

Androgens and cardiac diseases

Androgeni e cardiopatie

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ABSTRACT: *Androgens and cardiac diseases. V. Bianchi, A. Mezzani.*

Although androgens have been considered deleterious for the cardiovascular system, recent data have demonstrated favourable testosterone effects on cardiac and vascular remodeling and clinical outcome. However, the cardiovascular risk-benefit profile of testosterone therapy remains largely elusive due to lack of well-designed and adequately powered randomized clinical trials. In any case, a large body of clinical evidence underlines that low plasma testosterone levels should be considered a risk factor for

cardiovascular disease, and that the evaluation of sex steroids should be included in the routine clinical evaluation of cardiac patients. A better understanding of the mechanism regulating the effects of testosterone on cardiovascular system could lead to novel therapeutic strategies in several cardiac patient populations, such as chronic heart failure patients and those who recently underwent cardiac surgery.

Keywords: *testosterone, androgens, cardiac disease, cardiovascular risk.*

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Androgens in normal humans

Human androgens comprise testosterone (T), dihydrotestosterone (DHT), androstenedione and dehydroepiandrosterone (DHEA) and its sulfate. Most of T is secreted by the testis in males and by the ovary in females. Approximately 5% of serum T is transformed in DHT by a 5 α -reduction process, with DHT having a threefold greater affinity than T and a 15- to 30-fold greater affinity than adrenal androgens for androgen receptors. DHEA and dehydroepiandrosterone sulfate, the most abundant adrenal steroids in humans, are precursors of the intracellular production of androgens and estrogens in non-reproductive tissues. Most T is bound to plasma proteins, namely, 40-50% to albumin and 50-60% to sex hormone-binding globulin, with 1-2% being free [1]. Part of T is converted by the aromatase enzyme in estradiol, so that T is active through three ways: i) by directly activating the androgen receptors, ii) by indirectly activating the androgen receptors as DHT, and iii) by activating the estrogen receptors α and β (ER α and ER β) after conversion to estradiol [2] (Figure 1).

Androgens and aging

Many cross-sectional studies have demonstrated lower concentrations of circulating and/or free T in elderly men [3-6]. The study by Harman [7] is the largest longitudinal evaluation of the effects of aging on male gonadal hormone function reported to date, strongly supporting the concept of an age-re-

lated lowering of both total and bioavailable circulating T levels at a relatively constant rate, independently of obesity, illness, medications, cigarette smoking and/or alcohol intake. Moreover, a prospective cohort study about endocrine functioning in men found that the decline in total and free serum T is associated not only to aging, but to lifestyle as well [8], namely, nutrition and physical activity. Of note, asymptomatic hypogonadism has a high prevalence in the general US population, on average equal to 5.6% in men 30-79 years of age, and increases with increasing age. Hence, the aging of the western countries male population will likely cause a large increase of androgen deficiency [9].

Androgens effects on cardiovascular system

Androgens and heart remodeling

Information about the important role played by the androgen receptors system on cardiovascular function has been gained by male androgen receptors-knockout mice. Experimental use of these mice with inactivated androgen receptors has provided insights into the functional activities of androgens in adipocytes [10], brain [11], bone [12] and cardiovascular system [13].

Androgen receptors are present in cardiac myocytes of multiple species, including normal men and women, allowing androgens to modulate the cardiac phenotype and produce hypertrophy by direct, receptor-specific mechanisms [14]. The studies of Ikeda [13] demonstrated that in male mice, the androgen receptors system participates in normal

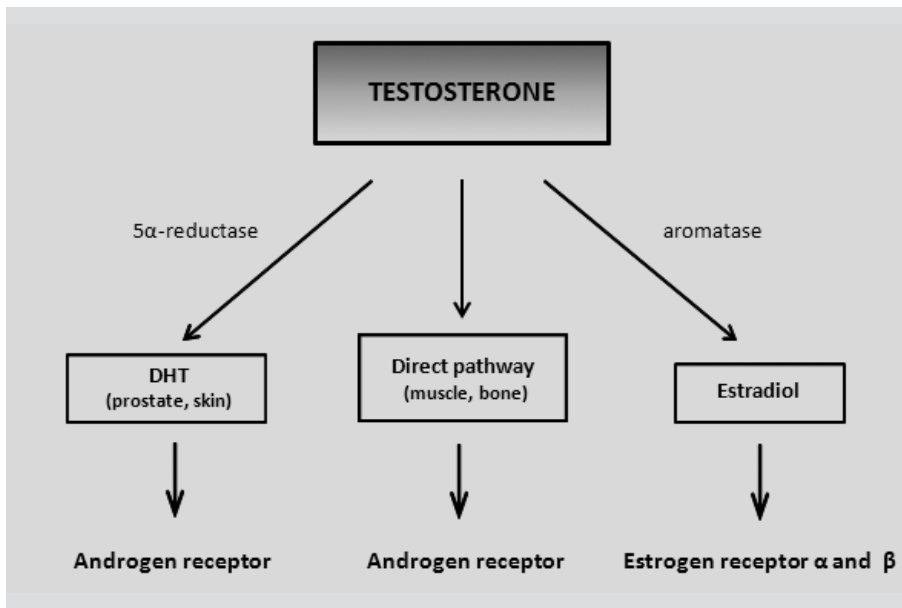


Figure 1. Pathways of testosterone action.

Testosterone directly activates the androgen receptors. In some organs rich of the 5 α -reductase enzyme, such as prostate and hair follicles, the effect of testosterone is amplified after transformation in dihydrotestosterone (DHT). Another pathway of testosterone action is through its aromatization into estrogen, that interacts with estrogen receptors α and/or β .

cardiac growth. Moreover, heart androgen receptors modulate adaptive hypertrophy and fibrosis during the process of cardiac remodeling under hypertrophic stress, and protect the heart from both angiotensin II-induced vascular remodeling [15] and doxorubicin-induced cardiotoxicity [16]. Androgen receptors also exist in cardiomyocytes [17] and play an important role in the modulation of cardiac hypertrophy and cardiac remodeling after myocardial infarction (MI) [18, 19]. Of note, when estrogen levels are reduced T worsens cardiac dysfunction and remodeling [20]. Grohe [17] demonstrated that the enzyme cyp450 aromatase is expressed in cardiac myocytes, and that the local estrogen biosynthesis in the heart is effective to activate both the receptor ER α and ER β . Accordingly, in the myocardium T operates both by activation of androgen receptors and local aromatization in estradiol acting on ER α and ER β . Many studies have demonstrated the preventive effect of estrogens on myocardial hypertrophy, while androgens induced cardiac hypertrophy [20-22]. These studies evidenced that T and estrogen interact physiologically modulating the effect on cardiac hypertrophy and contractile function, which underscores the need to evaluate both T and estrogen circulating levels in the clinical setting.

Androgens and vascular function

A direct effect of T on vascular function is mediated by the expression of the androgen receptors in vascular cells, which has been demonstrated in rabbits, dogs, monkeys and humans [23] in vascular smooth muscle cells, endothelial cells, macrophages, megakaryocytes and platelets [24]. In addition, these cells express aromatase and 17 β -hydroxysteroid-dehydrogenase, so that also estradiol can be produced locally from both T and DHEA [25-27]. ER α , ER β and membrane estrogen receptors are expressed in endothelial cells, smooth muscle cells, macrophages

and platelets as well as in coronary arteries of monkey and man [28-31]. In rabbit aorta, T was found to stimulate the expression of androgen receptors and to inhibit neointimal plaque formation, indicating autoregulatory effects [23].

The effects of androgen-son vascular function are still controversial. It has long been hypothesized that androgens promote atherosclerosis, and several in vitro and in vivo studies have shown that androgens increase expression of atherogenic factors [32-35]. Conversely, other studies have demonstrated a correlation between advanced atherosclerosis and low T levels. Muller showed that serum free T concentrations were inversely related to the mean progression of intima-media thickness of

the common carotid artery, independently of cardiovascular risk factors [36, 37]. Low plasma T levels were also associated with endothelial dysfunction and poor vasodilation of brachial artery in men [38]. T-induced vasodilation was first reported in 1945 [39]. This effect involves primarily the vascular smooth muscle cells without requiring the presence of endothelium, and the rapidity of the response evidences that T acts through a non-genomic way. T induces vasodilation in all arterial beds studied, including coronary, mesenteric, iliac, renal, and femoral arteries [40], and the vasodilator responsiveness of coronary arteries reduced with age [41]. The direct infusion of T causes acute coronary vasodilation, as demonstrated by intracoronary infusion of T at physiological concentration in patients with coronary artery disease (CAD) [42, 43] and this concept is supported by numerous experimental findings both in animals and humans [32, 42, 44].

The mechanism of T action is the arterial androgen receptors mRNA up-regulation, that reduces neointimal plaque formation in male rabbits [23], associated with a 50% increase of the amount of androgen receptor mRNA in the arterial segments treated with T. The beneficial effects of T on post-injury plaque development underlines, at least in males, the important role played by androgens in the vascular system. Physiological levels of DHT attenuated the development of atherosclerosis by androgen receptor-mediated suppression of the formation of intimal foam cells by macrophages [45]. The pathophysiological role of androgen receptors activity in the cardiovascular system has been studied in male androgen receptors-knockout mice under vascular stress [15], that exhibited exaggerated angiotensin II-induced medial thickening and perivascular fibrosis in the coronary arteries and aorta. Furthermore, physiological T supplementation inhibited cholesterol-enriched diet-induced

fatty streak formation in mice with a deletion in the gene encoding the classical androgen receptor [46]. These data suggest that androgen exerts an athero-protective effect via androgen receptor-dependent and -independent signaling.

Androgens and cardiac electrophysiology

The effects of T on cardiac electrophysiology are poorly described, but evidence is accumulating about the impact of sex steroids on human cardiac rhythm and arrhythmias [47]. Charbit [48] showed that the difference in QT-interval duration between men and women might be explained by differences in T levels. An involvement of gonadal steroids in morphologic differences in ventricular repolarization between males and females has also been hypothesized [47, 49]. A reduced QT dispersion in heart failure patients treated with T has been observed [50]. Lower QTc intervals in men with higher serum T levels could be due to the association of serum T with prolongation of the RR interval [51]. A non-genomic action of T and progesterone on cardiac ion channels likely contributes to gender differences in cardiac repolarization process [52]. Repolarization of canine ventricular myocardium is significantly modified by T, but not by estrogen, in both genders. This effect is likely due to augmentation of expression of K⁺-channel proteins, and thus may provide protection against arrhythmias via increasing the repolarization reserve [53]. The protective role of T in male hearts has been evidenced by [54] and Bigi [55], who demonstrated a QTc interval ≤ 380 ms among professional bodybuilders abusing of anabolic steroids.

Androgens and cardiac diseases

Coronary risk factors

T plays an important role in metabolism regulation. Low T levels are associated with obesity, metabolic syndrome and diabetes in men [56, 57], and are now recognized as an independent risk factor for such diseases [58]. T replacement improves glycemic control, visceral adiposity and hypercholesterolemia in hypogonadal men with type 2 diabetes [59]. High T levels are associated to a low incidence of type 2 diabetes in men, but not in women [60]. In a recent review, the current knowledge on the metabolic actions of T, the effects of T deficiency on obesity, metabolic syndrome and type 2 diabetes and the role of T replacement are discussed [61]. In older men, lower total T is associated with insulin resistance independently of measures of central obesity [62]. T is also involved in lipid homeostasis in insulin-responsive tissues, such as liver, adipose tissue and skeletal muscle [63].

Coronary artery disease and estrogens

CAD is the leading cause of death worldwide for both men and women [64], with the prevalence of CAD being significantly higher and the life expectancy significantly shorter in men as compared to women [65]. Historically, the different prevalence of CAD between men and women has been interpreted as an estrogen-induced protective effect against atherosclerosis. This concept has been

challenged by randomized clinical trials testing the effects of combined estrogen/progestin therapy in post-menopausal women, that showed no benefits as to CAD incidence [66, 67]. Furthermore, hormone replacement strategies in postmenopausal women have been associated with an increased risk of breast and endometrial malignancy and thromboembolic disease with resulting increased mortality. In a study conducted on 2763 postmenopausal women, the treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate for 4.1 years did not reduce the overall rate of CAD events [66]. In addition, a recent review showed that, in elderly postmenopausal women with established CAD, daily use of conjugated equine estrogen and combination of medroxyprogesterone acetate plus estrogen did not reduce the overall risk of MI and coronary death during an average follow-up of 4.1 years [68]. In men, estrogen plasma level is related to the incidence of CAD [69].

Coronary artery disease and androgens

The effects of androgens on CAD are even more controversial. Previous studies have evidenced an increased risk of cardiovascular risk in all ages in men after administration of T [70-72]. A correlation between the use of androgens and MI has been reported in body-builders using supraphysiological doses of androgens [73-81]. Such doses of androgens were considered toxic on the cardiovascular system [82, 83, 84], but no clear evidence about an epidemic of acute cardiac events has been associated with the increase of anabolic steroids abuse during the last decades [85, 86].

Despite these reports, an increasing body of literature indicates that men with CAD have significantly lower T levels than those without CAD. An increased development of atherosclerosis has been shown in male animals after castration and reversed with androgen replacement therapy [46] (see above '*Androgens and vascular function*'). The relationship between serum T level and CAD in humans has been evaluated in a complete review by Wu [87]. Thirty-two cross-sectional studies were analyzed; in 16 studies, a lower level of T was found in patients with CAD as compared to controls, whereas other 16 studies showed no differences in T level between patients and controls. The Caerphilly Heart Study enrolled 2512 men [88], showing a modest reduction in T in survivors of MI. The association, however, became not significant when adjusted for plasma insulin and triglycerides. Conversely, Phillips [89] demonstrated a significant relationship between low free T level and the degree of coronary occlusion in 55 men undergoing angiography. Another study on 900 men found that both total and bioavailable T were significantly lower in men with CAD than in those without [90]. Similar results were reported by Dunajska [91], who showed that men with CAD had lower total T levels, T/estradiol ratio and free androgen index as compared to controls; moreover, men with CAD were more insulin-resistant than controls and had an atherogenic lipid profile. A positive association between low serum androgen levels and severe internal carotid artery

atherosclerosis in men has been evidenced by Debing et al. [92], suggesting a protective role of physiological levels of androgens from the development of atherosclerosis. Similar results have been evidenced in the study of health in Pomerania [93] and further confirmed recently [94, 95].

In women, the relationship between androgen level and CAD has been poorly investigated. In women with polycystic ovary syndrome, two long-term longitudinal studies showed no significant increase of CAD incidence [96]. High free T and androstenedione levels within the physiological range have also been correlated with reduced carotid artery atherosclerosis in premenopausal and postmenopausal women [97]. More recently, in postmenopausal women decreased T levels have been found to be associated with CAD independently of other risk factors. Hormonal replacement therapy tends to increase T level, which may further support the beneficial role of hormone replacement therapy in postmenopausal women [98]. Evidence of a positive association between low serum androgen levels and severe internal carotid artery atherosclerosis in postmenopausal women has been provided, and suggests that higher, but still physiological, levels of androgens in postmenopausal women have a protective role from the development of CAD [99]. He [100] showed a more complex interaction between sex hormones and CAD. In both men and postmenopausal women with angiographic CAD, there were significant differences (relative to age-matched control subjects) in sex hormone ratios, suggesting that an abnormality in sex hormones could influence coronary health. A lower estradiol-to-progesterone ratio was associated with the predisposition to coronary atherosclerosis in males, whereas lower estradiol-to-progesterone and estradiol-to-T ratios were associated with the same condition in females.

Angina pectoris

Several studies have demonstrated the effect of T therapy in angina pectoris and are reported in Table 1. The first studies were reported in 1942 by Hamm [101] and Walker [102]. These authors showed that T supplementation in patients with angina pectoris produced significant clinical improvement, reduced cardiac symptoms and increased time to ischemia. These data have been confirmed recently [103]. English [104] found that low-dose supplemental T reduces exercise-induced myocardial ischemia in men with chronic stable angina. Long-term benefits of T therapy were observed during 12 months of treatment in men with low T levels and angina; T increased time to ischemia without side effects [105]. In a randomized study on 50 men with exercise-induced ST segment depression, Jaffe [106] showed that a treatment with T cypionate, 200 mg intramuscularly weekly, significantly reduced ST segment depression after 8 weeks of treatment; no effects were observed in the placebo group. In a crossover study, conducted on 62 men with ischemic heart disease treated with T undecanoate or placebo [107], angina pectoris was relieved by 77% and myocardial ischemia in ECG and Holter recordings was reduced by 69% and 75%, respectively. Moreover, administration of low doses of T in men with chronic stable angina reduced exercise-induced myocardial ischemia [104], resulting in an increase in time to 1-mm ST-segment depression after 12 weeks of treatment.

Myocardial infarction

A limited number of studies are available on the relationship between T levels and MI. After MI in male patients, a transient decrease in T has been observed [112]. Chronic T administration showed no detrimental effects on left ventricular remodeling

Table 1. - Effect of testosterone treatment in men with coronary artery disease

		Patient n.	Dosage	Treatment duration	Clinical effect
Chronic administration	Hamm L ¹⁰¹	7	75 mg/week	1/2 months	↑↑
	Walker TC ¹⁰²	12	100 → 10 mg/day	4 months	↑↑
	Sigler LH ¹⁰⁸	16	50 mg/week	6/7 weeks	↑↑
	Jaffe MD ¹⁰⁶	50	200 mg/week	2 months	↑↑
	Wu SZ ¹⁰⁷	62	40-120 mg/day	1 month	↑↑
	English KM ¹⁰⁴	46	5 mg/day	3 months	↑↑
	Mathur A ¹⁰⁵	15	1 g/3 months	12 months	↑↑
Acute administration	Webb CM ¹⁰⁹	14	2.3 mg i.v.	10 min	↑↑
	Rosano GM ¹¹⁰	14	2.5 mg i.v.	5 min	↑↑
	Thompson PD ¹¹¹	32	2-6 times baseline plasmatic level	20 min	-

The clinical effect cumulates the reduction of the number of anginal episodes and both the prolongation of time to and the increase of heart rate at ischemic threshold during ergometric stress test.

↑↑ = clinical improvement; - = no effect.

after MI [113]. In a study conducted on 65 regularly menstruating women aged 33-48 years with recent MI, a significantly higher concentration of T was found in women with a family history of CAD than in those without [114]. Due to the young age of these women, data are not conclusive and need verification.

Chronic heart failure

Several authors have considered the effects of T administration in chronic heart failure (CHF) patients at physiological doses, evidencing positive clinical outcomes [115-119]. In patients with CHF, a low level of plasma T has been observed [120-122]. Particularly, CHF due to idiopathic dilated cardiomyopathy is associated with a significant decrease in growth hormone, insulin-like growth factor 1 and T concentrations [122], underlying the concept that a catabolic state is strictly related to this clinical condition. Wehr [123] showed that low free T level is independently associated with increased CHF mortality, with no association with total T levels. The T treatment in men with CHF determined a significant improvement in exercise capacity and symptoms [115]. Anabolic hormones (T, DHEA sulfate, insulin-like growth factor 1) are related to physical capacity in healthy men, and in CHF patients low circulating T are independent predictors of exercise intolerance [124].

In a randomized double-blind placebo-controlled trial, T administration for a 12-month period in men with moderate-to-severe CHF was associated to an improvement in exercise capacity and symptoms, without changes in muscular strength [115]. In a similar protocol, T replacement was studied in men with moderate-to-severe CHF; T therapy improved exercise capacity and NYHA class compared with placebo [117]. Pugh [118] demonstrated that the administration of T increases cardiac output acutely, apparently via a reduction of left ventricular afterload. In a recent review [125], T appears to be a promising therapy to improve exercise capacity in patients with CHF. Caminiti [116] showed that long-acting T therapy improves exercise capacity, muscle strength, glucose metabolism and baroreflex sensitivity in men with CHF. T therapy improved both peak VO_2 and ventilatory efficiency, as assessed by the VE/VCO_2 slope.

T benefits seem to be mediated by metabolic and peripheral effects. Recently, T supplementation has been used in a 12-week program of exercise rehabilitation in elderly male patients with CHF and a low T status, positively impacting on a range of key health outcomes [126]. Iellamo [119] showed that women with stable CHF who received T transdermal patch, improved functional capacity, insulin resistance and muscle strength without side effects. In a recent meta-analysis, Toma [125] observed that T appears to be a promising therapy to improve exercise capacity in patients with CHF.

Testosterone and prognosis

Recent epidemiological studies revealed that low T levels in men were associated with higher cardiovascular mortality rates [90, 127-131]. Low

plasma level of T and estradiol predict mortality in elderly men [129]. Furthermore, anti-androgen therapy in men affected by prostate cancer is associated with significant increases in the risk of CAD and incident heart failure [132]. Moreover, in men treated by orchiectomy, a twofold increase of CAD mortality over a 10-year period has been demonstrated [133].

Shores [134], using the Veteran's Affairs clinical database, reported that men with low T level had a 88% relative increase in all-cause mortality risk when compared with those with normal T levels, and concluded that hypotestosteronemia was a marker of increased mortality risk. An increased risk of death associated with the decline in anabolic hormone levels during a 6-year follow-up was reported in the InChianty study [135]. Laughlin [128] studied a group of 794 men for 20 years, and found that the risk of death was 44% greater between the lowest and highest quartiles of total T after adjusting for age, adiposity and lifestyle choices. The European Prospective Investigation in Norfolk [127] investigated all-cause and cardiovascular mortality in 11606 healthy men between 40 and 79 years of age, observing a statistically significant association between baseline serum T level and all-cause, cardiovascular- and cancer-related death. The authors concluded that T concentrations are inversely related to cardiovascular and all-cause mortality. Recently, Malkin [90] followed 930 men with angiographically proven CAD over a 7-year period, and found that in androgen-deficient men the mortality was 21% versus 12% in the eugonadal group. Furthermore, the biological available T – and not total T – was significantly associated to all-cause and cardiovascular mortality (Figure 2). This data suggest that bioavailable T is the most sensitive assay for mortality risk stratification.

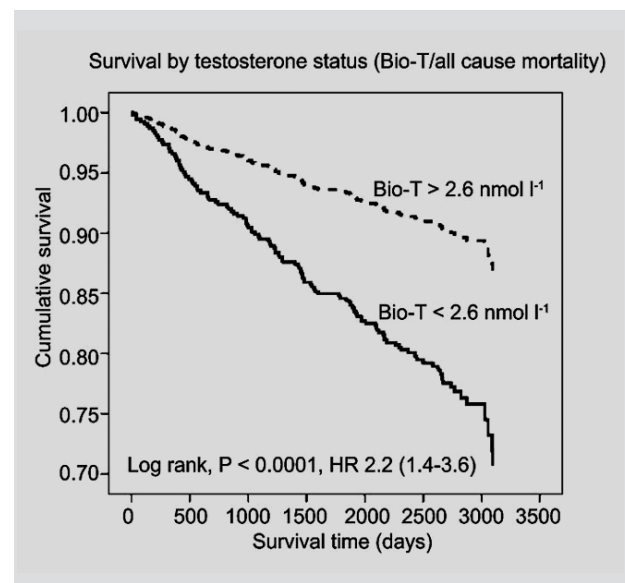


Figure 2. - Survival curves of all-cause mortality based on bio-available testosterone (Bio-T) levels.

The solid line represents patients with baseline Bio-T less than 2.6 nmol/l, the broken line represents patients with Bio-T greater than 2.6 nmol/l. Follow-up duration was 6.9 ± 2.1 years.

HR = hazard ratio.

Reproduced with permission from Malkin [90].

Conclusions

Although androgens have been considered deleterious for the cardiovascular system, recent data have demonstrated favorable T effects on cardiac and vascular remodeling and clinical outcome. However, Ruige [136] in a recent review affirms that the cardiovascular risk-benefit profile of T therapy remains largely evasive in view of a lack of well-designed and adequately powered randomized clinical trials. Discrepancies between studies might be explained by differences in methodology, dose and duration of T administration, and effects of other important hormones, such as estrogens and insulin-like growth factor 1. In any case, a large body of clinical evidence underlines that low plasma T levels should be considered a risk factor for cardiovascular disease, and that the evaluation of sex steroids should be included in the routine clinical evaluation of cardiac patients. A better understanding of the mechanism regulating the effects of T on cardiovascular system could lead to novel therapeutic strategies in several cardiac patient populations, such as CHF patients and patients who recently underwent cardiac surgery.

Riassunto

Sebbene gli androgeni siano stati considerati dannosi per il sistema cardiovascolare, dati recenti hanno dimostrato effetti favorevoli del testosterone sul rimodellamento cardiaco e vascolare e sulla prognosi. Tuttavia, il rapporto rischio-beneficio cardiovascolare della terapia con testosterone rimane elusivo per la mancanza di trial clinici randomizzati ben disegnati e dotati di adeguata potenza statistica. In ogni caso, una notevole evidenza clinica suggerisce che bassi livelli di testosterone plasmatico dovrebbero essere considerati un fattore di rischio cardiovascolare, e che il dosaggio degli steroidi sessuali dovrebbe essere incluso nella routine clinica dei pazienti cardiopatici. Una miglior comprensione dei meccanismi che regolano gli effetti del testosterone sul sistema cardiovascolare potrebbe condurre a nuove strategie terapeutiche in molte popolazioni di pazienti cardiopatici, quali quelli con scompenso cardiaco cronico e quelli recentemente sottoposti a cardiocirurgia.

Parole chiave: testosterone, androgeni, cardiopatia, rischio cardiovascolare.

ABBREVIAZIONI

T = testosterone
DHT = diidrotestosterone
DHEA = deidroepiandrosterone
ER α = estrogen receptors α
ER β = estrogen receptors β
MI = myocardial infarction
CAD = coronary artery disease
NYHA = New York Heart Association

References

- Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. *Journal of Clinical Endocrinology and Metabolism* 1981; 53: 58-68.
- Kuiper GG, Enmark E, Peltö-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. *Proceedings of the National Academy of Sciences of the United States of America* 1996; 93: 5925-5930.
- Vermeulen A, Rubens R, Verdonck L. Testosterone secretion and metabolism in male senescence. *Journal of Clinical Endocrinology and Metabolism*. 1972; 34: 730-735.
- Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *Journal of Clinical Endocrinology and Metabolism* 1983; 56: 1278-1281.
- Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: Response to clomiphene citrate. *Journal of Clinical Endocrinology and Metabolism* 1987; 65: 1118-1126.
- Gray A, Berlin JA, McKinlay JB, Longcope C. An examination of research design effects on the association of testosterone and male aging: Results of a meta-analysis. *Journal of Clinical Epidemiology* 1991; 44: 671-684.
- Harman SM. Testosterone in older men after the institute of medicine report: Where do we go from here? *Climacteric* 2005; 8: 124-135.
- Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *Journal of Clinical Endocrinology and Metabolism* 2007; 92: 549-555.
- Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *Journal of Clinical Endocrinology and Metabolism*. 2007; 92: 4241-4247.
- Sato T, Matsumoto T, Yamada T, Watanabe T, Kawano H, Kato S. Late onset of obesity in male androgen receptor-deficient (arko) mice. *Biochemical and Biophysical Research Communications* 2003; 300: 167-171.
- Sato T, Matsumoto T, Kawano H, et al. Brain masculinization requires androgen receptor function. *Proceedings of the National Academy of Sciences of the United States of America* 2004; 101: 1673-1678.
- Kawano H, Sato T, Yamada T, et al. Suppressive function of androgen receptor in bone resorption. *Proceedings of the National Academy of Sciences of the United States of America* 2003; 100: 9416-9421.
- Ikeda Y, Aihara K, Sato T, et al. Androgen receptor gene knockout male mice exhibit impaired cardiac growth and exacerbation of angiotensin II-induced cardiac fibrosis. *Journal of Biological Chemistry* 2005; 280: 29661-29666.
- Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ. Androgen receptors mediate hypertrophy in cardiac myocytes. *Circulation* 1998; 98: 256-261.
- Ikeda Y, Aihara K, Yoshida S, et al. Androgen-androgen receptor system protects against angiotensin II-induced vascular remodeling. *Endocrinology* 2009; 150: 2857-2864.
- Ikeda Y, Aihara K, Akaike M, et al. Androgen receptor counteracts doxorubicin-induced cardiotoxicity in male mice. *Molecular Endocrinology* 2010; 24: 1338-1348.
- Grohe C, Kahlert S, Lobbart K, Vetter H. Expression of oestrogen receptor alpha and beta in rat heart: Role of local oestrogen synthesis. *Journal of Endocrinology* 1998; 156: R1-7.
- Marcus R, Krause L, Weder AB, Dominguez-Meja A, Schork NJ, Julius S. Sex-specific determinants of increased left ventricular mass in the tecumseh blood pressure study. *Circulation* 1994; 90: 928-936.
- Mendelsohn ME, Karas RH. Estrogen and the blood vessel wall. *Current Opinions in Cardiology* 1994; 9: 619-626.
- Cavasin MA, Sankey SS, Yu AL, Menon S, Yang XP. Estrogen and testosterone have opposing effects on chronic cardiac remodeling and function in mice with myocardial

- infarction. *American Journal of Physiology. Heart and Circulatory Physiology* 2003; 284: H1560-1569.
21. Weinberg EO, Thienelt CD, Katz SE, *et al.* Gender differences in molecular remodeling in pressure overload hypertrophy. *Journal of the American College of Cardiology* 1999; 34: 264-273.
22. Malhotra A, Buttrick P, Scheuer J. Effects of sex hormones on development of physiological and pathological cardiac hypertrophy in male and female rats. *American Journal of Physiology* 1990; 259: H866-871.
23. Hanke H, Lenz C, Hess B, Spindler KD, Weidemann W. Effect of testosterone on plaque development and androgen receptor expression in the arterial vessel wall. *Circulation* 2001; 103: 1382-1385.
24. Fujimoto R, Morimoto I, Morita E, Sugimoto H, Ito Y, Ito S. Androgen receptors, 5 alpha-reductase activity and androgen-dependent proliferation of vascular smooth muscle cells. *Journal of Steroid Biochemistry and Molecular Biology* 1994; 50: 169-174.
25. Harada N, Sasano H, Murakami H, Ohkuma T, Nagura H, Takagi Y. Localized expression of aromatase in human vascular tissues. *Circulation Research* 1999; 84: 1285-1291.
26. Diano S, Horvath TL, Mor G, *et al.* Aromatase and estrogen receptor immunoreactivity in the coronary arteries of monkeys and human subjects. *Menopause* 1999; 6: 21-28.
27. Schmidt M, Kreutz M, Loffler G, Scholmerich J, Straub RH. Conversion of dehydroepiandrosterone to downstream steroid hormones in macrophages. *Journal of Endocrinology* 2000; 164: 161-169.
28. Karas RH, Patterson BL, Mendelsohn ME. Human vascular smooth muscle cells contain functional estrogen receptor. *Circulation* 1994; 89: 1943-1950.
29. Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. *Circulation* 1994; 89: 1501-1510.
30. Hodges YK, Tung L, Yan XD, Graham JD, Horwitz KB, Horwitz LD. Estrogen receptors alpha and beta: Prevalence of estrogen receptor beta mRNA in human vascular smooth muscle and transcriptional effects. *Circulation* 2000; 101: 1792-1798.
31. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *New England Journal of Medicine* 1999; 340: 1801-1811.
32. Adams MR, Williams JK, Kaplan JR. Effects of androgens on coronary artery atherosclerosis and atherosclerosis-related impairment of vascular responsiveness. *Arteriosclerosis, Thrombosis, and Vascular Biology* 1995; 15: 562-570.
33. McCrohon JA, Jessup W, Handelsman DJ, Celmajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999; 99: 2317-2322.
34. Ng MK, Quinn CM, McCrohon JA, *et al.* Androgens up-regulate atherosclerosis-related genes in macrophages from males but not females: Molecular insights into gender differences in atherosclerosis. *Journal of the American College of Cardiology* 2003; 42: 1306-1313.
35. Nheu L, Nazareth L, Xu GY, *et al.* Physiological effects of androgens on human vascular endothelial and smooth muscle cells in culture. *Steroids* 2011; 76: 1590-1596.
36. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation* 2004; 109: 2074-2079.
37. Makinen J, Jarvisalo MJ, Pollanen P, *et al.* Increased carotid atherosclerosis in andropausal middle-aged men. *Journal of the American College of Cardiology* 2005; 45: 1603-1608.
38. Akishita M, Hashimoto M, Ohike Y, *et al.* Low testosterone level is an independent determinant of endothelial dysfunction in men. *Hypertension Research* 2007; 30: 1029-1034.
39. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. *Endocrine Reviews* 2003; 24: 313-340.
40. Molinari C, Battaglia A, Grossini E, Mary DA, Vassaneli C, Vacca G. The effect of testosterone on regional blood flow in prepubertal anesthetized pigs. *The Journal of Physiology* 2002; 543: 365-372.
41. English KM, Jones RD, Jones TH, Morice AH, Channer KS. Aging reduces the responsiveness of coronary arteries from male wistar rats to the vasodilatory action of testosterone. *Clinical Science* 2000; 99: 77-82.
42. Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation* 1999; 100: 1690-1696.
43. Chou TM, Sudhir K, Hutchison SJ, *et al.* Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation* 1996; 94: 2614-2619.
44. Costarella CE, Stallone JN, Rutecki GW, Whittier FC. Testosterone causes direct relaxation of rat thoracic aorta. *Journal of Pharmacology and Experimental Therapeutics* 1996; 277: 34-39.
45. Qiu Y, Yanase T, Hu H, *et al.* Dihydrotestosterone suppresses foam cell formation and attenuates atherosclerosis development. *Endocrinology* 2010; 151: 3307-3316.
46. Nettleship JE, Jones TH, Channer KS, Jones RD. Physiological testosterone replacement therapy attenuates fatty streak formation and improves high-density lipoprotein cholesterol in the tfm mouse: An effect that is independent of the classic androgen receptor. *Circulation* 2007; 116: 2427-2434.
47. Pham TV, Rosen MR. Sex, hormones, and repolarization. *Cardiovascular Research* 2002; 53: 740-751.
48. Charbit B, Christin-Maitre S, Demolis JL, Soustre E, Young J, Funck-Brentano C. Effects of testosterone on ventricular repolarization in hypogonadic men. *American Journal of Cardiology* 2009; 103: 887-890.
49. Surawicz B, Parikh SR. Differences between ventricular repolarization in men and women: Description, mechanism and implications. *Annals of Noninvasive Electrocardiology* 2003; 8: 333-340.
50. Malkin CJ, Morris PD, Pugh PJ, English KM, Channer KS. Effect of testosterone therapy on qt dispersion in men with heart failure. *American Journal of Cardiology* 2003; 92: 1241-1243.
51. van Noord C, Dorr M, Sturkenboom MC, *et al.* The association of serum testosterone levels and ventricular repolarization. *European Journal of Epidemiology* 2010; 25: 21-28.
52. Kurokawa J, Furukawa T. Non-genomic action of sex steroid hormones and cardiac repolarization. *Biological & Pharmaceutical Bulletin* 2013; 36: 8-12.
53. Fulop L, Banyasz T, Szabo G, *et al.* Effects of sex hormones on ecg parameters and expression of cardiac ion channels in dogs. *Acta Physiologica* 2006; 188: 163-171.
54. James AF, Choisy SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. *Progress in Biophysics and Molecular Biology* 2007; 94: 265-319.
55. Bigi MA, Aslani A, Aslani A. Short qt interval: A novel predictor of androgen abuse in strength trained athletes. *Annals of Noninvasive Electrocardiology* 2009; 14: 35-39.
56. Grossmann M. Low testosterone in men with type 2 diabetes: Significance and treatment. *Journal of Clinical Endocrinology and Metabolism* 2011; 96: 2341-2353.
57. Stanworth RD, Jones TH. Testosterone in obesity, metabolic syndrome and type 2 diabetes. *Frontiers of Hormone Research* 2009; 37: 74-90.
58. Jones TH. Effects of testosterone on type 2 diabetes and components of the metabolic syndrome. *Journal of Diabetes* 2010; 2: 146-156.
59. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance,

- glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *European Journal of Endocrinology* 2006; 154: 899-906.
60. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA* 2006; 295: 1288-1299.
 61. Kelly DM, Jones TH. Testosterone: A metabolic hormone in health and disease. *Journal of Endocrinology* 2013; 217: R25-45.
 62. Yeap BB, Chubb SA, Hyde Z, *et al.* Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: The health in men study. *European Journal of Endocrinology* 2009; 161: 591-598.
 63. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and t2dm in men. *Nature reviews. Endocrinology* 2013; 9: 479-493.
 64. Lloyd-Jones D, Adams R, Carnethon M, *et al.* Heart disease and stroke statistics-2009 update: A report from the american heart association statistics committee and stroke statistics subcommittee. *Circulation* 2009; 119: e21-181.
 65. Kalin MF, Zumoff B. Sex hormones and coronary disease: A review of the clinical studies. *Steroids* 1990; 55: 330-352.
 66. Hulley S, Grady D, Bush T, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (hers) research group. *JAMA* 1998; 280: 605-613.
 67. Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
 68. Jyotsna VP. Postmenopausal hormonal therapy: Current status. *Indian Journal of Endocrinology and Metabolism* 2013; 17: S45-S49.
 69. Callou de Sa EQ, Feijo de Sa FC, e Silva Rde S, *et al.* Endogenous oestradiol but not testosterone is related to coronary artery disease in men. *Clinical Endocrinology* 2011; 75: 177-183.
 70. Calof OM, Singh AB, Lee ML, *et al.* Adverse events associated with testosterone replacement in middle-aged and older men: A meta-analysis of randomized, placebo-controlled trials. *Journal of Gerontology. Series A, Biological Sciences and Medical Sciences* 2005; 60: 1451-1457.
 71. Haddad RM, Kennedy CC, Caples SM, *et al.* Testosterone and cardiovascular risk in men: A systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clinic Proceedings* 2007; 82: 29-39.
 72. Fernandez-Balsells MM, Murad MH, Lane M, Lampropoulos JF, *et al.* Clinical review 1: Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2010; 95: 2560-2575.
 73. Huie MJ. An acute myocardial infarction occurring in an anabolic steroid user. *Medicine and Science in Sports and Exercise* 1994; 26: 408-413.
 74. Wysoczanski M, Rachko M, Bergmann SR. Acute myocardial infarction in a young man using anabolic steroids. *Angiology* 2008; 59: 376-378.
 75. Stergiopoulos K, Brennan JJ, Mathews R, Setaro JF, Kort S. Anabolic steroids, acute myocardial infarction and polycythemia: A case report and review of the literature. *Vascular Health and Risk Management* 2008; 4: 1475-1480.
 76. Kennedy C. Myocardial infarction in association with misuse of anabolic steroids. *Ulster Medical Journal* 1993; 62: 174-176.
 77. McNutt RA, Ferencick GS, Kirilin PC, Hamlin NJ. Acute myocardial infarction in a 22-year-old world class weight lifter using anabolic steroids. *American Journal of Cardiology* 1988; 62: 164.
 78. Bowman S. Anabolic steroids and infarction. *BMJ* 1990; 300: 750.
 79. Goldstein DR, Dobbs T, Krull B, Plumb VJ. Clenbuterol and anabolic steroids: A previously unreported cause of myocardial infarction with normal coronary arteriograms. *Southern Medical Journal* 1998; 91: 780-784.
 80. Fisher M, Appleby M, Rittoo D, Cotter L. Myocardial infarction with extensive intracoronary thrombus induced by anabolic steroids. *British Journal of Clinical Practice* 1996; 50: 222-223.
 81. Kennedy MC, Lawrence C. Anabolic steroid abuse and cardiac death. *Medical Journal of Australia* 1993; 158: 346-348.
 82. Weidemann W, Hanke H. Cardiovascular effects of androgens. *Cardiovascular Drug Reviews* 2002; 20: 175-198.
 83. Sullivan ML, Martinez CM, Gennis P, Gallagher EJ. The cardiac toxicity of anabolic steroids. *Progress in Cardiovascular Diseases* 1998; 41: 1-15.
 84. Parssinen M, Seppala T. Steroid use and long-term health risks in former athletes. *Sports Medicine* 2002; 32: 83-94.
 85. Wilson JD. Androgen abuse by athletes. *Endocrine Reviews* 1988; 9: 181-199.
 86. Yesalis CE, Kennedy NJ, Kopstein AN, Bahrke MS. Anabolic-androgenic steroid use in the united states. *JAMA* 1993; 270: 1217-1221.
 87. Wu FC, von Eckardstein A. Androgens and coronary artery disease. *Endocrine Reviews* 2003; 24: 183-217.
 88. Yarnell JW, Beswick AD, Sweetnam PM, Riad-Fahmy D. Endogenous sex hormones and ischemic heart disease in men. The caerphilly prospective study. *Arteriosclerosis and Thrombosis* 1993; 13: 517-520.
 89. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. *Arteriosclerosis and Thrombosis* 1994; 14: 701-706.
 90. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart* 2010; 96: 1821-1825.
 91. Dunajska K, Milewicz A, Szymczak J, *et al.* Evaluation of sex hormone levels and some metabolic factors in men with coronary atherosclerosis. *Aging Male* 2004; 7: 197-204.
 92. Debing E, Peeters E, Duquet W, Poppe K, Velkeniers B, Van Den Brande P. Men with atherosclerotic stenosis of the carotid artery have lower testosterone levels compared with controls. *International Angiology* 2008; 27: 135-141.
 93. Dorr M, Wallaschofski H, Friedrich N. Association of low total testosterone levels and prevalent carotid plaques: Result of the study of health in Pomerania. *European Journal of Epidemiology* 2009; 24: 389-391.
 94. Li L, Guo CY, Jia EZ, *et al.* Testosterone is negatively associated with the severity of coronary atherosclerosis in men. *Asian Journal of Andrology* 2012; 14: 875-878.
 95. Hu X, Rui L, Zhu T, *et al.* Low testosterone level in middle-aged male patients with coronary artery disease. *European Journal of Internal Medicine* 2011; 22: e133-136.
 96. Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. *Journal of Clinical Epidemiology* 1998; 51: 581-586.
 97. Bernini GP, Sgro M, Moretti A, *et al.* Endogenous androgens and carotid intimal-medial thickness in women. *Journal of Clinical Endocrinology and Metabolism* 1999; 84: 2008-2012.
 98. Kaczmarek A, Reczuch K, Majda J, Banasiak W, Ponikowski P. The association of lower testosterone level with coronary artery disease in postmenopausal women. *International Journal of Cardiology* 2003; 87: 53-57.
 99. Debing E, Peeters E, Duquet W, Poppe K, Velkeniers B, Van den Brande P. Endogenous sex hormone levels in postmenopausal women undergoing carotid artery endarterectomy. *European Journal of Endocrinology* 2007; 156: 687-693.
 100. He H, Yang F, Liu X, *et al.* Sex hormone ratio changes in men and postmenopausal women with coronary artery disease. *Menopause* 2007; 14: 385-390.

101. L. H. Testosterone propionate in the treatment of angina pectoris. *Journal of Clinical Endocrinology* 1942; 2: 325-328.
102. TC. W. The use of testosterone propionate and estrogenic substance in the treatment of essential hypertension, angina and peripheral vascular disease. *Journal of Clinical Endocrinology* 1942; 2: 560-568.
103. Morris PD, Channer KS. Testosterone and cardiovascular disease in men. *Asian Journal of Andrology* 2012; 14: 428-435.
104. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. *Circulation* 2000; 102: 1906-1911.
105. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *European Journal of Endocrinology* 2009; 161: 443-449.
106. Jaffe MD. Effect of testosterone cypionate on postexercise ST segment depression. *British Heart Journal* 1977; 39: 1217-1222.
107. Wu SZ, Weng XZ. Therapeutic effects of an androgenic preparation on myocardial ischemia and cardiac function in 62 elderly male coronary heart disease patients. *Chinese Medical Journal* 1993; 106: 415-418.
108. Sieger LH. Treatment of angina pectoris by testosterone propionate. *New York Journal of Medicine* 1943; 43: 1424-1428.
109. Webb CM, Adamson DL, de Zeigler D, Collins P. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *American Journal of Cardiology* 1999; 83: 437-439, A439.
110. Rosano GM, Leonardo F, Pagnotta P, *et al.* Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation* 1999; 99: 1666-1670.
111. Thompson PD, Ahlberg AW, Moyna NM, *et al.* Effect of intravenous testosterone on myocardial ischemia in men with coronary artery disease. *American Heart Journal* 2002; 143: 249-256.
112. Wang C, Chan V, Tse TF, Yeung RT. Effect of acute myocardial infarction on pituitary-testicular function. *Clinical Endocrinology* 1978; 9: 249-253.
113. Nahrendorf M, Frantz S, Hu K, *et al.* Effect of testosterone on post-myocardial infarction remodeling and function. *Cardiovascular Research* 2003; 57: 370-378.
114. Ablewska U, Jankowski K, Rzewuska E, Liszewska-Pfejfer D, Hryniewiecki T. A levels of endogenous gonadal hormones and their relationship with selected coronary artery disease risk factors among young women post myocardial infarction. *Acta Biochimica Polonica* 2011; 58: 385-389.
115. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. *Heart* 2004; 90: 446-447.
116. Caminiti G, Volterrani M, Iellamo F, *et al.* Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *Journal of the American College of Cardiology* 2009; 54: 919-927.
117. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS. Testosterone therapy in men with moderate severity heart failure: A double-blind randomized placebo controlled trial. *European Heart Journal* 2006; 27: 57-64.
118. Pugh PJ, Jones TH, Channer KS. Acute haemodynamic effects of testosterone in men with chronic heart failure. *European Heart Journal* 2003; 24: 909-915.
119. Iellamo F, Volterrani M, Caminiti G, *et al.* Testosterone therapy in women with chronic heart failure: A pilot double-blind, randomized, placebo-controlled study. *Journal of the American College of Cardiology* 2010; 56: 1310-1316.
120. Moriyama Y, Yasue H, Yoshimura M, *et al.* The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *Journal of Clinical Endocrinology and Metabolism* 2000; 85: 1834-1840.
121. Jankowska EA, Biel B, Majda J, *et al.* Anabolic deficiency in men with chronic heart failure: Prevalence and detrimental impact on survival. *Circulation* 2006; 114: 1829-1837.
122. Kontoleon PE, Anastasiou-Nana MI, Papapetrou PD, *et al.* Hormonal profile in patients with congestive heart failure. *International Journal of Cardiology* 2003; 87: 179-183.
123. Wehr E, Pilz S, Boehm BO, Marz W, Grammer T, Obermayer-Pietsch B. Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography. *European Journal of Heart Failure* 2011; 13: 482-488.
124. Jankowska EA, Filippatos G, Ponikowska B, *et al.* Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. *Journal of Cardiac Failure* 2009; 15: 442-450.
125. Toma M, McAlister FA, Coglianese EE, *et al.* Testosterone supplementation in heart failure: A meta-analysis. *Circulation Heart Failure* 2012; 5: 315-321.
126. Stout M, Tew GA, Doll H, *et al.* Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: A double-blind randomized controlled feasibility study. *American Heart Journal* 2012; 164: 893-901.
127. Khaw KT, Dowsett M, Folkard E, *et al.* Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (Epic-Norfolk) Prospective Population Study. *Circulation* 2007; 116: 2694-2701.
128. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *Journal of Clinical Endocrinology and Metabolism* 2008; 93: 68-75.
129. Tivesten A, Vandenput L, Labrie F, *et al.* Low serum testosterone and estradiol predict mortality in elderly men. *Journal of Clinical Endocrinology and Metabolism* 2009; 94: 2482-2488.
130. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2011; 96: 3007-3019.
131. Corona G, Monami M, Boddi V, *et al.* Low testosterone is associated with an increased risk of male lethality in subjects with erectile dysfunction. *Journal of Sexual Medicine* 2010; 7: 1557-1564.
132. Martin-Merino E, Johansson S, Morris T, Garcia Rodriguez LA. Androgen deprivation therapy and the risk of coronary heart disease and heart failure in patients with prostate cancer: A nested case-control study in UK primary care. *Drug Safety* 2011; 34: 1061-1077.
133. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *Journal of the National Cancer Institute* 2007; 99: 1516-1524.
134. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Archives of Internal Medicine* 2006; 166: 1660-1665.
135. Maggio M, Lauretani F, Ceda GP, *et al.* Relationship between low levels of anabolic hormones and 6-year mortality in older men: The aging in the Chianti area (InChianti) study. *Archives of Internal Medicine* 2007; 167: 2249-2254.
136. Ruige JB, Ouwens DM, Kaufman JM. Beneficial and adverse effects of testosterone on the cardiovascular system in men. *Journal of Clinical Endocrinology and Metabolism* 2013; 98: 4300-4310.