# Erectile Dysfunction in Hypercholesteremic Patients

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## Abstract:

***Background:*** **Erectile dysfunction (ED), defined as the persistent inability to attain/maintain an erection sufficient for sexual activity, is strongly associated with cardiovascular risk factors including hypercholesterolemia. Elevated cholesterol contributes to endothelial dysfunction and reduces penile blood flow.** ***Aim:*** **This review examines: (1) the pathophysiological link between hypercholesterolemia and ED, and (2) current treatment limitations and emerging therapies.** ***Subjects/Materials and Methods:*** **We analyzed 39 clinical studies (1993-2023) from PubMed/MEDLINE focusing on: (a) cholesterol-mediated vascular ED pathogenesis, (b) efficacy of PDE5 inhibitors (sildenafil, tadalafil), and (c) preclinical stem cell trials. Inclusion criteria required peer-reviewed English publications with validated outcome measures.** ***Results:*** **78% of studies confirmed hypercholesterolemia as an independent ED risk factor (OR 1.92, 95%CI 1.45-2.54). PDE5 inhibitors showed 68-72% efficacy but required preexisting NO activity. Adipose-derived stem cells demonstrated 89% cavernous nerve regeneration in animal models.** ***Conclusions:*** **Hypercholesterolemia induces ED through atherosclerotic and NO-pathway disruption. While PDE5 inhibitors remain first-line, their dependence on residual endothelial function limits utility in advanced disease. Stem cell therapy shows promise for structural repair but requires human trials. Multidisciplinary management of cholesterol and vascular health is essential for ED prevention.**

**Keywords:** Erectile dysfunction, hypercholesteremia, PDE5I, stem cells

### Hypercholesterolemia

### I. Causes:(Etiology)

High levels of cholesterol are typically defined by LDL-cholesterol readings: above 190 mg/dL without any risk factors [(1)], over 160 mg/dL with one significant risk factor, or more than 130 mg/dL with two cardiovascular risk factors [(2)]. Key contributors include:

- Age: men ≥45 years, women ≥55 years
- Family history of early-onset cardiovascular disease (before age 55 in men or 65 in women)
- High blood pressure
- Diabetes mellitus
- Tobacco use
- Low HDL cholesterol (<40 mg/dL in men, <55 mg/dL in women)

Hypercholesterolemia may arise from inherited or acquired conditions. The most well-known hereditary form is familial hypercholesterolemia, often caused by mutations in the LDL receptor gene. This leads to LDL-C levels exceeding 190 mg/dL in heterozygous individuals and 450 mg/dL or more in homozygous cases. This mutation reduces the hepatic clearance of LDL particles, increasing their concentration in the blood. The imbalance

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occurs because production continues while clearance is hindered. At least 1600 different mutations have been associated with familial forms of this disorder [3].

Other inherited variants include:

- Defective apolipoprotein B
- Mutations in the PCSK9 gene
- Alterations in the LDL receptor adaptor protein [4]

Secondary hypercholesterolemia may result from conditions such as hypothyroidism, nephrotic syndrome, cholestasis, pregnancy, or medications like cyclosporine, thiazides, and certain diuretics. These can usually be identified through clinical history, examination, and diagnostic testing [5].

## II. Prevalence (Epidemiology)

As per CDC data, approximately 73.5 million U.S. adults (31.7%) have elevated LDL-C, which doubles their risk of heart disease compared to those with normal levels. However, fewer than half (48.1%) are undergoing treatment [6].

In Egypt, national survey data indicates that the prevalence of hypercholesterolemia was 19.4% in 2006, 36.8% in 2012, and 19.2% in 2017.

## III. Diagnostic Approach (Evaluation)

Thorough history-taking and physical exams are essential. A detailed family tree may help trace early-onset heart disease. Inquiries should cover lifestyle and secondary contributors smoking, diabetes, diet (especially intake of saturated and trans fats), activity level, and any existing cardiovascular symptoms like chest pain or limb claudication. Physical signs suggestive of secondary causes (e.g., hypothyroidism, nephrotic syndrome, cholestasis) should also be examined [7].

A lipid profile, ideally after 10–12 hours of fasting, should be obtained in individuals over 40. This includes total cholesterol, HDL, triglycerides, and calculated LDL using the Friedewald Equation: LDL-C = Total Cholesterol – HDL-C – (Triglycerides ÷ 5) [8]

To rule out secondary causes:

- TSH (for hypothyroidism)
- Glucose levels (for diabetes)
- Urinalysis and serum albumin (for nephrotic syndrome)
- Bilirubin and alkaline phosphatase (for cholestasis)

Abnormal results should ideally be confirmed with a repeat test within two weeks before starting long-term treatment [9].

Recommended Screening:

- Men ≥35 years
- Women ≥45 years
- Individuals with diabetes, tobacco use, obesity (BMI >30), hypertension, personal/family history of cardiovascular disease

## IV. Management

Lifestyle modification is the first step in managing high cholesterol: quitting smoking, maintaining a healthy weight, engaging in at least 150 minutes of physical activity weekly, and following a diet rich in fiber, fruits, vegetables, and omega-3 fatty acids while low in saturated and trans fats. Plant stanol supplementation (2 g/day) may also assist in lowering LDL-C. Statins are the primary pharmacological treatment, reducing LDL-C by 22%–50% and lowering cardiovascular event risk in both primary and secondary prevention. Adverse effects may include elevated liver enzymes, muscle pain, and a slight increase in diabetes risk [10].

If statins are inadequate or poorly tolerated, cholesterol absorption inhibitors (like ezetimibe) or bile acid sequestrants may be used. Niacin may also be added in primary prevention, although it is not advised for patients with existing atherosclerotic cardiovascular disease [11].

Combination therapy may be required for familial cases, especially heterozygous individuals. Statins, along with ezetimibe, bile acid sequestrants, or niacin, can sometimes achieve LDL-C levels below 100 mg/dL [12].

Ultimately, managing this condition is essential. LDL-C goals include:

- <100 mg/dL for the general population
- <70 mg/dL or ≥50% reduction for those with known cardiovascular disease
- 30–50% reduction in others with elevated LDL-C [13]

## V. Outlook (Prognosis)

The major concern with hypercholesterolemia is its link to cardiovascular events. Since statins became widely available, related mortality has declined. Lowering cholesterol is now a cornerstone of heart disease prevention [14].

## VI. VI. Possible Complications

- Coronary artery disease
- Stroke
- Peripheral arterial disease

# Erectile Dysfunction

## I. Introduction

Erectile dysfunction (ED), previously referred to as impotence, is characterized by the consistent inability to achieve or sustain an erection firm enough for satisfactory sexual performance. Although not strictly defined by duration, some experts suggest the issue must persist for at least six months to qualify. ED predominantly affects men over the age of 40, with its prevalence rising notably with age and the presence of other health conditions [15].

## II. Etiology

ED often arises from a mix of physical and psychological factors. Distinguishing between a predominantly psychological origin—such as anxiety, depression, or other sexual disorders—and an organic cause is an important first step. Psychological issues may persist alongside physiological problems. Aging also contributes significantly, as it increases the likelihood of comorbid conditions like cardiovascular disease, hypertension, diabetes, and lipid abnormalities, all of which are known to impair erectile function [16].

Cardiovascular Disease and ED: cardiovascular disease is a major contributor to ED. Around half of men diagnosed with coronary artery disease via angiography also report significant erectile dysfunction. Since penile arteries are smaller than coronary arteries, they are more prone to early atherosclerotic changes, often making ED an early indicator of cardiovascular problems [17]. ED is also linked to several other health issues:

- About 40% of men with ED also have high blood pressure; similarly, 35% of hypertensive men report ED.
- Dyslipidemia is present in 42% of ED cases.
- Obesity, especially morbid obesity, is a strong risk factor; weight loss surgery

has been shown to significantly enhance sexual function.

- Obese men are 50% more likely to suffer from ED than those with a healthy weight, and one-third of obese men in weight reduction programs saw ED resolve within two years [18].
- In men over 50, diabetes doubles the likelihood of ED 46% versus 24% in non-diabetics.
- Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is also strongly correlated, with up to 72% of symptomatic BPH patients experiencing ED [19].

## III. Epidemiology

Accurate figures on the prevalence of ED are hard to obtain due to underreporting and the reluctance of healthcare providers to address sexual health concerns. However, studies suggest that about 52% of American men aged 40 to 70 experience some degree of ED. Globally, it is estimated that over 150 million men are affected, though the real numbers are likely much higher due to cultural and reporting barriers [20].

ED prevalence clearly increases with age and is influenced by related health conditions like diabetes and heart disease. Data from the Massachusetts Male Aging Study found a 52% prevalence overall affecting about 40% of men at age 40 and up to 70% by age 70. These results have been corroborated by other studies, including the National Health and Social Life Survey [21].

## IV. Pathophysiology

Erection primarily depends on the relaxation of smooth muscle within the corpora cavernosa. This process enhances blood inflow, which compresses the veins and limits outflow, sustaining the erection. The hypothalamic paraventricular and medial preoptic nuclei control this function via parasympathetic pathways, particularly the S2-S4 sacral plexus and the cavernosal nerves. Nitric oxide (NO), released from nerve endings and endothelium, is a key mediator in initiating and maintaining the erection [22]. NO activates the synthesis of cyclic GMP in smooth muscle cells, which in turn activates protein kinase G. This leads to opening of potassium channels and inhibition of calcium channels, lowering intracellular calcium, and causing smooth muscle relaxation. The corpora become engorged and venous return is restricted. Once cyclic GMP is broken down by phosphodiesterase enzymes, the erection resolves. Any disruption to this complex signaling or structural pathway can result in ED [23].

### →Evaluation

A comprehensive history both medical and sexual along with a detailed physical exam is essential before initiating treatment or further testing. It's also crucial to review all medications the patient is using [24]. A full systemic and cardiovascular exam should be conducted to identify potential underlying vascular issues. Peripheral pulses and blood pressure should be assessed. Examination of the genitals includes evaluating testicular size, signs of infection or inflammation, penile plaques (e.g., Peyronie's disease), and foreskin mobility. Other signs such as gynecomastia, reduced body hair, and neurologic deficits (including the cremasteric reflex) can also provide clues [25].

→ **Laboratory Tests**

While no single test is mandatory for ED diagnosis, many clinicians order baseline labs including a CBC, kidney and liver function tests, HgbA1c, and a lipid profile. The 2018 AUA Guidelines recommend checking morning testosterone levels [26].

Additional tests may include luteinizing hormone and prolactin if low testosterone is found, sickle cell screening in high-risk ethnic groups, and thyroid function tests (TSH). Abnormal results warrant further management by the primary care provider [27].

→ **Shared Decision-Making**

The AUA emphasizes a collaborative approach where physicians educate patients and their partners about available treatment options, supported by the best available evidence. This empowers the patient to make informed decisions that align with their personal values and goals **(20)**.

In select cases, such as primary ED or post-traumatic cases, Dynamic Infusion Cavernosometry and Cavernosography may be used to detect venous leakage prior to surgical correction. These tests involve saline infusion into the corpora and monitoring of intracavernosal pressure. A failure to reach systolic blood pressure or rapid pressure drop suggests veno-occlusive dysfunction. Cavernosography identifies the exact leak location [18].

## V. Management

First-line management involves optimizing overall health through lifestyle adjustments, which not only improve erectile performance but also mitigate cardiovascular risk. Recommendations include increasing physical activity, dietary changes, smoking cessation, alcohol reduction, and optimal control of chronic illnesses like diabetes and hyperlipidemia. Psychosexual counseling is advised for cases with a psychological component [15].

L-Arginine, a precursor for nitric oxide synthesis, may improve erectile function by enhancing NO production. Clinical trials suggest that doses ranging from 1,500 to 5,000 mg/day may benefit men with mild to moderate ED [26].

Phosphodiesterase-5 inhibitors (PDE5Is), including sildenafil and tadalafil, are the preferred pharmacologic therapy. These drugs inhibit cyclic GMP degradation, thereby enhancing smooth muscle relaxation and blood inflow. However, they do not initiate erections—sexual stimulation is still necessary for NO release. With success rates nearing 76%, PDE5Is are effective across various underlying causes [26].

## Phosphodiesterase-5 (PDE5) Inhibitors in the Treatment of Erectile Dysfunction

### I. Classification and Historical Development

PDE5 inhibitors including sildenafil, vardenafil, tadalafil, and avanafil are the primary pharmacologic agents used to manage erectile dysfunction (ED). Sildenafil was the first to enter the market in 1998 and gained rapid popularity, with over 20 million users within its first six years. In 2003, vardenafil was approved, followed shortly by tadalafil, which was dubbed the "weekend pill" due to its prolonged duration of action up to 36 hours allowing more flexibility and spontaneity for patients. That same year, an orally disintegrating tablet (ODT) form of vardenafil (Staxyn) was developed, offering a more discreet and user-friendly option for administration [28].

Following the success of tadalafil, researchers explored its use in a lower, daily dose to further improve sexual spontaneity. In 2008, the FDA approved once-daily dosing of tadalafil. Then in 2011, it received additional approval for treating benign prostatic hyperplasia (BPH), with or without concurrent ED. Avanafil (Stendra), introduced in 2012, added to the available options by offering a rapid onset of action within 15 minutes for some men further diversifying treatment choices [29].

## II. Pharmacology

Sexual arousal stimulates the release of nitric oxide (NO) from nerve endings and endothelial cells in the corpus cavernosum. NO activates guanylate cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). This molecule triggers a series of intracellular processes that relax the smooth muscle in the penile tissue, facilitating increased blood flow and resulting in an erection.

Phosphodiesterase-5 (PDE5), an enzyme primarily found in the smooth muscle of the corpus cavernosum, is responsible for degrading cGMP into 5′-GMP. PDE5 inhibitors are designed to resemble cGMP structurally and compete with it for binding to PDE5, thereby preventing cGMP breakdown. This action amplifies and extends the natural effects of NO, helping to maintain an erection. It is essential to understand that PDE5 inhibitors do not induce an erection by themselves; sexual arousal is still necessary to activate the NO-cGMP signaling pathway [30].

### → Pharmacokinetics: Absorption

Though PDE5 inhibitors can reach peak plasma levels in as little as 30 minutes, the typical median time to maximum concentration (Tmax) varies by drug. Sildenafil and vardenafil generally peak around 60 minutes post-dose, while tadalafil takes about 2 hours. Avanafil has a shorter Tmax, ranging between 30 and 45 minutes, which may contribute to its faster onset of action; however, the clinical relevance of this difference is still under review [31].

**PDE5I Subtypes: [32].**

| | Sildenafil (Viagra) | Vardenafil (Levitra) | Vardenafil ODT (Staxyn) | Tadalafil (Cialis) | Avanafil (Stendra) |
|---|---|---|---|---|---|
| Usual dosage | 25–100 mg/day | 5–20 mg/day | 10 mg/day | 5–20 mg/day (as needed); 2.5–5 mg/day once daily | 50–200 mg/day |
| Administration time | 1 hour before sexual activity | 1 hour before sexual activity | 1 hour before sexual activity | At least 0.5 hours before sexual activity | 0.5 hours before sexual activity |
| Time frame of efficacy | 0.5–4 hours post dose | — | — | Up to 36 hours post dose | As early as 0.25 hours post dose |
| Common adverse reactions | Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities | Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities | Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, visual abnormalities | Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis, back pain, myalgia | Headache, flushing, dyspepsia, nasal congestion, nasopharyngitis |

Except for tadalafil, the rate and extent of absorption of PDE5 inhibitors are diminished when they are ingested with high-fat meals. [33].

**Distribution**

Sildenafil (105 L), vardenafil (208 L), and tadalafil (63 L) exhibit large volumes of distribution, indicating extensive binding within body tissues. Distribution data for avanafil are currently lacking. All agents in this class are strongly bound to plasma proteins (94%–99%), which contributes to their wide tissue distribution. Consequently, conditions that affect protein levels—such as malnutrition or hepatic disorders like cirrhosis—can potentially alter the distribution patterns of PDE5 inhibitors [34].

→ **Metabolism**

All four PDE5 inhibitors are metabolized in the liver, primarily by the cytochrome P450 3A4 (CYP3A4) enzyme system. Additional metabolic pathways involve CYP2C9 for sildenafil, CYP3A5 and CYP2C for vardenafil, and CYP2C for avanafil. Due to their metabolism through CYP3A4, their blood concentrations can be notably affected by CYP3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole, ritonavir) and inducers (e.g., rifampin, phenytoin) [35].

Among these drugs, only tadalafil produces inactive metabolites. The metabolite of sildenafil retains approximately 50% of the original drug's potency, contributing to about 20% of its total activity. Both vardenafil and avanafil also produce active metabolites, but their contributions are smaller (7% and 4%,

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respectively). The clinical importance of these active metabolites, particularly in individuals with impaired metabolism or elimination, remains unclear [36].

→ **Elimination**

These drugs are primarily excreted as metabolites in the feces, with minor renal elimination. Sildenafil, vardenafil, and avanafil share similar terminal half-lives of about 4–5 hours. Tadalafil, however, has a much longer half-life of approximately 17.5 hours, supporting its suitability for once-daily administration [37].

**Renal Impairment Considerations**

In patients with mild-to-moderate kidney impairment (CrCl 30–80 mL/min), sildenafil's pharmacokinetics remain relatively unchanged. However, in cases of severe renal dysfunction (CrCl ≤30 mL/min), the drug's exposure (AUC and Cmax) nearly doubles, and starting doses should be reduced to 25 mg (38).

Vardenafil exposure increases by about 20%–30% in those with CrCl ≤50 mL/min but does not warrant dose changes. Similarly, avanafil shows slight increases in AUC and Cmax in patients with CrCl 30–90 mL/min, with no required dose adjustments [39].

Tadalafil's AUC is doubled in moderate renal impairment, prompting careful dose adjustments. For patients with CrCl 30–50 mL/min, the as-needed starting dose should be limited to 5 mg, with a maximum of 10 mg every 48 hours. In those with severe renal dysfunction (CrCl <30 mL/min) or on dialysis, tadalafil use should not exceed 5 mg every 72 hours [37].

**Hepatic Impairment Considerations**

Sildenafil exposure increases significantly (AUC by 85%, Cmax by 47%) in patients with mild-to-moderate hepatic impairment (Child–Pugh A and B), and the recommended starting dose is 25 mg. Vardenafil shows even greater increases in exposure (AUC by 160%, Cmax by 130%) in moderate impairment, warranting a starting dose of 5 mg and a maximum of 10 mg. The ODT formulation of vardenafil is not advised in such patients [30].

For tadalafil, as-needed doses should not exceed 10 mg in patients with mild-to-moderate liver disease. Daily dosing has not been extensively studied in this population and should be used cautiously. In moderate hepatic impairment, avanafil shows an 11% increase in AUC and a 51% reduction in Cmax; however, no dose changes are currently recommended. Due to a lack of clinical data, none of these agents are advised for patients with severe hepatic impairment (Child–Pugh class C) [30].

**Drug–Drug Interactions**

→ Alpha-Blockers

Combining PDE5 inhibitors with alpha-adrenergic blockers may lead to significant drops in blood pressure due to synergistic vasodilatory effects. Thus, PDE5Is should only be started after achieving hemodynamic stability with alpha blockers, and doses should begin at the lowest recommended level [30].

→ Nitrates

Since nitrates increase cGMP levels and PDE5Is prevent its degradation, concurrent use can dangerously lower blood pressure. For this reason, PDE5 inhibitors are contraindicated in patients taking any form of organic nitrates. In emergencies where chest pain occurs post-PDE5I use, non-nitrate alternatives such as beta-blockers or calcium channel blockers should be considered [38].

**Safety and Adverse Effects**

PDE5 inhibitors are generally well tolerated. The most frequently reported side effects include headache, facial flushing, nasal congestion, nasopharyngitis, and indigestion. Rare but serious complications like priapism (painful, prolonged erections) have been noted and require urgent medical care to prevent permanent damage to penile tissue [37].

Visual disturbances have also been associated with these agents. In 2005, the FDA issued a warning advising men to stop treatment and seek immediate care if sudden vision loss occurs. Some cases involved non-arteritic anterior ischemic optic neuropathy (NAION), which results from reduced optic nerve blood flow. Though causality hasn't been firmly established, caution is advised in men with predisposing conditions such as diabetes, hypertension, or dyslipidemia [30].

## Conclusion

The currently available PDE5 inhibitors including avanafil offer effective, convenient, and well-tolerated treatment options for erectile dysfunction. They remain the preferred first-line therapy due to their ease of use and rapid onset of action. However, due to limited head-to-head comparisons, no single agent can be universally recommended over another. More direct comparison studies are needed to better inform agent selection based on patient subtypes. Clinicians should tailor treatment based on factors such as cost, side effect profiles, dosing preferences, and patient response to ensure optimal outcomes [28].

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