**Sample Journal Club Items**

The items below are based on the following study: Jamerson K, Weber MA, Bakris GL, et al; for the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417-28.

1. The ACCOMPLISH study was a double-blind study. What does *double-blind* mean within the context of this study?

1. The study team knew the medication combination each subject received, but the treating physician did not know the medication combination each subject received
2. The study team did not know the medication combination each subject received, and the treating physician did not know the medication combination each subject received
3. The study team did not know the medication combination each subject received, but the treating physician knew the medication combination each subject received
4. The study team did not know the medication combination each subject received, and the subjects did not know which medication combination they received

**Answer: D**

Rationale: *Double-blind* is a term used to describe an experiment in which neither the group of people who are doing the experiment (study team) nor the people who are the subjects of the experiment know which of the groups being studied is the control group and which is the test group. Blinding does not refer to the individual treating physician. Single blinding refers to a situation in which either the treatment team OR the study subject knows which treatment was received.

2. Which one of the following sets of outcomes was included in the primary composite outcome of the ACCOMPLISH trial?

A. Stroke, hospitalization for unstable angina, and sudden death from myocardial infarction (MI)

B. Nonfatal MI, hospitalization for heart failure, and coronary revascularization

C. Resuscitation after sudden cardiac arrest, death from sudden cardiac causes, and hypertensive urgency

D. Stroke, nonfatal MI, and hospitalization for diabetic ketoacidosis (DKA)

**Answer: A**

Rationale: The primary end point was a composite of cardiovascular (CV) events (defined as nonfatal MI, stroke, hospitalization for unstable angina, coronary revascularization, or resuscitation after sudden cardiac arrest) and death from CV causes (death from sudden cardiac causes, MI, stroke, coronary intervention, congestive heart failure, or other CV cause). Neither hypertensive urgency nor hospitalization for heart failure or DKA was defined within the composite outcome.

3. What was the null hypothesis of the ACCOMPLISH trial?

1. Treatment with amlodipine/benazepril would result in better cardiovascular outcomes than treatment with benazepril/hydrochlorothiazide.
2. Treatment with benazepril/hydrochlorothiazide would result in better cardiovascular outcomes than treatment with amlodipine/benazepril.
3. No differences would be observed in blood pressure changes between treatment with amlodipine/benazepril and treatment with benazepril/hydrochlorothiazide.
4. Treatment with either amlodipine/benazepril or benazepril/hydrochlorothiazide would result in no significant differences in cardiovascular outcomes.

**Answer: D**

Rationale: The ACCOMPLISH trial used a superiority design to test whether treatment with amlodipine/benazepril would result in better cardiovascular outcomes than treatment with benazepril/hydrochlorothiazide. The null hypothesis is therefore that there are no differences between the two treatments in those outcomes.

4. True or False: The end points reported by the ACCOMPLISH study investigators are considered adjudicated endpoints.

**Answer: False**

Rationale: Adjudication is the process whereby end points reported by study investigators are verified as actual study end points. This usually involves a blinded independent committee that follows an a priori process to obtain medical records or other source documentation to review and confirm whether the event meets the criteria as an end point.

5. The study was powered using an α of 0.05 and a β of 0.90. Which is a correct interpretation of this in relation to the null hypothesis of the study?

1. There is a 10% chance of concluding there is no difference between treatments when one actually exists.
2. There is a 90% chance of concluding there is a difference between treatments when one does not actually exist.
3. There is less than a 5% chance of concluding there is no difference between treatments when one actually exists.
4. There is a 95% chance of concluding there is a difference between treatments when there is not.

**Answer: A**

Rationale: The null hypothesis is that the two treatments are equal (or not different). β reflects the probability of a type II error, which is failure to find a difference between the two treatments when one actually exists. A power of 0.90 leaves a 10% chance of mistakenly accepting the null hypothesis.

6. Which factor was **least** likely to bias the findings of the trial in favor of the amlodipine/benazepril group?

1. Hydrochlorothiazide was used at a 25-mg dose, which may have been less effective at lowering blood pressure.
2. The two treatment groups did not achieve the same levels of blood pressure lowering.
3. Uncorrected hypokalemia in the benazepril/hydrochlorothiazide group may have led to increased cardiovascular events.
4. Calcium channel blockers are known to reduce revascularization rates, which may have driven the primary composite to significance.

**Answer: B**

Rationale: In ACCOMPLISH, the subjects in the amlodipine/benazepril group achieved slightly lower levels of blood pressure than did the subjects receiving benazepril/hydrochlorothiazide. However, although this may have contributed to the finding of better cardiovascular outcomes in the amlodipine/benazepril group, it would not be considered a bias. Biases are usually factors present at the outset of the study that may influence the final outcome. For example, biases would exist had unconventional doses of benazepril/hydrochlorothiazide, or different goal blood pressures and strategies to obtain them with add-on therapies, been study factors established at the outset.

7. “Written informed consent” for the ACCOMPLISH study refers to which one of the following?

1. A member of the study team asks the treating physician to sign a form indicating that it is acceptable for the physician’s patients to participate in the trial.
2. A member of the study team asks the patient to sign a form indicating his or her willingness to participate in the trial.
3. A member of the study team asks both the patient and the treating physician to sign a form indicating the patient’s willingness to participate in the trial.
4. The treating physician asks the patient to sign a form indicating his or her willingness to participate in the trial.

**Answer: B**

Rationale: Informed consent is permission granted in the knowledge of the possible consequences, by a patient to the study team, with full knowledge of the possible risks and benefits.

8. What is the number needed to treat (NNT) with amlodipine/benazepril to prevent one additional cardiovascular end point compared with benazepril/hydrochlorothiazide?

1. 12
2. 282
3. 39
4. 46

**Answer: D**

Rationale: NNT = 1/ARR, where ARR is absolute risk reduction. The primary end point occurred in 9.6% of subjects receiving benazepril/amlodipine and in 11.8% of subjects receiving benazepril/hydrochlorothiazide. NNT = 1/(0.118 − 0.096) = 45.5. When determining the NNT, the calculated number should always be rounded up; therefore, an NNT of 45.5 would be rounded to 46.

9. True or False: When considering the secondary end points in the ACCOMPLISH trial, patients receiving benazepril/amlodipine had a significant reduction in cardiovascular events versus those receiving benazepril/hydrochlorothiazide.

**Answer: True**

Rationale: For the secondary end point of death from cardiovascular causes plus nonfatal myocardial infarction and nonfatal stroke, 288 events (5.0%) occurred in the benazepril/amlodipine group compared with 364 events (6.3%) in the benazepril/hydrochlorothiazide group, representing an absolute risk reduction of 1.3 percentage points and a relative risk reduction of 21.2% (hazard ratio 0.79; p=0.002). For the secondary end point of cardiovascular events, there were 494 events (8.6%) in the benazepril/amlodipine group and 592 events (10.3%) in the benazepril/hydrochlorothiazide group , representing an absolute risk reduction of 1.7 percentage points and a relative risk reduction of 17.4% (hazard ratio 0.83; p=0.002).

10. The hazard ratio (95% confidence interval [CI]) for the primary composite end point in ACCOMPLISH was 0.80 (95% CI, 0.72–0.90) in favor of the benazepril/amlodipine group compared with the benazepril/hydrochlorothiazide group. Which of the following statements best describes the risk of the end point between the treatment groups?

1. There was a 20% relative risk reduction in the primary composite end point in favor of treatment with benazepril/amlodipine.
2. There was an 80% relative risk reduction in the primary composite end point for patients treated with benazepril/amlodipine.
3. There is a 5% chance that the true hazard ratio falls between 0.72 and 0.90.
4. There is a 95% chance that the true relative risk reduction between groups is between 72% and 90%.

**Answer: A**

Rationale: A hazard ratio of 1.0 would reflect no difference in the event rate between groups. 1 ‒ 0.80 = 0.20, or a 20% reduction in the relative risk of the composite end point. The 95% CI does not cross 1.0, so we are 95% certain that the true hazard ratio lies between 0.72 and 0.90 (as much as a 28% reduction in risk or as little as a 10% reduction in risk).

**References:**

1. Jamerson K, Weber MA, Bakris GL, et al; for the ACCOMPLISH Trial Investigators. [Benazepril plus amlodipine or hydrchlorthiazide for hypertension in high-risk patients](http://www.ncbi.nlm.nih.gov/pubmed/19052124). N Engl J Med 2008;359:2417-28.

2. DiCenzo R, ed. Clinical Pharmacist’s Guide to Biostatistics and Literature Evaluation. Lenexa, KS: American College of Clinical Pharmacy, 2011.

3. Hulley SB, Cummings SR, Browner WS, et al. Designing Clinical Research, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2013.

4. Riegelman RK. Studying a Study and Testing a Test: Reading Evidence-Based Health Research, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2013.

5.Tripepi G, Jager KJ, Dekker FW et al. [Measures of effect: Relative risks, odds rations, risk difference, and ‘number needed to treat’](http://www.ncbi.nlm.nih.gov/pubmed/17653136). Int Soc Neph. 2007: 789-791.

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