Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them

Paul L. Nguyen a,*, Shabbir M.H. Alibhai b, Shehzad Basaria c, Anthony V. D’Amico a, Philip W. Kantoff d, Nancy L. Keating e, David F. Penson f, Derek J. Rosario g, Bertrand Tombal h, Matthew R. Smith i

a Department of Radiation Oncology, Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA, USA; b Department of Medicine, University Health Network, Toronto, Canada; c Section on Men’s Health, Aging and Metabolism, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; d Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; e Division of General Internal Medicine, Department of Medicine, Brigham and Women’s Hospital, and Department of Health Care Policy, Harvard Medical School, Boston, MA, USA; f Department of Urologic Surgery and the Center for Surgical Quality and Outcomes Research, Vanderbilt University, and the VA Tennessee Valley Geriatric Research, Education, and Clinical Center, Nashville, TN, USA; g Academic Urology Unit, Department of Oncology, Royal Hallamshire Hospital, University of Sheffield, Sheffield, UK; h Division of Urology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; i Department of Hematology-Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA

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Abstract

Context: Androgen-deprivation therapy (ADT) is a key component of treatment for aggressive and advanced prostate cancer, but it has also been associated with adverse effects on bone, metabolic, cardiovascular, sexual, and cognitive health as well as body composition.

Objective: To review the current literature on the adverse effects of ADT and strategies for ameliorating harm from ADT.

Evidence acquisition: The Medline database (through PubMed) was searched from inception to August 1, 2013, for studies documenting the side effects of ADT and for randomized and prospective trials of interventions to mitigate those side effects.

Evidence synthesis: Adverse effects of ADT include decreases in bone mineral density; metabolic changes such as weight gain, decreased muscle mass, and increased insulin resistance; decreased libido and sexual dysfunction; hot flashes; gynecomastia; reduced testicle size; anemia; and fatigue. Several observational studies suggest an increased risk of diabetes and cardiovascular events, although most published studies report that ADT is not linked to greater cardiovascular mortality. Randomized trials have found value in treatments for some adverse effects including bone loss (bisphosphonates, denosumab, selective estrogen receptor modulators), markers of metabolic syndrome (exercise, diet, metformin), gynecomastia (tamoxifen, prophylactic radiation), muscle loss (resistance and aerobic exercise), and hot flashes (venlafaxine, medroxyprogesterone, cyproterone acetate, gabapentin).

Conclusions: Androgen deprivation therapy is often a necessary component of the treatment of aggressive prostate cancer, yet it has known harms that can impair health and quality of life. Clinicians should be aware of interventions that can help mitigate these adverse effects.

Patient summary: Androgen deprivation therapy is a critical component of the management of aggressive and advanced prostate cancer, but it causes adverse effects including bone loss, metabolic changes, gynecomastia, muscle loss, hot flashes, and possibly increased cardiovascular events. Clinicians should be aware of interventions that can help mitigate these adverse effects.

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1. Introduction

Androgen deprivation therapy (ADT) is a mainstay of prostate cancer treatment and has been shown in randomized trials to improve overall survival when used with radiation for intermediate- and high-risk localized disease [1,2], as well as locally advanced [3,4] and node-positive disease [5], and after surgery for node-positive disease [6]. Although ADT can improve survival, it can also cause significant morbidity and a decrement in quality of life (QOL). This narrative review describes the adverse consequences of ADT and provides an up-to-date summary of evidence-based interventions that can prevent or reduce these side effects (Tables 1 and 2).

2. Evidence acquisition

A Medline search was conducted to identify original articles and review articles published from January 1, 1966, to August 1, 2013, that focused on the side effects of ADT and methods to mitigate those side effects. Keywords included androgen deprivation therapy and side effects. The articles with the highest level of evidence within each of the side effect categories examined were identified with the consensus of all of the collaborative authors and were reviewed. For the treatment of ADT-related side effects, the initial selection of articles within each category was limited to randomized controlled trials and then expanded to prospective noncontrolled trials only if

<table>
<thead>
<tr>
<th>Problem</th>
<th>Intervention</th>
<th>Study</th>
<th>Patients, n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone health</td>
<td>Pamidronate</td>
<td>Smith et al. [15]</td>
<td>47</td>
<td>Prevents decrease in bone mineral density on ADT</td>
</tr>
<tr>
<td></td>
<td>Risedronate</td>
<td>Choo et al. [16]</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zoledronic acid</td>
<td>Smith et al. [17]</td>
<td>106</td>
<td>Increase in bone mineral density while on ADT</td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>Greenspan et al. [18]</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Klotz et al. [19]</td>
<td></td>
<td>191</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raloxifene</td>
<td>Smith et al. [22]</td>
<td>48</td>
<td>Increase in bone mineral density while on ADT; decreased fracture risk</td>
</tr>
<tr>
<td></td>
<td>Denosumab</td>
<td>Smith et al. [21]</td>
<td>1468</td>
<td>Increase in bone mineral density while on ADT; decreased fracture risk</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Metabolic syndrome</td>
<td>Resistance training</td>
<td>Segal et al. [40]</td>
<td>155</td>
<td>Increase in upper and lower body fitness; no effect on BMI or waist circumference</td>
</tr>
<tr>
<td></td>
<td>Resistance vs aerobic exercise</td>
<td>Santa Mina et al. [41]</td>
<td>66</td>
<td>Aerobic-training group engaged in significantly more physical activity than the resistance-training group</td>
</tr>
<tr>
<td></td>
<td>Cognitive-behavioral therapy for exercise</td>
<td>Carmack Taylor et al. [42]</td>
<td>134</td>
<td>No increase in exercise or QOL</td>
</tr>
<tr>
<td></td>
<td>Resistance and exercise</td>
<td>Nobes et al. [39]</td>
<td>40</td>
<td>Decrease in abdominal girth, BMI, weight, and systolic BP</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Intermittent ADT</td>
<td>Crook et al. [73]</td>
<td>1386</td>
<td>Increased libido; no decrease in survival compared with continuous ADT in nonmetastatic men</td>
</tr>
<tr>
<td></td>
<td>Aerobic and resistance exercise</td>
<td>Hussain et al. [74]</td>
<td>1535</td>
<td>Increased erectile function, but treatment failed noninferiority for survival in metastatic patients</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia</td>
<td>Widmark et al. [80]</td>
<td>253</td>
<td>Significant reduction in gynecomastia</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td>Tyrrell et al. [78]</td>
<td>106</td>
<td>Maintained sexual activity and interest in sex</td>
</tr>
<tr>
<td></td>
<td>Breast radiation vs tamoxifen</td>
<td>Di Lorenzo et al. [82]</td>
<td>102</td>
<td>RT and tamoxifen both reduce gynecomastia compared with observation, but tamoxifen reduces it more</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perdona et al. [83]</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Aerobic and resistance exercise</td>
<td>Galväo et al. [88]</td>
<td>57</td>
<td>Reduced fatigue compared with usual care</td>
</tr>
<tr>
<td></td>
<td>Segal et al. [40]</td>
<td>155</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cullos-Reed et al. [90]</td>
<td>100</td>
<td></td>
<td>Reduced fatigue compared with usual care</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Gabapentin</td>
<td>Bourke et al. [62]</td>
<td>50</td>
<td>High-dose gabapentin reduced hot flash frequency</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine/ medroxyprogesterone/ cyproterone</td>
<td>Irani et al. [93]</td>
<td>311</td>
<td>All treatments reduced hot flashes; medroxyprogesterone reduced more than venlafaxine and interfered with ADT less than cyproterone</td>
</tr>
<tr>
<td></td>
<td>Soy protein/Venlafaxine</td>
<td>Vitolins et al. [95]</td>
<td>120</td>
<td>Neither soy protein or venlafaxine, or a combination of the two, reduced hot flashes</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; BMI = body mass index; BP = blood pressure; DVT = deep vein thrombosis; QOL = quality of life; RT = radiation therapy.
Table 2 – Summary of evidence-based strategies to reduce androgen deprivation therapy side effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Evidence-based strategies to reduce effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased bone health</td>
<td>Calcium (1000–1200 mg daily from diet and supplements)</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Vitamin D (800–1000 IU daily)</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>For men with FRAX risk of hip fracture &gt;3%:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Denosumab (increased BMD and decreased fractures)</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td>• Zoledronic acid (increased BMD, alternative if denosumab not available)</td>
<td>[17,20,27]</td>
</tr>
<tr>
<td></td>
<td>• Alendronate (increased BMD, alternative if denosumab not available)</td>
<td>[18,19]</td>
</tr>
<tr>
<td>Metabolic consequences</td>
<td>Exercise (aerobic and resistance)</td>
<td>[39–41,43,44]</td>
</tr>
<tr>
<td></td>
<td>ATP III and AHA/ACC guidelines for lipids</td>
<td>[36,47]</td>
</tr>
<tr>
<td>Increased diabetic risk</td>
<td>ADA guidelines for screening high-risk patients</td>
<td>[45,46]</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Intermittent ADT for rising PSA after radiation</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>Use shortest acceptable duration of ADT</td>
<td>[76]</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Prophylactic radiation</td>
<td>[78,80]</td>
</tr>
<tr>
<td></td>
<td>Prophylactic tamoxifen</td>
<td>[81,82]</td>
</tr>
<tr>
<td>Reduced penile/testis size</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Exercise (aerobic and resistance)</td>
<td>[87–91]</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Medroxyprogesterone</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>[92]</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

ADA = American Diabetes Association; ADT = androgen-deprivation therapy; AHA/ACC = American Heart Association/American College of Cardiology; ATP III = Adult Treatment Panel III; BMD = bone mineral density; FRAX = World Health Organization Fracture Risk Assessment Tool; PSA = prostate-specific antigen.

randomized trials were not available in that particular category.

3. Evidence synthesis

3.1. Impact of androgen deprivation therapy on bone health and strategies for prevention

ADT is associated with decreases in bone mineral density (BMD) and increased risk of fracture. Prospective studies suggest that BMD decreases by 5–10% in the first year after initiating ADT for prostate cancer [7–10]. Two studies based on the Surveillance Epidemiology and End Results (SEER)–Medicare database reported an increased fracture rate with ADT that increased with longer duration of ADT. One study noted a 21% relative increase in clinical fractures with ADT use [11], and another study of > 50 000 men reported a fracture rate among men surviving at least 5 yr of 19.4% with ADT versus 12.6% without ADT [12].

Calcium and vitamin D are commonly recommended for men receiving ADT, although no randomized trials have tested whether supplementation improves BMD for men on ADT. A 2012 systematic review found that 12 clinical trials testing other agents for BMD preservation used calcium (500–1000 mg/d) and vitamin D (200–500 IU/d) in the control arms (doses likely too low to prevent bone loss) [13]. A calcium intake of at least 1200 mg daily (from diet and supplements) and supplemental vitamin D of 800–1000 IU/d is currently recommended for all men > 50 yr of age by the National Osteoporosis Foundation and would be a reasonable recommendation for all men on ADT [14].

Bisphosphonates have been shown in randomized trials to increase BMD or reduce BMD loss in men receiving ADT. In 2001, a randomized trial of 47 men found that in men assigned to leuprolide alone, there was a 3.3% decrease in BMD at the lumbar spine, 2.1% in the trochanter, and 1.8% in the hip, but no decreased BMD in the group receiving leuprolide plus pamidronate 60 mg every 12 wk [15]. Similarly, a recent trial of risedronate versus placebo found no significant loss in BMD after 2 yr of ADT in the risedronate arm compared with bone loss in the control arm [16]. Increased BMD has been seen with zoledronic acid or alendronate given with ADT. In a 2003 randomized trial, 4 mg zoledronic acid given every 3 mo for 1 yr increased mean BMD by 5.6% in men receiving zoledronic acid; BMD decreased by 2.2% in the placebo group \( (p < 0.001) \), and similar results were seen in the femoral neck, trochanter, and total hip [17]. Increases in BMD with alendronate were seen in two randomized trials [18,19]. The most recent, published in 2013, found that compared with calcium 100 mg and vitamin D 400 IU, the addition of weekly oral alendronate 70 mg improved spine BMD by 1.7% versus a –1.9% change in the placebo group \( (p < 0.001) \), with similar findings in the hip [19]. A systematic review and meta-analysis published in 2012 found that in 15 trials of 2634 participants, bisphosphonates as a class showed a substantial effect in preventing fractures (risk ratio [RR]: 0.80; \( p = 0.005 \)) and osteoporosis (RR: 0.39; \( p < 0.00001 \)) [20].

Denosumab is a humanized monoclonal antibody against the receptor activator of nuclear factor-\( \kappa \) ligand that blocks the maturation of preosteoclasts to osteoclasts. A large randomized trial of 1468 men published in 2009 found that 60 mg subcutaneous denosumab increased lumbar spine BMD at 24 mo by 5.6% compared with a 1.0% loss in the placebo group \( (p < 0.001) \). Similar results were seen in the total hip, femoral neck, and radius. In addition, denosumab led to a decreased incidence of new vertebral fractures at 3 yr (1.5% vs 3.9%; RR: 0.38; 95% confidence interval [CI],...
1.21; 95% CI, 0.99–1.50) in the metastatic setting. Antiandrogen monotherapy was associated with a near-2.42% at 2 yr versus a 5.40% loss with placebo that bicalutamide increased BMD in the lumbar spine by 3.2. Metabolic consequences of androgen deprivation therapy. An early prospective study of 32 men newly exposed to ADT found that men on ADT and those randomized to 80 mg oral toremifene daily had a 50% reduction in the 2-yr incidence of new vertebral fractures (4.9% for placebo vs 2.5% for toremifene; \( p < 0.001 \)), although venous thromboembolic events occurred more frequently in the toremifene group (1.1% for placebo vs 2.6% for toremifene) [23]. Raloxifene and toremifene are not currently approved by the US Food and Drug Administration (FDA) for the indication of preventing ADT-related bone loss.

Finally, two trials examined bone loss with bicalutamide monotherapy (150 mg daily) versus leuprolide. One trial of 52 men found that BMD of the lumbar spine increased by 2.5% in the bicalutamide group; it decreased by 2.5% at 1 yr in the leuprolide group [24]. A second trial of 103 men found that bicalutamide increased BMD in the lumbar spine by 2.42% at 2 yr versus a 5.40% loss with placebo [25]. However, this strategy cannot be routinely recommended because a meta-analysis of 2717 patients found that compared with luteinizing hormone-releasing hormone (LHRH) agonists, antiandrogen monotherapy was associated with a near-significant decline in overall survival (hazard ratio [HR]: 1.21; 95% CI, 0.99–1.50) in the metastatic setting [26].

Based on the data just cited, in addition to vitamin D and calcium supplementation for all men on ADT, the current National Comprehensive Cancer Network guidelines recommend treatment with either denosumab (60 mg subcutaneously every 6 mo), zoledronic acid (5 mg intravenously annually), or alendronate (70 mg orally weekly) for men with a 10-yr risk of hip fracture \( \geq 3\% \) based on the Fracture Risk Assessment Tool algorithm released by the World Health Organization [27]. A baseline BMD scan should also be obtained in these high-risk men, and a follow-up scan after 1 yr of therapy is recommended by the International Society for Clinical Densitometry for men on long-term ADT [28].

3.2. Metabolic consequences of androgen deprivation therapy

The metabolic consequences of ADT have been established in both prospective and population-based studies. An early prospective study of 32 men newly exposed to 12 mo of gonadotropin-releasing hormone (GnRH) agonists found a 2.4% weight gain, 9.4% increase in body fat percentage, and 2.7% decrease in lean body mass at 12 mo [29]. A subsequent prospective study of 25 patients without diabetes found that just 12 wk of combined androgen blockade resulted in a 12.8% decrease in insulin sensitivity and a 25.9% increase in fasting plasma insulin [30]. Also, a cross-sectional study of 18 men on \( > 1 \) yr of ADT and 35 age-matched controls found that men on long-term ADT had significantly higher fasting glucose (131 vs 103; \( p < 0.01 \)) and greater insulin resistance (17 vs 6; \( p < 0.01 \)), and that 44% of the men on ADT had fasting glucose in the diabetic range (\( \geq 126 \) mg/dl) compared with 11–12% for the controls [31].

The concern about the possible link between ADT and diabetes raised by the patient-level studies was later confirmed by several large population-based studies. First, a study based on 73 196 men \( > 65 \) yr of age with prostate cancer in the US-based SEER-Medicare database found that men being treated with a GnRH agonist had a 44% increased risk of incident diabetes [32]. These findings were confirmed in another US-based study of 37 443 veterans with prostate cancer. In this study, 36% of the men were treated with ADT, and among those receiving GnRH agonists, there was a 28% increase in the risk of incident diabetes (36.1 events per 1000 person-years with GnRH agonist vs 21.1 events per 1000 person-years for no ADT) [33,34]. A large study from the administrative databases in Ontario, Canada, examined 19 079 men \( \geq 66 \) yr of age who received either bilateral orchiectomy or \( > 6 \) mo ADT and found that ADT was associated with a 16% increase in the risk of incident diabetes [35].

The constellation of the metabolic effects of ADT shares some features of the hallmarks of metabolic syndrome. Per the Adult Treatment Panel III (ATP III) guidelines, the diagnosis of metabolic syndrome requires the presence of three of the following five criteria: (1) serum triglycerides \( \geq 150 \) mg/dl, (2) high-density lipoprotein (HDL) \( < 40 \) mg/dl, (3) fasting serum glucose \( > 110 \) mg/dl, (4) waist circumference \( \geq 40 \) inches, and (5) blood pressure \( \geq 130/85 \) [36]. As noted earlier, patients receiving ADT are at risk for higher fasting serum glucose and increased waist size due to central weight gain. Triglycerides have also been reported to rise by 26.5% (\( \pm 10\% \); \( p = 0.01 \)) with 1 yr of ADT [29]. Although ADT has not consistently been linked to increased blood pressure, a prospective study of 22 men on ADT for 6 mo found an increase in arterial stiffness [37]. Not surprisingly, an increase in the incidence of metabolic syndrome was observed in a cross-sectional study of 58 men that found metabolic syndrome was present in \( > 50\% \) of men on long-term ADT and that this rate was significantly higher than patients with prostate cancer not on ADT (\( p < 0.01 \)). This difference was driven largely by men on ADT meeting the hyperglycemia, abdominal girth, and elevated triglycerides criteria, rather than the hypertension or HDL criteria [38]. It should be noted that the metabolic profile resulting from ADT differs slightly from the metabolic syndrome in that ADT appears to result in an increase in HDL rather than a decrease, although it is unclear if this has any cardioprotective effect [29].

Several trials have examined whether various exercise strategies can counteract the metabolic effects of ADT. Nobes et al. found that among 40 men beginning ADT for the first time, 6 mo of metformin and exercise led to significant improvements in abdominal girth (\( p = 0.05 \)), weight (\( p < 0.001 \)), body mass index (\( p < 0.001 \)), and systolic blood pressure (\( p = 0.01 \)) compared with control, although there was no difference in the biochemical markers of insulin resistance [39]. Prior to that, Segal et al. reported
that randomization to 12 wk of resistance training versus observation resulted in higher levels of upper body \( (p = 0.009) \) and lower body \( (p < 0.001) \) muscular fitness, although there was no difference in body weight, body mass index, waist circumference, or subcutaneous skinfolds [40]. A recently reported randomized trial compared resistance training with aerobic exercise in men on ADT and found that the aerobic group engaged in significantly more physical activity than the resistance group, although the resistance group had significant improvements in health-related QOL [41]. The challenges of encouraging physical activity were demonstrated in a randomized trial of 134 men on ADT that found that a lifestyle program implementing a cognitive-behavioral curriculum focused on increasing physical activity did not result in increases in routine physical activity or changes in QOL [42]. Given the relatively small sample sizes and preliminary nature of many of these studies, larger randomized trials are needed to assess the benefit of strategies to mitigate metabolic syndrome in men on ADT. Additional randomized trials of exercise versus observation are currently in progress for this patient population [43,44]. Another promising strategy is the use of metformin, although currently there is insufficient evidence to support its routine use in this setting.

It remains uncertain exactly to what degree exercise can alleviate the metabolic harms of ADT; nevertheless, both aerobic and resistance exercises are very rational recommendations for all men undergoing ADT. There are currently no specific recommendations regarding the management of insulin resistance and lipid increases for men on ADT. Given the increased risk of diabetes associated with ADT, one strategy would be to consider men on ADT as high risk for developing diabetes and follow the American Diabetic Association recommendations for screening in high-risk individuals [45]. Similarly, given the worsening of diabetes control among men treated with ADT [46], regular monitoring of diabetes control and adjustment of medications when needed is recommended for men with existing diabetes treated with long-term ADT. Lipid abnormalities can be treated per the ATP III guidelines [36], or clinicians may consider the new American Heart Association (AHA)/American College of Cardiology guidelines that de-emphasize the specific low-density lipoprotein (LDL) targets of ATP III and instead recommend initiating statin therapy based on a combination of LDL levels, diabetes, and current and future risk of atherosclerosis [47].

### 3.3. The controversy about cardiovascular harm

Whereas the metabolic consequences of ADT are reasonably well established, whether ADT also increases the risk of cardiovascular (CV) events and CV mortality has been more controversial. Awareness of the problem began in 2006 with the publication of the observational SEER-Medicare study by Keating et al. [32]. In addition to the increased risk of diabetes, it also found a 16% increased risk of coronary heart disease, 11% increased risk of myocardial infarction (MI), and a 16% increased risk of sudden cardiac death among men receiving ADT compared with prostate cancer patients not on ADT. Interestingly, this risk of excess events was not seen with orchietomy, raising the possibility that the events could be related to the GnRH agonists themselves, although relatively few men underwent orchietomy [32]. Further retrospective data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry suggested that among men >65 yr of age receiving radical prostatectomy, those who also received ADT had a significantly higher risk of fatal CV events [48]. Another study examined CV mortality among men on ADT by pooling data from two randomized trials, the Dana-Farber Cancer Institute 95-096 and TROG 96-01, and found that among the subgroup of men >65 yr of age, assignment to the 6-mo ADT arms resulted in a significantly shorter time to fatal MI \( (p = 0.017) \), although the total number of cardiac events by 7 yr was the same [49]. Another study identified an association between ADT and coronary heart disease, MI, sudden cardiac death, and stroke in a US veterans’ population [33,34]. These studies led to a science advisory jointly released in 2010 by the American Urological Association, the AHA, American Cancer Society, and American Society of Radiation Oncologists stating that “at this point, it is reasonable, on the basis of the above data, to state that there may be a relation between ADT and cardiovascular events and death” [50]. That same year, the FDA issued a drug safety communication requiring manufacturers of GnRH agonists to modify their labeling to warn of an “increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke)” [51].

Since this report, additional large observational studies have been published finding an association between ADT and CV disease and related outcomes including stroke in a UK database [52], peripheral arterial disease and venous thromboembolism in the SEER-Medicare database [53], CV disease in the Swedish national prostate cancer register [54], and MI and stroke in the Danish cancer registry [55]. However, not all studies have found the same results. Notably, the case-control study from Ontario reported by Alibhai et al. of nearly 20 000 men did not find ADT to be associated with acute MI \( (HR: 0.91; 95% \text{ CI}, 0.84–1.00) \) for ADT vs no ADT) or sudden cardiac death \( (HR: 0.96; 95\% \text{ CI}, 0.83–1.10) \) [35].

Although most of the published large observational studies found an association between ADT and CV events, most studies examining CV death did not find an association with ADT. A retrospective analysis of the CaPSURE database using propensity matching to adjust for possible confounders among 1391 men did not demonstrate any difference in CV mortality associated with ADT [56]. Similarly, several reanalyses of randomized trials comparing ADT with no ADT did not find an association between ADT and increased CV death, including a reanalysis of RTOG 85-31 that compared radiation plus lifelong ADT versus radiation alone and found no increase in CV death on the ADT arm \( (8.4\% \text{ with ADT vs } 11.4\% \text{ without ADT}; p = 0.17) \), even after censoring patients in the control arm who received salvage ADT [57]. There was also a reanalysis of RTOG 86-10 comparing radiation plus 4 mo of ADT versus radiation alone showing 12.5% versus 9.1% fatal cardiac events at
and a reanalysis of TROG 96.01 showing 6.44% versus 7.54% fatal cardiac events at 10 yr with and without 6 mo of ADT (p = 0.65) [59]. In addition, a reanalysis of RTOG 92-02 did not find excess CV death in long-term (28 mo) versus short-term (4 mo) ADT [60]. These findings were supported by a meta-analysis of 4141 patients in eight randomized trials of ADT versus no ADT or delayed ADT in men with nonmetastatic prostate cancer that found the risk of CV death on the ADT arms (11.0%) was not different than the risk on the no-ADT arms (11.2%) (RR: 0.93; 95% CI, 0.79–1.10; p = 0.41) [61].

It has been noted that in the meta-analysis just cited, many of the patients in the control arm eventually received ADT, which may have limited the ability to detect a difference in CV mortality. Also, these trials were not specifically powered to detect a difference in CV outcomes [62]. In addition, the meta-analysis was not able to stratify by baseline comorbidity, and so it remains possible that there is a vulnerable subpopulation of men with high levels of existing comorbidity who could experience increased CV death when treated with ADT. Evidence for this hypothesis comes from a stratified reanalysis of the Dana-Farber randomized trial in which men with minimal or no comorbidity by the Adult Comorbidity Evaluation-27 index [63] had a highly significant survival benefit with ADT, but men with moderate to severe baseline comorbidity (24% of the study population) had a near-significant increase (HR: 1.85; p = 0.08) in all-cause mortality (ACM) on ADT, presumably due to an increase in CV death [1]. Similarly, a retrospective analysis of >5000 men treated with radiation found that ADT use was associated with an increase in ACM only among the small subgroup (5% of study population) of patients who had a prior MI or diagnosis of congestive heart failure (CHF) (HR for ACM: 1.96; 95% CI, 1.04–3.71; p = 0.04) [64], and another retrospective study suggested the increased risk of ACM with ADT in men with CHF or prior MI (9% of study population) also held for men with high-risk prostate cancer (HR: 2.57; 95% CI, 1.17–5.67; p = 0.019) [65]. However, a large SEER-Medicare study did not find that baseline comorbidity modified the impact of ADT on the risk of MI [66], although men with preexisting CV disease had a greater absolute risk of MI. This larger absolute risk could explain why some smaller studies observed differences only in higher risk subgroups. In addition, separate reanalyses of the RTOG 85-31 and RTOG 92-02 by comorbidity did not find that men with preexisting CV disease had excess CV deaths due to either short- or long-course ADT [57, 60].

To summarize, the available data suggest that ADT results in unfavorable metabolic changes and may increase risk for CV events, although most published studies report that ADT is not linked to greater CV mortality. Further investigation into the precise populations of men who may experience the greatest harm from ADT and the precise mechanism of harm is needed.

Currently, the best way to limit the CV harms of ADT is to avoid using it in patients who do not need it from a cancer perspective. It is also possible that the exercise interventions mentioned in the metabolic section will eventually translate into prevention of excess CV events. Another possible consideration is to evaluate alternatives to GnRH agonists because much of the data for the CV harms of ADT have been in men receiving mainly GnRH agonists. For example, in both the SEER-Medicare study and the Danish registry study, the excess risk of CV events on ADT was seen only in men receiving GnRH agonists and not in men receiving orchiectomy [32, 55], raising the possibility that orchiectomy may be associated with lower CV risk. There has also been recent interest in GnRH antagonists as an alternative to GnRH agonists and whether they could have a different risk profile. One randomized trial of 1 yr of leuprolide versus degarelix found no significant differences in CV events [67]. A pooled analysis of 1708 patients who participated in trials of degarelix found that for the overall population, the rate of CV events was similar before and after administration of degarelix (5.5 vs 6.1 per 100 person-years; p = 0.45), although among the subset of men with baseline CV disease, the event rate was significantly higher after degarelix (5.3 vs 10.5 events per 100 person-years; p = 0.0013) [68]. Most recently, a study that pooled 2328 patients from six randomized trials of degarelix versus leuprolide found that degarelix was associated with a lower risk of CV events than leuprolide (HR: 0.60; 95% CI, 0.38–0.94; p = 0.025) and that this effect was particularly seen in the 705 men (31% of patients) with baseline CV disease (HR: 0.476; 95% CI, 0.260–0.871; p = 0.016) but not in the men without a history of CV disease [69]. This raises the possibility that GnRH antagonists could be a good alternative to GnRH agonists for men with preexisting CV disease. However, some caution is needed because this was a post hoc analysis of pooled data, and further follow-up is needed to fully evaluate the long-term efficacy of GnRH antagonists versus GnRH agonists.

3.4. **Sexual dysfunction**

The decrease in testosterone due to ADT results in both loss of libido in a large proportion of men and a decrease in erectile function due to venous leakage, decreased arterial flow, and impaired nitric oxide, leading to sexual dysfunction in >90% of men [70–72]. Two strategies that are sometimes considered to try and reduce the sexual sequelae are the use of intermittent androgen deprivation, the use of shorter courses of ADT, or the use of antiandrogen monotherapy as an alternative to GnRH agonists.

Intermittent ADT may be a viable option for men with rising prostate-specific antigen (PSA) after local therapy but no evidence of metastases. This strategy was tested in a 1386-patient noninferiority trial that randomized patients with rising PSA after either primary or salvage radiotherapy to continuous ADT versus intermittent ADT and found no difference in overall survival with a 6.9-yr median follow-up (HR for death: 1.02; 95% CI, 0.86–1.21). However, desire for sexual activity was significantly better in the intermittent group (p < 0.001) [73]. For men with metastatic disease, intermittent ADT cannot be recommended as a strategy to reduce sexual dysfunction. In a randomized noninferiority trial of 1535 men with newly diagnosed...
nonmetastatic prostate cancer, intermittent versus continuous ADT was associated with significantly better erectile function \( (p < 0.001) \), but after a median follow-up of 9.8 yr it was not possible to conclude that intermittent therapy was noninferior to continuous therapy because the CI of the HR for death did not exclude the upper bound of 1.20 (HR: 1.10; 90% CI, 0.99–1.23) \[74\].

Reducing the duration of ADT could also provide improvements in sexual function, but it cannot be recommended in situations where this would lead to a survival decrement. For example, the European Organization for Research and Treatment of Cancer (EORTC) performed a noninferiority trial of radiation plus 6 versus 36 mo of ADT in men with high risk to locally advanced prostate cancer and found a significant improvement in sexual function and activity with the shorter course of ADT \( (p < 0.001) \), but there was also a significant increase in mortality (HR for death: 1.42; 95.7% CI, 1.09–1.85) \[75\]. Although there is no direct QOL comparison between 18 and 36 mo of ADT, the TROG 03-04 trial randomized men to 6 versus 18 mo of ADT and found that on the 18-mo arm of ADT, sexual activity was worse at 18 mo but not significantly worse by 36 mo. This seems to compare favorably with the 36-mo arm of the EORTC trial where sexual symptoms remained qualitatively worse than the 6-mo arm even at 3.5 yr, suggesting that 18 mo would provide sexual health benefits as compared with 36 mo \[76\]. Whether 18 mo can be recommended as an alternative to 36 mo remains an open question. A recent study reported in abstract form randomized 630 men with high-risk or locally advanced prostate cancer to radiation plus 18 versus 36 mo of ADT, and it did not find a difference in overall survival (HR: 1.15; 95% CI, 0.83–1.59; \( p = 0.398 \)), but it was underpowered and not designed as a noninferiority trial. The current 95% CI suggests it is not possible to rule out up to a 59% increase in the risk of death on the 18-mo arm as compared with the 36-mo arm, and further follow-up and more events will be needed to narrow this CI.

A third option to limit sexual side effects would be to use antiandrogen monotherapy instead of a GnRH agonist. A randomized trial of leuprolide versus bicalutamide 150 mg found less of a decline in sexual interest in the bicalutamide group \[24\]. However, as noted in the bone section, this strategy cannot be routinely recommended given the data suggesting that currently available antiandrogen monotherapy is not oncologically equivalent to GnRH agonists in a primarily metastatic setting \[26\]. Whether they are oncologically equivalent in the high-risk or locally advanced or biochemically recurrent settings remains untested.

Finally, there may be some significant benefit of exercise therapy. Cormie et al. investigated the effect of a 12-wk exercise program on sexual activity in 57 prostate cancer patients undergoing ADT. There was a significant \( (p = 0.045) \) adjusted group difference in sexual activity following the 12-wk intervention. At baseline, 20.6% and 22.2% of participants in the exercise and control groups, respectively, reported a major interest in sex. Following the intervention, the exercise group had a significantly higher percentage of participants reporting a major interest in sex (exercise: 17.2% vs control: 0%; \( p = 0.024 \)) \[77\]. Further confirmation of these results in larger randomized studies will be helpful in further assessing these strategies.

### 3.5. Gynecomastia

Gynecomastia and breast pain can be bothersome side effects for men on ADT. The incidence of gynecomastia was as high as 85% in a randomized trial of men receiving high-dose antiandrogen monotherapy (bicalutamide 150 mg daily) \[78\], although the incidence is substantially lower (13–22%) in men receiving combined androgen blockade \[79\]. Prophylactic radiotherapy and prophylactic tamoxifen are the two main strategies that have been tested in randomized trials to address gynecomastia. Single-fraction prophylactic radiation (10–15 Gy) reduced gynecomastia from antiandrogen monotherapy from 71% to 28% at 1 yr in one trial \[80\] and from 85% to 52% in another \[78\]; tamoxifen (20 mg/d) reduced gynecomastia from 73% to 10% in a third trial \[81\]. Another trial that compared tamoxifen versus radiation versus observation found a greater benefit of prophylactic tamoxifen (8% gynecomastia) as compared with prophylactic radiation (34% gynecomastia), although both were better than the control group that had 67% gynecomastia. This trial also randomized patients who developed gynecomastia to tamoxifen versus radiation as treatment and found that once gynecomastia develops, tamoxifen is superior to radiation in reversing gynecomastia (only 9% still had gynecomastia 6–9 mo after tamoxifen as compared with 54% after radiation; \( p < 0.05 \)) \[82\]. There were no significant differences in QOL between tamoxifen and radiation, and similar results were seen in another randomized trial \[83\].

### 3.6. Reduction in penile and testicular size

A rarely discussed side effect that can be very distressing for patients who experience it without warning is that ADT can induce reductions in both penile and testicular size. One pathologic study of 24 testes in men who had previously been treated with a mean of 1 yr of buserelin found pronounced interstitial fibrosis with total atrophy of the Leydig cells in 92% of the testes and severe generalized atrophy of the seminiferous tubules in 50% of the testes \[84\]. A prospective study of 47 men undergoing radiation plus GnRH agonists found that stretched penile length was significantly shorter after 18 mo, dropping from a mean of 14.2 cm to 8.6 cm \( (p < 0.001) \) \[85\]. This potential side effect should be discussed with patients before initiating ADT because reduced penile length after prostate cancer treatment has been associated with greater treatment regret \[86\]. There are currently no known ways to mitigate this side effect.

### 3.7. Fatigue

Fatigue is a noticeable side effect of ADT for many men. The main strategy to reduce fatigue is exercise, and a number of randomized trials reported that exercise significantly reduced fatigue for men on ADT \[87\]. One randomized trial of 57 men on ADT found that a program of resistance
and aerobic exercise for 12 wk led to less fatigue ($p = 0.021$) [88], and another trial of 12 wk of resistance exercise three times a week in 155 men had similar results ($p < 0.001$) [40]. These results were supported by a third trial of 12 wk of aerobic and resistance exercise plus dietary advice versus usual care in which fatigue was again significantly reduced ($p = 0.002$) [89]. A trend toward improved fatigue was seen with 16 wk of individualized aerobic and resistance training [90]; this concept is also being tested in another ongoing study [91].

3.8. Hot flashes

Vasomotor flushing can be a significant impediment to QOL for men on ADT. A randomized trial of 214 men on ADT who received either placebo or 4 wk of 300, 600, or 900 mg daily of gabapentin found that only the highest dose of gabapentin reduced hot-flash frequencies compared with placebo ($p = 0.02$) [92]. Another trial randomized 311 men on ADT with hot flashes to either venlafaxine 75 mg daily, medroxyprogesterone acetate 20 mg daily, or cyproterone acetate 100 mg daily. After 1 mo, hot-flash scores decreased significantly with each treatment (−47.2% for venlafaxine, −94.5% for cyproterone, −83.7% for medroxyprogesterone; all $p < 0.001$ from baseline). Pairwise comparisons showed that the decreases in the cyproterone and medroxyprogesterone groups were significantly larger than the decreases in the venlafaxine group ($p < 0.001$). Because cyproterone is a prostate cancer treatment that could interfere with ADT, the authors suggest that medroxyprogesterone should be considered the standard treatment for ADT-induced hot flashes [93].

Alternative remedies have also been tested to try to reduce hot flashes. Soy protein was tested in a randomized trial of 33 men undergoing ADT but showed no improvement in vasomotor symptoms [94]. A $2 \times 2$ randomized trial of soy protein, venlafaxine, and a combination of the two found no reduction in hot flashes for either soy protein or venlafaxine compared with placebo [95]. Acupuncture has also been evaluated. A systematic review identified six studies of acupuncture for hot flashes, of which none were randomized and placebo controlled [96]. One prospective study of 60 men receiving auricular acupuncture weekly for 10 wk found that 95% of men experienced a decrease in symptoms [97]. A more recent study of 14 men found that acupuncture decreased hot-flash scores by 89.2% from 37.41 to 4.05 ($p = 0.0078$) at 6 wk [98]. These results must be considered tentative, and randomized placebo-controlled trials are needed to further evaluate the role of acupuncture for ADT-related hot flashes.

3.9. Cognition

Hypogonadism has been linked to cognitive declines in several studies including a cohort study from the Baltimore Longitudinal Study of Aging that found that among 407 men 50–91 yr of age at baseline and followed for 10 yr, hypogonadism was associated with poorer memory and visuospatial performance and a faster rate of decline in visual memory [99]. The exact impact of ADT on cognition remains a matter of ongoing study. The strongest data for a deleterious effect come from a single trial by Green et al. [100] in 2002 that randomized 82 men to an LHRH agonist, cyproterone acetate, or observation. They found that half the men assigned to therapy had a clinically significant decline in one or more cognitive tests at 6 mo compared with none of the men in the observation group. However, these results were not confirmed in the largest prospective study on the issue conducted by Alibhai et al. that enrolled 241 men with prostate cancer treated with ADT, prostate cancer and no ADT, or no prostate cancer. After adjusting for age and education, the study found no consistent effect of ADT on 14 different cognitive tests across 8 cognitive domains [101]. The study did find individual tests of immediate memory ($p = 0.029$), working memory ($p = 0.031$), and visuospatial ability ($p = 0.034$) that were worse in the ADT group at 12 mo but were not confirmed by other tests looking at the same domains. Nevertheless, given the potential that ADT could have some subtle influences on cognition, an ongoing randomized trial is evaluating the impact of exercise on reducing the cognitive and psychosocial side effects of ADT [102].

3.10. Anemia

Anemia is a very common side effect of patients receiving ADT [103]. For example, one prospective study of orchietomy found that 78% of men had a median decrease in hemoglobin of at least 1 g/dl [104], another study of 110 men who received ADT prior to radiation found that by 3 mo, average hemoglobin had dropped from 14.8 to 12.9 g/dl [105], and a third study of 250 men with a mean hemoglobin of 14.1 g/l found that men on ADT had an 0.89 g/dl drop by 12 mo compared with a 0.056 g/dl hemoglobin drop for prostate cancer controls [106]. For most patients this leads to a mild asymptomatic normochromic and normocytic anemia, and the degree to which this anemia contributes to fatigue or other QOL decrements remains unknown [103]. Treatment with erythropoietin would not be considered except for symptomatic patients. Interestingly, some studies have suggested that larger declines in hemoglobin due to ADT are associated with poorer prostate-specific outcomes [105,107], but whether treating this anemia could improve prostate cancer–specific outcomes remains unknown.

4. Conclusions

Although ADT can improve survival for men in certain settings, ADT also has a variety of potential harms. Methods of preventing bone loss are now well established, and exercise may prove to be a good way to reduce the body composition changes and fatigue from ADT, but these results will require further confirmation. For several other side effects, there are presently no effective mitigating interventions. At this point, the only certain way to prevent many of the adverse effects is to avoid using ADT for situations in which it is not warranted, such as with radiation
for low-risk disease [2], as monotherapy for localized disease [108], or as neoadjuvant therapy before prostatectomy [109]. For situations in which ADT is necessary, clinicians should intervene to reduce the harms of ADT.

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