Androgen deprivation therapy complications

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Abstract

Androgen deprivation therapy (ADT) is increasingly used to treat advanced prostate cancer and is also utilised as adjuvant or neo-adjuvant treatment for high-risk disease. The resulting suppression of endogenous testosterone production has deleterious effects on quality of life, including hot flushes, reduced mood and cognition and diminished sexual function. Cross-sectional and longitudinal studies show that ADT has adverse bone and cardiometabolic effects. The rate of bone loss is accelerated, increasing the risk of osteoporosis and subsequent fracture. Fat mass is increased and lean mass reduced, and adverse effects on lipid levels and insulin resistance are observed, the latter increasing the risk of developing type 2 diabetes. ADT also appears to increase the risk of incident cardiovascular events, although whether it increases cardiovascular mortality is not certain from the observational evidence published to date. Until high-quality evidence is available to guide management, it is reasonable to consider men undergoing ADT to be at a higher risk of psychosexual dysfunction, osteoporotic fracture, diabetes and cardiovascular disease, especially when treated for extended periods of time and therefore subjected to profound and prolonged hypoandrogenism. Health professionals caring for men undergoing treatment for prostate cancer should be aware of the potential risks of ADT and ensure appropriate monitoring and clinical management.

Key Words

prostate cancer
androgen deprivation therapy
quality of life
bone
osteoporosis
fracture
cardiovascular disease
diabetes

Introduction

Prostate cancer is the most commonly diagnosed cancer in men in both the USA, with an age-adjusted incidence rate of 152/100,000 men per year (http://www.cancer.gov/cancertopics/types/commoncancers; accessed 15th June 2013) and a lifetime risk of one in seven (http://seer.cancer.gov/statfacts/html/prost.html; accessed 12th October 2013), and in the UK, with an age-adjusted incidence rate of 106/100,000 men per year and a lifetime risk of one in eight (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/incidence/; accessed 12th October 2013).

With the median age at diagnosis decreasing, now 66 years in the USA, and survival rates improving (current death rate 23.0/100,000 men per year), an increasing
number of men are living for extended periods with prostate cancer. Hence, the potential long-term adverse effects of prostate cancer treatments are an important consideration in the overall management of these men. In a study of 208,601 men diagnosed with prostate cancer between 1988 and 2002, the 5-year mortality from cardiovascular disease (CVD) was similar to that from prostate cancer (Ketchandji et al. 2009). Men with early-stage disease (representing 75% of all men diagnosed with prostate cancer) were more likely to die from CVD than prostate cancer, with diabetes and congestive heart failure being important predictors of mortality in these men.

The role of androgen deprivation therapy (ADT) in the treatment of prostate cancer has been extended in recent years from being used predominantly in symptomatic metastatic disease to asymptomatic metastatic disease, primary therapy in localised disease when men are considered unfit for surgery or radiotherapy, adjunct treatment in high-risk disease treated with radiotherapy and salvage therapy following a biochemical relapse after surgery or radiotherapy for presumed localised disease (Roach et al. 2008, Studer et al. 2008, Abrahamsson 2010, Engel et al. 2010). We have estimated that, in Australia, 6500 men used ADT in 1999/2000, with a steady increase to about 21,800 men in 2009/2010 (over 300% increase; Medicare Australia, Pharmaceutical Benefits Schedule item statistics, retrieved July 2010: www.medicareaustralia.gov.au/statistics/pbs_item.shtml; Allan et al. 2012); this trend reflects those seen in the USA and UK. Androgen deprivation can be achieved surgically by orchietomy (castration) or medically with a gonadotropin-releasing hormone (GNRH) agonist or a GNRH antagonist. Anti-androgens can be combined with GNRH agonists to produce combined androgen blockade.

The profound testosterone deficiency resulting from ADT is associated with a range of potential adverse short- and long-term consequences affecting physical and psychological health (Table 1). In particular, the growing recognition of the adverse cardio-metabolic profile associated with ADT led the US Food and Drug Administration to release a Drug Safety Communication in October 2010 regarding possible increased risks of diabetes and certain CVDs associated with the use of GNRH agonists (US Food and Drug Administration (2010)). FDA Drug Safety Communication: update to ongoing safety review of GNRH agonists, US FDA, www.fda.gov/Drugs/DrugSafety/ucm229986.htm; accessed June 2011). Similarly, an expert advisory group representing the American Heart Association, the American Cancer Society and the American Urological Society has published a science advisory statement recommending the assessment of cardiovascular risk in men receiving ADT (Levine et al. 2010).

These trends in prostate cancer diagnosis and survival, and the multi-system impact of ADT, underscore the need for appropriate surveillance strategies and treatment paradigms. This review addresses the psychosexual, bone, metabolic and cardiovascular effects of ADT in men being treated for prostate cancer and suggests an approach to monitor and prevent/treat these adverse effects.

### Quality of life

Given the growing number of men being diagnosed with prostate cancer, who are living longer with or without treatment, it is important for the treating doctor to consider the overall impact of treatment on quality of life. There are validated and widely used clinical research questionnaires such as the EORTC QLQ-C30 or more specifically for prostate cancer the EORTC QLQ-PR25 (van Andel et al. 2008) that assess symptoms and problems specifically related to the disease process. They generally include questions regarding mobility, eating, urination and bowel movements, depression, anxiety, pain, finances and sexual function. Whilst not always useful in the consulting room, the breakdown of these domains gives the treating doctor a framework in which to consider the patient’s overall health status.

Interestingly, a study of urologists caring for men with localised prostate cancer demonstrated a poor correlation between physician and patient assessment of quality of life that did not alter either for the worse or better over time (Sonn et al. 2013). This highlights the need for a more standardised approach, possibly in the form of pre-formatted questionnaires that patients can complete before consultation.

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Mood and cognitive function

In the retrospective observational study of Surveillance, Epidemiology, and End Results (SEER), data based on 50,613 elderly men receiving ADT and surviving at least 5 years after diagnosis were compared with that of men without prostate cancer (Shahinian et al. 2006). The incidence of at least one depressive, cognitive or constitutional diagnosis was higher among men with prostate cancer than in men without prostate cancer (31.3 vs 23.7%, respectively, P<0.001). After adjustment for age, co-morbidity and tumour characteristics; however, the risks associated with ADT were substantially reduced or abolished.

In a study of ADT on cognitive function (Alibhai et al. 2010a), after 12 months of ADT, there was a reduction in scores pertaining to immediate span of attention, working memory and visual–spatial function when compared with a control group. A review of nine studies (but with the largest cohort including only 57 men receiving ADT and 51 controls (Joly et al. 2006)) found that 47–69% of men on ADT experienced a decline in at least one cognitive domain, most commonly in visual–spatial abilities and executive functioning; however, the individual study findings were inconsistent (Nelson et al. 2008). Furthermore, it is possible that the additional side effects of ADT, including hot flushes and fatigue, may indirectly influence cognitive function. A recent review of nine clinical studies has also suggested an effect of ADT on spatial memory, but the authors importantly note that only one study was randomised and it did not assess spatial memory (Jamadar et al. 2012). Assessment of cognitive and mood parameters in 20 ADT-naïve men at baseline and after 3 and 9 months of treatment, with reassessment after a further 3 months of no treatment, showed a significant decline in spatial reasoning, spatial abilities and working memory during treatment, most evident after 3 months. Significant changes in self-rated mood including increased depression, tension, anxiety, fatigue and irritability occurred during treatment. Many but not all of these changes returned to baseline after cessation of ADT (Cherrier et al. 2009).

Hot flushes

Hot flushes affect over 50% of men receiving ADT (Charig & Rundle 1989, Schow et al. 1998, Sarosdy et al. 1999). They are a result of the abrupt withdrawal of sex hormones from the circulation, which lowers the temperature set-point in the pre-optic area of the anterior hypothalamus thus causing the peripheral thermoregulatory mechanisms to be activated inappropriately. Noted triggers include increased ambient temperature, stress, anxiety, certain foods and alcohol.

Described as an uncomfortable sensation of heat or sweating that can even be associated with extreme distress, light-headiness, palpitations and marked sleep disturbances; hot flushes are a major contributor to the discontinuation of ADT.Whilst flushes may wane over time this is not always the case with some men continuing to experience symptoms over a number of years (Karling et al. 1994). It is important that the treating practitioner recognises the frequency of this adverse effect and specifically asks all patients regarding this symptom. Usually a simple explanation will do much to alleviate anxiety and is all that is required along with simple lifestyle modifications such as the avoidance of trigger factors, maintenance of a healthy body weight, regular exercise and the use of appropriate clothing, particularly at night. However, sometimes other strategies need to be employed, such as the use of non-hormonal therapies including selective serotonin reuptake inhibitors (Quella et al. 1999), clonidine (Loprinzi et al. 1994), or gabapentin (Loprinzi et al. 2009) or hormonal therapies such as cyproterone acetate, medroxyprogesterone acetate or diethylstilbesterol (Irani et al. 2010). Acupuncture and relaxation techniques (Beer et al. 2010, Ashamalla et al. 2011) may also be considered. All these methods are variably effective with their own set of side effects making a short-term trial approach, usually of up to 4 weeks duration for each agent alone or in combination, necessary (Quella et al. 1999, Loprinzi et al. 2009).

Sexual function

Sexual dysfunction is near universal in men receiving ADT for prostate cancer (Potosky et al. 2002, Traish & Guay 2006). The withdrawal of androgens results in a disruption to both libido and erectile function. It is a problem that should be viewed as a couples issue in the context of the patient’s overall physical and mental health. Sexual counselling may be indicated.

The withdrawal of androgens impairs erectile function through i) a decreased tissue response to vasodilators, such as nitric oxide, resulting in reduced blood ‘inflow’ and ii) decreased tissue compliance causing increased ‘outflow’ and thus the inability to achieve an adequate erection (Aversa et al. 2000). There is also the impact of radiotherapy and surgery over which ADT may be superimposed. It is important for the treating doctor to
appreciate that sexual dysfunction is a significant morbidity of prostate cancer treatment that the patient may be hesitant to discuss. Given that there are effective treatment options, it is important to allow the patient to raise this significant quality of life issue. The first step in treatment is to explain to the patient that loss of sexual function is a common side effect resulting from ADT. For those wishing to pursue options, the PDE-5 inhibitors are the medication of first choice. However, it must be remembered that the efficacy of these drugs is greatly reduced in the face of decreased androgens. Men with ischaemic heart disease should be counselled about the risks of treatment with PDE-5 inhibitors (Kostis et al. 2005). Their use is contraindicated in men receiving nitrates. A trial should include at least four doses (Wespes et al. 2006) ideally given on an empty stomach. Second-line therapies include intracorporeal injections, vacuum devices and penile prosthesis.

Additional side effects

Many men develop a mild, normochromic anaemia. Fatigue is also common and the anaemia may further exacerbate this. Gynaecomastia is frequently seen, being most common with antiandrogen monotherapy. This in turn may affect body image and further negatively impact on quality of life. Gynaecomastia is often associated with breast tenderness.

Bone

ADT accelerates bone loss in men, with five- to tenfold increases in the rate of loss reported at all skeletal sites (Greenspan et al. 2005). This in turn increases the risk of fracture (Diamond et al. 2004, Shahinian et al. 2005). In the SEER retrospective observational study of 50 613 men, fracture rate in those surviving 5 years after diagnosis was 19.4% with ADT use compared with 12.6% in men not receiving ADT ($P<0.001$; Shahinian et al. 2005). Fracture risk increased according to duration of ADT. The relative risk of fracture in men with low grade, non-metastatic disease who received nine or more doses of GNRH agonist therapy within 12 months of diagnosis was 1.37. The 30% of men in the SEER cohort who received ADT were older with more co-morbidities and a higher grade and stage of disease. This finding of increased fracture risk is supported by data from Medicare claims with a relative risk of 1.21 for fracture risk with ADT (Smith et al. 2006a).

The rate of bone loss appears to be maximal in the first year of treatment, with reductions in bone mineral density (BMD) of 4% at the spine and 2.5% at the total hip (Greenspan et al. 2005). Bone loss continues at both sites to a lesser degree thereafter with no recovery when ADT is ceased. A decrease in BMD of 10–15% doubles the risk of fracture. Importantly, up to one in three men diagnosed with prostate cancer has pre-existing osteopaenia or osteoporosis (Hussain et al. 2003). ADT does not have a significant effect on the levels of calcium, PTH or vitamin D (Shahinian et al. 2005).

A number of randomised controlled studies have demonstrated that antiresorptive therapy can prevent bone loss and reduce fracture risk. 1.v. pamidronate (Diamond et al. 2001, Smith et al. 2001a) and zoledronic acid (Smith et al. 2003, Michaelson et al. 2007) have been shown to increase bone mass at the hip (total hip/femoral neck) and spine when compared with placebo. A single dose of zoledronic acid led to differences in BMD between the treated and placebo groups, 7.1% at the spine and 2.6% at the total hip after 12 months (Michaelson et al. 2007). Oral bisphosphonates are less well studied, but aledronate prevented bone loss over 12 months (Greenspan et al. 2007, 2008) and beyond. A meta-analysis of 15 bisphosphonate studies including 2634 men receiving ADT documented a reduction in fracture risk (RR, 0.80; $P=0.005$) and osteoporosis (RR, 0.39; $P<0.00001$) when compared with placebo. Zoledronic acid was the most effective agent with a number needed to treat (NNT) of 14.9 and 2.68 for prevention of fracture and osteoporosis respectively (Serpa Neto et al. 2012).

Denosumab (a MAB to RANK ligand which inhibits osteoclast function) subcutaneously administered at a dose of 60 mg every 6 months for a total of 36 months increased BMD at the lumbar spine and femoral neck by 6.7 and 3.9%, respectively, at 24 months (primary end-point for study) when compared with placebo. The incidence of new vertebral fractures was reduced by 62% (denosumab 1.5% and placebo 3.9%; $P=0.0006$) after 36 months (Smith et al. 2009).

The Selective Oestrogen Receptor Modulators (SERMS) raloxifene (Smith et al. 2004) and toremifene (Smith et al. 2013) also prevent bone loss in men receiving ADT, the latter being shown to reduce the incidence of new vertebral fractures after 2 years (relative risk reduction by 50% when compared with placebo).

Addressing bone risk in men receiving ADT

Evidence-based guidelines for the management of bone health in men receiving ADT are lacking; however, a number of consensus guidelines and expert
recommendations for optimising bone health have been published (Holmes-Walker et al. 2006, Greenspan 2008, Grossmann et al. 2011, Lattouf et al. 2011, Lee et al. 2011, Watts et al. 2012, Ahmadi & Daneshmand 2013). These include recommendations for the frequency of monitoring bone density and for lifestyle and pharmacological interventions to optimise bone health and reduce fracture risk. The US Endocrine Society recommends pharmacological treatment for osteoporosis in men with prostate cancer receiving ADT who have a high risk of fracture (Watts et al. 2012). High risk of fracture is defined according to clinical fracture status, dual-energy X-ray absorptiometry (DEXA) evaluation and WHO Fracture Risk Assessment Tool (FRAX)-based algorithms (Watts et al. 2012). One limitation of this recommendation, however, is that algorithms to predict fracture risk developed for men have not been validated in the context of ADT. A small cross-sectional study using the FRAX tool suggests that this may have limited predictive usefulness in men receiving ADT (Neubecker et al. 2011), but there are no prospective data to support this finding. Seventeen of 22 men with a vertebral fracture in this study were asymptomatic with the diagnosis made radiologically.

Men with prostate cancer treated with ADT should have DEXA assessment of BMD at baseline (Grossmann et al. 2011, Lee et al. 2011, Watts et al. 2012), with repeat DEXA studies performed at intervals according to baseline BMD and duration of ADT. Lifestyle factors should be optimised by smoking cessation and limitation of alcohol consumption. Regular exercise is recommended and ongoing trials of resistance, aerobic and impact-loading exercises should better define the role of exercise in the maintenance of skeletal health (Newton et al. 2012). There is no consensus regarding calcium and vitamin D supplementation.

The National Comprehensive Cancer Network (NCCN) Guidelines, version 4.2013 (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp; accessed 12th October 2013) support the recommendations of the National Osteoporosis Foundation for the screening and treatment of osteoporosis as per the general population. All men should be treated with supplemental calcium (1200 mg/day) and vitamin D3 (800–1000 units daily). In men without bone metastases treated with long-term ADT, antiresorptive therapy is indicated when the 10-year probability of hip fracture is ≥3% or the 10-year probability of a major osteoporosis-related fracture is ≥20%.

Body composition

Adverse changes in body composition, specifically a reduction in skeletal muscle and increase in body fat (Smith et al. 2002, Haseen et al. 2010), occur as early as 3–6 months after initiation of ADT (Boxer et al. 2005, Smith et al. 2006a). In an uncontrolled study of 79 men with non-metastatic cancer, treatment with ADT for 12 months led to an 11% increase in fat mass and a 4% decrease in lean mass (Smith 2004). A cross-sectional study of 20 men treated with ADT for a minimum of 12 months noted a higher percentage fat mass in these men compared with those with non-metastatic prostate cancer who did not receive ADT and healthy controls (Basaria et al. 2002). A review of 16 studies documented an average 7.7% increase in body fat and 2.8% reduction in lean body mass, although the rate and extent of these changes varied considerably (Haseen et al. 2010). Overall, a longer duration of treatment was associated with greater change; however, an attenuation over time was reported in a study of 65 men wherein a longer duration of ADT exposure before entry into the study was associated with reduced changes in body composition during the 12 month trial (Lee et al. 2005), and in a prospective 2-year observational study comparing men receiving more or less than 6 months of ADT (van Londen et al. 2008).

Contradictory results of the impact of ADT on regional fat mass have been reported. Whilst one study showed accumulation of fat to be primarily subcutaneous rather than visceral following 12 months of treatment (Smith et al. 2002), a similarly designed study found increases in both visceral and subcutaneous abdominal fat (Hamilton et al. 2011).

The loss of skeletal muscle is associated with reduced muscle strength and poorer physical performance (Storer et al. 2012). A prospective longitudinal study evaluating the impact of ADT on objective and subjective parameters of physical function in 87 men aged 50–87 years documented declines in endurance and upper extremity strength, and deteriorating physical aspects of health-related quality of life within 3 months of starting treatment (Alibhai et al. 2010b).

Lipid profiles

The reported effects of ADT on lipid profiles are variable. Long-term use of ADT (12 months or longer) was associated with higher total and LDL cholesterol in men with normal glucose tolerance and lipid profiles at baseline (Braga-Basaria et al. 2006). In an uncontrolled
prospective study of 32 men, increases in total and LDL cholesterol and triglycerides, but also an increase in HDL cholesterol, were observed after 48 weeks of ADT (Smith et al. 2002). Others have shown significant increases in total and HDL cholesterol, but no change in LDL cholesterol and triglycerides after 3 months of ADT (Dockery et al. 2003), or no change in any lipid component after a similar interval (Smith et al. 2001b). Furthermore, a recent study has found that the increases in total and LDL cholesterol observed at 6 months were no longer evident after 12 months of ADT (Salvador et al. 2013). Whether or not the reported increase in HDL cholesterol offers cardiovascular protection is uncertain.

**Insulin resistance and type 2 diabetes mellitus**

ADT is associated with increased insulin resistance, independent of age and body composition (Basaria et al. 2006). The relationship between ADT and insulin resistance appears to be a continuum, with short-term therapy leading to reduced insulin sensitivity and long-term ADT resulting in hyperglycaemia and increased risk of metabolic syndrome and finally overt type 2 diabetes mellitus (Basaria 2008). Supporting this theory, a small study of men treated with combined androgen blockade (GNRH agonist and an anti-androgen) found increased fasting insulin levels and decreased insulin sensitivity after 12 weeks, with no change in glucose levels (Smith et al. 2006b). A cross-sectional study of longer term ADT (mean duration 45 months) documented higher fasting glucose levels with ADT (n=18) compared with men with non-metastatic prostate cancer not exposed to ADT (n=17) and a non-cancer control group (n=18). Men treated with ADT also had higher fasting insulin, fasting leptin and insulin resistance after adjustments for age and BMI (Basaria et al. 2006). It may be, therefore, that the relatively rapid development of insulin resistance occurring with ADT is a compensatory mechanism to maintain normal glucose levels; however, after prolonged treatment, the hyper-insulinaemic response becomes inadequate to maintain euglycaemia (Shahani et al. 2008). ADT-associated adverse body composition changes are likely to further exacerbate insulin resistance.

Type 2 diabetes mellitus appears to be more common with prolonged ADT. Amongst 18 men treated for an average of 45 months, 44% satisfied the fasting glucose criterion for diabetes, compared with 12% of men with treated metastatic prostate cancer who did not receive ADT (n=17) and 11% of a non-cancer control group (n=18) (Basaria et al. 2006). The risk of incident diabetes in observational studies comparing men treated with ADT to those not receiving ADT have reported significantly elevated risks, with hazard ratios (adjusted for confounders) ranging from 1.16 to 1.44 (Keating et al. 2006, 2010, Alibhai et al. 2009). Two studies included only men aged 66 years or older (Keating et al. 2006, Alibhai et al. 2009) while in the third cohort over 40% of the cohort were younger than 66 years (Keating et al. 2010). The risk of developing diabetes with ADT was independent of known risk factors (Keating et al. 2013).

Glycaemic control may deteriorate in men with type 2 diabetes diagnosed before initiation of ADT. In a retrospective analysis of 77 men with pre-existing type 2 diabetes treated with ADT, almost 20% experienced a minimum 10% increase in HbA1c level (Derweesh et al. 2007).

**CVD incidence and mortality**

A number of large observational studies (Keating et al. 2006, 2010, Saigal et al. 2007, Tsai et al. 2007, Alibhai et al. 2009) and randomised controlled trials (some of which were not designed to assess CVD mortality specifically) (D’Amico et al. 2007, Roach et al. 2008, Efstathiou et al. 2009) have investigated the relationship between ADT and CVD endpoints. Comparison of these studies is restricted by their differing population characteristics (e.g. age, ethnicity and prostate cancer stage/grade), duration of ADT and length of observed follow-up.

An analysis of the SEER Medicare database of 73 196 men aged 66 years and older followed for 10 years concluded that ADT was associated with a 16% increase in the risk of each of coronary heart disease and sudden cardiac death, with the excess risk already evident after 4 months of treatment (Keating et al. 2006). A subsequent observational study of 37 443 men of similar age with local or regional prostate cancer, identified from the Veterans Healthcare Administration and followed from 2001 to 2005, confirmed these findings with an increase in the adjusted risk of coronary heart disease, myocardial infarction and sudden cardiac death in men receiving GNRH agonist therapy (Keating et al. 2010). A Swedish study of 76 600 men on the National Prostate Cancer Register reported moderately higher risks (standardised incidence ratios ~1.3; adjusted for history of circulatory disease, socioeconomic status and prostate cancer stage) for fatal and non-fatal CVD compared with the general population, irrespective of the type of treatment they received (Van Hemelrijck et al. 2010). Those treated with endocrine therapy (including anti-androgens,
orchietomy and GnRH agonists) were at higher risk than those who had curative treatment or surveillance, for both fatal and non-fatal CVD. Cardiovascular endpoints included myocardial infarction, arrhythmia, ischaemic heart disease, heart failure and stroke (Van Hemelrijck et al. 2010).

A retrospective single institution study of 5077 men stratified according to co-morbidities, established coronary artery disease and the presence of cardiovascular risk factors, found that the excess risk was confined to those men with a history of acute myocardial infarction or congestive heart failure (Nanda et al. 2009). Following a median duration of ADT usage of 4 months, after 5 years of follow-up these men had a twofold increase in all-cause mortality with no increase observed in men with either no co-morbidities or a single cardiovascular risk factor (Nanda et al. 2009). Some studies have suggested the increased cardiovascular mortality risk is limited to older men (>65 years; D’Amico et al. 2007) whilst others have found younger men to be at similar risk (Tsai et al. 2007). Overall, although there are inconsistencies between studies, the evidence points to a moderate effect of ADT on incident coronary heart disease and myocardial infarction (Keating et al. 2006, 2010, Saigal et al. 2007). The evidence for an association with CVD mortality is less convincing (Tsai et al. 2007, Roach et al. 2008, Alibhai et al. 2009, Efstathiou et al. 2009). A meta-analysis of 4141 men in eight randomised trials did not find an association with CVD for either short (<6 months) or longer (≥3 years) term use of ADT (Nguyen et al. 2011). Importantly, the authors noted that the analysis was limited by a lack of baseline stratification according to pre-existing cardiovascular morbidity.

Limited data examining the relationship of ADT with stroke are inconclusive (Keating et al. 2010, Azoulay et al. 2011, Chung et al. 2012).

**Addressing cardio-metabolic risk in men receiving ADT**

As CVD and diabetes are the leading causes of non-cancer deaths in prostate cancer survivors (Ketchandji et al. 2009), we advise that men who receive ADT undergo documentation of their cardio-metabolic profile before commencement of therapy and periodically thereafter, according to their cardiovascular risk stratification. Importantly, however, there are no randomised controlled trial data to guide expert recommendations, and the risks of ADT treatment are not fully understood, particularly regarding the characteristics of those men who will be at greatest cardiovascular risk as a result of the induced hypogonadism. The American Heart Association, American Cancer Society and American Urological Association have published a science advisory to guide physicians caring for men receiving ADT (Levine et al. 2010). This suggests evaluation of blood pressure, lipids and glucose within 3–6 months of initiating therapy, but does not stipulate a follow-up schedule, although it does propose annual assessment with long-term therapy. Recommendations for lipid, blood pressure and glucose targets are in keeping with national guidelines for men with pre-existing CVD, but do not specifically address primary cardiovascular prevention. Others have advised primary prevention measures based on expert recommendations, but these are not specific for men receiving ADT (Saylor et al. 2009). Guidelines for the management of hypertension and hyperlipidaemia are based upon absolute CVD risk, determined using one of several available risk calculators based on the Framingham risk equation. A significant limitation to the interpretation of the risk calculators is that the contribution of ADT to overall risk is unknown, and thus the applicability of these guidelines to men who will receive ADT but who do not have established CVD is uncertain. Additionally, there is no evidence base to support the notion that reversing these risk factors will negate the cardio-metabolic risks attributed to ADT. The role of aspirin for primary cardiovascular protection for men treated with ADT has not been studied, and there is no consensus about its role in primary prevention more generally. The European Society of Cardiology does not recommend its use (Perk et al. 2012), but guidelines from the American College of Chest Physicians, also published in 2012, advise the use of low-dose aspirin in men from the age of 50 years (Vandvik et al. 2012).

Whilst there remains a lack of evidence, it would seem prudent to assume that ADT places men at a higher risk of accelerated CVD (including myocardial infarction, cerebrovascular accident and sudden cardiac death) and thus in a previous publication we have recommended the following (Allan et al. 2012; see Table 2):

i) Maintenance of ideal weight (BMI) and waist circumference (diet and exercise).

ii) Smoking cessation.

iii) Blood pressure: targets set according to national guidelines and individualised, dependent upon the presence of co-morbid disease including pre-existent CVD.

iv) Lipid control: targets for fasting total, LDL and HDL cholesterol and triglycerides set according to
Table 2  Managing cardiovascular risk in men receiving ADT

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<th>Lifestyle modification to prevent weight gain (especially abdominal)</th>
<th>Dietary</th>
<th>Exercise</th>
<th>Smoking cessation</th>
<th>Optimise blood pressure control</th>
<th>Screen for and treat hyperlipidaemia</th>
<th>Screen for and treat type 2 diabetes mellitus</th>
<th>Aspirin therapy with established cardiovascular disease (role in primary prevention uncertain)</th>
</tr>
</thead>
</table>

- National guidelines. Individual targets and the use of lipid lowering therapies (statins and fibrates) will depend upon the presence of co-morbid disease including pre-existent CVD.
- Blood glucose/diabetes mellitus: annual screening for diabetes mellitus with a formal 2-h oral glucose tolerance test should be considered. We also recommend aggressive lifestyle intervention with impaired fasting plasma glucose (6.2–6.9 mmol/l) and/or impaired glucose tolerance (fasting plasma glucose <7 mmol/l and 2-h plasma glucose ≥7.8 and <11.1 mmol/l (World Health Organization and International Diabetes Federation (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. Geneva: World Health Organization) to prevent progression to type 2 diabetes mellitus.
- Aspirin: aspirin therapy should be considered for men without overt CVD at high risk of an event (according to a validated risk calculator), in whom the risk of bleeding is considered low. Men with established CVD, and no contra-indication, should routinely be prescribed antiplatelet therapy.

**Conclusion**

ADT is a valuable tool in the management armament for advanced prostate cancer in a variety of clinical situations. By being aware of the potential detrimental impact on quality of life, sexual function, cardio-metabolic health, and bone density and fracture risk, health professionals assisting men in making informed decisions about the role of ADT in their treatment regimen for prostate cancer are able to formulate comprehensive management and surveillance strategies. This is particularly important given the higher cardiovascular risk generally experienced by men in this age group. Although the clinical outcome data examining the effectiveness of managing CVD risk in men using ADT are limited, extrapolating from the principals of monitoring and managing CVD risk in the general male population, and incorporating and extending these to men receiving ADT treatment, appears warranted. It is appropriate that physicians and nurses treating men with advanced prostate cancer take into account these additional potential psycho-sexual, bone and cardio-metabolic morbidities and monitor accordingly. This could be done alone or in combination by any of the following – the urological team, the medical or radiation oncologist, an endocrinologist/andrologist, or the general practitioner/primary care physician, in addition to a cardiologist for men at high risk for or with established CVD, to ensure the optimal quality of care for men with prostate cancer managed with ADT.

**Declaration of interest**

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**References**


Joly F, Alibhai SM, Galica J, Park A, Yi QL, Wagner L & Tannock IF 2006 Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic


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