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Research paper

Cardiovascular toxicities associated with abiraterone compared to enzalutamide—A pharmacovigilance study

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ABSTRACT

Background: Androgen deprivation therapy (ADT) is standard-of-care for advanced prostate cancer. Studies have generally found increased cardiovascular risks associated with ADT, but the comparative risk of newer agents is under-characterized. We defined the cardiac risks of abiraterone and enzalutamide, using gonadotropic releasing hormone (GnRH) agonists to establish baseline ADT risk.

Methods: We used VigiBase, the World Health Organization pharmacovigilance database, to identify cardiac adverse drug reactions (ADRs) in a cohort taking GnRH agonists, abiraterone, or enzalutamide therapy for prostate cancer, comparing them to all other patients. To examine the relationship, we used an empirical Bayes estimator to screen for significance, then calculated the reporting odds ratio (ROR), a surrogate measure of association. A lower bound of a 95% confidence interval (CI) of ROR > 1 reflects a disproportionality signal that more ADRs are observed than expected due to chance.

Findings: We identified 2,433 cardiac ADRs, with higher odds for abiraterone compared to all other VigiBase drugs for overall cardiac events (ROR 1•59, 95% CI 1•48—1•71), myocardial infarction (1•35, 1•16—1•58), arrythmia (2•04, 1•82—2•30), and heart failure (3•02, 2•60—3•51), but found no signal for enzalutamide. Patients on GnRH agonists also had increased risk of cardiac events (ROR 1•21, 95% CI 1•12—1•30), myocardial infarction (1•80, 1•61—2•03) and heart failure (2•06, 1•76—2•41).

Interpretation: We found higher reported odds of cardiac events for abiraterone but not enzalutamide. Our data may suggest that patients with significant cardiac comorbidities may be better-suited for therapy with enzalutamide over abiraterone.

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1. Introduction

Reduction of testosterone to castrate levels is a standard-of-care treatment for advanced prostate cancer. First-line androgen deprivation therapy (ADT) utilizes gonadotropic releasing hormone (GnRH) agonists and antagonists to disrupt pituitary stimulus of testosterone production [1]. Unfortunately, prostate cancer can develop castrate resistance as quickly as a median of 7–11 months of first-line ADT in the metastatic setting [2-4]. In recent years, abiraterone acetate and enzalutamide have been shown to improve overall survival when added to first-line ADT (most commonly a GnRH agonist) in multiple settings [5,6].

However, modulating androgen activity has consequence, and cardiac toxicities remain a significant source of non-cancer related morbidity and mortality in patients with prostate cancer. GnRH agonists have been linked to cardiac adverse drug reactions (ADRs), especially in individuals with pre-existing cardiac conditions [7]. Abiraterone and enzalutamide have been linked to an increased risk of hypertension [8], and abiraterone has additionally been associated with an increase in heart failure [9]. Prescribing information for abiraterone cites risks of cardiac arrythmia, chest discomfort, and cardiac failure, while enzalutamide cites only cardiac ischemia risk [10,11]. Nevertheless, their comparative risk profile, especially in relation to first-line therapy alone, remains under-characterized, although recent work pooling patients taking abiraterone or enzalutamide did find a higher rate of severe cardiac ADRs than in patients taking similarly indicated taxane therapy [12].

These medications work via different mechanisms. Abiraterone is an inhibitor of 17α-hydroxy/17,20-lyase, which decreases both androgen and corticosteroid synthesis, resulting in compensatory increases in adrenocorticotropic hormone and mineralocorticoid synthesis. For this reason, abiraterone requires coadministration with a corticosteroid to

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Research in context

Evidence before this study

Advanced prostate cancer is treated with various forms of androgen deprivation therapy, all of which has previously been associated with cardiac risks, described both in package inserts and primary literature. Whether and how much newer agents such as enzalutamide and abiraterone elevate cardiac risks is unclear both in comparison to older medications and to each other.

Added value of this study

Using the world's largest pharmacovigilance database, we identified cardiac events associated with androgen deprivation for prostate cancer with traditional gonadotropic releasing hormone agonists and with the newer agents abiraterone and enzalutamide. We found expected increased cardiac risks associated with traditional therapy and with abiraterone, but found no high reported odds of cardiac events for enzalutamide.

Implications of all the available evidence

Clinicians prescribing androgen deprivation therapy for advanced prostate cancer, especially for patients with elevated cardiac risk profiles, should consider the prescription of agents associated with lower reported risks of cardiovascular adverse drug reactions. Our data may preliminarily suggest that a patient with significant cardiac comorbidities may be better suited for therapy with enzalutamide over abiraterone.

avoid mineralocorticoid excess which can contribute to worsened cardiac risks [13]. Enzalutamide directly antagonizes the androgen receptor with stronger affinity than is seen in first-generation antagonists and also prevents its nuclear translocation, preventing transcription of oncologic genes necessary for cancer growth and survival [14].

We hypothesized that differences in the mechanism of action of these new agents may lead to differences in cardiac toxicity profiles. Given that the most common non-cancer cause of death in prostate cancer patients is cardiovascular disease [15], we therefore conducted a pharmacovigilance study to evaluate the relative cardiac toxicity of GnRH agonist therapy alone, of abiraterone, and of enzalutamide.

2. Methods

We used VigiBase, the World Health Organization global database of individual case safety reports, which collects data from more than 130 countries, to extract all drug-adverse reaction pairs for a pharmacovigilance analysis. VigiBase is managed by the Uppsala Monitoring center, and contains more than 20 million safety reports of suspected medication adverse drug reactions (ADRs), dating to 1967. These reports originate from a variety of sources, including physicians, other healthcare professionals, patients, and pharmaceutical companies [16].

Using standardized Medical Dictionary for Regulatory Activities (MedRA) terminology, we identified all cardiovascular events captured by Vigibase at any time and reported in patients taking 1) GnRH agonists (leuprolide, goserelin, triptorelin, histrelin) but not abiraterone or enzalutamide, 2) abiraterone but not enzalutamide, and 3) enzalutamide but not abiraterone, all for an indication of prostate cancer. All terms in the MedRA cardiovascular hierarchical family were captured. Patients taking abiraterone and enzalutamide were assumed to be taking a first-line GnRH agonist or antagonist. GnRH agonists were chosen to provide a baseline for prostate cancer therapy related ADRs as they are the most-frequently utilized form of first-line ADT globally [17]. Non-standard doses were excluded, as were women and individuals under 18-years-old. Events were subcategorized as myocardial infarction (MI), heart failure (HF), carditis (cardiomyopathies, pericarditis, or myocarditis), new valvular dysfunction, new arrythmias, and other. Patient demographic data, duration of therapy, reported reaction, MedRA classification terms, onset date, end date, seriousness, and final outcome were extracted. Means with standard deviations (SDs) were calculated when appropriate. The research was IRB-approved (2019P000832).

We used disproportionality analysis to evaluate if cardiac ADRs were reported more frequently than would be expected with a given drug. As VigiBase lacks a comparison group of patients taking the drug of interest but not experiencing an ADR, all individuals in the database taking unrelated drugs and experiencing the ADR were used as a comparator, per standard pharmacovigilance methodology, forming a case/non-case study. If the proportion of individuals taking a drug who report a specific ADR is significantly higher than the proportion of individuals taking any other drug in the database who experience the same ADR, it represents a disproportionality signal, suggesting an association between drug and ADR [18,19]. As the measure of interest is a ratio, duration of drug availability does not intrinsically bias it. The expected count is generated by examining ADRs reported for every other drug in the pharmacovigilance database (Vigibase) over the examined period, which is then compared to the count for the examined drugs to determine whether a disproportional number of reports were generated. We examined one-year periods for cumulative incidence and the duration of drug availability for the total period [18,19].

Disproportionality analysis is reported in two ways: using an empirical Bayes estimator (EBE) or a reporting odds ratio (ROR). The ROR is a frequentist measure of association, similar to relative risk, using all reactions other than the one of interest as non-cases, with a lower bound of an ROR's 95% confidence interval (CI) > 1 reflecting a disproportionality signal (more ADRs than expected due to chance) [17,18,20,21]. Although easier to interpret than EBE, ROR has large sampling variability with low event counts, yielding large confidence intervals. The EBE is also a proxy of relative risk but is less susceptible to variability with low counts. In brief, the EBE assumes a Poisson distribution for each cell count with an unknown true mean, then fits prior and posterior distributions for each ratio, allowing calculation of posterior values. As EBEs are more valid for both small and large counts, the more conservative approach is to calculate the 5th percentile of the EBE for cardiac ADRs, using this value as a cutoff for significance [22]. We did so, then for any ADRs with significant EBEs we calculated the ROR and 95% CIs to allow for easier reporting and interpretation [23]. Analyses were performed using R (v3•6•1, RStudio) with an alpha of 0•05, correcting for multiple comparisons using the Bonferroni correction, and reported according to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) extension of the STrengthening Reporting of OBservational studies in Epidemiology (STROBE) guidelines [24].

2.1. Role of funding source

This study received no direct funding and no declared funders or interests had any input into or role in the research.

3. Results

We identified 278,848 total ADRs and 2433 cardiac ADRs associated with the included agents. GnRH agonists were associated with 122,284 overall ADRs (765 cardiac), abiraterone was associated with 29,776 ADRs (738 cardiac), and enzalutamide was associated 126,788 ADRs (930 cardiac). Most reports originated in Europe or the Americas, but all global VigiBase regions contributed reports. The first ADR was reported for a GnRH agonist in 1978, the first for abiraterone in 2009, and the first for enzalutamide in 2012, with the first cardiac ADRs reported in 1990, 2010, and 2013 respectively (see Figs. 1 and 2 for trends). Most ADRs were reported outside of a clinical trial (77%), with 1 in 3 reported

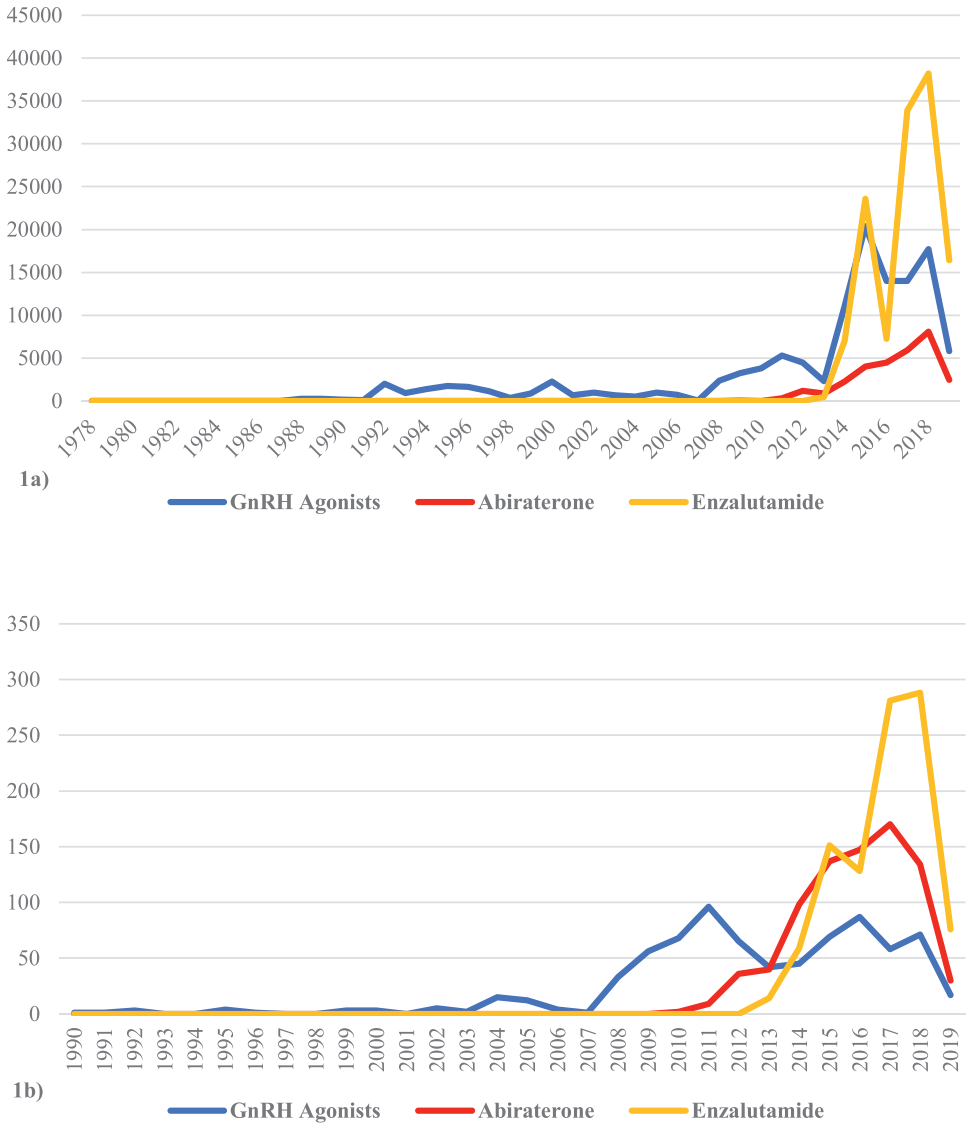

Fig. 1. Cumulative counts of any adverse drug events (ADRs) (1a) and cardiac ADRs (1b) for GnRH agonists, abiraterone, and enzalutamide over time.

by non-clinicians. Most patients were 65 or older. Among ADRs, MI (n = 696) and HF (n = 555) were the most frequent and also the most fatal, with ADR-associated death occurring in 27.7% of MI reports and 25.6% of HF reports. Full details can be found in Table 1.

Abiraterone-associated cardiac events were reported 56% more than the time-adjusted expected count based on all-other cause rates in the database, and 20% more than expected for GnRH agonists. Abiraterone and GnRH agonists were therefore associated with significantly increased odds of cardiac ADRs in VigiBase (ROR 1•59, 95% CI 1•48—1•71, and ROR 1•21, 95% CI 1•12—1•30 respectively). Abiraterone was associated with higher reporting rates of HF (ROR 3•02, 95% CI 2•60—3•51), MI (ROR 1•35, 95% CI 1•16—1•58), and was the only drug studied to show an association with arrhythmia (ROR 2•04, 95% CI 1•82—2•29). GnRH agonists were also associated with higher reporting of HF (ROR 2•06, 95% CI 1•76—2•41) and MI (ROR 1•80, 95% CI 1•61—2•03). Disproportionality analysis of VigiBase revealed no significant association of enzalutamide with increased odds of cardiac ADRs overall or any subtype of cardiac ADR. Full results for all studied reactions are in Table 2.

Time to onset of cardiac ADRs was more than one year after initiation of therapy for MI (mean 438 days, SD 824) and almost one year for HF (mean 353, SD 763). All three therapies had similar times to ADR onset for the studied cardiac complications, with more than 10% of HF and MI ADRs reported greater than 2 years after initiation of therapy. Cumulative incidence curves are displayed in Fig. 2, and all results remained significant after multiple comparison correction.

Reports of cardiac ADRs including more than one the drug as suspected agents occurred in 19•3% of cases (15•7% of GnRH ADRs, 20•9% of abiraterone ADRs, 21•3% of enzalutamide ADRs). We examined co-reported drugs occurring in more than 1% of reports for a given drug. We found that patients taking GnRH agonists and experiencing cardiac ADRs most commonly also reported taking bicalutamide (6•4%), zoledronic acid (4•4%), and docetaxel (1•3%), while reports for patients taking abiraterone also reported co-administration of prednisone (15•2%) and leuprolide (1•6%), and enzalutamide was co-administered with leuprolide (3•1%), docetaxel (1•3%), gabapentin (1•3%), tamsulosin (1•3%), pravastatin (1•1%), and hydrochlorothiazide (1•1%).

4. Discussion

Using the world's largest pharmacovigilance database, we identified important cardiac toxicities associated with androgen-modulating agents. Specifically, abiraterone increased the risk of cardiac adverse drug reactions, including myocardial infarction, heart failure and cardiac arrhythmias. GnRH increased the risk of myocardial infarction and heart failure. No increased cardiac risk was observed in patients on enzalutamide. The vast majority of reports were severe, and resulted in patient death in one in five reports of HF and MI.

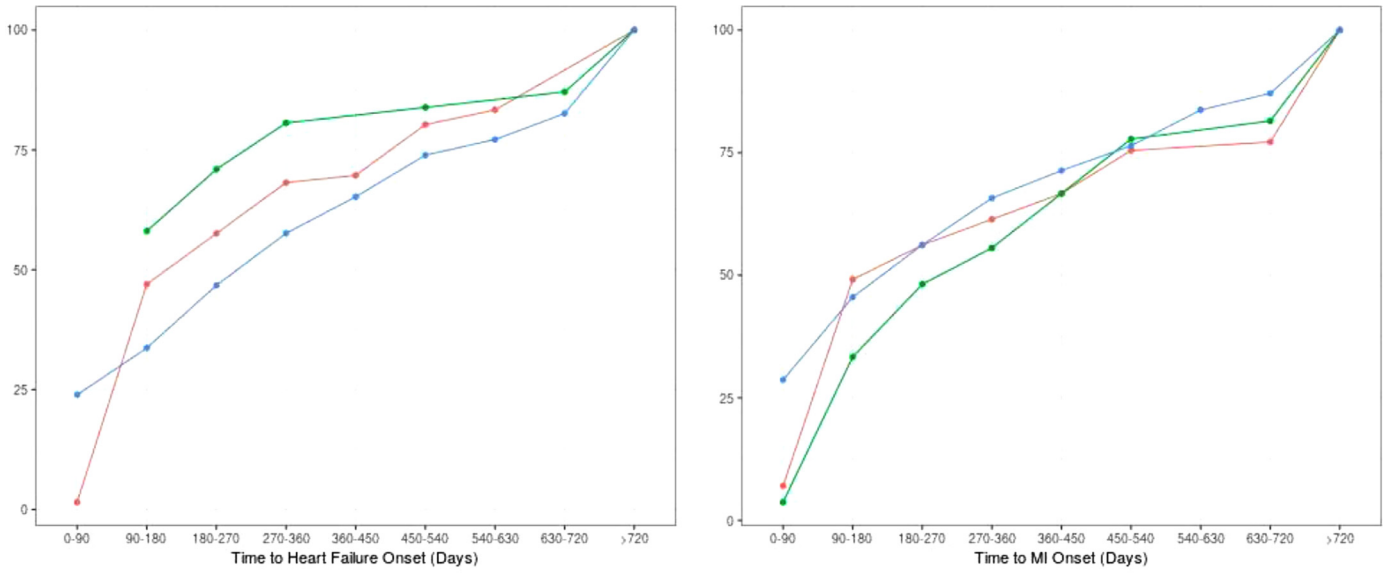

Fig. 2. Cumulative incidence of time to onset of heart failure and myocardial infarction (MI) from initiation of androgen deprivation therapy abiraterone (red), GnRH agonist monotherapy (blue), or enzalutamide (green). Enzalutamide's trend line begins in the 90–180 day period as its first HF event occurred after 90 days with none reported within 0–90 days of therapy initiation.

The finding of increased cardiac risk associated with GnRH agonists and with abiraterone therapy is consistent with prior work demonstrating an increase in cardiovascular events in patients on ADT, even in clinical trials where patients with significant cardiovascular disease were excluded [25-27]. It has also been shown that hypogonadal men who receive testosterone supplementation had a decreased risk of developing cardiac arrhythmias, indicating a protective effect of eugonadal levels [26]. Although enzalutamide is an extremely effective means of modulating androgen activity, it was not associated with an increased risk of cardiac ADRs in VigiBase's comprehensive international database.

The fact that we observed an increased cardiac risk both in patients receiving first-line ADT and in patients receiving androgen receptor signaling inhibitors via abiraterone, suggest that the increased risk is at least in part due to the androgen deprivation itself, not just the coadministration of abiraterone with corticosteroids. However, corticosteroids could certainly be contributing to the worsened overall cardiac risk profile, as is consistent with their association with hypertension [28], and could help explain the risk of HF specifically associated with abiraterone as compared to baseline ADT with a GnRH agonist. Abiraterone and corticosteroid coadministration has been linked to increased brain natriuretic peptide levels, evidence of volume overload consistent with chronic hypertension and eventual HF, as was seen in our study [9].

We did not find an increased reported risk of cardiac ADRs with enzalutamide, which is somewhat unexpected given that Grade III or higher cardiac ADRs were reported at low rates in some trials[29,30] involving the drug, although no significant differences were found in other prospective trials [6,31-33]. We note that prior studies have demonstrated that leuprolide decreases tissue levels of androgen, and that abiraterone plus leuprolide lower levels even more dramatically [34,35]. However, when enzalutamide is used in addition to

Table 1
Characteristics of cardiac ADRs associated with GnRH agonist, abiraterone, and enzalutamide therapy for prostate cancer in VigiBase (last accessed 11/23/2019).[a,b].

Adverse Drug Reaction	Arrythmia *N* = 736	Carditis *N* = 76	Heart Failure *N* = 617	MI *N* = 716	Other *N* = 386	Valvular *N* = 34
Region Reporting						
Americas	385 (56•0)	46 (62•2)	277 (49•9)	457 (65•7)	265 (69•4)	19 (55•9)
Europe	262 (38•1)	14 (18•9)	189 (34•1)	173 (24•9)	105 (27•5)	14 (41•2)
Australia	41 (6•0)	14 (18•9)	88 (15•9)	62 (8•9)	11 (2•9)	1 (2•9)
Asia	0 (0.0)	0 (0•0)	0 (0•0)	3 (0•4)	1 (0•3)	0 (0•0)
Africa	0 (0.0)	0 (0•0)	0 (0•0)	1 (0•1)	0 (0•0)	0 (0•0)
Eastern Mediterranean	0 (0.0)	0 (0•0)	1 (0•2)	0 (0•0)	1 (0•3)	0 (0•0)
Reported Outside Clinical Trial	534 (77•7)	64 (86•5)	431 (77•8)	490 (70•4)	284 (74•7)	25 (73•5)
Reported by non-healthcare worker	180 (26•8)	19 (26•0)	138 (26•4)	226 (34•6)	172 (46•5)	13 (39•4)
Age at onset (years)						
75 or older	309 (44•9)	36 (48•6)	311 (56•0)	299 (43•0)	142 (37•2)	20 (58•8)
65–74	154 (22•4)	15 (20•3)	90 (16•2)	143 (20•5)	72 (18•8)	5 (14•7)
45–64	37 (5•4)	1 (1•4)	14 (2•5)	46 (6•6)	23 (6•0)	0 (0•0)
unknown	188 (27•3)	22 (29•7)	140 (25•2)	208 (29•9)	145 (38•0)	9 (26•5)
Suspected drugs						
Only drug of interest	513 (74•4)	50 (64•9)	455 (82•0)	583 (83•8)	331 (86•6)	29 (85•3)
1 other drug	123 (17•9)	12 (16•2)	70 (12•6)	73 (10•5)	36 (9•4)	4 (11•8)
2+ other drugs	53 (7•7)	15 (18•9)	30 (5•4)	40 (5•7)	15 (3•9)	1 (2•9)
Time to ADR (days): mean (SD)	291•9 (568•5)	123•5 (136•7)	353•1 (762•7)	437•7 (823•6)	386•7 (671•7)	296•7 (283•1)
Severe ADR[c]	403 (69•7)	53 (80•3)	463 (86•9)	547 (83•0)	219 (68•0)	19 (61•3)
Death as outcome	51 (7•4)	3 (4•1)	142 (25•6)	193 (27•7)	41 (10•7)	5 (14•7)

[a] Values are reported as n (%) or n/N (%) unless otherwise indicated. MI = Myocardial Infarction.
[b] Percentage ratios may vary by category owing to missing data (i.e., 1 event may account for a different column percent in Region Reporting vs Time to ADR).
[c] Defined in VigiBase as life-threatening, leading to persistent or significant disability, birth defect, congenital anomaly, or to any other medically important condition, requiring hospitalization of causing death.

Table 2
Number of reports, expected number, empirical Bayes estimator (EBE), and reporting odds ratio for cardiac events in patients with prostate cancer taking a GnRH agonist but not abiraterone or enzalutamide, abiraterone and not enzalutamide, or enzalutamide and not abiraterone. EBE reports the lower (5th percentile) bounds of the posterior distribution of odds. ADRs with concordant significant findings for EBE and ROR in bolded italics.

	Count	Expected Count	Empirical Bayes Estimator (5th percentile)	Reporting Odds Ratio (95% CI)
Any cardiac event				
GnRH Agonist	765	637	1•13	1•21 (1•12–1•30)
Abiraterone	738	473	1•47	1•59 (1•48–1•71)
Enzalutamide	930	2148	0•41	NA
Heart Failure				
GnRH Agonist	160	78.0	1•77	2•06 (1•76–2•41)
Abiraterone	173	578	2•60	3•02 (2•60–3•51)
Enzalutamide	222	262•6	0•75	NA
Myocardial Infarction				
GnRH Agonist	290	161•9	1•61	1•80 (1•61–2•03)
Abiraterone	162	120•1	1•17	1•35 (1•16–1•58)
Enzalutamide	244	545•9	0•40	NA
Carditis				
GnRH Agonist	18	27•9	0•42	NA
Abiraterone	16	20•7	0•49	NA
Enzalutamide	40	94•1	0•32	NA
Arrythmia				
GnRH Agonist	167	193•4	0•76	NA
Abiraterone	290	143•5	1•82	2•04 (1•82–2•29)
Enzalutamide	231	652•1	0•32	NA
Valvular Dysfunction				
GnRH Agonist	10	21•7	0•26	NA
Abiraterone	10	16•1	0•35	NA
Enzalutamide	14	73•0	0•12	NA
Other				
GnRH Agonist	118	152•3	0•66	NA
Abiraterone	85	113•0	0•62	NA
Enzalutamide	179	513•5	0•31	NA

GnRH agonist therapy, tissue levels of androgen can rise [36]. One speculative hypothesis for the comparatively decreased odds of cardiac ADRs with enzalutamide is therefore that the higher levels of intracellular androgen are somehow cardioprotective. More work is clearly required to tease out the underlying mechanisms for the cardiac risk associated with some ADT.

We observed wide variability in the duration of time from initiation of therapy with GnRH agonist or abiraterone to the time of onset of the cardiac ADR. The majority of events occurred 6 months or more after initiation of therapy, with 10% or more occurring greater than 2 years after initiation of therapy (Table 1, Fig. 1). This finding stands in contrast to prior reports that heart failure and arrythmias usually occurred within the first 3 months of abiraterone treatment [9]. We observed even longer mean times to onset of MI or HF, with the majority occurring after more than 1 year of therapy. Additionally, two thirds of cardiac ADRs were reported outside a clinical trial, and one third. These points underscore the importance of pharmacovigilance studies using databases such as VigiBase. They are one of the only methods available with long enough time frames to capture delayed ADRs, and unlike the tightly selected patient cohorts in clinical trials, reflect a truly 'real world' patient population, with no exclusion criteria limiting generalizability.

One limitation of this work is that VigiBase reports originate from a variety of sources and the probability that an adverse event is drug related is not the same in all cases, nor can more granular information be collected about each case. The lack of reliable comorbidity data weakens our ability to compare the two groups, although this is mitigated by the lack of evidence that patients with more significant cardiac risks are preferentially prescribed abiraterone versus enzalutamide. Reporting bias is possible, but we identified no evidence supports bias in either direction. The variety report sources is both a strength and weakness, as non-clinical personnel may report detailed clinical information less reliably. Some ADRs are also likely not reported to national authorities for inclusion in VigiBase, but this is mitigated by the breadth of data collection (130+ countries) and sheer number of reports, enabling signal capture for rare ADRs and broad, global generalizability. Missing information and lack of access to the database population intrinsic with a global pharmacovigilance database limited our ability to adjust for duration of therapy, comorbidities (which would have required imputation of questionable validity via co-administered medications), setting (castration resistant or hormone sensitive), or sequencing (abiraterone before enzalutamide or vice versa). This specifically limited our ability to perform regression analysis to describe the effect of covariates on ADRs. Future studies, either prospective or of more granularly detailed databases, will be required to tease out these associations. We also note that although more than four in five reported cardiac ADRs were isolated to the medication of interest, the remainder had one or more additionally reported suspect medications, although the most frequently co-reported drugs are common prostate cancer-related medications (docetaxel chemotherapy, steroids for abiraterone, zoledronic acid, etc.).

Statistically we must emphasize that although RORs are functionally equivalent to relative risk, one cannot then assume that RORs less than one indicate a protective effect. By only calculating RORs for significant EBEs we hope to lessen the chances of spurious conclusions given the unfamiliar nature of pharmacovigilance statistics to many clinicians. Lastly, the exact denominator of patients exposed to GnRH agonist/antagonist therapy cannot be ascertained, requiring use of EBE and ROR, as is common in the pharmacovigilance literature [20].

Despite its limitations, disproportionality analysis of spontaneous adverse drug reaction reports is vital to monitor the safety of drugs in the post-marketing space [37]. Many ADT trials exclude patients with high cardiac risk profiles, as these patients are known to be at significant risk of cardiac events when on ADT [3,4]. As these patients still may receive ADT via GnRH agonists, GnRH antagonists, abiraterone, or enzalutamide outside the confines of a trial, the real-world data provided by comparative pharmacovigilance studies provide critical information for the practicing clinician considering two drugs with similar benefit.

Using disproportionality analysis, we found increased cardiac risks, especially for myocardial infarction and heart failure, for abiraterone and GnRH agonists, but not for enzalutamide. The worsened cardiac

risk profile of abiraterone compared to GnRH agonists and the absence of increased cardiac reporting risk for enzalutamide may suggest that the mechanism of androgen modulation plays a critical but as-yet undefined role in the development of cardiac toxicities, and deserves future study. Our data may preliminarily suggest that a patient with significant cardiac comorbidities may be better suited for therapy with enzalutamide over abiraterone. At a minimum they provide an important context for patient and provider education as to the cardiac risk associated with both traditional and newer forms of ADT.

Data sharing agreement

VigiBase, the WHO global database of individual case safety reports, can be made available to anyone with a health profession degree (physician, dentist, nurse, pharmacist) via request at subscription@who-umc.org – the authors of this manuscript are unable to share the rare data but can share source code with approved VigiBase users via appropriate request to the corresponding author.

Author contributions

All authors contributed to conceptualization and writing of all drafts and approved the final draft. Dr. Nabi assisted with data curation, Mrs. Marchese performed the formal analysis, as informed by the methodology developed by Drs. Cone, Reese, and Trinh and Mrs. Marchese. Drs. Trinh, Cone, and Marchese had access to and verified the underlying data.

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Declaration of Competing Interest

QDT reports personal fees from Astellas, Bayer, Janssen, Insightec and Intuitive Surgical, as well as a Health Services Research pilot test grant from the Defense Health Agency, and an unrestricted educational grant from the Vattikuti Urology Institute. Rana McKay reports advisory board roles for Novartis, Exelixis, Pfizer/Astellas, Bristol-Myers Squibb, and Johnson and Johnson. No other authors report disclosures.

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References

[1] Mohler JL, Antonarakis ES. NCCN guidelines updates: management of prostate cancer. J Natl Compr Canc Netw 2019;17(5.5):583–6.
[2] Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 2008;26(28):4563–71.
[3] Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20(5):686–700.
[4] Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 Chaarted trial. J Clin Oncol 2018;36(11):1080–7.
[5] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995–2005.
[6] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187–97.
[7] Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014;65(3):565–73.
[8] Iacovelli R, Ciccarese C, Bria E, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer 2018;16(3):e645–e53.
[9] Bretagne M, Lebrun-Vignes B, Pariente A, et al. Heart failure and atrial tachyarrhythmia on abiraterone: a pharmacovigilance study. Arch Cardiovasc Dis 2019.
[10] Janssen. ZYTIGA (abiraterone acetate): highlights of prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210308s000lbl.pdf: Food and Drug Administration; 2018.
[11] Pfizer. XTANDI (enzalutamide): highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf : Food and Drug Administration; 2019.
[12] de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381(26):2506–18.
[13] Attard G, Reid AH, Auchus RJ, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab 2012;97(2):507–16.
[14] Culig Z. Molecular mechanisms of enzalutamide resistance in prostate cancer. Curr Mol Biol Rep 2017;3(4):230–5.
[15] Satariano WA, Ragland KE, Van Den Eeden SK. Cause of death in men diagnosed with prostate carcinoma. Cancer 1998;83(6):1180–8.
[16] Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J 2008;42(5):409–19.
[17] Prostate Cancer Therapeutics Market Analysis By Drugs (Zytiga, Gonax, Lupron, Zoladex, Decapeptyl, Eligard, Vantas, Casodex, Xtandi, Taxotere, Jevtana, Provenge, Xofigo), By Region, And Segment Forecasts, 2018 - 2025: grand View Research, 2017.
[18] Bohm R, von Hehn L, Herdegen T, et al. OpenVigil FDA - inspection of U.S. American adverse drug events pharmacovigilance data and novel clinical applications. PLoS One 2016;11(6):e0157753.
[19] Chakraborty BS. Pharmacovigilance: a data mining approach to signal detection. Indian J Pharmacol 2015;47(3):241–2.
[20] van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Saf 2003;26(5):293–301.
[21] Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009;18(6):427–36.
[22] Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol 2019;74(13):1667–78.
[23] DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 1999;53(3).
[24] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7.
[25] Martin-Merino E, Johansson S, Morris T, Garcia Rodriguez LA. Androgen deprivation therapy and the risk of coronary heart disease and heart failure in patients with prostate cancer: a nested case-control study in UK primary care. Drug Saf 2011;34(11):1061–77.
[26] Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation. J Am Heart Assoc 2017;6(5).
[27] Bhatia N, Santos M, Jones LW, et al. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate cancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. Circulation 2016;133(5):537–41.
[28] Grossman E, Messerli FH. Drug-induced hypertension: an unappreciated cause of secondary hypertension. Am J Med 2012;125(1):14–22.
[29] Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol 2017;71(2):151–4.
[30] Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016;17(2):153–63.
[31] Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34(18):2098–106.
[32] Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37(32):2974–86.
[33] Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381(2):121–31.
[34] Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol 2014;32(33):3705–15.
[35] Zang T, Taplin ME, Tamae D, et al. Testicular vs adrenal sources of hydroxy-androgens in prostate cancer. Endocr Relat Cancer 2017;24(8):393–404.
[36] Efstathiou E, Titus M, Wen S, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. Eur Urol 2015;67(1):53–60.
[37] Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol 2011;72(6):905–8.