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Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer

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Abstract

Androgen deprivation therapy (ADT) is a central part of prostate cancer (PCa) treatment. Pharmacologic androgen deprivation includes gonadotropin-releasing hormone (GnRH) agonism and antagonism, androgen receptor inhibition, and CYP17 inhibition. Studies in the past decade have raised concerns about the potential for ADT to increase the risk of adverse cardiovascular events such as myocardial infarction, stroke, and cardiovascular mortality, possibly by exacerbating cardiovascular risk factors. In this review, we summarize existing data on the cardiovascular effects of ADT. Among the therapies, abiraterone stands out for increasing risk of cardiac events in meta-analyses of both RCTs and observational studies. We find a divergence between observational studies, which show consistent positive associations between ADT use and cardiovascular disease, and randomized controlled trials (RCTs), which do not show these associations reproducibly.

Graphic Abstract

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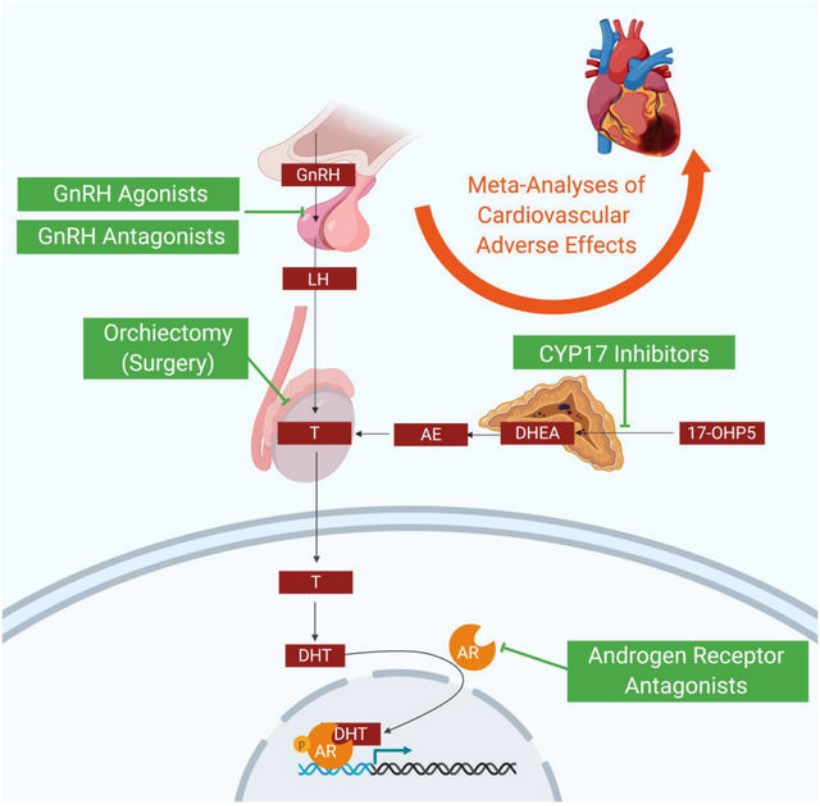

Keywords

cardio-oncology; androgen deprivation therapy; prostate cancer; cardiotoxicity; gonadotropin releasing hormone agonists

Introduction

Prostate cancer (PCa) is the second most common cancer in men, with an estimated incidence of 1,276,000 cases and 359,000 deaths globally in 2018[1]. In the United States, 174,650 new cases and 31,620 deaths are projected to occur in 2019[2]. The cornerstone of systemic treatment for PCa is pharmacologic or surgical androgen deprivation therapy (ADT). Pharmacologic ADT traditionally refers to treatment with a gonadotropin-releasing hormone (GnRH) agonist (e.g. leuprolide) or GnRH antagonist (e.g. degarelix). Suppression of androgen signaling can also be accomplished with androgen receptor (AR) inhibitors (e.g. enzalutamide) or CYP17 inhibitors (e.g. abiraterone). The inhibition of testosterone secretion by ADTs and AR-directed therapies results in a state of low plasma testosterone, a condition referred to as androgen deprivation. As advances in therapy improved the survival of PCa patients, growing reports have suggested a contribution of ADT to cardiovascular (CV) adverse sequelae. These reports led the American Heart Association, American Cancer Society, and American Urological Association to jointly issue a science advisory on the increased CV risks of ADT[3]. This review will summarize existing meta-analyses of the cardiovascular adverse effects of traditional ADTs as well as meta-analyses of AR-directed

therapy. While the state of low testosterone may arise from a multitude of etiologies, in this review we will focus on androgen deprivation resulting from the drugs used in the treatment of prostate cancer for prostate cancer patients.

Physiology

PCa is an androgen-sensitive cancer that relies on signaling from the HPG axis. The HPG axis begins at the hypothalamus, which releases luteinizing hormone releasing hormone (LHRH) in a pulsatile manner (Figure 1). Binding of LHRH to the LHRH receptors on the anterior pituitary causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates LH receptors on Leydig cells in the testes to produce testosterone.

In the testes, and to a lesser degree in the adrenal glands, testosterone synthesis from cholesterol relies on a cascade of CYP17-dependent reactions involving the conversion pregnenolone to dehydroepiandrosterone (DHEA) and progesterone into androstenedione, both of which are converted to testosterone and subsequently dihydrotestosterone (Figure 1). Dihydrotestosterone binding to the androgen receptor (AR) in the ligand binding pocket causes translocation of AR from the cytoplasm to the nucleus, where it binds to DNA and promotes transcription of cancer growth-promoting genes. When testosterone levels are depleted during PCa treatment, PCa cells can continue to respond to androgens synthesized in the adrenal gland. This pathway was the rationale for developing CYP17 inhibitors, which block synthesis of androgens in adrenal gland.

Types of Androgen Deprivation Therapy

GnRH agonists

The most common type of ADT are the GnRH agonists. GnRH agonists bind to GnRH receptors on gonadotropin-producing cells in the anterior pituitary[4]. The resulting continuous (non-pulsatile) release of GnRH causes a transient surge in LH and FSH and increase in testosterone production from Leydig cells. Subsequently, the negative feedback downregulates GnRH receptors on gonadotropin-producing cells, decreased pituitary production of LH and FSH, and testosterone is reduced to castration levels. Leuprolide, goserelin, triptorelin, buserelin, and histrelin are examples of GnRH agonists. Their pharmacology has been described previously[5] (Supplemental Table 1). All are available as intramuscular or subcutaneous formulations and are typically administered once every 1 to 6 months.

GnRH antagonists

GnRH antagonists bind to GnRH receptors on gonadotropin-producing cells in the anterior pituitary to inhibit release of LH or FSH without an initial increase in testosterone release[6]. Degarelix is an example of a GnRH antagonist. Degarelix is administered as a monthly subcutaneous injection. Degarelix causes a rapid fall in testosterone levels within 2–3 days, which is significantly more rapid than GnRH agonists.[7,8] Degarelix causes greater and more rapid PSA reduction than GnRH agonists, and has a lower rate of PSA failure[9]. Degarelix also causes greater and more rapid LH and FSH reduction than GnRH agonists[9]. Degarelix

is more likely to cause injection site reactions than GnRH agonists, while flushing is equally common in both groups[10]. Interestingly, degarelix causes improved health-related quality of life compared to GnRH agonists[11]. GnRH antagonists are less susceptible to the resistance that GnRH agonists may experience due to decreased sensitivity of the GnRH receptor from continuous exposure to GnRH agonists[8].

Androgen receptor antagonists

Androgen receptor antagonists, also known as antiandrogens, competitively inhibit dihydrotestosterone binding to the androgen receptor (AR) at the androgen binding site[12]. These agents inhibit nuclear translocation of the AR and interaction of the AR with the promoter at the AR response element. The inhibition of AR-dependent transcription impairs cell proliferation and triggers apoptosis. Nonsteroidal androgen receptor antagonists, discussed below, spare the patient from anti-mineralocorticoid, anti-gonadotropic, and progestogenic effects. Flutamide, nilutamide, and bicalutamide are first-generation androgen receptor antagonists. Enzalutamide, apalutamide, and darolutamide are next-generation (more potent) androgen receptor antagonists[5]. They are administered orally. A new compound that is a hybridization of abiratarone and enzalutamide has shown promising results for treating enzalutamide-resistant PCa[13]. AR antagonists are commonly used with GnRH agonists to alleviate the effects of the testosterone surge that occurs with a GnRH agonist. Extended AR antagonists may be used with GnRH agonists or antagonists to achieve combined androgen blockade (CAB).

CYP17 inhibitors

CYP17, an enzyme found in the testes, adrenal glands, and prostate tumor tissue, possesses both 17α-hydroxylase and C17,20-lyase activity, which generate testosterone from testosterone precursors[14]. CYP17 inhibitors block these reactions. Additionally, CYP17 inhibition reduces cortisol synthesis and may induce increased ACTH release promoting synthesis of mineralocorticoid precursors, leading to hypertension, edema, and hypokalemia. Corticosteroids are thus co-administered to prevent unwanted ACTH release. Ketoconazole and abiraterone are CYP17 inhibitors. Although androgen receptor antagonists and CYP17 inhibitors are androgen axis directed therapies rather than strictly androgen deprivation therapies, they have been grouped under the umbrella of ADTs in many studies, and will be treated as such in the data synthesis below.

Cardiovascular Adverse Effects of ADT

Keating and colleagues first identified an increased risk of incident diabetes, coronary heart disease, myocardial infarction (MI), and sudden cardiac death in association with GnRH agonists in a Surveillance, Epidemiology, and End Results (SEER)-Medicare database[15]. This finding has spurred numerous observational studies and retrospective studies from randomized controlled trials (RCTs).

Cardiovascular Adverse Effects of ADTs as a Pooled Group

Among the three available meta-analyses of observational trials, ADTs had positive associations (although not always significant) with CV events, CV death, and MI (Table

1)[16–18]. The comparator (non-ADT) group in these studies could include radical prostatectomy, radiotherapy, or watchful waiting. When the comparator group was watchful waiting, ADT was significantly associated with any non-fatal CV disease and stroke[17,18]. The strengthened effect size when the comparator group was restricted to watchful waiting suggests that there is CV risk associated with some non-ADT therapies, which may be minimizing the true CV effect difference between ADT and non-ADT. Among the three available meta-analyses of RCTs, there were no significant associations with CV outcomes except for a positive association with non-fatal CV disease compared in one analysis[15]. Therefore, in patients with low cardiovascular risk enrolled in RCTs, there is a suggestion but no conclusive increase in risk of cardiovascular adverse effects from ADT.

Cardiovascular Adverse Effects of GnRH Agonists

Among the ADTs, the strongest CV adverse event signal comes from observational studies of the GnRH agonists. In the three meta-analyses of GnRH agonists compared to non-ADT, positive associations were found between GnRH agonists and CV death, non-fatal CV disease, MI, and stroke (Table 2)[16,17,20]. There are currently no meta-analyses of RCTs of GnRH agonists and CV adverse events.

Cardiovascular Adverse Effects of Androgen Receptor Antagonists

The CV adverse effect signal from androgen receptor antagonists was mixed. In the three meta-analyses of observational studies of androgen receptor antagonists compared to non-ADT, there were mixed associations between ADT and non-fatal CV disease and MI[17,20], and no associations between ADT and CV death and stroke[16,17] (Supplemental Table 2). There are currently no meta-analyses of RCTs of androgen receptor antagonists and CV adverse events.

Cardiovascular Adverse Effects of Combined Androgen Blockade

Combined androgen blockade, which refers to the use of a GnRH agonist together with an androgen receptor antagonist, showed increased risk for CV adverse effects. In two meta-analyses of observational studies which examined combined androgen blockade compared to non-ADT, there was a positive association with CV death, non-fatal CV disease, and stroke[16,17] (Supplemental Table 3). The association with MI was not statistically significant[17].

Cardiovascular Adverse Effects of Orchiectomy

Individuals undergoing orchiectomy may have increased risk of CV events. In three meta-analyses of observational data examining orchiectomy compared to non-ADT, there was a positive association between orchiectomy and non-fatal CV disease[16,17,20] (Supplemental Table 4). Individual associations between orchiectomy and CV death, MI, and stroke were positive but did not achieve statistical significance. There are currently no meta-analyses of RCTs of orchiectomy CV adverse events.

Cardiovascular Adverse Effect Differences Between ADT Types

The mechanism of specific ADTs may differently affect CV event risk. In one meta-analysis, GnRH antagonists were associated with lower CV events than GnRH agonists (HR 0.44, CI 0.26–0.74, p=0.002, I2=42%, N=3)[21]. In a broader meta-analysis comparing all types of ADT with each other (Supplemental Table 5)[22], orchiectomy had the most unfavorable CV risk profile. Orchiectomy had a near-doubling of MI risk compared to combined androgen blockade (CAB), which appears to have the least harmful CV risk profile. Differences were modest among the other ADT types. GnRH antagonists were associated with a 58% decreased risk of MI compared to GnRH agonists[21,22]. Between continuous ADT and intermittent ADT, there was no difference in the development of CV events or thromboembolic events, but there was a marginally significant increase in CV death from continuous ADT[23].

Cardiovascular Adverse Effects of Abiraterone and Enzalutamide

Two agents, enzalutamide (an androgen receptor antagonist) and abiraterone (a CYP17 inhibitor), have drawn specific attention for their association with CV risk. In a meta-analysis of observational studies and a meta-analysis of RCTs, enzalutamide did not increase risk of cardiac events, but increased the risk of hypertension (Supplemental Table 6)[24,25]. Abiraterone was associated with increased risk of cardiac events and the risk of hypertension in both meta-analyses (Table 3). The strength of abiraterone's association with any cardiac events and hypertension suggests that further scrutiny should be given to the CYP17 inhibitors in future clinical trials. Furthermore, pharmacovigilance studies show that abiraterone have increased risk of atrial tachyarrhythmias and heart failure compared to other ADTs[26], an area that should be studied in future meta-analyses.

The Impact of Study Population on Cardiovascular Risk

Several factors related to trial design could partially explain these divergent results between meta-analyses of RCTs and meta-analyses of observational studies. RCTs may underestimate CV risk because the primary endpoints in RCTs are measures of PCa disease control, not CV events. Firstly, CV events in RCTs for PCa therapies are not defined or adjudicated in a standardized way as done in large prospective CV outcomes trials. Secondly, these RCTs are not sufficiently powered to look for unexpected CV events. Thirdly, the duration of follow-up is rarely as long as in observational studies. Fourthly, patients in the control arm in some trials did end up receiving ADT as well, just in a deferred time frame, thus attenuating any positive effect of ADT on CV risk. Fifthly, PCa RCTs suffer from selection bias as they exclude patients with high CV risk from enrolment.

On the other hand have greater susceptibility to confounding, less control over adherence to treatment, and may have outcome reporting bias, potentially leading to an overestimation of CV risk. Population-based databases, such as SEER, do not exclude elderly patients or those with concurrent CV disease or CV risk factors, thus more closely resembling the population of patients who get PCa[27]. The critical role that baseline CV risk factors and comorbidities play in overall survival was demonstrated in a study on a long-term follow-up of a prostate cancer RCT[28].

Finally, the heterogeneity varies widely between the studies, ranging from 0–100%, so results should be interpreted with caution. Studies varied greatly in follow-up time and regions included (Supplemental Table 7). On balance, the data support a cardiovascular risk association that needs to be further characterized. Pragmatic trials may overcome these limitations and offer the methodological innovation needed to address this research question.

Mechanisms

The increased risk of adverse CV outcomes from ADT is thought to be related to its role in promoting atherosclerosis, dyslipidemia, adiposity, and insulin resistance.

ADT and atherosclerosis

Multiple murine models of androgen deprivation have supported the hypothesis that androgen deprivation worsens atherosclerosis lesion formation. Firstly, orchiectomized LDL-receptor knockout (*Ldlr*$^{-/-}$) mice consuming a high fat diet developed larger atherosclerotic lesions as compared to sham-treated mice[29]. Testosterone supplementation in the orchiectomy model significantly reduced atherosclerotic lesion size compared to placebo, but this reduction did not occur if testosterone was administered in the presence of an aromatase inhibitor, which blocks conversion of testosterone to 17β-estradiol. This suggests that testosterone may inhibit atherosclerosis indirectly through its conversion to 17β-estradiol. Indeed, 17β-estradiol supplementation reduced atherosclerotic lesion size to the same degree as testosterone treatment[29].

Secondly, androgen receptor knockout (ARKO) in the context of an apolipoprotein E deficiency model led to larger atherosclerotic lesions in the aortic root compared to animals with an intact androgen receptor[30]. As in the *Ldlr*−/− model, testosterone supplementation reduced lesion size in both ARKO and wild-type mice, although the effect was blunted in ARKO mice. This suggests disruption of testosterone signaling is atherogenic via both AR-dependent and AR-independent mechanisms.

Thirdly, *in vitro*, testosterone dose-dependently augmented cholesterol efflux from human monocyte-derived macrophages via upregulation of scavenger receptor B1, thereby providing a possible mechanism for how testosterone can reduce the cholesterol content of atherosclerotic lesions[31]. Collectively, these preclinical models support the hypothesis that androgen deprivation drives atherosclerosis.

ADT and adiposity

ADT increases visceral and subcutaneous fat[32] while decreasing lean body mass[33]. This may occur via loss of androgen-mediated inhibition of stem cell differentiation into adipocytes[34], as well as loss of androgen-mediated stimulation of lipolysis and androgen-mediated reduction of lipid accumulation[35]. Of note, 90% of the gain in adiposity is subcutaneous rather than visceral[36].

ADT and insulin resistance

ADT leads to insulin resistance. Among men without diabetes, ADT has been associated with worsening fasting insulin, fasting glucose, leptin, and $HOMA_{IR}$ (homeostasis model of insulin resistance)[37,38]. More importantly, ADT has been associated with increased risk of developing diabetes[39]. Among men with diabetes, ADT has been associated with worsening A1c control[40]. This is plausible as testosterone has dose- and time-dependent effects on increasing cellular expression of insulin receptor substrate-1 and glucose transporter 4[41].

ADT and metabolic syndrome

In a meta-analysis of 9 studies of men treated with ADT for prostate cancer, ADT was associated with an increased risk of developing metabolic syndrome (relative risk: 1.75; CI: 1.27–2.41; I^2: 0%)[42]. However, ADT raises both LDL and HDL levels, instead of decreasing HDL levels, as in metabolic syndrome[43–45]. The fat accumulation in ADT is primarily subcutaneous, rather than the visceral accumulation of metabolic syndrome[36]. Moreover, there is no significant increase in waist-to-hip-ratio. These data suggest that ADT acts via pathways other than the traditional insulin resistance-mediated development of metabolic syndrome.

ADT and hypertension

ADT was hypothesized to lead to hypertension since androgen-deprived states were shown to increase arterial stiffness[46,47]. However, only abiraterone and enzalutamide have consistently demonstrated associations with hypertension[24]. Increased mineralocorticoid production from an increase in ACTH resulting from suppression of cortisol has been suggested as a mechanism for abiraterone's hypertensive effect[48].

ADT and endothelial cell function

At the cellular level, ADT leads to endothelial cell (EC) dysfunction. In ECs from patients with diabetes, androgen signaling was negatively enriched[49]. However, despite this previously identified biology, GnRH agonists improved conduit artery flow-mediated vasodilation (FMD) in men with PCa at 3 months[50]. Discontinuation of GNRH agonist resulted in return of FMD to baseline after 6 months. The improvement in FMD occurred despite worsening insulin resistance and dyslipidemia. Other cross sectional studies have described similar effects of ADT on EC function,[51] suggesting that EC dysfunction may not be a major determinant of atherosclerosis from ADT.

ADT and Arrhythmia

ADT, especially enzalutamide, may be associated with increased QT interval and acquired long QT syndrome (LQT)[52]. Testosterone shortens while estradiol lengthens QT prolongation (thus explaining, in part, the long standing observation that men have shorter QT than women)[53]. Similarly, an association between hypogonadism in men and LQT and risk of torsade de pointes (TdP) has been observed[54,55]. This association appears to be causal, as correction of hypogonadism by testosterone replacement therapy reduces QT prolongation[56]. These results suggest electrocardiographic monitoring may have a role in the surveillance of men treated with ADT.

GnRH Receptors Outside the Pituitary

Pituitary cells and cardiac myocytes have increased mRNA expression of GnRH receptor, LH receptor, and FSH receptor compared to other human cells[57]. In mice, GnRH has been shown to increase cardiac contractility via the protein kinase A (PKA) pathway[58]. However, further studies remain to be done to characterize the link between GnRH agonist use and GnRH receptor stimulation on cardiac myocytes. There is no evidence yet about whether this may be related to the QT interval prolongation reported from GnRH agonist use[59]. Intriguingly, FSH levels were positively associated with QT duration in two observational studies[54,60].

Synopsis of Mechanisms

The aforementioned atherosclerosis, visceral adiposity, lipolysis inhibition, insulin resistance, and endothelial dysfunction result in an unfavorable cardiovascular risk profile predisposing to MI, stroke, and hypertension[61,62]. In addition to these structural changes, conduction abnormalities arise as androgen deprivation prolongs the QT interval. Plaque destabilization and insulin resistance are further worsened by the increased state of inflammation caused by elevated pro-inflammatory cytokines and adiponectin from androgen receptor-dependent and -independent mechanisms[63].

Management

The CV adverse effects of ADT, such as atherosclerotic plaque growth, are insidious. The cornerstone of management relies on prevention. Prior to initiating an ADT, ideal management involves a multidisciplinary discussion with the patient about the risks and benefits of ADT. Physicians initiating ADT in patients with multiple CV risk factors or history of CV events should consider referral to cardiology or cardio-oncology. The components of cardiac prevention in prostate cancer survivors can be remembered by the ABCDE mnemonic: A for awareness and aspirin; B for blood pressure control; C for cholesterol and cigarettes; D for diabetes and diet; and E for exercise[64]. These principles do not differ from the principles of cardiac prevention in the general population.

Conclusion

In conclusion, meta-analyses demonstrate a recurring pattern whereby GnRH agonists, GnRH antagonists, androgen receptor antagonists (combined androgen blockade), and orchiectomy for prostate cancer show positive associations with CV events and CV death in observational studies. These effects are not consistently reproducible in RCTs. Notably, the CYP17 inhibitor abiraterone increases risk of CV events in both observational studies and RCTs. Animal and human studies suggest that the mechanisms by which ADT increases CV risk include increased atherosclerosis, dyslipidemia, metabolic syndrome, and insulin resistance. Our current work can provide the basis for a living network meta-analysis. Further pragmatic trials and meta-analyses are necessary to definitively characterize the impact of ADT and AR directed therapies on CV events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACTH	adrenocorticotropic hormone
ADT	androgen deprivation therapy
AR	androgen receptor
ARKO	androgen receptor knockout
CAB	combined androgen blockade
CI	confidence interval
CV	cardiovascular
DHEA	dehydroepiandrosterone
EC	endothelial cell
FMD	flow-mediated vasodilation
FSH	follicle stimulating hormone
GnRH	gonadotropin-releasing hormone
HOMA	homeostasis model of insulin resistance
HPG	hypothalamic-pituitary-gonadal
HR	hazard ratio
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LQT	long QT syndrome
MI	myocardial infarction
OR	odds ratio
PCa	prostate cancer
PKA	protein kinase A
RCT	randomized, controlled trial

RR	relative risk
SEER	Surveillance, Epidemiology, and End Results
TdP	torsade de pointes

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Highlights

- As a pooled group, androgen deprivation therapy (ADT) had positive associations (although not always significant) with cardiovascular (CV) events, CV death, and myocardial infarction (MI) among the three meta-analyses of observational studies, but among none of the three meta-analyses of randomized controlled trials (RCTs).
- GnRH agonists had strong positive associations with CV death, CV disease, MI, and stroke, among the three meta-analyses of observational trials.
- GnRH antagonists had mixed associations with CV disease and MI, and no associations with CV death and stroke, among the three meta-analyses of observational studies.
- Combined androgen blockade had positive associations with CV death, CV disease, and stroke, among two meta-analyses of observational studies
- CYP17 inhibitors had positive associations with CV events and hypertension, among two meta-analyses of RCTs

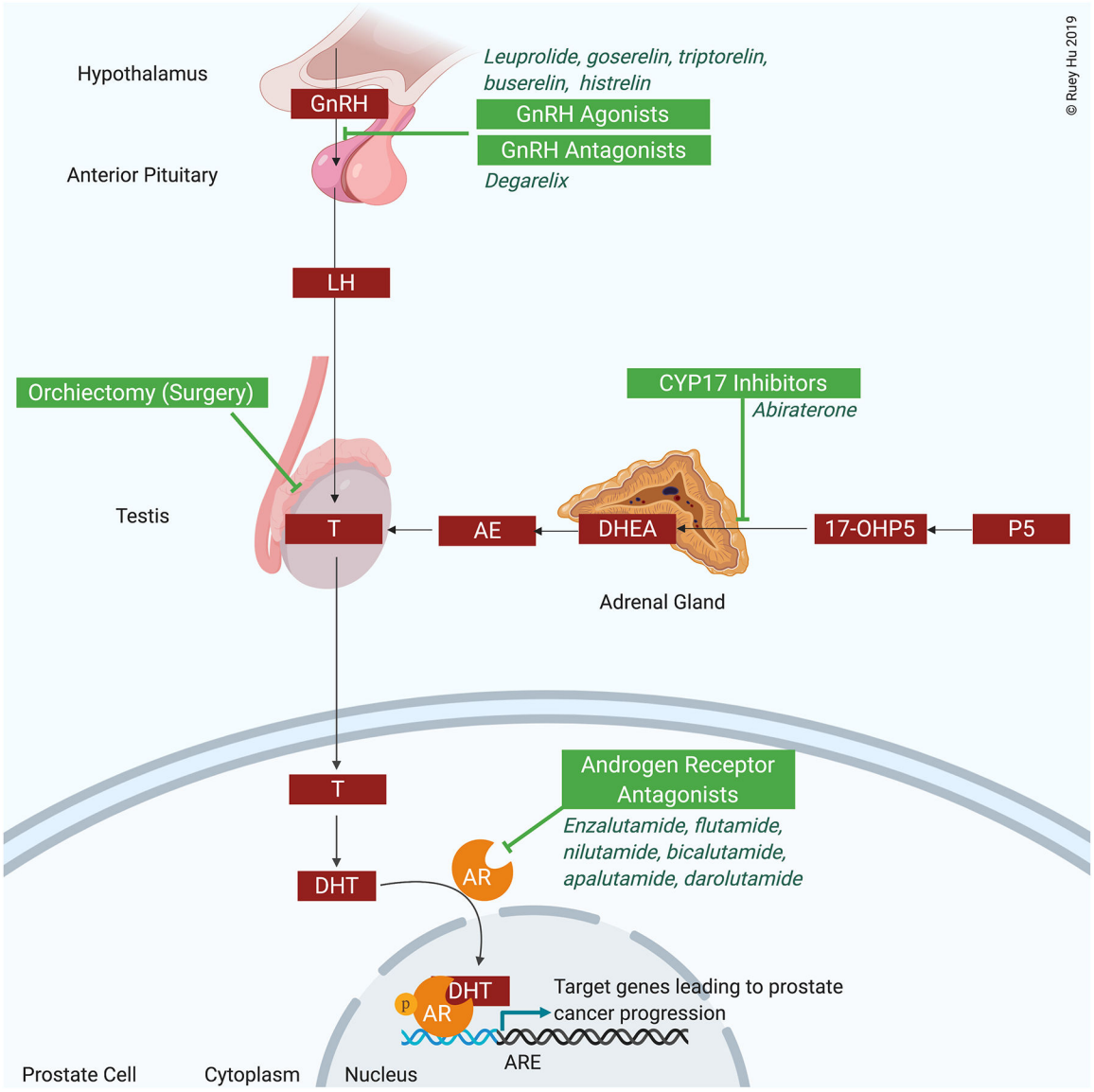

Figure 1:

The hypothalamic-pituitary-gonadal axis and targets for androgen deprivation therapy in prostate cancer

Abbreviations: 17-OHP5: 17α-hydroxypregnenolone; AE: androstenedione; AR: androgen receptor; DHEA: dihydroepiandrosterone; DHT: dihydrotestosterone; GnRH: gonadotropin releasing hormone; LH: luteinizing hormone; P5: pregnenolone; T: testosterone

Table 1:

Cardiovascular mortality and cardiovascular disease associated with androgen deprivation therapy (ADT) as a pooled group compared to non-ADT, according to results of meta-analyses from 2010 to 2019.

	Type	Treatment Agent (no. of patients)	Comparator Agent (no. of patients)	CV mortality	Any non-fatal CVD	Myocardial Infarction	Stroke
Nguyen 2011	RCT	ADT (n=2200)	Non-immediate ADT (n=1941)	RR 0.93 (CI 0.79–1.10, p=0.41, I^2=0%, N=8)			
Bourke 2013	RCT	ADT (n=1065)	Non-immediate ADT (n=814)	RR 1.06 (CI 0.80–1.40, p=0.69, I^2=0%, N=4)			
Zhao 2014	Obs.	ADT (n=129,802)^	Non-ADT (n=165,605)^	**HR 1.17** (CI 1.04–1.32, p = 0.01, I^2=57%, N=6)	HR 1.10 (CI 1.00–1.21, p = 0.06, I^2=72%, N=6)	HR 1.10 (CI 0.97–1.26, p=0.14, I^2=68%, N=6)	
Zhao 2014	Obs.	ADT (n=39,465)^	Watchful waiting (n=43,648)^	**HR 1.30** (CI 1.13–1.50, p=0.0003, I^2=0%, N=4)	**HR 1.19** (CI 1.08–1.30, p=0.0004, I^2=0%, N=3)		
Carneiro 2015	Obs.	ADT (n= 52,308)	Non-ADT (n=74,590)	OR 1.92 (CI 0.79–4.68, p 0.15, I^2=97%, N=3)	OR 1.06 (CI 0.70–1.61, p<0.78, I^2=100%, N=2)	**OR 2.05** (CI 1.93–2.17, p<0.00001, I^2=100%, N=2)	OR 1.07 (CI 0.66–1.72, p=0.79, I^2=99%, N=2)
Carneiro 2015	RCT	ADT (n=8,388)	Non-ADT (n=8,411)	OR 0.97 (CI 0.81–1.18, p 0.79, I^2 0%, N=6)	**OR 1.55** (CI 1.09–2.20, p=0.01, I^2 0%, N=3)	OR 1.23 (CI 0.92–1.64, p=0.16, I^2: 0%, N=2)	OR 1.02 (CI 0.71–1.46, p=0.93, I^2=0%, N=2)
Meng 2016	Obs.	ADT (n=74,538)	Non-ADT (n= 85,947)				HR 1.12 (CI 0.95–1.32, p=0.16, I2=85%, N=6)
Meng 2016	Obs.	ADT (n=39,029)	Watchful waiting (n=42,073)				**HR 1.16** (CI 1.03–1.31, p = 0.01, I^2=0%, N=2)

Abbreviations: RR: relative risk; OR: odds ratio; HR: hazard ratio; CI: confidence interval; ADT: androgen deprivation therapy; CV: cardiovascular: CVD: cardiovascular disease: MI: myocardial infarction; RCT: meta-analysis of randomized controlled trials; Obs.: meta-analysis of observational studies

Small n: total number of patients examined in the meta-analysis

Large N: number of studies or trials available for that outcome in the meta-analysis

^The exact participant count in Zhao (2014) varies by outcome.

Table 2:

Cardiovascular mortality and cardiovascular disease associated with GnRH agonists compared to non-ADT, according to results of meta-analyses from 2010 to 2019.

	Type	Treatment Agent (no. of patients)	Comparator Agent (no. of patients)	CV death	Any non-fatal CVD	Myocardial Infarction	Stroke
Zhao 2014	Obs.	GnRH agonist (n=89865)^	Non-ADT (n=126219)^	**HR 1.36** (CI 1.10, 1.68, p=0.004, I^2=91%, N=4)	**HR 1.19** (CI 1.04, 1.36, p = 0.01, I^2=86%, N = 3)	**HR 1.20** (CI 1.05–1.38, p = 0.008, I^2=82%, N = 4)	
Bosco 2015	Obs.	GnRH agonist	Non-ADT		**RR 1.38** (CI 1.29–1.48, p <0.001, I^2=85%, N=16)	**RR 1.57** (CI 1.26–1.94, p <0.001, I^2=92%, N=6)	**RR 1.51** (CI 1.24–1.84, p<0.001, I^2=90%, N=5)
Meng 2016	Obs.	GnRH agonist (n = 49292)	Non-ADT (n= 47309)				**HR 1.20** (CI 1.12–1.28, P<0.001, I2 = 0%, N=3)

Abbreviations: RR: relative risk; OR: odds ratio; HR: hazard ratio; CI: confidence interval; ADT: androgen deprivation therapy; CV: cardiovascular: CVD: cardiovascular disease: MI: myocardial infarction; RCT: meta-analysis of randomized controlled trials; Obs.: meta-analysis of observational studies

^The exact participant count in Zhao (2014) varies by outcome.

Small n: total number of patients examined in the meta-analysis

Large N: number of studies or trials available for that outcome in the meta-analysis

Table 3:

Cardiovascular events associated with abiraterone (a CYP17 inhibitor) compared to non-ADT, according to results of meta-analyses from 2010 to 2019.

	Type	Treatment Agent (no. of patients)	Comparator Agent (no. of patients)	Any cardiac events	CTCAE Grade ≥3 cardiac events	Any hypertension	CTCAE Grade ≥3 hypertension
Moreira 2017	RCT	Abiraterone and prednisone (n=1,343)	Prednisone (n=940)	**RR 1.28** (CI 1.06–1.55, P = 0.01, I^2=0%, N=2)	**RR 1.76** (CI1.12–2.75, P=0.01, I^2=0%, N=2)		
Iacovelli 2018	RCT	Abiraterone and prednisone (n=2,878)	Prednisone (n=2,496)	**RR 1.41** (CI 1.21–1.64, P<0.001, I^2=0%, N=4)	**RR 2.22** (CI 1.60–3.27, P<0.001, I^2=0%, N=4)	**RR 1.79** (CI 1.45–2.21, P<0.001, I^2=68%, N=4)	**RR 2.19** (CI 1.73–2.78, P<0.001, I^2=34%, N=4)

Abbreviations: RR: relative risk; CI: confidence interval; ADT: androgen deprivation therapy; CTCAE: Common terminology criteria for adverse events; RCT: meta-analysis of randomized controlled trials; Obs.: meta-analysis of observational studies

Small n: total patients examined in the meta-analysis

Large N: number of studies or trials available for that outcome in the meta-analysis