Questions

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

The Cardio-Renal Advisory Committee is asked whether an observed mortality difference can be a compelling finding far out of proportion to its place in a study's formal hypothesis testing.

Carvedilol is indicated for the reduction of mortality and the reduction of hospitalization in patients with mild to moderate heart failure. With the results of the CAPRICORN study, the sponsor seeks to extend the indication for carvedilol to patients with left ventricular dysfunction subsequent to myocardial infarction.

In CAPRICORN, 1959 subjects with left ventricular ejection fraction <40% and no heart failure, within 21 days of myocardial infarction, were randomized to placebo or to carvedilol 6.25 mg bid, titrated as tolerated to 25 mg bid over several weeks, and then followed for a mean of 15 months. The primary end point was overall mortality, but, as a result of a protocol amendment late in the study, there were two primary end points, time to cardiovascular hospitalization or death from any cause (assigned alpha of 0.045) and time to death alone (assigned alpha of 0.005). After a single interim analysis, conducted after the change in end point, the final results were as follows:

	Events		**Hazard ratio (95% CI)**	**P value**	**Alpha**
	Placebo N=984	**Carvedilol N=975**			
Death or CV hospitalization	367	340	0.92 (0.80-1.07)	0.297	0.045
Death	151	116	0.77 (0.60-0.98)	0.031	0.004

Studies are designed to test a formal hypothesis. We usually, but arbitrarily, say a study is "successful" if the null hypothesis is rejected at $p<0.05$, meaning that, on average and without considering other internal data from this study or data from other studies, no more than once in 20 times (or once in 40 times for a *favorable* result) will we be misled into believing a result that is not reproducible. Furthermore, to consider a finding to be compelling, we usually expect evidence equivalent to more than one study successful at $p=0.05$. Let us define "discovery" as any opportunity to declare a finding to be compelling

outside of formal hypothesis testing. Discovery comes at the cost of increasing the false positive rate.

1.1. How much are you willing to inflate the false positive rate in order to enable discovery?

1.2. For every potential discovery one can make in a study, the risk of a false positive result increases. How many opportunities should a study have for discovery?

1.3. When should a discovery be confirmed in a separate formal hypothesis test?

1.4. Do you believe it is always possible to discover something about mortality; i.e., is mortality always a primary end point? If so, of what value is making it a formally tested hypothesis?

2. Without formally specifying how we do so, we may be comforted or discomforted about a finding by other information derived from the study. In considering the mortality effect discovery in CAPRICORN, how do the following affect your confidence?

2.1. The effect on cardiovascular hospitalization.

2.2. Consistency of the mortality effect across prespecified subgroups.

2.3. Consistency of the mortality effect across non-prespecified subgroups.

2.4. Other secondary end points suggestive of a mechanism for the mortality effect.

3. Without formally specifying how we do so, we may be comforted or discomforted about a finding by information derived from other studies. In considering the mortality effect discovery in CAPRICORN, how do the following affect your confidence?

3.1. COPERNICUS

3.1.1. How relevant and supportive are the COPERNICUS data (overt heart failure remote from any myocardial infarction) for establishing a mortality effect in the post-MI population, given…

3.1.1.1. … the relationship between the two populations?

3.1.1.2. … the types of deaths apparently affected by treatment in the two settings?

3.1.1.3. … the time course over which the effects on mortality were manifest?

3.1.2. How concordant are the findings on cardiovascular hospitalization?

3.2. CHAPS

3.2.1. How relevant and supportive are these data for establishing a mortality effect in the post-MI population, given…

3.2.1.1. … the relationship between the two populations?

3.2.1.2. ... the types of deaths apparently affected by treatment in the two settings?
3.2.1.3. ... the time course over which the effects on mortality were manifest?
3.2.1.4. ... the high withdrawal rate?
3.3. Any other relevant studies?

4. Without formally specifying how we do so, we may be comforted or discomforted about a finding by information derived from studies of related drugs.
   4.1. If one were to do that with post-MI use of carvedilol, would one include any drug with any of its pharmacological properties—beta blocker, alpha blocker, free radical scavenger, anti-hypertensive—or only drugs with all of these properties?
   4.2. Would one be interested in survival trials only, any trials with survival data, or other end points as well?
   4.3. Are there relevant results with other drugs?

5. All things considered, how likely is it that the mortality effect in CAPRICORN represents an effect attributable to carvedilol?

6. Should carvedilol be indicated to reduce mortality in patients with left ventricular dysfunction after myocardial infarction?

7. The Sponsor also seeks a claim for reduction in recurrent MI, based on the observation of 45 adjudicated events on placebo and 27 on carvedilol (of which 16 and 12 were fatal). Do these data support a claim?