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# Proton pump inhibitor use may not prevent high-grade dysplasia and oesophageal adenocarcinoma in Barrett's oesophagus: a nationwide study of 9883 patients

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## SUMMARY

### Background
Proton pump inhibitors (PPI) may potentially modify and decrease the risk for development of oesophageal adenocarcinoma in Barrett's oesophagus (BO).

### Aim
To investigate if the intensity and adherence of PPI use among all patients with BO in Denmark affected the risk of oesophageal adenocarcinoma.

### Methods
We performed a nationwide case–control study in Denmark among 9883 patients with a new diagnosis of BO. All incident oesophageal adenocarcinomas and high-grade dysplasias were identified, and risk ratios were estimated on the basis of prior use of PPIs. Sex- and age-matched BO patients without dysplasia or malignancies in a 10:1 ratio were used for comparison. Conditional logistic regression was used for analysis, adjusting for low-grade dysplasia, gender and medication.

### Results
We identified 140 cases with incident oesophageal adenocarcinomas and/or high-grade dysplasia, with a median follow-up time of 10.2 years. The relative risk of oesophageal adenocarcinoma or high-grade dysplasia was 2.2 (0.7–6.7) and 3.4 (95% CI: 1.1–10.5) in long-term low- and high-adherence PPI users respectively.

### Conclusions
No cancer-protective effects from PPI's were seen. In fact, high-adherence and long-term use of PPI were associated with a significantly increased risk of adenocarcinoma or high-grade dysplasia. This could partly be due to confounding by indication or a true negative effect from PPIs. Until the results from future studies hopefully can elucidate the association further, continuous PPI therapy should be directed at symptom control and additional modalities considered as aid or replacement.




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## INTRODUCTION

Barrett's oesophagus (BO) and its connection to gastro-oesophageal reflux was described by Normann Barrett in the early 1950s,[1] and defines a replacement of normal squamous epithelium in the oesophagus by intestinal metaplasia.[2] Harmful exposure to the gastric refluxate is one of several proposed factors, which may facilitate metaplastic development. BO is a relatively common endoscopic finding in an estimated 6–10% of patients with reflux and 1–2% of the general population,[3–5] and has been identified as a pre-cancerous lesion accountable for more than 95% of oesophageal adenocarcinoma (OAC) cases.[6] However, with estimated OAC incidences between 0.1% and 0.5% per year the majority of patients will never develop OAC.[7–9] Great efforts have therefore been made to define high-risk patients, markers for progression to OAC and effective preventive measures.

In BO, the metaplastic cells have a higher proliferative rate than the normal squamous epithelium. It has been shown, that this activity increase during both persistent and pulsatile acid exposure via mitogen activated protein kinase pathways, transmitting growth regulatory signals in order to enhance proliferation and decrease apoptosis.[10, 11] Inhibiting these pathways, by minimising acid--induced stimulation, might therefore be beneficial in preventing progression from BO to high-grade dysplasia (HGD) or OAC.

First line medical treatment is therefore acid inhibition with proton pump inhibitors (PPI's). Apart from relieving symptoms, inhibition of acid production should decrease the reflux of acid into the oesophagus, thereby decreasing the ongoing inflammation, proliferation and risk of dysplasia in the epithelia. Especially in BO patients, with most to gain from acid inhibition, this effect is desired.[8] The use of PPIs has risen rapidly – but so have the incidence of OAC.[12] Studies investigating the potential protective effects of PPI's on BO have found some or none protective effect from PPIs.[13–19] However, the majorities of published studies had methodological limitations, were limited in size and follow-up and relied on selected patient cohorts.

Further studies of whether the use and adherence of acid-inhibiting drugs would influence the risk of OAC and HGD among patients with BO are needed. To address this, we conducted a large cohort study in patients with BO to assess: (i) the potential effect of acid lowering drugs on the risk of developing OAC or HGD in BO; (ii) the effect of duration and/or adherence (intensity) of medication use.

## MATERIAL AND METHODS

### Study design and information sources

We conducted this nested case–control study in a cohort of all patients diagnosed with BO in Denmark from 1995 to 2009. Denmark has free, tax supported health care, and therefore hospital services are basically population based. Previously we have described the incidence of OAC within this cohort.[8]

In all Danish medical registries, patients are identified by a civil registration number. These numbers are unique identifiers, assigned at birth and allow unambiguous linkage of individual-level data among registries.[20]

The National Danish Pathology Registry contains pathology reports and other information about all biopsies and specimens examined by all hospitals and private practitioners in Denmark. Several studies have documented a very high validity and completeness (above 98%) of this Registry.[21] Specimens are categorised according to the SNOMED classification (Systematized Nomenclature of Medicine), and based on histological specimens, localised by the accompanying text from the clinician and evaluated by specialised pathologists.

### Cases with OAC or HGD

We used the Pathology Registry to identify all 9,883 patients in Denmark who from 1995 to 2009 had a SNOMED diagnosis of Barrett's oesophagus (T62 in combination with M 73320 or M73330). BO was defined as presence of specialised intestinal metaplasia in oesophageal biopsies. Within this cohort, we identified patients with HGD (T62 in combination with M 74B09 or M74C09) and low-grade dysplasia (LGD) (T62 in combination with M 74009 or M 74A09). In addition, the cohort of BO patients were linked, by means of their civil registration numbers, to the Danish Cancer Registry in order to identify those who – before December 31st, 2009 – had received a diagnosis of OAC (ICD-10 codes C15 in combination with 74C09, 82603, 84803, 84903, 82113, 81433, 73320 or 81403). Patients with a diagnosis of HGD or OAC, made before or up to 1 year after the diagnosis of BO, were excluded from the cohort.

### Controls

Index date for the cases was defined as the first date of diagnosing HGD or OAC. For each patient, we selected 10 control subjects from the BO cohort, who were alive and had no diagnosis of HGD or OAC before the

diagnosis date of the patient, matched according to birth date (calliper matched ± 2.5 years) and date of BO (calliper matched ± 6 month).

The study was approved by the Danish Data Protection Agency (J.nr. 2010-41-4594).

### Prescription data

The Danish Prescription Database records all prescriptions in Denmark since January 1st 1995, linking civil registration number and prescription data, including date, type of drug and quantity according to the Anatomical Therapeutic Chemical (ATC) Classification System.[22] Using these databases, ensuring a minimum of 2 years of prescription history, we identified all prescriptions for cases and controls. Use of statins, aspirins and NSAIDs were identified, to adjust for potential effect on OAC and HGD incidence.

For PPI, we defined 'ever users' as individuals with >2 prescriptions and 'never/rare users' as those with less than 2 prescriptions during the study period. Ever users were further divided into recent users (>2 prescriptions during the period starting 2 years before the case date) and former users (>2 prescriptions overall, but <2 during the latest 2-year period). Duration of use was classified as short term (<7 years) or long term (>7 years), based on the number of days between the first and last prescription dates, as done in previous studies.[23] We also did calculations using 5 years as cut-off point yielding minimal differences in risk estimates (data not shown).

To further refine the medicine intake among cases and controls, all prescribed drugs were assessed in Defined Daily Dosages (DDD), which is the daily, approved dosage in milligrams for each drug. The adherence of use/intensity of PPI therapy was defined as the total number of DDD's divided by the total duration of use. Duration of use was the number of days from the date of the first prescription to the date of the last prescription plus the number of DDD's in the last prescription. Using this definition, PPI use was classified in low adherence (<75%) or high adherence (>75%). To minimise confounding by indication, PPI use within 1 year of either the OAC or HGD diagnosis (or corresponding index date in the control) was excluded from the analysis (cut-off in previous studies is between 0 and 1 year).

### Statistical analysis

Logistic regression analysis, conditioned on matched factors, was used to calculate odds ratios as a measure of the relative risks of OAC and HGD. In all analyses, never or rare users were defined as the reference group. Adding former users into the comparison group yielded minimal differences in risk estimates (data not shown). For each analysis, adjustment for potential confounding factors, e.g. presence of LGD, gender, use of statins, NSAIDs, low-dose aspirin, high-dose aspirin and anti-diabetics, was performed. All estimates of association were accompanied by a 95% confidence interval (95% CI) calculated by the profile likelihood method.

Because a comparison between PPI users and never/rare users could be confounded by the indication for PPI use, we also carried out a sub-analysis among PPI users, looking at risk differences associated with the adherence of use, recent or former use and duration of treatment.

As 70% of the cases had no prior use of H2-blockers, and only 4.3% reported a recent use of these, we did not perform further risk analysis in this therapeutic group.

## RESULTS

We diagnosed 9,883 patients with BO, consisting of 6,570 males (66.5%) and 3,313 females (33.5%), with a total follow-up time of 66,037 years. Median age at BO diagnosis was 62.6 years (interquartile range 52.4–72.9) and median follow-up time 5.7 years (interquartile range 3.4–9.3).

Within this cohort we identified 140 cases of OAC or HGD with a median age of 67.7 (interquartile range 60.7–76.1) and a median follow-up time of 10.2 years (interquartile range 7.2–12.5), and matched a total of 1297 controls from the cohort of BO patients. No major statistical differences in use of NSAID, aspirin or statins were found between cases and controls (Table 1). Fifty cases (35.7%) and 97 controls (7.5%) were diagnosed with LGD after their BO diagnosis – 143 of them among PPI users.

### Risk of OAC

Among the cases of OAC, 45 (75%) were recent users, with 23 (38.3%) being high-intensity users. The corresponding proportions among comparable controls were 341 (61.9%) and 176 (31.9%). Among all cases of OAC, high PPI-use adherence was short term in 31.7% and long term in 16.7%. For controls, the respective percentages were 32.5% and 11.4% (data not shown).

A nonsignificant statistical trend of an increased risk of OAC related to PPI usage (data not shown) was markedly diminished after adjusting for the presence of LGD (Table 2).

**Table 1 |** Characteristics of controls and cases with oesophageal adenocarcinoma and high-grade dysplasia

| Characteristic | Cases, *n* (%) | Controls, *n* (%) |
|---|---|---|
| Total | 140 (100) | 1297 (100) |
| Age, years (median)* | 67.7 (60.7–76.1)* | 67.6 (60.1–75.6)* |
| Follow-up, years (median)† | 10.2 (7.2–12.5)† | 10.1 (7.9–12.5)† |
| Male sex | 113 (80.7) | 855 (65.9) |
| Use of PPI | | |
| Never | 6 (4.3) | 125 (9.6) |
| Recent use | 116 (82.9) | 848 (65.4) |
| Former use | 18 (12.9) | 324 (25.0) |
| Short term | 97 (69.3) | 888 (68.5) |
| Long term | 37 (26.4) | 284 (21.9) |
| Use of NSAID | | |
| Never | 56 (40.0) | 415 (32.0) |
| Recent use | 24 (17.1) | 297 (22.9) |
| Former use | 60 (42.9) | 585 (45.1) |
| Use of statins | | |
| Never | 117 (83.6) | 1070 (82.5) |
| Recent use | 19 (13.6) | 200 (15.4) |
| Former use | 4 (2.9) | 27 (2.1) |
| Use of aspirin | | |
| Never | 98 (70) | 900 (69.4) |
| Recent use | 33 (23.6) | 312 (24.1) |
| Former use | 9 (6.4) | 85 (6.6) |
| Use of anti-diabetics | | |
| Never | 136 (97.1) | 1193 (92.0) |
| Recent use | 4 (2.9) | 94 (7.2) |
| Former use | 0 (0) | 10 (0.8) |

* Median age is provided with interquartile range in ().

† Median follow-up time is provided with interquartile range in ().

**Table 2 |** Duration and intensity of proton pump inhibitor use and risk of oesophageal adenocarcinoma

| PPI Use | Cases, *n* (%) | Controls, *n* (%) | Adjusted RR (95% CI)* |
|---|---|---|---|
| Never use | 4 (6.7) | 54 (9.8) | 1.0 |
| Short term† | | | |
| Low adherence‡ | 18 (30.0) | 175 (31.8) | 0.7 (0.2–2.9) |
| High adherence‡ | 19 (31.7) | 179 (32.5) | 0.7 (0.2–2.7) |
| Long term† | | | |
| Low adherence‡ | 9 (15.0) | 80 (14.5) | 0.5 (0.1–2.7) |
| High adherence‡ | 10 (16.7) | 63 (11.4) | 0.9 (0.2–4.6) |

* Adjusted for gender, LGD and use of H2 blockers, aspirin and non-aspirin NSAIDs, statins and anti-diabetics.

† Duration of PPI use categorised as short (<7 years) or long term (>7 years).

‡ Adherence of PPI use as measured by <75% (low) or >75% (high) of the daily defined dosage.

**Table 3 |** Frequency of proton pump inhibitor use and combined risk of oesophageal adenocarcinoma and high-grade dysplasia

| PPI Use | Cases, *n* (%) | Controls, *n* (%) | Adjusted RR (95% CI)* |
|---|---|---|---|
| Never use | 6 (4.3) | 125 (9.6) | 1.0 |
| Ever use | 134 (95.7) | 1172 (90.4) | 1.9 (0.7–4.9) |
| Recent use† | 116 (82.9) | 848 (65.4) | 2.1 (0.8–5.6) |
| Former use‡ | 18 (12.9) | 324 (25.0) | 1.1 (0.4–3.3) |

* Adjusted for gender, LGD and use of H2 blockers, aspirin and non-aspirin NSAIDs, statins and anti-diabetics.

† Use of PPI within the last 2 years.

‡ More than 2 years since last PPI prescription.

### Risk of either OAC or HGD

Looking at the outcome of either OAC or HGD combined, 116 (82.9%) of the cases were recent users of PPI and 70 (50%) were high-adherence PPI users. Among the controls, the corresponding numbers were 848 (65.4%) and 589 (45.4%). In total, 26.4% of the case patients and 21.9% of controls received long-term PPI therapy (Tables 1, 3 and 4).

The relative risk of OAC or HGD among BO patients using PPI compared to never/rare users, was 1.1 (95% CI: 0.4–3.3) in former PPI users, 1.9 (95% CI: 0.7–4.9) in ever users and 2.1 (95% CI: 0.8–5.6) in recent users, see Table 3. Long-term PPI use yielded a relative risk of OAC or HGD of 2.2 (95% CI: 0.7–6.7) in the low-adherence group and 3.4 (95% CI: 1.1–10.5) in high-adherence users (Table 4).

## DISCUSSION

In this population-based study among patients with Barrett's oesophagus, we were not able to prove a preventive effect from proton pump inhibitors, instead we found an increased risk of oesophageal adenocarcinoma and high-grade dysplasia related to long-term PPI therapy. Although methodological bias may limit the conclusions, this may in part lead to a re-evaluation of the treatment strategy for Barrett's oesophagus.

### Comparison to previous studies

Patients with BO have an increased risk of developing pre-malignant or malignant transformation of the metaplastic epithelium, although the risk is lower than previously believed.[8, 9] As BO is the main risk factor for developing OAC, studies regarding cancer prevention in

**Table 4 |** Duration and intensity of proton pump inhibitor use and combined risk of oesophageal adenocarcinoma and high-grade dysplasia

| PPI Use | Cases, *n* (%) | Controls, *n* (%) | Adjusted RR (95% CI)* |
|---|---|---|---|
| Never use | 6 (4.3) | 125 (9.6) | 1.0 |
| Short term† | | | |
| Low adherence‡ | 44 (31.4) | 420 (32.4) | 1.7 (0.6–4.7) |
| High adherence‡ | 53 (37.9) | 468 (36.1) | 1.7 (0.6–4.6) |
| Long term† | | | |
| Low adherence‡ | 20 (14.3) | 163 (12.6) | 2.2 (0.7–6.7) |
| High adherence‡ | 17 (12.1) | 121 (9.3) | 3.4 (1.1–10.5) |

* Adjusted for gender, LGD and use of H2 blockers, aspirin and non-aspirin NSAIDs, statins and anti-diabetics.

† Duration of PPI use categorised as short (<7 years) or long term (>7 years).

‡ Adherence of PPI use as measured by <75% (low) or >75% (high) of the daily defined dosage.

this group of patients are of great clinical importance. Previously reflux symptoms have been described as an independent risk factor for OAC,[17] and oesophageal acid exposure as the prominent factor in the malignant transformation from BO into OAC. This assumption has justified widespread routine prescription of PPI to BO patients, despite present international guidelines recommend PPI's as symptomatic treatment only.[24, 25]

In a case–control study from the UK using the general practitioners database, the use of PPI was associated with significantly increased risks of developing OAC. However, when adjusting for reflux symptoms as reported by the doctors, the association was attenuated (although still significant for long-term usage). Even though this is a very solid study, it is important to note that estimates were made using regular population controls and contained no information about BO status.[17]

A study in a large cohort of veterans with BO found no significant association between the use of PPIs and of OAC.[16] However, the study used a selected patient group, and a follow-up of less than 2 years. A follow-up time of more than 5 years, as in our study, might also be considered as a minimum to obtain a plausible evaluation of the OAC risk during PPI therapy.

In another veterans study of 236 BO patients, the incidence of dysplasia was reduced in PPI users and there was an inverse correlation with duration of use. However, the number of cases was rather small and PPI treatment length after BO diagnosis was less than 2 years. Calculating risk estimates for OAC was not possible due to few cases ($N = 2$).[13] Similarly two studies from Australia have shown that absence or delay of PPI therapy before and after BO diagnosis increased the risk of dysplastic progression among BO patients.[14, 18]

A recent Dutch prospective study containing 540 BO patients found a significant preventive effect from PPIs on the risk of both HGD and OAC associated to increasing treatment duration and adherence.[19] The authors suggest that this neoplastic prevention may obviate the need for future expensive endoscopic treatment procedures (EMR, resection). Irrespective of the strong study design, however, the conclusions may be premature due to the relatively small cohort diluted into several stratified groups and a small control group of non-PPI users.

Our results extend the current knowledge in several important ways. The finding of an increased risk of OAC or HGD combined, among high-adherence patients is problematic, and several possible explanations should be taken into account. First, it should be stressed that there is more to reflux than just acid. Gastro-oesophageal reflux is often a mixture of gastric and duodenal contents.[26] Bile has been shown to induce inflammation and cell proliferation in the oesophageal mucosa, and recent *in vitro* studies have shown a possible increased mutagenic effect associated with alkalisation of refluxed bile.[27–29] Hence – although further studies are necessary – PPI use may facilitate the formation of carcinogenic bile acids, explaining some of our findings.

Second, increased gastrin production may also influence the scenario. Gastrin is secreted from the gastric antrum and duodenum and has a stimulating effect on cells throughout the gastrointestinal system. The gastrin level may increase 5–10 fold during PPI therapy, and may have anti-apoptotic and proliferative effects that contribute to neoplasia.[30] This may increase the risk of gastrointestinal tumours.[31, 32] Previous studies have been conflicting. A recent study investigating colorectal cancer risk found no such association.[23] In BO, a recent *in vivo* and *vitro* study found no association between length of oesophageal metaplasia and gastrin level,[33] whereas two other studies found a significant correlation between gastrin and the risk of dysplasia and OAC.[34, 35]

Third, confounding by indication, as discussed below, can play an important role in the observed associations.

## Strength and limitations

The strength of our study includes the large cohort, including all BO patients nationwide, the use of registries with validated high data coverage and the complete prescription and hospital history. We report the longest follow-up time compared to previous studies. Long fol-

low-up time and large cohorts are important when assessing diseases with low incidence, as emphasised by the only 60 incident cancers among our 9,883 patients. Secondly, as all prescription medication was recorded prospectively, there is no recall bias, and the use of the unique civil registration number allows a population-based design, complete follow-up and linkage across registries. Most studies have not been able to identify type and dosage, but rather number of prescriptions of PPI and therefore we could not use previous definitions, which were also subject to more bias. In our study we have taken great effort in developing definitions of PPI usage, adherence and length of treatment, thereby presenting the most accurate medication intake presented in a study so far. This has been done to best present the clinical setting and also by looking at the way previous studies have defined PPI usage.[23]

Although controlled for several important potential confounders (sex, diabetes, NSAIDs, aspirins, statins), our study has some methodological factors that might affect our estimates. We did not have information about body mass index, tobacco and alcohol consumption or *H. pylori* status, which may be important factors in dysplastic progression. As in the previous published studies we were not able to adjust for BO length and the possible increased reflux and risk of dysplastic progression in these patients. As the diagnosis of LGD could drive an increased prescription of PPI's, the reported estimates are adjusted for the presence of LGD, even though it is in causal relation to OAC/HGD. This adjustment influences the estimates towards less statistical significance.

PPI has been available in small, low-dose packages over-the-counter during the last years of this study, and this has not been recorded by the nationwide prescription database. However, this confounding is minimal, as patients with a need for long time ongoing medication are likely to use prescribed medication that is partly reimbursed by the national health insurance. This is supported by previous studies describing this bias.[36, 37]

We did not have data on the patients' actual compliance to the prescribed drugs. However, PPIs are only partly reimbursed, which minimises continuous prescriptions combined with noncompliance, and furthermore residual confounding is expected to be evenly distributed between groups.

Although we have excluded use within 1 year of OAC or HGD diagnosis in order to minimise confounding, difficulties with adjusting the PPI use to the level of reflux can induce confounding by indication, i.e. it is the severity of reflux that predisposes to cancer, not the PPIs used to treat the reflux. It is very likely that a large proportion of the registered PPI usage is symptom driven and reflux symptoms have also been associated to the risk of OAC in persons with no known BO status.[38] However, it is a well-known fact that reflux symptoms correlate poorly with the actual amount of reflux in GORD patients, and that the presence of BO may make patients more hyposensitive to acid reflux.[5, 39–41] PPI usage and severity of reflux is therefore not necessarily linear. Hence, the risk correlation between PPI and incidence of OAC reflects the therapeutic picture – not measurable reflux.[41, 42] When we take these important bias into account we must conclude that should severe reflux be the cause and PPI use the measurable outcome, then the results show that PPI use seem to be unsatisfactory for cancer protection. This is in line with national guidelines, which recommends PPIs for symptom control and not for the prevention of OAC.[24, 25]

## CONCLUSIONS

In patients with Barrett's oesophagus, we found no evidence of a protective effect from PPI on the development of OAC or HGD. In fact, we observed an increased risk for developing high-grade dysplasia and adenocarcinoma in the oesophagus with long-term PPI usage. This association can partly be due to bias associated to symptom driven PPI intake. Until the results from future studies can further elucidate the association, PPIs should be restricted to symptom control according to current guidelines. Hence, PPI may not protect against malignant progression in BO patients and in selected high-risk patients, clinicians may consider adding or replacing long-term medical treatment with other modalities.

## AUTHORSHIP

*Guarantor of the article*: Asbjørn Mohr Drewes.

*Author contributions*: Frederik Hvid-Jensen: Designed the study, criteria and outcome, searched previous published studies, collected and interpreted data and wrote the article. Lars Pedersen: Designed the study, collected data and performed statistical analyses and contributed to 'materials & methods' section. Asbjørn Mohr Drewes and Peter Funch-Jensen: Designed the study, interpreted data and wrote the article. All authors approved the final version of the manuscript.

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