The Journal of Sexual Medicine, 2023, **00**, 1–27
https://doi.org/10.1093/jsxmed/qdad163
Special Report

Princeton IV consensus guidelines: PDE5 inhibitors and cardiac health

Robert A. Kloner, MD, PhD[1,2,*], Arthur L. Burnett, MD, MBA[3], Martin Miner, MD[4], Michael J. Blaha, MD[5], Peter Ganz, MD[6], Irwin Goldstein, MD[7], Noel N. Kim, PhD[7], Tobias Kohler, MD[8], Tom Lue, MD, ScD[6], Kevin T. McVary, MD[9], John P. Mulhall, MD, MSc[10], Sharon J. Parish, MD[11,12], Hossein Sadeghi-Nejad, MD[13], Richard Sadovsky, MD[14], Ira D. Sharlip, MD[6], Raymond C. Rosen, PhD[6]

[1]Department of Cardiovascular Research Pasadena, Huntington Medical Research Institutes, CA 91105, United States
[2]Department of Medicine, Keck School of Medicine at University of Southern California, Los Angeles, CA, United States
[3]Department of Urology, Johns Hopkins University, Baltimore, MD, United States
[4]Men's Health Center, Miriam Hospital, Providence, RI, United States
[5]Cardiology and Epidemiology, Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Baltimore, MD, United States
[6]Department of Medicine (PG); Department of Urology (TL, IDS); Department of Psychiatry and Behavioral Sciences, (RCR), University of California, San Francisco, San Francisco, CA, United States
[7]Department of Sexual Medicine, Institute for Sexual Medicine, Alvarado Hospital, San Diego, CA, United States
[8]Mayo Clinic, Rochester, MN, United States
[9]Center for Male Health, Stritch School of Medicine at Loyola University Medical Center, Maywood, IL, United States
[10]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[11]Weill Cornell Medicine, New York, NY, United States
[12]Department of Medicine and Psychiatry White Plains, Westchester Behavioral Health Center, NewYork-Presbyterian Hospital, NY, United States
[13]Department of Urology NY, NYU Langone Grossman School of Medicine, NY, United States
[14]Department of Family and Community Medicine, SUNY Downstate Health Sciences University, Brooklyn, NY, United States

*Corresponding author: Huntington Medical Research Institutes, 686 South Fair Oaks Avenue, Pasadena, CA 91105, United States.
Email: robert.kloner@hmri.org

Abstract

Background: In 1999, 1 year after the approval of the first oral phosphodiesterase type 5 (PDE5) inhibitor for the treatment of erectile dysfunction (ED), the first Princeton Consensus Conference was held to address the clinical management of men with ED who also had cardiovascular disease. These issues were readdressed in the second and third conferences. In the 13 years since the last Princeton Consensus Conference, the experience with PDE5 inhibitors is more robust, and recent new data have emerged regarding not only safety and drug–drug interactions, but also a potential cardioprotective effect of these drugs.
Aim: In March 2023, an interdisciplinary group of scientists and practitioners met for the fourth Princeton Consensus Guidelines at the Huntington Medical Research Institutes in Pasadena, California, to readdress the cardiovascular workup of men presenting with ED as well as the approach to treatment of ED in men with known cardiovascular disease.
Method: A series of lectures from experts in the field followed by Delphi-type discussions were developed to reach consensus.
Outcomes: Consensus was reached regarding a number of issues related to erectile dysfunction and the interaction with cardiovascular health and phosphodiesterase-5 inhibitors.
Results: An algorithm based on recent recommendations of the American College of Cardiology and American Heart Association, including the use of computed tomography coronary artery calcium scoring, was integrated into the evaluation of men presenting with ED. Additionally, the issue of nitrate use was further considered in an algorithm regarding the treatment of ED patients with coronary artery disease. Other topics included the psychological effect of ED and the benefits of treating it; the mechanism of action of the PDE5 inhibitors; drug–drug interactions; optimizing use of a PDE5 inhibitors; rare adverse events; potential cardiovascular benefits observed in recent retrospective studies; adulteration of dietary supplements with PDE5 inhibitors; the pros and cons of over-the-counter PDE5 inhibitors; non–PDE5 inhibitor therapy for ED including restorative therapies such as stem cells, platelet-rich plasma, and shock therapy; other non–PDE5 inhibitor therapies, including injection therapy and penile prostheses; the issue of safety and effectiveness of PDE5 inhibitors in women; and recommendations for future studies in the field of sexual dysfunction and PDE5 inhibitor use were discussed.
Clinical Implications: Algorithms and tables were developed to help guide the clinician in dealing with the interaction of ED and cardiovascular risk and disease.
Strengths and Limitations: Strengths include the expertise of the participants and consensus recommendations. Limitations included that participants were from the United States only for this particular meeting.
Conclusion: The issue of the intersection between cardiovascular health and sexual health remains an important topic with new studies suggesting the cardiovascular safety of PDE5 inhibitors.

Keywords: erectile dysfunction; phosphodiesterase type 5 inhibitors; cardiovascular risk factors; sexual dysfunction; major adverse cardiovascular events.

Received: September 6, 2023. **Revised:** October 22, 2023. **Accepted:** October 24, 2023

Introduction

Twenty-five years have passed since the first oral phosphodiesterase type 5 (PDE5) inhibitor was approved in the United States for the treatment of erectile dysfunction (ED), a milestone event in drug development and sexual medicine practice.[1] Shortly after its approval, it became clear that new guidelines were needed for the clinical management of sexual dysfunction in patients with overt or latent cardiovascular disease (CVD). To address this need, an interdisciplinary panel of experts was convened in Princeton, New Jersey, in June 1999 to consider the available data at that time, and to develop recommendations for clinical management of sexual dysfunction in patients with CVD. The findings and consensus recommendations from this meeting were published in the *American Journal of Cardiology* in 2000.[2] Two subsequent Princeton meetings were convened in 2004 and 2010, with important additions and modifications to the guidelines.[3,4] The third Princeton Consensus Conference (P3) Recommendations focused on 2 central concepts: (1) men who present with ED may have the same cardiovascular (CV) risk factors that are associated with atherosclerotic CVD (ASCVD) and therefore, an evaluation and management strategy for the potential CV risk in men with ED was needed; and (2) the need to re-evaluate and modify the cardiac risk associated with sexual activity itself, whether spontaneous or assisted by the use of PDE5 inhibitors. This included assessing the patient's exercise capacity and stress testing, if indicated, to assure that men could achieve the physical demands of sexual activity prior to prescribing treatment for ED. The P3 also addressed the issue of testosterone replacement therapy and the surrounding controversies.

In the intervening decade since the most recent Princeton guidance,[4] new questions have arisen regarding optimal treatment of sexual dysfunction in men with underlying or comorbid CVD. Most importantly, there is now a far more robust, long-term database of clinical experience in the use of PDE5 inhibitors by men with ED,[5] with comprehensive safety analyses, including in-depth investigation of patients taking a variety of antihypertensive drugs or α-blockers for benign prostatic hyperplasia (BPH), and also in men prescribed both PDE5 inhibitors and nitrates (despite the contraindication).[6,7] There have been significant advances also in both basic and applied science of PDE5 inhibition and nitric oxide regulation, in addition to mounting experience with PDE5 inhibitors used for other indications, such as pulmonary artery hypertension in both men and women, in which PDE5 inhibitors are now first-line therapy. Significant advances have also taken place in new treatment approaches for ED, including therapies derived from regenerative medicine and shockwave therapy. New guidelines have also been published for optimal evaluation of patients with multiple risk factors for ASCVD.[8] There are also emerging data on the use of PDE5 inhibitors in women, in addition to centrally acting compounds for treating components of female sexual dysfunction (FSD). Recently, there has been an emerging literature suggesting that PDE5 inhibitors may have cardioprotective effects and may play a role in preventative cardiology.

Princeton 4 (P4) was convened on March 10 to 11, 2023, at The Huntington Medical Research Institutes, a nonprofit biomedical research facility in Pasadena, California. The program content and presenters were determined by the organizing committee (R.A.K., R.C.R., A.L.B., M.M.), which included senior investigators in cardiology (R.A.K.), urology (A.L.B.), sexual medicine (R.C.R.), and men's health (M.M.). A multispecialty group of U.S. experts was selected by the organizing committee to critically evaluate our current evidence base regarding the relationship between ED and CV health, to update the CV workup in the ED patient, reassess when and how to treat ED patients with known CVD, and reassess the accuracy and relevance or previous Princeton management algorithms. The panel also assessed the overall safety and role of PDE5 inhibitors in relationship to CV health, examining new studies indicating a potential cardioprotective role of PDE5 inhibitors and preventative cardiology, and re-examining the role of PDE5 inhibitors in women. In addition, newer non–PDE5 inhibitor therapies for the treatment of ED and FSD were considered. A noteworthy omission was the topic of testosterone replacement therapy and the surrounding controversy. Because there was an ongoing randomized, prospective, controlled study of testosterone replacement therapy with CV outcomes as major endpoints, the results of which were forthcoming at the time of the meeting, the organizing committee thought it best to wait for those results to become available before developing further clinical guidelines for testosterone use in men with ED or other conditions. Since the meeting, the results of this study have been published and are briefly discussed in the section on clinical management of ED. The meeting was funded by an unrestricted educational grant from Sanofi, whose staff were not involved in the selection of speakers, topics, or any aspect of the content of the meeting. Prior to the meeting, each panelist was responsible for providing a written summary of published literature on their assigned topic, focusing on studies published since the prior Princeton meeting.[4] These summaries were then circulated in advance of the meeting and panelists presented major findings on each topic, along with panel discussion, during the open portion of the meeting on March 10. For the closed session on day 2, a modified Delphi approach was used to develop consensus on the major recommendations and management algorithms, following the same process as in the previous consensus meetings.[2-4]

We are deeply honored to dedicate the P4 to the memory of Professor Graham Jackson, MD, FESC, FRCP, FACC (1947-2016), who was a pioneer in the field of the intersection of sexual health and CV health.[9] His decades-long contributions to cardiology, sexual medicine, and men's health have served as a guiding inspiration to his many patients, colleagues, friends, and family. We honor Dr Jackson with heartfelt appreciation and are saddened by his loss.

Epidemiology and pathophysiology revisited

Sexual activity and cardiac risk: can he climb 2 flights of stairs?

A major issue of concern for the 1999 Princeton Consensus Conference[2] was the cardiac load or stress on the heart that is likely to occur with sexual intercourse or other sexual activity.[2] This is especially relevant for men with preexisting CV conditions, including angina pectoris, congestive heart failure, arrhythmias, and others. Epidemiologic data available at the time indicated a slight, albeit statistically significant association between sexual activity and incident cardiac events.[10] However, the absolute risk differences were estimated to be minimal: "In the United States, a 50-year-old

man has a baseline annual risk of myocardial infarction (MI) of about 1%, which increases to only 1.01% as a consequence of sexual activity." The annual risk associated with sexual activity increases to only 1.10%, even in high-risk men with known CVD or risk factors.[2] In a subsequent meta-analysis of 10 confirmatory studies, the absolute risk increase associated with 1 hour of additional physical or sexual activity per week was estimated as 2 to 3 per 10 000 person-years for MI and 1 per 10 000 person-years for sudden cardiac death. Regular exercise was found in this meta-analysis to further attenuate this marginally increased risk.[11]

Based on available evidence, P1 panelists concluded that sexual intercourse or activity of approximately 30 minutes duration with a usual partner in a long-standing relationship corresponds to a workload of approximately 2 to 3 metabolic equivalents of task (METS) and would not normally pose a greater risk than climbing 2 flights of stairs without cardiac symptoms.[2] For patients who fail to meet this simple benchmark, further cardiac assessment is indicated, including a simple exercise stress test to confirm the patient's self-report of exercise intolerance. Conclusions reached by P1 concerning cardiac risk of sexual activity were incorporated into the P2 and P3 guidelines[2-4] and are retained in the current version. It should be noted that in more recent analyses, some estimates report higher expenditures of METS for moderately intense sexual activity in young couples of 5 to 6 METS, which corresponds to about 4 minutes on a standard Bruce Protocol Treadmill Test.[12] In younger individuals with CV risk factors, 5 to 6 METS on a treadmill without evidence of ischemia suggests that, in general, sexual activity is safe.

Erectile dysfunction and CVD: is ED a harbinger of future events?

Epidemiologic studies have examined the association between ED and CV risk factors generally and its predictive relationship to MI, stroke, cardiac death, and other major CV outcomes (see Table 1).[13-21] For example, it has been found that ED symptoms precede clinically evident CVD by as long as 2 to 5 years, making the diagnosis of ED especially useful as a marker of probable subclinical CVD.[14,15] In men with ED, but without overt cardiac symptoms, cardiac events occurred in 4.2% of men within 2 years of incident ED and 12.3% of men at 5 years.[15] In another study, incident ED was associated with an adjusted hazard ratio of 1.25 (95% CI=1.02-1.53; p=0.04) for subsequent cardiovascular events over 5 years.[20] Further supportive evidence in favor of ED as a harbinger of future CV events comes from the National Institutes of Health–funded prospective MESA (Multi-Ethnic Study of Atherosclerosis) study.[21] A total 1757 participants contributed data on sexual function and ED for this well-designed, multicenter study, in which the presence of ED almost doubled the man's odds for developing subsequent major adverse CV events (MACE) (hazard ratio [HR],1.9; 95% confidence interval [CI], 1.1-3.4).[21] There has been controversy about whether ED is more predictive of coronary artery disease (CAD) in younger or older men,[14,15,17] a topic that is addressed in detail in the section on clinical management of ED.

Taken together, a diverse group of independent, multinational studies have shown consistent evidence that ED predicts subsequent CV events and cardiac deaths, regardless of the confounding effects of age, body mass index, prior CVD, and other relevant risk factors. The rate of adverse cardiac events was almost twice as high in some studies when men with ED were compared with others in their age cohort without ED.[13,16,17] Other studies have shown a dose-response effect as men with more severe ED at baseline have proportionately higher rates of subsequent CVD events.[13,19,21] All major studies to date have been strongly confirmatory, regardless of the study population or outcome measures reported. The consistency and robustness of this finding across study populations is compelling and demonstrates beyond doubt the role of ED as an important harbinger for future CV events.

Conversely, men with cardiometabolic risk factors, including obesity, diabetes, hypogonadism, and hypertension, are at increased risk for incident ED, compared with healthy men of similar age and risk profile.[16,22-24] The co-occurrence of ED with hypertension, hyperlipidemia, and diabetes provides further support for vasculogenic ED, considered a downstream symptom or pathophysiological sign of impaired endothelial function.[22-24] In short, converging lines of evidence from both basic science and clinical studies have corroborated the role of vascular mechanisms in ED, which in turn has been established as a reliable predictor of future CV risk.

Inflammatory disorders, including lower urinary tract symptoms (LUTS),[25] respiratory illness,[26] HIV-AIDS,[27] and most recently, long-term COVID,[28] have all been implicated as risk factors or comorbidities for ED in large, community-based studies. Moreover, the long-acting PDE5 inhibitor, tadalafil, has been approved by the Food and Drug Administration (FDA) since 2011 for the treatment of LUTS, with efficacy comparable to α-blockers and a high level of patient acceptance and tolerability.[25] The role of endocrine factors and hypogonadism in ED was not addressed by the conference.

Psychogenic factors: how distressed is the man or his partner?

A clinically meaningful association between ED and psychological distress was first documented in the MMAS (Massachusetts Male Aging Study) study in the mid-1990s.[29] In this landmark study, men with ED were found to be more than twice as likely to report depressed mood compared with controls, regardless of age and other confounding factors. These findings have been replicated in both longitudinal and cross-sectional study designs, in treated and untreated patient populations, and across different geographic settings (see Table 2).[29-37] The consistency and bidirectionality of these results has been confirmed in 2 separate meta-analyses.[38,39]

There is compelling evidence that the direction of causality is bidirectional (ie, psychological distress has been implicated as both a cause and consequence of ED).[38] Longitudinal studies have shown that presence of depression or anxiety increases the incidence of ED over time[32]; conversely, successful treatment of ED has been associated in multiple studies with significant improvements in mood in patients with concomitant ED and depression.[40-42] Improvements in mood and overall quality of life have also been reported in multiple studies of ED treatment.

Of note also, there is mounting evidence also that psychogenic ED may be a harbinger of increased CVD risk, not dissimilar to the risk level for vasculogenic ED. A systematic review in 2017 reported that psychogenic ED was associated with an increased risk of CVD after adjusting

Table 1. ED as a harbinger for CVD: supportive epidemiologic findings.

Study	Study population	Study design/data collection	Main findings
Thompson 2005[20]	Placebo treated men >55 years of age (n= 9500) in U.S. prostate cancer prevention trial.	Longitudinal assessment of ED, labs with clinical follow-up from 1994 to 2003.	Men with incident ED have higher risk of CV events comparable to smoking or family history of MI.
Montorsi 2006[18]	Italian community sample of men (N = 285) with ED and CAD.	Cross-sectional comparison of CAD risk in men with and without ED.	In patients with observable CAD, ED onset precedes CAD by approximately 2-3 y.
Schouten 2008[19]	Dutch, community sample (n = 1248) of men aged 50-75 years of age without CVD during baseline period (1995-1998).	Longitudinal follow-up up to 8 y. Extensive annual data collection.	Men with ED at baseline predicts cardiac events at follow-up. Dose-response effect—more severe ED predicts more CV events irrespective of age and other risk factors.
Gazzaruso 2008[16]	Italian men with T2DM (n = 291) with silent CAD.	Longitudinal follow-up to 48 mo.	ED associated with increased MACE (HR, 2.1). PDE5 use associated with lower rates of MACE.
Inman 2009[17]	Olmsted County longitudinal study of U.S. men aged 40-70 years of age from 1996 to 2005 (N = 1402).	Longitudinal study of male health in the general population.	ED associated with an approximately 80% higher risk of later CAD—a stronger effect in younger men.
Chew 2010[15]	Western Australian men with ED (N = 1660) and without CVD at baseline, 45-70 years of age.	Retrospective linked data design health records for follow-up.	Incidence of atherosclerotic CV events in men with ED were twice the rate observed in general male population (SIRR, 2.1; 95% CI, 1.9-2.4)
Banks 2013[14]	Australian men in national health survey from 2006-2009 (N = 95 038).	Proportional hazards modeling of ED on CV outcomes.	ED strongly predictive of subsequent CV events and death in men with and without prior CV history.
Uddin 2018[21]	Subsample (n = 1914) of U.S. men in the MESA study from 2000 to 2012.	Proportional hazards modeling of ED effects on CV outcomes.	Strong, independent effects of ED on subsequent CV events after multiple controls for other potential causes.
Adam 2020[13]	Male participants (N = 573) of mixed ages in epidemiological studies in 4 European countries.	Systematic review and meta-analysis of pooled data from 4 separate studies.	ED is highly significant harbinger of CV events after controlling for all other risk factors.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ED, erectile dysfunction; HR, hazard ratio; MACE, major adverse cardiovascular events; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; SIRR, standardized incidence rate ratio

for traditional CV risk factors such as age, smoking, hypertension, and diabetes.[43] Similar results were reported in a large, European meta-analysis.[30] Overall, these studies suggest that psychogenic ED may be a risk marker for CVD, independent of a potential vascular component, and that men with psychogenic ED may benefit from CV risk assessment and management. However, more research is needed to further elucidate the relationship between psychogenic ED and CVD.

Clinical management of ED: updated guidelines

CV risk management in men who present with ED without overt cardiac symptoms or disease

Given the prevalence and clinical impact of overt and covert CVD in men, in addition to increasing evidence for a harbinger effect of ED summarized in the previous section, the panel considered management guidelines for men with ED, with or without overt cardiac symptoms or disease. Epidemiologic data indicate that CVD is a leading cause of death in men, with as many as 1 in 3 adult males in the United States having some form of CVD.[44-47] Between 70% and 89% of sudden cardiac events occur in men.[48] Half of the men who die suddenly of coronary heart disease have no previous symptoms of CVD.[47,48]

Because of the common risk factors and pathophysiologic processes, men with CVD are more likely to have ED and vice versa.[49-53] ED severity has been correlated with atherosclerotic coronary disease, and in some studies, the presence of ED has been independently associated with CVD events.[54,55] Perhaps more importantly, it has been found that ED symptoms precede clinically evident CVD by an average of 2 to 5 years, making the diagnosis of ED especially useful as a marker of probable subclinical CVD.[18] Further stratification of ED severity further amplifies predictive cardiac risk with several studies revealing greater degree of number and narrowing in cardiac vessels. Thus, men with ED should be considered at risk for potentially sudden fatal cardiac events until proven otherwise.[53]

ED can be categorized as organic (including vasculogenic), psychogenic, or mixed. In general, primary vasculogenic ED is characterized by a gradual onset with symptoms extending beyond 6 months.[56] Erectile rigidity may be weakened, duration may be shortened, or both. These changes are evident under most or all circumstances, including the morning erection, nocturnal erection, sexually stimulated erection, and masturbation. The most common type of organic ED is vasculogenic ED, which shares physiologic underpinning risk factors of heart disease and endothelial dysfunction including but not limited to age, abdominal obesity, smoking, and metabolic syndrome.[15,53,57,58] Situational ED, such as that occurring with a partner but not with morning erections or masturbatory behavior, is usually considered largely psychogenic in origin.[56] Given the overlap of organic and psychogenic causes of ED, men regardless of ED etiology may benefit from CV evaluation and utilization of psychosexual intervention. Even

Table 2. Observational studies of ED and psychological distress: a bidirectional association.

Study	Study population	Study design/data collection	Main findings
Araujo 1998[29]	MMAS study population: representative sample (N = 1700) men 40-70 years of age in the Boston area.	Prospective, 15-y follow-up study with measures of ED and depression.	Strong, bidirectional association of ED and depression at baseline and follow-up. Three times greater risk of ED for men with severe depression at baseline.
Rosen 2004[36]	Large, multinational survey of men 20-75 years of age in 8 countries (N = 27 800).	Cross-sectional, survey of ED and HRQoL.	ED strongly associated with low mood and adverse effects on HRQoL.
De Berardis 2005[32]	N = 1456 Italian men with T2DM.	Longitudinal, prospective study with 3-y follow-up and multiple measures.	Onset of depressive symptoms preceded ED; conversely, onset of ED associated with significant deterioration in mood and HRQoL.
Sugimori 2005[37]	N = 1419 Japanese men 40-64 years of age.	Cross-sectional survey of ED, anxiety, and depression across age groups.	ED associated significantly with depression and anxiety status only in late 40s to early 50s.
Chou 2015[31]	Large, Taiwanese cohort study of men in national insurance database (N = 12 635).	Longitudinal, prospective study of ED and depression over 5 y.	Men with ED at baseline have markedly higher risk of depression at follow-up (adjusted HR, 2.24).
Goldstein 2018[33]	Large, community-based sample (N = 48 000) of men in U.S. commercial insurance database.	Cross-sectional study of ED and mental health compared with control individuals.	Men with ED have increased rates of depression after controlling for other relevant variables.
Calzo 2021[30]	Ongoing survey population in Growing Up Today Study of sexually active men (18-32 years of age).	Cross-sectional study of young men with and without ED.	Both depression and anxiety strongly associated with ED. Antidepressant use 3 times higher prevalence of ED.
Nackeeran 2021[35]	Large, federal database of EHR (N = 260 000).	Retrospective cohort study of men with or without ED and CV risk and depression.	Rates of major depressive disorder were double (odds ratio, 2.0) within 3 y in men with ED.
Manalo 2022[34]	Large claims database of young men (18-40 years of age) with ED (n = 181 000) compared with matched control individuals (n = 181 000).	Prospective study with ED, depression/anxiety measures at baseline, 12 mo, and 36 mo.	Elevated prevalence and incidence of depression and anxiety in young men with ED at all times.

Abbreviations: CV, cardiovascular; ED, erectile dysfunction; EHR, electronic health record; HR, hazard ratio; HRQoL, health-related quality of life; MMAS, Massachusetts Male Aging Study; T2DM, type 2 diabetes.

those presenting with psychogenic ED should be questioned about any cardiac history and assessed for the presence of CV risk factors such as hypertension, dyslipidemia, diabetes, and smoking. If men present with vasculogenic ED, then an assessment using the 10-year atherosclerotic CV risk calculation developed by the American College of Cardiology/American Heart Association (ACC/AHA) is suggested.[8]

Role of ED as a risk marker and risk-enhancing factor

It is important to clarify risk marker nomenclature. A risk marker is "a factor that is noncausally associated with the risk of a disease. It may be used as an indicator of such risk but it is not a causal factor."[59] A risk factor is a risk marker that is causally linked to CVD. Examples include hypertension, elevated low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol levels. For atherosclerotic disease, risk-enhancing factors refer to high-risk features that may guide the earlier use of therapies such as lipid-lowering agents, especially in those patients that are at intermediate or borderline risk. Current examples may include premature CAD in family members, metabolic syndrome, chronic inflammation, hypercholesterolemia that does not quite meet high levels usually associated with pharmacologic therapy, and chronic kidney disease. The panel concluded that there is insufficient evidence supporting the concept of ED is a major independent, causal risk factor for atherosclerotic heart disease (although it is likely that there will be continued discussion regarding this issue). There was consensus that ED is a risk marker, as well as a risk-enhancing factor for atherosclerotic disease, and when diagnosed must include a serious investigation into whether the patient has underlying vascular risk factors or outright CVD.

A strong case can be made for including ED as a risk marker and risk-enhancing factor in future guidelines. Current U.S. guidelines do not include it as such. Currently, only female-specific risk factors are included on the list of risk-enhancing factors for CVD, without any male-specific factors. Given the increased risk conferred by ED, however, many male patients will need advanced risk stratification to further refine their diagnostic and management plan.

As a risk marker, ED is likely to serve as an indicator, or biomarker of the severity of the underlying pathologic processes including atherosclerosis, endothelial dysfunction, and smooth muscle dysfunction.[21,60] ED quantifies the gradient in CVD risk with increasing degrees of ED because "this relationship is likely to inform the potential usefulness of ED as a risk marker in predicting events and in discriminating at what level clinical concerns should be raised."[14] The relationship of severity of ED to the different types of CVD was similar for those with and without a prior history of CVD, indicating that ED remains a risk marker even in those with known CVD.

Development of ED has been found to have similar or greater predictive value for future CV events when compared with traditional CVD risk factors like family history of MI, smoking, and hyperlipidemia.[16,17,20] Araujo et al[61] found that while ED was a strong predictor of CVD (HR, 1.42,

95% CI, 1.05-1.90), it did not improve much upon traditional Framingham risk calculations, allowing ED to have only a minimal effect on reclassification of CV risk. Perhaps the most epidemiologically robust analysis was performed by Uddin et al[21] from the prospective MESA study. A total 1757 participants answered a single MMAS study question regarding ED status. These individuals were followed for a mean of 3.8 years for MI, stroke, and CVD. Importantly, models were adjusted for race/ethnicity, socioeconomic status, β-blocker use, and depression. In the fully adjusted models, ED was robustly associated with CV events (HR, 1.9; 95% CI, 1.1-3.4).[21]

ED as a risk marker in younger vs older men.

Other studies have suggested that ED may have greater prognostic significance in younger men. Results from the Olmstead County Study showed that ED was more predictive of CAD in men 40 to 49 years of age when compared with older men.[17] Another study found that the incidence of CV events in men <40 years old with ED was more than 7 times higher than a reference group.[15] Riedner et al[58] performed a case-control study of 242 men referred for elective coronary angiography. CAD and ED were associated in patients younger than 60 years of age (ED in 68.8% of patients with CAD vs 46.7% of patients without CAD; P = .009) and the association was independent of CV risk factors, testosterone, and C-reactive protein (risk ratio, 2.3, 95% CI, 1.04-5.19). Severity of CAD was higher in patients younger than 60 years of age with ED.[62] Summarily, studies have focused on ED as a particularly significant harbinger of CVD in 2 populations: men <60 years of age and those with diabetes.[14,16,17,21,54,57,62-64] These studies suggest that ED is an early marker of generalized CVD and supports the need for CV workup in younger men and diabetic men with vasculogenic ED.

Review of the results of a large prospective population-based Australian study published following P3 (the 45 and Up Study) linking ED questionnaire data from 2006 to 2009 with hospitalization and death, found risks of CVD and death increased steadily with severity of ED, yet risk did not differentiate among younger and older men. Thus, Banks et al[14] found that among men without previous CVD, the risk ratio of more specific CVDs increased significantly with severe vs no ED, including acute MI (1.66; 95% CI, 1.22-2.26), heart failure (8.00; 95% CI, 2.64-24.2), atrioventricular and left bundle branch block (6.62; 95% CI, 1.86-23.56), and peripheral atherosclerosis (2.47; 95% CI, 1.18-5.15), yet with no significant difference in risk for conditions such as primary hypertension (0.61; 95% CI, 0.16-2.35) and intracerebral hemorrhage (0.78; 95% CI, 0.20-2.97).[14]

This study is an order of magnitude larger than any previous prospective study of ED and CVD and provides the strongest evidence to date of a relationship of increasing CVD risk with increasing self-reported severity of ED. These results lend strong support to prior studies among men without known CVD at baseline; those with moderate or severe ED have increased risks of a subsequent CVD event, including ischemic heart disease, stroke, and peripheral vascular disease, as well as all-cause mortality, compared with men with mild or no ED.[17,20,65,66] The finding on the relationship between severity of ED and future admissions for heart failure is novel, and no other prospective studies demonstrate increased risks of chronic ischemic heart disease and atrioventricular and left bundle branch block with increasing levels of ED.[14]

These findings highlight the need to consider ED in relation to the risk of a wide range of CVDs that extends beyond ischemic heart disease and stroke and includes conditions such as heart failure and conduction disorders. They also provide evidence that CVD risk is elevated across the spectrum of severity of ED and that men with mild or moderate ED should be considered at increased risk, in addition to those with severe disease. Nevertheless, this does not translate automatically into utility as part of a clinical risk score, such as using ED, in addition to the Framingham, ASCVD, and other risk scores.[64] Rather, the findings provide general support for P3 that men with ED require assessment for CVD risk, while the quantitative ability of ED to predict risk in the clinical setting, over and above clinically measured risk factors, requires specific testing.[4] Thus far, only the QRISK-3 calculator (https://www.qrisk.org/) has incorporated ED into its risk calculator (as binary, not severity related), increasing risk by about 25% when positive.[67]

Several small-to-medium studies implicate younger men as higher risk for future cardiac events. The most robust study with several-fold higher power refutes this claim only after adjustment for confounding factors. Despite ambiguity in this area, the need for cardiac screening in young men with ED remains imperative. Younger age screening gives greater opportunity, time, and margin for error of preventative approaches. In addition, young men are perhaps more easily convinced to augment behavior utilizing the fulcrum of improved sexual function instead of abstract future risks for asymptomatic conditions such as hypertension and high lipids.

What testing should be considered?

The 2023 P4 meeting was convened to examine the present ED guidelines and determine the appropriate CVD risk stratification and assessment of the man with primarily vasculogenic ED. There remains a need for specific guidance and selective use of prognostic tests for further CVD risk assessment. The P4 panel agreed that ED continues to be underreported and undervalued as a risk marker for future CVD events. While P3 prioritized an age stratification of 40 to 60 years as the greatest risk, and potential risk stratification based on the Framingham risk score including exercise treadmill testing, ankle-brachial index, carotid intima-media thickness, and computed tomography calcium, we propose utilizing the 2019 ACC/AHA ASCVD risk score for all men undergoing evaluation for predominantly vasculogenic ED. This risk assessment utilizes the Pooled Cohort Equations (PCE), which are based on age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (BP), and whether the patient is receiving treatment for high BP, has diabetes, or smokes.[8] This tool gives an estimate of the patient's risk of a CV event within the next 10 years, and the ASCVD risk estimator can be readily accessed (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/) and provides an estimate of the patient's risk of a major CV event within the next 10 years categorized as follows: low risk, < 5%; borderline risk, 5% to <7.5%; intermediate risk, ≥7.5% to <20%; and high risk, ≥20%. The panel considered this to be an appropriate starting point for risk stratification.[8,68-71] However, because of the reliance on the small number of traditional risk factors and the strong reliance on age in the risk estimates, we propose more advanced testing for all younger men (40-60 years of age) with vasculogenic ED and borderline

Table 3. CV workup and management

CV workup of men who present with ED and no known CV disease.

1) ED is a risk marker and risk enhancing factor for ASCVD.
2) Patients presenting with vasculogenic ED should have an assessment of their 10-year ASCVD risk based on the American College of Cardiology/American Heart Association risk score (see text and Figure 1 to link for calculating this score; see algorithm 1; applies primarily to men 40-79 years of age).
3) Borderline to intermediate-risk score (5%-20% 10 year risk of ASCVD) should have coronary artery computed tomography calcium scoring.
4) CAC Score of 0 results in lifestyle interventions.
5) CAC Score of 1-100: lifestyle modification plus moderate-to-high-intensity statins. Control other CV risk factors (hypertension, diabetes, stop smoking).
6) CAC Score of >100: high-intensity statins. Control other risk factors. Consider low-dose aspirin. Refer to preventative cardiologist.

How to manage ED in men with known CV disease

1) After initial sexual query, confirming ED, assess the patient's exercise ability for age.
2) Categorize the risk of having a cardiac event during sexual activity into low risk, intermediate or indeterminable (indeterminate) risk, or high risk as described in the text.
3) Intermediate or indeterminable (indeterminate) risk: may require additional testing to determine exercise capacity/development of ischemia with stress. This includes exercise stress testing; for those who cannot exercise, a chemical stress test (such as dobutamine echocardiogram or chemical nuclear stress test) is appropriate. Achieving 5-6 METS (in 4 min on a standard Bruce Protocol Treadmill Test) without ischemia (chest pain/electrocardiographic changes/wall motion abnormality) suggests patient can achieve desired exercise tolerance required for sexual activity and is low risk. Those who develop ischemia, especially at a low level of exercise, are then reclassified as high risk and require a CV consultation.
4) Low risk: patient may receive therapy for ED. If patient has a prescription for nitrates, make a determination whether nitrates are really needed. For example, some patients who have had successful coronary artery revascularization continue to carry nitrates but never need or use them. If nitrates are not needed, do not prescribe and consider PDE5 inhibitor therapy.
5) High risk: these are unstable cardiovascular patients who need a referral to a cardiologist. In some cases, revascularization procedures (preventive coronary intervention–angioplasty stenting) may be required before they can be reclassified as low risk.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CV, cardiovascular; ED, erectile dysfunction; METS, metabolic equivalents of task; PDE5, phosphodiesterase type 5.

or intermediate risk (5%-20%), as these patients normally do not score as high risk with the ACC/AHA risk estimator and are therefore likely have significant unaccounted for CVD risk.[69] While the P3 guidelines recommended that men with ED and an intermediate 10-year risk score undergo an exercise treadmill stress test based on the 2010 ACC/AHA ASCVD risk guidelines, the P4 guidelines recommend that all men with this range of risk deserve further risk enhancement evaluation with a coronary artery calcium (CAC) measurement. Based on this evaluation, further risk stratification and/or use of statin therapy will be initiated. At any point in time the clinician can refer to a preventative cardiologist for further guidance (Table 3).

The role of CAC scoring as a risk factor.

CAC scores (coronary artery calcium scores; determined by specialized CT scanning) are widely endorsed for advanced risk assessment in patients at borderline to intermediate risk in whom decisions about preventive therapy are uncertain. CAC scoring is widely accessible, fast (10-15 minutes today), and inexpensive (~$75-$150), and can be performed without heart rate control or intravenous contrast. One of the most common applications for CAC scoring in clinical practice is for precise risk assessment in patients with risk-enhancing factors—that is, patients who have risk conditions that place them at higher risk than would be expected based on traditional risk scores like the sex- and race-specific PCE.

Given the close correlation between ED and subclinical atherosclerosis as defined by CAC, and the fact that CAC scores are the single strongest predictors of CVD risk in current prevention guidelines, a strong case can be made for wider use of CAC as a risk marker in patients with ED. In particular, patients who would otherwise be borderline risk to intermediate risk using the PCE (many young adult men), presence of ED should be used as a rationale to engage in CAC scoring to guide earlier, personalized use of effective preventive therapies like statins, nonstatin therapy (ie, lifestyle optimization), and aspirin. Figure 1 (algorithm 1 and Table 3) shows the proposed CV workup of men who present with vasculogenic ED, as recommended by the P4 group.

ED management in men with overt CV symptoms and/or CVD

Sexual activity has been found to increase concurrent and proximal adverse cardiac events to a minimal degree.[11,72] The objective of algorithm 2 (Figure 2 and Table 3) is to estimate the CV risk associated with sexual activity in patients with ED and known CVD. CVD is defined as the full range of CV disorders including but not limited to ischemic disorders, arrhythmias, and cardiac output pathology. Risk refers to the likelihood of mortal or morbid events during or shortly after sex. The current panels' recommendations are similar to those developed during P3.[4] However, the current recommendations extend to include the appropriateness of treatment with PDE5 inhibitors among low-risk patients currently using or who have easy access to nitrates that they might use. The possibility of withdrawing nitrate use/access is also reviewed.

Sexual inquiry

ED and CVD share common risk factors, and ED is a risk marker and risk-enhancing factor of CVD. Thus, assessment of sexual function should be incorporated into the initial CV

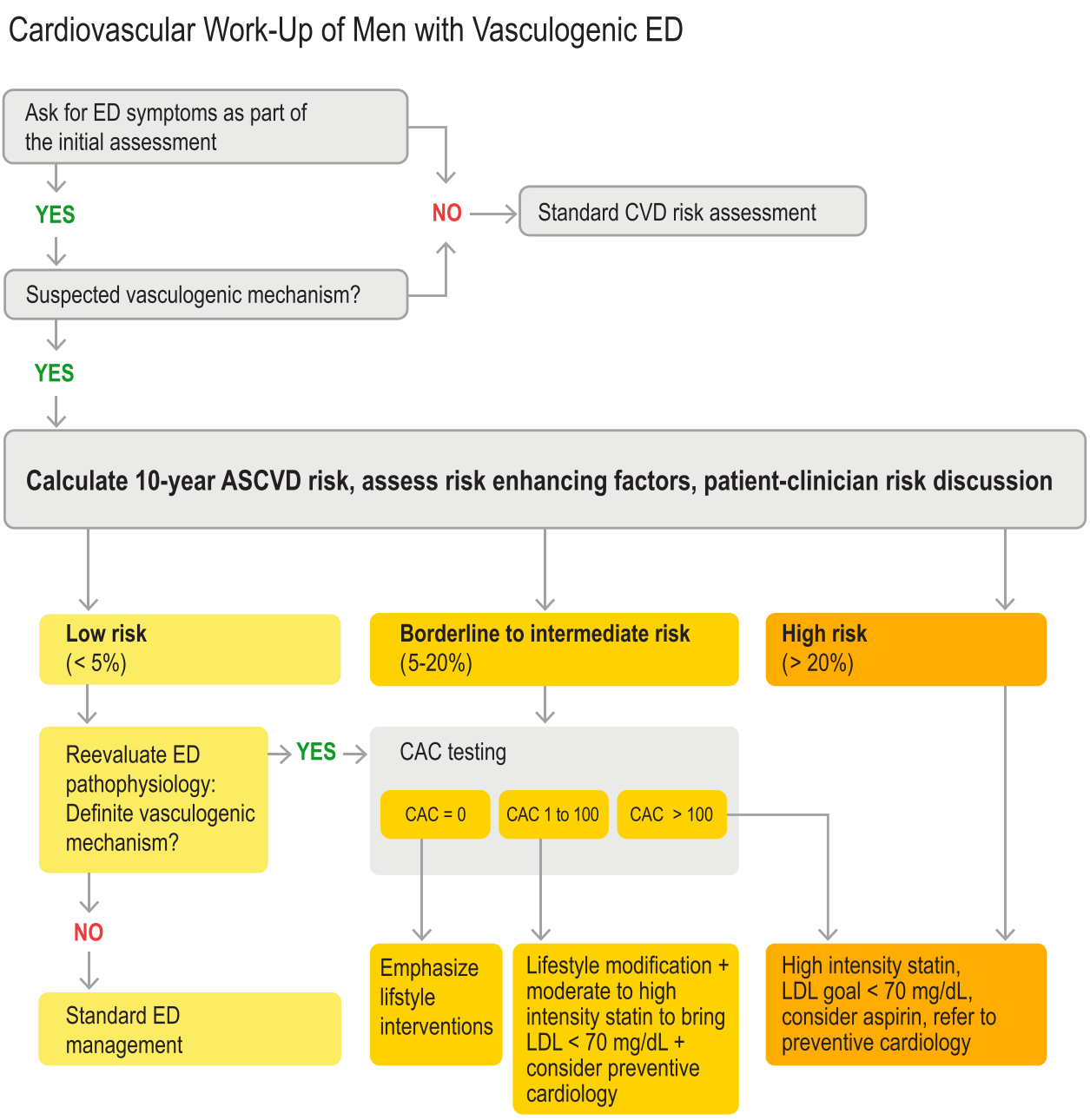

Figure 1. CV risk assessment of ED patient with no overt disease or cardiac symptoms. Algorithm 1 is derived from previous key papers with modifications: Evaluation and management of cardiovascular risk in men with vasculogenic ED but no known CVD is recommended. This applies primarily to men 40 to 79 years of age. Symptomatic men are presumed to have CVD and are therefore at high risk for CVD events. A thorough CV history, physical examination (including BP history) and measures, smoking history, lipid history, and lipid measurements (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol), diabetes history and measures (fasting plasma glucose, hemoglobin A1C, measures of visceral adiposity), assessment of ED severity and duration, 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. Thereafter, 10-year ACC/AHA ASCVD risk is calculated with therapeutic intervention based on score. The ACC/AHA risk score can be found online (https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/). Persons with complex or unclear clinical situations (eg, borderline results) may be referred to a urologist, cardiologist, or other subspecialist as indicated. Modified with permission from Miner et al,[56] Shah et al,[70] and Arnett et al.[8]

evaluation for all men, regardless of the presence or absence of known CVD.

Exercise ability and sexual activity risk stratification

High levels of habitual exercise have been shown to attenuate the association between acute cardiac events and the episodic physical activity of sex.[11,72] Thus, a patient's self-report of sedentary vs active lifestyle may guide the physician to an estimate of CV risk associated with sexual activity. The exertion of sexual activity between couples in a longstanding relationship equates to approximately 2 to 3 METS, which is equivalent to walking 1 mile on a flat surface in 20 minutes or climbing 2 flights of stairs in 10 seconds. Younger couples may expend 5 to 6 METS while engaging in more intense sexual activity (equivalent to approximately 4 minutes of standard Bruce Protocol Treadmill Test). Exercise tolerance should be

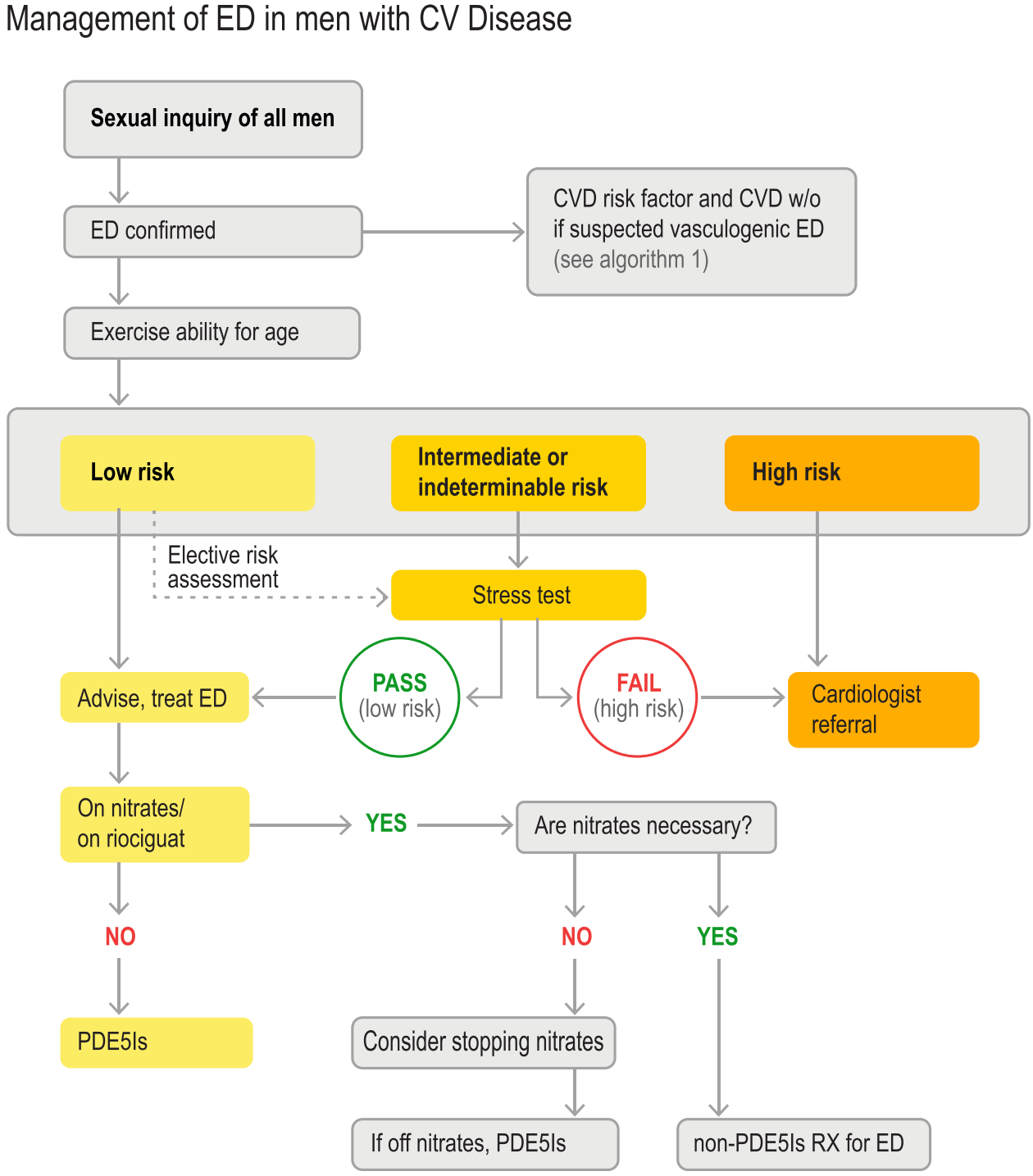

Figure 2. ED management in men with overt CV symptoms and/or CVD. Algorithm 2. w/o=work up. Risk of cardiovascular event with sexual activity is stratified based on exercise ability for age and thereafter on presence or absence of use of nitrates in management of CAD. Sexual activity with a usual partner in a long-standing relationship is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds. More moderate or vigorous intensity sexual activity is equivalent to 4 minutes of the Bruce Protocol Treadmill Test (5-6 METS). If patient is at low risk and has a prescription for nitrates, the health care provider may determine whether nitrates are really needed. In some cases, they may not be needed or other antianginal therapies can be considered. If nitrates are not needed, then PDE5 inhibitors may be considered. If nitrates are needed, then other therapies for ED besides PDE5 inhibitors are considered. Modified with permission from Nehra et al[4] and Miner et al.[72]

established before the initiation of ED therapy in all men, regardless of CV risk.[73] There was overlap in authorship of this P4 Consensus with that of the AHA Scientific Statement on Sexual Activity and Cardiovascular Disease,[74] so there are similarities in recommendations. 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 and 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 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 profiles include unstable or refractory angina pectoris, uncontrolled hypertension, congestive heart failure (New York Heart Association [NYHA] functional class IV), recent MI without intervention (<2 weeks), high-risk arrhythmia (exercise-induced ventricular tachycardia, implantable cardioverter-defibrillator with frequent shocks, and poorly controlled atrial fibrillation).

Intermediate-risk or indeterminable (or indeterminate) risk patients. These patients include those with mild or moderate stable angina pectoris, past MI (2-8 weeks) without intervention awaiting exercise electrocardiography, congestive heart failure patients (NYHA functional class III), and noncardiac sequelae of atherosclerotic disease (eg, peripheral arterial disease, history of stroke or transient ischemic attack). Further examination using exercise stress testing is required for indeterminate-risk patients before resuming sexual activity. Completing 4 minutes of the standard Bruce Protocol Treadmill Test (5-6 METS) without symptoms, arrhythmias, or a fall in systolic BP identifies the safety of sexual activity.[2,3] Based on stress test results, they will be reassigned to low- or high-risk groups as recommended by prior Princeton Consensus Conferences. If patients cannot complete a standard exercise test (owing to a disabling condition such as arthritis), a chemical stress test with echocardiography or nuclear imaging can be performed. Patients with suspected atherosclerotic disease may need additional vascular disease testing using CAC, carotid intima-media thickness or the ankle-brachial index that may be helpful in reclassifying to high- or low-risk categories.

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.

PDE5 inhibitors are widely used to treat ED. Their safety and appropriate use were reviewed in P2 and more recent analysis of placebo-controlled and postmarketing surveillance data have demonstrated no new concerns regarding CV events.[75] Additional considerations for treatment of ED may include testosterone replacement therapy for men with low serum total testosterone (either as an initial treatment or added to PDE5 inhibitor therapy after PDE5 inhibitor failure),[76,77] non–PDE5 inhibitor approaches,[24] exercise and weight loss,[24,78] and partner and relationship factors.[79-83] CV safety of long-term testosterone therapy in hypogonadal men with existing CV disease or risk factors was recently reported.[84] Based on results of a prospective, placebo-controlled trial of testosterone gel vs placebo in 5246 men 45 to 80 years of age, testosterone was not associated with increased overall major adverse CV risk, despite a higher incidence of pulmonary embolism, acute kidney injury, and atrial fibrillation in the testosterone group.[84]

Management of ED should be considered secondary to maintaining cardiac function and a healthy lifestyle. Conversely, as discussed in P3, agents used to treat CV disorders and risk factors may negatively impact ED.[4] Medication adjustments may help to relieve ED severity.[80] Placebo-controlled studies of ED in men taking medications to control other CV risk factors and known CVD 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 are recommended.

ED management in patients taking nitrate-containing medications or substances

The concurrent use of a PDE5 inhibitor with a nitrate-containing substance is currently contraindicated due to concern about the nitrate–PDE5 inhibitor interaction with resultant hypotension. Recommendations are to avoid using a shorter-acting PDE5 inhibitor (eg, sildenafil, vardenafil, avanafil) within 24 hours of a nitrate-containing substance and within 48 hours of a longer-acting PDE5 inhibitor (eg, tadalafil).[72]

There remain questions about the potential benefit of long-term nitrates in stable ischemic heart disease with evidence of the development of endothelial dysfunction and tolerance.[85] Although there are conflicting reports from various studies, nonrandomized studies have suggested an increase in the incidence of acute coronary syndrome with long-term nitrates.[86]

P4 discussed the likelihood that nitrates are being overused in current clinical practice and may not be necessary in many situations or could be stopped or substituted with other medications in many situations. The Consensus recommends that low-risk patients be asked if they are taking or being exposed to nitrates in any form. If the response is affirmative, the actual need for the nitrate can be discussed and the patient could, as appropriate, be encouraged to stop using the preparation or substitute some other medication if needed. For example, stable patients who have been recently revascularized and may still be taking a nitrate preparation could be evaluated for cessation of the medication. "Optimal utilization of nitrate therapy requires a greater interaction and understanding between the clinician and patient, to assess the severity of symptoms, the preferences and convenience of each patient and then tailor the treatment plan to ensure better quality of life and optimum adherence to treatment."[87] Conversations about nitrates often need to be patient-centered, especially if the patient has been taking the medication for a long time.

If the patient with ED has a true indication for nitrates such as continued angina or congestive heart failure, or nitrates are being used successfully off-label for other potential indications such as anal fissures, esophageal spasms, or the recreational aspect of "poppers," and there is no other treatment, then the clinician must consider other ways to manage ED.

Riociguat is a treatment for pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension that is a soluble guanylate cyclase stimulator and can increase levels of cyclic guanosine monophosphate (cGMP); it is contraindicated with PDE5 inhibitors.[88]

Drug–drug interactions and CV safety of PDE5 inhibitors

PDE5 performs a highly specialized biologic function, with respect to its mechanisms of action and in the way that this

enzyme is regulated. PDE5 was initially characterized as a high-affinity binding protein for the cyclic nucleotide, cGMP, with early studies showing its localization in platelets and the lung.[89,90] Its recognized role in the smooth muscle tone of vasculature was later identified and notably showcased in the biomedical arena with the discovery of PDE5 inhibitors (eg, sildenafil) that effectively treat such vascular conditions as ED and pulmonary hypertension.[1,91]

Current knowledge in the field of PDE5 biology establishes that this enzyme operates in an intricate molecular signaling cascade. Nitric oxide, a gaseous upstream molecule, activates guanylate cyclase to produce cGMP, which drives the downstream signaling of protein kinase G to phosphorylate contractile regulatory proteins and ion channels in vasculature resulting in vasodilation.[92] PDE5 inhibitors serve acutely to inhibit PDE5's selective hydrolysis of cGMP, promoting the action of this molecular effector.

PDE5 inhibitors have also been demonstrated to be protective in the vasculature and heart, a biologic role that denotes the extensive effects of cGMP.[93,94] Postulated therapeutic benefits of PDE5 inhibitors include decreased systemic BP, inflammation, tissue fibrosis and thrombosis development, and enhanced cardiac contractility.[93] The molecular biologic mechanisms for these effects are diverse: protection against ischemia-reperfusion injury (via activation of calcium-activated BK channels), coronary microvascular endothelial activation, oxidative stress reduction; enhancement of calcium signaling in cardiomyocytes, regulation of platelet protein, control of fibroblast-to-myofibroblast differentiation, and inhibition of transforming growth factor β signaling.[93,94]

Remarkably, PDE5 is a complex and mutable molecule, controlled by a dynamic, tight regulatory system. The activity of the enzyme can be upregulated or downregulated. The molecular structure of PDE5 accounts for this regulatory potential, a feature exploited by a host of regulatory conditions. The enzyme contains a highly conserved catalytic domain near its C-terminus, whereby the enzyme binds cGMP and terminates its actions; distinctly, at its N-terminus regulatory domain. PDE5 possesses an allosteric cGMP-binding site as well as a phosphorylation site.[95] The promoter region of the PDE5 gene contains cGMP-responsive elements. On this basis, activators of guanylate cyclase, such as continuous nitric oxide release, exert a feedforward upregulatory activation of PDE5 that attenuates cGMP effects. Upregulation of PDE5 essentially then contributes to a decline in cGMP and protein kinase G signaling. In a converse manner, guanylate cyclase inactivation, under such conditions as nitric oxide deficiency, downregulates PDE5 function resulting in elevated cGMP effects.

Regular PDE5 inhibitor use may also influence this signaling pathway's feedback regulatory control mechanism. Under such conditions, cGMP actions are prolonged resulting in PDE5 upregulation,[96] such that excessive vasodilation conceivably does not occur. This scientific principle likewise could apply to chronic nitrate exposure. It is quite plausible that chronic nitrate exposure upregulates PDE5 function in a manner that restrains excessive vasodilation. Hence, the coadministration of a PDE5 inhibitor under these conditions may not necessarily result in dangerous hypotension because the induced feedback control mechanism provides a safeguard.

Optimizing therapy with PDE5 inhibitors

The success in using PDE5 inhibitors for treating ED begins with basic education of patients (and partners, if available) in using the medications correctly and extends to applying strategies to optimize their effects. Such management includes maximally exploiting the pharmacologic and molecular biologic properties of this therapy, promoting practices favoring therapeutic responses, and addressing conditions hampering therapeutic responses. In particular, partner sexual function and readiness and/or willingness to resume sexual activity with PDE5 inhibitor therapy should be assessed and addressed, when indicated. Sample questions might include 1 or more of the following: "Have you spoken with your partner about your erection problem?"; "Is your partner supportive of you getting treatment to improve your erection?"; "Does your partner have any concerns about the treatment?"; "Would your partner like to talk with me or another clinician about improving your sex life together?"; "Do you know if your partner has any concerns about their own sexual function, pain with sexual activity, or about any other related health issues?"; and "Is there anything else I should know to help me understand this problem?"

The pharmacology of PDE5 inhibitors relates to such parameters as their onset of action, time for maximal effect, and time for elimination (T-half-life). In an on-demand mode, these medications require lead time intervals of approximately 30 to 60 minutes after ingestion, although differences exist in the duration to their peak serum concentrations (ie, approximately 30 minutes for avanafil, 1 hour for sildenafil and vardenafil, and 2 hours for tadalafil).[97] Duration of effect ranges from as much as 36 hours for tadalafil to approximately 4 to 8 hours for the other medications, corresponding with the pharmacology of drug elimination.[97]

Accordingly, using PDE5 inhibitors within their specifications of pharmacologic action is fundamental. Daily dosing using tadalafil to achieve steady state efficacy is an alternative dosing scheme that has been approved at the FDA regulatory agency level, thereby affording patients greater convenience in having sexual intercourse using this agent.[98] Additional pharmacologic factors include reducing food intake prior to dosing (as applies to sildenafil, avanafil, and vardenafil) to optimize drug absorption and escalating drug dosing to maximal dosing levels as needed.[97] It is also reasonable to try an alternate PDE5 inhibitor[97] and PDE5 inhibitors in combination,[99] while understanding that efficacies of the medications may differ between patients.

The arousal associated with sexual stimulation is a prerequisite for liberating nitric oxide from nerves and vascular endothelium of the penis, in accordance with the science of the molecular pathway required for producing the erection response and enhanced by PDE5 inhibitors.[100] Thus, optimal sexual stimulation should be applied to facilitate erection responses. Additionally, patients may be advised to observe partner interactions and stimulation (eg, arousal) that may influence medication responsiveness.[101]

Testosterone replacement in the hypogonadal patient with ED may also promote erection responses to PDE5 inhibitors, provided that the patient is documented to have low testosterone at baseline.[73] Scientific work suggests that a normalized testosterone milieu primes the function of the nitric oxide regulatory pathway.[102] As noted in the clinical management section, a recent trial using testosterone supplementation did not show an increase in MACE but an increase in pulmonary embolism and atrial fibrillation.[84] Similarly, correcting or improving adverse health conditions that compromise erection responses (eg, glycemic control, hyperlipidemic control, cigarette smoking discontinuation) may also promote therapeutic efficacy.[101]

Behavioral counseling offers another strategy to improve erection responses to PDE5 inhibitors. Repeated attempts of sexual activity using the medications is reported to afford maximal probability of success.[103] In this study, 55% of 137 treated patients who were previously not successful with sildenafil became successful after re-education and counseling, which included information on patient and partner expectations, how to properly take the drug, titration to maximum dose, and a minimum trial of 8 attempts for efficacy assessment.[103]

This outcome may relate to having sufficient opportunities to identify and employ the best stimulatory conditions to respond to this therapy. Addressing adverse psychosocial factors that may hinder stimulatory conditions (eg, sexual performance anxiety) may also be considered and invoke the service of a mental health counselor.[101]

Combination therapy in the setting of PDE5 inhibitor use has also been utilized to achieve erection success.[104] Options for combination therapy include vasoactive penile injections and vacuum erection devices.[105,106]

Interactions of PDE5 inhibitors with nitrates and other CV drugs

Safety concerns related to the interactions between PDE5 inhibitors and nitrates

Within 6 months of the introduction of sildenafil (Viagra) in early 1998, a total of 69 deaths were reported to the FDA in patients who had used Viagra.[107] In response, the ACC made recommendations on the use of sildenafil in patients with CVD.[107] One major concern addressed was the interaction of nitrates with PDE5 inhibitors, potentially leading to life-threatening hypotension. The biology of this interaction was well understood. Nitrates are donors of nitric oxide, which is a potent activator of soluble guanylate cyclase and its production of cGMP. Accumulation of cGMP leads to a reduction in intracellular calcium and (vascular) smooth muscle relaxation. The degradation of cGMP into its inactive form, GMP, is catalyzed predominantly by PDE5. Notably, inhibition of cGMP breakdown by PDE5 inhibitors simultaneous with its increased generation by nitrates can lead to extreme cGMP elevations with synergistic effects on vasodilation and hypotension. Based on the half-life of sildenafil of ~4 hours, it was recommended that nitrates should not be administered within 24 hours after the last dose of sildenafil. Subsequent to these recommendations for sildenafil, interactions of PDE5 inhibitors with nitrates have been investigated extensively in pharmacological studies under carefully controlled conditions.[108-113] Based on the totality of evidence, use of nitrates remains a contraindication for all PDE5 inhibitors (a class effect), specifically within 24 hours after the last dose of sildenafil, avanafil, and vardenafil (all with half-life ~4 hours) and 48 hours after the last dose of tadalafil (half-life ~17.5 hours).[5]

Real-world observations of coprescribed PDE5 inhibitors and nitrates: pharmacological studies of the interaction of nitrates and PDE5 inhibitors on BP have typically tested the worst-case scenarios, with the administration of the 2 agents timed to achieve a maximal hypotensive effect and participants' BP tested in an upright position. Nunes et al[7] investigated whether PDE5 inhibitors and nitrate coprescription (referred to as co-possession) is associated with increased rates of adverse CV outcomes in a real-world setting. Their review of U.S. electronic health record database (2012-2016) indicated that co-possession of nitrate and PDE5 inhibitor prescriptions while under the care of a physician was not associated with increased rates of adverse CV outcomes, relative to possession of nitrates alone. Medical records documented a discussion between physicians and patients in many cases prior to the first co-possession period regarding the hazards of coadministration and strategies to minimize harm, possibly accounting for the safe trends observed. In a retrospective study of Danish men with ischemic heart disease, covering 2000 to 2018, coprescriptions of PDE5 inhibitors and nitrates increased 20-fold during this period.[6] Despite this surge in coprescribing, the investigators did not observe any increase in adverse CV outcomes, reaching the same conclusion about the apparent safety record of coprescriptions, as the U.S. study[7] —patients with ED are able to successfully manage their co-possession of PDE5 inhibitors and nitrates without increasing their risk of CV outcomes. Notably, these studies have important limitations: (1) the observations were based on nitrate and PDE5 coprescriptions, without knowledge of how these medications were taken in relation to each other; (2) the subpopulation of patients with coprescriptions may have been exceptionally well informed, generally healthier, and adherent to physician guidance than the general population; and (3) even if taken on the same day, the 2 agents were likely not overlapped, with nitrates more likely taken in the mornings and PDE5 inhibitors in the evenings. Clinical implications of these co-possession studies are not yet resolved. Some experts have called for reassessment of whether the absolute contraindication should be lessened to a warning for well-informed, compliant patients. There is agreement that any contemplated change in current clinical practice should be ultimately tested in a well-designed prospective clinical trial that will accurately inform the risks and benefits of PDE5 inhibitor/nitrate coadministration.[7]

Interactions between PDE5 inhibitors and sacubitril/valsartan

Sacubitril/valsartan (Entresto) is a combination of a neprilysin inhibitor and angiotensin receptor antagonist approved for treatment of heart failure.[114] Neprilysin is an endopeptidase that cleaves a variety of proteins/peptides such as natriuretic peptides, bradykinin, adrenomedullin, endothelin, substance P, and angiotensin I and II.[115] Inhibition of neprilysin by sacubitril thus leads to increases in natriuretic peptide (as well as other proteins/peptides) and in cGMP.[115] Coadministration of sacubitril/valsartan and sildenafil resulted in a greater, but modest decreases in BP (–5/–4/–4 mm Hg ambulatory systolic BP/diastolic BP/mean BP) compared with sacubitril/valsartan alone.[114] While the coadministration of sacubitril/valsartan and sildenafil was generally clinically well tolerated, it is recommended that the coadministration of sacubitril/valsartan with sildenafil (and other PDE5 inhibitors) should be prescribed cautiously.

Interactions between PDE5 inhibitors and riociguat

Riociguat (Adempas) is a drug used to treat PAH and nonsurgical chronic thromboembolic pulmonary hypertension.[116] It potently stimulates soluble guanylate cyclase and its effects on augmenting cGMP are synergistic which PDE5 inhibitors. Coadministration of all PDE5 inhibitors and riociguat (and other soluble guanylate cyclase stimulators)

is contraindicated due to the risk of excessive systemic hypotension.[116,117]

Interactions between PDE5 inhibitors and α-1 receptor blockers

BPH, associated LUTS, and ED frequently coexist among aging men. α-1 blockers are currently the first-line treatment for LUTS due to BPH.[118] There are 2 subtypes of α-1 receptors: the α1A receptors are located in the prostate and bladder neck and are considered uroselective, whereas α1B receptors are located in the vasculature and are involved in BP regulation. Tamsulosin, silodosin and alfuzocin are uroselective whereas doxazosin and terazosin are nonuroselective α1-blockers.[118] Hypotension, particularly orthostatic hypotension, is an important side effect of coadministration of α1-blockers and PDE5 inhibitors and carries a package insert warning.[119] The risk of hypotension is lower with uroselective agents. For example, tadalafil augmented the hypotensive effects of doxazosin but had little hemodynamic interaction with uroselective tamsulosin.[120] Thus, in patients with both ED and BPH, combination of tadalafil with tamsulosin 0.4 mg may have a particularly safe BP profile.

Current PDE5 inhibitor package inserts state that these agents can potentiate the hypotensive effects of α-blockers and state that "caution is advised when PDE5 inhibitors are coadministered with α-blockers. Concomitant use can lower BP significantly leading to symptomatic hypotension (e.g., dizziness, light headedness, fainting)." Package inserts recommend that patients be stable on their current α-blocking therapy before starting PDE5 inhibitors and that PDE5 inhibitors be initiated at the lowest dose. Factors such as intravascular volume depletion and other antihypertensive medicines should be considered.[119]

Interactions between PDE5 inhibitors and antihypertensive therapies

When PDE5 inhibitors are administered to patients with hypertension who are taking most standard antihypertensive agents (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel antagonists, diuretics, and β-blockers), there are usually small additive decreases in BP without a significant increase of adverse events.[5] Thus, administration of most antihypertensive therapies along with PDE5 inhibitors is generally safe, with only the caution about coadministration with α1-blockers.

Rare adverse events associated with PDE5 inhibitors

PDE5 inhibitors are the leading drugs for the treatment of ED, being recommended as a first-line treatment by most major urological guidelines. Publications since the last Princeton guidelines show that the PDE5 inhibitors are safe from a CV standpoint, yet men with ED should be informed regarding the treatment option of PDE5 inhibitors, including discussion of benefits and risks/burdens. Most adverse events associated with the administration of PDE5 inhibitors are mild to moderate. Despite their demonstrated safety, rare and more significant adverse drug reactions have been associated with PDE5 inhibitors. The characteristics of these adverse events fall into 4 imprecise categories: (1) visual disturbances, (2) auditory alterations, (3) skin abnormalities, and (4) other.

Visual disturbances

Perception of blue color

The human retina contains an abundance of the PDE6 enzyme, which shares 80% homology with the PDE5, most common in the penis. PDE6 is present exclusively in rod and cone photoreceptors and plays a critical role in color perception—particularly blue and green. At the highest recommended oral doses, sildenafil causes mild and transient visual symptoms in a minority of patients by inhibition of the retinal PDE6 enzyme resulting in a visual field awash in shades of blue. The effects of sildenafil have been systematically investigated in visual function studies in volunteers and in patients with eye disease; sildenafil does not affect visual acuity, visual fields, and contrast sensitivity. The only definite effect is transient, mild impairment of color discrimination occurring around the time of peak plasma levels.[121] In clinical trials, abnormal vision occurred in 1% of users taking the 25-mg dosage, 2% of users taking the 50-mg dosage, and 11% of users taking the 100-mg dosage. Associated vision changes may include predominantly a color tinge change, but also blurred vision and increased sensitivity to light.[122] No consistent pattern has emerged to suggest any long-term effect of sildenafil on the retina or other structures of the eye. Based on this experience, intermittent, short-term, partial inhibition of PDE5 or PDE6 by sildenafil is unlikely to induce any long-term visual change.

Nonarteritic anterior ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is a rare visual condition characterized by the sudden onset of loss of vision in one eye. The estimated annual incidence is 2.5 to 11.8 cases per 100 000 men >50 years of age. Caucasian ethnicity, small optic discs with low cup-to-disc ratio, and various kinds of vascular conditions appear to confer greater risk.[123] Studies have suggested that PDE5 inhibitor use is associated with an increased risk of NAION, although the absolute risk is small (3 additional cases per 100 000 men >50 years of age).[124] Men in higher-risk groups (eg, older men, men of Caucasian ethnicity, men with vascular risk factors) should be counseled about this small increased risk, including the fact that the absolute risk of NAION is extremely low with or without the use of PDE5 inhibitors, and that the association does not imply causation.

Serous retinal detachment

The evidence behind serous retinal detachment (SRD) is mostly in the form of case reports or small epidemiologic studies that produced imprecise estimates for this risk[125]: because of the rarity of these events, they were not adequately studied in the original clinical trials of these drugs. In one meta-analysis, patients with SRD were more likely than those in the control group to have hypertension, diabetes, CVD, or sleep apnea. The adjusted incidence rate ratio for SRD in men receiving PDE5 inhibitors as individual outcome was 2.58 (95% CI, 1.55-4.30), and the incidence was 3.8 cases per 10 000 person-years. There is a paucity of evidence regarding the pathogenesis of PDE5 inhibitor–induced SRD. One hypothesis suggests that PDE5 inhibitors increase choroidal blood flow and congestion of the retinal blood vessels thus precipitating an SRD; however, further research is needed to elucidate these mechanisms.

There are no systematic controlled studies regarding the issue of safety of administering PDE5 inhibitors to patients with retinitis pigmentosa.

Ototoxicity

Auditory disturbances (sensorineural hearing loss and tinnitus) associated with PDE5 inhibitor use have been reported, but few studies have evaluated the causal link.

Recent concerns regarding these drugs and sudden sensorineural hearing loss have resulted in an FDA requirement for more stringent labeling. The evidence for this association is only based on case reports, as the number of patients affected is very low. In one review of 25 case reports, 15 (88%) patients experienced the event within 24 hours of taking a PDE5 inhibitor.[126] Eight (32%) patients had associated vertigo concurrently with their hearing loss. Ninety-six percent of reported cases were unilateral. Complete resolution of hearing loss was noted in 5 (20%) patients, whereas 3 (12%) other patients had at least partial improvement. Therefore, 8 (32%) patients had documented improvement in their hearing from the initial presentation. Overall, the possibility that PDE5 inhibitors cause sensorineural hearing loss remains uncertain.

The evidence for an association between tinnitus and PDE5 inhibitor exposure is based on a small number of case reports, some of which were associated with sensorineural hearing loss. In a study by Manna et al,[127] the authors reported 9 patients who had an association between PDE5 inhibitor use and hearing loss. Two (22%) of the 9 experienced tinnitus. Among prospective multipatient studies, there was no significant association between PDE5 inhibitor use and ototoxicity. As stated in package inserts,[122] "it is not possible to determine whether hearing loss and/or tinnitus are related directly to the use of PDE5 inhibitors or to other factors."

Melanoma

Several investigations have addressed the possible relationship between PDE5 inhibitor use and increased risk for skin cancers, particularly malignant melanoma. Overall, the available findings fail to convincingly satisfy most of Hill's causal criteria (ie, strength, consistency, specificity, temporality, biological gradient in which higher levels of exposure increase risk, and plausibility) for determining whether an epidemiological association constitutes a causal relationship. A study by Wayne et al[128] failed to show any increase in melanoma associated with PDE5 inhibitor use. The American Urological Association guidelines state that these data indicate that there is no increased risk of skin cancers reliably associated with PDE5 inhibitor use.[73]

Prostate cancer recurrence

Several studies have focused on the possible relationship between PDE5 inhibitor use after prostate cancer treatment and an increased risk of prostate cancer recurrence.[129-131] One study by Danley et al[132] suggested that PDE5 inhibitors were associated with a decrease in prostate cancer recurrence. The American Urological Association guidelines state that these data indicate that there is no increased risk of prostate cancer recurrence associated with PDE5 inhibitor use after prostate cancer treatment.[73]

Potential CV benefits and low rates of CV events in recent retrospective/observational studies

PDE5 inhibitors were initially developed for cardiac problems such as angina pectoris, but it was the serendipitous finding of improved erections that became their first indication. There were some basic science findings suggesting that these drugs may have CV-protective features, and it is well known that PDE5 is found not only in the blood vessels supplying the genitals, but also throughout the body. The enzyme can cause systemic vasodilation and can improve endothelial function. Desouza et al[133] determined the acute and prolonged effects of low-dose sildenafil (25 mg) on flow-mediated vasodilation of the brachial artery in men with type 2 diabetes with ED. Oral sildenafil both acutely and chronically improved flow-mediated vasodilation. The effect persisted at least 24 hours after the last dose. Another report by Rosano et al[134] noted the positive effects of the long-acting PDE5 inhibitor tadalafil on endothelial function. Thirty-two patients with increased CV risk received either tadalafil 20 mg on alternate days or matching placebo for 4 weeks; then, the patients had endothelial function assessed by evaluation of brachial artery flow-mediated dilation studies. Tadalafil treated participants showed improved flow-mediated vasodilation (from 4% to 9%; $P < .01$) compared with placebo (4% to 4%); the benefit was sustained at 6 weeks. These benefits were associated with an increase in nitrite/nitrate plasma levels and a decrease in endothelin-1 levels. The authors concluded that chronic therapy with the PDE5 inhibitor tadalafil improved endothelial function regardless of their degree of ED. This study set the stage for analyses of the effect of PDE5 inhibitors on major adverse cardiovascular events (MACE) and mortality.

Additional reports have been published suggesting that PDE5 inhibitors may have cardioprotective effects and are safe from a CV perspective (Table 4). In 2008, Gazzaruso et al[16] published an article following type 2 diabetic patients with silent CAD and observed that the prevalence of ED was greater in those who developed major adverse cardiac events; ED predicted MACE (HR, 2.1; 95% CI, 1.6-2.6; $P < .001$). Among patients with CAD plus ED, statin plus PDE5 inhibitor use was associated with lower rates of MACE. Treatment with PDE5 inhibitors was borderline significant for lower MACE (HR, 0.68; 95% CI, 0.46-1.01; $P = .056$). More recent observational/retrospective analyses have confirmed that PDE5 inhibitors may be protective in diabetic patients. Anderson et al[135] showed in 2016 that in a series of nearly 6000 men with type 2 diabetes, those prescribed PDE5 inhibitors experienced lower risk of all-cause mortality (HR, 0.69; 95% CI, 0.64-0.79; $P < .001$); this reduction persisted after accounting for a number of confounding variables. PDE5 inhibitors also showed a lower rate of incident MIs and lower rates of mortality with infarction. Hackett et al[136] studied 857 men with diabetes and stratified them by normal testosterone levels, low testosterone levels, PDE5 inhibitors treated vs nontreated, and statin untreated vs treated. Age, low testosterone (treated), PDE5 inhibitor treated, and statin treated were associated with lower mortality.

There have also been observational/retrospective studies suggesting that PDE5 inhibitors may be cardioprotective in men with known CAD and previous MI. In a 2017 article, Andersson et al[137] assessed a Swedish nationwide cohort of men (>43 000), of whom 7.1% had ED medication dispensed.

Table 4. Retrospective studies supporting CV safety/benefits of PDE5 inhibitors.

Study	Study population	Study design/data collection	Main findings
Anderson 2016[135]	UK men 40-89 years of age with T2DM.	PDE5 users (n = 1359) compared with nonusers (n = 4600).	PDE5 users had lower MI and mortality rates vs nonusers (25.7% vs 40.1%) over 7 y.
Andersson 2017[137]	Swedish men less than 80 years of age with MI.	Men taking PDE5 inhibitors (n = 2814) vs men taking alprostadil (n = 254).	PDE5 users had lower mortality (33%) and reduced hospitalization for heart failure. No effect for alprostadil.
Hackett 2017[136]	UK men 18-80 years of age with T2DM.	Subanalysis of data from a large trial. Men on PDE5 inhibitor (n = 175) vs nonusers (n = 682).	Lower mortality in PDE5 inhibitor users compared with TRT and nonusers.
Vestergaard 2017[141]	Danish men 40-80 years of age with ED.	Men taking PDE5 inhibitor (n= 71 000) compared with general male population of Denmark.	Significant reduction in MI and heart failure rates with PDE5 inhibitor use but only for the first 3 y of follow-up.
Andersson 2021[138]	Swedish men 18-80 years of age with stable CAD and ED.	Men taking PDE5 inhibitor (n = 16 548) vs men taking alprostadil (n = 1994).	Significant reduction in all CV outcomes for PDE5 users vs alprostadil use.
Nunes 2021[7]	U.S. men >21 years of age in a commercial database.	Men taking PDE5 inhibitor plus nitrate vs men taking nitrates or PDE5 inhibitor alone.	No increase in CV events or adverse outcomes in PDE5 inhibitor + nitrate users.
Nunes 2022[143]	U.S. men >21 years of age in a commercial database.	Men taking tadalafil + anti-HTN meds.	No increase in CV events or adverse outcomes with tadalafil + HTN meds
Wilton 2021[140]	U.S. men with RA and control individuals.	Men with RA + ED (n = 260) taking PDE5 inhibitor vs control individuals.	Significant decrease in death rate for men taking PDE5 inhibitor; trend toward lower incidence of CV events.
Goberdhan 2022[139]	U.S. men with LUTS and MACE in a large research database.	Men taking tadalafil alone (n = 5004) compared with tadalafil with α-blocker or α-blocker only (n = 327 482).	Tadalafil use associated with decreased risk of MACE regardless of prior or current use of α-blockers.
Kloner 2023[142]	U.S. men >21 years of age without MACE in past year.	Men taking PDE5 inhibitor between 2006 and 2020 (n = 23 816) compared with nonusers (n = 48 682).	PDE5 inhibitor users had lower incidence of MACE, CV-related death, and all-cause mortality. Dose-response effect.

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; ED, erectile dysfunction; HTN, hypertension; LUTS, lower urinary tract symptoms; MACE, major adverse cardiac events; MI, myocardial Infarction; PDE5, phosphodiesterase type 5; RA, rheumatoid arthritis; T2DM, type 2 diabetes, TRT, testosterone replacement therapy.

Men treated for ED had a 33% lower mortality rate and a 40% lower rate of heart failure hospitalization compared with those not treated. Treatment for ED was associated with a lower rate of both CV and non-CV death. The adjusted risk of death was observed to be lower with PDE5 inhibitors compared with treatment with alprostadil. A follow-up study from the same author group[138] studied all Swedish men with a prior MI or revascularization who received either a PDE5 inhibitor to treat ED or alprostadil for ED.[138] There were 16 548 men who received PDE5 inhibitors and 1994 men who received alprostadil, with a mean follow-up of 5.8 years. Those men receiving PDE5 inhibitors had lower rates of mortality compared with alprostadil (HR, 0.88; 95% CI, 0.79-0.98 with multivariable adjustments); a 19% lower rate of MI; and lower rates of hospitalizations for heart failure, CVDs, and revascularization. Those men receiving the highest quintiles of PDE5 inhibitors had the lowest rates of all-cause mortality. There also have been observational studies suggesting reduced adverse cardiac events in men receiving PDE5 inhibitors for ED in subgroups of men with lower urinary tract symptoms[139] and in men with ED and rheumatoid arthritis.[140]

A study by Vestergaard et al[141] assessed the risk of CVD for men receiving ED medicines in a large nationwide cohort study in Denmark; it included 71 710 men receiving their first ED medicines from 2000 to 2012. In the first 3 years of treatment, adjusted risk for overall CVD in the ED-treated cohort was lower in the first 3 years compared with the general male population (relative risk, 0.92; 95% CI, 0.87-0.97; P = .003); the benefit was lost after 3 years. There was a persistent lower risk of MI; the risk of heart failure was lower during the first 3 years. Our research group recently reported the results of a retrospective study assessing a large integrated medical and pharmacy claims data base of >70 000 men with ED comparing those treated with PDE5 inhibitors vs those not exposed, correcting for baseline variables and examining outcomes over a 15-year period.[142] The overall incidence of major adverse CV events was 13% lower in the PDE5 exposed vs nonexposed men (HR, 0.87; 95% CI, 0.79-0.95; P = .001), and there was a 25% lower incidence of all-cause mortality (P < .001) in PDE5 exposed vs nonexposed group, a 15% lower rate of need for coronary revascularization, a 17% lower rate of heart failure, a 22% lower rate of unstable angina, and a 39% lower rate of CV mortality (all statistically significant). Kaplan-Meier curves showed that the curves for the PDE5 inhibitor–exposed group continued to separate from the unexposed group over 150 months. In men with no history of known CAD but with risk factors for CAD, the findings were similar. In men with diabetes the incidence of MACE was 21% lower with PDE5 inhibitor exposure. In the main cohort of men with ED, those receiving the highest doses of PDE5 inhibitor had the lowest rates of MACE, MI, and stroke compared with those on the lowest doses.

Taken together, the studies described previously suggest that PDE5 inhibitors may have cardioprotective effects and might play a role in preventative cardiology in the future. However, these studies have limitations including the fact that they are retrospective, showing an association between PDE5 inhibitors and improved outcomes but not proving

causality of the benefit of the PDE5 inhibitors, which would require a prospective randomized controlled study. In addition, unknown confounders could play a role. Is the benefit a direct effect of the pharmacology of the PDE5 inhibitors or the sexual activity that is protective? Further prospective studies are needed to address this question. The dose response seen in the Anderson et al[138] and Kloner et al[142] studies, and the fact that the PDE5 inhibitors but not alprostadil were protective, but both enable sexual activity, does suggest that the PDE5 inhibitors themselves may be cardioprotective. Potential mechanisms for this include improvement in endothelial function, vasodilation with small reductions in BP and afterload, a direct protective effect on the myocardium, and anti-inflammatory and antiplatelet effects.

These studies support the concept that the PDE5 inhibitors are safe from a CV standpoint and support several other recent publications made available since P3, which confirm their CV safety in large numbers of patients (Table 4).[7,135-143]

Regulatory and public health perspectives

The P4 panel considered 2 broad issues of concern regarding the regulatory status of PDE5 inhibitors. These were the following:

Marketing of dietary supplements with PDE5 inhibitor components

In 1994, the U.S. Congress passed into law the U.S. Dietary Supplement Health and Education Act (DSHEA). This Act of Congress defines dietary supplements (DS) as foods, not as pharmaceutical products or drugs. Accordingly, DS manufacturers are not subject to the evidentiary processes and procedures which regulate the pharmaceutical industry. As a result of the legislation and, more recently, the profound impact of internet marketing, the number of DS has increased exponentially from about 4000 products in 1994 to over 75 000 products in 2023. Annual consumer spending on supplements has increased from about $4 billion in 1994 to approximately $50 billion in 2022. Unfortunately, consumers all too often assume that if a DS is publicly advertised, the supplement has been reviewed, tested, and approved by a legitimate health authority as being safe and/or efficacious. Unfortunately, vetting of DS is not required under DSHEA and is not performed.

Some supplements have nutritional or possible health benefits, while others have minimal or no value, and some may entail risk of adverse events. Regrettably, there are remarkably few data on the incidence of adverse events related to the use of supplements. Based on a 2015 study reported in the *New England Journal of Medicine*,[144] there were 23 005 annual emergency department visits due to adverse events from DS in the years 2004 through 2013. These visits resulted in over 2000 hospitalizations annually. The most common DS that caused adverse events were products marketed for sexual dysfunction, decreased energy, and weight loss. Since 2015, the incidences of adverse events and resulting hospitalizations due to DS are likely to have increased, along with the substantial increase in use of these supplements.

Of importance to the P4 panel, it was noted that some DS may be adulterated and may contain therapeutic levels of known pharmaceutical agents. Although supporting data are needed, it is to be expected that some if not many DS being marketed for male impotence or ED contain significant amounts of PDE5 inhibitors. There are some published data from at least 1 study.[145] Between 2007 and 2016, the FDA reported on 776 adulterated products which had been manufactured separately by 146 different companies. Of these adulterated products, **45% were products intended for enhancement of sexual activity and 47% contained sildenafil**.

The panel noted the implications of these findings, and the potential risks for consumers. From a CV perspective, a DS clandestinely adulterated with a PDE5 inhibitor and being used by someone (man or woman) simultaneously taking an organic nitrate drug for angina pectoris could cause serious hypotension, syncope, acute MI, and/or sudden cardiac death. Because there is no oversight of labeling of DS products, there is no incentive for companies marketing the products to properly notify users of the risks. This could in turn have important public health implications. The panel noted some action steps that might be taken to address this concerning situation. Steps that might reduce the risks of fraudulent DS adulteration and misleading advertising include the following:

1. Political and legislative efforts to increase funding for the FDA and the Federal Trade Commission to often perform spot reviews of DS contents and marketing of DS. The scope and impact of the problem needs to be defined more clearly.
2. Modify and upgrade the 29-year-old DSHEA (1994) mandate to meet modern standards of computer-based development, production and marketing of DS.
3. Improve efforts by the DS industry to police itself for DS adulteration and fraudulent advertising.
4. Marketing research to understand whether making PDE5 inhibitors available to the public without a prescription would satisfy consumers' desire for access to effective ED treatment, thereby lessening consumers' appetite for sexual performance-enhancing DS, some of which may dangerously contain undeclared PDE5 inhibitors.

Should PDE5 inhibitors be available without prescription? Is it time for FDA to consider this change in status, and the implications for consumers and health practitioners?

Given comprehensive and long-term data on use of PDE5 inhibitors in the general population, there are arguments in favor of changing the regulatory status of these drugs to over-the-counter (OTC) status. The rationale for this includes broad potential benefits in patient quality of life, reduced costs to consumers, and other benefits of the drug class to a larger number of men and their partners. Recent exposure to telemedicine and internet based prescribing companies are adding to this pressure. Such a change could have expected or unanticipated ripple effects, although there are tangible benefits to be anticipated.

Experience from other countries can be informative. For example, the United Kingdom has recently taken steps to move PDE5 inhibitors to pharmacy available by the reclassification of PDE5 inhibitors to pharmacy medicine status (P-medicine), requiring only an interaction with a pharmacist.[146] In assessing long-term outcomes associated with this status change, investigators noted that men accessing sildenafil-P had a higher number of healthcare providers (HCPs) and pharmacist visits for any reason than controls. Encouragingly, sildenafil-P use was also associated with higher sexual and nonsexual quality-of-life ratings, as well as HCP visits in men

obtaining sildenafil-P according to the UK regulations. These results are encouraging in suggesting broad benefits associated with the change in status of PDE5 inhibitors in the United Kingdom. In summary, the panel recommended consideration of the following if regulatory changes are to be made:

1. The recent experience in the United Kingdom with reclassification of PDE5 inhibitors to P-medicine was associated with a higher number of HCP and pharmacist visits for any reason in men accessing the medicine as such. It is assumed that such increased engagement between men and HCPs will lead to improved health outcomes, although this has yet to be demonstrated in a prospective study.
2. Evidence from clinical trials shows that patients who use PDE5 inhibitors report better quality of life and partner relationships, in addition to improved mood and self-esteem. As part of the initial P-medicine experience men on PDE5 inhibitors were noted to have a higher total and domain (sexual relationship and self-esteem) score on the Self-Esteem and Relationship (SEAR) questionnaire and better quality of life.
3. As noted previously, men increasingly purchase adulterated DS to improve their putative ED. Part of this risky behavior is attributed to a relatively high bar in accessing PDE5 inhibitors given the current U.S. prescribing protocols. If PDE5 inhibitors were switched to an easier access process (OTC), then patient safety would potentially be improved, as men would be encouraged to source their medication through more controlled and reliable channels. This would need to be monitored to ensure manufacturing quality.
4. Recent retrospective reports reveal evidence of cardioprotection (lower MACE, CV death, and overall mortality risk), based on the level of PDE5 inhibitor exposure.[142] Should PDE5 inhibitors move to an OTC setting, then it is likely that PDE5 inhibitor–related cardioprotection would be seen at the population health vantage point.
5. Optimal pharmacologic management of diseases comorbid with ED, such as CVD, depression, diabetes, dyslipidemia, and hypertension, is dependent on long-term treatment compliance and may be complicated by poor adherence to medication use.[147] Concomitant ED management may improve treatment outcome, decreased healthcare costs, and possibly prevent or even improve deterioration in medical conditions comorbid with ED. Because ED is a silent marker and predictor of such comorbidities, especially CVD, earlier diagnosis of ED may provide an opportunity to prevent future CV events. Should PDE5 inhibitors move to an OTC setting then it is likely that compliance with other drugs that may adversely affect erectile function will improve in a much broader population of men.

Risks of OTC availability of PDE5 inhibitors

The panel noted 2 potential risks that would need to be taken into account with an OTC switch:

1. Nitrates remain an absolute contraindication to PDE5 inhibitor use. If PDE5 inhibitors move to an OTC setting, then it is possible that some men will gain access to this class of medication (despite whatever warnings, labeling, and other safeguards that are employed), coadministrated with nitrates resulting in nitrate–PDE5 inhibitor–related CV events.
2. Abuse of the PDE5 inhibitor class is more likely among younger and recreational users. If PDE5 inhibitors moved to an OTC setting, it is possible that some men would gain inappropriate access to this class of medication and that significant adverse events might occur. Again, this would need to be monitored over time.

Therapies for ED beyond PDE5 inhibitors

Restorative therapy for ED: stem cells, platelet-rich plasma, and shock waves

Not all men with ED are candidates for PDE5 inhibitors due to contraindications, underlying heart disease, or in some cases, lack of efficacy. The next 2 sections review potential other therapies either in development or already on the market. The currently available ED treatments, such as a PDE5 inhibitor, vacuum erection device, penile injection, urethral insert, or penile prosthesis do not correct the pathological deficits that underlie ED. Regenerative medicine is a field that focuses on the development of therapies that can regenerate or replace damaged or diseased tissues and organs. This is achieved through a range of approaches, including stem cell therapy, tissue engineering, gene therapy, and other innovative techniques.[148] To address restorative therapies of ED, we only discuss stem cells, platelet-rich plasma (PRP), and shock waves.[149]

In stem cell therapy for ED, the 2 main types of stem cells used for ED are adipose-derived stem cells and bone marrow–derived stem cells.[150,151] The mechanism of action of stem cell therapy for ED is thought to involve several different pathways, including neovascularization, anti-inflammatory effects, tissue regeneration, and neuroprotection by the paracrine effects of the injected stem cells. A review of 7 published clinical phase 1 or phase 1/2 clinical trials found no significant adverse effects associated with the therapy. Some improvements in erectile function, as measured by the International Index of Erectile Function (IIEF) score, were reported, but the number of patients in each study is small. At the current time, stem cell therapy for ED should be considered experimental and investigational.

In PRP therapy for ED, the PRP contains various growth factors and cytokines that have been shown to have regenerative and healing properties.[152,153] The proposed mechanisms of action of PRP therapy include growth factor release, anti-inflammatory effects, recruitment of stem cells, neovascularization, and immune modulation. In a review by Anastasiadis et al,[152] one double-blinded placebo-controlled study reported a minimal clinically important difference in IIEF Erectile Function scores, but the number of patients in each group comprised only 30 men with mild-to-moderate ED.[152] A very recent report of a randomized, prospective placebo-controlled study did not show that PRP improved mild-to-moderate ED.[154] More studies are needed to establish safety and efficacy of this potential therapy.

Low-intensity extracorporeal shock wave therapy (Li-ESWT) has shown efficacy in some studies for ED.[155-157] It is thought to work through several different mechanisms, including neovascularization, improvement of endothelial function, anti-inflammatory effects, neural regeneration, and activation of penile tissue-resident stem cells.[158-161] In a

meta-analysis of 16 randomized controlled trials comprising 1064 participants, the efficacy was evaluated by standard methodology. Results of the IIEF questionnaire and Erectile Hardness Score were both improved after treatment.[149] The overall mean difference in IIEF scores was 3.18 (95% CI, 1.38-4.98), less than the generally accepted minimal clinically important difference of 4. The positive response rate on questions 2 and 3 of the Sexual Encounter Profile was not statistically significant. Overall, because of the heterogeneity among these studies, the true efficacy of Li-ESWT cannot be determined at this time.

Regarding future implications, restorative therapies for ED have shown promising results in preclinical and clinical studies.[162] However, none of the previously mentioned therapies has been approved by the FDA for ED. The American Urological Association considers Li-ESWT and stem cell therapy to be investigational and PRP to be experimental. The European Association of Urology determined that there is weak evidence supporting Li-ESWT in patients with mild ED as a first-line therapy and insufficient evidence to recommend stem cell or PRP. Overall, the field of restorative therapy for ED is rapidly evolving, and ongoing research is needed to determine the safety, efficacy, and accessibility of these therapies for patients with ED.

Second line therapy

For patients who cannot tolerate PDE5 inhibitors, because of cost or side effects, or for those for whom PDE5 inhibitors are contraindicated such as, nitroglycerin or guanylate cyclase stimulator users, and for patients with serious retinal conditions, including macular degeneration or retinitis pigmentosa, second-line therapies play a vital role.

Intracavernosal injection therapy

Intracavernosal injections involve injecting vasoactive medications directly into the corpora cavernosa. Intracavernosal papaverine was introduced in 1982 by Virag[163] followed in 1983 by a report on phenoxybenzamine by Brindley.[164] Currently, PGE1 and or papaverine with/without phentolamine are the main agents used.

The injections are usually self-administered using a tiny (27-30 g) needle. The vasorelaxant medication increases arterial inflow, resulting in an erection. In-office training is necessary to ensure appropriate technique, minimizing side effects and maximizing efficacy. Intracavernosal injections should be used with caution in men with poor vision, with poor manual dexterity, and at increased risk of priapism, and are contraindicated in men using monoamine oxidase inhibitors.

Penetration hardness rates are as high as 80% to 90%.[73] The onset of erection is typically within 5 to 10 minutes after the injection, which can last for up to an hour or more. It is most effective in men who have healthy cavernosal smooth muscle.

Common side effects include discomfort and bruising at the injection site, priapism (0.5%-5%), and some believe fibrosis of cavernosal smooth muscle.

Intraurethral vasoactive agents

The delivery of vasoactive agents into the corpus spongiosum has been shown to induce erection. The first such transurethral agent received FDA approval in 1997 (Muse; Viatris).[165]

This strategy entails the application of a small suppository into the urethra (3 doses: 250, 500, or 1000 μg).[73] After urinating, the patient stays standing and inserts a tiny PGE1-containing pellet into the distal urethra. The medication is transferred via venous channels from the corpus spongiosum into the corpora cavernosa.

Approximately 40% of patients are considered responders.[165] Its limitation is a lack of spontaneity, given the fact that the patient needs to void, stand, administer the suppository and then massage the penis and stay standing for some period of time (10-15 minutes). The purpose of this is to dilate the venous channels between the corpus spongiosum and cavernosum to permit absorption of the medication.

The risk of priapism is very low (<5%). Urethral bleeding (<5%), vaginal irritation (1%), and PGE1-mediated penile pain have also been reported in certain populations (penile autonomic neuropathy), and rare syncopal episodes have also been reported.

Vacuum devices

Vacuum erection devices operate on the principle of creating negative pressure around the penis, drawing blood into the corpora cavernosa to generate a rigid erection.[73]

A manual or battery-operated pump is used to remove the air from the cylinder, which is placed over the penile shaft, creating a vacuum. This causes mixed venous blood to fill the corpora in a retrograde fashion resulting in an erection.[73] A constriction band or tension ring is then placed at the base of the penis to maintain the erection.

Vacuum devices have success rates (erection sufficient for sexual intercourse) ranging from 60% to 90%.[73] They are contraindicated in men who have penile sensation loss or cognitive impairment, lest the constriction ring used with these devices is left on the penis for excessive periods of time, resulting in penile gangrene. Generally, the constriction ring should stay on for no longer than 30 minutes.

Penile discomfort, bruising, temporary numbness, coolness, or color changes in the penis can occur, all related to the constriction band.

Penile implant surgery

Penile implant (prosthesis) surgery is typically recommended for individuals with severe or irreversible ED unresponsive to other treatments. It may also be considered for those with anatomical abnormalities, such as Peyronie's disease, associated with ED.[73]

A prosthetic device is placed into the corpora cavernosa to induce an erection. There are 2 main types of penile implants: inflatable and semi-rigid (malleable). Inflatable implants consist of 2 cylinders that are implanted in the penis, a pump placed in the scrotum, and a reservoir of fluid placed in the extraperitoneal space. By squeezing the pump, the cylinders fill with fluid and create an erection. Semi-rigid implants, on the other hand, consist of bendable rods that are permanently implanted in the penis, allowing the user to manually position the penis for sexual activity.

Penile implants result in fully rigid erections usually in less than half a minute. Most men report high levels of satisfaction (65%-90%).[73]

Complications include infection (3%); bleeding, pain, scarring, or device malfunction (20% at 10 years); or erosion.

Topical therapy

Topical treatments are portrayed to offer a noninvasive, easily administered, well-tolerated and fast-acting treatment option for ED. A recent FDA approved, OTC product, Eroxon is a specialized, nonmedicated, hydroalcoholic gel formulation. It is applied directly to the head (glans) of the penis, exerting a rapid cooling-warming effect on the skin that supposedly stimulates local nerve endings involved in the erection response. Controlled clinical trials demonstrated its significant benefits: rapid onset (erection response within 10 minutes), efficacy (minimally clinical important difference of 5.73 units by IIEF Erectile Function score at 24 weeks vs baseline), and safety (no serious adverse events) (A. Burnett, MD, personal communication; June 12, 2023). In addition, a topical glyceryl trinitrate formulation was shown to be efficacious for ED.[166]

PDE5 inhibitors in women: treatment of FSD and other indications

FSD definitions, clinical presentations, and treatments were presented at the P4 meeting. The purpose of discussing FSDs was to provide context for understanding the role of PDE5 inhibitors in the treatment paradigms for female arousal disorders and other FSDs. Addressing partner sexual function was viewed by the panel as integral to the clinical assessment of ED. Partner assessment might include domains of (1) communication (eg, "Have you spoken with your partner about your erection problem?"), (2) emotional response/supportiveness (eg, "Is your partner supportive of your seeking treatment to improve your erection?"), (3) treatment concerns (eg, "Does your partner have any concerns or anxiety about the treatment?"), and (4) partner function or FSD (eg, "Would your partner like to talk with me or another clinician about improving your sex life together?"; "Do you know if your partner has any concerns about their own sexual function, pain with sexual activity, or about any other related health issues?") (adapted from Dean et al).[167]

Diagnostic and treatment guidelines for FSD

Sexual dysfunctions in women are often chronic conditions that affect the 3 phases of the sexual response cycle (desire, arousal, and orgasm) and/or are associated with sexual pain. Their etiology is commonly multifactorial with biological, psychological, interpersonal, social, and cultural risk factors and contributors. The optimal biopsychosocial approach to FSDs includes the identification and management of modifiable contributing factors and employs evidence-based pharmacological and nonpharmacological therapies.[168] Because pharmacological approaches have included trials of PDE5 inhibitors in women, both for sexual and nonsexual indications, a consideration of the safety and efficacy of PDE5 inhibitors in women and the cardiac implications were considered in depth by the panel.

Efficacy of PDE5 inhibitors in women

PDE5 inhibitor therapy has been used to treat various conditions in women, including sexual dysfunctions, pulmonary artery hypertension (PAH) , Raynaud's phenomenon, infertility, preeclampsia, and fetal growth restriction. Several randomized, double-blind, placebo-controlled trials have assessed the efficacy of sildenafil in treating FSDs. In one large trial that included pre- and postmenopausal women, sildenafil did not improve physical response during sexual activity or the ability to participate in sexual activity.[169] In subanalyses, no differences were observed between estrogenized and estrogen-deficient women. However, while all women were diagnosed with female sexual arousal disorder (FSAD), this trial included women with concomitant desire, orgasm, and sexual pain disorders. FSAD was identified as the primary presenting problem in less than half (48%) of study subjects. Thus, the interpretation of these findings was complicated by the inclusion of women with multiple sexual dysfunctions, the majority of whom did not report FSAD as their most important problem. In a meta-analysis of 14 placebo-controlled studies, data were grouped into subanalyses, dependent on outcome measures that were assessed.[170] Use of PDE5 inhibitors resulted in statistically significant improvements in sexual desire (2 of 5 studies), arousal (8 of 9 studies), orgasm (5 of 7 studies), and satisfaction (3 of 5 studies) compared with placebo. Thus, while findings from individual studies were equivocal, pooled data from meta-analyses suggest that treatment with PDE5 inhibitors could be an effective treatment option for several types of FSD. PDE5 inhibitors may also be effective in treating women with antidepressant-induced sexual dysfunction. In a randomized, double-blind, placebo-controlled study, flexible dosing of sildenafil (50-100 mg) significantly improved overall sexual function (Clinical Global Impression) in premenopausal women being treated with nonselective serotonin reuptake inhibitors with arousal and/or orgasm impairment after 8 weeks.[171] However, in a larger double-blind, placebo-controlled, flexible-dose study in women with spinal cord injury and FSAD, sildenafil treatment resulted in no clinically meaningful benefit.[172] Thus, consideration of the multidimensional aspects of sexual function and appropriate selection of patients are important in treating women with sexual dysfunction.

To date, PAH is the only indication approved by the FDA for PDE5 inhibitor use in women. Both sildenafil and tadalafil therapy increased 6-minute walk distance over baseline that was significantly greater than placebo.[173,174] While the trials in PAH patients included both men and women, 75% of the sildenafil PAH study and 78% of the tadalafil PAH study subjects were women. Limited data indicate that women with PAH may derive less benefit from PDE5 inhibitor therapy than men with PAH.[175] However, the underlying reasons for this potential difference remain unclear.

Raynaud's phenomenon is another condition that has greater prevalence in women.[176] Despite their off-label use, PDE5 inhibitors have become established in management algorithms for primary or secondary Raynaud's phenomenon.[177] In meta-analyses of 6 randomized controlled trials that included treatment of secondary Raynaud's phenomenon with sildenafil (2 trials), tadalafil (3 trials), and vardenafil (1 trial), PDE5 inhibitor therapy significantly reduced the mean Raynaud's condition score and also decreased the frequency and duration of ischemic episodes.[178] Overall, PDE5 inhibitors were deemed to have statistically significant but moderate efficacy in treating secondary Raynaud's symptoms in a combined cohort that was 84% female (4 out of 6 trials reported the number of female participants). On-demand sildenafil has also been observed to consistently improve Raynaud's symptom score in a small case series of 38 patients (74% female), although the clinical relevance of these changes remained questionable due to substantial heterogeneity of the study cohort.[179]

Table 5. AEs associated with PDE5 inhibitor therapy in clinical trials in women.

AE	PDE5 inhibitor	Placebo	Rate difference	Comments
Gao et al, 2016[170]				
Flushing	22.3 (775)	3.8 (497)	18.5	• Meta-analysis of 14 placebo-controlled trials
Headache	20.9 (896)	8.1 (618)	12.8	• Women with different sexual dysfunctions ± comorbidities
Vision changes	5.9 (817)	1.1 (544)	4.8	• Oral sildenafil, 10-100 mg, prn
Basson et al, 2002[169]				• 1 d to 24 wk treatment duration
Estrogenized women				• Double-blind, randomized, placebo-controlled trial
Flushing	20.9 (426)	1.3 (151)	19.6	• Premenopausal and postmenopausal women with female sexual
Headache	17.8 (426)	4.6 (151)	13.2	arousal disorder with other concomitant sexual dysfunctions
Rhinitis	5.4 (426)	0.7 (151)	4.7	• Oral sildenafil, 10-100 mg, taken as needed
Visual disturbances	5.4 (426)	0.7 (151)	4.7	• 12-wk parallel treatment period
Nausea	2.6 (426)	2.0 (151)	0.6	• Median number of doses = 15-21
Dyspepsia	1.9 (426)	0.0 (151)	1.9	
Estrogen-deficient women				
Headache	40.0 (103)	11.9 (101)	28.1	
Flushing	33.0 (103)	6.9 (101)	26.1	
Rhinitis	17.5 (103)	1.0 (101)	16.5	
Dyspepsia	4.9 (103)	0.0 (101)	4.9	
Visual disturbances	4.9 (103)	2.0 (101)	2.9	
Nausea	3.9 (103)	2.0 (101)	1.9	
PAH pivotal trials				
Sildenafil (AEs ≥ 3%)[174]				
Nasal bleeding	9 (69)	1 (70)	8	• Randomized, double-blind, placebo-controlled trial
Headache	46 (69)	39 (70)	7	• Patients with pulmonary arterial hypertension, WHO functional
Dyspepsia	13 (69)	7 (70)	6	class II or III; 75% women
Flushing	10 (69	4 (70)	6	• Oral sildenafil, 20 mg, three times a day
Insomnia	7 (69)	1 (70)	6	• 12 wk treatment duration
Erythema	6 (69)	1 (70)	5	
Dyspnea	7 (69)	3 (70)	4	
Rhinitis	4 (69)	0 (70)	4	
Diarrhea	9 (69)	6 (70)	3	
Myalgia	7 (69)	4 (70)	3	
Pyrexia	6 (69)	3 (70)	3	
Gastritis	3 (69)	0 (70)	3	
Sinusitis	3 (69)	0 (70)	3	
Paresthesia	3 (69)	0 (70)	3	
Tadalafil (AEs ≥9%)[173]				
Headache	42 (79)	15 (82)	27	• Randomized, double-blind, placebo-controlled trial
Flushing	13 (79)	2 (82)	11	• Patients with pulmonary arterial hypertension, WHO functional
Myalgia	14 (79)	4 (82)	10	class II or III; 78% women
Pain in extremity	11 (79)	2 (82)	9	• Oral tadalafil, 40 mg, once a day
Dyspepsia	10 (79)	2 (82)	8	• 16 wk treatment duration
Nasal congestion	9 (79)	1 (82)	8	
Respiratory tract infection	13 (79)	6 (82)	7	
Nasopharyngitis	13 (79)	7 (82)	6	
Nausea	11 (79)	6 (82)	5	
Back pain	10 (79)	6 (82)	4	
Ferreira et al, 2019[181]				
Headache	37.0 (135)	29.2 (144)	7.8	• Meta-analysis of 7 studies • Pregnant women with preeclampsia, intrauterine growth restriction, oligohydramnios • Sildenafil, 25-80 mg, tid or qd • Dosing duration from recruitment at 22-30 wk of pregnancy through delivery
Turner et al, 2022[182]				
Nasal bleeding	6.6 (151)	0.0 (152)	6.6	• Meta-analysis of 10 randomized, placebo-controlled trials
Headache	21.4 (416)	16.0 (420)	5.4	• Pregnant women treated for fetal growth restriction, preeclampsia,
Flushing	5.9 (389)	1.0 (400)	4.9	and prevention of operative birth for intrapartum fetal compromise
Rhinitis	4.6 (108)	0 (108)	4.6	• Sildenafil, 50-3788 mg/d (8 trials)
Nausea/vomiting	13.2 (395)	9.1 (408)	4.1	• Tadalafil, 350-926 mg/d (2 trials)
Palpitations	4.3 (163)	1.2 (166)	3.1	• Initiation of treatment at <37 wk gestation, mean duration of 23 d
Arthralgia	4.0 (177)	1.6 (188)	2.4	
Dizziness	5.0 (282)	3.1 (287)	1.9	
Diarrhea	1.9 (369)	2.2 (372)	−0.3	
Visual disturbances	4.3 (326)	5.2 (328)	−0.9	
Gastritis	6.1 (261)	7.6 (264)	−1.5	

Values are % (n), unless otherwise indicated. Abbreviations: AE, adverse event; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; WHO, World Health Organization.

PDE5 inhibitors are also increasingly used in women to treat infertility and during pregnancy to treat both maternal and fetal conditions. In a meta-analysis of 12 randomized controlled trials, endometrial thickness was improved in women undergoing ovarian stimulation and taking oral sildenafil in doses ranging from 25 to 75 mg/d.[180] However, clinical and chemical pregnancy rates were increased only in women engaging in timed intercourse vs in vitro fertilization or intrauterine insemination.[181] In pregnant women with preeclampsia and/or intrauterine growth restriction or oligohydramnios, a meta-analysis of 7 placebo-controlled studies demonstrated that oral sildenafil (20-80 mg/d), initiated at 24 to 30 weeks' gestational age, resulted in significantly greater abdominal circumference growth velocity or fetal weight at birth.[182] Analyses of other outcomes (eg, umbilical artery pulsatility index, delivery due to fetal distress or imminent eclampsia) showed no clear benefit of sildenafil therapy.

Safety of PDE5 inhibitors in women

Across numerous independent trials studying various conditions in women, PDE5 inhibitors, used at a wide range of doses and treatment regimens, have consistently been shown to be safe.[169,170,173,174,181,182] In clinical trials evaluating PDE5 inhibitors for sexual dysfunction, PAH, and conditions associated with pregnancy, the following were reported as being among the most common adverse events that occurred in the PDE5 inhibitor group at rates greater than placebo: nasal bleeding, headache, flushing, rhinitis, nausea, visual disturbances, and dyspepsia (Table 5). As expected, rates of mild adverse events in women with various medical conditions increased with increasing PDE5 inhibitor dose. Adverse events attributed to PDE5 inhibitor therapy were transient in duration and mild to moderate in severity. Thus, PDE5 inhibitors were relatively safe with no significant CV events in women.

Recently, sildenafil has also been evaluated in heart failure patients. The SilHF (Sildenafil in Heart Failure) trial was a randomized, placebo-controlled, multicenter trial that evaluated chronic sildenafil treatment (up to 40 mg 3 times/d) for 24 weeks in male and female patients with heart failure with reduced ejection fraction and pulmonary hypertension.[183] Only 69 patients were recruited into the trial with 11 women treated with sildenafil and 2 women treated with placebo. Nevertheless, even in this high-risk cohort of patients with heart failure, the investigators reported that sildenafil had adverse event rates similar to placebo (data not shown). There was a higher proportion of discontinuations in the sildenafil group, but all cases were due to non-CV symptoms that were deemed unrelated to sildenafil therapy.

Conclusion

A number of major themes emerged from P4 that are new and that expand the findings from P3. ED is a risk marker and risk enhancer for ASCVD, and men who present with ED, especially vasculogenic ED, should have an assessment of their atherosclerotic CV risk as outlined by the ACC/AHA algorithms. Those patients at the borderline to intermediate risk for CV events should undergo CAC scoring by computed tomography scanning. The CAC score will aid in determining therapy and need to refer to a cardiologist, which is also a newer aspect of the guidelines since P3. In addition, even psychogenic ED may be a harbinger for CVD, and there should at least be an inquiry about CVD and its risk factors in men presenting with this type of ED.

The management of ED in men with CVD begins with a sexual inquiry. If ED is confirmed and treatment for ED is requested, then patients are characterized into low risk, intermediate risk or indeterminable risk, or high risk of developing a cardiac event associated with sexual activity. This risk is largely assessed by the patient's exercise ability for age and may require a stress test to assess the ability of the patient to achieve what is deemed a relatively safe exercise level (usually about 4 minutes into a standard Bruce Protocol Treadmill Test) without evidence of ischemia. If the patient has good exercise tolerance without ischemia and is classified as low risk, then ED can be treated. If the patient is not on nitrates or riociguat, then PDE5 inhibitors can be started. If the patient is on nitrates or riociguat then PDE5 inhibitors are contraindicated. However, in P4, it was recognized that many patients may have a prescription for nitrates but either are not using them or do not need them (especially if they have been revascularized by percutaneous coronary intervention or coronary artery bypass surgery and are free of angina or evidence of myocardial ischemia). So, a decision should be made by the HCPs whether nitrates are necessary or whether they may be stopped, or whether other antianginal agents may be substituted. If nitrates are not necessary, then consideration should be given to stopping them and trying PDE5 inhibitors to treat ED, a new concept added since P3. However, if it is deemed that nitrates are indeed necessary, then other non PDE5 inhibitors should be considered to treat ED. Patients who are deemed high risk for cardiac events with sexual activity or who develop ischemia during a stress test, especially at a low level of exercise, should be referred to a cardiologist for additional care.

PDE5 inhibitors continue to show CV safety after about 25 years of experience on the market. Since P3, there has also been discussions and consideration of making the PDE5 inhibitors for the treatment of ED available OTC, a concept that is still being studied by regulatory agencies.

Acknowledgments

The authors thank Sanofi for an unrestricted grant that was used to sponsor the fourth Princeton Consensus Conference meeting. Sanofi did not participate in any aspect of the planning, selection of topics, speakers, or content of the meeting. Sanofi did not participate in the writing or concepts of the current manuscript.

Author contributions

R.A.K. and R.C.R. conceived of the article, wrote the outline, and contributed to the writing of several of the sections and supervised writing and editing. A.L.B. and M.M. served on the steering committee and wrote and supervised writing and editing. The other authors all contributed to writing sections and editing.

Conflicts of interest

R.A.K. has received grant funds from and served as a paid consultant for Sanofi, unrelated to this manuscript. A.L.B. has financial relationships with the following entities: American Medical Systems, Futura Medical, the National Institutes of Health, Novartis Pharmaceuticals, and the Urology Times Editorial Council. M.M. has served as an American Urological Association Erectile dysfunction, Testosterone, and Peyronie's Guideline Panel Member, American Urological Association Prostate Cancer Screening Guideline Panel Member, Acerus Advisor/Research Investigator, and Halozyme Advisor Literature Support and consultant. P.G. has served on the medical advisory board for SomaLogic, for which he has accepted no financial remuneration of any kind; and as a scientific advisor for Riparian Pharma, which is developing a

pharmacological agent to reverse endothelial dysfunction. I.G. has been associated with Adamo Bioscience and Cynosure. N.N.K. has served as a consultant for Pfizer, Prometheus Laboratories, TriangleRX Consult, Softwave TRT, and Sprout Pharmaceuticals. T.K. has served consultant for Coloplast. T.L. is a shareholder and board member of AWCT, using modified shockwave for different indication, not erectile dysfunction related. K.T.M. has served as a principal investigator and consultant for the National Institute on Diabetes and Digestive and Kidney Diseases, ProDeon, Boston Scientific, and SRS Medical; has received a fellowship grant from Boston Scientific; has served as the DSMB Chair for Francis, Urotronic, and Zenflow; has served as a consultant for Sanofi, Urotronic, Rivermark, Zenflow; owns equity in Rivermark and Uronext; and holds a patent for Penile Prosthesis, Magnetic induction SMA. S.J.P. has served as a consultant for Dara Bioscience; an advisor for Ms. Medicine Physician Executive Group; and a lecturer for AstraZeneca Israel (unrestricted content). R.C.R. has served as a paid consultant for Sanofi Pharmaceuticals, Strategic Solutions Technology, and Huntington Medical Research Institutes. All other authors disclose no conflicts.

References

1. Goldstein I, Burnett AL, Rosen RC, Park PW, Stecher VJ. The serendipitous story of sildenafil: an unexpected oral therapy for erectile dysfunction. *Sex Med Rev*. 2019;**7**(1):115-128.
2. DeBusk R, Drory Y, Goldstein I, *et al.* Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton consensus panel. *Am J Cardiol*. 2000;**86**(2):175-181. https://doi.org/10.1016/s0002-9149(00)00896-1.
3. Kostis JB, Jackson G, Rosen R, *et al.* Sexual dysfunction and cardiac risk (the second Princeton consensus conference). *Am J Cardiol*. 2005;**96**(12b):85m-93m. https://doi.org/10.1016/j.amjcard.2005.12.018.
4. 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. https://doi.org/10.1016/j.mayocp.2012.06.015.
5. Kloner RA, Goldstein I, Kirby MG, Parker JD, Sadovsky R. Cardiovascular safety of phosphodiesterase type 5 inhibitors after nearly 2 decades on the market. *Sex Med Rev*. 2018;**6**(4):583-594.
6. Holt A, Blanche P, Jensen AKG, *et al.* Adverse events associated with Coprescription of phosphodiesterase type 5 inhibitors and oral organic nitrates in male patients with ischemic heart disease: a case-crossover study. *Ann Intern Med*. 2022;**175**(6):774-782.
7. Nunes AP, Seeger JD, Stewart A, Gupta A, McGraw T. Cardiovascular outcome risks in patients with erectile dysfunction coprescribed a phosphodiesterase type 5 inhibitor (PDE5i) and a nitrate: a retrospective observational study using electronic health record data in the United States. *J Sex Med*. 2021;**18**(9):1511-1523.
8. Arnett DK, Blumenthal RS, Albert MA, *et al.* ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;**74**(10):e177-e232.
9. Cooper A, Ferro A, Lloyd G, O'Kane P, Waring E, Citrome L. In memoriam: Dr Graham Jackson, 1947-2016. *Int J Clin Pract*. 2019;**70**(8):638-639.
10. Muller JE, Mittleman MA, Maclure M, Sherwood JB, Tofler GH. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of myocardial infarction onset study investigators. *JAMA*. 1996;**275**(18):1405-1409. https://doi.org/10.1001/jama.275.18.1405.
11. Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. *JAMA*. 2011;**305**(12):1225-1233. https://doi.org/10.1001/jama.2011.336.
12. Frappier J, Toupin I, Levy JJ, Aubertin-Leheudre M, Karelis AD. Energy expenditure during sexual activity in young healthy couples. *PLoS One*. 2013;**8**(10):e79342. https://doi.org/10.1371/journal.pone.0079342.
13. Adam A, McDowall J, Aigbodion SJ, Enyuma C, *et al.* Is the history of erectile dysfunction a reliable risk factor for new onset acute myocardial infarction? A systematic review and meta-analysis. *Curr Urol*. 2020;**14**(3):122-129. https://doi.org/10.1159/000499249.
14. Banks E, Joshy G, Abhayaratna WP, *et al.* Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalisation and all-cause mortality: a prospective cohort study. *PLoS Med*. 2013;**10**(1):e1001372. https://doi.org/10.1371/journal.pmed.1001372.
15. 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):192-202. https://doi.org/10.1111/j.1743-6109.2009.01576.x.
16. 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. https://doi.org/10.1016/j.jacc.2007.10.069.
17. 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. https://doi.org/10.4065/84.2.108.
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. https://doi.org/10.1093/eurheartj/ehl142.
19. 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. https://doi.org/10.1038/sj.ijir.3901604.
20. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005;**294**(23):2996-3002. https://doi.org/10.1001/jama.294.23.2996.
21. Uddin SMI, Mirbolouk M, Dardari Z, *et al.* Erectile dysfunction as an independent predictor of future cardiovascular events: the multi-ethnic study of atherosclerosis. *Circulation*. 2018;**138**(5):540-542. https://doi.org/10.1161/circulationaha.118.033990.
22. Clavijo RI, Miner MM, Rajfer J. Erectile dysfunction and essential hypertension: the same aging-related disorder? *Rev Urol*. 2014;**16**(4):167-171.
23. De Leonardis F, Colalillo G, Finazzi Agrò E, Miano RA-O, Fuschi A, Asimakopoulos AA-OX. Endothelial dysfunction, erectile deficit and cardiovascular disease: an overview of the pathogenetic links. *Biomedicines*. 2022;**10**(8):1848. https://doi.org/10.3390/biomedicines10081848.
24. Esposito K, Giugliano F, Di Palo C, *et al.* Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *JAMA*. 2004;**291**(24):2978-2984. https://doi.org/10.1001/jama.291.24.2978.
25. Gacci M, Andersson KE, Chapple C, *et al.* Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol*. 2016;**70**(1):124-133. https://doi.org/10.1016/j.eururo.2015.12.048.
26. Way B, Griffin K, Kraus SW, Tsai J, Pietrzak R. Erectile dysfunction in a U.S. National Sample of male military veterans. *Military Medicine*. 2023;**188**(9-10):2837–2843. https://doi.org/10.1093/milmed/usac187.

27. Huntingdon B, Muscat DM, de Wit J, Duracinsky M, Juraskova I. Factors associated with erectile dysfunction among men living with HIV: a systematic review. *AIDS Care*. 2020;**32**(3):275-285. https://doi.org/10.1080/09540121.2019.1653443.
28. Zhang J, Shi W, Zou M, *et al.* Prevalence and risk factors of erectile dysfunction in COVID-19 patients: a systematic review and meta-analysis. *J Endocrinol Investig*. 2023;**46**(4):795-804. https://doi.org/10.1007/s40618-022-01945-w.
29. 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. https://doi.org/10.1097/00006842-199807000-00011.
30. Yannas D, Frizza F, Vignozzi L, Conona G, Maggi M, Rastrelli GJ. Erectile dysfunction is a hallmark of cardiovascular disease: Unavoidable matter of fact or opportunity to improve men's health? *Clin Med*. 2021;**10**(10):2221.
31. Chou PS, Chou WP, Chen MC, *et al.* Newly diagnosed erectile dysfunction and risk of depression: a population-based 5-year follow-up study in Taiwan. *J Sex Med*. 2015;**12**(3):804-812. https://doi.org/10.1111/jsm.12792.
32. De Berardis G, Pellegrini F, Franciosi M, *et al.* Longitudinal assessment of quality of life in patients with type 2 diabetes and self-reported erectile dysfunction. *Diabetes Care*. 2005;**28**(11):2637-2643. https://doi.org/10.2337/diacare.28.11.2637.
33. Goldstein I, Chambers R, Tang W, Stecher V, Hassan T. Real-world observational results from a database of 48 million men in the United States: relationship of cardiovascular disease, diabetes mellitus and depression with age and erectile dysfunction. *Int J Clin Pract*. 2018;**72**(4):e13078. https://doi.org/10.1111/ijcp.13078.
34. Manalo TA, Biermann HD, Patil DH, Mehta A. The temporal Association of Depression and Anxiety in young men with erectile dysfunction. *J Sex Med*. 2022;**19**(2):201-206. https://doi.org/10.1016/j.jsxm.2021.11.011.
35. Nackeeran S, Havanur A, Ory J, Althof S, Ramasamy R. Erectile dysfunction is a modifiable risk factor for major depressive disorder: analysis of a federated research network. *J Sex Med*. 2021;**18**(12):2005-2011. https://doi.org/10.1016/j.jsxm.2021.09.016.
36. Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, Sand M. The multinational Men's attitudes to life events and sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. *Curr Med Res Opin*. 2004;**20**(5):607-617. https://doi.org/10.1185/030079904125003467.
37. Sugimori H, Yoshida K, Tanaka T, *et al.* Relationships between erectile dysfunction, depression, and anxiety in Japanese subjects. *J Sex Med*. 2005;**2**(3):390-396. https://doi.org/10.1111/j.1743-6109.2005.20354.x.
38. Liu Q, Zhang Y, Wang J, *et al.* Erectile dysfunction and depression: A systematic review and meta-analysis. *J Sex Med*. 2018;**15**(8):1073-1082. https://doi.org/10.1016/j.jsxm.2018.05.016.
39. Shiri R, Koskimäki J, Tammela TL, Häkkinen J, Auvinen A, Hakama M. Bidirectional relationship between depression and erectile dysfunction. *J Urol*. 2007;**177**(2):669-673. https://doi.org/10.1016/j.juro.2006.09.030.
40. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *J Sex Med*. 2012;**9**(6):1497-1507. https://doi.org/10.1111/j.1743-6109.2012.02709.x.
41. Nurnberg HG, Seidman SN, Gelenberg AJ, Fava M, Rosen R, Shabsigh R. Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression. *Urology*. 2002;**60**(2):58-66. https://doi.org/10.1016/s0090-4295(02)01691-6.
42. Rosen R, Shabsigh R, Berber M, *et al.* Efficacy and tolerability of vardenafil in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. *Am J Psychiatry*. 2006;**163**(1):79-87. https://doi.org/10.1176/appi.ajp.163.1.79.
43. Nguyen HM, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men – A review of the prevalence and risk factors. *Sex Med Rev*. 2017;**5**(4):508-520.
44. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham heart study. *Circulation*. 2004;**110**(5):522-527.
45. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, *et al.* Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;**127**(1):e6-e245.
46. Kuller L, Cooper M, Perper J. Epidemiology of sudden death. *Arch Intern Med*. 1972;**129**(5):714-719.
47. Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. *Clin Cardiol*. 2005;**28**(11 Suppl 1):I3-I11.
48. Ni H, Coady S, Rosamond W, *et al.* Trends from 1987 to 2004 in sudden death due to coronary heart disease: the atherosclerosis risk in communities (ARIC) study. *Am Heart J*. 2009;**157**(1):46-52.
49. 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.
50. Grover SA, Lowensteyn I, Kaouache M, *et al.* The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. *Arch Intern Med*. 2006;**166**(2):213-219.
51. Kloner RA, Mullin S, Shook T, *et al.* Erectile dysfunction in the cardiac patient: how common and should we treat? *J Urol*. 2003;**170**(2 Pt 2):S46-S50.
52. Sasayama S, Ishii N, Ishikura F, *et al.* Men's Health Study: Epidemiology of erectile dysfunction and cardiovascular disease. *Circ J*. 2003;**67**(8):656-659.
53. Solomon H, Man JW, Wierzbicki AS, Jackson G. Relation of erectile dysfunction to angiographic artery disease. *Am J Cardiol*. 2003;**91**(2):230-231.
54. Araujo AB, Travison TG, Ganz P, *et al.* Erectile dysfunction and mortality. *J Sex Med*. 2009;**6**(9):2445-2454.
55. Greenstein A, Chen J, Miller H, Matzkin H, Villa Y, Braf Z. Does severity of ischemic coronary disease correlate with erectile function? *Int J Impot Res*. 1997;**9**(3):123-126.
56. Miner M, Nehra A, Jackson G, *et al.* All men with vasculogenic erectile dysfunction require a cardiovascular workup. *Am J Med*. 2014;**127**(3):174-182.
57. Miner M, Seftel AD, Nehra A, *et al.* Prognostic utility of erectile dysfunction for cardiovascular disease in younger men and those with diabetes. *Am Heart J*. 2012;**164**(1):21-28. https://doi.org/10.1016/j.ahj.2012.04.006.
58. 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. https://doi.org/10.1111/j.1743-6109.2011.02224.x.
59. Porta M. *A Dictionary of Epidemiology*. 6th ed. Oxford University Press; 2016.
60. Osondo CU, Vo B, Oni E, *et al.* The relationship of erectile dysfunction and subclinical cardiovascular disease. *A systematic review and meta-analysis. Vasc Med*. 2018;**23**(1):9-20.
61. 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.
62. Dsouza SC, Rahman O. Association of erectile dysfunction with coronary artery disease in type 2 diabetes mellitus. *Ghana Med J*. 2023;**57**(1):43-48.
63. 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.
64. 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. https://doi.org/10.1016/j.eururo.2005.05.014.
65. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol*. 2011;**58**(13):1378-1385.
66. Guo W, Liao C, Zou Y, *et al*. Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. *J Sex Med*. 2010;**7**(8):2805-2816.
67. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;**357**(May 23):j2099.
68. Blaha M, Blumenthal R. Risk factors: new risk assessment guidelines: more or less personalized? *Nat Rev Cardiol*. 2014;**11**(3):136-137.
69. Brennan CR, Osei AD, Uddin SMF, *et al*. ACC/AHA guidelines: personalized care to prevent cardiovascular disease. *Cleve Clin J Med*. 2020;**87**(4):231-239.
70. Shah NP, Cainzos-Achirica M, Feldman DI, *et al*. Cardiovascular disease prevention in men with vascular erectile dysfunction: the view of the preventative cardiologist. *Am J Med*. 2016;**129**(3):251-259.
71. 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.
72. Miner M, Tilkemeier P, Nehra A. Relationship of sexual activity and the heart in the aging male: use of the Princeton consensus panel guidelines for practical therapy. *Clin Geriatr*. 2009;**17**(1):34-40.
73. Burnett AL, Nehra A, Breau RH, *et al*. Erectile dysfunction: AUA guideline. *J Urol*. 2018;**200**(3):633-641.
74. Levine GN, Steinke EE, Bakaeen FG, *et al*. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2012;**125**(8):1058-1072.
75. Yafi FA, Sharlip I, Becher E. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. *Sex. Med Rev*. 2018;**6**(2):242-252.
76. Buvat J, Jaoude G. Combination therapy with phosphodiesterase type V inhibitors and testosterone. *Curr Sex Health Rep*. 2008;**5**(3):135-140.
77. 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.
78. Wing RR, Rosen RC, Fava JL, *et al*. Effects of weight loss intervention on erectile dysfunction in older men with type 2 diabetes in the look AHEAD trial. *J Sex Med*. 2010;**7**(1):156-165.
79. Fisher WA, Eardley I, McCabe M, Sand M. Erectile dysfunction (ED) is a shared sexual concern of couples II: association of female partner characteristics with male partner ED treatment seeking and phosphodiesterase type 5 inhibitor utilization. *J Sex Med*. 2009;**6**(11):3111-3124.
80. Mobley D, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. *Postgrad Med J*. 2017;**93**(1105):679-685.
81. Riley A. The role of the partner in erectile dysfunction and its treatment. *Int J Impot Res*. 2002;**14**(suppl 1):S105-S109.
82. Riley A. When treating erectile dysfunction, do not forget the partner. *Int J Clin Pract*. 2008;**62**(1):6-8.
83. Westheimer RK. Partner and relationship issues in the treatment of erectile dysfunction. *Am J Manag Care*. 2000;**6**(12 Suppl):S639-S640.
84. Lincoff AM, Bhasin S, Flevaris P, *et al*. Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med*. 2023;**389**(2):107-117.
85. Giusseppe C, Paul J, Hans-Ulrich I. Use of nitrates in ischemic heart disease. *Exp Opin Pharmacother*. 2015;**16**(11):1567-1572.
86. Nakamura Y, Moss AJ, Brown MW, Kinoshita M, Kawai C. Long-term nitrate use may be deleterious in ischemic heart disease. A study using the database from two large postinfarction studies. *Multicenter Myocardial Ischemia Research Group. Am Heart J*. 1999;**138**(3 Pt 1):577-585.
87. Soman B, Vijayaraghaven G. The role of organic nitrates in the optimal medical management of angina. *e-J Card Pract*. 2017;**15**(2). Accessed September 2023. https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/The-role-of-organic-nitrates-in-the-optimal-medical-management-of-angina.
88. Wardle A, Seager MJ, Wardle R, Tulloh RMR, Gibbs JSR, Cochrane Airways Group. Guanylate cyclase stimulators for pulmonary hypertension. *Cochrane Database Syst Rev*. 2016;**2016**(8):CD011205. https://doi.org/10.1002/14651858.CD011205.pub2.
89. Francis SH, Lincoln TM, Corbin JD. Characterization of a novel cGMP binding protein from rat lung. *J Biol Chem1980*. 1980;**255**(2):620-626.
90. Lincoln TM, Hall CL, Park CR, Corbin JD. Guanosine 3':5'-cyclic monophosphate binding proteins in rat tissues. *Proc Natl Acad Sci U S A*. 1976;**73**(8):2559-2563.
91. Galie N, Ghofrani HA, Torbicki A, *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;**353**(20):2148-2157.
92. Corbin JD, Francis SH. Cyclic GMP phosphodiesterase-5: target of sildenafil. *J Biol Chem*. 1999;**274**(20):13729-13732.
93. Friebe A, Sandner P, Schmidtko A. Meeting report of the 8th international conference on cGMP "cGMP: generators, effectors, and therapeutic implications" at Bamberg, Germany, from June 23 to 25, 2017. *Naunyn Schmiedebergs Arch Pharmacol*. 2017;**390**(12):1177-1188.
94. Kukreja RC. Cardiovascular protection with sildenafil following chronic inhibition of nitric oxide synthase. *Br J Pharmcol*. 2007;**150**(5):538-540.
95. Francis SH, Bessay EP, Kotera J, *et al*. Phosphorylation of isolated human phosphodiesterase-5 regulatory domain induces an apparent conformational change and increases cGMP binding affinity. *J Biol Chem*. 2002;**277**(49):47581-47587.
96. Blount MA, Zoraghi R, Bessay EP, Beasley A, Francis SH, Corbin JD. Conversion of phosphodiesterase-5 (PDE5) catalytic site to higher affinity by PDE5 inhibitors. *J Pharmcol Exp Ther*. 2007;**323**(2):730-737.
97. Porst H, Burnett A, Brock G, *et al*. SOP conservative (medical and mechanical) treatment of erectile dysfunction. *J Sex Med*. 2013;**10**(1):130-171.
98. Shabsigh R, Donatucci C, Costabile R, *et al*. Reliability of efficacy in men with erectile dysfunction treated with tadalafil once daily after initial success. *Int J Impot Res*. 2010;**22**(1):1-8.
99. Cui H, Liu B, Song Z, *et al*. Efficacy and safety of long-term tadalafil 5 mg once daily combined with sildenafil 50 mg as needed at the early stage of treatment for patients with erectile dysfunction. *Andrologia*. 2015;**47**(1):20-24.
100. Burnett AL. Phosphodiesterase 5 mechanisms and therapeutic applications. *Am J Cardiol*. 2005;**96**(12B):29M-31M.
101. Sadovsky R, Brock GB, Gutkin SW, Sorsaburu S. Toward a new 'EPOCH': optimizing treatment outcomes with phosphodiesterase type 5 inhibitors for erectile dysfunction. *Int J Clin Pract*. 2009;**63**(8):1214-1230.
102. Gur S, Alzweri L, Yilmaz-Oral D, *et al*. Testosterone positively regulates functional responses and nitric oxide expression in

the isolated human corpus cavernosum. *Andrology*. 2020;**8**(6):1824-1833.
103. McCullough AR, Barada JH, Fawzy A, Guay AT, Hatzichristou D. Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. *Urology*. 2002;**60**(2 Suppl 2):28-38.
104. Lee M, Sharifi R. Non-invasive management options for erectile dysfunction when a phosphodiesterase type 5 inhibitor fails. *Drugs Aging*. 2018;**35**(3):175-187.
105. Canguven O, Bailen J, Fredriksson W, Bock D, Burnett AL. Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. *J Sex Med*. 2009;**6**(9):2561-2567.
106. Labairu-Huerta L, Padillo-Fernandez B, Arrondo-Arrondo JL, *et al.* PDE-5 inhibitors in monotherapy verses combination therapy in a sample of 1200 patients with erectile dysfunction. *Arch Ital Urol Androl*. 2015;**87**(3):204-209.
107. Cheitlin MD, Hutter AM Jr, Brindis RG, *et al.* ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. *American College of Cardiology/American Heart Association. J Am Coll Cardiol*. 1999;**33**(1):273-282.
108. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol*. 2003;**42**(10):1855-1860.
109. Oliver JJ, Kerr DM, Webb DJ. Time-dependent interactions of the hypotensive effects of sildenafil citrate and sublingual glyceryl trinitrate. *Br J Clin Pharmacol*. 2009;**67**(4):403-412.
110. Parker JD, Bart BA, Webb DJ, *et al.* Safety of intravenous nitroglycerin after administration of sildenafil citrate to men with coronary artery disease: a double-blind, placebo-controlled, randomized, crossover trial. *Crit Care Med*. 2007;**35**(8):1863-1868.
111. Swearingen D, Nehra A, Morelos S, Peterson CA. Hemodynamic effect of avanafil and glyceryl trinitrate coadministration. *Drugs Context*. 2013;**2013**(212248):1-10.
112. Webb DJ, Freestone S, Allen MJ, Muirhead GJ. Sildenafil citrate and blood-pressure-lowering drugs: results of drug interaction studies with an organic nitrate and a calcium antagonist. *Am J Cardiol*. 1999;**83**(5A):21C-28C.
113. Webb DJ, Muirhead GJ, Wulff M, Sutton JA, Levi R, Dinsmore WW. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol*. 2000;**36**(1):25-31.
114. Hsiao HL, Langenickel TH, Petruck J, *et al.* Evaluation of pharmacokinetic and pharmacodynamic drug-drug interaction of Sacubitril/valsartan (LCZ696) and sildenafil in patients with mild-to-moderate hypertension. *Clin Pharmacol Ther*. 2018;**103**(3):468-476.
115. Bozkurt B, Nair AP, Misra A, Scott CZ, Mahar JH, Fedson S. Neprilysin inhibitors in heart failure: the science, mechanism of action, clinical studies, and unanswered questions. *J Am Coll Cardiol Basic Trans Science*. 2023;**8**(1):88-105.
116. Humbert M, Ghofrani H-A. The molecular targets of approved treatments for pulmonary arterial hypertension. *Thorax*. 2016;**71**(1)73-83.
117. Benza R, Corris P, Ghofrani A, Kanwar MK, McLaughlin VV, Raina A, Simonneau G. EXPRESS: switching to riociguat: A potential treatment strategy for the management of CTEPH and PAH. *Pulm Circ*. 2019;**10**(1):2045894019837849.
118. Adamou C, Ntasiotis P, Athanasopoulos A, Kallidonis P. The hemodynamic interactions of combination therapy with alpha-blockers and phosphodiesterase-5 inhibitors compared to monotherapy with alpha-blockers: a systematic review and meta-analysis. *Int Urol Nephrol*. 2020;**52**(8):1407-1420.
119. Kloner RA. Pharmacology and drug interaction effects of the phosphodiesterase 5 inhibitors: focus on alpha-blocker interactions. *Am J Cardiol*. 2005;**96**(12B):42M-46M.
120. Kloner RA, Jackson G, Emmick JT, *et al.* Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 alpha-blockers, doxazosin and tamsulosin in healthy normotensive men. *J Urol*. 2004;**172**(5 Pt 1):1935-1940.
121. Laties A, Zrenner E. Viagra, sildenafil citrate and ophthalmology. *Prog Retin Eye Res*. 2002;**21**(5):485-506. https://doi.org/10.1016/s1350-9462(02)00013-7.
122. Food and Drug Administration. Viagra (SILDENAFIL CITRATE) product insert. Accessed May 11, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/20895s039s042lbl.pdf.
123. Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. *Eye (Lond)*. 2015;**29**(1):61-79.
124. Pomeranz HD. The relationship between phosphodiesterase-5 inhibitors and nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol*. 2016;**36**(2):193-196.
125. Etminan M, Sodhi M, Mikelberg FS, Maberley D. Risk of ocular adverse events associated with use of phosphodiesterase 5 inhibitors in men in the US. *JAMA Ophthalmol*. 2022;**140**(5):480-484.
126. Maddox PT, Saunders J, Chandrasekhar SS. Sudden hearing loss from PDE-5 inhibitors: A possible cellular stress etiology. *Laryngoscope*. 2009;**119**(8):1586. https://doi.org/10.1002/lary.20511.
127. Manna S, Gray ML, Raul VF, Wanna G. Phosphodiesterase-5 (PDE5) inhibitor and ototoxicity: A systematic review. *Otol Neurotol Mar*. 2019;**40**(3):276-283.
128. Wayne G, Demus T, Jivanji D, *et al.* Use of phosphodiesterase-5 inhibitors and the incidence of melanoma. *Cancer Epidemiol*. 2022 Dec;**81**:102251. https://doi.org/10.1016/j.canep.2022.102251.
129. Gallina A, Bianchi M, Gandoglia G. A detailed analysis of the association between postoperative phosphodiesterase type 5 inhibitor use and risk of biochemical recurrence after radical prostatectomy. *Eur Urol Nov*. 2015;**68**(5):750-753.
130. Loeb S, Folkvaljon Y, Robinson D, Schlomm T, Garmo H, Stattin P. Phosphodiesterase type 5 inhibitor use and disease recurrence after prostate cancer treatment. *Eur Urol Nov*. 2016;**70**(5):824-828.
131. Michl U, Molfenter F, Graefen M. Use of phosphodiesterase type 5 inhibitors may adversely impact biochemical recurrence after radical prostatectomy. *J Urol*. 2015;**193**(2):479-483.
132. Danley KT, Tan A, Catalona WJ, *et al.* The association of phosphodiesterase-5 inhibitors with the biochemical recurrence-free and overall survival of patients with prostate cancer following radial prostatectomy. *Urol Oncol*. 2022;**40**(2):57.e1-57.e7. https://doi.org/10.1016/j.urolonc.2021.05.031.
133. Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca V. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilation in type 2 diabetes. *Diabetes Care*. 2002;**25**(8):1336-1339. https://doi.org/10.2337/diacare.25.8.1336.
134. Rosano GM, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur Urol*. 2005;**47**(2):214-222.
135. Anderson SG, Hutchings DC, Woodward M, *et al.* Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality. *Heart*. 2016;**102**(21):1750-1756.
136. Hackett G, Jones PW, Strange RC, Ramachandran S. Statin, testosterone and phosphodiesterase 5- inhibitor treatments and age related mortality in diabetes. *World J Diabetes*. 2017;**8**(3):104-111.
137. Andersson DP, Lagerros YT, Grotta A, *et al.* Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction. *Heart*. 2017;**103**(16):1264-1270.
138. Andersson DP, Landucci L, Lagerros YT, *et al.* Association of phosphodiesterase-5 inhibitors versus alprostadil with survival in men with coronary artery disease. *J Am Coll Cardiol*. 2021;**77**(12):1535-1550.
139. Goberdhan S, Blachman-Braun R, Nackeeran S, Masterson TA 3rd, Ramasamy R. Is tadalafil associated with decreased risk

of major adverse cardiac events or venous thromboembolism in men with lower urinary tract symptoms? *World J Urol*. 2022;**40**(7):1799-1803.
140. Wilton KM, Achenbach SJ, Davis JM 3rd, Myasoedova E, Matteson EL, Crowson CS. Erectile dysfunction and cardiovascular risk in men with rheumatoid arthritis: A population-based cohort study. *J Rheumatol*. 2021;**48**(11):1641-1647. https://doi.org/10.3899/jrheum.201226.
141. Vestergaard N, Sogaard P, Torp-Pederson C, Aasbjerg K. Relationship between treatment of erectile dysfunction and future risk of cardiovascular disease: A nationwide cohort study. *Eur J Prev Cardiol*. 2017;**24**(14):1498-1505.
142. Kloner RA, Stanek E, Crowe CL, *et al*. Effect of phosphodiesterase type 5 inhibitors on major adverse cardiovascular events and overall mortality in a large nationwide cohort of men with erectile dysfunction and cardiovascular risk factors: A retrospective, observational study based on healthcare claims and national death index data. *J Sex Med*. 2023;**20**(1):38-48. https://doi.org/10.1093/jsxmed/qdac005.
143. Nunes AP, Seeger JD, Stewart A, Gupta A, McGraw T. Retrospective observational real-world outcome study to evaluate safety among patients with erectile dysfunction (ED) with co-possession of tadalafil and anti-hypertensive medications (anti-HTN). *J Sex Med*. 2022;**19**(1):74-82.
144. Geller AI, Shehab N, Weidle NJ, *et al*. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med*. 2015;**373**(16):1531-1540. https://doi.org/10.1056/NEJMsa1504267.
145. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. *JAMA Netw Open*. 2018;**1**(6):e183337. https://doi.org/10.1001/jamanetworkopen.2018.3337.
146. Lee LJ, Maguire TA, Maculaitis M, *et al*. Increasing access to erectile dysfunction treatment via pharmacies to improve healthcare provider visits and quality of life: results from a prospective real-world observational study in the United Kingdom. *Int J Clin Pract*. 2021 Apr;**75**(4):e13849. https://doi.org/10-111113849.
147. Scranton RE, Goldstein I, Stecher VJ. Erectile dysfunction diagnosis and treatment as a means to improve medication adherence and optimize comorbidity management. *J Sex Med*. 2013;**10**(2):551-561. https://doi.org/10.1111/j.1743-6109.2012.02998.x.
148. Towe M, Peta A, Saltzman RG, Balaji N, Chu K, Ramasamy R. The use of combination regenerative therapies for erectile dysfunction: rationale and current status. *Int J Impot Res*. 2022;**34**(8):735-738.
149. Yao H, Wang X, Liu H, *et al*. Systematic review and meta-analysis of 16 randomized controlled trials of clinical outcomes of low-intensity extracorporeal shock wave therapy in treating erectile dysfunction. *Am J Mens Health*. 2022; **16**(2):15579883221087532.
150. Nazim SM, Ahmad S. Stem cells in urology. *J Pak Med Assoc*. 2023;**73**(**Suppl 1**)(2):S69-S74.
151. Zhang H, Albersen M, Jin X, Lin G. Stem cells: novel players in the treatment of erectile dysfunction. *Asian J Androl*. 2012;**14**(1):145-155.
152. Anastasiadis E, Ahmed R, Khoja AK, Yap T. Erectile dysfunction: is platelet-rich plasma the new frontier for treatment in patients with erectile dysfunction? A review of the existing evidence. *Front Reprod Health*. 2022 Aug 16;**4**:944765.
153. Israeli JM, Lokeshwar SD, Efimenko IV, Masterson TA, Ramasamy R. The potential of platelet-rich plasma injections and stem cell therapy for penile rejuvenation. *Int J Impot Res*. 2022;**34**(4):375-382.
154. Masterson TA, Molina M, Ledesma B, *et al*. Platelet-rich plasma for the treatment of erectile dysfunction: A prospective, randomized, double-blind, placebo-controlled clinical trial. *J Urol*. 2023;**210**(1):154-161.
155. Akande TO, Akinwunmi OM, Adebayo SA, Akinyinka AO, Shittu OB. Efficacy and safety of low-intensity extracorporeal shockwave therapy for treatment of vascular erectile dysfunction in Nigerian men: report of A study in Ibadan, south-West Nigeria. *Ann Ibadan Postgrad Med*. 2021;**19**(1):8-14.
156. Geyik S. A single-Centre result of two courses of low-intensity shockwave therapy (Li-SWT) in erectile dysfunction. *Andrologia*. 2022;**54**(2):e14324. https://doi.org/10.1111/and.14324.
157. Ong WLK, Lechmiannandan S, Lim YL, Manoharan D, Lee SB. Early outcomes of short-course low intensity shockwave therapy (LiSWT) for erectile dysfunction: A prospective, randomized, double-blinded, sham-controlled study in Malaysia. *Andrologia*. 2022;**54**(9):e14518. https://doi.org/10.1111/and.14518.
158. Li H, Matheu MP, Sun F, *et al*. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. *J Sex Med*. 2016;**13**(1):22-32.
159. Lin G, Reed-Maldonado AB, Wang B, *et al*. In situ activation of penile progenitor cells with low-intensity extracorporeal shockwave therapy. *J Sex Med*. 2017;**14**(4):493-501.
160. Peng D, Yuan H, Liu T, *et al*. Smooth muscle differentiation of penile stem/progenitor cells induced by microenergy acoustic pulses in vitro. *J Sex Med*. 2019;**16**(12):1874-1884.
161. Peng D, Reed-Maldonado AB, Zhou F, *et al*. Exosome released from Schwann cells may be involved in microenergy acoustic pulse-associated cavernous nerve regeneration. *J Sex Med*. 2020;**17**(9):1618-1628.
162. Manfredi C, Castiglione F, Fode M, *et al*. News and future perspectives of non-surgical treatments for erectile dysfunction. *Int J Impot Res*. 2022 Jul 27. https://doi.org/10.1038/s41443-022-00602-3.
163. Virag R. Intracavernous papaverine for erectile failure. *Lancet*. 1982 Oct 23;**2**(8304):938. https://doi.org/10.1016/s0140-6736(82)90910-2.
164. Brindley G. Cavernosal alpha-blockade: a new technique for investigating and treating erectile impotence. *Br J Psychiatry*. 1983;**143**(4):332-337. https://doi.org/10.1192/bjp.143.4.332.
165. Padma-Nathan H, Hellstrom WJ, Kaiser FE, *et al*. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated urethral system for erection (MUSE) study group. *N Engl J Med*. 1997;**336**(1):1-7.
166. Ralph DJ, Eardley I, Taubel J, Terrill P, Holland T. Efficacy and safety of MED2005, a topical glyceryl Trinitrate formulation, in the treatment of erectile dysfunction: A randomized crossover study. *J Sex Med*. 2018;**15**(2):167-175. https://doi.org/10.1016/j.jsxm.2017.12.003.
167. Dean J, Rubio-Aurioles E, McCabe M, *et al*. Integrating partners into erectile dysfunction treatment: improving the sexual experience for the couple. *Int J Clin Pract*. 2008;**62**(1):127-133. https://doi.org/10.1111/j.1742-1241.2007.01636.x.
168. Parish SJ, Hahn SR, Goldstein SW, *et al*. The International Society for the Study of Women's sexual health process of Care for the Identification of sexual concerns and problems in women. *Mayo Clin Proc*. 2019;**94**(5):842-856. https://doi.org/10.1016/j.mayocp.2019.01.009.
169. Basson R, McInnes R, Smith MD, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Gend Based Med*. 2002;**11**(4):367-377. https://doi.org/10.1089/152460902317586001.
170. Gao L, Yang L, Qian S, Li T, Han P, Yuan J. Systematic review and meta-analysis of phosphodiesterase type 5 inhibitors for the treatment of female sexual dysfunction. *Int J Gynaecol Obstet*. 2016;**133**(2):139-145. https://doi.org/10.1016/j.ijgo.2015.08.015.
171. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA*. 2008;**300**(4):395-404. https://doi.org/10.1001/jama.300.4.395.

172. Sipski ML, Rosen RC, Alexander CJ, Hamer RM. Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology*. 2000;**55**(6):812-815. https://doi.org/10.1016/s0090-4295(00)00493-3.
173. Adcirca (tadalafil); Package insert. Indianapolis, IN: Eli Lilly; 2020.
174. *Revatio (Sildenafil), Oral Tablet, Oral Suspension, Injectable*. New York, NY: Pfizer Labs; 2014.
175. Mathai SC, Hassoun PM, Puhan MA, Zhou Y, Wise RA. Sex differences in response to tadalafil in pulmonary arterial hypertension. *Chest*. 2015. **147**(1):188-197. https://doi.org/10.1378/chest.14-0263.
176. Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. *BMJ Open*. 2015;**5**(3):e006389.
177. Curtiss P, Svigos K, Schwager Z, Lo Sicco K, Franks AG Jr. Part II: the treatment of primary and secondary Raynaud's phenomenon. *J Am Acad Dermatol*. 2022 Jul 6:S0190-9622(22)02249-6. https://doi.org/10.1016/j.jaad.2022.05.067.
178. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis*. 2013;**72**(10):1696-1699. https://doi.org/10.1136/annrheumdis-2012-202836.
179. Roustit M, Giai J, Gaget O, *et al*. On-demand sildenafil as a treatment for Raynaud phenomenon: A series of n-of-1 trials. *Ann Intern Med*. 2018;**169**(10):694-703. https://doi.org/10.7326/m18-0517.
180. Marin L, Andrisani A, Bordin L, *et al*. Sildenafil supplementation for women undergoing infertility treatments: A systematic review and meta-analysis of randomized controlled trials. *J Clin Med*. 2021;**10**(19):4346.
181. da Silva Ferreira RD, Negrini R, Bernardo WM, Simões R, Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. *PLoS One*. 2019;**14**(7):e0219732.
182. Turner JM, Russo F, Deprest J, Mol BW, Kumar S. Phosphodiesterase-5 inhibitors in pregnancy: systematic review and meta-analysis of maternal and perinatal safety and clinical outcomes. *BJOG*. 2022;**129**(11):1817-1831. https://doi.org/10.1111/1471-0528.17163.
183. Cooper TJ, Cleland JGF, Guazzi M. Effects of sildenafil on symptoms and exercise capacity for heart failure with reduced ejection fraction and pulmonary hypertension (the Sil HF study): a randomized placebo-controlled multicentre trial. *Eur J Heart Fail*. 2022;**24**(7):1239-1248. https://doi.org/10.1002/ejhf.2527.