Why consider ADT modality? | How does MOA differ? | What is the evidence?

Managing CV risk in patients with prostate cancer

- There is a long-standing association between ADT and increased risk of CV events[1]
- ADT-treated patients with pre-existing CVD seem to be at an even higher risk.[1] Treatment with LHRH agonists is associated with increased risk of CHD, MI and sudden cardiac death[2]
- Recent evidence suggests that initiation with a GnRH antagonist (Firmagon®), rather than an LHRH agonist, may reduce CV risk in those patients with pre-existing CVD or CVD risk factors.[3,4] In this changing landscape of PCa, personalising treatment right from the start and considering the most appropriate ADT modality may reduce overall risk to patients[5]

Why is it important to consider ADT modality?

The CV risk association is clear for LHRH agonists, as the FDA has required that LHRH agonist manufacturers include additional safety information on their drug labels to reflect the higher level of risk.[6] When initiating ADT treatment in patients, it is important to consider a CV risk assessment to identify pre-existing CVD and then choose the most appropriate ADT modality.[5]

Men with PCa are at increased risk of CVD. Men with PCa and pre-existing CVD treated with ADT are at an even greater risk. ADT modality should be considered in order to reduce the risk of further CV events in patients[2]

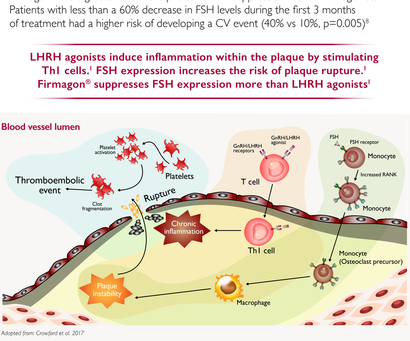
ADT, androgen deprivation therapy; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; FDA, Food and Drug Administration; GnRH, gonadotrophin-releasing hormone; LHRH, luteinising hormone-releasing hormone; MI, myocardial infarction; MOA, mode of action; PCa, prostate cancer.

How does the MOA of Firmagon® differ to LHRH agonists in patients with pre-existing CVD?

Differences between Firmagon® and LHRH agonists are multifactorial, but all stem from their distinct MOA resulting in different CV risk. Differences in MOA occur in both FSH and T lymphocyte systems:[1,4,8]

- Preclinical data has led to the hypothesis that unlike the GnRH antagonist, LHRH agonists activate GnRH receptors present on T lymphocytes, leading to increased cytokine expression.[1] This promotes a pro-inflammatory environment and increases the risk of plaque rupture and the occurrence of thromboembolic events[1]
- FSH receptors are associated with an increased risk of CVD with preclinical studies suggesting a role in endothelial dysfunction, lipid metabolism and fat accumulation.[4] Firmagon® has a greater and more profound FSH suppression than LHRH agonists.[1,4] Patients with less than a 60% decrease in FSH levels during the first 3 months of treatment had a higher risk of developing a CV event (40% vs 10%, p=0.005)[8]

LHRH agonists induce inflammation within the plaque by stimulating Th1 cells.[1] FSH expression increases the risk of plaque rupture.[1] Firmagon® suppresses FSH expression more than LHRH agonists[1]



Adapted from: Crawford et al. 2017

CV, cardiovascular; CVD, cardiovascular disease; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LHRH, luteinising hormone-releasing hormone; MOA, mode of action; RANK, receptor activator of NF-κB; Th1, T helper type 1.

What is the evidence to support a reduced CV risk with GnRH antagonists vs LHRH agonists?

In a **retrospective pooled analysis** (N=2,328) of PCa patients with pre-existing CVD, initiating Firmagon® compared with LHRH agonist therapy, **the absolute risk reduction during the first year was 8.2%** and the NNT to avoid one CV event or death was 12[4]

An **Italian observational study** carried out to evaluate incidence of CV events in a large cohort (N=9,785) concluded that the **incidence rate of CV events was significantly higher in patients treated with LHRH agonists rather than Firmagon®** (8.80 vs 6.24 per 100 person-year, p=0.002)[9]

In a **prospective randomised trial** of 80 patients with pre-existing CVD,[7] nine patients developed a MACCE. **Eight (20.5%) of these patients randomised to an LHRH agonist had a MACCE compared with one (2.4%) treated with the antagonist** (p=0.013; NNT=6)[3]

Real-world data from a UK primary care database of patients treated with LHRH agonists or Firmagon® (N=9,081) showed that **significantly more patients treated with an agonist had a CV event after initiation of therapy compared with Firmagon®** (6.9% vs 17.7%; 0.39 [0.191, 0.799]; p=0.01; NNT=9)[10]

Results from a **pharmacovigilance study** reported **higher increased odds of cardiac events in patients treated with LHRH agonists** (805 [7.7%]) vs in patients treated with a GnRH antagonist (102 [6.4%])[11]

In a **Phase III HERO trial**,[3] 622 patients received an oral GnRH antagonist and 308 received an LHRH agonist over 48 weeks. **Incidence of MACE was 2.9% in the GnRH antagonist group and 6.2% in the LHRH agonist group** (HR, 0.46; 95% CI: 0.24–0.88)[3]

**Study did not meet its primary endpoint of endothelial dysfunction, but did meet the predefined endpoint of developing a new CV event. MACCEs were defined as death, myocardial infarction, cerebrovascular event and heart catheterisation with stent insertion. †The oral GnRH antagonist is not available in the UK. In the study design MACE were not a primary or secondary endpoint but reported as a prespecified safety analysis. MACE were defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause.*

The NNT when initiating Firmagon® vs LHRH agonists to avoid one CV event or death:

Real-world data[10]	Retrospective pooled analysis[4]	Prospective randomised trial[3]
9	12	6

"When considered together, these trials raise the question of whether the use of a GnRH antagonist might result in improved CV outcomes, especially for those at higher risk."[7]

In summary, the GnRH antagonist consistently demonstrated lower probability of CV events in patients with pre-existing CVD compared with LHRH agonists in both RCTs and in real-world settings

Consider the right ADT modality for patients with pre-existing CVD to help minimise additional CV risk.[7] Firmagon® is currently the only GnRH antagonist that is commercially available to treat adult male patients with advanced hormone-dependent PCa[13]

ADT, androgen deprivation therapy; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GnRH, gonadotrophin-releasing hormone; HR, hazard ratio; LHRH, luteinising hormone-releasing hormone; MACCE, major adverse cardiovascular and cerebrovascular event; MACE, major adverse cardiovascular event; NNT, number needed to treat; PCa, prostate cancer; RCT, randomised controlled trial.

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13. Firmagon® (degarelix) Summary of Product Characteristics, July 2020.

Prescribing Information: Firmagon® (degarelix) 120mg and 80mg powder and solvent for solution for injection. **Please consult the full Summary of Product Characteristics before prescribing. Name of Product:** Firmagon 120mg and 80mg powder and solvent for solution for injection **Composition:** Each vial contains 120mg or 80mg degarelix (as acetate). **Indication:** Firmagon is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer. **Dosage and administration:** For subcutaneous use only. Starting dose – 240mg administered as two subcutaneous injections of 120mg each. Maintenance dose – 80mg administered monthly as one subcutaneous injection. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings and Precautions:** Long-term androgen deprivation therapy may prolong the QT interval. The benefit/risk ratio must be thoroughly appraised in patients with a history of a corrected QT interval over 450 msec, in patients with a history of or risk factors for torsades de pointes and in patients receiving concomitant medicinal products that might prolong the QT interval as Firmagon has not been studied in these patients. A thorough QT study showed that there was no intrinsic effect of Firmagon on QT/QTc interval. Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment. Firmagon has not been studied in patients with severe renal impairment; patients with a history of severe untreated asthma, anaphylactic reactions or severe urticaria; or angioedema. It can be anticipated that long periods of testosterone suppression in men will have effects on bone density. Diabetic patients may require more frequent monitoring of blood glucose when receiving androgen deprivation therapy. Cardiovascular disease such as stroke and myocardial infarction has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be considered. **Side Effects:** Very Common: hot flush, injection site adverse reactions. Common: anaemia, weight increase, insomnia, dizziness, headache, diarrhoea, nausea, liver transaminases increased, hyperhidrosis (incl. night sweats), rash, musculoskeletal pain and discomfort, gynaecomastia, testicular atrophy, erectile dysfunction, chills, pyrexia, fatigue, influenza-like illness. Uncommon: hypersensitivity, hyperglycaemia/ diabetes mellitus, cholesterol increased, weight decreased, appetite decreased, changes in blood calcium, depression, libido decreased, mental impairment, hypoaesthesia, vision blurred, cardiac arrhythmia (incl. atrial fibrillation), palpitations, QT prolongation, hypertension, vasovagal reaction (incl. hypotension), dyspnoea, constipation, vomiting, abdominal pain, abdominal discomfort, dry mouth, bilirubin increased, alkaline phosphatase increased, urticaria, skin nodule, alopecia, pruritus, erythema, osteoporosis/osteopenia, arthralgia, muscular weakness, muscle spasms, joint swelling/ stiffness, pollakiuria, micturition urgency, dysuria, nocturia, renal impairment, incontinence, testicular pain, breast pain, pelvic pain, genital irritation, ejaculation failure, malaise, peripheral oedema. Rare: neutropenic fever, anaphylactic reactions, myocardial infarction, cardiac failure. Please consult the full Summary of Product Characteristics for further information about side effects. **Presentation:** Firmagon 120mg contains 2 vials of 120mg powder for solution for injection and 2 solvent prefilled syringes, 2 vial adaptors and 2 administration needles; Firmagon 80mg contains 1 vial of 80mg powder for solution for injection and 1 solvent pre-filled syringe, 1 vial adaptor and administration needle. Solvent for both 120mg and 80mg Water for injection. **Marketing Authorisation Number:** 80mg: EU/1/08/504001, 120mg: EU/1/08/504002. **Marketing Authorisation Holder:** Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, DK-2300 Copenhagen S, Denmark. **Legal category:** POM. **Basic NHS price:** Firmagon 120mg - £260.00; Firmagon 80mg - £129.37. **Date of preparation:** July 2018. Firmagon® is a registered trademark. **PI Job Code:** FIN123020180UK(1).

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Ferring Pharmaceuticals Ltd. Tel: 0800 111 4126. Email: medical.uk@ferring.com

Ferring Pharmaceuticals Ltd., Drayton Hall, Church Road, West Drayton, UB7 7PS. Telephone: 0844 931 0050, Fax: 0844 931 0057, www.ferring.co.uk

Firmagon® is a registered trademark.
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