Recent literature: what does it mean for practice?

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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.
- Define the role of azithromycin in the treatment of early syphilis.
- Summarize the latest paper on the interaction between clopidogrel + proton pump inhibitors.
- Explain how the NAVIGATOR trial affects diabetes prevention strategies.
- Discuss the current controversy surrounding the JUPITER trial.

Outline

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

Please select the response that best describes your status:

1. Student
2. Resident
3. Pharmacist
4. Technician

Azithromycin vs. Penicillin

- Syphilis (*T. pallidum*) – parenteral penicillin G preferred for all stages of disease
- Primary, secondary, tertiary
- Latent infection (early, late, or unknown)

Benzathine penicillin G 2.4 million units IM x 1 dose for primary, secondary, or early latent disease in adults

MMWR Recomm Rep. 2006;55(RR-11):1-94.

Alternative treatments for syphilis

Doxycycline 100 mg po bid x 14 days
Tetracycline 500 mg po qid x 14 days
Ceftriaxone 1 g qd IM or IV x 8 to 10 days
Azithromycin single dose (preliminary data)

MMWR Recomm Rep. 2006;55(RR-11):1-94.

Azithromycin vs. Penicillin

- No alternatives for pregnant women
- Lack of data in patients with HIV
- *Medical Letter* (July 2010): routine use azithromycin not recommended for treating syphilis in US due to resistance concerns

MMWR Recomm Rep. 2006;55(RR-11):1-94.
Treat Guidel Med Lett. 2010;8(95):53-60.

Azithromycin vs. Penicillin

- Limitations of PCN?
  - Drug shortages
  - Medication errors
    - Benzathine
    - Aqueous procaine
    - Aqueous crystalline

Azithromycin vs. Penicillin

- Objective: to compare cure rates of azithromycin vs. benzathine penicillin G in patients with early syphilis
- Methods
  - OL
  - Randomized
  - Multicenter
  - Noninferiority/equivalence

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

- Inclusion criteria
  - 18 to 55 years of age
  - Early syphilis (primary, secondary, or early latent)
  - RPR results
- Exclusion criteria
  - Patients with HIV
  - Pregnant women

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

- Interventions
  - Directly observed single dose therapy
  - 2.4 million units benzathine PCN G given as two IM injections of 1.2 million units (n=262)
  - Azithromycin 2 grams po (n=255)
  - Observed for 30 minutes
- Primary outcome: serological cure at 6 months

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

- Demographic data
  - Mean age 27 years
  - Syphilis stage
    - 26% primary
    - 46% secondary
    - 28% early latent

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

	Azithro	PCN G	Difference	Lower bound limit of 95% CI
Cure rate	180/232 (77.6%)	186/237 (78.5%)	-0.9%	-7.2%

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

- Non-serious adverse events
  - Azithromycin 61.5%
    - GI
    - CNS
  - Penicillin 46.3% ($p<0.001$)
    - Local site reactions
- 4 treatment failures with azithromycin

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

Conclusion

A single dose of azithromycin is potentially useful for the treatment of early syphilis; however, concerns exist regarding resistance and use in patients with HIV.

J Infect Dis. 2010;201(11):1729-1735.

Azithromycin vs. Penicillin

- Strengths
  - Appropriate methodology
  - Benzathine penicillin G dose
- Limitations
  - No follow-up at 12 months
  - External validity
  - Resistance (23S rRNA mutation)

In which of the following patients would azithromycin be preferred over benzathine PCN G for early syphilis?

1. pregnant woman
2. patient with HIV
3. history of anaphylaxis to PCN
4. Otherwise healthy; NKDA

Is pantoprazole safer than other PPIs in terms of interaction with clopidogrel?

1. Yes
2. No

Clopidogrel + PPIs

- Proton pump inhibitors (PPIs) often prescribed for gastroprotection in patients receiving antiplatelet therapy
- Plethora of literature; not high quality evidence
- Several questions remain

Circulation. 2008;118(18):1894-1909.

Clopidogrel + PPIs

- Objective: to determine if patients taking clopidogrel and a PPI have a higher rate of rehospitalization after stent placement vs. those on clopidogrel alone
- Methods
  - Retrospective cohort study
  - Medicare and commercial members
  - Pharmacy and medical claims data
  - >7000 subjects

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

- Inclusion criteria
  - 18 to 84 years of age
  - Clopidogrel Rx during study period
  - Acute MI hospitalization or stent placement
- Exclusion criteria
  - Renal/hepatic failure
  - GI conditions

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

- 2 groups
  - PPI during 90 days before or after index date with at least 1 refill
  - No PPI during above time period
- Matched 1:1 to minimize selection bias
- Main outcome: rehospitalization for MI or stent over 360 days
- Subanalysis: effect with pantoprazole

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

- 1033 in each group; close to 5000 eliminated from clopidogrel group due to inability to match
- PPI distribution
  - Pantoprazole (63.8%)
  - Rabeprazole (15.4%)
  - Omeprazole (8.3%)
  - Lansoprazole (8%)
  - Esomeprazole (4.5%)

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

Re-hospitalization outcome (per 100 patient yrs)	PPI	No PPI	HR (95% CI)
MI	9.7	4.1	1.93 (1.05 to 3.54)
MI or stent	27.6	14.3	1.64 (1.16 to 2.32)

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

Pantoprazole subgroup

- Rehospitalization for MI or stent vs. no PPI: HR 1.91, 95% CI (1.19 to 3.06, p=0.008)
- Not enough events to find a difference in MI rehospitalization

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

Conclusion

Clopidogrel recipients who received concurrent PPI therapy had a higher risk of rehospitalization vs. those who did not receive a PPI.

Arch Intern Med. 2010;170(8):704-710.

Clopidogrel + PPIs

- Strengths
  - Propensity score
  - Expanded population vs. previous literature (women and >65 years of age)
  - Pantoprazole
- Limitations
  - Retrospective
  - ASA use (not billed through pharmacy)

The heart.org: http://www.theheart.org/article/1070797.do

What does this paper add to practice?

1. PPIs should be avoided in patients receiving clopidogrel
2. Pantoprazole may not be any safer than other PPIs
3. Dual antiplatelet therapy recipients are more likely to receive a PPI

NAVIGATOR

- Prevention of diabetes
  - 5% to10% weight loss
  - ⇧ physical activity to 150 min/week

Isn't there a pill for that?

Diabetes Care. 2010;33(Suppl 1):s11-s61.

NAVIGATOR

- Objective: to determine whether nateglinide or valsartan would reduce the risk of diabetes among patients with impaired glucose tolerance & CVD or CV risk factors
- Methods
  - RCT, DB, MC
  - 2 x 2 factorial design

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

- Inclusion criteria
  - Impaired glucose tolerance
  - 1 or more CV risk factors or known CVD
- Exclusion criteria
  - ACE-I or ARB for hypertension; concurrent ACE-I for other indications okay
  - Antidiabetic therapy within previous 5 years

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

- Interventions
  - Valsartan 160 mg/day (n=4631)
  - Placebo (n=4675)
  - Each with nateglinide or placebo
  - Lifestyle modifications (5% weight loss, reduced intake of fat, and increased physical activity)

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

- Coprimary outcomes
  - DM & composite (CV death, nonfatal MI, nonfatal stroke, hospitalization for HF, revascularization, or hospitalization for UA)
  - Added a third endpoint (composite CV as per above without revascularization or hospitalization for UA)

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

Results

- Median follow-up 5 years (66% of subjects receiving drug at year 5)
- 24.3% had CVD
- Weight loss: 0.31 ± 3.9 kg valsartan vs. 0.6 ± 4 kg placebo (difference .28 kg, 95% CI 0.12 to 0.44, p<0.001)
- BP reduced with valsartan (SBP -6.3 mmHg vs. -3.8 mmHg placebo, p<0.001)

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

Incidence of diabetes

	Valsartan	Placebo	Statistics
DM	1532 (33.1%)	1722 (36.8%)	HR 0.86 (95% CI 0.8 to 0.92); p<0.001

ARR=3.7%; NNT=27 over about 5 years

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

Results (cont.)

- No difference in CV outcomes
- Valsartan associated with hypotensive events (42.4% vs. 35.9% placebo, p<0.001)

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

Conclusion

Valsartan, when added to lifestyle modifications can reduce the risk of developing diabetes among patients with impaired glucose tolerance; there are no benefits for prevention of CV outcomes.

N Engl J Med. 2010;362(16):1477-1490.

NAVIGATOR

- Strengths
  - Randomization procedure (block, stratified)
  - Duration of follow-up
- Limitations
  - Results for valsartan plus nateglinide not presented
  - Adequacy of lifestyle modifications?
  - Clinical significance?
  - Non-study use of ACE-I/ARBs
  - Use of placebo

N Engl J Med. 2010;362(16):1533-1535.

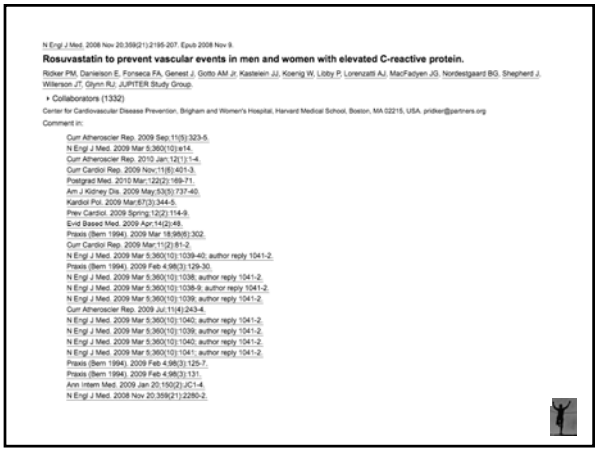
Is there a role for valsartan in preventing diabetes?

1. Yes
2. No

Statins for High-Risk Primary Prevention

- JUPITER 2008
  - Nearly 18,000 patients with normal LDL & elevated CRP
  - Rosuvastatin 20 mg/day vs. placebo
  - Terminated after 1.9 years follow-up (planned for 5 years)
  - RRR in incidence of a major CV event was 43%; ARR=1.2%
  - Need-to-treat 95 patients for 2 years to prevent 1 event

N Engl J Med. 2008;359(21):2195-2207.



N Engl J Med. 2008 Nov 20;359(21):2195-207. Epub 2008 Nov 9.

Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group.

▸ Collaborators (1332)

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Comment in:

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N Engl J Med. 2008 Nov 20;359(21):2280-2.

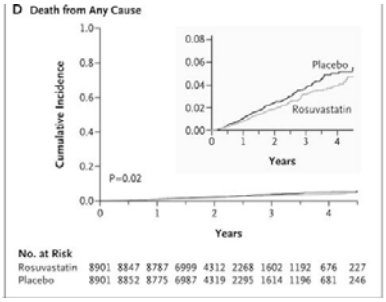
Statins for High-Risk Primary Prevention

Archives of Internal Medicine June 28, 2010

- COI raised, lead author, DSMB chair
- Early termination
- Composite endpoint ("hard" and "soft" components)
- Missing data
- Kaplan-Meier Curve

Arch Intern Med. 2010;170(12):1032-1036.

Figure 1D JUPITER



N Engl J Med. 2008;359(21):2195-2207.

Statins for High-Risk Primary Prevention

- Meta-analysis objective: to determine if statin therapy reduces all-cause mortality among intermediate to high-risk patients without CVD
- Methods
  - Meta-analysis
  - PubMed, Cochrane Collaboration
  - Random-effects model

Arch Intern Med. 2010;170(12):1024-1031.

Statins for High-Risk Primary Prevention

- Trial inclusion criteria
  - RCTs statins vs. placebo
  - All-cause mortality evaluated
  - Patient without CVD at baseline
- Contacted trial investigators for raw data
- Primary outcome: all-cause mortality

Arch Intern Med. 2010;170(12):1024-1031.

Statins for High-Risk Primary Prevention

Results

- 11 RCTs involving 65,229 patients
- 244,00 person-years of follow-up
- 1447 deaths among 32,606 placebo recipients; 1346 deaths among 32,623 statin recipients (risk ratio 0.91, 95% CI 0.83 to 1.01)

Arch Intern Med. 2010;170(12):1024-1031.

Statins for High-Risk Primary Prevention

Conclusion

The evidence does not support a benefit of statin therapy for reducing all-cause mortality among high-risk patients without CVD.

Arch Intern Med. 2010;170(12):1024-1031.

Statins for High-Risk Primary Prevention

- Strengths
  - Analysis limited to patients without CVD
  - No significant heterogeneity
  - Use of raw data
- Limitations
  - Cannot definitively establish cause/effect
  - Insufficient data to conduct subgroup analyses
  - Unable to obtain raw data from 4 additional papers

Arch Intern Med. 2010;170(12):1007-1008.

Are the results of JUPITER diminished by the meta-analysis and editorials?

1. Yes
2. No

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Azithromycin vs. benzathine penicillin

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Clopidogrel + PPIs

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2. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med*. 2010;170(8):704-710.

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Clopidogrel + PPIs (cont.)

3. The heart.org. PPIs plus clopidogrel associated with more MIs. http://www.theheart.org/article/1070797.do. Accessed July 6, 2010.

NAVIGATOR

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ICHP Annual Meeting 2010
Lodolce – Recent Literature: What Does It Mean for Practice?
121-000-10-060-L01-P

Post Test Questions

1. In which of the following patients would azithromycin be preferred over benzathine penicillin G for early syphilis?
    a. Pregnant woman
    b. Patient with HIV
    c. Patient with a history of anaphylaxis to penicillin
    d. Otherwise healthy patient with no known drug allergies

2. Based on the data presented, is pantoprazole safer than other proton pump inhibitors in terms of interaction with clopidogrel?
    a. Yes
    b. No

3. True/False. Proton pump inhibitors should be avoided in patients receiving clopidogrel.
    a. True
    b. False

4. Based on the results of the NAVIGATOR trial, there is no apparent role for valsartan in the prevention of diabetes?
    a. True
    b. False

5. What is the primary criticism of JUPITER is raised by de Lorgeril and colleagues?
    a. It is too expensive to prescribe rosuvastatin for primary prevention.
    b. The absolute risk reduction of 1.2% is not clinically important.
    c. The editorialists suggest that rosuvastatin should have been compared to another statin instead of placebo.
    d. The editorialists suspect bias in reporting data due to the presence of conflicts of interest.