Risk of major adverse cardiovascular events (MACE) with darolutamide versus enzalutamide in patients with advanced prostate cancer: A real-world observational study

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Darolutamide was associated with up to 19% and 15% lower risks of 3-point MACE (non-fatal MI, non-fatal stroke, or CV death) and 4-point MACE (plus angina or coronary revascularization), respectively, than enzalutamide in advanced prostate cancer, including mHSPC, where reductions were up to 27% (3-point MACE) and 20% (4-point MACE)

CLINICAL RELEVANCE

- EAU guidelines identify darolutamide as a preferred option for patients with CV comorbidities;[1] ESC guidelines report the lowest ARPI-related CV toxicity with darolutamide[2]
- CV-related death is the most common noncancer cause of death among patients with prostate cancer[3]

- Darolutamide was associated with lower risk of 3-point and 4-point MACE compared with enzalutamide

- Consider different CV impact from systemic treatment when selecting and managing patients with advanced prostate cancer (nmCRPC and mHSPC)

BACKGROUND

- Patients with advanced prostate cancer are often medically complex, with the majority having pre-existing CV comorbidities at treatment initiation[4]
- Hormonal treatments, including, ARPIs increase the risk of CV events,[5,6] including major adverse cardiovascular events (MACE), which can compromise patient survival and independence[4]
- CV risk varies across ARPIs; darolutamide has fewer drug–drug interactions than other ARPIs, and is often considered a preferred option for patients with CV comorbidities[1,7]
- Real-world comparative data on MACE outcomes with darolutamide vs enzalutamide in advanced prostate cancer remain limited

OBJECTIVE

- This study was designed to evaluate 3-point MACE and 4-point MACE outcomes among patients with advanced prostate cancer (nmCRPC and mHSPC) treated with darolutamide or enzalutamide; a prespecified subgroup analysis was conducted in the mHSPC population

METHOD

DESIGN & DATA
- Retrospective, observational, real-world cohort study using the US Optum Clinformatics Data Mart database
- Optum Claims contains deidentified data for >180 million individuals enrolled in fully insured commercial and Medicare Advantage plans

POPULATION
- Men aged ≥55 years with ≥12 months of baseline data before initiating darolutamide or enzalutamide for advanced prostate cancer (nmCRPC or mHSPC) between August 2019 to January 2026*
- Analyses included the overall population and mHSPC subgroup

PRIMARY ENDPOINTS
- **3-point MACE**: non-fatal MI, non-fatal stroke, or CV death†
- **4-point MACE**: 3-point MACE + unstable angina or coronary revascularization

ANALYSIS
- Multivariable Cox regression and doubly adjusted inverse probability of treatment weighting (IPTW) models‡ assessed the association between index treatment and time to MACE composite events
- Cumulative MACE incidence and absolute event rates were estimated using doubly adjusted IPTW Kaplan–Meier plots

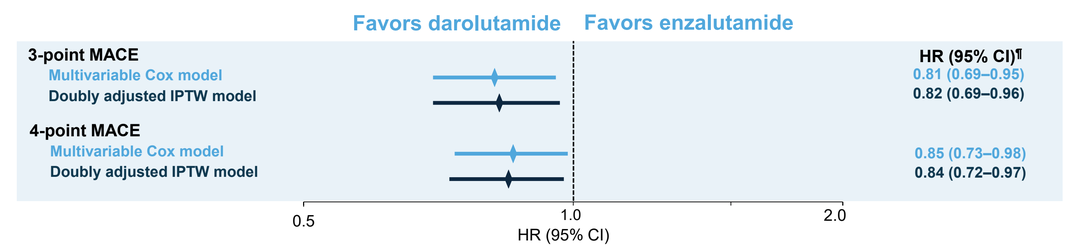
PATIENT BASELINE CHARACTERISTICS

- Baseline demographics and comorbidity profiles were similar between cohorts, including median age (76–77 years) and mean Charlson Comorbidity Index scores (2.2 vs 2.2)
- Prior CV events were broadly similar, although atrial fibrillation and recent hospitalization were slightly more frequent in the darolutamide cohort

Patient baseline characteristics	Darolutamide (n=1737)	Enzalutamide (n=4373)
Age, median (range), years	76 (55.0–89.0)	77 (55.0–89.0)
Race, n (%)		
White	1099 (63.3)	2729 (62.4)
African American/Black	292 (16.8)	821 (18.8)
Other	346 (19.9)	823 (18.8)
Region, n (%)		
Northeast	239 (13.8)	422 (9.7)
North Central	391 (22.5)	924 (21.1)
South	717 (41.3)	2002 (45.8)
West	390 (22.5)	1025 (23.4)
Disease state, n (%)		
nmCRPC	634 (36.5)	2084 (47.7)
mHSPC	1103 (63.5)	2289 (52.3)
Charlson Comorbidity Index		
Mean (SD)	2.2 (2.2)	2.2 (2.2)
Prior CV events, n (%)		
Hospitalization in past 6 months	319 (18.4)	627 (14.3)
Diabetes	617 (35.5)	1559 (35.7)
Hypertension	1330 (76.6)	3368 (77.0)
Prior 3-point MACE§	352 (20.3)	850 (19.4)
Prior 4-point MACE§	377 (21.7)	903 (20.6)
Acute MI	57 (3.3)	125 (2.9)
Stroke	54 (3.1)	167 (3.8)
Atrial fibrillation	373 (21.5)	716 (16.4)
IHD	556 (32.0)	1377 (31.5)

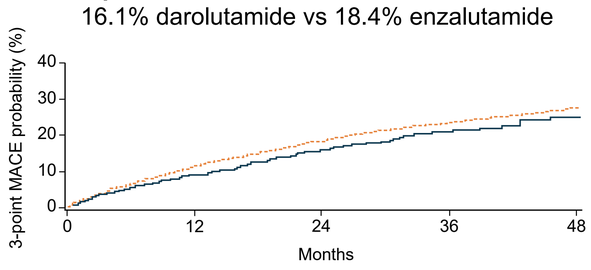
MACE OUTCOMES: OVERALL COHORT

- In the overall advanced prostate cancer population, **darolutamide was associated** with up to a **19% lower risk of 3-point MACE**, and up to a **15% lower risk of 4-point MACE** compared with enzalutamide

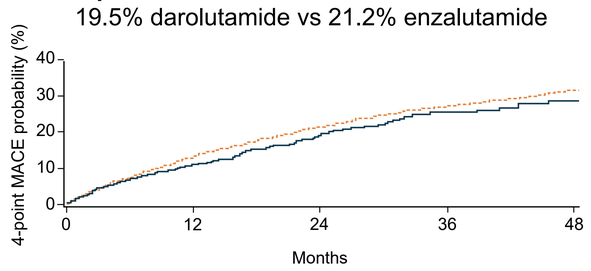


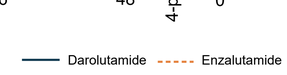
In the darolutamide and enzalutamide cohorts, respectively, 203 and 802 3-point MACE, and 244 and 922 4-point MACE occurred; median follow-up was 11 and 16 months. Forest plot estimates were derived using multivariable Cox proportional hazard models adjusted for treatment, age, race, region, metastasis, prior 3-/4-point MACE,§ prior hospitalization, hypertension, IHD, and diabetes; a doubly adjusted IPTW approach was also applied

At 24 months, probability of 3-point MACE was:
16.1% darolutamide vs 18.4% enzalutamide



At 24 months, probability of 4-point MACE was:
19.5% darolutamide vs 21.2% enzalutamide



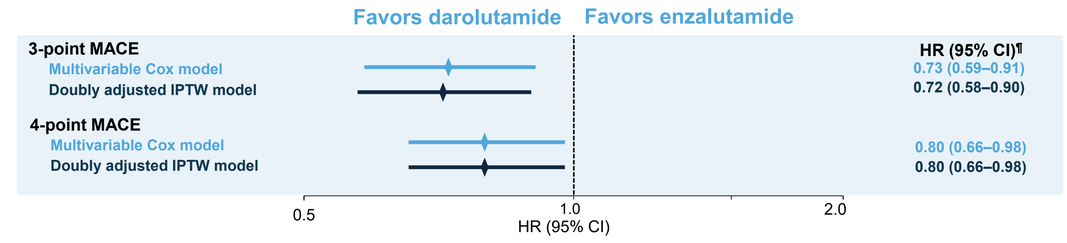


BASELINE FACTORS ASSOCIATED WITH MACE

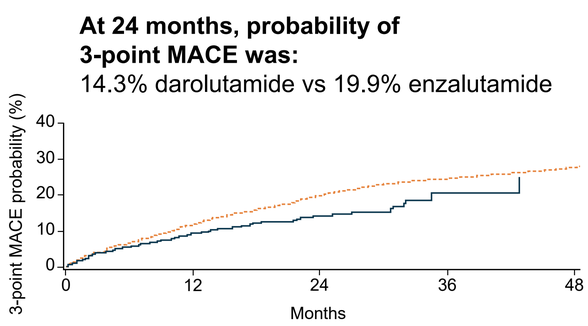
- MACE outcomes were associated with clinical history, age, race, and region
- Across covariates, similar associations were observed for 3-point and 4-point MACE
  - Prior MACE§ showed the strongest association for both outcomes

MACE OUTCOMES: mHSPC COHORT

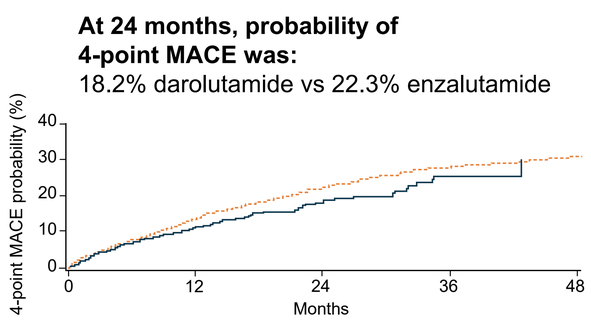
- In the mHSPC cohort, **darolutamide was associated** with up to a **27% lower risk** of 3-point MACE, and **20% lower risk of 4-point MACE** compared with enzalutamide



At 24 months, probability of 3-point MACE was:
14.3% darolutamide vs 19.9% enzalutamide



At 24 months, probability of 4-point MACE was:
18.2% darolutamide vs 22.3% enzalutamide



CONCLUSIONS

- This retrospective, real-world claims analysis supports the hypothesis that darolutamide is associated with a lower CV risk than enzalutamide. Residual confounding, event misclassification, and nonrandomized treatment allocation may have influenced the observed differences in MACE outcomes. Considering these limitations, the findings support EAU recommendations for darolutamide use in patients with CV risk

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Footnotes
*Data differ from those in the submitted abstract, because an updated analysis using a later data cut-off was conducted after abstract submission.
†CV death was defined as death within 30 days following MI, ischemic or non-traumatic stroke, heart failure, IHD, or cardiac arrest.
‡Propensity scores were estimated by logistic regression to create more comparable treatment groups; average treatment effect weights for darolutamide and enzalutamide were applied, and models were additionally adjusted for covariates that remained imbalanced after weighting. Kaplan–Meier curves were estimated in the same manner.
§Excludes CV death, but includes events leading to CV death within 30 days, including MI, ischemic or non-traumatic stroke, heart failure, IHD, or cardiac arrest.
¶The multivariable Cox regression and doubly adjusted IPTW models included treatment, age, race, region, and clinical history variables.

Abbreviations
ARPI, androgen receptor pathway inhibitor; **CI**, confidence interval; **CV**, cardiovascular; **EAU**, European Association of Urology; **ESC,** European Society of Cardiology; **HR**, hazard ratio; **IHD**, ischemic heart disease; **IPTW**, inverse probability of treatment weighting; **MACE**, major adverse cardiovascular events; **mHSPC**, metastatic hormone-sensitive prostate cancer; **MI**, myocardial infarction; **nmCRPC**, nonmetastatic castration-resistant prostate cancer.

References
1. EAU Prostate Cancer Guidelines. Available at https://uroweb.org/guidelines/prostate-cancer (Accessed October 2026); **2**. Lyon AR, et al. *Eur Heart J* 2022;43:4229–4361; **3**. Weiner AB, et al. *Cancer* 2021;127:2895–2904; **4**. Davey P, et al. *Int J Clin Pract* 2022;2022:2976811; **5.** O'Farrell S, et al. *J Clin Oncol* 2015;33:1243–1251; **6.** Matsukawa A, et al. *Prostate Cancer Prostatic Dis* 2025;28:298–308; **7.** Duong A, et al. *J Oncol Pharm Pract* 2025;10781552251406879.

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