

Table S1. Variable codes

Variable label	Definition	Length of history used before the start of abiraterone /enzalutamide (T0)	ICD-10 codes for hospitalisation or Long-term/chronic diseases (LTD)	Medical act code	ATC code	Biology codage
EXCLUSION CRITERIA						
Other active cancer	Other active cancer than Prostate cancer identified before abiraterone or enzalutamide exposure	Since 2009	C00.x-C97.x, D00.x-D09.x, excluding C61.x, D075			
EXPOSURE						
ABI treatment	Abiraterone exposure	No reimbursement in the 3 years before T0			L02BX03	
ENZ treatment	Enzalutamide exposure	No reimbursement in the 3 years before T0			L02BB04	
HISTORY OF DISEASES AND DRUGS EXPOSURE						
Chemotherapy session	At least 1 chemotherapy session for prostate cancer (chemo session or hospitalisation for prostate cancer)	In the 3 years before T0	main diagnosis = Z51.1 and related diagnosis = C61 or main diagnosis = C61 and associated diagnosis = Z51.1			
ADT exposure	At least one reimbursement of ADT drug or surgical orchiectomy	In the 3 years before T0		JHFA010	L02AE, L02BB, G03HA, L02BX02	
Curietherapy - brachytherapy	At least 1 curietherapy – brachytherapy session	In the 3 years before T0		JGNL001		
Prostatectomy	History of prostatectomy	In the 3 years before T0		JGFC001, JGFA006, JGFA011, JDFA019, JDFA020, JDFA021, JDFA022, JDFA023, JDFA024, JDFA025		
Radiotherapy	History of radiotherapy session	In the 3 years before T0		ZZNL.x in patients with ICD-10 C61 and exclusion of all ICD-10 codes of cancer		
Diabetes (with or without organ damage)	History of diabetes	3 years before T0	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149, E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	BGNA001, BGNP001, BGNP004, BGNP006, BGNP007, BGNP008	A10% (at least 3 reimbursements)	
Liver insufficiency	History of liver insufficiency	3 years before T0	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7			
Pancreatitis	History of pancreatitis	1 year before T0	K85.x			
HIV infection	History of HIV hospitalization or use of related treatment	1 year before T0	B20.x-B24.x, F02.4, R75.x, Z21.x		At least 2 reimbursements J05AE01-J05AE10, J05AF01-J05AF07, J05AF09, J05AG01, J05AG03-J05AG05, J05AR01-J05AR04,	

					J05AR06, J05AR08- J05AR10, J05AR13, J05AX05, J05AX07-09, J05AX12	
alcohol use disorders	History of alcohol use disorders	1 year before T0	F10.x, K70.x, T51.x, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z50.2, Z71.4, Z72.1,		At least 1 reimbursement N07BB	
Chronic Renal insufficiency (using Bannay et al definition*)	History of renal insufficiency	1 year before T0	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2	JVJF004, JVJF008, JVJB001, JVJF003		
Hypertension	History of hypertension hospitalization or use of related treatment	Drugs → 1 year before T0	See algorithm ⁵			
Reimbursement of drugs licensed for hypertension or cardiac failure	Reimbursement of drugs licensed for hypertension or cardiac failure				C02A + C02B + C02CA06 + C02D + C02L + C03 + C07 (exclusion of propranolol = C07AA05 + C08 + C09)	
Ischemic heart diseases	History of MI, angina or other ischemic heart diseases	3 years before T0	I20.x, I21.x, I22.x, I23.x, I24.x, I25.x			
Atherosclerosis and peripheral embolism	History of atherosclerosis and peripheral embolism	3 years before T0	I70.x, I74.x			
Coronary revascularisation	History of coronary revascularisation	3 years before T0		DDAF.x, DDPF002, DDMA.x, DDFF001, DDFF002		
Carotid and Peripheral angioplasty	History of angioplasty on carotid arteries and lower limbs	3 years before T0		DHCA004 EBAA002 EBAF001 EBAF003 EBAF004 EBAF005 EBAF006 EBAF009 EBAF010 EBAF011, EBCA001 EBCA002 EBCA004 EBCA008 EBCA010 EBCA011 EBCA013 EBCA015 EBCA017 EBEA003 EBEA005 EBKA001, EBKA002 EBKA003, EBKA004 ECFA003 ECFA004 ECLF004 EDCA004 EDCA005 EEEA002 EEAF001 EEAF002 EEAF003, EEAF004 EEAF005 EEAF006 EECA001 EECA002 EECA003 EECA005 EECA006 EECA007 EECA008 EECA010 EECA012, EEGA001 EEGA002 EEKA001 EELF002, EGAF003 EGCA003 EGFA006 EJCA002 EJCA003 EJEA001 EMSA001 ENAF001, ENAF002 ENFA005 EPCA002 EZCA002 EZCA003 EZCA004 EZFA003 EZPA001		
Ischemic stroke	history of ischemic stroke	3 years before T0	I63.0-I63.5, G45.x			
Heart diseases (including cardiomyopathy)	history of hospitalisation for heart failure or LTD for heart failure	3 years before T0	I099, I110, I130, I132, I42.x, I43.x, I50.x			
Cardiac valve disorders	History of hospitalisation for cardiac valve disorders	3 years before T0	I05-I08 I34-I39 T820 T826 Z952-54			
Anticoagulant	History of anticoagulant reimbursement	1 year before T0			At least 3 reimbursements B01AA, B01AE07,	

					B01AF01, B01AF02	
Antiplatelet inhibitors	History of antiplatelet inhibitors reimbursement	1 year before T0			At least 3 reimbursements B01AC04, B01AC05, B01AC06, B01AC07, B01AC22, B01AC24, B01AC30, C10BX02 and specific drug "Aspegic (aspirin) 100mg nourrissons®" (CIP7: 3189363, CIP13: 3400931893639)	
Drugs affecting bone structure and mineralisation	History of drugs affecting bone structure and mineralisation reimbursement	1 year before T0			At least 1 reimbursement M05BA04, M05BA07, M05BB03, M05BB04, G03XC01, H05AA02, Excluding [M05BA02, M05BA05]	
drug preventing the tumor bones complications	History of preventing the tumor bones complications reimbursement	1 year before T0			At least 1 reimbursement M05BA03, M05BX04	
Opioids and derivates	history of opioids and derivates reimbursement	1 year before T0			At least 2 reimbursements N02A	
Atrial fibrillation	History of atrial fibrillation	3 years before T0	See algorithme ^f			
Dyslipidemia drugs	History of dyslipidemia drugs reimbursement	1 year before T0			At least 1 reimbursement C10AA, C10AB, C10AX, C10B	
Smoking or chronic obstructive pneumopathy disorders	History of smoking or chronic obstructive pneumopathy disorders	3 years before T0	F17.x, I731, J41.x-J44.x, T652, Z716, Z720		R03AC18, R03AC19, R03BB05, R03BB04, R03BB07, R03BB06, R03AL04, R03AL05, R03AK04, N07BA, N06AX12	
Obesity	History of overweight	3 years before T0	E66.x	HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFMA009, HFMA010, HFMC006, HFMC007, HGCA009, HGCC027, HFLE002, HFLE900, HFGC900, HFKC001, HFKA002, HFMC008, HFMA011, HFKA001		
Liver disease	History of liver disease	3 years before T0	B15.0, B15.9, B16.0-16.2; B16.9, B17.0-B17.2, B17.8, B18.0-B18.2, B18.8-B18.9, B19.0, B19.9, B25.1, B94.2, K71.3-71.5, K71.7, K72.1, K73.0-K73.2, K73.8-K73.9, K74.0-K74.2, K74.4-K74.6, K75.0-K75.1, K75.3-K75.4, K75.8-K75.9, K76.0-K76.1, K76.3-K76.9, K77.0, K77.8, R16.0, R17, R740, R79.1, R82.2, R94.5, T86.4, D68.4, K71.1, K71.1, K712, K716, K718, K719, K710,		J05AF08, J05AF10-J05AF11, J05AB04, J05AE11, J05AE12, J05AX14-16, J05AX65-67, L03AB05, L03AB09-10, L03AB11	

			K752, K759, K762, K767, Z944			
Antiepileptic drugs or chronic / neuropathic pain drugs	History of antiepileptic drugs reimbursement	6 months before T0			At least 2 reimbursements: N03AA02, N03AA03, N03AB02, N03AB05, N03AD01, N03AD03, N03AE01, N03AF01, N03AF02, N03AF03, N03AF04, N03AG01, N03AG02, N03AG03, N03AG04, N03AG05, N03AG06, N03AX03, N03AX07, N03AX09, N03AX10, N03AX11, N03AX12, N03AX13, N03AX14, N03AX15, N03AX16, N03AX17, N03AX18, N03AX21, N03AX22, N05BA09	
Convulsive disorders	History of convulsive disorders	1 year before T0	G40.x, G41.x			
Seizure risk factor (adapted from Poon et al. Clin Genit Cancer. 2018)	History of ischemic stroke or transient stroke	1 year before T0	I63.0-I63.5, G45.x			
	History of traumatic brain or head injury within the last 12 months	1 year before T0	S02.0, S02.1, S02.7, S02.9, S06.x, S07.x			
	History of arteriovenous malformations of the brain	1 year before T0	Q28.2			
	History of brain infection (i.e., abscess, meningitis, or encephalitis),	1 year before T0	G04.x - G07.x			
	Presence of Alzheimer's disease	1 year before T0	F00.x-F03.x, F05.1, G30.x, G31.1			
	Presence of meningioma	1 year before T0	D32.x			
	Other disorders of brain	1 year before T0	G93.x (excluding .3 and .7)			
Use of BZD	Current use of benzodizepine	2 months before T0			At least 1 reimbursement: N05BA, excluding N05BA09	
Current use of medication that may modify seizure threshold	Current use of medication that may modify seizure threshold	6 months before T0			At least 1 reimbursement: N05A, N06A, J01M, J01FA, J01DB, J01DC, J01DD, J01DE, J04AC01, J04AM03, J04AC51, J04AM01, J04AM04, J04AM05, J04AM06, R03DA04, R03DA54, R03DA74, R03DB04	
Torsade de pointe or acquired long QT syndrome	Hospitalization for Torsade de pointe and QT interval prolongation (included ventricular tachycardia)	3 years before T0	I47.2, I45.8, I49.0, I49.8			
PSA testing	Prostate specific antigen testing	1 year before T0				7320, 7318, 7319
Liver test monitoring	Alanine transaminase (ALT)	6 months before				0514, 0522

	Aspartate aminotransferase (AST) Alkaline phosphatase (ALP)					
Charlson comorbidity index according to the Bannay et al definition*:						
- Myocardial infarction		1 year before T0	I21.x			
- Ischemic heart disease		1 year before T0	I20.x, I21.x, I22.x, I23.x, I24.x, I25.x			
- Congestive heart failure		1 year before T0	I110, I130, I132, I50.x			
- Peripheral vascular disease		1 year before T0	I70.x, I71.x, I731.x, I738.x, I739.x, I771.x, I790.x, I792.x, K551.x, K558.x, K559.x Z958.x, Z959.x	EFAF.x, ECPF.x, ECFA.x, EBFA.x,, EENF.x, EEPF.x, EEFA.x, EECA.x, ENNF.x, ENFA.x, DGAF.x, EDAF.x, DGFP.x, EDPF.x, DGFA.x, EDFA.x, DGCA.x, EDCA.x, EDPF.x, EDJF.x, EDKA.x, EDEA.x, EDLF.x, EDNF.x, EDPF.x, EDJF.x, EDMA.x, EANF002, ECNF002, ECJF001, ECCA007, ECCA009, ECCA003, ECCA002, ECMA001, ECKA002, EBNF001, EDEA001, EDLF007, EEJF001, EDCA005, ENAF001, ENAF002, DGKA004, EDNF003, EDKA002		
- Cerebrovascular disease		1 year before T0	G45.x, G46.x, H34.0, I60.x - I69.x			
- Dementia		1 year before T0	F00.x–F03.x, F05.1, G30.x, G31.1		N06D% (at least 3 reimbursements)	
- Chronic pulmonary disease		1 year before T0	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3		R03% except R03AA, R03AB, R03CA, R03CB (at least 3 reimbursements)	
- Rheumatologic disease Connective tissue disease		1 year before T0	M05.x, M06.x, M315, M32.x-M34.x, M351, M353, M360			
- Peptic ulcer disease Ulcer disease		1 year before T0	K25.x-K28.x			
- Mild liver disease		1 year before T0	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4			
- Moderate or severe liver disease		1 year before T0	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7			
- Diabetes Without complication		1 year before T0	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149		A10% (at least 3 reimbursements)	
- Diabetes with end-organ damage		1 year before T0	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	BGNA001, BGNP001, BGNP004, BGNP006, BGNP007, BGNP008		
- Hemiplegia		1 year before T0	G04.1, G11.4, G80.1, G80.2, G81.x,			

			G82.x, G83.0–G83.4, G83.9		
- Moderate or severe renal disease		1 year before T0	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	JVJF004, JVJF008, JVJB001, JVJF003	
- Any malignancy, including leukemia and lymphoma		1 year before T0	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x		
- Metastatic solid tumor		1 year before T0	C77.x–C80.x		
- AIDS/HIV		1 year before T0	B20.x–B22.x, B24.x, Z21.x		
OUTCOMES					
Acute cardiac failure or decompensation	Hospitalization for Acute cardiac failure or decompensation	/	I50.x		
Ischemic stroke	Hospitalization for Ischemic stroke	/	I63, G45		
Ischemic heart diseases	Hospitalization for ischemic heart diseases)		I21, I22, I23, I24, I20.0, I20.0+0		
Atrial fibrillation	Hospitalization for Atrial fibrillation	/	See algorithm £		
Torsade de pointe and QT interval prolongation (included ventricular tachycardia)	Hospitalization for Torsade de pointe and QT interval prolongation (included ventricular tachycardia)	/	I47.2, I45.8, I49.0, I49.8		
Convulsion/seizure	Hospitalization for Convulsion/seizure	/	G40, G41, “R56.8 + introduction of an anticoagulant in the 2 following months”		
Acute kidney injury	Hospitalization for Acute renal failure	/	N141, N142, N144, N990, N17, N19 ou R392	JVJB001, JVJF002, JVJF003, JVJF004, JVJF005 or JVJF008	
Hepatitis	Hospitalization for Hepatitis	/	K710, K711, K712, K716, K718, K719, K720, K752, K759, K762, K767, Z944		
Close liver test monitoring that might suggest hepatic injury	≥ 4 liver tests per months between the first and third month after the drug initiation and/or ≥ 3 liver tests per months after the third month of treatment	/			0514 , 0516, 0517, 0522
Cardiovascular morbidity	History of Hospitalization for [ischemic heart diseases or Atrial fibrillation or Torsade de pointe and QT interval prolongation (included ventricular tachycardia) regardless the vital status] + death / sudden death which occurred in a context of cardiovascular disease	/	I21, I22, I23, I24, I20.0, I20.0+0 I47.2, I45.8, I49.0, I49.8 + death identified with the following codes: I080, I469, R092, I498, I499, I359, I779, I080, I251, I110, I249, I258, I259, I519, I248, R99, I491, I749, I482, I48, I489, I490, I10, I634, I635, I632, I633, I639, I210, I219, I500, I509, I501, I516, R960, I420, I255, I428, I350		

* Bannay et al. Med Care. 2016.

\$ Hypertension algorithm:

If in the previous year, ICD-10 code « I10 » in the main or related or associated diagnosis

OR

If in the previous year, ICD-10 code « I15 » in the main or related or associated diagnosis

OR

If patient has a « long term disease » with ICD-10 code « I10 »

OR

Reimbursement for HTA drugs (ATC classes C02A + C02B + C02CA06 + C02D + C02L + C03 + C07 (**exclusion** of propranolol = C07AA05 + C08 + C09) but patients **without** history of:

- ischemic stroke: ICD10 codes in main diagnosis “I63”,

- and/or myocardial infarction: ICD10 codes in main diagnosis “I21”,

- and/or coronaropathy diseases: ICD10 codes in main diagnosis “I20% / I21% / I22% / I23% / I24% / I25%”,

- and/or congestive heart failure (thanks to French Quan** algorithm) defined as, in main or related or associated diagnosis (but excluding ICD-10 code “I25”, already in

Coronaropathy disease algorithm) or long-term disease with the following ICD10 codes:

I099/I110/I130/I132/I420/I425/I426/I427/I428/I429/I43%/I50%/P290;

- and/or arterial thrombosis diseases: main diagnosis with ICD10 codes “I74” + and/or medical acts (CCAM) for thrombosis:

('EEAF%' or 'ECPF%' or 'ECFA%' or 'EBFA%' or 'EENF%' or 'EPPF%' or 'EEFA%' or 'EECA%' or 'ENNF%' or 'ENFA%' or 'DGAF%' or 'EDAF%' or 'DGFP%' or 'EDPF%' or 'DGFA%' or 'EDFA%' or 'DGCA%' or 'EDCA%' or 'EDPF%' or 'EDJF%' or 'EDKA%' or 'EDEA%' or 'EDLF%' or 'EDNF%' or 'EDPF%' or 'EDJF%' or 'EDMA%' or cdc_act

in ('EANF002', 'ECNF002', 'ECJF001', 'ECCA007', 'ECCA009', 'ECCA003', 'ECCA002', 'ECMA001', 'ECKA002', 'EBNF001', 'EDEA001', 'EDLF007', 'EEJF001', 'EDCA005', 'ENAF001', 'ENAF002', 'DGKA004', 'EDNF003', 'EDKA002'.)

£ Atrial fibrillation algorithm:

- ICD-10 code « I48 »
- And/or medical acts DEQP003, DERP003, DERP004, DEPF001, DEPF006, DEPF012, DEPF014, DEPF025, DEPF033,
- And/or [medical acts DAQM003, DEQP001, DEQP004, DEQP005, DKRP004, DZQJ001, DZQJ006, DZQJ008, DZQM002, DZQM005, DZQM006, EQRP002, GLRP004 + ATC class for oral anticoagulant B01AA02, B01AA03, B01AA07, B01AA11, B01AE07, B01AF01, B01AF02].

**Quan algorithm for congestive heart failure (ICD-10 codes): I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0.

Table S2. Planned sub-groups analyses in the overall population.

Outcome	Sub-groups analyses
Acute heart failure	<ul style="list-style-type: none"> - In patients with history of heart failure[£] - In patients with drugs for antihypertension or cardiac failure* and without history of heart diseases[£] - In patients without drugs for antihypertension or cardiac failure* or history of heart diseases[£]
Ischemic stroke & Ischemic heart diseases	<ul style="list-style-type: none"> - In patients with history of hospitalization for stroke[£], ischemic heart diseases[£] or cardiac angioplasty[£], cerebral or peripheral angioplasty[£] or recent use/reimbursement of antiplatelet inhibitor* or dyslipidemia drugs*. - In patients with history of smoking[£] or COPD[£] or obesity[£] or chronic renal insufficiency[£] or atrial fibrillation[£] or recent use of anticoagulant* or diabetes[£] and without history of hospitalization for stroke[£], ischemic heart[£] diseases or cardiac angioplasty[£], cerebral or peripheral angioplasty[£] or recent use/reimbursement of antiplatelet inhibitor* or dyslipidemia drugs*. - In patients without history smoking[£] or COPD[£] or obesity[£] or chronic renal insufficiency[£] or atrial fibrillation[£] or recent use of anticoagulant* or diabetes[£] and without history of hospitalization for stroke[£], ischemic heart diseases[£] or cardiac angioplasty[£], cerebral or peripheral angioplasty[£] or recent use/reimbursement of antiplatelet inhibitor* or dyslipidemia drugs*.
Atrial fibrillation	<ul style="list-style-type: none"> - In patient with history of atrial fibrillation[£] - In patients without history of atrial fibrillation[£]
Acute kidney injury	<ul style="list-style-type: none"> - In patient with history of moderate or severe renal disease[£] - In patients without history of moderate or severe renal disease[£]
Seizure	<ul style="list-style-type: none"> - In patients with antiepileptic drugs* - In patients with benzodiazepine (BZD) drugs[§] but without antiepileptic drugs* - In patients with drugs modifying seizure threshold*, without antiepileptic drugs* or benzodiazepine (BZD)[§] - In patients with history of seizure[£] or non-drug seizure risk factor[£] but without drugs modifying seizure threshold*, or antiepileptic drugs or benzodiazepine (BZD)[§] - In patients without history of seizure[£] or non-drug seizure risk factor* but without drugs modifying seizure threshold*, or antiepileptic drugs or benzodiazepine (BZD)[§]

Outcome	Sub-groups analyses
Hepatitis	<ul style="list-style-type: none"> - In patient with non-drug induced liver injury or liver insufficiency[£] - In patients without history of non-drug induced liver injury or liver insufficiency[£]
Close liver test monitoring	<ul style="list-style-type: none"> - In patient with non-drug induced liver injury or liver insufficiency[£] - In patients without history of non-drug induced liver injury or liver insufficiency[£]
Torsade de pointe	<ul style="list-style-type: none"> - In patients with history of cardiac valve disorders[£] - In patients with history of congenital QT interval prolongation[£] - In patients with drugs that have a risk of causing QT prolongation and/or torsade de pointe* - In patients without history of cardiac valve disorders[£] or congenital QT interval prolongation[£] or use of drugs that have a risk of causing QT prolongation and/or torsade de pointe*.

§ History of reimbursed drug identified in the 2 months before initiation of abiraterone or enzalutamide.

* History of diseases or reimbursed drug identified in the 1 year before initiation of abiraterone or enzalutamide.

£ History of diseases were identified in the 3 years before initiation of abiraterone or enzalutamide.

Table S3. Exclusion criteria definition to select the “sub-population”.

HISTORY OF DISEASES AND DRUGS EXPOSURE	Definition	Length of history used before the start of abiraterone /enzalutamide (T0)	ICD-10 codes for hospitalisation or Long-term/chronic diseases (LTD)	Medical act code	ATC code	Biology codage
Liver insufficiency	History of mild to severe liver disease	3 years before T0	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5–K76.7			
Chronic Renal insufficiency	History of chronic renal insufficiency	3 year before T0	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	JVJF004, JVJF008, JVJB001, JVJF003		
Ischemic heart diseases	History of MI, angina or other ischemic heart diseases	1 years before T0	I20.x, I21.x, I22.x, I23.x, I24.x, I25.x			
Heart failure		1 year before T0	I110, I130, I132, I50.x			
Convulsive disorders	History of convulsive disorders or use of antiepileptic drugs (or that may modify threshold)	1 year before T0	G40.x, G41.x		At least 1 reimbursement: N05A, N06A, J01M, J01FA, J01DB, J01DC, J01DD, J01DE, J04AC01, J04AM03, J04AC51, J04AM01, J04AM04, J04AM05, J04AM06, R03DA04, R03DA54, R03DA74, R03DB04	

Table S4. Distribution of the number of cumulative outcome and type of outcome among the overall population (n = 15340).

Cumulative number of outcome	N	%	Atrial fibrillation	Ischemic stroke	Heart failure	Ischemic heart diseases	Torsade de pointe	Hepatitis	Hepatic injury observed on the liver test monitoring	Acute kidney injury	Seizure
0	7564	49.3	0	0	0	0	0	0	0	0	0
1	4871	31.8	1	0	0	0	0	0	0	0	0
1	1058	6.9	0	0	0	0	0	0	1	0	0
1	72	0.5	0	0	0	0	0	0	0	1	0
1	45	0.3	0	0	1	0	0	0	0	0	0
1	16	0.1	0	1	0	0	0	0	0	0	0
1	13	0.1	0	0	0	1	0	0	0	0	0
1	< 5	< 0.03	0	0	0	0	1	0	0	0	0
2	835	5.4	1	0	0	0	0	0	1	0	0
2	267	1.7	1	0	1	0	0	0	0	0	0
2	176	1.2	1	0	0	0	0	0	0	1	0
2	128	0.8	1	0	0	1	0	0	0	0	0
2	84	0.6	1	1	0	0	0	0	0	0	0
2	12	0.08	1	0	0	0	1	0	0	0	0
2	7	0.05	0	0	0	0	0	0	1	1	0
2	5	0.03	1	0	0	0	0	1	0	0	0
2	5	0.03	1	0	0	0	0	0	0	0	1
2	< 5	< 0.03	0	1	0	0	0	0	1	0	0
2	< 5	< 0.03	0	0	1	0	0	0	1	0	0
2	< 5	< 0.03	0	0	0	1	0	0	1	0	0
2	< 5	< 0.03	0	1	0	1	0	0	0	0	0
2	< 5	< 0.03	0	0	1	0	0	0	0	1	0
2	< 5	< 0.03	0	0	1	0	0	1	0	0	0
2	< 5	< 0.03	0	0	1	1	0	0	0	0	0

Cumulative number of outcome	N	%	Atrial fibrillation	Ischemic stroke	Heart failure	Ischemic heart diseases	Torsade de pointe	Hepatitis	Hepatic injury observed on the liver test monitoring	Acute kidney injury	Seizure
3	37	0.2	1	0	1	0	0	0	1	0	0
3	34	0.2	1	0	0	0	0	0	1	1	0
3	20	0.1	1	0	1	1	0	0	0	0	0
3	17	0.1	1	0	0	1	0	0	1	0	0
3	16	0.1	1	1	0	0	0	0	1	0	0
3	8	0.05	1	0	1	0	0	0	0	1	0
3	7	0.05	1	0	0	1	0	0	0	1	0
3	5	0.03	1	0	1	0	1	0	0	0	0
3	< 5	< 0.03	1	1	1	0	0	0	0	0	0
3	< 5	< 0.03	1	1	0	1	0	0	0	0	0
3	< 5	< 0.03	1	0	0	0	1	0	1	0	0
3	< 5	< 0.03	1	0	0	1	1	0	0	0	0
3	< 5	< 0.03	1	0	1	0	0	1	0	0	0
3	< 5	< 0.03	1	0	0	1	0	1	0	0	0
3	< 5	< 0.03	1	1	0	0	0	0	0	1	0
4	< 5	< 0.03	1	0	1	0	0	0	1	1	0
4	< 5	< 0.03	1	0	1	0	1	0	0	1	0
4	< 5	< 0.03	1	0	1	1	0	0	1	0	0
4	< 5	< 0.03	1	1	1	0	0	0	1	0	0
5	< 5	< 0.03	1	0	1	1	1	0	1	0	0

Figure S1. Incidence rate for each outcome per period.

Incidence rates of atrial fibrillation and of liver test monitoring that may suggest hepatic injury were not represented with other outcomes, as the scale was different. For atrial fibrillation with abiraterone, incidence rates at the 1st quarter, 2nd quarter, 2nd half-year, and 2nd year were 747, 245, 249 and 200 per 1000 person-year, respectively; for enzalutamide, they were 744, 259, 233 and 183 per 1000 person-year, respectively. For liver test monitoring that may suggest hepatic injury with abiraterone, they were 827, 1, 0 and 0 per 1000 person-year; for enzalutamide, they were 288, 1, 0 and 0 per 1000 person-year.

ABI: abiraterone; ENZ: enzalutamide.

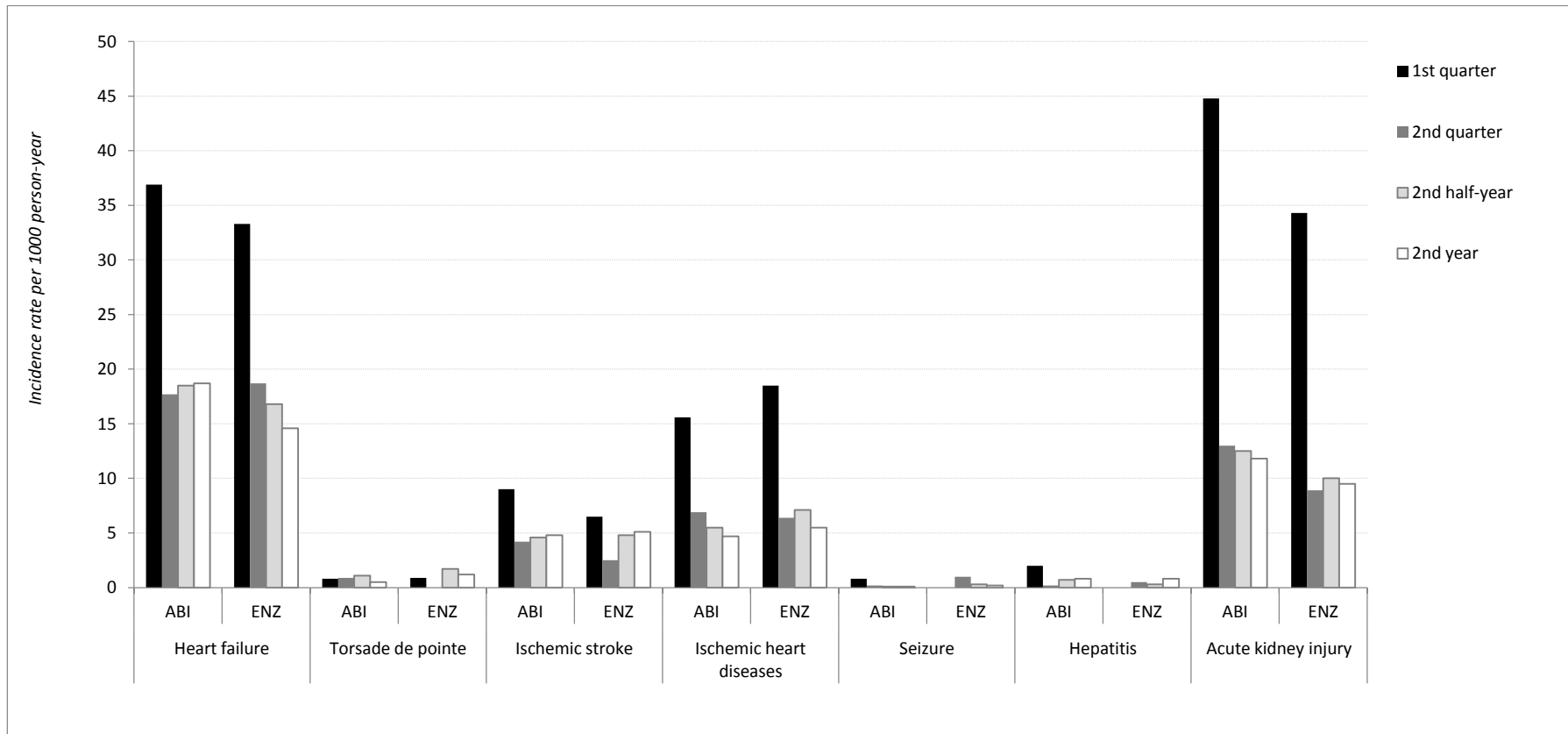


Table S5. Number of outcomes and incidence rates in sub-groups of patients from the overall population (n=15 340).

If less than 50 occurrences were identified for any of the events, descriptive sub-group analyses were not performed.

Outcome and sub-group analysis	Abiraterone			Enzalutamide		
	n	Person-year	Incidence per 1000 pers-year (95% CI)	n	Person-year	Incidence per 1000 per-year (95% CI)
Atrial fibrillation	4533	8763.2	517.28 (502.4- 532.6)	2016	4134.5	487.6 (466.8 -509.4)
- In patient with history of Atrial fibrillation	1507	1741.9	865.1 (822.5 -909.9)	762	951.4	800.9 (746.0- 859.8)
- In patients without history of Atrial fibrillation	3026	7021.3	431.0 (415.9 -446.6)	1254	3183.1	393.95 (372.7 -416.4)
Acute heart failure	286	12167.1	23.5 (20.9-26.4)	117	5674.3	20.6 (17.2 -24.7)
- In patients with history of heart failure	69	593.6	116.2 (91.8 -147.2)	37	352.1	105.1 (76.1- 145.0)
- In patients with drugs for antihypertension or cardiac failure and without history of heart failure	181	7635.4	23.7 (20.5- 27.4)	76	3606.2	21.1 (16.8- 26.4)
- In patients without history of heart failure or drugs for hypertension or cardiac failure	36	3938.0	9.1 (6.6- 12.7)	4	1715.9	2.3 (0.9- 6.2)
Ischemic stroke	91	12144.4	7.4 (6.1-9.1)	38	5708.8	6.66 (4.84-9.15)
- In patients with history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	63	5956.1	10.6 (8.3 -13.5)	25	2992.6	8.4 (5.6 -12.4)
- In patients with history of smoking or COPD or obesity or chronic renal insufficiency or atrial fibrillation or recent use of anticoagulant or diabetes and without history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	11	2397.0	4.6 (2.5 -8.3)	7	1081.0	6.5 (3.1 -13.6)
- In patients without history smoking or COPD or obesity or chronic renal insufficiency or atrial fibrillation or recent use of anticoagulant or diabetes and without history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	487	3891.3	4.4 (2.7 -7.0)	6	1635.3	3.7 (1.7 -8.2)
Ischemic heart diseases	125	12196.8	10.3 (8.6-12.2)	72	5684.7	12.7 (10.05-15.96)
- In patients with history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	88	5924.2	14.9 (12.1 -18.3)	52	2976.6	17.5 (13.3 -22.9)
- In patients with history of smoking or COPD or obesity or chronic renal insufficiency or atrial fibrillation or recent use of anticoagulant or diabetes and without history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	17	2390.7	7.1 (4.4 -11.4)	9	1078.4	8.4 (4.3 -16.0)

- In patients without history smoking or COPD or obesity or chronic renal insufficiency or atrial fibrillation or recent use of anticoagulant or diabetes and without history of hospitalization for stroke, ischemic heart diseases or cardiac angioplasty, cerebral or peripheral angioplasty or recent use/reimbursement of antiplatelet inhibitor or dyslipidemia drugs.	20	3881.9	5.2 (3.3 -8.0)	11	1629.6	6.8 (3.7 -12.2)
Torsade de pointe - In patients with history of cardiac valve disorders. - In patients with history of congenital QT interval prolongation. - In patients with drugs that have a risk of causing QT prolongation and/or torsade de pointe. - In patients without history of cardiac valve disorders or congenital QT interval prolongation or use of drugs that have a risk of causing QT prolongation and/or torsade de pointe.	17	12297.1	1.4 (0.9- 2.2)	9	5732.1	1.6 (0.8 -3.0)
Close liver test monitoring that might suggest hepatic injury - In patient with non-drug induced liver injury or liver insufficiency - In patients without history of non-drug induced liver injury or liver insufficiency	1724 35 1689	9887.7 194.4 9693.3	174.4 (166.3-182.8) 180.1 (129.3- 250.8) 174.2 (166.1 -182.8)	296 9 287	5323.9 154.4 5169.4	55.6 (49.6-62.3) 58.3 (129.3-250.8) 55.5 (49.5 -62.3)
Hepatitis - In patient with non-drug induced liver injury or liver insufficiency - In patients without history of non-drug induced liver injury or liver insufficiency	8	12299.9	0.7 (0.3 -1.3)	1	5735.7	0.2 (0.02 -1.2)
Acute kidney injury - In patient with history of moderate or severe renal disease - In patients without history of moderate or severe renal disease	237 48 189	12194.6 203.8 11990.8	19.4 (17.1 -22.1) 235.5 (177.5-312.5) 15.8 (13.7-18.2)	75 22 53	5699.4 135.7 5563.7	13.2 (10.5 -16.5) 162.1 (106.7-246.2) 9.5 (7.3-12.5)
Seizure - In patients with antiepileptic drugs - In patients with benzodiazepine (BZD) drugs but without antiepileptic drugs - In patients with drugs modifying seizure threshold, without antiepileptic drugs or benzodiazepine (BZD) - In patients with history of seizure or non-drug seizure risk factor but without drugs modifying seizure threshold, or antiepileptic drugs or benzodiazepine (BZD) - In patients without history of seizure or non-drug seizure risk factor but without drugs modifying seizure threshold, or antiepileptic drugs or benzodiazepine (BZD)	2	12299.6	0.16 (0.04 -0.65)	3	5731.8	0.5 (0.2 -1.6)

Table S6. Baseline characteristics of the sub-population of patients without contraindications or precautions for use according to the first line castration-resistant prostate cancer treatment (n=11 534).

	Overall		Abiraterone		Enzalutamide		Standardized difference
	n	%	n	(%)	n	(%)	
	11534	100	8137	70.5	3397	29.5	
Mean age in years (sd)			76.3 (9.1)		77.3 (9.3)		
Chemo-naïve	10364	89.9	7172	88.1	3192	94.0	0.094
<i>Cardiovascular risk factors</i>							
Hypertension	7362	63.8	5153	63.3	2209	65.0	0.035
Recent use of drugs licensed for hypertension or cardiac failure	7314	63.4	5130	63.0	2184	64.3	0.026
Obesity	500	4.3	314	3.9	186	5.5	0.077
Diabetes (with or without organ damage)	2057	17.8	1369	16.8	688	20.3	0.088
Smoking or chronic obstructive pneumopathy disorders	869	7.5	588	7.2	281	8.3	0.039
Recent use of dyslipidemia drugs	4114	35.7	2878	35.4	1236	36.4	0.021
<i>Cardiovascular diseases</i>							
Atrial fibrillation	2489	21.6	1718	21.1	771	22.7	0.038
Heart diseases (heart failure excluding cardiomyopathy)	0	0.0	0	0.0	0	0.0	
Cardiomyopathy	254	2.2	183	2.2	71	2.1	-0.011
Torsade de pointe	0	0.0	0	0.0	0	0.0	
Cardiac valve disorders	191	1.7	136	1.7	55	1.6	-0.004
Ischemic stroke	177	1.5	118	1.5	59	1.7	0.023
Atherosclerosis and peripheral embolism	185	1.6	130	1.6	55	1.6	0.002
Ischemic heart diseases and/or Coronary revascularisation	219	1.9	149	1.8	70	2.1	0.017
Carotid and Peripheral angioplasty	56	0.5	37	0.5	19	0.6	0.015
Recent use of anticoagulant [§]	1287	11.2	882	10.8	405	11.9	0.034
Recent use of antiplatelet inhibitors [§]	2720	23.6	1886	23.2	834	24.6	0.032
<i>Chronic renal insufficiency</i>	0	0.0	0	0.0	0	0.0	
<i>Non-drug induced liver injury:</i>							
Liver disease	47	0.4	29	0.4	18	0.5	0.026
Pancreatitis	10	0.1	7	0.1	3	0.1	0.001
HIV infection	19	0.2	16	0.2	3	0.1	-0.029
Alcohol use disorders	147	1.3	105	1.29	42	1.2	-0.005

<i>Factors modifying seizure risk</i>							
Convulsive disorders	13	0.1	7	0.1	6	0.2	0.025
Current use of BZD	2374	20.6	1722	21.2	652	19.2	-0.049
Current use of medication that may modify seizure threshold	4668	40.5	3418	42.0	1250	36.8	-0.107
Recent use of Antiepileptic drugs or chronic / neuropathic pain drugs	3	0.0	2	0.0	1	0.0	0.003
Other seizure risk factors and brain disorders [£]	0	0	0	0	0	0	

\$ these variables are considered as proxy of cardiovascular diseases.

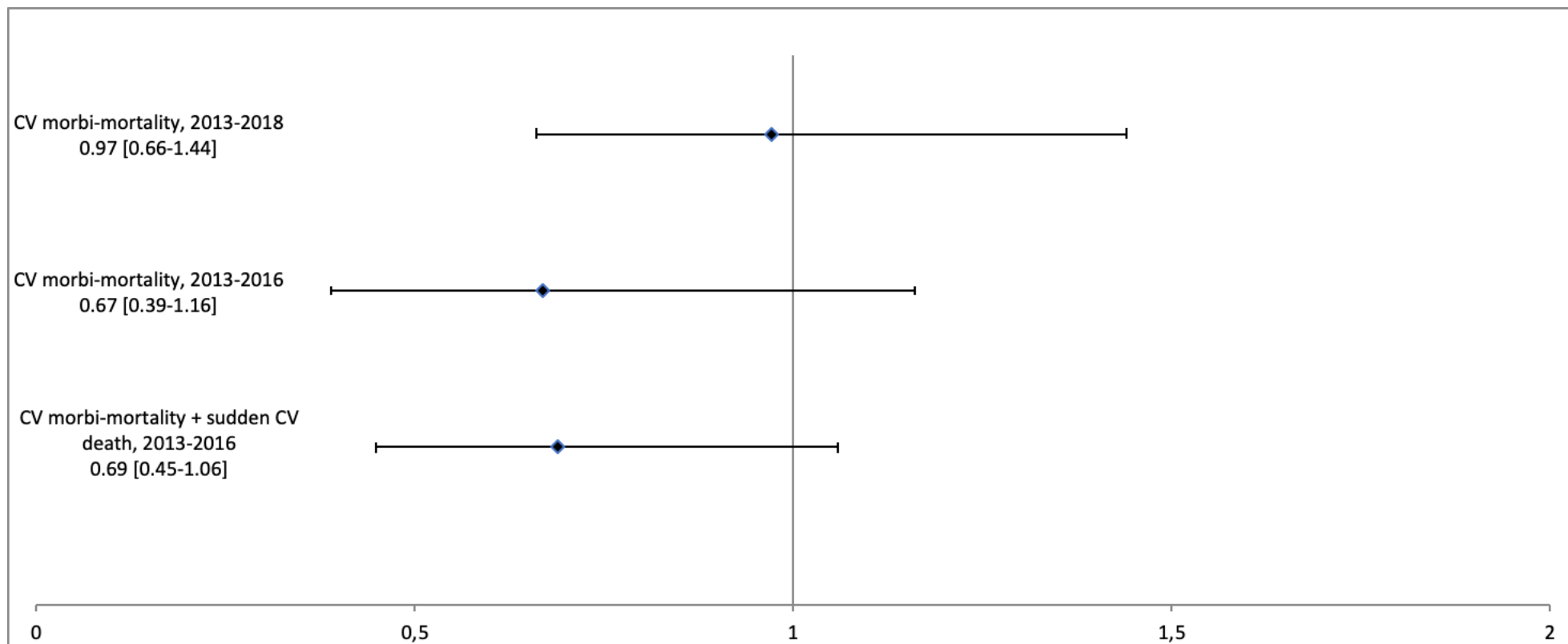
£ including traumatic brain or head injury within the last 12 months, arteriovenous malformations of the brain, brain infection (i.e. abscess, meningitis, or encephalitis), Alzheimer's disease, meningioma.

Table S7. Number of outcomes and crude incidence rates in the sub-population (n = 11 534)

Outcome definition	Abiraterone (N = 8755)			Enzalutamide (N = 2965)		
	n	Person-year	Incidence per 1000 person-year (95% CI)	n	Person-year	Incidence per 1000 person-year (95% CI)
Atrial fibrillation	3235	7160.6	451.8 (436.5 -467.6)	1303	3226.5	403.9 (382.5 -426.4)
Acute heart failure	165	9658.3	17.1 (14.7 -19.9)	54	4239.7	12.7 (9.8 -16.6)
Ischemic stroke	70	9693.8	7.2 (5.7 -9.1)	25	4244.3	5.9 (4.0 -8.7)
Ischemic heart diseases	72	9673.2	7.4 (5.9 -9.4)	32	4238.6	7.6 (5.3 -10.7)
Torsade de pointe & QT interval prolongation	9	9734.5	0.9 (0.5 -1.8)	5	4259.8	1.2 (0.5 -2.8)
Close liver test monitoring suggesting hepatic injury	1338	7827.5	170.9 (162.0 -180.3)	221	3958.0	55.8 (48.9 -63.7)
Hepatitis	7	9735.7	0.7 (0.3 -1.5)	1	4261.8	0.2 (0.03 -1.7)
Acute kidney injury	139	9679.1	14.4 (12.2 -17.0)	43	4248.4	10.1 (7.5 -13.7)
Seizure / convulsion	2	9735.4	0.2 (0.05 -0.8)	2	4260.4	0.5 (0.1 -1.9)
<i>Sensitivity analyses</i>						
Cardiovascular morbidity, 2013-2018	80	9670.3	8.3 (6.6 -10.3)	36	4236.6	8.5 (6.1 -11.8)
Cardiovascular morbidity, 2013-2016	55	6683.0	8.2 (6.3 -10.7)	17	1393.5	12.2 (7.58 -19.6)
Cardiovascular morbidity + sudden cardiac death*, 2013-2016	89	6683.0	13.3 (10.8 -16.4)	27	1393.5	19.4 (13.3 -28.3)

* Over the period 2013-2016, among the 4328 patients who died, the cause of death was unknown in 10.0% (n = 434) of them due lack of linkage between the death database and the SNDS

Figure S2. Incidence rates ratio of cardiovascular morbidity-mortality comparing abiraterone to enzalutamide, according to the period of interest.



Enzalutamide was the reference group.

CV: cardiovascular