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Androgen deprivation therapy and cardiological risks in patients with prostate cancer. Are all drugs the same?

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Prostate cancer (PCa) is one of the leading cancer diagnosis among men world wide. For a long time, long-term androgen deprivation therapy (ADT) decreasing native testosterone levels has been the foundation of medicinal treatment of PCa. At the time of PCa diagnosis, 2/3 of males have various risk factors for cardiovascular diseases (CVDs) or established CVDs (one fourth of the patients have CVDs associated with atherosclerosis; 45 % have a diagnosis of arterial hypertension). ADT is associated with increased risk of CVD and cardiovascular complication (CVC) development. Patients with PCa have two main mortality causes: directly due to cancer or due to CVD. Previously, luteinizing hormone-releasing hormone (LHRH) antagonists were considered to have a better safety profile compared to LHRH agonists. Comparison of all LHRH agonists (leuprorelin, triptorelin, goserelin, buserelin) with LHRH antagonists in meta-analyses showed that the risk of major adverse cardiovascular events (MACE) during LHRH antagonist therapy was 43 % lower than during agonist therapy. However, comparison of leuprorelin with antagonists did not show a significant difference in MACE rate. Leuprorelin is a drug with the most favorable profile of cardiological safety among the ADT drugs and the most frequently used LHRH agonist in the world. Considering the high risk of CVDs and CVCs in patients with PCa, along with treatment of the main disease, careful control and reduction of risks of CVD development from the moment of PCa diagnosis should be implemented. The patients must be informed on the necessity of healthy lifestyle, established CVDs should be treated with rational regimens of antihypertensive, lipid-lowering and hypoglycemic drugs. Risk control and reduction, as well as CVD treatment, should be performed for the entire duration of ADT treatment. The article proposes an algorithm of cardiometabolic risk stratification prior to ADT initiation and during ADT.

Keywords: prostate cancer, overall survival, androgen deprivation therapy, cardiovascular complication, luteinizing hormone-releasing hormone agonist, luteinizing hormone-releasing hormone antagonist, leuprorelin

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Background

Prostate cancer (PCa) is one of the most common malignancies in males. A total of 1,414,259 new cases of PCa were reported by the Global Cancer Statistics in 2020 [1]. In Russia, as many as 51,946 new PCa cases were detected in 2023 [2]. Pharmacotherapy of PCa relies primarily on androgen deprivation therapy (ADT), which has been used for several decades. ADT is indicated for patients with metastatic PCa, as a part of combined hormonal/radiation therapy for patients with a high risk of disease progression, patients with lymph node metastasis after radical prostatectomy, patients with locally advanced PCa non-eligible for surgery, and those with a biochemical relapse after surgery [3].

Several large studies have reported an increased risk of both fatal (2- to 5-fold) and non-fatal cardiovascular complications (CVCs) in patients receiving ADT [4–7]. Moreover, PCa patients with cardiovascular risk factors or history of cardiovascular diseases (CVDs) are particularly prone to CVCs [6, 7]. The main causes of death are CVDs, including coronary artery disease (CAD), ischemic heart disease (IHD), stroke, heart failure (HF), peripheral artery disease and a number of others [8].

According to the report on the Global Burden of Cardiovascular Diseases and Risks published in December 2023, age-standardized CVD mortality rates by region ranged from 73.6 per 100,000 in high-income Asia Pacific

region to 432.3 per 100,000 in Eastern Europe. Global CVD mortality decreased by 34.9 % from 1990 to 2022. IHD had the highest global age-standardized DALYs (disability-adjusted life years) among all diseases – 2,275.9 per 100,000. Intracerebral hemorrhage and ischemic stroke were next most important CVDs. Age-standardized CVD prevalence ranged from 5,881.0 per 100,000 in South Asia to 11,342.6 per 100,000 in Central Asia. High systolic blood pressure accounted for the largest number of attributable age-standardized CVD DALYs at 2,564.9 per 100,000 globally [9].

Risk of cardiovascular disease development in cancer patients

Cancer patients are at higher risk of developing CVDs [10–12], in particular due to adverse events associated with antitumor therapy [13]. Advances in the diagnosis and management of different cancers increased the population of monitored cancer patients receiving treatment (a 21 % increase over the last five years from 2019 to 2023) [2], which resulted in an increased prevalence of CVD [14].

A large population-based study which included 3,234,256 patients from the USA demonstrated that the risk of death due to CVD in PCa patients reached 16.6 %. Between 1973 and 2012, the highest absolute number of CVD-related deaths among 28 cancer types was observed in patients with PCa and breast cancer [15].

The sooner a patient is diagnosed with any type of cancer, the higher is the mortality risk due to CVD, but not cancer. Of note, CVD mortality in cancer patients aged 15–35 is very low with 340 cases of death between 1973 and 2012. For cancer patients aged 55 years and younger, the risk of CVD-associated death is more than 10-fold greater than in the general population. Risk of death associated with CVD in cancer patients gradually decreases as age at cancer diagnosis increases (55–64 years of age: standardized mortality ratio (SMR) 7.5; 65–74 years of age: SMR 3.8; 75–84 years of age: SMR 2.4), and this trend is maintained currently, since the risk of CVD death in the general population increases with age. The first year after cancer diagnosis is considered to be the period with highest risk of CVD-related death [15].

Some authors report that more than 70 % of men already have a high risk of CVD upon PCa diagnosis with ≥1 uncontrollable risk factors [16–19]. Testosterone levels in males start to decrease after the age of 40, which is associated with an increased risk of CVD mortality [20].

Pathogenesis of cardiovascular diseases development in PCa patients receiving androgen deprivation therapy

There are several mechanisms underlying the increased CVD risk in PCa patients receiving ADT. In preclinical animal studies, testosterone was shown to have a positive effect on the QT interval by increasing the expression of K+ channels in mouse cardiomyocytes [21] and exerted cardioprotective effects preventing myocardial ischemia [22]. Furthermore, testosterone can induce arterial vasodilation by increasing the production of nitric oxide in the vascular endothelium [23] or by blocking calcium channels [24]. Lowered serum testosterone during ADT impairs above-mentioned physiological processes and produces a negative impact on the cardiovascular system.

ADT was also demonstrated to have a pro-inflammatory and a prothrombotic effect, triggering the development or progression of atherosclerotic plaques, which increases the risk of ischemic events [25]. Panagiotis et al. analyzed cardiovascular health in males with metastatic PCa on ADT and found substantially increased stiffness of major arteries and aorta after 3–6 months of observation due to atherosclerosis and fibrosis of vascular walls [26]. Another mechanism depends on the ability of luteinizing hormonereleasing hormone (LHRH) agonists to make atherosclerotic plaques more vulnerable by stimulating LHRH receptors on T-lymphocytes, which escalates the risk of plaque destabilization, their rupture and subsequent thrombotic complications [28]. In addition to that, elevated Follicle-stimulating hormone (FSH) observed in men after bilateral orchiectomy can also contribute to atherosclerotic plaque development [29]. Some studies suggest that ADT leads to insulin resistance and changes in the lipid profile, which predisposes to CVD [30–32]. Weight gain as a well–known side effect of ADT represents one of the CVD risk factors and is also associated with CV mortality [33–35].

Comparing cardiovascular adverse events between Luteinizing hormone-releasing hormone agonists and antagonists

A systematic review by Nelson et al. compared major adverse cardiovascular events (MACE) of LHRH agonists (goserelin, leuprorelin) and antagonists (degarelix, relugolix). Eleven prospective studies were included in a meta-analysis with a total of 4,248 patients and a maximum duration of observation between 3 and 36 months. MACE were registered in 152 patients, including 76 individuals (2.9 %) among 2655 LHRH antagonist-treated patients and 76 (4.8 %) among 1593 LHRH agonist-treated patients. Comparing the effect of LHRH antagonist with LHRH agonist, the pooled odds ratio (OR) for MACE development was 0.57 (95 % confidence interval (CI) 0.37–0.86); for all-cause mortality, OR was 0.58 (95 % CI 0.32–1.08). Authors inferred that therapy with LHRH antagonist is associated with fewer cardiovascular events and probably lower mortality compared with LHRH agonist therapy [36].

A large retrospective study by Cicione et al. (2023), assessed cardiovascular adverse events (AEs) associated with a LHRH antagonist degarelix and LHRH agonists buserelin, goserelin, leuprorelin, and triptorelin. Analyzed cardiovascular adverse events included arrhythmia, atrial fibrillation, cardiac arrest, cerebrovascular accident, stroke, coronary thrombosis, hypertension, acute myocardial infarction, venous thrombosis, transient ischemic attack (TIA).

The total number of AEs including data from the Food and Drug Administration (FDA) Adverse Reporting System (FDA-FAERS) database and EudraVigilance database of the European Medicines Agency (EMA) was 5,128 for degarelix, 628 for buserelin, 12,145 for goserelin, 71,160 for leuprorelin and 4,969 for triptorelin. Among them, CVCs were reported in 315/5,128 (6 %) for degarelix, in 55/628 for buserelin (9 %), in 843/12,145 (7 %) for goserelin, in 3395/71,160 (5 %) for leuprorelin and in 214/4,969 (5 %) for triptorelin. In general, degarelix demonstrated a similar CVC risk when compared to all LHRH agonists. However, degarelix presented a lower CVC risk when compared to buserelin (pooled relative risk (PRR) = 0.13, p <0.05) and goserelin (PRR = 0.88, p <0.05) while the differences were not statistically significant when compared to leuprorelin and triptorelin (p >0.05). Triptorelin was more likely to be associated with hypertension, arrhythmia, and non-fatal coronary thrombosis than degarelix (Fig. 1) [37].

According to both FDA and EudraVigilance databases, leuprorelin is the most frequently used LHRH agonist; the incidence of CVCs associated with this drug for the entire period of use was similar to that of degarelix. Pooled relative risk of cardiovascular AEs was similar for degarelix and leuprorelin; there was no significant difference in the incidence of CVCs (including arrhythmia, atrial fibrillation, cardiac arrest, cerebrovascular accident, stroke, venous thrombosis, hypertension, acute myocardial infarction, transient ischemic attack), except for coronary thrombosis, the incidence of which was higher for all LHRH agonists compared to degarelix (Fig. 1) [37].

The assumption that LHRH antagonists are safer in terms of CVCs in PCa patients with atherosclerosis remains therefore controversial. An international, multi-center, prospective, open-label, randomized trial PRONOUNCE analyzed 545 PCa patients with atherosclerosis from 113 medical centers in 12 countries. Study participants were randomized 1:1 to receive degarelix or leuprorelin for 12 months. The results suggest no difference in MACE incidence between the groups. The primary endpoint of the study was the time to first occurrence of centrally adjudicated MACE (the composite endpoint included all-cause death, myocardial infarction or stroke) during 12 months. Mean patient age was 73 years; 49.8 % of participants had localized PCa, whereas 26.3 % and 20.4 % of patients were diagnosed with locally-advanced and metastatic PCa, respectively. MACE were registered in 15 (5.5 %) of patients receiving degarelix and 11 (4.1 %) of patients receiving leuprorelin (hazard ratio (HR) 1.28; 95 % CI 0.59–2.79; p = 0.53). The study was terminated prematurely due to a smaller than planned number of recruited patients and the absence of significant differences in the MACE incidence during 1 year between patients receiving degarelix and leuprorelin [38]. Based on results of the PRONOUNCE study, there were some amendments in the local Canadian guideline on ADT in 2022. It was decided to delete a paragraph about the preferential use of LHRH antagonist in patients with a history of myocardial infarction or stroke [39].

A large-scale retrospective study by Crawford et al. (2024) analyzed 45,059 PCa patients from the USA who received at least one injection of hormonal therapy. It has been demonstrated that the risks of MACE and all-cause mortality were slightly lower in the first year after ADT initiation compared to subsequent years. The risk of MACE was higher for the LHRH antagonist compared to LHRH

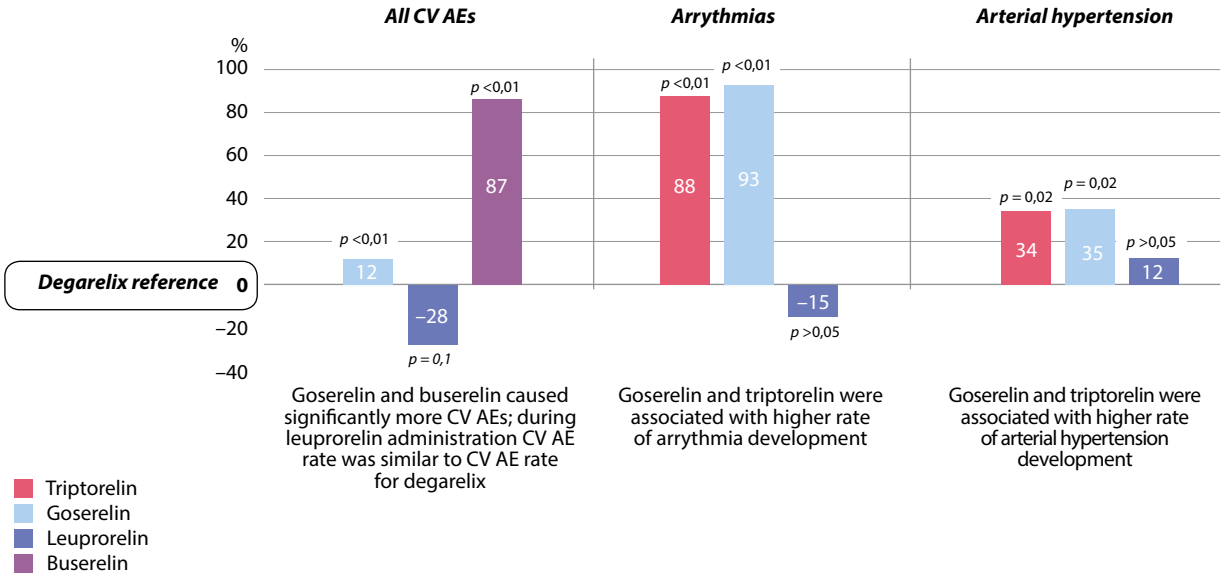


Fig. 1. *Frequency (%) of cardiovascular adverse events (CV AEs) caused by luteinizing hormone-releasing hormone agonists compared to luteinizing hormone-releasing hormone antagonist degarelix (adapted from [37])*

agonists (HR 1.62; 95 % CI 1.21–2.18; p = 0.001). Moreover, the risk of all-cause mortality was also higher for the LHRH antagonist *vs* LHRH agonists (HR 1.87; 95 % CI 1.39–2.51; p <0.001). The adjusted CVC risk, as well as the risk of all-cause mortality was higher in patients receiving LHRH antagonist compared to the LHRH agonists (by 62 % and 87 %, respectively) [40]. The following covariates were used for calculating the adjusted risks: age, treatment settings (oncology *vs* urology), CVD history, smoking, race, baseline body mass index, baseline prostate specific antigen, ethnicity, family history of CVD, hypertension, statin use, diabetes mellitus (DM), and duration of ADT. It should be noted, that in the USA leuprorelin is the most commonly used LHRH agonist prescribed to 90 % of patients; therefore, the majority of study participants received specifically leuprorelin as a LHRH agonist [41].

A meta-analysis of 10 retrospective comparative studies of real-world evidence published in September 2024 compared safety profiles of LHRH agonists and degarelix and found that degarelix was associated with an increased risk of cardiovascular AEs compared to controls (PRR 1.31, 95 % CI 1.14–1.51). The authors deduced that treatment with degarelix produces higher risks of cardiovascular AEs than LHRH agonists. However, this study has a limitation due to its retrospective nature [42].

Based on all facts mentioned above, leuprorelin is the safest LHRH agonist for PCa in terms of CVC risks. Leuprorelin was the first synthetic LHRH agonist [43, 44] and, due to its high tolerability, **is by far the most commonly used drug for ADT globally** [45, 46]. Leuprorelin acetate is manufactured as 1-, 3-, 4-, 6- and 12-month depot forms under various trademarks around the world [41, 47]. Among various forms of this drug, it was specifically leuprorelin acetate in the second-generation depot formulation (Eligard®, Recordati SpA), which ensured consistent and controlled release of leuprorelin between injections and a more effective reduction of testosterone levels compared to conventional LHRH agonists [48]. Eligard® is a leuprorelin acetate with a long-term action with Atrigel® delivery system. Atrigel® has become the most effective system for *in situ* implants since its development in 1989. It consists of a biodegradable polymer dissolved in a biocompatible, non-toxic and water-miscible solvent where the drug is either dissolved or dispersed [49]. After subcutaneous or intramuscular injection, the solvent diffuses into the surrounding fluids, causing gelation/precipitation of the polymer *in situ* as an implant with an active drug. This allows for a prolonged and controlled release of the drug from the depot [50].

Cardiovascular complications associated with second-generation antiandrogens, abiraterone

The majority of PCa patients that are on ADT for a long period eventually develop castration-resistant PCa (CRPCa), and therefore start second-generation antiandrogens (such as enzalutamide, apalutamide, darolutamide) or an androgen synthesis inhibitor (abiraterone acetate), chemotherapeutic drugs (docetaxel, cabazitaxel). These drugs can also cause some cardiovascular AEs. For example, chemotherapy with docetaxel was shown to cause left ventricular diastolic dysfunction and heart failure [51, 52].

Hypertension is the most common CVC associated with enzalutamide in patients with metastatic CRPCa. In the AFFIRM study, new cases of hypertension were registered in 6.6 % of patients [53], while in PREVAIL and ENZAMET studies, their number reached 13 % [54] and 8 % [55], respectively. Less common CVCs included atrial fibrillation (2 % in the PREVAIL study) [54]. In the PROSPER study in patients with non-metastatic CRPCa (nm-CRPCa), the most frequently occurring CVC was hypertension (12 %), followed by acute myocardial infarction, cerebrovascular hemorrhage, ischemia, and heart failure cumulatively observed in 5 % of patients. The authors emphasized that risk factors for such complications include age >75 years, history of CVDs, hypertension, DM, and dyslipidemia [56]. According to Salem J.E. et al., men receiving enzalutamide + ADT are at risk of a prolonged QT interval and Torsades de Pointes [57].

In patients with nm-CRPCa receiving apalutamide, hypertension was the most common CVC as well: it was observed in 24.8 % of patients in SPARTAN [58] and in 17.7 % of patients in TITAN [59]. Furthermore, IHD was reported in 4 % and 4.4 %, respectively.

Administration of darolutamide in nm-CRPCa patients is associated with fewer CVCs. In the ARAMIS, serious AEs in the darolutamide arm were reported in 25 % of participants and caused death in 3.9 %. Fatal CVCs included heart failure (0.3 %), cardiac arrest (0.2 %), and pulmonary embolism (0.2 %). IHD (4.0 % *vs* 3.4 % in the placebo arm) and heart failure (2.1 % *vs* 0.9 %) cases were also registered. No significant differences were observed in the incidence of hypertension between the darolutamide and the placebo arm [60].

The ARASENS study tested a triple combination of ADT + docetaxel + darolutamide for metastatic hormone-sensitive PCa (mHSPCa). The only CVC, which incidence was higher in the ADT + docetaxel + darolutamide arm than in the placebo arm, was hypertension observed in 6.4 % among all patients and 7.9 % in the European subgroup [61]. It is worth mentioning that there are currently no studies evaluating CVCs caused by apalutamide or darolutamide alone.

Abiraterone acetate is a selective inhibitor of CYP17A1 (17-alpha-hydroxylase/C17,20-lyase) responsible for androgen synthesis. Abiraterone inhibits the conversion of 17-hydroxypregnenolone to dehydroepiandrosterone, which, in turn, leads to lowering of serum testosterone [62]. Additionally, abiraterone downregulates serum cortisol levels associated with physiological stimulation of the hypothalamic-pituitary axis and the release of adrenocorticotropic hormone [62]. An adaptive increase in the level of adrenocorticotropic

hormone leads to the mineralocorticoid accumulation, which ultimately causes clinical complications such as fluid retention, hypertension or hypokalemia [63]. Therefore, abiraterone is used in combination with prednisone or methylprednisolone.

According to the COU-AA-301 study, patients with metastatic CRPCa after chemotherapy demonstrated no significant difference in CVC incidence between the abiraterone and placebo arms (13 % *vs* 11 %; $p = 0.14$). The most common cardiovascular AEs associated with abiraterone were tachycardia (3 %) and atrial fibrillation (2 %) [64].

In the COU-AA-302 study, patients with metastatic CRPCa after chemotherapy developed CVCs (such as IHD, acute myocardial infarction, supraventricular tachyarrhythmia, ventricular tachyarrhythmia, and heart failure) in 19 % and 16 % of cases in the abiraterone and placebo arm, respectively [65]. The LATITUDE tested the combination of abiraterone and ADT in patients with mHSPCa and found that grade III hypertension affected 20 % of patients receiving abiraterone and 10 % of patients receiving placebo [66].

A meta-analysis of prospective randomized clinical trials involving a total of 5,445 patients demonstrated that abiraterone therapy was associated with a significantly increased risk of hypertension of all grades with a relative risk of 1.80 (95 % CI 1.47–2.19 %; $p < 0.001$) and high grade with a relative risk of 2.11 (95 % CI 1.66–2.68 %; $p < 0.001$) in comparison with controls [67]. Moreover, administration of abiraterone was associated with an acquired QT prolongation and Torsades de Pointes [68].

Administration of second-generation antiandrogens significantly increases CVC incidence in patients with metastatic PCa [67]. A population-based retrospective study ($n = 3876$) based on the Surveillance, Epidemiology, and End Results (SEER) Program involving patients treated with abiraterone or enzalutamide demonstrated that men with concomitant CVD had a higher risk of mortality compared to those with no history of CVD [70]. Nevertheless, proper control of concomitant CVDs prior to PCa treatment initiation can substantially lower the risks of CVCs [71].

Guidelines on cardio-oncology by the European Society of Cardiology

In 2022, the European Society of Cardiology (ESC) issued the first guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), European Society for Therapeutic Radiology and Oncology (ESTRO) and International Cardio-Oncology Society (IC-OS) [72]. The description of ADT-related cardiovascular toxicity from the ESC guidelines is shown on Fig. 2.

Prior to initiation of antitumor therapies with a known cardiovascular toxicity profile, the cardio-oncology team should collect the information on the earlier diagnosed CVDs, identify and manage CVD risk factors, and define an appropriate prevention and surveillance plan for early identification and appropriate management of potential CVCs. After completing antitumor therapy, the focus shifts to coordination of long-term follow-up and treatment. For patients on long-term cancer therapies with cardiovascular toxicity risks, including PCa patients, monitoring should continue until the treatment is finished.

A multidisciplinary approach should be adopted for all types of cancer, including PCa, encompassing CVD management, healthy lifestyle promotion, and pharmacological, technological, and surgical treatments. The optimal time to consider CVD prevention strategies in PCa patients is at the time of cancer diagnosis and prior to the initiation of cancer treatment. So far, no definitive methods for stratifying patients by their cardiovascular risk have been developed. Thus, it is recommended to use clinical evaluation, physical examination, electrocardiography (ECG), echocardiography, ultrasound examination of blood vessels, as well as other instrumental methods and various scales. Since dedicated cardiovascular toxicity risk calculators have not been developed for PCa patients receiving ADT, experts reached a consensus to recommend SCORE [73, 74], SCORE2 or SCORE2-OP [75] to stratify cardiovascular risk in patients without previous CVD receiving ADT. In Russia, the application of SCORE2 and SCORE2-OP is limited because of the low accessibility and economic inexpediency of lipid profile assessment in a population-based screening [73]. Moreover, Russia refers to countries with extremely high cardiovascular risk; therefore, Russian guidelines, in particular, "Practical guidelines for the correction of cardiovascular toxicity" by the Russian Society of Clinical Oncology (RUSSCO) recommend the original SCORE [73, 74].

The main CVCs to be considered before initiation of ADT are hypertension, DM, IHD, and heart failure related to antitumor therapy [76, 77]. ADT is rarely associated with a prolonged QT interval and Torsades de Pointes due to the inhibition of the testosterone effects on ventricular repolarization [68, 78]. ECG monitoring and correction of factors triggering QT prolongation are recommended for PCa patients if they had a prolonged QT interval at the time of cancer diagnosis [72, 75].

PCa patients receiving ADT with no CVD at the moment of cancer diagnosis should undergo a baseline assessment of cardiovascular risks, as well as estimation of 10-year fatal and non-fatal CVD risk using SCORE [73, 74], SCORE2 or SCORE2-OP [75]. PCa patients at risk of QT prolongation should have regular ECG during ADT [72]. An annual assessment of cardiovascular risks during ADT treatment is recommended. Follow-up diagnostic procedures should include measuring of blood pressure, determining serum levels of lipids, fasting glucose, glycated hemoglobin and performing regular ECGs. In addition to that, patients should be educated on healthy lifestyle decisions and CVD risk factor control.

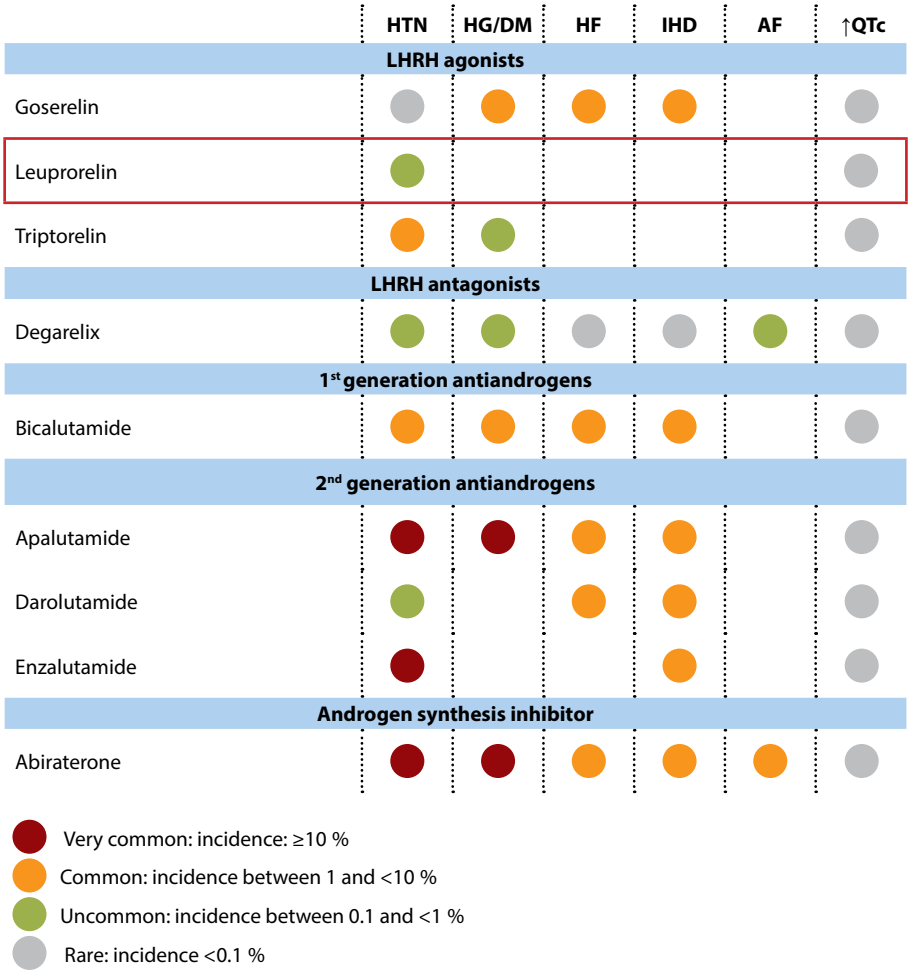


Fig. 2. *Cardiovascular toxicity associated with androgen deprivation therapy (adapted from [72]). Adverse reactions reported in multiple clinical trials or post-registration use are listed by organ system class (in MedDRA) and frequency. If the frequency is unknown or cannot be estimated from available data, the cell was not filled in. HTN – arterial hypertension; HG/DM – hyperglycemia/diabetes mellitus; HF – heart failure; IHD – ischemic heart disease; AF – atrial fibrillation; ↑QTc – QT interval prolongation; LHRH – luteinizing hormone-releasing hormone*

Guidelines on cardio-oncology by the Prostate cancer 360 Working Group

In 2024, the Prostate cancer 360 (PC360) Working Group published their guidelines on comprehensive care of PCa patients receiving ADT. It includes both general recommendations for managing ADT-related AEs and specific recommendations across 5 domains (cardiometabolic, bone, sexual, psychological, and lifestyle) [79].

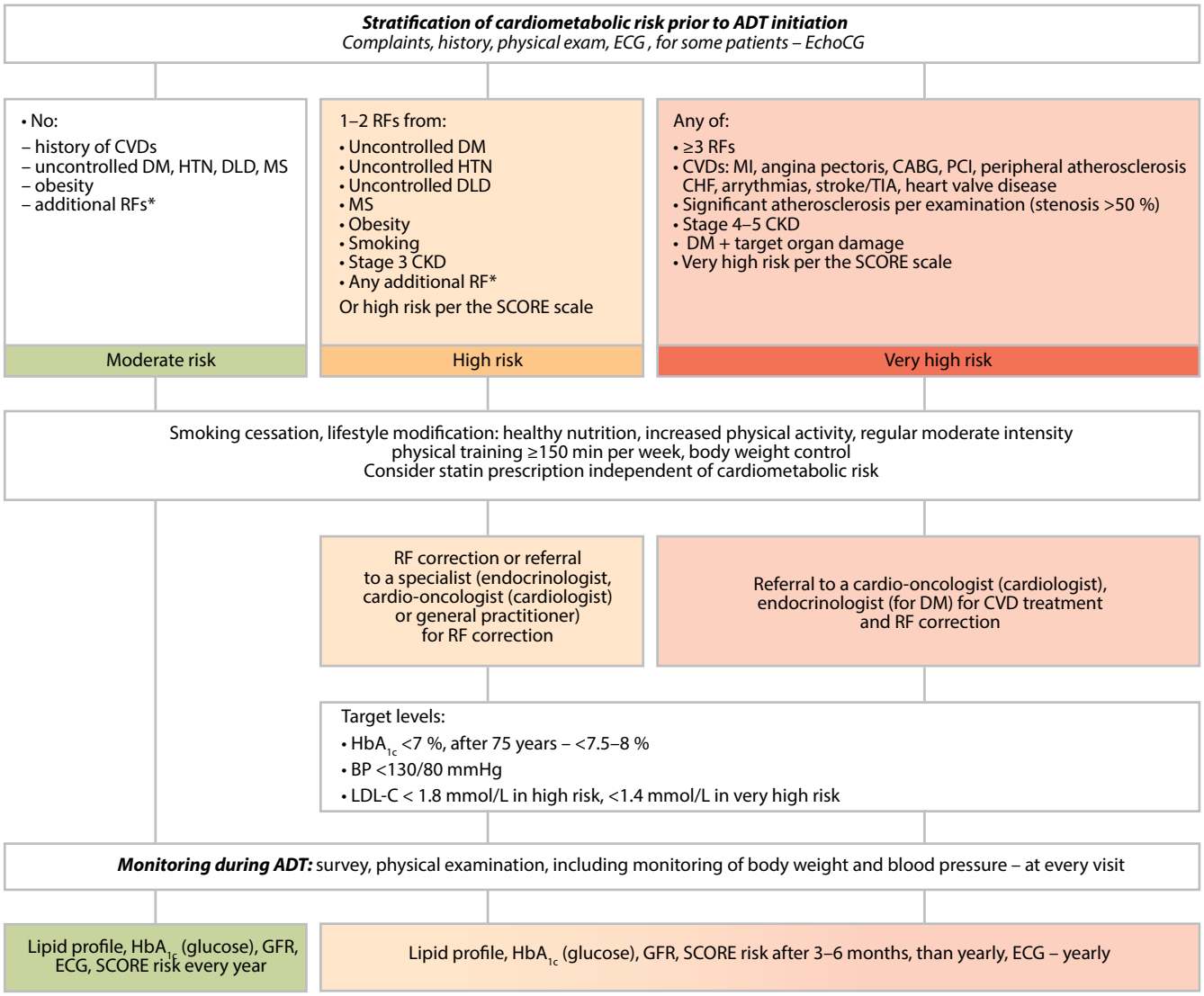
Based on the facts mentioned above, HCPs prescribing pharmacotherapy should be aware that the vast majority of patients starting ADT already have concomitant CVDs or risk factors for CVD. Thus, PC360 recommends CVC evaluation and management both before and during ADT. CVC assessment can be performed by either the oncologist, prescribing ADT, or by the cardiologist (less commonly by general practitioner), whom the patient can be referred to. There are various scales and calculators of cardiovascular risk. PC360 recommends the atherosclerotic CVD (ASCVD) risk calculator developed by the American Heart Association (AHA), which predicts the risk of an ASCVD event in the next 10 years for a patient without baseline ASCVD [80]. In Russia, SCORE, SCORE2, and SCORE2-OP are recommended [73].

To stratify CVC risk, the PC360 Working Group suggests a classification with 3 risk groups. Given that ADT itself is a risk factor, this classification has no low-risk group and the lowest CVC risk is considered as borderline, when no risk factors (dyslipidemia, metabolic syndrome, hypertension, DM, obesity, smoking, etc.) are observed. The risk is considered intermediate when patient has 1–2 risk factors and high when the patient has ≥3 risk factors or earlier diagnoses of CVD, heart failure, heart valve lesions or arrhythmias (in the guidelines by ESC and Russian Society of Cardiology for Cardiovascular Prevention, these

groups correspond to moderate, high and very high CVD risks, respectively) [72, 73, 79]. Similar to the ESC guidelines, the PC360 document encourage informing all patients about CVC risks and explaining the importance of regular examination and healthy lifestyle.

Patients with a borderline risk are recommended to start statins. In a meta-analysis of 25 cohort studies that included 119,878 PCa patients, concomitant statin usage was associated with improved overall survival by 27 % and PCa-specific mortality by 35 % [81]. Intermediate-risk patients should also initiate statin therapy, correct risk factors, and undergo a coronary calcium scan. High-risk patients should follow all recommendations for the previous group plus should be followed up by a cardiologist or cardio-oncologist.

For PCa patients in Russia, an algorithm of cardiovascular risk stratification prior to ADT initiation and monitoring during ADT is proposed (Fig. 3).



*Family history of early ischemic heart disease or stroke, systemic inflammatory diseases, age ≥ 65 years, history of antitumor therapy, including radiotherapy of the thoracic cage, head, neck

Fig. 3. *Algorithm of cardiovascular risk stratification prior to androgen deprivation therapy (ADT) initiation and monitoring during ADT for patients with prostate cancer. ECG – electrocardiography; EchoCG – echocardiography; CVDs – cardiovascular diseases; DM – diabetes mellitus; HTN – arterial hypertension; DLD – dyslipidemia; MS – metabolic syndrome; RF – risk factors; CKD – chronic kidney disease; MI – myocardial infarction; CABG – coronary artery bypass grafting; PCI – percutaneous intervention; CHF – chronic heart failure; TIA – transient ischemic attack; HbA1c – glycosylated hemoglobin; BP – blood pressure; LDL-C – low density lipoprotein cholesterol; GFR – glomerular filtration rate*

Conclusion

PCa patients usually demonstrate an increased CVD risk or already have some cardiovascular pathology at the time of cancer diagnosis. Given that ADT itself is a risk factor and causes CVCs, we should use a comprehensive approach to address this problem, starting from CV risk stratification and risk factors correction at early stages of treatment to choosing the safest available drug. So far, no robust evidence of higher LHRH antagonist safety in terms of CVCs over LHRH agonists has been presented. The most commonly used LHRH agonist is leuprorelin characterized by CV safety similar to that of LHRH antagonists. Leuprorelin is potentially safer in patients receiving LHRH agonists as a monotherapy or in combination with other drugs with a certain cardiovascular toxicity. Also, leuprorelin was shown to have no interactions with apalutamide [82]. The safest combination for mHSPCa patients is yet to be discovered and requires additional randomized clinical trials evaluating cardiovascular toxicity of drug combinations. No such analyses have been conducted so far.

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