

# Aspirin in CKD and in Diabetes

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# Questions

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- 1. Does aspirin reduce CVD outcomes in CKD and DM ?**
- 2. Does aspirin interferes with CKD progression ?**

- Aspirin has been shown to reduce stroke and myocardial infarction when given to patients with previous cardiovascular events (**secondary prevention**), but its effects in subjects without a history of cardiovascular disease (**primary prevention**), are controversial.

# Aspirin in Secondary Prevention Trials

16 secondary prevention trials

Major coronary event ( $\chi^2_1=0.6$ ;  $p=0.4$ )

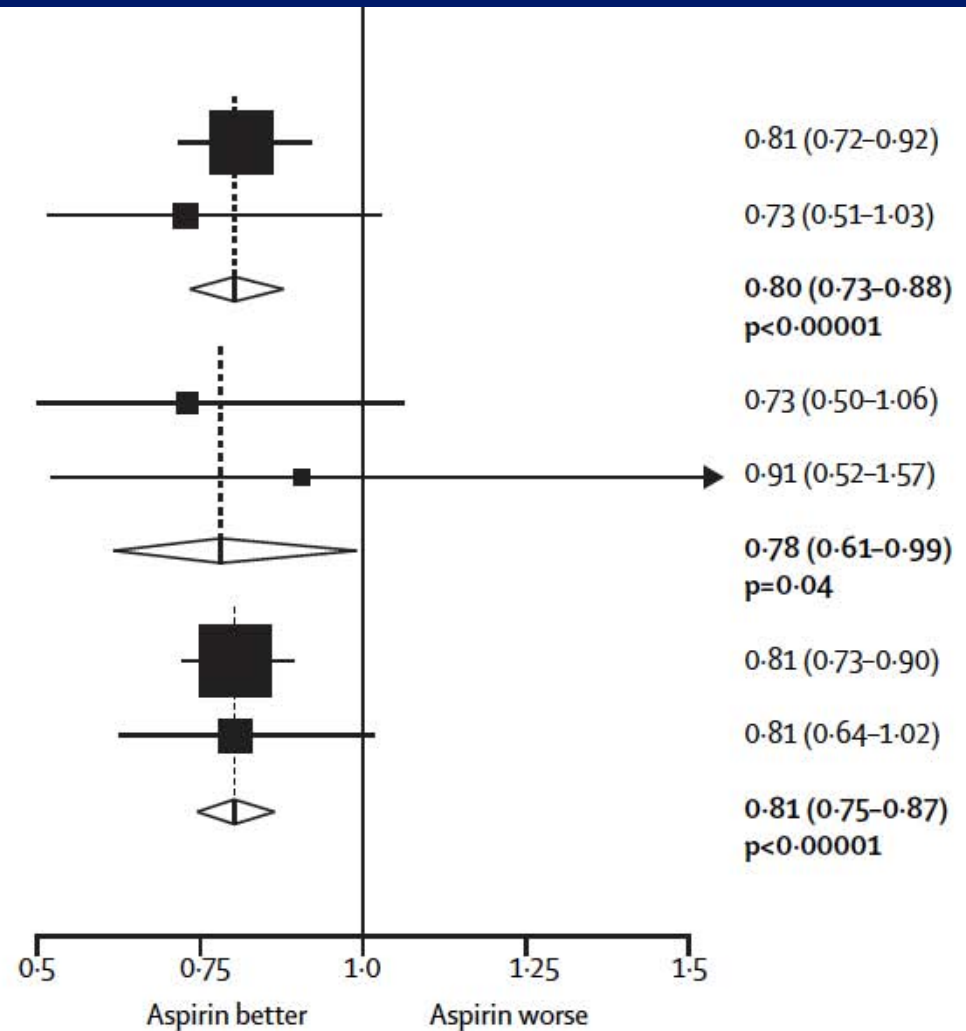
Male	880 (4.70)	1057 (5.79)
Female	115 (2.59)	157 (3.36)
Total	995 (4.30)	1214 (5.30)

Ischaemic stroke ( $\chi^2_1=0.7$ ;  $p=0.4$ )

Male	95 (0.51)	123 (0.67)
Female	45 (1.04)	53 (1.17)
Total	140 (0.61)	176 (0.77)

Serious vascular event\* ( $\chi^2_1=0.0$ ;  $p=1.0$ )

Male	1255 (6.88)	1487 (8.45)
Female	250 (5.88)	314 (7.14)
Total	1505 (6.69)	1801 (8.19)



# Primary Cardiovascular Prevention Trials with Aspirin

<b>Trial</b>	<b>Year</b>	<b>Duration</b>	<b>N</b>	<b>Males</b>	<b>Dose</b>
<b>1. British Doctors Study</b>	<b>1988</b>	<b>5.6</b>	<b>5139</b>	<b>100%</b>	<b>500 mg/d</b>
<b>2. US Physicians</b>	<b>1988</b>	<b>5.0</b>	<b>22071</b>	<b>100%</b>	<b>325 mg/2d</b>
<b>3. Thrombosis Prevention Trial</b>	<b>1998</b>	<b>6.7</b>	<b>5085</b>	<b>100%</b>	<b>75 mg/d</b>
<b>4. Hypertension Optimal Treatment</b>	<b>1998</b>	<b>3.8</b>	<b>18790</b>	<b>53%</b>	<b>75 mg/d</b>
<b>5. Primary Prevention Project</b>	<b>2001</b>	<b>3.7</b>	<b>4495</b>	<b>43%</b>	<b>100 mg/d</b>
<b>6. Women's Health Study</b>	<b>2005</b>	<b>10.0</b>	<b>39876</b>	<b>0%</b>	<b>100 mg/2d</b>

# Aspirin in Primary Prevention Trials

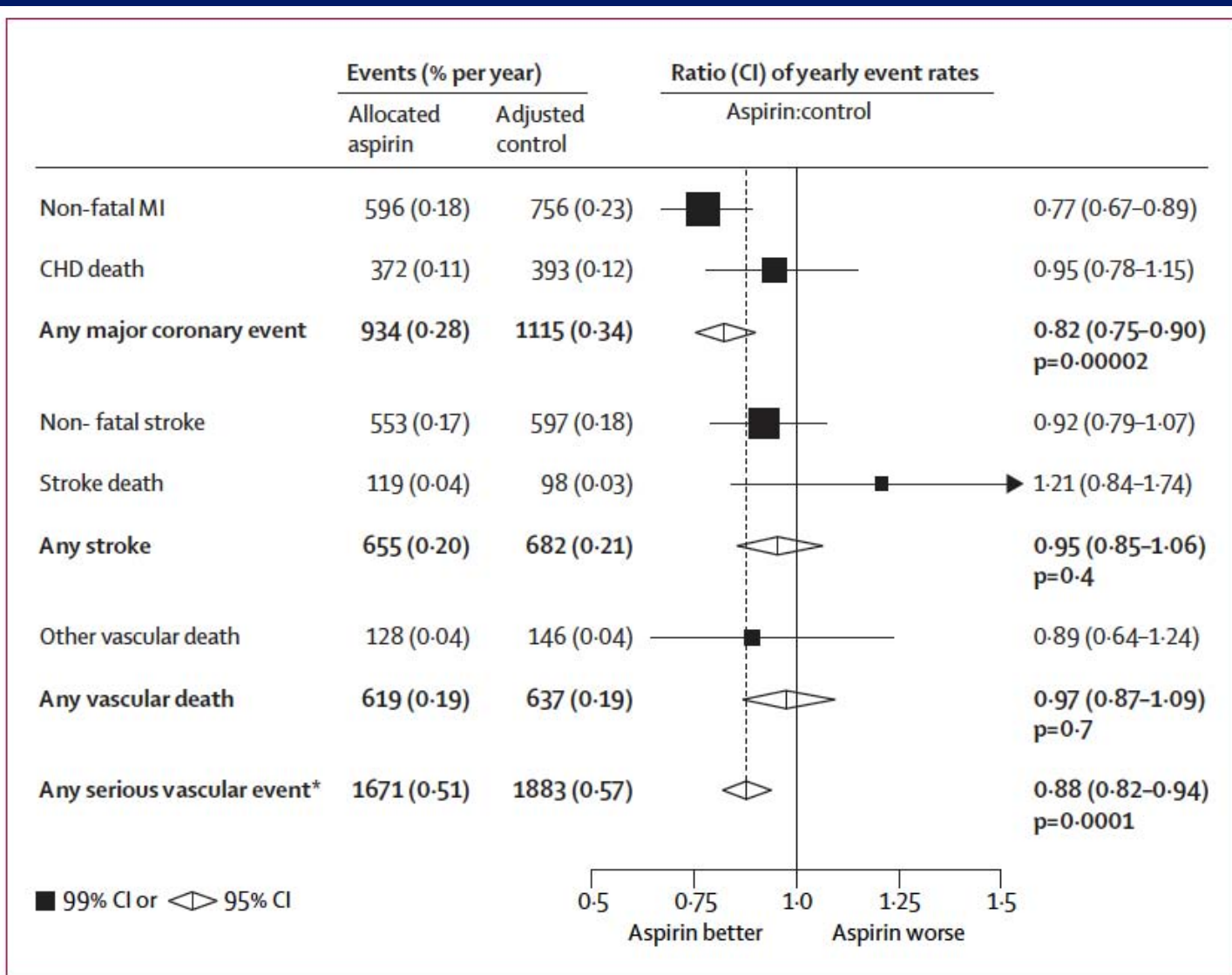


Figure 1: Serious vascular events in primary prevention trials—proportional effects of aspirin allocation

# Absolute Effects of Aspirin

- Secondary prevention** - 1.49 major CV event % for year
- Primary prevention** - 0.07 major CV event % for year

# **Benefits to Harm Relation of Aspirin**

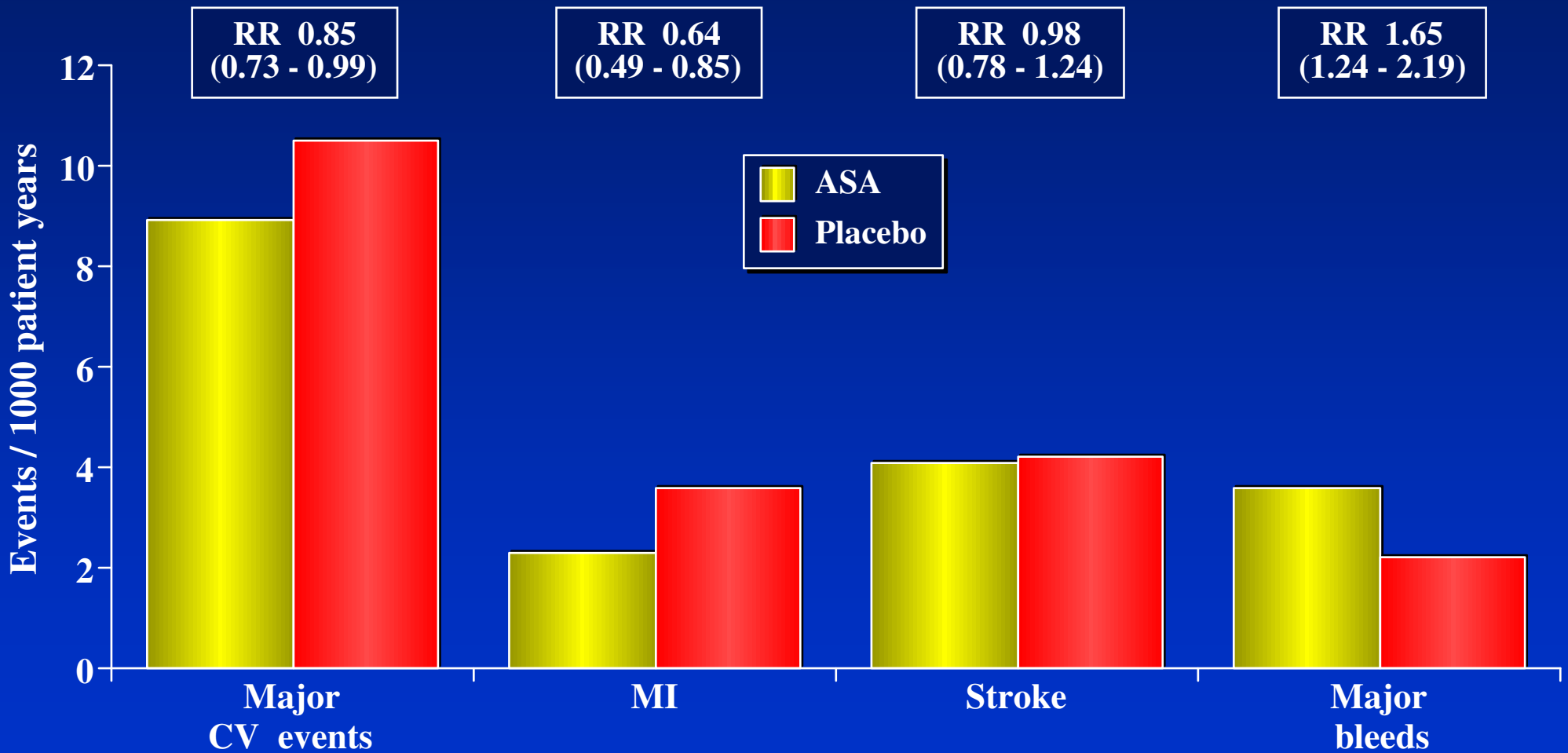


# Effects of Aspirin in Primary and Secondary Prevention Trials

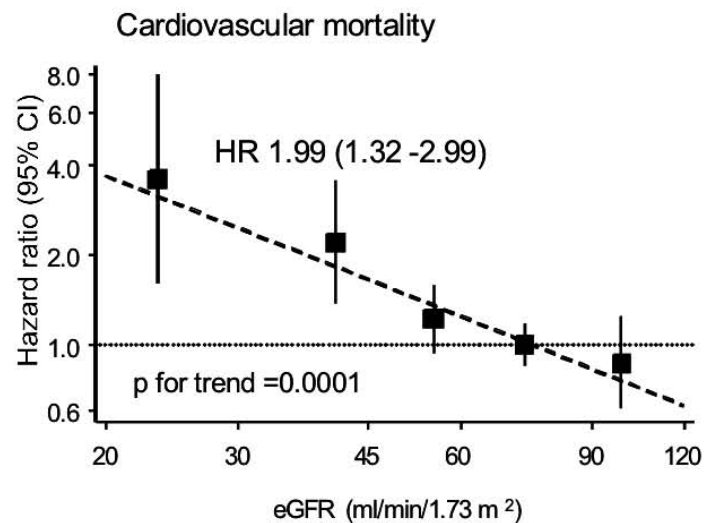
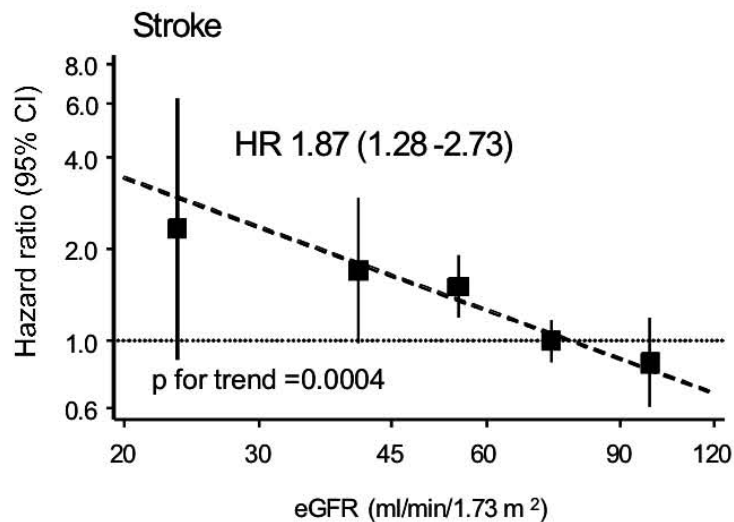
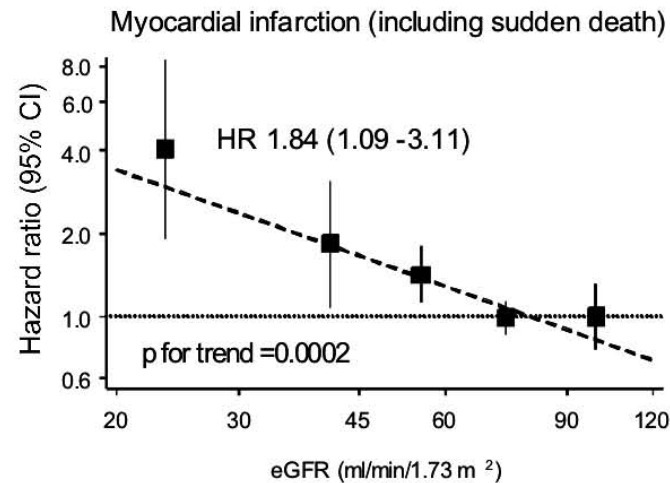
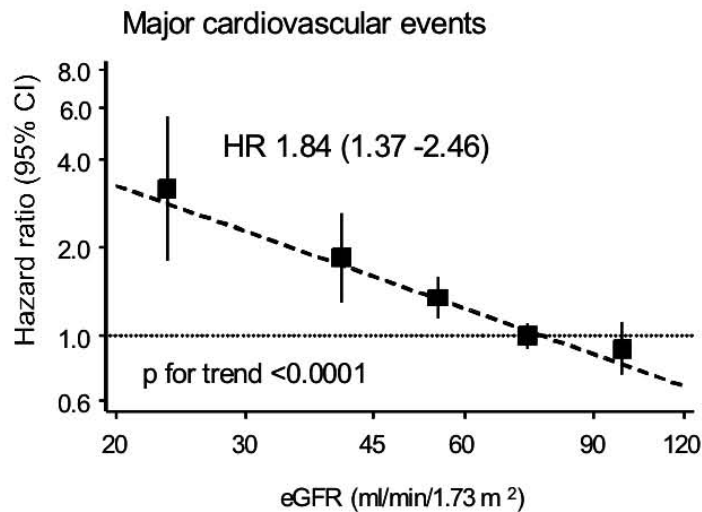
	Number of events (aspirin vs control)		Net effects	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary	Secondary
Major coronary event	934 vs 1115	995 vs 1214		
Non-fatal MI	596 vs 756	357 vs 505		
CHD mortality	372 vs 393	614 vs 696		
Stroke	655 vs 682	480 vs 580		
Haemorrhagic	116 vs 89	36 vs 19	+ 27	+ 17
Ischaemic	317 vs 367	140 vs 176		
Unknown cause	222 vs 226	304 vs 385		
Vascular death	619 vs 637	825 vs 896		
Any serious vascular event	1671 vs 1883 (0.51% vs 0.57% per year)	1505 vs 1801 (6.69% vs 8.19% per year)	- 212	- 296
Major extracranial bleed	335 vs 219	23 vs 6	+ 116	+ 17

**Among patients without previous CV events not  
all are at the same low risk**

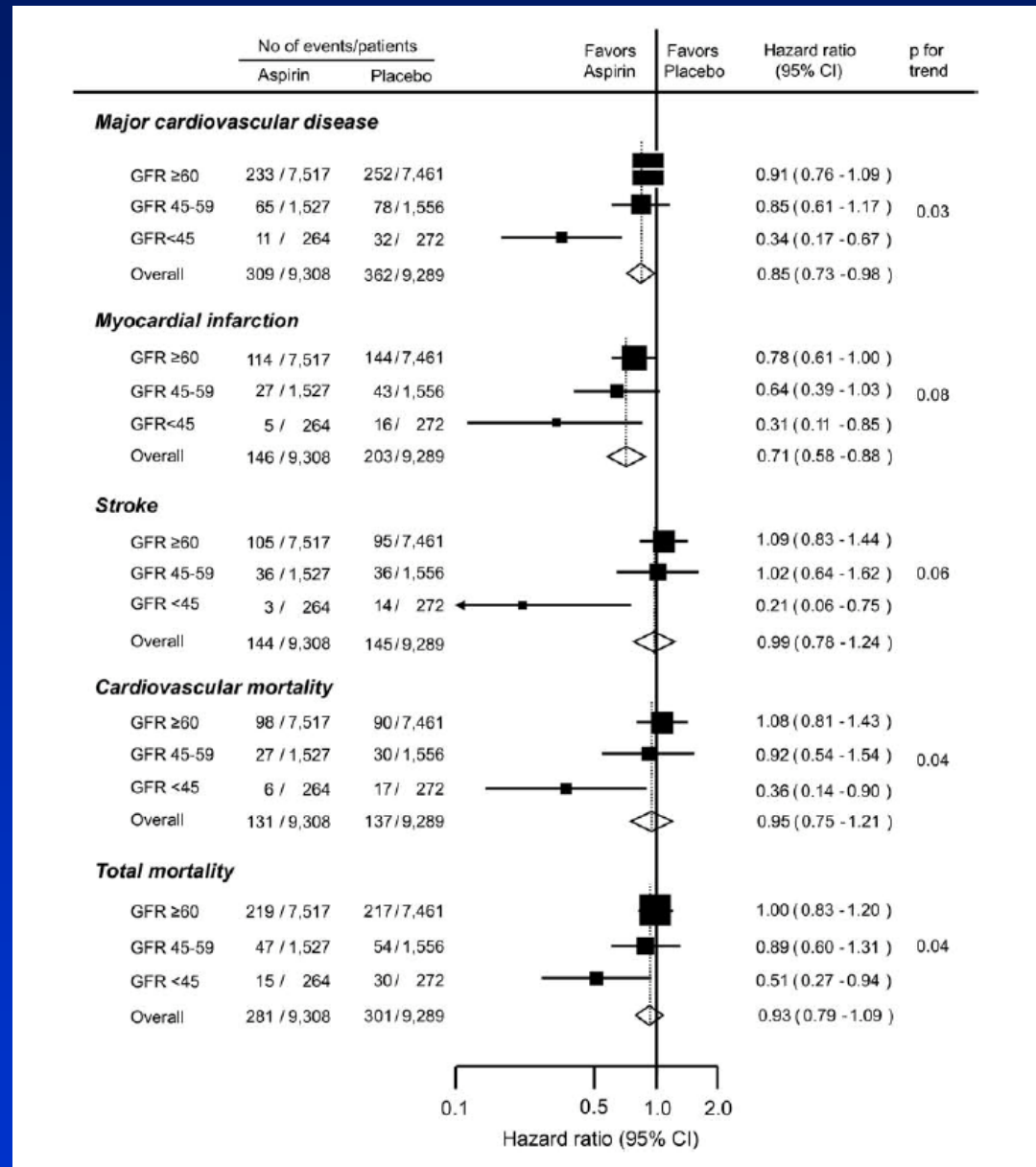
# HOT Study: Low-Dose Aspirin vs Placebo



# HOT Study : Hazard Ratios for CV Events as eGFR Declines

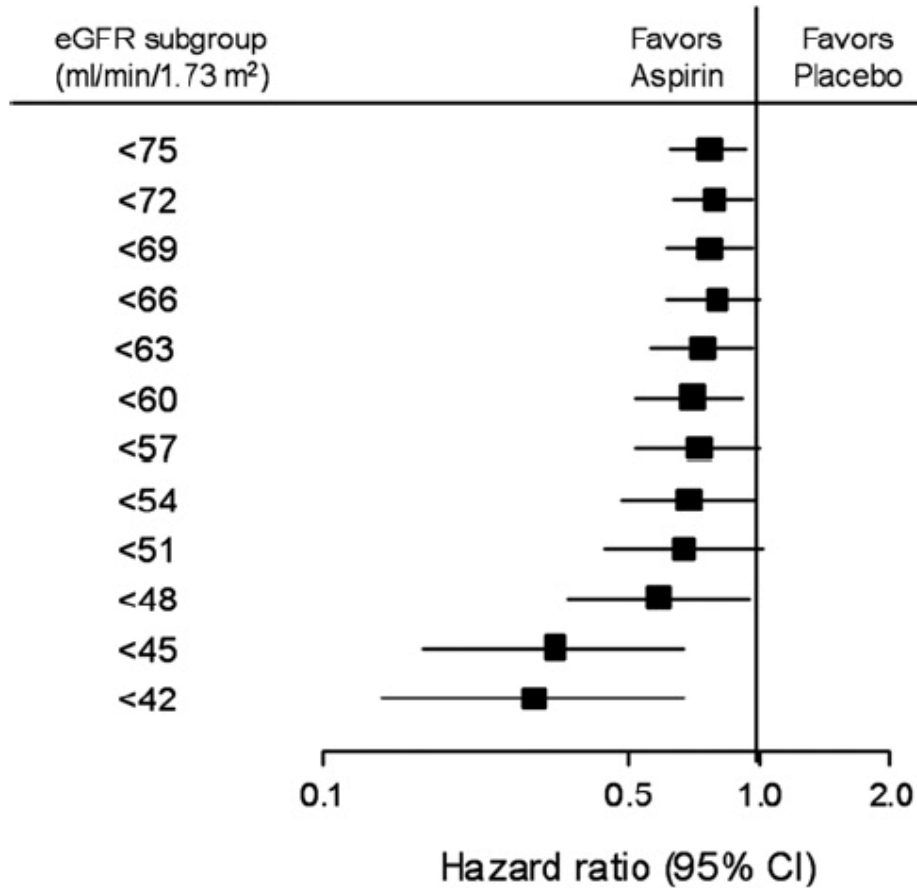


# HOT Study : Effects of Aspirin According to eGFR Category

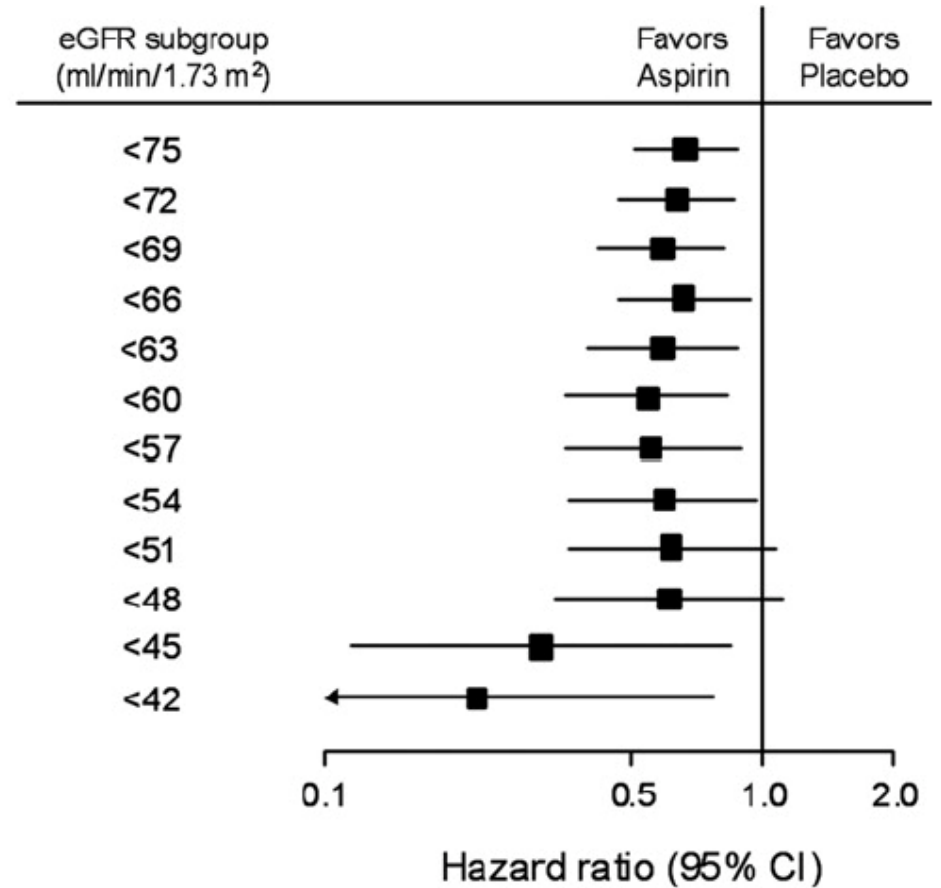


# HOT Study : Effects of Aspirin at Different eGFR Levels

## Major cardiovascular events



## Myocardial infarction



**Table 2****Events Prevented and Caused by Aspirin Therapy for Every 1,000 Patients Treated According to eGFR Category**

	eGFR, ml/min/1.73 m <sup>2</sup>			Overall
	≥60	45–59	<45	
<b>Events prevented by aspirin therapy</b>				
Major cardiovascular events	3 (–3 to 8)	8 (–7 to 22)	76 (31 to 121)	6 (0 to 11)
Myocardial infarctions	4 (0 to 8)	10 (–1 to 20)	40 (7 to 72)	6 (2 to 10)
Stroke	–1 (–5 to 2)	0 (–11 to 10)	40 (11 to 69)	0 (–3 to 4)
Cardiovascular mortality	–1 (–5 to 3)	2 (–8 to 11)	40 (6 to 74)	1 (–3 to 4)
Total mortality	0 (–5 to 5)	4 (–9 to 17)	54 (7 to 100)	2 (–3 to 7)
<b>Events caused by aspirin therapy</b>				
Major bleeding	4 (1 to 8)	4 (–2 to 10)	27 (–1 to 55)	6 (3 to 8)
Minor bleeding	4 (1 to 8)	12 (3 to 21)	12 (–8 to 31)	6 (2 to 9)
Any bleeding	8 (3 to 12)	16 (5 to 27)	39 (5 to 72)	10 (6 to 14)

Values are absolute risk change (95% confidence interval) per 1,000 patients treated for an average of 3.8 years.

eGFR = estimated glomerular filtration rate.

# Aspirin in DM Patients

<b>Study</b>		<b>n</b>	<b>OR</b>	<b>(95% CI)</b>
Meta-analysis ATC	2002	4961	0.93	
Meta-analysis ATC	2009	~ 10000	0.88	(0.67-1.15)
POPADAD	2008	1276	0.98	(0.76-1.26)
JAPAD	2008	2539	0.80	(0.58-1.10)

**Note : ASCEND and ACCEPT-D ongoing**



# Questions

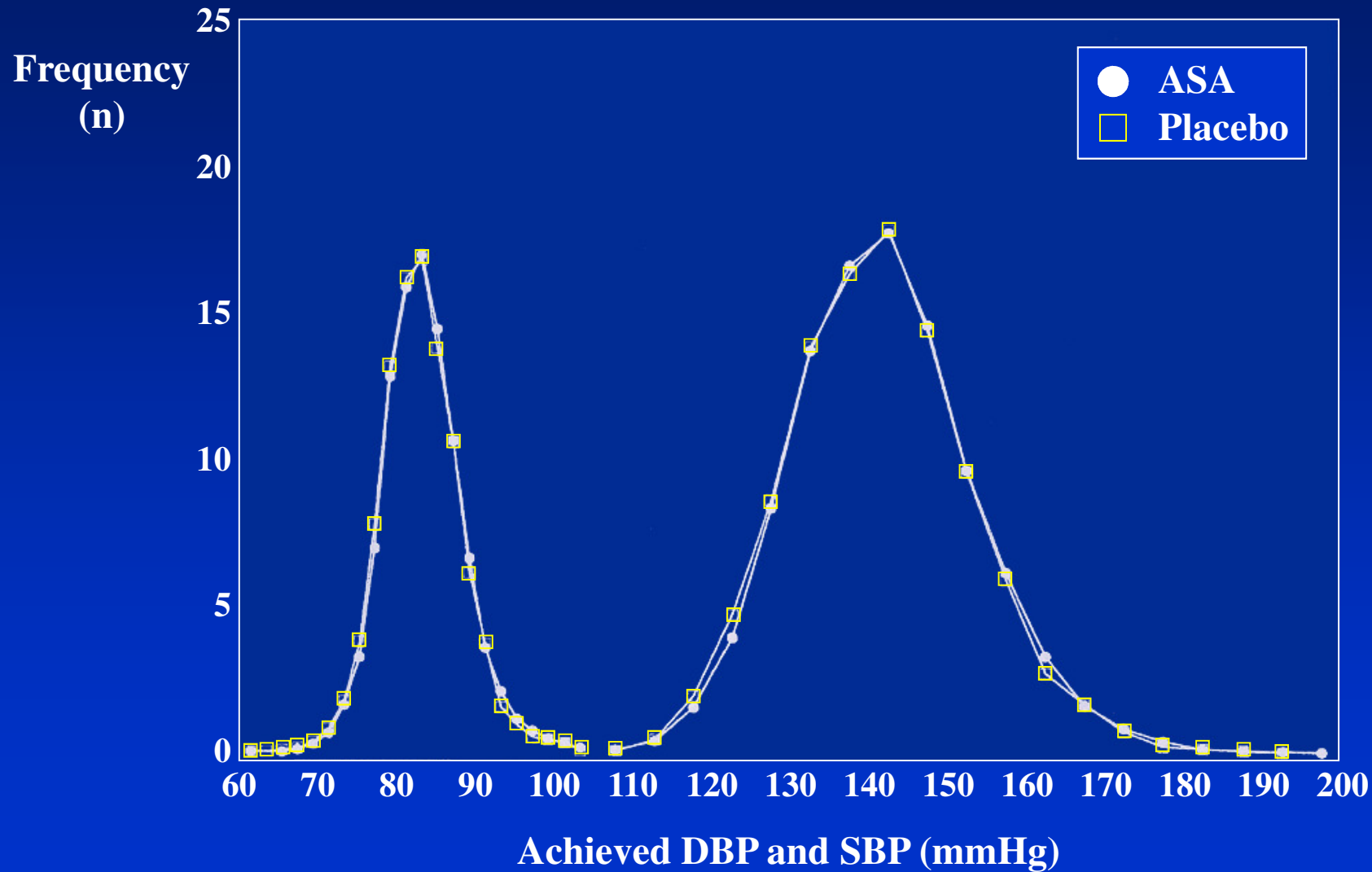
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- 1. Does aspirin reduce CVD outcomes in CKD and DM ?**
- 2. Does aspirin interferes with CKD progression ?**

# Open Questions about Aspirin in Hypertension

- 1. Does aspirin interfere with the BP lowering action of ACE-inhibitors (and other antihypertensive agents)?**
- 2. Does aspirin attenuate the cardiovascular benefits of ACE-inhibitors?**  
(suggestions from subanalyses of SOLVD and CONSENSUS II CHF trials)
- 3. Does aspirin worsen renal function in hypertensive patients?**

# Frequency Distribution of SBP and DBP Values Achieved by Treatment in the HOT Study in All Patients Randomized to Aspirin (ASA) or Placebo



## Mean Blood Pressure Values and Mean Dose Titration Step at the Final visit

Patient group	Mean SBP		Mean DBP		Mean treatment step	
	ASA	Placebo	ASA	Placebo	ASA	Placebo
High-very high risk	144.1 (12.5)	143.7 (12.3)	83.4 (5.6)	83.0 (5.5)	2.6	2.6
Medium risk	139.6 (10.4)	139.0 (10.3)	83.2 (5.1)	82.9 (5.0)	2.3	2.3
<b>Diabetes</b>	<b>146.4 (11.9)</b>	<b>145.5 (11.0)</b>	<b>83.1 (5.5)</b>	<b>82.7 (5.2)</b>	<b>2.5</b>	<b>2.6</b>
<b>No diabetes</b>	<b>141.5 (11.6)</b>	<b>141.0 (11.6)</b>	<b>83.3 (5.3)</b>	<b>83.0 (5.3)</b>	<b>2.4</b>	<b>2.4</b>
IHD	145.0 (12.0)	143.7 (11.4)	83.2 (5.2)	82.8 (5.2)	2.6	2.6
No IHD	141.3 (11.6)	140.9 (11.6)	83.3 (5.4)	83.0 (5.3)	2.4	2.4
Smoking	141.3 (11.7)	141.2 (11.5)	83.0 (5.3)	82.9 (5.0)	2.5	2.5
No smoking	142.0 (11.7)	141.4 (11.6)	83.4 (5.3)	83.0 (5.3)	2.4	2.4
S-cholesterol > 6.8 mmol/l	143.2 (11.4)	142.6 (11.8)	83.7 (5.3)	83.1 (5.2)	2.4	2.4
S-cholesterol ≤ 6.8 mmol/l	141.5 (11.8)	140.9 (11.5)	83.2 (5.3)	82.9 (5.3)	2.5	2.5
<b>S-creatinine &gt; 115 μmol/l</b>	<b>140.6 (12.9)</b>	<b>140.2 (11.9)</b>	<b>82.8 (5.4)</b>	<b>82.6 (5.3)</b>	<b>2.7</b>	<b>2.7</b>
<b>S-creatinine ≤ 115 μmol/l</b>	<b>142.0 (11.6)</b>	<b>141.4 (11.5)</b>	<b>83.3 (5.3)</b>	<b>83.0 (5.2)</b>	<b>2.4</b>	<b>2.4</b>
Men	140.8 (11.6)	140.4 (11.5)	83.5 (5.4)	83.2 (5.3)	2.6	2.6
Women	143.1 (11.7)	142.4 (11.5)	83.0 (5.2)	82.7 (5.2)	2.3	2.3
Older (≥ 65 years)	145.5 (11.6)	144.9 (11.6)	82.4 (5.1)	82.0 (5.1)	2.3	2.3
Younger (< 65 years)	140.2 (11.4)	139.7 (11.2)	83.7 (5.4)	83.4 (5.3)	2.5	2.5
SBP ≥ 180 mmHg	149.8 (11.7)	149.0 (11.6)	83.2 (5.7)	82.8 (5.5)	2.6	2.6
SBP 160 - <180 mmHg	142.0 (10.4)	141.4 (10.3)	83.3 (5.2)	83.0 (5.3)	2.4	2.4
SBP < 160 mmHg	134.8 ( 9.8)	134.4 ( 9.5)	83.4 (5.2)	83.1 (5.0)	2.4	2.4
DBP ≥ 107 mmHg	142.7 (12.3)	142.2 (12.2)	84.4 (5.8)	84.0 (5.7)	2.8	2.8
DBP 104 - <107 mmHg	141.9 (11.4)	141.4 (11.5)	83.2 (5.1)	82.8 (5.0)	2.4	2.4
DBP < 104 mmHg	141.2 (11.4)	140.6 (11.1)	82.5 (4.9)	82.3 (5.0)	2.2	2.2
All patients	141.9 (11.7)	141.3 (11.6)	83.3 (5.3)	83.0	2.4	2.4

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# Benefits of Aspirin (vs Placebo) in HOT Study Patients Treated or Never Treated with ACEI Inhibitors

Event and Treatment

Relative Risk (95% CI)

## Major CV events

ACEI never

ACEI during part of follow-up

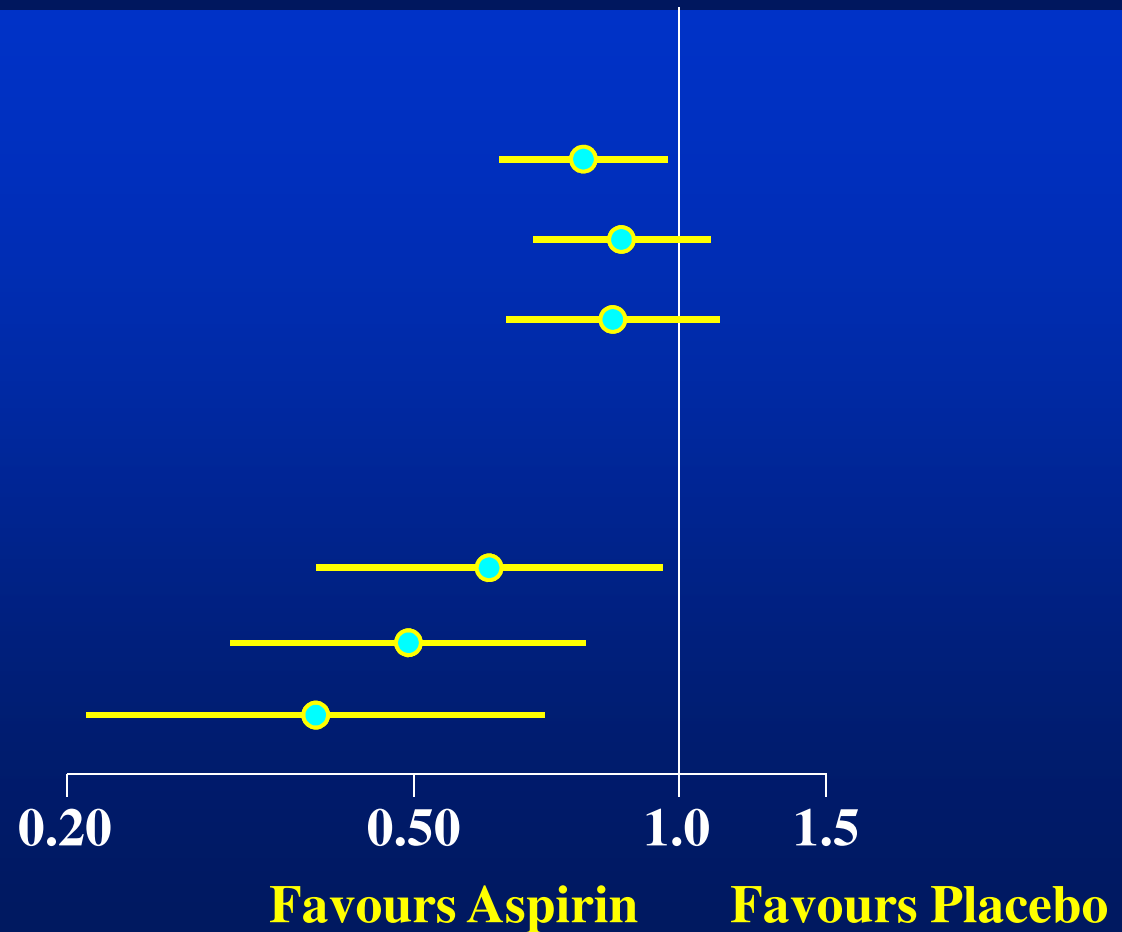
ACEI continuously during follow-up

## Myocardial infarction

ACEI never

ACEI during part of follow-up

ACEI continuously during follow-up



**Table 3****Difference in Change in Renal Function During Follow-Up Between Group Randomized to Aspirin and Group Randomized to Placebo, According to eGFR Categories**

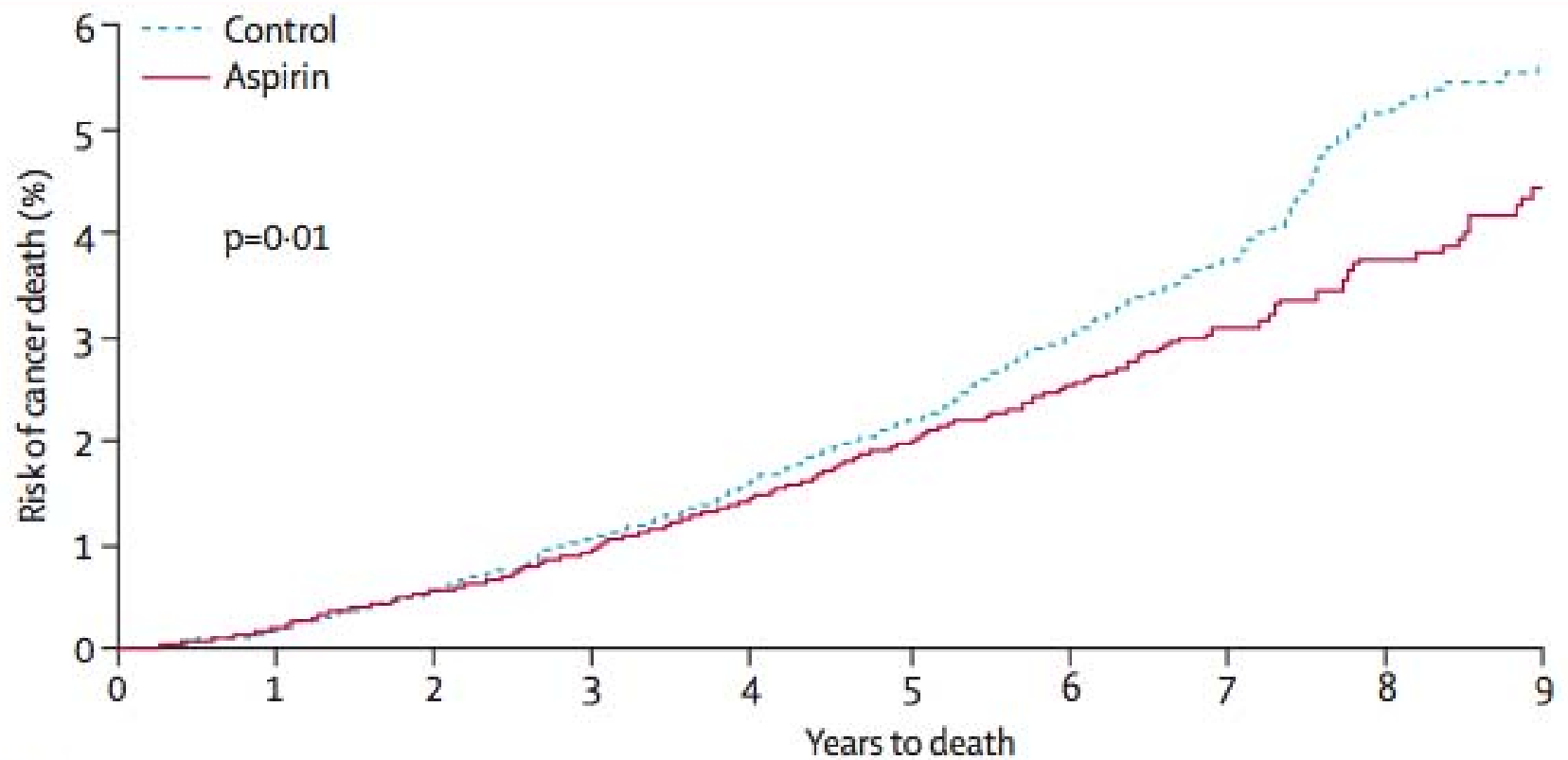
eGFR Levels at Baseline (ml/min/1.73 m <sup>2</sup> )	Annual Change in eGFR During Follow-Up for Aspirin Group Versus Placebo Group (ml/min/1.73 m <sup>2</sup> yr)	
	Mean (95% Confidence Interval)*	p Value
eGFR ≥60	-0.16 (-0.33 to 0.01)	0.06
eGFR 45-59	-0.08 (-0.37 to 0.21)	0.57
eGFR <45	0.30 (-0.74 to 1.34)	0.57
Overall	-0.15 (-0.30 to 0.00)	0.06

# European Guidelines Reappraisal

In conclusion, the prudent recommendations of the 2007 ESH/ESC guidelines can be reconfirmed: antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with previous cardiovascular events; it can also be considered in hypertensive patients without a history of cardiovascular disease with reduced renal function or with a high cardiovascular risk. In patients receiving aspirin, careful attention should always be given to the increased possibility of bleeding, particularly gastrointestinal.

**Should data increasingly suggesting a protective role of aspirin in cancer incidence and mortality modify these cautious recommendations ?**





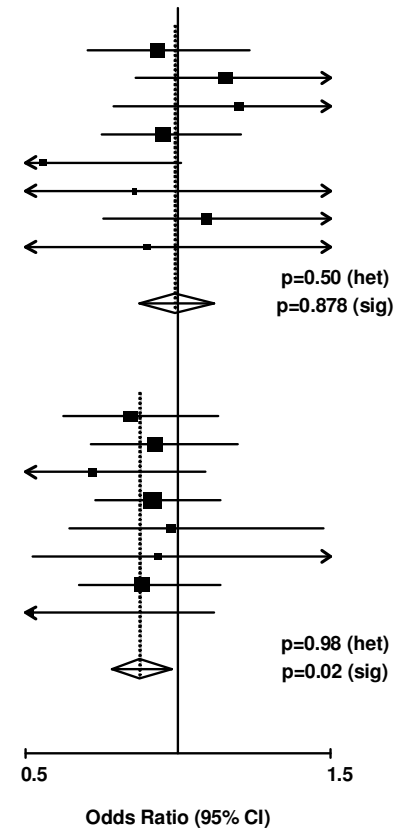
**Number at risk**

Aspirin	13 026	12 849	12 371	11 919	10 964	9 264	7 385	3 384	1 676	977
Control	10 509	10 351	10 026	9 720	8 881	7 339	5 933	3 438	1 671	969

**Figure 2: Effect of allocation to aspirin versus control on risk of death due to cancer during the trial treatment periods in a pooled analysis of the 23 535 patients in seven trials<sup>17-21,23,24</sup>**

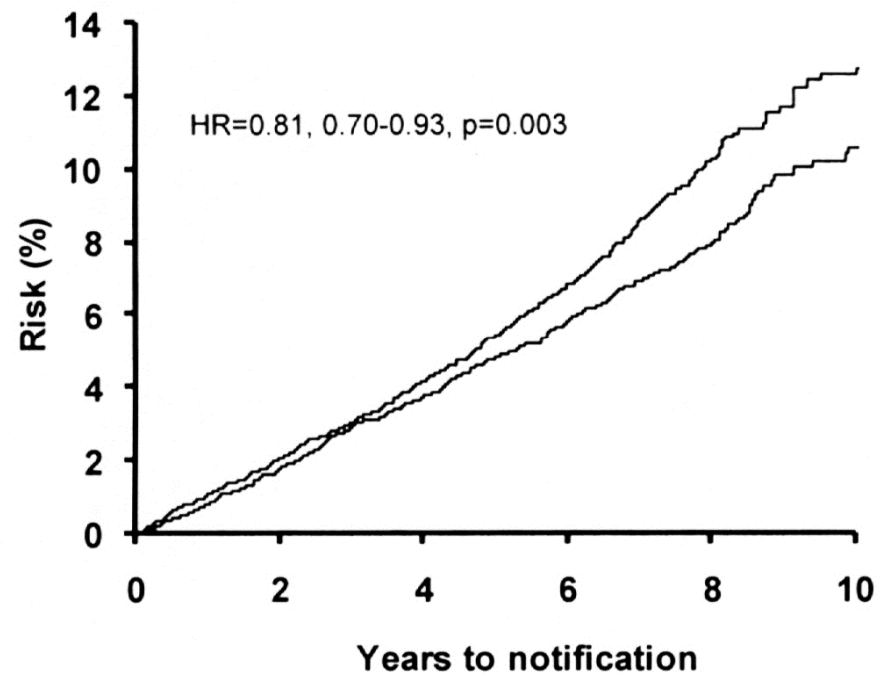
Meta-analysis of the effect of aspirin on risk of vascular death and non-vascular death during 12 randomised trials of daily aspirin versus control in predominantly primary prevention of vascular events.

	Events / Subjects		Odds Ratio	95% CI
	Aspirin	Control		
<b>Vascular death</b>				
BDAT	148 / 3429	79 / 1710	0.93	0.70-1.23
TPT	101 / 2545	88 / 2540	1.15	0.86-1.54
POPADAD	52 / 638	44 / 638	1.20	0.79-1.82
HOT	133 / 9399	140 / 9391	0.95	0.75-1.20
PPP	17 / 2226	31 / 2269	0.56	0.31-1.01
JAPD	11 / 1262	13 / 1277	0.85	0.38-1.92
AAAT	61 / 1675	56 / 1675	1.09	0.76-1.58
5 small trials	19 / 843	21 / 839	0.90	0.48-1.68
<b>Total</b>	<b>542 / 22017</b>	<b>472 / 20339</b>	<b>0.99</b>	<b>0.87-1.12</b>
Deaths adjusted for randomisation ratio	542	551		
<b>Non-vascular death</b>				
BDAT	122 / 3429	72 / 1710	0.84	0.62-1.13
TPT	115 / 2545	124 / 2540	0.92	0.71-1.20
POPADAD	42 / 638	57 / 638	0.72	0.47-1.09
HOT	151 / 9399	165 / 9391	0.91	0.73-1.14
PPP	45 / 2226	47 / 2269	0.98	0.65-1.47
JAPD	23 / 1262	25 / 1277	0.93	0.52-1.65
AAAT	115 / 1675	130 / 1675	0.88	0.68-1.14
5 small trials	10 / 843	18 / 839	0.55	0.25-1.19
<b>Total</b>	<b>623 / 22017</b>	<b>638 / 20339</b>	<b>0.88</b>	<b>0.78-0.98</b>
Deaths adjusted for randomisation ratio	623	710		



Pooled analysis of effect of allocation to aspirin on incidence of cancer during six randomised trials of daily low-dose (75-100mg daily) aspirin versus placebo in primary prevention of vascular events<sup>16-21</sup> in all patients (A) and in all patients with scheduled duration of trial treatment of at least 5 years (B).

B. Patients with scheduled duration of trial treatment  $\geq 5$  years



Aspirin	4668	4549	4394	3761	1592	504
Control	4664	4532	4383	3761	1568	493

Summary of meta-analyses of the effect of aspirin on risks of incident cancer, major vascular events, and major extracranial bleeds during six randomised trials of daily low-dose aspirin versus control in primary prevention of vascular events<sup>16-21</sup> stratified by period of trial follow-up (0-2.9; 3-4.9; <sup>3</sup> 5 years).

