EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

10TH CONGRESS OF THE EUROPEAN SOCIETY FOR SEXUAL MEDICINE (ESSM)

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CARDIAC SEXOLOGY: CAN WE SAVE A PATIENT'S LIFE AND HIS LOVE LIFE?

There is now a large body of evidence that erectile dysfunction (ED) is closely linked with underlying cardiovascular and metabolic conditions, and can act as a sentinel for cardiovascular disease. Endothelial dysfunction is likely to be the common pathological factor underlying ED and cardiovascular disease. The latest research in this emerging area of sexual medicine was discussed at a satellite symposium at the 10th ESSM Congress in Lisbon.

New horizons in erectile and endothelial dysfunction research and therapies

Every physiological event that happens in the penile erectile tissue in response to sexual stimulation depends on the vascular endothelium, said François Giuliano (Neuro-Uro-Andrology Unit, Department of Physical Medicine and Rehabilitation, Raymond Poincaré Hospital, Garches, France). There is activation of the autonomic pathway to the penis, vasodilation in the penile arteries and relaxation of the smooth muscle in the sinusoidal spaces of the erectile tissue. Endothelial tissue is present in the sinusoidal spaces as well as the blood vessels. Vascular and penile endothelium is fundamental in the regulation of vascular tone because it releases a variety of factors that affect the contraction and relaxation of the underlying vascular smooth muscle. The endothelium is also responsible for the homeostasis of the vascular bed. When there is endothelial dysfunction, vascular homeostasis is impaired and vascular disease results. The same mechanisms lead to erectile dysfunction.

Nitric oxide (NO) serves many biological functions. As a neurotransmitter, NO is responsible for relaxation of the smooth-muscle fibres in the erectile tissue, leading to penile erection. There are two main sources of NO: neural terminations and endothelial cells. The erectile process is initiated by release of NO at the neural termination but sustained by NO from the endothelial cells, Dr. Giuliano noted. Neural activation of NO in response to sexual stimulation is reversible and brief, but the resulting vasorelaxation causes increased blood flow and physical expansion of the penile vasculature and the sinusoidal spaces. The resulting shear force on the endothelium of these structures activates more sustained NO release [1].

The prevalence of both endothelial dysfunction and erectile dysfunction (ED) increases with age. The presence of cardiovascular conditions and cardiovascular risk factors is also closely associated with ED. The placebo arm of the Prostate Cancer Prevention Trial followed a cohort of over 9,000 men aged 55 or over from 1994 till 2003. In addition to looking for prostate cancer, the study collected data on ED and cardiovascular events. Forty-seven per cent of men had some degree of ED at study entry. Of those without ED at baseline, 65% reported its onset by seven years of follow-up. There was a striking association between the onset of ED and the first occurrence of an acute cardiovascular event [2]. The authors concluded that the occurrence of ED has the same prognostic value for cardiovascular disease as smoking or a family history of myocardial infarction. "It is very likely that ED is a sentinel, not only for cardiovascular risk factors but for acute cardiovascular events," said Dr. Giuliano. Endothelial dysfunction is very likely to be the unifying alteration occurring in the pathogenesis of cardiovascular disease, ageing, and ED.

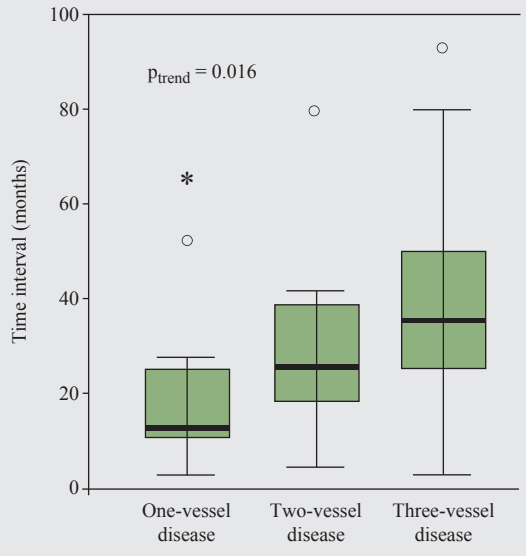
Many studies have now confirmed the close link between ED and cardiovascular disease. Gazzaruso and coworkers compared 133 men with apparently uncomplicated type 2 diabetes and silent coronary artery disease (CAD, diagnosed by imaging) with 127 similar diabetic men who had no CAD. They found that ED was present in 33.8% of men with CAD and only 4.7% of those without, suggesting a

strong and independent association between ED and silent CAD in these patients [3]. Chiurlia and coworkers compared 70 men with ED and no symptomatic heart disease with 73 matched controls without ED but with similar cardiovascular risk factors [4]. They found that men with ED had significantly higher levels of high-sensitivity C-reactive protein, more impairment of flow-mediated dilatation of the brachial artery, and more frequent coronary artery calcification. Men with ED were 3.7 times more likely than controls to have a calcification score above the 75th percentile. They concluded that coronary atherosclerosis is more severe in patients with ED and that ED predicts the presence and extent of coronary atherosclerosis independently of traditional risk factors for cardiovascular disease. ED can thus be seen as additional early warning sign of coronary atherosclerosis.

Prevention of cardiovascular disease by early identification of ED

The artery size hypothesis postulates that the penile arteries, which are 1–2 mm in diameter, will be affected clinically (in the form of ED) by levels of artery disease that are asymptomatic in the larger coronary and carotid arteries [5]. However, even small atherosclerotic lesions in the coronary arteries pose a significant danger because they are liable to rupture, said Graham Jackson (Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, UK).

Figure 1 **TIME INTERVAL BETWEEN ONSET OF ERECTILE DISEASE AND CORONARY ARTERY DISEASE SYMPTOMS**



Source: Montorsi P, et al. Eur Heart J 2006;27:2632–2639.

ED prevalence and time of onset was studied in 300 consecutive men presenting with acute chest pain and CAD [6]. The prevalence of ED among all patients was 49%. Of the men presenting with coexisting ED and CAD, 67% said ED had preceded their first onset of CAD symptoms. The mean time interval from onset of ED to onset of CAD symptoms was 38.8 months (range 1–168 months). Thus, in this study one third of men presenting to a coronary care unit had ED, with an average time of onset of three years previously. This strongly supports the idea that ED predicts an acute coronary syndrome, Dr. Jackson noted. Several other studies report similar findings. In the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial, which evaluated ED in 285 patients with CAD, Montorsi and colleagues found that the degree of severity of ED is related to the extent of CAD [7]. They also found that in patients with established CAD, ED comes before CAD by an average of two up to three years (Figure 1). "Approximately half to two thirds of men with CAD have ED, and approximately 50% of men with ED have silent CAD," said Dr. Jackson in summary.

The Princeton guidelines on sexual dysfunction and cardiac risk note that 'the recognition of ED as a warning sign of silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise.' They recommend that men with ED and other cardiovascular risk factors, such as obesity or sedentary lifestyle, should be counselled in lifestyle modification [8]. Unfortunately, the large cardiovascular risk reduction studies have not collected data on ED.

Dr. Jackson described a study from his own hospital of 19 men with ED and no cardiac symptoms [9]. They had normal blood pressure, although seven were on antihypertensive therapy. On evaluation, many men were found to have silent cardiac disease or significant risk factors. Seventeen had elevated low-density lipoprotein cholesterol and nine had abdominal obesity. Exercise ECGs were abnormal in four patients, but with no chest pain. Coronary calcium score was significantly raised in 10 and marginally raised in four. Computerised tomography coronary angiography revealed significant CAD in all 10 patients with raised calcium scores, and single atherosclerotic plaques in the four with marginally raised scores. Of the 10 patients with significant CAD, seven had normal exercise ECGs. He then asked delegates to vote on whether ED should be used as a means of preventing cardiovascular events. Ninety-one per cent agreed that it should.

ED can be a marker of silent CAD, even when exercise ECG is normal, emphasised Dr. Jackson in his concluding remarks. Physicians should consider aggressive cardiovascular risk reduction for all men with ED and no cardiac symptoms. "We have a time window of two to five years to reduce the risk of events," he said. This will involve team work between the family doctor, nurse, urologist, and cardiologist. A comprehensive education programme is needed so that men with ED will seek treatment sooner rather than later.

Understanding individuals' response to erectile dysfunction

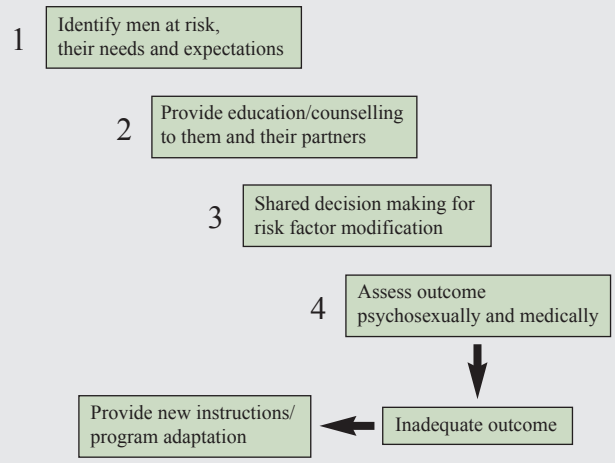
ED is highly prevalent in men with cardiovascular diseases, yet frequently underrecognised and underdiagnosed in

clinical practice. Many men do not seek help for their ED [10]. Dimitrios Hatzichristou (Center for Sexual and Reproductive Health, Aristotle University of Thessaloniki, Thessaloniki, Greece) described a study by his group assessing life satisfaction and quality of life in 69 men with ED. They found that men with moderate ED perceived the same impact of ED on their life satisfaction and satisfaction with their sexual life as did men with severe ED [11]. There was evidence that men with ED turn to other domains of life to compensate for low levels of overall life satisfaction: they gave higher satisfaction scores relating to finance and hobbies than men without ED.

Health professionals typically approach management of chronic illnesses from a disease-centred rather than a patient-centred perspective, Dr. Hatzichristou said. This may not adequately include the patient's perspective. In turn, patients frequently state that they are not understood by physicians in a whole-person context. The course of both ED and cardiovascular disease requires continuous adjustment by men and their partners as they adapt to the chronicity of cardiovascular disease and the new reality in their sexual lives. Partners often have fears about the risk of a myocardial infarction being triggered by intercourse. Working with these patients is complex and requires a holistic approach.

Goldstein described cardiovascular disease, ED, and depression as a mutually reinforcing triad [12]. Treating ED can reduce psychological distress. Bocchio and coworkers investigated the effect of tadalafil or placebo on self-evaluated psychological distress, erectile function, and quality of sexual life in 36 men with ED and cardiovascular risk factors [13]. Sexual life satisfaction (LiSat-2) was significantly improved after tadalafil and after placebo, but a strong positive correlation was observed between LiSat-2 and Sexual Health Inventory for Men (SHIM) score after tadalafil treatment ($p = 0.0003$) and not after placebo ($p = 0.189$). Psychological features were significantly changed after treatment, although a specific effect of tadalafil versus placebo was observed only for interpersonal sensitivity ($p = 0.042$). Obsessive-compulsive dimension, depression, anxiety, and psychoticism were significantly improved in both the tadalafil and the placebo groups, although the improvement was more relevant after treatment with tadalafil. These preliminary data suggest that a short treatment of ED reduced psychological distress and improved quality of sexual life in men with vascular risk factors. Dr. Hatzichristou concluded by presenting an algorithm for a common, patient-centred prevention strategy for ED and cardiovascular disease (Figure 2)

Figure 2 **ALGORITHM FOR A COMMON PREVENTION STRATEGY FOR ED AND CARDIOVASCULAR DISEASE**



ED = erectile dysfunction

Source: Hatzichristou D, Tsimtsiou Z. Am J Cardiol 2005;96(Suppl. 2):80M–84M.

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