MAYO CLINIC

The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease

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Abstract

The Princeton Consensus (Expert Panel) Conference is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health. The third Princeton Consensus met November 8 to 10, 2010, and had 2 primary objectives. The first objective focused on the evaluation and management of cardiovascular risk in men with erectile dysfunction (ED) and no known cardiovascular disease (CVD), with particular emphasis on identification of men with ED who may require additional cardiologic work-up. The second objective focused on reevaluation and modification of previous recommendations for evaluation of cardiac risk associated with sexual activity in men with known CVD. The Panel's recommendations build on those developed during the first and second Princeton Consensus Conferences, first emphasizing the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED, and second highlighting the link between ED and CVD, which may be asymptomatic and may benefit from cardiovascular risk reduction.

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The Princeton Consensus Conference is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health. The first conference convened in June 1999 to develop recommendations for clinical management of sexual dysfunction in men and women with known cardiovascular disease (CVD). This conference also provided a multidisciplinary forum for evaluation of the potential cardiovascular risk posed by sexual activity in at-risk patients. The first Princeton Consensus Conference recommendations[1] included stratification of patients by level of cardiac risk associated with sexual activity based on existing CVD. Those at low risk could initiate or resume sexual activity and be treated for sexual dysfunction. For those at high risk, sexual activity was deferred until the cardiac condition was stabilized. The second Princeton Consensus Conference convened in June 2004 and expanded the recommendations of the first conference to emphasize risk factor evaluation and lifestyle management for all men with erectile dysfunction (ED).[2] The second conference recommendations also incorporated new information on the appropriate use of phosphodiesterase type 5 (PDE5) inhibitors in men with ED and concomitant CVD.

The third Princeton Consensus Conference took place November 8 to 10, 2010, in Miami Beach, Florida. The group revisited and updated their 2005 recommendations regarding the cardiovascular risk associated with sexual activity in men with known CVD.[2] In addition, the third conference focused on the predictive value of vasculogenic ED in assigning cardiovascular risk in men of all ages, with the primary objective being development of an approach to cardiovascular risk assessment in younger men with ED and no known CVD. The role of testosterone in erectile function and cardiovascular health and the utility of testosterone replacement therapy (TRT) were also examined.

Recommendations were developed via the same process used in the first and second conferences.[1,2] Briefly, an international panel of 22 experts provided state-of-the-art presentations pertaining to the epidemiologic and physiologic links among hypogonadism, ED, and CVD; benefits and risks of testosterone depletion and repletion; evaluation of traditional and emerging cardiometabolic

risk factors and assessment tools; and available treatments for ED. After the presentations, a representative consensus panel met to review the information and, based on available scientific evidence, to develop recommendations for clinical practice and further research. The recommendations were modified and finalized through electronic communication and were approved by final consensus of the panel.

RECOMMENDATIONS

The recommendations of the third Princeton Consensus Conference focus on (1) evaluation and management of cardiovascular risk in men with ED and no known CVD, (2) reevaluation and modification of the second conference recommendations for evaluation of cardiac risk associated with sexual activity in men with known CVD, and (3) the role of TRT in ED and CVD management.

EVALUATION AND MANAGEMENT OF CARDIOVASCULAR RISK IN THE PATIENT WITH ED WITH NO KNOWN CVD

The consensus panel defines cardiovascular risk as the risk of morbid events over a 3- to 5-year interval from the onset of ED (American College of Cardiology Foundation/American Heart Association [ACCF/AHA] class Ib)[3,4] and provides recommendations for the evaluation and management of cardiovascular risk in men with ED and no known CVD. The panel's approach broadens the use of the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults to address an at-risk patient population that the guideline does not mention: men with ED. The rationale for each step in the panel's approach is detailed herein. The 2010 ACCF/AHA guideline[5] provides recommendations and levels of evidence (LOEs) for some of the recommended assessments, and we provide them for others.

Sexual Inquiry of All Men

- ED provides an opportunity for CVD risk reduction.[6]
- ED not only shares risk factors with CVD[7,8] but also is, in itself, an independent marker of increased risk for CVD (ACCF/AHA class Ia).[9-15]
- ED is a marker of significantly increased risk of CVD, coronary artery disease (CAD), stroke, and all-cause mortality.

Incident ED has a similar or greater predictive value for cardiovascular events as traditional risk factors, such as family history of myocardial infarction (MI), smoking, and hyperlipidemia.[16,17] Erectile dysfunction commonly occurs in the presence of

silent CAD,[3,18-20] with a time window between ED onset and a CAD event of 2 to 5 years (class Ia).[3,4,21] Furthermore, evidence suggests that ED is predictive of peripheral arterial disease (PAD)[22] and stroke.[23] In a population-based study of men 40 to 70 years of age, addition of ED status to the Framingham Risk Score (FRS) in a multivariate statistical model resulted in reclassification of 5 of 78 low-risk patients (<5% risk) to intermediate risk (5% to <10% risk).[9] In addition, data from the Olmsted County Study suggest that ED is far more predictive of CAD in men 40 to 49 years of age than in older men,[24] and the incidence of atherosclerotic cardiovascular events in men younger than 40 years with ED was more than 7 times the incidence in a reference population representative of the general male population in Western Australia.[25] Thus, ED may be particularly useful in assessing cardiovascular risk in younger men[26] and in minorities,[27] whose risk may be underestimated by global risk assessments such as the FRS. Finally, assessment of ED must include ED severity because more severe ED has been associated with greater risk of major cardiovascular events,[28] CAD,[23,29] extent of CAD,[19,21,30] and risk of PAD (ACCF/AHA class Ia).[22] These recommendations are supported by a meta-analysis of 12 prospective studies involving 36,744 men (Table 1).[31] In this study and in a study of ED in men with known CVD, ED was found to be an independent marker of cardiovascular events and all-cause mortality additional to conventional risk factors (eg, age, weight, hypertension, diabetes, hyperlipidemia, and cigarette smoking).

Limitations of the FRS in Men With ED

- ED is a marker of increased CVD risk independent of the FRS.

The FRS is a useful tool for estimating the 10-year risk of MI or coronary death and is supported by the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults (ACCF/AHA class I, LOE B).[5] It incorporates age, sex, total and high-density lipoprotein (HDL) cholesterol levels, smoking status, systolic blood pressure (BP),

TABLE 1. Relative Risks for Men With Erectile Dysfunction

	Relative risk	95% Confidence interval	P value
Overall	1.48	1.25-1.74	<.001
Coronary heart disease	1.46	1.31-1.63	<.001
Stroke	1.35	1.19-1.54	<.001
All-cause mortality	1.19	1.05-1.34	.005

Adapted from *J Am Coll Cardiol*.[15]

and use of antihypertensive medications.[32] However, it is important to note that the Framingham study and other long-term observational studies include few data from patients younger than 40 years. Thus, the FRS may not adequately estimate risk in younger patients. The FRS also lacks some important risk factors (eg, family history, fasting glucose level, serum creatinine level [estimated glomerular filtration rate], urinary albumin to creatinine ratio, and, potentially, testosterone level) that should be considered when estimating cardiovascular risk in men with ED. Therefore, although the consensus panel recommends the FRS as a starting point for estimating the likelihood of subclinical atherosclerosis in men with ED, the presence of ED per se, especially in men aged 30 to 60 years, should alert the physician to the possibility of increased CVD risk independently of the FRS. The checks recommended should, therefore, be used to modify risk after FRS determination in men with ED.

Recommended Assessments and Risk Clarification

- A man with organic ED should be considered at increased CVD risk until recommended checks suggest otherwise.
- ED identifies increased CVD risk in the presence or absence of CVD symptoms or history.

The consensus panel recommends the following risk assessments, which may be used to identify men with ED and no known CVD who may require additional cardiologic work-up. In the broadest sense, this risk refers to experiencing a significant cardiac event, including MI, acute coronary syndromes, angina pectoris, heart failure, and death.

- Patient history, including age, presence or absence of comorbid conditions (eg, abdominal obesity, hypertension, dyslipidemia, prediabetes, and symptoms suggestive of obstructive sleep apnea), family history of premature atherothrombotic CVD (father aged <55 years or mother aged <65 years; ACCF/AHA class I, LOE B), and lifestyle factors (eg, diet, excessive use of alcohol, limited physical activity, and smoking)
- Physical examination noting BP, waist circumference (WC), body mass index (BMI), fundal arterial changes, cardiac auscultation, carotid bruits, and palpation of femoral and pedal pulses
- ED severity (International Index of Erectile Function score or Sexual Health Inventory of Men) and duration
- Resting electrocardiogram (ACCF/AHA class IIa, LOE C in asymptomatic adults with hypertension or diabetes and ACCF/AHA class IIb, LOE C in

asymptomatic adults without hypertension or diabetes)
- Fasting plasma glucose level
- Serum creatinine level (estimated glomerular filtration rate) and albumin to creatinine ratio
- Total testosterone (TT) level (before 11 AM)
- Plasma lipid levels (total, low-density lipoprotein, and HDL cholesterol and triglyceride values)

Findings from a study of 4883 men and women 65 years and older who were followed up for 10 years suggest that 9 of 10 new cases of diabetes would have been avoided if patients were in the low-risk group for each of 5 lifestyle factors (physical activity, diet [combining intake of fiber, polyunsaturated vs saturated fat, trans fats, and glycemic index], smoking habits, alcohol use, and adiposity [measured by BMI or WC]).[33] Recent evidence suggests that measures of abdominal adiposity (eg, WC and waist to hip ratio) are better predictors of adverse cardiovascular outcomes than is BMI.[34,35] Abdominal obesity is associated with secretion of excess free fatty acids, release of inflammatory cytokines, and reduced secretion of adiponectin.[36] Furthermore, diabetes is associated with a 2-fold increase in the prevalence of CVD,[37] and estimated glomerular filtration rates less than 60 mL/min and urinary albumin to creatinine ratios greater than 10 mg/g are associated with increased cardiovascular mortality independent of other risk factors.[38,39]

The consensus panel recommends that testosterone levels be measured in all men with a diagnosis of organic ED, especially in those for whom PDE5 inhibitor therapy failed.[6] This recommendation may be controversial, and it differs from the guideline published by the American College of Physicians,[40] which does not recommend for or against routine hormonal blood tests or treatment in patients with ED. However, the British Society for Sexual Medicine and the International Society for Sexual Medicine advocate testosterone measurements (≥2) in all men with ED. The American College of Physicians urges physicians to consider the presence or absence of symptoms of hormonal dysfunction (eg, decreased libido and decreased spontaneous erection) and of physical findings (eg, testicular or muscle atrophy) when considering whether to measure testosterone levels in individual patients with ED. The consensus panel recommendation for evaluation of testosterone levels in all men with ED is based on evidence from an accumulation of recent studies linking low testosterone levels to ED and CVD.[41] Testosterone is a key central and peripheral modulator of erectile function in animal studies.[42-45] Consistent with these observations, a single-center study of 1050 men seeking new consultation for sexual dysfunction found that 36% had hypogonadism.[46] Buvat and Bou Jaoude,[47] in a compilation of data

TABLE 2. Low Testosterone Levels and Increased Mortality Rates in Recent Publications With Populations Greater Than 500					
Reference	HR (95% CI)	Study design	Men (No.)	Mean follow-up (y)	Mortality
Shores et al,[51] 2006	1.88 (1.34-2.63)	Retrospective	858	8.0	All-cause
Laughlin et al,[52] 2008	1.40 (1.14-1.71)	Prospective	794	20.0	All-cause
	1.38 (1.02-1.85)				CVD
Khaw et al,[53] 2007	2.29 (1.60-3.26)	Prospective	2314 of 11,606	10.0	All-cause and CVD
Haring et al,[54] 2010	2.32 (1.38-3.89)	Prospective	1954	7.2	All-cause
	2.56 (1.15-6.52)				CVD
Malkin et al,[55] 2010	2.27 (1.45-3.60)	Prospective	930	6.9	All-cause in men with coronary disease
Tivesten et al,[56] 2009	1.65 (1.29-2.12)	Prospective	3014	4.5	All-cause
Menke et al,[57] 2010	1.43 (1.09-1.87)	Prospective	1114	9.0	All-cause
Vikan et al,[58] 2009	1.24 (1.01-1.54)	Prospective	1568	11.2	All-cause
Corona et al,[59] 2010	7.1 (1.8-28.6)	Prospective	1687	4.3	CVD
CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.					

from 7000 men with ED in 9 large series, reported serum testosterone levels less than 300 ng/dL (to convert to nmol/L, multiply by 0.0347) in 12%, including 4% before and 15% after age 50 years. Hypogonadism is a potential cause of lack of response to PDE5 inhibitor therapy,[48,49] and TRT improves response.[49] This finding suggests that a minimal level of testosterone is required for a complete effect of PDE5 inhibitor therapy.[49,50] However, testosterone assay methods differ, and there are no generally accepted lower limits of normal TT.

Several epidemiologic studies have associated low testosterone levels with increased all-cause and cardiovascular mortality (Table 2).[51-59] However, a 2010 meta-analysis limited to longitudinal (cohort) studies in middle-aged men found no association between endogenous TT levels and risk of CVD in middle-aged men.[60] A more recent study by Corona et al[61] found significant associations between low TT levels and high estradiol levels and CVD in a meta-analysis of 49 cross-sectional studies. Conversely, in a meta-analysis of 10 longitudinal studies, TT levels were significantly lower in patients with incident overall and cardiovascular mortality compared with controls, but there were no differences in baseline TT and estradiol levels between cases and controls for incident CVD.[60] The authors of both studies acknowledged that low testosterone levels may be a marker of poor general health rather than CVD risk per se. Consistent with this notion, androgen deficiency has been associated with insulin resistance, type 2 diabetes mellitus, metabolic syndrome, and increased deposition of visceral fat.[62-65] In the TIMES2 (Testosterone Replacement In Hypogonadal Men With Either Metabolic Syndrome or Type 2 Diabetes) study, 6 to 12 months of transdermal TRT (vs placebo) significantly improved insulin resistance and glycemic control in a

large randomized study of hypogonadal men with type 2 diabetes mellitus (ACCF/AHA class Ib).[66] A meta-analysis of 5 other randomized controlled trials (including 3 placebo-controlled trials) with mean follow-up of 58 weeks found that TRT was associated with a significant reduction in fasting plasma glucose levels, homeostasis model assessment of insulin resistance index, triglycerides, and WC. An increase in HDL cholesterol level was also observed, whereas no significant differences were observed for total cholesterol level, BP, or BMI.[67] In summary, the panel recommended:

- All men with ED should have their cardiovascular risk assessed.
- Testosterone level should be routinely measured.

Treatment, Additional Cardiovascular Evaluation, and Referral

- In all patients, lifestyle changes are likely to reduce cardiovascular risk and improve erectile function.
- All men with ED should have their testosterone level measured and replacement considered when appropriate.

A meta-analysis of lifestyle modification strengthened the evidence for improvement in ED and maintenance of sexual function as well as cardiovascular risk reduction in addition to previous reviews.[31] Lifestyle advice should include the following: smoking cessation, regular dynamic exercise, weight loss, a healthy diet (eg, the Mediterranean diet, which emphasizes fruits, vegetables, beans and legumes, whole grains, nuts, fish, poultry, lean red meat, cheese, and yogurt),[68] and moderate alcohol consumption (<14 U/wk for women and <21 U/wk for

men, in which number of units is calculated as percentage of alcohol × volume/1000).

Although compliance with lifestyle advice can be difficult to achieve, population-based studies suggest that changes in lifestyle may be most important for primary prevention. Managing cardiovascular risk with lifestyle change also permits avoidance or reduction of adverse drug effects. In a meta-analysis of prospective cohort studies of patients with coronary heart disease, smoking cessation reduced total mortality by 36%.[69] The pleiotropic effects of physical activity (eg, improved lipid profiles, BP, glucose-insulin homeostasis, endothelial function, inflammatory markers, and psychological well-being)[70-73] likely account for 30% to 50% reductions in incident type 2 diabetes and coronary heart disease in physically active vs sedentary individuals.[72] Diet can reduce death from coronary heart disease by up to 36% and can improve many established risk factors.[73]

Consistent with the British Society for Sexual Medicine's guidelines on the management of ED,[74] the Third International Consultation of Sexual Medicine,[75] the Endocrine Society guidelines,[41] and a combined guidance of the International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, and American Society of Andrology,[76] the panel agreed that a TT level greater than 350 ng/dL does not usually require substitution and that men with TT levels less than 230 ng/dL usually benefit from TRT. If there are no contraindications, symptomatic men (decreased libido or ED) with TT levels of 231 to 346 ng/dL may be considered for a 4- to 6-month trial of TRT but only after careful discussion about the potential risks and benefits. Beyond 6 months, TRT should be continued only in cases of clinical benefit.[77] Caution is warranted in men with a history of congestive heart failure (risk of fluid retention); repletion goals should be in the middle range (ie, 350-600 ng/dL) for this group. In patients older than 70 years and those with chronic illness, the consensus panel suggests use of an easily titratable testosterone formulation (eg, gel, spray, or patch) rather than intermediate and long-acting injectable formulations. Also note that randomized trials are needed to establish the risks and benefits of TRT regarding cardiovascular risk and all-cause mortality. Baseline hematocrit and prostate-specific antigen testing and 6-month monitoring are necessary.

As the consensus panel considers all men with ED who are older than 30 years to be at increased CVD risk, a thorough noninvasive and, when indicated, invasive evaluation of CVD status is recommended.

A collaborative management approach incorporating primary care and cardiology expertise should include lifestyle advice and pharmacotherapy to aggressively control cardiovascular risk factors (eg, BP, hyperlipidemia, and hyperglycemia), with follow-up at routine intervals.

Noninvasive cardiovascular evaluation may include measurement of biomarkers and physiologic stress testing for ischemia or anatomical clarification by coronary computed tomographic angiography (CCTA) for diagnosis of asymptomatic or undiagnosed CAD.[78-81] This evaluation can be requested by a cardiologist, primary care physician, andrologist, or urologist with specialized training in cardiovascular risk assessment. The 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults[5] provides recommendations and LOEs for the following techniques:

- Exercise stress testing (EST) (ACCF/AHA class IIb, LOE B in asymptomatic, intermediate-risk adults, particularly when nonelectrocardiogram markers are considered [ie, exercise capacity] rather than ST-segment changes)[5,82]
- Carotid intima-media thickness (CIMT) (ACCF/AHA class IIa, LOE B in asymptomatic, intermediate-risk adults)
- Computed tomography for coronary artery calcium scoring (CACS) (ACCF/AHA class IIa, LOE B in asymptomatic, intermediate-risk men ≥40 years old; ACCF/AHA class IIb, LOE B in low- to intermediate-risk [6%-10% 10-year risk] men ≥40 years old)
- Ankle-brachial index (ABI) (ACCF/AHA class IIa, LOE B in asymptomatic, intermediate-risk adults)
- CCTA (ACCF/AHA class III, LOE C in asymptomatic patients)
- Pulse wave velocity (PWV) (ACCF/AHA class III, LOE C in asymptomatic patients)
- Noninvasive assessment of endothelial function (ie, brachial artery flow-mediated dilation) (ACCF/AHA class III, LOE B in asymptomatic adults)

Despite its limitations in detecting CVD without significant stenosis, EST (with or without imaging) can further define the cardiovascular risk in patients with ED and may be particularly helpful for identifying silent CAD in patients with diabetes. In a study of patients with type 2 diabetes, ED was significantly more prevalent in men with silent CAD (33.8%) identified by EST than in those without silent CAD (4.7%).[18] Chemical stress tests (dipyridamole [Persantine, Boehringer Ingellheim GmbH, Ingelheim, Germany] or adenosine with nuclear imaging) are appropriate for patients who cannot complete an EST (eg, inability to exercise due to a disabling condition such as arthritis). If the baseline electrocardiogram makes EST unavailable or noninterpretable, the consensus panel recommends refer-

ral to a cardiologist or a practice with cardiology expertise for further evaluation.

The order of testing that men with ED should undergo is the decision of the primary care physician or cardiologist. However, it makes sense for noninvasive tests (ie, EST, CIMT, and ABI) to be performed before those that require radiation/contrast (eg, CCTA and CACS). However, CCTA or CACS as the first test may be appropriate for younger patients (aged <50 years) with a family history of CVD, severe ED, diabetes, or multiple risk factors. Invasive coronary angiography should be considered when noninvasive evaluation suggests significantly increased CVD risk.

The 2010 ACCF/AHA guideline asserts that it is "reasonable" to perform CIMT, CACS, and ABI during assessment of intermediate-risk patients.[5] The Society for Heart Attack Prevention and Eradication task force issued a stronger recommendation, suggesting that all asymptomatic men 45 to 75 years of age and women 55 to 75 years of age who do not have very-low-risk characteristics (ie, absence of any traditional cardiovascular risk factors) or a documented history of CVD undergo CACS or CIMT screening for the detection of subclinical atherosclerosis.[83] In an analysis from the Atherosclerosis Risk in Communities study, addition of CIMT and plaque detection via ultrasonography to traditional risk factors improved coronary heart disease risk prediction.[84] In the Multi-Ethnic Study of Atherosclerosis, CACS was a better predictor of CVD than was CIMT.[85] In a meta-analysis of 16 population-based cohort studies, a low ABI (≤0.90) was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rates compared with the overall rate in each FRS category,[86] suggesting that ABI assessment may improve cardiovascular risk prediction beyond the FRS. Although the ACCF/AHA does not currently recommend assessment of arterial stiffness (eg, PWV) for cardiovascular risk determination in asymptomatic individuals, a meta-analysis of 17 longitudinal studies (mean follow-up, 7.7 years) showed that participants with high aortic PWV were at higher risk for total cardiovascular events, cardiovascular mortality, and all-cause mortality compared with participants with low PWV.[87] Similarly, impaired endothelial dysfunction detected by EndoPAT (Itamar Medical Ltd, Caesarea, Israel) was an independent predictor of cardiac death, MI, revascularization or cardiac hospitalization in symptomatic outpatients over 7-year follow-up.[88] Similarly, endothelial function assessed in the brachial artery by flow-mediated dilation[89,90] or in the forearm microvasculature by Doppler[91] predicted outcome independently of FRS. However, the role of measures of endothelial function in the evaluation of men with ED has yet to be established.

Assessment of circulating or noncirculating biomarkers may also help detect subclinical CVD in the indeterminate-risk patient. Consistent with the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults,[5] the consensus panel recommends that physicians consider evaluation of the following nontraditional risk factors: high-sensitivity C-reactive protein (hsCRP) level (ACCF/AHA class IIb, LOE B in asymptomatic, intermediate-risk men ≤50 years),[5] glycated hemoglobin level (ACCF/AHA class IIb, LOE B in asymptomatic adults without a diagnosis of diabetes),[5] urinary albumin excretion (ACCF/AHA class IIa, LOE B in asymptomatic adults with hypertension or diabetes; and ACCF/AHA class IIb, LOE B in asymptomatic, intermediate-risk adults without hypertension or diabetes),[5] serum uric acid level, and lipoprotein-associated phospholipase A2 level (ACCF/AHA class IIb, LOE B in asymptomatic, intermediate-risk adults).[5]

The hsCRP level is an independent predictor of incident coronary events after adjustment for traditional risk factors (ie, age, total cholesterol level, HDL cholesterol level, smoking status, BMI, diabetes, history of hypertension, exercise level, and family history of coronary disease).[92-94] Thus, in 2003, the Centers for Disease Control and Prevention and the AHA endorsed measurement of the hsCRP level as an adjunct to global risk prediction, particularly in patients at intermediate risk (10%-20% over 10 years).[95] More recently, the hsCRP level improved the predictive value of the FRS in patients at high risk for coronary heart disease.[96] The independent prognostic value of the hsCRP level was also evident in a meta-analysis of 160,309 people without a history of vascular disease (ie, 1.31 million person-years at risk and 27,769 fatal or nonfatal disease outcomes) from 54 long-term prospective studies.[97] Ridker[98] reviewed evidence that hsCRP level correctly reclassifies a substantial proportion of patients at intermediate risk for CVD into clinically relevant higher- or lower-risk groups.

Although not specifically addressed in the 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults,[5] the consensus panel recommends evaluation of serum uric acid levels. Similar to hsCRP levels, the recent literature supports the serum uric acid level as an inexpensive marker of increased cardiovascular risk.[99] There is inconsistency regarding the incremental benefit of adding the glycated hemoglobin level or microalbuminuria to standard risk factors in prediction of CVD and reclassification of cardiovascular risk. However, a recent analysis of data from the Atherosclerosis Risk in Communities study showed that addition of the glycated hemoglobin level to predic-

tion models incorporating traditional risk factors and the fasting glucose level improved coronary heart disease risk prediction in nondiabetic patients with no history of CVD.[100] In a meta-analysis of 26 cohort studies, microalbuminuria was associated with a 50% greater risk of coronary heart disease, and macroalbuminuria more than doubled coronary heart disease risk.[101] Finally, the lipoprotein-associated phospholipase A2 level seems to be an independent predictor of CVD events in apparently healthy adults after adjustment for hsCRP levels and standard risk factors.[102-105] The 2010 ACCF/AHA guideline[5], p.e66 states that measurement of lipoprotein-associated phospholipase A2 "might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults."

MANAGEMENT OF ED IN THE PATIENT WITH KNOWN CVD

The objective of this algorithm is to estimate the cardiovascular risk associated with sexual activity in patients with ED and known CVD (Figure). Herein, *risk* refers to the likelihood of mortal or morbid events during or shortly after sexual activity. The panel's recommendations are similar to those developed during the first and second Princeton Consensus Conferences.[1,2] However, the current recommendations classify patients with New York Heart Association (NYHA) class II as low risk rather than intermediate risk as in previous recommendations.

Patients with NYHA class III have been moved from high to intermediate risk. Patients with mild, stable angina and those with past MI (>6-8 weeks) have been reclassified as intermediate risk rather than low risk as in previous recommendations.

Sexual Inquiry

As reviewed previously herein, ED and CVD share risk factors, and ED is an independent predictor of CVD. Thus, assessment of sexual function should be incorporated into the initial cardiovascular evaluation for all men, regardless of the presence or absence of known CVD.

Exercise Ability and Sexual Activity Risk Stratification

A recent meta-analysis of 10 studies established a significant association between acute cardiac events and episodic physical and sexual activity that was attenuated among individuals with high levels of habitual physical activity.[106] Thus, exercise ability discerned by review of patient history may guide the physician to an estimate of cardiovascular risk associated with sexual activity. Exercise tolerance should be established before the initiation of ED therapy in all men regardless of cardiovascular risk. Members of the Princeton III Consensus contributed to "Sexual Activity and Cardiovascular Disease," the focus of an AHA Scientific Statement.[107] To aid practice, common patient profiles are provided for each level of risk.

Low-Risk Patients. As in previous recommendations, the low-risk group is limited to patients for whom sexual activity does not represent significant cardiac risk. These patients can generally perform exercise of modest intensity without symptoms. Low-risk patients include successfully revascularized (eg, via coronary artery bypass grafting, stenting, or angioplasty) individuals, patients with asymptomatic controlled hypertension, those with mild valvular disease, and patients with left ventricular dysfunction/heart failure (NYHA classes I and II) who achieved 5 metabolic equivalents of the task (Mets) without ischemia on recent exercise testing.

High-Risk Patients. High-risk patients are those with cardiac conditions severe or unstable enough to pose a significant risk with sexual activity. Most are moderately or severely symptomatic. Common high-risk patient profiles include unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), recent MI without intervention (<2 weeks), high-risk arrhythmia (exercise-induced ventricular tachycardia,
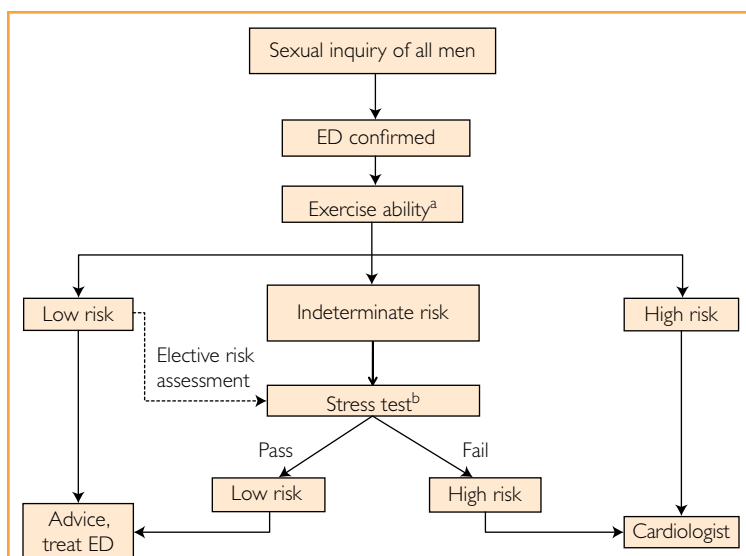

FIGURE. Management of erectile dysfunction (ED) in all men with ED, especially those with known cardiovascular disease. [a]Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds. [b]Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.

implanted internal cardioverter defibrillator with frequent shocks, and poorly controlled atrial fibrillation), obstructive hypertrophic cardiomyopathy with severe symptoms, and moderate to severe valve disease, particularly aortic stenosis.

Indeterminate-Risk Patients. Further evaluation using EST is required for indeterminate-risk patients before resuming sexual activity. Sexual activity between couples in a longstanding relationship equates to approximately 3 Mets. Completing 4 minutes of the standard Bruce treadmill protocol (5-6 Mets) without symptoms, arrhythmias, or a fall in systolic BP identifies the safety of sexual activity.[1,2,6] Based on stress test results, they will be reassigned to low- or high-risk groups as recommended after the first and second Princeton Consensus Conferences. Chemical stress tests (eg, dipyridamole or adenosine with nuclear imaging) are appropriate if the patient cannot complete a standard exercise test (eg, owing to a disabling condition such as arthritis). Indeterminate-risk patients include those with mild or moderate stable angina pectoris, past MI (2-8 wks) without intervention awaiting exercise electrocardiography, congestive heart failure (NYHA class III), and noncardiac sequelae of atherosclerotic disease (eg, PAD and a history of stroke or transient ischemic attack); this patient with ED may require assessment for additional vascular disease using CIMT or the ABI and subsequent reclassification to low or high risk.

ED Treatment (Low-Risk Patient) or Referral to a Cardiologist (High-Risk Patient)

- Most low-risk patients can initiate or resume sexual activity and begin ED treatment without further testing or evaluation.

The PDE5 inhibitors (eg, sildenafil, tadalafil, and vardenafil) are widely used to treat ED. Their safety and appropriate use was reviewed in the second Princeton Consensus Conference recommendations,[2] and more recent analyses of placebo-controlled and postmarketing surveillance data have demonstrated no new concerns regarding cardiovascular events.[108,109] In fact, a variety of studies have demonstrated a potential role for PDE5 inhibition in the management of hypertension[110-113] and endothelial dysfunction[114-116] in patients at risk for CVD. Effects on endothelial function are believed to underlie the beneficial effect of PDE5 inhibition in patients with pulmonary hypertension, for which sildenafil and tadalafil are licensed for use. Additional considerations for treatment of ED should include TRT for men with low (<230 ng/dL) or intermediate (230-350 ng/dL) serum TT levels (either as initial

treatment or added to PDE5 inhibitor therapy after PDE5 inhibitor failure),[49,117] non–PDE5 inhibitor approaches,[2] exercise and weight loss,[118,119] and partner and relationship factors.[120-123]

Management of ED should always be considered secondary to maintaining cardiovascular function. Thus, treatment for ED should not negatively affect cardiovascular health. Conversely, potential effects on erectile function of agents used to treat cardiovascular risk factors should be considered. For example, the β-blocker nebivolol, which has direct vasodilating properties, is less likely to cause ED than are other β-blockers.[124-126] Angiotensin receptor blockers are also less likely to cause ED than are other antihypertensive agents (eg, diuretics).[127,128] There have been several reports of improvements in erectile function among men using statins with and without PDE5 inhibitors.[129-132] However, these findings are not consistent with those of Solomon et al,[133] who reported new-onset ED in 22% of 93 high-risk men after 6 months of statin use. Placebo-controlled studies of erectile function in men taking medications to control other cardiovascular risk factors are lacking.

In high-risk patients, sexual activity should be deferred until the cardiac condition has been stabilized and sexual activity can be safely resumed. These patients should be referred to a cardiologist for further evaluation and should be managed with a collaborative approach to primary prevention. In all cases, patient follow-up and reassessment is recommended.

RECOMMENDATIONS

Consistent with other guidelines, the recommendations of the third Princeton Consensus Panel emphasize an approach to risk assessment that integrates multiple aspects of cardiometabolic health. Sexual function should be incorporated into CVD risk assessment for all men, and ED may allow identification of at-risk men who require further cardiovascular evaluation. The scientific evidence suggests that a comprehensive approach to cardiovascular risk reduction will improve overall vascular health, including sexual function. Similar to the first and second Princeton Consensus panels, the third Princeton Consensus also provides an approach to ensuring that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED. Finally, the panel encourages a collaborative approach to the management of men's sexual function and cardiovascular risk, incorporating general, urologic, endocrine, and cardiologic expertise.

Abbreviations and Acronyms ABI = ankle-brachial index; **ACCF** = American College of Cardiology Founda-

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