Comparing Cardiovascular Outcomes With Degarelix or Leuprolide as Prostate Cancer Therapy—Applying Real-world Data to Clinical Trial Emulation

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Since the early 1980s, androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) agonist or antagonist therapies has remained the primary systemic therapy for men with prostate cancer, owing to the fundamental reliance of the disease on oncogenic androgen signaling. While the intense androgen suppression achieved with ADT imparts near-universal initial therapeutic response in prostate cancer, it is also associated with numerous adverse cardiometabolic health consequences. In particular, GnRH agonist therapies have carried an advisory from the US Food and Drug Administration, warning of increased treatment-related cardiovascular risks, including myocardial infarction, stroke, and sudden cardiac death. However, risk differences related to ADT treatment selection may exist, as several retrospective studies have suggested an improved cardiovascular risk profile with GnRH antagonist therapies compared with GnRH agonist approaches. A 2020 large phase 3 randomized trial further indicated similar potential cardioprotective benefit with GnRH antagonist therapies, particularly in those patients with underlying cardiovascular disease history. Until recently, however, no prospective studies directly comparing the cardiovascular risks of GnRH agonist vs antagonist therapies as a primary end point have been published, and the relative cardiovascular safety of GnRH antagonist vs agonist therapies remains unresolved and a topic of clinical interest in contemporary prostate cancer management.

Wallach and coauthors report results from a retrospective study comparing the cardiovascular safety of GnRH antagonist (degarelix) vs agonist (leuprolide) therapy using a data set of individuals with commercial insurance and Medicare Advantage beneficiaries. Importantly, the study population and clinical outcomes of interest, derived from this real-world data set, were selected to emulate the Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease (PRONOUNCE)—a randomized phase 3b clinical trial comparing the cardiovascular safety of degarelix vs leuprolide as a prespecified and centrally adjudicated primary end point in men with prostate cancer and underlying atherosclerotic cardiovascular disease (NCT02663908). At the time of this real-world data set analysis, the primary study results from PRONOUNCE were not yet published, and the authors therefore sought to estimate clinical outcomes from an ongoing and unreported randomized clinical trial. Among 2226 propensity score–matched patients, Wallach and authors reported no significant difference in the risk of major adverse cardiovascular events for patients initiating degarelix when compared with patients initiating leuprolide (10.18 vs 8.60 events per 100 person-years; hazard ratio [HR], 1.18; 95% CI, 0.86-1.61). Moreover, while degarelix was associated with a higher risk of any-cause death (HR, 1.48; 95% CI, 1.01-2.18), it was not associated with increased risk of myocardial infarction (HR, 1.16; 95% CI, 0.60-2.25), stroke (HR, 0.92; 95% CI, 0.45-1.85), or angina (HR, 1.36; 95% CI, 0.43-4.27).

The authors' selection of the PRONOUNCE study represents a compelling application of this novel methodologic approach. Indeed, several aspects of this international randomized trial lend nicely to a real-world data comparative analysis. First, neither leuprolide nor degarelix is a novel therapeutic, and both are commonly used in routine clinical practice. Second, while the prospective randomized PRONOUNCE trial represents the criterion standard of comparative evidence, the actual conduct of the study was unfortunately plagued by restrictive patient eligibility, truncated projected enrollment, and potential loss of power to address the clinical end points of interest. (While 900
participants were planned for target study accrual, only 545 patients from 113 sites across 12 countries were ultimately randomized over a 4-year accrual period.  

However, some caution should be observed in the clinical interpretation of these real-world data results, and notably, the reported findings are contrary to some published literature evaluating relative cardiovascular risks of antagonist vs agonist therapies. As the authors acknowledge, the higher risk of death, but not adverse cardiovascular events, with degarelix suggests potential confounding by indication, with degarelix initiation preferentially used for patients with prostate cancer presentations with poor prognostic features, given the favorable testosterone suppression kinetics with antagonist therapies. Moreover, the presence of missing data (eg, serum prostate-specific antigen levels, metastatic disease burden) for most patients highlights the ever-present risk of residual confounding with real-world data for these important prognostic measures that would be anticipated to affect all-cause mortality not due to an adverse cardiovascular event. Finally, the complex and variable administration of GnRH antagonist and agonist therapies in real-world practice introduce further limitations with the reported results. Notably, 722 of 1131 patients (64.8%) initiating degarelix therapy ultimately crossed over to leuprolide therapy during study follow-up, thus muddling intention-to-treat analyses by ADT exposure. In routine clinical practice, degarelix is often initiated for 1 to 2 months, prior to therapeutic switch to leuprolide (to obviate the need for anti-androgen pretreatment). Consistent with this practice, the median duration of degarelix exposure in this real-world data set was 48 days (with 16% of patients changing to leuprolide within 30 days of degarelix initiation). Similar to contamination in a randomized clinical trial, this real-world crossover would be anticipated to bias results to the null. On the contrary, the PRONOUNCE trial intended 1 full year of either degarelix or leuprolide exposure as protocol-specified therapy. Thus, while the eligibility and outcomes of a randomized clinical trial are feasibly represented with this approach, the spirit of the intended criterion-standard randomized comparison proves more challenging to emulate with real-world data.

While the clinical implications of these study results from Wallach et al remain uncertain, the authors should be commended for thoughtfully exploring this novel methodologic application of real-world data for a compelling clinical question. Although real-world data sets have often been used to recapitulate published randomized trial evidence, here the authors sought to predict the results of a clinical trial that was ongoing and unreported at the time of data analysis. Notably, the 2021 publication of primary study results from PRONOUNCE ultimately noted no significant difference between degarelix and leuprolide exposure in major adverse cardiovascular events, a composite of all-cause death, myocardial infarction, or stroke through 12 months. Therefore, as Wallach and coauthors suggest, the stage is now set for future comparisons of these real-world study findings to the now published PRONOUNCE randomized trial results to better understand the utility and limitations of this approach. Critically, notable distinctions between the real-world data analysis and PRONOUNCE include differences in baseline study populations, time on intended study therapy, ascertainment and adjudication of adverse cardiovascular events, and concurrent longitudinal monitoring by cardiologist clinicians (required in PRONOUNCE).

This novel application of real-world data is particularly timely, given the recent emphasis from the 21st Century Cures Act for increased use of real-world evidence to support regulatory decision-making, including approval of new indications for approved drugs. Undoubtedly, the use of such data sets can help to generalize study findings to real-world cancer populations. Only approximately 25% of patients exposed to ADT in this real-world cohort ultimately met PRONOUNCE trial eligibility criteria, highlighting the often restrictive barriers to cancer clinical trial enrollment. Additionally, while therapeutic prostate cancer trials have historically been plagued with low enrollment of participants from minority racial and ethnic populations, 18% of patients with prostate cancer in this real-world data set were Black individuals (a near-doubling of historic rates). Indeed, in the now published PRONOUNCE study results, more than 90% of enrolled participants were White, and only approximately 5% identified as Black. Thus, as real-world health-related data sets rapidly evolve and expand, their novel applications for efficient, generalizable, low-cost, and rigorous evidence generation will be an important and complementary asset for informing clinical practice.
ARTICLE INFORMATION


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REFERENCES


