Erectile dysfunction affects an estimated one in ten men in the United States. According to one study, the prevalence of impotence at all degrees is approximately 52% in men aged 40 to 70 years. This prevalence rate might be underestimated, given patients’ reluctance to discuss the issue with their physicians. Erectile dysfunction is often accompanied by comorbid conditions because of overlapping risk factors. It is important that physicians be aware of the frequency of this coexistence so that they may monitor all potential health concerns and treat patients optimally.

Erectile dysfunction (ED) is the persistent inability to achieve and maintain an erection sufficient for satisfactory sexual activity. It is estimated that ED affects one in ten men in the United States.1 According to the Massachusetts Male Aging Study (MMAS),2 the prevalence of impotence at all degrees is approximately 52% in men aged 40 to 70 years. This prevalence might be underestimated, given patients’ reluctance to discuss the issue with their physicians.3

The current American Association of Clinical Endocrinologists (AACE) Guidelines4 for the workup of sexual dysfunction suggests that if possible, the patient and partner should be evaluated together. This evaluation may reveal underlying relationship and adjustment issues, as well as difficulties in communication. Sexual history should focus on the degree of ED, its frequency, and the duration of the problem. Longstanding ED may involve performance anxiety and require psychological therapy as well as medical treatment. Medical history should evaluate common risk factors for ED, as well as concomitant medications. A history of emotional or psychological problems (or both), or a history of previous surgical procedures should also be noted.

In addition to the usual physical examination parameters, anatomic abnormalities should be assessed, as well as sensory adequacy of the nerves serving the penis. Abnormalities that are suggestive of hormonal dysfunction should be worked up as needed. Diagnostic tests can help identify possible comorbidities. Hormonal assays may include thyroid function, if indicated, and measurement of testosterone concentration; testosterone concentrations should be assessed in the morning. Vascular assessment may include penile Doppler ultrasound examination to assess blood flow to the corpus cavernosum.4,5

Before initiating specific treatment modalities for ED, the physician should first eliminate hypogonadism, other hormonal factors, and decreased libido as primary causes. The AACE sexual dysfunction workup strategy should help identify these causes. Patients should receive treatment for any previously untreated comorbidities detected during workup. In addition to the direct impact on patient health and risk for complications and other comorbidities, such treatment may increase the effectiveness of ED-specific modes of therapy.

Erectile dysfunction is often accompanied by comorbid conditions because of overlapping risk factors.6 It is important that physicians be aware of the frequency of this coexistence so that they may monitor all potential health concerns and treat patients optimally.

Obstacles to discovering ED are substantial, including reticence or embarrassment on the part of the patient, physician, or both. An understanding of the etiology of ED may lead to an early rather than a delayed diagnosis of ED. The use of simple, straightforward screening questions can pave the way to a more comprehensive workup. Diagnosis of ED can help uncover previously undiagnosed comorbidities, and vice versa. The association of ED with a number of common disorders suggests an important role for “reciprocal diagnosis.”

Regular screening for disorders frequently observed in aging men can open the conversation to a discussion of ED. Conversely, including a screening process for ED during a routine physical examination may help point to previously undetected comorbidities. For example, Burchardt et al7 found that hypertensive patients with ED had a significantly higher prevalence of cardiovascular complications (P < .05) than those without ED.

Patients with diagnosed conditions that are frequently comorbid with ED provide an outstanding opportunity to facilitate discussions of sexual health. Patients with established cardiovascular disease, hypertension, dyslipidemia or hyperlipidemia, diabetes mellitus,
depression, or lower urinary tract symptoms should be evaluated for the presence of ED at every checkup.

A recent survey of male patients visiting a university-based urology clinic showed that the average number of ED risk factors was 2.1; however, of the 83% of patients who reported having a primary care physician, only 23% had been screened for ED.9,10

The Massachusetts Male Aging Study2 also has provided perhaps the best early description of the association of various degrees of ED with a wide range of comorbidities (Figure 1). Depression, established heart disease, hypertension, diabetes, and low levels of high-density lipoprotein cholesterol were all associated with substantial increases in risk for ED.

The risk of ED associated with depression is particularly striking, with 90% of severely depressed patients having moderate to complete ED; this statistic helps to spotlight the substantial psychological component of ED. Considerable overlap exists in these populations, and many men have two or more of these risk factors. It is not atypical to evaluate a patient with early-onset diabetes and uncover hypertension and early-onset coronary artery disease, as well.2

High rates of ED are observed in a variety of patient populations with one or more comorbidities. Of the comorbidities associated with high ED risk, three have been most intensively studied in clinical trials of phosphodiesterase-5 (PDE-5) inhibitors: patients with cardiovascular disease, patients with diabetes mellitus, and patients who have undergone prostatectomy for treatment of prostate cancer. In addition to posing increased risk for the development of ED, these comorbidities may increase the severity of ED and represent additional treatment challenges in comparison with those encountered in the general population.

Cardiovascular Disease, Risk Factors, and Erectile Dysfunction
Cardiovascular disease is associated with far higher rates of ED, and far higher rates of severe ED, than those observed in the general population. Data from the Massachusetts Male Aging Study2 confirmed that heart disease in nonsmokers is associated with a greater than twofold elevation in the risk for complete ED, and nearly a twofold elevation in the risk for moderate to complete ED when compared with the general population. Patients with heart disease who smoke face even worse odds: the risk of complete ED is more than fivefold, and that of moderate to complete ED more than twofold the comparable rates observed in the general population. The presence of hypertension doubles the risk for complete ED.

The diagnosis of ED is based on a comprehensive sexual history, medical history, physical examination, and diagnostic tests appropriate to the specific condition of the patient. The initial decision to treat is based on the underlying etiology of the patient’s ED and on assessment of cardiovascular risk. Cardiovascular risk assessment should be based on the risk of sexual activity per se. The use of oral PDE-5 inhibitors, based on clinical trials and postmar-
keting experience, does not add to cardiovascular risk.

Risk Factors
Risk factors for cardiovascular disease are also associated with increased risk for ED. A low high-density lipoprotein cholesterol level increases the risk of both complete and moderate to complete ED (Figure 2). The presence of hypertension is associated with a significant increase in the risk of the development of ED.

In a survey of male outpatients at the Hypertension Center of Columbia University using the International Index of Erectile Function (IIEF), Burchardt and colleagues found that 71 (68.3%) of the 104 respondents (mean age, 62 years) had some degree of ED. Of the 71 hypertensive patients with ED, 47 (66%) had complete ED, 16 (23%) had moderate ED, and 8 (11%) had mild ED. These data strongly suggest that hypertension is correlated not only with the presence of ED, but also with increased severity of ED.

A great deal of work during the past two decades has illustrated the critical role dysfunction of the vascular endothelium plays in linking disease states with outcomes. Conditions that lead to oxidative stress, such as hypertension, tobacco use, diabetes, and others, may be the common denominator in producing endothelial dysfunction. This dysfunction in turn leads to atherosclerosis, which may be a causative factor in many cases of ED.

The assessment of cardiovascular risk should focus on the risk of sexual activity itself. Sexual activity can trigger myocardial infarction (MI), but in a study of patients who had a nonfatal MI, only about 1% were associated with sexual activity during the preceding 2 hours. Even for patients with a 10% annual risk of MI, sexual activity causes only a transient increase in risk from 10 in 1 million per hour to 20 in 1 million per hour. The estimated energy used for sexual intercourse is approximately equivalent to that of climbing one flight of stairs and less than that of golf or dancing.

Treatment
Cardiovascular risk is an important consideration in prescribing phosphodiesterase type 5 (PDE-5) inhibitors for ED because of the frequent association between ED and cardiovascular disease and cardiovascular risk factors.

The cardiovascular safety profile of PDE-5 inhibitors, demonstrated both in clinical trials and postmarketing evaluations, strongly suggests that risk assessment should be based on the inherent risk of sexual activity and that PDE-5 inhibitors do not increase that risk. However, PDE-5 inhibitors should never be prescribed for, or used by, patients taking nitrates. A synergistic interaction between nitrates and PDE-5 inhibitors may lead to dangerous hypotension.

In general, the patient with ED comorbid with cardiovascular disease will benefit from the current strategies for cardiovascular risk assessment and risk management. Safety data from a range of clinical trials indicate that PDE-5 inhibitors do not add incremental risk to existing risk based on preexisting cardiovascular status.

Diabetes Mellitus and Erectile Dysfunction
Diabetes mellitus is a profound comorbidity for ED. Diabetes may contribute to ED in several ways. Diabetic neuropathy may compromise neural pathways important in the erectile response. Occlusive diabetic vasculopathy may limit blood flow into the corpus cavernosum. Impairment of nitric oxide–dependent smooth muscle relaxation may also prevent adequate blood flow to support erectile function. Endothelial dysfunction is believed to be the common denominator in diabetic vasculopathy, associated with pathologic effects in both small and large vessels. These effects may be the primary link between diabetes and ED.

Prevalence
The prevalence of ED among men with diabetes is higher than that among non-diabetic men at all ages. The risk of diabetes-associated ED is correlated with increasing age, duration of diabetes, and development of diabetic neuropathy and microangiopathy. The dramatic increase in diabetes-associated ED with increased age may account for a substantial fraction of the age-dependent increase in prevalence observed in the overall population.

The Massachusetts Male Aging Study showed that the prevalence of ED is high among diabetic men, and the proportion of diabetic men with moderate to complete ED is higher than the proportion in the general population. The odds ratio is a measure of the comparative likelihood of the development of a given condition between two different populations. The Cologne Male Survey, a study of 8000 men in Germany by Braun and colleagues, evaluated the impact of various factors on the risk of ED. The study showed that the odds ratio for the development of ED in diabetic men versus nondiabetic men was 3.95; that is, the presence of diabetes increased the likelihood of the development of ED by nearly fourfold.

Treatment
In assessing the results of placebo-controlled trials among diabetic men, all three PDE-5 inhibitors demonstrated significant improvement versus placebo. After 12 weeks of treatment with sildenafil, diabetic patients with ED responding to Sexual Encounter Profile (SEP) questions 2 and 3 (Q2, Q3) reported significant improvements over placebo in achieving and maintaining erections. However, in this study, efficacy in patients with severe ED was not discerned. In a study of vardenafil hydrochloride in men with diabetes, a subset analysis demonstrated significant improvement in erectile function versus placebo in men with severe ED at baseline (IIEF erectile function domain score <11). Improvement was assessed in this study using the stringent SEP Q3. Likewise, after 3 months of treatment with tadalafil, patients with diabetes who had moderate ED recorded clinically significant improvements in the ability to achieve and maintain erections compared with patients receiving placebo. Vardenafil also demonstrated sustained improvement in erectile function for 6 months.

Androgen Deficiency and Erectile Dysfunction
Prevalence
Currently available evidence indicates that ED and androgen deficiency are two
independently distributed disorders with some degree of overlap. A clear correlation does not appear to exist between erectile function and testosterone concentration. Buvat and Lemaire evaluated serum testosterone concentrations in 1022 men with ED. Only 10% (107) were found to have a low testosterone concentration (<300 ng/dL) on initial assay; of these, 40% had a testosterone concentration in the normal range on a repeated assay.21

Korenman and colleagues studied testosterone concentrations in young (aged 20 to 44 years) potent men, potent men older than 50 years, and impotent men older than 50 years to assess the relationship, if any, between impotence and testosterone concentration. Testosterone concentrations in impotent and potent older men were comparable; both groups had significantly lower levels than younger potent men. The fraction of bioavailable testosterone was significantly \((P<.001)\) higher in younger men than in older men (both impotent and potent older men had similar levels of bioavailable testosterone). Forty-eight percent of older potent men and 39% of impotent older men were hypogonadal, defined as having a mean bioavailable testosterone concentration of less than 2.3 nmol/L, which was 2.5 SD below the mean level in younger potent men. Korenman and colleagues concluded that no clear correlation existed between testosterone or bioavailable testosterone levels and erectile function, and that secondary hypogonadism and impotence are common, but independently distributed, conditions in aging men.

**Diagnosis**

The definition of androgen deficiency is not clear-cut; the AACE recommends using a combination of history, physical examination, and laboratory evaluations. Clinical problems that may be associated with decreased testosterone concentrations in older men include sexual dysfunction, muscle wasting and weakness, increased ratio of fat to lean body mass, osteopenia, increased fractures in the central skeleton (hip and vertebrae), decreased body hair, decreased hematopoiesis, and memory loss. There exists no unambiguous definition for low testosterone concentration; testosterone levels fluctuate on a diurnal basis and may vary significantly hour to hour.

"Normal" testosterone concentrations are defined differently depending on the reference source:
- The Merck Manual lists a range of 294 ng/dL to 833 ng/dL;
- the prescribing information for testosterone gel lists a range of 298 ng/dL to 1043 ng/dL; and
- the AACE guidelines for treating hypogonadism suggest a range of 280 ng/dL to 800 ng/dL.

The initial laboratory criterion for diagnosis of hypogonadism is the total testosterone concentration; the AACE suggests that the free testosterone or the sex hormone-binding globulin level may be useful in cases in which clinical findings and laboratory values are difficult to reconcile.

The AACE recommends that prior to initiating testosterone replacement, a complete physical examination and laboratory workup should be conducted, focusing on the identification of possible prostate or breast cancer. This examination should include a digital rectal examination, prostate-specific antigen (PSA) test, and careful evaluation of the breast. Absolute contraindications to testosterone replacement therapy are prostate cancer and breast cancer.

**Treatment**

Considerations of relative contraindications to testosterone replacement therapy should be based on the patient’s specific status. A prolatin-inhibiting tumor should be ruled out if the testosterone concentration is low and the luteinizing hormone level is low. Testosterone replacement will not be successful if an untreated prolactinoma is present. Both sleep apnea and polycythemia can be exacerbated by testosterone supplementation.

The patient’s age should also be considered in light of the increased incidence of prostate cancer after age 60 years. Testosterone replacement reduces sperm counts and fertility; therefore, it should not be used in men wishing to sustain fertility. Any existing symptomatic prostatism should be carefully evaluated and treated prior to testosterone supplementation.

Administration options for testosterone supplementation include:
- an injection of 200 mg every 2 weeks, or 300 mg every 3 weeks (this regimen should restore the serum level of testosterone to mid-normal after 1 week);
- scrotal transdermal patch, one patch every morning (this option should restore the serum level of testosterone to mid-normal after 4 hours);
- nonscrotal transdermal patch, one patch every evening (this option should restore the serum level to mid-normal after 8 to 12 hours);
- testosterone gel, 5 g, 7.5 g, or 10 g every morning (this modality should restore the serum level of testosterone to mid-normal range after 4 hours).

Absolute contraindications to any form of testosterone supplementation include suspected or confirmed prostate or breast cancer and desired fertility. The AACE recommends frequent, regular follow-up in men receiving testosterone replacement therapy. For the first year of therapy, follow-up examinations and laboratory values should be scheduled every 3 to 4 months, and every 6 to 12 months thereafter for the first 18 months. Follow-up assessments should include:
- confirmation of normal-range serum testosterone concentrations;
- digital rectal examination;
- PSA test;
- breast examination for breast cancer or gynecomastia;
- hematocrit testing (the AACE recommends hematocrit testing every 6 months for the first 18 months of therapy; if the hematocrit is stable, testing should be done annually thereafter); and
- assessment of sleep apnea, which may manifest as obviously disordered sleep or as daytime fatigue. (A more detailed sleep study may be indicated if sleep apnea is a possibility.)

Testosterone replacement therapy should be discontinued in patients with an abnormal finding on digital rectal examination, elevated or increasing PSA level, symptomatic prostatism (which should be evaluated and treated before reinitiating therapy), hematocrit greater than 0.50 (may decrease or discontinue...
testosterone replacement therapy), or sleep apnea.23

In a review of a small, limited selection of studies of testosterone therapy in men with various forms of sexual dysfunction, Tenover27 found that men with low libido had general improvement in libido with testosterone therapy, but ED was only occasionally improved by testosterone therapy.

The possibility that the physician’s ability to detect prostate cancer may be different for hypogonadal than for eugonadal men suggests that patients should be screened for prostate cancer before testosterone replacement therapy. The treatment decision should be based on the elimination of absolute contraindications (prostate cancer, breast cancer, and desired fertility); and on consideration of relative contraindications (sleep apnea, polycythemia, age relative to prostate cancer risk). Prolactinoma should be ruled out.

Follow-up
Follow-up of men receiving testosterone replacement therapy should be scheduled every 3 to 4 months for the first year of therapy, then every 6 to 12 months thereafter. Follow-up should include digital rectal examination, PSA test, breast evaluation, hematocrit, serum lipid levels, and assessment of possible sleep apnea. Testosterone therapy should be discontinued in patients who have abnormal findings on digital rectal examination, elevated or increasing PSA level, symptomatic prostatism, hematocrit greater than 0.50, or sleep problems. Under no circumstances should oral androgen preparations be used for testosterone supplementation.

Diminished Libido in Men and Erectile Dysfunction
Erectile dysfunction, androgen deficiency, and decreased libido appear to be independently distributed, but overlap to some extent. Androgen deficiency or decreased libido or both may play a causative role in some cases of ED, but many or most cases of ED appear to be primarily vasculogenic. Decreased libido may be the result of androgen deficiency, but it also may be psychogenic.

Although the term libido is frequently used to simply denote sexual desire, the Oxford English Dictionary definition hints at the true complexity of the term.28 Libido involves spontaneous sexual thoughts and fantasies, as well as attentiveness to external sexual stimuli that may be visual, auditory, or tactile.

Prevalence
The “true” incidence or prevalence rates of low sexual desire disorders are elusive and difficult to assess. Laumann and colleagues29 analyzed data from the National Health and Social Life survey, a 1992 study of sexual behavior in a sample of 1749 women and 1410 men (aged 18 to 59 years) selected to be demographically representative of the US population. Laumann and his colleagues estimated the prevalence of low-desire disorders to be about 5% in men and 22% in women.29 Panser and colleagues,30 in a survey of 2215 men (aged 40 to 79 years) using a self-administered questionnaire, found a clear increase with age for all sexual dysfunctions. Of men aged 70 to 79, 25.9% reported absent sexual drive, versus 0.6% of men aged 40 to 49 years (P<.001).

Segraves and Segraves31 studied the frequency of hypoactive sexual desire disorder (HSDD) among a group of 906 men and women recruited for a multisite pharmaceutical study based on a complaint of sexual dysfunction. In this highly selected population, 89% of the women and 30% of the men had a primary diagnosis of HSDD. Among the women with a primary HSDD diagnosis, 41% had at least one other sexual dis-
order; among the men with a primary HSDD diagnosis, 47% also reported some degree of ED. Other secondary disorders included inhibited ejaculation.\textsuperscript{31}

**Risk Factors and Sexual Response**

Low libido is associated with a number of risk factors. It may develop as a secondary condition because of other disorders, including:

- androgen deficiency;
- use of certain medications, including selective serotonin-reuptake inhibitors and antiandrogens;
- other sexual disorders such as ED due to fear of humiliation;
- psychiatric or psychological problems such as depression; and
- systemic illnesses such as arthritis.\textsuperscript{4}

The male cycle of sexual response (Figure 3) can be divided into four phases:

- libido (desire), consisting of fantasies and thoughts about sexual activity and the desire to have sexual activity;
- erection (arousal), involving a subjective sense of sexual pleasure accompanied by physiologic changes, ie, penile tumescence and erection;
- ejaculation/orgasm, comprising a peaking in sexual pleasure, a sensation of ejaculatory inevitability, and ejaculation of semen; and
- satisfaction/resolution, consisting of a sense of muscular relaxation and general well-being.

Sexual dysfunction is characterized by a disturbance in the processes that make up the cycle of sexual response, including:

- diminished or excessive libido;
- ED, priapism, or erectile deformity;
- premature, delayed, or retrograde ejaculation;
- anorgasmia; or
- anejaculation.

Sexual dysfunction also includes pain associated with sexual intercourse, caused by conditions such as fibrous cavernitis (Peyronie’s disease) or chronic pelvic pain syndrome. Although this model is not entirely evidence-based, it may be helpful to physicians seeking to diagnose various conditions that may occur at different points in the cycle of sexual response. For example, if a patient has reduced sexual desire, the physician may consider organic causes such as hormonal deficiencies, or psychogenic causes such as stress or partnership issues.\textsuperscript{32}

**Evaluation**

As with other sexual disorders, workup of suspected low libido should begin with a detailed sexual and medical history involving the couple. The sexual history may reveal other underlying problems to which low libido is secondary, such as relationship issues or organic ED. The medical history and evaluation (using appropriate diagnostic tests) can help rule out systemic illness, depression or other psychological problems, alcohol or drug abuse, medication side effects, and androgen deficiency. Self-administered questionnaires such as the Sexual Desire Inventory developed by Spector and colleagues\textsuperscript{33} may also be useful.\textsuperscript{1,4}

Disorders of libido can be an important contributor to and cause of sexual dysfunction. Libido disorders are frequently difficult to diagnose, are often overlooked, and not adequately treated. Libido disorders may be secondary to other sexual dysfunction, and they can affect the response to therapy for ED. Because low sexual desire may not be pathologic, self-reported distress is an essential component of the diagnosis. Androgen deficiency can reduce libido and is reversible on treatment; this cause should be excluded at the outset of any workup of libido problems.

**Treatment**

Testosterone deficiency is associated with decreased overall sexual desire and a reduced frequency of sexual fantasies and spontaneous erections. On testosterone supplementation in androgen-deficient men, studies have demonstrated increased overall sexual activity, sexual desire, sexual fantasies, and sleep-related erections. Although testosterone supplementation in androgen-deficient men seems to increase overall sexual desire and activity, it has no clear-cut effect on erectile capability.\textsuperscript{34-36}

Testosterone has been shown to be an important regulator of spontaneous sexual thoughts and feelings, the attentiveness to erotic stimuli, and spontaneous erections, but it does not appear to affect erectile response to visual erotic stimuli.

Erectile dysfunction, androgen deficiency, and libido are independently distributed conditions. Erectile dysfunction does not imply androgen deficiency; less than 10% of older men with ED are hypogonadal. Testosterone supplementation may not improve ED. Testosterone is not necessary for stimulus-evoked erections. Decreased libido may be related to androgen deficiency. Thus, testosterone supplementation may increase libido, and improved libido may increase the response to PDE-5 inhibitors and other treatment modalities for ED.

**Comment**

The prevalence of ED is rising sharply worldwide as the result of population growth overall and “graying” population trends. The presence of ED in a patient is frequently an indicator of comorbidities, including cardiovascular disease, diabetes, dyslipidemia, and depression. Despite its prevalence and an increasing awareness among the affected population, ED remains severely underdiagnosed and patients undertreated for it. Erectile dysfunction can result from psychological or organic causes, or a mixture of both; regardless of the underlying etiology, psychological factors are almost always involved.

In patients with comorbid diseases and ED, treatment should start with lifestyle and medication modification, followed by a combination of psychosocial counseling and oral therapy. Oral PDE-5 inhibitors have been shown to provide excellent efficacy in the treatment of ED in the general population and across a range of ages and background comorbidities. Oral PDE-5 inhibitors have also been shown to demonstrate an excellent safety and tolerability profile. Side effects are typically transient and related to the vasodilatory effects of the agents.\textsuperscript{18-20}

Aging is associated with a gradual decrease in bioavailable testosterone and an increase in the prevalence of androgen deficiency. Testosterone replacement therapy in hypogonadal men has been shown to increase strength, bone mass, and lean body mass. Testosterone
replacement therapy in hypogonadal men has also been correlated with increased libido and improved sense of well-being. Testosterone replacement has no clear-cut effect on ED, although it may improve the effectiveness of pharmacologic modes of therapy for ED. Testosterone replacement in hypogonadal men restores prostate volume and PSA levels to those seen in age-matched eugonadal men. Testosterone replacement therapy may increase hematocrit and lead to fluid retention and sleep apnea. Primary care physicians should understand the importance of detecting disorders of libido. Untreated low libido may lead to emotional gridlock between partners and the cessation of physical affection. Low libido can lead to ED and other organic and psychogenic sexual disorders. Low libido can also influence the effectiveness of therapeutic modalities used to treat other sexual dysfunctions. Finally, some cases of low libido are associated with androgen deficiency, for which patients can be treated.

References