Erectile dysfunction in primary care: a focus on cardiometabolic risk evaluation and stratification for future cardiovascular events

Martin Miner, MD,[1] Matt T. Rosenberg, MD,[2] Jack Barkin, MD[3]

[1]Departments of Family Medicine and Urology, Miriam Hospital, Brown University, Providence, Rhode Island, USA
[2]Mid Michigan Health Centers, Jackson, Michigan, USA
[3]Department of Surgery, University of Toronto, Humber River Regional Hospital, Toronto, Ontario, Canada

MINER M, ROSENBERG MT, BARKIN J. Erectile dysfunction in primary care: a focus on cardiometabolic risk evaluation and stratification for future cardiovascular events. Can J Urol 2014;21(Suppl 2):25-38.

An association between erectile dysfunction (ED) and cardiovascular disease has long been recognized, and studies suggest that ED is an independent marker of cardiovascular disease risk and even further, a marker for the burden of both obstructive and non-obstructive coronary artery disease. Therefore, the primary care physician (PCP) must assess the presence or absence of ED in every man > 39 years of age, especially if that man is asymptomatic of signs and symptoms of coronary artery disease. Assessment and management of ED may help identify and reduce the risk of future cardiovascular events, particularly in younger middle-aged men. The initial ED evaluation should distinguish between predominantly vasculogenic ED and ED of other etiologies. For men believed to have predominantly vasculogenic ED, we recommend that initial cardiovascular risk stratification be based on the Framingham Risk Score. Management of men with ED who are at low risk for cardiovascular disease should focus on risk factor control; men at high risk, including those with cardiovascular symptoms, should be referred to a cardiologist. Intermediate risk men should undergo noninvasive evaluation for subclinical atherosclerosis. A growing body of evidence supports the use of selected prognostic markers to further understand cardiovascular risk in men with ED, particularly CT calcium scoring. In conclusion, we support cardiovascular risk stratification and risk factor management in all men with vasculogenic ED.

Key Words: erectile dysfunction, cardiovascular, primary care

Introduction

Erectile dysfunction (ED), defined as the inability to maintain and achieve an erection sufficient for satisfactory intercourse, has a high prevalence and incidence worldwide.[1] A systematic review of epidemiologic evidence undertaken in 2002 showed a clear increase in prevalence in with advancing age, with rates for men younger than 40 years ranging from approximately from 2%-9%, compared with 18%-86% for those older than 80 years.[2] Although not life-threatening, it may be a precursor or marker of more serious conditions, particularly coronary artery disease (CAD). Inman et al[3] have shown when ED occurs in younger men, particularly less than 50 years old, it is associated with a marked increase in the risk of future cardiac events. Overall ED may be associated with an approximately 80% higher risk of subsequent CAD.[3]

Sexual function is a complex, multifactorial process. The implementation of sexual inquiry in primary care should occur at a minimum during the health surveillance visit or during the initiation of another therapy that might affect sexual function (e.g. hypertension management). The development of ED is attributable to both psychogenic factors and physiologic alterations in neural, vascular, hormonal and metabolic perturbations, all mediated through endothelial and smooth muscle dysfunction. The fact that ED often coexists with hypertension, hyperlipidemia, and diabetes[2] provides support for a vasculogenic etiology of ED. Beyond its association with vascular risk factors, vasculogenic ED has been recently recognized as a marker of both early endothelial and smooth muscle dysfunction and the first of many factors influencing the cascade of future cardiovascular (CVS) events. Consequently, the identification of largely organic ED through history-taking and sexual inquiry and the subsequent work up and potential identification of "plaque burden" in the younger middle-aged man have significant prognostic import.

Definition and prevalence

For years, the terms impotence and ED were used interchangeably to denote the inability of a man to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse.[4] Social scientists objected to the impotence label, because of its pejorative implications and lack of precision.[5] An NIH Consensus Development Conference suggested that ED be used in place of the term impotence to signify "an inability of the male to achieve an erect penis as part of the overall multifaceted process of male sexual function."[6] This de-emphasized intercourse as the sine qua non of sexual life and gave equal importance to other aspects of male sexual behavior. Sigal et al studied data on men 20 years and older collected via The National Health and Nutrition Examination Survey (NHANES) that included medical histories in which specific queries were made regarding sexual function.[7] ED was reported by nearly 1 in 5 respondents.[7] Hispanic men were more likely to report ED (odds ratio [OR], 1.89), after controlling for other factors. The prevalence of ED increased substantially with advanced age, and 77.5% of men ≥ 75 years were affected.[7]

ED can be categorized as organic (vasculogenic) or psychogenic or mixed, Table 1. In general, primary vasculogenic ED is characterized by a gradual onset. Erectile rigidity may be weakened, duration may be shortened, or both. These changes occur slowly, initially irregularly, and eventually are evident under most or all circumstances, be it with the morning erection, nocturnal erection, or sexually-stimulated erection.[8] Situational ED, such as that occurring with a partner but not with morning erections or masturbatory behavior, is usually considered psychogenic in origin.[8]

Either Doppler duplex penile imaging or nocturnal penile tumescence testing (Rigiscan) can validate this, though is often not necessary in primary care management.

Comorbidities and cardiometabolic risk

As mentioned, the cascade of metabolic parameters associated with ED can lead to early endothelial dysfunction and eventually, late CVS events. This article will initially focus on the metabolic work up of the ED patient and the evolving concept of "cardiometabolic risk."

Cardiometabolic risk entails the risk of developing any of the following: type 2 diabetes (T2DM), cardiovascular disease (CVD), or metabolic syndrome (MetS). The assessment of cardiometabolic risk uses traditional risk factors such as smoking, high LDL-C cholesterol, hypertension, and elevated serum glucose as well as emerging risk factors closely related to abdominal obesity, especially intra-abdominal or visceral obesity. The relationship between traditional CVS risk factors (hypercholesterolemia, hypertension and smoking) and the occurrence of CVS events is well understood. Our increasing understanding of the pathophysiology of CVD is now defining value of a range of new CVS risk factors. Risk stratification for future CVS events requires measurement tools of CVD risk that must be valid in the general male population, and measurement tests or biomarkers that help predict cardiac risk.[9] Though not included in most CVS risk engines such as Framingham, ED should become part of this CVD risk assessment in the male.

Traditional models of CVS risk such as Framingham Risk Score (FRS) are weighted toward age, and 80% of

TABLE 1. Differential characteristics of psychogenic versus organic erectile dysfunction[8,13]

Characteristic	Predominantly psychogenic ED	Predominantly organic ED
Onset	Acute	Gradual
Circumstances	Situational	Global
Course	Intermittent	Constant
Noncoital erection	Rigid	Poor
Nocturnal/early morning erections	Normal	Inconsistent
Psychosexual problems	Long history	Secondary to ED
Partner problems	At onset	Secondary to ED
Anxiety/fear	Primary	Secondary to ED

ED = erectile dysfunction

men age 40-59 will have a low 10 year risk.[10] Lifetime risk is not determined in the FRS. Incorporating some assessment of lifetime risk has been proposed as an added step to evaluate CVS risk in this young middle-age population noted by Inman with ED to be at particularly elevated CVS risk.[3]

New data have emerged to justify a new version, though controversial, to better target both risk and lipid management therapies for the reduction of CVS events in the adult population.[11] New guidelines have attempted to address the shortcomings of older risk models. ED guidelines such as Princeton III[12] have attempted to utilize evidence-based evaluation to further stratify men for CVS risk following the utilization of keen history taking and traditional risk models to establish the presence of predominantly vasculogenic ED and the volume of subclinical atherosclerotic burden which are markers for subsequent CVS events of MI and CVA in men.[13]

Key questions in ED management

- Is a history of largely organic ED a harbinger for future CVS risk? If so, does a timeframe or "window of opportunity" exist to lower the risk of future CVD events?
- Are there cost-effective, sensitive, and specific metabolic or imaging tests that might indicate increased CVS risk?
- Will these tests delineate treatment based on identification of either obstructive CAD or atherosclerotic burden and thereby lower future CVS risk and improve erectile function?

The metabolic syndrome (MetS): a cluster of findings increasing risk of type 2 DM and CVD-the cardiometabolic nexus of ED

MetS is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. MetS is defined by a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), other forms of atherosclerotic cardiovascular disease (ASCVD), and type 2 DM.[14] Its main components are dyslipidemia [elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins (small dense LDL subparticles), and low high density lipoproteins (HDL)], hypertension, and deregulated glucose homeostasis.[14] While abdominal obesity and/or insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome, other abnormalities such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver

disease and sleep apnea have been added to the entity of the syndrome, making its definition even more complex.[15] Besides the many components and clinical implications of MetS, there is still no universally accepted pathogenic mechanism or clearly defined diagnostic criteria. Furthermore, there is still debate as to whether this entity represents a specific syndrome or is a surrogate of combined risk factors that put the individual at particular risk.[15]

The most current definition incorporates the International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) definitions and requires a patient to have any three of the following five conditions.[14]

- Elevated waist circumference (ethnicity specific values, e.g. European males > 94 cm [40 in] and females > 80 cm)
- Triglycerides 1.7 mmol/L or greater 150 mg/dL
- HDL-chol below 1.03 mmol/L [< 40 mg/dL]
- BP > 135/85 mmHg
- Fasting glucose > 5.6 mmol/L [> 100 mg/dL]

ED has been linked to multiple selected aspects of the metabolic syndrome, including type 2 diabetes mellitus,[7,16] increased fasting blood glucose,[17,18] arteriosclerotic disease manifestations,[19-21] hypertension,[7,17,22-24] and obesity.[7,17,18] Moreover, Bal et al[18] noted that the risk of ED increased in line with the number of factors of the MetS exhibited by a patient. Several interrelated mechanisms may explain the observed relationship between the MetS and ED. One obvious mechanism could be a low testosterone level, which has been shown to be associated with moderate and severe ED,[25] possibly via a mechanism of diminished NO synthesis.[26] This hypothesis was supported by a report that testosterone treatment increases cavernosal expression of NO synthetase mRNA in rats.[27] In this way, hypogonadism as a manifestation of the MetS could result in a diminished NO synthesis and subsequent ED. Another mechanism is peripheral arterial insufficiency due to an atherosclerotic disease. The presence of arterial vasculogenic ED is associated with ischemic heart disease in men > 40 years old in several studies.[28] Furthermore, men with ED are twice as likely to have sustained a myocardial infarction compared with men without ED, and the risk becomes more pronounced with increasing age.[28] Increasing alpha adrenergic activity has been linked to several established aspects of the MetS, and is an attractive potential mechanism that could explain the link between the MetS and ED. Evidence supporting this mechanism has come from a study demonstrating that men with organic ED have significantly higher sympathetic activity than those without ($p < 0.05$).[29] This mechanism

has been supported by studies that have concluded that treatment with alpha-receptor antagonists, doxazosin,[30] and alfuzosin[31,32] may improve sexual function including ED. This mechanism is also attractive because it explains the link between ED and lower urinary tract symptoms (LUTS), which was confirmed by the Multinational Survey of the Aging Male (MSAM7) study.[33] This study included more than 14,000 men, aged 50-80 years, representative of the population of six European countries and the United States.[34]

A fourth mechanism explaining the link between the MetS and ED involves increased activation of the Rho/Rhokinase pathway, acting downstream of norepinephrine and endothelin1 receptors. Diabetes and hypertension have been linked to increased activity in this pathway.[35] Increased activity in Rho/Rho-kinase pathway results in the inhibition of smooth muscle and subsequent smooth muscle contraction.[36] Although this mechanism has not been specifically demonstrated in erectile tissue, it adds to the body of evidence suggesting that ED is also an expression of the MetS and could arise via this mechanism.[37]

There are several hypotheses concerning the mechanism linking the MetS and male hypogonadism. Obesity, especially visceral obesity, is an established aspect of the MetS. Activity of aromatase, an adipose enzyme that is involved in the irreversible conversion of testosterone into estradiol,[38] is higher in men who are obese and, consequently, they tend to have a decreased testosterone level and increased estradiol level.[38,39] Thus, the MetS provides an endocrine mechanism to explain the development of hypogonadotropic hypogonadism, as it is believed that the effect of estradiol on gonadotropin suppression is more potent than that of testosterone.[40] The findings of Zumoff and colleagues,[41] who treated obese men with oral testolactone (an aromatase inhibitor), support this conclusion. After 6 weeks, men treated with testolactone had higher levels of testosterone and LH and decreased levels of estrogen compared with their baseline levels.[41]

The hypothalamic–pituitary–adrenal (HPA) axis provides yet another mechanism that could explain the link between the MetS and hypogonadism. The HPA axis has been shown to be overactive in subjects suffering from the MetS,[42] and it is well established that cortisol inhibits the reproductive axis at several levels including secretion of GnRH and LH and also at the level of the testes themselves.[43] This emerging link between the MetS and male hypogonadism via increased aromatase activity, hypogonadotropic hypogonadism and increased activity of the HPA axis seems to suggest that male hypogonadism is also a urological aspect of the MetS.

Primary care cardiometabolic evaluation of ED

Symptomatic men are presumed to have CVD and are therefore at high risk for CVD events. A thorough history, physical exam (including measures of visceral adiposity), assessment of ED severity and duration, and evaluation of fasting plasma glucose, resting electrocardiogram, serum creatinine (estimated glomerular filtration rate) and albumin: creatinine ratio, and presence or absence of the metabolic syndrome may be used to further characterize CVS risk.[13]

Because ED is a well-established, independent marker for CVD risk[44-48] all men should be questioned about their sexual history and functioning as part of the initial assessment of CVD risk. For all men with ED, particularly those with vasculogenic ED, we recommend that initial risk stratification be based on the FR10 or the 2013 ACC/AHA Risk Calculator,[11] the former which estimates the 10 year CVS event risk; the latter which estimates the 10 year and lifetime ASCVD risk for both myocardial infarction or stroke.

The Framingham risk score is unique because it is dominated by chronologic age, systolic blood pressure, total cholesterol and HDL-C cholesterol, and cigarette smoking. We also know its limitations: it assesses the 10 year risk of non-fatal myocardial infarction or coronary heart disease death rather than a longer term risk, potentially depriving younger subjects and women of more intensive therapies. The Framingham study involved only 5200 patients from Framingham, Massachusetts. It is unclear whether this population is generalizable to others, particularly non-Caucasian populations.[48-50] In addition, the Framingham risk score does not include family history of premature coronary heart disease, and concepts of exercise and diet, and other risk factors that may be of great importance for future CVD risk. It also does not consider some of the novel biomarkers, such as C-reactive protein. The authors are therefore concerned that the Framingham risk score underestimates coronary heart disease (CHD) risk in the ED patient under the age of 60 years.

The Framingham risk calculator has now been altered in the form of a new downloadable American College of Cardiology and American Heart Association risk calculator for 2013.[11] This risk calculator not only determines 10 year risk of myocardial infarction (MI) but also risk for other ASCVD events including cerebrovascular accident (CVA). In addition it determines both 10 year ASCVD and lifetime ASCVD for men up to age 59.[11]

The following may be used to identify men with ED whose CVS risk may exceed that determined

based on the FRS or the 2013 ASCVD risk calculator: a thorough history; physical examination (including measures of visceral adiposity); assessment of ED severity and duration; evaluation of fasting plasma glucose; resting electrocardiogram; serum creatinine (estimated glomerular filtration rate) and albumin; creatinine ratio; and presence or absence of other features of the Met S.[12,13]

Based on results of the aforementioned assessments, the physician may encourage lifestyle changes which are likely to reduce CVS risk and improve erectile function.[51,52] Pharmacotherapy to control specific CVS risk factors (eg, hypertension, diabetes, hyperlipidemia) may also be appropriate. Men who appear to be at high risk for CVS events should be referred to a cardiologist. We suggest that intermediate risk men (per FRS or 2013 Risk Calculator defined as low 10 year ASCVD risk but high lifetime ASCVD risk) with vasculogenic ED and no overt CVD undergo further noninvasive evaluation of CVS risk using exercise stress testing (EST) to exclude obstructive disease, carotid intima-media thickness (CIMT), ankle-brachial index (ABI), or coronary artery calcium scoring (CACS) to determine the extent of subclinical atherosclerotic plaque burden, Figure 1. Neither the most appropriate order of testing nor the prognostic superiority of one test over another has been established. Tests should be selected based on clinical judgment, availability, and cost. All are considered a class IIB where the benefit appears to outweigh the risk and one or another of the tests may indicate plaque burden in an asymptomatic intermediate risk patient.

Exercise stress testing (EST): including myoview or echocardiographic stress testing
The 2010 ACCF/AHA guidelines recommend EST and CIMT for noninvasive evaluation of subclinical CVD in intermediate-risk patients.[53] Although EST does not detect non-flow-limiting lesions, it detects silent, inducible ischemia, thus providing further understanding of CVD risk. Data

suggest that this tool may be particularly helpful in identifying silent CAD in men with ED and diabetes.[53,54]

Carotid intima media thickness (CIMT)
Although the value of CIMT has not been evaluated in men with ED, ACCF/AHA,[53] and more emphatically, the Society for Heart Attack Prevention and Eradication (SHAPE) task force,[55] assert that it is reasonable to perform CIMT assessment during evaluation of intermediate risk patients. Studies published since these guidelines were developed support the value of this methodology in CVS risk assessment. In an evaluation of 441 asymptomatic subjects < 65 years of age (mean age, 50 years ± 8 years) with no history of CAD or diabetes, Eleid et al[56] reported that 38% of the 336 subjects deemed low risk based on the FRS had high risk carotid ultrasound findings (ie, CIMT ≥ 75th percentile adjusted for age, sex, and race or presence of plaque). Similarly, Naqvi et al[57] found that 50% of 136 asymptomatic subjects (mean age, 57 years ± 11 years) with no history of vascular events and FRS < 10% had CIMTs ≥ 75th percentile. However, Den
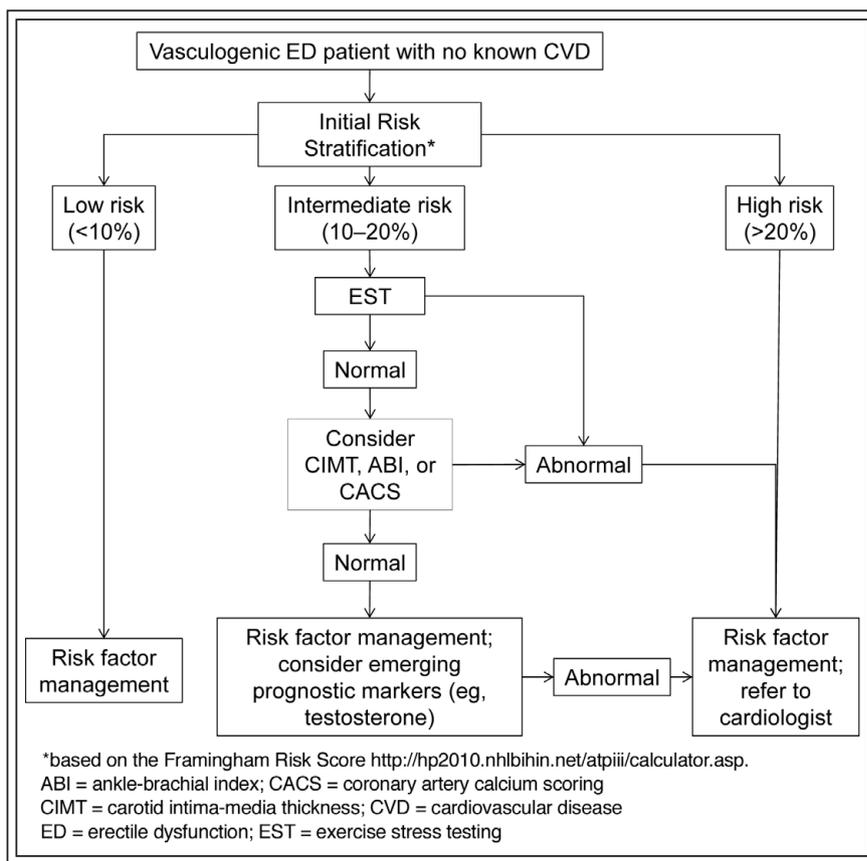

Figure 1. Recommended evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction but no known CVD for the primary care physician.

Ruijter et al[58] performed a meta-analysis of 14 studies (mean patient age, 58 years [range, 35-75]) that showed little improvement in 10 year risk prediction of first-time myocardial infarction or stroke when common CIMT measurements were added to the FRS. The incorporation of CIMT into CVS risk assessment is further complicated by the fact that thresholds for abnormal CIMT must be adjusted for age, sex, and race and are operator dependent.[59]

Ankle brachial index (ABI)
CVD has been identified in men with established ED by using various measures of general atherosclerotic burden, which are also considered surrogate markers of CVD. For example, ABI, the ratio of blood pressure in the dorsalis pedis artery to that in the brachial artery, is widely used to detect PAD. The ACCF/AHA considers measurement of ABI to be reasonable for CVS risk assessment in asymptomatic adults at intermediate risk.[53] In a study evaluating the relationship between ED and peripheral arterial disease (PAD), Polonsky et al showed that ABI successfully identified PAD in men with ED and suggested that men with ED undergo ABI examination.[60] ACCF/AHA guidelines state that ABI < 0.9 indicates the presence of PAD.[53]

Coronary artery calcium scoring (CACS)
CACS is another measure that has been prospectively validated as a predictor of CVD,[61] and for which the literature provides limited support in the ED population. Similar to ABI and CIMT, the ACCF/AHA considers CACS reasonable for CVS risk assessment in intermediate risk adults.[53] Jackson

and Padley performed maximal treadmill EST and CACS in 20 men aged 39 to 69 years with ED and no cardiac symptoms.[62] CACS were > 50 in 11 men, all of whom had angiographic CAD on coronary computed tomography, and 9 of whom had normal ESTs.[62] This study suggests that ED is a predictor of subclinical, non–flow-limiting CAD not detectable by EST, and that methods such as CACS and coronary computed tomography angiography may help detect CAD in patients with normal EST. More recently, in a comparison of the ability of six risk markers (CACS, CIMT, ABI, brachial flow-mediated dilation, high-sensitivity C-reactive protein [hsCRP], and family history of coronary heart disease) to improve prediction of incident coronary heart disease/CVD in FRS intermediate risk patients (10 year risk, > 5% and < 20%) enrolled in the Multi-Ethnic Study of Atherosclerosis, CACS provided superior improvements in risk estimation versus the other risk markers.[63] Noninvasive CVS evaluation may include other emerging prognostic markers, which are discussed in the next section.

Role of additional emerging prognostic markers in predicting CVS risk in men with ED

Although we recommend EST, CIMT, ABI, and/or CACS for noninvasive evaluation of subclinical CVD in intermediate risk patients, additional emerging prognostic markers may provide meaningful information pertinent to CVS risk in some patients. Table 2 summarizes evidence supporting these markers for assessment of CVS risk in men with ED, along with

---

TABLE 2. **Summary of evidence supporting emerging prognostic markers of cardiovascular disease in men with erectile dysfunction[13]**

Biomarkers	LOE[a]: association With CVD Prevalence in ED	LOE[a]: CVD Prognostic Value in ED	Availability	Cost
CIMT[81]	2b	NE	Somewhat limited	Medium
CACS[60,82]	2b	NE	Limited	High
ABI[22]	2b	NE	High	Low
Testosterone[67,68]	NE	2c	High	Low
Aortic stiffness (ie, PWV)[64]	NE	2c	Somewhat limited	Medium
Albuminuria[7]	NE	2c	High	Low

[a]per Center for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=1025); 2b = exploratory cohort study with good reference standards; 2c = outcomes research
ABI = ankle-brachial index; CACS = coronary artery calcium scoring; CIMT = carotid intima-media thickness; CVD = cardiovascular disease; ED = erectile dysfunction; LOE = level of evidence; NE = no evidence; PWV = pulse-wave velocity

their relative costs and availabilities. Although most of these markers have not undergone rigorous enough study to achieve guideline endorsement, prognostic markers represent a rapidly growing area of clinical research.

Vlachopoulos et al[64] investigated arterial prognostic markers in ED patients. The study employed carotid-femoral pulse wave velocity (PWV), a measure of aortic stiffness, and CIMT. Both indices were significantly increased in men with ED versus without, suggesting an increased CVS risk in men with ED. The European Society of Cardiology/European Society of Hypertension guidelines recommends PWV for the evaluation of the hypertensive patient.[65] Recent data show an independent predictive ability of PWV for future CVD events specifically in ED patients.[66] Pulse pressure, a crude index of aortic stiffness, was also found to be predictive of CVD events in ED patients.[66]

Prognostic markers that can be evaluated from routine blood sampling are particularly useful, and several candidates have been evaluated in men with ED. Total testosterone (TT) is a relatively low cost option, and a meta-analysis of seven population-based studies concluded that there was a (borderline-significant) 25% increased risk in CVD mortality associated with a 2.18 standard deviation decrease in serum testosterone. The authors highlighted significant between-study heterogeneity and concluded that low testosterone is likely to be a marker of poor general health.[67] Among patients with ED, Corona et al reported that TT levels < 8 nmol/L (230 ng/dL) were associated with a significant increase in fatal major adverse cardiovascular events versus those with levels ≥ 8 nmol/L.[68] This finding was supported by a recent analysis of data from the European Male Aging Study showing that TT < 8 nmol/L (230 ng/dL) and sexual symptoms were independently and additively associated with increased all-cause and CVD mortality in men between 40 and 79 years of age.[69] Although an observational cohort study of male US veterans with low TT levels (≤ 250 ng/dL) showed that testosterone treatment was associated with decreased mortality compared with no testosterone treatment,[70] it cannot be concluded that testosterone treatment reduced mortality.[71] In agreement with the British Society of Sexual Medicine,[72] Third International Consultation on Sexual Medicine,[73] and Princeton III Consensus,[11] we recommend that TT levels be measured as a potential cause and prognosticator of ED, particularly in those for whom phosphodiesterase type 5 inhibitors have failed. Although there are no generally accepted lower limits of normal TT, there is general agreement that TT > 350 ng/dL (12 nmol/L) does not usually

require substitution and, based on data from young hypogonadal men, those with TT < 230 ng/dL (8 nmol/L) usually benefit from testosterone treatment. A 3 to 6 month trial of testosterone therapy should be considered for symptomatic patients with TT 230 ng/dL-350 ng/dL (8 nmol/L-12 nmol/L).[74] Testosterone replacement improves sexual desire[75] and may improve and erectile function[76] and quality-of-life[77] but requires careful monitoring.

Waist circumference (intra-abdominal adiposity) (IAA) in men with ED drives the progression of multiple risk factors directly, through the secretion of excess free fatty acids and inflammatory adipokines, and decreased secretion of adiponectin. The important contributions of IAA to dyslipidemia and insulin resistance provide an indirect, though clinically important, link to the genesis and progression of atherosclerosis and CVD.[78-80] Presence of excess IAA is an important determinant of cardiometabolic risk. IAA is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic/proinflammatory states. Excess IAA typically is accompanied by elevated levels of C-reactive protein and free fatty acids (FFAs), as well as decreased levels of adiponectin. Abdominal obesity has been shown to be associated with the inflammation cascade, with adipose tissue expressing a number of inflammatory cytokines. Inflammation is now believed to play a role in the development of atherosclerosis and type 2 DM. Elevated levels of CRP are considered to be predictive of CVD and insulin resistance.[80,81]

These components help to explain why excess abdominal adiposity is considered to be a great threat to CVS and metabolic health. Abdominal obesity is associated with multiple cardiometabolic risk factors, including dyslipidemia,[82] elevated blood glucose,[83] and inflammation[84] – all factors leading to the development of CVD and DM in male ED patients. DM is, after age, the greatest risk factor for ED.[2] Patients with DM were three times more likely to develop ED than those who did not have DM.[84,85] The prevalence for ED in these patients was as high as 75%.[86-88] The Cologne Male Survey noted a 4-fold increase in ED in men with DM as compared to the general population.[89] In the Health Professionals Follow-up Study, which involved greater than 30,000 subjects, Bacon et al[90] found duration of DM strongly associated with incidence of ED. Rhoden et al[91] found higher glycosolated hemoglobin levels in patients with DM to be significantly associated with more severe ED (p < 0.05). The risk of ED in men with DM is also significantly associated with other diabetic complications such as diabetic neuropathy (p < 0.05).[92]

Adipocytes generate inflammatory cytokines, and patients with obesity and T2DM tend to have a higher

inflammatory profile. Inflammatory markers, such as IL-6,[93,94] TNF-apha,[93] or hsCRP,[94] are elevated and have been associated with impaired endothelial function, CVS events, and ED.[93,94]

High-sensitivity C-reactive protein is a potential marker of incident or future CVD that has not been tested in ED-specific populations.[95] However, hsCRP has been endorsed by the Centers for Disease Control and Prevention and the AHA as an adjunct to global risk prediction.[96] The ACCF/AHA guidelines[53] state that measurement of hsCRP may be reasonable in asymptomatic, intermediate risk men ≤ 50 years of age. Results of the JUPITER study suggest that measurement of hsCRP may useful in the selection of patients for statin therapy.[97]

Although data supporting the use of these emerging markers to predict CVD outcomes in men with ED are limited, evidence supporting the utility of these markers in other populations is expected to extend to ED populations.[53]

From the above evidence and our experience, we propose the following metabolic investigation of men with ED, including anthropomorphic and vital sign measurements:

- 2013 ASCVD Risk Estimator
- Waist circumference measured at the umbilicus
- Blood pressure/heart rate
- Fasting insulin and glucose levels
- Baseline renal function (BUN/creatinine)
- Fasting lipid profile
- Morning total testosterone level
- hs CRP
- Vitamin D325(OH)D$_3$

If any doubt with use of the 2013 ASCVD Risk Estimator, then CT calcium scoring may clarify risk and treatment options.

When we examine the use of biomarkers, we must distinguish between screening to define a population at risk that we are not currently treating, or reducing surrogate endpoints (eg. MI, acute coronary syndrome, stroke). These questions, together with the issue posed by Thompson:[45] "Could erectile dysfunction serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?" can only be answered by further studies of CVD prevention strategies in men with largely vasculogenic ED. Men with primary organic ED with or without CVS risk factors, should be considered an 'intermediate' risk group for future CVS events. It is this group of men, particularly under the age of 60 years, who may benefit from utilization of some of these surrogate markers of cardiometabolic risk in a cost-effective manner to stratify them for subsequent aggressive treatment of

preventative CVS risk factors. These men, many of whom may be missed by the traditional Framingham risk criteria, may find this risk elaborated with prudent use of these biomarkers or imaging studies. Only further studies of men with vasculogenic ED and preventative measures will provide evidence as to which of the surrogate markers are impactful and efficacious in the delineation of such risk.

Treatment of ED

Treatment plans need to be goal oriented, ideally aimed at satisfying the needs of both the man and his partner and maximizing the chance of achieving patient satisfaction. Based on the desired outcome, treatment can be simply pharmacologic, or may require further comprehensive psychosocial and relationship counseling. In many cases, the partner can be brought in to participate in the discussion about the goal of treatment improving the chance of success.

Educational and psychosocial interventions
In most cases, regardless of etiology, the treatment options of the physiologic impairment of ED are the same. Education is the first step in treatment and is personalized to the needs of the specific patient. The normal physiological changes associated with aging are often misunderstood by patients and lead to problems. Myths and misunderstandings about sexual activity can directly cause sexual difficulties as well as generate anxiety, guilt and worry that negatively impact on sexual response and erectile ability.[98,99] Helping men to have realistic expectations and to better understand healthy function and honest, constructive communication with partners can encourage more satisfactory sexual interaction and a healthier sense of sexual function. Research has demonstrated that the amount of sexual intimacy correlates with relationship satisfaction.[100,101]

The easily obtained erection begins to disappear in older men, especially those with chronic illness, such as diabetes, hypertension, or renal disease. Direct tactile stimulation of the penis may be needed to obtain and maintain an erection. The man becomes increasingly anxious thereby causing further erectile difficulties with the enhancement of "performance anxiety". Thus, information from the clinician about these changes of aging can be extremely reassuring.

Partner issues vary widely. Issues around partner choice, partner participation in sexual activity, and partner physiology may influence erectile function. When vaginal dryness, or vaginal atrophy leads to loss of lubrication and pain, women often lose interest in continued sexual activity.

Lifestyle and medication changes

Making healthy lifestyle changes may reduce the symptoms of ED and improve general physical health.[102] Patients need to understand that what is bad for the heart is bad for the penis. Elimination of smoking tobacco is helpful in reducing incident ED.[102] Dietary issues including reduced cholesterol and trans-fats, eliminating hyperglycemia when present, and decreasing salt intake when salt-sensitive hypertension is noted, all help to diminish vascular insufficiency progression. Exercise will increase cardiac output and improve peripheral circulation.[102] A recent study of obese men with ED without diabetes, hypertension, or dyslipidemia, found that reducing caloric intake and increasing physical activity was associated with improved sexual function in about one third of obese men.[51] These positive changes were associated with significant improvements in erectile function, which were highly correlated with both amount of weight loss and increased activity levels.[51] Exercise training improves endothelial function in the coronary[103] and peripheral circulation.[104] Endurance programs clearly have a positive effect on vasculature probably by moving endothelial function related to an increase in NO production and decreased oxidative stress, which leads to an increase in NO availability.[105] These recommendations will help men be healthier and, hopefully, happier, although their effect on erectile functioning may not be instantly apparent.

Changing medication regimens to remove ED causative agents can be tried when clinically possible. Examples of this might be discontinuing a thiazide diuretic and substituting an alpha-adrenergic blocker (although it may lead to ejaculatory dysfunction), or weaning the patient from digoxin or a beta-blocker if the medication is not necessary. Treatment of antidepressant-induced sexual dysfunction can sometimes be managed by reducing drug dosages, altering timing of drug dosages, taking drug holidays, adding an adjunctive drug, and switching to an alternative antidepressant.[106] These substitutions and eliminations may meet with some success, but need to be individualized depending on clinical circumstances.

Direct pharmacologic and surgical treatment

Specific treatment regimens for ED include oral medications, transurethral suppositories, intracavernosal injection, vacuum devices, and surgery. First-line therapies include oral medications and vacuum constriction devices. The FDA approved oral treatments include 1) sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra) and avanafil (Stendra - not available in Canada).[107] PCPs are writing about 80%-85% of all the prescriptions for PDE5 inhibitors in the United States.[108]

Other pharmacologic treatments being used primarily by the urologist and much less often by PCPs include intraurethral or intracavernosal injections of vasodilating medications, apomorphine, a dopamine agonist that causes central initiation of an erection through specific action in the brain, is available in Europe but not in the United States or Canada. Vacuum devices are a reasonable choice for many men who are in a stable relationship and their partners are willing to accept the inconvenience and loss of spontaneity.[109]

Testosterone augmentation, available as patches, gels, underarm solution, buccal patch (not in Canada), injection, or insertion of subcutaneous pellets (not in Canada) is best reserved for patients with documented hypogonadism based on the morning serum testosterone level. Generally, testosterone augmentation is associated with enhanced libido. This may improve erectile status by restoring interest and perhaps through other neurohormonal mechanisms, but relying solely on testosterone to restore erectile function in the dysfunctional male is inappropriate. Testosterone treatment for testosterone deficiency requires thorough evaluation and monitoring for changes in both Hct and PSA.

The most common surgical treatment for ED is penile implant surgery that is primarily performed by urologists. This is a successful therapy in the properly identified patient and should be reserved for those patients who have considered or at least tried several other treatments. The surgery should be considered irreversible since the normal function of the corpora cavemosa is obliterated with this procedure. There are two types of implants – the inflatable and non-inflatable or semi-rigid. These implants are essentially mechanical devices and as such can suffer from mechanical failures, that requires another surgical procedure to fix the "failure."

Some clinicians have advised that ED can be managed naturally, although no controlled trials exist. A dietary program rich in whole foods including vegetables, fruits, whole grains, and legumes has been suggested with key nutrients including zinc, essential fatty acids, vitamin A, vitamin B-6, L-arginine, and vitamin E being recommended. Herbal supplements such as ginseng, gota kola, and saw palmetto have also been discussed. Spices reported to increase sexual desire include nutmeg, saffron, parsley, vanilla, avocado, carrot oil, and celery.

Optimizing oral treatment with PDE5 inhibitors

Phosphodiesterase type 5 inhibitors (PDEi) have been available for the treatment of ED since 1998. The

rationale for their use is based on the fact that the NO-cGMP pathway is the primary mechanism by which relaxation of the corporal smooth muscle as well as the muscle of the penile vessels occurs.[110] Of the four available PDEi today, both sildenafil and vardenafil have comparable pharmacokinetics i.e. peak levels in the blood occur about 1 hour after oral ingestion and the serum half life is about 6 to 8 hours. Both agents require an empty stomach for optimum reabsorption. Avanafil, the first oral PDE5i to be approved by the FDA in the past 10 years may have an earlier onset of action then the previous three agents and absorption is reported to be not be affected by food. On the other hand, tadalafil reaches a peak level in the blood stream about 2 to 3 hours after ingestion while its half-life is more extended to about 17 to 18 hours. The absorption of this agent from the gut is not negatively impacted by food.

The PDE5i all have common side effects usually referable to vasomotor function. These include headache, flushing, lightheadedness, etc. Sildenafil is associated at times with visual changes e.g. seeing blue tint while tadalafil has been associated with back discomfort and muscle aches. All of the aforementioned side effects are dose dependent and reversible. Extremely rare but troubling side effects include non-arteritic ischemic optical neuropathy (NAION) and hearing loss both of which do not seem to be dose related

The success rates for the PDEi in rigorous scientific studies range from 60%-80% in most populations and early expectations of similar success among the general population were similarly high. Unfortunately, in real life a certain percentage of men with ED do not seem to be achieving their desired or expected goal with these agents. The discontinuation rate for PDE5i use among men diagnosed as having ED by their physicians appears to be high even among those who initially responded to the medication, reaching up to 57% in a 3 year follow up.[111,112]

Discussions about appropriate expectations are key to optimize PDE5i therapy outcomes. Myths and misunderstandings about sexual activity can directly cause sexual difficulties as well as generate anxiety, guilt and worry that negatively impact on sexual response and erectile ability. Helping men to have realistic expectations and to understand healthy function, and honest, constructive communication with their partners and a focus on less genital touch, can encourage more satisfactory sexual interaction and a healthier sexual life in a non-pharmacologic means. Men need to be told that although the medication is likely to have a positive and significant effect on erectile function in men with ED, the degree of effect can vary based on a variety of physiologic and psychosocial factors. The PDE5i biochemical effect does not provide 100% success in all men, and appears to be significantly decreased in men with diabetes or who have had a radical prostatectomy.[113,114]

A step-wise approach meant to deal with oral treatment ED failures includes reevaluation and adjustment of therapy with 1) hypogonadism treatment if present, 2) dose titration, and 3) patient instruction on optimal use of medication. If the man is still not satisfied, this algorithm suggests considering alternative oral or local therapy with additional education and counseling followed by referral to a specialist if needed.[115]

Our goal as clinicians for men with ED is to 1) help improve sexual function and regain self-esteem, 2) improve the man's sense of well-being, and 3) improve relationships.[116] We know that improving physiologic erectile function in men with ED is an important part, but only one part of the desired outcome. Many other issues can influence the likelihood of achieving the desired outcomes including 1) the man's psychosocial milieu, 2) the presence of other sexual issues or risk factors for physical sexual dysfunction, 3) the availability and receptivity of a partner, and 4) partner interaction. A trusting physician-patient partnership enhances the likelihood of a successful therapeutic outcome. Optimism is an essential management tool for PCPs to use in responding to sexual issues.

Follow up for treatment of ED

Follow up is an essential part of management of erectile dysfunction. Patients should be seen at 4-6 weeks after initiation of treatment to evaluate progress. Comparison to baseline can be done by verbal exchange or by using the standardized questionnaire measuring erectile function (SHIM). Reviewing the success or lack of success of treatment, any adverse effects, and considering dose or treatment alterations is more likely to achieve the patient's goal. Further education and/or basic sex counseling can be provided to the patient with or without his partner.

When to refer

Consultation with subspecialists may be appropriate at varying intervals when managing a man with ED. The major factor is the PCP's comfort in discussing and managing treatment options. The obligation of the PCP is to recognize ED and make the patient feel comfortable about seeking help. Initial work up and

treatment can be planned by the PCP who has good communication skills about sexual activity and who is knowledgeable about first-line treatments. Common indications for referral to an appropriate specialist include 1) significant penile anatomic disease, 2) a younger patient with a history of pelvic or perineal trauma, 3) cases requiring vascular or neurosurgical intervention, 4) complicated endocrinopathies, 5) complicated psychiatric or psychosocial problems, or 6) patient or physician desire for further evaluation. Urologists can be helpful in difficult or complex ED situations or when the patient presents with an anatomical problem such as Peyronie's disease. An endocrinologist or andrologist may be consulted to assist in managing men with difficult to control diabetes, hypogonadism, or evidence of pituitary dysfunction.

Sex therapists are practitioners in the medical or mental health field who, in addition to their basic clinical education, have had additional training in sex therapy including evaluation and treatment options. Sex therapists have more time to talk with the patient, to work with couples suggesting enhancement techniques, and to educate couples that there are many ways of having pleasurable sexual relations without a firm erection. These could be physicians, ministers, and mental health professionals. The American Association of Sex Therapists and Counselors can provide a directory for your state of trained, certified sex therapists. (www.aasect.org/Home/). Most major teaching hospitals have such a trained individual on their staffs.

Conclusion

The metabolic investigation of ED involves primarily the investigation of metabolic sequellae of visceral adiposity leading to type 2 DM or CVD. This is known as cardiometabolic risk. Older models of cardiovascular risk assessment (FRS) have generally underestimated risk in younger and middle-aged populations. The authors of the new risk models make adjustments for this and introduce the idea of balancing 10 year risk with lifetime risk to aid in decision-making in younger and middle-aged adults. Whether it's lifetime risk or ED that is used to enhance 10 year risk assessment, the concept is the same: to discern those who have started down the path of inflammation, endothelial dysfunction and vulnerable plaque formation, and thereby intervene somewhere upstream from the first ASCVD event. Lifetime risk may be something abstract to most patients, and current evidence does not support its use to guide pharmacotherapy. The value is to motivate therapeutic

lifestyle changes. ED is something tangible. It affects mental health and quality-of-life. Young and middle-aged male patients with ED are likely to make changes that will have an immediate impact on both their CVS risk and overall sexual function.

Disclosure

Dr. Martin Miner has been a consultant for Abbvie and Endo. He has also done research for Forest. Dr Matt T. Rosenberg has been a speaker and consultant for Astellas, Easai, Ferring, Forest, Horizon, Ortho-McNeil, Lilly, Pfizer and Bayer. Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Actavis, AstraZeneca, Astellas, Pfizer and Triton. □

References

1. Hatsimouratidis K, Amar E, Eardley I et al. Guidelines on male sexual dysfunction and premature ejaculation. *Eur Urol* 2010; 57(5):804-814.
2. Prins J, Blanker MH, Bohnen AM et al. Prevalence of erectile dysfunction: a systematic review of population–based studies. *Int J Impot Res* 2002;14(6):422-432.
3. Inman BA, St Sauver JL, Jacobson DJ et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009;84(2):108-113.
4. Krane RJ, Goldstein I, Saenz de Tejada I. Impotence. *N Engl J Med* 1989;321(24):1648-1659.
5. Rosen RC, Leiblum SR. An overview of historical trends and clinical perspectives. In: RRCLS R, editor. Erectile Disorders: Assessment and Treatment. New York: Guilford 1992;p. 3-26.
6. Bacon CG, Mittleman MA, Kawachi I, et al. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. *Ann Intern Med* 2003;139(3): 161-168.
7. Saigal CS, Wessells H, Pace J et al. Predictors and prevalence of erectile dysfunction in a racially diverse population. *Arch Intern Med* 2006;166(2):207-212.
8. Persu C, Cauni V, Gutue S et al. Diagnosis and treatment of erectile dysfunction–a practical update. *J Med Life* 2009;2(4): 394-400.
9. Marma AK, Berry JD, Ning H, et al. Distribution of 10-Year and Lifetime Predicted Risks for Cardiovascular Disease in US Adults Findings From the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes* 2010;3(1):8-14.
10. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *Am J Cardiol* 2009;103(10):1403-1407.
11. Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce astherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol* 2013;Epub ahead of print.
12. Nehra A, Jackson G, Miner M et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012;87(8):766-778.

13. Miner M, Nehra A, Jackson G et al. All men with vasculogenic ED require a cardiovascular workup. *Am J Med* 2014;127(3):174-182.

14. Alberti KG, Eckel RH, Grundy SM et al. International Diabetes Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity: harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120(16):1640-1645.

15. Kassi E, Pervanidou P, Kaltsas G et al. Metabolic syndrome: definitions and controversies. *BMC Med* 2011;9:48-61.

16. Aslan Y, Sezgin T, Tuncel A et al. Is type 2 diabetes mellitus a cause of severe erectile dysfunction in patients with metabolic syndrome. *Urology* 2009;74(3):561-564.

17. Demir T, Demir O, Kefi A et al. Prevalence of erectile dysfunction in patients with metabolic syndrome. *Int J Urol* 2006; 13(4):385-388.

18. Bal K, Oder M, Sahin AS et al. Prevalence of metabolic syndrome and its association with erectile dysfunction among urologic patients: metabolic backgrounds of erectile dysfunction. *Urology* 2007;69(2):356-360.

19. El-Sakka AI, Morsy AM. Screening for ischemic heart disease in patients with erectile dysfunction: role of penile Doppler ultrasonography. *Urology* 2004;64(2):346-350.

20. El-Sakka AI, Morsy AM, Fagih BI, Nassar AH. Coronary artery risk factors in patients with erectile dysfunction. *J Urol* 2004;172(1):251-254.

21. Jackson G. Sexual response in cardiovascular disease. *J Sex Res* 2009;46(2-3):233-236.

22. Al-Hunayan A, Al-Mutar M, Kehind EO, Thalib L, Al-Ghorory M. The prevalence and predictors of erectile dysfunction in men with newly diagnosed with type 2 diabetes mellitus. *BJU Int* 2007; 99(1):130-134.

23. Tomada N, Tomada I, Botelho F, Cruz F, Vendeira P. Are all metabolic syndrome components responsible for penile hemodynamics impairment in patients with erectile dysfunction? The role of body fat mass assessment. *J Sex Med* 2011;8(3):831-839.

24. Kupelian V, Shabsig R, Araujo AB, O'Donell AB, McKinlay JB. Erectile dysfunction as a predictor of the metabolic syndrome in aging men: results from the Massachusetts male aging study. *J Urol* 2006;176(1):222-226.

25. Corona G, Mannucci E, Ricca V et al. The age-related decline of testosterone is associated with different specific symptoms and signs in patients with sexual dysfunction. *Int J Androl* 2009;32(6): 720-728.

26. Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. *Rev Urol* 2010;12(4):157-180.

27. Reilly CM, Zamorano P, Stopper VS, Mills TM. Androgenic regulation of NO availability in rat penile erection. *J Androl* 1997; 18(2):110-115.

28. Chen C J, Kuo TB, Tseng, YJ, Yang CC. Combined cardiac sympathetic excitation and vagal impairment in patients with non-organic erectile dysfunction. *Clin Neurophysiol* 2009;120(2): 348-352.

29. Kirby RS, O'Leary MP, Carson C. Efficacy of extended-release doxazosin and doxazosin standard in patients with concomitant benign prostatic hyperplasia and sexual dysfunction. *BJU Int* 2005;95(1):103-109.

30. De Rose AF, Carmignani G, Corbu C et al. Observational multicentric trial performed with doxazosin: evaluation of sexual effects on patients with diagnosed benign prostatic hyperplasia. *Urol Int* 2002;68(2):95-98.

31. Liguori G, Trombetta C, De Giorgi G et al. Efficacy of combined oral therapy with tadalafil and alfuzosin: an integrated approach to management of patients with lower urinary tract symptoms and erectile dysfunction. Preliminary report. *J Sex Med* 2009; 6(2):544-552.

32. Kaplan SA, Gonzeles RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. *Eur Urol* 2007; 51(6):1717-1723.

33. Rosen R, Altwein J, Boyle P et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol* 2003;44(6): 637-649.

34. McVary K. Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathphysiology. *BJU Int* 2006; 97(Suppl 2):23-28.

35. De Rose AF, Carmignani G, Corbu C et al. Observational multicentric trial performed with doxazosin: evaluation of sexual effects on patients with diagnosed benign prostatic hyperplasia. *Urol Int* 2002;68(2):95-98.

36. Faris JE, Smith MR. Metabolic sequele associated with androgen deprivation therapy for prostate cancer. *Curr Opin Endocrinol Diabetes Obes* 2010;17(3):240-246.

37. Hammarsten J, Peeker R. Urologic aspects of the metabolic syndrome. *Nat Rev Urol* 2011;8(9):483-494.

38. Cohen PG. Obesity in men: the hypogonadal- estrogen receptor relationship and its effect on glucose homeostasis. *Med Hypotheses* 2008;70(2):358-360.

39. Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab* 1993; 76(5):1140-1146.

40. Cohen PG. The role of estradiol in the maintenance of secondary hypogonadism in males in erectile dysfunction. *Med Hypotheses* 1998;50(4):331-333.

41. Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. *Metabolism* 2003;52(9):1126-1128. 42. Rosmond R., Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab* 1998;83(6):1853-1859.

43. Chrousos G.P. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. *Ann NY Acad Sci* 1998;851:311-335.

44. Araujo AB, Hall SA, Ganz P et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? *J Am Coll Cardiol* 2010;55(4):350-356.

45. Thompson IM, Tamgen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005;294(23):2296-3002.

46. Gazzaruso C, Solerte SB, Pujia A et al. Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. *J Am J Cardiol* 2008;51(21): 2040-2044.

47. Ma RC, So WY, Yang X et al. Erectile dysfunction predicts coronary artery disease in type 2 diabetics. *J Am Coll Cardiol* 2008;51(21): 2045-2050.

48. Schouten BW, Bohnen AM, Bosch JL et al. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. *Int J Impot Res* 2008;20(1):92-99.

49. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97(18): 1837-1847.

50. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham Heart Disease Prediction Score: results of a multiple ethnic groups investigation. *JAMA* 2001;286(2):180-187.

51. Esposito K, Giugliano F, DiPalo C et al. Effect of lifestyle changes in erectile dysfunction in obese men. A randomized controlled trail. *JAMA* 2004;291(24):2978-2984.

52. Gupta BP, Murad MH, Clifton MM et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011;171(20):1797-1803.

53. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010;122(25):e584-636.

54. Gazzaruso C, Giordanetti S, De Amici E et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation* 2004;110(1):22-26.

55. Naghavi M, Falk E, Hecht HS et al. From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. *Am J Cardiol* 2006;98(2A):2H-15H.

56. Eleid MF, Lester SJ, Wiedenbeck TL et al. Carotid ultrasound identifies high risk subclinical atherosclerosis in adults with low framingham risk scores. *J Am Soc Echocardiogr* 2010;23(8):802-808.

57. Naqvi TZ, Mendoza F, Rafii F et al. High prevalence of ultrasound detected carotid atherosclerosis in subjects with low Framingham risk score: potential implications for screening for subclinical atherosclerosis. *J Am Soc Echocardiogr* 2010;23(8): 809-815.

58. Den Ruijter HM, Peters SA, Anderson TJ et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;308(8):796-803.

59. Howard G, Sharrett AR, Heiss G et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. *Stroke* 1993;24(9):1297-1304.

60. Polonsky TS, Taillon LA, Sheth H et al. The association between erectile dysfunction and peripheral arterial disease as determined by screening ankle-brachial index testing. *Atherosclerosis* 2009;207(2):440-444.

61. Greenland P, Bonow RO, Brundage BH et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007;49(3):378-402.

62. Jackson G, Padley S. Erectile dysfunction and silent coronary artery disease: abnormal computed tomography coronary angiogram in the presence of normal exercise ECGs. *Int J Clin Pract* 2008;62(6):973-976.

63. Yeboah J, McClelland RL, Polonsky TS et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308(8):788-795.

64. Vlachopoulos C, Aznaouridis K, Ioakeimidis N et al. Arterial function and intima-media thickness in hypertensive patients with erectile dysfunction. *J Hypertens* 2008;26(9):1829-1836.

65. Mancia G, Grassi G. The new European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines. *Ther Adv Cardiovasc Dis* 2008;2(1):5-12.

66. Vlachopoulos C, Ioakeimidis N, Aznaouridis K et al. Prediction of cardiovascular events with aortic stiffness in patients with erectile dysfunction. *J Am Coll Cardiol* 2012;59(13s1):E2072.

67. Araujo AB, Dixon JM, Suarez EA et al. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96(10):3007-3019.

68. Corona G, Monami M, Boddi V et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. *J Sex Med* 2010;7(4 Pt 1):1557-1564.

69. Pye SR, Huhtaniemi IT, O'Neill TW et al. editors. Late-onset hypogonadism (LOH) and mortality in European men. Endocrine Society 2012; Houston, TX.

70. Shores MM, Smith NL, Forsberg CW et al. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97(6):2050-2058.

71. Wu FC. Caveat emptor: does testosterone treatment reduce mortality in men? *J Clin Endocrinol Metab* 2012;97(6):1884-1886.

72. Hackett G, Kell P, Ralph D et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. *J Sex Med* 2008;5(8):1841-1865.

73. Buvat J, Maggi M, Gooren L et al. Endocrine aspects of male sexual dysfunctions. *J Sex Med* 2010;7(4 Pt 2):1627-56.

74. Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. *J Sex Med* 2013;10(1):245-284.

75. Bolona ER, Uraga MV, Haddad RM et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82(1):20-28.

76. Buvat J, Montorsi F, Maggi M et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). *J Sex Med* 2011;8(1):284-293.

77. Hackett G. Long acting testosterone undecanoate improved ageing male symptom scores but not depression versus placebo in a hypogonadal population with type 2 diabetes. 14th European Society of Sexual Medicine Congress. 2011; Milan, Italy.

78. Rathmann W, Haastert B, Herder C et al. Differential association of adiponectin with cardiovascular risk markers in men and women? The KORA survey 2000. *Int J Obes* 2007;31(5):770-776.

79. Yamauchi T, Kamon J, Minokoshi Y et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;8(11):1288-1295.

80. Snijder MB, Heine RJ, Seidell JC et al. Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the hoorn study. *Diabetes Care* 2006;29(11):2498-2503.

81. Silvestro A, Brevetti G, Schiano V et al. Adhesion molecules and cardiovascular risk in peripheral arterial disease. Soluble vascular cell adhesion molecule-1 improves risk stratification. *Thromb Haemost* 2005;93(3):559-563.

82. Nikoobakht M, Nasseh H, Pourkasmaee M. The relationship between lipid profile and erectile dysfunction. *Int J Impot Res* 2005; 17(6):523-526.

83. Burke JP, Jacobson DJ, McGree ME et al. Diabetes and sexual dysfunction: results from the Olmsted County Study of Urinary Symptoms and health status among men. *J Urol* 2007; 177(4):1438-1442.

84. Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. *Eur Urol* 2005;47(1):80-85.

85. Saigal CS, Wessells H, Pace J, Schonlau M, Wilt TJ for the Urologic Diseases in America Project. Predictors and prevalence of erectile dysfunction in a racially diverse population. *Arch Intern Med* 2006;166(2):207-212.

86. Fonseca V, Jawa A, Endothelial and erectile dysfunction, diabetes mellitus, and the metabolic syndrome: Common pathways and treatments? *Am J Cardiol* 2005;96(12B):13-18.

87. Vinik A, Richardson D. Erectile dysfunction in diabetes. *Diabetes Rev* 1998;6:16-33.

88. Fedele D, Coscelli C, Santeusanio F et al for the Gruppo Italiano Studio Deficit Erecttile nei Diabetici. Erectile dysfunction in diabetic subjects in Italy. *Diabetes Care* 1998;21(11):1973-1977.

89. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Imp Res* 2000;12(6):305-311.

90. Bacon CG, Hu FB, Giovannucci E, Glasser DB, Mittleman MA, Rimm EB. Association and type and duration of diabetes with erectile dysfunction in a large cohort of men. *Diabetes Care* 2002;25(8):1458-1463.

91. Rhoden EL, Ribeiro EP, Riedner CE, Teloken C, Souto CA. Glycosolated hemoglobin levels and the severity of erectile function in diabetic men. *BJU Int* 2005;95(4):615-617.

92. Gazzaruso C, Pujia A, Solerte SB et al. Erectile dysfunction and angiographic extent of coronary artery disease in type II diabetic patients. *In J Impot Res* 2006;18(3):311-315.

93. Naya M, Tsukamoto T, Morita K et al. Plasma interleukin-6 and tumor necrosis factor-alpha can predict coronary endothelial dysfunction in hypertensive patients. *Hypertens Res* 2007;30(6):541-548.

94. Vlachopoulos C, Aznaouridis K, Ioakeimidis N et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J* 2006; 27(22):2640-2648.

95. Giugliano F, Esposito K, Di Palo C et al. Erectile dysfunction associates with endothelial dysfunction and raised proinflammatory cytokine levels in obese men. *J Endocrinol Invest* 2004;27(7):665-669.

96. Pearson TA, Mensah GA, Alexander RW et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107(3):499-511.

97. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359(21):2195-2207.

98. Weeks GR, Gambescia N. Erectile dysfunction: integrating couples therapy, sex therapy, and medical treatment. New York, WW Norton and Co. 2000:43-44.

99. Mosher D. Sex guilt and sex myths in college men and women. *J Sex Res* 1979;15(3):224-234.

100. Blumstein P, Schwartz, P. "American Couples: money, work, and sex." New York: William Morrow, 1983.

101. Sprecher S, McKinney, K. "Sexuality." Newbury Park, CA: Sage, 1993.

102. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007;120(2):151-157.

103. Hambrecht R, Wolf A, Gielen S et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *New Eng J Med* 2000;342(7):454-460.

104. Gokce N, Vita JA, Bader DS et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. *Am J Cardiol* 2002;90(2):124-132.

105. Edwards DG, Schofield RS, Lennon SL et al. Effect of exercise training on endothelial function in men with coronary artery disease. *Am J Cardiol* 2004;93(5):617-620.

106. Moore BE, Rothschild AJ. Treatment of antidepressant-induced sexual dysfunction. *Hosp Pract* 1999;34(1):89-91,95-96.

107. Sadovsky R. Selecting patients appropriate for treatment. *J Fam Pract* 2005;Suppl 5-14.

108. Data on File, IMS, Eli Lilly and Company 2007.

109. Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G. Objective measurement of the effectiveness, therapeutic success, and dynamic mechanisms of the vacuum device. *Br J Urol* 1995;75(6):786-791.

110. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. *New Engl J Med* 1992;326(2):90-94.

111. Helstrom WJG. Management recommendations for family physicians. *J Fam Pract* 2005 Suppl:32-40.

112. Jiann BP, Yu CC, Su CC, Tsai JY. Complaince of sildenafil treatment for erectile dysfcutnion and factors affecting it. *Int J Impot Res* 2006;18(2):146-149.

113. Vickers MA, Satyanarayana R. Phosphosdiesterase type 5 inihibotrs for the treatment of erectile dysfunction in patients with diabetes mellitus. *Int J Impot Res* 2002:14(6):466-471.

114. Montorsi F, Burnett AL. Erectile dysfunction after radical prostatectomy. *BJU Int* 2004;93(1):1-2.

115. Carson CC, Lue TF. Phosphodiesterase type 5 inihibotrs for erectile dysfunction. *BJU Int* 2005;96(3):257-280.

116. Nusbaum MR. Therapeutic options for patients returning to sexual activity. *J Am Osteopath Assoc* 2004:104(3 suppl 4):S2-S5.