Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review

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Abstract

Purpose

Androgen deprivation therapy (ADT) has broad application in the treatment of prostate cancer (PC) and is associated with numerous, debilitating adverse effects. Increasing use of ADT for PC, longer timeframe for treatment (increased uptake of PSA testing and earlier diagnosis), as well as improved survival and an ageing population, means patients can live for a considerable period of time on or after ADT, experiencing these adverse effects. A number of systematic reviews of adverse effects of ADT for PC exist, however, no single systematic review has previously examined the evidence for all adverse effects, including newer forms of ADT.

Methods

A systematic review of existing systematic reviews of ADT for PC was conducted (2010 – February 2019), as per Cochrane guidelines, to identify the highest level of risk/incidence evidence available, supplemented by evidence drawn from individual studies where no systematic review existed.

Results

Incidence data was generated for 19 adverse effect sub groups, classified according to the common terminology criteria for adverse events (CTCAE).

Conclusion

Incidence of adverse effects provides valuable information for future burden of disease studies. This information can better guide clinical management to reduce symptoms for patients and assist patients to make more informed decisions about their treatment, potentially improving disease outcomes. It also highlights the importance of supportive care for PC patients receiving ADT and their carers. For analysts conducting economic evaluations, the inclusion of adverse effects in PC decision analytic models can provide more comprehensive and accurate information for decision makers.

Key words: prostate cancer, androgen deprivation therapy, adverse effects, incidence

Introduction

Since the advent of PSA testing in the 1990s, the rising incidence and burden of prostate cancer (PC) has been a cause for concern. Treatment options for men with PC are varied and depend on a number of factors such as expected survival, risk of progression, stage and grade of cancer at diagnosis, age and health of the patient, family history, personal preferences of the patient and adverse effects of treatment. Androgen deprivation therapy (ADT) suppresses the production of androgen, which fuels the growth of PC. It has broad application in the treatment of PC and many types of ADT are currently in use in Australia (Table 1). ADT is predominantly used for intermediate or higher risk disease as well as advanced and metastatic cancer. It is also maintained when cancer becomes castration resistant. In addition, it is used as neo-adjuvant, concurrent and adjuvant therapy with prostatectomy and radiotherapy(1-4).

Table 1. Androgen deprivation medications currently used in Australia

Type	Technical name	What it does	Format
GnRH/LHRH agonist	gosrelin leuprolelin triptorelin	Inhibits GnRH release from the testes with continuous delivery to suppress testosterone production	injection
GnRH/LHRH antagonist	degarelix	Inhibits GnRH release from the testes by binding to pituitary GnRH receptors decreasing circulating levels of testosterone	injection
Androgen receptor blockers (anti-androgens)			
Steroidal	cypoterone acetate	Inhibits androgen receptor (AR) & central nervous system effects	tablet
Non-steroidal -1 st generation	bicalutamide flutamide nilutamide	Inhibits AR, thereby reducing the stimulation of PC cells	tablet
Non-steroidal - 2 nd generation	enzalutamide apalutamide	Blocks several steps in the AR signalling pathway: binding to the AR; nuclear translocation of activated receptor; and association of the translocated receptor with DNA	tablet
Adrenal androgen inhibitors	abiraterone acetate + prednisone/ methylprednisolone	Inhibits androgen production at all sources: adrenal glands, testes, tumour	tablet

Key: GnRH gonadotropin-releasing hormone; LHRH luteinising hormone-releasing hormone

ADT for PC is associated with numerous and often debilitating adverse effects. The National Institute of Cancer defines an adverse effect as: “an unexpected medical problem that happens during treatment with a drug or other therapy. Adverse effects may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given. Also called an adverse event.”(5). The increasing use of ADT for PC, the longer timeframe for treatment (an outcome of increased uptake of PSA testing and earlier diagnosis), as well as improved survival and an ageing population, means patients can live for a considerable period of time on, or after, ADT, experiencing these adverse effects(6).

While much has been published on the adverse effects of ADT for PC in recent years, and a number of systematic reviews exist(7-29), some of these do not include current studies or newer ADTs. No single systematic review has previously comprehensively examined the evidence for all adverse effects.

Characterising adverse effects is beneficial for several reasons. Firstly, incidence of adverse effects will

provide valuable information for future burden of disease studies and better guide clinical management to reduce symptoms for patients. Secondly, in this era of shared decision making, such information will assist patients to make more informed decisions about their treatment, thus facilitating compliance with their treatment plan and potentially improving disease outcomes. For analysts conducting economic evaluations, inclusion of adverse effect incidence in PC decision analytic models can provide more comprehensive and accurate information for decision makers. The purpose of this paper, therefore, is to systematically review the current literature on ADT for PC to identify the highest available level evidence of risk/incidence of common adverse effects. Given the nature of current evidence, this review will comprise a review of existing systematic reviews, supplemented where necessary by evidence drawn from individual studies.

Methods

Using an *a priori* defined protocol, this systematic review was conducted as per Cochrane guidelines (30). In order to locate the most recent high-level evidence and not duplicate previous research, a systematic search was conducted as outlined below.

Identification - search strategy

A PRISMA compliant systematic search of the literature on the adverse effects of ADT for PC was conducted for the years 2010-February 2019)(30, 31). Figure 1 shows the search process (identification, screening, eligibility & inclusion). The study screening and selection process consisted of three phases. First, a search was conducted to identify original articles in the following electronic databases: Medline, Embase, PsycInfo, and Cochrane Library. The search strings comprised terms for PC, adverse effects and ADT medications (Online Resource 1). Where databases allowed, searches were limited to English language, humans. Language limitations were based on review time frames and language capacity of team members; pre-clinical trial research using animals was not relevant to adverse effect incidence, and given the rapidly changing landscape of PC treatment, a period of ten years of evidence generation was deemed adequate by the research team. A Google Scholar search of adverse effects of ADT for PC was also conducted.

Classification of studies

Identified studies were then classified using a three-step process.

Step 1: Screening

Titles and abstracts of the retrieved articles were screened following the PICOS criteria in Table 2.

Table 2. PICOS inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Men with prostate cancer (PC) receiving androgen deprivation therapy (ADT)	Men with prostate cancer not receiving ADT
Intervention	ADT for PC	Other forms of PC treatment
Comparator	No ADT or other PC treatment	-
Outcomes	Major adverse effects of ADT; incidence, rate or risk	Adverse effects without incidence, rate or risk evidence
Study design	Systematic review, RCT, observational study, population-based study, cohort study	Irrelevant/not PC; not a peer-reviewed article; descriptive or review article; not English language; does not involve human subjects

Step 2a: Classification of adverse effect groupings

The remaining records were classified into adverse effect groupings using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0(32) to enable comparison of available evidence for specific adverse effects (Table 3).

Step 2b: Identifying highest level of evidence

In order to have incidence data supported by the highest level of evidence available, classification of articles was guided by the Oxford Centre for Evidence-based Medicine (OECBM) 2011 Levels of Evidence(33, 34). Studies were classified into: A. systematic reviews; B. analytic studies, comprising i) experimental studies such as RCTs and ii) observational studies; and C. descriptive studies. Systematic reviews were prioritised; where they did not provide the evidence required, RCTs were the next level of evidence included. Observational studies were maintained until step three, in the event that higher level studies did not address adverse effect incidence. Descriptive studies were excluded.

The full text versions of the remaining records were obtained and independently assessed for eligibility by two reviewers (KE & HT). Disagreements were resolved through consensus. Where studies of equal quality and evidence level were found, all results were recorded to strengthen the evidence collected. Remaining lower evidence articles were then excluded. The following exclusion criteria were applied with the benefit of full text information: not highest level of evidence available; no incidence information; more recent but equivalent evidence available. Finally, the reference lists of included studies were manually reviewed to identify articles not located by the electronic database search.

Data extraction

Data was extracted from the included studies by one reviewer (KE) and independently reviewed by a second reviewer (HT). For each study, information was recorded on: first author, year and country where study was conducted; sample size and setting; study type, study outcomes or incidence data; and risk of bias or quality assessment.

Methodological quality of systematic reviews and single studies

Quality assessment of included systematic reviews was conducted using the AMSTAR 2, a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both(35). Included individual studies were critically appraised using Cochrane Collaboration recommended tools ROB 2(36) for RCTs and the Newcastle-Ottawa Scale(NOS)(37) for cohort studies(30, 38). Risk of bias or quality ratings were independently assessed by KE and HT to address the possibility of rating error. Any discrepancies were addressed via consensus. Systematic reviews receiving a critically low rating were excluded from the evidence synthesis.

Analysis

Given that the purpose and characteristics of the included individual studies (sample populations, treatment types, PC stages, patient age, control groups, adverse effect examined and outcomes measured) varied considerably across studies, a meta-analysis was not appropriate for the purposes of this review. Instead, evidence of the highest level available was collected and compared for each adverse effect and a range of scores recorded to ensure the most rigorous incidence data was generated by this systematic review.

<.....Fig 1 about here....>

Results

The search of databases located 1,253 records. Google Scholar and a survey of reference lists generated a further six records (n=1,259). Thirty-one duplicates were removed electronically. A total of 1,228 records remained for screening. After preliminary screening of titles and abstracts, 1110 studies that did not match the inclusion criteria were removed. A total of 118 studies remained. Thirty-two full text systematic reviews met the inclusion criteria and were evaluated for adverse effect incidence. Evidence was generated for incidence of body composition changes, bone loss, osteoporosis, metabolic syndrome, diabetes, hypertension, cardiovascular disease (CV) risk, thromboembolisms, hepatotoxicity, fatigue, body feminisation, vasomotor flushing, depression, cognitive function and dementia. The remaining single studies (n=86) were then examined for evidence of adverse effect incidence not generated by the systematic reviews (osteoporosis, hepatotoxicity, gait disturbance, fracture, sexual function) (Table 3). The highest level of evidence generating comprehensive data (e.g. including sufficient stages of PC and types of ADT) were included in the evidence synthesis for these adverse effects. Thirty-nine studies (25 systematic reviews + 14 individual studies) were judged eligible for inclusion in the review. Detailed information extracted from the 39 studies was recorded in the summary of findings table (Online Resource 2).

The following section examines each of the adverse effect sub groups in turn, summarising study characteristics and adverse effect incidence.

Table 3. Adverse effect groups and evidence consulted for incidence

Group	Adverse effect (CTCAE)	Adverse effect sub group	Studies (n)
1	Musculoskeletal changes	a) Bone loss	1 (SR)
		b) Osteoporosis	1 (IS)
		c) Fracture	8 (IS)
2	Metabolic changes	a) Body composition changes	1 (SR)
		b) Metabolic syndrome	1 (SR)
		c) Diabetes	2 (SR)
3	Cardiac disorders	a) Cardiovascular events	11 (SR)
4	Nervous system disorders	a) Cognitive impairment	2 (SR)
		b) Stroke	3 (SR)
		c) Dementia	1 (SR)
5	Vascular disorders	a) Hypertension	4 (SR)
		b) Thromboembolic events	2 (SR)
		c) Hot flashes	5 (SR)
6	Hepatobiliary disorders	a) Hepatic disorders	2 (SR); 1 (IS)
7	Reproductive system disorders	a) Gynaecomastia and breast pain	3 (SR)
		b) Sexual dysfunction	2 (SR); 2 (IS)
8	Psychiatric disorders	a) Depression	2 (SR)
9	General disorders	a) Fatigue	3 (SR)
		b) Gait disturbance	4 (IS)

Key: SR systematic review; IS individual study; CTCAE Common Terminology Criteria for Adverse Events

NB: Some studies have multiple adverse effect outcomes so may count more than once

1 Musculoskeletal changes

1a. Bone loss

ADT increases bone turnover and causes significant, progressive decrements in bone mineral density (BMD) in men with PC, contributing to an increased risk of osteoporosis and fractures. The magnitude of bone loss rates tends to be higher early in treatment, but also decreases steadily during long term treatment(39). The extent of bone loss differs for measurement site and duration of ADT. One systematic review included five prospective cohort studies of localised or advanced PC treated with orchiectomy, luteinising hormone releasing hormone (LHRH) agonist or anti-androgen (13). Controls varied across the studies as did treatment duration, with heterogeneity ranging from 82-99%. Pooled analysis of four studies (n=483) determined mean percent bone loss for lumbar spine of -3.6% (95% CI -6.72, -0.47, $p=0.02$). Five studies (n=515) recorded bone loss for femoral neck of -3.11% (95% CI -4.73, -1.48, $p=0.02$). Mean per cent bone loss for total hip derived from four studies (n=483) was -1.59% (95% CI -2.99, -0.19, $p=0.03$)(13).

1b Osteoporosis

ADT induced bone loss is further exacerbated by already high levels of osteoporosis in the ageing population. Studies in UK(40)and US(41) have reported levels of around 40% for osteoporosis and between 40% and 50% for osteopenia in men with PC initiating ADT. The risk of osteoporosis is heightened by age and comorbidities common in this population. One recent retrospective cohort study conducted in Australia using Pharmaceutical Benefits Scheme (PBS) data involved a 10% random sample of the PC population receiving their first ADT between 2004 and 2010 compared to a matched population not receiving anti-neoplastic agents or having no comorbidities at baseline(42). There was significant risk

of developing osteoporosis in the ADT PC population: hazard ratio (HR) 1.65 (95% CI 1.48, 1.85). An adjusted HR was also calculated for incidence of osteoporosis stratified by duration of ADT exposure: ≤ 1 year 1.38 (95% CI 1.10,1.72) and > 1 year 1.77 (1.55-2.02)(42).

1c Fracture

Two RCTs and six cohort studies with data on incidence of fractures in men receiving ADT met the inclusion criteria for this review. Two studies focussed on localised PC; one included recipients of ADT alone, curative treatment and ADT, and orchiectomy(43), the other men received radical prostatectomy or radiotherapy with/without ADT(44). Four studies focussed on advanced cancer, one included only men with non-metastatic PC receiving any type of ADT or orchiectomy(45), another, men with metastatic PC comparing gonadotropin releasing hormone (GnRH) agonists with orchiectomy(46), the third, men with advanced cancer receiving intermittent ADT (IADT)(47), and the fourth, men receiving GnRH agonists only with non-metastatic or metastatic PC(48). Two RCTs examined second generation treatments for non-metastatic(49) and metastatic castrate resistant PC (CRPC)(50). These studies established a significant association between ADT and incidence of fracture across the disease spectrum, and identified factors that elevate risk such as age, ADT dose and duration, time from last dose, osteoporosis, metastases and dementia (Table 4).

Table 4. Fracture incidence

First author (year)	Treatment	Fracture incidence
Smith (2018) (49)	apalutamide	11% apalutamide vs 6.5% placebo
Graff (2016)(50)	enzalutamide	enzalutamide vs placebo any fracture <75 years 9.9% vs 3.6%; ≥ 75 years 15.8% vs 7.9% non-pathological fractures <75 years 6.5% vs 1.8%; ≥ 75 years 10.1% vs 5.1%
Shao (2013) (43)	ADT alone ADT + curative therapy orchiectomy	All ADT: 26.83% one fracture; 8.8% hospitalisation. 23% of all fractures hip fractures (increased risk of mortality) Incidence for different fracture risks: high 58%, low 38%, no ADT 31%. Hazard ratio (95% CI) ADT alone (18 dose): low risk HR 1.53 (1.44-1.62); high risk 1.27 (1.20-1.35) vs no ADT. ADT + curative: low risk HR 1.37 (1.27-1.49); high risk HR 1.20 (1.09-1.33). Mortality risk 40% higher after a fracture
Wallis (2016) (44)	Radical Prostatectomy +/- ADT; Radiotherapy +/- ADT	Hazard ratio (95% CI) Any Fracture HR 1.28 (1.16, 1.41; $P < 0.0001$) Fracture requiring hospitalisation HR 1.32 (1.19-1.46; $P < 0.0001$)
Alibhai (2010) (45)	LHRH agonists, non-steroidal or steroidal anti-androgens alone or in combination & orchiectomy	ADT 9% vs non-ADT 5.9% - fragility fracture of spine, lower arm, hip/femur Adjusted hazard ratio (95% CI) aHR 1.65 (1.53-1.78); any fracture 17.2% vs 12.7% aHR 1.46 (1.39-1.54) significant increase for most fracture sites
Sun (2016) (46)	GnRHa, Orchiectomy	Any fractures incidence GnRHa 37.7% vs Orchiectomy 31.4% HR (95% CI) 0.77 (0.62, 0.94; $P = 0.01$) sub analysis GnRHa duration

		18-34 months HR 1.48 (1.17, 1.97; <P 0.001) ≥35 months HR 1.80 (1.45, 2.24; <P 0.001)
Tsai (2017) (47)	IADT	Hazard ratio (95% CI) IADT lower risk of fracture than CADT HR 0.52 (0.38-0.70)
Beebe-dimmer (2012)(48)	GnRH agonist	HR 1.31 (1.29-1.39) dose related; Adjusted hazard ratio (95% CI) Metastasis aHR 1.52 (1.36-1.67) Orchiectomy aHR 1.62 (1.42-1.84) among M0 & Met aHR 1.54 (1.26-1.88). Risk highest for men currently receiving ADT or within 6 months of last dose aHR 1.67 (1.56-1.78). Risk for men who received <6 doses or discontinued ADT 18 months ago aHR 1.06 (0.99-1.14). Similar for men with metastases. Mortality risks within 6 & 12 months of experiencing any fracture 8.3% & 12.2%, respectively. Fracture associated with two-fold increase in rate of death aHR 2.05; (1.98-2.12) aHR 2.82 for fracture requiring hospitalisation (2.68-2.97)

Key: HR hazard ratio; aHR adjusted hazard ratio; GnRHa gonadotrophin releasing hormone agonists; IADT intermittent androgen deprivation therapy; CADT continuous androgen deprivation therapy; MO not metastatic; Met metastatic

2 Metabolic changes

2a Body composition changes

Body composition changes increase with duration of treatment and comorbidities; they tend to be greater in the first three months and continue over time but less rapidly to six months and longer(51). A meta-analysis by Haseen et al.(51) reported significant changes in body composition for men receiving ADT. Pooled analysis was conducted from 16 studies (14 cohort and 2 RCTs) which varied in type of ADT and stage of PC. Analyses included seven studies for increases in body fat mass of 7.7% (95% CI 4.3,11.2, $p<0.00001$), six for decreases in lean mass of 2.8% (95% CI -3.6, -12.0, $p<0.00001$), nine for increases in body weight of 2.1% (95% CI 1.35, 2.94, $p<0.00001$) and eight for increases in body mass index (BMI) of 2.2% (95% CI 1.16, 3.14, $p<0.0001$). Heterogeneity was quite high across the studies included for each body composition change, 99%, 73%, 55% and 63%, respectively. Sub analyses for ADT type showed that luteinising hormone releasing hormone (LHRH) had greater impact on body composition changes than combination therapy with anti-androgen.

2b Metabolic syndrome

Men receiving ADT tend to experience adverse changes in the following metabolic features: decreased lean mass, increased fat mass (together known as sarcopenic obesity), increased waist circumference, alterations in lipids and decreased insulin sensitivity(52, 53). One systematic review of ADT induced metabolic syndrome incorporated data for meta-analysis from four cohort studies and five cross sectional studies(8). The type of ADT varied across studies from any type of ADT in five studies, GnRH agonist, combined androgen blockade, orchiectomy and anti-androgens in one study and orchiectomy alone in two. The relative risk (RR) of acquiring metabolic syndrome was 75% higher for men with PC receiving ADT compared to those not receiving ADT (RR 1.75; 95% CI 1.27, 2.41)(8).

2c Diabetes

Two systematic reviews generated data on diabetes incidence. The Bosco *et al.* (8) review mentioned above reported a RR of 1.36 (95% CI 1.17, 1.58) for men receiving ADT. Wang *et al.*(27), pooled data

for meta-analysis from four cohort and four cross sectional studies. Incidence of diabetes amongst men receiving ADT (GnRH agonists, combined androgen blockade or orchiectomy) was 10.9% (27). The risk of diabetes was 39% higher for these men than for men not receiving ADT or men on watchful waiting or active surveillance (RR 1.39; 95%CI 1.27-1.53, $P<0.001$)(27). Sub group analyses for ADT type and duration showed that GnRHa, combined androgen blockade and orchiectomy are significantly associated with risk of diabetes, and longer duration of ADT with elevated risk(27).

3 Cardiac disorders: Cardiovascular (CV) complications and mortality

Since a large observational analysis of Surveillance, Epidemiology and End Results (SEER) Medicare data demonstrated a significant association between GnRH and incident coronary heart disease, hospital admission for myocardial infarction (MI) and sudden cardiac death in men with PC, the question of whether ADT increases the risk of CV events or CV mortality has been raised(54). A systematic review conducted in 2009 showed that ADT is associated with a 17% increased risk of cardiovascular mortality(55). This analysis, however, was based on only two observational studies and two RCTs. Since that time, studies of CV risk for ADT recipients have proliferated and systematic reviews have been conducted of CV risk factors such as hypertension, as well as CV events including MI and CV mortality. While the included systematic reviews focus on CV adverse events, the outcomes measured differ, as do type of ADT, stage of PC and comparators. Attempts were made to address heterogeneity via pooled meta-analyses, within trial analyses or analyses by study (Table 5).

There was an increased risk of CV mortality for all types of ADT and for MI or stroke from GnRH agonists, anti-androgens and orchiectomy combined. For ADT type, orchiectomy has the highest risk ratio and anti-androgens(7, 28) or IADT(12, 15) the lowest risk compared to no ADT. The risk for CV events was similar across types of ADT and varied dependent largely on the comparator, as the study by Scailteux shows(24). One systematic review found no significant differences in risk for CV mortality between ADT and controls across all included studies(21). In other reviews, degarelix reduced the risk of CV events compared to GnRHa, as did IADT(12, 15, 25). There was a strong association between grade 3 cardiac adverse events and grade 3/4 vascular events and abiraterone acetate + prednisone compared to placebo(23). This impact was lower for all grade events. The relative risk of CV events with enzalutamide was lower than that for abiraterone acetate(29, 56).

Table 5. Incidence CV mortality and CV adverse events

First author (year)	Treatment	CV mortality	CV adverse events
Bosco 2015a(7)	GnRHa orchiectomy anti-androgen	Fatal MI or stroke: RR 1.51 (1.24-1.84)	Relative risk (95% CI) GnRH agonists i. any type CVD: RR 1.38 (1.29-1.48); ii. non-fatal IHD: RR 1.39 (1.26-1.54); iii. non-fatal MI or stroke: RR 1.57 (1.26-1.94); Orchiectomy i. any non-fatal CVD: RR 1.44 (1.28-1.62); Anti-androgen (AA) i. Any non-fatal CVD: RR 1.21 (1.07-1.37)
Jin 2016(12)	IADT	Relative risk (95% CI) No statistically significant difference: RR 0.85 (0.71-1.00)	Relative risk (95% CI) No statistically significant difference: RR 0.95 (0.83-1.08)
Magnan 2015(15)	IADT	Hazard ratio (95% CI) No statistically significant difference: HR 0.86 (0.73-1.02)	NA
Zhao 2014(28)	GnRHa GnRHa + anti-androgen Orchiectomy	11.7% of all ADT users hazard ratio (95% CI) Overall CVM 1.17 (1.04, 1.32, $P=0.01$) subgroup analyses ADT type: GnRH HR 1.36; (1.10, 1.68; $P = 0.004$), GnRH + AA HR 1.44 (1.33– 1.57; $P<0.001$); AA alone HR 0.95 (0.70–1.27; $P=0.72$) orchiectomy HR 1.69 (1.06–2.71; $P = 0.03$). ADT monotherapy vs WW/AS 1.30 (1.13, 1.50, $P<0.001$)	17.8% of all ADT users hazard ratio (95% CI) Overall CV events 1.10 (1.00-1.21, $P=0.06$) subgroup analyses ADT type: GnRH HR 1.19 (1.04–1.36; $P = 0.010$); GnRH + AA HR 1.46 (1.03–2.08; $P = 0.04$). AA alone HR 0.94 (0.85–1.03; $P = 0.16$) or orchiectomy HR 1.15 (0.92–1.43; $P = 0.23$) ADT monotherapy vs WW/AS 1.19 (1.08-1.30, $P=0.0004$) ADT & MI 1.10 (0.97-1.26, $P=0.14$) sub group analyses AMI GnRH HR 1.20 (1.05-1.38, $P=0.008$); AA alone HR 0.88 (0.81-0.96, $P=0.002$)
Nguyen 2011(21)	GnRH	GnRH 11% (8.3-14.5) relative risk (95% CI) RR 0.93 (7.9-1.10) no statistically significant difference	NA

Scailteux 2016(24)	Any ADT	NA	<p><u>Myocardial Infarction</u> Relative risk (95% CI) Observational studies Orchiectomy vs AA 2.04 (0.66, 8.33); GnRHa vs Orchiectomy 0.61 (0.30, 0.92); CAB vs Orchiectomy 0.49 (0.19, 0.89); CAB vs GnRHa 0.97 (0.63, 1.47); GnRHa vs AA 1.43 (1.10, 1.85); CAB vs AA 1.34 (0.87, 2.06) RCTs CPT vs AA 0.49 (0.04, 5.39); GnRHa vs GnRHant 0.42 (0.23, 0.77)</p>
Sciarra 2016(25)	Degarelix	NA	<p>Degarelix 1.6% vs GnRHa 3.6% Odds ratio (95% CI) OR 0.55 (0.26-1.14, p>0.1)</p>
Rydzewska 2017(23)	ADT + abiraterone acetate + prednisone/ prednisolone	NA	<p>Peto odds ratio (95% CI) Grade III acute cardiac events Peto OR 2.93 (1.74, 4.93, <i>P</i><0.001); Grade III-IV vascular events Peto OR 2.28 (1.71, 3.03, <i>P</i><0.001)</p>
Iacovelli 2018(56)	Abiraterone acetate vs placebo Enzalutamide vs bicalutamide	NA	<p>Both ADT All grade 11.7% vs 8.6% Relative risk (95% CI) RR 1.36 (1.13-1.64, <i>P</i>=0.001); high grade 3.7% vs 2.0% RR 1.84 (1.21-2.80, <i>P</i>=0.004); Abiraterone acetate all grade 13.7% & high grade 4.5% RR 1.41 (1.21-1.64 <i>P</i><0.001) & RR 2.22 (1.60-3.07, <i>P</i><0.001); Enzalutamide all grade 8.6% & high grade 2.5% RR 1.25 (0.99-1.59 <i>p</i>=0.3) & 1.28 (0.45-3.66, <i>p</i>=0.7); comparison between abiraterone & enzalutamide no difference in RR.</p>
Roviello 2016(22)	Abiraterone acetate + prednisone	NA	<p>Within trial incidence Abiraterone acetate vs control (COU-AA-301 %all, %high); (COU-AA-302 % all, % high): 301: 21 vs 15, 5 vs 3; 302: 23 vs 18; 8 vs 5. All grade AEs Relative risk (95% CI) RR 1.47 (1.27, 1.70, <i>P</i><0.00001); High grade AEs</p>

			RR 1.55 (1.18, 2.05, $P=0.02$)
Zhu 2018(29)	Abiraterone acetate + prednisone Enzalutamide	NA	Significant events Relative risk (95% CI) Abiraterone acetate: all grades RR 1.40 (1.22, 1.62) high grade AEs RR 1.93, (1.42, 2.61)

Key: CV cardiovascular; CVD cardiovascular disease; GnRHa gonadotrophin releasing hormone agonist; MI myocardial infarction; IHD ischaemic heart disease; RR relative risk; HR hazard risk; NA not applicable; CVM cardiovascular mortality, AA anti-androgen; WW watchful waiting; AS active surveillance; GnRHant gonadotrophin releasing hormone antagonist; CAB combined androgen blockade; RCTs randomized controlled trials; OR odds ratio; AEs adverse effects.

4 Nervous system disorders

4a Cognitive impairment

Two systematic reviews examined incidence of cognitive impairment from ADT(16, 26). Sun *et al.*(26) conducted a meta-analysis of six cohort studies, two of which were prospective and resulted in an odds ratio (OR) of 1.56 (0.50, 4.91, $p=0.441$). The remaining four retrospective sub groups included men with senile dementia and Alzheimer's disease, and while the risk of cognitive impairment was higher, it was not statistically significant (HR 1.28; 95% CI 0.93, 1.76 $p=0.130$). They concluded that results could not reliably confirm the relationship between ADT and cognitive impairment. A second meta-analysis of 14 studies suggested that for men receiving ADT for PC, there was insufficient evidence to support cognitive decline with the exception of compromised visuomotor skills, where a significant decline was reported. The weighted average effect was -0.67 (95% CI -1.17, -0.17; $P=0.008$)(16). The extent of the deficit was also larger with shorter time to follow-up. However, there was insufficient evidence to determine whether these deficits were primarily motor related, that is arising from ADT related muscle loss, or evidence of low testosterone related deficits in visuospatial skill. The authors concluded that ADT recipients can expect cognitive functioning to be similar to that of men with PC not receiving ADT and men without PC, however, clinicians and patients need to be aware of the potential for visuomotor impairment when deciding on treatment(16).

4b Stroke

Two meta-analyses were conducted to determine incidence of stroke. Meng *et al.*(17) found a significant association between stroke and some types of ADT. Pooled analyses of GnRH alone resulted in a HR of 1.20 (95% CI 1.12, 1.28, $P<0.001$); GnRH + anti-androgen, a HR of 1.23 (95% CI 1.13, 1.34, $P<0.001$); and orchiectomy a HR. 1.37 (1.33-1.46, $P<0.001$). The HR for all ADT showed a higher incidence for ADT recipients compared to control groups, (HR1.12; 95% CI 0.95, 1.32), but no significant association. Another meta-analysis conducted pooled analyses of a range of different types of ADT showing a significant association between stroke and ADT(24). For example, in the only RCT, RR of GnRH agonist compared to GnRH antagonist was 3.44 (95% CI 0.22, 1.32). In observational studies, results varied considerably between different types of ADT with greater relative risk for GnRH agonists and orchiectomy compared to anti-androgens and combined androgen blockade (CAB) (Online Resource 2).

4c Dementia

Men receiving ADT have increased circulating β -amyloid protein levels, the accumulation of which characterizes Alzheimer's disease(19). Men diagnosed with dementia tend to have lower testosterone levels and impaired cognitive function, which for recipients of ADT, has been noted from as early as six months post treatment initiation(19). One systematic review conducted a meta-analysis of studies reporting any dementia outcome showed an increased risk associated with ADT (HR 1.47; 95% CI 1.08, 2.00; $p=0.02$). Studies reporting all cause dementia and Alzheimer's disease were also analysed separately resulting in hazard ratios of 1.46 (95% CI 1.05–2.02; $p<0.001$) and 1.25 (95% CI 0.99, 1.57; $p<0.06$), respectively. Current evidence thus suggests that ADT may be associated with an increased risk of dementia(19).

5 Vascular disorders

5a Hypertension

Hypertension is one of the strongest risk factors for all CV diseases and is strongly associated with age. ADT, particularly second generation hormonal agents such as abiraterone acetate and enzalutamide, is associated with significant increases in risk of hypertension. Four systematic reviews generated data on the incidence of hypertension for men receiving ADT for PC (22, 29, 56, 57). One showed a higher incidence of long-term hypertension with radiotherapy and GnRH agonists than with the use of anti-androgens (12% vs 4%)(57). Abiraterone acetate and enzalutamide compared to placebo or other forms of ADT was associated with a high risk of hypertension higher than that for CV events in three systematic reviews (22, 29, 56) (Online Resource 2).

5b Thromboembolic events

Population-based studies of men receiving ADT for PC have revealed an association between ADT and increased risk of thromboembolic events such as deep vein thrombosis (DVT) and pulmonary embolus (PE). Two meta-analyses examined the evidence for ADT associated thromboembolic events(10, 18). One restricted the analysis to five cohort studies which compared GnRH agonists alone, GnRH agonists + anti-androgens, anti-androgens alone and orchiectomy with no ADT(10). In this meta-analysis, DVT was significantly associated with GnRH agonist alone (HR 1.47; 95% CI 1.07, 2.03 $p=0.017$), GnRH agonist + anti-androgen (HR 2.55; 95% CI 2.1, 2.94, $p<0.001$) and anti-androgen alone (HR 1.49; 95% CI 1.13, 1.96, $p=0.004$), but not with orchiectomy (HR 1.80 95% CI 0.93, 3.47, $p=0.07$). Pulmonary embolism was significantly associated with GnRH agonist alone (HR 2.26; 95% CI 1.78, 2.86, $p<0.001$) and orchiectomy (HR 2.12; 95% CI 1.44, 3.11, $p<0.001$)(10). The other systematic review included oestrogens in addition to the above-mentioned forms of ADT and drew evidence from 20 studies comparing ADT with no ADT, short term ADT and IADT(18). In this meta-analysis, ADT without oestrogen in 10 studies caused a significant increase in risk of thromboembolic events (RR 1.43; 95% CI 1.15, 1.77, $p<0.001$) as did oestrogen alone in 9 nine studies (RR 3.72; 95% CI 1.78, 7.80, $p<0.001$). Sub analyses comparing disease stage demonstrated a significantly increased risk of thromboembolic events from ADT without oestrogen and oestrogen alone for both localized (RR 1.10; 95% CI 1.05, 1.16, $p<0.001$) and metastatic disease (RR 1.58; 95% CI 1.24, 2.03, $p<0.001$), but not for studies of continuous vs intermittent ADT. Sub analyses examining impact of ADT duration showed a significantly increased risk of thromboembolic events for duration >12months. Significant heterogeneity was resolved in ADT without oestrogen analysis for localized disease (0%) but not for the metastatic disease analysis (84%) or the oestrogen only analysis (71%)(18).

5c Hot flashes

Five systematic reviews referred to incidence of vasomotor flushing across various treatments and stages of PC from locally advanced to metastatic CRPC(14, 15, 25, 29, 57). Anti-androgens have a significantly lower risk of flashing than orchiectomy (RR 0.23; 95% CI 0.10, 0.27)(14) and GnRH agonists (<1% vs 45%)(57). Enzalutamide has a significantly increased risk of flashing compared to bicalutamide or placebo (RR 1.94; 95% CI 1.55, 2.42)(29). There was no significant difference in flashing between CADT and IADT(15) or between degarelix and GnRH agonists(25).

6 Hepatobiliary disorders

Two systematic reviews examined incidence of hepatotoxicity; one from ADT + abiraterone acetate + prednisone compared to placebo for metastatic hormone sensitive PC (HR 3.09; 95% CI 2.12, 4.50, $P<0.001$)(23), and one from abiraterone acetate + prednisone compared to placebo for CRPC (all grade RR 1.93; 95% CI 1.15, 3.24, $p=0.01$ & high grade RR 2.94; 95% CI 0.95, 9.08, $p=0.06$) (22). A large population-based study ($n=82,938$) using SEER-Medicare data for 1992-2009 found a significantly increased risk of any liver disease (HR 1.47, 95% CI 1.35, 1.60), non-alcoholic fatty liver disease (NAFLD) (HR 1.54, 95% CI 1.40, 1.68), liver cirrhosis (HR 1.35, 95% CI 1.12, 1.60), and liver necrosis (HR 1.41, 95% CI 1.15, 1.72) for men with PC receiving GnRH agonists and antagonists(58).

7 Reproductive system disorders

7a Gynaecomastia and breast pain

Gynaecomastia and breast pain are common adverse effects of non-steroidal anti-androgen therapy (bicalutamide, flutamide), and less so, GnRHa therapy, that can seriously impact men's masculinity and quality of life(9, 59). Three systematic reviews analysed the incidence data(14, 15, 57). Two studies reported that, compared to GnRH agonists, non-steroidal anti-androgen therapy was associated with a significantly increased risk of gynaecomastia (RR 8.43; 95% CI 3.19-22.28)(14) and 70% vs 11%(57). One of these studies also reported a 23 fold increased risk of breast pain pooled from eight studies (RR 22.97; 95% CI 14.79, 35.67)(14). There was a lower risk of gynaecomastia for IADT compared to CADT (RR 0.63; 95% CI 0.36, 1.10) but the difference was not statistically significant(15).

7b Sexual dysfunction

Sexual dysfunction, which here refers to erectile dysfunction and decreased libido, is a common and often distressing experience for both men receiving ADT for PC and their partners. Two systematic reviews included RCTs with incidence of sexual dysfunction or decreased libido, one comparing erectile dysfunction between degarelix and GnRH agonists (RR 0.94 95% CI 0.700, 1.26, $p=0.686$)(25), the other IADT and continuous CADT for erectile dysfunction (RR 1.03; 95% CI 0.74, 1.43) and decreased libido (RR 1.01; 95% CI 0.95, 1.07) (15). No significant differences were found for erectile dysfunction or decreased libido between types of ADT. There is a paucity of data on sexual dysfunction, however, two RCTs examined the effect of short-term neoadjuvant ADT before radiotherapy and compared ADT recipients to those receiving radiation only, reported significant declines in sexual function from two months ADT administration(60, 61). Daly et al.(60) compared duration of ADT; 54% of men in the 4-month arm and 39% in the 8-month arm, who had sexual function at baseline, retained sexual function at one year. There were no statistically significant differences between arms and smaller decreases in sexual function were recorded after one year(60). This study found that 26% of men can expect to retain erectile function five years after receiving three or four months of ADT with age the only significant risk factor(60). Similar results were obtained in a second RCT comparing men receiving neoadjuvant ADT and radiotherapy and those receiving radiotherapy alone. There was a statistically significant difference between arms: number of men who always or almost always had erectile function at baseline in the ADT arm decreased by over 50% one year after ADT initiation(61).

8 Psychiatric disorders: Depression

Depression and anxiety are often unaddressed adverse effects among patients with PC and are associated with increased health service use, costs and mortality(62-64). Two systematic reviews examined the incidence of depression among men with PC receiving ADT(15, 20). One conducted a pooled analysis of 18 studies, both prospective and retrospective, involving a variety of forms of ADT from primary anti-androgen, radiotherapy or radical prostatectomy plus adjuvant ADT, and orchiectomy. Comparators included lesser exposed ADT group (e.g. no ADT, short term ADT or IADT). Relative risk of depression was 1.41 (95% CI 1.18-1.70, $p<0.001$) (20). The second systematic review analysed 15 RCTs of which three generated evidence of depression experienced by recipients of continuous and intermittent ADT and found no significant difference between IADT and CADT (RR 0.91; 95% CI 0.39, 2.13)(15).

9 General disorders

9a Fatigue

Two systematic reviews examined the incidence of fatigue for men receiving ADT for PC. One conducted a pooled analysis of all stages of PC and found no significant difference between IADT and CADT, but an incidence of fatigue that favoured IADT (HR 0.94; 95% CI 0.60, 1.48)(15). However, for men receiving new hormonal agent-based therapies for metastatic CRPC, enzalutamide or abiraterone acetate, fatigue is one of the most common adverse effects. A significant difference in incidence was discovered from pooled analyses of both all grade (RR 1.27; 95% CI 1.13, 1.43) and grade 3 or greater fatigue (RR 1.25; 95% CI 0.92, 1.71, $p=0.02$)(65).

9b Gait disturbance, physical function and falls

Clinically meaningful declines in physical functioning occur within 3-6 months after ADT initiation and stabilise or worsen over time(66-68). Alibhai et al.(66) report that for each 5-kg reduction in grip strength over 4 years, there was a 24% increased mortality risk, and with each 5% loss of relative grip strength, a 6% increased mortality risk. In a secondary analysis of this same population, the incidence of falls was higher for men receiving CADT, with a trend towards increased risk ($p=0.083$)(69). Graff et al.(70) conducted a sub-group analysis (≥ 75 years) of participants in the PREVAIL RCT, where there was a much higher incidence of falls, suggesting enzalutamide may further increase the risk of falls because all men in the trial were receiving ADT. In a Phase III, double-blinded RCT examining apalutamide versus placebo, Smith found a higher incidence of falls for participants receiving apalutamide(49) (Online Resource 2).

Methodological quality of included studies

Systematic reviews

Twenty-five systematic reviews (24 incorporating a meta-analysis) were assessed using the AMSTAR 2 tool (Online Resource 3). Confidence in overall results of the review rating varied, 10 were rated as low, 11 as moderate, and four as high. Results were impacted by lack of data or diversity of studies available. ADT is used broadly across the spectrum of PC, so patient characteristics differ as do the type and duration of ADT administration. In addition, studies involved different comparators or control groups,

making comparison across studies difficult. Heterogeneity between studies within reviews was often quite high. Risk of bias or quality assessments were not always conducted or just not reported in lower rated studies, despite their critical importance. Similarly, publication bias was overlooked in a number of reviews. Overall, systematic reviews brought together a comprehensive collection of the best available evidence on the adverse effects of ADT for PC and provide a sound evidence base.

Randomised Controlled Trials

Four RCTs were assessed for risk of bias using the ROB-2 tool generating ratings such as low, some concerns, or high risk of bias (Online Resource 4). Three of the four trials rated an overall low risk of bias and two of these were studies based on well-known trials (ICORG 97-01; PREVAIL); all four were published in high ranking journals by recognised authors/clinicians in the PC field, however, all four also had varying degrees of conflict of interest from author association with pharmaceutical companies.

Cohort studies

Ten cohort studies were assessed for quality using the Newcastle Ottawa Scale (NOS) for a possible rating of good, fair or poor (Online Resource 5). All achieved a rating of good and only three had weaknesses which were not considered sufficient to require a downgrading, given their other strengths. One study had missing outcome data that was not addressed and no measures to prevent confounding from previous falls or exercise(69); another had a 40% loss to follow up(66) and the third matched their experimental and control cohorts for age and no prior comorbidity only(42).

Discussion

This comprehensive systematic review of adverse effects (n=19) of ADT for PC confirms that many are commonly experienced by patients and survivors. A broad spectrum of ADT is represented, comprising GnRH agonists, GnRH antagonists, anti-androgens (steroidal and non-steroidal) and combinations of these drugs or neoadjuvant and adjuvant therapy with curative treatments like RP or RT. Intermittent ADT is also represented. Second generation non-steroidal anti-androgens, abiraterone acetate and enzalutamide, figured strongly in the systematic reviews. Statistically significant increased risks were evident in all the most common adverse effects from the CTCAE groupings (musculoskeletal, metabolic, cardiac, nervous system, vascular, hepatobiliary, reproductive system, psychiatric and general disorders). The dominant factor across all adverse effect incidence was type of ADT.

For musculoskeletal events duration of ADT was also a factor; for fractures, ADT dose, age, presence of osteoporosis, metastases and dementia impacted on incidence. ADT impacted combined CVD morbidity and the risk of specific CV diseases such as myocardial infarction and ischaemic heart disease. Risk was associated with type(7, 28), adverse event grade(22, 23, 29) and duration of ADT(71). Cardiac mortality was less common but increased risk was identified for all ADT, ADT monotherapy and GnRH agonists(28). Increased risk of stroke was associated with orchiectomy, CAB and GnRH agonist alone(17). There was also a significant association between ADT and hypertension, particularly for second generation therapies, abiraterone and enzalutamide. Other vascular disorders like thromboembolic events also showed a significant association with GnRH alone, CAB, anti-androgen alone, oestrogen and orchiectomy(10, 18). For vasomotor flushing, enzalutamide had a significant increased risk and anti-

androgens a significantly lower risk than other types of ADT (14, 15, 25, 29, 57). GnRH agonists and antagonists showed a strong association with hepatotoxicity(58), as did abiraterone acetate, two to three times higher than placebo for men with CRPC(22, 23).

Reproductive disorders were common with significantly increased risk of gynaecomastia and breast pain for anti-androgens over GnRH agonists(14, 57). Sexual function was significantly impacted by ADT with only 26% of men expected to retain some sexual function five years from initiation of ADT(60). There was no evidence to suggest a significant difference in relation to type of ADT(15, 25). The impact of ADT on the risk of depression was confirmed in the systematic review by Nead *et al.* which showed a 40% higher risk of depression for men receiving ADT which, like sexual function, was associated with exposure (20). Fatigue is a complex adverse effect associated with many cancer treatments but for men receiving enzalutamide and abiraterone for PC, there was a 27% greater risk of fatigue and a 50% greater risk for prechemotherapy men initiating ADT(65). Potentially related to fatigue and other adverse effects, declines in physical function and higher incidence of falls were also associated with ADT, significantly more-so with enzalutamide(70) and apalutamide(49).

Cognitive disorders were the exception amongst the adverse effect groupings with an inconclusive result from two systematic reviews(16, 26). Similarly, the systematic review of dementia suggested only that there may be an association between ADT and risk of dementia(19). Interestingly, McGinty *et al.* found a statistically significant increased risk associated with visuospatial cognitive skills, suggesting a possible link to increased incidence of falls and fractures for this population(16).

Such a broad range of adverse effects, some with high levels of incidence, poses problems, not only for the patient and their family who bear the consequences of increased morbidity or mortality and reduced quality of life, but also for society. There are significant cost implications of suffering these adverse effects in the form of their management, supportive care and increased health services utilisation, without considerations of productivity losses for those men in this population still actively employed or their carers. Management of adverse effects can take a number of forms from medications or counselling to exercise interventions; each involving increased resource utilisation as well as out of pocket costs for the patient.

In recent years, interest in adverse effects has increased, evidenced by the number of systematic reviews included in this review. There is growing awareness of the impact of many of these adverse effects on the part of clinicians, patients, economists and decision makers, from both a quality of life and a cost perspective. Bourke *et al.* raised the need for clearly defined adverse effects, in order that a better understanding of potential risks and subsequent treatment costs is developed to accurately inform the costs and effects associated with these drugs(72). Pearce *et al.* make a similar point, advising that economic evaluations should include all adverse effects regardless of severity(73). While the adverse effects associated with ADT are many, varied and complex, it is important that economic evaluations include consideration of them to ensure models are developed that accurately reflect the impact of adverse effects on drug cost-effectiveness, particularly given the current emphasis on personalised care. No single systematic review has previously provided such a comprehensive review of this topic. This review, conducted and reported following Cochrane guidelines, updates the current knowledge across all

common adverse effects of ADT for PC(30). We employed an *a priori* designed protocol and carried out an extensive literature search using multiple databases, Google Scholar and bibliographic hand search. Methodological quality of included studies was assessed using three Cochrane approved instruments and, with few exceptions, provided moderate to strong evidence of ADT adverse effects. This systematic review also includes new ADT medications like apalutamide, enzalutamide and abiraterone acetate, and through the weight of recent evidence, confirms effects previously considered contentious, such as cardiovascular toxicity, or rare, such as hepatotoxicity.

This review was limited by available data; while the full range of PC stages from localized to metastatic CRPC were represented, not all types of ADT or all stages of PC were captured for all adverse effects, particularly for newer therapies. Studies were characterised by considerable heterogeneity in study design, aims, outcomes, sample size, exclusion criteria, geographical location, number of sites involved and length of follow up. While all study participants were men with PC receiving ADT, there was considerable variation between and across studies in relation to age, PC stage, treatment, comorbidities, and demographics. Heterogeneity was not always addressed in meta-analysis. While a rigorous search of the literature was conducted, it is possible that not all studies reporting the adverse effects of ADT for PC were identified.

Conclusion

This review provides the first comprehensive incidence of the most common adverse effects of ADT for PC based on currently available evidence. These findings are significant for clinicians, researchers, health providers, health economists, PC patients, their carers and society. It is evident that more research is needed in adverse effects of ADT for prostate cancer; questions also remain in terms of potential recovery and management. It is hoped this review will assist in stimulating further questions and research around adverse effects, as well as the development of suitable interventions to decrease their risk. These findings also highlight the importance of supportive care for PC patients receiving ADT and their carers. Consideration of adverse effects and their management in economic evaluations of PC treatment is also important, particularly given their potential to add further costs to what is already costly treatment.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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