



# Questions

doxazosin  
24 May 2001

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

The Cardio-Renal Advisory Committee is asked to consider what labeling changes, if any, are appropriate for doxazosin, based on the currently available data from the ALLHAT study.

1. Consider the following issues related to the interpretation of the ALLHAT findings regarding doxazosin.
  - 1.1 The ALLHAT protocol restricted the maximum dose of doxazosin to 8 mg, but the label encourages use up to 16 mg. ALLHAT had dose titration at 1-month intervals, but the label encourages titration at 1- to 2-week intervals. Do the results of ALLHAT apply to doxazosin when it is used as labeled?
  - 1.2 At 3 years, only 76% of subjects randomized to doxazosin were still taking it. How should subjects not taking doxazosin be included in any analysis?
  - 1.3 Diastolic blood pressure control was similar in the doxazosin and chlorthalidone treatment groups, but systolic control was less similar. Might any differences in outcome be attributable to the degree of systolic blood pressure control?
  - 1.4 The primary end point in ALLHAT was the combined incidence of fatal coronary heart disease plus nonfatal myocardial infarction. The primary hypotheses were that the three comparator arms would be superior to chlorthalidone; this was not an equivalence study.
    - 1.4.1 Did ALLHAT demonstrate a difference between doxazosin and chlorthalidone for the primary end point?
    - 1.4.2 If not, how should one interpret any secondary end point when the primary end point showed no significant difference?
  - 1.5 The secondary end point that worried the DSMB was combined cardiovascular disease, one of numerous pre-specified secondary end points. How is the interpretation of a p-value for one secondary end point affected by this setting?
  - 1.6 The publications attribute the excess cardiovascular events in the doxazosin arm largely to excess CHF. This analysis was retrospective.
    - 1.6.1 How was CHF diagnosed?
    - 1.6.2 Was there a potential for bias in the diagnosis of CHF?
    - 1.6.3 Chlorthalidone and lisinopril are used to treat heart failure. How might the inclusion of these drugs in the study have affected the reporting of the signs and symptoms of heart failure?
  - 1.7 ALLHAT is still in progress. The data from ALLHAT are not available for FDA review. Are there questions of interpretation that can be addressed only by review of the complete data from all four arms of the completed trial?

2. Which of the following can be taken today as adequately established?
  - 2.1 Doxazosin is less effective than other treatments for (the ALLHAT primary end point of) prevention of fatal coronary heart disease and nonfatal myocardial infarction.
  - 2.2 Doxazosin is less effective than other treatments for (the ALLHAT secondary end points of) ...
    - 2.2.1 ... all cause mortality.
    - 2.2.2 ... combined coronary heart disease plus revascularization procedures plus hospitalized angina.
    - 2.2.3 ... stroke.
    - 2.2.4 ... left ventricular hypertrophy by ECG.
    - 2.2.5 ... renal disease by slope and reciprocal of serum creatinine or by need for chronic dialysis or transplant.
    - 2.2.6 ... health-related quality of life.
    - 2.2.7 ... major costs of medical care.
    - 2.2.8 ... fatal or nonfatal cancer.
    - 2.2.9 ... gastrointestinal bleeding.
    - 2.2.10 ... combined coronary heart disease plus stroke plus coronary revascularization procedures plus angina (hospitalized or medically treated) plus CHF (hospitalized or medically treated) plus peripheral arterial disease (hospitalized or outpatient revascularization procedure).
  - 2.3 Doxazosin is less effective than other treatments for (the ALLHAT other protocol-specified outcome measurements or end points of) ...
    - 2.3.1 ... mortality from coronary heart disease.
    - 2.3.2 ... mortality from other cardiovascular disease.
    - 2.3.3 ... mortality from neoplastic disease.
    - 2.3.4 ... mortality from other medical causes.
    - 2.3.5 ... mortality from non-medical causes.
    - 2.3.6 ... myocardial infarction.
    - 2.3.7 ... angina.
    - 2.3.8 ... peripheral arterial disease.
    - 2.3.9 ... nonfatal accidents and attempted suicides.
    - 2.3.10 ... CHF.
3. If you answered in the affirmative for any part of question 2, ...
  - 3.1 ... was doxazosin worse than placebo would have been?
  - 3.2 ... in comparison with which other treatments is doxazosin less effective?
  - 3.3 ... do the findings generalize to other drugs ...
    - 3.3.1 ... with predominant alpha-adrenergic antagonist activity?
    - 3.3.2 ... with alpha-adrenergic antagonist activity, in part?
    - 3.3.3 ... that block alpha-adrenergic transmission?
    - 3.3.4 ... with similar effects on systolic and diastolic pressure?
4. Should an antihypertensive agent be considered as "second line" if it is ...
  - 4.1 ... less safe than another agent?
  - 4.2 ... less effective at reducing systolic or diastolic pressure?
  - 4.3 ... less effective in reducing cardiovascular events? If so, which ones?
  - 4.4 ... less effective in reducing mortality?

5. What action is now indicated for doxazosin?
  - Withdraw marketing approval.
  - Change label to ...
    - ... remove indication for essential hypertension.
    - ... indicate for second-line use in hypertension.
    - ... add a "black box warning".
    - ... add a "bolded warning".
    - ... describe clinical trial findings.
  - Other actions.
  - No action.
  
6. What action is indicated ...
  - 6.1 ... for drugs with a similar mechanism of action?
  - 6.2 ... for drugs with a similar profile of effects on systolic versus diastolic pressure?
  - 6.3 ... for chlorthalidone?