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REVIEW

Erectile dysfunction as a harbinger for increased cardiometabolic risk

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In August 2003, the Minority Health Institute (MHI) convened an Expert Advisory Panel of cardiologists and urologists to design a new practice model algorithm that uses erectile dysfunction (ED) as a clinical tool for early identification of men with systemic vascular disease. The MHI algorithm noted ED as a marker for the presence of cardiovascular disease and suggested that ED may well be a cardiovascular risk equivalent warranting aggressive secondary prevention management strategies, even in the absence of other cardiac or peripheral vascular symptoms. The MHI algorithm stipulates that all men 25 years of age and older should be asked about ED as a routine part of the cardiovascular history during any office visit. The presence of ED should prompt an aggressive assessment for occult vascular disease; many men with erectile difficulty would benefit from early, aggressive management of cardiovascular risk factors with both lifestyle modification and pharmacotherapy to achieve optimal target goals under the existing treatment guidelines. Since publication of the algorithm in 2005, additional research studies have further supported the advisory panel recommendations.
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Introduction

Erectile dysfunction (ED) is a prevalent vascular disorder that like cardiovascular disease (CVD) is now believed to be caused by endothelial dysfunction.[1,2] In fact, a burgeoning literature is now available that suggests that ED may be an early marker for atherosclerosis, increased cardiovascular risk and subclinical systemic vascular disease.[3–5] The emerging awareness of ED as a barometer for vascular health and occult CVD represents a unique opportunity to improve preventive cardiovascular health in all men, and particularly in high-risk and underserved minority populations. African Americans, Hispanics, Native Americans and other ethnic minorities are particularly at risk for CVD and related comorbidities, such as hypertension, dyslipidemia and diabetes mellitus.[6–8]

Recognizing the need to provide informed guidance, the Minority Health Institute (MHI), a nonprofit organization that seeks to address the poor health status and inferior health care delivery among African Americans and other minority groups in the United States, convened an Expert Advisory Panel in August 2003, at the National Medical Association Annual Meeting in Philadelphia, Pennsylvania. The MHI Expert Advisory Panel, composed of cardiologists and urologists, developed a new practice model algorithm that uses ED as a clinical tool for early identification of men with systemic vascular disease. Comments from participants in a primary care symposium were considered in the development of the final algorithm.[9]

The goal of the MHI Expert Advisory Panel was to develop a management algorithm that would serve as a starting point for further discussion and clinical research studies investigating the role of ED as a marker for subclinical CVD. Based on a review of the

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available literature in 2003, the advisory panel made some bold clinical recommendations regarding risk assessment and management of men with ED. A summary of the key recommendations is listed below.[9]

1. All men 25 years of age and older should be questioned about ED as a routine part of the cardiovascular history and the clinical review of systems, regardless of their reason for seeking medical evaluation or level of sexual function.
2. Patients who are discovered to have ED must be thoroughly and aggressively assessed for cardiovascular risk and occult systemic vascular disease. Many men are good candidates to consider for diagnostic testing of the coronary, carotid, abdominal/pelvic and lower extremity arteries.
3. Most men with ED should be treated as if they already have vascular disease. While all men should be started on lifestyle modification (improved diet, exercise, smoking cessation), many men are also good candidates for aggressive management with pharmacotherapy to achieve optimal goals under the current published treatment guidelines.

The clinical algorithm developed by the MHI Expert Advisory Panel represents one of the first attempts to objectively manage ED both as an early marker of CVD and a possible cardiovascular risk equivalent. Since the original publication of the MHI algorithm in 2005,[9] new research studies and consensus panels have provided further support for the emerging role of ED as a marker for atherosclerosis. This special communication represents an extensive revision of the original article and is designed to reaffirm the value and applicability of the MHI algorithm in the context of newly published research studies.

The Second Princeton Consensus Conference on sexual dysfunction and cardiac risk was held in Princeton, NJ, USA in June 2004. The Princeton conference paper, 'Sexual Dysfunction and Cardiac Risk,' recommended that an assessment for sexual function should be incorporated into the initial cardiovascular evaluation for all men, and that all men with ED should undergo a thorough assessment of cardiovascular risk factors for classification into categories of low, indeterminate and high risk with respect to exertion from sexual activity. The panel also felt that lifestyle intervention (weight loss and increased physical activity) should be emphasized in all men with ED and CVD.[10]

Another recent study investigated the association between ED and subsequent CVD.[11] These investigators studied 4247 men aged 55 years and older in the placebo group of the Prostate Cancer Prevention Trial. None of the men had ED or CVD at the start of the study. After 7 years, 65% of the men reported the development of ED (incident ED). Multivariate assessment showed that men with incident ED are at increased risk for developing cardiac events, and ED is as strong a risk factor as current cigarette smoking, family history of coronary artery disease or dyslipidemia.[11]

The MHI algorithm

The rationale for the MHI cardiovascular risk assessment and management algorithm (Figure 1) is based on the fundamental assumption that ED is an early clinical manifestation of systemic vascular disease. Any man aged 25 years and older who has persistent difficulty (lasting 3 months or more) in achieving or maintaining an erection should undergo a thorough cardiovascular risk assessment as part of the medical management for ED. The MHI Expert Advisory Panel believes that age 25 is a reasonable starting point, because the National Cholesterol Education Program Adult Treatment Panel III report recommends that a full-fasting lipid panel be obtained in men aged 20 and older,[12] and dyslipidemia is a well-documented risk factor for ED.[13]

Workup for cardiovascular risk

All men with ED should be considered at increased risk for CVD until proven otherwise (Figure 1). The workup for cardiovascular risk factors in men with ED should include pertinent history (cardiac disease and other cardiovascular risk factors, lifestyle, tobacco and alcohol use, depression, current medications), appropriate laboratory measurements (blood pressure, fasting blood sugar, fasting lipoproteins, body mass index) and assessment for metabolic syndrome and/or insulin resistance. Assessment of cholesterol should include a routine fasting lipid profile (ongoing studies are investigating the potential role for the more advanced lipid particle size assays). Assessment for insulin resistance in overweight individuals can easily be performed using fasting insulin levels, fasting triglyceride levels or the triglyceride/high-density lipoprotein (HDL) cholesterol ratio.

Given the emerging data revealing ED as an early manifestation of systemic vascular disease, aggressive medical management of cardiovascular risk factors is a reasonable clinical approach to ED in the primary care setting. Although the evidence base for the link between ED and CVD is still developing, it is reasonable to assume that most men with ED may have early clinical vascular disease and should be considered for management as secondary prevention patients according to the most stringent standards of existing guidelines. Such an approach to ED is similar to past associations between hyperlipidemia and coronary heart disease (CHD), where aggressive treatment protocols were developed long before the evidence was accumulated through clinical trials.

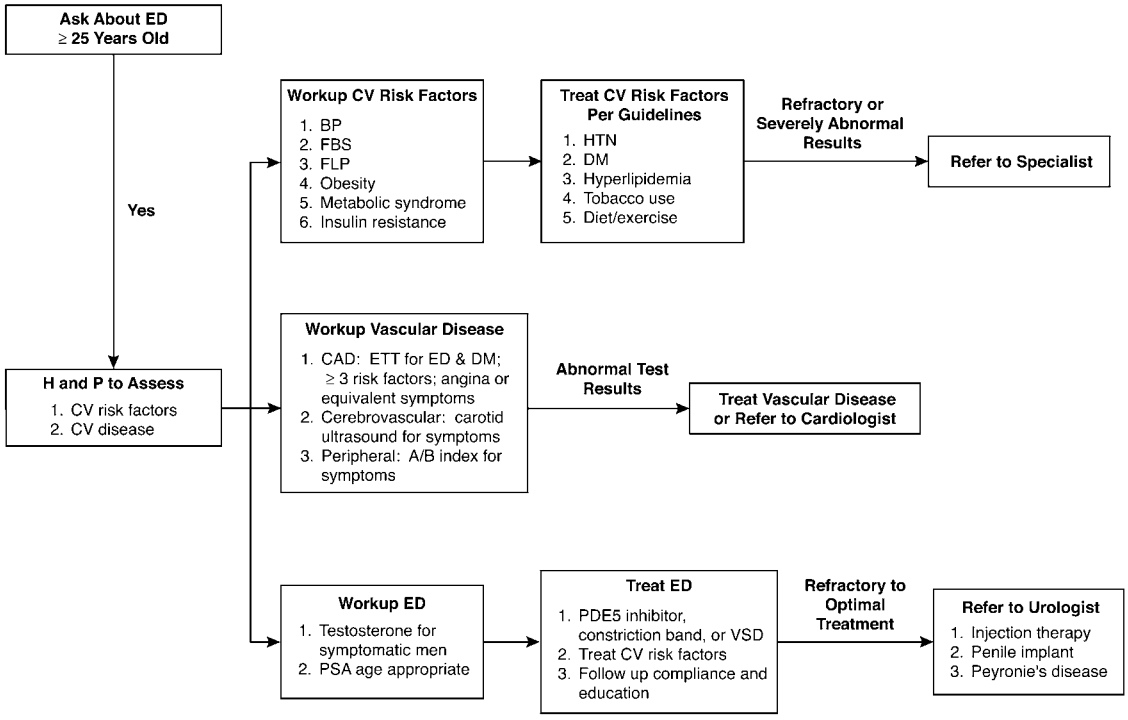

Figure 1 Minority Health Institute (MHI) Expert Advisory Panel's cardiovascular risk assessment and management algorithm for men with ED (reproduced with permission from KL Billups).

Aggressive management of cardiovascular risk factors, as an adjunct to standard medical therapy for ED (that is, PDE5 inhibitors), is an important part of overall management of ED in primary care patients. For example, patients who smoke should be educated about smoking cessation and offered assistance in the form of medication and counseling.[14] Hypertension should be treated according to the guidelines of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Optimal blood pressure is $<120/80$ mm Hg, and a blood pressure of 120–139/80–89 mm Hg is considered to be prehypertensive. Patients with blood pressure $\geqslant 140/90$ mm Hg should be managed with lifestyle modification and antihypertensive agents.[15]

Current guidelines for management of elevated lipids are based on the underlying degree of cardiovascular risk. An optimal lipid panel would include the following values: low-density lipoprotein (LDL) levels <70 mg per 100 ml (in individuals classified as very high risk), HDL levels $\geqslant 40$ mg per 100 ml, triglycerides <150 mg per 100 ml and total cholesterol <200 mg per 100 ml.[12] Given the evidence that many men with ED have clinical vascular disease, it seems reasonable for physicians to consider managing men with ED to optimal fasting lipid levels. Data from the Heart Protection Study[16] and the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm study[17] have shown the clear benefits of aggressive lipid lowering in men considered at increased risk for developing CVD. These benefits were seen despite the fact that their lipid levels were unremarkable.

In addition, aggressive lowering of LDL levels using statins has been shown to improve erectile function in three recent clinical research studies.[18–20] Bank *et al.*[20] recently showed in a placebo-controlled study that both quinapril and atorvastatin significantly improved erectile function in men with moderate to severe ED taking 100 mg of sildenafil. Together these three studies provide further evidence supporting the contention that ED and CVD are causally linked and that pharmacologic treatment of the shared risk factors can improve both conditions simultaneously.

An increasing number of persons in the United States have an especially lethal combination of major risk factors and body composition that together constitute a virulent pattern of cardiovascular risk known as metabolic syndrome. It has been estimated that 47 million persons in the United States have metabolic syndrome,[21] with a prevalence rate of more than 20%.[22,23] Hispanic Americans and African Americans are at particular risk of metabolic syndrome.[22,24] Persons with metabolic syndrome can be identified by a distinct pattern of abdominal obesity (waist circumference >40 inches in men), atherogenic dyslipidemia (triglycerides $\geqslant 150$ mg per 100 ml, HDL <40 mg per 100 ml, small LDL particles and normal or slightly elevated LDL), hypertension ($\geqslant 130/85$ mm Hg), insulin resistance

(fasting blood glucose $\geqslant$100 mg per 100 ml), and elevated levels of prothrombotic and proinflammatory markers.[25] Metabolic syndrome and insulin resistance are closely linked to ED. In one recently conducted study of 120 men with ED and no evidence of diabetes, 40% of patients fulfilled strict criteria for metabolic syndrome, and 73% were insulin resistant.[26]

Workup for vascular disease

In addition to a workup for cardiovascular risk, all men who present with ED should be assessed for the presence and severity of vascular disease (Figure 1). High-risk patients with ED and clinical coronary artery disease should undergo exercise treadmill testing. In this context, high-risk patients are those with ED plus diabetes, three or more cardiovascular risk factors, angina or a CHD risk equivalent. Peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes and multiple risk factors with a 10-year CHD risk greater than 20% constitute CHD risk equivalents.[12] Patients with ED and evidence of cerebrovascular disease should be assessed with carotid ultrasound. Symptoms of circulatory insufficiency that suggest peripheral vascular disease in men with ED should be evaluated using the ankle/brachial (A/B) index. Patients with an A/B index $<$0.90 should be managed with risk modification (smoking cessation, optimized treatment for hyperlipidemia, hypertension, diabetes), exercise and medications or surgery when needed.[27,28] It seems reasonable that at least men with ED who fall into the Princeton Conference indeterminate category (ED with three or more traditional cardiovascular risk factors)[10] are good candidates for evaluation with carotid ultrasound and/or A/B index testing. Future research studies may show that these additional tests are useful even in men who fall into the Princeton low-risk category.

Recent clinical studies have investigated the prevalence of carotid and/or lower extremity arterial disease in men with vascular ED documented by penile ultrasound studies. One study found that penile artery insufficiency is associated with carotid and/or lower limb artery ultrasound abnormalities (atheroma or marked intima-media thickness) approximately 75% of the time.[29] Another study found that the severity of ED based on penile Doppler ultrasound correlates with associated ultrasound abnormalities in the carotid artery, lower limb arteries or both vascular beds. Men with ED and both carotid and lower limb abnormalities had the most severe penile artery disease based on ultrasound assessments of all three vascular beds.[30] Both of these studies support the concept that many men with vascular ED should be regarded as having generalized vascular atherosclerosis. Additional evaluation of the carotid and lower limb peripheral vascular beds may help to identify men who, after presenting with ED as their initial clinical symptom, would benefit from additional diagnostic testing and/or aggressive pharmacologic intervention for risk factor management.

Workup for erectile dysfunction

All patients who present with ED should be worked up for cardiovascular risk as outlined above (Figure 1). In addition to a medical history, sexual history and physical examination, the proper assessment of ED requires selective laboratory tests, including fasting serum glucose or hemoglobin A1c, fasting lipid profiles and serum testosterone assays (total, free or bioavailable).[31–33] While a full review of testosterone therapy is beyond the scope of this article, in general, men with ED and symptoms of hypogonadism (diminished libido and erections, poor responders to PDE-5 inhibitor therapy, less energy, depressed mood, diminished muscle mass and strength) should be assessed with a morning total and free serum testosterone. Low testosterone levels (total testosterone less than 300 ng per 100 ml) in symptomatic men can identify potential candidates for testosterone replacement therapy.

Erectile dysfunction as an ideal barometer of atherosclerosis and increased cardiovascular risk

Endothelial dysfunction, which is associated with impaired vasodilatation, precedes the development of atherosclerotic lesions[34] and can be caused by vascular insults such as diabetes, cigarette smoking, hyperlipidemia and hypertension.[35] At the cellular level, endothelial dysfunction results in impaired bioavailability of nitric oxide (NO). Oxidative stress (that is, free radical damage), which interferes with the NO pathway and also is directly toxic to the endothelium, is a causal factor in clinically evident occlusive CVD and the vascular damage associated with preclinical disease. Free radical damage and impaired bioavailability of NO also result in increased adhesion and aggregation of platelets and neutrophils and the release of vasoconstrictor substances.[1,3]

The penis is a richly vascularized organ, and penile erections are, in large part, a vascular event. The penile anatomy consists of the two corpus cavernosa and the ventral corpus spongiosum that surrounds the urethra. The corpus cavernosa are supplied by the dorsal and cavernous arteries, with venous return occurring via the subtunical venular plexus, the deep dorsal vein and others (Figure 2). Penile erection is the result of a complex and coordinated series of events involving vascular response, neuronal pathways and psychosomatic stimulation. The NO pathway is activated upon

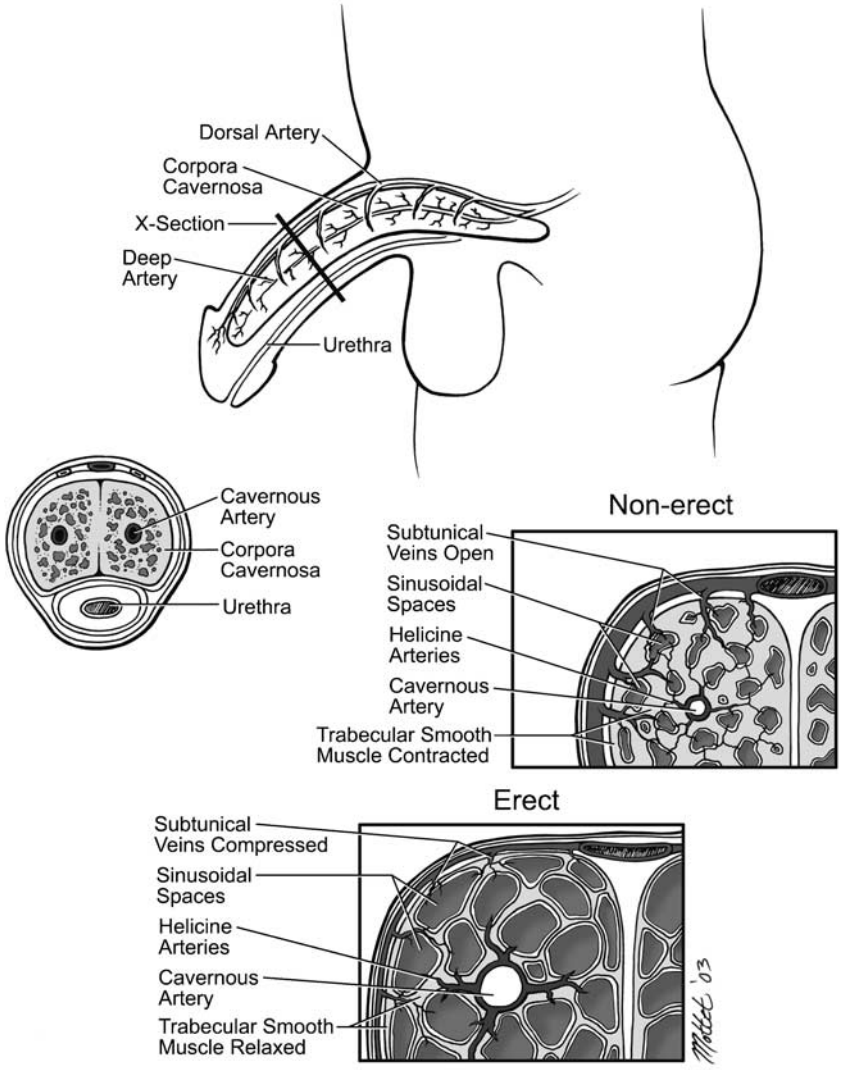

Figure 2 Anatomy of penile erection and detumescence (reproduced with permission from KL Billups).

sexual stimulation, and NO is released from both the vascular endothelium of the penis and the autonomic, cavernous nerve terminals. Within the penile smooth muscle, NO activates guanylyl cyclase, which increases the concentration of the second messenger, cyclic guanosine monophosphate (cGMP). The elevated concentrations of cGMP result in relaxation of arterial smooth muscle in the penis and a marked rise in penile blood flow. In addition, cGMP relaxes trabecular smooth muscle, which facilitates engorgement of the sinusoidal spaces and compression of the subtunical venules. The net result is complete occlusion of penile venous outflow and trapping of blood within the corpus cavernosa. Detumescence, or flaccidity, occurs following release of norepinephrine and contraction of the intracorporeal smooth muscle.[36,37]

The penis, as a vascular organ, is sensitive to changes in oxidative stress and systemic NO. The small diameter of the cavernosal arteries and the relatively high content of endothelium and smooth muscle on a per-unit volume tissue basis compared to other organs[38] suggests that the penile vascular bed may be a sensitive indicator of systemic vascular disease. ED may result from occlusion of the cavernosal arteries by atherosclerosis (that is, structural vascular ED), impairment of endothelial-dependent and/or -independent smooth muscle relaxation (that is, functional vascular ED) or a combination of these factors. Supporting this contention, Kaiser *et al*.[4] showed that brachial artery endothelial and smooth muscle dysfunction was present in relatively young men with ED and no known CVD.

Erectile dysfunction is clearly, in part, an occlusive atherosclerotic disease. Because the smaller arteries of the penis are more susceptible to atherosclerotic occlusion than the larger vessels of the

heart and limbs,[35,39,40] atherosclerotic lesions may first become clinically manifest in the penile arteries.[41] Many research studies have hypothesized that occlusion of the smaller penile arteries (1–2 mm in diameter) occurs well before occlusion of the coronary (3–4 mm) or peripheral (5–7 mm carotid or 6–8 mm femoral) arteries. This artery size/lumen occlusion hypothesis is one reason used to explain why the symptom of erectile difficulty occurs before other clinical vascular symptoms.[42]

Erectile dysfunction is also caused by functional vascular factors, such as increased oxidative stress and decreased availability of NO, that occur very early in the course of atherosclerosis. The early symptom of erectile difficulty (that is, inability to maintain rigidity) caused by endothelial cell and smooth muscle dysfunction probably occurs before the development of structural, occlusive penile arterial disease and may therefore be one of the first signs of systemic vascular disease.

The concept that ED begins as a functional, nonobstructive process early in the course of cardiovascular risk factor development and atherosclerosis is relatively new. Given that it is the lipid-rich minor lesions (less than 50% stenosis) in the coronary or peripheral arteries that are most likely to rupture with adverse clinical consequences,[43] detecting ED early in the cascade of atherosclerosis gives the best opportunity to modify risk factors and prevent occurrence of vascular events. Over time, the same systemic risk factors that contribute to functional ED likely lead to the development of chronic occlusive CVD.[3]

The idea that ED is often the first clinical symptom of generalized atherosclerosis may have special significance for cardiovascular health care in minority men. Recent studies have shown greater impairment of endothelial function in African Americans when compared with various control populations.[44,45] Androne *et al.*[46] recently investigated individuals with congestive heart failure and found that endothelium-dependent flow-mediated vasodilation was significantly decreased in African Americans compared with non-African American patients even after adjustment for hypertension. Using ED as an early marker for endothelial and smooth muscle dysfunction in minority populations warrants further clinical investigation.

Conclusions

The recognition of ED as a harbinger of systemic CVD represents a remarkable opportunity for prevention. The MHI clinical algorithm is based on the belief that ED-driven intervention on cardiovascular events could dramatically improve male preventive health care, particularly among high-risk and underserved populations such as African American and Hispanic men. Future large-scale, longitudinal studies that prospectively monitor cardiovascular risk and emergent disease in young men with ED will ultimately validate the aggressive diagnostic and treatment recommendations of the MHI advisory panel. It is time to change the perception of ED from a quality-of-life issue to a serious public health concern associated with cardiovascular health.

Abbreviations

A/B index, ankle/brachial index; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ED, erectile dysfunction; ETT, exercise treadmill testing; FBS, fasting blood sugar; FLP, fasting lipoproteins; H and P, history and physical; HTN, hypertension; PDE5 inhibitor, phosphodiesterase-5 inhibitor; PSA, prostate-specific antigen; VSD, vacuum suction devices.

Conflict of Interest

Dr Billups—research/grant support/speakers' bureau (Pfizer Inc.); consultation (Pfizer Inc., Bayer, Eli Lilly); stock holdings (none).

Dr Bank—consultancy, honoraria, research grants (Pfizer Inc.).

Dr Padma-Nathan—research support/consultation (Pfizer Inc., Bayer/GSK, Lilly ICOS, Novartis, Lilly, Schering Plough, Dong A, Vivus, Sepracor, TAP Pharmaceuticals, Abbott Labs, Palatin Technologies, Nastech); lecturer (Pfizer Inc., Bayer/GSK); stock (none, inclusive of family members).

Dr Katz—honoraria, research support (Pfizer Inc.).

Dr Williams—honoraria, consultation, research support (Nitromed, Pfizer Inc., AstraZeneca).

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