Nebivolol Advisory Committee

Shona Pendse, MD, MMSc (Clinical)

John Lawrence, Ph.D (Statistics)

January 11, 2010

Agenda

- Review issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

Agenda

- Review issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

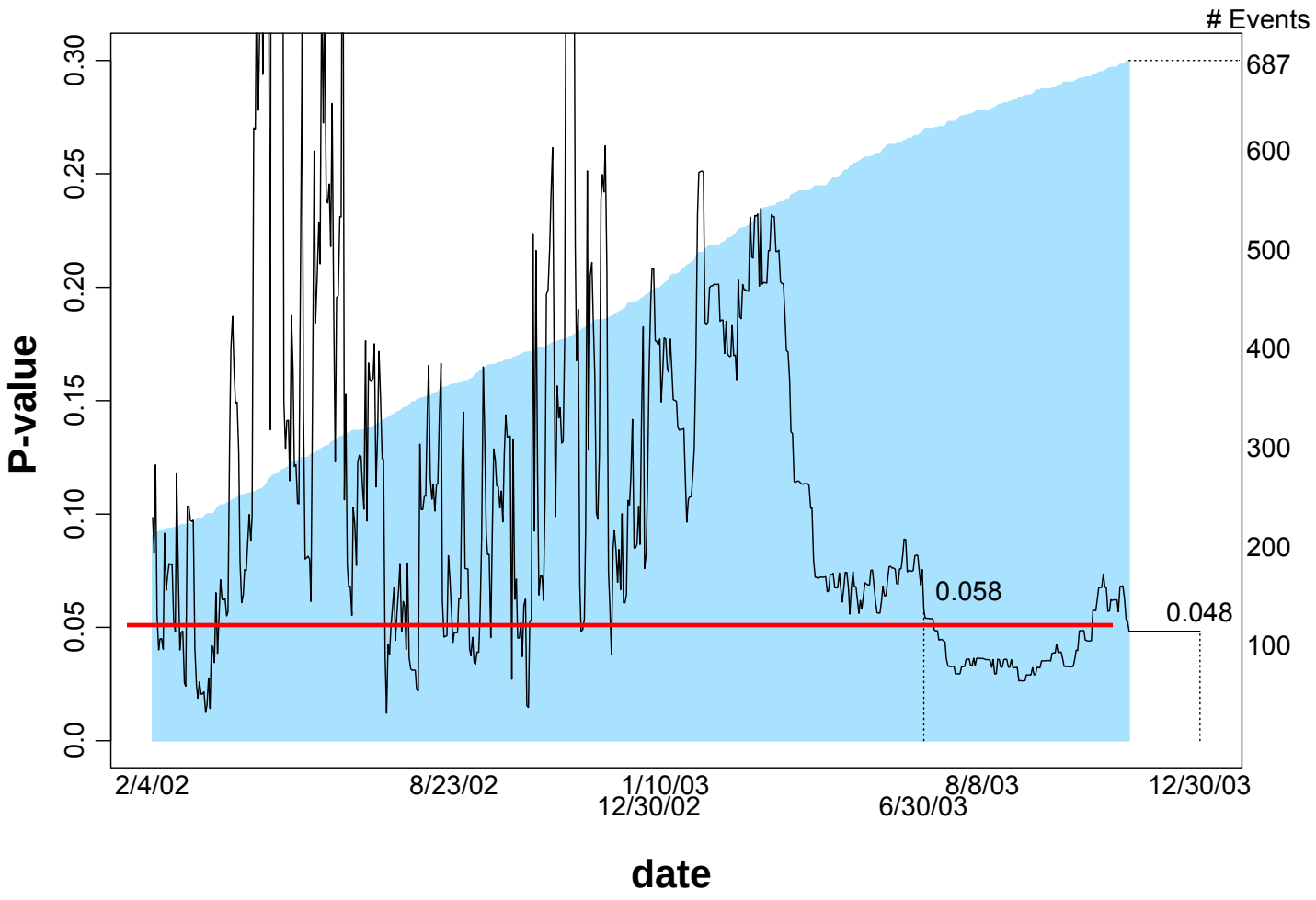
Review Issues

- Single trial with results that are not robust
- Two changes made late in the conduct of the trial
- Relevance of the composite endpoint of all cause mortality and cardiovascular hospitalization
- Generalizability of results

Agenda

- Key issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

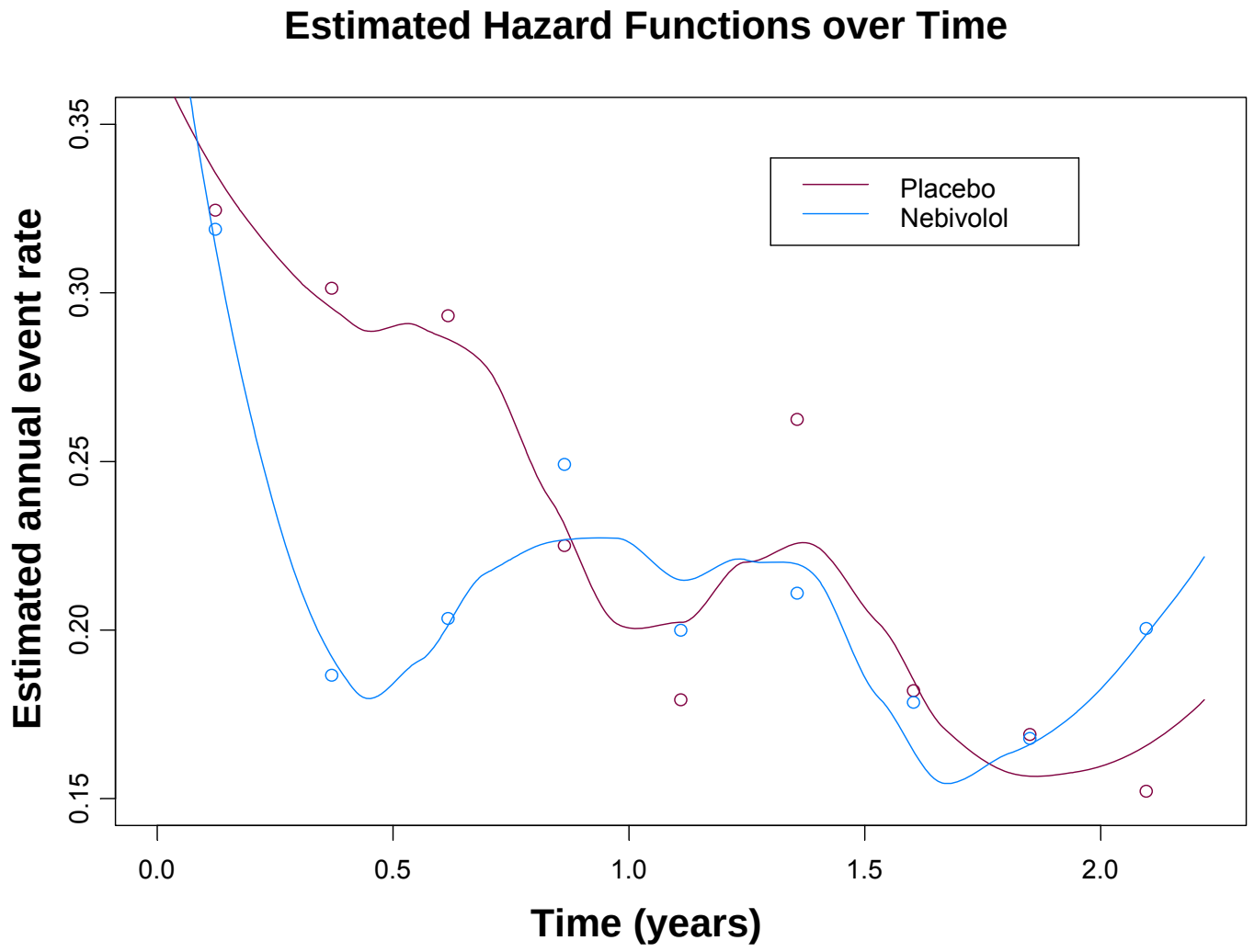
Results were not Robust



A Change in Outcomes of a Few Subjects Changes the Results

- The number of subjects whose outcomes needed to change p-value from 0.039 to greater than 0.05:
  - two fewer events in the placebo group
  - three more events in the nebivolol group

Hazard Functions and Ratio are Not Constant



Trial Design

Already presented by the Applicant this morning

Agenda

- Key issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

Changes in the SENIORS study

1. Increase in the minimum time subjects were followed from 6 to 12 months
2. Late change in analytic plan to include vital status (but not hospitalization) of discontinued subjects in primary analysis

1st Change: Length of Follow-up

- The original protocol stipulated that subjects were to be followed for a minimum of 6 months
- The Steering Committee [SC], during their meeting in September 2002, discussed whether to increase the duration of follow-up
  - Per the SC minutes, the reason was to “increase the power of the study”

Prolongation of the Study was Allowed only for Increasing the Power

NOTE TO FILE

Dated March 25, 2003

Statement of the SENIORS Steering Committee
Issue: Prolongation of study

On March 25, 2003 the Steering Committee decided to increase the power of the study by prolongation of the minimum observation period for all patients from 6 to 12 months. Furthermore, it was decided to make all efforts to reinforce compliance and whenever possible to restart study medication intake. Attempts are being made to obtain follow-up data for all patients who withdrawn the trial.

The decision was based on the recommendation of the Data Safety and Monitoring Committee given after the review of the data of the 3rd Interim Analysis (see encl.).

The prolongation of the study is in compliance with the SENIORS study protocol as mentioned in chapter 13.3 Prolongation of Study:
"The study can be prolonged by the Steering Committee until the study is adequately powered."

Notes of the SC - Events Required to Achieve 90% Power

Post meeting note: 578 events would be required to reach 90% power (α 0.05, risk reduction 25%, log rank test, 20% non-compliance to treatment). This number is not given in the protocol. Currently there have been 339 events reported and about 50% of the patient years observed.

- The SC notes indicate that a total of 578 events would be required to achieve 90% power
- By that time, 339 events had accrued (>50% of the necessary events) and ~ 50% of the trial had been completed
- Thus, the trial was already well on its way to achieving adequate power

SC Decision is Based on Data Safety and Monitoring Committee (DSMC) Recommendation

NOTE TO FILE

Dated March 25, 2003

Statement of the SENIORS Steering Committee
Issue: Prolongation of study

On March 25, 2003 the Steering Committee decided to increase the power of the study by prolongation of the minimum observation period for all patients from 6 to 12 months. Furthermore, it was decided to make all efforts to reinforce compliance and whenever possible to restart study medication intake. Attempts are being made to obtain follow-up data for all patients who withdrawn the trial.

The decision was based on the recommendation of the Data Safety and Monitoring Committee given after the review of the data of the 3rd Interim Analysis (see encl.).

The prolongation of the study is in compliance with the SENIORS study protocol as mentioned in chapter 13.3 Prolongation of Study:
"The study can be prolonged by the Steering Committee until the study is adequately powered."

DSMC Recommendation

1. The DSMC reiterates its strong support to any plan of the Steering Committee to increase the power of the study by extending minimum follow-up from 6 to 12 months.

SENIORS DSMC: Summary of guidelines and procedures

4. The DSMC will be unblinded to treatment group in these interim analyses, so that the respective tabulations will be labelled 'nebivolol' and 'placebo'. All interim analyses will be by intention-to-

Increase in Duration of Follow-up Decreases p-value for the 1° Endpoint

- If only data through 6 months of follow-up is analyzed ** (original protocol), p value is not significant [p = 0.058]
- Increase to 12 month follow-up [p = 0.048] **

** Analysis as planned in original protocol, i.e. without including deaths from discontinued subjects and without adjustment for covariates of LVEF, sex, or age

2nd Change: Inclusion of Vital Status in the 1° Endpoint

- January 20th, 2004

Based on the recommendation of the Data Safety and Monitoring Committee given after their meeting on October 16, 2002 the Steering Committee decided that all attempts should be done to obtain follow-up vital status data on all patients who discontinued the trial (see enclosure 1).

Statistical analysis of the vital status information:

Vital status data will be handled as additional information and analysed by descriptive statistics.

Inclusion of Information From Only One Component of the 1° Endpoint

- July 9th, 2004 (one day prior to data lock)
  - The applicant subsequently amended the analytic plan to include mortality but not cardiovascular hospitalization data from discontinued subjects in the analysis of the composite primary endpoint

"These data will be considered in the primary outcome as long as the information has been obtained from a reliable source and if the date of death is available"

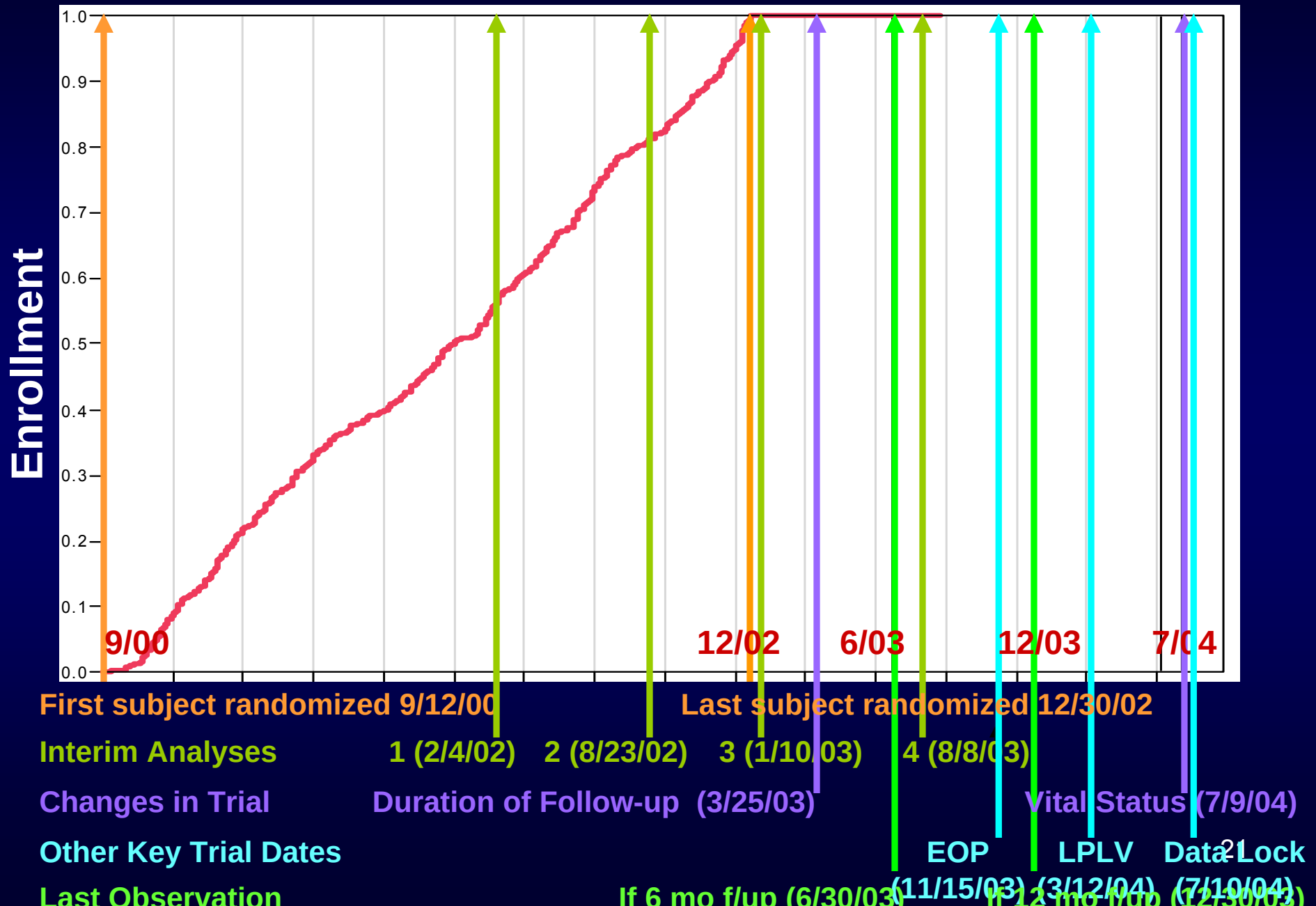
Eliminating 'Vital Status' Subjects Increases the P-value

- Subject deaths found by telephone inquiry*:
  - 8 deaths in 61 discontinued subjects (nebivolol)
  - 12 deaths in 54 discontinued subjects (placebo)
- P-value increases to 0.049 ** for the treatment effect (0.039 if not included)

* Vital status not obtained for 16 (nebivolol) and 21 (placebo) subjects

** Using the extended follow-up period of 12 months and adjusting for age, sex, and LVEF – but eliminating the 'vital status' deaths (if no adjustment for age, sex, and LVEF is done, the p-value using the 12 month follow-up is 0.048)

Trial Time-Line



Agenda

- Key issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

Risk of All-Cause Hospitalization: Similar in Both Treatment Groups

Cause for Hospitalization	Nebivolol n=1067	Placebo n=1061
Cardiovascular	256 (24.0%)	276 (26.0%)
Non-Cardiovascular	164 (15.4%)	148 (13.9%)
All-Cause	420 (39.4%)	424 (39.9%)

Adjudication of Bradycardia

- Sinus bradycardia leading to pacemaker placement.
- Investigator cites the cause for hospitalization as “sinus bradycardia”
- “chephalea with right cervicalgy” and “...sensations lasting several weeks of occipital and retro-ocular heaviness”.
- Admission pulse 57
- Carotid sinus massage was performed
  - Revealed “hypersensibility” of the carotid sinus with a greater than 4 second pause
  - pacemaker placed 13 days after the admission
- Adjudicated to be non-CV hospitalization

Adjudication of Bradycardia

- Presented with a non-serious AE of hypoglycemia and a SAE of sinus bradycardia
- Symptoms included asthenia, hypoglycemia, and sinus bradycardia
- Vital signs measurements or ECG tracings to document the degree of bradycardia were not provided to the endpoint committee
- Adjudicated to be a non-CV hospitalization

Adjudication

- Difficult for the endpoint committee if the information is
  - Difficult to interpret
  - Missing critical data (i.e. heart rate in the case of bradycardia)

Beta Blockers for Heart Failure

	COPERNICUS **Carvedilol (n = 2289)**	MERIT-HF **Metoprolol (n = 3991)**	SENIORS **Nebivolol (n = 2135)**
Age: Criteria/Mean	> 18 / ~ 63	40-80 / ~ 64	≥ 70 / ~ 76
Race (Af-Am)	5-6%	5%	0.1%
EF: Criteria/Mean	<25% / 20%	≤ 40% / 28%	None / 36%
Mean follow-up	10.4 months	12 months	21 months
Risk Reduction (All-cause mortality)	34%, p = 0.001 132 (11.4%) ßBl vs 191 (16.9%)	34%, p = 0.006 145 (7.3%) ßBl vs 217 (10.8%)	12%, p = 0.214 169 (15.8%) ßBl vs 192 (18.1%)

Agenda

- Key issues
- Results
- Changes in conduct and analysis of the trial
- Cardiovascular versus all-cause hospitalization
- Points to consider

Points to Consider

- Single trial with results that were not robust
  - Changing how a few outcomes are handled can alter the results importantly
- Two changes were made late in the trial
  - Extension of the minimum follow-up period
    - Based on recommendation of the unblinded DSMC
  - Change in primary endpoint: addition of mortality information for discontinued subjects (1 day prior to data lock)

Points to Consider (2)

- For discontinued subjects, only all-cause mortality information was ascertained, not hospitalization information
  - Is it proper to add information pertaining only to one component of a composite when the other is unknown? Should both or neither have been included?
  - Since 80% of the observed endpoint events in the 1° analysis were cardiovascular hospitalizations, should we be concerned about not capturing hospitalization in some subjects?

Points to Consider (3)

- No difference in risk of all-cause hospitalization despite apparent difference in cardiovascular hospitalization
  - If the endpoint committee is given records which are difficult to interpret or missing critical data (i.e. heart rate in a case of bradycardia), adjudication becomes difficult
  - Bradycardia not systematically adjudicated as a cardiovascular hospitalization

Points to Consider (4)

- The applicant claims the nebivolol is effective in treating all adult patients with HF but the trial enrolled only subjects greater than 70 years of age
  - If the data from this trial are adequate to support a claim, should the claim apply only to elderly patients?