Updates in Gastroenterology and Hepatology

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Disclosures

- None
Outline

Part One
- “Burden” of GERD and PPI Use
- Concern regarding side-effects of PPIs

Part Two
- Advances in the treatment of Hepatitis C
- Assessment of Liver Fibrosis
Burden of GERD

- A very common disease
- Up to 60% of adults will experience GERD within a 12 month period
  - 20-30% will have weekly symptoms
- 5-25% of adults worldwide have some symptoms within a 3 month period
- GERD diagnosis increased 216% from 1998 to 2005

Healthline.com
Healthcare Utilization

- In 2004:
  - 18.3 million ambulatory care visits in ERs, clinics
  - 3.1 million hospitalizations
- Addressed in 5% of all primary care clinic visits
- ACG reported that GERD symptoms cost $2 billion per week in lost productivity (2005)

Liker H et al. JABFM 2005:393-400.
NIH.GOV
ACG: GI.ORG
Proton Pump Inhibitor Drugs
Walgreens – Downtown Tampa
Proton Pump Inhibitors

- In 2007, over 108 million prescriptions were written for PPIs
  - 6th ranked class of medication in terms of # of prescriptions
- In 2008, U.S. sales of PPIs reached $13.9 Billion,
  - 3rd highest grossing class of medication

Healthline.com
## Top 100 Drugs By Sales (2013)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug (brand name)</th>
<th>Sales, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abilify</td>
<td>$6,460,215,394</td>
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<tr>
<td>2</td>
<td>Nexium</td>
<td>$6,135,667,614</td>
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<td>3</td>
<td>Humira</td>
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</tr>
<tr>
<td>4</td>
<td>Crestor</td>
<td>$5,310,818,889</td>
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</table>
GERD

- Common challenge that PCPs and gastroenterologists address daily
- Expensive problem
- Extensive PPI use
- PPI use is big business

Concerns Regarding Side Effects

- Over the last decade
- Patients on either short-term or chronic PPI therapy
- Extensive press
Study Finds Growing Reason to Be Wary of Some Reflux Drugs
Heartburn Drugs May Be Linked to Dementia in Seniors

Claire Groden / Fortune  |  Feb. 16, 2016

The study followed instances, not a cause-and-effect relationship of the drugs and dementia

A popular group of heartburn drugs may be linked to dementia in seniors.

A German study published in the medical journal JAMA Neurology found that seniors who regularly took proton-pump inhibitors like Nexium, Prilosec, and Prevacid
PROTON PUMP INHIBITORS CAN INCREASE RISK OF DEMENTIA BY 44%
Have you heard about the latest side effect of your acid reflux medication?

Examples of Proton Pump Inhibitors (PPIs):
Nexium,Prevacid, Prilosec, Protonix

PPIs are now associated with an increased risk of DEMENTIA according to an article published online by JAMA Neurology

Acupuncture is a safe and effective treatment for acid reflux

Save your brain, schedule an appointment today!

SIDE EFFECTS OF ACUPUNCTURE MAY INCLUDE: bliss, sense of euphoria, increased well-being, relaxation, happiness, pain-free digestion, and better mental focus.
COMMON DRUG WARNING

STUDY: HEARTBURN MEDS LINKED TO KIDNEY DISEASE
Heartburn drugs linked to serious kidney problems.
PROTON PUMP INHIBITORS
(used to treat acid reflux & heartburn)
CARRY A RISK OF
SERIOUS SIDE EFFECTS:
DEMENTIA, HEART ATTACK,
& KIDNEY FAILURE
Long-term use can result in drug
dependence.

Commonly Used PPIs Include:
Nexium, Prilosec, Prevacid,
Kapidex, Dexilant, Protonix,
Zegerid, & AcipHex.

http://protonpumpinhibitors.help/ppi-side-effects/
What Patients Have Told Me

- “I don’t want to get demented or Alzheimer's”
- “I have strong bones and want to keep them that way”
- “I have osteopenia”
- “I have osteoporosis”
- “Don’t you need to check my electrolytes or something if I stay on it?”
- “I have a friend on dialysis. I don’t want that.”
So…

- This is a big deal / issue / concern for patients
- Are these concerns justified?
PPI Side-Effects: Will Our Patients End Up with a Broken Hip, Demented, and on Dialysis...?
PPI Side Effects / Concerns

1) Vitamin B12 deficiency
2) Hypomagnesemia
3) Bone disease
4) Infection
   - C. difficile infection
   - Pneumonia
   - Spontaneous bacterial peritonitis
5) PPIs and Plavix
PPI Side Effects

6) Renal disease
7) Dementia
8) CVAs
B12 Deficiency

- How could this happen?
- B12 absorption occurs after enzyme pepsin releases B12 from dietary protein
- Pepsin requires acid for activation
B12 Deficiency

- 2010 Study, Delaware: J Nutr Elder
- Looked at
  - 1) Whether institutionalized older individuals taking PPIs for > 12 months were more likely to have B12 deficiency than patients not taking a PPI
  - 2) Whether cyanocobalamin nasal spray would improve B12 level
- Long-term care residents, aged 60-89
- 17 PPI users; 19 non-PPI users
- PPI users treated with nasal spray for 8 weeks; non-PPI users were not treated
- Serum B12 and methylmalonic acid levels at baseline and at the end of 8 weeks

B12 Deficiency

- 2010 Study, Delaware: J Nutr Elder
- Significant difference in mean B12 and MMA levels between the two groups at baseline
- After treatment → increase in B12 concentration

Conclusions:
- Institutionalized older individuals on PPI for more than 12 months are more likely to be B12 deficient than non-PPI users
- B12 nasal spray for 8 weeks can improve levels

B12 Deficiency

- 2008 Study: Netherlands
- 125 long-term (> 3 years) PPI users recruited from PCP offices
- 125 non-PPI using partners served as the reference group
- Patients > age 65
- Checked B12, homocysteine, and MCV

B12 Deficiency

- 2008 Study: Netherlands
- No difference in mean B12 levels between the groups (345 vs 339)
  - After adjustment for age, gender, H. pylori status, and CRP levels
- No differences observed in homocysteine levels and MCV
- Conclusion:
  - No association between long-term PPI use and B12 status
  - Regular testing for low vitamin B12 levels in elderly patients on PPIs is therefore not recommended

B12 Deficiency - Conclusions

- Small studies
- Relationship between PPIs and B12 deficiency not firmly established
- No formal recommendation to check B12 levels in patients on PPI therapy
Hypomagnesemia

- Well-established, but rare side effect of long-term PPI use
- Has been associated with all PPIs
  - Class effect
Hypomagnesemia – FDA March 2011

FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary

Safety Announcement

[3-2-2011] The U.S. Food and Drug Administration (FDA) is informing the public that prescription proton pump inhibitor (PPI) drugs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.

PPIs work by reducing the amount of acid in the stomach and are used to treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus. In 2009, approximately 21 million patients filled PPI prescriptions at outpatient retail pharmacies in the United States. Patients who take prescription PPIs usually stay on therapy for an average of about 180 days (6 months).
Hypomagnesemia

- Mechanism is not firmly established
- Symptoms:
  - Ataxia
  - Paresthesias
  - Tetany
  - Arrhythmias
- Magnesium replacement alone does not always correct levels
- Patients have to discontinue therapy
Hypomagnesemia

- FDA recommendation:
  - Consider checking serum levels prior to initiation of a PPI
  - Consider checking levels periodically thereafter for patients
    - Expected to be on prolonged treatment
    - Who also take other medications that can cause hypomagnesemia (ex: digoxin or diuretics)
Bone Disease

- An area of significant concern
- Women > Men
- Role PPIs play in inhibiting bone resorption
  - Increased risk of osteoporosis, bone fractures
- Osteoclasts have proton pumps in their cell membranes!
- Acid suppression may inhibit calcium absorption
- Clinical trial data is mixed
Bone Disease

- 2011 Study – Am J Gastro
- Systematic review and meta-analysis of controlled observational studies
  - Evaluate the risk of PPI use and fracture
- 10 studies (4 cohort and 6 case-control)
- 223,210 fracture cases

Am J Gastroenterol 2011;106:1209-18
Bone Disease

- 2011 Study – Am J Gastro
- Among PPI users, ORs were:
  - Hip fracture 1.25 (95% CI 1.14-1.37)
  - Vertebral fracture 1.50 (95% CI 1.32-1.72)
  - Wrist/Forearm fracture 1.09 (95% CI 0.95-1.24)
- No duration effect!
  - Short-term PPI use associated with higher risk of hip fracture, but long-term PPI use was not
- Conclusion:
  - A modest association between PPI use and increased risk of hip and vertebral fractures, but no evidence of duration effect in subgroup analysis
  - Results must be interpreted with caution
Bone Disease

- 2014 Study: J Bone Miner Res
- Long-term PPI therapy (> 1 year) associated with increased:
  - 1) Falls      OR 2.17 (95% CI 1.25-3.77)
  - 2) Fracture-related hospitalizations
    OR 1.95 (95% CI 1.20-3.16)

Bone Disease

- 2014 Study: UK
- Identified patients age 40-89 with a hip fracture
- Relative to non-use, an increased risk of hip fracture was seen with medium and high doses of PPIs
  - OR 1.11 (95% CI 1.01-1.22)
Bone Disease – No Association

- 2015 – Large Study – J Bone Miner Res
- Changes in BMD in
  - 207 PPI users
  - 185 H2RA users
  - 1,676 patients who did not take either
- Medium follow-up period of 9.9 years
- Adjusted for known RFs for osteoporosis
  - BMI, lifestyle factors, menopausal transition stage

Bone Disease – No Association

- 2015 – Large Study – J Bone Miner Res
- Finding:
  - No difference in BMD change in the hip, femoral neck, or lumbar spine in PPI users

Bone Disease – No Association

- 2010 – Manitoba BMD Database
- PPI use over a 5 year period
- Not associated with osteoporosis of the:
  - Hip OR 0.84 (95% CI 0.55-1.34)
  - Lumbar spine OR 0.79 (95% CI 0.59-1.06)

Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. (Strong recommendation, moderate level of evidence)
Infections
C. *difficile*

- One of most common and feared causes of diarrhea in hospitalized patients
- Numerous studies have shown that PPI use is a RF
- Lack of gastric acid → Inability to neutralize spores
- Change in gut flora → Increased susceptibility
C. difficile

- In critically ill / ICU patients
  - PPI use is an independent RF
- Independent RF for recurrent infection

Barletta. Crit Care 2014;18:714
Deshpande A et al. Infect Control Hosp Epidemiol 2015;36:452-60
McDonald EG et al. JAMA Intern Med 2015.
C. difficile – ACG Guidelines

PPI therapy can be a risk factor for Clostridium difficile infection and should be used with care in patients at risk. (Strong recommendation, moderate level of evidence)

Clinical Practice ➔
Continually evaluate inpatients for their need for PPI therapy; use lowest dose

Pneumonia

- Relationship between chronic PPI therapy and PNA not firmly established

Pneumonia – Summary of Studies

- Meta-analysis of 8 observational studies
  - Both PPIs and H2RAs increased overall risk
- Meta-analysis of 23 RCTs
  - Only H2RAs associated with hospital-acquired PNA
- Meta-analysis of 6 nested case-control studies
  - Short PPI course associated with increased risk
  - Chronic use was not

Eom SC et al. Cmaj 2011;183:310-9
Johnstone J et al. Aliment Pharmacol Ther 2010;31:1165-77
Pneumonia – Summary of Studies

- Different study with similar findings:
  - Risk of CAP increased if:
    - PPI started within the previous 2, 7, and 14 days
  - No relationship between PNA and longer-term PPI use

Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)
SBP

- How might this happen?
SBP

- Frequent complication of cirrhosis
- Decreased gastric acid secretion → bacterial colonization of UGI tract → may predispose to bacterial overgrowth and translocation
SBP – Increased Risk

- 2009 Study – Am J Gastroenterol
- 70 cirrhotics with SBP (2002-2007)
- Matched 1:1 (for age, Child class) with cirrhotics with ascites
- Outpatient PPI use at time of admission
SBP – Increased Risk

- **2009 Study – Am J Gastroenterol**
- **Findings**
  - SBP patients had significantly higher rate of PPI use (69%) vs ascitic cirrhotics without SBP (31%)
  - Multivariate analysis: PPI use independently associated with SBP  OR 4.31
  - 47% of cirrhotics on PPIs had no documented indication

Bajaj JS et al. Am J Gastroenterol 2009;104(5):1130-4
SBP – Increased Risk

- 2014 Study
- Retrospective cohort
- 1554 cirrhotic patients with ascites
- 512 on chronic PPIs
- SBP incidence rate between PPI and non-PPI groups

SBP – Increased Risk

- 2014 Study
- Findings:
  - Annual SBP incidence rate
    - PPI group 10.6%
    - Non-PPI group 5.8%  \( p=0.002 \)
  - Multivariate analysis
    - PPI use was an independent RF for SBP

http://emedicine.medscape.com/article/809744-technique
SBP – Decreased Risk

- 2015 Study – J Hepatol – Argentina
- Large nationwide prospective study
  - 23 hospitals
- Consecutive admissions of decompensated cirrhotics
- Exclusion criteria:
  - Active GIB
  - Recent antibiotic use
  - HIV positive / immunosuppressed
- Evaluated for PPI use within the previous 3 months

SBP – Decreased Risk

- 2015 Study – J Hepatol – Argentina
- Findings:
  - No significant difference in PPI use between:
    1) Infected and non-infected patients (44.3% versus 42.8% respectively)
    2) SBP patients and patients with ascites without SBP (46% versus 42% respectively)

Duration of PPI use did not affect SBP

SBP – ACG Guidelines

- Not addressed
- No clear consensus
- Clinical practice
  - Reassess cirrhotic patients’ need for PPI
PPIs and Clopidogrel

- Both agents use the same CYP2C19 pathway for metabolism
- Fear that PPIs may interfere with clopidogrel’s ability to inhibit platelet aggregation
- Mostly based on *in vitro* studies
- Extensively researched
  - Fear is overblown
PPIs and Clopidogrel

In setting of co-prescription, the evidence remains weak for diminished antiplatelet activity
PPI therapy does not need to be altered in concomitant clopidogrel users as clinical data does not support an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)
Renal Disease

- PPIs linked to acute interstitial nephritis
- ? Association with CKD

www.medcitynews.com
Renal Disease – JAMA Intern Med 2016

- Compared rates of incident CKD between patients taking and not taking PPIs among:
  - 10,482 subjects in the Atherosclerosis Risk in Communities (ARIC) Study
    - Median follow-up 13.9 years
    - 322 (3.1%) were taking PPIs
  - Replicated approach using data from 248,751 Geisinger Health System patients
    - Median follow-up 6.2 years
    - 16,900 (6.8%) were taking PPIs
- Patients had GFR > 60

Lazarus B et al. JAMA Intern Med 2016;176(2)238-46
Renal Disease – JAMA Intern Med 2016

- Incident CKD definitions:
  - Hospital codes at discharge or death in the ARIC group
  - Sustained GFR < 60 in the Geisinger cohort
ARIC Study

- 56 incident CKD events among 322 baseline users
  - (14.2 per 1000 person-years)
- 1382 incident CKD events among 10,160 nonusers
  - (10.7 per 1000 person-years)
- Unadjusted analysis
  - Patients using PPIs had 1.45 (95% CI, 1.11- 1.90; P = .006) times the risk of incident CKD relative to that of nonusers
ARIC Study

- Among 322 baseline PPI users:
  - 10-year estimated absolute risk of CKD: 11.8%
  - The expected risk had they not used PPIs: 8.5%

- Absolute risk difference = 3.3%
Geisinger Study

- 1,921 incident CKD events among 16,900 baseline users
  - (20.1 per 1,000 person-years)
- 28,226 incident CKD events among 231,851 nonusers
  - (18.3 per 1,000 person-years)
Geisinger Study

- Among 16,900 baseline PPI users:
  - 10-year estimated absolute risk of CKD: 15.6%
  - The expected risk had they not used PPIs: 13.9%

- Absolute risk difference = 1.7%
Recurrent AKI → CKD

- Analyzed association between PPI and AKI
- ARIC
  - PPI users had 1.64 times the risk for incident AKI as non-users
- Geisinger
  - Adjusted risk 1.31 with a dose effect
    - Twice daily dosing > once daily dosing
Authors’ Conclusion

- PPI use an independent RF for CKD and AKI
Limitations / Thoughts

- Large observational study
- Cannot assign causality
- PPI users may be at higher CKD risk for reasons unrelated to PPI use
  - In both arms, PPI patients more likely to be
    - Obese
    - Have HTN
    - Carry a greater burden of medications
- If the CKD risk is real, is it reversible
Dementia – JAMA Neurology 2016

- Germany
- Prospective cohort using observational data from 2004-2011
- Largest German health insurance database
- Data on inpatient and outpatient diagnosis and drug prescriptions
- PPI use = At least 1 PPI Rx in each quarter of an 18 month interval
- Dementia = Codes present in at least 2 of the 6 quarters of an 18 month interval

Dementia – JAMA Neurology 2016

- Potential confounding factors
  - Age and gender
  - Polypharmacy
  - CVA
  - Depression
  - Ischemic heart disease
  - Diabetes
Dementia – JAMA Neurology 2016

- 73,679 patients included (> age 75 without dementia)
- 2,950 patients regularly used a PPI
  - 78% female, age 84
- 70,729 did not use a PPI
Dementia – JAMA Neurology 2016

- Over course of the study:
  - 29,510 (40%) total patients diagnosed with dementia
  - 59% diagnosed with at least 2 different types of dementia
    - 31% unspecified dementia
    - 3% Alzheimer’s only
    - 6% vascular dementia
    - 59% two types of dementia
Dementia – JAMA Neurology 2016

- PPI users had significantly increased risk of dementia
  - HR 1.44 (95%CI, 1.36-1.52; p < .001)

- Of all potential confounders, depression (HR 1.28) and prior stroke (1.37) had the highest risk of dementia

- Remove all confounders → HR increased to 1.66 (95% CI, 1.57-1.66)
Major Limitations / Concerns

- Does not establish cause and effect
- No accounting for the chronology of progression of symptoms
  - Cognitive, functional symptoms develop slowly over years before a diagnosis is made
- Only 3% had AD (typically 60-80%)
- Diagnosis in at least 2 of 6 quarters
  - Not a high standard
  - Irreversible, progressive conditions that should manifest and be coded for from dx to death
Major Limitations / Concerns

- Unusual ICD codes (Leigh’s syndrome)
- Confounders
  - Heart disease a risk factor for dementia (vascular)
  - This study: associated with a lower risk of dementia
  - Runs counter to the preponderance of evidence
What is more likely?

- Dementia and PPI use are 2 common co-occurring phenomena in patients > age 75
- Not likely that PPIs cause dementia over a few years

- If data was reversed?
  - Prescribe PPIs to lower patients’ risk of dementia?
Dementia

- How might this happen?
- PPIs crossing blood-brain barrier
- Interact with brain enzymes → increase beta amyloid
- B12 deficiency
Abstract 18462: Proton Pump Inhibitor Use Increases the Associated Risk of First-Time Ischemic Stroke. A Nationwide Cohort Study

Thomas S Sehested, Emil L Fosbel, Peter W Hansen, Mette G Charlot, Christian Torp-Pedersen and Gunnar H Gislason

Circulation. 2016;134:A18462

Abstract

Introduction: Use of proton pump inhibitors has been linked with endothelial dysfunction and increased risk of myocardial infarction.

Hypothesis: We hypothesize that use of proton pump inhibitors (PPIs) increases the risk of ischemic stroke.

Methods: Using nationwide Danish registries, we performed a retrospective cohort study. We identified all individuals above 30 years, who had an elective gastroscopy between 1997 and 2012. Patients were excluded due to prior cardiovascular disease at baseline. Association between PPI exposure and risk of first-time ischemic stroke was analyzed in a time-dependent multivariable-adjusted Poisson regression model.

Results: A total of 244,679 individuals were included in the study (mean age was 57.0 years). Approximately 44% filed a prescription for a PPI. In comparison with nonusers, PPI users were older and had more comorbidities, including atrial fibrillation at baseline (3.4 vs. 3.8%). During follow-up, there were 9,489 (3.9%) events of first-time stroke. Time-dependent PPI exposure was associated with stroke with an incidence rate ratio (IRR) of 1.21 (95% CI 1.16-1.27; P-value < 0.0001) adjusted for age, sex, atrial fibrillation, hypertension, diabetes, heart failure, peptic ulcer, cancer, chronic kidney disease and NSAID use. Histamine H2 receptor antagonists demonstrated no association with stroke risk with an IRR of 0.99 (95% CI 0.83-1.21; P-value 0.99). We observed a dose-response relationship between PPI use and associated increased risk of ischemic stroke (Figure).
CVA

- Retrospective study from Denmark
- All patients > 30 who had an elective EGD from 1997 – 2012
- Evaluated association between PPI exposure and risk of first-time ischemic CVA
CVA

- 244,679 patients (mean age 57)
- 44% filled a prescription for a PPI
- PPI users were older and had more comorbidities including afib
- 9,489 (3.9%) of first-time CVA
- PPI exposure associated with CVA with an incidence rate ratio of 1.21 (95% CI 1.16-1.27, p < 0.0001)
  - Adjusted for age, afib, HTN, DM, heart failure, cancer, CKD, NSAID use
- Higher risk associated with higher dosages
CVA – Higher Risk with Higher Dosages

<table>
<thead>
<tr>
<th>Type of PPI</th>
<th>Dose per day</th>
<th>Incidence rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonusers</td>
<td>Reference</td>
<td>1.00 (1.00-1.00) Ref.</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>10 mg</td>
<td>0.95 (0.59-1.50) 0.8</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>0.91 (0.82-1.02) 0.09</td>
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<tr>
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<td>&gt;= 40 mg</td>
<td>1.40 (1.23-1.59) &lt;0.0001</td>
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<tr>
<td></td>
<td>80 mg</td>
<td>1.19 (1.03-1.38) 0.02</td>
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<tr>
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<td>150 mg</td>
<td>1.26 (1.14-1.39) &lt;0.0001</td>
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<td>200 mg</td>
<td>1.94 (1.63-2.29) &lt;0.0001</td>
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<td>300 mg</td>
<td>1.94 (1.63-2.29) &lt;0.0001</td>
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<td>400 mg</td>
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<td>500 mg</td>
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<td>1000 mg</td>
<td>1.94 (1.63-2.29) &lt;0.0001</td>
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IRR: Incidence Rate Ratio
CI: Confidence Interval
P-value: Statistical significance of the difference
Complications of Proton Pump Inhibitor Therapy

Michael F. Vaezi,¹ Yu-Xiao Yang,² and Colin W. Howden³
Hill Criteria

**Table 2. Hill Criteria**

- Strength of association
- Consistency
- Specificity
- Temporality
- Biological gradient
- Biological plausibility
- Coherence
- Experiment
- Analogy

**Questions**

- Is the association of high magnitude?
- Are the findings reproducible?
- Is the outcome predicted based only on the exposure to PPIs?
- Does the use of PPIs precede the observed outcome?
- Is there a direct relationship between dose or duration of PPI use and the outcome?
- Is there a rational and theoretical basis for the proposed association?
- Any conflicts with what is known about the natural history and biology of the disease?
- Are the data based on experiments?
- Are there features of association similar to other associations judged to be causal?
Hill Criteria

- **Strength of Association**
  - Moderate level
    • Bacterial Enteric Infections
    • *C. difficile* infection
  - ALL OTHERS WEAK

- **Consistency**
  - Yes: Bacterial Enteric Infections and hypoMg
  - No: ALL OTHERS
### Relative and Absolute Risk for Adverse Events Associated With Long-Term PPIs

<table>
<thead>
<tr>
<th>Potential Adverse Event</th>
<th>Relative Risk</th>
<th>Absolute Risk</th>
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<tbody>
<tr>
<td>Chronic Kidney Disease</td>
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<td>Dementia</td>
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<td>Bone Fracture</td>
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<tr>
<td>Myocardial Infarction</td>
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<td>SBP</td>
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<td><em>C. difficile</em> infection</td>
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<td>Pneumonia</td>
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<tr>
<td>Micronutrient Deficiencies</td>
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General Thoughts

- PPIs have transformed the treatment of GERD
- Many patients are on PPIs unnecessarily
- Many patients who are appropriately on PPIs receive excessively high doses
- **Use the lowest effective dose**
- Continuously reassess the need for PPI tx
General Thoughts

- Current data regarding associations of PPI use with long-term outcomes mostly based on observational studies
- Most higher-quality studies have produced lower risk estimates
- Most current evidence linking PPIs to long-term adverse events is weak
- Some patients inappropriately discontinue PPI therapy
- Weak/inconclusive data should not be presented as facts
Advances in the Treatment of Hepatitis C
Epidemiology and Healthcare

Natural History

Acute HCV Infection (100)

Recovery & Clearance of HCV (20)

Chronic Infection (80)

Mild (24)

Chronic Hepatitis

Moderate (32)

Cirrhosis

Severe (24)

End-Stage Liver Disease

Hepatocellular CA

Decompensated Cirrhosis and HCC

Decompensated cirrhosis
Hepatocellular cancer

Brief History of Treatment

Peg-IFN + RBV
IFN-free Combos
IFN + RBV
PI + PegIFN + RBV
Advances in Standard of Care

- Interferon
- Interferon + ribavirin
- Peginterferon + ribavirin
- Peginterferon + ribavirin + PI
- Interferon-free combination

Sustained virological response rates (%)

- 1990: 7-10%
- 1998: 25%
- 2001: 40-50%
- 2011: 60-70%
- 2014: >90%

Case

- 65 year-old asymptomatic female presents for evaluation of recent positive hepatitis C antibody

- What labs should you check?
  - CBC, CMP, PT/INR
  - HCV VL and genotype
  - Hep A Total Ab
  - HBsAg, sAb, core total Ab
  - HIV
### Recommendation for When and in Whom to Initiate Treatment

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.</td>
<td>I, A</td>
</tr>
</tbody>
</table>
Welcome to HCVGuidelines.org

The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a guidance section below, or use the search box to begin.

- Contents and Introduction - Select a Page
- Testing, Evaluation, and Monitoring of Hepatitis C - Browse Topics
- Initial Treatment of HCV Infection - Choose Patient Genotype
- Retreatment of Persons in Whom Prior Therapy Has Failed - Choose Patient Genotype

Search the Guidance
Enter your keyword: Search
Contents and Introduction - Select a Page

Testing, Evaluation, and Monitoring of Hepatitis C - Browse Topics

Initial Treatment of HCV Infection - Choose Patient Genotype

- Initial Treatment of HCV Infection
- Treatment-Naive Genotype 1
- Treatment-Naive Genotype 2
- Treatment-Naive Genotype 3
- Treatment-Naive Genotype 4
- Treatment-Naive Genotype 5 or 6
The following pages include guidance for management of treatment-naive patients with genotype 1 infection.

- Treatment-Naive Genotype 1a Without Cirrhosis
- Treatment-Naive Genotype 1b Without Cirrhosis
- Treatment-Naive Genotype 1a With Compensated Cirrhosis
- Treatment-Naive Genotype 1b With Compensated Cirrhosis
# Treatment-Naive Genotype 1b Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Patients Genotype 1b Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>8 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is &lt;6 million IU/mL</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily simeprevir (150 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
</tbody>
</table>

*a This is a 3-tablet coformulation. Please refer to the prescribing information.

*b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
### Table 1: LDV/SOF Phase III trials for the treatment of patients with chronic hepatitis C genotype 1 infection

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient characteristics</th>
<th>Treatment regimen</th>
<th>Number of pts</th>
<th>Duration (weeks)</th>
<th>SVR12 (%)</th>
<th>Relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1⁹</td>
<td>Treatment-naïve</td>
<td>LDV/SOF</td>
<td>214*</td>
<td>12</td>
<td>210/213 (99)</td>
<td>1/212 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>217</td>
<td>12</td>
<td>211 (97)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>217</td>
<td>24</td>
<td>212 (98)#</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>217*</td>
<td>24</td>
<td>215 (99)</td>
<td>0</td>
</tr>
<tr>
<td>ION-2¹⁶</td>
<td>Treatment-experienced</td>
<td>LDV/SOF</td>
<td>109</td>
<td>12</td>
<td>102 (94)</td>
<td>7 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>111</td>
<td>12</td>
<td>107 (96)</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>109</td>
<td>24</td>
<td>108 (99)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>111</td>
<td>24</td>
<td>110 (99)#</td>
<td>0</td>
</tr>
<tr>
<td>ION-3¹⁷</td>
<td>Treatment-naïve</td>
<td>LDV/SOF</td>
<td>215</td>
<td>8</td>
<td>202 (94)</td>
<td>11 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF + RBV</td>
<td>216</td>
<td>8</td>
<td>201 (93)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDV/SOF</td>
<td>216</td>
<td>12</td>
<td>208 (95)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

12 Weeks of Sofosbuvir-Velpatasvir in HCV Genotype 3 (ASTRAL-3)

SVR12 Among Patients with HCV GT 3, According to Cirrhosis Status and Prior Tx

SOF/VEL (Epclusa) for 12 Weeks Across All Genotypes

SVR12 (%)

Total 98 98 99 95 100 97 100

GT 1 1015/1035 323/328 237/238 264/277

GT 2 2 relapse 2 LTFU 1 D/C

GT 3 11 relapse 2 D/C

GT 4 100/116 116/116

GT 5 97/34 35/41

GT 6 100/41

Agarwal K, et al. EASL 2016; Poster #SAT-195
Jacobson I, et al. EASL 2016; Poster #SAT-168
### Table 2 Wholesale acquisition cost of direct-acting antivirals

<table>
<thead>
<tr>
<th>Direct-acting antiviral</th>
<th>Pharmaceutical company</th>
<th>WAC for 12 week course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir (Sovaldi)</td>
<td>Gilead sciences</td>
<td>$84,000</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir (Harvoni)</td>
<td>Gilead sciences</td>
<td>$94,500</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir + Dasabuvir (Viekira Pak)</td>
<td>AbbVie</td>
<td>$83,319</td>
</tr>
<tr>
<td>Daclatasvir (Daklinza) + Sofosbuvir (Sovaldi)</td>
<td>Bristol-Myers Squibb and Gilead</td>
<td>$147,000</td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir (Zepatier)</td>
<td>Merck</td>
<td>$54,600</td>
</tr>
</tbody>
</table>
Special Considerations

- Drug-Drug Interactions
  - Amiodarone
  - Statins
  - PPIs

- Regimens available for CKD patients

- Side-Effects
  - Nausea
  - Headaches
  - Fatigue

- ~ High 90s% chance of cure
Fibrosis Assessment
## Required in Every Patient

### Recommendation for Pretreatment Assessment

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate decision making regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening).</td>
<td>I, A</td>
</tr>
</tbody>
</table>

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Why Is This Important?

- Need to identify patients at high-risk for cirrhosis / liver-related complications
  - Future treatment
  - HCC / Varices
  - Referral for liver transplantation
- **Plan for long-term management**
- Increasing prevalence of fatty liver disease
Liver Biopsy

- Long the gold-standard for diagnosing fibrosis
- Benefits:
  - Also yields information on inflammation, necrosis, steatosis, iron deposits
- Downsides:
  - Invasive
  - Risk of complications
  - Sampling error (up to 25% of cases)
Trend Toward Non-Invasive Assessment

- HCV screening recommendations
- Increasing prevalence of fatty liver disease
- Patient preference
Non-Invasive Fibrosis Assessment

Serum Markers
- Indirect
  - APRI
  - FIB-4
- Direct
  - FibroTest or FibroSure

Imaging-Based Technologies
- Ultrasound Elastography
- MR Elastography
Indirect Serum Markers

\[
\text{FIB-4} = \frac{\text{Age(years)} \times \text{AST(U/L)}}{\text{Platelet count}(10^9/L) \times [\text{ALT(U/L)}]^{1/2}}
\]

\[
\text{APRI} = \frac{\text{AST(ULN*)}}{\text{Platelet count}(10^9/L)} \times 100
\]
Table 1. Comparison of FIB-4 Index and Liver Biopsy Results

<table>
<thead>
<tr>
<th>FIB4 Index</th>
<th>F0-F1-F2</th>
<th>F3-F4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.45</td>
<td>94.7% (n = 521)</td>
<td>5.3% (n = 29)</td>
<td>550</td>
</tr>
<tr>
<td>1.45-3.25</td>
<td>73.0% (n = 168)</td>
<td>27.0% (n = 62)</td>
<td>230</td>
</tr>
<tr>
<td>&gt;3.25</td>
<td>17.9% (n = 12)</td>
<td>82.1% (n = 55)</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>82.8% (n = 701)</td>
<td>17.2% (n = 146)</td>
<td>847</td>
</tr>
</tbody>
</table>
Direct Serum Marker - Fibrosure

- Blood test
  - Alpha-2-macroglobulin
  - Apolipoprotein A1
  - Haptoglobin
  - \( \gamma \)-glutamyltranspeptidase
  - Bilirubin
- Cost ~ $250
- Inconsistent insurance coverage
Transient Elastography - Fibroscan

Fibroscan(R) uses low-frequency ultrasound to measure hepatic transient elasticity (stiffness) and fibrosis for the staging of liver injury.
- Mechanical vibrator produces a shear wave that propagates through the liver
- Ultrasounds track this wave and measure its velocity
  - The stiffer the tissue, the faster the wave propagates
- How is it done?
  - Tip of the probe is placed between the intercostal spaces
  - A minimum of 10 valid measurements are required, and the final result is the median of the successful measurements (expressed in kPa)
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>F0 to F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>2 to 7 kPa</td>
<td>8 to 9 kPa</td>
<td>8 to 11 kPa</td>
<td>18 kPa or higher</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>2 to 7 kPa</td>
<td>8 to 9 kPa</td>
<td>9 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td><strong>HIV/HCV Coinfection</strong></td>
<td>2 to 7 kPa</td>
<td>7 to 11 kPa</td>
<td>11 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td><strong>Cholestatic Disease</strong></td>
<td>2 to 7 kPa</td>
<td>7 to 9 kPa</td>
<td>9 to 17 kPa</td>
<td>17 kPa or higher</td>
</tr>
<tr>
<td><strong>NAFLD/NASH</strong></td>
<td>2 to 7 kPa</td>
<td>7.5 to 10 kPa</td>
<td>10 to 14 kPa</td>
<td>14 kPa or higher</td>
</tr>
<tr>
<td><strong>Alcohol Related Disease</strong></td>
<td>2 to 7 kPa</td>
<td>7 to 11 kPa</td>
<td>11 to 19 kPa</td>
<td>19 kPa or higher</td>
</tr>
</tbody>
</table>
Fibroscan and HCV

Question 1. In adults with chronic HCV, is the overall diagnostic performance of VCTE superior to other noninvasive markers of liver fibrosis (APRI, FIB-4) for detection of cirrhosis?

Key message. In adults with chronic HCV, VCTE has superior sensitivity and specificity, and lower FP and FN rates, suggesting better diagnostic performance compared with APRI and FIB-4 for detection of cirrhosis. (Moderate quality of evidence).

Question 6. In adults with NAFLD, is the overall diagnostic performance of VCTE (M-mode) superior to other noninvasive markers of liver fibrosis (APRI, FIB-4) for detection of cirrhosis?

Key message. In adults with NAFLD, VCTE (M-mode) has superior sensitivity and specificity, and lower FP and FN rates, suggesting superior diagnostic performance, as compared to APRI and FIB-4 for detection of cirrhosis. (Very low quality of evidence).
Fibrosis Assessment - Conclusions

- All markers are imperfect
- Combination approach is often required
  - Fibrosis-4 Score and Fibroscan
- Fibroscan can easily be ordered in the primary care setting
- Required in HCV patients
- Remember to use these tools in other liver patients
Acknowledgements

- Dr. Joel Richter
- Dr. Mohamed Kaif
Thank you!