

# **Characterising potentially inappropriate prescribing of proton pump inhibitors in older people in primary care in Ireland from 1997 to 2012**

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## **Abstract**

**Background/objectives:** Concerns have been raised regarding overprescribing of proton pump inhibitors (PPIs). This study characterises prescribing of PPIs and medicines which increase gastrointestinal bleeding risk (ulcerogenic) in older people from 1997 to 2012 and assesses factors associated with maximal-dose prescribing in long-term PPI users.

**Design:** Repeated cross-sectional study of pharmacy claims data.

**Setting:** Eastern Health Board region of Ireland.

**Participants:** Individuals aged  $\geq 65$  from a means-tested scheme in 1997, 2002, 2007, and 2012 (range 78,489-133,884 individuals).

**Measurements:** PPI prescribing prevalence was determined per study year, categorised by duration ( $\leq$  or  $>8$  weeks), dosage (maximal or maintenance) and co-prescribed drugs.

Logistic regression in long-term PPI users determined if age, gender, polypharmacy and ulcerogenic medicines use were associated with being prescribed a maximal dose rather than a maintenance dose. Adjusted odds ratios (OR) with 95% confidence intervals (CI) are presented.

**Results:** Half of this older aged population received a PPI in 2007 and 2012. Long-term use ( $>8$  weeks) of maximal doses rose from 0.8% of individuals in 1997 to 23.6% in 2012. While some ulcerogenic medicines and polypharmacy were significantly associated with maximal PPI doses, any NSAID use was significantly associated with lower odds of maximal PPI dose (adjusted OR 0.85, 95%CI 0.81-0.88), as were aspirin use and increasing age. Adjusting for medication and demographic factors, odds of being prescribed a maximal PPI dose were significantly higher in 2012 compared to 1997 (adjusted OR 6.3, 95%CI 5.76-6.88).

**Conclusions:** Long-term maximal dose PPI prescribing is highly prevalent in older populations and is not consistently associated with gastrointestinal bleeding risk factors. Interventions involving prescribers and patients may promote appropriate PPI use, reducing costs and adverse effects of PPI overprescribing.

## Introduction

Proton pump inhibitors (PPIs) were first marketed in the late 1980's and since this time, the volume prescribed has surpassed other acid-suppressant agents such as H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) due to superior pharmacokinetics and efficacy to make PPIs one of the most commonly prescribed drug classes.[1–3] They were initially marketed for the treatment and prevention of gastric acid-related symptoms and diseases, however, these indications do not fully account for the rising number of prescriptions observed in recent years.[4] Their widespread use has prompted concerns regarding overprescribing of PPIs and that their use by many patients may cause more harm than benefit, particularly in patients at low risk of gastrointestinal (GI) adverse events.[1,5]

Use of PPIs for longer than indicated in older people is a particular source of concern, as illustrated by the addition of this prescribing to the recently updated Beers criteria.[6] The Screening Tool for Older Person's Prescriptions (STOPP) also defines use of PPIs at therapeutic dose or higher for longer than 8 weeks as potentially inappropriate for people aged 65 and over.[7] Studies suggest this is the optimal duration of high-dose prescribing to maximise ulcer healing and symptom resolution and minimise rebound acid secretion.[5] This is one of the most prevalent types of potentially inappropriate prescribing defined by STOPP in several European countries,[8] with a recent study showing that almost a quarter of older participants received this type of potentially inappropriate prescribing.[3] As PPIs are regarded as having a good safety profile and high efficacy,[5] such prescribing is often seen as a conservative approach to reduce the likelihood of GI bleeds in patients who are at elevated risk of such adverse events. However, using high doses for longer than indicated is

not cost-effective and, as well as increasing drug burden for patients, may also put patients at risk of other adverse events, including fractures and *Clostridium difficile* infection.[5,9,10]

The objectives of this study are: (1) to characterise how PPI prescribing and co-prescribed ulcerogenic medicines have changed in community-dwelling older people in Ireland (aged  $\geq 65$  years) from 1997 to 2012 and (2) for long-term PPI users, to determine what co-prescribed medications and demographic factors are associated with prescription of maximal dose (rather than maintenance dose) and which factors account for the increase in long-term use of maximal doses from 1997 to 2012.

## **Methods**

### **Study design**

This is a repeated cross-sectional study using administrative pharmacy claims data available from the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS). The study population includes all individuals aged  $\geq 65$  years eligible for the General Medical Services (GMS) scheme in the former Eastern Health Board region of Ireland (representing one third of older people nationally) in the years 1997, 2002, 2007, and 2012. The GMS scheme is a form of public health cover in Ireland with means-tested eligibility, however, from 2002 to 2008 all people aged 70 years or over were automatically eligible for the scheme and since January 2009, a higher income threshold was applied to this age group compared to the general population still covering 96.5% of this population.[11]

### **Analysis**

#### ***PPI use***

For each study year, we determined the percentage of the study population prescribed a PPI (ATC code A02BC and combinations), categorised by duration ( $\leq$  and  $>$  8 weeks for short- and long-term use respectively) and for those prescribed a long-term PPI, the dosage prescribed for this period (either maximal i.e. treatment dosage or higher, or maintenance i.e. less than treatment dose). Individuals with long-term periods at both maximal and maintenance doses were categorised as the former. Treatment doses were classified as 40mg daily for omeprazole, pantoprazole, and esomeprazole, 30mg daily for lansoprazole and 20mg daily for rabeprazole, consistent with other studies and United Kingdom treatment guidelines.[12,13] These doses are in some cases higher than those indicated on

Food & Drug Administration (FDA) labels and so estimates of potential overprescribing are likely to be more conservative than if FDA dose recommendations had been used.

For individuals prescribed a long-term PPI at maximal dose we also examined their concomitant use of medicines that can increase risk of GI bleeding (ulcerogenic agents including non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, other antiplatelet or anticoagulant drugs, and oral corticosteroids prescribed for 3 months or greater).

Concomitant use was classified as a dispensing of the ulcerogenic medicine within the period of long-term PPI use. Data were only available on doctor-prescribed drugs. We calculated prevalence estimates with 95% confidence intervals (CIs) for each of these scenarios as a percentage of all persons aged 65 years and over eligible for the GMS scheme in the final month of each study year.

### ***Factors associated with dosage of long-term PPIs***

Among long-term PPI users across all years, we used logistic regression to assess medication and demographic factors associated with being prescribed a maximal dose (considered potentially inappropriate prescribing) compared to a lower, more appropriate maintenance dose after 8 weeks. Factors included as explanatory variables were concomitant use of ulcerogenic medicines, age group (categorised as 65-69 years (reference), 70-74 years, or  $\geq 75$  years), gender, and level of polypharmacy (number of regular medication classes prescribed to an individual for 3 months or longer, categorised as 0-4 (reference), 5-9, or 10 or more regular medicines). Study year was also included to assess if risk of long-term users being prescribed a maximal dose changed with time, controlling for demographic and medication factors. Adjusted odds ratios (OR) with 95% CI are presented. Multicollinearity was assessed using the variance inflation factor. Some individuals may be included at



multiple time points, so a sensitivity analysis was undertaken to account for clustering/non-independence of repeated observations of a patient in estimating standard errors. All analyses were performed using Stata version 12 (Stata Corporation, College Station, TX, USA) and significance was assumed at  $p < 0.01$ .

## Results

The number of individuals aged 65 years and over included in this study was 78,489 in 1997, 121,726 in 2002, 129,162 in 2007, and 133,884 in 2012. Previous analysis found the percentage of these older adults on five or more regular medicines (i.e. with polypharmacy) increased steadily from 17.8% in 1997 to 60.4% in 2012, while those on 10 or more regular medicines rose from 1.5% to 21.9% over this period.[3]

Approximately half of participants were prescribed any PPI in 2007 and 2012, up from 10.7% in 1997 (see Table 1). Long-term prescribing became more common, with the percentage of participants on a PPI for greater than 8 weeks increasing from 4.1% in 1997 to 35.5% in 2012. The prevalence of potentially inappropriate prescription of a PPI (i.e. treatment dosage or higher for greater than 8 weeks) also rose over this period, from 0.8% of individuals in 1997 to 23.6% of those in 2012. Long-term use at maximal dosages increased both as a proportion of those prescribed any PPI and those on a long-term PPI, as illustrated in Figure 1 and in all cases the trend across years was statistically significant. Excluding individuals also receiving a concurrent prescription for an ulcerogenic agent, 4.7% of the 2012 study population were prescribed a potentially inappropriate PPI with no concurrent medicines that increase the risk of GI bleeding. The corresponding percentages were 0.3% of individuals in 1997, 1.4% in 2002, and 2.7% in 2007, a statistically significant trend.

Adjusted logistic regression analysis of individuals prescribed a long-term PPI found that concurrent anticoagulant, antiplatelet (excluding aspirin), or long-term corticosteroid use, and being on five or more regular medicines were significantly associated with higher odds of being prescribed a potentially inappropriate maximal dose (Table 2). Concurrent NSAID (adjusted OR 0.87, 95% CI 0.85-0.89) or aspirin use (OR 0.95, 95% CI 0.92-0.97) as well as

female gender and older age were associated with lower odds of being prescribed a maximal dose among long-term PPI users. The increased odds of a long-term PPI user in 2012 being on a maximal dose compared to in 1997 remained significantly higher after adjusting for concomitant ulcerogenic medicines, age group, gender and polypharmacy in the multivariate model (adjusted OR 6.30, 95% CI 5.76-6.88, see Table 2). In sensitivity analysis, accounting for patient clustering of repeated observations across years did not significantly alter the results.

## Discussion

### Principal findings and interpretation

Although the proportion of older people in this study prescribed PPIs was four times higher in 2012 compared to 1997, the prevalence of potentially inappropriate long-term PPI at maximal dose increased almost thirtyfold over this period. Discounting instances where an ulcerogenic drug was co-prescribed (even though higher doses of PPIs would not necessarily be indicated for gastroprotection in such cases), there were still almost 5% of people on a potentially inappropriate PPI in 2012. It was hypothesised that long-term PPI users with GI bleeding risk factors would be more likely to be prescribed a maximal dose; however, maximal-dose use was not consistently associated with such risk factors, including aspirin and NSAID use and increasing age. The rise in potentially inappropriate PPI use from 1997 to 2012 was not fully explained by changes in demographics and medication co-prescribing over this time period.

Behavioural economic theories may provide some explanation of the decision-making processes leading to increased use of maximal-dose PPIs long term. The availability heuristic, estimating the probability of events based on how easily one recalls similar events could play a role.[14] The threat of a GI bleed is well established and may be more widely recognised by prescribers than PPI-associated adverse effects such as *Clostridium difficile* infection and fracture, for which evidence is newer and mainly observational.[9,10]

Omission bias, which leads to risks from acts of omission being underestimated relative to acts of commission, may also influence decision making.[14] The more passive approach of continuing a PPI at treatment dose may be favoured relative to the risk of the act of commission of dose reduction/discontinuation, for fear of adverse consequences of altering

the status quo.[15] Patient resistance to change due to beliefs that continuation is beneficial to their health may also impede deprescribing.[16]

The unexpected association of NSAID use with lower doses of PPI could be due to the presence of confounding not measured in this study, for example a factor associated with the outcome of maximal-dose PPI prescribing and inversely associated with NSAID use, such as history of peptic ulcer disease (PUD) or symptomatic gastro-oesophageal reflux disease (GORD). Given that GI mucosal protective mechanisms are impaired with age, the relationship between increasing age and lower odds of maximal-dose PPI is also surprising and unlikely to be explained by confounding due to PUD/GORD.[17]

### **Findings in the context of previous research**

Research has shown a consistent upward trend in PPI utilisation, up to a 13-fold increase in the 12 years up to 2006 in Australia.[18–21] A Dutch study found a rise in PPI prescribing to primary care patients initiated on low-dose aspirin or an NSAID from 2000 to 2012, and this increase was observed in patients across levels of risk for upper GI bleeding.[21] Regarding trends in maximal dose prescribing, a growing prevalence of high-intensity PPI use was noted in a Canadian study.[22] Considering prescribing between 1997 and 2004 in this Canadian research, polypharmacy was associated with use of high doses, while increasing age was associated with reduced odds, consistent with our study. Interestingly the authors concluded that severity of GORD symptoms was a weak predictor of maximal-dose use.

An important finding was that demographics and concomitant ulcerogenic medicines dispensed did not account for much of the increase in maximal treatment dose prescribing from 1997 to 2012. This suggests that prescribing practices have changed independent of these factors and that many patients may not require this level of PPI prescribing. This is

consistent with other studies, where a small proportion of PPI prescribing (13.5%) was associated with regular indications of PUD or taking an NSAID in French nursing homes,[23] while non-specific morbidity accounted for 46% of new prescriptions in an English primary-care setting in 1995.[18] The former study concluded that much prescribing was probably inappropriately related to general health vulnerability, reflected by polypharmacy and comorbidities.[23]

### **Strengths and limitations**

Strengths of this study are the large numbers included and their representativeness of older Irish adults. The long study duration provides better evidence of actual changes in prescribing practice rather than short-term fluctuations. Due to lack of clinical information, we were unable to include possible predictors of prolonged use of maximal-dose PPIs such as PUD, GORD, or GI bleeding history. However, with the exception of Barrett's oesophagus and Zollinger-Ellison (ZE) syndrome, long-term PPI use at higher treatment doses is no more effective than maintenance doses for these conditions.[22] The lack of data on the setting of initiation (i.e. hospital or ambulatory care) or the indication for PPI prescriptions precluded examination of potentially important contributors to PPI overuse such as stress ulcer prophylaxis.[5,24] Similar to concomitant ulcerogenic drugs, conditions such as PUD may offer some justification for maximal-dose use, however, this would still be contrary to treatment guidelines and unlikely to benefit patients.[13,22]

The use of pharmacy claims data captured all prescribed medicines and allowed for medicines use of individuals to be analysed rather than population-level drug consumption. Although the primary focus was prescribing of these agents, it was assumed that dispensed medications were then consumed. While this is a limitation, long-term use indicated by

repeated dispensing here is more likely to indicate actual consumption compared to once-off or intermittent dispensing. We lacked information on non-prescription use of medicines, including NSAIDs, aspirin, PPIs or alternative gastroprotective medicines (e.g. antacids, H2RA), however, patients would have to purchase these themselves; given the extra cost, this is probably uncommon. Although this is not the first study to examine factors associated with maximal-dose PPI use in older people, this does appear to be the first since the continued increase in long-term prescribing over the last decade.

### **Clinical and policy implications**

Deprescribing of PPIs targeted at patients at low risk of GI bleeding, through dose reduction or discontinuation where tolerated, may help reduce the occurrence of PPI-associated adverse effects for patients and associated costs.[9] Sub-optimal use of PPIs has been identified as a significant source of drug expenditure and rationalising prescribing in this area could yield substantial cost savings.[12,20] A recent systematic review has shown interventions to improve PPI prescribing are feasible, with discontinuation rates without symptom control deterioration ranging from 14% to 64%.[25] Approaches to optimise prescribing more generally in older patients may also provide improvements. OPTI-SCRIPT, a multi-faceted intervention including academic detailing by a pharmacist and medication review with web-based treatment algorithms, targeted potentially inappropriate prescribing in Irish general practice and was effective in reducing the use of maximal-dose PPIs long term (OR 0.3, 95% CI 0.14-0.68, comparing the intervention group to control).[26]

Reducing overuse needs involvement of both healthcare professionals, to discuss PPI use, offer alternative treatments and trial discontinuation, as well as patients, who if fully informed of the risks and benefits may be more likely to try other approaches such as

lifestyle changes.[4] Strategies to optimise such prescribing should extend beyond primary care as many long-term prescriptions are hospital initiated.[27] PPIs commenced in secondary care without appropriate indications, for example for stress ulcer prophylaxis, are often continued inappropriately following discharge, particularly if communication of indication at the transition of care is lacking.[1,24,28,29] Providing clear information to prescribers initiating or continuing PPIs regarding indicated dosage and duration of treatment may help reduce inappropriate long-term use in ambulatory care.[30]

### **Conclusions**

This study contextualises the growing trend in potentially inappropriate PPI use in recent years and demonstrates that a significant portion of this maximal-dose PPI prescribing in older patients may not be justified. Further research should focus on determining the most effective interventions to optimise prescribing in this area and ways to implement these in practice in order to reduce PPI overuse while enhancing patient care.



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### Conflict of Interest Disclosures:

Elements of Financial/Personal Conflicts	FM		KB		CC		TF	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds		X		X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

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Figure

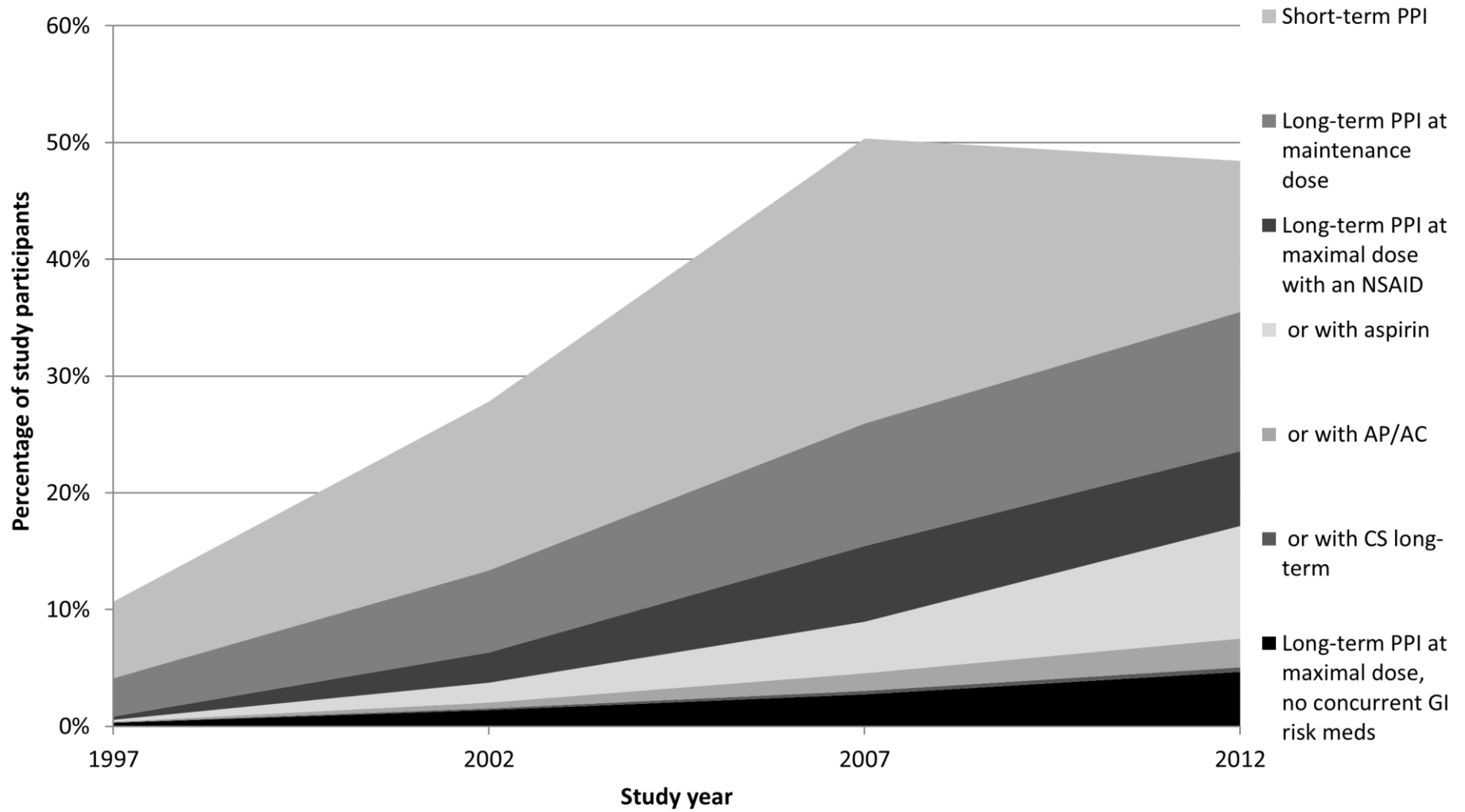


Figure 1 Prescribing of PPIs and ulcerogenic medicines to General Medical Services scheme-eligible population of Eastern Health Board region of Ireland aged  $\geq 65$  years in 1997, 2002, 2007 and 2012. Abbreviations: PPI = proton pump inhibitor; NSAID = non-steroidal anti-inflammatory drug; AP = antiplatelet drug (excluding aspirin); AC = anticoagulant drug; CS= corticosteroid; GI = gastrointestinal



## Tables

Table 1 Number and Percentage of Individuals Prescribed a Proton Pump Inhibitor (PPI) in 1997, 2002, 2007 and 2012, Categorized by Duration of Use, Dosage and Concurrent Medications Use

	1997 (n=78,489) <sup>a</sup>		2002 (n=121,726) <sup>a</sup>		2007 (n=129,162) <sup>a</sup>		2012 (n=133,884) <sup>a</sup>	
	n	% prevalence (95% CI)	n	% prevalence (95% CI)	n	% prevalence (95% CI)	n	% prevalence (95% CI)
Prescribed a PPI	8385	10.7 (10.5, 10.9)	33867	27.8 (27.6, 28.1)	65031	50.3 (50.1, 50.6)	64842	48.4 (48.2, 48.7)
Short-term PPI (≤8 weeks)	5148	6.6 (6.4, 6.7)	17606	14.5 (14.3, 14.7)	31527	24.4 (24.2, 24.6)	17317	12.9 (12.8, 13.1)
Long-term PPI (>8 weeks)	3237	4.1 (4.0, 4.3)	16261	13.4 (13.2, 13.5)	33504	25.9 (25.7, 26.2)	47525	35.5 (35.2, 35.8)
Long-term PPI, maintenance dose <sup>b</sup>	2575	3.3 (3.2, 3.4)	8561	7.0 (6.9, 7.2)	13557	10.5 (10.3, 10.7)	15967	11.9 (11.8, 12.1)
Long-term PPI, maximal dose <sup>b</sup>	662	0.8 (0.8, 0.9)	7700	6.3 (6.2, 6.5)	19947	15.4 (15.2, 15.6)	31558	23.6 (23.3, 23.8)
- with an NSAID <sup>c</sup>	226	0.3 (0.3, 0.3)	3151	2.6 (2.5, 2.7)	8375	6.5 (6.3, 6.6)	8582	6.4 (6.3, 6.5)
- with aspirin <sup>c</sup>	212	0.3 (0.2, 0.3)	3603	3.0 (2.9, 3.1)	11226	8.7 (8.5, 8.8)	17712	13.2 (13.0, 13.4)
- with an antiplatelet <sup>d</sup> or anticoagulant drug <sup>c</sup>	62	0.1 (0.1, 0.1)	1537	1.3 (1.2, 1.3)	5574	4.3 (4.2, 4.4)	8106	6.1 (5.9, 6.2)

	1997 (n=78,489) <sup>a</sup>		2002 (n=121,726) <sup>a</sup>		2007 (n=129,162) <sup>a</sup>		2012 (n=133,884) <sup>a</sup>	
	n	% prevalence (95% CI)	n	% prevalence (95% CI)	n	% prevalence (95% CI)	n	% prevalence (95% CI)
- with a long-term ( $\geq 3$ months) corticosteroid <sup>c</sup>	70	0.1 (0.1, 0.1)	759	0.6 (0.6, 0.7)	1769	1.4 (1.3, 1.4)	2477	1.9 (1.8, 1.9)
Long-term PPI, maximal dose <sup>b</sup> , none of above medicines	243	0.3 (0.3, 0.3)	1699	1.4 (1.3, 1.5)	3540	2.7 (2.7, 2.8)	6251	4.7 (4.6, 4.8)

<sup>a</sup> Total number of people aged  $\geq 65$  years eligible for General Medical Services scheme in Eastern Health Board region for each study year

<sup>b</sup> Dose classified as maximal i.e. greater than or equal to treatment dosage recommend by the United Kingdom National Institute for Clinical and Care Excellence (40mg daily for omeprazole, pantoprazole, and esomeprazole, 30mg daily for lansoprazole and 20mg daily for rabeprazole), or maintenance i.e. less than treatment dose.[13]

<sup>c</sup> Categories not mutually exclusive, individuals may have been co-prescribed more than one type of ulcerogenic medicine

<sup>d</sup> Antiplatelet drugs excluding aspirin

Table 2 Unadjusted and adjusted odds ratios and 95% CIs for factors associated with maximal dose compared to maintenance dose in long-term PPI users

	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>b</sup>
<b>Concurrent aspirin</b>	1.13 (1.11, 1.16)	0.95 (0.92, 0.97)
<b>Concurrent NSAID</b>	0.84 (0.82, 0.86)	0.87 (0.85, 0.89)
<b>Concurrent antiplatelet<sup>a</sup>/anticoagulant</b>	1.64 (1.59, 1.69)	1.36 (1.31, 1.41)
<b>Concurrent corticosteroid for ≥3 months</b>	1.19 (1.13, 1.24)	1.09 (1.04, 1.15)
<b>Age group</b>		
65-69 years (reference)	1.00	1.00
70-74 years	0.90 (0.86, 0.94)	0.90 (0.86, 0.93)
75+ years	0.94 (0.91, 0.97)	0.86 (0.83, 0.89)
<b>Female (vs male)</b>	0.89 (0.87, 0.91)	0.90 (0.88, 0.92)
<b>Level of polypharmacy</b>		
0-4 medicines (reference)	1.00	1.00
5-9 medicines	1.45 (1.40, 1.50)	1.28 (1.24, 1.34)
10+ medicines	2.39 (2.30, 2.49)	1.91 (1.83, 2.00)
<b>Study year</b>		
1997 (reference)	1.00	1.00
2002	3.50 (3.20, 3.83)	3.28 (2.99, 3.59)
2007	5.72 (5.24, 6.25)	4.86 (4.45, 5.32)
2012	7.69 (7.04, 8.39)	6.30 (5.76, 6.88)

<sup>a</sup> Antiplatelet drugs excluding aspirin.

<sup>b</sup> Mean variance inflation factor for all included covariates was 4.05 indicating no serious multicollinearity.