FDA Advisory Committees: Message to Pharmaceutical Industry and Academia

Michael Proschan

NIAID

Disclaimer

- This is a bait and switch talk
- I don’t really have general messages to the pharmaceutical industry and academia
- My comments concern participation as an FDA Advisory Committee panel member or as a presenter to an FDA Advisory Committee

Introduction

- FDA Advisory Committees are outside experts without major conflicts of interest
  - MDs with expertise in specialty under study
  - Statisticians & epidemiologists
  - Other experts as needed
  - Patient/Consumer Representative
  - Industry representative (non-voting)

Introduction

- FDA asks specific questions like:
  - Do you have significant safety concerns with respect to liver toxicity with Product X?
  - Has the sponsor demonstrated efficacy of product X with respect to CHD?
- Committee discusses issues, votes on questions & recommendations to FDA
- FDA makes ultimate decision on approval

Introduction

- Typical order of meetings
  - Sponsor presents
  - Committee asks “clarifying” questions
  - FDA presents
  - Committee asks “clarifying” questions
  - Public Hearing portion
  - Advisory Committee discussion/deliberation
  - Advisory Committee votes & explains vote

Interpretations, not Datasets

- Before meeting, you get briefing documents—FDA's and sponsor's interpretations of data, not datasets
  - Good: not as much work
  - Bad: you can't do your own analyses
- Given that you get only 2 interpretations, want to quickly find where they disagree
  - I read FDA briefing document first
  - If FDA has no issues, easy decision

They Don't Give You The Easy Ones

- Very rarely, decisions are easy
  - Sometimes the FDA is required to have FDA Advisory Committee meetings, even if they agree with sponsor (e.g., when there is a new molecular entity)
- Usually the FDA and Sponsor disagree about some things
- You usually don't get the easy ones
  - If they were easy, they wouldn't need you!

Analogous to Criminal Trial

- Advisory Committees have commonalities with criminal trials
  - Sponsor is like prosecutor: must prove case beyond reasonable doubt
  - FDA is like defense: makes sponsor prove their case
  - Advisory Committee like jury
    - Sometimes 1 or 2 members are very influential
    - Difference from jury: experts, not peers

Analogous to Criminal Trial

- Each side has its own experts
- Each side presents case separately
  - Evidence can seem overwhelming after one side, but then change when other side presents
- Discovery process: each side sees other side's evidence before trial
- Good strategic decision to present your side's weaknesses before other side does
  - Never want to give impression of hiding something

Analogous to Criminal Trial

- One important difference from criminal trial: jury (Advisory Committee) sees evidence in advance
  - Voluminous materials sent out weeks in advance (though “jury” doesn’t always read them)
- Still, sometimes things come up and you have to think fast
- Example: LOTS trial of Pompe disease

LOTS Trial and Minimization

- 10/21/2008 Endocrinologic and Metabolic Drugs Advisory Committee meeting on Pompe disease
  - Very rare, debilitating neuromuscular disease
    - Infant onset, juvenile onset, adult onset
  - Infant onset is most deadly, adult onset is still bad
  - Patients often progress to wheelchair dependence, ventilator, and death

LOTS Trial and Minimization

- Genzyme conducted Late Onset Treatment Study (LOTS)
- 90 patients with late onset Pompe disease
- Primary outcome: 6 minute walk test
- 2:1 allocation to drug/placebo using *minimization*
    - Try to balance on site, BL 6 minute walk (≤300m, >300m), and forced vital capacity (≤55% pred., >55% pred.)

LOTS Trial and Minimization

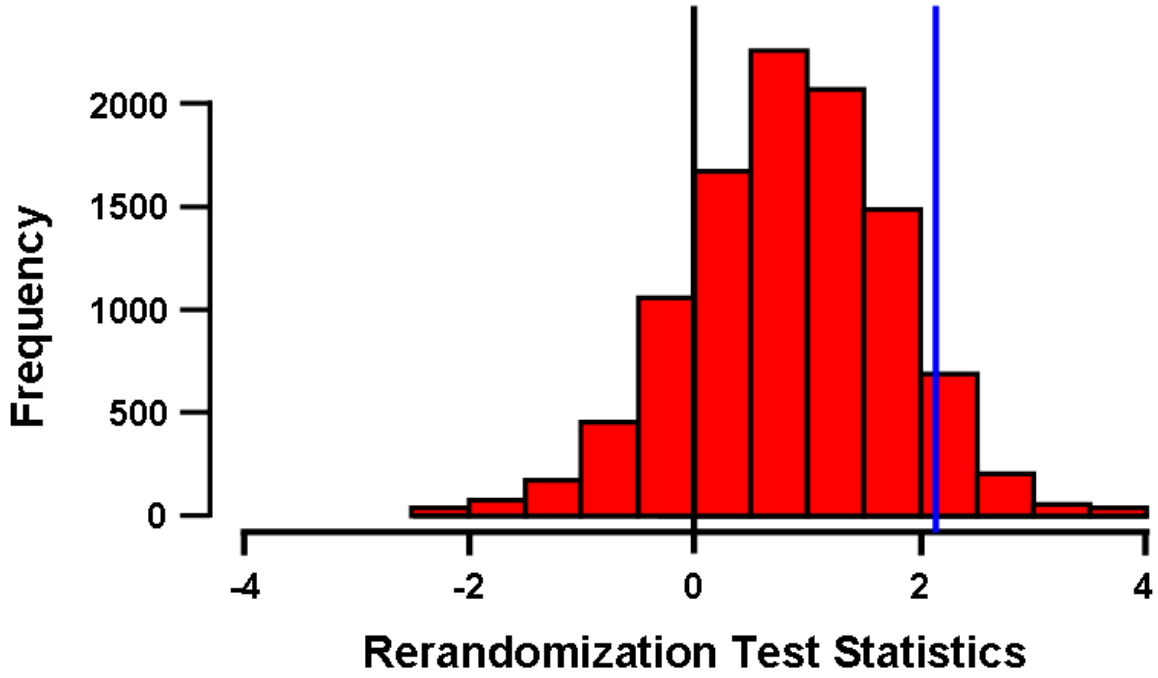
- The FDA is skeptical about minimization, so they require companies to use a re-randomization test
  - Compute observed test statistic T_{obs}
  - Fix data, regenerate treatment labels using allocation algorithm, compute T, and repeat thousands of times
  - Compute p-value by seeing where T_{obs} is in this *re-randomization distribution*

LOTS Trial and Minimization

- Proponents of minimization argue that you can do a re-randomization test, but it is unnecessary because you get about same answer as t-test
- The statistician argued that re-randomization test doesn’t work in LOTS

Problem with Application of Rerandomization Test in Analysis of 6MWT

- Distribution of 6MWT ANCOVA test statistics



ANCOVA p=.035

Re-randomization p=.06

LOTS Trial and Minimization

- Big problem: mean of re-randomization distribution is NOT 0 because of 2:1 allocation
  - It is 0 for standard randomization methods
- Nonzero mean causes loss of efficiency of re-randomization test: no longer close to t-test even for very large sample sizes
- Problem is that minimization severely limits amount of randomization

LOTS Trial and Minimization

- For more details on LOTS trial, see Van der Ploeg et al (2010) *NEJM* **362**, 1396-1406
- For more details about statistical problems minimization caused, see:

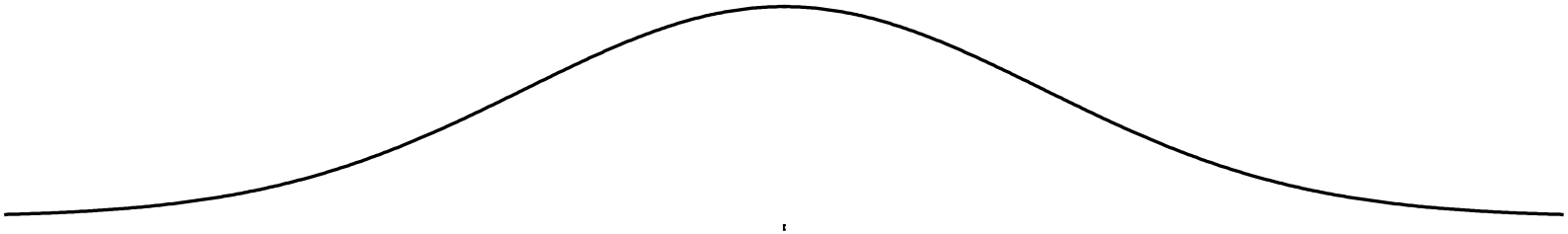
  Proschan, M., Brittain, E., and Kammerman, L. (2011). Minimize the use of minimization with unequal allocation. *Biometrics* **67**, 1135-1141

Experts and Presentation

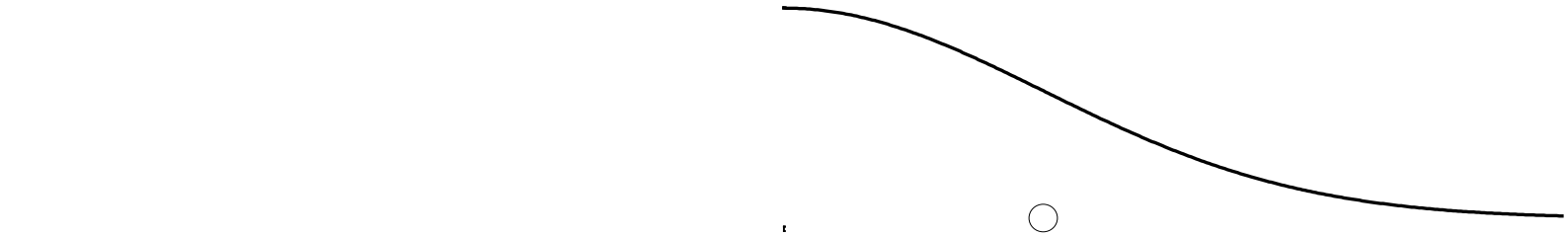
- Most important job for expert is to communicate effectively to statisticians and non-statisticians
  - Try to explain, not to impress
  - Give analogies
    - A p-value of .03 is like rolling a pair of sixes
    - Interaction:
      - 2 kids in the back seat
      - Will better team still win in soccer if it rains

Experts and Presentation

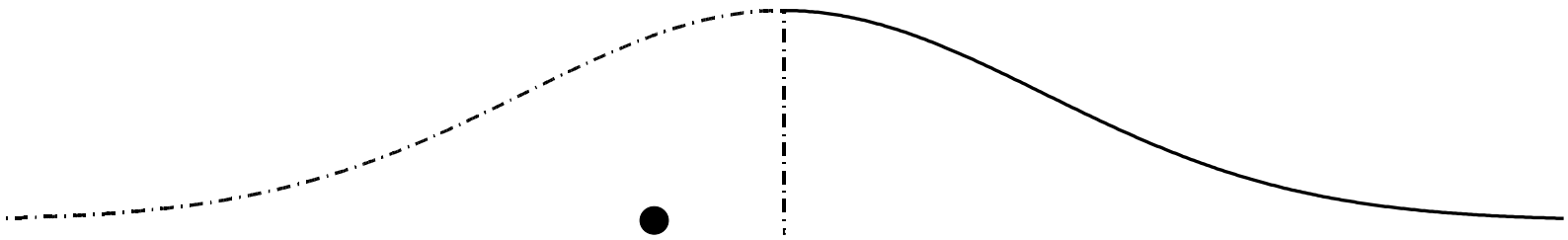
- Use graphs whenever possible
- Graphs are very helpful for illustrating statistical concepts
- E.g., for regression to the mean:



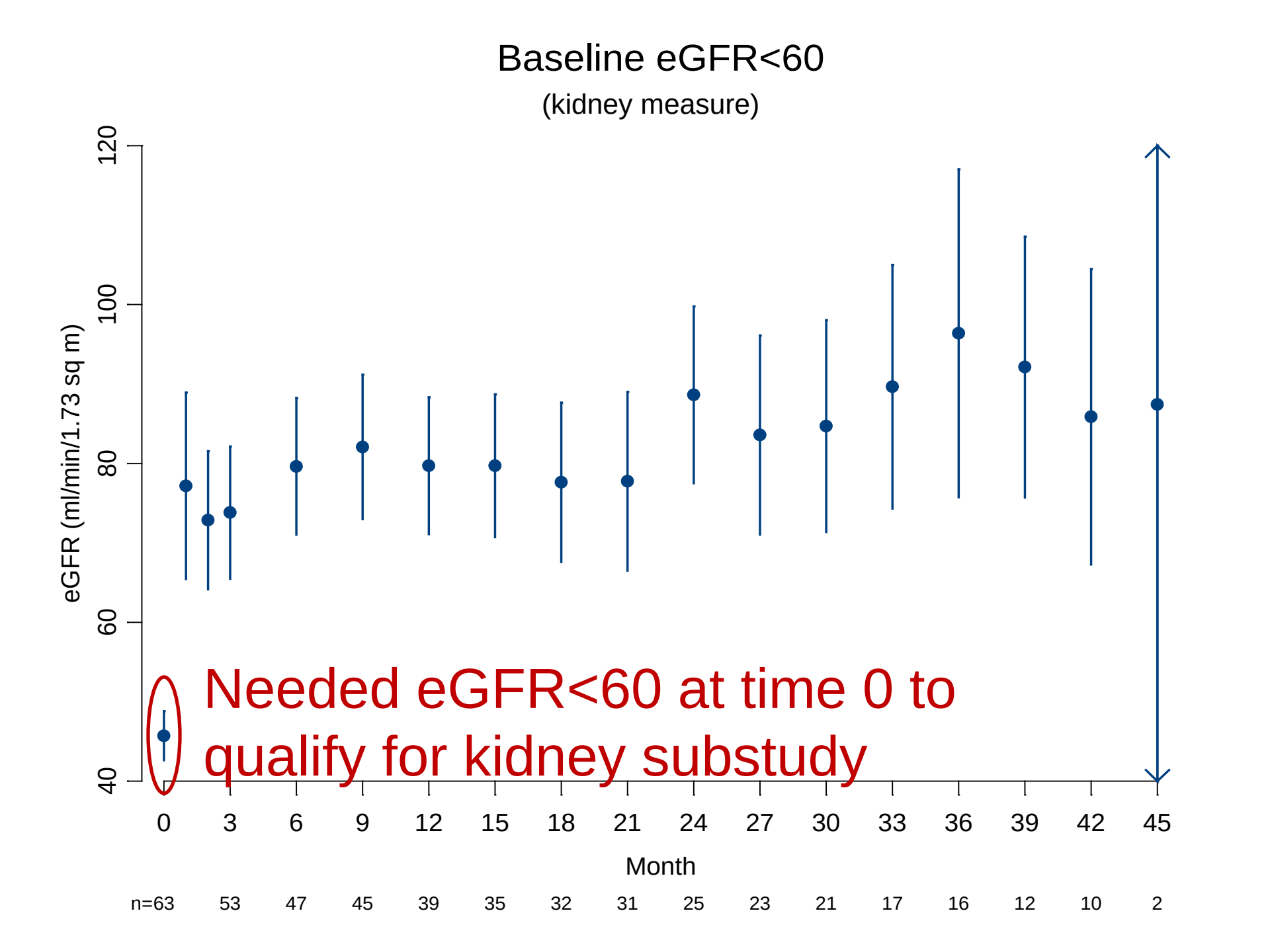
Cholesterol

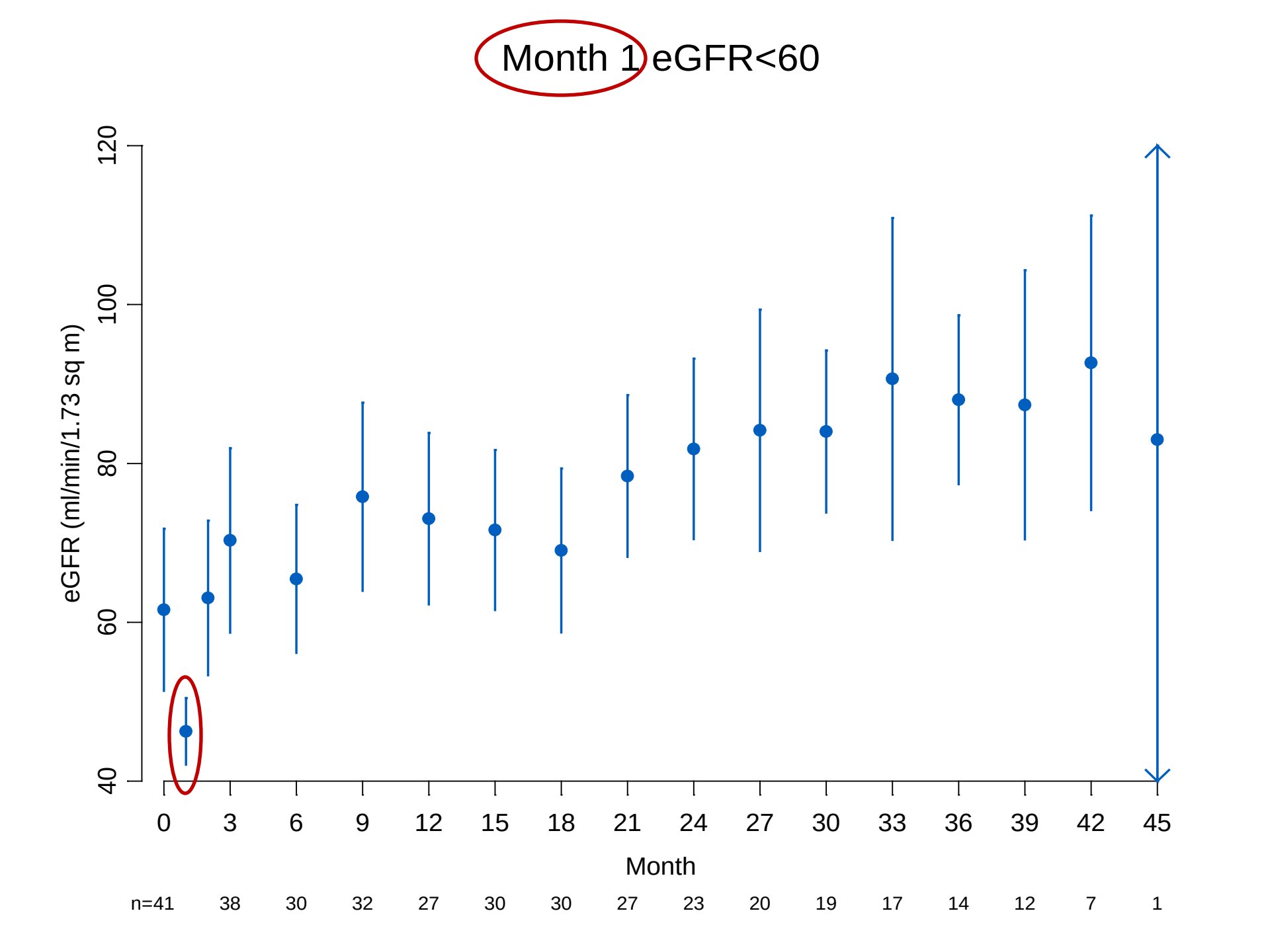


Baseline



End of Study


Baseline eGFR<60
(kidney measure)
eGFR (ml/min/1.73 sq m)
120
100
80
60
40
Needed eGFR<60 at time 0 to qualify for kidney substudy
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
Month
n=63
53
47
45
39
35
32
31
25
23
21
17
16
12
10
2

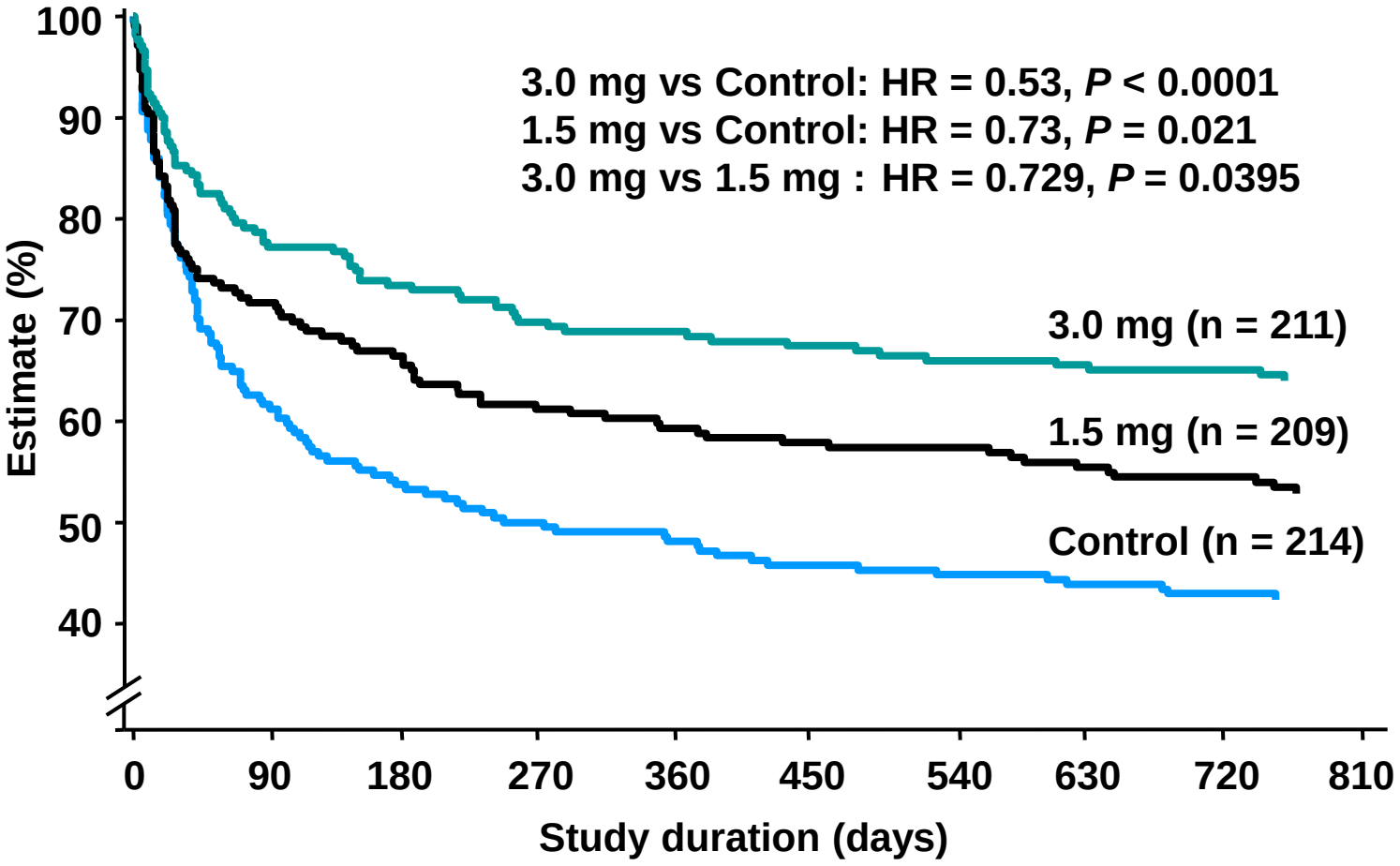

Month 1 eGFR<60
eGFR (ml/min/1.73 sq m)
120
100
80
60
40
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
45
Month
n=41
38
30
32
27
30
30
27
23
20
19
17
14
12
7
1

Experts and Presentation

- What to avoid in graphs:
  - Overcrowding with labels
  - Needless 3-dimensionality
  - Gratuitous use of colors
    - Think carefully about choice of colors (use placid blue for your drug, alarming red for placebo)
  - Scaling games

Freedom From Efficacy Failure Through 24 months

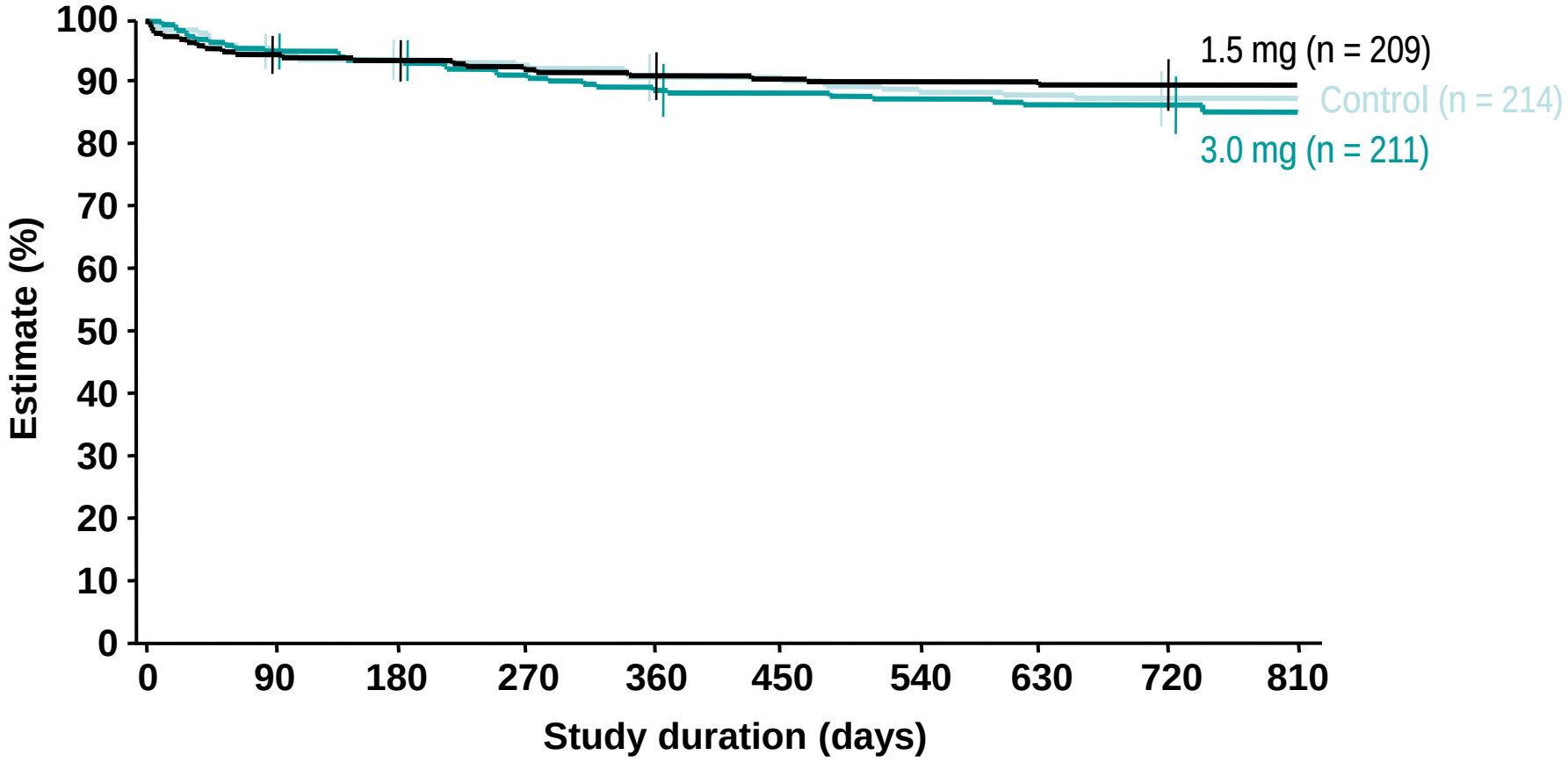
Study XXX—Kaplan-Meier Analysis



Prevention of rejection of heart in heart transplant

Survival* Through 24 months

Study XXX—Kaplan-Meier Analysis



95% CIs and number of patients at risk shown at 3, 6, 12, and 24 months.
***Freedom from graft loss/death/lost to follow-up through 24 months.**

Experts and Presentation

- Sometimes the experts are very well known (e.g., L.J. Wei, Richard Peto, Donald Rubin, etc.)
- If you are on AC, the FDA wants YOUR opinion; don’t be swept away if expert is famous
- No-no: “We have some world renowned experts here—let’s ask them”

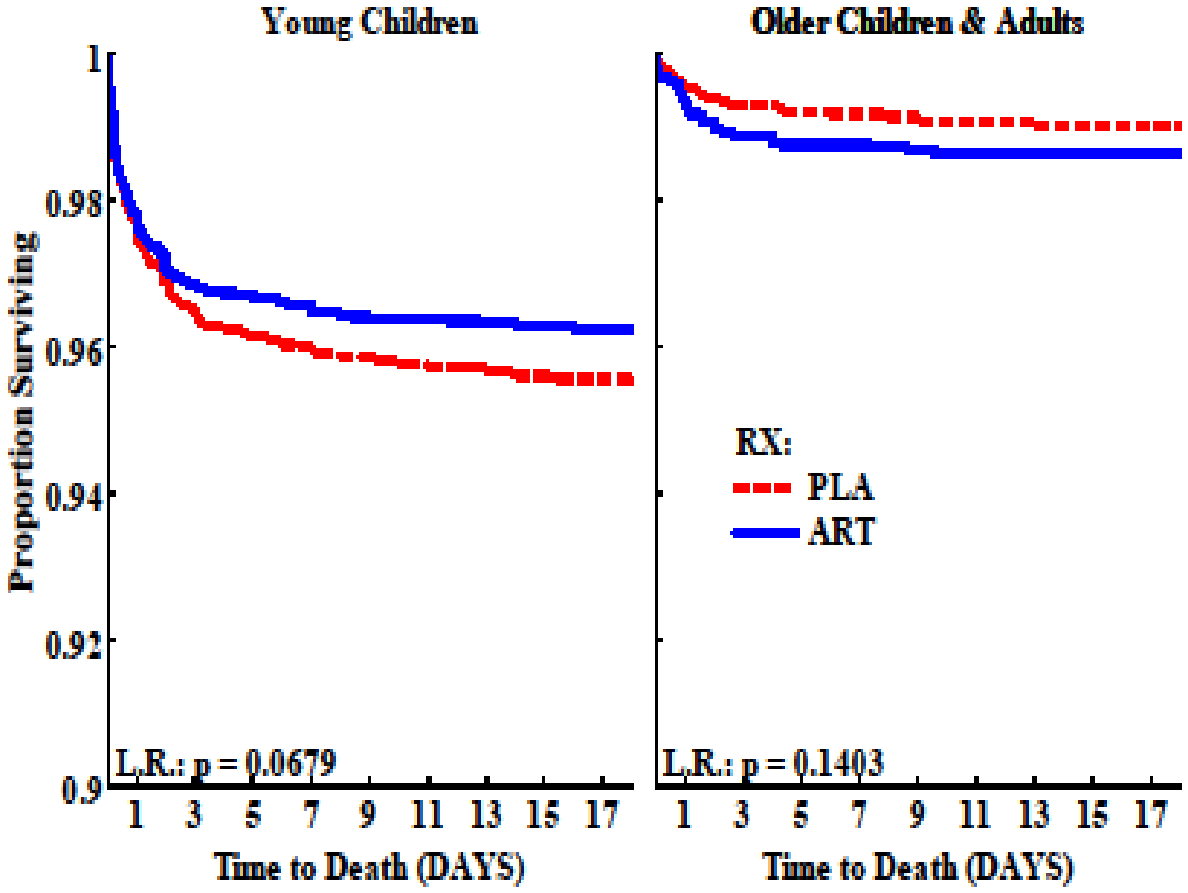
Example: Artesunate for Malaria

- 4/29/2010 FDA Anti-Infective Drugs Advisory Committee meeting:
- In remote locations, malaria sometimes kills people before they can reach the hospital
- Artesunate suppositories intended to reduce parasites & keep person alive until they reach a hospital

Example: Artesunate for Malaria

- Trial 13 compared artesunate suppository to placebo suppository
  - Children under 6 got 100mg dose
  - Adults & children over 6 got 400mg
- Analysis plan called for separate analyses in the two age subgroups
- Results suggested benefit for young children, harm for older children
- Is this real?

Figure 4. Kaplan-Meier Survival Curves for Time to Death, All Randomized Patients



Younger Children Bangladesh/Chittagong		Older Children/Adults Bangladesh/Chittagong	
ART	PLA	ART	PLA
14/1022 (1.4%)	31/988 (3.1%)	31/2009 (1.5%)	14/2009 (0.7%)
RR=0.43 (0.2,0.8) p=.007		RR=2.2 (1.1,4.2) p=.01	

Modified ITT Population

Example: Artesunate for Malaria

- Richard Peto argued conflicting results are due to play of chance
- As with many other AC meetings, I had not made up my mind in advance
- It is okay to have doubts
  - The FDA values your thinking
    - Talk! Don’t be afraid your questions are dumb
  - People with no doubts may be *less* convincing

Example: Artesunate for Malaria

- Expert was Richard Peto:
  - Famous & brilliant
  - Excellent at explaining things to statisticians and non-statisticians
- I began thinking:
  - I can't disagree with Peto!
  - He's probably right—he usually is
    - Cholesterol lowering and suicide/victim of homicide

Example: Artesunate for Malaria

- In the end, you have to go with your gut
- You are there to give an independent opinion
- If you are not convinced, it doesn’t matter how famous the expert is
- We decided that differences between younger and older children were probably not the play of chance

Not JUST A Statistician

- Statisticians also need to use non-statistical judgment as well, e.g. :
- 12/14-15/2006 Anti-Infective Drugs AC and Drug Safety and Risk Mangement AC
  - Ketek for 3 different conditions:
    - Community acquired pneumonia (CAP)
    - Acute exacerbations of chronic bronchitis (AECB)
    - Acute bacterial sinusitis (ABS)

Not JUST A Statistician

- Rare, but troubling side effect-diplopia
  - Concern about driving
- I thought it should be approve for more serious condition (CAP) because less likely to drive
  - Patients with CAP are less likely to feel well enough to drive

Respect the Public Hearing: You Might Learn Something

- Advisory Committee members sometimes ignore public speakers
  - They talk, read e-mails, etc.
- This is bad on several levels
  - Disrespectful to people who may already be afraid of public speaking
  - It gives an impression that you don't care about patients suffering from the disease
  - You might learn something useful
    - Better understanding of disease and patients

Respect the Public Hearing: You Might Learn Something

- I have been on several ACs involving weight loss drugs
- Some have had troubling side effects, especially in large doses
- One public speaker talked about how desperate extremely obese people are:
  - Likely to take more than prescribed dose
- Had a big effect on my deliberations

May Not Want to Participate if You Have the Disease

- I have kidney disease (IGA nephropathy)
- On 10/16/2007 I was a consultant on the Cardiovascular and Renal Drugs AC meeting
  - Phosphate binders for treatment of hyperphosphatemia in patients with chronic kidney disease (CKD)
- Sponsor presented slide with these bullet points:

May Not Want to Participate if You Have the Disease

- 11.3 million Americans have CKD, and excessively high mortality risk due to cardiovascular disease
- Most patients with CKD die before reaching dialysis
- Risk of death is extreme in end stage kidney failure
- 30 year old person with CKD Stage 5 on dialysis has risk of death equivalent to 90 year old

Summary

- FDA AC participation is great way to help the FDA and a great learning experience
  - Exciting learning experience as a spectator too
- Talk! The FDA wants to hear your reasoning
  - Try to explain, not to impress
- Use both statistical reasoning and common sense
- Don’t ignore the public speakers
- Avoid ACs for diseases you have!