

CARDIOVASCULAR DRUGS

Relevant Scientific Statements

AHA/ESC 2013 consensus document on sexual counselling in CVD

Sexual counselling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). *Eur Heart J*. 2013;**34**:3217–35.

AHA 212 Statement on sexual activity and CVD

Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1058-72.

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Drug Interactions

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that catalyse the oxidation of organic substances, and they are the major enzymes involved in drug metabolism. Permeability glycoprotein (P-gp) mediates the export of drugs from cells located in the small intestine, blood-brain barrier, hepatocytes, and kidney proximal tubule, serving a protective function for the body against foreign substances. Intestinal absorption, biliary excretion, and urinary excretion of P-gp substrates can therefore be altered by either the inhibition or induction of P-gp. A wide spectrum of drugs including cardiovascular drugs are known CYP or P-gp substrates and/or inhibitors, and may interfere with each other's concentrations.¹ Digoxin, amiodarone, warfarin and new oral anticoagulant agents (thrombin and Xa inhibitors), calcium channel blockers, beta blockers, and antiplatelet agents may be affected by the concomitant administration of anticancer drugs, antibiotics, and steroids (Appendix 1). Interactions are discussed in relevant chapters.

Antiarrhythmic Drugs

Beta blockers are discussed in the Chapters on Hypertension and Heart Failure. Other antiarrhythmic agents are discussed in the Chapters on Tachyarrhythmias.

Antiplatelet Agents

Aspirin and P2Y₁₂ receptor blockers are discussed mainly in the Chapter on UA/NSTEMI.

Anticoagulants

Heparins, warfarin and new anticoagulants such as thrombin and Xa inhibitors are mainly discussed in the Chapters on UA/NSTEMI, Valve Disease, and AF.

Beta blockers, Diuretics, ACEIs, ARBs, CCBs

They are discussed in the Chapters on Hypertension and Heart Failure.

Statins, Fibrates

They are mainly discussed in the Chapter on Stable CAD.

Drugs for Erectile Dysfunction

Erectile dysfunction is common, affecting almost 40% of men over 40 years of age (with varying degrees of severity) and increases in frequency with age.^{2 3} It can be psychogenic, organic, or mixed. The most common causes of organic erectile dysfunction are cardiovascular risk factors (diabetes, hypertension, dyslipidemia, obesity) and testosterone deficiency. Erectile dysfunction is a predictor of coronary artery disease, especially in men >60 years of age.³

Phosphodiesterase-5 (PDE5) inhibitors (PDE5Is) (*sildenafil*, *varденаfil*, *tadalafil*, and *varденаfil*) are used for erectile dysfunction. Sildenafil and tadalafil are also prescribed for pulmonary hypertension (see chapter). There is now evidence that PDE5Is do not significantly affect the incidence of adverse cardiovascular events,⁴ and may be associated with reduced mortality in patients with stable ischemic heart disease as well as those with recent myocardial infarction.⁵ Tadalafil, in particular, has fewer effects on the cardiovascular system than the other PDE5Is, as exemplified by its minimal effects on BP in healthy control subjects. Sildenafil (50-100 mg) and vardenafil (10-20 mg) lead to peak plasma levels in 60 min and have a half-life of 3-5 hours. Tadalafil (10-20 mg) peaks at 2 hours, has a half-life of 17.5 h and its absorption is not influenced by food. Reduced initial doses are required for patients with hepatic impairment, creatinine clearance < 30 ml/min, and age >65 years.

PDE5Is improve erectile function by enhancing nitric oxide availability in the penis and its supplying vasculature, resulting in vasodilation and increased blood flow. Since phosphodiesterase-5 is also located elsewhere in the body, including the pulmonary and systemic vasculature and in hypertrophied myocardium, PDE5Is are also used for pulmonary arterial hypertension. Initial evidence also suggests beneficial effects in congestive heart failure, secondary pulmonary hypertension, high-altitude pulmonary edema, high-altitude pulmonary hypertension, and Raynaud's phenomenon.⁶

Flibanserin an agonist of the serotonin 5-HT_{1A} receptor, has been approved by the FDA for the treatment of hypoactive sexual desire disorder (HSDD) in women.⁷ It is given orally (100 mg) at bedtime and offers improvement in approximately 10% of patients.

Side Effects and Precautions

PDE5 inhibitors

Most common side effects are mild headache and flushing. Priapism is rare. A direct link between PDE5Is and optic neuropathy could not be established, but a possible link between these drugs, especially sildenafil, and hearing impairment has been reported.² A potential association of sildenafil with melanoma has also been reported.⁸ In a Swedish cohort of men, the use of PDE5 inhibitors was associated with a modest but statistically significant increased

risk of malignant melanoma. However, the pattern of association (eg, the lack of association with multiple filled prescriptions) raises questions about whether this association is causal.⁹

PDE5I can be safely given with antihypertensive medications.

Care is needed with nitrates and α -blockers (Table 1).¹⁰

Nitrates

Penile erections and endothelium-mediated vasodilation are mediated through cGMP, which promotes trabecular and vascular smooth muscle relaxation. PDE5Is prevent the breakdown of cGMP. Nitric oxide donors (ie, nitrates) increase the production of cGMP. Because both PDE5Is and nitrates increase cGMP, coadministration can generate excess accumulation of cGMP and can trigger marked vasodilation and severe hypotension. Thus all nitrates are contraindicated for at least 24 h after sildenafil/vardenafil and 48 h after tadalafil.

In case of hypotension due to concomitant administration of nitrates, placing the patient in the Trendelenburg position, aggressive fluid resuscitation, and if necessary an α -agonist (phenylephrine) or a β -agonist (norepinephrine) are recommended.⁶ There is no antidote to PDE5Is.

α -blockers

"Uroselective" α -blockers (tamsulosin, alfuzosin) preferentially inhibit α_{1A} and α_{1D} receptors found primarily in the prostate and benefit patients with benign prostatic hypertrophy. Other α -blockers (terazosin) are less selective, and some (doxazosin) are used as third-line agents for hypertension because of their higher affinity for α_{1B} receptors, which are abundant in the peripheral vasculature. All α -blockers can cause vasodilation and orthostatic hypotension, and coadministration with PDE5Is increases the risk of a clinically significant decrease in BP. This risk is reduced with tadalafil, with uroselective α -blockers, when low doses of α -blockers are used, when dosing is separated by several hours (instead of simultaneously), and when patients are on stable therapy with 1 agent before the other drug class is administered.⁴

Other drug interactions

PDE5I are metabolized mainly by the cytochrome P450 (mainly 3A4 cytochrome) pathway and their concentrations may be increased by drugs such as cimetidine, erythromycin, clarithromycin, and ciprofloxacin (mainly sildenafil), ketoconazole (mainly vardenafil tadalafil), and ritonavir (all of them). Rifampin and bosentan may reduce their levels. QT prolongation is minimal with PDE5Is. Vardenafil and sildenafil have been studied and produced no increase of absolute QT and only similar, small increases of the QTc interval, with a shallow dose-response curve.¹¹

Flibanserin

Hypotension, somnolence and syncope may occur especially when the drug is taken during the day and with alcohol. Concomitant use of P-4503A4 (CYP3A4) inhibitors and alcohol

excess (more than 2 glasses of wine) is generally avoided. Activities requiring full alertness, such as driving, should be undertaken at least 6 hours after taking the drug.⁷

References

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Table 1. AHA 2012 Scientific Statement on Sexual Activity and Cardiovascular Disease. Use of PDE5 inhibitors

PDE5 inhibitors are useful for the treatment of erectile dysfunction in patients with stable CVD.	I-A
The safety of PDE5 inhibitors is unknown in patients with severe aortic stenosis or HCM.	IIb-C
PDE5 inhibitors should not be used in patients receiving nitrate therapy.	III-B
Nitrates should not be administered to patients within 24 hours of sildenafil or vardenafil administration or within 48 hours of tadalafil administration.	III-B