Metformin for patients with metastatic prostate cancer starting androgen deprivation therapy: a randomised phase 3 trial of the STAMPEDE platform protocol

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See Comment page 982

*A full list of STAMPEDE investigators and collaborators is provided in the appendix (pp 198–336)

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Summary

Background Metformin is a widely used anti-diabetic drug. Several studies have suggested that metformin has anticancer activity in some malignancies, including prostate cancer. Metformin might also mitigate the adverse metabolic effects of androgen-deprivation therapy (ADT). We hypothesised that metformin might improve survival in patients with metastatic hormone-sensitive prostate cancer and reduce metabolic complications associated with ADT.

Methods The STAMPEDE multi-arm, multi-stage, randomised phase 3 trial recruited patients with high-risk locally advanced or metastatic adenocarcinoma of the prostate staged by conventional imaging with isotope bone and CT scanning. This publication reports findings for the most recent STAMPEDE research question, testing the addition of metformin to standard of care for non-diabetic (glycated haemoglobin [HbA1c] <48 mmol/mol [equivalent to <6·5%]) patients with metastatic disease with adequate renal function (glomerular filtration rate ≥45 ml/min/1·73 m²) and WHO performance status 0–2. This trial recruited from 112 hospitals in the UK and Switzerland to the STAMPEDE protocol. Patients were randomly allocated (1:1) to standard of care or standard of care plus metformin 850 mg twice daily. Random assignment was by telephone using minimisation with a random element of 20% (developed and maintained by the MRC Clinical Trials Unit at UCL), stratified for randomising hospital, age (<70 years *vs* ≥70 years), WHO performance status (0 *vs* 1 or 2), type of ADT, regular long-term use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs; yes *vs* no), pelvic nodal status (positive *vs* negative), planned radiotherapy (yes *vs* no), and planned docetaxel or androgen receptor pathway inhibitor (ARPI) use (docetaxel *vs* abiraterone, enzalutamide, or apalutamide *vs* none). Standard of care comprised ADT with or without radiotherapy and with or without docetaxel or ARPI. The primary outcome measure was overall survival, defined as the time to death from any cause, assessed in the intention-to-treat population. Safety was assessed in patients who started treatment. The trial is registered with ClinicalTrials.gov, NCT00268476 and ISRCTN, ISRCTN78818544.

Findings Between Sep 5, 2016, and Mar 31, 2023, 1874 patients with metastatic disease were randomly allocated to standard of care (n=938) or standard of care plus metformin (n=936). The median patient age was 69 years (IQR 63-73) and the median PSA was 84 ng/mL (24–352). 1758 (94%) of 1874 patients were newly diagnosed with metastatic disease and 116 (6%) were diagnosed with metachronous relapsing disease. 1543 (82%) of 1874 patients received ADT plus docetaxel and 52 (3%) received abiraterone, enzalutamide, or apalutamide. The median time to most recent case report form follow-up was 60 months (IQR 49–72). 473 deaths were reported in the standard of care group; median survival was 61·8 months (IQR 29·7 to not reached). There were 453 deaths in the metformin group; median survival was 67·4 months (32·5 to not reached; HR 0·91, 95% CI 0·80–1·03; p=0·15). Grade 3 or worse adverse events were reported in 487 (52%) of 938 patients in the standard of care group and 523 (57%) of 921 patients in the standard of care plus metformin group. 61 (7%) patients in the standard of care group and 84 (9%) patients in the standard of care plus metformin group reported at least one grade 3 or worse gastrointestinal adverse event; all other body systems showed no difference in grade 3 adverse events. There were six drug-related deaths in the standard of care group and one in the standard of care plus metformin group.

Interpretation We did not find significant evidence of an overall survival benefit of adding metformin to standard of care in the overall population of patients with metastatic hormone-sensitive prostate cancer. The side-effect profile of metformin was as expected and consisted mainly of diarrhoea. Adverse metabolic side-effects of ADT were significantly reduced in the metformin group compared with the standard of care group.

Funding Cancer Research UK, Prostate Cancer UK, and UK Research and Innovation Medical Research Council.

Introduction

Combination therapies have improved outcomes for patients with metastatic hormone-sensitive prostate cancer.[1] The standard of care for systemic treatement in metastatic hormone-sensitive prostate cancer consists of androgen deprivation therapy (ADT) plus an androgen-receptor pathway inhibitor (ARPI) with or without docetaxel,[1] but ADT monotherapy is commonly used in older patients and patients with frailty.[2] ADT and ADT combination therapies are effective but induce adverse metabolic effects, most notably weight gain,[3] loss of muscle or bone mass,[4] and an increase in serious cardiovascular events.[5] The population with incident prostate cancer also has a high proportion of older patients and patients with comorbidities, who are already affected by these conditions.[6] Additionally, ARPIs are costly, resulting in low availability in low-income and middle-income countries. In these countries, a substantial increase in the number of patients diagnosed with advanced prostate cancer is expected in the future.[7] Therefore, cheaper yet safe therapeutic strategies for use in common cancers, such as prostate cancer, are needed.

Metformin is an oral agent that is widely used to manage type 2 diabetes.[8] Metformin does not induce hypoglycaemia, is well tolerated, and is inexpensive.[8] Epidemiological evidence suggests that metformin use can reduce cancer risk and cancer deaths among people with diabetes.[9] Metformin also has the potential to mitigate the metabolic changes known to be induced by ADT.

Various anticancer mechanisms for metformin have been suggested. Metformin is associated with activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of mTOR, leading to reduced cellular metabolic activity, growth, and proliferation.[10–12] High endogenous insulin concentrations, which are reduced by metformin, are also associated with mitogenic effects and tumour growth and proliferation.[12]

Clinical trials have addressed the utility of metformin in the treatment of prostate cancer, but only in small-scale trials and in various settings including both monotherapy and combination therapy. Outcome measures in these studies vary, with some focusing on metabolic effects alone and others focusing only on the effect on cancer progression.[13,14] None of these studies have been sufficiently powered to test the effect of metformin treatment on survival.

The STAMPEDE trial has tested new combination therapies in patients with locally-advanced or metastatic

Research in context

Evidence before this study

We searched PubMed for reports of clinical trials published between Jan 1, 2000, and March 1, 2025, in English, using the terms ("metformin") and ("metastatic prostate cancer" or "metastatic prostatic neoplasm" or "mHSPC" or "mCRPC"). We also searched abstract books of major cancer conferences using the terms ("metformin") and ("prostate cancer") between Jan 1, 2020, and March 1, 2025. We identified six phase 2 trials (NCT01620593, MetAb-Pro, SAKK 08/09, TAXOMET, MANSMED, and SAKK 08/14), a small, randomised pilot study, and two post-hoc analyses from three phase 3 trials (CHAARTED, COU-AA-301, and COU-AA-302) investigating metformin with androgen deprivation therapy (ADT) either as monotherapy or in combination with other treatments in patients with metastatic prostate cancer. These trials showed conflicting results and were also not powered to give a conclusive result. To our knowledge, no phase 3 clinical trials have been done in patients with metastatic hormone-sensitive prostate cancer to assess whether addition of metformin to standard of care could improve outcomes in this patient population.

Added value of this study

This study, using the STAMPEDE trial platform, is, to our knowledge, the first large-scale randomised trial to test the addition of metformin to standard of care therapy in patients with metastatic hormone-sensitive prostate cancer. Randomised trials investigating this strategy have been small and underpowered. Metformin might also mitigate adverse metabolic changes, including metabolic syndrome, a substantial clinical problem induced by ADT, which is an essential component of standard of care in metastatic prostate cancer. Our results show that in the general population with metastatic hormone-sensitive prostate cancer, adding metformin to standard of care did not bring significant oncological or survival improvement overall. However, in patients with high-volume disease there was some evidence of a potential anticancer effect. Addition of metformin to standard of care was also beneficial in mitigating the adverse effects of ADT in patients with metastatic hormone-sensitive prostate cancer, irrespective of metastatic disease volume.

Implications of all the available evidence

Addition of metformin, a widely used, safe, and cheap metabolic regulatory drug to standard of care is not recommended for patients with metastatic hormone-sensitive prostate cancer in general. Further work is needed to better understand the potential anticancer effect observed in patients with high-volume disease and to identify patients who might benefit most from the addition of metformin to treatment.

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See Online for appendix

For more on the **STAMPEDE trial** see www.stampedetrial.org

hormone-sensitive prostate cancer. The metformin arm of the STAMPEDE trial tested the standard of care plus metformin to ascertain the additive effect of metformin on survival and the potential mitigation of the adverse metabolic effects of ADT. Here, we report the results for patients with metastatic disease.

Methods

Study design and participants

The STAMPEDE multi-arm, multi-stage, randomised phase 3 trial recruited patients with high-risk locally advanced or metastatic adenocarcinoma of the prostate staged by conventional imaging with isotope bone and CT scanning. Since trial initiation in 2005, ten research questions have been tested: this publication reports findings for the most recent research question, testing the addition of metformin to standard of care for non-diabetic (glycated haemoglobin [HbA1c] <48 mmol/mol [equivalent to <6·5%]) patients with metastatic disease with adequate renal function (glomerular filtration rate ≥45 ml/min/1·73 m²) , and WHO performance status 0–2. There were no age restrictions. All patients were planned to receive long-term ADT, but could also receive additional standard of care treatments according to clinician choice. These treatments included radiotherapy to the prostate, docetaxel, or, from 2021, an ARPI. Full inclusion and exclusion criteria are provided in the protocol (appendix). This trial recruited from 112 hospitals in the UK and Switzerland to the STAMPEDE protocol as presented previously.[15,16] Patients were recruited to the study by the treating clinical team following clinical diagnosis and recorded centrally at the Medical Research Council (MRC) Clinical Trials Unit. Recruitment was higher than planned, partly because of the addition of a metabolic sub-study to explore in more detail the mechanisms underlying the metabolic effects of ADT and their potential mitigation using metformin; this sub-study opened in October, 2021. There have been six amendments to the protocol since the start of this comparison and all details are in section 22.1 of the protocol (appendix).

The trial was sponsored by University College London (UCL) and conducted by the MRC Clinical Trials Unit at UCL. All patients provided written informed consent, and the trial was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, with relevant regulatory and ethics approval. Ethics approval was granted by West Midlands Research Ethics Committee, now West Midlands, Edgbaston Reasearch Ethics Committee (04/MRE07/35). The STAMPEDE trial is registered with ClinicalTrials.gov, NCT00268476 and ISRCTN, ISRCTN78818544. Full details are available in the trial protocol (appendix).

Randomisation and masking

Patients were randomly assigned (1:1) to standard of care (control) or standard of care plus metformin. Random assignment was by telephone using minimisation with a random element of 20% (developed and maintained by the MRC Clinical Trials Unit at UCL), stratified for randomising hospital, age (<70 years *vs* ≥70 years), WHO performance status (0 *vs* 1 or 2), type of ADT, regular long-term use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs; yes *vs* no), pelvic nodal status (positive *vs* negative), planned radiotherapy (yes *vs* no), and planned docetaxel or ARPI use (docetaxel *vs* abiraterone, enzalutamide, or apalutamide *vs* none). The trial was open label. Radiological images from patients were retrieved and analysed centrally to categorise disease volume independent of the treatment group patients were assigned to.

Procedures

Standard of care with long-term ADT started within 12 weeks before random assignment. Patients could receive additional docetaxel, abiraterone, enzalutamide, or apalutamide according to local protocols. Prostate radiotherapy was permitted.

Metformin was administered orally at a starting dose of 850 mg once daily, and increased to 850 mg twice daily after 4–6 weeks if tolerated. Metformin was recommended to be continued life-long for patients with metastatic disease if well tolerated. Dose reductions were allowed; detailed information is provided in the protocol (appendix). Patients could stop metformin at any time based on unacceptable toxic effects or patient choice. Reasons for cessation were documented by the trial team in the End of Research treatment case report form.

Patients were followed up every 6 weeks within the first 6 months, then every 12 weeks up to 2 years, then every 6 months up to 5 years, then annually. Assessments included prostate-specific antigen (PSA) testing, safety laboratory blood tests, and ascertainment of adverse events. Morphometric and metabolic parameters, measured at baseline and at regular intervals thereafter, included bodyweight, waist measurement, blood lipid concentrations, and glucose concentrations. Blood pressure was measured at baseline. The nadir PSA concentration was defined as the lowest PSA concentration within 24 weeks after random assignment; subsequent rises were defined as PSA progression (biochemical failure), as per the trial protocol (appendix). After random assignment, imaging frequency occurred according to local practice or clinician choice. Investigator-determined radiographic or local progression was reported according to the STAMPEDE protocol (appendix).

Metastatic disease volume was assessed by central review of baseline staging investigations. Retrospective collection of pre-randomisation bone and CT scans was done, with scans stored at the Christie Hospital (Manchester, UK) central imaging repository after completion of accrual but before analysis. Physicians (AS, OE-T, and YJ) classified patients by high-volume or

low-volume disease using the CHAARTED criteria[17] based on the number and site of bone metastases on isotope bone scan, and whether local sites identified visceral disease on CT scan.

Outcomes

The primary outcome measure was overall survival, defined as the time to death from any cause. All survival-based outcome measures were timed from random assignment.

Information on death for patients living in England and Wales was supplemented by linking patients to Civil Registrations of Death (CRD); these data were used in overall survival and prostate cancer-specific survival analysis but not for other cancer outcomes, where censoring for non-fatal events was uncertain. Causes of death were determined from death certificates in those linked with CRD and by site-assigned cause of death for those unlinked with CRD (predominantly patients in Scotland, Northern Ireland, and Switzerland).

Secondary outcome measures were prostate cancer-specific survival (time to prostate cancer death), metastatic progression-free survival (time to new metastases or progression of existing metastases or prostate cancer death), progression-free survival (as for metastatic progression-free survival, with the addition of local or lymph node progression), and failure-free survival (as for progression-free survival, with the addition of biochemical progression). Morphometric and metabolic outcome measures included change in weight, waist circumference, fasting glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and HbA1c. Symptomatic skeletal events, major adverse cardiac events, further metabolic outcomes, quality of life, and cost effectiveness will be analysed separately. Race and ethnicity data were not recorded.

Adverse events were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0) at all follow-up visits. Safety reporting of serious adverse events continued

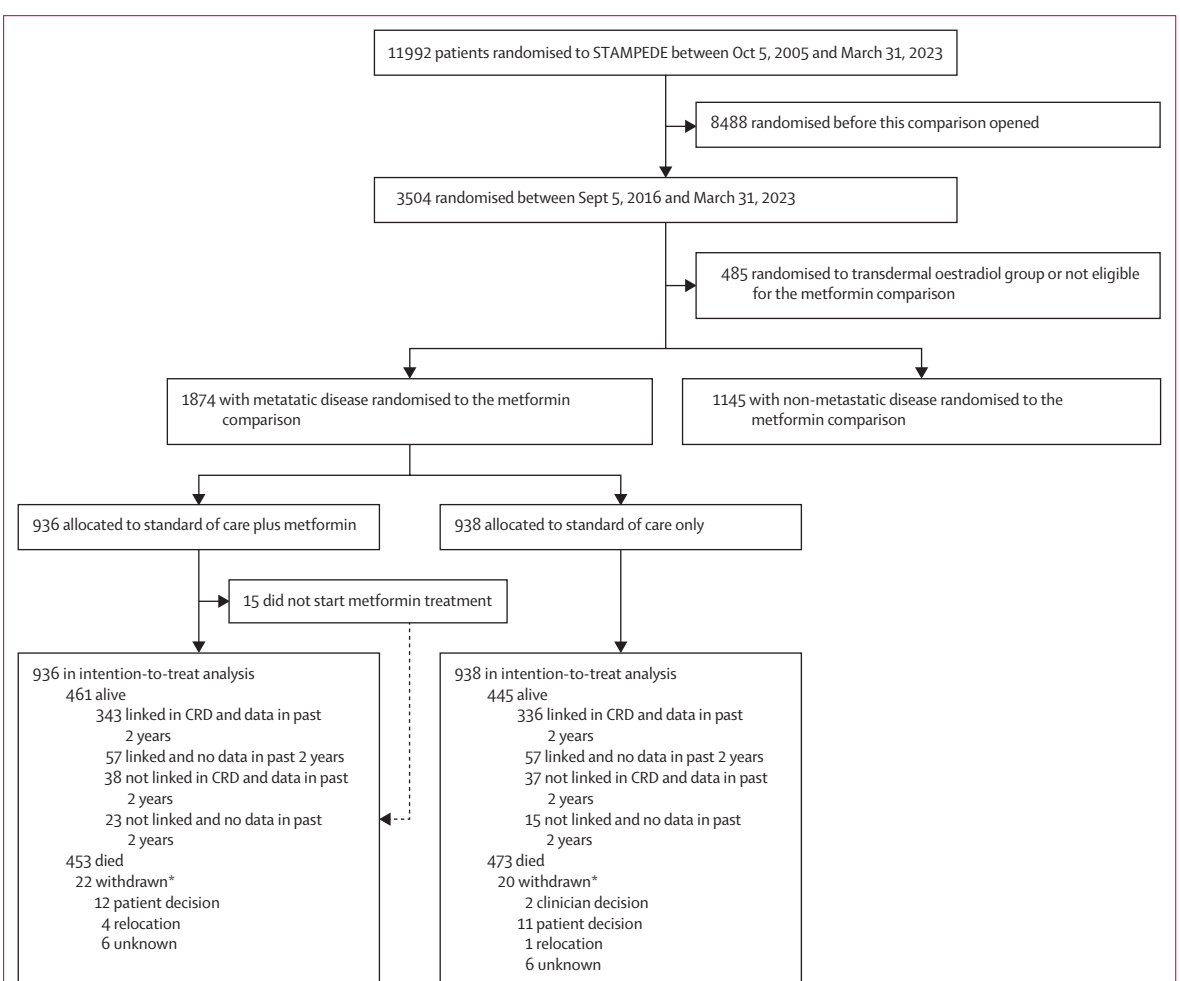


Figure 1: **Trial profile**

CRD=civil registrations of death (provided by the Office for National Statistics). *Withdrawn does not include patients with data in the last 2 years. Patients who withdrew were censored at last known contact.

until disease progression or 30 days after cessation of metformin.

Statistical analysis

A prespecified statistical analysis plan was signed off before data extraction and is available in the appendix. A target sample size of 1800 men with metastatic disease was calculated using the nstage command in Stata version 13. The sample size assumed a median overall survival of 54 months in the control group, targeting a hazard ratio (HR) of 0·8, with 86% power and a 2·5% one-sided significance level after accounting for the shared use of the control group with one other experimental research group. One interim analysis went ahead, with data frozen on April 17, 2020, and presented at a meeting on May 15, 2020, with a one-sided α of 0·40, and the independent data monitoring committee recommended continuation based on the HR threshold for lack of sufficient activity not being met. The final analysis was triggered by the occurrence of at least 473 deaths in the control group—these were observed by July 3, 2024.

	Standard of care (n=938)	Standard of care plus metformin (n=936)
Disease category		
De novo	881 (94%)	877 (94%)
Relapsing	57 (6%)	59 (6%)
Regional nodal status		
N0	272 (29%)	285 (30%)
N+	638 (68%)	620 (66%)
NX	28 (3%)	31 (3%)
Bone metastases		
No	134 (14%)	117 (13%)
Yes	804 (86%)	819 (88%)
Visceral metastases		
No	834 (89%)	828 (88%)
Yes	104 (11%)	108 (12%)
Distant nodal metastases		
No	619 (66%)	606 (65%)
Yes	319 (34%)	330 (35%)
CHAARTED volume		
Low	419 (45%)	390 (42%)
High	404 (43%)	420 (45%)
Scans not available	115 (12%)	126 (13%)
WHO performance status		
0	701 (75%)	701 (75%)
1	227 (24%)	216 (23%)
2	10 (1%)	19 (2%)
Systemic therapy (standard of care)		
ADT alone	135 (14%)	144 (15%)
ADT plus docetaxel	778 (83%)	765 (82%)
ADT plus androgen receptor pathway inhibitor	25 (3%)	27 (3%)
Local radiotherapy planned		
No	822 (88%)	830 (89%)
Yes	116 (12%)	106 (11%)
Age at random assignment, years		
Median (IQR)	69 (63–73)	69 (63–74)
Range	41–86	44–89
Prostate-specific antigen at random assignment, ng/mL		
Median (IQR)	80 (24–296)	87 (25–414)
Range	0–10 178	0–9132

Data are n (%), unless otherwise indicated. ADT=androgen deprivation therapy.

Table 1: **Baseline characteristics**

Primary analyses used the intention-to-treat population (all randomly assigned patients) except for recorded adverse events, which were analysed in the safety population (defined as patients starting treatment within randomly assigned groups), reported as the maximum grade per patient for each event. Serious adverse events were reported until disease progression in the control group and until both disease progression and 30 days after cessation of metformin in the research group. Median follow-up was calculated using a Kaplan-Meier method with reverse-censoring on death.

Time-to-event data were presented using Kaplan-Meier curves and analysed using Cox regression modelling to present HRs for treatment effect adjusted for stratification factors (excluding randomising hospital and type of long-term hormone therapy) and stratified for relevant time periods, defined by other recruiting comparisons and changes to standard of care. For overall survival and prostate cancer-specific survival outcomes, patients without an event were censored when last known to be alive; for patients linked to CRD data this date is defined as 30 days before the date of production of the CRD report by NHS England, and for patients not linked, this date is defined as the most recent date of any action received on follow-up forms. For other time-to-event outcome measures, patients were censored at the date of most recent follow-up or progression report (if not the progression event of interest). Medians are presented from flexible parametric models fitted to the data with five degrees of freedom. Prostate cancer-specific survival, failure-free survival, progression-free survival, and metastatic progression-free survival used a competing risks approach, with death from non-prostate cancer causes as the competing risk.

For Cox models, hazard ratios (HR) less than 1 favour adding metformin. Non-deviation from proportional hazards was checked using scaled Schoenfeld residuals regressed against the log of time.

Seven subgroup analyses of interest were prespecified in the statistical analysis plan: stratification factors (age, WHO status, aspirin or non-steroidal anti-inflammatory use, pelvic nodal status, planned radiotherapy, planned systemic therapy) and CHAARTED disease volume. Subgroup analyses were not formally designed (in terms of direction and size of effects or power) for identification of differing effects in these subgroups.

Changes in morphometric and metabolic factors were analysed at 24, 48, and 104 weeks using linear regression,

adjusted for baseline value, height, and stratification factors as above.

All analyses were done in Stata version 18.

Role of the funding source

Cancer Research UK approved the study design and subsequent amendments. The funders of the study had no role in data collection, data analysis, data interpretation, or writing of the report.

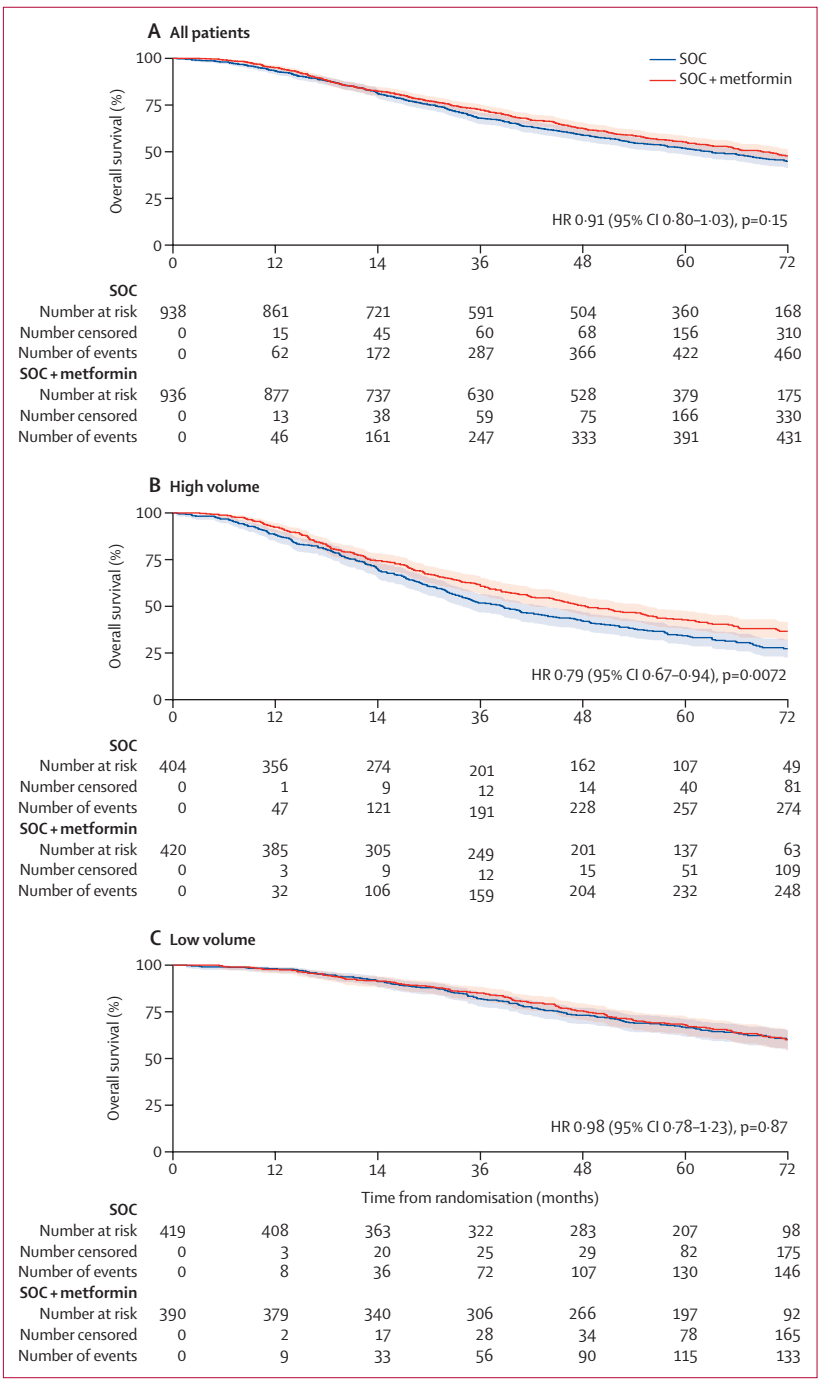
Results

Between Sep 5, 2016, and Mar 31, 2023, 1874 patients with metastatic disease were randomly allocated to standard of care (n=938) or standard of care plus metformin (n=936; figure 1; appendix p 11). 1145 patients with non-metastatic disease were also recruited during this period; results for these patients will be reported separately. The STAMPEDE trial closed recruitment on March 31, 2023, and this report presents the final primary analysis for patients with metastatic disease in the metformin comparison followed up to July 3, 2024.

Baseline characteristics were similar across treatment groups (table 1). The median patient age was 69 years (IQR 63–73) and the median PSA was 84 ng/mL (24–352). 1758 (94%) of 1874 patients were newly diagnosed with metastatic disease and 116 (6%) were diagnosed with metachronous relapsing disease. 1543 (82%) of 1874 patients received ADT plus docetaxel and 52 (3%) received ADT plus abiraterone, enzalutamide, or apalutamide. For additional baseline characteristics and baseline morphometric and metabolic parameters by randomly assigned group see the appendix (pp 2–3). 809 (43%) of 1874 patients had low-volume disease according to the CHAARTED definition[18] and 824 (44%) had high-volume disease. Scans were not available for 241 (13%) patients.

897 (96%) of 936 patients in the standard of care plus metformin group were confirmed to have started metformin treatment, 24 (3%) patients had a missing metformin start date but were assumed to have started treatment, and 15 (2%) patients did not start metformin treatment. 28 (3%) of 897 patients stopped metformin within the first 30 days of treatment. The median time from random assignment to starting metformin was 7 days (IQR 3 to 14) and to stopping metformin was 39 months (IQR 13 to not reached). At database lock on July 3, 2024, 287 (58%) of 497 patients who remained in the trial were still receiving metformin. 134 (26%) of 510 patients who reported stopping metformin gave the reason excessive toxicity. 42 (2%) of 1874 patients stopped their participation in trial follow-up early and were censored at last contact. During follow-up, 26 (3%) of 938 patients in the control group reported starting metformin at some point. The median time to most recent case report form follow-up was 60 months (IQR 49 to 72). The median time to date last known to be alive was 69 months (60 to 79; using CRD data).

When incorporating data from CRD, 473 deaths were reported in the standard of care group; median survival was 61·8 months (IQR 29·7 to not reached). There were 453 deaths in the metformin group; median survival was 67·4 months (32·5 to not reached; HR 0·91, 95% CI 0·80–1·03; p=0·15; figure 2). We found no evidence of non-proportional hazards (p=0·14). Causes of death are

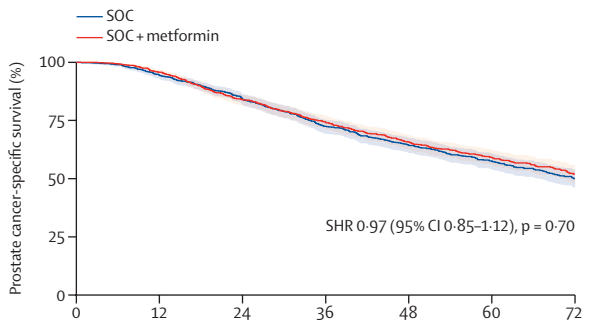


	0	12	14	36	48	60	72
SOC							
Number at risk	938	861	721	591	504	360	168
Number censored	0	15	45	60	68	156	310
Number of events	0	62	172	287	366	422	460
SOC + metformin							
Number at risk	936	877	737	630	528	379	175
Number censored	0	13	38	59	75	166	330
Number of events	0	46	161	247	333	391	431

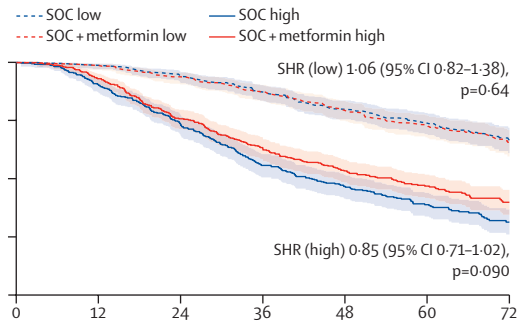
	0	12	14	36	48	60	72
SOC							
Number at risk	404	356	274	201	162	107	49
Number censored	0	1	9	12	14	40	81
Number of events	0	47	121	191	228	257	274
SOC + metformin							
Number at risk	420	385	305	249	201	137	63
Number censored	0	3	9	12	15	51	109
Number of events	0	32	106	159	204	232	248

	0	12	14	36	48	60	72
SOC							
Number at risk	419	408	363	322	283	207	98
Number censored	0	3	20	25	29	82	175
Number of events	0	8	36	72	107	130	146
SOC + metformin							
Number at risk	390	379	340	306	266	197	92
Number censored	0	2	17	28	34	78	165
Number of events	0	9	33	56	90	115	133

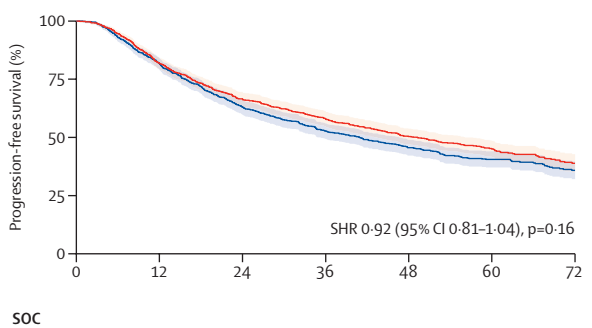
Figure 2: **Overall survival by treatment and metastatic disease volume**
Shaded areas indicate 95% CIs. HR=hazard ratio. SOC=standard of care.



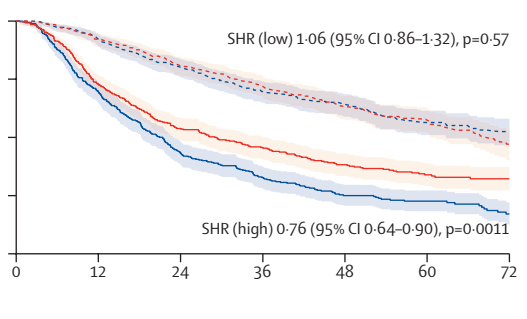
SOC							
Number at risk	938	858	719	590	503	343	155
Number censored	0	30	78	110	132	244	397
Number of events	0	50	141	238	303	351	386
SOC + metformin							
Number at risk	936	874	732	627	521	361	161
Number censored	0	23	60	83	119	231	397
Number of events	0	39	144	226	296	344	378



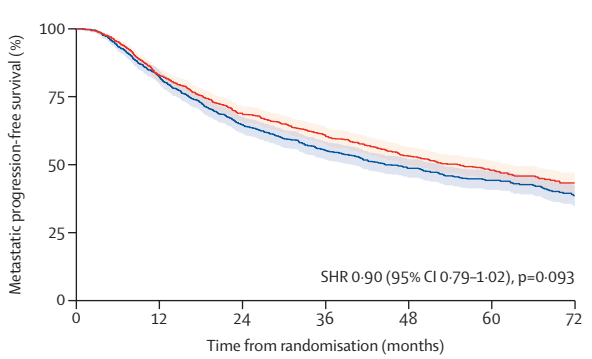
Number at risk (events)							
SOC low	419	406	362	322	283	200	90
	(0)	(5)	(24)	(49)	(76)	(95)	(110)
SOC + metformin low	390	376	337	304	262	188	86
	(0)	(5)	(24)	(46)	(72)	(93)	(107)
SOC high	404	355	274	201	162	98	46
	(0)	(38)	(104)	(168)	(200)	(225)	(240)
SOC + metformin high	420	385	304	249	201	133	56
	(0)	(29)	(99)	(149)	(187)	(209)	(225)



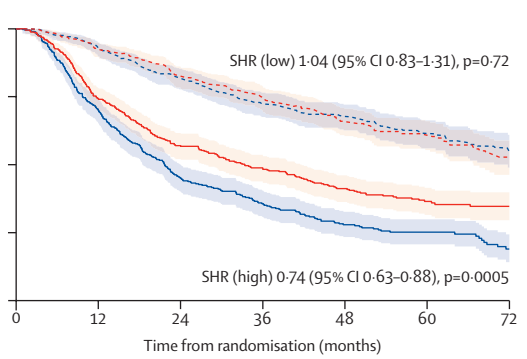
SOC							
Number at risk	938	741	524	409	305	169	71
Number censored	0	30	84	116	167	273	356
Number of events	0	167	330	413	466	496	511
SOC + metformin							
Number at risk	936	746	565	459	347	196	77
Number censored	0	23	67	104	158	277	375
Number of events	0	167	304	373	431	463	484



Number at risk (events)							
SOC low	419	378	302	248	199	113	47
	(0)	(33)	(80)	(118)	(138)	(159)	(165)
SOC + metformin low	390	353	284	241	186	109	41
	(0)	(30)	(72)	(102)	(131)	(146)	(161)
SOC high	404	273	158	112	72	42	15
	(0)	(120)	(220)	(258)	(283)	(289)	(297)
SOC + metformin high	420	299	212	165	122	70	29
	(0)	(133)	(190)	(221)	(247)	(259)	(262)

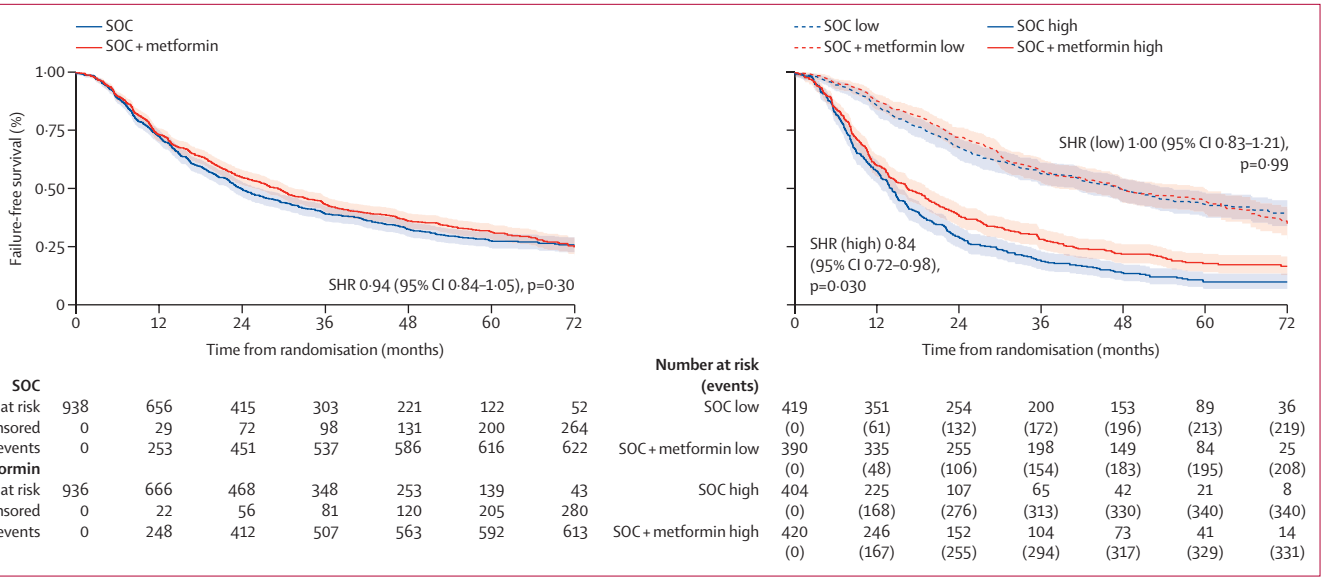


SOC							
Number at risk	938	747	538	428	325	181	76
Number censored	0	30	85	119	173	291	379
Number of events	0	161	315	391	440	466	483
SOC + metformin							
Number at risk	936	756	583	480	364	206	81
Number censored	0	23	71	109	167	294	403
Number of events	0	157	282	347	405	436	452



Number at risk (events)							
SOC low	419	381	308	256	209	120	50
	(0)	(30)	(73)	(108)	(124)	(141)	(150)
SOC + metformin low	390	355	288	248	193	116	44
	(0)	(28)	(66)	(92)	(120)	(133)	(145)
SOC high	404	275	165	122	81	45	15
	(0)	(118)	(213)	(247)	(272)	(279)	(287)
SOC + metformin high	420	305	225	178	131	72	30
	(0)	(107)	(177)	(208)	(235)	(248)	(251)

(Figure 3 continues on next page)



SOC							
Number at risk	938	656	415	303	221	122	52
Number censored	0	29	72	98	131	200	264
Number of events	0	253	451	537	586	616	622
SOC + metformin							
Number at risk	936	666	468	348	253	139	43
Number censored	0	22	56	81	120	205	280
Number of events	0	248	412	507	563	592	613

Number at risk (events)							
SOC low	419	351	254	200	153	89	36
	(0)	(61)	(132)	(172)	(196)	(213)	(219)
SOC + metformin low	390	335	255	198	149	84	25
	(0)	(48)	(106)	(154)	(183)	(195)	(208)
SOC high	404	225	107	65	42	21	8
	(0)	(168)	(276)	(313)	(330)	(340)	(340)
SOC + metformin high	420	246	152	104	73	41	14
	(0)	(167)	(255)	(294)	(317)	(329)	(331)

Figure 3: **Prostate cancer-specific, progression-free, metastatic progression-free, and failure-free survival by treatment and metastatic disease volume**
Shaded areas indicate 95% CIs. SHR=sub-hazard ratio (from competing risks analysis). SOC=standard of care.

presented in the appendix (p 3); the main cause of death was prostate cancer. A forest plot of the seven prespecified subgroup analyses is shown in the appendix (p 13). We found no strong suggestion of heterogeneity of effect for any of the prespecified subgroups. In patients with high-volume versus low-volume disease (as per CHAARTED),[18] HRs for patients treated with metformin versus those who received standard of care were 0·79 (95% CI 0·67–0·94; p=0·0072) and 0·98 (0·78–1·23; p=0·87), respectively (figure 2). The p value for interaction was 0·12.

400 deaths in the standard of care group and 396 deaths in the metformin group were attributed to prostate cancer; we found no evidence of an effect of metformin on prostate cancer-specific survival in the overall population (HR 0·97, 95% CI 0·85–1·12; p=0·70; figure 3), nor any strong suggestion of heterogeneity of effect for any of the prespecified subgroups. In patients with high-volume versus low-volume disease, HRs for prostate cancer-specific survival were 0·85 (0·71–1·02; p=0·090) and 1·06 (0·82–1·38; p=0·64), respectively. The p value for interaction was 0·11.

There were 515 progression-free survival events in the standard of care group and 494 in the metformin group. We found no evidence that metformin affected progression-free survival in the overall population (HR 0·92, 95% CI 0·81–1·04; p=0·16; figure 3). However, we found some evidence of an interaction with metastatic volume in patients with high volume disease (HR 0·76, 95% CI 0·64–0·90; p=0·0011) compared with patients with low-volume disease (1·06, 0·86–1·32; p=0·57). The p value for interaction between treatment arm and volume of disease was 0·012. A similar pattern was seen for metastatic progression-free survival, with 486 events in the standard of care group and 461 events in the metformin group (overall HR 0·90, 95% CI 0·79–1·02; p=0·093), with a suggestion of metastatic volume interaction (HR 0·74, 95% CI 0·63–0·88; p=0·00054; and 1·04, 0·83–1·31; p=0·72 for high-volume and low-volume, respectively; p value for interaction was 0·013). We found no apparent benefit of metformin for failure-free survival (HR 0·94, 95% CI 0·84–1·05; p=0·30; (625 events in the standard of care group and 618 events in the metformin group; 877 [71%] of 1243 events were PSA failures) nor substantial indication of interaction with baseline disease volume. HRs were 0·84 (95% CI 0·72–0·98; p=0·030) and 1·00 (0·83–1·21; p=0·99) in high-volume disease and low-volume disease, respectively. The p value for interaction was 0·15.

At 24, 48, and 104 weeks, weight gain differed significantly between treatment groups (p<0·0001 at all timepoints). Based on the 583 participants with weight available at baseline and 104 weeks, patients who received standard of care gained a mean of 4·40 kg (95% CI 3·57 to 5·24) by 104 weeks whereas patients who received metformin gained a mean of 2·00 kg (1·31 to 2·69; mean difference −2·48, 95% CI −3·55 to −1·41). Statistically significant differences favouring metformin were also seen between groups at 104 weeks for changes in fasting glucose (n=685; mean difference −0·17 mmol/L, 95% CI −0·29 to −0·05; p=0·0044), total cholesterol (n=817; mean difference −0·16 mmol/L, −0·29 to −0·03; p=0·013), LDL cholesterol (n=747; mean difference −0·17 mmol/L, −0·29 to −0·05; p=0·0043), HbA1c (n=806; mean difference −1·01 mmol/mol, −1·56 to −0·46; p<0·0001), and waist measurements (n=324; −1·74 cm, −3·39 to −0·09; p=0·038). Differences at 24 weeks and 48 weeks were consistent with these groups differences,

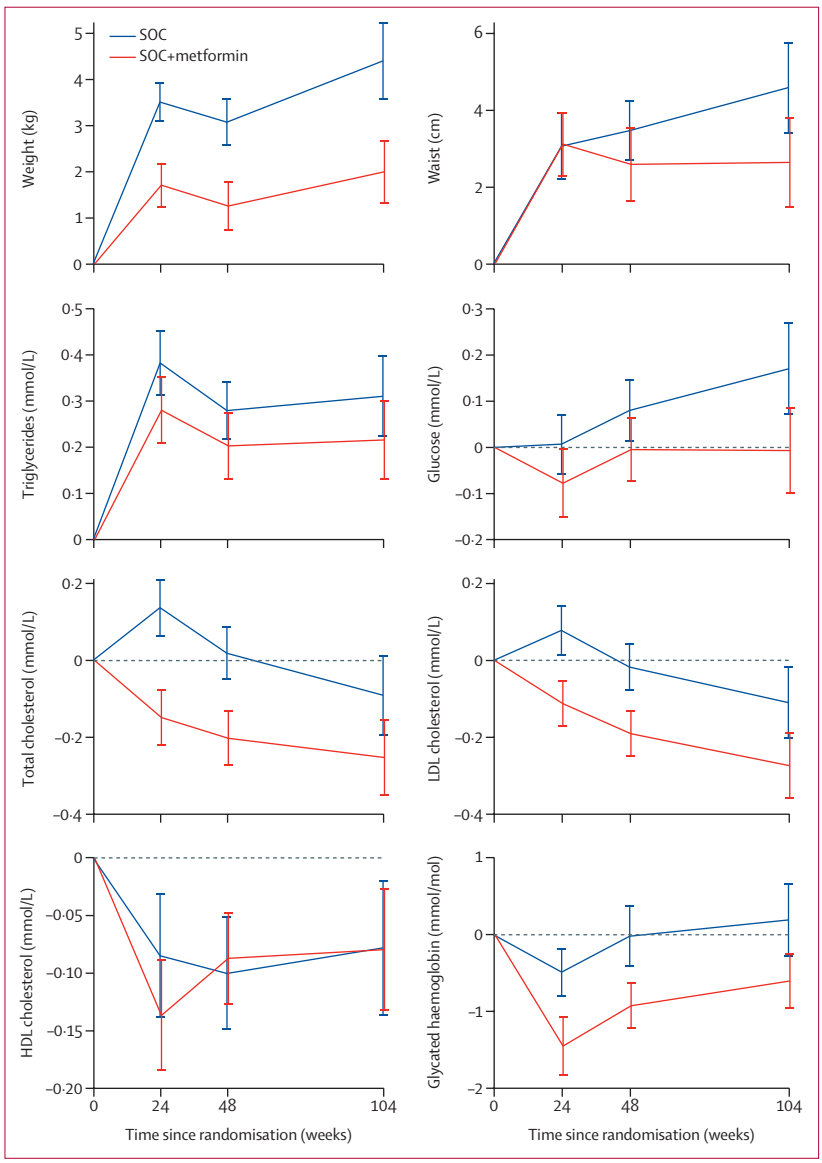


Figure 4: **Morphological and metabolic outcomes by treatment (change from baseline)**
Data shown are mean (95% CI). SOC=standard of care.

except for waist measurements, which were not significantly different at 24 weeks and 48 weeks. We found no evidence of difference in fasting triglycerides (n=751; –0·09 mmol/L, –0·21 to 0·02; p=0·10) or HDL cholesterol (n=816; –0·02 mmol/L, –0·08 to 0·05; p=0·62; figure 4; appendix p 4). There were no relevant differences in morphometric and metabolic factors, including BMI category, between patients with high-volume versus low-volume disease at baseline (appendix p 5).

Similar proportions of patients reported CTCAE grade 1–5 adverse events in both study groups during the course of follow-up, with the exception of gastrointestinal and renal and urinary adverse events (table 2). Gastrointestinal adverse events were more common with metformin: 789 (86%) of 921 patients reported any gastrointestinal event versus 629 (67%) of 938 patients in the standard of care group. The difference was mostly driven by 600 (65%) of 921 patients in the metformin group and 350 (37%) of 938 patients in the standard of care group reporting diarrhoea and 292 (32%) patients in the metformin group and 215 (23%) patients in the standard of care group reporting nausea. Grade 3 diarrhoea was reported in 46 (5%) of 921 patients in the metformin group versus 29 (3%) of 938 patients in the standard of care group. Grade 1–2 renal and urinary adverse events were more common with metformin: 612 (66%) of 921 patients reported a grade 1–2 event versus 584 (62%) of 938 patients in the standard of care group. However, we found no significant difference in grade 3–5 renal and urinary events (39 [4%] of 921 patients in the metformin group and 34 [4%] of 938 patients in the standard of care arm reported a grade 3–5 event; table 2; appendix pp 6–9). The number of dose reductions for metformin is shown in the appendix (p 10). Grade 3 or worse adverse events were reported in 487 (52%) of 938 patients in the standard of care group and 523 (57%) of 921 patients in the standard of care plus metformin group. There were 286 serious adverse reactions, generally related to standard of care docetaxel (appendix p 10). Nine of 14 serious adverse reactions to metformin were in the gastrointestinal system. There was one hormone therapy-related death in each study group (cardiac disorders) and five docetaxel-related deaths in the standard of care group (one musculoskeletal and connective tissue, two infections, and two blood and lymphatic).

Discussion

Evidence of oncological benefit with metformin use in prostate cancer has been reported in epidemiological studies[8,9] but, to date, although some randomised clinical trials in advanced prostate cancer have suggested an oncological benefit[13,14] they have been too small for definitive comment. This open-label, randomised controlled trial within the STAMPEDE trial platform is the first to report the effects of metformin added to standard of care in patients with metastatic hormone-sensitive prostate cancer, tested at large scale. The data show that addition of metformin given orally at standard dose was generally well tolerated but did not result in the targeted benefit of a 20% reduction in risk of death in an unselected population. However, for men with high-volume disease, assessed centrally using CHAARTED criteria[17] on conventional imaging with isotope bone scan and CT-MRI,[18] there was some indication of potential oncological benefit in the prespecified subgroup analysis. However, although prespecified, these subgroup analyses were not formally powered to test such an interaction and therefore should be considered hypothesis-generating.

	Standard of care (n=938)				Standard of care plus metformin (n=921)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Blood and lymphatic	409 (44%)	73 (8%)	13 (1%)	1 (<1%)	458 (50%)	68 (7%)	17 (2%)	1 (<1%)
Cardiac	48 (5%)	21 (2%)	4 (<1%)	3 (<1%)	49 (5%)	35 (4%)	4 (<1%)	3 (<1%)
Ear and labyrinth	10 (1%)	1 (<1%)	0	1 (<1%)	5 (1%)	1 (<1%)	0	0
Endocrine	10 (1%)	1 (<1%)	0	0	11 (1%)	0	0	0
Eye	75 (8%)	6 (1%)	2 (<1%)	0	77 (8%)	10 (1%)	1 (<1%)	0
Gastrointestinal	568 (61%)	54 (6%)	4 (<1%)	3 (<1%)	705 (77%)	82 (9%)	2 (<1%)	0
Diarrhoea	321 (34%)	29 (3%)	0	0	554 (60%)	46 (5%)	0	0
Nausea	211 (22%)	4 (<1%)	NA	NA	285 (31%)	7 (1%)	NA	NA
Vomiting	47 (5%)	4 (<1%)	0	0	68 (7%)	5 (1%)	0	0
Flatulence	76 (8%)	0	0	0	149 (16%)	0	0	0
Dyspepsia	96 (10%)	1 (<1%)	0	0	156 (17%)	0	0	0
General disorders and administration site conditions	748 (80%)	53 (6%)	2 (<1%)	1 (<1%)	745 (81%)	57 (6%)	3 (<1%)	5 (1%)
Fatigue	749 (80%)	34 (4%)	NA	NA	746 (81%)	33 (4%)	NA	NA
Hepatobiliary	4 (<1%)	0	0	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)	0
Immune system	21 (2%)	3 (<1%)	0	0	26 (3%)	3 (<1%)	0	0
Infections	189 (20%)	80 (9%)	9 (1%)	3 (<1%)	212 (23%)	72 (8%)	9 (1%)	5 (1%)
Injury	16 (2%)	19 (2%)	0	1 (<1%)	21 (2%)	25 (3%)	1 (<1%)	0
Investigations	426 (45%)	65 (7%)	16 (2%)	0	434 (47%)	64 (7%)	32 (3%)	0
Metabolism and nutrition	280 (30%)	16 (2%)	3 (<1%)	1 (<1%)	325 (35%)	19 (2%)	4 (<1%)	0
Musculoskeletal	600 (64%)	70 (7%)	0	1 (<1%)	608 (66%)	68 (7%)	1 (<1%)	0
Neoplasms	11 (1%)	9 (1%)	3 (<1%)	3 (<1%)	5 (1%)	15 (2%)	1 (<1%)	9 (1%)
Nervous system	473 (50%)	30 (3%)	2 (<1%)	2 (<1%)	453 (49%)	44 (5%)	4 (<1%)	1 (<1%)
Psychiatric	468 (50%)	26 (3%)	3 (<1%)	0	488 (53%)	22 (2%)	0	0
Renal and urinary	584 (62%)	32 (3%)	2 (<1%)	0	612 (66%)	37 (4%)	2 (<1%)	0
Acute kidney injury	28 (3%)	4 (<1%)	0	0	24 (3%)	8 (1%)	0	0
Chronic kidney disease	96 (10%)	2 (<1%)	0	0	92 (10%)	3 (<1%)	2 (<1%)	0
Reproductive	334 (36%)	128 (14%)	0	0	315 (34%)	129 (14%)	0	0
Respiratory	323 (34%)	25 (3%)	1 (<1%)	0	298 (32%)	18 (2%)	5 (1%)	0
Skin	468 (50%)	4 (<1%)	0	0	424 (46%)	11 (1%)	1 (<1%)	0
Social circumstances	0	1 (<1%)	0	0	2 (<1%)	1 (<1%)	0	0
Surgical or medical procedures	9 (1%)	8 (1%)	0	0	3 (<1%)	5 (1%)	0	0
Vascular	664 (71%)	91 (10%)	1 (<1%)	1 (<1%)	661 (72%)	96 (10%)	3 (<1%)	1 (<1%)

NA=not applicable (grade 4/5 does not exist in this side-effect term).

Table 2: **Adverse events in the safety population by body system and specific adverse events of interest in this population (not necessarily treatment-related)**

The biological rationale for such an anticancer effect might relate to the pleiotropic actions, including regulation of energetic function and dysfunction, and immunomodulatory properties of metformin.[19] The regulation of cellular energy use is mainly driven by activation by metformin of the metabolic regulator, AMPK. AMPK is a key regulator of many intracellular metabolic processes, including intracellular energy control, glucose metabolism, macrophage-linked inflammation, and the immune response, all of which are important in cancer development and progression.[19] Genetic aberrations associated with cancer are fundamentally linked to disordered metabolism and energy dysregulation through multiple cellular regulatory pathways.[20,21] In-vivo studies in animals have shown that genetic and pharmacological activation of AMPK provides a protective effect on prostate cancer progression by inducing catabolic metabolic reprogramming of prostate cancer cells. This catabolic state is characterised by increased mitochondrial gene expression, increased fatty acid oxidation, decreased lipogenic potential, decreased cell proliferation, and decreased cell motility, all of which are associated with prostate cancer metastasis and progression.[22] Such mitochondrial aberrations are evident in human prostate cancer, where alterations in mitochondrial mass and mitochondrial complex 1 protein are observed.[23] However, this finding does not explain the differential effect linked to disease volume that has been documented radiologically. High-volume disease is considered a more aggressive subtype of metastatic

hormone-sensitive prostate cancer and is associated with heightened glycolytic activity (ie, Warburg effect) and reduced mitochondrial oxidative phosphorylation. Inhibition of mitochondrial complex I by metformin might selectively stress these metabolically inflexible cancer cells, which already operate near their energetic limits.[24–26] This effect might account for the observed greater clinical benefit in this subgroup. Notably, there were no more patients with overweight or obesity with potentially higher insulin concentrations in the subgroup with high-volume disease compared with the subgroup with low-volume disease, a factor which might be a possible explanation for a difference in the effect of metformin in patients with high-volume or low-volume disease. Further elucidation and studies of the mechanisms underlying the observed oncological effect reported here are planned in translational studies linked to the STAMPEDE trial to understand which individuals might benefit most from addition of metformin to treatment. These studies include evaluation of metabolic and molecular alterations within the tumour and host at baseline and during treatment, which will allow investigation of the tumour–host interactions underpinning the observed response to metformin in patients with high-volume disease.

Addition of metformin to standard of care produced clear metabolic benefits irrespective of disease volume, inducing significant and sustained reductions in circulating glucose and HbA1c and total cholesterol and LDL cholesterol concentrations. Additionally, metformin significantly reduced clinically relevant weight gain induced by systemic treatment with ADT. These findings are novel and represent a substantial and potentially valuable treatment benefit for men with this lethal form of prostate cancer. Use of metformin as a supplement to ADT-based standard of care will have to be weighted against side-effects, namely diarrhoea.

Reduction in glucose and HbA1c is likely secondary to the known ability of metformin to reduce hepatic gluconeogenesis,[27] and the control of key lipid levels by metformin is likely attributable to the AMPK-linked reduction in hepatic lipogenesis and cholesterol synthesis.[19] These changes were accompanied by improved control of weight gain after starting ADT. ADT, which is essential for the treatment of metastatic prostate cancer, has recognised adverse side-effects, including reduced bone mineral density,[28] metabolic changes—comprising weight gain, decreased muscle mass, increased insulin resistance, and increased visceral and subcutaneous abdominal fat[29–31]—and an increase in the cardiovascular event rate, particularly after combination treatment with ADT plus ARPI.[5] Therefore, mitigation of these side-effects might be important when an ADT plus ARPI combination treatment is given. In this study, only a small number of patients had ADT plus ARPI combination therapy; most patients received ADT plus docetaxel. Addition of metformin to the regimen for men undergoing ADT, either as monotherapy or with intensification, provides an opportunity to reduce morbidities by using an inexpensive, widely available, low toxicity drug. These positive metabolic effects might, with longer observation, translate into reduced cardiovascular deaths; therefore, we will continue the follow-up of participants in our trial to test this hypothesis.

There are several limitations of this study. First, the open-label nature of the design is a potential limitation. However, identification of progression events is unlikely to be affected by clinicians' or patients' knowledge of use of metformin. Furthermore, outcomes of mortality and metabolic parameters are objective measures that would not be affected by the open-label design. Second, patient diaries for assessment of compliance were not included in this trial, therefore limiting our certainty about adherence to metformin. The population of patients included in the trial was also a limitation. Most patients had synchronous disease; therefore, extrapolation of the data to the population with metachronous disease is difficult. There was also a paucity of patients who received ADT plus an ARPI in the hormone-sensitive setting; it is unclear if the results of our study can be extrapolated to this current standard of care. However, despite ADT plus ARPI combination therapy being recommended in many guidelines, real-world evidence shows that the combination of ADT plus ARPI is not always used, and in some countries ARPIs are not reimbursed.

In conclusion, the addition of metformin to ADT with or without docetaxel therapy did not result in a significant improvement in survival compared with ADT with or without docetaxel in the overall population of patients with metastatic hormone-sensitive prostate cancer. However, there was some evidence of a potential anticancer effect in patients with high-volume disease. In our study, only 3% of participants received an ADT plus ARPI combination because most patients were accrued before ARPIs were approved for this indication in the UK. Further work is needed to assess the true utility of metformin when used in the population with high-volume disease alongside ADT plus ARPI (with or without docetaxel) combinations, which are the current standard of care. There was a substantial and significant improvement with the addition of metformin in key metabolic parameters known to be affected adversely by ADT, independent of disease volume. Such metabolic effects might translate into improved outcomes. As the addition of ARPI to ADT both increases survival[1] and cardiovascular risk,[5] the metabolic benefits of metformin might be even more relevant given the shift in standard of care to ADT plus ARPI since trial inception. Metformin is an inexpensive, well tolerated, and widely available medication. Although it would be inappropriate to recommend metformin to all patients for improving oncological outcomes, we found some evidence of benefit

in a subgroup of patients with high-volume disease. We also found a beneficial effect on metabolic parameters in all comers. Some patients and doctors might consider these findings sufficient to consider adding metformin to ADT-based therapy in some patients who are at increased risk of cardiovascular disease and who are unable to change their lifestyle to mitigate the adverse consequences induced by impaired metabolic status after treatment with ADT.

Contributors

Conceptualisation: SGi, NDJ, GA, DPD, RJ, ZM, MDM, WC, CP, MRS, MKBP, and NWC. Data curation: LM, MRS, MKBP, LCB, AS, OE-T, CMu, CA, and MB. Formal analysis: LM, MKBP, PD-M, and LCB. Funding acquisition: SGi, AS, MKBP, NDJ, and NWC. Investigation: SGi, NDJ, AS, OE-T, NWC, GA, HA-A, MV, JG, SB, NS, AJB, SC, DPD, OD, SGr, EG, UH, AMH, YJ, GJ, RJ, MK, ZM, MP-M, OP, CP, HR, MR, RS, SS, and JST. Methodology: MRS, LM, LCB, and MKBP. Project administration: CA, KC, PD-M, DCG, CG, REL, CMc, AM, CMu, MP-M, and LCB. Resources: SGi, NDJ, AS, OE-T, NWC, GA, HA-A, MV, JG, SB, NS, AJB, SC, DPD, OD, SGr, EG, UH, AMH, YJ, GJ, RJ, MK, ZM, MP-M, OP, CP, HR, MR, RS, SS, and JST. Supervision: SGi, AIA, NWC, NDJ, MRS, LCB, and MKBP. Validation: SGi, LM, NWC, NDJ, GA, LCB, and MKBP. Visualisation: LM, LCB, MRS, SGi, NDJ, GA, and NWC. Writing—original draft: SGi, LM, FT, NDJ, GA, and NWC. Writing—review and editing: all authors. RM, DM, and PW are the patient and public involvement representatives in the trial management group. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. SGi, LM, FT, NDJ, LCB, and NWC have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

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All other authors declare no competing interests.

Data sharing

Individual participant data can be requested via the general enquiries email: mrcctu.ctuenquiries@ucl.ac.uk, as per the moderated access approach of the Medical Research Council Clinical Trials Unit at University College London. Upon approval, individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices), will be provided with a data dictionary, protocol, and case record forms relevant to the data.

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