

Probability of Cardiovascular Death in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy (ADT): A Comprehensive Analysis

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Background. ADT, or androgen deprivation therapy, is one of the most effective treatments for prostate cancer. It works by reducing testosterone levels to levels that would cause castration either medication or surgery. ADT has been associated with a significant improvement in cancer-related survival; however, reports of cardiovascular (CV) problems connected to ADT treatment are on the rise.

Objectives. To demonstrate the risk of cardiovascular death in patients with prostate cancer treated with ADT.

Methods. This study demonstrated compliance with the parameters set forth by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. With this search strategy, articles published between 2014 and 2024 were taken into consideration. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, SagePub, and Google Scholar. Review articles, previously published works, and partially completed works were all selected not to be considered.

Results. We found 221 papers in the PubMed database, 47 articles on SagePub, and 9050 items on Google Scholar as a result of our search. 7287 records were removed before screening, hence 2030 articles were received for review. Following a record-exclusion screening, we assembled ten publications in total. Five studies that fulfilled the requirements were included.

Conclusion. ADT is frequently a crucial component of the treatment of prostate cancer; patients should also receive counselling regarding their elevated risk of cardiovascular events and should think about taking preventative measures to lower that risk.

Keywords: Androgen deprivation therapy, prostate cancer, cardiovascular mortality.

Introduction

Androgen deprivation therapy (ADT) is the standard of care for men diagnosed with unfavourable-risk prostate cancer who are treated with definitive radiation therapy (RT). ADT is administered for 4 to 6 months for intermediate-risk disease and 18 to 36 months for high-risk illness. The use of ADT in this setting may have been linked to an increased risk of a number of cardiovascular end points, such as diabetes, coronary artery disease, myocardial infarction, stroke, transient ischemic attack, and cardiovascular death, according to a

number of previous reports, including observational data and a secondary analysis of randomized trials. Nonetheless, alternative research has yielded conflicting results and has not established a connection of any kind between ADT and the risk of cardiac death. ADT's potential cardiovascular toxicity remains unclear, however a number of theories have been brought out, including the possibility of metabolic changes brought on by low testosterone levels and the instability of atherosclerotic plaques as a result of gonadotropin receptor agonists directly stimulating immune cells [1].

The most important treatment for advanced prostate cancer is ADT. Numerous regimens, such as gonadotropin-releasing hormone (GnRH) agonists and antagonists, anti-androgens, and androgen receptor inhibitors, have become the standards of care in advanced prostate cancer treatment. The basic principle of ADT for advanced prostate cancer is ongoing androgen blocking, which is maintained even in the late castration-resistant stage. As a result, the longer an advanced prostate cancer patient lives, the longer ADT treatment is administered. Extended use of ADT will result in more problems even though it improves overall survival. In relation to androgen loss, decreased libido, gynecomastia, weight gain, cognitive deficit, overactive bladder, metabolic disorders (hyperglycemia, hyperlipidemia, cardiovascular events), and skeletal related problems were the most often reported side events linked to ADT. Considering their potentially fatal nature and effects, subgroup investigations focused mostly on cardiovascular events [2].

Over the past few decades, there has been a lot of research done on the function of androgens in the CV system. It has long been thought that the primary androgen, testosterone, raises the risk of cardiovascular disease (CVD); studies have shown that men are twice as likely as women to get CVD. Nevertheless, this gender disparity diminishes when women go through menopause, and it is generally acknowledged that the premenopausal estrogen's cardioprotective function plays a major part in this gender disparity. However, there is still some debate over testosterone's effects on the heart [3]. According to certain retrospective studies, men who use supplemental testosterone are more likely to experience cardiovascular events, indicating that high testosterone levels may actually hasten the onset of CVD. On the other hand, low or insufficient endogenous testosterone has also been linked to a higher risk of CVD, an adverse metabolic profile, and a detrimental effect on the cardiovascular system, suggesting that testosterone has complicated and possibly bimodal effects on the cardiovascular system [4].

Materials and Methods

In order to ensure that this study complied with the requirements, the author followed the guidelines established by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. To make sure that the results derived from the investigation are correct, this is done.

In this study, we investigate the disparities in the risk of cardiovascular death among patients with prostate cancer treated with androgen deprivation therapy. Researching or exploring the risk of cardiovascular death in patients with prostate cancer treated with androgen deprivation therapy is achievable. The main objective of this study is to demonstrate the significance of the challenges that have been recognized.

To be eligible to participate in the study, researchers had to choose articles that met the following requirements: The study must be prepared in English and assess the risk of cardiovascular death in individuals with prostate cancer receiving androgen deprivation therapy. The manuscript must fulfil both of these conditions in order to be considered for publication. A few of the examined studies had been published after 2014, but prior to the time frame considered relevant by this systematic review.

We used "risk of cardiovascular mortality in prostate cancer patients managed with androgen deprivation therapy." as keywords. Using the PubMed and SagePub databases, the search for studies to be included in the systematic review was conducted by entering the terms: (("Prostate cancer"[MeSH Subheading] OR "Androgen deprivation therapy"[All Fields] OR "Treatment of prostate cancer" [All Fields]) AND ("management of prostate cancer"[All Fields] OR "Benefit of androgen deprivation therapy"[All Fields]) AND ("Risk factor of cardiovascular mortality with androgen deprivation therapy"[All Fields]) OR ("Cardiovascular mortality in prostate cancer"[All Fields]) used in searching the literature.

Upon reviewing each study abstract and title, the authors conducted an analysis to ascertain if the research met the inclusion requirements. Subsequently, the authors determined which prior studies to include as references in their paper and selected those that were appropriate. All submissions must be made in English and must not have been published elsewhere.

The publications included in the systematic review were limited to those that met all of the inclusion criteria. As a result, only relevant results remain after the reduction in the number of results. The findings of any study that does not meet our standards are not taken into consideration. Subsequently, an extensive analysis of the research findings will be conducted. Names, authors, publication dates, locations, study activities, and parameters were among the details that came to light during the investigation conducted for this study.

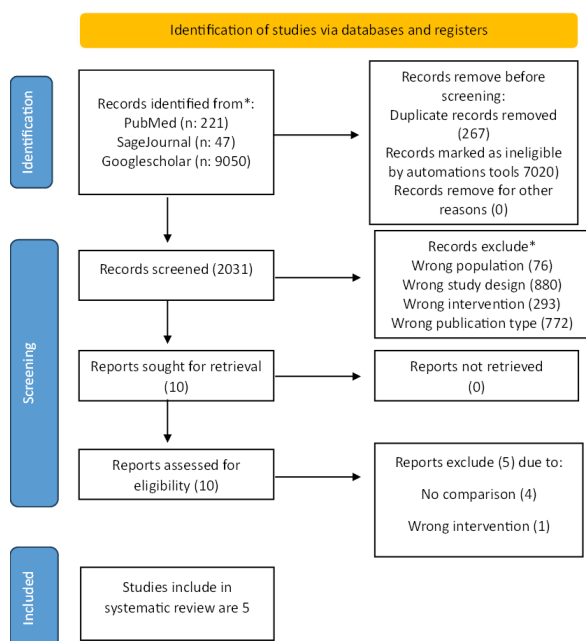


Figure 1. Flowchart for article search

Results and Discussions

We obtained 221 articles from the PubMed database, 47 articles from SagePub, and 9050 items from Google Scholar as a result of our search. We receive 2030 items for screening since 7287 records were removed prior to screening. Following a record-exclusion screening, we assembled ten publications in total. Five studies that satisfied the requirements were included.

According to Forster, RB *et al.* (2022), there is evidence linking ADT for nonmetastatic PCa to an increased risk of CVD events, particularly in patients who had some CVD risk factors at the time of diagnosis and were receiving treatment for a longer period of time [5]. Patients receiving ADT also had greater all-cause mortality, according to our findings. Nonetheless, additional research utilizing more comprehensive cancer data, particularly about cancer aggressiveness, is required to ascertain the clinical significance of these results in relation to the overall advantages of ADT. When planning a treatment for patients, clinicians should carefully assess the advantages and disadvantages of ADT, possibly taking early management for CVD risk factors into account.

GnRH agonists and degarelix were linked to a higher risk of cardiovascular disease, according to research by Cardwell, CR *et al.* (2020). According to this study, degarelix use is associated with an elevated risk of cardiovascular disease. Further research is warranted as the cause of this connection is not well understood [6].

When compared to ADT non-users, Jonusas, J. *et al.* (2022) showed that ADT usage is linked to a

higher risk of CVD-related death among individuals diagnosed with prostate cancer [7]. Stroke and ischemic heart disease were determined to carry the highest mortality risk. Furthermore, all cumulative duration groups had an increased risk of death from CVD, and starting in the second year following diagnosis, ADT users had a significantly higher risk of death than non-users. Lastly, in the older cohort of patients with prostate cancer diagnosed and receiving ADT treatment, we find a markedly elevated risk of mortality from CVD.

According to Li, Y. *et al.* (2022), there was no correlation between ADT and a higher risk of major cardiovascular events among males of Southeast Asian descent who got curative radiation, when two forms of propensity score adjustments were included [8].

The Middle East and Lebanon are known to have a high prevalence of CV risk factors, and Hassan, MA *et al.* (2022) demonstrated that this is the first study on cardiac risks and events in patients on ADT from these regions [9]. The study discovered that among this Middle Eastern patient cohort, one-third had coronary artery disease at baseline, and 9.5% had recorded cardiac events. Additionally, a noteworthy proportion of the population had CV risk factors at the time of ADT beginning. Our study draws attention to the shortcomings in the evaluation of CV risk for this high-risk subset of prostate cancer patients. Prior to beginning ADT therapy, risk and resource-stratified algorithms are required for the best possible CV health. To maximize patient treatment, cardiologists, urologists, and oncologists must work together more and establish referral protocols and increased awareness.

In terms of cancer incidence and cancer-related mortality among American men, prostate cancer (PCa) ranks second in the country. High 5-year survival rates, nearly 100%, are observed for localized and regional PCa. Since prostate cancer seldom spreads to other organs and results in mortality, active surveillance has shown to be a successful long-term treatment plan. ADT, on the other hand, is the mainstay of treatment for prostate cancer that has developed, and it can be highly successful in bringing blood testosterone levels down to castrate levels in as few as 2-4 weeks. ADT has been linked to a higher incidence of CV adverse events, despite its great results. In addition to other adverse effects, it has been discovered that patients have an increased risk of myocardial infarction (MI), stroke, hypertension (HTN), and arrhythmia. In men with prostate cancer, cardiovascular disease (CVD) is the second most common cause of death, and two-thirds of patients have an elevated risk of CVD [10,11].

Table 1. The articles included in this study

Author	Method	Sample Size	Result
Forster, RB et al., 2022⁵	Longitudinal cohort study	30923	8449 (27%) of the 30 923 PCa patients that were included in our study received main ADT. For CVD events and death, the mean follow-up was 2.9 and 3.8 years, respectively. We determined a correlation between ADT and the following conditions: heart failure (1.23: 1.13-1.35), myocardial infarction (1.18: 1.05-1.32), stroke (1.21: 1.06-1.38), and composite CVD (adjusted HR 1.13: 95% CI 1.05-1.21). For more than seven months, these correlations remained in people with low to intermediate CVD risk and ADT. All-cause mortality and ADT were found to be correlated, particularly in patients with moderate CVD risk and prolonged treatment duration.
Cardwell, CR et al., 2020⁶	Cohort study	22366	During 73,570 people, during which time there were 3,853 cardiovascular incidents, the cohort of 20,216 patients with prostate cancer was monitored. An increase in cardiovascular events of 30% was linked to ADT (adjusted HR=1.3 95% CI 1.2, 1.4). Adjusted HR=1.3 95% CI 1.2, 1.4 for GnRH agonists and HR=1.5 95% CI 1.2, 1.9 for degarelix, but not for bicalutamide monotherapy (adjusted HR=1.0 95% CI 0.82, 1.3) indicated increases in cardiovascular events.
Jonusas, J et al., 2022⁷	Retrospective cohort study	13343	Compared to ADT non-users, the cohort of patients receiving ADT had a greater risk of suffering from CVD (HR 2.14, 95% CI [1.86–2.45], p <0.001). In addition, ADT users had a higher risk of suffering from ischemic heart disease and stroke (HR 1.42, 95% CI [1.16–1.73] and 1.70, 95% CI [1.18–2.45]). Lastly, the age group of ADT users aged 70–79 had the highest risk of death from CVD (HR 4.78, 95% CI [3.79–6.04]).
Li, Y et al., 2022⁸	Prospective study	1940	Patients who underwent either RT alone (n = 494) or RT plus ADT (n = 1446) between 2000 and 2019 were included in the analysis. The cumulative incidence of MACE at 1, 3, and 9 years was 1.2, 5 and 16.2% in the RT group and 1.1, 5.2 and 17.6% in the RT+ ADT group, respectively, following a median follow-up of 10 years (RT) and 7.2 years (RT+ ADT). The incidence of MACE did not differ between the two groups (HR 1.01, 95% CI 0.78–1.30, p = 0.969). Eighty percent of patients had pre-treatment CV risk factors, and cardiovascular disease (15.9%) was the second highest cause of death, behind prostate cancer (21.1%). Older age, being Indian or Malay, having pre-existing CV risk factors, and having a history of MACE were all linked to a higher risk of MACE on univariate analysis. Multivariable analysis showed no significant changes in MACE risk between the RT+ADT and RT groups after propensity score adjustments.
Hassan, MA et al., 2022⁹	Retrospective study	234	ADT therapy was administered to 234 patients with prostate cancer who were treated in a tertiary care facility in Lebanon. The study was done retrospectively. CV incidents on ADT and baseline CV risk variables were examined. The age range with a median of 68 years was 48–92 years. At diagnosis, 49.6% of patients had stage 4 illnesses, and their median time on ADT was 12 months. Within our group, 24.4% had a body mass index greater than 30, 52.1% had smoked before, 25.6% had diabetes, 19.7% had experienced coronary artery disease, 9.8% had experienced heart failure, and 52.9% had hypertension. At baseline, less than half of the patients had a lipid profile that had been documented. Following the start of ADT, 22 individuals (9.5%) had reported cardiac incidents.

For men with intermediate/high-risk or locally advanced prostate cancer (PCa), external-beam radiation therapy (RT) combined with ADT

employing GnRH agonist therapy reduces cancer-specific mortality and, in certain situations, all-cause mortality. GnRH agonist therapy use has

significantly grown in the past 20 years among men with PCa, including those with lower stage disease and older men with major competing causes of mortality. This is partly because of the established survival benefit in intermediate/high-risk disease. But because the risk-benefit ratio is less clear in these patient populations, caution has been raised regarding the use of ADT with special consideration given to those who are least likely to benefit (lower risk disease with fewer competing causes of mortality) and those who are most likely to be harmed (significant comorbidities like high-risk cardiovascular status) [12,13].

Male hypogonadism has often been linked to a poorer metabolic profile and an elevated risk of CVD. It is crucial to note that there is still a lot of disagreement on the latter association. Low testosterone (T) in particular, which is seen in patients at higher risk for cardiovascular disease (CVD), may be an adaptive protective mechanism that shuts down T-dependent processes (including sexual and/or reproductive activity) when a patient's physical health deteriorates. Consequently, a substantial amount of research has shown that acute or long-term medical conditions may disrupt the hypothalamic-pituitary-testis axis, which may result in the emergence of primary or, more commonly, secondary hypogonadism [14].

GnRH agonists and antagonists may differ in their effects on cardiovascular risk, which is an interesting finding. Unlike GnRH agonists, which predominantly reduce LH, GnRH antagonists suppress both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This could have an impact on how these substances affect fat accumulation, lipid metabolism, and endothelial function. Remarkably, a recent pooled study of six randomized controlled trials discovered that the risk of cardiac events was twice as high for men receiving GnRH agonist treatment than for men receiving GnRH antagonist treatment among men with pre-existing CVD. Prospective studies are required to provide more conclusive information about which type of ADT is best for men with the highest cardiovascular risk, even though they are hypothesis generating [15].

Not a single prospective trial has conclusively shown that exposure to ADT raises the risk of CVD or CV mortality, despite well-established negative effects on CV risk factors and a potential link between ADT exposure and increased CV morbidity. Nonetheless, the overwhelming body of research indicates that men with pre-existing cardiovascular disease (CVD), such as a history of myocardial infarction or congestive heart failure, are most at risk of experiencing CV events when exposed to ADT, particularly in the first six months after ADT

initiation. Therefore, frequent monitoring is necessary [15,16].

Conclusions

ADT is frequently a crucial component of the treatment of prostate cancer; patients should also receive counselling regarding their elevated risk of cardiovascular events and should think about taking preventative measures to lower that risk.

Conflict of interest

The authors declare no conflict of interest.

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