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Risk of Cardiovascular Toxicity and Hypertension in Prostate Cancer Patients Treated with the Combination of a PARP Inhibitor and Abiraterone: A Systematic Review and Meta-Analysis

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Abstract

Background: Combinations of an Androgen Receptor Signaling inhibitor (ARSi, i.e., abiraterone acetate) and a PARPi (i.e., olaparib, niraparib) have recently shown to significantly improve clinical outcomes of metastatic Castration–Resistant Prostate Cancer (mCRPC) patients compared to ARSi monotherapy. These combinations have been associated with a potential increased risk of Cardiovascular Toxicity (CVT) and hypertension. We analyzed the incidence and the relative risk of developing CVT and hypertension in mCRPC treated with abiraterone and PARPi.

Methods: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined Relative Risks (RRs) and 95% Confidence Intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. The statistical analyses were performed with RevMan software for meta-analysis (v.5.2.3).

Results: Three articles were selected for this meta-analysis, including a total of 1,361 patients who were used to evaluate the CVT. The incidence of treatment-related CVT of any- and high-grade was 12.7% and 7.4%, respectively. Treatment with the association of abiraterone and a PARPi was associated with a significant increased risk of any grade CVT (RR=1.57, 95% CI 1.14-2.17; p=0.005) but not with high-grade CVT (RR=3.39; p=0.36) compared to abiraterone monotherapy. Moreover, the combination of abiraterone and a PARPi did not significantly increase the risk of hypertension of any grade (RR=1.07; p=0.74) and high-grade (RR=1.11; p=0.60) compared to control.

Conclusion: Treatment with abiraterone associated with a PARPi has a manageable safety profile in terms of cardiac disorders, with a significantly increase of the risk of CVT of any-grade, but not of high-grade, compared to controls. The incidence and relative risk of hypertension of any-grade and high-grade were not significantly augmented by this therapeutic approach

Keywords: mCRPC; Prostate cancer; PARPi; Abiraterone; Cardiovascular toxicity; Hypertension

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Introduction

Prostate Cancer (PC) is the second most frequent malignancy in men and the second leading cause of cancer-related deaths, which are mainly associated with metastatic spread [1]. PC is an androgen-dependent tumor; therefore, Androgen Deprivation Therapy (ADT) historically represents the cornerstone of treatment for metastatic disease, both in Castration-Sensitive (CSPC) and in Castration-Resistant (CRPC) phases of the disease [2]. In the last years, it has become clear that adding taxane chemotherapy and/or a new Androgen Receptor Signaling inhibitor (ARSi) to ADT significantly prolongs Overall Survival (OS) of either metastatic CSPC and CRPC patients [3]. Despite these advantages, the 3-years OS rate for mCRPC patients do not reach 50% [4]. Therefore, there is an urgent unmet necessity to improve the outcome of mCRPC patients.

DNA Damage Response and repair (DDR) encompasses a variety of cellular mechanisms that, when defective, can lead to developmental issues, tumorigenesis, and cellular death. DDR

comprises genes involved in the Homologous Recombination Repair (HRR), including *BRCA2*, *BRCA1*, *CDK12*, *FANCA*, *ATM*, *RAD1B*, and *RAD51C* [5]. Around 25% to 30% of mCRPC tumors carries inactivating somatic or germline mutations in HRR genes with BRCA-2 representing the most frequent mutated one [6]. HRR inactivating gene mutations have been associated with poor prognosis [7-10], but confer sensitivity to the pharmacological inhibition of DNA repairing enzymes, including poly (ADP-ribose) polymerase (PARP). PARP inhibitors (PARPi), by trapping PARP at sites of DNA damage and causing an accumulation of DNA double-strand breaks, lead to synthetic lethality in HRR deficient cells [11,12]. Several PARPi have demonstrated a significant anti-tumor activity in HRR-carriers mCRPC tumors, mainly with *BRCA2* mutations [13-17]. Lately, preclinical data have suggested a synergism between the Androgen Receptor (AR) pathway inhibition and PARPi in mCRPC, regardless of HRR mutational status. Indeed, ADT determines up-regulation of PARP-mediated repair pathways, which are key elements for prostate cancer cells survival [18]. Moreover, PAPR inhibition might increase the activity of ARSi by enhancing AR-dependent transcription, and ARSi can induce HRR mutations leading to an increased PARPi activity [19].

To confirm these findings, combinations of an ARSi (i.e., abiraterone acetate) and a PARPi (i.e., olaparib, niraparib) have recently shown to significantly improve clinical outcomes of mCRPC patients compared to an ARSi monotherapy [20-22]. Of note, these combinations have been associated with a potential increased risk of Cardiovascular Toxicity (CVT). Therefore, we have analyzed the incidence and the relative risk of developing CVT (several types of cardiac events) and hypertension in mCRPC patients treated with abiraterone and a PARPi.

Patients and Methods

Definition of outcomes

The objective of this analysis was to assess the incidence and Relative Risk (RR) of either CVT and of hypertension in mCRPC patients treated with the combination of an Androgen Receptor Signaling inhibitor (ARSi) plus a PARPi. CVT encompassed a wide spectrum of events, including myocardial infarction, chronic and acute cardiac failure, ischemic stroke, arterial and venous thromboembolic events, pulmonary embolism, and arrhythmia.

For each trial, the combination of an ARSi and a PARPi was considered as the experimental arm and the ARSi as the control. Both all-grades (grades 1-4) and high-grade (grades 3-5) events were considered as the main outcomes, and the analysis was conducted in order to identify a significant difference between the two treatment arms.

Selection of studies

We reviewed MEDLINE/PubMed, the Cochrane Library, and the ASCO Library abstracts for citations up to September 12th, 2022. The search criteria were limited to articles published in the English language and phase III or phase II RCTs in patients with prostate cancer. We included randomized trials reporting data of CVT with combinations of a PARP inhibitor and abiraterone. Principal exclusion criteria were overlapping publications, trials not reporting data about cardiovascular toxicity. The MeSH terms used for the search of PubMed and the Cochrane Library were 'prostate cancer', 'PARP inhibitor', 'mCRPC', 'ARSi', or the name of the drugs (i.e., abiraterone, apalutamide, enzalutamide, niraparib, olaparib, talazoparib). For the search in the ASCO Library, we used the name of the drugs and the terms 'phase II' or 'phase III'. 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 [23].

Data extraction

Two authors (CC and RI) conducted the data extraction independently. It was performed according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement [24], and any types of discrepancies were resolved by consensus. The data extracted for each trial were first author's name, year of publication, trial phase, number of enrolled patients, type of treatment, number and type of all-grades and high-grades CVT and hypertension events in both populations.

Statistical methods

The calculation of incidence was performed from the data available in each study. The proportion of patients with CT 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 PARPi plus abiraterone compared to the control (abiraterone plus placebo) in the same study. To calculate the 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method [25]. Statistical heterogeneity between the trials included in the meta-analysis was assessed using Cochrane's Q statistic, and inconsistency was quantified with an I^2 statistic (100% × [Q-df)/Q]) [26]. The assumption of homogeneity was considered to be invalid for p values less than 0.1. 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 [27], which considers both within- and between-study variations [26]. A two-tailed p-value of less than 0.05 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) [28].

Results

Search results

The electronic search revealed 205 citations, after screening 39 full text articles were reviewed for further assessment and 36 citations were excluded because did not meet the inclusion criteria.

This reviewed process (Figure 1) led to the selection of three articles considered for final analysis based on their adequate quality and relevance for inclusion in the meta-analysis [20-22]. Two were randomized phase III trials; one was a randomized phase II study. All the three studies used abiraterone acetate as ARSi; the PARPi was Olaparib in two trials, while the other study evaluated the efficacy of niraparib. The comparator was abiraterone acetate associated with placebo across all the three studies. A total of 1,361 patients were

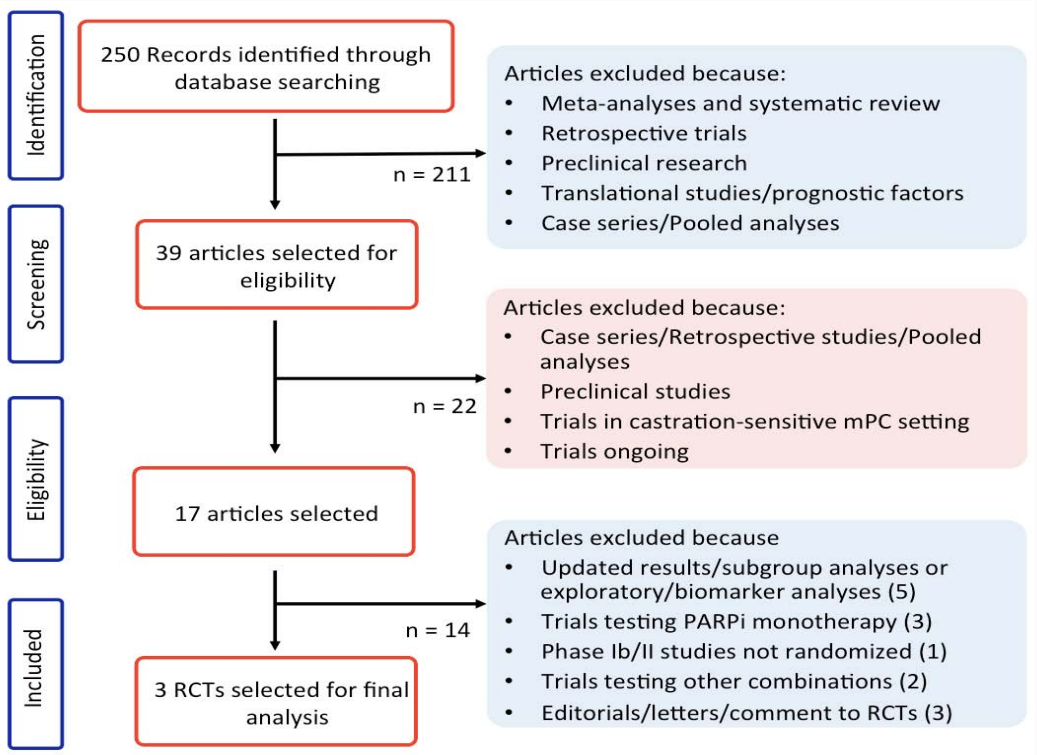

Figure 1: Selection of the included studies.

available for meta-analysis: 682 in the experimental arms, and 679 in the control arms. The characteristics of each trial analyzed in this study are shown in Table 1.

Incidence and relative risk of cardiovascular toxicity

For incidence of CVT of any grade, all studies were included in final analysis, encompassing a total of 1,361 patients. Among them, 682 were treated in the experimental arms with the combination of abiraterone and a PARPi (niraparib or Olaparib), while 679 received standard therapy (abiraterone plus placebo) in the control arms. CVT events described in the selected trials include myocardial infarction, chronic and acute cardiac failure, ischemic stroke, arterial and venous thromboembolic events, pulmonary embolism, and arrhythmia. In the overall cohort, CVT of any grade was reported in 87 of 682 patients treated with abiraterone plus a PARPi, corresponding to an incidence of 12.7%, compared to 8.1% in the control arms (55 cases of PT among 679 patients) (Table 2).

Treatment with abiraterone associated with a PARPi significantly increased the risk of any grade CVT compared to controls (fixed-effects, RR=1.57, 95% CI, 1.14-2.17; p=0.005). No significant heterogeneity was found in this analysis (Chi^2=1.12, p = 0.57; I^2=0%) (Figure 2A).

As concern the incidence of CVT of high grade, data were available for two out of the three studies, encompassing a total of 565 patients. The incidence of high-grade CVT was 7.4% in the experimental arms (21 events among 283 patients) and 3.5% in the control arms (10 reported cases in 282 patients) (Table 2). Treatment with abiraterone plus a PARPi did not significantly increase the risk of high-grade CVT (random-effect, RR=3.39, 95% CI, 0.25-46.78; p=0.36). Significant heterogeneity was documented in the RR analysis for high-grade CT (Chi^2=3.39, p=0.07; I^2=70%) (Figure 2B).

Incidence and relative risk of hypertension

With regard to the risk of hypertension of any grade, data were available from all the three studies, with a total of 1,359 patients. Hypertension of any grade was reported in 128 out of 681 patients treated with abiraterone plus a PARPi, corresponding to an incidence of 18.7%, compared to 17.4% in the control arms (118 cases of hypertension among 678 patients) (Table 3).

Treatment with the association of abiraterone and a PARPi did not significantly increase the risk of hypertension of any grade compared to controls (random-effects, RR=1.07, 95% CI, 0.70–1.64; p=0.74). Significant heterogeneity was observed in this analysis (Chi^2=4.91, p=0.09; I^2=59%) (Figure 3A).

As concern the incidence of hypertension of high grade, all the three studies were included in the analysis. The incidence of high-grade hypertension was 7.2% in the experimental arms (49 events among 681 patients) and 6.5% in the control arms (44 reported cases in 678 patients) (Table 3). Therefore, similarly to what observed for all-grades hypertension, treatment with abiraterone plus a PARPi did not significantly increase the risk of high-grade hypertension (fixed-effect, RR=1.11, 95% CI, 0.76-1.62; p=0.60). No significant heterogeneity was found in this analysis (Chi^2=0.39, p=0.82; I^2=0%) (Figure 3B).

Quality of the studies

At the time of this analysis, only one out of three studies were published. The Jadad's scale could be applied only to this trial, which was of good quality (score ≥ 3). The Jadad's scale could not be applied for the remaining two studies presented at the 2022 ASCO Genitourinary Symposium but not yet published (Table 1).

Discussion

Combinations of abiraterone acetate and a PARPi (i.e., Olaparib

Table 1: Selected studies for final analysis.

Trial	Phase	Trial Design				Disease setting	HRR mutation status		Median follow-up	rPFS (Exp/Ctr) (HR, 95% CI; p value)	mOS (Exp/Ctr) (HR, 95% CI; p value)	Jadad
		Exp		Ctr			Exp	Ctr				
		Drug	Pts (N)	Drug	Pts (N)							
NCT01972217	2	ABI + OLAPARIB	71	ABI + pbo	71	Pre-treated mCRPC	HRR mut=11 (15%) HRR WT=15 (21%) HRR partially characterized = 45 (63%)	HRR mut=10 (14%) HRR WT=20 (28%) HRR partially characterized = 41 (58%)	15.5 mo (exp) 24.5 mo (ctr)	ITT=13.8 *vs.* 8.2 mo (HR 0.65, 0.44-0.97, p=0.034) HRR mut=17.8 *vs.* 6.5 mo (HR 0.74, 0.26-2.12; nominal p=0.58) HRR WT=15.0 *vs.* 9.7 mo (HR 0.52, 0.24-1.15); nominal p=0.11)	22.7 *vs.* 20.9 mo (HR 0.91 0.60-1.38); p=0.66)	5
PROpel	3	ABI + OLAPARIB	399	ABI + pbo	397	1st line mCRPC	HRR mut= 111 (27.8%) HRR WT= 279 (69.9%) HRR unknown= 9 (2.3)	HRR mut= 115 (29.0%) HRR WT= 273 (68.8%) HRR unknown= 9 (2.3)	NR (Events 457, for rPFS) Events 319, maturity 40.1% for OS)	25.0 *vs.* 16.4 mo (HR 0.67, 0.56–0.81, p<0.0001)* HRR WT= 24.1 *vs.* 19.0 mo (HR 0.76, 0.49-0.74)* HRR Mut= NR *vs.* 13.9 mo HR 0.50 (0.34-0.73)* BRCA WT=24.1 *vs.* 19.0 mo (HR 0.76, 0.61-0.94)* BRCA Mut=HR 0.23 (0.12-0.43)*	NR *vs* NR (HR 0.83, 0.66-1.03); p=0.11	NE
MAGNITUDE	3	ABI + NIRAPARIB	212#	ABI + pbo	211#	1st line mCRPC	HRR mut= 212 BRCA1/2= 98	HRR mut= 211 BRCA1/2= 92	18.6 months	HRR mut 16.5 *vs.* 13.7 (HR 0.73, 0.56-0.96); p=0.0217** HRR mut=19.0 *vs.* 13.9 (HR 0.64, 0.49-0.89); p=0.0022* BRCA1/2 mut=16.6 *vs.* 10.9 (HR 0.53, 0.36-0.79); p=0.0014**	NE *vs.* NE (HR 0.767, 0.525-1.119), p=0.1682	NE

ABI: Abiraterone; CI: Confidence Interval; HR: Hazard Ratio; HRR: Homologous Recombination Repair; mCRPC: metastatic Castration-Resistant Prostate Cancer; mo: months; mOS: median Overall Survival; mPFS: median Progression-Free Survival; mut: mutation positive; N: Number of Patients; NE: Not Evaluable; NR: Not Reached; pbo: placebo; vs: versus; WT: Wild Type

*: investigator-assessment

#: HRR mutation positive

Table 2: Overall incidence of all- and high-grade cardiovascular toxicity from all included trials.

Study	Experimental Drug	Evaluable Patients		Cardiovascular toxicity							
				Any-Grade				High-Grade			
		ABI+PARPi	ABI+Pbo	ABI+PARPi		Control		ABI+PARPi		Control	
				N Events	Incidence	N Events	Incidence	N Events	Incidence	N Events	Incidence
NCT01972217	ABI+OLAPARIB	71	71	9	12.7%	3	4.2%	8	11.3%	0	0.0%
PROpel	ABI+OLAPARIB	399	397	43	10.8%	28	7.0%	NR	NR	NR	NR
MAGNITUDE	ABI+NIRAPARIB	212	211	35	16.5%	24	11.4%	13	6.1%	10	4.7%
	Total	682	679	87	12.7%	55	8.1%	21	7.4%	10	3.5%

Legend: ABI: Abiraterone; N: Number of Patients; NR: Not Reported; Pbo: Placebo

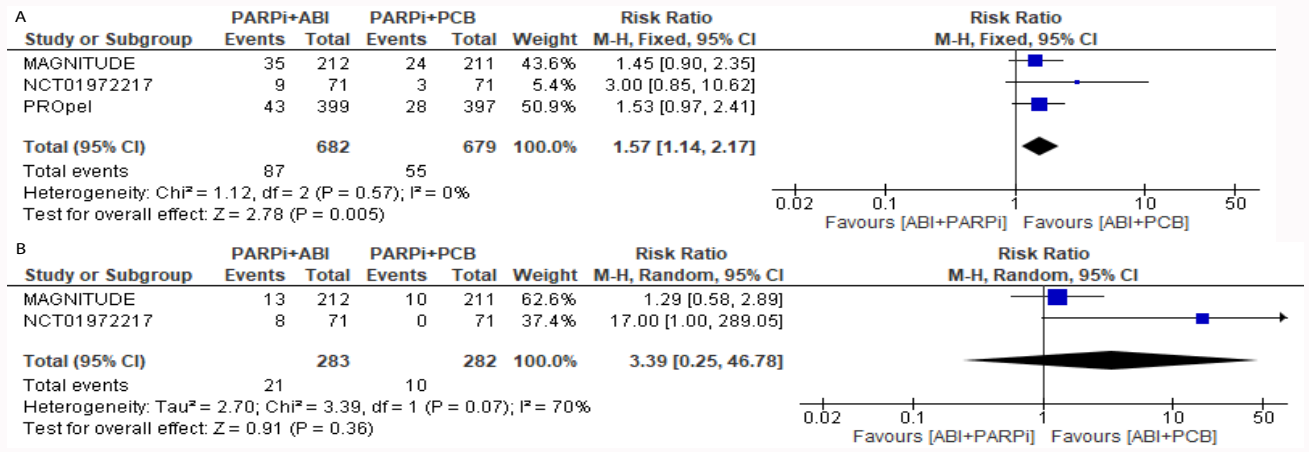

Figure 2: Cardiovascular toxicity of any grade (A) and high-grade (B) of abiraterone acetate plus a PARPi compared to abiraterone acetate plus placebo.

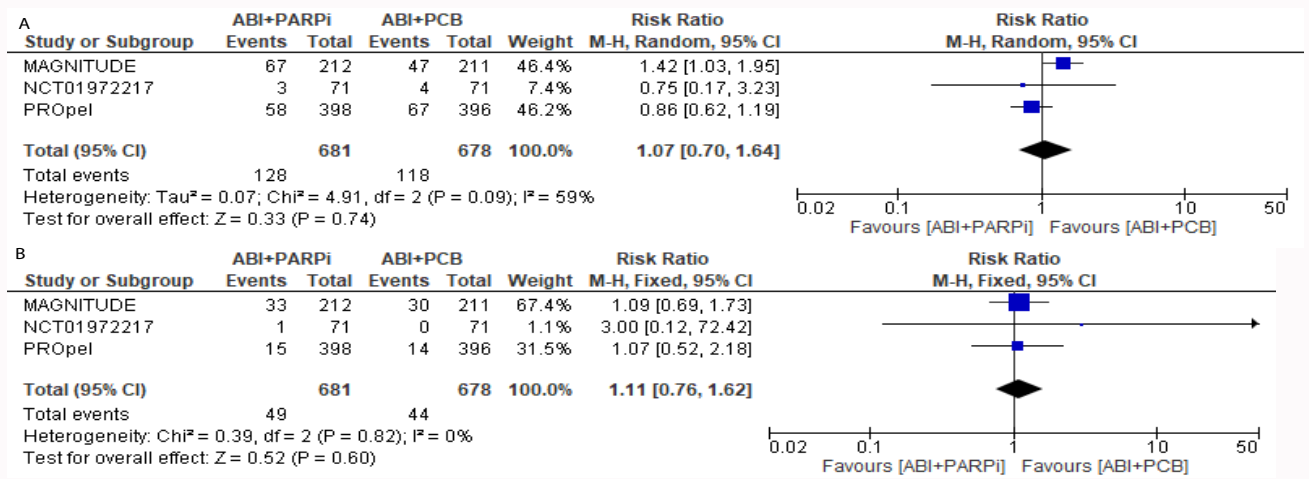

Figure 3: Hypertension of any grade (A) and high-grade (B) of abiraterone acetate plus a PARPi compared to abiraterone acetate plus placebo.

or niraparib) represent a recently investigated strategy that could in the near future be considered as a first-line option for mCRPC patients. Two international phase 3 trials, MAGNITUDE and PROpel studies, demonstrated the superiority of abiraterone plus niraparib and abiraterone plus Olaparib, respectively, compared to abiraterone plus placebo in mCRPC patients [21,22]. Notably, abiraterone plus Olaparib significantly improved radiographic Progression Free Survival (rPFS) over abiraterone plus placebo (HR=0.66; p<0.0001) irrespective of HRR mutational status in the PROPel trial; while a significant benefit of abiraterone plus niraparib was restricted to the mCRPC patients' population carrying HRR gene alterations (rPFS HR=0.53, p=0.0014 in BRCA1/2 mutated patients, HR=0.73, p=0.02 in HRR positive tumor) but not in patients without HRR mutations. Final OS analyses are warranted to clearly state the impact of this strategy in mCRPC patients' management.

With respect to the safety profile of these combinations, concerns have been raised in terms of CVT. The correlation between anti-androgen therapies and CVT is a debated topic in prostate cancer. In previous papers our group reported a significant increase of the relative risk of all-grades (RR 1.41; 95% CI 1.21-1.64; p<0.001) and high-grade (RR 2.22; 95% CI 1.60-3.07; p<0.001) CVT in CRPC patients treated with abiraterone compared to ADT alone. Of note, the improved risk of CVT was evident for mCRPC but not for

Table 3: Overall incidence of all- and high-grade hypertension from all included trials.

Study	Experimental Drug	Evaluable Patients		Hypertension							
				Any-Grade				High-Grade			
		ABI+PARPi	ABI+Pbo	ABI+PARPi		Control		ABI+PARPi		Control	
				N Events	Incidence	N Events	Incidence	N Events	Incidence	N Events	Incidence
NCT01972217	ABI+OLAPARIB	71	71	3	4.2%	4	5.6%	1	1.4%	0	0%
PROpel	ABI+OLAPARIB	398	396	58	14.6%	67	16.9%	15	3.8%	14	3.5%
MAGNITUDE	ABI+NIRAPARIB	212	211	67	31.6%	47	22.3%	33	15.6%	30	14.2%
Total		681	678	128	18.7%	118	17.4%	49	7.2%	44	6.5%

Legend: ABI: Abiraterone; N: Number of Patients; NR: Not Reported; Pbo: Placebo

mCSPC, suggesting that the length of therapy with abiraterone, longer in mCSPC patients, was not directly related to the increased risk of cardiac events. On the contrary, the longer duration of ADT in mCRPC patients might explain the increased risk of CVT in this disease setting [29,30]. Similarly, treatment with abiraterone significantly increased the incidence of all-grade and high-grade hypertension compared with placebo [29,30].

To the best of our knowledge, this is the first analysis at investigating the impact on the cardiovascular system of the combinations of abiraterone plus a PARPi. We demonstrated that these combinations significantly increased the risk of CVT of any-grade (RR=1.57; p=0.005) compared to abiraterone plus placebo. Despite that, an increased incidence of high-grade CVT was found (7.4% *vs.* 3.5%), but the difference in the RR was not significant (p=0.36). It is important to underline that the incidence of high-grade CVT reported in our analysis were substantially in line to that observed with abiraterone monotherapy, further confirming the lack of a significant contribution of PARP inhibitors in terms of cardiotoxicity [30]. Treatment with PARPi alone is not commonly associated with increased cardiac toxicity in patients affected by mCRPC, ovarian or breast cancer [31-34]. A potential dose-dependent increase in QT interval has been described with PARPi [35], even if at recommended daily doses niraparib and Olaparib are not responsible for clinically relevant changes in Electrocardiographic (ECG), including QTc prolongation [36,37]. In EudraVigilance database in the last year, 115 cases of cardiac disorders related to Olaparib therapy have been reported, mainly among women (due to the indication of PARPi for ovarian and breast cancer) with only 7 cases described in men. In the majority of cases, these cardiac events were recovering/recovered, while they were considered fatal in 18 patients. The same database has reported 130 cases of hypertension, recovered in 65% of cases and fatal only for one patient. As concern niraparib, EudraVigilance database has reported 354 cardiac disorders events (only 13 of which in men), responsible for patients' death in only 4 cases and recovering/recovered in 15.7% of cases. Moreover, 325 hypertension events have been reported, none of which fatal [38].

In terms of hypertension, the incidence and relative risk of developing hypertension of any-grade and high-grade were not significantly improved with the addition of a PARPi to abiraterone, supporting once again the manageable safety profile of these combinations. It is interesting to note that niraparib monotherapy is the only PARPi to be associated with hypertension, caused by an off-target interference of dopamine and noradrenaline metabolism [39]. In the phase I study testing the safety of niraparib associated with abiraterone, the incidence of hypertension of high-grade (in the cohort of niraparib at 200 mg daily) was 21%, considerably higher than that found in our larger cohort of patients (7.0%), thus downsizing a potential adverse event of interest [40].

One of the major limits of our analysis was the lack of important clinical information (i.e., patient's comorbidities, metabolic syndrome, age, body mass index) and other possible data that might be associated with an increased risk of cardiovascular toxicity. Moreover, the definition of cardiovascular toxicity included different medical conditions that could not be standardized over the trials included.

In conclusion, our analysis demonstrated that treatment with abiraterone associated with a PARPi has a manageable safety profile in terms of cardiac disorders, with a significantly increase of the risk of cardiovascular toxicity of any-grade, but not of high-grade, compared to controls. The incidence and relative risk of hypertension of any-grade and high-grade were not significantly augmented by this therapeutic approach. These results suggest a careful clinical evaluation of patients under treatment, paying particular attention to cardiovascular toxicity and those expected toxicities, first of all anemia, which could indirectly be responsible for an increase in adverse cardiac events in a daily clinical practice population.

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