

Title: Cardiovascular risks and survival with abiraterone vs enzalutamide in chemotherapy-naïve metastatic castration-resistant prostate cancer in **Germany**: AVENGER study

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Table S1. Identification codes used to define eligibility

ITEM		IDENTIFICATION
<i>Diagnoses</i>		
Prostate cancer	Malignant neoplasm of the prostate	ICD-10-GM C61
Metastatic cancer	Secondary malignant neoplasms	ICD-10-GM C77–C79 with the exception of C77.5
Malignant neoplasms in tissues adjacent to the prostate	Malignant neoplasm of the rectum	ICD-10-GM C20
	Malignant neoplasm of the of bone and articular cartilage of limbs	ICD-10-GM C40
	Malignant neoplasm of the bone and articular cartilage of other and unspecified sites	ICD-10-GM C41
	Malignant melanoma of the skin	ICD-10-GM C43, C44
	Malignant neoplasm of overlapping male genital organs	ICD-10-GM C63.8
	Malignant neoplasm of male genital organ, unspecified	ICD-10-GM C63.9
	Malignant neoplasm of the bladder	ICD-10-GM C67
	Malignant neoplasm of other and unspecified urinary organs	ICD-10-GM C68
	Malignant neoplasm, without specification of site	ICD-10-GM C80
<i>Treatments and procedures</i>		
ARPI	Enzalutamide	ATC L02BB04, OPS 6-007.6
	Abiraterone	ATC L02BX03, OPS 6-006.2
	Darolutamide	ATC L02BB06, OPS 6-00d.8
	Apalutamide	ATC L02BB05, OPS 6-00c.1
Other antiandrogens	Flutamide	ATC L02BB01
	Bicalutamide	ATC L02BB03, L02AE51 (combination with leuporelin)

Chemotherapy/ Antineoplastic agents	Docetaxel	ATC L01CD02, OPS 6-002.h
	Cabazitaxel	ATC L01CD04, OPS 6-006.1
	Axitinib	ATC L01EK01, OPS 6-006.g
	Carboplatin	ATC L01XA02
	Cisplatin	ATC L01XA01
	Doxorubicin	ATC L01DB01, OPS 6-001.b, 6-002.8
	Estramustine	ATC L01XX11
	Etoposide	ATC L01CB01
	Mitoxantrone	ATC L01DB07
	Olaparib	ATC L01XK01, OPS 6-009.0
	Paclitaxel	ATC L01CD01, OPS 6-001.f, 6-005.d
	General inpatient chemotherapy	OPS 8-542, 8-543, 8-544, 8-546
Radiotherapy	Radium-223-dichloride	ATC V10XX03, OPS 8-530.10 (therapy with alpha-emitting radionucleotides)
Medical castration/ADT	LHRH agonists	ATC L02AE
	LHRH antagonists	ATC L02BX01, L02BX02
	Antiandrogens	ATC G03HA01
Surgical castration	Orchiectomy	OPS 5-622, 5-601, 5-602, 5-603, 5-604

ADT: androgen-deprivation therapy; ARPI: androgen receptor pathway inhibitors; ATC: Anatomical Therapeutic Chemical Classification; LHRH: luteinizing hormone-releasing hormone; OPS: operation and procedure key; ICD-10-GM: International Statistical Classification of Diseases and Related Health Problems – Version 10 – German Version

Table S2. Codes for identification of CV-related diagnoses

Category	Item	Identification (ICD-10-GM CODE)
Hypertension	Essential (primary) hypertension	I10
	Hypertensive heart disease	I11
	Hypertensive renal disease	I12
	Hypertensive heart and renal disease	I13
	Secondary hypertension	I15
Heart failure	Hypertensive heart disease with (congestive) heart failure	I11.0
	Hypertensive heart and renal disease with (congestive) heart failure	I13.0
	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2
	Heart failure	I50
Ischemic heart disease	Angina pectoris	I20
	Acute myocardial infarction	I21
	Subsequent myocardial infarction	I22
	Certain current complications following acute myocardial infarction	I23
	Other acute ischemic heart diseases	I24
	Chronic ischemic heart diseases	I25
Nonrheumatic valve disorders	Nonrheumatic mitral valve insufficiency	I34
	Nonrheumatic aortic valve disorders	I35
	Nonrheumatic tricuspid valve disorders	I36
Atrioventricular block	Atrioventricular and left bundle-branch block	I44
Arrhythmia	Paroxysmal tachycardia	I47
	Atrial fibrillation and flutter	I48
	Other cardiac arrhythmias	I49
Cerebrovascular disease	Subarachnoid hemorrhage	I60
	Intracerebral hemorrhage	I61
	Other nontraumatic intracranial hemorrhage	I62
	Cerebral infarction	I63
	Stroke, not specified as hemorrhage or infarction	I64

	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	I65
	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	I66
	Other cerebrovascular diseases	I67
	Cerebrovascular disorders in diseases classified elsewhere	I68
	Sequelae of cerebrovascular disease	I69
	Transient cerebral ischemic attacks and related syndromes	G45
Peripheral vascular disease	Atherosclerosis	I70
	Aortic aneurysm and dissection	I71
	Other aneurysm	I72
	Other peripheral vascular diseases	I73
	Arterial embolism and thrombosis	I74
	Other disorders of arteries and arterioles	I77
	Disorders of arteries, arterioles, and capillaries in diseases classified elsewhere	I79
Pulmonary circulation disorders	Pulmonary embolism	I26
	Other pulmonary heart diseases	I27
Deep vein thrombosis	Phlebitis and thrombophlebitis	I80
Cardiac arrest	Cardiac arrest	I46

CV: cardiovascular; ICD-10-GM: International Classification of Diseases, 10th revision, German Modification

Table S3. Balance assessment in propensity score matching

BALANCE ASSESSMENT		UNADJUSTED SAMPLE		ADJUSTED SAMPLE		
AOK						
Covariates	Mean AA	Mean ENZA	SMD	Mean AA	Mean ENZA	SMD
Propensity score	0.37	0.43	0.52	0.42	0.42	0.00
# of urologist visits	6.90	7.58	0.32	7.38	7.50	0.06
Age in years	76.70	78.15	0.19	78.04	77.95	−0.01
Arrhythmia	0.30	0.36	0.07	0.34	0.35	0.01
Anticoagulant use	0.12	0.18	0.06	0.16	0.18	0.02
Renal failure	0.40	0.46	0.06	0.44	0.45	0.01
Diabetes without complications	0.14	0.18	0.05	0.17	0.18	0.00
Diabetes with complications	0.14	0.18	0.04	0.17	0.18	0.01
Skin cancer	0.07	0.11	0.04	0.09	0.10	0.01
Congestive heart failure	0.38	0.42	0.04	0.39	0.41	0.02
Obesity	0.21	0.25	0.04	0.23	0.24	0.01
Dyslipidemia drug use	0.40	0.42	0.02	0.42	0.42	0.00
IHD or coronary revascularization	0.40	0.42	0.02	0.40	0.42	0.02
Antiplatelet use	0.18	0.19	0.01	0.19	0.19	0.00
Hypertension	0.86	0.87	0.01	0.87	0.87	0.00
Urinary tract infection	0.27	0.28	0.01	0.30	0.28	−0.02
Hyperlipidemia	0.53	0.53	0.00	0.54	0.53	0.00
Opioid use	0.29	0.28	−0.01	0.29	0.28	−0.01
COPD	0.15	0.14	−0.01	0.13	0.14	0.01
Surgical castration	0.20	0.19	−0.01	0.20	0.19	−0.01
Total DDD of ADT	564.70	560.72	−0.02	553.30	562.86	0.04
Bone drug use	0.28	0.26	−0.02	0.27	0.26	−0.01
Cerebrovascular disease	0.26	0.24	−0.03	0.23	0.24	0.00
Antiandrogen use	0.76	0.73	−0.03	0.72	0.74	0.02
Radiotherapy	0.18	0.14	−0.04	0.16	0.14	−0.02
Hospitalization days	15.61	14.37	−0.06	14.82	14.30	−0.02
GWQ						
Propensity score	0.33	0.36	0.39	0.36	0.36	0.01
# of urologist visits	9.09	9.95	0.19	9.75	9.71	−0.01

Age in years	74.60	75.81	0.14	75.16	75.64	0.06
Total DDD of ADT	528.93	546.45	0.08	543.13	542.63	0.00
Obesity	0.19	0.25	0.06	0.24	0.24	0.00
Renal failure	0.28	0.34	0.06	0.34	0.33	-0.01
Opioid use	0.22	0.27	0.04	0.25	0.26	0.01
Hospitalization days	15.26	16.24	0.04	16.44	16.32	-0.01
Hyperlipidemia	0.53	0.57	0.04	0.55	0.56	0.01
Arrhythmia	0.28	0.31	0.03	0.31	0.31	0.00
Diabetes w/o complications	0.06	0.09	0.03	0.08	0.09	0.01
IHD or coronary revascularization	0.31	0.34	0.03	0.33	0.33	0.00
Antiplatelet use	0.10	0.13	0.03	0.13	0.12	-0.01
Hypertension	0.77	0.79	0.02	0.80	0.79	-0.01
COPD	0.11	0.13	0.02	0.12	0.13	0.01
Bone drug use	0.19	0.21	0.02	0.19	0.21	0.01
Urinary tract infection	0.26	0.27	0.01	0.25	0.27	0.02
Skin cancer	0.13	0.14	0.01	0.14	0.14	0.00
Surgical castration	0.17	0.18	0.01	0.20	0.18	-0.02
Diabetes w/ complications	0.16	0.17	0.00	0.18	0.16	-0.02
Antiandrogen use	0.75	0.75	0.00	0.75	0.75	0.00
Anticoagulant use	0.15	0.14	-0.01	0.14	0.15	0.01
Congestive heart failure	0.28	0.26	-0.02	0.27	0.27	0.00
Cerebrovascular disease	0.23	0.21	-0.02	0.21	0.21	0.01
Dyslipidemia drug use	0.37	0.34	-0.02	0.34	0.35	0.00
Radiotherapy	0.29	0.24	-0.05	0.23	0.24	0.01

AA: abiraterone acetate; ADT: androgen-deprivation therapy; COPD: chronic obstructive pulmonary disease; DDD: defined daily dose; ENZA: enzalutamide; IHD: ischemic heart diseases

Table S4. Sensitivity and competing risk analysis for time to first CV event and overall survival

	HR (95% CI) (ENZA vs AA)	P-value	I ²
Time to first CV events			
Main analysis (PSM, ITT)	0.70 (0.57–0.86)	0.001	0%
Sensitivity analyses for main analysis			
IPTW, ITT	0.78 (0.65–0.94)	0.010	0%
PSM, on treatment	0.75 (0.57–0.98)	0.037	0%
IPTW, on treatment	0.76 (0.51–1.15)	0.200	61%
Competing risk analysis [§]			
AOK			
Main analysis – PSM, ITT	Event-CV event: 0.72 (0.55–0.94)	0.014	NA
	Competing event-death: 0.76 (0.64–0.90)	0.001	NA
Sensitivity analysis – PSM, on treatment	Event-CV event: 0.80 (0.56–1.15)	0.226	NA
	Competing event-death: 0.69 (0.52–0.91)	0.009	NA
GWQ			
Main analysis – PSM, ITT	Event-CV event: 0.68 (0.50–0.93)	0.014	NA
	Competing event-death: 0.85 (0.70–1.04)	0.106	NA
Sensitivity analysis – PSM, on treatment	Event-CV event: 0.67 (0.44–1.03)	0.072	NA
	Competing event-death: 1.00 (0.71–1.40)	1.000	NA

AOK and GWQ	Event-CV event: 0.70 (0.57–0.86)	0.001	0%
Overall survival			
Sensitivity analyses (AOK and GWQ)			
IPTW, ITT	0.85 (0.76–0.95)	0.005	14%
PSM, on treatment	0.79 (0.65–0.96)	0.017	0%
IPTW, on treatment	0.86 (0.66–1.13)	0.281	51%

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; IPTW: inverse probability of treatment weighting; ITT: intention-to-treat; NA: not applicable; PSM: propensity score matching

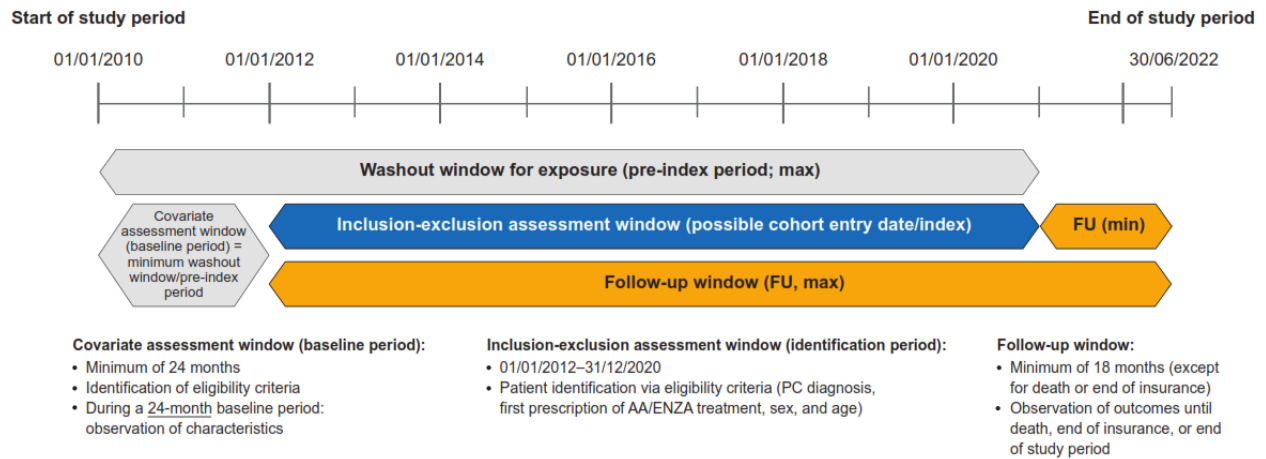
Table S5. Adverse events of special interest in the on-treatment PSM cohorts

	ENZA (N = 796)	AA (N = 796)	SMD
Measured among all patients, n (%)			
Severe fractures	0 (0.0)	2 (0.3)	0.00
Severe falls	12 (1.5)	8 (1.0)	0.01
Incident events only, n/N (%)			
Diarrhea	2/794 (0.3)	0/795 (0.0)	0.00
Dyspepsia	12/746 (1.6)	4/749 (0.5)	0.01
Peripheral edema	23/706 (3.3)	38/694 (5.5)	-0.02
Asthenia/Fatigue	54/714 (7.6)	47/704 (6.7)	0.01
Urinary tract infection	35/577 (6.1)	49/576 (8.5)	-0.02
Sepsis	12/774 (1.6)	28/773 (3.6)	-0.02
Hypokalemia	23/718 (3.2)	88/704 (12.5)	-0.09
Hypertriglyceridemia	8/671 (1.2)	8/654 (1.2)	0.00
Amnesia/memory disorder	1/793 (0.1)	0/792 (0.0)	0.00
Dysgeusia	1/796 (0.1)	0/796 (0.0)	0.00
Headache	3/772 (0.4)	3/773 (0.4)	0.00
Restless leg syndrome	4/768 (0.5)	1/772 (0.1)	0.00
Anxiety	15/697 (2.2)	11/726 (1.5)	0.01
Hematuria	22/613 (3.6)	27/620 (4.4)	-0.01
Gynecomastia	1/770 (0.1)	1/755 (0.1)	0.00
Rash	3/778 (0.4)	1/792 (0.1)	0.00
Pruritus	7/776 (0.9)	1/772 (0.1)	0.01

AA: abiraterone acetate; ENZA: enzalutamide; PSM: propensity score matching; SMD: standardized mean difference

Adverse events identified via documentation of at least one respective ICD-10-GM code between cohort entry date until earliest of 180 days post-cohort entry date, index treatment discontinuation/switch, death, study end, or end of insurance.

Figure S1. Overview of study and selection periods



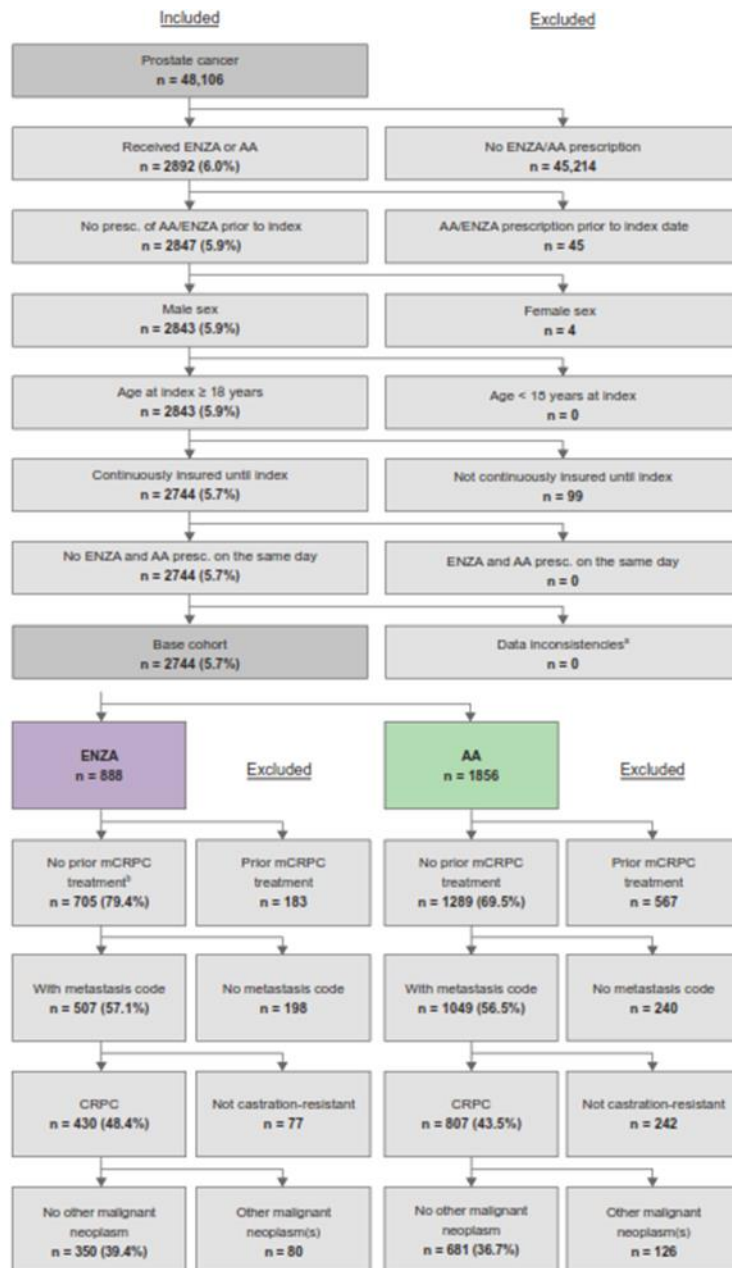
AA: abiraterone; ENZA: enzalutamide; FU: follow-up; min: minimum; max: maximum; PC: prostate cancer

Figure S2. Patient attrition

A. AOK database



B. GWQ database



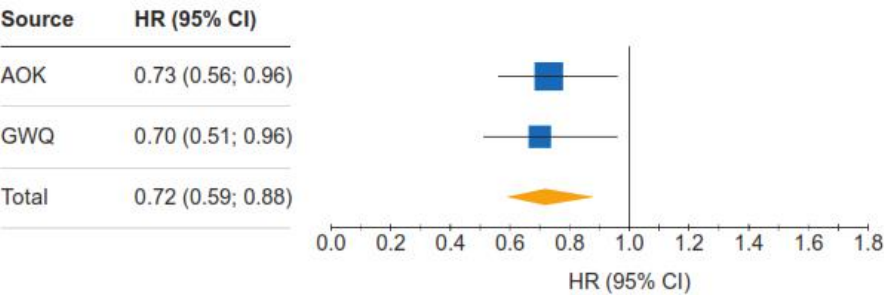
C. Sample size summary before and after adjustment for cohort differences

Summary of sample sizes before/after adjustment for cohort differences						
	AOK		GWQ		AOK & GWQ	
	ENZA	AA	ENZA	AA	ENZA	AA
Unmatched cohorts	478	731	350	681	828	1412
Matched: PSM	457	457	339	339	796	796
Weighted: IPTW	479.7	731.7	350.1	680.6	829.8	1412.3

AA: abiraterone; CRPC: castration-resistant prostate cancer; ENZA: enzalutamide; IPTW: inverse probability of treatment weighting; mCRPC: metastatic castration-resistant prostate cancer; PSM: propensity score matching

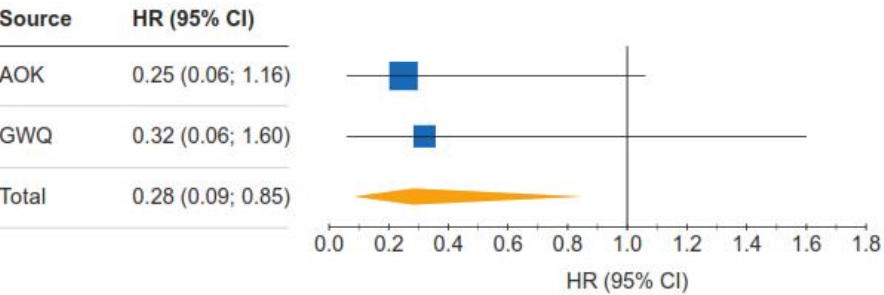
Figure S3. Time to first CV events in patients with and without CV disease in propensity score-matched cohorts

Subgroup: Prior CV disease (PSM, ITT) (n = 711)



Heterogeneity: $\chi^2_1 = 0.04$ ($P^* = 0.85$), $I^2 = 0\%$

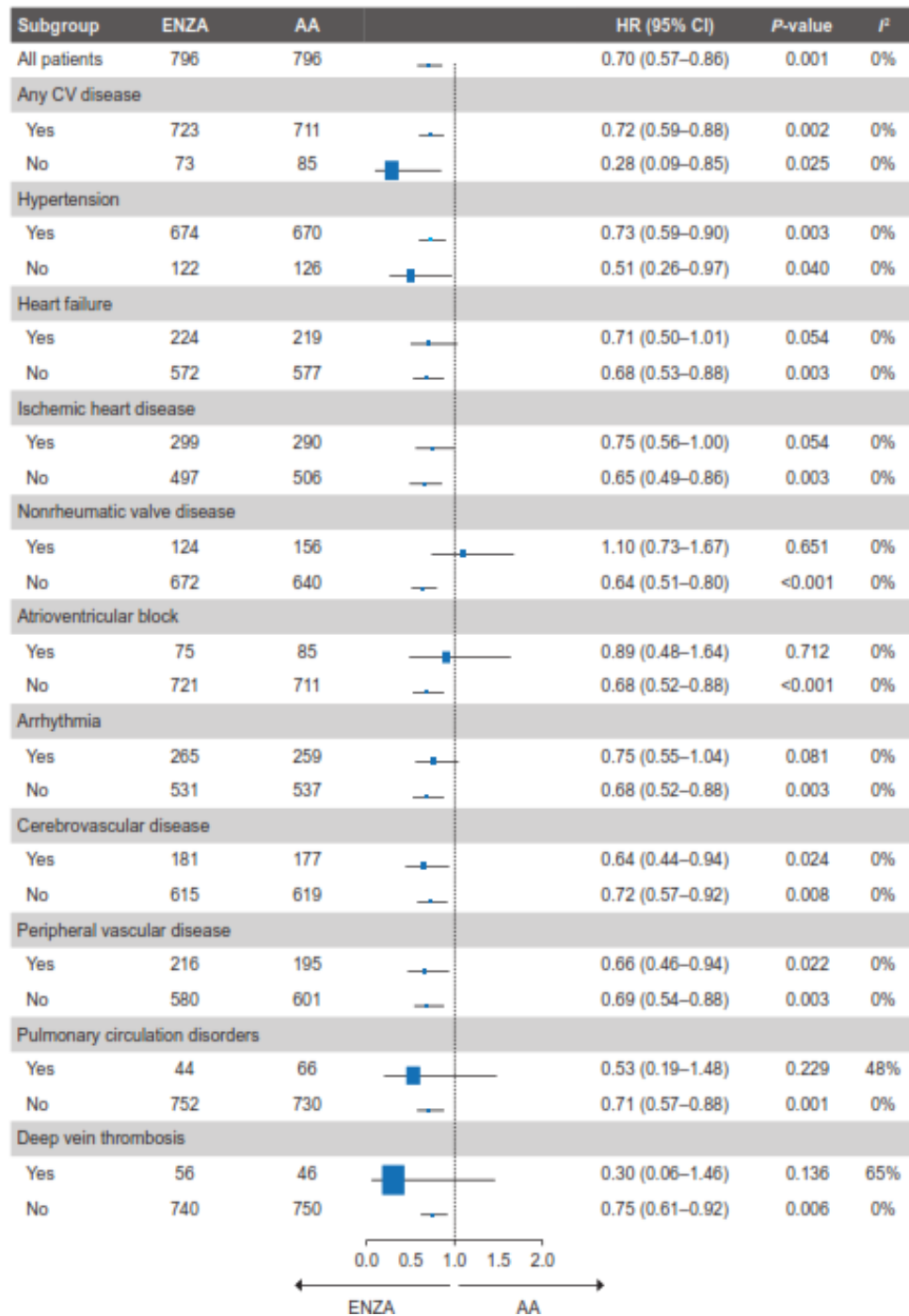
Subgroup: No prior CV disease (PSM, ITT) (n = 85)



Heterogeneity: $\chi^2_1 = 0.05$ ($P^* = 0.83$), $I^2 = 0\%$

AA: abiraterone acetate; CI: confidence interval; CV: cardiovascular; ENZA: enzalutamide; HR: hazard ratio; ITT: intention-to-treat; PSM: propensity score matching
**P*-value for heterogeneity indicating no meaningful difference.

Figure S4. Time to first CV event in patients with/without prior CV diseases



AA: abiraterone acetate; CI: confidence interval; CV: cardiovascular; ENZA: enzalutamide; HR: hazard ratio

I² threshold: 0%–40% indicates no important heterogeneity; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity.