HHS Public Access

Author manuscript

Biochim Biophys Acta Rev Cancer. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Biochim Biophys Acta Rev Cancer. 2020 August ; 1874(1): 188383. doi:10.1016/j.bbcan.2020.188383.

Cardiovascular risks and toxicity - the Achilles heel of androgen deprivation therapy in prostate cancer patients

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Abstract

Androgen deprivation therapy (ADT) is the primary systemic therapy for treating locally advanced or metastatic prostate cancer (PCa). Despite its positive effect on PCa patient survival, ADT causes various adverse effects, including increased cardiovascular risk factors and cardiotoxicity. Lifespans extension, early use of ADT, and second-line treatment with next-generation androgen receptor pathway inhibitors would further extend the duration of ADT and possibly increase the risk of ADT-induced cardiotoxicity. Meanwhile, information on the molecular mechanisms underlying ADT-induced cardiotoxicity and measures to prevent it is limited, mainly due to the lack of specifically designed preclinical studies and clinical trials. This review article compiles up-to-date evidence obtained from observational studies and clinical trials, in order to gain new insights for deciphering the association between ADT use and cardiotoxicity. In addition, potential cardioprotective strategies involving GnRH receptors and second messenger cGMP are discussed.

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Declaration of interests

SKB is one of the co-founders of Sanguine Diagnostics and Therapeutics, Inc.

LX is a co-founder of Xiamen Innovo Medical Technology Co. Ltd., China

BAT has served as a paid advisor/consultant to Janssen Pharmaceuticals.

Other authors declare no conflicts of interest.

Keywords

Androgen deprivation therapy; cardiotoxicity; GnRH agonists; cGMP; sildenafil citrate; prostate cancer

1. Introduction

Prostate cancer (PCa) is still one of the most common cause of mortality and morbidity among men globally [1]. In 2016, 1.4 million new cases of PCa were reported and 381,000 men died because of PCa [1]. Since 2000, the number of PCa survivors are increasing and are expected to increase further due to age, early screening and better therapeutics for PCa [2]. Androgen deprivation therapy (ADT) has been the primary systemic therapy for metastatic PCa during the past 75 years. ADT is also given as a neoadjuvant, concurrent or adjuvant therapy with radiation for localized or locally advanced PCa. Since 1990, the majority of locally advanced and metastatic PCa patients received gonadotropin-releasing hormone (GnRH) agonists as the first-line ADT treatment. Despite the survival benefit, ADT is associated with significant adverse effects, including sexual dysfunction, vasomotor flushing, loss of libido, fatigue, gynecomastia, anemia, osteoporosis, insulin insensitivity, diabetes and cardiovascular disease [3, 4]. Recent observational studies and a randomized controlled trials (RCT) have suggested that ADT, particularly GnRH agonists, is associated with increased incidence of cardiovascular (CV) events.

Epidemiological studies have estimated that ~50% of PCa patients will undergo ADT at some point in their treatment course [5] and at least 20–30% of these patients will develop risk for CV events, particularly with GnRH agonists [6–8]. A recent study using the Surveillance, Epidemiology, and End Results (SEER) database and Swedish cancer registry estimated that cardiovascular disease (CVD) is the most common cause of death in PCa patients who survive longer than 10 years after cancer diagnosis [9]. Since PCa patients are surviving longer, GnRH agonists-mediated CV events is a growing concern. Although the association between GnRH agonists and cardiac risk events is well established, several clinical studies have not supported this association. A possible explanation is that clinical trials often exclude patients at highest risk of CVD. Also, the survival benefit of GnRH agonists may undermine the risk ratio associated with CV adverse events. In fact, no RCT has been designed to determine the CV risk events/death from ADT as a primary endpoint of analysis except the PRONOUNCE trail (NCT02663908). The PRONOUNCE trial is currently recruiting advanced PCa patients with predefined CVD to determine the CVD related death among the patients treated with GnRH agonist (leuprolide) and GnRH antagonist (degarelix), but the results are expected only in 2021. For these reasons, understanding of cardiac events associated with ADT is incomplete, which impedes the design of preventive or curative interventions for CV risks/toxicity. Here, we review the currently available evidence on the association between various types of ADT and CV events. We also focus on the possible underlying molecular mechanisms of ADT-associated CV events, including the role of GnRH receptor (GnRHR). Finally, we have outlined our perspectives on the role of cGMP-hydrolyzing phosphodiesterase 5 (PDE5) inhibitors in possible management of risk for CV toxicity in PCa patients treated with GnRH agonists.

2. Prostate cancer and androgen deprivation therapy

In 1941, Huggins and Hodges first showed that androgen deprivation, primarily by surgical castration or estrogen treatment reduces PCa growth [10]. Since then, various approaches have been developed to target the androgen signaling axis (Fig. 1). The principle of ADT is to reduce the physiological concentration of circulating androgens (300–1000 ng/dl) to the castrated levels (≤50 ng/dl) [11]. ADT is achieved either by the surgical removal of the testis (bilateral orchiectomy) or chemically blocking the hypothalamus/pituitary/testicular axis (using GnRH agonists or antagonists and/or antiandrogens) to reduce the effect of androgen signaling on the prostate (Fig. 2). In contemporary days, the patients who undergo bilateral orchiectomy is very few and hence mostly chemical castration is prevalent in the management of PCa.

GnRH agonists: the first-line systemic therapeutic agent for ADT

The high affinity GnRH agonists were originally developed as birth control agents. Contrary to natural pulsatile stimulation, these agonists continuously stimulate the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Chronic administration of agonists desensitizes the GnRHR and thus reduces gonadotropin secretion and testosterone synthesis [12]. The first report of the clinical benefit of GnRH agonists in PCa in 1982 suggested that GnRH agonists could serve as an alternative ADT strategy [13]. Since then, various GnRH agonists (leuprolide, goserelin, triptorelin, histrelin) have been developed and largely replaced the use of Diethylstilbestrol (DES) and surgical orchiectomy (Fig. 1).

GnRH antagonists were developed as an alternative for GnRH agonists. These antagonists bind to GnRHRs and competitively prevent the native peptide from binding and thereby preventing the release of LH. GnRH antagonists do not cause a testosterone flare in PCa patients and thus can prevent the additional use of antiandrogens [14]. Earlier generations of GnRH antagonists were not well received in the clinic because of their limited solubility and induction of histamine release [14], whereas more recent GnRH antagonists have overcome these limitations. GnRH agonists and GnRH antagonists were generally well tolerated in clinical trials, except an incidence of anaphylaxis was reported in the patients receiving GnRH antagonists [15, 16]. Further, GnRH agonists are easier to administer than antagonists due to lower dose frequency and cost, as well as simpler drug compound reconstitution.

3. Testosterone and cardiovascular system

Typically, testosterone (androgens) is known to play a vital role in the development of male reproductive system and masculine features such as increased muscle, bone mass, and the growth of body hair. In addition, though studies are scant, it has been shown that testosterone has multitude of cardioprotective effects, which may account for maintaining lipid profiles and minimizing inflammation at physiological concentrations of testosterone. These cardio protective effects are supported by androgen receptor (AR) expression in cardiovascular tissues [17, 18]. In cardiac tissues, androgen can executes its function either through its conventional AR signaling (Fig. 2) or the non-genomic signaling through MAPK, PI3K/Akt, PKC, etc [19]. Further, androgens have also been shown to induce NO-

mediated cGMP production which results in vascular relaxation In general, low physiological levels of testosterone are associated with increased cardiovascular risk events such as coronary artery disease (CAD), congestive heart failure (CHF) and metabolic changes including altered lipid profile and insulin resistance, and diabetes [21, 22]. Indirectly, pre-existing risk factors such as altered lipid profiles and insulin resistance, and diabetes may increase CV risk and related mortality. On the other hand, few studies have shown that testosterone supplementation in hypogonadal men are associated with increased CV risk, which is further complicated by gender discrepancy, protective effect of estrogen, and deleterious effect of supraphysiological testosterone levels [22]. Overall, though it is not clinically proven, majority of the studies and experimental evidence show that circulating testosterone has beneficial effects on cardiovascular system [21].

In a completely different scenario such as intentional androgen deprivation for PCa, the association with CV risk events is still unclear and several hypotheses have been proposed. In the following section, we provide details of the underlying possible mechanism of various form of ADT agents induced CVD and how ADT-induced cardiotoxicity is different from physiological dysfunction.

4. ADT-related cardiovascular risk and adverse events

Despite the clinical success of ADT (GnRH agonists) in the management of PCa, there is a growing body of data suggesting that ADT is associated with increased CV adverse events [3, 6–8, 23–27]. European Society of Cardiology (ESC) classifies cancer therapy-induced CV complications into the following nine major categories: i) myocardial dysfunction and heart failure (HF), ii) coronary artery disease (CAD), iii) valvular disease, iv) arrhythmias (especially QT prolongation), v) hypertension, vi) thromboembolic disease, vii) peripheral vascular disease and stroke, viii) pulmonary hypertension, and ix) pericardial complications [28]. Long-term administration of GnRH agonists may lead to some of the CV risk events such as myocardial dysfunction, HF, CAD, arrhythmias, thromboembolic disease, and stroke, which are further discussed below.

In an observational study using the SEER database, Keating et al. [7] first showed in 2006 that GnRH agonist use is associated with significantly increased risk of developing diabetes, CAD, myocardial infarction (MI), and sudden cardiac death among patients with loco-regional PCa. Subsequent studies confirmed these associations, particularly between GnRH agonists use and CV risk events among PCa patients [6–8, 23–27, 29–32], as summarized in Table 1. For example, Tsai et al. [27] found that GnRH agonists and antiandrogens significantly increased risk of CVD-related mortality. Similarly, Van Hemelrijck and colleagues reported that ADT increased the risk of CVD, which was highest in patients treated with GnRH agonists compared to orchiectomy and combined androgen blockade, and lowest among those who received antiandrogens [24]. In addition, ADT was not only linked to cardiac dysfunction [25] but also to vascular dysfunction caused by peripheral arterial disease and venous thromboembolism [25, 26, 33].

The PCa patients receiving ADT for 1 year had 20% higher CV-related morbidity compared to the ones who did not receive ADT [8]. CVD risk was also significantly higher during the

first 12 months of ADT treatment, as compared with the following months. Similarly, Veterans Healthcare Administration data indicated that the current use of GnRH agonists significantly increased risk of MI, whereas increased incidence of CAD, sudden cardiac death, stroke, and diabetes were observed among both current and past users of GnRH agonists [6]. Few retrospective analyses revealed that 4-month neo-adjuvant ADT use was associated with an increased risk of all-cause mortality among low-risk PCa patients [34] and those with preexisting CV risk factors [35]. In contrary, Alibhai et al. [36] reported that continuous ADT for 6 months or more was likely to cause diabetes and fragility fracture, but not CV events. The later discrepancies could be due to the difference in the treatment period, treatment combination (GnRH agonists with or without antiandrogens) [34, 35], and pooled analyses of all form of ADT vs. non ADT [36].

Besides the observational studies, a number of meta-analyses have focused on the association between ADT and CV risk [37–41] which is summarized in Table 2. Meta-analyses of the European Organization for Research and Treatment of Cancer [EORTC] trial did not find significant CV risk associated with ADT [42]. Also, three phase III randomized clinical trials with a follow-up of at least eight years did not reveal a close association between GnRH agonist use and increased risk of CV mortality. Further, a meta-analysis of eight trials comprising 4141 PCa patients showed no increased risk of CV death following GnRH agonist therapy [39]. Similarly, in 2012 Wilcox et al. showed no increase in cardiac events following six month neoadjuvant use of GnRH agonists as compared with radiation therapy alone [40]. The disagreements between population-based studies and RCTs could be due to the fact that most of the RCTs included only the PCa patients with minimal or no risk of CVD. To the contrary, the population studies are based on more practical and inclusive representation of the real-world population. Interestingly, a pooled analysis of six phase III prospective trials in 2328 patients showed that the users of GnRH antagonists had significantly lower cardiac events (Hazard ratio = 0.44, 95% CI, 0.26–0.74; $p = 0.002$) than the patients who received GnRH agonists [41]. Supportively, a recent multinational randomized phase 3 trial reported that compared to leuprolide (GnRH agonist), relugolix (GnRH antagonist) treatment reduced adverse CV events by 54% in advanced PCa patients [43]. The later reports support the notion that GnRH agonist is associated with increased CV risk events.

Few observational studies also suggest that antiandrogen monotherapy is associated with increased CAD, MI, arrhythmia, heart failure and stroke (Table 1). Using VA database Keating et al., showed that antiandrogen monotherapy treatment had 27% increase in CAD [6]. Similarly, Van Hemelrijck et al. using Swedish database showed that antiandrogen monotherapy is associated with slight increase in CVD events but not related deaths [24]. Further, the same group with an updated dataset showed that PCa patients receiving antiandrogen had increased risk of CVD during the first year when they had 2 or more CV events in past year [30]. The antiandrogen associated CV risk events reduced after 12 months [30]. Studies also show mixed observations on CV risk events in PCa patients who had received orchiectomy as their primary therpay when compared to PCa patients without any form of ADT [6, 32–35, 38–40, 44]. However, in contemporary days, the number of patients receiving orchiectomy is minimal [32, 39, 42] and the procedure is becoming less common due to various confounders. To maintain the focus of review on current treatment

trends, we excluded any details which solely compare the orchiectomy associated CV effect to other type of ADT.

5. Potential mechanisms of ADT-induced cardiovascular adverse effects

The mechanism by which GnRH agonists mediate CV risk and cardiotoxic events is still unclear, although several hypotheses have been proposed, which are summarized in Figure 3. Since testosterone maintains lean body mass, it has been suggested that ADT-induced hypogonadism is a causative factor for the development of metabolic syndrome [44]. In fact, there is a significant correlation between men with higher testosterone level and lower incidence of CVD and vice versa [21, 45]. Initial studies suggested that lower testosterone level and decreased metabolic function contribute to the increased CV risk [44, 46–48]. In 1990, Tayek et al. [49] demonstrated that 12-month GnRH agonist (buserelin) use led to an increase in body weight, cholesterol, and fat mass, which are linked to CV risk. The adverse effects on body composition occurred as early as 3–6 months after initiation of ADT [50]. A significant increase in fat mass was also reported in men who had undergone treatment with ADT for 12 months [51]. The ADT-associated alteration in body fat and mass was associated with altered lipid profiles [46–48]. Similar findings of increased fat percentage and body weight with a decline in lean body mass were also reported under androgen deprivation conditions [48]. Thus it appears that the longer the duration of ADT, the stronger the correlation with body mass increase [51]. Further, the median age of 66 years among PCa patients and predisposing factors such as diabetes, altered metabolic profiles make them generally vulnerable to CVD risk.

Obesity and insulin resistance are independent and established risk factors for type 2 diabetes and CVD [52]. Evidence also linked the use of GnRH agonists to insulin resistance [53] and the progression of diabetes mellitus, supporting a potential correlation between ADT and metabolic complications in men with PCa. ADT-mediated alterations in lipid profiles could lead to the development of metabolic syndrome and CVD, which is supported by various clinical studies [6, 7, 36]. The metabolic alterations can also accelerate atherosclerosis, a major predisposing factor for CVD [54] as illustrated in Figure 3. GnRH agonists had a significantly greater effect on metabolic profile as compared with surgical orchiectomy [7]. However, ADT-mediated alterations of metabolism are apparently different from the classical metabolic profiles associated with diabetes and CVD [48, 55].

GnRH agonists may also induce cardiac injury by destabilizing established atherosclerotic plaques during the initial testosterone surge [56]. The increased testosterone may also promote angiogenesis or neutrophil migration. GnRH agonists can act on GnRHR present on T-lymphocytes to induce interferon-γ production, which in turn drives the pro-inflammatory environment and increases the risk of plaque rupture. These events can reduce atherosclerotic plaque stability, which subsequently leads to platelet activation and increased risk for clot formation [56].The destabilization of atherosclerotic plaques is thought to precede the ischemic CVD events triggered by blood clots [57, 58]. Recently, it was shown that GnRH agonist administration induced atherosclerosis in mice. Four months treatment of GnRH agonists alone induced atherosclerosis in low density lipoprotein receptor (LDLR) knockout mice with normal chow diet [59]. In addition, 4 weeks of leuprolide acetate

administration destabilized established atherosclerotic plagues in apolipoprotein E (ApoE) knockout mice by recruiting macrophages and inducing necrosis [60]. Both *in vitro* and *in vivo* studies have shown that T cells of atherosclerotic plaques express GnRHR, and GnRH agonists induced proliferation and activation of these cells through GnRH receptor type I [60, 61]. Furthermore, GnRH receptors favor the generation of Th1-type cells [62], which promote atherosclerosis.

The pituitary axis contributing to the hormonal imbalance has also been proposed as an underlying mechanism but not clinically proven. GnRH agonist could potentially alter male hormones and the modulation may differ from physiological state or with other ADT treatment regimen. These GnRH agonist-mediated hormonal imbalance may affect the cardiac function outside the direct action of testosterone. For example, GnRH agonists lead to an initial surge in LH and FSH, which is in contrast to the rapid inhibition of these hormones by GnRH antagonists (*e.g.* degarelix) [63]. Importantly, FSH levels did not reach the level of GnRH agonists -mediated decline even after 12 months of GnRH agonist (leuprolide) treatment [43, 63]. The spike and continued presence of trace FSH levels are important in the context of low-level expression of FSH receptors in cardiac myocytes [56, 64] and human adipocytes [65]. An increase in FSH was also observed after orchiectomy along with higher LH and reduced anti-Mullerian hormone (AMH) [66], whereas GnRH agonist use decreased LH while sustaining AMH levels [67]. GnRH agonists also decrease the serum inhibin level, which causes a secondary FSH surge, creating a feedback loop under GnRH agonist treatment [67]. The altered hormonal levels during ADT (particularly with GnRH agonists) may affect cardiac function and CVD risk. In particular, FSH may promote atherosclerotic plaque formation and other metabolic changes associated with ADT [68].

The third possible mechanism by which GnRH agonists contribute to CV risk is via direct action on cardiomyocytes. GnRHR expression has been reported in various extra-gonadal tissues including heart, kidney, and immune cells [69, 70]. In addition, GnRH binding has been detected in multiple tissues and tumors, including the hypothalamus, pituitary, gonads, breast, and prostate cancers. Mechanistically, GnRH agonists trigger the release of gonadotropins in the pituitary gland through the inositol trisphosphate-protein kinase C (PKC) pathway [71] and MAPK-dependent phospholipase A_2 [71]. Calcium mobilization also plays a major role in the release of sex hormone. Even though human cardiac tissues express GnRHR mRNA, there is no evidence which suggests that the GnRH agonists mediate calcium accumulation in human cardiac cells. A preclinical study by Dong et al. [72] suggested that GnRH agonists have positive effects on cardiomyocyte contractile function. As opposed to the classical GnRH/PKC-mediated intracellular calcium accumulation and gonadotropin release in the pituitary, the cardiac contractility and intracellular calcium concentration increases via a GnRHR/protein kinase A (PKA)-dependent mechanism. GnRH activates PKA, which phosphorylates several important substrates in cardiomyocytes, including phospholamban, an L-type calcium channel on the sarcolemma and components of the contractile apparatus. PKA could have an essential role in a GnRH-associated cardiac response [73]. PKA may phosphorylate the ryanodine receptor/Ca^{2+} release channel, which in turn regulates channel conductance in cardiomyocytes [74]. Exposure of mouse cardiomyocytes to GnRH agonists resulted in a

significant change in myocardial intracellular calcium concentration, thus altering the cells contractility [72]. High doses of GnRH analogs increased intracellular Ca^{2+} in the myocardium under resting and electrostimulation conditions through non-conventional GnRH/PKA receptor signaling [72]. As illustrated in Figure 3, this non-conventional signaling can phosphorylate the sarcolemmal L-type calcium channel and phospholamban, which in turn modulate contractile function in cardiomyocytes. In addition, electrolytes modification could play a role in the cardiac QT prolongation observed during a six-month treatment with GnRH agonists [75]. The non-classical action of GnRH/PKA is further supported by the *in vitro* observation that GnRH can act through both PKA and PKC mediated signaling mechanisms in the mature gonadotrope LbetaT2 cell line [76].

The extra gonadal (adrenal gland and intraprostatic) steroidogenesis is responsible for 5–10% of circulating androgens. In clinics, this extra-gonadal androgen biosynthesis and prostate AR signaling were managed by non-steroidal antiandrogens and androgen biosynthesis inhibitor (Figs. 1 & 2). Though, the antiandrogen monotherapy is not common across the globe, still it is given in few Asian and European countries during clinical management of PCa. The androgen biosynthesis inhibitor and antiandrogens will inhibit CYP17A1-mediated androgen precursor synthesis and AR signaling, respectively (Fig. 2). The extra gonadal steroidogenesis has limited influence on physiological testosterone. In fact, antiandrogen monotherapy may slightly increase the circulating testosterone than the normal physiological level [77]. In this scenario, these elevated testosterone levels may be associated with elevated CV risk, as seen with supraphysiological testosterone administration associated with elevated hematocrit [78]. Yet, the higher peripheral testosterone can be regulated through negative feed-back hypothalamic-pituitary-adrenal [HPA] axis [21, 22]. This might be different from the supra physiological testosterone levels observed during androgen supplementation. It is currently undetermined whether the antiandrogens associated normal or supra physiological testosterone levels have any causal relationship with CVD in men with PCa. Few observational studies (Table 1) suggest that antiandrogen monotherapy is associated with increased CHD, MI, arrhythmia, heart failure and stroke (Table 1). Hemelrijck and group suggested that antiandrogen monotherapy increased the CV risk events during the first year of therapy and the risk become non-significant over the time [30]. Similarly, the thromboembolic disease events are reduced in PCa patients who received antiandrogens monotherapy compared to age-matched PCa patients [31]. Interestingly, a multicenter observational study revealed that patients who received antiandrogen monotherapy had reduced CV risk events compared to the PCa patients who received GnRH agonists as ADT [79]. The protective effect of testosterone in general may contribute to the reduced/non-significant observation between antiandrogens and CVD risk [31]. There is also a possibility that the patients who receive antiandrogens monotherapy are younger and have less aggressive PCa [30]. In addition, the patients may receive antiandrogens for a short time, and will cross over to systemic ADT such as GnRH agonists treatment which will further dilute the real risk ratio. Further, most of the observational studies describing the associations derive these conclusion from either cancer registry or institutional data base which do not mention about the testosterone levels during antiandrogen monotherapy.

6. Proposed strategies to reduce CV risk and toxicity induced by GnRH agonists: PDE5 inhibition and cGMP signaling

As summarized in Table 3, various types of anticancer drugs have been shown to induce cardiotoxic effects. However, the cellular and molecular mechanisms underlying GnRH agonist-induced cardiotoxicity may be fundamentally different than other major anticancer drugs (Table 3). Despite abundant evidence linking ADT and CVD risks and cardiotoxicity, currently, there is a paucity of studies to identify, develop or even conceptualize strategies to address ADT-induced CVD risk factors and cardiac dysfunction. In order to fill this apparent gap of knowledge, we hypothesize that a class of cGMP-specific phosphodiesterase 5 (PDE5) inhibitors may be effective in reducing CVD adverse effects. Since early 2002, we have described the powerful cardioprotective effects of PDE5 inhibitors (*i.e.* sildenafil, vardenafil, tadalafil) against myocardial infarction, heart failure, and doxorubicin-induced cardiomyopathy [80–87]. As of today, close to 160 clinical trials with PDE5 inhibitors (http://www.clinicaltrials.gov) have focused on potential CV benefits. However, no study has evaluated the efficacy of PDE5 inhibitors in limiting CVD events in patients with PCa receiving GnRH agonists.

As mentioned above, the possible underlying mechanism(s) of GnRH agonist-induced cardiac dysfunction and toxicity relates to GnRHR expression in the heart. Therefore, targeting GnRHR/PKA signaling may be a therapeutic strategy to prevent these CV adverse events [72]. PDE5 inhibitors trigger a cardioprotective effect against doxorubicin-induced cardiotoxicity, by generating therapeutic levels of nitric oxide (NO) and cGMP. The activation of cGMP-dependent protein kinase G (PKG) signaling can potentially modulate the PKA-dependent mechanism that controls cardiomyocyte contractility and viability (Figure 4). In fact, cross-talk between cGMP and cAMP signaling pathways has been demonstrated in human platelets by Li et al. [88] in 2003. However, it remains largely unknown how PKG and PKA interact in the setting of co-treatment with a GnRH agonist and PDE5 inhibitor. Further in-depth studies are clearly needed to fully address this unsolved issue.

7. Summary and perspectives

Given the probability of long-term survival of men with PCa and prolonged treatment with ADT, the systemic and metabolic side effects of this therapy on vital organs and functions is an emerging concern. In particular, the close association between ADT and CVD leads to decreased quality of life as well as life span. This relationship was supported by the fact that CVD is the primary reason for death among men with PCa [9].

A plethora of observational studies have provided evidence that ADT results in various levels of CV risk events, and the risk of CVD is not uniform among different modes of ADT. CV risk events in PCa patients due to orchiectomy and antiandrogen have mixed observations compared to PCa patients who did not received any form of ADT [6, 23–26, 29–31, 36]. Besides, the second generation antiandrogens are not given as first line monotherapy. Nevertheless, observational studies coupled with preclinical evidence suggest that patients with a history of cardiac events may be at higher risk of death among PCa

patients who receive GnRH agonists as ADT strategy. Further, ADT-induced metabolic alterations may also cause CV events [46, 48, 51]; which would likely manifest later than the observational time frame of less than a year. Intriguingly, a randomized study which reported that GnRH agonist has higher adverse CV events compared to GnRH antagonist [43]. Thus, further studies to understand the cellular and molecular mechanisms of GnRH agonist-associated cardiotoxicity are still needed, which can help in identifying novel therapeutic targets for alleviating ADT toxicity.

The direct evidence of GnRH agonists on CV predisposing events was shown in various experimental models, supported by the explanation of increased fat mass, insulin sensitivity, and altered metabolism-mediated arterial stiffness and atherosclerosis. Of interest, one preclinical study showed that GnRH agonists could induce adverse CV events through an altered GnRH/PKA axis but further validation is needed [72]. These studies have tested the hypothesis that common strategies of managing PCa patients with CV risk events may not be enough. Significant efforts have been made in the past to intervene in the ADT-induced adverse CV events, but not CVD [3]. Therefore, it is important to consider a safer pharmacological agent to use as a preventive agent irrespective of ADT type. We have built a compelling case for the potential use of PDE5 inhibitors (e.g., sildenafil citrate) in preventing and/or treating ADT (GnRH agonist)-induced cardiotoxicity in PCa patients. Because PDE5 inhibitors are FDA approved and widely prescribed drugs outside the context of PCa, these drugs hold great promise as a repurposed cardioprotectant that could be used in conjunction with ADT for local, advanced or metastatic PCa patients.

Considering the efficacy and number of patients receiving ADT, providers should discuss the increased CVD risk and monitor patients closely. Because of the recent change in the treatment landscape of ADT to ADT with enzalutamide or chemo-hormonal therapy for advanced PCa, there is an increase in the number of patients under ADT and hence, the interest in the associated CVD risk events also increased. Interestingly, a recent meta-analysis by Iacovelli et al. [89] revealed that the use of the second-generation hormonal agent abiraterone acetate also significantly increased CVD risk. The risk is higher during the early period of ADT (up to 12 months) treatment; hence the concurrent monitoring of hormones such as androgens, insulin, FSH, ACTH might be useful to track the development of metabolic disease, which is considered one of the causes of CVD. Further, a baseline cardiac risk assessment should be performed to tailor the cancer treatment and cardiac management strategy. Therefore, until pharmacological agents like the one proposed above are validated in a prospective clinical trial, physicians should consider a comprehensive effort to minimize/mitigate ADT-induced adverse events. If needed, a collaborative, multidisciplinary approach should be considered by involving oncologists and cardiologists to overcome cardiac comorbidities.

Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms “androgen deprivation therapy”, “heart”, “toxicity”, and “prostate cancer” from 1985 until March 2020. Articles were also identified through searches of the authors’ own files.

Only papers published in English were reviewed. The final list of 89 references was generated on the basis of originality and relevance to the broad scope of this review.

Acknowledgments

We thank Dr. Jessica Mercer for her editorial contributions. The authors are in part supported by grants from the National Institutes of Health (UO1 CA185148 to SKB; RO1 CA221813, DK120866, HL118808 to RCK; and RO1 HL134366 to RCK & AD) and the Department of Defense Idea Award (PC170891 to SKB & RCK). LX is a recipient of the Pauley Pilot Research Grant from the VCU Pauley Heart Center. The funding agencies had no involvement in the conception, design or views presented in the review.

Abbreviations

ADT	Androgen deprivation therapy
AMH	Anti-Müllerian hormone
Apa	Apalutamide
ApoE	Apolipoprotein E
AR	Androgen receptor
ARPI	AR pathway inhibitors
CAD	Coronary artery disease
cGMP	Cyclic guanosine monophosphate
CV	Cardiovascular
CVD	Cardiovascular disease
CYP17A1	Cytochrome P450 family 17 subfamily A member 1
DES	Diethylstilbestrol
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
eNOS	Endothelial nitric oxide synthase
EORTC	European Organization for Research and Treatment of Cancer
ESC	European Society of Cardiology
FSH	Follicle-stimulating hormone
GC	Guanylate cyclase
GnRH	Gonadotropin-releasing hormone
GnRH	Gonadotropin-releasing hormone
GTP	Guanosine-5′-triphosphate

iNOS	Inducible NOS
LDLR	Low density lipoprotein receptor
LH	Luteinizing hormone
LH	Luteinizing hormone
MPTP	Mitochondrial permeability transition pore
NO	Nitric oxide
PCa	Prostate cancer
PDE5	Phosphodiesterase 5
PKA	Protein kinase A
PKA	Protein kinase A
PKG	Protein kinase G
PSA	Prostate-specific antigen
RCT	Randomized controlled trials
SEER	Surveillance, Epidemiology, and End Results
T	Testosterone

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Highlights

- Androgen deprivation therapy (ADT) causes various adverse effects, including increased risk of cardiovascular events
- Improved life span and novel androgen receptor inhibitors further extend the risk of cardiovascular disease among cancer survivors
- Among various ADT agents, gonadotropin releasing hormone agonists are associated with higher cardiotoxicity
- The underlying molecular mechanisms of ADT-induced cardiotoxicity is still limited

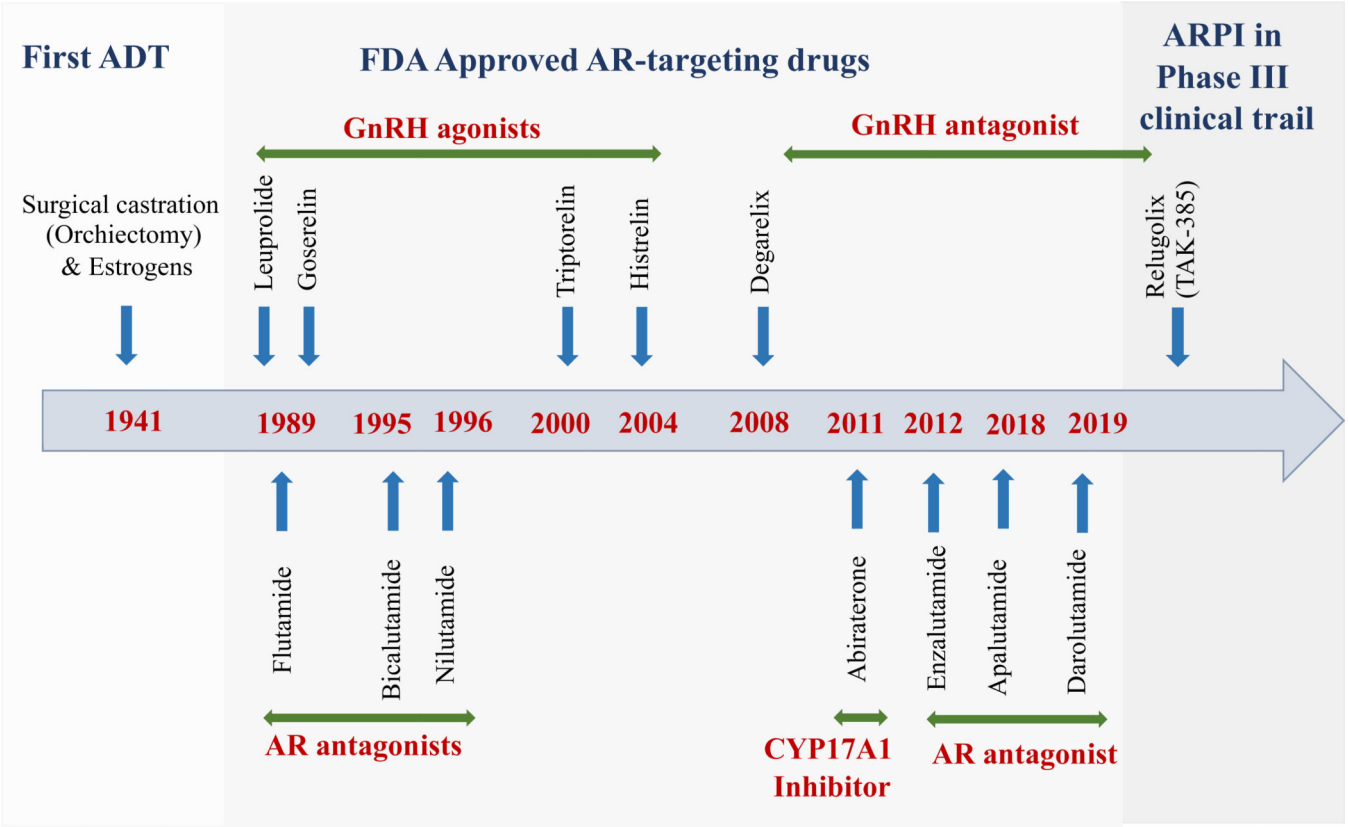

Figure 1. Landmarks in targeted therapies of androgen signaling approved for advanced prostate cancer management.

Graphical representation of drugs targeting the AR pathway for prostate cancer, starting from surgical castration to currently approved and in-use drugs. Drugs were classified according to their targets; novel agent still in clinical trials is given at the end.

Abbreviations: AR – androgen receptor, CYP17A1 – cytochrome P450 family 17 subfamily A member 1, GnRH – gonadotropin-releasing hormone.

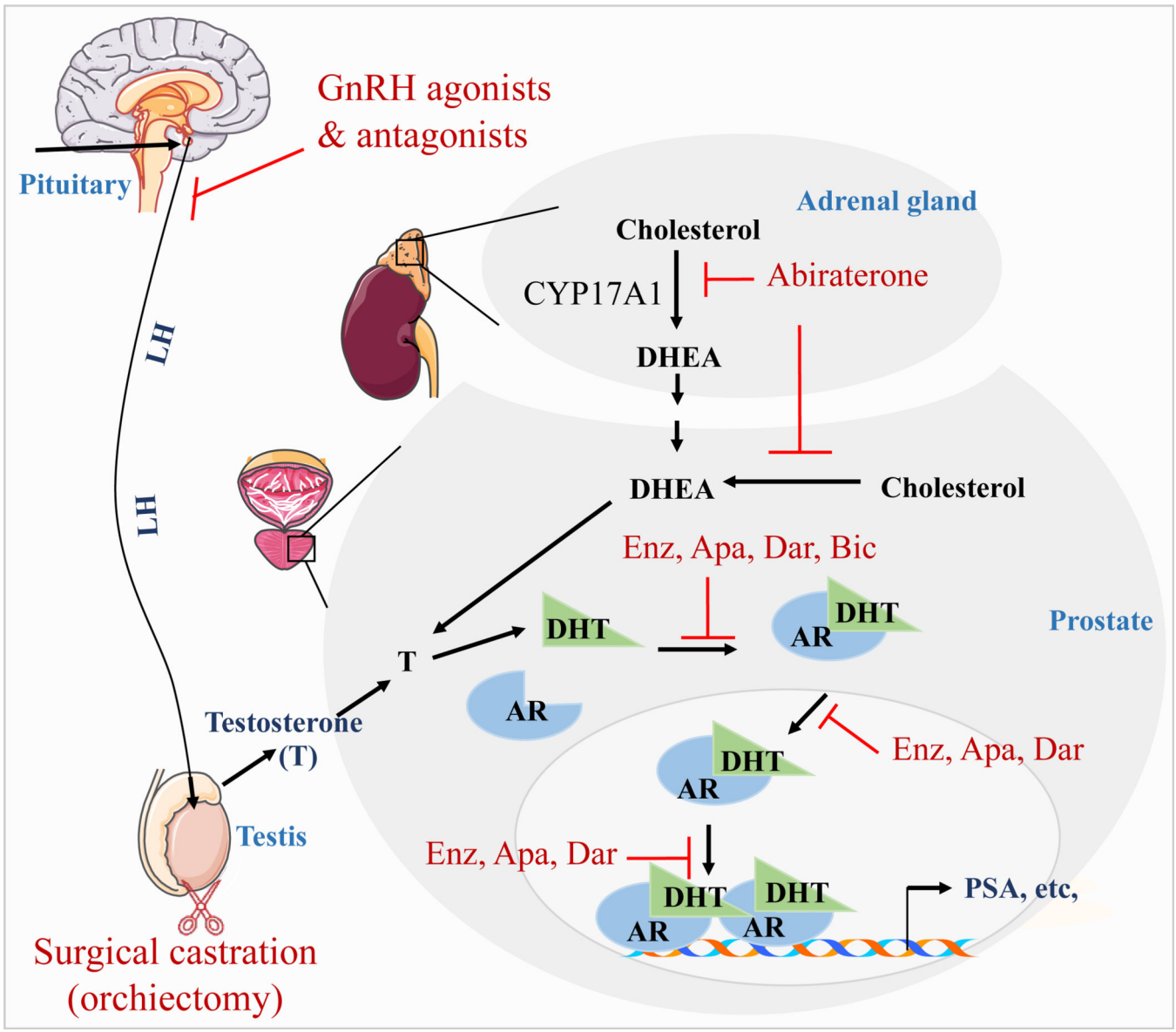

Fig. 2. Androgen receptor pathway inhibitors and their mechanism of action.

Testosterone, the major driver of prostate cell proliferation and survival, is synthesized by the testis under the control of LH, which is regulated by the hypothalamus/pituitary axis. De novo testosterone then reaches the prostate and is converted into more potent DHT form by the enzyme 5-α reductase. Either T or DHT forms a complex with AR, which then binds with an AR-specific DNA sequence and induces transcription of genes. Since 1941 various strategies were developed to inhibit the AR signaling axis in prostate cancer. A surgical procedure to remove the testis, to eliminate the source of T. The drugs which act on various organs are indicated in red. Part of the figure icons are obtained from Servier Medical Art (http://smart.servier.com), licensed under a Creative Common Attribution 3.0. (https://creativecommons.org/licenses/by/3.0/). The male urinary tract is simplified to show only urinary bladder and prostate. Abbreviations: Apa – apalutamide, AR – androgen receptor, CYP17A1 – cytochrome P450 family 17 subfamily A member 1, Dar - darolutamide, DHEA

– dehydroepiandrosterone, DHT –dihydrotestosterone, Enz – enzalutamide, GnRH – gonadotropin-releasing hormone, LH – luteinizing hormone, PSA – prostate-specific antigen, and T – testosterone.

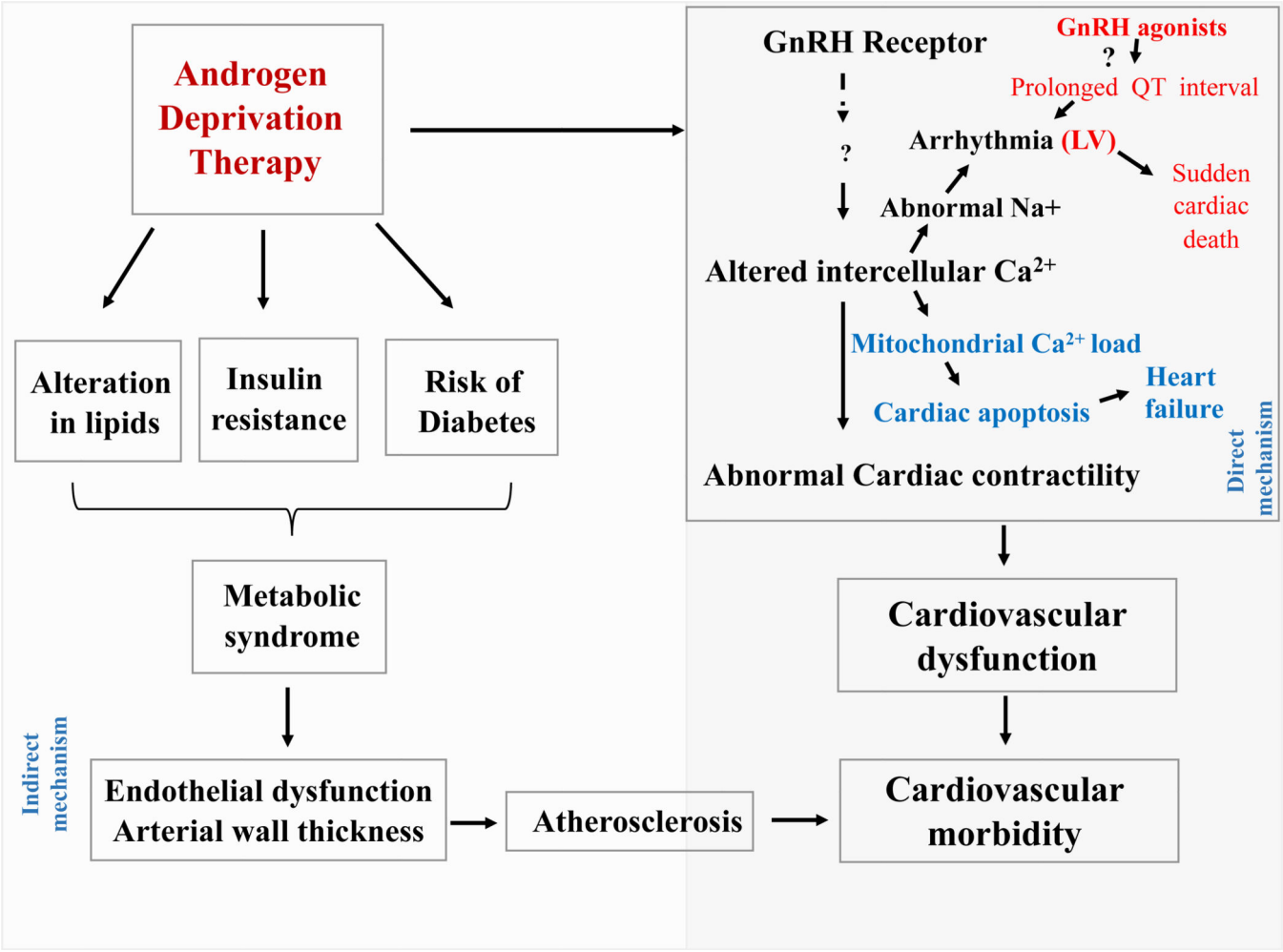

Fig. 3. ADT (GnRH agonist)-associated adverse events and pathogenic mechanisms.

ADT alters lipid profiles and insulin resistance. These alterations can induce the development of metabolic syndrome. Further, the accumulation of lipids can lead to endothelial dysfunction and arterial wall thickness, which can result in the development of atherosclerosis. Mechanistically, ADT can alter the intracellular calcium in cardiomyocytes through GnRH receptors. This abnormal calcium gradient can alter a plethora of normal cardiac functions such as cardiac contractility cardiac apoptosis, and heart rate.

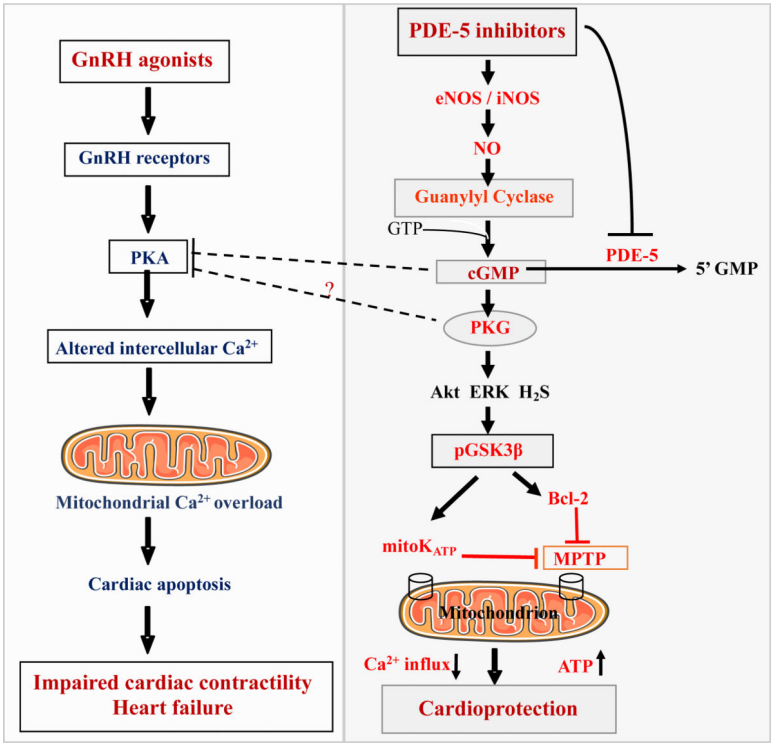

Fig. 4. Cross-talk between ADT (GnRH agonists) and cGMP-mediated signaling: potential adverse events and possible preventive mechanisms.

GnRH agonists can regulate PKA signaling in cardiac cells via GnRHRs thereby altering the intracellular calcium. The altered calcium can lead to mitochondrial influx and induce cardiomyocyte apoptosis, eventually impairing cardiac contractility or causing heart failure. PDE5 inhibitors can upregulate NO in cardiac cells through constitutively active eNOS. The increased NO can upregulate cGMP which may protect cardiomyocytes through cGMP/PKG signaling and inhibition of mitochondrial calcium uptake. The GnRH agonists mediated potential CV events are given in the left box and the our perspective are given in the right box along with posssible mechanistic relation. The mitochondrion icon is from Servier Medical Art (http://smart.servier.com), licensed under Creative Common Attribution 3.0. (https://creativecommons.org/licenses/by/3.0/). Abbreviations : cGMP – cyclic guanosine monophosphate, eNOS – endothelial nitric oxide synthase, GC – guanylate cyclase, GTP – guanosine-5′-triphosphate, H_2S - hydrogen sulfide, iNOS – inducible NOS, mitoKATP - ATP-sensitive mitochondrial potassium channel, MPTP - membrane permeability transition pore, PDE5 – phosphodiesterase type 5, PKA – protein kinase A, PKG – protein kinase G, MPTP – mitochondrial permeability transition pore, NO – nitric oxide.

Table 1:

Evidence from population-based observational studies for the relationship between GnRH agonists use, and CV/outcomes risk events.

Study/Database (Study period)	Number of patients with stage and age	Type of ADT and duration	CV risk event and median follow-up	Cardiovascular risk events/ mortality incidence	Adjusted HR; p-value
Keating et al. [7] SEER (1992–1999)	73,196 Men with locoregional PCa Mean age - 72 years	GnRH agonist and/or AA vs. No ADT Median - 4.5 years	Until first CV risk event with Median follow-up of 4.55 years.	CHD	1.16 (1.10–1.21); p=0.001
				MI	1.11 (1.01–1.21); p=0.03
				SCD	1.16 (1.05–1.27); p=0.004
Tsai et al. [27] US CaPSURE (1995–2004)	4,892 Men with localized PCa Median age - 64 yrs	GnRH agonist and/or AA vs. No ADT Median - 4.1 months	Median follow-up of 3.8 years	CV mortality with RP	2.6 (1.4–1.7); p=0.002
				CV mortality with EBRT, BT or CT	1.07 (1.02–1.1); p=0.004
Saigal et al. [8] SEER (1992–1996)	22,816 Men with PCa >65 years of age	Any medical ADT vs. No ADT Mean - 21 months	Follow-up of 5 years after diagnosis	CV morbidity	1.20 (1.15–1.26); ND 20% higher CV morbidity among the patients who received ADT vs. No ADT for 1 year.
Alibhai et al. [36]	19,079 Men with PCa	GnRH agonist and/or AA	Mean follow-up of 6.47 years	MI	0.92 (0.84–1.00); NS
				SCD	0.96 (0.83–1.10); NS
Ontario Cancer Registry (1995–2005)	>66 (mean 75) years of age	Orchiectomy vs. No ADT		Diabetes	1.24 (1.15–1.35); p<0.05
Keating et al. [6] US VHA (2001–2004)	37,443 Men with locoregional PCa until Dec 2005 or death	GnRH agonists, vs. no ADT Ever vs. never users	Mean follow-up of 2.6 years	CHD	1.17 (1.09–1.25); p=0.001
				MI	1.11 (0.95–1.30); p=0.18
				SCD	1.44 (1.28–1.64); p=0.01
				Stroke	1.17 (1.03–1.33); p=0.02
		AA monotherapy vs. no ADT (unadjusted)		CHD	1.27 (1.05–1.53)
Van Hemelrijck et al. [24] PcBaSE Sweden (1997–2007)[a]	76,600 Men with PCa vs. matched non-cancer men	GnRH agonist use (SIR) [b]	Until death	MI	1.28 (1.11–1.47) [a]
				Arrhythmia	1.27 (1.10–1.47) [a]
				IHD	1.30 (1.17–1.45) [a]
				Heart failure	1.46 (1.28–1.67) [a]

Study/Database (Study period)	Number of patients with stage and age	Type of ADT and duration	CV risk event and median follow-up	Cardiovascular risk events/ mortality incidence	Adjusted HR; p-value
		GnRH agonist use (SMR) [b]		Stroke	1.27 (1.12–1.43) [a]
				MI	1.28 (1.07–1.53) [a]
				Arrhythmia	0.64 (0.38–1.09) [a]
				IHD	1.01 (0.88–1.16) [a]
				Heart failure	1.23 (0.89–1.71) [a]
				Stroke	1.01 (0.77–1.34) [a]
		Antiandrogens (SIR) [b]		MI	1.12 0.94 to 1.34
				Arrhythmia	1.38 1.16 to 1.65
				IHD	1.13 0.99 to 1.30
				Heart failure	1.15 0.95 to 1.41
				Stroke	1.19 1.02 to 1.40
		Antiandrogens (SMR) [b]		MI	0.98 0.75 to 1.27
				Arrhythmia	0.38 0.17 to 0.87
				IHD	0.79 0.65 to 0.96
				Heart failure	0.53 0.28 to 0.99
				Stroke	0.81 0.54 to 1.20
Azoulay et al. [25] UK GPRD) (1988–2008)	15,375 men received ADT Mean age 72.3 years.	Current users of GnRH agonists CAB Oral antiandrogens	Mean follow-up of 3.9 years	Stroke/TIAs	1.18 (1.00–1.39)
					1.26 (0.93–1.72)
					1.47 (1.08–2.01)
Hu et al. [26] SEER (1992–2007)	182,757 Men with locoregional PCa >65 yrs of age	GnRH agonist vs. No ADT	Mean follow-up of 5.1 years	PAD	1.16 (1.12–1.21); p<0.001
				VTE	1.10 (1.04–1.15); p<0.001
Jespersen et al. [29] Danish Cancer Registry (2002–2010)	31,571 Men with PCa Median age at PCa diagnosis was 71 years.	GnRH agonist/AA vs. No ADT adjusted	Median follow-up of 3.3 years	MI	1.33 (1.15–1.53)
				Stroke	1.21 (1.05–1.39)
Gandaglia et al. [23] SEER (1995–2009)	140,474 Men with non-metastatic PCa >65 years of age	GnRH agonist vs. No ADT	Mean (median) follow-up of 75.3 months (6.3 years)	CAD	1.11 (1.07–1.15); p<0.001
				AMI	1.09 (1.04–1.15); p<0.001
				SCD	1.18 (1.12–1.24); p<0.001
O'Farrell et al. [30] PCBaSe Sweden 2.0	41362 Men with Prostate cancer	GnRH agonist vs. age-matched men w/o PCa	All incidental CVD	CVD	1.21 (1.18–1.25)

Study/Database (Study period)	Number of patients with stage and age	Type of ADT and duration	CV risk event and median follow-up	Cardiovascular risk events/ mortality incidence	Adjusted HR; p-value
			W/o baseline risk factors	CVD	1.19 (1.14–1.24)
			Men with a history of Statin use	CVD	1.20 (1.12–1.28)
		AA vs. age-matched men w/o PCa	All incidental CVD W/o baseline risk factors Men with a history of Statin use	CVD	0.87 (0.82–0.91)
				CVD	0.81 (0.75–0.87)
				CVD	0.86 (0.78–0.95)
O'Farrell et al. 2016 [31] PCBaSe Sweden 3.0	42 263 men with PCa	GnRH agonists vs. No ADT		DVT	1.67 (1.40–1.98)
				PE	1.61 (1.42–1.82)
		AA vs. No ADT		DVT	0.49 (0.33–0.74)
				PE	0.58 (0.45–0.75)
Morgia et al., [79] Italian multicenter,	1075 patients with PCa		GnRH agonists vs. AA alone	CV complications	OR= 3.95 (1.01–15.34) p<.05
cross-sectional study (2010 to 2012)			CAB (GnRH agonists +AA) vs. AA alone	CV complications	OR= 3.37(1.10–10.30) p<.05

Abbreviations: AA-antiandrogen; AMI - acute myocardial infarction; AS-active surveillance; BT-brachytherapy; CAD-coronary artery disease; CaPSURE - Cancer of the Prostate Strategic Urologic Research Endeavour; CHD-coronary heart disease; CT-cryotherapy; EBRT-external beam radiation therapy; CVD- Cardiovascular disease [(IHD- ischemic heart disease), arrhythmia, HF & stroke]; DVT-Deep vein thrombosis; GnRH-gonadotropin-releasing hormone; ID- Incidental diabetes; MI-myocardial infarction; PcBaSE-Prostate Cancer data Base Sweden; ND- no detail; NS- not significant; OR- Odds ratio; PAD-peripheral artery disease; PE - Pulmonary embolism; RP- radical prostatectomy; SCD-sudden cardiac death; SEER-surveillance, epidemiology, and end results; SES- socio economic status; SIR-standardized incident ratios; SMR-standardized mortality ratios; US-United States; TIAs- transient ischemic attacks; VHA-Veterans Healthcare Administration; VTE-venous thromboembolism; WW-watchful waiting.

[a] The data were shown only to GnRH agonist use for SIRs and SMRs and were adjusted for the circulatory disease at baseline, SES, and PCa stage.

[b] SIR and SMR is higher than AA, Orchiectomy, GnRH agonists with short-term AAs and curative treatment.

Table 2:

Meta-analyses of randomized controlled trials for relationship between GnRH agonists use and CV/outcomes risk events.

Study/Database (Study period)	Type of study	Type of ADT vs. control group	Cardiovascular risk bevents/ mortality incidence	Adjusted HR; p-value
Nyguen et al. [39] 4141 men with PCa Median follow-up of 7.6 years to 13.2 y ears	Meta-analysis of eight RCT s Cardiovascular death as the separate endpoint	GnRH agonist- based ADT versus no immediate use of ADT	CV mortality	0.93 (0.79–1.10) p=0.41
Wilcox et al. [40] 802 men with PCa	TROG 96.01 trial	Radiotherapy (RT) versus RT plus 3 or 6 months neoadiuvant ADT	Cumulative fatal cardiac events RT for RT plus 6-mo ADT	7.5% (4.8–11.1) 6.4% (3.9–9.9)
Albertson et al. [41] 2328 men with PCa	Pooled analysis of six RCTs	GnRH agonists vs. antagonists	CV adverse events within 1 year of ADT in men with pre-existing CVD conditions	0.44 (0.26–0.74)
Bosco et al. [37]	Meta-analysis of eight observational studies	GnRH agonists, orchiectomy and antiandrogens vs. No ADT	The relative risk of nonfatal CVD (GnRH agonists) CVD (Orchiectomy) CVD (Antiandrogens) Non-fatal ID (Agonists) Non-fatal MI (Agonists) Fatal MI (Agonists).	1.38 (1.29–1.48) 1.44 (1.28–1.62) 1.21 (1.07–1.36) 1.39 (1.26–1.54 1.57 (1.26–1.94) 1.51 (1.24–1.84)
Guo et al. [38] 170,851 ADT users vs. 256,704 non-ADT users.	Pooled meta-analysis of five retrospective population-based cohort studies	GnRH agonists, Antiandrogens (AA) GnRH agonists plus AA, & orchiectomy vs. Non-ADT	DVT (GnRH agonists) DVT (GnRH agonists plus oral AA) DVT (AA alone) DVT (Orchiectomy) PE (GnRH agonists) PE (Orchiectomy)	1.47 (1.07– 2.03); p=0.017; I^2=96.3% 2.55 (2.21–2.94); p<0.001; I^2=0.0%, 1.49 (1.13–1.96); p=0.004; I^2=0.0% 1.80 (0.93–3.47);p=0.079; I^2=94.8% 2.26 (1.78–2.86);p< 0.001 2.12 (1.44–3.11);p< 0.001; I^2=57.2%)

Abbreviations: AA-antiandrogen; ADT-androgen deprivation therapy; CVD-cardiovascular disease; DVT-Deep venous thrombosis; GnRH-gonadotropin-releasing hormone; ID-ischemic disease; MI-myocardial infarction; PE- pulmonary embolism.

Table 3:

Comparative summary of adverse effects of the commonly used systemic anticancer drugs on cardiovascular health.

Class of Anticancer Drugs	Types of Drugs in Clinical Use	Potential Events and/or Mechanisms of Anticancer Drug-induced Adverse Effects on Cardiovascular Health
Androgen-deprivation therapy (ADT)	***GnRH agonists:*** Buserelin, Goserelin, Histrelin, Leuprolide, Triptorelin, ***GnRH antagonists:*** Abarelix, Degarelix, ***Androgen receptor blockers:*** Abiraterone acetate, Apalutamide Bicalutamide, Cyproterone, Darolutamide, Flutamide, Nilutamide, Seviteronel	GnRH agonists increase intracellular Ca^{2+} and activate PKA signaling that phosphorylates sarcolemmal L-type calcium channel and phospholamban in cardiomyocytes; Prolongation of cardiac QT- interval; Hyperlipidemia; Diabetic complications; Peripheral arterial disease.
Alkylating agents	Cyclophosphamide, Cisplatin	Endothelial dy sfunction; Arterial vasoconstriction; Ventricular dysfunction; Microbiota dysbiosis; Renal and vascular damage
Anthracyclines	Doxorubicin, Daunorubicin, Epirubicin, Idarubicin	Oxidative stress, DNA damage; Necrotic and apoptotic cell death in heart and blood vessels; Fibrotic and inflammatory changes in vascular wall and myocardium; Endothelial dysfunction; Ventricular dy sfunction; Mitochondrial injury.
Cancer immune checkpoint blockade therapy	***CTLA-4 inhibitors:*** Ipilimumab ***PD-1 inhibitors:*** Nivolumab, Pembrolizumab ***PD-L1 inhibitors:*** Atezolizumab, Avelumab, BMS-946559, Durvalumab	Myocarditis and pericarditis; Heart block; Cardiomyopathy; Myocardial fibrosis; Ventricular dysfunction.
Fluoropyrimidines antimetabolites	Capecitabine, Carmofur, Doxifluridine, 5-Fluorouracil, T egafur	Coronary vasospasm and subsequent myocardial ischemia; Endothelial and myocardial cell apoptosis; Oxidative stress; Mitochondrial dysfunction; Inflammation; Thrombi formation.
Tyrosin kinase inhibitors	Pazopanib, Sorabenib, Sunitinib	Endothelial dysfunction; Reduced NO bioavailability; Vascular rarefaction; Hypothyroidism
VEGF inhibitors	Bevacizumab, Vandetanib	Endothelial dysfunction; Reduced NO bioavailability; Increased endothelin production and arterial vasoconstriction; Ventricular dysfunction; Platelet aggregation; Myocardial inflammation.

Abbreviations: ADT-androgen-deprivation therapy; CTLA-4-cytotoxic T-lymphocyte associated protein 4; GnRH-gonadotropin-releasing hormone; NO-nitric oxide; PD-1-programmed cell death 1; PD-L1-ligand of programmed cell death 1; PKA-protein kinase A; VEGF-vascular endothelial growth factor.