tion study, in which 6602 such patients were allocated to receive aspirin (25 mg twice daily), modified release dipyridamole (200 mg twice daily), both, or neither in a 2×2 factorial design.[17] Overall, among 18 270 patients in 21 trials (compared with 10 255 patients in 18 trials previously[1]), allocation to a mean duration of 29 months of antiplatelet therapy resulted in 36 (6) fewer serious vascular events per 1000 patients (fig 2). This benefit reflects a large and highly significant reduction in non-fatal stroke (25 (5) fewer/1000; $P<0.0001$: fig 3c), along with a smaller but still significant reduction in non-fatal myocardial infarction (6 (2) fewer/1000; $P=0.0009$).

Although the reduction in vascular mortality of 7 (4) per 1000 was only marginally significant ($P=0.04$), the highly significant reductions in non-fatal vascular events and in all cause mortality (15 (5) fewer deaths/1000; $P=0.002$) strongly reinforce the conclusion that prolonged antiplatelet therapy reduces the risk of death in such patients. These benefits clearly exceeded the estimated excess risk of bleeding of about 1-2 additional major extracranial bleeds per 1000 patients per year.

Patients with acute ischaemic stroke

Almost no information about the effects of antiplatelet therapy in acute ischaemic stroke was available for the previous analyses (table 1).[1] Subsequently, results have emerged from the international stroke trial of 300 mg daily aspirin versus open control[18] and the Chinese acute stroke trial of 160 mg daily aspirin versus placebo.[19] These trials each included about 20 000 patients with suspected acute ischaemic stroke.[20] Overall, among 40 821 such patients in seven trials, allocation to a mean duration of three weeks of antiplatelet therapy produced an 11% (3%) proportional reduction in vascular events (fig 1), which was somewhat smaller than in other high risk categories. The resulting absolute reduction of 9 (3) fewer serious vascular event per 1000 patients (fig 2) reflects significant reductions in non-fatal stroke (4 (2) fewer/1000; $P=0.003$; fig 3d) and in vascular deaths (5 (2) fewer/1000; $P=0.05$), with information on non-fatal myocardial infarction not recorded in either the international stroke trial or Chinese acute stroke trial.

For 40 428 patients in four of these trials,[18 19 21 22] it was possible to separate the stroke outcomes into those considered to be due to haemorrhage and those that were considered to be ischaemic (or of unknown cause). Antiplatelet therapy produced an absolute excess of 1.9 (SE 1.0) haemorrhagic strokes per 1000 patients, which was counterbalanced by an absolute reduction of 6.9 (1.4) fewer ischaemic strokes per 1000, yielding the overall reduction in the risk of any further stroke (including those of unknown cause) of 5.4 (1.9) per 1000. The excess risk of major extracranial

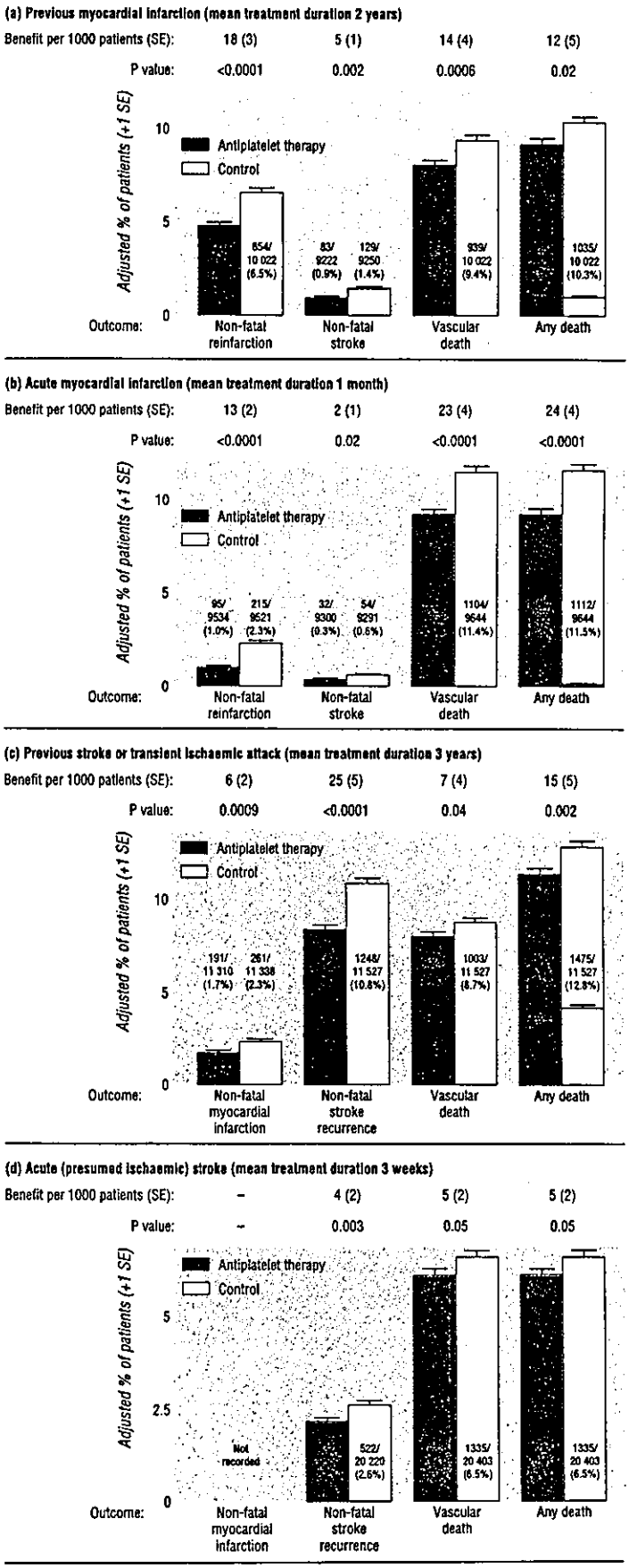


Fig 3 Absolute effects of antiplatelet therapy on various outcomes in patients with (a) previous myocardial infarction (12 trials); (b) acute myocardial infarction (15 trials); (c) previous stroke or transient ischaemic attack (21 trials); and (d) acute (presumed ischaemic) stroke (seven trials). Adjusted control totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once. In "any death" columns, non-vascular deaths are represented by lower horizontal lines (and may be calculated by subtracting vascular deaths from any deaths)

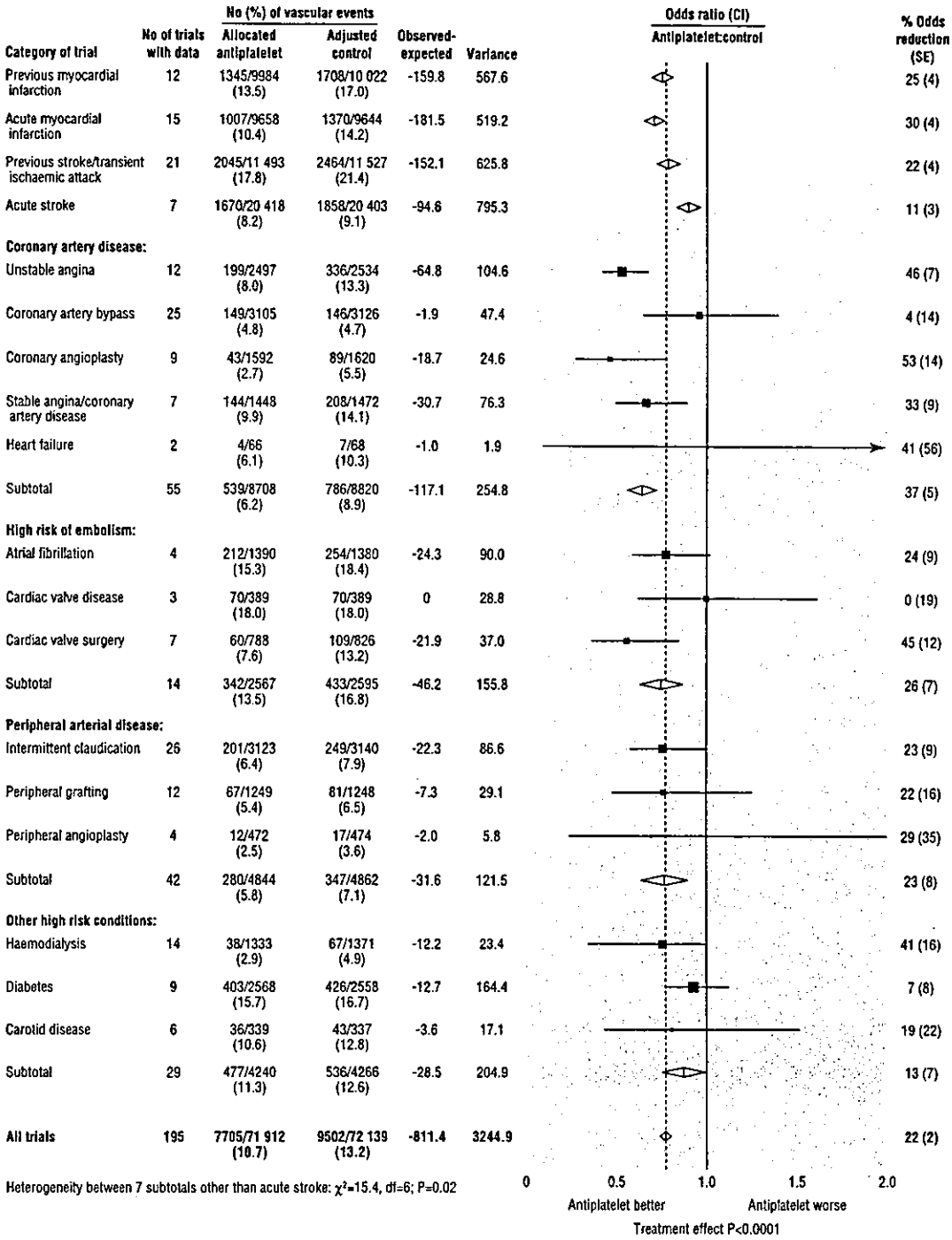


Fig 4 Proportional effects of antiplatelet therapy on vascular events in 195 trials in high risk patients subdivided by disease category. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analysis of results for each main category and for all trials (and 95% confidence interval) is represented by an open diamond. Adjusted control totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, but other statistical calculations are based on actual numbers from individual trials

bleeding was estimated at about three additional such bleeds per 1000 allocated antiplatelet therapy, and more detailed analysis of the international stroke trial suggested that much of this excess occurred when antiplatelet therapy was given in conjunction with heparin (absolute excess 9 (2) per 1000 with heparin *v* 2 (1) per 1000 without heparin).[18]

Effects in other high risk categories

In the previous cycle of analyses,[1] information was available on serious vascular events from 104 trials among about 20 000 patients with various other conditions associated with an increased risk of vascular events. Subsequently, more information has become available for certain of these conditions, which we have

grouped into four main categories: coronary artery disease (which includes unstable angina, coronary artery bypass grafting, coronary angioplasty, stable angina, and heart failure); high risk of embolism (which includes non-rheumatic atrial fibrillation, cardiac valve disease, and cardiac valve surgery); peripheral arterial disease (which includes intermittent claudication, peripheral grafting, and peripheral angioplasty); and other high risk conditions (which includes haemodialysis patients having fistula or shunt placement, diabetes mellitus, and carotid disease).

In patients in each of the four main categories and their 14 components, the practical medical question is whether to give antiplatelet therapy. For that, it may suffice to know that the overall results for these "other high risk" categories show substantial reductions in myocardial infarction, stroke, and vascular death. This general conclusion can then be applied semiquantitatively in each of the 14 separate components, even if the results in one particular component considered separately do not indicate significant benefit.

Many of the odds ratios for individual components are associated with confidence intervals that are at least as wide as the likely magnitude of any treatment benefit (fig 4). Thus, even if antiplatelet therapy were of similar efficacy in all circumstances, several false negative results would be expected just from the play of chance. For example, the lack of evidence of benefit in patients randomised because of diabetes is not good evidence of lack of benefit in diabetic patients. (Indeed, even without any allowance for multiple comparisons, the 99% confidence interval for the proportional risk reduction in diabetic patients includes a risk reduction of one quarter, and the risks among diabetic patients are so high that the absolute benefit from such a risk reduction would be substantial.) Even if it is accepted, however, that antiplatelet treatment will produce an appreciable risk reduction in each type of patient at high risk of occlusive vascular disease, it is still of some interest to consider whether there is good evidence that the proportional risk reductions are different in different subcategories.

Other high risk patients with coronary artery disease

Overall, among 15 828 patients with coronary artery disease in 55 trials (compared with 9731 patients in 35 such trials previously[1]) there was a highly significant 37% (5%) proportional reduction in serious vascular events ($P<0.0001$; fig 4). The substantial increase in information available about the effects of antiplatelet therapy among patients with stable angina is due mainly to the results of the Swedish angina pectoris aspirin trial, in which 2035 patients were allocated to receive 75 mg aspirin daily or placebo.[23] There were independently significant benefits among patients with unstable angina (46% (7%) reduction, $P<0.0001$), those having coronary angioplasty (53% (14%) reduction, $P<0.0002$), and those with stable angina (33% (9%) reduction, $P=0.0004$).

The proportional risk reduction among patients who had recently had coronary artery bypass grafting was smaller (4% (14%)), but the confidence interval is wide and includes a risk reduction of one quarter. Hence, the apparent lack of effect of antiplatelet therapy on vascular events immediately after coronary artery bypass surgery may—given the clear evidence of benefit among other patients with coronary artery disease—be largely or wholly due to chance. Only 134 patients have been included in trials of antiplatelet therapy for heart failure, but most such patients have coronary artery disease,[24] for which antiplatelet therapy is of known benefit.

Patients at high risk of embolism

Several cardiac and vascular conditions are associated with an increased risk of embolism to the brain or peripheral circulation, including atrial fibrillation (which was predominantly non-rheumatic), cardiac valve disease, and cardiac valve replacement. Overall, among 5162 patients at high risk of embolism in 14 trials (compared with 3190 such patients in nine trials previously[1]) there was a highly significant 26% (7%) proportional reduction in serious vascular events ($P=0.0003$; fig 4).

Atrial fibrillation is the commonest cardiac condition giving rise to embolism and is an important cause of stroke among elderly people.[25] Most of the additional information about the effects of antiplatelet therapy among patients with atrial fibrillation was provided by the European atrial fibrillation trial,[26] in which high risk patients with a previous stroke or transient ischaemic attack were randomised to aspirin or placebo (or oral anticoagulant, if eligible). Overall, among 2770 patients with atrial fibrillation in four trials there was a proportional reduction of 24% (9%) in serious vascular events (or 23% (10%) if one small trial of indobufen *v* placebo that also included some patients without atrial fibrillation is excluded[27]).

Patients with peripheral arterial disease

Overall, among 9214 patients with peripheral arterial disease in 42 trials (compared with 4939 such patients in 33 trials previously[1]) there was a proportional reduction of 23% (8%) in serious vascular events ($P=0.004$; fig 4), with similar benefits among patients with intermittent claudication, those having peripheral grafting, and those having peripheral angioplasty (heterogeneity test $\chi^2=3.8$, $df=3$; NS). Much of the new evidence came from the atherosclerotic disease evolution by picotamide trial, in which 2304 patients with intermittent claudication were allocated to receive the thromboxane synthase inhibitor picotamide or placebo.[6]

Other high risk conditions

Other groups of patients at high risk of occlusive arterial disease that have been studied include haemodialysis patients having shunt or fistula replacement, patients with diabetes, patients having carotid endarterectomy, and patients with asymptomatic carotid stenosis. Studies of antiplatelet therapy among haemodialysis patients after placement of a dialysis shunt or fistula included in the previous meta-analysis[1] had typically lasted only a few weeks, but several of the more recent trials assessed the effects of 12-18 months of treatment. Overall, among 2632 patients in 14 trials (compared with only 525 patients in 10 trials previously[1]), antiplatelet therapy produced a 41% (16%) proportional reduction in serious vascular events. Even though this result is based on only 99 vascular events among such patients, it is consistent with the benefits seen in other circumstances. Chronic renal failure is associated with impaired haemostasis, but only 46 major extracranial bleeds (27/

Category of trial	No of trials with data	No (%) of vascular events: Regimen 1	Regimen 2	Observed-expected	Variance	% Odds reduction (SE)
Higher v lower aspirin doses:						
500-1500 mg v 75-325 mg*	7	227/1608 (14.1)	231/1589 (14.5)	-3.1	93.0	3 (10)
≥75 mg v <75 mg†	3	254/1795 (14.2)	234/1775 (13.2)	8.5	104.3	-8 (10)
Subtotal	10	481/3403 (14.1)	465/3364 (13.8)	5.4	197.3	-3 (7)
Another antiplatelet drug v aspirin:						
Sulfinpyrazone	5	85/526 (16.2)	88/673 (13.1)	5.5	34.1	-18 (19)
Triflusal	3	135/1331 (10.1)	146/1344 (10.9)	-4.6	61.8	7 (12)
Ridogrel	2	50/519 (9.6)	64/524 (12.2)	-7.0	23.4	26 (18)
Dipyridamole	3	298/1783 (16.7)	293/1775 (16.5)	2.0	121.4	-2 (9)
Indobufen	3	37/704 (5.3)	29/705 (4.1)	4.0	15.7	-29 (29)
Ticlopidine	4	397/1884 (21.1)	443/1907 (23.2)	-20.7	160.2	12 (7)
Clopidogrel	1	970/9599 (10.1)	1063/9586 (11.1)	-47.2	454.4	10 (4)
Another antiplatelet‡	6	10/797 (1.3)	11/795 (1.4)	-0.3	4.6	6 (45)
Subtotal	27	1982/17 143 (11.6)	2137/17 309 (12.3)	-68.3	875.6	8 (3)
Aspirin + another antiplatelet v aspirin:						
Aspirin + dipyridamole	25	614/5198 (11.8)	648/5206 (12.4)	-17.1	268.5	6 (6)
Aspirin + sulfinpyrazone	2	38/283 (13.4)	49/283 (17.3)	-5.6	18.4	26 (20)
Aspirin + ticlopidine	1	26/546 (4.8)	33/557 (5.9)	-3.2	14.0	20 (24)
Aspirin + intravenous GP IIb/IIIa inhibitor	15	1334/13 541 (9.9)	1610/13 591 (11.8)	-121.6	583.2	19 (4)
Subtotal	43	2012/19 568 (10.3)	2340/19 637 (11.9)	-147.5	884.1	15 (3)

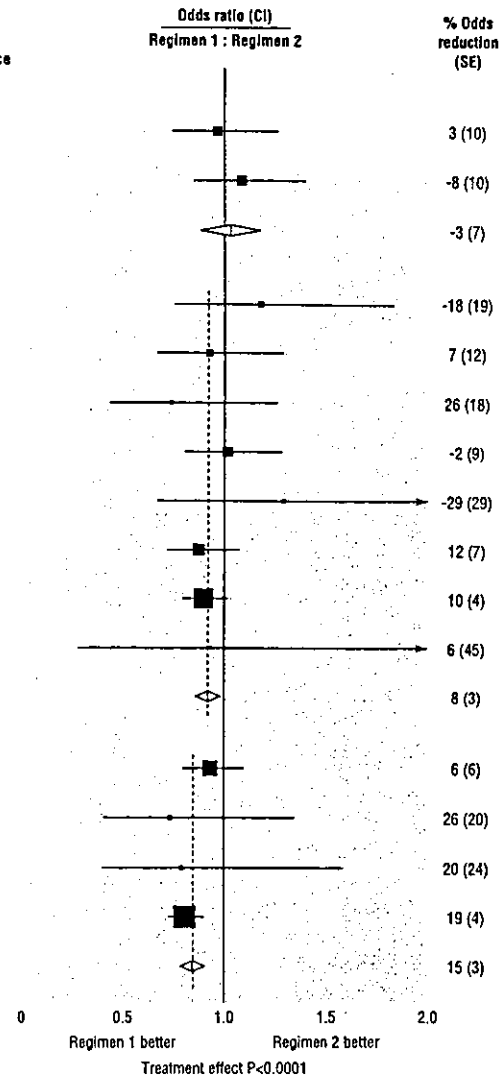


Fig 5 Direct comparisons of proportional effects of different antiplatelet regimens on vascular events in high risk patients. Only meta-analyses involving a total of 500 or more high risk patients are shown. *Includes one trial comparing 1400 mg/day v 350 mg/day,[30] and another (excluding those with acute stroke) comparing 1000 mg/day v 300 mg/day among patients who were also given dipyridamole.[31] †Includes two trials comparing 75-325 mg aspirin daily v <75 mg aspirin daily[32 33] and one trial of 500-1500 mg aspirin daily v <75 mg aspirin daily.[34] ‡Includes cilostazol, sulotroban, trapidil, E5510, eptifibatide, and GR32191B. Stratified ratio of odds of an event in regimen 1 group to that in regimen 2 group is plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analysis of results for all trials for a particular comparison (and 95% confidence interval) is represented by an open diamond

1333 (2.0%) antiplatelet v 31/1371 (2.3%) adjusted control; NS) were recorded in these trials, so the size of any bleeding hazards cannot be reliably estimated.

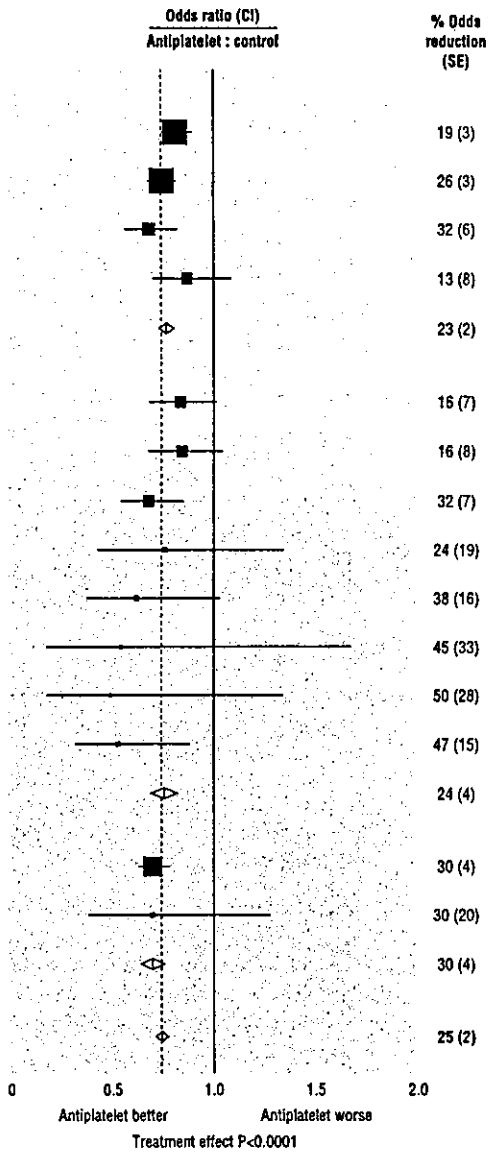
Diabetes mellitus is also associated with an increased risk of vascular events, even in the absence of diagnosed cardiovascular disease. Much of the new information comes from the early treatment diabetic retinopathy study,[28] in which 3711 people with diabetes (and, generally, no history of myocardial infarction or stroke) were allocated to receive 650 mg aspirin daily or placebo. Overall, among 4961 patients with diabetes in nine trials (compared with 1365 patients in seven trials previously[1]), antiplatelet therapy was associated with only a 7% (8%) proportional reduction in serious vascular events (which remains consistent, however, with the reduction of about one quarter observed overall). None of the trials reported major extracranial bleeds, but the early treatment diabetic retinopathy study indicated that aspirin did not increase the risk of vitreous or retinal haemorrhage.[29]

Relatively small numbers of patients with carotid atherosclerosis have been studied. The overall results in five trials of antiplatelet therapy after carotid endarterectomy and one among patients with asymptomatic carotid disease (36/339 (10.6%) antiplatelet v 43/337 (12.8%) adjusted control; 19% (22%) reduction; NS) are consistent with those observed in other patients at high risk of stroke.

Comparisons of different antiplatelet regimens

Many small trials compared different antiplatelet drugs, but the analysis in figure 5 is restricted to direct randomised comparisons in which a total of at least 500 patients had been studied. The effects of different

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	No (%) of vascular events: Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Aspirin alone (mg daily):						
500-1500	34	1621/11 215 (14.5)	1930/11 236 (17.2)	-147.1	707.8	19 (3)
160-325	19	1526/13 240 (11.5)	1963/13 273 (14.8)	-219.9	742.6	26 (3)
75-150	12	366/3370 (10.9)	517/3406 (15.2)	-72.0	183.8	32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	-18.9	136.5	13 (8)
Any aspirin*	65	3829/29 652 (12.9)	4764/29 743 (16.0)	-452.3	1717.0	23 (2)
Other antiplatelet drugs:						
Dipyridamole	15	392/2696 (14.5)	458/2734 (16.8)	-30.9	173.0	16 (7)
Sulfinpyrazone	19	315/2411 (13.1)	361/2416 (14.9)	-23.8	140.7	16 (8)
Ticlopidine	42	278/3435 (8.1)	385/3475 (11.1)	-50.5	132.3	32 (7)
Suloctidil	6	47/364 (12.9)	59/367 (16.1)	-5.6	20.5	24 (19)
Picotamide	4	41/1583 (2.6)	66/1602 (4.1)	-12.2	25.8	38 (16)
Sulotroban	4	8/406 (2.0)	14/409 (3.4)	-3.2	5.3	45 (33)
Triflusal	2	10/314 (3.2)	19/309 (6.1)	-4.7	6.7	50 (28)
Other†	9	41/647 (6.3)	73/641 (11.4)	-16.1	25.6	47 (15)
Any other single agent	101	1132/11 856 (9.5)	1435/11 953 (12.0)	-147.0	529.9	24 (4)
Aspirin + another antiplatelet drug:						
Aspirin + dipyridamole	46	1036/9703 (10.7)	1393/9738 (14.3)	-172.6	488.7	30 (4)
Aspirin + sulfinpyrazone	2	38/283 (13.4)	50/278 (18.0)	-6.5	18.5	30 (20)
Any combination	48	1074/9986 (10.8)	1443/10 016 (14.4)	-179.1	507.2	30 (4)
All trials	**188**	**6035/51 494 (11.7)**	**7644/51 736 (14.8)**	**-715.7**	**2449.6**	**25 (2)**



Heterogeneity of odds reductions between:
Different aspirin doses: χ^2=7.7, df=3; P=0.05
Other antiplatelet *v* any aspirin: χ^2=10.8, df=8; P>0.1

Fig 6 Indirect comparisons of proportional effects of different antiplatelet regimens on vascular events in high risk patients (excluding those with acute stroke). Only meta-analyses involving 500 or more high risk patients are shown. *Some trials contributed to more than one comparison. †Includes indobufen, flurbiprofen, GR32191B, dazoxiben, and trapidil. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analysis of results for each main comparison and for all trials (and 95% confidence interval) is represented by an open diamond. Adjusted control totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, but statistical calculations are based on actual numbers from individual trials

regimens can also be compared indirectly by comparing the size of the protective effect observed in the trials of one particular antiplatelet regimen versus control with the size of the protective effect in trials of another antiplatelet regimen versus control (fig 6). Such indirect comparisons need to be interpreted more cautiously than direct comparisons because there is some potential for bias if patients in the trials had different types of disease. Much of this bias can, however, be avoided by restricting attention to proportional reductions among high risk patients other than those with acute stroke (in whom antiplatelet therapy has a significantly smaller proportional effect on serious vascular events).

Effects of different doses of aspirin

Aspirin doses below 75 mg daily have been suggested to be more effective than higher doses because such low doses are reported to "spare" prostacyclin (a platelet antiaggregant and vasodilator) and cause less gastrointestinal toxicity.[5] Since the previous meta-analysis, much more information has become available from both direct and indirect comparisons on very low daily aspirin doses (table 1). Overall, among 3570 patients in three trials directly comparing aspirin ≥75 mg daily *v* aspirin <75 mg daily there was no significant difference between the different aspirin regimens (fig 5). However, aspirin doses of <75 mg have been less widely assessed than doses of 75-150

mg daily, so there remains uncertainty about whether such low doses are as effective as daily doses of ≥75 mg. Among the trials of higher daily doses of aspirin *v* no aspirin (fig 6), no particular range of aspirin dose was preferable for the prevention of serious vascular events. The proportional reduction in vascular events was 19% (3%) with 500-1500 mg daily, 26% (3%) with 160-325 mg daily, and 32% (6%) with 75-150 mg daily. However, daily doses <75 mg seemed to have a somewhat smaller effect (proportional reduction 13% (8%); $\chi^2=7.7$, df=3; P=0.05; fig 6).

There was no good evidence to support the suggestion that aspirin doses of ≥1000 mg daily might be preferable for the prevention of serious vascular events among patients at high risk of stroke.[35 36] This observation is reinforced by the aspirin and carotid endarterectomy trial (which was not included in this meta-analysis as it was reported after 1997). In that study the risk of the composite outcome of myocardial infarction, stroke, or death within three months of carotid endarterectomy was significantly lower among patients taking 81 mg or 325 mg aspirin daily than in those taking 625-1300 mg.[37]

In trials comparing aspirin with control, the proportional increase in the risk of a major extracranial bleed was similar with all daily aspirin doses <325 mg (odds ratios 1.7 (95% confidence interval 0.8 to 3.3) for <75 mg; 1.5 (1.0 to 2.3) for 75-150 mg; and 1.4 (1.0 to 2.0) for 160-325 mg). Two trials that compared 75-325 mg aspirin daily with <75 mg daily also found no significant difference in major extracranial bleeds (39/1576 (2.5%) with 75-325 mg *v* 28/1555 (1.8%) with <75 mg; NS).

Effects of antiplatelet drugs other than aspirin

Overall, after trials among patients with acute stroke had been excluded, 81 731 patients were included in 166 trials comparing a single antiplatelet drug with control among high risk patients (compared with 73 218 patients in 141 trials previously[1]). Indirect comparisons of the different antiplatelet drugs provided no clear evidence of any differences in the effects on serious vascular events (χ^2 for heterogeneity between any aspirin regimen and the other antiplatelet drugs = 10.8, df = 8; NS; fig 6), indicating that no large differences exist.

Direct randomised comparisons of different antiplatelet regimens could, if they were large enough, assess more reliably any modest differences that might exist. Most direct comparisons have assessed the effects of replacing aspirin with another antiplatelet (fig 5). Large scale randomised evidence was available only for clopidogrel versus aspirin.[7] Overall, among 19 185 patients with a history of myocardial infarction, stroke, or peripheral arterial disease, clopidogrel reduced serious vascular events by 10% (4%) compared with aspirin (970/9599 (10.1%) clopidogrel *v* 1063/9586 (11.1%) aspirin; P=0.03). This is similar to the 12% (7%) reduction observed in trials of ticlopidine (a thienopyridine drug similar to clopidogrel) versus aspirin. The clopidogrel versus aspirin in patients at risk of ischaemic events trial also showed that the drug was relatively safe.[38] However, the true size of any difference between clopidogrel and aspirin could not be reliably estimated, since the 99% confidence interval ranged from a negligible benefit to a 20% further reduction in serious vascular events.

Effects of adding another antiplatelet drug to aspirin

Although the size of any difference between aspirin and other antiplatelet drugs may only be small, the addition to aspirin of an antiplatelet drug that acts through a different pathway might provide more substantial benefit than aspirin alone. The effects of adding dipyridamole, sulfinpyrazone, ticlopidine, or intravenous glycoprotein IIb/IIIa antagonists have been tested in randomised trials (fig 5).

Overall, among 10 404 patients in 25 trials comparing dipyridamole plus aspirin with aspirin alone (compared with 5317 in 14 trials previously[1]), the addition of dipyridamole to aspirin was associated with only a non-significant further 6% (6%) reduction in serious vascular events (614/5198 (11.8%) aspirin plus dipyridamole *v* 648/5206 (12.4%) aspirin alone; fig 5). This overall result includes 183 *v* 236 patients with non-fatal stroke, 150 *v* 134 with non-fatal myocardial infarction, and 286 *v* 279 vascular deaths (with 5 *v* 1 having both a non-fatal myocardial infarction and a non-fatal stroke). The apparent reduction in non-fatal stroke was derived mainly from one large study (109 *v* 158),[17] but this result was not supported by the findings for non-fatal stroke in the other studies (74 *v* 78) or by the overall findings for non-fatal myocardial infarction or for vascular death.

Experimental and clinical studies have indicated that the platelet antiaggregatory effects of ticlopidine and aspirin may be additive.[39] The combination has been studied among patients having coronary artery stenting, although mainly in non-randomised comparisons and case series.[40] Several randomised trials have compared the combination of ticlopidine and aspirin with the combination of an oral anticoagulant and aspirin, but only two randomised trials have compared ticlopidine plus aspirin versus aspirin, and only one (the stent anticoagulation restenosis study[41]) was unconfounded. In that study, the addition of ticlopidine to aspirin was associated with a non-significant 21% (24%) further reduction in serious vascular events (fig 5). There was, however, a non-significant increase in major extracranial bleeds (15/546 (2.8%) ticlopidine plus aspirin *v* 8/557 (1.4%) aspirin alone). Further evidence that adding a thienopyridine to aspirin produces additional benefit among patients at acute risk of coronary occlusion has recently been provided by the clopidogrel in unstable angina to prevent recurrent events trial,[42] but these results are not included as they were reported after September 1997.

The final common pathway of platelet aggregation is thought to be mediated by activation of platelet glycoprotein IIb/IIIa receptors by a platelet agonist (such as ADP, collagen, or thrombin) followed by crosslinking of activated receptors by circulating fibrinogen molecules.[43] Drugs that block this receptor might therefore be especially effective. Many such drugs have now been developed, and in September 1997, 15 trials were available comparing aspirin plus a short (12-96 hour) intravenous infusion of a glycoprotein IIb/IIIa antagonist with aspirin alone (one small study had studied an oral drug). Overall, among 24 802 patients in these 15 trials, the addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin produced a highly significant 19% (4%) proportional reduction in serious vascular events (P<0.0001),

corresponding to the avoidance of about 20 vascular events per 1000 patients in just one month.

The proportional reduction in vascular events was significantly larger among patients having percutaneous coronary intervention than among patients not having such intervention (32% (6%) *v* 12% (5%); heterogeneity test $\chi^2=8.7$, df = 1; $P=0.003$). However, since patients with acute coronary syndromes not having a coronary procedure were at high risk of vascular events, addition of a glycoprotein IIb/IIIa antagonist was still associated with a worthwhile absolute benefit (15 vascular events avoided for 1000 treated during one month $P<0.02$). Overall, these benefits were offset by an absolute excess of 23 major extracranial bleeds per 1000 patients treated, although fatal bleeding was rare. The absolute risk of bleeding after percutaneous coronary intervention may be minimised by early removal of the sheath and reducing the dose of heparin.[44] There were few intracranial haemorrhages (20/12 791 (0.2%) glycoprotein IIb/IIIa antagonist plus aspirin *v* 13/12 833 (0.1%) adjusted aspirin alone; NS).

Discussion

Since the previous meta-analysis,[1] large amounts of information have become available from trials in patients having coronary artery procedures and in patients with acute stroke, stable angina, atrial fibrillation, peripheral arterial disease, and diabetes mellitus. Consequently, this analysis extends the direct evidence of benefit from antiplatelet therapy to a much wider range of patients at high risk of occlusive vascular disease. Antiplatelet therapy reduced the risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by about one quarter, not just among patients with unstable angina, acute myocardial infarction, stroke, or transient ischaemic attacks[1] but also among other patients with coronary or peripheral arterial disease and those at high risk of embolism. Overall mortality was also significantly reduced in these high risk patients, and, compared with these benefits, the absolute risk of fatal and major non-fatal bleeds was small.

Generalisability of findings to types of patients not studied directly

Because these proportional risk reductions in vascular events were statistically reliable and seemed roughly homogeneous over the wide range of settings studied in these trials (fig 4) the protective effects of antiplatelet therapy should be expected to apply to an even wider range of high risk patients than those categories for which the present meta-analysis provides direct evidence of benefit. Thus, it would be inappropriate to base conclusions about the effects of antiplatelet therapy in each small subcategory of patients solely on the results from that subcategory. Compare, for example, the apparently contrasting effects on vascular events among patients having coronary angioplasty (in whom antiplatelet therapy seems to halve the risk) and those having coronary artery bypass grafting (in whom it seems to have no effect). Given the overall evidence for a reduction in serious vascular events of about one quarter among such a wide range of patients at high risk of occlusive vascular disease, it would not be reasonable to conclude that antiplatelet therapy halves vascular events after angioplasty but has no protective effect after coronary artery bypass surgery (particularly when antiplatelet therapy has been shown to produce a massively significant reduction in thrombotic occlusion of bypass grafts[2]).

Similarly, although antiplatelet therapy was associated with only a non-significant 7% (8%) proportional reduction in serious vascular events among patients with diabetes mellitus (but, predominantly, no history of myocardial infarction or stroke), these results do not provide reliable evidence of a lack of worthwhile benefit in such patients. Indeed, taken as a whole they indicate the converse, although direct evidence from further randomised trials of antiplatelet therapy among diabetic patients would still be helpful. However, our previous finding that antiplatelet therapy is similarly effective among patients with pre-existing symptomatic vascular disease who do and do not have diabetes[1] suggests that aspirin is likely to be effective for the primary prevention of vascular events among diabetic patients. Furthermore, there is now good evidence that antiplatelet therapy is not associated with any special risks (such as bleeding in the eye) in patients with diabetes.[29] Hence, it may be appropriate to consider antiplatelet therapy in diabetic patients who are at substantial risk of a first vascular event (such as those with proteinuria)[45] and non-diabetic patients at high risk because of pre-existing vascular disease, even if there is no direct evidence of benefit (as for patients undergoing coronary artery surgery or those with heart failure[46]), provided that there are no special risks of bleeding that might outweigh the benefit. Thus, these findings can reasonably be extrapolated to a far wider range of high risk patients than those studied, but the further the extrapolation goes, the more desirable it is to have direct evidence—for example, for patients with renal disease, who are at high risk of myocardial infarction and ischaemic stroke[47] but who also have special risks of bleeding.

Acute stroke

The randomised evidence that is available from about 40 000 patients with acute stroke shows that, although antiplatelet therapy is associated with about two more major extracranial bleeds per 1000 treated in the absence of concomitant heparin,[18] there will be about four fewer patients with a non-fatal stroke and five fewer patients dying from a vascular cause. Moreover, even among acute stroke patients who did not have computed tomography to exclude pre-existing cerebral haemorrhage before starting treatment, antiplatelet therapy seemed to produce net benefit.[20] Hence, there is now good reason to consider starting antiplatelet therapy as soon as possible after suspected acute ischaemic stroke, preferably after confirmation by computed tomography (unless this would result in undue delay). This complements the previous evidence that continuing antiplatelet therapy for some years after the acute phase of ischaemic stroke produces substantial further reductions in risk.[1]

Benefits of different antiplatelet regimens

The available data allow three main questions about treatment regimens to be examined: which range of aspirin doses seems most promising; is some other antiplatelet drug better than aspirin; and does any antiplatelet drug add to the net benefit of aspirin?

Aspirin regimens

Within a few days of beginning 75 mg aspirin daily, cyclo-oxygenase is virtually completely inhibited in platelets, producing an antithrombotic effect.[5] The present analyses indicate that high doses of 500-1500 mg aspirin daily (which are more gastrotoxic[48]) are no more effective than medium doses of 160-325 mg/day or low doses of 75-150 mg/day (figs 5 and 6). Results from trials of lower doses are less conclusive. Hence, the available evidence supports daily doses of aspirin in the range 75-150 mg for the long term prevention of serious vascular events in high risk patients. In clinical situations where an immediate antithrombotic effect is required (such as acute myocardial infarction, acute ischaemic stroke, unstable angina), a loading dose of about 150-300 mg, which is sufficient to produce rapid and complete inhibition of thromboxane mediated platelet aggregation,[49] should probably be given.

Other antiplatelet drugs

Even though aspirin can prevent about one quarter of serious vascular events in a wide range of high risk patients, the residual risk may still be high. Hence, antiplatelet regimens are needed that are more effective than aspirin alone. Any real differences between two antiplatelet drugs are likely to be smaller than the differences between antiplatelet therapy and no antiplatelet therapy, so reliable comparisons between different drugs may require direct randomisation of many thousands, or even tens of thousands, of high risk patients. Such evidence exists only for clopidogrel versus aspirin, and this indicates that clopidogrel may be slightly more effective than aspirin (particularly when the evidence for ticlopidine, which is similar in structure and mechanism of action to clopidogrel, is also considered).[50]

Addition of other antiplatelet drugs to aspirin

Addition to aspirin of an antiplatelet drug that prevents platelet aggregation through some other pathway may well produce a further reduction in the risk of serious vascular events. This has now been shown for short term treatment. Large randomised trials among patients having percutaneous coronary interventions have found that adding a short intravenous infusion of glycoprotein IIb/IIIa antagonist reduces the risk of early arterial or stent thrombosis.[43] In the present meta-analysis, evidence of benefit was limited to a follow up of only around one month, but recently published studies show that the benefit of glycoprotein IIb/IIIa antagonists is maintained for at least six months (and possibly longer).[51-53] Despite this, the oral IIb/IIIa-antagonists have not been found to add to the effects of aspirin.[54]

Similarly, the addition of dipyridamole to aspirin has not been shown clearly to produce additional reductions in serious vascular events, although one trial suggested that there may be a worthwhile further reduction in stroke.[17] Reasons for this apparent effect on stroke in that study include the possibility that the newer (and more bioavailable) formulation of dipyridamole was more effective than the older preparation. It is also plausible that these findings (which were not supported by other studies) arose largely or wholly by the play of chance, or were due to an insufficient daily aspirin dose or a slight antihypertensive effect of dipyridamole. Dipyridamole is being tested further in the European and Australian stroke prevention in reversible ischaemia trial.[55]

Clopidogrel and ticlopidine, which are both thienopyridines, act by blocking ADP dependent activation of platelets. The effects of their antiplatelet properties on occlusive vascular events could therefore be complementary to those of aspirin, which inhibits thromboxane dependent activation. A large trial that assessed the effects of adding clopidogrel to aspirin among patients with unstable angina recently reported promising results,[42] and the second Chinese cardiac study is assessing this question among patients with acute myocardial infarction.[56] Long term studies of the effects of adding clopidogrel to aspirin might also be useful among other types of patients at high risk of occlusive vascular disease. Such studies could also examine the important question of whether adding clopidogrel is effective in patients who were taking aspirin when the event occurred (so called aspirin failures).

In the high risk setting of percutaneous coronary intervention or among high risk patients with an acute coronary syndrome, intensification of antiplatelet therapy by adding an intravenous glycoprotein IIb/IIIa antagonist or thienopyridine to aspirin may be appropriate. In other circumstances, however, aspirin at a dose of 75-150 mg daily is likely to be an appropriate antiplatelet regimen unless patients have a definite contraindication to aspirin—for example, definite allergy or appreciable gastric symptoms even with low dose aspirin. Clopidogrel might be an appropriate alternative in such patients.

Benefits exceed hazards in most high risk patients

Our results suggest that among individuals at high risk of occlusive vascular disease, the proportional risk reductions with antiplatelet therapy are roughly similar in most categories of patient (although they are smaller in acute stroke). Consequently, a patient's absolute risk is likely to be more important than the proportional reduction in serious vascular events in determining the likely benefit of antiplatelet therapy. In patients at particularly high risk of vascular events, the benefits of antiplatelet therapy are large. For example, among 1000 patients with acute myocardial infarction who are given one month of aspirin and then continue to take low dose aspirin for some years, about 40 would avoid a serious vascular event during the first month and about a further 40 would avoid a vascular event in the next couple of years. Similar sized long term benefits are likely to be seen if antiplatelet therapy is started soon after stroke or transient ischaemic attack and continued long term. Even in patient populations at intermediate risk (2-3% a year of serious occlusive vascular events) such as some patients with no previous vascular event but with stable angina, atrial fibrillation, or peripheral arterial disease, antiplatelet therapy for a couple of years would be expected to prevent about 10-15 vascular events for every 1000 patients treated.

The present evidence suggests that the proportional increase in the risk of major bleeding of about one half is similar among a wide range of categories of patient. Population based observational studies have found that regular use of aspirin (at a dose of ≤300 mg/day) is associated with around a twofold increased

risk of upper gastrointestinal bleeding (or perforation).[57] It therefore seems likely that the benefits of antiplatelet therapy will far outweigh any hazards unless the absolute risk of bleeding is high (such as among haemodialysis patients) or the absolute risk of a vascular event is low (as in apparently healthy people). Consequently, unless some definite contraindication exists, antiplatelet therapy should be considered routinely for all patients whose medical history implies a significant risk of occlusive vascular disease over the next few months or years, and it should generally be continued for as long as the risk remains high.

Potential for wider use of antiplatelet therapy in high risk patients

Recent audits have shown that the use of antiplatelet therapy has increased during the past few years but that a substantial proportion of high risk patients still do not receive it. For example, only about half (or less) of all patients with a history of myocardial infarction, angina, or peripheral arterial disease are currently receiving antiplatelet therapy, and rates tend to be lower in older people despite their higher absolute risk.[58-60] Use of aspirin among patients with diabetes is even more limited, with one survey suggesting that less than a quarter of those with a clear history of coronary artery disease were taking regular aspirin,[58] and another study finding that only 7% of those without a history of coronary artery disease were taking aspirin.[60] Similarly, only about one third of patients with atrial fibrillation receive oral anticoagulants, the most effective treatment for the prevention of strokes in this condition.[61 62] This may be because of the associated risks of bleeding and the need for anticoagulation monitoring. But less than half of such patients who are not taking anticoagulants receive antiplatelet therapy despite the high risk of stroke (especially in elderly people).[63 64]

These results reinforce the value of ensuring that antiplatelet therapy with 75-150 mg aspirin daily (or some other effective antiplatelet regimen) is considered routinely for all such patients at high or intermediate risk of occlusive vascular events (more than about 2% a year), irrespective of whether they have already had a major vascular event. An unanswered question, however, is whether it is possible to identify particular groups of apparently healthy people who may be at increased risk of myocardial infarction or stroke and for whom the benefits of daily aspirin outweigh the hazards. This is currently being investigated in an analysis of primary prevention trials. For most healthy individuals, however, for whom the risk of a vascular event is likely to be substantially less than 1% a year, daily aspirin may well be inappropriate.

What is already known on this topic

Antiplatelet therapy is effective for short term treatment of patients with suspected acute myocardial infarction and unstable angina

Long term treatment is beneficial for patients who have had a myocardial infarction, stroke, or transient ischaemic attack

Daily aspirin doses of 75-325 mg are effective

What this study adds

Antiplatelet therapy protects against vascular events among patients with stable angina, intermittent claudication, and (if oral anticoagulants are unsuitable) atrial fibrillation

Antiplatelet therapy can be started promptly during acute presumed ischaemic stroke and continued long term

Daily aspirin doses of 75-150 mg seem to be as effective as higher doses for long term treatments (and clopidrogel is an appropriate alternative for patients with a contraindication to aspirin)

Short term addition of a glycoprotein IIb/IIIa antagonist to aspirin prevents vascular events in patients having percutaneous coronary intervention and those with unstable angina but causes increased bleeding

This paper is dedicated to Gale Mead (1943-2001), who typed this and the previous reports from this collaboration.

Contributors: Writing committee: C Baigent, C Sudlow, R Collins, R Peto. Details of collaborators are available on bmj.com. The current cycle of this collaborative study was coordinated by CB and CS. CB, CS, RC, and RP all contributed to drafting the manuscript, which was circulated to collaborators for comment and subsequent revision. The collaborators all provided trial data or other trial related information either in a previous cycle of the Antiplatelet Trialists' Collaboration or in the current cycle of the Antithrombotic Trialists' Collaboration. CB, CS, RC, and RP are the study guarantors.

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Chlamydia pneumoniae infection is not involved in carotid artery stenosis

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Abstract

Recent studies have suggested the existence of a close relationship between *Chlamydia pneumoniae* infection and atherosclerosis. However, it has been speculated that *C. pneumoniae* infection is not associated with early atherosclerosis but with advanced atherosclerosis. In the present study, we test this hypothesis. In 524 consecutive patients who underwent cerebral angiography were recruited for the study. From the films obtained during angiography, percent stenosis of neck internal carotid artery was calculated according to the method of the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Serum *C. pneumoniae* IgG and IgA antibodies were measured by a commercial ELISA enzyme immunoassay kit. Cerebrovascular risk factors such as age, gender, hypertension, diabetes mellitus, hyperlipidemis and smoking were assessed by interview. Old age above 60 years and diabetes mellitus were found to be independent risk factors for carotid artery stenosis in this study after adjustment for cerebrovascular risk factors. When we defined carotid artery stenosis as the presence of greater than 30% stenosis of one artery, there was no association after adjustment for other risk factors between *C. pneumoniae* IgG and IgA seropositivity and the presence of carotid artery stenosis for any cut-off value of seropositivity. When we defined carotid artery stenosis as the presence of greater than 70%, there was also no association between *C. pneumoniae* IgG and IgA seropositivity and the presence of carotid artery stenosis for any cut-off value of seropositivity. These results suggest that *C. pneumoniae* infection is not associated with carotid artery atherosclerosis.

Keywords: Atherosclerosis; *Chlamydia pneumoniae*; Neck carotid artery stenosis

1. Introduction

There is a growing body of evidence that certain infectious agents play roles in the pathogenesis of atherosclerosis. Associations of atherosclerotic plaque and fatty streaks in the aorta, coronary arteries of autopsy cases, in coronary arterectomy specimens, and in carotid endoarterectomy specimens with *Chlamydia pneumoniae* elementary bodies have been reported [1,2]. Previous studies have reported associations between *C. pneumoniae* seropositivity and coronary heart disease or carotid stenosis [3,4]. In a study of normal population individuals, no association between *C. pneumoniae* IgG and IgA seropositivity and carotid artery stenosis was found [5]. These results suggest the hypothesis that *C. pneumoniae* infection is not associated with the earlier stages of atherosclerosis but instead with the later stages of it. The present prospective study was designed to test this hypothesis by analysis of serum *C. pneumoniae* IgG and IgA antibodies and angiographic measurement of neck carotid artery stenosis in a group of subjects with a variety of neurosurgical diseases including earlier and advanced stage of neck carotid artery stenosis.

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2. Methods

2.1. Patients

A total of 524 consecutive patients who underwent cerebral angiography were recruited for the study between July 2000 and February 2001. They were treated at the Departments of Neurosurgery of the following hospitals in Japan: Shakaihoken Takaoka Hospital, Saiseikai Takaoka Hospital, Seieikai Neurosurgical Tsukamoto Hospital, Red Cross Toyama Hospital, Asahi General Hospital, Toseikai Yatsuo General Hospital, Kamiichi Kosei Hospital, Koseren Namerikawa Hospital and Toyama Medical and Pharmaceutical University in Toyama; Saito Memorial Hospital in Niigata; Sekishinkai Kawasakisaiwai Hospital, Sanshikai Tomei-Atsugi Hospital and Meihoukai Yokohama Shintoshi Neurosurgical Hospital in Kanagawa; Sekishinkai Sayama Hospital in Saitama; Tokai Memorial Hospital in Aichi; and Yao Tokushukai Hospital and Ikuwakai Memorial Hospital in Osaka.

The patients had visited the above hospitals for various conditions: 110 patients (21%) with cerebral infarction, 67 (13%) with subarachnoid hemorrhage due to ruptured cerebral aneurysms, 57 (11%) with incidental cerebral aneurysms, 36 (7%) with brain tumor, 34 (6%) with intracerebral hematoma including seven with arteriovenous malformation and two with dural arteriovenous fistula, 15 (3%) with non-bleeding dural arteriovenous fistula, nine (2%) with traumatic subarachnoid hemorrhage, five (1%) with non-bleeding arteriovenous malformation, and 191 other patients with headache and vertigo (36%).

This study was approved by the Committees on Medical Ethics of Toyama Medical and Pharmaceutical University and all other participating hospitals. Informed consent was obtained from all participants before examination. Cerebrovascular risk factors were assessed by interview. Diabetes mellitus was diagnosed for patients with a history of dietary treatment or additional oral anti-diabetic or insulin medication; hypertension was diagnosed for patients with history of anti-hypertensive treatment, and hyperlipidemia for patients taking lipid-lowering medication or history of cholesterol levels >240 mg/dl.

2.2. Angiography and serological analysis

Blood samples were drawn from each subject via a catheter before angiography using contrast medium. Serum was centrifuged at $4000 \times g$ for 10 min, immediately divided into aliquots, and frozen at -80 °C until analysis. *C. pneumoniae* IgG and IgA antibodies were measured by a commercial ELISA enzyme immunoassay kit (HITAZYME, Hitachi Kasei, Japan). Results are provided by the manufacturer in the form of indices, relative to the concentrations of antibodies. The coefficients of variation for the ELISA of *C. pneumoniae* IgG within runs (three runs) were 4.0% (run 1), 10.0% (run 2) and 10.7% (run 3), respectively, while the coefficients of variation for the ELISA of *C. pneumoniae* IgA within runs (three runs) were 3.8% (run 1), 10.7% (run 2) and 5.7% (run 3), respectively. The coefficients of variation for the ELISA of *C. pneumoniae* IgG among lots of antibody (three samples) were 7.5% (sample 1), 4.5% (sample 2) and 8.2% (sample 3), respectively, while the coefficients of variation for the ELISA of *C. pneumoniae* IgA among lots of antibody (three samples) were 3.5% (sample 1), 1.3% (sample 2) and 5.9% (sample 3), respectively. Selective carotid angiography was performed. From the films obtained during angiography, the narrowest luminal diameter of the neck carotid artery (A), and the diameter of the normal artery beyond the carotid bulb (B) were determined. Percent stenosis was calculated according to the method of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6], with the formula $(1-A/B) \times 100\%$. All angiographic measurements were made blind to clinical details and serological results. Serological assays were performed blind to clinical details and the results of angiographic measurements.

2.3. Statistical analysis

Two sections of analysis were performed: first, the relationship between *C. pneumoniae* seropositivity and carotid artery stenosis was examined, and then the relationship between conventional risk factors and carotid artery stenosis. For each section, univariate analysis was performed, followed by multivariate analysis using multiple logistic regression to allow adjustment for other risk factors. P-values <0.05 were considered significant.

3. Results

Background data for the 524 patients were as follows: age: 61 ± 11 year (mean $\pm$ SD), male/female ratio: 314/210, smoking: 189 (36.3%), hypertension: 248 (47.6%), diabetes mellitus: 99 (19.0%), hyperlipidemia: 138 (26.7%), *C. pneumoniae* IgG antibody: 1.10 ± 0.73 (mean $\pm$ SD) and *C. pneumoniae* IgA antibody: 1.30 ± 0.88 (mean $\pm$ SD). When we defined carotid artery stenosis as the presence of greater than 30% stenosis of one artery, it was detected in 103 of the 524 subjects (20.4%). After adjustment for other risk factors (age, gender, hypertension, diabetes mellitus, hyperlipidemia and smoking) using a multiple logistic regression model, there was no close association between *C. pneumoniae* IgG and IgA seropositivity and the presence of carotid artery stenosis for any cut-off value of seropositivity

Table 1
Odds ratios for association of *C. pneumoniae* IgG and IgA with neck carotid artery stenosis

	Cut-off value	Adjusted[a] odds ratio (95% CI) stenosis > 30%	*P*-value	Adjusted[a] odds ratio (95% CI) stenosis > 70%	*P*-value
C. pneumoniae IgG	0.9	1.02 (0.64–1.65)	0.924	1.97 (0.76–5.75)	0.180
	1.1	1.05 (0.66–1.69)	0.824	1.07 (0.43–2.63)	0.880
	1.5	1.02 (0.60–1.68)	0.954	1.36 (0.52–3.36)	0.514
	2.5	1.12 (0.34–3.08)	0.842	1.18 (0.06–6.77)	0.881
C. pneumoniae IgA	0.9	1.13 (0.69–1.86)	0.634	1.52 (0.56–4.85)	0.436
	1.1	0.88 (0.55–1.42)	0.596	1.72 (0.66–5.02)	0.288
	1.5	0.86 (0.53–1.39)	0.863	1.24 (0.50–3.05)	0.645
	2.5	1.67 (0.85–3.17)	0.125	1.96 (0.60–5.52)	0.225

[a] Adjusted for age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoking status using a multiple logistic regression model.

(Table 1). When we defined carotid artery stenosis as the presence of > 70%, it was detected in 24 (4.8%). The all odds ratios of association between *C. pneumoniae* IgG and IgA seropositivity and the presence of carotid artery stenosis increased for any cut-off value of seropositivity, although they were not statistically significant (Table 1). We next estimated the relationship between carotid artery stenosis > 30% stenosis of one artery and risk factors such as old age above 60 years (age > 60), male sex, hypertension, diabetes mellitus, hyperlipidemia, smoking and evidence of *C. pneumoniae* seropositivity such as *C. pneumoniae* IgG antibody index greater than 1.1 or *C. pneumoniae* IgA antibody index greater than 1.1 (Table 2). Multivariate odds ratios were also calculated using a multiple logistic regression model with age as a binary variable, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking, and either *C. pneumoniae* IgG or IgA as a cut-off point of 1.1. Although there was a significant association between carotid artery stenosis and age > 60 years (OR 2.47, 95% CI 1.53–4.10, $P = 0.0003$), male sex (OR 1.85, 95% CI 1.17–2.98, $P = 0.010$), and diabetes mellitus (OR 2.12, 95% CI 1.26–3.50, $P = 0.0037$) before adjustment for other risk factors, the association between carotid artery stenosis and two variables such as age > 60 (OR 2.47, 95% CI 1.49–4.23, $P = 0.0007$) and diabetes mellitus (OR 1.91, 95% CI 1.09–3.28, $P = 0.021$) was significant after adjustment (Table 2).

4. Discussion

Although *C. pneumoniae* infection has been implicated in the pathogenesis of atherosclerosis, its role in an early stage of this condition has been suspicious [5]. Markus et al. reported that *C. pneumoniae* infection is not associated with the earlier stage of carotid atherosclerosis and speculated that it may be associated with the later stages of the disease [5]. In the present study, age > 60 years and diabetes mellitus were found to be independent risk factors for carotid artery stenosis in this study. After adjustment for cerebrovascular risk factors, we found no association between *C. pneumoniae* seropositivity and the presence of carotid artery stenosis > 30% for any cut-off value of seropositivity. However, the all odds ratios for association of *C. pneumoniae* IgG and IgA seropositivity with neck carotid artery stenosis > 70% of one artery increased for any cut-off value of seropositivity, although they were not statistically significant. The low ratio (4.8%) of neck carotid artery stenosis greater than 70% may be the reason why these associations are not statistically significant. Our findings

Table 2
Odds ratios for association of risk factors with more than 30% neck carotid artery stenosis of one artery

Risk group	Univariate odds ratio (95% CI)	*P*-value	Multivariate[a] odds ratio (95% CI)	*P*-value
Elderly (> 60 years)	2.47 (1.53–4.10)	0.0003	2.47 (1.49–4.23)	0.0007
Male	1.85 (1.17–2.98)	0.010	1.64 (0.96–2.85)	0.075
Smoking	1.32 (0.84–2.05)	0.226	1.23 (0.73–2.07)	0.441
Hypertension	1.49 (0.96–2.30)	0.075	1.21 (0.75–1.96)	0.426
Diabetes mellitus	2.12 (1.26–3.50)	0.0037	1.91 (1.09–3.28)	0.021
Hyperlipidemia	1.26 (0.77–2.02)	0.344	1.12 (0.65–1.90)	0.675
C. pneumoniae IgG index > 1.1	1.26 (0.81–1.95)	0.301	1.11 (0.69–1.77)	0.658
C. pneumoniae IgA index > 1.1	1.17 (0.76–1.81)	0.484	0.92[b] (0.57–1.48)	0.725

[a] A multiple logistic model was used with risk factors including age (as a binary variable), gender, smoking, hypertension, diabetes mellitus, hyperlipidemia, and either *C. pneumoniae* IgG or IgA index as a cut-off point of 1.1. Values are shown as determined using the model with *C. pneumoniae* IgG.
[b] Obtained from a multiple logistic model with risk factors and *C. pneumoniae* IgA.

are similar to those of Markus et al. in the mild neck carotid stenosis and support their hypothesis that there may be a trend with the advancing atherosclerosis [5].

Next, it is important whether *C. pneumoniae* is merely an innocent bystander or play a pathogenic role in the progression of atherosclerosis. Inflammation is one of the primary mechanisms in atherosclerosis [7]. It has been suggested that *C. pneumoniae* infection may contribute to pathogenesis of atherosclerosis by causing chronic systemic inflammation [7]. However, no association between *C. pneumoniae* seropositivity and markers of chronic inflammation have been reported in the large community population [5]. Our data are consistent with the concept that *C. pneumoniae* infection is not significantly associated with carotid artery atherosclerosis.

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Original Articles

Effect of Pravastatin-Induced LDL-Cholesterol Reduction on Coronary Heart Disease and Cerebrovascular Disease in Japanese: Hokuriku Lipid Coronary Heart Disease Study-Pravastatin Atherosclerosis Trial (Holicos-PAT)

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The purpose of Holicos-PAT was to investigate the efficacy of serum lipid lowering by pravastatin against coronary heart disease (CHD) and cerebrovascular disease (CVD) in the Japanese population. Hypercholesterolemic men and women (n = 2,232), aged 40-70 years, were followed up for 5 years, while they were receiving pravastatin (group P, n = 1,422) or only diet therapy (group C, n = 810). The primary endpoint was CHD (a composite of onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, death from CHD including heart death or sudden death). The secondary endpoints were comprised of CVD, total mortality, variation of serum lipid and apoprotein levels, and a relationship between the LDL-C level and occurrence of CHD. For several reasons (proving to meet the exclusion criteria after registration, etc.), 1,290 cases of group P and 749 cases of group C were used as subjects for the primary analysis. The mean follow-up period was 4.5 years in group P and 4.2 years in group C for events of CHD. The mean LDL-C level (SD) in group P was 176 (29) mg/dl and decreased to 134 (29) mg/dl one year later. This effect continued during the follow-up period. CHD events occurred in 9.2/1000 patient-years for men and 2.4/1000 patient-years for women without a history of CHD. CHD events occurred in 55.3/1000 patient-years for men and 23.6/1000 patient-years for women with a history of CHD, which was 6 times higher in men and 10 times higher in women than in those without a history of CHD, respectively. The adjusted relative risk ratio of group P to group C for CHD events was 0.74 (95%CI: 0.47-1.19). In the patients with a history of CHD, the ratio was 0.55 (95%CI: 0.30-1.00). The effect was apparent in the patients with a history of CHD. The incidence of myocardial infarction in Japanese patients with hypercholesterolemia living in the Hokuriku district was apparently lower, than the worldwide incidence, indicative that pravastatin may have a tendency to inhibit the occurrence of events of arteriosclerotic disease. ***J Atheroscler Thromb, 2002; 9: 251-259.***

Key words: Pravastatin, Coronary heart disease, Cerebrovascular disease, Prospective study

Introduction

Epidemic studies have proved that hypercholesterolemia is a risk factor for CHD (1-3). In Japan, this was supported by the Research Group of the Ministry of Welfare, investigating primary hypercholesterolemia of specific diseases (4).

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In Western countries, the usefulness of lipid reduction therapy for CHD was demonstrated in large-scale clinical studies using the statins, WOS, AFCAPS/TexCAPS, 4S, CARE, and LIPID (5-9). There have been some reports of its usefulness for CVD (cerebral infarction and hemorrhage) (7, 9, 10). However, the usefulness of treatment with statins has not been confirmed in elderly populations with a low incidence of CHD. The mean life expectancy in Japan, determined in 2000, is 77.64 years for men and 84.62 years for women, and it is estimated that 84.1% of men and 92.2% of women survive until the age of 65. The results of prospective clinical trials on CHD have been reported in Japan by CARS (11) and J-MIC (S) (12), in which coronary arteriosclerosis was prevented from progressing, KLIS (13), in which male patients were used as subjects, and PATE (14), in which aged patients were used as subjects. However, not enough data is available on the incidence and mortality of CHD or CVD in a range of hypercholesterolemic patients in Japan, including relatively young subjects and women. Moreover, there have been only a few reports describing the usefulness of serum cholesterol-lowering therapy for the above populations. Thus the results of clinical trials in the Japanese, who have a low rate of mortality for CHD (15,16) and different life style and hereditary predisposition from the West, are thought to provide valuable infromation on lipid-lowering therapy in low-risk populations.

As for Holicos-PAT, we followed up men and women who had hypercholesterolemia with or without pravastatin treatment, so as to investigate the incidence of CHD events, CVD events, and total mortality. Hypercholesterolemia was defined as a serum cholesterol level of 220 mg/dl (5.69 mmol/l) or higher. Moreover, the treatment effect was compared between those receiving pravastatin and a diet therapy group controlling for risk factors. Furthermore, the relationship between LDL-C reduction and occurrence of CHD was investigated.

Methods

Study design

Hypercholesterolemic men and women, aged 40-70 years, were followed up for 5 years, while receiving pravastatin (group P) or diet only therapy (group C). The administration of pravastatin was not randomized. Treatment was determined by the doctor based on daily medical examinations. If an antilipidemic agent had already been used, the study was initiated with a TC level of 220 mg/dl or higher after the drug had been withdrawn for at least 4 weeks. When sufficient diet therapy had already been achieved, patients with a TC level of 200 mg/dl or higher were used as subjects.

Patients with familial hypercholesterolemia (FH), secondary hypercholesterolemia (hypothyroidism, nephrotic syndrome, type 1 diabetes, severe diabetes using insulin, and others), or complications such as severe liver disease or nephropathy, and patients whom physicians deemed inappropriate, were excluded from the study.

This study was planned according to the Helsinki declaration.

Study organization

The study organization was constructed by an Excutive Committee, an Event Evaluation Committee, and a Statistician as described in Appendix 1.

Administration of drugs and monitoring

During the follow-up period, both group P and group C were examined for diet and non-smoking. The administration in group P started with 10 mg/day and increased to 20 mg/day when the doctor decided that the effect was insufficient. In group C, when the doctor judged that the therapeutic effect was inadequate, the prescription of antilipidemic agents was allowed if needed. In this case, antilipidemic agents other than statin or fibrate were prescribed to the patient. As for treatment for hypercholesterolemia during the follow-up period, the treatment conducted at the time of registration was continued as a rule.

The patient's background included gender, age, BMI level, complication, presence or absence of history of ischemic heart disease and family history of hypercholesterolemia or CHD. During the follow-up period, we examined serum lipid levels, CHD, CVD, adverse events (including death) and medication. The serum lipid levels were measured at each institution under medical supervision everyday, and the LDL-C level was calculated using the Friedewald formula. When CHD or CVD occurred, a precise record was prepared, and the event was evaluated by the Event Evaluation Committee.

Ethical and safety monitoring was performed under the surveillance of the Executive Committee.

Definition of evaluation items and evaluation methods

The primary endpoint was CHD and the secondary endpoints were CVD, total mortality, serum lipid level, apoprotein level, and the relationship between the LDL-C level and occurrence of CHD. When similar events occurred multiple times, time to the first event was adopted. An event of CHD was defined as the onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, and death from CHD including heart death and sudden death. An event of CVD was defined as the onset or recurrence of cerebral infarction, the onset of cerebral hemorrhage, or death (cerebral infarction or hemorrhage). Causes of death were classified into myocardial infarction, heart failure, sudden death, cerebral infarction, cerebral hemorrhage, cancer, trauma and suicide, and other diseases.

As for event cases, the treatment group was masked

and two members of the Event Evaluation Committee evaluated the same case independently. When the results were not identical, the case was reviewed at the Event Evaluation Committee and the result was regarded as the final evaluation. When the committee considered that the case needed to be investigated again, a decision was based on the re-investigation, and the result was regarded as the final evaluation.

Statistical analysis

Because the selection of a treatment method was voluntary, the statistical analyses were conducted as in an observational study.

In comparisons of patient background between the two groups, the χ^2 test was used for gender, history of angina pectoris, myocardial infarction and cerebral infarction, complications of hypertension and diabetes, smoking, and family history of CHD, and Fisher's exact test for history of cerebral infarction. Wilcoxon test was used for mean age, SBP, DBP, BMI, and serum lipid level (TC, LDL-C, HDL-C, TG). If TG > 400 mg/dl, the case was regarded as lacking a measured level (17). These factors are based on doctor's report. The comparison of background factors between the groups was aimed at confirming the degree of imbalance and only P-values are shown. As for the incidence of events, the number of occurrences per 1,000 patient-years was calculated after age adjustment. For lipid variation, a comparison of the measured levels at each evaluation time between the two groups was conducted by Wilcoxon test with the Bonferroni method. The primary endpoint was CHD and a comparison between group P and group C was conducted for each evaluation item. The relative risk (risk ratio) and 95% confidence interval on administration of pravastatin were obtained using the Cox proportional hazard model. Adjustment factors were history of CHD, gender, age, TC level, HDL-C level, TG level, diabetes, and smoking. Similar analyses were also conducted for events of cerebrovascular disease and total mortality. All P-values shown as test results were two-sided and the significance level was 5%.

For the analyses, the statistical package SAS version 6.12 (SAS Institute, Inc., Carry, Northcarolina) was used.

Results

A total of 2,232 cases (1,422 cases in group P, 810 cases in group C) had been registered during the period from October 1989 to November 1993, and followed up by 132 physicians at 70 facilities until the end of the study. Among those cases, 132 from group P (12 cases meeting the exclusion criteria, one case rejected immediately after registration, 98 cases lacking measured lipid levels at registration, 21 cases not coming after registration) and 61 cases from group C (10 cases meeting the exclusion criteria, 4 cases rejected immediately after registration, 22 cases lacking measured lipid levels at registration, 24 cases not coming after registration, and one case of unknown date of event occurrence) were excluded (a total of 193 cases). Consequently, 2,039 cases were used for analyses.

Patient background

Table 1 shows the background of patients in both groups. The ratio of men was significantly lower in group P than group C ($p = 0.001$). The mean age was significantly higher in group P ($p < 0.001$). The history of diabetes was signifi-

Table 1. Summary of baseline of characteristics of patients

Variable	Pravastatin (n = 1,290)	Only diet therapy (n = 749)	P value
Gender (men%/women%)	33.4/66.6	43.7/56.3	0.001 †*
Age (year)	57.8 ± 8.9	55.1 ± 9.4	< 0.001 §*
Angina pectoris (%)	14.3	13.5	0.591 †
Myocardial infraction (%)	4.8	3.7	0.258 †
Cerebral infraction (%)	3.0	2.3	0.316 †
Cerebral hemorrhage (%)	0.2	0.1	1.000 ‡
Hypertension (%)	38.3	35.8	0.258 †
Diabetes mellitus (%)	13.0	18.6	0.001 †*
Current smoking (%)	22.6	29.2	0.001 †*
Family history of CHD (%)	7.5	7.2	0.797 †
Systolic blood pressure (mmHg)	134.5 ± 19.7	132.0 ± 21.9	0.001 §*
Diastolic blood pressure (mmHg)	80.3 ± 11.6	78.8 ± 12.6	0.009 §*
Body mass index (kg/m²)	23.7 ± 2.9	23.5 ± 2.8	0.107 §

*$p < 0.05$

† Based on the chi-square test (for dichotomous variables)

‡ Based on Fisher's exact test

§ Based on the Wilcoxon test

cantly lower in group P ($p = 0.001$). Smoking was significantly lower in group P. SBP and DBP were significantly higher in group P ($p = 0.001$, $p = 0.009$, respectively). No difference in BMI levels was seen between the two groups. Group P showed significantly higher levels of TC, LDL-C, and TG ($p < 0.001$). No difference in HDL-C levels was seen between the groups. No differences between the groups were found in history of angina pectoris, myocardial infarction, and cerebral hemorrhage, complication of hypertension, and family history of CHD.

Follow-up

The cumulative discontinuation rate due to absence at 60 months was 28.0% in group P and 36.3% in group C, being higher in the latter group. As for confirmed final outcome including missing cases, 23 out of 2,039 cases could not be confirmed for death or survival. The mean follow-up period was 4.5 years in group P and 4.2 years in group C for events of CHD, and 4.7 years in group P and 4.4 years in group C for total mortality. Pravastatin was discontinued or changed to some other antilipidemic agent in 38.9% of patients in group P, and a antilipidemic agent was given to 18.2% of patients in group C. The mean dose of pravastatin was 10.1 mg/day in group P.

Treatment effects on lipids

Fig. 1 shows the variations of TC, LDL-C, TG, and HDL-C levels for five years after initiation of the study. LDL-C levels in group P decreased from 176.3 mg/dl initially to 133.8 mg/dl (– 24.1%) one year later, and this effect continued throughout the study period. LDL-C levels in group C decreased from 156.8 mg/dl to 149.1 mg/dl (– 4.9%) one year later and similar variation was seen during the study period. As for the difference between groups, group P showed a significantly higher level at the start of the study ($p < 0.05$) and a significantly lower level during the study period after one year ($p < 0.05$). The TC level shifted similarly to the LDL-C level. The HDL-C level in group P did not change, being 51.4 mg/dl at the start and 53.6 mg/dl (+ 4.3%) one year later, and similar variation was seen during the study period. Group C also showed no change in the HDL-C level from 51.9 mg/dl to 52.1 mg/dl (+ 3.9%) one year later, and similar variation was seen during the study period. No significant difference was found between the groups. The TG level in group P decreased from 165.3 mg/dl initially to 148.9 mg/dl (– 9.9%) one year later, and this effect continued throughout the study period. The TG level in group C increased from 139.3 mg/dl to be 143.1 mg/dl (+ 2.7%) one year later, and similar variation was seen during the study period. As for the difference between the groups, group P showed a significantly higher level initially ($p < 0.05$), and no significant difference between the groups was seen during the study period after one year. ApoA-I in group P increased from 130.7 mg/dl ($n = 864$) at the start to 137.3 mg/dl (+ 5.3%, $n = 527$) one year later and then to 145.2 mg/dl (+ 11.1%, $n = 286$) five years later. ApoA-I in group C increased from 129.5 mg/dl ($n = 523$) to be 133.1 mg/dl (+ 2.8%, $n = 274$) one year layer and then 139.8 mg/dl (+ 8.0%, $n = 135$) five years later. No significant difference was seen between the two groups. ApoB in group P decreased from 124.7 mg/dl ($n = 866$) to be 106.3 mg/dl

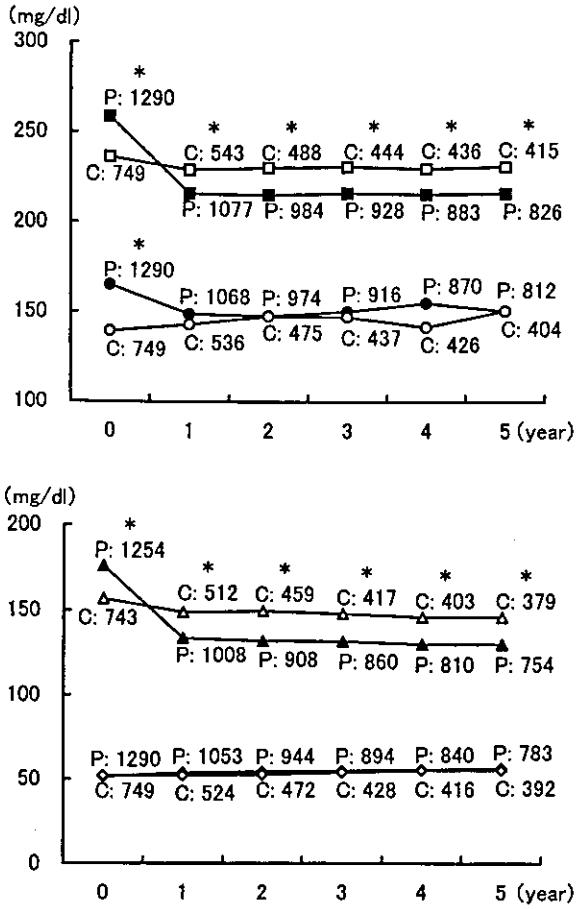

Fig. 1. Effects of pravastatin treatment on serum lipid levels
Numbers of patients are shown over or under the curve.
P = pravastatin; C = only diet therapy
total cholesterol (Group P) =closed square; total cholesterol (Group C) =open square; Triglyceride (Group P) = closed circle; Triglyceride (Group C) = open circle; LDL-cholesterol (Group P) = closed triangle; LDL-cholesterol (Group C) = open triangle; HDL-cholesterol (Group P) = closed diamond; HDL-cholesterol (Group C) = open diamond. LDL-C levels in group P decreased from 176.3 mg/dl at the start to 133.8 mg/dl (– 24.1%) one year later, and this effect continued throughout the study period. LDL-C levels in group C decreased from 156.8 mg/dl to 149.1 mg/dl (– 4.9%) one year later. Group P showed a significantly higher level at the start of the study and a lower level during the study period after one year than group C.
*$p < 0.05$ (Wilcoxon test with Bonferroni's method)