Erectile dysfunction and cardiovascular disease - a suitable case for treatment and prevention?

Professor Paul Collinson.

Departments of Clinical Blood Sciences and Cardiology

St George's University Hospitals NHS Foundation Trust and St George's University of London.

Cranmer Terrace, London SW17 0QT

paul.collinson@stgeorges.nhs.uk

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Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection for satisfactory sexual performance. The prevalence of ED has been estimated as nearly 40% of men > 40 years of age [1] although these figures are contested [2]. ED increases in frequency with age and is estimated to affect 15% of men 40-50 years, 45% of men in their 60s and 70% of men older than 70 years [3]. Successful erection is a complex system involving reflex action (peripheral nerves and spinal cord), the limbic system (psychogenic stimuli) and the release of nitric oxide. Adequate levels of testosterone are required, hence an intact hypothalamo/pituitary/testicular axis. Hence, ED can result from disease or treatment that produces hormonal deficiency, neurological impairment, problems with penile blood flow, disorders of tissue mechanics, psychological factors or any combination of these.

Logically, ED secondary to testosterone deficiency should be treated by testosterone replacement. Testosterone levels in men decrease with age [4]. Both epidemiological and observational studies have demonstrated reduced testosterone is associated with increased cardiovascular risk. One meta-analysis showed lower testosterone and higher 17β oestradiol as significant risk predictor despite adjustment for age and body mass index [4]. Patients with coronary artery disease have been found to have lower testosterone levels than controls and there is inverse correlation between testosterone and the incidence of major cardiovascular disease (CVD) [4]. A significant negative correlation has been reported between total testosterone levels and Framingham risk score [4]. However, it has been pointed out that "It is unclear if this is a causal association or due to low testosterone being a biomarker of poor health" [4]. Testosterone replacement as a treatment for ED is controversial. Meta-analysis of studies has suggested a neutral impact of testosterone replacement on major adverse CVD events [4]. However, clinical trials of testosterone replacement and cohort studies of men receiving replacement therapy have shown contradictory and diametrically opposed results [4]. To date there have been no trials specifically designed to assess replacement in patients

with CVD. Similarly there is interest in the use of testosterone as a therapeutic option in a range of CVD related conditions. The role of testosterone as a risk modifier or a therapeutic agent in CVD remains a situation in flux [4].

Endothelial dysfunction is one of the first changes in cardiovascular disease. ED and cardiovascular disease share many common risk factors including age, hypertension, diabetes, insulin resistance, smoking, increased body mass index, cholesterol and low high density lipoprotein, metabolic syndrome, sedentary lifestyle and depression [1 3 5]. Numerous studies and meta-analyses have confirmed the association between ED and coronary artery disease (CAD). ED is associated with asymptomatic CAD [1 3 5]. ED precedes CAD and referral for coronary artery disease by periods ranging from 2 to 5 years [1]. Compared with controls, patients with ED have a higher risk for total CV events (44%), MI (60%) and all-cause mortality (25%) [1]. ED also appears to be a marker of the severity of CVD with ED associated with increased risk of CVD mortality with a hazard ratio 1.48 in a large meta-analysis of 12 prospective cohort studies [3].

In the well-characterised multi-ethnic study of atherosclerosis (MESA) study 1862 men free of known cardiovascular disease were well-characterised with comprehensive baseline subclinical vascular disease phenotyping. ED status was assessed at the fifth visit with a standardised questionnaire on ED symptoms [6]. Patients with ED had a higher coronary artery calcification score, increased carotid intima medial thickness and plaque score, reduced carotid and aortic distensibility and reduced brachial flow mediated dilation. However, out of all of these, only coronary artery calcification and carotid plaque score were significantly associated with the ED. The authors concluded that subclinical vascular disease is common in men who later self-report ED [6]. Assessment of CVD risk factors in men with ED with or without established CVD is a Class IIa Level C recommendation in the joint European Society of Cardiology (ESC) 2016 European Guidelines on cardiovascular disease prevention

in clinical practice[1]. It is less well-established whether ED is a sentinel event for CVD[3] but the inclusion of ED symptoms as part of a cardiovascular risk assessment has been advocated[5]. However the ESC guidelines consider that there is a gap in the evidence on the benefits of routine screening for ED and what is the most effective tool to assess ED is unclear. A note of caution is required. Some workers consider that sexual functioning is a mirror of overall male health irrespective of cardiovascular risk factors [7].

The advent of the phosphodiesterase 5 (PDE5) inhibitors, including sildenafil (Viagra™), vardenafil (Levitra™) and tadalafil (Cialis™) has transformed the treatment of ED by directly targeting endothelial dysfunction. The clinical development of the first in class agent, sildenafil was, according to medical urban myth, consequent to an interesting side effect noted in early human volunteer studies. This is in fact true. Sildenafil was originally investigated as a potential antihypertensive agent, a role which it maintains in the treatment of pulmonary arterial hypertension. Sildenafil produces vasodilatation in vascular beds which have high concentrations of PDE5 including the corpus cavernosum and the lungs. Sildenafil produces targeted vasodilatation and is a very successful agent for the treatment of ED. It is remarkable that this drug is one of the few to have achieved trade name recognition in popular culture including being directly mentioned by Sir Michael Caine in a memorable scene in the second Austin Powers film "Goldmember".

Cardiological interest in PDE5 inhibitors was initially as a safety concern due to the potential to interact with nitrates (which remains as a contraindication to their use). Other concerns were that cardiovascular events might be precipitated by the physical activity involved post administration. One cardiologist recommended anyone contemplating treatment with PDE5 inhibitors should have a full cardiological assessment prior to administration. In this issue of Heart, Andersson and colleagues have performed an analysis of data from the enviable Swedish registries looking at the instance of cardiac events in patients receiving treatment for

ED. They performed a Swedish nation-wide cohort study of all men < 80 years of age without prior MI, or cardiac revascularization, hospitalized for MI from 2007 to end 2013. They used prescription of PDE5 inhibitors or alprostadil (a prostaglandin), as surrogate for the presence of ED and examined how this was related to risk of death, MI, cardiac revascularization or heart failure. Those treated with PDE5 inhibitors but not alprostadil had a 33% lower mortality and 40% lower risk of hospitalization for heart failure. The risk was proportionally lower more PDE5 inhibitors were dispensed.

There are some caveats to this study. Men who receive ED medication are more likely to be in a caring relationship, a factor known to reduce CVD risk. In addition those requesting ED medication are likely to be healthier, a factor the authors acknowledge and discuss. Finally, the study looks at prescription of ED medication rather than ED itself. This may be strength rather than a weakness.

The first conclusion is that treatment with PDE5 inhibitors appears to be safe. Therefore cardiologists may recommend PDE5 inhibitors to their patients (with appropriate clinical assessment and medication review). The second is much more intriguing. PDE5 inhibitors may be cardioprotective and a new therapeutic option for treatment or prevention. This is not such an outrageous suggestion. Sildenafil has been shown to reduce cardiac infarct size following ischaemia/reperfusion injury [8]. The subject has recently been reviewed with the suggestion that PDE5 inhibitors may have a role in a range of cardiac and non-cardiac conditions [8].

At this point the findings of Andersson and colleagues must be interpreted with caution but PDE5 inhibitors appear to be safe and may even be have a role in therapy for prevention or treatment of CVD. This is an area worthy of further study. Perhaps there will be yet another serendipitous but useful side effect of sildenafil treatment. The concept of the combined

preparation of sildenafil and atorvastatin may not be so far-fetched. Improved compliance for prevention is likely (and the patient will not roll out of bed at night).

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