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The risk of cardiovascular disease in prostate cancer patients receiving androgen deprivation therapies.

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Running title

Androgen deprivation and cardiovascular disease.

Conflicts of interest

None declared. None of the authors has a potential conflict of interest.

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Data access

Data could be accessed, at a cost, through the Information Services Division (ISD) of National Health Service (NHS) Scotland (<https://www.isdscotland.org/Products-and-Services/eDRIS/>). Analysis code is available from authors upon request.

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ABSTRACT

Background

Androgen deprivation therapy (ADT), which has a proven role in prostate cancer management, has been associated with various cardiovascular diseases. However few studies have investigated these associations by type of ADT, particularly for newer ADTs such as the gonadotropin-releasing hormone (GnRH) antagonist degarelix. We investigated the risk of cardiovascular disease by type of ADT in a real world setting.

Methods

Men newly diagnosed with prostate cancer, from 2009 to 2015, were identified from the Scottish Cancer Registry. ADTs were identified from the nationwide Prescribing Information System. Cardiovascular events were based upon hospitalisation (from hospital records) or death from cardiovascular disease (from death records). Cox regression calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular events with time-varying ADT exposure, comparing ADT users with untreated patients, after adjusting for potential confounders including prior cardiovascular disease.

Results

The cohort contained 20,216 prostate cancer patients, followed for 73,570 person years, during which there were 3,853 cardiovascular events. ADT was associated with a 25% increase in cardiovascular events (adjusted HR=1.25 95% CI 1.16, 1.35). This reflected increases in cardiovascular events associated with GnRH agonists (adjusted HR=1.26 95% CI 1.16, 1.36), degarelix (adjusted HR=1.49 95% CI 1.16, 1.90), but not bicalutamide monotherapy (adjusted HR=1.01 95% CI 0.82, 1.25).

Conclusions

There were increased risks of cardiovascular disease with use of GnRH agonists and degarelix, but not with bicalutamide monotherapy. This is the first study to observe increased cardiovascular risks with degarelix, but the cause of this association is unclear and merits further investigation.

Keywords

Androgen deprivation therapy, Bicalutamide, Cardiovascular Diseases, Gonadotropin-releasing hormone, Prostatic neoplasms

Introduction

Androgen deprivation therapy (ADT) has long been used in advanced prostate cancer [1] and more recently in localised disease [2,3] with clear survival benefits alone or with radiotherapy. ADT has been linked to various side-effects including cardiovascular disease [4], for which several mechanisms have been proposed [5]. For instance, ADT increases established cardiovascular disease risk factors including obesity and dyslipidaemia [5], and ADT suppresses protective effects of androgens on atherosclerosis [5,6].

The association between ADT and cardiovascular disease remains controversial. Since 2010 the US Food and Drug Administration has required manufacturers of GnRH (gonadotropin-releasing hormone) agonists to include safety information warning of increased risks of cardiovascular disease [7]. This is consistent with a 2015 meta-analysis of observational studies (including 6 studies of GnRH agonists and 3 of antiandrogens) which observed increases in cardiovascular disease [8] but not a 2011 meta-analysis of trials that did not show increases in fatal cardiovascular disease [9]. The different findings could reflect confounding in observational studies or the inclusion of healthier trial populations [9].

Recently authors have suggested that the different mechanisms of specific ADTs could alter cardiovascular disease risk [5]. A post-hoc analysis of a systematic review of trials suggested that the GnRH antagonist degarelix had a weaker adverse effect on cardiovascular disease, compared with GnRH agonists [10]. However only one observational study [7] which had limited statistical power due to only 12 ischaemic events in degarelix users has investigated this association.

Therefore, we investigated the risk of cardiovascular disease by type of ADT in a large population-based prostate cancer cohort.

Methods

Data sources

The study utilised the following linked databases [11]: the Scottish Cancer Registry; the Scottish National Prescribing Information System (PIS), which captures all community dispensed medications in Scotland; the General / Acute Inpatient and Day Case dataset (SMR01), which captures hospital diagnoses and operations; the Outpatient Attendance dataset (SMR00), which captures diagnoses and procedures from outpatient clinics; and, the National Records of Scotland Death Records which captures date and cause of death. These databases covered Scotland from January 1999 to July 2017, apart from the PIS which was available from January 2009 to July 2017. Linkages between data sources were conducted using the Community Health Index number (unique to each Scottish resident) [11]. The study was approved by the Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland (number:1617-0374).

Study design

A cohort of men newly diagnosed with prostate cancer (ICD10, International Classification of Diseases 10th revision, code C61) between January 2009 and December 2015, was identified from the Scottish Cancer Registry. Men were excluded if they: had a previous cancer diagnosis (apart from non-melanoma skin cancer or in-situ tumours); had inconsistent dates (specifically a record of ADT or radical prostatectomy, RP, more than 6 months prior to prostate cancer diagnosis).

The primary outcome was a cardiovascular event consisting of either death from cardiovascular disease or hospitalisation for cardiovascular disease. Death from cardiovascular disease was identified by ICD10 codes I20 to I99 and G45, as the underlying cause of death, within National Records of Scotland Death Records up to July 2017.

Hospitalisation for cardiovascular disease was identified, using the same ICD10 codes, from the primary condition for hospitalisation within SMR01 to July 2017. Analysis were also conducted by cardiovascular disease type using previous definitions for angina (I20, I24, I25 [12]), acute myocardial infarction (I21, I22 [12]), stroke (I60-64, G45 [13]), venous thromboembolism (I26, I80, I82.1-2.9 [14]), heart failure (I50, I11.0 [12]), arrhythmia (I44-49[13]) and other cardiovascular disease (all remaining I codes not previously categorised).

Exposure

ADT consisted of GnRH agonists (including goserelin, leuprorelin, triptorelin, and histrelin), oral antiandrogens (including bicalutamide, enzalutamide, flutamide and cyproterone acetate), the GnRH antagonist degarelix, estrogens and orchidectomy. Medical ADT was identified from dispensed medications from the PIS. The pack size and strength was used to calculate the number of days use based upon the daily defined doses (DDDs) as given by the World Health Organisation [15]. The Scottish Cancer Registry provided data on initial curative radiotherapy, RT. Orchidectomy (ICD10 codes N051, N052, N061 and N063 [16]) and RP (code M61 [16]) were taken from SMR01.

Confounders

The Scottish Cancer Registry provided Gleason score, and stage (based upon pathological stage, where recorded, or clinical stage). Cardiovascular diseases named previously and other comorbidities from the Charlson comorbidity index (specifically dementia, pulmonary disease, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, connective tissue disorder, renal disease and severe liver disease, using previous ICD10 codes [17]) were identified before prostate cancer diagnosis from hospital admissions data (SMR00 and SMR01). The following medications were determined from PIS records in

the year prior to diagnosis: non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications. Deprivation level was determined from postcode of residence using the 2009 Scottish Index of Multiple Deprivation [18].

Statistical analysis

In the primary analysis, prostate cancer patients were followed from prostate cancer diagnosis to the earliest of the date of first cardiovascular event, date of death, date of leaving Scotland or July 2017. Treatment was coded as a single time-varying and hierarchical variable to reflect treatment pathways [19,20]. Specifically, participants were initially in the untreated group and entered the ADT group on the date of their first dispensed ADT (regardless of future or past RP or RT) and remained in the ADT group for the rest of follow-up. Participants entered the RP group on the date of RP (where RP occurred before first ADT) and remained in the RP group for the rest of follow-up or until the date of first ADT. Participants entered the RT group on the date of RT (where RT occurred before ADT) and remained in the RT group for the rest of follow-up or until the date of first ADT or RP (see Figure 1A).

Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for cardiovascular events comparing the ADT, RT and RP exposure to untreated patients (receiving active surveillance or watchful waiting). The main model contained year of diagnosis, age, deprivation, comorbidities (stated above, at any time before diagnosis) and other medications (stated above, in the year before diagnosis using separate variables for each). Separate analyses, restricted to patients diagnosed 2012 to 2015, when stage was routinely recorded, were conducted additionally adjusted for stage (including

stage X[unstaged/stage unknown] as a category) and Gleason score (restricted to those with available data). A separate analysis was also conducted using a complete case analysis to adjust for stage and Gleason score, treating stage X as missing. In dose response analysis using a time-varying covariate, patients were deemed non-users prior to their first dispensed ADT, a short-term user from this time to 365 days of use (based upon DDDs) and a long-term user from then on (see Figure 1B). Analyses were repeated with ADT type coded as a single time-varying and hierarchical variable into the following hierarchical categories (to reflect treatment pathways[19,20]): GnRH agonists (with or without other ADT), degarelix (with or without antiandrogens, oestrogen or orchidectomy), bicalutamide 150 mg (analysed separately as predominantly used as monotherapy; with or without other antiandrogens, oestrogens or orchidectomy) and other antiandrogens (with or without oestrogens or orchidectomy).

Additional analyses were conducted. First, analyses were repeated using a primary outcome of death from cardiovascular disease only and, separately, repeated for cardiovascular disease incidence. Second, analyses were repeated stratifying by stage, age and cardiovascular disease before diagnosis. Third, analyses were conducted in which ADT users who subsequently received RT were allocated to a separate “ADT then RT” exposure category on the date of RT receipt. Fourth, analyses were conducted on an “intention-to-treat” exposure model with treatment groups based solely upon initial treatment (except for individuals simultaneously starting GnRH and antiandrogens who were allocated to GnRH exposure, as such antiandrogens were likely used short-term for tumour flare). Fifth, avoiding hierarchical exposure assignment, a separate analysis was conducted comparing each ADT individually (GnRH, degarelix, bicalutamide and other antiandrogens) with no treatment, regardless of use of another ADT. Sixth, analyses were repeated with death based upon a

cardiovascular disease code as any cause of death, and incidence based upon a cardiovascular disease code anywhere in SMR00 and SMR01.

Current use of ADT was investigated using a start/stop time-varying exposure in which patients became a user upon the date of each dispensed ADT and remained a user for the duration of the prescription, based upon the DDD, plus a residual effect period. The duration of the residual effect was taken from a previous study [21] and was 3 months for GnRH agonists and antagonists and 1 month for antiandrogens and estrogens (see Figure 1C). The exposure period between the end of one prescription and start of the next was allocated to past use. All analyses were conducted using STATA 14 (StataCorp, College Station, TX, USA).

Results

Overall 22,366 patients were identified with prostate cancer between 2009 and 2015. Of these 1,839 had prior cancer, 169 had date inconsistencies, 142 had events on the date of prostate cancer diagnosis. The final cohort contained 20,216 prostate cancer patients, 73,570 person years, and 3,853 cardiovascular events (52 per 1,000 person years).

Patient Characteristics

ADT users, compared with untreated patients, were older, less deprived, and had higher stage and Gleason score (see Table 1). ADT users had similar rates of medication use and cardiovascular disease before diagnosis, compared with untreated patients.

ADT and cardiovascular events

Table 2 shows, compared with untreated patients, the rates of cardiovascular events were similar in the radical prostatectomy and radiotherapy groups but higher in ADT users (adjusted HR=1.25 95% CI 1.16, 1.35). More marked associations (adjusted HR=1.36 95% CI 1.24, 1.48) were seen after receiving more than a year supply, 365 DDDs, of ADT. An increase in cardiovascular events was seen for GnRH agonists (adjusted HR=1.26 95% CI 1.16, 1.36), degarelix (adjusted HR=1.49 95% CI 1.16, 1.90), non-bicalutamide antiandrogens (adjusted HR=1.30 95% CI 1.07, 1.57) but not bicalutamide (adjusted HR=1.01 95% CI 0.82, 1.25). The difference between unadjusted and adjusted results partly reflected adjustment for age (see eTable 1). These associations were similar after further adjustment for stage and Gleason score and when based solely upon incidence of cardiovascular disease, but were slightly attenuated when based upon death from cardiovascular disease (eTable 2 and 3)

Table 3 shows analysis by specific cardiovascular events. Overall, ADT users compared with untreated patients had higher risks of myocardial infarction (adjusted HR=1.23 95% CI 1.03, 1.46), arrhythmia (adjusted HR=1.21 95% CI 1.01, 1.45), venous thromboembolism (adjusted HR=2.28 95% CI 1.76, 2.97) and unclassified other cardiovascular events (adjusted HR=1.28 95% CI 1.11, 1.47). These associations largely reflected GnRH agonists, but numbers were limited to investigate ADT types. After further adjustment for stage and Gleason score (shown in eTable 4) associations were similar, except for venous thromboembolism (adjusted HR=1.26 95% CI 0.76, 2.09).

Secondary \ sensitivity analyses

The association between ADT and cardiovascular events appeared similar in patients with and without prior cardiovascular disease (adjusted HR=1.22 95% CI 1.09, 1.36 and 1.34 95% CI 1.21, 1.49, see Table 4), by stage (see eTable 5) and by age (see eTable 6). Treating stage X as missing, and analysing the data as complete case had little impact on the results (see eTable 7). The associations were little altered after analyses assigning RT to a separate category, analyses based upon “intention-to-treat”, or analyses comparing each ADT individually with no treatment, regardless of use of another ADT (see eTables 8 and 9). Associations were generally attenuated when analyses were repeated with death based upon cardiovascular disease as any cause of death, and incidence based upon cardiovascular disease codes anywhere in hospital admissions data (see eTable 10).

Finally, current use of ADT (adjusted HR=1.33 95% CI 1.23, 1.44) was associated with cardiovascular events whilst past use (adjusted HR=1.06 95% CI 0.95, 1.18) was not, see Table 5. Current ADT use had generally similar associations with specific cardiovascular diseases as any ADT use (see eTable 11).

Discussion

We observed approximately a 25% increase in the risk of cardiovascular events in ADT users compared with untreated patients that mainly reflected increases for GnRH agonists and the GnRH antagonist degarelix. These associations followed a dose response and were apparent for current, but not past, ADT use. There was generally no association between bicalutamide use and cardiovascular events. ADT was associated with increased risks of venous thromboembolism, myocardial infarction and arrhythmia, but these associations were not robust across all analyses.

Our main ADT findings are largely consistent with a 2015 meta-analysis of observational studies that observed evidence of around 40% increases in cardiovascular disease risk with GnRH agonist based upon 6 studies [8]. Furthermore, since then additional studies have been conducted comparing ADT users to non-users which have shown increased risks of cardiovascular disease by 37% [22], increased risk of heart failure by 27%, arrhythmia by 17% [12] and venous thromboembolism by 84% [14].

The only previous observational study investigating cardiovascular disease risk with degarelix observed no difference in the risk of myocardial infarction or stroke in degarelix users compared with GnRH antagonists [7]. Similarly, we observed an increased risk of cardiovascular events with degarelix use similar to that seen for GnRH agonist use, compared with untreated patients. Furthermore, this pattern was similar in patients with pre-existing cardiovascular disease although our power was reduced in this group. Consequently, our findings do not appear to support a meta-analysis of trials suggesting that degarelix had a lower cardiovascular disease risk, compared with GnRH agonists in patients with pre-existing cardiovascular disease [10]. This difference in findings could reflect confounding within our study. For instance, degarelix users have more advanced prostate cancer which could increase cardiovascular disease risk and although we adjusted for stage and grade, these

variables were not complete. Alternatively, the difference could reflect Type 1 error or the inclusion of a real world population in our study with fewer comorbidity restrictions. Further research on the association between degarelix and cardiovascular events is merited and a trial is ongoing but is not due to report until 2021 [23].

We observed, in general, lower cardiovascular disease risk with bicalutamide monotherapy, which could reflect higher testosterone levels [24]. This should provide some reassurance to clinicians using bicalutamide in locally advanced non-metastatic prostate cancer [25] and complements studies which have shown a reduced impact of bicalutamide on bone health [24] and comorbidities more generally [26].

Strengths of our study include use of a large cohort of prostate cancer patients with high completeness[27] and detailed information on use and timing of ADT and access to a wide range of confounders including prior cardiovascular disease, cancer stage and Gleason score. Cardiovascular events were based upon National death and hospital records, which have high accuracy for various conditions including cardiovascular diseases [28], and of reassurance, results were similar when incidence or mortality data were analysed separately.

There is the possibility of residual confounding by incompletely recorded (stage, Gleason score) or unavailable variables (such as lifestyle cardiovascular disease risk factors including obesity, smoking or alcohol intake). ADT use was determined from dispensing records and medication adherence cannot be confirmed. However, the limited evidence that exists, suggests high adherence to oral ADT medications [29]. Finally, patients receiving ADT may have increased exposure to health care professionals increasing the likelihood of cardiovascular disease being identified.

In conclusion, GnRH agonists and degarelix were associated with increased cardiovascular disease risk. This is the first study to observe increased risks of

cardiovascular disease with degarelix. The cause of this association is unclear and merits further investigation.

Table 1. Characteristics of prostate cancer cohort by treatment group.

	Untreated	Radiotherapy ^a	Radical prostatectomy ^a	ADT ^a	ADT type			
					GnRH ^a	Degarelix ^a	Bicalutamide 150 mg ^a	Other antiandrogen ^a
Year of diagnosis: 2009	686 (14%)	134 (13%)	285 (12%)	1728 (14%)	1550 (15%)	5 (1%)	88 (20%)	81 (13%)
2010-11	1297 (26%)	293 (28%)	657 (28%)	3371 (28%)	3015 (29%)	22 (6%)	123 (27%)	206 (34%)
2012-13	1436 (29%)	381 (36%)	657 (28%)	3397 (28%)	2989 (29%)	114 (29%)	116 (26%)	177 (29%)
2014-15	1484 (30%)	243 (23%)	723 (31%)	3444 (29%)	2926 (28%)	246 (64%)	124 (27%)	145 (24%)
Age at diagnosis: <60	593 (12%)	233 (22%)	696 (30%)	886 (7%)	776 (7%)	23 (6%)	46 (10%)	39 (6%)
60-69	1789 (36%)	496 (47%)	1371 (59%)	3848 (32%)	3379 (32%)	112 (29%)	168 (37%)	187 (31%)
70-79	1543 (31%)	309 (29%)	251-255 ^c	5017 (42%)	4459 (43%)	156 (40%)	167 (37%)	232 (38%)
≥ 90	978 (20%)	13 (1%)		2189 (18%)	1866 (18%)	96 (25%)	70 (16%)	151 (25%)
Deprivation: 5 th fifth (most deprived)	1211 (25%)	273 (26%)	696 (30%)	2541 (21%)	2255 (22%)	61 (16%)	109 (24%)	113 (19%)
Gleason score: ≤ 6	1808 (62%)	231 (37%)	441 (32%)	658 (10%)	596 (10%)	19 (5%)	35 (15%)	8 (2%)
7	505 (17%)	311 (50%)	840 (61%)	2326 (34%)	2084 (35%)	45 (13%)	124 (52%)	72 (22%)
8	41 (1%)	35 (6%)	69 (5%)	812 (12%)	727 (12%)	27 (8%)	19 (8%)	39 (12%)
9	51 (2%)	27 (4%)	30 (2%)	1546 (23%)	1361 (23%)	71 (20%)	31 (13%)	81 (25%)
10	5 (0%)	6 (1%)	< 5	151 (2%)	110 (2%)	17 (5%)	< 5	21 (7%)
Missing	510 (17%)	14 (2%)	< 5	1348 (20%)	1037 (18%)	181 (50%)	27-31 ^c	101 (31%)
T stage ^b : 1	870 (30%)	92 (15%)	54 (4%)	461 (7%)	376 (6%)	36 (10%)	36 (15%)	13 (4%)
2	1401 (48%)	430 (69%)	883 (64%)	2020 (30%)	1794 (30%)	49 (14%)	98 (41%)	77 (24%)
3	219 (8%)	82 (13%)	432 (31%)	2801 (41%)	2482 (42%)	103 (29%)	80 (33%)	135 (42%)
4	57 (2%)	6 (1%)	5 (0%)	706 (10%)	600 (10%)	78 (22%)	< 5	24 (7%)
X	373 (13%)	14 (2%)	6 (0%)	853 (12%)	663 (11%)	94 (26%)	22-26 ^c	73 (23%)
N stage ^b : 0	1946 (67%)	543 (87%)	1233 (89%)	3881 (57%)	3497 (59%)	72 (20%)	180 (75%)	131 (41%)
1	64 (2%)	18 (3%)	23 (2%)	1181 (17%)	1004 (17%)	99 (28%)	13 (5%)	63 (20%)
X	910 (31%)	63 (10%)	124 (9%)	1779 (26%)	1414 (24%)	189 (53%)	47 (20%)	128 (40%)
M stage ^b : 0	1665 (57%)	493 (79%)	1002 (73%)	3826 (56%)	3459 (58%)	58 (16%)	161 (67%)	147 (46%)
1	217 (7%)	8 (1%)	< 5	2022 (30%)	1616 (27%)	263 (73%)	12 (5%)	128 (40%)
X	1038 (36%)	123 (20%)	372-378 ^c	993 (15%)	840 (14%)	39 (11%)	67 (28%)	47 (15%)
Medications in year prior ^d : Aspirin	1471 (30%)	230 (22%)	293 (13%)	3696 (31%)	3209 (31%)	146 (38%)	148 (33%)	188 (31%)
Statin	2078 (42%)	408 (39%)	637 (27%)	5414 (45%)	4722 (45%)	206 (53%)	214 (47%)	266 (44%)
Nitrate	493 (10%)	73 (7%)	72 (3%)	1213 (10%)	1035 (10%)	64 (17%)	64 (14%)	49 (8%)
Metformin	321 (7%)	64 (6%)	86 (4%)	951 (8%)	818 (8%)	50 (13%)	40 (9%)	43 (7%)
Comorbidities prior ^e : Angina	793 (16%)	111 (11%)	110 (5%)	1880 (16%)	1593 (15%)	94 (24%)	98 (22%)	90 (15%)
MI	234 (5%)	38 (4%)	37 (2%)	607 (5%)	508 (5%)	37 (10%)	32 (7%)	29 (5%)
Heart failure	208 (4%)	21 (2%)	13 (1%)	468 (4%)	376 (4%)	31 (8%)	30 (7%)	31 (5%)
Stroke	235 (5%)	25 (2%)	23 (1%)	519 (4%)	443 (4%)	29 (7%)	20 (4%)	27 (4%)
VTE	102 (2%)	9 (1%)	20 (1%)	181 (2%)	157 (1%)	5 (1%)	8 (2%)	11 (2%)
Arrhythmia	542 (11%)	50 (5%)	70 (3%)	1137 (10%)	955 (9%)	67 (17%)	57 (13%)	57 (9%)
Any cardiovascular	1661 (34%)	233 (22%)	367 (16%)	3818 (32%)	3267 (31%)	173 (45%)	179 (40%)	194 (32%)

MI, myocardial infarction; VTE, venous thromboembolism.

^aParticipants allocated to the following mutually exclusive treatment categories based upon any use after diagnosis: ADT (with or without RP or RT), RP (with or without RT but without ADT) and RT (without ADT or RP). ADT users allocated to the following categories based upon any use after prostate cancer diagnosis: GnRH (with or without any other ADT), degarelix (with or without an antiandrogen but without GnRH), bicalutamide 150 mg (with or without any other antiandrogen but without degarelix and GnRH) and other antiandrogen (without GnRH, deagaralex, bicalutamide 150 mg).

^bStage unavailable for prostate cancer patients diagnosed 2009 to 2011.

^cRange given to avoid disclosure of small counts.

^dMedications at any time prior to prostate cancer diagnosis.

^eComorbidities at any time prior to prostate cancer diagnosis.

Table 2. Association between androgen deprivation therapy and cardiovascular events.

		Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
<i>Diagnosed 2009 to 2015</i>								<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and Gleason)</i>					
Untreated		1105	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		511	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
Radical prostatectomy		253	9350	0.61 (0.53,0.70)	<0.001	0.94 (0.81,1.09)	0.404	104	3836	0.63 (0.51,0.78)	<0.001	0.98 (0.77,1.24)	0.847
Radiotherapy		135	4450	0.68 (0.57,0.82)	<0.001	0.85 (0.71,1.02)	0.076	53	1929	0.65 (0.49,0.86)	0.003	0.82 (0.61,1.11)	0.206
ADT:	Any use	2360	37180	1.38 (1.28,1.49)	<0.001	1.25 (1.16,1.35)	<0.001	1069	16562	1.46 (1.31,1.64)	<0.001	1.32 (1.12,1.54)	0.001
	0-365 DDDs	979	16495	1.23 (1.12,1.34)	<0.001	1.15 (1.05,1.26)	0.002	493	8259	1.28 (1.13,1.46)	<0.001	1.21 (1.02,1.43)	0.029
	365+ DDDs	1381	20685	1.56 (1.43,1.70)	<0.001	1.36 (1.24,1.48)	<0.001	576	8303	1.73 (1.51,1.98)	<0.001	1.59 (1.31,1.93)	<0.001
GnRH:	Any use	2075	33023	1.37 (1.27,1.48)	<0.001	1.26 (1.16,1.36)	<0.001	920	14575	1.43 (1.28,1.60)	<0.001	1.33 (1.13,1.56)	0.001
	0-365 DDDs	990	16606	1.24 (1.14,1.36)	<0.001	1.18 (1.08,1.29)	<0.001	487	8101	1.31 (1.15,1.49)	<0.001	1.26 (1.06,1.49)	0.007
	365+ DDDs	1085	16417	1.55 (1.41,1.69)	<0.001	1.36 (1.24,1.49)	<0.001	433	6473	1.65 (1.43,1.90)	<0.001	1.55 (1.26,1.89)	<0.001
Degarelix:	Any use	71	726	2.01 (1.58,2.56)	<0.001	1.49 (1.16,1.90)	0.001	64	657	2.12 (1.63,2.76)	<0.001	1.47 (0.99,2.18)	0.054
	0-365 DDDs	41	393	1.98 (1.45,2.71)	<0.001	1.45 (1.06,2.00)	0.02	37	361	2.05 (1.47,2.88)	<0.001	1.33 (0.79,2.24)	0.28
	365+ DDDs	30	333	2.01 (1.39,2.89)	<0.001	1.52 (1.05,2.19)	0.026	27	296	2.20 (1.49,3.26)	<0.001	1.81 (1.05,3.12)	0.032
Bicalutamide:	Any use	95	1711	1.22 (0.98,1.50)	0.07	1.01 (0.82,1.25)	0.913	37	620	1.35 (0.97,1.89)	0.079	1.13 (0.77,1.65)	0.524
	0-365 DDDs	33	539	1.24 (0.88,1.76)	0.219	1.08 (0.76,1.53)	0.67	15	250	1.28 (0.76,2.14)	0.35	0.97 (0.52,1.83)	0.929
	365+ DDDs	62	1172	1.22 (0.94,1.58)	0.13	0.99 (0.76,1.28)	0.939	22	370	1.44 (0.93,2.21)	0.098	1.29 (0.82,2.03)	0.279
Other antiandrogen:													
	Any use	117	1659	1.53 (1.26,1.85)	<0.001	1.30 (1.07,1.57)	0.008	47	697	1.52 (1.13,2.06)	0.006	1.27 (0.85,1.91)	0.238
	0-365 DDDs	103	1520	1.47 (1.20,1.80)	<0.001	1.28 (1.04,1.56)	0.019	42	667	1.43 (1.04,1.97)	0.026	1.25 (0.82,1.91)	0.303
	365+ DDDs	14	139	2.43 (1.43,4.12)	0.001	1.57 (0.92,2.67)	0.099	5	30	4.21 (1.74,10.18)	0.001	2.98 (0.94,9.48)	0.064

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and Gleason score.

Table 3. Association between androgen deprivation therapy and type of cardiovascular events in patients diagnosed 2009 to 2015.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P
Angina						
Untreated	260	24089	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	510	40923	1.13 (0.97,1.32)	0.122	1.02 (0.88,1.20)	0.769
GnRH	440	36370	1.09 (0.93,1.28)	0.261	1.01 (0.86,1.19)	0.885
Degaralex	16	818	1.71 (1.03,2.84)	0.038	1.07 (0.64,1.79)	0.801
Bicalutamide	30	1853	1.48 (1.01,2.17)	0.042	1.13 (0.77,1.65)	0.537
Other antiandrogen	24	1816	1.20 (0.79,1.83)	0.393	1.14 (0.75,1.73)	0.546
Myocardial infarction						
Untreated	201	24308	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	440	41352	1.38 (1.16,1.64)	<0.001	1.23 (1.03,1.46)	0.023
GnRH	386	36759	1.36 (1.14,1.63)	0.001	1.23 (1.03,1.47)	0.025
Degaralex	12	819	1.83 (1.02,3.28)	0.043	1.26 (0.70,2.29)	0.442
Bicalutamide	26	1869	1.79 (1.19,2.71)	0.005	1.46 (0.97,2.21)	0.073
Other antiandrogen	16	1841	1.12 (0.67,1.88)	0.652	0.95 (0.57,1.59)	0.855
Arrhythmia						
Untreated	184	24221	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	414	41064	1.33 (1.11,1.59)	0.002	1.21 (1.01,1.45)	0.038
GnRH	357	36501	1.29 (1.07,1.54)	0.007	1.19 (0.99,1.43)	0.069
Degaralex	14	809	2.27 (1.32,3.92)	0.003	1.55 (0.89,2.72)	0.121
Bicalutamide	17	1879	1.19 (0.72,1.96)	0.5	1.01 (0.61,1.67)	0.957
Other antiandrogen	25	1811	1.83 (1.20,2.78)	0.005	1.64 (1.07,2.49)	0.022
Heart failure						
Untreated	104	24454	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	229	41639	1.41 (1.11,1.80)	0.005	1.21 (0.95,1.55)	0.12
GnRH	197	37018	1.37 (1.07,1.76)	0.014	1.21 (0.94,1.55)	0.142
Degaralex	8	821	2.23 (1.08,4.60)	0.03	1.22 (0.58,2.58)	0.597
Bicalutamide	16	1881	2.20 (1.29,3.73)	0.004	1.87 (1.10,3.20)	0.021
Other antiandrogen	8	1854	1.10 (0.54,2.27)	0.787	0.80 (0.39,1.65)	0.547
Stroke						
Untreated	226	24198	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	437	41206	1.15 (0.98,1.36)	0.093	1.04 (0.88,1.22)	0.682
GnRH	394	36621	1.17 (0.99,1.39)	0.068	1.06 (0.90,1.26)	0.489
Degaralex	6	818	0.80 (0.35,1.80)	0.586	0.58 (0.25,1.31)	0.187
Bicalutamide	12	1883	0.69 (0.39,1.24)	0.214	0.62 (0.35,1.12)	0.112
Other antiandrogen	24	1822	1.44 (0.94,2.19)	0.094	1.18 (0.77,1.81)	0.436
Venous thromboembolism						
Untreated	89	24459	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	273	41460	2.34 (1.80,3.03)	<0.001	2.28 (1.76,2.97)	<0.001
GnRH	243	36837	2.35 (1.80,3.05)	<0.001	2.31 (1.77,3.01)	<0.001
Degaralex	10	814	3.85 (1.99,7.45)	<0.001	3.74 (1.91,7.32)	<0.001
Bicalutamide	5	1902	0.92 (0.37,2.27)	0.852	0.86 (0.35,2.13)	0.745
Other antiandrogen	15	1842	2.78 (1.60,4.83)	<0.001	2.64 (1.51,4.61)	0.001
Other CVD events						
Untreated	320	23967	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	726	40390	1.38 (1.20,1.58)	<0.001	1.28 (1.11,1.47)	<0.001
GnRH	657	35853	1.41 (1.22,1.62)	<0.001	1.32 (1.14,1.52)	<0.001
Degaralex	22	804	2.07 (1.34,3.20)	0.001	1.73 (1.11,2.68)	0.015
Bicalutamide	19	1843	0.79 (0.50,1.26)	0.332	0.70 (0.44,1.11)	0.133
Other antiandrogen	28	1826	1.17 (0.80,1.73)	0.418	1.02 (0.69,1.51)	0.912

^aModel contains for year of diagnosis, age, deprivation, comorbidities in the year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease,

dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications).

Table 4. Association between androgen deprivation therapy and cardiovascular events stratified by previous cardiovascular disease.

Table 4. Association between androgen deprivation therapy and cardiovascular events stratified by previous cardiovascular disease.												
	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
	Diagnosed 2009 to 2015						Diagnosed 2012 to 2015 (additionally adjusted for stage and Gleason)					
	CVD prior											
Untreated	555	5950	1.00 (ref. cat.)		1.00 (ref. cat.)		268	3001	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	1074	10281	1.21 (1.09,1.35)	0.001	1.14 (1.02,1.27)	0.017	537	4890	1.31 (1.12,1.53)	0.001	1.35 (1.07,1.69)	0.01
GnRH	931	8934	1.21 (1.08,1.35)	0.001	1.16 (1.04,1.30)	0.009	451	4183	1.29 (1.10,1.52)	0.002	1.34 (1.06,1.69)	0.013
Degarelex	40	287	1.51 (1.09,2.08)	0.012	1.22 (0.88,1.69)	0.239	35	264	1.51 (1.06,2.16)	0.023	1.46 (0.88,2.41)	0.14
Bicalutamide	54	573	1.10 (0.83,1.46)	0.494	0.97 (0.73,1.29)	0.844	29	243	1.45 (0.98,2.13)	0.062	1.38 (0.88,2.15)	0.159
Other antiandrogen	49	468	1.21 (0.90,1.62)	0.203	1.03 (0.76,1.38)	0.868	22	191	1.38 (0.89,2.13)	0.151	1.24 (0.67,2.28)	0.497
	No CVD prior											
Untreated	550	16639	1.00 (ref. cat.)		1.00 (ref. cat.)		243	7836	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	1286	26899	1.50 (1.36,1.67)	<0.001	1.34 (1.21,1.49)	<0.001	532	11672	1.55 (1.32,1.82)	<0.001	1.27 (1.02,1.59)	0.033
GnRH	1144	24088	1.49 (1.34,1.66)	<0.001	1.33 (1.20,1.48)	<0.001	469	10392	1.53 (1.30,1.80)	<0.001	1.31 (1.04,1.63)	0.02
Degarelex	31	440	2.18 (1.52,3.14)	<0.001	1.82 (1.26,2.63)	0.001	29	393	2.47 (1.68,3.65)	<0.001	1.51 (0.79,2.87)	0.213
Bicalutamide	41	1138	1.13 (0.82,1.56)	0.446	1.01 (0.74,1.39)	0.942	8	378	0.72 (0.35,1.45)	0.352	0.67 (0.31,1.44)	0.309
Other antiandrogen	68	1191	1.79 (1.39,2.30)	<0.001	1.61 (1.25,2.07)	<0.001	25	506	1.67 (1.10,2.53)	0.016	1.28 (0.75,2.21)	0.365

^aModel contains for year of diagnosis, age, deprivation, comorbidities in the year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and Gleason score.

Table 5. Association between current use of androgen deprivation therapy and cardiovascular events.

		Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
		<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Untreated		1105	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		511	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	1752	24196	1.54 (1.42,1.66)	<0.001	1.33 (1.23,1.44)	<0.001	857	11896	1.60 (1.42,1.79)	<0.001	1.40 (1.18,1.66)	<0.001
	Previous use	608	12984	1.04 (0.93,1.15)	0.482	1.06 (0.95,1.18)	0.276	212	4666	1.05 (0.89,1.24)	0.579	1.17 (0.96,1.43)	0.117
GnRH:	Current use	1550	21724	1.52 (1.40,1.64)	<0.001	1.33 (1.23,1.44)	<0.001	735	10529	1.55 (1.37,1.74)	<0.001	1.41 (1.18,1.67)	<0.001
	Previous use	525	11299	1.03 (0.92,1.15)	0.609	1.07 (0.96,1.19)	0.246	185	4046	1.06 (0.88,1.26)	0.538	1.19 (0.97,1.46)	0.091
Degarelix:	Current use	66	683	2.02 (1.57,2.59)	<0.001	1.50 (1.16,1.93)	0.002	59	621	2.08 (1.58,2.73)	<0.001	1.47 (0.97,2.24)	0.072
	Previous use	5	43	2.50 (1.04,6.01)	0.041	1.60 (0.66,3.85)	0.299	5	36	3.15 (1.31,7.62)	0.011	1.97 (0.73,5.33)	0.182
Bicalutamide:	Current use	61	962	1.34 (1.03,1.74)	0.027	1.04 (0.80,1.35)	0.778	27	398	1.50 (1.01,2.21)	0.042	1.22 (0.78,1.90)	0.378
	Previous use	34	749	1.01 (0.71,1.42)	0.97	0.96 (0.68,1.35)	0.807	10	223	1.03 (0.55,1.94)	0.92	0.96 (0.49,1.88)	0.914
Other antiandrogen:													
	Current use	47	501	1.94 (1.45,2.60)	<0.001	1.44 (1.07,1.93)	0.016	21	223	2.05 (1.32,3.17)	0.001	1.40 (0.74,2.65)	0.307
	Previous use	70	1158	1.32 (1.03,1.68)	0.026	1.21 (0.95,1.54)	0.128	26	474	1.24 (0.83,1.84)	0.287	1.23 (0.75,2.01)	0.411

^aModel contains year of diagnosis, age, deprivation, comorbidities in the year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and Gleason score.

^aDuration of user time depends on the number of DDD in the prescription plus a residual period as described.

^bAssuming on receipt of 3rd dispensed ADT usage exceeds 365 DDDs.

Figure 1. Figure illustrating the study design for the main analyses of ADT and secondary analysis of current use of ADT.

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eTable 1. Association between androgen deprivation therapy and cardiovascular events adjusting for age.

		Case	Person years	Unadjusted HR (95% CI)	P	Age-adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Age-adjusted ^a HR (95% CI)	P
		<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Untreated		1105	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		511	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
Radical prostatectomy		253	9350	0.61 (0.53,0.70)	<0.001	0.83 (0.72,0.96)	0.013	104	3836	0.63 (0.51,0.78)	<0.001	0.84 (0.67,1.05)	0.121
Radiotherapy		135	4450	0.68 (0.57,0.82)	<0.001	0.81 (0.68,0.97)	0.023	53	1929	0.65 (0.49,0.86)	0.003	0.75 (0.56,0.99)	0.045
ADT:	Any use	2360	37180	1.38 (1.28,1.49)	<0.001	1.26 (1.17,1.35)	<0.001	1069	16562	1.46 (1.31,1.64)	<0.001	1.32 (1.18,1.47)	<0.001
	0-365 DDDs	979	16495	1.23 (1.12,1.34)	<0.001	1.15 (1.05,1.25)	0.003	493	8259	1.28 (1.13,1.46)	<0.001	1.18 (1.04,1.34)	0.013
	365+ DDDs	1381	20685	1.56 (1.43,1.70)	<0.001	1.38 (1.26,1.50)	<0.001	576	8303	1.73 (1.51,1.98)	<0.001	1.52 (1.33,1.74)	<0.001
GnRH:	Any use	2075	33023	1.37 (1.27,1.48)	<0.001	1.25 (1.15,1.35)	<0.001	920	14575	1.43 (1.28,1.60)	<0.001	1.29 (1.15,1.45)	<0.001
	0-365 DDDs	990	16606	1.24 (1.14,1.36)	<0.001	1.17 (1.07,1.28)	0.001	487	8101	1.31 (1.15,1.49)	<0.001	1.21 (1.06,1.37)	0.005
	365+ DDDs	1085	16417	1.55 (1.41,1.69)	<0.001	1.35 (1.23,1.48)	<0.001	433	6473	1.65 (1.43,1.90)	<0.001	1.43 (1.24,1.66)	<0.001
Degarelix:	Any use	71	726	2.01 (1.58,2.56)	<0.001	1.73 (1.36,2.20)	<0.001	64	657	2.12 (1.63,2.76)	<0.001	1.83 (1.41,2.38)	<0.001
	0-365 DDDs	41	393	1.98 (1.45,2.71)	<0.001	1.73 (1.27,2.37)	0.001	37	361	2.05 (1.47,2.88)	<0.001	1.80 (1.29,2.52)	0.001
	365+ DDDs	30	333	2.01 (1.39,2.89)	<0.001	1.71 (1.19,2.46)	0.004	27	296	2.20 (1.49,3.26)	<0.001	1.88 (1.27,2.78)	0.002
Bicalutamide:	Any use	95	1711	1.22 (0.98,1.50)	0.07	1.14 (0.93,1.41)	0.214	37	620	1.35 (0.97,1.89)	0.079	1.25 (0.90,1.75)	0.185
	0-365 DDDs	33	539	1.24 (0.88,1.76)	0.219	1.19 (0.84,1.68)	0.337	15	250	1.28 (0.76,2.14)	0.35	1.21 (0.73,2.03)	0.458
	365+ DDDs	62	1172	1.22 (0.94,1.58)	0.13	1.13 (0.88,1.47)	0.34	22	370	1.44 (0.93,2.21)	0.098	1.31 (0.85,2.01)	0.225
Other antiandrogen:													
	Any use	117	1659	1.53 (1.26,1.85)	<0.001	1.34 (1.10,1.62)	0.003	47	697	1.52 (1.13,2.06)	0.006	1.36 (1.01,1.84)	0.044
	0-365 DDDs	103	1520	1.47 (1.20,1.80)	<0.001	1.29 (1.05,1.58)	0.014	42	667	1.43 (1.04,1.97)	0.026	1.29 (0.94,1.77)	0.111
	365+ DDDs	14	139	2.43 (1.43,4.12)	0.001	1.98 (1.16,3.36)	0.012	5	30	4.21 (1.74,10.18)	0.001	2.99 (1.23,7.25)	0.015

^aModel contains age.

eTable 2. Association between androgen deprivation therapy and cardiovascular disease based upon incidence.

		Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
		<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Untreated		990	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		462	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
Radical prostatectomy	Radiotherapy	243	9350	0.65 (0.56,0.75)	<0.001	0.94 (0.81,1.09)	0.412	99	3836	0.66 (0.53,0.82)	<0.001	0.96 (0.75,1.23)	0.75
		129	4450	0.73 (0.61,0.88)	0.001	0.87 (0.72,1.05)	0.14	51	1929	0.68 (0.51,0.92)	0.011	0.85 (0.63,1.15)	0.293
ADT:	Any use	2082	37180	1.36 (1.26,1.48)	<0.001	1.25 (1.15,1.35)	<0.001	951	16562	1.43 (1.27,1.61)	<0.001	1.33 (1.13,1.56)	0.001
	0-365 DDDs	863	16495	1.21 (1.10,1.33)	<0.001	1.14 (1.04,1.25)	0.007	436	8259	1.25 (1.09,1.43)	0.001	1.22 (1.02,1.45)	0.025
	365+ DDDs	1219	20685	1.54 (1.41,1.69)	<0.001	1.36 (1.24,1.50)	<0.001	515	8303	1.69 (1.47,1.95)	<0.001	1.61 (1.32,1.97)	<0.001
GnRH:	Any use	1845	33023	1.36 (1.26,1.48)	<0.001	1.26 (1.16,1.37)	<0.001	830	14575	1.42 (1.26,1.60)	<0.001	1.35 (1.15,1.60)	<0.001
	0-365 DDDs	888	16606	1.25 (1.13,1.37)	<0.001	1.19 (1.08,1.30)	<0.001	441	8101	1.30 (1.14,1.49)	<0.001	1.28 (1.08,1.53)	0.005
	365+ DDDs	957	16417	1.52 (1.38,1.68)	<0.001	1.36 (1.24,1.50)	<0.001	389	6473	1.61 (1.39,1.88)	<0.001	1.59 (1.29,1.97)	<0.001
Degarelix:	Any use	60	726	1.89 (1.46,2.46)	<0.001	1.44 (1.10,1.88)	0.007	55	657	2.00 (1.51,2.65)	<0.001	1.43 (0.94,2.17)	0.094
	0-365 DDDs	35	393	1.89 (1.35,2.65)	<0.001	1.43 (1.01,2.01)	0.042	32	361	1.96 (1.37,2.82)	<0.001	1.29 (0.74,2.25)	0.362
	365+ DDDs	25	333	1.86 (1.25,2.78)	0.002	1.45 (0.97,2.17)	0.071	23	296	2.04 (1.34,3.12)	0.001	1.77 (0.99,3.18)	0.054
Bicalutamide:	Any use	77	1711	1.10 (0.87,1.39)	0.418	0.92 (0.73,1.17)	0.51	28	620	1.12 (0.76,1.65)	0.557	1.04 (0.69,1.57)	0.852
	0-365 DDDs	27	539	1.14 (0.78,1.67)	0.512	0.99 (0.68,1.45)	0.963	11	250	1.03 (0.57,1.88)	0.917	0.94 (0.48,1.84)	0.865
	365+ DDDs	50	1172	1.10 (0.82,1.46)	0.521	0.90 (0.68,1.20)	0.476	17	370	1.21 (0.75,1.98)	0.437	1.15 (0.70,1.91)	0.574
Other antiandrogen:													
	Any use	98	1659	1.43 (1.16,1.76)	0.001	1.24 (1.01,1.53)	0.044	37	697	1.31 (0.94,1.84)	0.112	1.21 (0.78,1.86)	0.395
	0-365 DDDs	88	1520	1.40 (1.13,1.75)	0.003	1.24 (1.00,1.55)	0.052	32	667	1.20 (0.83,1.72)	0.328	1.16 (0.73,1.83)	0.531
	365+ DDDs	10	139	1.93 (1.04,3.61)	0.038	1.29 (0.69,2.42)	0.432	5	30	4.58 (1.89,11.09)	0.001	3.54 (1.11,11.28)	0.032

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and othaer diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and gleason score.

eTable 3. Association between androgen deprivation therapy and cardiovascular disease based upon mortality.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
<i>Diagnosed 2009 to 2015</i>							<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Untreated	221	24580	1.00 (ref. cat.)				95	11509	1.00 (ref. cat.)			
Radical prostatectomy	16	10087	0.18 (0.11,0.30)	<0.001	0.62 (0.37,1.05)	0.074	5	4033	0.16 (0.07,0.41)	<0.001	0.56 (0.21,1.48)	0.241
Radiotherapy	10	4804	0.24 (0.13,0.45)	<0.001	0.47 (0.25,0.88)	0.019	< 5	2036	0.26 (0.10,0.72)	0.009	0.38 (0.11,1.26)	0.113
ADT: Any use	571	41954	1.57 (1.33,1.85)	<0.001	1.35 (1.15,1.59)	<0.001	227	18175	1.65 (1.27,2.13)	<0.001	1.04 (0.66,1.65)	0.864
0-365 DDDs	197	17922	1.26 (1.03,1.54)	0.023	1.23 (1.01,1.50)	0.043	94	8800	1.37 (1.02,1.86)	0.038	0.85 (0.50,1.42)	0.531
365+ DDDs	374	24032	1.87 (1.56,2.24)	<0.001	1.45 (1.21,1.74)	<0.001	133	9376	2.01 (1.49,2.71)	<0.001	1.32 (0.78,2.22)	0.3
GnRH: Any use	491	37285	1.51 (1.28,1.79)	<0.001	1.34 (1.13,1.58)	0.001	185	15971	1.52 (1.17,1.98)	0.002	1.01 (0.63,1.61)	0.964
0-365 DDDs	185	18097	1.16 (0.95,1.42)	0.143	1.16 (0.95,1.43)	0.146	86	8653	1.28 (0.94,1.75)	0.112	0.98 (0.59,1.63)	0.947
365+ DDDs	306	19188	1.94 (1.60,2.34)	<0.001	1.50 (1.24,1.81)	<0.001	99	7318	1.90 (1.38,2.62)	<0.001	1.08 (0.62,1.86)	0.792
Degarelix: Any use	20	832	2.81 (1.77,4.46)	<0.001	1.71 (1.07,2.74)	0.026	17	753	2.97 (1.76,5.02)	<0.001	1.58 (0.61,4.10)	0.346
0-365 DDDs	9	440	2.24 (1.14,4.38)	0.019	1.41 (0.72,2.78)	0.32	8	399	2.47 (1.19,5.15)	0.015	1.15 (0.26,5.03)	0.858
365+ DDDs	11	392	3.37 (1.83,6.22)	<0.001	2.05 (1.10,3.82)	0.025	9	354	3.56 (1.77,7.16)	<0.001	2.04 (0.66,6.32)	0.218
Bicalutamide: Any use	28	1908	1.68 (1.13,2.50)	0.01	1.39 (0.93,2.06)	0.107	11	676	2.14 (1.14,4.03)	0.018	1.17 (0.47,2.94)	0.731
0-365 DDDs	11	585	2.13 (1.16,3.92)	0.014	1.85 (1.00,3.41)	0.049	5	260	2.49 (1.01,6.15)	0.047	0.76 (0.10,5.61)	0.788
365+ DDDs	17	1323	1.53 (0.93,2.52)	0.094	1.21 (0.73,2.00)	0.452	6	416	1.99 (0.86,4.58)	0.107	1.36 (0.49,3.72)	0.553
Other antiandrogen: Any use	31	1864	1.92 (1.32,2.80)	0.001	1.41 (0.96,2.06)	0.077	13	763	2.26 (1.26,4.06)	0.007	1.13 (0.42,3.07)	0.811
0-365 DDDs	25	1687	1.74 (1.15,2.64)	0.009	1.31 (0.86,1.99)	0.202	9-13	724	2.24 (1.22,4.11)	0.009	1.28 (0.47,3.50)	0.632
365+ DDDs	6	177	4.11 (1.82,9.29)	0.001	2.22 (0.97,5.06)	0.058	< 5	38	3.66 (0.51,26.44)	0.198		

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and othaer diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and gleason score.

eTable 4. Association between androgen deprivation therapy and type of cardiovascular events (restricted to patients diagnosed 2012 to 2015).

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P
Angina						
Untreated	135	11315	1.00 (ref. cat.)			
ADT	240	17833	1.08 (0.86,1.34)	0.516	1.13 (0.84,1.53)	0.427
GnRH	205	15666	1.04 (0.83,1.31)	0.712	1.13 (0.83,1.53)	0.431
Degarelix	13	740	1.42 (0.80,2.52)	0.227	1.01 (0.45,2.27)	0.975
Bicalutamide	13	659	1.58 (0.89,2.80)	0.118	1.33 (0.70,2.55)	0.383
Other antiandrogen	9	755	0.96 (0.49,1.88)	0.894	0.74 (0.27,2.07)	0.568
Myocardial infarction						
Untreated	91	11419	1.00 (ref. cat.)			
ADT	183	17973	1.39 (1.06,1.81)	0.016	1.32 (0.89,1.96)	0.163
GnRH	153	15806	1.32 (1.00,1.73)	0.049	1.27 (0.85,1.90)	0.239
Degarelix	12	742	2.11 (1.15,3.87)	0.016	1.55 (0.62,3.84)	0.349
Bicalutamide	10	665	2.05 (1.06,3.95)	0.033	1.91 (0.90,4.05)	0.09
Other antiandrogen	8	747	1.46 (0.70,3.02)	0.311	1.22 (0.42,3.51)	0.713
Arrhythmia						
Untreated	78	11419	1.00 (ref. cat.)			
ADT	185	17879	1.56 (1.18,2.07)	0.002	1.38 (0.94,2.03)	0.102
GnRH	158	15713	1.51 (1.14,2.02)	0.004	1.40 (0.94,2.07)	0.096
Degarelix	13	733	2.68 (1.48,4.85)	0.001	1.72 (0.70,4.27)	0.239
Bicalutamide	6	670	1.35 (0.58,3.10)	0.485	1.06 (0.41,2.69)	0.91
Other antiandrogen	8	750	1.62 (0.78,3.36)	0.198	1.41 (0.54,3.66)	0.485
Heart failure						
Untreated	46	11456	1.00 (ref. cat.)			
ADT	112	18028	1.67 (1.16,2.39)	0.006	1.25 (0.68,2.30)	0.467
GnRH	96	15845	1.63 (1.12,2.36)	0.01	1.22 (0.65,2.27)	0.538
Degarelix	8	743	2.66 (1.25,5.67)	0.011	0.88 (0.19,4.07)	0.872
Bicalutamide	< 5	668	2.02 (0.80,5.12)	0.139	2.43 (0.88,6.71)	0.087
Other antiandrogen	< 5	758	1.06 (0.33,3.44)	0.917	0.51 (0.06,3.99)	0.519
Stroke						
Untreated	99	11381	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	185	17924	1.18 (0.92,1.53)	0.197	0.99 (0.67,1.44)	0.946
GnRH	165	15755	1.20 (0.93,1.56)	0.164	1.02 (0.70,1.50)	0.912
Degarelix	< 5	739	0.63 (0.23,1.70)	0.358	0.21 (0.03,1.59)	0.131
Bicalutamide	< 5	670	0.86 (0.35,2.11)	0.734	0.60 (0.18,1.93)	0.388
Other antiandrogen	10	748	1.53 (0.79,2.94)	0.203	1.44 (0.62,3.33)	0.395
Venous thromboembolism						
Untreated	47	11460	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	119	17993	2.05 (1.43,2.96)	<0.001	1.26 (0.76,2.09)	0.378
GnRH	102	15816	2.00 (1.38,2.91)	<0.001	1.33 (0.79,2.21)	0.281
Degarelix	9	735	3.44 (1.67,7.07)	0.001	0.79 (0.18,3.49)	0.753
Bicalutamide	< 5	675	0.45 (0.06,3.30)	0.434	0.37 (0.05,2.77)	0.331
Other antiandrogen	7	754	2.81 (1.26,6.27)	0.012	1.40 (0.47,4.23)	0.547
Other CVD events						
Untreated	137	11331	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	319	17693	1.55 (1.25,1.91)	<0.001	1.68 (1.24,2.27)	0.001
GnRH	282	15538	1.55 (1.25,1.93)	<0.001	1.73 (1.28,2.35)	<0.001
Degarelix	20	730	2.32 (1.45,3.72)	<0.001	2.60 (1.35,4.99)	0.004
Bicalutamide	5	663	0.64 (0.26,1.58)	0.336	0.73 (0.29,1.82)	0.5
Other antiandrogen	12	749	1.37 (0.75,2.47)	0.303	1.64 (0.80,3.36)	0.179

^aModel contains t stage, n stage, m stage, gleason score, year of diagnosis, age, deprivation, comorbidities in the year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications).

eTable 5. Association between androgen deprivation therapy and cardiovascular events stratifying by stage.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and Gleason)</i>						
No metastases (M stage 0)						
Untreated	287	6743	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	588	10159	1.37 (1.18,1.59)	<0.001	1.39 (1.15,1.68)	0.001
GnRH	523	9238	1.34 (1.15,1.55)	<0.001	1.40 (1.15,1.70)	0.001
Degarelex	14	119	2.70 (1.58,4.62)	<0.001	1.80 (0.98,3.28)	0.057
Bicalutamide	30	420	1.68 (1.15,2.45)	0.007	1.32 (0.87,2.00)	0.192
Other antiandrogen	21	380	1.30 (0.84,2.04)	0.241	1.16 (0.69,1.96)	0.584
Metastases (M stage 1)						
Untreated	52	465	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	327	3948	0.86 (0.59,1.25)	0.425	1.94 (0.79,4.75)	0.148
GnRH	268	3231	0.87 (0.60,1.27)	0.466	2.00 (0.81,4.95)	0.133
Degarelex	40	470	0.88 (0.55,1.40)	0.585	1.73 (0.61,4.92)	0.301
Bicalutamide	<5	29	0.34 (0.05,2.48)	0.287		
Other antiandrogen	17	208	0.85 (0.47,1.54)	0.59	2.33 (0.72,7.48)	0.156
Low risk (T1N0M0 or T2N0M0)						
Untreated	197	5311	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	233	4187	1.62 (1.32,1.97)	<0.001	1.49 (1.17,1.89)	0.001
GnRH	213	3790	1.63 (1.33,2.00)	<0.001	1.54 (1.21,1.96)	<0.001
Degarelex	<5	34	2.48 (0.79,7.76)	0.119	2.04 (0.64,6.54)	0.229
Bicalutamide	13	222	1.69 (0.96,2.97)	0.069	1.20 (0.66,2.21)	0.551
Other antiandrogen	<5	139	0.83 (0.31,2.23)	0.711	0.73 (0.27,2.00)	0.538

^aModel contains for year of diagnosis, age, deprivation, comorbidities in the year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications), t stage, n stage, m stage and Gleason score.

eTable 6. Association between androgen deprivation therapy and cardiovascular events stratifying by age.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
	<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Age < 70												
Untreated	418	12771	1.00 (ref. cat.)		1.00 (ref. cat.)		199	6178	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	710	16204	1.38 (1.22,1.57)	<0.001	1.29 (1.14,1.47)	<0.001	315	7253	1.41 (1.17,1.69)	<0.001	1.19 (0.93,1.52)	0.156
GnRH	627	14347	1.38 (1.21,1.57)	<0.001	1.30 (1.14,1.48)	<0.001	275	6317	1.41 (1.16,1.71)	<0.001	1.24 (0.97,1.59)	0.086
Degarelix	19	277	2.04 (1.28,3.23)	0.003	1.60 (1.00,2.56)	0.048	17	266	1.99 (1.21,3.28)	0.007	1.02 (0.50,2.08)	0.953
Bicalutamide	32	854	1.19 (0.83,1.71)	0.343	0.97 (0.67,1.39)	0.863	12	340	1.14 (0.64,2.05)	0.655	0.76 (0.41,1.40)	0.377
Other antiandrogen	32	696	1.46 (1.01,2.09)	0.042	1.47 (1.02,2.11)	0.038	11	329	1.09 (0.59,2.01)	0.78	1.23 (0.65,2.35)	0.527
Age ≥ 70												
Untreated	687	9818	1.00 (ref. cat.)		1.00 (ref. cat.)		312	4659	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	1650	20976	1.21 (1.10,1.33)	<0.001	1.24 (1.13,1.36)	<0.001	754	9309	1.29 (1.13,1.49)	<0.001	1.39 (1.12,1.72)	0.002
GnRH	1448	18675	1.19 (1.08,1.31)	<0.001	1.25 (1.13,1.37)	<0.001	645	8258	1.25 (1.08,1.44)	0.003	1.37 (1.10,1.70)	0.004
Degarelix	52	449	1.71 (1.29,2.26)	<0.001	1.43 (1.07,1.91)	0.015	47	391	1.86 (1.37,2.54)	<0.001	1.76 (1.09,2.85)	0.021
Bicalutamide	63	857	1.13 (0.87,1.46)	0.358	1.03 (0.79,1.33)	0.843	25	280	1.42 (0.94,2.14)	0.093	1.61 (0.99,2.62)	0.057
Other antiandrogen	85	964	1.34 (1.07,1.68)	0.011	1.25 (1.00,1.57)	0.054	36	368	1.54 (1.09,2.18)	0.015	1.32 (0.79,2.23)	0.292

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and Gleason score.

eTable 7. Association between androgen deprivation therapy and cardiovascular events, adjusting for stage and grade, treating stage X as missing.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>						
Untreated	213	6210	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	590	10843	1.60 (1.35,1.88)	<0.001	1.48 (1.21,1.80)	<0.001
GnRH	528	9836	1.58 (1.33,1.86)	<0.001	1.49 (1.22,1.82)	<0.001
Degarelix	18	208	2.47 (1.52,4.00)	<0.001	1.74 (1.05,2.90)	0.033
Bicalutamide	24	393	1.80 (1.18,2.75)	0.007	1.29 (0.83,2.01)	0.248
Other antiandrogen	19	400	1.40 (0.87,2.24)	0.165	1.32 (0.81,2.15)	0.269

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including separately aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications), t stage, n stage, m stage and Gleason score.

eTable 8. The association between androgen deprivation therapy and cardiovascular events (incidence and mortality) in sensitivity analyses (a) assigning radiotherapy to a separate category and (b) basing treatment solely upon initial treatment.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
<i>Diagnosed 2009 to 2015</i>							<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
(a) Radiotherapy after ADT³												
Untreated	1105	22590					511	10837	1.00 (ref. cat.)			
ADT	1608	21625	1.58 (1.46,1.71)	<0.001	1.30 (1.20,1.41)	<0.001	722	9469	1.67 (1.49,1.88)	<0.001	1.31 (1.10,1.57)	0.002
ADT and radiotherapy	752	15555	1.06 (0.96,1.17)	0.236	1.15 (1.04,1.27)	0.005	347	7093	1.11 (0.96,1.29)	0.143	1.32 (1.10,1.58)	0.003
GnRH	1382	18689	1.57 (1.45,1.71)	<0.001	1.31 (1.21,1.42)	<0.001	604	8017	1.65 (1.46,1.86)	<0.001	1.34 (1.12,1.60)	0.001
GnRH and radiotherapy	693	14334	1.06 (0.96,1.17)	0.253	1.16 (1.05,1.28)	0.004	316	6558	1.10 (0.94,1.27)	0.224	1.31 (1.09,1.58)	0.004
Degarelix	63	668	1.94 (1.51,2.51)	<0.001	1.43 (1.10,1.85)	0.007	57	601	2.06 (1.57,2.72)	<0.001	1.32 (0.85,2.05)	0.215
Degarelix and radiotherapy	8	58	2.88 (1.43,5.77)	0.003	2.30 (1.14,4.62)	0.02	7	56	2.77 (1.31,5.86)	0.008	2.41 (1.12,5.16)	0.024
Bicalutamide	68	987	1.47 (1.15,1.88)	0.002	1.12 (0.88,1.44)	0.349	25	360	1.52 (1.02,2.27)	0.041	1.20 (0.75,1.92)	0.449
Bicalutamide and radiotherapy	27	724	0.82 (0.56,1.21)	0.315	0.80 (0.55,1.18)	0.263	12	260	1.05 (0.59,1.87)	0.864	1.04 (0.58,1.86)	0.905
Other antiandrogen	99	1313	1.61 (1.31,1.98)	<0.001	1.28 (1.04,1.58)	0.019	38	503	1.67 (1.20,2.32)	0.003	1.24 (0.77,2.00)	0.382
Other antiandrogen + RT	18	346	1.13 (0.71,1.81)	0.602	1.39 (0.87,2.21)	0.171	9	194	1.05 (0.54,2.03)	0.885	1.35 (0.69,2.65)	0.38
(b) Treatment group based upon first treatment⁴												
Untreated	1105	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		511	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	2323	36035	1.40 (1.30,1.51)	<0.001	1.26 (1.17,1.36)	<0.001	1057	16165	1.48 (1.32,1.65)	<0.001	1.32 (1.13,1.54)	0.001
GnRH	1836	29326	1.36 (1.26,1.47)	<0.001	1.25 (1.16,1.35)	<0.001	822	13214	1.41 (1.25,1.58)	<0.001	1.30 (1.11,1.53)	0.001
Degarelix	82	805	2.11 (1.68,2.64)	<0.001	1.59 (1.27,2.01)	<0.001	75	747	2.20 (1.72,2.81)	<0.001	1.58 (1.10,2.27)	0.014
Bicalutamide	176	2741	1.41 (1.20,1.65)	<0.001	1.15 (0.98,1.36)	0.083	66	907	1.65 (1.27,2.13)	<0.001	1.42 (1.05,1.91)	0.022
Other antiandrogen	227	3113	1.59 (1.37,1.83)	<0.001	1.31 (1.13,1.51)	<0.001	93	1282	1.64 (1.31,2.05)	<0.001	1.32 (0.98,1.78)	0.07

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ²Adjusted models contain all terms in ¹ as well as t stage, n stage, m stage and gleason score. ^b ADT users who received RT after the date of their ADT were allocated to a separate ADT and RT exposure category on the date of their RT. ⁴ Treatment group based solely upon initial treatment.

eTable 9. Sensitivity analyses comparing cardiovascular events between each ADT individually (GnRH, degarelix, bicalutamide and other antiandrogens) with no treatment, regardless of use of another ADT.

		Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
		<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
Untreated		1105	22590	1.00 (ref. cat.)		1.00 (ref. cat.)		511	10837	1.00 (ref. cat.)		1.00 (ref. cat.)	
GnRH:	Any use	2075	33023	1.37 (1.27,1.48)	<0.001	1.26 (1.16,1.36)	<0.001	920	14575	1.43 (1.28,1.61)	<0.001	1.32 (1.13,1.56)	0.001
	0-365 DDDs	990	16606	1.24 (1.14,1.36)	<0.001	1.18 (1.08,1.29)	<0.001	487	8101	1.31 (1.15,1.49)	<0.001	1.26 (1.06,1.49)	0.007
	365+ DDDs	1085	16417	1.55 (1.41,1.69)	<0.001	1.36 (1.24,1.50)	<0.001	433	6473	1.65 (1.43,1.90)	<0.001	1.55 (1.26,1.89)	<0.001
	Current use	1550	21724	1.52 (1.40,1.64)	<0.001	1.33 (1.23,1.44)	<0.001	735	10529	1.55 (1.37,1.74)	<0.001	1.40 (1.18,1.67)	<0.001
	Past use	525	11299	1.03 (0.92,1.15)	0.61	1.07 (0.96,1.19)	0.246	185	4046	1.06 (0.88,1.26)	0.54	1.19 (0.97,1.46)	0.091
Degarelix:	Any use	91	891	2.12 (1.71,2.63)	<0.001	1.62 (1.30,2.02)	<0.001	82	809	2.23 (1.76,2.82)	<0.001	1.71 (1.21,2.40)	0.002
	0-365 DDDs	54	499	2.16 (1.64,2.84)	<0.001	1.64 (1.24,2.17)	<0.001	49	460	2.24 (1.67,3.02)	<0.001	1.63 (1.06,2.49)	0.025
	365+ DDDs	37	391	2.07 (1.49,2.88)	<0.001	1.60 (1.15,2.23)	0.006	33	349	2.21 (1.55,3.16)	<0.001	1.82 (1.13,2.93)	0.014
	Current use	71	744	1.96 (1.54,2.49)	<0.001	1.49 (1.17,1.91)	0.001	63	676	2.03 (1.56,2.64)	<0.001	1.42 (0.95,2.12)	0.086
	Past use	20	146	3.00 (1.93,4.68)	<0.001	2.38 (1.52,3.71)	<0.001	19	133	3.35 (2.11,5.31)	<0.001	2.80 (1.64,4.78)	<0.001
Bicalutamide:	Any use	299	4909	1.35 (1.18,1.53)	<0.001	1.14 (1.00,1.30)	0.05	109	1542	1.61 (1.31,1.99)	<0.001	1.43 (1.11,1.85)	0.006
	0-365 DDDs	198	3153	1.36 (1.17,1.59)	<0.001	1.19 (1.02,1.39)	0.024	78	1057	1.66 (1.30,2.11)	<0.001	1.58 (1.18,2.11)	0.002
	365+ DDDs	101	1756	1.31 (1.07,1.61)	0.01	1.05 (0.85,1.29)	0.666	31	485	1.51 (1.05,2.18)	0.027	1.17 (0.77,1.78)	0.471
	Current use	94	1473	1.32 (1.07,1.64)	0.009	1.03 (0.83,1.27)	0.793	44	576	1.65 (1.21,2.25)	0.001	1.33 (0.91,1.93)	0.137
	Past use	205	3437	1.36 (1.16,1.58)	<0.001	1.20 (1.03,1.40)	0.018	65	966	1.59 (1.22,2.06)	0.001	1.50 (1.10,2.04)	0.01
Other antiandrogen:													
	Any use	1729	27419	1.38 (1.28,1.50)	<0.001	1.29 (1.19,1.40)	<0.001	783	12770	1.39 (1.24,1.57)	<0.001	1.30 (1.11,1.53)	0.001
	0-365 DDDs	1628	26113	1.36 (1.26,1.48)	<0.001	1.28 (1.18,1.38)	<0.001	760	12437	1.39 (1.23,1.56)	<0.001	1.30 (1.10,1.53)	0.002
	365+ DDDs	101	1307	1.84 (1.49,2.26)	<0.001	1.53 (1.24,1.88)	<0.001	23	333	1.70 (1.12,2.60)	0.014	1.84 (1.14,2.99)	0.013
	Current use	354	4755	1.54 (1.36,1.73)	<0.001	1.34 (1.19,1.51)	<0.001	170	2268	1.61 (1.35,1.92)	<0.001	1.46 (1.16,1.84)	0.001
	Past use	1375	22664	1.34 (1.23,1.46)	<0.001	1.28 (1.17,1.39)	<0.001	613	10501	1.33 (1.17,1.51)	<0.001	1.27 (1.07,1.50)	0.006

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and gleason score.

eTable 10. Association between androgen deprivation therapy and cardiovascular disease based upon (a) cardiovascular death or incidence mentioned anywhere in hospital discharge records or death certificate, (b) cardiovascular death mentioned anywhere on death certificate and (c) cardiovascular death mentioned on death certificate.

	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P	Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^b HR (95% CI)	P
	<i>Diagnosed 2009 to 2015</i>						<i>Diagnosed 2012 to 2015 (additionally adjusted for stage and grade)</i>					
	(a) Cardiovascular events (based upon cardiovascular disease anywhere in hospital discharge records and anywhere on death certificate)											
Untreated	2135	20707	1.00 (ref. cat.)		1.00 (ref. cat.)		1131	10019	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	4050	32623	1.44 (1.36,1.52)	<0.001	1.27 (1.20,1.34)	<0.001	1922	14746	1.40 (1.29,1.52)	<0.001	0.98 (0.87,1.10)	0.707
GnRH	3517	29094	1.40 (1.32,1.48)	<0.001	1.25 (1.18,1.33)	<0.001	1628	13048	1.34 (1.24,1.46)	<0.001	0.98 (0.87,1.10)	0.725
Degarelix	137	598	2.34 (1.97,2.78)	<0.001	1.64 (1.37,1.95)	<0.001	127	543	2.30 (1.91,2.77)	<0.001	0.97 (0.73,1.29)	0.814
Bicalutamide	167	1433	1.34 (1.14,1.57)	<0.001	1.07 (0.91,1.26)	0.396	71	530	1.43 (1.12,1.82)	0.004	0.95 (0.72,1.25)	0.719
Other antiandrogen	224	1447	1.76 (1.53,2.02)	<0.001	1.48 (1.29,1.70)	<0.001	95	614	1.65 (1.33,2.03)	<0.001	1.03 (0.76,1.38)	0.863
	(b) Cardiovascular death (based upon cardiovascular disease anywhere on death certificate)											
Untreated	551	24580	1.00 (ref. cat.)		1.00 (ref. cat.)		257	11509	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	1635	41954	1.92 (1.73,2.12)	<0.001	1.64 (1.48,1.81)	<0.001	717	18175	2.00 (1.71,2.33)	<0.001	1.23 (0.91,1.67)	0.183
GnRH	1406	37285	1.85 (1.66,2.05)	<0.001	1.62 (1.46,1.80)	<0.001	586	15971	1.84 (1.57,2.16)	<0.001	1.26 (0.92,1.71)	0.148
Degarelix	85	832	4.90 (3.89,6.18)	<0.001	2.84 (2.23,3.61)	<0.001	78	753	5.13 (3.96,6.64)	<0.001	1.40 (0.82,2.41)	0.22
Bicalutamide	58	1908	1.48 (1.13,1.94)	0.005	1.20 (0.91,1.58)	0.186	18	676	1.34 (0.83,2.16)	0.239	0.89 (0.44,1.79)	0.744
Other antiandrogen	82	1864	2.13 (1.69,2.70)	<0.001	1.59 (1.26,2.02)	<0.001	34	763	2.23 (1.55,3.20)	<0.001	1.06 (0.55,2.04)	0.858
	(c) Cardiovascular incidence (based upon cardiovascular disease anywhere in hospital discharge records)											
Untreated	1964	20707	1.00 (ref. cat.)		1.00 (ref. cat.)		1044	10019	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT	3606	32623	1.39 (1.31,1.47)	<0.001	1.23 (1.16,1.31)	<0.001	1704	14746	1.34 (1.23,1.46)	<0.001	0.97 (0.87,1.10)	0.668
GnRH	3140	29094	1.36 (1.28,1.44)	<0.001	1.22 (1.15,1.30)	<0.001	1455	13048	1.29 (1.19,1.41)	<0.001	0.98 (0.87,1.10)	0.722
Degarelix	105	598	1.94 (1.60,2.37)	<0.001	1.39 (1.13,1.69)	0.001	97	543	1.89 (1.53,2.33)	<0.001	0.88 (0.65,1.21)	0.434
Bicalutamide	153	1433	1.33 (1.13,1.57)	0.001	1.07 (0.90,1.26)	0.445	65	530	1.41 (1.09,1.81)	0.008	0.93 (0.70,1.25)	0.646
Other antiandrogen	204	1447	1.74 (1.50,2.01)	<0.001	1.48 (1.28,1.72)	<0.001	86	614	1.61 (1.29,2.01)	<0.001	1.05 (0.78,1.43)	0.739

^aModel contains year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and othaer diabetic medications). ^bAdjusted models contain all terms in ^a as well as t stage, n stage, m stage and gleason score.

eTable 11. Association between current use of androgen deprivation therapy and cardiovascular events by type in patients diagnosed 2009 to 2015.

diagnosed 2009 to 2015.							
		Case	Person years	Unadjusted HR (95% CI)	P	Adjusted ^a HR (95% CI)	P
Angina							
Untreated		260	24089	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	353	26434	1.19 (1.01,1.40)	0.042	1.02 (0.87,1.21)	0.774
	Past use	157	14489	1.01 (0.82,1.24)	0.933	1.02 (0.83,1.26)	0.844
GnRH:	Current use	301	23705	1.13 (0.95,1.33)	0.174	1.00 (0.84,1.18)	0.977
	Past use	139	12665	1.02 (0.82,1.27)	0.832	1.04 (0.84,1.30)	0.695
Degarelex:	Current use	14	768	1.61 (0.94,2.75)	0.086	1.02 (0.59,1.76)	0.945
	Past use	<5	51	3.40 (0.85,13.70)	0.085	1.60 (0.40,6.49)	0.507
Bicalutamide:	Current use	20	1045	1.71 (1.08,2.70)	0.021	1.23 (0.78,1.95)	0.369
	Past use	10	809	1.16 (0.61,2.19)	0.647	0.96 (0.51,1.82)	0.91
Other antiandrogen:							
	Current use	11	547	1.85 (1.01,3.38)	0.046	1.44 (0.79,2.65)	0.236
	Past use	13	1268	0.92 (0.53,1.61)	0.776	0.96 (0.55,1.68)	0.893
Myocardial infarction							
Untreated		201	24308	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	336	26610	1.62 (1.35,1.94)	<0.001	1.35 (1.12,1.62)	0.001
	Past use	104	14742	0.88 (0.69,1.14)	0.336	0.92 (0.72,1.19)	0.534
GnRH:	Current use	300	23857	1.62 (1.34,1.94)	<0.001	1.37 (1.13,1.65)	0.001
	Past use	86	12902	0.83 (0.64,1.09)	0.18	0.88 (0.68,1.15)	0.361
Degarelex:	Current use	12	769	2.01 (1.12,3.60)	0.02	1.38 (0.76,2.50)	0.29
	Past use	<5	50				
Bicalutamide:	Current use	14	1048	1.71 (0.99,2.94)	0.054	1.26 (0.73,2.17)	0.412
	Past use	12	820	1.81 (1.01,3.27)	0.048	1.76 (0.97,3.17)	0.061
Other antiandrogen:							
	Current use	6	559	1.34 (0.59,3.02)	0.483	0.94 (0.42,2.13)	0.884
	Past use	10	1282	1.00 (0.53,1.90)	0.992	0.95 (0.50,1.80)	0.87
Arrhythmia							
Untreated		184	24221	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	301	26447	1.51 (1.25,1.82)	<0.001	1.30 (1.07,1.57)	0.007
	Past use	113	14617	0.98 (0.77,1.25)	0.87	1.02 (0.79,1.30)	0.899
GnRH:	Current use	262	23729	1.46 (1.20,1.77)	<0.001	1.28 (1.05,1.56)	0.013
	Past use	95	12772	0.94 (0.72,1.21)	0.625	0.98 (0.75,1.27)	0.874
Degarelex:	Current use	12	756	2.14 (1.19,3.84)	0.011	1.46 (0.80,2.66)	0.215
	Past use	<5	53	4.90 (1.21,19.76)	0.026	3.39 (0.83,13.76)	0.088
Bicalutamide:	Current use	11	1043	1.41 (0.77,2.59)	0.271	1.11 (0.60,2.05)	0.737
	Past use	6	837	0.89 (0.39,2.02)	0.788	0.86 (0.38,1.96)	0.723
Other antiandrogen:							
	Current use	9	542	2.23 (1.14,4.35)	0.019	1.80 (0.92,3.53)	0.087
	Past use	16	1268	1.64 (0.98,2.74)	0.06	1.55 (0.93,2.60)	0.094
Heart failure							
Untreated		104	24454	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	193	26699	1.77 (1.38,2.27)	<0.001	1.35 (1.05,1.73)	0.02
	Past use	36	14939	0.62 (0.42,0.93)	0.02	0.78 (0.52,1.16)	0.221
GnRH:	Current use	172	23944	1.77 (1.37,2.28)	<0.001	1.38 (1.07,1.78)	0.014
	Past use	25	13074	0.49 (0.31,0.78)	0.002	0.64 (0.41,1.01)	0.058
Degarelex:	Current use	7	766	2.19 (1.01,4.72)	0.046	1.20 (0.54,2.65)	0.654
	Past use	<5	54	4.82 (0.67,34.62)	0.118	2.20 (0.30,16.04)	0.435
Bicalutamide:	Current use	10	1049	2.33 (1.21,4.46)	0.011	1.70 (0.88,3.28)	0.114
	Past use	6	832	1.86 (0.81,4.27)	0.145	2.23 (0.97,5.16)	0.06
Other antiandrogen:							
	Current use	<5	560	0.43 (0.06,3.07)	0.399	0.24 (0.03,1.71)	0.153
	Past use	7	1294	1.38 (0.64,2.98)	0.411	1.21 (0.56,2.62)	0.634
Stroke							
Untreated		226	24198	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT:	Current use	312	26491	1.29 (1.08,1.54)	0.005	1.07 (0.90,1.28)	0.45
	Past use	125	14715	0.89 (0.71,1.12)	0.335	0.95 (0.76,1.20)	0.683
GnRH:	Current use	286	23754	1.32 (1.10,1.58)	0.003	1.11 (0.92,1.33)	0.272
	Past use	108	12866	0.88 (0.69,1.12)	0.303	0.95 (0.75,1.22)	0.705
Degarelex:	Current use	6	764	0.88 (0.39,1.97)	0.748	0.62 (0.28,1.42)	0.26
	Past use	<5	54				

Bicalutamide: Current use	8	1046	0.84 (0.42,1.71)	0.632	0.68 (0.34,1.38)	0.285
Past use	<5	838	0.49 (0.18,1.33)	0.164	0.53 (0.20,1.44)	0.213
Other antiandrogen:						
Current use	7	549	1.39 (0.65,2.95)	0.393	1.00 (0.47,2.14)	0.994
Past use	17	1272	1.44 (0.88,2.36)	0.151	1.27 (0.77,2.10)	0.339
Venous thromboembolism						
Untreated	89	24459	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT: Current use	234	26596	2.95 (2.28,3.82)	<0.001	2.89 (2.22,3.75)	<0.001
Past use	39	14864	0.89 (0.60,1.32)	0.561	0.91 (0.61,1.36)	0.645
GnRH: Current use	210	23844	2.98 (2.29,3.88)	<0.001	2.93 (2.24,3.82)	<0.001
Past use	33	12993	0.86 (0.56,1.31)	0.482	0.89 (0.58,1.35)	0.58
Degarelix: Current use	9	760	3.84 (1.92,7.67)	<0.001	3.73 (1.85,7.53)	<0.001
Past use	<5	54	6.87 (0.95,49.53)	0.056	7.63 (1.05,55.37)	0.045
Bicalutamide: Current use	<5	1056	0.92 (0.29,2.91)	0.886	0.83 (0.26,2.65)	0.758
Past use	<5	846	0.80 (0.20,3.29)	0.762	0.81 (0.20,3.32)	0.771
Other antiandrogen:						
Current use	6	558	3.10 (1.35,7.10)	0.007	2.98 (1.29,6.85)	0.01
Past use	9	1285	2.44 (1.22,4.89)	0.012	2.36 (1.17,4.74)	0.016
Other CVD events						
Untreated	320	23967	1.00 (ref. cat.)		1.00 (ref. cat.)	
ADT: Current use	484	26157	1.41 (1.22,1.63)	<0.001	1.24 (1.07,1.44)	0.004
Past use	242	14233	1.32 (1.10,1.57)	0.002	1.36 (1.14,1.63)	0.001
GnRH: Current use	429	23449	1.39 (1.20,1.62)	<0.001	1.24 (1.07,1.44)	0.005
Past use	228	12403	1.43 (1.19,1.71)	<0.001	1.50 (1.25,1.80)	<0.001
Degarelix: Current use	22	754	2.21 (1.43,3.41)	<0.001	1.82 (1.17,2.83)	0.008
Past use	<5	50				
Bicalutamide: Current use	9	1033	0.66 (0.34,1.29)	0.223	0.54 (0.28,1.05)	0.07
Past use	10	810	0.97 (0.51,1.82)	0.917	0.96 (0.51,1.82)	0.912
Other antiandrogen:						
Current use	15	555	2.07 (1.23,3.48)	0.006	1.56 (0.92,2.62)	0.097
Past use	13	1271	0.78 (0.45,1.36)	0.385	0.73 (0.42,1.27)	0.266

^aModel contains for year of diagnosis, age, deprivation, comorbidities in year before prostate cancer diagnosis (myocardial infarction, angina, cerebral vascular accident, heart failure, venous thromboembolism, arrhythmia, other cardiovascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, severe liver disease) and other medication use in the year before prostate cancer diagnosis (including aspirin, beta-blockers, ACEIs, ARBs, diuretics, statins, warfarin, digoxin, clopidogrel, dipyridamole, nitrate, insulin, sulfonylureas, metformin and other diabetic medications).