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Androgen deprivation therapies and changes in comorbidity: A Comparison of gonadotropin releasing hormone agonists and anti-androgen monotherapy as primary therapy in men with high risk prostate cancer

Short Title: **Androgen deprivation therapies and changes in comorbidity**

Authors: Kerri Beckmann[1,2], Hans Garmo[3], Jan Adolfsson[4], Cecilia Bosco[2], Eva Johansson[5], David Robinson[6], Lars Holmberg[2], Par Stattin[5], Mieke Van Hemelrijck[2,7]

Affiliations:

[1] University of South Australia, **Australian Centre for Precision Health,** Adelaide, Australia

[2] King's College London, School of Cancer and Pharmaceutical Sciences, Translational Oncology & Urology Research (TOUR), London, UK

[3] Regional Cancer Centre Uppsala, Uppsala University Hospital, Uppsala, Sweden.

[4] CLINTEC-department, Karolinska Institutet, Stockholm, Sweden

[5] Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden

[6] Department of Urology, Ryhov Hospital, Jönköping, Sweden

[7] Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Corresponding author:

Kerri Beckmann

Translational Oncology and Urology Research, School of Cancer and Pharmaceutical Studies, King's College London

3rd Floor, Bermondsey Wing, Guy's Hospital, London SE1 9RT, UK

Kerri.beckmann@kcl.ac.uk

+44 (0) 20 7188 7188, ext. 57380

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Abstract

Background: Some studies suggest that Gonadotropin releasing hormone (GnRH) agonists are associated with higher risk of adverse events than anti-androgens (AA) 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 non-metastatic prostate cancer (PCa) who received primary AA (n=2,078) or GnRH agonists (n=4878) and age-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 5yrs before through to 5yrs 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 year, $p<0.001$). Risk of any new CCI change after ADT was greater for GnRH agonists than AA (Hazard ratio: 1.32; 95% confidence interval: 1.20-1.44).

Conclusion: 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 non-metastatic PCa who are unsuitable for curative treatment.

Patient Summary: Hormone therapies for advanced prostate cancer can increase the risk of other diseases (e.g. 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 GnRH agonists) than for those on AA monotherapy.

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, non-steroidal anti-androgen monotherapy (AA), and gonadotrophin releasing hormones (GnRH) agonists – the latter being most commonly used.

Current European Association of Urology (EAU) 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 150mg bicalutamide, which is the current standard dose in Sweden[3]. Also, most studies included men with metastatic disease. Subgroup analyses, however, showed similar overall survival for men with non-metastatic PCa on 150 mg bicalutamide daily[1].

Adverse effects [AE] 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 adverse effects 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 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 ADT´s 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 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.

Methods

Study population and data collection

This study used data from PCBaSe3.0, a database which links the National Prostate Cancer Register (NPCR) of Sweden to the National Patient Registry, the National Prescribed Drug Register and the Swedish longitudinal integration dataset for health insurance and labour market studies using the unique Swedish personal identity number. Nationwide capture of PCa cases in NPCR is 98% compared to 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 Jan 1, 2006 to Dec 31, 2013 with high-risk PCa (defined as Gleason Grade Group (GGG) ≥4, and/or clinical stage T3, and/or

prostate specific antigen (PSA) >20-50ng/ml, and N0, M0/MX) or regionally metastatic PCa (defined as clinical stage T4, and/or PSA >50-100ng/ml, and/or N1, and 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=6,956). 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 (~40% of men on AA switched within 5 years) 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 Charlson Comorbidity index (CCI)[20], based on 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. Firstly, we calculated CCI at five years prior to the start of ADT, based on hospital admissions occurring during the previous 10 years, 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) until the date of censoring due to death, emigration, or the end of study (31, Dec 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.

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 AA monotherapy using multivariable least squares linear regression. Models 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 Gleason Grade Group (GGG), PSA and stage at diagnosis, for post-ADT differences).

The second approach involved multivariable Cox proportional hazards regression with age as a time-scale 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 (<75years, ≥75years) 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-year 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 S1.

Since follow-up time differed across groups, we also undertook sensitivity analyses restricted to the first 3 years 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 v 14.0 (STATA corporation, College Station, Texas USA). This study was approved by the Research Ethics Board at Umeå University, Sweden.

Results

The study comprised 2,078 men on AA monotherapy and 4,878 men on GnRH agonists, along with 9,337 and 21,808 PCa-free men within their respective comparison groups (**Table 1)**. Median follow-up time was 3.1 years for men on AA and 3.7 years 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 education level. The distribution of CCI five years before staring ADT, at initiation of ADT and at the end of follow-up is provided in **Supplementary Table 2**.

Figure 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, while 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 the Supplementary Tables **(Tables S3 and S4)**. Little difference was seen in the profile of diseases contributing to changes in CCI before ADT across study groups (**Table S3**), 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%) (**Table S4**).

Table 2 shows the mean CCI scores at three time points for each study group (five years 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 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 men on AA monotherapy after starting ADT (5.7% per year, $p<0.001$). No difference in excess rates of CCI change was observed between men on GnRH and those on AA for the 5-year period before starting ADT (0.7% per year, $p=0.162$).

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 (HR: 1.31; 95%CI: 1.20-1.44) for men on GnRH than for those on AA. Analyses restricted to 3 years 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 years than men ≥ 75 years ($p=0.031$ 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 AA

users (**Table 4**). Risk of dementia was also elevated in men on GnRH agonists compared with AA, but the difference did not reach statistical significance.

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 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 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 adverse effects 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 AA[8,22]. Figure 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, non-metastatic 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.

Due to 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 Charlson Comorbidity Index 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 was 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 since identical measures of CCI were applied to all groups. Another limitation is the lack of information about additional treatment in PCBaSe (e.g. 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 (e.g. 50mg/daily), 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 to men on AA monotherapy. If correct, this has important implications for selecting ADT therapies for men with advanced non-metastatic disease, who are not suitable candidates for curative treatment, especially those who will receive ADT for long time-periods. These findings require confirmation through further RCTs to inform guideline development.

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