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The Efficacy and Safety of Relugolix Compared with Degarelix in Advanced Prostate Cancer Patients: A Network Meta-analysis of Randomized Trials

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Abstract

Context: Degarelix is associated with high rates of injection site reaction. The US Food and Drug Administration approved relugolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, for the treatment of advanced prostate cancer patients.
Objective: This systematic review and network meta-analysis aimed to compare the efficacy and safety of relugolix versus degarelix.
Evidence acquisition: A systematic search was performed using major web databases for studies published before January 30, 2021, according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) extension statement for a network meta-analysis. Studies that compared the efficacy (12-mo castration rate with testosterone ≤50 ng/dl) and safety (adverse events [AEs]) of relugolix or degarelix and of the control group (GnRH agonists) were included. We used the Bayesian approach in the network meta-analysis.
Evidence synthesis: Four studies (n = 2059) met our eligibility criteria. The main efficacy analysis was conducted for two different treatments (relugolix and all doses of degarelix vs GnRH agonists); relugolix (risk ratio [RR] 1.09, 95% credible interval [CrI]: 0.95–1.23) and degarelix (RR 0.98, 95% CrI: 0.91–1.06) were not associated with different 12-mo castration rates. In the subgroup analysis, degarelix 480 mg was significantly associated with a lower castration rate (RR 0.46, 95% CrI: 0.07–0.92). In all

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efficacy ranking analyses, relugolix achieved the best rank. The safety analyses showed that relugolix (RR 0.99, 95% CrI: 0.6–1.6 and RR 0.72, 95% CrI: 0.4–1.3, respectively) and degarelix (RR 1.1, 95% CrI: 0.75–1.35 and RR 1.05, 95% CrI: 0.42–2.6, respectively) were not associated with either all AE or serious AE rates. In the ranking analyses, degarelix achieved the worst rank of all AEs and the best rank of serious AEs. Relugolix (RR 0.44, 95% CrI: 0.16–1.2) and degarelix (RR 0.74, 95% CrI: 0.37–1.52) were not associated with different cardiovascular event (CVE) rates; both were associated with lower CVE rates than GnRH agonists in the ranking analyses.

Conclusions: We found that the efficacy and safety of relugolix are comparable with those of degarelix, albeit with no injection site reaction. Such data should be interpreted with caution until large-scale direct comparison studies with a longer follow-up are available.

Patient summary: We found that relugolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, has comparable efficacy and safety with degarelix, a parenteral GnRH antagonist, for the treatment of advanced prostate cancer patients.

1. Introduction

Recently, the US Food and Drug Administration (FDA) approved relugolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, for the treatment of patients with advanced prostate cancer (PCa) based on the efficacy and safety of the HERO trial [1,2]. The favorable characteristics of GnRH antagonists (eg, degarelix) over GnRH agonists have been shown as an androgen deprivation therapy (ADT) in PCa patients [3–6]. Indeed, a lack of testosterone surge after initiating treatment, a profound suppression of follicle-stimulating hormone, and lower cardiovascular event (CVE) rates [7] are the most important of these characteristics. Nevertheless, the high injection site reaction rate (around 40%) and the need for monthly injection might result in suboptimal utilization of degarelix in clinical practice [8].

Relugolix as an oral formulation of GnRH antagonists has been shown to be noninferior and superior with a 7.9 percentage point difference; moreover, it has a 54% lower risk of major CVEs versus GnRH agonists [1]. Consequently, the use of oral GnRH antagonists in clinical practice appears promising and appealing because this avoids the need for frequent injections and eliminates the injection site reaction. To date, there is no direct assessment of relugolix compared with degarelix, and there is a need to know whether this new formulation of antagonists has different efficacy and safety profiles. Thus, this systematic review and network meta-analysis aimed to assess the 12-mo efficacy and safety of degarelix compared with those of relugolix, including only phase III randomized trials.

2. Evidence acquisition

2.1. Literature search

A protocol for this study was registered a priori on the International Prospective Register of Systematic Reviews (ID: CRD42021258881). Our search was performed using electronic databases PubMed, Web of Science, Embase, Scopus, and Cochrane Library's CENTRAL for studies published before January 30, 2021; moreover, we renewed our search results in June 2021. This systematic review and network meta-analysis of randomized controlled trials (RCTs) for the efficacy and safety of relugolix or degarelix were conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) extension statement for a network meta-analysis [9]. The following search terms were used: “relugolix” AND “degarelix” AND “GnRH agonist” AND “GnRH antagonist” AND “efficacy” OR “safety” AND “(randomized controlled trial [Filter])”. Manual searches of reference lists of relevant articles were also performed to identify additional studies. The primary outcome of interest was efficacy and safety.

2.2. Inclusion and exclusion criteria

Studies were included if they investigated patients with advanced PCa (patients) who had received the GnRH antagonist ADT relugolix or degarelix, including monthly or 3-monthly doses (intervention), compared with those treated with a GnRH agonist (comparison) to assess the efficacy (ie, sustained castration with testosterone <50 ng/dl) and safety (outcomes) in a randomized control study only. We excluded observational studies, reviews, letters, editorials, meeting abstracts, replies from authors, case reports, and articles not published in English. References of all papers included were scanned for additional studies of interest. Studies were included only if they involved patients who received a GnRH agonist as the control arm.

2.3. Study selection

We selected RCTs that used GnRH antagonists (eg, relugolix or degarelix) and agonists (eg, leuprolide or goserelin) as an ADT to induce castration in PCa patients. Two investigators performed initial screening based on the titles and abstracts of the article, to identify eligible and ineligible reports. Reasons for exclusion were noted. Potentially relevant

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reports were subjected to a full-text review, and the relevance of the reports was confirmed after the data extraction process. Disagreements were resolved via consensus with the coauthors and consultation with the senior author.

2.4. Data extraction

Two investigators independently extracted the following information from the included articles: first author's name, publication year, period of patient recruitment, number of patients, type of treatment and doses, age, study design, study funding and/or support, and efficacy for induced sustained castration and adverse events (AEs). Subsequently, the number of patients with 12 mo of sustained castration and the number of AEs was retrieved. The castrate level was defined as a testosterone level of $\leq$ 0.5 ng/ml. All discrepancies regarding data extraction were resolved by consensus with the coauthors or by discussion with the senior author.

2.5. Methodological quality

The "risk-of-bias" (RoB version 2) evaluation of each study was assessed according to the Cochrane Collaboration's tool for assessing a risk of bias [10]. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. RoB 2 of each study was assessed independently by two authors. Disagreements were resolved by consultation with the coauthors or discussion with the senior author. The robvis tool was used to create risk-of-bias plots [11].

2.6. Statistical analysis

We conducted a network meta-analysis using random and fixed-effect models with a Bayesian approach for direct and indirect treatment comparisons with GnRH agonists as the common comparator arm [12,13]. Degarelix 80 mg monthly is the recommended dose in clinical practice. Consequently, the first subgroup analysis was conducted by including trial arms that used degarelix80 mg. The second subgroup analysis was conducted by including trial arms that used degarelix 80, 160, and 480 mg separately. The risk ratio (RR) was used to denote the results with a 95% credible interval (CrI), indicating the strength of association between treatments and outcomes. In Bayesian statistics, CrI is the interval within which an unobserved value falls with a particular probability. Pooled RRs and their 95% CrIs were also calculated. Statistical significance was established with two-sided $p < 0.05$ or 95% CrI that did not include a value of 1. All treatments were ranked according to the surface under the cumulative ranking curve (SUCRA) probability. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of the proportion of patients. All Bayesian statistical calculations were performed using MetaInsight software [13] from the R package gemtc (gemtc: Network Meta-Analysis Using Bayesian Methods R package version 0.8-2) and R package BUGSNET (BUGSnet: Bayesian inference Using Gibbs Sampling to conduct NETwork meta-analysis version 1.0.3) [14]. Statistical significance was set at $p < 0.05$.

3. Evidence synthesis

3.1. Results

3.1.1. Search results

Our initial search identified 48 trials, and after the elimination of duplicates, 26 publications were available. A total of 17 articles were excluded after screening the titles and abstracts, and a full-text review was performed for nine articles. Supplementary Figure 1 illustrates the flowchart of the selection process.

3.1.2. Characteristics of the studies included

Based on the selection criteria, we identified four phase III randomized control trials comprising 2059 patients for this systematic review and network meta-analysis [1,3,15,16]. Extracted data from the four studies and their characteristics, and the primary and secondary outcomes are outlined in Supplementary Tables 1 and 2. Three studies included all stages of PCa patients, for whom ADT was indicated [3,15,16]; however, the HERO trial indicated the characteristics of patients in detail, including naïve hormone-sensitive metastatic disease in addition to the patients who needed ADT after localized therapy (Supplementary Table 1). All studies were published between 2008 and 2020, which included a total of three two-arm studies and one multiarm study with five different interventions (Fig. 1). A sustained castration rate during 12 mo was defined as the efficacy of ADT in PCa patients.

3.1.3. Network meta-analysis

The network of eligible comparisons is graphically represented in network plots in terms of the efficacy of ADT to induce castration and the safety in AEs (Fig. 1).

3.1.3.1. The efficacy outcome. A network meta-analysis of two different interventions including relugolix and degarelix (ie, all degarelix doses: 80, 160, and 480 mg) was conducted for the primary endpoint of the castration rate during 12 mo. Compared with GnRH agonists, relugolix (RR: 1.09, 95% CrI: 0.95–1.23) and degarelix (RR: 0.98, 95% CrI: 0.91–1.06) were not associated with a significantly higher likelihood of 12-mo castration rate. The main results of the network meta-analysis are illustrated in Figure 2. Based on Bayesian analysis and analysis of the treatment ranking according to SUCRA, it was highly likely that relugolix was the top treatment to induce sustained castration (Fig. 2).

In the first subgroup analysis, we included only trial arms that used degarelix 80 mg as stated in the previous section. Relugolix and degarelix 80 mg were compared with GnRH agonists. We found that relugolix (RR: 1.09, 95% CrI: 0.98–1.2) and degarelix 80 mg (RR: 1.02, 95% CrI: 0.95–1.1) were not associated with a significantly higher likelihood of 12-mo castration rate. A summary of the analysis results is

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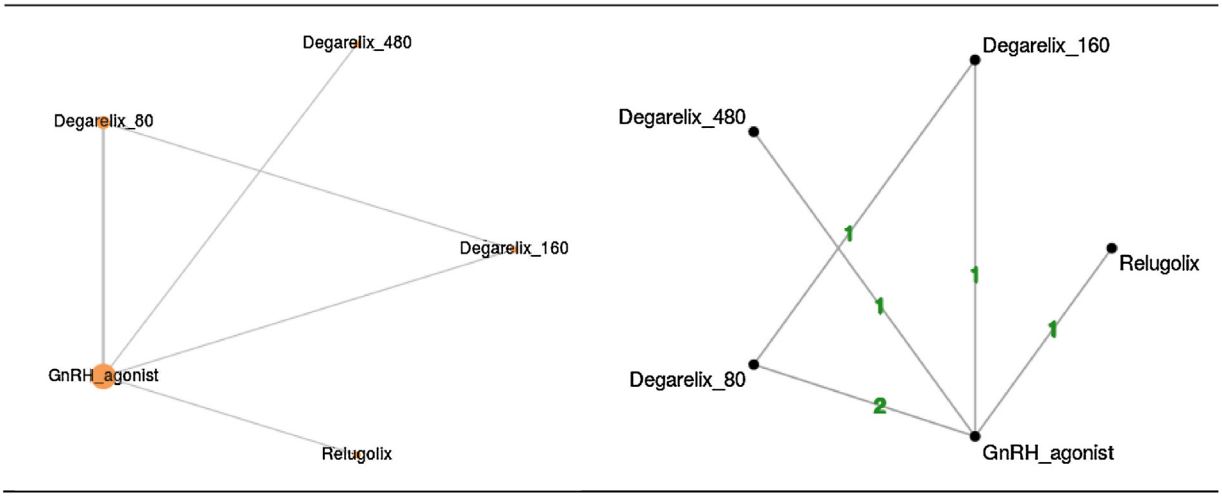

Fig. 1 – The network plot of RCTs that assessed the efficacy and safety of relugolix or degarelix versus a GnRH agonist. The number of trials is shown on the line and the number of people indicated by the size of the node. The number of interventions is 5, number of studies 4, total number of patients in the network 2059, and total possible pairwise comparisons 10. The total number of pairwise comparisons with direct data is 5, number of two-arm studies 3, number of multiarm studies 1, total number of events in the network 1969, and number of studies with no zero events 4. GnRH = gonadotropin-releasing hormone; RCT = randomized controlled trial.

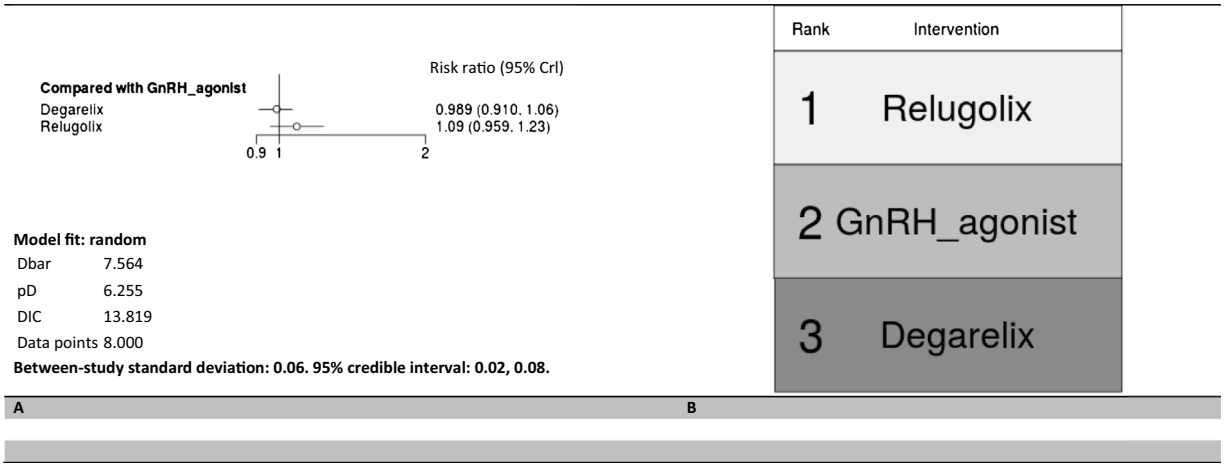

Fig. 2 – Summary of the Bayesian network meta-analysis for the efficacy of treatment. (A) Forest plot of Bayesian random-effect consistency model for all studies compared with a GnRH agonist. (B) Ranking with all studies—a network meta-analysis median rank chart. The total number of patients in the network is 2059 and the total number of events in the network 1969. CrI = credible interval; GnRH = gonadotropin-releasing hormone.

shown in Supplementary Figure 2. Based on SUCRA probability ranking analysis, it was highly likely that relugolix was better than degarelix 80 mg and GnRH agonists to induce sustained castration (Supplementary Fig. 2).

In the second subgroup analysis, four different interventions including relugolix and degarelix (ie, degarelix 80, 160, and 480 mg) were compared with GnRH agonists; relugolix (RR: 1.09, 95% CrI: 0.98–1.2), degarelix 160 mg (RR: 1.03, 95% CrI: 0.93–1.13), and degarelix 80 mg (RR: 1.02, 95% CrI: 0.95–1.1) were not associated with a significantly higher likelihood of 12-mo castration rate. Degarelix 480 mg (RR: 0.46, 95% CrI: 0.07–0.92) was associated with a significantly lower 12-mo castration rate. A summary of the analysis is illustrated in Figure 3. Based on Bayesian analysis and analysis of the treatment ranking according to SUCRA, it was highly likely that relugolix was the top treatment to induce sustained castration and degarelix 480 mg had the lowest rank (Fig. 3).

3.1.3.2. Adverse events (all AEs, serious AEs, and CVEs). Supplementary Table 3 summarized the number of the AEs in intervention and control groups that were reported in the four included RCTs. A network meta-analysis of two different interventions including relugolix and degarelix (ie, all degarelix doses: 80, 160, and 480 mg) was conducted for all AEs. Compared with GnRH agonists, relugolix (RR: 0.99, 95% CrI: 0.6–1.6) and degarelix (RR: 1.1, 95% CrI: 0.75–1.35) were not associated with a lower likelihood of 12-mo all AE rates. Figure 4A illustrates a

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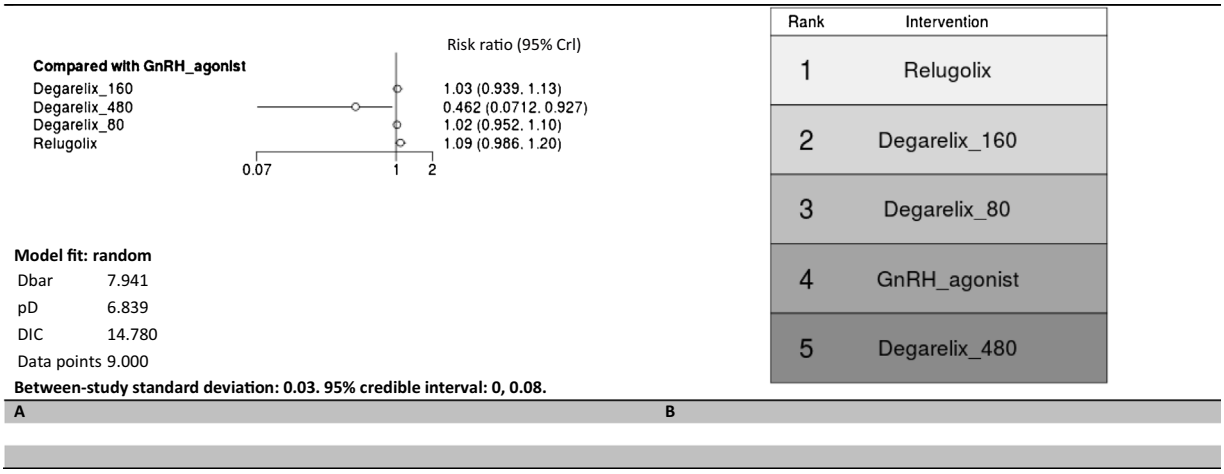

Fig. 3 – Summary of the subgroup Bayesian network meta-analysis for the efficacy of treatment. (A) Forest plot of Bayesian random-effect consistency model for all studies compared with a GnRH agonist. (B) Ranking with all studies—a network meta-analysis median rank chart. The total number of patients in the network is 2059 and the total number of events in the network 1969. CrI = credible interval; GnRH = gonadotropin-releasing hormone.

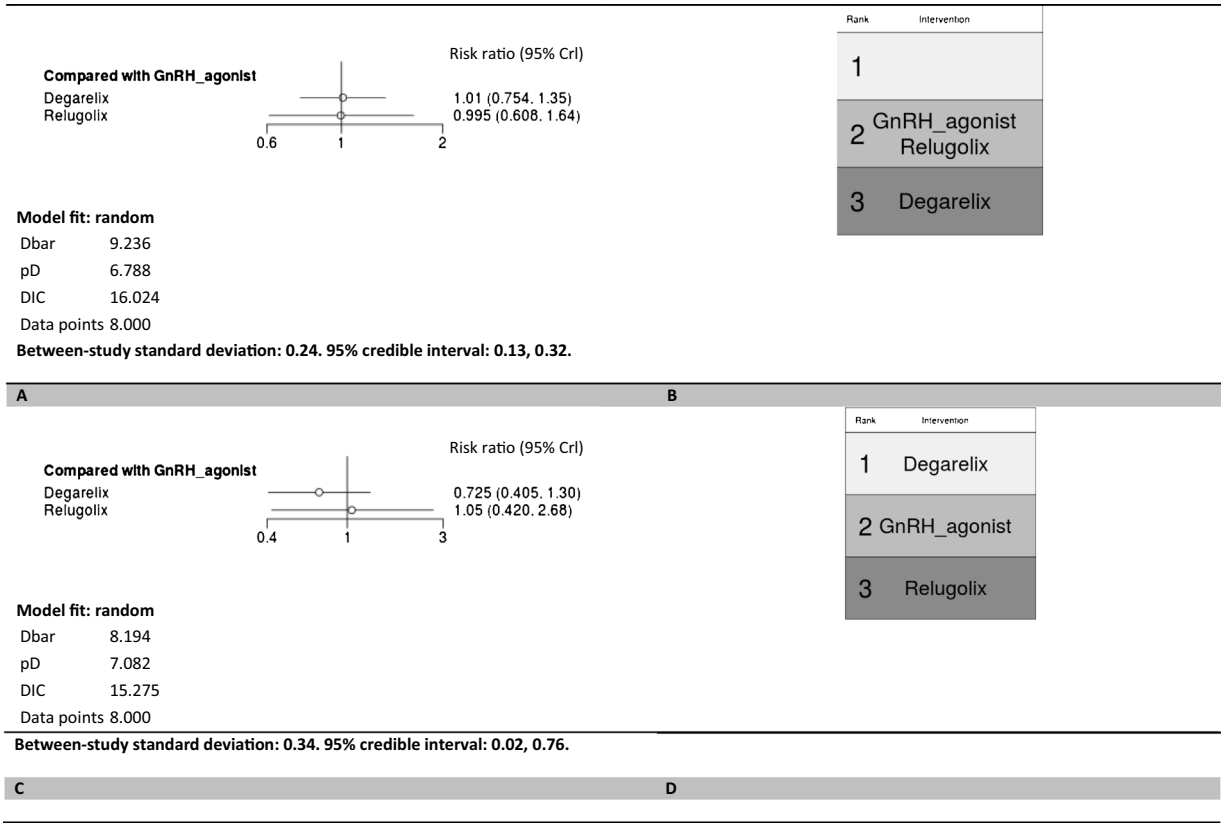

Fig. 4 – Summary of the Bayesian network meta-analysis for all adverse events and serious adverse events of all included studies. (A and C) Forest plot of Bayesian random-effect consistency model for all studies compared with a GnRH agonist. (B and D) Ranking with all studies—a network meta-analysis median rank chart. CrI = credible interval; GnRH = gonadotropin-releasing hormone.

summary of this analysis. Based on the Bayesian analysis and analysis of treatment ranking according to SUCRA, it was highly likely that both relugolix and GnRH agonists were the best treatment options in terms of a lower likelihood of all AEs (Fig. 4B).

In the first subgroup analysis, two different interventions including relugolix and degarelix (ie, all degarelix doses: 80, 160, and 480 mg) were conducted for serious adverse events (SAEs). Compared with GnRH agonists, we found that degarelix (RR: 0.72, 95% CrI: 0.4–1.3) and relugolix (RR: 1.05,

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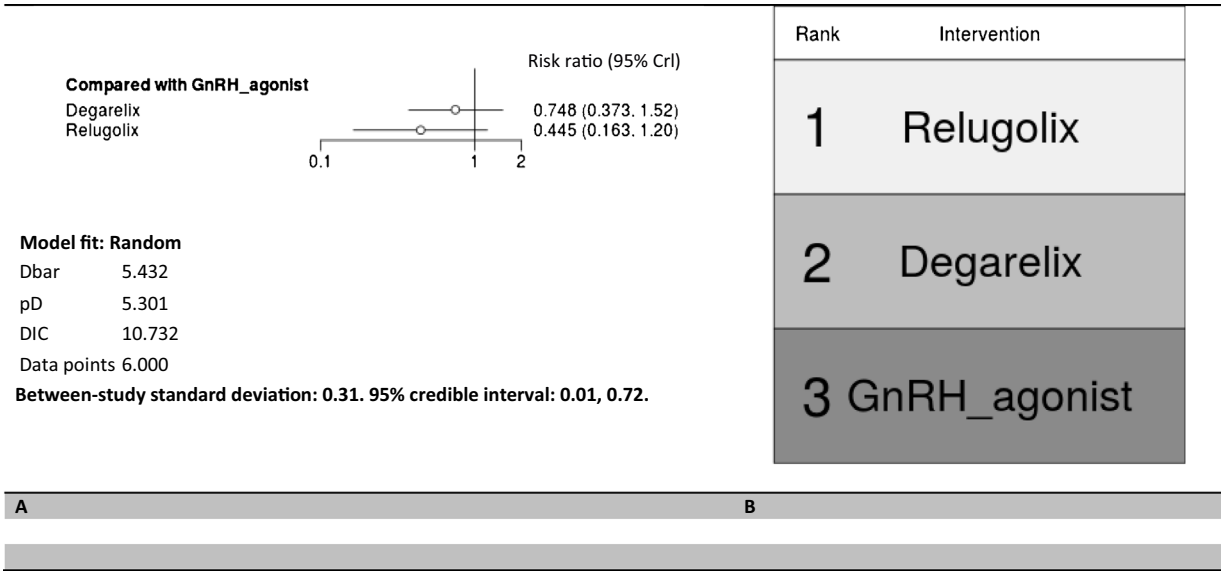

Fig. 5 – Summary of the Bayesian network meta-analysis for cardiovascular events. (A) Forest plot of Bayesian random-effect consistency model for all studies compared with a GnRH agonist. (B) Ranking with all studies—a network meta-analysis median rank chart. The total number of patients in the network is 1823 and the total number of events in the network 126. CrI = credible interval; GnRH = gonadotropin-releasing hormone.

95% CrI: 0.42–2.6) were not associated with a lower likelihood of 12-mo SAE rates (Fig. 4C). Based on SUCRA probability ranking analysis, it was highly likely that degarelix was better than GnRH agonists and relugolix in terms of a lower likelihood of 12-mo SAEs (Fig. 4D).

In the second subgroup analysis, two different interventions including relugolix and degarelix (all degarelix doses: 80, 160, and 480 mg) were conducted for CVEs. Compared with GnRH agonists, we found that relugolix (RR: 0.44, 95% CrI: 0.16–1.2) and degarelix (RR: 0.74, 95% CrI: 0.37–1.52) were not associated with a lower likelihood of 12-mo CVE rates (Fig. 5). However, based on SUCRA probability ranking analysis, it was highly likely that relugolix was better than degarelix and GnRH agonists in terms of a lower likelihood of 12 mo CVE (Fig. 5)

3.1.4. *Risk of Bias assessment*

An assessment of the risk of bias in the RCTs was performed following the Cochrane recommendations; the results are presented in Supplementary Figure 3. Generally, studies included in this systematic review and network meta-analysis had a low risk of bias, and deviation from intended intervention was a more affected domain.

3.2. *Discussion*

We found that the FDA-approved GnRH antagonists (relugolix and degarelix) were comparable with GnRH agonists in terms of the 12-mo sustained castration rates with testosterone levels <50 ng/dl. Moreover, there was no statistically significant difference between oral and parenteral GnRH antagonists except for the 3-mo formulation of degarelix (480 mg). Efficacy ranking analyses showed that relugolix was the most effective medical castration drug to induce 12-mo sustained castration. Moreover, both monthly GnRH antagonists (80 and 160 mg) were more effective than the GnRH agonists in the ranking analysis. Regarding the safety analyses, both relugolix and degarelix (regardless of doses) had no significant difference in AE and SAE rates. However, ranking analyses showed that degarelix had worse "all AE" rates and conversely the best SAE rates. Indeed, these inconsistent results may reflect the high injection site reaction rate in the degarelix group; however, this AE was not severe enough to be categorized as an SAE. When we considered CVEs for a subgroup safety analysis, RRs of both GnRH antagonists suggested lower CVE rates than that of GnRH agonists, although no statistical significance was reached. Nevertheless, the ranking analysis showed that relugolix and degarelix (regardless of doses) had the top rank and the second rank, respectively.

We hypothesized that changing of the formulation and administration method of individual therapeutic components could have changed the efficacy and safety. Such efficacy change had been shown when the 3-mo formulation of degarelix (480 mg 3 monthly) was used [16,17]. Indeed, the 28–364-d castration rate of degarelix 480 mg was lower than that of GnRH agonists and monthly formulation of degarelix (160 and 80 mg). However, we confirmed that the efficacy of the oral and the monthly parenteral formulation of GnRH antagonists was comparable in inducing sustained castration. Nevertheless, relugolix cannot be used with intensified cancer treatment, as it has not been studied adequately in combination with potent androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, and abiraterone, as well as in combination with chemotherapeutic agents such as docetaxel and cabazitaxel. Until recently, degarelix was the only FDA-approved GnRH antagonist, but its utilization was limited due to the high rate of injection site reactions and manual administration, despite the clinically favorable characteristics compared with those of GnRH agonists [3–6]. Most

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injection site reactions were due to an inadequate injection technique; indeed, proper injection education has been shown to diminish injection site reactions significantly [18].

Relugolix not only is as effective as GnRH agonists, but also overcomes the main barrier of using degarelix in clinical practice (ie, injection site reaction and need to the frequent injections). The all AE results of the ranking network meta-analysis showed that both relugolix and GnRH agonists were better than degarelix, which might be only due to the higher injection site reactions associated with degarelix. However, in the subgroup analysis of SAEs, degarelix and relugolix achieved the top and the lowest rank, respectively; indeed, degarelix had the lowest number of SAEs. It seems that we have to wait for a longer follow-up of the HERO trial and more data on the clinical use of relugolix for reliable conclusions. Indeed, the last molecular agent of relugolix "16b (TAK-385)" is a highly potent and orally active GnRH antagonist as a clinical candidate without (P450) CYP3A4 inhibition and with improved in vivo efficacy [19]. Still, there is a potential interaction between relugolix and other drugs that can induce or inhibit CYP3A4; moreover, the risk of QT prolongation was mentioned, and this risk could increase with a positive past or family history of cardiac arrhythmia, electrolytes disturbance, and concomitant use of diuretics [20]. Urologists should be cautioned about patient comorbidities and medications.

The advantage of GnRH antagonists over agonists is the lower incidence of CVEs with the former [7]. Our results confirmed that both oral and parenteral GnRH antagonists had a lower rate of CVEs than GnRH agonists. However, there are no trial results that assessed major CVEs as a primary endpoint [21]. Moreover, the definition of CVEs was different among the efficacy and safety trials [1,3,15], and these trials did not report the various CVE results in detail. Consequently, a subgroup analysis according to the various CVEs was not feasible. Despite there being no level 1 evidence addressing this point, there is a trend to recommend that GnRH antagonists were used commonly in PCa patients with risk factors for cardiovascular disorders or a history of major CVEs.

The main limitation of this network meta-analysis was that in contrast to the multiple reports of the CS21 trial from 2008 [3–6] that led to the approval of degarelix by the FDA, the HERO trial has reported only a 12-mo follow-up with still not data on the biochemical recurrence rate. Consequently, a longer follow-up comparison was not feasible in the current network meta-analysis. Cardiac diseases, metabolic syndrome, and cognitive disorders are the main AEs of long-term ADT [7,22]. Thus, we have to be cautious about the results of the present study and wait for the longer follow-up results of the HERO trial. Another important limitation was a lack of stage-categorized analysis results among the included studies; therefore, a subgroup analysis according to the stage (ie, biochemical or clinical relapse after definitive local therapy, hormone naïve hormone-sensitive metastatic disease, and high-risk locally advanced disease) was not feasible. Additionally, the HERO trial assessed and reported the testosterone recovery rate at 90 d and diarrhea rate as among specific AEs that were significantly more than the rates in the leuprolide arm; however, both of these rates were not reported in the degarelix trials, making it impossible to assess these endpoints.

4. Conclusions

While there is no direct comparison between relugolix and degarelix, the results of the present network meta-analysis confirmed that the 12-mo efficacy and safety of the oral GnRH antagonist are comparable with those of parenteral GnRH antagonists and superior to those of GnRH agonists, except the 3-mo formulation of degarelix (480 mg). Relugolix is a promising GnRH antagonist to overcome the injection site reaction that is the main usage barrier of degarelix. However, until longer follow-up results are known, we have to be cautious regarding the wide clinical use of relugolix and its SAEs. The current data suggest that both relugolix and monthly degarelix could be considered as the recommended ADT for PCa patients who need to receive ADT and suffer from cardiovascular disorders and/or risk factors at the same time.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sari Motlagh, Shariat.
Acquisition of data: Abufaraj, Mori, Aydh, Rajwa, Katayama, Grossmann, Laukhtina, Mostafai, Pradere, Quhal.
Analysis and interpretation of data: Sari Motlagh, Abufaraj.
Drafting of the manuscript: Sari Motlagh, Abufaraj.
Critical revision of the manuscript for important intellectual content: Karakiewicz, Enikeev, Shariat.
Statistical analysis: Sari Motlagh, Abufaraj.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euo.2021.07.002.

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