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Cardiovascular Morbidity Associated with Gonadotropin Releasing Hormone Agonists and an Antagonist

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Abstract

Background: Androgen deprivation therapy (ADT) is associated with increased cardiovascular morbidity.
Objective: To determine whether cardiovascular morbidity differs following initiation of gonadotropin-releasing hormone (GnRH) agonists compared with an antagonist.
Design, setting, and participants: Pooled data from six phase 3 prospective randomized trials that recruited 2328 men between 2005 and 2012 to compare the efficacy of GnRH agonists against an antagonist. Men recruited had pathologically confirmed prostate cancer, an Eastern Cooperative Oncology Group score <2, a minimum life expectancy of 12 mo, and were naïve to ADT. Men were excluded if they had a prolonged baseline QT/corrected QT interval, other risk factors for heart failure, hypokalemia or a family history of long QT syndrome, or had another cancer diagnosed within 5 yr.
Intervention: Men were randomized to receive a GnRH agonist or an antagonist for either 3–7 mo ($n = 642$) or 12 mo ($n = 1686$). Treatment groups were balanced for common baseline characteristics.
Outcome measurements and statistical analysis: Event analysis was based on death from any cause or cardiac events. Data documenting adverse experiences were classified based on the Medical Dictionary for Regulatory Activities. The following conditions defined a cardiac event: arterial embolic or thrombotic events, hemorrhagic or ischemic cerebrovascular conditions, myocardial infarction, and other ischemic heart disease. Kaplan-Meier curves and log-rank tests were used to compare time to a cardiovascular event or death.
Results and limitations: Among men with preexisting cardiovascular disease, the risk of cardiac events within 1 yr of initiating therapy was significantly lower among men treated with a GnRH antagonist compared with GnRH agonists (hazard ratio: 0.44; 95% confidence interval, 0.26–0.74; $p = 0.002$). Since our analysis is post hoc, our findings should only be interpreted as hypothesis generating.
Conclusions: GnRH antagonists appear to halve the number of cardiac events experienced by men with preexisting cardiovascular disease during the first year of ADT when compared to GnRH agonists.

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1. Introduction

Ever since Huggins and Hodges published their landmark study, clinicians have relied on androgen deprivation therapy (ADT) to treat men with prostate cancer (PCa). In 1959, the Veterans Administration Cooperative Urological Research Group was established to facilitate large-scale, prospective, randomized trials to define safe and effective treatments for PCa. They noted significantly increased rates of cardiovascular (CV) morbidity among men receiving higher doses of diethylstilbestrol as compared with men undergoing orchiectomy.

Gonadotropin-releasing hormone (GnRH) agonists were introduced in the 1990s to lower the risks of cardiac events associated with estrogens. A growing body of literature, however, has described several side effects associated with GnRH agonist therapy that include a 10–50% increased risk of bone fractures, peripheral insulin sensitivity, coronary heart disease, myocardial infarction, and sudden cardiac death, in addition to adverse effects on body mass, cholesterol, and quality of life [1,2]. In a recent mini-review, Bourke et al. commented that "a cause and effect relationship between ADT and increased risk of CV disease remains a plausible hypothesis that is yet to be falsified" [3]. Concerns regarding increased CV risks prompted the US Food and Drug Administration (FDA) to mandate in 2010 that manufacturers of GnRH agonists include additional safety information to the warnings and precautions section of drug labels.

Still, the relationship between ADT and CV disease remains controversial [4]. One theory suggests that ADT exacerbates preexisting cardiac risk factors, making them more evident during treatment [5,6]. CV mortality among PCa patients receiving radiation therapy was higher among men receiving concomitant ADT when compared to those who did not, and was observed primarily among men with moderate to severe preexisting CV disease [5,7].

We explored this hypothesis using data previously collected for phase 3 and 3B randomized trials of an FDA-approved GnRH antagonist. Specifically, we investigated whether these two drug classes had a similar impact on the short-term risk of CV events among men initiating GnRH therapy.

2. Methods

2.1. Data sources

Six prospective, phase 3, randomized controlled trials ($n = 2328$) were conducted by Ferring Pharmaceuticals to test the efficacy of a new GnRH antagonist compared to GnRH agonists. These trials included two 12-mo trials (CS21, $n = 610$; and CS35, $n = 848$), one 7-mo trial (CS37, $n = 403$), and three 3-mo trials (CS28, $n = 40$; CS30, $n = 245$; and CS31, $n = 182$). These six trials include all of the phase 3 trial data collected by Ferring Pharmaceuticals concerning the performance of the GnRH antagonist, degarelix. These trials are summarized in Table 1.

This analysis was prompted by the concerns raised by the FDA in 2010 concerning CV side effects associated with ADT [8]. Using funds provided by an independent cancer research foundation, the lead author (P.A.) analyzed these data with a statistician (J.G.) who has no connection with Ferring Pharmaceuticals. The quality of the study data was evaluated for bias using the Cochrane Collaboration tool. All data were available for analysis and were drawn from trials randomizing patients to either a novel GnRH antagonist (degarelix, $n = 1491$) or an existing GnRH agonist (either leuprolide, $n = 379$; or goserelin, $n = 458$). Most patients (72%) received treatment for 1 yr, while the remaining patients were treated for 3–7 mo. Men participating in the 3-mo studies (CS28, CS30, and CS28) and receiving a GnRH agonist were also given an antiandrogen (bicalutamide) for 1 mo as flare protection. Approximately 11% of the men participating in the 12-mo study also received an antiandrogen (bicalutamide) for 1 mo at the discretion of the investigator. None of the patients participating in the 7-mo study received antiandrogen therapy. All patients randomized had pathologically confirmed PCa and were naïve to ADT. All patients were recruited from community and academic practices in Europe and North America and were initially evaluated for existing comorbid diseases. Treatment groups were balanced for common baseline characteristics and characteristics related to CV disease.

Patients included in the trials had an Eastern Cooperative Oncology score <2, a life expectancy of >12 mo, and an indication for ADT, including biochemical recurrence after prostatectomy or radiotherapy given with curative intention or other clinical evidence of progressive PCa. Patients were excluded if they had previously received any type of ADT for PCa or had a cancer diagnosis other than PCa during the previous 5 yr, including men with surgically removed basal cell or squamous cell carcinomas of the skin. Patients with risk factors for torsade de pointes ventricular arrhythmias (eg, heart failure, hypokalemia, or a family history of a long QT syndrome), a QT or corrected QT (QTc) interval >450 ms at baseline, or taking medications that prolonged the QT/QTc interval were excluded. The exclusion related to the QT/QTc interval was mandated by regulatory requirements. Men currently treated with 5α-reductase inhibitors were also excluded. All six trials were designed and initiated before regulatory approval of the GnRH antagonist.

Data documenting preexisting comorbid diseases or adverse experiences were recorded and classified at the time of collection by study investigators (M.D.) in the field. They were instructed to assess preexisting conditions and adverse experiences according to the Medical Dictionary for Regulatory Activities. Serious CV events were evaluated and recorded according to the Major Adverse Cardiovascular Event Criteria (MACE) by an independent CV expert blinded to the study arm. Study investigators recorded all data before this study was planned. All studies had the same inclusion/exclusion criteria with regard to CV parameters and CV comorbidities. The most frequently reported adverse events were related to the effect of androgen deprivation and were similar in both treatment groups in terms of frequency and severity.

2.2. Study end points

We tallied the number of deaths from any cause and the number of cardiac events among all men receiving any form of ADT. Cardiac events were tallied if any of the following were documented: arterial embolic and thrombotic events, hemorrhagic or ischemic cerebrovascular conditions, myocardial infarction or other ischemic heart disease.

2.3. Statistical analysis

Kaplan-Meier curves and log-rank tests were used to compare time to a CV event or death using the LIFETEST procedure in SAS (SAS Institute Inc, Cary, NC, USA). Cox regression models were used to estimate adjusted hazard ratios [HR] and 95% confidence intervals [CI] using the PHREG procedure in SAS [8]. The forest plot was created from HRs estimated in PHREG and produced in Comprehensive Meta-Analysis v.2 using a fixed effects approach. We report two values assessing heterogeneity: $Q = 3.4$ ($p = 0.18$) and $I^2 = 41.9$. Our decision to combine studies was based on these values suggesting a low to moderate level of heterogeneity.

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Table 1 – Summary of the six randomized controlled trials combined in this analysis

Trial, location	Patients (ratio of antagonist/agonist with or without antiandrogen)	Main prostate cancer inclusion criteria	Length of follow-up	Median duration of LHRH agonist/degarelix therapy	Primary end point	Frequency of the three most common AEs
CS28, United Kingdom	$N = 40$ (LHRH agonist: $n = 13$; degarelix: $n = 27$; 3:1 bicalutamide added as flare protection for agonist patients) Cardiovascular history ($n = 3$) Degarelix ($n = 1$) LHRH agonist ($n = 2$) Cardiovascular events, no. (deaths): 0 (0)	• PSA level at screening >10 ng/ml • TNM staging at baseline: T3/4, any N, any M • IPSS ≥12 • Q_{max} ≤12 ml/s	3 mo	LHRH agonist: 8.57 wk Degarelix: 8.14 wk	• Change from baseline in total IPSS at Week 12 using the LOCF approach	Injection-site pain (LHRH agonist: 0%; degarelix: 22%) Hot flush (LHRH agonist: 15%; degarelix: 19%) Cystitis (LHRH agonist: 11%; degarelix: 11%)
CS30, Scandinavia	$N = 245$ (LHRH agonist: $n = 64$; degarelix: $n = 181$; 3:1 bicalutamide added as flare protection for agonist patients) Cardiovascular history ($n = 41$) Degarelix ($n = 33$) LHRH agonist ($n = 8$) Cardiovascular events, no. (deaths): 0 (0)	• Planned for radical radiotherapy treatment and in whom neoadjuvant is indicated • TNM stage: T2 (b or c)/T3/T4, N0, M0; or Gleason score ≥7 or PSA level ≥10 ng/ml	3 mo	LHRH agonist: 12.7 wk Degarelix: 12.1 wk	• Mean percentage reduction in prostate volume at 12 wk as compared to baseline	Injection-site pain (LHRH agonist: 2%; degarelix: 33%) Hot flush (LHRH agonist: 63%; degarelix: 60%) Injection-site erythema (LHRH agonist: 0%; degarelix: 25%)
CS31, USA and western Europe	$N = 182$ (LHRH agonist: $n = 98$; degarelix: $n = 84$, 1:1 bicalutamide added as flare protection for agonist patients) Cardiovascular history ($n = 44$) Degarelix ($n = 23$) LHRH agonist ($n = 21$) Cardiovascular events, no. (death): 0 (0)	• TNM stage: any T, any N, any M • PSA level at screening >2 ng/ml • Prostate >30 ml	3 mo	LHRH agonist: 12.1 wk Degarelix: 12.5 wk	• Mean percentage reduction in prostate volume measured with TRUS at 12 wk compared to baseline	Injection-site pain (LHRH agonist: 0%; degarelix: 14%) Hot flush (LHRH agonist: 17%; degarelix: 10%) Hyperhidrosis (LHRH agonist: 5%; degarelix: 5%)
CS37, USA	$N = 403$ (LHRH agonist continuous: $n = 178$; degarelix intermittent: $n = 175$; degarelix continuous: $n = 50$, 9:7) Cardiovascular history ($n = 143$) Degarelix ($n = 88$) LHRH agonist ($n = 55$) Cardiovascular events, no. (deaths): 13 (3) Degarelix: 3 (1) LHRH agonist: 10 (2)	• Rising PSA after having undergone primary therapy for localized prostatic carcinoma	14 mo	LHRH agonist (continuous): 4 mo phase A and 6 mo phase B Degarelix (intermittent): 6 mo phase A and 6 mo phase B Degarelix (continuous): 6 mo phase A and 6 mo phase B	• Proportion of subjects with a serum PSA level ≤4.0 ng/ml in subjects receiving degarelix intermittent treatment vs continuous androgen deprivation (leuprolide and degarelix combined) at 14 mo	Phase A + B Injection-site pain (LHRH agonist continuous: 11%; degarelix intermittent: 45%; degarelix continuous: 58%) Hot flush (LHRH agonist continuous: 62%; degarelix intermittent: 50%; degarelix continuous: 52%) Injection-site erythema (LHRH agonist continuous: <1%; degarelix intermittent: 24%; degarelix continuous: 34%)

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Table 1 (*Continued*)

Trial, location	Patients (ratio of antagonist/agonist with or without antiandrogen)	Main prostate cancer inclusion criteria	Length of follow-up	Median duration of LHRH agonist/degarelix therapy	Primary end point	Frequency of the three most common AEs
CS21, Global	$N = 610$ (LHRH agonist: $n = 201$; degarelix 240/160 mg: $n = 202$; degarelix 240/80 mg: $n = 207$; 2:1, antiandrogen could be added as flare protection at investigator's discretion) Cardiovascular history ($n = 192$) Degarelix ($n = 130$) LHRH agonist ($n = 62$) Cardiovascular events, no. (deaths): 13 (11) Degarelix: 8 (5) LHRH agonist: 5 (6)	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intention. • PSA level at screening >2 ng/ml	12 mo	LHRH agonist: 12.1 mo Degarelix: 12.1 mo	• Probability of testosterone ≤0.5 ng/ml from day 28 through day 364	Injection-site pain (LHRH agonist: <1%; degarelix 240/160 mg: 30%; degarelix 240/80 mg: 28%) Injection-site erythema (LHRH agonist: 0%; degarelix 240/160 mg: 24%; degarelix 240/80 mg: 17%) Hot flush (LHRH agonist: 21%; degarelix 240/160 mg: 26%; degarelix 240/80 mg: 26%)
CS35, Global	$N = 848$ (LHRH agonist: $n = 283$; degarelix: $n = 565$; 2:1, antiandrogen could be added as flare protection at investigator's discretion) Cardiovascular history ($n = 285$) Degarelix ($n = 188$) LHRH agonist ($n = 97$) Cardiovascular events, no. (deaths): 18 (8) Degarelix: 10 (3) LHRH agonist 8 (5)	• TNM stage: any T, any N, any M, except for neoadjuvant hormonal therapy • Includes rising PSA after having undergone prostatectomy or radiotherapy with curative intention. • PSA level at screening >2 ng/ml	12 mo	LHRH agonist: 52.1 wk Degarelix: 52.1 wk	• Cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from day 28 to day 364 with degarelix • Difference in cumulative probability of testosterone at castrate level (≤0.5 ng/ml) from day 3 to day 364 between degarelix and goserelin	Injection-site pain (LHRH agonist: 1%; degarelix: 31%) Injection site erythema (LHRH agonist: 0%; degarelix: 22%) Hot flush (LHRH agonist: 27%; degarelix: 28%)

AE = adverse event; IPSS = International Prostate Symptom Score; LHRH = luteinizing hormone-releasing hormone; LOCF = last observation carried forward; PSA = prostate-specific antigen; Q_{max} = maximum flow rate; TRUS = transrectal ultrasound.

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3. Results

The study cohort consisted of 2328 patients who received either GnRH agonists ($n = 837$) or an antagonist ($n = 1491$). The two treatment groups were balanced for CV history and baseline characteristics such as a history of diabetes, elevated blood pressure, elevated cholesterol levels, and the use of statin medications (Table 2). The baseline incidence of CV disease was approximately 30% in both treatment groups (Table 3). The most frequent preexisting event was myocardial ischemia (11%), followed by coronary artery disease (8%), myocardial infarction (7%), cerebrovascular accident (3%), angina pectoris (3%), and coronary artery bypass (3%).

During the initial year of treatment, 42 men died: 22 patients who received the GnRH antagonist and 20 patients who received a GnRH agonist. During this same period, 37 patients who received the GnRH antagonist experienced a cardiac event compared with 42 patients who received a GnRH agonist. A Cox proportional hazard model showed a 40% lower risk of a cardiac event or death (HR: 0.60; 95% CI, 0.41–0.87; $p = 0.008$). These findings are displayed in a Kaplan-Meier plot (Fig. 1). No differences in the incidence of either death from any cause or the incidence of cardiac events was seen among the men who had no preexisting

Table 2 – Baseline characteristics of the two treatment groups

Variable	GnRH antagonist ($n = 1491$)	GnRH agonist ($n = 837$)
Age, yr (range)	71.7 (46–94)	71.6 (51–98)
Body mass index	27.2	27.5
Body mass index >30, % (no.)	22.4 (334)	23.9 (200)
History of cardiovascular disease, % (no.)	31.1 (463)	29.3 (245)
History of smoking, % (no.)	47.4 (707)	51.6 (432)
History of alcohol use, % (no.)	59.6 (889)	56.8 (475)
History of hypertension, % (no.)	74.9 (1117)	73.5 (615)
Serum cholesterol level >6.2 mmol/l, % (no.)	26.8 (399)	29.5 (247)
Statin medication use, % (no.)	26.8 (400)	28.0 (234)
History of diabetes, % (no.)	14.8 (221)	15.3 (128)

GnRH = gonadatropin-releasing hormone.

Table 3 – Baseline history of cardiovascular disease among men in the two treatment groups

CVD	GnRH antagonist, % (no.) ($n = 1491$)	GnRH agonist, % (no.) ($n = 837$)	Total, % no. ($n = 2328$)
Any CVD event	31.1 (463)	29.3 (245)	30.4 (708)
Myocardial ischemia	11.6 (173)	9.7 (81)	10.9 (254)
Coronary artery disease	7.4 (110)	8.7 (73)	7.9 (183)
Myocardial infarction	6.9 (103)	6.1 (51)	6.6 (154)
Cerebrovascular accident	3.9 (58)	2.8 (23)	3.5 (81)
Angina pectoris	3.5 (52)	3.0 (25)	3.3 (77)
Coronary artery bypass	3.0 (45)	3.2 (27)	3.1 (72)

CVD = cardiovascular disease; GnRH = gonadotropin-releasing hormone.

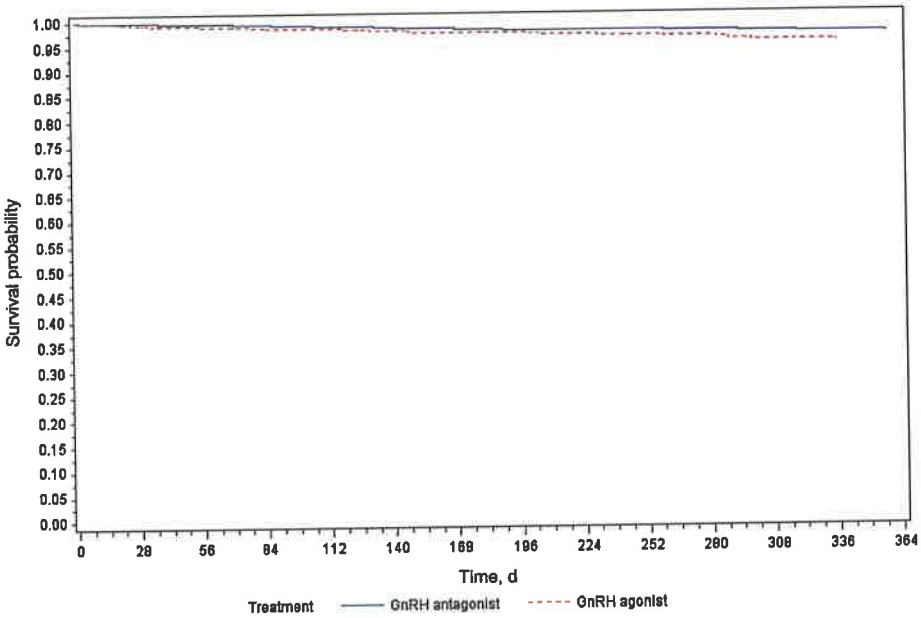

Fig. 1 – Kaplan-Meier plot of time to first cardiovascular event or death among all men enrolled in the prospective randomized trials. GnRH = gonadatropin-releasing hormone.

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Table 4 – Hazard ratios from a Cox regression for predictors of a cardiac event or death among trial participants with a baseline cardiovascular history (n = 707)

	Hazard ratio	95% CI	p value
GnRH antagonist vs GnRH agonist	0.438	0.260–0.736	0.0018
Statin medication use	0.539	0.282–1.030	0.0614
Alcohol use	0.433	0.243–0.774	0.0047
Hypertension	2.088	1.075–4.055	0.0296
Smoker	1.259	0.722–2.193	0.4169
Serum cholesterol	1.136	0.619–2.083	0.6807
Type 2 diabetes treated	0.825	0.340–1.997	0.6689
Hypertension treated	0.632	0.322–1.239	0.1816
Baseline age	1.027	0.990–1.066	0.1524
Baseline testosterone level	0.786	0.656–0.941	0.0089
Baseline BMI	0.970	0.909–1.035	0.3571

BMI = body mass index; CI = confidence interval; GnRH = gonadatropin-releasing hormone.

CV disease at baseline. Moderate alcohol consumption and a low baseline serum testosterone level were the only other predictors of a lower risk of a cardiac event or death (Table 4).

Among those patients reporting CV disease at baseline (n = 708), 22 men died during the initial year of treatment: 13 patients who received the GnRH antagonist and 9 patients who received a GnRH agonist. During the same period, 23 patients who received the GnRH antagonist experienced a cardiac event compared with 21 patients who received a GnRH agonist. For men with preexisting CV disease at baseline, there were significantly fewer cardiac events or deaths experienced by patients receiving a GnRH antagonist (8.0%) compared with patients receiving GnRH agonists (11.8%) (Fig. 2). Among the men reporting CV disease at baseline, a Cox proportional hazard model showed a 56% lower risk of a cardiac event or death during the initial year of treatment for men receiving the GnRH antagonist compared with men receiving a GnRH agonist (HR: 0.44; 95% CI, 0.26–0.74; p = 0.002). The absolute risk reduction during the first year was 8.8%, which yielded a number needed to treat of 11. Cardiac events occurred only in the three longer trials; none occurred in the three shorter trials. These events are displayed in the forest plot (Fig. 3).

Based on the Cochrane Collaboration's tool, our findings are subject to bias because both patients and study

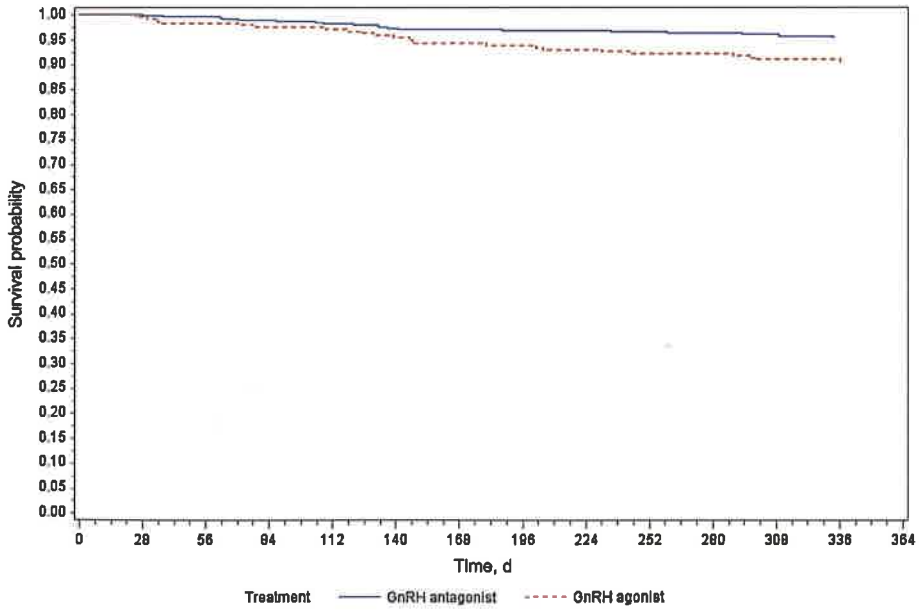

Fig. 2 – Kaplan-Meier plot of time to first cardiovascular event or death among men with preexisting cardiovascular disease.

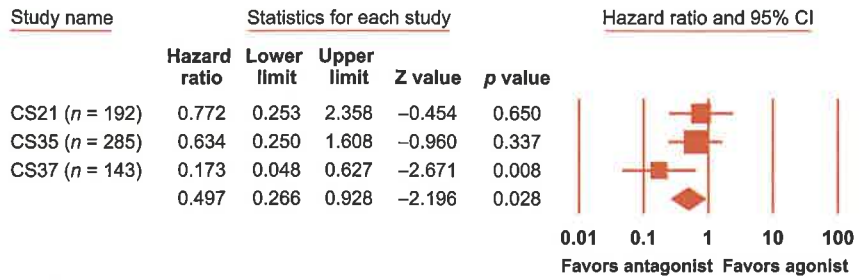

Fig. 3 – Forest plot documenting the hazard ratio of cardiovascular events in each of the individual trials. For the fixed effects model, I^2 = 41.9; Q = 3.4; p = 0.18. CI = confidence interval; CVD = cardivascular disease.

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personnel were aware of which patients were allocated to receive a GnRH agonist or antagonist. This risk of bias was mitigated in part by having all serious CV events evaluated and recorded by a CV expert who was blinded to the treatment given. Furthermore, participants in all six trials were assigned treatment by a computer-generated random sequence and no patients were lost to follow-up during the study period.

4. Discussion

Our analysis suggests that ADT may be an independent risk factor for CV events. Patients with preexisting CV disease who were treated with a GnRH antagonist appear to have had a significantly lower risk of experiencing a CV event or death when compared to patients receiving a GnRH agonist within 1 yr of initiating ADT. The relative risk reduction appears to be as high as 50%, while the absolute risk reduction is about 3.8%. We did not see a similar reduction among men without preexisting CV disease. Although we have not demonstrated a cause-and-effect relationship, we hypothesize that ADT increases the risk of atherosclerotic plaque rupture and that this risk is partially mitigated by GnRH antagonists.

In contemporary practice, many clinicians begin ADT when evidence exists for systemic PCa [9]. For most men, a rise in serum levels of prostate-specific antigen following definitive treatment with either radical surgery or radiation therapy is a sufficient trigger. As a consequence, men now receive ADT for considerably longer periods of time, resulting in a greater recognition of the side effects associated with treatment. These include hot flushing, loss of libido, sexual dysfunction, fatigue, anemia, bone loss, and metabolic changes that include obesity, insulin resistance, and lipid alterations that contribute to CV risks [10].

Despite the numerous studies documenting outcomes of men receiving ADT with GnRH agonists, the potential association with CV toxicity and death is still controversial. Conteduca et al. recently published an extensive review of this subject and noted that CV disease, rather than PCa itself, is the most common cause of mortality in men with early stage PCa [4]. They concluded that the potential risk of androgen deprivation on CV events needs to be evaluated and compared with the expected benefits of treatment. Nanda et al. suggested that the increased risk of CV disease was restricted to men with preexisting cardiac disease [6]. Our study supports this finding by demonstrating that among men with preexisting CV disease, those receiving GnRH agonists had twice the incidence of cardiac events when compared to men receiving a GnRH antagonist. There was no difference in the incidence of cardiac events among men without preexisting CV disease.

The mechanisms by which ADT interacts with CV disease remain to be elucidated. Previous studies have clearly established that low testosterone levels are associated with increased CV risk [11–14]. This risk has been attributed to metabolic changes similar to those observed in subjects with metabolic syndrome, including low high-density lipoprotein cholesterol, hypertriglyceridemia, and insulin resistance. Although low baseline levels of testosterone were undoubtedly an independent predictor of cardiac events or death in this study, the metabolic effects of lowering testosterone are more likely to affect CV disease over the long term rather than during the first 12 mo of therapy. The observation that the incidence of cardiac events differs whether a patient receives a GnRH antagonist versus an agonist also argues against lower testosterone as the sole cause of CV disease among patients undergoing ADT. Previous reports have showed that both classes of drugs induce castrate levels of testosterone.

An alternative explanation for the adverse effect of GnRH therapy on CV disease could be the destabilization of established vascular lesions. Most acute CV events, including myocardial infarction and stroke, are caused by rupture of an atherosclerotic plaque [15–17]. If this rupture occurs in a small to midsized artery, such as in a coronary artery, a thrombus will form that, in many instances, occludes the vessel and infarcts tissue distal to the obstruction. Plaque ruptures in larger arteries, such as the carotids, and usually gives rise to a nonobstructing thrombus that embolizes into the cerebral arteries, causing a stroke or a transient ischemic attack. The mechanisms involved in atherosclerotic plaque destabilization and rupture have been extensively studied. Plaques prone to rupture are characterized by a large core of lipids and necrotic debris covered by a thin cap of smooth muscle cells and connective tissue [18–20]. The rupture is caused by a degradation of the cap connective tissue by infiltrating macrophages releasing matrix-degrading proteases [19–22]. Lymphocytes of the proinflammatory T-helper 1 (Th1) type are important macrophage activators and are the dominant T-cell type in atherosclerotic plaques [23–25]. T cells express GnRH receptors, and activation of these receptors has been shown to stimulate T-cell expansion and differentiation into the Th1 phenotype, suggesting that GnRH agonists may promote destabilization of atherosclerotic plaques [26–28].

GnRH antagonists suppress both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as opposed to GnRH agonists, which primarily suppress LH. FSH receptors have been found on the luminal endothelial surface of proliferating tissue and may also play a role in endothelial cell function, lipid metabolism, and fat accumulation that may increase the risk of CV disease in men receiving GnRH agonist therapy [29]. These hypotheses are all supported by our observation that a GnRH antagonist is associated with a lower incidence of cardiac events only in subjects with preexisting CV disease and that this difference becomes apparent within a treatment period of <1 yr and appears to be most pronounced within 7 mo.

Our study also documented a lower risk of cardiac events for men with moderate alcohol consumption. These findings are consistent with a body of epidemiologic studies that demonstrate a J-shaped association between alcohol consumption and CV disease [30].

Our study has several limitations that confine our findings to hypothesis generation. Since results from six trials were pooled and reflect a post hoc analysis, we cannot exclude the possibility of uncontrolled bias in CV risk

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factors. Although we noted no differences between the study groups with respect to age, body mass index, CV history, hypertension, diabetes, statin treatment, smoking, or alcohol consumption, other factors such as plasma lipoprotein lipids, glucose levels, and blood pressure that were not monitored during the trials may have influenced the outcome. Patients and study personnel were not blinded to treatment allocation and, therefore, we cannot exclude the possibility that the observed differences in cardiac events were due to underreporting of CV events among men receiving GnRH antagonists. Another important limitation of this analysis stems from the fact that cardiac events were reported as adverse events, not as independent study end points. Although the trials were randomized, reported cardiac events were not systematically validated.

5. Conclusions

GnRH antagonists appear to halve the risk of CV events among men with preexisting CV disease when compared to GnRH agonists. One possible explanation could be the activation of T cells to the Th1 phenotype, resulting in atherosclerotic plaque destabilization. Animal models, as well randomized clinical trials, will be needed to validate this observation and define the mechanism.

Author contributions: Peter C. Albertsen 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: Albertsen, Olesen, Nilsson.
Acquisition of data: Klotz, Tombal, Olesen.
Analysis and interpretation of data: Albertsen, Grady.
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References

[1] D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420–5.
[2] Keeting NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.
[3] Bourke L, Kirkbride P, Hooper R, Rosario AJ, Chico TJ, Rosario DJ. Endocrine therapy in prostate cancer: time for reappraisal of risks, benefits and cost-effectiveness? Br J Cancer 2013;108:9–13.
[4] Conteduca V, DiLorenzo G, Tartarone A, Aieta M. The cardiovascular risk of gonadotropin releasing hormone agonists in men with prostate cancer: an unresolved controversy. Crit Rev Oncol Hematol 2013;86:42–51.
[5] D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289–95.
[6] Nanda AN, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009;302:866–73.
[7] Saigal CS, Gore JL, Krupski TL, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–500.
[8] Levine GN, D'Amico AV, Berger P, et al. Androgen deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and the American Urological Association: endorsed by the American Society of Radiation Oncology. Circulation 2010;121:833–40.
[9] Ginzburg S, Albertsen PC. The timing and extent of androgen deprivation therapy for prostate cancer: weighing the clinical evidence. Endocrinol Metab Clin N Am 2011;40:615–23.
[10] Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol 2012;61:11–25.
[11] Mohile SG, Mustian K, Bylow K, Hall W, Dale W. Management of complications of androgen deprivation therapy in older man. Crit Rev Oncol Hematol 2009;70:235–55.
[12] Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:3007–19.
[13] Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol 2011;165:687–701.
[14] Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol 2013;217:R25–45.
[15] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685–95.
[16] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317–25.
[17] Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
[18] Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481–8.
[19] Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003;108:1664–72.
[20] Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. Am J Cardiol 1989;63:114E–20E.
[21] Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90:1385–91.

[22] Van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36–44.
[23] Frostegard J, Ulfgren AK, Nyberg P, et al. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. Atherosclerosis 1999;145:33–43.
[24] Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol 2011;12:204–12.
[25] Lichtman AH, Binder CJ, Tsimikas S, Witztum JL. Adaptive immunity in atherogenesis: new insights and therapeutic approaches. J Clin Invest 2013;123:27–36.
[26] Chen HF, Jeung EB, Stephenson M, Leung PC. Human peripheral blood mononuclear cells express gonadotropin-releasing hormone (GnRH), GnRH receptor, and interleukin-2 receptor gamma-chain messenger ribonucleic acids that are regulated by GnRH in vitro. J Clin Endocrinol Metab 1999;84:743–50.
[27] Tanriverdi F, Gonzalez-Martinez D, Hu Y, Kelestimur F, Bouloux PM. GnRH-I and GnRH-II have differential modulatory effects on human peripheral blood mononuclear cell proliferation and interleukin-2 receptor gamma-chain mrna expression in healthy males. Clin Exp Immunol 2005;142:103–10.
[28] Dixit VD, Yang H, Udhayakumar V, Sridaran R. Gonadotropin-releasing hormone alters the t helper cytokine balance in the pregnant rat. Biol Reprod 2003;68:2215–21.
[29] Radu A, Pichon C, Camparo P, et al. Expression of follicle-stimulating hormone receptor in tumor blood vessels. N Eng J Med 2010;363:1621–30.
[30] Costanzo S, Di Castelnuovo A, Donati MB, Iacoviello L, de Gaetano G. Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. Circulation 2010;121:1951–9.

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