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Supplementary webappendix

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Supplement to: Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373:** 1849–60.

Webappendix for "Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials" Lancet 2009; 373: 1849-60

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* For some secondary prevention trials, the numbers of events have been updated slightly from those published previously (BMJ 1994; BMJ 2002). Specifically, the current report includes an additional 5 vs 8 (aspirin vs adjusted control) non-fatal myocardial infarctions, 13 vs 18 non-fatal strokes, 16 vs 26 serious vascular events (AICLA [0 vs 2], AMIS [3 vs 2], Canadian Co-op [1 vs 0] and UKTIA [12 vs 11x2]), and 2 vs 1 major extracranial bleeds (Britton [0 vs 1] and UKTIA [2 vs 0]). (Two aspirin-allocated patients had both a non-fatal MI and a non-fatal stroke.) These events were previously omitted from the 2002 report because an earlier definition (BMJ 1994) of a non-fatal event was applied in error. None of these minor changes affect the conclusions of previous reports.

Web Table 1: Baseline characteristics of the primary and secondary prevention trials

	Number of participants	Male	Age, years	Blood pressure (SBP/DBP), mmHg	Total cholesterol, mmol/L	Current smokers	Body mass index, kg/m ²	Diabetes mellitus	Hypertension	Any vascular disease
Primary prevention trials										
British Doctors Study	5139	100%	61 (7)	136 (17) / 83 (10)	-	31%	24.4 (2.5)	2%	10%	8%
US Physicians Health Study	22071	100%	53 (10)	126 (12) / 79 (8)	5.5 (1.2)	11%	24.9 (3.0)	2%	24%	1%
Thrombosis Prevention Trial	5085	100%	57 (7)	139 (18) / 83 (10)	6.4 (1.0)	41%	27.4 (3.6)	2%	16%	<1%
Hypertension Optimal Treatment Trial	18790	53%	61 (7)	170 (14) / 105 (3)	6.0 (1.1)	16%	28.4 (4.7)	8%	100%	3%
Primary Prevention Project	4495	43%	64 (8)	145 (16) / 85 (8)	6.1 (1.2)	15%	27.6 (4.7)	17%	68%	4%
Women's Health Study	39876	0%	54 (7)	124 (13) / 77 (8)*	5.2 (1.0)*	13%	26.0 (5.1)	3%	26%	<1%
Subtotal: 6 trials	95456	46%	56 (9)	136 (22) / 84 (13)	5.6 (1.1)	16%	26.3 (4.6)	4%	41%	2%
Secondary prevention post-MI trials										
Cardiff-I	1239	100%	55 (8)	-	-	-	-	-	-	100%
Cardiff-II	1725	85%	56 (10)	143 (29) / 90 (18)	-	-	-	5%	-	100%
PARIS-I	1216	87%	56 (8)	132 (18) / 83 (9)	-	-	-	10%	-	100%
AMIS	4524	89%	55 (8)	128 (16) / 80 (9)	-	-	-	11%	-	100%
CDP-A	1529	100%	56 (7)	132 (18) / 81 (10)	-	-	-	14%	-	100%
Gamis	626	78%	59 (7)	-	-	-	-	20%	19%	100%
Subtotal: 6 trials	10859	90%	56 (8)	132 (21) / 82 (12)	-	-	-	11%	19%	100%
Secondary prevention post TIA / stroke trials										
AITIA	319	70%	58 (14)	-	-	-	-	-	-	100%
UK-TIA	2435	73%	60 (9)	151 (25) / 88 (12)	-	-	-	4%	27%	100%
Reuther	60	65%	58 (10)	-	-	-	-	17%	50%	100%
CA Co-op	283	67%	61 (9)	146 (23) / 85 (11)	-	-	-	8%	37%	100%
Toulouse TIA	303	86%	63 (9)	-	-	-	-	-	-	100%
AICLA	402	68%	64 (10)	150 (21) / 90 (12)	-	-	-	23%	64%	100%
Danish Co-op	203	73%	59 (9)	138 (22) / 84 (12)	-	-	-	6%	-	100%
Britton	505	62%	68 (10)	-	-	-	-	17%	46%	100%
Danish Low Dose	301	65%	59 (8)	149 (23) / 85 (12)	-	-	-	7%	-	100%
SALT	1359	66%	67 (7)	-	-	-	-	13%	47%	100%
Subtotal: 10 trials	6170	70%	62 (10)	149 (24) / 87 (12)		-	-	9%	38%	100%

- = Not available, MI = myocardial infarction, TIA = transient ischaemic attack. * In the Women's Health Study, individual blood pressure and cholesterol levels were imputed based on categories provided by the investigators (in 10 mmHg ranges for SBP, 5 mmHg ranges for DBP and 10 mg/dL [~0.25 mmol/L] ranges for cholesterol). Continuous data are presented as mean (SD). Percentages are based on the proportions among those participants with data available. Some patients in the primary prevention trials were found, after randomisation, to have had vascular disease (i.e. prior history of myocardial infarction, cerebrovascular disease, angina pectoris, peripheral arterial disease or heart failure).

							Mortality							
Trial	Serious vascular event	Major coronary events	Non fatal myocardial infarction	Any stroke	Stroke of unknown cause	CHD	Stroke	Other vascular	Any known vascular	Non vascular	Unknown cause	All causes	Major extracranial bleed	Fatal bleed
Primary prevention trials														
British Doctors Study (2:1†)	434	267	149	133	87	136	42	46	224	194	3	421	30	4
US Physicians Health Study	686	459	342	219	10	127	22	28	177	205	62	444	78	2
Thrombosis Prevention Trial	468	353	233	100	22	141	25	28	194	197	48	439	33	5
Hypertension Optimal Treatment Trial	712	345	182	317	291	170‡	51	63	284	305	0	589	176	10
Primary Prevention Project	112	46	36	39	6	10	7	35	52	76	12	140	9	4
Women's Health Study	999	493	365	487	4	134	58	55	247	850	154	1251	218	1
Subtotal: 6 trials	3411	1963	1307	1295	420	718	205	255	1178	1827	279	3284	544	26
Secondary prevention post-MI trials														
Cardiff-I	133	129	25	1	0	104	1	2	107	6	1	114	0	0
Cardiff-II	316	306	96	10	7	206	10	4	220	10	0	230	0	0
PARIS-I (2:1†)	212	195	84	20	18	110	5	3	118	19	0	137	0	0
AMIS	795	707	317	101	97	388	10	10	408	52	5	465	0	0
CDP-A	178	146	59	25	24	85	5	14	104	6	0	110	0	0
Gamis	78	61	26	2	0	35	2	7	44	7	8	59	0	0
Subtotal: 6 trials	1712	1544	607	159	146	928	33	40	1001	100	14	1115	0	0
Secondary prevention post TIA / stroke trial	s													
AITIA	61	17	6	40	39	7	6	10	23	3	0	26	3	0
UK-TIA (2:1†)	558	245	77	320	224	163	55	35	253	77	13	343	15	2
Reuther	7	1	0	6	4	1	2	0	3	0	0	3	1	0
CA Co-op	63	16	4	43	43	12	9	5	26	5	0	31	0	0
Toulouse TIA	27	7	2	16	16	5	5	4	14	11	0	25	0	0
AICLA	79	15	11	53	49	4	6	5	15	12	10	37	0	0
Danish Co-op	50	20	10	32	29	10	4	1	15	5	1	21	0	0
Britton	114	42	21	63	15	15	20	22	57	14	0	71	5	0
Danish Low Dose	42	16	2	21	20	14	1	3	18	4	2	24	0	0
SALT	307	119	53	180	11	54	32	34	120	35	5	160	4	0
Subtotal: 10 trials	1308	498	186	774	450	285	140	119	544	166	31	741	28	2

† Allocation ratio 2:1; in tables or figures where adjusted numbers of controls are given, the number of events in the control group of this study is doubled. ‡Includes 149 sudden deaths.

Web Table 3: Rate ratios associated with risk factors for selected outcomes among people with no known vascular disease in primary prevention trials

Variable	Serious vascular event	Non fatal MI	CHD death	Major coronary event	Probably ischaemic stroke	Haemorrhagic stroke	Any stroke	Non fatal MI or probably ischaemic stroke	Major GI or other extracranial bleed	Non fatal major GI or other extracranial bleed
Age, per decade	2.08 (1.99,2.17)	1.63 (1.52,1.75)	2.37 (2.15,2.62)	1.84 (1.74,1.95)	2.46 (2.27,2.65)	1.59 (1.33,1.90)	2.29 (2.13,2.46)	1.91 (1.81,2.02)	2.15 (1.93,2.39)	2.10 (1.88,2.34)
Male gender *	1.86 (1.60,2.16)	2.58 (1.91,3.49)	2.21 (1.58,3.07)	2.43 (1.94,3.04)	1.44 (1.14,1.82)	1.11 (0.52,2.34)	1.39 (1.12,1.74)	1.85 (1.52,2.24)	1.99 (1.45,2.73)	1.98 (1.42,2.75)
Diabetes	2.43 (2.16,2.74)	2.80 (2.31,3.40)	2.42 (1.86,3.15)	2.66 (2.28,3.12)	2.06 (1.67,2.54)	1.74 (0.95,3.17)	2.02 (1.66,2.46)	2.39 (2.06,2.78)	1.55 (1.13,2.14)	1.55 (1.11,2.16)
Current smoker	2.03 (1.87,2.20)	1.96 (1.72,2.23)	2.17 (1.83,2.58)	2.05 (1.85,2.28)	2.00 (1.72,2.31)	2.18 (1.57,3.02)	2.02 (1.77,2.31)	1.97 (1.78,2.17)	1.56 (1.25,1.94)	1.50 (1.20,1.88)
Mean blood pressure	1.79 (1.67,1.92)	1.59 (1.42,1.77)	2.10 (1.83,2.42)	1.73 (1.59,1.89)	2.00 (1.77,2.26)	2.18 (1.65,2.87)	2.02 (1.81,2.26)	1.76 (1.62,1.92)	1.32 (1.09,1.58)	1.32 (1.09,1.60)
Cholesterol	1.10 (1.06,1.14)	1.23 (1.16,1.31)	1.09 (1.00,1.18)	1.18 (1.12,1.24)	1.02 (0.95,1.09)	0.90 (0.77,1.07)	1.00 (0.94,1.06)	1.13 (1.08,1.19)	0.99 (0.90,1.08)	0.98 (0.89,1.08)
BMI (per 5 kg/m²)	1.07 (1.02,1.11)	1.10 (1.03,1.18)	1.07 (0.97,1.18)	1.09 (1.03,1.15)	1.06 (0.98,1.14)	0.85 (0.71,1.02)	1.02 (0.96,1.09)	1.08 (1.03,1.14)	1.24 (1.13,1.35)	1.22 (1.11,1.34)

* The relevance of male gender can be assessed only in the two trials that included both men and women, so the confidence intervals for its relevance are wide, particularly for stroke.

GI = Gastrointestinal.

Total cholesterol was not available in the British Doctors Study.

Excluding the 2% of participants with known history of vascular disease.

Rate ratios for cholesterol are per 1mmol/L and for mean blood pressure per 20mmHg.

Web Figure 1: MAJOR CORONARY EVENTS in primary prevention trials - subgroup analyses Symbols and conventions as in text - figure 2

Subgroup	Allocated aspirin	Adjusted control	Ratio of annual event rates (& Aspirin : Control	CI)
Age; years (χ_1^2 =	0-1; P = 0-8)			
< 65	592	716	0.81 (0	.70
65+	(0·21%/y) 342	(U·25%/y) 399	0.83 (0	9.68
- · · · · · -	(0.67%/y)	(0·79%/y)		,.00
Gender ($\chi_1^2 = 4.7$; P = 0·03)			
Male	635 (0-57%/y)	801 (0∙72%/y)		ŀ67
Female	299 (0·14%/v)	314 (0·14%/v)	0.95 (0).77
Prior vascular d	isease ($\chi_1^2 = 0.2$	2; P = 0-6)		
Yes	66	81 ←	0.76 (0	.48
No	(1.63%/y) 868 (0.26%/y)	(1.99%/y) 1034 (0.32%/y)	0·83 (0	.73
Prior diabetes (χ	ζ ² ₁ = 0·8; Ρ = 0·4	ł)		
Yes	101 (0•93%/v)	107 (1.01%/v)	0.92 (0	ŀ64
No	(0.00/0/y) 775 (0.24%/y)	944 (0·30%/y)).71
Prior hypertensi	ion (χ ₁ ² = 0·1; Ρ	= 0.7)		
Yes	456 (0·42%/v)	552 (0·51%/v)		.69
No	478 (0·21%/y)	561 (0·25%/y)		0.71
Current smoker	$(\chi_1^2 = 3.6; P = 0)$	0.06)		
Yes	303 (0.60%/v)	327 (0.64%/y)	0.94 (0	.76
No	630 (0·22%/y)	785 (0·28%/y)	0.78 (0	.68
SBP; mm Hg (tre	end χ_1^2 = 0.2; P	= 0.7)		
< 140	396 (0·17%/v)	480 (0∙21%/v)	0.82 (0	.69
140 – 159	256 (0.49%/y)	307 (0.59%/y)	0.80 (0	.64
160+	229 (0.65%/y)	259 (0.75%/y)		.68
DBP; mm Hg (tre	end $\chi_1^2 = 0.1; P$	= 0-8)		
< 80	259 (0.14% /v)	303 (0.17%/y)	0.83 (0	.67
80 – 89	284 (0.419/ M)	323 (0.47%/y)	0.85 (0	.68
90+	(0.41%) 338 (0.50%/y)	(0.47%/y) 420 (0.62%/y)	0.81 (0	.66
Cholesterol; mm	nol/l (trend χ_1^2 =	• 0•6; P = 0•))	
< 5.0	119	171 -	0·70 (0	.52
5.0 – 5.9	(0·13%/y) 183 (0.21%/y)	(0·16%/y) 223 (0·25%/y)	0.82 (0	.64
6.0+	(0·2 1 70/y) 282 (0·45%/y)	347 (0.57%/y)	0.80 (0	.65
BMI; kg/m² (tren	d χ_1^2 = 0.0; P =	1-0)		
< 25.0	364 (0.23%/\/)	435 (0.28%/y)		.67
25•0 – 29•9	405 (0.35%/y)	480 (0.41%/v)	0.84 (0	.71
30.0+	(0.33%/y) 149	187	0.79 (0	.60
Predicted 5-yea	(0·27%/y) r CHD risk*; %	(0.34%) (trend $\chi_1^2 =$	0-0; P = 1-0)	
< 2.5	383	438	0.86 (0	0.72
2·5, < 5	(0·14%/y) 226	(0·16%/y) 285	0·76 (0	.60
5, < 10	(0·62%/y) 188	(0·79%/y) 241	0.78 (0	.60
10+	(1∙14%/y) 71 (1∙89%/v)	(1·43%/y) 70 (1·85%/v)	1.06 (0	.67
Total	934 (0·28%/v)	1115 (0∙34%/v)	0-82 (0 P =	.75 0.0
		,		

N.B. Unknown values not plotted

Excluding patients with history of vascular disease
 Note that the regression model may have slightly overestimated risk in the high risk group.

Web Figure 2: MAJOR CORONARY EVENTS in primary prevention trials, by study Symbols and conventions as in text - figure 2

Churcher	Events (% Allocated	per annum) Adjusted	Ratio of annual ev	vent rates (& CI)
Study	aspirin	control	Aspirin :	Control
(a) Non–fatal MI (χ^2_5	= 20·4; P =	= 0-001)	i	
British Doctors' Study	104 (0∙54%/y)	90 (0∙47%/y)		1.15 (0.73 – 1.79)
US Physicians' Health Study	129 (0·24%/y)	213 ← (0·39%/y)	-	0.61 (0.46 - 0.81)
Thrombosis Prevention Trial	96 (0∙58%/y)	137 ← (0·83%/y)		0.70 (0.50 – 0.98)
Hypertension Optimal Treatment Trial	68 (0∙19%/y)	114 <i>←</i> (0·32%/y)	-	0.60 (0.41 - 0.88)
Primary Prevention Proje	ect 15 (0⋅18%/y)	21 ← (0·25%/y)		$ \xrightarrow{0.72} (0.31 - 1.71) $
Women's Health Study	184 (0∙09%/y)	181 (0∙09%/y)		1.02 (0.78 – 1.33)
(a) Subtotal	596 (0∙18%/y)	756 (0-23%/y)		0·77 (0·69 − 0·86) P < 0·00001
(b) CHD death (χ_5^2 =	3-7; P = 0-	6)		
British Doctors' Study	89	94		0.94 (0.59 - 1.50)
US Physicians' Health	(0.46%/y) 60	(0·49%/y) 67		0.90 (0.57 - 1.41)
Study Thrombosis Prevention	(0·11%/y) 78	(0·12%/y) 63		1.25 (0.81 − 1.92)
Trial Hypertension Optimal	(0∙46%/y) 80	(0∙37%/y) 90		0.89 (0.60 - 1.32)
Treatment Trial	(0·22%/y)	(0·25%/y)		0.68 (0.13 - 3.46)
Primary Prevention Proje	ect 4 (0∙05%/y)	6 ← (0·07%/y)		> 0·84 (0·54 – 1·30)
Women's Health Study	61 (0·03%/y)	73 (0·04%/y)		
(b) Subtotal	372 (0-11%/y)	393 (0-12%/y)		> 0.95 (0.82 − 1.10) P = 0.5
(a or b) Major coror	nary event	(χ ₂ ² = 12·6; Ι	P = 0·03)	
British Doctors' Study	181 (0∙95%/y)	172 (0∙90%/y)		1.05 (0.75 – 1.46) ■
US Physicians' Health Study	186 (0∙34%/y)	273 (0·50%/y)		0.68 (0.54 - 0.87)
Thrombosis Prevention Trial	160 (0∙97%/y)	193 (1·17%/y)		
Hypertension Optimal Treatment Trial	145 (0·41%/y)	200 (0∙57%/y)		0.72 (0.55 – 0.95)
Primary Prevention Proje	ect 19 (0·23%/y)	27 <i>←</i> (0·33%/y)		0.71 (0.33 – 1.52)
Women's Health Study	243 (0·12%/y)	250 (0·13%/y)	-	0.97 (0.77 – 1.23)
(a or b) Total	934 (0-28%/y)	1115 (0·34%/y)	\Leftrightarrow	0•82 (0•75 – 0•90) P = 0∙00002
-∎- 99% or <⇒ 95% cor	nfidence intervals	; L		
		0.5	0.75 1.0 Aspirin better) 1·25 1·5 Aspirin worse

Web Figure 3: STROKE SUBTYPES (first stroke only) in primary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual ev Aspirin :	vent rates (& CI) Control
(a) Haemorrhagic f	iret etroko	(v ² – 4.7: P	- 0.5)	
(a) Haemorrhagic I	II ST STIORE	(x ₅ = 4.7, F	= 0.3)	0.92 (0.27 - 3.13)
British Doctors' Study	13 (0⋅07%/y)	14 (0·07%/y)		>´
US Physicians' Health	24	12		1.95 (0.83 – 4.60)
Study	(0·04%/y)	(0·02%/y)		2.23 (0.71 – 7.07)
Thrombosis Prevention Trial †	14 (0∙08%/y)	6 (0·04%/y)		>
Hypertension Optimal Treatment Trial	12 (0∙03%/y)	14 (0∙04%/y)		0.85 (0.31 - 2.35)
Primary Prevention Proj	ect 2	2 (0.02%/b)		1.01 (0.08 – 13.32)
Waman's Haalth Study	(0·02%/y)	(0·02%/y)		1.24 (0.73 – 2.12)
women's realth Study	(0·03%/y)	(0·02%/y)		_ >
(a) Subtotal	116 (0.04%/v)	89 (0.03%/y/)	-	
	(0.04 /8/9)	(0·03 ///y)		1-32 (1-00 – 1-75 P = 0-05 adverse
(b) Ischaemic first	stroke (χ² ₌	= 6·1; P = 0·2	2)	
British Doctors' Study	- 19	14		1.33 (0.45 – 3.88)
2	(0·10%/y)	(0·07%/y)		1.11 (0.75 – 1.64)
US Physicians' Health Study	91 (0·17%/y)	82 (0·15%/y)		,
Thrombosis Prevention Trial †	23 (0·14%/y)	35 (0·21%/y)		0.67 (0.34 – 1.31)
Hypertension Optimal Treatment Trial ††				
Primary Prevention Proj	ect 14 (0·17%/y)	15 (0-18%/y)		0.95 (0.36 – 2.47)
Women's Health Study	170 (0·09%/y)	221 (0·11%/y)		0.77 (0.59 – 1.00)
(b) Subtotal	317 (0∙11%/y)	367 (0·12%/y)	${\Leftrightarrow}$	0·86 (0·74 − 1·00 P = 0·05
(a) Any first straka	including	unknown ti	$m_{2} (\alpha^{2} - 7.4; P - 1)$	0.2)
(c) Any hist stroke	, menuanny	unknown ty	$\chi_{5} = 7.4, P = 0$	1.08 (0.67 – 1.73)
British Doctors' Study	91 (0·47%/y)	84 (0•44%/y)		
US Physicians' Health	121	98		1·23 (0·87 – 1·75) —
Study	(0-22%/y)	(0·18%/y)		1.01 (0.60 - 1.69)
Trial †	0.30%/y)	0.30%/y)		
Hypertension Optimal Treatment Trial	156 (0·44%/v)	161 (0·46%/v)		0·97 (0·72 – 1·29)
Primary Prevention Proj	ect 16	23		0.71 (0.31 – 1.62)
	(0·20%/y)	(0·28%/y)	_	
Women's Health Study	221 (0∙11%/y)	266 (0·13%/y)		0.83 (0.66 – 1.05)
(c) Total	655 (0-20%/y)	682 (0∙21%/y)	\Diamond	> 0.95 (0.85 – 1.06 P = 0.4; NS
- ■ - 99% or <-> 95% co	nfidence intervals	_		

† Aspirin vs. control in the half not allocated warfarin in TPT: 4 vs. 2 haemorrhagic, 12 vs. 19 ischaemic and 5 vs. 6 unknown strokes.

 $\ensuremath{\ensuremath{\mathsf{+}}}\xspace$ Non–haemorrhagic strokes in HOT were not further subdivided.

Page 7 of Aspirin in the primary and secondary prevention of vascular disease web appendix (Lancet 2009)

Web Figure 4: PROBABLY ISCHAEMIC STROKE in primary prevention trials - subgroup analyses Symbols and conventions as in text - figure 2

Subgroup	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual event rates (& CI) Aspirin : Control
Age; years (χ^2_4 =	= 0-0; P = 0-9)		
< 65	284	313	
65+	(0·10%/y) 255	(0·11%/y) 280	
	(0·50%/y)	(0·56%/y)	
Gender ($\chi_1^2 = 8.0$); P = 0·005)		1 00 (0 05 1 1
Male	312 (0⋅28%/v)	292 (0·26%/v)	1.06 (0.85 - 1.5
Female	227 (0.10%/v)	301 (0.14%/v)	0.75 (0.60 – 0.5
Prior vascular o	lisease ($\chi_1^2 = 3$	•4; P = 0•07)	
Yes	45	30	1.38 (0.74 – 2.5
No	(1·13%/y) 494 (0·15%/y)	(0-72%/y) 563 (0-17%/y)	0.87 (0.74 – 1.0
Prior diabetes ($\chi_1^2 = 0.3; P = 0.3$	6)	
Yes	56	66 —	0.81 (0.51 – 1.5
No	(0⋅51%/y) 468	(0⋅62%/y) 513	0.90 (0.76 – 1.0
	(0·15%/y) 2	(0·16%/y)	
Prior hypertens	ion ($\chi_1^2 = 0.0$; F	P = 0·9)	
Yes	329 (0⋅30%/y)	362 (0∙34%/y)	0.90 (0.74 – 1.0
No	208 (0·09%/y)	231 (0⋅10%/y)	0.89 (0.69 - 1.
Current smoker	$(\chi_1^2 = 5.1; P =$	0-02)	
Yes	158	143	1.13 (0.83 – 1.5
No	(0-31%/y) 378	(0-28%/y) 449	0.83 (0.69 - 0.5
SBP· mm Ha (tr	(0.13%/y) and v ² – 0.0: F	(0·16%/y) P – 1.0)	-
< 140	μ ₁ - 0.0, 1	- 1-0)	-
140 - 159	(0.08%/y)	(0.09%/y)	0.95 (0.04 – 1.1 0.95 (0.71 – 1.2
140 - 155	(0·30%/y)	(0·32%/y)	
	(0·45%/y)	(0·54%/y)	0.03 (0.03 1)
DBP; mm Hg (ti	rend $\chi_1 = 1.2; F$	² = 0·3)	
< 80	136 (0⋅07%/y)	179 (0⋅10%/y)	0.76 (0.57 - 1.0
80 - 89	123 (0⋅18%/y)	124 (0⋅18%/y)	
90+	241 (0⋅36%/y)	268 (0∙40%/y)	0·90 (0·71 – 1·
Cholesterol; mr	nol/l (trend χ^2_1	= 0·1; P = 0·	7)
< 5.0	108 (0.11%/v)	119 (0.12%/v)	<u> </u>
5.0 – 5.9	(0-14%/y) 128 (0-14%/y)	(0·12/0/y) 147 (0·16%/y)	0.87 (0.64 – 1.
6.0+	(0·22%/v)	156 (0.26%/y)	0.86 (0.64 − 1.
BMI; kg/m ² (tren	nd $\chi_1^2 = 0.0; P =$	= 0·9)	
< 25.0	214	235	0·87 (0·68 – 1·
25.0 – 29.9	(0-14%/y) 217	(0.15%/y) 233	<u> </u>
30.0+	(0.19%/y) 102	(0.20%/y) 122	0.84 (0.59 – 1.
Predicted 5-yea	(۵۰۱۹%/۷) ar CHD risk*; ۹	(0.22%/y) 6 (trend χ^2_{1} =	= 3·9; P = 0·05)
< 2.5	242	301	0.80 (0.64 – 1.0
2.5 < 5	(0·09%/y) 100	(0·11%/y) 114	0.85 (0.60 - 1.2
5. < 10	(0·27%/y) 104	(0·32%/y) 106	1.04 (0.72 – 1.5
10+	(0.63%/y) 48	(0.62%/y) 42	1.15 (0.65 - 2.0
	(1·29%/y)	(1·11%/y)	-
Total	539 (0.16%/v)	593 (0-18%/v)	0.90 (0.80 – 1 P = 0.08
	(c. (c, (a, j))	(2.2/0/3/	
- 99% or < > 95	% confidence intervals	0-5	0.75 1.0 1.25 1.
eterogeneity on 11	df: χ ² ₁₁ = 22-0; P =	= 0-02	Aspirin better Aspirin worse

N.B. Unknown values not plotted * Excluding patients with history of vascular disease

Treatment effect P = 0.08

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Web Figure 5: FIRST STROKE (any type) in primary prevention trials - subgroup analyses Symbols and conventions as in text - figure 2

Age; years (χ_1^2 =	0.1: P = 0.8)	• • • • • •
1	,,	
< 65	358 382	0.94 (0.78 – 1
65+	(0·13%/y) (0·14%/y) 297 300	0.97 (0.78 – 1
	(0.59%/y) (0.60%/y)	
Gender ($\chi_1^2 = 8.3$; P = 0·004)	1.12 (0.91 – 1
Male	371 332 (0·33%/y) (0·30%/y)	
Female	284 350 (0·13%/y) (0·16%/y)	0.81 (0.66 – 0.
Prior vascular d	isease (χ ₁ ² = 4·1; Ρ = 0·04	4)
Yes	51 31	1.50 (0.83 – 2
No	(1.28%/y) $(0.74%/y)604$ $651(0.18%/y)$ $(0.20%/y)$	0.93 (0.80 - 1
Prior diabatas ((0.18%) $(0.20%)$	
Yoo	(₁ = 0.6, F = 0.4)	0.82 (0.52 – 1
No	(0.56%/y) (0.69%/y)	
NO	(0·18%/y) (0·19%/y)	0.96 (0.83 - 1
Prior hypertens	ion (χ ₁ ² = 0·1; P = 0·8)	
Yes	378 398 (0.35% k) (0.37% k)	
No	(0·35%/y) (0·37%/y) 275 284	0.97 (0.77 – 1
Current smoker	(0.12%/y) $(0.13%/y)(x^2 - 3.9 P - 0.05)$	
Voc	($\chi_1 = 3.3, 1 = 0.03)$	 1.14 (0.86 – 1
No	(0.38%/y) (0.33%/y)	0.89 (0.75 - 1
110	(0·16%/y) (0·18%/y)	
SBP; mm Hg (tr	end χ ₁ ² = 0·1; Ρ = 0·8)	
< 140	243 $267(0.11%/y) (0.11%/y)$	0.92 (0.73 – 1
140 – 159	184 184 (0.35%/y) (0.35%/y)	<u> </u>
160+	(0.03 %/y) $(0.03 %/y)185 203(0.53%/y)$ $(0.59%/y)$	0.88 (0.67 – 1
DBP; mm Hg (tr	end $\chi_1^2 = 0.7$; P = 0.4)	
< 80	180 214	0.84 (0.65 – 1
80 - 89	(0.10%) $(0.12%)152$ $147(0.22%)$ $(0.21%)$	<u> </u>
90+	(0.22%) $(0.21%)279 294(0.42%)$ $(0.44%)$	0.95 (0.76 – 1
Cholesterol; mn	nol/l (trend $\chi_4^2 = 0.6$; P =	0-4)
< 5.0	139 141	1.00 (0.73 – 1
5.0 – 5.9	(0·15%/y) (0·15%/y) 154 168	<u> </u>
6.0+	(0·17%/y) (0·19%/y) 160 178	0.88 (0.67 – 1
BMI: ka/m² (tren	(0.25%/y) $(0.29%/y)d \gamma^2 = 0.0; P = 1.0)$	
< 25.0	265 285	0.90 (0.72 – 1
25.0 - 29.9	(0·17%/y) (0·18%/y)	1.04 (0.83 – 1
30.0+	(0.23%/y) (0.22%/y) 115 133	0.86 (0.62 – 1
Dredicted 5	(0.21%/y) (0.24%/y)	-
Fredicted 5-yea	I UTU ISK"; $\%$ (trend χ_1^-	= 5·0; P = 0·03)
< 2.5	305 355 (0·11%/y) (0·13%/y)	
2.5, < 5	122 136 (0·33%/y) (0·38%/y)	
5, < 10	120 115 (0·73%/y) (0·68%/y)	1.30 (0.76 – 2
10+	57 45 (1·53%/y) (1·18%/y)	1.50 (0.70 - 2)
Total	655 682	0.95 (0.85 – 2
	(0·20%/y) (0·21%/y)	P = 0-4

N.B. Unknown values not plotted * Excluding patients with history of vascular disease

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Web Figure 6: GASTRO–INTESTINAL BLEED (or other major extracranial bleed) in primary prevention trials, by study

Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	<u>Ratio of annu</u> Aspi	al even rin : Co	t rates (8 ntrol	k CI)	
					1·0ģ	(0.37 – 2	2.70)
British Doctors' Study	20 (0∙10%/y)	20 (0∙10%/y)		-	1 50	(0.80	→ 2 94)
US Physicians' Health Study	48 (0∙09%/y)	30 (0∙05%/y)				(0·09 — .	2·04) →
Thrombosis Prevention	20	13			1.54	(0.63 - 3	3·77) →
Trial	(0·12%/y)	(0·08%/y)			1.81	(1·22 —)	2.66)
Treatment Trial	114 (0⋅32%/y)	62 (0·18%/y)			1.98	_	→ 1.02)
Primary Prevention Proje	ect 6 (0⋅07%/y)	3 (0∙04%/y)					>
Women's Health Study	127 (0∙06%/y)	91 (0∙05%/y)			1.39 ■	(0.98 –	1·97) _
Total †	335 (0-10%/y)	219 (0-07%/y)				>	
	(0-10/0/9)	(0.01 /019)			1.54 (P	1∙30 — < 0∙0000 adverse	1.82) 01
- - 99% or <i><</i> 95% cor	nfidence intervals	 0	0-5	1.0	1.5		 2·0
eneity between 6 trials: χ	$c_{5}^{2} = 3.1; P = 0$	-7	Aspirin better		Aspirin v	vorse	
			Treatment effect	t P < 0-0	00001, ad	dverse	

† Includes 9 vs. 20 fatal bleeds, P = 0.07 reduction.

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Web Figure 7: GASTRO-INTESTINAL BLEED (or other major extracranial bleed) in primary prevention trials subgroup analyses. Symbols and conventions as in text - figure 2

Subgroup	Allocated Adjusted Ratio aspirin control	of annual event rates Aspirin : Control	<u>s (& CI)</u>
Age; years (χ	${}^{2}_{1} = 0.0; P = 1.0)$	· ·	
< 65	206 134		1.53 (1.16 – 2.03
65+	(0.07%/y) (0.05%/y) 129 85	i	1.55 (1.08 – 2.2
Gender (χ^2_4 =	(0.25%/y) (0.17%/y) 0.0; P = 0.9)		
Male	166 108		1.56 (1.13 – 2.15
Female	(0·15%/y) (0·10%/y) 169 111		1.52 (1.11 – 2.00
Prior vascula	(0·08%/y) (0·05%/y) r disease (χ ² = 0·3; P = 0·6)	,	1 1
Yes	11 10		1.17 (0.35 – 3.93
No	(0·27%/y) (0·24%/y) 324 209		1.55 (1.24 – 1.9
Prior diaboto	(0.10%/y) $(0.06%/y)$		
	$\chi_1 = 1.3, F = 0.2)$		1.10 (0.52 – 2.3
No	25 22 (0·23%/y) (0·21%/y)		1.60 (1.27 – 2.03
INU	(0·10%/y) (0·06%/y)		
Prior hyperte	nsion (χ ₁ ² = 0·1; Ρ = 0·8)		, , , ,, , ,, , ,, , ,, , ,, , ,, , ,, , , , , , , , , , , , , , , , , , , ,
Yes	195 123 (0·18%/y) (0·11%/y)		1.57 (1.17 – 2.10
No	140 96 (0.04%/y) (0.04%/y)		1.49 (1.06 – 2.10
Current smol	$\operatorname{ker}\left(\chi_{1}^{2}=1.9; \mathrm{P}=0.2\right)$		
Yes	65 56		1.22 (0.75 – 1.98
No	(0·13%/y) (0·11%/y) 270 162		1.64 (1.28 – 2.1
SBP: mm Ha	(0.10%/y) (0.06%/y) (trend $\gamma^2 = 0.0$: P = 0.9)		
< 140	159 92		1.72 (1.24 – 2.3
140 – 159	(0.07%/y) (0.04%/y) 66 55		1.20 (0.74 – 1.92
160+	(0.12%/y) (0.10%/y) 103 58		1.76 (1.17 – 2.6
	(0.29%/y) (0.17%/y)		
DBP; mm Hg	(trend $\chi_1^- = 1.0$; P = 0.3)		1.41 (0.95 2.0)
< 80	101 71 (0·06%/y) (0·04%/y)		1.64 (1.02 2.6
80 – 89	76 48 (0·11%/y) (0·07%/y)		1.72 (1.23 – 2.4
90+	151 86 (0·22%/y) (0·13%/y)		
Cholesterol;	mmol/l (trend χ_1^2 = 5.6; P =	0-02)	1 1 1
< 5.0	77 53 (0.08%/y) (0.06%/y)		1.48 (0.94 – 2.3
5.0 – 5.9	72 71 (0.08%) (0.0		1.02 (0.66 – 1.5
6.0+	(0.08%y) $(0.08%y)113 41(0.18%y)$ $(0.07%y)$		2.50 (1.65 – 3.75
BMI; kg/m² (ti	rend $\chi_1^2 = 0.6$; P = 0.5)		1 1 1
< 25.0	106 77		1.40 (0.95 – 2.0
25.0 – 29.9	(0·07%/y) (0·05%/y) 159 79	_	1.99 (1.42 – 2.78
30.0+	(0·14%/y) (0·07%/y) 66 60		1.10 (0.70 – 1.75
Predicted 5-v	(0·12%/y) (0·11%/y) /ear CHD risk*: % (trend γ ²	= 2·2: P = 0·1)	1 1
< 2.5	203 122	, - ,	1.64 (1.23 – 2.19
2.5. < 5	(0.07%/y) $(0.04%/y)69 40$		1.73 (1.05 – 2.86
5, < 10	(0.19%/y) (0.11%/y) 38 31		
10+	(0·23%/y) (0·18%/y) 14 16 -		0.93 (0.34 – 2.52
	(0·37%/y) (0·41%/y)	-	1 1 1
Total	335 219 (0∙10%/y)(0∙07%/y)		1-54 (1-30 – 1-4 P < 0-00001 adverse
- -99% or <>95%	6 confidence intervals —		
		1-0	2.0 3

Treatment effect P < 0.00001, adverse

N.B. Unknown values not plotted * Excluding patients with history of vascular disease

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Web Figure 8: SERIOUS VASCULAR EVENTS in secondary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual e Aspirin :	vent rates (& Cl) Control
(a) Post myocardi	al infarction	I		
Cardiff–I	57 (8·81%/y)	76 (12·30%/y) ←		0·72 (0·46 – 1·13)
Cardiff-II	129 (17∙06%/y)	187 — (25∙03%/y)		0.70 (0.52 – 0.93)
Paris-I	130 (5∙24%/y)	164 — (6∙86%/y)		0·76 (0·52 − 1·10)
AMIS	382 (5∙80%/y)	413 (6·41%/y)		0·89 (0·74 − 1·06)
CDP-A	76 (5∙81%/y)	102 — (7∙86%/y)		0.74 (0.50 – 1.09)
Gamis	33 (7·93%/y)	45 ← (11·11%/y)		0.08 (0.37 - 1.27)
(a) Subtotal	807 (6-62%/y)	987 (8·29%/y)		0·79 (0·72 – 0·87) P < 0·00001
Heterogeneity between 6 tria	als: χ ₅ ² = 4·7; Ρ	= 0.5		
Micristin	65 (4·84%/y)	106 ← (7·93%/y)	o	0.57 (0.38 – 0.87)
(b) Post transient	ischaemic a	ttack or stro	oke	
AITIA	26 (12⋅38%/y)	35 ← (18·52%/y)		0.67 (0.32 – 1.39)
UK-TIA	354 (5∙98%/y)	408 (7·03%/y)		0·85 (0·67 – 1·07)
Reuther	2 (3·45%/y)	5 (8∙93%/y)		0.42 (0.06 – 2.96)
СА Со–ор	33 (9·51%/y)	30 (8·70%/y)		1.08 (0.57 – 2.08) ■>
Toulouse TIA	11 (2⋅62%/y)	16 ← (3·33%/y)		0·73 (0·27 − 1·96) →
AICLA	31 (5∙70%/y)	48 (9·23%/y) ←	-	
Danish Co-op	23 (9⋅62%/y)	27 (11·74%/y)≪		0.84 (0.41 - 1.75)
Britton	59 (13∙69%/y)	55 (12·97%/y)	 	1.05 (0.65 - 1.71)
Danish Low Dose	21 (7⋅64%/y)	21 ← (7·75%/y)		0.98 (0.44 – 2.18)
SALT	138 (7·48%/y)	169 (9∙51%/y)		0.79 (0.59 − 1.06)
(b) Subtotal	698 (6-78%/y)	814 (8-06%/y)		0•83 (0•75 – 0•93) P = 0•001
Heterogeneity between 10 tria	als: $\chi_9^2 = 6.3$; P	= 0.7		
ESPS-II	293 (8·88%/y)	332 (10∙07%/y)		0·86 (0·68 – 1·08)
Total (a+b)	1505 (6·69%/y)	1801 (8-19%/y)	\Rightarrow	0-81 (0-75 – 0-87) P < 0⋅00001
- 99% or <>> 95% o	onfidence intervals	0.5	0.75 1.	0 1.25 1.5
treatment effects in 2 subtotals:	$\chi_1^2 = 0.4; P = 0$	0.5	Aspirin better	Aspirin worse

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Web Figure 9: NON-FATAL MYOCARDIAL INFARCTION in secondary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Events (% p Allocated aspirin	er annum) Adjusted control	Ratio of a	annual event rates (& CI) Aspirin : Control
(a) Post myocard	lial infarction			
Cardiff–I	10 (1⋅55%/y)	15 <i>←</i> (2·43%/y)		0.64 (0.23 – 1.79)
Cardiff-II	31 (4·08%/y)	65 (8∙67%/y) ←	•	- 0.49 (0.29 - 0.83)
Paris–I	50 (2·00%/y)	68 (2·82%/y) ←		0.70 (0.38 – 1.27)
AMIS	142 (2∙14%/y)	175 (2⋅69%/y)		
CDP-A	27 (2·05%/y)	32 (2·45%/y)		■ 0·84 (0·43 – 1·65) →
Gamis	11 (2·64%/y)	15 <i>←</i> (3·70%/y)		0.71 (0.25 – 1.98)
(a) Subtotal	271 (2·21%/y)	370 (3-08%/y)		- 0·71 (0·60 − 0·83) P = 0·00003
Heterogeneity between 6 tr	ials: χ ₅ ² = 4·5; Ρ =	= 0.5		
Micristin	22 (1·64%/y)	35 <i><</i> (2·62%/y)	O	0.62 (0.31 – 1.24)
(b) Post transien	t ischaemic at	tack or str	oke	
AITIA	4	2 <		1.91 (0.23 - 15.89)
UK-TIA	(1.81 %/y) 42 (0.67%/y)	(0.99 %/y) 70 < (1.11%/y)		0.59 (0.31 – 1.09)
Reuther	0 (0·00%/y)	0 (0·00%/y)		
СА Со–ор	4 (1⋅06%/y)	0 (0-00%/y)		7.16 (0.54 - 94.17)
Toulouse TIA	0 (0·00%/y)	2 (0·41%/y)		
AICLA	2 (0·35%/y)	9 ← (1·58%/y)		0.28 (0.06 - 1.32)
Danish Co–op	2 (0·76%/y)	8 (3·24%/y) ←		0.30 (0.06 - 1.52)
Britton	11 (2·42%/y)	10 <i>←</i> (2·24%/y)		<u> </u>
Danish Low Dose	0 (0·00%/y)	2 (0·70%/y)		0.65 (0.22 1.22)
SALT	21 (1∙08%/y)	32 ← (1·66%/y)		
(b) Subtotal	86 (0·79%/y)	135 (1∙24%/y)		→ 0.64 (0.48 - 0.86) P = 0.003
Heterogeneity between 9 tr	ials: χ ₈ ² = 14·8; Ρ	= 0-06		
ESPS-II	17 (0∙52%/y)	22 ← (0·67%/y) ←		0.77 (0.34 - 1.77)
Total (a+b)	357 (1-54%/y)	505 (2·20%/y)		0-69 (0-60 – 0-80) P < 0-00001
- ■ - 99% or <=> 95% Difference between	confidence intervals	_	0.5 0.75	1.0 1.25
treatment effects in 2 subtotals	s: $\chi_1^2 = 0.4$; P = 0.	5	Aspirin be Treatment	effect P < 0.00001

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Web Figure 10: CHD DEATH in secondary prevention trials, by study

Symbols and conventions as in text - figure 2

Study	Deaths (% Allocated aspirin	per annum) Adjusted control	Ratio of annual death rates (& CI) Aspirin : Control
(a) Post mvocardia	al infarction	1	
Cardiff_I	45	59 -	0.74 (0.45 – 1.23)
Oardin-r	(6·87%/y)	(9·31%/y)	
Cardiff-II	89 (11·47%/y)	117 - (14∙96%/y)	● 0.77 (0.54 – 1.11)
Paris-I	67 (2-58% (小)	86 ←	0·77 (0·46 − 1·29)
AMIS	203	185	1.06 (0.82 – 1.38)
CDP-4	(2·96%/y)	(2·71%/y)	0.77 (0.44 – 1.35)
	(2·76%/y)	(3·56%/y) ⊂	0.56 (0.23 – 1.38)
Gamis	13 (3·10%/y)	22 ← (5·35%/y)	•
(a) Subtotal	454 (3·59%/y)	517 (4·11%/y)	0.87 (0.76 – 0.99 P = 0.04
Heterogeneity between 6 tria	als: $\chi_5^2 = 7.4$; P	= 0-2	
Micristin	12 (0⋅89%/y)	31—	0.40 (0.18 – 0.89)
(b) Post transient	ischaemic a	attack or stro	oke
AITIA	4 (1∙77%/v)	3 ← (1·46%/v)	1.30 (0.18 – 9.26)
UK–TIA	109 (1·70%/y)	108 (1.66%/y)	1.02 (0.67 – 1.57)
Reuther	0 (0·00%/y)	1 (1∙72%/y)	0.50 /0.44
CA Co-op	4 (1∙05%/y)	8 ← (2·13%/y)	>
Toulouse TIA	2 (0∙47%/y)	3 (0·61%/y) ≪	0.70 (0.07 - 6.99)
AICLA	1 (0⋅17%/y)	3 ← (0·51%/y)	0.38 (0.03 – 4.96)
Danish Co-op	4	6 ←	• • • • • • • • • • • • • • • • • • • •
Britton	(1·49/8/y) 6	(2·23 /₀/y) 9 ←	0.66 (0.17 – 2.49)
Danish Low Dose	(1·28%/y) 9	(1·96%/y)	1.80 (0.45 – 7.13)
	(3·19%/y)	(1·74%/y)	0.64 (0.32 – 1.29)
SALI	21 (1·05%/y)	33 ← (1·65%/y)	
(b) Subtotal	160 (1-44%/v)	179 (1.59%/v)	
	(117,3,3)	(100/04))	0·87 (0·69 – 1·1 ⁻ P = 0·3
Heterogeneity between 10 tria	als: $\chi_9^2 = 7.3$; P	= 0-6	1.16 (0.58 - 2.22)
ESPS-II	30 (0∙91%/y)	26 (0·79%/y)	
Total (a+b)	614 (2·59%/y)	696 (2-92%/y)	0.87 (0.78 – 0.98 P = 0.02
-∎- 99% or <=> 95% c fference between	onfidence intervals	0.5	0.75 1.0 1.25 1.5
treatment effects in 2 subtotals:	χ ₁ ² = 0·0; Ρ = 1	-0	Aspirin better Aspirin worse

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Web Figure 11: MAJOR CORONARY EVENTS in secondary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual eve Aspirin : C	ent rates (& CI) ontrol
(a) Post myocardia	I infarction	I		
Cardiff-I	55 (8∙50%/y)	74 <i>≪</i>		
Cardiff-II	124 (16∙40%/y)	182 ← (24·36%/y)		0.66 (0.48 - 0.91)
Paris-I	118 (4∙73%/y)	154 <i>←</i> (6·40%/y)		— 0.73 (0.49 – 1.09)
AMIS	346 (5,22%小/)	361 (5 . 54%小)		0·92 (0·76 – 1·12)
CDP-A	65 (4·95%/y)	81 — (6·20%/y)		0.80 (0.52 – 1.22)
Gamis	24 (5·77%/y)	37 (9·14%/y) ←	-	0.61 (0.30 – 1.21)
(a) Subtotal	732 (5∙97%/y)	889 (7-41%/y)		0-80 (0-73 – 0-89) P = 0-00003
Heterogeneity between 6 tria	ls: χ ₅ ² = 7·8; Ρ	= 0-2		
Micristin	34 (2·53%/y)	66 ≪— (4·94%/y)		0.50 (0.29 - 0.85)
(b) Post transient i	schaemic a	attack or stro	oke	
AITIA	10	7 ←		1.40 (0.39 – 5.06)
	(4·52%/y)	(3·47%/y)		0.86 (0.61 – 1.22)
UK-TIA	155 (2·46%/y)	180 (2∙85%/y)		
Reuther	0 (0·00%/y)	1 (1·72%/y)		0.97 (0.27 - 3.53)
CA Co-op	8 (2·12%/y)	8 ← (2·15%/y)		>
Toulouse TIA	2 (0∙47%/y)	5 (1·03%/y) ←		0·44 (0·06 − 3·11) →
AICLA	3 (0.52% (v)	12 ←		0·30 (0·08 – 1·14)
Danish Co-op	(0.52 %/y)	(2·11 /ø/y) 14 ←		0.44 (0.14 – 1.39)
Britton	(2·28%/y) 21	(5·67%/y) 21 <−	_	0.98 (0.44 – 2.17)
Britton	(4·63%/y)	(4·71%/y)	-	1.30 (0.36 – 4.72)
Danish Low Dose	9 (3·20%/y)	7 <i><</i> — (2∙45%/y)		•>
SALT	49 (2·52%/y)	70 (3·63%/y) ←	-	
(b) Subtotal	263 (2·41%/y)	325 (2·98%/y)		0·79 (0·66 − 0·95) P = 0·01
Heterogeneity between 10 tria	ls: χ ₉ ² = 10·5;	P = 0·3		
ESPS-II	47 (1·43%/y)	48 (1·46%/y)		0·98 (0·57 − 1·67) →
Total (a+b)	995 (4·30%/y)	1214 (5∙30%/y)	\Rightarrow	0-80 (0-73 – 0-88) P < 0-00001
99% or <-> 95% co	nfidence intervals	0.5	0.75 1.0	1.25 1.5
treatment effects in 2 subtotals:	$\chi_1^2 = 0.0; P = 0$).9	Aspirin better	Aspirin worse
			Treatment effect	P < 0.00001

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Web Figure 12: HAEMORRHAGIC STROKE in secondary prevention trials, by study

Symbols and conventions as in text - figure 2

Study	Events (% per annun Allocated Adjuste aspirin control	n) d <u>Ratio of annual e</u> Aspirin	event rates (& CI) : Control
(a) Post myocard	dial infarction		
Cardiff-I	1 0 (0·15%/y) (0·00%/y	()	
Cardiff-II	2 0 (0·26%/y) (0·00%/y	()	
Paris–I	0 0 (0·00%/y) (0·00%/y	()	
AMIS	0 1 (0·00%/y) (0·01%/y	()	
CDP-A	0 1 (0·00%/y) (0·07%/y	()	
Gamis	0 2 (0·00%/y) (0·49%/y	()	
(a) Subtotal	3 (0·02%/y) (0·03%/	y)	0.74 (0.17 – 3.27) P = 0.7
Heterogeneity between 5 t	rials: χ ₄ ² = 6·9; Ρ = 0·1		
Micristin	8 10 (0⋅60%/y) (0⋅75%/y	·)	0.79 (0.23 – 2.69)
(b) Post transien	t ischaemic attack or	stroke	
ΑΙΤΙΑ	1 0 (0∙47%/y) (0∙00%/y	()	
UK–TIA	14 4 (0·23%/y) (0·07%/y	·)	2.52 (0.64 – 9.92)
Reuther	0 1 (0·00%/y) (1·79%/y	()	
CA Co-op	0 0 (0·00%/y) (0·00%/y	()	
Toulouse TIA	0 0 (0·00%/y) (0·00%/y)	0.99 (0.08 – 13.03)
AICLA	2 2 (0·37%/y) (0·37%/y	<	>
Danish Co–op	1 1 (0·41%/y) (0·41%/y	()	0.99 (0.12 – 8.07)
Britton	3 3 (0.68%/y) (0.69%/y	()	
Danish Low Dose	1 0 (0·36%/y) (0·00%/y	()	2.48 (0.66 – 9.38)
SALT	11 4 (0·58%/y) (0·22%/y	()	/
(b) Subtotal	33 15 (0-32%/y) (0-14%/	y)	1.90 (1.06 – 3.44) P = 0.03
Heterogeneity between 8 t	rials: χ ₇ ² = 4·5; Ρ = 0·7		adverse
ESPS-II	9 10 (0·27%/y) (0·30%/y	′)°	
Total (a+b)	36 19 (0·16%/y) (0·08%/	y)	1.67 (0.97 – 2.90) P = 0.07 adverse
- 99% or <⊃ 95% Difference between	confidence intervals	0.1 0.25 0.5 1	•0 2•5 5•0 10
treatment effects in 2 subtotal	s: χ ₁ = 1·3; Ρ = 0·2	Aspirin better Treatment effect	Aspirin worse P = 0-07, adverse

Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total. NB: Most strokes of known cause were in just three trials (UK-TIA, Britton and SALT), all in patients with prior cerebral vascular disease. Page 16 of Aspirin in the primary and secondary prevention of vascular disease web appendix (Lancet 2009)

Web Figure 13: DEFINITELY ISCHAEMIC STROKE in secondary prevention trials, by study

Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual Aspirin	event rates (& CI) : Control
(a) Post myocardia	al infarction	1		
Cardiff-I	0 (0·00%/y)	0 (0·00%/y)		
Cardiff-II	0 (0·00%/y)	1 (0∙13%/y)		
Paris-I	2 (0∙08%/y)	0 (0·00%/y)		
AMIS	0 (0·00%/y)	3 (0∙04%/y)		
CDP-A	0 (0·00%/y)	0 (0·00%/y)		
Gamis	0 (0·00%/y)	0 (0·00%/y)		
(a) Subtotal	2 (0.02%/y/)	4 – (0.03%/v)		
	(0·02 /0/y)	(0·03 /8/y)		0·35 (0·07 – 1·83) P = 0·2
Heterogeneity between 3 tria	ls: χ ₂ ² = 4·0; Ρ	= 0-1		0.60 (0.21 1.72)
Micristin	9 (0·67%/y)	15 < (1·12%/y)	ai	>
(b) Post transient i	schaemic a	attack or st	roke	
AITIA	0 (0·00%/y)	0 (0·00%/y)		
UK-TIA	48 (0·80%/y)	64 < (1∙07%/y)	•	0.74 (0.40 - 1.36)
Reuther	0 (0·00%/y)	1 (1∙79%/y)		
CA Co-op	0 (0·00%/y)	0 (0·00%/y)		
Toulouse TIA	0 (0·00%/y)	0 (0∙00%/y)		
AICLA	0 (0·00%/y)	0 (0·00%/y)		
Danish Co-op	1 (0-41%/y)	0 (0·00%/y)		0.98 (0.44 – 2.17)
Britton	21 (4·74%/y)	21		>
Danish Low Dose	0 (0·00%/y)	0 (0·00%/y)		0.77 (0.51 – 1.16)
SALT	68 (3·59%/y)	86 – (4∙69%/y)		
(b) Subtotal	138 (1-32%/y)	172 (1·66%/y)		- 0.79 (0.62 – 1.00) P = 0.05
Heterogeneity between 5 tria	ls: χ ₄ ² = 2·6; Ρ	= 0-6		
ESPS-II	122 (3∙70%/y)	158 (4·79%/y)		0.76 (0.55 – 1.04)
Total (a+b)	140 (0∙61%/y)	176 (0-77%/y)		0·78 (0·61 – 0·99 P = 0·04
- ■ - 99% or <=> 95% co Difference between	onfidence intervals	。 0-5	0-75 1	-0 1·25 1·5
treatment effects in 2 subtotals:	χ ₁ ² = 0·9; P = 0).3	Aspirin better Treatment e	Aspirin worse ffect P = 0·04

Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total. NB: Most strokes of known cause were in just three trials (UK-TIA, Britton and SALT), all in patients with prior cerebral vascular disease. Page 17 of Aspirin in the primary and secondary prevention of vascular disease web appendix (Lancet 2009)

Web Figure 14: PROBABLY ISCHAEMIC STROKE in secondary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Allocate aspirin	d Adjusted control	Ratio of annu Aspir	al event rates (& CI) in : Control
(a) Post r	nyocardial infarction	on		
Cardiff-I	0 (0·00%/y	0 /) (0·00%/y)		
Cardiff-II	5 (0·64%/)	3 ← /) (0·38%/y)		1.67 (0.27 – 10.32)
Paris-I	12 (0·46%/y	16 ← /) (0·63%/y)		0.73 (0.21 – 2.49)
AMIS	39 (0.57%/)	61 ←		0.62 (0.37 - 1.03)
CDP-A	(0.97%) 13 (0.97%)	() (0.30767y) 11 ← () (0.82%/y)		1·18 (0·41 – 3·39)
Gamis	(0 01 /0) 0 (0.00%/y	0 (0.00%/y)		
(a) Subt	otal 69 (0-55%/	91 y) (0·73%/y)		0.74 (0.54 − 1.02 P = 0.06
Heterogeneity be	tween 4 trials: χ_3^2 = 3-5	; P = 0·3		
Micristin	9 (0-67%/)	15 ← /) (1·12%/y)		0.60 (0.21 – 1.73)
(b) Post t	ransient ischaemie	c attack or str	oke	
AITIA	12 (5·58%/y	27 ← /) (14·14%/y)		- 0.40 (0.17 - 0.97)
UK–TIA	187 (3·11%/)	234 /) (3·92%/y)		0.79 (0.57 – 1.08)
Reuther	2 (3·45%/y	3 ← /) (5·36%/y)	-	0.67 (0.07 - 6.67)
CA Co-or	o 23 (6·55%/y	20 – /) (5·76%/y)		1.13 (0.51 – 2.47)
Toulouse	TIA 7 (1.67%/)	9 ← /) (1·86%/y)		0.82 (0.23 – 2.99)
AICLA	18 (3·30%/\	31 < /) (5·76%/y)	-	0.59 (0.28 – 1.22)
Danish Co	o–op 17 (7.05%/y	13 - /) (5·28%/y)		1.34 (0.52 – 3.44)
Britton		29 ← ⁄) (6·67%/y)		● 0.95 (0.48 - 1.87)
Danish Lo	ow Dose 8 (2·91%/)	12 ← /) (4·41%/y)		0.66 (0.21 – 2.09)
SALT	73 (3·85%/y	92 – /) (5·02%/y)		0.77 (0.52 – 1.15)
(b) Subt	otal 375 (3·58%/	470 y) (4·53%/y)		0·78 (0·68 – 0·91 P = 0·001
Heterogeneity betw	veen 10 trials: $\chi_9^2 = 9.2$; P = 0·4		
ESPS-II	188 (5·70%/y	225 /) (6·82%/y)		0.81 (0.62 - 1.07)
Total (a⋅	+b) 444 (1·93%/	561 y) (2·46%/y)		0·78 (0·68 – 0·89 P = 0·0002
- ∎ - 99% or	→ 95% confidence interview.	/als	0.7E	
ence between eatment effects in 2	subtotals: $\chi_4^2 = 0.1$; P	0·5 = 0·7	U•75 Aspirin better	1.0 1.20 1.5

Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total. NB: Most strokes of known cause were in just three trials (UK-TIA, Britton and SALT), all in patients with prior cerebral vascular disease. Page 18 of Aspirin in the primary and secondary prevention of vascular disease web appendix (Lancet 2009)

Web Figure 15: ANY STROKE in secondary prevention trials, by study Symbols and conventions as in text - figure 2

Study	Events (% Allocated aspirin	per annum) Adjusted control	Ratio of annual eve Aspirin : Co	nt rates (& CI) ontrol
(a) Post myocardi	al infarction	1		
Cardiff-I	1 (0∙15%/y)	0 (0·00%/y)		
Cardiff-II	7 (0·90%/y)	3 < (0·38%/y) <		2.25 (0.44 - 11.47)
Paris-I	12 (0·46%/y)	16 ← (0·63%/y)		0·73 (0·21 – 2·49)
AMIS	39 (0:57%/v)	62 ← (0.92%/y)	-	0.61 (0.36 – 1.02)
CDP-A	13 (0.97%/y)	(° ° ⊆ /«,)) 12 ← (0.90%/v)		1.08 (0.39 − 3.04) >
Gamis	0 (0.00%/y)	2 (0·49%/y)		
(a) Subtotal	72 (0∙57%/y)	95 (0·76%/y)		0·74 (0·54 – 1·01) P = 0·06
Heterogeneity between 6 tria	als: χ_5^2 = 7-8; P	= 0-2		
Micristin	17 (1⋅26%/y)	25 ← (1·87%/y)		0.67 (0.30 – 1.50)
(b) Post transient	ischaemic a	attack or stre	oke	
AITIA	13 (6∙05%/y)	27 <i>←</i> (14·14%/y)		0.43 (0.18 – 1.04)
UK-TIA	201 (3⋅34%/y)	238 (3∙99%/y)		— 0.83 (0.61 – 1.13)
Reuther	2 (3·45%/y)	4 ← (7·14%/y)		0.51 (0.06 - 4.18)
СА Со-ор	23 (6·55%/v)	20 – (5·76%/v)		1·13 (0·51 − 2·47)
Toulouse TIA	7 (1.67%/v)	9 ← (1.86%/v)		0·82 (0·23 − 2·99) →
AICLA	20 (3.67%/v)	(1 00707)) 33 ← (6.13%/\/)		0.61 (0.30 – 1.24)
Danish Co-op	(3.07 %/y) 18	(0.13 %/y) 14 –		1·32 (0·53 – 3·27) ■→>
Britton	(7.47%/y) 31	(5·69%/y) 32 <		0.95 (0.50 − 1.82)
Danish Low Dose	(7.00%/y) 9	(7·36%/y) 12 ←		0.74 (0.24 – 2.28)
SALT	(3·27%/y) 84 (4·43%/y)	(4·41%/y) 96 (5·23%/y)		0·85 (0·58 – 1·25)
(b) Subtotal	408 (3-90%/v)	485 (4-68%/v)		0·83 (0·72 – 0·96) P = 0·01
Heterogeneity between 10 tria	als: $\chi_9^2 = 8.4$; P	= 0.5		
ESPS-II	197 (5·97%/y)	235 (7·13%/y)	<u></u>	0.82 (0.63 - 1.07)
Total (a+b)	480 (2·08%/y)	580 (2·54%/y)		0·81 (0·71 – 0·92) P = 0·002
- 99% or <>> 95% c	onfidence intervals	ي 0-5	0.75 1.0	1.25 1.5
treatment effects in 2 subtotals:	$\chi_1^2 = 0.4; P = 0$).5	Aspirin better	Aspirin worse

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Web Figure 16: VASCULAR DEATH in secondary prevention trials, by study

Symbols and conventions as in text - figure 2

Study	Deaths (% Allocated aspirin	per annum) Adjusted control	Ratio of annual de Aspirin : (ath rates (& CI) Control
(a) Post myocardia	al infarction	l		
Cardiff-I	47 (7·18%/v)	61 <i>←</i> (9·62%/v)		0.75 (0.46 – 1.23)
Cardiff-II	98 (12.63%/v)	122 (15.60%/v)		0.82 (0.58 – 1.16)
Paris-I	(12 00 %)) 73 (2.81%/y)	(10 007/a/y) 90 ← (3:50%/y)		0.80 (0.49 – 1.33)
AMIS	214	(0-007677) 199 (2.01% (v)		1·04 (0·81 – 1·34)
CDP-A	(3·12/0/y) 43	(2·91 /0/y) 61 ←		0.71 (0.43 – 1.18)
Gamis	(3.21%)	(4.53%/y) $30 \leftarrow (7.30\%/y)$		0.70 (0.33 – 1.47)
(a) Subtotal	497 (3·93%/y)	563 (4-48%/y)	\triangleleft	0•87 (0•77 − 0•99 P = 0•03
Heterogeneity between 6 tria	als: χ ₅ ² = 5·9; Ρ	= 0-3		
Micristin	34 (2∙53%/y)	56 <i>←</i> (4·19%/y)		0.59 (0.34 - 1.03)
(b) Post transient	ischaemic a	ttack or stro	oke	
AITIA	10 (4·42%/y)	13 ← (6·34%/y)		0.73 (0.24 – 2.22)
UK-TIA	180 (2·81%/y)	172 (2·64%/y)		1.06 (0.76 – 1.48)
Reuther	0 (0.00%/y)	3 (5·17%/y)		
СА Со-ор	11 (2·89%/y)	15 ← (4·00%/y)		0.71 (0.26 – 1.96)
Toulouse TIA	7 (1·64%/y)	7 ← (1·43%/y)		1.04 (0.26 – 4.14)
AICLA	13 (2·26%/y)	12 ← (2·04%/y)		1.11 (0.40 − 3.11)
Danish Co-op	8 (2·97%/v)	8 < (3·00%/v)		1.01 (0.28 − 3.65) →
Britton	28 (6:00%/v)	29 ← (6·30%/v)		0·95 (0·48 − 1·88) →
Danish Low Dose	(3 30 / 30 / 30 / 30 / 30 / 30 / 30 / 30	7 (2.44%/y)		1.85 (0.59 − 5.87) →
SALT	58 (2.90%/y)	67 (3.36%/y)		0.87 (0.55 – 1.37)
(b) Subtotal	(2.9078/y) 328	333		>
	(2·96%/y)	(2·96%/y)		0·98 (0·83 − 1·16 P = 0·8
Heterogeneity between 10 tria	als: χ ₉ ² = 7·1; Ρ	= 0-6		0.95 (0.67 - 1.34)
ESPS-II	118 (3⋅58%/y)	124 (3·76%/y)		
Total (a+b)	825 (3-47%/y)	896 (3·76%/y)		0·91 (0·82 – 1·00 P = 0·06
	onfidence intervals	0.5	0.75 1.0	1.25 1.5
treatment effects in 2 subtotals:	$\chi_1 = 1.1; P = 0$	1.3	Aspirin better Treatment effe	Aspirin worse ect P = 0.06

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Web Figure 17: GASTRO-INTESTINAL BLEED (or other extracranial bleed) in secondary prevention trials, that reported at least one such event

Symbols and conventions as in text - figure 2



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Web Figure 18: SERIOUS VASCULAR EVENTS in primary and secondary prevention trials by study

Denominators are numbers of participants randomised and percentages are proportions with an event. For trials that randomised in a 2:1 ratio the control group is multiplied by two in the "adjusted control" column, but not in other calculations. Other conventions as in text - figure 2.

Study	Allocated	Adjusted control	Ratio of annual event rates (& CI) Aspirin : Control	
(a) Primary preventi	on (χ ² = 4	ŀ-3; P = 0·5)		
British Doctors' Study	291/3429 (8·5%)	2×(143/1710) (8·4%)	1.01 (0.78 – 1	1.31)
US Physicians' Health Study	313/11037 (2·8%)	373/11034 (3·4%)	0.84 (0.69 – 1	1.02)
Thrombosis Prevention Trial	215/2545 (8·4%)	253/2540 (10·0%)	0.84 (0.67 – 1	1.07)
Hypertension Optimal Treatment Trial	329/9399 (3·5%)	383/9391 (4·1%)	0.85 (0.70 – 1	1.04)
Primary Prevention Project	ct 46/2226 (2·1%)	66/2269 (2·9%)	——— 0·71 (0·43 – 1	1.15)
Women's Health Study	477/19934 (2·4%)	522/19942 (2·6%)		1.07)
(a) Subtotal	1671/ 48570 (3•4%)	1883/ 48596 (3·9%)	O·88 (0·82 − P = 0·000 ⁻	0.94 1
(b) Post myocardial	infarctior	n (χ ₅ ² = 4·7; Ρ	= 0·5)	
Cardiff–I	57/615 (9-3%)	76/624 (12·2%)	0.72 (0.46 - 1	1.13)
Cardiff-II	129/847 (15·2%)	187/878 (21·3%)).93)
Paris-I	130/810 (16·0%)	2×(82/406) (20·2%)		1.10)
AMIS	382/2267 (16·9%)	413/2257 (18·3%)	0.89 (0.74 – 1	1.06)
CDP-A	76/758 (10·0%)	102/771 (13·2%)	0.74 (0.50 - 1	1.09)
Gamis	33/317 (10·4%)	45/309 (14·6%)	0·68 (0·37 – 1	1.27)
(b) Subtotal	807/ 5614 (14·4%)	987/ 5651 (17·5%)	↔ 0.79 (0.72 – P < 0.0000	0-87 01
Micristin	65/672 (9·7%)	106/668 (15·9%)	0.57 (0.38 – 0	J-87)
(c) Post TIA or strok	$xe(\chi_9^2 = 6.3)$	3; P = 0·7)	0.07.(0.22.4	1.20)
AITIA	26/162 (16·0%)	35/157 (22·3%)		1.29)
UK-TIA	354/1621 (21·8%)	2×(204/814) (25·1%)	0.85 (0.67 - 1	1.07)
Reuther	2/30 (6·7%)	5/30 – (16·7%)	0.42 (0.06 - 2	2·96) →
СА Со-ор	33/144 (22·9%)	30/139 (21·6%)	1.08 (0.57 - 2	2.08)
Toulouse TIA	11/147 (7-5%)	16/156 (10·3%)	0.73 (0.27 - 1	- -
AICLA	31/198 (15·7%)	48/204 (23·5%)	0.63 (0.35 – 1	1.12)
Danish Co-op	23/101 (22·8%)	27/102 (26·5%)	0.84 (0.41 – 1	1.75)
Britton	59/253 (23·3%)	55/252 (21·8%)	<u> </u>	1.71)
Danish Low Dose	21/150 (14·0%)	21/151 (13·9%)	0.98 (0.44 - 2	2·18) →
SALT	138/676 (20·4%)	169/683 (24·7%)	0·79 (0·59 − 1	1.06)
(c) Subtotal	698/ 3482 (20·0%)	814/ 3502 (23·2%)	<⊅ 0.83 (0.75 – P = 0.001	0-93 I
ESPS-II	293/1649 (17·8%)	332/1649 (20·1%)	0-86 (0-68 – 1	1.08)
	3176/	3684/	 0·85 (0·80 − 	0-89

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Statistical Appendix

Estimating the event rate ratio associated with baseline prognostic factors for selected major outcomes among the 94 000 people without prior vascular disease at baseline (see table 3 and webtable 3)

Among patients without prior vascular disease, the event rate ratio for selected major outcomes (serious vascular event; non-fatal MI; CHD death; major coronary event; probable ischaemic stroke; haemorrhagic stroke; total stroke and major gastrointestinal [or other extracranial] bleed) associated with baseline prognostic factors was modelled as follows. For patient *i* in study *j* receiving treatment *k* (where *k*=0 corresponds to placebo and *k*=1 corresponds to aspirin), let Y_{ijk} denote the occurrence or otherwise for that patient of the outcome under consideration during the trial, and let T_{ijk} denote the number of years of follow-up. The logarithm of the expected annual event rate was modelled through the Poisson regression model:

$$\ln\left(\frac{E(Y_{ijk})}{T_{ijk}}\right) = \alpha_j + (\boldsymbol{x_{ijk}} - \bar{\boldsymbol{x}}_{\cdot j0})'\boldsymbol{\beta}$$

where α_j is the average (log) annual event rate observed in the placebo group in study j, x_{ijk} is the vector of baseline characteristics for patient i in study j (including an indicator variable corresponding to randomisation to aspirin), $\overline{x}_{.j0}$ is the vector of mean baseline risk exposure levels observed among the placebo patients in study j, and β is the vector of regression coefficients (including a regression coefficient associated with aspirin allocation). In addition to aspirin allocation, the baseline prognostic factors included in each model were: age (per decade); male gender; history of diabetes; cigarette smoking status (current vs ex/never); total cholesterol (per 1 mmol/L); the average of systolic and diastolic blood pressure (per 20 mmHg) and body mass index (per 5 kg/m²). Missing values of baseline characteristics were imputed based on the study-specific average levels in the placebo group $\overline{x}_{.j0}$. For the British Doctors' Study, in which total cholesterol was not available, the mean value across all the other trials was used.

Separating individuals at "very low", "low", "moderate" and "high" predicted risk of a major coronary event for the analysis in figure 7, and the subgroup analyses (figure 2 and the corresponding webfigures [1, 4, 5 & 7])

For major coronary events, the log event rate ratios β described above were re-estimated based on the 47 000 patients in the control groups only (so patients allocated aspirin and the term associated with aspirin allocation were removed). These log event rate ratios (which were similar to those estimated among all participants) were then used in conjunction with the estimated average (log) annual event rates $\hat{\alpha}_1, \ldots, \hat{\alpha}_6$ in the six trials to predict the average 5-yearly major coronary event risk P_{ijk} that would be expected in the absence of aspirin use, where

$$P_{ijk} = 100 \times (1 - (1 - e^{\eta_{ijk}})^5)$$

and

$$\eta_{ijk} = \hat{\alpha}_j + (\boldsymbol{x_{ijk}} - \bar{\boldsymbol{x}_{j0}})'\hat{\boldsymbol{\beta}}$$

Individuals were categorised as "very low" (<2.5%), "low" (2.5-5%), "moderate" (5-10%), or "high" (\geq 10%) predicted 5-year risk of a major coronary event without aspirin on the basis of P_{ijk} . (Note that the regression model may have slightly overestimated risk in the small high risk group.) The proportional and absolute effects of aspirin allocation on specific endpoints was then estimated separately within each of these subgroups (as described in the main Statistical Methods section).