Proton Pump Inhibitors and Renal Disease/RAAS Blockade Reconsidered

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Disclosures

- None, just working for The Man
- No maker of any PPI supported this talk either!
Objectives

• Understand the significant risks of PPI use and acute and chronic renal disease
• Understand the role of PPIs in various electrolyte abnormalities and increased risk of death
• Understand the lack of information on RAAS blockade in advanced CKD and potential risks of continued use
• Understand the potential trade off between lower BP and advanced CKD
IS NOTHING SACRED?
Proton Pump Inhibitors and Kidney Disease
Historical Perspectives

• The besetting malady of the country is dyspepsia... From it about one half of the income of doctors is derived, and at least two thirds of that of the patent medicine vendors.¹

Osler

• The platter kills more than the sword.²

Osler

2. Osler, W, Principles and Practice of Medicine 7th Ed. 1909 D. Appleton, New York, p.460
Proton Pump Inhibitors (PPI)

- 1989 Omeprazole first introduced, by prescription
- 2003 FDA approved PPI’s for OTC sales
- $10 billion in sales in 2012
- NHANES Study estimated 7.8% of adults used a PPI within the past 30 days (2015)
- 25-70% may not have appropriate indications
- Part of some admitting standing orders sets, “just in case”

*JAMA.* 2015;314:1818-1831

*US Pharm.* 2017;42:4-7

Mechanism of Action of PPI’s

- PPI’s covalently bind to the Gastric H-K ATPase Pump of the Parietal Cells
- No effect on Renal H-K ATPase Pump
- Metabolized via Cytochrome P450-CYP2C19 and CYP3A4

*J Nephrol 2016;29:611-619*
But then....
PPI’s linked to Numerous Adverse Effects

- Since 2007 FDA has issues warnings to people taking PPI’s for increased risk:
  - Fractures
  - Decreased effectiveness of clopidogrel w/ omeprazole
  - *C. difficle* diarrhea
  - Pneumonia (community and hospital acquired)
  - Cutaneous Lupus reactions
  - Renal effects

FDA.gov:
Renal Side Effects Linked to PPI’s

• Acute interstitial nephritis
• Acute kidney injury (AKI) from pneumonia or \textit{C. diff.} diarrhea
• Chronic interstitial nephritis
• Hyponatremia
• Hypomagnesemia
• Hypokalemia
• ESRD

\textit{J Gastroenterol Hepatol} 2017;32:1295-1302.

\textit{J Nephrol.} 2016;29:611-616
Acute Interstitial Nephritis (AIN)

• Most common cause of AKI linked to PPIs
• 1st described in 1992 with omeprazole
• Relatively infrequent cause of AKI but can occur in 20-30% of in hospital renal biopsies
• Frequently overlooked as a cause (because everyone is on one?)
• Does not follow the classic time frame of 7-14 day use before onset of symptoms, _if any_
• Mean time of ~9.9 weeks of use prior to recognition

*Clin Nephrol 2007;68:65-72*

Risk of PPI Induced AIN

• New Zealand 2005-2009
• 572,661 patients nested case control
• Odds Ratio of AIN was 5.16 for current PPI users
• Higher Risk >60 y.o. 20/yr. cases of AIN per 100,000 vs 2/yr. per 100,000 age 15-49

Kidney Int. 2014;86:837-844
AKI and AIN

- Ontario 2002-2011
- 290,592 patients hospitalized, those w/ AKI and had taken a PPI within 120 days before admit, >65 y.o
- All AKI and AIN subgroup
- **AKI** (all cause) 13.46 per 1000 person years in PPI vs 5.46 per 1000 person years non PPI-Hazard Ratio 2.52
- **AIN** 0.32 per 1000 patient years in PPI group vs 0.11 per 1000 Patient years in the non-PPI group

*CMAJ.* 2015;3:E166-E171
PPI Induced AIN

• Does not present with the classic allergic manifestations (e.g. methicillin, TMP-STX) of fever, rash, malaise and eosinophiluria

• Does not present with the bland manifestations of NSAID induced AIN

• When re-challenged with another PPI, will cause more rapid onset of AIN

Features of PPI-AIN (or lack of)

- <50% have fever
- <10 have rash
- <30% have Eosinophiluria
- <10% have classic triad of fever, rash and eosinophiluria, thus making Dx more difficult
- 22-39% will have fatigue, nausea and weakness
- Hypersensitivity to drug or metabolite which bind to the tubular basement membrane, stimulating an immune response

Laboratory Findings in PPI-AIN

- Elevated BUN and Creatinine
- Minimal proteinuria
- WBCs, WBC casts (sterile pyuria), microscopic hematuria, eosinophilia and eosinophiluria (only 30% of All cases of AIN)
- ESR may be elevated and C₃ and/or C₄ may be low
- While the above is suggestive of PPI-AIN the diagnosis can only be made by renal biopsy

Renal Biopsy in AIN

- Diffuse infiltration of the interstitium with inflammatory cells and eosinophils
- Production of ROS, cytokines and antioxidants which damage the tubule
- Acute inflammation leads to interstitial fibrosis and chronic interstitial nephritis
Clinical Course

• Frequently overlooked as a causative agent, delay of diagnosis/association leads to progression to Chronic Interstitial Nephritis (CIN) and then ESRD

• Even when diagnosed early, residual renal impairment is frequently seen

• Steroids may be of little value

AIN Can Progress to CIN

Acute Interstitial Nephritis

Chronic Interstitial Nephritis
PPIs and Chronic Renal Disease Risk (1)

- Atherosclerosis Risk in Communities (ARIC)
- 10,482 patients w/ GFR>60 ml/min/1.73m²
- Compared baseline values (1996-1999) to December 2011
- H₂ antagonist were considered negative control and active comparator
- 20-50% risk incidence of CKD
- Twice daily use further increased risk of CKD
- Highest risk group: obese, white, taking antihypertensives

JAMA Internal Med. 2016;176:238-246
PPIs and Chronic Renal Disease Risk (2)

- VA Upstate New York, 71,516 patients
- Examined risk of CKD and PPIs 4/2001-4/2008
- 24,149 (34%) developed CKD during this period of these 24.4% on PPI
- Odds ratio of CKD 1.10 for CKD in PPI users vs non-PPI users
- Odds ratio of death was 1.76 in PPI users vs non-PPI users
- Patients <53 y.o had a higher risk of CKD

*BMC Nephrology* 2016; 112-120.
PPI Induced Hyponatremia

• Elderly are at highest risk
• Hyponatremia of any cause is an independent risk factor for death
• May aggravate other meds associated with hyponatremia (e.g. thiazides) or act alone
• SIADH (Euvolemic hyponatremia)

PPI Induced Hypomagnesemia/Hypocalcemia

- Usually with an inappropriately **low** PTH level
- Low magnesium stimulates PTH but very low levels suppress PTH
- 1st described in 2006
- Related to **decreased** magnesium absorption from the gut as renal excretion was appropriately decreased
- **Risk factors are:** age, duration of treatment,
- Hypomagnesemia is a cardiac risk factor and can lead to hypokalemia via **increased** K secretion by the kidney

PPI’s Can Induce Hypokalemia

• Can be aggravated by hypomagnesemic induced renal K loss
• Can be aggravated chronic interstitial nephritis induced K loss
• Can be aggravated by other medications e.g. diuretics
• Can be aggravated by PPI’s alone
• PPI usually have no effect on the H-K ATPase pump in the distal tubule
• However in certain conditions such as increased acid load, K is secreted in the urine and PPIs may activate the renal H-K ATPase

Effect of Chronic Hypokalemia on CKD

• Chronic hypokalemic nephropathy 1st described 1978
• Impaired ammoniagenesis (unable to excrete acid load) leads to acidosis, interstitial fibrosis and CKD
• Another potential cause of CKD related to chronic PPI therapy

*J Clin Invest 1987;79:1447-1458*
PPI’s and Risk of Death of All Causes

• VA National Database, population based observational study
• 349,312 patients
• Compared PPI use vs H₂ Blockers vs neither class of medications and all cause mortality
• Follow up time 5.71 years, mainly older, white male veterans

PPI and All Cause Mortality

- Overall increased mortality of PPIs vs H₂ Blockers  HR 1.25
- PPI increased mortality vs no PPI                  HR 1.15
- PPI increased mortality vs no PPI or H₂ Blockers HR 1.23

PPI use compared to a cohort w/o GI Condition

- PPI increased mortality vs H₂ Blockers             HR 1.24
- PPI increased mortality vs no PPI                  HR 1.19
- PPI increased mortality vs no PPI or H₂ Blockers  HR 1.22

Survival curves for PPI and H2 blockers.

Yan Xie et al. BMJ Open 2017;7:e015735
Duration of PPI exposure and risk of death among new PPI users (n=166 098).

Yan Xie et al. BMJ Open 2017;7:e015735
In Summary

• PPI’s are safe in most patients
• Risks for renal problems increase with age, duration of therapy, and other medications
• AKI may not present with many specific s/s, if it is on a med list d/c if possible until there is improvement in renal function
• If re-challenging with a PPI, be sure to closely monitor renal function
• Make sure that a PPI is appropriate and for short term use, not “just in case”
ACE-i/ARBs Reconsidered
Background

• RAAS Blockade has been central to nephrology, endocrine, cardiology and other specialties for well over two decades

• Countless studies have demonstrated their benefit in diabetic and non diabetic renal disease, hypertension, CHF and post MI (Captopril, IDNT, RENAAL, REIN, REIN-2, HOPE, LIFE, ALLHAT, SOLVD, CHARM, ALLHAT to mention a few

• Many of us (nephrologists and other) have advocated NOT stopping an ACE-I/ARB, regardless of the renal function
But

- The studies that recommendations were based on were in patients with Stages 1-3 CKD, not Stages 4 or 5
  - CKD 3 eGFR< 60ml/min. 1.73m²
  - CKD 4 eGFR< 30 ml/min 1.73m²
  - CKD 5 eGFR<15 ml/min. 1.73m²
- What is the big deal with Stage 4/5 CKD?

KDIGO Kidney Intl Suppl. 2013;3;1-150
CKD by Stages

![Graph showing CKD by stages from 1988-1994, 1999-2004, and 2007-2012.](image-url)

- **Stage 1**: Percentage of the population
- **Stage 2**: Percentage of the population
- **Stage 3**: Percentage of the population
- **Stage 4**: Percentage of the population
- **Stage 5**: Percentage of the population
Kidney Disease = Cardiovascular Disease

**Mediators**
- Inflammation
  - CD8+ cells
  - TNFα, IL-1β, IL-8
- Endothelial dysfunction
  - Uric acid
  - L-arginine synthesis
  - NO signalling
  - Renin-angiotensin-system
  - ox-LDL
- Redox perturbations
  - ROS, RNS
  - Antioxidant enzyme activity
  - Mitochondria
  - Nrf2/keap1/ARB pathway
RAAS Blockade in CKD

“A rise in the serum creatinine of up to 30% of baseline (given baseline up to 3 mg/dl) that remains stable in the absence of hyperkalemia (K>6 mg/dl) correlated with slower renal disease progression.”

Bakris & Weir Arch Int Med 2000; 160:685-693
Lesson from History

• Damn the Creatinine! Continue the ACE-I!!!
But!

• The 30% recommendation was based on a review of 12 studies of 1,102 patients and not based on a focused trial
• Data from ONTARGET, ACCOMPLISH, and other studies have questioned this thinking
• For “renoprotective effect” the urine protein must be >500-1,000 mg/da
• At CKD 4 or 5 the vasculature stiffens and statins (and RAAS blockade) lose their effectiveness, more hyperkalemia, all cause mortality
• Further RAAS blockade may accelerate this decline
• RAAS blockade mediated renoprotection may be lost in advanced CKD

Controversies

• Should we maximize the blockade of the RAAS (aldosterone blockade and direct renin inhibitors)?

• Should albuminuria reduction be a target of treatment in antihypertensive therapy?

• Should ACEi/ARB be discontinued in Stage 4/5 CKD to avoid further compromising residual renal function?

• Low blood pressure (SBP<120 mm Hg) in CKD risks advancing CKD and earlier ESRD (SPRINT)-Less CV deaths, more ESRD²

Effect of Stopping RAAS Blockage on Renal Function

- 52 patients with advanced CKD on ACE-I or ARB
- 21 female, 31 male
- Average *increase* eGFR 10 ml/min/1.73 m over 12 months over 12 months in all but 4 patients
- Slight increase in MAP of 90 to 94 mm Hg
- No effect on proteinuria

*Nephrol Dial Transplant* 2010;25: 3977-3982
From: The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease


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Double-edged Sword

• ? Increase CV mortality in stopping RAAS blockade in advanced CKD?
• Swedish Registry compared mortality of CKD 4/5 vs HD/PD:

<table>
<thead>
<tr>
<th>Patients</th>
<th>#</th>
<th>Ave. age yrs.</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 4/5</td>
<td>3040</td>
<td>66</td>
<td>12/100 person yrs (95% CI 11-13)</td>
</tr>
<tr>
<td>PD</td>
<td>725</td>
<td>60</td>
<td>17/100 person yrs (95% CI 15-19)</td>
</tr>
<tr>
<td>HD</td>
<td>1791</td>
<td>62</td>
<td>25/100 person yrs (95% CI 23-27)</td>
</tr>
</tbody>
</table>

HR for mortality for dialysis vs CKD:
- PD 1.7 (95% CI 1.4-2.1)
- HD 2.6 (95% CI 2.3-2.9)

Neovius, BMJ Open 2014; 4:e004251.
What about long-term use of RAAS blockade?

- 6102 patients, 102 developed ESRD matched to 4129 controls
- Relative to Thiazide use the adjusted rate ratio of ESRD after 3 yrs:
  - ACE-i Total          2.5 (95% CI 1.3-4.7)
  - ACE-i 1st 3 yrs     0.8 (95% CI 0.3-2.5)
  - ACE-i >3 yrs        4.2 (95% CI 2.0-9.0)
  - Beta-blockers       0.8 (95% CI 0.5-1.4)
  - CCB                0.7 (95% CI 2.0-9.0)

Is RAAS blockade only effective early (Stage 1-3) in CKD and for only 3 yrs?

Suissa S Kidney Int 2006;69:913-919
McGill University
Can the RAAS Blockade Romance be Ending?
STOP-ACEi Trial (2014-present)

- **Aim of the study:** To test the hypothesis that stopping treatment with ACEi, ARB or a combination of both, compared with continuing on these treatments, improves or stabilizes renal function in patients with progressive stage 4 or 5 Chronic Kidney Disease (CKD).

- **Study design:** Open-label randomized controlled trial (RCT).

- **Sample size:** 410 patients will be recruited into the study (205 in each arm) over a 2 year period.

- **Study Duration:** The accrual period is for 2 years and all patients will be followed up for 36 months. The end of trial will be 6 months after the last data capture. The total study duration is 6 years.

- **Timeframes:** NIHR/MRC EME programed grant start date: 1\textsuperscript{st} February 2014. Trial set up will take place in 6 months, recruitment will take 24 months, all patients will be followed up for 36 months.


University of Birmingham, UK
CKD patients stage 4-5
ACEi/ARB treatments

Eligible for STOP-ACEi study?

Yes

No

Excluded
Not meeting criteria
Declined
Other reason

Randomize 1:1 ratio, N=410

Control Arm: Continue ACEi/ARB N=205

Experimental Arm: Discontinue ACEi/ARB N=205

3-year follow-up

Routine tests (eGFR, FBC, BCP, urinary PCR), BP,
documentation of ESA dose, adverse events,
compliance and changes in medication

QOL questionnaire, weight and BMI, 6-minute walk
test, ECG, bloods for C-reactive protein, cystatin-C,
NT-proBNP, ACE/renin levels and biomarkers

Analysis

Interim analysis of efficacy and safety carried out for data monitoring
and ethics committee

First analysis once the last randomized participant completes the
3-year follow-up.
But until the results are in...

I'LL JUST WAIT

PATIENTLY

memegenerator.net
Conclusions

• RAAS blockade is an essential cornerstone of therapy for DM, CHF, proteinuria renal disease and HTN, especially in Stage 1-3 CKD

• But does the effect only last 3 years or longer?

• Should we consider stopping or deceasing the dose at CKD 4/5?
Thank You

Questions?

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