Luteinising Hormone-Releasing Hormone Antagonists in Prostate Cancer: Myths and Facts

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Meeting Summary

Androgen deprivation therapy (ADT) has long been a foundation in the management of prostate cancer. Since the introduction of gonadotropin-releasing hormone (GnRH) agonists in 1985, the treatment landscape has evolved significantly. A major advancement came with the introduction of GnRH antagonists in the early 2000s, offering rapid testosterone suppression without the need for antiandrogens to prevent the flare of symptoms associated with the initial testosterone surge seen with agonists. The more recent emergence of an oral GnRH antagonist represents a significant step forward, providing a non-injectable ADT option that allows clinicians to tailor treatment based on clinical factors, such as disease burden, comorbidities, and patient preference.

This article summarises the presentations delivered during a symposium held on 22nd March 2025 at the European Association of Urology (EAU) 2025 Congress in Madrid, Spain. Four globally recognised experts explored the key differences between GnRH antagonists and agonists in the management of prostate cancer. Through relatable and commonly encountered patient case studies, the faculty guided attendees in translating the latest evidence into their clinical practice.

The symposium explored how clinical considerations, such as cardiovascular disease (CVD) and lower urinary tract symptoms (LUTS), influence the selection of ADT and impact treatment outcomes. The multidisciplinary panel brought perspectives from a urologist, radiation oncologist, medical oncologist, as well as the critical viewpoint of a cardiologist.

Alberto Briganti, Full Professor of Urology, San Raffaele Hospital, Milan, Italy, and Chair of the meeting, opened the session with an overview of the agenda and initiated audience polling. A near-even split in ADT preferences emerged, with a slight preference towards GnRH agonists. Fast testosterone decline was identified by attendees as the most influential factor in ADT choice. Teresa Lopez Fernandez, Senior Consultant Cardiologist, La Paz University Hospital, IdiPAZ Research Institute, Madrid, Spain, provided insights into the cardiovascular impact of ADT choice from a cardiologist's perspective. Opening with a representative case study of a prostate cancer patient with a history of cardiovascular (CV) risk factors, the significant overlap between prostate cancer and CVD was highlighted. Lopez Fernandez discussed the results of a systematic review and a post hoc analysis from the HERO trial, which showed that GnRH antagonists are associated with a lower major adverse cardiovascular events (MACE) risk compared with agonists. Verane Achard, Radiation Oncologist, Institut Bergonié, Bordeaux, France, and University of Geneva, Switzerland, focused on patients with LUTS. Achard presented data from three degarelix (GnRH antagonist) studies, each demonstrating improved International Prostate Symptom Score (IPSS) in patients with IPSS ≥13 compared with goserelin (GnRH agonist). Giuseppe Banna, Consultant Medical Oncologist and Honorary Associate Professor, Portsmouth Hospitals University NHS trust, UK, concluded the series of talks with a discussion on the use of GnRH antagonists versus agonists in patients with metastatic

prostate cancer. Banna provided an overview of the clinical benefits of the oral GnRH antagonist, relugolix, compared with the agonist, leuprolide. Data from the HERO trial demonstrated that relugolix provides rapid, sustained, and deep testosterone suppression, along with a rapid prostate-specific antigen (PSA) reduction superior to that seen with leuprolide. These findings support the use of the oral GnRH antagonist relugolix over an agonist in patients with metastatic prostate cancer.

Introduction

At the Accord Healthcare-sponsored symposium, 'LHRH Antagonists in Prostate Cancer: Myths and Facts', held on 22nd March 2025 at the EAU 2025 Congress in Madrid, Spain, expert speakers from Italy, Spain, France, and the UK shared insights on the increasingly important topic of oral GnRH antagonist therapy in prostate cancer. The symposium aimed to update attendees' knowledge on GnRH antagonists in prostate cancer, explore how CVD and LUTS in patients with prostate cancer might influence the choice of ADT, and provide attendees with a comprehensive understanding of key clinical considerations surrounding the use of GnRH antagonists versus agonists in metastatic prostate cancer.

Briganti opened the meeting by providing an overview of the meeting agenda and objectives, encouraging audience engagement through a series of polling questions. The initial polling question aimed to understand what types of ADT attendees currently prefer for their patients when aiming to achieve medical castration. Approximately 50% of respondents opted for a GnRH agonist, while ~30% selected an oral GnRH antagonist and ~20% an injectable GnRH antagonist. The second polling question addressed key clinical factors influencing ADT selection. Around 30% of respondents selected rapid testosterone decline as an important consideration, while ~20% consider overall safety profile and CV safety profile as important clinical considerations.

Beyond Prostate Cancer: Do Androgen Deprivation Therapy Choices Impact Cardiovascular Outcomes?

Lopez Fernandez opened her session with an illustrative case study of a 68-year-old male with a history of localised prostate cancer that was treated with radical prostatectomy and adjuvant radiotherapy 4 years ago. His medical history included hypertension, dyslipidaemia, and obesity (BMI: 28 kg/m^2). One year prior, he experienced an acute coronary syndrome and percutaneous coronary revascularisation with non-ST-elevation myocardial infarction, for which he received appropriate treatment. Subsequently, the patient presented with a rising PSA level and multiple bone lesions on prostate-specific membrane antigen PET/CT. Lopez Fernandez stated that the 2022 European Society of Cardiology (ESC) Guidelines on Cardio–Oncology recommend that patients with a history of CV risk factors be referred to a cardiologist, and emphasised the importance of early risk stratification.[1] Key information, including cancer prognosis and less cardiotoxic treatment options, should be discussed with the treating oncologist.[1]

Prostate cancer and CVD frequently coexist, with data from national cancer registries, such as the Surveillance, Epidemiology, and End Results programme, indicating an increased risk of death from heart disease among patients with prostate cancer.[2] Around 20% of patients with prostate cancer have established CVD, and over half have more than three poorly controlled CV risk factors.[3,4] This elevated burden is partially attributable to the fact that prostate cancer predominantly affects older individuals (>65 years), and that certain oncologic therapies may adversely affect cardiac function.[5]

ADT, a cornerstone of prostate cancer treatment, has been associated with increased CV risk.[6] Several randomised controlled trials (RCT) have demonstrated that GnRH agonists are linked to a higher incidence of CV mortality and CVD compared to non-ADT therapies.[7] This might be caused by hypogonadism from ADT, promoting metabolic disturbances that accelerate atherosclerosis and coronary artery disease.[6] It has also been reported that prolonged ADT duration is associated with increased CVD risk and CV mortality.[8,9] Given this association, consideration should be given to choosing agents with a more favourable CV profile, particularly in patients with pre-existing CVD.

Evidence from a systematic review of RCTs suggests that GnRH antagonists are associated with a lower risk of MACE in men with prostate cancer.[10] This difference in CV risk may be partially explained by the physiological differences between GnRH antagonists and agonists. Unlike agonists, GnRH antagonists provide rapid and sustained testosterone suppression without the initial micro-surge,[11] a factor that might contribute to their favourable cardiovascular outcomes. This is supported by safety data from the HERO trial.[12,13] A post hoc analysis showed that relugolix was associated with a lower MACE risk compared with leuprolide, in patients with (odds ratio: leuprolide versus relugolix: 5.8; 95% CI: 1.5–23.3) and without a history of MACE (odds ratio: 1.5; 95% CI: 0.7–3.4).[12, 13] This is particularly relevant considering the high prevalence of underlying CVD (~20%) in the prostate cancer population.[3]

In the 2022 ESC Cardio–Oncology guidelines, the importance of early risk stratification of CV risk factors is emphasised.[1] It is also noted that GnRH antagonists offer an alternative treatment to agonists, with the majority of the data suggesting significantly lower overall mortality and CV events compared with agonists.[1]

Following the conclusion of Lopez Fernandez's talk, Briganti polled the audience on whether they routinely refer their patients for cardiology assessment prior to initiating ADT. Few hands were raised, highlighting a lack of communication between oncologists and cardiologists, and the potential underassessment of CV risk in these patients.

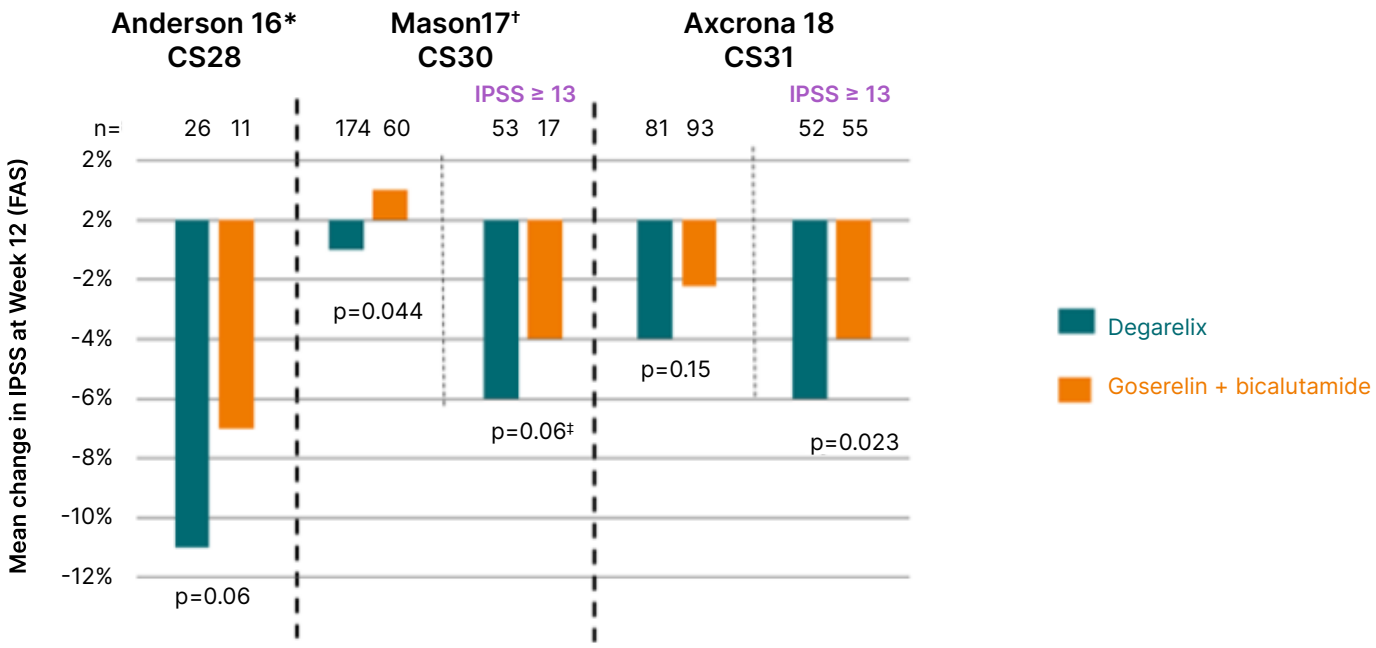
Patients with Lower Urinary Tract Symptoms: Does the Choice of Androgen Deprivation Therapy Matter?

To address whether the choice of ADT matters in patients with LUTS, Achard presented a case study of a 75-year-old male with a PSA of 5 ng/mL, Geriatric 8 score of 14, and a Karnofsky performance status of 90. The patient underwent an MRI prior to prostatic embolisation for LUTS (IPSS 17), and is planned to receive radiotherapy (RT). When polled on preferred hormonal therapy, over half of the audience recommended short-course ADT with a GnRH antagonist.

Moderate-to-severe LUTS are known to be frequent in men undergoing RT+ADT for localised prostate cancer. This is supported by a single-centre study showing that over 40% of men diagnosed with localised prostate cancer experience moderate-to-severe LUTS.[14] However, what is less known is the impact of RT+ADT on LUTS. Treatment with a GnRH agonist plus RT has been shown to improve obstructive symptoms in patients with moderate-to-severe LUTS, whereas patients with mild LUTS may experience a worsening of urinary function.[15]

Three clinical studies provide information on the impact of the GnRH antagonist degarelix with the GnRH agonist goserelin on LUTS: clinical study (CS) 28, CS30, and CS31. Achard highlighted that in the CS30 and CS31 trials, patients with an IPSS ≥13 had improved IPSS scores with degarelix compared with goserelin.[16,17] In the CS28 trial, most patients also had an IPSS ≥13, although this specific subgroup was not assessed (Figure 1).[18] These data demonstrated a statistically significant reduction in IPSS scores over time in all patients and in patients with IPSS ≥13 with degarelix compared to goserelin.[19]

Figure 1: The mean change in IPSS at Week 12 from three RCT evaluating degarelix versus goserelin plus bicalutamide.[16,17,18]



Inferiority study: Degarelix was non-inferior to goserelin arm (upper limit of the 2-sided 95% CI of the mean difference between the two arms: 1.6 and -0.3 for the full and PP analyses sets (below the non-inferiority margin of 3).

†Mean change from baseline IPSS was statistically significant: -1.71±-0.42 versus 0.11±-0.65 in the degarelix arm and goserelin arm, respectively (p=0.044).

‡Statistically significant difference between the groups (p<0.05).

§Mean IPSS decrease in degarelix-treated patients: -4.4±0.7 (>3-point threshold for clinical significance), in the goserelin + bicalutamide group <3-point threshold (-2.7±0.6). The adjusted mean difference between treatment groups was non-significant (-1.2, 95% CI: -2.9–0.4; p=0.15).

IPSS: International Prostate Symptom Score; RCT: randomised controlled trials.

It is important to consider whether the improvement in IPSS score observed with GnRH antagonists compared with agonists is clinically meaningful. The minimal important difference, representing a perceptible improvement from the patient's perspective, is typically defined as a reduction of 3 points in IPSS score, a threshold often achieved regardless of the type of ADT used.[20,21] However, treatment with a GnRH antagonist provides an additional reduction of approximately 2.6 points in patients with an IPSS score ≥13.[19] This additional improvement contributes to a total score change considered clinically significant, as seen in multiple studies assessing patient-reported outcome measures.[16,17,18]

Preliminary data for other GnRH antagonists are available from the REVELUTION trial, suggesting a class effect.[22] Patients receiving relugolix plus RT were significantly less impacted in IPSS urinary score, compared to leuprolide plus RT.[22] The clinical benefits of GnRH antagonists in patients with LUTS may be due to their direct effects on the bladder and prostate, which is supported by preliminary evidence from preclinical studies in rats demonstrating that GnRH antagonists act directly on benign prostatic hyperplasia cells and the bladder.[23,24,25]

Achard concluded her presentation by revisiting the initial case study, recommending a GnRH antagonist as

an alternative treatment for this patient based on the clinical evidence presented. It was highlighted that GnRH antagonists might improve LUTS control compared to agonists and be preferable in patients with moderate-to-severe LUTS (IPSS ≥13).

Before the next session, Briganti polled the audience on their current practice: whether they routinely assess LUTS using IPSS, whether LUTS influences their ADT selection, and if they prefer GnRH antagonists in this context. Approximately half of the attendees raised their hands for each question, suggesting that LUTS are not yet a key consideration in deciding what ADT to use.

Debunking the Debate in Metastatic Prostate Cancer: Agonist versus Antagonist Showdown

Commensurate with the format of previous sessions, Banna began with a case study of a 76-year-old male diagnosed with *de novo* metastatic prostate adenocarcinoma and a history of CVD and hypertension, currently managed with antiplatelets and an angiotensin-converting enzyme inhibitor. The patient was initiated on degarelix at the end of 2024, and within 1 month, the patient showed early symptom relief, improved mobility, a PSA (236 ng/mL to 10.8 ng/mL) and alkaline phosphatase (294 UI/L to 192 UI/L) decline, and, importantly, sustained castration. Banna followed the case study presentation with a polling question, asking attendees: what are the key therapeutic goals for this patient beyond overall survival and progression-free survival? Approximately 50% of respondents selected all of the above, encompassing secondary endpoints such as quality of life improvement and de-escalation strategies.

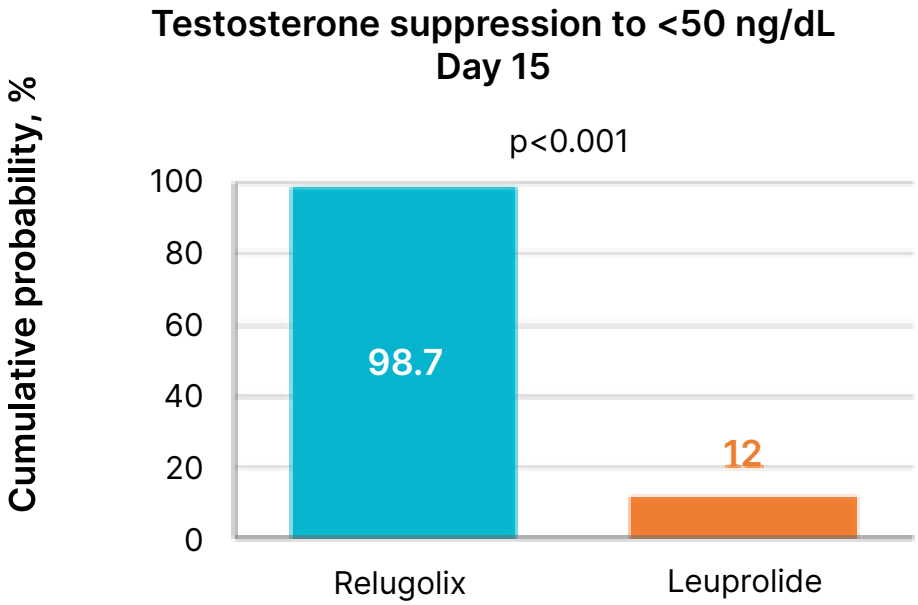
ADT is the primary systemic therapy for metastatic hormone-sensitive prostate cancer, used in up to 40% of patients with prostate cancer at some point during treatment for both localised and metastatic disease.[26] A critical difference between GnRH antagonists and agonists is the initial testosterone surge. As mentioned previously, LHRH agonists cause an initial testosterone surge, whereas LHRH antagonists rapidly suppress testosterone without the need for adding an antiandrogen to prevent the flare of symptoms.[27]

Evidence for the differences in testosterone suppression between GnRH antagonists and agonists is provided by the HERO trial, a RCT comparing the oral GnRH antagonist relugolix with the GnRH agonist leuprolide.[12] By Day 4, mean testosterone levels had dropped significantly to 38 ng/dL in the relugolix group, compared with 625 ng/dL in the leuprolide group, demonstrating the rapid and superior testosterone suppression achieved with relugolix. The primary endpoint was the sustained castration rate below 50 ng/dL from Day 29 to Week 49, with relugolix demonstrating superiority to leuprolide, after non-inferiority was first shown. Focusing on testosterone suppression, by Day 15, approximately 99% of patients in the relugolix group had testosterone levels <50 ng/dL, compared with only 12% in the leuprolide group (Figure 2). These data highlight that relugolix offers rapid, sustained, testosterone suppression superior to that of leuprolide.[12]

Banna presented the results of a meta-analysis of eight RCTs, which demonstrated a 50% reduction in CV events and a 52% reduction in mortality with GnRH antagonists compared to agonists.[28] This difference may potentially be linked to the rapid and profound testosterone suppression seen with GnRH antagonists.[12]

To conclude, Banna noted that PSA response may also result in improved clinical outcomes. A post hoc analysis of the TITAN study showed that deep PSA reduction at 3 months correlated with improved overall survival, radiographic progression-free survival, and time to complete response.[29] A rapid PSA reduction was observed with relugolix in the HERO trial, with 80% of patients in the relugolix arm achieving a PSA response by Day 15, compared with 20% in the leuprolide group (Figure 3).[12]

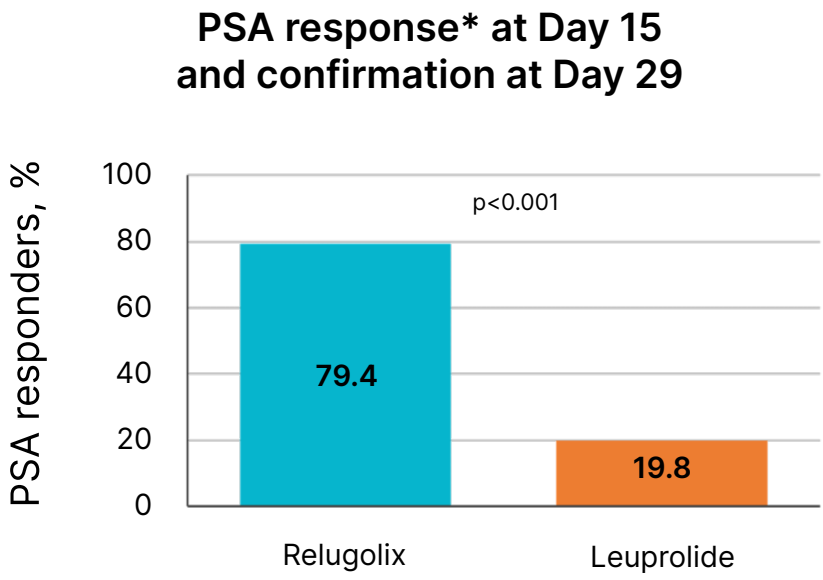
Figure 2: HERO study: Testosterone suppression with relugolix versus leuprolide.[12]



Adapted from Shore et al.[12]

Depicts the cumulative probability of testosterone suppression to <50 ng/dL on Day 15.

Figure 3: HERO study: PSA response with relugolix versus leuprolide.[12]



Adapted from Shore et al.[12]

*Defined as decrease of ≥50% in PSA level.

PSA: prostate-specific antigen.

Panel Discussion

Following the final presentation, an open panel discussion moderated by Briganti gave attendees the opportunity to have their questions answered by the expert panel. Lopez Fernandez began by addressing a question on the rationale behind the reduced risk of CV events observed with GnRH antagonists compared with agonists. Lopez Fernandez explained that, while the exact mechanism remains unclear, one possible explanation involves the direct effects of GnRH antagonists on the hypothalamic–pituitary axis. Bertrand Tombal, a member of the audience, expanded on this, proposing three potential mechanisms: the presence of surface androgen receptors on the heart, GnRH receptors in the coronary arteries, and the suppression of follicle-stimulating hormone levels by GnRH antagonists.

When asked about the early termination of the PRONOUNCE trial, Lopez Fernandez cautioned against interpreting the results as negative, reiterating that the trial was stopped prematurely. Tombal added that six randomised trials have demonstrated an overall 50% reduction in CV events with GnRH antagonists compared to agonists, emphasising that the PRONOUNCE trial should not be considered in isolation.

To close the meeting, Briganti rechallenged the audience with the same questions posed at the start of the meeting. In this instance, there was a marked increase in respondents opting for an oral GnRH antagonist and a greater number considering CV safety and the presence of LUTS when choosing an ADT agent.

Conclusion

The management and treatment of prostate cancer continue to evolve in response to patient needs and the overarching goal of improving outcomes. A key development is the introduction of oral ADT, which offers rapid and profound testosterone suppression without the initial testosterone surge associated with GnRH agonists, thereby eliminating the need for concurrent antiandrogen use. This advancement not only avoids exposing patients to the additional side effects seen with antiandrogens, but also enables clinicians to tailor treatment according to key clinical factors such as CV history and the presence of LUTS. Through a series of case-based presentations, expert faculty from various specialities explored how CVD, LUTS, and metastatic disease influence the choice of ADT.

Lopez Fernandez, emphasised the importance of following the ESC guidelines to assess CV risk in patients with prostate cancer, and the timely communication and referral to a cardiologist when risk factors are identified. To minimise CV events during ADT treatment, the use of less cardiotoxic agents is recommended.

Achard discussed improved clinical outcomes seen in patients with LUTS treated with GnRH antagonists versus agonists, with emerging data suggesting a potential class effect.

Banna provided an overview of the debate surrounding the use of GnRH antagonists versus agonists in patients with metastatic prostate cancer, presenting evidence that supports the use of the oral GnRH antagonist relugolix. Relugolix demonstrated rapid, sustained, and profound testosterone suppression, as well as PSA suppression that was superior to that seen with the GnRH agonist leuprolide.

The panel discussion and final polling reflected a shift towards more personalised ADT selection, with clinical practice shifting towards the consideration of clinical factors such as CV risk and LUTS to optimise treatment outcomes for patients with prostate cancer.

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