

Complications of Proton Pump Inhibitor Therapy

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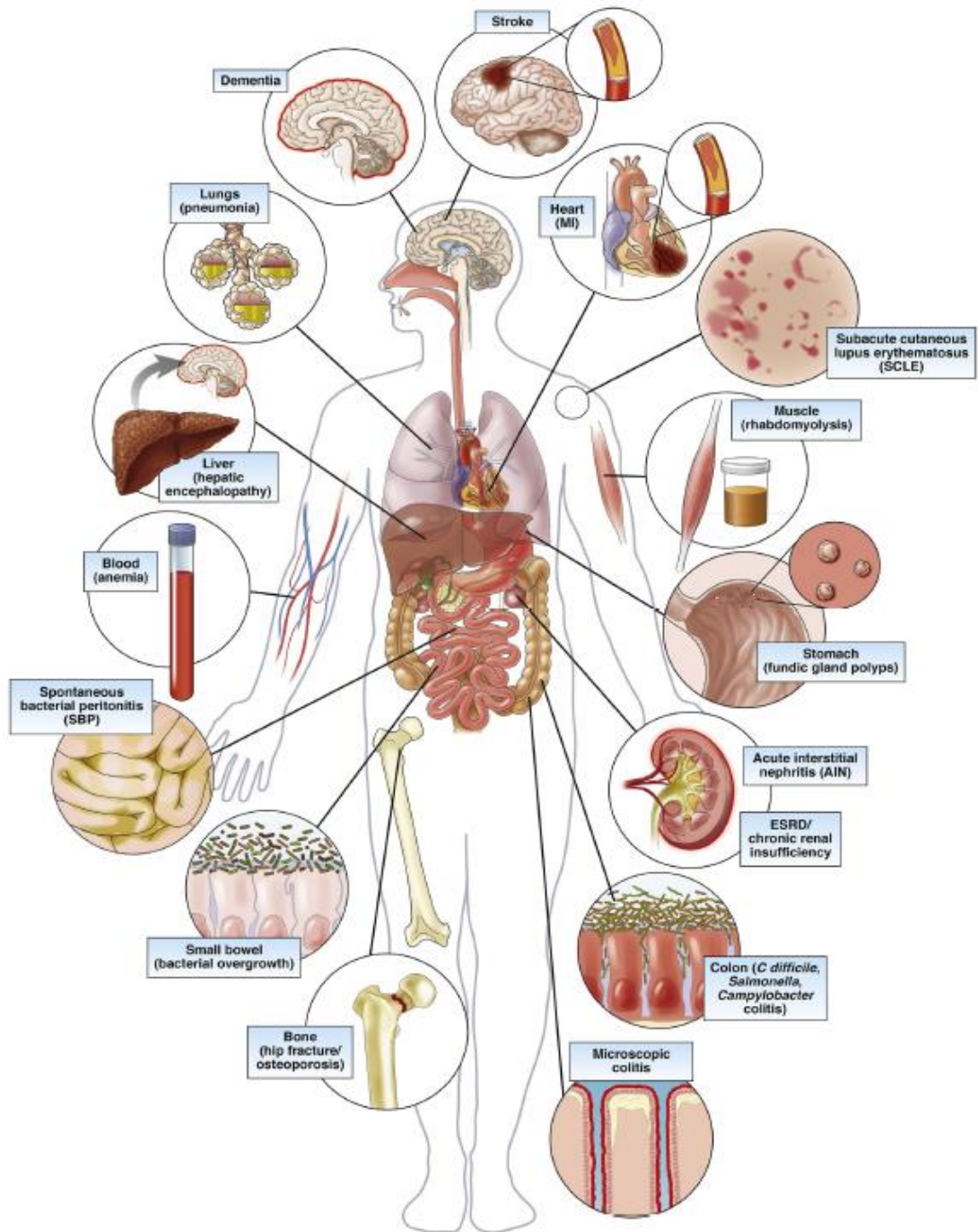
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Background

- Proton pump inhibitors (PPIs) are among the most commonly prescribed medicines for gastroesophageal reflux disease (GERD) and peptic ulcer disease.
- PPIs block acid production by irreversibly inhibiting H⁺/K⁺ adenosine tri-phosphatase in gastric parietal cells.
- As such, PPIs are often treatment of choice for acid-related disorders.

Food and Drug Administration Indication for PPI Use

- Healing of erosive esophagitis
 - Maintenance of healed erosive esophagitis
 - Treatment of GERD
 - Risk reduction for gastric ulcer associated with NSAIDs
 - *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence in combination with antibiotics
 - Hypersecretory conditions including Zollinger-Ellison syndrome
 - Short-term and maintenance treatment of duodenal ulcer
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Background

- **Safety issues associated with proton pump inhibitors (PPIs)** have recently attracted widespread media and lay attention.
- Gastroenterologists are frequently asked about the **appropriateness of PPI therapy** for specific patients
- Furthermore, some patients may have had PPI therapy discontinued abruptly or inappropriately due to safety concerns.

Aim

- **To provide perspective on the likelihood of causality versus association based on available observational studies.**

False Alarms

- The current evidence regarding associations of PPI use with adverse long-term outcomes is predominantly based on observational studies.
- But, such epidemiologic studies often trigger “**False Alarms**”.
- Reported associations may be false due to inappropriate design or confounding due to poorly adjusted study parameters applied to retrospective analyses.

Hill Criteria

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

Strength of Association

- Is the **Association of high magnitude**?
- Assessing the strength of association is critical in causality evaluation.
- Because most adverse outcomes are multifactorial conditions, it is not surprising that the reported relationships between PPI therapy and adverse outcomes are quite modest, particularly on the absolute scale.

Absolute and RRs for Adverse effects associated with long-term PPIs

Potential Adverse Effect	Relative Risk	Reference for Risk Estimate	Reference for Incidence Estimate	Absolute Excess Risk
Chronic kidney disease ^a	10% to 20% increase	Lazarus et al ⁴⁸	Lazarus et al ⁴⁸	0.1% to 0.3% per patient/y
Dementia ^b	4% to 80% increase	Haenisch et al ⁹⁰	Haenisch et al ⁹⁰	.07% to 1.5% per patient/y
Bone fracture ^c	30% to 4-fold increase	Yang et al ²⁷	Yang et al ²⁷	0.1% to 0.5% per patient/y
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al ⁹¹	None available	Unable to calculate
<i>Campylobacter</i> or <i>Salmonella</i> infection	2-fold to 6-fold increase	Bavishi et al ²⁶	Crim et al ⁹²	.03% to 0.2% per patient/y
Spontaneous bacterial peritonitis ^d	50% to 3-fold increase	Xu et al ⁹³	Fernandez et al ⁹⁴	3% to 16% per patient/y
<i>Clostridium difficile</i> infection ^e	No risk to 3-fold increase	Furuya et al ⁹⁵	Lessa et al ⁹⁶	0% to .09% per patient/y
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies ^f	60% to 70% increase	Lam et al ⁹⁷	Bailey et al ⁹⁸	0.3% to 0.4% per patient/y
Gastrointestinal malignancies	No association in RCTs	—	—	—

Strength of Association

- If the magnitude of the association exceeds what one would expect, it may indicate unmeasured confounding or another source of bias.
- For example, the concern related to PPI therapy and clopidogrel interaction is based on the notion that a PPI would reduce the antiplatelet effect of clopidogrel through competition for binding sites at CYP2C19.
- As such, the magnitude of potential harm conferred by the interaction of clopidogrel with PPIs is inherently limited by the magnitude of cardiovascular benefit conferred by clopidogrel.

Strength of Association

- Therefore, studies that reported larger effect estimates for concomitant use of PPIs should actually raise suspicion about the validity of the findings.
- Furthermore, an association that is weak does not preclude a causal relationship and does not necessarily imply a lack of clinical importance

Consistency

- Are the findings are **Reproducible**?
- Some of the proposed associations with PPI use have not been consistently demonstrated.

Consistency – PPI with hip fracture

- Among the reported adverse events associated with long-term PPI use, the possible increased risk of fracture has attracted widespread attention.
- A meta analysis of 10 studies reported a pooled OR for hip fracture associated with PPI use 1.25 (95% confidence interval 1.14-1.37)
- Six studies had demonstrated a positive association with hip fracture (all with ORs >2), and the remaining 4 had shown no significant association, 2 of which actually demonstrated lower fracture incidence among PPI users than controls.
- Three of the 4 cohort studies had not shown a significant association, whereas 5 of 6 case-control studies had; all of the case control studies had quantitatively small ORs between 1.20 and 1.62.
- In general, higher-quality studies have produced lower estimates of risk than lower-quality studies.

Consistency – PPI with CAP

- Similarly, for community-acquired pneumonia, the association was initially suggested by a retrospective study conducted among patients with GERD.
- However, this was not subsequently confirmed in a study examining PPI use and CAP among patients using NSAIDs.
- Subsequent studies have shown no association between PPI use and CAP.

Consistency

- Consistency among studies carries more weight if the studies used different designs and patients groups, and still arrived at the same conclusion.
- Conversely, if all the studies had used the same methodology, they could just have consistently replicated the same inherent bias.

Specificity

- Is the **Outcome predicted based only on the exposure to PPIs?**
- The specificity criterion has limited utility because so many conditions are of multifactorial etiology.

Specificity

- For example, there are many possible etiological or predisposing factors for both hip fracture and CAP
- It is likely that the association between PPI use and hip fracture risk may simply have been a result of confounding, and its significance has been overinterpreted.
- Some of the adverse events attributed to PPIs are idiopathic in nature, and, therefore, nonspecific.

Temporality

- Does the **use of PPIs precede the observed outcome?**
- Most published reports on PPI safety issues are case control studies.
- Cohort studies and RCTs have been reported much less often.
- Only incident outcome events are considered in these study designs.

Temporality

- In addition, for most potential adverse effects, there is a long induction period between the PPI exposure and outcome.
- Therefore, the mechanically relevant exposure has generally been intermediate- to long-term PPI therapy.

Epidemiological terminologies used

Terminology	Definition	Example
Protopathic bias (also called reverse causality)	This bias occurs when the drug is initiated in response to the first symptoms of the disease that is, at this point, undiagnosed.	PPIs initiated for epigastric pain resulting from a yet to be diagnosed gastric cancer give the false appearance that they cause gastric cancer.
Residual confounding	This bias occurs when there is persistence of a portion of the confounding effect of a measured confounder.	Despite collecting data on and adjusting for comorbidity status, which is a plausible confounder for most PPI-related adverse effects, measurement error in comorbid condition status or inability to capture disease severity could result in confounded PPI-adverse effect association.

Biological gradient

- Is there a direct relationship between **Dose or Duration** of PPI use and outcome?
- A gradient effect refers to the presence of a monotonic dose- or duration- response relationship between the exposure and outcome.

Biological gradient

- The presence of such an effect has not been consistently demonstrated for many of the PPI safety issues.
- A meta-analysis on PPI use and bone fracture found neither a dose-response nor a duration-response effect for PPI use and fracture risk, although substantial heterogeneity among studies made it difficult to interpret the pooled effect estimates.

Biological gradient

- First, most of the data sources are not life-time databases and cannot capture PPI use before a patient was included in the database.
- Second, some causal associations may be characterized by a threshold effect rather than a monotonic trend.
- Third, a monotonic trend with increasing levels of exposure is not necessarily casual.

Plausibility and Experiment

- Is there **a Rational and Theoretical basis** for the proposed association?
- Are the **data based on experiments**?

Plausibility and Experiment

- A biologically plausible explanation for any proposed association provides a rational and theoretical basis for the link between the proposed exposure and the observed outcome.
- The overarching biological explanations proposed for the adverse outcomes linked to chronic PPI therapy have generally been based on gastric acid suppression or idiosyncratic effects of these agents.

Proposed mechanism of chronic complications of PPI therapy

Kidney	Recurrent AIN
Brain	a) Decreased gastric acidity leading to vitamin B ₁₂ deficiency b) Beta-amyloid deposition
Bone	a) Decreased gastric acidity leading to reduced calcium and vitamin B ₁₂ absorption b) Hypergastrinemia leading to hyperparathyroidism
Heart	a) Inhibiting clopidogrel activation (Cytochrome P2C19) b) Increased asymmetric dimethylarginine leading to reduced endothelial nitrous oxide resulting in thrombosis
Colon	a) Decreased gastric acidity altering intestinal normal flora b) Trophic effect of hypergastrinemia on colonocytes
Lungs	a) Decreased gastric acidity and overgrowth of gastric bacteria b) Antineutrophilic effect of PPIs
Muscle	CYP3A4 enzyme inhibition
Blood	Decreased gastric acidity leading to iron and vitamin B ₁₂ deficiencies
Liver	a) Altered gut microbiota due to gastric acid suppression b) Vitamin B ₁₂ deficiency due to reduced gastric acid
Stomach	Acid suppression induced parietal cell hyperplasia

Coherence

- Any **Conflicts with what is known about the natural history and biology of the disease?**
- Coherence between epidemiological and laboratory findings has been difficult to demonstrate.

Coherence

- Indeed, it may still be widely perceived that PPIs "cause" osteoporosis
- But, the evidence does not support this.
- Recent studies have shown no significant difference between BMD values in women taking and not taking a PPI long term.

Analogy

- For the association between PPI use and bacterial enteric infection, the experience with H2RAs may serve as an analogy.
- A meta analysis had shown a weak association between H2RA use and bacterial enteric infection (OR 2.03;95% CI, 1.05-3.92) and a stronger association with PPI use (OR, 3.33;95% CI, 1.84-6.02).
- Intuitively, this makes biological sense and could be considered as indirect evidence of a dose-response relationship between gastric acid suppression and risk of bacterial enteric infection.

Residual Confounding

- Although not one of the Hill criteria, confounding is arguably the most important extraneous factor that could best explain many of the putative associations between PPI therapy and adverse outcomes.
- Specifically, the central question is whether the observed positive associations are due to the effects of a PPI or the reasons why it was prescribed.

Residual Confounding

- The real concern is that PPI users generally have worse overall health status than nonusers.
- This imbalance has been demonstrated in the study population of virtually all published studies addressing PPI safety concerns.
- Furthermore, because patients with worse health status are also more likely to develop adverse clinical outcomes, health status could confound the association between PPI therapy and adverse outcomes.

Residual Confounding

- Except for the descriptive case reports and case series of rare, idiosyncratic reactions virtually all published studies on PPI safety issues used some measures to account for this confounding effect.
- Although randomization is the most effective way to address this issue, post-marketing RCTs are rarely feasible due to cost and ethical reasons.

Residual Confounding

- **Matching and statistical adjustment** were strategies used to control for this effect in most nonrandomized studies.
- This approach often fails to take the severity of the comorbidities into consideration, which may lead to residual confounding.
- For example, dementia is an important determinant of overall health status and is also a risk factor for falls and fractures; it is thus a potential confounder for the association between PPI therapy and hip fracture.

Conclusions

- Virtually the entire evidence base regarding PPI-related safety concerns consists of observational studies.
- We need to have a clear understanding of the meaning of a "statistically significant" but modest association from such studies.
- Statistical significance only takes random errors related to sample size into consideration ; it ignores systematic errors.

Conclusions

- Observational studies, no matter how well performed, may be inherently incapable of accurately discerning weak associations from null effect due to their susceptibility to systematic errors of bias/confounding and other methodological weakness.
- Therefore, we advise a pragmatic, “common-sense” approach to this issue.

Conclusions

- Patients with a clear indication for PPI treatment should continue to receive it in the lowest effective dose.
- Multiple “false alarms” related to the safety of PPIs could ultimately lead to inappropriate discontinuation of treatment with potentially serious consequences for some patients.

Conclusions

- The media should take a more balanced, critical, and responsible approach in their reporting of epidemiological data so that weak and inconclusive results are not overinterpreted and presented to the lay public as facts.
- Researchers engaged in investigations on PPI safety issues should devote more effort toward RCTs whenever possible as well as studies that will advance our understanding of the physiological effects of PPI therapy on mechanistically relevant biomarkers.

Conclusions

- The investigators also should use appropriate methodological tools to mitigate the effect of confounding and quantify how robust the observed associations are to potential unmeasured or uncontrolled confounding.
- Most importantly, they need to understand the limitations of the observational studies and be more skeptical about their own findings from such studies.

Conclusions

- Much of the current evidence linking PPI use to serious long-term adverse consequences is weak and insubstantial.
- It should not deter prescribers from **using appropriate doses of PPIs for appropriate indications.**