Questions

PHARM Study
April 26, 2006

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Committee is asked to opine on the continued use of placebo in studies of antihypertensive drugs. If antihypertensive drugs, regardless of class, can be expected to reduce death and stroke, and possibly myocardial infarction and other irreversible outcomes as well, how can it be ethical to continue the current practice of including a placebo control in studies of new agents?

1. To address the risk, there are two meta-analyses. The first was conducted by Dr Al-Khatib and colleagues and based on published reports of placebo-controlled trials. Combining death, stroke, MI, and CHF among 25 trials, they found a net placebo-active difference of 0, ruling out a difference as high as 0.6 per 1000 patients enrolled.

    1.1. Assuming these trials were on the order of 8 weeks duration, the upper limit corresponds to about 0.1 per 1000 patient-years, which is considerably smaller than the benefit of treatment is expected to be. How do you explain that?

    1.2. Are you concerned about …

        1.2.1. …publication bias for the component studies?

        1.2.2. …the effectiveness of agents employed?

        1.2.3. …other adverse effects not part of the end point?

2. The second meta-analysis (PHARM) was based on 93 NDAs (590 studies and 86137 randomized patients).

    2.1. Are you concerned about …

        2.1.1. …studies in INDs that never led to NDAs (analogous to publication bias)?

        2.1.2. …trends in safety of active agents over 1973-2001?

The table below is based on the PHARM report. It is sorted by the absolute value of the “Excess” column, which shows the placebo minus active treatment difference in events per 1000 patient-years.

Event	Placebo	Active	RR	Excess
Any	3056	6580	1.33	+251
Treatment failure	1266	1384	2.53	+246
Other cardiovascular	52	417	0.33	-28
Hypertensive emergency	134	145	2.75	+26
Administrative	840	2241	1.09	+23
Other adverse event	653	2081	0.87	-18
Arrhythmia	17	73	0.64	-2
CHF	15	29	1.47	+2
Angina pectoris	27	72	1.07	+1
Myocardial infarction	22	55	1.06	+1
Stroke	12	28	1.43	+0.8
Death	10	33	0.72	-0.4
Transient ischemic attack	8	22	0.81	-0.2

2.2. The primary analysis was the relative risk for simply any reason for withdrawal, an analysis that counted treatment failure and MI equally. Was this reasonable?

2.3. The overwhelming majority of events in the PHARM analysis were discontinuations for treatment failure, not surprisingly much more common on placebo than on drug. Is this alone reason for concern about the use of placebo, or is it just a reflection that trial procedures appropriately caught most cases of need for treatment?

The second most important class of events contributing to differences in overall event rates was other cardiovascular events, which included such things as angioedema, dependent edema, hypotension, syncope, and nonspecific chest pain or ECG changes. These events were more common on active drug.

2.4. The third biggest contributor to placebo-active treatment was hypertensive emergency events. The clear intent was to capture a class of withdrawal more ominous than the treatment failures. Did it do that?

2.4.1. Hypertensive emergencies were defined by the combination of clinical signs or symptoms and blood pressure criteria.

2.4.1.1. The clinical presentation was supposed to include new end-organ damage or symptoms plausibly related to blood pressure. Were these criteria sufficient to establish that

the hypertensive emergency events were clearly worse than the treatment failures?

2.4.1.2. Which of the following cited evidence of end organ involvement should have been the basis for declaring hypertensive emergency?

- Retinopathy
- Eye hemorrhage
- Visual disturbance
- CNS alteration
- Headache
- Chest pain
- Palpitations
- Dizziness
- Edema
- Shortness of breath
- Erectile dysfunction
- Flu-like syndrome
- Rash
- Vomiting

2.4.1.3. The blood pressure criteria were either a diastolic pressure greater than 120 mmHg or a rise by 10 mmHg to >110 mmHg. Were these criteria sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures?

2.5. Please comment on the Mangano analysis of "hypertensive emergency" and "other cardiovascular" events.

2.5.1. What was the rationale for looking at those two classes in isolation?

2.5.2. Different 0-10 severity grading systems were employed for hypertensive emergency and other cardiovascular events, and then the scores were combined. Was this reasonable?

2.5.3. What scores represented permanent end-organ damage? How many of these events were there?

2.5.4. Is it appropriate to consider a threshold for severity, or is some integral appropriate?

2.5.5. What was an appropriate threshold score for considering events to be severe?

2.5.6. What would be an appropriate nominal p-value for considering a relative risk to be significant?

2.6. The fourth biggest contributor to placebo-active treatment differences was administrative events. This was the category with the largest number of total events. Why do you think these events were somewhat more common on placebo (p=0.03)?

The fifth biggest contributor to placebo-active treatment differences was other adverse events, which included headache, lab abnormalities, rash, and fatigue. These were more common on active treatment than placebo.

2.7. The next largest contributor to placebo-active treatment differences is 10-fold less common, but generally the remaining event classes (arrhythmia, heart failure, angina, myocardial infarction, stroke, death, and transient ischemic attack) represent serious, often fixed, outcomes, mostly those that one would expect to be better on drug than on placebo.

2.7.1. The net excess on placebo is about 2 events per 1000 patient-years, Is this what one should expect for the benefits of active treatment?

2.7.2. Together, death, stroke, and myocardial infarction (not quite the Al-Khatib end point) give a relative risk of 1.03 (p=0.9). Is that what one should expect for the benefits of active treatment?

3. If placebo-controlled studies continue, what do you advise to minimize risk?
   - Minimize the duration of exposure to placebo
   - Avoid study of patients at high risk because of high blood pressure or other risk factors
   - Minimize the time between visits
   - Set more strict criteria for remaining in study
   - Others?

4. Under which, if any, of the following circumstances should placebo controls be discouraged? Please vote.
   - Dose-ranging studies for a new molecular entity
   - Withdrawal studies intended to show long-term effectiveness
   - Factorial studies for approved drugs
   - Others?