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

QUESTIONS

Questions for the Joint Committee of the
Nonprescription Drugs Advisory Committee and the
Cardiovascular and Renal Drugs Advisory Committee

BACKGROUND INFORMATION

Current Agency Status of Professional Labeling Indications For Aspirin:

1. Indications Accepted:

   a. TIA
   b. Recurrent Myocardial Infarction
   c. Unstable Angina Pectoris
   d. Suspected Acute Myocardial Infarction
   e. Minor Ischemic Stroke

2. Indication Not Accepted:

   - Prevention of First Myocardial Infarction in Healthy People

3. Indication Under Consideration:

   - Stable Angina Pectoris

4. Additional Indications Requested by the Petition:

   a. Patients undergoing coronary, cerebral or peripheral arterial revascularization procedures (CABG, PTCA, carotid endarterectomy, peripheral artery grafts, surgically created peripheral arterial fistula, peripheral angioplasty).
   b. Patients with chronic non-valvular atrial fibrillation.
   c. Patients requiring hemodialysis access with a fistula or shunt.
   d. Major completed stroke
   e. Other 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.

QUESTIONS

1. In your opinion, do the SAPAT data support the conclusion that aspirin is beneficial in the primary prevention of non-fatal myocardial infarction in patients with stable angina pectoris?

2. In the past, the Agency has required specific clinical data to support each indication (e.g., prevention of stroke, TIA, MI) for aspirin. In your opinion, can extrapolations be made from the available data on aspirin to patient populations which have not been studied in formal clinical trials but are at risk for occlusive vascular events? (Revised)

3. If the answer to question #2 is yes, which populations listed under Background Information #4 would you specify, which not, and why?

4. If the answer to question #2 is yes and extrapolations can be made, how would the dose and duration of treatment for these patient populations and indications be determined?

5. Please comment on the use of data from studies of anti-platelet drugs other than aspirin to approve new professional uses of aspirin.

6. Please comment on the use of aspirin in patients who have not had a signal event (symptom or sign) but are considered to be at high risk for the development of occlusive vascular disease (i.e., family history, diabetes, hypercholesterolemia, etc). Define high risk.

Open Public Hearing Speakers

Am. College of Chest Physicians	Dr. Paul Stein	In support, based on 4th ACCP Consensus Conference on Antithrombotic Therapy
National Stroke Assn.	Dr. Fletcher McDowell	In Support
Bayer Corp.	TBA	In support
McNeil Corp	Dr. Anthony Temple	In support
Aspirin Foundation	Dr. Thomas Bryant	TBA
Am. Heart Assn.	TBA	In support
Am. College of Cardiology	Dr. Noel Bairey Merz (If not acting as Industry Representative for NDMA)	TBA

FROM: Joan C. Standaert, Executive Secretary, Cardiovascular and Renal Drugs Advisory Committee

TO: Director, HFD-1

SUBJECT: 79th meeting, Cardiovascular and Renal Drugs Advisory Committee, jointly with Nonprescription Drugs Advisory Committee, January 23, 1997. INFORMATION ALERT MEMORANDUM

The joint advisory committees convened to discuss a citizen's petition from the Aspirin Strategy Group, seeking broadened indications for professional labeling for aspirin to include anyone at risk for heart attack and stroke. The committees heard presentations from interested professional organizations and corporations, in open public hearing and in open session from the Aspirin Strategy Group.

The committees unanimously recommended that results from the Swedish Angina Pectoris Antiplatelet Trial supported the benefits for low-dose aspirin in patients with stable angina pectoris. The committees also unanimously recommended that low-dose aspirin be extended to patients with arterial revascularization procedures, i.e., CABG or PTCA. The committees gave a conditional recommendation for the use of aspirin in patients with ischemic stroke pending the agency's acceptance of data from the European Stroke Prevention Trial 2 (ESPS2).

The committees recommended that available data on aspirin not be extrapolated to patients with occlusive peripheral arterial vascular disease (11 no, 4 yes).

Ten questions, of which the first is much the most important, that could be put to the cardio-renal advisory committee on 23 January 1997, at the hearings on the 1994 citizens' petition on aspirin. Note: The full 1994 citizens' petition to FDA is several hundred pages long. Even if members do not have time to scrutinise all of it in full detail, it would be helpful if, before considering these questions, they were able to scrutinise in it the text and, particularly, the Discussion (p.93) of Part I of the 1994 APT report (BMJ 308: 81-106: copy attached).

ASPIRIN: CONTRAINDICATIONS, INDICATIONS AND UNCERTAINTIES

Neither the petitioners, nor the FDA, wish to recommend the use of aspirin by people who are not already at appreciable risk of occlusive vascular disease, because if the current risk without aspirin is small then any benefits of aspirin would currently be small, and may well not justify the small but definite increase in the risk of cerebral haemorrhage or other major bleeding. Conversely, neither the petitioners, nor (presumably) the FDA, would want to perpetuate the under-use of aspirin in those who are already at such high risk of occlusive vascular disease (i.e. myocardial infarction or occlusive stroke) that the risk reduction from aspirin greatly exceeds any hazard. Finally, both would agree that there are some categories of patient (including the large majority of those people who do not yet have evidence of occlusive arterial disease) where the balance of risk and benefit remains unclear, and so no professional labelling can yet be justified. What is needed is advice from the committee as to how, in practical terms, such categories can be defined clearly enough for unambiguous and appropriate professional labelling to follow quickly.

NEED FOR CLEAR CATEGORIES: NOT TOO NARROW, NOR TOO WIDE

One problem with the 1994 citizens' petition is that the category of patients for which professional labelling is requested varies slightly from place to place in the document (e.g. on page 1 it is all who are at high risk for occlusive vascular events, irrespective of the reason for this; on page 2 it includes only those who are at high risk due to

prior cardiovascular disease history; on page 4 it includes haemodialysis patients with a recent fistula or shunt, irrespective of their risk of occlusive vascular disease). Perhaps, therefore, it would be appropriate for the first questions to the committee to be concerned with exactly which category of patients to treat. For example:

QUESTION I: PRE-EXISTING OCCLUSIVE ARTERIAL DISEASE

Is aspirin (at a maintenance dose of at least 75 or 81 mg/day: see below) indicated for all patients who have already been diagnosed as having had some occlusive arterial disease, and who currently have no special contraindication to low-dose aspirin?

Notes:

(1) This is the key category; it is simple to state and simple to understand, yet it includes the great majority of those who could, on present evidence, be claimed to benefit substantially, and it does not appear to include any for whom substantial concerns about inappropriate over-treatment can be justified.

(2) Question I implies treatment for stable angina, unstable angina, suspected or definite acute myocardial infarction, a previous history of myocardial infarction, transient cerebral ischaemia, occlusive acute stroke, any current or previous history of occlusive stroke, coronary, carotid or peripheral arterial occlusion, and both perioperative and longer-term treatment for those who have had arterial grafts, angioplasty or other arterial procedures.

(3) The category of patients in Question I differs from that in the 1994 citizens' petition in that it does **not** include those who have not yet developed occlusive arterial disease but who are at substantial risk of doing so in the near future because of severe diabetes, severe hypertension, very high blood cholesterol (or other lipid abnormalities), or renal failure (even though haemodialysis patients

have death rates from occlusive vascular disease that are an order of magnitude greater than those of the general population).

(4) Question I does not specify whether patients who have been hospitalised for acute occlusive stroke should start aspirin immediately after their CT scan, or whether they should wait until the time of hospital discharge. (Randomised evidence on 33,000 acute stroke patients was, however, presented at the 1996 international stroke conference at Munich that strongly indicated that the earlier aspirin starts in hospital the better).

(5) Although there is convincing randomised evidence that in certain types of patient (e.g. those undergoing maior surgical procedures) aspirin can substantially reduce the incidence of deep vein thrombosis and can approximately halve the incidence of pulmonary embolism (see Part III of the 1994 APT overview, which is provided in the citizens' petition), venous thromboprophylaxis should, to avoid confusion, be considered only on some other occasion, and is not discussed at all in these proposed questions.

Questions II-VII then consider possible extensions of the main indication in Question I, and the remaining questions (VIII, IX & X) then relate to other matters.

QUESTION II: DIABETICS without evidence of occlusive arterial disease
Is aspirin likewise (i.e. as in Question I) indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated medically for diabetes, but who have not yet been found to have any occlusive arterial disease?

QUESTION III: RENAL PATIENTS without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated for renal insufficiency, but who have not yet been found to have any occlusive arterial disease? (Note: This question is not related to the maintenance of haemodialysis shunt patency.)

QUESTION IV: ATRIAL FIBRILLATION without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease (especially stroke) in those with chronic atrial fibrillation, but who have not yet been found to have any occlusive arterial disease?

QUESTION V: HYPERTENSIVES without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease in those who are being treated for hypertension, but who have not yet been found to have any occlusive arterial disease?

QUESTION VI: HYPERLIPIDEMICS without evidence of occlusive arterial disease
Is aspirin likewise indicated in middle or old age for the prevention of occlusive vascular disease (especially myocardial infarction) in those who are being treated for elevated blood cholesterol, but who have not yet been found to have any occlusive arterial disease?

QUESTION VII: <u>ANY</u> OTHER HIGH-RISK CATEGORY without evidence of occlusive arterial disease? (This could include, or go beyond, II-VI)
Among those who have **not** yet been found to have any occlusive arterial disease, can **any** category of patient be defined, in a way that might be clear enough to lead to professional labelling, where aspirin is clearly indicated for the prevention of myocardial infarction, occlusive stroke or other occlusive arterial disease? (Note: This question excludes the use of aspirin for the prevention of deep vein thrombosis.)

General note: After discussing the trial evidence and some general statistical principles, an uncomplicated, unqualified positive answer to Question I will be strongly recommended by the petitioners. But, Questions II to VII are more open to differences of opinion, and the current answers to them may well be modified by further research.

Questions on other subjects

QUESTION VIII: SEX, AGE, BLOOD PRESSURE, DIABETES

Among those who are to receive low-dose aspirin for the prevention of myocardial infarction, occlusive stroke, or other occlusive arterial disease, should any be denied treatment on the grounds of gender, age, blood pressure or diabetes? (Probably not: see Figure 7 on page 92 of the 1994 APT report.)

QUESTION IX: CONTRAINDICATIONS TO ASPIRIN USE

Should any specific contraindications be listed (e.g. definitely known allergy to aspirin, recent intra-cranial bleed, current gastric bleed or ulcer), and should these be clearly specified as **relative** contraindications?

Note: In circumstances where the immediate benefits of aspirin are substantial (e.g. acute MI), it is important to forego them only for **really major** contraindications; even a currently active gastric ulcer may be relatively less important, and a past history of ulceration would almost certainly be so: see Figure. (As an example of inappropriate professional labelling of possible side-effects, before the ISIS-2 trial one stated "contraindication" to streptokinase on the data sheet was the use of aspirin!)

QUESTION X: ASPIRIN DOSAGE

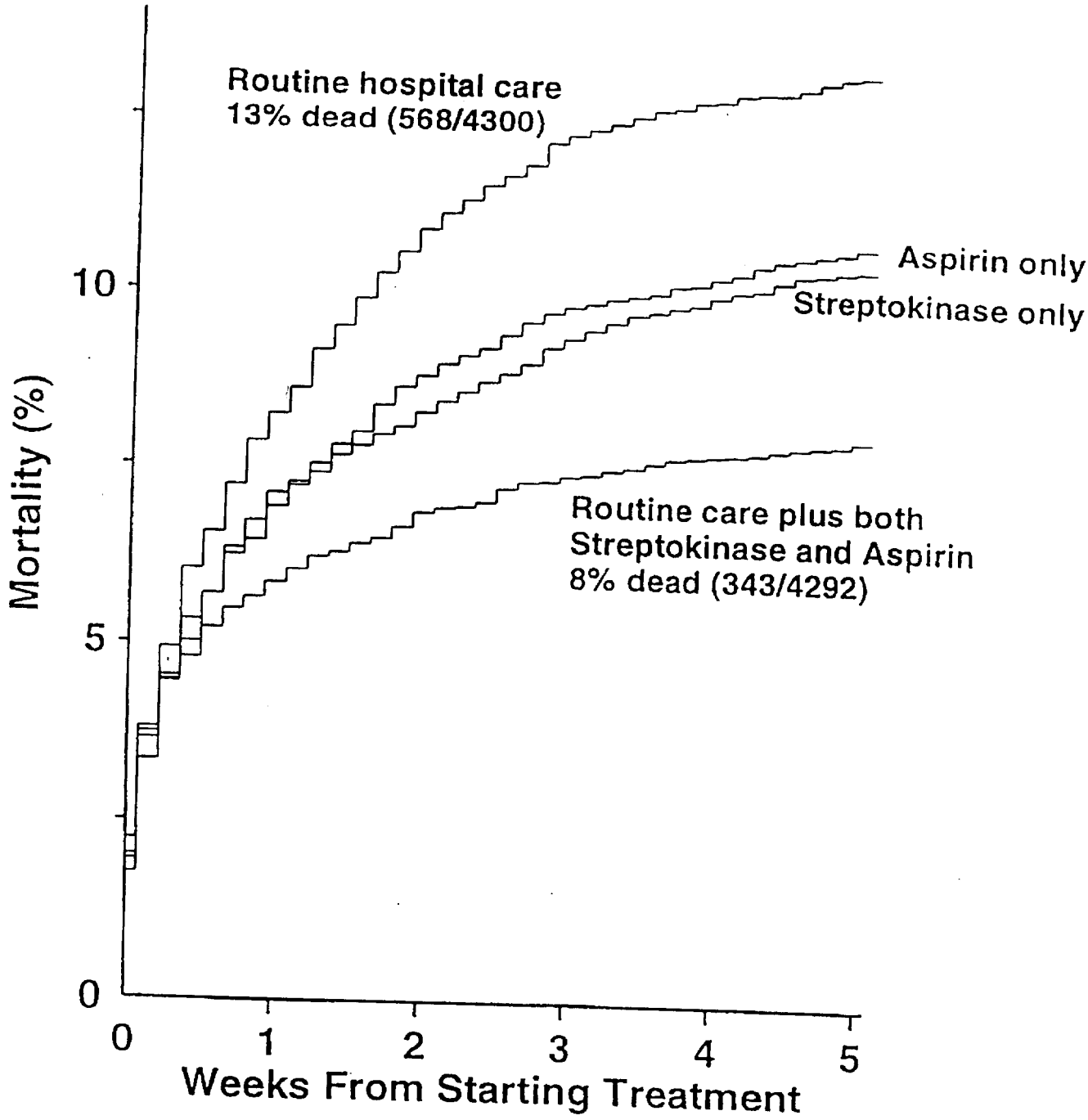
In the light of the 1994 APT report and the additional trials since then, does the committee concur with the conclusion on the final page of the Discussion of the 1994 APT report that "Medium-dose aspirin (75-325 mg/day) is the most widely tested ..... regimen, and no other regimen appeared significantly more effective [in patients with some pre-existing occlusive arterial disease] at preventing myocardial infarction, stroke, or death"?

Notes:

(1) Question I suggested a **maintenance** dose of at least 75 or 81 mg/day, but did not specify what the **initial** dose should be. In most medical circumstances no special initial dose is needed, but in acute ischaemic conditions treatment should begin with enough aspirin to guarantee that a virtually complete effect is obtained rapidly after the first dose, which should therefore be at least 162 mg, as in ISIS-2, or even 250, 300 or 325 mg, rather than, for example, 75 or 81 mg.

(2) In various parts of Western Europe, aspirin doses of 75, 100, 150, 250 or 300 mg may be conveniently prescribable, while in North America doses of 81, 162 or 325 mg may be conveniently prescribable. Some trials have demonstrated clearly significant benefits with 75 mg/day, but substantially lower doses have been much less extensively studied for their effects on clinical endpoints and they may not suffice to maintain full inhibition of platelet cyclo-oxygenase. Thus, although the 1994 citizens' petition suggests recommending aspirin at a dose of "at least 81 mg/day", a more appropriate recommendation might be "at least 75 or 81 mg/day". Higher doses are more gastrotoxic, and have not been reliably shown to be more effective than 75-325 mg/day: the current recommendation of 1300 mg/day for stroke cannot be justified (see Discussion of 1994 APT report).

(3) If the committee cannot agree on which dose to recommend, then it is important not to let this prevent recommending that aspirin should be used for an appropriately wide range of patients. (It would, for example, be possible for the committee to recommend the use of aspirin "at the lowest effective dose", or "at an appropriate dose", leaving FDA to decide subsequently what this implies.)



Cumulative Vascular Mortality From Days 0 to 35 in the ISIS-2 Trial.

17,187 patients randomly assigned within 24 hours of the onset of suspected acute myocardial infarction to receive (i) placebo infusion and placebo tablets, (ii) placebo infusion and 162.5 mg aspirin daily for one month, (iii) 1,500,000 units of streptokinase infusion over one hour and placebo tablets, or (iv) both