Side Effects of Long-Term Proton Pump Inhibitor Use: A Review

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Running title: Side effects of proton pump inhibitors

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Abstract: Proton pump inhibitors (PPIs) are widely used, and concerns about overuse have been raised. Therefore, side effects are important to be aware of and several suggested side effects of long-term use have been studied. In this MiniReview, we sum up the evidence of side effects related to long-term PPI treatment. Suspected side effects are mainly related to increased susceptibility to infections, secondary hypergastrinaemia, impeded absorption of micronutrients or idiosyncratic reactions. Most of the potential side effects have only been evaluated in observational studies demonstrating conflicting and weak associations with a substantial risk of confounding. However, a high probability of causality seems to be established for the side effects increased risk of gastrointestinal infections and rebound acid hypersecretion following discontinuation of treatment due to secondary hypergastrinaemia. The risk of side effects should not be a reason to withhold PPIs from patients with a true indication, and worry about poorly proven side effects should not lead to unnecessary discontinuation. The most important safety issue regarding PPI therapy is to critically evaluate the indication when initiating treatment and reconsidering the indication in long-term-treated patients.

Gastric acid-related disorders such as gastroesophageal reflux disease and peptic ulcer are common reasons for patients to obtain medical treatment. Antacids have a quick but not sustainable effect on acid-related symptoms. Histamine-2-receptor antagonists (H2RAs) inhibit gastric acid secretion but their effects may diminish over time (and they do not block the stimulatory effects of other hormones on acid secretion). In order to inhibit gastric acid secretion more powerfully, the proton pump inhibitors (PPIs) were developed. Five PPIs are marketed (Table 1) and all share a common pharmacophore. Due to different pKa values, the reactivity of the PPI subtypes differ and equipotent dosages are different from one PPI subtype to another (Table 1) [1].

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Proton pump inhibitors are highly effective, and during the past decades the PPIs have overtaken the role as the drug of choice in the treatment of gastric acid-related disorders. This is reflected in drug utilization studies demonstrating increasing purchase of PPIs [2]. Incident and prevalent PPI use is growing and more than 10% of the Danish population redeem a prescription for a PPI annually [3, 4]. Concerns have been raised that PPIs are over-prescribed and often used on questionable grounds [5]. One of the reasons for continuous increasing use of PPIs could be initial empirical prescribing. However, response to PPI cannot be used as a diagnostic test to evaluate whether or not upper gastrointestinal symptoms are acid-related [6, 7]. Nevertheless, if a patient experiences positive response, it may cause continuation of therapy and initiate long-term treatment with PPIs despite the positive response might be due to a placebo response or the fluctuating nature of dyspepsia and not because of inhibited acid secretion.

PPIs are generally considered to be well tolerated with few (and minor) side effects, especially related to short-term use. Patients have reported unspecific symptoms during short-term PPI therapy, such as headache, rash and dizziness and gastrointestinal symptoms such as nausea, abdominal pain, flatulence and constipation or diarrhoea [8, 9]. There is no concern of serious side effects with short-term use (two weeks) of PPIs at approved dosing [10]. However, awareness of potential adverse effects related to PPI therapy is increasingly emerging, particularly with longer-term use. Therefore, we conducted this MiniReview to sum up the evidence of side effects related to long-term PPI treatment with the intention of providing an evidence-based basis for clinicians to guide and inform patients about possible side effects to PPIs.
Materials and methods

We searched the databases PubMed and EMBASE in October 2017 for relevant articles. We used the keywords: proton pump inhibitor, proton pump inhibitors, side effects, adverse effects and complications. Each title was evaluated by the two first authors to determine relevance. If there was any doubt about the relevance of the article based on the title, the abstract was inspected. Any discrepancies in evaluation were solved through consensus. From the articles found in the primary search, we extracted possible side effects related to PPI therapy. Afterwards, we conducted a search for each specific side effect found in the primary search (e.g. proton pump inhibitor AND pneumonia). We also supplemented our search by hand-searching relevant journals and identifying articles from the reference lists of eligible studies.

Only papers written in English or Scandinavian language were included. Each unique abstract was inspected by the first and the second author to determine relevance. Any doubts regarding eligibility of a study were resolved through consensus among the authors. Data extraction was performed by the first and the second author and reviewed by the entire group. Any disagreements were resolved through consensus among the authors. We described risk measures as reported in eligible studies (odds ratios, hazard ratios, relative risk; absolute risk, number needed to harm [NNH] were described, if available).

Results

The initial search resulted in 6490 papers. After determining relevance of the papers based on the title (and in case of doubt, the abstract or the entire article) 67 unique papers (case reports, clinical studies and reviews) reporting possible side effects related to PPI therapy were identified (Fig. 1). From the 67 papers, a total of 15 different side effects were identified. Suspected side effects were related to the following: Increased susceptibility to infections due to PPI-induced hypochlorhydria and altered intestinal
microbiome, side effects related to secondary hypergastrinaemia, impeded absorption of micronutrients or idiosyncratic reactions causing kidney disease or dementia.

**Side effects associated with long-term use of PPIs**

Concerns about possible side effects related to long-term use of PPIs have been raised in terms of infections, impaired absorption of nutrients, dementia, kidney disease and hypergastrinaemia-related side effects. Below, we briefly summarize the evidence for each side effect.

**Infections**

The PPI-induced hypochlorhydria has been hypothesized to impair one of the natural defence mechanisms against ingested bacteria, leading to bacterial colonization, altered intestinal flora and increased susceptibility to enteric infections. The possible association between PPIs and bacterial enteric infections has been demonstrated with consistence among various studies [11, 12].

*Clostridium difficile infection*

The seriousness of *Clostridium difficile* infection varies. Age and recent exposure to antibiotics are well-known risk factors. However, use of PPIs has also been linked to an increased risk of both incident and recurrent *Clostridium difficile* diarrhoea in observational studies. Compared to non-users of PPI, the users of PPI had an odds ratio (OR) of 1.74 (95% CI 1.47-2.85) for incident *Clostridium difficile* infection and an OR of 2.51 (95% CI 1.6-5.44) for recurrent *Clostridium difficile* infection [13, 14].

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Other enteric infections

The relative risk (RR) of infectious gastroenteritis has been assessed to be 3.33 (95% CI 1.84-6.02) [11]. For non-typhoid *Salmonella*, a RR of 4.2 (95% CI 2.2-7.9) has been demonstrated [11]. For *Campylobacter* infection, the RR has been assessed ranging from 3.5 (95% CI 1.1-12.0) to 11.7 (95% CI 2.5-54.0) [12]. The latter becomes of special clinical interest with the increasing incidence of *Campylobacter* infections [15].

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is associated with increased morbidity and mortality and is a feared complication in cirrhotic patients with ascites. Translocation of bacteria from the gut to ascites is thought to play a key role and two meta-analyses based on numerous patients have demonstrated a two- to threefold increase in odds of SBP among patients treated with PPIs [16, 17]. However, the results are inconsistent, as other studies have shown that there is no increased risk of SBP among PPI users [18, 19]. Whether PPI therapy in cirrhotic patients constitutes a real increased risk of SBP or not remains controversial.

Liver diseases

It has recently been demonstrated that PPI-induced hypochlorhydria can cause intestinal bacterial overgrowth of *Enterococci*, which may exacerbate alcoholic liver disease [20]. The hypothesis that PPIs cause small intestinal bacterial overgrowth has furthermore led to an explanation of the increased risk of hepatic encephalopathy in patients with cirrhosis using PPIs [21, 22]. However, few studies about PPIs and liver diseases have been conducted and it appears still too premature to draw conclusions about causality.

Community-acquired pneumonia

It has been hypothesized that micro-aspiration of gastric contents containing more bacteria due to PPI-induced hypochlorhydria may lead to lung colonization and subsequent pneumonia. Both case-control studies [23], cohort studies [24] as well as meta-analyses [25] have demonstrated an association between
use of PPI and community-acquired pneumonia. However, the results are inconsistent because other studies have not been able to establish an association [26, 27].

Overall, studies about the association between PPI use and community-acquired pneumonia are conflicting. Important life style factors such as smoking status have not been taken into account and the positive association demonstrated in some studies might be due to unmeasured confounding lifestyle factors.

**Impaired absorption related to PPI-induced hypochlorhydria**

*Bone fractures*

Gastric acid dissolves and ionizes poorly soluble calcium salts enabling absorption of calcium ions. Therefore, it has been theorized that hypochlorhydria reduces calcium absorption and may lead to accelerated bone mineral loss, subsequent osteoporosis and increased bone fracture risk. Additionally, it has been argued that hypergastrinaemia may induce secondary hyperparathyroidism [28] that could lead to subsequent bone mineral loss. Observational studies and meta-analyses of observational studies have demonstrated an association between PPI use and bone fractures [29-32]; however, the associations found are weak and conflicting as other studies have found that neither changes in bone mineral density, bone structure nor manifest osteoporosis have been proven related to PPI use [33, 34].

*Vitamin B12 deficiency*

Vitamin B12 requires the presence of gastric acid and activated pepsin in order to be released from its protein bond and subsequently bind with the intrinsic factor necessary for it to be absorbed in the terminal ileum. Therefore, it has been hypothesized that PPI-induced hypochlorhydria may cause reduced

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absorption of vitamin B12. It has been demonstrated that use of PPIs for more than two years is significantly associated with an increased risk of incident vitamin B12 deficiency, OR 1.65 (95% CI 1.58-1.73) [35]. However, there are also studies with conflicting findings of no association between PPI therapy and vitamin B12 deficiency [36] and the biological plausibility and clinical consequences of slightly impeded absorption with standard use of PPIs has been questioned [37]. Therefore, there is no evidence for (or against) routine testing for vitamin B12 in patients taking long-term PPIs.

**Hypomagnesaemia**

Hypomagnesaemia from PPIs is thought to be caused by decreased gastrointestinal absorption of magnesium [38]. A 2015 review article examined the body of evidence behind PPI use and hypomagnesaemia and concluded that any associated risk was particularly increased in patients on diuretics [39]. For example, a 2014 case-control study (n=1,830) found that PPI use was associated with hypomagnesaemia in patients on diuretics (OR 1.73, 95% CI 1.11 to 2.70) but not in those who were not taking diuretics (OR 1.25, 95% CI 0.81 to 1.91) [40]. Two systematic reviews and meta-analyses have reported an increased risk of hypomagnesaemia associated with PPI use [41, 42]. However, there was high statistical and clinical heterogeneity in pooled studies (for example, differences in exposure definition, definition of hypomagnesaemia and patient population). A 2017 open-label prospective study (n=250) reported no increased risk of hypomagnesaemia associated with PPI use though this study was not randomized and the authors did not adjust for confounders [43].

Overall, available evidence points to a possible increased risk of hypomagnesemia with PPI use, which may be most pronounced in diuretic users. However, meta-analysis findings are limited by heterogeneity across studies.
**Iron deficiency**

Most iron is ingested as non-haem iron in the reduced ferric form, Fe$^{3+}$. To be absorbed in the duodenum, ferric iron has to be oxidized to the ferrous form, Fe$^{2+}$. The solution of ferric iron and oxidation to ferrous iron is facilitated by gastric acid (and vitamin C actively secreted in gastric juice). Therefore, a possible negative effect of PPIs on iron absorption has been proposed and an association between PPI therapy and anaemia has been found [44, 45]. However, the results are conflicting, as other studies have failed to show an association [46]. None of the studies have demonstrated an increased risk of symptomatic anaemia requiring treatment. Thus, impeded iron absorption and anaemia is not considered a clinically relevant side effect to PPI therapy.

**Side effects related to PPI-induced hypergastrinaemia**

**Gastric hyperplasia/metaplasia**

Several studies have demonstrated that inhibition of the gastric proton pump causes compensatory raising secretion of stimulatory gastrin [47, 48]. Gastrin is known to have a proliferative effect on cell growth, and hypergastrinaemia has been shown to have a trophic effect on enterochromaffin-like (ECL) cells and a concern about increased risk of gastric cancer was raised. Some studies have despite ECL hyperplasia not found increased risks of neuroendocrine tumours or adenocarcinomas in humans [48, 49]. However, recent studies reintroduce the worry and a possible increased risk cannot yet be ruled out [50, 51].

**Rebound acid hypersecretion**

When a PPI is stopped abruptly, gastric acid production appears to rise above pre-PPI treatment levels. This has been termed “rebound acid hypersecretion” (RAHS), and the biological mechanism and pathophysiology of this phenomenon has been established [52]. Lodrup et al. systematically reviewed the
clinical relevance of RAHS [53]. They identified two RCTs in healthy asymptomatic volunteers, and three RCTs in participants with healed upper GI symptoms or oesophagitis. The authors report that withdrawal of PPIs appeared to cause rebound upper GI symptoms in healthy symptomatic volunteers (44% of patients in the PPI arm experienced acid-related symptoms after withdrawal compared to 15% who had been receiving placebo; absolute difference 29%). However, the results in patients treated with PPIs for upper GI disorders were inconsistent and it was unclear if symptoms were caused by RAHS when PPIs were withdrawn or by underlying GI disease.

Other suggested side effects related to long-term use of PPIs

Kidney disease and acute kidney injury

PPIs have been reported to have adverse effects on the kidneys. The mechanism is not clearly established but has been hypothesized to be related to acute interstitial nephritis (AIN) [54]. Development of AIN could then lead to acute kidney injury (AKI) and/or chronic kidney disease (CKD) [55].

The clinical evidence in this area is summarized by three systematic review and meta-analyses published in 2017 [54-56]. These meta-analyses found that PPI use was associated with an increased risk of CKD (NNH = 20, 95% CI 10 to 105), end-stage renal disease (NNH not available), AKI (NNH=27, 95% CI 13 to 147) and AIN (NNH not available). However, the authors reported substantial statistical heterogeneity and differences in how diseases were classified across studies. Sub-group analysis for AKI found that risk of AKI may have been higher in studies where baseline PPI users were excluded [54]. One systematic review conducted formal quality assessment and noted several limitations in the studies of PPIs and kidney events to date [55]. Specifically, selection bias, misclassification bias and residual confounding was a concern in many of the studies.

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Overall, meta-analyses suggest that PPI use may be associated with an increased risk of adverse kidney events. However, the meta-analysis conducted by Nochaiwong et al., which included quality assessment, found the quality of evidence to be low or insufficient.

Dementia

Amyloid-beta (Aβ) protein appears to accumulate in the brains of patients with Alzheimer’s disease (AD). This protein is broken down in acidic lysosomes which are acidified by proton pumps. The lysosomes of patients taking PPIs may be less acidic and thus less able to degrade Aβ protein, potentially leading to accumulation [57].

Clinical evidence on the association between PPI use and dementia is available. A 2017 systematic review located four non-randomized studies specifically examining PPI use and dementia. Three of these studies reported an increased risk of developing dementia in patients who were PPI users [58-60], while one case-control study reported a reduced risk[61]. There were important methodological concerns in all studies, particularly related to residual confounding and detection bias.

Two additional non-randomized studies have been published since the systematic review described above. An observational longitudinal study (n=10,486) found that continuous and intermittent PPI use reduced risk of developing AD and converting from MCI to AD [62]. However, this study was at risk of misclassification bias due to self-reporting of PPI use and missing data. A retrospective cohort study of 15,726 patients in Taiwan found that PPI use increased risk of developing dementia compared to non-use [63]. These authors also reported that the risk of developing dementia increased with higher doses of PPIs. Residual confounding was an important concern with this study as several important confounders were not adjusted for.
Overall, data surrounding the association between PPI use and risk of dementia are conflicting. Studies have involved heterogeneous populations and have important methodological limitations. Thus, the available evidence does not convincingly demonstrate that PPI users are at increased risk of developing dementia.

Discussion

During the past decades, use of PPIs has been increasing and concerns of various possible side effects have been raised. Suspected side effects are related to increased susceptibility to infections due to PPI-induced hypochlorhydria and altered intestinal microbiome, side effects related to secondary hypergastrinaemia, impeded absorption of micronutrients or idiosyncratic reactions causing kidney disease or dementia.

For most of the suggested side effects the concern has been raised based on associations between the suspected side effect and long-term use of PPIs demonstrated in observational studies. Observational studies of side effects related to drug use have the advantage that they are based on “real world” observations. This means that the effects (and side effects) of a drug can be studied in the population that actually is the target of the drug and not in a selected group of test subjects. Furthermore, uncommon side effects and side effects related to long-term use of a drug are seldom measureable in premarketing safety studies of drugs due to the limited number of test subjects and often narrow observation time. Furthermore, studying suspected side effects in a randomized, controlled design can be ethically impossible if the suspected side effect is serious. However, there are also several disadvantages related to observational studies. One of the major challenges when studying side effects in observational studies is that they cannot prove causality between drug use and suspected side effect, merely association. No simple checklist is available to assess causation but applying the Hill criteria as a guidepost rather than a checklist could be one way of making reasonable judgement about whether the relationship between drug
and outcome shows causal traits [64]. When applying the Hill criteria to the observational studies included in this MiniReview (Table 2), it shows that the side effects related to hypergastrinaemia seem to have a higher probability of causality than the other side effects found to be associated with long-term use of PPIs. This is further supported by the fact that the only side effect demonstrated in randomized, controlled blinded studies is hypergastrinaemia and occurrence of acid-related symptoms in previously asymptomatic subjects when the PPI is withdrawn [53, 65].

One of the explanations for lack of causality for suggested side effects found associated with long-term use of PPIs is residual confounding. The concern is that PPI users may not be comparable to non-PPI users in terms of lifestyle and overall health status. It has been demonstrated that the prevalence of smoking is significantly higher among PPI users than non-users [66]. This means that, for example, the increased risk of pneumonia found in PPI users could just as well be explained by the smoking status as the PPI use and smoking confounds the association between PPI therapy and pneumonia. Several of the studies included in this MiniReview address the issue by matching and statistical adjustments; however, complete information about all possible confounding factors is missing which may lead to residual confounding despite the effort to account for confounding effects. Another analytical issue to keep in mind when assessing the studies in this MiniReview, is the fact that the studies use statistical significance testing to judge whether the outcome and the exposure are associated. It is important to remember that statistical significance testing should not be over-emphasized, given that the systematic error often can be greater than the random error in large-scale observational studies comprising vast number of subjects. [67] Confounding by indication may also be a concern with some of associations discussed. Finally, most of the studies we identified reported relative measures of association (e.g. OR, HR, RR) versus absolute measures. Absolute measures allow for a more clinically meaningful interpretation of results. We included absolute measures wherever possible; however, these were available in few studies. Given that many of the adverse effects we describe are quite rare, the absolute risk of adverse effects is likely low.

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In the light of the current evidence some of the proposed side effects related to long-term PPI therapy have been disproven. For others, the evidence is insufficient to regard PPI therapy as a threat, primarily due to observational studies of the associations where unmeasured or residual confounding may the cause of association rather than causality. For now, there is no evidence for long-term PPI users to routinely raise their intake of magnesium, iron or calcium beyond the Recommended Dietary Allowance, and long-term PPI users should not be regularly screened for serum levels of micronutrients, creatinine or bone mineral density solely due to their use of PPI.

One of the most important side effects where the causality is established is RAHS and therefore one of the important factors to take into account as a clinician when initiating PPI therapy is to carefully evaluate the indication and duration of treatment. Initiating PPI treatment for more than a few weeks in patients with ambiguous symptoms that are not truly acid-related entails the risk of causing truly acid-related symptoms when the discontinuing treatment, necessitating continuous PPI treatment. However, while RAHS appears to occur physiologically, the clinical significance in patients treated with long-term PPIs is not well-established based on the current evidence. The authors point out that it is difficult to evaluate whether return of symptoms is due to RAHS or underlying disease in patients treated with PPI on a long-term basis. Nevertheless, when reducing PPI therapy, evidence-based guidance suggests tapering or using on-demand as this appears to lead to a greater success rate and a lower risk of symptoms returning compared to abruptly stopping. [68, 69]

Another side effect where a moderate association was consistently found is increased risk of enteric bacterial infections. Therefore, this risk should be kept in mind when initiating long-term use of PPIs and the indication for continuous PPI use should be critically reevaluated in patients with Clostridium difficile infections.
Although the findings are controversial, the recent studies reintroducing the concerns about a possible increased risk of gastric malignancies in long-term users of PPIs call for further investigations in light of the seriousness of possible increased cancer risk.

Since our aim was to provide a broad overview and summary of the literature on the long-term safety of PPIs, we felt a narrative review to be an appropriate format. However, our review was limited by its non-systematic search process. As such, it is possible that we missed studies reporting adverse events related to PPIs.

In conclusion, based on the evidence reviewed, the risk of long-term side effects should not be a reason to withhold PPIs from patients with a true indication for acid suppressive therapy. If side effects are merely associated with PPI therapy due to residual confounding, it may cause unnecessary discontinuation of PPI with serious consequences for patients at risk (for example, those at high risk of peptic ulcer bleeding).

However, as with all drugs, PPIs should be prescribed in the lowest effective dose and the indication should be reviewed on a regular basis.

References


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<table>
<thead>
<tr>
<th>Proton pump inhibitor</th>
<th>Maintenance dose/gastric protection</th>
<th>Treatment dose</th>
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<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Esomeprazole</td>
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<tr>
<td>Lansoprazole</td>
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<td>Rabeprazole</td>
<td>10 mg</td>
<td>20 mg</td>
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</tbody>
</table>

Table 1. Overview of the proton pump inhibitors and their equipotent dosages [70]
Table 2. Application of the Hill criteria to the suggested side effects of long-term use of PPIs

<table>
<thead>
<tr>
<th>Hill criteria</th>
<th>Bone fractures</th>
<th>GI infections</th>
<th>Pneumonia</th>
<th>Kidney events</th>
<th>Dementia</th>
<th>Hypomagnesemia</th>
<th>RAHS</th>
<th>Iron/B12 absorption</th>
<th>Gastric cancer</th>
<th>Liver disease</th>
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<tbody>
<tr>
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*Spontaneous bacterial peritonitis not included
RAHS: rebound acid hypersecretion

Table 3. Summary of adverse effects.

<table>
<thead>
<tr>
<th>Category of adverse effects</th>
<th>Specific adverse effects that have been associated with PPI use</th>
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<tbody>
<tr>
<td>Infections due to hypochlorhydria</td>
<td><em>C. difficile</em> infection&lt;br&gt;Enteric infections&lt;br&gt;Spontaneous bacterial peritonitis&lt;br&gt;Liver diseases&lt;br&gt;Community-acquired pneumonia</td>
</tr>
<tr>
<td>Impaired absorption of nutrients due to hypochlorhydria</td>
<td>Bone fractures&lt;br&gt;Vitamin B12 deficiency&lt;br&gt;Hypomagnesemia&lt;br&gt;Iron deficiency</td>
</tr>
<tr>
<td>PPI-induced hypergastrinemia</td>
<td>Gastric hyperplasia/metaplasia&lt;br&gt;Rebound acid hypersecretion</td>
</tr>
<tr>
<td>Other</td>
<td>Kidney disease and acute kidney injury&lt;br&gt;Dementia</td>
</tr>
</tbody>
</table>
Figure 1. Flow chart demonstrating study selection

Primary search (keywords: proton pump inhibitor, proton pump inhibitors, side effects, adverse effects, and complications)
N=6490

Studies examining side effects related to PPI therapy
N=67

Exclusion due to irrelevancy (not studies of side effects related to PPI therapy) or duplication
N=6423