CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: JOINT MEETING OF THE NONPRESCRIPTION DRUGS AND CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEES

DATE OF MEETING: 01/23/97

SUMMARY MINUTES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

A JOINT MEETING OF THE

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

AND THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

MINUTES

Thursday, January 23, 1997

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
Center for Drug Evaluation and Research

CHAIRMAN

Ralph B. D'Agostino, Ph.D.

MEMBERS

Cage S. Johnson, M.D.
Theodore G. Tong, Pharm. D.
Lynn McKinley-Grant, M.D.

OTHER PARTICIPANTS

Dr. Randy Juhl
Mary Ann Koda-Kimbell

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

CHAIRMAN

Barry Massie, M.D.

EXECUTIVE SECRETARY

Joan C. Standaert

MEMBERS

Cynthia Raehl, Pharm. D.
Michael Weber, M.D.
Lemuel Moye, M.D., Ph.D.
Udho Thandani, M.D., FRCP
Robert Califf, M.D.
John DiMarco, M.D.
Marvin Konstam, M.D.
Dan Roden, M.D.C.M.

OPEN PUBLIC HEARING SPEAKERS

Darrell R. Abernethy, M.D., Ph.D.
Paul Stein, M.D.
Thomas Bryant, M.D.
Richard W. Frank
Steven Weisman, M.D.
Anthony Temple, M.D.
Fletcher McDowell, M.D.

FDA STAFF

Michael Weintraub, M.D.
Dr. Robert Temple, FDA
Dr. D. Bowen
Dr. D. Feigal

PRESENTERS

Charles Hennekens, M.D.
Rory Collins, M.D.
Colin Baigent, M.D.
Richard Peto
Stephen Kimmel, M.D.
Jeffrey Carson, M.D.
Stephen Fredd, M.D.
Mohammad Huque, Ph.D.

A joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee was called to order at 8:30 a.m., Thursday, January 23, by the chairman of the Nonprescription Drugs Advisory Committee, Ralph D'Agostino, PhD.

Advisory committee members and invited speakers were introduced and the executive secretary, Joan C. Standaert, entered the conflict of interest statement into the record. Waivers for this discussion of professional labeling for aspirin were granted to Drs. Lemmuel Moye, Barry Massie, Randy Juhl and Mary Ann Koda-Kimbell. Copies of these waivers may be obtained by writing to the FDA's Freedom of Information Office, Room 12-A-30, Parklawn Building.

Dr. Weintraub presented an award of special recognition to the Nonprescription Drugs Manufacturing Association for their assistance in helping FDA develop clear and understandable labeling for nonprescription drug products. The award was accepted by Dr. Bill Soller.

Dr. D'Agostino proceeded to the open public hearing. Six presenters were on the agenda. Dr. Darrell Abernathy spoke on behalf of the American Heart Association. He expressed the view that aspirin should be indicated for secondary prevention of heart attack in patients with documented coronary and other atherosclerosis.

Dr. Paul Stein presented on behalf of the American College of Chest Physicians. They advocated use of daily doses of 160-125 mg of aspirin for primary prevention for individuals with coronary artery disease over age 50, based on data from the Physicians Health Study. The College also recommended use of aspirin for patients with stable angina, atrial fibrillation and certain revascularizations.

Dr. Thomas Bryant presented on behalf of the Aspirin Foundation, an organization sponsored by major aspirin manufacturers. Dr. Bryant advocated an FDA recommendation for use of low-dose aspirin for primary prevention.

Mr. Richard Frank and Dr. Steven Weisman spoke on behalf of Bayer Corporation. Bayer will continue to support research and physician and consumer education about appropriate uses for aspirin. Dr. Weisman discussed the evidence from the Physician's Health Study, SPAT, ISIS-2 and the APT meta-analysis, which supported a variety of cardiovascular benefits for all levels of cardiovascular risk.

Dr, Anthony Temple, McNeil Consumer products, cautioned that with increasing numbers of patients consuming low dose aspirin, the FDA should indicate in labeling that increased risk of GI bleeding could occur when consumers ingest higher doses for fever reduction and that it might be appropriate to advise that a doctor be consulted before using increased aspirin doses.

Dr. Fletcher McDowell represented the National Stroke Association. He addressed the difference between a transient ischemic attack (TIA) and a completed stroke, where TIA could be considered the mildest completed stroke. Completed stroke carries a high risk of recurrence and Dr. McDowell advocated the use of aspirin to prevent recurrence of all degrees of completed stroke.

Dr. Michael Weintraub, Director, Office of Drug Evaluation V, presented a summary of FDA problems with the aspirin data. He described them as 4 pronged: extrapolation of data obtained from antiplatelet drugs to aspirin indications; substitution of meta-analysis results for clinical trials: the definition of high risk patients and the adverse effects of bleeding.

His remarks were amplified by Dr. Robert Temple, Director, Office of Drug Evaluation I. Dr. Temple noted that meta-analysis as a basis for primary approval has not been common. Initial approval of aspirin for use post-infarction was based on at least three specific studies that showed an effect on a combined endpoint of death plus recurrent infarction. A meta analysis was done and played a supportive role, suggesting an effect on survival, but that claim has never appeared in labeling.

Addressing the claims proposed in Dr. Henneken's petition of June 6, 1994, two seem likely to turn on extrapolation of other data. These would be patients undergoing revascularization procedures and patients deemed to be at elevated risk due to some form of vascular disease or other condition, implying an increased risk of occlusive vascular disease. Noting the types of claims currently being promoted for aspirin, Dr. Temple urged the committee to be conscious of the implications for advertizing that could result from any recommendations.

Prior to initiating formal presentations from the petitioners, Dr. D'Agostino summarized the issues the committee should address regarding the professional labeling for aspirin. The issues included extrapolation of data from minor strokes to major strokes, to atrial fibrillation and cardiac procedures, extrapolation of data from anti-platelet trials to aspirin, how to define patients at high risk and the role of meta analysis in answering these questions.

Dr. Charles Hennekens summarized the content of the citizens petition filed in 1994 . Recognizing that some data on strokes and vascular deaths remains inconclusive, the new and expanded labeling indications would approve aspirin at a maintenance dose of 75-81 mg a day for all patients who have already been diagnosed as having some occlusive arterial disease and have no special contraindications to aspirin. Dr. Hennekens estimated that underutilization or non-use of aspirin for such patients contributes to as many as 10,000 premature deaths each year in the United States.

The Anti-Platelet Trialists Collaboration (APT) published its first series of papers in the British Medical Journal in 1988. This included a meta analysis of the 25 completed trials of

aspirin, dipyridamole and/or sulfinpyrazone, conducted among 29,073 men and women with a history of MI, stroke, TIA or unstable angina. Results were significant for all patient classes as well as for a combined endpoint. Lower daily doses of aspirin were shown to be as effective as higher doses and were accompanied by reduced side effects.

ISIS-2 was a randomized trial of 17,187 patients with suspected acute MI admitted within 24 hours of onset of symptoms. Streptokinase was compared to 160 mg aspirin, streptokinase plus aspirin or placebo. The primary endpoint was 30 day mortality. This trial showed a clear benefit for the aspirin and aspirin plus streptokinase groups over streptokinase and placebo.

The ATP trials were updated in 1994 and these results were reported by Dr. Rory Collins. This data base now included 159 trials of antiplatelet therapy versus control in approximately 100,000 patients. About two thirds of these data were from trials of aspirin versus control. Individual patient report forms were obtained for analysis. The results showed no evidence that aspirin therapy was beneficial for primary prevention in low risk patients.

However in high risk patients post myocardial infarction there was a 25% reduction in vascular events, a 29% reduction in acute myocardial infarction and a 22% reduction in major vascular events including nonfatal MI, nonfatal stroke and vascular death. Adverse effects were also demonstrated. After several years of antiplatelet therapy there was an excess of one per thousand hemorrhagic strokes and 3 per thousand major noncerebal, nonfatal bleeds. On balance the benefits far outweighed the risks, particularly for patients at high risk.

Dr. Baigent summarized data published after the 1994 reanalysis. Two large international studies from Munich and China have provided evidence for aspirin's effectiveness in recurrent stroke. In the early period aspirin avoids about ten per thousand strokes in the first month and with long term use prevents another 10 per thousand per year.

The Swedish Aspirin Low-Dose Trial (SALT) randomized 1,360 patients who had a TIA, minor ischemic stroke or retinal artery occlusion within the previous six months, to aspirin 75 mg or placebo control. The primary endpoint was stroke or death. Aspirin prevented 10 per 1,000 nonfatal strokes or death.

The Swedish Angina Pectoris Aspirin Trial (SAPAT). This randomized 200 patients to SALT, who had evidence of chronic stable angina and were started on sotalol. The primary endpoint was fatal MI, with a mean follow-up of about four years. This trial showed a 30% reduction in the odds of a vascular event. These two trials taken together provide very supportive evidence for the efficacy of low dose aspirin in high risk patients. The most disappointing fact emerging from these and other trials is that aspirin was not prescribed for 24% of elderly patients upon discharge from hospital, after a vascular event.

The statistical aspect of the interpretation of the anti-platelet trials was addressed by Professor Richard Peto. He began by mentioning some of the particular problems with the Citizen's Petition as it was submitted. The petition generated some difficulties for FDA because it did not recommend a specific action. He had reduced the petition content to 7 categories of patients who might be considered for long term aspirin therapy. A copy of this proposal is appended to these minutes. Dr. Peto recommended approval of only category 1. That is aspirin, at a dose of 75-81 mg day, be approved for patients who have been diagnosed as having some occlusive arterial disease and who currently have no special contraindication to aspirin.

At the conclusion of Dr Peto's presentation Committee reviewers were encouraged to ask questions of the presenters. Dr. Califf expressed some concern about the separation of vascular death from all cause mortality. Total mortality was not the primary outcome of meta-analyses but effects of vascular mortality and total mortality were similar.

He also asked about differences in treatment effects across all categories of disease, which could not be clearly addressed from these data and found the use of the term occlusive vascular disease unclear and suggested that perhaps a more functional definition of the patient population could be developed.

Dr. Moye asked at what point the background of metaanalytic noise begins to overwhelm the signal. Dr. Hennekens responded that the magnitude of the finding for aspirin was considerable and sometimes in excess of other drugs already recommended for such cardiovascular indications.

Dr. D'Agostino noting that the meta analysis was impressive, asked for guidance on interpretation of the results. Should meta analysis replace individual trials? Because the results were so highly significant and the veracity of these data so well researched, Dr. Peto thought the results were well beyond the limits of chance.

Dr. D'Agostino also asked if a clinical argument was being put forward for equivalence of all antiplatelets and aspirin. Dr Collins responded that claims were not made that effects were the same in all categories of patients. There was clear evidence of benefit in each of the different settings and the results in the different settings reinforced each other.

Questions from other committee members were mainly concerned with isolating effects attributable to aspirin alone from the antiplatelet studies included in the meta analysis or alternatively aspirin efficacy described in other trials. The committee was also concerned about the definition of patients with peripheral occlusive disease.

At 12:35 the committee adjourned for lunch to reconvene at 1:25 p.m., when Dr. Barry Massie, chairman of the Cardiovascular and Renal Drugs Advisory Committee, assumed the chair. He introduced Dr. Stephen Kimmel who addressed the topic of aspirin and primary prevention of cardiovascular disease.

Dr. Kimmel reviewed data related to the risks and benefits of aspirin in prevention of first heart attack and stroke. He concluded that the benefit of a 17% reduction in risk of dying and a 25-30% reduction in occurrence of an event, outweighed the 1% risk of a GI bleed. Dr. Kimmel also supported the extrapolation of SAPAT data to permit an indication for arterial disease even though there were no studies of aspirin in these patients.

The adverse effects of long term aspirin were discussed by Dr. Jeffrey Carson. Studies clearly show that aspirin is associated with a dose related increased risk of GI bleeding. There was no evidence that this risk was reduced by enteric coated preparations. Dr. Carson concluded that the benefit of aspirin far outweighed the risks of GI adverse effects.

The FDA review of the 1994 Citizen's Petition was presented by Dr. Steven Fredd. He wished to address the heterogeneity of the antiplatelet agents and underlying "occlusive diseases" contained in the meta-analysis and the development of direct randomized evidence that may support a uniform effect in various occlusive diseases. He concluded that aspirin could be recommended for use in patients with chronic stable angina but that the use of aspirin alone to prevent periprocedural events was not established. Dr. Fredd also concluded that claims for Peripheral Vascular Disease was not established by data from use in patients with Peripheral Vascular Disease.

At this time the committee began consideration of the questions asked by the FDA. A copy of these questions is appended to these minutes.

The committee unanimously recommended that the results of the SAPAT trial supported the conclusion that aspirin was beneficial for prevention of vascular events in patients with stable angina pectoris. The second question was revised to ask, "In major completed stroke is their evidence that aspirin prevents recurrent vascular events including stroke, myocardial infarction and vascular death. The committee recommended approval if the analysis of the recently completed ESPS-2 trial supported the claimed efficacy endpoint.

The committee discussed possible labeling for aspirin use in revascularized patients. They supported an indication for patients who have had revascularization for symptomatic or clinically manifest coronary disease (CABG and PCTA). The last clinically manifest vascular disease to be discussed was peripheral vascular disease. The difficulty with this indication was the extrapolation of results from non-aspirin anti-platelet trials to the aspirin indication. Results from aspirin studies alone were weak.

Some members were convinced that generalizations could be based on the view that all types of vessel disease were the result of an atherosclerotic process. Diagnosis of the severity of this disease was limited by the fact that many of these patients were asymptomatic because their coronary artery disease prevented them from exertion. The committee recommended 11-4 that professional labeling should not include an indication for use in peripheral vascular disease because the evidence did not meet usual standards for approval.

Dose and duration were also addressed. Evidence indicates that doses of 75-81 mg of

aspirin will produce complete inhibition of platelet-dependent cyclooxygenase for the life of the platelet over a two day period. Higher doses must be used to produce a rapid effect. Side effects also appeared to be dose related. Differing doses have been demonstrated to have efficacy in differing disease states. This information should be provided to the health care professional who advises the patient. The meeting was then adjourned at 4:30 p.m..

I certify that I attended the January 23, 1997, joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Ralph D'Agostino,PhD.,
Chairman Nonprescription Drugs Advisory Committee

Barry Massie, M.D., Chairman
Chairman Cardiovascular and Renal Drugs Advisory Committee

Joan C. Standaert M.S.
Executive Secretary, Cardiovascular and Renal Drugs Advisory Committee