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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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

* 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).

Web Table 2: Number of events in the primary and secondary prevention trials

Trial	Serious vascular event	Major coronary events	Non fatal myocardial infarction	Any stroke	Stroke of unknown cause	Mortality							Major extracranial bleed	Fatal bleed
						CHD	Stroke	Other vascular	Any known vascular	Non vascular	Unknown cause	All causes		
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 trials														
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.

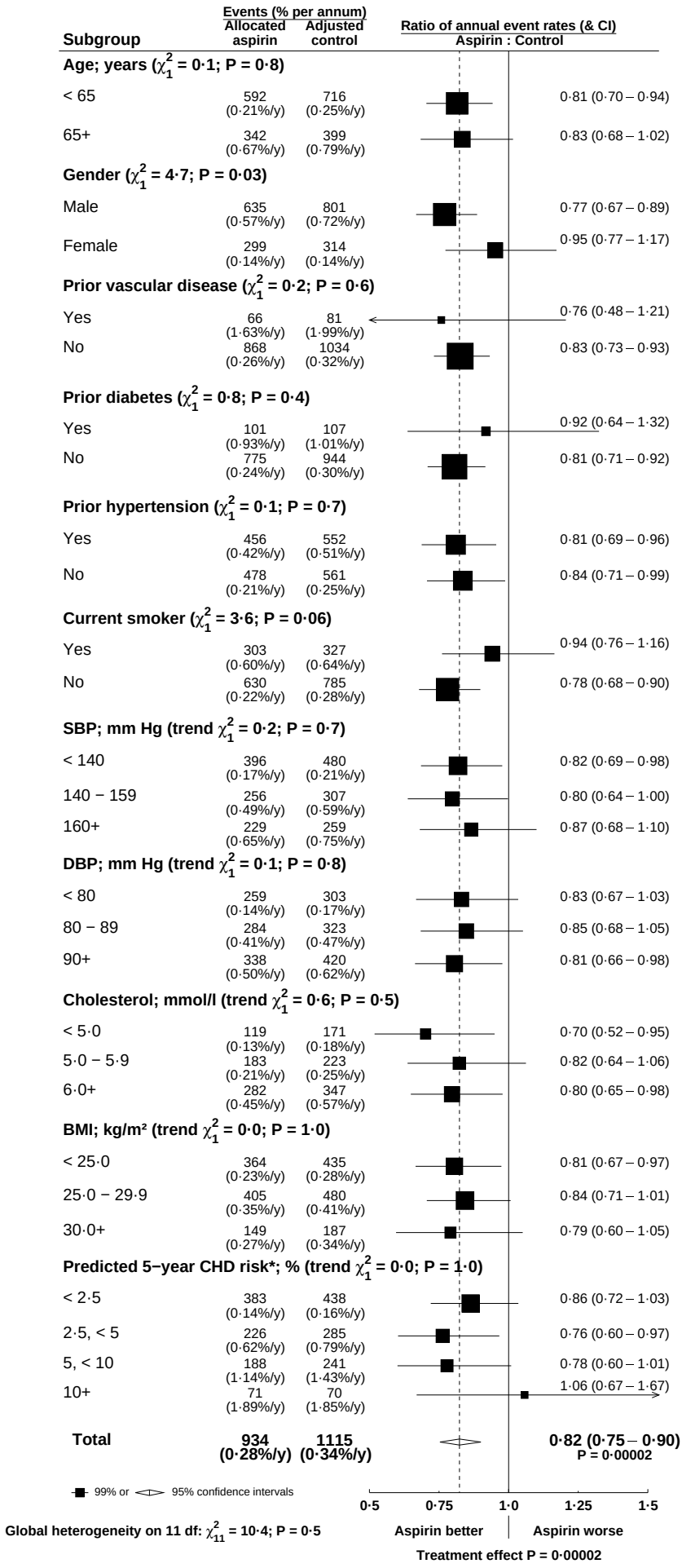
GI = Gastrointestinal.

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

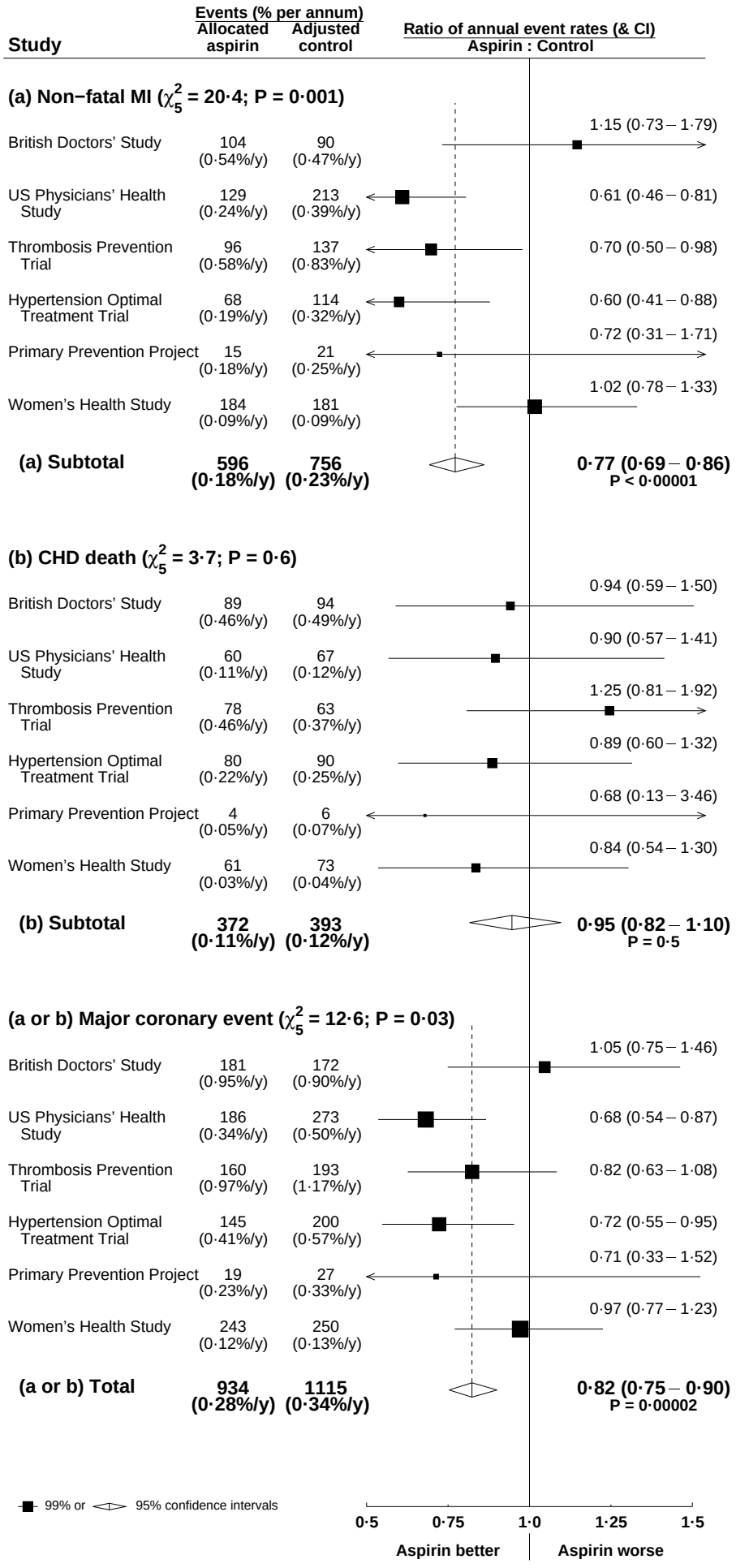


N.B. Unknown values not plotted

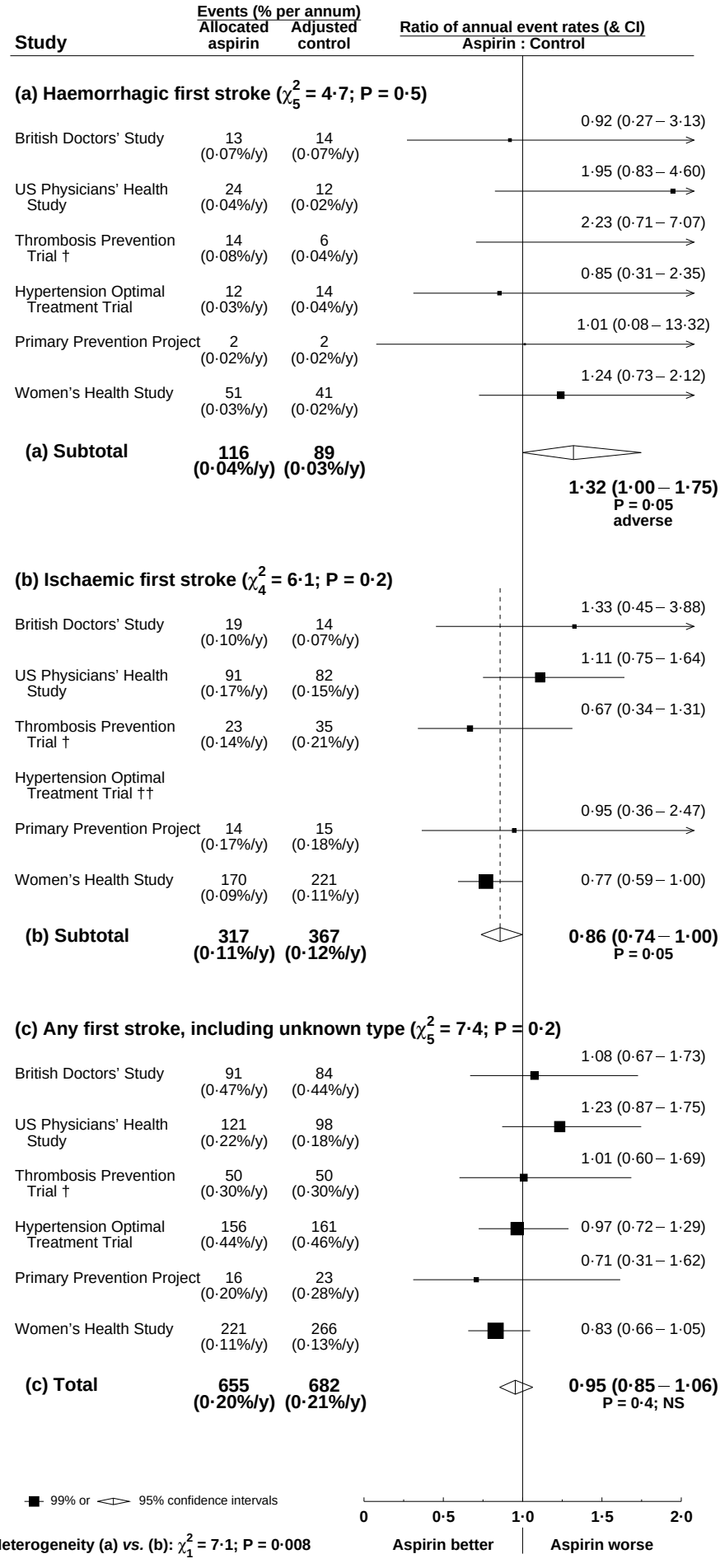
* Excluding patients with history of vascular disease

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



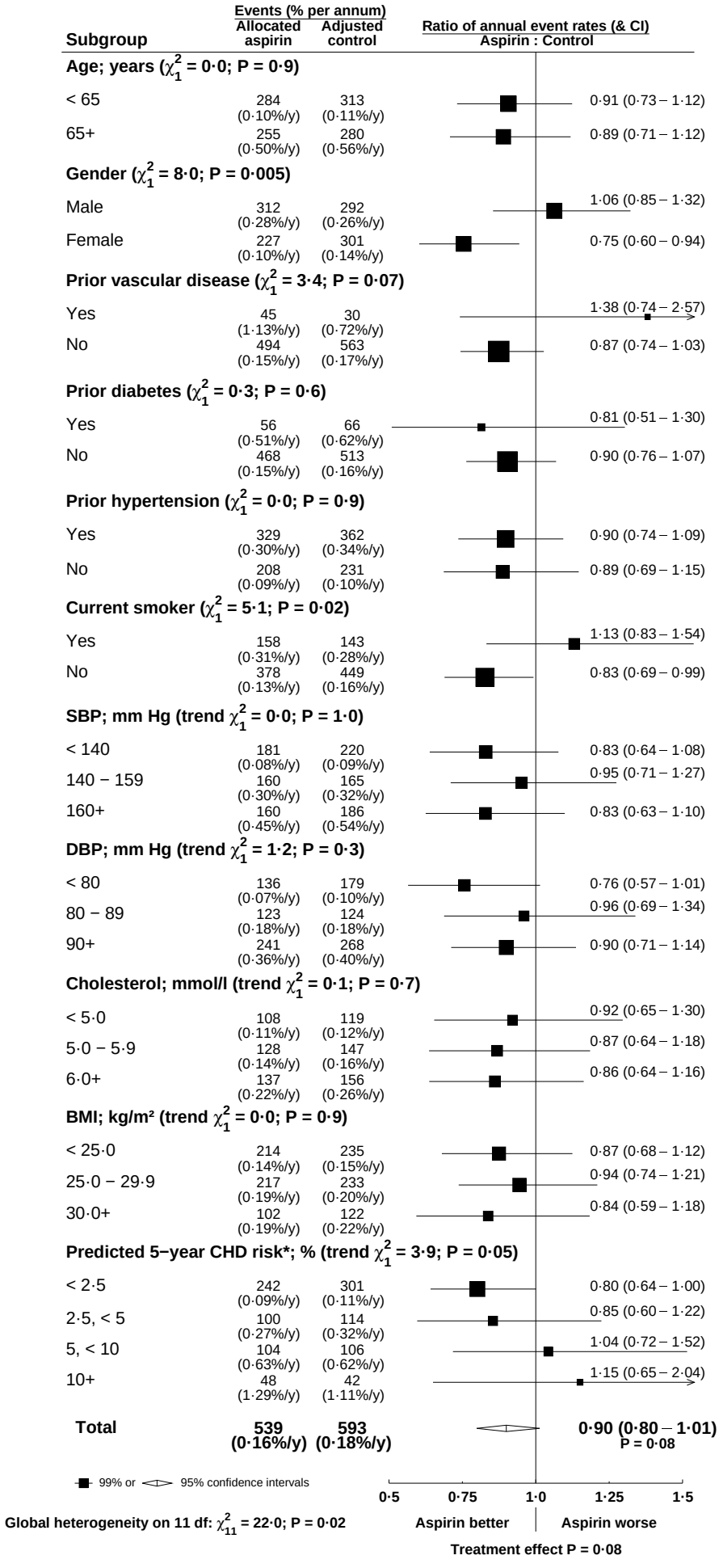
Web Figure 3: STROKE SUBTYPES (first stroke only) in primary prevention trials, by study
Symbols and conventions as in text - figure 2



† 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.

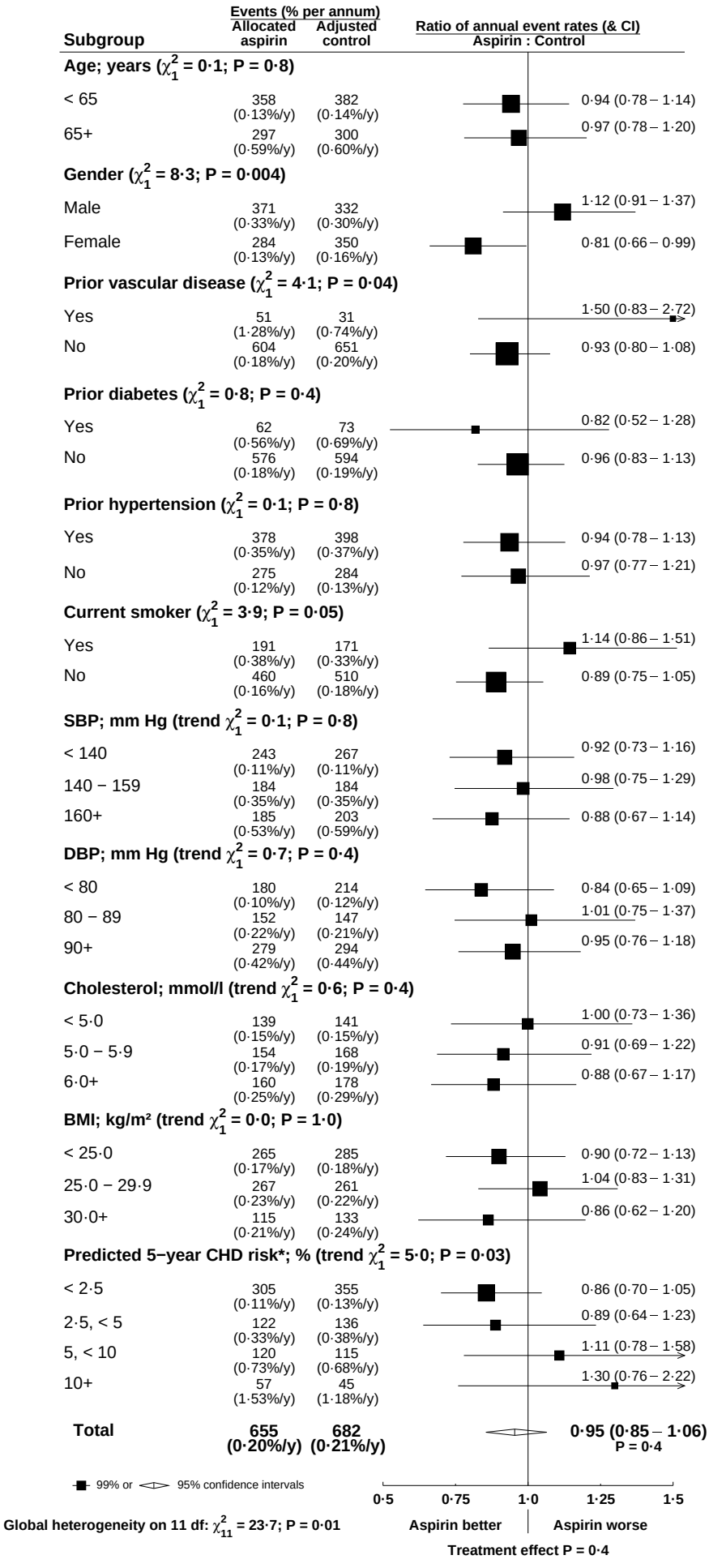
†† Non–haemorrhagic strokes in HOT were not further subdivided.

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



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

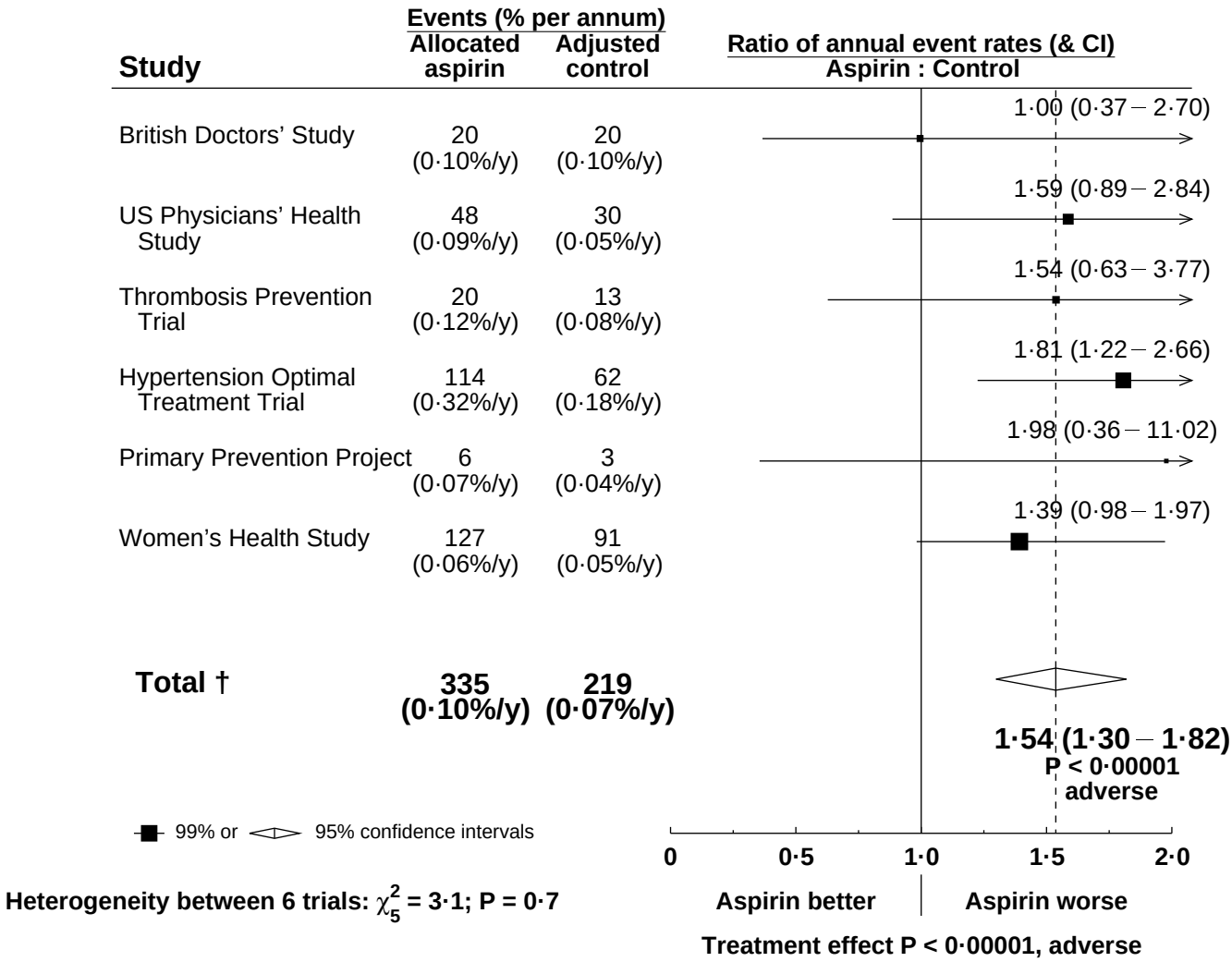
Web Figure 5: FIRST STROKE (any type) in primary prevention trials - subgroup analyses
Symbols and conventions as in text - figure 2



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

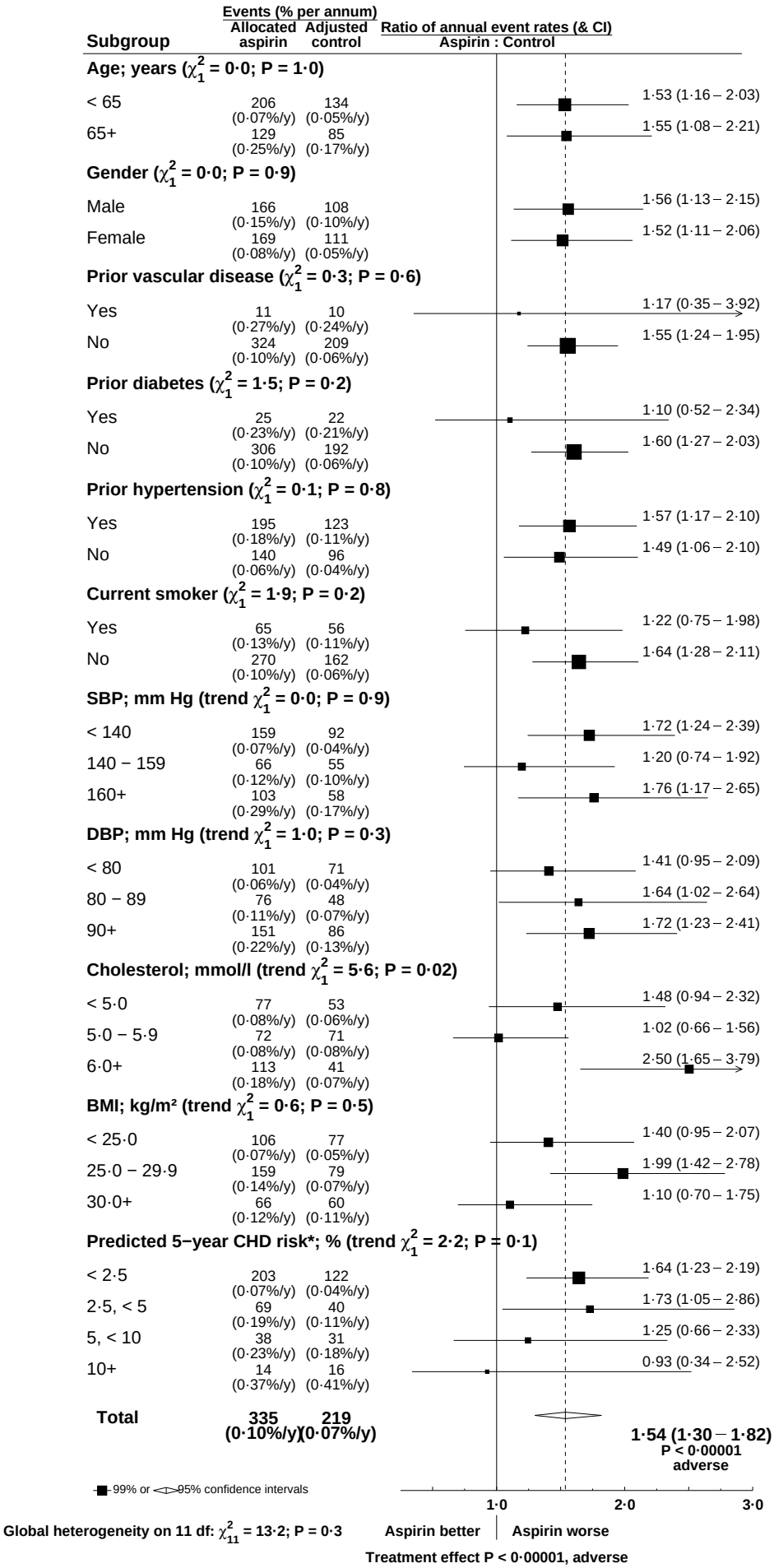
Web Figure 6: GASTRO−INTESTINAL BLEED (or other major extracranial bleed) in primary prevention trials, by study

Symbols and conventions as in text - figure 2



† Includes 9 vs. 20 fatal bleeds, P = 0·07 reduction.

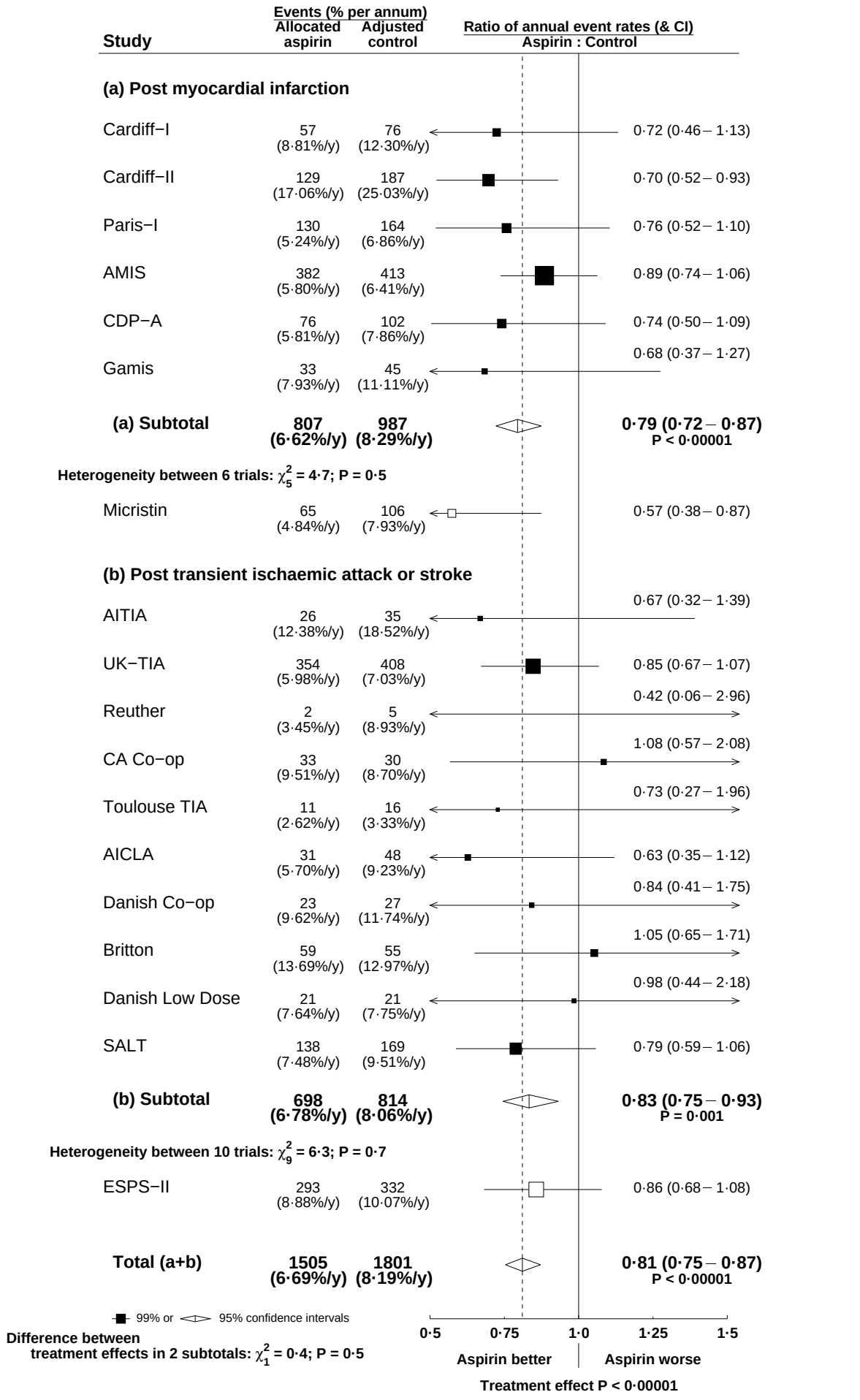
Web Figure 7: GASTRO−INTESTINAL BLEED (or other major extracranial bleed) in primary prevention trials - subgroup analyses. Symbols and conventions as in text - figure 2



N.B. Unknown values not plotted

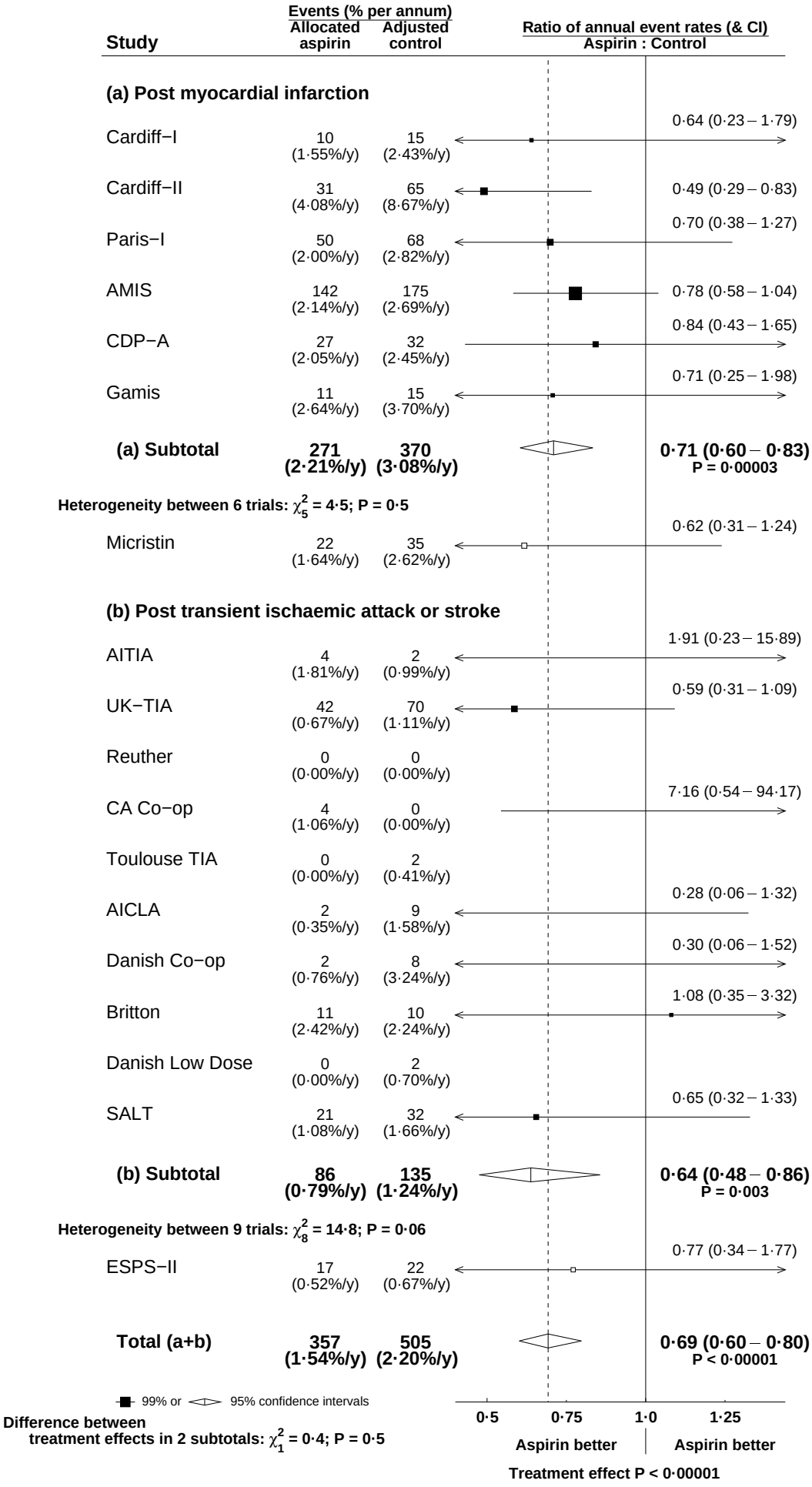
* Excluding patients with history of vascular disease

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



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

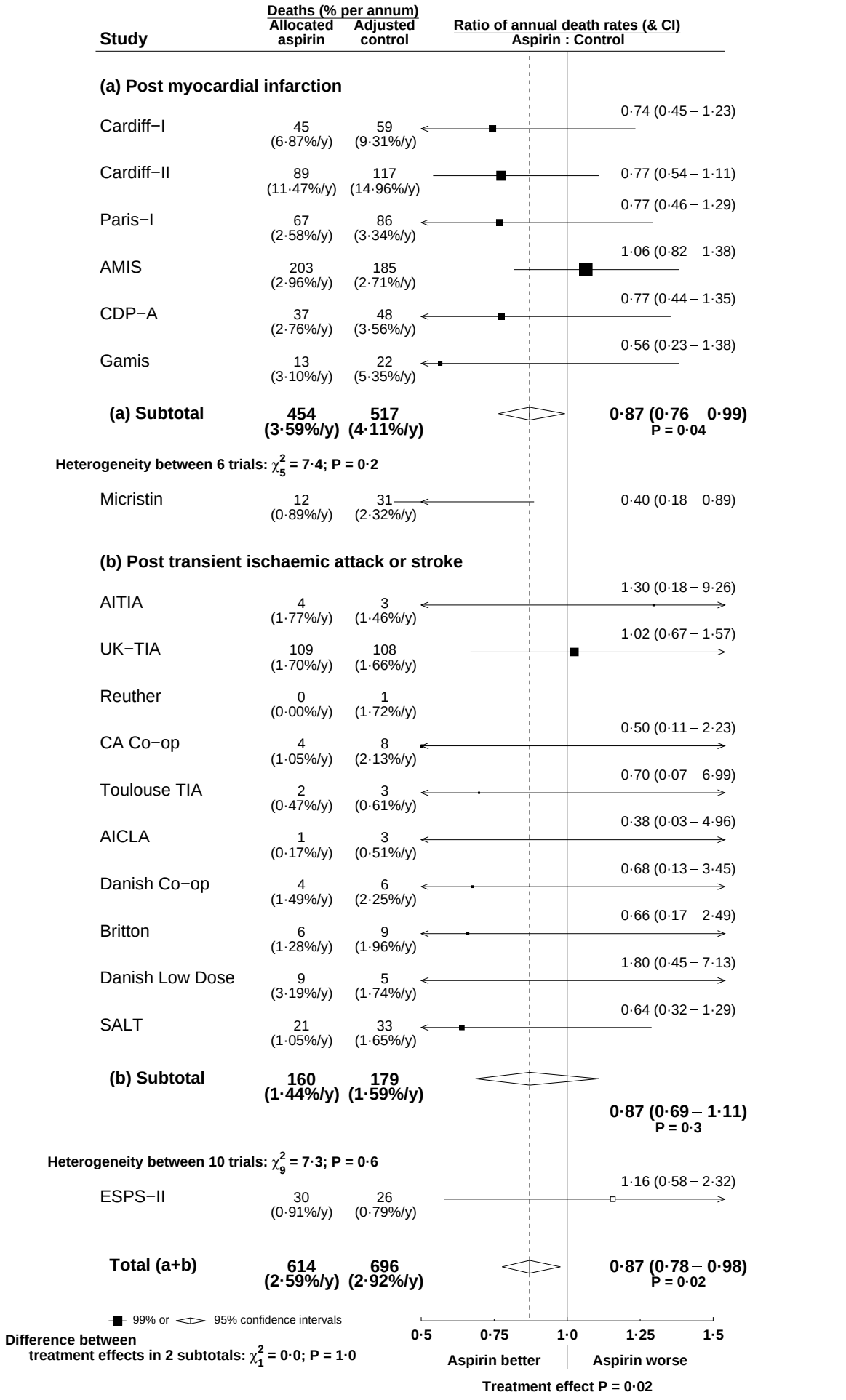
Web Figure 9: NON−FATAL MYOCARDIAL INFARCTION in secondary prevention trials, by study
Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

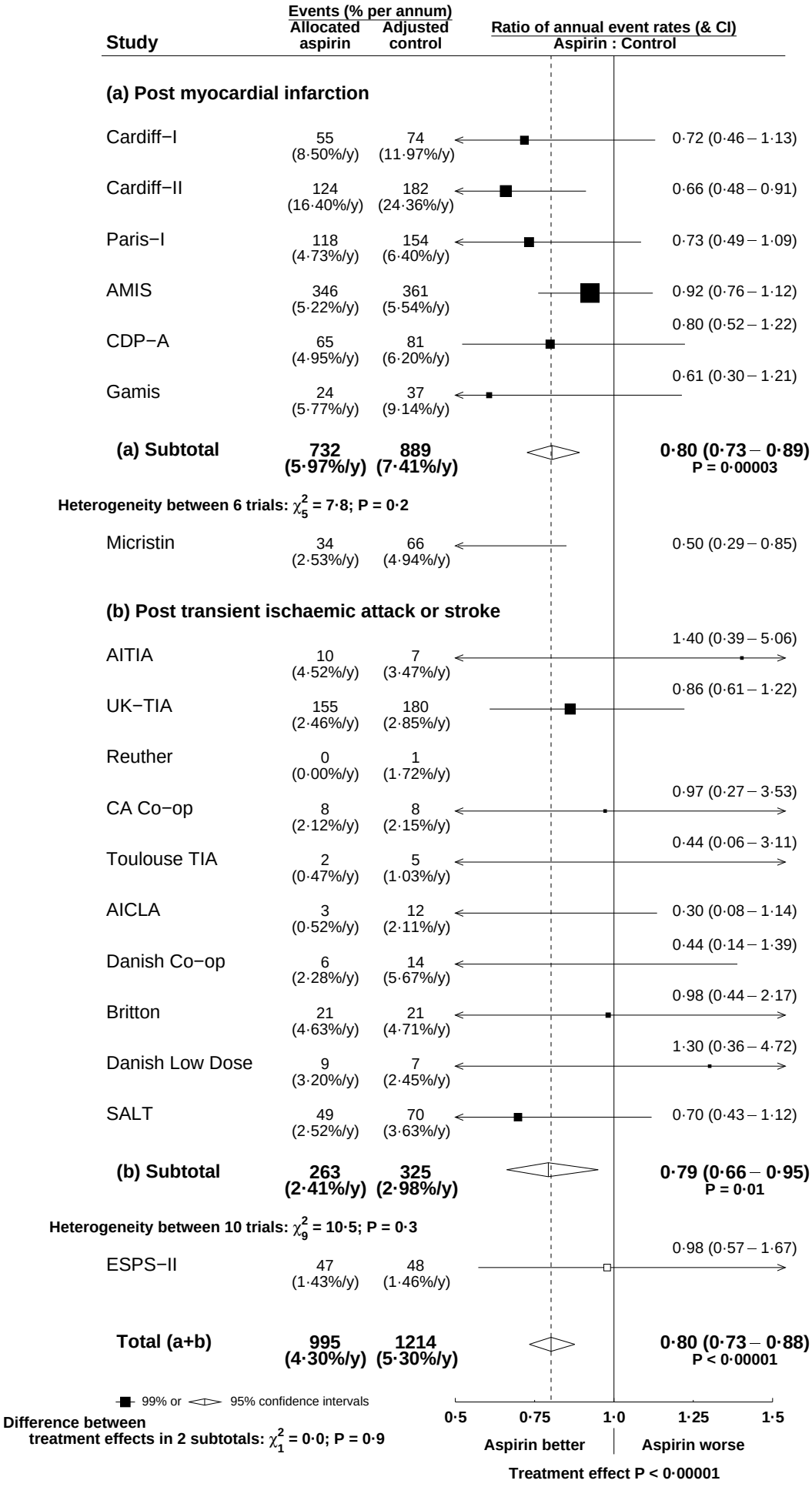
Web Figure 10: CHD DEATH in secondary prevention trials, by study

Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

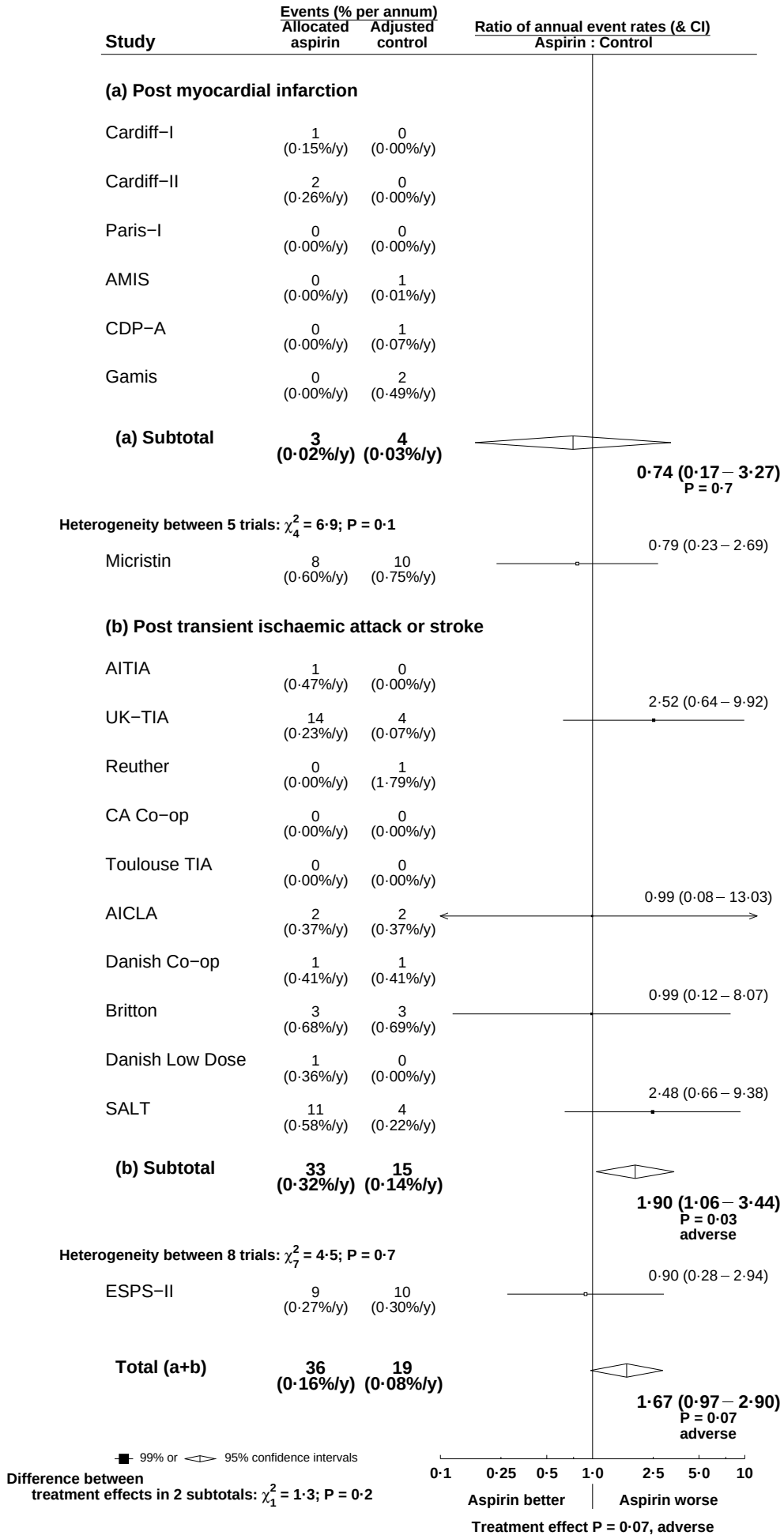
Web Figure 11: MAJOR CORONARY EVENTS in secondary prevention trials, by study
Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

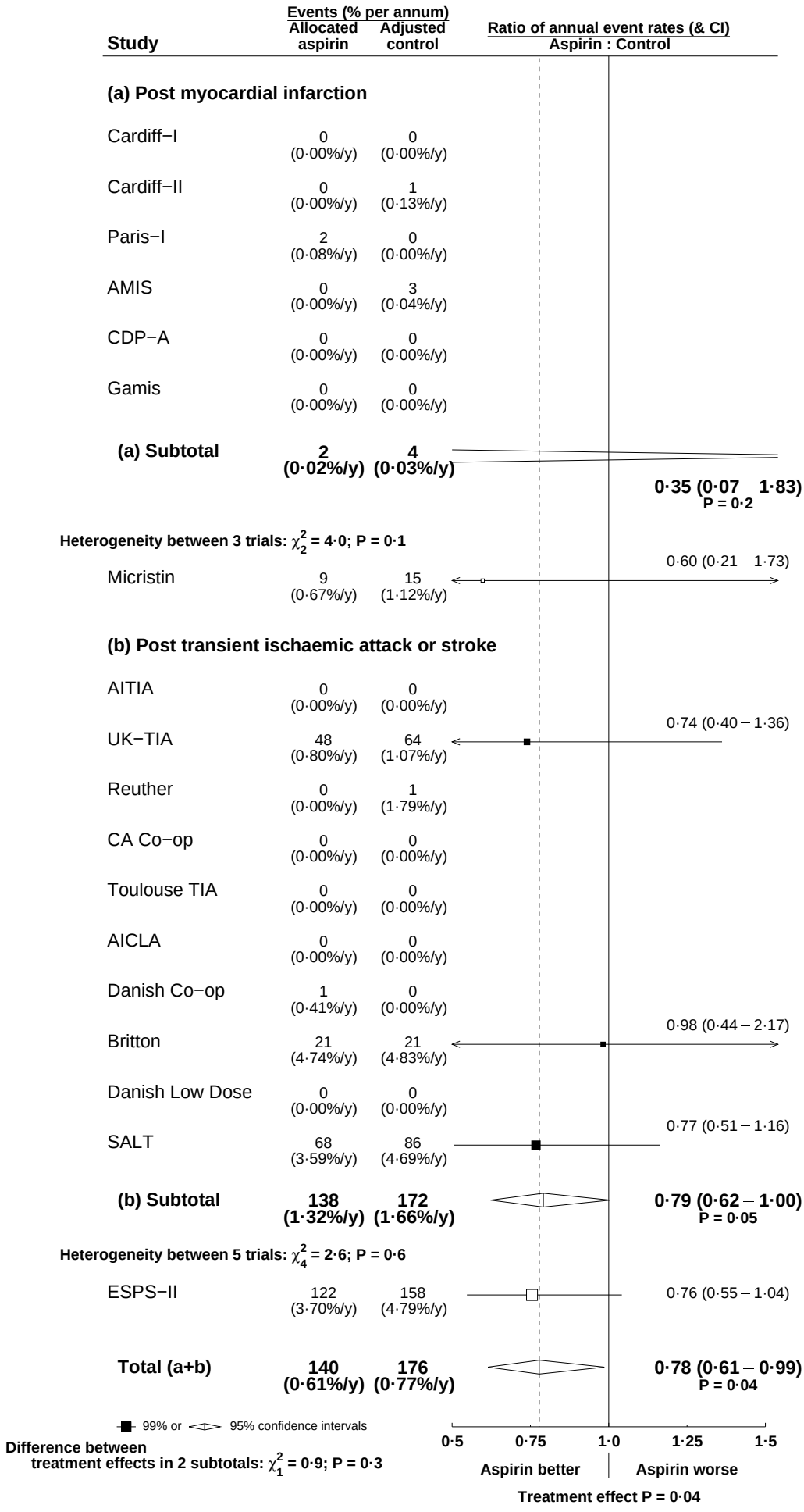
Web Figure 12: HAEMORRHAGIC STROKE in secondary prevention trials, by study

Symbols and conventions as in text - figure 2



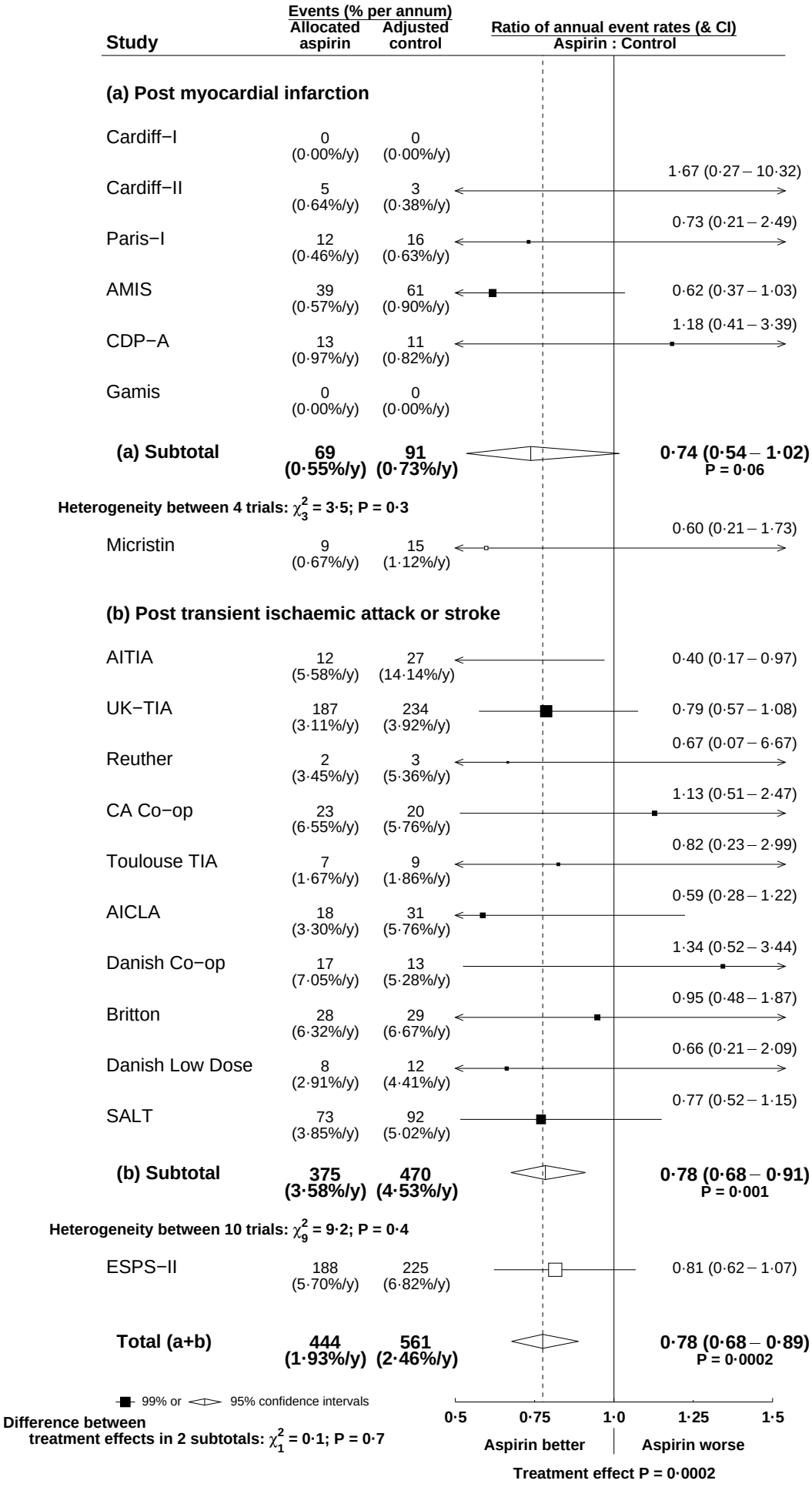
Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.
NB: Most strokes of known cause were in just three trials (UK-TIA, Britton and SALT), all in patients with prior cerebral vascular disease.

Web Figure 13: DEFINITELY ISCHAEMIC STROKE in secondary prevention trials, by study
Symbols and conventions as in text - figure 2



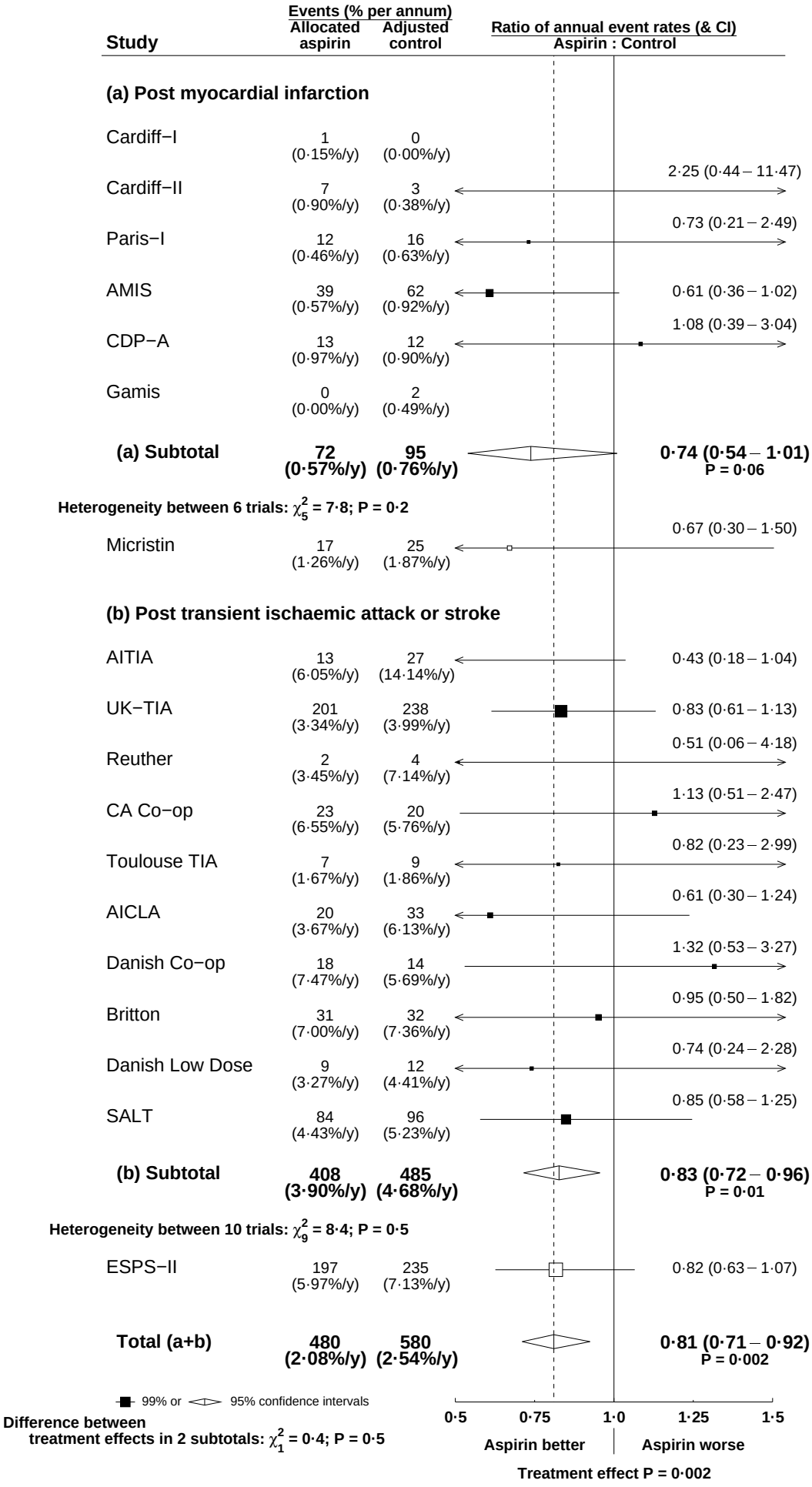
Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.
NB: Most strokes of known cause were in just three trials (UK-TIA, Britton and SALT), all in patients with prior cerebral vascular disease.

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



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.

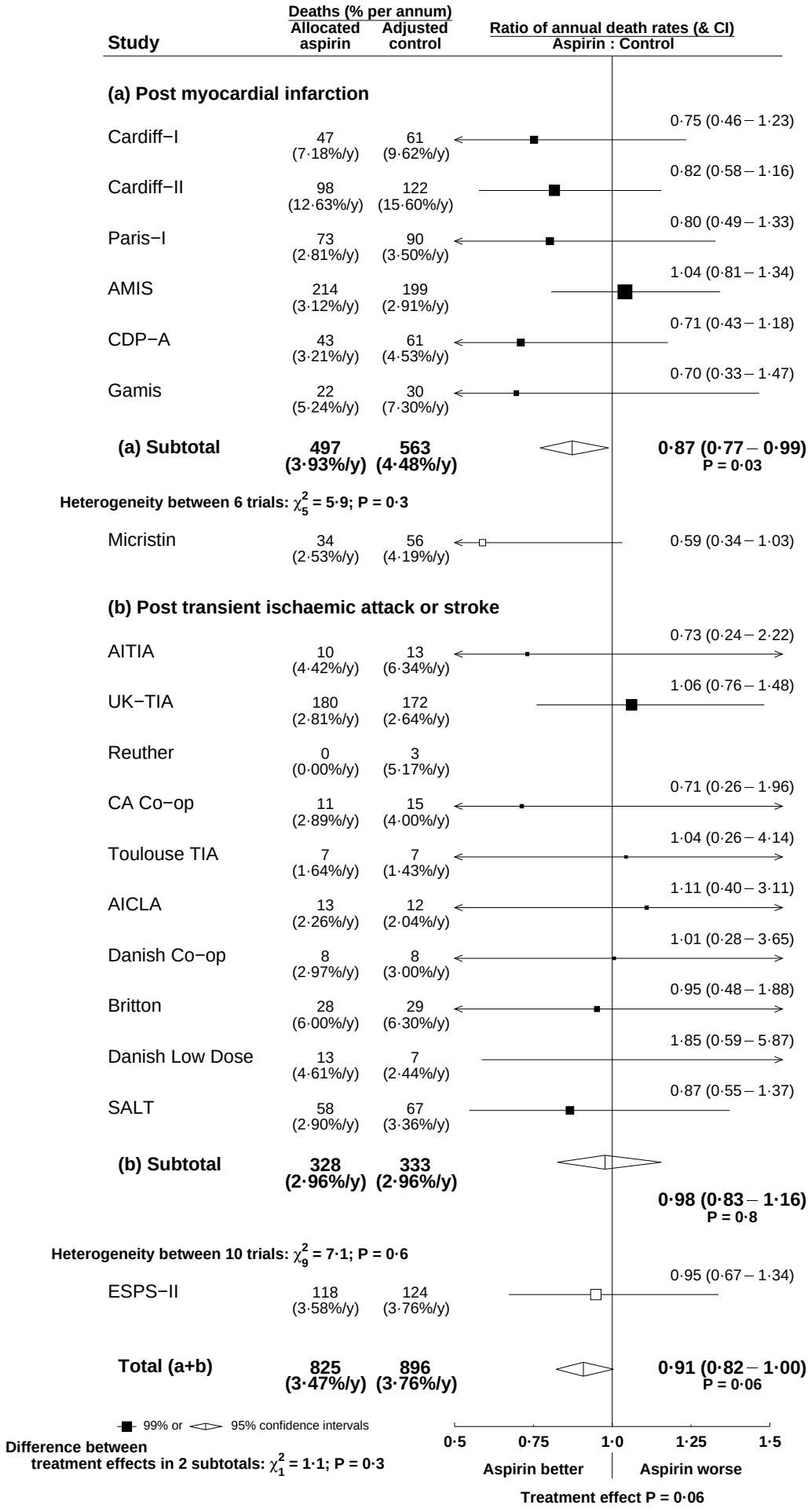
Web Figure 15: ANY STROKE in secondary prevention trials, by study
Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

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

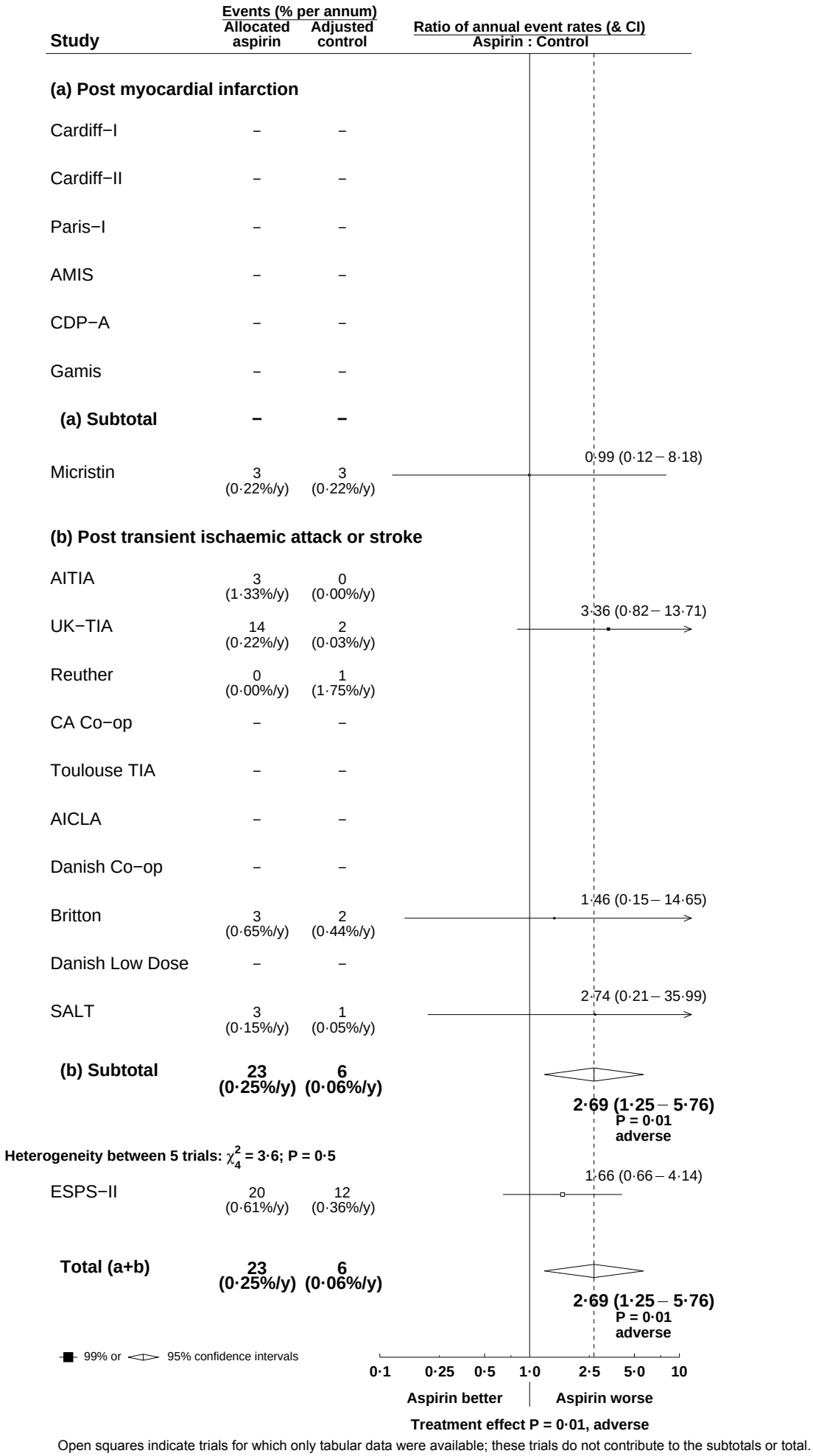
Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

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

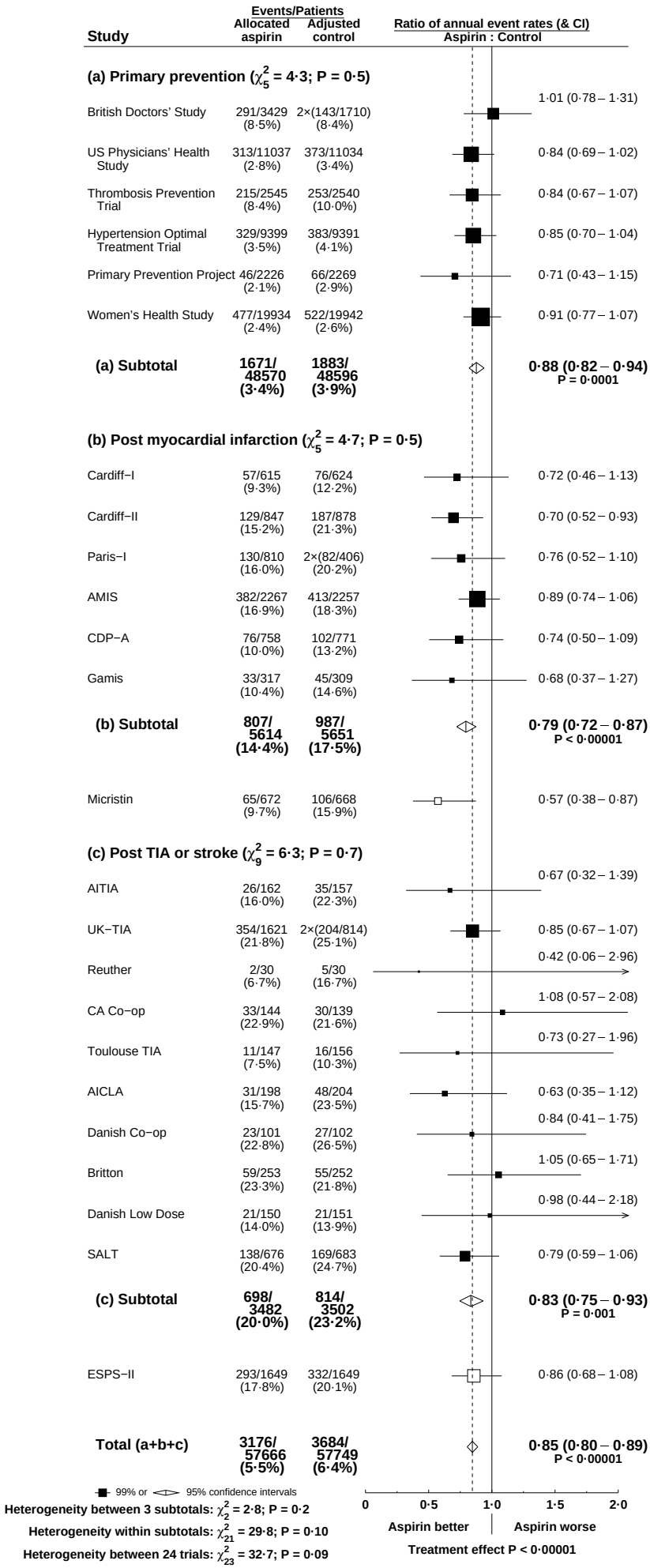
Symbols and conventions as in text - figure 2



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

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.



Open squares indicate trials for which only tabular data were available; these trials do not contribute to the subtotals or total.

References for secondary prevention trials

1. Elwood PC, Cochrane AL, Burr ML, Sweetnam PM, Williams G, Welsby E, et al. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J* 1974; **1**: 436-40.

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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:

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

where α_j is the average (log) annual event rate observed in the placebo group in study *j*, $\boldsymbol{x_{ijk}}$ is the vector of baseline characteristics for patient *i* in study *j* (including an indicator variable corresponding to randomisation to aspirin), $\bar{\boldsymbol{x}}_{\cdot \boldsymbol{j0}}$ is the vector of mean baseline risk exposure levels observed among the placebo patients in study *j*, and $\boldsymbol{\beta}$ 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/m^2). Missing values of baseline characteristics were imputed based on the study-specific average levels in the placebo group $\bar{\boldsymbol{x}}_{\cdot \boldsymbol{j0}}$. 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 $\boldsymbol{\beta}$ 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

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

and

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

Individuals were categorised as "very low" (<2.5%), "low" (2.5-5%), "moderate" (5-10%), or "high" (≥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).