Post-diagnostic use of beta-blockers and the risk of death in patients with prostate cancer

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Abstract ***Background:*** Recent observational studies have produced conflicting results with respect to beta-blocker use after prostate cancer diagnosis and mortality outcomes.
Objective: To determine whether post-diagnostic use of beta-blockers is associated with prostate cancer mortality and all-cause mortality.
Patients and methods: A cohort of 6270 men newly-diagnosed with non-metastatic prostate cancer between 1st April 1998, and 31st December 2009, followed until 1st October 2012, was identified using large population-based electronic databases from the United Kingdom. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality outcomes associated with post-diagnostic use of beta-blockers. Secondary analyses were performed to examine the independent effects of non-selective beta-blockers, as well as cumulative duration of use.
Results: During a mean follow-up time of 3.8 years (standard deviation: 2.7 years), 1761 deaths occurred, including 715 from prostate cancer. Post-diagnostic use of beta-blockers was not associated with a decreased risk of prostate cancer mortality (HR: 0.97, 95% CI: 0.72–1.31) and all-cause mortality (HR: 0.97, 95% CI: 0.81–1.16). There was no statistically significant association for non-selective beta-blockers (prostate cancer mortality, HR: 1.05, 95% CI: 0.72–1.53 and all-cause mortality, HR: 0.94, 95% CI: 0.74–1.18), and no statistically significant trends of cumulative duration of use for both mortality outcomes.
Conclusion: The use of beta blockers, including those of the non-selective type, was not associated with a decreased risk of prostate cancer and all-cause mortality.

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1. Introduction

Beta-blockers have recently been under investigation for their antineoplastic effects [1,2]. Indeed, preclinical data have shown that activation of β-adrenergic receptors is involved in tumour cell proliferation, angiogenesis and tumour migration [3,4]. Moreover, laboratory models have demonstrated that catecholamines such as epinephrine and norepinephrine can induce tumour cell invasion and migration [1,5]. Thus, the inhibitory potential of beta-blockers has become the focus of several *in vitro* studies on tumour progression and metastasis, which included prostate and other tumour types [1,6,7].

To date, several observational studies have reported strong risk reductions in metastasis and cancer-specific mortality with the use of beta-blockers in patients with certain cancer types [2,8–13]. With respect to prostate cancer, observational studies have reported conflicting results [13–16]. These studies had a number of methodological limitations, including small sample sizes [16] and possible immortal time bias [13,17–19]. Furthermore, none of these studies examined the effects of the less commonly prescribed non-selective beta blockers, such as propranolol, which have been associated with decreased metastasis in animal models [1,3,4].

Thus, given the potential anti-tumour effects of beta-blockers, and recent and conflicting evidence in patients with prostate cancer, we conducted a large-population based cohort study to assess whether post-diagnostic use of these drugs is associated with a decreased risk of cancer-specific and all-cause mortality in men diagnosed with prostate cancer. Secondary objectives were to assess whether these effects varied with cumulative duration of use, and whether beta-blocker selectivity had an impact on these outcomes.

2. Patients and methods

2.1. Data sources

This study was conducted by linking the following four large electronic databases from the United Kingdom (UK): the National Cancer Data Repository (NCDR), Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) database, and the Office for National Statistics (ONS) database. The NCDR contains tumour information, including site of primary growth (coded using the International Classification of Diseases, 10th Revision [ICD-10]) and tumour characteristics (such as grade, stage and primary treatments received). The CPRD contains data on more than 13 million individuals enrolled in more than 680 general practices. Furthermore, the recorded information on drug exposures and diagnoses in the CPRD has been validated and proven to be of high quality [20–24]. The HES database contains dates of hospital admissions, primary and secondary diagnoses (coded using the ICD-10 classification), and procedures (coded using the ICD-10 classification and Office of Population Censuses and Surveys Classification of Interventions and Procedures, Fourth Version). Finally, the ONS contains the electronic death certificates of all citizens living in the United Kingdom and was used to identify the underlying cause of death (coded using the ICD-10 classification) for all patients who died during follow-up. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

2.2. Study population

A population-based retrospective cohort study was conducted within the databases described above. First, we used the NCDR to identify all men newly-diagnosed with prostate cancer (ICD-10 code: C61) between 1st April 1998, and 31st December 2009. These patients were then linked to the CPRD, HES and ONS databases.

We excluded patients diagnosed with metastatic disease and those with less than 1 year of up-to-standard medical history in the CPRD before the prostate cancer diagnosis. The cohort was also restricted to patients who received at least one prescription for an antihypertensive drug (consisting of beta-blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], alpha-blockers and others [diuretics, aldosterone antagonist and vasodilators]) in the year prior to diagnosis. Restricting the cohort to patients with a history of antihypertensive drug use was necessary to minimise potential confounding by indication, which was a major limitation of some of the previous studies [2,8,14,25]. Furthermore, all patients were required to have at least 1 year of follow-up, which was necessary for latency considerations. Thus, cohort entry was set to the year after the prostate cancer diagnosis, and all patients were observed until death (either from prostate cancer or from other causes), end of registration with the general practice or end of study period (1st October 2012), whichever came first.

2.3. Beta-blocker exposure assessment

The use of beta-blockers (listed in Supplemental Table 1) after the prostate cancer diagnosis was entered as a time-dependent variable in the models, allowing patients to move from a period of non-exposure to a period of exposure. Furthermore, beta-blocker exposure was lagged by 1 year to take into account a biologically meaningful latency time window, as short duration exposures are unlikely to have any biological effects. Thus, patients were considered unexposed to beta-blockers up until the 1 year after the time of a first

prescription and then considered exposed for the remainder of follow-up.

Post-diagnostic beta-blocker exposure was expressed in the following two ways: post-diagnostic use and cumulative duration of use. For the first approach, post-diagnostic use of beta-blockers was compared with never use up until the time of the risk set (i.e. time of the case event and corresponding time of the cohort still at risk). For the second approach, it was of interest to determine whether there was a trend with beta-blocker cumulative duration of use and the mortality outcomes. Therefore, cumulative duration of use was defined, in a time-dependent fashion, as the total number of months of beta-blocker use which was calculated by summing the durations of all prescriptions between cohort entry and the time of the risk set. This variable was then classified into the following four categories: <12 months, 12–24 months, 24–36 months, and >36 months of use. In a secondary analysis, we examined the effects of non-selective beta-blockers both in terms of post-diagnostic use and cumulative duration of use. The latter was classified into two categories due to the few exposed patients: <24 months and ⩾24 months of use. Finally, we also assessed whether pre-diagnostic use of beta blockers modified the association between post diagnostic use of beta blockers and the two mortality outcomes.

2.4. Statistical analysis

Descriptive statistics were used to describe the characteristics of the cohort. Time-dependent Cox proportional hazards models were used to estimate hazards ratios (HRs) with 95% confidence intervals (CIs) of prostate cancer mortality and all-cause mortality associated with the post-diagnostic use and cumulative duration of use of beta-blockers. All models were adjusted for of the following potential confounders measured at the date of the prostate cancer diagnosis: age, year of cohort entry, ethnicity, excessive alcohol use, obesity ($\geqslant 30$ kg/m^2), smoking status and socio-economic status using the Townsend Material Deprivation Score [26]. This is a composite score calculated using census data on unemployment, overcrowding, access to a car and home ownership. Patients were assigned a score based on the area where their general practice is located. The scores were stratified into quintiles, from Q1 (the least deprived quintile) to Q5 (most deprived quintile). Other potential confounders, also measured before the prostate cancer diagnosis, were cardiovascular comorbidities (at any time before diagnosis), and use of antihypertensive drug use, statins, aspirin, other non-steroidal anti-inflammatory drugs, antiplatelet drugs, beta-agonists and anti-diabetic drugs (metformin, sulfonylureas, insulins and other anti-diabetic drugs), all measured in the year prior to diagnosis. The models also considered the following prostate cancer related variables: prostate-specific antigen (PSA) level prior to diagnosis, Gleason score, as well as prostate cancer-related treatments (prostatectomy, radiation therapy, androgen deprivation therapy (ADT) and chemotherapy), all measured in the year between prostate cancer diagnosis and cohort entry. Stage information was only available for 10% of patients, and thus it was not included in the models. Finally, the use of antihypertensive drugs (ACEIs, ARBs, CCBs, alpha-blockers and others) used during follow-up was included as time-dependent covariate in the models, and lagged by 1 year as with the main exposure variable.

Finally, for the prostate cancer mortality analysis, we conducted a sensitivity analysis to account for competing risks as a result of death from other causes using the sub-distribution hazards model proposed by Fine and Gray [27]. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and the competing risk analyses were performed using R software version 3.0.2.

3. Results

Of the 15,540 patients diagnosed with prostate cancer during the study period, 6270 met the study inclusion criteria (Fig. 1). The mean duration of follow-up was 3.8 years (standard deviation (SD): 2.7), and the crude incidence rates of prostate cancer mortality and all-cause mortality were 29.6 per 1000 per year (95% CI: 27.8–32.2) and 71.6 per 1000 per year (95% CI: 70.0–77.4), respectively.

The characteristics of the cohort members are presented in Table 1. The mean age at cohort entry was 72.3 (standard deviation [SD]: 8.3) years, and the majority of the cohort members were white (75.8%). In terms of antihypertensive drug use in the year prior to diagnosis, the most prevalent class was alpha-blockers (39.5%) while beta-blockers were used by 30.5% of the cohort (of which 13.3% were the non-selective type). The use of statins (38.0%) and aspirin (39.3%) represented the most prevalent other non-antihypertensive drugs used prior to diagnosis. As expected, the majority of patients had a diagnosis for hypertension (59.8%) followed by coronary heart disease (32.3%). As for prostate cancer treatments, the majority of patients received radiation therapy (58.0), followed by radical prostatectomy (44.1%), while few patients received chemotherapy (2.5%). ADT was prescribed to close to 60% of the cohort (Table 1).

The results of the primary analysis are presented in Table 2. Overall, post-diagnostic use of beta-blockers was not associated with a decreased risk of prostate cancer mortality (HR: 0.97, 95% CI: 0.72–1.31). This remained consistent in a sensitivity analysis that considered competing risks from other causes deaths (Supplemental Table 2). There was also no evidence of

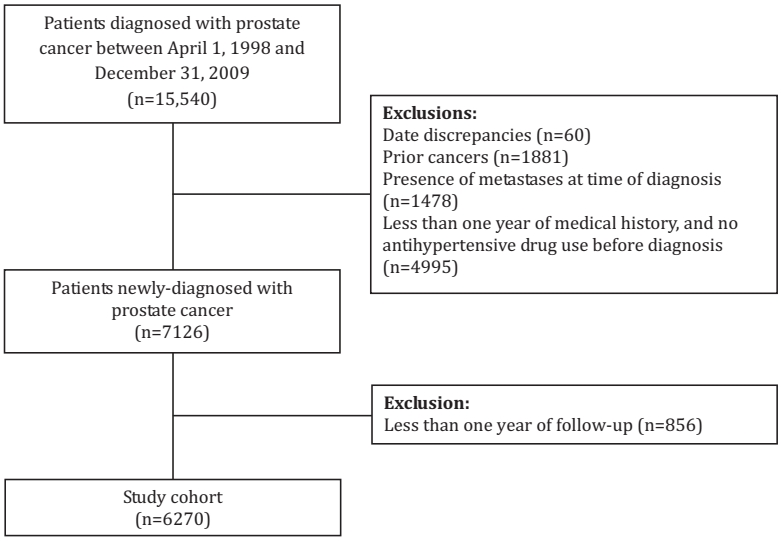

Fig. 1. Study flow chart.

a duration-response relationship between the use of these drugs and prostate cancer mortality (p value for trend = 0.61), with all HRs above the null value and statistically non-significant (Table 2).

The results for the secondary outcome of all-cause mortality are presented in Table 3. Post-diagnostic use of beta-blockers was not associated with a decreased risk of this outcome (HR: 0.97, 95% CI: 0.81–1.16), and there was no association with cumulative duration of use (p value for trend = 0.91) (Table 3).

Table 4 presents the results for prostate cancer mortality and all-cause mortality associated with the post-diagnostic use of non-selective beta-blockers. Overall, the use of these drugs was not associated with prostate cancer mortality, and there was no evidence of duration-response relationship ($p = 0.81$). These results remained consistent in a sensitivity analysis that considered competing risks for other non-prostate cancer deaths (Supplemental Table 2). Similar null findings were observed for all-cause mortality overall, and by cumulative duration of use (p value for trend = 0.80) (Table 4). Finally, pre-diagnostic use of beta blockers did modify the association between post diagnostic use of beta-blockers and the two mortality outcomes (Supplemental Table 3).

4. Discussion

In this large population-based cohort of men newly-diagnosed with non-metastatic prostate cancer, the use of beta-blockers after diagnosis was not associated with a decreased risk of prostate cancer mortality and all-cause mortality. In a secondary analysis, there were no cumulative duration-responses with these outcomes. Furthermore, there was no evidence that the use of non-selective beta-blockers was associated with a decreased risk of prostate cancer mortality and all-cause mortality.

To our knowledge, four observational studies have been conducted to assess whether the use of beta-blockers is associated with a decreased risk of prostate cancer mortality [13–16]. Our results are consistent with one study [15], but contrast with those of the three other studies which reported decreased [13,16] and increased risks [14]. Such discrepancies are likely related to some methodological shortcomings. Specifically, the two studies that reported decreased risks in prostate cancer mortality (with HRs ranging between 0.14 [86% decreased risk] and 0.79 [21% decreased risk]), likely suffered from immortal time bias [17]. This bias results from misclassifying the unexposed person-time before exposure as exposed person-time, which is also immortal because no deaths could have occurred during that time [28]. In the other study that reported an increased risk [14], the authors compared users of beta-blockers to non-users, which primarily consisted of individuals without hypertension or heart failure. As such, that study likely suffered from confounding by indication. Our study was specifically designed to avoid these biases. Specifically, exposure was considered a time-dependent variable in the models, effectively eliminating the possibility of immortal time bias, and we restricted the cohort to patients who had used antihypertensive drugs prior to diagnosis to minimise confounding by indication.

The selectivity of beta-blockers has been of particular interest given that several *in vitro* studies have shown that tumour progression is mediated specifically through the beta-2 adrenergic pathway and is inhibited by beta-2 receptor antagonists such as propranolol [2,6,29,30].

Table 1
Baseline characteristics of patients with prostate cancer with a history of antihypertensive drug use.

Baseline characteristics	Cohort ($n = 6270$)	Pre-diagnostic use of beta blockers	
		Use ($n = 1909$)	Non-use ($n = 4361$)
Age, mean (SD)	72.3 (8.3)	72.3 (8.0)	72.3 (8.5)
Ethnicity, *n* (%)			
White	4750 (75.8)	1481 (77.6)	3269 (76.0)
Black	90 (1.4)	27 (1.4)	63 (1.4)
Other	974 (15.5)	271 (14.2)	703 (16.1)
Unknown	456 (7.3)	130 (6.8)	326 (7.5)
Excessive alcohol use, *n* (%)	273 (4.4)	87 (4.6)	186 (4.3)
Body mass index, *n* (%)			
<30 kg/m^2	3399 (54.2)	1095 (57.4)	2304 (52.8)
$\geqslant 30$ kg/m^2	927 (14.8)	327 (17.1)	600 (13.8)
Unknown	1944 (31.0)	487 (25.5)	1457 (33.4)
Smoking status, *n* (%)			
Never	2818 (45.2)	877 (46.1)	1941 (44.8)
Ever	3421 (54.8)	1026 (53.8)	2395 (55.2)
unknown	31 (0.05)	6 (0.03)	25 (0.05)
Townsend Deprivation Score, *n* (%)			
Quartile 1	1788 (28.5)	547 (28.7)	1241 (28.5)
Quartile 2	1694 (27.0)	536 (28.1)	1158 (26.6)
Quartile 3	1293 (20.6)	406 (21.3)	887 (20.3)
Quartile 4	969 (15.5)	278 (14.6)	691 (15.8)
Quartile 5	514 (8.2)	135 (7.1)	379 (8.7)
Unknown	12 (0.2)	7 (0.4)	5 (0.1)
Anti-hypertensive drugs			
Beta-blockers, *n* (%)	1909 (30.5)	1909 (30.5)	0 (0.0)
Angiotensin converting enzyme inhibitors, *n* (%)	2228 (35.5)	714 (37.4)	1514 (34.7)
Angiotensin receptor blockers, *n* (%)	734 (11.7)	215 (11.3)	519 (11.9)
Calcium channel blockers, *n* (%)	2147 (34.2)	660 (34.6)	1487 (34.1)
Alpha blockers, *n* (%)	2469 (39.5)	522 (27.3)	1957 (44.9)
Other antihypertensive drugs, *n* (%)	43 (0.7)	13 (0.7)	30 (0.7)
Other drugs			
Statins, *n* (%)	2385 (38.0)	957 (50.1)	1428 (32.7)
Aspirin, *n* (%)	2462 (39.3)	1000 (52.4)	1462 (33.5)
Other non-steroidal anti-inflammatory drugs, *n* (%)	1652 (26.4)	501 (26.2)	1151 (26.4)
Beta-agonists, *n* (%)	854 (13.6)	82 (4.3)	772 (17.7)
Metformin *n* (%)	401 (6.4)	141 (7.4)	260 (6.0)
Sulfonylureas *n* (%)	306 (4.9)	101 (5.3)	205 (4.7)
Insulin, *n* (%)	129 (2.1)	45 (2.4)	84 (1.9)
Other anti-diabetic drugs, *n* (%)	75 (1.2)	24 (1.3)	51 (1.2)
Cardiovascular comorbidities			
Hypertension *n* (%)	3751 (59.8)	1335 (69.9)	2416 (55.4)
Heart failure *n* (%)	713 (11.4)	228 (11.9)	485 (11.1)
Coronary heart disease *n* (%)	2024 (32.3)	893 (46.8)	1131 (25.9)
Rhythmic disorders *n* (%)	135 (2.1)	53 (2.8)	82 (1.9)
Valve disorders *n* (%)	362 (5.8)	131 (6.9)	231 (5.3)
Prostate cancer-related variables			
PSA level before diagnosis, *n* (%)			
0–4	227 (3.6)	67 (3.5)	160 (3.6)
4–10	1535 (24.5)	459 (24.0)	1076 (24.7)
>10	2766 (44.1)	864 (45.3)	1902 (43.6)
Unknown	1742 (27.8)	519 (27.2)	1223 (28.0)
Gleason score, *n* (%)			
4–6	152 (2.4)	55 (2.9)	97 (2.2)
7	2369 (37.8)	701 (36.7)	1668 (38.3)
8–10	735 (11.7)	211 (11.1)	524 (12.0)
Unknown	3014 (48.1)	942 (49.4)	2072 (47.5)
Prostatectomy, *n* (%)	2766 (44.1)	767 (40.2)	1999 (45.8)
Radiation therapy, *n* (%)	3635 (58.0)	1067 (55.9)	2568 (58.9)
Androgen deprivation therapy, *n* (%)	3678 (58.7)	1190 (62.3)	2488 (57.1)
Chemotherapy, *n* (%)	154 (2.5)	42 (2.2)	112 (2.6)

Abbreviations: HR, hazard ratio; CI, confidence interval; SD, standard deviation; PSA, prostate-specific antigen.

Table 2
Crude and adjusted hazard ratios of prostate cancer mortality associated with the post-diagnostic use of beta-blockers.

Post-diagnostic use of beta-blockers	Events ($n = 715$)	Person-years	Crude rate (per 1000/year)	Crude HR	Adjusted HR (95% CI)[†]
Non-use	437	14,721	29.7	1.00	1.00 (Reference)
Use	278	9388	29.6	1.01	0.97 (0.72–1.31)
Cumulative duration of use					
<12 months	96	2679	35.8	1.18	1.06 (0.77–1.46)
12–24 months	63	1900	33.2	0.97	0.86 (0.57–1.29)
24–36 months	31	1473	21.0	0.92	0.83 (0.50–1.35)
⩾36 months	88	3336	26.4	0.92	0.81 (0.53–1.24)

Abbreviations: HR, hazard ratio; CI, confidence interval.
[†] Adjusted for age, year of cohort entry, race, excessive alcohol use, obesity ($\geqslant 30$ kg/m^2), smoking status, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, beta agonists, other antiplatelet drugs, non-steroidal anti-inflammatory drugs, metformin, sulfonylureas, insulin and other anti-diabetic drugs. Prostate cancer related variables: PSA, Gleason score, cancer treatments during first year of after diagnosis: chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy. The model was also adjusted for antihypertensive drug use during follow up which was entered as time-dependent covariate.

Table 3
Crude and adjusted hazard ratios of all-cause mortality associated with the post-diagnostic use of beta-blockers.

Post-diagnostic use of beta-blockers	Events ($n = 1761$)	Person-years	Crude rate (per 1000/year)	Crude HR	Adjusted HR (95% CI)[†]
Non-use	1088	14,721	73.9	1.00	1.00 (Reference)
Use	673	9388	71.6	0.96	0.97 (0.81–1.16)
Cumulative duration of use					
<12 months	197	2679	73.5	1.00	0.97 (0.79–1.18)
12–24 months	150	1900	78.9	1.05	1.01 (0.79–1.30)
24–36 months	89	1473	60.4	0.92	0.93 (0.70–1.25)
⩾36 months	237	3336	71.0	0.88	0.89 (0.70–1.18)

Abbreviations: HR, hazard ratio; CI, confidence interval.
[†] Adjusted for age, year of cohort entry, race, excessive alcohol use, obesity ($\geqslant 30$ kg/m^2), smoking status, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, beta agonists, other antiplatelet drugs, non-steroidal anti-inflammatory drugs, metformin, sulfonylureas, insulin and other anti-diabetic drugs. Prostate cancer related variables: PSA, Gleason score, cancer treatments during first year after diagnosis: chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy. The model was also adjusted for antihypertensive drug use during follow up which were entered as time-dependent covariates.

Table 4
Crude and adjusted hazard ratios of mortality outcomes associated with the post-diagnostic use of non-selective beta-blockers.

Post-diagnostic use of beta-blockers	Events ($n = 715$)	Person-years	Crude rate (per 1000/year)	Crude HR	Adjusted HR (95% CI)[†]
Prostate cancer mortality					
Non-use	682	22,893	29.8	1.00	1.00 (Reference)
Use	33	1220	27.1	0.93	1.05 (0.72–1.53)
Cumulative duration of use					
0–24 months	22	804	27.4	0.91	0.98 (0.63–1.53)
⩾24 months	11	416	26.4	0.97	1.23 (0.66–2.30)
All-cause mortality					
Non-use	1672	22,893	73.0	1.00	1.00 (Reference)
Use	89	1220	73.0	0.98	0.94 (0.74–1.18)
Cumulative duration of use					
0–24 months	61	804	75.9	1.03	0.96 (0.73–1.25)
⩾24 months	28	416	67.3	0.89	0.88 (0.60–1.31)

Abbreviations: HR-hazard ratio-CI-confidence interval.
[†] Adjusted for age, year of cohort entry, race, excessive alcohol use, obesity ($\geqslant 30$ kg/m^2), smoking status, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, beta agonists, other antiplatelet drugs, non-steroidal anti-inflammatory drugs, metformin, sulfonylureas, insulin and other anti-diabetic drugs. Prostate cancer related variables: PSA, Gleason score, cancer treatments during first year after diagnosis: chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy. The model was also adjusted for antihypertensive drug use during follow up which were entered as time-dependent covariates.

To our knowledge, our study is the first study to have examined the independent effects of non-selective beta-blockers on mortality outcomes in patients with prostate cancer. Our null findings, despite promising animal models, can perhaps be explained by higher doses and a stronger sympathetic response in mouse models [4,31–34]. Further studies are needed to explore the discrepancies between the preclinical and observational literature.

This population-based study has a number of strengths and some limitations. To our knowledge, this is the largest population-based study to have investigated the use of beta-blockers in the context of prostate cancer mortality with up to 15 years of follow-up. Furthermore, by restricting the cohort to patients with a history of antihypertensive drug use, we minimised confounding by indication. Our exposure definition took into account a biologically meaningful latency time, and was time dependent thus allowing exposure status to change over time. Furthermore, by linking the NCDR, CPRD, HES and ONS databases, we were able to adjust for a number of potential important confounders, including smoking, ethnicity, body mass index, prostate cancer treatments and PSA levels. Unfortunately, it was not possible to adjust for tumour stage, because this information was missing for nearly 90% of patients in the NCDR. Drug information in the CPRD represents prescriptions written by general practitioners. As such, it is unknown whether prescriptions were actually filled at the pharmacy. This misclassification of exposure can lead to a dilution of the point estimates. Furthermore, some antihypertensive drugs, such as alpha-blockers, can be used for conditions other than hypertension (i.e. benign prostatic hypertrophy). It is important to note that such conditions have not been previously associated with the outcome of interest (i.e. prostate cancer mortality), and should thus not affect the internal validity of the study. Moreover, the vast majority (88%) of patients using alpha-blockers were those who used other anti-hypertensive drugs concurrently and/or had a diagnosis of hypertension. With respect to the primary outcome of interest, prostate cancer mortality, it is possible that some cancer-related deaths were misclassified as non-cancer deaths, and vice versa. Such non-differential misclassification of the outcome would dilute the point estimates, although in contrast to other cancers, prostate cancer mortality has been shown to be generally well recorded in death certificates [35]. Another limitation of the CPRD is the lack of information on certain potential risk factors. These include diet, physical activity and family history of cancer. While these variables may be associated with prostate cancer mortality, it is unclear how these variables would influence physicians to prescribe beta-blockers. Thus, we believe that these unmeasured variables are unlikely to affect the internal validity of the study.

In summary, the use of beta-blockers after prostate cancer diagnosis was not associated with prostate cancer mortality and all-cause mortality in patients with a history of antihypertensive drug use. Overall our findings do not provide evidence of any beneficial effect of beta-blockers on these outcomes.

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