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Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study

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Abstract

Background: The use of proton-pump inhibitors (PPIs) has increased over the last decade. The objective of this study was to provide detailed utilization data on PPI use over time, with special emphasis on duration of PPI use and concomitant use of ulcerogenic drugs.

Methods: Using the nationwide Danish Prescription Registry, we identified all Danish adults filling a PPI between 2002 and 2014. Using descriptive statistics, we reported (i) the distribution of use between single PPI entities, (ii) the development in incidence and prevalence of use over time, (iii) measures of duration and intensity of treatment, and (iv) the prevalence of use of ulcerogenic drugs among users of PPIs.

Results: We identified 1,617,614 adults using PPIs during the study period. The prevalence of PPI use increased fourfold during the study period to 7.4% of all Danish adults in 2014. PPI use showed strong age dependency, reaching more than 20% among those aged at least 80 years. The proportion of users maintaining treatment over time increased with increasing age, with less than10% of those aged 18–39 years using PPIs 2 years after their first prescription, compared with about 40% among those aged at least 80 years. The overall use of ulcerogenic drugs among PPI users increased moderately, from 35% of users of PPI in 2002 to 45% in 2014.

Conclusions: The use of PPIs is extensive and increasing rapidly, especially among the elderly.

Keywords: proton-pump inhibitor, prescription registry, general population, prevalence, incidence, ulcerogenic drugs

Introduction

Proton-pump inhibitors (PPIs) have for many years been the cornerstone of treatment of gastroesophageal reflux disease (GERD) and in the healing and prevention of gastroduodenal ulcers. With an increasing number of patients receiving GERD therapy and an increased awareness of the need for ulcer prophylaxis [Valkhoff *et al.* 2010; Abraham *et al.* 2010; El-Serag *et al.* 2014], a concomitant rise in PPI users has been observed. However, inappropriate prescriptions and unjustified long-term use consequently seems to drive the use of PPIs [Batuwitage *et al.* 2007]. While side effects related to PPI use are generally few and mild (flatus, loose stools and abdominal pain), some data suggest several potential detrimental effects, such as *Clostridium difficile* infection, community-acquired pneumonia, bone fractures, and low levels of magnesium and B12 vitamin, mostly observed in the elderly population [Reimer, 2013]. Further, concerns have been raised regarding possible associations between long-term PPI use and increased risk of neuroendocrine gastrointestinal tumours, but so far, this has only been shown in rodents [Reimer, 2013; Ko *et al.* 2016]. These health-related concerns are complemented by concerns for the financial costs related to the extensive use of PPIs.

In previous surveys and register-based studies of the general population, the prevalence of PPI users has varied considerably, both over time and among studies. Most of the studies date several years back, have clustered PPI use with use of histamine type-2 receptor antagonists (H2RA) and were not carried out in a nationwide setting. Furthermore, the studies applied different definitions of long-term use, based on either duration of therapy or used defined daily doses (DDDs) per year, without taking both parameters into account

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[Hungin *et al.* 1999; Jacobson *et al.* 2003; van Soest *et al.* 2006; Reimer and Bytzer, 2009; Lødrup *et al.* 2014; Haastrup *et al.* 2014].

There is a need for more detailed information regarding the changes in PPI use within the general population, both with regard to duration and dosing, and to what extent such therapy might be related to concomitant use of ulcerogenic medicine. Also, it has been found that the majority of PPI users choose to be on demand therapy instead of continuous therapy; but how this may be reflected in the prescription pattern of PPI is not known.

In this study, we used nationwide Danish register-based data to describe use of PPIs over time, specifically describing the duration and magnitude of PPI use as well as concomitant use of ulcerogenic drugs.

Method

In this descriptive utilization study, we accounted for the use of PPI drugs among adults in Denmark between 2002 and 2014.

Data Sources

The Prescription Registry [Kildemoes *et al.* 2011] contains data on all prescription drugs dispensed to Danish citizens since 1995. The data include the type of drug, date of dispensing, and quantity. The dosing information and the indication for prescribing are not available, and no information is available on drug use dispensed at hospital level. Drugs are categorized according to the anatomic therapeutic chemical (ATC) index, a hierarchical classification system developed by the World Health Organization (WHO), and the quantity dispensed for each prescription is given by the number and strength of the pharmaceutical entities (e.g. tablets), as well as the DDDs [WHO Collaborating Centre for Drug Statistics Methodology].

The Civil Registration System [Pedersen, 2011] contains data on date of death and migration to and from Denmark. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968 [Pedersen, 2011].

Population and study drugs

We included all adults filling a PPI prescription between 1 January 2002 and 31 December 2014.

Table 1. Proton-pump inhibitors with marketing authorization in Denmark.

Drug	ATC	DDD (mg)
Omeprazole	A02BC01	20
Pantoprazole	A02BC02	40
Lansoprazole	A02BC03	30
Rabeprazole	A02BC04	20
Esomeprazole	A02BC05	30

ATC, anatomical therapeutic chemical; DDD, defined daily dose.

The adult Danish population increased from 4.19 to 4.49 million individuals during the study period. Children and adolescents were excluded from the analysis. During the study period, this pertained to 63,549 individuals less than 18-years old filling 181,698 prescriptions. The median age among the children and adolescent users was 12 years (interquartile range 5–15 years).

PPIs were defined as all drugs within ATC group, A02BC. The five single PPIs marketed in Denmark, along with DDD definitions, are shown in Table 1. Rabeprazole (ATC, A02BC04) is rarely used in Denmark.

For several analyses, we had to estimate whether an individual was a 'current user' of a PPI at a given date. We achieved this by regarding an individual as a 'current user' if they had filled a PPI prescription with enough PPI doses to cover that day. The duration of each prescription was estimated as the number of tablets dispensed, that is, assuming a consumption of one tablet per day, while adding 25% to the duration to account for noncompliance and irregular prescription refills.

Analyses

First, we calculated the annual use of PPIs (measured as amount of dispensed DDDs), specified by type of PPI and study year (2002–2014).

Second, we calculated the annual incidence and point prevalence proportions, that is, the number of first-ever and current adult users per 1000 adults in the population from 2002 to 2014. Both measures used the total Danish adult population on 1 January of the relevant year as the denominator. Further, the sex and age-specific (using 1-year intervals) prevalence proportion was reported by the end of the study period (i.e. end

of 2014), as well as for the end of years 2002, 2006 and 2010.

Third, to describe duration of treatment, we used the 'proportion of patients covered' (PPC) method. In brief, we followed all individuals from the date of their first PPI prescription, that is, incident users. Over time, we estimated the proportion of all subjects still alive after X days that still used PPI at that day. As such, an individual could be regarded as 'dropped out of treatment' at one point in time and later be reclassified as 'current user' upon filling a new prescription. Subgroup analyses were carried out according to age, sex, and calendar year of first prescription.

Fourth, we identified individuals who, after their first PPI prescription, filled at least one prescription for a PPI each year for 5 consecutive years (defined as years from first prescription and not calendar years). Among these 'longer-duration users', we estimated the median number of DDDs used per year. Subgroup analyses were carried out according to age, sex, and calendar year of first prescription.

Fifth, in order to explore potential reasons for using PPIs, we estimated the prevalence of ulcerogenic drug use among users of PPI. To do this, we calculated the annual proportion of PPI users that had filled one or more prescriptions for the following drugs known to be ulcerogenic or to increase the risk of bleeding peptic ulcer [Bhatt *et al.* 2008; Dall *et al.* 2009; Gómez-Outes *et al.* 2013; Narum *et al.* 2014]: acetylsalicylic acid (ATC code: B01AC06, N02BA01 and B01AC30), NSAIDs (M01A excl M01AX), oral anticoagulants [vitamin K antagonists (B01AA) and the newer oral anticoagulants (B01AE, B01AF and B01AX06)], and platelet inhibitors [dipyridamole (B01AC07 and B01AC30) and ADP-receptor blockers (B01AC04, B01AC22 and B01AC24)]. Only prescriptions filled by individuals currently using PPIs or during the 30 days leading up to PPI use were included. As a sensitivity analysis, we also analysed this using a 90-day run in.

Other

Stata Version 14.0 (StataCorp, College Station, TX, USA) was used for all analyses. The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board [Thygesen *et al.* 2011].

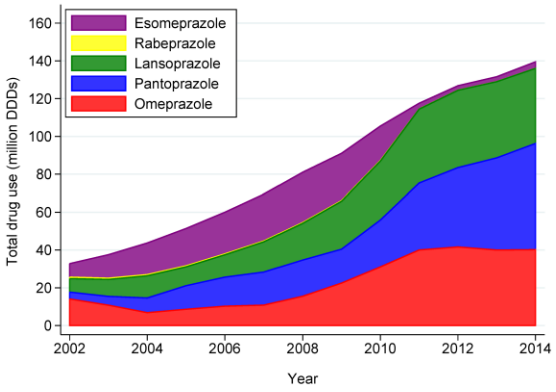

Figure 1. Total amount of proton-pump inhibitor used per calendar year during the study period, measuered as the total amont of dispensed defined daily doses. DDDs, defined daily doses.

Results

We identified 1,617,614 adults filling 18,963,535 prescriptions for PPIs throughout the study period. 517,000 (32%) filled only one prescription, whereas 449,272 (28%) and 739,339 (46%) filled two to four, and five-plus prescriptions, respectively. The median number of DDDs filled per prescription was 56 (interquartile range 28–98).

The use of PPIs increased substantially over the study period, reaching 140 million DDDs filled in 2014 (Figure 1). The number of users of PPIs (point prevalence) increased fourfold during the study period, reaching 7.4% of all Danish adults by 2014 (Figure 2A). This was accompanied by an increase from 21.5 to 36.4 incident users per 1000 person-years (Figure 2B). The prevalence of use increased with age and only marginally with female sex, with the prevalence reaching 14.0%, and 16.3% among men and women above 60 years (Supplementary Figure S1). The full age spectrum for prevalence of use at the end of the study period (2014) is provided in Figure 3, showing a steadily increasing use with increasing age, reaching a prevalence of over 20% among those aged at least 80 years. Corresponding figures for use in 2002, 2006 and 2010 are provided in Supplementary Figure S2A–C.

The proportion of incident users that used PPI over time following their first prescription was found to be heavily dependent on age, as presented in Figure 4, showing that with increasing age the proportion of incident users still using PPIs 2 years later increased. Additional analyses showed that these proportions were stable up to 5 years following the index prescription (Supplementary

Figure 3), and that the results were only marginally affected by sex (Supplementary Figure S4A) and unrelated to calendar time (Supplementary Figure S4B).

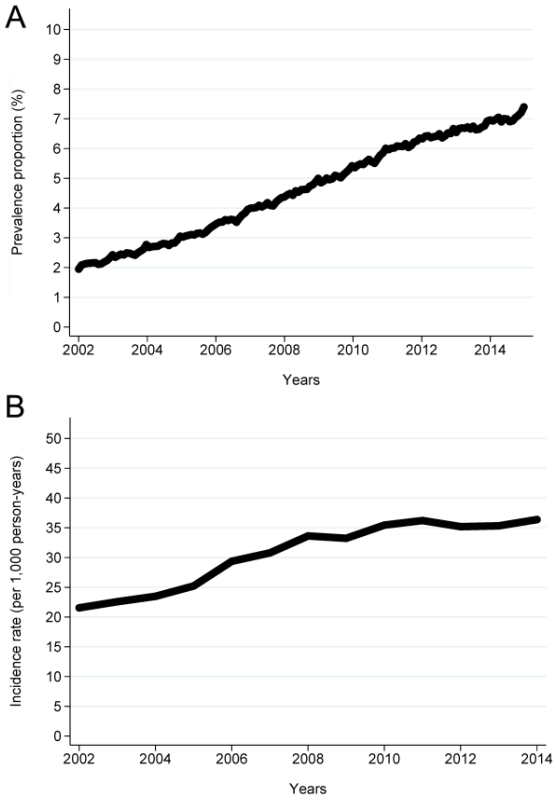

Figure 2. (A) Number of users (point-prevalence proportion), and (B) number of new users (incidence rate) of proton-pump inhibitor use among adults (⩾18 years) in Denmark from 2002 to 2014.

About 14% of incident users maintained PPI therapy for each year of the first 5 years following their index prescription, while 30% received therapy for at least 3 of the five 5 years. Among those using it each year, we found the distribution of annual use measured in DDDs to be relatively stable, although with an increase in the 90th percentile of use (Figure 5). This increase in the 90th percentile was more pronounced with increasing age (data not shown).

Concomitant use of drugs known to be ulcerogenic or to increase the risk of bleeding peptic ulcer increased slightly over time with 45% filling at least one such drug concomitantly with their use of PPI in 2014 (Figure 6). The largest increase was seen for oral anticoagulants (increasing from 2.1% to 6.1%) and platelet inhibitors other than acetylsalicylic acid (from 3.2% to 7.0%), while use of acetylsalicylic acid and NSAIDs was more stable (16.9% and 24.8%, respectively, in 2014). Varying the definition of concomitant use (see Methods) had only marginal effect on these estimates (data not shown).

In a *post-hoc* analysis to investigate the large proportion of individuals filling only one prescription, we determined the proportion of PPI prescriptions that could potentially be attributed to *Helicobacter pylori* eradication treatment (defined as PPI prescriptions filled within 1 day from an antibiotic treatment with two different antibiotics being filled). This was the case for 0.7% (n = 127,755) of all PPI prescriptions and 2.4% (n = 12,226) of individuals filling only one prescription during the study period.

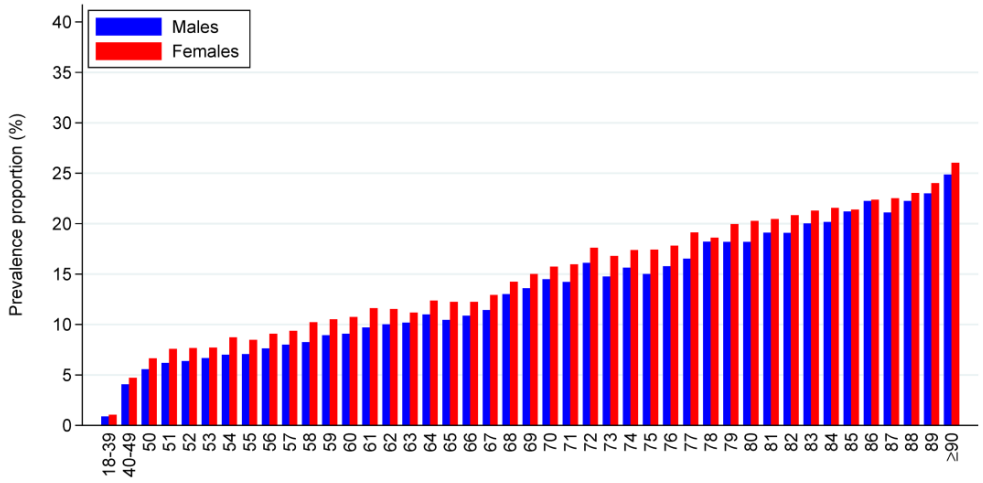

Figure 3. Age and sex-specific prevalence proportion of proton-pump inhibitor drug use by end of 2014.

Discussion

In our nationwide study, we have documented a marked increase in the use of PPIs in Denmark between 2002 and 2014. This increase was primarily driven by an accumulation of prevalent PPI users rather than an increase in the incidence of use. While we noted a slight increase in the use of ulcerogenic drugs among PPI users, this did not explain the observed increase in use of PPI.

The principal strength of the study is the nationwide setting allowing analysis of the use of PPIs in the entire Danish population regardless of, for example, socioeconomic or insurance status. Further, the use of the Danish Prescription Registry allowed analyses to be conducted over a 13-year period with no risk of recall bias or drop-out. Lastly, the use of acid-suppressive medicine in Denmark has been found to be similar to that seen in Europe [National Institutes for Health and Drug Consumption in Denmark, Norway and Sweden].

The most important limitation of the study is the lack of data on the underlying reason for PPI use at the individual level. Further, acid-suppressive medicine sold over the counter or dispensed at hospitals is not covered by our data source. However, this only pertains to 2% of PPIs used during the study period [Statens Serum Institut, 2015]. Lastly, we were not able to account for dosing regimens using more than one daily dosage, for example, twice a day, which may be applied on a regular basis by 10–20% of GERD patients on a PPI and which is also commonly used for treatment of gastroduodenal ulcers [Hungin *et al.* 2012].

We found that, on any given day in the last year of our study period, 7% of the adult population would be covered by a PPI prescription; 14% for persons aged over 60 years. This finding is in accordance with previous register-based studies [Lassen *et al.* 2004; van Soest *et al.* 2006]. The most common reason for starting PPI therapy is GERD. At the end our study period, we may assume that our study population had a yearly prevalence of GERD close to, or, due to a continuing increase in the worldwide GERD prevalence, slightly above of what was found in the Kalixanda study [Ronkainen *et al.* 2005a, 2005b], in which weekly GERD symptoms were

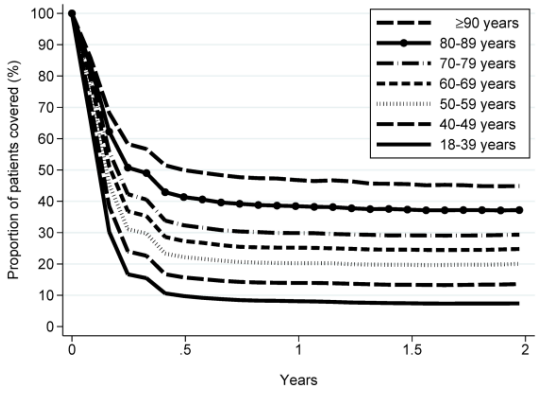

Figure 4. Duration of proton-pump inhibitor therapy, calculated as the proportion of patients covered, specified by age, up to 2 years following each individual's first prescription.

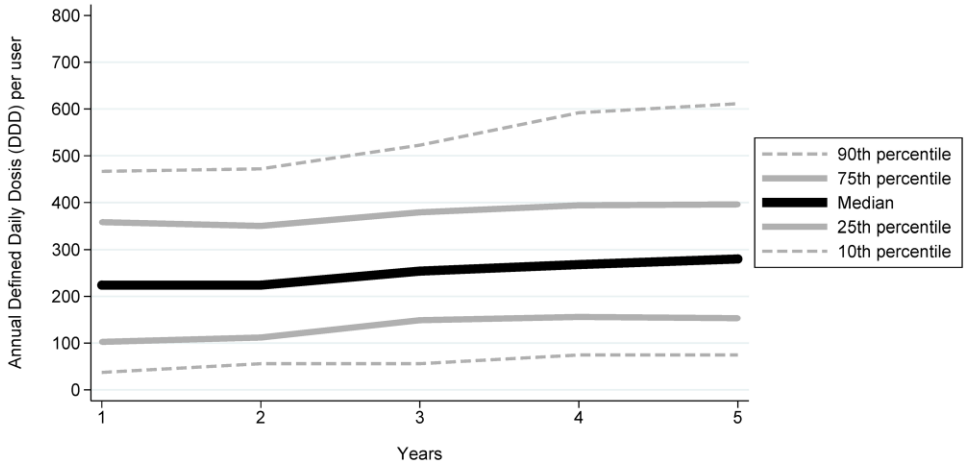

Figure 5. Doses used over time in the first 5 years among individuals filling a minimum of one prescription for each year for at least 5 years following their first prescription.

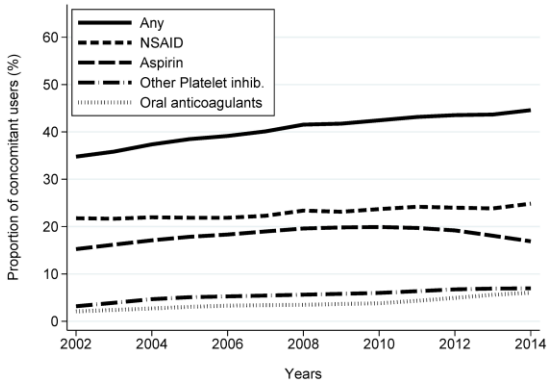

Figure 6. NSAID, nonsteroidal anti-inflammatory drug; inhib, inhibitor.
Concomitant use of ulcerogenic drugs or drugs with increased risk of bleeding peptic ulcer among users of proton-pump inhibitors.

found in 20% of the general population, mild-to-moderate erosive esophagitis (Los Angeles grade A/B) in 15%, severe erosive esophagitis (Los Angeles grade C/D) in 0.5% and Barrett's Esophagus with confirmed intestinal metaplasia in 1.6%. This does not adequately explain the prevalence of PPI use found in our study, and in particular, not the proportion of new PPI users who were covered with PPI prescriptions 2 years after their first PPI prescription, which was more than 30% for persons aged over 70 years. In the latest National Institute for Health and Care Excellence (NICE) guideline [NICE, 2014], initial short-term PPI treatment for 4–8 weeks is advised for the vast majority of GERD patients who are without severe erosive esophagitis or Barrett's Esophagus, and periodic medication reviews are recommended if PPI treatment is prolonged. Furthermore, up to one third of long-term PPI users have been shown not to have undergone upper endoscopy to confirm presence of erosive esophagitis [Lassen *et al.* 2004], making the indication for long-term treatment doubtful. However, getting such patients off PPI has proven difficult [Batuwitage *et al.* 2007; Reimer and Bytzer, 2010; Ahrens *et al.* 2012; Wermeling *et al.* 2014; Zwisler *et al.* 2015], and this could, at least in part, be a reason for the prevalence of use observed in our study. One possible reason for continuing PPI use in patients without a well established indication could be rebound-acid hypersecretion, that is, acid hypersecretion following withdrawal of PPI therapy. This phenomenon has been shown to lead to reflux symptoms in healthy volunteers, but its clinical significance in patients with regard to restarting PPI therapy is not clear [Björnsson *et al.* 2006; Lødrup *et al.* 2013]. In our study, 32% of PPI users only redeemed one prescription throughout the study period, suggesting that PPIs are often prescribed for mild and intermittent symptoms where over-the-counter drugs such as antacids or alginates probably would have sufficed. In such patients, acid-rebound hypersecretion may have a detrimental clinical impact if it leads to otherwise unnecessary long-term PPI therapy.

The modest increase in PPI users redeeming at least one prescription for an ulcerogenic drug (35% in 2002 *versus* 45% in 2014) indicates that the rise in PPI use is not mainly driven by ulcer-prophylactic initiatives. This corresponds well with concerns that PPI is not only overutilized (as discussed above), but also underutilized in patients taking ulcerogenic drugs [van Soest *et al.* 2011].

In previous studies on health-related risks associated with PPI use, much attention has been given to 'long-term PPI use', although this has not been uniformly defined across studies. In our data, we note that only a small proportion of individual patients maintain treatment for each of the first 5 years following their first prescription while we at the aggregate level see a high and stable prevalence of PPI users during the same period (Supplementary Figure S3). This illustrates that many patients drop in and out of PPI therapy after redeeming their first prescription, while only a minority uses PPI continuously. As such, it seems that the term 'long-term users' could include both chronic and recurring PPI users, and this pattern needs to be taken into consideration in future studies on long-term PPI use and potential health-related risks.

In conclusion, we document a considerable increase in the use of PPIs over the last decade, especially among elderly individuals. Further, a large proportion of new PPI users maintain their treatment over a longer period. In light of this, initiatives to assess the appropriateness of the use of these drugs might be warranted.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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