Major Adverse Cardiovascular Events in high risk localised and metastatic hormone sensitive prostate cancer in four phase III STAMPEDE platform protocol trials

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Background
Major Adverse Cardiovascular Events (MACE) are a leading cause of non-cancer death in men with locally advanced (M0) and metastatic (M1) prostate cancer (PCa), of whom up to 30% have pre-existing CV disease. Although the Systemic Coronary Risk Evaluation (SCORE2) model estimates 10-year MACE risk in the general population, its performance in PCa is untested. We evaluated incidence of MACE across 4 phase 3 STAMPEDE trials and tested the utility of SCORE2 for risk stratification.

Methods
MACE were identified using a prespecified coding framework of ICD10 and OPCS codes through linkage of health systems data (up to March 2023) for STAMPEDE trial participants recruited to the docetaxel (DOC) ± zoledronic acid (ZA), abiraterone (AAP), AAP ± enzalutamide (ENZA) and radiotherapy (RT) trials. Flexible parametric competing risks models estimated 5 and 10-year cumulative incidence and sub-distribution hazard ratios (SDHR). Discrimination, calibration, and the clinical utility of SCORE2 was subsequently assessed.

Results
Linked data were available for 6,292 patients (M0 2,369, M1 3,923). The 10-year model based cumulative incidence of MACE in the DOC trial for M0 and M1 patients treated with ADT alone was 16% (95% CI, 12-22%) and 12% (9-17%) respectively; ADT+DOC for M0 and M1 patients was 17% (13-22%) and 12% (9-16%) respectively. In AAP and AAP+ENZA trials both M0 and M1 cohorts had a 5-year incidence of 7% (5–10%) with ADT alone, which remained similar with ADT+AAP or ADT+AAP+ENZA. Notably, patients with a prior CVD history had a significantly higher risk of MACE regardless of treatment allocation (M0 SDHR 2.17 (1.53-3.06), M1 2.16 (1.54-3.02)). Complete SCORE2 data were available for 4,239 (M0 1,595, M1 2,644) (70%) patients. SCORE2 demonstrated poor discriminative ability in this population (AUROC 0.61, at 10 years), with calibration characterised by systematic overprediction.

Conclusions
In this relatively fit population of STAMPEDE patients, the incidence of MACE was lower than that observed in real-world studies. Although treatment intensification did not significantly increase MACE risk overall, the elevated risk among patients with prior CVD and the poor performance of SCORE2 highlights the need for PCa-specific CV risk models in patients receiving systemic therapy.

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