

Proton pump inhibitor prescribing patterns in the United Kingdom: a primary care database study.

Running title: Proton pump inhibitor prescribing patterns in the UK

Authors:

Fatmah Othman, Timothy R Card, Colin J Crooks

Authors' affiliation: Division of Epidemiology and Public Health, The University of Nottingham

Corresponding Author

 Fatmah Othman

Division of Epidemiology and Public Health, The University of Nottingham, Clinical Sciences Building 2, Nottingham City Hospital, NG5 1PB, UK

msxfo1@nottingham.ac.uk

t: +44 (0) 115 8231376

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KEY POINTS:

- The prevalence of PPI use in the UK general population is high and still increasing.
- The majority of patients only use PPIs short term, with only 26% using them long-term.
- Clear attempts to step down long-term use were identified in two fifths of the patients, so there remain further opportunities for reducing the cost and side effects of PPI use through improving adherence to recommended withdrawal strategies.

COMPETING INTERESTS:

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1 **Abstract:**

2 **Purpose:** To determine the prevalence and pattern of proton pump inhibitor (PPI)
3 prescription, and the practices employed to reduce PPI use in the UK general population.

4 **Method:** The UK's Clinical Practice Research Database was used to identify individuals who
5 were issued with ≥ 1 PPI prescription during the period 1990-2014. Point and period
6 prevalence of PPI use were estimated annually. Additionally, new users of PPI therapy who
7 had five years of follow-up data were included in a cohort analysis to describe patterns of
8 cessation and duration of PPI use.

9 **Results:** Both the period and point prevalence of PPI use increased between 1990 and 2014
10 (period prevalence increased from 0.2% to 15.0% and point from 0.03 % to 7.7%). A total of
11 596,334 new users of PPI therapy in the cohort study received 8,784,272 prescriptions. Of
12 these, 26.7% used PPI therapy long-term (≥ 1 year continuously) while 3.9% remained on PPI
13 therapy for five years. Clear attempts to step down dose were identified in 39.9% of long-
14 term users while this was 47% in patients whose initial indication did not mandate long-term
15 use.

16 **Conclusion:** A considerable increase in PPI use was observed in UK general practice. 60% of
17 long-term PPI users did not have an attempt to discontinue or step down. Considerable
18 opportunities may therefore exist to reduce the cost and side effects of PPI use through
19 improving adherence to recommended withdrawal strategies.

20 INTRODUCTION

21 The introduction of proton pump inhibitors (PPIs) has revolutionised the management of
22 acid-related gastrointestinal disorders¹. In the United Kingdom (UK), 11,126 thousand
23 prescriptions for PPIs were dispensed in 2000², and this increased to 43,127 thousand in
24 2011³. Although the expenditure on PPIs has decreased in the UK since 2006 as a result of
25 government efforts to encourage the use of low-cost generic PPIs^{4,5}, there has still been an
26 overall increase in the total number of PPI prescriptions dispensed⁴. For instance, in 2010,
27 PPIs became one of the top 20 drugs with the greatest net ingredient cost in the UK⁴.

28 The importance of reducing any overuse of PPIs is not limited to the associated costs, but
29 also to the risks of taking the drugs on a long-term basis⁶. As PPIs have become commonly
30 used for long-term maintenance, concerns have been raised about the safety of such use⁶.
31 Studies have showed that PPI use is associated with malabsorption of vitamins and
32 minerals^{7,8}, an increased risk of infections, such as pneumonia⁹ and enteric infection¹⁰, and
33 an increased fracture risk^{11,12}. These potential side effects can be minimized through
34 appropriate prescription practices in terms of stepping down the dose or stopping long-term
35 treatment altogether.

36 As a consequence of this dramatic increase in PPI use and the associated potential risks,
37 clinical guidelines in the UK have recommended rationing the use of the PPI in the primary
38 care setting, either by stepping down the dose or stopping treatment all together¹³.
39 However, very few research studies have examined the extent to which the clinical guidelines
40 are being followed in the UK¹⁴⁻¹⁹. The aim of this study was to determine the prevalence of
41 PPI use and assess the practices employed to reduce PPI use in the general UK population. It

42 is anticipated that research of this nature will help to inform future attempts to moderate the
43 use of PPIs.

44 METHODS

45 Study type and data source

46 We conducted an observational study with repeated cross-sectional analyses to estimate the
47 prevalence of PPI use annually and a cohort design to describe the patterns of PPI utilization
48 by using data from the UK Clinical Practice Research Datalink (CPRD)²⁰. CPRD is a large
49 database drawn from the computerised records of primary care practices throughout the UK
50 and encompassing a representative sample of around 6% of UK population²¹⁻²³. The CPRD
51 comprises data about patients' medical diagnoses, GPs' prescriptions, investigations, hospital
52 referrals and discharges, together with basic demographic information. The information on
53 prescriptions includes their issue dates, the drug prescribed, numeric daily dose, daily
54 quantity and the number of packs/pack size prescribed. Many studies have validated CPRD
55 for use in pharmacoepidemiological research^{21,24}.

56 Study population

57 We studied adult patients with at least one month of prospective records after either the
58 date of their current registration or the date after the practice became "up to standard"
59 (UTS) on CPRD²¹ whichever was the latest, and an "acceptable" registration status as defined
60 by CPRD²¹ between 1st Jan 1990 and 31st December 2014. This population formed our
61 denominator for studies of prevalence. Patients who received ≥ 1 PPI prescription (BNF 1.3.5
62 ²⁵) were classified as exposed subjects in the study (i.e. the numerator).

63 Prescription duration

64 The earliest PPI prescription for each patient was considered their index date. Prescription
65 duration was taken as the number of treatment days recorded by the GP, or calculated from
66 the prescribed quantity and numeric daily dose prescribed. If information on both was

67 missing, the individual median duration was imputed. The duration was recalculated if the
68 calculated prescription duration was less than or equal to seven days assuming that the
69 prescription quantity was referring to the number of individual product packs prescribed.

70 **Prescribing patterns**

71 To describe the prescribing practices of long-term PPI use in general practice in term of
72 discontinuation, stepping down or switching to histamine 2 receptor antagonists (H2RA), we
73 identified new PPI therapy users i.e. patients with at least 12 months of registration on CPRD
74 prior to their index date who had ≥ 5 years of prospective follow-up data. We

75 The NICE guidelines¹³ were used to determine what constitutes expected long-term PPI
76 use within this study. PPIs are used for the short-term management in conditions such as
77 dyspepsia, gastro-oesophageal reflux disease (GORD), and gastric and duodenal ulcers. Long-
78 term PPI therapy is often prescribed to prevent recurrence of GORD complications, and as
79 prophylactic therapy to prevent peptic ulcers in patients who are co-prescribed non-steroidal
80 anti-inflammatory (NSAID) therapy¹³.

81 Exposure to PPIs was considered to begin on the date of a prescription for them and end
82 after its calculated duration unless another prescription was issued ≤ 30 days after this date in
83 which case we considered exposure continuous. We refer to one set of continuous
84 prescriptions as one course. Courses were classified as short (< 12 months) or long (≥ 12
85 months), this time period being chosen as 12 months is the minimum frequency with which
86 NICE recommends that these prescriptions should be reviewed and stopped or stepped down
87 if possible. Individuals receiving exclusively short courses were classified as short-term users
88 while individuals who received at least one long course were classified as long-term users
89 even if their records contained other short courses.

90 Discontinuation (no subsequent PPI prescription issued within 30 days after the end of
91 the previous one) was categorized as temporary (patients subsequently re-prescribed PPI) or
92 permanent (no further prescriptions received up to the end of the patient's follow-up). A step
93 down of PPI therapy was defined as a reduction in daily dose of the subsequent PPI
94 prescription. If a following prescription was for a different PPI, the dose was converted to an
95 equivalent dose based on the recommended dosing in the BNF²⁵. A successful step down
96 was defined as maintaining the stepped down dose for 12 months from the step down date.
97 Lastly, a switch to H2RA medication was defined as receiving H2RA prescription within one
98 month before or after discontinuation or stepping down attempt.

99 **Covariates**

100 We abstracted data on patients' age at the index date (in 10-year age bands), gender, and
101 socioeconomic status (derived through linking CPRD to the Index of Multiple Deprivation
102 (IMD) 2007). For each course, the potential indications as specified in the BNF²⁵ were
103 identified by the presence of relevant Read codes on the first prescription date of a course,
104 or within 30 days before and 12 month after that date. We considered prevention and
105 treatment of NSAID-associated ulcer the indication if NSAID prescription date fell on the
106 same date as the PPI prescription. Potential indications were then classified into 8 categories
107 (supplementary Table1) and missing initial indication was recorded in a separate category.

108 **Statistical analysis**

109 *Prevalence of PPI use*

110 For each year we calculated the period prevalence by dividing the number of patients who
111 received at least one PPI prescription during that year by the corresponding mid-year adult
112 population of the CPRD. We also calculated annual point prevalence as the number of

113 patients with an ongoing PPI prescription on 30th June divided by the corresponding mid-
114 year population. We stratified these prevalence estimates by gender and age (calculated on
115 June 30th and grouped into 10 years age bands).

116 *Patterns of PPI use*

117 The baseline patient characteristics and the use of PPIs among new users were described as
118 proportions of age bands, genders and quintiles of IMD (to represent socioeconomic status).
119 We calculated the percentage of patients who continued their first PPI course, from the index
120 date to the end of five years of follow-up during the study period.

121 Kaplan Meier survival curves were constructed among all new PPI patients to
122 graphically describe: 1) time to discontinuation (permanent or temporary) of the first PPI
123 course during the five years follow-up, 2) time to permanent discontinuation of all PPI
124 therapy during the five years follow-up. Time to discontinuation of the first PPI course was
125 calculated from the index date to the first PPI course's end date. Time to permanent
126 discontinuation was calculated from the index date to the end date of the last PPI course that
127 each patient received during the follow-up period.

128 The proportions of patients, who stepped down, or substituted PPIs, were calculated
129 for long-term users as NICE guidelines¹³ recommends reviewing long-term PPI user on an
130 annual basis at a minimum. To determine successful step down attempts accurately patients
131 were required to have a 12 month window after the step down date. The analysis of
132 successful step down attempts was therefore limited to patients who had stepdown
133 attempts within the first 4 years of the follow-up to allow adequate follow up within the final
134 year of the cohort. We repeated this analysis restricted to patients who started PPI therapy
135 as long-term and whose indication might not suggest an ongoing need for long-term PPI use,

136 therefore patients with recorded indication of complicated GORD, NSAID-associated ulcers
137 prophylaxis or reducing the degradation of pancreatic enzyme supplements were excluded.

138 Analyses were performed using STATA 12 (Stata Corp, College Station, Texas).

139 RESULTS

140 Prevalence of prescribing

141 We identified 31,956,396 PPI prescriptions in 1,828,141 adult patients during the study
142 period. The point and period prevalence of PPI increased between 1990 and 2014 (Figure 1-
143 a) and it varied substantially by age group (Figure 1-b). The point prevalence of PPI use was
144 similar between males and females, increasing during the study period from 0.04% in 1990 to
145 7.05% in 2014 in males, and from 0.03% in 1990 to 8.35% in 2014 in females. The female to
146 male prevalence ratio of PPI use was 1.14 (95% confidence intervals (CI) 1.12-1.17) from
147 1990 to 2014.

148 Prescribing patterns

149 During the study period, 596,334 new users of PPI therapy with at least five years of follow-
150 up data were identified. Their mean age was 54.2 years (Standard Deviation SD: 16.3) and
151 55% were females. They received a total of 8,784,272 prescriptions and 26.5% had one PPI
152 prescription recorded. The median duration for all PPI prescriptions was 28 days
153 (interquartile range (IQR) 18-56 days).

154 Individual prescriptions were combined to create 1,708,513 PPI courses. The median
155 duration of all courses was 55 days (IQR 28-125 days) and there were a median of 2 courses
156 per patient (IQR 1-4 courses). Patients received prescriptions for enough PPI to cover 96.69%
157 (95%CI 96.68-96.71) of days in these courses.

158 1,505,758 (88.1%) of the courses were categorised as short courses and 202,755(11.8%)
159 were categorised as long courses with median durations of 28 days (IQR 28-79 days) and 805
160 days (IQR 526-1345 days) for short and long courses respectively. 73.2% of the cohort
161 received exclusively short courses with a mean age of 51.6years (SD 16.3 years), and 26.7%

162 received at least one long course with a mean age of 61.2years (SD 14.3 years)(Table 1).
163 Within this cohort, 230,766 patients (38.7%) had only one PPI course, and 365,568 (61.3%)
164 patients had multiple courses. Around 16.3% and 11.4% of patients remained continuously
165 on PPI therapy for 6 and 12 months from their index date, respectively. At the end of 5 years
166 of follow-up, 23,607 (3.9%) patients had remained on PPI continuously from the index date.

167 **Prescription indications**

168 Initially, 365,481 PPI courses (21.3%) had no coded indication for PPI prescription. This fell to
169 14.0% after assuming prescriptions concurrent with NSAID prescriptions were intended for
170 gastro-protection. Dyspepsia was the most frequent recorded indication (Table2).

171 **Discontinuation, step-down, and substitution**

172 Figure 2 shows the proportion of patients who discontinued the first PPI course (Figure 2-A),
173 and patients who permanently discontinued all PPI courses (Figure 2-B). When considering
174 only long-term PPI patients, 25% had temporarily discontinued their therapy at one year and
175 three months after starting their long-term PPI course, 50% at one year and seven months
176 and by two years and three months 75% had temporarily discontinued their long term PPI
177 course. Of those discontinuing, 9,557 (9%) received a prescription for H2RA within one
178 month before or after this occurred.

179 Of the 159,259 patients who received long term PPIs, 63,640 (39.9%) had an attempt to
180 step down their PPI dose (Table3). Of these 6,388 (10%) had received an H2RA prescription
181 within one month before or after stepping down PPI dose.

182 Of 59,734 patients in whom the initial indication for PPI prescription did not suggest a
183 recognised need for PPI use to be prolonged, un-complicated GORD was the most frequent

184 recorded indication and 39,164 (65.5%) discontinued PPI therapy (temporarily or
185 permanently). For those patients who temporarily discontinued their PPI therapy the median
186 time to this was 3 years and 3 months after starting their PPI course. In those using PPI long
187 term without recognised indication for such use a step down attempt was identified in 47%
188 (Table4).

189 DISCUSSION

190 Summary

191 This study describes the pattern of PPI prescription in UK general practice in terms of its
192 prevalence and the practices employed to reduce long-term use. The proportion of the
193 population using PPIs within each year increased from 0.2% in 1990 to 15.0% in 2014. Of
194 those new PPI users who had five years of follow up available, 26.7% used PPI therapy for
195 more than one year, and 3.9% remained on PPI therapy for five full years. Clear attempts to
196 step down long-term use were identified in about 39%, and 8.7% of long-term users received
197 a H2RA prescription around the time they attempted to step down and/or discontinue their
198 use of PPI. Amongst patients whose initial PPI prescription indication did not necessarily
199 warrant long term PPI use, 47% had attempts to step down their PPI dose.

200 Comparison with previous work

201 Our findings pertaining to the prevalence of PPI use in the early years of our study were
202 consistent with the findings of earlier studies involving general practice in the UK^{14,16,18,26} in
203 addition, our result revealed that the use of PPI has continued to rise. These trends are not
204 limited to the UK: similar increases in prescription rates have been observed in the United
205 States²⁷, Australia²⁸, and many European countries. This widespread increase supports the
206 evidence that PPI prescriptions remain highly prevalent in many healthcare systems despite
207 the extensive literature that indicates overprescribing PPI in both the primary and secondary
208 care setting^{29,30}.

209 In this study, the proportion of patients who were on long-term PPI (26%) was higher
210 than that reported in previous studies¹⁶⁻¹⁸, which have reported rates of long-term PPI usage
211 between 0.05% and 4.4%, according to varying definitions of long-term use. Studies have

212 shown that repeat prescription practices account for approximately 32 to 81% of the total
213 cost of prescribed drugs³¹. The continuous increase in PPI use, specifically the increase in the
214 proportion of long-term users, may therefore have important cost implications despite the
215 availability of low-cost PPI.

216 PPIs provide effective symptomatic relief for patients who suffer from dyspepsia
217 symptoms. However, while clinical guidelines suggest the use of PPI therapy over short
218 durations to treat dyspepsia symptoms¹³, it seems that PPIs had been prescribed as a form
219 of maintenance therapy without specific underlying cause. Our study revealed that dyspepsia
220 symptoms were the initial indication in 23% of long-term PPI courses. However, as most
221 patients on first presentation in primary care will not have a final endoscopic diagnosis, it is
222 inevitable that the GPs will have recorded less-specific indications in subjects who had other
223 underlying diagnoses. Our results concur with those of several studies that have reported
224 that the majority of patients on PPI therapy are prescribed PPI for the purpose of relieving
225 symptoms without any other clear indications^{32,33}. In addition, although its clinical relevance
226 is unproven, it has been proposed that rebound acid hypersecretion following PPI therapy
227 withdrawal may help perpetuate the use of PPIs in patients with uncertain indications or who
228 have received them for symptomatic relief of relatively mild symptoms for more than six
229 weeks³⁴. The issue of appropriateness in terms of prescription practices has been discussed
230 in existing literature^{29,35,36}. Despite this, PPIs are still being administered to patients for a
231 variety of complaints that are not known to be acid-induced and over a long-term basis.

232 In the view of the emerging concerns regarding adverse events from long-term PPI
233 use, clinical guidelines¹³ have encouraged GPs to use PPIs carefully and to continually review
234 long-term patients to try to step down or stop treatment. Our results suggest that GPs are

235 actively attempting to reduce PPI use by stepping down and substituting alternative
236 medication. Previous studies^{36–39} reported discontinuation rates that differed from those
237 identified in our study; however, these can be explained by variations in the study population
238 and the discontinuation strategies employed³⁸. Reports regarding the outcomes of step-
239 down therapy have been conflicting^{40,41}. For example, one study reported that more than
240 half of the patients involved in the study remained asymptomatic after the step down⁴¹ while
241 another reported that 19% of patients whose PPI therapy was stepped down experienced
242 relapsed symptoms and resumed PPI use⁴⁰. In our study, 60% of the long-term PPI users
243 maintained lower doses for more than one year. However, while we identified an appreciable
244 proportion of long-term PPI users who could potentially reduce the use of the drug, we were
245 unable to find evidence of such attempts in a large proportion of those individuals. Non-
246 adherence to the step down therapy, therefore, allows the maintenance of inappropriate PPI
247 prescription which may sustains overuse of PPIs.

248 **Strengths and limitations**

249 Our study used data from a large database of UK primary care records which has been
250 extensively used and validated for pharmacoepidemiological research^{21,24}. The population in
251 our study is therefore representative of the general practice population of the UK to whom
252 our results should be generalizable²¹. The large sample size has allowed us to stratify our
253 analyses by age groups and gender, and to show trends in PPI use over time. It has also
254 provided us with adequate power to identify the relatively small proportion of patients who
255 took PPIs on a long-term basis and describe the management of their prescriptions.

256 Weaknesses in our study include that we may have underestimated PPI use since neither
257 hospital prescriptions nor over the counter (OTC) use are captured in the data. However,

258 since secondary care initiated PPI treatment will often be continued by GPs afterwards³⁵, and
259 prescribed PPI use continued to rise after they became available OTC ⁴² we think it unlikely
260 that this has led to massive underestimation. Additionally, we focused on long-term users
261 who would be the most likely to obtain their prescriptions from their GPs. Furthermore, the
262 period of PPI exposure for those who took PPI intermittently may have been underestimated,
263 since the calculation of the prescription duration was based on the assumption that the
264 dispensed prescription was consumed as directed. Indeed, CPRD only contains information
265 about the prescriptions of medications; as such, it is not possible to assess whether patients
266 actually collected or consumed the prescribed medication. In addition, our definition of a
267 successful stepdown may underestimate the proportion of patients whose long-term PPI
268 therapy was stepped down but then required a smaller increase in dose lower than the initial
269 dose. However, including this in our definition only identified an additional 997 patients (an
270 additional 1.5% of attempted step downs) so for clarity we retained our initial stricter
271 definition. Furthermore, our method of estimating successful step down attempts within the
272 initial 4 years of follow-up would not have led to a substantial underestimation, as it is
273 expected that long-term patients should have been offered a step down attempt at least
274 within the first year of their continuous use of PPI therapy.

275 **CONCLUSION:**

276 During the study period, a considerable increase in the administration of PPI prescriptions
277 was observed in UK general practice. The majority of patients use PPIs on a short-term basis
278 with 26% of the identified use long term. Our results suggest that GPs are actively attempting
279 to decrease the use of PPI by stepping down and discontinuing prescriptions; however, this is
280 not universally practised, nor is it always successful when attempted. If the cost and potential
281 risks of the continuing increase of PPI are to be minimised, a proactive clinical review and
282 adherence to the guidelines is likely to be required.

Ethical approval:

This study was approved by the Independent Scientific Advisory Committee (ISAC) with CPRD number 13_214, and 13-214Mn.

CONTRIBUTORS:

TC & CC supervised FO in conducting this study .TC proposed the original idea. All authors were involved in the study design and concept, and interpretation of results. FO analysed the data set and wrote the initial manuscript draft. TC &CC critically reviewed and edited the drafts of the manuscript. All authors approved the submitted final version. All authors had full access to all of the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

References:

1. Robinson M. Review article: the pharmacodynamics and pharmacokinetics of proton pump inhibitors--overview and clinical implications. *Aliment Pharmacol Ther* 2004; **20 Suppl 6**: 1–10.
2. Department of Health. *Prescription Cost Analysis: England 2000*. London, 2000.
3. Health and Social Care Information Centre, Prescribing and Primary Care Services. *Prescription Cost Analysis England 2011*. London, 2012.
4. The NHS Information Centre, Prescribing and Primary Care Services. *Prescriptions Dispensed in the Community: England, Statistics for 2000 to 2010*. London, 2011.
5. Cahir C, Fahey T, Tilson L, Teljeur C, Bennett K. Proton pump inhibitors: potential cost reductions by applying prescribing guidelines. *BMC Health Serv Res* 2012; **12**: 408.
6. Chen J, Yuan YC, Leontiadis GI, Howden CW. Recent safety concerns with proton pump inhibitors. *J Clin Gastroenterol* 2012; **46**: 93–114.
7. Joel J. Heidelbaugh, Kathleen L. Goldberg JMI. Adverse Risks Associated With Proton Pump Inhibitors: A Systematic Review. *Gastroenterol Hepatol (N Y)* 2009; **5**: 725.
8. Zipursky J, Macdonald EM, Hollands S, *et al*. Proton pump inhibitors and hospitalization with hypomagnesemia: a population-based case-control study. *PLoS Med* 2014; **11**: e1001736.
9. Eom C-S, Jeon CY, Lim J-W, Cho E-G, Park SM, Lee K-S. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011; **183**: 310–9.
10. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011; **34**: 1269–81.
11. Yang Y-X, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296**: 2947–53. doi:10.1001/jama.296.24.2947.
12. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton Pump Inhibitors and Risk of Fractures: A Meta-Analysis of 11 International Studies. *Am J Med* 2011; **124**: 519–526.
13. National Institute for Clinical Excellence. NICE. *Dyspepsia and gastro-oesophageal reflux disease Investigation and management of dyspepsia, NICE clinical guideline 184.*, 2014.
14. Bashford JNR, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. *BMJ* 1998; **317**: 452–456.
15. Martin RM, Lim AG, Kerry SM, Hilton SR. Trends in prescribing H2-receptor antagonists and proton pump inhibitors in primary care. *Aliment Pharmacol Ther* 1998; **12**: 797–805.
16. Hungin A, Rubin G, O’Flanagan H. Long-term prescribing of proton pump inhibitors in general practice. *Br J Gen Pract* 1999: 451–453.
17. Raghunath AS, O’Morain C, McLoughlin RC. Review article: the long-term use of

- proton-pump inhibitors. *Aliment Pharmacol Ther* 2005; **22 Suppl 1**: 55–63. doi:10.1111/j.1365-2036.2005.02611.x.
18. Ryder SD, O'Reilly S, Miller RJ, Ross J, Jacyna MR, Levi AJ. Long term acid suppressing treatment in general practice. *BMJ* 1994; **308**: 827–30.
 19. Prach A, McGilchrist M, Murray F, Johnston D, MacDonald T. Prescription of acid-suppressing drugs in relation to endoscopic diagnosis: a record-linkage study. *Aliment Pharmacol Ther* 1999: 397–405.
 20. The Clinical Practice Research Datalink. Available at: www.cprd.com. Accessed June 25, 2015.
 21. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. *Ther Adv Drug Saf* 2012; **3**: 89–99. doi:10.1177/2042098611435911.
 22. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: A systematic review. *Br J Clin Pharmacol* 2010; **69**: 4–14. doi:10.1111/j.1365-2125.2009.03537.x.
 23. Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**: 827–836.
 24. Jick SS, Kaye JA, Vasilakis-Scaramozza C, *et al*. Validity of the General Practice Research Database. *Pharmacotherapy* 2003; **23**: 686–689.
 25. BNF. 1.3.5 Proton pump inhibitors: British National Formulary. Available at: <https://www.medicinescomplete.com/mc/bnf/current/PHP431-proton-pump-inhibitors.htm>. Accessed September 11, 2014.
 26. Jick H, Wilson A, Wiggins P, Chamberlain DP. Comparison of prescription drug costs in the United States and the United Kingdom, part 2: proton pump inhibitors. *Pharmacotherapy* 2012; **32**: 489–92.
 27. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting, 2002–2009. *PLoS One* 2013; **8**: e56060.
 28. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. *Pharmacoepidemiol Drug Saf* 2010; **19**: 1019–24.
 29. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008; **336**: 2–3.
 30. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012; **5**: 219–32.
 31. De Smet PAGM, Dautzenberg M. Repeat Prescribing. *Drugs* 2004; **64**: 1779–1800.
 32. Van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MCJM, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. *Aliment Pharmacol Ther* 2006; **24**: 377–85. doi:10.1111/j.1365-2036.2006.02982.x.
 33. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. *Br J Clin Pharmacol* 2009; **68**: 936–47.

34. Lødrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scand J Gastroenterol* 2013.
35. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot J-F. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. *Int J Clin Pract* 2012; **66**: 767–773.
36. Björnsson E, Abrahamsson H, Simrén M, *et al.* Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; **24**: 945–54. doi:10.1111/j.1365-2036.2006.03084.x.
37. Jonasson C, Tvette IF, Hatlebakk JG. Patterns of proton pump inhibitor utilization in gastroesophageal reflux disease and the effect of restrictions on reimbursement: a nationwide prescription database study. *Scand J Gastroenterol* 2013; **48**: 1010–7. doi:10.3109/00365521.2013.812140.
38. Haastrup P, Paulsen MS, Begtrup LM, Hansen JM, Jarbøl DE. Strategies for discontinuation of proton pump inhibitors: a systematic review. *Fam Pract* 2014; **31**: 625–30.
39. Gadzhanova S V., Roughead EE, Mackson JM. Initiation and duration of proton pump inhibitors in the Australian veteran population. *Intern Med J* 2012; **42**. doi:10.1111/j.1445-5994.2010.02259.x.
40. Ramser KL, Sprabery LR, Hamann GL, George CM, Will A. Results of an intervention in an academic Internal Medicine Clinic to continue, step-down, or discontinue proton pump inhibitor therapy related to a tennessee medicaid formulary change. *J Manag Care Pharm* 2009; **15**: 344–50.
41. Inadomi JM, Jamal R, Murata GH, *et al.* Step-down management of gastroesophageal reflux disease. *Gastroenterology* 2001; **121**: 1095–1100.
42. MHRA. Medicines & Healthcare products Regulatory Agency. Available at: <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>. Accessed November 4, 2014.

Tables and figures:

Table 1: Descriptive characteristics of new users of proton pump inhibitor (PPI) therapy with ≥ 5 years of follow-up data(patients with exclusively short-term courses and patients with at least one long-term course), and the duration (in days) for the first short and long courses.

Patients characteristics	Total number		Patients with exclusively short course		Duration of first short course Median(IQR)	Patients with at least one long course in their records		Duration of first long course Median(IQR)
	N=596,334		N=437,075			N=159,259		
		%	Number	%		Number	%	
Age								
18-30	50,318	8.4	46,683	92.7	28(28-28)	3,635	7.2	705(484-1172)
31-40	83,579	14.1	72,475	86.7	28(28-49)	11,104	13.2	769(502-1314)
41-50	113,746	19.1	91,721	80.6	28(28-56)	22,025	19.3	816(524-1403)
51-60	120,553	20.3	86,466	71.7	28(28-56)	34,087	28.2	876(544-1491)
61-70	115,470	19.4	73,854	63.9	28(28-56)	41,616	36.0	935(568-1568)
71-80	80,968	13.6	48,034	59.3	28(28-56)	32,934	40.6	978(582-1610)
>80	27,997	4.7	15,216	54.3	28(28-59)	12,781	45.6	1014(592-1656)
Gender								
Male	262,765	44.0	190,947	72.6	28(28-56)	71,818	27.3	920(559-1556)
Female	333,569	55.9	246,128	73.7	28(28-56)	87,441	26.2	882(546-1496)
Index of Multiple Deprivation** (quintiles)								
Unavailable	263,562	44.2	191,426	72.6	28(28-56)	72,136	27.3	905(553-1530)
1(least deprived)	75,711	12.7	57,276	75.6	28(28-56)	18,435	24.3	865(538-1467)
2	78,619	13.1	57,893	73.6	28(28-56)	20,726	26.3	894(550-1512)
3	66,880	11.2	48,987	73.2	28(28-56)	17,893	26.7	905(555-1532)
4	64,654	10.8	47,256	73.0	28(28-56)	17,398	26.9	914(561-1535)
5(most deprived)	46,908	7.8	34,237	72.9	28(28-53)	12,671	27.0	908(557-1574)

IQR=interquartile range

** Socioeconomic status is based on Index of multiple deprivations (IMD) and figures are percent of the people who have available deprivation status

Table 2: Recorded indication for all proton pump inhibitor(PPI)courses(all short courses in exclusively short-term PPI users and all long courses in patients with at least one long-term PPI course).

Indication category	Total number N=596,334		Patient with exclusively short courses N=437,075		Patients who had at least one long-term course N=159,259	
	All PPI courses 1,708,513	%*	Short PPI courses 1,158,705	%*	Long PPI courses 202,755	%*
Dyspepsia	612,842	35.8	452,651	39.0	47,086	23.2
un-complicated GORD	495,288	28.9	309,204	26.6	70,485	34.7
NSAID prophylaxis	132,426	7.7	90,380	7.8	17,926	8.8
Gastritis & duodenitis	125,300	7.3	73,089	6.3	23,037	11.3
peptic ulcer below oesophagus	51,137	2.9	27,871	2.4	10,356	5.1
Helicobacter therapy	24,466	1.4	18,755	1.6	1,581	0.7
GORD complicated	13,146	0.7	5,464	0.4	2,935	1.4
Reduction of pancreatic enzyme degradation	3,450	0.2	1,924	0.1	560	0.2
missing	250,458	14.0	179,367	15.4	28,789	14.2

* column percentage; GORD= Gastro-oesophageal reflux disease; NSAID nonsteroidal anti-inflammatory drugs

Table 3: Numbers and percentages of long-term proton pump inhibitor (PPI) users who attempted a step down in dose, were successful at 12 months, and were prescribed histamin2 receptor antagonists (H2RA) by age, time, and indication.

	Patients with at least one long PPI course	Number of patients who had step down to lower PPI dose		Number of patients who maintained lower dose after step down attempt for 12 months**		Number of patients who received H2RA substitution at time of step down and /or discontinuation	
		Number	%*	Number	%	Number	%*
	159,259	63,640	39.9	36,006	60.5	13,954	8.7
Age group							
18-30	3,632	1,559	42.9	695	47.7	315	8.6
31-40	11,095	4,774	43.0	2,344	52.5	910	8.2
41-50	22,001	9,127	41.4	4,720	55.5	1,568	7.1
51-60	34,040	14,037	41.2	7,777	59.5	2,611	7.6
61-70	42,822	17,205	40.2	9,892	61.5	4,042	9.4
71-80	32,917	12,503	37.9	7,766	66.3	3,271	9.9
>80	12,752	4,435	34.7	2,812	67.9	1,237	9.7
Time when GP attempt to step down							
2 month		25,240	39.6	18,536	73.5	3,986	15.7
6 month		14,414	22.6	8,152	57.7	1,722	11.9
12 month		9,171	14.4	3,819	45.7	6,295	6.0
More than 12 month		14,815	23.2	5,474	46.8	1,951	13.1
Indication							
GORD un-complicated	55,450	26,402	47.6	14,674	59.2	6,125	11.0
Dyspepsia	37,011	14,897	40.2	8,802	63.2	3,203	8.6
Gastritis & duodenitis	18,383	7,889	42.9	3,656	50.3	1,968	10.7
NSAID prophylaxis	13,695	3,591	26.2	2,575	75.9	537	3.9
peptic ulcer below oesophagus	8,188	3,838	46.8	2,306	63.6	780	9.5
GORD complicated	2,209	675	30.5	380	60.8	124	5.6
Helicobacter therapy	1,257	444	35.3	238	57.0	99	7.8
Reduction of pancreatic enzyme degradation	416	129	31.0	59	48.7	28	6.7
missing	22,650	5,775	25.5	3,316	62.2	1,090	4.8

GORD=Gastro-oesophageal reflux disease; NSAID= non-steroidal anti-inflammatory drugs
H2RA=Histamine 2 Receptor antagonist

*percentages were calculated from the total number of long-PPI patients

** percentages were calculated from the number of step down patients who stepped down within the first 4 years of follow-up and successfully stepped down for 12 months(number of patients (59,458))

Table 4 : Numbers and percentages of long-term proton pump inhibitor (PPI) users who attempted a step down in dose, were successful at 12 months, and were prescribed histamin2 receptor antagonists (H2RA) by age, time, and indication. Analysis restricted to indications unsuitable for step down.

	Patients with at least one long proton pump inhibitor course	Number of patients who had step down to lower PPI dose		Number of patients who maintained lower dose after step down attempt for 12 months**		Number of patients who received H2RA substitution at time of step down and /or discontinuation	
		Number	%*	Number	%	Number	%*
	59,734	28,113	47.0	16,907	61.5	5,567	9.3
Age group							
18-30	1,075	569	52.9	282	50.2	105	9.7
31-40	3,586	1,912	53.3	969	51.4	299	8.3
41-50	7,648	3,783	49.4	2,110	56.8	593	7.7
51-60	12,417	6,063	48.8	3,519	59.2	1,003	8.0
61-70	16,347	7,675	46.9	4,679	62.4	1,603	9.8
71-80	13,254	5,902	44.5	3,870	67.4	1,413	10.6
>80	5,407	2,209	40.8	1,478	69.0	551	10.1
Time when GP attempt to step-down							
2 month		11,602	41.2	8,323	71.7	2,019	17.4
6 month		6,922	24.6	4,157	60.0	2,339	6.0
12 month		3,407	12.1	1,683	49.4	433	12.7
More than 12 month		6,182	21.9	2,744	49.5	776	12.5
Indication							
GORD un-complicated	22,173	12,290	55.4	7,290	60.4	2,524	11.3
Dyspepsia	13,686	6,426	46.9	4,116	65.5	1,268	9.2
Gastritis & duodenitis	7,761	3,731	48.0	1,948	53.5	791	10.1
peptic ulcer below oesophagus	4,126	2,101	50.9	1,343	65.4	396	9.6
Helicobacter therapy	402	192	47.0	111	59.0	35	8.7
missing	11,586	3,373	29.1	2,099	64.5	553	4.7

GORD=Gastro-oesophageal reflux disease; H2RA=Histamine 2 Receptor antagonist

* percentages were calculated from the total number of long-PPI patients

** percentages were calculated from the number of step down patients who stepped down within the first 4 years of follow-up and successfully stepped down for 12 months(number of patients (27,473))