

ORIGINAL**The Association between PDE5 Inhibitors and Aneurysm/Arterial Dissection : A Pharmacovigilance Study Using WHO Safety Database**

Koji Miyata¹, Yuki Izawa-Ishizawa^{1,2}, Takahiro Niimura^{1,3}, Hirofumi Hamano^{3,4}, Fuka Aizawa^{1,5}, Kenta Yagi^{1,3}, Kei Kawada^{1,6}, Yoshito Zamami^{1,4}, Mitsuhiro Goda^{1,5}, and Keisuke Ishizawa^{1,3,5}

¹Department of Clinical Pharmacology and Therapeutics, Tokushima University Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan, ²Department of General Medicine, Taoka Hospital, Tokushima, Japan, ³Clinical Research Center for Developmental Therapeutics, Tokushima University Hospital, Tokushima, Japan, ⁴Department of Pharmacy, Okayama University Hospital, Okayama, Japan, ⁵Department of Pharmacy, Tokushima University Hospital, Tokushima, Japan, ⁶Department of Clinical Pharmacy Practice Pedagogy, Tokushima University Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan

Abstract : Aneurysm and arterial dissection have been reported as adverse drug events, associated with angiogenesis inhibitors and fluoroquinolones. Specifically, several cases of severe arterial disease following cGMP-specific phosphodiesterase type 5 (PDE5) inhibitors usage have recently been reported. It is necessary to ascertain the risks of serious adverse events caused by PDE5 inhibitors. We aimed to evaluate the association of aneurysm and artery dissection with PDE5 inhibitors using VigiBase, which is a World Health Organization database of spontaneously reported adverse events, for explorative hypothesis-generating analysis. We performed disproportionality analysis using a dataset from inception in 1967 to December 2022 and calculated reporting odds ratios (ROR) between PDE5 inhibitors and arterial diseases. We extracted 195,839 reports on PDE5 inhibitors with 254 reports of arterial disease as adverse events from VigiBase. Disproportionality analysis showed disproportional signals for PDE5 inhibitors (ROR, 2.30 ; 95% confidence intervals, 2.04-2.61) ; disproportional signals were detected in analyses restricting the lesion site to the aorta or cerebral arteries. From stratified analysis, disproportional signals were noted in females, as well as males, generally recognized as a risk factor for artery diseases. This real-world data analysis suggests that PDE5 inhibitors may play a role in the development of lethal arterial disease. *J. Med. Invest.* 71 : 134-140, February, 2024

Keywords : PDE5 inhibitors, Aneurysm, Arterial dissection, Pharmacovigilance, Adverse event

INTRODUCTION

Aortic aneurysm and dissection are common acute aortic diseases with high mortality. Once an abdominal aortic aneurysm ruptures, in-hospital mortality is reported to be more than 50% (1). In cases of type A and type B aortic dissection, in-hospital mortalities were 22-31% and 12-14%, respectively (2). There is a need, therefore, for elucidation of the causes of these acute aortic diseases and the establishment of new preventive methods.

The well-known risk factors for aortic aneurysm and dissection include hypertension, smoking, dyslipidemia, arteriosclerosis, aging, male sex, and connective tissue diseases. In addition to these known risk factors, aortic aneurysm and dissection have recently been reported as adverse events associated with some drugs. Usage of fluoroquinolones is considered as a risk factor for acute aortic diseases. Based on animal studies, observational studies, and pharmacovigilance studies, the U.S. Food and Drug Administration (FDA) updated its warning against the use of fluoroquinolones in 2018 (3-6). Many countries have also warned against aneurysm and artery dissection as adverse events caused by systemic vascular endothelial growth factor pathway

inhibitors, such as bevacizumab, sunitinib, and sorafenib (7-9).

Although no guidelines have been issued, several cases of aortic dissection or intracranial aneurysm have recently been reported with the use of cGMP-specific phosphodiesterase type 5 (PDE5) inhibitors (10-14). Zhang *et al.* reported that sildenafil, a PDE5 inhibitor, exacerbates the development of experimental abdominal aortic aneurysm in mice (15). These studies suggest that PDE5 inhibitors may increase the risk of aortic disease. PDE5 inhibitors are widely used to treat erectile dysfunction (ED) and pulmonary hypertension (PH). Sales of drugs for ED, containing PDE5 inhibitors have reportedly increased markedly during the COVID-19 pandemic (16). Therefore, it can be assumed that a large number of patients are at risk of experiencing adverse events. Examination of the association between the use of PDE5 inhibitors and aneurysm or arterial dissection is, thus, urgent.

In the present study, we report our results using data from a large-scale medical database. The database of Individual Case Safety Reports (ICSRs) collected from spontaneous reporting systems reflects the actual clinical settings and can be used to assess drug safety and identify adverse drug events (17, 18). VigiBase is the World Health Organization's (WHO) global database of ICSR and a leading source of pharmacovigilance research. This study aimed to evaluate the association between PDE5 inhibitors and aneurysm or arterial dissection using VigiBase.

Received for publication December 11, 2023 ; accepted January 12, 2024.

Address correspondence and reprint requests to Keisuke Ishizawa, Department of Clinical Pharmacology and Therapeutics Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto, Tokushima 770-8503, Japan and Fax : +81-88-633-7472. E-mail : ishizawa@tokushima-u.ac.jp

METHODS

Data sources

For this study, we used the WHO database, VigiBase, which is managed and developed by the Uppsala Monitoring Centre (Uppsala, Sweden). VigiBase contains more than 20 million ICSRs collected from various sources, such as physicians, healthcare professionals, and patients from over 130 countries. ICSRs include information on patient backgrounds (including age, sex, reporting date), drugs (including indications, Anatomical Therapeutic Chemical (ATC) classification, and dosage), and adverse drug reactions. With the information being multi-sourced, the probability that a suspected adverse effect is drug-related is not same in all cases. In this study, we assembled ICSRs from VigiBase, from its inception in 1967, through December 1, 2022. VigiBase contains duplicate reports; hence, reports determined by the Uppsala Monitoring Centre as having the potential for duplicate reporting, were excluded from the analysis. Downloaded data were processed using SQLite databases 3.30.1 (SQLite Consortium, Charlotte, NC, USA). This study did not require informed consent since anonymized data from VigiBase was used.

Procedures

Within the VigiBase, the terms aneurysm and artery dissection were identified systematically, using the preferred terms in the lower layer of High Level Group Term (HLGT) as “Aneurysms and artery dissections” in the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J), version 25.0, which is developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). For disproportionality analyses by artery lesions, cases of aneurysm and dissection of aorta or the cerebral vasculature were identified systematically, using the preferred terms in the lower layer of HLGT as, respectively, “Aortic aneurysms and dissections,” and “Cerebrovascular aneurysms and dissections.” PDE5 inhibitors included in the search were sildenafil, tadalafil, vardenafil, and avanafil. Given the differences in background or usage by various indications, we verified the disproportionality analyses of PDE5 inhibitors used for each indication (using the full database as comparator group). We selected two indications, ED and PH, from the list of indications in the MedDRA/J or the International Classification of Disease Tenth Revision (ICD10).

Stratified Analysis

For disproportionality analyses stratified by sex and age, we divided, respectively, the data into two groups; male and female, and four groups; ≤ 44 years, 45 - 64 years, 65 - 74 years, and ≥ 75 years. For disproportionality analysis in only high-risk patients with cardiovascular events, patients using anti-dyslipidemia drugs (as defined by the ATC code C10) were considered as cases of cardiovascular risk associated with dyslipidemia, and those using agents acting on the renin-angiotensin system (as defined by the ATC code C09), that is anti-hypertensive drugs, were considered as cases of cardiovascular risk associated with hypertension. To verify whether PDE5 inhibitors were associated with higher reports of aneurysm and artery dissection within the cardiovascular risk groups, we analyzed whether PDE5 inhibitor users had disproportional signals of aneurysm and artery dissection among anti-dyslipidemia and anti-hypertensive drug users.

Statistical Analysis

The risk of adverse events was evaluated by signal detection using the reporting odds ratio (ROR) and a 95% confidence interval (CI). For each of the four PDE5 inhibitors, cases were classified into four groups: (A) patients who used the drug of interest

and reported aneurysm and artery dissection; (B) patients who used the drug of interest and did not report aneurysm and artery dissection; (C) patients who did not use the drug of interest and reported aneurysm and artery dissection; (D) patients who did not use the drug of interest and did not report aneurysm or artery dissection. The ROR and 95% CI were calculated using the following equations:

$$\text{ROR} = (A/B)/(C/D)$$

$$95\% \text{ CI} = \exp \left\{ \log(\text{ROR}) \pm 1.96 \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} \right\}$$

The disproportional signal was considered to be present when the lower limit of the 95% CI for ROR was > 1 (19, 20). The reporting rate of the drug of interest was also assessed using Fisher's exact tests. The analysis was performed using R statistical software version 4.1.2.

RESULTS

Demographics of aneurysm and artery dissection cases and non-cases associated with PDE5 inhibitors

Among the 32,520,983 ICSRs registered in VigiBase, 195,839 were identified as reports with PDE5 inhibitors and 254 of them were identified as cases of aneurysm and arterial dissection (Figure 1). These ICSRs included 173 males (68.1%), 74 females (29.1%), and 7 with sex unknown (2.8%). The most common age group was 45–64 years (82, 32.3%). The Region of the Americas had the largest number of reports (212, 83.5%), followed by the European Region (35, 13.8%). Additional demographic data is shown in Table 1. The site of lesions of aneurysm and dissection were aortic in 86 patients (33.9%) and cerebroarterial in 55 patients (21.7%). The outcomes of patients with aneurysm and artery dissection in PDE5 inhibitor-related ICSRs were as follows: 50 “Death” (19.7%), 14 “Life threatening” (5.5%), and 95 “Caused Prolonged Hospitalization” (37.4%) (Figure 2).

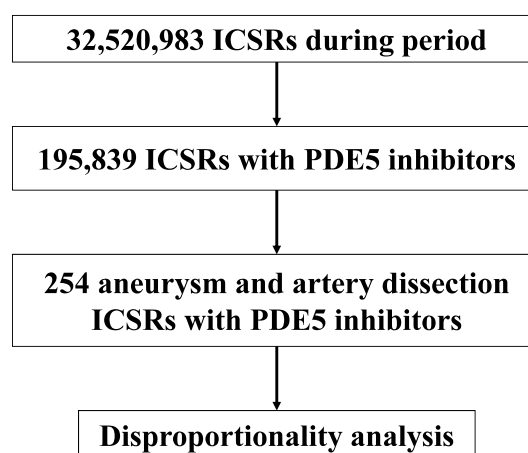


Figure 1. Flow diagram representing the study design. Abbreviations: PDE5 = phosphodiesterase type 5; ICSRs = individual case safety reports.

Reporting odds ratios (RORs) of PDE5 inhibitors for aneurysm and artery dissection

From the results of disproportionality analyses (Figure 3), disproportional signals for aneurysm and arterial dissection were identified with the use of PDE5 inhibitors ($n=254$; $\text{ROR}=2.30$

Table 1. Demographics of aneurysm and artery dissection cases and non-cases associated with PDE5 inhibitors.

Characteristic	Patients without aneurysm and artery dissection, n = 195,585	Patients with aneurysm and artery dissection, n = 254
Age		
≤ 44	23,130 (11.8)#	25 (9.8)
45_64	54,727 (28.0)	82 (32.3)
65_74	32,153 (16.4)	54 (21.3)
≥ 75	19,176 (9.8)	22 (8.7)
Unknown	66,399 (33.9)	71 (28.0)
Sex		
Female	72,690 (37.2)	74 (29.1)
Male	113,644 (58.1)	173 (68.1)
Unknown	9,251 (4.7)	7 (2.8)
Reporting Regions		
African Region	375 (0.2)	0 (0.0)
Eastern Mediterranean Region	605 (0.3)	0 (0.0)
European Region	20,039 (10.2)	35 (13.8)
Region of the Americas	162,847 (83.3)	212 (83.5)
South-East Asia Region	688 (0.4)	0 (0.0)
Western Pacific Region	11,031 (5.6)	7 (2.8)
Reporting Type		
Other	1,276 (0.7)	2 (0.8)
PMS/Special monitoring	111 (0.1)	5 (2.0)
Report from study	32,625 (16.7)	47 (18.5)
Spontaneous	158,542 (81.1)	195 (76.8)
Unknown	3,031 (1.5)	5 (2.0)
PDE5 inhibitors*		
Sildenafil	117,039 (59.8)	175 (68.9)
Tadalafil	74,936 (38.3)	80 (31.5)
Vardenafil	8,317 (4.3)	8 (3.1)
Avanafil	783 (0.4)	0 (0.0)

* Patients could have used one or more PDE5 inhibitors.

#Figures represent number of patients; per cent values are enclosed in parenthesis.

Abbreviations : PDE5 = phosphodiesterase type 5.

[2.04-2.61]). In individual analyses for each PDE5 inhibitor, sildenafil (n=175 ; ROR=2.65 [2.28-3.07]) and tadalafil (n=80 ; ROR=1.88 [1.51-2.35]) showed disproportional signals for aneurysm and arterial dissection, but vardenafil (n=8 ; ROR=1.69 [0.85-3.39]) did not. The ICSRs with avanafil had no report of aneurysm and artery dissection. Moreover, in the individual analysis for each indication, disproportional signals for aneurysm and arterial dissection were detected in both, ED (n=51 ; ROR=3.16 [2.40-4.17]) and PH (n=36 ; ROR=3.15 [2.27-4.37]). Even when the analysis was performed with respect to the site of the lesion i.e., aorta or cerebrovascular arteries, the use of PDE5 inhibitors overall or sildenafil alone, showed disproportional signals (Figure 3).

Stratified analysis by age, sex, and concomitant drug use

In disproportionality analyses stratified by age and sex, PDE5

inhibitors had disproportional signals for aneurysm and arterial dissection in all layers (male : n=173 ; ROR=2.51 [2.16-2.92], female : n=74 ; ROR=2.11 [1.68-2.65], <= 44 years : n=25 ; ROR=5.08 [3.42-7.54], 45 - 64 years : n=82 ; ROR=2.78 [2.23-3.46] and 65 - 74 years : n=54 ; ROR=2.37 [1.81-3.10]) except >= 75 years : n=22 ; ROR=1.51 [0.99-2.30] (Table 3). For further stratification, two high-risk groups with cardiovascular events based on concomitant medications were extracted : anti-hypertensive drug users (hypertension group) and anti-dyslipidemia drug users (dyslipidemia group) (Table 2). PDE5 inhibitors had disproportional signals for aneurysm and arterial dissection in these stratified groups of anti-hypertensive drug users (n=49 ; ROR=1.95 [1.47-2.59]) and anti-dyslipidemia drug users (n=54 ; ROR=1.78 [1.36-2.33]) (Table 3).

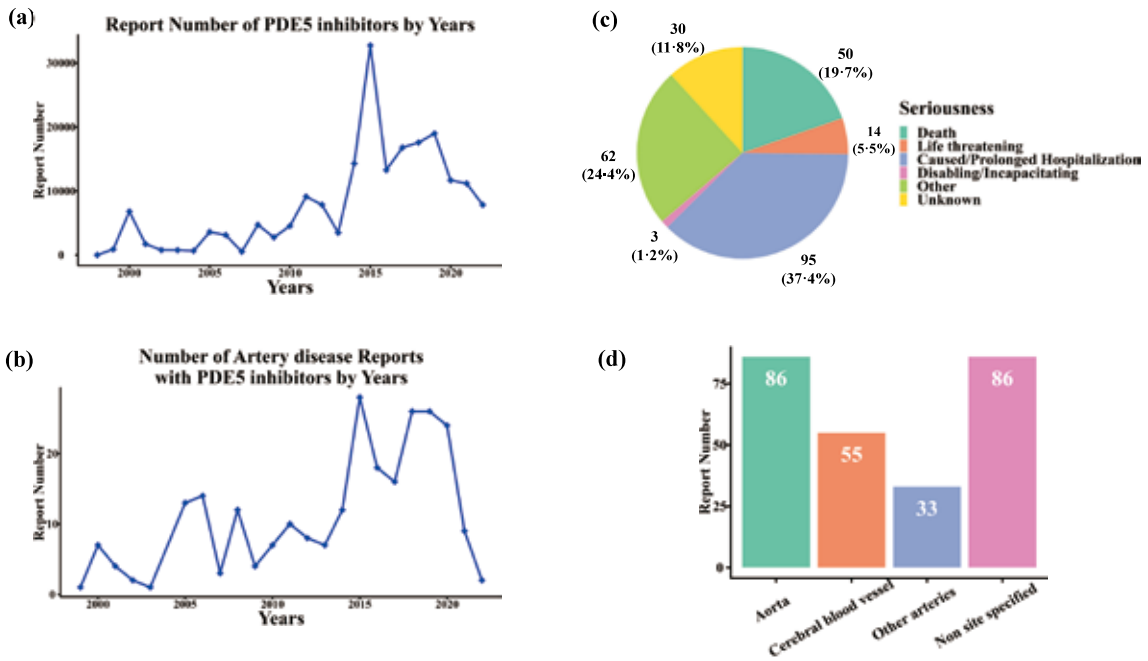


Figure 2. Characteristics of aneurysm and artery dissection cases with PDE5 inhibitors. a) Time trend of all adverse event reports with PDE5 inhibitors. b) Time trend of aneurysm and artery dissection reports with PDE5 inhibitors. c) Outcomes of patients with aneurysm and artery dissection using PDE5 inhibitors. d) Bar plot shows numbers of ICSRs by artery lesion site, in aneurysm and artery dissection reports with PDE5 inhibitors. Patients could have one or more sites of aneurysm and artery dissection. Abbreviations : PDE5 = phosphodiesterase type 5 ; ICSRs = individual case safety reports.

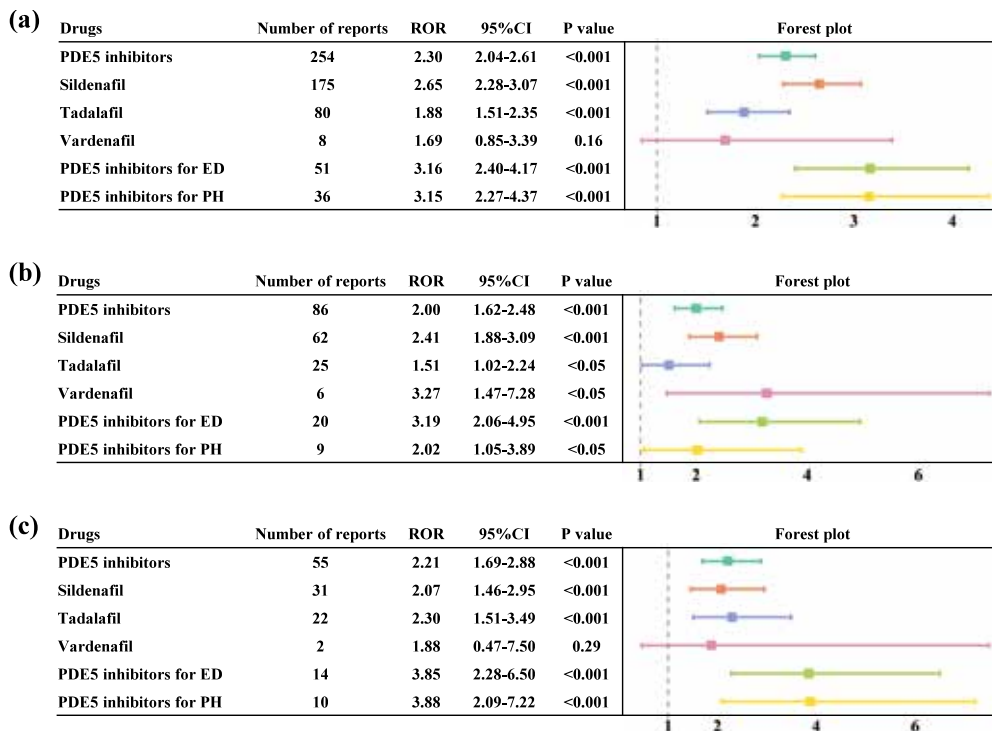


Figure 3. Reporting odds ratios (RORs) of PDE5 inhibitors for aneurysm and artery dissection. a) All aneurysm and artery dissection b) Aortic aneurysm and artery dissection c) Cerebrovascular aneurysm and artery dissection. ICSRs with avanafil had no reports of aneurysm and artery dissection. Statistical analysis was conducted using Fisher's exact test. Abbreviations : PDE5 = phosphodiesterase type 5 ; ROR = reporting odds ratios ; CI = confidence intervals ; ED = erectile dysfunction ; PH = pulmonary hypertension.

Table 2. Reporting odd ratios (RORs) of cardiovascular agents for aneurysm and artery dissection.

drug of interest	with drug of interest	without drug of interest	ROR (95%CI)	P value
anti-hypertensive drugs	2,076 (0.13%)	16,388 (0.05%)	2.38 (2.28-2.50)	<0.001
anti-dyslipidemia drugs	2,163 (0.13%)	16,301 (0.05%)	2.51 (2.40-2.63)	<0.001

Abbreviation : ROR = reporting odds ratios ; CI = confidence intervals.

Table 3. Stratified analysis by age, sex, and concomitant drug use.

Characteristics	Reporting rate (number of reports) of aneurysm and artery dissection		ROR (95%CI)	P value
	with PDE5 inhibitors	without PDE5 inhibitors		
Age				
≤44	25 (0.11%)	1,979 (0.02%)	5.08 (3.42-7.54)	<0.001
45 - 64	82 (0.15%)	4,264 (0.05%)	2.78 (2.23-3.46)	<0.001
65 - 74	54 (0.17%)	2,604 (0.07%)	2.37 (1.81-3.1)	<0.001
≥75	22 (0.11%)	2,151 (0.08%)	1.51 (0.99-2.3)	0.06
Sex				
Male	173 (0.15%)	7,189 (0.06%)	2.51 (2.16-2.92)	<0.001
Female	74 (0.10%)	8,976 (0.05%)	2.11 (1.68-2.65)	<0.001
Concomitant drugs				
anti-hypertensive drugs	49 (0.24%)	2,027 (0.13%)	1.95 (1.47-2.59)	<0.001
anti-dyslipidemia drugs	54 (0.23%)	2,109 (0.13%)	1.78 (1.36-2.33)	<0.001

Abbreviation : PDE5 = phosphodiesterase type 5 ; ROR = reporting odds ratios ; CI = confidence intervals.

DISCUSSION

To the best of our knowledge, this is the first largest pharmacovigilance study to show that PDE5 inhibitors may be associated with a risk of aneurysm and arterial dissection. We used VigiBase for an explorative hypothesis-generating analysis. As shown in Figure 2, the use of sildenafil and tadalafil resulted in high reporting rates for aneurysm and arterial dissection. A clinical study examining the effects of tadalafil in patients with chronic obstructive pulmonary disease reported a case of ruptured abdominal aortic aneurysm in the tadalafil group (21). Disproportional signals for aneurysm and arterial dissection were detected with respect to the cerebrovascular arteries and the aorta (Figure 3). This result is consistent with previous case reports, in which the foci of aneurysm and arterial dissection in PDE5 inhibitor users were not only in the aorta but also in the cerebral and vertebral arteries (10-14).

PDE5 inhibitors are used for various indications. The drug course depends on the background of the patient and the underlying disease. For example, it is usually administered as a single dose to ED patients but has continued dosing in patients with PH. Therefore, we focused on the signal analysis of either ED or PH. As shown in Figure 3, even after the analysis was narrowed down by ED or PH, disproportional signals were detected in both cases. These results suggest that PDE5 inhibitors may increase the risk of aneurysm and arterial dissection, regardless of their indications. Additionally, we performed a stratified analysis using several factors to eliminate bias due to patient

background. The results of the disproportionality analysis stratified by sex and age showed disproportional signal for aneurysm and arterial dissection in both sexes and in most age groups, except for those over 75 years of age. These results indicate that the effect of PDE5 inhibitors on arterial disease is independent of age and sex. Disproportional signals were also detected in the stratified analyses of the population at risk of cardiovascular events using anti-hypertensive or anti-dyslipidemia medication concomitantly. Since hypertension or dyslipidemia is considered high-risk for cardiovascular events, adverse events were reported more frequently in these groups than in other populations even without the use of PDE5 inhibitors. However, the disproportional signals associated with PDE5 inhibitor use indicates a further increase in incidence of these cardiovascular events in these high-risk groups. Based on these findings, we note that PDE5 inhibitors may increase the risk of aneurysm and arterial dissection as adverse events, regardless of their usage method, age, sex, or presence of preexisting hypertension or dyslipidemia.

For PDE5 inhibitor-induced aneurysm and arterial dissection, evidence from clinical studies is still insufficient ; however, several basic studies have suggested an association. Zhang *C et al.* reported that sildenafil aggravated the development of abdominal aortic aneurysm in mice (15). Cesarini *V et al.* demonstrated the relevance of down-regulated PDE5 mRNA expression with aortic aneurysm in human aortic tissue (22). As a possible molecular mechanism, cGMP, which is degraded by PDE5, binding to, and activating cGMP-dependent protein kinase type 1 (PKG1) to regulate smooth muscle cell contractility might be

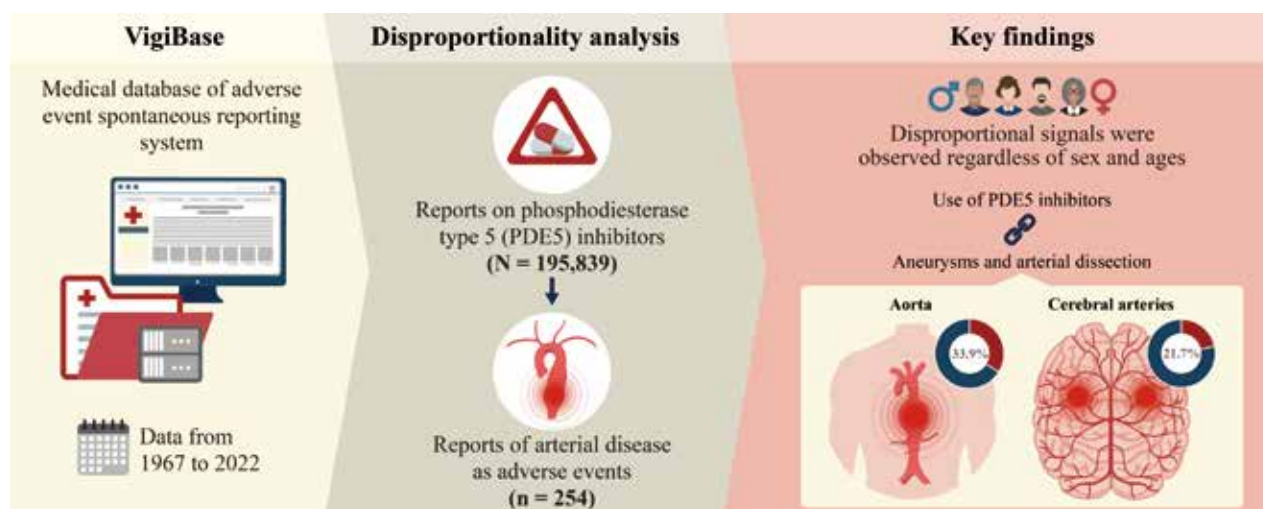


Figure 4. Graphical Abstract of Current study.

considered. Guo *et al.* reported that mutations in *PRKG1* gene, which encodes PKG1, caused genetic aortic disease by promoting smooth muscle cell relaxation (23). It has also been reported that cGMP-PKG1 overactivation causes aortic disease in Marfan syndrome (24, 25). In our study, the disproportional signals were detected even in younger age, ≤ 44 years. This result implies that some genetic background could be involved. The detailed molecular mechanisms, involving *PRKG1*, in PDE5 inhibitor-induced arterial diseases need to be elucidated.

Although large-scale medical databases are expected to reflect the real-world situation, there are several intrinsic limitations to spontaneous reporting database systems. First, it is not possible to calculate the actual incidence of adverse events because all reports in VigiBase are of only some adverse events of a drug, while the denominator of actual drug users is unknown. It is difficult to accurately determine the actual number of people taking PDE5 inhibitors since many people obtain them without a prescription, for curiosity or for recreation (26-29). Supplements containing PDE5 inhibitors are also widely available (30). Therefore, the risk signal calculated from VigiBase refers to the reported rate of aneurysm and arterial dissection among PDE5 inhibitor users, relative to all adverse event reports and not the difference in the actual incidence of adverse events with or without PDE5 inhibitor use. Second, the influence of confounding factors on the risk signals cannot be completely controlled. It is well known that ED is correlated with cardiovascular factors such as hypertension or arteriosclerosis. Chronic obstructive pulmonary disease, a cause of PH, is strongly associated with a history of smoking. These are also other risk factors for aneurysm and arterial dissection. Further research, including population-based studies, is required to understand the effects of these confounding factors. Despite these limitations, the value of this pharmacovigilance study cannot be underestimated. Pharmacovigilance studies have been established as a very useful first step in validating potentially rare adverse drug events such as aneurysm and arterial dissection, which are difficult to detect in prospective studies.

In conclusion, the present pharmacovigilance study supports the validity of PDE5 inhibitor-associated cardiovascular risks in the real world. This study suggests that physicians prescribing PDE5 inhibitors as well as patients, should consider the associated risk of vascular toxicity regardless of sex, age, or nature of underlying disease.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

FUNDING INFORMATION

This study was supported by JSPS KAKENHI (21H02646 to K.I., 22K06863 to Y.I-I.) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and JST SPRING program (JPMJSP2113 to K.M.).

ACKNOWLEDGEMENTS

The study results and conclusions do not represent the opinion of the Uppsala Monitoring Centre, National Centres, or WHO. This work was supported by JST SPRING, Grant Number JPMJSP2113. We would like to thank Editage (www.editage.com) for English language editing.

REFERENCES

1. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM: Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet* 383(9921): 963-969, 2014
2. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmet T, Larsen M, Harris KM, Greason K, Di Eusanio M, Bossone E, Montgomery DG, Eagle KA, Nienaber CA, Isselbacher EM, O'Gara P: Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol* 66(4): 350-358, 2015
3. Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC: Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med* 175(11): 1839-1847, 2015
4. LeMaire SA, Zhang L, Luo W, Ren P, Azares AR, Wang Y, Zhang C, Coselli JS, Shen YH: Effect of Ciprofloxacin on Susceptibility to Aortic Dissection and Rupture in Mice.

- JAMA Surg 153(9) : e181804, 2018
5. Sommet A, Bénévent J, Rousseau V, Chebane L, Douros A, Montastruc JL, Montastruc F : What Fluoroquinolones Have the Highest Risk of Aortic Aneurysm? A Case/Non-case Study in VigiBase®. *J Gen Intern Med* 34(4) : 502-503, 2019
 6. Newton ER, Akerman AW, Strassle PD, Kibbe MR : Association of Fluoroquinolone Use With Short-term Risk of Development of Aortic Aneurysm. *JAMA Surg* 156(3) : 264-272, 2021
 7. Oshima Y, Tanimoto T, Yuji K, Tojo A : Association Between Aortic Dissection and Systemic Exposure of Vascular Endothelial Growth Factor Pathway Inhibitors in the Japanese Adverse Drug Event Report Database. *Circulation* 135(8) : 815-817, 2017
 8. Guyon J, Gouverneur A, Maumus-Robert S, Bérard X, Pariente A, Bikfalvi A, Noize P : Association Between Antiangiogenic Drugs Used for Cancer Treatment and Artery Dissections or Aneurysms. *JAMA Oncol* 7(5) : 775-778, 2021
 9. Wang S, Chen M, Zhang X, Zhang L, Jia M, Shen Z, Wang J, Zhao B, Gong Y, Gong J : Aneurysm and Artery Dissection Following the Use of Vascular Endothelial Growth Factor Inhibitor : A Real-World Analysis Using a Spontaneous Reporting System. *J Am Heart Assoc* 10(23) : e020844, 2021
 10. Nachtnebel A, Stöllberger C, Ehrlich M, Finsterer J : Aortic dissection after sildenafil-induced erection. *South Med J* 99(10) : 1151-1152, 2006
 11. Tiryakioglu SK, Tiryakioglu O, Turan T, Kumbay E : Aortic dissection due to sildenafil abuse. *Interact Cardiovasc Thorac Surg* 9(1) : 141-143, 2009
 12. Lameijer CM, Tielliu IF, van Driel MF, Zeebregts CJ : Type B aortic dissection after the use of tadalafil. *Ann Thorac Surg* 93(2) : 651-653, 2012
 13. Dersch R, Anastasopoulos C, Hader C, Stich O : Vertebral artery dissection associated with sildenafil abuse. *J Clin Neurosci* 20(5) : 742, 2013
 14. Adiga A, Edriss H, Nugent K : Intracranial aneurysm and sildenafil. *Proc (Bayl Univ Med Cent)* 29(2) : 178-180, 2016
 15. Zhang C, Mohan A, Shi H, Yan C : Sildenafil (Viagra) Aggravates the Development of Experimental Abdominal Aortic Aneurysm. *J Am Heart Assoc* 11(2) : e023053, 2022
 16. Hernandez I, Gul Z, Gellad WF, Davies BJ : Marked Increase in Sales of Erectile Dysfunction Medication During COVID-19. *J Gen Intern Med* 36(9) : 2912-2914, 2021
 17. Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano JP, Balko JM, Bonaca MP, Roden DM, Johnson DB, Moslehi JJ : Cardiovascular toxicities associated with immune checkpoint inhibitors : an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 19(12) : 1579-1589, 2018
 18. Salem JE, Manouchehri A, Bretagne M, Lebrun-Vignes B, Groarke JD, Johnson DB, Yang T, Reddy NM, Funck-Brentano C, Brown JR, Roden DM, Moslehi JJ : Cardiovascular Toxicities Associated With Ibrutinib. *J Am Coll Cardiol* 74(13) : 1667-1678, 2019
 19. Rothman KJ, Lanes S, Sacks ST : The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf* 13(8) : 519-523, 2004
 20. Chakraborty BS : Pharmacovigilance : A data mining approach to signal detection. *Indian J Pharmacol* 47(3) : 241-242, 2015
 21. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD : Tadalafil in patients with chronic obstructive pulmonary disease : a randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2(4) : 293-300, 2014
 22. Cesarini V, Pisano C, Rossi G, Balistreri CR, Botti F, Antonelli G, Ruvolo G, Jannini EA, Dolci S : Regulation of PDE5 expression in human aorta and thoracic aortic aneurysms. *Sci Rep* 9(1) : 12206, 2019
 23. Guo DC, Regalado E, Casteel DE, Santos-Cortez RL, Gong L, Kim JJ, Dyack S, Horne SG, Chang G, Jondeau G, Boileau C, Coselli JS, Li Z, Leal SM, Shendure J, Rieder MJ, Bamshad MJ, Nickerson DA, Kim C, Milewicz DM : Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. *Am J Hum Genet* 93(2) : 398-404, 2013
 24. Milewicz DM, Trybus KM, Guo DC, Sweeney HL, Regalado E, Kamm K, Stull JT : Altered Smooth Muscle Cell Force Generation as a Driver of Thoracic Aortic Aneurysms and Dissections. *Arterioscler Thromb Vasc Biol* 37(1) : 26-34, 2017
 25. de la Fuente-Alonso A, Toral M, Alfayate A, Ruiz-Rodríguez MJ, Bonzón-Kulichenko E, Teixido-Tura G, Martínez-Martínez S, Méndez-Olivares MJ, López-Maderuelo D, González-Valdés I, García-Izquierdo E, Mingo S, Martín CE, Muiño-Mosquera L, De Backer J, Nistal JF, Forteza A, Evangelista A, Vázquez J, Campanero MR, Redondo JM : Aortic disease in Marfan syndrome is caused by overactivation of sGC-PRKG signaling by NO. *Nat Commun* 12(1) : 2628, 2021
 26. Bechara A, Casabé A, De Bonis W, Helien A, Bertolino MV : Recreational use of phosphodiesterase type 5 inhibitors by healthy young men. *J Sex Med* 7(11) : 3736-3742, 2010
 27. Schnetzler G, Banks I, Kirby M, Zou KH, Symonds T : Characteristics, behaviors, and attitudes of men bypassing the healthcare system when obtaining phosphodiesterase type 5 inhibitors. *J Sex Med* 7(3) : 1237-1246, 2010
 28. Alshahrani S, Ahmed AF, Gabr AH, Al Ansari A, El-Feky M, Elbadry MS : Phosphodiesterase type 5 inhibitors : Irrational use in Saudi Arabia. *Arab J Urol* 14(2) : 94-100, 2016
 29. Gebreyohannes EA, Bhagavathula AS, Gebresillassie BM, Tefera YG, Belachew SA, Erku DA : Recreational Use of Phosphodiesterase 5 Inhibitors and Its Associated Factors among Undergraduate Male Students in an Ethiopian University : A Cross-Sectional Study. *World J Mens Health* 34(3) : 186-193, 2016
 30. Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M : Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. *JAMA Netw Open* 1(6) : e183337, 2018