Cardiac and cognitive effects of androgen deprivation therapy: are they real?

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ABSTRACT

With androgen deprivation therapy being used ever earlier and longer in the course of prostate cancer, concerns have emerged about a variety of adverse effects, including cardiovascular disease and cognitive dysfunction. Conflicting data in both areas have led to controversy and confusion. Here, we review published data in an attempt to clarify those issues.

KEY WORDS

Prostatic neoplasms, androgen deprivation therapy, cardiac disease, cognition, adverse effects

1. INTRODUCTION

Androgen deprivation therapy (ADT) has been used to treat prostate cancer since 1941 [1]. With expanding use of the therapy, data suggest that 40%–50% of men diagnosed with prostate cancer in the current era will receive ADT at some point [2,3]. With increasing experience and use of ADT earlier (and for longer) in the disease course, concerns have emerged about a variety of adverse effects, including cardiovascular disease [4] and cognitive dysfunction [5]. However, conflicting data in both areas have led to controversy and confusion. Here, we review published data in an attempt to clarify those issues.

2. DISCUSSION

2.1 Effects of ADT on Cardiovascular Morbidity and Mortality

In theory, ADT increases the risk of cardiovascular events by inducing or aggravating some of the established risk factors for cardiovascular diseases, such as increased low-density lipoprotein (LDL), increased body fat, and reduced insulin sensitivity. A number of studies have demonstrated increased percentage body fat mass in patients initiating ADT [6–9], often within 3–6 months of use [10]. Insulin sensitivity, hyperglycemia, and a greater incidence of the development of diabetes mellitus have also been demonstrated [2,11–15], with some suggestion of greater risk with prolonged ADT use [16]. In addition, numerous studies have shown that ADT increases levels of serum triglycerides and LDL [8,17,18]. Collectively, these metabolic changes would lead to an increased risk of cardiovascular events in ADT users.

Several retrospective studies have shown a positive correlation between ADT and both morbidity and mortality from cardiovascular events. The strongest evidence comes from two population-based trials using the Surveillance, Epidemiology, and End Results (SEER) database [2,13]. The first paper, an observational study of a population-based cohort of 73,196 patients with localized prostate cancer, found that ADT was associated with a greater risk of coronary artery disease, myocardial infarction (MI), and sudden cardiac death. For the ADT group, as compared with a matched non-ADT control group, adjusted hazard ratios (AHRS) for MI, coronary artery disease, and sudden cardiac death were 1.11 [95% confidence interval (CI): 1.01 to 1.21; $p = 0.03$], 1.16 (95% CI: 1.10 to 1.21; $p < 0.001$), and 1.16 (95% CI: 1.05 to 1.27; $p = 0.004$) respectively [13]. A second, more recent study by the same authors, using current SEER data, found similar results [2]: among 37,443 men with nonmetastatic prostate cancer, 14,597 of whom used ADT (median of 2.6 years of follow-up), the risk of MI (AHR: 1.28; 95% CI: 1.08 to 1.52) and sudden cardiac death (AHR: 1.19; 95% CI: 1.10 to 1.28) were increased. A third study, by Saigal *et al.,* also using the SEER database, reported that compared with 18% of ADT nonusers, 24% of men undergoing ADT experience a cardiovascular event (not well-defined in the manuscript) within 1–4 years of starting therapy (AHR: 1.2; $p < 0.001$) [19]. Those investigators also found a positive correlation between duration of ADT use and risk of cardiovascular events.

In addition to evidence from the above three studies that used administrative data, one study used a prospectively maintained clinical database, CAPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor). Among 4892 patients undergoing either radical prostatectomy or 1 of 3 types of radiation, ADT

use was associated with an increased risk of death from cardiovascular disease. After a median follow up of 3.8 years, the AHR for ADT users compared with nonusers was 2.6 ($p = 0.002$) among radical prostatectomy patients, but only 1.2 among radiation therapy patients ($p = 0.40$). The total number of events was relatively small at 131 [20].

Supportive evidence also comes from several randomized controlled trials (RCTs). In a secondary analysis of pooled data from three RCTs of short-term adjuvant ADT in men undergoing radiation, D'Amico *et al.* found that 6 months of ADT was associated with a shorter time to fatal MI ($p = 0.017$), but that the risk seemed to be confined to men over the age of 65 [21]. Finally, one prospective RCT of radiation therapy with or without 6 months of ADT in 206 patients showed that ADT increases the risk of cardiac death, but only in patients with moderate-to-severe comorbidities [22]. Notably, few cardiovascular events were observed in these studies, which are summarized in Table I.

In contrast, several studies have demonstrated no relationship between ADT and cardiovascular events, also summarized in Table I. Three large phase III RCTs [Radiation Therapy Oncology Group (RTOG) 85-31, RTOG 86-10, and RTOG 92-02)] with sample sizes ranging from 456 to 1554 men and with follow-up of 8–10 years (Table II) all found no statistically significantly increased risk of cardiovascular mortality with ADT use [24,25,27]. Although each of the studies used ADT in a different fashion in conjunction with external-beam radiotherapy (adjuvant vs. salvage ADT in RTOG 85-31, ADT vs. no ADT in RTOG 86-10, and 4 months vs. 24 months of adjuvant ADT in RTOG 92-02), the results were remarkably similar across studies. However, nonfatal MIs were not recorded, and relatively few fatal MIs were observed in each trial.

Two additional RCTs led by European groups [European Organisation for Research and Treatment of Cancer (EORTC) 22961 and 30891] not only failed to show any increased risk of cardiovascular toxicity from ADT, but both studies suggested a trend toward fewer fatal cardiovascular events in ADT users [23,26]. In EORTC 22961, in which 1113 men with locally advanced prostate cancer received either 6 months or 36 months of ADT along with external-beam radiotherapy, 4% of men in the 6-month ADT arm experienced cardiovascular mortality as compared with 3% in the 36-month ADT arm. In EORTC 30891, 985 men who were not suitable to undergo radical therapy were randomized to immediate or deferred ADT. Cardiovascular mortality was 17.9% in the immediate ADT arm compared with 19.7% in the deferred ADT arm (Table I).

Lastly, a large retrospective cohort study recently conducted by our group used administrative data from Ontario, Canada. Among 19,079 matched pairs of ADT users and nonusers 66 years of age or older, after extensive adjustment for comorbidities, medication use, socioeconomic factors, and prior treatment, the AHRs for MI and sudden cardiac death were 0.91 (95% CI: 0.84 to 1.00) and 0.96 (95% CI: 0.83 to 1.10) respectively [12].

2.1.1 Reconciling Differences in Study Findings

How does one reconcile these disparate findings?

Although the highest-quality evidence should be obtained from RCTs, the nine RCTs to date provide conflicting results. Although the significant differences in study populations and the varying follow-ups across trials might account for the different results, another key factor is the relatively small number of events observed in many studies. Additionally, most studies recorded only cardiovascular mortality, which is obviously clinically important but subject to attribution bias and considerably less common than nonfatal MI. Most of the RCTs did not report results stratified by age or comorbidity, but at least one study has suggested that ADT–related cardiovascular toxicity is observed predominantly in older adults [40]. Even in the large administrative databases that have sample sizes sufficient and follow-up adequate enough to capture nonfatal MIs (as can be seen in Table I), the inconsistent results can only partly be explained by differences in study methodology or definitions of endpoints. Clearly, further studies—including additional analyses of nonfatal cardiovascular endpoints from RCTs and prospective cohort studies—are needed. Meanwhile, what are clinicians to do?

Clearly, ADT increases the risk of diabetes and leads to unfavourable alterations in lipid profile. Thus, it seems reasonable to obtain a fasting blood glucose and lipid profile before initiating ADT and to ensure that patients with metabolic abnormalities are treated based on established guidelines. Screening for diabetes is particularly important, because a significant proportion of diabetics are asymptomatic and unaware of their diagnoses [41]. It is also reasonable to repeat blood glucose and lipid testing every 1–2 years while a man remain on ADT, or sooner if he experiences a cardiovascular event.

It is equally important to consider whether the cumulative risks of ADT (on outcomes ranging from quality of life to fractures) are outweighed by benefits with respect to cancer control and cancer-specific survival. For men with non-high-risk localized prostate cancer or biochemical relapse after radical therapy in particular, the benefits of ADT are far from established [42,43], but the risks are independent of ADT indication. Based on a recent scientific advisory from the American Heart Association, the American Cancer Society, and the American Urological Association, there is no indication for additional cardiovascular evaluation (for example, stress-testing or echocardiography) in men initiating ADT beyond the screening already mentioned, a careful clinical assessment, and a consideration of both the risks and the benefits of ADT [4].

TABLE I Studies of the cardiovascular (CV) effects of androgen deprivation therapy (ADT) in men with prostate cancer (PCa)

Reference	*Study type*	*Comparison*	*Population*	*Cardiovascular events*	*Duration of follow-up (years)*	*Main results*	*Evidence for worse CV outcomes with ADT?*	*Comment*
Keating *et al.*, 2006 [13]	Retrospective population-based cohort	ADT vs. no ADT	73,196 patients, >66 yrs of age, with LPCa diagnosed between 1992 and 1999 (SEER database)	MI: 3917 SCD: 3301 CAD: 15,116	4.55 (median)	Adjusted HR[a] (95% CI): MI: 1.11 (1.01 to 1.21) $p = 0.03$ SCD: 1.16 (1.05 to 1.27) $p = 0.004$ CAD: 1.16 (1.10 to 1.21) $p<0.001$	Yes	
Studer *et al.*, 2006 [23] (EORTC 30891)	RCT	Immediate ADT vs. deferred ADT	985 patients not suitable for curative therapy	185 CV deaths (541 deaths total)	7.8 (median)	CV mortality (%): immediate ADT: 17.9; deferred ADT: 19.7; p=NR	No	Relatively few CV deaths; nonfatal MI not captured
D'Amico *et al.*, 2007 [21]	Secondary pooled analysis of 3 RCTs	RT plus varying durations of ADT: 0 vs. 3 vs. 6 mos., 3 vs. 8 mos., 0 vs. 6 mos.	1372 men enrolled between 1995 and 2001	RCT 1: 802 men, 29 fatal MIs; RCT 2: 364 men, 6 fatal MIs; RCT 3: 206 men, 16 fatal MIs	RCT 1: 5.9 (median) RCT 2: 6.7 (median) RCT 3: 4.8	Time to fatal MI shorter in ADT users, p=NR	Yes	Relatively few MI events; total MIs not different between ADT users and non-users; effect seen primarily in men aged 65 and older
Saigal *et al.*, 2007 [19]	Population-based retrospective cohort	ADT patients and newly diagnosed PCa controls	22,186 patients newly diagnosed between 1992 and 1996 (SEER database)	CV events (%) 12–60 mos. after treatment start: ADT group: 24; controls: 18	5	HR (95% CI) for CV event (ADT vs. non-ADT): 1.2 (NR), $p<0.001$	Yes	ADT users and non-users unmatched; CV events not clearly defined
Tsai *et al.*, 2007 [20]	Retrospective cohort	ADT users or non-users undergoing RT (including EBRT, brachytherapy, cryotherapy) or RP	4892 patients (1015 ADT users; CAPSURE database)	131 total CV deaths (61 in RP group, 70 in RT group)	3.8 (median)	HR (95% CI) ADT vs. no ADT: RP group: 2.6 (1.4 to 4.7) $p = 0.002$; RT group: 1.2 (0.8 to 1.9) $p = 0.40$	Yes	Relatively few CV deaths; subgroup analyses by age

TABLE I *(Continued)*

Reference	*Study type*	*Comparison*	*Population*	*Cardiovascular events*	*Duration of follow-up (years)*	*Main results*	*Evidence for worse CV outcomes with ADT?*	*Comment*
D'Amico *et al.*, 2008 [22]	RCT	EBRT with 6 mos. of ADT vs. no ADT	206 Patients with CLPCa	RT + ADT group: 30 total deaths, 13 cardiac deaths; RT-alone group: 44 total deaths, 13 cardiac deaths	7.6 (median)	No difference overall (p=NR)	No	Most cardiac deaths in ADT group occurred in men with moderate to severe comorbidity
Efstathiou *et al.*, 2008 [24] (RTOG 92-02)	RCT	EBRT plus 4 mos. of ADT vs. 24 mos. of ADT	1554 Men with locally advanced PCa	85 CV deaths	8.1 (median)	HR (95% CI) no ADT vs. ADT: 1.19 (0.78 to 1.80), $p = 0.43$	No	Relatively few CV deaths; nonfatal MI not captured; all patients received some ADT
Roach *et al.*, 2008 [25] (RTOG 86-10)	RCT	EBRT plus ADT vs. EBRT alone	456 Men with locally advanced PCa	348 Total deaths, 57 CV deaths	10	Fatal MI at 10 yrs (%): ADT: 12.5; no ADT: 9.1; $p = 0.32$	No	Relatively few CV deaths; nonfatal MI not captured
Alibhai *et al.*, 2009 [12]	Matched retrospective population-based cohort	ADT use vs. no ADT use	19,079 Matched pairs of PCa patients (linked administration data from ICES)	ADT users vs. non-users (n): MIs: 949 vs. 1085; SCDs: 399 vs. 436	6.47 (mean)	Adjusted HR[a] (95% CI) ADT users to non-users: MI: 0.91 (0.84 to 1.00), $p = 0.059$; SCD: 0.96 (0.83 to 1.10), $p = 0.53$	No	Extensive adjustment for comorbidity and other variables; missing stage and grade
Bolla *et al.*, 2009 [26] (EORTC 22961)	RCT	EBRT plus 6 mos. of ADT vs. 36 mos. of ADT	1113 Men with locally advanced PCa	6-month group: 132 total deaths, 31 cardiac deaths; 36-month group: 98 total deaths, 25 cardiac deaths	6.4 (median)	Cardiac deaths (%) 6-month group vs. 36-month group: 4 vs. 3 p=NR	No	Relatively few CV deaths; nonfatal MI not captured
Efstathiou *et al.*, 2009 [27] (RTOG 85–31)	RCT	EBRT plus adjuvant ADT (median: 4.2 yrs) vs. salvage ADT	945 Men with locally advanced or node-positive PCa between 1987 and 1992	574 total deaths, 117 CV deaths	8.1 (median)	Adjusted HR[a] (95% CI) for CV mortality at 9 years salvage vs. adjuvant ADT: 0.73 (0.47 to 1.15), $p = 0.16$	No	Relatively few CV deaths; nonfatal MI not captured; 64% in control arm received salvage ADT at median 3.0 years

TABLE I *(Continued)*

Reference	*Study type*	*Comparison*	*Population*	*Cardiovascular events*	*Duration of follow-up (years)*	*Main results*	*Evidence for worse CV outcomes with ADT?*	*Comment*
Keating *et al.*, 2010 [2]	Retrospective population-based cohort	ADT users vs. non-users	37,443 Men with non-metastatic PCa (14,597 ADT users; SEER database)	MI: 847 total SCD: 1337 total CAD: 4775 total	2.6 (median)	*n*/1000 person–years and adjusted HR[a] (95% CI): MI: 12.8 vs. 7.3, 1.28 (1.08 to 1.52), *p*=NR SCD: 21.6 vs. 11.5, 1.35 (1.18 to 1.54), *p*=NR incident CAD: 144 vs. 81.4, 1.19 (1.10 to 1.28), *p*=NR	Yes	Separate results for orchiectomy, anti-androgen monotherapy, and combined androgen blockade

[a] From time-to-event analyses.
(CL)PCa = (clinically localized) prostate cancer; SEER = Surveillance, Epidemiology, and End Results; MI = myocardial infarction; SCD = sudden cardiac death; CAD = coronary artery disease; HR = hazard ratio; CI: = confidence interval; RCT = randomized controlled trial; NR = not reported; RT = radiotherapy; EBRT = external-beam radiation therapy; RP = radical prostatectomy; ICES = Institute for Clinical Evaluative Sciences.

2.2 Effects of ADT on Cognitive Function

A significant body of literature involving both animal and human studies of hypogonadism treated with testosterone replacement therapy points to cognitive effects of testosterone [44–48]. Neuroanatomic studies have demonstrated both testosterone and estrogen receptors in varying densities in various parts of the brain [49]. Thus, there is good reason to observe cognitive effects with ADT, which leads to profound reductions in testosterone and a shift in the testosterone:estrogen ratio. In particular, based on studies in both animals and older men, alterations in testosterone may preferentially affect working memory and visuospatial function more than they affect other cognitive domains [5,49].

A dozen studies have been published examining the effects of ADT on a variety of cognitive domains in men with prostate cancer. Most of these studies were summarized in a recent review, in which Nelson *et al.* concluded that ADT leads to subtle but significant cognitive declines in men with prostate cancer, particularly in the areas of visuospatial ability and executive functioning [5]. However, those conclusions deserve further scrutiny, given the significant methodologic limitations of published studies and the contrasting findings across studies.

Table II summarizes the published studies, including one that was published after the review by Nelson *et al.* [39]. In general, studies have included men with nonmetastatic prostate cancer receiving either continuous or intermittent ADT. Most studies have included a control group of healthy age- and education-matched men. Studies have generally been small, with sample sizes ranging from 18 to 62 participants. They also have generally been longitudinal and observational in nature, with 2–3 assessments over a 6- to 12-month period. Cognitive assessments have ranged from a traditional battery of pen-and-paper tasks to customized cognitive testing software. Few studies have adjusted for multiple statistical comparisons, a potentially significant issue given the large number of cognitive tests (typically 6–15 different tests); and even fewer studies have adjusted for practice effects (subjects become more familiar with tests over time, leading to better performance in subsequent test sessions) [50,51].

Considering the findings as summarized in Table II, most studies have reported few statistically significant differences between ADT users and controls, which is a bit surprising given the number of cognitive and statistical tests involved. Moreover, although several studies have reported worse performance in verbal memory and visuospatial abilities [28,29,34,36,37,39], others have reported no such differences [29,30,33,38]. Several studies reported worse processing speed [28,36], but those results were not confirmed in other studies [30,33]. At least one study reported worse verbal fluency [36], but at least one study reported improved verbal fluency with ADT use [30].

Thus, based on our review of published studies, we do not believe that valid conclusions can yet be drawn about cognitive effects of ADT. We recently presented results on cognitive outcomes from a matched prospective cohort study of 84 men with nonmetastatic prostate cancer on ADT and 2 control groups (ADT nonusers with prostate cancer and healthy controls), all matched on age and education and assessed at 3 time points over 12 months. Using a variety of analytic methods, we found no consistent effect of ADT on 14 different cognitive tests across 6 cognitive domains [52].

No studies have examined whether ADT leads to impaired function in daily tasks such as financial management, medication management, or shopping. Similarly, no reported study has examined whether ADT affects self-reported cognitive function or leads to dementia. Arguably, these endpoints are more clinically relevant than are subtle cognitive impairments that might be detectable only by detailed neuropsychological assessment. Additionally, cognitive effects of ADT, if present, may require a follow-up longer than 12 months. Our study is continuing to follow our 3 cohorts of men for 2 more years; it may be able to shed further light in this regard.

3. SUMMARY

Although ADT has a variety of unfavourable metabolic side effects that increase the risk of cardiovascular toxicity, published studies using a variety of designs have demonstrated inconsistent effects of ADT on cardiovascular endpoints ranging from MI to cardiovascular mortality. Far fewer, and methodologically weaker, studies have examined effects of ADT on cognitive function, and the results are even less conclusive. Further studies are clearly needed.

In the interim, clinicians should screen for, and manage, cardiovascular risk factors such as diabetes and hyperlipidemia according to the usual guidelines for men without prostate cancer, and should carefully consider the risks and benefits of ADT before initiating it. With respect to cognition, the evidence is insufficient to determine whether ADT has any effects. Patients with complaints of memory loss or cognitive dysfunction should therefore be referred back to their primary care physician or to a relevant specialist (neurologist, geriatrician) for further evaluation—a recommendation that is no different than it would be for a general population of older adults with such complaints.

4. ACKNOWLEDGMENTS

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TABLE II Studies of the cognitive effects of androgen ablation therapy in men with prostate cancer (PCa)

Reference	*Participants*	*Design*	*Cognitive tests*	*Main results*	*Comments*
Green *et al.*, 2002 [28]	77 Men with metastatic PCa (62 ADT, 15 controls)	Randomized trial of 3 types of ADT vs. observation	Assessments: baseline, 6 mos.; WMS-R, AVLT, Rey–Osterrieth Complex Figure Test, TMT A and B, COWAT	No significant differences in most tests; ↓ performance on AVLT (verbal memory) with goserelin; ↑ verbal memory with cyproterone acetate; ↓ processing time with leuprolide	No correction for multiple significance testing; no healthy controls; no correction for practice effects
Cherrier *et al.*, 2003 [29]	19 Men with biochemical relapse (intermittent ADT), 15 healthy controls	Longitudinal case–control study	Assessments: baseline, 9 mos., 12 mos. (3 mos. after ADT stopped); Puget Sound Route Learning Test, WAIS III Block Design Task, Mental Rotation Task, WMS-R Story Recall Test, COWAT, Stroop test	No significant differences in verbal memory and spatial memory; ↓ spatial rotation with ADT; improved verbal memory and mental rotation ability 3 mos. after stopping ADT	Adjusted for multiple significance testing; no correction for practice effects
Salminen *et al.*, 2003 [30], 2004 [31], 2005 [32]	25 Men with nonmetastatic PCa (ADT), 52 healthy controls	Longitudinal case–control study	Assessments: baseline, 6 mos., 12 mos.; CogniSpeed software[a]	No significant differences in most tests; ↓ sustained attention with ADT at 6 and 12 mos.; ↑ visual memory and delayed recall at 6 mos.; ↑ verbal fluency at 12 mos.	Controls tested only at baseline; inconsistent results and slightly different sample sizes in different publications; no adjustment for multiple significance testing; no correction for practice effects
Almeida *et al.*, 2004 [33]	37 Men (intermittent ADT)	Cohort study	Assessments: 8 during 1 year (3 after ADT stopped); CAMCOG, WAIS III Block Design Task, WMS III Word List, Verbal Paired Association, Visual Reproduction Tasks	No significant differences in all tests from baseline to 36 weeks on ADT; ↑ verbal memory (2 tests) 3 mos. after ADT stopped	No controls; no adjustment for multiple significance testing; no correction for practice effects
Green *et al.*, 2004 [34]	77 Men with metastatic PCa (62 ADT, 15 controls)	Randomized trial of 3 types of ADT vs. observation	Assessments: baseline, 6 mos., 12 mos.; WMS-R, AVLT, Rey–Osterrieth Complex Figure Test, TMT A and B, COWAT	No significant differences in most tests from 6 to 12 mo; ↓ verbal memory with ADT	Extension of 2002 study; no correction for multiple significance testing; no healthy controls; no correction for practice effects

TABLE II *(Continued)*

Reference	*Participants*	*Design*	*Cognitive tests*	*Main results*	*Comments*
Bussiere, 2005 [35]	14 Men (ADT), 16 controls	Cross-sectional case–control study	Assessments: baseline, 2 min., 12 min.; 3-phase memory task	Similar performance at immediate retention; worse performance among ADT users at 2 min. and borderline worse at 12 min.	4 ADT users had prior chemotherapy; no longitudinal follow-up; mean duration of ADT use: 5.5 years
Jenkins, 2005 [36]	32 Men with nonmetastatic PCA (ADT), 18 healthy controls	Longitudinal case–control study	Assessments: baseline, 3 mos., 6 mos.; NART, AVLT, Rey–Osterrieth Complex Figure Test, WMS-III Digit Span, KACA, COWAT	No between-group differences on any task; ADT users had ↓ verbal fluency, verbal learning, and processing speed at 3 and 9 mos.	Corrected for practice effect
Beer *et al.*, 2006 [37]	18 Men (ADT), 18 starting estradiol, 17 healthy controls	Longitudinal case–control study	Assessments: baseline, 4 weeks; Paragraph Recall, TMT A and B, Story Recall Test	↓ Long-term memory with estradiol; ↓ immediate and delayed verbal memory with ADT	Short duration of follow-up; corrected for multiple significance testing
Joly *et al.*, 2006 [38]	57 Men with nonmetastatic PCA (ADT), 51 healthy controls	Cross-sectional study	Single assessment; Folstein Mini-Mental Status Exam, HSCS	No differences	No longitudinal follow-up; mean duration of ADT use: 1.8 years
Cherrier *et al.*, 2009 [39]	20 Men with biochemical relapse (intermittent ADT), 19 healthy controls	Longitudinal case–control study	Assessments: baseline, 3 mos., 9 mos., 12 mos. (3 mos. after ADT stopped); Puget Sound Route Learning Test, WAIS-R Block Design, Mental Rotation Test, Proactive Interference Test, WMS-R Story Recall, COWAT, Stroop test, Subject Ordered Pointing Task	No significant differences in most tests; ↓ visual working memory and spatial ability at 3 mos., but not 9 mos. in ADT users compared with controls	Corrected for practice effect and multiple significance testing; most changes returned to baseline by 9–12 mos. in ADT users

[a] Activity Stones, Ulvila, Finland.

ADT = androgen deprivation therapy; WMS-R = Wechsler Memory Scale–Revised; AVLT = Auditory Verbal Learning Test, TMT = Trail Making Test; COWAT = Controlled Word Association Test; WAIS III = Wechsler Adult Intelligence Scale III; CAMCOG = Cambridge Examination for Mental Disorders; WMS III = Wechsler Memory Scale III; NART = National Adult Reading Scale; KACA = Kendrick Assessment of Cognitive Ageing; HSCS = High Sensitivity Cognitive Screen.

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