Original Investigation

Androgen Deprivation Therapy and Risk of Acute Kidney Injury in Patients With Prostate Cancer

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IMPORTANCE The use of androgen deprivation therapy (ADT) in the treatment of advanced prostate cancer has been shown to delay the clinical progression of the disease. However, the testosterone suppression associated with this therapy may lead to a hypogonadal condition that can have detrimental effects on renal function, thus raising the hypothesis that ADT-induced hypogonadism could potentially lead to acute kidney injury (AKI).

OBJECTIVE To determine whether the use of ADT is associated with an increased risk of AKI in patients newly diagnosed with prostate cancer.

DESIGN AND SETTING A nested case-control analysis using medical information extracted from the UK Clinical Practice Research Datalink linked to the Hospital Episodes Statistics database.

PARTICIPANTS Men newly diagnosed with nonmetastatic prostate cancer between January 1, 1997, and December 31, 2008, were selected and followed up until December 31, 2009. Cases were patients with incident AKI during follow-up who were randomly matched with up to 20 controls on age, calendar year of prostate cancer diagnosis, and duration of follow-up.

MAIN OUTCOMES AND MEASURES Conditional logistic regression was used to estimate odds ratios (ORs) with 95% CIs of AKI associated with the use of ADT. ADT was categorized into 1 of 6 mutually exclusive groups: gonadotropin-releasing hormone agonists, oral antiandrogens, combined androgen blockade, bilateral orchiectomy, estrogens, and combination of the above.

RESULTS A total of 10 250 patients met the study inclusion criteria. During a mean follow-up of 4.1 (SD, 2.9) years, 232 incident cases of AKI were identified (rate, 5.5/1000 person-years). Overall, current use of any ADT was associated with an increased risk of AKI when compared with never use (OR, 2.48 [95% CI, 1.61-3.82]), generating a rate difference of 4.43/1000 persons per year (95% CI, 1.54-7.33). This association was mainly driven by a combined androgen blockade consisting of gonadotropin-releasing hormone agonists with oral antiandrogens (OR, 4.50 [95% CI, 2.61-7.78]), estrogens (OR, 4.00 [95% CI, 1.06-15.03]), other combination therapies (OR, 4.04 [95% CI, 1.88-8.69]), and gonadotropin-releasing hormone agonists (OR, 1.93 [95% CI, 1.20-3.10]).

CONCLUSIONS AND RELEVANCE In a cohort of patients with newly diagnosed nonmetastatic prostate cancer, the use of ADT was significantly associated with an increased risk of AKI. These findings require replication in other well-designed studies as well as further investigation of their clinical importance.

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Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer. While this therapy has been traditionally reserved for patients with advanced disease, ADT is increasingly being used in patients with less severe forms of the cancer, such as in patients with biochemical relapse who have no evidence of metastatic disease.[1]

Although ADT has been shown to have beneficial effects on prostate cancer progression, serious adverse events can occur during treatment.[2] Specifically, ADT reduces testosterone levels leading to a hypogonadal condition marked by metabolic changes, such as dyslipidemia,[3] hyperglycemia,[4] and an increase in fat mass.[5] With respect to the renal system, hyperglycemia and dyslipidemia may disrupt glomerular function by expanding and thickening the interstitial tubular membrane.[6] Furthermore, by lowering testosterone to castration levels, ADT may antagonize the vasodilating effects of testosterone on renal vessels[7] while also creating an estrogen deficiency, which can negatively affect renal tubular function.[8] Thus, it is possible that through these mechanisms, the use of ADT may increase the risk of acute kidney injury (AKI).

ADT *androgen deprivation therapy*

AKI *acute kidney injury*

GnRH *gonadotropin-releasing hormone*

NSAIDs *nonsteroidal anti-inflammatory drugs*

PSA *prostate-specific antigen*

SSRIs *selective serotonin reuptake inhibitors*

Although there is one case report associating the use of the oral antiandrogen flutamide with AKI,[9] to our knowledge there are no observational studies investigating this association. Thus, given the increasing use of ADT in patients with earlier-stage disease[10] and the high mortality rate in patients with AKI (around 50%),[11] the objective of this study was to determine whether the use of ADT is associated with an increased risk of AKI in patients newly diagnosed with prostate cancer.

Methods

Data Sources

This study was conducted using the United Kingdom Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database, and the Hospital Episodes Statistics (HES) database.

Since its inception in 1987, the CPRD has stored information on demographics, drug prescriptions, clinical events, specialist referrals, and deaths on more than 12 million patients across 650 general practices.[12] Furthermore, the CPRD collects information on lifestyle variables such as body mass index (BMI), smoking, and excessive alcohol use. The Read classification system is used to code medical diagnoses and procedures. Recent reviews have found that medical data recorded in the CPRD are of high validity.[13,14]

For the purposes of this study, the CPRD was linked to the HES database. The HES database contains discharge diagnoses (coded using the *International Statistical Classification of Diseases, 10th Revision* [*ICD-10*]) and procedures (coded using the *ICD-10* classification and the *Classification of Interventions and Procedures, 4th version* [*OPCS-4*]).

Patient informed consent was not necessary because the data were anonymized for research purposes. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

Study Population

Within the CPRD population, we assembled a cohort of patients newly diagnosed with prostate cancer between January 1, 1998, and December 31, 2008, with follow-up until December 31, 2009, which was linked to the HES database. To be included in the cohort, all patients were required to have at least 1 year of "up-to-standard" medical history in the CPRD at the time of the prostate cancer diagnosis (cohort entry), and patients had to be at least 40 years old at the time of diagnosis. Men with metastatic disease recorded at any time before cohort entry up until the first 3 months after cohort entry (to account for potential delays in the recording of metastases) were excluded, as well as those with a history of any other cancers (other than nonmelanoma skin cancer), history of AKI, chronic kidney failure, dialysis-related procedures, hepatitis, systemic connective tissue diseases, rheumatoid arthritis, crush injury, human immunodeficiency virus infection, and any drug abuse (*ICD-10* and Read codes for these and other conditions are available on request).

Thus, all patients were followed up from the date of their prostate cancer diagnosis until a first-ever hospitalization for AKI, the occurrence of one of the exclusion criteria (the exception was metastasis because it is a known indication for ADT use, but was considered an additional censoring criterion in a sensitivity analysis), death from any cause, end of registration with the general practice, or end of the study period (December 31, 2009), whichever came first.

Selection of Cases and Controls

A nested case-control analysis was conducted within the cohort defined above. This analytic approach was chosen because of the time-varying nature of exposure, the size of the cohort, and the long duration of follow-up.[15] In comparison to a time-dependent survival analysis, a nested case-control analysis is computationally more efficient,[16] while producing odds ratios (ORs) that are unbiased estimators of incidence rate ratios, with little or no loss in precision.[15,17]

Cases consisted of patients hospitalized for the first time with AKI during follow-up (primary or secondary *ICD-10* codes: N17, N17.0-2, N17.8-9).[18,19] The admission date of the AKI event defined the index date. Among these cases, we also identified those who had evidence of a dialysis procedure (*ICD-10* codes: Z99.2, Z49.0, Z49.1[18,19]; *OPCS-4* codes: X40.1,3,8,9; X41.8,9; X42.8,9; X43.1) in the 30 days before or after the AKI hospitalization. In the event that the dialysis procedure preceded the AKI admission, the index date was set as the date of the procedure.

Using risk set sampling, up to 20 controls were randomly selected from the case's risk set and matched to each case on age (year of birth), calendar year of cohort entry, and dura-

tion of follow-up. The date of the risk set was the index date for the controls.

Exposure Assessment

Patients were considered currently exposed to ADT if the duration of the last prescription plus a residual effect period (since hypogonadism may persist after discontinuation of therapy[20,21]) overlapped the 90 days immediately prior to the index date. We considered a residual effect period of 3 months for gonadotropin-releasing hormone (GnRH) agonists and 1 month for oral antiandrogens and estrogens. Thus, the primary exposure definition classified cases and matched controls into 1 of 3 mutually exclusive groups: (1) current use, defined as ADT overlapping the 90 days immediately prior to the index date; (2) past use, defined as ADT used at any time during follow-up, but not overlapping the current time window; and (3) never use, defined as no use of any ADT between cohort entry and index date.

We also considered 2 secondary exposure definitions. In the first, we further classified current users of ADT according to their specific types. Thus, patients were categorized into 1 of 6 mutually exclusive groups: (1) GnRH agonists (leuprolide, goserelin, triptorelin), (2) oral antiandrogens (cyproterone acetate, flutamide, bicalutamide, nilutamide), (3) combined androgen blockade (GnRH agonists + oral antiandrogens), (4) bilateral orchiectomy, (5) estrogens, and (6) combinations of the above. In the second approach, we assessed whether the risk of AKI varied according to ADT duration among current users. For this approach, continuous use was defined as when the duration plus the residual effect period of a prescription overlapped with the date of the next prescription.

Potential Confounders

The risk estimates were adjusted for comorbidities and prescription drugs known to be associated with AKI, which could also influence the use of ADT. Thus, all models were adjusted for hypertension, heart failure, ischemic stroke, coronary artery diseases, rhythm disorders, and diabetes, all measured at any time before cohort entry. The models were also adjusted for excessive alcohol use (based on alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and liver failure), smoking status, and BMI, all based on the last measure before the index date. To minimize the effect of prostate cancer severity, the models were further adjusted for number of hospitalizations, metastasis, prostatectomy, radiation therapy, and chemotherapy, all measured between cohort entry and index date, as well as the last prostate-specific antigen (PSA) value measured prior to cohort entry. Finally, the models were adjusted for the use of antipsychotics; selective serotonin reuptake inhibitors (SSRIs); anticoagulants; aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs); angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, and other antihypertensives (including thiazide and loop diuretics); digoxin; clopidogrel; antiarrhythmics; statins; antibiotics; immunosuppressive drugs; paracetamol/acetaminophen; and corticosteroids, all measured in the 90 days before the index date. Because some of the aforementioned variables may be in the causal pathway between ADT exposure and AKI, we conducted a sensitivity analysis by adjusting all variables at cohort entry.

Statistical Analysis

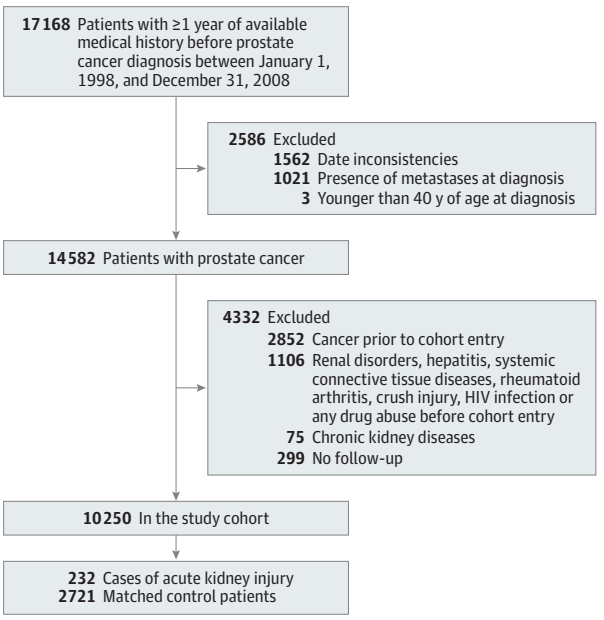
The incidence rate of AKI was estimated by dividing the total number of cases by the total number of person-years of follow-up, with 95% CIs based on Poisson distribution. Conditional logistic regression was used to compute ORs of AKI associated with the use ADT.

For the primary analysis, we assessed whether current use and past use of ADT were associated with an increased risk of AKI when compared with never use. In 2 secondary analyses, we estimated the OR of AKI with respect to current use of specific ADTs and by duration of use. For the latter analysis, duration of use was categorized in tertiles based on the distribution of use among the controls. We also computed the attributable risk of AKI associated with the use of ADT by applying the ORs to the incidence rate derived from the unexposed person-time in the cohort (which was determined to be 3.0/1000 person-years). In addition to year of birth, year of cohort entry, and duration of follow-up on which the logistic regression was conditioned, all models were adjusted for the potential confounders listed above.

We conducted 10 sensitivity analyses to assess the robustness of our findings. In the first 3, we evaluated the accuracy of the event definition by (1) restricting AKI cases to those with a primary diagnosis, (2) assessing the effect of new Quality and Outcomes Framework guidelines in the United Kingdom[22] over the study period (which may have affected the recording and treatment of kidney diseases) by stratifying cases and matched controls on calendar period (1998-2003, 2004-2009), and (3) repeating the analyses by excluding at baseline and censoring for the occurrence of ureteroscopy, nephrostomography, other percutaneous insertion of ureteric stent, and nephrostomy tube in an attempt to minimize the potential presence of postrenal AKI.

In the fourth to seventh sensitivity analyses, we assessed the impact of confounding by indication on the results (for example, a situation in which advanced carcinoma may lead to kidney complications by direct extension into the trigone and bladder)[23] by (1) comparing current users vs past users, 2 exposure groups likely to have had similar indications for ADT use, (2) additionally censoring for the occurrence of metastases, prostatectomy, radiation therapy, and chemotherapy during follow-up, (3) additionally excluding patients with abnormal baseline creatinine levels,[24] and following up the remaining patients for a maximum of 2 years, while additionally censoring on the occurrence of metastases and use of chemotherapy (limiting follow-up to 2 years was meant to minimize the inclusion of patients who may have used ADT because of disease progression), and (4) repeating the primary analyses using a falsification exposure consisting of 5α-reductase inhibitors, a drug class often used to lower prostate volumes in patients with prostate cancer. In the eighth sensitivity analysis, we repeated the analyses by varying the length of the residual effect periods of ADT (ie, GnRH agonists: 6 months; oral antiandrogens: 2 months). In the ninth sensitivity analysis, we

Figure. Selection of Cohort and Design of Case-Control Study of Acute Kidney Injury in Prostate Cancer



varied the current exposure time window of 90 days with 60 and 30 days. Finally, we assessed the impact of baseline kidney function on the association by excluding cases and controls with abnormal baseline creatinine levels.[24]

All analyses were 2-tailed and $P < .05$ was considered significant. Analyses were conducted with SAS version 9.2.

Results

A total of 10 250 patients met the study inclusion criteria (**Figure**). During the 42 070 person-years of follow-up, 232 cases with a first-ever AKI admission (incidence rate, 5.5 [95% CI, 4.8-6.3] per 1000 person-years) were identified (including 9 who had undergone dialysis) and matched with 2721 controls. All cases were matched with at least 1 control, with 55 cases (23.7%) matched with 20 controls, 135 (58.2%) with at least 10 controls, and 187 (80.6%) with at least 4 controls.

Table 1 shows the demographic and clinical characteristics of the cases and matched controls. As expected, cases were more likely to have used alcohol excessively, to have been smokers, to have diabetes and cardiovascular diseases, and have a greater number of hospitalizations. The prevalence of metastases, prostatectomy, and chemotherapy were also proportionally higher among cases than controls, while cases had lower use of radiation therapy. Moreover, cases were more likely to have used antipsychotics, SSRIs, aspirin and other NSAIDs, anticoagulants, clopidogrel, antihypertensive drugs (with the exception of calcium channel blockers), antiarrhythmics, digoxin, statins, antibiotics, immunosuppressive drugs, paracetamol/acetaminophen, and corticosteroids.

Table 2 depicts the demographic and clinical characteristics of ADT users (current and past) vs never users among

Table 1. Characteristics of AKI Cases and Matched Controls

Characteristics	No. (%) Cases (n = 232)	Controls (n = 2721)
Age, mean (SD), y[a]	80.2 (7.8)	80.2 (6.6)
Duration of follow-up, mean (SD), y[a]	4.1 (2.8)	4.1 (2.6)
Excessive alcohol use	24 (10.3)	200 (7.4)
Smoking status		
Never	73 (31.5)	1034 (38.0)
Ever	149 (64.2)	1607 (59.1)
Unknown	10 (4.3)	80 (2.9)
Body mass index		
<30	165 (71.1)	2132 (78.4)
≥30	40 (17.2)	403 (14.8)
Unknown	27 (11.6)	186 (6.8)
Prostate-specific antigen, ng/mL		
<4	22 (9.5)	260 (9.6)
4-10	30 (12.9)	473 7.4)
>10	81 (34.9)	1010 (37.1)
Unknown	99 (42.7)	978 (35.9)
Comorbidities		
Hypertension	99 (42.7)	1021 (37.5)
Coronary artery disease	52 (22.4)	339 (12.5)
Diabetes	40 (17.2)	298 (11.0)
Rhythm disorders	25 (10.8)	194 (7.1)
Congestive heart failure	18 (7.8)	85 (3.1)
Ischemic stroke	17 (7.3)	99 (3.6)
No. of hospitalizations, mean (SD)	5.5 (6.8)	2.0 (3.4)
Metastasis[b]	35 (15.1)	91 (3.3)
Radiation therapy	15 (6.5)	246 (9.0)
Prostatectomy	45 (19.4)	467 (17.2)
Chemotherapy	7 (3.0)	31 (1.1)
Medications[c]		
Angiotensin-converting enzyme inhibitors	70 (30.2)	638 (23.5)
Angiotensin II receptor blockers	22 (9.5)	241 (8.9)
Calcium channel blockers	48 (20.7)	654 (24.0)
β-Blockers	41 (17.7)	504 (18.5)
Other antihypertensives (including diuretics)	111 (47.8)	825 (30.3)
Antibiotics	105 (45.3)	537 (19.7)
Paracetamol/acetaminophen	106 (45.7)	613 (22.5)
Aspirin	94 (40.5)	866 (31.8)
Statins	73 (31.5)	848 (31.2)
Corticosteroids	41 (17.7)	256 (9.4)
Antiarrhythmics	32 (13.8)	281 (10.3)
Other nonsteroidal anti-inflammatory drugs	24 (10.3)	191 (7.0)
Anticoagulants	21 (9.1)	188 (6.9)
Selective serotonin reuptake inhibitors	20 (8.6)	107 (3.9)
Digoxin	14 (6.0)	128 (4.7)
Clopidogrel	12 (5.2)	89 (3.3)
Immunosuppressive agents	4 (1.7)	38 (1.4)
Antipsychotics	3 (1.3)	17 (0.6)

Abbreviations: AKI, acute kidney injury; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Matching variables (along with year of cohort entry).

[b] Captured in both the Clinical Practice Research Datalink and Hospital Episode Statistics database.

[c] Measured in the 90 days before the index date.

controls. Current and past ADT users were generally more similar than those never exposed to ADT in terms of smoking, BMI, baseline PSA levels, number of hospitalizations, and use of statins, corticosteroids, NSAIDs, SSRIs, clopidogrel, and antipsychotics. In contrast, excessive alcohol use was slightly higher among current users compared with past and never users, and most of the cardiovascular diseases along with related medications were proportionally higher among current users. Moreover, the prevalence of metastases was the highest for current use, while the prevalence of use of radiation therapy and prostatectomy was the highest among past and never users, respectively.

The results of the primary analysis are shown in **Table 3**. Compared with never use, current use of ADT was significantly associated with an increased risk of AKI (OR, 2.48 [95% CI, 1.61-3.82]), while the OR was lower and not statistically significant for past use (OR, 1.25 [95% CI, 0.68-2.29]). A sensitivity analysis adjusting for all potentially confounding variables at cohort entry yielded similar results (current use: adjusted OR, 2.68 [95% CI, 1.81-3.98]; and past use: adjusted OR, 1.20 [95% CI, 0.68-2.10]). Current use of ADT generated a rate difference of 4.43 per 1000 persons per year (95% CI, 1.54-7.33).

The results of the secondary analyses are shown in **Table 4**. Current use of a combined androgen blockade therapy was associated with an increased risk of AKI. The ORs for current use of other combination therapies were also increased and most associations were statistically significant (a total of 19 exposed cases, mainly to GnRH agonists plus estrogens [n = 10] and GnRH agonists plus oral antiandrogens plus estrogens [n = 5], estrogens, oral antiandrogens, and GnRH agonists). The ORs for current use of oral antiandrogens and bilateral orchiectomy were above 1.0 but were not statistically significant.

Finally, when we estimated the OR of AKI as a function of duration of ADT, the first tertile of exposure (<386 days) produced the highest OR (2.80 [95% CI, 1.66-4.72]). The ORs decreased with longer durations of use but remained significantly elevated (second tertile [≥386 to <1106 days]: OR, 2.41 [95% CI, 1.43-4.04]; and third tertile [≥1106 days]: OR, 2.29 [95% CI, 1.36-3.87]; *P* for interaction for the 3 duration categories = .31).

Sensitivity Analyses

When the analyses were restricted to the 62 cases with AKI as the primary diagnosis, the OR for current use of ADT remained statistically significant, with the point estimate higher than the one estimated in the primary analysis (eTable 1 in the Supplement). When we stratified by calendar period, the ORs for the 2 time bands (1998-2003 and 2004-2009) were elevated and in the same direction as those obtained in the primary analysis, although OR for the 1998-2003 time was higher (eTable 2 in the Supplement). Furthermore, excluding and censoring cases and matched controls based on the presence of procedures suggestive of postrenal AKI led to results consistent with those of the primary and secondary analyses (eTable 3). When current users were compared with past users, the OR remained elevated and in the same direction as that of the primary

Table 2. Characteristics of Androgen Deprivation Therapy Users Among Controls

Characteristics	Use, No. (%)		
	Never (n = 842)	Current (n = 1420)	Past (n = 459)
Age, mean (SD), y	77.2 (7.2)	80.2 (6.1)	77.4 (5.8)
Duration of follow-up, mean (SD), y	3.6 (2.5)	3.5 (2.7)	4.3 (2.3)
Excessive alcohol use	60 (7.1)	113 (8.0)	27 (5.9)
Smoking status			
Never	317 (37.7)	533 (37.5)	184 (40.1)
Ever	504 (59.9)	837 (58.9)	266 (58.0)
Unknown	21 (2.5)	50 (3.5)	9 (2.0)
Body mass index			
<30	666 (79.1)	1102 (77.6)	364 (79.3)
≥30	119 (14.1)	216 (15.2)	68 (14.8)
Unknown	57 (6.8)	102 (7.2)	27 (5.9)
Prostate-specific antigen, ng/mL			
<4	79 (9.4)	134 (9.4)	47 (10.2)
4-10	252 (29.9)	136 (9.6)	85 (18.5)
>10	186 (22.1)	643 (45.3)	181 (39.4)
Unknown	325 (38.6)	507 (35.7)	146 (31.8)
Comorbidities			
Hypertension	309 (36.7)	565 (39.8)	147 (32.0)
Coronary artery disease	98 (11.6)	208 (14.6)	33 (7.1)
Diabetes	83 (9.9)	155 (10.9)	60 (13.1)
Rhythm disorders	60 (7.1)	110 (7.8)	24 (5.2)
Congestive heart failure	24 (2.9)	57 (4.0)	4 (0.9)
Ischemic stroke	26 (3.1)	63 (4.4)	10 (2.2)
No. of hospitalizations, mean (SD)	2.1 (4.0)	1.8 (2.9)	2.2 (3.6)
Metastasis[a]	5 (0.6)	77 (5.4)	9 (2.0)
Radiation therapy	47 (5.6)	91 (6.4)	108 (23.5)
Prostatectomy	217 (25.8)	183 (12.9)	67 (14.6)
Chemotherapy	4 (0.5)	16 (1.1)	11 (2.4)
Medications[b]			
Angiotensin-converting enzyme inhibitors	190 (22.6)	357 (25.1)	91 (19.8)
Angiotensin II receptor blockers	73 (8.7)	120 (8.5)	48 (10.5)
Calcium channel blockers	203 (24.1)	335 (23.6)	116 (25.3)
β-Blockers	141 (16.8)	285 (20.1)	78 (17.0)
Other antihypertensives (including diuretics)	221 (26.3)	513 (36.1)	91 (19.8)
Antibiotics	163 (19.4)	300 (21.1)	74 (16.1)
Paracetamol/acetaminophen	174 20.7)	365 (25.7)	74(16.1)
Aspirin	267 (31.7)	462 (32.5)	137 (29.9)
Statins	254 (30.2)	448 (31.6)	146 (31.8)
Corticosteroids	61 (7.2)	147 (10.4)	48 (10.5)
Antiarrhythmics	25 (3.0)	238 (16.8)	18 (3.9)
Other nonsteroidal anti-inflammatory drugs	51 (6.1)	107 (7.5)	33 (7.2)
Anticoagulants	50 (5.9)	109 (7.7)	29 (6.3)
Selective serotonin reuptake inhibitors	30 (3.6)	60 (4.2)	17 (3.7)
Digoxin	32 (3.8)	79 (5.6)	17(3.7)
Clopidogrel	25 (3.0)	47 (3.3)	17 (3.7)
Immunosuppressive agents	16 (1.9)	18 (1.3)	4 (0.9)
Antipsychotics	6 (0.7)	10 (0.7)	1 (0.2)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Captured in both the Clinical Practice Research Datalink and Hospital Episode Statistics database.

[b] Measured in the 90 days before the index date.

Table 3. Risk of Acute Kidney Injury Associated With Androgen Deprivation Therapy According to Timing of Use

	Exposure to Androgen Deprivation Therapy		
	Never	Current (≤90 d of Index Date)	Past (≥91 d of Index Date)
No. (%)			
Cases (n = 232)	40 (17.2)	168 (72.4)	24 (10.3)
Controls (n = 2721)	842 (30.9)	1420 (52.2)	459 (16.9)
OR (95% CI)			
Crude	1 [Reference]	2.66 (1.83-3.85)	1.12 (0.66-1.93)
Adjusted[a]	1 [Reference]	2.48 (1.61-3.82)	1.25 (0.68-2.29)

Abbreviation: OR, odds ratio.

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol/acetaminophen, aspirin, statins, corticosteroids, antiarrhythmics, other nonsteroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, and antipsychotics.

Table 4. Risk of Acute Kidney Injury Associated With Androgen Deprivation Therapy According to Type of Therapy

	No. (%)		OR (95% CI)	
Exposure to Androgen Deprivation Therapy	Cases (n = 232)	Controls (n = 2721)	Crude	Adjusted[a]
Never	40 (17.2)	842 (30.9)	1 [Reference]	1 [Reference]
Current[b]				
Combined androgen blockade	43 (18.5)	208 (7.6)	4.51 (2.80-7.27)	4.50 (2.61-7.78)
Estrogen only	5 (2.2)	15 (0.6)	7.03 (2.35-21.04)	4.00 (1.06-15.03)
Other combination therapies	19 (8.2)	69 (2.5)	5.56 (2.97-10.38)	4.04 (1.88-8.69)
Oral antiandrogens only	10 (4.3)	112 (4.1)	2.03 (0.97-4.23)	2.18 (0.95-5.01)
GnRH agonists only	85 (36.6)	949 (34.9)	1.99 (1.32-3.00)	1.93 (1.20-3.10)
Bilateral orchiectomy	6 (2.6)	67 (2.5)	1.59 (0.61-4.11)	1.84 (0.64-5.28)

Abbreviations: GnRH, gonadotropin-releasing hormone; OR, odds ratio.

[a] Adjusted for excessive alcohol use, smoking status, obesity, prostate-specific antigen, hypertension, coronary artery disease, diabetes, rhythm disorders, congestive heart failure, ischemic stroke, number of hospitalizations, metastasis, radiation therapy, prostatectomy, chemotherapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers, other antihypertensives (including diuretics), antibiotics, paracetamol/acetaminophen, aspirin, statins, corticosteroids, antiarrhythmics, other nonsteroidal anti-inflammatory drugs, anticoagulants, selective serotonin reuptake inhibitors, digoxin, clopidogrel, immunosuppressive agents, antipsychotics.

[b] *P* value for interaction across the different ADT exposure groups was .001.

analysis (eTable 4). Censoring on metastases, prostatectomy, radiation therapy, and chemotherapy during follow-up led to ORs consistent with those of the primary and secondary analyses (eTable 5 in the Supplement). Additionally excluding patients with abnormal creatinine values and following the remaining cohort for up to 2 years led to nonsignificant results due to the fewer exposed cases, but with point estimates in the same direction as that of the primary analysis (eTable 6). Repeating the primary analysis yielded a falsification exposure consisting of 5α-reductase inhibitors was not associated with an increased risk of AKI, with the OR for current use nonsignificant and below the null value (eTable 7). When we varied the length of the residual effect periods of ADT, and the exposure window of 90 days with alternate windows of 30 and 60 days, the ORs were similar to those estimated in both primary and secondary analyses (eTables 8-10 in the Supplement). Finally, excluding the 54 cases and 842 controls with abnormal baseline creatinine levels yielded results consistent with those of the primary analysis (eTable 11).

Discussion

To our knowledge, this is the first population-based study to investigate the association between the use of ADT and the risk of AKI in men with prostate cancer. In this study, the use of ADT was associated with an increased risk of AKI, with variations observed with certain types of ADTs. This association remained continuously elevated, with the highest OR observed in the first year of treatment. Overall, these results remained consistent after conducting several sensitivity analyses.

Although only one case report of flutamide-related AKI has been published to date,[11] ADT and its hypogonadal effect have well-known consequences consistent with our findings. We previously reported that oral antiandrogen therapy and bilateral orchiectomy are associated with increased risks of stroke and transient ischemic attack.[25] Others have reported that current use of GnRH agonists was associated with increased risks of incident diabetes and coronary heart disease.[26] Since these studies support an association between the use of ADT and an

increased risk of metabolic syndrome and cardiovascular diseases, a similar rationale can be postulated for the risk of AKI. Patients with metabolic syndrome have been shown to have a higher prevalence of tubular atrophy and interstitial fibrosis on histological studies. As such, dyslipidemia and hyperglycemia may disrupt glomerular functions by expanding and thickening the interstitial tubular membranes.[6] Furthermore, dyslipidemia is a known risk factor for thrombosis, which as observed in patients with hyperlipidemia undergoing postcardiac surgery increases the risk of AKI by inducing oxidative stress.[27,28]

In addition, there is preclinical evidence suggesting a protective effect of testosterone on the peripheral circulation. Specifically, testosterone appears to protect the kidneys by inducing vasodilation in the renal vessels and by enhancing the production of nitric oxide.[7] Thus, the use of ADT might antagonize testosterone, thereby increasing the risk of damage to the glomerulus. Furthermore, ADT-induced hypogonadism leads to estrogen deficiency, with the latter shown to play a protective role in ischemic renal injury by reducing glomerular endothelial permeability.[8] Supporting this notion is our falsification analysis using 5α-reductase inhibitors, a group of drugs that directly block the conversion of testosterone to dihydrotestosterone, leading to an increase of testosterone as well as estradiol through the process of aromatization. In that analysis, 5α-reductase inhibitors were not associated with an increased risk of AKI, with a nonsignificant OR below the null value for current use (0.62) and one closer to the null value for past use (1.11). While this analysis likely lacked statistical power due to the few exposed cases, the direction of the point estimates are suggestive of a potential renoprotective role of testosterone and estrogens on AKI. Finally, given the known association between cardiovascular diseases and AKI,[29-31] it is not possible to exclude an intermediate effect due to ADT-related cardiovascular events as the leading cause for AKI.

With respect to ADT types, the highest OR was observed in patients taking combination therapies, such as those concurrently using GnRH agonists with oral antiandrogens. This finding suggests a possible additive effect exerted by ADT on both receptor antagonism and reduction of testosterone excretion. Furthermore, the highest OR of AKI was also observed in the earliest period of treatment, though the OR remained continuously elevated with longer durations of use. The former might be related to an early and severe deteriorating effect of ADT in susceptible patients[32] who probably experience subtle reductions in kidney functions.

This study has a number of strengths. First, we assembled a population-based cohort by linking the CPRD and HES databases, which allowed access to detailed patients' medical histories, including lifestyle information such as smoking, alcohol use, and BMI measurements. We were therefore able to adjust for several potentially important confounders often absent in administrative databases. Second, both exposure and covariates definitions were time-dependent based on the risk set sampling used to select controls in this nested case-control design. Third, exposure to ADT was prospectively recorded in the CPRD, thus eliminating the possibility of recall bias.

This study also has some limitations. First, we did not perform a formal validation of AKI cases. However, our overall incidence rate of AKI is greater than what has been estimated in the general population (5.5 vs 1.8 per 1000 person-years[33]), which is expected in a cohort of men with prostate cancer. In addition, in sensitivity analyses, consistent results were observed when AKI cases were restricted to those with a primary diagnosis code, when we stratified the analysis by calendar period, and when we excluded at baseline and censored patients with procedures suggestive of postrenal AKI. Second, there may be some concerns regarding residual confounding due to unmeasured variables, such as the grade and stage of prostate cancer at diagnosis and cancer progression during follow-up. Nevertheless, we observed consistent results after comparing current users with past users, 2 populations likely similar in terms of clinical characteristics and indications of use, and adjusting or censoring for major potential confounders (ie, the occurrence of metastases, with an incidence rate of 3.1% per year in our cohort, in line with previous reports[34]).

In addition, given the magnitude of the ORs observed, a confounder very strongly associated with both the exposure and outcome would be needed to completely confound the association[35] (eFigure in the Supplement). Finally, although the 90-day current exposure time window is biologically consistent with the expected time frame of AKI occurrence, there are no conclusive data on this regard. Nonetheless, we obtained similar results when we repeated the analyses using shorter exposure windows of 60 and 30 days.

Conclusions

In summary, in this study of patients newly diagnosed with nonmetastatic prostate cancer, the use of ADT was associated with a significantly increased risk of AKI. These findings require replication in other carefully designed studies as well as further investigation of their clinical importance.

ARTICLE INFORMATION

Author Contributions: Dr Suissa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lapi, Azoulay, Benayoun, Suissa.
Acquisition of data: Suissa.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Lapi, Suissa.
Critical revision of the manuscript for important intellectual content: Azoulay, Niazi, Yin, Benayoun, Suissa.
Statistical analysis: Lapi, Azoulay, Yin, Suissa.
Administrative, technical, or material support: Suissa.
Study supervision: Suissa.

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