

Putting the literature into context: summary and evaluation of recent clinical trials

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I have no actual or potential conflicts of interest in relation to this program.

Learning Objectives

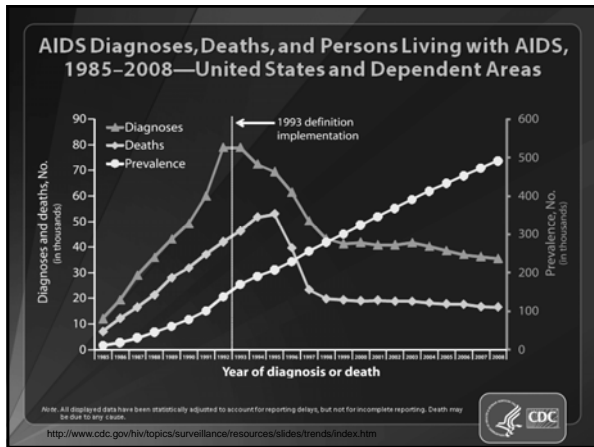
- Describe the methods and key findings of the papers presented.
- Explain how the iPrEx trial affects HIV prevention strategies.
- Summarize the findings and implications for practice of the POET-COPD trial.
- Compare and contrast fidaxomicin and vancomycin for treatment of CDAD.
- Discuss the role of dabigatran in prevention of stroke and embolism among patients with atrial fibrillation.

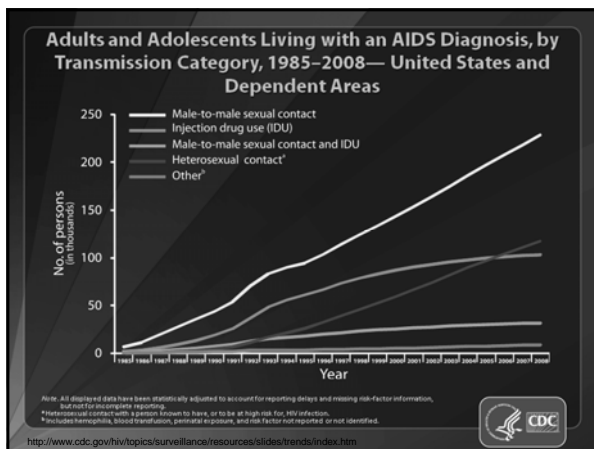
Outline

- Pertinent background
- Study objective
- Methods
- Results
- Critique/clinical implications

Audience Demographics

- 1. Student
- 2. Resident
- 3. Technician
- 4. Pharmacist
- 5. Other





Diagnoses of HIV Infection among Adult and Adolescent Males, 2006–2009—40 States and 5 U.S. Dependent Areas


Of the 171,020 diagnoses of HIV Infection among adults and adolescents during 2006 through 2009,

- 75% were in males
 - 71% of diagnosed HIV infections in males were attributed to male-to-male sexual contact
 - 18% of diagnosed HIV infections in males during 2006 through 2009 were aged 13-24
 - 87% of diagnosed HIV infections in males aged 13-24 were attributed to male-to-male sexual contact

In 2009, 56% of HIV infections diagnosed among adults and adolescents were attributed to male-to-male sexual contact.*

Note: Data include persons with a diagnosis of HIV infection regardless of stage of disease or diagnosis. All displayed data have been statistically adjusted for reporting delay and missing data. Partial observations, but not for incomplete reporting. Data exclude men who reported sexual contact with other men and injection drug use.

http://www.cdc.gov/hiv/topics/surveillance/resources/slides/msm/index.htm



HIV Prevention

- Occupational PEP
 - 2-drug regimen: zidovudine + lamivudine; zidovudine + emtricitabine; tenofovir + emtricitabine; tenofovir + lamivudine)
 - ≥3-drug regimen: basic + lopinavir/ritonavir
- Nonoccupational PEP
 - NNRTI-based: efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir)
 - PI-based: lopinavir/ritonavir + (lamivudine or emtricitabine) + zidovudine

MMWR Recomm Rep. 2005;54(RR-9):1-17
MMWR Recomm Rep. 2005;54(RR-2):1-20

HIV Prevention

What about preexposure prophylaxis?

iPrEx

Preexposure Prophylaxis Initiative trial

- Objective: to evaluate the safety and efficacy of emtricitabine + tenofovir given daily for prevention of HIV among MSM
- Methods
 - MC, DB, PC, RCT
 - HIV negative MSM (age ≥18 years) at high risk for HIV

N Engl J Med. 2010;363(27):2587-2599

iPrEx

Interventions:

- Tenofovir 300 mg + emtricitabine 200 mg once daily (n=1251) vs. placebo (n=1248)
- Standard prevention interventions
 - HIV testing
 - Counseling, condoms
 - Diagnosis and treatment of STIs
 - PEP referral
- Follow-up visits every 4 weeks

N Engl J Med. 2010;363(27):2587-2599

iPrEx

- Primary endpoint: HIV infection
- Other outcomes:
 - Adherence
 - Sexual practices
 - Safety
 - Resistance
 - Drug level detection and prophylactic effect
 - Effect of study drug on HIV infection

N Engl J Med. 2010;363(27):2587-2599

iPrEx

Demographics

- Median follow-up 1.2 years (max 2.8 years)
- 10 were found to be positive at enrollment
- Majority of subjects were from South America; ~4% from US in each group
- About half were 18 to 24 years of age

N Engl J Med. 2010;363(27):2587-2599

iPrEx

Results

| | TFC-TDF (n=1251) | Placebo (n=1248) |
|-----------------|-------------------------|-------------------------|
| HIV acquisition | 36 (2.88%) | 64 (5.13%) |

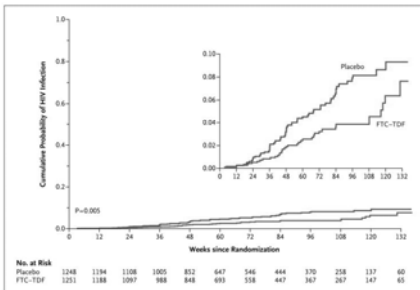
Relative reduction 44% (95% CI 15 to 63, p=0.005)

Absolute risk reduction: 2.25%

NNT = 44

N Engl J Med. 2010;363(27):2587-2599

iPrEx



N Engl J Med. 2010;363(27):2587-2599

iPrEx

Results

- Adherence (self-reported): lower with FTC-TDF at weeks 4 ($p < 0.001$) and 8 ($p = 0.006$)
- Decreased during 1st year based on dates and quantities (99% to 91%) in contrast to self-report & pill counts
- Sexual practices: similar between groups, safer as study progressed

N Engl J Med. 2010;363(27):2587-2599

iPrEx

Results

- Safety: elevated SrCr (2% FTC-TDF vs. 1% placebo, $p = 0.08$); nausea ($p = 0.04$) & weight loss ($p = 0.04$) more common with FTC-TDF
- Resistance: FTC resistance detected in 2 subjects who were positive at baseline; no resistance among 100 infections during trial

N Engl J Med. 2010;363(27):2587-2599

iPrEx

Results

- Drug level/prophylactic effect: at least 1 component detected in the serum of 3 (9%) of 34 subjects who developed HIV and in 22 (51%) of seronegative controls
- Detectable drug reduced the odds of infection by a factor of 12.9 (95% CI 1.7 to 99.3, $p < 0.001$)
- Effect of study drug on HIV infection: viral load and CD4+ counts similar in both groups

N Engl J Med. 2010;363(27):2587-2599

iPrEx

| | |
|--|--|
| <p>Strengths</p> <ul style="list-style-type: none"> - Large, well designed trial - Standard interventions - Close follow-up - Adherence assessments | <p>Limitations</p> <ul style="list-style-type: none"> - Difficult to fully assess safety (e.g. renal insufficiency) - Not large enough to assess efficacy at each site - Cost of treatment/economic considerations - Risk compensation? |
|--|--|

N Engl J Med 2010;363(27):2663-2665
N Engl J Med 2011;364(14):1372-1373
N Engl J Med 2011;364(14):1374

iPrEx

- CDC interim guidance: released to prevent unsafe practices
- Several steps for safe use:
 - Determine eligibility
 - Prescribe a limited quantity initially
 - Risk reduction counseling
 - Follow-up every 2 to 3 months
- Safe discontinuation also addressed

MMWR Morb Mortal Wkly Rep. 2011;60(3):65-68.

Which patient is a candidate for PrEP?

1. Bisexual female with multiple partners
2. MSM with multiple partners
3. MSM with a single partner; the partner has HIV
4. Pregnant woman with HIV

Which long-acting bronchodilator is preferred for COPD?

1. Long-acting beta₂-agonist
2. Inhaled anticholinergic
3. Either agent is appropriate.

POET-COPD

Management of COPD – GOLD guidelines

| Stage | FEV ₁ (% of predicted) | Short-acting bronchodilator (prn) | Long-acting bronchodilator | Inhaled steroid |
|------------------|---|-----------------------------------|----------------------------|-----------------|
| I (mild) | FEV ₁ ≥80% | ✓ | | |
| II (moderate) | 50% < FEV ₁ <80% | ✓ | ✓ | |
| III (severe) | 30% ≤ FEV ₁ <50% | ✓ | ✓ | ✓ |
| IV (very severe) | <30% or <50% with chronic respiratory failure | ✓ | ✓ | ✓ |

<http://www.goldcopd.org/guidelines-publications-reviewed-2010.html>

POET-COPD

Prevention of Exacerbations with Tiotropium in COPD

- Objective: to directly compare the effects of tiotropium with salmeterol on the risk of moderate and severe exacerbations
- Methods
 - RCT, MC, DB, DD
 - 1 year
 - Patients with moderate to very severe COPD

N Engl J Med. 2011;364(12):1093-1103

POET-COPD

Interventions (following 2- week run-in):

- Tiotropium 18 mcg once daily (n=3708)
- Salmeterol 50 mcg twice daily (n=3669)
- Matching placebos
- Usual COPD medications allowed except:
 - Anticholinergic drugs
 - LABAs

POET-COPD

- Primary endpoint: time to first COPD exacerbation (visits, telephone contact, records)
- Secondary/safety:
 - Time-to-event and number-of-event endpoints (further detail on exacerbations)
 - Serious adverse events
 - Death

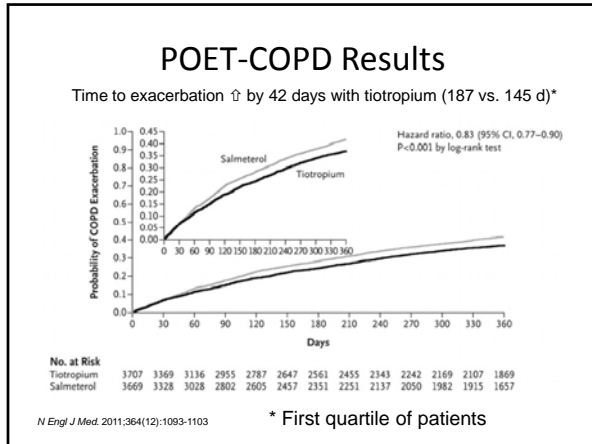
N Engl J Med. 2011;364(12):1093-1103

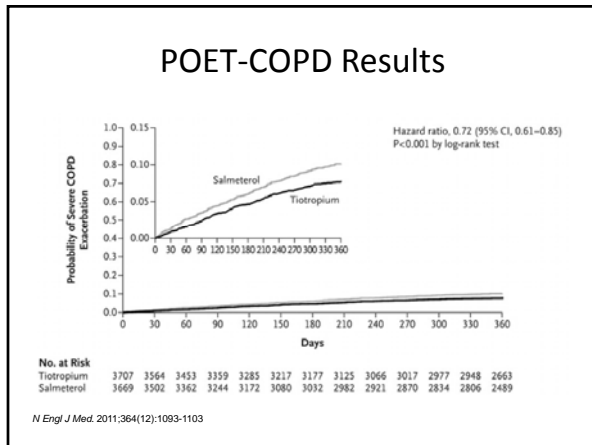
POET-COPD

Demographics

- Mean age 74 years
- 48% current smokers
- GOLD classification: 49% stage II, 43% stage III, 8% stage IV
- Fewer tiotropium recipients withdrew, 585 (15.8%) vs. 648 (17.7%), HR 0.88, 95% CI 0.78 to 0.98

N Engl J Med. 2011;364(12):1093-1103





POET-COPD

Exacerbation results (tiotropium vs. salmeterol): risk reduction

- Moderate: 14% (HR 0.86, 95% CI 0.79 to 0.93)
- Severe: 28% (HR 0.72, 95% CI 0.61 to 0.85)
- Steroids: 23% (HR 0.77, 95% CI 0.69 to 0.85)
- Antibiotics: 15% (HR 0.85, 95% CI 0.78 to 0.92)
- Both: 24% (HR 0.76, 95% CI 0.68 to 0.86)

N Engl J Med. 2011;364(12):1093-1103

POET-COPD

Annual rate of exacerbations

| | Overall | Moderate | Severe | Steroids | Antibiotics | Both |
|--------------------------------|--------------------------|----------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Tiotropium | 0.64 | 0.54 | 0.09 | 0.33 | 0.53 | 0.23 |
| Salmeterol | 0.72 | 0.59 | 0.13 | 0.41 | 0.59 | 0.28 |
| Reduction (Rate ratio, 95% CI) | 11% (0.89, 0.83 to 0.96) | 7% (0.93, 0.86 to 1) | 27% (0.73, 0.66 to 0.82) | 18% (0.82, 0.76 to 0.90) | 10% (0.90, 0.84 to 0.97) | 20% (0.80, 0.73 to 0.88) |

Results consistent among prespecified subgroups

N Engl J Med. 2011;364(12):1093-1103

POET-COPD

Safety

- SAEs: 14.7% tiotropium vs. 16.5% salmeterol
- Deaths: 64 in the tiotropium group vs. 78 with salmeterol (HR 0.81, 95% CI 0.58 to 1.13)

N Engl J Med. 2011;364(12):1093-1103

POET-COPD

| | |
|--|--|
| <p>Strengths</p> <ul style="list-style-type: none"> • Design • Duration • Clinically important outcome • Reporting of outcomes | <p>Limitations</p> <ul style="list-style-type: none"> • Exacerbation rate lower than some previous trials • SABA allowed (role of dual bronchodilators?) • High-risk patients with cardiac disease excluded |
|--|--|

N Engl J Med. 2011;364(12):1093-1103

Should the GOLD guidelines be updated based on POET-COPD?

1. Yes
2. No

Fidaxomicin vs. Vancomycin

IDSA/SHEA guidelines 2010

- Metronidazole 500 mg po tid x 10 to 14 days for mild-to-moderate infection
- Vancomycin 125 mg po qid x 10 to 14 days for severe infection
- 1st recurrence: usually same regimen
- No metronidazole beyond 1st recurrence
- Severe, complicated infection: po and rectal vancomycin +/- metronidazole

Infect Control Hosp Epidemiol. 2010;31(5):431-455

Fidaxomicin vs. Vancomycin

SHEA/IDSA Treatment Criteria

| Definition (expert opinion) | Clinical data* |
|-----------------------------|--|
| Mild or moderate | •WBC ≤15,000 cells/μL •SrCr <1.5 x baseline |
| Severe | •WBC ≥15,000 cells/μL •SrCr ≥1.5 x baseline |
| Severe, complicated | •Hypotension/shock •Ileus •Megacolon |

*Age is also considered.

Infect Control Hosp Epidemiol. 2010;31(5):431-455

Fidaxomicin vs. Vancomycin

- Objective: to compare the safety and efficacy of fidaxomicin to vancomycin in treating *C difficile* infection
- Methods
 - RCT, MC, DB, NI
 - ≥16 years with CDAD (primary or 1st recurrence)
 - Up to 4 doses of prior treatment allowed
 - Could have failed at least a 3-day course of metronidazole
 - Excluded: life-threatening infection, toxic megacolon, IBD, >1 occurrence within 3 months

N Engl J Med. 2011;364(5):422-431

Fidaxomicin vs. Vancomycin

Interventions:

- Stratification based on primary or 1st recurrence
- Fidaxomicin 200 mg po q12h (n=287)
- Vancomycin 125 mg po q6h (n=309)
- Both given for 10 days
- Patients who were cured were followed for 28 days after last dose for recurrence

N Engl J Med. 2011;364(5):422-431

Fidaxomicin vs. Vancomycin

- Primary endpoint: clinical cure
- Secondary endpoint: recurrence (assessed between days 36 and 40)
- Other
 - Microbiologic evaluation
 - PK
 - Safety

N Engl J Med. 2011;364(5):422-431

Fidaxomicin vs. Vancomycin

Demographics

- 596 mITT population, 548 PP, 623 safety
- Mean age 62 years, 56% female
- 59% inpatient
- 5% lack of response to metronidazole
- 39% treated within previous 24 hours
- 17% previous episode of *C difficile*
- 38% NAP1/BI/027

N Engl J Med. 2011;364(5):422-431

Fidaxomicin vs. Vancomycin

Results

- Clinical cure (mITT): 253 (88.2%) of 287 fidaxomicin vs. 265 (85.8%) of 309 vancomycin (lower bound CI limit of -3.1%, met NI criteria)
- Recurrence (mITT): 39 (15.4%) of 253 fidaxomicin vs. 67 (25.3%) of 265 vancomycin (reduction 9.9%, 95% CI -16.6 to -2.9)
- Recurrence rates similar among those with NAP1/BI/027 (11 [24.4%] of 45 fidaxomicin vs. 13 [23.6%] of 55 vancomycin, p=0.93)

N Engl J Med. 2011;364(5):422-431

Fidaxomicin vs. Vancomycin

Safety:

- No significant differences in SAEs
- More SAEs related to laboratory abnormalities with fidaxomicin (4.7% vs. 1.2%, p=0.01) – no obvious patterns

More common with fidaxomicin:

- Dizziness (4% vs. 1.2%, p=0.0405)
- Rash (3% vs. 0.6%, p=0.0315)

N Engl J Med. 2011;364(5):422-431
http://www.nejm.org.proxy.cc.uic.edu/doi/suppl/10.1056/NEJMoa0910812/suppl_file/nejm0910812_appendix.pdf

Fidaxomicin vs. Vancomycin

| | |
|---|--|
| <p>Strengths</p> <ul style="list-style-type: none"> • NI design is appropriate • Reasonable to assess superiority once NI is established • Vancomycin dose appropriate • External validity (US and Canada) | <p>Limitations</p> <ul style="list-style-type: none"> • 10 days of therapy • NAP1/BI/027 • Antibody levels to <i>C difficile</i> toxin A • Disease severity • Pretreatment • Pharmacoeconomics? |
|---|--|

N Engl J Med. 2011;364(5):473-475
 N Engl J Med. 2011;364(19):1875

True/false. Fidaxomicin demonstrated less recurrence of *C difficile* among patients with the NAP1/BI/027 strain.

1. True
2. False

RE-LY

- Increased risk for stroke and death with atrial fibrillation (AF); 15% of stroke in US due to AF
- Vitamin K antagonists (VKA) – standard of care
- Numerous limitations to VKA therapy
 - Drug/dietary interactions
 - Dosage adjustments
 - Bleeding risk

Chest. 2008;133(6 Suppl):546e-592e

RE-LY

- CHADS₂ Score
 - 2 points history of TIA/stroke
 - 1 point for:
 - Age ≥75 years
 - Hypertension
 - Diabetes
 - Recent CHF

Chest. 2008;133(6 Suppl):546s-592s

RE-LY

Randomized Evaluation of Long-Term Anticoagulation Therapy

- Objective: to compare dabigatran to warfarin for anticoagulation in patients with AF
- Methods
 - RCT, partially blinded, MC, NI
 - AF plus at least 1 CHADS₂ factor
 - Exclusion: CrCl <30 mL/minute, liver disease, recent stroke, increased risk for hemorrhage

N Engl J Med. 2009;361(12):1139-1151

RE-LY

Interventions:

- Dabigatran 110 mg bid (n=6015)
- Dabigatran 150 mg bid (n=6076)
- Warfarin to a target INR of 2.0 to 3.0 (n=6022)
- Aspirin <100 mg/day or antiplatelet agents permitted
- Follow-up every 3 to 4 months

N Engl J Med. 2009;361(12):1139-1151

RE-LY

- Primary endpoint: stroke or embolism
- Primary safety endpoint: major hemorrhage
- Secondary endpoints:
 - Stroke, embolism separately
 - Death
- Other: MI, PE, and hospitalization; net clinical benefit

N Engl J Med. 2009;361(12):1139-1151

RE-LY

Demographics

- Mean age 71 years
- 63.6% male
- 50% received previous VKA therapy
- Mean CHADS₂ score: 2.1
- Previous stroke: 20%
- Median follow-up: 2 years
- Aspirin used in about 20% of patients
- Mean time INR was in the therapeutic range: 64%

N Engl J Med. 2009;361(12):1139-1151

RE-LY

- Primary endpoint: both dabigatran doses met NI criteria when compared to warfarin
 - Dabigatran 110: 1.53% per year
 - Dabigatran 150: 1.11% per year
 - Warfarin: 1.69% per year
- Dabigatran 150 superior to warfarin (RR 0.66, 95% CI 0.53 to 0.82)

N Engl J Med. 2009;361(12):1139-1151

RE-LY

- Major bleeding (incidence per year): 3.36% with warfarin, 2.71% with dabigatran 110 (RR 0.80, 95% CI 0.69 to 0.93), and 3.11% with dabigatran 150 (RR 0.93, 95% CI 0.81 to 1.07)
- Hemorrhagic stroke (incidence per year): 0.38% warfarin, 0.12% dabigatran 110 (RR 0.31, 95% CI 0.17 to 0.56), and 0.10% dabigatran 150 (RR 0.26, 95% CI 0.14 to 0.49)

N Engl J Med. 2009;361(12):1139-1151

RE-LY

Results (secondary endpoints/other):

- No significant differences in rates of death
- MI (incidence per year):
 - 0.53% warfarin
 - 0.72% dabigatran 110 (RR 1.35, 95% CI 0.98 to 1.87)
 - 0.74% dabigatran 150 (RR 1.38, 95% CI 1 to 1.91)
- PE: no significant differences

N Engl J Med. 2009;361(12):1139-1151

RE-LY

Results (other):

- Hospitalization: Less frequent with dabigatran 110 vs. warfarin (RR 0.92, 95% CI 0.87 to 0.97)
- Net clinical benefit (incidence per year):
 - 7.64% warfarin
 - 7.09% dabigatran 110 (RR 0.92, 95% CI 0.84 to 1.02)
 - 6.91% dabigatran 150 (RR 0.91, 95% CI 0.82 to 1.00)
- No differences in elevated liver function tests

N Engl J Med. 2009;361(12):1139-1151

RE-LY

- Large trial
- Appropriate for NI trial
- Mix of CHADS₂ scores (30% 0 or 1, 36% 2, 32% 3 to 6)
- Appropriate endpoints
- Individualized dosing?
- Rate of bleeding with warfarin (use of aspirin)
- Renal insufficiency
- OL warfarin
- Pharmacoeconomics

N Engl J Med. 2009;361(27):2671-2672
N Engl J Med. 2009;361(27):2674

Which of the following reflects a reasonable conclusion from RE-LY?

1. Dabigatran should replace warfarin since it is more effective and causes less bleeding.
2. Dabigatran is not worse than warfarin, and the 150 mg dose appears to be more effective.
3. Liver failure is a concern with dabigatran.
4. The incidence of MI is higher with warfarin.

References

iPrEx

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RE-LY

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ICHP 2011 Annual Meeting
Putting the Literature into Context
Amy Lodolce, PharmD

Post Test:

Which of the following is NOT a concern with use of emtricitabine/tenofovir for preexposure prophylaxis?

- a. Cost of therapy
 - b. Potential for renal impairment
 - c. Development of resistant HIV
 - d. Lack of efficacy
2. True/false. The Centers for Disease Control and Prevention recommends HIV testing prior to initiation of preexposure prophylaxis.
- a. True
 - b. False
3. Which of the following is a surrogate outcome measure?
- a. Death
 - b. COPD exacerbation
 - c. Change in FEV₁
 - d. None of the above
4. True/false. Fidaxomicin demonstrated less recurrence of *Clostridium difficile* among patients with the NAP1/BI/027 strain.
- a. True
 - b. False
5. Which of the following statements is TRUE regarding noninferiority trials?
- a. The standard of care is used as the active control.
 - b. Placebo is used as the control.
 - c. Superiority cannot be assessed.
 - d. Confidence intervals that contain "0" or "1" are not significant.
6. Which of the following statements is a reasonable conclusion from the RE-LY trial?
- a. Dabigatran should replace warfarin since it is more effective and causes less bleeding.
 - b. Dabigatran is not worse than warfarin, and the 150 mg dose appears to be more effective in preventing stroke/embosлизм.
 - c. Liver failure is a concern with dabigatran.
 - d. The incidence of MI is higher with warfarin.