

# Cardiovascular effects of hormone therapy for prostate cancer

Jason F Lester<sup>1</sup>  
Malcolm D Mason<sup>1,2</sup>

<sup>1</sup>Velindre Hospital, Whitchurch,

<sup>2</sup>School of Medicine, Cardiff

University, Heath Park, Cardiff, UK

**Abstract:** Androgen deprivation therapy (ADT) has been the mainstay of treatment for advanced prostate cancer for decades, and has been shown to control disease and improve symptoms. In addition, for men with high-risk localized or locally advanced prostate cancer, short-course ADT in combination with radiotherapy improves survival. There is evidence that ADT increases cardiovascular risk, particularly in men with preexisting cardiovascular disease. This increased risk may apply even with short-course ADT. In an individual patient, the benefits of ADT should be balanced against the risk, and patients who require ADT should have risk factors for cardiovascular disease optimized. There is some evidence to suggest that more contemporary methods of delivering ADT may reduce cardiovascular risk.

**Keywords:** androgen deprivation therapy, testosterone, cardiovascular risk, hypercoagulability, prostate cancer patients, dihydrotestosterone, androgen receptor

## Basic physiology

One of the key drivers of prostate cancer is the androgen testosterone. The production of testosterone primarily occurs in the testes, and this process is regulated by luteinizing hormone (LH) produced by the anterior pituitary gland. In turn, the production of LH is regulated by gonadotropin-releasing hormone (GnRH) (also called luteinizing hormone-releasing hormone [LHRH]), produced by the hypothalamus. Testosterone acts as a “negative feedback” to maintain physiological levels; high levels of testosterone will lead to inhibition of GnRH and LH production, reducing subsequent testosterone production.

Manipulating the hypothalamic–pituitary–gonadal axis to achieve castrate levels of testosterone is a key therapeutic intervention in men with advanced prostate cancer. However, the testes produce only 90% of the testosterone present in the adult male. The remaining 10% is derived from adrenal steroid synthesis. The adrenal glands secrete the weak androgens dehydroepiandrosterone and androstenedione that can be converted into testosterone in peripheral tissues and the prostate gland. Newer hormone treatments have been developed to target the production of androgen precursors in the adrenal gland, and have shown to be effective in the treatment of advanced prostate cancer.

Despite the undoubted benefit of lowering testosterone in men with advanced prostate cancer, there may be unwanted side effects as these hormones have other physiological roles in the body. The potential consequences of androgen deprivation therapy (ADT) are described in this review.

Correspondence: Jason F Lester  
Velindre Hospital, Whitchurch, Cardiff,  
CF14 2TL, UK

Email Jason.lester2@wales.nhs.uk

## Introduction: an historical background

In 1941, Huggins et al published their historic studies, which heralded the age of hormone therapy (perhaps more correctly referred to as ADT) for human prostate cancer.<sup>1,2</sup> In 2010, a science advisory was jointly published by the American Heart Association, the American Cancer Society, and the American Urological Association, highlighting the link between ADT for prostate cancer and cardiovascular risks.<sup>3</sup> It seems fair to say that there is now a high level of awareness on the part of cancer physicians and surgeons of the detrimental effects of ADT in terms of cardiovascular risk, but this is now expressed as a general feeling that ADT is bad for men, and, as others have noted, patients who would benefit from ADT might be under-treated if a careful balance is not maintained.<sup>4</sup> Before addressing the – now high-profile – complications of ADT, let us begin with a clear and unequivocal statement of its benefits. For metastatic prostate cancer ADT, usually using orchidectomy or LHRH agonists, is the mainstay of treatment. In addition, ADT is frequently used in combination with radiotherapy, and the evidence is quite unequivocal that ADT improves survival when given in addition to radiotherapy for high-risk disease.<sup>5–8</sup> In addition, it might improve cancer outcomes when given in addition to radiotherapy for intermediate-risk prostate cancer.<sup>9</sup>

It is informative to look at the evolution of hormone therapy for prostate cancer when discussing cardiovascular risk with ADT. The Veterans Administration Cooperative Urologic Research Group (VACURG) carried out a series of trials in the 1960s looking at treating all stages of prostate cancer. The first, and arguably most important trial randomized patients with stage I and II prostate cancer to radical prostatectomy and either diethylstilbestrol (DES) or placebo, and stage III and IV patients to placebo, DES 5 mg, orchidectomy and DES 5 mg or orchidectomy and placebo.<sup>10</sup> In stage III patients, there was an excess of cancer deaths in the arms treated with placebo but quite unexpectedly, an excess of cardiovascular deaths in the DES arms. A similar pattern was also seen in the stage I and II patients and importantly, there were more total deaths in the DES arms of the trial. A retrospective review of patients' medical records suggested a history of cardiovascular disease was a predisposing factor to early death.<sup>11</sup> Patients randomized to placebo did, however, derive significant benefit when given DES later on for symptom control. The excess of cardiovascular deaths in the first VACURG trial did not appear to be driven by androgen deprivation – patients randomized to orchidectomy did not appear to be at greater

risk. One criticism of the first VACURG trial was the high dose of DES used. The second VACURG trial attempted to address this by using three doses of DES (0.2 mg, 1 mg, and 5 mg). In addition, cardiovascular data were also collected prospectively, to try and understand the surprising findings from the first trial showing excess cardiovascular deaths in the DES arms.<sup>12</sup> The second trial showed that 0.2 mg DES was ineffective, and that the 1 mg dose was as effective as the 5 mg dose in controlling prostate cancer, but did not seem to be associated with excess risk of cardiovascular death. Tellingly, the placebo arms in stage III patients were still superior to all DES arms with regard to survival and this was thought due to excess noncancer deaths in those taking DES. Taking data from the VACURG trials into consideration, it was recommended that 1 mg DES should be used in preference to 5 mg but to withhold treatment until required.<sup>13</sup>

In the following decades, an increasing knowledge of the androgen pathway led to the development of new hormone treatments to either inhibit androgen production or block the effect of androgen on target cells.<sup>14–18</sup> LHRH agonists have been tested in a large number of randomized trials that compared the various approaches to androgen-ablative therapies (such as orchidectomy, estrogen administration, and LHRH agonists). The received wisdom from these studies is that all approaches are equally effective, reducing tumor growth in 70%–80% of symptomatic patients, though the robustness of this conclusion is debatable.<sup>19</sup> On the basis of these studies, LHRH agonists have become the preferred method for androgen-ablative therapy. LHRH antagonists, which directly inhibit the LHRH receptor, have also been developed as prostate cancer therapeutics.<sup>20</sup> These antagonists were initially developed for contraceptive purposes. Several of these antagonists have been tested in clinical trials as treatment for men with advanced prostate cancer. Preliminary data indicate that these agents are as effective as the LHRH agonists in lowering serum testosterone, but do not cause the testosterone flare that is synonymous with the LHRH agonists.

## Testosterone and cardiovascular risk

To look at the potential effects of ADT on cardiovascular risk, it is useful to look at the effects of testosterone on the cardiovascular system. Herring et al have carried out a comprehensive basic science review on this subject, and it seems that testosterone might have both beneficial and harmful effects.<sup>21</sup> Testosterone has been shown to exhibit potential antiarrhythmic properties, and in animal models,

reduces myocardial infarct size by modulating the myocardial K (adenosine triphosphate [ATP]) channel, enhancing vasodilation, attenuating atherosclerosis, and improving lipid metabolism. There are, however, studies that found testosterone may cause vasoconstriction, inflammation, and result in death signaling. These findings suggest a complex interaction between the cardiovascular system and testosterone.

The population-based evidence on the effect of testosterone on cardiovascular risk is also very variable in its findings, and testosterone may not be the only androgen involved. In men, approximately 5% of testosterone undergoes 5 $\alpha$ -reduction to form the more potent androgen dihydrotestosterone (DHT). This enzymatic conversion is carried out in the prostate, testes, hair follicles, and adrenal glands. DHT has two to three times greater androgen receptor (AR) affinity than testosterone, and given its potency, several studies have looked at the effect of both testosterone and DHT on cardiovascular risk. Yeap et al measured plasma total testosterone and DHT in early morning samples from 3,690 community-dwelling men aged 70–89 years.<sup>22</sup> Higher testosterone or DHT was associated with a lower incidence of stroke, but not of myocardial infarction.

In a longitudinal cohort study, Shores et al evaluated whether total testosterone, calculated free testosterone, DHT, and calculated free DHT were associated with cardiovascular disease and mortality in 1,032 men in the Cardiovascular Health Study who were free of cardiovascular disease at the time of the study.<sup>23</sup> In models adjusted for cardiovascular risk factors, total testosterone and calculated free testosterone were not associated with incident cardiovascular disease or all-cause mortality, whereas DHT and calculated free DHT were so, in a nonlinear fashion, with the lowest incidence of stroke associated with a total DHT concentration just above the mean, at approximately 65–70 mg/mL, while free DHT had an inverse correlation with risk.

Shores et al also looked at whether testosterone or DHT was associated with incident ischemic stroke in the same cohort of men.<sup>24</sup> Total testosterone and free testosterone were not significantly associated with stroke risk, while DHT had a nonlinear association with incident stroke. The lowest risk of stroke was at DHT levels of 50–75 ng/dL, with a greater risk of stroke at DHT levels >75 ng/dL or <50 ng/dL. Thus, variable results have been reported in both basic science and population-based studies on the relationship between androgens on the cardiovascular system. Further studies are needed to better define this relationship and establish whether in fact there is an optimal androgen range associated with the least risk of adverse outcomes.

The metabolic syndrome is a cluster of the most dangerous risk factors for cardiovascular disease.<sup>25</sup> Patients with metabolic syndrome have a two-fold increase in cardiovascular disease risk.<sup>26</sup> The International Diabetes Federation defines patients as having the metabolic syndrome if they have central obesity plus two any of the following four factors:

- raised triglycerides;
- reduced high-density lipoprotein (HDL) cholesterol;
- raised blood pressure;
- raised fasting plasma glucose.

A low serum testosterone concentration predicts or is associated with the metabolic syndrome, and type 2 diabetes mellitus.<sup>27,28</sup> As might be expected, men with the metabolic syndrome and type 2 diabetes mellitus often have low testosterone levels.<sup>29</sup> It is worth noting though, that the mechanisms whereby a low testosterone level increases the risk of death may be complex. A prospective, population-based study of 794 men aged 50–91 years reported low testosterone was associated with an increase in mortality that was independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease.<sup>30</sup>

The link between low testosterone and increased cardiovascular risk has also been reported in observational studies. Brand et al conducted an individual participant data meta-analysis of 20 observational studies.<sup>31</sup> Mixed effects models were used to assess cross-sectional and prospective associations of total testosterone, sex hormone-binding globulin, and free testosterone with metabolic syndrome and its individual components. Men with low concentrations of total testosterone, sex hormone-binding globulin, and free testosterone were more likely to have metabolic syndrome compared to those having high sex hormone concentrations. The associations were independent of age and lifestyle factors. Interestingly, the association between total testosterone and metabolic syndrome was strongest in men with a body mass index (BMI) <25 kg/m<sup>2</sup>. The reason for this interaction is not clear, but the weaker association in overweight men suggests a dominant role for non-androgenic risk factors, or perhaps the emergence of relative androgen insensitivity with increasing BMI. In children, an inverse association between BMI and AR sensitivity has been reported, but no studies so far have explored this association in middle-aged and older men.<sup>32</sup>

Several trials have shown that elevating low testosterone levels may improve features of the metabolic syndrome and glycemic control, and hence modify cardiovascular risk factors. In a single blind, 52-week randomized clinical trial,

the effects of supervised diet and exercise with or without transdermal testosterone administration on components of the metabolic syndrome in hypogonadal men with the metabolic syndrome and newly diagnosed type 2 diabetes were assessed. Glycosylated hemoglobin, fasting plasma glucose, HDL cholesterol, triglyceride concentrations, and the waist circumference improved in both treatment groups after 52 weeks of treatment, but were significantly better in the testosterone-supplemented group.<sup>33</sup>

In a prospective, observational, long-term study, 181 obese (BMI  $\geq 30$  kg/m<sup>2</sup>) hypogonadal men (serum testosterone  $< 12.1$  nmol/L), with and without type 2 diabetes mellitus, were treated with testosterone over 5 years.<sup>34</sup> In the total study population, there was an improvement in all cardiovascular risk factors. Significant improvements were seen in lipid profile, blood pressure, fasting glucose, HbA<sub>1c</sub>, and liver function. In the diabetic subgroup, there were significant improvements in fasting glucose and HbA<sub>1c</sub> with comparatively greater decreases seen in the diabetic subgroup than in the general population.

Testosterone has been studied as a treatment for congestive heart failure (CHF). Three randomized placebo-controlled trials showed that testosterone therapy for men with CHF improved various functional CHF outcomes, such as exercise capacity, peak oxygen consumption, and New York Heart Association heart failure class, but did not improve left ventricular function.<sup>35–37</sup> Thus, studies show that testosterone for heart failure improves patient functional status, exercise capacity, and ventilatory efficiency, with most evidence showing an absence of changes in cardiac anatomy or left ventricular function. Therefore, the benefits are likely because of peripheral effects of testosterone, perhaps relating to testosterone's vasodilator effects, its effects on glucose metabolism, and its ability to improve skeletal muscle function. According to the muscle hypothesis, improvement in skeletal muscle function might improve cardiac function by neurohumoral, autonomic nervous system, or hemodynamic mechanisms, or because improvement in skeletal muscle physiology might result in a delay of muscle converting to anaerobic metabolism during exercise.

There are, however, studies that suggest a detrimental effect of testosterone on the cardiovascular system. A retrospective national cohort study of men with low testosterone levels who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011 showed that testosterone was associated with an increased risk of adverse events (all-cause mortality, myocardial infarction, or stroke).<sup>38</sup>

It is clear that there is a complex interaction between testosterone and the cardiovascular system. To complicate the picture further, ADT may result in men acquiring some but not all aspects of the metabolic syndrome, and some of the changes seen may be different. Smith et al carried out an open-label prospective study on 26 men with recurrent or locally advanced prostate cancer who were treated with leuprolide (LHRH agonist) for 12 months.<sup>39</sup> In this trial, in contrast to the metabolic syndrome, leuprolide increased subcutaneous fat mass, HDL cholesterol, and adiponectin, and did not alter the waist-to-hip ratio or blood pressure.

In summary, most animal models and population-based research strongly suggest a beneficial effect of testosterone on cardiovascular risk, but there are studies with conflicting results. Low serum testosterone is associated with the metabolic syndrome, but it is possible that the changes induced by ADT for prostate cancer are different from those seen in classical metabolic syndrome, making any estimation of cardiovascular risk from ADT more difficult.

## The role of the AR

Both testosterone and DHT bind to the AR to exert their physiological functions.<sup>40</sup> The androgen-activated AR regulates the transcription of a variety of target genes through the interaction with different coregulators, forming a complex signaling network. Yu et al have studied the molecular aspects of mechanisms linking ADT to the metabolic syndrome using AR-knockout (ARKO) mouse models.<sup>41</sup>

They found that global deletion of AR (GARKO) in male mice resulted in central obesity in middle age, and was associated with elevations of circulating lipids, altered lipid metabolism in adipose tissue, and excessive deposition of lipids in non-adipose tissue, including liver and muscle.<sup>42</sup> GARKO mice also demonstrated fasting hyperglycemia, glucose intolerance, and insulin resistance – all risk factors for cardiovascular disease. The development of late-onset visceral obesity was also seen in several parallel studies using mouse models with genetic AR deletion.<sup>43,44</sup>

As expected, circulating testosterone levels were very low in GARKO male mice due to atrophic testes. Hence, the observed metabolic abnormalities may have been a result of low serum testosterone, rather than the absence of the active AR. To exclude this, the androgen DHT was given to male GARKO mice but was not able to reverse the metabolic abnormalities and insulin resistance.<sup>42</sup> These findings strongly suggest that nongenomic actions of androgen cannot directly account for the development of obesity and insulin resistance, and that the AR is critical

in mediating the effects of androgens to regulate glucose and lipid metabolism.

The molecular mechanisms by which AR signaling influences metabolism in men are likely to involve multiple factors and cross-talk among insulin target tissues. Cell type-specific AR targeting in mice with physiological testosterone levels has shown that the AR may have different roles in different tissues. Hepatic AR and neuronal AR signaling have been shown to be involved in cellular insulin signaling, regulating systemic insulin sensitivity, as well as glucose and lipid homeostasis.<sup>45,46</sup> In addition, AR signaling in myocytes has been shown to increase systemic oxidative metabolism by changing muscle fiber compositions in skeletal muscle.<sup>47</sup> It is likely then, that the AR is crucial in modulating the effect of androgens on metabolic homeostasis. In addition, these findings suggest promising targets for tissue-selective treatments to manage metabolic complications found in patients with prostate cancer during ADT.

## Hypercoagulability

It is well known that cancer patients are at a higher risk for thromboembolism compared to the normal population. Conventional coagulation tests have limited capacity in evaluating coagulability. In a pilot study, Toukh et al investigated whether the assessment of global hemostasis using thromboelastography and quantification of plasma procoagulant microparticles could determine the risk of adverse thrombotic events in 32 patients with prostate cancer compared to a control group with a negative prostate cancer biopsy.<sup>48</sup> Hypercoagulability was more marked in the prostate cancer patients compared to the control group, particularly in those with advanced disease on ADT. These initial results need larger confirmatory studies, but suggest that prostate cancer results in a hypercoagulable state, and ADT may exacerbate this state. This hypercoagulability may contribute to the excess noncancer mortality seen in patients with prostate cancer. It is known that higher serum levels of fibrinogen are associated with coronary artery disease and increased cardiovascular risk.<sup>49</sup> Ziaran et al looked at 97 patients with locally advanced prostate cancer and showed that after 12 months of ADT, patients had significantly higher fibrinogen in comparison with a control group, suggesting that the elevation of fibrinogen may contribute to increased cardiovascular risk in men on ADT for prostate cancer.<sup>50</sup>

It is likely that prostate cancer induces a hypercoagulable state, which may be exacerbated by ADT. This may in part explain the excess noncancer deaths seen in several prostate cancer studies and indeed, venous

thromboembolism is associated with excess mortality in prostate cancer patients.<sup>51</sup>

## Clinical data on risks of ADT in prostate cancer patients

The first definitive evidence of adverse cardiovascular effects associated with ADT for prostate cancer came from an analysis of data from the Surveillance, Epidemiology and End Results database.<sup>52</sup> In this study, a population of over 73,000 men with locoregional disease were analyzed for their risks of coronary heart disease, diabetes, myocardial infarction, and sudden cardiac death. The use of LHRH agonists was associated with a significantly increased risk of coronary heart disease, myocardial infarction, diabetes, and sudden cardiac death. In contrast, orchidectomy resulted in an increased risk of diabetes, but not of myocardial infarction. Other population-based studies have shown similar effects, and the major ones<sup>53–59</sup> have been summarized in a recent meta-analysis, combining data from over 295,000 men from the US, Scandinavia, and the UK.<sup>60</sup> With the caveats that, in two of the studies, hazard ratios had to be recalculated as they were not in the original publication, this meta-analysis shows a fairly consistent effect. For cardiovascular mortality, there was a significantly increased risk associated with ADT compared with other treatments (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.04–1.32). For cardiovascular disease, there was a trend toward a greater risk with ADT (HR 1.10, 95% CI 1.00–1.21). With the exception of one study,<sup>55</sup> the effect seems consistent. Other studies, not included in the meta-analysis, add to the weight of evidence that ADT is associated with all forms of cardiovascular disease.<sup>61,62</sup>

A study of patients with localized disease, being treated with radical prostatectomy, external beam radiotherapy, brachytherapy, or cryotherapy showed that patients receiving ADT had an increased risk of cardiovascular death.<sup>63</sup> Among patients 65 years or older treated with radical prostatectomy, the 5-year cumulative incidence of cardiovascular death was 5.5% (95% CI 1.2%–9.8%) in those who received ADT and 2.0% (95% CI 1.1%–3.0%) in those who did not. Among patients 65 years or older treated with external beam radiotherapy, brachytherapy, or cryotherapy, ADT use was associated with a higher cumulative incidence of death from cardiovascular causes, but the difference did not reach statistical significance. Patients in this study were only on ADT for a median of 4.1 months, suggesting that any adverse effect of ADT on cardiovascular risk happens early and may persist despite relatively short periods of androgen deprivation.

Despite the majority of published evidence supporting the association of ADT with cardiovascular risk, there is research that contradicts this finding. A meta-analysis of cardiovascular mortality in patients entered into randomized trials showed no significant differences in patients treated with or without ADT.<sup>64</sup> This might suggest that more fit patients (those most likely to be entered into randomized trials) are less at risk, and supports the view that those patients on ADT with preexisting cardiovascular disease may be at a greatest risk.

Much has been made of the heterogeneity evident between studies that hampers comparison and makes meta-analysis less robust, but given the number of variables it is hardly surprising that this should be the case. Several variables (eg, tumor stage, grade, comorbidities, type of ADT, duration of ADT, outcome measure) could all affect the estimation of risk.

## Differential effects with different forms of ADT

From data on the cardiovascular complications of hypogonadism, it might be expected that any agent that lowered serum testosterone levels would have similar effects per se. However, there is randomized trial and population-based data suggesting that different methods of achieving castrate levels of testosterone may confer different cardiovascular risks. In addition, not all agents reduce serum testosterone levels; antiandrogens act by competing with androgens for the binding site on the AR.

A Swedish randomized trial of 100 patients compared intramuscular and oral estrogens with orchidectomy, and concluded that the risks of a cardiovascular event were significantly lower in patients receiving an orchidectomy.<sup>65</sup> Increasing the dose of estrogen achieved parity with orchidectomy in terms of disease control, but also resulted in an increase in cardiovascular complications.<sup>66</sup> A much larger Finnish randomized trial of over 400 patients reported 2% cardiovascular deaths in patients undergoing orchidectomy compared to 6% in patients receiving intravenous polyestradiol phosphate. Increasing the dose of estrogen achieved parity with orchidectomy in terms of disease control, but also resulted in an increase in cardiovascular complications.<sup>66</sup> The route of administration may be important in relation to estrogen therapy. The PATCH trial randomized patients with locally advanced and metastatic prostate cancer to GnRH agonists or transdermal estrogen, and safety data have shown no difference in the incidence of cardiovascular events between the two arms.<sup>67</sup>

The VA carried out a population-based study of 37,443 men who were diagnosed with local or regional prostate cancer looking at the effects of different forms of ADT (orchidectomy, GnRH agonist therapy, combined GnRH agonist, and antiandrogen therapy), and antiandrogen monotherapy on cardiovascular disease.<sup>54</sup> Overall, 14,597 (39%) of the 37,443 patients were treated with ADT or antiandrogen monotherapy, and these men were compared to the remaining 61% of men who received no hormone manipulation. All forms of hormone therapy were associated with an increased risk of diabetes and cardiovascular disease including coronary heart disease, myocardial infarction, sudden cardiac death, and stroke. Higher risks of cardiac disease were seen with orchidectomy compared to GnRH agonist or antiandrogen monotherapy, but a smaller increased risk of diabetes for orchidectomy compared with GnRH agonists was observed. The addition of antiandrogens to GnRH agonists did not result in a further excess of cardiovascular complications, and overall, the lowest risk was seen in patients on antiandrogen monotherapy. A meta-analysis of population-based studies reported antiandrogens had no effect on cardiovascular risk, supporting the VA findings.<sup>60</sup>

An earlier study reported similar findings to the one described above. GnRH agonist use was associated with increased risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death. Men treated with orchidectomy were more likely to develop diabetes but not coronary heart disease, myocardial infarction, or sudden cardiac death.<sup>53</sup>

In a Canadian population-based cohort study, over 19,000 men aged 66 years or older with prostate cancer who were given continuous ADT for at least 6 months or who underwent bilateral orchidectomy were matched with men with prostate cancer who had never received ADT. ADT use was associated with an increased risk of diabetes but not with myocardial infarction or sudden cardiac death. An increasing duration of ADT was associated with an excess risk of diabetes but not cardiac outcomes.<sup>55</sup>

More recently, there has been great interest in the possibility that GnRH antagonists might be associated with lower risks of cardiovascular effects. In an experimental model, low-density lipoprotein knockout mice were treated with orchidectomy, GnRH agonists, or GnRH antagonists.<sup>68</sup> Mice treated with orchidectomy or with GnRH agonists developed more visceral fat, and larger atherosclerotic plaques than those treated with GnRH antagonists. Similar differences were also noted with fasting blood glucose and glucose tolerance tests.<sup>68</sup>

Clinical data from a randomized trial that compared the GnRH antagonist degarelix with the GnRH agonist leuprolide showed similar rates of cardiac arrhythmias, incident ischemic heart disease, cardiac failure, and stroke.<sup>69</sup> Similar results were seen when pooling six Phase II and III studies on the same agents.<sup>70</sup> On the other hand, a further analysis from the same pooled study database suggested that, for men with preexisting cardiovascular disease, the risks of a subsequent cardiovascular event or death were approximately half in men treated with degarelix compared with men treated with leuprolide.<sup>71</sup> This finding was from a post hoc analysis, however, and can only be regarded as suggestive, but it is noteworthy that it is concordant with the animal data.

In summary, it is extremely difficult to draw firm conclusions about the “safest” form of ADT from the data available; <1% of men in the VA studies were treated with orchidectomy, and it is difficult to extract comparable data from other observational studies. In historical trials, estrogens appear to confer a significantly higher risk than orchidectomy or more contemporary forms of pharmacological ADT, but this risk may be reduced by transdermal administration. There are some data to suggest the GnRH antagonist degarelix may have a more favorable cardiovascular risk profile than the GnRH agonists, but this observation needs prospective validation.

## Identification of patients at risk

An obvious question would be whether patients with preexisting cardiovascular disease are at more risk following ADT, and the extent to which this modifies the risk in patients without such risk factors. Data from the Scandinavian randomized trial of intramuscular estrogen showed that as many as 33% of patients with a history of pretreatment cardiovascular disease had a subsequent cardiovascular event during estrogen therapy.<sup>72</sup> Patients with no preexisting cardiovascular disease were still at moderate risk during estrogen therapy, raising the argument that the excess risks of ADT are not confined to men with preexisting cardiovascular disease.

Retrospective data from 1,378 patients with a previous history of myocardial infarction or CHF who were undergoing brachytherapy with or without external beam radiotherapy showed that the use of ADT was associated with increased rates of death from any cause.<sup>73</sup> Importantly, this was the case even in men with high-risk prostate cancer. However, due to the retrospective nature of the data, it was not possible to further interrogate the cause of death. It seems reasonable to conclude that care should be taken in advocating the use of ADT in men with preexisting cardiovascular disease,

weighing up their competing risks from prostate cancer and from the complications of ADT.

The effect of ADT on cardiovascular risk may occur early on during therapy and persist even in patients on short-term ADT.<sup>63</sup> Further prospective studies are needed to identify the risk factors that predict cardiovascular morbidity and mortality to better define the groups of patients who may benefit from intervention to modify risk. In the interim, in men undergoing ADT, the monitoring and management of cardiovascular risk factors (hyperglycemia, hyperlipidemia, hypertension, and obesity) should be seen as an integral part of patient management.<sup>74</sup>

## Therapeutic and other interventions to ameliorate toxicity

Given the importance of diet and exercise in the prevention and ongoing management of cardiovascular disease, it is obvious that these interventions should be investigated in the context of ADT for prostate cancer. A systematic review of exercise interventions identified ten studies that suggest some benefits to an exercise program but variable effects on cardiovascular risk factors. Only two randomized trials looked at this important facet; one showed a reduction in C-reactive protein after 12 weeks of exercise, but no differences in systolic blood pressure, blood glucose, or lipids was demonstrated.<sup>75</sup> A further prospective randomized trial of dietary and exercise intervention is underway,<sup>76</sup> but while these important studies may yield benefits to prostate cancer patients, they are unlikely to be able to demonstrate whether such interventions are capable of ameliorating the risks associated with ADT.<sup>74-77</sup> What is clear is that in the general population, cardiac rehabilitation programs that primarily utilize exercise produce compelling and consistent clinical results in men with preexisting cardiovascular disease. Randomized trials have shown that cardiac rehabilitation reduces the probability of suffering additional cardiac events and is associated with a broad range of benefits, including reduced mortality. It is reasonable to assume that similar programs may benefit men on ADT.

A recent randomized trial compared no interventions, with a combination of metformin, diet, and exercise in 40 men starting ADT.<sup>78</sup> Patients in the intervention arm showed significant improvements in abdominal girth, systolic blood pressure, and BMI, though the relative contribution of the individual components could not be assessed.

Finally, the question of whether transdermal estrogens might be a viable treatment option if the transdermal route is able to abrogate the cardiovascular effects associated with

oral estrogens is being evaluated in the UK Medical Research Council “PATCH” study, which randomizes men starting long-term hormone therapy to either transdermal estrogen patches, or to “conventional” ADT with GnRH agonists. The results from the safety analysis of this study are encouraging, with no differences in the incidence of cardiovascular events between the two arms.<sup>67</sup>

## Conclusion

It is clear that overall, the use of ADT in the treatment of prostate cancer is associated with an increased risk of cardiovascular complications. However, for the most part the excess risk is modest though significant, and must be weighed against the equally clear benefits of ADT in appropriate patients. In the future, better identification of patients at risk – particularly those with a previous history of myocardial infarction or CHF – and perhaps more tailoring of the form and duration of ADT in an individual patient, might ameliorate the risk. However, awareness and management of the risks of cardiovascular complications must not result in the under-use of ADT, which for all its shortcomings is still a supremely important modality nearly 74 years after Charles Huggins’ original publication.

## Disclosure

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