Recent literature: what does it mean for practice?

Amy E. Lodolce, PharmD, BCPS
Assistant Director
UIC Drug Information Group

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

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)
Azithromycin vs. Penicillin

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

---

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

---
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


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


Azithromycin vs. Penicillin

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

Azithromycin vs. Penicillin

<table>
<thead>
<tr>
<th></th>
<th>Azithro</th>
<th>PCN G</th>
<th>Difference</th>
<th>Lower bound limit of 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure rate</td>
<td>180/232 (77.6%)</td>
<td>186/237 (78.5%)</td>
<td>-0.9%</td>
<td>-7.2%</td>
</tr>
</tbody>
</table>


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


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.

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

Sources:

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

Sources:

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

Sources:
**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**

<table>
<thead>
<tr>
<th>Rehospitalization outcome (per 100 patient yrs)</th>
<th>PPI</th>
<th>No PPI</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>9.7</td>
<td>4.1</td>
<td>1.93 (1.05 to 3.54)</td>
</tr>
<tr>
<td>MI or stent</td>
<td>27.6</td>
<td>14.3</td>
<td>1.64 (1.16 to 2.32)</td>
</tr>
</tbody>
</table>

**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


Clopidogrel + PPIs

Conclusion

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


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% to 10% weight loss
  - Physical activity to 150 min/week

Isn’t there a pill for that?


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

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

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)

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)
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)


NAVIGATOR

Incidence of diabetes

<table>
<thead>
<tr>
<th></th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>1532</td>
<td>1722</td>
<td>HR 0.86 (95% CI 0.8 to 0.92); p&lt;0.001</td>
</tr>
<tr>
<td>(%)</td>
<td>(33.1%)</td>
<td>(36.8%)</td>
<td></td>
</tr>
</tbody>
</table>

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


NAVIGATOR

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


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


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


- **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.
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

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

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)

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

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

1. Yes
2. No

References

Azithromycin vs. benzathine penicillin

Clopidogrel + PPIs

Clopidogrel + PPIs (cont.)

NAVIGATOR

Statins for High-Risk Primary Prevention


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 rosvastatin for primary prevention.
   b. The absolute risk reduction of 1.2% is not clinically important.
   c. The editorialists suggest that rosvastatin 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.