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EDITORIAL COMMENT

Cardiovascular Toxicity During Advanced Prostate Cancer Treatment

Minding the Heart*

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Despite some heterogeneity in the literature, there is overall consensus that androgen deprivation therapy (ADT), most commonly using luteinizing hormone-release hormone (LHRH) analogues, is associated with negative metabolic consequences and increased cardiovascular morbidity/mortality.[1] Urologists and oncologists, whose primary focus is ensuring patients do not succumb to prostate cancer itself, acknowledge that the elevated risk of cardiovascular morbidity may be a necessary compromise. However, it is undoubtedly preferable to simultaneously avoid adverse outcomes due to cardiovascular causes. Thus, the development of LHRH antagonist therapies, with apparently greater cardiovascular safety, represented an important advance in the treatment of prostate cancer.[2] However, questions have remained regarding the validity of early analyses,[3] because the studies were not specifically designed to examine cardiovascular outcomes.

In this issue of *JACC: CardioOncology*, Nelson et al[4] review the cardiovascular risk from contemporary studies of LHRH agonists vs antagonists to provide greater confidence in the differential cardiovascular safety of these agents. With a pooled odds ratio of 0.57 derived from an analysis of 4,248 patients, this analysis supports the assertion that LHRH antagonists are associated with a lower rate of cardiovascular events including myocardial infarction, cerebrovascular accident, and death particularly in patients with pre-existing cardiovascular disease (CVD).

As the investigators point out, the mechanism by which LHRH therapy may contribute to cardiovascular risk remains incompletely defined and may be different in the short term (testosterone/follicle stimulating hormone surge) vs during long-term treatment (metabolic syndrome and atherosclerosis).[5] The analysis was limited to short-term therapy with median ADT duration of the included trials being 12 months. It is possible different results would be seen in patients receiving long-term ADT if the deeper testosterone suppression achieved by LHRH antagonists[6] would translate into more significant metabolic disruption. However, the differences seen in this analysis speak to the fact that even when short-term use of ADT is planned, cardiovascular morbidity should be considered. Reassuringly, the incidence of overall major adverse cardiovascular events (MACE) was relatively low, at 4.8% in agonist-treated patients and 2.9% in antagonist-treated patients. However, it is important to consider a recent study that reported a 2.1% rate of 1-year MACE among patients without known prostate cancer, but with established atherosclerotic disease (mean age 69 years) and 1.1% among patients with multiple cardiovascular risk factors.[7] These findings suggest that the event rates among prostate cancer patients on ADT may indeed be elevated, compared with non-cancer patients with pre-existing CVD. Therefore, although the benefits of cancer control with ADT often outweigh the associated cardiovascular risk, prostate cancer patients being considered for ADT, in particular those with those with pre-existing CVD or

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CVD risk factors, should be closely monitored with parallel efforts to optimize their cardiovascular risk.

A limitation of the analysis is the shifting landscape in prostate cancer therapeutics toward greater usage of doublet therapy with agents such as androgen synthesis inhibitor (eg, abiraterone) or androgen receptor antagonists (apalutamide, darolutamide, and enzalutamide). The differential cardiovascular morbidity of the LHRH component may become less significant if there are added cardiovascular toxicities from the partner agents. Although data on this topic are limited, existing evidence suggests a heightened risk of cardiovascular events, including hypertension, associated with abiraterone as well as androgen receptor-targeted agents.[8-10] There are also more drug-drug interactions involving cardiovascular medications including direct oral anticoagulants, antiarrhythmics, and even antihypertensive agents. Thus, it is crucial to foster closer collaboration between cardiologists and prostate cancer specialists to minimize what may be preventable cardiovascular events related to drug-drug interactions.

It is important to call attention to the concern that the lack of equitable access to LHRH antagonists may exacerbate health disparities. A retrospective analysis of a Southern California population found that cost was a significant barrier to use of relugolix in both Medicare and privately insured patients.[11] If insurers refuse to cover relugolix, which offers flexibility in the clinic visit schedule given its oral formulation, working patients may find the monthly degarelix injection schedule a barrier in terms of time off work, whereas LHRH agonists can be administered with a 3-, 4-, or 6-month depot formulation. Additionally, considering the relatively recent Food and Drug Administration approval of relugolix, the information regarding the potential differences between LHRH agonists and antagonists in terms of cardiovascular outcomes may not have penetrated into all oncology and urology practices. This knowledge gap can contribute to further disparities in the care of those on ADT. Thus, dedicated efforts should be made to enhance physician education and dissemination of up-to-date information regarding the cardiovascular risks and benefits associated with different LHRH therapies.[12] Furthermore, studies are warranted to assess the practice patterns and barriers to accessibility of LHRH antagonists, especially to patients with elevated cardiovascular risk, which may be enriched for underserved populations.

It is also important to emphasize that the availability of a less cardiotoxic treatment option (eg, LHRH antagonists) does not exempt oncologists and urologists from devoting attention to cardiovascular risk when treating prostate cancer patients. Regular monitoring of blood pressure, lipid panels, fasting glucose levels, and weight changes are still essential and should be done ideally in collaboration with primary care or appropriate specialists. Additionally, appropriate pharmaceutical and lifestyle strategies to mitigate adverse cardiometabolic consequences should be implemented.[13] As noted by the investigators, there was greater medication prescription for lipid and blood pressure management in PRONOUNCE (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease), in which cardiology consultation was mandatory for each patient, than in other ADT studies. Regardless of the use of LHRH agonist or antagonist therapy, there should be consistent attention to these parameters,[14] and we therefore call for increased educational efforts and patient-empowering innovations to promote comprehensive care of prostate cancer patients receiving ADT.

Finally, although population-based retrospective studies and ad hoc analyses of available clinical trial results such as this work offer valuable insights into the cardiovascular impact of ADT, there is a need for prospective studies and/or randomized trials that specifically examine how contemporary approaches (eg, doublet therapy) influence cardiovascular outcomes. One ongoing study, REPLACE-CV (Randomized Study to Evaluate MACE in Patients With Prostate Cancer Treated With Relugolix or Leuprolide Acetate; NCT05605964) will randomize 2,250 patients with prostate cancer to relugolix or leuprolide, while allowing additional standard treatments, and should provide definitive data given the design with a rigorous, blinded adjudication of MACE by an independent clinical event adjudication committee. Additionally, it would be essential to examine how pre-existing cardiovascular risk factors influence outcomes when undergoing various ADT treatments and, ideally, when there is a standardized approach to risk management. Such studies can enhance our understanding of the cardiovascular implications of different ADT regimens and lead to the development of optimized strategies for identifying and mitigating cardiovascular risks in patients because, for the foreseeable future, ADT will continue to play a crucial role in the treatment of prostate cancer.

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REFERENCES

1. Hu JR, Duncan MS, Morgans AK. Bet al. Cardiovascular effects of androgen deprivation therapy in prostate cancer: contemporary meta-analyses. *Arterioscler Thromb Vasc Biol*. 2020;40(3):e55–e64. https://doi.org/10.1161/ATVBAHA.119.313046

2. Shore ND, Saad F, Cookson, et al, HERO Study Investigators. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187–2196. https://doi.org/10.1056/NEJMoa2004325

3. Abufaraj M, Iwata T, Kimura S, et al. Differential impact of gonadotropin-releasing hormone antagonist versus agonist on clinical safety and oncologic outcomes on patients with metastatic prostate cancer: a meta-analysis of randomized controlled trials. *Eur Urol*. 2021;79(1):44–53. https://doi.org/10.1016/j.eururo.2020.06.002

4. Nelson AJ, Lopes RD, Hong H, et al. Cardiovascular effects of GnRH antagonists compared with agonists in prostate cancer: a systematic review. *J Am Coll Cardiol CardioOnc*. 2023;5:613–624.

5. Kim J, Freeman K, Ayala A, Mullen M, Sun Z, Rhee JW. Cardiovascular impact of androgen deprivation therapy: from basic biology to clinical practice. *Curr Oncol Rep*. 2023;25:965–977. https://doi.org/10.1007/s11912-023-01424-2

6. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*. 2008;102(11):1531–1538. https://doi.org/10.1111/j.1464-410X.2008.08183.x

7. Miao B, Hernandez AV, Alberts MJ, Mangiafico N, Roman YM, Coleman CI. Incidence and predictors of major adverse cardiovascular events in patients with established atherosclerotic disease or multiple risk factors. *J Am Heart Assoc*. 2020;9(2):e014402. https://doi.org/10.1161/JAHA.119.014402

8. Bretagne M, Lebrun-Vignes B, Pariente A, et al. Heart failure and atrial tachyarrhythmia on abiraterone: a pharmacovigilance study. *Arch Cardiovasc Dis*. 2020;113(1):9–21. https://doi.org/10.1016/j.acvd.2019.09.006

9. Fizazi K, Foulon S, Carles J, et al. PEACE-1 investigators. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022;399(10336):1695–1707. https://doi.org/10.1016/S0140-6736(22)00367-1

10. Moreira RB, Debiasi M, Francini E, et al. Differential side effects profile in patients with mCRPC treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials. *Oncotarget*. 2017;8(48):84572–84578. https://doi.org/10.18632/oncotarget.20028

11. Kasparian S, Wei O, Tsai NC, et al. A practical guide to relugolix: early experience with oral androgen deprivation therapy. *Oncologist*. 2023;28(8):699–705. https://doi.org/10.1093/oncolo/oyad036

12. Fazal M, Malisa J, Rhee JW, Witteles RM, Rodriguez F. Racial and ethnic disparities in cardio-oncology: a call to action. *J Am Coll Cardiol CardioOnc*. 2021;3(2):201–204. https://doi.org/10.1016/j.jaccao.2021.05.001

13. Okwuosa TM, Morgans A, Rhee JW, et al. American Heart Association Cardio-Oncology Subcommittee of the Council on Clinical Cardiology and the Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and Council on Cardiovascular Radiology and Intervention. Impact of hormonal therapies for treatment of hormone-dependent cancers (breast and prostate) on the cardiovascular system: effects and modifications: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2021;14(3):e000082. https://doi.org/10.1161/HCG.0000000000000082

14. Bhatia N, Santos M, Jones LW, et al. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate cancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. *Circulation*. 2016;133(5):537–541. https://doi.org/10.1161/CIRCULATIONAHA.115.012519

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