Cardiovascular Toxicities of Androgen Deprivation Therapy

Azariyas A. Challa, MD, PhD
Adam Christopher Calaway, MD
Jennifer Cullen, PhD, MPH
Jorge Garcia, MD
Nihar Desai, MD, MPH
Neal L. Weintraub, MD
Anita Deswal, MD
Shelby Kutty, MD, PhD
Ajay Vallakati, MBBS, MPH
Daniel Addison, MD
Ragavendra Baliga, MD, MBA
Courtney M. Campbell, MD, PhD
Avirup Guha, MD

Address
*Correspondence: Avirup Guha, MD, Harrington Heart and Vascular Institute, UH Cleveland Medical Center, Cleveland, OH, USA

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Opinion statement

Prostate cancer is the second leading cause of cancer death in men, and cardiovascular disease is the number one cause of death in patients with prostate cancer. Androgen deprivation therapy, the cornerstone of prostate cancer treatment, has been associated with adverse cardiovascular events. Emerging data supports decreased cardiovascular risk of gonadotropin releasing hormone (GnRH) antagonists compared to agonists. Ongoing clinical trials are assessing the relative safety of different modalities of androgen deprivation therapy. Racial disparities in cardiovascular outcomes in prostate cancer patients are starting to be explored. An intriguing inquiry connects androgen deprivation therapy with reduced risk of COVID-19 infection susceptibility and severity. Recognition of the cardiotoxicity of androgen deprivation therapy and aggressive risk factor modification are crucial for optimal patient care.

Introduction

Prostate cancer is the second most common cancer overall and the second leading cause of cancer death in men [1]. Androgen deprivation therapy (ADT) is widely used in prostate cancer treatment because excessive androgen receptor activation in prostate cancer cells leads to uncontrolled cell proliferation [2, 3]. ADT reduces testosterone levels to castration levels, disrupting the hypothalamus-pituitary-gonadal axis. ADT can be achieved surgically via bilateral orchiectomy. However, hormone therapy with gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists is most commonly used.

Within 6 months of diagnosis, 40% of patients with prostate cancer undergo ADT. Almost 50% of patients receive ADT at some point during their illness [4, 5]. ADT is increasingly being used even in the early stages of the disease, along with radiotherapy [6, 7]. When combined with radiotherapy, ADT has been shown to prevent localized prostate cancer progression with high-risk features and improve survival. ADT is also recommended as first-line systemic therapy for metastatic prostate cancer. Exposure to ADT is anticipated to increase with the aging population and earlier prostate cancer detection.

Despite its efficacy in treating prostate cancer, ADT has been associated with several adverse effects, including, but not limited to, insulin resistance, dyslipidemia, obesity, and osteoporosis [8–10]. Notably, the accrued body of evidence from several observational and randomized clinical trials (RCTs) have demonstrated increased risk of cardiovascular (CV) adverse events with ADT. Recent studies and currently ongoing clinical trials seek to determine the safety of GnRH antagonists relative to GnRH agonists from a CV risk perspective.

Cardiovascular disease (CVD) is the leading cause of death in patients with prostate cancer, according to data from the Surveillance, Epidemiology, and End Results (SEER) [11, 12]. Patients with prostate cancer have a higher incidence of CVD than patients without prostate cancer [11]. Death from CVD accounts for 32% (ischemic heart disease 26%, cerebrovascular 6%), while death from prostate cancer stands at number two (20%), followed by death from other causes (14%) [13]. How ADT contributes to CVD in patients with prostate cancer remains an area of active investigation. It is important to remember that CVD and prostate cancer in men have multiple shared risk factors,
including smoking, dyslipidemia, obesity, old age, and male gender [14–16]. In a cohort study of men with intermediate- or high-risk localized prostate cancer, high Framingham risk scores were found in 65% of patients emphasizing the high degree interaction of common risk factors in these two conditions [17].

This review discusses the CVD toxicities of ADT, emphasizing recent areas of inquiry, including different CVD risk profiles between GnRH agonists versus antagonists, racial disparities in CV outcomes for prostate cancer patients, and the connection between COVID-19 infection susceptibility and ADT.

**ADT and risk of cardiovascular disease**

The association of ADT with adverse CV outcomes has been a controversial topic due to conflicting results in early published works [18]. Initial sizeable observational cohort studies and a meta-analysis reported no association between ADT and CV morbidity and mortality [19–21]. Subsequently, several large observational cohorts and clinical trial meta-analyses have validated the association between ADT and increased CVD mortality and morbidity [22–34]. For instance, a meta-analysis of eight large observational studies demonstrated that ADT with GnRH agonists was associated with increased risk of the CVD endpoint of nonfatal myocardial infarction (MI), fatal MI, or stroke (RR 1.57) [30]. In a large population-based study of 22,810 newly diagnosed prostate cancer patients, patients receiving a GnRH agonist for at least 1 year were found to have a 20% higher risk of CV events (hazard ratio [HR] 1.2) over a 5-year follow-up period compared with patients who did not receive ADT [25]. In a pooled analysis of three RCTs that included 1372 men, patients with prostate cancer aged ≥65 years receiving radiation therapy along with 6 months of ADT had shorter times to fatal MI when compared with those who received radiotherapy alone [31].

ADT was strongly associated with increased risk of CV morbidity and mortality in a subset of prostate cancer patients who had preexisting CVD or one or more risk factors for CVD [23, 26–28, 32, 33]. In a retrospective cohort study, among 1378 patients with a history of congestive heart failure or MI treated with radiation, adding ADT was associated with increased all-cause mortality with an adjusted HR of 1.76 [33]. The 5-year all-cause mortality for patients with and without ADT was 22.71% and 11.62%, respectively [33]. In a large observational cohort study involving 26,959 men who received GnRH agonists, there was an increased risk of CV events (HR: 1.21) [28]. This risk was further increased (HR: 1.91) in patients with a history of two or more CV events before initiating therapy with GnRH agonists [28]. In addition to preexisting CVD, age >75 years and the presence of comorbidities were found to increase susceptibility to ADT-associated CV adverse effects [35]. A detailed appraisal of the evidence for the association of ADT with adverse CV events and possible explanations for inconsistent data in the literature can be found in our recent review [18].

The evidence for increased CV risk in patients with prostate cancer on ADT outweighs the evidence against it, as recognized by national organizations. In 2010, the American Heart Association, American Cancer Society, and American Urological Association published a joint scientific statement to make clinicians and patients aware of the association between ADT and the risk of CV events.
In the same year, the US Food and Drug Administration (FDA) issued a statement requiring the addition of safety warning of increased risk of CVD, including heart attack, sudden cardiac death, and stroke on the labeling of GnRH agonist medications. The National Comprehensive Cancer Network (NCCN) guidelines also address ADT-associated CVD risk in prostate cancer patients. In patients with a prior history of significant CVD, referral to a cardiologist before initiating ADT is recommended. NCCN also recommends a multidisciplinary team approach that includes the primary care provider, a geriatrician, and a cardiologist or cardio-oncologist. NCCN further stipulates the assessment of traditional risk factors for CV disease using the ABCDE approach (Awareness and Aspirin, Blood pressure, Cholesterol, and Cigarette smoking, Diet and Diabetes, Exercise) in patients undergoing ADT for prostate cancer [37].

### GnRH agonists vs. antagonists: comparison of cardiovascular risk

Although ADT is associated with increased CVD risk, the relative CVD risk between ADT types is now more appreciated. Specifically, evidence of a difference in the CV risk profile of GnRH antagonists (degarelix, abarelix, and relugolix) versus agonists (leuprolide, goserelin, and triptorelin) has been accumulating over the past decade from observational studies, RCTs, and meta-analyses (see Table 1). GnRH agonists are generally preferred by most oncologists, given the long-term experience and the less frequent administration associated with these agents.

Large observational retrospective cohort studies have shown a higher CV risk for GnRH agonists compared with GnRH antagonists. In a retrospective cohort study involving 9785 prostate cancer patients who received ADT, the incidence of CV events was significantly higher in those treated with GnRH agonists rather than antagonists. In the multivariable regression analysis, the risk of adverse CV events was significantly lower in patients treated with GnRH antagonist compared to those treated with GnRH agonists with HR of 0.76 [38]. Similar results were observed in patients without a prior CVD history. In a population-based cohort study conducted in the UK involving 9081 patients, the relative risk of cardiac events was lower with degarelix, a GnRH antagonist, compared with GnRH agonists (HR = 0.39) [39].

Meta-analyses of randomized clinical trials have also found a difference in the CV risk profiles of GnRH agonists versus antagonists [40–42]. In a large meta-analysis of pooled data from five phase III RCTs consisting of 1925 patients, degarelix improved prostate-specific antigen (PSA) progression-free survival and overall survival compared to GnRH agonists with HR: 0.71 and HR: 0.47, respectively [41]. The authors inferred that the difference in overall survival was likely due to reduced adverse CV events in the patients who received degarelix. Another large meta-analysis analyzed eight RCTs comprising 2632 men with metastatic prostate cancer who received ADT with either GnRH agonist or antagonist. Their analysis revealed that GnRH antagonist treatment was associated with fewer CV adverse events than GnRH agonists (RR: 0.52) [42]. Patients treated with GnRH antagonists also had lower overall mortality rates than patients who received GnRH agonists.
Other studies of patients treated with GnRH agonists versus antagonists have focused on the risk of CV events in patients with preexisting CVD. Using data from a pooled meta-analysis of 6 RCTs comprising a total of 2328 men, the use of degarelix, a GnRH antagonist, was associated with a 40% reduced risk of major adverse CV events and mortality in patients with preexisting CVD compared to GnRH agonist use [43]. Another meta-analysis compared risk of CV events in GnRH antagonist- and agonist-treated patients using pooled RCT and observational data from four studies. Patients treated with GnRH antagonists had decreased CV risk compared to those treated with GnRH agonists (HR 0.597); the risk reduction was more significant in patients with preexisting CV disease (HR 0.44) [44]. A phase 2 randomized clinical trial compared GnRH agonists with antagonists in 80 men with prostate cancer and preexisting CVD. Within 1 year from initiation of ADT, the incidence of adverse CV events was higher in patients who received GnRH agonists (20%) than those who received GnRH antagonists (3%) [45]. Most recently, a phase 3 trial involving 930 patients with advanced prostate cancer studied the efficacy and CV safety of relugolix, a new oral GnRH antagonist, compared to leuprolide, a GnRH agonist [46]. The incidence of major adverse CV events was 2.9% in the relugolix group and 6.2% in the leuprolide group (HR: 0.46; 95% CI, 0.24 to 0.88), representing a 54% CV risk reduction. For men with a history of

| Authors, year | Study type | Number of patients | Study population | Relative risk of CV events |
|---------------|------------|--------------------|------------------|---------------------------|
| Shore et al., 2020 | RCT | 930 | All patients | ↑ |
| Abuferaj et al., 2020 | Meta-analysis of 8 RCTs | 2632 | All patients | ↑ |
| Perone et al., 2020 | Retrospective cohort | 9785 | All patients | ↑ |
| Margel et al., 2019 | RCT | 80 | In patients with pre-existing CVD | ↑ |
| Meseburger et al., 2016 | Mixed meta-analysis of pooled RCTs and pooled cohorts | 126,806 | All patients | ↑ |
| Davey et al., 2020 | Retrospective cohort | 9081 | All patients | ↑ |
| Albertson et al., 2014. | Meta-analysis of 6 phase III RCTs | 2328 | In patient without pre-existing CVD | ↑ |

Table 1. GnRH agonists versus antagonists: comparison of cardiovascular risk
preexisting CVD, the difference in the incidence of adverse CV events was more pronounced, 3.6% vs. 17.8% in the GnRH antagonist and GnRH agonist groups, respectively.

GnRH antagonist treatment in patients with prostate cancer is associated with lower CV adverse events than GnRH agonist treatment. Clinicians may find this updated information on CV safety helpful when choosing between the two hormonal ADT options to treat prostate cancer patients, particularly in patients with preexisting CVD.

**Abiraterone**

Abiraterone is a selective inhibitor of androgen biosynthesis by irreversibly blocking the CYP17 enzyme in the adrenals. Inhibition of the CYP17 enzyme decreases the synthesis of the precursors for androgen and cortisol [47]. When used in combination with ADT, abiraterone was associated with improved survival in men with locally advanced or metastatic prostate cancer compared to ADT alone [48]. However, clinical trials have shown that abiraterone is associated with worsening baseline hypertension and new hypertension diagnosis [49]. The mechanism by which abiraterone causes hypertension is thought to be increased production of mineralocorticoids due to the lack of negative feedback on ACTH production due to decreased cortisol production. To decrease the effect on the adverse effect of mineralocorticoid excess, concomitant administration of abiraterone with low prednisone doses has become the standard. However, ADT combined with abiraterone and prednisone was also associated with an increased incidence of hypertension (20% vs. 0%) compared to ADT alone. In addition, there was also an increased incidence of atrial fibrillation in the abiraterone group atrial fibrillation [50]. A recent meta-analysis revealed that the use of abiraterone acetate significantly increased cardiac toxicity in addition to increased risk of hypertension. The risk of cardiac toxicity was higher during the early period of ADT treatment [51].

**Potential mechanisms for CV risk profile differences between GnRH agonists and antagonists**

ADT in general is associated with metabolic derangements that aggravate CVD risk factors, such as insulin resistance, diabetes, dyslipidemia, and obesity. However, the relative increase of CV events associated with GnRH agonists likely results from unique mechanisms, as both GnRH antagonists and orchiectomy are associated with fewer adverse CV events than GnRH agonists [22, 52]. The reasons for the increased CV risk associated with GnRH agonists are not well understood. Hypotheses for increased CV risk related to GnRH agonists include testosterone fluctuations, follicle-stimulating hormone (FSH) suppression, and immune system activation.

Testosterone fluctuations unique to GnRH agonists may account for the differential risk profiles. In brief, GnRH agonists achieve decreased testosterone levels by exerting negative feedback on the hypothalamus-pituitary axis (Fig. 1). The first administration of GnRH agonists is associated with a significant surge in testosterone levels [53, 54], and
Fig. 1. Potential mechanisms of gonadotropin releasing hormone (GnRH) agonist and antagonist cardiotoxicity. GnRH agonist can lead to testosterone microsurges, promote endothelial dysfunction through follicle stimulating hormone (FSH), and directly activate monocytes and T lymphocytes. Together, these actions may promote atherosclerotic plaque formation, disruption, and thrombosis. In contrast, GnRH antagonists do not lead to testosterone microsurges and more rapidly decrease FSH secretion. Both GnRH agonists and antagonists decrease testosterone levels resulting in wide-ranging effects including insulin resistance, adiposity, dyslipidemia, and increased pro-inflammatory mediators.
each subsequent administration is related to microsurges of testosterone levels [55]. In general, patients treated with GnRH agonists may require weeks or months for a nadir testosterone level to be reached [41]. To counteract the initial testosterone surge, GnRH agonists are frequently administered with androgen receptor blockers (e.g., flutamide, enzalutamide) or androgen synthesis inhibitors (e.g., abiraterone) [56–58], which have been independently associated with adverse CV events [59–61].

In contrast, GnRH antagonists, by directly inhibiting GnRH receptors in the anterior pituitary, rapidly suppress testosterone within a few days [62, 63]. Treatment with GnRH antagonists may confer CV benefits by preventing the CV system’s exposure to testosterone surges (Fig. 1), assuming testosterone microsurges are harmful to the CV system. However, both murine and human studies demonstrate that androgens exert beneficial effects on the vasculature with vasodilatory, proliferative, anti-inflammatory, and anti-thrombotic effects [64–68]. Similarly, several animal and human studies have reported that loss of androgens is associated with adverse CV effects. These effects include vascular stiffness, endothelial dysfunction, increased cholesterol content of atherosclerotic lesions, increased plaque vulnerability, prolonged QTc, and increased pro-atherogenic cytokines, fibrinogen, and adiponectin [69–74]. Not all studies have reported consistent findings, however, as endothelial injury was reported to be similar in patients with prostate cancer treated with GnRH agonists versus GnRH antagonists [45]. Reconciling these potentially beneficial and deleterious effects of testosterone requires a deeper understanding of factors such as the duration of endothelial exposure to testosterone, the effects of variable serum levels of testosterone on the vasculature, the heterogeneity of endothelial androgen receptors and downstream signaling pathways, and genetic variability (i.e., polymorphisms).

Additionally, FSH levels are significantly more suppressed in patients treated with GnRH antagonists than those who received the GnRH agonists [41, 46]. FSH receptors are found in vascular endothelial cell membranes and promote cell adhesion molecule expression in human tissue culture and animal models (Fig. 1) [75]. FSH has been reported to play a role in cell proliferation, adiposity, and fat distribution [76]. FSH may facilitate endothelial injury and subsequent atheroma formation and progression. Increased levels of FSH have also been associated with prolonged QTc [77]. The clinical significance of these observed changes in the development of CV events in patients treated with GnRH agonists is unknown.

Lastly, GnRH agonists may directly alter the immune system to promote atherosclerotic plaque instability (Fig. 1). In a mouse model, GnRH antagonists were associated with fewer atherosclerotic plaques with instability features than GnRH agonists [78]. In vitro experiments using human peripheral monocytes revealed that GnRH controls the expression of GnRH receptors and interleukin-2 receptor gamma at the messenger RNA level [79, 80]. GnRH agonist signaling could promote T cell differentiation into an inflammatory phenotype in atherosclerotic plaques, thereby facilitating plaque disruption, plaque rupture, and thrombus formation [81, 82].
To delineate the molecular, cellular, and physiologic reasons underpinning the CV risk profile differences between GnRH antagonists and agonists, carefully designed mechanistic studies (both basic and translational) are needed.

**Ongoing randomized clinical trials addressing the cardiotoxic effects of GnRH agonists vs. antagonists**

In response to the accruing evidence supporting the superior CV safety profile of GnRH antagonists over agonists, three randomized clinical trials are currently ongoing or are in the planning phase (see Table 2). The PRONOUNCE trial (NCT02663908) is a multi-country phase 3 randomized clinical trial in patients with advanced prostate cancer and preexisting atherosclerotic CVD. The CV safety of degarelix, a GnRH antagonist, will be compared prospectively to leuprolide, a GnRH agonist. The primary endpoint is the time from randomization to the first confirmed occurrence of the composite major adverse cardiovascular event (MACE). Although the original plan was to enroll 900 participants, the study enrolled 575 patients before recruitment concluded [83]. NCT04182594 is a smaller phase 2 RCT superiority study comparing the occurrence of CV events in 80 patients with prostate cancer and preexisting CV risk factors receiving degarelix or GnRH agonist in addition to chemotherapy with docetaxel or the newer hormonal agents abiraterone, enzalutamide, or apalutamide [84]. The interventional arm will receive two initial loading doses of 120-mg degarelix for 1 month, followed by 80 mg monthly for eleven additional months. The control arm receives a GnRH agonist at the discretion of the treating urologist/oncologist for 1 year. The primary endpoint will be the time to first composite MACE (see Table 2). PEGASUS is a phase IIIb randomized trial comparing radiation therapy plus long-term adjuvant ADT with GnRH antagonist or GnRH agonist plus flare protection in patients with high-risk localized or locally advanced prostate cancer [85]. The trial's primary objective is to assess progression-free survival. The principal safety endpoint is the incidence of clinically significant CV events in the subgroup of patients with a prior history of CVD.

When completed, these trials are anticipated to validate the accumulating evidence of the favorable CV safety profile of GnRH agonists compared with GnRH antagonists in patients with preexisting CVD. The studies will also assess whether the superior CV safety of GnRH antagonists persists when treatment is combined with modern regimens of chemotherapy and novel hormonal agents. We propose that a similar high-quality randomized study designed to quantify CV event rates in patients without any prior history of CVD treated with GnRH agonists and antagonists would be an excellent addition to these prospective trials.

**Racial disparities in CV outcomes of prostate cancer therapy**

Beyond relative CV risks of ADT in prostate cancer therapy, significant racial disparities may adversely impact CV outcomes of patients treated with ADT. African American men are 2.5 times more likely than white men to die from prostate cancer [86]. Between 2008 and 2011, African American men had a
| Study name/trial number | Comparison groups | No. (pts.) | Inclusion criteria | Exclusion criteria | Follow-up duration | Outcome measures | Expected DoC |
|-------------------------|------------------|------------|--------------------|-------------------|-------------------|-----------------|--------------|
| PRONOUNCE/ NCT02663908 | Degarelix<sup>2</sup> (GnRH antagonist) versus leuprolide (GnRH agonist) | 545 | - Men with advanced PCA  
- With pre-existing atherosclerotic CVD  
- Who have indications to start ADT | - Previous or current hormonal therapy for PCA  
- Acute cardiovascular disease in the previous 30 days | Up to 336 days | Primary end point is time from randomization to the first confirmed occurrence of MACE (as death due to any cause, or non-fatal MI, or non-fatal stroke) | April 2021 |
| NCT04182594 | Degarelix + docetaxel, or one of the novel<sup>b</sup> hormonal agents versus GnRH agonist + docetaxel, or one of the novel hormonal agents | 80 | - Men age < 90 y/o with locally advanced or metastatic PCA, and pre-existing CVD, or CVA, or PAD or two or more major CV risk factors  
- Who are scheduled to receive primary ADT for 1 year, and a second line chemotherapy with docetaxel or one of the novel hormonal agents  
- Life expectancy of 1 year and WHO performance status of 0–2 | - Prior use of ADT in past 6 months prior to randomization  
- Known allergic reaction to degarelix  
- Any situation potentially hampering compliance with the study protocol and follow-up schedule | 1 year | Primary end point is time to first composite MACE (death due to any cause, MI, TIA, Cardiac ED visits, or heart catheterizations) | January 2023 |
| PEGASUS/ NCT02799706 | Degarelix + EBRT versus GnRH agonist + EBRT  
EBRT: total of 78–80 Gy (5× per wk) | 885 | - Men age < 80 y/o with high-risk localized or locally advanced prostate cancer scheduled to receive ADT and EBRT  
- Testosterone level > 200 ng/dl  
- Creatinine clearance > 50 ml/min  
- WHO performance 0–1 | - Prior use of ADT  
- Hx of severe asthma, GEs that interferes with drug absorption, pituitary or adrenal dysfunction, uncontrolled DM, severe liver dis, uncontrolled HTN, MI or arterial thrombotic event in the past 6 months, severe or unstable angina, NYHA class III/IV CHF or EF < 50% at baseline, PCI or multivessel CABG, carotid artery or iliofemoral artery revascularization within the last 30 days | Minimum of 18 months | Secondary end point is the incidence of clinical cardiovascular events including arterial embolic or thrombotic events including CVA, MI, and other ischemic heart disease in those with prior CV events, and those without history of such events | September 2024 |
| Study name/ trial number | Comparison groups | No. (pts.) | Inclusion criteria | Exclusion criteria | Follow-up duration | Outcome measures | Expected DoC |
|-------------------------|------------------|-----------|-------------------|-------------------|------------------|-----------------|-------------|
|                         |                  |           |                   | - Prior hx of malignancies other than skin cancers unless in remission for > 3 yrs - Family history of a long QT syndrome or QTc > 450 ms at baseline |                  |                 |              |

Abbreviations: ADT, androgen deprivation therapy; CABG, coronary artery bypass graft; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes; DoC, date of completion; DS, disease or disorder; EBRT, external beam radiation therapy; ED, emergency department; EF, ejection fraction; HTN, hypertension; GI, gastro-intestinal; GnRH, gonadotropin releasing hormone; HTNL, hypertension; MACE, major cardiovascular adverse events; MI, myocardial infarction; No., number; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCA, prostatic cancer; Pts, patients; TIA, transient ischemic attacks

* Dose of degarelix for all the above three studies is loading dose of 240 mg subcutaneous on day 1, followed by 80 mg monthly for the remainder of the study period
* The three novel anti-androgenic hormonal agents are abiraterone, enzalutamide, and apalutamide
* This is a joint study of the European Organization for Research and Treatment of Cancer (EORTC) Radiation Oncology Group (ROG) and Genitourinary Cancer Group (GUCG)
* The primary endpoint of this study is progression free survival defined as the time in days from randomization to death, clinical or biochemical progression, whichever comes first.
mortality rate of 43 per 100,000—significantly higher than men who identified as Caucasian (19.8 per 100,000), Hispanic (17.8 per 100,000), and Asian/Pacific Islanders (9.4 per 100,000) [87]. Studies demonstrate that African American men present at a younger age and with a more aggressive disease at the time of diagnosis and have worse clinical outcomes after radical prostatectomy [88–90].

Not only are African Americans disproportionately affected by mortality from prostate cancer, but they also have the highest age-adjusted CV mortality rates. The high mortality from prostate cancer may thus be due in part to higher underlying CV risk and increased adverse CV events associated with ADT. A retrospective cohort involving 7252 men assessed outcomes of low-risk or favorable intermediate-risk prostatic cancer treated with brachytherapy followed by either ADT for a median of 4 months or no ADT [91]. In patients who received ADT, African Americans had significantly increased all-cause mortality (HR 1.77) and non-prostate cancer mortality (HR 1.86) compared to non-African Americans. These racial associations were not observed among men who did not receive ADT.

The underlying causes of these racial disparities are likely multifactorial, complex, and intertwined. Several basic and translational studies have attempted to understand the genetic and molecular basis for the poor outcomes of African American patients with prostate cancer [92–94]. However, none of the molecular and genetic factors identified thus far fully explain such a wide gap in mortality from prostate cancer among the different races. Social determinants of health may contribute to the disproportionate deleterious effect of prostate cancer in African American men. These previously described factors include racism, bias, limited access to health care, distrust of the medical community due to prior negative experiences, personal or historical, and low representation in clinical trials.

A study analyzing oncology clinical trials leading to drug approvals between 2008 and 2018 found that although African Americans account for 22% of all cancers in the USA, they constituted just 3.1% of trial participants [95]. Moreover, while one-third of prostate cancer deaths in the USA occur in African Americans, they represented < 5% of participants in sizeable multicenter prostate cancer trials [96]. Improved enrollment of African Americans in clinical trials could be pivotal in defining the best therapies to improve outcomes and reducing adverse CVD events in this community.

**ADT in prostate cancer therapy and susceptibility to COVID infection**

In the era of the COVID-19 pandemic, cancer is independently associated with adverse outcomes in patients infected with severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2). Patients with a history of cancer and CVD are at significantly higher risk of COVID-19 associated adverse outcomes [97]. Interestingly, ADT-treated prostate cancer patients may experience reduced COVID-19 infections and severity. Using a database from 68 Italian hospitals, researchers identified four COVID-19 infections out of 5273 patients with prostate cancer on ADT [98]. In
| Study name/trial No.                  | Comparison groups                                                                 | No. (pts.) | Inclusion criteria                                                                 | Exclusion criteria                                                                                      | Outcome measures                                                                                   | Expect. DoC |
|-------------------------------------|------------------------------------------------------------------------------------|------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------|
| RECOVER/NCT04374279                | Standard of care and bicalutamide + versus Standard care only                      | 60         | - ≥18 years of age                                                                   - COVID-19 infection, confirmed by PCR                                                                  - Unable to take orally; pregnant, or breastfeeding                                                | Percentage of patients with clinical improvement at day 7 after randomization                        | Dec. 2021   |
| NCT04509999                        | Standard of care and bicalutamide + versus standard of care only                   | 100        | - Men ≥ 36 years old with at least one T. ≥ 100.4 F., or new cough, or new dyspnea, and +ve COVID-19 by standard local lab. assay | - Admission to hospital at time of screening                                                          - Percent of pts with improved COVID-19 symptoms at day 28                                         | Sept. 2022  |
| NCT04446429                        | Standard of care and dutasteride + or proxalutamide versus standard of care only   | 381        | - Male; age ≥ 50 years old                                                             - Positive COVID-19 in the past 7 days                                                                  - Pt. enrolled in another study drug for COVID-19 drug                                              | Percentage of pts hospitalized due to COVID-19 over the one month period                              | Jan. 2021   |
| HITCH/NCT04397718                  | Standard of care + degarelix versus standard of care alone                          | 198        | - Male veterans admitted to a VA hospital                                              - Severity of illness of level 3, 4 or 5 on ISS                                                       - Hx of severe hypersensitivity to degarelix                                                       | Primary end point is composite of mortality, ongoing need for hospitalization, or requirement for mech. vent./ECMO at day 15 after randomization | Dec. 2020   |
| Study name/trial No. | Comparison groups | No. (pts.) | Inclusion criteria | Exclusion criteria | Outcome measures | Expect. DoC |
|---------------------|-------------------|------------|--------------------|-------------------|------------------|------------|
| COVIDENZA/NCT04475601 | Enzalutamide + standard of care versus standard of care alone | 500 | - The subject or legal rep. must consent to trial | hydroxychloroquine, chloroquine, or azithromycin; use of any drug known to prolong QT interval within 30 days of day 1; MI in the past 6 mos, UA, or NYHA class III/IV heart ds | Severe allergy to enzalutamide; Pregnant or breast-feeding women; Need of immediate mechanical ventilation; Current medication includes enzalutamide treatment; Hx of CVA, or TIA, or seizure ds., unstable CVD; Treatment for HIV, or severe immunosuppressive disease; Treatment with tamoxifen, or immunosuppressive agents; Treatment with warfarin or NOACs; Other serious illness or medical condition | Primary end points are time to worsening of ds. and time to improvement (up to 30 days after inclusion for both worsening and improvement) | May 2022 |

Abbreviations: ds, disease or disorder; DoC, date of completion; ECMO, extracorporeal membrane oxygenation; hx, history; in-patient, inpatient; ISS, influenza severity scale; NIPPV, non-invasive positive pressure ventilation; NH, Norwood Hamilton; No., number; NOACs, non-vit K antagonist oral anticoagulants; NYHA, New York Heart Association; pt, patient; sxs, symptoms; LFTs, liver function enzymes; mech. vent., mechanical ventilation; NPSS, nasopharyngeal swab sample; O2, oxygen; +ve, positive; rep, representative; req, requirement; RR, respiratory rate; TIA, transient ischemic attack; UA, unstable angina

*Dose and duration of bicalutamide: 150 mg daily for 7 days. In addition to those listed above, exclusion criteria also include allergy to bicalutamide or other androgen receptor inhibitor

* Dose and duration of bicalutamide: 150 mg daily for up to 28 days. Allergy to bicalutamide or other androgen receptor inhibitors is part of exclusion criteria

* Standard care is ivermectin + azithromycin for up to 30 days. In addition, patients in the experimental arm will receive either dutasteride at 0.5 mg daily, or proxalutamide 200 mg daily

* Patients > 85 years can be enrolled if there is no history of chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, hypertension, diabetes mellitus, or active malignancy

* Other exclusion criteria for HITCH include enrollment in another study drug within 30 days of day 1, planned discharge within 24 h of treatment initiation, known psychiatric or substance abuse disorder that interferes with study, Child-Pugh class C liver disease, use androgen receptor antagonists and agonists within 4 weeks, use of ketoconazole or abiraterone acetate within 2 weeks, use of estrogens or progestins within 2 weeks, and pts unwilling or unable to comply with the study protocol

* Enzalutamide 160-mg tablets will be given orally once daily for up to 5 days (to be given only during hospitalization and stop if starting mechanical ventilation or at discharge from hospital)
contrast, 114 COVID-19 infections were identified in 37,161 cancer patients, resulting in a positivity rate of 0.075% (odds ratio 4.05). However, in a northern Italian study investigating only prostate cancer patients, ADT treatment was not associated with decreased COVID-19 infection rates [99]. An American study assessed the clinical course of 58 patients with prostate cancer infected with COVID-19 [100]. After controlling for age, cardiac disease, and pulmonary disease, ADT use was associated with lower hospitalization rates (OR 0.23) and lower supplemental oxygen requirements (OR 0.26). Higher levels of androgens are associated with more severe COVID-19 infections in observational studies of men with androgenic alopecia compared to an age- and race-matched general population [101–103].

The biological basis of these clinical observations may be related to androgen regulation of the type II transmembrane serine protease (TMPRSS2). SARS-CoV-2 binds to angiotensin-converting enzyme 2. Then, TMPRSS2 cleavage of the S protein allows the fusion of the virus with the human cellular membrane [104]. The reduction of androgens by ADT may prevent the virus' entry into cells. Five clinical trials aiming to treat COVID-19 infections with hormonal therapy targeting androgens are currently recruiting or in preparation to recruit (see Table 3).

Conclusion and future directions

ADT-associated cardiotoxicity is linked to increased morbidity and mortality in patients with prostate cancer. Nevertheless, promising data are emerging regarding the improved safety of GnRH antagonists. The risk-benefit ratio between GnRH agonists and antagonists should be carefully considered. It is imperative to identify, monitor, and manage CV risks and complications in prostate cancer patients, especially in older patients with a prior history of significant CVD. The striking racial disparity in prostate cancer mortality among blacks compared to all other races, plus their high mortality from CV disease, warrants prompt attention by the research community. The need for novel strategies to maximize enrollment of these high-risk populations into clinical trials for prostate cancer therapy cannot be overemphasized. More high-quality trials that directly examine adverse CV events as a primary endpoint are needed. Despite the associated cardiotoxicity, ADT intriguingly may confer protection against COVID-19 infection through limiting the virus' entry into cells.

Compliance with Ethical Standards

Conflict of Interest
Azariyas A. Challa declares that he has no conflict of interest. Adam Christopher Calaway declares that he has no conflict of interest. Jennifer Cullen declares that she has no conflict of interest. Jorge Garcia declares that he has no conflict of interest. Nihar Desai declares that he has no conflict of interest. Neal L. Weintraub declares that he has no
conflict of interest. Anita Deswal declares that she has no conflict of interest. Shelby Kutty declares that she has no conflict of interest. Ajay Vallakati declares that he has no conflict of interest. Daniel Addison declares that he has no conflict of interest. Ragavendra Baliga declares that he has no conflict of interest. Courtney M. Campbell declares that she has no conflict of interest. Avirup Guha declares that he has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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