Investigating potential confounding by indication when considering the association between proton pump inhibitor use, infection, hepatic encephalopathy and mortality in hospitalised decompensated cirrhosis: a post-hoc analysis of the ATTIRE trial

Louise China,[a,g] Thais Tittanegro,[a,g] Dominic Crocombe,[a] Ewan Forrest,[b] Yiannis Kallis,[c] Stephen D. Ryder,[d] Gavin Wright,[e] Nick Freemantle,[f] and Alastair O'Brien[a,f,*]

[a]Institute of Liver and Digestive Health, University College London, United Kingdom
[b]Glasgow Royal Infirmary, Glasgow, United Kingdom
[c]Barts and the London School of Medicine and Dentistry Queen Mary University of London, United Kingdom
[d]National Institute for Health Research Nottingham Biomedical Research Centre at Nottingham University Hospitals NHS Trust and the University of Nottingham, Queens Medical Centre, Nottingham, United Kingdom
[e]Mid and South Essex NHS Foundation Trust, Basildon & Thurrock University Hospitals NHS Foundation Trust, Gastroenterology, Hepatology and Hepatobiliary Medicine, The Royal Free Hospital, University College London, Kings College London, United Kingdom
[f]Comprehensive Clinical Trials Unit, University College London, United Kingdom

eClinicalMedicine 2023;58: 101924

Published Online xxx https://doi.org/10.1016/j.eclinm.2023.101924

Summary

Background Proton pump inhibitors (PPIs) are commonly prescribed to prevent and treat upper gastrointestinal ulceration and bleeding. Studies have identified increased incidence of spontaneous bacterial peritonitis and hepatic encephalopathy (HE) in cirrhosis patients taking PPIs. However, results are conflicting, and as PPIs are prescribed for variceal bleeding, a major risk factor for infection and HE, it is challenging to discern whether these associations are causal.

Methods In this post-hoc analysis of the ATTIRE trial, we pooled all patient data to investigate the effects of PPI use on clinical outcomes. ATTIRE was a multicentre, open-label, randomised trial of targeted 20% human albumin solution (HAS) daily infusions versus standard care involving 777 adults with decompensated cirrhosis hospitalised with acute complications and albumin <30 g/L. Study recruitment was between Jan 25, 2016, and June 28, 2019, at 35 hospitals across England, Scotland, and Wales. Key exclusion criteria were advanced hepatocellular carcinoma with life expectancy <8 weeks and patients receiving palliative care. In ATTIRE, patients were grouped by PPI use at trial entry. We studied infection and HE at baseline and incidence of hospital acquired infection, new onset HE, renal dysfunction and mortality. We attempted with propensity score matching to account for differences in disease severity.

Findings Overall PPI use at baseline was not associated with increased incidence of infection, renal dysfunction or mortality, but was associated with significantly increased incidence of grade III/IV HE during hospital stay ($P = 0.011$). This was only significant for those taking intravenous PPIs and these patients had >10 times the incidence of variceal bleeding and near double the 28-day mortality compared to non-PPI patients. However, propensity score matching was not possible as there was such a strong selection of patients for PPI use, that we could not find sufficient non-PPI patients to match to. We found no impact of PPI use on plasma markers of bacterial translocation, infection or systemic inflammation.

Interpretations Our real-world data from a completed randomised trial show that PPIs are widely prescribed in the UK and judicious use appears safe in patients hospitalised with decompensated cirrhosis. However, patients prescribed PPIs had fundamentally different phenotypes to those not prescribed PPIs, a form of confounding by indication, which should be strongly considered when interpreting studies and making recommendations about their use.

*Corresponding author. UCL Institute for Liver and Digestive Health, Upper 3rd Floor, Division of Medicine, Royal Free Campus, Rowland Hill Street London, NW3 2PF, United Kingdom.
E-mail address: a.o'brien@ucl.ac.uk (A. O'Brien).
[g]Joint first authors.

Funding Wellcome Trust and Department of Health and Social Care.

Keywords: Spontaneous bacterial peritonitis; Variceal bleeding; Bacterial translocation

Research in context

Evidence before this study

Proton pump inhibitors (PPIs) have well known benefits in terms of acid suppression and are used to prevent and treat ulceration and bleeding from gastrointestinal bleeding. In cirrhosis, several studies have identified an increased incidence of spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy (HEs) in patients taking PPIs. However, results are conflicting and, given that PPIs are prescribed for variceal bleeding—itself a major risk factor for infection and HE—it is challenging to discern whether these associations are causal or because of confounding. Nevertheless, the Baveno consensus guidelines recommend PPIs be stopped immediately after endoscopy unless there is a strict indication to continue them.

Added value of this study

PPI use at baseline in patients hospitalised with decompensated cirrhosis in the ATTIRE trial did not increase incidence of infection, renal dysfunction or mortality up to 6 months from study entry but was associated overall with significantly increased grade III/IV HE during their hospital stay.

This risk appeared appreciably associated with the increased use of PPIs in patients with suspected variceal bleed at hospitalisation. Our analyses suggest that factors other than PPI use are likely to be significant potential confounders for HE, such as the variceal bleed itself or use of sedation or anaesthetic for endoscopy. Consistent with this, we found no increase in grade I/II HE in those taking PPIs. We attempted propensity score matching to ensure we had not missed a possible effect of PPI use but were unable to achieve a balance between PPI use and non-use, which was remarkably challenging. It appears that these were two very different, discrete groups of patients, and thus a matched comparison was not possible.

Our mechanistic analyses showed no impact of PPI use on plasma markers of bacterial translocation, infection or systemic inflammation at baseline, day 5 or day 10 of trial entry.

Implications of all the available evidence

PPIs were widely prescribed during ATTIRE and there was no associated increased risk of infection nor 6-month mortality. Our data were consistent with the possibility that the reported association between PPIs and HE represents an example of potential confounding by indication and a true major casual factor is variceal bleeding and endoscopic variceal treatment under sedation or anaesthetic. We cannot exclude a modest casual effect of these drugs on HE but were unable to perform propensity score matching—even when variceal bleed patients were excluded— because of other important confounders (such as non-selective beta-blocker use, serum bilirubin levels and numbers with alcohol-induced cirrhosis), all of which have been associated with increased HE. Our work supports the notion that patients prescribed PPIs had fundamentally different phenotypes to those not, which should be strongly considered when interpreting studies on their use in acutely decompensated cirrhosis.

Introduction

Proton pump inhibitors (PPIs) reduce gastric acid secretion, promote clotting of gastrointestinal bleeding and are commonly prescribed to cirrhosis patients with established benefits for peptic ulcer disease and to prevent rebleeding immediately post endoscopic banding of gastroesophageal varices.[1,2] However, PPIs do not prevent bleeding from gastroesophageal varices or portal hypertensive gastropathy[3] and are frequently prescribed without a clear indication.

Many studies have identified that PPIs may cause harm, with four meta-analyses identifying a statistically significant association between PPI use and increased risk for spontaneous bacterial peritonitis (SBP).[4–7] Other infections possibly associated with PPIs include hospital-acquired pneumonia and *Clostridium difficile* enterocolitis.[8,9] Furthermore, PPI use in cirrhosis has been associated with increased incidence of hepatic encephalopathy (HE) and even mortality.[10–13] A potential underlying mechanism is PPI use may lead to increased small intestinal bacterial overgrowth which promotes bacterial translocation leading to greater systemic inflammation and impaired immunity.[14] These concerns are reflected in the recent Baveno consensus that included a new recommendation, "Proton pump inhibitors, when started before endoscopy, should be stopped immediately after the procedure unless there is a strict indication to continue them".[15] However, many studies have been limited by retrospective or case–control deign.[16–20] Importantly, PPIs are more likely to be prescribed following variceal haemorrhage, which itself increases the risks of infection and HE, thus

limiting interpretation of these data due to potential confounding by indication.[21–23] Indeed, the only multicentre prospectively designed study investigating SBP risk and PPI use, did not show a significant association.[18]

As such, there remains considerable uncertainty over the true risks of PPI use in acutely decompensated cirrhosis. This is important as use could be causing widespread harm or alternatively, they may be unnecessarily withheld when there is a valid indication, based on misinterpretation of existing data. Therefore, we studied the ATTIRE (albumin to prevent infection in chronic liver failure) trial[24] dataset to investigate whether PPI use at baseline was associated with increased rates of infection, HE or mortality. We examined intravenous (iv) use and patients with suspected variceal bleeding separately to directly address these potential confounders. We also analysed plasma biomarkers of bacterial translocation and systemic inflammation in PPI users and non-users during hospitalisation.[14]

Methods

ATTIRE trial

ATTIRE was a trial of targeted human albumin solution (HAS) infusions versus standard care involving 777 hospitalised patients with decompensated cirrhosis from 35 hospitals across England, Wales and Scotland (2016–2019).[24]

ATTIRE was a multicentre, randomised, open-labelled trial to evaluate the effect of daily intravenous 20% human albumin infusions to raise and maintain serum albumin ≥30 g/L compared to standard medical care in treatment of decompensated cirrhosis patients hospitalised with acute complications and albumin <30 g/L. Patients were aged >18 years hospitalised with a clinical diagnosis of acute complications of decompensated cirrhosis and serum albumin <30 g/L within 72 h after hospital admission (as early therapy was more likely to be beneficial) and anticipated hospital length of stay ≥5 days at randomization. Patients hospitalised with community-onset infection were eligible as they have high rates of nosocomial infection. Recruitment was between 25-Jan-2016 to 28-Jun-2019, at 35 hospitals across England, Scotland and Wales. Key exclusion criteria were advanced hepatocellular carcinoma with life expectancy <8 weeks and patients receiving palliative care (Supplementary Fig. S1). See supplementary methods for more details on enrolment.

As the overall trial was null, we pooled all patient data to investigate the effects of PPI use on clinical outcomes. In ATTIRE patients grouped by PPI use at trial entry, we studied infection and HE at baseline and incidence of hospital acquired infection, new onset HE, renal dysfunction and mortality. We attempted with propensity score matching to account for differences in disease severity.

Hypothesis

This post-hoc analysis tested the hypotheses that use of PPIs at ATTIRE trial entry would be associated with:

(i) An increased risk of infection, HE, and increased markers of bacterial translocation at baseline (trial entry).
(ii) An increased incidence of hospital acquired infection (HAI – defined as infection >48 h after trial entry) and new brain dysfunction (HE) during the trial treatment period (days 3–15).
(iii) As a result of (ii), an increased incidence of renal dysfunction and mortality during the trial treatment period and increased mortality at 28-, 90- and 180-days follow-up.

Data collection

ATTIRE trial data were collected daily from trial entry until: discharge from hospital, death, being declared medically fit for discharge from hospital, or at 15 days. Mortality data was collected at 28-, 90- and 180-days from trial entry.

PPI use was defined as use at any point during hospitalisation and was extracted from the concomitant medication (ConMed) case report forms (CRFs). PPI non-use was defined as no use during hospitalisation. Name, dose, and start and stop dates for all medications were recorded from patient drug charts during the trial from day 1 of trial entry and inputted into the ATTIRE database at the UCL Comprehensive Clinical Trials Unit. These data did not differentiate between medication started at hospital admission or prior to hospitalisation nor was any information regarding indications for medication use collected.

Search terms: 'esomeprazole', 'omeprazole', 'omeprazole (n)', 'omeprazole capsule', 'omeprazole capsules', 'omperazole', 'pantoprazole', 'pantoprazole + 250 ml of 0.2% nacl', 'pantoprazole + 250 ml of 0.9% nacl', 'pantoprazole + 250 ml of 5% glucose', 'pantoprazole inj', 'pantoprazole injection', 'pantotrazole', 'lansaprazole', 'lansoprazole', 'lansoprazole 'I', 'lansoprazole caps'ke', 'lansopraz'lw', 'lanzopraz'le'.

We searched for intravenous (iv), oral, nasogastric or sublingual administration of PPIs. We only included those taking PPIs on the day of randomisation. We considered the earliest day when comparing duplicated entries. We did not consider those without a start date, nor without a randomisation date.

Patient selection

The schema for our analyses for all patient groups is shown in Fig. 1. As ATTIRE trial outcomes were reported from day 3 of participation, patients that took PPIs for 2 or fewer days and those that started PPIs on day 3 or later were excluded from our main analyses. For these analyses, we divided patients into the

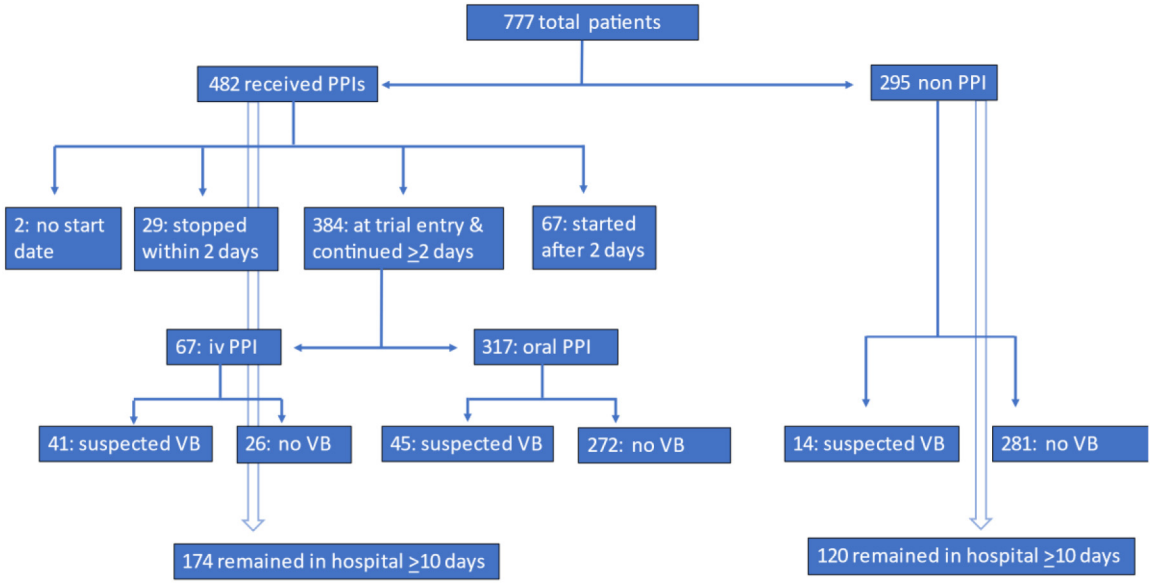

***Fig. 1:* Study profile showing the patient groups from ATTIRE trial that were analysed in this post-hoc analysis**. PPI – Proton pump inhibitor, iv – intravenous, VB – suspected variceal bleed.

following categories, as variceal bleeding and sedation required for endoscopy has been shown to be associated with increased incidence of HE and infection:

(a) All patients taking PPI at baseline - 482.
(b) Patients prescribed only iv PPI at baseline - 67 (as these patients were likely to have a greater incidence of large volume gastrointestinal haemorrhage, which we hypothesised might represent a confounding variable).
(c) Patients prescribed only oral PPI at baseline - 317.
(d) Patients prescribed oral PPI at baseline that did not have suspected variceal bleeding - 272.
(e) Patients in the comparator group did not take PPIs at any point during their hospitalisation for the ATTIRE trial, or at hospital discharge - 295.

We also performed analyses on the following subgroups:

(f) All patients taking PPIs at baseline (IV and oral) compared with patients not prescribed PPIs.
(g) All patients taking PPIs at baseline (IV and oral) compared with patients not prescribed PPIs – 298, with patients diagnosed with suspected variceal bleeding at baseline excluded - 281.
(h) Baseline characteristics and clinical outcomes of all patients taking PPIs at baseline (IV and oral) that were continued for ≥10 days–174, compared with patients not prescribed PPIs that also remained in the trial for >10 days - 120.

Primary analyses

We compared baseline characteristics and outcomes of patients taking PPIs or not at trial entry and examined (a) Incidence of infection and HE at hospitalisation and (b) Development of hospital acquired infection (HAI) and new brain dysfunction (either Grade I/II or III/IV HE) on days 3–15 of the trial.

Infection was defined according to the attending clinician's diagnosis and for HAIs sites were asked to complete infection CRFs with supporting clinical, biochemical, microbiological and radiological data. This was used for blinded validation for infection diagnosis by a physician panel but was not a mandated requirement for sites. Blood test results were obtained from hospital sites. Suspected variceal bleeding was defined according to attending clinician diagnosis.

Renal dysfunction was defined as serum creatinine increase ≥50% compared to randomisation, rise in serum creatinine ≥0.3 mg/dL within 48 h or patient initiated on renal replacement therapy (patients receiving renal replacement at baseline could not reach this outcome). HE was defined as grade III (Drowsy) or grade IV encephalopathy (coma) using the Westhaven Criteria to grade HE (based on modified components of the Chronic liver failure-sequential organ failure assessment (CLIFSOFA) score (Supplementary Table S2), was recorded.[25] ***Propensity Scoring to examine the effect of PPI use on HAI, HE and mortality was attempted to account for baseline differences in disease severity***.

We calculated a propensity score for each patient, using the fitted value on the logit scale from a logistic regression model which included baseline use of antibiotics, suspected variceal bleed (categorised as suspected because CRFs were often completed prior to endoscopy as patients could be enrolled at the point of hospitalisation), new-onset or worsening ascites, HE, diagnosis of alcoholic hepatitis, use of antibiotics, use of non-selective beta-blockers (NSBBs), gender, age, MELD score, serum albumin, creatinine, white cell count (WCC), C-reactive protein, and randomised group. Hospital site and randomised group were considered in the propensity score analysis, however in the main analysis of the trial including sites as random intercept terms made no material difference to the results of the trial (and very flat), which was also neutral for randomised condition. We planned that once adequate matching was achieved, the matched data set would be locked before proceeding to preplanned outcome analyses.[26,27] Please see supplementary methods for more details.

Secondary analyses

(a) We investigated renal dysfunction and mortality on days 3–15 of the trial between patients prescribed PPIs or not at baseline. The ATTIRE protocol defined renal dysfunction as a serum creatinine increase ≥50% from randomisation, or patient initiated on renal replacement therapy, or a rise in creatinine ≥26.5 μmol/L within 48 h.

(b) We investigated mortality at 28-, 90- and 180-days during trial follow-up between patients prescribed PPIs or not at baseline, choosing a categorical analysis approach rather than Kaplan Meier as we were examining short-term outcomes and all patients had the same follow-up times.

(c) We compared plasma markers of bacterial translocation (Endotoxin binding protein (LBP) and soluble CD14 (sCD14), systemic inflammation (Tumour Necrosis Factor (TNF); Interleukins (IL) 1,4 and 6; CD163; CCL8/MCP-2), infection, (Procalcitonin (PCT)) and the neutrophil associated chemokine Interleukin-8 (IL8)) between patients taking PPIs or not at baseline. Data were taken from our published dataset in which samples from both study arms were blindly analysed.[28] All patients selected were enrolled in the trial for at least 5 days. We divided patients into those taking PPIs (n = 63) or not (n = 51) at baseline prior to albumin treatment, day 5 (n = 49, PPIs and 43 not) and day 10 (n = 14 PPI and 13 non-PPI). LBP, sCD14, TNF, ILs-1, 4, 6 and 8, CD163, CCL8/MCP-2 and PCT was measured by Luminex assay (R&D Systems, Minneapolis, MN) as manufacturer's instructions (supplementary material and Supplementary Table S1). PGE_2 was measured using Amersham Prostaglandin E2 Biotrak Enzymeimmunoassay (EIA) System (GE Healthcare) as manufacturer's instructions. We previously showed that while EIA measurements of PGE_2 were 20x higher than liquid chromatography-tandem mass spectrometry (LC-MS/MS), EIA reproducibly produced qualitative differences between sample groups consistent with LC-MS/MS data.[29]

Statistical analysis

A statistical analysis plan, prior to analyses, was approved by all authors. All authors vouch for completeness and accuracy of data. Confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Microsoft Excel was used for extraction of data from ATTIRE databases, producing tables and graphs. We did not undertake a sample size calculation because our sample is fixed (and thus there is little reason to account for sampling error) but more fundamentally the planned analyses were exploratory with no alpha spend, and our approach was based on estimation to inform future inferential studies on new study material.

IBM SPSS – Version 27 was used for bivariate tests of statistical significance (T-tests for continuous variables with unpaired t-test for normally distributed data and Mann Whitney with log rank testing for non-normally distributed data, and Fishers exact or Chi-squared tests for categorical variables). Normality was addressed through routinely examining comparative histograms, normal and kernel densities, box plots and QQ plots.

Hospital site and randomised group were considered in the propensity score analysis, however in the main analysis of the trial including sites as random intercept terms made no material difference to the results of the trial (and very flat), which was also neutral for randomised condition.

Data are presented as mean (SD) or median (CI) according to distribution. Other analyses performed using SAS software, version 9.4 (SAS Institute; Carey NC).

Ethics

The ATTIRE trial was approved by the London–Brent Research Ethics Committee (ref:15/LO/0104) and the Medicines and Healthcare Products Regulatory Agency (MHRA, ref: 20363/0350/001-0001). Written informed consent was obtained from patients. For incapacitated patients, a legal representative provided written informed consent until the patient regained capacity.

Role of the funding source

The funders had no role in the design of this study and had no role in data collection, data analyses, interpretation, or writing of the report and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Results

482 patients (62%) were recorded as receiving PPIs and 295 (38%) had no PPI prescription at any point during the trial treatment period (enrolment up until discharge, medically fit for discharge or day 15, whichever was earliest). 29 patients had the PPI stopped within 2 days of trial entry, 67 had the PPI commenced after day 2 of trial entry and 2 patients had no start date provided for the PPI. As hospital endpoints were reported from day 3 of trial, we did not believe that PPI use could be accurately assessed to have contributed to clinical outcomes for these 98 patients, who were thus excluded from our main analyses.

The remaining 384 who had PPIs prescribed (67 intravenous (iv), 317 oral) at trial entry, which was on average day 2 of hospitalisation, and continued for 3 days or longer were included. Of these, 332 were recorded as taking PPIs at discharge of the 714 patients that were alive at this point. For patients that had the PPI stopped beyond day 2 but prior to discharge, the median duration of prescription was 6.5 days (95% confidence interval 5–9). For the oral PPIs, 64.5% were taking omeprazole, 33.5% lansoprazole, 1% esomeprazole and 0.5% pantoprazole. For iv PPIs, 64% were taking omeprazole, 30% pantoprazole and 6% esomeprazole, all these patients were commenced on oral PPIs following cessation of iv administration.

When compared to patients not prescribed PPIs during hospitalisation or at discharge, those prescribed PPIs at baseline and for greater than 2 days had similar age, gender, MELD score presence of ascites and serum albumin. PPI patients had significantly increased suspected variceal bleeds (22.6% vs 4.75%, P = 1.64194E-10) and were prescribed more NSBBs (24% vs 12.5%, P = 0.0002) and antibiotics (56.5% vs 46.4%, P = 0.01), both of which were likely to be related to variceal bleed management. PPI patients also had significantly reduced serum bilirubin and white cell count (WCC) and there were slightly more PPI patients with alcohol-induced cirrhosis, though not alcoholic hepatitis and fewer with ascites diagnosed at admission (Table 1).

When just those receiving iv PPIs at baseline were examined, we found more than 60% had suspected variceal bleeding and greater than 80% received antibiotics, both highly significantly increased compared to non-PPI patients (P = 3.97574757773517E-31 and P = 0.000014, respectively). However, there were no differences in serum WCC, bilirubin nor NSBB use (Table 2).

When only those receiving oral PPIs were examined, there were increased suspected variceal bleeds, use of NSBBs, serum WCC and bilirubin (Table 3). Finally, when patients with suspected variceal bleeds were excluded from the analyses, the oral PPI group had increased NSBB use and reduced bilirubin and WCC.

Similarly, when all patients prescribed PPIs at any point during the trial or those prescribed PPIs for >10 days were compared to those not prescribed, there were significantly higher numbers with suspected variceal bleed or NSBB use in the PPI group (Supplementary Tables S3 and S5). When patients prescribed iv and po PPIs with suspected variceal bleeds excluded were compared to those not prescribed PPIs, there were significantly more patients taking NSBBs in the PPI group (Supplementary Table S4).

There was an equal incidence of all-cause infection at hospitalisation when all patients taking PPIs at baseline that were continued for >2 days were compared to those not prescribed PPIs at any point of their hospital admission (27.1% vs 27.1%, P = 0.97). This null effect was consistent when PPI patients were subdivided into those given iv or oral medication or when suspected variceal bleeds were excluded (Tables 1–4 and Supplementary Tables S3–S5).

Similarly, there was an almost equal incidence of development of HAIs between those taking PPIs or not (18.2% vs 18.3%, P = 0.98), again with findings consistent across all subgroups (Tables 1–4 and Supplementary Tables S3–S5). There were no differences between groups prescribed high dose prednisolone ≥30 mg. Infection case report forms were completed for all HAIs in patients taking PPIs and for 45 of the 54 HAIs in the non-PPI group. The most commonly diagnosed infection was lower respiratory tract infection (approximately 35%, Supplementary Table S6). Of these HAIs, 10 patients were diagnosed with SBP (8% of HAIs), of whom 5 were taking PPIs and 5 not (P = 0.67). There was only one HAI that was recorded as *C. difficile*, and this patient did not receive a PPI during their admission.

There was a trend towards an increased incidence of HE at baseline, observed overall in patients taking PPIs at baseline compared to those not (21.8% vs 15.6%, P = 0.054, Table 1), which reached significance when only those taking iv PPIs were considered (P = 0.001, Table 2). However, there was no significant difference in HE at baseline between groups when those only taking oral PPIs or when those taking oral PPIs with no suspected variceal bleeding, were compared (Tables 3 and 4).

There was a significant increase in development of new onset grade III/IV HE during hospitalisation in those taking PPI at baseline (8.6% vs 3.7%, P = 0.01, Table 1) including when all patients given PPI during the trial were considered (P = 0.044, Supplementary Table S3). This difference was greatest when those taking iv PPIs were compared (P = 0.0004; Table 2) but did not reach significance when those taking oral PPIs with or without suspected variceal bleed were examined (Tables 3 and 4). When we examined patients with twice daily dosing for oral PPIs, there were 2/48 patients that developed grade III/IV HE (4%) compared to 11/294 in the non-PPI group (P = 0.89) demonstrating no apparent dose related effect. When patients taking iv

	PPI at baseline	Non-PPI at baseline	*P* value
Baseline clinical characteristics			
Number	384	295	
Mean age (yrs, SD)	53.7 (10.6)	53.5 (10.6)	0.80
Male	275 (71.6%)	208 (70.5%)	0.86
Female	109 (28.4%)	87 (29.5%)	0.86
Alcohol	356 (92.7%)	257 (87.1%)	0.03*
Alcoholic Hepatitis	96 (25.2%)	70 (23.7%)	0.75
Albumin treatment	194 (50.5%)	150 (50.8%)	0.93
NSBB use	92 (24%)	37 (12.5%)	0.0002*
Suspected Variceal Bleed	86 (22.6%)	14 (4.75%)	1.64194E-10*
Ascites	241 (63.1%)	208 (70.5%)	0.037
Use of antibiotics	217 (56.5%)	137 (46.4%)	0.01*
Use of Prednisolone ≥30 mg od	53 (13.8%)	28 (9.5%)	0.09
MELD Score - median (95% CI)	18.94 (17.9–20.1)	19.58 (18.6–20.6)	0.10
Serum Albumin g/L - median (95% CI)	24 (23–24)	24 (23–24)	0.81
Creatinine mmol/L - median (95% CI)	69 (66–73)	66 (63–69)	0.09
WCC $x10^9$/L - median (95% CI)	7.2 (6.8–7.7)	8.1 (7.5–8.8)	0.003*
CRP mg/L - median (95% CI)	24 (21–28)	23 (21–29)	0.57
Bilirubin mg/L - median (95% CI)	84.5 (72–96)	109 (94–127)	0.002*
Primary Clinical Outcomes			
Diagnosis of infection at randomisation	104 (27.1%)	80 (27.1%)	0.97
Incidence of new infection (days 3–15)	70 (18.2%)	54 (18.3%)	0.98
New infection reported as SBP	5 (1.3%)	5 (1.7%)	0.67
HE at randomisation (all grades)	83 (21.8%)	46 (15.6%)	0.054
Incidence of new grade III/IV HE (days 3–15)	33 (8.6%)	11 (3.7%)	0.011*
Incidence of new grade I/II HE (days 3–15)	31 (8.1%)	22 (7.5%)	0.77
Secondary Clinical Outcomes			
Incidence of renal dysfunction (days 3–15)	51 (13.3%)	32 (10.9%)	0.34
Incidence of death during hospitalisation (days 3–15)	30 (7.8%)	24 (8.5%)	0.88
28-day mortality	60 (15.2%)	40 (13.6%)	0.45
90-day mortality	90 (22.8%)	67 (22.7%)	0.82
180-day mortality	120 (30.5%)	95 (32.2%)	0.79

*P values < 0.05.

Table 1: **Baseline characteristics and clinical outcomes of all patients taking PPIs at baseline that were continued for >2 days compared with patients not prescribed PPIs during hospitalisation or at discharge.**

and oral PPIs for >10 days and those taking iv and oral PPIs with suspected variceal bleed at baseline excluded were compared to those not taking PPIs, there was a greater incidence of new onset grade III/IV HE (P = 0.015 and 0.04 respectively, Supplementary Tables S4 and S5). There were no differences between groups in diagnosis of new grade I/II HE during the trial treatment period for overall PPI use or across all subgroups.

We were unable to match patients effectively using propensity scores, failing to achieve the prespecified standardised mean difference criterion or qualitatively important differences between cases and controls. This included an attempt to match the patients without variceal bleeding by bilirubin alone as this was significantly different between the two groups.

Use of PPIs overall at baseline and throughout hospitalisation was not associated with increased renal dysfunction or in-hospital mortality (Table 1). However, use of iv PPI was associated with increased mortality (16.4% vs 8.5%, P = 0.04) despite both groups having a similar MELD score, although PPI patients had four times the rate of suspected variceal bleed (Table 2); There were no differences for renal dysfunction or mortality between groups when those taking oral PPIs with or without suspected variceal bleeding were compared (Tables 3 and 4) or across other subgroup analyses (Supplementary Tables S3–S5).

28-, 90- and 180-day mortality

There were no differences in mortality between patients taking PPIs overall at baseline or not (Table 1). Use of iv PPIs was associated with increased 28-day mortality (25.4% vs 13.6%, P = 0.02) but not 90- or 180-day (Table 2); with similar findings seen in those given iv and oral PPIs that were continued for ≥10 days

	IV PPI at baseline	Non-PPI at baseline	*P* value
Baseline Clinical Characteristics			
Number	67	295	
Mean age, yrs (SD)	54 (9.3)	53.5 (10.6)	0.90
Male	46 (68.7%)	208 (70.5%)	0.71
Female	21 (31.3%)	87 (29.5%)	0.71
Alcohol	63 (94%)	257 (87.1%)	0.14
Alcoholic Hepatitis	10 (15.2%)	70 (23.7%)	0.11
Albumin treatment	36 (53.7%)	150 (50.8%)	0.31
NSBB use	9 (13.4%)	37 (12.5%)	0.85
Suspected Variceal Bleed	41 (62.1%)	14 (4.75%)	3.97574757773517E-31*
Ascites	38 (56.7%)	208 (70.5%)	0.02*
Use of antibiotics	55 (82.1%)	137 (46.4%)	0.000014*
MELD Score – median (95% CI)	19.2 (17.5–21.6)	19.58 (18.6–20.6)	0.69
Serum Albumin g/L – median (95% CI)	24 (23–25)	24 (23–24)	0.70
Creatinine mmol/L – median (95% CI)	74 (67–79)	66 (63–69)	0.06
WCC x10^9/L – median (95% CI)	7 (6.5–8.7)	8.1 (7.5–8.8)	0.14
CRP mg/L - median (95% CI)	20 (14–28)	23 (21–29)	0.25
Bilirubin mg/L - median (95% CI)	85 (64–109)	109 (94–127)	0.13
Primary Clinical Outcomes			
Diagnosis of infection at randomisation	19 (28.4%)	80 (27.1%)	0.86
Incidence of new infection (days 3–15)	16 (23.9%)	54 (18.3%)	0.30
New infection reported as SBP	1 (1.5%)	5 (1.7%)	N/A
HE at randomisation (all grades)	22 (33.3%)	46 (15.6%)	0.0011*
Incidence of new grade III/IV HE (days 3–15)	10 (14.9%)	11 (3.7%)	0.0004*
Incidence of new grade I/II HE (days 3–15)	6 (8.95%)	22 (7.5%)	0.68
Secondary Clinical Outcomes			
Incidence of renal dysfunction (days 3–15)	12 (17.9%)	32 (10.9%)	0.11
Incidence of death during hospitalisation (days 3–15)	11 (16.4%)	24 (8.5%)	0.04*
28-day mortality	17 (25.4%)	40 (13.6%)	0.02*
90-day mortality	18 (26.9%)	67 (22.7%)	0.47
180-day mortality	23 (34.3%)	95 (32.2%)	0.74

*P values < 0.05.

Table 2: **Baseline characteristics and clinical outcomes of patients taking only iv PPIs at baseline compared with patients not prescribed PPIs during hospitalisation or at discharge.**

compared with patients not prescribed PPIs that also remained in the trial for ≥10 days (Supplementary Table 5). Use of oral PPIs, with or without suspected variceal bleeding, was not associated with increased mortality (Tables 3 and 4). Nor were any differences observed in other subgroup analyses (Supplementary Tables S3 and S4).

There were no differences in any plasma marker of bacterial translocation, inflammation, and infection between those taking PPI or not at baseline, day 5 or day 10 (Table 5). When patients only taking oral PPIs were considered, there were also no differences (Supplementary Table S7).

Discussion

PPIs were prescribed in over 60% of ATTIRE patients. Use was not associated with an increased risk of all cause infection either at or during hospitalisation, including SBP. Use was associated with an increased overall incidence of development of grade III/IV HE during hospitalisation, with a trend seen for increased HE at hospitalisation. This risk appeared appreciably associated with the increased use of PPIs in patients with suspected variceal bleed at hospitalisation, with subgroup analyses showing that this only reached significance when either iv alone (at hospitalisation) or when iv and oral patients combined were considered and, in these patients, incidence of suspected variceal bleed was up to five times higher than those not prescribed PPIs. We do not think that these analyses suggest that iv administration of PPIs has a greater effect on HE than oral but rather factors other than PPI use are likely to be significant potential confounders for HE, such as the variceal bleed itself or use of sedation or anaesthetic for endoscopy.[30] Furthermore, these patients are often extremely unwell and therefore endoscopy is recommended to take place in a high dependency

	PPI at baseline	Non-PPI at baseline	*P* value
Baseline Clinical Characteristics			
Number	317	295	
Mean age (yrs)	53.71 (10.9)	53.5 (10.6)	0.81
Male	229 (72.2%)	208 (70.5%)	0.73
Female	88 (27.8%)	87 (29.5%)	0.73
Alcohol	293 (92.4%)	257 (87.1%)	0.05
Alcoholic Hepatitis	86 (27.3%)	70 (23.7%)	0.37
Albumin treatment	158 (49.8%)	150 (50.8%)	0.28
NSBB use	83 (26.2%)	37 (12.5%)	2.36489E-05*
Suspected Variceal Bleed	45 (14.3%)	14 (4.75%)	8.95954E-05*
Ascites	203 (64.4%)	208 (70.5%)	0.08
Use of antibiotics	162 (51.1%)	137 (46.4%)	0.30
MELD Score - median (95% CI)	18.9 (17.7–20.1)	19.58 (18.6–20.6)	0.08
Serum Albumin g/L - median (95% CI)	24 (23–24)	24 (23–24)	0.89
Creatinine mmol/L -median (95% CI)	68 (63–72)	66 (63–69)	0.19
WCC $x10^9$/L - median (95% CI)	7.3 (6.7–7.7)	8.1 (7.5–8.8)	0.0038*
CRP mg/L - median (95% CI)	26 (22–30)	23 (21–29)	0.79
Bilirubin mg/L median (95% CI)	84 (70–98)	109 (94–127)	0.0027*
Primary Clinical Outcomes			
Diagnosis of infection at randomisation	85 (26.8%)	80 (27.1%)	0.89
Incidence of new infection (days 3–15)	54 (17%)	54 (18.3%)	0.68
New infection reported as SBP	4 (1.3%)	5 (1.7%)	N/A
HE at randomisation (all grades)	61 (19.4%)	46 (15.6%)	0.26
Incidence of new grade III/IV HE (days 3–15)	21 (6.6%)	11 (3.7%)	0.11
Incidence of new grade I/II HE (days 3–15)	25 (7.9%)	22 (7.5%)	0.84
Secondary Clinical Outcomes			
Incidence of renal dysfunction (days 3–15)	39 (12.3%)	32 (10.9%)	0.57
Incidence of death during hospitalisation (days 3–15)	19 (6%)	24 (8.5%)	0.3
28-day mortality	43 (13.6%)	40 (13.6%)	0.99
90-day mortality	72 (22.7%)	67 (22.7%)	0.99
180-day mortality	97 (30.6%)	95 (32.2%)	0.67

*P values < 0.05.

Table 3: **Baseline characteristics and clinical outcomes and clinical outcomes of patients taking only oral PPIs at baseline that were continued for >2 days compared with patients not prescribed PPIs during hospitalisation or at discharge.**

setting within 24 h[31] and patients may continue to be sedated overnight in case of high risk of rebleed. Those that continued to be intubated and ventilated would be classified as grade IV HE and even those that had been extubated may well remain significantly drowsy for 12–24 h and thus be classified as grade III HE. Consistent with this, we found no increase in grade I/II HE in those taking PPIs. When those taking oral PPIs were considered, this increased incidence of grade III/IV HE did not reach statistical significance nor when suspected variceal bleed patients were excluded. When we examined all patients taking oral and iv PPIs at baseline with suspected variceal bleed at baseline excluded, there was a significant increase in new onset grade III/IV HE compared to those not taking PPIs, however twice as many PPI patients were taking NSBBs which has been associated with increased HE.[32] Furthermore, there were significant imbalances in baseline characteristics between groups for ascites, serum bilirubin levels and numbers with alcohol-induced cirrhosis, all of which have been associated with increased HE and are therefore additional potential confounders.[32,33] Finally, there was an increase in short term mortality in those prescribed iv PPIs, but these patients had four times the incidence of suspected variceal bleed and increased mortality was not seen in those taking oral PPIs with or without suspected variceal bleeding. We attempted propensity score matching to ensure we had not missed a possible effect of PPI use but were unable to achieve a balance between PPI use and non-use, which was remarkably challenging. It appears that these were two very different, discrete groups of patients, and thus a matched comparison was not possible. We also considered a multivariable analysis to investigate possible predictors of grade III/IV HE in addition to use of PPIs, however, the failure of the propensity score matching, in spite of considerable analytic effort, indicates that we are not comparing 'like

	PPI at baseline	Non-PPI at baseline	*P* value
Baseline Clinical Characteristics			
Number	272	281	
Mean age, yrs (SD)	53.6 (11)	53.38 (10)	0.81
Male	197 (72.4%)	198 (71%)	0.70
Female	75 (27.6%)	87 (29.5%)	0.70
Alcohol	250 (91.9%)	248 (88.2%)	0.28
Alcoholic Hepatitis	76 (28.1%)	68 (24.2%)	0.37
Albumin treatment	130 (48.3%)	140 (49.8%)	0.55
NSBB use	69 (25.4%)	32 (11.4%)	2.28903E-05*
Suspected Variceal Bleed	0	0	
Ascites	182 (67.4%)	202 (69.6%)	0.18
Use of antibiotics	128 (47.1%)	126 (45.5%)	0.71
MELD Score median (95% CI)	19.47 (17.6–20.3)	19.88 (19–20.9)	0.06
Serum Albumin g/L -median (95% CI)	24 (23–24)	24 (23–24)	0.86
Creatinine mmol/L -median (95% CI)	68 (63–74)	66 (64–70)	0.22
WCC $x10^9$/L - median (95% CI)	7.4 (6.8–8)	8.2 (7.5–9)	0.0068*
CRP mg/L - median (95% CI)	28 (23–32)	24 (21–29)	0.70
Bilirubin mg/L - median (95% CI)	85 (72–99)	111 (102–134)	0.0027*
Primary Clinical Outcomes			
Diagnosis of infection at randomization	78 (28.7%)	78 (27.8%)	0.87
Incidence of new infection (days 3–15)	49 (18.0)	50 (17.8%)	0.95
New infection reported as SBP	3 (1.1%)	5 (1.7%)	N/A
HE at randomization (all grades)	56 (20.7%)	45 (16%)	0.19
Incidence of new grade III/IV HE (days 3–15)	19 (7.0)	10 (3.6)	0.07
Incidence of new grade I/II HE (days 3–15)	23 (8.5%)	22 (7.8%)	0.79
Secondary Clinical Outcomes			
Incidence of Kidney dysfunction	36 (13.2)	29 (10.3)	0.29
Incidence of death during hospitalisation	14 (5.1)	22 (7.8)	0.20
28-day mortality	36 (13.2)	38 (13.5)	0.92
90-day mortality	62 (22.8)	65 (23.1)	0.92
180-day mortality	84 (30.9)	92 (32.7)	0.64

*P values < 0.05.

Table 4: **Baseline characteristics and clinical outcomes of patients taking only oral PPIs at baseline that were continued for >2 days compared with patients not prescribed PPIs during hospitalisation or at discharge, with patients diagnosed with suspected variceal bleed at baseline excluded.**

with like' and attempts to account for these systematic differences through multivariable analysis cannot overcome this substantial limitation. Exploratory analyses, such as matched subgroups or adjusted sensitivity analyses may provide more information regarding the differences between patients prescribed PPIs or not but we considered this would introduce too much inference and the only way to resolve this would be a RCT of PPI use versus non-use.

Studies have shown statistically significant, but quantitatively small, associations between SBP and PPI use, however, prospectively conducted studies have not,[18] including one with a 5-year follow-up.[34] A recent meta-analysis concluded that there was a weak but statistically significant association between SBP and PPI use, but the size of this possible association diminished when analyses focused on higher quality data.[35] We did not record SBP diagnosis at baseline, but all cause infection rates were identical in overall analyses and extremely similar in all subgroup analyses. The HAIs categorised as SBP were extremely similar in both groups (5/70 in PPI group and 5/54 in non-PPI group). There was an increased use of antibiotics in those prescribed PPIs overall, likely related to prescription for variceal bleeding, which might mask an effect on infection and represents further confounding by indication when comparing patients prescribed PPIs or not. However, when those prescribed oral PPIs were considered, there were no differences in antibiotic prescription at baseline.

The absence of an effect of PPIs on incidence of infection and HE (outside of iv administration) was consistent with our analyses of plasma samples from approximately 50 patients per group at baseline and day 5, with limited numbers of samples analysed at day 10, in which there were no increased markers of bacterial translocation, infection nor systemic inflammation in those prescribed PPIs during hospitalisation compared

(a)

Plasma marker of infection/inflammation Baseline	PPI at baseline (oral and IV) Median (95% CI) *(numbers of patients)*	Non-PPI at baseline Median (95% CI) *(numbers of patients)*	*P* value
Interleukin 1-βeta (IL- 1β pg/ml)	0 (0–1) *(62)*	0 (0-0) *(51)*	0.28
Interleukin-6 (IL-6 pg/ml)	13 (8.8–19.8) *(62)*	12.6 (10.3–18.1) *(51)*	0.90
Interleukin-10 (IL-10 pg/ml)	0 (0–0.3) *(62)*	0 (0-0) *(51)*	0.84
Tumour necrosis factor alpha (TNF-α pg/ml)	4 (3.2–5) *(62)*	4.2 (3.1–5) *(51)*	0.64
Interleukin-4 (IL-4 pg/ml)	0 (0-0) *(62)*	0 (0-0) *(51)*	0.73
Interleukin-8 (IL-8 pg/ml)	115.2 (45.8–155.9) *(62)*	76 (38.2–154.3) *(51)*	0.88
Procalcitonin (PCT ng/ml)	158.9 (124.6–279.2) *(62)*	128.8 (93.8–214.5) *(51)*	0.65
Lipopolysaccharide binding protein (LBP ng/ml)	1895 (1450–3010) *(63)*	1780 (1330–3400) *(51)*	0.50
Soluble CD 14 (sCD14 ng/ml)	3075 (1570–7520) *(63)*	2230 (1410–3870) *(51)*	0.71
CD163 (ng/ml)	2221 (1758–2872) *(63)*	2746 (2527–3281) *(49)*	0.18
Chemokine ligand 8/monocyte chemoattractant protein 2 (CCL8/MCP-2 pg/ml)	53.5 (47.4–63.1) *(62)*	46.5 (39–54) *(49)*	0.22
Prostaglandin E_2 (PGE_2, pg/ml)	647.9 (550–993) *(62)*	742.8 (537–936) *(50)*	0.97

(b)

Plasma marker of infection/inflammation Day 5	PPI at baseline (oral and IV) Median (95% CI) *(numbers of patients)*	Non-PPI at baseline Median (95% CI) *(numbers of patients)*	*P* value
IL1-β (pg/ml)	0 (0–1.3) *(46)*	0 (0-0) *(42)*	0.27
IL-6 (pg/ml)	10.1 (8–12.9) *(46)*	9.8 (6.2–14) *(42)*	0.82
IL-10 (pg/ml)	0 (0-0) *(46)*	0 (0-0) *(42)*	0.70
TNF-α (pg/ml)	3.8 (2.7) *(46)*	4.15 (3.1–5.2) *(42)*	0.61
IL-4 (pg/ml)	0 (0-0) *(46)*	0 (0-0) *(42)*	0.47
IL-8 (pg/ml)	39.8 (20–91.8) *(46)*	45 (23.3–93.1) *(42)*	0.98
PCT (ng/ml)	110.4 (66.4–231.2) *(46)*	226.5 (69.8–284.4) *(42)*	0.32
LBP (ng/ml)	1540 (1190–1930) *(49)*	1645 (1330–2250) *(44)*	0.41
sCD14 (ng/ml)	5210 (1980–7370) *(49)*	2310 (1440–7820) *(44)*	0.59
CD163 (ng/ml)	2153 (18189–2731) *(46)*	2853 (2382–3290) *(41)*	0.06
CCL8/MCP-2 (pg/ml)	56.1 (41.4–65) *(46)*	45.5 (39.1–53.8) *(41)*	0.22

(c)

Plasma marker of infection/inflammation Day 10	PPI at baseline (oral and IV) Median (95% CI) *(n = 14)*	Non-PPI at baseline Median (95% CI) *(n = 13)*	*P* value
IL1-β (pg/ml)	0 (0–0.2)	0 (0–0)	0.62
IL-6 (pg/ml)	10.75 (4.2–24)	11 (7.2–24.5)	0.79
IL-10 (pg/ml)	0 (0–3)	0 (0–0)	0.20
TNF-α (pg/ml)	2.9 (1.7–4.9)	3.7 (0.7–6.2)	0.90
IL-4 (pg/ml)	0 (0–4)	0 (0–5.8)	0.36
IL-8 (pg/ml)	42.15 (16.6–321.2)	20 (9.8–203.1)	0.46
PCT (ng/ml)	118 (40.5–287.3)	107.8 (48.9–211.4)	0.65
LBP (ng/ml)	3205 (1170–9010)	6070 (1180–6910)	0.55
sCD14 (ng/ml)	1007 (624–7100)	1200 (817–2410)	0.72
CD163 (ng/ml)	2391 (1224–3780)	2761 (867–4274)	0.94
CCL8/MCP-2 (pg/ml)	38.2 (20.7–59.5)	45.3 (22.1–72.8)	0.59
PGE_2 (pg/ml)	680.3 (353–1275)	904.3 (392–2655)	0.51

Table 5: **Plasma markers of bacterial translocation and inflammation/infection at (a) baseline, (b) day 5 of trial and (c) day 10 of trial.**

to those not. There are studies to suggest that albumin use might affect these markers, but day 1 samples were prior to albumin infusions, we did not see an effect of albumin at day 5 using these samples,[28] and albumin use was evenly matched between groups. Therefore, we do not believe targeted albumin infusions to be a confounder. Our data are consistent with a study of greater than one thousand patients that showed no association between PPI use and small intestine bacterial overgrowth.[36] We did not assess cellular oxidative burst that has been shown to be reduced in cirrhosis patients that are taking PPI compared to those not.[37] The reduction in WCC at baseline in the PPI group was most probably related to increased use of NSBBs that we

and others have shown is associated with reduced values.[38,39]

We can only be certain that patients were prescribed PPIs at hospitalisation as we have no data from prior to this. Infection diagnoses were only recorded during the trial treatment period (3–15 days with a median stay of 9 days) and so, we cannot exclude a difference in infections after discharge. However, a study comparing SBP in cirrhotic patients on PPIs for the previous 7 days to those that had taken them for 8–90 days concluded the increased risk of SBP was only in those prescribed for 7 days.[16] Furthermore, completion of infection case report forms was not a mandatory requirement and most, but not all infection diagnoses were recorded. HE assessment was performed by research nurses in collaboration with the clinical teams in the context of a clinical trial rather than dedicated expert assessment using psychometric testing or serum arterial ammonia. Given this limitation we feel that the diagnosis of grade III/IV HE is more robust than I/II as the phenotypes are far more severe and relatively easily identified. Following hospital discharge, we only collected data on mortality or liver transplantation. We do not have data on medications prescribed for patients after they had left hospital to inform whether PPIs were started or stopped following discharge. 4 patients were transplanted during 180-day follow-up, and we did not collect data on transplant listing, ongoing alcohol consumption, or hospital readmissions after discharge. Finally, the vast majority of patients studied had alcohol-induced cirrhosis and findings might differ in patients with other etiologies.

This was a large cohort of patients with frequent PPI prescription from 35 clinical sites throughout the UK with very granular data collected during a high quality RCT in which infection and mortality were part of the primary composite endpoint and grade III/IV HE a secondary one.

It is important to contextualise our analyses. We can be reasonably confident that short-term PPI use had no appreciable effect on infections, renal dysfunction, mortality and probably not even HE during an episode of acute decompensation, and no effect on mortality seen for 180-day follow-up. However, we have not shown that PPIs have no influence on infection or HE in cirrhosis in other contexts, for example stable refractory ascites patients, or over longer periods of time.

In conclusion, PPIs were widely prescribed during ATTIRE in acutely decompensated patients and there was *no* associated increased risk of infection nor mortality. Our data were consistent with the possibility that the reported association between PPIs and HE represents an example of confounding by indication and a major casual factor is variceal bleeding or endoscopic variceal treatment under sedation or anaesthetic. However, when we omitted variceal bleed patients from our analyses, we were unable to perform propensity score matching, due to other important potential confounders between patients prescribed PPIs or not and so we cannot exclude a modest casual effect on grade III/IV HE. Our data support the notion that patients prescribed PPIs had fundamentally different phenotypes to those not, a form of confounding by indication, which should be strongly considered when interpreting studies on PPIs and making recommendations concerning use.

Contributors

Databases were created by LC and TT and verified by AOB and NF. TT, AOB and NF performed statistical analyses. AOB wrote manuscript first draft, with contributions from all authors. All authors read and approved the final version of the manuscript.

Data sharing statement

Data sharing can be made available upon reasonable request.

Declaration of interests

All authors declare no competing interests.

Acknowledgments

This work was funded by the Health Innovation Challenge fund awarded to Dr O'Brien (Wellcome Trust and Department of Health and Social Care); HICF reference HICF-R8-439, WT grant number WT102568.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101924.

References

1 Dultz G, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther*. 2015;41(5):459–466.
2 Chavez-Tapia NC, Tellez-Avila FI, Garcia-Leiva J, Valdovinos MA. Use and overuse of proton pump inhibitors in cirrhotic patients. *Med Sci Monit*. 2008;14(9):CR468–C472.
3 Garcia-Saenz-de-Sicilia M, Sanchez-Avila F, Chavez-Tapia NC, et al. PPIs are not associated with a lower incidence of portal-hypertension-related bleeding in cirrhosis. *World J Gastroenterol*. 2010;16(46):5869–5873.
4 Deshpande A, Pasupuleti V, Thota P, et al. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol*. 2013;28(2):235–242.
5 Khan MA, Kamal S, Khan S, Lee WM, Howden CW. Systematic review and meta-analysis of the possible association between pharmacological gastric acid suppression and spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol*. 2015;27(11):1327–1336.
6 Xu HB, Wang HD, Li CH, et al. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. *Genet Mol Res*. 2015;14(3):7490–7501.
7 Yu T, Tang Y, Jiang L, Zheng Y, Xiong W, Lin L. Proton pump inhibitor therapy and its association with spontaneous bacterial peritonitis incidence and mortality: a meta-analysis. *Dig Liver Dis*. 2016;48(4):353–359.
8 Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301(20):2120–2128.
9 Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. *Arch Intern Med*. 2010;170(9):772–778.
10 Nardelli S, Gioia S, Ridola L, Farcomeni A, Merli M, Riggio O. Proton pump inhibitors are associated with minimal and overt hepatic encephalopathy and increased mortality in patients with cirrhosis. *Hepatology*. 2019;70(2):640–649.

11 Dam G, Vilstrup H, Watson H, Jepsen P. Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. *Hepatology*. 2016;64(4):1265–1272.
12 Tsai CF, Chen MH, Wang YP, et al. Proton pump inhibitors increase risk for hepatic encephalopathy in patients with cirrhosis in a population study. *Gastroenterology*. 2017;152(1):134–141.
13 Kuan YC, Huang KW, Lin CL, Luo JC, Kao CH. Short-term proton pump inhibitor use and hepatic encephalopathy risk in patients with decompensated cirrhosis. *J Clin Med*. 2019;8(8).
14 Alexopoulou A, Agiasotelli D, Vasilieva LE, Dourakis SP. Bacterial translocation markers in liver cirrhosis. *Ann Gastroenterol*. 2017;30(5):486–497.
15 de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF. Baveno VII - renewing consensus in portal hypertension. *J Hepatol*. 2022;76(4):959–974.
16 Goel GA, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. *Clin Gastroenterol Hepatol*. 2012;10(4):422–427.
17 Ratelle M, Perreault S, Villeneuve JP, Tremblay L. Association between proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Can J Gastroenterol Hepatol*. 2014;28(6):330–334.
18 Terg R, Casciato P, Garbe C, et al. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: a multicenter prospective study. *J Hepatol*. 2015;62(5):1056–1060.
19 Mandorfer M, Bota S, Schwabl P, et al. Proton pump inhibitor intake neither predisposes to spontaneous bacterial peritonitis or other infections nor increases mortality in patients with cirrhosis and ascites. *PLoS One*. 2014;9(11):e110503.
20 O'Leary JG, Reddy KR, Wong F, et al. Long-term use of antibiotics and proton pump inhibitors predict development of infections in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2015;13(4):753–759.e1-2.
21 Khan MA, Cholankeril G, Howden CW. Are proton pump inhibitors a threat for spontaneous bacterial peritonitis and hepatic encephalopathy in cirrhosis? Not so fast. *Hepatology*. 2017;65(1):393.
22 Moon AM, Hayashi PH, Barritt AS. Letter to the editor: proton pump inhibitors in cirrhosis: a marker of morbid conditions or a cause of mortality? *Hepatology*. 2019;70(2):761–762.
23 Khan MA, Cholankeril G, Howden CW. Proton pump inhibitors and the possible development of hepatic encephalopathy in cirrhotic patients: true association or residual confounding? *Gastroenterology*. 2017;152(8):2076.
24 China L, Freemantle N, Forrest E, et al. A randomised trial of albumin infusions in hospitalised patients with cirrhosis. *N Engl J Med*. 2021;384(9):808–817.
25 China L, Skene SS, Bennett K, et al. ATTIRE: albumin to prevenT Infection in chronic liveR failurE: study protocol for an interventional randomised controlled trial. *BMJ Open*. 2018;8(10):e023754.
26 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424.
27 Haukoos JS, Lewis RJ. The propensity score. *JAMA*. 2015;314(15):1637–1638.
28 China L, Becares N, Rhead C, Tittanegro T, Freemantle N, O'Brien A. Targeted albumin infusions do not improve systemic inflammation or cardiovascular function in decompensated cirrhosis. *Clin Transl Gastroenterol*. 2022;13(5):e00476.
29 Maini AA, Becares N, China L, et al. Monocyte dysfunction in decompensated cirrhosis is mediated by the prostaglandin E2-EP4 pathway. *JHEP Rep*. 2021;3(6).
30 European Association for the Study of the Liver. Electronic address eee, European association for the study of the L. EASL clinical practice guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022;77(3):807–824.
31 Tripathi D, Stanley AJ, Hayes PC, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*. 2015;64(11):1680–1704.
32 Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and risk factors for hepatic encephalopathy in a population-based cohort of Americans with cirrhosis. *Hepatol Commun*. 2019;3(11):1510–1519.
33 Tapper EB, Parikh ND, Sengupta N, et al. A risk score to predict the development of hepatic encephalopathy in a population-based cohort of patients with cirrhosis. *Hepatology*. 2018;68(4):1498–1507.
34 Miozzo SA, Tovo CV, John JA, de Mattos AA. Proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhosis: an undesirable association? *J Hepatol*. 2015;63(2):529–530.
35 Alhumaid S, Al Mutair A, Al Alawi Z, et al. Proton pump inhibitors use and risk of developing spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. *Gut Pathog*. 2021;13(1):17.
36 Ratuapli SK, Ellington TG, O'Neill MT, et al. Proton pump inhibitor therapy use does not predispose to small intestinal bacterial overgrowth. *Am J Gastroenterol*. 2012;107(5):730–735.
37 Garcia-Martinez I, Frances R, Zapater P, et al. Use of proton pump inhibitors decrease cellular oxidative burst in patients with decompensated cirrhosis. *J Gastroenterol Hepatol*. 2015;30(1):147–154.
38 Tittanegro T, China L, Forrest E, et al. Use of non-selective B-blockers is safe in hospitalised decompensated cirrhosis patients and exerts a potential anti-inflammatory effect: data from the ATTIRE trial. *eClinicalMedicine*. 2023;55:101716.
39 Mookerjee RP, Pavesi M, Thomsen KL, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol*. 2016;64(3):574–582.