Fracture-related hospitalisations in *de novo* advanced or metastatic hormone-sensitive prostate cancer: secondary analysis of the STAMPEDE abiraterone acetate plus prednisone +/- enzalutamide and M1|RT phase 3 trials using health systems data

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Background
Androgen deprivation therapy (ADT) has been the mainstay of treatment for patients with de novo metastatic (M1) and locally-advanced (M0) prostate cancer (PCa). Addition of androgen receptor signalling inhibitors (ARSI), including abiraterone acetate + prednisolone (AAP) or enzalutamide (ENZ) have shown significant survival benefits. Combination ADT+ARSI is now considered a standard-of-care. There is an urgent need to understand the long-term effects on bone health and fracture risk of ARSIs and prostate radiotherapy (RT) added to ADT.

Methods
We accessed health systems data (HSD) through Hospital Episode Statistics (HES) up to Mar-2021 for STAMPEDE participants (pts) in England randomised in the AAP, AAP with ENZ and RT trials. Pts were stratified by metastatic status: metastatic (M1); or non-metastatic (M0). Fracture related hospitalisations (FRH) were identified using a prespecified coding framework of ICD10 diagnosis and OPCS procedure codes. Flexible parametric competing-risk models were used to estimate 5-year cumulative incidence of FRH and sub-distribution hazard ratios (SDHR).

Results
Between Jan-2013 and Sept-2016, patients were randomised to the STAMPEDE AAP, AAP with ENZ and RT trials. Linked data were available for: 1,453 (82%) of 1,774 (734 M0, 1,308 M1) eligible pts from the AAP trial; 1,649 (89%) of 1,843 pts (900 M0, 749 M1) from the AAP+Enza trial; and 1,724 (85%) of 2,024 from the M1-RT trial. The 5yr model-based cumulative incidence of FRH was high in both M0 and M1 randomised to ADT alone (AAP trial: M0=15%, 95% CI 12-18%; M1=30%, 25-34%). FRH risk was significantly reduced in M1 pts allocated AAP (SDHR 0.77, 95% CI 0.59-0.99; p=0.044) or AAP+Enza (SDHR 0.69, 95% CI 0.54-0.88; p=0.002) but not M0 pts (AAP: SDHR 0.98, p=0.897; AAP+Enza: SDHR 0.76, p=0.104) or M1 pts allocated RT (SDHR 0.92, p=0.299).

Conclusions
The cumulative incidence of FRH was high in both M0 and M1 PCa participants. Treatment intensification with ASRIs significantly reduced FRH in M1 pts. No difference was seen in M0 pts or in M1 pts allocated local RT. These linked HSD data support the notion that the anti-cancer effect of ARSIs in metastatic hormone-sensitive prostate cancer significantly reduces the incidence of FRH.

Funding Acknowledgements: Prostate Cancer Foundation, John Black Charitable Foundation

Conflicts of Interest Disclosure Statement: AS reports travel support from Airamatrix.