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CARDIOVASCULAR DISEASES AND ANDROGEN DEPRIVATION THERAPY

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SUMMARY – The leading cause of death in patients with prostate cancer are cardiovascular diseases. Androgen deprivation therapy is the mainstay of treatment in prostate cancers. The latter has numerous perplexed disadvantaging effects to cardiovascular health. ADT alternates the metabolic profile, insulin resistance and glucose metabolism, causes loss of lean body mass, an increase in adipose tissue, obesity, worsening of atherosclerosis and heart failure. It is important to point out that prostate cancer survivors have increased prevalence of coronary artery disease, cerebrovascular stroke, myocardial infarctions and cardiovascular mortality. Due to these reasons particular care on prevention and treatment of cardiovascular diseases should become a standard of care in patients with prostate cancer.

Key words: *Prostate Cancer; Androgen Deprivation Therapy (ADT); Cardiovascular Diseases; Myocardial Infarction*

Introduction

Cardiovascular diseases are the most common cause of non-cancer related death in patients with prostate carcinoma^{1,2}. A number of studies reported on an increased prevalence of major adverse cardiovascular events, particularly myocardial infarction, cerebrovascular stroke and cardiac death in patients treated for prostate carcinoma using androgen deprivation therapy (ADT)^{3,4}. Interestingly, in a meta-analysis performed on 4,800 patients there was no difference in thromboembolic risk for patients with therapeutically deprived testosterone, although the cardiovascular mortality was increased in patients with intermittent androgen deprivation⁵.

Besides traditional cardiovascular risk factors, especially age or male gender, therapeutic decrease of

testosterone levels can have multiple perplexed effects on metabolism, lipoprotein profile and other factors which convene an increase of cardiovascular risk. Through the suppression of gonadotrophin stimulating hormone or blockade of androgen receptors, those lead to decreased stimulation of cancerous cells production by chemical orchidectomy. On the other side, these effects decrease insulin sensitivity, worsen dyslipidemia and increase arterial stiffness⁶⁻⁸. Several studies reported on higher prevalence of diabetes and worsening of therapeutic control of diabetes in patients with ADT^{9,10}. Preclinical studies on mice revealed more pronounced atherosclerosis in animals with testosterone/androgen receptor deficiency¹¹. Analogous findings on increased prevalence of coronary artery disease was also reported in a large retrospective cohort study¹². In another large population-based observational study, GnRH agonists were associated with higher incidence of peripheral artery disease and venous thrombosis¹³. Furthermore, therapeutic decrease of testosterone levels causes loss of lean body mass, loss of muscle tissue, increase of fat tissue and development of obesity, which is associated with higher cardiovascular risks^{14,15}. An-

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drogen deprivation therapy was found to be associated with higher prevalence of arterial hypertension, in a study that analyzed GnRh agonist vs. antagonist during a 3 year follow-up¹⁶.

Negative effects of ADT are furthermore pronounced because of lowered functional performance, i.e. limited lifestyle interventions capacity, increased fatigue and significantly decreased physical activity in patients with prostate cancer and therapeutically decreased testosterone levels¹⁷. In the propensity score-matched cohort study, the adjusted HR for developing heart failure among androgen deprivation therapy users was 1.92 (95%CI, 1.15–3.18) to propensity score-matched prevalence in nonusers¹⁸. Data exist on ADT having effect on the prolongation of corrected QT interval (QTc), which might be responsible for higher incidence of sudden cardiac deaths observed in patients with prostate cancer¹⁹. It is worthwhile to note that in the case of localized prostate cancer, patients' cardiovascular risk has not increased, probably due to a shorter duration of ADT²⁰.

Epidemiology

A large population-based observational study on 37,443 men who were diagnosed with local or regional prostate cancer and who were treated with ADT in the Veterans Healthcare Administration, reported an increase of cardiovascular comorbidities⁹. Surprisingly, the oral antiandrogen therapy was not correlated with any outcome studied⁹. Arm with GnRH agonists, monotherapy was found to be in correlation with increased risk of incident diabetes (for GnRH agonist therapy, 159.4 events per 1,000 person-years vs 87.5 events for no-androgen deprivation therapy; adjusted hazard ratio [aHR] = 1.28, 95% CI = 1.19 to 1.38), myocardial infarction (12.8 events per 1,000 person-years for GnRH agonist therapy vs 7.3 for no-androgen deprivation therapy, difference = 5.5, 95% CI = 5.4 to 5.6; aHR = 1.28, 95% CI = 1.08 to 1.52), newly diagnosed coronary heart disease (aHR = 1.19, 95% CI = 1.10 to 1.28), sudden cardiac death (aHR = 1.35, 95% CI = 1.18 to 1.54), and cerebrovascular stroke (aHR = 1.22, 95% CI = 1.10 to 1.36)⁹. Complete androgen blockade was associated with a more pronounced risk of incident coronary heart disease (aHR = 1.27, 95% CI = 1.05 to 1.53), whilst only orchiectomy was associated with an increase of coronary heart disease (aHR = 1.40, 95% CI = 1.04 to 1.87), as

well as myocardial infarction (aHR = 2.11, 95% CI = 1.27 to 3.50)⁹.

The risk of incident coronary artery disease was found to be pronounced within the first four months of treatment²¹. An increase of 20% of serious cardiovascular comorbidity during a 5-year follow-up of patients on ADT was reported¹. A six-months use of ADT in patients older than 65 years was shown to shorten the period of incident myocardial infarction by 2 years, compared to controls without ADT³.

One must note that the relation between ADT and cardiovascular diseases and comorbidities might not be defined only as straightforward. GnRH antagonists were found to have protective effects in respect to the increase of cardiovascular risk, whilst other types of ADT's increase the risk of cardiovascular diseases²². Other study reported no increase in all-cause mortality with ADT treatment, where the sub-group analysis found no increase of mortality for patients without cardiovascular risk factors or with no known cardiovascular disease, whilst all-cause mortality was higher; adjusted HR 1.96, 95% CI 1.04 to 3.71 in sub-group of patients with myocardial infarction or congestive heart failure due to coronary artery disease²³. In addition, several studies and meta-analyses also did not report of an increase of cardiovascular diseases in patients with prostate cancer and ADT, making the overall connection somewhat controversial^{24–26}. The reasons for discrepancy might be different study settings, the number or selection of patients, various disease and treatment modalities. Further studies are necessary to systematically outweigh the cardiovascular risk associated with ADT²⁷.

Treatment and prevention

Given the potential of ADT to increase cardiovascular risks, all patients should be advised to reassess their cardiovascular risk profile with their general physician. Science Advisory from the American Heart Association, American Cancer Society, and American Urological Association issued a recommendation that an initial reassessment should be performed within 3–6 months after initiation of ADT, while further follow-up would be tailored individually^{28,29}. Basic laboratory exams would be recommended on a yearly basis or otherwise in particular cases²⁸. There is a general consensus that prior to the initiation of the ADT no

particular additional routine assessment by cardiologists, internists or endocrinologists should be done²⁸. In the circumstance of significant cardiovascular comorbidity, the initiation of ADT should be reassessed by the treating specialist i.e. urologist or oncologist. Currently, there is a lack of evidence-based studies on potential benefits of random or non-incident, case-based clinical assessment by cardiologists, including stress tests, cardiovascular imaging, coronarography or other diagnostic modalities³⁰. It is important to change the lifestyle, correct the diet, increase physical activity and cease with the nicotine abuse^{17,33,34}.

Conclusion

Androgen deprivation therapy has numerous perplexed negative effects on cardiovascular health. ADT generally has negative effects on commonly known cardiovascular risk factors, especially metabolic ones. Prostate cancer survivors have increased prevalence of significant cardiovascular diseases and major adverse effects as coronary artery disease, myocardial infarctions, cerebrovascular stroke and cardiovascular mortality. Due to these reasons particular care on prevention and treatment of cardiovascular diseases should become a standard of care in patients with prostate cancer

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References

1. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007;110:1493-500.
2. Ketchandji M, Kuo YF, Shahinian VB, Goodwin JS. Cause of death in older men after the diagnosis of prostate cancer. *J Am Geriatr Soc* 2009;57:24-30.
3. D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007;25:2420-5.
4. Chen DY, See LC, Liu JR, Chuang CK, Pang ST, Hsieh IC, et al. Risk of Cardiovascular Ischemic Events After Surgical Castration and Gonadotropin-Releasing Hormone Agonist Therapy for Prostate Cancer: A Nationwide Cohort Study. *J Clin Oncol* 2017;35:3697-705.
5. Jin C, Fan Y, Meng Y, Shen C, Wang Y, Hu S, et al. A meta-analysis of cardiovascular events in intermittent androgen-deprivation therapy versus continuous androgen-deprivation therapy for prostate cancer patients. *Prostate Cancer Prostatic Dis* 2016;19:333-9.
6. Di Sebastiano KM, Pinthus JH, Duivenvoorden WCM, Mourtzakis M. Glucose impairments and insulin resistance in prostate cancer: the role of obesity, nutrition and exercise. *Obes Rev* 2018;19:1008-16.
7. Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab* 2001;86:4261-7.
8. Smith MR, Lee H, Fallon MA, Nathan DM. Adipocytokines, obesity, and insulin resistance during combined androgen blockade for prostate cancer. *Urology* 2008;71:318-22.
9. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010;102:39-46.
10. Keating NL, Liu PH, O'Malley AJ, Freedland SJ, Smith MR. Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. *Eur Urol* 2014;65:816-24.
11. Wilhelmson AS, Lantero Rodriguez M, Svedlund Eriksson E, Johansson I, Fogelstrand P, Stubelius A, et al. Testosterone Protects Against Atherosclerosis in Male Mice by Targeting Thymic Epithelial Cells-Brief Report. *Arterioscler Thromb Vasc Biol* 2018;38:1519-27.
12. Wallis CJ, Mahar AL, Satkunasivam R, Herschorn S, Kodama RT, Lee Y, et al. Cardiovascular and Skeletal-related Events Following Localized Prostate Cancer Treatment: Role of Surgery, Radiotherapy, and Androgen Deprivation. *Urology* 2016;97:145-52.
13. Hu JC, Williams SB, O'Malley AJ, Smith MR, Nguyen PL, Keating NL. Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. *Eur Urol* 2012;61:1119-28.
14. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 2002;87:599-603.
15. Smith MR, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. *Cancer* 2008;112:2188-94.
16. Hupe MC, Hammerer P, Ketz M, Kossack N, Colling C, Merseburger AS. Retrospective Analysis of Patients With Prostate Cancer Initiating GnRH Agonists/Antagonists Therapy Using a German Claims Database: Epidemiological and Patient Outcomes. *Front Oncol* 2018;8:543.
17. Ashton RE, Tew GA, Robson WA, Saxton JM, Aning JJ. Cross-sectional study of patient-reported fatigue, physical activity and cardiovascular status in men after robotic-assisted radical prostatectomy. *Support Care Cancer* 2019.

18. Kao HH, Kao LT, Li IH, Pan KT, Shih JH, Chou YC, et al. Androgen Deprivation Therapy Use Increases the Risk of Heart Failure in Patients With Prostate Cancer: A Population-Based Cohort Study. *J Clin Pharmacol* 2019;59:335-43.
19. Gagliano-Juca T, Trivison TG, Kantoff PW, Nguyen PL, Taplin ME, Kibel AS, et al. Androgen Deprivation Therapy Is Associated With Prolongation of QTc Interval in Men With Prostate Cancer. *J Endocr Soc* 2018;2:485-96.
20. Voog JC, Paulus R, Shipley WU, Smith MR, McGowan DG, Jones CU, et al. Cardiovascular Mortality Following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08. *Eur Urol* 2016;69:204-10.
21. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448-56.
22. Agarwal M, Canan T, Glover G, Thareja N, Akhondi A, Rosenberg J. Cardiovascular Effects of Androgen Deprivation Therapy in Prostate Cancer. *Curr Oncol Rep* 2019;21:91.
23. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA* 2009;302:866-73.
24. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360:2516-27.
25. Efsthathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol* 2009;27:92-9.
26. Nguyen PL, Je Y, Schutz FA, 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* 2011;306:2359-66.
27. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Causes of death in men undergoing androgen suppression therapy for newly diagnosed localized or recurrent prostate cancer. *Cancer* 2008;113:3290-7.
28. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation* 2010;121:833-40.
29. Holmes JA, Anderson RF, Hoffman LG, Showalter TN, Kasibhatla M, Collins SP, et al. Cardiovascular Preventive Care and Coordination of Care in Prostate Cancer Survivors: A Multi-Institutional Prospective Study. *Int J Radiat Oncol Biol Phys* 2019;103:112-5.
30. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur Heart J Acute Cardiovasc Care* 2019;2048872619858285.
31. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315-81.
32. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019.
33. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. *BJU Int* 2013;111:543-8. 10.1111/j.1464-410X.2012.11774.x:
34. Tzortzis V, Samarinas M, Zachos I, Oeconomou A, Pisters LL, Bargiota A. Adverse effects of androgen deprivation therapy in patients with prostate cancer: focus on metabolic complications. *Hormones (Athens)* 2017;16:115-23.

Sažetak

KARDIOVASKULARNE BOLESTI I ANDROGEN DEPRIVACIJSKA TERAPIJA

M. Boban

Vodeći uzrok smrti u bolesnika s karcinomom prostate su kardiovaskularne bolesti. Terapija deprivacije androgena (ADT) temelj je liječenja raka prostate. Potonja ima brojne nepovoljne učinke na kardiovaskularno zdravlje. ADT pogoršava metabolički profil, inzulinsku rezistenciju i metabolizam glukoze, uzrokuje gubitak mišićne tjelesne mase i povećanje mase masnog tkiva, posreduje u razvoju pretilosti, pogoršava aterosklerozu i dovodi do zatajenja srca. Valja naglasiti u studijama pronađenu dodatno povećanu učestalost bolesti koronarnih arterija, moždanog udara, infarkta miokarda i kardiovaskularnog mortaliteta kod bolesnika s karcinomom prostate i ADT-om. Iz navedenih razloga potrebna je dodatna briga oko prevencije i liječenja kardiovaskularnih bolesti, a navedeno bi trebalo postati standard zdravstvene skrbi.

Ključne riječi: *karcinom prostate; terapija deprivacije androgena; kardiovaskularne bolesti; infarkt miokarda*