Safety of Abiraterone and Enzalutamide in prostate cancer patients treated with anticoagulants

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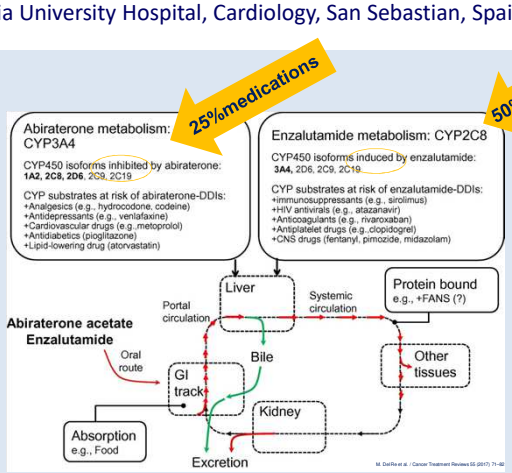
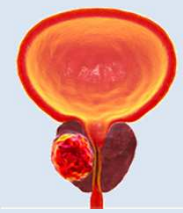
Introduction:

- **Abiraterone acetate** (AA) and **Enzalutamide** (EZ) are used for the treatment of advanced metastatic prostate cancer with similar benefits in clinical outcomes but they have not been compared head-to-head.
- These metabolic effects in patients treated **with vitamin K antagonists and direct oral anticoagulants** (AC) can derive into sub- or supratherapeutic anticoagulant drug levels with the subsequent appearance of **bleeding and thrombotic related-adverse events** (AEs).



Enzyme inhibition
=↑drug levels
= toxicity

Enzyme induction
=↓drug levels
= loss of efficacy



Objectives:

1. Evaluate the incidence of AEs in patients treated with EZ or AA into the EudraVigilance (EV) database.
2. Search for differences in AEs between patients with reported use of AC

Methods:

Observational analyses of the EV reference population treated with Rivaroxaban, Edoxaban, Dabigatran, Apixaban and AVK for stroke prevention in non-valvular atrial fibrillation and AA or EZ.

Each report collected data on age, gender, seriousness, suspected and concomitant drugs and causality.

EUROPEAN MEDICINES AGENCY — EudraVigilance Human

Post-marketing adverse events (hemorrhagic/thrombotic) reported between January 2011-September 2018

AE GROUP	Vascular & Blood lymphatic disorders	Gastrointestinal disorders	Cardiac disorders, Renal & Urinary disorders	Respiratory, thoracic and mediastinal disorders	Nervous System disorders
AE Selected	Anaemia	Colitis ischaemic	Acute coronary syndrome	Epistaxis	Aphasia
	Arterial occlusive disease	Diarrhoea haemorrhagic	Acute myocardial infarction	Pulmonary embolism	Brain stem haemorrhage
	Blood disorder	Duodenal ulcer haemorrhage	Angina pectoris		Cerebellar haemorrhage
	Coagulopathy	Gastric haemorrhage	Angina unstable		Cerebral haematoma
	Deep vein thrombosis	Gastric ulcer haemorrhage	Coronary artery disease		Cerebral haemorrhage
	Disseminated intravascular coagulation	Gastrointestinal haemorrhage	Coronary artery occlusion		Cerebral infarction
	Haematoma	Haematemesis	Cystitis haemorrhagic		Cerebral thrombosis
	Haemolytic anaemia	Intestinal haemorrhage	Haematuria		Cerebrovascular accident
	Haemorrhage	Intestinal ischaemia	Haemorrhage urinary tract		Coma
	Haemorrhagic anaemia	Large intestinal haemorrhage	Myocardial infarction		Dysarthria
	Infarction	Melaena	Myocardial ischaemia		Haemorrhage intracranial
	Internal haemorrhage	Mouth haemorrhage	Urethral haemorrhage		Hemiparesis
	Iron deficiency anaemia	Oesophageal haemorrhage			Hemiplegia
	Normocytic anaemia	Rectal haemorrhage			Hypoaesthesia
	Peripheral artery thrombosis	Upper gastrointestinal haemorrhage			Ischaemic cerebral infarction
	Shock				Ischaemic stroke
	Thrombocytopenia				Lacunar infarction
	Thrombosis				Monoplegia
	Thrombotic thrombocytopenic purpura				Optic neuritis
	Venous thrombosis				Speech disorder
					Thalamus haemorrhage
					Transient ischaemic attack
					Visual field defect

Results:

- A total of 2,115 AE were reported
- 71.2% associated to EZ and 28.8% to AA.
- Adverse events by concomitant use of anticoagulants and by suspected drug:

Concomitant use of ACs	Product	All adverse events (AE) Total number	Proportion
Use of AC	Abiraterone	36	22,2%
	Enzalutamide	126	**77,8%**
No use of AC	Abiraterone	809	32,1%
	Enzalutamide	1710	**67,9%**
Total	Abiraterone	845	31,5%
	Enzalutamide	1836	**68,5%**

Differences Use vs. No Use	Enzalutamide	Abiraterone
Difference	**9,9%**	**9,9%**
95% CI	1,59% to 16,65%	-6,26% to 20,90%
P	**0,0209**	**0,2118**

- There are significant differences when EE and AC are reported as concomitant. There are no differences with AA + AC vs AA .

- According to the criteria and methods that we decided to apply to perform the analysis, these results can show that there are significant differences within EZ reports AE when AC are reported as concomitant. On the other hand, there are no significant differences within AA reports AEs whether ACs are reported or not as concomitant for this treatment:

Concomitant use of ACs	Product	TOTAL AEs Group Selected Total number	Proportion	Vascular & Blood lymphatic disorders Total number	Proportion	Gastrointestinal disorders Total number	Proportion	Cardiac disorders, Renal & Urinary disorders Total number	Proportion	Respiratory, thoracic and mediastinal disorders Total number	Proportion	Nervous System disorders Total number	Proportion
Use AC	AA	25	18,0%	16	38,1%	1	7,1%	4	14,8%	2	12,5%	2	5,0%
	EZ	**114**	**82,0%**	**26**	**61,9%**	**13**	**92,9%**	**23**	**85,2%**	**14**	**87,5%**	**38**	**95,0%**
No use AC	AA	584	29,6%	259	38,5%	48	34,5%	147	36,0%	18	16,8%	112	17,2%
	EZ	**1392**	**70,4%**	**413**	**61,5%**	**91**	**65,5%**	**261**	**64,0%**	**89**	**83,2%**	**538**	**82,8%**
Total	AA	609	28,8%	275	38,5%	49	32,0%	151	34,7%	20	16,3%	114	16,5%
	EZ	**1506**	**71,2%**	**439**	**61,5%**	**104**	**68,0%**	**284**	**65,3%**	**103**	**83,7%**	**576**	**83,5%**

Differences AC. vs. No AC.	Enza	Abi	Enza	Abi	Enza	Abi	Enza	Abi	Enza	Abi	Enza	Abi
Difference	**11,6%**	**11,6%**	**0,4%**	**0,4%**	**27,4%**	**27,4%**	**21,3%**	**21,2%**	**4,3%**	**4,3%**	**12,2%**	**12,2%**
95% CI*	3,20% to 18,05%	-7,64% to 22,67%	-19,16% to 7,05%	-24,07% to 20,52 %	0,394% to 39,19%	-48,57% to 43,16%	1,027% to 32,26%	-26,85% to 36,48%	-21,89% to 17,28%	-57,75% to 29,75%	-0,08% to 17,20%	-52,13% to 21,60%
P-value*	**0,0085**	0,2116	0,967	0,974	**0,0469**	0,5708	**0,0404**	0,3834	0,6864	0,8792	**0,0498**	0,6502

Conclusions:

- There seems to be an increasing number adverse events reported with EZ and AA when ACs are concomitant drugs.
- In our analysis with EV, AA shows smaller number of AEs compared to EZ when ACs are prescribed.
- Despite these results a randomized clinical trial would be needed to confirm these findings. In addition, analyses of real-world data may provide additional insights and establish a strategy to manage this subgroup of patients.

There is no conflict of interest