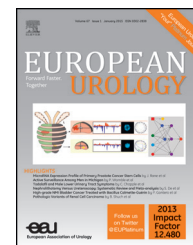


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## Platinum Priority – Review – Prostate Cancer

Editorial by Paul L. Nguyen and Anthony V. D'Amico on pp. 397–398 of this issue

# Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis

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### Abstract

**Context:** Whether androgen deprivation therapy (ADT) for men with prostate cancer (PCa) increases the risk of cardiovascular disease (CVD) remains controversial. Pooled analyses using data from randomised controlled trials suggest no increased risk of fatal CVD following ADT, but no pooled analyses exist for observational studies.

**Objective:** To perform a meta-analysis using observational data on ADT and risk of CVD events in men with PCa.

**Evidence acquisition:** PubMed and Embase were searched using predefined inclusion criteria to perform meta-analyses on associations between types of ADT and nonfatal and fatal CVD outcomes using information from observational studies. Random effects meta-analyses were conducted to estimate relative risks (RRs) and 95% confidence intervals (CIs).

**Evidence synthesis:** A total of eight observational studies were identified studying at least one type of ADT and a nonfatal or fatal CVD outcome. The RR for risk of any type of nonfatal CVD was 1.38 (95% CI, 1.29–1.48) for men with PCa on gonadotropin-releasing hormone (GnRH) agonists, compared with men not treated with ADT. When analysing nonfatal ischemic heart disease only, the RR was 1.39 (95% CI, 1.26–1.54). The associations between GnRH agonists and nonfatal or fatal myocardial infarction or stroke were even stronger: RR: 1.57 (95% CI, 1.26–1.94) and RR: 1.51 (95% CI, 1.24–1.84), respectively. The results for other types of ADT in relation to the risk of any nonfatal CVD were RR: 1.44 (95% CI, 1.28–1.62) for orchiectomy and RR: 1.21 (95% CI, 1.07–1.367) for antiandrogens.

**Conclusions:** Observational data show a consistent positive association between ADT and the risk of CVD. This finding supports the need for future randomised trials of PCa patients that include older patients and men with multiple comorbidities to better reflect the general population.

**Patient summary:** We investigated all the available data from observational studies on hormonal treatment for prostate cancer and its possible cardiovascular adverse effects. We found consistent evidence that this treatment may increase the risk of cardiovascular disease.

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## 1. Introduction

Androgen deprivation therapy (ADT) is the mainstay treatment for advanced prostate cancer (PCa). Since its discovery in 1941 [1], different types of treatments to impede androgen tumour growth stimulation have been developed including gonadotropin-releasing hormone (GnRH) agonists (ie, buserelin, goserelin, leuprorelin, and triptorelin), orchiectomy, GnRH antagonists (ie, abarelix, degarelix), oestrogens (diethylstilbestrol), and antiandrogens (cyproterone acetate, nilutamide, flutamide, and bicalutamide) [2]. For locally advanced and metastatic PCa, ADT has been shown to improve survival rates, palliate symptoms effectively, and delay cancer progression [3]. Men on ADT may remain under treatment for prolonged periods of time [4]; thus adverse effects are important to consider when making treatment decisions. Reported adverse effects include hot flashes, erectile dysfunction, loss of libido, bone fractures, obesity and sarcopaenia, lipid alterations and insulin resistance, metabolic syndrome, diabetes, and cardiovascular disease (CVD) [5].

Several recent meta-analyses have focused on ADT-related cardiovascular (CV) morbidity and mortality using data from randomised controlled trials (RCTs) with different primary end points. No association was found for CV mortality; however, investigators were not able to stratify by baseline cardiac comorbidity [6]. Together with a large retrospective study [7], some very recent data [8] suggest that ADT is associated with increased mortality (especially cardiac-specific mortality) only amongst men with a history of cardiac disease (eg, congestive heart failure or myocardial infarction [MI]). In addition, a meta-analysis by Albertsen et al, based on six RCTs comparing treatment efficacy of GnRH agonists versus antagonist, showed that the risk of nonfatal CVD and all-cause mortality was particularly high in men with preexisting CVD. This risk was also observed to be higher for those treated with GnRH agonists rather than GnRH antagonists [9].

As a result of the increasing number of studies finding a positive association between ADT and CVD, the European Association of Urology's 2012 PCa guidelines comment on the association of ADT with nonfatal CVD but state that the evidence regarding ADT and CVD mortality risk is not consistent [5]. Several large observational studies have identified an association between ADT and CVD [10–17] including some studies that examined both nonfatal and fatal CVD. RCTs provide the highest grade of evidence for the assessment of the effectiveness of treatments [18]. Nonetheless, these trials tend to exclude older patients or those with a higher number of comorbidities [19]. For instance, in the meta-analysis on RCTs by Nguyen et al, authors highlight that given that they analysed phase 3 RCTs, it is likely that participants had fewer comorbidities than the general population, making them less susceptible to ADT-related CV adverse effects [6].

The RCTs of ADT were not designed to ascertain CV outcomes other than death. Observational studies, when well conducted, have been shown to provide similar

estimate effects to RCTs. Elderly participants and those with comorbidities, two common characteristics of PCa patients receiving ADT, do not need to be excluded [20]. Including these men in the study population will provide results that are more applicable to the general population of interest. Finally, observational studies also allowed examination of CV outcomes other than death.

Therefore, we performed the first meta-analysis on ADT and risk of fatal and nonfatal CVD using data from observational studies. This study is novel because it specifically focuses on observational studies to address some of the limitations of RCTs as previously described (ie, selection of healthier population and a focus on CVD mortality only).

## 2. Evidence acquisition

### 2.1. Literature search strategy

We used computerised literature search databases (PubMed search followed by Embase) to identify full texts and abstracts published as of June 15, 2014. Our searches included *cardiovascular diseases* as search/Medical Subject Heading (MeSH) terms for the outcome variable of interest. In addition, *prostatic neoplasms* and *androgen deprivation therapy, antineoplastic agents hormonal/adverse effects or endocrine treatment* were used as search/MeSH terms for the exposure variable of interest. Our search strategy was limited to publications with a focus on humans. By not restricting the search to research papers, we made it possible to include grey literature, such as letters and abstracts presented at relevant conference meetings, to address the effects of ADT on CV morbidity and mortality. All references of selected articles were checked, including hand searches, which is an effective practical way to cross-check the completeness of the electronic searches.

### 2.2. Inclusion criteria

The selected articles were chosen based on the following inclusion criteria: the publication pertained to an epidemiological observational study that measured exposure to ADT, the comparison group was clearly defined, CVD (fatal or nonfatal) was assessed as an outcome, CVD events were clearly defined, the study focused on men with PCa and disease stage was clearly described, and ADT type was specified. Titles of articles were first reviewed to ascertain whether they might potentially fit the inclusion criteria. After assessing the abstract, a more thorough subsequent assessment was performed when there was doubt whether the paper would fit the inclusion criteria. The list of potential articles was further shortened by performing evaluations of the methods and results of each remaining paper. Figure 1 provides detailed information regarding the progressive flow of the study exclusion process. Figure 2 shows how the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria were also used to evaluate the quality of included studies [21].

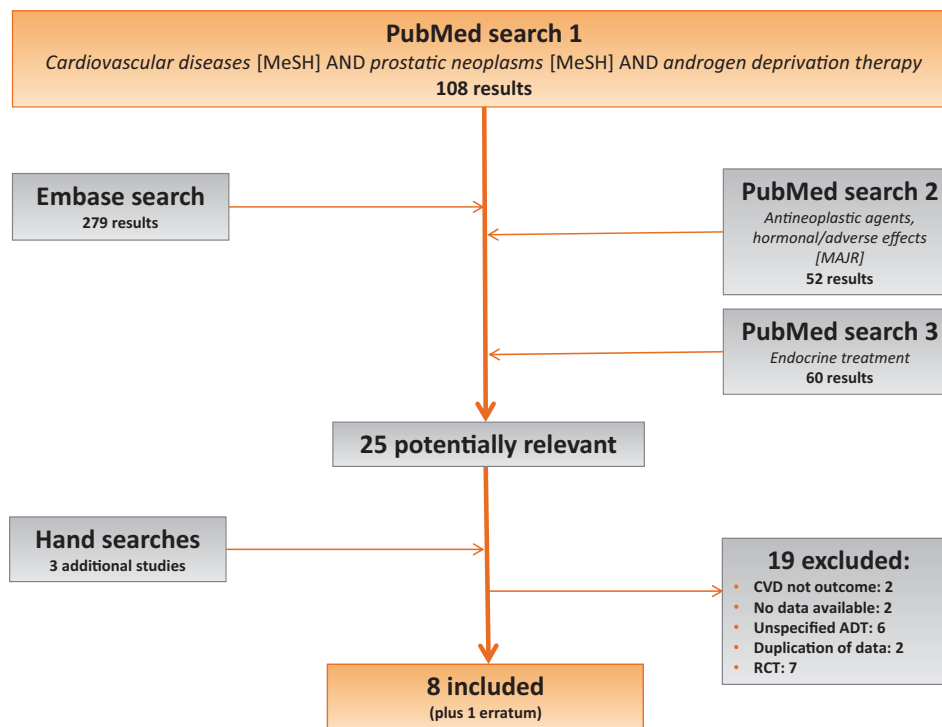


Fig. 1 – Flowchart of study selection procedure.

ADT = androgen deprivation therapy; CVD = cardiovascular disease; MeSH = Medical Subject Heading; RCT = randomised controlled trial.

### 2.3. Data extraction

For each study, we considered author, year of publication, ADT type and exposure (binary), study type (case control or cohort), outcome, and number of cases and total subjects for each level of ADT. The outcome was defined as fatal or nonfatal CVD based on the CVD definition provided by the World Health Organisation [22]: coronary heart disease (CHD), ischemic heart disease (IHD), acute MI, arrhythmia, sudden cardiac death, peripheral artery disease, deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial embolism, and stroke and transient ischemic attack. However, it is arguable whether thromboembolic disease (TED) should be included because from an aetiological point these may differ from CV outcomes such as MI and stroke. It is known that recent surgery as well as PCa disease progression may also be linked to the risk of TED [11]. Therefore, we also performed a sensitivity analysis excluding those studies where DVT or PE was the main outcome. Heart failure was not included as an outcome due to its wide range of clinical aetiologies. First, we assessed the risk of any nonfatal CVD event. When a distinction between a fatal and nonfatal CVD event was not made, the study was included and the events were considered nonfatal. However, an additional sensitivity analysis was performed including only the five studies explicitly specifying nonfatal events. Next, we focused specifically on nonfatal IHD to further disentangle the possible associations with ADT. Lastly, we investigated the association between ADT and MI and stroke. For the latter, we did

not make a distinction between nonfatal and fatal because these are thought to be equally relevant clinically.

### 2.4. Statistical methods

The effect of ADT compared with no ADT on the risk of CVD amongst men with PCa was evaluated by calculating the random effects summary relative risk (RR). Forest plots were created to display the RR estimates for each study. Potential heterogeneity of the study results was evaluated using the  $I^2$  statistic as well as a “remove-one” analysis. Potential publication bias was assessed with a contour-enhanced funnel plot [23] and by conducting the Egger test [24]. ADT was grouped into different types of treatment: GnRH agonists, orchiectomy, and antiandrogens (no studies of GnRH antagonists were identified).

Because our analyses did not allow for adjustment, we examined the robustness of estimated treatment effects to potential observed and unobserved confounders [25–27]. To do this, we assumed there was a confounder such as diabetes (observed) or smoking (unobserved), associated with both intake of ADT and development of nonfatal CVD (our outcome with the lowest risk ratio). We then reestimated the effect of ADT on CVD after adjusting for these additional variables under specific assumptions regarding the prevalence of the confounder in men who were on ADT and those who were not as well as the confounder’s relationship with the outcome. For age, existing evidence suggests that men with diabetes have twice the risk of CVD as men without diabetes [28]. In one

Article Section	STROBE key points for observational studies assessment	Keating SEER	Keating Veterans	Van Hemelrijck DVT PE	Van Hemelrijck CVD	Azoulay	Hu	Jespersen	Martin Merino
<b>Title and abstract</b>	1	Indicate the study's design with a commonly used term in the title or the abstract	✓	✓	✓	✓	✓	✓	✓
		Provide in the abstract an informative and balanced summary of what was done and what was found	✓	✓	✓	✓	✓	✓	✓
<b>Introduction</b>									
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓	✓	✓	✓	✓	✓	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓	✓	✓	✓	✓	✓	✓
<b>Methods</b>									
Study design	4	Present key elements of study design early in the paper	✓	✓	✓	✓	✓	✓	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	✓	✓	✓	✓	✓	✓
Participants	6	<i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓	✓	✓	✓	✓	✓	✓
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	✓	✓	✓	✓	✓	✓	✓
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	✓	✓	✓	✓	✓	✓	✓
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	✓	✓	✓	✓	✓	✓
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	✓	✓	✓	✓	✓	✓
Bias	9	Describe any efforts to address potential sources of bias	✓	✓	✓	✓	✓	✓	✓
Study size	10	Explain how the study size was arrived at	✓	✓	✓	✓	✓	✓	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓	✓	✓	✓	✓	✓	✓
Statistical methods	12	Describe all statistical methods, including those used to control for confounding	✓	✓	✓	✓	✓	✓	✓
		Describe any methods used to examine subgroups and interactions	✓	✓	✓	✓	✓	✓	✓
		Explain how missing data were addressed	✓	✓	✓	✓	✓	✓	✓
		<i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	✓	✓	✓	✓	✓	✓	✓
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	✓	✓	✓	✓	✓	✓	✓
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	✓	✓	✓	✓	✓	✓	
		Describe any sensitivity analyses	✓	✓	✓	✓	✓	✓	
<b>Results</b>									
Participants	13	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	✓	✓	✓	✓	✓	✓
		Give reasons for non-participation at each stage	✓	✓	✓	✓	✓	✓	✓
		Consider use of a flow diagram	✓	✓	✓	✓	✓	✓	✓
Descriptive data	14	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓	✓	✓	✓	✓	✓	✓
		Indicate number of participants with missing data for each variable of interest	✓	✓	✓	✓	✓	✓	✓
		<i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	✓	✓	✓	✓	✓	✓	✓
Outcome data	15	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	✓	✓	✓	✓	✓	✓	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	✓	✓	✓	✓	✓	✓	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	✓	✓	✓	✓	✓	✓	
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	✓	✓	✓	✓	✓	
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✓	✓	✓	✓	✓	✓	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓	✓	✓	✓	✓	✓	
<b>Discussion</b>									
Key results	18	Summarise key results with reference to study objectives	✓	✓	✓	✓	✓	✓	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓	✓	✓	✓	✓	✓	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	✓	✓	✓	✓	✓	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓	✓	✓	✓	✓	✓	✓
<b>Other information</b>									
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓	✓	✓	✓	✓	✓	✓

**Fig. 2 – Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies included in our meta-analyses.**  
**CVD = cardiovascular disease; DVT = deep vein thrombosis; PE = pulmonary embolism.**

study, the observed prevalence of diabetes was 12% in men on ADT and 11% in men not on ADT [12], although other evidence suggests rates of diagnosed diabetes in the United States of approximately 20% [29]. We assumed rates of diabetes were 15% for men not on ADT and 30% for men on ADT. For smoking, prior evidence suggests that smoking increases the risk of CVD approximately 2.5-fold [30]. Overall, about 20% of adult men in the United States smoke [31]. We assumed that smoking rates in men not on ADT were 15% and in men on ADT were 30%.

To further identify possible sources of heterogeneity across different subgroups/patient population, we performed subgroup analyses by publication year and region for the meta-analysis focused on GnRH agonists and any type of nonfatal CVD. All analyses were performed using Stata software v. 12.

### 3. Evidence synthesis

The initial search for ADT and fatal and nonfatal CVD resulted in 108 articles via PubMed and 279 via Embase. After extracting information from the abstracts, 25 articles were selected for further investigation (Fig. 1). Three additional studies were identified via hand searches. Finally, eight studies that included different types of ADT and CVD outcomes were selected for the primary data analysis (Table 1). Based on the previously defined inclusion criteria, we excluded 19 studies. Amongst these, two did not have CVD as an outcome, two were excluded due to lack of data, six did not specify the type of ADT, seven were RCTs, and two had analysed the same data as studies that were already included in this meta-analysis [14,32–49]. One additional publication, an erratum for an already included study, was also included [50].

The random effects analysis evaluating GnRH agonists and the risk of any type of CVD indicated a RR of 1.38 (95% confidence interval [CI], 1.29–1.48) for men with PCa who were treated versus men who were not treated with ADT (Fig. 3a). The  $I^2$  statistic suggested heterogeneity ( $I^2 = 85%$ ), even though every individual estimate indicated a positive association. The “remove-one” analysis did not indicate major influences of one specific study. Both the pooled RR and the  $I^2$  did not alter dramatically upon removal of any of the included studies (results not shown). Next we analysed GnRH agonists and nonfatal IHD only, which resulted in an RR of 1.39 (95% CI, 1.26–1.54). To address potential heterogeneity in outcome, we also excluded both studies by Keating et al [12,13] and the study by Jespersen et al (15) because these analysed the risk of fatal or nonfatal CVD combined. However, the results were similar to the findings cited earlier: RR of 1.38 (95% CI, 1.27–1.50). For nonfatal IHD, the results did not change upon exclusion of these studies: RR was 1.44 (95% CI, 1.36–1.54).

When assessing publication bias, the funnel plot showed an area where missing studies are perceived that includes regions of both low and high statistical significance, suggesting that both studies that showed ADT to be nonsignificantly and significantly inversely associated with CVD were missing (Fig. 3b). Therefore, publication bias

cannot be accepted as the only cause of funnel asymmetry if it is believed that studies are being suppressed because of a mechanism based on two-sided  $p$  values. The Egger test showed an estimated bias coefficient of  $-2.72$ , with a standard error of 7.12, giving a  $p$  value of 0.7. The test thus did not provide evidence for the presence of small-study effects.

Subgroup analyses by publication year and region for the meta-analysis of GnRH agonists and any type of nonfatal CVD showed the following results. Studies published before 2010 showed an RR of 1.31 (95% CI, 1.20–1.41) and those from 2010 onwards had an RR of 1.44 (95% CI, 1.30–1.59). Studies conducted in the United States resulted in an RR of 1.41 (95% CI, 1.27–1.56), whereas those published in Europe resulted in an RR of 1.36 (95% CI, 1.23–1.51).

In analyses assessing the sensitivity of our findings to confounders, we first considered differences in diabetes. We assumed that rates of diabetes were two times higher in men on ADT (30%) than men not on ADT (15%). In this case, the association between ADT and risk of CVD would be statistically significant (RR: 1.22; 95% CI, 1.14–1.31). Even if rates of diabetes were three times higher (45% vs 15%), the difference would still be statistically significant (RR: 1.09; 95% CI, 1.02–1.17). We also considered a confounder, such as smoking status, and assumed that the prevalence of smoking was two times higher in men on ADT (30%) than in men not on ADT (15%). If 30% of men on ADT smoked, the association between ADT and risk of CVD would still be statistically significant (RR: 1.26; 95% CI, 1.18–1.36). However, if the rate of smoking amongst men on ADT was three times higher (45%), this association would no longer be statistically significant (RR: 1.01; 95% CI, 0.94–1.08).

We performed a sensitivity analysis excluding those studies where DVT and PE were the main outcome, but again the results did not alter: RR was 1.36 (95% CI, 1.27–1.47) with  $I^2 = 84%$ .

The results for other types of ADT in relation to risk of any nonfatal CVD were RR of 1.44 (95% CI, 1.28–1.62) for orchiectomy and 1.21 (95% CI, 1.07–1.367) for antiandrogens (Fig. 3c and 3d). Exclusion of those studies not making a distinction between fatal or nonfatal outcome again resulted in similar findings: RR was 1.38 (95% CI, 1.20–1.57) and 1.12 (95% CI, 1.04–1.21), respectively. The associations between GnRH agonists and nonfatal or fatal MI or stroke were even stronger: RR was 1.57 (95% CI, 1.26–1.94) and 1.51 (95% CI, 1.24–1.84), respectively (Figs. 4 and 5).

#### 3.1. Discussion

In this first meta-analysis evaluating observational studies for the association between ADT and CVD, we found that GnRH agonists were associated with a 38% increased risk of any type of nonfatal CVD compared with men with PCa not treated with ADT. For orchiectomy and antiandrogens, this increase was 44% and 21%, respectively. The associations between GnRH agonists and nonfatal or fatal MI or stroke were even stronger: 57% and 51%, respectively.

CV morbidity and mortality as a consequence of ADT in men with PCa have been the subject of several systematic reviews and meta-analyses of RCTs [6,49]. A recent pooled



**Table 1 – Description of all eight studies included in our meta-analysis using observational data for the association between androgen deprivation therapy and cardiovascular disease**

Study	Database	Year	Study type	ADT type	No. of patients	Age distribution, yr	Outcome: no. of events/no. exposed (no. of events/no. unexposed)	Main finding
Azoulay et al [14]	UKGPRD	2011	Case control	GnRH agonists, orchiectomy, antiandrogens combined androgen blockade, medical or surgical ADT	7986 men with PCa	78.5 (mean)	Nonfatal stroke: 453/4026 (361/3960)	Compared with nonusers of ADT, current users of GnRH agonists, oral antiandrogens, bilateral orchiectomy increased risk of stroke/TIA
Hu et al [16]	SEER	2012	Prospective cohort	GnRH agonists, orchiectomy	182 757 men with nonmetastatic PCa	66–69, 70–74, 75–79, 80–84, >85	Nonfatal peripheral arterial disease: 2773/91 379 (1919/91 379) Venous thromboembolism: 1227/91 379 (950/91 379)	GnRH agonists and orchiectomy are associated with an increased risk of peripheral artery disease and venous thromboembolism
Keating et al [12]	SEER	2006	Prospective cohort	GnRH agonists, orchiectomy	73 196 men with locoregional PCa	66–69, 70–74, 75–79, 80–84, >85	Nonfatal/fatal CHD: 2241/31 621 (2549/41 575) Nonfatal/fatal MI: 425/31 621 (453/41 575)	GnRH agonists associated with increased risk of incident diabetes, CHD MI, and sudden cardiac death
Keating et al [13]	US VHA	2010	Prospective cohort	GnRH agonists, orchiectomy, antiandrogens, combined androgen blockade	37 443 men with PCa	<55, 56–60, 61–65, 66–70, 71–75, >75	Nonfatal/fatal CHD: 705/14 563 (712/23 964) Nonfatal/fatal MI: 183/14 563 (177/23 964) Nonfatal/fatal stroke: 274/14 563 (271/23 964)	GnRH agonist associated with increased risk of incident CHD MI, sudden cardiac death. Combined androgen blockade associated with an increased risk of incident CHD. Orchiectomy associated with CHD and MI
Jespersen et al [15]	Danish Cancer Registry	2014	Prospective cohort	GnRH agonists, orchiectomy	31 571 men with PCa	30–59, 60–69, 70–79, ≥80	Nonfatal/fatal MI: 164/11 264 (223/20 307) Nonfatal/fatal stroke: 188/11 264 (244/20 307)	GnRH agonists associated with increased risk of MI and stroke
Martín-Merino et al [17]	UKGPRD	2011	Prospective cohort	GnRH agonists, orchiectomy, antiandrogens, combined androgen blockade	5103 men with PCa	51–69, 70–84	Nonfatal MI: 198/1455 (199/1709)	Combination therapy with GnRH agonists and antiandrogens associated with significant increases in the risk of CHD, AMI, incident HF, and hospitalized HF
Van Hemelrijck et al [10]	PcBaSE Sweden	2010	Prospective cohort	GnRH agonists, orchiectomy, antiandrogens, combined androgen blockade, medical or surgical ADT	76 601 men with PCa	<65, 65–74, ≥75	Fatal MI: 749/17 797 (139/45 058) Fatal IHD: 1309/17 797 (1591/45 958) Fatal arrhythmia: 115/17 707 (139/45 958) Fatal stroke: 335/17 797 (426/45 958) Nonfatal MI: 1293/17 797 (2252/45 958) Nonfatal arrhythmia: 1000/17 797 (2287/45 958) Nonfatal stroke: 1551/17 797 (2958/45 958) Nonfatal IHD: 2020/17 797 (3945/45 958)	Increased relative risks of nonfatal and fatal CVD found amongst all men with PCa, especially those treated with endocrine therapy
Van Hemelrijck et al [11]	PcBaSE Sweden	2010	Prospective cohort	GnRH agonists, orchiectomy, antiandrogens, combined androgen blockade, medical or surgical ADT	76 601 men with PCa	<65, 65–74, ≥75	Nonfatal DVT: 259/17 797 (331/45 958) PE: 220/17 797 (493/45 958)	All men with PCa at higher risk of thromboembolic diseases, with highest risk for those on endocrine therapy

ADT = androgen deprivation therapy; AMI = acute myocardial infarction; CHD = coronary heart disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; GnRH = gonadotropin-releasing hormone; HF = heart failure; IHD = ischemic heart disease; MI = myocardial infarction; PCa = prostate cancer; PE = pulmonary embolism; SEER = Surveillance, Epidemiology, and End Results Medicare database; TIA = transient ischemic attack; UKGPRD = UK General Practice Research Database; VHA = Veterans Health Administration.

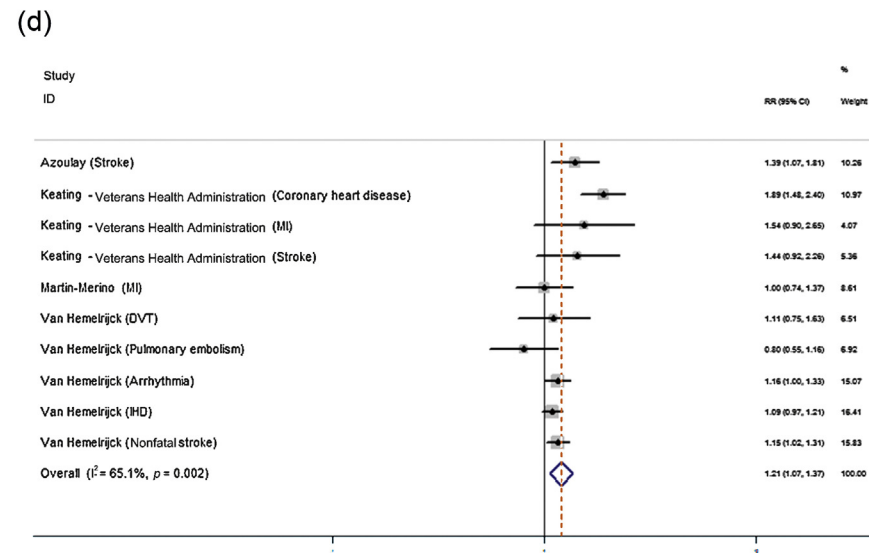
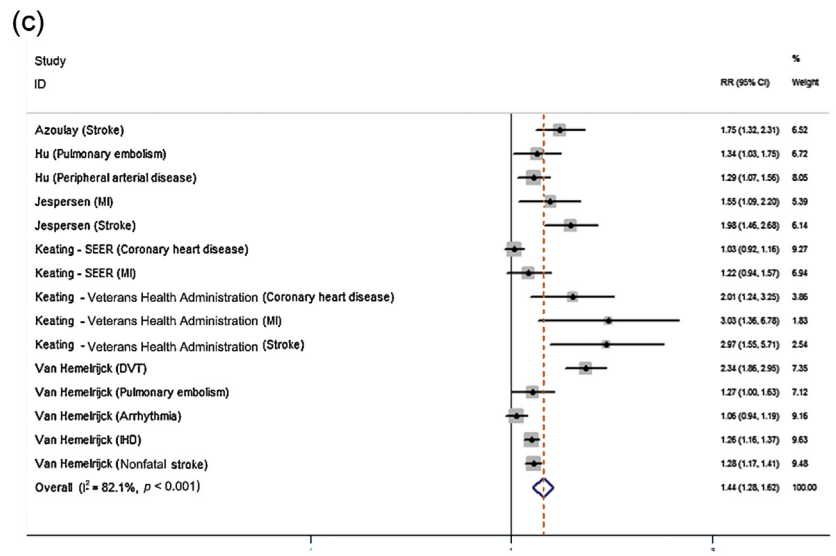
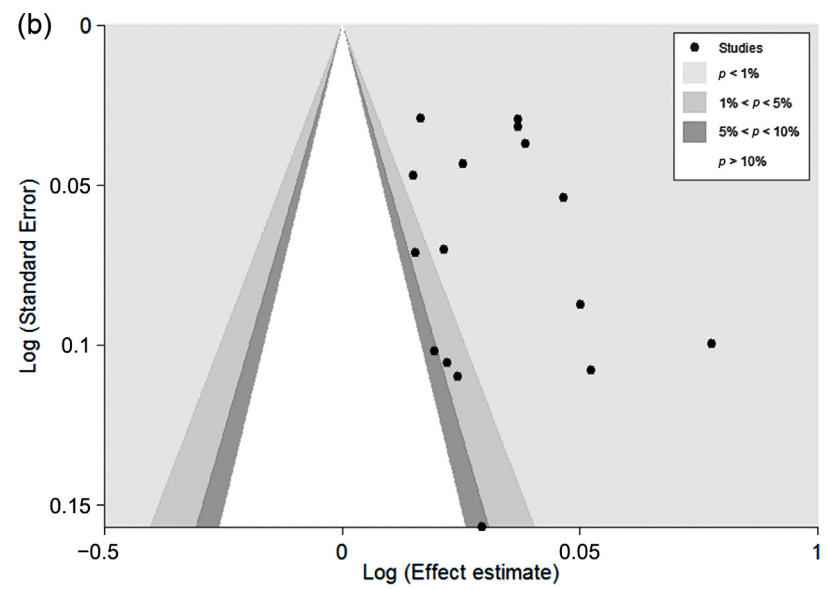
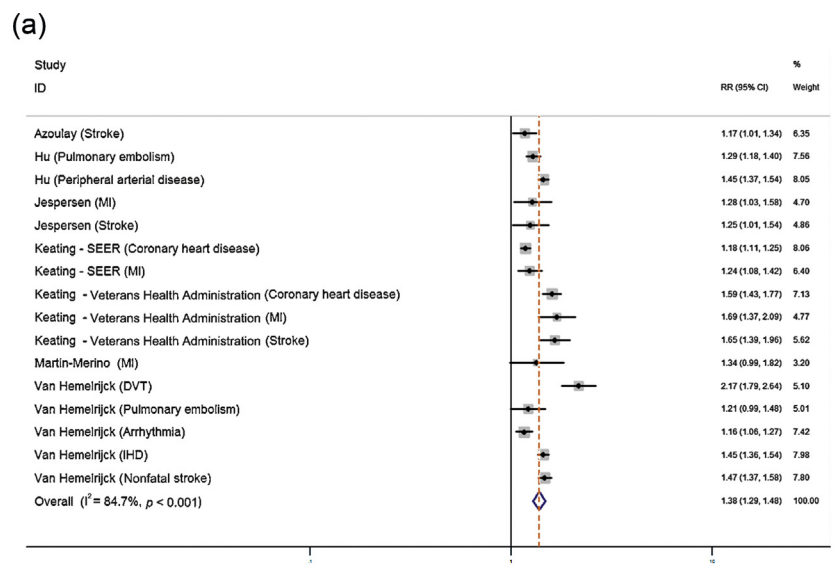
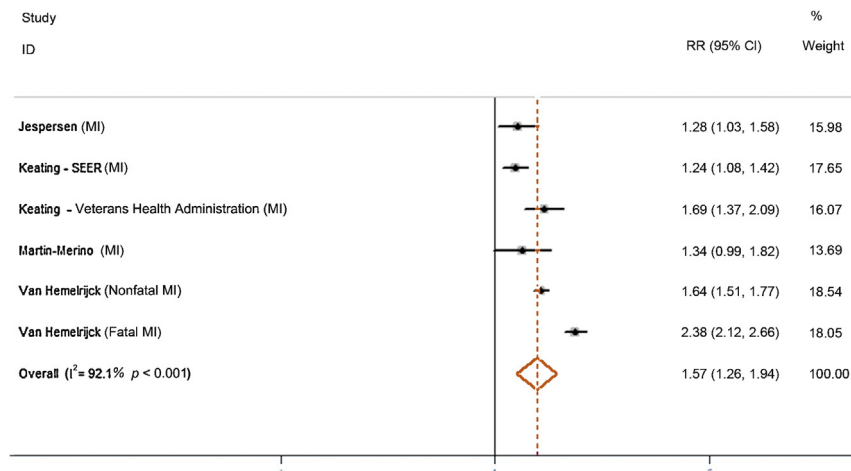


Fig. 3 – (a) Forest plot for the association between gonadotropin-releasing hormone (GnRH) agonists and nonfatal cardiovascular disease (CVD) events; (b) contour-enhanced funnel plot for the association between GnRH agonists and nonfatal CVD events; (c) forest plot for the association between orchiectomy and nonfatal CVD events; (d) forest plot for the association between antiandrogens and nonfatal CVD events. CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis; GnRH = gonadotropin-releasing hormone; IHD = ischemic heart disease; MI = myocardial infarction; RR = relative risk; SEER = Surveillance, Epidemiology, and End Results.



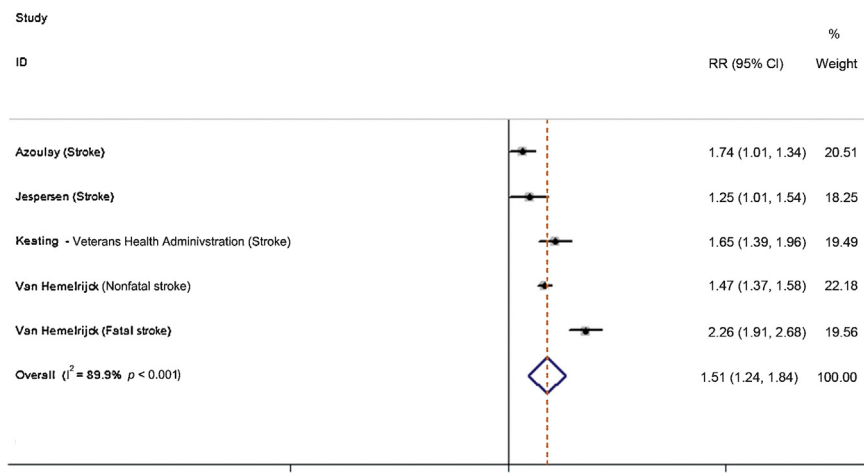
**Fig. 4 – Forest plot for the association between gonadotropin-releasing hormone agonists and nonfatal or fatal myocardial infarction.** CI = confidence interval; MI = myocardial infarction; RR = relative risk; SEER = Surveillance, Epidemiology, and End Results.

analysis of RCTs (where CVD was not the primary end point) showed that ADT was associated with early onset of fatal MI in men aged  $\geq 65$  yr or men who had been under treatment  $>6$  mo compared with those who were not receiving ADT [36]. A meta-analysis of RCTs comparing GnRH agonists versus antagonists showed that ADT may be an independent risk factor for CVD in men with preexisting CVD [9].

Our results suggest that GnRH agonists and orchiectomy have similar effects on nonfatal CVD events. Keating et al previously reported in two different publications that (1) treatment with GnRH agonists and orchiectomy, compared with no ADT, is positively associated with an increased risk of diabetes, CHD, MI, and sudden cardiac death and that (2) orchiectomy was not associated with CVD events, possibly due to small sample sizes [12,13]. In a study by Jespersen et al, MI or stroke were positively associated with GnRH agonists but not with orchiectomy [15]. Given that both treatments lead to castration androgen levels, it is to be expected that results would be similar with variations according to the number of patients being analysed, as

suggested by Keating et al [12,13]. It has been shown that human heart tissue expresses the GnRH receptor, and an experimental study on rat heart tissue showed that stimulation of the cells with GnRH agonists causes changes in the contractility of the cardiomyocytes [51,52]. Although most studies on ADT and CVD have found that ADT increases the risk of having a CVD event, more experimental and epidemiological studies are needed to differentiate the CV effects of different types of ADT.

Both indirect and direct biologic mechanisms have been suggested for the link between ADT and increased risk of CVD. The main indirect mechanism by which ADT is thought to increase the risk of CVD is by reducing circulating testosterone levels [53]. Low levels of androgens have shown to increase levels of low-density lipoprotein, triglycerides, and insulin, all defined as components of the metabolic syndrome, which is a strong risk factor for CVD [54]. In addition to the metabolic effects of testosterone, it has been proposed that testosterone may have a protective effect against the development of atheromatous plaques by causing coronary artery dilation and



**Fig. 5 – Forest plot for the association between gonadotropin-releasing hormone agonists and nonfatal or fatal stroke.** CI = confidence interval; RR = relative risk.



by inhibiting the effect of proinflammatory cytokines [55]. Normal levels of testosterone have been shown to decrease the risk of CV events compared with lower testosterone values [9]. Direct effects are thought to occur via the immune system. The GnRH receptor has been found to be expressed on T lymphocytes [56]. These cells are known to be part of atheromatous plaques, and their activation leads to interferon- $\gamma$  production and activation of macrophages causing plaque instability and increasing the risk of thromboembolic complications [57]. Experimental studies have shown that GnRH agonists can activate T lymphocytes and induce their proliferation. However, these effects were not observed when using GnRH antagonists [56,58]. These mechanisms could potentially explain the strong association we found between GnRH agonists and nonfatal or fatal MI and stroke. As suggested by experimental studies and the Albertsen et al meta-analysis [9], other types of ADT, such as GnRH antagonists, may therefore have fewer adverse effects on CVD. However, to date no observational data are yet available to analyse the association between GnRH antagonists and the risk of CVD.

In contrast to the corroborating findings from RCTs and observational studies for the association between ADT and nonfatal CVD, the findings for fatal CVD are less in agreement. Nguyen et al concluded in their RCT meta-analysis that ADT does not increase the risk of fatal CVD [6]. Using data from observational studies, our meta-analysis showed an increased risk of all MI and stroke associated with GnRH agonists (including nonfatal and fatal events), as well as in sensitivity analyses restricting to studies that explicitly focused on fatal events. Even though most studies show that ADT has an impact on the risk of CVD, inconsistent findings for fatal CVD are likely explained by the differences between the studies analysed, especially RCTs and observational studies. One has to be aware that RCTs often do not assess nonfatal events, and some observational studies do not make a distinction between fatal and nonfatal events. Most CVD events are nonfatal; thus it is more difficult for an RCT to find a positive association, particularly because men enrolled in RCTs are generally healthier than the general population and will experience fewer fatal CVD events [19]. Also, as mentioned previously, RCTs tend to exclude older patients or those with more comorbidities, whereby the latter may potentially also reflect differences in dietary and lifestyle habits associated with the risk of CVD [19]. The lower risk of CVD events amongst healthier younger and RCT patients could explain the absence of an association observed in these studies. Furthermore, these RCTs did not take into account a history of CVD, making it possible that subgroups of men with PCa with preexisting CVD could have an increased risk of a fatal CVD associated with ADT [6].

Observational studies are less expensive and easier to implement than RCTs. When conducted well and based on large and well-documented databases, the results often reflect a broader patient population and therefore may be more applicable to the general population and everyday clinical practice [59]. Although it has been reported that observational studies find stronger treatment effects than

RCTs, a more recent publication comparing results between these types of study designs showed that the estimates of the treatment effects were similar [20].

It is thus reasonable to assume that the studies included in this meta-analysis represent general populations of men with PCa: UK General Practice Research Database; PcBaSe Sweden, based on the National Prostate Cancer Register of Sweden; the US Veterans Health Administration; the Surveillance, Epidemiology, and End Results (SEER)–Medicare database; and the Danish Cancer Registry.

Nevertheless, an important limitation of observational studies is the possibility of bias introduced by selection of men to receive treatment. Men who are treated with ADT may differ from men who are not in ways that are also associated with a risk for CVD. Although most of the studies included in this meta-analysis conducted analyses adjusting for observed confounders, we could only rely on crude event rates because most studies did not provide sufficient data to allow us to account for potential confounders in our analyses. In future studies it would be of interest to add sensitivity analyses focused on specific subgroups of patients such as those with or without a history of CVD.

We made every effort to include all relevant publications available to date through various sources, including grey literature, and three main online databases. In addition, clearly defined objective criteria for exposure, outcome, and other study characteristics were specified a priori. One limitation of our study is that CVD definitions were not always available, so we had to assume they were comparable amongst the different studies. The overall results showed a rather larger amount of heterogeneity as described by the  $I^2$  statistic, but the “remove-one” analysis and sensitivity analyses as well as the direction of individual study findings suggests that our findings are robust. The funnel plot indicated that there is no publication bias and that the heterogeneity is most likely explained by other differences between the studies: study design and potential differences in underlying biologic mechanisms due to variety in the study population and exposure or outcome assessment.

Another limitation is that we could not make a distinction between patients with and without a history of CVD. This difference could have shown whether ADT increases even more the risk of CVD events in a subgroup of patients with CVD history, as previously suggested by some studies [38] but not all [60]. Information on when ADT was given (primary, (neo)adjuvant, or salvage therapy) was not available, so it was not possible to perform a subgroup analysis related to the scheduling and duration of ADT.

Limitations reported by the included studies comprise risk estimate imprecisions due to the small number of patients experiencing CVD events, incomplete data on disease stage, prostate-specific antigen and Gleason score, lack of randomisation, confounding bias, study population age restrictions, and incomplete data on CVD history.

#### 4. Conclusions

This first meta-analysis analysing observational studies showed consistent positive associations between ADT,

especially GnRH agonists and orchiectomy, and the occurrence of CVD events. This contrast with meta-findings from RCTs may be due to differences in study design. However, data from observational studies represent a broader population with fewer age and comorbidity restrictions, which can lead to more applicable results to the general population. The present study supports the need for future RCTs of PCa patients to include older patients and those with multiple comorbidities to better reflect the general population of men with PCa [19]. The differences observed for GnRH agonists and orchiectomy need to be further disentangled, both biologically and epidemiologically.

**Author contributions:** Cecilia Bosco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Van Hemelrijck, Bosnyak, Malmberg.

**Acquisition of data:** Van Hemelrijck, Bosco.

**Analysis and interpretation of data:** Van Hemelrijck, Bosco, Bosnyak, Malmberg, Adolfsson, Keating.

**Drafting of the manuscript:** Van Hemelrijck, Bosco.

**Critical revision of the manuscript for important intellectual content:** Van Hemelrijck, Bosco, Bosnyak, Malmberg, Adolfsson, Keating.

**Statistical analysis:** Van Hemelrijck, Malmberg, Adolfsson.

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**Supervision:** Van Hemelrijck, Adolfsson, Keating.

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