Cardiovascular and Renal Drugs Advisory Committee Meeting
December 8, 2003

Committee Questions

The Cardio-Renal Advisory Committee is asked to opine on the use of aspirin for the primary prevention of myocardial infarction. This meeting is in response to a Citizen Petition, filed 11 February 2003 by Bayer Healthcare, requesting an amendment to the professional labeling for aspirin. The Petition cites the five studies summarized below.

The British Doctors' Trial (BDT; British Medical Journal, 1988) was conducted between 1978 and 1984 among 5139 healthy male British doctors. age 50 to 78. The comparison was between aspirin 500 mg daily and no treatment. The primary end point was fatal or non-fatal MI, stroke, or TIA; p=NS.

The Physician's Health Study (PHS; New England Journal of Medicine, 1989) was conducted between 1982 and 1987 among 22071 healthy male US physicians, age 40 to 84. The comparison was between aspirin 325 mg every other day and placebo. The primary end point was cardiovascular mortality; p=0.87. This study was terminated early because of a 44% reduction in fatal and non-fatal MI (nominal $p<0.00001$).

The Thrombosis Prevention Trial (TPT; Lancet, 1998) was conducted between 1984 and 1989 among 5085 British males at high risk, age 45 to 69. The comparison was between controlled-release aspirin 75 mg daily and placebo. The primary end point was "coronary death and fatal and non-fatal MI"; p=0.04 (p=0.07 including silent MI).

The Hypertension Optimal Treatment study (HOT; Lancet, 1998) was conducted in 26 countries between 1992 and 1997 among 19196 men and women with mild-to-moderate hypertension and no stroke or MI within 12 months. The comparison was between aspirin 75 mg daily and placebo. The primary end point was cardiovascular death and non-fatal MI or stroke; p=0.17 (p=0.03 excluding silent MI).

The Primary Prevention Project (PPP; Lancet 2001) was conducted in Italy between 1994 and 1998) among 4495 men and women over age 50 with some additional cardiovascular risk. The comparison was between enteric aspirin 100 mg daily and no treatment. The primary end point was cardiovascular death and non-fatal MI or stroke; p=NS.

Of the 5 studies, a study protocol and source data were reviewed only for HOT (PHS having been previously reviewed), and the FDA review of HOT suggests a

substantially weaker result than is published. The primary end point in HOT included silent MI, while in TPT silent MI was assessed (but it unclear whether it is included in the reported analyses) and in the other 3 studies silent MI was, apparently, not collected. Assessed end points in the published studies are shown in the table below:

	BDT	PHS	TPT	PPP
All-cause mortality	√	√	√	√
Cardiovascular mortality	√	√	√	√
CV death + MI + stroke	√			√
Fatal MI + fatal stroke	√			
Fatal or non-fatal MI	√	√	√	√
Fatal or non-fatal stroke	√	√	√	√
Non-fatal MI	√	√	√	√
Non-fatal stroke	√	√	√	√
Silent MI			√	

1. Are there other studies that should be considered?

2. In considering how to interpret these trials with respect to primary prevention of MI, whether by formal or informal meta-analysis, ...
   - 2.1. ...what is the significance of each of the following?
     - 2.1.1. The study protocol is unavailable for BDT, TPT, and PPP.
     - 2.1.2. The source data are unavailable for BDT, TPT, and PPP.
     - 2.1.3. No study had primary prevention of MI as a primary end point.
     - 2.1.4. Only one study appears to have shown an effect on its pre-specified primary end point.
     - 2.1.5. The studies varied with respect to what MIs were captured.
     - 2.1.6. The dose, regimen, and biopharmaceutical properties of aspirin varied.
     - 2.1.7. The baseline risk factors varied.
   - 2.2. ...do you conclude that a meaningful synthesis is possible?

3. Aspirin has a claim for *secondary* prevention of myocardial infarction.
   - 3.1. How much, if at all, does this lower the evidentiary burden for *primary* prevention of myocardial infarction?
   - 3.2. Aspirin also has secondary prevention claims related to strokes and overall cardiovascular mortality. Since effects of aspirin on strokes and cardiovascular mortality are not evident in these primary prevention studies, how much, if at all, does this discrepancy *raise* the evidentiary burden for primary prevention of myocardial infarction?

4. What do the available data say was the effect of aspirin on primary prevention of myocardial infarction? If there was an effect, ...
   - 4.1. ...is this opinion based on selected studies or the formal meta-analysis?
   - 4.2. ...name the effect and define what constituted a myocardial infarction.

4.3. ...how do you explain differences in outcome among these studies?
4.4. ...what was the effect in relevant demographic subgroups (gender, age, and race)?

5. What do the available data say about the safety of aspirin in primary prevention setting? What do you know about ...
   5.1. ...risks in demographic subgroups (gender, age, race)?
   5.2. ...interactions with underlying disease?
   5.3. ...use with various concomitant drugs?

6. Should professional labeling for aspirin recommend its use for primary prevention of MI?
   6.1. If so, ...
      6.1.1. ...what patient population can expect to benefit from aspirin?
      6.1.2. ...what dose, regimen, and form of aspirin should be recommended?
   6.2. If not, describe the study that would provide compelling evidence for this indication.

7. If aspirin were to be approved for primary prevention of myocardial infarction, comment on the petitioner's proposal to identify a target population using an integrated risk assessment score.
   7.1. How confident are you that the proposed scoring system appropriately identifies patients most likely to benefit from aspirin?
   7.2. Can physicians use this?
   7.3. Can patients understand it?