Proton Pump Inhibitors and Kidney Disease

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Disclosures

- None, just working for The Man
- No maker of any PPI supported this talk either! As you will see

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

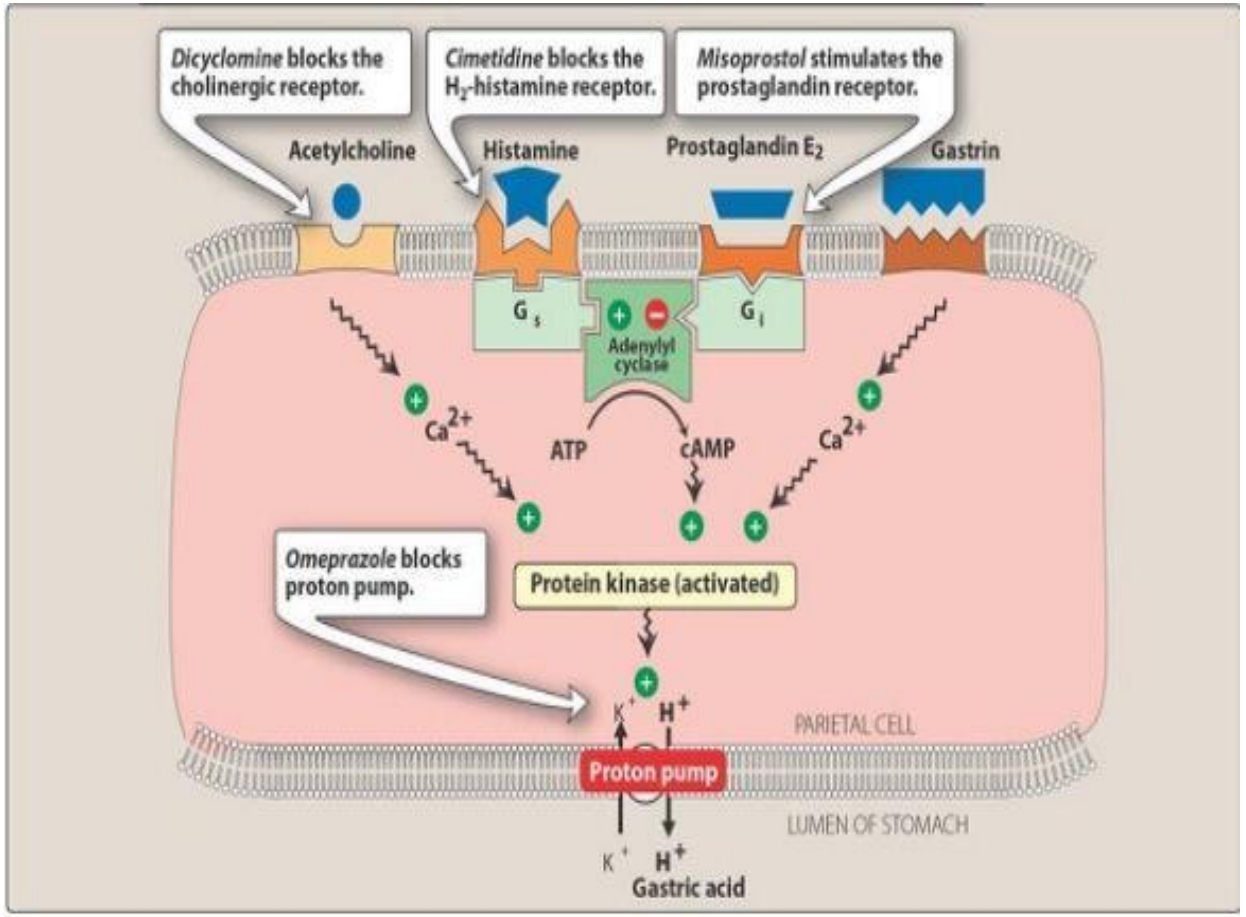
1. Bliss, M, *William Osler A Life in Medicine.* 1999 Oxford University Press, New York, p.273
2. Osler, W, *Principles and Practice of Medicine* 7th Ed. 1909 D. Appleton, New York, p.460

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, BMJ. 2008;336:2-3.

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….


ernst
LUBITSCH'S
"TROUBLE IN PARADISE"
WITH
MIRIAM HOPKINS · KAY FRANCIS · HERBERT MARSHALL
CHARLIE RUGGLES AND EDWARD EVERETT HORTON
FROM THE PLAY BY LASZLO ALADAR
A Paramount Picture

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 (omeprazole) *FDA* 2010
- *C. difficle* diarrhea
- Pneumonia (community and hospital acquired)
- Cutaneous Lupus reactions
- Renal effects

FDA.gov:
8/9/2007,12/10/2007,5/28/2010,6/26/2010,4/5/2011,3/2/2011,3/11/2011,3/23/2011,4/5/2011, 2/8/2012,6/24/2016,8/30/2016, 11/1/2016, 2/23/2017

Renal Side Effects Linked to PPI's

- Acute interstitial nephritis
- Acute kidney injury from pneumonia or *C. diff.* diarrhea
- Chronic interstitial nephritis
- ESRD
- Hyponatremia
- Hypomagnesemia
- Hypokalemia

J Gastroenterol Hepatol 2017;32:1295-1302. *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. *Am J Med 1992;93:472-43,*

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 AKI and had taken a PPI within 120 days before admit, >65 y.o
- All AKI and AIN subgroup
- AKI 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

Clin Nephrol 2007;68:65-72. *Am J Kidney Disease.* 2014;64:558-566.

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 may bind to the tubular basement membrane, stimulating an immune response

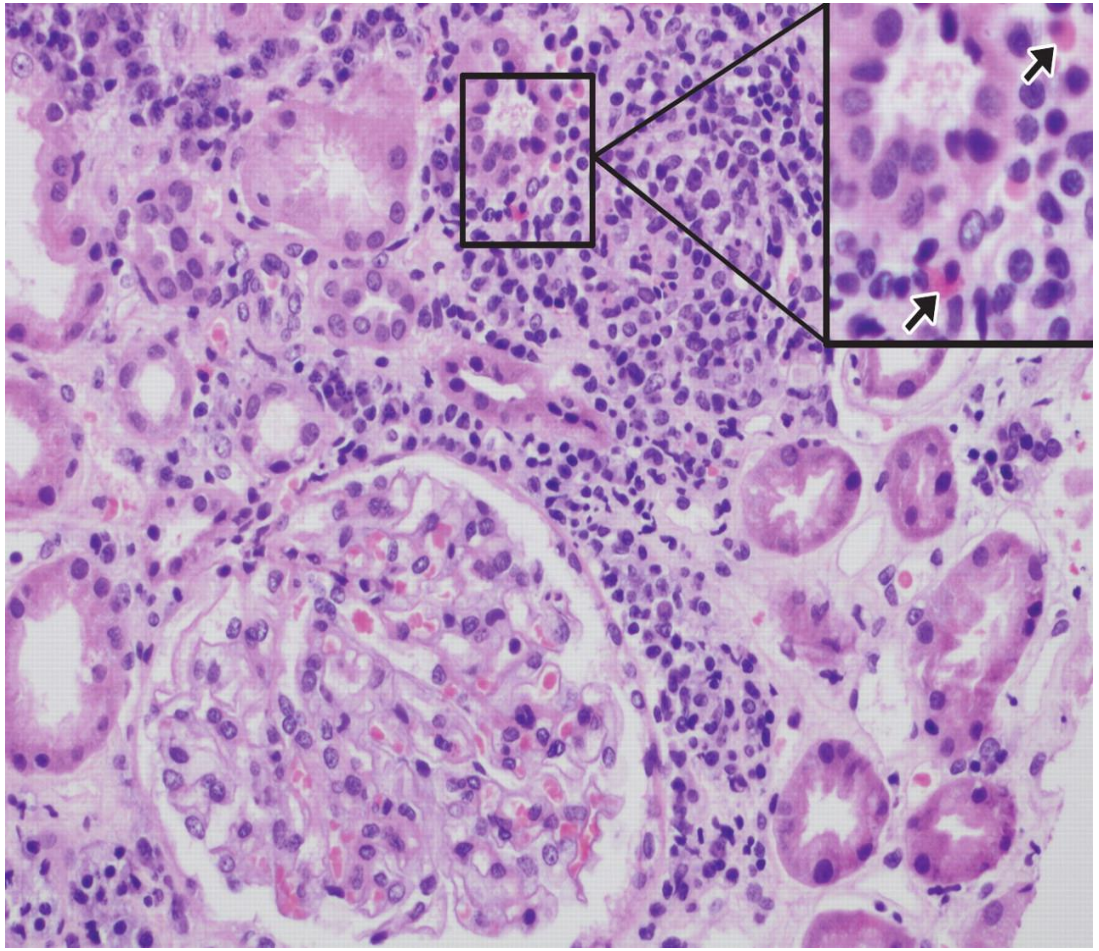
Br J Clin Pharmacol 2007;6:819-823. *Clin Nephrol* 2007;68:65-72.

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 C_3 and/or C_4 may be low
- While the above is suggestive of PPI-AIN the diagnosis can only be made by renal biopsy

Am J Kidney Disease. 2014;64:558-566.

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

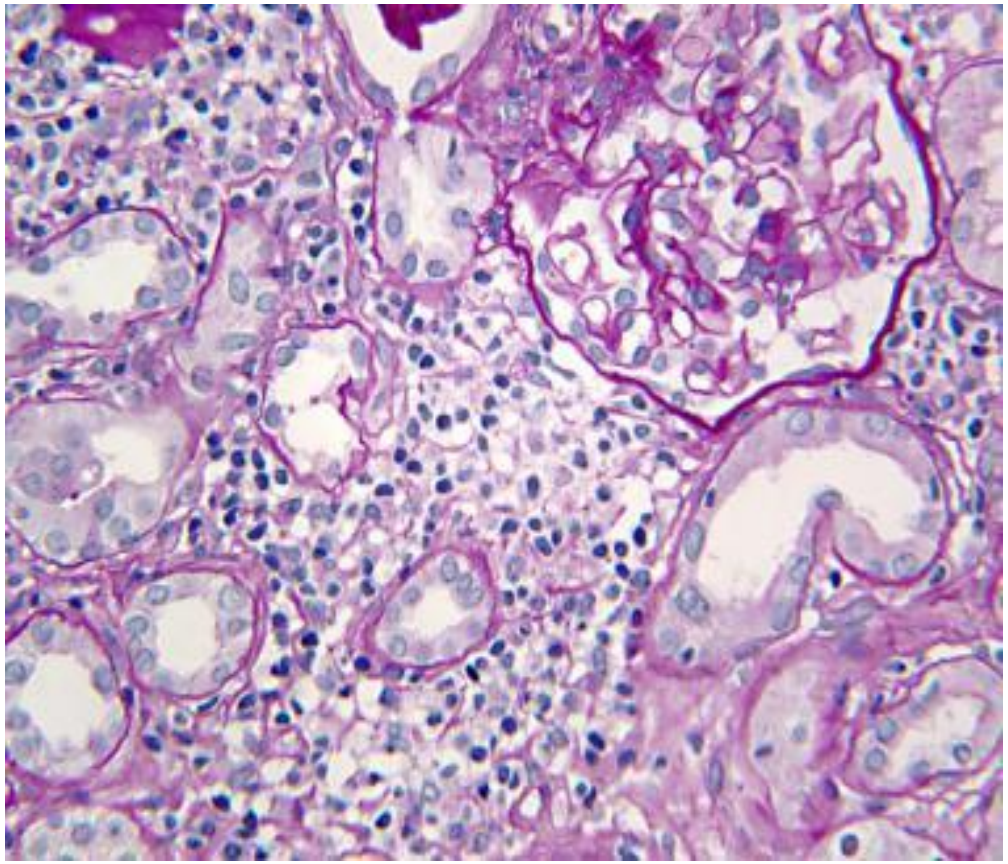
Clinical Course

- 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

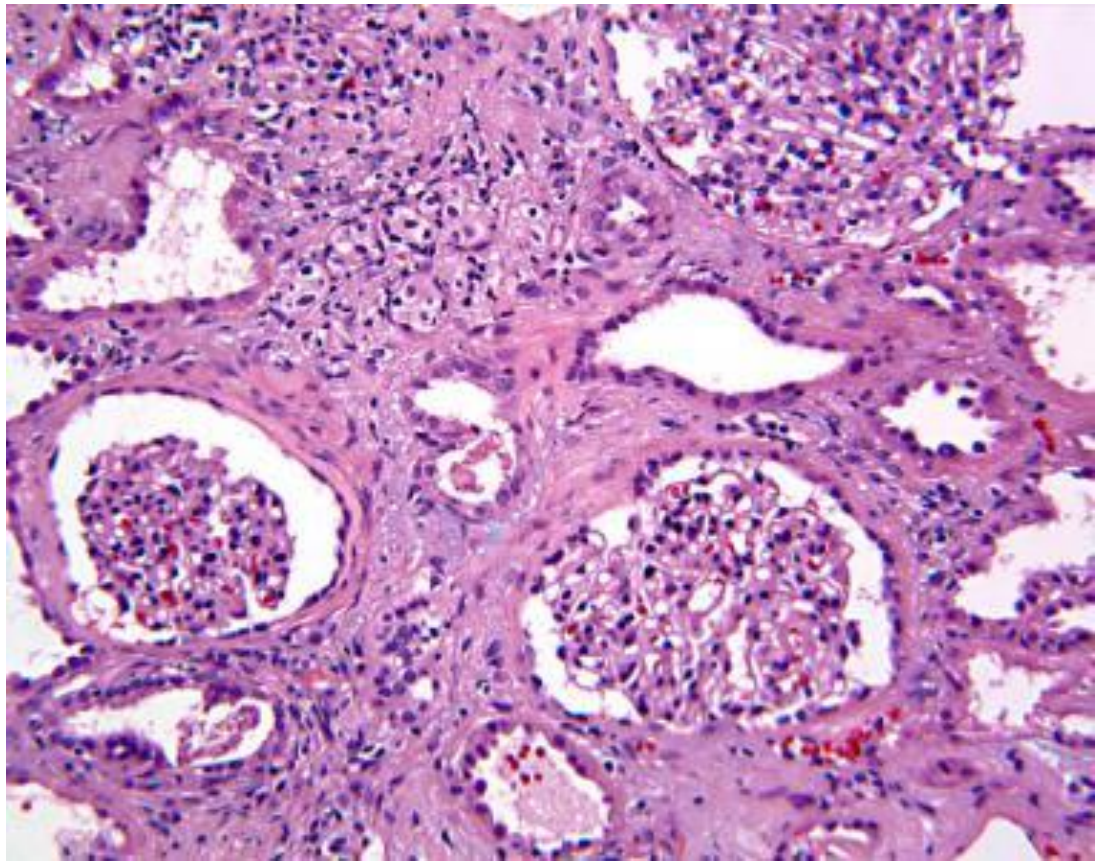
Am J Kidney Disease. 2014;64:558-566.

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/1.73m^2
- Compared baseline values (1996-1999) to December 2011
- H_2 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 mortality 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
- May aggravate other meds associated with hyponatremia (e.g. thiazides) or act alone
- SIADH (Euvolemic hyponatremia)

Ferreira F, Mateus S, Santos AR, Moreira H, Ribeiro Ferreira N. Pantoprazole-related symptomatic hyponatemia. *EJCRIM* 2016;**3**:doi:10.12890/2015_000341Can precipitate SIADH which improved with stopping medication Accessed August 18, 2017

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

Curr Opin Nephrol Hyperten. 2002;4:403-410. *N Engl J Med* 355;1834-1836. *Ann Pharmacother* 2013;47:773-780

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

Intern Med 2011;50:1045-1050.

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
- Compared PPI use vs H_2 Blockers vs neither class of medications and all cause mortality
- Follow up time 5.71 years, mainly older, white male veterans

Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017;7:e015735. doi: 10.1136/bmjopen-2016-015735 accessed August 18, 2017

PPI and All Cause Mortality

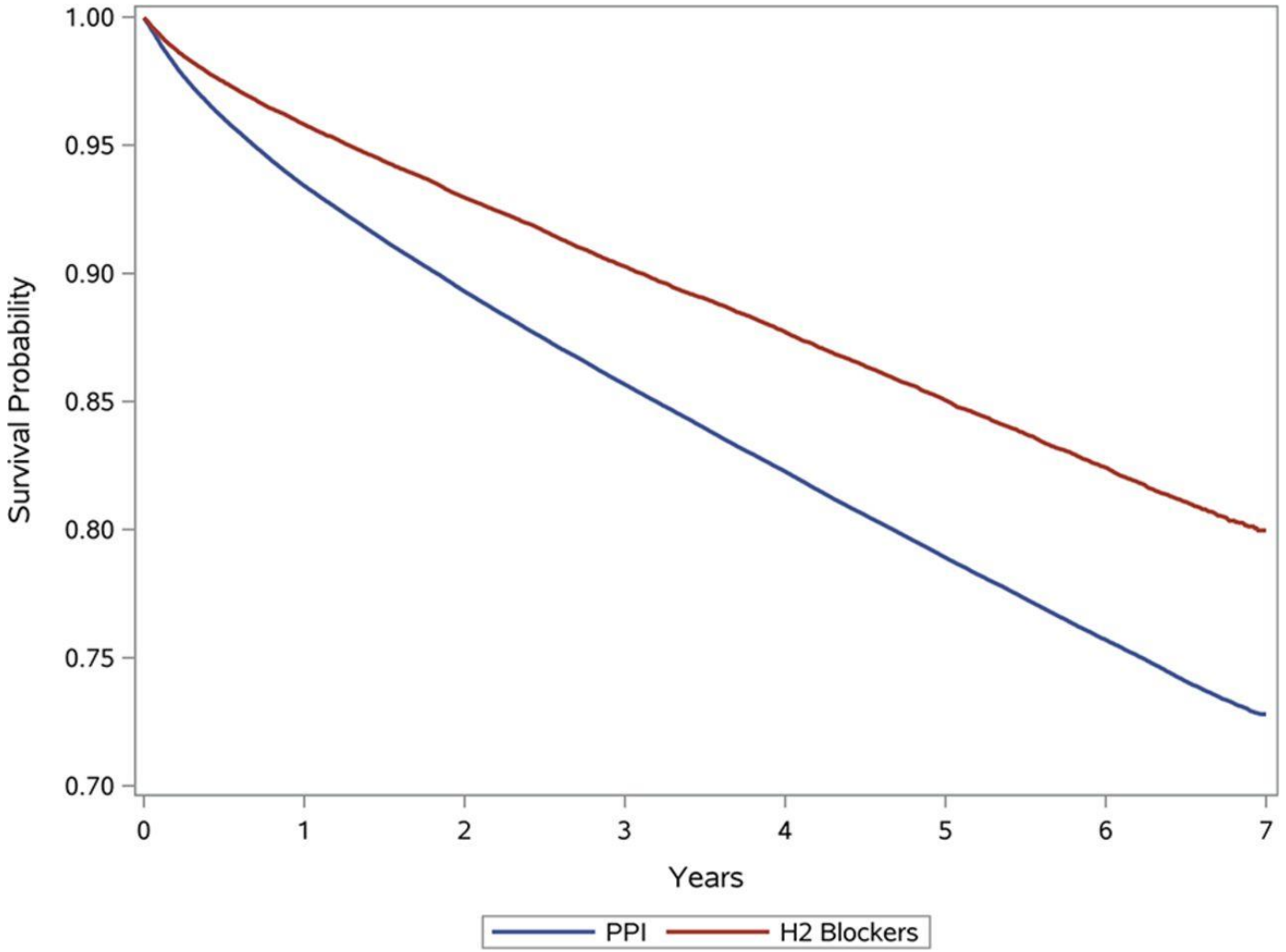
- Overall increased mortality of PPIs vs H_2Blockers HR 1.25
- PPI increased mortality vs no PPI HR 1.15
- PPI increased mortality vs no PPI or H2 Blockers HR 1.23

<u>PPI use compared to a cohort w/o GI Condition</u>

- 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

Xie Y, Bowe B, Li T, et al. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017;7:e015735. doi: 10.1136/bmjopen-2016-015735 accessed August 18, 2017

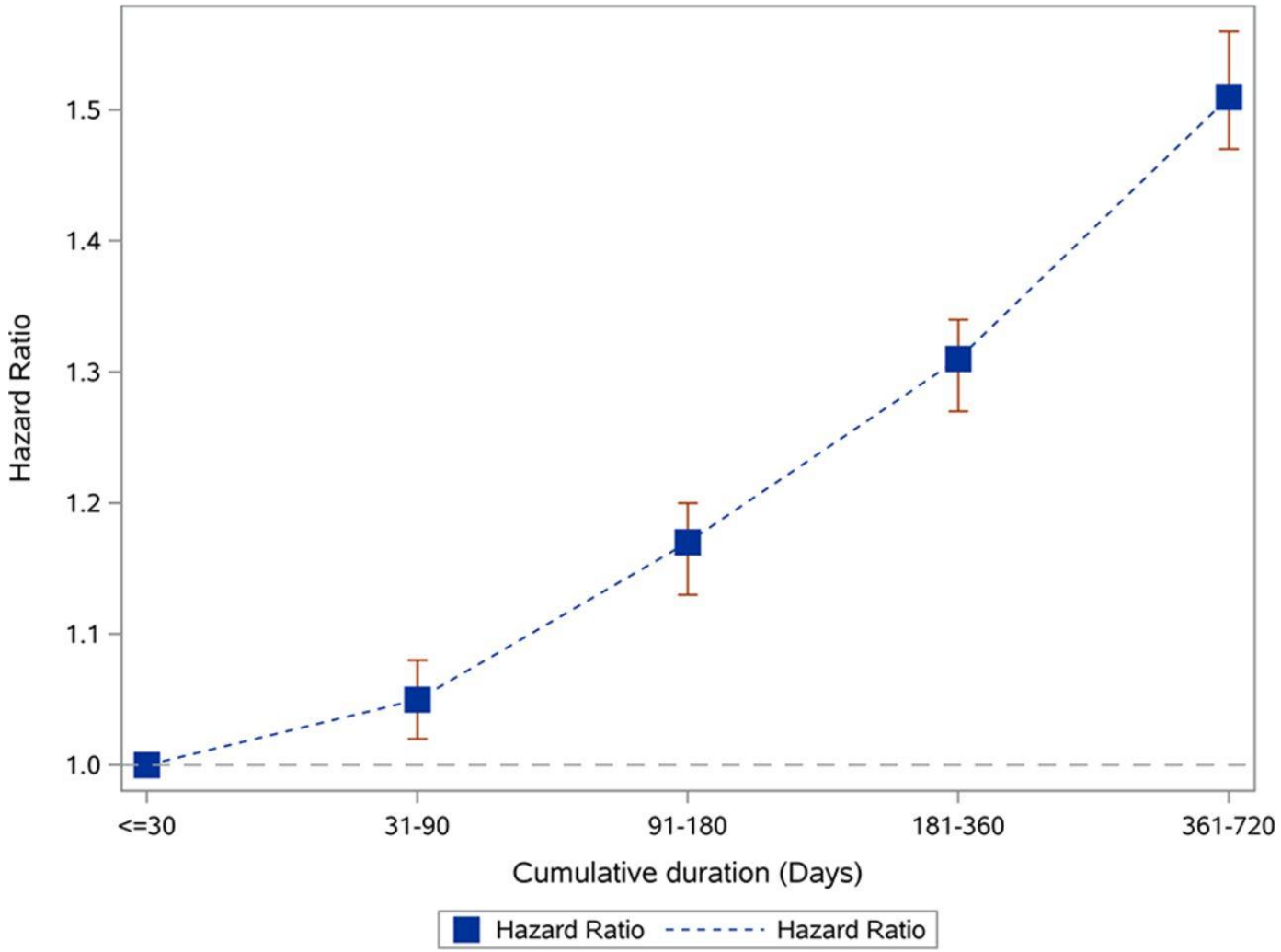
Survival curves for PPI and H2 blockers.



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

BMJ Open

Duration of PPI exposure and risk of death among new PPI users (n=166 098).



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

BMJ Open

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"

Thank You

Questions?

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