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Androgen Deprivation Therapy and the Risk of Coronary Heart Disease and Heart Failure in Patients with Prostate Cancer

A Nested Case-Control Study in UK Primary Care

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Abstract

Background: Androgen deprivation therapy (ADT) is used to delay tumour development and improve survival in patients with prostate cancer. However, several randomized controlled trials and observational studies have suggested that ADT may increase the risk of cardiovascular events.

Objective: The aim of the study was to evaluate the risk of coronary heart disease (CHD) and heart failure (HF) in patients with prostate cancer receiving ADT in UK primary care, and to evaluate the risks associated with individual ADT and combination ADT.

Methods: The UK General Practice Research Database was used to identify a cohort of patients with a first prostate cancer diagnosis during 1999–2005. These patients were followed up to assess the occurrence of acute myocardial infarction (AMI), death from CHD, incident HF and hospitalization due to acute decompensated HF. Nested case-control analyses were performed to assess the risk of these outcomes associated with anti-androgen therapy, as well as different types of ADT and combinations of ADT.

Results: Current anti-androgen use was associated with a significant increase in the risk of hospitalization due to HF (odds ratio [OR] 2.15; 95% CI 1.08, 4.29), but not of incident HF, CHD or AMI. When assessed individually, there was no significant association of bicalutamide or cyproterone use with the risk of AMI or CHD. Current use of bicalutamide 50 mg/day was associated with a significant increase in the risk of HF (OR 3.28; 95% CI 1.31, 8.18); however, this increased risk of HF was only found in patients taking bicalutamide 50 mg/day in combination with luteinizing hormone-releasing hormone (LHRH) receptor agonists. There were no cases of hospitalized HF in patients taking bicalutamide 50 mg/day as monotherapy and there was no significant association between current use of bicalutamide 150 mg/day and

the risk of hospitalized HF. Combination therapy with LHRH agonists and anti-androgens was associated with a significant increase in the risk of CHD (OR 4.35; 95% CI 1.94, 9.75), AMI (OR 3.57; 95% CI 1.44, 8.86), incident HF (OR 3.19; 95% CI 1.10, 9.27) and hospitalized HF (OR 3.39; 95% CI 1.07, 10.70) compared with non-use of these drugs.

Conclusions: In men with prostate cancer, combination therapy with LHRH agonists and anti-androgens is associated with significant increases in the risk of CHD, AMI, incident HF and hospitalized HF. Individual therapies do not appear to increase the risk of these outcomes.

Background

Prostate cancer is the most frequently diagnosed cancer in men and most cases are detected in men older than 70 years of age.[1] Prognosis is generally favourable; in England, men diagnosed with prostate cancer have a relative 1-year survival rate of 95.8%,[2] and 5-year survival rate has been reported at 77.0%.[3] In the US, over 90% of men are diagnosed with local or regional disease and have a 5-year relative survival rate approaching 100%.[4]

Prostate cancer treatments aim to prevent the actions of androgens such as testosterone, which drive the progression of the disease in its early stages.[5] Androgen deprivation therapies (ADTs) either reduce hormone levels (luteinizing hormone-releasing hormone [LHRH] receptor agonists) or block the hormone's action (anti-androgens) in order to delay tumour development and improve survival.[6] Originally used to treat men with advanced disease, ADTs are now increasingly administered to men with local or regional disease;[7] however, they are known to increase cholesterol levels, reduce insulin sensitivity and increase body fat deposition, which are all risk factors for diabetes mellitus and cardiovascular events.[8-11] Several randomized controlled trials[12-15] and observational studies[16-24] have evaluated the association between ADT and risk of cardiovascular events, yet have reported equivocal findings. Nonetheless, it would be prudent for treatment options for patients with local or regional prostate cancer to be considered carefully to ensure that treatment-related adverse events do not impact on the patient's overall health more than the prostate cancer itself.

Most studies investigating the association between ADTs and cardiovascular disease have examined the risk associated with LHRH agonists or a combination of different types of ADTs. We feel it is important to determine the relative risk of individual ADTs in relation to cardiovascular disease. The aims of this study were therefore to evaluate the risk of coronary heart disease (CHD) and heart failure (HF) in patients with prostate cancer who were (i) treated with anti-androgen drugs (primary aim) and (ii) treated with different types and combinations of ADTs (secondary aim).

Methods

Study Design and Database

A cohort study with nested case-control analyses was performed using data from the UK General Practice Research Database (GPRD). The GPRD contains computerized information on almost 5 million active patients entered by around 600 primary care physicians (PCPs).[25] The database provides information on demographics, medical diagnoses, PCP visits, consultant and hospital referrals, laboratory test results and records of all prescriptions issued, and also includes a free-text section for the recording of any additional comments.[26] Several studies have validated the accuracy and completeness of the data in the GPRD as a whole,[27] specifically for the diagnosis of prostate cancer.[28,29]

Selection of Source Population

We identified all men enrolled on the database aged 50–84 years during January 1999–December

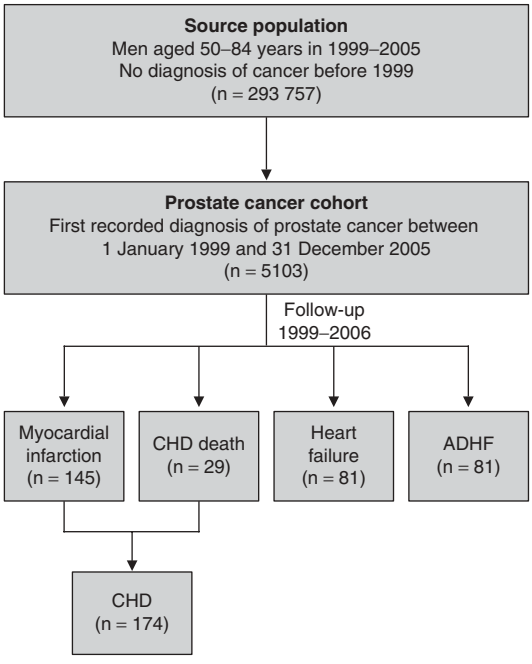

Fig. 1. Study design and case ascertainment. **ADHF** = acute decompensated heart failure; **CHD** = coronary heart disease.

2005 who had a patient registration status of 'permanent' or 'died'. For information quality assurance, patients were eligible to become members of the study population on the date (eligibility date) that they met the following inclusion criteria: at least 2 years enrolment with a PCP, at least one computer entry in the previous year and a computerized prescription history of at least 1 year. Patients who were 'elderly without visit' (aged 80 years or more at their eligibility date and fewer than two computer entries over a follow-up period >1 year) were excluded as a proxy for incomplete data recording. Patients with Read codes for any type of cancer (except non-melanoma skin cancer) prior to the date they became eligible members of the study population were also excluded. All remaining patients constituted the final study population of 293 757 men free of any recorded cancer (figure 1).

Cohort Selection and Follow-up

Identification of Prostate Cancer Cohort

All members of the study population with a Read code for prostate cancer (n = 5555) were identified and their computerized patient profiles, including free-text comments, were reviewed manually. Patients deemed to be prevalent cases (n = 136) and those with an unconfirmed or incorrect prostate cancer diagnosis (n = 82) were excluded. Patients who died on the same day or the day following their prostate cancer diagnosis (n = 12), and patients who had a diagnosis for another cancer within 60 days of their prostate cancer diagnosis (n = 222) were also excluded (these criteria were adopted to be certain of only selecting cases of prostate cancer that were a primary malignancy), leaving a final prostate cancer cohort (incident prostate cancer cases) comprising 5103 patients. Previous validation studies[28,29] have shown a high confirmation rate of prostate cancer diagnoses in the GPRD; therefore, no further validation of prostate cancer diagnoses was undertaken in this study. Each patient's start date was set as the date of prostate cancer diagnosis.

Follow-Up, Case Ascertainment and Validation

Two separate follow-up studies were performed: the first assessed the occurrence of acute myocardial infarction (AMI) or overall CHD (non-fatal AMI plus death due to CHD), and the second assessed the incidence of HF and hospitalizations from acute decompensated HF.

In study 1, all members of the prostate cancer cohort were followed up from the date of diagnosis until the occurrence of the first of the following (right censoring date): hospitalization from AMI; death due to AMI or CHD; death from another cause; age 85 years; or 31 December 2006. The computerized profiles (including free-text comments) of all patients with a code for AMI or a record of death due to CHD were reviewed manually to ascertain potential cases. Cases of non-fatal AMI were only included if the patient also had a code compatible with a hospitalization due to the event. Following this review, 145 hospitalizations from AMI and 29 deaths due to CHD (including sudden deaths or cardiac arrests) were identified. The index date was defined as the date of hospitalization for AMI and date of death for CHD death. Previous studies have found that PCP validation of AMI diagnoses and records of death due to CHD results in a high

confirmation rate;[30,31] therefore, no further validation was performed in this study.

In study 2, all members of the prostate cancer cohort were followed up from the date of diagnosis until the occurrence of the first of the following (right censoring date): diagnosis of HF; death; age 85 years; or 31 December 2006. Patients with a history of CHD or HF were excluded from the follow-up to incident HF but not from the follow-up to hospitalization due to HF. Computerized profiles of all potential cases were reviewed manually. A patient was considered a case if they presented with dyspnoea together with at least one of the following: clinically or radiographically confirmed pulmonary oedema; peripheral oedema and raised jugular venous pressure (on clinical examination); evidence of heart disease (either by clinical examination, ECG or echocardiogram). When the diagnosis of HF was based on post-mortem findings, or when the diagnosis of HF was confirmed by the PCP even in the absence of symptoms, these patients were also deemed to be cases. For hospitalization due to HF, patients were deemed only to be a potential case if they had a code compatible with a hospitalization due to the event. Following this review, a total of 85 cases of incident HF and 68 cases of incident hospitalizations due to HF were identified. The index date was defined as the date of HF diagnosis or hospitalization due to HF. PCPs were requested to confirm, via questionnaires, the HF diagnoses and the hospitalizations from HF. After PCP validation, the final number of incident HF cases was 81 (67 of these were identified following the manual review of possible incident HF cases; 14 were identified following manual review of possible hospitalized HF and then later confirmed through this validation process as being incident HF cases) and the final number of hospitalization for HF was also 81 (63 of these were identified following the manual review of possible hospitalized HF cases; 18 were identified following manual review of possible incident cases of HF and then later confirmed through this validation as having been hospitalized). Based on the questionnaires received, this represents a confirmation rate for HF and hospitalized HF of 94.4% and 90.9%, respectively.

Control Selection

Controls were free of the outcome of interest and were selected by incidence density sampling from the prostate cancer cohort, in which the probability of being selected as a control is proportional to the person-time at risk. Three groups of 1000 controls were selected and frequency-matched to each of the three case types by interval between start and right censoring date (within periods of 90 days). The index date for the controls was a date generated at random by a computer programme within the interval between their start and right censoring date.

Risk Factors and Therapy Exposure

Information on the patients' demographics, lifestyle characteristics, use of healthcare services, co-morbidity (yes/no), prostate-specific antigen (PSA) level (ng/mL) and Gleason value at the date of prostate cancer diagnosis was obtained from the computerized patient files. Information on prostate cancer treatment was obtained and included therapeutic procedures (including prostatectomy and radiotherapy) and ADT used during the period from prostate cancer diagnosis to the index date. Four subgroups for ADT exposure were defined: current use, recent use, past use and non-use. Current users were defined as patients whose most recent prescription ended 0–30 days before the index date; recent users were those whose most recent prescription ended 31 days–1 year before the index date; past users were those whose most recent prescription ended more than 1 year before the index date; and non-users were those who had never had a prescription for that drug (they could have been exposed to other types of ADT). For bicalutamide, data were collected on the two different doses that are available – 50 mg/day and 150 mg/day.

Statistical Analysis

Case-control analyses nested in the prostate cancer cohort were performed to evaluate the association between the different prostate cancer treatments and the cardiovascular outcomes. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models

adjusted for the following potential confounding variables: age, body mass index, smoking status, alcohol use, number of PCP visits, duration of follow-up and the following co-morbidities present at the start date: ischaemic heart disease, HF, atrial fibrillation, cerebrovascular disease, diabetes, hypercholesterolaemia, hypertension, chronic obstructive pulmonary disease and anaemia.

Results

Baseline Characteristics

Of the 5103 men with prostate cancer, 64.4% of patients were 70 years or older at the time of diagnosis (mean = 72). Prostate biopsy results were recorded for 36.1% of patients, and 34.6% of patients had a Gleason score. Among patients with Gleason information, 49% had a low Gleason score (1–6), 30.5% had an intermediate score (equal to 7) and 19.4% had a high score (8–10). Only 11.4% of patients had data on clinical disease stage recorded. PSA tests were recorded for 84.3% of patients. Among those with a PSA assessment within 90 days of the prostate cancer diagnosis (n = 2812; 55.1%), 87.0% had PSA levels ≥6 ng/mL, 10.7% had PSA <6 ng/mL and 2.3% were not assigned a value (although a PSA test was recorded). The distribution of demographic and lifestyle characteristics, co-morbidity, PSA level and Gleason value among cases and controls are reported in table I for CHD and table II for HF.

Study 1: Risk of Coronary Heart Disease

The risk of AMI and overall CHD among men receiving different prostate therapies is shown in table III.

Anti-Androgens

Compared with non-use of anti-androgens, current use of any anti-androgen (with or without other treatments) was not associated with a significant difference in the risk of hospitalization due to AMI (OR 1.02; 95% CI 0.55, 1.90) or the risk of overall CHD (OR 1.28; 95% CI 0.75, 2.20). When current use of anti-androgen therapy was analysed by individual anti-androgen therapy, none were associated with a significant change in risk of hospitalization due to AMI or CHD compared with non-use. Compared with men receiving neither anti-androgens nor LHRH agonists, current use of anti-androgen monotherapy was not associated with a significant change in risk of overall CHD (OR 0.66; 95% CI 0.31, 1.43) or the risk of hospitalization due to AMI (OR 0.51; 95% CI 0.21, 1.22).

Luteinizing Hormone-Releasing Hormone (LHRH) Agonists

Current use of LHRH agonists (with or without other treatments) was associated with a significant increase in the overall risk of CHD (OR 1.61; 95% CI 1.04, 2.51) and a numerically greater risk of hospitalization due to AMI (OR 1.49; 95% CI 0.93, 2.40) compared with non-use of LHRH agonists. However, when the analysis was restricted to current users of LHRH agonist monotherapy, there was no significant increase in the risk of CHD (OR 1.21; 95% CI 0.73, 2.01) compared with patients receiving neither LHRH agonists nor anti-androgens.

Combination Therapy

Current use of a combination of LHRH agonists and anti-androgens was associated with a significantly increased risk of CHD (OR 4.35; 95% CI 1.94, 9.75) and hospitalization due to AMI (OR 3.57; 95% CI 1.44, 8.86) compared with men with not receiving either therapy.

Other Treatments

Only a small proportion of patients underwent prostatectomy or orchiectomy, and these procedures were not associated with an increased risk of cardiovascular events. However, radiotherapy was associated with a decreased risk of both hospitalization due to AMI (OR 0.51; 95% CI 0.26, 1.00) and CHD (OR 0.53; 95% CI 0.28, 0.99) when compared with no radiotherapy.

Study 2: Risk of Heart Failure

The risk of HF and hospitalization due to HF among men receiving different prostate therapies is shown in table IV.

Anti-Androgens

Current use of any anti-androgen (with or without other treatments) was associated with a

Table I. Baseline characteristics: coronary heart disease (CHD) cases and controls

Independent variable	Controls (n = 1000) [n (%)]	Hospitalization due to AMI		CHD (hospitalization due to AMI + CHD death)	
		AMI cases (n = 145) [n (%)]	OR (95% CI)	CHD cases (n = 174) [n (%)]	OR (95% CI)
Age (y)					
51–69	296 (29.6)	26 (17.9)	Ref	28 (16.1)	Ref
70–84	704 (70.4)	119 (82.1)	1.59 (0.99, 2.55)	146 (83.9)	1.77 (1.12, 2.78)
BMI (kg/m^2)					
13–19.9	24 (2.4)	0 (0)	NA	2 (1.1)	0.46 (0.10, 2.15)
20–24.9	285 (28.5)	34 (23.4)	Ref	43 (24.7)	Ref
25–29.9	436 (43.6)	66 (45.5)	1.40 (0.87, 2.24)	76 (43.7)	1.23 (0.80, 1.90)
30–59.9	141 (14.1)	30 (20.7)	1.82 (1.02, 3.26)	34 (19.5)	1.61 (0.93, 2.77)
Unknown	114 (11.4)	15 (10.3)	1.03 (0.45, 2.34)	19 (10.9)	0.82 (0.38, 1.77)
Smoking					
Never	402 (40.2)	47 (32.4)	Ref	56 (32.2)	Ref
Current	108 (10.8)	23 (15.9)	1.87 (1.03, 3.37)	28 (16.1)	1.95 (1.13, 3.36)
Former	462 (46.2)	70 (48.3)	0.96 (0.63, 1.47)	81 (46.6)	0.94 (0.64, 1.40)
Unknown	28 (2.8)	5 (3.4)	1.34 (0.38, 4.76)	9 (5.2)	2.71 (0.91, 8.08)
Alcohol use (units/week)					
None	307 (30.7)	56 (38.6)	Ref	64 (36.8)	Ref
1–15	449 (44.9)	57 (39.3)	0.86 (0.57, 1.31)	68 (39.1)	0.88 (0.59, 1.31)
16–41	131 (13.1)	16 (11.0)	0.78 (0.42, 1.46)	20 (11.5)	0.84 (0.47, 1.50)
≥42	16 (1.6)	0 (0)	NA	1 (0.6)	0.52 (0.07, 4.20)
Unknown	97 (9.7)	97 (9.7)	1.29 (0.57, 2.91)	21 (12.1)	1.23 (0.57, 2.67)
Hospitalizations					
0–1	835 (83.5)	103 (71.0)	Ref	122 (70.1)	Ref
>1	165 (16.5)	42 (29.0)	2.32 (1.49, 3.60)	52 (29.9)	2.24 (1.48, 3.37)

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Table I. Contd

Independent variable	Controls (n = 1000) [n (%)]	Hospitalization due to AMI		CHD (hospitalization due to AMI + CHD death)	
		AMI cases (n = 145) [n (%)]	OR (95% CI)	CHD cases (n = 174) [n (%)]	OR (95% CI)
PCP visits					
0–2	84 (8.4)	7 (4.8)	Ref	8 (4.6)	Ref
3–10	226 (22.6)	25 (17.2)	1.45 (0.58, 3.66)	34 (19.5)	1.97 (0.82, 4.72)
≥11	690 (69.0)	113 (77.9)	2.27 (0.95, 5.48)	132 (75.9)	2.50 (1.08, 5.81)
Co-morbidity					
IHD	232 (23.2)	71 (49.0)	2.72 (1.80, 4.09)	81 (46.6)	2.29 (1.56, 3.37)
AF	77 (7.7)	9 (6.21)	0.46 (0.21, 1.01)	19 (10.9)	0.83 (0.45, 1.53)
HF	53 (5.3)	17 (11.7)	1.52 (0.78, 2.96)	28 (16.1)	2.11 (1.18, 3.74)
CVD	88 (8.8)	25 (17.2)	1.53 (0.90, 2.61)	31 (17.8)	1.46 (0.89, 2.39)
Diabetes mellitus	105 (10.5)	25 (17.2)	1.25 (0.74, 2.10)	30 (17.2)	1.26 (0.77, 2.05)
Hypercholesterolaemia	187 (18.7)	32 (22.1)	0.74 (0.45, 1.19)	38 (21.8)	0.79 (0.50, 1.24)
Hypertension	399 (39.9)	75 (51.7)	1.31 (0.89, 1.92)	89 (51.2)	1.37 (0.96, 1.96)
COPD	71 (7.1)	18 (12.4)	1.55 (0.84, 2.86)	24 (13.8)	1.67 (0.97, 2.88)
Anaemia	44 (4.4)	11 (7.6)	1.10 (0.52, 2.33)	15 (8.6)	1.23 (0.63, 2.41)
PSA value (ng/mL)					
≤5	107 (10.7)	12 (8.3)	Ref	13 (7.5)	Ref
6–15.9	300 (30.0)	34 (23.5)	1.06 (0.51, 2.19)	39 (22.4)	1.11 (0.55, 2.23)
16–39.9	187 (18.7)	26 (17.9)	1.12 (0.52, 2.41)	27 (15.5)	1.02 (0.48, 2.13)
≥40	144 (14.4)	26 (17.9)	1.31 (0.60, 2.84)	35 (20.1)	1.51 (0.73, 3.14)
Unknown	262 (26.2)	47 (32.4)	1.66 (0.82, 3.40)	60 (34.5)	1.78 (0.90, 3.52)
Gleason value					
<5	31 (3.1)	6 (4.1)	Ref	6 (3.5)	Ref
5–7	269 (26.9)	23 (15.9)	0.39 (0.14, 1.09)	29 (16.7)	0.48 (0.18, 1.30)
8–10	55 (5.5)	5 (3.5)	0.36 (0.09, 1.36)	8 (4.6)	0.59 (0.18, 1.98)
Unknown	645 (64.5)	111 (76.6)	0.70 (0.27, 1.80)	131 (75.3)	0.73 (0.28, 1.87)

AF = atrial fibrillation; **AMI** = acute myocardial infarction; **BMI** = body mass index; **COPD** = chronic obstructive pulmonary disease; **CVD** = cerebrovascular disease; **HF** = heart failure; **IHD** = ischaemic heart disease; **NA** = not applicable; **OR** = odds ratio; **PCP** = primary care practitioner; **PSA** = prostate-specific antigen; **Ref** = reference.

Table II. Baseline characteristics: heart failure (HF) cases and controls

Independent variable	Incident HF			Hospitalization from HF		
	cases (n = 81) [n (%)]	controls (n = 1000) [n (%)]	OR (95% CI)	cases (n = 81) [n (%)]	controls (n = 1000) [n (%)]	OR (95% CI)
Age (y)						
51–69	11 (13.6)	359 (35.9)	Ref	11 (13.6)	327 (32.7)	Ref
70–84	70 (86.4)	641 (64.1)	3.79 (1.92, 7.49)	70 (86.4)	673 (67.3)	2.58 (1.30, 5.11)
BMI (kg/m^2)						
13–19.9	2 (2.5)	28 (2.8)	0.87 (0.18, 4.16)	2 (2.5)	12 (1.2)	1.74 (0.33, 9.27)
20–24.9	18 (22.2)	281 (28.1)	Ref	20 (24.7)	273 (27.3)	Ref
25–29.9	36 (44.4)	432 (43.2)	1.45 (0.79, 2.67)	36 (44.4)	451 (45.1)	1.05 (0.57, 1.92)
30–59.9	14 (17.3)	134 (13.4)	1.83 (0.84, 3.97)	15 (18.5)	147 (14.7)	1.10 (0.50, 2.44)
Unknown	11 (13.6)	125 (12.5)	2.13 (0.87, 5.22)	8 (9.9)	117 (11.7)	1.09 (0.40, 2.93)
Smoking						
Never	25 (30.9)	409 (40.9)	Ref	24 (29.6)	400 (40.0)	Ref
Current	16 (19.8)	122 (12.2)	2.34 (1.13, 4.81)	16 (19.8)	111 (11.0)	2.79 (1.34, 5.82)
Former	39 (48.1)	436 (43.6)	1.19 (0.69, 2.05)	40 (49.4)	467 (46.7)	1.21 (0.69, 2.14)
Unknown	1 (1.2)	33 (3.3)	0.27 (0.03, 2.18)	1 (1.2)	22 (2.2)	0.58 (0.06, 5.88)
Alcohol use (units/week)						
None	18 (22.2)	293 (29.3)	Ref	25 (30.9)	325 (32.5)	Ref
1–15	37 (45.7)	446 (44.6)	1.59 (0.86, 2.92)	36 (44.4)	433 (43.3)	1.22 (0.69, 2.16)
16–42	16 (19.8)	133 (13.3)	2.27 (1.08, 4.78)	12 (14.8)	140 (14.0)	1.19 (0.55, 2.58)
≥42	1 (1.2)	20 (2.0)	0.74 (0.09, 6.20)	1 (1.2)	8 (0.8)	2.10 (0.23, 19.01)
Unknown	9 (11.1)	108 (10.8)	1.80 (0.69, 2.05)	7 (8.6)	94 (9.4)	1.49 (0.53, 4.16)
Hospitalizations						
0–1	58 (71.6)	802 (80.2)	Ref	57 (70.4)	823 (82.3)	Ref
>1	23 (28.4)	198 (19.8)	1.50 (0.87, 2.60)	24 (29.6)	177 (17.7)	1.82 (1.04, 3.18)
PCP visits						
0–2	3 (3.7)	55 (5.5)	Ref	3 (3.7)	56 (5.6)	Ref

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Table II. Contd

Independent variable	Incident HF			Hospitalization from HF		
	cases (n = 81) [n (%)]	controls (n = 1000) [n (%)]	OR (95% CI)	cases (n = 81) [n (%)]	controls (n = 1000) [n (%)]	OR (95% CI)
3–10	13 (16.0)	264 (26.4)	0.83 (0.22, 3.12)	10 (12.3)	242 (24.2)	0.66 (0.16, 2.65)
≥11	65 (80.2)	681 (68.1)	1.55 (0.44, 5.48)	68 (84.0)	702 (70.2)	1.53 (0.41, 5.67)
Co-morbidities						
IHD	NA	NA	NA	28 (34.6)	225 (22.5)	1.19 (0.67, 2.10)
AF	10 (12.4)	39 (3.9)	2.24 (1.01, 4.99)	18 (22.2)	61 (6.1)	2.75 (1.42, 5.32)
HF	NA	NA	NA	14 (17.3)	32 (3.2)	3.97 (1.81, 8.73)
CVD	11 (13.6)	65 (6.5)	1.89 (0.89, 4.00)	16 (19.8)	97 (9.7)	1.58 (0.82, 3.06)
Diabetes mellitus	10 (12.4)	82 (8.2)	1.53 (0.72, 3.26)	14 (17.3)	102 (10.2)	1.84 (0.93, 3.64)
Hypercholesterolaemia	5 (6.2)	121 (12.1)	0.52 (0.20, 1.35)	13 (16.1)	170 (17.0)	0.68 (0.34, 1.39)
Hypertension	32 (39.5)	390 (39.0)	0.82 (0.49, 1.37)	38 (46.9)	422 (42.2)	0.97 (0.58, 1.61)
COPD	10 (12.4)	61 (6.1)	1.66 (0.76, 3.59)	10 (12.4)	64 (6.4)	1.14 (0.52, 2.50)
Anaemia	4 (4.9)	36 (3.6)	0.84 (0.27, 2.62)	4 (4.9)	34 (3.40)	0.88 (0.27, 2.86)
PSA value (ng/mL)						
≤5	6 (7.4)	127 (12.7)	Ref	5 (6.2)	110 (11)	Ref
6–15.9	12 (14.8)	298 (29.8)	0.65 (0.23, 1.83)	18 (22.2)	308 (30.8)	1.04 (0.36, 3.00)
16–39.9	12 (14.8)	165 (16.5)	0.80 (0.28, 2.34)	10 (12.4)	172 (17.2)	0.70 (0.22, 2.25)
≥40	21 (25.9)	163 (16.3)	1.55 (0.58, 4.20)	23 (28.4)	156 (15.6)	1.95 (0.68, 5.62)
Unknown	30 (37.0)	247 (24.7)	1.75 (0.68, 4.49)	25 (30.9)	254 (25.4)	1.48 (0.52, 4.20)
Gleason value						
<5	0 (-)	31 (3.1)	NA	1 (1.2)	32 (3.2)	Ref
5–7	11 (13.6)	261 (26.1)	NA	10 (12.4)	251 (25.1)	0.76 (0.09, 6.54)
8–10	1 (1.2)	68 (6.8)	NA	3 (3.7)	59 (5.9)	0.78 (0.07, 8.47)
Unknown	69 (85.2)	640 (64,0)	NA	67 (82.7)	658 (65.8)	1.79 (0.23, 14.17)

AF = atrial fibrillation; **BMI** = body mass index; **COPD** = chronic obstructive pulmonary disease; **CVD** = cerebrovascular disease; **IHD** = ischaemic heart disease; **NA** = not applicable; **OR** = odds ratio; **PCP** = primary care practitioner; **PSA** = prostate-specific antigen; **Ref** = reference.

Table III. Association between prostate cancer therapy and risk of acute myocardial infarction (AMI) and coronary heart disease (CHD)

Prostate cancer therapy	Controls (n = 1000) [n (%)]	Hospitalization due to AMI			CHD (hospitalization due to AMI + CHD death)		
		MI cases (n = 145) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]	CHD cases (n = 174) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]
Any anti-androgen							
Non-use	594 (59.4)	86 (59.3)	Ref	Ref	99 (56.9)	Ref	Ref
Current	96 (9.6)	16 (11.0)	1.15 (0.65, 2.05)	1.02 (0.55, 1.90)	23 (13.2)	1.44 (0.87, 2.38)	1.28 (0.75, 2.20)
Recent	126 (12.6)	17 (11.7)	0.93 (0.54, 1.62)	0.76 (0.42, 1.38)	23 (13.2)	1.10 (0.67, 1.79)	0.86 (0.50, 1.47)
Past	184 (18.4)	26 (17.9)	0.98 (0.61, 1.56)	0.92 (0.54, 1.55)	29 (16.7)	0.95 (0.61, 1.48)	0.88 (0.53, 1.44)
Bicalutamide							
Non-use	777 (77.7)	118 (81.4)	Ref	Ref	140 (80.5)	Ref	Ref
Current (mg)	69 (6.9)	12 (8.3)	1.15 (0.60, 2.18)	1.04 (0.52, 2.05)	18 (10.3)	1.45 (0.84, 2.51)	1.38 (0.77, 2.49)
50	29 (2.9)	6 (7.4)	1.36 (0.55, 3.35)	1.24 (0.48, 3.16)	9 (5.2)	1.72 (0.80, 3.72)	1.64 (0.73, 3.67)
150	40 (4.0)	6 (7.4)	0.99 (0.41, 2.38)	0.88 (0.34, 2.27)	9 (5.2)	1.25 (0.59, 2.63)	1.19 (0.53, 2.64)
Recent	64 (6.4)	6 (4.1)	0.62 (0.26, 1.46)	0.49 (0.20, 1.20)	7 (4.0)	0.61 (0.27, 1.35)	0.49 (0.21, 1.15)
Past	90 (9.0)	9 (6.2)	0.66 (0.32, 1.34)	0.70 (0.33, 1.50)	9 (5.2)	0.56 (0.27, 1.13)	0.58 (0.28, 1.24)
Cyproterone							
Non-use	831 (83.1)	110 (75.9)	Ref	Ref	131 (75.3)	Ref	Ref
Current	22 (2.2)	4 (2.8)	1.37 (0.46, 4.06)	1.21 (0.37, 3.97)	5 (2.9)	1.44 (0.54, 3.87)	1.15 (0.39, 3.44)
Recent	57 (5.7)	11 (7.6)	1.46 (0.74, 2.86)	1.22 (0.58, 2.56)	15 (8.6)	1.67 (0.92, 3.04)	1.32 (0.68, 2.58)
Past	90 (9.0)	20 (13.8)	1.68 (0.99, 2.83)	1.67 (0.94, 3.00)	23 (13.2)	1.62 (0.99, 2.66)	1.62 (0.94, 2.80)
Flutamide							
Non-use	961 (96.1)	142 (97.9)	Ref	Ref	168 (96.6)	Ref	Ref
Current	5 (0.5)	0	NA	NA	0	NA	NA
Recent	11 (1.1)	1 (0.7)	0.62 (0.08, 4.80)	0.67 (0.08, 5.63)	2 (1.2)	1.04 (0.23, 4.73)	0.86 (0.16, 4.53)
Past	23 (2.3)	2 (1.4)	0.59 (0.14, 2.52)	0.56 (0.12, 2.58)	4 (2.3)	0.99 (0.34, 2.92)	0.95 (0.30, 3.01)

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Table III. Contd

Prostate cancer therapy	Controls (n = 1000) [n (%)]	Hospitalization due to AMI			CHD (hospitalization due to AMI + CHD death)		
		MI cases (n = 145) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]	CHD cases (n = 174) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]
LHRH agonists							
Non-use	511 (51.1)	62 (42.8)	Ref	Ref	72 (41.4)	Ref	Ref
Current	179 (17.9)	40 (27.6)	1.84 (1.20, 2.84)	1.49 (0.93, 2.40)	51 (29.3)	2.02 (1.36, 3.01)	1.61 (1.04, 2.51)
Recent	218 (21.8)	34 (23.5)	1.29 (0.82, 2.01)	0.88 (0.54, 1.45)	42 (24.1)	1.37 (0.91, 2.07)	0.99 (0.62, 1.57)
Past	92 (9.2)	9 (6.2)	0.81 (0.39, 1.68)	0.65 (0.29, 1.46)	9 (5.2)	0.69 (0.34, 1.44)	0.59 (0.27, 1.29)
LHRH agonists and anti-androgen combination							
None	405 (40.5)	51 (35.2)	Ref	Ref	57 (32.8)	Ref	Ref
Only LHRH agonist	158 (15.8)	31 (21.4)	1.56 (0.96, 2.52)	1.13 (0.66, 1.94)	38 (21.8)	1.71 (1.09, 2.68)	1.21 (0.73, 2.01)
Only anti-androgens current	75 (7.5)	7 (4.8)	0.74 (0.32, 1.70)	0.51 (0.21, 1.22)	10 (5.8)	0.95 (0.46, 1.94)	0.66 (0.31, 1.43)
Both current	21 (2.1)	9 (6.2)	3.40 (1.48, 7.83)	3.57 (1.44, 8.86)	13 (7.5)	4.40 (2.09, 9.27)	4.35 (1.94, 9.75)
Remaining	341 (34.1)	47 (32.4)	1.09 (0.72, 1.67)	0.80 (0.50, 1.29)	56 (32.2)	1.17 (0.79, 1.73)	0.88 (0.56, 1.37)
Procedures							
Prostatectomy	100 (10.0)	11 (7.6)	0.74 (0.39, 1.41)	1.30 (0.63, 2.66)	11 (6.3)	0.61 (0.32, 1.16)	1.12 (0.55, 2.28)
Radiotherapy	160 (16.0)	11 (7.6)	0.43 (0.23, 0.82)	0.51 (0.26, 1.00)	13 (7.5)	0.42 (0.24, 0.76)	0.53 (0.28, 0.99)
Orchiectomy	8 (0.8)	1 (0.7)	0.86 (0.11, 6.94)	1.03 (0.12, 8.86)	2 (1.2)	1.44 (0.30, 6.85)	2.10 (0.42, 10.53)
TURP	140 (14.0)	23 (15.9)	1.16 (0.72, 1.87)	1.03 (0.62, 1.72)	30 (17.2)	1.28 (0.83, 1.97)	1.15 (0.72, 1.83)
Overall treatment							
No treatment (watchful waiting)	289 (28.9)	41 (28.3)	Ref	Ref	46 (26.4)	Ref	Ref
Only prostatectomy	74 (7.4)	7 (4.8)	0.67 (0.29, 1.55)	1.01 (0.40, 2.51)	7 (4.0)	0.59 (0.26, 1.37)	0.96 (0.39, 2.37)
Only pharmacological treatment or orchiectomy	232 (23.2)	46 (31.7)	1.40 (0.89, 2.20)	1.10 (0.66, 1.84)	59 (33.9)	1.60 (1.05, 2.44)	1.26 (0.78, 2.02)
Only radiotherapy	33 (3.3)	1 (0.7)	0.21 (0.03, 1.60)	0.23 (0.03, 1.82)	2 (1.2)	0.38 (0.09, 1.64)	0.44 (0.10, 1.98)
More than one treatment	372 (37.2)	50 (34.5)	0.95 (0.61, 1.47)	0.78 (0.47, 1.28)	60 (34.5)	1.01 (0.67, 1.53)	0.87 (0.54, 1.39)

a Adjusted by age, body mass index, smoking, alcohol use, time of follow-up, primary care physician visits, and the following co-morbidity before the start date: ischaemic heart disease, heart failure, atrial fibrillation, cerebrovascular disease, diabetes mellitus, hypercholesterolaemia, hypertension, chronic obstructive pulmonary disease and anaemia.

LHRH = luteinizing hormone-releasing hormone; **MI** = myocardial infarction; **NA** = not applicable; **OR** = odds ratio; **Ref** = reference; **TURP** = transurethral resection of the prostate.

Table IV. Association between prostate cancer therapy and risk of heart failure (HF)

Prostate cancer therapy	Incident HF				Hospitalization due to HF			
	controls (n = 1000) [n (%)]	HF cases (n = 81) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]	controls (n = 1000) [n (%)]	HF cases (n = 81) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]
Any anti-androgen								
Non-use	594 (59.4)	36 (44.4)	Ref	Ref	589 (58.9)	36 (44.4)	Ref	Ref
Current	117 (11.7)	14 (17.3)	1.97 (1.03, 3.78)	1.70 (0.85, 3.40)	110 (11.0)	15 (18.5)	2.23 (1.18, 4.21)	2.15 (1.08, 4.29)
Recent	129 (12.9)	16 (19.8)	2.05 (1.10, 3.80)	1.64 (0.84, 3.19)	132 (13.2)	13 (16.1)	1.61 (0.83, 3.12)	1.35 (0.65, 2.80)
Past	160 (16.0)	15 (18.5)	1.55 (0.83, 2.90)	1.41 (0.71, 2.83)	169 (16.9)	17 (21.0)	1.65 (0.90, 3.00)	1.24 (0.62, 2.47)
Bicalutamide								
Non-use	756 (75.6)	61 (75.3)	Ref	Ref	751 (75.1)	58 (71.6)	Ref	Ref
Current (mg)	76 (7.6)	6 (7.4)	0.98 (0.41, 2.34)	0.72 (0.29, 1.82)	84 (8.4)	10 (12.4)	1.54 (0.76, 3.13)	1.54 (0.72, 3.28)
50	28 (2.8)	5 (6.2)	2.21 (0.83, 5.94)	1.54 (0.53, 4.49)	36 (3.6)	7 (8.6)	2.52 (1.07, 5.91)	3.28 (1.31, 8.18)
150	48 (4.8)	1 (1.2)	0.26 (0.04, 1.90)	0.20 (0.03, 1.52)	48 (4.8)	3 (3.7)	0.81 (0.24, 2.68)	0.63 (0.18, 2.23)
Recent	76 (7.6)	9 (11.1)	1.47 (0.70, 3.07)	1.22 (0.56, 2.68)	71 (7.1)	7 (8.6)	1.28 (0.56, 2.90)	1.18 (0.48, 2.90)
Past	92 (9.2)	5 (6.2)	0.67 (0.26, 1.72)	0.63 (0.24, 1.68)	94 (9.4)	6 (7.4)	0.83 (0.35, 1.97)	0.58 (0.22, 1.50)
Cyproterone								
Non-use	833 (83.3)	63 (77.8)	Ref	Ref	832 (83.2)	58 (71.6)	Ref	Ref
Current	34 (3.4)	5 (6.2)	1.94 (0.73, 5.15)	2.32 (0.80, 6.75)	24 (2.4)	4 (4.9)	2.39 (0.80, 7.12)	2.49 (0.74, 8.37)
Recent	63 (6.3)	5 (6.2)	1.05 (0.41, 2.70)	0.92 (0.35, 2.46)	57 (5.7)	8 (9.9)	2.01 (0.92, 4.42)	1.67 (0.70, 3.98)
Past	70 (7.0)	8 (9.9)	1.51 (0.70, 3.28)	1.30 (0.55, 3.04)	87 (8.7)	11 (13.6)	1.81 (0.92, 3.58)	1.54 (0.71, 3.34)
Flutamide								
Non-use	975 (97.5)	69 (85.2)	Ref	Ref	972 (97.2)	75 (92.6)	Ref	Ref
Current	7 (0.7)	3 (3.7)	6.06 (1.53, 23.94)	8.16 (1.70, 39.15)	3 (0.3)	1 (1.2)	4.32 (0.44, 42.04)	6.04 (0.47, 78.08)
Recent	4 (0.4)	3 (3.7)	10.60 (2.33, 48.30)	6.82 (1.06, 43.96)	9 (0.9)	1 (1.2)	1.44 (0.18, 11.52)	1.79 (0.20, 15.87)
Past	14 (1.4)	6 (7.4)	6.06 (2.26, 16.25)	5.65 (1.96, 16.26)	16 (1.6)	4 (4.9)	3.24 (1.06, 9.94)	4.02 (1.18, 13.66)
LHRH agonists								
Non-use	519 (51.9)	24 (29.6)	Ref	Ref	530 (53.0)	24 (29.6)	Ref	Ref
Current	188 (18.8)	21 (25.9)	2.42 (1.31, 4.44)	1.81 (0.93, 3.52)	195 (19.5)	21 (29.6)	2.38 (1.29, 4.37)	2.07 (1.06, 4.05)

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Table IV. Contd

Prostate cancer therapy	Incident HF				Hospitalization due to HF			
	controls (n = 1000) [n (%)]	HF cases (n = 81) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]	controls (n = 1000) [n (%)]	HF cases (n = 81) [n (%)]	crude OR (95% CI)	OR (95% CI)[a]
Recent	220 (22.0)	31 (38.3)	3.05 (1.75, 5.31)	2.39 (1.29, 4.41)	182 (18.2)	29 (25.9)	3.52 (2.00, 6.20)	2.90 (1.55, 5.42)
Past	73 (7.3)	5 (6.2)	1.48 (0.55, 4.00)	1.20 (0.41, 3.56)	93 (9.3)	7 (8.6)	1.66 (0.70, 3.97)	1.36 (0.52, 3.57)
LHRH agonists and anti-androgen combination								
None	390 (39.0)	18 (22.2)	Ref	Ref	411 (41.1)	16 (19.8)	Ref	Ref
Only LHRH agonist	153 (15.3)	15 (18.5)	2.12 (1.04, 4.32)	1.44 (0.66, 3.13)	156 (15.6)	16 (19.8)	2.63 (1.29, 5.40)	1.99 (0.90, 4.40)
Only anti-androgens current	82 (8.2)	8 (9.9)	2.11 (0.89, 5.03)	1.55 (0.61, 3.94)	71 (7.1)	10 (12.4)	3.62 (1.58, 8.29)	3.09 (1.25, 7.67)
Both current	35 (3.5)	6 (7.4)	3.71 (1.38, 9.96)	3.19 (1.10, 9.27)	39 (3.9)	5 (6.2)	3.29 (1.14, 9.47)	3.39 (1.07, 10.70)
Remaining	340 (34.0)	34 (42.0)	2.17 (1.20, 3.91)	1.74 (0.91, 3.31)	323 (32.3)	34 (42.0)	2.70 (1.47, 4.99)	2.06 (1.04, 4.06)
Procedures								
Prostatectomy	122 (12.2)	2 (2.5)	0.18 (0.04, 0.75)	0.35 (0.08, 1.48)	103 (10.3)	2 (2.5)	0.22 (0.05, 0.91)	0.45 (0.11, 1.95)
Radiotherapy	145 (14.4)	7 (8.6)	0.56 (0.25, 1.23)	0.66 (0.29, 1.51)	162 (16.2)	9 (11.1)	0.65 (0.32, 1.32)	0.73 (0.33, 1.60)
Orchiectomy	11 (1.1)	0 (-)	NA	NA	14 (1.4)	1 (1.2)	0.88 (0.11, 6.78)	0.59 (0.07, 5.02)
TURP	128 (12.8)	6 (7.4)	0.55 (0.23, 1.28)	0.46 (0.19, 1.13)	162 (16.2)	6 (7.41)	0.41 (0.18, 0.97)	0.35 (0.15, 0.85)
Overall treatment								
No treatment (watchful waiting)	261 (26.1)	16 (19.8)	Ref	Ref	278 (27.8)	12 (14.8)	Ref	Ref
Only prostatectomy	85 (8.5)	2 (2.5)	0.38 (0.09, 1.70)	0.73 (0.15, 3.44)	83 (8.3)	2 (2.5)	0.56 (0.12, 2.54)	1.09 (0.22, 5.29)
Only pharmacological treatment or orchiectomy	241 (24.1)	30 (37.0)	2.03 (1.08, 3.82)	1.60 (0.79, 3.3)	239 (23.9)	32 (39.5)	3.10 (1.56, 6.16)	2.72 (1.27, 5,82)
Only radiotherapy	34 (3.4)	0 (0)	NA	NA	39 (3.9)	1 (1.2)	0.59 (0.08, 4.69)	0.73 (0.08, 6.43)
More than one treatment	379 (37.9)	33 (40.8)	1.42 (0.77, 2.63)	1.27 (0.64, 2.50)	361 (36.1)	34 (42.0)	2.18 (1.11, 4.29)	2.02 (0.95, 4.32)

a Adjusted by age, body mass index, smoking, alcohol use, time of follow-up, primary care physician visits, and the following co-morbidity before the start date: ischaemic heart disease, HF, atrial fibrillation, cerebrovascular disease, diabetes mellitus, hypercholesterolaemia, hypertension, chronic obstructive pulmonary disease and anaemia.

LHRH = luteinizing hormone-releasing hormone; **NA** = not applicable; **OR** = odds ratio; **Ref** = reference; **TURP** = transurethral resection of the prostate.

significantly increased of risk of hospitalization due to HF (OR 2.15; 95% CI 1.08, 4.29) and a numerically increased risk of incident HF (OR 1.70; 95% CI 0.85, 3.40) compared with non-use of anti-androgens. Recent and past use of any anti-androgen was associated with non-significant increases in the risk of these cardiovascular events. When use of each anti-androgen was analysed individually, use of flutamide was associated with a significant increase in the risk of incident HF. However, the small numbers of individuals in each of the flutamide exposure groups makes these results hard to interpret. Bicalutamide and cyproterone use was not associated with a significant change in risk of incident HF.

A significant increase in the risk of hospitalization due to HF was found to be associated with current use of bicalutamide 50 mg/day (OR 3.28; 95% CI 1.31, 8.18) and past use of flutamide (OR 4.02; 95% CI 1.18, 13.66) when compared with non-use of the respective drug. Further analysis showed that the increase in risk associated with current use of bicalutamide 50 mg/day was only found when this therapy was used in conjunction with LHRH agonists (OR 4.33; 95% CI 1.68, 11.13). No hospitalizations from HF were identified in patients taking bicalutamide 50 mg/day as monotherapy and there were no other significant associations between the risk of hospitalization from HF and the use of individual anti-androgen drugs.

Compared with non-use of anti-androgens or LHRH agonists, anti-androgen monotherapy was associated with a significant increase in the risk of hospitalization from HF (OR 3.09; 95% CI 1.25, 7.67), but not of incident HF (OR 1.55; 95% CI 0.61, 3.94).

LHRH Agonists

Use of LHRH agonists in the year before the index date was associated with a significant increase in the risk of hospitalization from HF (OR 2.07; 95% CI 1.06, 4.05 for current use, and OR 2.90; 95% CI 1.55, 5.42 for recent use) compared with non-use of LHRH agonists. The risk of incident HF was also significantly increased among recent users of LHRH agonists (OR 2.39; 95% CI 1.29, 4.41), but the association between current use of LHRH agonists and incident HF did not reach statistical significance (OR 1.81; 95% CI 0.93, 3.52).

Combination Therapy

Patients with prostate cancer who were currently taking a combination of LHRH agonists and anti-androgens had a significantly increased risk of incident HF (OR 3.19; 95% CI 1.10, 9.27) and hospitalization due to HF (OR 3.39; 95% CI 1.07, 10.70) compared with men not taking either therapy.

Other Treatments

There was no significant association between other treatments, such as prostatectomy, orchiectomy and radiotherapy, and the risk of HF.

Discussion

This large, population-based study showed that certain types and combinations of hormonal treatments are associated with increased risk of cardiovascular events in men with prostate cancer. Current use of anti-androgens (in combination with other therapies or as monotherapy) was associated with a significant increase in the risk of hospitalization from HF; however, there was no significant association between the use of anti-androgens and any of the other outcomes studied. Although the remaining subanalyses are exploratory, thus increasing the chance of random errors, the following observations are considered worthy of note. We found that current use of LHRH agonists (in combination with other therapies or as monotherapy) to be associated with a significant increase in the risk of CHD and hospitalization from HF. However, these associations were no longer significant when the analyses were restricted to users of LHRH agonist monotherapy. In particular, we found combination therapy with LHRH agonists and anti-androgens to be associated with a significant increase in the risk of all of the studied outcomes (incident HF, CHD and hospitalization from AMI or HF). Our findings suggest that LHRH agonists, rather than anti-androgen therapy, may play a role in increasing the risk of cardiovascular events in these men.

Our findings are somewhat in agreement with a number of other studies reporting a link between ADT and cardiovascular events in men with prostate cancer;[14-23] however, findings are inconsistent with several other studies reporting no association.[12,13,24] In most of these studies, patients with prostate cancer were taking ADTs consisting of either LHRH agonists alone or LHRH agonists in combination with anti-androgens. Few have analysed the association of different individual ADTs on the risk of cardiovascular events. Robinson et al.[23] reported a statistically significant increase in risk of IHD associated with the use of gonadotropin-releasing hormone (GnRH) agonists, regardless of co-medication. Keating et al.[16] similarly reported current use of a GnRH agonist to be associated with statistically significant increased risks of incident CHD, as well as myocardial infarction, sudden cardiac death and stroke.

To the best of our knowledge, our study is the first observational study to have performed a detailed analysis of the relationship between individual ADTs and cardiovascular risk. Some RCTs have identified small numerical increases in the incidence of cardiovascular events, particularly HF, in patients with prostate cancer receiving bicalutamide 150 mg/day compared with patients taking placebo.[14,15] However, in our study, no evidence was found for an increased risk of AMI, CHD or HF with use of bicalutamide 150 mg/day compared with patients not receiving bicalutamide. When stratified by the type of anti-androgen used, the risk of hospitalization from HF was only significantly increased in current users of bicalutamide 50 mg/day and past users of flutamide. The sample sizes for the flutamide analyses were very small, therefore the results should be interpreted with caution. Bicalutamide 50 mg/day was associated with a significant increase in the risk of hospitalization from HF and non-significant increases in the risk of the other outcomes studied; however, these increases were only found in patients who received concomitant treatment with LHRH agonists. This provides further support to our suggestion that the use of LHRH agonists or combination therapy with LHRH agonists results in a higher risk of cardiovascular events.

Combination therapy with LHRH agonists and anti-androgens tends to be prescribed either at initiation of treatment to combat the tumour 'flare' that can occur when LHRH agonist therapy is begun, or at later stages of the disease when the cancer has become more advanced and potentially resistant to some forms of hormone therapy. Patients at this stage of their disease are likely to have a poor prognosis and be at increased risk of cardiovascular events regardless of the treatment they receive.

The increase in cardiovascular risk observed in this study may be explained at the physiological level by the cardioprotective properties of testosterone.[32-34] ADT-mediated inhibition of endogenous androgens may reduce this cardioprotection and make patients more vulnerable to cardiovascular episodes. ADT has also been associated with an increase in fat mass, glycaemia resistance and hypertriglyceridaemia, metabolic factors that increase the risk for cardiovascular episodes.[35,36]

A key strength of this study is that it was conducted using data collected from a large representative sample of the population registered with PCPs in the UK. The accuracy and completeness of the GPRD for diagnoses of prostate cancer and all the cardiovascular events in this study have been validated previously[28,30] or were subject to validation during this study. Another strength of the study is that by matching cases and controls by calendar period, we ensured that we compared patients who had the same probability of being prescribed certain treatments. This is important as any changes in the guidelines for pharmacotherapy of prostate cancer during the study period may have affected the comparability of patients.

Our study does, however, have some limitations. Firstly, some of the risk estimates could be imprecise due to the small numbers of patients experiencing the various cardiovascular events. For the majority of cardiovascular outcomes, the number of patients taking anti-androgens, LHRH agonists, or both, were sufficient, but for some of the individual anti-androgen treatments the numbers of patients were often less than 10 and CIs were large. Our choice of nested case-control analysis could also potentially reduce the power of the

analysis compared with a time-dependent Cox regression model. However, as we used all incident cases ascertained in the follow-up and sampled a large group of controls, the power of the nested case-control analysis is virtually identical to that afforded by a cohort type analysis, but with fewer computational and logistical requirements than a time-dependent Cox regression approach.[37] Secondly, data on the clinical disease stage of the recorded prostate cancer diagnosis, be it coded or in free-text comments, was incomplete. This information would have been beneficial to better understand the baseline risk of cardiovascular disease in patients with localized, locally advanced or metastatic prostate cancer, and to control for it when assessing the risk associated with the treatment. Also, an important percentage of patients had a missing value of PSA or Gleason score, therefore we could not use these variables in the adjustment. We consider that a deeper analysis must be performed to resolve any potential confounding by indication in that the type of hormonal therapy prescribed is related to the stage and differentiation of the cancer. Finally, the study was only designed to look at some very specific aspects of cardiovascular disease: HF, non-fatal AMI and death due to CHD. As a result, the incidence of other cardiovascular conditions in the prostate cancer cohort was not assessed.

This study evaluated the risk of cardiovascular disease in patients with prostate cancer according to pharmacological treatments and procedures. Further work should address the relative risk of cardiovascular disease in prostate cancer patients prescribed individual ADTs as monotherapy and evaluate the role of testosterone levels in the development of cardiovascular events.

Conclusions

In men with prostate cancer, anti-androgens did not show an increase in the risk of CHD but a tendency to increase the incident HF and a significant increase in the hospitalization for HF. Combination therapy with LHRH agonists and anti-androgens is associated with a significant increase in the risk of incident HF, CHD, AMI and hospitalization from HF.

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This study is based in part on data from the Full Feature General Practice Research Database obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone.

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