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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 CS31) 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.