

Supplementary Material

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Supplementary Method 1. High Dimensional propensity score analysis

Residual confounding was assessed by stratifying subjects into mutually exclusive subsets of high, dimensional propensity score deciles. The high dimensional propensity score is a method that empirically selects covariates based on their prevalence and potential for confounding.¹ Thus, for each patient, we used multivariate logistic regression to calculate a propensity score, i.e. the probability of being exposed to ADT compared to non-use conditional, based upon use within the first 6 months of follow-up, on 500 empirically identified and 20 predefined covariates measured at cohort entry (covariates included in primary analyses as listed in text). The empirical covariates were estimated from 7 data dimensions (drug prescriptions from CPRD, procedures from CPRD and HES, diagnoses from CPRD and HES, disease history from CPRD, and administrative information from CPRD).

References

1. Schneeweiss S, Rassen JA, Glynn RJ, et al: High, dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 20:512–22, 2009

Supplementary Method 2. Marginal structural Cox proportional hazards model.

We conducted a marginal structural Cox proportional hazards model to address potential residual time, dependent confounding over the 18 year follow, up period. This method is designed to adjust for time, dependent confounding associated with time, varying exposures.^{1,2} Firstly, two pooled logistic regression models were fitted to estimate the conditional probability of being exposed to ADT at 30-day intervals during follow, up; one for the numerator and one for the denominator of the stabilized inverse, probability, of, treatment weights (IPTWs). The numerator treatment model included baseline covariates (the covariates included in the primary analysis, listed in the text) and follow-up time. The denominator model included covariates (the same as those listed in the text as well as metastases and radical prostatectomy) measured at each time interval and follow-up time. In both the numerator and denominator models, follow-up time was modelled using a restricted cubic spline with five knots to reduce bias due to model misspecification from linearity assumptions.³ We also estimated inverse probability of censoring weights (IPCWs) in a similar fashion. Stabilized IPTW and IPCW for each patient were computed using the predicted probabilities from the two treatment and censoring models. The product of these stabilized IPTWs and IPCWs was then used to reweight the cohort, in which we estimated the hazard ratios of hospitalisation for community-acquired pneumonia associated with the use of ADT, with 95% confidence intervals, calculated using robust variance estimators.²

References

1. Robins JM, Hernán MA, Brumback B: Marginal structural models and causal inference in epidemiology. *Epidemiology* 11:550–60, 2000
2. Hernán MA, Brumback B, Robins JM: Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV, positive men. *Epidemiology* 11:561–70, 2000
3. Cole SR, Hernán MA: Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 168:656–64, 2008

Supplementary Table 1. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (varying grace period)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI)†
90-day grace period					
Non use	147	38,535	3.8 (3.2 to 4.5)	1.00 [Reference]	1.00 [Reference]
Current use	351	28,886	12.2 (10.9 to 13.5)	3.32	1.79 (1.45 to 2.21)
Past use	123	18,879	6.5 (5.4 to 7.8)	1.54	1.30 (1.01 to 1.67)
1-year grace period					
Non use	147	38,535	3.8 (3.2 to 4.5)	1.00 [Reference]	1.00 [Reference]
Current use	381	32,017	11.9 (10.7 to 13.2)	3.28	1.81 (1.47 to 2.22)
Past use	93	15,748	5.9 (4.8 to 7.2)	1.33	1.17 (0.89 to 1.54)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Per 1000 Person-Years.

† Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 2. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (Alternative Outcome Definition*)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)[†]	Crude HR	Adjusted HR (95% CI)[‡]
Non use	250	38,535	6.5 (5.7 to 7.3)	1.00 [Reference]	1.00 [Reference]
Current use	600	30,052	20.0 (18.4 to 21.6)	3.22	1.77 (1.51 to 2.08)
Past use	177	17,713	10.0 (8.6 to 11.6)	1.40	1.17 (0.96 to 1.44)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Alternative outcome definition includes a diagnosis of pneumonia recorded in the primary or secondary position.

[†] Per 1000 Person-Years.

[‡] Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 3. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (Alternative Time Window for Hospital-acquired Pneumonia*)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)[†]	Crude HR	Adjusted HR (95% CI)[†]
Non use	145	38,535	3.8 (3.2 to 4.4)	1.00 [Reference]	1.00 [Reference]
Current use	346	30,052	11.5 (10.3 to 12.8)	3.20	1.75 (1.42 to 2.16)
Past use	100	17,713	5.6 (4.6 to 6.9)	1.34	1.16 (0.89 to 1.51)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Censoring on hospital-acquired pneumonia which was defined as a diagnosis of pneumonia >2 days after hospital admission and up to 14 days after discharge.

[†] Per 1000 Person-Years.

[‡] Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 4. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (Additional Censoring*)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)[†]	Crude HR	Adjusted HR (95% CI)[‡]
Non use	130	34,806	3.7 (3.1 to 4.4)	1.00 [Reference]	1.00 [Reference]
Current use	284	24,773	11.5 (10.2 to 12.9)	3.22	1.66 (1.32 to 2.09)
Past use	79	11,813	6.7 (5.3 to 8.3)	1.55	1.30 (0.97 to 1.74)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Additionally censoring upon incident metastases or receipt of radiotherapy during follow-up

[†] Per 1000 Person-Years.

[‡] Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 5. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (Multiple Imputation)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI)†
Non use	147	38,535	3.8 (3.2 to 4.5)	1.00 [Reference]	1.00 [Reference]
Current use	364	30,052	12.1 (10.9 to 13.4)	3.32	1.83 (1.49 to 2.26)
Past use	110	17,713	6.2 (5.1 to 7.5)	1.44	1.24 (0.95 to 1.60)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Per 1000 Person-Years.

† Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 6. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (HDPS)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI)†
Non use	44	14,222	3.1 (2.2 to 4.2)	1.00 [Reference]	1.00 [Reference]
Current use	99	10,049	9.9 (8.0 to 12.0)	3.46	2.33 (1.50 to 3.60)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Per 1000 Person-Years.

† Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

Supplementary Table 7. Crude and Adjusted HRs for the Association Between the Use of ADT and the Risk of Community-acquired Pneumonia (Marginal Structural Model)

Exposure to ADT	Events	Person-years	Incidence rate (95% CI)*	Crude marginal HR in weighted model	Adjusted marginal HR (95% CI)†
Non use	147	38,535	3.8 (3.2 to 4.5)	1.00 [Reference]	1.00 [Reference]
Current use	364	30,052	12.1 (10.9 to 13.4)	2.61	1.81 (0.94 to 3.50)
Past use	110	17,713	6.2 (5.1 to 7.5)	0.99	1.24 (0.95 to 1.60)

Abbreviations: ADT, androgen deprivation therapy, CI, confidence interval, HR, hazard ratio

* Per 1000 Person-Years.

† Adjusted for age, year of prostate cancer diagnosis, body mass index, smoking status, alcohol related disorders, seasonality, prostate-specific antigen, previous cancer, chronic obstructive pulmonary disease, asthma, bronchitis and bronchiectasis, use of immunosuppressive agents, inhaled bronchodilators, inhaled and oral corticosteroids, oral antibiotics, inhaled and oral corticosteroids, influenza and pneumococcal vaccines.

