

## ORIGINAL ARTICLE

# Fracture-related hospitalisations in newly diagnosed high-risk localised or metastatic hormone-sensitive prostate cancer: secondary analysis of the STAMPEDE phase III trials of docetaxel and zoledronic acid using healthcare systems data

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**Background:** Androgen deprivation therapy (ADT), the mainstay systemic treatment for high risk non-metastatic (M0) and metastatic (M1) prostate cancer is associated with bone loss and increased fracture risk. The STAMPEDE trial tested the addition of zoledronic acid (ZA)  $\pm$  docetaxel (with prednisolone) to ADT. Both regimens may impact bone health. However, long-term fracture incidence remains uncertain.

**Patients and methods:** Health systems data were obtained for patients recruited from England and randomised to standard-of-care (SOC) ADT compared with SOC plus ZA or docetaxel or both docetaxel and ZA. ICD10 diagnosis and OPCS procedure codes from inpatient hospital admissions were used to identify fracture-related hospitalisations. Flexible parametric competing risks models were used to estimate 5- and 10-year cumulative incidence and sub-distribution hazard ratios (SDHR).

**Results:** 2140 of 2705 (79%) patients recruited from trial sites in England were eligible for this secondary analysis. Linked data were available for 2042/2140 (96%) pts (734 M0, 1308 M1). 5-year cumulative incidence of fracture for M0 and M1 patients treated with SOC only was 11% [95% confidence interval (CI), 8% to 15%] and 23% (95% CI, 19% to 28%), respectively. 10-year cumulative incidence in M0 patients was 26% (95% CI, 20% to 33%). Allocation to ZA significantly reduced the risk of fracture in M1 patients (SDHR 0.73, 95% CI 0.55-0.97;  $P = 0.015$ ) but not M0 patients (SDHR 0.88, 95% CI 0.59-1.32;  $P = 0.549$ ). Docetaxel had no clear effect on the risk of fracture in M0 ( $P = 0.570$ ) or M1 ( $P = 0.264$ ) patients.

**Conclusions:** High cumulative incidence of fracture was observed in both M0 and M1 prostate cancer patients receiving ADT. The addition of ZA to ADT  $\pm$  docetaxel significantly reduced long-term fracture risk in M1 participants but had no clear effect in M0 disease. These data support the use of bone protective agents to reduce fracture risk in men with M1 prostate cancer undergoing ADT.

**Key words:** prostate cancer, androgen deprivation therapy, fracture, zoledronic acid, docetaxel, health systems data

## INTRODUCTION

Prostate cancer (PCa) is the second most common male cancer worldwide and androgen deprivation therapy (ADT) is the mainstay systemic treatment. However, suppression of circulating androgens disrupts healthy bone remodelling, causing bone mineral density (BMD) loss.<sup>1,2</sup> This loss and disruption of bone microarchitecture is most rapid within 12 months of starting ADT<sup>3,4</sup> and it continues for the duration of

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treatment,<sup>5,6</sup> increasing the long-term risk of osteoporosis and fracture.<sup>7</sup>

The STAMPEDE trial recruited people with high-risk non-metastatic (M0) and metastatic (M1) hormone-sensitive PCa between 2005 and 2023, serially demonstrating improved survival advantage with early intensification of treatment ([www.thestampedetrial.org](http://www.thestampedetrial.org)). Trial results showed no evidence of an overall survival benefit with the addition of zoledronic acid (ZA) to ADT.<sup>8</sup> A survival advantage was demonstrated with addition of docetaxel (with or without ZA) across this trial population, though long-term analyses showed that a sustained improvement in overall survival was limited only to M1 patients.<sup>9</sup> Treatment intensification has resulted in improved survival outcomes among patients with advanced PCa, and a key focus is the maintenance of physical function and quality-of-life.

The impact of treatment intensification on bone health and the risk of adverse events, such as fractures, has not been examined comprehensively. International guidelines for men with hormone-sensitive PCa recommend routine risk assessment and consideration for bone protection only in patients at high risk of fracture.<sup>10-12</sup> Bisphosphonates (e.g. ZA) and RANKL inhibitors (e.g. denosumab) are frequently used for castrate-resistant disease to reduce skeletal morbidity,<sup>13</sup> and have been shown to help preserve BMD in men with newly diagnosed PCa treated with ADT.<sup>14</sup> However, studies to date have shown no evidence that ZA affects fracture risk in men with hormone-sensitive PCa receiving ADT.<sup>8,15</sup>

Hospital Episode Statistics (HES) provide a reliable, accurate, and detailed nationally collated record of clinical diagnoses and procedures for patients admitted to hospitals in England.<sup>16,17</sup> They contain Civil Registrations of Death (CRD), which are the central records of deaths registered to the General Register Office of England & Wales, as well as deaths reported by an NHS service, such as in-hospital deaths, for which integrity and provenance has also been demonstrated.<sup>18</sup> Linked healthcare systems data (HSD) through HES and CRD for STAMPEDE trial participants in England facilitates long-term assessment of fracture risk beyond standard trial follow-up. The objectives of this study were to evaluate the effect of treatment intensification with docetaxel and/or ZA on the cumulative incidence and risk of fracture.

## PATIENTS AND METHODS

### Trial design

The STAMPEDE multiarm multistage (MAMS) trial (NCT00268476, ISRCTN78818544) recruited men with high-risk M0 or M1, hormone-sensitive PCa between 2005 and 2023 from 126 UK and Swiss sites. The STAMPEDE protocol was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (full protocol provided in [Supplementary Appendix C](#), available at <https://doi.org/10.1016/j.annonc.2025.07.005>). Ethics approval was granted by West Midlands Research Ethics Committee (REC), now West Midlands, Edgbaston REC (REC number 04/MRE07/35), and all

patients were required to provide written informed consent. Patients were recruited between October 2005 and March 2013 to the original STAMPEDE trial comparisons, testing the effect of adding ZA and/or docetaxel to standard of care (SOC) with ADT ([Supplementary Figure S1](#), available at <https://doi.org/10.1016/j.annonc.2025.07.005>). To ascertain the risk of a clinical fracture we utilised a prespecified coding framework of International Classification of Disease 10th Revision (ICD-10) and OPCS Classification of Interventions and Procedures version 4 (OPCS-4) built on work developed by the National Prostate Cancer Audit.<sup>19</sup> Patients with relapsed disease were excluded due to the potential influence of prior ADT exposure on fracture risk.

HES records and CRD data were linked to STAMPEDE by NHS England and provided to the MRC Clinical Trials Unit (CTU) at UCL for analysis for (i) participants providing explicitly recorded consent for linkage and (ii) participants recruited before February 2013 whose consent for linkage was unknown under NHS Act 2006 section 251 approval by the Confidentiality Advisory Group (21/CAG/0048). While the STAMPEDE trial recruited 2962 participants from UK and Switzerland, such health systems data were only available for 2140 trial participants recruited in England (79% of the overall trial cohort).

### Randomisation and masking

Participants were randomised centrally by the MRC CTU. Randomisation was performed using the method of minimisation over a number of clinically important stratification factors with an additional random element ([Supplementary Table S1](#), available at <https://doi.org/10.1016/j.annonc.2025.07.005>). The number of patients with high-risk localised and M1 disease was not fixed. Allocation in the original comparisons of STAMPEDE included a 2 : 1 : 1 : 1 ratio to ADT-only as the standard-of-care (SOC), or SOC plus ZA, or SOC plus docetaxel, or SOC plus ZA and docetaxel. All allocations were open-labelled.

### Procedures

Standard-of-care ADT for M0 participants was administered for at least 2 years with gonadotrophin-releasing hormone agonists or antagonists (or oral bicalutamide anti-androgen therapy between 2006 and 2011). Primary-site radiotherapy for node-negative M0 participants was encouraged until November 2011 and then mandated; radiotherapy was optional for node-positive M0 participants. ADT was lifelong for M1 participants.

If allocated, ZA (4 mg intravenous infusion) was given for six 3-weekly cycles, then 4-weekly for 2 years with routine vitamin D and calcium supplementation, and if allocated, docetaxel (75 mg/m<sup>2</sup> intravenous infusion) given for six 3-weekly cycles with daily oral prednisolone (10 mg). Trial therapies were discontinued after disease progression or intolerable adverse events. As reported previously,<sup>8</sup> 40% of patients allocated to receive ZA completed 2 years of ZA treatment. The median duration of ZA was 16.6 months (IQR 7.8-23.2) for SOC + ZA and 19.5 months (IQR 9.1-23.4)

for SOC + ZA + Docetaxel, with the difference being driven by differences in time to progression.

### Outcome measures

The primary outcome measure for this secondary analysis was time to first fracture-related hospitalisation (FRH), defined from randomisation until the date of a hospital admission with a fracture diagnosis. FRHs were identified as Admitted Patient Care episodes containing at least one clinical fracture diagnosis (See [Supplementary Table S2](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>) and/or one coded fracture reduction or fixation procedure (See [Supplementary Table S3](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>). This definition did not cover fractures leading to an attendance at an emergency department which were not followed by an inpatient or day case hospitalisation. To focus on events occurring after trial recruitment, FRHs within a washout period of 60 days of a discharge from another FRH taking place before randomisation were discarded.

In patients with no FRH, time to FRH was censored on the earliest of: (1) HES dataset end date (31 March 2021) or (2) date of most recent English NHS hospital activity + 730 days, either hospital discharge from an English NHS hospital (HES-admitted patient care dataset) or attended outpatient appointment (HES outpatient dataset) post randomisation (see [Supplementary Table S4](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>). Criteria 2 was used to censor individuals lost to follow-up in HES or with discrepancies in data linkage. Death from any cause was determined using the earliest of (1) date reported on the STAMPEDE death case report form and (2) date in the Death Registrations provided by NHS England.

Osteonecrosis of the jaw (ONJ) is a rare, but significant, complication arising from use of ZA and other bisphosphonates.<sup>20</sup> This risk was examined by reporting the proportion of patients with at least one ONJ ICD-10 diagnosis code after randomisation (See [Supplementary Table S2](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>).

### Statistical analysis

Statistical analysis was conducted at the MRC CTU at UCL in accordance with a pre-specified Statistical Analysis Plan v2.0 ([Supplementary Appendix B](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>) (data extraction 04 May 2023). The study objective was to test the treatment effect of ZA, docetaxel, and the combination thereof in addition to ADT on the cumulative incidence of FRH, using flexible parametric Fine–Gray models (using death as a competing risk).<sup>21</sup> This objective was pursued separately in the high-risk M0 and M1 patient cohorts. The target of inference was the change in partial log-likelihood when adding a binary variable indicating allocation to the experimental arm of a comparison, similar to a Fine–Gray test. A minimum of 247 and 380 events, respectively, were required to detect a hazard ratio of 0.70 and 0.75 with 80% power at the 5% significance level.<sup>22</sup>

This analysis, like the main analysis for the trial, followed an intention-to-treat approach and a multiarm rather than factorial approach: models included an interaction effect for allocation to both docetaxel and ZA. Significance tests were performed in the following order: (1) docetaxel, (2) ZA, and (3) their interaction. The cumulative incidence of FRH was estimated using regression standardisation and the delta method from cause-specific hazard models using the *stpm2* and *standsurv* libraries.<sup>23–26</sup> The cause-specific hazard ratios (CSHR) are reported alongside sub-distribution hazard ratios (SDHR) from a Fine–Gray competing risk model fitted using the *stpm2cr* library. CSHRs measure the effect on the hazard of FRH in individuals who remain at risk (alive). SDHRs, however, measure the treatment effect on the cumulative incidence (absolute risk) of FRH, taking account the competing risk of death.<sup>27,28</sup> All models were covariate-adjusted for randomisation minimisation factors (age  $\geq 70$ , regional nodal involvement (N stage), WHO performance status, intended method of ADT, NSAID or aspirin use, planned radiotherapy). Parametric baseline hazards were estimated with 5 degrees of freedom in each failure type. The proportional hazards assumption was tested. Median time from randomisation to loss to follow-up was estimated using the reverse Kaplan–Meier method, by censoring on death from any cause.

### Sensitivity analyses

The primary analyses were replicated in three sensitivity analyses: (1) excluding FRH within  $\pm 90$  days of a pathological fracture code, in an attempt to focus on osteoporotic fractures plausibly related to prolonged ADT exposure ([Supplementary Table S2](https://doi.org/10.1016/j.annonc.2025.07.005), available at <https://doi.org/10.1016/j.annonc.2025.07.005>); (2) excluding non-primary ICD-10 clinical diagnoses (those not listed in the top 3 codes); and (3) using only OPCS-4 procedure codes, to focus on high-morbidity events, where surgical intervention was deemed necessary.

### RESULTS

Between 05 October 2005 and 31 Mar 2013, 2962 participants were enrolled into the STAMPEDE trial, randomised to receive ADT only as SOC or, SOC with ZA, docetaxel or docetaxel + ZA. 257 participants were excluded: 166 participants had previously received treatment and 91 participants refused consent for data linkage or opted out of additional data collection when stopping their trial participation early. Of the remaining 2705 eligible men, 2140 (79%) were recruited from sites in England of whom 2042/2140 (95%) could be linked successfully with HSD ([Figure 1](https://doi.org/10.1016/j.annonc.2025.07.005)). The linked cohort comprised 817 participants allocated to SOC, 404 to SOC + ZA, 407 to SOC + docetaxel and 414 to SOC + docetaxel and ZA. Baseline characteristics of the linked cohort were representative of the eligible trial cohort ([Table 1](https://doi.org/10.1016/j.annonc.2025.07.005)). Median follow-up duration was 9.9 years (IQR 9.7–10) for M0 patients and 10 years (IQR 9.7–10) for M1 patients ([Table 2](https://doi.org/10.1016/j.annonc.2025.07.005)). In total, 324/734 M0 and 1096/1308 M1 patients died during the study. Overall, 189/734 men with M0 disease at baseline experienced at least

one FRH compared with 386/1308 of those with M1 disease (Table 2). Fitted survival models found no evidence of non-proportional hazards for FRH or death.

### Non-metastatic disease

The treatment effect on the cumulative incidence of FRH with either ZA or docetaxel among patients with M0 disease was inconclusive (Table 3, Figure 2). There was no interaction effect between docetaxel and ZA ( $P = 0.805$ , Figure 3, Supplementary Table S7, available at <https://doi.org/10.1016/j.annonc.2025.07.005>). The cumulative incidence of FRH at 5 and 10 years in patients allocated to SOC was 11% [95% confidence interval (CI), 8% to 15%] and 26% (95% CI, 20% to 33%), respectively (Table 4). In patients allocated to SOC + docetaxel, the 5- and 10-year cumulative incidence of FRH was similar: 10% (95% CI, 7% to 13%) and 24% (95% CI, 19% to 30%), respectively. Zoledronic acid did not substantially reduce the 5-year cumulative incidence of FRH in those allocated to SOC or SOC + docetaxel: the absolute risk reduction was 1.2% (95% CI, -5.1% to 2.7%) and 1.2% (95% CI, -5.0% to 2.5%), respectively (Supplementary Table S5, available at <https://doi.org/10.1016/j.annonc.2025.07.005>). The most frequently occurring fracture code in M0 patients was 'O16 – Remanipulation of fracture of bone and fixation using plate', which contributed to 62% of first FRH events (Supplementary Table S6, available at <https://doi.org/10.1016/j.annonc.2025.07.005>).

### Metastatic disease

M1 patients allocated to ZA had a significantly decreased risk of FRH [SDHR 0.73, 95% CI (0.55-0.97);  $P = 0.015$ ] but there was no evidence of an effect on FRH with allocation to docetaxel

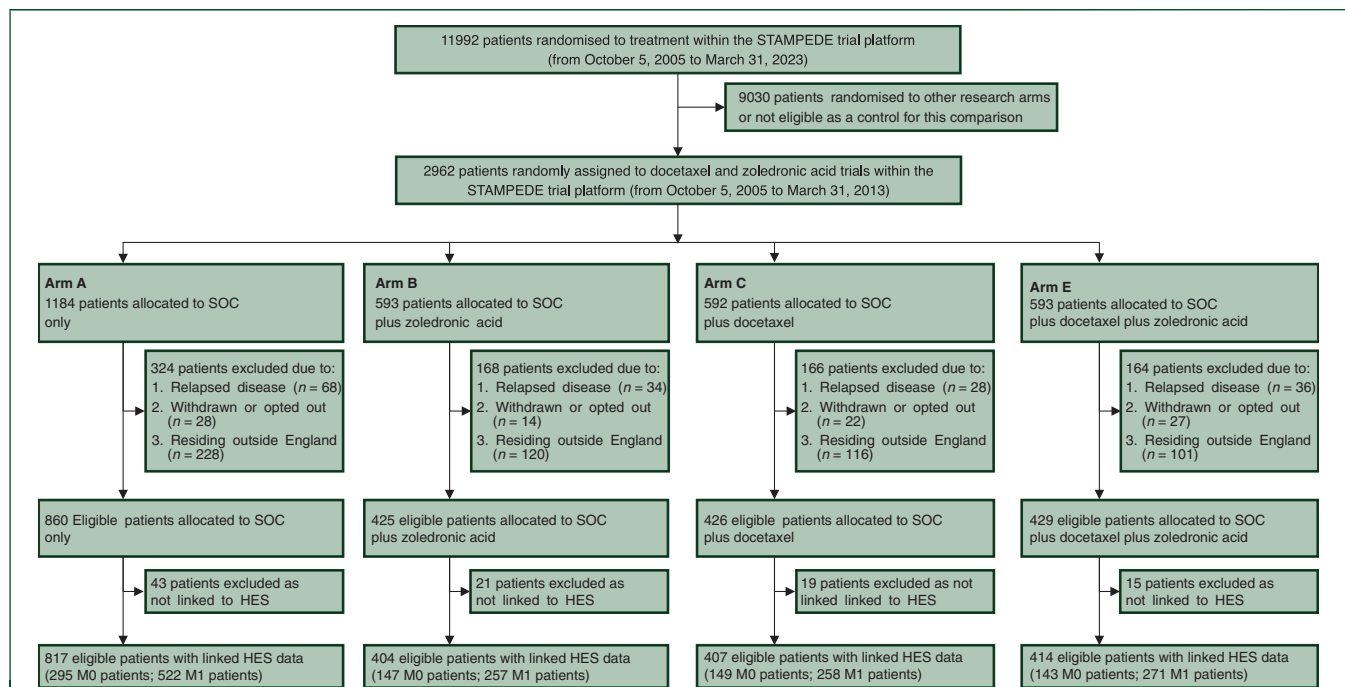
[SDHR 1.07, (95% CI, 0.82-1.38;  $P = 0.264$ )] (Figure 2). There was no interaction effect between docetaxel and ZA [interaction SDHR 1.14 (95% CI, 0.76-1.73;  $P_{\text{interaction}} = 0.526$ )] (Figure 3, Supplementary Table S7, available at <https://doi.org/10.1016/j.annonc.2025.07.005>). The cumulative incidence of FRH at 5 and 10 years in M1 patients allocated to SOC was 23% (95% CI, 19% to 28%) and 32% (95% CI, 27% to 37%), respectively (Table 3). In M1 patients allocated to SOC + docetaxel the 5-year incidence of FRH was similar: 23% (95% CI, 19% to 27%) (Table 3). In absolute terms, allocation to ZA reduced the 5-year cumulative incidence of FRH by 5.6% (95% CI, 0.4% to 10.3%) for those treated with SOC only, and a reduction of 5.4% (95% CI, 0.5% to 10.3%) in those treated with SOC + docetaxel (Supplementary Table S5, available at <https://doi.org/10.1016/j.annonc.2025.07.005>). Similar to the findings in M0 participants, the most frequently occurring fracture code in M1 participants was 'O16 – Remanipulation of fracture of bone and fixation using plate' which contributed to 64% of first FRH events (Supplementary Table S8, available at <https://doi.org/10.1016/j.annonc.2025.07.005>).

### Osteonecrosis of the jaw

The incidence of ONJ in both M1 and M0 participants allocated to ZA was 2.8% (23/818): this was significantly higher than those not allocated to ZA, where fewer than 10 events were identified [incidence <0.8% (<10/1224), corresponding to a risk ratio of >3.5 ( $P < 0.001$ )] (Supplementary Table S9, available at <https://doi.org/10.1016/j.annonc.2025.07.005>).

### Sensitivity analysis

There were no changes to the findings when limiting the analysis to primary diagnosis codes only and fracture



**Figure 1. CONSORT diagram.** Patients with non-metastatic or *de novo* metastatic prostate cancer recruited to the docetaxel and zoledronic acid trials within the STAMPEDE trial platform in England were eligible for inclusion. HES, Hospital Episode Statistics. SOC, standard of care.



**Table 1. Baseline characteristics of linked cohort compared with eligible trial cohort.**

| Characteristic <sup>a</sup>            | Linked, N = 2042 <sup>a</sup> | Not linked, N = 754 <sup>a</sup> | Overall, N = 2796 <sup>a</sup> |
|--|-------------------------------|----------------------------------|--------------------------------|
| <b>Trial arm</b>                       |                               |                                  |                                |
| A: SOC                                 | 817 (40%)                     | 299 (40%)                        | 1116 (40%)                     |
| B: SOC + zoledronic acid               | 404 (20%)                     | 155 (21%)                        | 559 (20%)                      |
| C: SOC + docetaxel                     | 407 (20%)                     | 157 (21%)                        | 564 (20%)                      |
| E: SOC + docetaxel + zoledronic acid   | 414 (20%)                     | 143 (19%)                        | 557 (20%)                      |
| <b>Age at randomisation</b>            |                               |                                  |                                |
| Under 70 years                         | 1421 (70%)                    | 560 (74%)                        | 1981 (71%)                     |
| 70 years and over                      | 621 (30%)                     | 194 (26%)                        | 815 (29%)                      |
| <b>Disease burden</b>                  |                               |                                  |                                |
| M0 node-negative                       | 433 (21%)                     | 204 (27%)                        | 637 (23%)                      |
| M0 node-positive                       | 301 (15%)                     | 120 (16%)                        | 421 (15%)                      |
| M1 low volume <sup>b</sup>             | 350 (17%)                     | 98 (13%)                         | 448 (16%)                      |
| M1 high volume <sup>b</sup>            | 473 (23%)                     | 138 (18%)                        | 611 (22%)                      |
| M1 unknown                             | 485 (24%)                     | 194 (26%)                        | 679 (24%)                      |
| <b>T stage</b>                         |                               |                                  |                                |
| T0-T2                                  | 205 (10%)                     | 67 (9%)                          | 272 (10%)                      |
| T3-T4                                  | 1708 (84%)                    | 650 (86%)                        | 2358 (84%)                     |
| TX                                     | 129 (6%)                      | 37 (5%)                          | 166 (6%)                       |
| <b>Gleason score</b>                   |                               |                                  |                                |
| <8                                     | 367 (20%)                     | 149 (21%)                        | 516 (20%)                      |
| ≥8                                     | 1507 (80%)                    | 548 (79%)                        | 2055 (80%)                     |
| Not assessed                           | 168                           | 57                               | 225                            |
| <b>Planned RT to prostate</b>          | 555 (27%)                     | 281 (37%)                        | 836 (30%)                      |
| <b>Baseline WHO performance status</b> |                               |                                  |                                |
| 0                                      | 1567 (77%)                    | 610 (81%)                        | 2177 (78%)                     |
| 1-2                                    | 475 (23%)                     | 144 (19%)                        | 619 (22%)                      |
| <b>PSA value</b>                       | 72 (27, 201)                  | 70 (28, 185)                     | 71 (27, 199)                   |

HES, Hospital Episode Statistics; M0, non-metastatic; M1, metastatic; PSA, prostate-specific antigen; RT, radiotherapy; SOC, standard of care (androgen deprivation therapy only); T, clinical local tumour staging according to TNM; WHO, World Health Organisation.

<sup>a</sup>N (%); Median (IQR).

<sup>b</sup>Disease burden for M1 participants was determined based on the CHAARTED definition (high being ≥4 bone metastases with ≥1 outside the spine and pelvis, or visceral metastases).

procedure codes only (Supplementary Tables S10-S13, available at <https://doi.org/10.1016/j.annonc.2025.07.005>). However, contrary to the primary findings, analysis limited to non-pathological fractures in M1 participants failed to demonstrate a significant effect of ZA on FRH (SDHR 0.82, 95% CI, 0.61-1.11;  $P = 0.175$ ) (Supplementary Tables S14 and S15, available at <https://doi.org/10.1016/j.annonc.2025.07.005>).

## DISCUSSION

The STAMPEDE trial has demonstrated a survival advantage with the addition of docetaxel to SOC ADT in participants with primary presenting M1 disease, but there was no survival benefit with addition of ZA.<sup>8</sup> Results from this secondary *post hoc* analysis show a significant reduction in fracture risk with the addition of ZA in M1 patients, but results for men with M0 disease were inconclusive.

Outcome data for this study were collated using HSD from HES on Admitted Patient Care (inpatient).<sup>16,17</sup> HES provides near universal coverage of hospital care in England due to the predominance of government funding in the UK (94% of total inpatient care expenditure in 2019).<sup>29</sup> It contains a record of clinical diagnoses and procedures, the quality, completeness and accuracy of which has improved over time.<sup>30</sup> In 2019, 50% of research-funded trials registered with the National Institute for Health Care and Research were planning to access and use HSD.<sup>31</sup> The UK National Prostate Cancer Audit has previously

demonstrated the utility of HES data to report the high incidence of skeletal-related events (SREs) in men with advanced and M1 PCa.<sup>19</sup> In our study, successful data linkage for eligible STAMPEDE participants from England with consent or permission was excellent (>95%). Our study demonstrates the considerable potential of HSD linkage for patients randomised to different trial treatments, identifying those requiring hospitalisation with a fracture, providing important long-term outcome data on bone health. Any potential biases in the data linkage and/or underreporting, misclassification and extraction of events will likely be balanced across the trial arms by nature of the randomised population, giving greater confidence that observed differences in outcome are likely to be real.

The effects of androgen deprivation on BMD<sup>1-3</sup> coupled with higher rates of osteoporosis in men presenting with advanced PCa<sup>32</sup> contribute to an increased risk of fracture.<sup>7</sup> There is good evidence that bone protective agents preserve BMD in men receiving ADT as part of treatment for PCa.<sup>33,34</sup> Randomised trials of ZA in bone-metastatic PCa have typically reported skeletal morbidity as SREs. This wider definition includes only pathological fractures, as well as spinal cord compression, surgery to bone, radiation to bone, or a change in systemic anti-cancer therapy due to bony pain. The CALBG 90202 trial in mHSPC with bone metastases showed no evidence of reduction in SREs with early ZA.<sup>15</sup> The ZAPCA trial in a similar population showed

**Table 2. Summary events by trial arm by time of analysis**

|  | Trial arm      |                       |                 |                                   | Overall        |
|--|----------------|-----------------------|-----------------|-----------------------------------|----------------|
|  | SOC only       | SOC + zoledronic acid | SOC + docetaxel | SOC + docetaxel + zoledronic acid |                |
| Non-metastatic (M0)                    |                |                       |                 |                                   |                |
| N                                      | 295            | 147                   | 149             | 143                               | 734            |
| Events                                 |                |                       |                 |                                   |                |
| 1+ FRH, alive                          | 28 (9.5%)      | 8 (5.4%)              | 19 (13%)        | 12 (8.4%)                         | 67 (9.1%)      |
| 1+ FRH, then died                      | 56 (19%)       | 26 (18%)              | 19 (13%)        | 21 (15%)                          | 122 (17%)      |
| No FRH, alive                          | 128 (43%)      | 69 (47%)              | 73 (49%)        | 73 (51%)                          | 343 (47%)      |
| No FRH, died                           | 83 (28%)       | 44 (30%)              | 38 (26%)        | 37 (26%)                          | 202 (28%)      |
| All cause deaths                       | 139 (47%)      | 70 (48%)              | 57 (38%)        | 58 (41%)                          | 324 (44%)      |
| Cumulative incidence of FRH            | 84 (28%)       | 34 (23%)              | 38 (26%)        | 33 (23%)                          | 189 (26%)      |
| Median survival (years)                | 11 (9.7, —)    | 11 (9.1, —)           | 13 (11, —)      | 13 (10, —)                        | 12 (11, 13)    |
| Median follow-up (years <sup>a</sup> ) | 10 (9.7, 10)   | 9.8 (9.4, 10)         | 9.9 (9.6, 11)   | 9.9 (9.4, 10)                     | 9.9 (9.7, 10)  |
| Metastatic (M1)                        |                |                       |                 |                                   |                |
| N                                      | 522            | 257                   | 258             | 271                               | 1308           |
| Events                                 |                |                       |                 |                                   |                |
| 1+ FRH, alive                          | 13 (2.5%)      | 9 (3.5%)              | 7 (2.7%)        | 12 (4.4%)                         | 41 (3.1%)      |
| 1+ FRH, then died                      | 152 (29%)      | 51 (20%)              | 78 (30%)        | 64 (24%)                          | 345 (26%)      |
| No FRH, alive                          | 60 (11%)       | 25 (9.7%)             | 49 (19%)        | 37 (14%)                          | 171 (13%)      |
| No FRH, died                           | 297 (57%)      | 172 (67%)             | 124 (48%)       | 158 (58%)                         | 751 (57%)      |
| All cause deaths                       | 449 (86%)      | 223 (87%)             | 202 (78%)       | 222 (82%)                         | 1096 (84%)     |
| Cumulative incidence of FRH            | 165 (32%)      | 60 (23%)              | 85 (33%)        | 76 (28%)                          | 386 (30%)      |
| Median survival (years)                | 3.5 (3.3, 3.8) | 3.5 (3.0, 4.3)        | 4.9 (4.3, 6.0)  | 4.5 (4.1, 5.0)                    | 3.9 (3.7, 4.2) |
| Median follow-up (years <sup>a</sup> ) | 10 (9.7, 11)   | 10 (9.3, —)           | 9.8 (9.3, 11)   | 10 (9.6, 11)                      | 10 (9.7, 10)   |

FRH, fracture-related hospitalisation; SOC, standard of care (androgen deprivation therapy only).

<sup>a</sup>Point and 95% interval reverse Kaplan—Meier estimator.

ZA significantly reduced time to the first SRE, with a median difference of 18.8 months. However, there was no evidence of an effect on time to PCa progression or overall survival.<sup>35</sup> A meta-analysis of 18 trials in people with PCa and bone metastases across hormone-sensitive and castrate-resistant states concluded that addition of bisphosphonates did not improve overall survival, but there was evidence of a significant reduction in the incidence of SREs, including pathological fractures.<sup>36</sup> Zoledronic acid and other bone protective agents are more commonly used in men with castrate-resistant PCa with bone metastases to prevent SREs, where they significantly reduce skeletal morbidity<sup>13</sup> and are currently recommended in international guidelines.<sup>11,12</sup> Notably, our definition of fracture-related events, based on hospitalisation records, likely underestimates the true fracture burden. This approach excludes non-hospitalised fractures, asymptomatic events detected radiographically, and other skeletal complications such as radiotherapy or spinal cord compression that are typically included in broader SRE definitions used in trials like CALGB 90202 and ZAPCA. However, it captures a

clinically meaningful subset of events associated with higher morbidity and healthcare resource use, while based on a substantially larger sample size and longer follow-up compared with these previous trials.

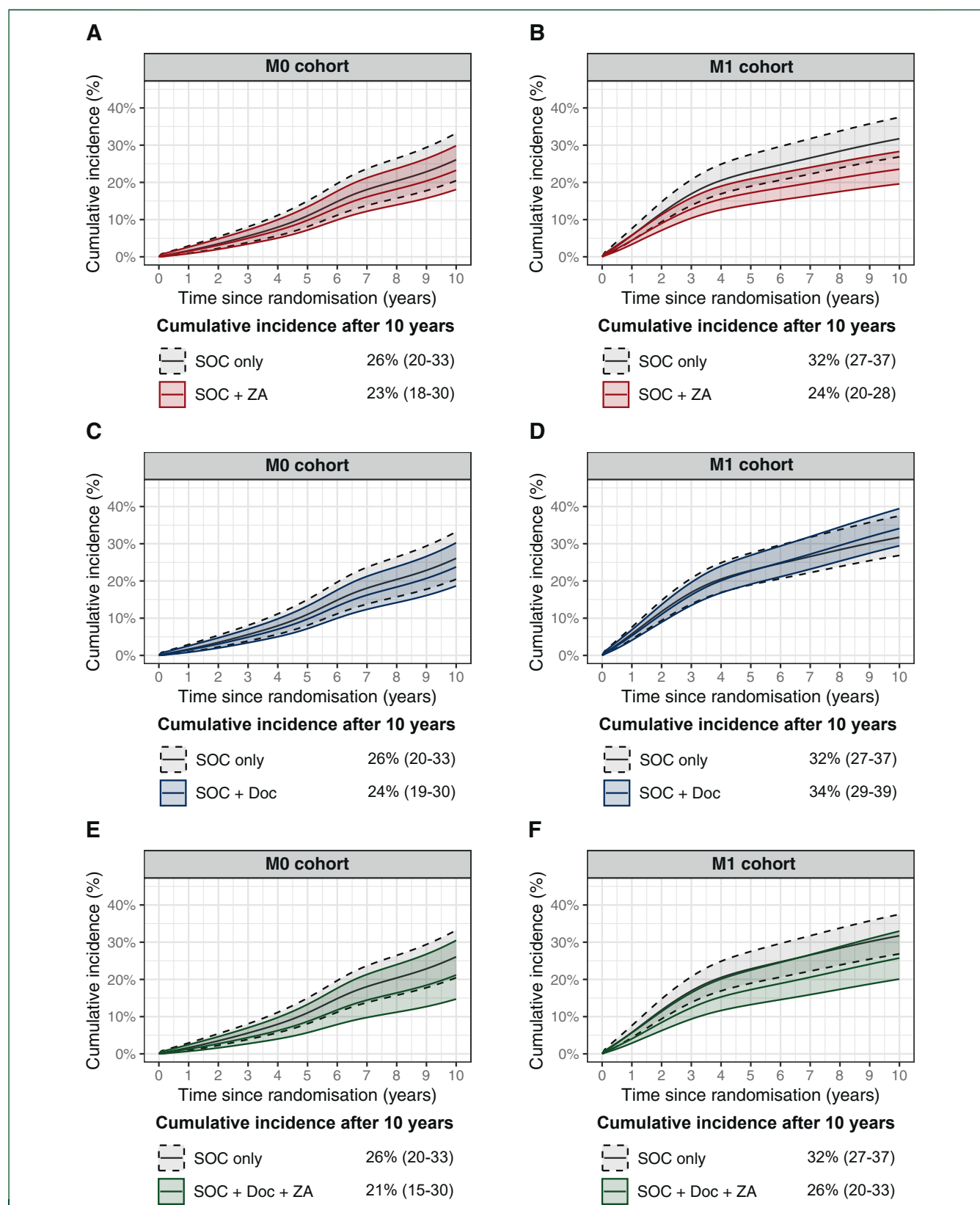
Given the relatively low event rate in patients with M0 disease, our estimates regarding the efficacy of ZA in this cohort remain inconclusive. The failure to detect a benefit of ZA in this population may potentially be driven by the relatively smaller sample size and the focus of our analyses on fractures that resulted in hospitalisation which would only capture a relatively small proportion of vertebral fractures, which significantly impact quality of life and contribute to pain. It may be that with longer follow-up and accrual of additional events; these effects may become more evident. Patients with M0 disease may therefore benefit from fracture risk assessment, including the use of biomarker-based assessments (e.g. serum-based or imaging-based), with those at increased fracture risk considered for early ZA treatment.

The ZA dose administered in STAMPEDE (4 mg 3-weekly for 6 doses then 4-weekly for 2 years) was an oncological

**Table 3. Point and interval estimates of FRH sub-distribution and cause-specific hazard ratios**

| Treatment                  | SDHR (95% CI) (treatment effect) | LRT<br><i>P</i> value | CSHR (95% CI) (treatment effect) | LRT<br><i>P</i> value |
|----------------------------|----------------------------------|-----------------------|----------------------------------|-----------------------|
| <b>Non-metastatic (M0)</b> |                                  |                       |                                  |                       |
| Zoledronic acid            | 0.88 (0.59-1.32)                 | 0.55                  | 0.89 (0.60-1.33)                 | 0.57                  |
| Docetaxel                  | 0.89 (0.62-1.30)                 | 0.57                  | 0.87 (0.59-1.28)                 | 0.46                  |
| <b>Metastatic (M1)</b>     |                                  |                       |                                  |                       |
| Zoledronic acid            | 0.73 (0.55-0.97)                 | 0.02                  | 0.76 (0.57-1.03)                 | 0.07                  |
| Docetaxel                  | 1.07 (0.82-1.38)                 | 0.26                  | 0.91 (0.70-1.18)                 | 0.68                  |

CI, confidence interval; CSHR, cause-specific hazard ratio; LRT: likelihood ratio test; SDHR: sub-distribution hazard ratio.



**Figure 2.** Flexible parametric competing risk model based cumulative incidence plots of FRH for each metastatic cohort (M0/M1) by allocated treatment. SOC versus SOC + zoledronic acid trial in (A) M0 cohort, and (B) M1 cohort; SOC versus SOC + docetaxel trial in (C) M0 cohort, and (D) M1 cohort; SOC versus SOC + docetaxel + zoledronic acid trial in (E) M0 cohort, and (F) M1 cohort. FRH, fracture-related hospitalisation; M0, non-metastatic; M1, metastatic; SOC, standard of care; ZA, zoledronic acid.

**Table 4. Model based estimates of the cumulative incidence function for fracture-related hospitalisations at 5 and 10 years by metastatic status at baseline**

| Treatment                         | Model-based cumulative incidence (95% CI) |              |                 |              |
|-----------------------------------|---|--------------|-----------------|--------------|
|                                   | Non-metastatic (M0)                       |              | Metastatic (M1) |              |
|                                   | 5 years (%)                               | 10 years (%) | 5 years (%)     | 10 years (%) |
| SOC only                          | 11 (8-15)                                 | 26 (20-33)   | 23 (19-28)      | 32 (27-37)   |
| SOC + zoledronic acid             | 10 (7-13)                                 | 23 (18-30)   | 17 (14-21)      | 24 (20-28)   |
| SOC + docetaxel                   | 10 (7-13)                                 | 24 (19-30)   | 23 (19-27)      | 34 (29-39)   |
| SOC + docetaxel + zoledronic acid | 9 (6-13)                                  | 21 (15-30)   | 17 (13-23)      | 26 (20-33)   |

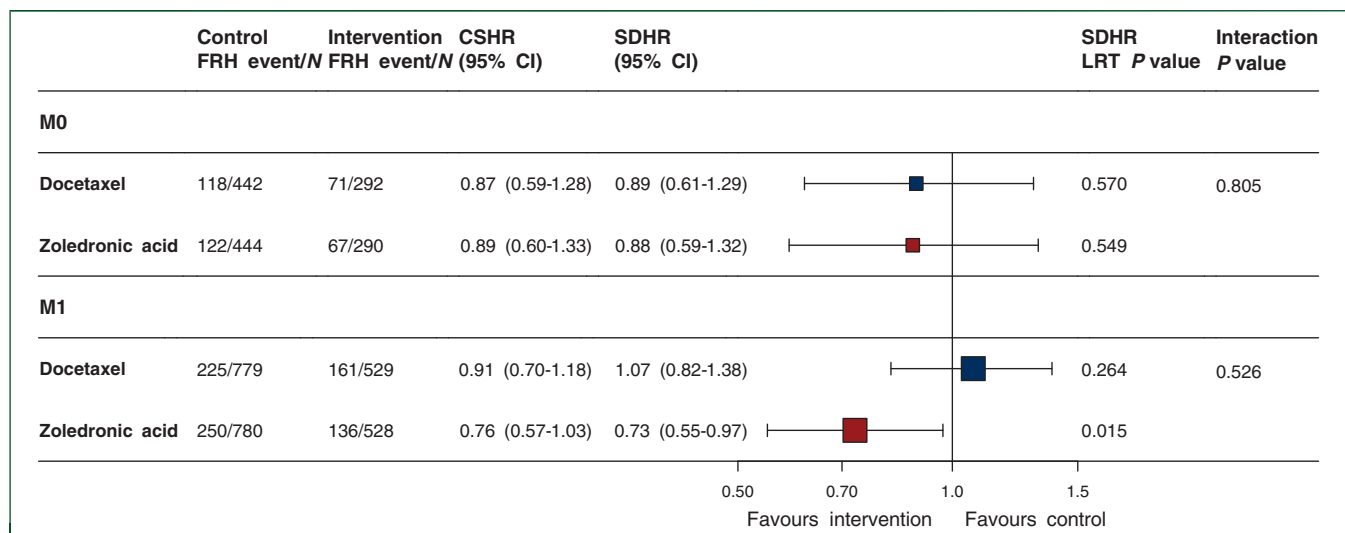
CI, confidence interval; SOC, standard of care (androgen deprivation therapy only).

dose and is considerably higher than is typically recommended for prevention of osteoporosis (5 mg yearly or 6-monthly). A randomised trial comparing 4-weekly 4 mg dosing to 12-weekly 4 mg dosing in patients with bone metastases, of whom 38% had PCa, showed no significant difference in SRE rate at 2 years.<sup>37</sup> These studies suggest that less frequent dosing of ZA, for example 6-monthly or annually, may be appropriate if widely adopted into routine clinical practice for people with M1 hormone-sensitive PCa. Such an approach is routinely used in early breast cancer, to reduce fracture risk in pre- and post-menopausal patients receiving hormonal therapy<sup>38</sup>: such regimens include ZA given 6-monthly.

Although other ZA-related adverse events (e.g. renal impairment, hypocalcaemia) were comprehensively documented in the original STAMPEDE report,<sup>8</sup> the risk of ONJ warrants distinct evaluation given its significant impact on quality of life and higher incidence with intensive treatment, with a cumulative incidence of 0.8% at year 1, increasing to 2.8% after year 3.<sup>39</sup> In our study the overall incidence of ONJ was 2.8% in patients allocated to ZA, in keeping with existing literature. Regular dental check-ups alongside vitamin D and calcium supplementation are recommended for all patients receiving bisphosphonates and other bone protective agents.<sup>40</sup>

The co-administration of prednisolone alongside docetaxel has been postulated to further affect bone health and increase fracture risk in addition to that already seen with ADT,<sup>10</sup> with mild to moderate risk of osteoporosis associated with >3 months duration with prednisolone dose between 2.5-5 mg.<sup>41</sup> In this trial, men were allocated to receive 10 mg prednisolone dose over six 3-weekly cycles, in which setting NOGG recommendations would recommend use of bone protective treatment. However, we found no evidence to support this notion: allocation to docetaxel with 10 mg prednisolone over six 3-weekly cycles did not alter the fracture risk for either M0 or M1 patients.

There are further limitations to this secondary analysis. Firstly, the linked cohort represents only 69% of the randomised trial cohort, largely due to the exclusion of patients not followed up in England (565/663 of excluded patients). Of eligible patients in England, data linkage was excellent (95%) and baseline characteristics of the study group were comparable with those of the whole trial cohort. Secondly, our methods would not have captured a patient who attended Accident and Emergency with a fracture not requiring a hospital admission or procedure. In addition, potential under-reporting or misclassification of events might further affect the incidence estimates. However, the sensitivity analyses using both procedure and primary



**Figure 3. Forest plot of the sub-distribution hazard ratios showing the relative effect of treatment on the risk of fracture-related hospitalisation by metastatic stage.** CSHR, cause-specific hazard ratio; FRH, fracture-related hospitalisation; LRT, likelihood ratio test M0, non-metastatic; M1, metastatic; SDHR, sub-distribution hazard ratio.



diagnosis codes separately support the primary findings that fractures were one of the primary reasons for hospitalisation, and most required procedural intervention (81%), contributing to increased morbidity. Analysis limited to non-pathological fractures failed to show a significant reduction in FRHs for M1 patients allocated ZA, potentially due to challenges in the coding of pathological fractures in this population. Finally, the median age of participants included in this analysis at trial enrolment was 65 years, much lower than the average patient diagnosed with M1 PCa in the UK.<sup>42</sup> Increasing age is associated with a greater risk of fracture, suggesting that the real-world fracture incidence in patients with PCa may be even higher than that reported here. Baseline DEXA scans were not mandated as part of the study, although randomisation should have balanced underlying fracture risk across groups. Though we observed a reduction in fracture incidence with the addition of ZA to SOC ADT in M1 patients, the contemporary SOC now includes upfront androgen receptor pathway inhibitors as part of doublet or triplet therapy, which may further increase fracture risk.<sup>43</sup> *Post hoc* analysis of the LATITUDE trial suggests that bone protection agents may also be beneficial in this setting,<sup>44</sup> though directly randomised evidence is currently lacking.

In conclusion, secondary analysis of the STAMPEDE trial using linked HSD demonstrates a high cumulative incidence of fracture-related hospitalisations in both M0 and M1 participants. Treatment with ZA significantly reduced the risk of fracture in patients with M1 disease, evidence providing strong support for a change in clinical practice whereby bone protective agents for *de novo* M1 PCa are used routinely as an SOC.

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WC reports personal fees from Janssen and Bayer, outside the submitted work.

RM and DM were patient representatives.

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