PDE5 inhibitors: A new mission for ischemic heart disease

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Abstract

This article briefly introduces and discusses main roles of phosphodiesterase type 5 inhibitors (PDE5i), single and combination treatment, and its long-term tolerability in patients with cardiovascular disease (coronary artery disease) beyond erectile dysfunction. At the same time, the author comments the Mendelian randomization (MR) analysis on PDE5i for ischemic heart disease and mortality in a recent study, as well as anti-tumor functions and applications of PDE5i in cancers, and other clinical uses, particularly combining with healthy lifestyle.

Introduction

As we all known, Phosphodiesterase 5 inhibitors (PDE5i) are widely used in clinical practice. Previous a series of clinical trials published in *The New England Journal of Medicine* showed that oral sildenafil is an effective, well-tolerated treatment for men with erectile dysfunction (ED),[1] and no adverse cardiovascular effects in men with severe coronary artery disease.[2]Moreover, it may improve exercise capacity and hemodynamics in patients with symptomatic pulmonary arterial hypertension (PAH).[3] In fact, the use of PDE5i could provide definite cardiovascular benefits beyond ED treatment, including cardioprotective effects and improving acute myocardial infarction (AMI) survival.[4] It is now a promising drug candidate for the treatment of not only cardiovascular disease (CVD),[5] but also neurocognitive or neurodegenerative disorders due to the potential of neuro-restorative and neuroprotective effects.[6,7]

Table 1 Major clinical applications and related molecular mechanisms [16-19]

Clinical Applications
Erectile dysfunction (ED) * Cardiovascular disease (CVD) Ischemic heart disease (IHD) or coronary artery disease (CAD),

Notes: Current PDE5i mainly includes avanafil, sildenafil (**Viagra**), tadalafil (Tada), and vardenafil. It can be used to treat ED in all patients (especially middle-aged and elderly ones), CVD, and others by monotherapies and combination treatment. Second-generation long-acting PDE5i (tadalafil) could be a promising new therapy.

Major clinical applications and related molecular mechanisms

So far, millions of patients with CVD are prescribed PDE5i for ED.[8] PDE5i treatment may reduce mortality after AMI in men with stable coronary artery disease (CAD),[9] with lower risks of death, recurrence of AMI, congestive heart failure (CHF), and revascularization. The use of PDE5i links to a lower risk for cardiovascular events and overall mortality.[4] Oral administration of a single dose of sildenafil improves exercise capacity and haemodynamic response to exercise in Fontan patients.[10]

Since ED is a frequent complication of CHF and stroke, as well as a possible predictor of cardiovascular events and mortality, treatment of ED in CHF patients should be individualized and multidisciplinary. As

the first-line therapy for ED, pulmonary artery hypertension (PAH), and lower urinary tract symptoms, PDE5i may improve both sexual function, cardiopulmonary parameters,[11] and the other clinical outcome. And PDE5i use was also associated with lower mortality and ischemic strokes after device implantation (such as left ventricular assist devices).[12]

As to combination treatment, both initial combination (e.g., tadalafil and ambrisentan)[13] or a fixed-dose combination (e.g., tadalafil and others) of PDE5i in a once-daily, single tablet could improve significantly clinical outcomes *vs* monotherapies in PAH patients with a safety and tolerability profile[14] due to related molecular mechanisms (Table 1). However, the use of a PDE5i in combination with nitrate medication in men with stable CAD may pose an increased risk for cardiovascular morbidity and mortality.[15] Long-term tolerability of PDE5i is good. Particularly, sildenafil, a selective PDE5i, is well tolerated in its intravenous and oral forms, and did not adversely affect any exercise parameter in men with CAD and ED.

Comments on Mendelian randomization analysis

In a recent **Mendelian randomization (MR)** study, **Xiao,*et al*** [20] provided genetic and real-world evidences about the protective role of PDE5 inhibition against ischemic heart disease (IHD), and found the potential of these drugs to be repurposed for IHD (CAD and AMI) prevention and treatment. Overall, this study on **MR analysis** is indeed a good job. However, further investigation, especially large-scale clinical trials are needed to enhance its strength, since the dose-response effects of PDE5i from more data on IHD prevention may provide additional information.

These excellent data in this study supported the protective role of PDE5i on IHD and other cardiovascular outcomes by a MR analysis, which offered the possibility of assessing causal relationships between genetically predicted risk factors and acquired CVD. It is an optimal study method to assess cardiovascular outcomes associated with risk factors of interest. It's believed that this study would be a new example and an influential MR study, since it revealed the protective role of PDE5 inhibition against IHD, and it is also pivotal for the development of PDE5i due to lowering CVD risk in high-risk individuals.

In fact, there are indeed the opportunities and challenges of MR studies for CAD, since MR analysis has tremendous potential for identifying therapeutic targets that are likely to be causal for CAD.[21] And MR has been increasingly used not only to predict the efficacy and safety of existing and novel drugs targeting risk factors of CVD but also to develop the repurposing potential of available PDE5i.[22]

As we know, there are the potential causal associations of lifestyle factors with risk of CVD, particularly CAD and ischaemic stroke, however, some MR studies indicated inconsistent results. On the one hand, this phenomenon is probably a gap between single and comprehensive risk factors; On the other hand, limitations of MR analysis are that "genetic variants have life-long effects, whereas trials assess the impact of short-term interventions". Herein, "MR studies may not reflect real-world practice, and trial endpoints often differ from outcomes in MR analyses".

However, in this study, Xiao, *et al* [20] added "a real-world study". Obviously, it enhanced the strengthen of this study. At the same time, sensitivity analysis is one of the key steps for a reliable and powerful MR study. Since MR analysis may help to evaluate the repurposing potential of available PDE5i, no doubt, this study is an excellent example. Of course, clinical trials are required to further investigate the efficacy of PDE5i on preventing IHD at both the population and the specific individual levels.

Some negative results of clinical trials

Unfortunately, there were also a series of negative results of clinical trials. Due to worse clinical outcomes, usage of sildenafil for corrected valvular heart disease and persistent PAH should be avoided,[23] and treatment with sildenafil did not reduce pulmonary artery pressures and did not improve heart failure with preserved ejection fraction (HFpEF).[24] In addition, adding sildenafil to bosentan did not significantly improve walking distance in Eisenmenger syndrome,[25] but did increase saturation at rest. In addition, regular users of PDE5i might have an increased risk for serous retinal detachment, retinal vascular occlusion, and ischemic optic

neuropathy.[26] No difference was found between placebo and PDE5i among men treated for ED after prostate surgery.[27]

Moreover, the use of PDE5i links to the increased risk for melanoma and basal cell carcinoma, but not for prostate cancer, and might have chemoprophylaxis effect on colorectal cancer. In fact, there are inadequate data and evidence regarding the role of PDE5i in cancer pathogenesis[28] including brain tumors (glioblastoma multiforme),[29] regardless of the promising anti-tumor functions of PDE5i (e.g., triggering apoptosis, suppressing tumor cell growth and invasion, and reversing tumor microenvironment immunosuppression in the brain). However, PDE5i has also some promising anti-tumor functions, for example, triggering apoptosis, suppressing tumor cell growth and invasion, and reversing tumor microenvironment immunosuppression in the brain. Herein, the repurposing PDE5i can target cancer-associated fibroblasts induced chemotherapy resistance.[30]

Conclusions and future perspectives

All in all, people expect PDE5i being more and better applied in clinical practice for CVD, but large-scale clinical trials are needed to indicate the clinical efficacy and practical applications of PDE5i. For example, we can apply excellent MR methods to discover more and better agents, therefore, better serving human health. In fact, as poly-pharmacological strategies for human health care, the E(e)SEEDi or the "magic polypill",[31] newly referred to as "Vitamin CH" or "Vitamin C2", and "Hot Pots" of both traditional Chinese and marine natural products,[32,33] may greatly improve clinical outcomes of both major non-communicable diseases and virus-infectious diseases. This means that if combining with healthy lifestyle and TCM, there will be more benefits from the use of PDE5i.

Currently, the intersection between cardiovascular and sexual health remains a vital topic,[34] and data on safety of PDE5i, drug-drug interactions, and a potential cardioprotective effect of these PDE5i drugs are increasing. Previous studies confirmed that PDE5i treatment for ED was associated with a decreased risk of AMI and CVD for the first 3 years.[35] Beyond most successful PDE5i for ED, the development of PDE3i for CHF and PDE4i for inflammatory airways disease have good prospects. Since PDE5 inhibition might be used as an effective strategy and a therapeutic candidate for the treatment of Alzheimer's disease (AD),[36,37] the development of agents of PDE5i with improved pharmacologic profile (e.g. higher potency, improved selectivity, and blood-brain barrier penetration) is also promising.

Other uses of PDE5i in clinical disorders include diabetic patients, treatment of Raynaud phenomenon[38] and COVID-19 infection. In addition, sildenafil therapy may reduce dyspnea in Eisenmenger syndrome by the role of J receptors,[39] the use of PDE5 inhibitors greatly increased (20-fold) among patients with IHD who were taking nitrates.[40] PDE5i may have cardiorenal protective effects with sex- and tissue-specific responses in diabetic cardiomyopathy.[41] Further high-quality research is warranted to confirm these findings and elucidate the underlying mechanisms.

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Declarations

Disclosure of Interest

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