The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer

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Abstract

We analyzed the cardiovascular toxicities related to the use of abiraterone and enzalutamide in prostate cancer. We found that these agents are associated with an increased risk of all- and high-grade cardiac toxicity as well as an increased risk of all- and high-grade hypertension. Follow-up for the onset of treatment-related cardiovascular events should be considered in these patients treated with abiraterone and enzalutamide.

Introduction: The cardiovascular toxicity related to abiraterone and enzalutamide has been previously studied by our group. In this analysis, we aim to update our previous findings related to abiraterone and enzalutamide, including the new available evidence, both in castration-resistant and hormone-sensitive prostate cancer. **Patients and Methods:** Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library, and ASCO Meeting abstracts. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods. **Results:** We included 7 articles in this meta-analysis, covering a total of 8660 patients who were used to evaluate cardiovascular toxicity. The use of new hormonal agents was associated with an increased risk of all-grade (RR, 1.36; 95% CI, 1.13-1.64; $P = .001$) and high-grade (RR, 1.84; 95% CI, 1.21-2.80; $P = .004$) cardiac toxicity. The use of new hormonal agents was also associated with an increased risk of all-grade (RR, 1.98; 95% CI, 1.62-2.43; $P = .001$) and high-grade (RR, 2.26; 95% CI, 1.84-2.77; $P = .004$) hypertension compared with the controls. Abiraterone was found to significantly increase the risk of both cardiac toxicity and hypertension, whereas enzalutamide significantly increases only the risk of hypertension. No differences were found based on the dose of prednisone used with abiraterone. The major limitation of this study is that data are available only as aggregate, and no single-patient information could be analyzed. **Conclusions:** Abiraterone and enzalutamide significantly increase the incidence and RR of cardiovascular toxicity in patients affected by metastatic prostate cancer. Follow-up for the onset of treatment-related cardiovascular events should therefore be considered in these patients.

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Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer in men, with 161,360 new cases and 26,730 deaths estimated to occur in 2017 in the United States.[1] Androgen deprivation therapy (ADT) is a cornerstone for treating locally advanced and metastatic disease. Recently, new hormonal agents able to prevent the synthesis of the testosterone by the inhibition of the cytochrome CYP17 (ie, abiraterone) or the intracellular binding (ie, enzalutamide) with the androgen receptor have demonstrated to increase the survival of patients with castration-resistant disease (CRPC) and, more lately, also of patients with metastatic hormone-sensitive disease (HSPC),

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naive to hormonal agents. Historically, ADT is the first step for medical treatment of PC and has been largely studied. ADT is characterized by a wide spectrum of toxicities and among those, cardiovascular toxicity is one of the most interesting with conflicting evidences.[2-5]

On the other hand, new hormonal agents are characterized by a favorable toxicity profile, with fluid retention, edema, hypokalemia, and transaminase increases peculiar to abiraterone, and fatigue and hot flashes typical of enzalutamide.

The cardiovascular toxicity related to abiraterone and enzalutamide has been previously studied by our group. We reported an increased incidence for all-grade but not for high-grade cardiovascular toxicity and the increase of both all- and high-grade hypertension in CRPC patients treated with new hormonal agents including abiraterone, enzalutamide, and orteronel.[6]

In this analysis, we aim to update our previous findings related to abiraterone and enzalutamide, including the new available evidences both in CRPC and in HSPC settings.

Materials and Methods
Definition of the Outcome
The objective of this analysis was to assess the incidence and relative risk (RR) of cardiovascular toxicity in patients treated with abiraterone and enzalutamide for PC. The cardiovascular toxicity considered included both arterial hypertension and cardiovascular toxicity. The latter was defined as the onset of any adverse cardiac event signs and symptoms.

For each trial, the abiraterone and enzalutamide ± prednisone group was considered to be the experimental arm and a placebo ± prednisone group the control. Both all-grade (grades 1-4) and high-grade (grades 3-5) events were considered to be the main outcomes, and the analysis was conducted in order to identify a significant difference between the 2 groups. A subgroup analysis was performed to highlight any differences in terms of the incidence and RR of cardiovascular toxicity between abiraterone and enzalutamide, and in patients treated with abiraterone, a subgroup analysis was performed based on the daily dose of prednisone used (ie, 10 vs. 5 mg).

Selection of the Studies
We reviewed MEDLINE/PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) University Meeting abstracts for citations from 2013 to June 15, 2017. The search criteria were limited to articles published in the English language and phase III or phase II randomized controlled trials in patients with PC. The MeSH terms used for the search of PubMed and the Cochrane Library were "abiraterone" or "enzalutamide." For the search in the ASCO meeting library, we used the name of the drugs and the terms "phase II" or "phase III"; the search was limited from 2013 to 2017 and to ASCO annual conferences and genitourinary cancer symposiums. The summaries for the product characteristics were searched for at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. If more than one publication was found for the same trial, the most recent, complete, and updated version was included in the final analysis.

Study quality was assessed using the Jadad 5-item scale, taking into account randomization, double blinding and withdrawals. The final score ranged from 0 to 5.[7]

Data Extraction
Two authors (R.I. and C.C.) independently conducted the data extraction according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement,[8] and a consensus approach was used to resolve any discrepancies. The data obtained for each trial included the first author's name, year of publication, trial phase, number of evaluable patients, number of arms, drugs used in the experimental and control arms, dosage, median follow-up, median treatment duration, and number of patients with any cardiac event or hypertension.

Statistical Method
The calculation of incidence was performed from the data available in each study. The proportion of patients who suffered cardiovascular events and the derived 95% confidence intervals (CIs) were calculated for each study. We also calculated the RR and CIs of events in patients assigned to treatment with new hormonal agents compared with the controls in the same study. To calculate the 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method.[9]

Statistical heterogeneity between the trials included in the meta-analysis was assessed using the Cochrane Q statistic, and inconsistency was quantified with an I^2 statistic {100% $\times$ [(Q−df)/Q]}.[10] The assumption of homogeneity was considered to be invalid for P values less than .1. Summary incidence and RRs were calculated using random- or fixed-effects models, depending on the heterogeneity of the included studies. When there was no substantial heterogeneity, the pooled estimate that was calculated based on the fixed-effects model was reported using the inverse variance method. When substantial heterogeneity was observed, the pooled estimate that was calculated based on the random-effects model was reported using the DerSimonian et al method,[11] which considers both within- and between-study variations.[10] An indirect comparison between the groups was performed using a χ^2 test. A 2-tailed P-value of less than .05 was considered to be statistically significant. All the data were collated using Microsoft Office Excel 2007. The statistical analyses were performed using the RevMan software for meta-analysis (v. 5.2.3).[12]

Results
Search Results
The electronic search revealed 2246 citations; after screening, 2035 records were eliminated because they did not match the initial requirements (Figure 1). At the end of the review process, 7 articles were included in the qualitative and quantitative syntheses.[13-19] Four studies compared abiraterone plus prednisone over a placebo plus prednisone, whereas the remaining 3 compared enzalutamide over a placebo in 2 studies and enzalutamide over bicalutamide in the last study. Five studies were performed in patients with metastatic CRPC and 2 in patients with metastatic HSPC. The characteristics of the studies are shown in Table 1.

The studies included in this analysis covered a total of 8660 patients. Among them, 2878 patients were treated with abiraterone and 1854 with enzalutamide in the experimental arms, whereas 3928 received a placebo ± prednisone in the control arms.

Figure 1   Flowchart of the Search Process
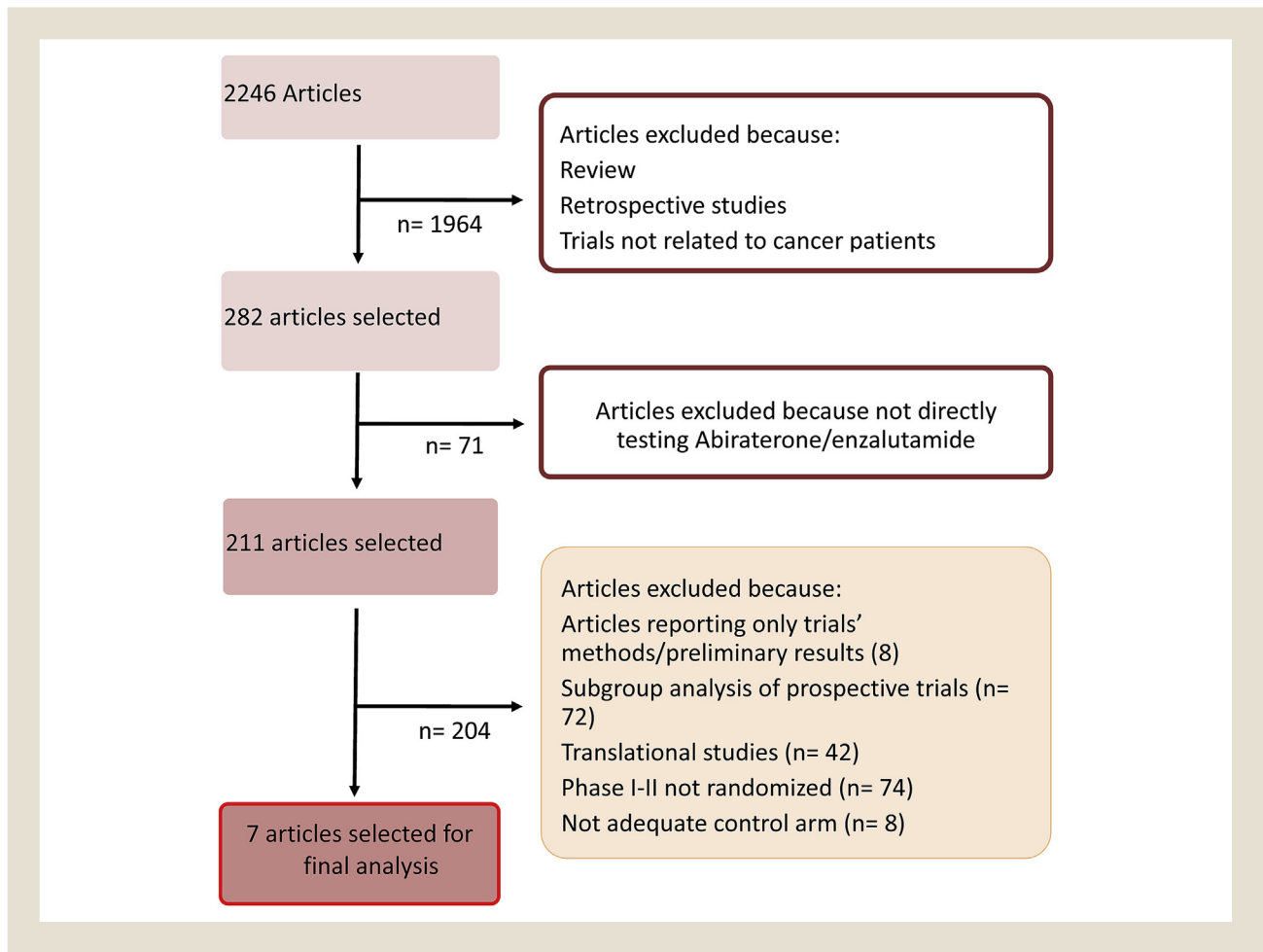
Cardiac Toxicity

In the experimental arm, the incidence of all-grade cardiac events was 11.7%, whereas in the control arm, it was 8.6%. Treatment with new hormonal agents increased the risk of all-grade toxicity by 36% (random effect: RR, 1.36; 95% CI, 1.13-1.64; $P = .001$). There was significant heterogeneity (χ^2, 11.7; $P = .07$; I^2, 49%).

The incidence of high-grades cardiac events was 3.7% in the experimental arms and 2.0% in the control arms. Treatment with new hormonal agents significantly increased the risk of high-grades cardiac toxicity (random effect, RR, 1.84; 95% CI, 1.21-2.80; $P = .004$), significant heterogeneity was found (χ^2, 13.3; $P = .04$; I^2, 56%) (Figure 2).

The incidence of all-grade and high-grade cardiac toxicity by the abiraterone was 13.7% and 4.5%, respectively; these were significantly increased compared with placebo (RR, 1.41; 95% CI, 1.21-1.64; $P < .001$ and RR, 2.22; 95% CI, 1.60-3.07; $P < .001$) (Table 2).

The incidence of all-grade and high-grade cardiac toxicity by the enzalutamide was 8.6% and 2.5%, respectively; these were not significantly increased compared with placebo (RR, 1.25; 95% CI, 0.99-1.59; $P = .3$ and RR, 1.28; 95% CI, 0.45-3.66; $P = .7$) (Table 2). No differences were found in the RR of both all-grade ($P = .9$) and high-grade ($P = .3$) cardiac toxicity between abiraterone and enzalutamide.

When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone with CRPC have significant major incidence of high-grade cardiac toxicity events compared with patients with HSPC, but no increase of all-grades cardiac toxicity was found. The same evidence was found for patients treated with placebo (see Supplemental Table 1 in the online version).

Hypertension

In the experimental arms, the incidence of all-grade hypertension was 19.6%, whereas in the control arms, it was 10.9%. Treatment with new hormonal agents increased the risk of all-grade hypertension by 98% (random effect, RR, 1.98; 95% CI, 1.62-2.43; $P = .001$). There was significant heterogeneity (χ^2, 12.0; $P = .006$; I^2, 67%).

The incidence of high-grade hypertension was 6.1% in the experimental arms and 3.1% in the control arms. Treatment with new hormonal agents more than doubled the risk of high-grade hypertension (fixed effect, RR, 2.26; 95% CI, 1.84-2.77; $P < .001$); no significant heterogeneity was found (χ^2, 6.68; $P = .35$; I^2, 10%) (Figure 3).

The incidence of all-grade and high-grade hypertension by the abiraterone was 26.2% and 6.9%, respectively; these were significantly increased compared with placebo (RR, 1.79; 95% CI,

Table 1 Main Characteristics of the Included Studies

Trial	Year	Previous Docetaxel	Required ADT	Experimental Arm		Control Arm		Median Treatment Duration, mos Exp./Ctr.	Median Follow-up, mos	CTCAE Version	Jadad Score
				No. Pts	Therapy	No. Pts	Therapy				
COU-AA-301	2012	Yes	Yes	791	Abiraterone + P 10 mg	394	Placebo + P 10 mg	8.0/4.0	12.8	3	5
COU-AA-302	2013	No	Yes	542	Abiraterone + P 10 mg	540	Placebo + P 10 mg	15.0/9.0	22.0	3	5
AFFIRM	2012	Yes	Yes	800	Enzalutamide	399	Placebo	8.3/3.0	14.4	4	5
PREVAIL	2014	No	Yes	872	Enzalutamide	845	Placebo	16.6/4.6	22.0	4	5
TERRAIN	2016	No	Yes	184	Enzalutamide	191	Bicalutamide	11.7/5.8	20.0/16.7	4	5
LATITUDE	2017	No	Yes	597	Abiraterone + P 5 mg	602	Placebo + P 5 mg	24/14	30.4	4	5
STAMPEDE	2017	No	Yes	948	Abiraterone + P 5 mg	960	NA	10.1/8.9	NA	NA	3

Abbreviations: ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; Ctr. = control group; Exp. = experimental group; mos = months; No. = number; NA = not available; P = prednisone; pts = patients.

1.45-2.21; $P < .001$ and RR, 2.19; 95% CI, 1.73-2.78; $P < .001$) (Table 2).

The incidence of all-grade and high-grade hypertension by the enzalutamide was 10.5% and 4.8%, respectively; these were significantly increased compared with placebo (RR, 2.66; 95% CI, 1.94-3.66; $P < .001$ and RR, 2.44; 95% CI, 1.64-3.63; $P < .001$) (Table 2). A significant difference was found in the RR for all-grade ($P = .04$) but not for high-grade ($P = .7$) hypertension between abiraterone and enzalutamide.

When studies performed in patients with HSPC were compared with those performed in patients with CRPC, patients treated with abiraterone for HSPC have major incidence of hypertension, but the difference was not significant. When the incidence of hypertension was compared in patients treated with placebo, patients with HSPC have a significantly increased incidence of adverse events compared with patients with CRPC (see Supplemental Table 2 in the online version).

Role of Prednisone Dose

A total of 2267 patients received prednisone 10 mg daily, and 3107 patients received prednisone 5 mg daily; among these 2 groups, 1333 and 1545 received abiraterone.

In the experimental arms, the incidence of all-grade cardiac toxicity was 18.9% and 9.2%, and in the control arms, 15.2% and 6.0%, when patients were treated with 10 mg or 5 mg of prednisone, respectively. No significant difference ($P = .4$) was found between the RR of all-grade toxicity in patients treated with 10 mg (RR, 1.33; 95% CI, 1.10-1.61; $P = .003$) or 5 mg (RR, 1.54; 95% CI, 1.20-1.97; $P < .001$).

In the experimental arms, the incidence of high-grade cardiac toxicity was 6.5% and 2.8%, and in the control arms, the incidence of high-grade cardiac toxicity was 3.4% and 1.1%, when patients were treated with 10 mg or 5 mg of prednisone, respectively. No significant difference ($P = .5$) was found between the RR of high-grade toxicity in patients treated with 10 mg (RR, 2.06; 95% CI, 1.38-3.08; $P < .001$) or 5 mg (RR, 2.62; 95% CI, 1.50-4.56; $P < .001$).

In the experimental arms, the incidence of all-grade hypertension was 16.3% and 33.5%, and in the control arms, the incidence of all-grade hypertension was 11.3% and 16.9%, when patients were treated with 10 mg or 5 mg of prednisone, respectively. No significant difference ($P = .3$) was found between the RR of all-grades hypertension in patients treated with 10 mg (RR, 1.61; 95% CI, 1.30-2.00; $P < .001$) or 5 mg (RR, 1.94; 95% CI, 1.41-2.71; $P < .001$).

In the experimental arms, the incidence of high-grade hypertension was 2.6% and 10.7%, and in the control arms, the incidence of high-grade hypertension was 1.9% and 4.6%, when patients were treated with 10 mg or 5 mg of prednisone, respectively. No significant difference ($P = .4$) was found between the RR of high-grade hypertension in patients treated with 10 mg (RR, 1.72; 95% CI, 0.97-3.06; $P = .06$) or 5 mg (RR, 2.31; 95% CI, 1.78-3.01; $P < .001$).

Quality of the Studies

All the studies were randomized, double-blind clinical trials, with the exception of the Systemic Therapy in Advancing or Metastatic

Figure 2 Relative Risk for All-grade (A) and High-grade (B) Cardiac Toxicity in Patients Treated With New Hormonal Agents or Control
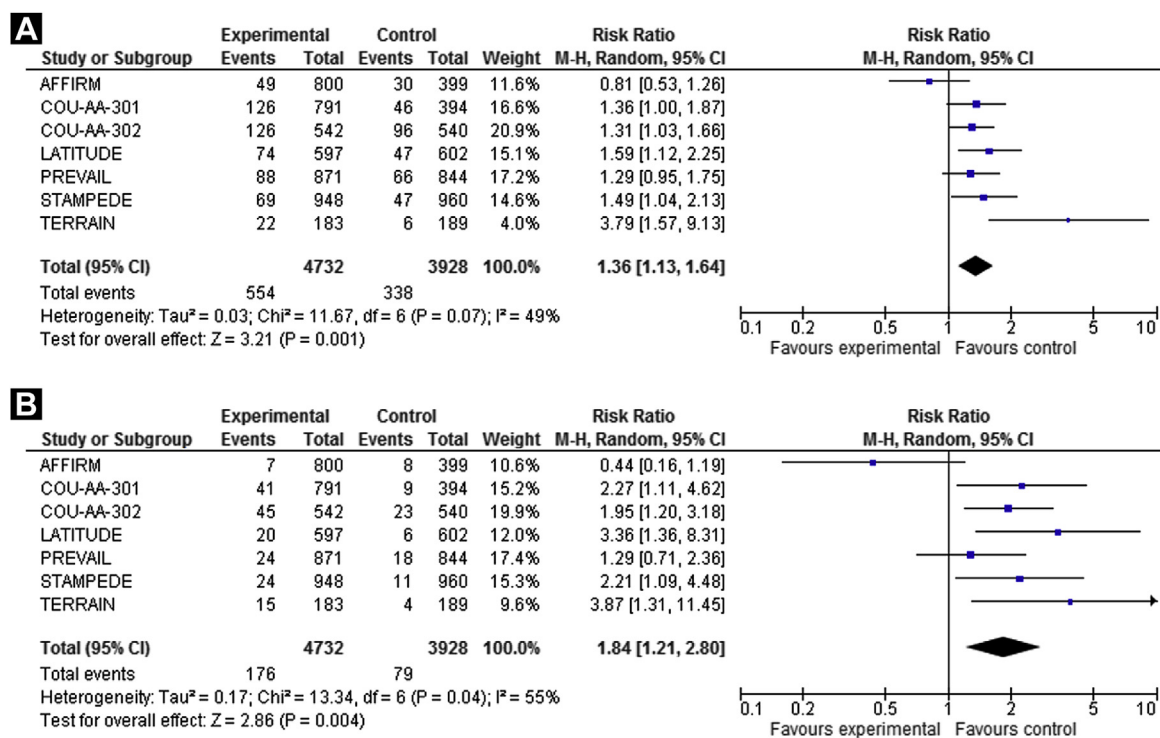
Abbreviations: CI = confidence interval; df = degrees of freedom.

Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, which was an open label study. This last trial has 3 points in the Jadad score, whereas all other studies have 5 points. The median value of 4.7 points confirms the good quality of studies included in the analysis.

Discussion

To our knowledge, this is the largest up-to-date meta-analysis investigating the incidence and the relative risk of cardiac toxicity and hypertension in patients treated with abiraterone and enzalutamide for PC. In a previous paper by our group, we reported a significant increase for all-grade cardiovascular toxicity but not for high-grade, with differences from CYP-17 inhibitors and enzalutamide.[6]

In this paper, more than 8600 patients were included in the final analysis, and we are able to confirm that new hormonal agents increase the risk of a cardiac event by 36% compared with ADT and the risk of high-grade toxicity by 84%, even if the incidence remains low in less than 12% and 4% of patients, respectively. Our results suggest that abiraterone significantly increases the RR of cardiovascular toxicity, whereas enzalutamide does not.

Regarding the incidence of hypertension, we found that such new hormonal therapies significantly increase the risk for both all- and high-grade hypertension, but this is more evident in patients treated with enzalutamide. A significant increase of the RR of all-grade toxicity was found in patients treated with enzalutamide compared with abiraterone.

Interestingly, we can describe 2 classes of drugs, both acting on the androgen axis and both used in patients with CRPC, which may have different patterns of cardiovascular toxicity, with abiraterone mainly generating cardiac events and enzalutamide primarily leading to hypertension. This difference may help the clinician to choose between the 2 agents.

Moreover, the increased incidence of cardiac toxicity in patients treated for CRPC but not for HSPC suggests that the length of therapy with abiraterone, longer in patients with HSPC, is not directly related to the increased risk of cardiac events. These are probably related to the longer duration of ADT in patients with CRPC. The increased incidence of hypertension in HSPC is probably related to the use of lower dose of prednisone in these trials and to the increased risk of abiraterone-related toxicities.

Recently, 2 trials presented at ASCO 2017 conference tested the addition or the sequence of new hormonal agents. A Phase 4, Randomized, Double-blind, Placebo-controlled Study Of Continued Enzalutamide Treatment Beyond Progression In Patients With Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (PLATO) trial investigated the addition of abiraterone or placebo to enzalutamide in patients with CRPC who progressed to enzalutamide. This study reported that the incidence of the high-grade hypertension was 9.6% in the combination arm compared with 1.6% in the group of patients treated with placebo and abiraterone.[20] On the other hand, a phase II study that randomized 202 patients to receive the sequence of abiraterone

Cardiovascular Effects of Abiraterone and Enzalutamide

Table 2 Incidence and Relative Risk of Cardiovascular Toxicities by Type of Treatment

Type of Toxicity	Toxicity Grade	Abiraterone				Enzalutamide			
		Exp. Arm, %	Ctr. Arm, %	RR (95% CI); P Value	Heterogeneity	Exp. Arm, %	Ctr. Arm, %	RR (95% CI); P Value	Heterogeneity
Cardiac	All	13.7	9.5	1.41 (1.21-1.64); <.001	$\chi^2 = 0.96$, $P = .81$; $I^2 = 0\%$	8.6	7.1	1.41 (0.75-2.63); 28	$\chi^2 = 9.82$, $P = .007$; $I^2 = 80\%$
	High	4.5	2.9	2.22 (1.60-3.27); <.001	$\chi^2 = 1.09$, $P = .8$; $I^2 = 0\%$	2.5	2.1	1.32 (0.85-2.06); .2	$\chi^2 = 8.44$, $P = .01$; $I^2 = 76\%$
Hypertension	All	26.2	14.8	1.79 (1.45-2.21); <.001	$\chi^2 = 9.47$, $P = .02$; $I^2 = 68\%$	10.5	4.2	2.74 (2.07-3.63); <.001	$\chi^2 = 2.36$, $P = .31$; $I^2 = 15\%$
	High	6.9	3.6	2.19 (1.73-2.78); <.001	$\chi^2 = 4.52$, $P = .21$; $I^2 = 34\%$	4.8	2.2	2.44 (1.64-3.63); <.001	$\chi^2 = 1.91$, $P = .39$; $I^2 = 0\%$

Abbreviations: CI = confidence interval; Ctr. = control; Exp. = experimental; I^2 = inconsistency; RR = risk ratio.

followed by enzalutamide (or vice versa) reported an increased incidence of high-grade hypertension in patients treated with abiraterone compared with enzalutamide (21% vs. 12%).[21] Both studies confirmed the cardiovascular toxicity of new hormonal agents and their addictive effect.

In this paper, we also analyzed the role of prednisone in the prevention of mineralocorticoid-related adverse events that arise because of CYP17 inhibition with abiraterone. In phase I to II trials, abiraterone acetate was administered without any glucocorticoid, and hypertension and hypokalemia were successfully managed with the mineralocorticoid receptor antagonist eplerenone.[22-24] Considering that, the use of 5 mg prednisone twice daily as a glucocorticoid replacement therapy was recommended. On the other hand, glucocorticoid-related adverse events include altered bone metabolism, immunosuppression, increased risk of hyperglycemia and diabetes, adverse impact on mood and cognitive function, and muscle weakness. Bearing in mind these events, 2 trials in metastatic HSPC have been designed with only 5 mg of prednisone per day, and results were recently presented at ASCO 2017 conference.[18,19] Both have been included in the meta-analysis, and the incidence and RR of cardiovascular toxicity has been compared with previous studies with abiraterone plus recommended dose of prednisone in patients with CRPC. Cardiac toxicity was not increased in patients treated with a reduced dose of prednisone. Despite that, an increased incidence of all-grade (33.5% vs. 16.3%) and high-grade (10.7% vs. 2.6%) hypertension was found, but the difference in the RR was not significant, probably because a comparable increase of events was also found in the control arms.

The evaluation of cardiovascular toxicity in this analysis must also account for several factors. First, not all the patients had previous therapy with ADT, and others could have several years of exposition and continue this treatment during the administration of new hormonal therapies. This analysis was also unable to explore the effect of several other factors such as a patient's medical history, age, and other possible data that may be predictive of cardiovascular toxicity. Moreover, the definition of cardiac toxicity includes several diseases that cannot be standardized over the trials included.

It is important to highlight that patients enrolled in clinical studies generally had adequate organ function, and those with chronic or concomitant disease were excluded. As a result of these selection criteria, the incidence of cardiovascular events is expected to be higher in the unselected population.

Despite these limitations, our analysis reported a significant increase of cardiac toxicity and hypertension in patients receiving abiraterone or enzalutamide for PC. Considering that, patients should be investigated for pre-existing risk factors in order to optimize those who are modifiable, and there should be careful follow-up for the onset of new treatment-related cardiovascular events.

Clinical Practice Points

- Abiraterone and enzalutamide are standard therapies for treatment of metastatic PC. Cardiovascular toxicity has not been well-addressed for these molecules.
- In this meta-analysis, we found that these 2 drugs increased the risk of cardiac toxicity by 36% for all-grade and by 84% for high-

Figure 3 Relative Risk for All-grade (A) and High-grade (B) Hypertension in Patients Treated With New Hormonal Agents or Control
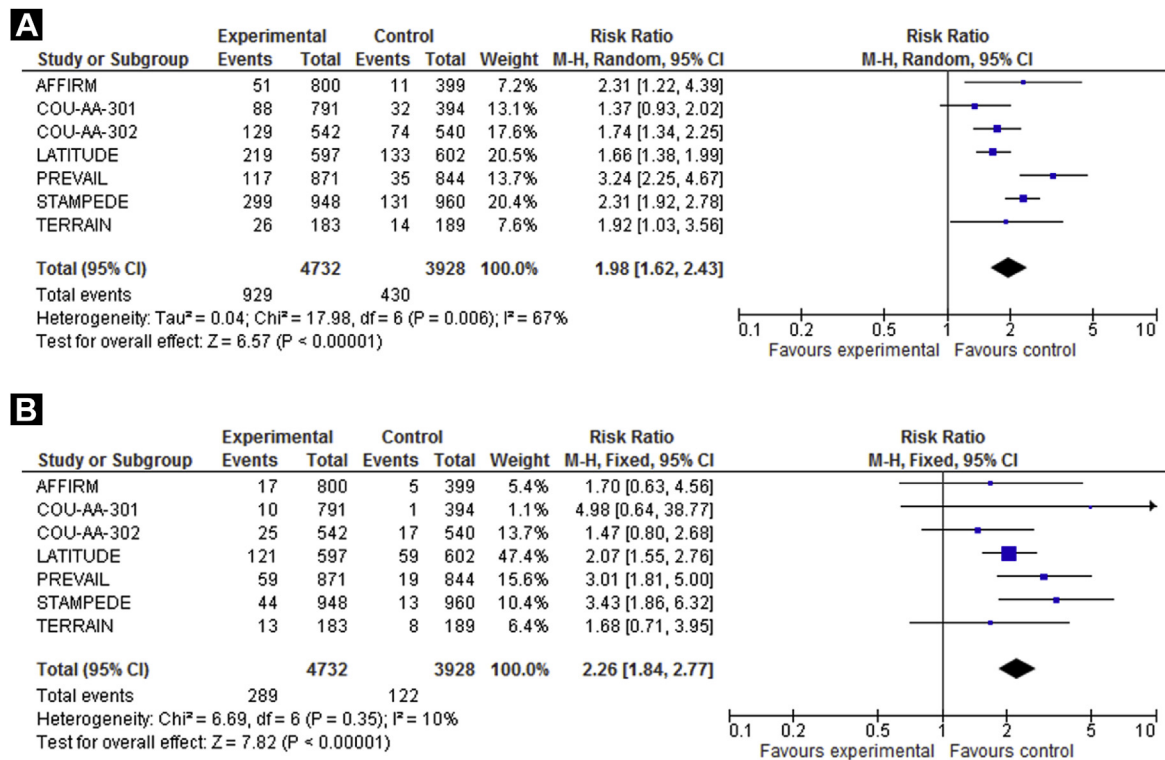
Abbreviations: CI = confidence interval; df = degrees of freedom.

grade events. In addition, the risk of arterial hypertension was increased by 100% for all-grade events and by 220% for high-grade events.

Disclosures

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2017.12.007.

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Supplemental Table 1	Incidence of Cardiac Toxicity Based on Type of Disease (ie, HSPC vs. CRPC)		
Disease	**Incidence, %**	χ^2	*P* Value
High-grade cardiac toxicity abiraterone			
HSPC	2.85	21.55	<.001
CRPC	6.45		
All-grade cardiac toxicity abiraterone			
HSPC	9.2	56.27	>.05
CRPC	19.9		
High-grade cardiac toxicity placebo			
HSPC	1.09	16.60	<.001
CRPC	3.43		
All-grade cardiac toxicity placebo			
HSPC	6.0	59.10	>.05
CRPC	15.2		

Abbreviations: CPRC = castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer.

Supplemental Table 2	Incidence of Hypertension Based on Type of Disease (ie, HSPC vs. CRPC)		
Disease	**Incidence, %**	χ^2	*P* Value
High-grade hypertension abiraterone			
HSPC	10.7	71.78	>.05
CRPC	2.6		
All-grade hypertension abiraterone			
HSPC	33.5	111.95	>.05
CRPC	16.3		
High-grade hypertension placebo			
HSPC	4.6	12.10	<.001
CRPC	1.9		
All-grade hypertension placebo			
HSPC	16.9	14.27	<.001
CRPC	11.3		

Abbreviations: CPRC = Castration-resistant prostate cancer; HSPC = hormone-sensitive prostate cancer.