Transdermal oestradiol for androgen suppression in prostate cancer: long-term cardiovascular outcomes from the randomised Prostate Adenocarcinoma Transcutaneous Hormone (PATCH) trial programme

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Summary

Background Androgen suppression is a central component of prostate cancer management but causes substantial long-term toxicity. Transdermal administration of oestradiol (tE2) circumvents first-pass hepatic metabolism and, therefore, should avoid the cardiovascular toxicity seen with oral oestrogen and the oestrogen-depletion effects seen with luteinising hormone releasing hormone agonists (LHRHa). We present long-term cardiovascular follow-up data from the Prostate Adenocarcinoma Transcutaneous Hormone (PATCH) trial programme.

Methods PATCH is a seamless phase 2/3, randomised, multicentre trial programme at 52 study sites in the UK. Men with locally advanced or metastatic prostate cancer were randomly allocated (1:2 from August, 2007 then 1:1 from February, 2011) to either LHRHa according to local practice or tE2 patches (four 100 µg patches per 24 h, changed twice weekly, reducing to three patches twice weekly if castrate at 4 weeks [defined as testosterone ≤1·7 nmol/L]). Randomisation was done using a computer-based minimisation algorithm and was stratified by several factors, including disease stage, age, smoking status, and family history of cardiac disease. The primary outcome of this analysis was cardiovascular morbidity and mortality. Cardiovascular events, including heart failure, acute coronary syndrome, thromboembolic stroke, and other thromboembolic events, were confirmed using predefined criteria and source data. Sudden or unexpected deaths were attributed to a cardiovascular category if a confirmatory post-mortem report was available and as other relevant events if no post-mortem report was available. PATCH is registered with the ISRCTN registry, ISRCTN70406718; the study is ongoing and adaptive.

Findings Between Aug 14, 2007, and July 30, 2019, 1694 men were randomly allocated either LHRHa (n=790) or tE2 patches (n=904). Overall, median follow-up was 3·9 (IQR 2·4–7·0) years. Respective castration rates at 1 month and 3 months were 65% and 93% among patients assigned LHRHa and 83% and 93% among those allocated tE2. 157 events from 145 men met predefined cardiovascular criteria, with a further ten sudden deaths with no post-mortem report (total 167 events in 153 men). 26 (2%) of 1694 patients had fatal cardiovascular events, 15 (2%) of 790 assigned LHRHa and 11 (1%) of 904 allocated tE2. The time to first cardiovascular event did not differ between treatments (hazard ratio 1·11, 95% CI 0·80–1·53; p=0·54 [including sudden deaths without post-mortem report]; 1·20, 0·86–1·68; p=0·29 [confirmed group only]). 30 (34%) of 89 cardiovascular events in patients assigned tE2 occurred more than 3 months after tE2 was stopped or changed to LHRHa. The most frequent adverse events were gynaecomastia (all grades), with 279 (38%) events in 730 patients who received LHRHa versus 690 (86%) in 807 patients who received tE2 (p<0·0001) and hot flushes (all grades) in 628 (86%) of those who received LHRHa versus 280 (35%) who received tE2 (p<0·0001).

Interpretation Long-term data comparing tE2 patches with LHRHa show no evidence of a difference between treatments in cardiovascular mortality or morbidity. Oestrogens administered transdermally should be reconsidered for androgen suppression in the management of prostate cancer.

Funding Cancer Research UK, and Medical Research Council Clinical Trials Unit at University College London.

Introduction

Prostate cancer treatment has evolved substantially over the past 20 years leading to improved outcomes, but as a result some men receive androgen-depleting therapies for many years, if not decades.[1] Androgen suppression is the cornerstone of management in metastatic disease and is also used in combination with radiotherapy (either adjuvant or neoadjuvant) in the locally advanced setting.

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See Online for appendix

Research in context

Evidence before this study

We did a systematic review before starting this study on the use of parenteral oestrogen for treatment of prostate cancer (Norman et al, 2008). Oestrogen is not routinely used to produce androgen suppression in men with prostate cancer because previous studies using oral oestrogen (diethylstilbestrol) have reported increased rates of cardiovascular embolic events. Administering oestradiol parenterally (eg, through a transdermal patch [tE2]) avoids first-pass hepatic metabolism and should avoid cardiovascular toxicity.

Added value of this study

The Prostate Adenocarcinoma Transcutaneous Hormone (PATCH) trial programme is a seamless phase 2/3 randomised trial comparing the safety and efficacy of luteinising hormone releasing hormone agonists (LHRHa) with tE2 patches in men with prostate cancer. Long-term data from the PATCH trial programme (median follow-up 3·9 [IQR 2·4–7·0] years) showed no evidence of a difference in cardiovascular mortality or morbidity between men receiving tE2 patches compared with LHRHa for the management of locally advanced and metastatic prostate cancer.

Implications of all the available evidence

Oestrogens in men are derived from the aromatisation of androgens. Therefore, most androgen suppression strategies used to treat prostate cancer (eg, LHRHa) cause a dual set of toxicities related to both androgen and oestrogen depletion. Using tE2 patches to produce castrate levels of testosterone in men with prostate cancer should mitigate the side-effects of LHRHa caused by oestrogen depletion (eg, hot flushes, osteoporosis, and adverse metabolic profiles) and avoids the cardiovascular toxicity seen with oral oestrogen. Oestrogens administered transdermally should be reconsidered for androgen suppression in the management of prostate cancer.

Currently, the most common method of achieving androgen suppression is with luteinising hormone releasing hormone agonists (LHRHa). Toxicities from LHRHa include erectile dysfunction and loss of muscle mass as a result of testosterone suppression.[2–4] Additionally, most androgen-depleting strategies also lower oestrogen levels (because oestrogens in men are derived from aromatisation of testosterone), thought to be the primary driver of osteoporosis, osteoporotic fractures, hot flushes, and adverse metabolic effects such as hyperlipidaemia and increased glucose levels.[5–8]

Exogenous oestrogen, through a negative feedback loop on the hypothalamus and pituitary,[9,10] is a potential strategy for achieving castrate levels of testosterone and avoids the physiological effects of oestrogen depletion. This approach was first investigated using oral oestrogen (diethylstilbestrol) but was found to cause increased thromboembolic cardiovascular disease,[11] and as a result the use of oestrogen in the management of prostate cancer was largely discontinued. However, because the thromboembolic events seen with oral oestrogen are attributed to first-pass hepatic metabolism and associated activation of coagulation pathways, transdermal administration of oestradiol (tE2) should avoid both the cardiovascular toxicity and the oestrogen-depletion effects. In women, the dose of oral oestrogen required to have the same therapeutic effect as transdermal administration is approximately ten-fold higher, highlighting the substantial effect of intestinal and hepatic metabolism on the pharmacokinetics of exogenous oestrogen. Levels of several proteins involved in the coagulation pathway are altered by oral oestrogen, including antithrombin III and coagulation factor VII.[12]

The PATCH (Prostate Adenocarcinoma Transcutaneous Hormone) trial programme is adaptive and designed to assess the safety and efficacy of tE2 patches compared with LHRHa for the treatment of advanced prostate cancer, using a seamless phased approach (appendix p 1). The first stage, a phase 2a evaluation,[13] assessed early toxicity and feasibility. Recruitment was then extended to a phase 2b evaluation to provide early data on efficacy. Following this phase, recruitment continued within the PATCH trial network sites and was extended into the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy [ISRCTN78818544]) trial network to widen experience with the transdermal patches in the treatment of advanced prostate cancer.[14] The aim of this current analysis is to compare long-term cardiovascular outcomes between patients who were recruited through PATCH trial sites receiving LHRHa and tE2.

Methods

Study design and participants

PATCH is a seamless phase 2/3, randomised, multicentre trial programme at 52 study sites in the UK. Throughout the study phases (phases 2a, 2b, and 3), men from participating centres were eligible if they had locally advanced (M0) or metastatic (M1) prostate cancer (newly diagnosed or relapsing after radical treatment) and were scheduled to start long-term (≥3 years) continuous hormonal therapy. Patients were required to have evidence of a controlled blood pressure before randomisation (systolic blood pressure <160 mm Hg and diastolic <100 mm Hg).

We excluded patients with a previous history of major cardiovascular disease, defined as: cerebral ischaemia (eg, stroke or transient ischaemic attack) within 2 years of randomisation; history of deep vein thrombosis or pulmonary embolus confirmed radiologically or a known

thrombophilic disorder; history of myocardial infarction or acute coronary syndrome within the past 6 months or more than 6 months with evidence of q-wave anterior infarct on electrocardiogram; unstable angina within the past year; angina that occurs on walking 100 m on the level or after climbing one flight of stairs at a normal pace and in normal condition, or angina that causes substantial limitation of ordinary physical activity or occurs at rest; New York Heart Association grade III or IV heart failure; and pulmonary oedema on chest radiography.

The protocol was approved by the Leeds East multicentre research ethics committee (MREC 05/Q1206/168) and all patients gave written informed consent to participate.

Randomisation and masking

Participants were randomly allocated without masking either LHRHa or tE2 patches 1:2 before February, 2011, and thereafter 1:1. The 1:2 ratio was used in the first phase of the evaluation (Aug 14, 2007, to Feb 17, 2011) to increase experience of using tE2 patches. Randomisation was done using a computer-based minimisation algorithm with a random element (80%) and several stratification factors: disease stage (newly diagnosed with categories based on tumour and node status, and patients with multiple sclerotic bone metastases and prostate specific antigen [PSA] >50 ng/mL but no histological confirmation, or patients who have received radical treatment previously with categories based on PSA doubling rates and absolute levels); age (<70 years or ≥70 years); smoking status (never, previous, or current); family history of cardiac disease (yes or no); intended LHRHa agent to be administered (leuprorelin, goserelin, triptorelin, or other); PSA at baseline (<50, ≥50 to <500, or ≥500 ng/mL); study centre; intention to give radical radiotherapy (from 2013; protocol version 8, approved December, 2013); and intention to give upfront docetaxel (from 2015; protocol version 10, approved September, 2015).

Procedures

Patients self-administered tE2 patches (four oestradiol patches, 100 µg per 24 h; FemSeven, LTS Lohmann Therapie-Systeme, Andernach, Germany; or Progynova TS, Bayer, Weimar, Germany), which were changed twice weekly during the first 4 weeks. If testosterone reached castration levels (≤1·7 nmol/L) at 4 weeks, the dose was reduced to three patches changed twice weekly. Amounts in serum of oestradiol and testosterone were monitored every 12 weeks up to 6 months and then every 6 months during follow-up to ensure appropriate testosterone suppression was maintained. LHRHa were administered intramuscularly or subcutaneously as per local practice. Prostate cancer radiotherapy was mandated (since January, 2014; protocol version 8, approved December, 2013) for all locally advanced (N0 M0) patients unless contraindicated, and use of upfront docetaxel was permitted for all patients (since October, 2015; protocol version 10, approved September, 2015), reflecting the evolving standard of care.

If evidence of cancer progression was seen, subsequent therapy was at the discretion of the treating clinician. Men could remain on their allocated first-line hormonal therapy with the addition of other treatments (eg, antiandrogen, corticosteroids, or cytotoxic chemotherapy). A switch to LHRHa for patients progressing on tE2 patches was permitted. Until May, 2019, the protocol mandated treatment with tE2 patches be discontinued if the patient had one of the predefined cardiovascular outcome events. Subsequently, clinician discretion was allowed when such an event occurred.

Cardiovascular outcome events were defined accordingly. Heart failure was defined as new symptoms or clinical signs consistent with a diagnosis of new or decompensated cardiac failure, with supporting evidence from chest radiography, echocardiography, or a rise in amounts of brain natriuretic peptide in serum. Acute coronary syndrome, including unstable angina, ST-elevation myocardial infarction, and non-ST-elevation myocardial infarction were defined as new-onset cardiac chest pain, confirmed as ischaemic in origin by ECG or a rise in troponin with or without coronary angiography, or both these. Thromboembolic stroke was defined as new neurological symptoms and clinical signs with confirmatory evidence from brain CT or MRI. For transient ischaemic attacks, corroborative data from carotid duplex scanning was sought along with evidence of pre-existing or new (persistent or paroxysmal) atrial fibrillation. Other arterial embolic events were defined as those detected by new clinical symptoms and supporting radiological evidence. Venous thromboembolism was defined as thromboses confirmed radiologically (doppler ultrasound scan or cross-sectional imaging) or pulmonary

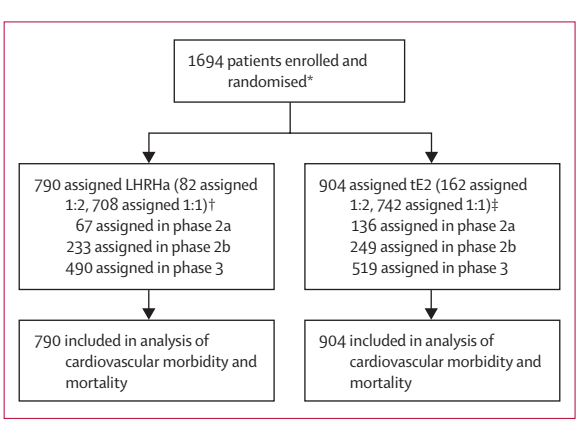

Figure 1: **Trial profile**
LHRHa=luteinising hormone releasing hormone agonist. tE2=transdermal oestradiol patch. *All 1694 patients were included in the analysis of cardiovascular outcomes. 51 additional patients randomised as part of the initial cohort, treated using a different tE2 dose, are excluded from all analyses. †One patient was randomised in error (previously received 3 years of LHRHa). ‡One patient was randomised in error (only short-term androgen-depletion therapy was planned) and one patient did not start tE2 treatment.

embolism confirmed by CT pulmonary angiography, ventilation and perfusion scans, or angiography. A death could be attributed to one of the above categories without meeting the predefined clinical investigations (eg, in the post-mortem report). Cardiac events were reported by investigators on follow-up forms (at 3 and 6 months and every 6 months thereafter) or as notable events, or they were identified from reports of serious adverse events and routinely obtained toxicity data. All potential events and requested supporting evidence (which included original investigation reports, clinic letters, and hospital discharge letters) were reviewed by REL, DCG, or AM (who were aware of treatment allocations) as they occurred, and they were reviewed again for consistency before the current analysis. Sudden or unexpected deaths were attributed to a cardiovascular category if a confirmatory post-mortem report was available. Sudden or unexplained deaths with no post-mortem report were classified as other relevant events, recognising that the most likely causes would include myocardial infarction or arrhythmia, pulmonary embolism, or a cerebrovascular event.

	LHRHa (n=790)	tE2 patches (n=904)	Total (n=1694)
Age at randomisation, years	73 (67–78)	73 (68–78)	73 (68–78)
Range	52–96	49–91	49–96
Inclusion criteria			
Newly diagnosed locally advanced prostate cancer	358 (45%)	414 (46%)	772 (46%)
Newly diagnosed node-positive or metastatic prostate cancer	312 (39%)	352 (39%)	664 (39%)
Newly diagnosed prostate cancer with bone metastases and PSA ≥50 ng/mL, without histology	74 (9%)	84 (9%)	158 (9%)
Relapsing with PSA ≥4 ng/mL	7 (1%)	15 (2%)	22 (1%)
Relapsing with PSA ≥20 ng/mL	18 (2%)	20 (2%)	38 (2%)
Relapsing with documented metastases and PSA ≥4 ng/mL	21 (3%)	19 (2%)	40 (2%)
Tumour status			
T0	5 (1%)	3 (<1%)	8 (<1%)
T1	5 (1%)	4 (<1%)	9 (1%)
T2	30 (4%)	43 (5%)	73 (4%)
T3	567 (72%)	660 (73%)	1227 (72%)
T4	124 (16%)	128 (14%)	252 (15%)
TX	59 (7%)	66 (7%)	125 (7%)
Nodal status			
N0	396 (50%)	416 (46%)	812 (48%)
N+	233 (29%)	251 (28%)	484 (29%)
NX	161 (20%)	237 (26%)	398 (23%)
Metastases			
No	469 (59%)	555 (61%)	1024 (60%)
Yes	321 (41%)	349 (39%)	670 (40%)
Bone metastases in M1 patient			
No	38 (12%)	40 (11%)	78 (12%)
Yes	283 (88%)	309 (89%)	592 (88%)
PSA at randomisation, ng/mL	35·0 (14·8–95·2)	34·9 (14·9–97·1)	35·0 (14·9–96·8)
Range	0·7–6247·0	0·6–6710·0	0·6–6710·0
Missing data	12 (2%)	8 (1%)	20 (1%)
Gleason sum score at diagnosis*			
4–6	46 (6%)	54 (6%)	100 (6%)
7	227 (29%)	280 (31%)	507 (30%)
8–10	443 (56%)	476 (53%)	919 (54%)
Newly diagnosed, without histology	54 (7%)	74 (8%)	128 (8%)
Missing or data not yet received	20 (3%)	20 (2%)	40 (2%)
WHO performance status			
0 (normal activity without restriction)	555 (70%)	642 (71%)	1197 (71%)
1 (strenuous activity restricted, can do light work)	208 (26%)	229 (25%)	437 (26%)
2 (up and about >50% of waking hours, capable of self-care)	27 (3%)	33 (4%)	60 (4%)

(Table 1 continues on next page)

Outcomes

The primary outcome measure for this analysis was cardiovascular morbidity and mortality, defined as the proportion of patients with a confirmed cardiovascular event or sudden or unexpected death. The PATCH trial programme is ongoing and the coprimary outcome for the PATCH phase 3 study is overall survival and progression-free survival; it is anticipated that these data will be available in 2023 or 2024.

Secondary outcomes presented here include castration rates, cardiovascular risk factors, and metabolic profiles at 6 and 12 months, and adverse events.

Statistical analysis

The current analysis was predefined to include all men recruited through the PATCH trial sites, since these centres had agreed to provide additional supporting data to verify the cardiovascular events at the end of the original phase 3 recruitment. The first 51 patients randomised in the PATCH trial were excluded from the current analysis as they received an initial dosing schedule of the patches that produced lower than anticipated castration rates.[15]

The original recruitment target for the phase 3 evaluation was 2150 patients but due to a lower than anticipated event rate, this target was extended to 2550 (protocol version 12, approved December, 2019). The non-inferiority margin hazard ratio (HR) for overall survival is 1·16 (with tE2 assumed to be associated with an absolute improvement in overall survival of 1% at 5 years compared with LHRHa) with 88% power and a one-sided significance level of 0·03. The progression-free survival analysis is planned with 88% power and one-sided significance level of 0·03 and a non-inferiority margin HR of 1·16.

No formal sample size calculation was specified for this current analysis but the nature and timing were prespecified in the protocol and scheduled for the end of

the original phase 3 recruitment period. A formal request was made to the independent data monitoring committee (IDMC) by the trial management group to permit publication of this analysis without knowledge of the cardiovascular data. The aim was to potentially provide further supporting evidence for ongoing research and information for patients and their doctors.

The proportion of patients with a confirmed cardiovascular event was summarised by original treatment allocation, stratified by randomisation period before and after the change in randomisation allocation ratio (since patients randomised under the 1:2 allocation ratio had a longer duration of follow-up). Kaplan-Meier methods were used to describe time to first cardiovascular event by treatment group, based on intention to treat. Follow-up of each patient was considered up to the date of first cardiovascular event, date of death, or last follow-up for those without an event. The treatment effect on cardiovascular risk was estimated using Cox proportional hazards models, adjusted for preselected stratification factors (age, smoking status, and family history of cardiac disease) and stratified by randomisation period (1:2 and 1:1). Heterogeneity of the treatment effect over the two randomisation periods (1:2 and 1:1) was checked by assessing the interaction between randomisation period and treatment, with the overall treatment effect presented if no evidence interaction was found. To assess whether cardiovascular risk varied with cumulative exposure time on original allocated treatment, follow-up in a given patient was divided according to time on treatment from randomisation (<12, 12 to <24, 24 to <36, and ≥36 months; due to small numbers the last two categories were combined into ≥24 months) and accounting for when treatment stopped, which was analysed as a time-varying covariate.

Castration rates were assessed at 4 weeks then at 3, 6, and 12 months, with patients being deemed castrate if their testosterone levels were 1·7 nmol/L or lower. Patients were included in the analysis of castration rate if they were still on their allocated treatment without additional systemic anticancer therapy and, for patients allocated tE2 patches, if they had an oestradiol level of at least 250 pmol/L. Data were included in the analysis of castration rate if tests were done at 4 weeks (2-week margin of error), and at 3, 6, and 12 months (6-week margin of error). The percentage of castrate patients in each treatment group is presented but was not formally compared.

Toxicities experienced while patients were receiving their original allocated treatment are summarised overall and separately for each randomisation cohort (1:2 and 1:1), according to Common Terminology Criteria for Adverse Events, version 3.0. The percentage of patients experiencing any adverse event, and toxicity of grade 3 or worse, are presented. The percentage of patients experiencing any adverse event in each treatment group is compared using a logistic regression model, with patients recruited in each randomisation cohort being combined using a fixed-effects meta-analysis. Toxicities were assessed at each follow-up visit, and data from a specific visit were excluded from summaries if the patient had stopped their allocated treatment before that visit. This exclusion was to ensure that only toxicities

	LHRHa (n=790)	tE2 patches (n=904)	Total (n=1694)
(Continued from previous page)			
Body-mass index, kg/m²†	27·0 (24·4–30·0)	27·1 (24·8–30·1)	27·1 (24·6–30·0)
Range	15·0–47·0	17·7–45·8	15·0–47·0
Missing or not initially collected	134 (17%)	164 (18%)	298 (18%)
Smoking status			
Never smoked	322 (41%)	372 (41%)	694 (41%)
Previous smoker	390 (49%)	440 (49%)	830 (49%)
Current smoker	78 (10%)	92 (10%)	170 (10%)
History of heart disease in first-degree relative‡			
No	551 (70%)	632 (71%)	1183 (71%)
Yes	234 (30%)	259 (29%)	493 (29%)
Regular long-term aspirin			
No	630 (80%)	684 (76%)	1314 (78%)
Yes	157 (20%)	219 (24%)	376 (22%)
Missing data	3 (<1%)	1 (<1%)	4 (<1%)
LHRHa treatment§			
Leuprorelin	359 (45%)	409 (45%)	768 (45%)
Goserelin	319 (40%)	377 (42%)	696 (41%)
Other	51 (6%)	49 (5%)	100 (6%)
Triptorelin	61 (8%)	69 (8%)	130 (8%)
First-line docetaxel§			
No	301 (38%)	325 (36%)	626 (37%)
Yes	90 (11%)	96 (11%)	186 (11%)
Missing or not initially relevant	399 (51%)	483 (53%)	882 (52%)
First-line docetaxel in M1 patients only			
No	79 (25%)	69 (20%)	148 (22%)
Not available, patient randomly assigned before October, 2015	161 (50%)	190 (54%)	351 (52%)
Yes	81 (25%)	90 (26%)	171 (26%)
Radiotherapy to the prostate§			
No	463 (59%)	541 (60%)	1004 (59%)
Yes	318 (40%)	347 (38%)	665 (39%)
Missing data	9 (1%)	16 (2%)	25 (1%)
Radiotherapy to the prostate, M0 patients only			
No	173 (37%)	216 (39%)	389 (38%)
Yes	290 (62%)	328 (59%)	618 (60%)
Missing data	6 (1%)	11 (2%)	17 (2%)

Data are n (%) or median (IQR), unless otherwise stated. LHRHa=luteinising hormone releasing hormone agonist. tE2=transdermal oestradiol. PSA=prostate specific antigen. *Of patients missing Gleason sum score, 20 (50%) of 40 are because the baseline case report form has not yet been received. †Data not initially reported. ‡Initial versions of the case report form asked about a personal history of cardiac disease, rather than a family history, and are not included in this table. Three of five patients assigned LHRHa and two of 13 patients assigned tE2 patches answered "yes" to a personal history of cardiac disease. In analyses that include history of cardiac disease as a covariate, personal history is used in lieu of family history for these patients. §Intended choice before randomisation.

Table 1: **Patients' characteristics at randomisation**

	1:2 cohort		1:1 cohort		Total (n=1694)
	LHRHa (n=82)	tE2 patches (n=162)	LHRHa (n=708)	tE2 patches (n=742)	
Events reviewed	38	73	88	112	311
Events fulfilling endpoint criteria (fatal)*	16 (6)	35 (5)	56 (9)	60 (6)	167 (26)
Type of event (fatal)					
Heart failure	2 (0)	4 (1)	7 (2)	12 (1)	25 (4)
Acute coronary syndrome	3 (1)	12 (2)	16 (2)	18 (3)	49 (8)
Thromboembolic stroke	5 (1)	6 (0)	16 (1)	15 (0)	42 (2)
Other arterial embolic events	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)
Venous thromboembolism	2 (0)	12 (1)	14 (1)	11 (0)	39 (2)
Other relevant event†	4 (4)	1 (1)	3 (3)	2 (2)	10 (10)
Patients with a cardiovascular endpoint event, including sudden death with no post-mortem report	14 (17%)	32 (20%)	50 (7%)	57 (8%)	153 (9%)
Patients with a confirmed cardiovascular endpoint event	11 (13%)	31 (19%)	47 (7%)	56 (8%)	145 (9%)

LHRHa=luteinising hormone releasing hormone agonist. tE2=transdermal oestradiol. *Of 95 events that occurred in patients initially assigned tE2 patches, 34 occurred when tE2 patches had been stopped and LHRHa started. †Other relevant events are unexpected death but for which no post-mortem report was done and, therefore, the endpoint definition could not be verified.

Table 2: **Cardiovascular events reviewed and classified as a cardiovascular endpoint**

	LHRH (n=790)	tE2 patches (n=904)
Overall rate		
By 12 months	2·8% (1·8–4·2)	2·8% (1·9–4·2)
By 24 months	5·3% (3·8–7·3)	6·4% (4·8–8·4)
By 36 months	7·2% (5·4–9·6)	8·0% (6·2–10·4)
Rate by previous exposure to treatment		
<6 months	3·5% (2·1–6·0)	3·5% (2·3–5·2)
6 to <12 months	2·5% (1·3–4·7)	2·7% (1·6–4·7)
≥12 months	2·4% (1·8–3·2)	2·8% (2·1–3·7)
Treatment status at time of event		
Number with event	64	89
Patient still on tE2	..	42 (47%)
Patient off tE2 treatment	..	47 (53%)
<3 months after stopping tE2	..	17
3 to <6 months after stopping tE2	..	3
6 to <12 months after stopping tE2	..	6
12 to <24 months after stopping tE2	..	9
≥24 months after stopping tE2	..	12

Data are % (95% CI), n, or n (%). LHRHa=luteinising hormone releasing hormone agonist. tE2=transdermal oestradiol.

Table 3: **Proportion of patients experiencing cardiovascular event or sudden death**

definitely attributed to their original allocated treatment were included.

Changes in cardiovascular risk factors (fasting blood glucose, fasting total cholesterol, and HDL cholesterol concentrations, weight, and blood pressure) at 6 and 12 months were compared between treatment groups using ANCOVA models, adjusting for baseline values and study cohorts. These analyses were based on patients still on their original allocated treatment without additional systemic anticancer therapy who had a fasting blood sample at the relevant follow-up assessments. Men allocated tE2 patches with oestradiol levels less than 250 pmol/L were considered not to be adhering to the patch regimen and were, therefore, excluded. Statistical analyses were done using Stata version 15.

The PATCH trial programme is registered with the ISRCTN registry, ISRCTN70406718.

Role of the funding source

The funders and study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 14, 2007, and July 30, 2019, 1694 patients were recruited through the PATCH trial network, including 203 patients in phase 2a (from Aug 14, 2007, to April 28, 2010), 482 patients in phase 2b (from July 21, 2010, to Oct 14, 2013), and 1009 patients in phase 3 (from Feb 10, 2014, to July 30, 2019). 790 patients were assigned LHRHa and 904 were allocated tE2 patches (figure 1). Baseline characteristics were similar between treatment groups (table 1). Median age of the overall cohort was 73 (IQR 68–78) years. 670 (40%) of 1694 patients had metastatic disease and median PSA at randomisation was 35·0 (IQR 14·9–96·8) ng/mL. For 426 (93%) of 458 M0 N0 patients, radical radiotherapy to the prostate was planned since this was approved in the protocol in December, 2013. Upfront docetaxel was planned in 171 (54%) of 319 M1 patients overall since September, 2015 (84 of 110 [76%] aged <70 years and 87 of 209 [42%] aged ≥70 years). Overall, median follow-up was 3·9 (IQR 2·4–7·0) years, with 1657 (98%) of 1694 participants having at least 3 months of follow-up data. Median follow-up for the 1:2 cohort was 10·6 years and for the 1:1 cohort it was 3·5 years.

Only one patient (assigned tE2) did not begin their allocated treatment (figure 1). At 4 weeks after randomisation, for men still receiving their allocated treatment without additional anticancer therapy, with oestradiol levels of at least 250 pmol/L in the tE2 group and a blood test within the analysis window, the proportion with testosterone concentrations of 1·7 nmol/L or lower (ie, meeting the definition of castrate) was 65% (415 of 640) among those allocated LHRHa and 83% (661 of 793) in those assigned tE2. By 3 months, the rates were very similar (643 of 693 [93%] with LHRHa and 721 of 776 [93%] with tE2) and remained so over time (appendix p 2). No evidence of an early testosterone surge was seen with tE2. The median oestradiol level at 4 weeks after randomisation was

70 (5th–95th centile range 18–124) pmol/L among men assigned LHRHa and 845 (376–2280) pmol/L in those allocated tE2 (appendix p 3).

311 cardiovascular events were reviewed (table 2), of which 157 experienced by 145 patients fulfilled study endpoint definitions, and a further ten events were classed as other relevant events (sudden unexplained deaths with no post-mortem report available to confirm the endpoint definition) resulting in a total of 167 events in 153 participants. These other relevant events are presented with the main analysis because the most likely clinical causes are cardiovascular (eg, myocardial infarction or arrhythmia and thromboembolic events such as pulmonary embolism). The 144 events deemed not to meet the primary outcome definitions included: non-cardiac chest pain, stable angina, or investigation for a silent myocardial infarction that was not confirmed (n=38); symptoms that might indicate congestive cardiac failure or venous thromboembolism, such as dyspnoea or leg swelling, but investigations did not confirm the diagnosis or symptoms were attributed to another cause (n=27); other cardiac events, including atrial fibrillation, hypotension, hypertension, collapse, valve disease, and non-embolic peripheral vascular disease (n=54); possible intracerebral bleed, acute transient ischaemic attack, or stroke that was not confirmed on imaging or associated history (n=13); death that on clinical review had sufficient evidence for a non-cardiovascular cause (eg, progression of prostate cancer, n=10); and other medical events (n=2).

Patients experiencing a cardiovascular event were more likely than were those without an event to be current or former smokers (104 of 153 [68%] *vs* 896 of 1541 [58%]) and were slightly older (median 75 [IQR 70–79] years *vs* 73 [IQR 68–78] years; data not shown). No other baseline factors were associated with having a cardiovascular event. No consistent differences were seen in the nature of the event between treatment groups (table 2). 26 (2%) of 1694 patients had fatal cardiovascular events, 15 (2%) of 790 who were assigned LHRHa versus 11 (1%) of 904 allocated tE2. The proportion of patients with at least one cardiovascular endpoint or sudden death was similar between treatment groups. Overall, 64 (8%) of 790 patients assigned LHRHa versus 89 (10%) of 904 allocated tE2 had an event; in the 1:2 cohort, 14 (17%) of 82 men assigned LHRHa versus 32 (20%) of 162 allocated tE2 had an event; and in the 1:1 cohort, 50 (7%) of 708 men assigned LHRHa versus 57 (8%) of 742 allocated tE2 had an event.

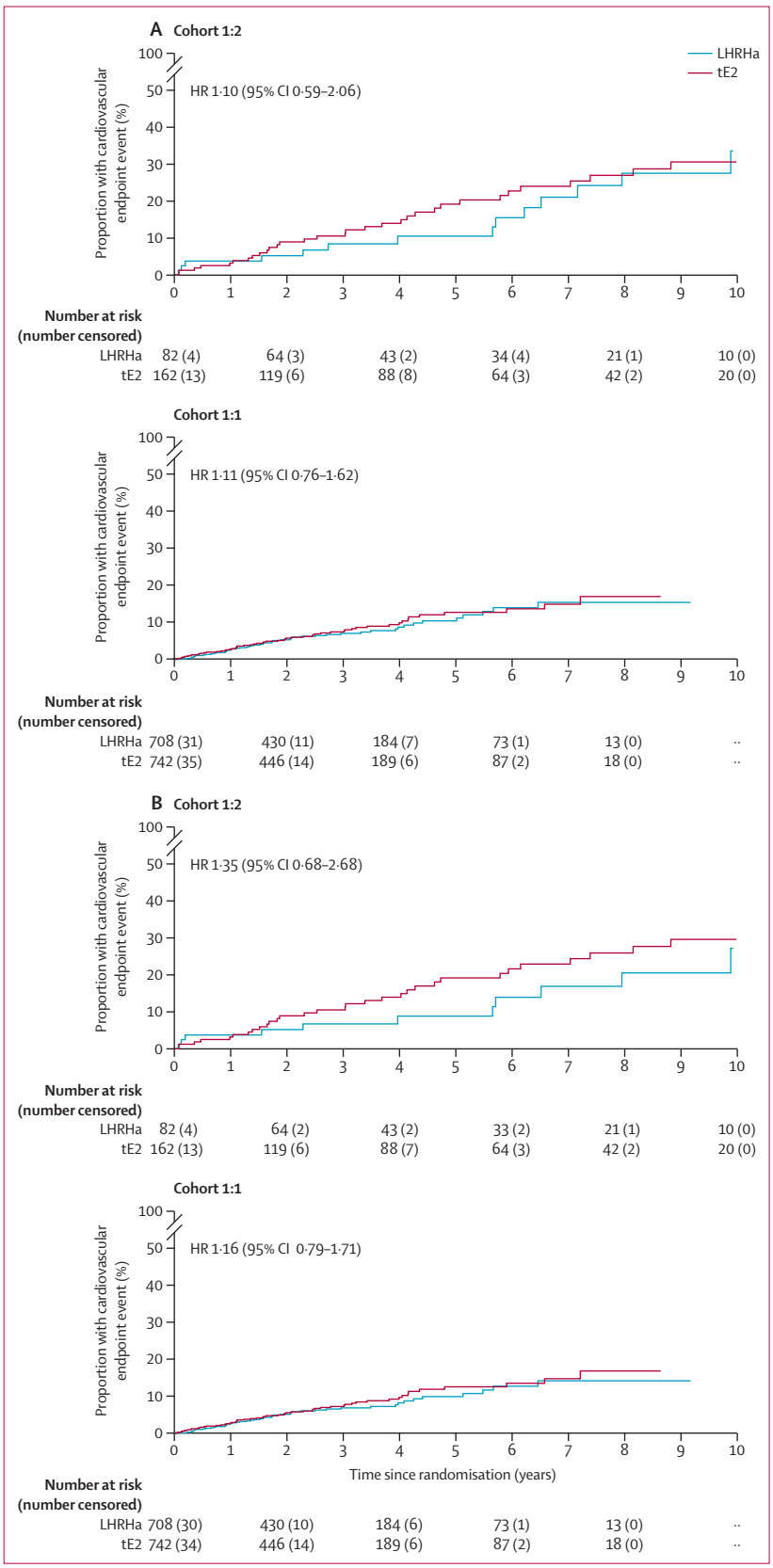

Figure 2: **Time to first cardiovascular endpoint event, intention-to-treat analysis**

Time to first cardiovascular endpoint event, including patients with sudden or unexplained death and no post-mortem report (A). Time to first cardiovascular endpoint event, confirmed events only (B). Overall (1:2 and 1:1 cohorts combined): in panel A, HR 1·11, 95% CI 0·80–1·53; in panel B, HR 1·20, 95% CI 0·86–1·68).

	n*	Mean change (95% CI)	Mean % change (95% CI)	Treatment effect p value†
Fasting glucose, mmol/L				
6-month change	..	..	..	<0·0001
LHRHa	531	0·14 (0·04 to 0·24)	3·1% (1·6 to 4·7%)	..
tE2 patches	553	−0·20 (−0·29 to −0·12)	−2·4% (−3·7 to −1·0%)	..
12-month change	..	..	..	<0·0001
LHRHa	433	0·31 (0·17 to 0·46)	5·9% (3·7 to 8·1%)	..
tE2 patches	473	−0·11 (−0·22 to −0·01)	−1·1% (−2·7 to 0·6%)	..
Fasting cholesterol, mmol/L				
6-month change	..	..	..	<0·0001
LHRHa	551	0·19 (0·11 to 0·26)	5·3% (3·7 to 6·9%)	..
tE2 patches	575	−0·32 (−0·38 to −0·26)	−5·3% (−6·5 to −4·1%)	..
12-month change	..	..	..	<0·0001
LHRHa	456	0·10 (0·01 to 0·18)	3·1% (1·4 to 4·8%)	..
tE2 patches	486	−0·34 (−0·40 to −0·28)	−5·7% (−7·0 to −4·5%)	..
Fasting HDL, mmol/L				
6-month change	..	..	..	0·023
LHRHa	528	0·05 (0·02 to 0·09)	6·7% (4·3 to 9·0%)	..
tE2 patches	554	0·11 (0·08 to 0·15)	11·6% (8·6 to 14·6%)	..
12-month change	..	..	..	0·19
LHRHa	432	0·04 (−0·01 to 0·08)	5·8% (2·4 to 9·2%)	..
tE2 patches	466	0·07 (0·04 to 0·11)	8·5% (6·0 to 11·0%)	..
Weight, kg				
6-month change	..	..	..	0·32
LHRHa	518	1·74 (1·17 to 2·30)	2·3% (1·7 to 2·9%)	..
tE2 patches	569	1·43 (0·85 to 2·01)	1·9% (1·3 to 2·5%)	..
12-month change	..	..	..	0·16
LHRHa	421	2·16 (1·51 to 2·80)	2·8% (2·0 to 3·5%)	..
tE2 patches	452	1·68 (1·09 to 2·28)	2·2% (1·7 to 2·7%)	..
Systolic blood pressure, mm Hg‡				
6-month change	..	..	..	<0·0001
LHRHa	547	1·90 (0·50 to 3·31)	1·9% (0·9 to 3·0%)	..
tE2 patches	609	−2·07 (−3·39 to −0·75)	−0·8% (−1·8 to 0·1%)	..
Diastolic blood pressure, mm Hg‡				
6-month change	..	..	..	<0·0001
LHRHa	547	1·27 (0·37 to 2·18)	2·6% (1·4 to 3·9%)	..
tE2 patches	608	−1·77 (−2·60 to −0·95)	−1·5% (−2·6 to −0·4%)	..

Patients with data at baseline and at 6 months were included in this analysis. *Includes patients still receiving their randomly allocated treatment at the time of assessment. For tE2 patients, oestradiol levels needed to be at least 250 pmol/L. Among patients who reported any cardiovascular risk factors, at 6 months, 54 patients assigned LHRHa and 111 allocated tE2 were excluded due to having stopped their allocated treatment, 25 tE2 patients were excluded due to having low oestradiol, and 13 tE2 patients were excluded due to not reporting an oestradiol value. At 12 months, 95 patients assigned LHRHa and 158 allocated tE2 were excluded due to having stopped allocated treatment, 19 tE2 patients were excluded for reporting low oestradiol, and seven tE2 patients were excluded for not reporting an oestradiol value. †p values are from ANCOVA models comparing mean change in each risk factor. ‡Blood pressure was only measured at 6 months.

Table 4: **6-month and 12-month changes from baseline in cardiovascular risk factors**

The higher rate in the 1:2 cohort is accounted for by the longer duration of follow-up of this cohort. At the time of this intention-to-treat analysis (data cutoff July, 2020), 417 of those allocated tE2 had changed treatment to LHRHa.

Overall, the time to first cardiovascular event did not differ between treatment groups (HR 1·11, 95% CI 0·80–1·53; p=0·54 [including patients with no post-mortem report]). The event rate by 36 months was 7·2% (95% CI 5·4–9·6) among men assigned LHRHa and 8·0% (6·2–10·4) among those allocated tE2 (table 3), with an absolute difference between event rates of 0·8% and an upper (95%) bound to the absolute difference estimate of 3·6%. For the confirmed group only, risk also did not differ between treatments (HR 1·20, 95% CI 0·86–1·68; p=0·29). Risk was also similar in both cohorts (1:2 cohort, HR 1·10, 95% CI 0·59–2·06 [including patients with no post-mortem report], and 1·35, 0·68–2·68 [in the confirmed group]; 1:1 cohort, 1·11, 0·76–1·62 [including patients with no post-mortem report], and 1·16, 0·79–1·71 [in the confirmed group]; figure 2). Within patients allocated tE2, 30 (34%) of 89 had an event more than 3 months after stopping tE2 treatment, with 27 (30%) occurring more than 6 months after tE2 was stopped (table 3).

The rate of cardiovascular events over time remained constant (table 3). The proportion of patients having a cardiovascular endpoint by 12 months was 2·8% (95% CI 1·8–4·2) for men assigned LHRHa and 2·8% (1·9–4·2) for those allocated tE2; corresponding figures by 24 months were 5·3% (3·8–7·3) and 6·4% (4·8–8·4). A potential cumulative effect was assessed by length of time on treatment, and the effect remained constant for both drugs over time (table 3). Inclusion of assigned treatment as a time-varying covariate also provided no evidence that the treatment effect differed with increased time on treatment. By including oestradiol level as a time-varying covariate, no evidence was seen that higher levels of oestradiol with patches were associated with increased risk of a cardiovascular event. Similarly, among 186 patients with metastatic disease (90 LHRHa, 96 tE2) who were planned to receive upfront docetaxel as part of first-line treatment, 7·0% (95% CI 2·2–21·1) assigned LHRHa and 7·9% (3·0–20·0) assigned tE2 had a cardiovascular event by 24 months, and among 626 patients with metastatic disease not receiving docetaxel (301 LHRHa, 325 tE2), 7·8% (95% CI 3·3–17·8) assigned LHRHa and 6·1% (2·3–15·4) allocated tE2 had a cardiovascular event by 24 months, suggesting no evidence of increased cardiovascular toxicity with tE2 when administered with docetaxel (appendix p 4).

At 6 and 12 months, changes in fasting glucose and total cholesterol concentrations differed significantly between treatment groups among men still on their original allocated treatment (p<0·0001 for all comparisons), with levels increasing from baseline among those assigned LHRHa but decreasing among those allocated tE2 (table 4). HDL cholesterol and weight increased by similar amounts in the two groups at 6 months and 12 months. Systolic and diastolic blood pressure increased between baseline and 6 months in patients allocated LHRHa and decreased in those assigned tE2, although the changes were relatively small (relevant data not collected at 12 months).

Other adverse events experienced while patients were known to be receiving their allocated treatment were as expected and predominantly grade 1–2 (table 5). Gynaecomastia was significantly more common in patients who received tE2 (p<0·0001) and hot flushes were more common in those who received LHRHa (p<0·0001). Sexual and reproductive toxicities were similar between the two groups, as expected.

	LHRHa			tE2 patches			p value*
	n	Any grade	Grade 3	n	Any grade	Grade 3	
Gynaecomastia							
Both cohorts	730	279 (38%)	6 (1%)	807	690 (86%)	34 (4%)	<0·0001
1:2	79	38 (48%)	1 (1%)	147	121 (82%)	19 (13%)	..
1:1	651	241 (37%)	5 (1%)	660	569 (86%)	15 (2%)	..
Hot flushes							
Both cohorts	730	628 (86%)	23 (3%)	807	280 (35%)	1 (0%)	<0·0001
1:2	79	66 (84%)	5 (6%)	147	52 (35%)	1 (1%)	..
1:1	651	562 (86%)	18 (3%)	660	228 (35%)	0 (0%)	..
Skin or subcutaneous toxicity							
Both cohorts	730	474 (65%)	11 (2%)	807	548 (68%)	2 (0%)	0·20
1:2	79	56 (71%)	3 (4%)	147	92 (63%)	0 (0%)	..
1:1	651	418 (64%)	8 (1%)	660	456 (69%)	2 (0%)	..
Sexual or reproductive toxicity							
Both cohorts	730	671 (92%)	48 (7%)	807	732 (91%)	56 (7%)	0·58
1:2	79	71 (90%)	13 (16%)	147	125 (85%)	34 (23%)	..
1:1	651	600 (92%)	35 (5%)	660	607 (92%)	22 (3%)	..

Data are n (%) unless otherwise stated. Table presents toxicities experienced while patients were known to be receiving allocated treatment. Patients were included in the analysis of adverse events if they returned any toxicity data while still receiving allocated treatment. *p values compare the rate of toxicity at any grade, using a logistic regression model and combining the two randomisation cohorts using a fixed-effects meta-analysis.

Table 5: **Adverse events**

Discussion

Our data confirm that administration of oestradiol transdermally via a patch, rather than orally as in previous studies,[11] abrogates the risk of thromboembolic cardiovascular complications. Over a prolonged follow-up period, no evidence of excess cardiovascular toxicity was seen with tE2 compared with LHRHa, which are the current standard globally and widely used to achieve androgen suppression. These data accord with findings of previous prostate cancer studies in which oestrogens were administered intramuscularly[16] and with data from hormone replacement studies in both cis-gender and transgender populations comparing oral and transdermal administration of oestrogens.[17–19]

tE2 patches have three key pharmacological characteristics that make them especially attractive for androgen suppression in men with prostate cancer. First, exogenous oestrogen avoids the oestrogen-depleting effects (loss of bone mineral density, adverse metabolic profiles, and hot flushes) seen with other androgen-depleting strategies and that are associated with long-term morbidity. Second, transdermal administration avoids the thromboembolic cardiovascular toxicity seen with oral oestrogen. Third, the absence of an early testosterone flare with tE2 negates the need for co-administration of antiandrogens, which is usually required with LHRHa.

We have previously shown[20] a significant difference in bone mineral density in the first 2 years of treatment with tE2 compared with LHRHa. For men who remained on allocated treatment, the mean percentage change in lumbar spine bone mineral density was −3·0% with LHRHa and 7·9% with tE2 (p<0·001).[20] Loss of bone mineral density with LHRHa is attributed to a reduction in circulating oestrogens. Additionally, we have published self-reported quality-of-life data from 727 men within the PATCH programme.[21] Overall, higher global quality-of-life scores were reported with tE2 compared with LHRHa (mean difference 4·2, 95% CI 1·2–7·1; p=0·006), attributed to a reduction in hot flushes and fatigue.[21] Our current data confirm the reduction in hot flushes with tE2 compared with LHRHa and, as anticipated, the increase in gynaecomastia.

Our current data also show clear differences in fasting glucose and lipid levels over time between the two treatment approaches. The rise in fasting glucose levels or insulin resistance on LHRHa accords with published work[22] and could contribute to the increased cardiovascular morbidity associated with LHRHa detected in epidemiological studies.[23,24] The improvement in metabolic variables with tE2 accords with findings in postmenopausal women showing that oestrogen improved lipid profiles[25] and in men with prostate cancer who received tE2 with LHRHa to alleviate side-effects.[26] To date, the improvement in metabolic variables we noted with tE2 compared with LHRHa has not translated into a clinical benefit in terms of cardiovascular outcomes, but further follow-up is required since the expected time to see such benefits would be 5–10 years. By comparison with LHRHa, the only increased toxicity seen with tE2 was gynaecomastia. Overall, skin toxicity was reported at similar rates between the two treatment groups, although the toxicity will most likely be due to different causes, with discomfort or irritation around the injection site more typical for patients receiving LHRHa, and with erythema or pruritus and issues with adherence more common for men receiving tE2.

Our study has several strengths, including its randomised nature, detailed review of all potential cardiovascular events, and length of follow-up. In epidemiological studies, LHRHa have been associated with increased risk of developing metabolic syndrome and cardiovascular disease,[23,24] although data from randomised trials primarily designed to evaluate oncological outcomes have been less consistent.[27,28] Endpoint review is common practice in cardiovascular trials because the symptoms associated with cardiovascular disease can be similar to, or subsequently attributed to, another disease process. We initially used a broad and conservative approach for events to be included in our

detailed cardiovascular review based on symptoms or initial reports, and we used additional clinical information received to confirm or refute our defined cardiovascular event, with only 167 (53%) of 311 events subsequently meeting our criteria. The initial inclusive approach minimised the risk of under-reporting cardiovascular events and provides confidence of accurate categorisation. Moreover, the intention-to-treat analysis (for which a substantial proportion of patients allocated tE2 had changed to LHRHa) provides data for the cardiovascular effect of any exposure to tE2 over a prolonged period, even when medication has been stopped. The frequency of cardiovascular disease that we noted accords with our original estimates based on published work.[29]

A limitation of our study was that the review of cardiovascular events was not blinded to treatment allocation, but it was supported by additional and confirmatory source data from study sites. Agreement on cases was reached by consensus of the clinical reviewers. A further limitation could be perceived to be the length of follow-up (median 3·9 [IQR 2·4–7·0] years). However, in the original Veterans Administration Cooperative Urological Research Group studies,[11] increased cardiovascular toxicity became apparent within the first year and the rate remained constant over time. No evidence of an increased rate of cardiovascular events with tE2 patches compared with LHRHa was seen over time; a planned extension of recruitment in PATCH means that follow-up will be ongoing.

The PATCH trial programme has evolved over 15 years. During that time, outcomes and treatment paradigms for M0 and M1 patients have diverged, with radiotherapy to the prostate becoming standard of care for M0 patients and upfront docetaxel (and abiraterone and other androgen-receptor targeting agents such as enzalutamide) entering clinical practice for more advanced disease.[1] Most clinical trials now consider M0 and M1 patients as two separate entities and, for this reason, we aim to continue recruiting to the PATCH trial programme to provide two separate cohorts for M0 and M1 patients, with conventional statistical power to assess prostate cancer efficacy based on a non-inferiority design. This analysis will include patients recruited from both the PATCH and STAMPEDE networks and it is anticipated that efficacy results for the M0 cohort will be available in 2023 and those for the M1 cohort in 2024. These results for efficacy will be required for a full assessment of this therapeutic approach and its role in the treatment of both locally advanced and metastatic prostate cancer. To ensure that the results of the PATCH programme remain pertinent to current clinical practice,[1] we have assessed tE2 alongside radiotherapy and docetaxel, and future work will include the androgen-receptor targeted agents (eg, abiraterone and enzalutamide). During this development programme, all accumulating data (including efficacy data) have been monitored by an IDMC, which has supported continued recruitment at each phase.

To date, the PATCH development programme has been a repurposing project using tE2 patches manufactured for the relief of menopausal symptoms in women. A practical limitation of this approach is that the current patches need to be changed twice weekly, and although this procedure is simple it contrasts with one intramuscular injection given monthly or every 3 months for LHRHa.

In a randomised trial comparing the LHRH antagonist relugolix with the LHRHa leuprolide, castration rates were higher and fewer serious adverse cardiovascular events were reported with relugolix.[30] The reason for the reduction in cardiovascular toxicity is unknown, although it has been seen in other trials of LHRH antagonists.[31] Toxicities associated with LHRH antagonists include the oestrogen-depletion effects of hot flushes, adverse metabolic profiles, and the risk of osteoporosis.

In view of our castration rate data, in particular that castration is achieved more quickly with tE2 compared with LHRHa, and the extensive toxicity data, there is arguably already sufficient information to support use of tE2 for short-term use (<6 months)—eg, alongside radiotherapy in men with localised intermediate risk prostate cancer. Equally, for patients who are greatly affected by the side-effects of LHRHa (or for whom the cost of standard therapy is prohibitive), these data provide the basis for a more detailed and personalised discussion around the different approaches to androgen deprivation.

Contributors

REL, MP, and Prof Paul Abel developed the trial and oversaw study conduct. The team at the coordinating trials unit was led by REL with the support of MP and DCG. Statistical analyses were done by TD and MN. SF and MW were responsible for trial coordination. AA, NWC, RK, HK, StMa, AM, and SDR were clinical members of the trial management group, with SDR providing cardiovascular expertise. REL, DCG, and AM reviewed all cardiovascular events for consistency. SKS, MEL, SD, SaMa, CM, AP, CDS, StMc, IAM, GNC, JW, STW, EP, AR, and JoMc recruited and treated patients. JoMa and JVD were participant representatives for the study. MN and TD had full access to the raw data and verified the analyses. All authors had access to the data presented, reviewed and approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

REL reports grants from Cancer Research UK (CRUK) and the UK Medical Research Council (MRC), during the conduct of the study; and personal fees from Aspirin Foundation, outside of the submitted work. IAM reports in the last 3 years that he received honoraria for advisory boards and chairing or speaking at educational or pharmaceutical meetings with Ipsen, EUSA Pharma, Novartis, and Pfizer. MP reports grants from CRUK and MRC, during the conduct of the study; and grants from Astellas, Clovis Oncology, Novartis, Pfizer, and Sanofi, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Data will be shared according to the MRC Clinical Trials Unit (CTU) controlled access approach, based on the following principles: no data should be released that would compromise an ongoing trial or study; there must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose; investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers; the resources required to

process requests should not be underestimated, particularly successful requests that lead to preparing data for release, thus adequate resources must be available to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources; and data exchange complies with Information Governance and Data Security Policies in all the relevant countries. Researchers wishing to access data from the PATCH study should contact mrcctu.pr09@ucl.ac.uk in the first instance.

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