

UPDATE – Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies

Summary of changes

Andrea Kokorovic¹, Alan I. So², Hosam Serag², Christopher French³, Robert J. Hamilton⁴, Jason P. Izard⁵, Jasmir G. Nayak⁶, Frédéric Pouliot⁷, Fred Saad¹, Bobby Shayegan⁸, Armen Aprikian⁹, Ricardo A. Rendon¹⁰

¹Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; ²Department of Urological Sciences, University of British Columbia, Vancouver, BC, Canada; ³Division of Urology, Department of Surgery, Memorial University, St. John's, NL, Canada; ⁴Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁵Department of Urology, Queen's University, Kingston, ON, Canada; ⁶Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; ⁷CHU de Quebec, Université Laval, Quebec, QC, Canada; ⁸Division of Urology, Departments of Surgery and Oncology, McMaster University, Hamilton, ON, Canada; ⁹McGill University Health Centre, Montreal, QC, Canada; ¹⁰Department of Urology, Dalhousie University, Halifax, NS, Canada

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Full-text guideline update available at cuaj.ca and cua.org

Due to the recent release of data from the PRONOUNCE trial, authors of the Canadian Urological Association (CUA) guideline on androgen deprivation therapy (ADT) felt updates to the 2021 document were warranted. A summary of changes is included herein. The full draft of the guideline, with revisions, can be viewed at cuaj.ca or cua.org.

Summary of changes

The PRONOUNCE trial failed to demonstrate a meaningful difference in cardiovascular disease (CVD) risk between gonadotropin-releasing hormone (GnRH) agonists and antagonists. It remains important for physicians to identify patients at high risk for major adverse cardiac events (MACE) so that these men receive cardiac optimization while undergoing cancer treatment. A systematic baseline cardiovascular risk assessment is important before initiating cancer therapies.

Based on results of the PRONOUNCE study, the ADT guideline panel has made the following changes to their recommendations:

- The following statement has been removed:
 - Use of a GnRH antagonist may be considered in men with a prior history of myocardial infarction (MI) or stroke (*LE 2, weak recommendation*).

- The statement, “In patients with a history of MI or stroke, referral to a cardiologist or cardio-oncologist may be considered for assessment and medical optimization prior to initiating ADT (*Expert opinion*),” has been modified to:

- Patients with a history of MI or stroke should be referred to a cardiologist or cardio-oncologist for assessment and medical optimization at the time of initiating ADT (*Expert opinion*).**

- The following statement has been added:

- All patients receiving ADT should undergo a baseline cardiovascular risk assessment and be monitored for cardiovascular complications while receiving therapy (*Expert opinion*).**

Rationale

The CUA guideline on ADT was published in June 2021 in an effort to highlight adverse events associated with therapy, and, importantly, strategies to mitigate these events.¹ The guideline panel strongly recommends that a multidisciplinary approach be used to decrease the risk of cardiovascular events in men receiving ADT. Emphasis is placed on the optimization of cardiometabolic parameters through the primary care provider or cardio-oncologist, particularly in high-risk men with a prior history of MACE. An important and controversial question is whether there is a difference in adverse cardiovascular outcomes in men receiving a GnRH agonist or antagonist, particularly in those with a prior history of MACE. The guideline panel recommends that a GnRH antagonist may be considered in these men to potentially decrease the risk of cardiovascular complications, albeit based on limited data. These recommendations were made before the results of PRONOUNCE — a trial comparing cardiovascular safety of degarelix vs. leuprolide in patients with advanced prostate cancer and cardiovascular disease — were published.²

PRONOUNCE is a multi-institutional, international, prospective, randomized controlled trial whose primary endpoint was to compare the effect of degarelix and leuprolide on MACE in patients with prostate cancer and a prior history of atherosclerotic cardiovascular disease (ASCVD). Patients due to receive ADT for a minimum duration of 12 months were randomized to receive degarelix or leuprolide in standard doses. The primary endpoint of the study was the time from randomization to first occurrence of centrally adjudicated MACE, a composite of all-cause death, MI, or stroke through 12 months.

The primary outcome of first occurrence of MACE (all-cause death, MI, or stroke) occurred in 15 (5.5%) patients receiving degarelix and 11 (4.1%) patients receiving leuprolide (hazard ratio [HR] 1.28, 95% confidence interval [CI] 0.59–2.79, $p=0.53$). Additional prespecified sensitivity analyses and secondary endpoints were analyzed, none of which yielded a difference in event rate between the groups. Importantly, using the HERO trial definitions for MACE,³ there were 18 events in the degarelix group compared to 21 events in the leuprolide group (HR 0.81, 95% CI 0.43–1.53).

PRONOUNCE is the first international, multi-institutional, randomized controlled trial that prospectively compares the cardiovascular risk of a GnRH antagonist vs. an agonist in men with prostate cancer. Overall, the trial results suggest there is no added cardiovascular risk in men receiving a GnRH agonist compared to an antagonist.

The trial has two major limitations. First, patient accrual closed early, with only approximately 60% of the targeted number of patients accrued. Second, the event rate was much lower than anticipated (4.8% actual event rate vs. 7.5% anticipated). PRONOUNCE is, therefore, underpowered to demonstrate a significant difference in the primary event rate.

Nonetheless, there is key take-away point from the PRONOUNCE study. The overall event rate was low in both groups at 4.8%, and was, in fact, much lower than what was observed in the HERO trial, where 17.8% of patients with prior MACE receiving leuprolide experienced an additional MACE on trial. The lower event rate in PRONOUNCE can likely be attributed to the fact that all enrolled participants

were followed by a cardiologist and underwent cardiac optimization for secondary prevention of cardiac events. This strongly suggests that routine monitoring of adverse events and optimization of cardiac risk factors throughout ADT treatment may reduce cardiac morbidity associated with ADT. This supports the guideline panel's recommendations for continuous monitoring and optimization of cardiometabolic parameters in patients receiving ADT, regardless of whether an agonist or antagonist is used.

Competing interests: Dr. So has been an advisory board member for Abbvie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Izard has received grant(s) or honoraria from Abbvie, Astellas, Bayer, Ferring, Janssen, and Sanofi; and has participated in clinical trials supported by Abbvie, Astellas, AstraZeneca, Bayer, Janssen, and Merck. Dr. Saad has been an advisory board member for and has received payment/honoraria from Abbvie, Amgen, Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Amgen, Astellas, Bayer, Janssen, and Sanofi. Dr. Shayegan has been an advisory board member for Astellas, Bayer, and Janssen; and has received a research grant from Janssen. Dr. Aprikian has been an advisory board member for Abbvie, Astellas, and Bayer; and has received grants from Abbvie, Astellas, Bayer, Sanofi, and TerSera. Dr. Rendon has been an advisory board and speakers' bureau member for and has received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. The remaining authors report no competing personal or financial interests related to this work.

Prior to publication, this guideline update was reviewed and approved by the CUA Guidelines Committee and the CUA Board of Directors.

References

1. Kokorovic A, So AI, Serag H, et al. Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies. *Can Urol Assoc J* 2021;15:E307-22. <http://dx.doi.org/10.5489/auaj.7355>
2. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular safety of degarelix vs. leuprolide in patients with prostate cancer: The primary results of the PRONOUNCE randomized trial. *Circulation* 2021;144:1295-1307. <https://doi.org/10.1161/CIRCULATIONAHA.121.056810>
3. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen deprivation therapy in advanced prostate cancer. *N Engl J Med* 2020;382:2187-96. <https://doi.org/10.1056/NEJMoa2004325>

Correspondence: Dr. Ricardo Rendon, Department of Urology, Dalhousie University, Halifax, NS, Canada; rrendon@dal.ca