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Short title: Mechanisms of cardiovascular risk with ADT

Abstract

Androgen deprivation therapy (ADT) is frequently used for the treatment of advanced prostate cancer. ADT is associated with numerous side effects related to its mode of action, namely the suppression of testosterone to castrate levels. Recently, several large retrospective studies have also reported an increased risk of diabetes and cardiovascular disease in men receiving ADT, although these risks have not been confirmed by prospective randomized trials. We review the literature to consider the risk of cardiovascular disease with different forms of ADT and examine in detail potential mechanisms by which any such risk could be mediated. Mechanisms discussed include the metabolic syndrome resulting from low testosterone and the potential roles of testosterone flare, gonadotropin releasing hormone receptors outside of the pituitary gland and altered levels of follicle-stimulating hormone. Finally, the clinical implications for men prescribed ADT for the treatment of advanced prostate cancer are considered.

Keywords: Androgen deprivation therapy; cardiovascular; prostate cancer

1. Introduction

Androgen deprivation therapy (ADT) is the foundation of medical treatment for advanced prostate cancer (PCa). The traditional method of ADT suppresses testosterone production by removing the testes, the primary organ of testosterone production, although nowadays this is most commonly achieved via disruption of the hypothalamic-pituitary-testicular axis. However, ADT is associated with many side effects including hot flashes, low libido, erectile dysfunction and decreased bone mineral density [1]. A further series of side effects include decreased lean body mass, increased body fat, dyslipidemia, hyperglycemia and insulin resistance [2, 3]. These changes in body homeostasis resulting from ADT may be associated with an increased risk of diabetes and cardiovascular disease (CVD) [4, 5], and are similar to those observed in subjects with metabolic syndrome. This is currently an area of active research.

1.1 CVD risk in patients receiving ADT for PCa

The risk of CVD may be increased in men having undergone bilateral orchiectomy [6-8], but the data are inconsistent [9, 10], possibly because of the relatively small sample sizes in the various reports. The original oral ADT modality using estrogens such as diethylstilbestrol has been discontinued as primary therapy because of the association with an increased risk of cardiovascular (CV) morbidity [11, 12] with one study showing that, despite a reduction in PCa-related death with estrogen treatment, overall survival was reduced due to the increase in deaths from CVD [11]. Ongoing studies of cutaneous estrogen patches have recently shown estrogens to be much safer, with the added potential benefit of reduced disruption of glucose and lipid metabolism [13], but until larger scale studies of these and other alternative approaches report, gonadotropin-releasing hormone (GnRH) agonists remain the most popular therapeutic choice for primary ADT. GnRH agonists, such as leuprolide and goserelin, produce a decline in testosterone after an initial testosterone surge in the first 1–3 weeks of therapy [14]. They are highly effective in suppressing circulating testosterone levels.

The use of GnRH analogs and their influence on CV toxicity remains controversial. Epidemiological and population-based studies have found that their use, with or without antiandrogens, is associated with increased CV risk [6, 7, 9, 10, 15-18] with, for example, an increased hazard ratio (HR) compared to men not receiving GnRH agonists of 1.11 to 1.47 for myocardial infarction and 1.18 to 1.27 for stroke. A summary of outcomes from all large population-based observational studies comparing the risk of CV events with ADT versus no ADT treatment in men with PCa is shown in Table 1. Not all observational studies found an increased risk of CV events with ADT [19]. Recently, two meta-analyses of population-based observational studies have been published. Zhao et al. analyzed seven studies comparing men treated with or without ADT and found that CVD (HR = 1.19; 95% CI 1.04–1.36) and CV mortality (HR = 1.36; 95% CI 1.10–1.64) were significantly increased with GnRH agonist treatment compared with controls [20]. The meta-analysis reported by Bosco et al. comprised eight observational studies, four of which were included in the analysis by Zhao et al. They report a significantly increased relative risk (RR) for non-fatal CVD with a GnRH agonist compared with men not treated with ADT (1.38; 95% CI 1.29–1.48) and an especially strong association was noted with GnRH agonist use and nonfatal or fatal myocardial infarction (RR=1.57; 95% CI 1.26–1.94) [21].

In contrast, results from randomized clinical trials reported no increase in CV risk with GnRH agonists [22-24]. This apparent discrepancy in CV outcomes may be accounted for by a number of factors, including selection bias in men offered ADT, statistical approaches that did not account for competing risks, a lack of sensitivity in determining CVD or unmeasured confounding factors. A meta-analysis of over 4000 patients from eight randomized clinical trials also found no added risk of CV mortality in randomized studies of ADT with a GnRH agonist versus no ADT with incidences of 11.0% and 11.2%, respectively (RR=0.93, p=0.041) [25]. Any impact of ADT on CV morbidity was not assessed in this study. The authors did note that an early increase in CV mortality could be

Table 1. Observational studies evaluating the association between GnRH agonists and CV outcomes in men with PCa

Study	Database (Years included)	Population	Control group	ADT type	Outcome	Adjusted HR (95% CI)[a]
Keating 2006 [9]	SEER (1992–1999)	73,196 men with locoregional PCa	No ADT	GnRH agonist and/or AA	CHD MI SCD	1.16 (1.10–1.21) 1.11 (1.01–1.21) 1.16 (1.05–1.27)
Tsai 2007 [15]	US CaPSURE (1995–2004)	4,892 men with localised PCa	No ADT	GnRH agonist and/or AA	CV mortality with RP CV mortality with EBRT, BT or CT	2.6 (1.4–1.7) 1.2 (0.8–1.9)
Saigal 2007 [16]	SEER (1992–1996)	22,816 men with PCa	No ADT	Any medical ADT	CV morbidity	1.20 (1.15–1.26)
Alibhai 2009 [19]	Ontario Cancer Registry (1995-2005)	19,079 men with PCa	No ADT	GnRH agonist and/or AA Orchiectomy	AMI SCD Diabetes	0.92 (0.84-1.00) 0.96 (0.83-1.10) 1.24 (1.15-1.35)
Keating 2010 [6]	US VHA (2001–2004)	37,443 men with locoregional PCa	WW/AS	GnRH agonists, Orchiectomy, AA, Combined androgen blockade	CHD MI SCD Stroke	1.17 (1.06–1.39) 1.21 (1.01–1.44) 1.28 (1.05–1.57) 1.18 (1.02–1.36)
Van Hemelrijck 2010 [7]	PcBaSE Sweden (1997–2007)	76,601 men with PCa	RP, WW/AS	GnRH agonist AA GnRH + AA	IHD MI Heart failure	1.34 (1.25–1.43)[b] 1.47 (1.35–1.60)[b] 1.67 (1.54–1.80)[b]

				Orchiectomy Medical or surgical ADT	Stroke	1.27 (1.17–1.38)[b]
Hu 2012 [17]	SEER (1992–2007)	182,757 men with loco-regional PCa	No ADT	GnRH agonist Orchiectomy	PAD VTE	1.15 (1.11–1.19) 1.10 (1.04–1.16)
Jespersen 2014 [10]	Danish Cancer Registry (2002–2010)	31,571 men with PCa	No ADT	GnRH agonist/AA Orchiectomy	MI Stroke	1.31 (1.16–1.49) 1.19 (1.06–1.35)
Gandaglia 2014 [18]	SEER (1995–2009)	140,474 men with non-metastatic PCa	No ADT	GnRH agonist Orchiectomy	AMI CAD SCD	1.09 (1.04-1.15) 1.11 (1.07-1.15) 1.18 (1.12-1.24)

[a]Where multiple ADT types are assessed separately, the HRs given refer to the GnRH agonist group vs control; [b]Standardised incident ratios
AA, antiandrogen; ADT, androgen deprivation therapy; AMI, acute myocardial infarction; AS, active surveillance; BT, brachytherapy; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavour; CHD, coronary heart disease; CT, cryotherapy; CV, cardiovascular; EBRT, external beam radiation therapy; HR, hazard ratio; IHD, ischaemic heart disease; MI, myocardial infarction; PCa, prostate cancer, SCD; sudden cardiac death; SEER, surveillance, epidemiology, and end results; US, United States; VHA, Veterans Healthcare Administration; WW, watchful waiting

missed as this effect would be diluted by the long-term follow-up (median follow-up of around 10 years) [25].

The association of ADT with CVD has thus far been examined mostly using retrospective analysis of administrative and clinical databases [6, 7, 9, 10, 15-19]. Many observational studies show an association between GnRH agonists and increased CVD risk, however, as there are no prospective randomized trials to provide level 1 evidence that ADT increases the risk of CVD, causality is yet to be demonstrated in humans. At present, no large studies have investigated the risk of CVD with the new treatment modalities abiraterone (a CYP17 enzyme inhibitor) or enzalutamide (an androgen receptor antagonist). Such studies are awaited with interest.

On the balance of available evidence, the United States Food and Drug Administration (FDA) mandated the inclusion of additional safety information to GnRH agonist drug labels in 2010 [26]. A science advisory notice, jointly issued by four American societies, also stated there may be a relationship between ADT and CV risk [27]. Similarly, in 2011, Health Canada issued a special notice to health providers and patients that "Labeling for GnRH agonist drugs has been updated to add a warning on the potential increased risk of heart-related side effects" [28]. The European Association of Urology specified in its 2013 prostate cancer guidelines the need for special attention to the risk-to-benefit ratio of ADT in patients with a higher risk of CV complications, especially if it is possible to delay starting ADT [29].

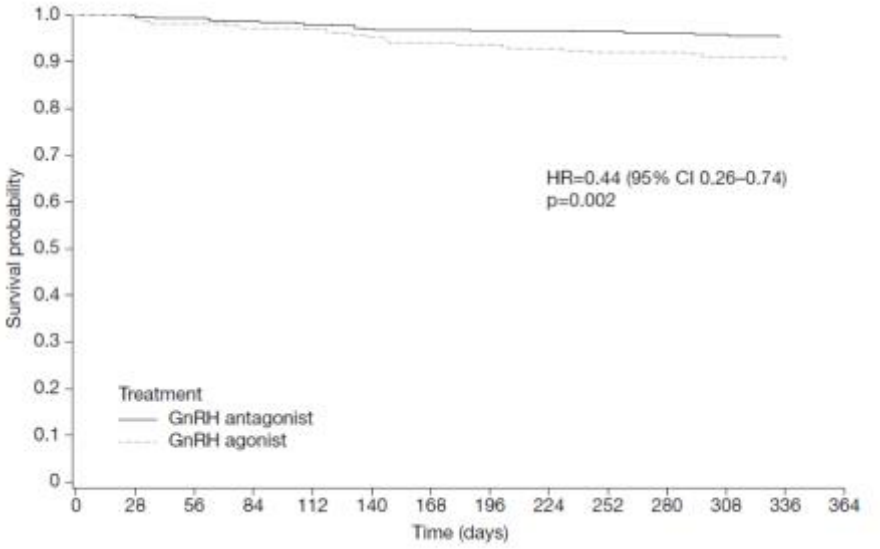
1.2 GnRH antagonists and CVD risk

In contrast to GnRH agonists, GnRH antagonists block GnRH receptors in the anterior pituitary gland, resulting in decreased secretion of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This leads to a decrease in testosterone production initiated within 24 hours, with no surge. Castrate levels (≤0.5 ng/mL) are achieved within 1–3 days of treatment initiation [30].

Analyses have investigated CV safety in patients treated with the GnRH antagonist degarelix. In a 1-year randomized comparative phase III study of degarelix versus leuprolide [31], there was no difference in mean change in electrocardiographic QT abnormalities in either treatment arm. The most frequently reported cardiac disorder during the trial was ischemic heart disease, which occurred in 4% of degarelix patients and 10% of leuprolide patients, although this was not statistically significantly different [30].

Two pooled analyses have also investigated the incidence of CV events with degarelix. In the first, data from degarelix-treated patients from nine phase II and III trials (n = 1,704) showed no increase in the baseline CV event rate once degarelix treatment was started [32]. In the second, data from all randomized phase III/IIIb trials comparing degarelix with GnRH agonists were pooled. Individual patient data from 2,328 men (degarelix; n = 1,491, GnRH agonists, n = 837) were analyzed for the incidence of cardiac events (classified as arterial embolic and thrombotic events, hemorrhagic or ischemic cerebrovascular conditions, myocardial infarction or other ischemic heart disease). Using a Cox proportional hazard model there was a 40% lower risk of a cardiac event or death with degarelix (HR = 0.60, 95% CI 0.41–0.87, P = 0.008). Among the 30% of patients reporting CVD at baseline, the relative risk of a cardiac event or death during the initial year of treatment was 56% lower for men receiving the GnRH antagonist compared with men receiving a GnRH agonist (Fig. 1), an absolute risk reduction of 8.2% during the first year [33]. The trial populations from the second analysis were mixed and there are important caveats to recognize in interpreting this data, including the risk of uncontrolled bias resulting from a post-hoc analysis and that CV events were not systematically validated or recorded as an independent study end point. Nonetheless, the results of the analysis warrant further study.

Fig. 1. Kaplan-Meier plot of time to first cardiovascular event or death among men with pre-existing CVD treated for up to 1 year with degarelix or a GnRH agonist.



Reprinted from European Urology, 65 (3), Albertsen PC et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist, 565–573, Copyright (2014), with permission from Elsevier.

The U.S. FDA requirement to add new safety information to GnRH agonist drug labels warned about the “increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke)” [26]. It should be noted that there is currently no evidence of sudden cardiac death associated with GnRH antagonist use [33].

2. Potential mechanisms of CV risk with ADT

Several hypotheses have been proposed to explain the increased risk of CVD with ADT. These have been informed by the observations that CV events occur mostly within the first 12 months after initiation of ADT [34, 35], that men most at risk are those aged over 65 [34] or with a history of CVD at treatment initiation [36, 37] and that, in some studies, GnRH agonists and orchiectomy both increase the risk of CV events [6-8]. A recent report shows that CV effects can occur even with short duration ADT [38].

2.1 Metabolic syndrome and low testosterone

Classically, metabolic syndrome can include atherogenic dyslipidemia with, for example, increased triglyceride and reduced high density lipoprotein (HDL) levels, increased waist circumference and fasting glucose levels, and hypertension [39]. Similar metabolic alterations are associated with ADT, although differences such as raised HDL and increased subcutaneous, rather than visceral, abdominal fat have been noted [3, 40]. Thus, physiologic changes associated with an increased risk of CVD occur in men receiving ADT but the impact on CV risk remains to be fully defined.

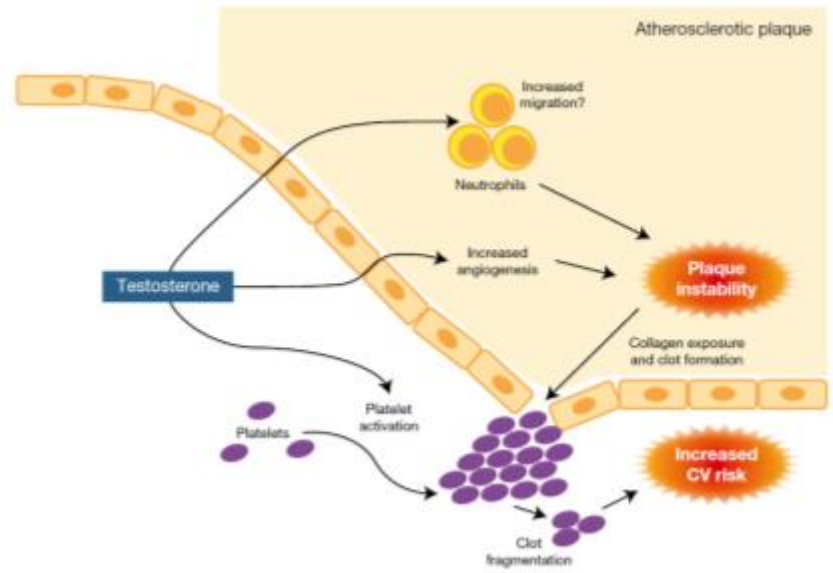
Previous studies have established that low androgen levels are associated with increased CV risk [41-44] and although the mechanisms are unknown, it may be hypothesized to be due to changes similar to those seen in metabolic syndrome. Preclinical studies showed testosterone may have atheroprotective actions as testosterone supplementation of orchiectomized mice reduced atherosclerotic lesion area [45]. Among several potential mechanisms linking testosterone to atheroprotection [46], testosterone enables HDL-related removal of excess cholesterol from arterial walls [47].

2.2 Testosterone flare

Some authors have discussed the notion that testosterone flare may have an adverse influence on CV risk. Firstly, three recent reports suggest an increased risk of CV events in the first year after initiation of testosterone therapy, especially for elderly men and men with pre-existing CVD [48-50]. These studies led the Endocrine Society to issue a statement advising patients be made aware of the increase in risk of CV events with testosterone therapy, especially in men aged over 65 or with a history of CVD [51]. Secondly, testosterone may promote angiogenesis [52] in atherosclerotic plaques, a process known to increase plaque growth and destabilization [53, 54] and, thirdly, testosterone may increase hematocrit and platelet aggregation [55]. Finally, in the absence of androgen receptor signaling in mice, neutrophil numbers and migratory capacity are reduced [56], therefore in

the presence of high testosterone levels it is possible neutrophil migration may increase and this in turn may affect atherosclerotic plaque stability. An increased neutrophil/lymphocyte ratio is known to be an independent predictor of death and myocardial infarction [57]. These possible mechanisms are summarized in Fig. 2. Importantly, whether testosterone flare, a feature of GnRH agonist but not GnRH antagonist treatment, contributes to the suggested differences in CV risk with these therapies is unknown.

Fig. 2. Potential mechanisms by which exogenous testosterone/testosterone flare may increase CV risk. Testosterone may drive the accumulation of neutrophils and promote angiogenesis in atherosclerotic plaques, increasing plaque instability. There may also be a direct activation effect on platelets, increasing clot formation around exposed collagen associated with disrupted plaques.

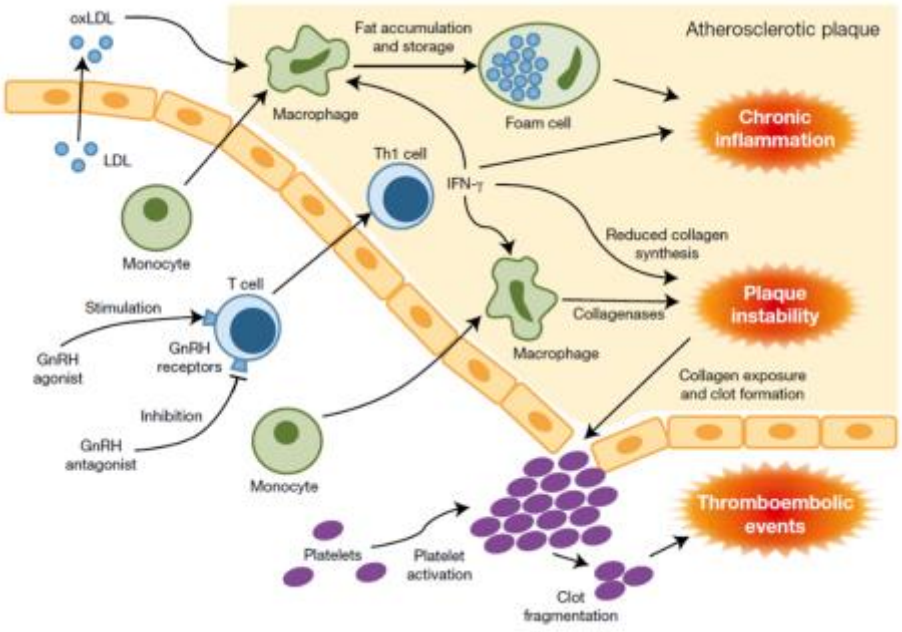


2.3 GnRH receptors, immune cells and atherosclerotic plaque destabilization

The destabilization of established atherosclerotic lesions has also been proposed as an explanation for the acute adverse effect of GnRH agonist therapy on CVD, potentially driven by the presence of GnRH receptors on T lymphocytes. Activation of these receptors stimulates T cell proliferation and differentiation to the Th1 (interferon [IFN]-γ producing)

phenotype [58]. Therefore it can be hypothesized that stimulation of GnRH receptors by GnRH agonists may promote destabilization of atherosclerotic plaques by stimulating an inflammatory process (Fig. 3). However, there is currently no conclusive evidence and definitive statements on the mechanisms responsible await further information. So-called "vulnerable" plaques are characterized by a thin fibrous cap, large lipid pool, inflammatory cell infiltration and a lack of smooth muscle cells [59]. When these rupture, the ensuing thrombotic complications include myocardial infarction and ischemic stroke. Loss of structural integrity of the fibrous cap is driven through a combination of reduced collagen synthesis and increased collagenase expression, driven by pro-inflammatory cytokines such as IFN-γ [60]. A pro-inflammatory cytokine microenvironment has also been linked to increased apoptosis of smooth muscle cells [61]. A summary of these events is shown in Fig. 3.

Fig. 3. Potential mechanisms by which immune cell stimulation may affect atherosclerotic plaques. The risk of plaque rupture is augmented by IFN-γ, which may be increased by GnRH agonist stimulation of GnRH receptors on T cells. The production of IFN-γ drives a pro-inflammatory environment, maturation of macrophages, reduced collagen synthesis and increased collagenase production. These latter mechanisms weaken the fibrous cap of the plaque increasing the risk of rupture and subsequent thrombotic complications.

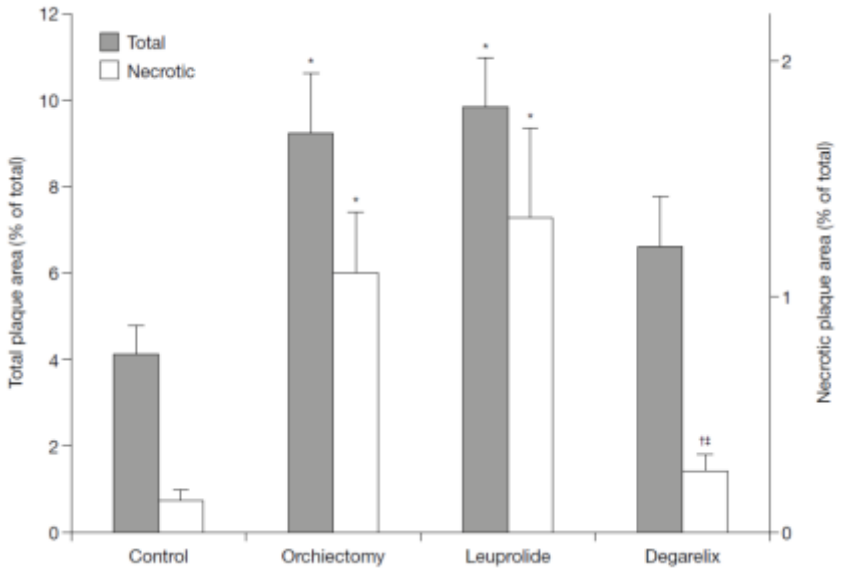


Monocyte/macrophages are another important cell type in plaque pathophysiology. Macrophages within plaques take up and store oxidized low-density lipoprotein (oxLDL), ultimately maturing into pro-inflammatory foam cells [62]. The phenotype of macrophages infiltrating the plaque is dependent on the cytokine environment – the presence of IFN-γ drives the development of M1 macrophages capable of producing collagenases, inflammatory cytokines, chemokines and reactive oxygen and nitrogen species that drive pathogenesis [62, 63] (Fig. 3).

A recent study by Hopmans et al. investigated the effects of different ADT modalities on the development of metabolic syndrome and atherosclerosis in a mouse model [64]. Using

LDL-receptor knockout mice ($LDLR^{-/-}$), the effects of orchiectomy plus vehicle (2.5% mannitol), sham surgery plus vehicle (control), sham surgery plus GnRH antagonist (degarelix) or sham surgery plus GnRH-agonist (leuprolide) on the development of aortic atherosclerotic plaques were compared. After 4 months, all mice developed fatty streaks in the ascending aorta, although they were very small in control mice. Leuprolide-treatment and orchiectomy more than doubled the amount of atherosclerotic plaque area compared to control (Fig. 4). On the other hand, the aortic atherosclerotic plaque area in mice treated with degarelix was not significantly different from control. Of importance, the necrotic core area of the plaques in degarelix-treated mice was significantly smaller compared to leuprolide-treated and orchiectomized mice. Notably, necrotic areas in atherosclerotic plaques associate with plaque progression and instability which can lead to CV events [65]. These data may support the notion that modes of ADT differentially affect plaque vulnerability and thereby the risk of CV events appearing within the first year of ADT [33].

Fig. 4. Comparison of total and necrotic aortic atherosclerotic plaque areas in LDLR$^{-/-}$ mice receiving orchiectomy, leuprolide or degarelix (n = 9–13/group) versus control at 4 months. (Plaque areas calculated as percentage of plaque and necrotic plaque area of aortic tissue). Data shown represent mean ± SEM. *P < 0.05 vs control; †P < 0.05 vs orchiectomy; ‡P < 0.05 vs leuprolide.



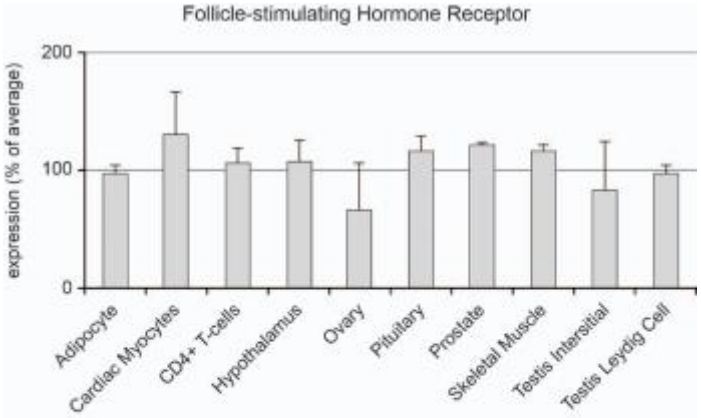
Reprinted from Urologic Oncology, doi: 10.1016/j.urolonc.2014.06.018, Hopmans SN, et al. GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model, copyright (2014), with permission from Elsevier.

2.4 GnRH receptors in other tissues

Aside from expression in the pituitary gland, GnRH receptors are expressed in numerous other tissues including the prostate, testes and on various tumors originating from both reproductive and non-reproductive tissues [66, 67]. Of particular interest here is expression in the heart (Fig. 5). In mice, GnRH, at similar concentrations to those attained during GnRH agonist treatment of men with prostate cancer, increases cardiomyocyte contractility [68] and GnRH receptor mRNA has been detected in the human heart [69]. This may be of relevance to previous data showing prolonged electrocardiographic QT interval

with GnRH agonist treatment [70]. However, a direct link between cardiac GnRH receptor stimulation and GnRH agonist use remains to be established.

Fig. 5. Relative mRNA expression of human hormone receptors in different cells and tissues. RNA expression is presented as a percentage of average expression in all human tissues examined [71]. Source BioGPS.org.


Follicle-stimulating Hormone Receptor
expression (% of average)
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Adipocyte
Cardiac Myocytes
CD4+ T-cells
Hypothalamus
Ovary
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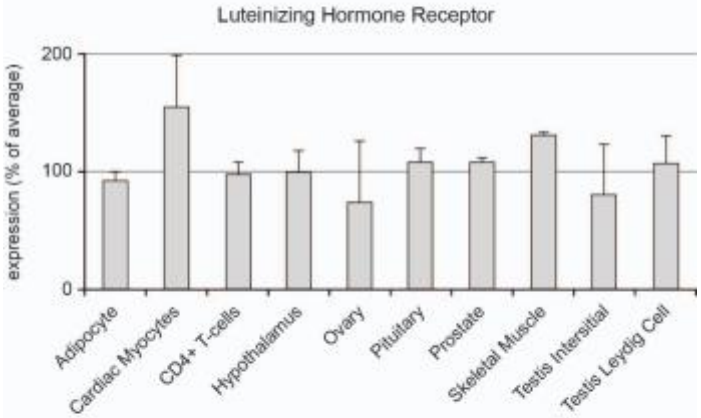
Prostate
Skeletal Muscle
Testis Intersitial
Testis Leydig Cell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Hypothalamus
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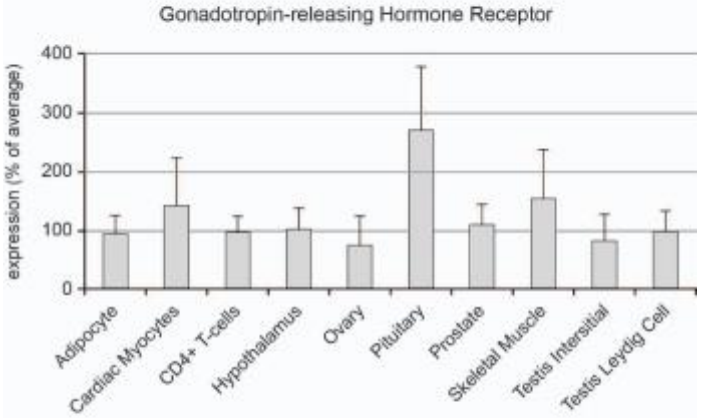
Skeletal Muscle
Testis Intersitial
Testis Leydig Cell


Gonadotropin-releasing Hormone Receptor
expression (% of average)
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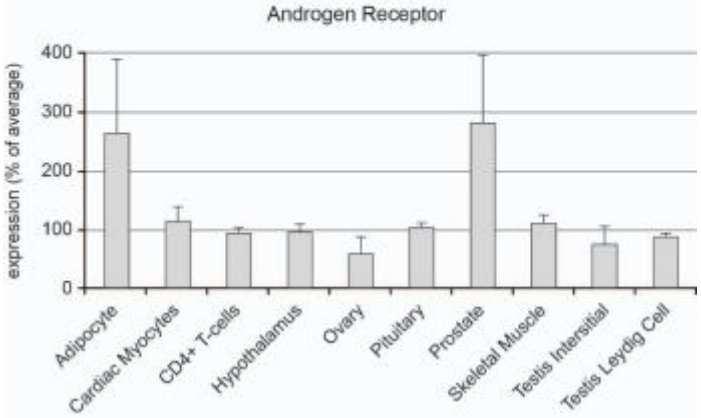
Prostate
Skeletal Muscle
Testis Intersitial
Testis Leydig Cell


Androgen Receptor
expression (% of average)
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Adipocyte
Cardiac Myocytes
CD4+ T-cells
Hypothalamus
Ovary
Pituitary
Prostate
Skeletal Muscle
Testis Intersitial
Testis Leydig Cell

2.5 Follicle-stimulating hormone

The differing methods of ADT have differential effects on LH and FSH. Orchiectomy decreases testosterone rapidly but FSH and LH rise. By contrast, GnRH antagonists rapidly suppress FSH and LH as well as testosterone. GnRH agonists have a different profile again; a phase III study comparing degarelix and leuprolide reported an initial peak in median LH and FSH levels in the leuprolide arm whereas levels fell rapidly after degarelix treatment. Ultimately, FSH levels did not fall to the same extent in the leuprolide arm [30]. In men, the receptor for FSH (FSHR) is expressed in testicular Sertoli cells and at low levels in the endothelial cells of the testis [72] as well as in cardiac myocytes (Fig. 5). In the prostate, FSHR is expressed in endothelial cells surrounding tumors but not in endothelial cells in normal tissue further than 1 cm from the tumor [73]. In orchiectomized men, FSH levels are raised above physiological levels [74] but the evidence for increased CV risk in this group is mixed [6-10]. Thus, it is currently difficult to draw firm conclusions about the association between FSH levels and CV disease.

Data from a preclinical mouse model suggest that treatment with degarelix leads to lower FSH levels than treatment with GnRH agonist or orchiectomy. Also, degarelix-treated mice have significantly lower perirenal fat weight and lean tissue mass than those treated with a GnRH agonist, suggesting reduced fat accumulation during degarelix treatment [64]. However, in men, changes in body composition are unlikely to explain the increased CV risk over the first few months of ADT, as discussed above.

3. Potential strategies to minimize CV morbidity and mortality during ADT

A recent review considered the management of patients receiving ADT in light of the recent evidence linking GnRH agonists with increased CVD risk [39]. It was suggested that prior to treatment initiation, the potential risk of CV events should be evaluated and balanced against expected treatment benefits. Therefore screening should be performed for known risk factors (abdominal girth, high blood pressure, and low- and high-density lipoproteins)

and, as CV events occur early after initiation of ADT, tests should be repeated every 3 months. The adoption of a healthy lifestyle including a low-fat diet, regular exercise, not smoking and moderating alcohol consumption should be encouraged.

For men with a history of CVD, it is important that guidelines for secondary prevention are followed closely, for example the European or American guidelines on CVD prevention in clinical practice [75, 76]. This applies to all patients with prevalent CVD but may be of particular importance for men on ADT for the reasons discussed above. Guidelines include the use of lipid-lowering therapies, most commonly statins and anti-platelet therapy such as irreversible cyclo-oxygenase inhibitors (acetylsalicylic acid; aspirin) or adenosine diphosphate receptor inhibitors (e.g. clopidogrel). Several observational studies also report hypertension as a risk factor for CV events during GnRH agonist therapy [8, 16, 19]: blood pressure should therefore be monitored and hypertension treated appropriately in these patients. ADT is also associated with increases in blood glucose [13]. Interventions include metformin combined with diet and exercise, which in non-diabetic men treated with ADT is associated with significant improvements in abdominal girth, weight, body mass index and systolic blood pressure [77], and toremifene, which may normalize lipid profiles in men receiving ADT [78]. For men on ADT without a history of CVD there may be an increased risk but this is not proven: careful monitoring and the treatment of established CV risk factors would be prudent. The treatment goals specified in the CVD prevention guidelines provide good help to the clinician in this regard [75, 76] and are summarized in Table 2.

The treatment of men with pre-existing CVD with a GnRH antagonist may be associated with a lower risk of a CV event than the use of a GnRH agonist [33]. These data suggest that, in men with a history of CVD, ADT with a GnRH antagonist may be considered as a primary option. However, this would not necessarily negate the risk of a CV event, which could still likely be higher than in men not receiving ADT. Thus, it is important to consider the use of concomitant preventative strategies whatever type of ADT is used. Equally important

Table 2. Recommendations for the management of CVD from the European and US secondary prevention guidelines.

Risk factor	Guideline	Recommendations*	Class and level of evidence†
Hyperlipidaemia	EU/US	Lifestyle changes including weight control, increased physical activity and a reduced intake of saturated fats	I B
	US	As well as lifestyle changes, statin therapy should be prescribed in the absence of contraindications or documented adverse effects	I A
	EU/US	In patients at high CVD risk, treatment should reduce LDL-C to <2.5 mmol/L (<100 mg/dL) and by at least 30%	I A/C
Hypertension	EU/US	Lifestyle changes including weight control, increased physical activity, alcohol moderation, sodium reduction and a healthy diet	I B
	US	Patients with blood pressure >140/90 mmHg should be treated, as tolerated, initially with β-blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve target blood pressure	I A
	EU	All major antihypertensive drug classes do not differ significantly in their BP-lowering efficacy and thus should be recommended for the initiation and maintenance of antihypertensive treatment	I A
	EU	Systolic BP should be lowered to <140 mmHg (and diastolic BP <90 mmHg) in all hypertensive patients	IIa A
	EU	Antiplatelet therapy, in particular low-dose aspirin, is recommended for hypertensive patients with cardiovascular events	I A
	US	ACE inhibitors should be prescribed indefinitely in all patients with LVSD (ejection fraction <40%) and in those with hypertension unless contraindicated	I A
	US	β-Blocker therapy should be used in all patients with LVSD with heart failure or prior myocardial infarction, unless contraindicated	I A
	US	β-Blocker therapy should be given for 3 years in all patients with normal left ventricular function who have had myocardial infarction or ACS	I B
	US	Chronic β-blocker therapy beyond 3 years is reasonable in all patients with normal left ventricular function who have had myocardial infarction or ACS	IIa B
	US	Chronic β-Blocker therapy may be considered for all other patients with coronary or other vascular disease	IIb C
Thrombosis	US	Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated	I A

	EU	In the chronic phase (>1 year) after myocardial infarction, aspirin is recommended for secondary prevention	I A
	US	A P2Y12 receptor antagonist plus aspirin is indicated in patients after ACS or PCI with stent placement	I A
	US	For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity, antiplatelet therapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) should be used	I A
	EU	In patients with non-cardioembolic TIA or ischaemic stroke, secondary prevention with either dipyridamole plus aspirin or clopidogrel alone is recommended	I A
	US	Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease	IIb B
Influenza	EU/US	Patients with CVD should have an annual influenza vaccination	I B
Depression	US	Screening for depression is reasonable, in collaboration with their primary care physician and a mental health specialist	IIa B
	EU/US	Treatment of depression has not been shown to improve CVD outcomes but may be reasonable for its reduction of mood symptoms and improvement of health-related quality of life	IIb C
Lack of cardiac rehabilitation	US	All eligible outpatients with a diagnosis of ACS, coronary artery bypass surgery or PCI, chronic angina and/or peripheral artery disease within 1 year should be referred to a cardiovascular rehabilitation programme	I A/B
	EU	All patients requiring hospitalisation or invasive intervention after an acute ischaemic event should participate in a cardiac rehabilitation programme	IIa B

*Further details on these recommendations and options for when a recommended treatment is contraindicated can be found in the full guidelines which are freely available [75, 76]. †Agency for Healthcare Research and Quality. Practice Guidelines and Recommendations: Assessing Cardiovascular Risk. March, 2012. Available at http://www.medscape.com/viewarticle/759314_9 (Accessed March 2014). Where the guidelines differ in class and level of evidence the lower level is given.

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LVSD, left ventricular systolic dysfunction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

is the decision as to whether ADT should be used as freely as it is currently. There are many circumstances where ADT use might be limited, postponed or even avoided altogether. For example, treatment may be delayed in men with locally advanced disease. Treatment delay has been associated with no difference in PCa survival or time to hormone-refractory disease, although fewer deaths from non-prostate cancer causes were reported with immediate ADT [79]. Intermittent ADT is another much discussed treatment option to reduce exposure to ADT; a recent study of over 1500 men with metastatic PCa found intermittent treatment provided small improvements in quality of life but was statistically inconclusive in terms of survival [80]. Therefore the risk of ADT use must be balanced carefully with the potential for benefit to the patient.

4. Summary

There appears, on the balance of the currently available evidence, to be an increased risk of CV events in men with PCa treated with one of several modalities of ADT. Recent data indicate the risk may be lower with the GnRH antagonist, degarelix, than with GnRH agonists but this needs to be proved definitively. Several mechanisms have been proposed that potentially explain the increased CV morbidity and mortality seen with ADT, although currently there are insufficient data available to confirm the mechanism(s) responsible or to explain why CV risk is prevalent and how this may differ between treatment modalities. Consequently, when initiating ADT it is important to consider the risk of CVD on an individual patient basis, with a prior history of CVD and patient age >65 years currently being the strongest known risk factors. Measures to lower the risk of a CV event should be considered in all men undergoing ADT.

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