Cardiovascular Safety of Degarelix versus Leuprolide in Patients with Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial

Running Title: *Lopes et al.; Cardiovascular Safety of Degarelix vs. Leuprolide in Prostate Cancer*

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This article was updated on 9/13/21 due to authors' request. In Table 1, four variables were inadvertently left out of the published table. This addition does not change the findings of the article. On pg 26, the third row's data changed, and the fourth row through the seventh row were added.

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Abstract

Background: The relative cardiovascular safety of gonadotropin-releasing hormone (GnRH) antagonists compared with GnRH agonists in men with prostate cancer and known atherosclerotic cardiovascular disease (ASCVD) remains controversial.

Methods: In this international, multicenter, prospective, randomized, open-label trial, men with prostate cancer and concomitant ASCVD were randomized 1:1 to receive the GnRH antagonist degarelix or the GnRH agonist leuprolide for 12 months. The primary outcome was the time to first adjudicated major adverse cardiovascular event (MACE) (composite of death, myocardial infarction, or stroke) through 12 months.

Results: Due to slower than projected enrollment and fewer than projected primary outcome events, enrollment was stopped before the 900 planned participants were accrued. From 3 May 2016 to 16 April 2020, a total of 545 patients from 113 sites across 12 countries were randomized. Baseline characteristics were balanced between study groups. The median age was 73 years, 49.8% had localized prostate cancer; 26.3% had locally advanced disease and 20.4% had metastatic disease. MACE occurred in 15 (5.5%) patients assigned to degarelix and 11 (4.1%) assigned to leuprolide (hazard ratio [HR] 1.28, 95% confidence interval [CI] 0.59–2.79; p=0.53).

Conclusions: PRONOUNCE is the first, international, randomized clinical trial to prospectively compare the cardiovascular safety of a GnRH antagonist and a GnRH agonist in patients with prostate cancer. The study was terminated prematurely due to smaller than planned number of participants and events and no difference in MACE at 1 year between patients assigned to degarelix or leuprolide was observed. The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02663908

Key Words: prostate cancer; atherosclerotic cardiovascular disease; cardiovascular events; GnRH antagonist; GnRH agonist

Non-standard Abbreviations and Acronyms

ADT=androgen deprivation therapy
ASCVD=atherosclerotic cardiovascular disease
CEC=clinical events classification
DCRI=Duke Clinical Research Institute
DSMB=data safety monitoring board
GnRH=gonadotropin-releasing hormone
HERO=A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer
IPSS=International Prostate Symptom Score
MACE=major adverse cardiovascular events
ORR=occurrence rate ratio
PFS=progression-free survival
PRONOUNCE=A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease
PSA=prostate-specific antigen

RADICAL PC=The Role of Androgen Deprivation Therapy in Cardiovascular Disease – A Longitudinal Prostate Cancer
SMQ=standardized MedDRA queries

Clinical Perspective

What is new?

- The relative cardiovascular safety of gonadotropin-releasing hormone (GnRH) antagonists compared with GnRH agonists in men with prostate cancer and known atherosclerotic cardiovascular disease (ASCVD) remains controversial.
- PRONOUNCE is the first, international, randomized clinical trial to prospectively compare the cardiovascular safety of a GnRH antagonist and a GnRH agonist in patients with prostate cancer.
- The study was terminated prematurely with smaller than the planned number of participants and events, and no difference in MACE was observed at 1 year between patients assigned to degarelix and leuprolide.

What are the clinical implications?

- The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.
- Cardiovascular events might be lower in patients with prostate cancer through better awareness and attention to cardiovascular risk factor control.
- In the light of improved cancer survivorship and the competing risk of cardiovascular disease, there is an ongoing need for rigorous cardio-oncology clinical trials.
- PRONOUNCE provides a model for interdisciplinary collaboration between urologists, oncologists and cardiologists with a shared goal of evaluating the impact of cancer therapies on cardiovascular outcomes.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading non-cancer cause of death in patients with prostate cancer.[1,2] In relation to common risk factors,[3] contemporary data suggest that two-thirds of patients with prostate cancer have high cardiovascular risk and almost a quarter have established ASCVD.[4,5] Androgen deprivation therapy (ADT), defined as lowering testosterone to castrate levels with orchiectomy or medical treatment, has been the cornerstone of advanced prostate cancer treatment for decades. There are over 3.1 million prostate cancer survivors in the United States,[6] with approximately 50% receiving ADT at some point during their lifetime.[7] Through different pituitary gonadotropin-releasing hormone (GnRH)-receptor mediated mechanisms, both GnRH agonists and antagonists indirectly or directly inhibit luteinizing hormone secretion, consequently inhibiting testosterone production.[8] GnRH agonists are the most commonly prescribed form of ADT, with only 3–4% patients treated with a GnRH antagonist.[9]

Use of ADT has been associated with higher cardiovascular morbidity and mortality in prior studies, particularly in men with cardiovascular risk factors and pre-existing ASCVD.[10-12] In the context of these observational studies and others linking ADT with higher rates of diabetes,[13] lower insulin sensitivity,[14,15] higher low-density lipoprotein- and high-density lipoprotein-cholesterol and triglycerides,[15-17] sarcopenia and higher fat mass,[18,19] and more thromboembolic events,[20,21] the U.S. Food and Drug Administration (FDA) mandated in 2010 that manufacturers of GnRH agonists include the potential increased risk of ASCVD in their product safety information. The European Medicines Agency (EMA) had a similar recommendation. Less is known, however, about whether the mode of testosterone suppression (GnRH agonist or GnRH antagonist) differentially impacts cardiovascular risk, particularly

among those with pre-existing ASCVD. Specifically, there are conflicting data about the cardiovascular safety of GnRH agonists compared with GnRH antagonists.[8,22-24] Recently, a new oral GnRH antagonist, relugolix, was compared with the GnRH agonist, leuprolide, in a prospective head-to-head efficacy trial. Cardiovascular adverse events were lower with relugolix than with leuprolide.[25] However, like all other previous trials evaluating ADT,[26] cardiovascular events were extracted from analyses of adverse event data rather than being collected as prespecified, centrally adjudicated study endpoints. The PRONOUNCE trial was performed to compare the effect of a GnRH antagonist, degarelix, and an agonist, leuprolide, on the occurrence of adjudicated major adverse cardiovascular events (MACEs) over 12 months in patients with prostate cancer and pre-existing ASCVD.

Methods

Trial Design and Oversight

PRONOUNCE (NCT02663908) was an international, multicenter, prospective, randomized, open-label trial with blinded endpoint adjudication comparing the effect of the GnRH antagonist, degarelix, with the GnRH agonist, leuprolide, on adjudicated MACE in patients with prostate cancer and established ASCVD.[27] The trial was designed and led by an academic steering committee comprised of cardiologists, oncologists, and urologists who were responsible for its conduct and reporting. The Duke Clinical Research Institute (DCRI, Durham, NC) was the academic coordinating center and the trial was sponsored by Ferring Pharmaceuticals A/S. The data used to conduct this research will not be made available.

At 113 sites in 12 countries, eligible patients were randomized 1:1 to either a 240 mg subcutaneous starting dose of degarelix followed by 11 maintenance doses of 80 mg injections every 28 days or a 22.5 mg intramuscular injection of leuprolide followed by 3 similar injections

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every 84 days. Randomization was stratified by baseline age (<75 or ≥75 years) and region (North America or other) in fixed blocks of 4. Investigators were required to ensure that a cardiologist was treating enrolled participants during the trial to ensure optimization of secondary prevention medications for ASCVD.

As the dose schedule (once a month vs. once every 3 months), mode of administration (subcutaneous vs. intramuscular), and frequency of injection site reactions differed between the study drugs, a double-blind, multiple sham injection placebo-controlled design was deemed impractical. The nurse administering the study drug, who was unblinded, was kept separate from the study team and had no role in assessing the occurrence of potential cardiovascular events. All patients had monthly study visits regardless of treatment assignment. Sites completed a specific clinical events page, inquiring about potential cardiovascular events, to ensure a systematic and consistent assessment of possible cardiovascular events in each arm.

A clinical event classification (CEC) committee was established to provide independent, blinded, adjudication of cardiovascular events throughout the trial. The CEC committee consisted of cardiologists, neurologists, and an oncologist not otherwise involved with recruiting patients in the trial. Adjudicated primary endpoint data were transferred directly from the CEC to an independent data safety monitoring board (DSMB) to keep those data blinded to the sponsor and investigators.

Appropriate national and institutional regulatory and ethics boards approved the protocol, and the trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to participation. An independent DSMB reviewed unblinded patient-level data at regular intervals during the trial.

All authors had full access to the data and assume responsibility for the completeness and accuracy of the data. Committee members and all participating investigators are listed in the Supplementary Appendix.

Study Population

Patients with histologically confirmed adenocarcinoma of the prostate and a history of ASCVD scheduled to receive at least 12 months of ADT were eligible for enrollment. Patients with prostate cancer were enrolled with localized disease, locally advanced disease, biochemical recurrence after definitive therapy, or metastatic disease. Included within the patient cohort were patients with very high-risk, high-risk, or intermediate-risk disease with features of unfavorable prognosis who would receive standard of care definitive radiation therapy in combination with at least 12 months of neoadjuvant/adjuvant ADT, patients with biochemical recurrence after local therapy who had a prostate-specific antigen (PSA) doubling time <12 months, or those eligible for salvage radiation therapy in combination with ADT. Patients had to be ADT naïve at the time of randomization with a serum testosterone of at least 150 ng/dL (5.2 nmol/L). Exceptions included those with a prior history of neoadjuvant/adjuvant ADT with definitive therapy for which the last injection of a depot ADT formulation was at least 12 months before randomization who were required to have a serum testosterone >50 ng/dL (≥1.73 nmol/L).

ASCVD was defined as prior history of myocardial infarction (MI); previous percutaneous or surgical revascularization of the carotid, coronary, iliac, femoral, or popliteal arteries; previous documentation of a stenosis of >50% in these vessels by angiography or carotid ultrasound; or peripheral artery disease with a diminished ankle-brachial pressure index less than 0.9. To assist sites in confirming the ASCVD inclusion criteria, supporting documentation for the first 3 patients enrolled by each site were reviewed centrally for eligibility

by a cardiologist at the DCRI. Complete inclusion and exclusion criteria are available in the

Supplementary Appendix.

Endpoints

The primary outcome was the time from randomization to first occurrence of centrally

adjudicated MACE, a composite of all-cause death, MI, or stroke through 12 months. Sensitivity

analyses for the primary outcome included time from randomization to a 4-point MACE

outcome (all-cause death, MI, stroke, or unstable angina requiring hospitalization); time from

randomization to MACE-related adverse event (Standardized MedDRA Queries [SMQ]

definitions for MI [broad SMQ], central nervous system hemorrhages and cerebrovascular

conditions [broad SMQ], and all-cause death); and the total occurrence, including first and

recurrent events, of each of the components of the primary outcome. Key secondary outcomes

were the time to first occurrence of cardiovascular-related death, nonfatal MI, or nonfatal stroke;

time to first occurrence of cardiovascular-related death; and time to first occurrence of MI. A

post-hoc analysis using adjudicated MACE plus MedDRA SMQ definitions that were used in the

HERO trial was also performed.[25] Prostate cancer-related outcomes included testosterone levels

at days 28, 168, and 336, progression-free survival (PFS) (defined as time to either death,

radiographic disease progression, introduction of additional prostate cancer therapies for

progression, or PSA failure), and lower urinary tract symptoms using the International Prostate

Symptom Score (IPSS) questionnaire.

Statistical Analysis

Over 12 months, primary outcome event rates were projected to be 5.1% for degarelix and 10.2%

for leuprolide.[22] Under this assumption, an estimated 876 patients would be required to yield 66

primary outcome events to provide the trial with 80% power to detect a hazard ratio of 0.49 for

degarelix versus leuprolide for the composite outcome using a 2-sided alpha level of 0.05. An interim analysis was planned after 33 adjudicated MACE events. Recruitment into the trial was slower than anticipated and the aggregated primary outcome rate was lower than initially projected. After discussion with the steering committee, the sponsor closed enrollment in March 2020 with 545 of the planned 900 patients. The planned 12 months of follow-up for all enrolled patients was completed.

Analyses were based on the full analysis set, which included all patients who were randomized and received at least 1 dose of study drug. Time-to-event endpoints were censored at the time when a patient started a new treatment or a different ADT, was lost to follow-up or withdrew from the study, or at day 336, whichever occurred first. Kaplan-Meier time-to-event curves were constructed and hazard rates within treatment groups were compared using log-rank tests and Cox regressions stratified by age group and geographic region. Endpoints for counts of total number of events were analyzed using a negative binomial regression adjusted for the logarithm of the duration of exposure to estimate the occurrence rate ratio (ORR) between treatment groups, along with a 95 percent confidence interval and a p-value for a hypothesis of ORR=1.

Results

Trial conduct

From 3 May 2016 to 16 April 2020, a total of 545 patients from 113 sites in 12 countries were randomly assigned to receive open-label degarelix or leuprolide. Incomplete follow-up occurred in 32 patients in the degarelix arm (11.6%) and 24 in the leuprolide arm (8.9%) with the most common reasons being an adverse event (4.4%) and withdrawal of consent (2.4%). Loss to

follow-up occurred in 1 patient in the degarelix group (0.4%) and 5 patients in the leuprolide

group (1.9%). Data on vital status was missing for 1 (0.2%) patient at the end of the trial (**Figure**

1).

Patients

The two groups were balanced with respect to baseline characteristics and cardiovascular

secondary prevention medications (**Table 1**). The median age was 73 years, 44% were above 75

years of age. Enrollment from North America was 48.3% and 51.7% from Europe with 1 site in

South Africa. Roughly half (49.8%) of patients had localized prostate cancer; a quarter (26.3%)

had locally advanced disease, and one-fifth (20.4%) had metastatic disease. Baseline median

testosterone level was 330 ng/dL and baseline median PSA level was 12.83 ng/dL.

Cardiovascular Outcomes

The primary outcome of all cause-death, MI, or stroke occurred in 15 patients in the degarelix

group (5.5%) and 11 in the leuprolide group (4.1%) (hazard ratio [HR], 1.28; 95% confidence

interval [CI] 0.59–2.79; p=0.53). The cumulative incidence of primary outcome events over the

12-month treatment period is shown in **Figure 2**. Details around the timing of MACE events are

shown in **Figure 3**.

Pre-specified sensitivity analyses of the primary endpoint using adjudicated data revealed

similar results (**Table 2**). An expanded 4-point MACE endpoint that included unstable angina

requiring hospitalization occurred in 17 (6.2%) patients assigned degarelix and 15 (5.6%)

assigned leuprolide (HR 1.07, 95% CI 0.53–2.13). Analysis of total events revealed 21 MACE in

patients assigned degarelix and 17 in patients assigned leuprolide (ORR 1.27, 95% CI 0.52–

3.11). A final prespecified sensitivity analysis using investigator-reported adverse events with

the application of a standardized MedDRA MACE definition by broad SMQ search used in the

HERO study, occurred in 14 patients assigned degarelix and 20 patients assigned leuprolide (HR 0.67, 95% CI 0.34–1.32).

Overall there were very few secondary outcome events. The composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 9 patients in the degarelix group and 7 in the leuprolide group (HR 1.20, 95% CI 0.45–3.23). There were a total of 8 events for the endpoint of MI (HR 1.59, 95% CI 0.38–6.67), and 6 events for the endpoint of cardiovascular death (HR 0.19, 95% CI 0.02–1.60). Finally, in the post-hoc analysis using adjudicated MACE plus MedDRA (version 22.0) SMQ definitions that were used in the HERO trial, there were 18 events in patients assigned to degarelix and 21 in patients assigned to leuprolide (HR 0.81, 95% CI 0.43–1.53).

Oncological Outcomes

Disease progression occurred in 24 patients assigned degarelix and 27 patients assigned leuprolide (HR 0.89, 95% CI 0.51–1.54) (**Figure 4**). Testosterone suppression to castration levels (<50 ng/dL or <1.73 nmol/L) at day 28 occurred in 96.6% of patients assigned degarelix and 96.5% assigned leuprolide (**Figure 5**). The rates of sustained castration at day 336 were similar between groups; 93.6% for degarelix and 94.8% for leuprolide, whereas profound castration (< 20 ng/dL) through day 336 was observed in 80% assigned to degarelix and 67.8% assigned to leuprolide (p=0.0003 for a log-rank test).

Other Adverse Events

The incidence of severe adverse events was similar between groups (21.5% in degarelix group; 20.4% in leuoprolide group). Injection site reactions were more common among those assigned degarelix than those assigned leuprolide (60.4% vs. 26.8%). Fatigue was more common among those in the degarelix group than the leuprolide group (18.2% vs. 12.6%), while hot flashes were

less common (38.9% vs. 44.6%). Adverse events leading to drug discontinuation were similar

between groups and occurred in 13 patients assigned degarelix (4.7%) and 11assigned leuprolide

(4.1%).

Discussion

In this international, multicenter, prospective, randomized, open-label trial with blinded endpoint

adjudication in patients with prostate cancer and pre-existing ASCVD, no difference was

observed in the rate of cardiovascular events with the GnRH antagonist degarelix compared with

the GnRH agonist leuprolide. However, accrual to the trial was stopped early and there were

fewer than the planned participants and number of MACE, resulting in wide confidence intervals

and low statistical power, and therefore, the relative cardiovascular safety of GnRH antagonists

and agonists remains unresolved. As expected, testosterone levels, rates of progressive disease,

and urinary symptoms were similar between the 2 agents.

Cardiovascular risk is a significant factor to consider when managing patients with

prostate cancer with ADT alone or in combination with novel hormonal agents.[28,29] The Role of

Androgen Deprivation Therapy in Cardiovascular Disease – A Longitudinal Prostate Cancer

(RADICAL PC) study reported that two-thirds of a cohort of 2492 men with prostate cancer had

high cardiovascular risk with 22% having established cardiovascular disease, 16% having

diabetes, 45% having hypertension, and 31% having obesity.[1] ASCVD is the leading cause of

non-cancer deaths in men with prostate cancer. ADT is the pillar of treatment for patients with

prostate cancer. GnRH agonists (leuprolide, goserelin, triptorelin, histrelin) and GnRH

antagonists (degarelix, relugolix) decrease luteinizing hormone levels, leading to testosterone

suppression to castrate levels. GnRH agonists and antagonists are both effective for the treatment

of prostate cancer and are used in men with intermediate- to high-risk localized disease in combination with radiation therapy, in selected patients with biochemical relapse, and as standard therapy in men with metastatic disease. Understanding the impact of ADT therapy on cardiovascular risk is critical because many of the risk factors associated with prostate cancer are also associated with cardiovascular disease. Novel hormonal agents such as abiraterone, enzalutamide, apalutamide, or darolutamide may also adversely affect cardiovascular risk in men already on ADT, as demonstrated by retrospective analyses of the phase III trials of each drug.[29,30]

The known unfavorable effects of ADT on cardiovascular risk factors including increasing lipids, blood pressure, and blood glucose and changing body composition, means that focusing on risk factor control is an important aspect of care for individuals on ADT.[3] A cross-sectional analysis of more than 90,000 U.S. veterans with prostate cancer showed that cardiovascular burden is high, under-assessed, and likely undertreated.[31] In a retrospective study of 616 patients undergoing exercise treadmill testing after a diagnosis of prostate cancer, prolonged ADT was associated with higher cardiovascular mortality in patients with high cardiovascular risk at baseline as well as with lower cardiorespiratory capacity.[4] These findings suggest the need for close attention and education, as well as innovative tools and interventions, to improve the identification and facilitate the earlier treatment of cardiovascular risk in patients with prostate cancer. In our study, all patients were followed by a cardiologist and the use of evidence-based cardiovascular therapies was high, and higher than that reported in prior studies.[8,32-35] Thus, a careful evaluation by cardiologists focusing on cardiovascular risk factors control may have a considerable impact on clinical outcomes of these patients. Additionally, changes in cardiovascular care since the Albertsen[22] data were generated, which are reflected in a

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higher use of cardiovascular therapies in PRONOUNCE, may also have impacted the overall rate of cardiovascular events in our trial. However, this suggests that cardiovascular events can be reduced in patients with prostate cancer through better awareness and attention to cardiovascular interventions, resulting in potential improved overall survival time.

There are conflicting data from both observational and randomized studies comparing GnRH antagonists with GnRH agonists. Numerous observational studies demonstrate an association between GnRH antagonist use and a lower risk of cardiovascular events and both cardiovascular and all-cause mortality, particularly in those with high cardiovascular risk or established ASCVD, compared with GnRH agonists.[22,23,32,34-36] Conversely, a more recent observational study using real-world data from Europe showed that men treated with GnRH antagonists with a history of ASCVD had a 30% higher risk of a cardiovascular event, 63% higher risk of an acute MI, and 74% higher risk of an arrhythmia compared with men treated with GnRH agonists.[32] Important limitations of all these observational studies include lack of randomization, differences in baseline cardiovascular risk, short duration of follow-up, and the absence of rigorous ascertainment or adjudication of cardiovascular outcomes.[37-39]

A meta-analysis of adverse event data from phase 2, randomized trials reported fewer cardiovascular events among patients treated with the GnRH antagonist, degarelix, compared with GnRH agonists.[40] However, another meta-analysis with slightly different inclusion criteria found no significant difference in cardiovascular outcomes between the two.[32] Variation in the baseline cardiovascular risk of the studied populations has been hypothesized as an explanation for the conflicting results as these data were not ascertained in a consistent way. A recently reported randomized open-label trial in patients with prostate cancer comparing the GnRH antagonist relugolix with the GnRH agonist leuprolide showed that the incidence of major

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adverse cardiac events, defined based on MedDRA coded adverse events, was 2.9% in the relugolix group and 6.2% in the leuprolide group.[25] The cardiac adverse events were not independently confirmed or adjudicated. Based on medical history, 90% of patients in HERO had at least 1 cardiovascular risk factor (lifestyle, tobacco use, diabetes, hypertension, and obesity) or a history of a cardiovascular event whereas patients in PRONOUNCE had to have had a history of ASCVD as defined above. In PRONOUNCE, using a similar MedDRA adverse event definition, we also noted numerically fewer major adverse cardiovascular events in the degarelix group than in the leuprolide group, though the difference was also not statistically significant. In many of these studies, analyses of coded investigator-reported adverse event data are challenged by the open label design and lack of blinded event adjudication, the variability of the adverse events included, and the fact that these analyses, with the exception of HERO, are often not prespecified.

Mechanistically, the association between GnRH agonists and cardiovascular events has been hypothesized to relate to the destabilization of existing vascular plaques seen in animal models.[41,42] CD3 positive T cells embedded in atherosclerotic plaque express GnRH receptors. Treatment with a GnRH agonist may result in destabilization of a vulnerable thin cap. Activation of T cells can cause release of cytokines and stimulation of macrophages to secrete collagenases leading to rupture of an atherosclerotic plaque causing an acute cardiovascular event.[41] In animals, treatment with a GnRH antagonist did not have this effect on plaque stability.[41]

PRONOUNCE has major limitations. The premature termination of enrollment and a lower than projected aggregate event rate resulted in wide confidence intervals and the inability to conclude on cardiovascular safety between degarelix and leuprolide. The lower than expected enrollment was in part due to changes in the standard of care during the years of enrollment

including the addition of docetaxel or abiraterone to ADT for men with metastatic hormone sensitive disease.[43-45] The trial was open-label, which could have led to differential treatment or event ascertainment; however, primary outcome events were adjudicated in a blinded fashion without knowledge of treatment assignment. Finally, a unique aspect of PRONOUNCE was that participants were required to have ongoing care of a cardiologist. This requirement, and the predominantly white population, may limit the external validity of these findings to other populations.

Conclusions

PRONOUNCE is the first, international, randomized clinical trial to prospectively compare the cardiovascular safety of a GnRH antagonist and a GnRH agonist in patients with prostate cancer. The study was terminated prematurely due to smaller than planned number of participants and events, and no difference in MACE at 1 year between patients assigned to degarelix or leuprolide was observed. The relative cardiovascular safety of GnRH antagonists and agonists remains unresolved. Nonetheless, PRONOUNCE provides a model for the interdisciplinary collaboration between urologists, oncologists and cardiologists with a shared goal of evaluating the impact of cancer therapies on cardiovascular outcomes.

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BDO: Employee of Ferring Pharmaceuticals A/S.

HK: Employee of Ferring Pharmaceuticals A/S.

LA: Nothing to report.

NWC: Personal fees from Janssen Pharmaceuticals.

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Supplemental Materials

Steering Committee, Operations Committee, Clinical Events Committee, and Data Safety Monitoring Board Members

Investigators

Criteria for Inclusion/Exclusion

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Table 1. Demographics and baseline characteristics

	Degarelix (n=275)	Leuprolide (n=269)	Total (N=544)
Age, mean (SD), yrs	73.3 (7.28)	73.1 (7.16)	73.2 (7.22)
Race, no. (%)			
American Indian or Alaska Native	2 (0.7)		2 (0.4)
Asian	3 (1.1)	5 (1.9)	8 (1.5)
Black or African American	16 (5.9)	12 (4.5)	28 (5.2)
White	252 (91.6)	251 (93.3)	503 (93.0)
All	273 (100.0)	268 (100.0)	541 (100.0)
Ethnicity, no. (%)			
Hispanic or Latino	16 (5.9)	14 (5.2)	30 (5.6)
Not Hispanic or Latino	256 (94.1)	254 (94.8)	510 (94.4)
All	272 (100.0)	268 (100.0)	540 (100.0)
Weight, mean, kg	86.01	87.10	86.55
BMI, no./No.	273/275	268/269	541/544
Mean, kg/m^2	28.38	28.58	28.48
Smoking status, no. (%)			
Current	34 (12.4)	48 (17.8)	82 (15.1)
Former	104 (37.8)	107 (39.8)	211 (38.8)
Never	73 (26.5)	68 (25.3)	141 (25.9)
Baseline BP (diastolic >90 or systolic >140 mm Hg), no. (%)	94 (34.2)	90 (33.5)	184 (33.8)
Total serum cholesterol, mean (SD), mmol/L	4.1 (1.09)	4.2 (1.09)	4.1 (1.09)
Type 2 diabetes mellitus, no. (%)	88 (32.0)	87 (32.3)	175 (32.2)
NT-proBNP, no./No.	266/275	263/269	529/544
Mean (SD), pg/mL	665.4 (1552)	675.0 (3154)	670.2 (2479)
High sensitivity C-reactive protein, no./No.	270/275	264/269	534/544
Mean (SD), mg/dL	0.6896 (1.825)	0.5707 (1.747)	0.6308 (1.786)
Troponin T, no./No.	267/275	257/269	524/544
Mean (SD), pg/mL	18.79 (17.78)	17.62 (17.66)	18.21 (17.71)
Prostate cancer therapy history, no. (%)			
Radiotherapy	42 (15.3)	31 (11.5)	73 (13.4)
Radical prostatectomy	37 (13.5)	27 (10.0)	64 (11.8)
Hormonal therapy	21 (7.6)	23 (8.6)	44 (8.1)
Other	13 (4.7)	11 (4.1)	24 (4.4)
Gleason score			
2–4	1 (0.4)	2 (0.7)	3 (0.6)
5–6	34 (12.4)	33 (12.3)	67 (12.3)
7–10	238 (86.5)	234 (87.0)	472 (86.8)
Stage of prostate cancer, no. (%)			
Localised	138 (50.2)	133 (49.4)	271 (49.8)
Locally advanced	63 (22.9)	80 (29.7)	143 (26.3)
Metastatic	63 (22.9)	48 (17.8)	111 (20.4)
Not classifiable	11 (4.0)	8 (3.0)	19 (3.5)
Testosterone, no./No.	274/275	269/269	543/544
Median (25th, 75th), ng/dL	325.5 (252, 416)	338.0 (249, 415)	330.0 (250, 416)
Prostate specific antigen, no./No.	275/275	268/269	543/544

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Median (25th, 75th), ng/mL	13.4 (5.9, 34.5)	12.7 (5.8, 29.8)	12.8 (5.8, 32.7)
Cardiac disorders, no. (%)	239 (86.9)	233 (86.6)	472 (86.8)
Myocardial infarction	127 (46.2)	125 (46.5)	252 (46.3)
Coronary carotid, or iliofemoral revascularization	199 (72.4)	194 (72.1)	393 (72.2)
Coronary, carotid, or iliofemoral stenosis >50% by angiography	108 (39.3)	120 (44.6)	228 (41.9%)
Carotid stenosis >50% by ultrasound	19 (6.9)	16 (5.9)	35 (6.4)
Ankle-brachial index <0.9	34 (12.4)	41 (15.2)	75 (13.8)
Atrial fibrillation	55 (20.0)	47 (17.5)	102 (18.8)
Dyslipidemia, no. (%)	106 (38.5)	91 (33.8)	197 (36.2)
Hypertension, no. (%)	232 (84.4)	235 (87.4)	467 (85.8)
Concomitant medications, no. (%)			
Cardiovascular medications	268 (97.5)	262 (97.4)	530 (97.4)
Lipid modifying agents	234 (85.1)	224 (83.3)	458 (84.2)
Agents acting on the renin-angiotensin system	202 (73.5)	194 (72.1)	396 (72.8)
Beta blockers	194 (70.5)	180 (66.9)	374 (68.8)

BMI indicates body mass index; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation.

Table 2. Clinical outcomes

Endpoint	Patients with Events, No. (%) Degarelix vs. Leuprolide	HR (95% CI)[*]	P-value[†]
Primary efficacy			
Time from randomization to first adjudicated MACE	15 (5.5%) vs. 11 (4.1%)	1.283 (0.589–2.794)	0.5294
Sensitivity of primary efficacy			
Time from randomization to first adjudicated MI, stroke, unstable angina requiring hospitalization, or all-cause death	17 (6.2%) vs. 15 (5.6%)	1.065 (0.532–2.134)	0.8580
Total occurrences of adjudicated MI, stroke, and all-cause death[‡]	21 vs. 17[‡]	1.265 (0.515–3.107)	0.6076
Time from randomization to first MACE-related AE according to broad SMQ	14 (5.1%) vs. 20 (7.4%)	0.665 (0.336–1.317)	0.2389
Time from randomization to first adjudicated occurrence of MACE (not censored at treatment discontinuation or change of ADT regimen)	15 (5.5%) vs. 11 (4.1%)	1.319 (0.606–2.873)	0.4835
Time from randomization to first adjudicated MACE over full trial duration[#]	17 (6.2%) vs. 12 (4.5%)	1.446 (0.677–3.088)	0.3382
Time from randomization to the first adjudicated MACE (using all CEC adjudicated events)	18 (6.5%) vs. 13 (4.8%)	1.468 (0.707–3.051)	0.3003
Key secondary efficacy[§]			
Time from randomization to first adjudicated occurrence of CV-related death, non-fatal MI, or non-fatal stroke	9 (3.3%) vs. 7 (2.6%)	1.204 (0.448–3.234)	0.7126
Time from randomization to first adjudicated CV-related death	1 (0.4%) vs. 5 (1.9%)	0.186 (0.022–1.595)	0.0853
Endpoints for MACE components			
Time from randomization to first adjudicated MI	5 (1.8%) vs. 3 (1.1%)	1.594 (0.381–6.673)	0.5196
Time from randomization to first adjudicated stroke	3 (1.1%) vs. 3 (1.1%)	0.899 (0.181–4.457)	0.8964
Time from randomization to all-cause death	8 (2.9%) vs. 9 (3.3%)	0.839 (0.324–2.176)	0.7184

*Hazard ratio and 95 percent confidence interval for degarelix versus leuprolide are estimated using a Cox regression stratified for age group and region.

†p-value of the log-rank test is based on comparison of the treatment groups stratified for age group and region.

‡For the total number of MACE, the occurrence rate ratio is presented along with a 95% confidence interval and the corresponding p-value derived from a negative binomial regression.

§Endpoints controlled for multiplicity by a closed testing sequence. Formally, by this procedure and endpoint is only statistically significant if all previous endpoints are having a p-value below 0.05, ordered from top to bottom.

#Over full trial duration indicates that this endpoint was not censored at day 336 and events occurring after 336 and before the end-of-study visit were included.

ADT indicates androgen deprivation therapy; CEC, clinical events committee; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; SMQ, Standardized MedDRA Queries.

Figure Legends

Figure 1. CONSORT diagram

Figure 2. Primary endpoint: Kaplan-Meier plot of time from randomization to first adjudicated

MACE, by treatment group

Figure 3. Timing of MACE by treatment group

Figure 4. Kaplan-Meier plot of progression-free survival (PFS), time from randomization to PFS

failure, by treatment group

Figure 5. Median measured values and interquartile ranges for testosterone

Enrollment

Assessed for eligibility (n=702)

Excluded (n=157)
- Not meeting inclusion criteria (n=118)
- Declined to participate (n=28)
- Other reasons (n=11)

Randomized (n=545)

Allocation

Allocated to degarelix (n=276)
- Received allocated intervention (n=275)
- Did not receive degarelix (screening failure randomized in error) (n=1)

Allocated to leuprolide (n=269)
- Received allocated intervention (n=269)

Follow-Up

Lost to follow-up (n=1)

Discontinued intervention (n=31)

Lost to follow-up (n=5)
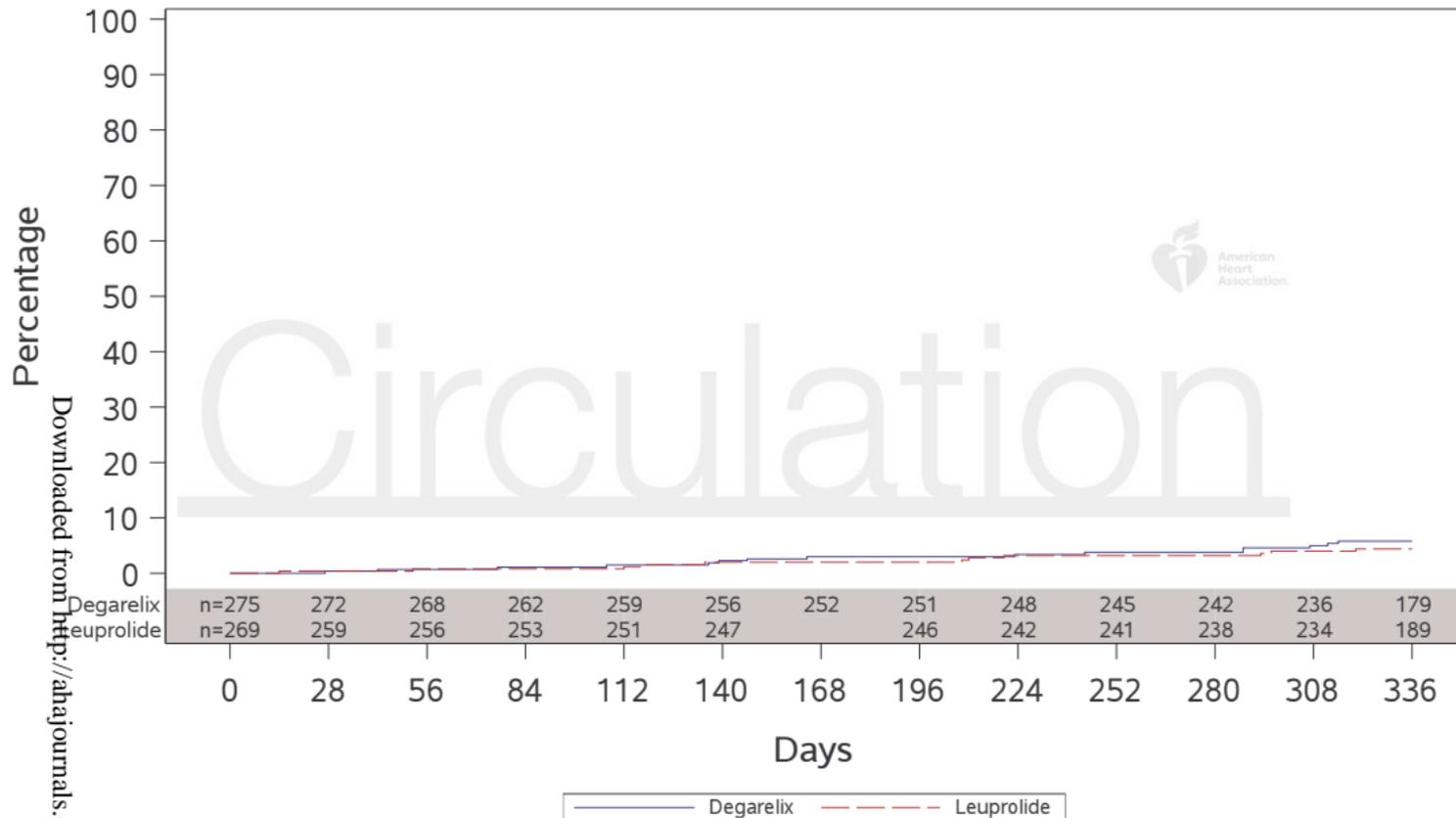
Discontinued intervention (n=19)

Analysis
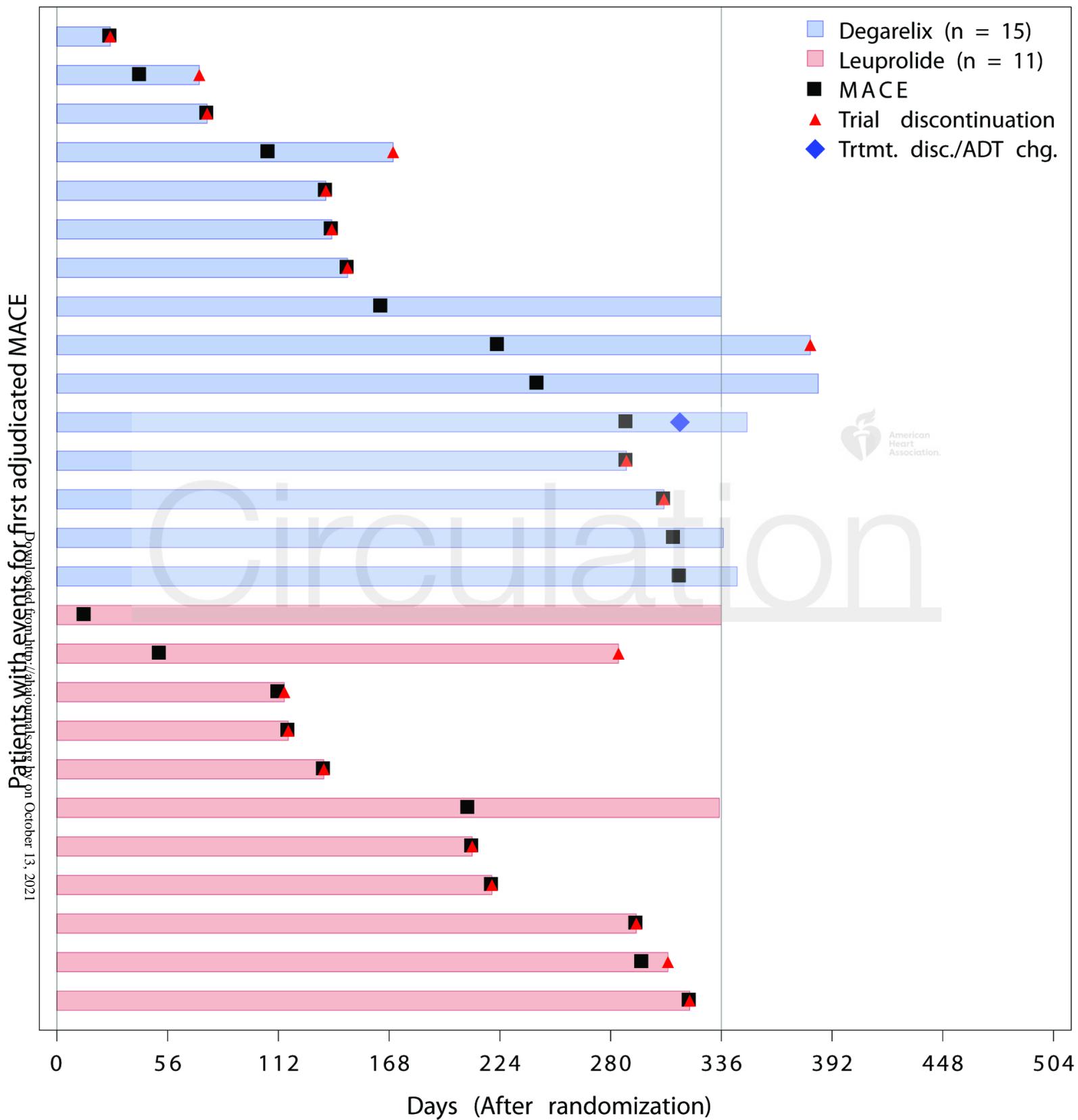
Analysed (n=275)
- Excluded from analysis: None

Analysed (n=269)
- Excluded from analysis: None

Primary endpoint: Inverted Kaplan-Meier estimates of the cumulative probability of first adjudicated MACE - Full Analysis Set

Degarelix	n=275	272	268	262	259	256	252	251	248	245	242	236	179
Leuprolide	n=269	259	256	253	251	247		246	242	241	238	234	189

Days

— Degarelix   — — — Leuprolide

FE200486/Prostate/000108/Report/18AUG2021-PESO/KM_EPS_ADTTE.sas

Primary endpoint: Swimmer plot for patients with events for first adjudicated MACE - Full Analysis Set

Legend:
- Degarelix (n = 15)
- Leuprolide (n = 11)
- M A C E
- Trial discontinuation
- Trtmt. disc./ADT chg.

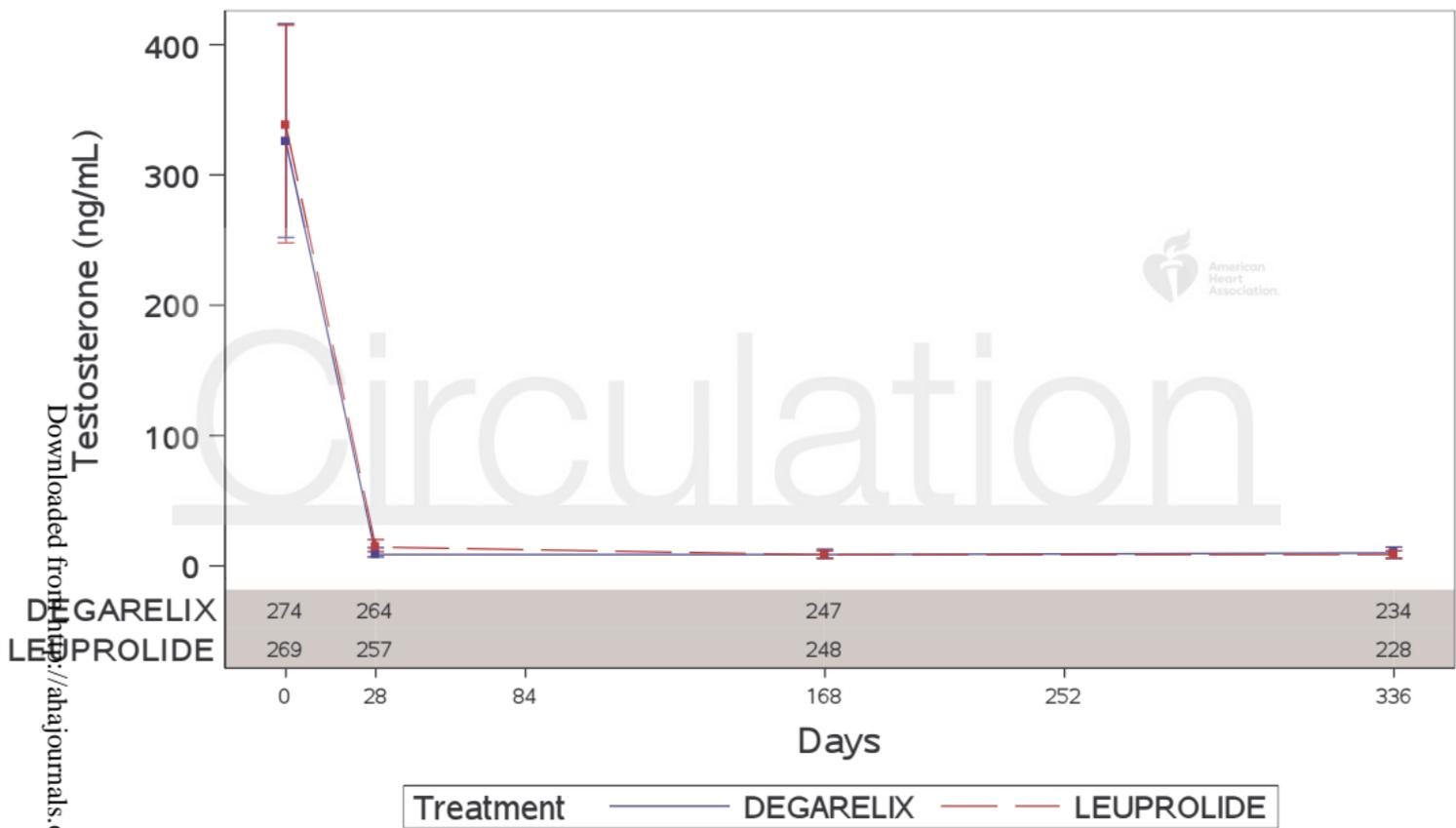Y-axis: Patients with events for first adjudicated MACE

X-axis: Days (After randomization)

Primary endpoint: Inverted Kaplan-Meier estimates of the cumulative probability of Progression-free survival (PFS) - Full Analysis Set

FE200486/Prostate/000108/Report/18AUG2021-PESO/KM_EPS_ADTTE.sas
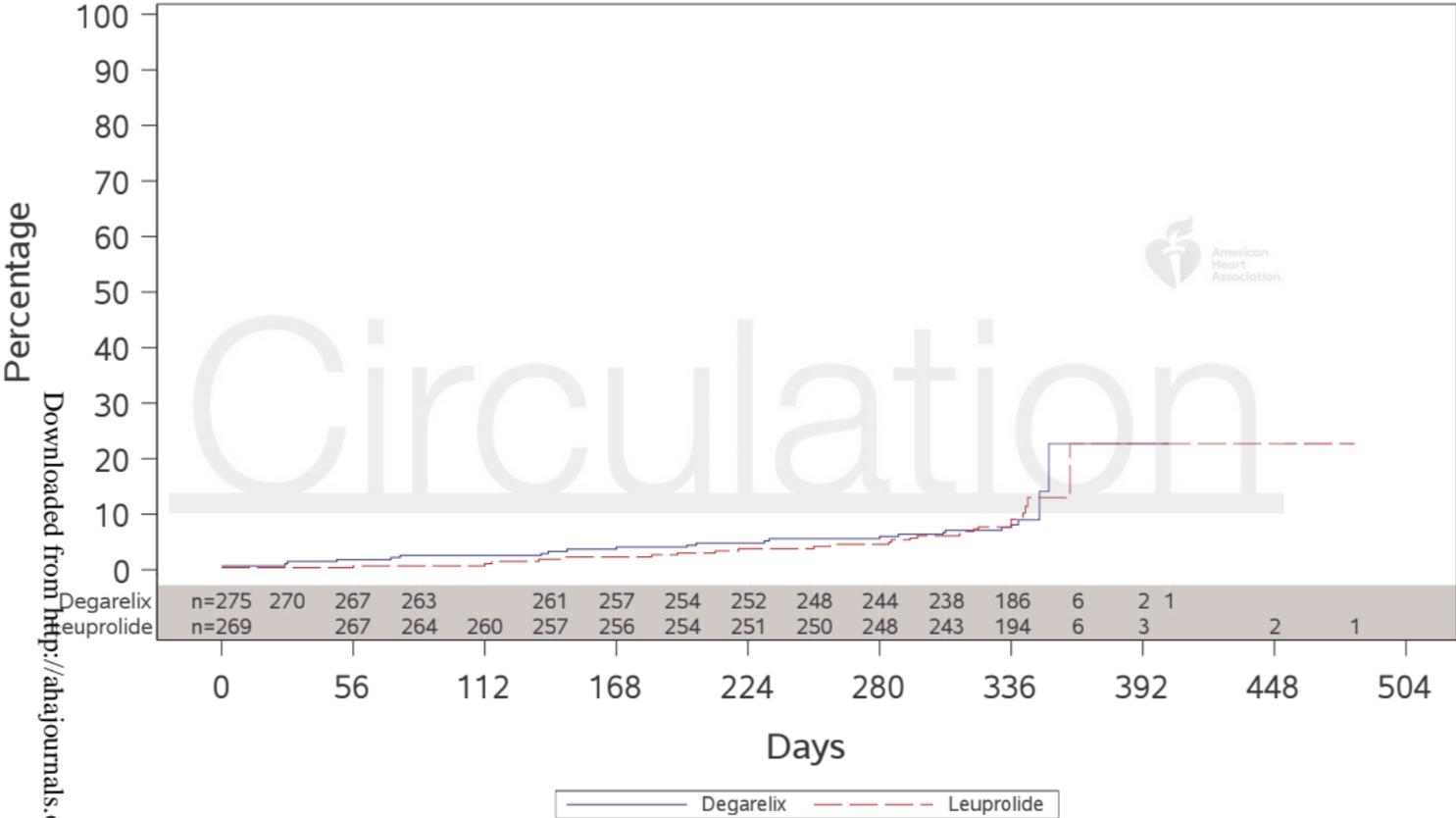
Median levels and interquartile ranges for testosterone, arithmetic values - Full Analysis Set

Treatment	0	28	168	336
DEGARELIX	274	264	247	234
LEUPROLIDE	269	257	248	228

Days

Testosterone (ng/mL)

Treatment — DEGARELIX — LEUPROLIDE