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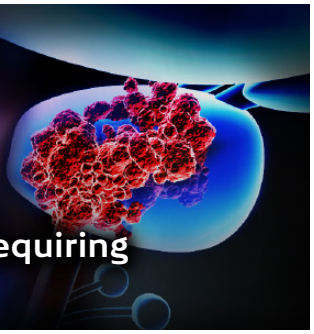
Managing Cardiovascular Risk in Patients with Prostate Cancer Requiring Androgen Deprivation Therapy



Making Education Easy 2025

Independent expert commentary provided by Professor Henry Woo

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This review is intended as an educational resource for healthcare professionals who treat men with prostate cancer, including urologists, medical oncologists, radiation oncologists and nurses, as well as general practitioners with an interest in prostate cancer. It summarises data highlighting the increased cardiovascular risk in men with prostate cancer receiving androgen deprivation therapy (ADT), and compares the risk associated with gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists. The review presents recommendations for cardiovascular risk assessment and management in men with prostate cancer receiving ADT, including specific recommendations regarding choice of ADT.

In Australia, degarelix is the only GnRH antagonist indicated for the treatment of prostate cancer in patients who require ADT.[1] It is listed on the Pharmaceutical Benefits Scheme for use in locally advanced or metastatic prostate cancer.[2]

Introduction

Prostate cancer is the most common solid organ malignancy in Australian men.[3] Men with prostate cancer have a high burden of cardiovascular risk factors, even at the time of diagnosis,[4] and cardiovascular disease is the most common cause of death.[5] Despite this, poor control of modifiable cardiovascular risk factors is common in men with prostate cancer.[6]

Androgen deprivation therapy (ADT) is used in 40% of men with prostate cancer as neoadjuvant and/or adjuvant therapy to radiotherapy or for biochemical relapse after surgery.[7] Gonadotropin-releasing hormone (GnRH) agonists are the most frequently prescribed ADT, but are associated with increased cardiovascular risk and mortality, particularly in patients aged >60 years.[7] GnRH antagonists are an alternative to GnRH agonists, and several studies have suggested they are associated with significantly lower overall mortality and cardiovascular events.[7]

In 2022, The European Society of Cardiology (ESC) published Cardio-Oncology guidelines, in collaboration with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society (ICOS).[7] The guidelines are designed to assist healthcare professionals providing care to patients with cancer before, during and after treatment with respect to cardiovascular health.[7] A cardiovascular risk assessment is recommended before initiation of ADT in men with prostate cancer, with subsequent care pathways dependent on baseline risk.[8] A GnRH antagonist is recommended over a GnRH agonist for men with pre-existing cardiovascular disease.[7]

Despite recommendations and evidence from clinical studies, real-world data indicate that GnRH antagonists are not widely adopted in clinical practice.[9] The Prostate Cancer Cardiovascular (PCCV) Expert Network, comprising specialists from Australia, Asia and Germany, was convened to develop feasible solutions for routine cardiovascular risk assessment and management in men with prostate cancer, and recommendations are included in this publication.[9]

ADT and cardiovascular risk

Cardiovascular risk in men with prostate cancer

The burden of cardiovascular risk is high in men with prostate cancer, as demonstrated by analyses from RADICAL-PC, a prospective cohort study of men with prostate cancer.[6,10] Among 2492 Canadian men with newly diagnosed prostate cancer or planning to start ADT enrolled in RADICAL-PC, 58% were current or former smokers, 22% had known cardiovascular disease, 16% had diabetes, 45% had hypertension, 31% had a body mass index ≥30 kg/m^2 and 24% had low levels of physical activity.[10] Overall, 69% had a Framingham risk score consistent with high cardiovascular risk.[10] Among 2811 men from Canada, Australia, Israel and Brazil enrolled in RADICAL-PC, 99% had ≥1 uncontrolled cardiovascular risk factor (high low-density lipoprotein cholesterol, high blood pressure, smoking, high waist:hip ratio, and physical inactivity), and 51% had poor overall risk factor control (≥3 of these risk factors).[6]

An analysis of data from the SEER programme, which collects data on cancer cases in the US, found that cumulative mortality from cardiovascular disease exceeded mortality from the primary neoplasm 5-15 years after cancer diagnosis in more than 300,000 men with prostate cancer aged ≥65 years.[11]

Association of cardiovascular risk with ADT

ADT has been associated with a number of cardiometabolic adverse events, including hypertension, type 2 diabetes and ischaemic heart disease.[5,7] ADT is also uncommonly associated with prolongation of the corrected QT interval and in rare cases, can cause torsade de pointes.[7]

Swedish registry data comprising 76,600 men with prostate cancer undergoing ADT, curative treatment or surveillance highlighted an increased risk of both nonfatal and fatal cardiovascular disease compared with the general population.[12] The highest risk was seen in men undergoing ADT.[12]

A recently published US retrospective cohort study of men with prostate cancer (n=5156) found an increased risk of cardiovascular events in those who received vs did not receive ADT; risk was further increased in those with pre-existing dyslipidaemia.[13]

In several observational studies, the increased cardiovascular risk associated with ADT has been specifically linked with GnRH agonist use.[5] A SEER database study of 73,196 men with prostate cancer found that GnRH agonist therapy was associated with an increased risk of diabetes, coronary artery disease, myocardial infarction and sudden cardiac death.[14] A further analysis of SEER data involving 140,474 men also found that GnRH agonist use was associated with an increased risk of cardiovascular disease compared with men who did not receive this treatment.[15] In both studies, the risk of cardiovascular disease was not increased in men who underwent orchidectomy.[14,15]

Twenty-year follow-up data from the randomised controlled RTOG 9202 trial revealed no statistically significant difference in cardiovascular mortality between 1520 men with locally advanced prostate cancer who received radiotherapy along with longer-term (28 months) vs short-term (4 months) GnRH agonist therapy.[16] However, the risk of death from myocardial infarction was significantly increased in those who received longer-term GnRH agonist therapy, particularly in men with pre-existing cardiovascular disease.[16]

Australian Product information leaflets for GnRH agonists now include warnings citing the increased risk of diabetes and cardiovascular events in men with prostate cancer, mirroring required changes to US labelling.[17-19]

Mechanisms of ADT-associated cardiovascular disease

Testosterone depletion as a result of surgical or chemical castration leads to an increase in adipose tissue.[19] The release of growth factors and cytokines from this adipose tissue leads to metabolic changes, and the development of insulin resistance and risk factors for cardiovascular disease.[19] These risk factors include inflammation, type 2 diabetes, atherosclerosis, atherogenic dyslipidaemia, hypertension and thrombosis.[19] Prolongation of the QT interval is thought to occur through blockade of testosterone effects on ventricular repolarisation.[7]

Other mechanisms for increased cardiovascular risk associated with ADT have been proposed, and may explain the differential effects of GnRH agonists and GnRH antagonists.[5] GnRH agonists are able to activate T cells, triggering an inflammatory cascade and increasing the risk of atherosclerotic plaque rupture, a frequent cause of fatal thromboembolic events (see **Figure 1**).[5] GnRH antagonists have no effect on T cells, thereby maintaining plaque stability.[5]

Follicle-stimulating hormone (FSH) has also been shown to promote inflammatory cytokine release from immune cells, providing another mechanism by which plaque stability may be disrupted (see **Figure 1**).[5] Clinical data has shown that men with prostate cancer who experience a <60% decrease in FSH levels during the first 3 months of ADT have a higher risk of cardiovascular events, and that GnRH antagonists suppress FSH levels to a greater extent than GnRH agonists.[5]

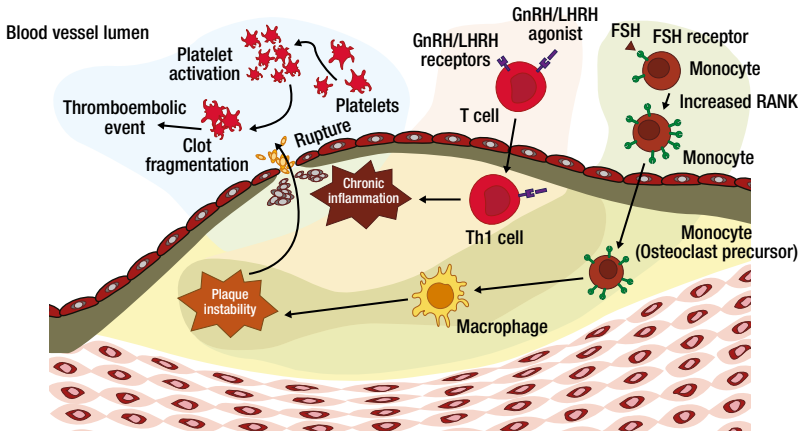

Figure 1. Proposed mechanism of differing cardiovascular risk between GnRH antagonists and GnRH agonists (reproduced from Davey P, et al. Int J Clin Pract. 2022 May 17;2022:2976811).[5]
FSH = follicle-stimulating hormone; **GnRH** = gonadotropin-releasing hormone; **LHRH** = luteinising hormone-releasing hormone.

Comparative cardiovascular risk with GnRH agonists and GnRH antagonists

Current data indicate that GnRH agonists increase the risk of cardiovascular events in men with prostate cancer, and that this increase is greatest in men with pre-existing cardiovascular disease.[5] While not definitive, GnRH antagonists may be associated with a lower risk of cardiovascular events compared with GnRH agonists, particularly in men with pre-existing cardiovascular disease.[5]

The randomised controlled PRONOUNCE trial evaluated cardiovascular safety of the GnRH antagonist degarelix compared with the GnRH agonist leuprorelin in men with prostate cancer and established atherosclerotic cardiovascular disease.[20] The primary endpoint was time to first major cardiovascular event (MACE; composite of death, myocardial infarction and stroke).[20] The trial was stopped early, after 545 rather than the planned 900 patients had been enrolled, due to slower recruitment and fewer outcome events than expected.[20] At 12 months, there was no significant difference between groups in MACE (5.5% [15/275] of degarelix recipients vs 4.1% [11/269] of leuprorelin recipients; hazard ratio [HR] 1.28; 95% confidence interval [CI] 0.59-2.79; p=0.53).[20]

However, the randomised controlled HERO trial comparing a different GnRH antagonist with leuprorelin in men with prostate cancer found a 54% lower risk of MACE at 48 weeks (2.9% [18/622] of GnRH antagonist recipients vs 6.2% [19/308] of leuprorelin recipients; HR 0.46; 95% CI 0.24-0.88).[21] In this trial, 92.5% of patients had ≥1 cardiovascular risk factor at baseline, and 13.9% had a history of MACE.[21] Among those with a history of MACE, the odds of having a subsequent event were 4.8 times higher in leuprorelin vs GnRH antagonist recipients (17.8% [8/45] vs 3.6% [3/84] of patients, respectively).[21] MACE was evaluated in a prespecified safety analysis; the primary trial endpoint was sustained castration rate.[21]

In a pooled analysis of six randomised controlled trials involving 2328 men with prostate cancer, of whom approximately 30% had pre-existing cardiovascular disease, there was a 40% lower risk of cardiac events within 1 year of initiating treatment with degarelix vs a GnRH agonist (HR 0.60; 95% CI 0.41-0.87; p=0.008).[22] In the subset of patients with pre-existing cardiovascular disease, there was a 56% lower risk of cardiac events with degarelix vs a GnRH agonist (HR 0.44; 95% CI 0.26-0.74; p=0.002).[22]

A meta-analysis of 11 randomised controlled trials involving a total of 4248 men with prostate cancer, including PRONOUNCE and HERO, found that GnRH antagonists were associated with a lower risk of MACE compared with GnRH agonists (2.9% [76/2655] vs 4.8% [76/1593] of patients, respectively; odds ratio [OR] 0.57; 95% credible interval [CrI] 0.37-0.86).[23] Risk of all-cause mortality was also non-significantly decreased with GnRH antagonists vs GnRH agonists (OR 0.58; 95% CrI 0.32-1.08).[23]

These findings were supported by more recently published meta-analyses comparing the cardiovascular safety of degarelix with GnRH agonists in men with prostate cancer.[24,25] Odat et al. analysed 13 studies, including six randomised controlled trials and seven observational studies (n=160,214).[24] Risk of MACE was significantly decreased with degarelix vs GnRH agonists (relative risk 0.60; 95% CI 0.41-0.88; p=0.008).[24] de Moraes et al. analysed 15 studies, including eight randomised controlled trials and seven observational studies (n=123,969).[25] Relative risk of MACE was 0.59 (95% CI 0.41-0.84; p=0.003) with degarelix vs GnRH agonists.[25] The risk of all-cause mortality was non-significantly decreased with degarelix vs GnRH agonists in both meta-analyses.[24,25]

Cardiovascular risk with androgen receptor signalling inhibitors

The use of androgen receptor signalling inhibitors in combination with a GnRH agonist or GnRH antagonist is the new standard of care for advanced prostate cancer.[26] Apalutamide, darolutamide and enzalutamide are second-generation androgen receptor pathway inhibitors that bind to the ligand-binding region of the androgen receptor, preventing androgen translocation to the nucleus and androgen-initiated transcription of DNA.[26] Abiraterone inhibits cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17) within adrenal cells and tumour cells to decrease testosterone levels.[26]

Second-generation androgen receptor pathway inhibitors are associated with an increased risk of hypertension, whereas abiraterone is associated with an increased risk of both cardiovascular events and hypertension.[7,27] In a meta-analysis of three randomised controlled trials involving 4117 patients with prostate cancer, the use of apalutamide, darolutamide or enzalutamide in combination with a GnRH agonist or GnRH antagonist significantly increased the risk of cardiovascular events, hypertension and death compared with use of a GnRH agonist or GnRH antagonist alone.[28]

Cardiovascular risk with combination therapy appears to be greater with use of a GnRH agonist compared with a GnRH antagonist,[27] as demonstrated in a pharmacovigilance study using the US FDA Adverse Event Reporting System.[29] The study analysed 6231 reports of cardiovascular adverse events from men with prostate cancer receiving a GnRH agonist, GnRH antagonist, first- or second-generation androgen receptor pathway inhibitor, and/or abiraterone.[29] Compared with any combination therapy with a GnRH agonist, combination therapy with a GnRH antagonist was associated with fewer cardiovascular events (adjusted reporting OR 0.64; 95% CI 0.50-0.81; p=0.0003).[29]

Expert comment

There is no disagreement amongst Australian clinicians that ADT is associated with an increased risk of cardiovascular events compared with men not receiving ADT. However, it is highly unlikely that most clinicians are undertaking routine cardiovascular risk factor assessment prior to commencing ADT in men with prostate cancer. The level of routine cardiovascular risk factor assessment is largely unknown and worthy of investigation in the Australian practice setting. That said, the extent to which any such data exists globally is minimal. One study that evaluated risk assessment in US veterans with prostate cancer found gaps in care and concluded that interventions were needed to improve cardiovascular risk factor mitigation in that population.[30]

Multiple clinical guidelines recommend that cardiovascular risk factor mitigation be undertaken in men commencing ADT. These guidelines are based upon high-level evidence demonstrating the potential to mitigate against cardiovascular morbidity with use of GnRH antagonists and cardiologist intervention. It is essential to understand that risk mitigation is more than simply modifying the type of ADT we prescribe for our patients, and must include risk-based involvement of a cardiologist either at onset of care or at commencement of treatment that may elevate the risk for cardiovascular events.

Management of cardiovascular risk in men receiving ADT

Assessment of baseline risk

Before initiation of cancer therapies with a known cardiovascular toxicity profile, including ADT, cardiovascular risk factors and pre-existing cardiovascular disease should be identified and treated.[8] A position paper from the ESC Heart Failure Association and ICOS recommended that baseline cardiovascular risk assessment includes the following elements:

- Age, sex, genetics
- Previous cardiovascular disease
- Previous cardiotoxic therapies
- Medical cardiovascular risk factors (e.g. diabetes, hypercholesterolaemia)
- Lifestyle cardiovascular risk factors (e.g. smoking, obesity)
- Electrocardiogram (ECG), transthoracic echocardiogram, cardiac biomarkers.[8]

Any prostate cancer patient with a previous history of cardiovascular disease is considered to be high risk.[8]

For patients with no history of cardiovascular disease, ESC Cardio-Oncology guidelines recommend using SCORE2[21] or SCORE2-OP[21] to stratify 10-year risk of events in those scheduled to ADT.[7] These risk calculators have been validated primarily in Europe and North Africa.[31] Alternative risk calculators include QRISK®3[32] (validated in the UK) and the ACC/AHA Atherosclerotic Cardiovascular Disease Risk Estimator[33] (validated in the US).[7]

The PCCV Expert Network has proposed a simplified and objective cardiovascular risk assessment tool for use in clinical practice, adapted from a tool first published by Davey et al. in 2022,[5] shown in **Figure 2**.[9] Patients are stratified as low, intermediate or high risk.[9] These categories are solely a guide to subsequent management rather than a predictor of future cardiovascular events.[9]

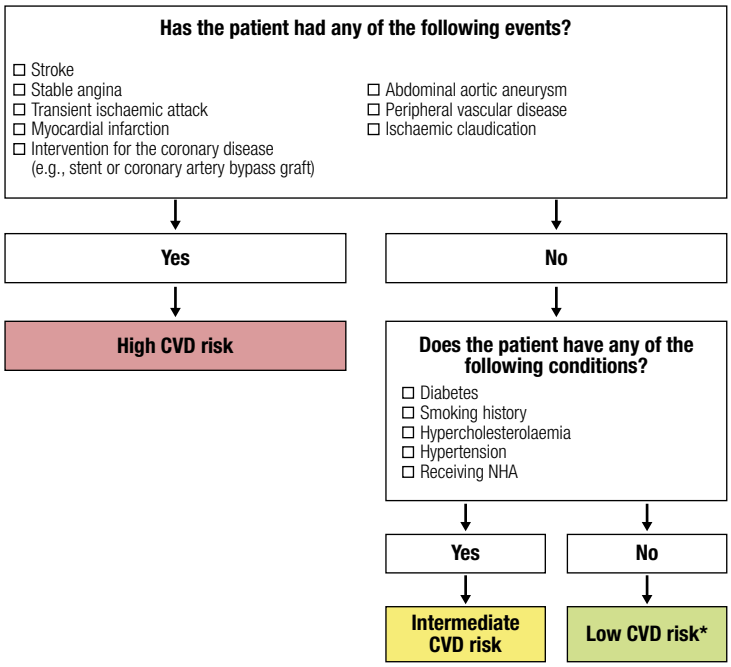

Figure 2. Checklist for cardiovascular risk assessment and stratification (reproduced from Merseburger AS, et al. World J Urol. 2024 Mar 14;42(1):156).[9]

*A patient's risk level may transition from "Low Risk" to "Intermediate Risk" or "High Risk" after 2 or 3 years of GnRH agonist/GnRH antagonist plus NHA treatment.

CVD = cardiovascular disease; **GnRH** = gonadotropin-releasing hormone; **NHA** = novel hormonal agent (apalutamide, darolutamide, enzalutamide or abiraterone).

Care pathways according to baseline cardiovascular risk

ESC Cardio-Oncology guidelines present a general approach to care after baseline cardiovascular risk assessment.[7] For low-risk patients, routine follow-up is sufficient, with referral to a cardiologist only necessary if a cardiac issue develops.[7] Moderate-risk patients require closer follow-up, and may warrant a cardiology referral before treatment start, whereas high-risk patients require a cardiology referral before treatment start, and will require close surveillance during treatment.[7]

Patients with low cardiovascular risk should start ADT as soon as possible.[9] For these patients, general practitioners may be assigned the responsibility of annual cardiovascular assessment and monitoring patient adherence with the cardiovascular health plan.[9] For other patients, risk factors for other patients should be optimised before, during and after ADT.[9]

Choice of ADT

The PCCV Expert Network has provided specific management steps for minimising cardiovascular risk at initiation of ADT in men with prostate cancer (see **Figure 3**).[9] The choice of therapy should be tailored to baseline cardiovascular risk status, and the toxicity profile of individual ADTs should be considered.[9]

Both ESC Cardio-Oncology guidelines and the PCCV Expert Network recommend that a GnRH antagonist is considered in place of a GnRH agonist for patients with pre-existing cardiovascular disease.[7,9] The PCCV Expert Network also recommend that a GnRH antagonist is considered for patients receiving combination treatment with an androgen receptor signalling inhibitor, to minimise cumulative cardiovascular risk.[9] In Australia, degarelix is the only GnRH antagonist indicated for the treatment of prostate cancer in patients who require ADT.[1] It is listed on the Pharmaceutical Benefits Scheme for locally advanced or metastatic prostate cancer.[2]

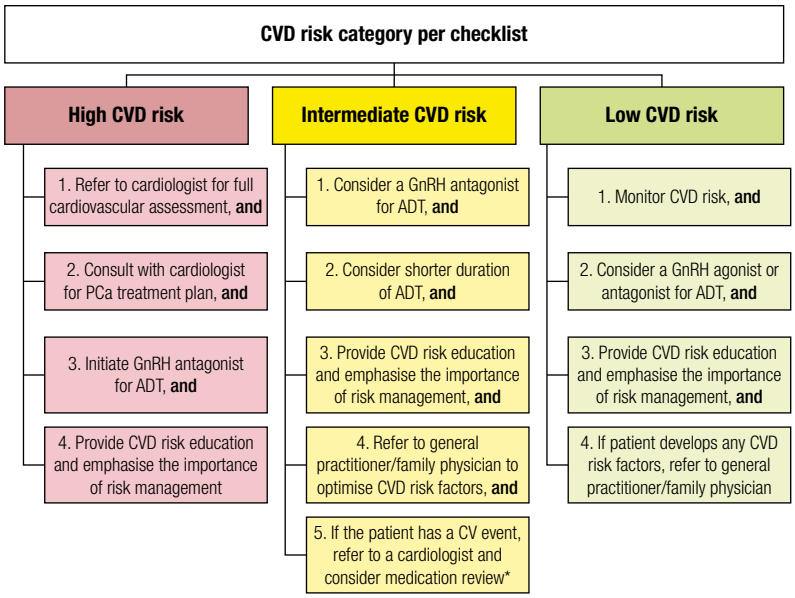

Figure 3. Management steps for minimising cumulative cardiovascular risk at ADT initiation (reproduced from Merseburger AS, et al. World J Urol. 2024 Mar 14;42(1):156).[9]

*Referral to a cardiologist is recommended but is subject to specific healthcare system and resources.

ADT = androgen deprivation therapy; **CVD** = cardiovascular disease; **GnRH** = gonadotropin-releasing hormone; **PCa** = prostate cancer.

The main adverse cardiovascular events associated with ADT are hypertension, diabetes mellitus, ischaemic heart disease and cancer therapy-related cardiac dysfunction.[7] The incidences of specific cardiovascular toxicities associated with different types of ADT are shown in **Figure 4**.[7]

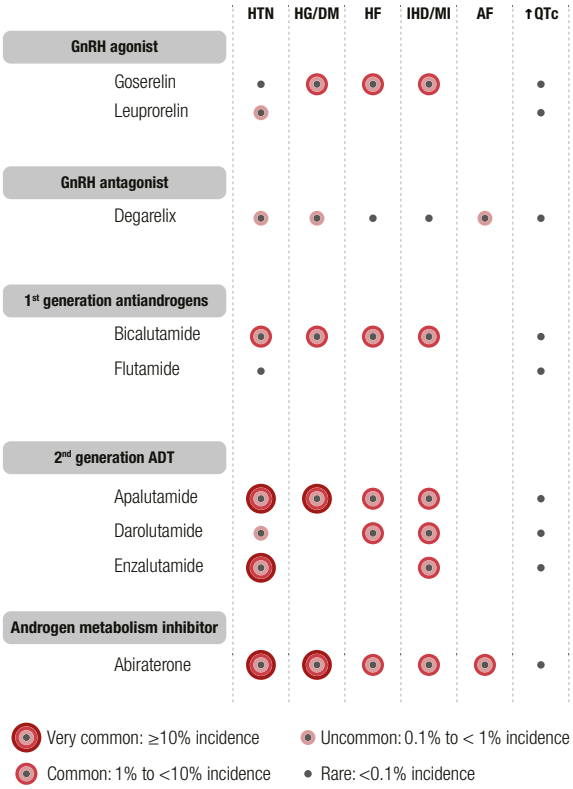

Figure 4. ADT-related cardiovascular toxicities (adapted from Lyon AR, et al. Eur Heart J. 2022 Nov 1;43(41):4229-4361).[7]

ADT = androgen deprivation therapy; **AF** = atrial fibrillation; **DM** = diabetes mellitus; **GnRH** = gonadotropin-releasing hormone; **HF** = heart failure; **HG** = hyperglycaemia; **HTN** = hypertension; **IHD** = ischaemic heart disease; **MI** = myocardial infarction; **↑QTc** = corrected QT interval prolongation.

Expert comment

The choice of ADT can influence management. It is commonplace to initiate men on a GnRH antagonist for rapid chemical castration or to avoid the complexities of short-term flare coverage with antiandrogens that is necessary with GnRH agonists. It is also commonplace that men initiated on a GnRH antagonist will be switched over to a GnRH agonist once the effects of ADT have become established. Appropriate consideration of cardiovascular risk should be undertaken prior to making this switch, which is usually made to allow patients the convenience of having a GnRH agonist injection once every 3 months rather than a monthly GnRH antagonist injection.

Clinical trials now dictate that the majority of men who require ADT should also receive an androgen receptor pathway inhibitor. These agents have the potential to further magnify cardiovascular risk factors. For men with existing cardiovascular risk factors, consideration should be given to using a GnRH antagonist rather than a GnRH agonist to mitigate cardiovascular adverse events.

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Cardiovascular monitoring

ESC Cardio-Oncology guidelines recommend ECG monitoring and management of QT prolongation precipitant factors during ADT if the baseline corrected QT interval is prolonged.[7] Furthermore, measurement of blood pressure, lipids, fasting glucose and glycosylated haemoglobin is recommended on an annual basis for all patients receiving ADT, as well as an annual ECG.[7] Patients should be counselled on healthy lifestyle and control of cardiovascular risk factors.[7]

One popular approach for cardiovascular care is the "ABCDE" paradigm,[34] which has been adapted for use in patients with prostate cancer receiving ADT (see **Table 1**).[31] Healthcare professionals should be able to recognise cardiovascular signs and symptoms, including dyspnoea, orthopnoea, lower extremity oedema, chest pain or pressure, dizziness, palpitations, and syncope.[31] Dyslipidaemia should be treated with a high-intensity statin independently of goal low-density lipoprotein levels, especially in the presence of type 2 diabetes or cardiovascular disease.[34] Plant-based and Mediterranean diets have been shown to reduce cardiovascular events in observational studies.[35] Muscle-strength training improves short-term cardiovascular health in men with prostate cancer.[31] Physical activity may also help mitigate the cardiometabolic adverse effects of ADT, including insulin resistance, obesity, and hypertension.[31]

Table 1. ABCDE paradigm for cardiovascular monitoring in patients with prostate cancer receiving ADT (adapted from Bhave A, et al. Prostate Cancer Prostatic Dis. 2025 Jul 14. Epub ahead of print).[31]

A	Awareness of cardiovascular signs and symptoms
	Aspirin for the prevention of cardiovascular events
B	Blood pressure ≤140/90 mm Hg
C	Cholesterol control with high-intensity statin
	Cigarette cessation
D	Diabetes mellitus control
	Diet (balanced, cultivated and high in calcium and vitamin D)
E	Exercise for 150 min/week at moderate intensity or 75 min/week at high intensity

ADT = androgen deprivation therapy.

Expert comment

The management of advanced prostate cancer has become more nuanced with the recognition that it is possible to mitigate against the full impact of adverse events associated with ADT treatment. Urologists do not need to undertake cardiovascular monitoring of men on ADT, but they do have a responsibility to ensure that an appropriate member of the multidisciplinary team has this covered. This is no different to the manner in which bone mineral density adverse effects are managed by either general practitioners or endocrinologists, under the recommendation of the clinician leading the patient's prostate cancer care. Clinicians must ensure that when appropriate, the general practitioner or cardiologist is aware of a patient's need for ADT and that the addition of an androgen receptor pathway inhibitor magnifies the cardiovascular risk.

Take-home messages

- Men with prostate cancer receiving ADT have an increased risk of cardiovascular events[5,7]
  - Cardiovascular risk appears to be higher in men receiving GnRH agonists compared with GnRH antagonists[5]
- A comprehensive assessment of cardiovascular risk should be undertaken before commencement of ADT in men with prostate cancer, with subsequent care pathways and choice of ADT tailored to the baseline risk[7-9]
  - GnRH antagonists are recommended over GnRH agonists for patients with pre-existing cardiovascular disease[7,9]
  - GnRH antagonists should be considered over GnRH agonists for patients receiving combination treatment with an androgen receptor signalling inhibitor[9]
- All patients receiving ADT should undergo annual measurement of blood pressure, lipids, fasting glucose and glycosylated haemoglobin, as well as an annual ECG[7]
  - Patients should be counselled on healthy lifestyle and control of cardiovascular risk factors.[7]

Expert concluding comments

ADT has been the mainstay of systemic treatment for men with advanced prostate cancer. With the development of androgen receptor pathway inhibitors, men will live longer, be on medications for longer and have a greater risk of cardiovascular events. It is essential for clinicians treating advanced prostate cancer to recognise that systemic treatments in the form of ADT and androgen receptor pathway inhibitors carry a measurable risk of cardiovascular events, and where appropriate, strategies should be in place to assess cardiovascular risk factors and to mitigate risk.

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