# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20839

## ADMINISTRATIVE DOCUMENTS

## ITEM 13. PATENT INFORMATION

BRANDNAME (clopidogrel bisulfate) drug, drug product, and method of use are covered by the following U.S. Patents. Sanofi Pharmaceuticals, Inc. believes that these patents would be infringed if a person, not licensed by the patent owner, engaged in the manufacture, use or sale of the drug product described in this application.

| United States Patent Number | Expiration Date | Type of Patent | Patent Owner |
|---|---|---|---|
| 4,529,596 | July 5, 2003 | Drug<br>Drug Product<br>Method of Use | Sanofi SA |
| 4,847,265 | February 12, 2008 | Drug<br>Drug Product | Sanofi |
| 5,576,328 | January 31, 2014 | Method of Use | Elf Sanofi |



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## ITEM 14. PATENT DECLARATION

The undersigned declares that U.S. Patent No. 4,529,596, U.S. Patent No. 4,847,265, and U.S. Patent No. 5,576,328 cover the formulation, composition and/or method of use of clopidogrel bisulfate. This product is the subject of this application for which approval is being sought.

**EXCLUSIVITY SUMMARY for NDA #** 20-839 **SUPPL #** _____

**Trade Name** Plavix **Generic Name** clopidogrel bisulfate
**Applicant Name** Sanofi Pharmaceuticals Inc **HFD-** 110

**Approval Date** Nov 17, 1997

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**



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**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.**

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) **Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?**

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /___/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /___/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

David L Roeder
Signature
Title: Regulatory Health Project Manager

8-22-97
Date

Ray Lipicky
Signature of Division Director

11/20/97
Date

cc: Original NDA Division File HFD-~~85~~ 93 Mary Ann Holovac

8/8/95

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-839 Trade (generic) names Plavix (clopidogrel bisulfate)

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

10/3/97
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

**Item 15. OTHER: Debarment Certification**

Sanofi Pharmaceuticals, Inc. certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act, in connection with this new drug application.

SEP 22 1997

# 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

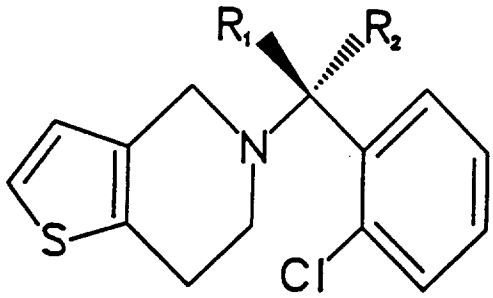
Date: 11 September 1997
From: Robert R. Fenichel (HFD-110) & James Hung (HFD-710)
Subject: clopidogrel (PLAVIX®, Sanofi), NDA 20-839
To: Raymond J. Lipicky, HFD-110

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, chemically similar to ticlopidine (TICLID®, Roche). Ticlopidine and clopidogrel share the formula




For ticlopidine, $R_1$ and $R_2$ are both H. For clopidogrel, an *S*-enantiomer, $R_1$ and $R_2$ are H and $COOCH_3$, respectively. To produce the SR26334 metabolite of clopidogrel (important in the development process and mentioned below), $R_2$ is hydrolyzed to COOH.

Minor CMC deficiencies were described to the firm in a letter dated 6 August. Under the new environmental-assessment rules, the sponsor plans to withdraw its environmental-assessment submission and to submit a claim for categorical exclusion. The proposed tradename (PLAVIX) is said to be unacceptable to the Nomenclature Committee because of potential confusion with LASIX, but Dr. Lipicky has announced his intention to overrule them.

## 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. Clopidogrel is inactive *in vitro*, and none of its isolated metabolites is active *in vitro* or *in vivo*, so the active molecular species is presumably an early, ephemeral intermediate.*

The *R*-enantiomer is inactive *in vitro* and *in vivo*.

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.

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

† Aprotinin (TRASYLOL®, Bayer) 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** (DDAVP®, Rhône-Poulenc Rorer), 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 >80%. The evanescence of clopidogrel's putative active moiety has already been noted. Under the circumstances, all of the drug-exposure data had to be obtained by following serum concentrations of SR26334, the main circulating metabolite. The appearance of SR26334 seems to be qualitatively and quantitatively similar in humans and (at least) baboons.

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. As estimated by measurements of SR26334 levels, drug exposure in the treated baboons was 1–2 orders of magnitude greater than exposure to be expected in humans who receive the proposed therapeutic dose.

Worrisome toxicity was not seen in reproductive studies, but tracer studies suggest that clopidogrel (or a metabolite) crosses the placenta and also appears in milk. 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. Clopidogrel's *R*-enantiomer was neurotoxic in some models, but only at exposures about 4 orders of magnitude higher than those to be expected from use of clopidogrel at proposed doses. The SR26334 metabolite, administered as a pure compound, was not more toxic than clopidogrel.

## 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. As in the animal studies, clopidogrel's human pharmacokinetics have been estimated by tracer studies and studies of the SR26334 metabolite.

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

**Absorption** of clopidogrel is at least 50%, and the $t_{max}$ of SR26334 is less than 1 hour. 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, the $C_{max}$ of SR26334 is about 3 mg/L, and over 90% of circulating SR26334 is bound to serum proteins, mainly albumin.

**Metabolism** of clopidogrel and of SR26334 is complex and extensive, including hydrolysis, oxidation, dimerization, and glucuronidation. The clopidogrel→SR26334 hydrolysis is performed by plasma esterases in rodents, but in humans it is dependent on hepatic enzymes, probably of the $P_{450}$ (1A) group. Neither racemization nor cleavage to ticlopidine were detected in human studies.

The **elimination** half-life of SR26334 was about 8 hours, but radioactivity from labeled clopidogrel had a half-life of about a week, presumably reflecting irreversible binding to platelets by the (hypothesized) active metabolite.

## 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.* Although peak levels of the SR26334 metabolite increased more than linearly with dose,† 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, page 7), for example, Hour-2 plasma concentration of SR26334 was 1.4±0.6 mg/L after a 100-mg dose and 14.6±3.8 mg/L after a 600-mg dose. In Study P1560 (Volume 1.79, page 248), the AUC of SR26334 was 1.96±0.44 μg•h/mL after a 25-mg dose and 70.41±18.17 μg•h/mL after a 400-mg dose.

‡ 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/mm³).

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 $[G/F,\ G\times F]$, where G is the geometric mean and F is a factor chosen so that the $[G/F,\ G\times F]$ 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 (on Day 10, from 1.9±1.5 ng/mL to 99.7±147.7 ng/mL). In contrast, the $C_{max}$ and AUC of SR26334 were only 10–30% higher in the cirrhotic group, and these differences were consistently dwarfed by the intersubject variation.

The non-difference in SR26334 kinetics better predicted the pharmacodynamics than the huge difference in clopidogrel kinetics. On Day 10, ADP-induced platelet aggregation as a percentage of baseline was 51±39% in the cirrhotics and 33±8% in the normals, neither of these different from the other or from the analogous results in Studies P1264 and P1404. Similarly, the bleeding times on Day 10 were 164±49% and 154±87% of the baseline times.

## Drug Interactions

In a series of *in vitro* studies, $P_{450}$(2C9)* was moderately inhibited by SR26334, but the other isozymes tested (1A2, 2A6, 2C19, 2D6, 2E1, 3A4) were inhibited by neither clopidogrel nor SR26334.

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,**¶ the clopidogrel/SR26334 $C_{max}$ ratio was reduced, 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% ($P=0.51$). 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 occurrence 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

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* 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 15538 (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 15634 patient-years of exposure to clopidogrel and 15626 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%) |

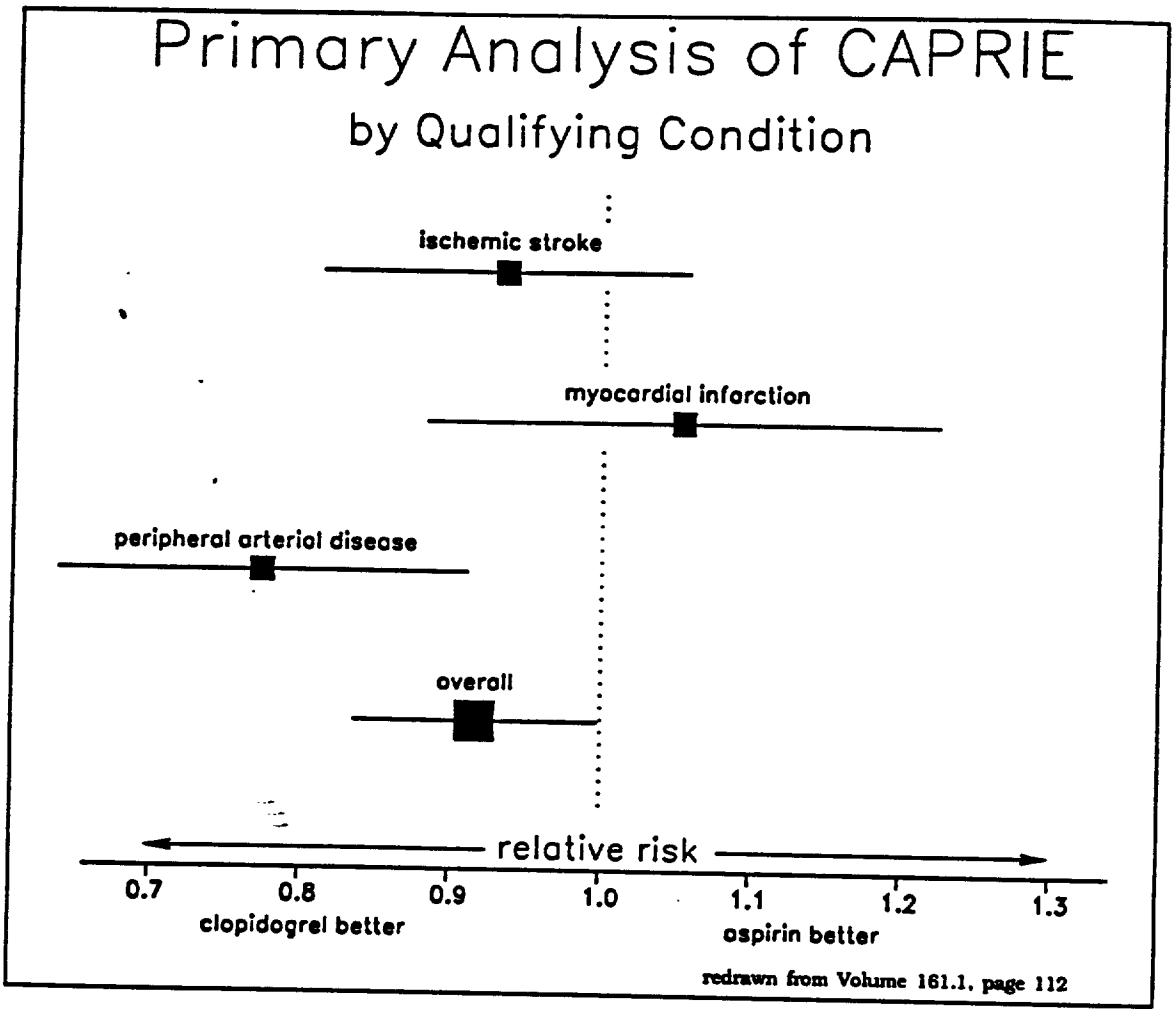
from Volume 161.1, page 101

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 ($\chi^2_3 = 1277$, $P<10^{-648}$). 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

| covariates included | Qualifying Condition 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%)‡ |
| angibedema | 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 (range 1–3 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



cc: NDA 20-839
HFD-110/RFenichel
HFD-110/SFredd
HFD-110/CGanley
HFD-111/DRoeder

# 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 | 1119 | 943 |
| 95th | 1071 | 943 |
| 90th | 823 | 882 |
| 75th | 545 | 712 |
| 50th | 420 | 520.5 |
| 25th | 246 | 244 |
| 10th | 48.5 | 46 |
| 5th | 25 | 42 |
| 1st | 22 | 29 |
| 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 | 1109 | 1109 |
| 95th | 1098 | 1098 |
| 90th | 1092 | 1092 |
| 75th | 873 | 881 |
| 50th | 726 | 725 |
| 25th | 488 | 488 |
| 10th | 364 | 364 |
| 5th | 358 | 358 |
| 1st | 120 | 121 |
| 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.
† $0.05<P<0.10$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

## 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) |

NDEL

JUL 9 1997

**Memo to the File**

Date: June 30, 1997

Application: NDA 20-839
Plavix (clopidogrel bisulfate) Tablets

Sponsor: Sanofi

Subject: Trade Name Review

Sanofi's proposed trade name "Plavix" was found to be unacceptable by the FDA's nomenclature committee in their review of February 11, 1997. I informed the sponsor of their recommendation on April 30, 1997. The sponsor responded with an argument in favor of the Plavix name in a submission dated June 16, 1997. I forwarded Sanofi's response and all related documents to Dr. Lipicky for his review. He concluded that the trade name "Plavix" is acceptable (see attachment). I call Ms. Terrie Maloney at Sanofi and conveyed this information to her.

David Roeder
Regulatory Health Project Manager

Attachment

cc: ~~Orig~~ NDA 20-839
HFD-110
HFD-110/CSO

Dr. Lipicky,

Sanofi proposed the trade name "Plavix" for clopidogrel prior to the NDA submission (when it was still with Dr. Fredd). The nomenclature committee didn't like it because it sounds too much like Lasix. The firm was anxious to get a ruling on the issue, so I suggested that they submit an argument in support of "Plavix" and that I would send it up to you for a decision. So, here it is.

I've included the report from the Nomenclature committee. They are anxious to get a decision as soon as possible since this is a "P" application and they wouldn't have much time if they have to find a new name. Let me know if you have any questions.

Dave

Plavix sounds fine to me. If it is only my call, I say O.K. Plavix it is.

Lipicky

PLAVIX
(clopidogrel bisulfate)
Tablets
75 mg once daily

Note: In a recent submission (Serial number 175), the applicant states that they just got the name PLAVIX registered.

Indication: The prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease.

Description: pink, round, biconvex, engraved with "75" film coated tablet

| Conflicting name | dosage form & dosage size | drug class | NDA approved |
|---|---|---|---|
| FLAREX | Ophthalmic suspension [HFD-550] | ophth-corticosteroid | 19-079 2/11/86 |
| FLAVINE (acriflavine) | a topical antiseptic used primarily in veterinary medicine. Dan Boring has stated in the April 18 e-mail that there is little potential for confusion with this product. NOTE: this was incorrectly spelled as FLAVIN in the consult response. | | |
| LASIX | Round, White Tablet<br>20, 40, & 80 mg<br>Injection & Oral Solution<br>20-80 mg once or twice daily.<br>[HFD-110] | a potent diuretic | 16-273 7/1/66 (Tablet) |

OPG

# REQUEST FOR TRADEMARK REVIEW

757

**To:** Labeling and Nomenclature Committee
**Attention:** Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

| | |
|---|---|
| **From:** Division of Gastrointestinal and Coagulation Drug Products | **HFD-180** |
| **Attention:** Michael Folkendt, Project Manager | **Phone:** (301) 443-0487 |
| **Date: February 11, 1997** 2/11/97 | |
| **Subject:** Request for Assessment of a Trademark for a Proposed New Drug Product | |
| **Proposed Trademark:** **PLAVIX** | **NDA/ANDA#** IND 34,663 (future NDA 20-839) |
| **Established name, including dosage form:** clopidogrel bisulfate | |
| **Other trademarks by the same firm for companion products:** -none- | |
| **Indications for Use (may be a summary if proposed statement is lengthy):** This drug is an antiplatelet agent for the reduction of the incidence of stroke, myocardial infraction, or vascular death in patients at risk. | |
| **Initial Comments from the submitter (concerns, observations, etc.):** -none- | |

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original IND 34,663; HFD-180/division file; HFD-180/M.Folkendt; HFD-180/J.Sieczkowski

Rev. December 95

Consult #757 (HFD-180)

PLAVIX clopidogrel bisulfate

The following look-alike/sound-alike conflicts were noted: FLAREX, FLAVIN, LASIX. The Committee believes there is a significant potential for mix-up between these products and the proposed name. There were no misleading aspects found in the proposed proprietary name.

The Committee finds the proposed proprietary name unacceptable.

D Boring 3/27/97, Chair
CDER Labeling and Nomenclature Committee