Managing cardiovascular risk in high-risk prostate cancer

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Men living with prostate cancer have a high rate of cardiovascular events, and many of them have risk factors that would be an indication for primary prevention under current guidance. These risks may be increased by certain androgen deprivation therapies. This article reports the outcome of a consensus meeting at which the authors discussed these issues. They suggest a simple assessment tool for use with prostate cancer patients to rapidly assess cardiovascular risk and allow appropriate risk-management strategies to be implemented.

Improved diagnosis, therapeutic advances, increased treatment in earlier-stage disease and better disease management have all contributed to a rapid increase in the numbers of men receiving androgen deprivation therapy (ADT) for prostate cancer (PC). Although the therapeutic benefits of ADT include improved survival rates, symptom palliation and delayed cancer progression, ADT is not without adverse events and complications, including decreased insulin sensitivity, adverse changes in lipid profiles, cardiovascular disease (CVD), effects on cognitive function, skeletal events, fatigue, loss of muscle mass, muscular pain, general pain, lower urinary tract symptoms and reduced quality of life.

PROSTATE CANCER AND CV RISK
Studies have shown increased cardiovascular (CV) mortality in men with PC, compared with an age-matched male population, with CVD being the second most common cause of death in men with PC. PC patients with pre-existing CVD have an increased risk of CV death, compared with a population with matched CV risk, but without PC. Furthermore, increased relative risk of CVD has been demonstrated in PC patients, compared with an age-matched population. These
CV risks might be increased by ADT, suggesting that careful consideration of ADT modality is required before initiating treatment. However, ADT should not be withheld from men when indicated, as the priority should be optimal PC treatment.

**Rationale for ADT**

Androgens stimulate the growth of PC cells. Reducing serum testosterone to castration levels is the standard strategy to control the proliferation of hormone-dependent PC cells. Collectively, these techniques are known as ADT and form the mainstay of treatment for advanced PC. This approach can be supplemented by agents that block androgen receptors. ADT has been shown to improve overall survival in men with locally advanced PC treated with radiotherapy.

Surgical orchiectomy has largely been supplanted by gonadotrophin-releasing hormone (GnRH) agonist- or antagonist-based ADT. These agents bind to GnRH receptors in the anterior pituitary gland to induce castrate levels of testosterone in the body. Anti-androgens (AA), which block the binding of androgens to their receptors, may be used in addition to GnRH agonists to provide the rapid onset of maximum androgen blockade.

Unlike GnRH agonists, which initially stimulate receptors leading to receptor downregulation, GnRH antagonists block GnRH receptors with immediate onset, providing more rapid and sustained testosterone suppression, compared with GnRH agonists, without the initial agonist-associated testosterone surge.

**Testosterone Depletion and CV Risk**

Testosterone in the body promotes increased muscle mass and decreases total fat mass. Consequently, testosterone depletion via surgical or chemical castration leads to fat accumulation and muscle wasting. When adipose tissue mass increases, the secretion of adipokines (growth factors and cytokines) leads to metabolic changes, and the development of insulin resistance and CV risk, making it reasonable to consider visceral fat a de facto endocrine organ (Figure 1).

**ADT and CV Risk**

Pharmacological ADT with GnRH agonists is associated with metabolic syndrome, weight gain, raised triglycerides and cholesterol, reduced insulin sensitivity, and type 2 diabetes, all of which represent risk factors for CVD.

CVD driven by these adverse metabolic changes may occur within six months of initiation of ADT. In a study of >40,000 patients receiving ADT (AA 10,656, GnRH 26,959 and surgical orchiectomy 3747), CV risk was increased for GnRH agonists (hazard ratio [HR] 1.21, 95% CI 1.18–1.25) and orchiectomy (HR 1.16, 95% CI 1.08–1.25), compared with the comparison cohort. CV risk was highest during the first six months after starting ADT in men who had previously experienced two or more CV events (GnRH agonist: HR 1.91, 95% CI 1.66–2.20; AA: HR 1.60, 95% CI 1.24–2.06; orchiectomy: HR 1.79, 95% CI 1.16–2.76) versus the comparison cohort.

GnRH agonist-based ADT is associated with an increased risk of CV events, including arterial embolic or thrombotic events, haemorrhagic or ischaemic cerebrovascular conditions, myocardial infarction (MI), heart failure and other ischaemic heart disease. ADT may increase aortic stiffness, and arterial wall thickening and endothelial dysfunction, thereby promoting formation of atherosclerotic plaques. Testosterone removal is not the only mechanism by which GnRH agonists elevate CV risk. In fact, CV morbidities may be a drug class effect of GnRH agonists, and not solely due to castration.

**Mechanisms of ADT-Associated CVD**

Although testosterone suppression is in itself associated with increased CV risk, there is concern that GnRH agonist therapy might have a separate action to elevate CV risk via hitherto unidentified mechanisms. A putative mechanism, whereby an agent may precipitate an acute CV event, is atherosclerotic plaque rupture, the underlying cause of most acute CV events. Atherosclerotic plaques are widespread throughout the arterial tree and are generally considered to exist in a ‘stable’ state, characterised by a fibrous cap covering a lipid core containing thrombogenic macrophages. Plaque rupture involves transition from this stable state to a vulnerable state where the thin fibrous plaque is rendered unstable and ruptures, leading to thrombosis and vessel occlusion. Plaque transition to a vulnerable state and subsequent plaque rupture is thought to be mediated primarily via T-lymphocytes, which act to destabilise vulnerable fibrous caps by two mechanisms: the release of pro-inflammatory cytokines that prevent the collagen synthesis required for the maintenance of the fibrous cap, and the release of CD40L that stimulates collagenase secretion by macrophages, resulting in degradation of the fibrous cap.

It has long been known that T-lymphocytes express GnRH receptors that are sensitive to GnRH agonists and antagonists. Agonist-based ADT may lead to increased proliferation and activity of T-cells, with resulting fibrotic cap disruption and plaque instability. This proliferative effect is not seen with GnRH antagonists. It is feasible that differential effects seen in vitro between GnRH agonists and antagonists on T-lymphocyte function might result in the difference in CV events seen during the first year of ADT between antagonist and agonist in the pooled analysis of Albertsen et al.

**Controversies in ADT-Associated CVD**

The association between agonist-based ADT and increased CV events remains controversial. While increased risk of CVD in patients receiving ADT has been demonstrated in a number of observational studies, these findings have been
contradicted by various phase 3 randomized controlled trials (RCTs) and subsequent meta-analyses (Table 1). The observational evidence linking ADT to increased CV risk is substantial (Table 1). An observational study comparing 76,000 men with PC with the general Swedish male population showed an increased risk of incident and fatal CVD among all men.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details</th>
<th>Outcome</th>
<th>Supportive of CV in PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keating 2006</td>
<td>SEER database study (n=73,196)</td>
<td>GnRH agonist therapy may be associated with increased risk of CVD, compared with no GnRH therapy</td>
<td>✓</td>
</tr>
<tr>
<td>D'Amico 2007</td>
<td>Study of three RCTs (n=1372)</td>
<td>ADT was associated with earlier onset of fatal MIs in men ≥65 years old</td>
<td>✓</td>
</tr>
<tr>
<td>Efstathiou 2008</td>
<td>Phase 3 randomised trial of ADT added to radiotherapy (RT) (n=456)</td>
<td>Addition of ADT to RT was not associated with statistically significant increase in fatal cardiac events</td>
<td>✗</td>
</tr>
<tr>
<td>Van Hemelrijk 2010</td>
<td>Swedish registry study (n=76,600)</td>
<td>Increased relative risks of non-fatal and fatal CVD were found among all men with PC, especially those treated with endocrine therapy</td>
<td>✓</td>
</tr>
<tr>
<td>Keating 2010</td>
<td>Observational study (n=37,443)</td>
<td>GnRH agonist therapy may be associated with increased risk of CVD, compared with no GnRH therapy</td>
<td>✓</td>
</tr>
<tr>
<td>Nguyen 2011</td>
<td>Meta-analysis (n=41,411)</td>
<td>ADT was not associated with increased risk of CV death</td>
<td>✗</td>
</tr>
<tr>
<td>Keating 2013</td>
<td>Observational study (n=185,106)</td>
<td>In men with no comorbidities, ADT was associated with increased risk of MI, compared with no ADT</td>
<td>✓</td>
</tr>
<tr>
<td>Jespersen 2014</td>
<td>National registry study (n=31,571)</td>
<td>Chemical ADT (but not orchiectomy) was associated with increased risk of MI and stroke</td>
<td>✓</td>
</tr>
<tr>
<td>Albertsen 2014</td>
<td>Pooled data from six phase 3 prospective randomised trials (n=2328)</td>
<td>GnRH antagonists appear to halve the number of CV events, compared with agonists in men with pre-existing CVD</td>
<td>✓</td>
</tr>
<tr>
<td>Gandaglia 2014</td>
<td>SEER database study (n=140,474)</td>
<td>GnRH agonist use (but not orchiectomy) was associated with higher risk of coronary artery disease, acute MI and sudden cardiac death</td>
<td>✓</td>
</tr>
<tr>
<td>O'Farrell 2015</td>
<td>Swedish registry study (n=41,362)</td>
<td>CVD risk was increased in men on GnRH agonists, compared with the comparison cohort</td>
<td>✓</td>
</tr>
<tr>
<td>Bosco 2015</td>
<td>Meta-analysis of observational studies</td>
<td>Consistent evidence that ADT may increase CV risk</td>
<td>✓</td>
</tr>
<tr>
<td>Voog 2016</td>
<td>Hypothesis-generating retrospective analysis (n=1979) of men receiving RT and ADT</td>
<td>Short-course ADT was not associated with increased risk of CV mortality</td>
<td>✗</td>
</tr>
<tr>
<td>Kohutek 2016</td>
<td>Retrospective study (n=2211)</td>
<td>Patients receiving ADT at the time of RT exhibited significantly higher incidence of CV events than those not receiving AD</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 1. Association of CV risk with ADT in clinical trials and observational studies
with PC: standardised incidence ratios of MI for men without circulatory disease history were 1.40; 95% CI 1.31–1.49, 1.15; 95% CI 1.01–1.31, and 1.20; 95% CI 1.11–1.30 for men undergoing endocrine treatment, curative treatment and surveillance, respectively. Together with a number of other studies, these data prompted the US Food and Drug Administration (FDA) to request that GnRH agonists be labelled as increasing the risk of diabetes and CV events.

Against this, there is evidence from RCTs, from secondary analyses and from a meta-analysis that have failed to identify any increased risk. Confusingly, Jespersen’s nationwide cohort study of >30,000 men found an association between ADT and increased risk of MI and stroke. Meanwhile, an RCT reported that longer duration of ADT did not increase CV mortality in men with locally advanced PC. However, this latter study has been criticised because only a small proportion of men remained on ADT for a significant period. Additionally, a meta-analysis of eight RCTs showed no significant increase in CV risk with agonist-based ADT versus no ADT (255/2200 versus 252/1941 events; incidence 11.0%; 95% CI 8.3%–14.5% versus 11.2%; 95% CI 8.3%–15.0%, relative risk 0.93; 95% CI 0.79–1.10; p=0.41). Once again, methodological flaws mean that the data are not conclusive; there were participants in the control group receiving ADT, and in the intervention group the median duration of ADT was only six months.

There are many potential reasons why these RCTs may have shown different results from observational studies, including the RCTs enrolling younger patients with less comorbidity and lower risk of CV events, while excluding patients with comorbidities and potentially less healthy lifestyles. Furthermore, non-fatal CV events are frequently under-reported in oncological RCTs, despite their significant impact on quality of life. Unfortunately, many of these studies did not stratify patients by baseline CV risk, and it appears that the association of ADT with cardiac-specific mortality occurs predominantly in men with a history of CVD.5

While the evidence linking CV risk with long-term ADT is generally considered to weigh in favour of ADT contributing the increased CV risk, the question of a difference between agonist and antagonist therapy is perhaps more contentious. Jespersen et al have reported an increased risk of CV events in men treated with GnRH agonists compared with orchiectomy in a registry-based study. Albertsen’s pooled analysis of six phase 3 RCTs compared GnRH antagonist- versus GnRH agonist-based ADT. In the total patient population there was a 40% reduction in relative risk of a CV event or death in patients treated with a GnRH antagonist, compared with those treated with an agonist (HR 0.60; 95% CI 0.41–0.87; p=0.008). In patients with pre-existing CVD at baseline, there was a 56% relative risk reduction of a CV event or death in patients treated with an antagonist, compared with patients treated with an agonist (HR 0.44; 95% CI 0.26–0.74; p=0.002). Although this post hoc analysis should be interpreted as hypothesis generating, it concluded that, compared with GnRH agonists, GnRH antagonists appear to halve the number of CV events.

Regardless of the mode of ADT administered, CV risk at initiation of treatment appears to be correlated with the degree of elevation of risk during ADT. Thus a strong case for CV risk assessment when ADT is being considered can be made and should be taken into account before deciding when and what type of ADT to administer.

**CV RISK REDUCTION IN THE PC TREATMENT PATHWAY**

Patients with PC represent a cohort in whom CV risk is higher than in the general population. Studies such as the Albertsen pooled trial reveal a population where approximately one third of patients have pre-existing CVD. Furthermore, CVD is the most common cause of death in men with PC who do not die of advanced PC. There is, therefore, a compelling argument that CV risk assessment should be carried out and risk-reduction measures implemented as standard when initiating ADT. Unfortunately, NHS data from 2013 to 2015 show that, in the UK, only 23% of the eligible population were offered an NHS Health Check. The clear need for improvement in primary prevention in the general population implies a significant unmet need for CV risk assessment in men, including those with PC.

CV risk assessment and management should be a consideration at all stages of the PC patient journey. As most PC patients first present to primary care, ideally GPs should carry out CV assessment and communicate their findings to the consultant urologist. Similarly, urology/ oncology nurses should complete CV assessments when patients are referred to the urologist or oncologist. Urologists and oncologists should also be aware of the importance of assessing CV risk and considering CV management as part of the patient’s treatment.

However, it is imperative that any CV risk assessment or management should not be a barrier to the initiation of ADT for advanced hormone-dependent PC. CV assessment should be simple and achievable within the limited resources of a typical GP surgery. A simple CV risk gradient tick-box assessment is proposed, whereby CV risk can be rapidly assessed and appropriate CV risk management strategies implemented (Table 2).

Once increased CV risk has been identified, patients should be offered guideline-based primary or secondary prevention treatment with medication and other risk-reduction strategies alongside the appropriate ADT modality. Interventions may include statins, antihypertensive agents, anticoagulants,
metformin for blood glucose control, antiplatelet agents, and behavioural changes including diet, activity/exercise and smoking cessation. GPs and specialist nurses should refer patients for professional support with lifestyle interventions. Such interventions have demonstrated improved quality of life and reduced fatigue in cancer patients, and might also improve endothelial function and reduce CV risk.

**CONCLUSIONS**

ADT is now the standard of care in patients with advanced PC; however, several studies suggest that ADT adversely affects traditional CV risk factors and is associated with an increased risk of CV events. Furthermore, there is evidence for the increased incidence of CV events in PC patients receiving GnRH agonist-based ADT, which is not seen with antagonist-based ADT.

Given the patient demographics of PC, as many as 30% of men with advanced PC are likely to be at high risk of a CV event – making CV risk a key factor in assessing patients for the optimal ADT modality. Therefore, a multidisciplinary change in clinical behaviour throughout the patient pathway is required to ensure that all patients with PC are assessed for CV risk and, where appropriate, CV management measures are introduced at ADT commencement. Such actions will ultimately save lives and reduce the overall burden placed on health services.

**Declaration of interests**

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### Table 2. Cardiovascular risk gradient tick-box assessment

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Description</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest risk for CV events</strong></td>
<td>Established CVD, MI (heart attack), angina, stroke, transient ischaemic attack, peripheral vascular disease, diabetes mellitus</td>
<td>Lifestyle advice, risk factor management and drug therapies in accordance with NICE guidance* (<a href="http://www.nice.org.uk/guidance/cg181">www.nice.org.uk/guidance/cg181</a>) Goal: Optimise lipid, glucose, blood pressure and weight management, smoking cessation</td>
</tr>
<tr>
<td><strong>Elevated risk for CV events</strong></td>
<td>All other patients &gt;40 years† Men &lt;40 years with familial hypercholesterolaemia</td>
<td>QRISK2 10-year CV risk assessment&lt;br&gt; If risk &gt;10%, patients should be offered lipid-lowering treatment with atorvastatin 20mg daily&lt;br&gt; → 43% reduction in low-density lipoprotein&lt;br&gt; → 38% relative-risk reduction in heart attack or stroke over the next 10 years</td>
</tr>
<tr>
<td><strong>Lower risk</strong></td>
<td>Patients ≤40 years†† Patients &gt;40 years with QRISK2 10-year risk &lt;10%</td>
<td>General lifestyle advice&lt;br&gt; Recommend home weight monitoring and reassess QRISK2 annually if long-term ADT therapy</td>
</tr>
</tbody>
</table>

*All patients with established CVD or diabetes should have received evidence-based prevention/rehabilitation programmes addressing lifestyle, risk-factor management and adherence to drug therapies in accordance with NICE guidance: 'Cardiovascular disease: risk assessment and reduction, including lipid modification', Clinical Guideline 181, 18 July 2014; www.nice.org.uk/guidance/cg181.

† Other patients >40 years should have their 10-year risk of a CVD event estimated using QRISK2. Those with a risk >10% should be offered lipid-lowering treatment (atorvastatin 20mg nocte). This is associated with a 43% reduction in low-density lipoprotein and a 38% reduction in the risk of a heart attack or stroke over the next 10 years.

†† Excludes patients aged <40 years with familial hypercholesterolaemia.

**REFERENCES**


