Is Androgen Deprivation Therapy for Prostate Cancer Associated with Cardiovascular disease ? A Meta-Analysis and systematic review.

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Abstract

Background: Whether androgen deprivation therapy (ADT) is associated with an increased risk of developing cardiovascular related disease is poorly defined. The aim of the present meta-analysis is to explore the relationship between ADT and the risk of cardiovascular disease (CVD). **Method:** For this systematic review and meta-analysis, we searched databases until April 2019 for randomized controlled trial (RCT) or observational studies that reported data on ADT administration and cardiovascular disease (CVD) incidence. The relationship was evaluated through estimate relative risk ratio (RR) and 95% confidence intervals (CIs) **Result:** A statistically significant difference was detected for acute myocardial infarction (AMI) (RR = 1.13; 95% CI, 1.10–1.15; $P < 0.05$) including a total of 142,186 cases and 174,404 controls. Significant difference between coronary heart disease (CHD) and ADT was also observed, with summary (RR=1.11; 95% confidence interval CI: 1.10-1.13), from 157,339 ADT users and 349,636 non-ADT users of 7 eligible studies. **Conclusions:** Pooled result demonstrated that ADT could significantly increase the risk of CHD, AMI and sudden cardiac death (SCD). Various ADT modalities have different impact on cardiovascular disease risk in different level. Our meta-analysis also suggests that the application of ADT in prostate cancer patients for over 5 years resulted in a significant increase in cardiovascular morbidity. Moreover, subgroup analyses for different types of ADT indicated that compared with the individual administration of ADT, GnRH plus AA (oral anti-androgens) is more likely significantly lead to AMI.

Background

Recognized as the most commonly diagnosed disease in male, the incidence and mortality of prostate cancer have been increasing in recent years [1, 2]. This situation can be attributed to population aging, improvement of diagnostic tools and the national surveillance programs for early prostate cancer detection [3].

Nearly half of the patients who were diagnosed prostate cancer (PCa) receive androgen deprivation therapy (ADT) [4] and commonly suffer from adverse side effects which would lead to the decline in quality of life (QOL)[5]. Owing to improvements in diagnosis and treatment of cancer, the quantity of prostate cancer survivors is increasing [6]. However, most of survivors are burdened with continuous adverse effects of ADT including cardiovascular complications.[7, 8] Keating et al[9] first reported an excess risk of acute myocardial infarction (AMI), sudden cardiac death (SCD) in a large group of patients for men 66 years or older. Since then several observational studies and randomized controlled trials have also assessed the association between risk of cardiovascular events and ADT, yet have demonstrated equivocal findings [10-12].

Nonetheless, there are considerable disagreements on the association between ADT and cardiovascular disease. Nanda et al. [13] indicated that all-cause mortality and coronary heart disease (CHD) specifically only happened in patients with preexisting CVD. Marti'n-Merino[14] demonstrated individual ADT therapy does not appear to increase the risk of CVD outcomes, only the combination of oral anti-androgens(AA) and Luteinizing Hormone Releasing Hormone (LHRH) is associated with significant increase in risk of cardiovascular disease[14]. Therefore, it is necessary to perform a meta-analysis of long duration of follow-up, large-scale studies with high quality of implementation and design.

Several meta-analysis have focused on ADT related cardiovascular mortality and morbidity through processing data from trials with different primary end points [15, 16]. However, investigators were not able to stratify the outcome by different kinds of ADT. Besides, the former meta-analysis did not detect a statistically significant difference between AMI and CHD, classification bias and insufficient data on such safety secondary outcomes prevent an explicit conclusion.

In light of uncertainties about this clinical issue and the limitations exist in former meta-analysis of for adverse-effect research, we performed a systematic review of existing literatures in bibliographic databases to further explore the relationship between the application of ADT for AMI, CVD, and SCD respectively.

Full Text

Is Androgen Deprivation Therapy for Prostate Cancer Associated with Cardiovascular disease ? A Meta-Analysis and systematic review.

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Abstract

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Conclusions: Pooled result demonstrated that ADT could significantly increase the risk of CHD, AMI and sudden cardiac death (SCD). Various ADT modalities have different impact on cardiovascular disease risk in different level. Our meta-analysis also suggests that the application of ADT in prostate cancer patients for over 5 years resulted in a significant increase in cardiovascular morbidity. Moreover, subgroup analyses for different types of ADT indicated that compared with the individual administration of ADT, GnRH plus AA (oral anti-androgens) is more likely significantly lead to AMI.

1. Background

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Nearly half of the patients who were diagnosed prostate cancer (PCa) receive androgen deprivation therapy (ADT) [4] and commonly suffer from adverse side effects which would lead to the decline in quality of life (QOL)[5]. Owing to improvements in diagnosis and treatment of cancer, the quantity of prostate cancer survivors is increasing [6]. However, most of survivors are burdened with continuous adverse effects of ADT including cardiovascular complications.[7, 8] Keating et al[9] first reported an excess risk of acute myocardial infarction (AMI), sudden cardiac death (SCD) in a large group of patients for men 66 years or older. Since then several observational studies and randomized controlled trials have also assessed the association between risk of cardiovascular events and ADT, yet have demonstrated equivocal findings [10-12].

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2. Method

The systematic literature review (SLR) was reported and conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement and the Cochrane Collaboration[17]. The systematic review includes electronic search in the Ovid versions of Pubmed, Embase, and Web of Science. A literature search was performed for studies published up to March 28th 2019 by two researchers independently. Any uncertainty about inclusion was checked by a third researcher. The search was not limited by geographic region or country; however, it was limited to English publications. The main key words used for search were: prostate cancer or prostate tumor or prostate carcinoma, androgen and deprivation or androgen suppression or endocrine treatment; and cardiovascular or myocardial infarction or coronary heart disease or cardiac death or heart disease. All identified publications went through a three-step parallel review of title, abstract, and full text, based on predefined exclusion criteria and inclusion criteria. Reviews of included studies were searched

manually to find out additional eligible studies. The author was contacted when the clinical trial method or results were unclear or sufficient data was not reported.

2.1 Study selection

Studies were included in our meta-analysis if (1) the type of study should be population-based cohort observation study or case control study with no subject selection bias; (2) both the experimental group and randomized controlled trials (RCT) were clearly prespecified, SCD, CHD and AMI were assessed as outcomes; (3) included studies had to provide sufficient data for the calculation of risk estimates with 95% confidence intervals (CIs); (4) ADT type for included patients should be specified in article; (5) baseline cardiac comorbidity should be separated from newly emerging cardiovascular disease.

2.2 Quality Assessment and Data extraction

Quality assessment of the included studies was evaluated through the Newcastle-Ottawa quality assessment scale (NOS) for observational study, a 9-item measure designed for observational studies with a focus on data quality, sample representativeness, and appropriateness of analysis with scores of <7 indicated low-quality studies and ≥ 7 indicated high-quality[18]. As for the included RCT studies, Cochrane Collaboration's tool for risk of bias was performed[19]. We evaluated the quality of each study by assessing the risk of bias in 7 domains: study participation and attrition, prognostic factor measurement, outcome measurement, confounding measurement, and statistical analysis and reporting. For each study, the criteria listed on the checklist was rated as a low, unclear, or high risk of bias. The evaluation was performed by two authors independently, and disagreements were resolved by discussion. The risk of bias summary and risk of bias graph were generated through Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009, Copenhagen, Denmark)

Data was extracted from the included studies independently by two sensors in this study. The following data will be extracted: details of study (year, design, total number of participants, number of ADT users, number of control group, follow-up duration) details of participants (median age, country/region outcomes measure of AMI, CHD and SCD).

2.3 Statistical Analysis

Statistics analyses were conducted using the pooled data unless otherwise stated. To assess the heterogeneity of the included studies, Cochran's Q and I^2 tests were used. An $I^2 > 50\%$ or $P < 0.05$ were defined as statistical significance. When more than one type of ADT were respectively compared with the same control group in one study, the random-effects model was then used for data analysis to combine different types of ADT groups. The effect of ADT compared with no ADT on the risk of CHD amongst men with PCa was quantified by computing the pooled risk ratio (RR) with 95% confidence interval (CI) through a random-effects model. Forest plots were generated to display the RR estimates for each study. Meta-analysis was subgrouped according to type of ADT. ADT was assigned into different types of treatment: orchiectomy, GnRH agonists, anti-androgens, and anti-androgens plus GnRH agonists. The data analyses were performed using STATA version 14.0 and Review Manager (version 5.2; The Cochrane Collaboration, Oxford).

2.4 Subgroups Analyses

To analyze the source of heterogeneity and potential factors, the random-effects model was also applied in the subgroups analysis. $P < 0.01$ was defined as statistically significant for subgroup analysis. We performed the subgroup meta-analysis on the various types of ADT (e.g. GnRH, AA, GnRH + AA and Orchiectomy) vs non-ADT to minimize existing heterogeneity.

3. Results

3.1 Literature Search and Characteristics

Figure 1 represents a flowchart demonstrated the selection process that met our criteria aforementioned, a total of 1541 potential records were initially identified from Embase, Pubmed and Web of Science through the search terms listed above. A total of 1541 articles were screened, out of which 531 duplicate studies were excluded. 50 were considered closely correlated to the concept of this study and underwent full text review. 14 studies were removed because they did not mention AMI, CHD or SCD as outcomes. 2 were excluded due to lack of data, 7 studies were excluded because ADT duration was shorter than 6 months, 6 did not specifically report the type of ADT. Additionally, we remove 9 retrospective researches from our study, 2 were excluded for using the same databases as studies that were already included. In the end, 8 articles were included in our meta-analysis of AMI[9, 14, 20-25], representing a total population of 316,590 patients. 7[9, 14, 21-23, 26, 27] studies were included in the CHD analysis, representing a total of 529,357 patients. 5 studies [12, 20, 21, 28, 29] were included in the SCD analysis, representing a total of 182,403 patients. All included studies were of observational design and published between 2008 and 2017. In the references of the primarily selected articles no additional articles were eligible with potential data for the meta-analysis.

Details of the included studies are summarized in Tables 1, which lists the basic characteristics of the included studies for SCD AMI and CHM. Quality assessment of observational studies was conducted via NOS and included studies were demonstrated to be of high quality. Information on RCT study quality is presented in Figure 2. The overall methodological quality of the included studies was high and no research was excluded for low quality.

3.2 Association between ADT and AMI

The subgroup analysis result indicated that the source of heterogeneity was due to the variation of ADT. 8 studies were identified to explore the relationship between ADT and AMI. The result indicated that the application of ADT for prostate cancer was associated with the risk of AMI. (RR = 1.13; 95% CI, 1.10–1.15; $P < 0.05$) (Figure 3) Data from 4 studies were eligible for AA [9, 14, 23, 24] subgroup-analyses; 3 [9, 14, 23] were available for GnRH plus AA, 4 [9, 14, 21, 23] for GnRH and 5 [9, 14, 21, 23, 25] for orchiectomy. Among 142,186 ADT users, 13,270 (9.3%) developed AMI compared with 15,598 events (8.9%) among 174,404 non-ADT users. Subgroup analysis by different type of ADT for meta-analysis showed the following results. A significant association was observed between AMI and AA (RR = 1.41; 95% CI, 1.24–1.59; $P < 0.05$); GnRH (RR = 1.20; 95% CI, 1.17–1.22; $P < 0.05$); GnRH plus AA (RR = 2.47; 95% CI 2.34–2.61; $P < 0.05$); orchiectomy (RR = 1.43; 95% CI 1.33–1.54; $P < 0.05$). (Figure 4) The I^2 statistic indicated heterogeneity ($I^2 = 95\%$), even though every individual estimate suggested a positive association.

3.3 Association between ADT and CHD

A total of 506,975 from 7 studies [9, 14, 21–23, 26, 27] were participated in study investigating the relationship between ADT and CHD. A significantly increased CHD risk was found in the prostate cancer patients treated with ADT. (RR = 1.11; 95% confidence interval CI: 1.10–1.13); (Figure 5) data from 5 studies [9, 14, 23, 26, 27] were eligible for AA subgroup-analyses. 4 [9, 14, 23, 27] reported data about GnRH plus AA; 5 [9, 14, 21, 23, 27] for GnRH and 5 [9, 14, 21, 23, 26] for orchiectomy. Among 157,339 ADT users, 22,382 (14.2%) developed CHD compared with 32,863 events (9.3%) among 349,636 non-ADT users. Significant association was found in every type of ADT, except for AA (RR = 0.94; 95% CI, 0.89–1.00; $P < 0.05$); GnRH (RR = 1.16; 95% CI, 1.14–1.18; $P < 0.05$); GnRH plus AA (RR = 1.77; 95% CI 1.66–1.88; $P < 0.05$); orchiectomy (RR = 1.37; 95% CI, 1.30–1.45; $P < 0.05$) respectively. (Figure 6)

3.4 Association between ADT and SCD

The relationship between ADT and SCD was also investigated in our study. A total of 822,403 events were identified, including 11,096 from 79,881 ADT users and 12,263 from 102,522 WW/AS (watchful waiting/ active surveillance) groups. The RRs for each study for different kinds of ADT are shown in Figure 7. We identified that ADT are related to increased incidence of SCD, the sum of included studies are quite limited so that it is difficult to perform a subgroup analysis based on different type of ADT (RR = 1.23; 95% CI 1.20–1.26; $P < 0.05$) (Figure 7).

3.5 Subgroup by duration of ADT

In order to reduce the impact of inconsistent endpoints on our conclusion, whether the duration of ADT application was associated with a significant effect on the risk of CVD events was also explored in our study. The included studies were separated into different groups based on the duration of ADT application, and we define the 5 year as the cut-off value. 3 studies [20, 21, 24] with 53,115 ADT users and 53,124 controls were assigned into the group with ADT application longer than 5 years, and others were distributed to the group with ADT application shorter than 5 years. For results of a subgroup meta-analysis of prospective cohort studies revealed a significant positive association between duration of ADT application and the incident for AMI. Pooled data suggested the incidence of AMI in >5 year group was 17.6% higher than that from <5 year group. (RR = 1.87, 95% CI: 1.81–1.92, $P < 0.05$, for >5 year group) (RR = 1.32, 95% CI: 1.24–1.40, $P < 0.05$ for ≤5 year group). As for the CHD group, the amount of included studies is quite limited so the subgroup analysis was not performed.

Discussion

Controversies still exist with potential risk of the concomitant use of ADT which remains to be solved in this new era. To the best of our knowledge, this is the first comprehensive assessment of the association between ADT and cardiovascular risk performed by meta-analysis based on different types of ADT and makes a distinction among SCD, AMI and CHD. Similar to the results of this present analysis, another meta-analysis [15] exploring the relationship between cardiovascular disease and ADT, 6 trials with a total number of 8282 patients showed that ADT is associated with both cardiovascular mortality (CVM) and CVD, especially GnRH alone and GnRH plus AA can significantly increase the incidence of cardiovascular events in PCa patients. O'Farrell et al. [26] indicated an invariable increase in risk of CVD in men with PCa treated with a GnRH agonist in a large observational study when compared with a matched PCa-free group. Similarly, Bosco et al. [30] revealed an increased risk of non-fatal CVD events (MI and stroke) in patients treated with ADT, particularly GnRH agonists, compared with those who do not receiving ADT (relative risk [RR] 1.38, 95% CI 1.29–1.48).

Our results suggest that the application of all kinds of ADT for prostate cancer was associated with AMI; long-term use of GnRH plus AA can significantly increase the risk of major adverse cardiac events such as AMI compared with the others. AA alone can only significantly increase

the incident of AMI, but have little impact on CHD. The pooled results for the duration of the ADT application investigation revealed that taking ADT more than 5 years leads to an increase in the risk of AMI. Both the individual use of GnRH agonists and orchiectomy could increase the risk of cardiac adverse effect significantly, and the risk of CHD was similar for men treated with GnRH agonists and men treated with orchiectomy. Three prior studies [20, 31, 32] are distinctly discordant with our result, demonstrating that AA use is not associated with an excess risk of AMI. The discordance was likely due to their small number of end points. In addition, several other studies reported that although the combination treatment with GnRH agonists and orchiectomy is positively associated with an increased risk of CHD, AMI, and SCD, orchiectomy alone was not associated with CHD events [33, 34]. This may owe to men treated with orchiectomy were older, presented with more advanced stage of prostate cancer and had more comorbidities, which in turn influenced the risk of endpoint [35]. The variation in inclusion criteria of patients and duration of ADT application may also contribute to the inconsistency, as suggested by Keating et al.[9]. Furthermore, three studies [36-38] did not report an association between ADT and cardiovascular related death, for the previous or later ADT users were not ruled out of consideration in control group.

The application of GnRH remains to be the cornerstone of management for patients with prostate cancer. However, there are many consequences of androgen deprivation including decreasing in physical function; reducing quality of life[39]; bone mineral density (BMD) loss [40, 41]; and increasing risk of metabolic [42]. Metabolic syndrome (MS) is known as a risk factor for cardiovascular disease[43]. Most data, predominantly derived from GnRH agonists was found to have an association between ADT and increase of triglyceride and LDL levels. Previous researches [44, 45] showed that deficiency of testosterone was thought to decrease lean body mass and increase fat, decrease glucose tolerance and increase insulin resistance, all of which could generate a state similar to the metabolic syndrome. The occurrence of metabolic syndrome would lead to the development of atherosclerosis which would accelerate the progress of cardiovascular events[46]. Besides, GnRH agonists is thought to have an indirectly impact on development of CHD by increasing the risk of metabolic changes such as dyslipidemia hyperglycemia, and obesity which are also well-established causal risk factors for the development of atherosclerosis [47]. Furthermore, it has been proved that human heart tissue express the GnRH receptor, and a basic study on rat heart tissue demonstrated that stimulation of the cells with GnRH agonists causes progression in the contractility of the cardiomyocyte [48].

Orchiectomy can lead to a low level of testosterone and it remains unclear how low testosterone levels trigger major cardiovascular events. Callou de Sá et al.[49] indicated that men with CHD have higher oestradiol and FEI levels. As a matter of fact, elevated level estrogen can increase heart attack risk by accelerating coagulation and platelet aggregation in coronary arteries[50]. The direct evidence provided by Thomsen et al. [33], comparing the impact of GnRH and orchiectomy on cardiovascular disease revealed that GnRH agonists do not increase the risk of CHD in comparison to orchiectomy. Although further studies are needed to determine whether interventions like orchiectomy that raise estrogen levels might have an impact on CHD disease risk in men, cautions are warranted for caregivers that they should consider the serious risk of CHD complications when deciding the type of androgen deprivation therapy for patient with prostate cancer.

From our subgroup analysis for the duration of ADT indicated that increasing duration of ADT was associated with an excess risk of AMI. In an observational study, Efsthathiou et al.[28] found no evidence to prove that longer-term ADT with a GnRH increased cardiovascular mortality compared with short-term in men with locally advanced prostate cancer. Bolla et al. [51] performed a random control study, one to receive short-term androgen suppression, and the other to receive 2-5 years of further treatment, the result revealed that overall mortality was higher with short-term than with long-term deprivation. As their endpoint was prostate cancer specific mortality and other efficacy endpoints, they draw a conclusion that overall quality of life did not differ significantly between the two groups. Evidence indicated that short-term ADT (3–6 months) results in the development of insulin resistance without causing hyperglycemia [52]. However, long-term ADT over 12 months is associated with hyperglycemia, frank diabetes, and metabolic syndrome all of which are risk factors for cardiovascular disease[53]. The optimum duration of ADT application should be adapted to comorbid conditions and risk factors of individual patients.

In our analysis, we found the application of ADT was also associated with excess cardiovascular mortality. Nguyen et al. [40] indicated the application of ADT is connected with a significantly increased risk of CAD, AMI, and, particularly, SCD in patients with non-metastatic PCa. This finding is corroborated by our study. However, multiple previous studies fail to demonstrate a correlation between ADT and the risk of CVD mortality. One of an important reason is most of these aforementioned studies are designed retrospectively, which means population included in these studies are relied on historical cohorts. In addition Nanda et al. [54] suggested that the excess SCD with ADT seemed to happen in only the first 6 to 24 months after. A significant improvement in prostate cancer-specific survival and overall survival was also detected for the administration of ADT. Therefore, periodic cardiovascular evaluation is required for patients before underwent ADT treatment.

Some intrinsic limitations in this meta-analysis should be taken into account in this study. First, unnegligible limitation of our study is that the CHD definitions of some included studies were not explicit so we had to hypothesize they were comparable amongst the different studies. Second, current meta-analysis included very few studies in every subgroup analysis which means publication bias could not be excluded as funnel plots included only 4 or 5 studies, besides, they suffered from substantial heterogeneity which could be related to methodological parameters and population characteristics. Third, our analysis pooled together both RCTs and observational studies, and subgroup analyses based on study design were not also performed in the AMI and CHD subgroup, because all the included studies are designed observationally for

the AMI and CHD subgroup. Fourth, data in some included studies are not provided completely, so we have to calculate the RRs by ourselves, this may affect the overall result of our study to some extent.

5. Conclusion

Pooled result demonstrated that ADT could significantly increase the risk of CHD, AMI, and SCD. In addition, our results support the hypothesis that the various ADT modalities have different impact on CVD risk in different level. Our meta-analysis also suggested that the application of ADT in prostate cancer patients for over 5 years resulted in a significant increase in cardiovascular morbidity. Moreover, subgroup analysis for different types of ADT indicated that compared with the individual administration of ADT, GnRH plus AA is more likely significantly lead to AMI. Therefore, ADT is associated with a significant negative impact on quality of life. Special attention and periodic cardiovascular assessment are required for these patients. More epidemiological and experimental studies are needed to differentiate the CVD effects on different types of ADT.

6. Conflict of interests: The authors declare that there are no conflicts of interest.

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8. Tables and figures legends

Table 1. Characteristics of randomized included studies

Figure 1. Article selection

Figure 2. Risk of bias for the included RCT studies

Figure 3. Acute myocardial infarction risk associated with ADT

Figure 4. RRs of acute myocardial infarction Related to different type of ADT.

Figure 5. Coronary heart disease risk associated with ADT

Figure 6. RRs of coronary heart disease Related to different type of ADT.

Figure 7. Sudden cardiac death risk associated with ADT

Figure 8. RRs of acute myocardial infarction Related to different duration of ADT application.

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Methods

The systematic literature review (SLR) was reported and conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement and the Cochrane Collaboration[17]. The systematic review includes electronic search in the Ovid versions of Pubmed, Embase, and Web of Science. A literature search was performed for studies published up to March 28th 2019 by two researchers independently. Any uncertainty about inclusion was checked by a third researcher. The search was not limited by geographic region or country; however, it was limited to English publications. The main key words used for search were: prostate cancer or prostate tumor or prostate carcinoma, androgen and deprivation or androgen suppression or endocrine treatment; and cardiovascular or myocardial infarction or coronary heart disease or cardiac death or heart disease. All identified publications went through a three-step parallel review of title, abstract, and full text, based on predefined exclusion criteria and inclusion criteria. Reviews of included studies were searched manually to find out additional eligible studies. The author was contacted when the clinical trial method or results were unclear or sufficient data was not reported.

2.1 Study selection

Studies were included in our meta-analysis if (1) the type of study should be population-based cohort observation study or case control study with no subject selection bias; (2) both the experimental group and randomized controlled trials (RCT) were clearly prespecified, SCD, CHD and AMI were assessed as outcomes; (3) included studies had to provide sufficient data for the calculation of risk estimates with 95% confidence intervals (CIs); (4) ADT type for included patients should be specified in article; (5) baseline cardiac comorbidity should be separated from newly emerging cardiovascular disease.

2.2 Quality Assessment and Data extraction

Quality assessment of the included studies was evaluated through the Newcastle-Ottawa quality assessment scale (NOS) for observational study, a 9-item measure designed for observational studies with a focus on data quality, sample representativeness, and appropriateness of analysis with scores of <7 indicated low-quality studies and ≥ 7 indicated high-quality[18]. As for the included RCT studies, Cochrane Collaboration's tool for risk of bias was performed[19]. We evaluated the quality of each study by assessing the risk of bias in 7 domains: study

participation and attrition, prognostic factor measurement, outcome measurement, confounding measurement, and statistical analysis and reporting. For each study, the criteria listed on the checklist was rated as a low, unclear, or high risk of bias. The evaluation was performed by two authors independently, and disagreements were resolved by discussion. The risk of bias summary and risk of bias graph were generated through Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009, Copenhagen, Denmark)

Data was extracted from the included studies independently by two censors in this study. The following data will be extracted: details of study (year, design, total number of participants, number of ADT users, number of control group, follow-up duration) details of participants (median age, country/region outcomes measure of AMI, CHD and SCD).

2.3 Statistical Analysis

Statistics analyses were conducted using the pooled data unless otherwise stated. To assess the heterogeneity of the included studies, Cochran's Q and I^2 tests were used. An $I^2 > 50\%$ or $P < 0.05$ were defined as statistical significance. When more than one type of ADT were respectively compared with the same control group in one study, the random-effects model was then used for data analysis to combine different types of ADT groups. The effect of ADT compared with no ADT on the risk of CHD amongst men with PCa was quantified by computing the pooled risk ratio (RR) with 95% confidence interval (CI) through a random-effects model. Forest plots were generated to display the RR estimates for each study. Meta-analysis was subgrouped according to type of ADT. ADT was assigned into different types of treatment: orchiectomy, GnRH agonists, anti-androgens, and anti-androgens plus GnRH agonists. The data analyses were performed using STATA version 14.0 and Review Manager (version 5.2; The Cochrane Collaboration, Oxford).

2.4 Subgroups Analyses

To analyze the source of heterogeneity and potential factors, the random-effects model was also applied in the subgroups analysis. $P < 0.01$ was defined as statistically significant for subgroup analysis. We performed the subgroup meta-analysis on the various types of ADT (e.g. GnRH, AA, GnRH + AA and Orchiectomy) vs non-ADT to minimize existing heterogeneity.

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Data was extracted from the included studies independently by two censors in this study. The following data will be extracted: details of study (year, design, total number of participants, number of ADT users, number of control group, follow-up duration) details of participants (median age, country/region outcomes measure of AMI, CHD and SCD).

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Statistics analyses were conducted using the pooled data unless otherwise stated. To assess the heterogeneity of the included studies, Cochran's Q and I^2 tests were used. An $I^2 > 50\%$ or $P < 0.05$ were defined as statistical significance. When more than one type of ADT were respectively compared with the same control group in one study, the random-effects model was then used for data analysis to combine different types of ADT groups. The effect of ADT compared with no ADT on the risk of CHD amongst men with PCa was quantified by computing the pooled risk ratio (RR) with 95% confidence interval (CI) through a random-effects model. Forest plots were generated to display the RR estimates for each study. Meta-analysis was subgrouped according to type of ADT. ADT was assigned into different types of treatment: orchiectomy, GnRH agonists, anti-androgens, and anti-androgens plus GnRH agonists. The data analyses were performed using STATA version 14.0 and Review Manager (version 5.2; The Cochrane Collaboration, Oxford).

2.4 Subgroups Analyses

To analyze the source of heterogeneity and potential factors, the random-effects model was also applied in the subgroups analysis. $P < 0.01$ was defined as statistically significant for subgroup analysis. We performed the subgroup meta-analysis on the various types of ADT (e.g. GnRH, AA, GnRH + AA and Orchiectomy) vs non-ADT to minimize existing heterogeneity.

Results

3.1 Literature Search and Characteristics

Figure 1 represents a flowchart demonstrated the selection process that met our criteria aforementioned, a total of 1541 potential records were initially identified from Embase, Pubmed and Web of Science through the search terms listed above. A total of 1541 articles were screened, out of which 531 duplicate studies were excluded. 50 were considered closely correlated to the concept of this study and underwent full text review. 14 studies were removed because they did not mention AMI, CHD or SCD as outcomes. 2 were excluded due to lack of data, 7 studies were excluded because ADT duration was shorter than 6 months, 6 did not specifically report the type of ADT. Additionally, we remove 9 retrospective researches from our study, 2 were excluded for using the same databases as studies that were already included. In the end, 8 articles were included in our meta-analysis of AMI [9, 14, 20-25], representing a total population of 316,590 patients. 7 [9, 14, 21-23, 26, 27] studies were included in the CHD analysis, representing a total of 529,357 patients. 5 studies [12, 20, 21, 28, 29] were included in the SCD analysis, representing a total of 182,403 patients. All included studies were of observational design and published between 2008 and 2017. In the references of the primarily selected articles no additional articles were eligible with potential data for the meta-analysis.

Details of the included studies are summarized in Tables 1, which lists the basic characteristics of the included studies for SCD AMI and CHM. Quality assessment of observational studies was conducted via NOS and included studies were demonstrated to be of high quality. Information on RCT study quality is presented in Figure 2. The overall methodological quality of the included studies was high and no research was excluded for low quality.

3.2 Association between ADT and AMI

The subgroup analysis result indicated that the source of heterogeneity was due to the variation of ADT. 8 studies were identified to explore the relationship between ADT and AMI. The result indicated that the application of ADT for prostate cancer was associated with the risk of AMI. (RR = 1.13; 95% CI, 1.10–1.15; $P < 0.05$) (Figure 3) Data from 4 studies were eligible for AA [9, 14, 23, 24] subgroup-analyses; 3 [9, 14, 23] were available for GnRH plus AA, 4 [9, 14, 21, 23] for GnRH and 5 [9, 14, 21, 23, 25] for orchiectomy. Among 142,186 ADT users, 13,270 (9.3%) developed AMI compared with 15,598 events (8.9%) among 174,404 non-ADT users. Subgroup analysis by different type of ADT for meta-analysis showed the following results. A significant association was observed between AMI and AA (RR = 1.41; 95% CI, 1.24–1.59; $P < 0.05$); GnRH (RR = 1.20; 95% CI, 1.17–1.22; $P < 0.05$); GnRH plus AA (RR = 2.47; 95% CI 2.34–2.61; $P < 0.05$); orchiectomy (RR = 1.43; 95% CI 1.33–1.54; $P < 0.05$). (Figure 4) The I^2 statistic indicated heterogeneity ($I^2 = 95\%$), even though every individual estimate suggested a positive association.

3.3 Association between ADT and CHD

A total of 506,975 from 7 studies [9, 14, 21-23, 26, 27] were participated in study investigating the relationship between ADT and CHD. A significantly increased CHD risk was found in the prostate cancer patients treated with ADT. (RR = 1.11; 95% confidence interval CI: 1.10-1.13); (Figure 5) data from 5 studies [9, 14, 23, 26, 27] were eligible for AA subgroup-analyses. 4 [9, 14, 23, 27] reported data about GnRH plus AA; 5 [9, 14, 21, 23, 27] for GnRH and 5 [9, 14, 21, 23, 26] for orchiectomy. Among 157,339 ADT users, 22,382 (14.2%) developed CHD compared with 32,863 events (9.3%) among 349,636 non-ADT users. Significant association was found in every type of ADT, except for AA (RR = 0.94; 95% CI, 0.89–1.00; $P < 0.05$); GnRH (RR = 1.16; 95% CI, 1.14–1.18; $P < 0.05$) GnRH plus AA (RR = 1.77; 95% CI 1.66–1.88; $P < 0.05$); orchiectomy (RR = 1.37; 95% CI, 1.30–1.45; $P < 0.05$) respectively. (Figure 6)

3.4 Association between ADT and SCD

The relationship between ADT and SCD was also investigated in our study. A total of 822,403 events were identified, including 11,096 from 79,881 ADT users and 12,263 from 102,522 WW/AS (watchful waiting/ active surveillance) groups. The RRs for each study for different kinds of ADT are shown in Figure 7. We identified that ADT are related to increased incidence of SCD, the sum of included studies are quite limited so that it is difficult to perform a subgroup analysis based on different type of ADT (RR=1.23; 95% CI 1.20–1.26; $P < 0.05$) (Figure 7).

3.5 Subgroup by duration of ADT

In order to reduce the impact of inconsistent endpoints on our conclusion, whether the duration of ADT application was associated with a significant effect on the risk of CVD events was also explored in our study. The included studies were separated into different groups based on the duration of ADT application, and we define the 5 year as the cut-off value. 3 studies [20, 21, 24] with 53,115 ADT users and 53,124 controls were assigned into the group with ADT application longer than 5 years, and others were distributed to the group with ADT application shorter than 5 years. For results of a subgroup meta-analysis of prospective cohort studies revealed a significant positive association between duration of ADT application and the incident for AMI. Pooled data suggested the incidence of AMI in >5 year group was 17.6% higher than that from <5 year group. (RR = 1.87, 95%CI: 1.81–1.92, $P < 0.05$, for >5 year group) (RR = 1.32, 95%CI: 1.24–1.40, $P < 0.05$ for ≤5 year group). As for the CHD group, the amount of included studies is quite limited so the subgroup analysis was not performed.

Discussion

Controversies still exist with potential risk of the concomitant use of ADT which remains to be solved in this new era. To the best of our knowledge, this is the first comprehensive assessment of the association between ADT and cardiovascular risk performed by meta-analysis based on different types of ADT and makes a distinction among SCD, AMI and CHD. Similar to the results of this present analysis, another meta-analysis [15] exploring the relationship between cardiovascular disease and ADT, 6 trials with a total number of 8282 patients showed that ADT is associated with both cardiovascular mortality (CVM) and CVD, especially GnRH alone and GnRH plus AA can significantly increase the incidence of cardiovascular events in PCa patients. O'Farrell et al. [26] indicated an invariable increase in risk of CVD in men with PCa treated with a GnRH agonist in a large observational study when compared with a matched PCa-free group. Similarly, Bosco et al. [30] revealed an increased risk of non-fatal CVD events (MI and stroke) in patients treated with ADT, particularly GnRH agonists, compared with those who do not receiving ADT (relative risk [RR] 1.38, 95% CI 1.29–1.48).

Our results suggest that the application of all kinds of ADT for prostate cancer was associated with AMI; long-term use of GnRH plus AA can significantly increase the risk of major adverse cardiac events such as AMI compared with the others. AA alone can only significantly increase the incident of AMI, but have little impact on CHD. The pooled results for the duration of the ADT application investigation revealed that taking ADT more than 5 years leads to an increase in the risk of AMI. Both the individual use of GnRH agonists and orchiectomy could increase the risk of cardiac adverse effect significantly, and the risk of CHD was similar for men treated with GnRH agonists and men treated with orchiectomy. Three prior studies [20, 31, 32] are distinctly discordant with our result, demonstrating that AA use is not associated with an excess risk of AMI. The discordance was likely due to their small number of end points. In addition, several other studies reported that although the combination treatment with GnRH agonists and orchiectomy is positively associated with an increased risk of CHD, AMI, and SCD, orchiectomy alone was not associated with CHD events [33, 34]. This may owe to men treated with orchiectomy were older, presented with more advanced stage of prostate cancer and had more comorbidities, which in turn influenced the risk of endpoint [35]. The variation in inclusion criteria of patients and duration of ADT application may also contribute to the inconsistency, as suggested by Keating et al. [9]. Furthermore, three studies [36–38] did not report an association between ADT and cardiovascular related death, for the previous or later ADT users were not ruled out of consideration in control group.

The application of GnRH remains to be the cornerstone of management for patients with prostate cancer. However, there are many consequences of androgen deprivation including decreasing in physical function; reducing quality of life [39]; bone mineral density (BMD) loss [40, 41]; and increasing risk of metabolic [42]. Metabolic syndrome (MS) is known as a risk factor for cardiovascular disease [43]. Most data, predominantly derived from GnRH agonists was found to have an association between ADT and increase of triglyceride and LDL levels. Previous researches [44, 45] showed that deficiency of testosterone was thought to decrease lean body mass and increase fat, decrease glucose tolerance and increase insulin resistance, all of which could generate a state similar to the metabolic syndrome. The occurrence of metabolic syndrome would lead to the development of atherosclerosis which would accelerate the progress of cardiovascular events [46]. Besides, GnRH agonists is thought to have an indirectly impact on development of CHD by increasing the risk of metabolic changes such as dyslipidemia hyperglycemia, and obesity which are also well-established causal risk factors for the development of atherosclerosis [47]. Furthermore, it has been proved that human heart tissue express the GnRH receptor, and a basic study on rat heart tissue demonstrated that stimulation of the cells with GnRH agonists causes progression in the contractility of the cardiomyocyte [48].

Orchiectomy can lead to a low level of testosterone and it remains unclear how low testosterone levels trigger major cardiovascular events. Callou de Sá et al.[49] indicated that men with CHD have higher oestradiol and FEI levels. As a matter of fact, elevated level estrogen can increase heart attack risk by accelerating coagulation and platelet aggregation in coronary arteries[50]. The direct evidence provided by Thomsen et al. [33], comparing the impact of GnRH and orchiectomy on cardiovascular disease revealed that GnRH agonists do not increase the risk of CHD in comparison to orchiectomy. Although further studies are needed to determine whether interventions like orchiectomy that raise estrogen levels might have an impact on CHD disease risk in men, cautions are warranted for caregivers that they should consider the serious risk of CHD complications when deciding the type of androgen deprivation therapy for patient with prostate cancer.

From our subgroup analysis for the duration of ADT indicated that increasing duration of ADT was associated with an excess risk of AMI. In an observational study, Efsthathiou et al.[28] found no evidence to prove that longer-term ADT with a GnRH increased cardiovascular mortality compared with short-term in men with locally advanced prostate cancer. Bolla et al. [51] performed a random control study, one to receive short-term androgen suppression, and the other to receive 2-5 years of further treatment, the result revealed that overall mortality was higher with short-term than with long-term deprivation. As their endpoint was prostate cancer specific mortality and other efficacy endpoints, they draw a conclusion that overall quality of life did not differ significantly between the two groups. Evidence indicated that short-term ADT (3–6 months) results in the development of insulin resistance without causing hyperglycemia [52]. However, long-term ADT over 12 months is associated with hyperglycemia, frank diabetes, and metabolic syndrome all of which are risk factors for cardiovascular disease[53]. The optimum duration of ADT application should be adapted to comorbid conditions and risk factors of individual patients.

In our analysis, we found the application of ADT was also associated with excess cardiovascular mortality. Nguyen et al. [40] indicated the application of ADT is connected with a significantly increased risk of CAD, AMI, and, particularly, SCD in patients with non-metastatic PCa. This finding is corroborated by our study. However, multiple previous studies fail to demonstrate a correlation between ADT and the risk of CVD mortality. One of an important reason is most of these aforementioned studies are designed retrospectively, which means population included in these studies are relied on historical cohorts. In addition Nanda et al. [54] suggested that the excess SCD with ADT seemed to happen in only the first 6 to 24 months after. A significant improvement in prostate cancer-specific survival and overall survival was also detected for the administration of ADT. Therefore, periodic cardiovascular evaluation is required for patients before underwent ADT treatment.

Some intrinsic limitations in this meta-analysis should be taken into account in this study. First, unnegligible limitation of our study is that the CHD definitions of some included studies were not explicit so we had to hypothesize they were comparable amongst the different studies. Second, current meta-analysis included very few studies in every subgroup analysis which means publication bias could not be excluded as funnel plots included only 4 or 5 studies, besides, they suffered from substantial heterogeneity which could be related to methodological parameters and population characteristics. Third, our analysis pooled together both RCTs and observational studies, and subgroup analyses based on study design were not also performed in the AMI and CHD subgroup, because all the included studies are designed observationally for the AMI and CHD subgroup. Fourth, data in some included studies are not provided completely, so we have to calculate the RRs by ourselves, this may affect the overall result of our study to some extent.

Conclusions

Pooled result demonstrated that ADT could significantly increase the risk of CHD, AMI, and SCD. In addition, our results support the hypothesis that the various ADT modalities have different impact on CVD risk in different level. Our meta-analysis also suggested that the application of ADT in prostate cancer patients for over 5 years resulted in a significant increase in cardiovascular morbidity. Moreover, subgroup analysis for different types of ADT indicated that compared with the individual administration of ADT, GnRH plus AA is more likely significantly lead to AMI. Therefore, ADT is associated with a significant negative impact on quality of life. Special attention and periodic cardiovascular assessment are required for these patients. More epidemiological and experimental studies are needed to differentiate the CVD effects on different types of ADT.

Declarations

Conflict of interests: The authors declare that there are no conflicts of interest.

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Tables

Table 1. Characteristics of randomized included studies

First author	Year	Country/region	Types of ADT	Treatment in control group	Definition of CVD	No. of ADT	No. Of Control	Age y(median/average)	Follow up(y)	Study type	NOS
Alibhai	2009	Canada	ADT	non-ADT	CHD/SCD	19079	19079	75	6.47	observational	7
Bolla	2010	France	GnRH agonist	RP	SCD	107	203	ADT:71 non-ADT:70	9.1	RCT	
Efstathiou	2009	USA	GnRH agonist	RP	SCD	477	468	70	8.1	RCT	
Farrel	2015	Sweden	AA; GnRH agonist; Orchiectomy; AA GnRH + AA	non-ADT	CHD	41362	187785	ADT:73.7 non-ADT:75.3	4	observational	9
Gandaglia	2014	Italy	GnRH agonist; Orchiectomy	non-ADT	CHD/AMI/SCD	59994	82535	median: 73 average:73.6	6.28	observational	9
Haque	2017	USA	ADT	non-ADT	CHD/AMI	2170	5457	NR	3.4	observational	9
Hemelryck	2010	UK	GnRH agonist; AA; GnRH + AA; Orchiectomy	RP	CHD/AMI	30642	45958	NR	4.1	observational	8
Iversen	2010	USA	AA	non-ADT	AMI	4052	4061	64.5	9.7	RCT	
Jespersen	2013	Denmark	GnRH/AA; Orchiectomy	non-ADT	AMI	11264	20307	71	3.3	observational	7
Keating	2009	USA	GnRH agonist AA; GnRH + AA; Orchiectomy	WW/AS	CHD/AMI/SCD	14579	22846	66.9	2.6	observational	9
Merino	2011	Spain	GnRH agonist AA; GnRH + AA; Orchiectomy	WW/AS	CHD/AMI	406	594	51	NR	observational	9
Robinson	2010	Sweden	GnRH agonist; AA; GnRH + AA	non-ADT	CHD	8168	30883	NR	1.9	observational	7
Roach	2008	USA	GnRH agonist AA	RP	SCD	224	232	70	13.2	RCT	

Figures

Figure 1

Article selection

Figure 2

Risk of bias for the included RCT studies

Figure 3

Acute myocardial infarction risk associated with ADT

Figure 4

RRs of acute myocardial infarction Related to different type of ADT

Figure 5

Coronary heart disease risk associated with ADT

Figure 6

RRs of coronary heart disease Related to different type of ADT

Figure 7

Sudden cardiac death risk associated with ADT

Figure 8

RRs of acute myocardial infarction Related to different duration of ADT application