# Potential beneficial impacts of tadalafil on cardiovascular diseases

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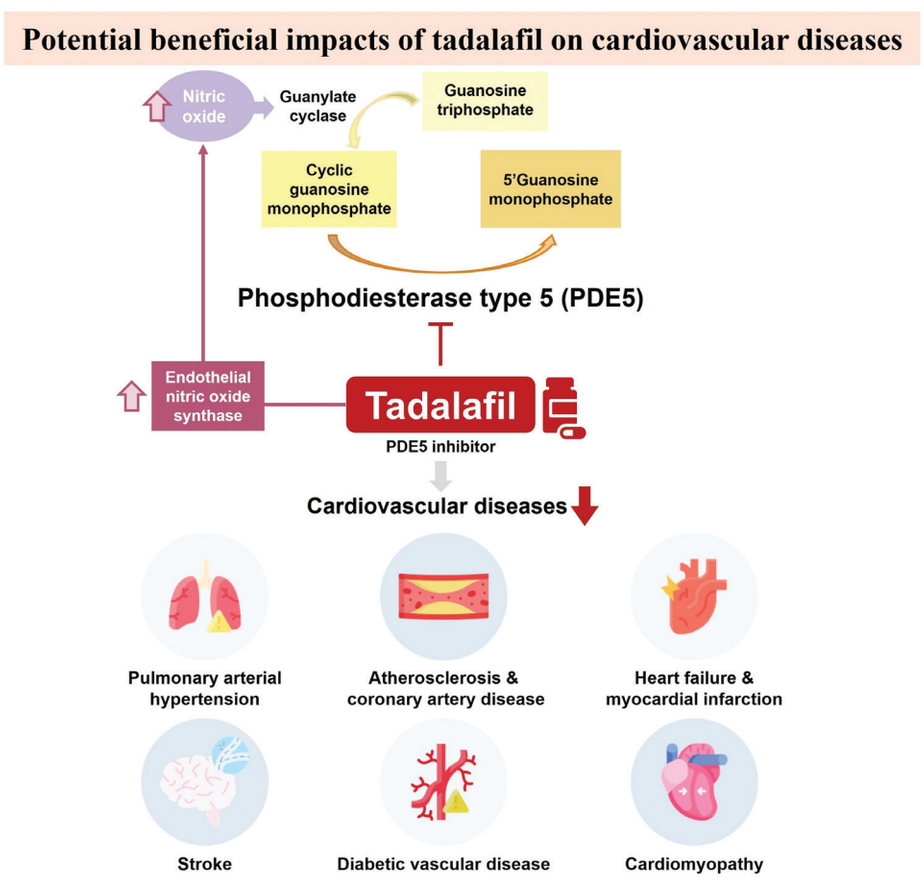
**Abstract**

Tadalafil is a selective phosphodiesterase type 5 (PDE5) inhibitor commonly used for the treatment of erectile dysfunction and benign prostatic hyperplasia. Its mechanism of action involves the inhibition of PDE5, leading to increased levels of nitric oxide and cyclic guanosine monophosphate in the corpus cavernosum, which facilitates smooth muscle relaxation. This article reviews studies using tadalafil in the treatment of cardiovascular diseases and emphasizes its potential advantages in conditions such as pulmonary arterial hypertension, atherosclerosis, coronary artery disease, myocardial infarction, heart failure, stroke, diabetic ulcers, and cardiomyopathy. Although tadalafil shows potential efficacy in treating cardiovascular disease, further experimental studies are needed to clarify its pharmacological effects on cardiovascular protection beyond PDE5 inhibition.

**Keywords:** Cardiovascular disease; Coronary artery disease; Tadalafil

Graphical abstract



## 1. INTRODUCTION

Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor commonly used for the treatment of adult men with erectile dysfunction (ED) and/or the symptoms of benign prostatic hyperplasia (BPH).[1] Although the mechanistic insights are not well elucidated, recent clinical data suggest the use of PDE5 inhibitors including tadalafil may be associated with reduced cardiovascular events and overall mortality in patients with ED.[2]

Tadalafil has a long half-life that allows for alternate-day administration.[3] Nitric oxide (NO) acts as an activator for soluble guanylyl cyclase, which induces cyclic guanosine monophosphate (cGMP) production. PDE5 is a cGMP-specific phosphodiesterase that converts cGMP to the inactive 5′-guanosine monophosphate form.[4,5] Tadalafil inhibits PDE5 in the penile corpus cavernosum and regulates smooth muscle relaxation by elevating intracellular NO and cGMP levels.[6] However, the mechanisms by which tadalafil enhances intracellular NO include, but are not limited to, increasing the bioavailability of NO[7] and stimulating endothelial NO synthase activity.[3] Therefore, tadalafil is contraindicated in patients taking any form of organic nitrates because of the risk of potentially life-threatening hypotension caused by a synergistic reduction in blood pressure via the NO/cGMP pathway.[8] Headache and dyspepsia are the most frequently reported adverse effects associated with tadalafil treatment. These adverse events decrease with continued administration.[9]

PDE5 is a member of the mammalian phosphodiesterase family that hydrolyzes cGMP and cyclic adenosine monophosphate (cAMP).[10] Three PDE5 isoforms are present in humans: PDE5A1, PDE5A2, and PDE5A3. Both PDE5A1 and PDE5A2 are expressed in renal vessels, glomeruli, tubular epithelial cells of the renal proximal tubule, and the medullary collecting duct. Notably, PDE5A2 is abundantly expressed in various tissues, including penile endothelium, penile smooth muscle, aortic smooth muscle, and aortic endothelium. In contrast, PDE5A3 is specifically expressed in vascular smooth muscle cells.[11] On the basis of the widespread distribution of PDE5 in multiple organs, the potential effects of tadalafil treatment on diseases beyond ED and BPH should be further considered.

Although the intersection between cardiovascular and sexual health continues to be an important issue, the PDE5 inhibitors are infrequently associated with major adverse cardiovascular events.[12,13] Furthermore, the use of PDE5 inhibitors primarily in men with or without known coronary artery disease (CAD) was associated with a lower risk for cardiovascular events and overall mortality, which highlights the potential clinical benefits of PDE5 inhibitors beyond ED treatment.[2,14] Among the current available PDE5 inhibitors, tadalafil was recognized with high cardiovascular safety in large numbers of patients.[15,16] Tadalafil could not only elevate intracellular NO and cGMP levels[6] but also stimulate endothelial NO synthase activity and increase the bioavailability of NO.[7] The above may provide a mechanistic rational to its potential clinical cardiovascular protection effects. In fact, tadalafil was shown to independently improve endothelial function in patients with increased cardiovascular risk, regardless of the degree of ED.[3,17,18] Given the significant impacts of vascular endothelial function on general cardiovascular diseases including hypertension, systemic atherosclerosis, CAD, peripheral artery disease, ischemic cardiomyopathy, and others one may speculate the universal NO-related cardiovascular benefits of tadalafil. However, the existing data may be varied with different PDE5 inhibitors in different diseases and might not be sufficient to support its general clinical use. Future large-scaled studies may be required to confirm the clinical role of PDE5 inhibitors, especially tadalafil in each individual cardiovascular disease.[2] In this article, we sought to review the currently available clinical evidence of tadalafil's efficacy for a rationale to its potential use in various cardiovascular diseases.

## 2. THE EFFECTS OF TADALAFIL IN CARDIOVASCULAR DISEASE

### 2.1. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is defined by a chronic increase in pulmonary artery pressure, which is characterized by vascular proliferation and remodeling. This condition can progress to right heart failure or even death.[19] Complex pathological mechanisms contribute to the progression of PAH, including endothelial dysfunction, inflammation, and dysregulation of the NO pathway. NO is synthesized from arginine in endothelial cells via NO synthase, leading to vasodilation through a complex pathway involving cGMP production in vascular smooth muscle cells. On the other hand, PDE5 degrades cGMP, which disrupts the vasodilatory pathway initiated by NO. Inhibition of PDE5 activates NO/cGMP signaling, leading to an increase in cytosolic cGMP levels. This activates cGMP-dependent protein kinase, which dilates pulmonary arterial smooth muscles and reduces pulmonary vascular resistance.[20] Tadalafil attenuates vascular remodeling by inhibiting cell proliferation, promoting apoptosis, and downregulating PDE5 expression in idiopathic PAH pulmonary arterial smooth muscle cells.[21] In fact, tadalafil reduces pulmonary arterial pressure in patients with PAH. Tadalafil also enhances exercise capacity and reduces clinical deterioration in patients with PAH.[22] A recent clinical trial showed that a fixed-dose combination of an endothelin receptor antagonist and tadalafil, administered once daily, significantly improved pulmonary vascular resistance.[23] Although tadalafil has received Food and Drug Administration (FDA) approval for the treatment of PAH,[24] further mechanistic insights and clinical studies are required to determine the optimal dose of tadalafil and its effects as an adjunctive therapy in PAH.

### 2.2. Atherosclerosis and CAD

Atherosclerotic lesions are localized thickenings of the innermost layer of the artery, composed of inflammatory cells, connective tissue, lipids, and debris. Myocardial infarction usually occurs when the atheroma ruptures because of vascular inflammation with the formation of a significant amount of thrombus in the coronary artery, which could happen with or without a significant atherosclerotic lesion obstructing blood flow. The above makes atherosclerosis the primary cause of CAD.[25] ED is often associated with a range of risk factors for CAD and reduced endothelial function. Given that endothelial dysfunction is an early step in the development of atherosclerosis, chronic tadalafil therapy could improve endothelial function in patients with increased cardiovascular risk, as assessed using brachial artery flow-mediated dilation and nitrite/nitrate and endothelin-1

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plasma levels.[3] Tadalafil reduces serum endothelin-1 and tissue-type plasminogen activator levels while retaining its inhibitory effects on circulating angiogenic cells and colony-forming units, implying a beneficial effect of tadalafil on endothelial cell damage.[26] Tadalafil also improves lower urinary tract symptoms suggestive of BPH.[27] Recent clinical evidence suggests that risk factors for atherosclerosis could be associated with the severity of lower urinary tract symptoms,[28,29] and long-term tadalafil treatment resulted in a reduction in arteriosclerosis by improving pulse wave velocity in elderly patients with these symptoms.[30]

On the other hand, treatment with a 20-mg dose of tadalafil showed no adverse effects on myocardial blood flow in patients with stable CAD, suggesting it might not affect or even improve myocardial blood flow during increased workload in both normal and poorly perfused myocardium.[31] Another study also demonstrated that tadalafil did not affect the duration of exercise-induced myocardial ischemia in individuals with CAD.[32] However, in patients with chronic stable angina as a common manifestation of CAD, reduced blood pressure was observed after a single oral dose of tadalafil.[33,34] Taken together, tadalafil might act as a mild systemic and/or coronary vasodilator, resulting in minimal decreases in blood pressure in patients with stable CAD. Moreover, tadalafil might enhance endothelial function in patients at high cardiovascular risk, suggesting its potential role in atherosclerosis. Further clinical trials are needed to justify if tadalafil could be prophylactic for atherosclerosis and CAD.

### 2.3. Heart failure and myocardial infarction

Heart failure is a complex clinical syndrome resulting from structural or functional heart impairment, with myocardial infarction as the most common complication.[35,36] The NO–cyclic GMP–protein kinase G axis has been demonstrated to provide anti-ischemic effects,[37] and PDE5 inhibitors, like tadalafil, may benefit heart failure by preventing cGMP degradation.

In a clinical trial, tadalafil improved arterial stiffness and left ventricular diastolic function in patients with ED without known atherosclerotic risk factors or cardiac diseases, showing its positive effects on endothelial dysfunction and cardiac function.[38] In a rat model of heart failure induced by aortocaval fistula, administration of tadalafil for 4 weeks reduced cardiac hypertrophy and improved left ventricular function. Furthermore, renal function and oxidative mechanisms were impaired in rats with heart failure, while tadalafil treatment improved both renal and oxidative parameters under heart failure conditions.[39] In another myocardial infarction mouse model with permanent left coronary artery ligation, tadalafil treatment for 4 weeks attenuated cardiac hypertrophy and pulmonary edema.[40] Furthermore, tadalafil has been shown to reduce myocardial infarct size in rats with coronary artery occlusion-induced acute myocardial infarction.[41] Altogether, tadalafil has demonstrated cardioprotective benefits in clinical and experimental animal models of heart failure and myocardial infarction. However, whether tadalafil has a clinical effect in treating heart failure and myocardial infarction still requires further study.

### 2.4. Stroke

Endothelial cell function is closely associated with cerebral vessel disease and can play a role in the pathogenesis of stroke.[42] Oral administration of tadalafil increased cerebral vascular density and the percentage of Bromodeoxyuridine (BrdU)-positive endothelial cells around the ischemic boundary, suggesting that tadalafil may improve angiogenesis and neurogenesis in rats with embolic middle cerebral artery occlusion.[43] In a clinical trial, tadalafil administration was associated with enhanced oxygenation of the cerebral microvasculature, indicating an improvement in perfusion within this vascular network among patients with stroke with cerebral small-vessel disease.[44] Although tadalafil has shown positive effects in some experimental and clinical studies of ischemic stroke, several cases have demonstrated the occurrence of stroke after tadalafil administration.[45,46] Another study showed that tadalafil administration to patients after a cerebral stroke was associated with a reduction in blood flow not only to regions adjacent to the stroke site but also to areas distant from the stroke.[47] Given the controversial effects of tadalafil in stroke, tadalafil should be used very carefully and/or even avoided in subjects at high risk of cerebrovascular ischemic events. Future research should further investigate this serious and potentially life-threatening association.

### 2.5. Diabetic vascular disease

Diabetes is a condition characterized by increased blood glucose levels, with a global prevalence.[48] Hyperglycemia can lead to both microvascular and macrovascular complications, posing a serious threat to patients with diabetes.[49] In diabetes, nonhealing ulcers often occur especially in the legs or foot because of reduced blood flow or tissue damage.[50] Previous studies showed that tadalafil administration improved apical limb width in patients with ED with type 2 diabetes.[51] Although current research suggests that tadalafil may enhance microvascular circulation in clinical patients with ED with type 2 diabetes, further mechanistic studies and clinical trials are needed to confirm these findings because of the complexity of diabetes pathology and its vascular complications.

### 2.6. Cardiomyopathy

Cardiomyopathies are myocardium disorders characterized by mechanical or electrical dysfunction, often manifesting as abnormal ventricular hypertrophy or dilation. These conditions can result in cardiovascular mortality or heart failure progression.[52] Tadalafil administration reduced cardiomyocyte atrophy/

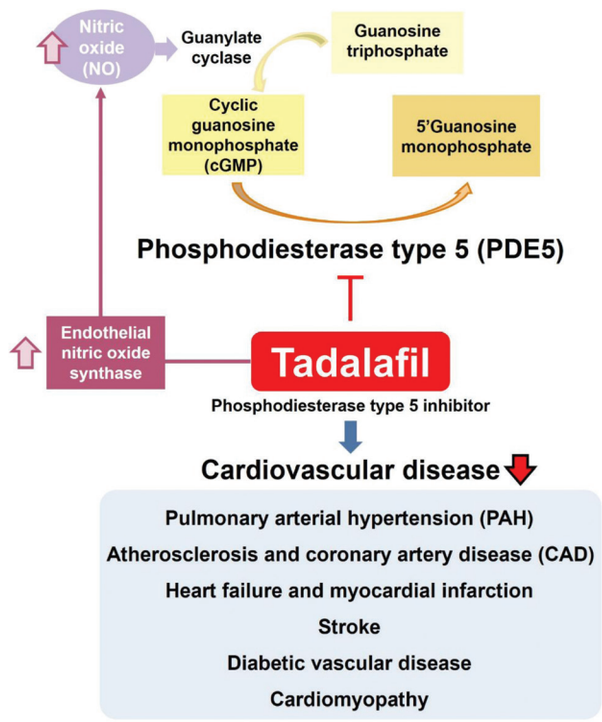


**Fig. 1** Tadalafil, a PDE5 inhibitor, demonstrates protective effects in cardiovascular diseases.

**Table 1**

**Summary of tadalafil used in cardiovascular disease in this review article**

| Cardiovascular disease | Samples | Tadalafil treatment | Key finding | References |
|---|---|---|---|---|
| Pulmonary arterial hypertension | Idiopathic pulmonary arterial hypertension—pulmonary arterial smooth muscle cells | 0.1, 1, 10, or 100 μM for 72 h | Reduced the cell viability of pulmonary arterial smooth muscle cells from patients with idiopathic pulmonary arterial hypertension | Yamamura et al[21] |
| | A total of 405 patients with pulmonary arterial hypertension | 2.5, 10, 20, or 40 mg orally daily for 16 wk | Increased walking distance and time to clinical worsening | Galiè et al[22] |
| Atherosclerosis | A total of 32 men with increased cardiovascular risk | 20 mg orally every other day for 4 wk | Improved endothelial function and these effects are sustained after discontinuation of therapy | Rosano et al[3] |
| | Mononuclear cells from healthy men were cultured with serum from patients with ED to obtain circulating angiogenic cells and colony-forming units | 20 mg orally every other day for 4 wk in patients with ED | Reduced endothelin-1 and plasminogen activator but did not improve circulating angiogenic cell and colony-forming units | Pelliccione et al[26] |
| | A total of 68 patients with lower urinary tract symptoms | 5 mg orally daily for 48 wk | The pulse wave velocity of 75 y or older group showed significant improvement at week 24 | Hayashi et al[30] |
| CAD | A total of 7 patients with stable CAD | 20 mg (single dose) | Improved myocardial blood flow during increased workload | Weinsaft et al[31] |
| | A total of 23 patients with stable CAD | 10 mg (single dose) | No significant effect on myocardial ischemia duration. But lower systolic blood pressure before, during, and after exercise | Patterson et al[32] |
| | A total of 50 patients with chronic stable angina | 5 and 10 mg orally (single dose) | Small decrease in systolic blood pressure and diastolic blood pressure | Kloner et al[34] |
| Heart failure | A total of 30 patients with ED | 20 mg orally (single dose) | Improved the arterial stiffness and left ventricular diastolic function | Özdabakoğlu et al[38] |
| | Male rats (aortocaval fistula model) | 5 mg/kg i.p. daily for 4 wk | Improved left ventricular function and overall cardiac function | Mora et al[39] |
| Myocardial infarction | Male mice (myocardial infarction model) | 1 mg/kg i.p. daily for 4 wk | Reduced cardiac hypertrophy and pulmonary edema | Salloum et al[40] |
| | Male rats (acute myocardial infarction model) | 10 mg/kg orally (single dose) | Reduced myocardial infarct size and ischemic cell death | Sesti et al[41] |
| Stroke | Male Wistar rats (embolic stroke model) | 2 and 10 mg/kg daily orally for 6 d | Increased cerebral vascular density and neurogenesis | Zhang et al[43] |
| | Patients with cerebral small-vessel disease | 20 mg orally (single dose) | Improved vascular parameters and cerebral perfusion | Ölmestig et al[44] |
| Diabetics vascular disease | A total of 20 patients with type 2 diabetes and have ED | 5 mg orally daily for 4 wk | Increased capillary width and the rate of blood flow | Lee et al[51] |
| Cardiomyopathy | Male C57BL/6J mice (doxorubicin-induced cardiomyopathy model) | 4 mg orally daily for 14 d | Attenuated left ventricular dilatation and dysfunction | Jin et al[53] |
| | Male CF-1 mice (doxorubicin-induced cardiomyopathy model) | 4 mg orally daily for 9 d | Improved left ventricular function and prevented cardiomyocyte apoptosis | Koka et al[54] |
| | Male mdx mice and golden retriever muscular dystrophy canines | 100 mg/L in drinking water for 6 wk or 7 mo in mice and 1 mg/kg orally daily for 16 mo in canines | Attenuated the onset of dystrophic cardiomyopathy | Hammers et al[55] |

CAD = coronary artery disease; ED = erectile dysfunction; i.p. = intraperitoneal.

degeneration, decreased myocardial fibrosis, and attenuated left ventricular dilatation and dysfunction induced by doxorubicin treatment. The study also showed that tadalafil's effects on alleviating doxorubicin cardiomyopathy occurred through the cGMP signaling pathway.[53] Moreover, tadalafil exhibited a cardioprotective effect in doxorubicin-induced cardiomyopathy via regulating mitochondrial superoxide dismutase, cardiac cGMP levels, and protein kinase G activity without interfering with the chemotherapeutic effects of doxorubicin.[54] In addition, tadalafil delayed the progression of cardiomyopathy in dystrophin-deficient hearts in the mdx mouse and golden retriever models of Duchenne muscular dystrophy.[55] Although tadalafil may have cardioprotective effects in some particular animal models of cardiomyopathy, further clinical investigations are still needed for some common causes, such as inflammation or ischemia-induced cardiomyopathy.

## 3. POTENTIAL MECHANISMS OF TADALAFIL IN DIFFERENT CARDIOVASCULAR DISEASES

The majority of the protective effects of tadalafil are suggested from its PDE5 inhibition characteristics. Endothelial dysfunction is often associated with NO production. Endothelial cells in the arterial vasculature release NO, which induces smooth muscle relaxation and exerts a variety of physiological effects, primarily through the activation of soluble guanylate cyclase, which enhances cGMP synthesis. This increase in cGMP concentrations subsequently leads to a reduction in intracellular calcium levels, promoting vasodilation. The degradation of cGMP is mediated by intracellular PDEs, which are widely distributed across various tissues and responsible for hydrolyzing cyclic nucleotides. Specifically, PDE5 plays a crucial role in the catabolism of cGMP. As a PDE5 inhibitor, tadalafil may be a promising therapeutic option for managing cardiovascular diseases (Fig. 1). However, it is not known if all the clinical mechanistic effects of tadalafil should be similar to that of other PDE5 inhibitors. Given the varied clinical effects of tadalafil on different cardiovascular diseases, the direct organ protection of tadalafil beyond PDE5 inhibition should be also considered especially in the case of cardiomyopathy.

In conclusion, in this review, in addition to treating ED and BPH, it was highlighted how tadalafil may exhibit significant potential to improve cardiovascular diseases (Table 1). In PAH, tadalafil has been shown to reduce pulmonary arterial pressure, improve exercise capacity, and reduce clinical deterioration. In atherosclerosis and CAD, tadalafil may help attenuate the progression of atherosclerosis and CAD. In heart failure and myocardial infarction, tadalafil has demonstrated cardioprotective effects by reducing cardiac hypertrophy, pulmonary edema, and myocardial infarct size. In stroke and diabetic vascular disease, tadalafil has led to improvements in microvascular perfusion, which may benefit patients with ischemic stroke and diabetic wounds. In cardiomyopathy, tadalafil has demonstrated potential in alleviating chemotherapy-induced cardiomyopathy and delaying muscular dystrophy-related cardiomyopathy in animal models. Although tadalafil has received approval from the FDA as a commercial medication for the treatment of ED, BPH, and PAH, it might be used cautiously in subjects at high risk of cerebrovascular ischemic events. Although tadalafil demonstrates potent efficacy in various cardiovascular diseases, its appropriate dosage and potential applications in different medical conditions continue to generate significant interest. Given the potentially wide application of tadalafil to clinical settings, its novel pharmacological effects on cardiovascular protection beyond PDE5 inhibition also require further experimental investigation.

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