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Original Article

Impact of Treatment Intensification with Abiraterone on Fracture-related Hospitalisation in Newly Diagnosed Prostate Cancer: A Secondary Analysis of Two Randomised Phase 3 Trials Within the STAMPEDE Trial Platform

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Abstract

Background: Prostate cancer (PCa) patients are at increased fracture risk due to the need for androgen deprivation therapy (ADT) and progressive bone metastases. Previous meta-analyses of randomised controlled trials suggest that androgen receptor pathway inhibitors (ARPIs) increase fracture risk.

Objective: We assessed the impact of abiraterone-based treatment intensification on fracture-related hospitalisation (FRH) within the STAMPEDE trial platform.

Design, setting and participants: We performed a secondary analysis of two STAMPEDE trials in patients with high-risk non-metastatic (M0) or metastatic (M1) disease.

Interventions: Patients were allocated to either standard of care (SOC) or SOC plus abiraterone with prednisolone (AAP) or, in a later comparison, SOC+AAP with enzalutamide (Enza).

Outcome measurements and statistical analysis: A prespecified coding framework within Hospital Episode Statistics (HES) identified FRHs. Flexible parametric competing-risk models estimated 5-year cumulative incidence of FRH and sub-distribution hazard ratios (SDHR), with death as a competing risk.

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Enzalutamide
Androgen receptor pathway
inhibitors
ARPIs
ADT
Health systems data

Outcome measurements and statistical analysis: Between Nov 2011 and Mar 2016, 3893 patients were randomised to the STAMPEDE AAPEnza trials. Linked HES data were available for 3102 patients in England. In M1 disease, 5-year FRH incidence was significantly lower with SOC + AAP than SOC alone (22% vs 30%; SDHR 0.77, 95%CI 0.59–0.99; $p = 0.04$) and with SOC + AAP + Enza than SOC alone (28% vs 38%; SDHR 0.69, 95%CI 0.54–0.88; $p = 0.002$). No significant difference was observed in M0 patients. Limitations include potential under-estimation of total fracture burden by exclusion of non-hospitalised fractures, lack of baseline assessment of fracture risk including bone mineral density, and longitudinal use of bone-protective therapy.

Conclusions: Abiraterone-based treatment intensification did not increase FRH compared to SOC alone. In M1 disease, abiraterone reduced rather than augmented fracture risk, most plausibly reflecting improved metastatic bone disease control.

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ADVANCING PRACTICE

What does this study add?

This study shows that abiraterone-based treatment intensification did not increase fracture-related hospitalisation in men with newly diagnosed hormone-sensitive prostate cancer. In men with metastatic disease, abiraterone with or without enzalutamide was associated with fewer fracture-related hospitalisations, most likely reflecting improved control of metastatic bone disease. These findings help reconcile previous adverse-event meta-analyses suggesting increased fracture risk with androgen receptor pathway inhibitors by showing that, when death is accounted for as a competing risk, clinically important hospitalised fracture events are not increased. The results support continued use of abiraterone-based intensification while reinforcing the need for routine fracture-risk assessment and bone-health optimisation in men receiving long-term androgen deprivation therapy.

Clinical Relevance

This secondary analysis of the randomized STAMPEDE platform provides high-quality evidence that abiraterone-based treatment intensification does not increase the risk of fracture-related hospitalization and, in men with metastatic hormone-sensitive prostate cancer, is associated with a clinically meaningful reduction in hospital-treated fractures. By leveraging long-term linked healthcare data and competing-risk analyses, the study challenges previous concerns derived from adverse-event meta-analyses, and suggests that improved metastatic bone disease control may outweigh the detrimental skeletal effects of intensified androgen suppression. For uro-oncologists, these findings support the use of abiraterone-based intensification without additional concern for severe fracture-related morbidity, while reinforcing the continued importance of systematic fracture risk assessment and appropriate bone-protective strategies in all patients receiving long-term androgen deprivation therapy. Associate Editor: Gianluca Giannarini, MD.

Patient Summary

We studied long-term hospital admissions for bone fractures in men with newly diagnosed prostate cancer treated in two STAMPEDE trials. Adding abiraterone, with or without enzalutamide, to standard hormone therapy did not increase fracture-related hospital admissions. In men whose cancer had spread, these treatments were linked to fewer fracture-related admissions, probably because they improved control of cancer that had spread to the bones.

1. Introduction

Androgen deprivation therapy (ADT) is a key component of standard treatment of newly diagnosed locally advanced or metastatic prostate cancer (PCa). ADT induces bone mineral density (BMD) loss, increasing fragility fracture risk [1,2], whereas metastatic bone progression compromises skeletal structure and predisposes to pathological fractures [3,4].

Such fractures affect quality of life [5] and overall survival [6].

Systemic therapy using combined ADT and androgen receptor pathway inhibitor (ARPI) was tested in two comparisons that did not overlap in time in the multiarm multistage STAMPEDE trial in patients with high-risk M0 or M1 hormone-naïve PCa. Cancer outcomes were improved in metastatic (M1) and nonmetastatic (M0) cohorts with the

addition of abiraterone acetate with prednisolone (AAP) [7,8], without additional benefit demonstrated with the addition of enzalutamide (Enza).

Evidence regarding the impact of ARPI treatment intensification on bone health remains sparse and conflicting, particularly in hormone-sensitive disease. In a PEACE-1 substudy, AAP did not significantly contribute to ADT-mediated BMD loss at 2 yr [9]. Bone turnover markers are reduced in patients with [10] and without [11] bone metastases when treated with both an ADT and an ARPI. Conversely, a previous meta-analysis of 17 randomised controlled trials showed an increased risk of fractures in patients treated with the addition of an ARPI [12]. However, adverse-event reporting in those trials was limited by inconsistent fracture definitions, variable follow-up, and an inability to account for the competing risk of death.

International guidelines [1315] recommend fracture risk stratification at diagnosis of hormone-sensitive PCa, with a risk-adapted approach that balances fracture prevention against the potential adverse effects of bone resorptive agents (BRAs). The use of Hospital Episode Statistics (HES) data to identify fracture-related hospitalisation (FRH) has been shown in earlier STAMPEDE comparisons. HES is a national dataset containing detailed records of all National Health Service (NHS) hospital attendances in England. FRH is a clinically meaningful outcome measure that captures fracture events that led to admission, including those occurring later than the traditional duration of trial adverse-event reporting [16]. We used this validated FRH framework to evaluate the impact of AAP, with or without Enza, on FRH in newly diagnosed hormone-sensitive PCa.

2. Patients and methods

2.1. Trial design

The STAMPEDE multiarm multistage trial (NCT00268476/ISRCTN78818544) recruited patients with high-risk M0 or M1 hormone-sensitive PCa between 2005 and 2023 from 126 UK and Swiss sites. Ethics approval was granted by the West Midlands Research Ethics Committee (number 04/MRE07/35); all patients provided written informed consent. This substudy analysed two trials that recruited between November 2011 and March 2016: standard of care (SOC) versus SOC with AAP (*the AAP trial*) and SOC versus SOC with AAP and Enza (*AAP + Enza trial*; [Supplementary Fig. 1](#)).

2.2. Procedures

Full procedural details of the STAMPEDE trial interventions have been published previously [7,8] and are available online (www.stampedetrial.org). SOC ADT was planned for at least 2 yr administration in patients with M0 disease and lifelong in patients with M1 disease. If allocated to treatment intensification, patients were planned for AAP given as abiraterone acetate (1000 mg) and prednisolone (5 mg) once daily or, in the AAP + Enza trial, AAP + Enza 160 mg orally once daily. Trial treatments were continued until progression, death, discontinuation because of side effects or up to 2 yr from randomisation in patients with

M0 disease. BRAs were used at clinician discretion. Baseline use of BRA was recorded on case report forms and follow-up use through systemic anticancer therapy records. Osteonecrosis of the jaw (ONJ) was assessed through HES using the prespecified International Classification of Diseases 10th Revision (ICD-10) codes: M87.18, M87.28 and K10.2 [17].

2.3. Inclusion/exclusion criteria

The full eligibility criteria for STAMPEDE have been published elsewhere [7,8]. Randomisation (1:1) was performed centrally ([Supplementary Table 1](#)). For this analysis, patients randomised after relapse from local treatment were excluded. Patients outside England were not HES-linked. HES records and Civil Registrations of Death (CRD) data were linked to STAMPEDE by NHS England for consenting patients or those recruited before February 2013 whose consent for linkage was unknown under NHS Act 2006 section 251 (Confidentiality Advisory Group [21/CAG/0048]). Linked data were securely transferred to the Medical Research Council (MRC) Clinical Trials Unit at University College London for analysis in a secure location.

2.4. Outcome measures

To ascertain the risk of a FRH, we used a prespecified coding framework of at least one ICD-10 code ([Supplementary Table 2](#)) diagnosis with/without accompanying Operating Procedure Code Supplement (OPCS) Classification of Interventions and Procedures version 4 (OPCS-4; [Supplementary Table 3](#)), as previously reported [16]. To focus on events occurring after trial recruitment, FRH events were excluded within a washout period of 60 d after discharge from any FRH taking place before randomisation.

The primary outcome measure was time to first FRH defined from randomisation until the date of the fracture event. Death from any cause was determined using the earliest of (1) the date reported on the STAMPEDE death case report form and (2) the date in the CRD dataset. Alive patients at the time of HES data extraction, without an FRH, were censored at the last known time of HES activity ([Supplementary Table 4](#)).

2.5. Statistical analysis

Statistical analysis was conducted in accordance with a pre-specified statistical analysis plan ([Appendix B](#)). The effect of adding either AAP or AAP + Enza on the cumulative incidence of FRH was tested separately in M0 and M1 disease using flexible parametric Fine-Gray models, using death as a competing risk [18]. The target of inference was the change in partial log likelihood of FRH when adding treatment allocation as a binary variable. The cumulative incidence of FRH was estimated using regression standardisation and the delta method from cause-specific hazard models [1922]. Cause-specific hazard ratios (CSHR) were reported alongside subdistribution hazard ratios (SDHR) from a Fine-Gray competing-risk model. CSHRs measured the effect on the hazard of FRH in individuals who remained alive and remained at risk. SDHRs measured the treatment effect on the cumulative incidence (absolute

risk) of FRH, taking account of the competing risk of death [23,24]. All models were covariate-adjusted for the minimisation factors used at randomisation (Supplementary Table 3). Parametric baseline hazards were estimated with 5 degrees of freedom. Median time from randomisation to loss to follow-up was estimated using the reverse Kaplan-Meier method by censoring on death from any cause.

Three sensitivity analyses were performed: excluding FRH within 90 d of pathological fracture codes, excluding nonprimary ICD-10 diagnoses, and restricting analyses to only OPCS-4 procedure codes to focus on clinically meaningful events requiring intervention. No indirect comparison of SOC + AAP and SOC + AAP + Enza was planned.

3. Results

Between November 2011 and January 2014, 1917 patients were recruited to the AAP trial, and between March 2014 and March 2016, 1976 patients were recruited to the AAP + Enza trial. In total, 3102 of the 3893 patients met eligibility criteria for this analysis. Exclusions were because of relapsed disease at presentation ($n = 200$) or lack of HES-linked FRH outcomes, including being outside England ($n = 601$; Fig. 1). Baseline characteristics between the HES-linked cohort and the overall trial cohort were comparable (Table 1). Among M1 patients in the linked cohort, metastatic burden was classified as low volume in 435 patients and high volume in 576 patients; metastatic burden was not assessed in 476 patients. Median follow-up was 7.8 yr for the AAP trial and 5.9 yr for the AAP + Enza trial, during which time 355 patients with M0 disease and 935 patients with M1 died (Table 2).

A total of 303 patients with M0 disease and 510 patients with M1 disease were detected as experiencing at least one FRH event (Table 2). The commonest site of fracture was the femur (Supplementary Tables 58). Only 8 patients were identified as having planned BRA use at baseline on trial CRFs. HES reported that ONJ was recorded in 2 patients, both allocated to SOC and who received a BRA within 2 yr after randomisation.

3.1. M0

No statistically significant difference in FRH risk was observed with the addition of an ARPI in patients with M0 disease (SDHR 0.98, 95% confidence interval [CI] 0.721.33; $p = 0.9$; Table 3; Fig. 2). The 5-yr cumulative incidence of FRH in patients with M0 disease was 15% (95% CI 12.18) for both arms of the AAP trial (Table 4). The average treatment effect of AAP on FRH over 5 yr was 0.2 (95% CI 4.3 to 3.9; Fig. 3; Supplementary Table 9).

Similar findings were observed in the AAP + Enza trial. A clinically relevant, nonstatistically significant reduction in fracture risk (SDHR 0.76, 95% CI 0.541.06; $p = 0.10$) was observed among patients allocated to receive SOC + AAP + Enza (Table 3). The 5-yr cumulative incidence of FRH was 15% (95% CI 12.18) with SOC compared to 11% (95% CI 9.15) with SOC + AAP + Enza (Table 4). The absolute risk reduction in FRH for SOC + AAP + Enza compared to SOC was 3.4% (95% CI 7.5 to 0.6; Supplementary Table 9).

Sensitivity analyses reflected the main findings, with no compelling evidence that the addition of ARPIs in the M0 setting affected FRH (Supplementary Tables 1015).

3.2. M1

A statistically significant reduction in FRH was observed in patients with M1 disease allocated to receive SOC + AAP (SDHR 0.77, 95% CI 0.590.99; $p = 0.04$; Table 4). The 5-yr cumulative incidence of FRH with SOC was 30% (95% CI 25.34) compared to 22% (95% CI 18.26) with SOC + AAP (Table 3).

Similar findings were also observed in the AAP + Enza trial, in which SOC + AAP + Enza significantly reduced the risk of FRH compared to SOC (SDHR 0.69, 95% CI 0.540.88; $p = 0.002$; Table 4). The 5-yr cumulative incidence of FRH was 38% (95% CI 33.43) in the SOC arm compared to 28% (95% CI 24.32) in the SOC + AAP + Enza arm (Table 3).

Sensitivity analyses detected a statistically significant reduction in patients with FRH and M1 disease allocated to SOC + AAP when analyses were limited to fracture events in the first 3 primary ICD-10 codes in HES events (Supplementary Tables 1213). No statistically significant differences were observed in FRH events in analyses limited to nonpathological fractures nor when limiting outcomes to procedural codes only (Supplementary Tables 14 and 15). Results of these sensitivity analyses were also replicated in the AAP + Enza trial. (Supplementary Tables 1015). In exploratory analyses stratified by metastatic site, the reduction in FRH with SOC + AAP + Enza was observed in patients with M1b disease, whereas estimates in the smaller M1a cohorts were imprecise with wide CIs (Supplementary Table 16).

4. Discussion

This prespecified secondary analysis of two STAMPEDE trials used linked NHS health system data to evaluate the impact of abiraterone-based treatment intensification on FRH in men with newly diagnosed hormone-sensitive PCA. Abiraterone-based intensification did not worsen FRH. In patients with M1 disease, SOC + AAP was associated with an absolute 8% lower 5-yr cumulative incidence of FRH and SOC + AAP + Enza with an absolute 10% lower incidence (Supplementary Table 9). These findings suggest that improved disease control with abiraterone-based intensification may reduce clinically meaningful hospitalised fracture events, potentially outweighing any adverse effect of intensified androgen signalling inhibition on skeletal fragility.

These findings contrast with aggregate adverse-event meta-analyses [12,25] and epidemiological studies [26] reporting increased fracture risk with ARPIs. Several factors may explain this apparent discordance. First, previous meta-analyses relied on adverse-event reporting, in which fracture definitions, attribution, severity thresholds, and follow-up duration vary across studies. In contrast, FRH is a validated hospitalisation endpoint capturing clinically meaningful fracture events requiring hospital-based care, which are known to affect quality of life [5]. However, it

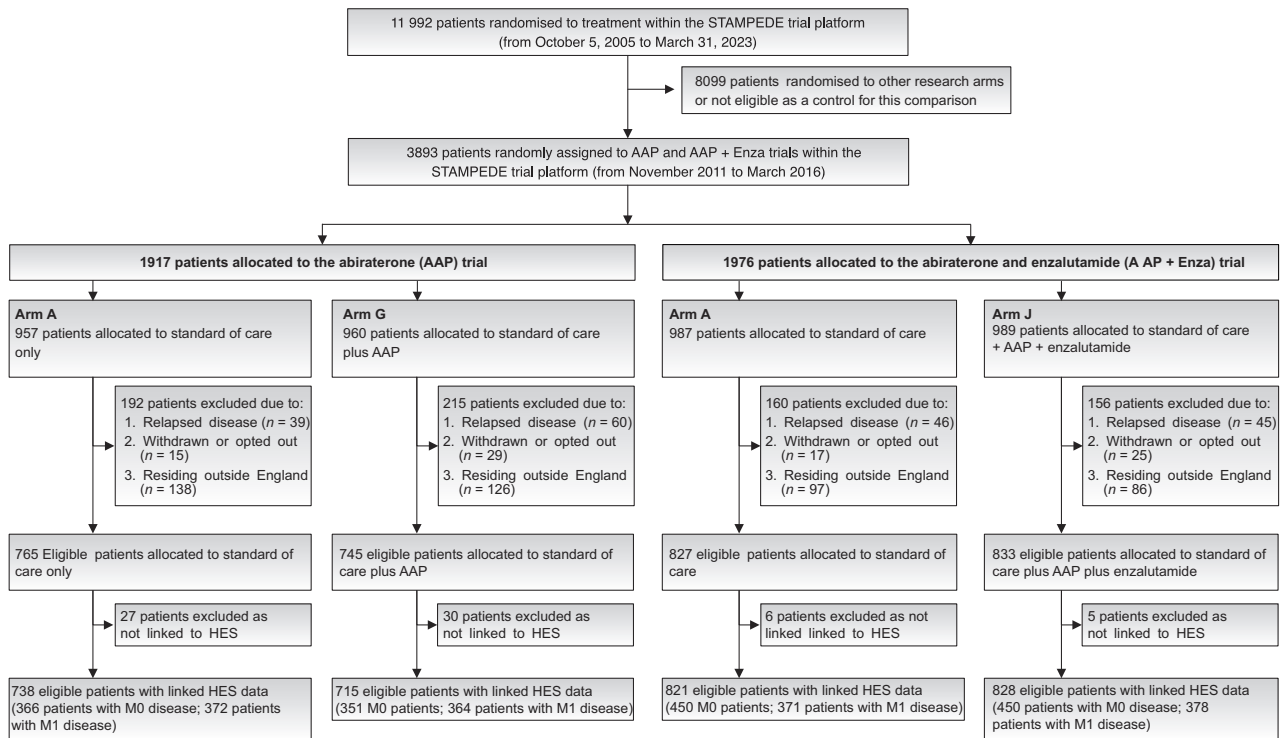


Fig. 1 – CONSORT diagram. Patients with newly diagnosed nonmetastatic or metastatic PCa recruited to the ARPI trials within the STAMPEDE trial platform in England were eligible for inclusion. PCa = prostate cancer; ARPI = androgen receptor pathway inhibitor; AAP = abiraterone acetate with prednisolone; Enza = enzalutamide; HES = Hospital Episode Statistics; M0 = nonmetastatic; M1 = metastatic; CONSORT = Consolidated Standards of Reporting Trials.

Table 1 – Baseline characteristics of linked cohort compared with the eligible trial cohort

	Linked cohort (N = 3103)		Eligible cohort (N = 3703)	
	n	%	n	%
Treatment arm				
A = ADT	1559	(50)	1859	(50)
G = ADT + AAP	715	(23)	900	(24)
J = ADT + AAP + enzalutamide	829	(27)	944	(25)
Age at randomisation (yr)				
<70	1830	(59)	2201	(59)
70	1273	(41)	1502	(41)
Disease burden				
M0 node negative	993	(32)	1161	(31)
M0 node positive	623	(20)	745	(20)
M1 low volume	435	(14)	536	(14)
M1 high volume	576	(19)	712	(19)
M1 not assessed	476	(15)	549	(15)
Tumour stage				
T0T2	240	(8)	275	(7)
T3T4	2743	(88)	3280	(89)
Not assessed	120	(4)	148	(4)
Gleason score				
<8	562	(18)	680	(18)
8	2489	(80)	2960	(80)
Not assessed	52	(2)	63	(2)
RT to prostate planned?				
No	1653	(53)	1982	(54)
Yes	1450	(47)	1721	(46)
Baseline WHO performance status				
0	2342	(75)	2838	(77)
12	761	(25)	865	(23)
Baseline PSA (g/L)				
049	1497	(48)	1772	(48)
50199	968	(31)	1147	(31)
200999	467	(15)	578	(16)
1000	171	(6)	206	(6)

ADT = androgen deprivation therapy; AAP = abiraterone acetate with prednisolone; RT = radiotherapy; M0 = nonmetastatic; M1 = metastatic; WHO = World Health Organization; PSA = prostate-specific antigen.

Table 2 – Summary of events by trial arm at time of analysis

Characteristic	AAP trial			AAP + Enza trial		
	SOC only	SOC + AAP	Overall	SOC only	SOC + AAP + Enza	Overall
Nonmetastatic						
Patients (n)	366	351	717	450	450	900
Status at analysis, n (%)						
1+ FRH, alive	29 (7.9)	37 (11)	66 (9.2)	40 (8.9)	38 (8.4)	78 (8.7)
1+ FRH, then died	56 (15)	42 (12)	98 (14)	39 (8.7)	22 (4.9)	61 (6.8)
No FRH, alive	219 (60)	223 (64)	442 (62)	319 (71)	357 (79)	676 (75)
No FRH, died	62 (17)	49 (14)	111 (15)	52 (12)	33 (7.3)	85 (9.4)
All-cause deaths	118 (32)	91 (26)	209 (29)	91 (20)	55 (12)	146 (16)
Cumulative incidence of FRH	85 (23)	79 (23)	164 (23)	79 (18)	60 (13)	139 (15)
FU (yr), mean (SD)	6.84 (1.81)	7.00 (1.87)	6.92 (1.84)	5.28 (1.19)	5.45 (1.03)	5.36 (1.11)
Metastatic						
Patients (n)	372	364	736	371	378	749
Status at analysis, n (%)						
1+ FRH, alive	12 (3.2)	23 (6.3)	35 (4.8)	23 (6.2)	24 (6.3)	47 (6.3)
1+ FRH, then died	124 (33)	83 (23)	207 (28)	130 (35)	91 (24)	221 (30)
No FRH, alive	75 (20)	124 (34)	199 (27)	102 (27)	167 (44)	269 (36)
No FRH, died	161 (43)	134 (37)	295 (40)	116 (31)	96 (25)	212 (28)
All-cause deaths	285 (77)	217 (60)	502 (68)	246 (66)	187 (49)	433 (58)
Cumulative incidence of FRH	136 (37)	106 (29)	242 (33)	153 (41%)	115 (30%)	268 (36%)
Mean yr FU (SD)	4.39 (2.67)	5.44 (2.78)	4.91 (2.78)	3.85 (1.90)	4.39 (1.91)	4.12 (1.92)

SOC = Standard of care; AAP = abiraterone acetate with prednisolone; FRH = fracture-related hospitalisation; FU = follow-up; Enza = enzalutamide; SD = standard deviation.

Table 3 – Point and interval estimates of FRH subdistribution and CSHRs

Treatment	SDHR (95% CI; treatment effect)	LRT p value	CSHR (95% CI; treatment effect)	LRT p value
Nonmetastatic				
Abiraterone	0.980 (0.7231.329)	0.897	0.973 (0.7151.324)	0.859
Abiraterone and enzalutamide	0.758 (0.5411.061)	0.104	0.737 (0.5261.032)	0.075
Metastatic				
Abiraterone	0.767 (0.5910.994)	0.044	0.633 (0.4900.818)	<0.001
Abiraterone and enzalutamide	0.689 (0.5410.877)	0.002	0.672 (0.5160.876)	0.003

CSHR = cause-specific hazard ratio; LRT = likelihood ratio test; SDHR = subdistribution hazard ratio; FRH = fracture-related hospitalisation; CI = confidence interval.

underestimates total fracture burden by excluding fractures managed without hospital admissions in emergency departments or outpatient settings, which are likely captured in aggregate adverse-event reporting.

Second, analyses based on aggregate adverse-event rates are vulnerable to competing-risk and survivorship bias. Patients allocated to effective treatment intensification, including abiraterone with ADT, live longer and therefore remain at risk of fracture for longer, increasing their absolute lifetime risk. If death is not accounted for, longer survival in the experimental arm may increase the observed number of fracture events, even if the treatment also reduces skeletal morbidity through improved cancer control. These analyses addressed this by using competing-risk models with death as a competing event rather than simply comparing crude event counts.

The reduction in FRH observed in M1 disease is biologically and clinically plausible. In metastatic hormone-sensitive PCa, fracture risk reflects both treatment-induced skeletal fragility and the structural consequences of progressive bone metastases. Individual trials have reported that AAP [7,8,27], Enza [28], and AAP + Enza [7,8] prolong time to skeletal-related events (SREs) in hormone-sensitive disease. Therefore, improved disease control may

reduce pathological skeletal complications, including events such as intractable bone pain and spinal cord compression. This interpretation is supported by the absence of a clear FRH reduction in M0 disease, in which metastatic bone progression is not a driver of skeletal instability. Given the absence of additional oncological benefit from adding Enza to AAP in STAMPEDE, the findings from the AAP + Enza comparison should not be interpreted as evidence that Enza independently reduces FRH.

The effect of ARPIs on bone health remains complex. Serum castration disrupts normal bone remodelling, increasing bone resorption with inadequate compensatory bone formation [29,30]. Coprescription of prednisolone remains a bone health concern with abiraterone [31], although direct comparisons of AAP versus Enza show similar SRE rates [32]. In PEACE-1, longitudinal BMD measurement showed rapid but comparable BMD loss in patients treated with ADT + AAP [9]. Bone turnover marker studies have also reported favourable changes with abiraterone in metastatic castration-resistant prostate cancer [10], and preclinical data suggest abiraterone may promote bone matrix deposition through inhibition of osteoclast differentiation and osteoblast activity [33]. Similarly, Enza monotherapy has been associated with preserved BMD

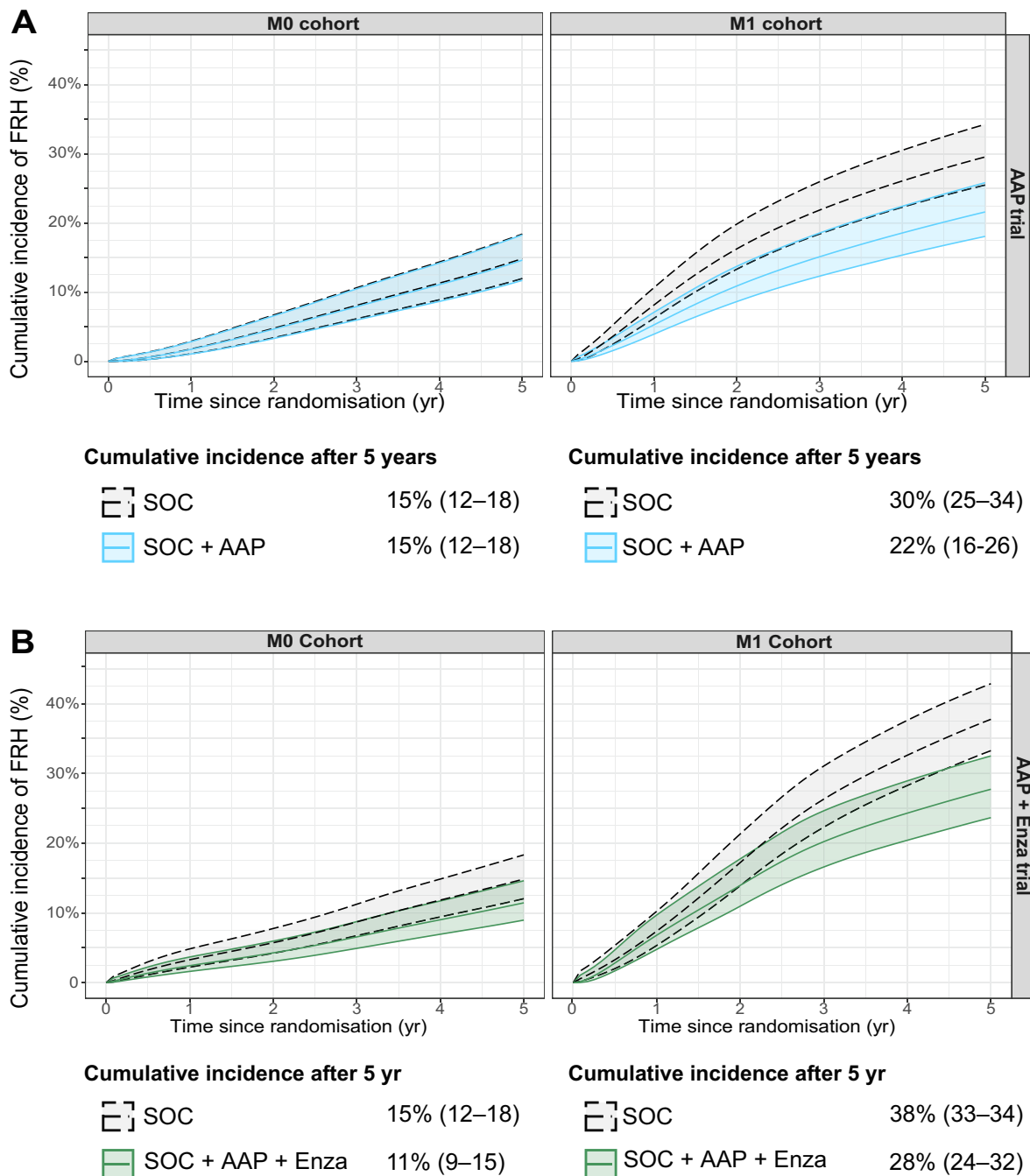


Fig. 2 – Flexible parametric competing risk model-based cumulative incidence of FRH for each cohort (M0/M1) by allocated treatment: (A) SOC only versus SOC + AAP and (B) SOC versus SOC + AAP + Enza. AAP = abiraterone acetate with prednisolone; Enza = enzalutamide; M0 = nonmetastatic; M1 = metastatic; SOC = Standard of care; FRH = fracture-related hospitalisation.

[34], a phenomenon previously observed with earlier-generation antiandrogen bicalutamide [35,36]. However, this mechanism is unlikely to apply when Enza is combined with ADT, where castration-driven bone loss predominates.

These observations are biologically plausible and hypothesis generating, but they should not be overinterpreted. The most plausible explanation for fewer FRHs in M1 disease is improved control of metastatic bone disease, although a direct favourable effect of abiraterone on skeletal biology cannot be excluded. The exploratory M1a/M1b

analysis is consistent with this interpretation, but the relationship between metastatic burden, treatment effect, and FRH remains inferential. More granular imaging-derived measures of osseous metastatic burden were not available in a standardised form, and this analysis was not powered to test treatment-effect heterogeneity by metastatic volume. Future imaging-based analyses are required to define how metastatic bone burden and distribution influence FRH risk. Overall, these findings suggest that abiraterone-based intensification may reduce clinically meaningful frac-

Table 4 – Model-based estimates of the cumulative incidence function for FRHs at 5 yr, stratified by metastatic status at randomisation

Trial arm	Cumulative incidence of FRH at 5 yr (95% CI)	
	Nonmetastatic	Metastatic
AAP trial		
SOC only	15% (1218)	30% (2534)
SOC + AAP	15% (1218)	22% (1826)
AAP + Enza trial		
SOC only	15% (1218)	38% (3343)
SOC + AAP + Enza	11% (915)	28% (2432)

FRH = fracture-related hospitalisation; AAP = abiraterone acetate with prednisolone; Enza = enzalutamide; SOC = standard of care; CI = confidence interval.

ture events requiring hospitalisation by delaying progression of bone metastases and reducing metastatic skeletal morbidity [29].

The strengths of this study include randomised comparisons within STAMPEDE; large M0 and M1 hormone-sensitive disease cohorts; long-term, linked, systematically recorded health system data; data collection beyond the usual duration and scope of trial adverse-event reporting; use of a prespecified FRH coding framework; and applications of competing-risk methods in a setting where treatment intensification substantially alters survival.

Several limitations should also be acknowledged. FRH captures only hospitalised fracture events and therefore does not measure the total incidence of fracture: asymp-

tomatic vertebral fractures, outpatient-managed events, or falls that did not result in admission. Established baseline predictors of fracture risk, such as those included in the FRAX[®] tool [37], BMD, falls history, frailty scores, sarcopenia, cognition status, and physical activity, were not systematically available and may be influenced by cancer treatments and disease progression. Although randomisation should balance measured and unmeasured fracture risk factors across treatment arms, these variables could not be directly modelled.

BRA use was uncommon at baseline, likely reflecting the treatment era and variation in clinical practice, with potentially incomplete capture during follow-up; therefore, the interaction between ARPI intensification and contemporary bone-protective strategies remains uncertain. Post hoc analyses of the LATITUDE [38] and BONENZA [39] trials suggested that BRAs can improve bone-health outcomes in men treated with ADT with or without AAP or Enza. Further research should define how baseline fracture risk, metastatic burden, ARPI treatment, and frailty interact to influence skeletal outcomes.

In conclusion, abiraterone-based treatment intensification did not increase FRH in newly diagnosed hormone-sensitive PCa. In M1 disease, SOC + AAP + Enza was associated with fewer FRHs, most plausibly reflecting improved control of metastatic bone disease. These findings are reassuring but do not remove the need for fracture-risk assessment, fall-risk mitigation, lifestyle optimisation, and appropriate bone-protective agents in people commencing long-term ADT.

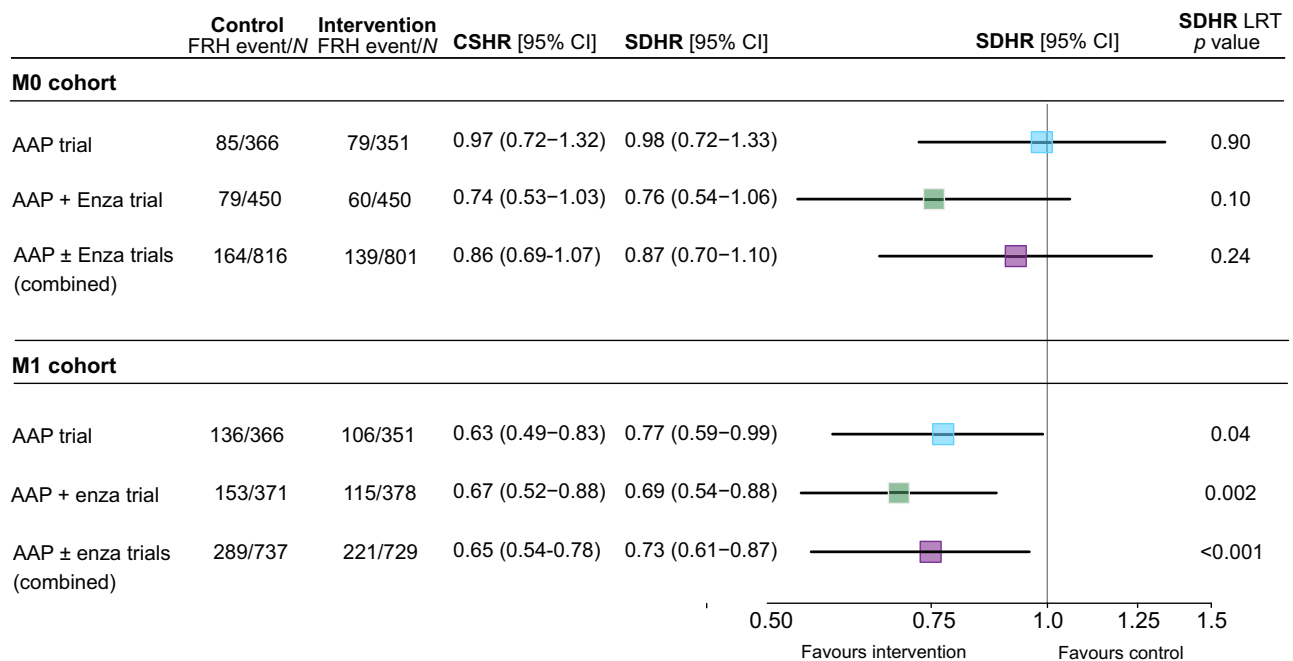


Fig. 3 – Forest plot of the SDHR showing the relative effect of treatment on the risk of FRH by metastatic stage. AAP = abiraterone acetate with prednisolone; Enza = enzalutamide; M0 = nonmetastatic; M1 = metastatic; FRH = fracture-related hospitalisation; CSHR = cause-specific hazard ratio; SDHR = subdistribution hazard ratio; CI = confidence interval; LRT = likelihood ratio test.

Author contributions: A. Sachdeva had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sachdeva, Jones, Clarke, Brown, McCloskey, Sydes.

Acquisition of data: Sydes, Murray, Dutey-Magni.

Analysis and interpretation of data: Dutey-Magni, Jones, Sachdeva, Gray, Clarke, Brown, McCloskey.

Drafting of the manuscript: Gray, Sachdeva, Clarke.

Critical revision of the manuscript for important intellectual content: All authors.

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Supplementary material

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