The Aging Male

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/itam20

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To cite this article: Justinas Jonušas, Mingailė Drevinskaitė, Aušvydas Patašius, Marius Kinčius, Ernestas Janulionis & Giedrė Smailytė (2022) Androgen-deprivation therapy and risk of death from cardio-vascular disease in prostate cancer patients: a nationwide lithuanian population-based cohort study, The Aging Male, 25:1, 173-179, DOI: 10.1080/13685538.2022.2091130

To link to this article: https://doi.org/10.1080/13685538.2022.2091130

Published online: 26 Jul 2022.

THE AGING MALE
2022, VOL. 25, NO. 1, 173–179
https://doi.org/10.1080/13685538.2022.2091130

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RESEARCH ARTICLE

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Androgen-deprivation therapy and risk of death from cardio-vascular disease in prostate cancer patients: a nationwide lithuanian population-based cohort study

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ABSTRACT

Purpose: The main purpose of this study was to evaluate the risk of CVD mortality in the national cohort of patients diagnosed with prostate cancer and treated with ADT compared with the ADT non-users.

Materials and methods: We performed a retrospective cohort study of patients aged 40–79 years and diagnosed with prostate cancer between 1 January 2012 and 31 December 2016 using the Lithuanian Cancer registry data. In total, 13 343 prostate cancer patients were included in the final study cohort who exclusively used gonadotropin-releasing hormone agonists. The primary outcomes that were registered during the follow-up of this study were overall CVD death.

Results: There was a higher risk of CVD death in the cohort of patients treated with ADT than in ADT non-users (HR 2.14, 95% CI [1.86–2.45], $p < 0.001$). Moreover, there was an increased risk of death from ischemic heart disease and stroke (HR 1.42, 95% CI [1.16–1.73] and 1.70, 95% CI [1.18–2.45], respectively) among ADT users. Finally, the risk of CVD-related mortality was highest in the 70–79 age group of ADT users (HR 4.78, 95% CI [3.79–6.04]).

Conclusions: This study shows that ADT usage is associated with increased CVD-related mortality risk for patients diagnosed with prostate cancer compared with ADT non-users. The highest mortality risk was found for ischemic heart disease and stroke. CVD-related mortality was increased in the elder group of patients also.

ARTICLE HISTORY
Received 20 January 2022
Revised 30 March 2022
Accepted 14 June 2022
Published online 24 June 2022

KEYWORDS
Prostate cancer; androgen deprivation; cardiovascular disease; mortality risk

1. Introduction

Prostate cancer is one of the most prevalent malignancy in the European male population [1]. In the most recent analysis, prostate cancer incidence rates in Lithuania were reported to be the highest globally in the period of 2008–2012 [2]. High prostate cancer incidence rates may be the result of the national prostate cancer screening program based on the serum prostate-specific antigen (PSA) testing introduced in Lithuania in 2006 [3,4].

Androgen deprivation therapy (ADT) is a "backbone therapy" for patients diagnosed with advanced, metastatic, and high-risk localized prostate cancer [5]. There are several options of ADT, such as bilateral orchidectomy, gonadotropin-releasing hormone agonist (GnRH), and antagonist, with agonist used most widely. There are many studies on association between cardiovascular event incidence ratio and ADT. For example, Keating et al. showed that usage of gonadotropin-releasing hormone agonists increases the risk of coronary heart disease (HR 1.16, 95% CI [1.10–1.21]), myocardial infarction (HR 1.11, 95% CI [1.01–1.21]), and sudden cardiac death (HR 1.16, 95% CI [1.05–1.27]) [6]. The latest study by Cone et al. showed similar results – GnRH agonist usage increased the risk of heart failure and myocardial infarction (Odds ratio (OR) 2.06 (95% CI [1.76–2.41]) and 1.80 (95% CI [1.61–2.03]) respectively) [7]. On the other hand, the EORTC study reported no statistically

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significant difference between ADT users and non-users regarding cardiovascular diseases (CVD) [8].

In large part, prostate malignancies are diagnosed in an elderly population. Usually, these males are diagnosed with CVD already [9]. A prominent South Korean population study analyzing patients diagnosed with prostate cancer reported twofold results – even though there was no correlation between ADT usage and the need for cardiovascular intervention after the cardiovascular event, the previous CVD significantly increased the risk of cardiovascular intervention in ADT users' cohort [10]. Consequently, identifying patients with CVD before ADT therapy plays an essential role in treatment optimization and decision-making for clinicians.

The main purpose of this study was to evaluate the risk of CVD mortality in the national cohort of patients diagnosed with prostate cancer and treated with ADT compared with the ADT non-users.

2. Materials and methods

We performed a retrospective cohort study of patients aged 40–79 years and diagnosed with prostate cancer between 1 January 2012 and 31 December 2016 using the Lithuanian Cancer registry data. All patients included in the study were primary patients diagnosed with prostate cancer. Lithuanian Cancer Registry is a population-based cancer registry containing information on diagnosis (cancer site, date of diagnosis, method of cancer verification) and death (date of death, cause of death) of all cancer patients in Lithuania. Lithuanian data on cancer incidence for decades have been included in the "Cancer Incidence in Five Continents", a longstanding collaboration between the International Agency for Research on Cancer and the International Association of Cancer Registries, which serves as a unique source of cancer incidence data from high-quality population-based cancer registries around the world [11].

All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database to obtain information on antiandrogens (AA) and GnRH agonists' prescriptions. NHIF system is used for the management, storage, exchange, analysis, and reporting of all the services provided by healthcare institutions. The national database contains demographic data and entries on the primary and secondary healthcare services provided, emergency and hospital admissions, and prescriptions of reimbursed medications. Data from the Lithuanian NHIF database cover the entire territory of the country [12].

Data linkage between databases was based on the personal identification code, which is unique to each resident in Lithuania.

There were 13,697 cases of prostate cancer diagnosed between 1 January 2012 and 31 December 2016 in Lithuania. Patients diagnosed with prostate cancer and whose date of prostate cancer diagnosis was equal to the date of death (267 cases) and patients treated with AA only (87 cases) were excluded from the following analysis. In total, 13,343 prostate cancer patients were included in the final study cohort. Patients who used gonadotropin-releasing hormone agonists and AA as initial treatment were included in the group of ADT users. It is worth mentioning that despite publically available treatment option with the gonadotropin-releasing hormone antagonists, none of these agents are state reimbursed, therefore not used in Lithuania. ADT non-users received standard care for prostate cancer recommended by the national treatment standards available in Lithuania (radiotherapy, surgery).

Patients were followed up from the date of diagnosis until 31 December 2019 or the date of death. The flowchart of the study design and the number of patients who have been analyzed is shown in Figure 1.

The primary outcomes that were registered during the follow-up of this study were overall CVD death (International Classification of Diseases, Tenth Revision [ICD-10]: I00-I99) and the following subtypes: ischemic heart disease (ICD-10: I20-I25) and myocardial infarction separately (ICD-10: I21), arrhythmia (ICD-10: I44-I49), heart failure (ICD-10: I50), and stroke (ICD-10: I60-I64).

Person-years at risk were calculated for each patient from the date of prostate cancer diagnosis until the end of the follow-up to estimate the risk of CVD development. Later on, Cox proportional-hazards model analysis was performed in order to evaluate the hazard ratio (HR) (with 95% CIs) of death from CVD between a group of patients diagnosed with prostate cancer and treated with ADT and those without ADT treatment. Multivariate analysis adjusted for age and stage of the disease. The ADT cumulative usage time stratified and CVD risk was estimated by dividing cumulative usage time into these intervals: 4–40 weeks, 44–104 weeks, and more than 108 weeks. Moreover, the risk of CVD death each year after prostate cancer diagnosis was also estimated in ADT users compared with the non-users group. In addition, the risk of CVD-related mortality was calculated for the 60–69 years and 70–79 years age groups. The 40–59 years age group was considered as the reference group.

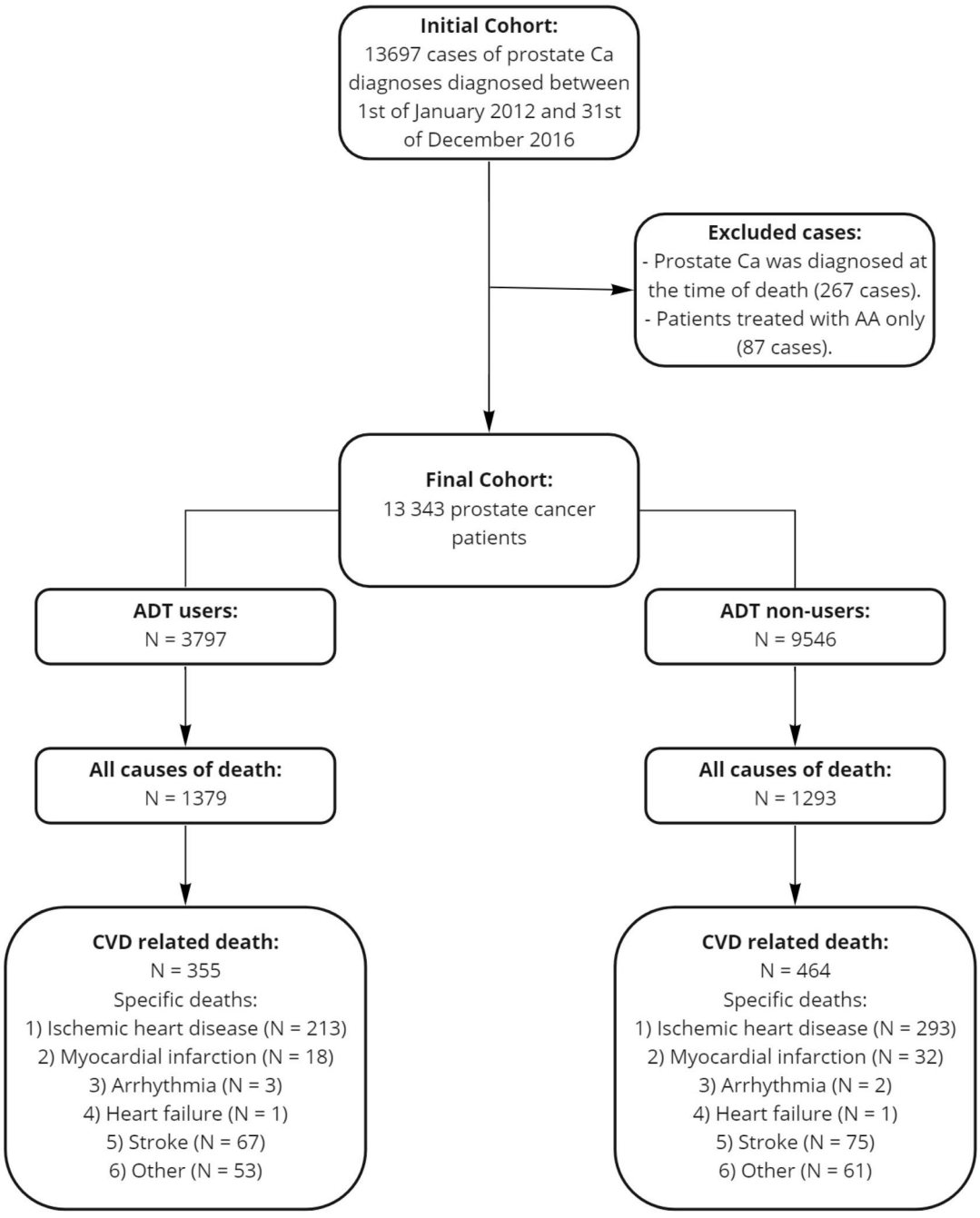

Figure 1. The flowchart of the study design and the number of patients who have been analyzed in the current study.

We determined three prostate cancer groups by cancer stage and TNM: localized (T1-T2N0M0 or stage I–II), advanced (T3-T4N0M0 or stage III), distant (any T, N1 or M1 or stage IV) and unknown.

All data for the retrospective cohort study were collected from the Lithuanian Cancer registry and NHIF databases with Vilnius regional bioethics committee approval (number 158200-16-879-388 on 28 November 2016.).

3. Results

Among the final cohort of patients, there were 3797 ADT users and 9546 ADT non-users. The mean follow-up time of ADT users was 4.63 years, while for ADT non-users, it was 5.13 years. ADT users were older than ADT non-users (67.86 years vs. 63.47 years). Detailed stage group distributions for ADT users and non-users are seen in Table 1.

Table 1. A detailed description of the final cohort of patients diagnosed with prostate cancer.

	All patients	ADT users	ADT non-users	Significance
N (%)	13343 (100.00)	3797 (28.46)	9546 (71.54)	–
Person-years	66529.62	17567.77	66529.62	
Mean follow-up time, years (SD)	4.99 (1.87)	4.63 (2.11)	5.13 (1.9)	$p < 0.05$
Mean age at diagnosis, years (SD)	64.72 (7.47)	67.86 (7.12)	63.47 (7.24)	$p < 0.05$
Stage N (%):				
Organ-confined	6851 (51.35)	1109 (29.21)	5742 (60.15)	$p < 0.05$
Locally advanced	2085 (15.63)	1312 (34.55)	773 (8.10)	$p < 0.05$
Distant	387 (2.90)	303 (7.98)	84 (0.88)	$p < 0.05$
Unknown	4020 (30.13)	1073 (28.26)	2947 (30.87)	$p < 0.05$

Table 2. Risk of CVD-related mortality in ADT user and ADT non-user cohorts. Multivariate model adjusted for stage and age groups.

	Unadjusted HR [95 % CI]	Significance	Multivariate-adjusted HR [95 % CI]	Significance
ADT non-users	1.00	Ref.	1.00	Ref.
ADT users	2.14 [1.86–2.45]	<0.001	2.03 [1.65–2.51]	<0.001

Table 3. Cumulative duration of ADT usage and risk for the development of CVD-related mortality. Multivariate model adjusted for stage and age groups.

	Unadjusted HR [95 % CI]	Significance	Multivariate-adjusted HR [95 % CI]	Significance
ADT non-users	1.00	Ref.	1.00	Ref.
4–40 weeks	2.35 [1.92–2.86]	<0.001	1.75 [1.42–2.15]	<0.001
44–104 weeks	1.85 [1.50–2.29]	<0.001	1.35 [1.08–1.68]	0.009
> 108 weeks	2.23 [1.83–2.71]	<0.001	1.51 [1.22–1.87]	<0.001

Table 4. Risk to develop the CVD-related mortality during the first five consecutive years after the diagnosis of prostate cancer in a cohort of ADT users. Multivariate model adjusted for stage and age groups.

	Unadjusted HR [95 % CI]	Significance	Multivariate-adjusted HR [95 % CI]	Significance
ADT non-users	1.00	Ref.	1.00	Ref.
≤ 12 months	1.85 [1.47–2.32]	0.021	0.99 [0.68–1.44]	0.972
≤ 2 years	2.22 [1.59–3.13]	<0.001	1.67 [1.14–2.45]	0.008
≤ 3 years	2.44 [1.75–3.41]	<0.001	1.94 [1.34–2.83]	0.001
≤ 4 years	2.65 [1.90–3.71]	<0.001	2.01 [1.39–2.91]	<0.001
> 5 years	2.15 [1.68–2.76]	<0.001	1.41 [1.07–1.85]	0.014

There was a statistically significant higher risk of CVD-related death in the cohort of patients diagnosed with prostate cancer and treated with ADT than in ADT non-users (Table 2). The unadjusted model showed more than a twofold increase in the risk (HR 2.14, 95% CI [1.86–2.45], $p < 0.001$). However, when the Cox model was adjusted for stage and age groups, a twofold increase in the risk of CVD death in the ADT user group remained, and it was statistically significant (HR 2.03, 95% CI [1.65–2.51], $p < 0.001$).

The cumulative usage time analysis showed a statistically significant higher risk for CVD-related death in all cumulative exposure groups (Table 3). However, when cumulative usage duration was adjusted for disease stage groups and patient age groups, CVD-related death risk decreased slightly but remained statistically significant.

When the risk of CVD death during the first five consecutive years was assessed in the group of patients treated with ADT, was found a higher risk of CVD death from the first to the fourth year after a prostate cancer diagnosis. The risk of CVD death five and more years after diagnosis remained twofold higher but slightly lower than in the second, third, and fourth years in the unadjusted model (Table 4). When the model was adjusted for the disease stage groups and patient age groups, it was found that there was a slight decrease in the risk of CVD death. In addition, a higher risk of CVD death was not observed during the first year after diagnosis, while from the second year, the risk of death in ADT users was significantly higher than in non-users (Table 4).

The risk of CVD-related mortality was estimated among different age groups. We have observed an

Table 5. Risk of CVD-related mortality among different age groups in a cohort of ADT users. Multivariate model adjusted for the stage.

	Unadjusted HR [95 % CI]	Significance	Multivariate-adjusted HR [95 % CI]	Significance
Age groups				
40–59	1.00	Ref	1.00	Ref
60–69	2.32 [1.83–2.95]	<0.001	2.29 [1.80–2.91]	<0.001
70–79	4.98 [3.95–6.29]	<0.001	4.78 [3.79–6.04]	<0.001

Table 6. The death risk from the specific heart diseases in a cohort of ADT users, compared to the ADT-free cohort. Multivariate model adjusted for stage and age groups.

	Unadjusted HR (95 % CI)	Significance	Multivariate-adjusted HR (95 % CI)	Significance
ADT non-users	1.00	Ref.	1.00	Ref.
Ischemic heart disease	2.03 [1.70–2.42]	<0.001	1.42 [1.16–1.73]	0.001
Myocardial infarction	1.59 [0.89–2.84]	0.114	1.02 [0.53–1.94]	0.964
Arrhythmia	4.08 [0.68–24.40]	0.124	0.95 [0.14–6.66]	0.959
Heart failure	2.75 [0.17–44.01]	0.475	2.28 [0.13–38.98]	0.569
Stroke	2.50 [1.80–3.47]	<0.001	1.70 [1.18–2.45]	0.005

almost fivefold higher risk of CVD death in the 70–79 age group of ADT users. The risk was lower among younger ADT users (60–69 years age group) but remained more than two times higher when compared with the reference male group (Table 5).

Finally, the mortality risks for the specific CVD were assessed for ADT users, compared with the ADT-free cohort. There was an increased death risk from all chosen CVD in the ADT user cohort. However, statistically significant results were obtained only in ischemic heart disease and stroke groups (Table 6). When the results were adjusted for the prostate cancer stage and age groups in multivariate analysis, an increase in death risk from ischemic heart disease and stroke remained statistically significant.

4. Discussion

The main finding of this study was that there is a higher risk of CVD death in a male population diagnosed with prostate cancer and treated with ADT compared with the ADT non-user patients diagnosed with prostate cancer. Secondly, the risk of CVD-related mortality was higher in all ADT cumulative usage groups. Moreover, the risk of CVD death was increased from the second year after the prostate cancer diagnosis. Furthermore, there is a massive increase in CVD-related mortality in the elder patient cohort. Finally, a higher risk of death from ischemic heart disease and stroke was observed in patients treated with ADT.

It has been shown in several studies that ADT usage for the treatment of advanced prostate cancer is associated with an increased risk of adverse cardiac events [6,13,14]. The adverse cardiovascular outcomes from ADT are thought to be related not only to the hypogonadism induced by the ADT treatment but also to the other factors such as prolonged QT interval, a decrease of 17β-estradiol level, increased arterial stiffness, higher insulin resistance, and suppressed lipolysis [15]. In addition, these pathological factors lead to atherosclerosis, type 2 diabetes, obesity, arterial hypertension, reduced hemoglobin levels, impotence, gynecomastia, decreased quality of life, cognitive dysfunction, and reduced bone mineral density [16,17]. Finally, these mentioned syndromes are well-known predisposing factors for CVD to manifest. Our results agree with previous studies and show that ADT added as a treatment option increases the overall risk of CVD-related death by more than twofold compared with the ADT non-users (HR 2.03, 95% CI [1.65–2.51]). Moreover, our study shows that the primary causes of CVD-related mortality during ADT treatment could be a stroke or ischemic heart disease. Death risks from these specific diseases were 42% and 70% higher, respectively, in the cohort of patients treated with ADT compared with the ADT non-users.

Keating et al. showed that the duration of ADT plays an essential role in CVD manifestation [6]. The author demonstrated that the incidence rate of CVD increases rapidly during the first 12 months after the start of ADT. A recent study by O'Farrell et al. showed the increased risk of CVD after the start of use of GnRH [14]. In the group of patients who had no previous CVD, the risk remained increased for the whole treatment duration. These data come in agreement with the meta-analysis published by D'Amico et al., who showed that the time till fatal myocardial infarction in elderly males was shorter in a group of patients diagnosed with prostate cancer and treated with ADT compared with the ADT non-users [13]. Our

investigation shows similar trends – multivariate analysis adjusted for age and disease stage shows a sharp increase in CVD-related mortality in the group of cumulative ADT treatment from 4 to 40 weeks. Giving thoughts to the observed trends that CVD deaths occur in much smaller time scale than CVD predisposing factors could occur because of ADT action, we can only agree with the notion published by Nguyen that there is a direct mechanism of ADT on cardiac outcomes [18]. However, later increase in the HR of CVD-related mortality (> 108 weeks after the start of ADT usage), we contribute to the developed afore-mentioned CVD risk factors related to the ADT usage.

One interesting aspect of our study is that we did not find a higher risk of CVD-related death during the first year after diagnosis in a cohort of males diagnosed with prostate cancer and treated with ADT. We stipulate that this may be related to the fact that ADT treatment is usually prescribed to the advanced, metastatic, or high-risk localized prostate cancer. Furthermore, according to our recent population-based study, most screened males in the Lithuanian population are detected at the early stages of prostate cancer [3]. Most of these men undergo radical prostatectomy, radiation therapy, or brachytherapy as a treatment option and are not treated with ADT. According to Milonas et al., most biochemical recurrences occur during the first year after the performed radical prostatectomy [19]. Therefore, hormone therapy is usually prescribed as a treatment modality to these patients. This comes in agreement with our results – it takes time for an advanced PC to be diagnosed, after which ADT is prescribed, and CVD-related death may manifest with risk increasing every year and reaching its peak at the fourth year.

A typical patient diagnosed with prostate cancer is an elder male who is older than 65 years [17]. Therefore, the majority of these patients have preexisting cardiovascular pathology [20]. Considering that ADT usage increases the risk of CVD-related death, elderly males become a population at risk. However, results from the before published studies show controversial results. Although Davis et al. argue that risk factors related to CVD are common among men receiving ADT, Jespersen et al. report that the risk of CVD-related death is lower for patients with preexisting CVD than those without previous CVD [21,22]. Therefore, our results show a significant, almost five-fold increase in CVD-related mortality in the elder cohort of males diagnosed with prostate cancer and treated with ADT (age group 70–79, HR 4.78 [3.79–6.04]). With such a tremendous increase in the risk of CVD death in the elderly cohort, we would like to express our notion that older males should be screened for preexisting CVD and their risk factors in order to minimize the risk of CVD-related mortality.

The main strength of this study was that this is the first paper that analyses ADT-induced CVD in the national cohort. Moreover, the study includes a decent amount of patients diagnosed with prostate cancer. Finally, our results based on real world data empower available scientific evidence. The limitations of this study are these: firstly, this is a retrospective observational study. In addition, all patients except those treated with AA only that were diagnosed with prostate cancer were included in this study, making cohorts of patients highly non-homogenous. Secondly, there is a lack of information regarding preexisting CVD and its risk factors. Moreover, there is a low number of cases of some specific CVD-related deaths (myocardial infarction, arrhythmia, heart failure), which can affect our results.

5. Conclusions

This study shows that ADT usage is associated with increased CVD-related mortality risk for patients diagnosed with prostate cancer compared with ADT non-users. The highest mortality risk was found for ischemic heart disease and stroke. In addition, an increased risk of overall CVD-related death was found in all cumulative duration groups, and from the second year after diagnosis the risk of death in ADT users was significantly higher than in non-users. Finally, we report a highly increased risk of CVD-related mortality in the elder group of patients diagnosed with prostate cancer and treated with ADT.

Disclosure statement

The authors report there are no competing interests to declare. The obtained data were anonymized, and there was no possibility to identify persons, added to the study.

Funding

This research received no external funding.

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Data availability statement

The data presented in this study are available on request from the corresponding author.

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