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Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

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Abstract

Proton pump inhibitors (PPIs) are commonly used drugs among cancer patients. Due to conflicting reports on their safety, we aimed to determine whether PPI use is associated with mortality among prostate cancer patients. In this population-based cohort study, we identified incident diagnoses of prostate cancer between 2007 and 2012 (n = 1058). Follow-up was from 12 months after diagnosis until death, emigration or end the of study. Post-diagnosis use was defined as ≥2 filled prescriptions following diagnosis. We used time-dependent Cox proportional hazard regression models to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific and all-cause mortality associated with post-diagnosis use of PPIs. We identified 347 (32.8%) post-diagnosis PPI users and 711 (67.2%) non-users after diagnosis. Of the 347 patients using PPIs after diagnosis, 59 (17.0%) died due to any cause and 22 (6.3%) due to prostate cancer, compared with 144 (20.3%) and 76 (10.7%) among non-users after diagnosis, respectively. Post-diagnosis PPI use was not associated with prostate cancer-specific mortality (HR 0.88; 95% CI: 0.52-1.48) or all-cause mortality (HR 1.02; 95% CI: 0.73-1.43). Contrary to a previous report, this study did not find evidence of an association between post-diagnosis PPI use and mortality among prostate cancer patients.

KEYWORDS

mortality, nationwide, pharmacoepidemiology, prostate cancer, proton pump inhibitors

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used drugs and their use has been increasing quite rapidly over the last decade.[1] As potent inhibitors of acid secretion, PPIs were originally developed to inhibit the activity of the H+/K+ ATPase, a type of proton pump that secretes gastric acid from parietal cells of the stomach.[2] However, they have also been shown to have an affinity for another proton pump, that is the vacuolar H+-ATPase (V-ATPase).[3,4] The V-ATPase is frequently seen overexpressed in the plasma membrane of cancer cells where they are believed to promote alkalization of the cytoplasm and acidification of the tumour microenvironment.[5-10] Increased tumour acidity has been associated with a malignant cancer phenotype characterized by increased invasiveness, metastatic potential and drug resistance.[11-13] Thus, due to the

ability of PPIs to inhibit V-ATPase function, their repositioning as potential antineoplastic agents has been suggested.[14] Studies, in vitro and in vivo, have reported a potential anticancer activity of PPIs[15-17] and a phase II trial among breast cancer patients with a metastatic disease reported increased efficacy of chemotherapy in patients pre-treated with PPIs.[18] Furthermore, a clinical study among osteosarcoma patients found that pre-treatment with PPIs improved the effectiveness of chemotherapy.[19] These results highlight a potential avenue for studying whether PPI use increases the effectiveness of cancer therapy in various cancer types.

The potential association between PPI use and cancer mortality has not been evaluated conclusively in epidemiological studies. A study among pancreatic cancer patients found no association between PPI use and survival.[20] Another study found that PPI use, and use of histamine receptor-2 antagonist (H2RA), was associated with improved overall survival among patients with head and neck squamous cell cancer.[21] However, a recent Danish study reported that PPI use was associated with increased cancer-specific mortality for a number of cancer types, including prostate cancer.[22]

Prostate cancer is the second most commonly diagnosed cancer among men and the fifth most frequent cause of cancer-specific death.[23] Given the conflicting results of the few epidemiological studies conducted so far, the increasing overall use of PPIs, and the high incidence of prostate cancer, we aimed to utilize the high-quality nationwide register data available in Iceland to examine the association between post-diagnosis PPI use and mortality among prostate cancer patients.

2 | METHODS

2.1 | Data sources

This was a population-based cohort study where we used unique personal identification numbers to link together data from the Icelandic Cancer Registry,[24] the Icelandic Medicines Registry, the Icelandic Population Register, the Cause of Death Register, and from electronic health records of Landspitali—The National University Hospital of Iceland.

2.2 | Study population

Eligible patients, identified using the Icelandic Cancer Registry, were all adult Icelandic residents between 40 and 85 years of age with a verified first-time diagnosis of prostate cancer (ICD-10: C61) between 1 January 2007 and 31 December 2012.

2.3 | Follow-up and mortality outcomes

The primary outcome in all analyses was prostate cancer-specific mortality. The secondary outcome was all-cause mortality. Prostate cancer-specific mortality was defined by the relevant ICD-10 code (C61) as the underlying cause of death. Eligible patients were followed from 12 months after prostate cancer diagnosis until their death, emigration or end of the study period (31 December 2015). We excluded those patients who died or emigrated from Iceland within 12 months after diagnosis.

2.4 | Exposure assessment

We obtained information on PPI use from the Icelandic Medicine Registry, a nationwide prescription register with a completeness ranging from 91% to 99%. Although PPIs became available over-the-counter (OTC) in 2009, the majority (>90%) of PPIs between 2009 and 2015 were obtained by prescription.[1] We considered the Anatomical Therapeutic Chemical (ATC)[25] code group A02BC as a PPI dispensing. Four PPI substances were prescribed within our cohort during the period under study: omeprazole (A02BC01), lansoprazole (A02BC03), rabeprazole (A02BC04) and esomeprazole (A02BC05). The information we received for every PPI prescription between 1 January 2003 and 31 December 2015, including date of dispensing, ATC code and number of dispensed "defined daily doses" (DDDs).

The primary exposure was post-diagnosis PPI use, defined as at least two or more dispensed PPI prescriptions after prostate cancer diagnosis. In all analyses, we considered the exposed person-time of post-diagnosis PPI users in a time-dependent manner to avoid time-related biases such as immortal time bias.[26] In the main analysis, patients were thus initially considered unexposed until they received a second PPI prescription, after which they were considered exposed for the remainder of follow-up. Furthermore, the exposed person-time was lagged by 12 months to account for the possibility of reverse causation and to allow for a biologically meaningful latency period, since it is unlikely that a short duration of drug use would influence mortality outcomes in a significant way. Patients that did not receive at least two PPI dispensing after diagnosis were thus considered as non-users after diagnosis.

For the purposes of secondary analyses, we explored the timing of PPI use by assessing pre-diagnosis PPI use. Patients were considered pre-diagnosis users if they received at least two PPI prescriptions in the 3 years prior to diagnosis. Pre-diagnosis use was modelled as a time-fixed covariate, that is a dichotomous yes/no variable. Thus, patients exposed to PPIs were either considered to be "new PPI users" or "continuing PPI users" based on their exposure status before and after diagnosis. We defined new users as those patients that only

used PPIs after diagnosis while those who used PPIs prior to and after diagnosis were considered as continuing PPI users. Additionally, we estimated the cumulative dose for each patient based on the total number of dispensed DDDs during exposed person-time (0 DDDs, 1-365 DDDs, >365 DDDs).

2.5 | Covariates

We considered a range of demographic and clinical factors for multivariable adjustments. Patient age at diagnosis and year of diagnosis were modelled as continuous variables. A medication-based comorbidity score was derived by identifying the number of different prescription drug groups that were dispensed in the 12 months prior to a cancer diagnosis (excluding filled PPI prescriptions in this period).[27,28] To be categorized in the same group, the drugs had to share the same initial four characters of the ATC classification system. The medication-based comorbidity score was then modelled as a continuous variable. Clinical stage at diagnosis according to the tumour-node-metastasis (TNM) system was classified into three categories if information on M was available: localized (M0), non-localized (M1) and unknown (Mx or information missing). We adjusted for the following clinical variables: Gleason score was grouped into five distinct categories (2-5, 6, 7, ≥8 and unknown). Cancer treatment in the 12 months following diagnosis was accounted for in the following way: cancer surgery was categorized into three categories (total excision of prostate, partial excision of prostate and no surgery), cancer drug treatment was grouped into four categories (chemotherapy, endocrine therapy, combination of chemotherapy and endocrine therapy, and no therapy), and radiotherapy was modelled as a dichotomous variable (radiotherapy, no radiotherapy).

2.6 | Data analysis

We used a time-dependent Cox proportional hazard regression models, with time since diagnosis as the underlying time-scale, to estimate crude and multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific mortality and all-cause mortality associated with post-diagnosis PPI use modelled as a time-dependent covariate where patients were considered unexposed until they had met the exposure criteria and then remained exposed throughout follow-up. In multivariable adjusted analyses, we adjusted for the aforementioned covariates, also listed in Table 1. We evaluated the validity of the proportional hazard assumptions using a Grambsch-Therneau test of the scaled Schoenfeld residuals from a Cox model.[29]

In the main analysis, we assessed PPI use following prostate cancer diagnosis, modelled as a time-dependent

TABLE 1 Descriptive characteristics of a cohort of Icelandic prostate cancer patients diagnosed between 1 January 2007 and 31 December 2012 by PPI exposure status

	Proton pump inhibitor use		
	Non-users after diagnosis	Post-diagnosis users	
		Continuing	New
	N = 711	N = 182	N = 165
Age at diagnosis—y			
Median (IQR)	69 (62-75)	70 (64-76)	68 (62-75)
Age groups (%)			
40-54	47 (6.6)	3 (1.6)	11 (6.7)
55-69	338 (47.5)	85 (46.7)	84 (50.9)
70-85	326 (45.9)	94 (51.7)	70 (42.4)
Year of diagnosis (%)			
2007-2009	349 (49.1)	97 (53.3)	111 (67.2)
2010-2012	362 (50.9)	85 (46.7)	54 (32.7)
Clinical stage			
Localized	549 (77.2)	149 (81.9)	134 (81.2)
Non-localized	59 (8.3)	11 (6.0)	11 (6.7)
Unknown	103 (14.5)	22 (12.1)	20 (12.1)
Gleason score			
<7	371 (52.2)	92 (50.5)	85 (51.5)
7	195 (27.4)	54 (29.7)	49 (29.7)
≥8	134 (18.8)	32 (17.6)	28 (17.0)
Unknown	11 (1.6)	4 (2.2)	3 (1.8)
Radiotherapy (%)[a]			
Yes	196 (27.6)	53 (29.1)	39 (23.6)
No	515 (72.4)	129 (70.9)	126 (76.4)
Cancer surgery (%)[a]			
Total excision of prostate	173 (24.3)	41 (22.5)	45 (27.3)
Partial excision of prostate	63 (8.9)	28 (15.4)	16 (9.7)
No surgery	475 (66.8)	113 (62.1)	104 (63.0)
Cancer drug treatment (%)[a]			
Yes	62 (8.7)	14 (7.7)	17 (10.3)
Chemotherapy (%)[a]			
Yes	8 (1.1)	0 (0.0)	1 (0.6)
Endocrine therapy (%)[a]			
Yes	43 (6.0)	14 (7.7)	10 (6.1)
Chemotherapy & endocrine therapy[a]			
Yes	11 (1.5)	0 (0.0)	6 (3.6)
Medication-based comorbidity			
Median (IQR)	5 (3-8)	9 (7-12)	6 (4-8)

[a]Treatment in first year after diagnosis.

covariate as described above. Exposed person-time was then lagged by 12 months following a second dispensing of a post-diagnosis PPI prescription. Furthermore, we performed three secondary analyses. Firstly, PPI use was stratified by pre-diagnosis PPI use. Additionally, we incorporated an interaction term between pre-diagnosis and post-diagnosis PPI use to assess whether pre-diagnosis PPI use acted as an effect modifier of the association between post-diagnosis PPI use and prostate cancer-specific mortality. Secondly, we stratified by clinical stage at diagnosis (localized versus non-localized). Thirdly, we stratified PPI use by cumulative dose (0 DDDs, 1-365 DDDs, >365 DDDs).

We performed two sensitivity analyses to assess the definition of PPI use. In the first one, post-diagnosis PPI use was defined as at least one filled PPI prescriptions following diagnosis and the exposure was modelled as a time-dependent covariate as in the main analysis. In the second sensitivity analysis, we defined post-diagnosis PPI use as at least two filled prescriptions within 12 months following the diagnosis of prostate cancer.

All analyses were performed using the survival package[30] in R.[31] This study was approved by the National Bioethics Committee in Iceland (study reference number: VSNb2015080004/03.03).

3 | RESULTS

We initially identified 1138 prostate cancer patients, but after implementing the exclusion criteria, 1058 were eligible for inclusion in the study (Figure 1). During 4810 person-years of follow-up, we identified a total of 203 patients (19.2%) that died, thereof 98 patients (9.3%) that died due to prostate cancer. The median follow-up time was 4.6 years. Among eligible patients, 347 (32.8%) were identified as post-diagnosis PPI users; thereof 182 (52.4%) were continuing PPI users and 165 (47.6%) new PPI users. Among the 347 post-diagnosis PPI users, we identified 59 patients (17.0%) that died from any cause and 22 patients (6.3%) that died from prostate cancer, compared with 144 patients (20.3%) and 76 patients (10.7%) among non-users after diagnosis, respectively. The median age among post-diagnosis PPI users was 69 years (interquartile range: 63-76) while it was 69 years (interquartile range: 62-75) among non-users after diagnosis. The majority of all patients were diagnosed with a localized disease; 81.6% among post-diagnosis PPI users and 77.2% among non-users after diagnosis. Compared with non-users after diagnosis, post-diagnosis PPI users had a higher median of medication-based comorbidity score (Table 1).

In the main analysis, we observed adjusted HRs of 0.88 (95% CI: 0.52-1.48) for prostate cancer-specific mortality and 1.02 (95% CI: 0.73-1.43) for all-cause mortality among post-diagnosis PPI users as compared with non-users after diagnosis

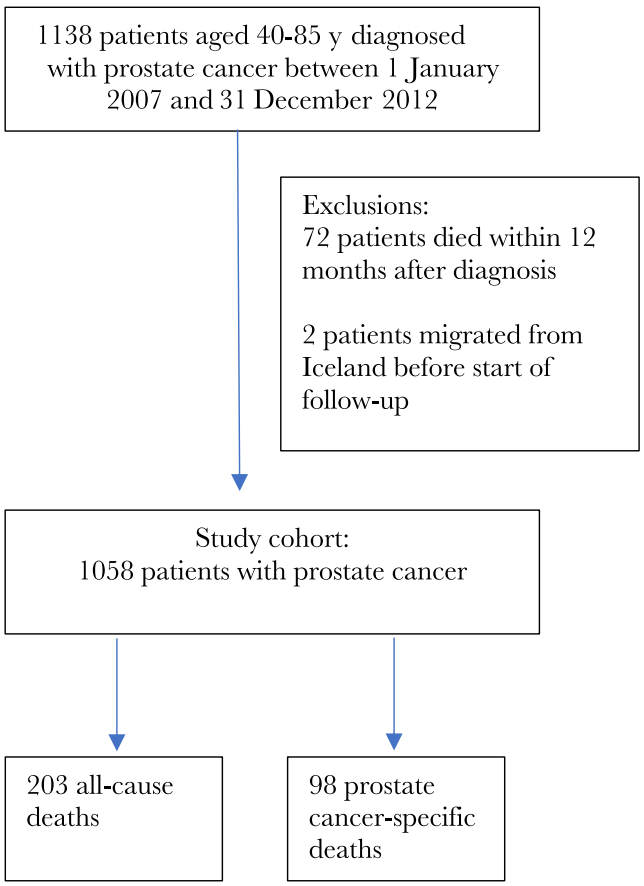

FIGURE 1 Study flowchart of cohort identification

(Tables 2 and 3). In secondary analyses for prostate cancer-specific mortality (Table 2), we observed adjusted HRs of 0.45 (95% CI: 0.21-0.98) among continuing PPI users and 1.12 (95% CI: 0.61-2.08) among new PPI users, when we stratified by pre-diagnosis PPI use (test for effect modification $P = .026$). Stratifying by clinical stage at diagnosis yielded adjusted HRs of 0.50 (95% CI: 0.22-1.16) and 1.00 (95% CI: 0.44-2.27) among patients with localized and non-localized disease, respectively. For cumulative dose, we observed an adjusted HR for cumulative use of 1-365 DDDs of 0.91 (95% CI: 0.43-1.90) and 0.86 (95% CI: 0.45-1.61) for >365 DDDs. For all-cause mortality (Table 3), the adjusted HRs were 0.67 (95% CI: 0.43-1.04) and 1.25 (0.82-1.92) among continuing and new PPI users, respectively. Analyses stratified by clinical stage at diagnosis yielded an adjusted HR of 0.74 (95% CI: 0.47-1.15) among patients with localized disease and 1.18 (95% CI: 0.58-2.34) among patients with non-localized disease. For cumulative PPI use, we observed adjusted HRs of 1.19 (95% CI: 0.76-1.87) and 0.91 (95% CI: 0.61-1.37) for patients using 1-365 DDDs and >365 DDDs, respectively.

Redefining post-diagnosis use as at least one filled prescription for a PPI drug yielded similar result as in the main analysis (Table S1). When we redefined the exposure opportunity window by assessing PPI use only in the 12 months following prostate cancer diagnosis, we observed HRs that

TABLE 2 Cox proportional hazard regression models for associations between post-diagnosis PPI use and prostate cancer-specific mortality among patients diagnosed with prostate cancer in Iceland between 2007 and 2012

Prostate cancer-specific mortality				
PPI exposure	**No of deaths**	**No of person-years**	**Age adjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**
Non-users after diagnosis	76	3640	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI users	22	1171	0.85 (0.52-1.38)	0.88 (0.52-1.48)
Timing of use				
Continuing PPI users	8	734	0.45 (0.22-0.93)	0.45 (0.21-0.98)
New PPI users	14	437	1.39 (0.77-2.53)	1.12 (0.61-2.08)
Clinical stage at diagnosis				
Localized	8	1006	0.55 (0.25-1.23)	0.50 (0.22-1.16)
Non-localized	9	39	0.92 (0.43-1.96)	1.00 (0.44-2.27)
Cumulative dose				
1-365 DDDs	9	390	1.04 (0.52-2.09)	0.91 (0.43-1.90)
>365 DDDs	13	780	0.75 (0.41-1.37)	0.86 (0.45-1.61)

Abbreviations: CI, confidence interval; DDD, defined daily doses; HR, hazard ratio.

[a]Adjusted for age at diagnosis.

[b]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy.

TABLE 3 Cox proportional hazard regression models for associations between post-diagnosis PPI use and all-cause mortality among patients diagnosed with prostate cancer in Iceland between 2007 and 2012

All-cause mortality				
PPI exposure	**No of deaths**	**No of person-years**	**Age adjusted HR (95% CI)[a]**	**Adjusted HR (95% CI)[b]**
Non-users after diagnosis	144	3640	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI users	59	1171	1.16 (0.85-1.59)	1.02 (0.73-1.43)
Timing of use				
Continuing PPI users	28	734	0.81 (0.54-1.22)	0.67 (0.43-1.04)
New PPI users	31	437	1.57 (1.04-2.36)	1.25 (0.82-1.92)
Clinical stage at diagnosis				
Localized	33	1006	0.99 (0.65-1.50)	0.74 (0.47-1.15)
Non-localized	13	39	1.08 (0.57-2.06)	1.18 (0.58-2.34)
Cumulative dose				
1-365 DDDs	27	390	1.61 (1.06-2.44)	1.19 (0.76-1.87)
>365 DDDs	32	780	0.93 (0.63-1.38)	0.91 (0.61-1.37)

Abbreviations: CI, confidence interval; DDD, defined daily doses; HR, hazard ratio.

[a]Adjusted for age at diagnosis.

[b]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy.

were slightly lower, but mostly in line with those observed in the main analysis (Table S2).

4 | DISCUSSION

In this population-based cohort study among Icelandic prostate cancer patients, we did not observe a clear association between post-diagnosis PPI use and mortality among prostate cancer patients. To our knowledge, this is only the second observational study to explore the association between PPI use and mortality among prostate cancer patients.

Proton pump inhibitors are commonly used among cancer patients,[32] often as a preventive measure against the risk of gastric ulceration following chemotherapy, radiotherapy

and steroid use.[33] Furthermore, PPI use has been shown to be associated with indicators of worse overall health[34,35] and among prostate cancer patients PPIs have been suggested to be related to decreased overall health.[36] Recently, post-diagnosis use of PPIs was reported to be associated with increased mortality among cancer patients; both overall (HR 1.29, 95% CI: 1.27-1.32) and among patients with certain site-specific cancers, including prostate cancer (HR 1.25, 95% CI: 1.14-1.36). Furthermore, that association was found to be substance-specific.[22] In contrast to these findings, previous clinical studies have reported that PPIs might actually enhance the effectiveness of chemotherapy.[18,19] However, there have also been reports of unwanted drug interactions between PPIs and oral anticancer agents suggesting a negative impact of PPIs on chemotherapeutic efficacy.[33,37] Unfortunately, we were unable to perform stratified analyses by chemotherapy or PPI substance in our study due to the small sample size leading to low numbers in stratified subgroups.

Our observations of null associations between PPI use and prostate cancer-specific and all-cause mortality are in contrast with the findings of Tvingsholm et al In their study, they found that the observed increased mortality seemed to be exclusively among new PPI users, while the increased risk was not observed among continuing PPI users.[22] Their results seem to suggest that there is some unmeasured confounding at play, since the increased mortality is only observed among patients that start their PPI use after they are diagnosed with prostate cancer. It seems likely, that if PPI use does in fact increase the risk of mortality among post-diagnosis users, that this would also be observed among continuing PPI users, who have been using PPIs for longer durations and consumed a greater cumulative quantity of the drugs. However, it could also be argued that the difference observed between patients that were exposed and unexposed to PPIs prior to diagnosis might stem from a form of detection bias, since pre-diagnosis PPI users might be expected to be in closer contact with the healthcare system in the months and years leading up to their diagnosis, potentially leading to a more timely diagnosis and a more favourable prognosis. In our study, although we observed slightly higher point estimates among new users of PPIs than among continuing users, our data did not indicate that initiating PPI use after diagnosis was associated with excess mortality.

This study has several limitations that might have influenced our observations. Firstly, we lacked information on clinical diagnoses to be able to adjust for underlying comorbidities. We attempted to counteract this limitation by using a medication-based comorbidity score as a proxy but still some confounding by indication may remain. Secondly, we did not have information on concomitant use of other drugs that might influence our estimates, for example statins which have been reported to be associated with decreased mortality among prostate cancer patients.[38,39] Thirdly, misclassification of PPI use might have resulted from use within the hospital setting and OTC use since we only had information on dispensed PPI drugs to the outpatient population. OTC use of PPIs was, however, minimal during the study period.[1] Fourthly, we were unable to obtain information on the measured level of prostate-specific antigen (PSA) at diagnosis; a variable that is used in clinical staging and could influence prognosis. Fifthly, as in all studies of this nature, our assessment of PPI use is based on dispensed drugs, which we cannot be sure are necessarily consumed. However, we tried to minimize the influence of this potential bias by the requirement of PPI users having received at least two filled prescriptions, in the main analysis. Finally, the modest sample size of our cohort limited our ability to draw definitive conclusions from our observations. The primary strength of our study was the clearly defined population-based cohort and our utilization of high-quality nationwide register data. Furthermore, utilization of register data removed the risk of recall bias.

In summary, contrary to a previous report, our findings do not indicate that post-diagnosis PPI use influences mortality risk among prostate cancer patients. Future studies should aim to further elucidate whether PPI use influences mortality among prostate cancer patients, using a larger cohort, longer follow-up time and minimizing as possible the potential impact of confounding by indication.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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