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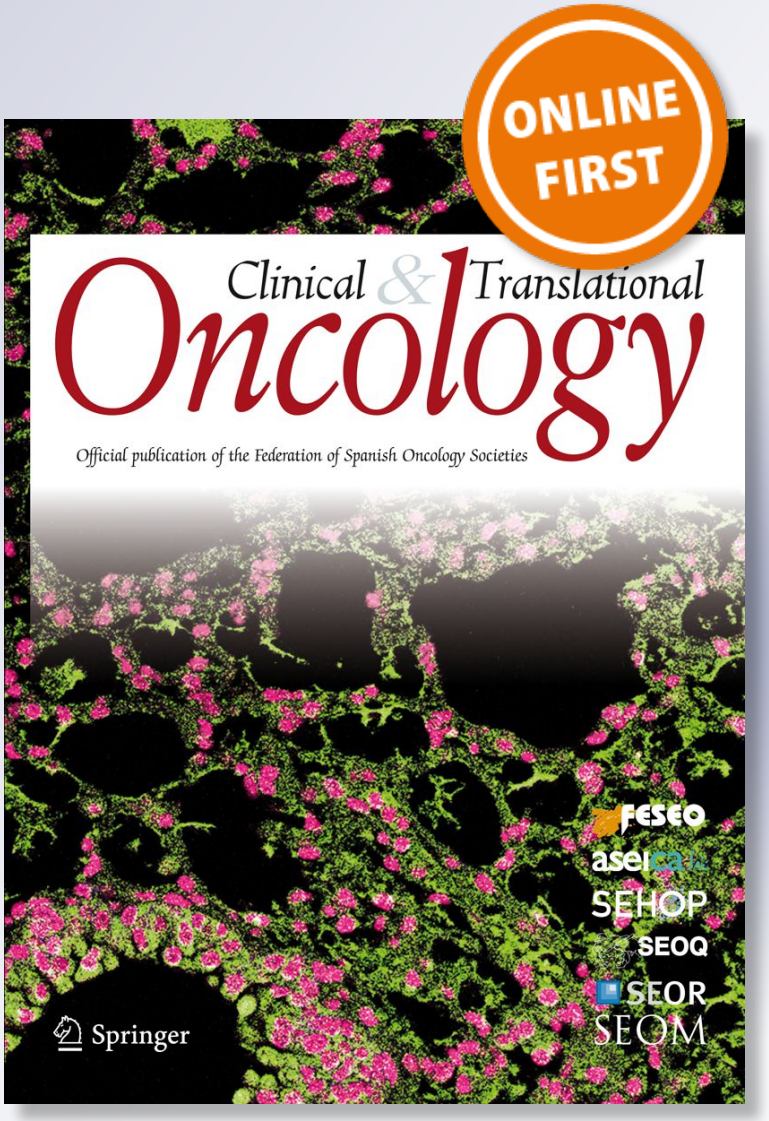

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RESEARCH ARTICLE

Effectiveness, safety and cost of abiraterone acetate in patients with metastatic castration-resistant prostate cancer: a real-world data analysis

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Abstract

Purpose New therapies with diverse mechanisms of action are available for metastatic castration-resistant prostate cancer (mCRPC). This study aims to evaluate the effectiveness, safety and cost of abiraterone acetate (AA) in patients with mCRPC.

Materials and methods Observational retrospective cohort study in which mCRPC patients who initiated AA between January 1, 2012 and December 31, 2017, were included. The patients were followed-up until death or March 31, 2018. Demographic, clinical and economic data were collected from the corporate electronic information systems. Survival distributions were estimated using the Kaplan–Meier method and compared using the log-rank test.

Results A total of 69 mCRPC patients were started on AA, of whom 18 (26.1%) received prior chemotherapy (post-CT) and 51 (73.9%) did not receive it (CT-naïve). A PSA decline of ≥ 50% was achieved in five (27.8%) post-CT and 32 (62.7%) CT-naïve patients ($p = 0.011$). Median time to PSA progression, progression-free survival (PFS) and overall survival (OS) were 4.4/7.9 months ($p = 0.003$), 5.1/7.5 months ($p = 0.034$) and 12.1/21.3 months ($p = 0.119$), respectively, for post-CT/CT-naïve patients. Treatment-related adverse events (AEs) occurred in 10 (55.6%) post-CT and 11 (21.6%) CT-naïve patients ($p = 0.007$). The most common AEs were hypokalaemia (11.6%), hypertension (8.7%) and fatigue (5.8%). The cost per median PFS month and per median OS month was €2818.4/€2784.3 and €1187.9/€980.4 for post-CT/CT-naïve patients, respectively.

Conclusions CT-naïve patients treated with AA obtained a better clinical benefit in terms of effectiveness, safety and cost-effectiveness ratio than post-CT patients. The effectiveness outcomes were poorer than those reported previously in the clinical trial setting.

Keywords Abiraterone acetate · Castration-resistant prostatic cancer · Chemotherapy · Cost-effectiveness analysis · Safety · Survival analysis

Introduction

Prostate cancer causes about 5.5% of all deaths from cancer and 1.5% of the total deaths from any cause in the European Union [1]. Metastatic castration-resistant prostate cancer (mCRPC) is the disease stage when biochemical or radiologic progression occurs despite maintaining adequate castrate level of serum testosterone below 50 ng/dl [2].

Docetaxel was the first treatment that showed a survival improvement of mCRPC and for nearly a decade, it was the only available option used to treat this patient population [3]. Nevertheless, new chemotherapeutic, immunotherapeutic and hormonal agents have been incorporated in clinical practice in recent years. In particular, abiraterone acetate (AA), a drug that blocks endogenous androgen synthesis by inhibiting the CYP17 enzyme, was associated in the clinical trial setting with significant survival advantage over placebo in both mCRPC patients pre-treated with docetaxel and in chemotherapy-naïve mCRPC patients [4, 5].

AA has been available since 2012 for mCRPC patients under Valencian Health System coverage via the Program of Medicines with High Health and Economic Impact [6].

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In the post-approved setting, several studies have reported results of the effectiveness and safety of AA [7–10]. Likewise, previous cost-effectiveness analyses (CEAs) of mCRPC treatments were conducted based on efficacy data from randomized clinical trials (RCT) [11, 12]. However, to the best of our knowledge, no study has evaluated the cost-effectiveness of AA using real-world data of both dimensions.

The aim of this study was to analyse the impact of AA on health outcomes in terms of effectiveness, safety and cost in mCRPC patients at the Health Department of Gandia (Valencia, Spain).

Materials and methods

Design and population of the study

An observational retrospective cohort study in which mCRPC patients who were referred to the Pharmacy Department and initiated AA between January 1, 2012 and December 31, 2017, were included. Treatment groups were defined as patients who received AA without prior chemotherapy (CT-naïve) and those who received AA after chemotherapy (post-CT). The follow-up period was defined as the start date of AA until death or March 31, 2018. This study was approved by the Teaching, Investigation and Ethics Commission of Gandia Health Department.

Data sources

Data were collected retrospectively from the corporate electronic information systems Abucasis (the ambulatory medical history), Farmasyst (the pharmacotherapeutic history), GestLab (the laboratory results application), Orion Clinic (the hospital electronic medical history) and Orion Logis (the purchase and storage management programme). The necessary data for the analysis were recorded in a database designed for this purpose using Microsoft Access 2010 SP2. This file is subject to safety requirements established by Law 15/1999 and Royal Decree 1720/2007 of personal data protection.

Study variables

Information about demographics, clinical outcomes, ongoing medication, laboratory and diagnostic tests was collected. Pharmacy electronic dispensing records were checked to evaluate adherence to AA and it was calculated as the sum of the dispensed units, divided by the total prescribed units during the study period. Prostate-specific antigen doubling time (PSA-DT) was calculated considering the three consecutive PSA levels before AA.

For the effectiveness analysis, PSA response rate and time to PSA progression were calculated according to the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria [13]. Progression-free survival (PFS) was defined as time from the onset of AA to the first radiological (spread or new metastasis) or clinical (worsening of performance status (PS) or pain) event or death for any reason. Radiographic controls were performed with CT scan when clinically indicated and PS was measured by the Eastern Cooperative Oncology Group (ECOG). Overall survival (OS) was calculated in two different manners: from the initial diagnosis of prostate cancer and from AA initiation to death for any reason. Additional effectiveness outcome was the rate of objective response based on RECIST criteria [14].

The adverse events (AEs) related to AA treatment were graded according to the standards of the Common Terminology Criteria for Adverse Events, version 4.0 [15].

The costs per median PFS month and per median OS month were calculated following the method used by Pilon et al. [11]. Only pharmacological costs (euros (€) 2018) were taken into account. Other direct costs were not considered, such as the cost of patient management or the handling of AEs. Cost of AA was obtained from the pharmaceutical provider for our institution, not reflecting any type of discount, and it was expressed as selling price plus 4% VAT. A multivariate sensitivity analysis (MSA) was performed to evaluate the impact on cost per median PFS month and per OS month. In this MSA the monthly cost and the treatment duration were varied simultaneously at a rate of €50 and 2 months within a range of 2200–3200 euros and 2–36 months, respectively.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR). Relative and absolute frequencies were used for categorical variables. Differences between treatment groups in patient characteristics and outcomes were analysed using Mann–Whitney U test and Chi-square tests for continuous and categorical variables, respectively. Median treatment duration, time to PSA progression and the survival distributions (PFS and OS) were estimated using the Kaplan–Meier method and differences among groups were compared using the log-rank test. The log-rank test was also used to assess the PFS and OS as a function of some factors which have been previously related to these survival outcomes [7, 8], but we also considered the adherence to AA as an additional factor. All tests were two-sided with a statistical confidence level of 95% and were performed using IBM SPSS Statistics for Windows, version 19.0 (Armonk, NY).

Results

Overall, 69 mCRPC patients were started on AA 1000 mg/day plus prednisone 10 mg/day between January 1, 2012 and December 31, 2017. Of these patients, 18 (26.1%) were post-CT and 51 (73.9%) were CT-naïve. Patient baseline characteristics are shown in Table 1. Other than age, multiple metastasis, previous radiotherapy and PSA baseline, there were no statistically significant differences in the distribution of these characteristics between treatment groups.

Table 1 Demographic and clinical characteristics of the patients according to treatment group

	All patients ($n=69$)	Post-CT ($n=18$)	CT-naïve ($n=51$)	p value
Age, years				
Median (IQR)	78.2 (71.4–82.0)	71.7 (67.4–76.9)	79.9 (75.2–83.1)	< 0.001*
≥ 75, *n* (%)	44 (63.8)	5 (27.8)	39 (76.5)	< 0.001†
ECOG performance status, *n* (%)				
0–1	61 (88.4)	15 (83.3)	46 (90.2)	0.421†
≥ 2	8 (11.6)	3 (16.7)	5 (9.8)	
Initial Gleason score, *n* (%)				
< 8	28 (40.6)	9 (50.0)	19 (37.2)	0.344‡
≥ 8	33 (47.8)	7 (38.9)	26 (51.0)	0.377‡
Unknown	8 (11.6)	2 (11.1)	6 (11.8)	1.000†
Metastasis on initial diagnosis, *n* (%)	19 (27.5)	4 (22.2)	15 (29.4)	0.761†
Sites of metastasis, *n* (%)				
Bone	54 (78.3)	17 (94.4)	37 (72.5)	0.093†
Nodes	37 (53.6)	11 (61.1)	27 (52.9)	0.549‡
Visceral (lung or liver)	6 (8.7)	2 (11.1)	4 (7.8)	0.647†
Multiple sites	25 (36.2)	10 (55.6)	15 (29.4)	0.047‡
Cancer therapy before AA, *n* (%)				
Hormonal	69 (100.0)	18 (100.0)	51 (100.0)	–
Surgery (RP, TR)	19 (27.5)	6 (33.3)	13 (25.5)	0.550†
Radiotherapy	18 (26.1)	10 (55.6)	8 (15.7)	0.002†
Chemotherapy	–	18 (100.0)	–	–
ADT response time, months, median (IQR)	31.3 (13.2–67.9)	28.8 (9.6–64.0)	31.3 (13.6–78.9)	0.382*
Previous CT regimens, *n* (%)				
1 (DT)	–	15 (83.3)	–	–
2 (ES → DT)	–	2 (11.1)	–	–
3 (DT → MTX → CBZ)	–	1 (5.6)	–	–
Time from initial diagnosis to AA, years, median (IQR)	3.5 (1.5–8.2)	5.6 (2.4–7.9)	3.0 (1.3–8.3)	0.507*
PSA level before AA, ng/ml, median (IQR)	46.4 (10.8–88.9)	71.4 (42.2–190.0)	31.4 (9.4–76.2)	0.022*
PSA doubling time, months, median (IQR)	3.0 (2.1–5.0)	2.7 (1.6–5.2)	3.1 (2.1–5.0)	0.750*
Medical history, *n* (%)				
Congestive heart failure	4 (5.8)	0 (0.0)	4 (7.8)	0.566†
Diabetes	17 (24.6)	2 (11.1)	15 (29.4)	0.203†
Hypertension	52 (75.4)	13 (72.2)	39 (76.5)	0.756†
Vascular disease (MI, PAD, stroke)	12 (17.4)	2 (11.1)	10 (19.6)	0.718†
Renal disease	19 (27.5)	4 (22.2)	15 (29.4)	0.761†
Atrial fibrillation	19 (27.5)	2 (11.1)	17 (33.3)	0.123†
Dyslipidemia	38 (55.1)	9 (50.0)	29 (56.9)	0.615‡
Liver disease	6 (8.7)	1 (5.6)	5 (9.8)	1.000†

AA abiraterone, *ADT* androgen deprivation therapy, *CBZ* cabazitaxel, *CT* chemotherapy, *DT* docetaxel, *ECOG* Eastern Cooperative Oncology Group, *ES* estramustine, *IQR* interquartile range, *MI* myocardial infarction, *MTX* mitoxantrone, *PAD* peripheral arterial disease, *PSA* prostate-specific antigen, *RP* radical prostatectomy, *TR* transurethral resection

*Estimated using Mann–Whitney *U* test

†Estimated using Fisher's exact test

‡Estimated using Pearson's Chi-squared test

Treatment duration

At the time of the last follow-up, one (5.6%) post-CT and 14 (27.5%) CT-naïve patients were still on AA, of whom one (6.7%) had complete response, three (20.0%) partial response and 11 (73.3%) stable disease. Median treatment duration was 5.3 months (IQR 2.4–15.7) and 7.7 months (IQR 4.1–22.8) for post-CT and CT-naïve group ($p=0.146$), respectively. Five (27.8%) post-CT and six (11.8%) CT-naïve patients received AA for less than 12 weeks. AA was stopped in eight (44.4%) post-CT and 31 (60.8%) CT-naïve patients due to disease progression (Table 2).

PSA response

A higher proportion of CT-naïve patients compared to post-CT patients achieved a decline in PSA of ≥ 50% at 12 weeks (56.9% vs. 27.8%, $p=0.034$) and at some point after 12 weeks (62.7 vs. 27.8%, $p=0.011$) (Table 2). A progressive PSA upsurge was observed since AA initiation in six (33.3%) post-CT and seven (13.7%) CT-naïve patients ($p=0.086$), with a median PSA increase of 155.6% (IQR 104.1–254.9) and 113.9% (IQR 76.9.4–544.6) at 12 weeks ($p=0.886$), respectively. The median time to PSA progression was 4.4 months (IQR 3.4–6.7) in post-CT and 7.9 months (IQR 4.8–18.0) in CT-naïve patients ($p=0.003$) (Fig. 1a). Prednisone was replaced by dexamethasone in 15 (21.7%) patients, of whom 5 (33.3%) had a biochemical response.

Table 2 Treatment and clinical outcomes of the patients according to treatment group

	All patients ($n=69$)	Post-CT ($n=18$)	CT-naïve ($n=51$)	p value
Follow-up, months, median (IQR)	12.1 (5.5–21.4)	11.5 (3.1–19.9)	13.3 (6.1–21.8)	0.482*
Time on AA, months, median (IQR)	7.0 (3.7–16.6)	5.3 (2.4–15.7)	7.7 (4.1–22.8)	0.146†
Adherence to AA, *n* (%)				
≥ 80%	61 (88.4)	15 (83.3)	46 (90.2)	0.421‡
< 80%	8 (11.6)	3 (16.7)	5 (9.8)	
Bone-targeted therapy, *n* (%)				
Denosumab	19 (27.5)	2 (11.1)	17 (33.3)	0.123‡
Zoledronic acid	18 (26.1)	13 (72.2)	5 (9.8)	< 0.001‡
≥ 50% PSA decline, *n* (%)				
At 12 weeks	34 (49.3)	5 (27.8)	29 (56.9)	0.034#
At any time point after 12 weeks	37 (53.6)	5 (27.8)	32 (62.7)	0.011#
Maximal PSA decline, %, median (IQR)	82.6 (58.4–93.8)	80.7 (30.3–92.5)	82.9 (58.9–95.7)	0.369*
Hospital admission, *n* (%)	18 (28.6)	7 (38.9)	13 (25.5)	0.281#
Length of stay, days, median (IQR)				
Any cause	5.5 (2.0–10.0)	7.0 (5.0–17.0)	5.0 (2.0–10.0)	0.339*
Related to prostate cancer	5.0 (2.3–8.8)	6.0 (1.0–17.0)	5.0 (2.5–6.5)	0.238*
Cause of AA completion, *n* (%)				
PSA and RX or CL progression	23 (33.3)	4 (22.2)	19 (37.3)	0.245#
PSA, RX and CL progression	6 (8.7)	4 (22.2)	2 (3.9)	0.036‡
RX and/or CL progression	8 (11.6)	0 (0.0)	8 (15.7)	0.101‡
PSA progression	2 (2.9)	0 (0.0)	2 (3.9)	1.000‡
Treatment-related AEs	2 (2.9)	2 (11.1)	0 (0.0)	0.065‡
Death	13 (18.8)	7 (38.9)	6 (11.8)	0.030‡
Post-AA therapy, *n* (%)				
Docetaxel	20 (29.0)	4 (22.2)	16 (31.4)	0.462#
Symptomatic treatment	20 (29.0)	6 (33.3)	14 (27.5)	0.636#
Radium-223	1 (1.4)	0 (0.0)	1 (2.0)	1.000‡

AA abiraterone, *AEs* adverse events, *CL* clinical, *CT* chemotherapy, *IQR* interquartile range, *PSA* prostate-specific antigen, *RX* radiographic

*Estimated using Mann–Whitney U test

†Estimated using Kaplan–Meier method

‡Estimated using Fisher's exact test

#Estimated using Pearson's Chi-squared test

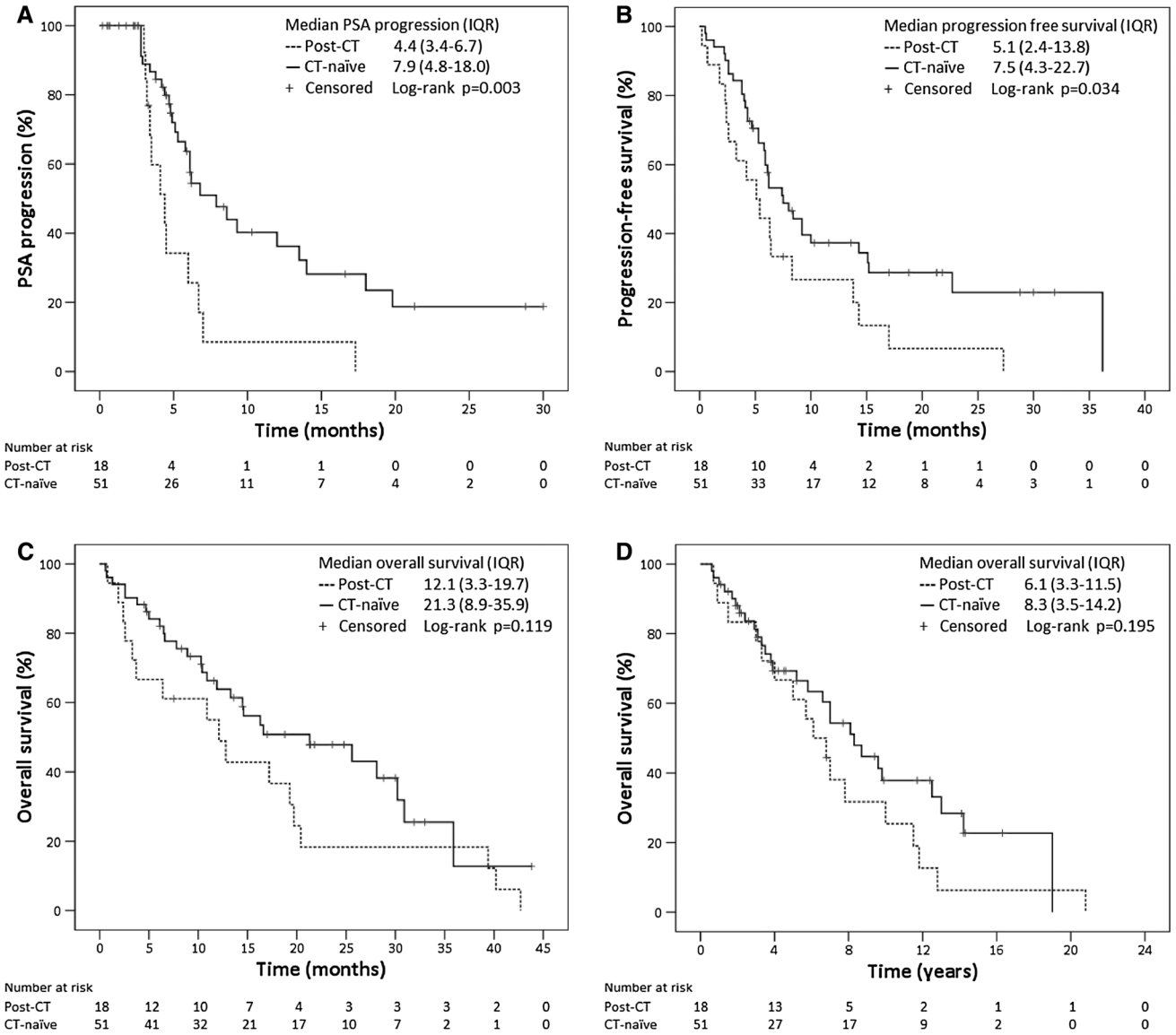

Fig. 1 Time to PSA progression (**a**), progression-free survival (**b**), overall survival from abiraterone initiation (**c**) and overall survival from the initial diagnosis for mCRPC patients treated with abiraterone with (post-CT) or without (CT-naïve) prior chemotherapy

Survival

By the last follow-up, 17 (94.4%) post-CT and 28 (54.9%) CT-naïve patients had died. Overall, the median PFS, OS from AA initiation and OS from the initial diagnosis were 6.3 months (IQR 4.0–15.2), 16.6 months (IQR 6.5–35.9) and 7.0 years (IQR 3.5–12.8), respectively. Figure 1b–d shows survival curves for each treatment group.

In univariate analysis (Table 3), ECOG-PS was significantly determinant of the PFS and OS in the post-CT group as was PSA response in the CT-naïve group. Time on AA was able to predict OS in both groups.

Safety

Treatment-related AEs occurred in 10 (55.6%) post-CT and 11 (21.6%) CT-naïve patients ($p = 0.007$). Hypokalaemia (11.6%), hypertension (8.7%) and fatigue (5.8%) were the most common AEs and the incidence of hypokalaemia and nausea/vomiting was higher in post-CT patients than in CT-naïve patients (Table 4). One post-CT patient was admitted for vomiting grade 3, one CT-naïve patient for hypokalaemia grade 4 and one CT-naïve patient for atrial flutter grade 3. The information about those hospitalisations occurred during AA treatment is shown in Table 2.

Owing to AEs, the initial dose of AA was reduced or discontinued in five (27.8%) post-CT and two (3.9%) CT-naïve

Table 3 Univariate analysis (log-rank test) of progression-free survival and overall survival in mCRPC patients treated with abiraterone

Variables	Post-CT				CT-naïve			
	PFS (months)		OS (months)		PFS (months)		OS (months)	
	Median (IQR)	*p* value	Median (IQR)	*p* value	Median (IQR)	*p* value	Median (IQR)	*p* value
Age < 75 years	5.6 (2.4–13.8)	0.937	19.3 (3.3–39.4)	0.194	7.2 (4.1–NR)	0.495	30.2 (10.4–30.9)	0.252
Age ≥ 75 years	5.4 (2.6–8.3)		12.1 (10.9–12.8)		6.5 (4.3–15.2)		16.3 (6.6–35.9)	
Gleason score < 8	6.4 (2.6–13.8)	0.685	12.8 (6.4–39.4)	0.459	15.1 (6.2–36.2)	0.120	30.2 (16.3–NR)	0.067
Gleason score ≥ 8	5.1 (1.8–6.3)		12.1 (3.3–19.7)		5.9 (3.0–14.3)		14.5 (6.6–30.9)	
ECOG-PS < 2	6.3 (3.3–13.8)	< 0.001	17.2 (6.4–20.4)	0.001	7.5 (4.7–22.7)	0.923	21.3 (8.9–30.9)	0.683
ECOG-PS ≥ 2	0.7 (0.2–1.8)		1.9 (0.8–3.7)		4.0 (3.8–NR)		10.9 (6.6–NR)	
No visceral metastasis	4.2 (2.3–6.4)	0.393	10.9 (2.6–19.7)	0.116	7.4 (4.1–22.7)	0.177	21.3 (7.8–35.9)	0.669
Visceral metastasis	13.8 (13.8–14.3)		19.3 (19.3–42.7)		NR		NR	
ADT-R ≥ 10 months	6.3 (4.2–13.8)	0.348	19.3 (6.4–39.4)	0.095	8.4 (5.3–22.7)	0.123	25.6 (8.9–35.9)	0.141
ADT-R < 10 months	2.6 (2.3–3.3)		3.7 (3.3–12.8)		4.0 (2.6–6.2)		13.3 (6.6–30.9)	
PSA prior AA < 20 ng/ml	14.3 (2.3–27.3)	0.153	40.2 (2.4–42.7)	0.064	10.0 (8.0–36.2)	0.069	NR (10.4–NR)	0.250
PSA prior AA ≥ 20 ng/ml	5.1 (2.4–8.3)		12.1 (3.3–19.3)		5.9 (4.0–15.2)		14.6 (7.8–30.9)	
PSA-DT ≥ 2 months	5.1 (2.6–13.8)	0.766	17.2 (3.7–20.4)	0.849	9.2 (5.3–36.2)	0.094	25.6 (10.3–35.9)	0.101
PSA-DT < 2 months	6.4 (2.3–8.3)		6.4 (2.4–10.9)		4.3 (2.6–8.4)		13.3 (5.0–16.6)	
PSA decline ≥ 50%	13.8 (8.3–14.3)	0.178	19.3 (10.9–20.4)	0.102	14.3 (6.1–36.2)	< 0.001	30.9 (14.6–35.9)	< 0.001
PSA decline < 50%	3.3 (2.3–5.4)		6.4 (2.6–17.2)		4.0 (2.3–7.5)		10.4 (2.6–16.6)	
Adherence ≥ 80%	5.1 (2.3–8.3)	0.083	10.9 (2.6–19.3)	0.110	8.4 (4.1–36.2)	0.199	25.6 (8.9–35.9)	0.164
Adherence < 80%	27.3 (4.2–27.3)		39.4 (39.4–40.2)		6.2 (5.3–7.5)		11.9 (10.4–14.5)	
AA duration ≥ 12 weeks	NA	NA	19.3 (12.1–39.4)	< 0.001	NA	NA	25.6 (10.9–35.9)	< 0.001
AA duration < 12 weeks			2.4 (1.9–2.6)				1.3 (0.7–2.6)	

AA abiraterone, *ADT-R* androgen deprivation therapy response, *CT* chemotherapy, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *IQR* interquartile range, *NA* not applicable, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *PSA* prostate-specific antigen, *PSA-DT* prostate-specific antigen doubling time

Table 4 Detected abiraterone-related adverse events

Cases, *n* (%)	All grades				Grade 3 and 4			
	All patients (*n* = 69)	Post-CT (*n* = 18)	CT-naïve (*n* = 51)	*P* value*	All patients (*n* = 69)	Post-CT (*n* = 18)	CT-naïve (*n* = 51)	*P* value*
ACS	1 (1.4)	0 (0.0)	1 (2.0)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
AST elevation	1 (1.4)	0 (0.0)	1 (2.0)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
Atrial flutter	1 (1.4)	0 (0.0)	1 (2.0)	1.000	1 (1.4)	0 (0.0)	1 (2.0)	1.000
Diarrhoea	1 (1.4)	0 (0.0)	1 (2.0)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
Fluid retention	3 (4.3)	1 (5.6)	2 (3.9)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	–
Fatigue	4 (5.8)	3 (16.7)	1 (2.0)	0.052	0 (0.0)	0 (0.0)	0 (0.0)	–
Hypertension	6 (8.7)	2 (11.1)	4 (7.8)	0.647	5 (7.2)	2 (11.1)	3 (5.9)	0.600
Hypokalaemia	8 (11.6)	5 (27.8)	3 (5.9)	0.024	5 (7.2)	3 (16.7)	2 (3.9)	0.107
Nausea/vomiting	3 (4.3)	3 (16.7)	0 (0.0)	0.016	1 (1.4)	1 (5.6)	0 (0.0)	0.261
Stomach pain	1 (1.4)	1 (5.6)	0 (0.0)	0.261	0 (0.0)	0 (0.0)	0 (0.0)	–

ACS acute coronary syndrome, *AST* aspartate aminotransferase, *CT* chemotherapy

*Estimated using Fisher's exact test

patients ($p = 0.011$), of whom AA was stopped in one post-CT patient AA due to vomiting grade 3 and one post-CT patient due to stomach pain and nausea grade 2.

Costs

The estimated monthly treatment cost for AA was €2712.0. The cost per median PFS month was €2818.4, €2784.3 and €3013.3 for post-CT patients, CT-naïve patients and overall cohort, respectively, whereas their respective costs per median OS (from AA initiation to death) month were €1187.9, €980.4 and €1143.6. Figure 2a, b shows the MSA using median PFS and median OS of the overall cohort and according to the monthly cost and the treatment duration.

Discussion

Our study, developed in the context of a quality improvement programme of healthcare, has reported the effectiveness, safety and costs of AA in routine clinical practice. In the setting of mCRPC, the best sequence of available treatments to achieve the maximal clinical benefit is a dilemma of emerging interest. Surprisingly, despite the early adoption of AA by the Valencian Health System in 2012, only 26.1% of our patients used it following a chemotherapeutic regimen; most received AA after androgen deprivation therapy because some of them were not candidates for chemotherapy as a first-line choice owing to medical criteria and others because AA was considered the best treatment following COU-AA-302 results [5].

A

Monthly treatment cost (€) \ Treatment duration (months)	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
2200	698,4	1396,8	2095,2	2793,7	3492,1	4190,5	4888,9	5587,3	6285,7	6984,1	7682,5	8381,0	9079,4	9777,8	10476,2	11174,6	11873,0	12571,4
2250	714,3	1428,6	2142,9	2857,1	3571,4	4285,7	5000,0	5714,3	6428,6	7142,9	7857,1	8571,4	9285,7	10000,0	10714,3	11428,6	12142,9	12857,1
2300	730,2	1460,3	2190,5	2920,6	3650,8	4381,0	5111,1	5841,3	6571,4	7301,6	8031,7	8761,9	9492,1	10222,2	10952,4	11682,5	12412,7	13142,9
2350	746,0	1492,1	2238,1	2984,1	3730,2	4476,2	5222,2	5968,3	6714,3	7460,3	8206,3	8952,4	9698,4	10444,4	11190,5	11936,5	12682,5	13428,6
2400	761,9	1523,8	2285,7	3047,6	3809,5	4571,4	5333,3	6095,2	6857,1	7619,0	8381,0	9142,9	9904,8	10666,7	11428,6	12190,5	12952,4	13714,3
2450	777,8	1555,6	2333,3	3111,1	3888,9	4666,7	5444,4	6222,2	7000,0	7777,8	8555,6	9333,3	10111,1	10888,9	11666,7	12444,4	13222,2	14000,0
2500	793,7	1587,3	2381,0	3174,6	3968,3	4761,9	5555,6	6349,2	7142,9	7936,5	8730,2	9523,8	10317,5	11111,1	11904,8	12698,4	13492,1	14285,7
2550	809,5	1619,0	2428,6	3238,1	4047,6	4857,1	5666,7	6476,2	7285,7	8095,2	8904,8	9714,3	10523,8	11333,3	12142,9	12952,4	13761,9	14571,4
2600	825,4	1650,8	2476,2	3301,6	4127,0	4952,4	5777,8	6603,2	7428,6	8254,0	9079,4	9904,8	10730,2	11555,6	12381,0	13206,3	14031,7	14857,1
2650	841,3	1682,5	2523,8	3365,1	4206,3	5047,6	5888,9	6730,2	7571,4	8412,7	9254,0	10095,2	10936,5	11777,8	12619,0	13460,3	14301,6	15142,9
2700	857,1	1714,3	2571,4	3428,6	4285,7	5142,9	6000,0	6857,1	7714,3	8571,4	9428,6	10285,7	11142,9	12000,0	12857,1	13714,3	14571,4	15428,6
2750	873,0	1746,0	2619,0	3492,1	4365,1	5238,1	6111,1	6984,1	7857,1	8730,2	9603,2	10476,2	11349,2	12222,2	13095,2	13968,3	14841,3	15714,3
2800	888,9	1777,8	2666,7	3555,6	4444,4	5333,3	6222,2	7111,1	8000,0	8888,9	9777,8	10666,7	11555,6	12444,4	13333,3	14222,2	15111,1	16000,0
2850	904,8	1809,5	2714,3	3619,0	4523,8	5428,6	6333,3	7238,1	8142,9	9047,6	9952,4	10857,1	11761,9	12666,7	13571,4	14476,2	15381,0	16285,7
2900	920,6	1841,3	2761,9	3682,5	4603,2	5523,8	6444,4	7365,1	8285,7	9206,3	10127,0	11047,6	11968,3	12888,9	13809,5	14730,2	15650,8	16571,4
2950	936,5	1873,0	2809,5	3746,0	4682,5	5619,0	6555,6	7492,1	8428,6	9365,1	10301,6	11238,1	12174,6	13111,1	14047,6	14984,1	15920,6	16857,1
3000	952,4	1904,8	2857,1	3809,5	4761,9	5714,3	6666,7	7619,0	8571,4	9523,8	10476,2	11428,6	12381,0	13333,3	14285,7	15238,1	16190,5	17142,9
3050	968,3	1936,5	2904,8	3873,0	4841,3	5809,5	6777,8	7746,0	8714,3	9682,5	10650,8	11619,0	12587,3	13555,6	14523,8	15492,1	16460,3	17428,6
3100	984,1	1968,3	2952,4	3936,5	4920,6	5904,8	6888,9	7873,0	8857,1	9841,3	10825,4	11809,5	12793,7	13777,8	14761,9	15746,0	16730,2	17714,3
3150	1000,0	2000,0	3000,0	4000,0	5000,0	6000,0	7000,0	8000,0	9000,0	10000,0	11000,0	12000,0	13000,0	14000,0	15000,0	16000,0	17000,0	18000,0
3200	1015,9	2031,7	3047,6	4063,5	5079,4	6095,2	7111,1	8127,0	9142,9	10158,7	11174,6	12190,5	13206,3	14222,2	15238,1	16254,0	17269,8	18285,7

B

Monthly treatment cost (€) \ Treatment duration (months)	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
2200	265,1	530,1	795,2	1060,2	1325,3	1590,4	1855,4	2120,5	2385,5	2650,6	2915,7	3180,7	3445,8	3710,8	3975,9	4241,0	4506,0	4771,1
2250	271,1	542,2	813,3	1084,3	1355,4	1626,5	1897,6	2168,7	2439,8	2710,8	2981,9	3253,0	3524,1	3795,2	4066,3	4337,3	4608,4	4879,5
2300	277,1	554,2	831,3	1108,4	1385,5	1662,7	1939,8	2216,9	2494,0	2771,1	3048,2	3325,3	3602,4	3879,5	4156,6	4433,7	4710,8	4988,0
2350	283,1	566,3	849,4	1132,5	1415,7	1698,8	1981,9	2265,1	2548,2	2831,3	3114,5	3397,6	3680,7	3963,9	4247,0	4530,1	4813,3	5096,4
2400	289,2	578,3	867,5	1156,6	1445,8	1734,9	2024,1	2313,3	2602,4	2891,6	3180,7	3469,9	3759,0	4048,2	4337,3	4626,5	4915,7	5204,8
2450	295,2	590,4	885,5	1180,7	1475,9	1771,1	2066,3	2361,4	2656,6	2951,8	3247,0	3542,2	3837,3	4132,5	4427,7	4722,9	5018,1	5313,3
2500	301,2	602,4	903,6	1204,8	1506,0	1807,2	2108,4	2409,6	2710,8	3012,0	3313,3	3614,5	3915,7	4216,9	4518,1	4819,3	5120,5	5421,7
2550	307,2	614,5	921,7	1228,9	1536,1	1843,4	2150,6	2457,8	2765,1	3072,3	3379,5	3686,7	3994,0	4301,2	4608,4	4915,7	5222,9	5530,1
2600	313,3	626,5	939,8	1253,0	1566,3	1879,5	2192,8	2506,0	2819,3	3132,5	3445,8	3759,0	4072,3	4385,5	4698,8	5012,0	5325,3	5638,6
2650	319,3	638,6	957,8	1277,1	1596,4	1915,7	2234,9	2554,2	2873,5	3192,8	3512,0	3831,3	4150,6	4469,9	4789,2	5108,4	5427,7	5747,0
2700	325,3	650,6	975,9	1301,2	1626,5	1951,8	2277,1	2602,4	2927,7	3253,0	3578,3	3903,6	4228,9	4554,2	4879,5	5204,8	5530,1	5855,4
2750	331,3	662,7	994,0	1325,3	1656,6	1988,0	2319,3	2650,6	2981,9	3313,3	3644,6	3975,9	4307,2	4638,6	4969,9	5301,2	5632,5	5963,9
2800	337,3	674,7	1012,0	1349,4	1686,7	2024,1	2361,4	2698,8	3036,1	3373,5	3710,8	4048,2	4385,5	4722,9	5060,2	5397,6	5734,9	6072,3
2850	343,4	686,7	1030,1	1373,5	1716,9	2060,2	2403,6	2747,0	3090,4	3433,7	3777,1	4120,5	4463,9	4807,2	5150,6	5494,0	5837,3	6180,7
2900	349,4	698,8	1048,2	1397,6	1747,0	2096,4	2445,8	2795,2	3144,6	3494,0	3843,4	4192,8	4542,2	4891,6	5241,0	5590,4	5939,8	6289,2
2950	355,4	710,8	1066,3	1421,7	1777,1	2132,5	2488,0	2843,4	3198,8	3554,2	3909,6	4265,1	4620,5	4975,9	5331,3	5686,7	6042,2	6397,6
3000	361,4	722,9	1084,3	1445,8	1807,2	2168,7	2530,1	2891,6	3253,0	3614,5	3975,9	4337,3	4698,8	5060,2	5421,7	5783,1	6144,6	6506,0
3050	367,5	734,9	1102,4	1469,9	1837,3	2204,8	2572,3	2939,8	3307,2	3674,7	4042,2	4409,6	4777,1	5144,6	5512,0	5879,5	6247,0	6614,5
3100	373,5	747,0	1120,5	1494,0	1867,5	2241,0	2614,5	2988,0	3361,4	3734,9	4108,4	4481,9	4855,4	5228,9	5602,4	5975,9	6349,4	6722,9
3150	379,5	759,0	1138,6	1518,1	1897,6	2277,1	2656,6	3036,1	3415,7	3795,2	4174,7	4554,2	4933,7	5313,3	5692,8	6072,3	6451,8	6831,3
3200	385,5	771,1	1156,6	1542,2	1927,7	2313,3	2698,8	3084,3	3469,9	3855,4	4241,0	4626,5	5012,0	5397,6	5783,1	6168,7	6554,2	6939,8

Cost per median OS/PFS month: 0-6000 € | Cost per median OS/PFS month: 6001-12000 € | Cost per median OS/PFS month: >12000 €

Fig. 2 Multivariate sensitivity analysis of the cost per median progression-free survival month (**a**) and cost per median overall survival (from abiraterone initiation to death) month (**b**) in the overall cohort according to the monthly cost and the treatment duration

In our analysis, AA was related to longer time to PSA progression and PFS and higher PSA response rate in the CT-naïve group compared to the post-CT group, but the increase in OS did not reach statistical significance. It is important to highlight that 45.1% of our CT-naïve patients were alive at the cut-off date. Therefore, a longer follow-up period of these patients could change our current OS results. These differences could probably be a consequence of patient characteristics. Bone and multiple metastasis were more prevalent and baseline PSA level was higher in our post-CT patients. Skeletal lesions are the primary source of morbidity and mortality related to prostate cancer [16]. In contrast to what we expected, post-CT and CT-naïve patients with visceral metastasis had non-significant longer PFS and OS. This might be due to the small number of cases with baseline visceral metastasis and differs from what was previously observed in other studies [8]. Therefore, new analyses which include more patients with this condition are required to clarify our current observation.

Furthermore, a lower baseline PSA level and higher PSA response rate have a positive impact on survival in mCRPC patients treated with AA [8–10]. The use of PSA decline of 50% or more as an effectiveness outcome was derived from analyses that have linked this degree of decline to survival [16]. In our cohort, the PFS and OS were significantly associated with PSA response in CT-naïve patients, but not in those treated with AA after chemotherapy. The lack of statistical significance in the post-CT cohort could be explained partly by a high percentage (33.3%) of patients who kept a progressive PSA upsurge after AA initiation. Emerging data suggest several possibilities determining resistance to AA and cross-resistance between chemotherapy treatments [17–19]. Then, the worse effectiveness results of AA obtained in this study in the post-chemotherapy setting could also be supported by this notion. Personalized and precision medicine is a goal for many translational and clinical investigators and the development of useful biomarkers will inform about proper choices for prostate cancer treatment [20].

Overall, the effectiveness observed in our series is poorer compared to that achieved in the RCT. In our post-CT patients, the median time to PSA progression, median PFS and median OS were less than that obtained in the COU-AA-301 trial (4.4 vs. 8.5 months, 5.1 vs. 5.6 months and 12.1 vs. 15.8 months, respectively) [4]. These outcomes were also much shorter in our CT-naïve patients than those reported in COU-AA-302 trial (7.9 vs. 11.1 months, 7.5 vs. 16.5 months and 21.3 vs. 34.7 months, respectively) [5]. As already mentioned, the inferior outcomes in this group may not be the ultimate result and another follow-up analysis will be carried out in the future.

The dissimilarity in efficacy-effectiveness results of AA between clinical and real-life setting has been previously described [7–10, 21, 22]. The baseline status of the patients could explain these differences. Our cohorts included a higher proportion of elderly (aged ≥ 75 years) and symptomatic (ECOG-PS ≥ 2) patients compared to pivotal trials. An ECOG-PS ≥ 2 was associated with poor survival in both pre-chemotherapy and post-chemotherapy patients [8, 10, 23]. Likewise, various definitions of progression criteria have been used [7–9, 24]. Methodological aspects like this and the fact that radiographic evaluation was performed regularly every 8 weeks in these pivotal trials, but it was requested in our patients when biochemical or clinical progression was observed, have a direct effect on the results. In any case, the evidence obtained from both the clinical and the real-world studies points to a better outcome of AA in the early stages of the disease. Along this view, the clinical benefit of AA has been evaluated in patients with metastatic castration-sensitive prostate cancer [25].

In terms of safety, AA had a good overall profile. As expected, hypokalaemia, hypertension and fatigue were the more commonly detected AEs. However, the incidence of fluid retention, cardiac disorders and hypertransaminasemia was low. In the vast majority of cases, AEs were grade 1–2 or required medical follow-up in primary healthcare services or outpatient oncology consultation, but hospital admission was necessary in three cases. A higher incidence of AEs was reported in the RCT [4, 5], being probably a consequence of the longer exposure to AA in these trials and the non-systematic record of AEs in the clinical history and its under-reporting in the real-life setting [26]. The incidence of overall AEs, hypokalaemia and nausea/vomiting was higher in the post-CT group. Moreover, there was a higher proportion of post-CT patients who discontinued or reduced the dose of AA due to AEs.

Dose reduction or discontinuation of a drug can lead to a lack of patient adherence to treatment and have a negative impact on healthcare results. Likewise, one of the criteria established to access to AA treatment in the Valencian Health System is that adherence can be guaranteed [6]. Sixty-one (88.4%) of our patients had an adherence ≥ 80% and it was related to non-significant numerically higher PFS and OS in the CT-naïve group, but not in those post-CT. The apparent inconsistency in survival outcomes in post-CT patients regarding adherence level is probably an artefact arising from a small number of cases with an adherence < 80%. The cut-off point of 80% was also used by Behl et al. to evaluate treatment patterns and patient adherence to AA therapy in real-world practice [27]. Adherence calculation using the electronic dispensing records may lead to an overestimation and time adherence or different types of adherence (one-time lapses, interruptions, etc.) cannot be measured. Also, an information bias exists because it assumes that the medication collection is equivalent to adherence.

On the other hand, we have estimated the cost per unit of clinical benefit of AA, and as far as we are aware, our study is one of the first that uses real-world data for this assessment. Previously, several CEAs of treatments for mCRPC have been conducted, using the efficacy results from RCT [11, 12]. Pilon et al. estimated a cost per median PFS month of $6794 and a cost per median OS month of $3231 in mCRPC patients treated with AA and who had not received prior chemotherapy [11]. Compared to these costs, our estimations are considerably lower because the time on AA in our cohorts was shorter than that observed in COU-AA-301 (5.3 vs. 7.4 months) and COU-AA-302 (7.7 vs. 13.8 months) trials [4, 5]. Also, the monthly treatment cost was €2712.0, being less than that used previously in other estimates [12]. Despite this, it remains a high price, influencing the decision to stop treatment at progression, and therefore, the treatment duration. Our analysis is limited to the cost of AA only, not taking into account other associated costs. Due to its oral administration, there is no increase in its cost due to the use of resources in the Oncology Day Clinic and its elaboration in the Pharmacy Department. Despite the good safety profile of AA, if the cost associated with AEs was to be considered, it would be the estimated amount of $198.7 per month [28].

Finally, apart from the aforementioned limitations it should be noted that this is an observational study and may be subject to residual confounding and unmeasured factors. Moreover, it includes a relatively small number of patients and there is an unbalanced proportion of patients between treatment groups, limiting direct comparisons and the detection of statistically significant differences in subgroup analyses. Due to all this, the conclusions reached must be interpreted cautiously.

Conclusions

The present study provides some interesting and updated information regarding AA in the real-world setting of the mCRPC and establishes a quality framework for the new therapies. Our data points toward a better effectiveness, safety and cost-effectiveness ratio of AA in CT-naïve patients than in those treated with AA after chemotherapy. This supports the notion of the clinical utility of administering AA early in the disease course. In comparison with the clinical trial setting, the survival outcomes were poorer, especially in the CT-naïve group. A future analysis is needed to completely evaluate the clinical benefit of AA in this patient population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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