Prostate Cancer

Androgen Deprivation Therapies and Changes in Comorbidity: A Comparison of Gonadotropin-releasing Hormone Agonists and Antiandrogen Monotherapy as Primary Therapy in Men with High-risk Prostate Cancer

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Article info

Abstract

Background: Some studies suggest that gonadotropin-releasing hormone (GnRH) agonists are associated with higher risk of adverse events than antiandrogens (AAs) monotherapy. However, it has been unclear whether this is due to indication bias.

Objective: To investigate rates of change in comorbidity for men on GnRH agonists versus AA monotherapy in a population-based register study.

Design, setting, and participants: Men with advanced nonmetastatic prostate cancer (PCa) who received primary AA (n = 2078) or GnRH agonists (n = 4878) and age- and area-matched PCa-free men were selected from Prostate Cancer Database Sweden 3.0. Increases in comorbidity were measured using the Charlson Comorbidity Index (CCI), from 5 yr before through to 5 yr after starting androgen deprivation therapy (ADT).

Outcome measures and statistical methods: Multivariable linear regression was used to determine differences in excess rate of CCI change before and after ADT initiation. Risk of any incremental change in CCI following ADT was assessed using multivariable Cox regression analyses.

Results and limitations: Men on GnRH agonists experienced a greater difference in excess rate of CCI change after starting ADT than men on AA monotherapy (5.6% per yr, $p < 0.001$). Risk of any new CCI change after ADT was greater for GnRH agonists than for AA (hazard ratio, 1.32; 95% confidence interval, 1.20–1.44).

Conclusions: Impact on comorbidity was lower for men on AA monotherapy than for men on GnRH agonists. Our results should be confirmed through randomised trials of effectiveness and adverse effects, comparing AA monotherapy and GnRH agonists in men with advanced nonmetastatic PCa who are unsuitable for curative treatment.

Patient summary: Hormone therapies for advanced prostate cancer can increase the risk of other diseases (eg, heart disease, diabetes). This study compared two common forms of hormone therapy and found that the risk of another serious disease was higher for those on gonadotropin-releasing hormone agonists than for those on antiandrogen monotherapy.

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1. Introduction

Androgen deprivation therapy (ADT) is often prescribed for advanced prostate cancer (PCa) when curative treatment is not a suitable option. There are several types of ADT including surgical castration, nonsteroidal antiandrogen (AA) monotherapy, and gonadotropin-releasing hormone (GnRH) agonists, with the latter being the most commonly used.

Current European Association of Urology guidelines recommend against AA monotherapy based on evidence from a Cochrane review which found higher overall survival for GnRH agonists as first-line ADT for advanced PCa [1]. Nevertheless, in Scandinavian countries AA monotherapy is frequently used as first-line ADT for high-risk or regionally metastatic PCa [2]. Most trials included in the Cochrane review compared GnRH agonists with 50 mg daily and not 150-mg bicalutamide, which is the current standard dose in Sweden [3]. In addition, most studies included men with metastatic disease. Subgroup analyses, however, showed similar overall survival for men with nonmetastatic PCa on 150-mg bicalutamide daily [1].

Adverse effects (AEs) have been reported for all types of ADT. For GnRH agonists, hot flushes, weight gain, loss of libido, and erectile dysfunction are most commonly described [4]. GnRH agonists are also associated with metabolic AEs including bone loss with increased risk of fractures [5–7], cardiovascular disease [8–12], stroke [10,11,13], thrombolytic events [14], type 2 diabetes [9,15,16], and dementia [17]. For AA, the most frequently reported adverse events are breast pain and gynaecomastia [18]. While previous studies suggest more AEs for GnRH agonists than for AA monotherapy, differences may reflect indication bias, whereby healthier men who are at lower risk of developing AE are preferentially selected for AA monotherapy over GnRH agonists. While several studies have reported multiple adverse events for GnRH agonists [9,11], none to date has compared different ADTs with respect to their cumulative effect on overall comorbidity.

This study aimed to compare the impact of primary therapy with either GnRH agonists or AA monotherapy on change in overall comorbidity among men with high-risk or regionally metastatic disease, using the Charlson Comorbidity Index (CCI) as the measure of comorbidity. We hypothesised that (1) rates of change in CCI would be greater for GnRH agonists than for AA monotherapy and (2) men on GnRH agonists would be at greater risk of developing new comorbidities following initiation of hormonal therapy. To address concerns about the potential for indication bias we have examined rates of change in comorbidities relative to men of the same age who were free of PCa, both before and after starting ADT.

2. Methods

2.1. Study population and data collection

This study used data from Prostate Cancer Database Sweden 3.0 (PCBaSe3.0), a database that links the National Prostate Cancer Register (NPCR) of Sweden to the National Patient Registry, the National Prescribed Drug Register, and the Swedish longitudinal integration data set for health insurance and labour market studies using the unique Swedish personal identity number. Nationwide capture of PCa cases in NPCR is 98% compared with the Swedish Cancer Registry to which reporting is mandated by law [19]. PCBaSe3.0 also includes five men without a PCa diagnosis at the date each case was diagnosed, matched on birth year and county of residence, to act as a comparison cohort.

Eligible participants included all men diagnosed from January 1, 2006, to December 31, 2013, with high-risk PCa [defined as Gleason Grade Group (GGG) ≥4, and/or clinical stage T3, and/or prostate-specific antigen (PSA) >20–50 ng/ml, and N0, M0/MX] or regionally metastatic PCa (defined as clinical stage T4, and/or PSA >50–100 ng/ml, and/or N1, M0/X), who received either AA monotherapy or GnRH agonists, with or without short-term AA for flare protection, as primary therapy within 6 months of diagnosis (n = 6956). Men who underwent orchiectomy were excluded, as were men with distant metastases at diagnosis. Androgen blockade therapy was included in the GnRH agonist group. Five PCa-free men were also selected for each man on ADT to provide a comparison of age-related changes, in the absence of PCa and related treatments (n = 31 145). Four groups of study participants were thus defined: those who received primary AA monotherapy; their comparison cohort of matched PCa-free men; those who received primary GnRH agonists; and their matched PCa-free comparison cohort.

The main exposure was type of ADT (AA monotherapy vs GnRH agonists) received as primary therapy for high-risk or regionally advanced PCa. Standard AA monotherapy in Sweden is 150-mg oral bicalutamide once daily. Type of ADT, start date, and date of switch from AA to GnRH (approximately 40% of men on AA switched within 5 yr) were determined from the Prescribed Drug Register. The main outcome variable was change in comorbidity following initiation of ADT. This was assessed in two ways: (1) as the rate of change over the follow-up period, and (2) as the time to any new change in comorbidity. Comorbidity was assessed using the CCI [20], based on International Classification of Diseases, 10th edition (ICD-10) diagnosis codes from previous hospital discharge records. Diagnoses of PCa and any metastases were excluded from CCI scores to ensure comparability across groups. First, we calculated CCI at 5 yr prior to the start of ADT, based on hospital admissions occurring during the previous 10 yr, then determined changes in CCI thereafter. This provided measures of CCI at initiation of ADT and end of follow-up, as well as rates of increase for equivalent periods before and after starting ADT. The date of any incremental change in CCI corresponded to the date of first hospital admission for any new conditions within a disease group not previously contributing to the cumulative CCI, while the size of the increment corresponded to the weighting assigned to the specific disease group. Scores for multiple conditions during a single hospital admission were combined. We also assessed the time to first incremental change in CCI following start of ADT. Follow-up time was calculated from the date of ADT initiation (or same date in matched controls) to the date of censoring due to death, emigration, or the end of study (December 31, 2014). Men on AA monotherapy were censored if they changed to GnRH agonists or orchiectomy. Men in the PCa-free comparison groups were censored at the date of any PCa diagnosis.

2.2. Statistical analyses

Two different approaches to analysis were used to test our hypotheses. The first analysis was a comparison of annual excess rates of CCI change, defined as the difference between rates of CCI change in men on AA and their five matched comparison men, and similarly for men on GnRH and their respective matched comparison men. We assessed differences in excess rates among men on GnRH agonists compared with those on AA monotherapy using multivariable least squares linear regression. Models

Table 1 – Characteristics of study cohort for AA users, AA comparison group, GnRH users, and GnRH comparison group

ADT type	Antiandrogen monotherapy		Gonadotrophin-releasing hormones (agonists)	
	AA users	Comparison group	GnRH users	Comparison group
Total no.	2078	9337	4878	21 808
Mean age at ADT start	76.7 (6.5)	76.4 (6.6)	78.0 (7.2)	77.7 (7.2)
Mean PSA at diagnosis	33 (22)	–	36 (24)	–
Civil status, %				
Married	1338 (67)	6014 (64)	3057 (63)	13 774 (62)
Single/widowed/divorced	689 (33)	3307 (35)	1820 (37)	8001 (38)
Missing	1 (0.1)	16 (0.2)	1 (0.1)	33 (0.2)
Education level, %				
High	392 (19)	1574 (17)	679 (14)	3639 (17)
Intermediate	716 (34)	3152 (34)	1590 (33)	7041 (32)
Low	948 (45)	4389 (47)	2532 (52)	10 659 (49)
Missing	22 (1)	222 (2)	77 (2)	469 (2)
Risk category at diagnosis, %				
High risk	1552 (74)	–	3262 (67)	–
Regional disease	526 (26)	–	1616 (33)	–
Gleason grade group				
1	282 (14)	–	414 (9)	–
2–3	886 (42)	–	1663 (34)	–
4–5	893 (43)	–	2707 (55)	–
Missing	35 (2)		94 (2)	
Detection				
Screening	562 (27)	–	933 (19)	–
Lower urinary tract symptoms	1016 (49)	–	2836 (58)	–
Other symptoms	431 (21)	–	966 (20)	–
Missing	69 (3)	–	143 (3)	–
Mean time Dx to ADT start (d)	57	–	43	–
All deaths by 5 yr post-ADT	303	1734	2147	5185
PCa deaths by 5 yr post-ADT	67	–	982	–
Median follow-up post-ADT (IQR; yr)	3.0 (2.0–4.8)	4.1 (2.7–5.0)	3.7 (2.3–5.0)	4.5 (2.9–5.0)

AA = antiandrogen monotherapy; ADT = androgen deprivation therapy; Dx = diagnosis; GnRH = gonadotrophin-releasing hormones; IQR = interquartile range; PCa = prostate cancer; PSA = prostate-specific antigen.

were performed for differences both prior to and after initiation of ADT. Models were adjusted for age at ADT initiation, education level, and marital status (plus GGG, PSA, and stage at diagnosis for post-ADT differences).

The second approach involved multivariable Cox proportional hazards regression with age as a timescale to assess the impact of ADT on time to the first incremental change in CCI after initiating ADT. Models comparing type of ADT were adjusted for education, marital status, CCI score at initiation of ADT, GGG, stage, and PSA at diagnosis. In separate models we also investigated whether effects of ADT type varied according to age or stage of disease by including interaction terms for age group (<75 yr, ≥75 yr) and likewise for stage (high risk, regionally metastatic).

To further check that results did not reflect indication bias we repeated the Cox regression analysis in a propensity-matched subset of men on ADT. Propensity scores were determined using a logit model for treatment type, which included age and year of diagnosis, detection mode, stage, grade, log-PSA, education level, marital status, 5-yr pre-ADT CCI, and CCI at ADT start. One-to-one matching with a calliper of 0.01 without replacement was used to select the analytic cohort comprising 1993 men in each treatment group. Characteristics of the matched cohorts are reported in Supplementary Table 1.

Because follow-up time differed across groups, we also undertook sensitivity analyses restricted to the first 3 yr of follow-up by censoring at this time point. We also undertook further sensitivity analyses whereby men receiving combined androgen blockade (CAB) were excluded from the GnRH study group (n = 231, 5%).

To determine associations between ADT type and specific diseases contributing to CCI change, further multivariate Cox regression analyses were undertaken in the propensity-matched cohort to assess risk for each component disease category within the CCI. In these analyses, myocardial infarction, congestive heart failure, and peripheral vascular disease were combined and analysed as a single outcome: cardiovascular disease (CVD). Likewise, mild and moderate to severe liver disease, and diabetes with and without complications were also combined and analysed as single outcomes.

All statistical analyses were undertaken using STATA version 14.0 (STATA Corporation, College Station, TX, USA). This study was approved by the Research Ethics Board at Umeå University, Sweden.

3. Results

The study comprised 2078 men on AA monotherapy and 4878 men on GnRH agonists, along with 9337 and 21 808 PCa-free men within their respective comparison groups (Table 1). Median follow-up time was 3.0 yr for men on AA and 3.7 yr for men on GnRH. Those on GnRH agonists were slightly older, had lower education level, were less likely to be married, and had more adverse clinical features at diagnosis than men on AA therapy. Compared with men in their comparison groups, AA users had a higher education level, while GnRH agonist users had a lower

Cumulative CCI scores
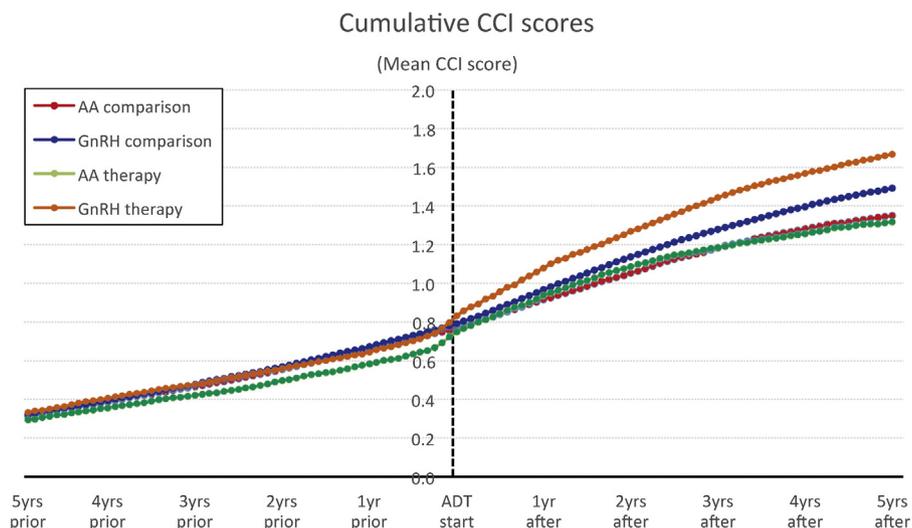
Fig. 1 – Cumulative changes in mean Charlson Comorbidity Index (CCI) score over time [relative to androgen deprivation therapy (ADT) initiation date] for men on antiandrogen monotherapy or gonadotropin-releasing hormone (GnRH) agonists, and their respective age- and area-matched comparison groups. AA = antiandrogen.

Table 2 – Differences in excess rate of change in CCI scores before and after initiation of ADT for men on GnRH agonists compared with men on AA monotherapy

ADT type	AA users	AA comparison	GnRH users	GnRH comparison
Measures				
Mean CCI score				
Pre-ADT	0.29 (0.69)	0.31 (0.76)	0.33 (0.75)	0.32 (0.75)
ADT start	0.75 (1.18)	0.77 (1.25)	0.83 (1.25)	0.79 (1.26)
Post-ADT	1.32 (1.63)	1.35 (1.72)	1.67 (1.77)	1.49 (1.77)
Mean annual change in CCI				
Pre-ADT period[a]	0.09 (0.19)	0.09 (0.18)	0.10 (0.18)	0.09 (0.18)
Post-ADT period[b]	0.21 (0.46)	0.19 (0.41)	0.31 (0.53)	0.23 (0.46)
Difference in rate of CCI change for AA versus GnRH relative to comparison men				
Regression analysis[c] (GnRH users vs AA users)	% Difference in annual CCI change		95% CI	p value
Crude				
Pre-ADT period	0.6		−0.4, 1.6	0.100
Post-ADT period	5.7		2.9, 8.5	<0.001
Adjusted				
Pre-ADT period	0.7		−2.9, 1.8	0.162
Post-ADT period	5.5		2.6, 8.5	<0.001

AA = antiandrogen monotherapy; ADT = androgen deprivation therapy; CCI = Charlson Comorbidity index; CI = confidence interval; GnRH = gonadotrophin-releasing hormone agonist.
[a] Pre-ADT rates calculated for 5 yr prior to ADT start.
[b] Post-ADT rates calculated to the end of follow-up, emigration, death, orchiectomy, or switch from AA to GnRH.
[c] Multivariable linear regression for difference in excess rate of CCI change comparing men on GnRH with those on AA monotherapy, adjusted for age at the start of ADT, education level, and marital status (plus Gleason grade group, stage, and PSA for post-ADT rate differences).

education level. The distribution of CCI 5 yr before staring ADT, at initiation of ADT, and at the end of follow-up is provided in Supplementary Table 2.

Fig. 1 shows changes in the mean cumulative CCI over time for each study group. Trajectories prior to ADT initiation were very similar for all study groups, though mean CCI was slightly lower among men who went on to receive AA. CCI increased at a greater rate during follow-up among men on GnRH agonists compared with controls, whereas CCI trajectories among men on AA

did not differ substantially from their controls. Disease groups contributing to change in CCI scores during the pre- and post-ADT periods are provided in Supplementary Tables 3 and 4. Little difference was seen in the profile of diseases contributing to changes in CCI before ADT across study groups (Supplementary Table 3), whereas profiles following ADT differed noticeably, particularly for chronic heart failure (GnRH users 12%; AA users 6%) and stroke (GnRH users 10%; AA users 6%; Supplementary Table 4).

Table 3 – Risk of any incremental increase in CCI score after commencing ADT among men on GnRH agonists compared with men on AA monotherapy

	No. events		Adjusted HR (95% CI)
	AA	GnRH	
Main analyses			
Complete cohort/full follow-up	618/2027	2093/4715	1.32 (1.20–1.44)
Sensitivity analyses			
Propensity-matched subset	612/1993	821/1993	1.28 (1.15–1.42)
Follow-up restricted to 3 yr	500/2027	1648/4712	1.32 (1.19–1.46)
CAB excluded from GnRH	618/2027	2018/4486	1.33 (1.21–1.45)

AA = antiandrogen monotherapy; ADT = androgen deprivation therapy; CAB = combined androgen blockade; CCI = Charlson Comorbidity Index; CI = confidence interval; GnRH = gonadotrophin-releasing hormone agonist; HR = hazard ratio.
Cox proportional hazards regression for time to first incremental change in CCI after ADT start date, using age as the time scale, adjusted for education, marital status, CCI score at the initiation of ADT, Gleason grade, stage, and PSA at diagnosis.

Table 4 – Risk of developing specific CCI subcategory diseases after commencing ADT, among men on GnRH agonists compared with men on AA monotherapy

Component conditions of CCI	No. events		Adjusted HR (95% CI)
	AA (n = 1993)	GnRH (n = 1993)	
Cardiovascular disease (MI, CHF or PVD)[a]	215	319	1.39 (1.14–1.69)
Stroke	126	168	1.26 (0.99–1.57)
Dementia	86	109	1.19 (0.89–1.59)
Chronic pulmonary disease	76	101	1.26 (0.93–1.70)
Rheumatic/connective tissue disease	28	26	0.89 (0.52–1.52)
Ulcerative disease	35	48	1.26 (0.81–1.96)
Diabetes (±complications)[a]	121	180	1.64 (1.26–2.13)
Liver disease (mild to severe)[a]	8	16	1.34 (0.55–3.28)
Paraplegia	24	33	1.23 (0.73–2.07)
Renal disease	97	110	1.01 (0.76–1.33)
Malignancy (other than PCa)	78	89	1.02 (0.75–1.39)

AA = antiandrogen monotherapy; ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; CHF = chronic heart failure; CI = confidence interval; GnRH = gonadotrophin-releasing hormone agonist; HR = hazard ratio; MI = myocardial infarction; PCa = prostate cancer; PSA = prostate-specific antigen; PVD = peripheral vascular disease.
Cox proportional hazards regression for time to disease incidence after ADT start date in the propensity-matched cohort, using age as the time scale, adjusted for education, marital status, CCI at initiation of ADT, Gleason grade, and PSA at diagnosis.
[a] Pertains only to incident cases occurring during follow-up within these combined groups.

Table 2 shows the mean CCI scores at three time points for each study group (5 yr before the date of ADT initiation, on the date of ADT initiation, and at the end of the follow-up period), along with rates of CCI change before and after the start of ADT. While there was little difference in rates of CCI change before initiation of ADT, differences were quite pronounced for the period after ADT. The differences in excess rate of change in CCI for men on GnRH compared with men on AA are shown in the lower section of Table 2. Multivariable regression analysis indicates a greater difference in excess rate of CCI change for men on GnRH agonists than for men on AA monotherapy after starting ADT (5.7% per yr, $p < 0.001$). No difference in excess rates of CCI change was observed between men on GnRH and those on AA for the 5-yr period before starting ADT (0.7% per yr, p = 0.162).

Results of multivariate Cox regression analyses examining the influence of ADT type on time to first incremental change in CCI (Table 3) show a higher risk of CCI increase [hazard ratio (HR), 1.31; 95% confidence interval (CI), 1.20–1.44] for men on GnRH than for those on AA. Analyses restricted to 3 yr of follow-up show a very similar increase for men on GnRH (HR, 1.32; 95% CI, 1.19–1.46). Exclusion of men undergoing CAB did not alter the findings nor did results substantially differ for the propensity-matched cohort (HR, 1.27; 95% CI, 1.15–1.42). Analyses investigating interaction by age revealed a stronger effect for GnRH than AA in men <75 yr than men ≥75 yr (p = 0.031 for interaction). However, no effect modification was observed in relation to stage of disease at diagnosis (results not shown).

With respect to specific diseases contributing to CCI changes, there were increases in risk of coronary heart disease (HR, 1.39; 95% CI, 1.14–1.69), diabetes (HR, 1.64; 95% CI, 1.26–2.13), and stroke (HR, 1.26; 95% CI, 0.99–1.57) among men on GnRH agonists compared with those on AA (Table 4). Risk of dementia was also elevated in men on GnRH agonists compared with those on AA, but the difference did not reach statistical significance.

Outcome	Estimate	Comparison
Coronary Heart disease		
Coronary heart disease		
	HR=1.19 (1.10-1.28)	GnRH vs no ADT
Keating 2010	HR=1.10 (0.80-1.53)	AA vs no ADT
Myocardial infarction		
	HR=1.28 (1.08-1.52)	GnRH vs no ADT
Keating 2010	HR=1.05 (0.47-2.35)	AA vs no ADT
	SIR=1.28 (1.11-1.47)	GnRH vs gen. pop.
Hemelrijck 2010	SIR=1.12 (0.94-1.34)	AA vs gen. pop.
Arrhythmia		
	SIR=1.27 (1.10-1.47)	GnRH vs gen. pop.
Hemelrijck 2010	SIR=1.38 (1.16-1.65)	AA vs gen. pop.
Ischemic heart disease		
	SIR=1.30 (1.17-1.45)	GnRH vs gen. pop.
Hemelrijck 2010	SIR=1.13 (0.99-1.30)	AA vs gen. pop.
	HR=1.45 (1.14-1.84)	GnRH vs controls
Robinson et al 2012	HR=1.40 (0.90-2.18)	AA vs controls
Heart failure		
	SIR=1.46 (1.28-1.67)	GnRH vs gen. pop.
Hemelrijck 2010	SIR=1.15 (0.95-1.41)	AA vs gen. pop.
Stoke		
	SIR=1.27 (1.12-1.43)	GnRH vs gen. pop.
Hemelrijck 2010	SIR=1.19 (1.02-1.40)	AA vs gen. pop.
	HR=1.21(1.05-1.40)	GnRH vs no ADT
Keating 2010	HR=0.86 (0.43-1.73)	AA vs no ADT
	HR=1.43 (1.08-1.77)	GnRH vs controls
Robinson 2012	HR=1.11 (0.67-1.84)	AA vs controls
Diabetes		
	HR=1.28 (1.19-1.38)	GnRH vs no ADT
Keating 2010	HR=1.02 (0.72-1.45)	AA vs no ADT
	HR=1.61 (1.36-1.91)	GnRH/Orch vs controls
Crawley 2016	HR=0.74 (0.65-0.84)	AA vs controls
Thromolitic events		
Deep vein thrombosis		
	HR=1.92 (1.62-2.27)	GnRH vs controls
O'Farrell 2016	HR=0.63 (0.43-0.93)	AA vs controls
Pulmonary embolism		
	HR=1.73 (1.53-1.95)	GnRH vs controls
O'Farrell 2016	HR=0.71 (0.55-0.91)	AA vs controls
Bone health		
Any bone fracture		
	SIR=1.6 (1.5-1.7)	GnRH vs gen. pop.
Thorstenson 2012	SIR=1.1 (0.9-1.3)	AA vs gen. pop.
Hip Fracture		
	SIR=1.6 (1.5-1.8)	GnRH vs gen. pop.
Thorstenson 2012	SIR=0.9 (0.7-1.1)	AA vs gen. pop.
Dementia		
All cause Dementia		
	HR=1.15 (1.07-1.23)	GnRH vs controls
*Robinson (unpublished)	HR=0.94 (0.84-1.05)	AA vs controls
Non-Alzheimer's dementia		
	HR=1.24 (1.14-1.36)	GnRH vs controls
*Robinson (unpublished)	HR=0.91 (0.78-1.06)	AA vs controls

0.10   1.00   10.00   Risk Estimate

Fig. 2 – Summary of evidence comparing adverse effects of gonadotropin-releasing hormone (GnRH) agonists versus antiandrogen (AA) monotherapy. ADT = androgen deprivation therapy; gen. pop = general population; Orch. = orchiectomy.

4. Discussion

In this population-based register study, we found a stronger increase in comorbidity among men with high-risk PCa on GnRH agonists than among men on AA monotherapy. This is indicated both by the excess rate of CCI change and by the increased risk of any increment in CCI after starting ADT among men on GnRH. Similarities in the rates of CCI change and the profiles of specific comorbidities prior to starting ADT, as well as the consistency of findings in the propensity-matched analysis, suggest that our results are not simply the result of indication bias.

Our findings regarding changes in CCI, particularly the increase in CVD, diabetes, and stroke, are consistent with evidence from several large population-based studies, which points to increased risk of serious AEs for GnRH agonists compared with AA. Reported AEs include coronary vascular disease (CVD) [9–12], diabetes and other metabolic syndrome components [9,16,21], thromboembolic events [14], and osteoporosis and bone fractures [7]. Recent meta-analyses also show higher risk of CVD morbidity and CVD mortality for GnRH agonists than for AA [8,22]. Fig. 2 summarises the evidence for the range of adverse outcomes, based on observational studies undertaken in Sweden and the USA.

Findings from a recent study of mortality following GnRH agonists or AA monotherapy for advanced, nonmetastatic PCa suggest equivalent cancer-specific mortality (adjusted HR, 1.08; CI, 0.95–1.23) but higher all-cause mortality (HR, 1.23; CI: 1.13–1.34) with GnRH use [23]. Given this evidence, along with our findings suggesting increased comorbidity, further investigation through well-run randomised controlled trials (RCTs) is warranted to inform treatment guidelines.

Because of the potential biases inherent in observational study designs, causality cannot be inferred. Despite adjustment for social and clinical factors in multivariable analyses we cannot rule out indication bias as possible explanation for our findings. The slightly lower mean baseline CCI in men on AA suggests some preferential selection of healthier men for AA monotherapy. Even though our statistical methods aimed to address potential biases, it is still possible that choice of primary AA over GnRH agonists was associated with other factors such as fitness or sexual functioning, which in turn are associated with risk of further comorbidity. Importantly, the similarity in CCI profiles before ADT initiation gives some assurance that differences in health status were not large.

While the CCI is a well-validated tool for assessing overall comorbidity, it does not include all adverse outcomes that may be associated with ADT. For example, bone fractures, thromboembolic events other than stroke, and components of metabolic syndrome other than diabetes are not included. Another limitation is the reliance on hospital admission data (reflecting more severe disease) to determine our outcome. The true extent of comorbidity may therefore have been underestimated. However, this should not affect comparison because identical measures of CCI were applied to all groups. Another limitation is the lack of information about additional treatment in PCBaSe (eg, chemotherapies), which may contribute to increased comorbidities in patients on ADT. Newer-generation ADT therapies such as abiraterone or enzalutamide were not available in Sweden before 2014. Finally, these results are not generalisable to men receiving bicalutamide at other doses (eg, 50 mg/d), those with metastatic disease, or populations with differing comorbidity profiles.

The strengths of this study include the use of high-quality population-based registries with reliable linkages to the Prescribed Drug Register, allowing for complete sampling of eligible cases, accurate measures of exposure to different types of ADT, and a large sample size. Furthermore, the consistency of results using two different approaches gives greater weight to our findings.

In conclusion, our findings suggest that men on GnRH agonists have a greater risk of additional comorbidities compared with men on AA monotherapy. If correct, this has important implications for selecting ADT therapies for men with advanced nonmetastatic disease, who are not suitable candidates for curative treatment, especially those who will receive ADT for long periods. These findings require confirmation through further RCTs to inform guideline development.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.022.

References

[1] Kunath F, Grobe HR, Rucker G, et al. Non-steroidal antiandrogen monotherapy compared with luteinizing hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer: a Cochrane systematic review. BJU Int 2015;116:30–6.

[2] Lycken M, Garmo H, Adolfsson J, Stattin P, Holmberg L, Bill-Axelson A. Patterns of androgen deprivation therapies among men diagnosed with localised prostate cancer: a population-based study. Eur J Cancer 2014;50:1789–98.

[3] Iversen P. Antiandrogen monotherapy: indications and results. Urology 2002;60:64–71.

[4] Walker LM, Tran S, Robinson JW. Luteinizing hormone-releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. Clin Genitourin Cancer 2013;11:375–84.

[5] Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154–64.

[6] Smith MR, Lee WC, Brandman J, Wang Q, Botteman M, Pashos CL. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23:7897–903.

[7] Thorstenson A, Bratt O, Akre O, et al. Incidence of fractures causing hospitalisation in prostate cancer patients: results from the population-based PCBaSe Sweden. Eur J Cancer 2012;48:1672–81.

[8] Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015;68:386–96.

[9] Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2010;102:39–46.

[10] Robinson D, Garmo H, Lindahl B, et al. Ischemic heart disease and stroke before and during endocrine treatment for prostate cancer in PCBaSe Sweden. Int J Cancer 2012;130:478–87.

[11] Van Hemelrijck M, Garmo H, Holmberg L, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. J Clin Oncol 2010;28:3448–56.

[12] O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol 2015;33:1243–51.

[13] Meng F, Zhu S, Zhao J, et al. Stroke related to androgen deprivation therapy for prostate cancer: a meta-analysis and systematic review. BMC Cancer 2016;16:180.

[14] O'Farrell S, Sandstrom K, Garmo H, et al. Risk of thromboembolic disease in men with prostate cancer undergoing androgen deprivation therapy. BJU Int 2016;118:391–8.

[15] Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979–83.

[16] Crawley D, Garmo H, Rudman S, et al. Association between duration and type of androgen deprivation therapy and risk of diabetes in men with prostate cancer. Int J Cancer 2016;139:2698–704.

[17] Nead KT, Sinha S, Nguyen PL. Androgen deprivation therapy for prostate cancer and dementia risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2017;20:259–64.

[18] Iversen P, McLeod DG, See WA, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int 2010;105:1074–81.

[19] Van Hemelrijck M, Wigertz A, Sandin F, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. Int J Epidemiol 2013;42:956–67.

[20] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[21] Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS One 2015;10:e0117344.

[22] Zhao J, Zhu S, Sun L, et al. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: a meta-analysis of population-based observational studies. PLoS One 2014;9:e107516.

[23] Thomsen F, Bosco C, Garmo H, et al. Anti-androgen monotherapy versus gonadotropin-releasing hormone agonists in men with advanced, non-metastatic prostate cancer: a register-based, observational study. Acta Oncol. In press. https://doi.org/10.1080/0284186X.2018.1529427.