Developing Antibacterial Drugs for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

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Anti-Infective Drugs Advisory Committee

November 4, 2011

Developing Clinical Trial Designs for HABP/VABP

- Challenges inherent to the disease process
  - Biology of infection
  - Acute disease where therapy needs to be started promptly
  - Effects of prior therapy
  - Diagnostic uncertainty
  - Limitations of the available scientific information
- Progress has been made to date
  - IDSA/FDA co-sponsored workshop on HABP/VABP clinical trial design
  - Draft HABP/VABP Guidance document
  - Comments to the docket on the draft HABP/VABP guidance document

Therapies for HABP/VABP

- Continued need for new antibacterial drug therapies for treatment of patients with HABP/VABP
  - Antimicrobial resistance
  - Patient tolerance e.g., allergy
  - Drug interactions
  - Adverse event profiles – better tolerated options
- Prudent use of new and existing antibacterial drugs essential to preserve utility

HABP/VABP Clinical Trials - 1

- HABP/VABP trial designs that are
  - Scientifically sound
  - Ethical
  - Feasible
- Evidenced-based designs for HABP/VABP trials
  - Non-inferiority trials
  - Limitations of the available information
- Comments to the docket and other fora regarding draft HABP/VABP guidance & HABP/VABP clinical trial designs
  - Feasibility and Practicality one of the issues frequently brought up

HABP/VABP Clinical Trials - 2

- Feasibility and practicality
- Inherent trade-offs in precision of estimates of efficacy and safety for a drug and practicality/feasibility of clinical trials
- Get to feasible, practical trials while maintaining scientifically sound, ethical, clinical trial designs for assessing the safety and efficacy of antibacterial drugs for HABP/VABP

Clinical Trials

- Scientifically sound, feasible, and ethical designs
- Options on later stage clinical development programs for drugs being developed to treat patients with HABP/VABP
- Seek your advice on these issues for future trials of antibacterial drugs for HABP/VABP
- Issues for further discussion at today's Advisory Committee meeting
  - Non-inferiority margins - timing of the endpoint
  - Prior antibacterial therapy
  - HABP/VABP development program

Question 1

DISCUSSION: Please discuss the merits and limitations of the single trial plus supportive information proposal for Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia (HABP/VABP). Please discuss the types of supportive evidence that would be considered acceptable if only a single HABP/VABP trial is conducted.

Question 2

DISCUSSION: Please discuss if a noninferiority margin of 10% will be acceptable if the active control mortality rate is less than 20%. Please discuss if the odds ratio or risk difference metric is preferred when the control mortality rate is less than 20%.

Question 3

DISCUSSION: Please discuss the preferred timing for the all cause mortality endpoint. Would an assessment at an earlier time point be preferred to the 28-day assessment?

Question 4

DISCUSSION: Please discuss the following scenarios regarding use of prior antibacterial drugs:

a. If empiric antibacterial treatment for HABP/VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound interpretation of the treatment effect of the study drug? Please describe your rationale. Please discuss what other information might be useful to address this question.

b. Should a patient who develops HABP/VABP while receiving antibacterial drugs for other infections be enrolled in a HABP/VABP trial? If so, please discuss some scenarios where this will be acceptable.

Thank you

Anti-Infective Drugs Advisory Committee Meeting

Hospital-Acquired Bacterial Pneumonia & Ventilator-Associated Bacterial Pneumonia: Regulatory Background

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November 4, 2011

Summary of the Presentation HABP/VABP: Regulatory Background

- Summary of 2009 HAP/VAP workshop
- Highlights of the draft guidance HABP/VABP
- Summary of comments to the docket in response to draft guidance HABP/VABP

Workshop for Hospital-Acquired and Ventilator-Associated Pneumonia March 31 & April 1 2009

- Co-sponsored by professional medical societies - IDSA, ATS, SCCM, ACCP - and FDA
- Goal to discuss scientific data addressing key issues in design of trials for HAP and VAP
  - Proceedings: Clin Infect Dis 1 Aug 2010 (51) Supplement 1

Summary of HAP/VAP Workshop Presentations

- Trial designs: noninferiority (NI)
- Review of published studies and assessment of treatment effects
- Review of recently-conducted trials
- Current therapeutic modalities
- Diagnostic evaluations
- Microbiologic etiologies
- FDA, industry and academia perspectives
- 16 discussion questions

Highlights of HAP/VAP Workshop Discussions

- Evaluating drugs for HAP/VAP challenging
  - Efforts to minimize hospital-acquired infections: CMS, Joint Commission
  - Multicenter trials: bacterial etiologies and ICU managements differs among centers
- All-cause mortality endpoint
  - Treatment effect from historical studies
  - Most in favor of this endpoint
  - Concerns with evaluating mortality due to non-respiratory events
  - Timing: 14 days – 28 days

Highlights of HAP/VAP Workshop Discussions

- Non-mortality endpoints discussed
  - “days in ICU”; “days on ventilator”, “PaO2/FiO2 ratio”
  - Lack of consistent evaluation of clinical endpoints in historical studies: treatment effects unknown
- Trials should be active-controlled, randomized, blinded: NI (mortality endpoint) or superiority
  - Evaluation of HAP and VAP: separate trials or together
- Definition of HAP and VAP for enrollment
  - Enrich for bacterial disease (CPIS scores for VAP)
  - Analysis population: micro-ITT (easier for VAP)
  - Role of quantitative cultures in mechanical ventilation

Highlights of HAP/VAP Workshop Discussions

- Enroll patients with sufficient severity at baseline/stratification
  - Discussion of several scores, e.g. APACHE-II
- Concomitant therapy poses unique challenges
  - Empirical broad-spectrum coverage, aminoglycosides
  - De-escalation of drugs rarely done
- Pediatric evaluations as early in development as is possible
- Consortia or cooperative groups could enhance protocol development and implementation

Draft Guidance HABP/VABP

- Incorporated topics addressed at the Spring 2009 workshop
- Included a summary of the work to justify NI margin
- Draft Guidance issued November 29, 2010
- 90-day comment period
  - Comment on guidance at any time

Draft Guidance HABP/VABP

- Enrollment criteria
  - Sufficiently ill trial population, mortality ~ 20%
  - HABP: >48 hours of hospitalization, within 7 days after discharge
  - VABP: >48 hours of mechanical ventilation, CPIS > 6 (enrich for VABP)
  - New radiographic findings
  - Clinical criteria (e.g. fever, cough, dyspnea, hypoxemia)
  - Microbiologic criteria

Draft Guidance HABP/VABP

- Efficacy Considerations
  - All-cause mortality primary endpoint
    - 28-days after randomization
    - Active-control NI trial design
    - Appendix justification NI margin
  - Recommend only VABP or only HABP trials
  - Efficacy/safety demonstrated in VABP support indication for both HABP and VABP
  - Efficacy/safety demonstrated in HABP support indication for HABP

Draft Guidance HABP/VABP

- Efficacy Considerations
  - Micro-ITT analysis population
  - No data on clinical endpoints from historical trials: Secondary endpoints
    - Clinical cure (resolution of signs and symptoms)
    - PaO2/FiO2 improvement over time
    - Clinical progression/rescue therapy

Draft Guidance HABP/VABP

- Other Considerations
  - Exclude patients with receipt of prior antibacterial drugs that have activity against pathogens that cause HABP/VABP
  - Acknowledged empirical use of concomitant antibacterial drugs for broad-spectrum
    - Avoid concomitant antibacterial drugs that have overlapping activity with investigational drug
  - Trials in patients with unmet need
    - Superiority finding of investigational drug

Comments to Draft Guidance HABP/VABP

- 14 responses submitted to the docket
  - Most from industry, several from individuals
  - All comments considered during final guidance prep: Thanks!
- 9 areas of criticism
  - In general, guidance is not practical
  - Efficacy endpoint: all-cause mortality
  - Statistical considerations
  - Comparator antibacterial drugs
  - Issue of prior antibacterial drugs
  - Trial population considerations
  - Clinical microbiology considerations
  - Entry criteria concerns
  - Trials in patients with unmet need

Comments to Draft Guidance HABP/VABP

For today's discussion focus on 5 areas

- **In general, guidance is not practical**
- **Efficacy endpoint: all-cause mortality**
- **Statistical considerations**
- **Comparator antibacterial drugs**
- **Issue of prior antibacterial drugs**
- Trial population considerations
- Clinical microbiology considerations
- Entry criteria concerns
- Trials in patients with unmet need

Comments to Draft Guidance HABP/VABP

- **In general, guidance is not practical**
- **Efficacy endpoint: all-cause mortality**

- Advances in ICU care, mortality < 20%
- Requirement for micro-ITT analysis population: trials too large
- Uncertainty about the timing of day 28 all-cause mortality

Comments to Draft Guidance HABP/VABP

– **Statistical considerations**

- Extensive discounting to arrive at NI margin
- 12.5% NI margin supportable
- Questions about choice of OR metric of 1.67
- Sample size estimates

Comments to Draft Guidance HABP/VABP

– Comparator antibacterial drugs

- Treatment guidelines for patient management might not be relevant today
- FDA-approved too restrictive
  - International flexibility
- Dosages may differ from labeling

Comments to Draft Guidance HABP/VABP

– **Issue of prior antibacterial drugs**

- Excluding prior use unjustified and impractical
- Perioperative antibacterial drugs commonly used in trauma/surgical patients

HABP & VABP: Regulatory Background

Summary of docket comments relevant to today's AIDAC

- All-cause mortality endpoint
  - We looked again and could not find support for NI margin based on any other endpoint
  - Issues of when mortality expected to be < 20%
  - Timing of the mortality endpoint
- Statistical considerations
  - Micro-ITT populations
  - Approach to NI: risk difference and odds ratio
  - Single trial + supportive data

HABP & VABP: Regulatory Background

Summary of docket comments relevant to today's AIDAC, cont.

- Issues of prior antibacterial drugs and choice of comparator drugs
  - Role of prior antibacterial drugs in setting of HABP/VABP
  - Role of comparator drugs

HABP & VABP: Regulatory Background

Many thanks to my FDA colleagues

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HABP/VABP Trials: An FDA Clinical Perspective

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Meeting of the Anti-infective Drugs' Advisory Committee
November 4, 2011

Outline

- Issues with prior trials for these indications
- Use of prior antibacterial drugs
- Use of concomitant antibacterial drugs
- Rationale for 28-day mortality as an endpoint
- Rationale for microITT as primary analysis population

Issues with prior trials

- Some trials/drugs failed with a clinical response endpoint:
  - Inadequate spectrum of activity
  - Inadequate dose for target bacteria
- Interpretation of trials for others problematic because:
  - Confounding by prior and concomitant antibacterial drug use including failure to de-escalate
  - Inability to determine whether bacteria isolated from culture were considered by the investigator to be pathogens requiring adjunctive antibacterial agents
  - Questionable interpretations of chest radiographs
  - Inconsistent or absent microbiological specimen collection and assessment
  - Concern that subjects did not have the disease of interest→ major issue for noninferiority trials b/c will lead to erroneous conclusion that study drug is noninferior to comparator

Confounding by prior antibacterial drug use: Drug A

	Study 1	Study 2
No prior abx use	17.8%	22.1%
No prior abx use w/in 24 h window	21.7%	26.1%
Prior abx use w/in 24 h window	60.5%	51.8%

Confounding by prior antibacterial drug use: Drug B

	Drug B	Comparator
No prior abx use w/in 7 d window	64.7%	57.6%
Prior abx use w/in 7 d window	30.4%	34.4%
Unable to determine	4.9%	8.0%

Confounding by prior antibacterial drug use: Drug C

	Drug C	Comparator
Prior abx use w/in 24 h window	64%	66%

- Overall, 85% of microITT subjects received a prior antibacterial drug for systemic use

Confounding by concomitant active antibacterial drug use and duration: Drug A

	Study 1	Study 2
Use of any anti-Pseudomonal coverage		
No	16.5%	73.8%
Yes	83.5%	26.2%
≤ 2 days	12.5%	11.7%
3-5 days	35.4%	8.8%
≥ 5 days	35.8%	5.6%

Confounding by concomitant active antibacterial drug use and duration: Drug C

	Drug C	Comparator
No	32%	34%
Yes	68%	66%
Mean duration (for 3 most commonly used abx)	6.2-7.2 days	
Median duration (for 3 most commonly used abx)	5-6 days	

Problems with CXRs

- Not consistent with pneumonia
- Lack of formal radiology reports
- Inconsistencies between radiologist interpretation and investigator-indicated chest radiograph findings in the CRF
- Unclear whether the radiologist or investigator interpreted the chest radiograph
- Missing radiology reports

Problems with micro specimens

- Inadequate sputum samples for culture (≥10 SEC/LPF or <25 WBCs on Gram stain)
- Sputum samples without Gram stain
- Inadequate endotracheal aspirate specimens for culture (≥10 SEC/LPF or no organisms present on Gram stain)
- No standardization of bacterial quantitation in bronchoscopically-obtained specimens to characterize isolate between investigational sites

Did subjects really have HABP/VABP?

- Unconvincing radiologic and microbiologic findings
- Patients enrolled without any findings of pneumonia such as fever, leukocytosis, purulent sputum
- Enrollment of subjects
  - with less likelihood of disease based on low CPIS scores
  - low risk of mortality based on APACHE II scores

Rationale for 28-d mortality endpoint

- No historical evidence of treatment effect for other endpoints
- Clinical response can be assessed as secondary
- Earlier assessment of mortality results in lower mortality rates
  - Mortality rates historically for control arms ~20%

Duration of Therapy

- Most trials allowed 7-14 days of dosing although few allowed 7-21 days of dosing
- In trials that allowed 7-14 days of dosing, very few patients received more than 15 days of dosing
- In trials that allowed 7-21 days of dosing, substantial proportion of patients (11-14%) received more than 14 days of dosing

All-Cause Mortality

Trial	Day			Mean (SD)	
-	14	21	28	Baseline Age	Baseline APACHE II
Study 1	16%	22%	26%	63.8 (18.6)	15.8 (6.1)
Study 2	15%	20%	24%	60.8 (18.2)	15.4 (6.2)
Study 3	8%	11%	17%	56.5 (18.8)	12.5 (5.4)
Study 4	10%	14%	18%	61.8 (18.0)	17.5 (6.2)

VABP All-Cause Mortality

Trial	Day			Mean (SD)	
-	14	21	28	Baseline Age	Baseline APACHE II
Study 1	15%	20%	25%	56.6 (19.0)	16.5 (5.6)
Study 2	20%	26%	28%	56.4 (19.7)	17.8 (5.6)
Study 3	10%	15%	19%	54.1 (18.6)	14.1 (5.6)
Study 4	12%	17%	20%	60.3 (19.1)	18.7 (6.1)

HABP All-Cause Mortality

Trial	Day			Mean (SD)	
-	14	21	28	Baseline Age	Baseline APACHE II
Study 1	17%	22%	26%	67.2 (17.4)	15.4 (6.3)
Study 2	12%	17%	21%	63.1 (17.1)	14.3 (6.2)
Study 3	8%	11%	17%	57.9 (18.8)	11.6 (5.0)
Study 4	8%	10%	12%	65.5 (14.6)	14.3 (5.2)

Rationale for microITT as 1° analysis population

- Increases confidence that study subjects have the disease of interest
- Diagnostic uncertainties when relying on clinical and radiologic findings alone
- High rates of isolation of bacterial organisms in previous trials
- Nonculture methods can be used to supplement conventional culture

Conclusions

- Although HABP/VABP trials are difficult to conduct, need to incorporate:
  - Strict enrollment criteria to ensure subjects have the disease of interest
  - Procedures for obtaining and evaluating chest radiographs
  - Procedures for obtaining and interpreting microbiologic specimens
  - Minimization of prior and concomitant antibacterial therapy
  - De-escalate concomitant antibacterial therapy once culture results are known
- microITT analysis population provides assurance that subjects have the disease of interest
  - Generally ~70% of subjects are microbiologically evaluable
- Mortality is the endpoint for which there is historical evidence of treatment effect
  - Assessment at 28 days reasonable to capture disease-related mortality without too much noise

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Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia: Proposed development pathways and clinical trial designs

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Anti-Infective Drugs Advisory Committee Meeting
November 4, 2011

Outline

- Microbiological evaluability rates
- Non-inferiority margin
- Risk difference and odds ratio measures
- Sample size requirement
- Proposed development pathways

VABP Microbiologic evaluability

VABP patients in trials of broad spectrum agents

Trial	Microbiologic evaluability rate%	≈ N
Study 1	72%	125
Study 2	78%	525
Study 3	75%	250
Study 4	84%	200

VABP Microbiologic evaluability for gram-positive pathogens

VABP patients in trials of gram-positive agents

Trial	Microbiologic evaluability rate%	≈ N
Study 1	56%	200
Study 2	63%	225
Study 3	63%	750

HABP Microbiologic evaluability

HABP patients in trials of broad spectrum agents

Trial	Microbiologic evaluability rate%	≈ N
Study 1	50%	675
Study 2	60%	325
Study 3	63%	575

HABP Microbiologic evaluability for gram-positive pathogens

HABP patients in trials of gram-positive agents

Trial	Microbiologic evaluability rate%	≈ N
Study 1	45%	550
Study 2	52%	375
Study 3	53%	525

Historical Evidence of Treatment Effect for Active Comparator

- Literature search: 36 published articles
- No placebo-controlled studies identified
- No placebo data for assessing clinical response identified
- Primary endpoint: All-cause mortality
- “Placebo”: used studies of patients receiving inappropriate, inadequate or delayed therapy
- Active comparator: used recent randomized clinical trials

Sorbello et al., DIJ (2010)

"Placebo" Mortality Rate

- 12 studies of patients receiving inadequate, inappropriate, or delayed therapy
- Mortality rate estimate from 2 studies most comparable to active control trials:

  62% with 95% CI (52%, 71%)
- Mortality rate estimate from all studies:

  60% with 95% CI: (49%, 69%)

Active Control Mortality Rate

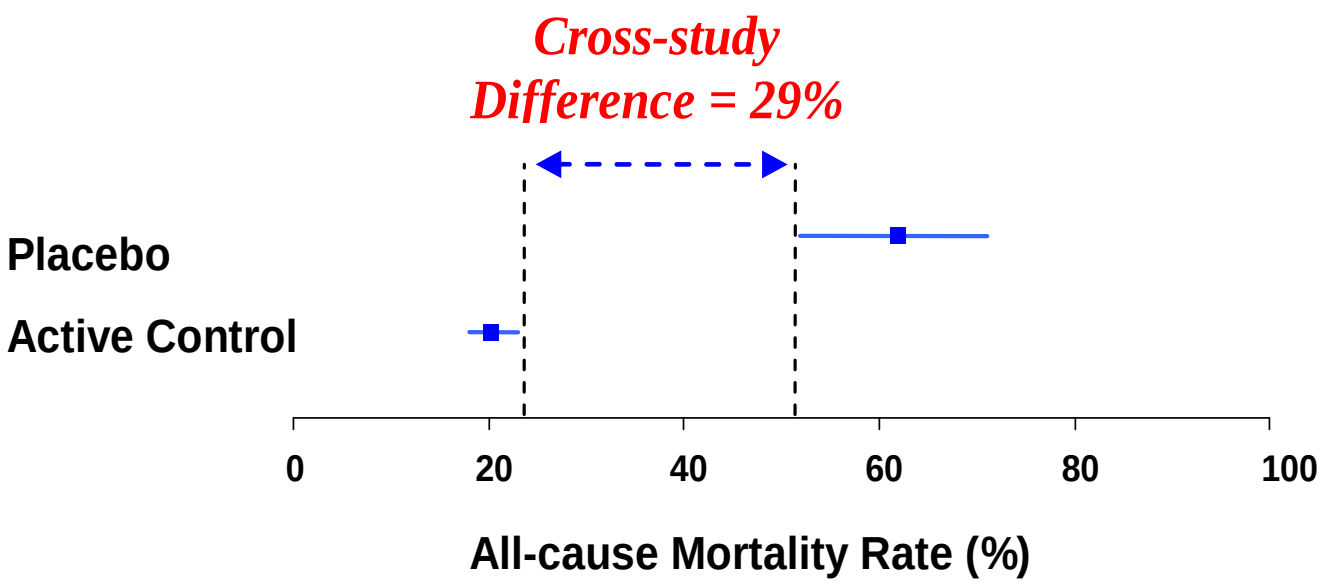
- 8 randomized clinical trials identified
- 5 trials used in analysis felt to be most comparable to “placebo” studies
- Mortality rate estimate from the five trials:

  20% with 95% CI: (18%, 23%)

Determination of M1

Cross-study difference in all-cause mortality rates between active control and "placebo" = 29%:

- based on comparison of 95% CIs, where the lower bound of the 95% CI for "placebo" was 52% and the upper bound of the 95% CI for active control was 23%



Limitations

- No placebo-controlled studies
- Observed treatment effect of HABP/VABP derived from only 7 studies: 2 “placebo” and 5 active control
- Some studies were open-label comparisons or observational studies - potential for bias
- Variability in baseline patient demographics and disease severity across studies
- Studies assessed mortality at different time points or did not state when mortality was assessed
- Cross-study comparisons create uncertainties
- Technological advances over time in ICU patient management lead to potential concerns on the constancy of treatment effect

Determination of M1: Discounting

- Discounting: performed to account for uncertainties in active comparator treatment effect
- Accounting for variability by taking difference in upper bound of active comparator rate and lower bound of placebo rate can be viewed as form of discounting but may not account for all these potential biases
- Further discounting resulted in M1 of 20%

M2: Clinical Margin

- Choice of M2: based on clinical judgment on the proportion of M1 (active comparator treatment effect) that can be lost but test drug still considered noninferior
- Large proportion (50%) of M1 was preserved because endpoint is all-cause mortality
- 10% NI margin based on 50% preservation

Risk Measures

Let P_t be the probability of an event in the "Test" group and P_c in the "control" group.

- Risk Difference (RD)

  The difference of probabilities: $P_t - P_c$
- Relative Risk (RR)

  Ratio of probabilities: P_t / P_c
- Odds Ratio (OR)

  The ratio of the odds of an event occurring in "test" group to the odds of it occurring in the "control" group

$$\frac{P_t/(1-P_t)}{P_c/(1-P_c)}$$

Risk Difference (RD)

Difference of probabilities: $P_t - P_c$

	Dead	Alive	
Test	**250**	750	**1000**
Control	**200**	800	**1000**
	450	1550	**2000**

Risk Difference $= 250/1000 - 200/1000$

$= 25\% - 20\%$

$= 5\%$

Relative Risk (RR)

	Dead	Alive	
Test	**250**	750	**1000**
Control	**200**	800	**1000**
	450	1550	**2000**

$$RR = \frac{P_t}{Pc} = \frac{(250/1000)}{(200/1000)} = \frac{0.25}{0.20}$$

$$= 1.25$$

Interpretation of Relative Risk

RR > 1: Increased risk of mortality for Test drug

RR < 1: Decreased risk of mortality for Test drug

RR = 1: Similar risk for Test and Control drug

Odds Ratio (OR)

	Dead	Alive	
Test	**250**	750	**1000**
Control	**200**	800	**1000**
	450	1550	**2000**

$$\text{OR} = \frac{(250/1000)\ /\ (750/1000)}{(200/1000)\ /\ (800/1000)} = \frac{0.25/0.75}{0.20/0.80} = 1.33$$

Interpretation of Odds Ratio

OR > 1: Increased odds of mortality in the Test group compared to Control

OR = 1: No difference in odds of mortality in the Test group compared to Control

OR < 1: Reduced odds of mortality in the Test group compared to Control

Symmetry of OR for Mortality/Survival

For instance, assume the mortality rate is 25% for the test drug and 20% for the active control.

For mortality, **OR** = (0.25/0.75) / (0.2/0.8) = 1.33

For survival, **OR** = (0.75/0.25) / (0.8/0.2) = 0.75

Note: 1/0.75 = 1.33; therefore, OR is symmetric.

Similarly for RR:

For mortality, RR= 0.25/0.2 = 1.25

For survival, RR= 0.75/0.8 = 0.94

However, $1/0.94 = 1.06 \neq 1.25$

Therefore, RR lacks symmetry

Comparison of OR and RR

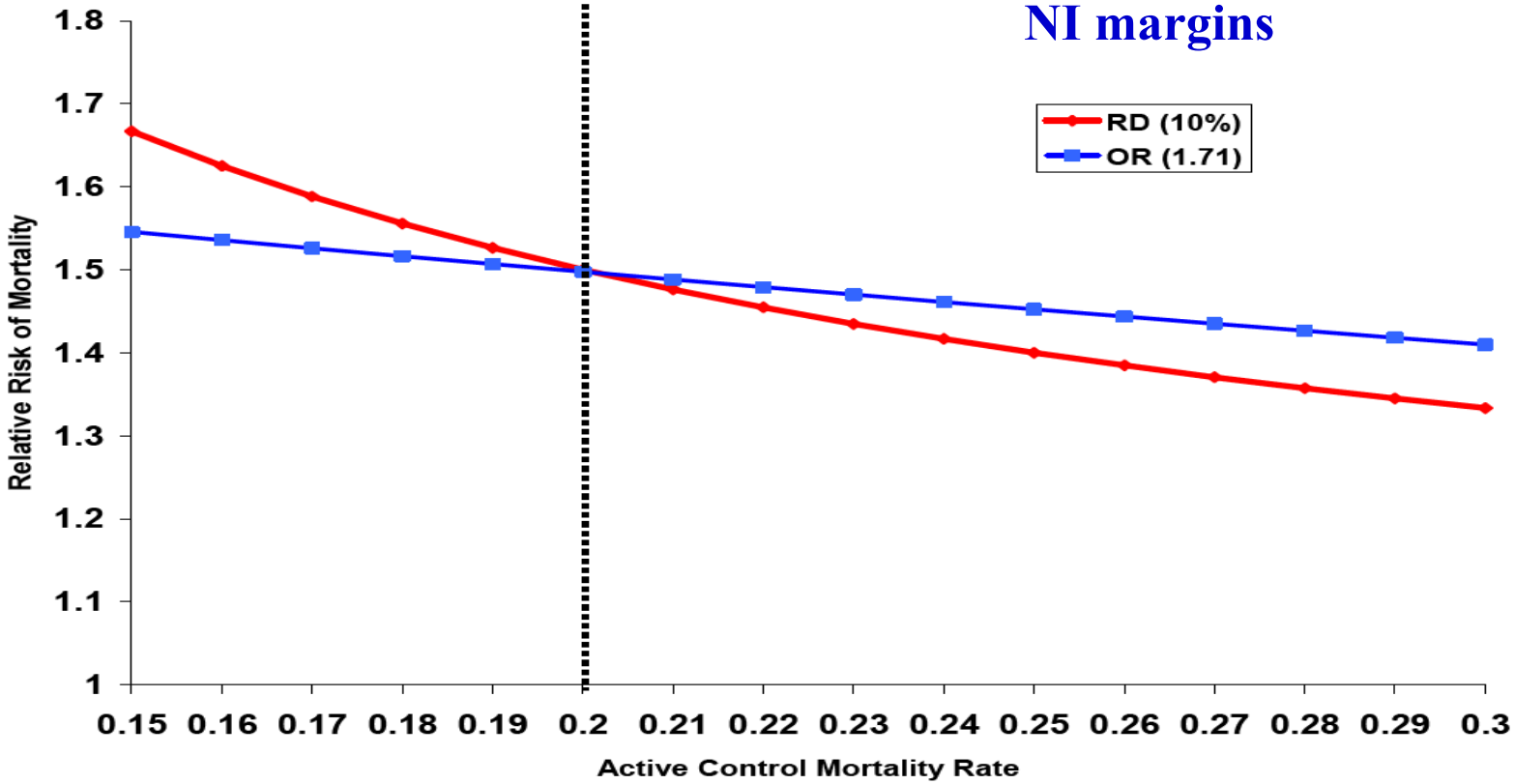
- OR has good mathematical properties
- OR is symmetric for mortality or survival
- RR is not symmetric
  - Major disadvantage
- OR approximates RR when the control event rate is low

Reasons to Consider Alternative Effect Metrics

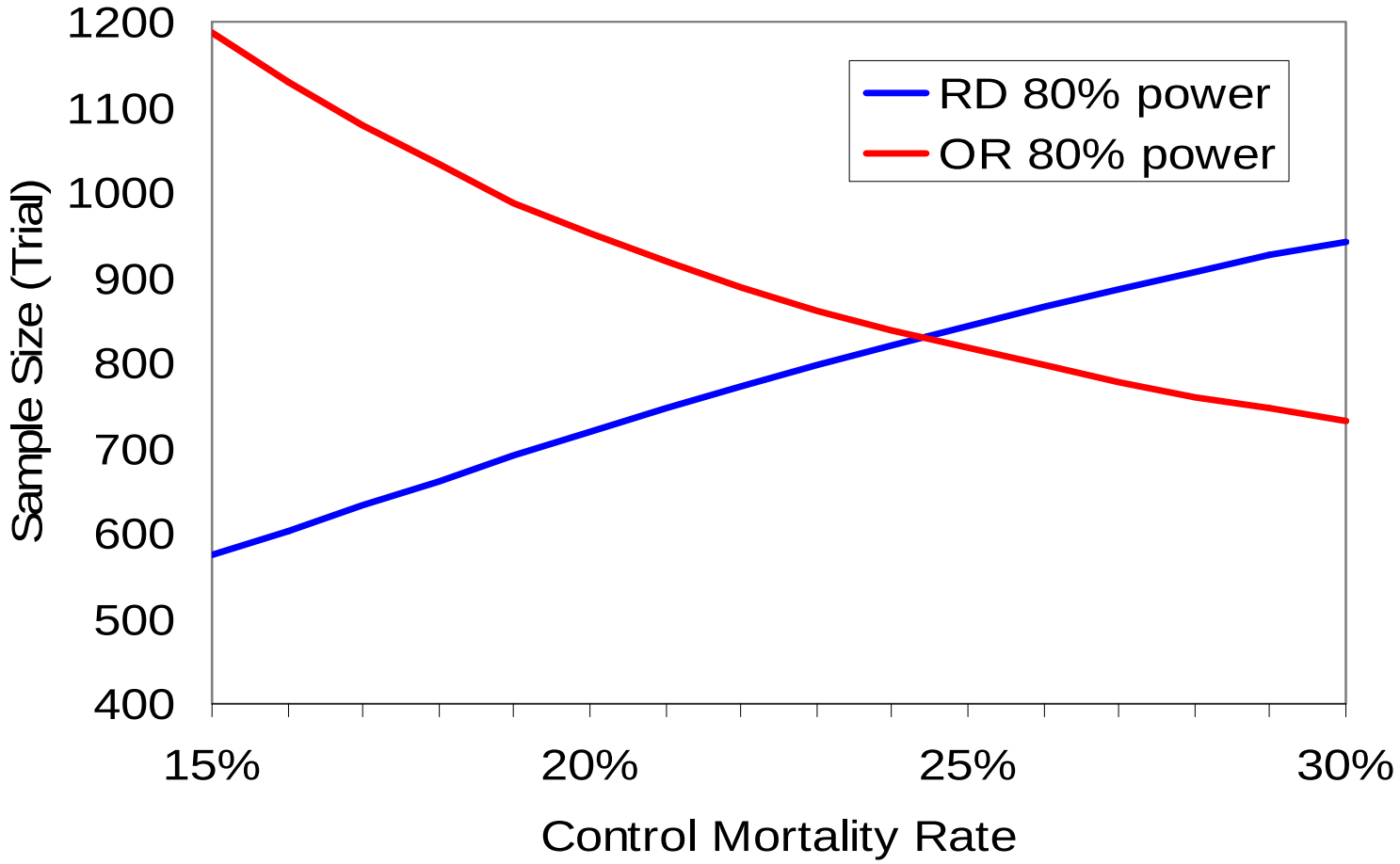
- If control rates are lower than historical data, then risk difference may not be an appropriate measure; odds ratio better?

- If control rates are higher than historical data, then odds ratio may have additional benefits

Relative risk of mortality based on RD and OR metrics



Sample Size: Odds Ratio and Risk Difference



Option 1: Single VABP Trial

- A single, adequate VABP trial
- Plus supportive evidence in related indication
- Provides evidence for both a VABP and HABP indication
- Total number of randomized patients
  - Risk difference, 10% NI margin
    - 720 patients (80% power)
    - 962 patients (90% power)
  - Odds ratio, 1.71 NI margin
    - 952 patients (80% power)
    - 1272 patients (90% power)
  - Assumes 20% control mortality rate and 70% microbiologic evaluability

Option 2: Single HABP Trial

- A single adequate well-controlled HABP trial
- Plus supportive evidence in related indication
- Provides evidence for HABP indication
- Total number of randomized patients
  - Risk difference, 10% NI margin
    - 840 patients (80% power)
    - 1124 patients (90% power)
  - Odds ratio, 1.71 NI margin
    - 1110 patients (80% power)
    - 1484 patients (90% power)
  - Assumes 20% control mortality rate and 60% microbiologic evaluability

Supportive Evidence

Adequate evidence of efficacy and safety in related indications such as:

- Complicated Intra-Abdominal Infections (cIAI)
  - Drugs primarily active against Gram-negative bacteria
- Community-acquired bacterial pneumonia (CABP)
  - Drugs with suitable spectrum of activity for the treatment of CABP
- Acute bacterial skin and skin structure infections
  - Drugs with activity against only Gram positive organisms including methicillin-resistant Staphylococcus aureus

Option 3: Two VABP Trials

- Two adequate, well-controlled VABP trials
- Provides evidence for both HABP and VABP indications
- Total number of randomized patients for program (two trials)
  - Risk Difference, 10% NI margin
    - 1440 patients (Both trials w/80% power)
    - 1924 patients (Both trials w/90% power)
  - Odds ratio, 1.71 NI margin
    - 1904 patients (Both trials w/80% power)
    - 2544 patients (Both trials w/90% power)

Option 4: one HABP and one VABP trial

- Two adequate, well controlled trials:
  One HABP and one VABP
- Provides evidence for both HABP and VABP indications
- Total number of randomized patients for program (two trials)
  - Risk Difference, 10% NI margin
    - 1560 patients (Both trials w/80% power)
    - 2086 patients (Both trials w/90% power)
  - Odds ratio, 1.71 NI margin
    - 2062 patients (2 trials w/80% power)
    - 2756 patients (2 trials w/90% power)

Summary

- Proposed development pathways
  - Single trial with supportive evidence
  - Two trials
- Primary endpoint: 28-day all-cause mortality
- Primary population: microbiological ITT
- Risk difference vs. odds ratio
- NI margin
  - 10% for risk difference
  - 1.71 for odds ratio

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