Gilbert Duncan (Orcid ID: 0000-0003-1859-7012)

Sydes Matthew R. (Orcid ID: 0000-0002-9323-1371)

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Authors	**Name** **ORCID** **Affiliation**
	Nicholas D James 0000-0002-7314-8204 Institute of Cancer Research, London, UK Twitter: @Prof_Nick_James
	Noel W Clarke 0000-0001-7776-8059 The Departments of Surgery & Urology, The Christie & Salford Royal Hospitals, Manchester, UK
	Adrian Cook 0000-0003-4417-2632 MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK
	Adnan Ali 0000-0002-8344-3776 The Christie NHS Foundation Trust, Manchester, UK
	Alex P Hoyle (none) Salford Royal HS Foundation Trust, Manchester. UK
	Gert Attard 0000-0002-4811-7983 UCL Cancer Institute, University College London, London, UK Twitter: @AttardLab
	Chris D Brawley 0000-0003-3641-278x MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK
	Simon Chowdhury (none) Guy's, King's, and St. Thomas' Hospitals, and Sarah Cannon Research Institute, London, UK Twitter: @SCSerendipity1

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William R Cross
0000-0001-9276-3053
St James University Hospital, Leeds, UK,

David P Dearnaley
0000-0002-3954-2806
The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK

Johann S de Bono
0000-0002-2034-595X
Institute of Cancer Research, London, UK

Carlos Diaz Montana
0000-0001-9082-4596
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK

Duncan Gilbert
0000-0003-1859-7012
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK

Silke Gillessen
0000-0001-5746-6555
Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland
Twitter: @Silke_Gillessen

Clare Gilson
0000-0001-6935-3232
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK;
Royal Marsden Hospital, London, UK

Rob J Jones
0000-0002-2904-6980
Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK

Ruth E Langley
0000 0002 9706 016x
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK

Zafar I Malik
(none)
The Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, UK

David J Matheson
0000-0002-3695-3167
University of Wolverhampton, Wolverhampton, UK

Robin Millman
(none)
(PPI) c/o MRC CTU at UCL

Chris C Parker
(none)
Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK
Twitter: @PCaParker

Cheryl Pugh
0000-0003-4584-9780
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK

Hannah Rush
0000-0001-9550-8808
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK & Guys and St Thomas' NHS Foundation Trust, London, United Kingdom

J Martin Russell
0000-0003-4594-4155
Institute of Cancer Sciences, University of Glasgow, Glasgow, UK; Beatson West of Scotland Cancer Centre, Glasgow, UK

Dominic R Berthold
0000-0002-1552-6617
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

Michelle L Buckner
(none)
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK

Malcolm D Mason
0000-0003-1505-2869
Velindre Hospital, Cardiff, UK

Alastair WS Ritchie
(none)
Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK

Alison J Birtle
0000-0002-2621-0909
Rosemere Cancer Centre, Lancashire Teaching Hospitals, University of Manchester, University of Central Lancashire, UK

Susannah J Brock
0000-0002-7561-0052
University Hospital Dorset, UK

Prantik Das
0000-0003-2976-4410
University Hospitals of Derby and Burton NHS Foundation Trust

Dan Ford
(none)
City Hospital, Cancer Centre at Queen Elizabeth Hospital, Birmingham

Joanna Gale
(none)
Portsmouth Hospitals University Trust, Portsmouth, UK

Warren Grant
0000-0002-9677-5198
Gloucestershire Oncology Centre, Cheltenham General Hospital, UK

Emma K Gray
(none)
Musgrove Park Hospital, Taunton, UK

Peter Hoskin
0000-0001-8323-9567
Mount Vernon Cancer Centre, Northwood, UK

Mohammad M Khan
(none)
Department of Oncology Castle Hill Hospital, Hull, UK; Scarborough General Hospital, Scarborough, UK

Caroline Manetta
(none)
Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

Neil J McPhail
(none)
Raigmore Hospital, Inverness, UK

Joe M O'Sullivan
0000-0001-6999-2739
Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK

Omi Parikh
0000-0003-4181-7124
Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, UK

Carla Perna
0000-0002-3035-2408
Royal Surrey NHS Foundation Trust, Guildford, UK

Carmel J Pezaro
0000-0003-2471-5265
Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Andrew S Protheroe
0000-0001-9413-0575
Oxford University Hospitals NHS Foundation Trust

Angus J Robinson
(none)
Sussex Cancer Centre, Brighton

Sarah M Rudman
(none)
Guy's & St Thomas' NHS Foundation Trust, London, UK

Denise J Sheehan
(none)
Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

Narayanan N Srihari
(none)
Shrewsbury & Telford Hospitals NHS Trust

Isabel Syndikus
0000-0001-5781-2067
The Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, UK

Jacob Tanguay
(none)
Velindre Cancer Centre, Cardiff

Carys W Thomas
(none)
Kent Oncology Centre, UK

Salil Vengalil
(none)
University Hospital North Midlands NHS Trust

John Wagstaff
0000-0002-1140-5981
Swansea University and the South West Wales Cancer Centre

James P Wylie
(none)
The Christie NHS Foundation Trust, Manchester, UK

Mahesh KB Parmar[1]
0000-0003-0166-1700
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK
Twitter: @MaxParmarMRCUCL

Matthew R Sydes[1]
0000-0002-9323-1371
MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, UCL, London, UK
Twitter: @MattSydes

[1] These authors contributed equally

Correspondence:
Professor Matthew R Sydes
E: m.sydes@ucl.ac.uk
CC: mrcctu.stampede@ucl.ac.uk
T: +44(0)7825995251
Twitter: @MattSydes, @MRCCTU

ABBREVIATION LIST

Abbreviation	Term
AA	Abiraterone acetate
AAP	Abiraterone acetate + prednisone/prednisolone
ADT	Androgen deprivation therapy
BP	Blood pressure
CI	Confidence interval
CRUK	Cancer Research UK
CT	Computerised Tomography (as in CT Scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
FFS	Failure-free survival
GnRH	Gonadotrophin-releasing hormone
HR	Hazard ratio
IQR	Inter-quartile range
mg	Milligrams
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR	National Institute of Health Research
NSAID	Non-Steroidal Anti-Inflammatory Drug
PSA	Prostate-specific antigen
QoL	Quality of Life
SAKK	Swiss Group for Clinical Cancer Research
SOC	Standard-of-care
SOC+AAP	Standard-of-care plus abiraterone acetate + prednisone/prednisolone
UCL	University College London
UK	United Kingdom
vs	Versus
WHO	World Health Organisation
yr	Year

NOVELTY AND IMPACT

Short version: STAMPEDE, the largest RCT of adding abiraterone to up-front hormone therapy for prostate cancer, including high-risk and low-risk metastatic disease, the only RCT incorporating this group. Long-term findings, with the longest patient exposure, support abiraterone as an effective treatment across newly-diagnosed metastatic prostate cancer. An updated, aggregate data meta-analysis of all available trials in this setting combines STAMPEDE with published long-term findings from LATITUDE, which recruited only patients with high-risk metastatic prostate cancer.

Long version: STAMPEDE is the largest randomised controlled trial of abiraterone added to upfront hormone therapy. This paper presents long-term follow-up data, representing in metastatic patients who have been on abiraterone for longer than in any other trial. STAMPEDE is the only trial to incorporate patients with low-risk metastatic disease. The findings support the utility of abiraterone as an effective treatment across the whole spectrum of patients with newly-diagnosed metastatic prostate cancer. The manuscript further combines the results with the published long-term findings of the LATITUDE trial, which recruited only patients with high-risk metastatic prostate cancer, and represents the first manuscript to present an updated meta-analysis of all the available trials in this setting.

ABSTRACT

Abiraterone acetate plus prednisolone (AAP) previously demonstrated improved survival in STAMPEDE, a multi-arm, multi-stage platform trial in men starting long-term hormone therapy for prostate cancer. This long-term analysis in metastatic patients was planned for 3yrs after the first results. Standard-of-care (SOC) was androgen deprivation therapy. The comparison randomized patients 1:1 to SOC-alone with or without daily abiraterone acetate 1000mg + prednisolone 5mg (SOC+AAP), continued until disease progression. The primary outcome measure was overall survival. Metastatic disease risk group was classified retrospectively using baseline CT and bone scans by central radiological review and pathology reports. Analyses used Cox proportional hazards & flexible parametric models, adjusted for baseline stratification factors. 1003 patients were contemporaneously randomized (Nov-2011--Jan-2014): median age 67yr; 94% newly-diagnosed; metastatic disease risk group: 48% high, 44% low, 8% un-assessable; median PSA 97ng/ml. At 6.1yr median follow-up, 329 SOC-alone deaths (118 low-risk, 178 high-risk) and 244 SOC+AAP deaths (75 low-risk, 145 high-risk) were reported. Adjusted HR=0·60 (95%CI:0·50—0·71; $p=0.31x10^{-9}$) favoured SOC+AAP, with 5-yr survival improved from 41% SOC-alone to 60% SOC+AAP. This was similar in low-risk (HR=0·55; 95%CI:0·41—0·76) and high-risk (HR=0·54; 95%CI:0·43—0·69) patients. Median and current maximum time on SOC+AAP was 2.4yr and 8.1yr. Toxicity at 4yr post-randomisation was similar, with 16% patients in each group reporting grade 3 or higher toxicity. A sustained and substantial improvement in overall survival of all metastatic prostate cancer patients was achieved with SOC + abiraterone acetate + prednisolone, irrespective of metastatic disease risk group.

INTRODUCTION

Intensifying Androgen Deprivation Therapy (ADT) with abiraterone, enzalutamide or apalutamide is effective for metastatic prostate cancer.[1-7] The LATITUDE trial defined metastatic disease risk groups and recruited only patients from a pre-defined "high-risk" group. That trial has reported a sustained improvement in survival after a median of 52 months. The primary analysis of the STAMPEDE "abiraterone comparison" was presented in 2017 and reported clinically meaningful and statistically significant improvements in overall and progression-free survival for adding abiraterone acetate with prednisolone to life-long ADT compared to life-long ADT alone.[6] A long-term analysis was planned for three years after the primary analysis. In 2019, the STAMPEDE Trial Steering Committee, which includes members independent of the Trial Management Group, agreed that future analyses should present results separately for metastatic (M1) and non-metastatic (M0) patients.

We present here the long-term results of metastatic patients in the STAMPEDE "abiraterone comparison" with an increase in median follow-up to 73 months and an increase >50% in the number of deaths. This analysis also incorporates the separation of cases by metastatic disease risk group, classified retrospectively, using the system adopted in the LATITUDE trial.[4,5] The extended follow-up from our previous paper[8] with additional events is of particular importance in clarifying treatment effects for patients with low-risk disease since they were excluded from the LATITUDE trial.[4,5]

METHODS

The patients, design, treatment, and analytic approach have been described in detail previously[6] and are summarised here.

Study Participants

For this comparison in STAMPEDE, eligible patients had metastatic prostate cancer that was newly-diagnosed or relapsing after previous local therapy and were initiating long-term androgen deprivation therapy (ADT) which had started no longer than 12 weeks prior to randomisation. There were no age restrictions, but patients were required to have no clinically significant cardiovascular history. For this analysis, patients had metastatic disease confirmed by scintigraphic bone scan and cross-sectional soft tissue imaging performed within twelve weeks of starting ADT.

Randomisation and masking

Patients were randomised centrally using a computerised algorithm, developed and maintained by the MRC Clinical Trials Unit. Minimisation with a random element of 20% was used, stratifying for hospital, age at randomisation (<70 vs ≥70 years), nodal involvement (negative vs positive vs indeterminate), WHO performance status (0 vs 1 or 2), planned SOC therapy, and regular aspirin or NSAID use (yes or no). Allocation was 1:1 to standard-of-care (SOC-alone) only group or SOC-alone with abiraterone acetate and prednisolone/prednisone group (SOC+AAP). There was no blinding to treatment allocation for practical reasons and the key efficacy outcome measures were objective.

Procedures

All patients received lifelong ADT using gonadotrophin-releasing hormone (GnRH) agonists, antagonists, or orchidectomy. Patients allocated to the SOC+AAP group were also planned to receive abiraterone (1000 mg daily) with prednisolone (5 mg daily). Treatment continued until progression

that usually included PSA but also required radiologic or clinical progression, or initiation of second-line therapy. Dose modifications were described in the protocol.

Patients were followed-up six-weekly until six months after randomisation, 12-weekly to two years, six-monthly to five years and then annually. PSA was measured at every follow-up visit; further tests were at the clinician's discretion. Nadir PSA was the lowest PSA reported within 24 weeks after randomisation. Regular safety monitoring was required as per the abiraterone product characteristics recommendations. Toxicities and symptoms were reported at regular follow-up visits, if associated with a change in treatment or when an adverse event was categorised as "serious". These were graded with Common Terminology Criteria (CTCAE) v3·0 until Feb-2015, v4.0 subsequently. Limited data were collected on long-term toxicity.

Metastatic disease risk group at randomisation was evaluated through whole body scintigraphy and CT or MRI staging scans. Bone scans were centralised and reviewed by two co-authors (AH and AA) with 10% independent review by a consultant uro-radiologist. Visceral metastases and Gleason score were recorded prior to randomization. Gleason score was reported locally by a clinically qualified pathologist. The metastatic disease risk group was classified according to the definition used in the LATITUDE trial,[1,2] with high-risk disease defined as at least 2 of: ≥3 bone metastases; visceral metastases; Gleason score ≥8.

Outcome measures and statistical analysis

The primary outcome for this comparison was overall survival, with secondary outcomes of failure-free survival, progression-free survival, metastatic progression-free survival, skeletal-related events, disease-specific survival, toxicity, and therapy for progression.

All analyses were by intention-to-treat. For time-to-event outcomes, the stratified log-rank test was used to test for differences between groups. Estimates of effect were obtained from stratified Cox regression models, with Kaplan Meier plots presented in KMunicate format.[9] The Grambsch-Therneau test was used to check the proportional hazards assumption, with restricted mean survival times from a flexible parametric model taking precedence in the presence of non-proportional hazards (shown where needed). Statistical significance was two-sided, taken as a p-value of 0.05, with no formal adjustment for interim analyses since this was pre-considered in the design. Differences in categorical variables were analysed using the Chi-squared test. The prevalence of adverse effects at two and four years after randomisation are presented for the solicited categories. Further drug treatment at any time after primary treatment failure is also presented.

A sensitivity analysis was undertaken to exclude patients who did not meet the strictest interpretation of all the protocol eligibility criteria, which primarily related to baseline blood pressure. The eligibility criteria excluded patients with uncontrolled hypertension. Patients reported as being fit for the trial, with no signs of uncontrolled hypertension or other severe cardiovascular history, but whose single baseline blood pressure (BP) reading was out-of-range were conservatively excluded in sensitivity analysis.

RESULTS

Between 15-Nov-2011 and 17-Jan-2014, 1917 patients were randomised to the arms of STAMPEDE constituting the "abiraterone comparison". Of these, all 1003 patients with metastatic disease were analysed here: 502 (50%) allocated to standard treatment (SOC-alone group) and 501 (50%) to standard treatment plus abiraterone and prednisolone (SOC+AAP group) (**Figure 1**). Median age at randomisation was 67 years (IQR 62-71), 941 (94%) had newly diagnosed disease (**Table 1**). Metastatic disease risk group was retrospectively classified as low-risk in 436 (43%) patients, high in 473 (47%) and was unclassified in a further 94 (9%). Bone metastases were detected in 882 (88%) patients and distant lymph node metastases in 293 (29%). All baseline disease characteristics were balanced between randomised groups.

The database was locked for this analysis on 03-Apr-2020. Median follow-up was 73 months (6.1 years). Median time on abiraterone in the SOC+AAP group was 29 months (IQR 12-71) and 126 (25%) participants were still on their trial supplies of abiraterone at the data freeze.

Deaths were reported in 573/1003 (57%) participants including 329 (66%) in the SOC-alone group and 244 (49%) in the SOC+AAP group: HR=0.60 for SOC+AAP (95%CI 0.50 to 0.71, p<0.0001) (**Table 2**, **Figure 2A**). There was no evidence of non-proportional hazards in the treatment effect (p=0.78). Median survival was 46 months (IQR 25, 92) in the SOC-alone group and 79 months (IQR 33, not reached) in the SOC+AAP group; 5-year survival was 41% (95%CI 37% to 45%) for SOC-alone and 60% (95%CI 50% to 71%) for SOC+AAP. The sensitivity analyses excluding 157 patients (16%) did not change the primary outcome measure results HR=0.62 (95% CI 0.52-0.75; $p=0.14x10^{-6}$).

Failure-free survival (FFS) events were reported for 437 (87%) in the SOC-alone group and 282 (56%) in the SOC+AAP group, HR=0.34 for SOC+AAP (95%CI 0.29 to 0.40, p<0.0001) (**Table 2**, **Figure 2B**). A statistically significant benefit of treatment with SOC+AAP, compared to SOC-alone, was observed in

all other secondary outcomes (**Table 2, Figures S1&S2**): progression-free survival (HR=0.58, 95%CI 0.49 to 0.69, p<0.0001), metastatic progression-free survival (HR=0.60, 95%CI 0.50 to 0.71, p<0.0001), skeletal-related events (HR=0.56, 95%CI 0.41,0.76, p=0.0008) and disease-specific survival (HR=0.49, 95%CI 0.39 to 0.60, p<0.0001).

Focusing on the 91% (909/1003) of patients for whom metastatic disease risk group could be calculated, the relative effect of SOC+AAP on overall survival was similar in both low-risk and high-risk metastatic disease risk groups (low-risk HR=0.55, 95%CI 0.41 to 0.76; high-risk HR=0.54, 95%CI 0.43 to 0.69 respectively) (**Table 3**, **Figure 3**). The effect of SOC+AAP was also observed to be similar in both low-risk and high-risk metastatic disease risk groups for the secondary outcomes of failure-free survival, progression-free survival, metastatic progression-free survival, skeletal-related events and disease-specific survival.

Further treatment was reported for most patients within 1 year of first disease progression (**Table S1, Figure S3**). Patients allocated to the SOC-alone group were more likely to receive abiraterone or enzalutamide within 1 year (abiraterone, 19% vs 2%, Chi-square p<0.0001; enzalutamide, 16% vs 8%, Chi-square p=0.002). Reported use of docetaxel within 1 year after first progression was higher among patients allocated to SOC+AAP (32% SOC-alone and 40% SOC+AAP, Chi-square p=0.048).

Adverse event data was reported at 2 years after randomisation for 136 patients in the SOC-alone group whose disease had not already progressed and 291 patients in the SOC+AAP group who were still on treatment. Of these, data was received from 133 (98%) SOC-alone and 286 (98%) SOC+AAP patients, respectively. The worst reported grade of toxicity was similar between randomised groups (p=0.29, **Table S2**) with grade 3 toxicity for 12 (9%) in the SOC-alone group patients and 20 (7%) in the SOC+AAP group, and no grade 4 or 5 toxicity. Four years after randomisation, the worst grade of toxicity reported was again similar between randomised groups (p=0.56).

DISCUSSION

This updated follow-up of the STAMPEDE "abiraterone comparison" demonstrated that the effects reported previously [6] were robust. With 57% participants now deceased and a median follow-up of more than 6 years, this represented a considerable increase in information over the previous report (**Table S3**): these results are unlikely to change meaningfully with any further follow-up.

There was no evidence of difference in effect size when the patients were separated by metastatic disease risk group using the system defined by researchers for the LATITUDE trial.[4, 5] This is important as, in many regions, both the licensed indication and reimbursement for the drug are restricted to the high-risk group defined by the eligibility criteria for the LATITUDE trial. We have shown previously that the "low-risk" metastatic disease risk group constitutes >40% of patients presenting with metastatic prostate cancer.[6, 10] We also carried out additional analyses using the definition of metastatic disease risk group employed in the CHAARTED trial.[11] Our previous analysis showed that the two systems for defining metastatic disease risk group largely coincided but that 18% (164/901) of patients were low-risk on one system and high-risk on the other (or vice versa). There was no evidence that the classifier used affected the overall conclusion with respect to the impact of disease burden on treatment effects.[8] The minority of patients for whom suitable imaging was unavailable are presented separately. This group will have had either missing scans or been staged using techniques such as PSMA-PET or whole-body MRI and thus are not directly classifiable using the separate systems for LATITUDE and CHAARTED. Our results strongly support the option for use of abiraterone for all patients starting long-term hormone therapy for metastatic prostate cancer, irrespective of metastatic disease risk group.

Table 4 shows the findings of STAMPEDE alongside the results from LATITUDE. Combining the aggregate results using standard meta-analysis methods further clarifies the survival advantage for SOC+AAP over SOC; this extended to the wider population of patients with metastatic prostate

cancer, not just those in the high-risk metastatic disease risk group defined for LATITUDE. Our long-term results are strikingly similar to those observed with both apalutamide[1, 2] and enzalutamide[3] in trials with similar eligibility criteria to the metastatic population into STAMPEDE. While those agents are androgen receptor antagonists, all three drugs work by targeting the androgen receptor axis. This suggests that a choice of any of these agents may be clinically reasonable and should be driven by secondary considerations such as side-effect profiles or cost rather than by primary efficacy or disease risk/metastatic burden. No additional toxicity data has been collected since the primary report in 2017, so we have not updated those aspects here. No further treatment for relapse had been reported for 29 of the 329 patients on the control arm who had died. Planned future access to national healthcare system data may facilitate reporting of additional long-term adverse events, such as late effects on cardiovascular effects, skeletal events and the need for additional systemic therapies.

Most patients in STAMPEDE had de novo metastatic disease, a higher proportion than most other trials in this setting and few patients had visceral metastatic disease at entry. Therefore, these trial data could not be used to explore whether there is a differential treatment effect by these characteristics.

The widely-accessible, alternative standard-of-care for men with hormone-sensitive metastatic prostate cancer is docetaxel.[11, 12] Controversy exists as to whether metastatic disease risk group predicts the effectiveness of the agent. Previous data from STAMPEDE supports the use of docetaxel as an alternative to androgen receptor targeting in all newly-diagnosed groups irrespective of metastatic disease risk group.[10, 13] Direct comparison of patient-related QoL outcomes previously supported the use of abiraterone over docetaxel,[14] however, costs of abiraterone are currently higher than docetaxel and hence reimbursement varies in different countries. As the abiraterone patent will be expired in most territories in the coming years, these costs can be expected to fall.

We have previously reported the effects of prostate radiotherapy for hormone-sensitive metastatic prostate cancer from another comparison in STAMPEDE.[15] Patients in that comparison did not receive upfront abiraterone hence we do not currently know the effect of the interaction between these two possible upfront therapies. The forthcoming data from the PEACE-1 trial, recently presented at ESMO, reports a failure free and overall survival advantage from the triplet compared to the ADT-abiraterone doublet. Further data are awaited from the ENZAMET and ARASENS trials on the same question. No trial has addressed the reverse question (should docetaxel be added to abiraterone). There will be quality of life plus relative fitness for docetaxel vs abiraterone issues that will likely limit uptake of the triplet therapy. Long-term follow-up of the complementary cohort of non-metastatic patients from this "abiraterone comparison" in STAMPEDE were analysed alongside first results from the trial "enzalutamide + abiraterone comparison" and show compelling evidence of improved metastases-free survival and overall survival with abiraterone-based therapy. Those non-metastatic patients did receive radiotherapy in the majority of cases, unless there was a clinical contraindication.[16]

In conclusion, this extended analysis further reinforces the body of data on the substantial benefits of upfront targeting of the androgen receptor pathway using abiraterone acetate in all men with hormone-sensitive metastatic prostate cancer, irrespective of metastatic disease risk group.

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Conflict of Interest:

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Ethics Statement:

Appropriate ethical review was in place for each participating country. All participants gave written, informed consent. The trial identification for

	STAMPEDE is NCT00268476 (clinicaltrials.gov) and ISRCTN78818544 (www.isrctn.com).
Author Contributions:	NDJ was the Chief Investigator. MP developed the MAMS concept. NDJ was the Comparison Chief Investigator. MKBP, NDJ, MRS, REL, NWC, MDM and DPD designed the trial. DPD, NDJ, MDM, MKBP, MRS and NWC were Grant holders (UK). NDJ, NWC, AC, GA, CDB, SC, WRC, DPD, JSdB, DG, SG, CG, RJJ, REL, ZIM, DJM, RM, CCP, CP, HR, JMR, MLB, MDM, AWR, MKBP and MRS were members of the Trial Management Group. CA, CP and MB were part of trial operations. All authors collated data. AC, NJ, NWC, AA, MKBP, and MRS wrote the Statistical Analysis Plan. AC, CB and MRS performed the analyses. All authors interpreted the data. NDJ, AC, NWC and MRS wrote critical sections of the manuscript. All authors reviewed, edited and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.
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TABLES AND FIGURES

Figure 1: CONSORT diagram

Figure 2: Overall survival by allocated treatment

Figure 3: Overall survival by allocated treatment and metastatic disease risk group

Table 1. Baseline characteristics

	SOC-alone n=502	SOC+AAP n=501	All n=1003
Age (years)			
Median (IQR)	67 (62-72)	67 (62-71)	67 (62-71)
Range	39-84	42-85	39-85
Eligibility category			
Newly diagnosed	475 (95%)	466 (93%)	941 (94%)
Relapsing	27 (5%)	35 (7%)	62 (6%)
PSA (ng/ml)			
Median (IQR)	97.2 (26.0-358)	96.3 (29-371)	96.9 (27.3-363)
Range	0.6-10530	0.1-21460	0.1-21460
Metastatic disease risk group			
Low-risk	220 (44%)	208 (42%)	428 (43%)
High-risk	232 (46%)	241 (48%)	473 (47%)
Unclassified	50 (10%)	52 (10%)	102† (10%)
Site of metastases*			
Bone	448 (89%)	434 (87%)	882 (88%)
Liver	8 (2%)	7 (1%)	15 (2%)
Lung	21 (4%)	21 (4%)	42 (4%)
Distant lymph nodes	150 (30%)	143 (29%)	293 (29%)
Other	26 (5%)	23 (5%)	49 (5%)

* patients can be in multiple categories

† includes 14 patients at Swiss sites for whom imaging could not be obtained

Key: IQR = Interquartile range; SOC = Standard-of-care; AAP = abiraterone acetate + prednisolone/prednisone

Table 2. Primary and Secondary outcomes

	SOC-alone n=502		SOC+AAP n=501		
Overall survival					
Events	329		244		
% alive at 5 yrs (95%CI)	41%	(37,45)	60%	(55,64)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.60	(0.50,0.71)	<0.0001
RMST (months), p(proportional hazards)	54	(51,57)	66	(63,69)	0.78
Failure-free survival					
Events	437		282		
% event-free at 5 yrs (95%CI)	13%	(11,17)	45%	(41,50)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.34	(0.29,0.40)	<0.0001
RMST (months), p(proportional hazards)	24	(21,27)	55	(51,59)	0.0001
Progression-free survival					
Events	323		241		
% event-free at 5 yrs (95%CI)	37%	(33,42)	54%	(50,59)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.58	(0.49,0.69)	<0.0001
RMST (months), p(proportional hazards)	47	(43,51)	62	(59,66)	0.038
Metastatic PFS					
Events	309		230		
% event-free at 5 yrs (95%CI)	40%	(36,45)	56%	(52,61)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.60	(0.50,0.71)	<0.0001
RMST (months), p(proportional hazards)	50	(46,53)	64	(60,67)	0.13
Skeletal-related events					
Events	100		76		
% event-free at 5 yrs (95%CI)	76%	(71,80)	82%	(78,86)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.56	(0.41,0.76)	0.0008
RMST (months), p(proportional hazards)	78	(74,81)	84	(82,87)	0.33
Disease-specific survival					
Events	255		156		
% event-free at 5 yrs (95%CI)	50%	(45,55)	72%	(67,76)	
HR=vs. SOC-alone (95%CI), p	(Reference)		0.49	(0.39,0.60)	<0.0001
RMST (months), p(proportional hazards)	60	(57,64)	75	(72,78)	0.97

Key: SOC = Standard-of-care; AAP = abiraterone acetate + prednisolone/prednisone; 95%CI = 95% confidence interval; RMST = restricted mean survival time; p = p-value; Reference = reference arm; yrs = years

Table 3. Primary and Secondary outcomes, by metastatic disease risk group using LATITUDE criteria

	Metastatic disease risk group											
	Low-risk				High-risk				Unclassified†			
	SOC-alone n=220		SOC+AAP n=208		SOC-alone n=232		SOC+AAP n=241		SOC-alone n=45		SOC+AAP n=43	
Overall survival												
Events	118		75		178		145		29		22	
% alive at 5 yrs, (95%CI)	55%	(48,61)	72%	(65,77)	28%	(22,34)	49%	(43,55)	40%	(26,54)	59%	(42,72)
HR=vs. SOC-alone (95%CI), p	0.54	(0.40,0.74)		<0.0001	0.54	(0.43,0.69)		<0.0001	0.63	(0.33,1.23)		0.180
Failure-free survival												
Events	178		92		215		165		40		22	
% event-free at 5 yrs, (95%CI)	21%	(16,26)	61%	(54,67)	6%	(3,9)	31%	(25,37)	18%	(8,30)	44%	(29,59)
HR=vs. SOC-alone (95%CI), p	0.32	(0.25,0.42)		<0.0001	0.28	(0.22,0.36)		<0.0001	0.33	(0.17,0.64)		0.002
Progression-free survival												
Events	118		73		169		146		32		19	
% event-free at 5 yrs, (95%CI)	50%	(43,57)	70%	(63,76)	25%	(19,31)	39%	(33,46)	36%	(22,49)	59%	(42,73)
HR=vs. SOC-alone (95%CI), p	0.55	(0.40,0.75)		<0.0001	0.56	(0.46,0.72)		<0.0001	0.38	(0.19,0.75)		0.007
Metastatic PFS												
Events	**113**		**66**		**164**		**142**		**30**		**19**	
% event-free at 5 yrs, (95%CI)	52%	(45,59)	73%	(66,79)	28%	(22,34)	41%	(34,47)	39%	(25,53)	59%	(42,73)
HR=vs. SOC-alone (95%CI), p	0.52	(0.37,0.72)		<0.0001	0.59	(0.47,0.75)		<0.0001	0.44	(0.22,0.88)		0.009
Skeletal-related events												
Events	35		24		55		44		9		8	
% event-free at 5 yrs, (95%CI)	84%	(78,89)	88%	(82,92)	65%	(56,73)	78%	(71,83)	77%	(57,88)	75%	(56,87)
HR=vs. SOC-alone (95%CI), p	0.47	(0.27,0.83)		0.010	0.51	(0.33,0.79)		0.008	0.83	(0.29,2.39)		0.82
Disease-specific survival												
Events	90		39		138		100		25		15	
% event-free at 5 yrs, (95%CI)	64%	(57,70)	86%	(80,90)	37%	(30,44)	60%	(53,66)	46%	(31,60)	72%	(54,84)
HR=vs. SOC-alone (95%CI), p	0.36	(0.24,0.54)		<0.0001	0.49	(0.37,0.65)		<0.0001	0.48	(0.22,1.04)		0.050

† Scans were unavailable for patients at sites in Switzerland, 14 further patients therefore do not appear in this table

Key: SOC = Standard-of-care; AAP = abiraterone acetate + prednisolone/prednisone; 95%CI = 95% confidence interval; RMST = restricted mean survival time; p = p-value; Ref = reference arm; yrs = years

Table 4. Combined analyses from STAMPEDE and LATITUDE

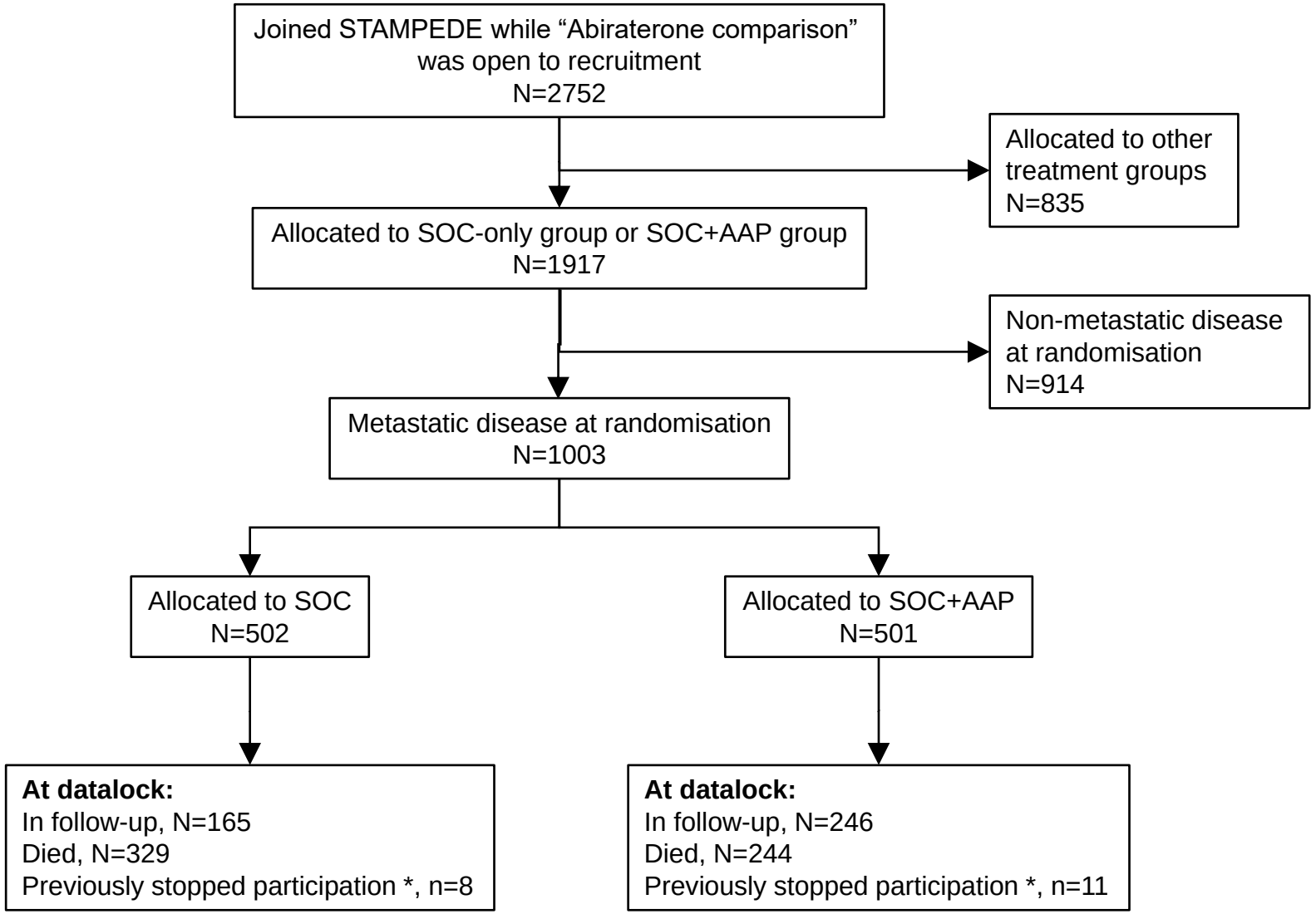
Trial & Population	Published	Pts	Control	Research	Hazard ratio (95% CI)
LATITUDE					
M1, High-risk	*First results: 2017*[4]	*1199*	*232 / 602*	*169 / 597*	*0·62 (0·51—0·76)*
	Updated results: 2019[5]	1199	305 / 602	230 / 597	0·66 (0·56—0·78)
STAMPEDE "abiraterone comparison"					
All: M0 and M1, any risk	*First results: 2017*[6]	*1917*	*262 / 957*	*184 / 960*	*0·63 (0·52—0·76)*
Subset: M1, any risk	*First results: 2017*[6]	*1002*	*218 / 502*	*150 / 501*	*0·61 (0·49—0·75)*
	Updated results (here)	1002	329 / 502	244/ 501	0·60 (0·50—0·71)
Subset: M1, high-risk	*First results: 2019*[18]	*473*	*136 / 232*	*94 / 241*	*0·54 (0·41—0·70)*
	Updated results (here)	473	178 / 232	145 / 241	0·54 (0·43—0·69)
Combined					
Metastatic, any risk			634 / 1104	182 / 1097	0·63 (0·50—0·71)
Metastatic, high-risk			483 / 843	182 / 829	0·62 (0·54—0·71)

Note: Risks defined using the metastatic disease risk group system used for LATITUDE.

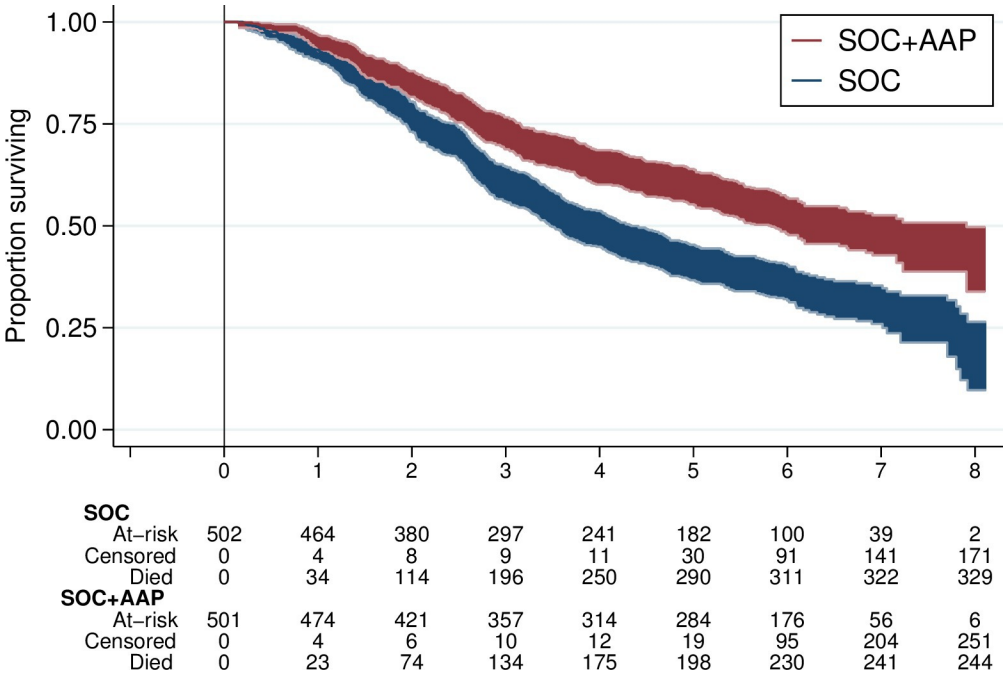
[1] Same data freeze as 2017 paper

Initial results from the STAMPEDE trial for advanced prostate cancer showed that adding abiraterone acetate and prednisone (AAP) to androgen deprivation therapy improved progression-free survival. Here, the authors present long-term results of metastatic patients in the STAMPEDE trial. Median follow-up increased from 52 to 73 months. They found that AAP improved overall survival of all metastatic prostate cancer patients, whether their disease was high-risk or low-risk.

Figure 1: Trial profile



* withdrew and refused permission for future health data to be collected
SOC = standard-of-care
AAP = Abiraterone acetate plus prednisolone/prednisone



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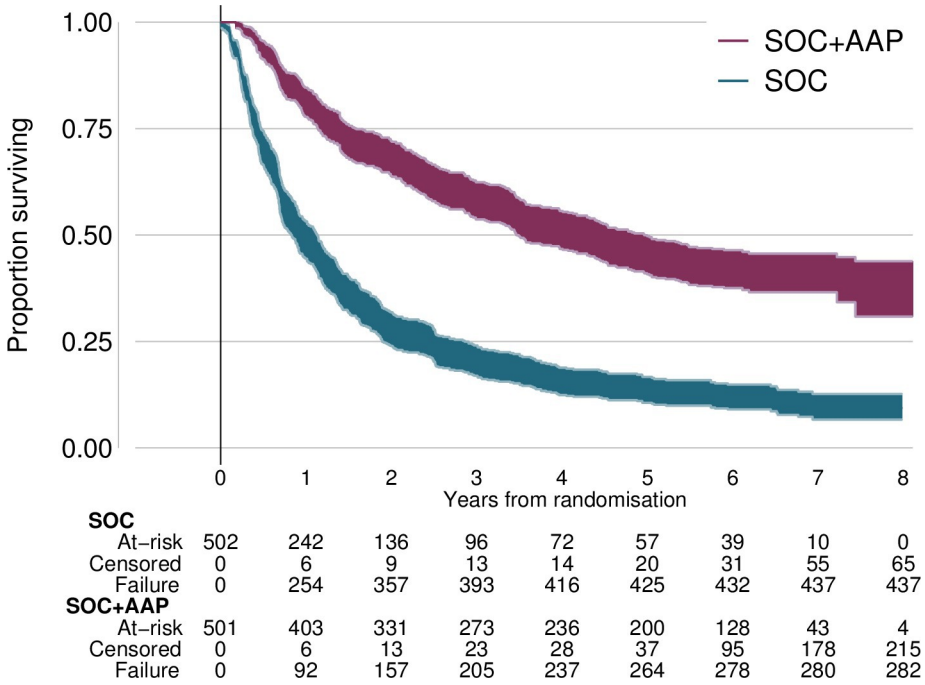
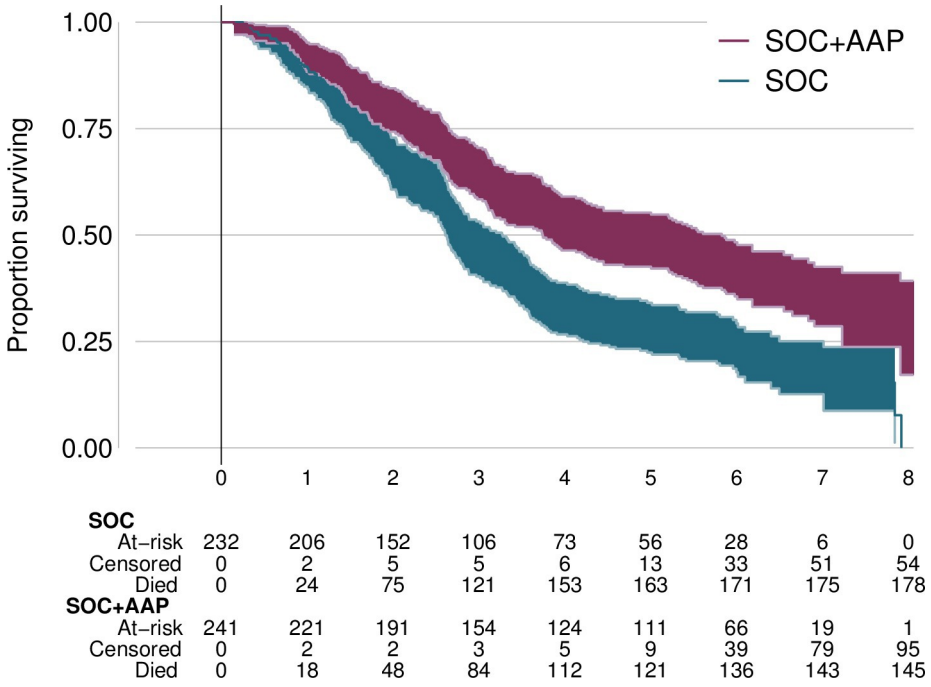


SOC									
At−risk	502	242	136	96	72	57	39	10	0
Censored	0	6	9	13	14	20	31	55	65
Failure	0	254	357	393	416	425	432	437	437
SOC+AAP									
At−risk	501	403	331	273	236	200	128	43	4
Censored	0	6	13	23	28	37	95	178	215
Failure	0	92	157	205	237	264	278	280	282

ijc_34018_figure-2b_ffs_all_kmunicate.eps



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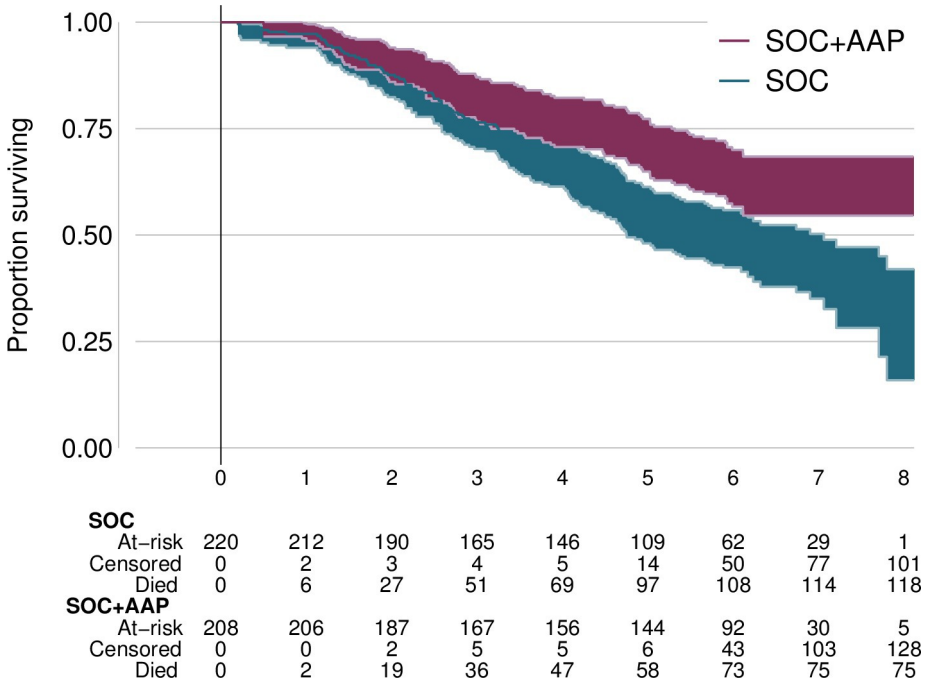

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