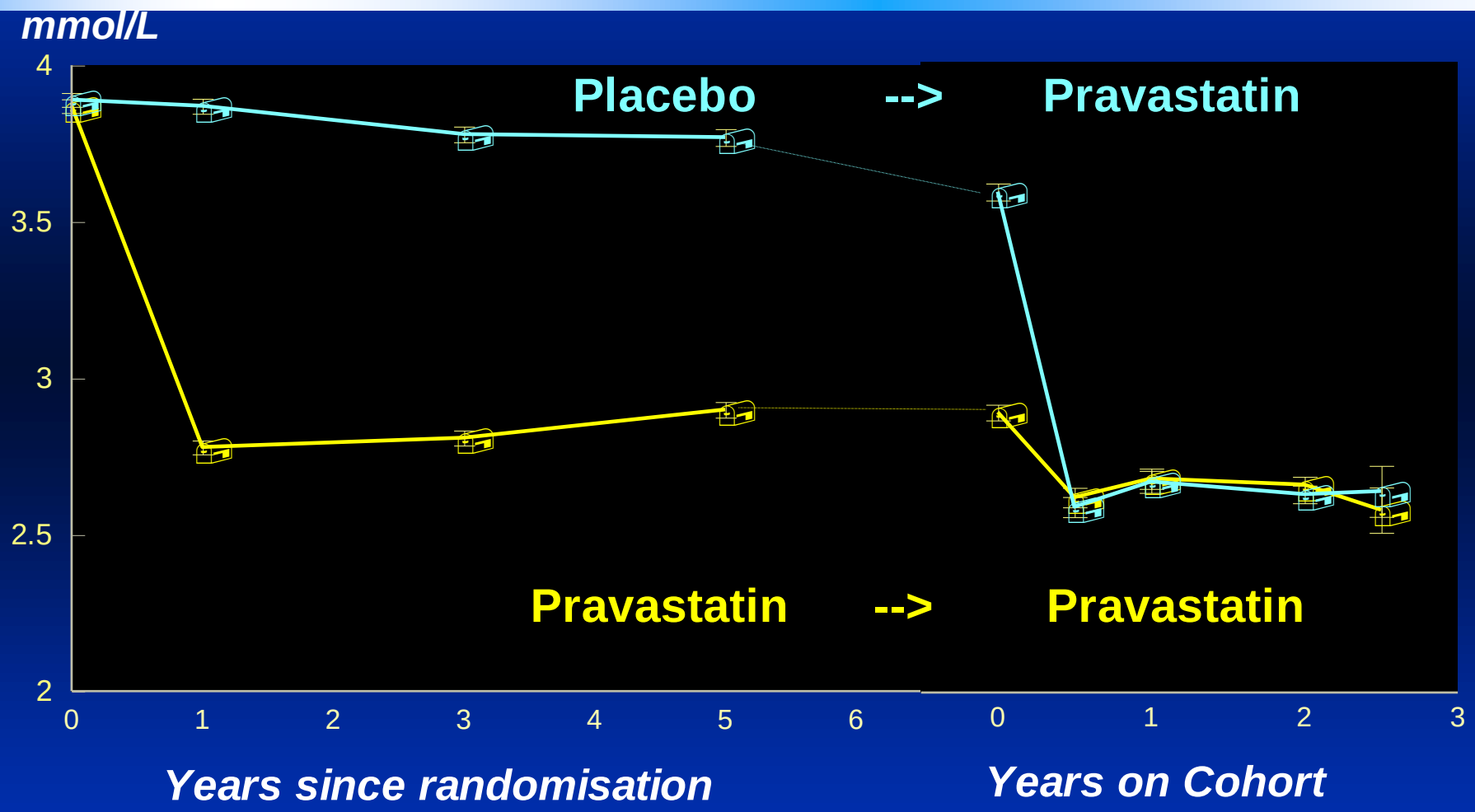
LIPID Trial Extension

Objectives

- Long term effectiveness and safety of treatment on
  - Cause-specific mortality
  - Cancer incidence
  - Other major adverse events
- Long-term cost-effectiveness
- Relationship between patient risk factors, blood markers, treatment and long-term outcomes

Change in LDL Cholesterol

Mean with 95% confidence intervals



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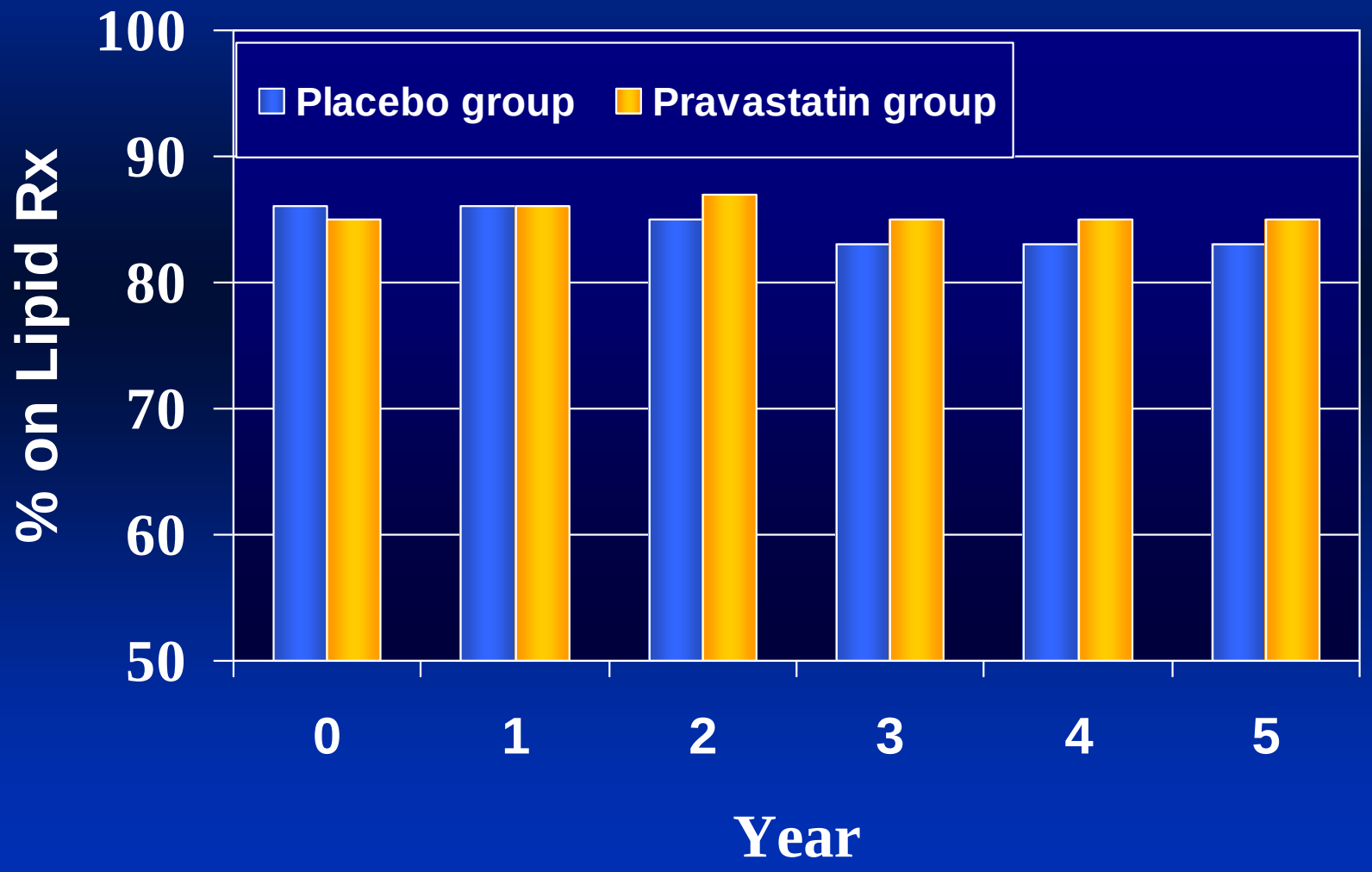
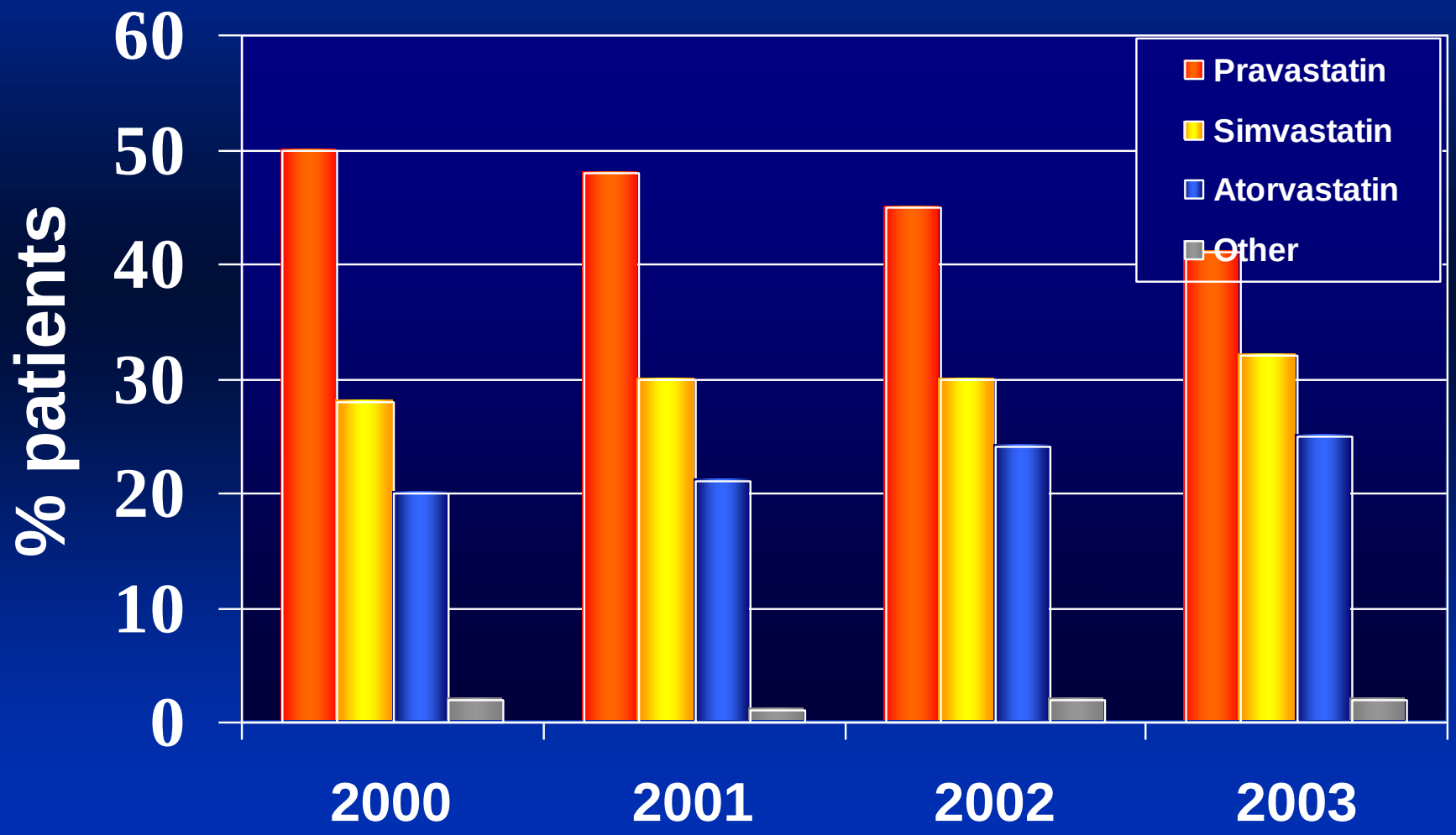
Use of Cholesterol Lowering Treatment
By randomised group



LIPID Cohort

Cholesterol treatment

Questionnaire follow-up



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Long term follow-up

Period	Number followed	Deaths	Not followed
Baseline	9014		
Completed main trial – Yr 6	7882	1131	1
Consented to extended FU	7721		161 (2.0%)
Completed 2 yr open-label phase – Yr 8	7246	474	1
Extended FU (Yr 8-11)*	6391	833	22 (0.3%)

*Contact by questionnaire, mail in > 99% .
All patients followed through national death registries (100%).

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Cause of Death

- Cause of death classified by Outcome Assessment Committee (blinded) over 1st 8 years in major groups as:
  - Coronary
  - Other Vascular: Stroke-related and other
  - Non- cardiovascular:
    - Cancer
    - Other non-vascular
- Deaths in extended follow-up were classified in same categories from the national death registry information based on ICD registry codes
- Validation study during main trial demonstrated reasonable concordance in major groupings (sensitivity 93%, specificity 90% for CVD death).

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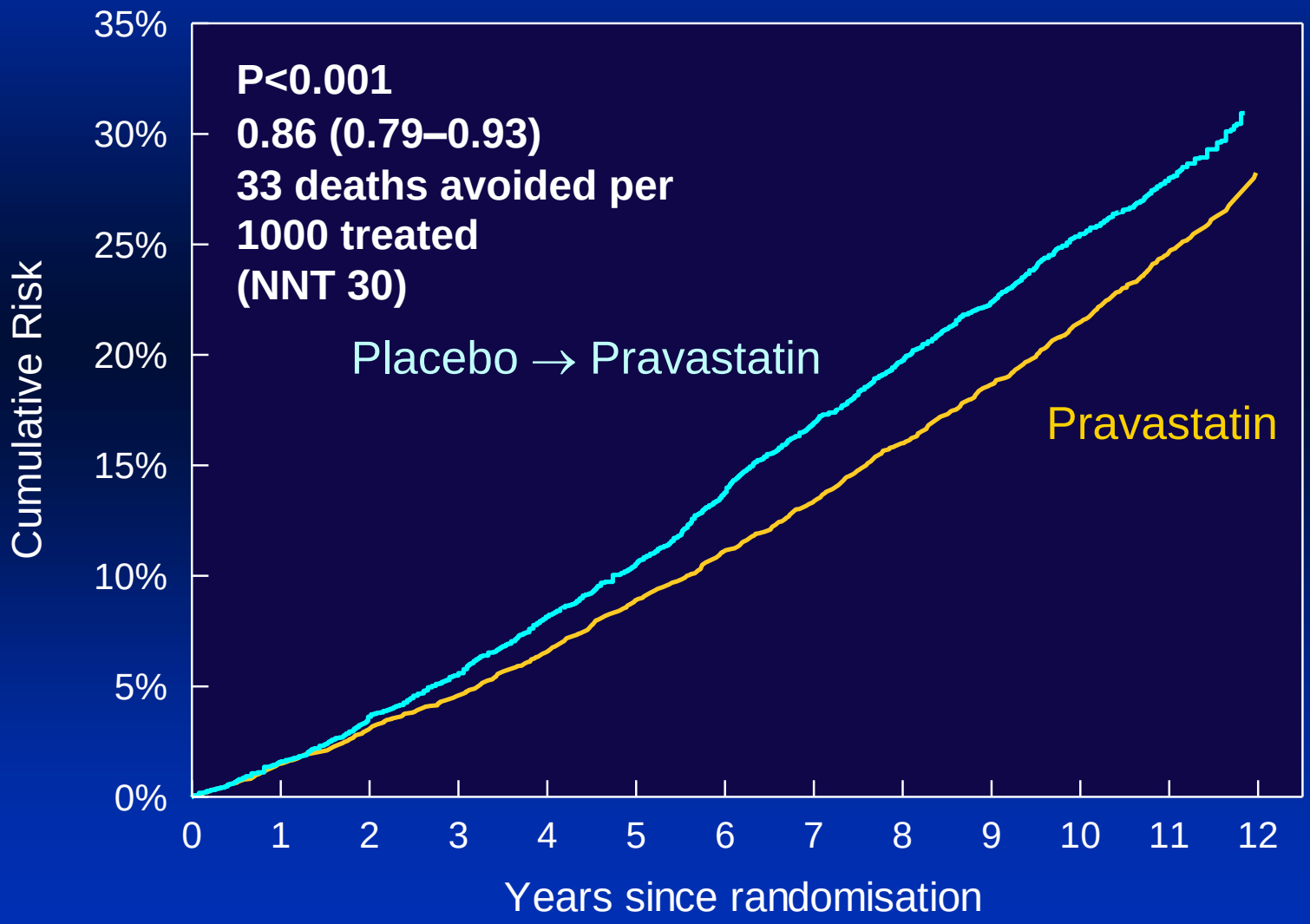
Cause of death

Cause of death	n	% cause	% died in LIPID
Coronary	1293	53%	14%
Stroke	136	6%	2%
Other CVD	111	5%	1%
Total CVD	1540	63%	17%
Cancer	619	25%	7%
Other non-CVD	279	11%	3%
Total	2438	100%	27%

LIPID Cohort

Total Mortality



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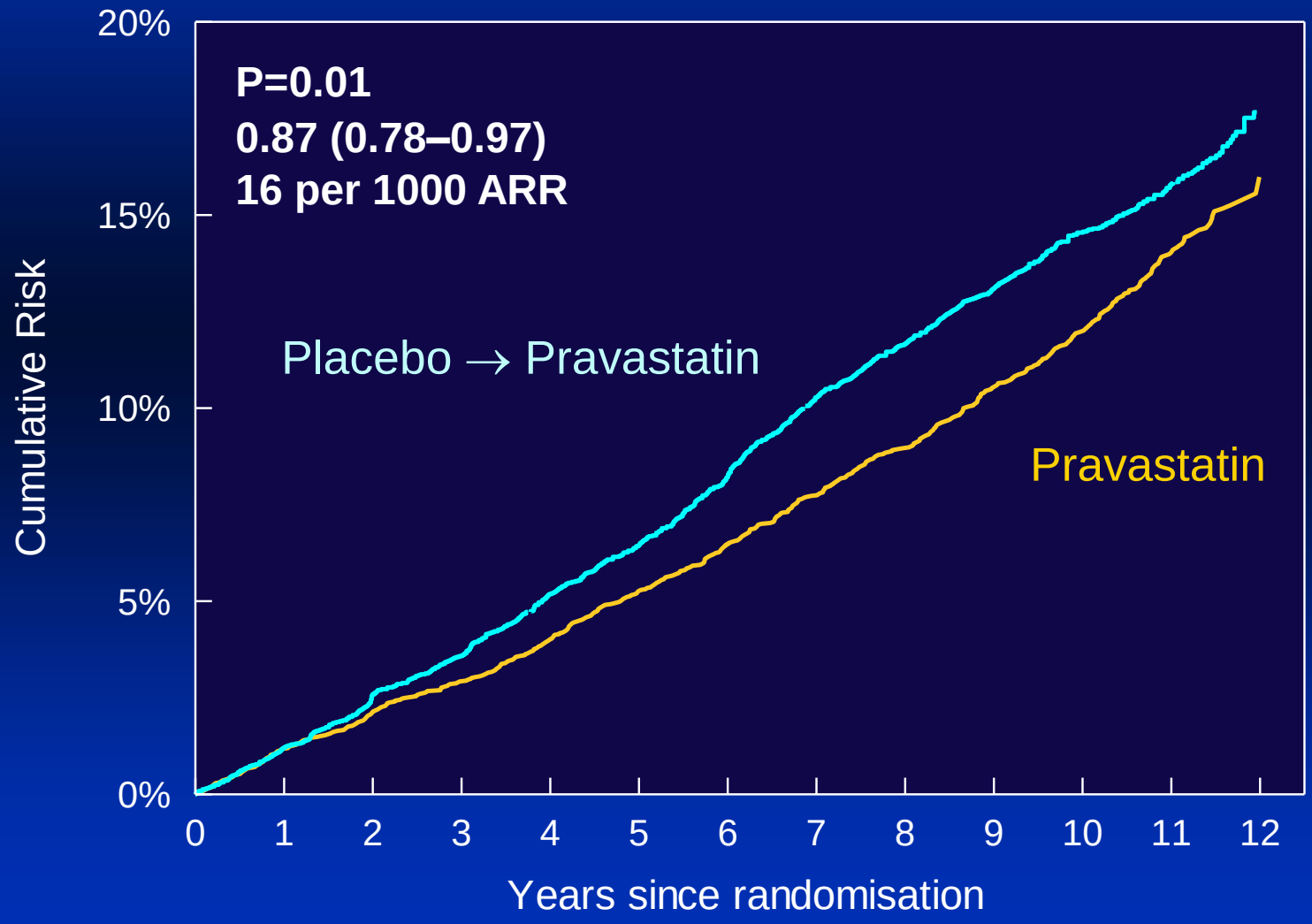
CHD Mortality



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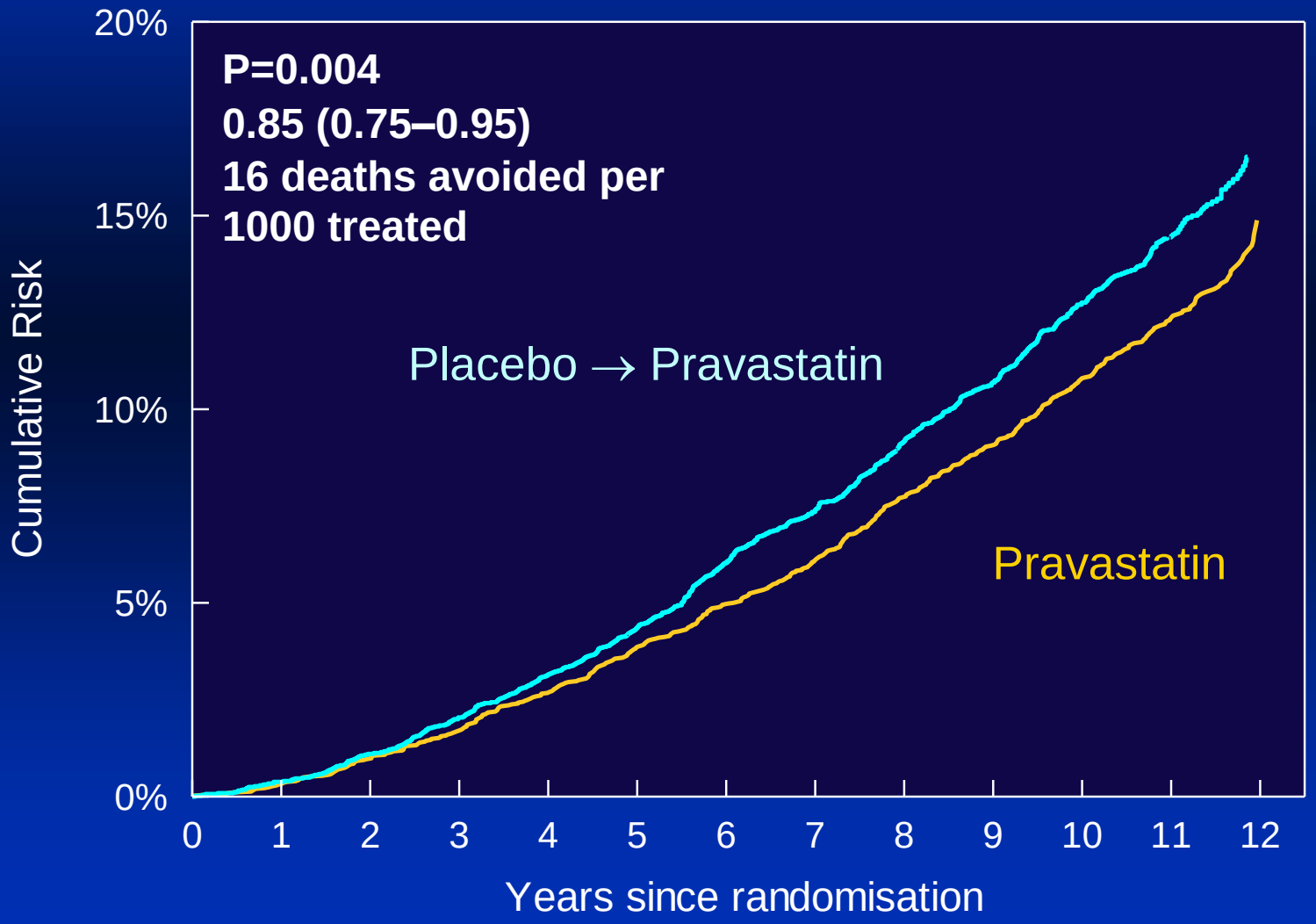
Non-CHD Mortality



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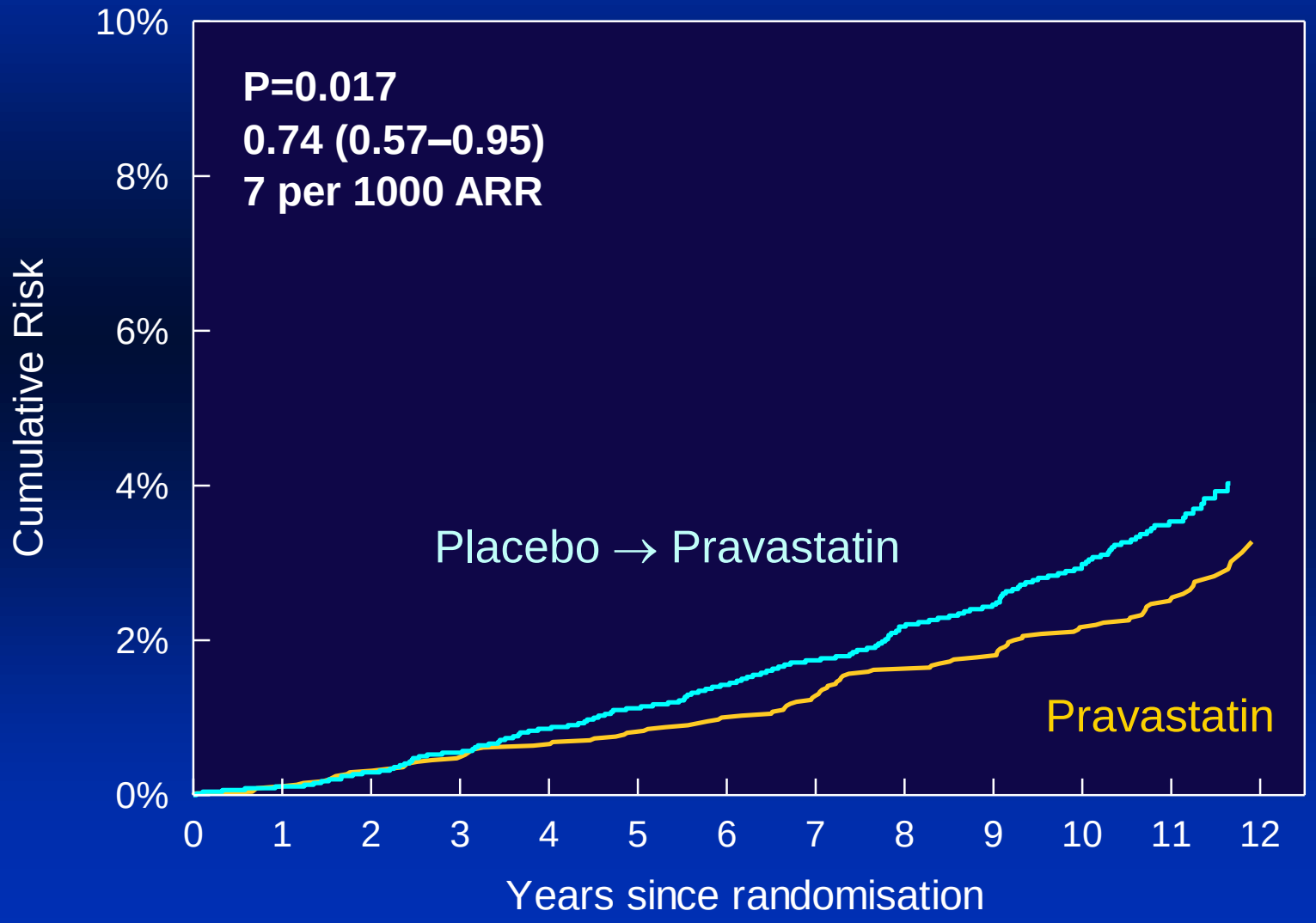
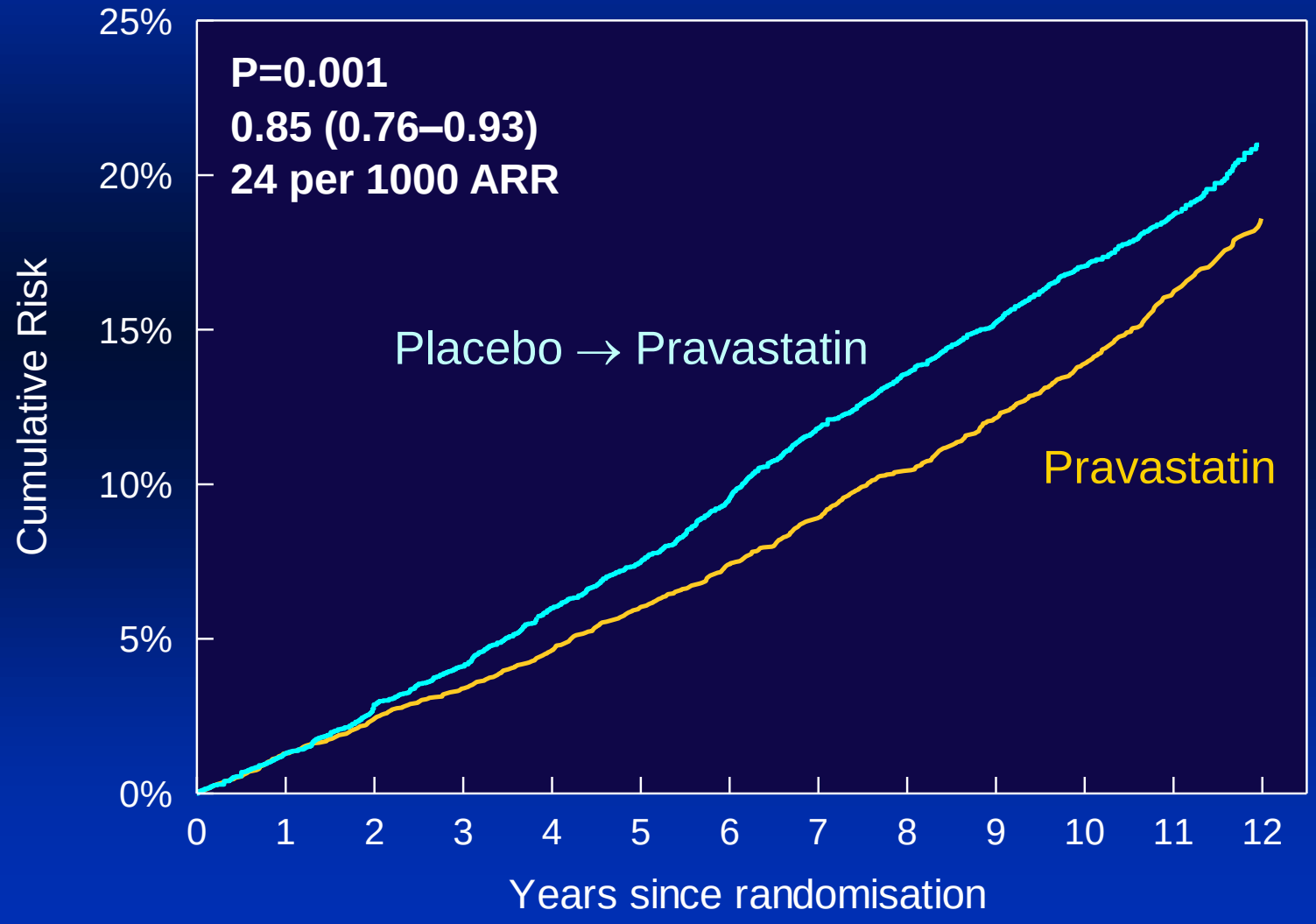
Vascular Mortality
Non-CHD



LIPID Cohort

CVD Mortality



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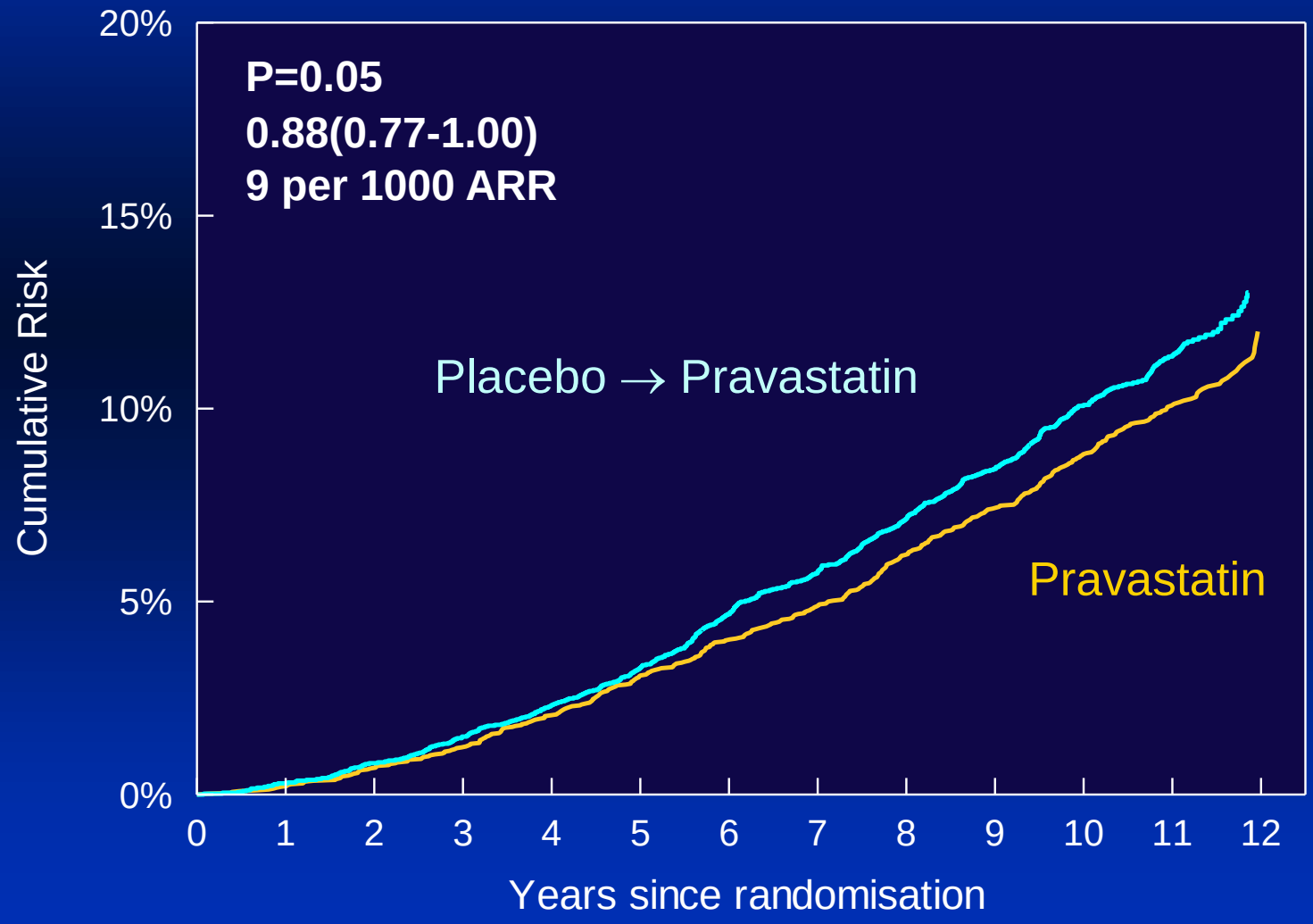
Non-CVD Mortality



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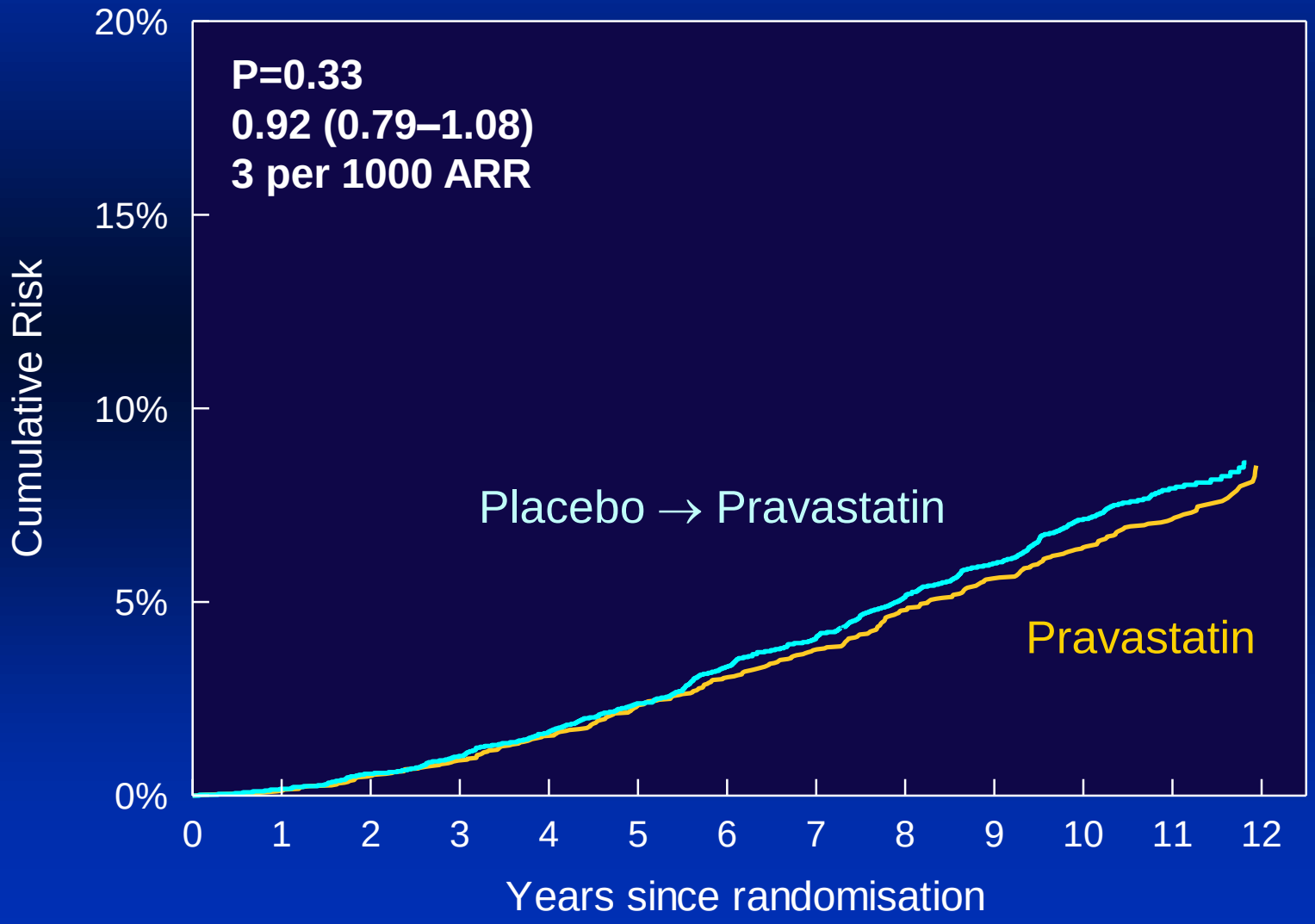
Cancer Mortality



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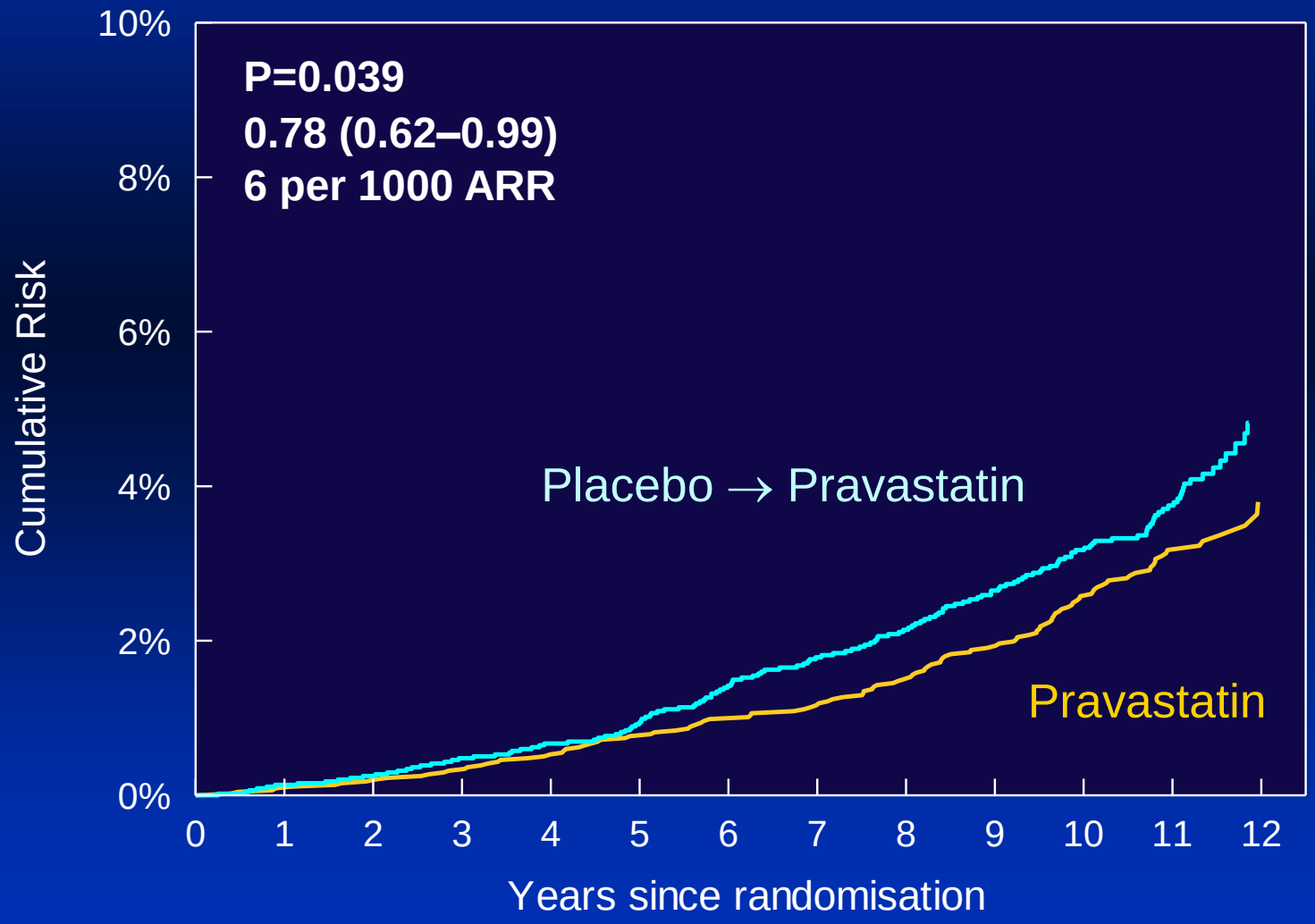
Other Mortality
Non-CVD Non-Cancer



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Cause-Specific Mortality

Cause of death	Placebo gp (%)	Pravastatin gp (%)	HR (95% CI)	P-value
Coronary	15.1	13.5	0.87 (0.78-0.97)	0.01
Other CVD	3.1	2.4	0.74 (0.57-0.95)	0.02
Stroke	1.7	1.3	0.76 (0.50-1.06)	0.11
Other Vascular	1.4	1.0	0.71 (0.49-1.04)	0.08
Total CVD	18.3	15.9	0.85 (0.76-0.93)	0.001
Cancer	7.0	6.7	0.92 (0.79-1.08)	0.33
Other Non-CVD	3.4	2.8	0.78 (0.62-0.99)	0.04
Total Non-CVD	10.4	9.5	0.88 (0.77-1.00)	0.05
Total	28.7	25.4	0.86 (0.79-0.93)	<0.001

Cause-Specific Mortality
Adjusted for CHD events*

Cause of death	HR (95% CI)	P-value	HR (95% CI)	P-value
	Unadjusted Analysis		Adjusted analysis	
Coronary	0.87 (0.78-0.97)	0.01	0.84 (0.75-0.93)	0.001
Other CVD	0.74 (0.57-0.95)	0.02	0.71 (0.55-0.92)	0.008
Total CVD	0.85 (0.76-0.93)	0.001	0.81 (0.74-0.90)	<0.001
Non-CHD	0.85 (0.75-0.95)	0.004	0.82 (0.73-0.92)	0.001
Non-CVD	0.88 (0.77-1.00)	0.05	0.85 (0.74-0.97)	0.014

* Adjusted for on-study CHD events in Cox regression analysis

LIPID Trial Extension

Discussion / Conclusions

- **Clear evidence of sustained survival benefit from initial pravastatin treatment for 5 years compared with delayed cholesterol lowering treatment**
- **No evidence of harm in terms of an increase in cancer deaths or deaths from any other cause**
- **These long term outcomes confirm findings previously reported in long term follow-up of 4S trial in a broader patient group with prior CHD**

LIPID Trial Extension

Discussion / Conclusions

- New evidence of a significant reduction in non-CVD death of uncertain significance
  - Possible chance finding
  - Not explained by a reduction in earlier non-fatal events
  - Possible misclassification of cause of death
  - Possible reduced CVD complications in patients dying from non-CVD causes
  - Not attributed to a specific non-CVD cause

LIPID Trial Extension

Discussion / Conclusions

- **Clear evidence of a significant reduction in vascular deaths not seen in CTT overview of statin trials (non-significant trend)**
- **Long-term follow-up of LIPID trial confirms long-term benefits of statin therapy and provides additional reassurance on safety**
- **Further follow-up and assessment of cancer incidence of LIPID trial in progress**

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Change in Total Cholesterol

Mean with 95% confidence intervals