Proton pump inhibitors reduce phlebotomy burden in patients with HFE-related hemochromatosis: a systematic review and meta-analysis

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Background and aims Proton pump inhibitors (PPIs) may reduce iron absorption and serum ferritin levels in patients with homeostatic iron regulator (HFE)-related hemochromatosis, reducing the need for frequent phlebotomies. Our study aimed to perform for the first time a meta-analysis of existing observational and randomized controlled studies to ascertain the overall effect of PPI use in patients with HFE-related hemochromatosis.

Methods Studies in adults reporting the outcomes of PPIs use in hereditary hemochromatosis patients from *Medline*, *Embase*, *Scopus* and *Google Scholar* databases from inception to December 2019 were systematically searched. The study outcomes were the serum ferritin levels and annual requirement for phlebotomies. Pooled mean difference, and 95% confidence intervals (CIs) were obtained by the random-effects model. Forrest plots were constructed to show the summary pooled estimate. Heterogeneity was assessed by using I^2 measure of inconsistency.

Results Following an initial search of 202 manuscripts, a total of three studies involving 68 patients with hemochromatosis (34 in the PPIs group and 34 in the placebo or non-PPI group) were included. A minimum duration of PPI use was 1 year. Patients who received PPIs therapy did not have a statistically significant lower serum ferritin levels (mean difference: −18.86, 95% CI: −60.44, 22.72, $P=0.37$, $I^2=88\%$) but required significantly less sessions of phlebotomies annually (mean difference: −3.10, 95% CI: −4.46, −3.08, $P<0.00001$, $I^2=93\%$). No publication bias was found on Egger ($P=0.94$) or Begg ($P=0.98$) tests.

Conclusion PPIs can be used as an adjuvant therapy to reduce phlebotomy burden in patients with HFE-related hemochromatosis. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Hemochromatosis secondary to homeostatic iron regulator (HFE) gene mutations results in the accumulation of iron in multiple organs including the liver, pancreas, and heart. Over the years, iron accumulation not properly addressed leads to chronic disease and organ failure [1,2]. The treatment of HFE-related hemochromatosis is centered on the reduction of total body iron. Routine phlebotomy began to be used to reduce total body iron levels in the early 1950s, and is a proven and widely accepted treatment strategy [3]. Phlebotomies, however, are associated with a number of side effects including fainting spells and loss of appetite in as many as 52% of patients, as well as clinical worsening in individuals with congestive heart failure [4]. Therefore, a reduction of intestinal iron absorption represents a preferred alternative mechanism to reduce serum iron and ferritin when possible. Iron is absorbed in the ferrous form in the duodenum via a divalent metal transporter-1 (DMT1) [5]. Nonheme iron, in contrast to heme or animal iron, requires gastric acid to reduce its ferric to ferrous form and so facilitate its absorption [6]. Reduction of gastric acid production by pharmacological means may therefore reduce the bioavailability of nonheme iron. Furthermore, individuals with homozygous C282Y mutation, the most frequent HFE gene profile in Caucasians with hemochromatosis, have increased expression of DMT1 as well as high levels of serum gastrin, leading to increased absorption of nonheme iron in this population [7,8]. Proton pump inhibitors (PPIs) have the ability of reducing gastric acid and therefore could reduce iron absorption in patients with HFE-related hemochromatosis and may reduce the frequency of phlebotomies.

Iron deficiency is generally not associated with routine PPI use, presumable as patients with normal iron regulatory mechanisms can adapt to these changes in bioavailability and upregulate intestinal iron absorption [9,10]. However, in the setting of HFE-related hemochromatosis, there is likely a significant reduction in iron absorption with PPI use [11]. Despite several studies evaluating the effect of PPI use in the reduction of serum ferritin and frequency of phlebotomies, there is no general consensus among the hepatology community on whether this is an evidence-based approach. Hence, we aimed to complement the available knowledge and improve the management of patients with HFE-related hemochromatosis, by systematically reviewing the literature and performing a

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meta-analysis to ascertain the overall effect of PPI use in patients with HFE-related hemochromatosis.

Methods

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Meta-analysis of Observational Studies Epidemiology guidelines [12,13].

Data sources and search strategy

A comprehensive search of the English language literature was carried out by an experienced librarian to identify articles that examined the effect on PPIs use on serum ferritin and annual phlebotomies in patients with HFE-related hemochromatosis. A systematic search of *Medline*, *Embase*, *Scopus* and *Google Scholar* databases for all studies published from inception to December 2019 was performed using the following MeSH, Emtree and keyword search terms: 'proton pump inhibitors', 'proton pump inhibitor', 'PPI', 'hemochromatosis', 'HFE-related hemochromatosis', 'familial hemochromatosis', 'genetic hemochromatosis', 'primary hemochromatosis', 'pigmentary cirrhosis' and 'iron storage disorder'. The search accounted for plurals and spelling variations. Abstracts were reviewed to determine their relevance, and full-text articles were obtained for all potential studies that met the eligibility criteria. References of all selected studies were examined to identify further relevant articles for inclusion. Two reviewers (A.D. and C.A) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any discrepancies were resolved by consensus. Quality assessment of studies is highlighted in Table 1.

Eligibility criteria

Studies (observational and randomized controlled) were included if they were conducted in an adult population (≥18 years), involving patients with HFE-related hemochromatosis, and had at least two groups for comparison (PPIs group and placebo or non-PPIs group). The following exclusion criteria were used: studies that did not evaluate patients with HFE-related hemochromatosis, studies that did not have PPIs as one of the interventions arms and studies that overlapped the selected studies (studies from the same study group, institution and period of inclusion), case reports, reviews, editorials and correspondence letters that did not report their own data. Finally, one study was excluded as it used a different statistical method to report results, and we could not adjust arithmetic means with accuracy for given geometric means [14].

Quality assessment

The Newcastle-Ottawa scale and the Cochrane tool for risks of bias were used to determine the methodological quality of observational studies and included randomized controlled trail, respectively. The Newcastle-Ottawa scale evaluates studies using the following categories: cohort selection (maximum four points), comparability of cohorts (maximum two points) and exposure/outcome (maximum three points). Studies could score a maximum of nine points, with a higher score indicating a higher quality study. In the Cochrane tool for assessing risk of bias, bias is assessed as a judgment for individual elements from five different domains (selection, performance, attrition, reporting and other).

Outcomes of interest

The outcome of interest was the annual phlebotomy burden in patients with HFE-related hemochromatosis on PPIs therapy.

Data synthesis and statistical analysis

Dichotomous outcomes were evaluated in terms of mean difference with their 95% confidence intervals (CIs) and summarized across studies through a random-effects model as described by DerSimonian and Laird for analysis. Forest plots were constructed to show the point estimates in each study about the summary pooled estimate. Two-sided *P* values of less than 0.05 were considered as statistically significant. Width of the point estimates in the Forrest plots corresponded to the assigned weight of the study. Heterogeneity across studies was assessed through the Q test based on $\chi 2$ statistics, and inconsistency was quantified through the I^2 statistics. I^2 above 50% explains substantial heterogeneity as described in the *Cochrane Handbook for Systematic Reviews for Interventions*, version 5.2.0, Part 2: General Methods for Cochrane Reviews. Sensitivity analysis for significant heterogeneity was performed. The robustness of the meta-analysis to the

Table 1. Quality assessment of included studies

Quality assessment of observational studies using Newcastle-Ottawa Quality Assessment Scale

	Selection				Outcomes				
Study	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at the start of study	Comparability	Assessment of outcomes	Length of follow up	Adequacy of follow up	Quality
Hutchinson et al [17]	*	*	*	*	**	*	*	*	High
Van Aerts et al [11]	*	*	*	*	**	*	*	*	High

Quality assessment of randomized controlled trial using Cochrane tool for assessing risk of bias

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Quality
Vanclooster et al. [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High

Each '*' denotes number of points
- Selection (maximum 4 points), comparability of cohorts (maximum 2 points), and exposure/ outcome (maximum 3 points)
- Studies can score a maximum of 9 points, with a higher score indicating a higher quality study

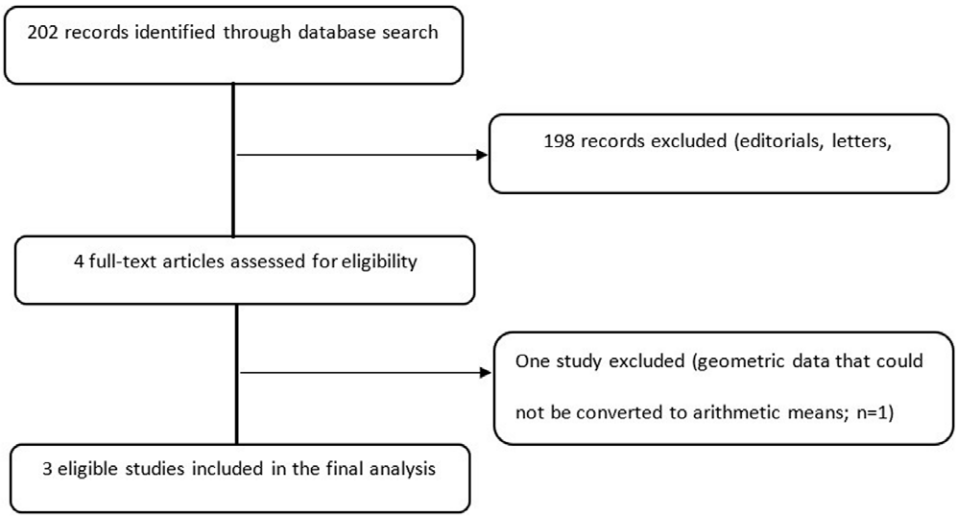

Fig. 1. PRISMA flowchart.

publication bias was assessed by various bias indicators, including Egger's test, Begg's test and by visual inspection of funnel plots for asymmetry [15].

Results

Eligible studies

An initial search strategy identified 202 articles. Titles and abstracts of articles were reviewed in accordance with the predefined exclusion criteria, yielding four potentially relevant articles that were considered in depth. Figure 1 highlights the search strategy and results. Among these, three studies ($n = 68$) that met the inclusion criteria were included in the present analysis [11,16,17]. There were a total of 34 subjects in each (PPIs versus placebo or no-PPIs) group. All the three studies were published as full-text articles in peer-reviewed journals. Baseline characteristics and salient features of each study are presented in Table 2.

Study outcomes

Serum ferritin levels

Analysis included 34 subjects in the PPIs group and 34 subjects in the placebo or non-PPIs group. The serum ferritin concentrations in the PPIs group compared with placebo or non-PPIs group was not statistically significant (mean difference: −18.86, 95% CI: −60.44, 22.72, $P = 0.37$, $I^2 = 88\%$) (Fig. 2).

Requirement for annual phlebotomies

All studies reported this outcome with 34 subjects with HFE hemochromatosis in the PPIs group and 34 subjects in the placebo or non-PPIs group. The need for annual phlebotomies was significantly lower in the PPIs group compared to placebo or non-PPIs group (mean difference: −3.10, 95% CI: −4.46, −3.08, $P < 0.00001$, $I^2 = 93\%$) (Fig. 3).

Quality assessment and publication bias

Included studies were of good quality in the representativeness of the cohorts, outcome assessment, and comparability of the two groups (PPI versus no PPI). The primary meta-analysis included all three studies and was evaluated using a random-effects model. No publication bias was found on Egger's test with a P value of 0.94 and Begg's test with a P value of 0.98.

Discussion

Our meta-analysis demonstrates that PPI use is superior to placebo or non-PPIs in reducing the annual phlebotomy burden in patients with HFE-related hemochromatosis (Fig. 3). To our knowledge, this is the first meta-analysis to evaluate the efficacy and utility of PPIs in patients with HFE-related hemochromatosis.

Iron overload in HFE-related hemochromatosis can result in cirrhosis, complicated by portal hypertension and in some cases hepatocellular carcinoma [18]. Although significant hard outcomes such as progression to cirrhosis, and mortality were not evaluated, the included studies evaluated the need for phlebotomies, which is a primary outcome measure in the treatment of patients with HFE-related hemochromatosis. The fact that the serum ferritin levels were the same in the two groups give credibility to the premise that PPIs indeed lessen the need for phlebotomy. The serum ferritin level is crucial in the diagnostic algorithm for patients with suspected or established hemochromatosis as the serum ferritin level >1000 µg/L predicts the potential for advanced fibrosis and consequent downstream effects of cirrhosis and portal hypertension [19,20]. Moreover, successful iron depletion may reverse cirrhosis and measurement of the serum ferritin level is recommended by international guidelines to monitor the need for phlebotomies.

Reduction of iron absorption is an indirect method of reducing serum ferritin. Using PPIs, a relative iron deficit can be induced in individuals with HFE-related hemochromatosis but not in normal individuals. In patients with HFE-related hemochromatosis, there is an increased expression of apical and basolateral iron transporters – DMT-1 and Ferroportin, due to a relative lack of hepcidin [17]. This oversaturated system results in increased iron absorption in the duodenum. PPI use in these individuals reduces the amount of available and potentially

Table 2. Baseline characteristics and salient features of individual studies

Studies [references]	Hutchinson *et al*. [17]		Van Aerts *et al*. [11]		Vanclooster *et al*. [16]	
Design	Retrospective cohort study		Retrospective cohort study		Prospective, randomized, double-blind, placebo-controlled study	
Country	UK		The Netherlands		The Netherlands/Belgium	
Year	2007		2016		2017	
Population	No PPIs	PPIs	No PPIs	PPIs	PPIs	Placebo
Sample size (n)	7	7	12	12	15	15
Age (years) at diagnosis	NR	NR	NR	NR	50.13 (±8.86)	47.13 (±11.04)
Age (years) at start of study	NR	NR	NR	NR	57.53 (±6.51)	53 (±10.5)
Males, *n* (%)	NR	NR	7 (58%)	7 (58%)	10 (67%)	12 (80%)
BMI	NR	NR	NR	NR	27.05 (±4.37)	27.8 (±3.39)
PPI therapy duration (years)	–	≥1	–	2–3	≥1	–
PPIs used	–	Lansoprazole (30 mg) omeprazole (20 mg) daily	–	Esomeprazole (40 mg), pantoprazole (40 mg), omeprazole (20 mg) daily	Pantoprazole (40 mg) daily	–
Recording period (years)	6.1 (0.2)	3.8 (0.9)	3.0(3)	3.0(3)	1	1
Hemoglobin (g/dl) mean (SEM)	14 (0.2)	14.3 (0.4)	NR	NR	NR	NR
Gastrin level (pg/mL)	NR	NR	NR	NR	96.64 (±71)	32.73 (±17.91)
Underwent liver biopsy, *n* (%)	5 (71.4%)	5 (71.4%)	NR	NR	NR	NR
Grade 4 sclerosis	5 (71.4%)	5 (71.4%)	NR	NR	NR	NR
Serum ferritin	81.4 (17.1) µg/L	38.5 (8.5) µg/L	50 (32.7–77.7) µg/L	70.1 (26.7–91.6) µg/L	90.53 (±46.18) U/L	125.80 (±37.06) U/L
Annual phlebotomy requirements	2.5 (0.2)	0.5 (0.2)	3.17 (2.08–3.66)	0.5 (0–0.66)	1.27 (±1.03)	2.60 (±1.55)

NR, not reported; PPIs, proton pump inhibitors.

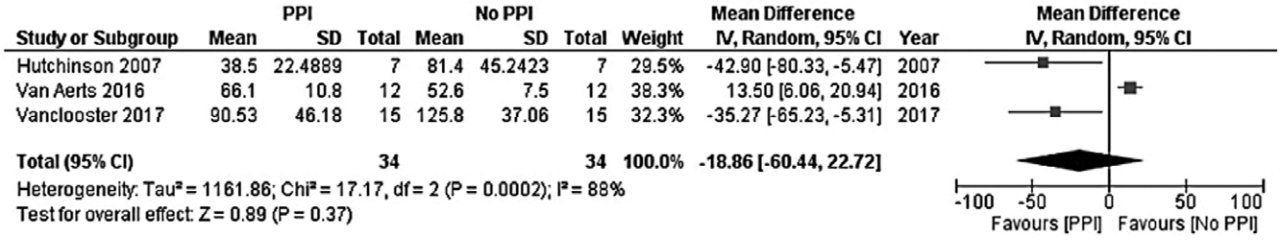

Fig. 2. Forrest plot depicting pooled mean difference in serum ferritin between two groups in patients with HFE-related homochromatosis.

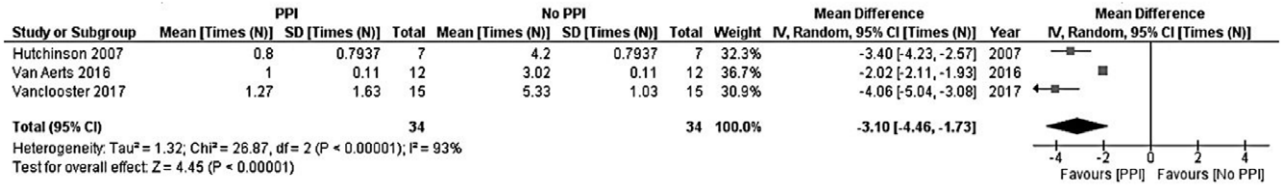

Fig. 3. Forrest plot depicting pooled mean difference in annual phlebotomies between two groups in patients with HFE-related homochromatosis.

absorbable iron. In contrast, when PPIs are administered to individuals with normal iron meabolism, the expression of DMT-1 and Ferroportin is increased to match the relative lack of potentially absorbable iron and so maintain a homeostasis [9,10].

Reduction of serum ferritin can be achieved with routine therapeutic phlebotomy. Despite the wide acceptance of this treatment modality, it is associated with fatigue, fainting spells and loss of appetite in 37% of patients on maintenance treatment [4]. Thus, reduction in the annual need for maintenance phlebotomies can reduce patient discomfort and costs from visits to healthcare facilities. Our meta-analysis found a statistically significant reduction in the need for annual phlebotomies in the PPIs group compared to placebo or non-PPIs group (Fig. 3) in the presence of a similar serum ferritin level.

Our findings suggest that use of PPIs in patients with HFE-related hemochromatosis results in lower annual phlebotomies compared to placebo or non-PPIs. In addition to the ease of compliance associated with daily medication compared to therapeutic procedures; PPIs, by reducing the annual burden of maintenance phlebotomies, may help reduce the overall cost of management of HFE hemochromatosis. According to consumer reports, generic forms of oral Omeprazole 20 mg daily and Pantoprazole 40 mg daily cost $58 per month supply and $66 per month supply, respectively [21]. In contrast, a session of therapeutic phlebotomy for HFE hemochromatosis is variable and based on location. It may range from $30 to $200 in a blood bank, $200 to $400 in a doctor's office and $400 to $1400 in a hospital/outpatient setting. Insurance coverage for each location vary, and patients generally undergo on average four sessions per month depending on serum ferritin levels [22].

Possible risks of chronic PPI use that have gained recent infamy include pneumonia, hip fracture, osteoporosis, dementia and chronic obstructive pulmonary disease, based on retrospective studies [23–26]. However, a large randomized prospective study of 17 600 patients did not find any statistically significant increase in the rates of these risks. There was a slightly increased risk of enteric infections, and a trend toward increased risk of *Clostridiodes difficile* infection [27]. Nonetheless, the relatively higher cost of phlebotomy and potential exposure to nosocomial infections associated with visits to clinics or hospitals may be a conceivable demerit when compared to the lower cost and simplicity of patients taking a daily PPI. Furthermore, in the included studies, no side effects were documented in the patients treated with PPIs.

Our meta-analysis has several limitations. First, it included only three studies in final analysis, two of which were observational, with an overall small sample size and thus a higher risk for publication bias. This is largely because of the paucity of available data on the efficacy and utility of PPIs in patients with HFE-related hemochromatosis. Second, long-term events and direct clinical outcomes such as progression of cirrhosis and decompensation, need for transplantation and transplant-free survival, in addition to overall mortality are lacking. Third, although we can attest to a high safety profile of PPIs, more prospective studies with follow-up of 5–10 years are required to help determine the overall long-term safety profile of these medications.

Based on this meta-analysis, PPIs, used as adjuvant therapy, is well tolerated and efficacious in reducing the phlebotomy burden in patients with HFE-related hemochromatosis. This may be achieved by increasing the gastric pH in this population thus reducing iron absorption.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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