Cardiovascular complications related to Androgen deprivation therapies for prostate cancer

Complications cardiovasculaires du traitement antiandrogénique dans les cancers de la prostate

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SUMMARY

Androgen deprivation therapy (ADT) used for prostate cancer treatment is related to an increase in cardiovascular (CV) disease.

The purpose of this review is to briefly summarize the biological mechanisms that may underlie the link between ADT and CV disease, the current clinical evidence supporting this association, and to propose a monitoring protocol for cardiovascular complications during ADT for prostate cancer.

KEYWORDS

Androgen deprivation therapy; Prostate cancer; Cardiovascular toxicity, Cardiovascular disease

RÉSUMÉ

La Suppression androgénique (SA) utilisée pour le traitement du cancer de la prostate est liée à une augmentation du risque des maladies cardiovasculaires.

Le but de cette revue est de résumer brièvement les mécanismes biologiques qui peuvent expliquer le lien entre la SA et les maladies cardiovasculaires, les preuves cliniques actuelles à l'appui de cette association, et de proposer un protocole de surveillance des complications cardiovasculaires pendant la SA au cours du cancer de la prostate.

MOTS-CLÉS

suppression androgénique, cancer de prostate, toxicité cardiovasculaire; maladie cardiovasculaire

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INTRODUCTION

Prostate cancer (PCa) is the 2nd most common urologic cancer among men (after bladder cancer) in Tunisia. Its incidence is continuously increasing due to the combined effect of the aging population and the progress of diagnostic means.

As PCa is a hormone-sensitive malignancy, androgen deprivation therapy (ADT) is the mainstay of systemic therapy for PCa and results in castrate serum levels of testosterone (<50ng/ml). ADT encompasses surgical castration and chemical castration with or without the addition of antiandrogen therapy. The duration of ADT therapy is variable but is often continued for months to years, if not indefinitely. Although ADT extends the lives of many men with prostate cancer, this benefit comes at a cost of significant side effects. ADT has long been known to cause hot flashes, fatigue, decreased libido, erectile dysfunction, and osteopenia (1). More recently, there has been rising awareness that ADT may also cause more silent but potentially lethal adverse effects related to cardiovascular (CV) disease. Therefore, consideration should be given to the most appropriate type of ADT for a given patient (2). The incidence of both PCa and CV disease is highest in older men, and CV disease is the second most common cause of death in men with PCa (3).

The purpose of this review is to briefly summarize the biological mechanisms that may underlie the link between ADT and CV disease, the current clinical evidence supporting this association, and to propose a monitoring protocol for cardiovascular complications during ADT for prostate cancer.

Anti-androgen therapy modalities and mechanism of action

The objective of ADT is to reduce the effects of androgens by three mechanisms: suppression of their secretion and suppression of their synthesis, both of which lead to castration (decrease in circulating androgens) and inhibition of the androgen receptor (which increases circulating androgens) (4).

• ***Surgical castration:*** pulpectomy. The delay before castration is 12 hours. It is an irreversible treatment.

• ***GnRH agonists :*** (such as leuprolide, goserelin, and triptorelin) bind to GnRH receptors on the pituitary gland, causing an initial release of luteinizing hormone (LH) and follicle-stimulating hormone (initial "flare" response), but with continuous administration, they desensitize the gland, determining a down-regulation of LH secretion, loss of stimulation of the Leydig cells. and subsequent fall in androgens levels (mainly testosterone). The delay before castration is 2 to 4 weeks.

• ***GnRH antagonists :*** (such as degarelix) bind in a competitive way to GnRH receptors in the pituitary gland, blocking the release of follicle-stimulating hormone and LH and leading to rapid suppression of testosterone release from the testes. The delay before castration is 48 to 72 hours

• ***First-generation non-steroidal antiandrogens:*** (such as bicalutamide) whose principle of action is the direct blocking of the androgen receptor due to a higher affinity than that of androgens.

• ***Steroidal antiandrogens :*** with a dual action (such as Cyproterone acetate): central action, similar to that of analogs, and peripheral action, similar to that of non-steroidal antiandrogens. Time to castration: 7 days. The thromboembolic risk is higher with this type of treatment, which contraindicates it in patients with a history of phlebitis or pulmonary embolism

• ***Abiraterone acetate :*** a selective inhibitor of androgen synthesis by irreversibly blocking CYP17. It leads to a reinforced inhibition of androgen synthesis (including at the adrenal level). The consequence is an accumulation of synthesis products (increased production of mineralocorticoids by the adrenal glands).

• ***Enzalutamide :*** a new family of androgen receptor inhibitors. It has a higher affinity to the receptor than first-generation anti-androgens

Mechanism of cardiovascular events in men using ADT

The putative detrimental effects of ADT on the development and progression of CV disease have classically been ascribed to ADT-induced atherogenic metabolic disturbances. Indeed, androgens appear to stimulate lipolysis and inhibit triglyceride synthesis from free fatty acids within adipocytes. Therefore, loss of androgen may cause dyslipidemia with high low-density lipoprotein (LDL), high triglyceride level, and low high-density lipoprotein (HDL) levels that have a causal

effect on atherosclerotic plaque development(1,2,5). Besides loss of androgen-mediated inhibition of stem cell differentiation into adipocytes causes decreased lean body mass, while increasing both visceral and subcutaneous fat and thus Obesity (6). This may lead to insulin resistance causing hyperglycemia or diabetes. Often, these metabolic perturbations occur together and form the metabolic syndrome (2).

Sex hormones may also play a more direct role in the pathophysiology of atherosclerosis by modulating the local inflammatory process through endothelial production of nitric oxide. Androgen deprivation could promote monocyte-endothelial cell binding and the resultant local inflammatory response that is a key player in plaque progression and rupture resulting in the formation of a clot that blocks coronary blood flow (figure 1). Thus increasing the risk of myocardial infarction, cerebral strokes, peripheral arterial damage, and venous thromboembolic diseases (5).

Beyond modulating the inflammatory process that leads to atherosclerosis and plaque rupture-induced thrombosis, androgens have also been shown to affect vascular and cardiac function in other ways. Androgens directly induce arterial dilatation, anti-arrhythmic properties, and a shorter QT interval. Some anti-androgen treatments can cause high blood pressure, and a longer QTc interval by altering the interaction of testosterone with myocardial ion channels, resulting in arrhythmias, myocardial infarction, and sudden cardiac death (7).

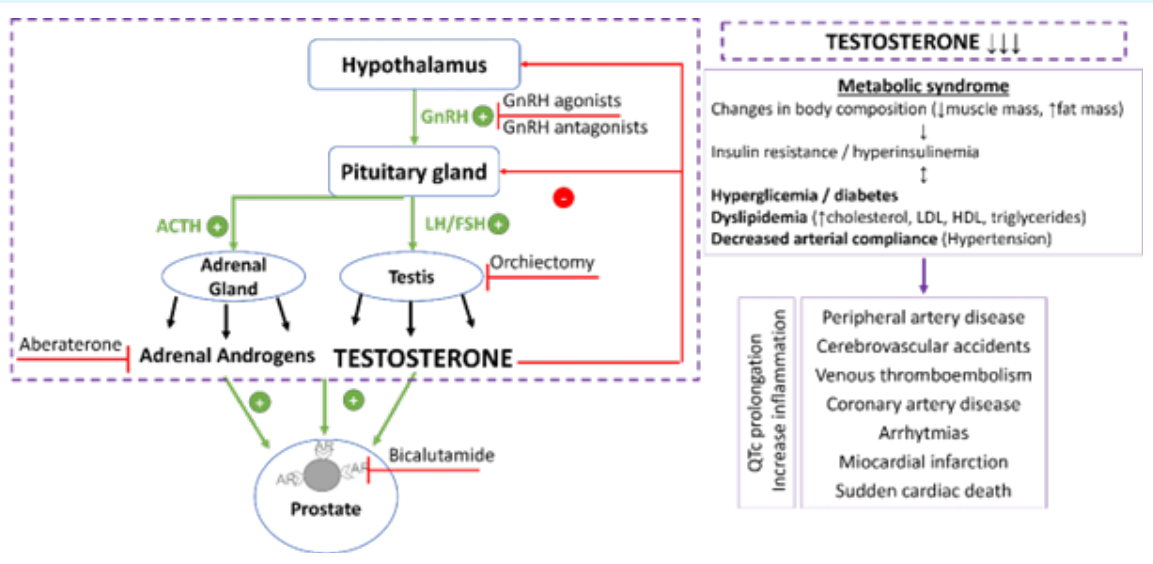


Figure 1. Mechanisms of hormone treatments' action for prostate cancer in the induction of metabolic and cardiovascular alterations

Clinical data

A review of the literature shows that data from retrospective and prospective clinical studies have yielded conflicting results on the effect of ADT on clinical CV events.

Several studies and two meta-analyses have reported an increase in coronary heart disease by up to 16% but also sudden death from cardiac stroke by up to 11% and lethal ventricular arrhythmias related to androgenic suppression (8–10).

Ziouziou et al reported that ADT increases the relative risk of vascular events by 10 to 30%. This risk was greater in elderly patients with cardiac comorbidity with an estimated risk of cardiovascular mortality of 17% (11).

Subgroup analysis by type of ADT showed that increased risk of CV disease was associated with GnRH agonists alone in 12.6% of patients and GnRH agonists plus antiandrogen (AA) and 26.1% of patients but not with AA alone or orchiectomy (12).

These results are contrasting with the publications of randomized trials of hormone-radiotherapy in which there was no evidence of an increased risk of cardiovascular events in post hoc analysis (13,14). A meta-analysis of eight randomized trials showed no significant difference in cardiovascular mortality between patients treated with ADT and those who did not receive patients who did not receive ADT.

Many factors have been called into play to try to explain these differences in study results, such as heterogeneity in the study population, in study design (including different follow-up periods/methods), treatment-specific factors such as lack of data on the type of ADT, extensive variability in the duration of ADT, or patient factors with and without existing CV disease, and CV events were not systematically collected or adjudicated(15).

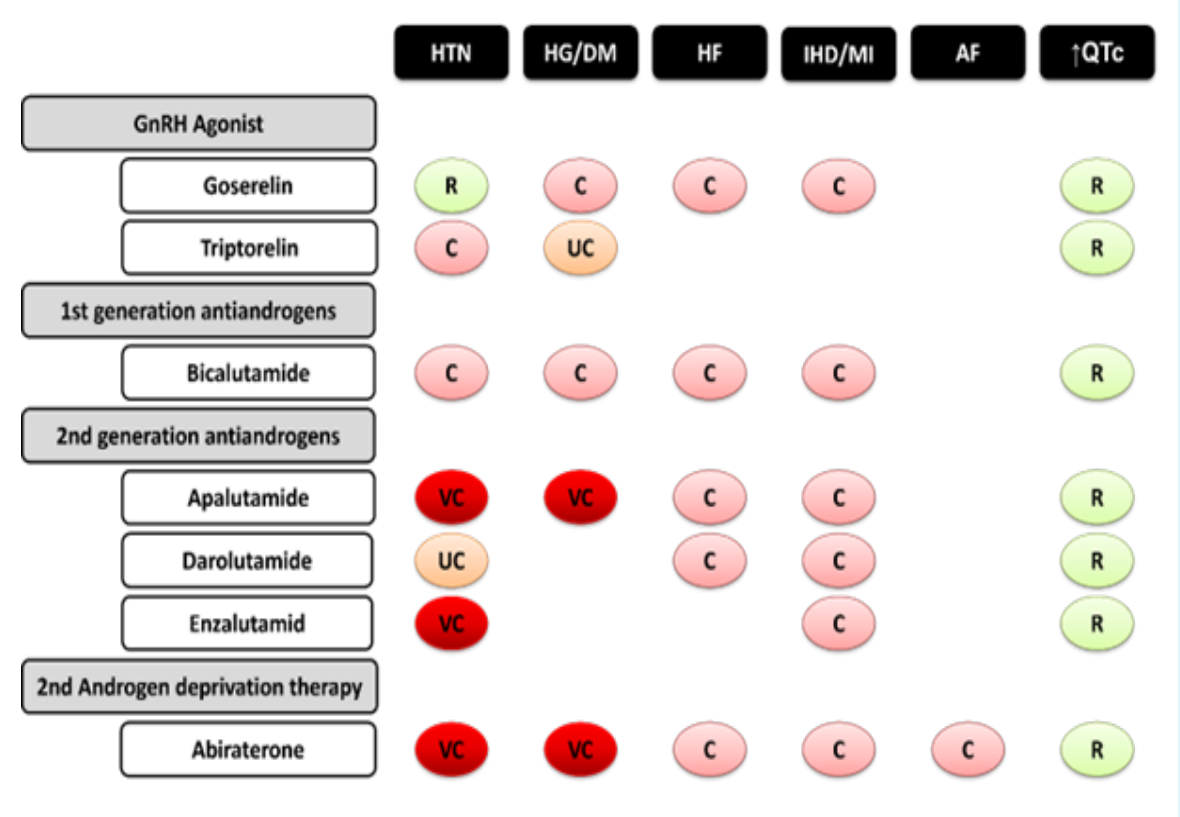
A cohort study was published in 2022 including 13343 patients aged 40 to 79 years, treated for prostate cancer between 2012 and 2016 with a follow-up between 4 and 5 years, and comparing the risk of death from cardiovascular disease in 3797 patients who received HT versus 9546 patients who did not. The analysis found a more than twofold increase in the risk of death from cardiovascular disease patients treated with HT with higher risk of cardiovascular death from cardiovascular disease starting in the second year after prostate cancer diagnosis: Hazard Ratio 2.14, 95% Confidence Interval [1,86-2,45]. The risk was five times higher for patients aged 70-79 years old who received ADT. The risk of death specifically related to stroke or coronary artery disease was 70% for patients treated with ADT versus 42% for patients who did not receive ADT (16).

Cardiac workup before starting ADT for prostate cancer

- Baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP are recommended in patients treated with ADT without pre-existing CVD (17).

- Baseline ECGs are recommended in patients at risk of length QTc interval during ADT therapy (17).

- Inform the patient of the eventual cardiovascular toxicities of ADT (Figure 2).



VC: Very common ≥10% incidence; C: common 1% to < 10% incidence; UC: uncommon 0.1 to <1% incidence; R: rare< 0.1% incidence

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;

Figure 2. Androgen deprivation therapy- related cardiovascular toxicities (17)

- Educate the patient about cardiovascular preventive measures (ABCDE Algorithm - Table 1), smoking cessation, healthy diet, diabetes control, exercise, and compliance with prescribed cardiovascular treatments (18) (Table 1).

Table 1. ABCDE measures for the prevention of cardiovascular disease in patients with prostate cancer (18)

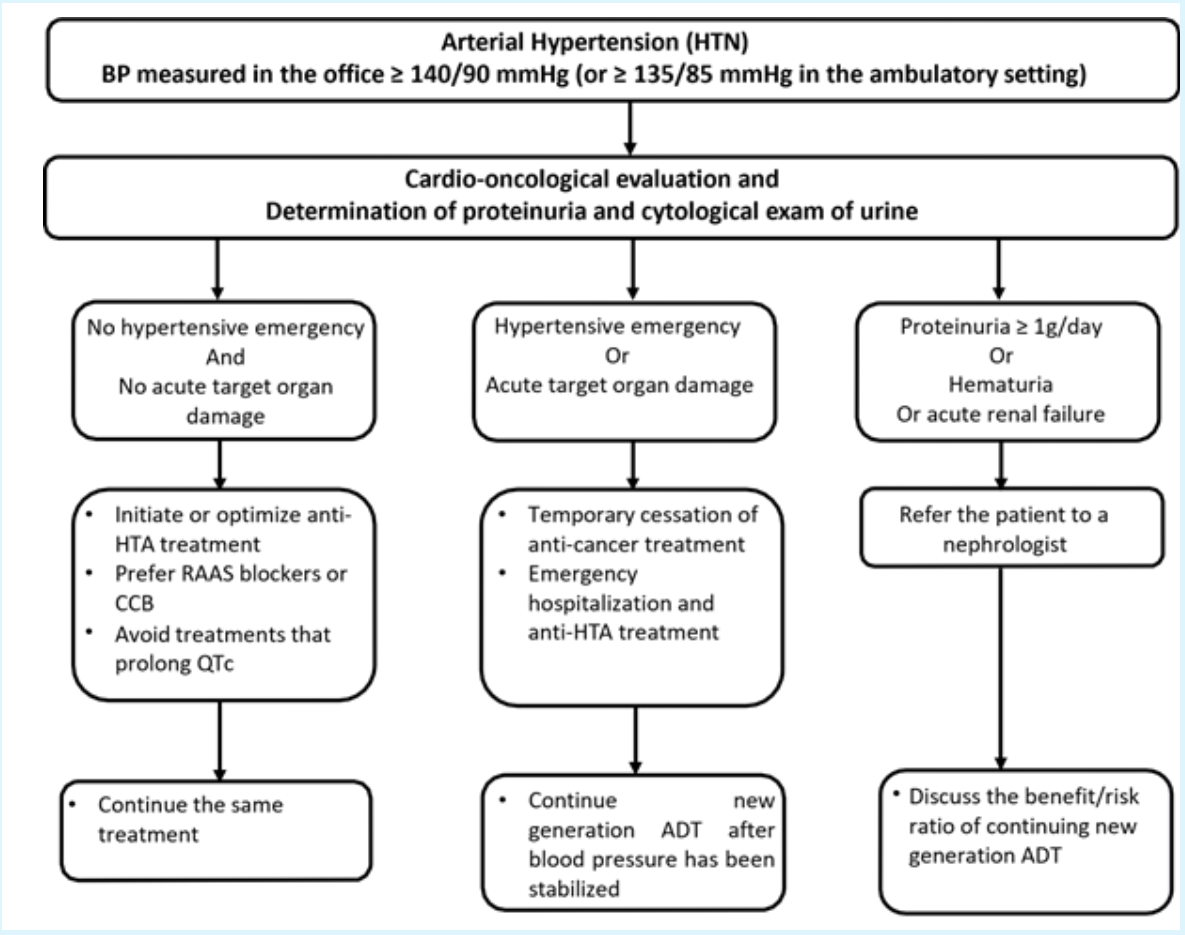
A	Aspirin and awareness	Aspirin 100 mg/day for secondary cardiovascular prevention
B	Blood pressure	Target BP < 140/90 mmHg
C	Cholesterol and Cigarettes	Statins if dyslipidemia Stop smoking Monitoring of blood glucose, HbA1C
D	Diabetes and Diet	Diet rich in fruits, vegetables, unsaturated fatty acids, Vit D 600 IU/day, and Calcium (1200mg/d)/ Avoid alcohol consumption
E	Physical activity	Moderate physical activity lasting 150 min/per week or intense activity lasting 75 min/per week

BP: blood pressure

Recommended monitoring and management of cardiovascular complications during ADT for prostate cancer

- Annual CV risk assessment is recommended during ADT to ensure that the risk factors are well controlled.

- In addition, for those on new generation ADT (abiraterone, apalutamide or enzalutamide), it is recommended that blood pressure be monitored every month after starting ADT (Figure 3).



ADT: Androgen deprivation therapy; BP: blood pressure; CCB : Calcuim channel blockers ; HTN : Hypertension; RAAS: Renin angiotensin aldosterone system

Figure 3. Proposed management algorithm for patients on new generation hormonotherapy presenting a blood pressure imbalance

- The cardiovascular monitoring visit should focus on monitoring:
  - body mass index, abdominal circumference, and blood pressure measurement
  - Lipid profile (total cholesterol, HDLch, LDLch, TG), blood glucose, and blood ionogram
  - QTc interval on electrocardiogram (Figure 4).

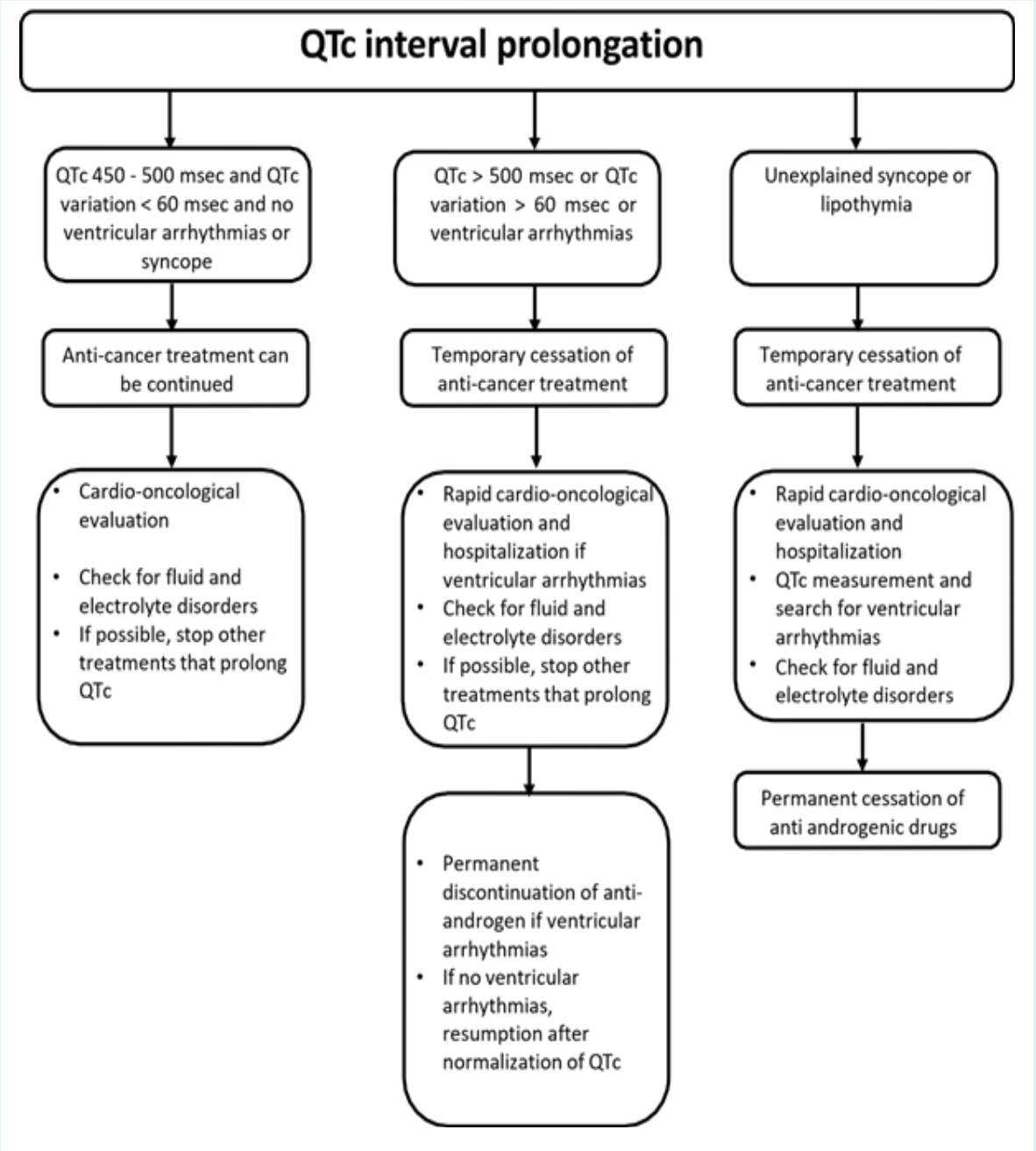


Figure 4. Proposed management algorithm for patients on anti-androgens who presenting QTc prolongation

- Patients on ADT may present with angina chest pain in association with atherosclerotic coronary disease. A specialized cardio-oncology consultation is indicated in these patients to decide on further treatment, including necessary cardiac investigations, cardiovascular treatment, and whether to continue ADT (19) (Figure 5).

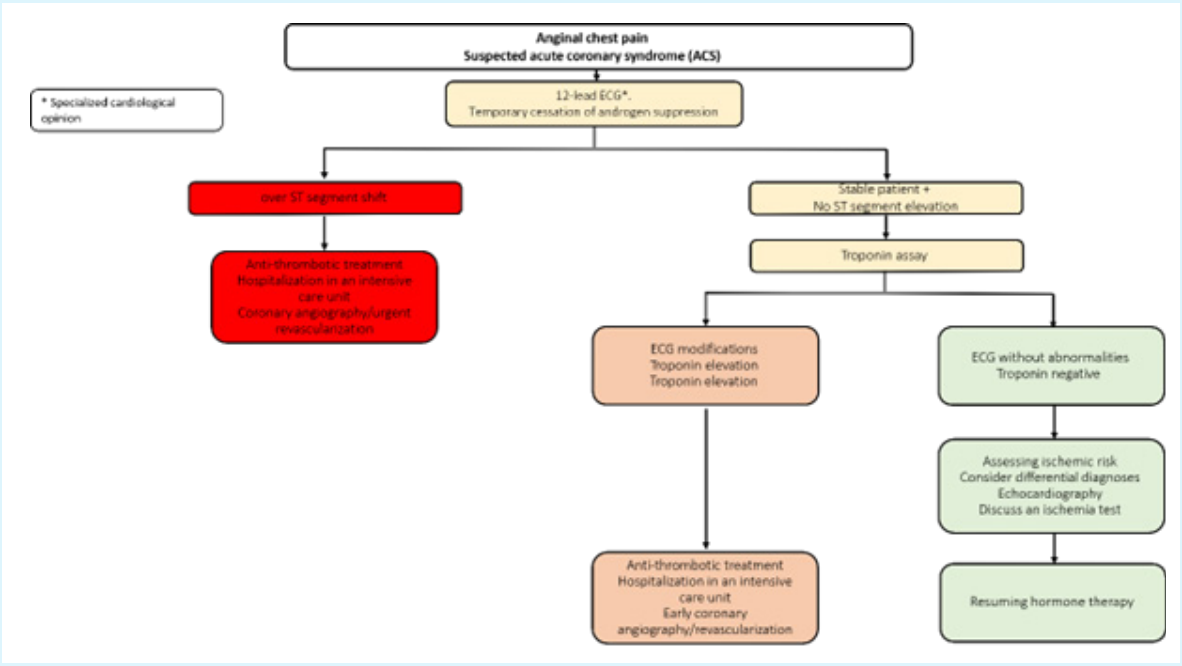


Figure 5. Proposed management algorithm for patients on androgen deprivation therapy who present with chest pain with suspected acute coronary syndrome

- Androgen suppression also increases the risk of venous thromboembolic (VTE) disease. A discussion of primary thrombo-prophylaxis with preventive dose anticoagulation is advised in patients with prostate cancer who are candidates for castration with a high thromboembolic risk (Khorana score ≥3) and low bleeding risk. Eligible patients can be put either on Low-molecular-weight heparin (LMWH) or direct oral anticoagulants (AOD) (rivaroxaban 10 mg/day or apixaban 2.5 mg X 2/day) respecting the contraindications of AOD essentially the absence of high risk of gastrointestinal or genitourinary bleeding (20).

- If VTE occurs in patients on ADT, curative anticoagulation should be initiated with a preference to AOD in the absence of high risk of gastrointestinal or genitourinary bleeding or LMWH and continuation of ADT is possible (17, 20).

CONCLUSION

Advances in early detection and efficient treatments have improved cancer-specific survival. With this prolonged survival, PCa patients are now living with the aging effects and are facing an increased risk of developing CV risk factors and CV disease. In the long term, CV mortality has become more common than cancer mortality for many cancer survivors. ADT seems to be associated with a higher risk of CV events, a risk that peaks within the first 6 months of treatment. The mechanism appears to be multifactorial, encompassing both immunomodulatory and metabolic changes, and the risk of subsequent events varies with the co-existing CV comorbidities and the type of ADT received. Therefore, because of the frequent co-occurrence of these two diseases, effective collaboration between oncologists, urologists, and cardiologists, is crucial to address the challenge of balancing cancer and CV outcomes to optimize survival.

REFERENCES

1. Nguyen PL, Alibhai SMH, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them. European Urology. mai 2015;67(5):825-36.
2. Melloni C, Roe MT. Androgen deprivation therapy and cardiovascular disease. Urologic Oncology: Seminars and Original Investigations. févr 2020;38(2):45-52.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J Clin. mai 2021;71(3):209-49.

4. Urofrance | Recommandations françaises du Comité de cancérologie de l'AFU – actualisation 2020–2022 : cancer de la prostate - Urofrance [Internet]. [cité 23 déc 2022]. Disponible sur: https://www.urofrance.org/recommandation/recommandations-francaises-du-comite-de-cancerologie-de-lafu-actualisation-2020-2022-cancer-de-la-prostate/
5. Zareba P, Duivenvoorden W, Leong DP, Pinthus JH. Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? Therapeutic Advances in Urology. 1 avr 2016;8(2):118-29.
6. Blouin K, Boivin A, Tchernof A. Androgens and body fat distribution. The Journal of Steroid Biochemistry and Molecular Biology. févr 2008;108(3-5):272-80.
7. Cereda V, Falbo PT, Manna G, Iannace A, Menghi A, Corona M, et al. Hormonal prostate cancer therapies and cardiovascular disease: a systematic review. Heart Fail Rev. janv 2022;27(1):119-34.
8. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis. European Urology. sept 2015;68(3):386-96.
9. Wilk M, Waśko-Grabowska A, Szmit S. Cardiovascular Complications of Prostate Cancer Treatment. Front Pharmacol. 22 déc 2020;11:555475.
10. Zhao J, Zhu S, Sun L, Meng F, Zhao L, Zhao Y, et al. Androgen Deprivation Therapy for Prostate Cancer Is Associated with Cardiovascular Morbidity and Mortality: A Meta-Analysis of Population-Based Observational Studies. Kyprianou N, éditeur. PLoS ONE. 29 sept 2014;9(9):e107516.
11. Ziouziou I, Karmouni T, El khader K, Koutani A, Iben attya andaloussi A. Complications de l'hormonothérapie anti-androgénique du cancer de la prostate. CUAJ. 11 mars 2014;8(3-4):159.
12. Zhang KW, Reimers MA, Calaway AC, Fradley MG, Ponsky L, Garcia JA, et al. Cardiovascular Events in Men with Prostate Cancer Receiving Hormone Therapy: An Analysis of the FDA Adverse Event Reporting System (FAERS). Journal of Urology. sept 2021;206(3):613-22.
13. Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, et al. Cardiovascular Mortality and Duration of Androgen Deprivation for Locally Advanced Prostate Cancer: Analysis of RTOG 92-02. European Urology. oct 2008;54(4):816-24.
14. Roach M, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, et al. Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610. JCO. 1 févr 2008;26(4):585-91.
15. Nguyen PL, Je Y, Schutz FAB, Hoffman KE, Hu JC, Parekh A, et al. Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer: A Meta-analysis of Randomized Trials. JAMA [Internet]. 7 déc 2011 [cité 23 déc 2022];306(21). Disponible sur: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2011.1745
16. 16. Jonušas J, Drevinskait□ M, Patašius A, Kinčius M, Janulionis E, Smailytė G. Androgen-deprivation therapy and risk of death from cardio-vascular disease in prostate cancer patients: a nationwide lithuanian population-based cohort study. The Aging Male. 31 déc 2022;25(1):173-9.
17. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). European Heart Journal. 1 nov 2022;43(41):4229-361.
18. Guan J, Khambhati J, Jones LW, Morgans A, Allaf M, Penson DF, et al. ABCDE Steps for Heart and Vascular Wellness Following a Prostate Cancer Diagnosis. Circulation [Internet]. 3 nov 2015 [cité 23 déc 2022];132(18). Disponible sur: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.115.012521
19. Corrigendum to: 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal. 21 nov 2020;41(44):4242-4242.
20. Farge D, Frere C, Connors JM, Khorana AA, Kakkar A, Ay C, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. The Lancet Oncology. juill 2022;23(7):e334-47