CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 10/23-24/97

SEP 2 2 1997

BRIEFING DOCUMENT

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Date: 11 September 1997
From: Robert R. Fenichel (HFD-110) & James Hung (HFD-710)
Subject: clopidogrel (PLAVIX®, Sanofi), NDA 20-839
To: Raymond J. Lipicky, HFD-110

With this application, the sponsor proposes to market clopidogrel bisulfate, to be indicated for the prevention of vascular ischemic events in patients with histories of symptomatic atherosclerosis.

Some of the contents of the application are present only as references to portions of IND In this review, cited volumes of the NDA are all from volumes 1.XXX–6.XXX; those of the IND are generally from serial submissions 161 and above, cited as 161.1 (submission 161, Volume 1), 161.2, and so on.

Chemistry

Clopidogrel is a thienopyridine
clopidogrel formula

The proposed tradename (PLAVIX)

Pharmacology

For a more detailed review of clopidogrel pharmacology, see the review by Dr. DeFelice.

In multiple species (mouse, rat, rabbit, and baboon), clopidogrel inhibits ADP-induced platelet aggregation. The effective doses (1–5 mg/kg/day) are the same whether the drug is given enterally or intravenously, and clopidogrel's activity is potentiated by inducers of cytochrome P_{450} (1A), suggesting that metabolic activation is the rate-limiting step.

After a single dose of clopidogrel, normal platelet aggregability returns slowly over a period of several days, and plasma from clopidogrel-treated animals (or humans) is inactive *in vitro*. These data suggest that the reaction between platelets and the (unidentified) active metabolite is irreversible.

In rats and rabbits, administration of clopidogrel caused dose-related prolongation of the bleeding time, without measurable effects on coagulation or fibrinolysis. In rats, the effect of clopidogrel could be antagonized by aprotinin,† but aprotinin was ineffective as an antagonist/antidote in human volunteers who received clopidogrel at the proposed therapeutic dose for 10–12 days.‡

Using doses in the same range as those used in the studies demonstrating inhibition of platelet aggregation, clopidogrel was protective in a variety of animal models of arterial and venous thrombosis. These models included one§ in which clopidogrel, apparently by suppressing accretion of new thrombus, effectively potentiated the thrombolytic activity of streptokinase. In another provocative study,‖ clopidogrel's platelet-calming activity appeared to reduce myointimal thickening in rabbits subjected to endovascular injury.

* For a reasonable-sounding argument that the active compound is probably the sulfoxide, see Volume 1.2, pages 93–94.

† Aprotinin is a protease inhibitor used in major surgery to mitigate the hemostatic defects that are associated with cardiopulmonary bypass and with any large-scale replacement of blood components.

‡ See Study INT1979 in Volume 1.170. Another human trial (Study P1629, described in Volume 1.165) examined the potential antidotal activity of **desmopressin** with similarly disappointing results. Two others (P1875 in Volume 1.166 and PDY2239 in Volume 1.167) evaluated **methylprednisolone** for this purpose, but it didn't work either.

§ See Volume 4, page 68.

‖ See Volume 2, page 1, and Volume 4, page 203.

Toxicology

Because of its rapid and extensive metabolism, clopidogrel was barely detectable in plasma in any of the species studied, including humans, even though absorption (from mass-balance data) was always The evanescence of clopidogrel's putative active moiety has already been noted.

In acute doses one or two orders of magnitude higher than those used to achieve full anti-platelet activity, clopidogrel caused a variety of toxicity (gastric erosions, renal tubular injuries, and pulmonary congestion) in dogs and rodents. Acute doses lower than these were nontoxic.

In subacute and chronic studies at similarly elevated doses, the same effects were seen. In addition, these doses in the test animals induced increases in platelet counts and in hepatic enzymes.

Worrisome toxicity was not seen in reproductive studies.

Carcinogenicity and mutagenicity tests were uniformly negative.

Clopidogrel was not myelotoxic in mice, rats, or baboons. The comfort derived from these results must be limited, inasmuch as ticlopidine (a known human myelotoxin) is similarly nontoxic in animal models.

Various other specialized studies (for immunotoxicity, phototoxicity, tumor promotion, and so forth) were also negative.

Human Pharmacokinetics

Pharmacokinetic evaluation of clopidogrel has been necessarily indirect. As noted above, clopidogrel itself is so rapidly removed from the mammalian circulation that off-peak concentrations have been impossible to measure. As also noted above, the active moiety of clopidogrel is believed to be a labile, early metabolite, but this molecule has not actually been identified. Finally, the sponsor has been unable to develop an intravenous formulation, so direct human measures of absolute bioavailability could not be made.

The tested formulations are said to be bioequivalent to the formulation proposed for marketing.

Absorption of clopidogrel is at least 50%,
In healthy volunteers, absorption of clopidogrel was not significantly affected by the co-ingestion of food or antacids. After a 75-mg dose of clopidogrel,

Metabolism of clopidogrel is complex and extensive

clopidogrel

Antihemostatic Dose-Response

The application describes approximately twenty trials whose main purpose was the estimation of the antihemostatic response to various doses of clopidogrel. The trials ranged in size from 6 to 150 subjects, most of whom were healthy male volunteers. In almost all of the trials, the laboratory measures of hemostasis used were (a) percent inhibition of platelet aggregation induced by 5 μM ADP, and (b) proportional bleeding-time prolongation.

The proper interpretation of these trials is not clear, given the remoteness of their endpoints from clinical benefit and the vagueness of the links between the known pharmacokinetics and the presumed mechanism of that benefit. The trials were undertaken with the apparent intent of (a) identifying regimens of clopidogrel whose antihemostatic effects are similar to those of the approved regimen of ticlopidine, and (b) possibly identifying regimens of clopidogrel that are so toxic that they should be avoided. In addition, one trial explored the extent to which clopidogrel's PK and PD are affected by hepatic dysfunction.

Doses larger than 150 mg were not studied in multiple-dose trials. Single doses in the 200–600-mg range were studied in a total of about 75 healthy male volunteers.*
the highest tested doses were not associated with observed adverse responses. The antihemostatic effects of these single high doses were generally similar to those seen with 75-mg doses in multiple-dose regimens.‡

* See studies P1062 (Volume 1.89), P1560 (1.79), MET0103 (1.9), P1305 (1.47), P1590 (1.79), P1298 (1.61), and P1064 (1.91).

† In Study P1062 (Volume 1.89,

Study P1560 (Volume 1.79,

‡ In Study P1062, the peak achieved inhibition of ADP-triggered platelet aggregation after

Almost all of the experience with **multiple-dose regimens of 150 mg** comes from Study P1264.§‖ This was a 16-day, escalating-dose trial in 32 normal male volunteers. The volunteers were divided into groups of 8; within each group, the subjects were randomized in double-blind fashion to receive either placebo or clopidogrel once daily, with the clopidogrel dose 25, 50, 100, or 150 mg, depending upon the group. The groups were not strictly comparable, since the 150-mg group was recruited and studied at one center, and the other groups at another center. The primary results (inhibition of platelet aggregation by ADP 5 μM and prolongation of Ivy-Nelson bleeding time) are shown in Table 1 below.

In the same table, we have included some of the results of Study P1404.¶ This was a 4-week, 139-patient, randomized, open-label trial in patients with atherosclerosis of the peripheral vessels, cerebrovascular circulation, or coronary arteries, objectively documented and sufficiently severe (as assessed by the investigator) to warrant antiplatelet therapy. Each patient received placebo; ticlopidine 250 mg bid; or clopidogrel 10, 25, 50, 75, or 100 mg qd. These results are tabulated with those of Study P1264 because they allow the antihemostatic effects of clopidogrel to be compared to those obtained with the conventional dose of ticlopidine.

Table 1
Antihemostatic effects of
Various Doses of Clopidogrel
As Percent of Baseline

	ADP-induced platelet aggregation		bleeding-time prolongation	
trial:	P1264	P1404	P1264*	P1404
placebo	100%	100%	110%	128%
clopidogrel 10 mg qd	---	86%	---	134%
clopidogrel 25 mg qd	68%	71%	148%	123%
clopidogrel 50 mg qd	52%	71%	164%	150%
clopidogrel 75 mg qd	---	61%	---	172%
clopidogrel 100 mg qd	46%	63%	278%	165%
clopidogrel 150 mg qd	27%	---	439%	---
ticlopidine 250 mg bid	---	54%	---	190%

* Geometric means.

from Volume 1.97, pp. 6–7, and Volume 1.12, pages 5–6

the 600-mg dose was 42±6%, and the peak prolongation factor of the the bleeding time was 1.7. In Study P1560, the analogous results with the 400-mg dose were 47±8% and 1.6. *Cf.* our Table 1 on the next page.

§ See Volume 1.97.

‖ The only other data come from Study LIN2264 (Volume 1.9). This was a 12-subject, 4-day, nonrandomized pharmacokinetic study that included doses of 50, 75, 100, and 150 mg.

¶ See Volume 1.112.

The results of these trials are consistent with the sponsor's expectation that the antihemostatic effects of clopidogrel 50–100 mg qd will be roughly similar to those of ticlopidine 250 mg bid, but more needs to be said. The results were characterized by wide inter- and intra-subject variation; for example, coefficients of variation of the aggregation data in Study P1264 were roughly 0.2–0.8.* In the same study, the bleeding-time results were so skewed that geometric means were thought to have been appropriate, and the confidence intervals around the tabulated figures are defined by factors about 1.4.†

In these trials, the observed increases in antihemostasis with increasing doses of clopidogrel were only weakly associated with increasing rates of bleeding and other hemostasis-related effects. In Study P1264, there was one withdrawal by a patient randomized to placebo, one (the only one related solely to hemostasis) by a patient randomized to 100 mg, and one by a patient randomized to 150 mg.‡ Another subject, receiving 50 mg of daily clopidogrel, did not withdraw despite bruising and prolonged bleeding from shaving nicks. These phenomena developed about midway through the trial, persisted for 7 days, and then remitted completely. On Day 16, his bleeding time was substantially prolonged (35 minutes).

In Study P1404, rate of withdrawal was not monotonically related to the dose of clopidogrel, and the only hemostasis-related withdrawal was in the ticlopidine group (for excessive inhibition of platelet aggregation). Hemostasis-related adverse effects that were reported but did not lead to withdrawal were seen in 1 of the 23 placebo patients (hemorrhoid problem); none of the 73 patients receiving 10–50 mg of clopidogrel; 2 of the 21 patients receiving 75 mg of clopidogrel (one hemorrhoid problem and one hemorrhage from a vessel torn during bleeding-time measurement); 2 of the 11 patients receiving 100 mg of clopidogrel (hematomas); and 1 of the 22 patients receiving ticlopidine (thrombocytopenia to 147 000/mm^3).

Study PDY3079§ was a 24-subject, 18-day, nonrandomized, open-label study of the effect of **hepatic dysfunction** on the pharmacokinetics and pharmacodynamics of clopidogrel. Half of the subjects had biopsy- or scintigraphy-proven hepatic cirrhosis, and the other half were normal subjects matched pair-

* See Volume 1.97, pages 92–93. The sponsor did not present coefficients of variation *per se*. Platelet aggregation at baseline was typically 60–65%, and on-treatment platelet aggregation was as low as 15%, with standard deviations said to be about 13% throughout.

† See Volume 1.97, pages 105–106. When geometric means are used, the conventional interval $[\mu-2\sigma,\ \mu+2\sigma]$ is replaced by an interval [G/F, G×F], where G is the geometric mean and F is a factor chosen so that the [G/F, G×F] interval contains as much of the distribution as $[\mu-2\sigma,\ \mu+2\sigma]$ usually does.

‡ The subject randomized to placebo withdrew because of eczema.

The subject randomized to 100 mg was withdrawn on Day 4 when ADP-induced platelet aggregation had declined to only 8%.

The subject randomized to 150 mg was withdrawn on Day 14 because of glucosuria thought to have been "possibly" related to therapy; it later developed that this man had a fixed low renal threshhold for glucose excretion. He had been noted to have excessively prolonged bleeding time (76.5 minutes) and low ADP-induced platelet aggregation (11%) on Day 12, and he was thereafter subjected to more aggressive surveillance. The glucosuria was an incidental finding of urinalysis performed to screen for hematuria, which was not found.

§ See Volumes 6.1 and 6.2.

wise for age (±5 years), weight (±15%), and sex. The cirrhotic subjects were all in Childs-Pugh class A or B; their baseline serum bilirubin levels ranged from 0.4 to 2.5 mg/dL, with a mean of 1.2. In contrast, none of the normal subjects' bilirubin levels was more than 1, and the mean was 0.6. The mean baseline AUC of indocyanine green was 1.9±1.5 μg•h/mL in the cirrhotic subjects and 1.04±0.22 μg•h/mL in the normal subjects.

Each subject received daily clopidogrel 75 mg for 10 days; pharmacokinetic measurements were made at baseline and on Days 1 and 10. Pharmacodynamic measurements (ADP-induced platelet aggregation and bleeding time) were made at baseline and on Days 7, 10, and 18.

Hepatic dysfunction was associated with spectacular increases in the C_{max} of parent clopidogrel

cirrhotic group, and these differences were consistently dwarfed by the intersubject variation.

Drug Interactions

other isozymes tested (1A2, 2A6, 2C19, 2D6, 2E1, 3A4) were inhibited by neither clopidogrel

In healthy volunteers, coadministration of clopidogrel did not cause any significant change in the pharmacokinetics of **digoxin**† or **theophylline.**‡ Conversely, the pharmacokinetics of clopidogrel were not importantly affected by coadministration of **cimetidine.**§ In postmenopausal women, the effects of clopidogrel were not obviously changed by short-term **estrogen replacement therapy,** but the only data come from a weak trial.‖ When volunteers' hepatic

* Drugs metabolized by P_{450}(2C9) include **tamoxifen, tolbutamide,** the more potent enantiomer of **warfarin,** at least some **HMG CoA reductase inhibitors,** and many **non-steroidal anti-inflammatory agents.** P_{450}(2C9) is also contributory, but inessential, to the metabolism of **carbamazepine** and **phenytoin.**

† See Study P1722, Volume 1.65.

‡ See Study INT1980, Volume 1.158.

§ See Study P1716 in Volume 1.135. Cimetidine did cause a statistically-significant decrease in clopidogrel-related inhibition of ADP-induced platelet aggregation, but the magnitude of effect was small, and there were no significant changes in bleeding time or clopidogrel-related inhibition of collagen-induced platelet aggregation.

‖ See Study P1435 in Volume 1.123. In the pertinent portion of this open-label, nonrandomized study, the pharmacokinetics and antihemostatic effects of clopidogrel were measured in 10 postmenopausal women, once after 2 weeks of coadministered clopidogrel and hormone replacement, and once after 2 weeks of clopidogrel monotherapy.

enzymes had been induced by pretreatment with **phenobarbital,**¶ and the change in platelet-inhibitory activity (an increase from 42% to 49% inhibition) was statistically significant; bleeding time was unaffected.

Study P1512# was intended to assess the effects of **atenolol** and **nifedipine** on clopidogrel's pharmacokinetics, but the trial was not randomized; the recruited patients were heterogeneous and poorly compliant; and the difficulties of detecting clopidogrel in plasma were beginning to be recognized. In the end, the intended assessment was abandoned.

Similarly, Study PDY2189** was intended to address the (speculative) possibility that clopidogrel might potentiate the CNS dysfunction induced by moderate doses of **ethanol.** No such potentiation was observed, but the investigator believed that the tests as administered had not been adequately sensitive to form the basis of firm conclusions. Perhaps because of a mixup in the investigators' supply of ethanol,†† the actual blood-alcohol levels achieved were only 20–30 mg/dL, and these are below those at which the tests used have been validated.

Potential interactions with **heparin** were assessed in Study INT2193.‡‡ This was a 12-subject, randomized, double-blind, crossover study consisting of two 12-day test periods separated by a 3-week washout. During each test period, subjects received either placebo or clopidogrel 75 mg qd. For the last 4 days of each test period, intravenous heparin was administered, titrated so as to achieve an activated partial thromboplastin time (APTT) of 1.7–2.3 times control.

Clopidogrel's influence upon the effects of heparin was to be evaluated by comparing the total heparin consumption in the placebo and clopidogrel periods. With somewhat less confidence (because administration of heparin was neither blinded nor separable from a time-on-clopidogrel effect), heparin's influence upon the effects of clopidogrel was evaluated by the sponsor's usual measures of antihemostasis (bleeding time and ADP-induced platelet aggregation). Other tests of coagulation and hemostasis were also performed at various times during the study.

The target APTT ratios were achieved with equal success in the clopidogrel and placebo groups, and the amounts of heparin required were identical to

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¶ See Study ENZ2556 in Volume 1.138.

See Volume 1.56.

** See Volume 1.120.

†† See Volume 1.120, page 244:
> Ethanol was obtained from the University Hospital in a single bulk container. The Hospital normally supplies ethanol for use in volunteers participating in medical research in two concentrations: 99.8% *[sic]* and 70%. The former was ordered for this study but apparently the latter was delivered. The label "guaranteeing" the concentration was accepted at face value. As none of the ethanol supply remained for analysis when the apparent mistake was discovered, it is impossible to verify its concentration.

‡‡ See Volume 1.149.

within 2% ($P \approx 0.51$). The bleeding-time tests were done only at baseline, during heparin administration, and during washout, so they were not useful for the detection of a clopidogrel-heparin interaction. Platelet aggregation studies were more usefully timed, and heparin did not appear to have any measurable effect on clopidogrel's inhibition of ADP-induced aggregation. Prothrombin times were unchanged throughout the trial, while thrombin times were greatly increased by heparin, significantly more in the absence of clopidogrel (3.3 times) than in its presence (2.4 times).*

A similar study was performed to look for interactions between clopidogrel and **warfarin.**† This was a 10-subject, randomized, double-blind, crossover study consisting of two 19-day test periods separated by a 3-week washout. During each test period, subjects were to receive either placebo or clopidogrel 75 mg qd. For the last 7 days of each test period, warfarin was to be administered, with doses adjusted so as to achieve a prothrombin time INR in the 1.8–2.2 range.

This study was a complete fiasco. As described on pages 29–31 of Volume 1.147, many of the protocol-specified laboratory studies were mistimed or omitted. Much more seriously, dosing of clopidogrel, placebo, and (especially) warfarin was almost whimsically irregular, and in the end "no subject received a complete, seven-day course of warfarin, and no subject received two complete 19-day periods of clopidogrel and placebo administration [emphasis added]." Some subjects received extraordinary doses of warfarin (up to 40 mg), with resulting INR values up to 4.01.

Minor Efficacy Studies

In Volume 1.79, the sponsor provides brief (2–5-page) descriptions of several small Phase II studies with clinical endpoints. These include

- Study P1742 (pages 266–269), an 8-week, open-label, forced-titration study of 10–75 mg of clopidogrel in 45 patients who had had thrombotic strokes. The investigator thought that during the course of the forced titration, patients got better.

- Study P1930 (pages 270–272), a 12-week, open-label, parallel-group study in 45 patients who had undergone successful thrombolysis after myocardial infarction. These patients were randomized to receive 10 mg or 50 mg of daily clopidogrel; the investigators could not distinguish the groups' outcomes.

- Study P2055 (pages 273–275), a 12-week, open-label, nonrandomized study of 25–75 mg of daily clopidogrel in 47 patients with atrial fibrillation. There were no interpretable events during the trial.

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* For all these results, see Volume 1.149, pages 26–32.

† See Study INT2240 in Volume 1.147.

● Study P2221 (pages 275–276), a 24-week, double-blind, parallel-group study of 25–75 mg of daily clopidogrel in 381 patients who had had strokes or transient ischemic attacks. There were no differences in the on-treatment incidences of new ischemic events.

● Study P2299 (pages 277–281), a 17-patient, open-label crossover trial consisting of two 4-week test periods. The patients were middle-aged adults with objectively verified peripheral arterial disease and reproducible claudication on treadmill exercise; they received placebo during one test period and clopidogrel 25–100 mg qd during the other. As measured by treadmill performance, patients dervived greater benefit from placebo than from clopidogrel.

● Study 2300 (pages 282–285), an open-label study in 49 hemodialysis patients who had problems with residual blood or clots in the dialyzer. The investigators thought that dialysis problems were less frequent as the clopidogrel dose was escalated.

CAPRIE

The Clopidogrel *vs.* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was a 19 185-patient, 1.6-year, 304-center, international, randomized, triple-blind, 2-armed, parallel-group study comparing clopidogrel to aspirin as secondary prevention of certain events related to atherosclerosis. Clopidogrel exposure in CAPRIE was 98% of all clopidogrel exposure reported in the application, and it was nearly 99% of the exposure in randomized, double-blind trials.

CAPRIE and its results were described in a paper in *The Lancet* (**348:** 1329–1339 (1996)); minor discrepancies between the paper and the study report are described on pages 331–332 of Volume 161.7.

The trial's protocol appears on pages 207–255 of Volume 161.2. Many details of the sort usually found in protocols are not included here, but they are instead found in the "Operations Manual"* that was produced on the same date (26 November 1991, about 4 months before the first patient was randomized). Although the study report states that the protocol was not amended,† the IND includes copies of the "bulletins" that were sent from the trial's coordinating center to its investigators.‡ Some of the bulletins dealt with pedestrian administrative matters, but others constituted what would normally be said to be amendments. For example, when it was decided to extend recruitment, effectively increasing the trial's patient population by about 30%, investigators got the news through bulletins from this series.

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* See Volume 161.3, pages 2–28.

† Volume 161.1, page 34.

‡ Volume 161.7, pages 296–322.

Eligibility for enrollment. A patient could become eligible for enrollment in any of three different ways.

- A patient could be enrolled if 1–26 weeks before randomization he or she had had an **ischemic stroke** (IS), thought likely to have been of atherosclerotic origin, confirmed by computerized tomography or magnetic resonance imaging,* and associated with residual neurological signs for at least a week.

- A patient could be enrolled because of a qualifying **myocardial infarction** (MI). Such an infarction was diagnosed if within the 35 days before randomization the patient had had at least two of (a) at least 20 minutes of characteristic pain; (b) elevation of CK, CK-MB, LDH, or AST to at least twice the laboratory's upper limit of normal, with no other explanation; and (c) development of new 40-ms Q waves in at least two adjacent electrocardiogram leads or development of a new dominant R wave of at least 1 mm in lead V_1.

- A patient could be enrolled because of **peripheral arterial disease** (PAD), manifest either as current claudication or as a history of major intervention for claudication. Current claudication was defined as leg pain of presumed atherosclerotic origin, induced by walking and relieved within 10 minutes after walking was stopped and the patient remained standing, with at least one ankle/arm systolic blood-pressure ratio less than 0.86 at rest on two assessments on separate days. The qualifying major interventions were amputations, reconstructive surgical procedures, and angioplasties of the legs, performed because of atherosclerotic disease and without persisting complications.

Each enrolled patient was counted as having been enrolled because of exactly one of the three conditions, even if the patient's history were sufficient for eligibility in one or both of the other categories too. In the application and in this review, there is continual mention of the three "diagnostic groups," referring to the three mutually-exclusive groups of patients who were *enrolled because of* the specified conditions, not the larger (and overlapping) groups of patients who *had* the specified conditions.

With very few exceptions, each investigator recruited patients in exactly one category: Neurologists recruited stroke patients, cardiologists recruited MI patients, and vascular surgeons recruited patients with PAD.

Qualification for randomization. Enrolled patients could be disqualified from randomization for most of the usual reasons (dementia, expected major surgery, contraindications to either test drug, short expected survival, concomi-

* Early in the course of the trial, the protocol was revised so that an otherwise-qualifying retinal infarction could be used as a qualifying IS event without tomographic imaging. See Volume 161.7, page 297.

tant use of other anticoagulants or antiplatelet agents, reasonable risk of pregnancy, and so on).* In addition, a patient was disqualified from randomization in the IS group if the qualifying stroke had been induced by carotid endarterectomy or angiography, or if he or she had had endarterectomy since the qualifying stroke.

Randomization of patients in the MI group was deferred, if necessary, until 48 hours after the completion of thrombolytic therapy.

Randomization. Randomization between clopidogrel and aspirin (1:1) was stratified by center and qualifying condition, and the treatment assignments are listed in Volumes 161.4 (pages 5–203), 161.5 (pages 1–350), 161.6 (pages 1–250), and 161.7 (pages 1–201). The randomization appears to have been generated in blocks of 4 patients at a time, but the procedure by which the codes were generated is not revealed in the application.

Randomization, drug packaging, and drug delivery were all performed by an outside vendor, independent of the sponsor, but the chairman of the Data Safety Monitoring Board (DSMB)† was also informed of treatment assignments as they were made, and the DSMB was provided with treatment-labeled data for its periodic safety assessments.‡

Patient Monitoring. Randomized patients were followed with routine examinations and laboratory studies. Because of concern that clopidogrel might turn out to be associated with myelotoxicity similar to that of ticlopidine, the protocol specified three different levels of monitoring. The first and most intensive level was to be followed for the first 500 patients. If blinded review of those patients' laboratory reports were reassuring, it was planned to relax monitoring to the middle level of intensity. Similarly, if no myelotoxic effect were evident on blinded review of the first 1000 patients' 3-month laboratory data, then it was planned to relax monitoring to the lowest level of intensity. The progressively-loosening monitoring scheme is described on pages 225–228 of Volume 161.2. At the least intensive level of monitoring, patients were seen every month for four months and every four months thereafter. There was no requirement for a final visit at the very end of the trial.

Drug regimens. Each patient was randomized to receive clopidogrel 75 mg or aspirin 325 mg, to be taken once daily with breakfast. A double-dummy technique was used, so each patient took two pills daily.

Trial duration. Whether or not still receiving blinded treatment, each patient was followed for three years or until the end of the trial, whichever came first. The trial was to continue until one year after the last patient had been randomized, so every patient's time on treatment was — unless the patient withdrew or an endpoint event intervened — at least one year.

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* Volume 161.2, pages 223–224.

† Throughout the application, the DSMB is consistently called the "External Safety and Efficacy Monitoring Committee," or "ESEMC."

‡ See Volume 161.3, page 17.

Planned analysis of results. The outcome events of interest were new ischemic events, including ischemic strokes, myocardial infarctions, and death from "other vascular causes."* Other events of interest included non-vascular deaths and above-ankle amputations not attributable to trauma or malignancy. Each reported event was to be evaluated by a blinded "Central Validation Committee" (CVC). The criteria that the CVC were to apply, and the procedures to be used for resolving disagreements, are described in considerable detail in the Operations Manual.† The criteria of ischemic stroke and myocardial infarction were similar to those used in determining eligibility for enrollment in the trial; the criteria for "vascular death" were inclusive rather than exclusive, so in the end "any . . . death that cannot be definitely ascribed to a nonvascular cause [was to be] classified as vascular death."

The primary test of efficacy was to be an unadjusted, intention-to-treat Mantel-Haenszel test of Kaplan-Meier survival curves, plotting the time to the first occurrencé of ischemic stroke, myocardial infarction, or vascular death.

Secondary analyses were to include similar tests of survival curves showing the time to

- ischemic stroke, myocardial infarction, amputation, or vascular death;
- vascular death;
- any stroke, myocardial infarction, or death from any cause; and
- death from any cause.

The protocol specified that if *post hoc* analysis revealed "important prognostic imbalance" between the aspirin and clopidogrel groups, then the trial would be reanalyzed, using *post hoc* stratification or adjustment via a Cox proportional-hazards model. The primary analysis and each of the secondary analyses was also to be performed both using the intention-to-treat model and using an "efficacy" model in which patients were to be censored 4 weeks after they were known to have discontinued study drug. There were thus 20 different intended life-table analyses,‡ but the protocol makes plain that the primary analysis should be the unadjusted, intention-to-treat analysis described above.

Interim analyses were planned for the times at which 25%, 50%, and 75% of the events had accrued, using a Peto-Haybittle rule that allocated a two-sided type I error of 0.001 to each interim analysis and a two-sided type I error of 0.048 for the final analysis. In addition, the study was to be stopped early if the upper limit of a 95% confidence interval for the risk reduction fell below 14%.§

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* See Volume 161.2, page 224.

† See Volume 161.3, pages 9–15.

‡ (1 primary + 4 secondary) × (adjust or not) × (intention-to-treat or efficacy); see Volume 161.2, page 235.

§ In April 1995, the DSMB decided that even if this threshhold were crossed, the Steering Committee would be encouraged *not* to stop the trial. See Volume 4.4, page 165.

In addition, the Operations Manual alludes to a variety of circumstances under which the trial might be aborted, generally when the safety and efficacy profiles of clopidogrel appeared insufficiently promising to justify continuing the trial. The Manual provides guidelines limiting communications between the DSMB and the Steering Committee, including the requirement that any such communications be in writing.

The planned analyses were intended to include patients from all three qualifying groups. The investigators believed that

> . . . there is no prior evidence to suggest that over a long period of time the relative efficiency of clopidogrel and aspirin should differ among the separate diagnostic groups, and thus the primary analysis will combine the treatment-effect estimates for stroke, myocardial infarction, and peripheral arterial disease patients. The consistency of these treatment effects across the three clinical disorders will be investigated.

To increase the credibility of the trial's overall result, the investigators planned to compare the pooled results from the North American centers with the pooled results from the European and Australian Centers.

Course of the trial. The first patient was randomized on 20 March 1992, and it was expected that it would take three years to recruit the target population of 15 000 patients. In fact, recruitment was more successful than had been anticipated, and the overall event rate was slightly lower. After considering the option to stop after the original target enrollment had been achieved, the Steering Committee instead elected to hold to (roughly) the original schedule; in order to balance the final population among the three diagnostic groups, recruitment was continued

- until 31 October 1994 in the PAD group;
- until 31 December 1994 in the MI group; and
- until 28 February 1995 in the IS group*

with the last followup visits about a year later in each group.

Pursuant to the plan described under "Patient monitoring" on page 12, hematological testing was initially intensive, but then became progressively looser when myelotoxicity appeared to be absent.†

Patients enrolled. The three qualifying conditions were approximately equally represented among the 19 185 randomized patients. About 40% of the patients were from North America, and the remainder were from Europe, Australia, and New Zealand. As might have been expected in a study this size, with randomization stratified by center and qualifying condition, the clopidogrel and aspirin groups were tightly matched, with the same mean age to within a month or two, the same mean weight to within an ounce or two, and so on. Differences in the racial composition of the two groups were nominally significant

* See Volume 161.7, pages 312 and 314–315.

† See Volume 161.7, pages 307–309.

($P=0.02$), but this result was driven by differences in the fractions of Black, Oriental, and Other Non-Caucasian patients, who together made up less than 6% of the total of either treatment group.

In contrast (but as might also have been expected), the three qualifying conditions were associated with patient populations that were sharply distinct from each other, at least in a statistical sense. As shown in table 2 below, the MI patients were generally younger than patients in the other two groups, they had fewer risk factors, and they had fewer signs of diffuse atherosclerosis. The PAD patients, although no older than the patients in the IS group, had more signs and risk factors.

Table 2
Characteristics of Patients
Recruited with Different
Qualifying Conditions

	Qualifying Condition		
	IS	MI	PAD
age <55	18.33%	37.59%	16.86%
55–64	28.11%	30.89%	29.49%
65–74	34.40%	23.48%	40.10%
>74	19.16%	8.03%	13.55%
(mean)	64.6	58.4	64.3
male	63.68%	80.78%	72.37%
white	90.95%	95.73%	97.57%
smoking current	22.19%	28.15%	38.24%
former	43.49%	50.34%	52.88%
never	34.32%	21.50%	8.88%
amaurosis fugax	2.33%	0.21%	2.06%
amputation	0.56%	0.17%	N/A
angioplasty	1.51%	2.05%	N/A
cardiac surgery	4.14%	8.25%	10.90%
cardiomegaly	5.89%	3.70%	4.23%
congestive failure	4.09%	7.03%	5.70%
claudication	7.79%	5.51%	N/A
diabetes	25.50%	14.39%	20.68%
hypercholesterolemia	37.96%	41.05%	44.62%
hypertension	65.29%	38.10%	50.91%
ischemic stroke	18.15%*	2.17%	5.97%
myocardial infarction	12.08%	16.84%*	21.19%
reconstructive surgery	2.04%	1.40%	N/A
stable angina	13.99%	24.79%	26.50%
TIA	15.53%	1.87%	6.46%
unstable angina	2.85%	17.14%	6.17%
digitalis glycosides	7.10%	9.10%	8.60%
antiepileptics	7.40%	1.50%	2.90%

* Before development of index condition.

from Volume 161.8, pp. 61–68, 71–76, and 80–82.

Patient retention. As of the end of the trial, 56 patients (0.3%) had been lost to followup; 1131 (5.9%) had died; 2460 (12.8%) had completed the maximum duration of randomized treatment (3 years); and 15 538 (81%) were still assigned to treatment with study drug.* The two treatment groups did not significantly differ with respect to the number of patients lost to followup (30 and 26 for clopidogrel and aspirin, respectively) or the duration of time on study before these patients were lost (428 ± 290 days and 475 ± 284 days).†

The mean duration of participation in the trial was 23 months; because the three diagnostic groups completed recruitment at different times, the average durations of trial participation differed slightly from one group to another,‡ but average length of participation did *not* differ between the clopidogrel and aspirin groups (698.99 ± 256.34 days and 698.91 ± 256.35 days, respectively).§

About a quarter of the patients discontinued treatment with study drug before the end of the study or the assigned three-year point. Of these patients, about half discontinued because of adverse events, including outcome events;‖ about 20% withdrew consent; about 10% began to receive a prohibited concomitant medication; about 1% were belatedly found not to have met the trial's inclusion criteria;¶ and the remainder were simply noncompliant or lost to followup. The mean duration of drug treatment was about 20 months, so there were 15 634 patient-years of exposure to clopidogrel and 15 626 patient-years of exposure to aspirin.

The 86 patients (0.4%) who never received study drug were about evenly split between the two assigned treatments. The great majority of these patients (described on pages 10–14 of Volume 161.35) withdrew consent; there were scattered instances of forbidden concomitant medication; and there were a few patients who turned out, on reconsideration, not to have had the qualifying condition after all.

Similarly, there were 60 patients (0.3%) who for various short periods were inadvertently given the opposite study drug from the one to which they had been assigned. These patients were about equally split between the two assigned treatments.

Overall efficacy *vs.* aspirin. The prespecified **primary analysis** was, as noted above, an intention-to-treat analysis using the Mantel-Haenszel test, looking at the time to first occurrence of protocol-defined ischemic stroke, myocardial infarction, or vascular death. As shown in Table 3 on the next

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* See Volume 161.1, page 79.

† For more detail, see Table A1 in the Appendix.

‡ See Volume 161.1, page 73.

§ For more detail, see Table A2 in the Appendix.

‖ After an outcome event, withdrawal from study drug was *not* required by the protocol.

¶ Of the randomized patients, 392 (2%) were in retrospect improperly enrolled. Many of these patients had had events of atherothrombotic origin, but not events that met the trial's criteria. When these patients were identified, treatment with study drug was continued (352 patients) or discontinued (40 patients) at the discretion of the investigators following them. These patients were of course retained in the study for purposes of the intention-to-treat analyses. See Volume 161.1, pages 80–83, and Volume 161.35, pages 4–6.

Table 3
Outcome Events of the
Primary Analysis

	clopidogrel	aspirin
patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
other vascular death	226 (2.35%)	226 (2.36%)
total	939 (9.78%)	1020 (10.64%)

from Volume 161.1, page 94

page, the clopidogrel patients had a lower incidence of events in every category, with an overall relative risk reduction of 8.7% (95% confidence interval 0.2–16.4%, $P \doteq 0.045$ by the stratified* logrank test). These results are only slightly affected (RRR still 8.7%, $P = 0.043$) when the calculations are revised so as to include the 14 patients who had been lost to followup but were located within a few days after the data lock.† Similarly, there is little change when the analysis uses the slightly different counts that appear when the investigators' reports are taken at face value, without endpoint adjudication by the CVC.‡ When non-first strokes and MIs are added, the pattern is slightly reinforced (1077 events in the clopidogrel group, 1182 in the aspirin group);§ when analysis is *limited* to non-first outcome events (that is, to new outcome events in patients who had survived an in-study IS or MI), the clopidogrel group again has lower rates of ischemic stroke (0.66% *vs.* 0.76%), myocardial infarction (0.29% *vs.* 0.44%), and vascular death (1.29% *vs.* 1.59%).‖ Even when the patients lost to followup are all treated as having had events at the time of their disappearances, the result is only slightly weakened (968 events *vs.* 1046, relative risk reduction 8.2% (-0.2–15.9%), $P = 0.055$).

The overall primary result in the European, Australian, and New Zealand centers (relative risk reduction of 7.0%) was not significantly different from the overall primary result in the North American centers (relative risk reduction of 10.9%). Not surprisingly, inasmuch as the overall trial result was only barely significant, neither of these regional results was nominally significant.¶

All of the prespecified intention-to-treat **secondary analyses** also favored clopidogrel, as did a revised primary endpoint that included all-cause mortality in place of "vascular" mortality. These results are shown in Table 4 on the next page; none of the differences was nominally significant ($0.08 \le P \le 0.71$). In the primary analysis and in each of the four secondary analyses, the numerical

* The protocol is somewhat ambiguous as to whether the logrank test was to be stratified, but various historical trial documents, provided by the sponsor with the submission of 13 August, convince us that stratification was intended.

† See Volume 161.1, page 107.

‡ See Volume 161.1, pages 104–107.

§ See Volume 161.1, page 97.

‖ See Volume 161.1, page 104.

¶ See Volume 161.1, pages 107–111.

Table 4
Outcome Events of the
Secondary Analyses

	clopidogrel	aspirin	relative risk reduction
patients	9599	9586	
IS, MI, amputation, vascular death	979 (10.2%)	1050 (11.0%)	7.5%
vascular death	350 (3.6%)	378 (3.9%)	7.6%
any stroke, MI, any death	1133 (11.8%)	1206 (12.6%)	6.9%
any death	560 (5.8%)	571 (6.0%)	2.2%
IS, MI, any death*	1108 (11.5%)	1173 (12.2%)	6.4%

* Reviewers' analysis, *not* protocol-specified.

from Volume 161.1, page 98

advantage of clopidogrel was visible by six months and (with one exception) sustained at one, two, and three years.*

As noted under "Patient retention" on page 16, about a quarter of the patients discontinued study drug prematurely, and only a minority of these discontinuations were related to outcome events. In another protocol-specified analysis, the investigators reexamined the primary endpoint, excluding events that occurred more than 4 weeks after study drug had been discontinued. As shown in Table 5 on the next page, these results are extremely similar to those of the primary analysis; the new relative risk reduction is 9.4%, with $P=0.046$.

Efficacy and qualifying condition. When the primary analysis is separately repeated on each of the three diagnostic groups, the results are heterogeneous. The treatment×group interaction is significant at $P=0.043$, and (as shown in Table 6 on the next page and in the figure on page 20) the point estimates for relative risk reduction vary from 23.7% in the PAD group down to -4% (that is, a relative risk *increase*) in the MI group.† As shown in Table 7 on page 21, the same pattern was seen in selected combinations of the secondary analyses. If the effect were really uniform across the three groups, then the likelihoods of results as extreme as those seen in the extremal strata (the MI and PAD groups) would have been 0.067 and 0.13, respectively.‡

In the MI group, a plot of event-free survival reveals a slight edge for aspirin at most times, but a slight edge for clopidogrel at a few others. In the IS group, clopidogrel is superior at every time point, but never by much. In

* The one exception was for all-cause mortality at two years, which was slightly higher (5.83% *vs.* 5.82%) in the clopidogrel group. See Volume 161.1, pages 96–97 and 99.

† Not surprisingly, inasmuch as the overall trial result and the treatment×group interaction were each only barely significant, the clopidogrel-aspirin differences in the MI and IS groups were not statistically significant ($P=0.64$ and $P=0.26$, respectively).

‡ These probabilities can be derived using the formula given by Inglefinger, Mosteller, Thibodeau, and Ware in *Biostatistics in Clinical Medicine*, 2nd edition (New York: Macmillan, 1987), page 281 or by using percentiles of the *P*-value distribution based on the overall effect size, as given by Hung, O'Neill, Bauer, and Köhne in *Biometrics* **53:** 12 (1997).

Table 5
Outcome Events of the
Primary Analysis, Censored
4 Weeks After Study Drug Discontinued

	clopidogrel	aspirin
patients	9553	9546
IS (fatal or not)	385 (4.03%)	403 (4.22%)
MI (fatal or not)	225 (2.36%)	283 (2.96%)
other vascular death	165 (1.73%)	166 (1.74%)
total	775 (8.11%)	852 (8.93%)

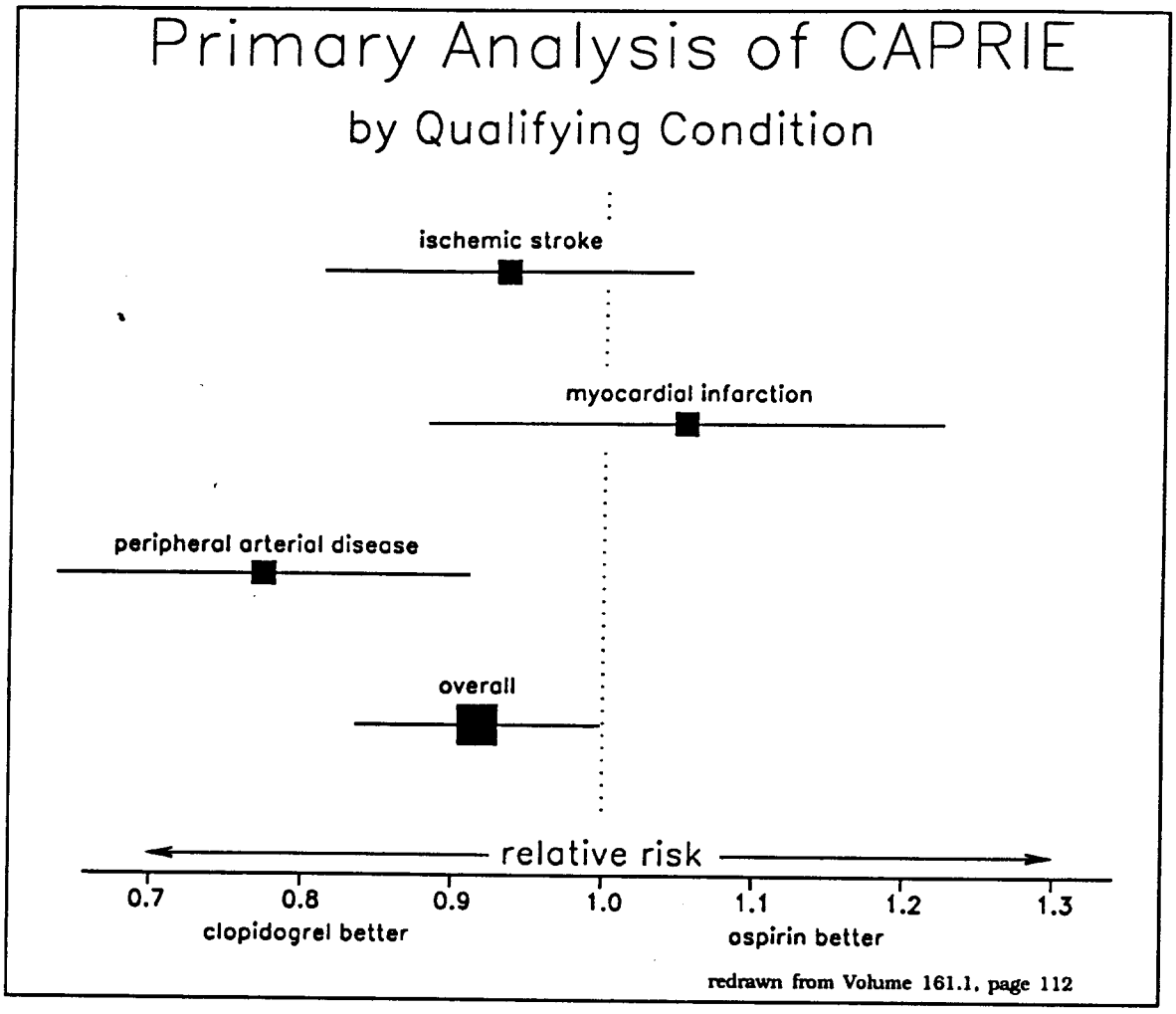
from Volume 161.1, page 101

IS group, clopidogrel is superior at every time point, but never by much. In the PAD group, the curves separate after two or three months, and they seem (see Volume 161.1, pages 113–115) to separate further over time.

Table 6
Outcome Events of the
Primary Analysis
by Diagnostic Group

	clopidogrel	aspirin	relative risk reduction (95% C.I.)
IS group			
patients	3233	3198	
IS (fatal or not)	315 (9.74%)	338 (10.57%)	
MI (fatal or not)	44 (1.36%)	51 (1.59%)	
other vascular death	74 (2.29%)	72 (2.25%)	
total	433 (13.39%)	461 (14.42%)	7.3% (-5.7, 18.7)
MI group			
patients	3143	3159	
IS (fatal or not)	42 (1.34%)	41 (1.30%)	
MI (fatal or not)	163 (5.19%)	174 (5.51%)	
other vascular death	86 (2.74%)	67 (2.12%)	
total	291 (9.26%)	282 (8.93%)	-4.0% (-22.5, 11.7)
PAD group			
patients	3223	3229	
IS (fatal or not)	81 (2.51%)	82 (2.54%)	
MI (fatal or not)	68 (2.11%)	108 (3.34%)	
other vascular death	66 (2.05%)	87 (2.69%)	
total	215 (6.67%)	277 (8.58%)	23.7% (8.9, 36.2)

from Volume 161.1, pages 73 and 111



Covariate Influence on Efficacy. Even though the heterogeneity among the three diagnostic groups is statistically significant, the point estimates cited above might not be the best estimates of the effect to be seen in patients like those who were recruited into the three respective diagnostic groups. Before the demonstrated heterogeneity can be turned into prediction, one must face difficult problems of estimation and of description.

Although CAPRIE was designed to detect heterogeneity in efficacy among the diagnostic groups, it was *not* designed to provide separate estimates of the effect size in each group. If the trial population had been (biologically) homogeneous, then the best estimates of effect for any subgroup would be obtained not from only the data pertaining to that subgroup, but rather from the parent population. Oppositely, when two or more subgroups are expected to experience totally unrelated effects of an intervention (for example, in an amantadine trial that recruited (a) patients with Parkinson's disease and (b) patients at risk of infection with influenza A virus), then the best statistics describing each group are of course computed from only the data obtained from that group. The situation here is intermediate, and there is no established procedure for weighting the group data against the overall data.

Table 7
Outcome Events of
Selected non-Primary Analyses
by Diagnostic Group

	clopidogrel	aspirin	relative risk reduction (95% C.I.)
IS group			
patients	3233	3198	
IS, MI, any death	511 (15.85%)	527 (16.48%)	4.3% (-8.1, 15.2)
any stroke, MI, any death	527 (16.30%)	550 (17.20%)	5.5% (-6.5, 16.1)
MI group			
patients	3143	3159	
IS, MI, any death	319 (10.15%)	312 (9.88%)	-3.0% (-20.4, 11.9)
any stroke, MI, any death	322 (10.24%)	315 (9.97%)	-3.0% (-20.3, 11.8)
PAD group			
patients	3223	3229	
IS, MI, any death	278 (8.63%)	334 (10.34%)	18.3% (4.2, 30.3)
any stroke, MI, any death	284 (8.81%)	341 (10.56%)	18.3% (4.3, 30.2)

In particular, it is difficult to decide whether the best estimate of effect in the MI group should really be adverse, as it is in Tables 6 and 7 and in the figure. From the test described by Gail and Simon,* the apparent adverse effect could easily be a result of chance ($P=0.71$), but our 10 000-run simulation shows that even if the point estimates of the tables and figure were correct, the Gail-Simon test would have only 5.5% power to detect the adverse effect. That is, the Gail-Simon test doesn't really help in deciding whether the apparent adverse effect was the result of chance.

Moreover, whatever estimate of within-group effect size one accepts, it is not clear which were the pivotal characteristics that caused the three groups to be associated with such different results. For example, as shown in Table 2 on page 15, many of the patients in the PAD and IS groups had had myocardial infarctions (although not necessarily within the qualifying time period). If the effect-determining characteristic of patients in the MI group were their histories of having had MIs, then one might expect the IS and PAD patients who had had infarctions to have derived less benefit from clopidogrel than infarction-free members of their respective cohorts.

Such was not the case. For patients in the IS and PAD groups, having had an MI was associated with a substantial increase in the incidence of primary outcome events during the trial, but (as shown in Table 8 on the next page) the relative benefit of clopidogrel over aspirin appeared to be *greater* in these patients than it was in their infarction-free colleagues.

* *Biometrics* **41:** 361-372 (1985).

Table 8
Outcome Events of the Primary Analysis
by non-MI Diagnostic Group
and History of MI

	clopidogrel	aspirin	relative risk reduction
IS group			
history of MI	86/413 (20.8%)	87/364 (23.9%)	12.9%
no such history	347/2820 (12.3%)	374/2834 (13.2%)	6.8%
PAD group			
history of MI	78/686 (11.4%)	109/681 (16.0%)	28.8%
no such history	137/2537 (5.4%)	168/2548 (6.6%)	18.2%

Clopidogrel's relatively poor performance in the MI group might somehow be related to the fact that those patients had all had *recent* infarctions, probably more recent than those experienced by any but a very few of the patients in the other two groups. This possibility has not been investigated.

Because they were specifically defined by the inclusion criteria, the three diagnostic groups are natural targets of analysis, but they are not the targets of any preferred analysis prespecified by the CAPRIE protocol. For this reason, exploratory analysis that tries to account for the observed heterogeneity should be free to look for other cofactors (*i.e.*, other than qualifying condition) that might better account for the observed variance. We have tried to identify such cofactors, but without success.

Increasing **age**, for example, was strongly associated with an increasing incidence of outcome events ($P=0.0001$); the clopidogrel/aspirin relative risk ratio was heterogeneous across the age groups ($P=0.009$); and the MI group was substantially younger than either of the others ($\chi^2_9 = 1277$, $P < 10^{-648}$). We anticipated that clopidogrel's advantage over aspirin would rise with age in every group, and that the relatively poor performance of clopidogrel in the MI group could arguably be better described as relatively poor performance in younger patients. As shown in Table 9 on the next page, however, this speculation is not borne out by the data. What is evident in Table 9 is that the clopidogrel/aspirin benefit actually *declines* with age in the IS and PAD groups, while its relation to age in the MI group is nonmonotonic.

A Cox regression analysis (which allowed age to be treated as a continuous, rather than categorical, variable) gave results that were consistent with those shown in Table 9. That is (as shown in Table A3 in the Appendix), age had some explanatory power in each of the three groups, but the effect varied from group to group.

As shown (in part) in Table 2 on page 15, the three diagnostic groups differed in many of their other pre-randomization characteristics. In a series of

Table 9
Outcome Events of the
Primary Analysis by
Diagnostic Group and Age

group and age	clopidogrel	aspirin
IS group		
<55	52 (8.6%)	60 (10.4%)
55–64	99 (10.7%)	111 (12.6%)
65–74	155 (14.2%)	167 (14.9%)
>75	127 (20.9%)	123 (19.7%)
MI group		
<55	65 (5.4%)	60 (5.1%)
55–64	69 (7.3%)	94 (9.4%)
65–74	94 (12.6%)	82 (11.2%)
>75	63 (24.5%)	46 (18.5%)
PAD group		
<55	15 (2.8%)	31 (5.7%)
55–64	54 (5.6%)	68 (7.2%)
65–74	93 (7.1%)	127 (9.9%)
>75	53 (12.7%)	51 (11.2%)

analyses shown in Tables A4–A20 in the Appendix, we attempted to identify one or more of these cofactors that might account for the apparent intergroup differences through a treatment×cofactor interaction. We examined smoking status, any concomitant disease reported to have been present in at least 10% of the population, and concomitant medications. With scattered small exceptions best attributed to chance, the performance of clopidogrel and aspirin in the identified subgroups (IS patients with/without hypertension, MI patients receiving/not receiving calcium antagonists, and so on) was similar to that seen in the larger groups.

Finally, we performed a series of multifactor Cox regression analyses, thinking that even though the treatment×qualifying-condition interaction could not be explained away by any single covariate, perhaps it would fall to an attack by many at once. Our ultimate analysis included 28 covariates; after all of that (as shown in Table 10 on the next page), the heterogeneity among the diagnostic groups was essentially unchanged.

Comparison to placebo. Because clopidogrel and placebo have never been compared in a single trial, any estimate of their relative efficacy must rest upon a combination of CAPRIE (clopidogrel/aspirin) and one or more other trials (aspirin/placebo).

The aspirin/placebo data have been exhaustively reviewed by the Oxford-based Antiplatelet Trialists' Collaboration ("the Trialists").* The work of the

* See, *inter alia*, their "Collaborative overview of randomised trials of antiplatelet therapy I" in *British Medical Journal* **308**: 81–106 (1994).

Table 10
Risk Reduction by Qualifying Condition
After Adjustments for Various Cofactors

	Qualifying Condition			
covariates included	IS	MI	PAD	overall*
none	7.3%	-4.1%	23.5%	8.5%
age, diabetes, smoking status	5.1%	-4.1%	22.7%	7.6%
everything except anchovies†	5.3%	-6.8%	19.2%	5.7%

* Adjusted for qualifying condition.
† Age, sex, diabetes, smoking status, cardiac surgery, congestive heart failure, hypercholesterolemia, hypertension, previous MI, cardiac arrhythmia, previous ischemic stroke, stable angina, unstable angina, transient ischemic attack, ACE inhibitors, antidiabetic therapy, anti-epileptic therapy, β-blockers, calcium-channel blockers, estrogens, anti-lipid products, coronary vasodilators, digitalis glycosides, diuretics, peripheral vasodilators, anti-inflammatory products, anti-thrombotic products, and peripheral surgical interventions.

Trialists has been reviewed by Dr. Ganley and one of us (JH), and we here include only the high points of that analysis.

The Trialists concluded that aspirin is more or less uniformly beneficial in patients at risk of atherothrombotic events. Their papers, however, are sufficiently data-rich that one may do one's own analysis and draw one's own conclusions.

Many of the trials analyzed by the Trialists (and by Ganley & Hung) recruited patients who were reasonably similar to the patients recruited into one or another of the diagnostic groups of CAPRIE. Other trials' patients were a looser fit to CAPRIE, notably those who had had TIAs as their only manifestation of cerebrovascular disease. As it turns out, the results of the Ganley-Hung analysis are not much affected by inclusion or exclusion of the TIA patients.

The results are also reasonably robust with respect to variation in meta-analytic technique. Our preferred technique is to compute overall results by weighting the individual study results by their sample sizes, but alternative schemes (weighting studies equally; pooling at the patient level) give results that are only trivially different. Similarly, we prefer to exclude studies in which no outcome events were observed, but inclusion of such studies has little effect here.

The results of our preferred analysis for the composite of stroke, MI, and cardiovascular death are shown in Table 11 on the next page. Table 12 on the next page is similar, with the endpoint expanded to include noncardiovascular death. In either table, one sees a strong protective effect of aspirin in the MI group and a slightly weaker effect in the IS/TIA group. In the PAD group, perhaps because of the much smaller population of patients studied, the results are equivocal. The best-estimate overall effect in a CAPRIE-like population is a risk reduction of 15–20%.

Table 11
Effect of Aspirin (*vs.* Placebo) on
Stroke, MI, and Cardiovascular Death

group	trials	patients ASA	patients placebo	odds ratio (95% C.I.)
MI	Cardiff I, Cardiff II Paris I, AMIS, CDP-A, GAMIS, Micristin	6286	5913	0.76 (0.68–0.84)
IS	AICLA, Britton, SALT	1127	1140	0.83 (0.68–1.01)
IS (& TIA)	AICLA, Britton, SALT, AITIA, UK-TIA, Canadian cooperative	3054	2250	0.84 (0.74–0.96)
PAD	Hess, Schoop-I, Munich-A, Munich-B	545	534	0.96 (0.48–1.92)

from Table 4 of the Ganley-Hung review

Moreover, the group-specific results are strangely complementary to those of CAPRIE. Where clopidogrel looks best against aspirin (that is, in the PAD group), aspirin is of unproved value *viz-à-viz* placebo. Where clopidogrel appears to be no better than aspirin (that is, in the MI group), aspirin is markedly superior to placebo.

In a report written for the sponsor (included in the submission of 20 August), Lloyd Fisher estimated that with respect to the primary composite endpoint of CAPRIE, the overall clopidogrel/placebo odds ratio was 70.5%. Dr. Fisher went on to compute confidence limits for this estimate of the

Table 12
Effect of Aspirin (*vs.* Placebo) on
Stroke, MI, and Death

group	trials	patients ASA	patients placebo	odds ratio (95% C.I.)
MI	Cardiff I, Cardiff II Paris I, AMIS, CDP-A, GAMIS, Micristin	6286	5913	0.78 (0.70–0.86)
IS	AICLA, Britton, SALT	1127	1140	0.81 (0.67–0.97)
IS (& TIA)	AICLA, Britton, SALT, AITIA, UK-TIA, Canadian cooperative	3054	2250	0.80 (0.70–0.90)
PAD	Hess, Schoop-I, Munich-A, Munich-B	545	534	1.07 (0.55–2.07)

from Table 5 of the Ganley-Hung review

clopidogrel/placebo odds ratio; the probability that this odds ratio could really be ≥ 100%; similar estimates, confidence limits, and *P*-values for components of the endpoint; similar estimates, confidence limits, and *P*-values for modified endpoints (*e.g.*, counting all-cause mortality instead of vascular mortality); and reanalyses by qualifying condition. We agree with Dr. Fisher that clopidogrel seems highly likely to be more effective than placebo in every identifiable subgroup.

We are unwilling to say more than that. As noted on page 3 of the Ganley-Hung review, the covariates that might influence the aspirin/placebo odds-ratio calculation include duration of treatment, duration of followup, secular changes in concomitant treatment, and many others. We believe that adequate adjustment for these covariates is not possible, so that while we do not quarrel with Dr. Fisher's calculations *per se*, we believe that any interpretation of his combined odds-ratio, confidence-limit, and *P*-value results is problematic.

Safety

Pre-CAPRIE trials. Exposure to clopidogrel in pre-CAPRIE trials was limited (about 270 patient-years, compared to almost 16 000 patient-years in CAPRIE), but the patients in the early trials were generally followed more closely than those of CAPRIE. Also, many of the early trials used ticlopidine and/or placebo controls, both of which were absent in CAPRIE.

All of the clopidogrel-exposed patients in CAPRIE received 75 mg daily, while dosing in the pre-CAPRIE trials included doses ranging from 10 to 600 mg. One might hope that subtle safety information might be teased out of dose-response observations, but the total exposure to doses other than 75 mg was only about 6 patient-years.

On pages 153–155 of Volume 1.173, the sponsor summarizes the data regarding each adverse event that occurred with frequency ≥ 2% in the pre-CAPRIE studies; a more detailed listing appears on pages 17–29 of Volume 1.175. In an attempt to expose dose-response signals, the clopidogrel exposures are tabulated by separating doses less than 75 mg, equal to 75 mg, or greater than 75 mg. The other columns of these displays are for placebo and "other drug" (usually ticlopidine). These tables must be interpreted together with the tables of ADR-related dropouts on pages 168–171 of Volume 1.73.

Many of the apparent findings in this sort of tabulation are likely to be spurious. For example, abnormal pre-CAPRIE laboratory findings are listed and described on pages 172–180 of Volume 1.73. The hematocrit dropped below the normal range in fully 20% of the clopidogrel-exposed patients, but in only 9% of the patients exposed to placebo. That sounds bad, but 38% of the clopidogrel cases turn out to have been patients who underwent coronary bypass surgery in a trial (P1398, Volume 1.129) that had no placebo control. When examining the pooled pre-CAPRIE data, one must remember that the various treatment groups were not selected from the same population. Without keeping this consideration in mind, one might (for example) have difficulty understanding the finding that

the incidence of "any event" in the 75-mg clopidogrel group was 43%, but the incidence in the subjects who received *higher* doses was only 12%.

Of the tabulated varieties of adverse event, many were no more common with clopidogrel than with placebo. Table 13 below lists the ADRs of interest.

- Most of the "autonomic nervous system disorders" were cases of **flushing.** In addition, "hot flushes" are recorded under the Body As A Whole category, where there were 1 case on low-dose clopidogrel, 4 cases on 75 mg of clopidogrel, and 1 case on placebo, for an incidence of 0.6% in each group.

- There was only one case of **chest pain** that was reported to be substernal, but we can't tell whether "chest pain" and "substernal chest pain" were recorded as overlap-

Table 13
Number (%) of pre-CAPRIE Subjects
With Adverse Events Occurring
More Often with Clopidogrel than with Placebo and
(a) Associated with Discontinuation or
(b) Seen in at least 2% of Subjects

	clopidogrel 75 mg	placebo
autonomic nervous system disorders	16 (2.2%)	0
chest pain	20 (2.8%)	3 (1.9%)
headache	63 (8.7%)	10 (6.5%)
diarrhea	20 (2.8%)	1 (0.7%)
ulcerative stomatitis	5 (0.7%)*	0
bleeding, clotting, or platelet disorder	72 (10.0%)	6 (3.9%)
hematoma	25 (3.5%)	0
laboratory abnormalities	15 (2.1%)†	0
pharyngitis	9 (1.2%)‡	1 (0.6%)
purpura	10 (1.4%)§	4 (2.6%)
rhinitis	19 (2.6%)	2 (1.3%)
skin disorders	35 (4.9%)	4 (2.6%)
white-cell and reticuloendothelial disorders	15 (2.1%)	0

* Listed because stomatitis was also reported in 3 (2.5%) of subjects exposed to clopidogrel doses greater than 75 mg.

† These included 1 subject with SGPT increased, 1 with "hepatocellular damage," 12 with unspecified hepatic enzymes increased (1 of whom also had increased creatine phosphokinase), and 1 with hypercholesterolemia. Of these subjects, only the patient with CPK elevation withdrew from treatment.

‡ Listed because pharyngitis was also reported in 4 (2.4%) of subjects exposed to clopidogrel doses less than 75 mg. In addition, it may be pertinent that coughing was reported by 4 (0.6%) of subjects receiving clopidogrel 75 mg, 1 subject (0.8%) receiving a higher dose, and no subjects receiving placebo. Three patients with pharyngitis and/or coughing withdrew from trials.

§ Listed because purpura was also reported in 5 (4.1%) of subjects exposed to clopidogrel doses greater than 75 mg.

ping or as mutually exclusive categories. Events in this area were, in any case, better studied in CAPRIE.

- The **headache** and **diarrhea** cases speak for themselves.

- The **pharyngitis/rhinitis/cough** entries are a little implausible, but of course that's what we once thought about ACE-inhibitor-induced cough, too. Should the subject with angioedema (now listed with the dermatologic problems; see below) have been listed here? Not counting the subject with angioedema, 4 of these subjects withdrew from treatment.

- The hemostasis-related events seen in these trials should be ignored, inasmuch as the same phenomena were better studied in CAPRIE.

- The "skin disorders" category included **rashes** (bullous, erythematous, folliculitic, maculopapular, psoriaform, urticarial/dermatographic, and unspecified), **itching**, and one case of **angioedema.** The angioedema patient and 14 others withdrew from treatment. The incidence of events was low in each of the subcategories, but something is definitely going on. Could the **stomatitis** cases have been lichen planus?

- We don't know what to make of the "white-cell and reticuloendothelial disorders" category. The 15 patients were associated with 18 reported events, consisting of eosinophilia (2, one of whom withdrew from treatment), granulocytopenia (2), leukocytosis (4), lymphadenopathy (2), cervical lymphadenopathy (1), monocytosis (1, who withdrew from treatment), neutropenia (1), and an unspecified white-cell disorder (5). This is such a mixed bag that we are inclined to believe that there is no signal worth tracking, unless something shows up in CAPRIE.

Ignoring the most flagrantly uninterpretable categories, and ignoring disorders of hemostatic mechanism (better studied in CAPRIE), the laboratory values of note are shown in Table 14 on the next page. The implications of these findings will be discussed with the findings of CAPRIE.

Clopidogrel was compared to **ticlopidine** in four pre-CAPRIE trials, but the total ticlopidine exposure in these trials was about 30 patient-months, so stable comparative results could not be obtained.

Fourteen early **Japanese** clopidogrel studies are also described in the application (Volume 1.173, pages 205–224). The total clopidogrel exposure in these studies was less than 2 patient-years, and the tabulated events and abnormalities are not different, better described, or different in frequency from those described elsewhere.

Table 14
Number (%) of pre-CAPRIE Subjects
With Laboratory Abnormalities Occurring
More Often with Clopidogrel than with Placebo and
Seen in at least 2% of Subjects

	clopidogrel 75 mg	placebo
leukopenia	115 (17.0%)	7 (5.5%)
lymphopenia	14 (2.2%)	1 (0.8%)
monocytopenia	17 (2.7%)	0
neutropenia	44 (6.8%)	3 (2.5%)
ALT increased	41 (6.1%)	0
AST increased	66 (9.8%)	0
hypercholesterolemia	13 (2.1%)	1 (0.9%)
creatinine increased	26 (4.0%)	0
hypertriglyceridemia	35 (6.8%)	6 (6.1%)

Safety findings of CAPRIE. Some adverse events reported in CAPRIE were of significantly different incidence between the treatment groups, and others are of interest because of findings in the pre-CAPRIE studies discussed above. Adverse-event findings of these varieties are displayed in Table 15 on the next page. Most of Table 15 is taken from the sponsor's table on pages 66–67 of Volume 1.173, but some entries had to be obtained by interrogation of the database in the sponsor's CANDA.

Some concerns raised by the pre-CAPRIE database are alleviated, or at least put into context, by the larger-scale database from CAPRIE. For example, while **flushing** was significantly more commonly reported with clopidogrel than with placebo in the early studies, the incidence of flushing in CAPRIE was slightly greater among aspirin patients than among clopidogrel patients. Similarly, the data shown in Table 15 should dissipate concerns about **angioedema** and **stomatitis**, and although **headache** was weakly associated with clopidogrel in the earlier trials, in CAPRIE it was only slightly more frequent with clopidogrel than with the analgesic aspirin. The **pharyngitis/rhinitis/cough** cluster is also no longer impressive, although one might have a small nagging worry that some cough might arise as an asthma equivalent, so that with respect to this adverse effect aspirin might be an (adversely) active control.

Other findings from the pre-CAPRIE studies are reinforced by CAPRIE, notably the associations of clopidogrel with **diarrhea** and with a wide range of **skin problems.***

* The reported dermatopathology ranges from alopecia through xerosis. Acutely life-threatening conditions (Stevens-Johnson syndrome, epidermal necrolysis, *etc.*) were not reported; the clopidogrel group included 22 bullous eruptions, while the aspirin group included 15 bullous eruptions and one "pemphigoid reaction." Many of the CANDA-tabulated data appear nonspecifically as "rash" or "skin disorder."

Table 15
Number (%) of CAPRIE Patients
With Adverse Events Occurring
(a) Significantly More Often in One Treatment Group, or
(b) Otherwise of Interest

	clopidogrel	aspirin
abdominal pain	541 (5.64%)	684 (7.14%)‡
angiobedema	8 (0.08%)	11 (0.11%)
constipation	228 (2.38%)	319 (3.33%)‡
cough	220 (2.29%)	175 (1.83%)*
diarrhea	428 (4.46%)	322 (3.36%)‡
dyspepsia	501 (5.22%)	585 (6.10%)†
flushing	21 (0.22%)	23 (0.24%)
headache	730 (7.60%)	694 (7.24%)
heart rate & rhythm disorders	409 (4.26%)	483 (5.04%)*
hypertension	415 (4.32%)	487 (5.08%)*
pharyngitis	22 (0.23%)	16 (0.17%)
purpura	506 (5.27%)	353 (3.68%)‡
rhinitis	403 (4.20%)	405 (4.22%)
skin disorders	1518 (15.81%)	1254 (13.08%)‡
stomatitis	31 (0.32%)	35 (0.37%)
bleeding, clotting, or platelet disorder	(see text)	
white-cell and reticuloendothelial disorders	(see text)	
other laboratory findings	(see text)	

* $P \leq 0.05$.
† $P \leq 0.01$.
‡ $P \leq 0.001$.

CAPRIE demonstrated that aspirin is associated with a slightly higher incidence of cardiac arrhythmias than is clopidogrel, but the reported arrhythmias ranged from extrasystoles to cardiac arrest, and these events seem to be hopelessly confounded with the outcome events. Table 15 also shows that aspirin is more likely than clopidogrel to cause **abdominal pain, constipation, dyspepsia,** and **hypertension,** but the differences in incidence are probably not sufficient to alter the behavior of clinicians. A number of other small differences in symptomatic endpoints are described on pages 68–80 of Volume 1.173; some of the differences were nominally statistically significant, but the comparisons are taken from among so many that they are not convincing.

Disorders of hemostasis were of course given special attention. Some of these (non-ischemic strokes) were scored as secondary outcome events, but many less serious events were also recorded. An intent-to-treat analysis of hemorrhage counted intracranial hemorrhages (fatal or not) and other hemorrhagic deaths. As shown in Table 16 on the next page, these events were infrequent, but consistently less frequent in the clopidogrel group than in the aspirin group. In addition, Table 17 on the next page lists all of the pertinent-seeming events we could find in the sponsor's CANDA. Incidence rates (percentages) are omitted to

Table 16
Major Hemorrhagic Events

	clopidogrel	aspirin
patients	9599	9586
nonfatal intracranial hemorrhage	14 (0.15%)	24 (0.25%)
fatal intracranial hemorrhage	16 (0.17%)	16 (0.17%)
other fatal hemorrhage	7 (0.07%)	11 (0.11%)

from Volume 161.1, page 100

conserve space, but the exposed groups were so nearly identical in size (9599 *vs.* 9586) that the raw counts are not misleading. As is seen Table 17, some events were much more common in one group than the other (more purpura with clopidogrel, $P<0.001$; more gastrointestinal bleeding with aspirin, $P<0.05$).

In clinical trials of the congener drug ticlopidine, 50/2048 patients (2.4%) developed **neutropenia** (counts less than 1.2 G/L), and a third of these patients had counts less than 0.45 G/L. As described under "Patient monitoring" on page 12, CAPRIE patients were (at least initially) intensively monitored in an attempt to detect any similar effect in association with clopidogrel. In the preplanned analysis, cases of apparent neutropenia were reviewed in blinded

Table 17
Number of CAPRIE Patients
With Bleeding-Related Adverse Events

	all events		events called serious	
	clop	ASA	clop	ASA
hemorrhagic duodenal ulcer	17	14	17	13
epistaxis	281	245	11	12
hemorrhagic gastric ulcer	8	12	7	11
rectal hemorrhage	52	75	5	15
hemorrhagic gastritis	4	4	4	4
peptic ulcer	6	13	3	5
purpura	506	353	3	0
hemothorax	4	1	2	1
perforated gastric ulcer	1	3	1	3
retroperitoneal hemorrhage	2	2	1	2
hyphema	16	9	1	0
hemorrhagic cystitis	3	0	1	0
respiratory tract hemorrhage	1	1	1	0
pulmonary hemorrhage	1	0	1	0
vaginal hemorrhage	18	15	0	4
hemopericardium	0	1	0	1
oral hemorrhage	2	5	0	1
aggravation of peptic ulcer	0	2	0	0
uterine hemorrhage	2	6	0	0

fashion by a hematologist; the hematologist, unlike the investigators, could reject some results as being laboratory errors or insignificant changes from low baseline values.

The reports of the investigators and the hematologist are summarized in Table 18 on the next page. In addition, capsule summaries of the 7 cases in which counts were below 0.45 G/L are tabulated on pages 84–85 of Volume 1.173. The aspirin patient rejected by the hematologist had a nadir neutrophil count of 0.397 G/L, but it had been only 0.866 G/L at baseline. In all 4 of the clopidogrel patients and one of the remaining aspirin patients, neutrophil counts returned to normal after the drug was discontinued; the other aspirin patient was an 81-year-old man who remained granulocytopenic despite withdrawal of aspirin.

Also, graphs on pages 102–112 of Volume 161.11 show that at almost every time of measurement, CAPRIE patients receiving clopidogrel had lower counts of basophils, eosinophils, lymphocytes, monocytes, platelets, and neutrophils than did the patients receiving aspirin. From the error bars and the values shown, the many differences are usually statistically significant, but never clinically so.*

Clopidogrel may have a weak neutropenic effect, and it may even be capable of causing agranulocytosis. CAPRIE clearly demonstrates, however, that this neutropenic effect (if it is real) is at least one or two orders of magnitude weaker than that of ticlopidine.

Clopidogrel and aspirin had statistically different effects on many different **laboratory values**, but most of the effects were clinically trivial. For example, total bilirubin was consistently significantly higher in the clopidogrel group, but the values at a typical time point were 0.570±0 005 mg/dL (clopidogrel) and 0.546±0.003 mg/dL (aspirin). Similar results were seen in measurements of albumin and calcium (trivially higher in the clopidogrel group) and of creatinine, cholesterol, sodium, alkaline phosphatase, uric acid,† and hepatocellular enzymes (trivially higher in the aspirin group). On some other tests (cholesterol, LDL cholesterol, triglycerides), the two treatment groups could not be distinguished statistically, let alone clinically.‡

Adverse events that led to **early discontinuation of therapy** are tabulated on page 94 of Volume 1.173. The overall rates of early discontinuation were almost identical (11.94% *vs.* 11.92%) in the two treatment groups. As grounds for withdrawal, categories of adverse events appeared in the two treatment groups in the same pattern as before: more gastrointestinal problems with aspirin, more dermatologic problems with clopidogrel, and so on.

---

* The opposite pattern was seen with hemoglobin and red-cell count. Both of these values rose steadily in both treatment groups, from 14.4 to 14.7 g/dL and 4.7 to 4.8 T/L, respectively. At almost every on-treatment time of measurement, each value in the clopidogrel group was statistically significantly higher than the corresponding value in the aspirin group, but these differences (and, for that matter, the overall differences from baseline) were all clinically meaningless.

† The incidence of frank gout was actually somewhat higher in the clopidogrel group than in the aspirin group (175 *vs.* 132, $P<0.025$).

‡ For all of these laboratory results, see pages 116–125 of Volume 1.173 and pages 89–101 of Volume 161.11.

Table 18
Number of CAPRIE Patients
With Certain Treatment-Emergent Neutrophil Counts

	per investigator		per hematologist	
	clop	ASA	clop	ASA
agranulocytosis	2	0	2	0
0 < count < 0.45 G/L	2	3	2	2
0.45 ≤ count < 1.2 G/L	22	20	4	12
count ≥ 1.2 G/L, but decreased	43	27	not done	

Conclusions

Biopharmaceutic issues. We do not frequently see applications for drugs whose active moiety is unidentified. Such a situation must always lead to concern that under one or another circumstance of metabolic derangement, the pharmacokinetics of the drug will be unpredictably altered, with corresponding unpredictable effects on pharmacodynamics.

Clopidogrel's high bioavailability provides some comfort. In addition, one can derive considerable reassurance from the results of Study PDY3079 (page 6 above). In that study, the pharmacodynamics of clopidogrel were essentially unchanged despite 50-fold increases in the peak levels of the parent compound.

Despite *in vitro* evidence that clopidogrel is a moderate inhibitor of P_{450} (2C9), there were no interpretable trials to estimate the magnitude of clopidogrel's effect upon the metabolism of drugs dependent upon this enzyme. The affected drugs include tamoxifen, tolbutamide, and warfarin.

Relative efficacy of clopidogrel and aspirin. Clopidogrel is probably more effective than aspirin in prevention of the secondary complications of atherosclerosis. We say that clopidogrel is only "probably" more effective because the data come from only a single trial (CAPRIE), and the results of that trial were only marginally significant. Even within CAPRIE, the results were heterogeneous, with clopidogrel showing no advantage in certain subpopulations.

In some other ways, however, CAPRIE demonstrated robust internal consistency. As described on pages 16–18 above, essentially all of the various efficacy results of CAPRIE supported the superiority of clopidogrel. Some of the results (*e.g.*, analysis using nonadjudicated endpoints) were so tightly correlated to the primary result that they could not possibly provide much additional information or comfort, but other results (*e.g.*, analyses of the separate components of the composite endpoint, or analysis of non-first outcome events) had a measure of confirmatory independence. When analyses excluded events that might have been expected to be unrelated to treatment (*e.g.*, non-vascular deaths, or any events occurring long after treatment was discontinued), the apparent benefit of clopidogrel was consistently increased.

Relative efficacy in various subpopulations. Over the population at risk as recruited into CAPRIE, the efficacy of clopidogrel relative to aspirin is heterogeneous. The heterogeneity is a robust finding, with the same sort of statistical significance and internal confirmation as is available for the primary result of the trial.

The benefit of clopidogrel appeared to be greatest in patients with peripheral vascular disease and additional risk factors, and weakest in patients whose sole major sign of vascular risk was a recent myocardial infarction. CAPRIE allows one to estimate the relative efficacy in these groups, but these estimates (as with any estimates of effect in extremal subgroups) are likely to overstate the expected value of the deviation from the overall observed relative efficacy.

Relative efficacy of clopidogrel and placebo. Clopidogrel seems highly likely to be more efficacious than placebo in reducing the incidence of secondary complications of atherosclerosis. In the CAPRIE subgroup in which clopidogrel's superiority to aspirin was equivocal, aspirin's superiority to placebo seems to be well established. Conversely, in the subgroup in which the efficacy of aspirin is not established, clopidogrel appeared to be strongly superior to aspirin, so that clopidogrel could fail to be superior to placebo only if aspirin turned out to be substantially *inferior* to placebo.

Safety of clopidogrel. At the doses used in CAPRIE (respectively 75 mg and 325 mg daily), clopidogrel was associated with significantly more dermatologic problems, and aspirin was associated with significantly more bleeding. Adverse reactions leading to withdrawal were equally common in the two groups.

Unlike the congener drug ticlopidine, clopidogrel does not appear to cause neutropenia or agranulocytosis.

Recommendations by RRF

● Clopidogrel should be approved, indicated for the reduction of atherosclerotic events in patients with atherosclerosis made evident by recent stroke, recent MI, or established peripheral arterial disease.

● The CAPRIE trial should be described in the **Clinical Pharmacology** section of the labeling in language similar to this:

> Essentially all of the clinical evidence of clopidogrel's efficacy is derived from the CAPRIE trial. This was a 19 185-patient, 304-center, international, randomized, triple-blind, parallel-group study comparing clopidogrel (75 mg daily) to aspirin (325 mg daily). The patients randomized had recent histories of myocardial infarction (within 35 days); recent histories of ischemic stroke (within 6 months) with at least of week of residual neurological signs; or objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years

> The trial's primary outcome metric was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. In general, deaths not easily attributable to nonvascular causes were all classified as vascular.
>
> As shown in the table [here would be a table similar to our Table 3], clopidogrel was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% *vs.* 10.64%) was 8.7%, $P=0.045$. Clopidogrel was also associated with somewhat lower rates of vascular deaths (3.6% *vs.* 3.9%); all-cause mortality (5.8% *vs.* 6.0%); composite endpoints that counted all-cause mortality and all-cause strokes instead of vascular mortality and ischemic strokes; and all types of non-first outcome events (that is, new outcome events in patients who had survived an in-study stroke or myocardial infarction).
>
> The efficacy of clopidogrel relative to aspirin was heterogeneous across the population studied ($P=0.043$). The relative benefit of clopidogrel appeared to be strongest in patients who were enrolled because of peripheral vascular disease and who had also experienced myocardial infarction; weaker in other peripheral-vascular-disease patients; and weaker still in stroke patients (especially those who had not experienced myocardial infarction). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel did not appear to be superior to aspirin. Although groups of the recruited patients differed in many demographic variables (patients in the myocardial infarction group were younger, patients in the peripheral-vascular-disease group were heavier smokers, and so on), adjustment for these variables did not reduce the intergroup differences in the relative efficacy of clopidogrel and aspirin.

- The "Drug Interactions" subsection of the **Precautions** section of the labeling should note that

> *In vitro*, clopidogrel inhibits P_{450} (2C9), and accordingly may be expected to interfere with the metabolism of **tamoxifen, tolbutamide, warfarin,** some **HMG CoA reductase inhibitors,** and many **non-steroidal anti-inflammatory agents.** There are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel.

- Other parts of the labeling should be noncontentious.

Robert R. Fenichel, M.D., Ph.D.

H. M. James Hung, Ph.D.

Concur: Dr. Mahjoob
Dr. Chi

9/22/97

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cc: NDA 20-839
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Appendix

Detailed Statistical Tables

Table A1
Time to censoring (days) of the
56 CAPRIE Patients Lost to Followup

	clopidogrel	aspirin
patients	30	26
Percentile		
99th		
95th		
90th		
75th		
50th		
25th		
10th		
5th		
1st		
Max		
Min		
Mean	428.3	474.6
s.d.	290.1	284.5

Table A2
Time in trial (days) of CAPRIE's
Intention-to-Treat Population

	clopidogrel	aspirin
Percentile		
99th		
95th		
90th		
75th		
50th		
25th		
10th		
5th		
1st		
Max		
Min		
Mean	698.99	698.91
s.d.	256.34	256.35

Table A3
Cox Regression Analyses of Primary Endpoint by Age and Treatment (T) for Each Qualifying Condition

QC	model	deviance
IS	T	15113.56
	T, age* **	15035.11
	T, age, age²†	15031.98
	T, age***, T×age	15033.48
	T, age, age²†, T×age	15030.46
	T, age, age², T×age, T×age²	15029.92
MI	T	9775.61
	T, age***	9635.56
	T, age, age²**	9628.09
	T†, age***, T×age*	9631.58
	T†, age, age², T×age†**	9624.84
	T, age, age², T×age, T×age²	9623.11
PAD	T**	8274.59
	T**, age***	8207.36
	T**, age, age²	8207.09
	T*, age*, T×age***	8203.46
	T*, age, age², T×age†	8203.26
	T, age, age², T×age, T×age²	8202.79

The "best" models are shown in boldface.
† $0.05<P<0.10$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

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Table A4
Primary Outcome Event Rate
by Qualifying Condition
and Smoking Status

Qualifying Condition	smoking status	patients (%) with event clop	ASA
IS	current	99 (14.0)	116 (16.1)
	former	199 (14.4)	184 (13.1)
	never	135 (11.9)	161 (15.1)
MI	current	64 (7.4)	79 (8.7)
	former	157 (9.8)	133 (8.5)
	never	69 (10.4)	70 (10.2)
PAD	current	70 (5.7)	113 (9.2)
	former	122 (7.1)	126 (7.5)
	never	23 (8.5)	38 (12.6)

Table A5
Primary Outcome Event Rate
by Qualifying Condition
and Diabetes Mellitus

Qualifying Condition	diabetes mellitus	patients (%) with event clop	ASA
IS	yes	147 (18.3)	163 (19.5)
	no	286 (11.8)	298 (12.6)
MI	yes	59 (13.2)	57 (12.4)
	no	232 (8.6)	225 (8.3)
PAD	yes	84 (12.6)	91 (13.7)
	no	131 (5.1)	186 (7.3)

Table A6
Primary Outcome Event Rate
by Qualifying Condition
and Hypertension

Qualifying Condition	hypertension	patients (%) with event clop	ASA
IS	yes	286 (13.5)	305 (14.6)
	no	147 (13.2)	156 (14.0)
MI	yes	128 (10.6)	130 (10.9)
	no	163 (8.5)	152 (7.7)
PAD	yes	135 (8.2)	158 (9.7)
	no	80 (5.1)	119 (7.5)

Table A7
Primary Outcome Event Rate
by Qualifying Condition
and Unstable Angina

Qualifying Condition	unstable angina	patients (%) with event clop	ASA
IS	yes	23 (24.0)	23 (26.4)
	no	410 (13.1)	438 (14.1)
MI	yes	62 (11.6)	62 (11.3)
	no	229 (8.8)	220 (8.4)
PAD	yes	25 (12.0)	26 (13.7)
	no	190 (6.3)	251 (8.3)

Table A8
Primary Outcome Event Rate
by Qualifying Condition
and Stable Angina

Qualifying Condition	stable angina	patients (%) with event clop	ASA
IS	yes	89 (19.1)	85 (19.6)
	no	344 (12.4)	376 (13.6)
MI	yes	111 (14.1)	97 (12.5)
	no	180 (7.6)	185 (7.8)
PAD	yes	98 (11.6)	120 (13.9)
	no	117 (4.9)	157 (6.6)

Table A9
Primary Outcome Event Rate
by Qualifying Condition
and History of Cardiac Surgery

Qualifying Condition	cardiac surgery	patients (%) with event clop	ASA
IS	yes	25 (18.1)	31 (24.2)
	no	408 (13.2)	430 (14.0)
MI	yes	30 (10.9)	29 (11.8)
	no	261 (9.1)	253 (8.7)
PAD	yes	40 (10.9)	62 (18.5)
	no	173 (6.1)	215 (7.4)

Table A10
Primary Outcome Event Rate
by Qualifying Condition
and Use of Coronary Vasodilators

Qualifying Condition	coronary dilators	patients (%) with event clop	ASA
IS	yes	127 (23.5)	126 (23.7)
	no	306 (11.4)	335 (12.6)
MI	yes	237 (11.6)	216 (10.5)
	no	54 (4.9)	66 (6.0)
PAD	yes	110 (14.3)	148 (18.1)
	no	105 (4.3)	129 (5.4)

Table A11
Primary Outcome Event Rate
by Qualifying Condition
and Use of β-Blockers

Qualifying Condition	β-blockers	patients (%) with event clop	ASA
IS	yes	130 (16.8)	141 (18.2)
	no	303 (12.3)	320 (13.2)
MI	yes	186 (8.2)	204 (8.7)
	no	105 (12.0)	78 (9.5)
PAD	yes	68 (9.6)	91 (12.5)
	no	147 (5.9)	186 (7.4)

Table A12
Primary Outcome Event Rate
by Qualifying Condition
and Use of Calcium Antagonists

Qualifying Condition	calcium antagonists	patients (%) with event clop	ASA
IS	yes	197 (15.0)	210 (16.6)
	no	236 (12.3)	251 (13.0)
MI	yes	143 (11.5)	128 (10.1)
	no	148 (7.8)	154 (8.1)
PAD	yes	112 (9.8)	153 (12.7)
	no	103 (5.0)	124 (6.1)

Table A13
Primary Outcome Event Rate
by Qualifying Condition
and Use of ACE Inhibitors

Qualifying Condition	ACE inhibitors	patients (%) with event clop	ASA
IS	yes	150 (14.5)	177 (16.3)
	no	283 (12.9)	284 (13.5)
MI	yes	142 (14.3)	143 (13.6)
	no	149 (6.9)	139 (6.6)
PAD	yes	82 (10.6)	105 (13.4)
	no	133 (5.4)	172 (7.0)

Table A14
Primary Outcome Event Rate
by Qualifying Condition
and Use of Diuretics

Qualifying Condition	diuretics	patients (%) with event clop	ASA
IS	yes	173 (17.2)	185 (17.6)
	no	260 (11.7)	276 (12.9)
MI	yes	161 (19.4)	144 (17.3)
	no	130 (5.6)	138 (5.9)
PAD	yes	99 (10.6)	143 (15.1)
	no	116 (5.1)	134 (5.9)

Table A15
Primary Outcome Event Rate
by Qualifying Condition
and Use of Any Antilipid Therapy

Qualifying Condition	antilipid therapy	patients (%) with event clop	ASA
IS	yes	61 (10.8)	64 (11.4)
	no	372 (13.9)	397 (15.1)
MI	yes	66 (6.0)	66 (5.8)
	no	225 (11.0)	216 (10.7)
PAD	yes	42 (5.4)	64 (8.6)
	no	173 (7.1)	213 (8.6)

Table A16
Primary Outcome Event Rate
by Qualifying Condition
and Use of HMG-CoA Reductase Inhibitors

Qualifying Condition	reductase inhibitors	patients (%) with event clop	ASA
IS	yes	41 (10.7)	38 (10.3)
	no	392 (13.8)	423 (15.0)
MI	yes	57 (6.3)	53 (5.7)
	no	234 (10.5)	229 (10.3)
PAD	yes	32 (5.7)	49 (8.8)
	no	183 (6.9)	228 (8.5)

Table A17
Primary Outcome Event Rate
by Qualifying Condition
and Use of Antidiabetic Therapy

Qualifying Condition	antidiabetic therapy	patients (%) with event clop	ASA
IS	yes	138 (19.6)	150 (21.0)
	no	295 (11.7)	311 (12.5)
MI	yes	51 (13.9)	63 (15.7)
	no	240 (8.7)	219 (7.9)
PAD	yes	75 (12.3)	83 (14.1)
	no	140 (5.4)	194 (7.4)

Table A18
Primary Outcome Event Rate
by Qualifying Condition
and Use of Anti-inflammatory Products

Qualifying Condition	anti-inflammatories	patients (%) with event clop	ASA
IS	yes	49 (12.5)	58 (16.3)
	no	384 (13.5)	403 (14.2)
MI	yes	28 (7.7)	30 (8.5)
	no	263 (9.5)	252 (9.0)
PAD	yes	28 (6.9)	37 (9.8)
	no	187 (6.7)	240 (8.4)

Table A19
Primary Outcome Event Rate
by Qualifying Condition
and Use of Antithrombotic Products

Qualifying Condition	anti-thrombotics	patients (%) with event clop	ASA
IS	yes	179 (33.0)	204 (38.2)
	no	254 (9.4)	257 (9.7)
MI	yes	174 (19.4)	180 (20.2)
	no	117 (5.2)	102 (4.5)
PAD	yes	88 (16.6)	134 (21.6)
	no	127 (4.7)	143 (5.5)

Table A20
Primary Outcome Event Rate
by Qualifying Condition
and Use of Estrogens

Qualifying Condition	estrogens	patients (%) with event clop	ASA
IS	yes	14 (9.7)	17 (11.6)
	no	419 (13.6)	444 (14.6)
MI	yes	7 (6.3)	3 (3.4)
	no	284 (9.4)	279 (9.1)
PAD	yes	3 (2.8)	6 (5.2)
	no	212 (6.8)	271 (8.7)

MEMORANDUM To NDA File #20-839

SEP 2 2 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 9/16/97
Subject: Review of Aspirin Effect in Prevention of Vascular Events in Patients with Prior history of MI, Stroke and Peripheral Vascular Disease
To: Dr. Lipicky, Dr. Fenichel, Dr. Fredd

Objective

The purpose of this report is to provide information on the relative effect of aspirin versus placebo for the prevention of vascular events in patients with atherosclerotic disease.

Rationale

In the clopidogrel NDA (#20-839), the primary clinical study is the CAPRIE[1] Trial. The CAPRIE Trial is a randomized, double-blind, controlled study in which patients with recent MI, recent stroke or peripheral atherosclerotic vascular disease were randomized to clopidogrel 75 mg or aspirin 325 mg once daily. The primary measure of efficacy was the time to first event for ischemic stroke, myocardial infarction or vascular death. As there is no placebo group, the treatment effect of clopidogrel can only be assessed against aspirin. In order to determine whether there is an overall clinical benefit, the clinical benefit of aspirin therapy (relative to placebo) in a population similar to that randomized in CAPRIE needs to be estimated.

Methods

Data was obtained from the Anti-Platelet Trialists' overview[2] of trials of prolonged anti-platelet therapy in patients with vascular disease or a condition that increases the risk for occlusive vascular disease. This overview provided a complete listing of data from clinical trials that had available data as of March 1990. The following procedure was followed.

(1) Categories of patients with backgrounds similar to those enrolled in CAPRIE (i.e. patients with Past MI, Past Stroke or Peripheral Arterial Disease) were identified in the Anti-Platelet Trialists' overview. [Note: Studies in the overview were categorized by the population enrolled (e.g. Past MI).]
(2) Within these patient categories, the placebo controlled trials that included an aspirin only treatment group were identified. From these studies, studies that enrolled patients similar to that enrolled in CAPRIE were identified. Only studies with greater than 30 days of treatment were included.
(3) Data on non-fatal MI, non-fatal stroke, cardiovascular mortality and all cause mortality was collected for the trials identified.
(4) From this data, the odds ratios were calculated for Placebo/Aspirin for the combined endpoints of non-fatal MI, non-fatal stroke and cardiovascular deaths and non-fatal MI, non-fatal stroke and all deaths.
5) Odds ratios for clopidogrel/aspirin were calculated from data in the CAPRIE trial.

The odds ratio for placebo/aspirin = $\frac{\text{odds of event on placebo}}{\text{odds of event on aspirin}}$ where the

odds of event = probability of the event/ probability of no event
= p/(1 - p) where p is probability.

The odds ratio for clopidogrel/aspirin = $\frac{\text{odds of event on clopidogrel}}{\text{odds of event on aspirin}}$.

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[1] CAPRIE Steering Committee. A Randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996;348:1329 - 39.
[2] Antiplatelet Trialists' Collaboration. Collaborative Overview Of Randomised Trials Of Antiplatelet Therapy - I: Prevention Of Death, Myocardial Infarction, And Stroke By Prolonged Antiplatelet Therapy In Various Categories Of Patients. BMJ 1994;308:81 - 106. (see appendix for reprint)

In the calculation of the odds ratio, aspirin served as the comparator for both placebo (Trialists' data) and clopidogrel (CAPRIE trial data). With aspirin as the common denominator in the odds ratio calculation, this permits a comparison (qualitative more than quantitative) of clopidogrel to placebo.

[NOTE: The data included in the Anti-Platelet Trialists' overview has not been validated by the FDA.]

Results

Table 1 lists the categories of patients provided in the Trialists' overview.

Table 1. Categories of Patients in Trialists' Overview

Patient Category	Patient Category
Prior MI	Rheumatic Valve Disease
Acute MI	Valve Surgery
Prior Stroke/TIA	Intermittent Claudication
Acute Stroke	Non-Coronary Grafting
Carotid Endarterectomy	Peripheral Angioplasty
Unstable Angina	Renal Hemodialysis
Post-Coronary Artery Bypass Grafting	Diabetes
Post-Percutaneous Transluminal Coronary Angioplasty	Deep Venous Thrombosis Prophylaxis
Stable Angina/Coronary Artery Disease	Miscellaneous
Atrial Fibrillation	Low Risk (Primary Prevention)

The CAPRIE Trial enrolled patients with one of the following characteristics: a focal neurological deficit likely to be of atherothrombotic origin[3] (Stroke subgroup), a myocardial infarction ≤ 35 days before randomization[4] (MI subgroup) or atherosclerotic peripheral arterial disease[5] (Peripheral Arterial Disease subgroup). The categories in the Trialists' overview that most closely resemble the populations enrolled in CAPRIE include Prior MI, Prior Stroke/TIA, Intermittent Claudication, Non-coronary Grafting and Peripheral Angioplasty. Table 2 lists the number of placebo controlled studies referenced in the Trialists' overview for these categories of patients and the number of studies that have an aspirin treatment arm and enrolled a CAPRIE-like population. The populations enrolled in these studies were determined from citations referenced in the overview. Foreign language publications could not be reviewed in time for completion of this review.

Table 2. Categories of Patients in Trialists' Overview Enrolling Population Similar to CAPRIE

Patient Category	# of Trials	# Trials With Aspirin Only Treatment Arm, > 1 month Duration	# Trials With Aspirin Only Treatment Arm, > 1 month Duration, CAPRIE-like Population
Prior MI	11	7	7
Prior Stroke/TIA	21	10	3 or 6
Intermittent Claudication	27	4	4
Non-Coronary Grafting	11	2	2
Peripheral Angioplasty	2	0	0

Tables A.1a. - A.1d. in the appendix provide additional details on the studies that included an aspirin treatment arm and enrolled a population similar to that enrolled in CAPRIE. For some of the Stroke/TIA and Non-Coronary Grafting trials, it is not clear whether the patients enrolled are similar to those enrolled in CAPRIE. In three of the Stroke/TIA trials (AITIA, Canadian Cooperative, UK-TIA), even though the primary objective was to enroll patients with a history of TIA, patients with neurological

[3] with the onset ≥ 1 week and ≤ 6 months prior to randomization, neurological signs persisting ≥ 1 week from stroke onset and CT or MRI ruling out hemorrhage or non-relevant disease

[4] with two of the following characteristics: elevation of CK, CK-MB, LDH, or AST to 2x the upper limit of normal, characteristic ischemic pain for ≥ 20 minutes or new ≥ 40 msec Q waves in at least two adjacent ECG leads or new dominant R wave in V1

[5] presenting as intermittent claudication of presumed atherosclerotic origin plus ankle/arm systolic BP ratio ≤ .85 in either leg at rest, or a history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from intervention

deficits were also enrolled. Consequently, odds ratios were calculated for the stroke population with and without these trials included in the analyses. Non-coronary grafting trials were included with the intermittent claudication trials because patients with peripheral arterial disease who underwent revascularization procedures were enrolled in CAPRIE. An analysis was also performed without these trials.

There are numerous covariates regarding trial design and conduct that influence the placebo/aspirin odds ratio calculation. For example, if the duration of follow-up is longer or a higher risk population is enrolled in a trial, the event rate in the trial will be greater than a trial with a shorter duration of follow-up or with patients at lessor risk. In the Prior MI category, the mean duration of follow-up in the trials varied from a mean of 1 year to 41 months. The event rate for stroke, MI and CV death varied from 9% to 17% and 12% to 21% in the aspirin and placebo groups respectively. This resulted in odds ratios for placebo/ aspirin in each trial ranging from 1.11 to 1.76. Consequently, it should be recognized that the odds ratio provides more of a qualitative estimate of the treatment effect as opposed to a some absolute value. The covariates that could influence the odds ratio and its confidence interval include:

- variation of the aspirin dose range among the studies;
- duration of treatment and follow-up after initiation of therapy;
- definition of endpoint event in each study;
- time period which the trial was conducted (i.e. study performed in the 1970's vs. 1980's);
- some studies did not document certain non-fatal events;
- number of subjects lost to follow-up;
- demographic characteristics of the populations enrolled;
- number of subjects randomized;
- deviation from the CAPRIE subgroup definitions (e.g. TIA vs. persistent neurologic deficit);
- time from the event (e.g. MI or stroke) that fulfills inclusion criteria.

Since these covariates cannot be adequately adjusted for in the calculation of the odds ratio, one must be realistic in the interpretation of any calculation of the odds ratio.

Table A.2a - A.2d in the appendix lists the event rates for each clinical trial whose data was used in the calculation of the odds ratios. Lost to follow-up is a problem in the prior MI and prior stroke trials where 2 - 3% of the patients were lost to follow-up. The distribution of lost to follow-up was similar between treatment groups. This missing data adds to the uncertainty of the calculation.

Table 3 list the number of patients in the aspirin and placebo treatment arms and the combined death, MI plus stroke event rates for each patient category. The event rates are the number of patients in each treatment group that experienced at least one of the endpoint events. Multiple events in the same patient only contribute one event to the count. Two populations for the Prior Stroke/ TIA and Intermittent Claudication categories were analyzed. There were three Prior Stroke/TIA studies (AICLA, Britton, SALT) that enrolled predominately patients with strokes. These three studies were analyzed as a group. There were three additional studies (AITIA, Canadian Cooperative, UK-TIA) that predominately enrolled patients with TIA but also included some patients with neurologic deficits. These three trials were combined with the three stroke studies and analyzed. Similarly, four trials of intermittent claudication were analyzed with and without two trials of non-coronary grafting.

Table 3. Incidence Of Non-Fatal Stroke, Non-Fatal MI And Death In Placebo/Aspirin Trials

Patient Category	# Trials	# Patients		Stroke, MI, CV Deaths		Stroke, MI, All Deaths	
		Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
Prior MI	7	6286	5913	867 (13.8%)	1008 (17.0%)	940 (15.0%)	1065 (18.0%)
Prior Stroke/TIA	3 [A]	1127	1140	253 (22.4%)	294 (25.8%)	276 (24.5%)	326 (28.6%)
Prior Stroke/TIA	6 [B]	3054	2250	653 (21.4%)	552 (24.5%)	720 (23.6%)	625 (27.8%)
Intermittent Claudication	4 [C]	314	304	18 (5.7%)	18 (5.9%)	21 (6.7%)	19 (6.3%)
Intermittent Claudication and Non-Coronary Grafting	6 [D]	545	534	18 (3.3%)	18 (3.4%)	21 (3.9%)	19 (3.6%)

[A] = data from AICLA, Britton, SALT trials

[B] = data from AICLA, Britton, SALT, AITIA, Canadian Cooperative, UK-TIA trials.

[C] = Hess, Schoop -I, Munich-A, Munich-B trials; [D] = Hess, Schoop -I, Munich-A, Munich-B, Rochester, Loew Bypass trials

Table 3a list the event rate for stroke, MI and death (cardiovascular or all) in subgroups of patients from the CAPRIE trial. The event rates in the MI and stroke subgroups of the CAPRIE trial were less than that observed in the Placebo/Aspirin trials (table 3). The event rate in the peripheral arterial disease subgroup was greater in the CAPRIE trial compared to the Placebo/Aspirin trials.

Table 3a. Incidence Of Non-Fatal Stroke, Non-Fatal MI And Death In CAPRIE

Patient Subgroup	# Patients		Stroke, MI, CV Deaths		Stroke, MI, All Deaths	
	Aspirin	Clopidogrel	Aspirin	Clopidogrel	Aspirin	Clopidogrel
Prior MI	3159	3143	282 (8.9%)	291 (9.3%)	315 (10.0%)	322 (10.2%)
Prior Stroke	3198	3233	461 (14.4%)	433 (13.4%)	550 (17.2%)	527 (16.3%)
Peripheral Arterial Disease	3229	3223	277 (8.6%)	215 (6.7%)	341 (10.6%)	284 (8.8%)

Table 4 list the odds ratio and 95% confidence interval for cardiovascular deaths, MI and stroke for the Placebo/Aspirin comparison. Table 5 list the odds ratio and 95% confidence interval for all deaths, MI and stroke for the Placebo/Aspirin comparison. The odds ratio is calculated by three different methods: equal weighting of individual studies[6], weighting individual studies by sample size[7] and pooling of studies[8]. Within a subgroup, the various methods of calculating the odds ratio yielded similar results. An odds ratio of 1 indicates that the odds of having an event on placebo is the same as the odds of having an event on aspirin. Odds ratios < 1 suggest that the odds of an event on placebo is less than the odds of an event on aspirin[9]. Odds ratios > 1 suggest that the odds of an event on placebo is greater than the odds of an event on aspirin. If the 95% confidence interval does not cross 1, then the odds for an event on placebo is significantly different than the odds for an event on aspirin.

Table 4. Cardiovascular Death, Stroke, MI Odds Ratio for Placebo/ASA (Trialists' Data)

	Equal Weighting of Individual Studies			Weighting Individual Studies by Sample Size			Pooling Studies		
Population	Upper 95% CI	Odds Ratio	Lower 95% CI	Upper 95% CI	Odds Ratio	Lower 95% CI	Upper 95% CI	Odds Ratio	Lower 95% CI
MI	1.59	1.40	1.24	1.46	1.32	1.19	1.42	1.28	1.16
Stroke[A]	1.53	1.21	0.96	1.47	1.21	0.99	1.46	1.20	0.99
Stroke[B]	1.44	1.20	1.00	1.36	1.19	1.04	1.36	1.19	1.05
PAD	1.96	0.94	0.45	2.10	1.04	0.52	2.03	1.04	0.53
PAD[A]							1.98	1.02	0.53

MI = Cardiff I, Cardiff II, Paris I, AMIS, CDP-A, GAMIS, Micristin;
Stroke[A] = AICLA, Britton, SALT; Stroke[B] = AICLA, Britton, SALT, AITIA, Canadian Cooperative, UK-TIA;
PAD (Peripheral Arterial Disease) = Hess, Schoop-I, Munich-A, Munich-B;
PAD[A] = Hess, Schoop-I, Munich-A, Munich-B, Rochester and Loew Bypass

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[6] equal weighting of individual studies: $1/S\ [\log OR_1 + \log OR_2 + ... \log OR_s]$ where S = number of studies and OR = odds ratio

[7] weighting individual studies by sample size: $[(N_1) \log OR_1 + (N_2) \log OR_2 + ...(N_s) \log OR_s] / [(N_1) + (N_2) + ... (N_s)]$ where N = number of patients in a study, OR = odds ratio and s = number of studies

[8] pooling of studies: the pooled data is treated as one study

[9] aspirin odds is set to 1

Table 5. All Cause Death, Stroke, MI Odds Ratio for Placebo/ASA (Trialists' Data)

	Equal Weighting of Individual Studies			Weighting Individual Studies by Sample Size			Pooling Studies		
Population	Upper 95% CI	Odds Ratio	Lower 95% CI	Upper 95% CI	Odds Ratio	Lower 95% CI	Upper 95% CI	Odds Ratio	Lower 95% CI
MI	1.54	1.36	1.21	1.42	1.29	1.17	1.38	1.25	1.14
Stroke[A]	1.53	1.23	0.98	1.49	1.24	1.03	1.49	1.24	1.02
Stroke[B]	1.47	1.24	1.04	1.42	1.25	1.10	1.41	1.25	1.10
PAD	1.71	0.87	0.44	1.82	0.94	0.48	1.77	0.93	0.49
PAD[A]							1.73	0.92	0.49

MI = Cardiff I, Cardiff II, Paris I, AMIS, CDP-A, GAMIS, Micristin;
Stroke[A] = AICLA, Britton, SALT; Stroke[B] = AICLA, Britton, SALT, AITIA, Canadian Cooperative, UK-TIA;
PAD (Peripheral Arterial Disease) = Hess, Schoop-I, Munich-A, Munich-B;
PAD[A] = Hess, Schoop-I, Munich-A, Munich-B, Rochester and Loew Bypass

Table 6 lists the odds ratios for clopidogrel/ASA. An odds ratio of 1 indicates that the odds of having an event on clopidogrel is the same as odds of having an event on aspirin. Odds ratios < 1 suggest that the odds of an event on clopidogrel is less than the odds of an event on aspirin[10]. Odds ratios > 1 suggest that the odds of an event on clopidogrel is greater than the odds of an event on aspirin. If the 95% confidence interval does not cross 1, then the odds for an event on clopidogrel is significantly different than the odds for an event on aspirin.

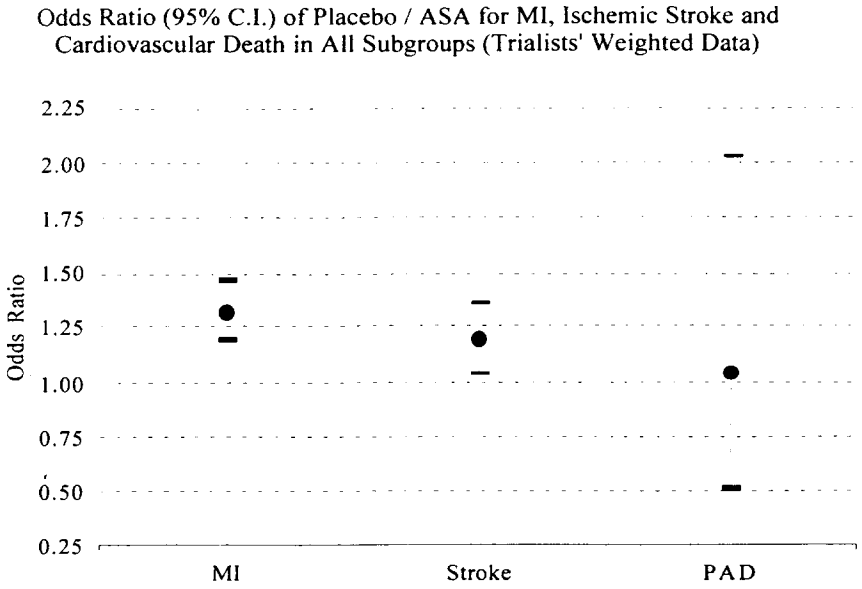
Table 6. Odds Ratio for Clopidogrel/ASA

Subgroup	Endpoint	Odds Ratio	95% C.I.
MI	MI, stroke, CV death	1.04	(0.88, 1.24)
	MI, stroke, all death	1.03	(0.87, 1.22)
Stroke	MI, stroke, CV death	0.92	(0.80, 1.06)
	MI, stroke, all death	0.95	(0.84, 1.09)
PAD	MI, stroke, CV death	0.76	(0.63, 0.92)
	MI, stroke all death	0.82	(0.69, 0.97)

Figure 1 lists the odds ratio (using weighting of studies by sample size) and 95% confidence interval for the Placebo/Aspirin comparison as a function of patient category. The large confidence interval for the PAD group reflects the small number of patients in this category. In figure 1, for the MI and stroke subgroups, the odds ratio 95% confidence interval does not intersect one. Consequently, there is a significant increase in the odds of having an event on placebo compared to aspirin. For patients on placebo, the odds are increased 1.32 - fold and 1.19 - fold in the MI and stroke subgroups respectively[11]. There was no significant difference in the odds of an event in the PAD group.

[10] aspirin odds is set to 1
[11] Based on the point estimates.

Figure 1.



MI odds ratio includes Cardiff I, Cardiff II, Paris I, AMIS, CDP-A, GAMIS, Micristin trials.
Stroke odds ratio includes data from AICLA, Britton, SALT, AITIA , Canadian Cooperative, UK-TIA trials.
PAD odds ratio includes Hess, Schoop-I, Munich-A, Munich-B trials
Calculation is based on weighting individual studies by sample size.

Figures 2a. - 4b plot the odds ratios and 95% confidence interval for Placebo/Aspirin and Clopidogrel/Aspirin for the endpoints MI, stroke plus cardiovascular deaths and MI, stroke plus all deaths in the patient subgroups of prior MI, prior stroke and peripheral arterial disease. There are essentially no differences in the odds ratios and 95% confidence intervals when all deaths are counted instead of cardiovascular deaths within each subgroup. In all plots, the odds for an event in the aspirin group is set to 1. Odds ratios < 1 suggest that the odds of an event on placebo or clopidogrel is less than the odds of an event on aspirin. Odds ratios > 1 suggest that the odds of an event on placebo or clopidogrel is greater than the odds of an event on aspirin.

The odds ratios for the MI subgroup are plotted in figures 2a and 2b. The odds of an event on placebo is significantly greater than the odds of an event on aspirin. As noted previously, the estimate of the placebo/aspirin odds ratio is influenced by numerous factors which lead to uncertainty in the accuracy of the point estimate. The odds (point estimate) of an event on clopidogrel are slightly greater than ASA but the 95% C.I. intersects 1.

For the stroke subgroup (figures 3a and 3b), the odds of an event are greater with placebo compared to ASA. The odds (point estimate) of an event on clopidogrel are slightly less than ASA but the 95% C.I. intersects 1.

In the PAD subgroup (figures 4a and 4b), there is sufficient overlap between the odds ratios for placebo/aspirin and clopidogrel/aspirin that they cannot be distinguished.

Figure 2a.

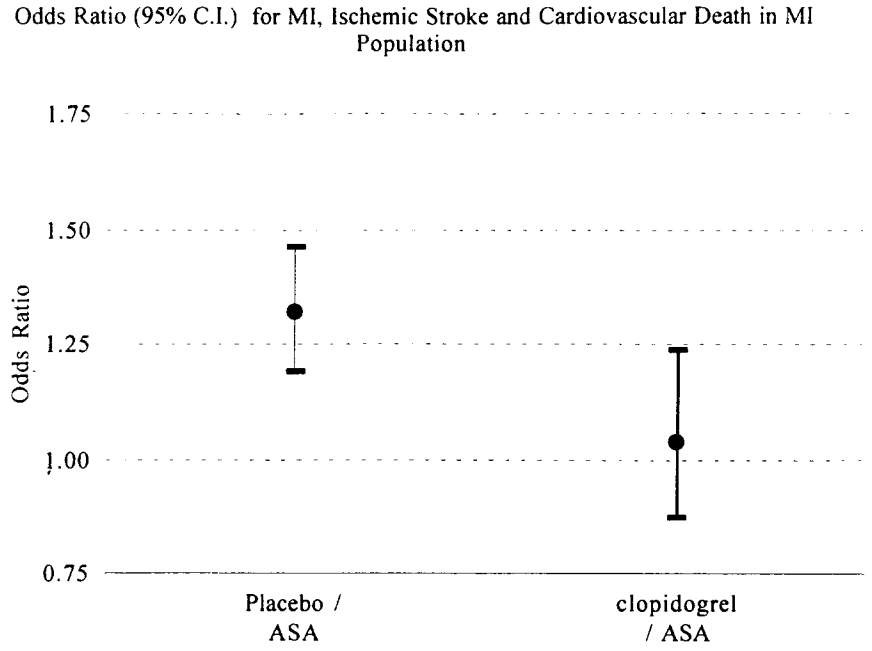


Figure 2b.

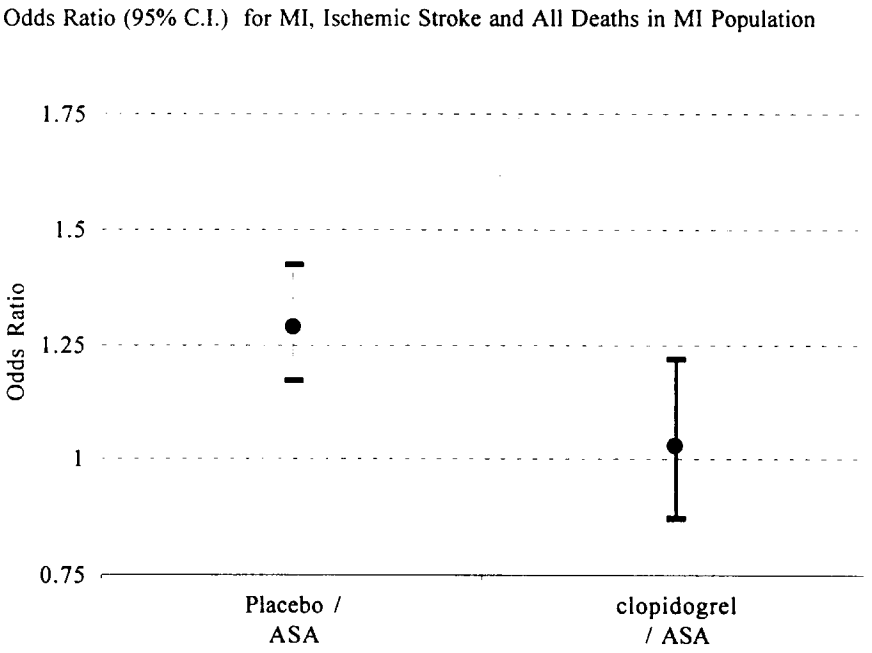
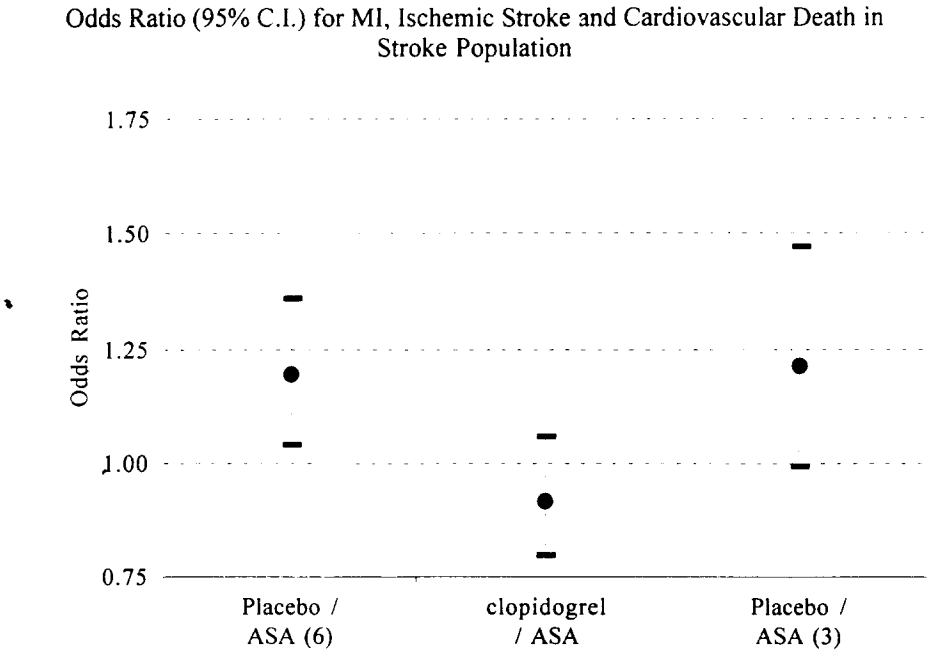
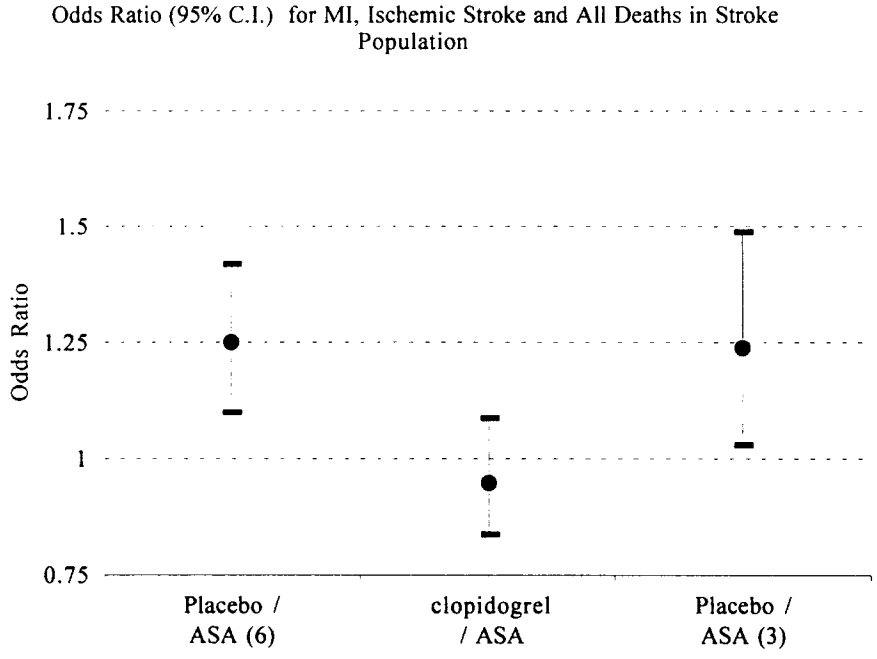


Figure 3a.



Stroke Placebo/ASA (6) odds ratio includes data from AICLA, Britton, SALT, AITIA, Canadian Cooperative, UK-TIA trials.
Stroke Placebo/ASA (3) odds ratio includes data from AICLA, Britton, SALT.

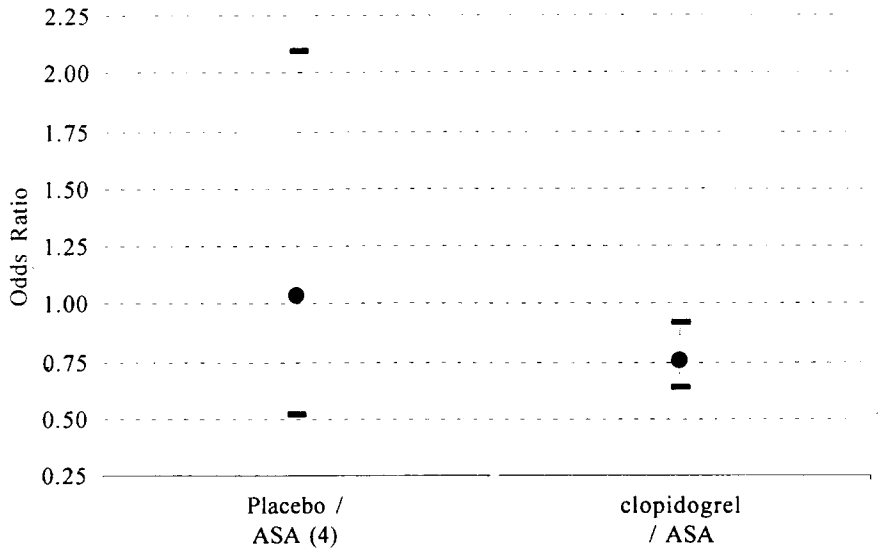
Figure 3b.



Stroke Placebo/ASA (6) odds ratio includes data from AICLA, Britton, SALT, AITIA, Canadian Cooperative, UK-TIA trials.
Stroke Placebo/ASA (3) odds ratio includes data from AICLA, Britton, SALT.

Figure 4a.

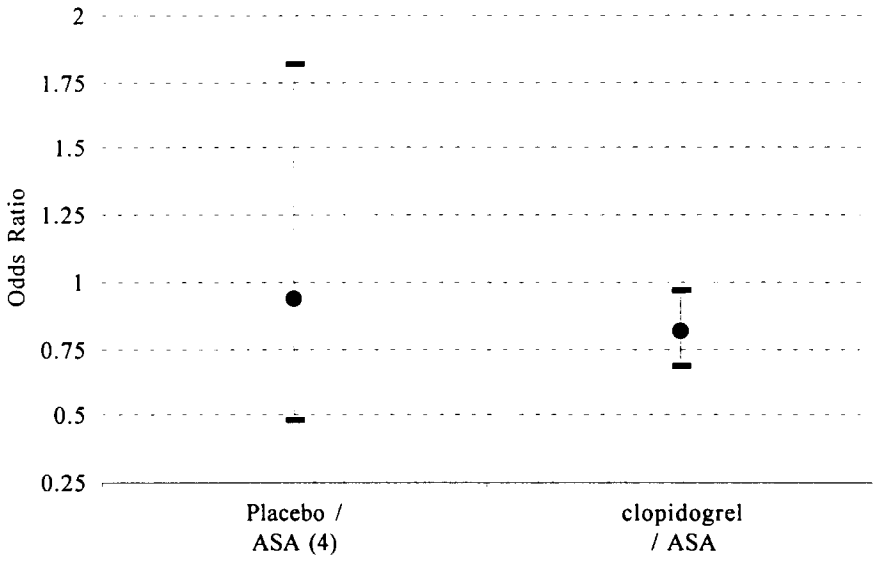
Odds Ratio (95% C.I.) for MI, Ischemic Stroke and Cardiovascular Death in PAD Population



PAD Placebo/ASA (4) odds ratio includes Hess, Schoop -I, Munich-A, Munich-B trials

Figure 4b.

Odds Ratio (95% C.I.) for MI, Ischemic Stroke and All Deaths in PAD Population



PAD Placebo/ASA (4) odds ratio includes Hess, Schoop -I, Munich-A, Munich-B trials

Discussion

The estimates for the placebo/ASA odds ratios are influenced by numerous factors (discussed earlier on page 3) which lead to uncertainty in the accuracy of the point estimate. For this reason, a direct comparison of the clopidogrel odds of an event to placebo odds of an event is not realistic. As a result, caution should be exercised in comparing the odds ratios for placebo/aspirin and clopidogrel/aspirin.

In both the MI (figure 2a and 2b) and stroke (figure 3a and 3b) subgroups, the odds ratios suggest that aspirin lessens the risk for developing an event for the combined endpoints of MI, stroke and cardiovascular or all cause mortality compared to placebo. Based on a qualitative assessment, clopidogrel appears more like aspirin and less like placebo for both subgroups. And hence, clopidogrel is likely to be superior to placebo in these subgroups.

In the peripheral arterial disease subgroup, a definitive statement regarding the odds of developing an event with placebo compared to aspirin (figures 4a and 4b) cannot be made. This is a reflection of the low event rate and small number of patients enrolled in PAD trials comparing aspirin to placebo. Although the odds ratio point estimates for placebo/aspirin for both endpoints are close to 1, the event rates are so low that the addition of just a few events can substantially alter the point estimate[12]. In addition, because of a limited number of patients studied with placebo versus aspirin, the confidence interval for the placebo/aspirin odds ratio is large (.52 - 2.1 from table 4 for MI, stroke or cardiovascular death). Because of the uncertainty in comparing placebo with aspirin, it is difficult to make a definitive statement regarding clopidogrel versus placebo based solely on the data available from the aspirin versus placebo PAD trials.

[NOTE: At the time of completion of this review, there are still unresolved issues in the validation of the data in the CAPRIE Trial. The major issues involve:

- completion of study participants prior to the 1 year follow-up date;
- explanation of termination dates that do not coincide with a scheduled visit;
- explanation of why patients completed the trial prior to the permitted termination date for their subgroup.

The previous discussion assumes that the remaining questions regarding the completion and termination of patients are answered in a satisfactory manner.]

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9/22/97

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[12] Eighteen subjects in both the aspirin and placebo treatment groups experienced events (MI, stroke, CV death). The placebo/aspirin odds ratio point estimate is 1.04. If 5 additional events are added in the aspirin subgroup and none in placebo group, the placebo/aspirin odds ratio point estimate is .80. Thus, the point estimate is unstable because of the small number of events and small number of patients in the trials.

Table A.1a. Study Details for Trials Enrolling Patients with Prior MI

Trial (Ref.)	Treatments [N]	Mean Duration of F/U; Trial Dates	Population	Endpoints
Cardiff I (18, 19)	• Aspirin 300 mg OD [615] • Placebo [624]	• 12.1 months • 11.7 months • 2/71 - 9/73	• men discharged from hosp. with DX of MI based on physicians diagnosis (no definition provided for enrollment into trial) • mean of 9.8 - 10.0 weeks from infarction to enrollment • 50% had < 6 weeks between time of infarction to enrollment	• not specified in methods section • strokes not reported • post-randomization myocardial infarction definition was not defined; does not report on MI incidence • cumulative mortality reported at 6 month intervals based on life table
Cardiff II (20, 21)	• Aspirin 300 mg TID [832] • Placebo [850]	• 1 year F/U	• 15% women • Dx confirmed by physician • 50% had infarct within 7 days; 47% had infarct > 7 days	• no stroke data documented • data on non-fatal MI were limited and uncertain • 228 withdrawals in each group
Paris I (22, 23)	• Aspirin 324 mg TID [810] • Aspirin 324 mg + Persantine 75 mg TID [810] • Placebo [406]	• mean 41 months • 5/75 - 7/79	• 87% men • 8 weeks to 60 months after MI • MI defined as enzyme elevations and verified abnormal ECG	• Total Mortality • Coronary Mortality • Coronary Deaths and non-fatal MI
AMIS (25, 26)	• Aspirin 500 mg BID[2267] • Placebo [2257]	• minimum 3 years • 1975 - 1979	• MI occurred 8 weeks to 5 years prior to enrollment (mean 25 months) • 89% male • 87% had one MI	• Total Mortality • Cardiovascular Mortality • Fatal or non-fatal stroke
CDP-A (27, 28, 29)	• Aspirin 324 mg TID [758] • Placebo [771]	• 10 - 28 months (mean 22 months) • 1972 - 1975	• men only • prior participation in Coronary Drug Project (dextrothyroxine or estrogen Rx group) • 75% had MI > 5 years prior to enrollment • 24% had > two MIs • mean age 61 years • 114 patients recruited but excluded from analysis (total of 1060 recruited, data provided on 946)	• Total Mortality • Cause Specific Mortality • non-fatal CV events (?)
GAMIS (30, 31, 32)	• Aspirin 500 mg TID [317] • Phenprocoumon [320] • Placebo [309]	• 2 year F/U • 1970 - 1977	• MI 30 - 42 day prior to randomization • meet WHO criteria for MI • 16% had heart failure • 20% had > 1 MI • 22% female	• Sudden death, death by MI and non-fatal MI [Note: phenprocoumon arm was open label; if patient had non-fatal MI, no longer treated as participant in the trial]

Table A.1a. Study Details for Trials Enrolling Patients with Prior MI

Trial (Ref.)	Treatments [N]	Mean Duration of F/U: Trial Dates	Population	Endpoints
Micristin (38, 39)	Foreign Language Publication			

(Ref.) = Reference Number from the BMJ 1994;308:81 - 106.

Table A.1b. Study Details for Trials Enrolling Patients with Prior Stroke/TIA

Trial (Ref.)	Treatments [N]	Duration of F/U	Population	Endpoints
AITIA (52, 53, 54)	Aspirin 650 mg BID [88] Placebo [90]	• 24 months • 1972	• TIA < 3 months prior to enrollment • disabling defect excluded • 28% had neurologic a deficit at randomization	• mortality and major morbidity (stroke)
Canadian Cooperative (57, 58, 59)	sulfinpyrazone 200 mg QID [156] sulfinpyrazone 200 mg QID + Aspirin 325 mg QID [146] Aspirin 325 mg QID [144] Placebo [139]	• 26 months • 11/71 - 6/76	• cerebral or retinal ischemic attacks lasting < 24 hours occurring within 3 months of study	• TIA • stroke • death (excluded events in the first week of therapy and > 6 months after premature discontinuation)
AICLA (62, 63)	Aspirin 330 mg TID [198] Aspirin 330 mg + Dypyridamole 75 mg TID [202] Placebo [204]	• 3 years •10/75 - 12/78	• an episode of cerebral or retinal atherothrombotic ischemic event ≤ 1 year previous • 77% < 3 months from ischemic event; 23% 3 months - 1 year from ischemic event • 84% completed strokes	• fatal and non-fatal cerebral infarction
Britton (65)	Aspirin 1.5 gram OD [253] Placebo [252]	• 2 year for all patients •10/78 - 8/84	• within 3 weeks of cerebral infarct • TIA not eligible	• stroke and death • acute MI recorded
UK-TIA (69, 70)	Aspirin 600 mg BID [815] Aspirin 300 mg OD [806] Placebo [814]	• mean 4 years • range years • 7/79 - 9/86	• recent TIA or minor ischemic stroke (deficit > 24 hours but < 7 days) • mean age 59 years • 71% with TIA, 73% men • 22% with stroke	• non-fatal major stroke •non-fatal MI • vascular death • non-vascular death
SALT (277)	Aspirin 75 OD [676] Placebo [684]	• mean 32 months	• TIA, minor ischemic stroke or retinal artery occlusion with the previous 3 months	• first event stroke or death • MI follows WHO criteria.

(Ref.) = Reference Number from the BMJ 1994;308:81 - 106.

Table A.1c. Study Details for Trials Enrolling Patients with Intermittent Claudication

Trial (Ref.)	Treatments [N]	Duration of F/U	Population	Endpoints
Hess (153)	• Aspirin 330 mg TID[80] • Aspirin 330 mg + Dipyridamole 75 mg TID [80] • Placebo [80]	• 2 years • 1977 - ?	• Occlusive arteriosclerosis • 80% male, mean age 62 years	• Occlusion of peripheral arteries (based angiogram changes)
Schoop-I (160 - 162)	• Aspirin 990 mg [100] • Aspirin 990 mg + dipyridamole 225 mg • placebo [Ref. #161 and #162 are Foreign Language Publications]			
Munich-A (168)	Foreign Language Publication			
Munich-B (168)	Foreign Language Publication			

(Ref.) = Reference Number from the BMJ 1994;308:81 - 106.

Table A.1d. Study Details for Trials Enrolling Patients with Non-Coronary grafting.

Trial (Ref.)	Treatments [N]	Duration of F/U	Population	Endpoints
Rochester (181)	• Aspirin 325 mg TID[16] • Aspirin 325 mg + Dipyridamole 75 mg TID [16] • Placebo [17]	• 1 year	• status post infrainguinal polytetrafluoro-ethylene grafts	• Patency rate of polytetrafluoroethylene grafts in infrainguinal region
Loew Bypass (186, 187)	Foreign Language Publication			

(Ref.) = Reference Number from the BMJ 1994;308:81 - 106.

Table A.2a. Mortality and Morbidity (non-fatal MI, non-fatal stroke) Data from Prior MI Trials

Trial	Regimen	Months	# Patients	# Patients	CV Death Or Unk	CV Death Or Unk	Stroke, MI, CV Deaths	Stroke, MI, CV Deaths	NV Death	NV Death	Stroke, MI, All Deaths	Stroke, MI, All Deaths	LTF	LTF
			Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
Cardiff I	A300	13	615	624	47	61	57	76	2	4	59	80	3	2
Cardiff II	A900	12	847	878	98	122	129	186	5	5	134	191	0	0
Paris I	A972	41	810	406	73	45	128	82	12	7	140	89	0	0
AMIS	A1000	38	2267	2257	214	199	379	411	32	20	411	431	5	4
CDP-A	A972	22	758	771	43	61	76	102	2	4	78	106	0	0
GAMIS	A1500	17	317	309	22	30	33	45	5	2	38	47	112	103
Micristin	A1500	24	672	668	34	56	65	106	15	15	80	121	11	13
Total			**6286**	**5913**	**531**	**574**	**867**	**1008**	**73**	**57**	**940**	**1065**	**131**	**122**

Table A.2b. Mortality and Morbidity (non-fatal MI, non-fatal stroke) Data from Prior Stroke (3) Trials

Trial	Regimen	Months	# Patients	# Patients	CV Death Or Unk	CV Death Or Unk	Stroke, MI, CV Deaths	Stroke, MI, CV Deaths	NV Death	NV Death	Stroke, MI, All Deaths	Stroke, MI, All Deaths	LTF	LTF
			Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
AICLA	A990	36	198	204	13	12	31	46	6	6	37	52	0	0
Britton	A1500	24	253	252	28	29	59	55	6	8	65	63	2	2
SALT	A75	32	676	684	50	51	163	193	11	18	174	211	0	0
Total			**1127**	**1140**	**91**	**92**	**253**	**294**	**23**	**32**	**276**	**326**	**2**	**2**

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Table A.2c. Mortality and Morbidity (non-fatal MI, non-fatal stroke) Data from Prior Stroke (6) Trials

Trial	Regimen	Months	# Patients	# Patients	CV Death Or Unk	CV Death Or Unk	Stroke, MI, CV Deaths	Stroke, MI, CV Deaths	NV Death	NV Death	Stroke, MI, All Deaths	Stroke, MI, All Deaths	LTF	LTF
			Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
AICLA	A990	36	198	204	13	12	31	46	6	6	37	52	0	0
Britton	A1500	24	253	252	28	29	59	55	6	8	65	63	2	2
SALT	A75	32	676	684	50	51	163	193	11	18	174	211	0	0
AITIA	A1300	17	162	157	10	13	26	35	0	3	26	38	59	51
Canadian Cooperative	A1300	34	144	139	11	15	32	30	3	2	35	32	2	4
UK-TIA	A300, A1200	50	1621	814	180	86	342	193	41	36	383	229	5	4
Total			**3054**	**2250**	**292**	**206**	**653**	**552**	**67**	**73**	**720**	**625**	**68**	**61**

Table A.2d. Mortality and Morbidity (non-fatal MI, non-fatal stroke) Data from Intermittent Claudication and Non-Coronary Grafting Trials

Trial	Regimen	Months	# Patients	# Patients	CV Death Or Unk	CV Death Or Unk	Stroke, MI, CV Deaths	Stroke, MI, CV Deaths	NV Death	NV Death	Stroke, MI, All Deaths	Stroke, MI, All Deaths	LTF	LTF
			Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
Hess	A990	24	80	80	1	0	3	3	1	0	4	3	0	0
Schoop-I	A990	60	100	100	2	4	6	7	0	0	6	7	2	4
Munick-A	A1500	24	92	84	2	4	5	6	1	0	6	6	0	0
Munich-B	A1500	24	42	40	3	1	4	2	1	1	5	3	2	2
Rochester	A975	12	16	17	0	0	0	0	0	0	0	0	0	0
Loew Bypass	A1500	12	215	213	0	0	0	0	0	0	0	0	0	0
Total			**545**	**534**	**8**	**9**	**18**	**18**	**3**	**1**	**21**	**19**	**4**	**6**

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Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients

Antiplatelet Trialists' Collaboration

This is the first of a three part overview of randomised trials of antiplatelet therapy. Part II, on maintaining vessel patency, will be published next week.

Antiplatelet Trialists' Collaboration
A full list of collaborators is given at the end of this report.

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BMJ 1994;308:81-106

Abstract

Objective—To determine the effects of "prolonged" antiplatelet therapy (that is, given for one month or more) on "vascular events" (non-fatal myocardial infarctions, non-fatal strokes, or vascular deaths) in various categories of patients.

Design—Overviews of 145 randomised trials of "prolonged" antiplatelet therapy versus control and 29 randomised comparisons between such antiplatelet regimens.

Setting—Randomised trials that could have been available by March 1990.

Subjects—Trials of antiplatelet therapy versus control included about 70 000 "high risk" patients (that is, with some vascular disease or other condition implying an increased risk of occlusive vascular disease) and 30 000 "low risk" subjects from the general population. Direct comparisons of different antiplatelet regimens involved about 10 000 high risk patients.

Results—In each of four main high risk categories of patients antiplatelet therapy was definitely protective. The percentages of patients suffering a vascular event among those allocated antiplatelet therapy versus appropriately adjusted control percentages (and mean scheduled treatment durations and net absolute benefits) were: (*a*) among about 20 000 patients with acute myocardial infarction, 10% antiplatelet therapy *v* 14% control (one month benefit about 40 vascular events avoided per 1000 patients treated ($2P < 0{\cdot}00001$)); (*b*) among about 20 000 patients with a past history of myocardial infarction, 13% antiplatelet therapy *v* 17% control (two year benefit about 40/1000 ($2P < 0{\cdot}00001$)); (*c*) among about 10 000 patients with a past history of stroke or transient ischaemic attack, 18% antiplatelet therapy *v* 22% control (three year benefit about 40/1000 ($2P < 0{\cdot}00001$)); (*d*) among about 20 000 patients with some other relevant medical history (unstable angina, stable angina, vascular surgery, angioplasty, atrial fibrillation, valvular disease, peripheral vascular disease, etc), 9% *v* 14% in 4000 patients with unstable angina (six month benefit about 50/1000 ($2P < 0{\cdot}00001$)) and 6% *v* 8% in 16 000 other high risk patients (one year benefit about 20/1000 ($2P < 0{\cdot}00001$)).

Reductions in vascular events were about one quarter in each of these four main categories and were separately statistically significant in middle age and old age, in men and women, in hypertensive and normotensive patients, and in diabetic and non-diabetic patients. Taking all high risk patients together showed reductions of about one third in non-fatal myocardial infarction, about one third in non-fatal stroke, and about one sixth in vascular death (each $2P < 0{\cdot}00001$). There was no evidence that non-vascular deaths were increased, so in each of the four main high risk categories overall mortality was significantly reduced. The most widely tested antiplatelet regimen was "medium dose" (75-325 mg/day) aspirin. Doses throughout this range seemed similarly effective (although in an acute emergency it might be prudent to use an initial dose of 160-325 mg rather than about 75 mg). There was no appreciable evidence that either a higher aspirin dose or any other antiplatelet regimen was more effective than medium dose aspirin in preventing vascular events. The optimal duration of treatment for patients with a past history of myocardial infarction, stroke, or transient ischaemic attack could not be determined directly because most trials lasted only one, two, or three years (average about two years). Nevertheless, there was significant ($2P < 0{\cdot}0001$) further benefit between the end of year 1 and the end of year 3, suggesting that longer treatment might well be more effective.

Among low risk recipients of "primary prevention" a significant reduction of one third in non-fatal myocardial infarction was, however, accompanied by a non-significant increase in stroke. Furthermore, the absolute reduction in vascular events was much smaller than for high risk patients despite a much longer treatment period (4·4% antiplatelet therapy *v* 4·8% control; five year benefit only about four per 1000 patients treated) and was not significant ($2P = 0{\cdot}09$).

Conclusions—Among a much wider range of patients at high risk of occlusive vascular disease than is currently treated routinely, some years of antiplatelet therapy—with aspirin 75-325 mg/day or some other antiplatelet regimen (provided there are no contraindications)—offers worthwhile protection against myocardial infarction, stroke, and death. Significant benefit is evident not only among patients with unstable angina, suspected acute myocardial infarction, or a past history of myocardial infarction, stroke, or transient ischaemic attack, but also among many other categories of high risk patients (such as those having vascular procedures and those with stable angina or peripheral vascular disease). There is as yet, however, no clear evidence on the balance of risks and benefits of antiplatelet therapy in primary prevention among low risk subjects.

Introduction

PREVIOUS ANTIPLATELET TRIALS AND AIMS OF CURRENT OVERVIEW

It is reliably established that antiplatelet therapy reduces the risk of vascular death by about one sixth and the risk of non-fatal myocardial infarction and stroke by about one third in patients with unstable

angina, suspected acute myocardial infarction, or a past history of myocardial infarction, stroke, or a transient ischaemic attack.[1-4] There remains uncertainty, however, whether antiplatelet therapy is beneficial in other patient populations at high risk of occlusive vascular disease or in certain subgroups of these "high risk" populations (for example, among women or among patients who are old, hypertensive, or diabetic). It is also uncertain whether the benefits of long term antiplatelet therapy would outweigh the side effects among subjects in whom the risks of occlusive vascular disease are much lower (for example, primary prevention in the general population with no relevant medical history) and which antiplatelet regimens are most effective.

The aim of this second cycle of the worldwide Antiplatelet Trialists' Collaboration[1] was therefore to assess the effects of antiplatelet therapy in more detail and in a much wider range of circumstances than before. This paper (part I in a series of three reports) describes the methods used in the collaborative overview process and then provides systematic overviews of the effects of "prolonged" antiplatelet therapy (that is, given for at least one month) in subjects at high risk and at low risk of occlusive vascular disease. The trials in high risk subjects are then subdivided more finely by the category of patients who were to be studied (prior myocardial infarction, acute myocardial infarction, prior stroke or transient ischaemic attack, and various other categories of patients considered to be at particular risk of vascular events because of their medical history). Where possible, the patients in those trials in high risk are also subdivided by certain personal characteristics (age, sex, blood pressure, diabetes) or by the type of antiplatelet regimen tested (aspirin at various doses, dipyridamole, ticlopidine, etc). In addition, the directly randomised comparisons of different antiplatelet regimens are reviewed. Randomised comparisons of different durations of treatment were not available, but the effects of antiplatelet therapy during year 1, during year 2, and during later times are examined separately to help assess any additional effects of more prolonged therapy.

Parts II and III will report overviews of 53 trials of antiplatelet therapy to maintain vessel patency after vascular procedures[5] and 77 trials to prevent venous thromboembolism after general and orthopaedic surgery.[6]

EVIDENCE THAT CAN BE GENERALISED TO A WIDE RANGE OF PATIENTS

Reliable detection (or refutation) of the sort of moderate sized benefits observed previously with antiplatelet therapy requires reliable exclusion both of moderate biases and of moderate random errors, either of which might obscure (or mimic) moderate treatment effects. Each requirement may be difficult to meet adequately without a proper overview of the unconfounded randomised trials, particularly if the aim is not only to distil clear findings from the overall material but also (by appropriate subgroup analyses) to help assess the generalisability of those findings.[7,8]

Analyses of the effects of treatment in particular subgroups will mainly involve "vascular events" (that is, non-fatal myocardial infarctions, non-fatal strokes, or vascular deaths) rather than vascular deaths alone. This is because such subgroup analyses may be statistically more reliable for vascular events (where, overall, there is a 13 standard deviation difference in favour of antiplatelet therapy; see results) than for vascular deaths alone (where there is "only" a six standard deviation difference in favour of antiplatelet therapy). Even for vascular events, however, separate analyses of the effects in an excessively large number of small subgroups of patients studied could well generate some false negative results merely by chance. Paradoxically, therefore, unless there are good reasons for expecting a difference in the direction of the effects of treatment in different settings the approximate benefit of antiplatelet therapy in some small subgroup of patients may best be assessed indirectly by approximate extrapolation from the proportional effect observed in a much wider class of patients.[9]

Materials and methods

DATA ACQUISITION

Identification of all unconfounded randomised trials

The aim was to seek collaboration between the coordinators of all unconfounded randomised trials, published or unpublished,[10,11] that could have been available for review by March 1990, in which antiplatelet therapy was compared with no antiplatelet therapy, or in which one antiplatelet regimen was compared with another (with the exception of trials of antiplatelet therapy for patients with subarachnoid haemorrhage[12-14] or for preventing pre-eclampsia[15] or migraine[16]). Trials were to be included only if they were believed to have been randomised in a manner that precluded prior knowledge of the next treatment (for example, where allocation was not alternate or based on odd or even dates), and they were considered to be unconfounded if one treatment group differed from another only in the treatment of interest. Thus a trial in which antiplatelet therapy plus heparin was compared with the same heparin regimen would have been included whereas a trial of antiplatelet therapy plus heparin versus no treatment (or of antiplatelet therapy versus anticoagulant therapy) would not.

Relevant randomised trials were identified by computer aided literature searches (Medline and Current Contents), by manual searches of journals, by scrutiny of the reference lists of trials and review articles, by scrutiny of abstracts and meeting proceedings, by collaboration with the trial register of the International Committee on Thrombosis and Haemostasis, by inquiry among colleagues (particularly those who had coordinated other such studies), and by inquiry of various manufacturers of antiplatelet agents. This process and the correspondence with collaborating trialists that it engendered (see below) took several years. The aim was to include trials of agents whose primary mode of action on the vascular system was thought to be through inhibition of platelet aggregation or adhesion, or both: cyclo-oxygenase inhibitors (aspirin, flurbiprofen, ibuprofen, indobufen, naproxen, sulphinpyrazone, triflusal), phosphodiesterase inhibitors (dipyridamole, E5510, RA233), platelet calcium ion channel inhibitors (suloctidil), phospholipase inhibitors (hydroxychloroquine), thromboxane synthetase inhibitors, receptor blockers, or both (dazoxiben, piracetam, picotamide, ridogrel, sulotroban, daltroban, GR32191), and agents with direct effects on platelet membranes (ticlopidine). Agents known also to have a major vasodilating action (such as epoprostenol, oxpentifylline, ketanserin, naftidrofuryl) or major anticoagulant action (such as heparin or warfarin) were not to be included.

Definition of outcome measures

In this report the effects of antiplatelet therapy were to be assessed principally in terms of their effects on vascular events, defined as non-fatal myocardial infarctions, non-fatal strokes, or vascular deaths. Outcome events were to be counted as "non-fatal" only if the patient subsequently survived to the end of the study treatment period scheduled for that patient; otherwise, only the death was to be counted. Survivors could have suffered more than one type of non-fatal event. Causes of death were subdivided into "non-

vascular" (that is, definitely non-vascular) and "vascular" (that is, definitely or possibly vascular, which includes all deaths attributed to cardiac, cerebral, haemorrhagic, embolic, other vascular, or unknown causes). Myocardial infarctions and strokes were to be counted if the investigator considered them to be either probable or definite. Transient ischaemic attacks (in brain or eye), angina, and "possible" myocardial infarctions or strokes were not to be counted as outcomes. Strokes (including subarachnoid haemorrhages) were to be counted only if symptoms persisted for at least 24 hours, and were subdivided into haemorrhagic (including those of "probably" haemorrhagic aetiology) and other (including those of probably ischaemic or of unknown aetiology). "Major" bleeds were those non-cerebral bleeds that required transfusion.

In trials among patients having vascular surgery or angioplasty or those having renal shunts or fistulas established, information on vessel or graft patency was sought (see part II[5]), and among all trials in which deep venous thromboses were looked for prospectively (usually among surgical patients) information on deep venous thromboses and pulmonary emboli was also sought (see part III[6]). Pulmonary emboli were to be counted if considered "probable" or "definite" by the investigator. There were differences between studies in the definitions of outcome measures, but because retrospective reclassification would have been impracticable (and potentially biased) the definitions preferred by the original investigators in each study were generally retained. The heterogeneity that this entailed does not invalidate the main overview results.[17]

"Summary data" from all contributing trials

For all studies that might have been randomised controlled trials of antiplatelet therapy a few simple details of trial design were requested from the principal investigators (including the exact method of treatment allocation, whether control patients received placebo, any other "blinding" of treatment allocation or outcome assessment, and the scheduled duration of trial treatment and of patient recruitment). Summary data were requested on the numbers of patients allocated to each treatment group and on the numbers of these who had suffered each of the outcomes of interest. These summary data were checked for internal consistency and for consistency with any published reports of the trials. When the data did not include information about outcome among all patients initially randomised or about all the outcomes of interest during the scheduled period of follow up, extra details were sought by correspondence with the principal investigators so that "intention to treat" analyses could be conducted. Before the final analyses, the data to be used were printed out for each trialist to check again.

Individual patient data from certain trial categories

For the trials among "low risk" subjects (that is, of primary prevention of vascular events) or among particular categories of "high risk" patients (those with unstable angina, acute myocardial infarction, prior myocardial infarction, stroke or transient ischaemic attack) data were sought for each individual randomised patient. These concerned certain baseline entry characteristics (age or date of birth, sex, blood pressure, and whether diabetic or not); the allocated treatments; and the dates of randomisation, of the scheduled end of trial treatment, of the actual end of treatment, of the last follow up, and of the first occurrence of any of the important vascular events defined above. More specific information about any non-vascular deaths and about the degree of disability associated with any strokes was also sought. In trials that recruited stroke or transient ischaemic attack patients information was sought on the nature of these qualifying cerebral events. The data from each investigator were checked for internal consistency of individual patient records, for balance of group sizes overall and according to certain prognostic categories, for consistency with the summary tabulations provided for each trial, and for some other indicators of possible anomalies.[6] Queries were referred back for clarification, and the complete set of information on each trial was also referred back for confirmation.

STATISTICAL METHODS

Proportional and absolute reductions

Both proportional and absolute reductions in clinical events can help in describing the size of any treatment effects. For example, overall in the 11 trials among patients with a history of myocardial infarction,[18-40] 13% of the patients allocated antiplatelet therapy and 17% of the controls suffered a vascular event (myocardial infarction, stroke, or vascular death; fig 1). This absolute reduction of 4% (that is, about 40 vascular events prevented per 1000 patients treated) corresponds to a proportional reduction of about one quarter. Proportional reductions may be more widely generalisable to different medical circumstances, while absolute reductions may be more directly relevant to deciding whether to use treatment in particular medical circumstances. For these reasons both proportional and absolute reductions are described in the results.

Simplest summary of trial results: adjusted totals and adjusted percentages

Suppose that findings are to be combined from several trials that were all evenly randomised (that is, with about half the subjects in each trial allocated treatment and half control). A simple method of comparison would entail adding together all the treatment groups, adding together all the control groups, and, finally, comparing these two grand totals. If any of the trials had included deliberately uneven treatment allocation (for example, two thirds treatment, one third control), then it could first be "adjusted" to an evenly randomised comparison by counting the control group more than once. For example, in figure 1 for trials of antiplatelet therapy after myocardial infarction the small control group in the PARIS-I study[22 23] would be counted fourfold to make it about the same size as the treatment group. The adjusted totals for the treatment and control groups would then be 262/1620 *v* 328/1624 in PARIS-I and 1331/9877 (13%) *v* 1693/9914 (17%) in all 11 trials together. In statistical principle these simple adjusted totals may not be ideal (see below) but if, as here, the overall difference between treatment and control is very highly statistically significant, then such adjusted percentages (13% *v* 17%) may well provide a simple description of the effects of treatment that is sufficient for most practical medical purposes.

Comparisons of like versus like based on combination of "observed minus expected" differences in each separate trial

Figure 1 also illustrates the more formal statistical methods used to combine the results from different trials (using the actual numbers rather than adjusted numbers). These methods are completely robust, entailing no unjustified assumptions. A fuller description of the methods and of why they are more appropriate than other methods for such overviews of randomised trials is given elsewhere.[17]

Within each separate trial the standard quantity "observed minus expected" (together with its "variance") is calculated for the numbers of events among treatment allocated patients.[17] (Note that in an evenly randomised trial the observed minus expected value equals only half the number of events that appear

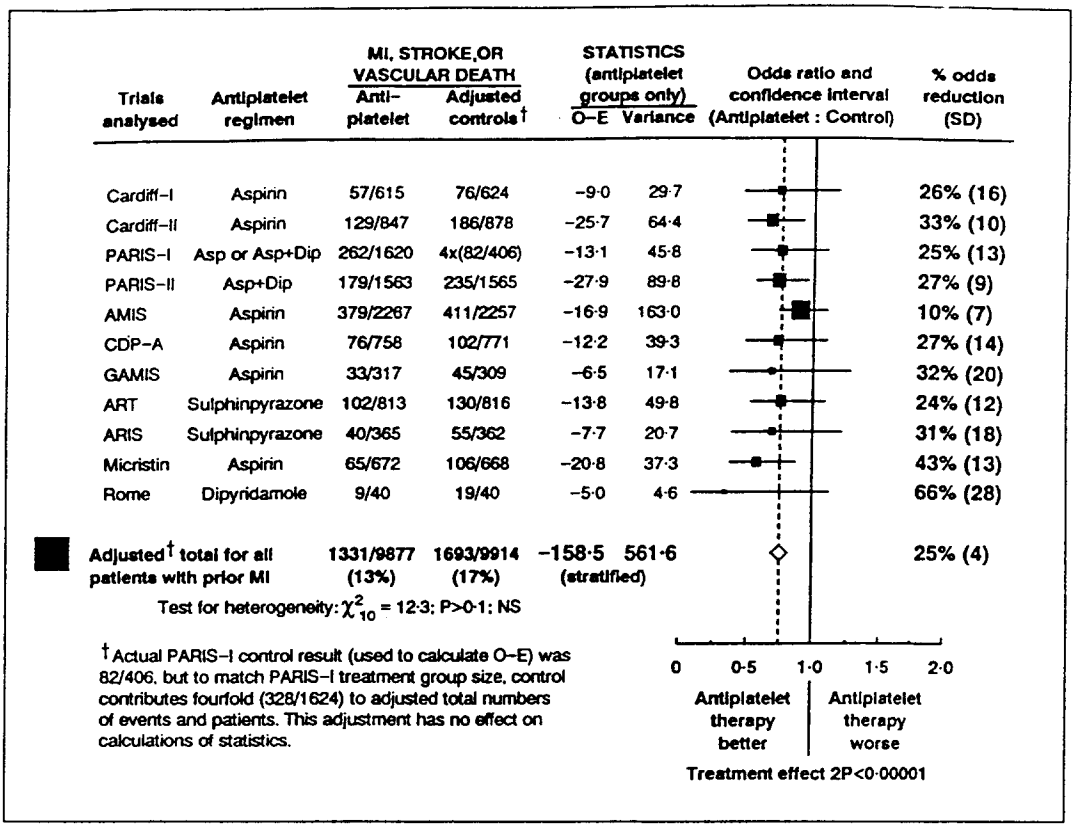


FIG 1—*Proportional effects on vascular events (myocardial infarction, stroke, or vascular death) in 11 randomised trials of prolonged antiplatelet therapy (for one month or more) versus control in patients with prior myocardial infarction. O–E=Observed minus expected. Asp=Aspirin. Dip=Dipyridamole. MI=Myocardial infarction*

(In most trials patients were allocated roughly evenly between treatment groups, but in some (for example, PARIS-I) more were deliberately allocated to active treatment. To allow direct comparisons between percentages suffering an event in each treatment group, in figure 1 and elsewhere adjusted totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once. Statistical calculations are, however, based on actual numbers from individual trials. Ratio of odds of an event in treatment group to that in control group is plotted for each trial (black square: area proportional to amount of statistical information contributed by trial) along with its 99% confidence interval (horizontal line). All black squares are to left of solid vertical line, indicating benefit (but benefit is significant at 2P<0·01 only where, in three trials, entire confidence interval is to left of line). Stratified overview of results of all trials (and 95% confidence interval) is represented by open diamond, indicating odds ratio of 0·75 (SD 0·04) or, equivalently, odds reduction of 25% (SD 4%))

to have been avoided by treatment.) To combine information from several different trials these observed minus expected values—one from each trial—can simply be added up. If treatment did nothing, then each of the separate observed minus expected values could equally well be positive or negative and their grand total would likewise differ only randomly from zero. On the other hand, if treatment reduced the risk of adverse outcome to some extent in most or all of the trials, then any individual observed minus expected value would be likely to be somewhat negative (that is, favouring treatment), so that when all these values are added up their grand total may be clearly negative. (These arguments do not assume that the size of the treatment effect is the same in all patients, or in all trials; indeed, it probably is not.) So, for example, in figure 1 the grand total of the individual observed minus expected values is −158·5. The negative sign indicates fewer vascular events in the patients allocated antiplatelet therapy than in the controls, and the numerical value of −158·5 suggests (very approximately) that about 320 vascular events were averted by treatment.

Variances and P values

The variance of the observed minus expected value is small in small trials and large in large, informative trials that estimate more accurately the proportional reduction in adverse events. Indeed, the variance of the observed minus expected value indicates the "statistical information content" of a trial.[17] For the grand total of several observed minus expected values, the variance is given simply by the sum of their individual variances, and the standard deviation is the square root of this sum. In figure 1 the grand total of −158·5 has a variance of 561·6 and hence a standard deviation of 23·7, so it differs from zero by nearly seven of its standard deviations. This indicates a highly significant protective effect of antiplatelet therapy (two sided P value (2P) <0·00001), as a difference of only two standard deviations would have been enough for conventional statistical significance (2P<0·05). P values ≥0·1 are denoted non-significant (NS).

Proportional odds reductions

The grand totals (G and V) of the individual observed minus expected values and of their variances can be used not only (as above) to calculate a P value to help test whether treatment has any effect but also to help describe the size of the treatment effect. This description entails calculating (by using the formula exp(G/V)) the "typical odds ratio," which gives the ratio of the odds of an unfavourable outcome among treatment allocated patients to the corresponding odds among controls, stratified by trial. In figure 1 allocation to antiplatelet therapy is associated with a typical odds ratio of 0·75, which corresponds to a reduction of 25% in the odds of a vascular event.

Proportional odds and risk reductions

When comparing outcome among treated and control patients in trial analyses where substantial proportions have not yet suffered the outcome of interest, "odds" reductions and "risk" reductions are not importantly different from each other as methods for describing the results. For example, if 100 control

patients suffered a vascular event and 500 did not, then the odds of suffering an event would be one to five, or 0·20, while the risk would be one in six. In this instance it can be shown that a 25% odds reduction (from 0·20 to 0·15) would correspond to a 22% risk reduction (from 100/600 to 78/600). The percentage reduction in odds will always be slightly larger, but the similarity of these reductions (25% and 22%) confirms that it does not matter which is used to describe the trial results. Odds ratios for overviews are simpler to calculate, and so use is chiefly made of percentage reductions in odds in this report.

Standard deviations and confidence intervals

A convenient way of describing the statistical reliability of an odds reduction is to give its standard deviation (SD). For example, the overall odds reduction in figure 1 is given as 25% (SD 4%). Two standard deviations below and above 25% would yield 17% (one sixth) and 33% (one third), indicating that unless a rather unlikely ($2P<0·05$) chance event has occurred the odds reduction lies somewhere in the range between one sixth and one third. A more precisely calculated version of this "95% confidence interval" (with ends at $\exp(G/V \pm 1·96/\sqrt{V})$ is denoted by an open diamond in figure 1 and subsequent figures. The odds ratio observed in each of the parts that contribute to the total is plotted as a black square, with the areas of the squares chosen to be approximately proportional to the numbers of events (that is, the "statistical information content") in each trial. The horizontal line through each black square indicates the 99% confidence interval for the odds ratio—that is, the range of odds ratios with which that result is reasonably comfortably compatible. Because, appropriately,[17] assumption free (that is, "fixed effect") statistical methods are used to combine trial results the standard deviations and confidence intervals describe the extent to which the play of chance during the randomisation process would be apt to affect the results, either of one particular trial or of an overview of several trials.

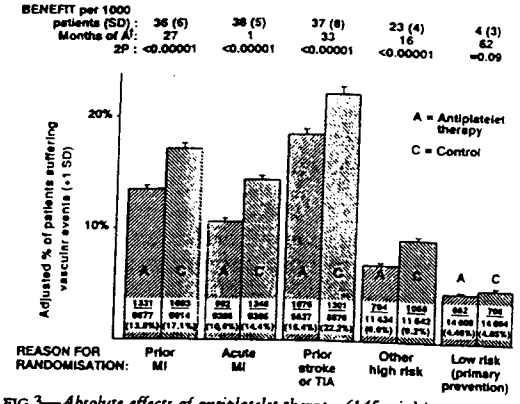


FIG 3—*Absolute effects of antiplatelet therapy (145 trials) on vascular events (myocardial infarction, stroke, or vascular death) in four main high risk categories of trial and in low risk (primary prevention) (Adjusted totals calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, for calculating adjusted percentages and events prevented per 1000 patients allocated antiplatelet therapy. Statistical significance (2P) based on stratified analyses of original, unadjusted numbers in each trial (see statistical methods))*

†Months of A = Means of scheduled antiplatelet durations. No trial lasted under one month.

DESCRIPTION OF TRIALS

A total of 413 apparently randomised trials of antiplatelet therapy could have been identified by March 1990.[18-30] On further investigation 49 were not properly randomised,[313-363] 51 were confounded or had extremely large numbers of subjects lost to follow up or included a crossover design[364-420] (plus A Lowenthal, personal communication), and two (Birmingham ticlopidine study and PACT) had never started. Data from one study (Zurich vein bypass study) were not available owing to the death of the investigator (A Bollinger, personal communication). Results from 53 studies, many of which were still in progress, were not available in March 1990[276-313] and, although results from some are now available (and, for the larger

Category of trial	No of trials with data	MI, STROKE, OR VASCULAR DEATH: Anti-platelet	MI, STROKE, OR VASCULAR DEATH: Adjusted controls†	STRATIFIED STATISTICS: O−E	STRATIFIED STATISTICS: Variance	Odds ratio and confidence interval (Antiplatelet : Control)	% odds reduction (SD)
Prior MI	11	1331/9877 (13.5%)	1693/9914 (17.1%)	−158·5	561·6		25% (4)
Acute MI	9	992/9388 (10.6%)	1348/9385 (14.4%)	−177·9	510·3		29% (4)
Prior stroke/TIA	18	1076/5837 (18.4%)	1301/5870 (22.2%)	−98·5	386·5		22% (4)
Other high risk	104	784/11 434 (6.9%)	1058/11 542 (9.2%)	−134·0	352·5		32% (4)
ALL HIGH RISK (four main categories)	142	4183/36 536 (11.4%)	5400/36 711 (14.7%)	−568·8	1810·9		27% (2)
ALL LOW RISK (primary prevention)	3	652/14 608 (4.46%)	708/14 604 (4.85%)	−28·5	273·5		10% (6)
ALL TRIALS† (high or low risk)	145	4835/51 144 (9.5%)	6108/51 315 (11.9%)	−597·3	2084·4		25% (2)

Heterogeneity of odds reductions:
- between four high risk categories $\chi^2_3 = 4.1$; NS
- between high risk and low risk $\chi^2_1 = 10.5$; P=0.001

†Crude, unadjusted control total = 5274/45 172.

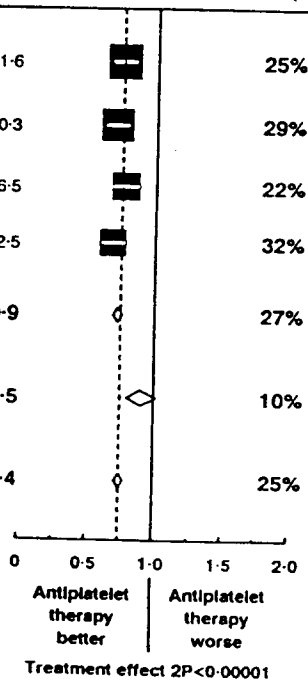
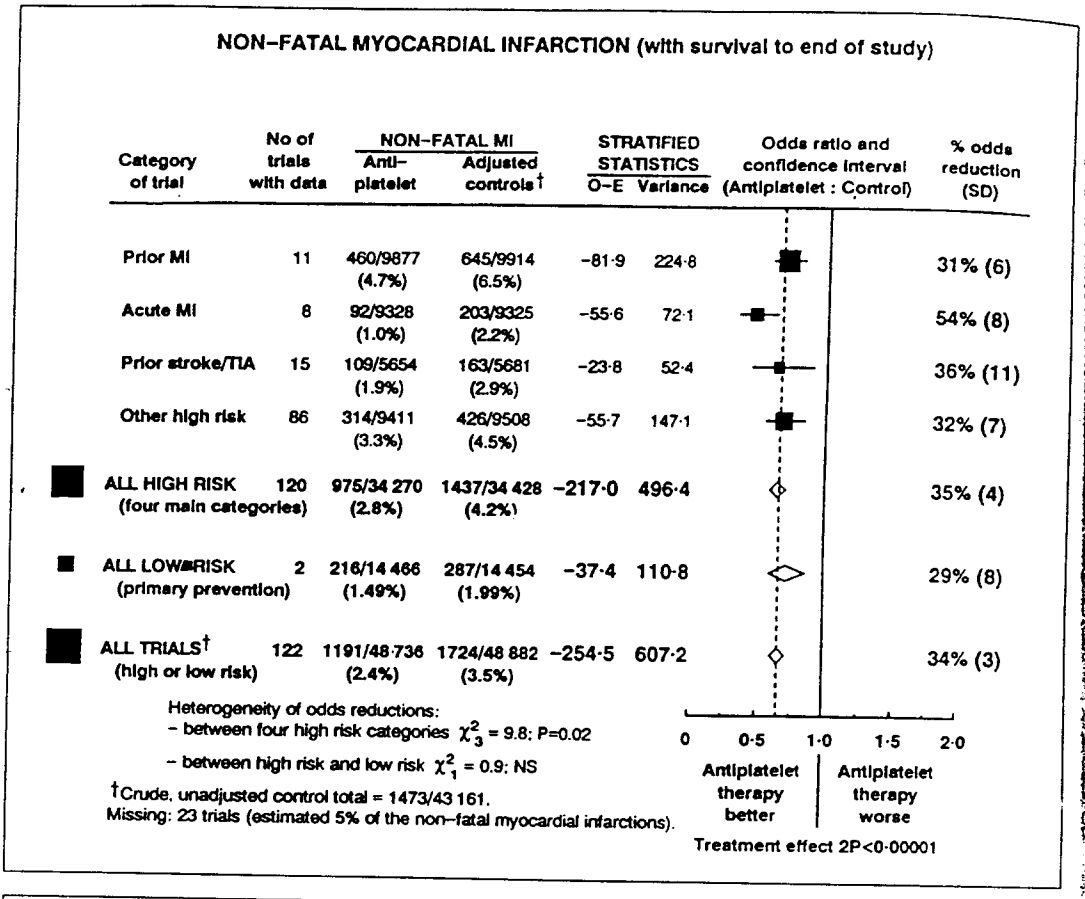


FIG 2—*Proportional effects of antiplatelet therapy (145 trials) on vascular events (myocardial infarction, stroke, or vascular death) in four main high risk categories of trial and in low risk (primary prevention). TIA = Transient ischaemic attack*

(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). Overviews of results for certain subtotals (and 95% confidence intervals) are represented by diamonds. Odds reductions observed in particular groups of trials are given to right of solid vertical line)

trials, are included in the appendices and discussion), they do not contribute to the main analyses. This left 257 eligible trials among 118 958 patients. Trials of less than one month of antiplatelet therapy were not to be included in the analyses in this report. They were, with few exceptions[248-275] (see appendices 1 and 2), mostly designed to assess efficacy in terms of vessel or graft patency (see part II[5]) or in terms of the prevention of deep venous thrombosis or pulmonary embolism after surgery (see part III[6]).



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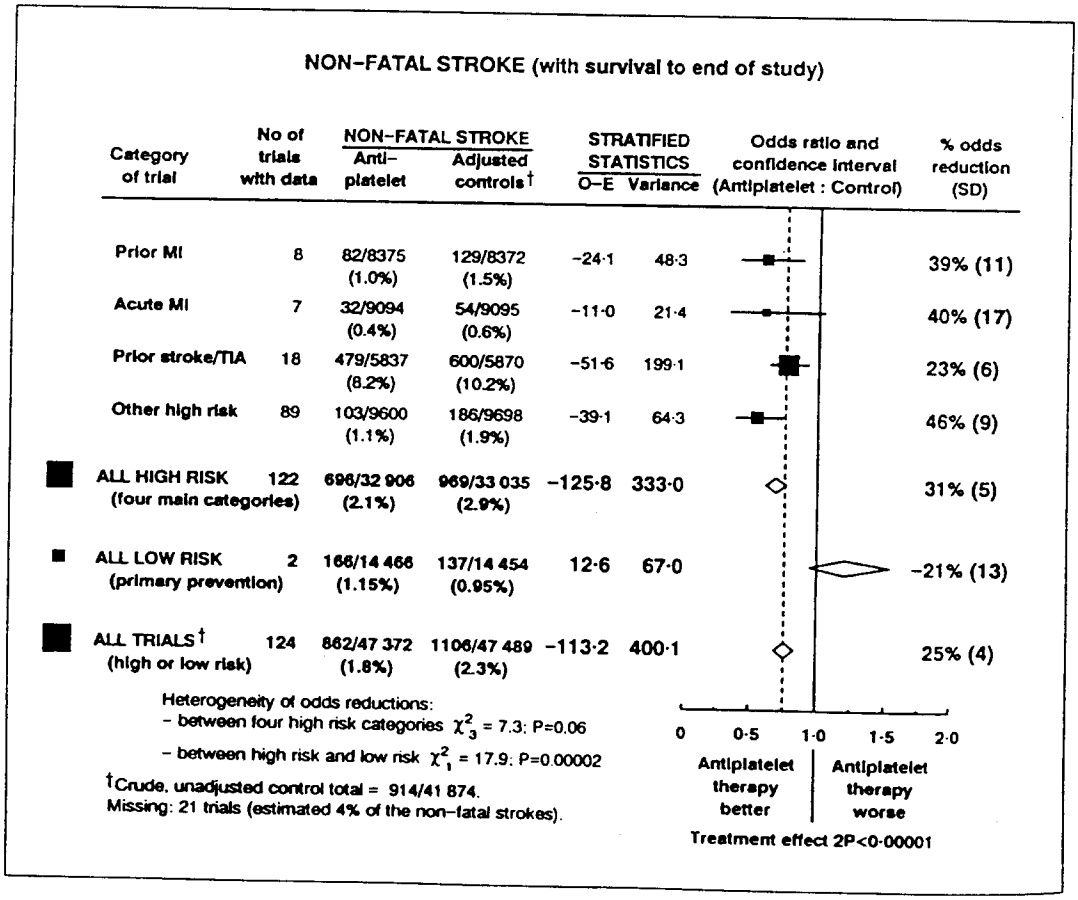


b

FIG 4 (a-d)—*Proportional effects of antiplatelet therapy (145 trials) on non-fatal myocardial infarction, non-fatal stroke, vascular death, and any death in four main high risk categories of trial and in low risk (primary prevention). Symbols and conventions as in figures 1 and 2*

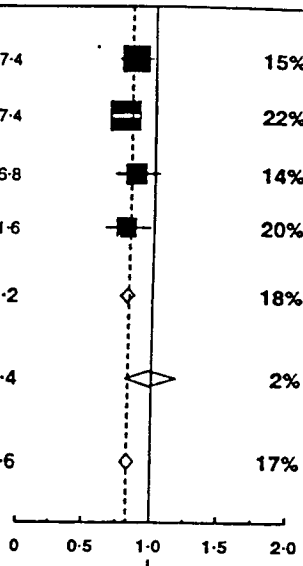
Appendices 1 and 2 give details of the 159 randomised trials of prolonged (that is, one month or more) antiplatelet therapy versus control among 96 935 patients (with individual patient data for 32 of these trials among 73 933 patients) and of the 32 trials comparing different prolonged antiplatelet regimens among 13 655 patients (with some patients in 16 of these trials also contributing to the comparison of antiplatelet versus control).[18-248] For some trials the results differ from those originally published,

c

VASCULAR DEATH (or death from unknown cause)

Category of trial	No of trials with data	VASCULAR DEATH: Anti-platelet	VASCULAR DEATH: Adjusted controls†	STRATIFIED STATISTICS: O−E	STRATIFIED STATISTICS: Variance	% odds reduction (SD)
Prior MI	11	797/9877 (8.1%)	933/9914 (9.4%)	−56·0	347·4	15% (5)
Acute MI	9	871/9388 (9.3%)	1094/9385 (11.7%)	−111·2	437·4	22% (4)
Prior stroke/TIA	18	497/5837 (8.5%)	562/5870 (9.6%)	−29·2	196·8	14% (7)
Other high risk	103	369/11 374 (3.2%)	446/11 488 (3.9%)	−38·6	171·6	20% (7)
ALL HIGH RISK (four main categories)	141	2534/36 476 (6.9%)	3035/36 657 (8.3%)	−235·1	1153·2	18% (3)
ALL LOW RISK (primary prevention)	3	281/14 608 (1.92%)	291/14 604 (1.99%)	−2·2	108·4	2% (10)
ALL TRIALS† (high or low risk)	144	2815/51 084 (5.5%)	3326/51 261 (6.5%)	−237·3	1261·6	17% (3)

Odds ratio and confidence interval (Antiplatelet : Control)



Heterogeneity of odds reductions:
- between four high risk categories $\chi^2_3 = 2.4$; NS
- between high risk and low risk $\chi^2_1 = 3.4$; P=0.07

†Crude, unadjusted control total = 2927/45 118.
NB: Non-vascular deaths NS in each category and overall (679/51 084 vs 742/51 261: O−E=−20.3, variance=291.3, NS).

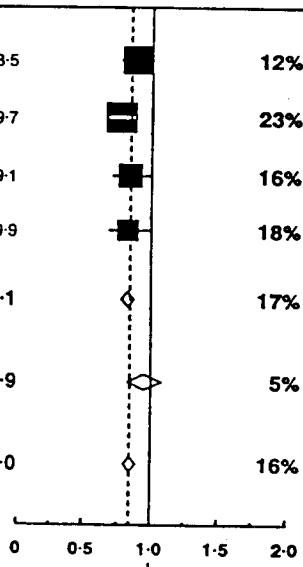
Treatment effect 2P<0·00001

d

DEATH FROM ANY CAUSE

Category of trial	No of trials with data	ALL DEATH: Anti-platelet	ALL DEATH: Adjusted controls†	STRATIFIED STATISTICS: O−E	STRATIFIED STATISTICS: Variance	% odds reduction (SD)
Prior MI	11	910/9877 (9.2%)	1029/9914 (10.4%)	−46·9	383·5	12% (5)
Acute MI	9	874/9388 (9.3%)	1102/9385 (11.7%)	−113·7	439·7	23% (4)
Prior stroke/TIA	18	675/5837 (11.6%)	780/5870 (13.3%)	−44·7	259·1	16% (6)
Other high risk	103	470/11 374 (4.1%)	554/11 488 (4.8%)	−40·4	209·9	18% (6)
ALL HIGH RISK (four main categories)	141	2929/36 476 (8.0%)	3465/36 657 (9.5%)	−245·8	1292·1	17% (3)
ALL LOW RISK (primary prevention)	3	565/14 608 (3.87%)	603/14 604 (4.13%)	−11·9	212·9	5% (7)
ALL TRIALS† (high or low risk)	144	3494/51 084 (6.8%)	4068/51 261 (7.9%)	−257·6	1505·0	16% (2)

Odds ratio and confidence interval (Antiplatelet : Control)



Heterogeneity of odds reductions:
- between four high risk categories $\chi^2_3 = 3.9$; NS
- between high risk and low risk $\chi^2_1 = 3.3$; P=0.07

†Crude, unadjusted control total = 3515/45 118.

Treatment effect 2P<0·00001

generally because of the considerable efforts taken to obtain complete follow up data on all randomised subjects (see above), including not only events while treatment actually continued but also events before the scheduled end of trial treatment (which was on a common date for all patients in some trials and at a fixed interval after randomisation in others).

Results

EFFECTS OF ANTIPLATELET THERAPY ON "VASCULAR EVENTS"

Information about vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) was available from 145 trials among a total of 51 144 patients allocated antiplatelet therapy and 45 172 controls (adjusted control total 51 315; fig 2) and was known to be unavailable from 14 small trials among a total of only 619 patients. The total numbers of patients suffering a vascular event among those allocated antiplatelet therapy were 4835 (9·5%) of 51 144, while the corresponding adjusted total among the controls was 6108 of 51 315 (11·9%). In the formal statistical analysis the grand total of observed minus expected values was about −600, indicating that about 1200 vascular events were prevented. Overall in these trials the typical reduction in the odds of suffering such events was 25% (SD 2%), which was very highly significantly favourable (13·1 standard deviations from zero; $2P < 0{\cdot}00001$) (fig 2).

Although the 145 trials did not all indicate exactly the same odds reduction, the amount of scatter between their separate results was no greater than might be expected by chance if the true odds reduction in each study was exactly 25%. But when the trials were subdivided into five main categories, the proportional reductions seemed to be somewhat greater in the four "high risk" categories than in the one "low risk category ($P = 0{\cdot}001$ for this heterogeneity; fig 2). The proportional reductions in vascular events were each about one quarter and highly significant ($2P < 0{\cdot}00001$) in each of the four high risk categories—namely, patients with a prior history of myocardial infarction, patients with suspected or definite acute myocardial infarction, patients with a prior history of stroke or transient ischaemic attack, and patients with other evidence of vascular disease or some condition associated with an increased risk of occlusive disease.

As the proportional reductions were bigger among the high risk patients, the absolute risk reductions were very much bigger (ranging from 23 to 38 vascular events averted per 1000 high risk patients allocated antiplatelet therapy; fig 3) than among the low risk "primary prevention" subjects studied. For the latter group, the proportional reduction was less extreme (10% (SD 6%)) and the absolute risk in the control group was low (only 4·8% of controls suffered an event during about five years of follow up; fig 3). Hence the absolute benefit of antiplatelet therapy seemed small (only about four vascular events averted for every 1000 patients treated for five years), and even this small benefit among such low risk subjects was statistically uncertain ($2P = 0{\cdot}09$).

Effects of antiplatelet therapy on fatal and non-fatal strokes, subdivided by stroke aetiology

Stroke aetiology and trial category	Fatal + non-fatal strokes/No of subjects (combined %)	
	Antiplatelet groups	Adjusted controls
Probably or definitely haemorrhagic strokes (in trials with at least one haemorrhagic stroke recorded)		
High risk:		
Prior myocardial infarction	6+5/ 5 476 (0·2)	6+8/ 5 507 (0·3)
Acute myocardial infarction†	6+0/ 8 821 (0·07)	1+1/ 8 830 (0·02)
Prior stroke or transient ischaemic attack	20+5/ 3 897 (0·6)	10+7/ 3 953 (0·4)
All other high risk	12+5/ 2 333 (0·7)	5+6/ 2 352 (0·5)
Low risk:		
Primary prevention	19+25/14 466 (0·3)	10+14/14 454 (0·2)*
All such trials	63+40/34 993 (0·3)	32+36/35 096 (0·2)*
Other strokes (ischaemic or unknown aetiology; in trials with at least one haemorrhagic stroke recorded)		
High risk:		
Prior myocardial infarction	17+40/ 5 476 (1·0)	17+65/ 5 507 (1·5)*
Acute myocardial infarction	8+29/ 8 821 (0·4)	14+51/ 8 830 (0·7)**
Prior stroke or transient ischaemic attack	73+306/ 3 897 (9·7)	86+396/ 3 953 (12·2)**
All other high risk	5+53/ 2 333 (2·5)	18+88/ 2 352 (4·5)***
Low risk:		
Primary prevention	24+141/14 466 (1·1)	22+123/14 454 (1·0)
All such trials	127+569/34 993 (2·0)	157+723/35 096 (2·5)*****
Strokes of any aetiology (in all trials with data on non-fatal strokes)		
High risk:		
Prior myocardial infarction	26+82/ 8 375 (1·3)	32+129/ 8 372 (1·9)***
Acute myocardial infarction	13+32/ 9 094 (0·5)	19+54/ 9 095 (0·8)**
Prior stroke or transient ischaemic attack	128+479/ 5 837 (10·4)	156+600/ 5 870 (11·2)****
All other high risk	28+103/ 9 600 (1·4)	38+186/ 9 698 (2·3)*****
Low risk:		
Primary prevention	43+166/14 466 (1·4)	32+137/14 454 (1·2)
All such trials	238+862/47 372 (2·3)	277+1106/47 489 (2·9)*****

*2P < 0·05. **2P < 0·01. ***2P < 0·001. ****2P < 0·0001. *****2P < 0·00001.
†In these acute myocardial infarction trials,[14 15] cerebral haemorrhage was found only among patients allocated fibrinolytic therapy, among whom proportions affected were 6/4526 (0·13%) versus 2/4530 (0·04%).

EFFECTS ON DIFFERENT MEASURES OF OUTCOME

Myocardial infarction

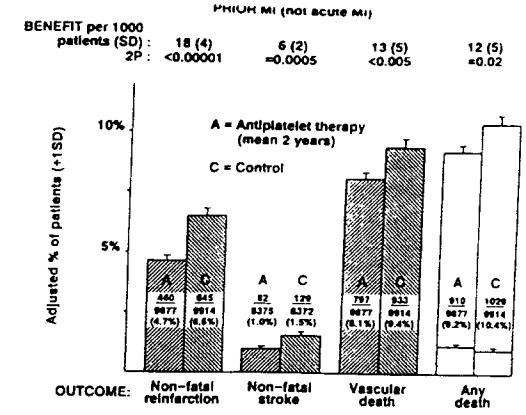
The information on non-fatal myocardial infarction was only about 95% complete, but the reductions in non-fatal myocardial infarction were so significantly and substantially different from zero that the unavailability of some data is unlikely to be important. Non-fatal myocardial infarctions were recorded in 122 trials, and the typical odds reduction produced by allocation to active treatment was 34% (SD 3%) ($2P < 0{\cdot}00001$; fig 4). This reduction in non-fatal myocardial infarction was highly statistically significant, not only in each of the four high risk categories but also in the low risk category, which suggests that a similar proportional reduction in myocardial infarction can be expected in a very wide range of settings.

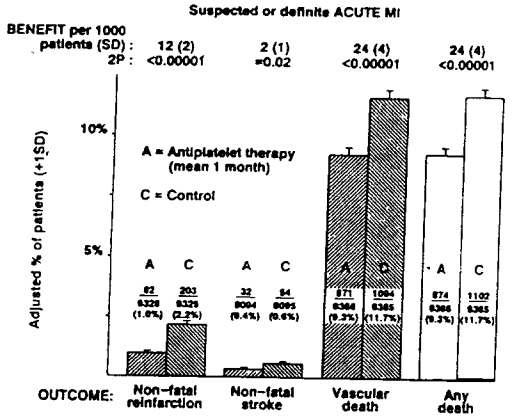
Stroke

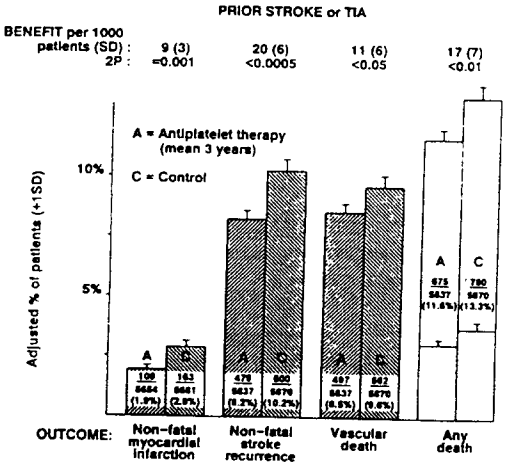
For non-fatal stroke, the information was also about 95% complete (124 trials provided results) and the typical odds reduction observed overall was large (25% (SD 4%)) and highly significant ($2P < 0{\cdot}00001$; fig 4). The reduction in non-fatal stroke among high risk patients was very definite (31% (SD 5%)) and about the same size as the reduction in myocardial infarction. There was no significant heterogeneity between the proportional odds reductions in stroke in the four high risk categories (fig 4), but the effects were very different in high risk and low risk subjects ($P = 0{\cdot}00002$ for heterogeneity). Indeed, in the low risk primary prevention studies the effect of antiplatelet therapy on non-fatal stroke appeared unfavourable. This unfavourable result was, however, statistically uncertain, and the true effect on stroke in such low risk subjects might still be about zero.

In addition to the 2000 non-fatal strokes recorded, about 500 fatal strokes were recorded during the scheduled treatment periods. Subdivision of all strokes, fatal or not, with respect to what is known of their aetiology (table) indicated that a probable small increase in haemorrhagic strokes was outweighed by a larger and very definite reduction in other strokes. The table shows that haemorrhage was considered to be the probable or definite aetiology of about 25% of fatal strokes but only about 5% of non-fatal strokes. This may help explain why the apparent effect on fatal strokes (15% (SD 9%) reduction; NS) was non-significantly smaller than the effect on non-fatal strokes (25% (SD 4%) reduction; $2P < 0{\cdot}00001$).

Reliable analyses of disabling and other non-fatal strokes were not separately available because in only 15 trials (14 high risk, one low risk[22]) could non-fatal strokes be divided into those that were "disabling"







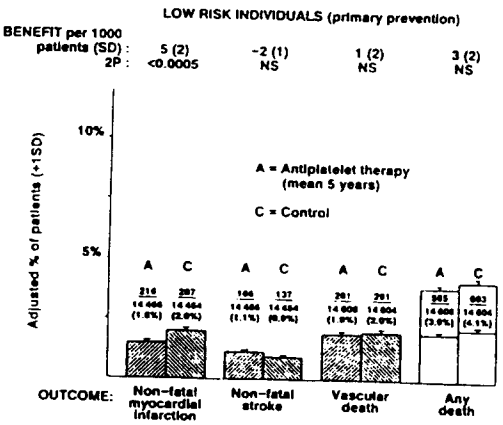


FIG 5—*Absolute effects of antiplatelet therapy on various outcomes in 11 trials in patients with prior (but not acute) myocardial infarction, five trials in patients with acute myocardial infarction (suspected or definite), 17 trials in patients with prior stroke or transient ischaemic attack, and three trials in people at low risk (primary prevention). Conventions as in figure 3. In "any death" columns non-vascular deaths are represented by lower horizontal lines (and may be calculated by subtracting vascular deaths from any deaths)*

(that is, severe interference to daily life persisting for some months after the stroke occurred) and those that were not. In these 14 high risk trials, antiplatelet therapy was associated with a 24% (SD 9%) reduction ($2P < 0{\cdot}01$) in disabling or fatal stroke and a 17% (SD 10%) reduction ($2P = 0{\cdot}09$) in non-disabling stroke with subsequent survival, the standard deviations of both reductions being large.

Vascular deaths

All but one of the 145 trials provided information on mortality, most deaths being attributed to vascular causes (which, by definition, include unknown causes). The overall effect of antiplatelet therapy on such "vascular" deaths was highly significantly favourable (6·7 standard deviations from zero; $2P < 0{\cdot}00001$), and the typical reduction in the odds of vascular death was 17% (SD 3%). Similar proportional reductions were observed in the four high risk categories, but little net effect on vascular death was observed in the primary prevention trials, and the difference between the definite mortality reduction in the high risk categories and the lack of apparent effect in the low risk primary prevention trials approached significance ($P = 0{\cdot}07$; fig 4).

Non-vascular and total deaths

There was also a slight but non-significant tendency for there to be fewer non-vascular deaths among patients allocated antiplatelet therapy than among controls (figs 4, 5). Consequently, total (all cause) mortality was significantly ($1P < 0{\cdot}01$) reduced in each high risk category of patients but not in low risk subjects (fig 4). If antiplatelet therapy has some unanticipated protective or adverse effect on some specific type of non-vascular deaths, a crude overall analysis of non-vascular mortality might well yield an uninformatively non-significant result. Fatal non-cerebral bleeding was recorded only rarely (11/51 069 (0·02%) patients among those allocated antiplatelet therapy versus 18/51 246 (0·04%) adjusted controls; NS) but there was a significant excess of three per 1000 "major" non-fatal non-cerebral bleeds (214/37 772 (0·6%) *v* 116/37 817 (0·3%); $2P < 0{\cdot}00001$).

In all but one[228 229] of the 32 trials for which individual patient data were obtained more specific details about the causes of other non-vascular deaths were available. Separate analysis of those trials also indicated a non-significant shortfall in all non-vascular deaths (352 observed, 378·2 expected) among antiplatelet allocated patients that was similar to that seen overall (679 observed, 699·3 expected; fig 4), with slightly, though non-significantly, fewer deaths both from cancer (183 observed, 196·6 expected) and from other non-vascular causes (169 observed, 181·6 expected). Site specific data on cancer deaths were not available, so the suggestion that aspirin might prevent intestinal cancer[421] or that it might cause renal cancer[422] could not be addressed directly (although analyses of one of the longest of the randomised trials of aspirin did not find any evidence of an excess of renal cancer[423]).

EFFECTS IN DIFFERENT CATEGORIES OF PATIENTS

Patients with history of myocardial infarction

The weighted (by study size) mean duration of antiplatelet therapy in trials among about 20 000 patients with a prior history of myocardial infarction was 27 months, and allocation to antiplatelet therapy produced a highly significant reduction ($2P < 0{\cdot}00001$) of about 36 per 1000 in the risk of suffering another vascular event (fig 3). The standard deviation of this risk reduction was only 6, so the real risk reduction was unlikely to be less than about 20 or 30 per 1000. Moreover, here, as in other statistically definite trial results, the benefits of actually taking

treatment tend to be underestimated by clinical trials because some patients did not comply fully with their random allocation (see discussion). Among patients with a prior history of myocardial infarction there were large and highly significant reductions in non-fatal reinfarction (18 (SD 4) prevented per 1000; $2P<0.00001$; (fig 5)) and in vascular death (13 (SD 5) per 1000; $P<0.005$: total mortality also significantly reduced) and a smaller but still highly significant reduction in non-fatal stroke (6 (SD 2) per 1000; $2P=0.0005$).

Patients with suspected or definite acute myocardial infarction

For acute myocardial infarction the overview was again based on almost 20 000 patients, nearly all of whom were in the ISIS-2 trial of one month of 160 mg aspirin daily in suspected acute myocardial infarction.[4] Allocation to antiplatelet therapy produced a highly significant reduction ($2P<0.00001$) of 38 per 1000 in the risk of suffering a subsequent vascular event (fig 3), again with a fairly small standard deviation. Most of this reduction was in vascular deaths (24 (SD 4) prevented per 1000; $2P<0.00001$ (fig 5)), but there was also a highly significant reduction in non-fatal reinfarction during the month of treatment (12 (SD 2) per 1000; $2P<0.00001$) and a smaller but still significant reduction in non-fatal stroke (2 (SD 1) per 1000; $2P<0.02$).

Patients with history of stroke or transient ischaemic attack

Among more than 10 000 patients with a prior history of stroke or transient ischaemic attack, allocation to a mean duration of 33 months of antiplatelet therapy produced a highly significant ($2P<0.00001$) reduction of 37 per 1000 in the risk of suffering another vascular event (fig 3), with a standard deviation of 8. Compared with patients after a myocardial infarction, patients after a stroke or transient ischaemic attack are at relatively high absolute risk of stroke recurrence and at relatively low absolute risk of non-fatal myocardial infarction. Among such patients, therefore, there was a large and highly significant absolute reduction in non-fatal stroke (20 (SD 6) prevented per 1000; $2P<0.0005$ (fig 5)) plus a somewhat smaller but still highly significant reduction in non-fatal myocardial infarction (9 (SD 3) per 1000; $2P=0.001$). Although the reduction of 11 (SD 6) per 1000 vascular deaths was only marginally significant ($2P<0.05$) on its own, the highly significant reductions in non-fatal vascular events and the significant ($2P<0.01$) reduction in all cause mortality strongly reinforce the conclusion that prolonged antiplatelet therapy reduces both the vascular and all cause mortality in patients with a history of stroke or transient ischaemic attack.

For 10 of the 12 such trials that provided individual patient data it was possible to categorise patients into those who had presented with completed stroke and those who had presented with transient ischaemic attack only. The proportional reduction in important vascular events in these cerebrovascular trials was 22% (SD 5%) overall and was similar for patients presenting with a completed stroke (23% (SD 7%) reduction; $2P<0.001$) and for those presenting with only a transient ischaemic attack (22% (SD 7%) reduction; $2P<0.01$).

Low risk "primary prevention" subjects

Among about 28 000 low risk "primary prevention" subjects studied, allocation to an average of just over five years of antiplatelet therapy produced a small but highly significant ($2P<0.0005$) reduction of 5 (SD 2) per 1000 in non-fatal myocardial infarction (fig 5), but the reduction in vascular events was slightly smaller and less clearly significant (figs 2, 3; $2P=0.09$). In contrast with the highly significant reduction in non-fatal strokes among high risk subjects there was no evidence of any decrease in non-fatal strokes among these low risk subjects—rather the reverse (2 (SD 1) per 1000 increase; NS).

When the aetiology of all strokes (fatal and not; table) observed among low risk subjects was considered there was not only a small, marginally significant ($2P<0.05$) excess of strokes attributed to haemorrhagic causes but also a non-significant excess of "other" strokes. This may be because other strokes included those of unknown cause, a few of which may have been haemorrhagic and caused by antiplatelet therapy. But as a large proportion of these other strokes were confirmed as occlusive, the adverse effects on stroke among these low risk subjects may well have been inflated to some extent by chance. Haemorrhagic strokes are more likely to be fatal, and a small excess of these with antiplatelet therapy among the low risk primary prevention subjects may account, at least in part, for the lack of any significant difference in vascular mortality (table, fig 5).

Other high risk patients

The remaining 20 000 high risk patients represented a mixed category of conditions associated with an increased risk of vascular events. Among them, the mean duration of antiplatelet therapy was only about half as long as in the post-myocardial infarction or post-stroke or transient ischaemic attack trials. Hence, although the event rates per month (and the benefits of antiplatelet therapy per month; see below) were about as large as in those trials, the cumulative rates of vascular events (and hence the cumulative benefits of antiplatelet therapy) were only about half as great. The benefits were, however, statistically definite ($2P<0.00001$; fig 3); allocation to an average of 16 months of antiplatelet therapy in these other high risk patients producing a reduction of 23 per 1000 in the risk of suffering a vascular event, again with a small standard deviation (SD 4). Among these patients there were separately significant reductions in non-fatal myocardial infarction, non-fatal stroke, vascular death, and total mortality (fig 4).

Figure 6 subdivides this fourth large category of high risk patients into 14 subcategories, comparing their results with each other and with the first three large categories (prior myocardial infarction, acute myocardial infarction, prior stroke or transient ischaemic attack). Patients in each of these three large categories and 14 small subcategories were, for one reason or another, at high risk of occlusive vascular disease. Thus in view of the overall results for high risk patients (odds reduction 27% (SD 2%)) some protection might be expected from antiplatelet therapy for each subcategory. But if there were a real benefit that was of roughly similar size in each subcategory, then what was likely to be observed was significant benefit in a few, non-significant benefit in most, and no particularly striking evidence of heterogeneity around the overall odds reduction of about a quarter (indicated by the vertical broken line in figure 6).

This is exactly what is shown in figure 6. Although almost all of the subcategory results appear to favour treatment, the reductions are conventionally significant at $2P<0.01$ (as indicated by the 99% confidence intervals not crossing the solid vertical line) only for patients with unstable angina (182 *v* 285 events; $2P<0.00001$), for those who had undergone percutaneous transluminal coronary angioplasty (32 *v* 61 events; $2P=0.002$), and for those who had undergone heart valve surgery (46 *v* 79 events; $2P<0.01$) and not for the other 11 subcategories. But there was no significant evidence of heterogeneity between the

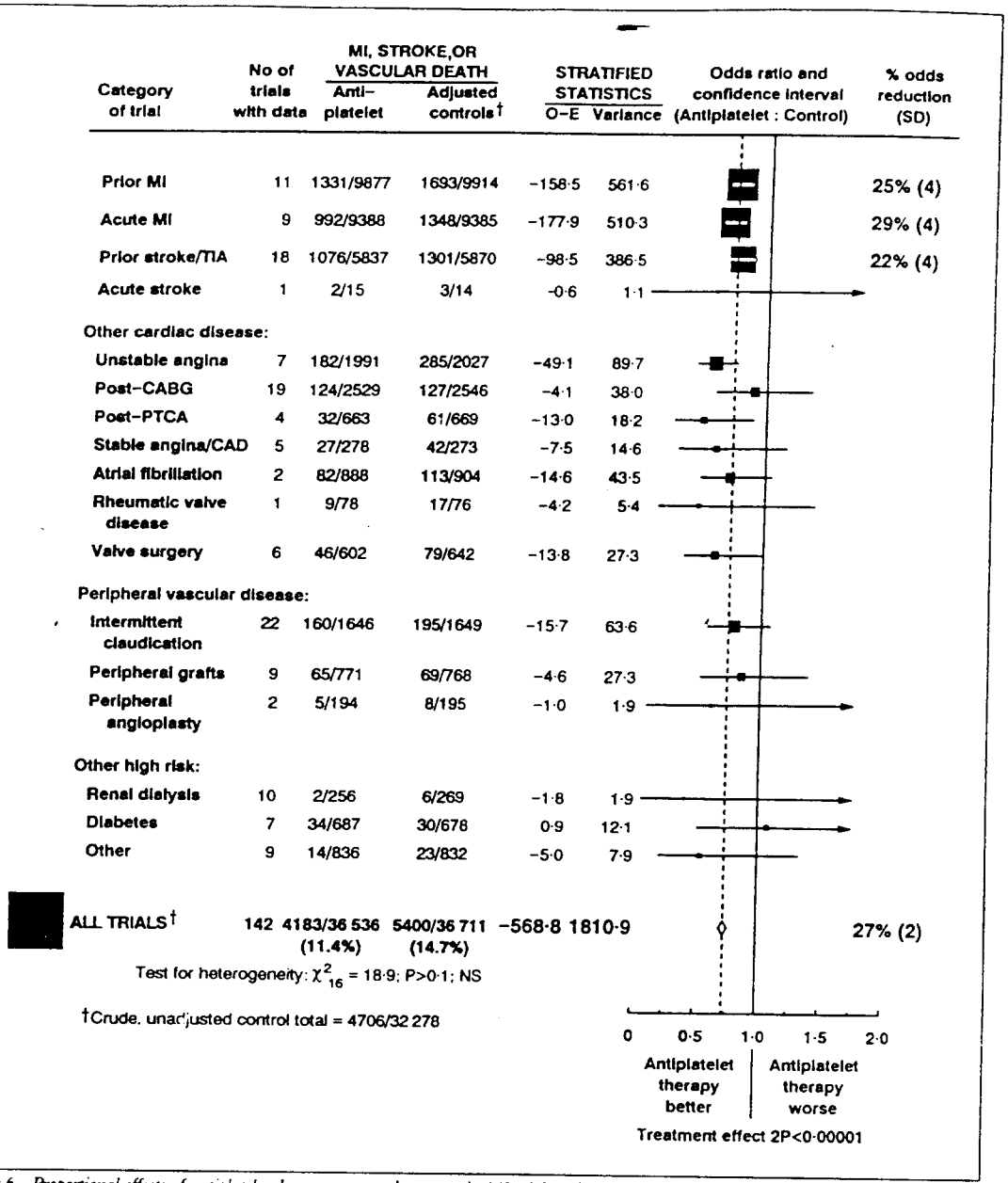


FIG 6—*Proportional effects of antiplatelet therapy on vascular events in 142 trials in high risk patients subdivided by type of trial. Symbols and conventions as in figures 1 and 2. CABG=Coronary artery bypass grafting. PTCA=Percutaneous transluminal coronary angioplasty. CAD=Coronary artery disease*

results in figure 6, and the most appropriate conclusion may well be that antiplatelet therapy is likely to be protective for any high risk patients with clinically evident occlusive vascular disease, unless there is some special contraindication (see discussion, which includes those major trials that became available only after March 1990).

Subdivision by other characteristics in high risk patients

In those trials in high risk patients where data for each subject were available, treatment produced similar proportional reductions in middle age and old age, in men and women, in hypertensive and normotensive patients, and in diabetic and non-diabetic patients (fig 7). None of these characteristics are therefore contraindications to antiplatelet therapy for patients who have occlusive vascular disease. In particular, women seem to derive about as much benefit as men, and elderly patients seem in the short term to derive even more benefit than middle aged patients might do (although, as middle aged patients have a long life expectancy, their long term benefit may be greater).

COMPARISONS OF DIFFERENT ANTIPLATELET REGIMENS

Direct comparisons between different regimens

Any real differences between two antiplatelet regimens are likely to be smaller than the differences between antiplatelet and no antiplatelet treatment. Hence tens of thousands of patients may need to be randomised directly between different antiplatelet regimens to ensure (by large numbers) small enough random errors and to avoid (by direct randomisation) important biases. Unfortunately, the numbers so far randomised between one antiplatelet regimen and another have been much smaller than this.

Figure 8 gives the four comparisons, where, in aggregate, at least 1000 patients were randomised, though the largest included only a few thousand patients. There was no significant difference between the protective effects of higher aspirin doses (500-1500 mg daily) and of medium aspirin doses (75-325 mg daily), but these direct randomised comparisons were based on only 396 vascular events in three trials. So, although these comparisons of different aspirin doses do not show any need for more than 300 or 325 mg daily (and a dose much higher than this would

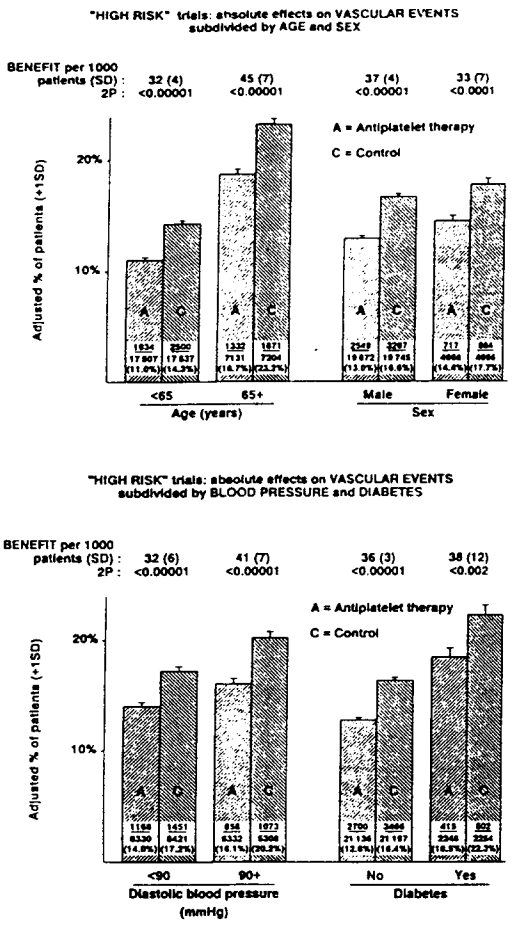


FIG 7—*Absolute effects of antiplatelet therapy on vascular events in the 29 trials in high risk patients with separate information available on each patient subdivided by age and sex and by diastolic blood pressure and diabetes. Conventions as in figure 3*

be significantly more gastrotoxic[69 70]), they cannot prove that no worthwhile differences exist (for example, of 10% or 20% in either direction). Similarly, in the direct comparisons of aspirin alone versus aspirin plus dipyridamole, of aspirin versus sulphinpyrazone, or of aspirin versus ticlopidine the differences in the combined outcome measure of vascular events were not statistically significant (though moderate differences cannot be ruled out).

Indirect comparisons between different regimens

The effects of different 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. Such indirect comparisons need to be interpreted more cautiously, for although many of the biases inherent in non-random methods (such as those involving historical controls) are avoided, some potential for bias remains.[17] This potential may, however, be reduced by restricting attention to the 142 trials of antiplatelet therapy versus control in high risk patients and by comparing proportional rather than absolute risk reductions. When this was done (fig 9) the effects of the different antiplatelet drug regimens that have been tested in these trials appeared remarkably homogeneous. None of these groups of antiplatelet regimens appeared to be much more or less effective than any other, irrespective of whether they were characterised just by the drugs they contain or, for aspirin, by the daily dosage. (The formal statistical comparisons confirm that there was no significant heterogeneity between the protective effects of the seven different drug combinations in figure 9.)

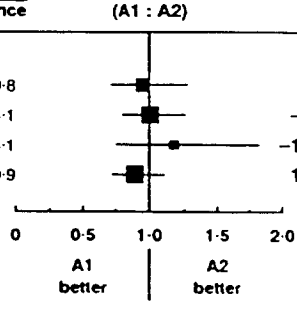
Aspirin regimens were much the most widely tested in such trials, accounting for two thirds of the data in figure 9. Overall, aspirin was associated with a highly significant 25% (SD 2%) proportional reduction ($2P < 0{\cdot}00001$) in vascular events, with at least as great an apparent effect in trials of "medium" daily doses of 75-325 mg daily (less than 160 mg daily (mostly 75-150 mg), 26% (SD 11%) reduction ($2P = 0{\cdot}01$); 160-325 mg daily, 28% (SD 3%) reduction ($2P < 0{\cdot}00001$)) as in trials of higher doses (500-1500 mg daily, 21% (SD 4%) reduction ($2P < 0{\cdot}00001$)). These aspirin trials, together with two more recent studies of 75 mg/day[277 279] (see discussion), provide substantial evidence that in emergency use (for example, in acute myocardial infarction[43]) doses as low as 160 mg are effective and that in long term use doses as low as 75 mg daily are effective; however, they provide no substantial evidence about daily doses of less than 75 mg.

The numbers studied in trials of the six other antiplatelet drug combinations were smaller, so that estimates of the sizes of the protective effects were less accurate than for aspirin alone. For three combinations (aspirin plus sulphinpyrazone, dipyridamole alone, and suloctidil alone) the numbers studied were so small that although the apparent effects were about as great as for aspirin, the confidence intervals included zero. For the three other drug regimens (aspirin plus dipyridamole, sulphinpyrazone alone, and ticlopidine alone) the numbers studied were larger and the protective effects were significantly different from zero; they were not, however, significantly different from each other or from the size of the reduction that can be produced by aspirin alone.

DURATION OF ANTIPLATELET TREATMENT

No large randomised trials have compared different

Regimens compared (A1 vs A2)	No of trials	MI, STROKE, OR VASCULAR DEATH A1	A2	STRATIFIED STATISTICS O−E	Variance	Odds ratio and confidence interval (A1 : A2)	% odds reduction (SD)
High† v medium Asp	3	195/1212	201/1213	−3·8	79·8		5% (11)
Asp + Dip v same Asp	14	316/2661	312/2656	1·0	134·1		−1% (9)
Sulphinpyrazone v Asp	5	98/674‡	88/673	5·5	34·1		−18% (19)
Ticlopidine v Aspirin	3	378/1730	414/1741	−16·6	149·9		10% (8)



†Aspirin doses(mg/day): high=500−1500, medium=75−325
‡Crude, unadjusted sulphinpyrazone total = 85/526

FIG 8—*Direct comparisons of proportional effects on vascular events of different antiplatelet regimens in trials in over 1000 high risk patients. Symbols and conventions as in figures 1 and 2*

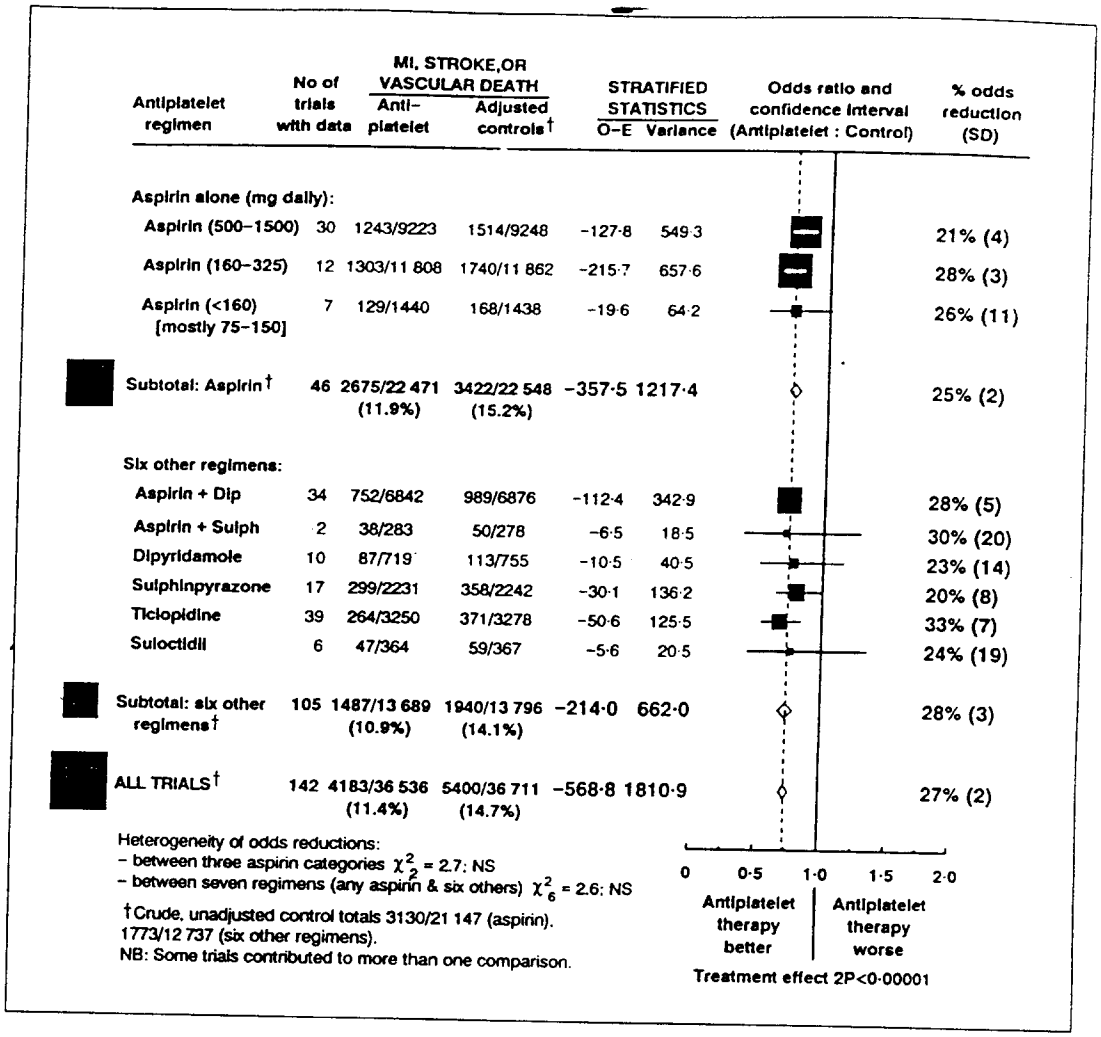


FIG 9—*Indirect comparisons of proportional effects on vascular events of different antiplatelet regimens in 142 trials in high risk patients. Symbols and conventions as in figures 1 and 2. Sulph = Sulphinpyrazone*

durations of antiplatelet treatment. Some information may be gained by determining whether in trials where treatment was prolonged the absolute benefits of treatment continued to grow with time. But such comparisons would eventually become somewhat biased against an effective treatment (see discussion). Hence whatever further divergence there may be between treatment and control in later years tends to underestimate the benefits that would be seen in an appropriately randomised comparison between stopping and continuing treatment.

For the trials of more than one year of antiplatelet therapy among patients with prior myocardial infarction, stroke, or transient ischaemic attack in which information was available on the times of each individual event, figure 10 shows the apparent effects of treatment in each separate year. The largest amounts of data, and the largest benefit, were seen in the first year, but the further benefit just during year 2 was highly significant (the odds reduction during that year alone was 24% (SD 5%); $2P < 0{\cdot}0001$), and even after year 2 there appeared to be some additional benefit (if non-significant). These year by year risk reductions are plotted[17] in figure 11, which shows that the absolute benefit among such high-risk patients was already substantial by the end of the first year, that it grew significantly larger by the end of year 3, and that there was no evidence that treatment stopped being protective. Figure 11 also shows substantial benefits at the end of only one month of treatment in patients with acute myocardial infarction ($2P < 0{\cdot}00001$) and at the end of six months of treatment in patients with unstable angina ($2P < 0{\cdot}00001$), but in primary prevention the absolute annual benefit even after five years was still small and not conventionally significant ($2P = 0{\cdot}08$).

Discussion

BENEFIT IN A WIDE RANGE OF PATIENTS AT HIGH RISK OF OCCLUSIVE VASCULAR DISEASE

These results strongly reinforce and extend the results of the first cycle of the Antiplatelet Trialists' Collaboration.[1] Antiplatelet therapy has been shown to reduce the risk of "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, or a past history of myocardial infarction, stroke, or transient ischaemic attack but also in the large category of other patients at increased risk of occlusive vascular disease (that is, patients having coronary vascular procedures and patients with stable angina, valvular heart disease, atrial fibrillation, or peripheral vascular disease). Vascular mortality and all cause mortality were also significantly reduced by antiplatelet therapy in these high risk patients, and compared with these benefits the absolute risk of fatal and major non-fatal bleeds was small.[4,5]

Because these proportional risk reductions were statistically reliable and appeared approximately homogeneous over the wide range of settings studied in these trials, protective effects of antiplatelet therapy against occlusive vascular disease should be expected for a range of high risk patients that is even wider than just those categories in which this overview provides direct evidence of benefit. This important conclusion depends partly on the definiteness and consistency of

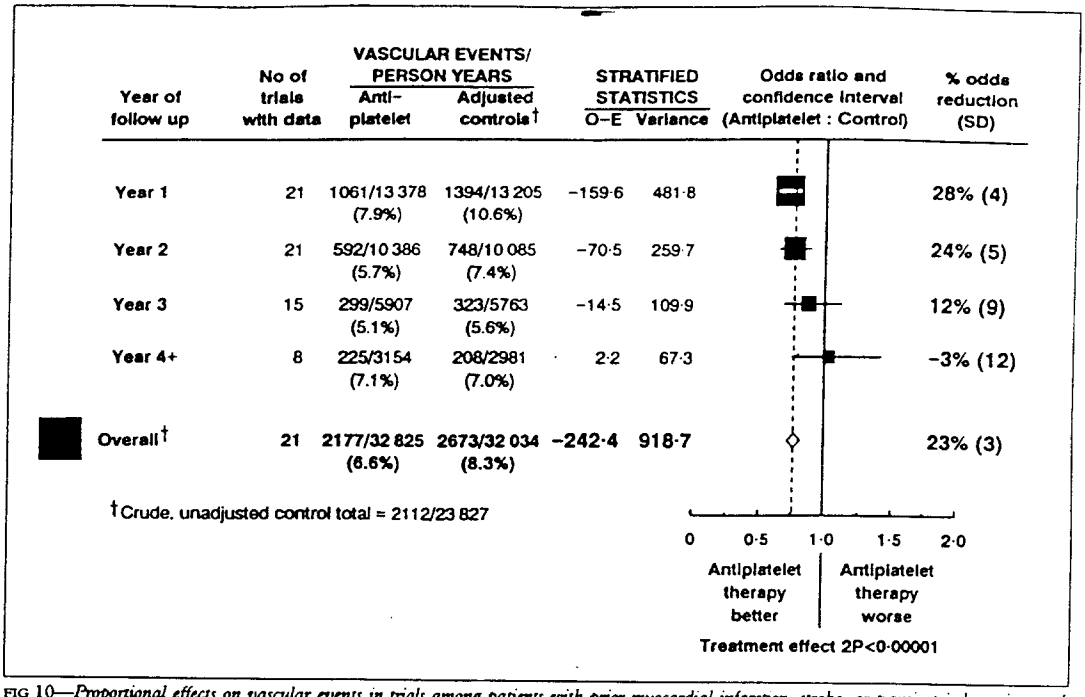


FIG 10—*Proportional effects on vascular events in trials among patients with prior myocardial infarction, stroke, or transient ischaemic attack showing additional benefits during different time periods of antiplatelet therapy. (Twenty one trials with more than one year of treatment and separate information on each patient.) Symbols and conventions as in figures 1 and 2. In the three primary prevention trials, comparable stratified observed minus expected and variance statistics were −12·5 and 51·3 (year 1); −7·2 and 56·1 (year 2); −3·5 and 50·3 (year 3); −12·2 and 51·4 (year 4); and 0·3 and 70·4 (year 5)*

the evidence of benefit in all categories of high risk patients that have been studied extensively (fig 2) and partly on the common sense notion that if antiplatelet therapy averts a certain proportion of occlusive vascular events in one category of patients, then although the proportion averted in another category may not be identical it is unlikely to be vastly different—and, in particular, is extremely unlikely to be zero. (The mathematical theory of James-Stein estimators[9] provides formal statistical support for this emphasis on the overall results.) It would therefore be inappropriate to draw conclusions about each small subcategory that are based only on the results from that subcategory.

Compare, for example, the apparently contrasting effects in figure 6 of antiplatelet therapy on vascular events in the trials among patients with coronary artery disease who had undergone percutaneous transluminal coronary angioplasty (32/663 *v* 61/669, an apparent halving of risk that was highly significantly different from zero) and among those who had undergone coronary artery bypass grafting (124/2529 *v* 127/2546, showing no apparent difference from zero). It is not reasonable to suppose that antiplatelet therapy halves vascular events during the months after angioplasty but has no effect on them in the months after bypass surgery, especially as we know (part II[3]) that some months of antiplatelet therapy after bypass surgery produces a massively significant reduction in the likelihood (measured angiographically) of the bypass becoming occluded.

Consequently, even though this overview of existing data does not provide *direct* evidence of benefit among certain categories of patient at high risk of occlusive vascular disease that have not been extensively studied, it provides *indirect* evidence that the net effects would be beneficial, unless there is some particular reason to expect serious side effects. It is possible to extrapolate too far and so reach mistaken conclusions that lead to inappropriate treatment, but it is also possible that taking too formal a view of the existing evidence and not extrapolating far enough may lead to inappropriately restrictive treatment policies that deny antiplatelet therapy to many patients who would benefit. Thus the information from trials in this overview may provide useful guidance in the treatment of a far wider range of high risk patients than just those studied, although the further the extrapolation the more desirable it might be to have direct evidence.

In particular, directly randomised evidence will certainly be needed in those conditions (such as acute stroke) where there are special risks of bleeding with antiplatelet therapy that might outweigh the reduction in occlusive disease (and for acute stroke this is currently being sought in the international stroke trial[125]). In other circumstances, however, it would be

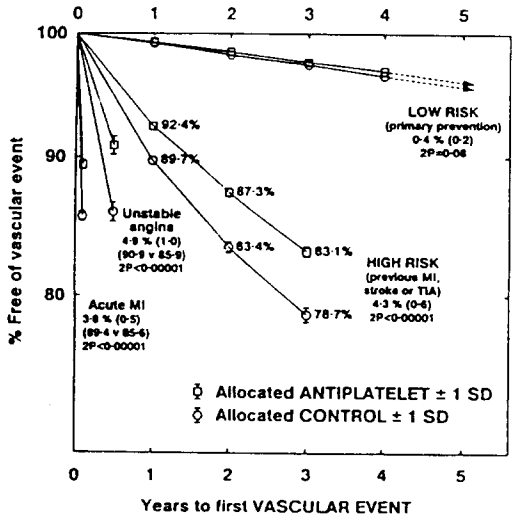


FIG 11—*Years to first vascular event after randomisation (stroke, myocardial infarction, or vascular death) in the 32 trials of antiplatelet therapy with separate information on each patient*

(Adaptation of standard life table method permitting unbiased combination of information from heterogeneous trials[11] was used to plot year by year results from figure 10 for high risk patients with previous myocardial infarction, stroke, or transient ischaemic attack and for primary prevention among low risk subjects. Median treatment duration was used to plot overall results from figure 6 for trials in acute myocardial infarction (one month) and in unstable angina (six months))

reasonable to infer that, provided there was no definite contraindication, antiplatelet therapy would probably be of net benefit for all categories of patients who are currently at high risk of occlusive vascular disease. Support for this conclusion is provided by studies reported after March 1990. For example, this overview included only about 600 patients with stable angina and did not on its own show clearly for such patients that antiplatelet therapy reduced the risk of vascular events. But after adding the recently reported results for vascular events from the SAPAT study in stable angina[279] (111/1009 aspirin *v* 159/1026 placebo; appendix 1) and the United States Physicians' health study[426] of patients who had stable angina at entry (24/178 aspirin *v* 25/155 placebo) there was a highly significant 33% (SD 9%) benefit ($2P < 0.0005$) among the new total of 3000 patients with stable angina, which was similar to the benefit in other high risk patient categories.

In contrast, for people whose absolute rates of ischaemic events are low (for example, "primary prevention" among apparently healthy people) or for people who are at particularly high risk of a major haemorrhagic event (for example, those with a recent history of possible cerebral haemorrhage) even a small increase in serious haemorrhagic events might outweigh the expected decrease in ischaemic events. For example, in the low risk primary prevention studies conducted so far, the non-significant reduction in vascular events ($2P = 0.09$; fig 3) combines a definite reduction in non-fatal myocardial infarction (29% (SD 8%) decrease; $2P < 0.0005$), a possible increase in non-fatal stroke (21% (SD 13%) increase; NS), and no apparent effect on vascular mortality (2% (SD 10%) reduction). Because of this uncertainty and because the numbers to whom this could be relevant are so large, more directly randomised evidence is needed on whether long term prophylactic antiplatelet therapy produces any worthwhile net benefit in "primary" prevention, both among subjects with raised levels of coronary risk factors (hypercholesterolaemia, hypertension, renal disease, etc) and among those without. Both are being sought (for example, in the thrombosis prevention trial,[309] the planned British Hypertension Society study, and the United States Women's Health study[427]).

BENEFIT IRRESPECTIVE OF AGE, SEX, BLOOD PRESSURE, AND DIABETES

In those studies of high risk subjects in which individual patient data were obtained, separate analyses were planned among older (aged 65 or over) and younger patients, among women and men, among hypertensive (diastolic blood pressure 90 mm Hg or over) and "normotensive" patients, and among diabetic and non-diabetic patients. In each case antiplatelet therapy for high risk patients appeared to reduce the odds of vascular events by a roughly similar proportion (fig 7). Thus the notion that women might not benefit from antiplatelet therapy (which arose from data dependent subgroup analyses of a few trials[57-59]) is contradicted by these much more reliable, prospectively planned overview analyses. Older patients, patients with hypertension, and diabetics tend to be at higher than average risk of vascular events, and if the proportional benefit is similar, then the absolute benefits of antiplatelet therapy may be greater than average among them (fig 7), certainly in the first few years of treatment. (Additional evidence among diabetic patients has recently been provided by the large ETDRS trial of five years of aspirin[282]; no special hazards of antiplatelet therapy for diabetics were seen[283] and vascular events appeared to be reduced, though not significantly (350/1856 *v* 379/1855 (NS); appendix 1).)

LACK OF EVIDENCE OF DIFFERENCES BETWEEN DIFFERENT ANTIPLATELET REGIMENS

Most of the trials tested aspirin, although a substantial minority tested other drugs. Two main questions may therefore be addressed. Firstly, if aspirin is to be used as the only drug, which range of doses seems most promising? Secondly, is some other antiplatelet drug or combination of drugs better than aspirin alone?

Aspirin pharmacology

Within a few days of beginning treatment with at least 75 mg aspirin daily the enzyme cyclo-oxygenase is virtually completely inhibited, both in platelets (producing an antithrombotic effect) and in arterial walls (which may possibly produce some impairment of the antithrombotic effect by reducing prostacyclin production in the vascular endothelium, although the relevance of this is disputed).[428-431] It is not known whether doses somewhat lower than this have a greater or lesser therapeutic effect. At 75 mg or more daily, however, across the 20-fold range of doses up to 1500 mg/day that have been studied widely in the trials in this overview, the pharmacological evidence on cyclo-oxygenase gives no reason to expect any material difference either on platelets or on vessel walls between different daily doses. Nevertheless, to achieve virtually complete inhibition immediately, aspirin treatment in emergency situations such as acute myocardial infarction, unstable angina, or crescendo transient ischaemic attack should perhaps begin for the first few days with a daily dose of at least 160 mg (as in the ISIS-2 trial[43]) or even about 300 mg.[432]

Aspirin regimens

The randomised evidence now available for comparing the effects of different antiplatelet regimens on the incidence of vascular events includes not only the trials in figures 8 and 9 but also five, more recent, major trials of aspirin (SALT,[277] SAPAT,[279] ETDRS,[282] Dutch TIA,[284] and EAFT[285]), the results of which are given in appendices 1 and 2. These increase from 3000 to 6000 the total number in figure 9 of high risk patients in trials of less than 160 mg aspirin daily. A total of 5000 of these patients were in trials of exactly 75 mg/day, and among them there was a very definite reduction in vascular events (351/2495 *v* 470/2517; odds reduction 29% (SD 7%) ($2P < 0.0001$)). Thus as well as the clear evidence in figure 9 that doses of 160-325 mg aspirin daily are effective (odds reduction 28% (SD 3%)), there is now strong evidence that doses of 75-160 mg/day are similarly effective. There is as yet, however, no statistically reliable trial evidence about the main effects of much lower doses. Indeed, in the only major trial that directly compares these lower doses with higher doses[284] the results for vascular events were compatible with a difference of 10-15% in either direction (appendix 2).

With respect to much higher doses, figures 8 and 9 suggest that doses of about 1000 mg/day (that is, at least 10 times more than is needed to inhibit cyclo-oxygenase dependent platelet aggregation), which were widely studied in the earlier trials, are no more effective than the "medium" doses of 75-325 mg/day that have now been more widely studied. It has been suggested that only for patients with a prior stroke or transient ischaemic attack[433] doses as high as 1000 mg/day may be preferable, although the trials provide little evidence for this. Even if attention were restricted just to patients with such cerebrovascular disease (including those in the recently reported SALT trial of 75 mg aspirin daily; appendix 1) there would be no significant difference between the protective effects of medium and of high doses of aspirin. However, the amount of evidence just on cerebrovascular patients in

aspirin trials is too limited for further subdivision of it into different aspirin regimens to be reliably informative. More important, in the unrestricted analyses in figures 2, 4, and 7 (and 9) there is approximate homogeneity of the effects of antiplatelet therapy, indicating that evidence from different types of patients can and should be combined. Hence it is neither necessary nor appropriate to review the evidence on aspirin dosage from cerebrovascular patients independently of that from other high risk patients.

Other antiplatelet regimens

After aspirin alone, the three most widely studied antiplatelet regimens in these trials were aspirin plus dipyridamole in combination, sulphinpyrazone, and ticlopidine. Significant reductions in vascular events were seen with each of these. But neither the directly randomised comparisons of them against aspirin alone (fig 8) nor the indirect comparisons between the trials of them versus control and the trials of aspirin versus control (fig 9) provided clear evidence of any greater or lesser effects with regimens based on these other drugs than with regimens based on aspirin alone.

Implications

Medium dose aspirin (75-325 mg/day) is now the most widely tested antiplatelet regimen and hence has the most extensive evidence of benefit among high risk patients. No other drug regimen in these trials has been shown to be significantly more effective than aspirin alone (figs 8, 9), and the protective effects of aspirin seem to be at least as great with medium doses as with higher and hence more gastrotoxic[424] doses (figs 8, 9). At present, therefore, on grounds of convenience and proved efficacy a medium dose aspirin regimen might be a reasonable first choice for patients who need routine antiplatelet therapy, except for the small minority with a clear contraindication to aspirin (for example, definite allergy or severe gastric symptoms even with medium dose enteric coated formulations). For these, some other antiplatelet drug (for example, ticlopidine) might be more appropriate.

The lack of any statistically significant differences between various antiplatelet regimens does not necessarily mean that those regimens are exactly equivalent. For example, although the direct comparisons of aspirin plus dipyridamole versus aspirin alone indicated that dipyridamole produces no worthwhile additional reduction in vascular events (316/2661 with aspirin plus dipyridamole *v* 312/2656 with aspirin alone; fig 8), it does not prove this. Similarly, although the direct comparisons of ticlopidine versus aspirin are non-significantly favourable to ticlopidine, the results are consistent with ticlopidine being either a little better or a little worse than aspirin. But figures 8 and 9 suggest that if there are real differences between one antiplatelet regimen and another in their effects on vascular events, then these differences are unlikely to be large. If, therefore, antiplatelet regimens are to be shown to differ from each other then direct randomised comparisons may be needed that are (in aggregate) of sufficient size, with a total of a few thousand vascular events, to detect the sort of moderate additional effects (perhaps involving odds reductions of only about 10% or, at most, 20%) that could realistically be hoped for in comparisons of other antiplatelet treatments against 75-325 mg aspirin daily.

OPTIMAL DURATION OF ANTIPLATELET TREATMENT

It is difficult to determine directly from the trials how long antiplatelet therapy should be continued, as there are as yet no large directly randomised comparisons of different durations of treatment. For those trials among patients with a history of myocardial infarction, stroke, or transient ischaemic attack that provided individual patient data, information was available on events occurring during the first, second, and subsequent years of the scheduled treatment period. There was an apparent pattern (figs 10, 11), of a greater effect during the earlier years which superficially suggested that the additional effects of antiplatelet therapy become smaller as treatment is continued. There are, however, difficulties in interpreting such patterns.

Firstly, as time goes by, non-compliance with allocated treatment (that is, stopping antiplatelet therapy in the treatment group and starting it in the control group, perhaps when non-fatal events occur) tends to increase so that any underestimation of the effects of actually using treatment provided by these "intention to treat" analyses tends to be more serious during later years (see below). Secondly, patients remaining at risk of a first event in the treatment group include some who would, in the absence of treatment, already have suffered a vascular event, biasing the comparisons in later years. In the absence of evidence to the contrary from some extensive direct randomised comparisons of different durations of antiplatelet therapy, therefore, it may be prudent to consider indefinite continuation of antiplatelet therapy in patients who remain at high risk of occlusive vascular events, unless some clear contraindication develops.

SIZE OF REDUCTIONS IN RISK PRODUCED BY THERAPY

Figure 11 illustrates the results of the intention to treat analyses that have, to avoid bias, been used throughout this overview. But because there is likely to be some non-compliance in both treatment and control groups in large trials, these analyses slightly underestimate the size of the effect produced by actually taking antiplatelet treatment. This is true for non-fatal events (such as the first non-fatal myocardial infarction or non-fatal stroke during the trial) that are typically of sudden onset, but it may be even more true for vascular death, as death may be preceded by some illness that results in deviations from the allocated trial treatment. Indeed, in some studies the occurrence of a non-fatal vascular event was to be a reason for stopping trial medication. Conversely, control patients thought to be at some particular risk of death, perhaps because they have suffered a non-fatal vascular event, may start taking antiplatelet treatment. In the main trials of prolonged antiplatelet therapy among patients with a history of prior myocardial infarction, stroke, or transient ischaemic attack the average compliance one year after randomisation appeared to have been no more than 80% (and in the months just before a vascular death it may well have been even less).[1] Hence the proportional reductions of about 15% in vascular death and 30% in non-fatal vascular events observed in these trials may reflect proportional reductions of about 20% and 35% respectively with actual use of antiplatelet therapy.

From a medical viewpoint what chiefly matters is not the proportional reduction in risk but the absolute reduction in risk. The results of the overview suggest that, at least among patients at particular risk of occlusive vascular disease (but possibly not in primary prevention among healthy subjects), the proportional risk reductions may be roughly similar in different categories of patients. Consequently, in estimating the absolute reduction in risk likely to be produced by antiplatelet therapy what matters most may not be whether the proportional reduction in vascular death is 15% or 20% but whether the absolute risk is "high" or "low." In patients at particularly high risk of vascular events the benefits of the actual use of antiplatelet therapy are large. For example, among 1000 patients with acute myocardial infarction about 40 vascular events would typically be prevented during the first

Clinical implications

- Antiplatelet therapy protects a wider range of patients at high risk of occlusive vascular disease than is currently treated routinely: it should be considered for almost all with suspected acute myocardial infarction, unstable angina, or a history of myocardial infarction, angina, stroke, transient ischaemic attack, arterial bypass surgery, or angioplasty
- There is, as yet, no clear evidence that antiplatelet therapy is indicated for routine use in "primary prevention" subjects at low risk of occlusive vascular events
- Medium dose aspirin (75-325 mg/day) is the most widely tested antiplatelet regimen, and no other regimen appeared significantly more effective at preventing myocardial infarction, stroke, or death

month and about a further 40 would be prevented in the next couple of years. And similar sized benefits are likely to be seen with prolonged antiplatelet therapy after stroke or transient ischaemic attack.

Even in a patient population at intermediate risk (such as patients with a history of stable angina, other cardiac disease, atrial fibrillation, or peripheral vascular disease), with "only" about a 5% risk of vascular death and an additional 5% risk of a non-fatal vascular event during two years of treatment, antiplatelet therapy would be expected to prevent about 10 deaths and 20 non-fatal events for every 1000 such patients treated. These benefits, which are now extraordinarily definitely established, compare very favourably to those of other treatments that are currently in wide use. Hence unless some specific 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.

Since the inception of this collaboration several years ago, staff and computing have been provided for the clinical secretariat in Edinburgh by grants from the Medical Research Council (United Kingdom), the Chest, Heart, and Stroke Association (United Kingdom and Scotland), and Edinburgh University (Sir Stanley and Lady Davidson Fund); and for the statistical secretariat by the Clinical Trial Service Unit (Nuffield Department of Clinical Medicine, University of Oxford), which is supported by the Medical Research Council, the British Heart Foundation, and the Imperial Cancer Research Fund, and by a Harvard visiting professorship for R Peto. In addition, support was provided (in ignorance of the final results) by Boehringer Ingelheim (UK), Ciba Geigy (USA), EISAI (Europe), European Aspirin Foundation, Glaxo (UK), Glenbrook Laboratories Division of Sterling Drugs (USA), ICI (UK), Lilly (UK), Reckitt and Colman (UK), and Sanofi (Europe).

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Appendix 1

INDIVIDUAL RESULTS OF UNCONFOUNDED RANDOMISED COMPARISONS OF PROLONGED ANTIPLATELET THERAPY (SCHEDULED DURATION ONE MONTH OR MORE) WITH CONTROL (A *v* C)

Trial name†	Reference No	Data provided‡	Regimen§	Months scheduled	No of patients A	No of patients C	Non-fatal myocardial infarction A	Non-fatal myocardial infarction C	Non-fatal stroke A	Non-fatal stroke C	Vascular death or not known A	Vascular death or not known C	Vascular events A	Vascular events C	Pulmonary embolism A	Pulmonary embolism C	Non-vascular death A	Non-vascular death C	Non-fatal major bleed A	Non-fatal major bleed C	Lost to follow up A	Lost to follow up C
Prior myocardial infarction																						
Cardiff-I	18, 19	AS—	A300	13	615	624	10	15	—	—	47	61	57	76	1	0	2	4	—	—	3	2
Cardiff-II	20, 21	ASBD	A900	12	847	878	31	64	—	—	98	122	129	186	1	1	5	5	—	—	0	0
PARIS-I	22, 23	ASBD	A972, A+Dip	41	1620	406×4‖	103	34	14	3	147	45	262	82	1	0	26	7	—	—	0	0
PARIS-II	24	ASBD	A990+Dip	23	1563	1565	64	104	18	30	98	105	179	235	3	1	13	9	—	—	6	2
AMIS	25, 26	ASBD	A1000	38	2267	2257	140	173	29	49	214	199	379	411	0	1	32	20	—	—	5	4
CDP-A	27-29	ASBD	A972	22	758	771	27	32	7	9	43	61	76	102	1	0	2	4	—	—	0	0
GAMIS	30-32	AS-D	A1500	17	317	309	11	15	0	0	22	30	33	45	—	—	5	2	—	—	112	103
ART	33-36	ASBD	Sp	20	813	816	33	38	4	10	65	82	102	130	0	0	9	7	—	—	0	0
ARIS	37	ASBD	Sp	30	365	362	14	26	1	4	25	25	40	55	0	0	4	2	0	0	3	2
Micristin	38, 39		A1500	24	672	668	22	35	9	15	34	56	65	106	6	8	15	15	2	2	11	13
Rome	40		Dip	72	40	40	5	7	—	—	4	12	9	19	0	0	0	0	—	—	0	0
Acute myocardial infarction																						
Gent AMI	41		Dip	1	60	60	2	4	1	0	8	3	11	7	2	0	1	0	—	—	2	2
ISIS pilot	42	AS-D	A325/48 h	1	313	306	7	9	1	2	25	35	33	46	—	—	0	0	1	1	47	61
ISIS-2	43	AS-D	A160	1	8587	8600	74	161	29	52	815	1026	915	1236	1	1	2	7	24	18	250	251
French	44		Flurbiprofen	6	234	230	7	23	—	—	2	3	9	26	0	0	0	0	1	1	0	0
Dutch-sulphinpyrazone	45		Sp	1	50	50	0	0	0	0	2	4	2	4	0	0	0	0	0	0	0	0
Dutch-aspirin	46-48	AS—	A100	3	50	50	2	6	1	0	9	12	12	18	0	1	0	0	0	0	0	0
Huddinge	49		A167	12	10	10	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Jones	50		Dazmxiben	1	60	60	—	—	—	—	10	11	10	11	0	1	—	—	—	—	0	0
Kausden-A	51		Ticlopidine	3	24	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
{Cardiff-III}	249		A300 (once only)	<1	1249	1281	—	—	—	—	159	172	159	172	0	0	0	0	—	—	422	403
{Johannessen}	250		A150+Dip	<1	11	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
{Wilcox}	251		Sp	<1	49	49	—	—	—	—	5	1	5	1	0	0	0	0	—	—	0	0
{Den Ottolander}	252		A1500+RA233	<1	14	14	0	0	0	0	3	3	3	3	2	2	—	—	0	0	0	0
{GRAND}	253		GR32191B	<1	63	64	0	2	0	0	3	5	3	7	0	0	0	0	0	0	1	0
{Frankfurt}	254		A1320, A+Dip	<1	25	14×2	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0
Prior stroke/transient ischaemic attack																						
AFTIA	52-54	AS—	A1300	17	162	157	4	2	12	20	10	13	26	35	—	—	0	3	3	0	59	51
Reuther	55, 56	AS-D	A1500	24	30	30	0	0	2	2	0	3	2	5	—	—	0	0	0	1	0	0
Canadian cooperative‡‡	57-59	ASBD	A1300, Sp, A+Sp	34	446	139×3	16	0	58	15	29	15	100	30	0	0	12	2	—	—	16	4
Toulouse-TIA	60, 61	AS—	A900, A+Dip	34	284	156×2	0	2	5	7	18	7	23	16	—	—	11	5	—	—	15	15
AICLA	62, 63	ASBD	A990, A+Dip	36	400	204×2	4	9	32	25	25	12	61	46	0	0	11	6	0	0	0	0
Danish cooperative	64	ASBD	A1000	33	101	102	2	8	14	12	8	8	23	27	—	—	3	2	0	0	0	0
Britton	65	AS-D	A1500	24	253	252	11	10	22	18	28	29	59	55	—	—	6	8	3	0	2	2
Danish low dose	66	ASBD	A50-100 (average 54)	23	150	151	0	2	8	12	13	7	21	21	—	—	1	3	—	—	46	44
ESPS-1	67, 68	ASBD	A975+Dip	23	1250	1250	21	35	83	128	79	105	183	263	5	5	28	50	—	—	12	8
UK-TIA	69, 70	ASBD	A300, A1200	50	1621	814×2	39	32	126	83	180	86	342	193	0	1	41	36	9	0	5	4
Stoke	71, 72		Dip	25	85	84	—	—	12	11	11	9	23	20	0	0	2	0	—	—	15	12
Memphis	73		Sp	48	73	75	—	—	10	6	9	16	19	22	0	0	0	0	—	—	0	0
Blakely-stroke	74	AS—	Sp	38	143	147	0	1	3	2	30	39	33	42	0	0	16	13	—	—	12	12
CATS	75, 76		Ticlopidine	28	531	541	9	15	64	85	35	43	108	143	2	0	31	22	—	—	3	1
Gent-stroke	77	AS—	Sulocridil	25	222	225	3	4	23	22	21	31	47	57	—	—	16	17	0	0	0	3
Ross Russell	78		Ticlopidine	3	11	11	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Birmingham-B	79		Sp	4	50	50	0	0	0	2	1	2	1	4	0	0	0	0	1	0	9	1
Charing Cross	80		Sp	18	25	30	—	—	5	5	0	2	5	7	0	0	0	0	—	—	0	0
{Toulouse-II}	255		A990+Dip	<1	40	40	—	—	—	—	7	5	7	5	1	0	0	0	—	—	0	0
{McKenna-III}	256		Ticlopidine	<1	27	26	0	0	2	0	0	2	2	2	0	2	0	0	0	0	0	0
{SALT}	277		A75	32	676	684	36	40	77	102	50	51	163	193	—	—	11	18	10	6	0	0
Acute stroke																						
Tokyo	81		Ticlopidine	2	15	14	—	—	2	1	0	2	2	3	0	0	0	0	0	0	0	0
{Ciuffetti}	257		Ticlopidine	<1	15	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carotid endarterectomy																						
{Toronto}	258		A990+Dip	<1	10	12	0	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0
{Bologna}	259		Ticlopidine	<1	14	17		0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
{McCollum}	260		Indobufen	<1	20	20	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Unstable angina																						
VA pilot	82	ASBD	A324	3	26	24	0	1	0	0	1	3	1	4	0	0	0	0	0	0	0	0
VA main	83	ASBD	A324	3	661	677	27	49	3	2	15	24	45	75	0	0	0	0	0	0	0	4
Canadian	84	ASBD	A1300, Sp, A+Sp	20	416	139×3	24	7	4	0	28	13	54	20	0	0	3	0	1	0	3	1
RISC	85-87		A75	14	474	471	36	69	1	0	9	16	46	85	0	0	2	2	0	0	0	0
ALDUSA pilot	88		A325, A40	12	56	28×2	5	0	1	0	1	1	7	1	0	0	0	0	—	—	0	0
STAI††	89, 90	ASBD	Ticlopidine	5	314	338	15	30	0	2	8	16	23	48	0	0	0	0	—	—	74	87
Prandoni	91	ASBD	A50+Dip	12	44	44	5	11	0	0	1	0	6	11	0	0	1	0	—	—	0	0
{Théroux}	261		A650	<1	243	236	6	12	0	0	0	2	6	14	—	—	0	0	4	2	0	0
{Florida UA}	262		Ticlopidine	<1	12	12	2	2	0	0	0	0	2	2	0	0	0	0	0	0	0	0
Post-coronary artery bypass grafting																						
McEnany	92		A1200	18	71	77	0	2	0	0	1	3	1	5	2	1	0	0	0	0	0	0
Brooks	93, 94		A990+Dip	12	160	160	—	—	—	—	8	4	8	4	0	0	0	0	3	1	0	0
Mayo-A	95-97		A975+Dip	12	202	205	—	—	—	—	5	6	5	6	0	0	—	—	0	1	0	0
Liege-I	98-100		Ticlopidine	3	75	75	0	0	0	1	0	1	0	2	3	1	0	0	0	0	0	1
Liège-II	101, 102		Ticlopidine	12	88	87	1	3	0	2	2	1	3	6	1	2	0	2	0	0	0	0
Pantely	103		A975+Dip	6	18	30	0	0	0	0	0	0	0	0	0	1	0	0	0	0	3	2
Wadsworth	104		A975, A+Dip	12	96	51×2	—	—	1	1	2	1	3	2	0	0	0	0	—	—	0	0
Lorenz	105, 106		A100	4	29	31	0	1	0	1	2	2	2	4	0	1	0	0	0	0	0	0
VA cooperative CABG	107, 108		A325, A975, Sp, A975+Dip	12	619	153×4	40	11	5	3	22	2	67	16	5	3	4	3	30	2	44	8
Brussels	109		A200+Dip	12	24	25	1	2	0	1	1	0	2	3	0	0	0	0	—	—	4	5
GESIC	110		A150, A+Dip	1	741	371×2	—	—	—	—	22	5	22	5	5	1	0	0	16	5	0	0
Basle	111		A50+Dip	9	62	63	0	1	—	—	0	0	0	1	0	0	0	0	0	0	0	0
Leeds-B	112		A990+Dip	6	61	64	0	0	0	0	1	1	1	1	0	0	0	0	1	1	0	0
Czech	113		A1000+Dip	12	47	46	0	2	0	0	0	1	0	3	0	0	0	0	0	0	0	0
Thaulow	114		A1000+Dip	3	34	35	0	2	0	0	1	1	1	3	1	0	0	0	2	0	0	0
Guiteras	115		A150+Dip	7	72	68	0	0	0	0	5	3	5	3	0	1	0	2	0	0	7	4
Sydney	116		A324	12	68	69	—	—	—	—	—	—	—	—	—	—	—	—	1	0	0	0
Des Moines	117		A20+Dip	12	60	54	—	—	0	1	—	—	0	1	—	—	—	—	—	—	0	0
Zurich	118		Ticlopidine	3	50	50	4	7	0	0	0	0	4	7	0	0	0	0	12	2	0	0
Knudsen-B	119		Ticlopidine	6	9	10	—	—	—	—	—	—	—	—	—	—	—	—	1	0	0	0
Romeo	120		Ticlopidine	3	20	20	—	—	—	—	0	0	0	0	0	0	0	0	—	—	0	0
Cade	121		Sp	6	22	22	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Green	122		A600	1	12	15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
{Baur}	263		Sp	<1	130	125	8	3	0	0	1	0	9	3	0	0	0	0	0	0	0	0
{Kohn}	264		Ticlopidine	<1	21	12×2	—	—	—	—	0	0	0	0	0	0	0	0	1	0	0	0
{Toronto dipyridamole-I}	265		Dip	<1	20	20	1	0	—	—	0	0	1	0	0	0	0	0	—	—	0	0
{Toronto dipyridamole-II}	266		A975+Dip, Dip	<1	40	18×2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Post-percutaneous transluminal coronary angioplasty																						
TACT	123		Ticlopidine	6	177	173	5	10	1	1	1	0	7	11	1	0	0	0	0	0	0	0
Toronto	124		A990+Dip	6	187	189	7	25	0	0	0	0	7	25	0	0	0	0	0	0	6	4
White	125, 126		A650+Dip, ticlopidine	6	245	127×2	14	10	0	1	2	1	16	12	0	0	0	0	0	0	0	0
Finci	127		Sulotroban	6	54	53	2	0	0	0	0	1	2	1	0	1	0	0	0	0	0	0
Stable angina/coronary artery disease																						
Atlanta	128		Dip	6	30	30	3	4	1	0	1	0	5	4	0	0	0	0	0	0	0	0
Becker	129		Dip	6	14	13	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0
Mayo-B	130		A975+Dip	54	185	185	10	22	0	4	11	12	21	38	0	0	0	0	0	0	0	0
Berglund	131, 132		Ticlopidine	2	21	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mexican	133		Dip	3	20	20	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0

Continued on next page

Appendix 1 (continued)

Trial name†	Reference No	Data provided‡	Regimen§	Months scheduled	No of patients A	No of patients C	Non-fatal myocardial infarction A	Non-fatal myocardial infarction C	Non-fatal stroke A	Non-fatal stroke C	Vascular death or not known A	Vascular death or not known C	Vascular events A	Vascular events C	Pulmonary embolism A	Pulmonary embolism C	Non-vascular death A	Non-vascular death C	Non-fatal major bleed A	Non-fatal major bleed C	Lost to follow up A	Lost to follow up C
Stable angina/coronary artery disease (continued)																						
Wirecki	134		Dip	7	28	28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Brown	135		A975+Dip	18	24	23	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
{Parry}	267		Dazoxiben, A250	<1	12	6×2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
[SAPAT]	279		A75	50	1009	1026	40	61	21	27	53	71	111	159	—	—	29	35	11	8	0	0
Atrial fibrillation																						
SPAF	136-138		A325	30	552	568	8	8	16	36	25	35	49	79	0	0	14	15	6	8	0	0
AFASAK	139, 140		A75	12	336	336	—	—	10	13	23	21	33	34	2	1	5	9	1	0	0	0
[EAFT]	293		A300	27	404	378	8	8	87	85	29	34	124	127	—	—	24	21	4	3	0	0
Rheumatic valve disease																						
Steele-RHD	141		Sp	48	78	76	0	0	2	10	7	7	9	17	0	0	0	1	0	0	2	16
Valve surgery																						
Sullivan	142, 143		Dip	12	79	84	2	1	3	9	10	8	15	18	2	0	2	2	2	5	0	0
Altman	144		A500	24	65	69	0	0	0	3	2	3	2	6	0	0	0	1	4	3	0	0
Norwegian	145		A1000	24	75	73	0	1	4	5	2	4	6	10	0	0	1	2	0	0	2	2
PACTE	146, 147		Dip	12	183	202	0	1	1	2	10	25	11	28	0	0	0	9	0	1	46	36
Leeds-A	148		Dip	27	68	87	0	0	1	7	6	7	7	14	0	0	2	0	—	—	0	0
Starkman	149		Dip	12	132	127	—	—	—	—	5	3	5	3	0	0	0	0	—	—	33	14
Ciavarella	150		Dip	1	25	25	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Intermittent claudication																						
VA cooperative	151, 152		A975+Dip	48	110	121	10	8	2	7	24	25	36	40	0	0	13	12	1	1	0	3
Hess	153		A990, A+Dip	24	160	80×2	2	0	0	3	3	0	5	3	0	0	2	0	0	0	0	0
STIMS	154		Ticlopidine	67	346	341	45	42	18	19	28	47	91	108	1	0	20	19	0	0	0	0
Aukland	155		Ticlopidine	12	33	32	0	1	0	0	1	1	1	2	0	0	0	0	0	0	7	4
ACT	156, 157		Ticlopidine	6	83	86	0	0	0	3	0	0	0	3	0	0	1	1	0	0	0	0
US ticlopidine	158		Ticlopidine	6	100	103	0	1	1	1	1	3	2	5	0	0	0	0	1	0	0	0
Stiegler	159		Ticlopidine	24	57	57	0	0	0	0	1	1	1	1	0	0	1	0	1	0	0	0
Schoop-I	160-162		A990, A+Dip	60	200	100×2	4	3	2	0	8	4	14	7	1	1	2	0	3	0	10	4
Kalkar	163		Sulocidil	6	18	22	0	1	0	0	0	0	0	1	0	0	0	1	0	0	1	2
Katsumura	164		Ticlopidine	1	93	100	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0
Coccheri	165		Ticlopidine	21	76	75	1	0	0	1	0	1	1	2	0	0	1	2	0	0	5	4
Hurlow	166		Ticlopidine	2	30	10×3	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Louvain-I	167		Sulocidil	2	15	15	—	—	—	—	0	1	0	1	—	—	0	0	—	—	0	0
Munich-A	168		A1500	24	92	84	2	2	1	0	2	4	5	6	1	0	1	0	2	0	0	0
Munich-B	168		A1500	24	42	40	1	0	0	1	3	1	4	2	0	1	1	1	1	1	2	2
Domenech Amar	169		Triflusal	6	50	50	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
London-A	170		Ticlopidine	12	8	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
London-B	171		Ticlopidine	2	15	8×2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Portsmouth-B	172		Ticlopidine	6	17	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bourde	173, 174		Ticlopidine	1	14	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Holm	175		Sulocidil	9	20	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cloarec	176		Ticlopidine	6	66	66	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4
Signorini	177		Indobufen	6	28	24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3
Krause	178		Ticlopidine	3	19	19	—	—	—	—	0	0	0	0	0	0	0	0	0	0	0	0
Drouin	179		Ticlopidine	2	10	10	—	—	—	—	—	—	—	—	—	—	0	0	—	—	1	2
Louvain-II	180		Sulocidil	6	27	24	0	0	0	0	0	0	0	0	0	0	0	0	—	—	0	0
[ADEP]	294		Picotamide	18	1150	1154	13	16	10	11	15	18	38	45	—	—	5	4	—	—	57	59
Non-coronary grafting																						
Rochester	181		A975, A+Dip	12	32	17×2	0	0	1	0	2	0	3	0	0	0	0	0	1	0	0	0
McCollum	182		A660+Dip	30	286	263	14	6	14	16	25	39	53	61	0	4	15	7	3	3	9	16
Kester	183, 184		A990+Dip	12	33	32	0	0	0	0	4	0	4	0	0	0	0	0	0	0	9	1
Kohler	185		A975+Dip	24	50	50	—	—	—	—	2	2	2	2	0	0	2	0	—	—	4	2
Loew bypass	186, 187		A1500	12	215	213	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0
Schettler	188		Sp	6	33	30	0	1	0	0	2	0	2	1	0	0	0	0	—	—	0	0
Blakely-PVD	189		Sp	36	75	90	0	0	0	1	1	2	1	3	0	1	0	0	—	—	0	0
Baselini	190		Ticlopidine	6	25	25	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0
Goldman	191, 192		A975+Dip	12	22	31	—	—	—	—	0	2	0	2	0	0	0	0	—	—	0	0
{Zekert-IV}	268		A1500	<1	148	150	0	0	0	0	1	3	1	3	1	4	3	2	0	1	0	0
{Harjola}	269		A1500, A+Dip, Dip	<1	300	100×2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Peripheral angioplasty																						
Heiss	193, 194		A300+Dip, A990+Dip	6	132	67×2	3	2	1	1	1	1	5	4	0	0	0	0	0	0	3	3
Bern/Zurich	195		Sulocidil	12	62	61	—	—	0	0	0	0	0	0	0	0	2	2	1	0	0	0
Renal haemodialysis																						
Pineo	196-198		Sp	6	30	32	—	—	—	—	1	3	1	3	0	0	0	0	2	1	1	3
Majerus	199		A160	5	19	25	—	—	—	—	1	1	1	1	0	0	0	0	0	0	0	0
Andrassy	200		A500	1	47	45	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0
Japanese-A	201		Ticlopidine	3	50	57	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0
Portsmouth-A	202		Ticlopidine	3	24	26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Edinburgh	203		Ticlopidine	1	13	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
London-C	204		Ticlopidine	1	8	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Swedish	205		Ticlopidine	1	21	21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Heidelberg-A	206		Ticlopidine	1	36	33	—	—	—	—	0	0	0	0	0	0	0	0	0	0	0	0
Norfolk	207		Sp	3	8	8	—	—	—	—	0	1	0	1	0	0	0	0	0	1	0	0
Diabetes																						
Birmingham-A	208		Ticlopidine	2	20	8×2	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0
London diabetes	209		Ticlopidine	12	38	40	0	0	0	1	1	1	1	2	0	0	0	0	0	0	1	1
Dutch	210		Sp	32	30	31	1	1	1	1	2	0	4	2	0	0	0	0	0	0	0	0
DAMAD	211		A990, A+Dip	36	318	157×2	21	5	—	—	3	3	24	8	0	0	1	1	—	—	19	14
TIMAD	212		Ticlopidine	32	220	215	1	3	2	2	1	2	4	7	0	0	2	2	0	0	55	42
BTRS	213		Ticlopidine	48	49	51	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Nyberg	214		Ticlopidine	12	12	11	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Turin	215		Dip	36	16	15	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Barnett	216		UK38, 485	4	18	18	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
{ETDRS}¶	282, 283		A650	60	1856	1855	55	72	67	53	253	281	375	406	—	—	87	85	—	—	3	3
Deep venous thrombosis prophylaxis																					15	19
Erfurt-A	217, 218		A1500	1	357	357	0	0	0	0	0	3	0	3	0	3	0	0	3	0	3	6
Erfurt- B	218		A1500	2	44	44	0	0	0	0	5	5	5	5	5	5	0	0	0	0	0	0
Chicago	219		A600+Dip	1	13	15	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Denver-I	220		Sp	3	14	14	0	0	0	0	1	0	1	0	0	0	0	0	—	—	0	2
Denver-II	221		A1200+Dip	18	19	19	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Ontario DVT	222		Sp	8	15	16	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Miscellaneous																						
Hugonot-A	223		Ticlopidine	2	109	115	0	0	2	0	1	1	3	1	0	1	1	1	0	0	0	0
Hugonot-B	223		Ticlopidine	2	195	194	0	0	0	0	1	0	1	0	0	0	0	0	0	0	63	66
Meyer	224		A325	36	37	33	0	0	2	8	3	5	5	13	0	0	0	0	0	0	0	0
Dutch ocular	225		Ticlopidine	6	48	41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	3
{Bedford}	270		A600	<1	31	31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Low risk (primary prevention)																						
Geriatric	226	ASBD	Sp	43	142	150	—	—	—	—	43	41	43	41	—	—	35	33	—	—	0	0
UK doctors	227	ASBD	A500	70	3429	1710×2	87	38	57	23	147	79	288	140	4	0	123	72	20	7	2	0
US physicians	228, 229	ASBD	A325/48 h	60	11037	11034	129	211	109	91	91	92	321	387	27	23	126	135	48	27	0	0

— Data not supplied.

†Trials named within braces {} were those with duration less than one month (excluding short trials of deep venous thrombosis prophylaxis after surgery, reviewed in part III). Trials named within square brackets [] were major trials (around 1000 patients or more) for which results became available after March 1990 deadline for overview.

‡For trials with individual patient data only: A=age, S=sex, B=blood pressure, D=diabetes, —=data not supplied.

§A=Aspirin (expressed with daily dosage in mg). Dip=Dipyridamole. Sp=Sulphinpyrazone.

"×2," "×3," "×4" denote control groups counted twice, thrice, four times in adjusted totals to balance larger treatment groups.

¶Non-fatal event in early treatment diabetic retinopathy study defined as "survival to scheduled end of study or death from another cause."

††Patients lost to follow up included 60 of 56 withdrawals and 14 of 31 lost to mortality follow up after non-fatal myocardial infarction.

‡‡Data not available for 64 patients ruled ineligible after randomisation.

Appendix 2

UNCONFOUNDED RANDOMISED TRIALS COMPARING ONE PROLONGED ANTIPLATELET REGIMEN WITH ANOTHER (A1 v A2)

Trial name†	Reference No	Regimen‡	Months scheduled	No of patients		Non-fatal myocardial infarction		Non-fatal stroke		Vascular death or not known		Vascular events		Pulmonary embolism		Non-vascular death		Non-fatal major bleed		Lost to follow up	
				A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2
Prior myocardial infarction																					
PARIS-I	22, 23	A + Dip v A972	41	810	810	54	49	8	6	74	73	134	128	0	1	14	12	—	—	0	0
Acute myocardial infarction																					
Mitra	229	A1150 + Dip v Sp	2	25	25	0	0	0	0	2	1	2	1	0	0	0	0	0	0	0	0
(Pisa)†	275	A50 v A324	< 1	5	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
(Hart)	271	A + Dip v A1500	< 1	44	46	—	—	—	—	0	0	0	0	0	0	0	0	—	—	0	0
(Frankfurt)	254	A + Dip v A1320	< 1	11	14	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
Prior stroke/transient ischaemic attack																					
Canadian cooperative	57-59	Sp v A1300	34	156	144	8	4	29	17	12	11	47	32	0	0	5	3	—	—	6	2
Canadian cooperative	57-59	A1300 + Sp v Sp	34	146	156	4	8	12	29	6	12	21	47	0	0	4	5	—	—	8	6
Canadian cooperative	57-59	A + Sp v A1300	34	146	144	4	4	12	17	6	11	21	32	0	0	4	3	—	—	8	2
Toulouse-TIA	60, 61	A + Dip v A900	34	137	147	0	0	1	4	11	7	12	11	—	—	5	6	—	—	3	12
AICLA	62, 63	A + Dip v A990	36	202	198	2	2	16	16	12	13	30	31	0	0	5	6	0	0	0	0
UK-TIA	69, 70	A300 v A1200	50	806	815	21	18	63	63	91	89	174	168	0	0	18	23	5	4	2	3
TASS	231, 232	Ticlopidine v A1300	42	1529	1540	83	75	156	189	131	131	370	395	5	2	44	67	1	12	7	7
Japanese-B	233, 234	Ticlopidine v A500	12	170	170	1	1	7	13	1	2	8	16	0	0	0	0	—	—	0	0
ATIAIS	235	Sp v A1000	22	63	64	1	0	2	2	2	1	5	3	1	0	0	0	0	0	2	1
ACCSG	236-238	A + Dip v A1300	30	448	442	11	10	38	45	31	31	79	85	0	0	15	8	—	—	17	21
(Capildeo)	272	A + Dip v A900	< 1	88	95	0	0	0	0	6	3	6	3	1	0	3	2	1	0	0	0
(Dutch TIA)†	284	A30 v A283	31	1555	1576	36	27	87	105	105	107	225	235	—	—	55	44	—	—	0	0
Unstable angina																					
Canadian	84	Sp v A1300	20	140	139	6	9	0	1	14	8	20	17	0	0	1	1	0	0	1	2
Canadian	84	A1300 + Sp v Sp	20	137	140	9	6	3	0	6	14	17	20	0	0	1	1	1	0	0	1
Canadian	84	A + Sp v A1300	20	137	139	9	9	3	1	6	8	17	17	0	0	1	1	1	0	0	2
ALDUSA pilot	88	A40 v A325	12	28	28	1	4	1	0	0	1	2	5	0	0	0	0	—	—	0	0
Post-coronary artery bypass grafting																					
Sharma	239	A + Dip v A975	12	60	64	—	—	—	—	0	0	0	0	0	0	0	0	—	—	0	0
Wadsworth	104	A + Dip v A975	12	49	47	—	—	0	1	1	1	1	2	0	0	0	0	—	—	0	0
VA Cooperative CABG	107, 108	A + Dip v A975	12	162	155	10	10	1	2	7	6	18	18	2	1	3	0	6	7	16	9
VA Cooperative CABG	107, 108	A325 v A975	12	154	155	11	10	2	2	5	6	18	18	0	1	1	0	12	7	11	9
VA Cooperative CABG	107, 108	Sp v A975, A325	12	148	309	9	21	0	4	4	11	13	36	2	1	0	1	5	19	8	20
VA Cooperative CABG	107, 108	A975 + Dip v Sp	12	162	148	10	9	1	0	7	4	18	13	2	2	3	0	6	5	16	8
GESIC	110	A + Dip v A150	1	368	373	—	—	—	—	9	13	9	13	3	2	0	0	8	8	0	0
SINBA	240	Indobufen v A975 + Dip	12	290	279	0	4	0	0	1	4	1	8	0	1	0	1	0	0	0	0
(Toronto dipyridamole-II)	266	A975 + Dip v Dip	< 1	19	21	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Post-percutaneous transluminal coronary angioplasty																					
White	125, 126	A650 + Dip v ticlopidine	6	123	122	5	9	0	0	0	2	5	11	0	0	0	0	0	0	0	0
Mufson	241	A80 v A1500	6	253	242	9	9	0	0	0	0	9	9	0	0	0	0	0	0	0	0
SIAC	242	Indobufen v A325	6	161	162	4	3	0	0	0	1	4	4	0	0	1	1	0	0	0	0
Ress	243	BM 13.177 v A500	3	7	7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
(Lembo)	273	A + Dip v A975	< 1	129	139	7	4	0	0	1	0	8	4	0	0	0	0	0	0	0	0
Stable angina/coronary artery disease																					
(Parry)	267	Dazoxiben v A250	< 1	6	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Intermittent claudication																					
Hess	153	A + Dip v A990	24	80	80	0	2	0	0	2	1	2	3	0	0	1	1	0	0	0	0
Libretti	244	A + Dip v A600	6	27	27	1	1	0	0	1	2	2	3	0	0	0	0	0	0	1	2
Schoop-I	160-162	A + Dip v A990	60	100	100	1	3	1	1	6	2	8	6	0	1	2	0	3	0	8	2
Schoop-II	245	Ticlopidine v A1500	24	31	31	0	0	0	0	0	3	0	3	0	0	0	2	0	0	0	0
London-B	171	Ticlopidine 250 v ticlopidine 500	2	7	8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Non-coronary grafting																					
Rochester	181	A + Dip v A975	12	16	16	0	0	1	0	2	0	3	0	0	0	0	0	0	1	0	0
Bollinger	246	A + Dip v A1000	24	41	40	3	0	1	0	2	0	6	0	0	0	1	2	0	0	0	0
(Harjola)	269	A1500 + Dip v Dip	< 1	100	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
(Harjola)	269	A + Dip v A1500	< 1	100	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
(Harjola)	269	Dip v A1500	< 1	100	100	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Peripheral angioplasty																					
Hess	193, 194	A300 + Dip v A990 + Dip	6	66	66	3	0	1	0	0	1	4	1	0	0	0	0	0	0	1	2
(Hess-PTA)	274	A + Dip v A990	< 1	55	55	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Renal haemodialysis																					
Albert	247	Sp v A1500	1	19	17	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
Heidelberg-B	248	Ticlopidine v A	1	10	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	0
Diabetes																					
DAMAD	211	A + Dip v A990	36	161	157	10	11	—	—	2	1	12	12	0	0	0	1	—	—	14	5

— Data not supplied

†Trials named within braces { } were those with duration less than one month (excluding short trials of deep venous thrombosis prophylaxis after surgery, reviewed in part III). Trials named within square brackets [ ] were major trials (around 1000 patients or more) for which results became available after March 1990 deadline for overview.

‡A = Aspirin (expressed with daily dosage in mg). Dip = Dipyridamole. Sp = Sulphinpyrazone.

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(Accepted 12 October 1993)