REVIEW

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All Men with Vasculogenic Erectile Dysfunction Require a Cardiovascular Workup

Martin Miner, MD,[a] Ajay Nehra, MD,[b] Graham Jackson, MD,[c] Shalender Bhasin, MD,[d] Kevin Billups, MD,[e,f] Arthur L. Burnett, MD,[f] Jacques Buvat, MD,[g] Culley Carson, MD,[h] Glenn Cunningham, MD,[i] Peter Ganz, MD,[j] Irwin Goldstein, MD,[k] Andre Guay, MD,[l] Geoff Hackett, MD,[m] Robert A. Kloner, MD, PhD,[n] John B. Kostis, MD,[o] K. Elizabeth LaFlamme, PhD,[p] Piero Montorsi, MD,[q] Melinda Ramsey, PhD,[p] Raymond Rosen, PhD,[r] Richard Sadovsky, MD,[s] Allen Seftel, MD,[t] Ridwan Shabsigh, MD,[u] Charalambos Vlachopoulos, MD,[v] Frederick Wu, MD[w]

[a]Departments of Family Medicine and Urology, Miriam Hospital and Brown University, Providence, RI; [b]Department of Urology, Rush University, Chicago, Ill; [c]Guy's & St. Thomas Hospital, London, UK; [d]Department of Medicine, Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Mass; [e]Department of Urologic Surgery, University of Minnesota, Minneapolis; [f]The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Md; [g]Centre d'Etude et de Traitement de la Pathologie de l'Appareil Reproducteur et de la Psychosomatique, Lille, France; [h]Department of Surgery, Division of Urologic Surgery, University of North Carolina, Chapel Hill; [i]Departments of Medicine, and Molecular & Cellular Biology, Baylor College of Medicine and St. Luke's Episcopal Hospital, Houston, Tex; [j]Division of Cardiology, San Francisco General Hospital and University of California, San Francisco; [k]San Diego Sexual Medicine, Calif; [l]Center For Sexual Function/Endocrinology, Lahey Clinic Medical Center, Peabody, Mass, Tufts University School of Medicine, Boston, Mass; [m]Good Hope Hospital, Birmingham, UK; [n]Heart Institute, Good Samaritan Hospital and Keck School of Medicine at University of Southern California, Los Angeles; [o]Cardiovascular Institute, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; [p]Complete Healthcare Communications, Inc., Chadds Ford, Pa; [q]Centro Cardiologico Monzino, IRCCS, Institute of Cardiology University of Milan, Italy; [r]New England Research Institutes, Inc., Watertown, Mass; [s]Department of Family Medicine, SUNY-Downstate Medical Center, Brooklyn, NY; [t]Department of Urology, Cooper University Hospital, Camden, NJ; [u]Division of Urology, Maimonides Medical Center, Brooklyn, NY, and College of Physicians and Surgeons of Columbia University, New York, NY; [v]1st Department of Cardiology, Athens Medical School, Athens, Greece; [w]Andrology Research Unit, Developmental & Regenerative Biomedicine Research Group, University of Manchester, Manchester Academic Health Science Centre, Manchester Royal Infirmary, UK.

ABSTRACT

An association between erectile dysfunction and cardiovascular disease has long been recognized, and studies suggest that erectile dysfunction is an independent marker of cardiovascular disease risk. Therefore, assessment and management of erectile dysfunction may help identify and reduce the risk of future cardiovascular events, particularly in younger men. The initial erectile dysfunction evaluation should distinguish between predominantly vasculogenic erectile dysfunction and erectile dysfunction of other etiologies. For men believed to have predominantly vasculogenic erectile dysfunction, we recommend that initial cardiovascular risk stratification be based on the Framingham Risk Score. Management of men with erectile dysfunction 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 emerging prognostic markers to further understand cardiovascular risk in men with erectile dysfunction, but few markers have been prospectively evaluated in this population. In conclusion, we support cardiovascular risk stratification and risk-factor management in all men with vasculogenic erectile dysfunction.

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Requests for reprints should be addressed to Martin Miner, MD, Men's Health Center, Department of Family and Community Medicine, Miriam Hospital, 164 Summit Ave., Providence, RI 02906.

E-mail address: martin_miner@brown.edu

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Cardiovascular disease is a leading cause of death in men. Erectile dysfunction is a common problem in men as they age and may help drive them to seek medical attention in the absence of other cardiovascular symptoms. The link between erectile dysfunction and cardiovascular disease is well established; however, this relationship has been previously characterized primarily by shared risk factors.[1-3] An emerging paradigm indicates that erectile dysfunction is, in fact, an independent marker of cardiovascular disease risk.[4-8] Thus, the presence of erectile dysfunction may provide the opportunity for cardiovascular disease risk mitigation in men with otherwise unrecognized cardiovascular disease. This article discusses the evaluation and management of cardiovascular risk in men with erectile dysfunction but no known cardiovascular disease in a primary care setting. It considers the fundamental question: do all men with presumed vasculogenic erectile dysfunction need a cardiovascular workup?

CLINICAL SIGNIFICANCE

- The prognostic value of erectile dysfunction for cardiovascular events is considerably greater in younger men.
- For men believed to have predominantly vasculogenic erectile dysfunction, initial cardiovascular risk stratification should be based on the Framingham Risk Score.
- Management of low-risk men with erectile dysfunction should focus on risk-factor control; men at high risk should be referred to a cardiologist.
- Intermediate-risk men should undergo noninvasive evaluation for subclinical atherosclerosis.

THE ERECTILE DYSFUNCTION/CARDIOVASCULAR DISEASE NEXUS

A number of risk factors are shared by erectile dysfunction and cardiovascular disease, including age,[9] sedentary lifestyle, obesity, smoking, hypercholesterolemia, metabolic syndrome,[10] insulin resistance,[11] hypertension,[12,13] and diabetes.[12] The common pathophysiologic bases for erectile dysfunction and cardiovascular disease are believed to include endothelial dysfunction,[14] inflammation,[15] and low testosterone.[14,16] Furthermore, numerous studies in men with clinically evident cardiovascular disease have established erectile dysfunction as an independent risk marker for cardiovascular disease[4-8,17] and shown that erectile dysfunction frequently precedes coronary artery disease,[18-21] peripheral arterial disease,[22] and stroke.[19] Erectile dysfunction symptoms appear approximately 2 to 5 years before the onset of cardiovascular symptoms,[18,23-25] and more severe erectile dysfunction has been correlated with greater atherosclerotic burden,[21] extent of coronary artery disease,[18,26] and risk of coronary artery disease,[19,20] peripheral artery disease,[22] and major cardiovascular events.[27]

Compared with traditional cardiovascular disease risk factors (eg, family history of myocardial infarction, smoking, hyperlipidemia), incident erectile dysfunction has demonstrated similar or greater predictive value for cardiovascular events.[28,29] Although addition of erectile dysfunction to the Framingham Risk Score resulted in only a slight improvement for predicting cardiovascular events in a group of men 40 to 70 years of age,[4] other studies demonstrated considerably greater prognostic value of erectile dysfunction in younger men.[30-32] Findings from the Olmstead County Study[30] showed that erectile dysfunction was far more predictive of coronary artery disease in men aged 40-49 years versus older men, whereas another retrospective study[31] showed that the predictive value for atherosclerotic cardiovascular events strengthened with younger age at erectile dysfunction development. Indeed, the incidence of atherosclerotic cardiovascular events in men <40 years of age with erectile dysfunction was >7 times the incidence in a reference group representative of the general male population. Most recently, Riedner et al[32] performed a case-control study involving 242 men (mean age, 58 years) referred for elective coronary angiography. Nearly half had significant coronary artery disease (stenosis of 50% or greater in ≥1 of the major epicardial vessels or their branches); the remaining men had no significant coronary artery disease. Men <60 years of age with coronary artery disease were significantly more likely to have erectile dysfunction than those without coronary artery disease. However, coronary artery disease was not associated with increased likelihood of erectile dysfunction in men aged ≥60 years. A statistical model controlling for the effects of cardiovascular risk factors, testosterone, and C-reactive protein showed that the probability of coronary artery disease was 2.3 times higher in men <60 years of age with erectile dysfunction versus those without erectile dysfunction. There was no association between erectile dysfunction and probability of coronary artery disease in men ≥60 years of age. Thus, current evidence suggests that erectile dysfunction is an early marker of generalized cardiovascular disease and supports cardiovascular workup in younger men with vasculogenic erectile dysfunction. We believe that the addition of erectile dysfunction to the Framingham Risk Score would improve risk prediction in younger men (aged 30-60 years), but additional studies are needed to make this determination.

DISTINGUISHING PREDOMINANTLY ORGANIC FROM PREDOMINANTLY PSYCHOGENIC ERECTILE DYSFUNCTION

Cases of erectile dysfunction may be classified as predominantly psychogenic in nature, predominantly organic, or mixed. Although many cases are mixed, identification of predominant etiology helps guide management of both cardiovascular and sexual health. Because vasculogenic erectile dysfunction is a harbinger of cardiovascular disease,

it is important to distinguish between men with predominantly vasculogenic erectile dysfunction and those with predominantly psychogenic erectile dysfunction or nonvasculogenic organic erectile dysfunction. Men with overtly vasculogenic erectile dysfunction will benefit from the most rigorous cardiovascular evaluation, and those with clearly psychogenic erectile dysfunction may require significant psychosexual intervention.

Psychogenic erectile dysfunction tends to be acute, situational, and of varying disease course. It is associated with rigid noncoital erections, a long history of psychosexual problems, partner problems from onset, and primary anxiety or fear (**Table 1**).[33] The underpinnings of predominantly psychogenic erectile dysfunction are multifactorial, and possible causes may include psychiatric disorders,[34-37] misconceptions about normal sexual functioning,[38] or interpersonal problems with the sexual partner.[39] Psychogenic causes of erectile dysfunction, such as depression, also may increase cardiovascular risk and should be identified and treated.[38,40,41]

The most common organic etiologies of erectile dysfunction are vasculogenic, hormonal, and neurogenic. Organic erectile dysfunction has a gradual onset, a constant disease course, and is associated with poor noncoital erections (**Table 1**).[33] The most common organic etiology of erectile dysfunction is vasculogenic. Reduced inflow may be due to atherosclerotic blockage or factors affecting endothelial function that prevent adequate vasodilation during sexual stimulation (eg, increased serum inflammatory markers, reduced testosterone). Increased outflow is commonly due to venous leak.[33,42,43] Furthermore, strong evidence supports a correlation between erectile dysfunction and various metabolic and vascular disorders. Indeed, age, visceral adiposity, and metabolic syndrome and its components, all risk factors for cardiovascular disease, also increase the risk for erectile dysfunction.[44,45] Thus, evidence of these disorders in men with erectile dysfunction suggests a vasculogenic etiology.

Several approaches may be used to distinguish predominantly organic from predominantly psychogenic erectile dysfunction. Initially, a review of the patient's medical history may reveal the presence or absence of the organic or psychogenic risk factors mentioned earlier. Furthermore, every erectile dysfunction patient should be questioned about the frequency and rigidity of nocturnal or early morning erections. In the absence of other risk factors, the presence of regular nocturnal or early morning erections is suggestive of normal vascular functioning, thereby indicating a psychogenic etiology.[46] It should be noted that reduced frequency or rigidity of morning erections may be due to reductions in morning rapid eye movement sleep observed in older individuals.[47,48] In cases that are difficult to distinguish, the treating physician may refer the patient to a urologist or sexual medicine practitioner with specialized training in erectile dysfunction evaluation.

RECOMMENDATIONS FOR EVALUATION AND MANAGEMENT OF CARDIOVASCULAR RISK IN MEN WITH ERECTILE DYSFUNCTION BUT NO KNOWN CARDIOVASCULAR DISEASE

Because erectile dysfunction is a well-established, independent marker for cardiovascular disease risk,[4-8] all men should be questioned about their sexual history and functioning as part of the initial assessment of cardiovascular disease risk. For all men with erectile dysfunction, particularly those with vasculogenic erectile dysfunction, we recommend that initial risk stratification be based on the Framingham Risk Score, which estimates the 10-year risk for myocardial infarction or coronary death. The Framingham Risk Score incorporates age, sex, total and high-density lipoprotein cholesterol, smoking, systolic blood pressure, and use of antihypertensive medications.[49] Initial risk stratification based on the Framingham Risk Score is recommended by the 2010 American College of Cardiology Foundation/American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults[50] and Princeton III Consensus.[51] Symptomatic men are presumed to have cardiovascular disease and are therefore at high risk for cardiovascular disease events. The following may be used to identify men whose cardiovascular risk may exceed that estimated by the Framingham Risk Score: a thorough history, physical examination (including measures of visceral adiposity), assessment of erectile dysfunction severity and duration, evaluation of fasting plasma glucose, resting electrocardiogram, serum

Table 1 Differential Characteristics of Psychogenic vs Organic Erectile Dysfunction[33,47,48]

Characteristic	Predominantly Psychogenic Erectile Dysfunction	Predominantly Organic Erectile Dysfunction
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 erectile dysfunction
Partner problems	At onset	Secondary to erectile dysfunction
Anxiety/fear	Primary	Secondary to erectile dysfunction

Adapted from: 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.[33]

creatinine (estimated glomerular filtration rate) and albumin:creatinine ratio, and presence or absence of the metabolic syndrome.[51] Given the evidence that treatment of obstructive sleep apnea can improve erectile function,[52,53] along with observational studies suggesting that treatment of obstructive sleep apnea may improve cardiovascular outcomes,[54,55] the physician also should consider evaluating patients with erectile dysfunction for sleep apnea. Based on results of the aforementioned assessments, the physician may encourage lifestyle changes (eg, diet, exercise, smoking cessation), which are likely to reduce cardiovascular risk and improve erectile function.[56,57] Interventions to control specific cardiovascular risk factors (eg, hypertension, diabetes, hyperlipidemia, obstructive sleep apnea) also may be appropriate. Men who appear to be at high risk for cardiovascular events should be referred to a cardiologist. We suggest that intermediate-risk men with vasculogenic erectile dysfunction and no overt cardiovascular disease undergo further noninvasive evaluation of cardiovascular risk using exercise stress testing, carotid intima-media thickness, ankle-brachial index, or coronary artery calcium scoring (**Figure**). 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.

Exercise Stress Testing

The 2010 American College of Cardiology Foundation/American Heart Association guidelines recommend exercise stress testing and carotid intima-media thickness for noninvasive evaluation of subclinical cardiovascular disease in intermediate-risk patients.[50] Although exercise stress testing does not detect non-flow-limiting lesions, it detects silent, inducible ischemia, thus providing further understanding of cardiovascular disease risk. Data suggest that this tool may be particularly helpful in identifying silent coronary artery disease in men with erectile dysfunction and diabetes.[58]

Carotid Intima-Media Thickness

Although the value of carotid intima-media thickness has not been evaluated in men with erectile dysfunction, American College of Cardiology Foundation/American Heart Association[50] and, more emphatically, the Society for

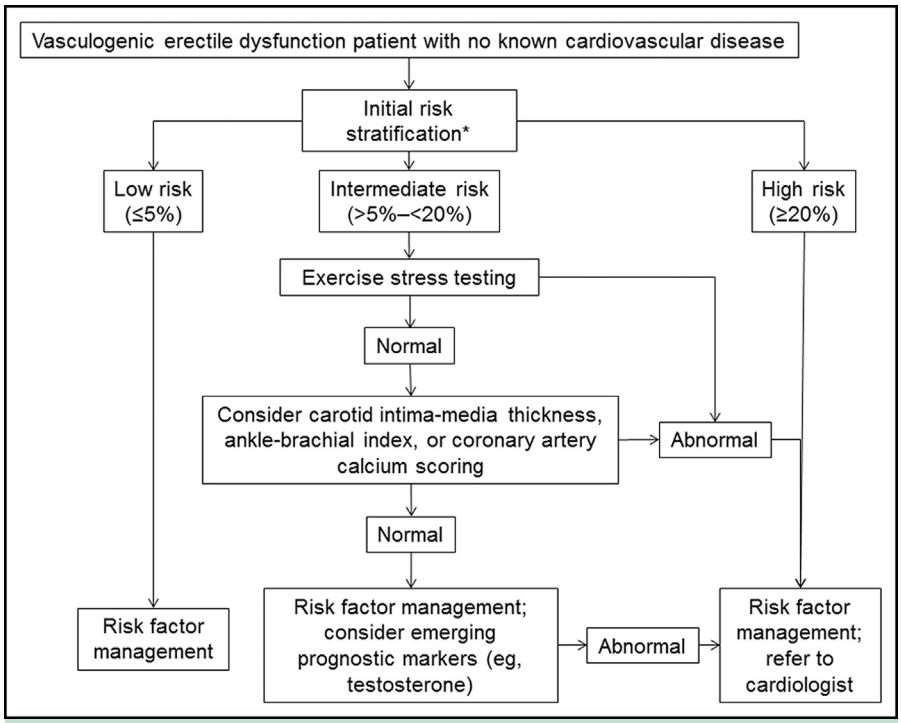

Figure Evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction but no known cardiovascular disease recommended for the primary care physician. Symptomatic men are presumed to have cardiovascular disease and are therefore at high risk for cardiovascular disease events. A thorough history, physical examination (including measures of visceral adiposity), assessment of erectile dysfunction 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 and obstructive sleep apnea may be used to further characterize cardiovascular risk. *Based on the Framingham Risk Score.[49] SCORE[58] is an appropriate alternate method for initial cardiovascular risk stratification.

Heart Attack Prevention and Eradication Task Force[59] assert that it is reasonable to perform carotid intima-media thickness assessment during evaluation of patients at intermediate risk. Studies published since these guidelines were developed support the value of this methodology in cardiovascular risk assessment. In an evaluation of 441 asymptomatic subjects <65 years of age (mean age, 50 ± 8 years) with no history of coronary artery disease or diabetes, Eleid et al[60] reported that 38% of the 336 subjects deemed low risk based on the Framingham Risk Score had high-risk carotid ultrasound findings (ie, carotid intima-media thickness ≥75th percentile adjusted for age, sex, and race or presence of plaque). Similarly, Naqvi et al[61] found that 50% of 136 asymptomatic subjects (mean age, 57 ± 11 years) with no history of vascular events and a Framingham Risk Score <10% had carotid intima-media thickness ≥75th percentile. However, Den Ruijter et al[62] performed a meta-analysis of 14 studies (mean patient age, 58 years [range, 35-75 years]) that showed little improvement in 10-year risk prediction of first-time myocardial infarction or stroke when common carotid intima-media thickness measurements were added to the Framingham Risk Score. The incorporation of carotid intima-media thickness into cardiovascular risk assessment is further complicated by the fact that thresholds for abnormal carotid intima-media thickness must be adjusted for age, sex, and race.[63]

Ankle-Brachial Index

Cardiovascular disease has been identified in men with established erectile dysfunction by using various measures of general atherosclerotic burden, which also are considered surrogate markers of cardiovascular disease. For example, ankle-brachial index, the ratio of blood pressure in the dorsalis pedis artery to that in the brachial artery, is widely used to detect peripheral artery disease. The American College of Cardiology Foundation/American Heart Association considers measurement of ankle-brachial index to be reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.[50] In a study evaluating the relationship between erectile dysfunction and peripheral artery disease, Polonsky et al[22] showed that ankle-brachial index successfully identified peripheral artery disease in men with erectile dysfunction and suggested that men with erectile dysfunction undergo ankle-brachial index examination. American College of Cardiology Foundation/American Heart Association guidelines[50] state that ankle-brachial index <0.9 indicates the presence of peripheral artery disease.

Coronary Artery Calcium Scoring

Coronary artery calcium scoring is another measure that has been validated prospectively as a predictor of cardiovascular disease[64] and for which the literature provides limited support in the erectile dysfunction population. Similar to ankle-brachial index and carotid intima-media thickness, the American College of Cardiology Foundation/American Heart Association considers coronary artery calcium scoring reasonable for cardiovascular risk assessment in intermediate-risk adults.[50] Jackson and Padley[65] performed maximal treadmill exercise stress testing and coronary artery calcium scoring in 20 men aged 39-69 years with erectile dysfunction and no cardiac symptoms; coronary artery calcium scores were >50 in 11 men, all of whom had angiographic coronary artery disease on coronary computed tomography and 9 of whom had normal exercise stress tests. This study suggests that erectile dysfunction is a predictor of subclinical, non-flow-limiting coronary artery disease not detectable by exercise stress tests, and that methods such as coronary artery calcium scoring and coronary computed tomography angiography may help detect coronary artery disease in patients with normal exercise stress tests. More recently, in a comparison of the ability of 6 risk markers (coronary artery calcium scoring, carotid intima-media thickness, ankle-brachial index, brachial flow-mediated dilation, high-sensitivity C-reactive protein, and family history of coronary heart disease) to improve prediction of incident coronary heart disease/cardiovascular disease in patients at intermediate risk (Framingham 10-year risk, >5%-<20%) enrolled in the Multi-Ethnic Study of Atherosclerosis, coronary artery calcium scoring provided superior improvements in risk estimation versus the other risk markers.[66] Noninvasive cardiovascular evaluation may include other emerging prognostic markers, which are discussed in the next section.

ROLE OF ADDITIONAL EMERGING PROGNOSTIC MARKERS IN PREDICTING CARDIOVASCULAR RISK IN MEN WITH ERECTILE DYSFUNCTION

Although we recommend exercise stress testing, carotid intima-media thickness, ankle-brachial index, or coronary artery calcium scoring for noninvasive evaluation of subclinical cardiovascular disease in intermediate-risk patients, additional emerging prognostic markers may provide meaningful information pertinent to cardiovascular risk in some patients. **Table 2** summarizes evidence supporting these markers for assessment of cardiovascular risk in men with erectile dysfunction, along with 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[67] investigated arterial prognostic markers in patients with erectile dysfunction. The study employed carotid-femoral pulse-wave velocity, a measure of aortic stiffness, and carotid intima-media thickness. Both indices were increased significantly in men with erectile dysfunction versus without, suggesting an increased cardiovascular risk in men with erectile dysfunction. The European Society of Cardiology/European Society of Hypertension guidelines recommend pulse-wave velocity for the evaluation of the hypertensive patient.[68] Recent data

Table 2 Summary of Evidence Supporting Emerging Prognostic Markers of Cardiovascular Disease in Men with Erectile Dysfunction

Biomarkers	Level of Evidence*: Association with Cardiovascular Disease Prevalence in Erectile Dysfunction	Level of Evidence*: Cardiovascular Disease Prognostic Value in Erectile Dysfunction	Availability	Cost
Carotid intima-media thickness[84]	2b	No evidence	Somewhat limited	Medium
Coronary artery calcium scoring[65,85]	2b	No evidence	Limited	High
Ankle-brachial index[22]	2b	No evidence	High	Low
Testosterone[71,72]	No evidence	2c	High	Low
Aortic stiffness (ie, pulse-wave velocity)[69]	No evidence	2c	Somewhat limited	Medium
Albuminuria[7]	No evidence	2c	High	Low

2b = exploratory cohort study with good reference standards; 2c = outcomes research.

*Centre for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine—levels of evidence (March 2009). University of Oxford. Available at: http://www.cebm.net/index.aspx?o=1025.

show an independent predictive ability of pulse-wave velocity for future cardiovascular events, specifically in erectile dysfunction patients.[69]

Prognostic markers that can be evaluated from routine blood sampling are particularly useful, and several candidates have been evaluated in men with erectile dysfunction. Total testosterone is a relatively low-cost option, and a meta-analysis of 7 population-based studies concluded that there was a (borderline-significant) 25% increased risk in cardiovascular disease 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.[70] Among patients with erectile dysfunction, Corona et al[71] reported that total testosterone 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. This finding was supported by a recent analysis of data from the European Male Aging Study showing that total testosterone <8 nmol/L and sexual symptoms were independently and additively associated with increased all-cause and cardiovascular disease mortality in men between 40 and 79 years of age.[72] Although an observational cohort study of male US veterans with low total testosterone levels (≤250 ng/dL) showed that testosterone treatment was associated with decreased mortality compared with no testosterone treatment,[73] it cannot be concluded that testosterone treatment reduced mortality.[74] In agreement with the British Society of Sexual Medicine,[75] Third International Consultation on Sexual Medicine,[76] and Princeton III Consensus,[51] we recommend that total testosterone levels be measured as a potential cause of erectile dysfunction, particularly in those for whom phosphodiesterase type 5 inhibitors have failed. Although there are no generally accepted lower limits of normal total testosterone, there is general agreement that total testosterone >350 ng/dL (12 nmol/L) does not usually require substitution and, based on data from young hypogonadal men, those with total testosterone <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 total testosterone between 230 and 350 ng/dL (8-12 nmol/L).[77] Testosterone replacement improves sexual desire[78] and may improve erectile function[79] and quality of life,[80] but requires monitoring.

Albuminuria is another option that has been tested in diabetic men with erectile dysfunction. In a cohort study of 2306 diabetic men without clinically evident cardiovascular disease, including 616 men with erectile dysfunction, a mean urinary albumin:creatinine ratio ≥25 mg/mmol was associated with a significantly increased risk for new cardiovascular events.[81] Another study evaluating men with type 2 diabetes and silent coronary artery disease found that those with erectile dysfunction and microalbuminuria (ie, albumin excretion rates 30-299 mg/d) showed a significantly higher risk for major adverse cardiovascular events compared with normoalbuminuric men with erectile dysfunction.[7]

High-sensitivity C-reactive protein is a potential marker of incident or future cardiovascular disease that has not been tested in erectile dysfunction-specific populations. However, high-sensitivity C-reactive protein has been endorsed by the Centers for Disease Control and Prevention and the American Heart Association as an adjunct to global risk prediction.[82] The American College of Cardiology Foundation/American Heart Association guidelines[50] state that measurement of high-sensitivity C-reactive protein may be reasonable in asymptomatic, intermediate-risk men ≤50 years of age. Results of the JUPITER[83] study suggest that measurement of high-sensitivity C-reactive protein may be useful in the selection of patients for statin therapy.

Although data supporting the use of these emerging markers to predict cardiovascular disease outcomes in men with erectile dysfunction are limited, evidence supporting the utility of these markers in other populations is expected to extend to erectile dysfunction populations.[50]

CONCLUSION

Vasculogenic erectile dysfunction should be regarded as a harbinger of silent or future cardiovascular disease. Thus,

strategies that aid in the identification and characterization of erectile dysfunction also may be clinically useful for assessing and managing cardiovascular risk. The first step is to establish reasonable certainty of predominantly organic etiology. In men with organic erectile dysfunction believed to be vasculogenic in etiology, cardiovascular risk should be further evaluated through assessment of traditional risk factors and noninvasive methods to detect subclinical cardiovascular disease. Emerging prognostic markers may be used to further characterize risk for cardiovascular events in men with erectile dysfunction, but few have been evaluated in this population. In conclusion, we strongly support cardiovascular risk stratification and risk factor management in all men with vasculogenic erectile dysfunction.

References

1. Bacon CG, Mittleman MA, Kawachi I, et al. A prospective study of risk factors for erectile dysfunction. *J Urol*. 2006;176(1):217-221.
2. 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.
3. Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. *J Am Coll Cardiol*. 2004;43(8):1405-1411.
4. 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.
5. Batty GD, Li Q, Czernichow S, et al. Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial. *J Am Coll Cardiol*. 2010;56(23):1908-1913.
6. Blumentals WA, Gomez-Caminero A, Joo S, Vannappagari V. Should erectile dysfunction be considered as a marker for acute myocardial infarction? Results from a retrospective cohort study. *Int J Impot Res*. 2004;16(4):350-353.
7. 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 Coll Cardiol*. 2008;51(21):2040-2044.
8. 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.
9. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994;151(1):54-61.
10. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol*. 2010;57(5):804-814.
11. Guay A, Jacobson J. The relationship between testosterone levels, the metabolic syndrome (by two criteria), and insulin resistance in a population of men with organic erectile dysfunction. *J Sex Med*. 2007;4(4 Pt 1):1046-1055.
12. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol*. 2004;171(6 Pt 1):2341-2345.
13. Sun P, Swindle R. Are men with erectile dysfunction more likely to have hypertension than men without erectile dysfunction? A naturalistic national cohort study. *J Urol*. 2005;174(1):244-248.
14. Guay AT. ED2: erectile dysfunction = endothelial dysfunction. *Endocrinol Metab Clin North Am*. 2007;36(2):453-463.
15. 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.
16. Yassin AA, Akhras F, El-Sakka AI, Saad F. Cardiovascular diseases and erectile dysfunction: the two faces of the coin of androgen deficiency. *Andrologia*. 2011;43(1):1-8.
17. Bohm M, Baumhakel M, Teo K, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *Circulation*. 2010;121(12):1439-1446.
18. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. *Eur Heart J*. 2006;27(22):2632-2639.
19. Ponholzer A, Temml C, Obermayr R, Wehrberger C, Madersbacher S. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? *Eur Urol*. 2005;48(3):512-518; discussion 517-518.
20. Salem S, Abdi S, Mehrsai A, et al. Erectile dysfunction severity as a risk predictor for coronary artery disease. *J Sex Med*. 2009;6(12):3425-3432.
21. Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic coronary artery disease. *Am J Cardiol*. 2003;91(2):230-231.
22. 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.
23. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol*. 2003;44(3):360-364; discussion 364-365.
24. Baumhakel M, Bohm M. Erectile dysfunction correlates with left ventricular function and precedes cardiovascular events in cardiovascular high-risk patients. *Int J Clin Pract*. 2007;61(3):361-366.
25. Hodges LD, Kirby M, Solanki J, O'Donnell J, Brodie DA. The temporal relationship between erectile dysfunction and cardiovascular disease. *Int J Clin Pract*. 2007;61(12):2019-2025.
26. Greenstein A, Chen J, Miller H, et al. Does severity of ischemic coronary disease correlate with erectile function? *Int J Impot Res*. 1997;9(3):123-126.
27. Hall SA, Shackelton R, Rosen RC, Araujo AB. Sexual activity, erectile dysfunction, and incident cardiovascular events. *Am J Cardiol*. 2010;105(2):192-197.
28. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005;294(23):2996-3002.
29. Araujo AB, Travison TG, Ganz P, et al. Erectile dysfunction and mortality. *J Sex Med*. 2009;6(9):2445-2454.
30. Inman BA, 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.
31. Chew KK, Finn J, Stuckey B, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. *J Sex Med*. 2010;7(1 Pt 1):192-202.
32. Riedner CE, Rhoden EL, Fuchs SC, et al. Erectile dysfunction and coronary artery disease: an association of higher risk in younger men. *J Sex Med*. 2011;8(5):1445-1453.
33. 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.
34. Cosgrove DJ, Gordon Z, Bernie JE, et al. Sexual dysfunction in combat veterans with post-traumatic stress disorder. *Urology*. 2002;60(5):881-884.
35. Shabsigh R, Klein LT, Seidman S, et al. Increased incidence of depressive symptoms in men with erectile dysfunction. *Urology*. 1998;52(5):848-852.

36. Lee IC, Surridge D, Morales A, Heaton JP. The prevalence and influence of significant psychiatric abnormalities in men undergoing comprehensive management of organic erectile dysfunction. *Int J Impot Res*. 2000;12(1):47-51.
37. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. *Psychosom Med*. 1998;60(4):458-465.
38. Bodie JA, Beeman WW, Monga M. Psychogenic erectile dysfunction. *Int J Psychiatry Med*. 2003;33(3):273-293.
39. Rosen RC. Psychogenic erectile dysfunction. Classification and management. *Urol Clin North Am*. 2001;28(2):269-278.
40. Serrano CV Jr, Setani KT, Sakamoto E, Andrei AM, Fraguas R. Association between depression and development of coronary artery disease: pathophysiologic and diagnostic implications. *Vasc Health Risk Manag*. 2011;7:159-164.
41. Farre JM, Fora F, Lasheras MG. Specific aspects of erectile dysfunction in psychiatry. *Int J Impot Res*. 2004;16(Suppl 2):S46-S49.
42. Bocchio M, Desideri G, Scarpelli P, et al. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol*. 2004;171(4):1601-1604.
43. Empen K, Lorbeer R, Dorr M, et al. Association of testosterone levels with endothelial function in men: results from a population-based study. *Arterioscler Thromb Vasc Biol*. 2012;32(2):481-486.
44. Ellsworth P, Kirshenbaum EM. Current concepts in the evaluation and management of erectile dysfunction. *Urol Nurs*. 2008;28(5):357-369.
45. Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, Wang C. Obesity, low testosterone levels and erectile dysfunction. *Int J Impot Res*. 2009;21(2):89-98.
46. Jannini EA, Granata AM, Hatzimouratidis K, Goldstein I. Use and abuse of Rigiscan in the diagnosis of erectile dysfunction. *J Sex Med*. 2009;6(7):1820-1829.
47. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004;27(7):1255-1273.
48. Fisher C, Gorss J, Zuch J. Cycle of penile erection synchronous with dreaming (REM) sleep. Preliminary report. *Arch Gen Psychiatry*. 1965;12:29-45.
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. 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-e636.
51. 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.
52. Shin HW, Park JH, Park JW, et al. Effects of surgical vs. nonsurgical therapy on erectile dysfunction and quality of life in obstructive sleep apnea syndrome: a pilot study. *J Sex Med*. 2013;10(8):2053-2059.
53. Khafagy AH, Khafagy AH. Treatment of obstructive sleep apnoea as a therapeutic modality for associated erectile dysfunction. *Int J Clin Pract*. 2012;66(12):1204-1208.
54. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest*. 2005;127(6):2076-2084.
55. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053.
56. 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.
57. Harte CB, Meston CM. Association between smoking cessation and sexual health in men. *BJU Int*. 2012;109(6):888-896.
58. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987-1003.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. 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.
68. 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.
69. 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.
70. 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.
71. 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.
72. 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.
73. Pye SR, Huhtaniemi IT, O'Neill TW, et al. Late-onset hypogonadism (LOH) and mortality in European men. Presented at: Endocrine Society, 2012; Houston, TX. Available at http://edrv.endojournals.org/cgi/content/meeting_abstract/33/03_MeetingAbstracts/OR28-2.
74. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab*. 2012;97(6):2050-2058.
75. Wu FC. Caveat emptor: does testosterone treatment reduce mortality in men? *J Clin Endocrinol Metab*. 2012;97(6):1884-1886.
76. 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.

77. Buvat J, Maggi M, Gooren L, et al. Endocrine aspects of male sexual dysfunctions. *J Sex Med*. 2010;7(4 Pt 2):1627-1656.
78. 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.
79. 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.
80. 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.
81. 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*. Milan, Italy; 2011.
82. Ma RC-W, So W-Y, Yang X, et al. Erectile dysfunction predicts coronary heart disease in type 2 diabetes. *J Am Coll Cardiol*. 2008;51(21):2045-2050.
83. 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.
84. 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.
85. Chang ST, Chu CM, Hsu JT, et al. Independent determinants of coronary artery disease in erectile dysfunction patients. *J Sex Med*. 2010;7(4 Pt 1):1478-1487.
86. Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol*. 2005;46(8):1503-1506.

Conflict of Interest: MM is a consultant to Abbott Laboratories, Chicago, IL, and conducts personal research for Forest Laboratories Inc, New York, NY, and Auxilium Pharmaceuticals Inc, Chesterbrook, PA. GJ is a speaker for Pfizer, New York, NY, Eli Lilly & Co, Indianapolis, IN, and Bayer, Leverkusen, Germany. KB is a consultant to Endo Pharmaceuticals, Chadds Ford, PA, and Abbott Laboratories. ALB is a consultant to Endo Pharmaceuticals, Abbott Laboratories, Timm Medical Technologies, Eden Prairie, MN, VIVUS Inc, Mountain View, CA, Auxilium Pharmaceuticals Inc., and Shionogi Inc., Florham Park, NJ; has received grant support from Pfizer; and has participated in clinical trials for VIVUS Inc and Auxilium Pharmaceuticals Inc.

JB is a consultant to Eli Lilly & Co and Nextmed, Tucson, AZ. CC is a consultant to and a speaker for GlaxoSmith-Kline, Eli Lilly & Co, Pfizer, and Auxilium Pharmaceuticals Inc. GC is a consultant to Abbott Laboratories, Endo Pharmaceuticals, GlaxoSmithKline, and Repros Therapeutics, The Woodlands, TX and is a speaker for Abbott Laboratories, Endo Pharmaceuticals, and Merck, Whitehouse Station, NJ. PG is a consultant to Pfizer, Gilead, Forest City, CA, and Roche, Basel, Switzerland. IG is a consultant to Coloplast, Humlebæk, Denmark, Medtronic Vascular, Fridley, MN, Slate Pharmaceuticals, Lake Forest, IL, and VIVUS Inc; a speaker for Abbott Laboratories, Auxilium Pharmaceuticals Inc, Coloplast, Eli Lilly & Co, Endo Pharmaceuticals, Medtronic Vascular, and Slate Pharmaceuticals; performs personal research for Auxilium Pharmaceuticals Inc., BioSante Pharmaceuticals, Lincolnshire, IL, Medtronic Vascular, Slate Pharmaceuticals, and Target Health, New York, NY; and is an expert witness for Pfizer and Bayer. AG is a consultant to Auxilium Pharmaceuticals Inc, Abbott Laboratories, Endo Pharmaceuticals, and Repros Therapeutics. GH is a speaker and conducts personal research for Bayer and Eli Lilly & Co. RAK is a speaker for Pfizer. JBK is a consultant to Merck and Palatin Technologies Inc, Cranbury, NJ; a speaker for Forest Laboratories, Merck, and Sanofi, Bridgewater, NJ; and has received research support from Medtronic and Novartis, Basel, Switzerland. RR is a consultant to Eli Lilly & Co., Boehringer Ingelheim, Palatin Technologies Inc, and Auxilium Pharmaceuticals Inc. RSa is a consultant to Pfizer, Boehringer Ingelheim, and Eli Lilly & Co. AS is a consultant to Auxilium Pharmaceuticals Inc, Endo Pharmaceuticals, Actient RSh is a consultant to Auxilium Pharmaceuticals Inc, Endo Pharmaceuticals, Bayer, and Mezzion Pharma Co., Ltd, Seoul, Korea. CV is a consultant to Eli Lilly & Co. and has received research support from Pfizer. FW is a consultant to Eli Lilly & Co, is a speaker for Galapagos NV, Mechelen, Belgium, and conducts personal research for Bayer. AN, SB, and PM have no conflicts of interest. KEL and MR are employees of Complete Healthcare Communications, Inc. who were paid consultants to Pfizer in connection with the development of this manuscript.