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Adverse Events Associated With Coprescription of Phosphodiesterase Type 5 Inhibitors and Oral Organic Nitrates in Male Patients With Ischemic Heart Disease

A Case-Crossover Study

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Background: Concomitant use of oral organic nitrates (nitrates) and phosphodiesterase type 5 (PDE5) inhibitors is contraindicated.

Objective: To measure temporal trends in the coprescription of nitrates and PDE5 inhibitors and to measure the association between cardiovascular outcomes and the coprescription of nitrates with PDE5 inhibitors.

Design: Case-crossover design.

Setting: Nationwide study of Danish patients from 2000 to 2018.

Patients: Male patients with International Classification of Diseases, 10th Revision (ICD-10) codes for ischemic heart disease (IHD), including those who had a continuing prescription for nitrates and a new, filled prescription for PDE5 inhibitors.

Measurements: Two composite outcomes were measured: 1) cardiac arrest, shock, myocardial infarction, ischemic stroke, or acute coronary arteriography and 2) syncope, angina pectoris, or drug-related adverse event.

Results: From 2000 to 2018, 249 541 male patients with IHD were identified. Of these, 42 073 patients had continuing prescriptions for nitrates. During this period, the prescription rate for PDE5 inhibitors in patients with IHD who were taking nitrates increased from an average of 0.9 prescriptions (95% CI, 0.5 to 1.2 prescriptions) per 100 persons per year in 2000 to 19.5 prescriptions (CI, 18.0 to 21.1 prescriptions) in 2018. No statistically significant association was found between the coprescription of nitrates with PDE5 inhibitors and the risk for either composite outcome (odds ratio [OR], 0.58 [CI, 0.28 to 1.13] for the first outcome and OR, 0.73 [CI, 0.40 to 1.32] for the second outcome).

Limitation: An assumption was made that concurrently filled prescriptions for nitrates and PDE5 inhibitors equaled concomitant use.

Conclusion: From 2000 to 2018, the use of PDE5 inhibitors increased 20-fold among Danish patients with IHD who were taking nitrates. A statistically significant association between concomitant use of these medications and cardiovascular adverse events could not be identified.

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Combining oral organic nitrates (nitrates) with phosphodiesterase type 5 (PDE5) inhibitors is contraindicated due to a synergistic effect on blood pressure (1, 2). Both nitrates and PDE5 inhibitors work by increasing cyclic guanosine monophosphate activity, thus relaxing smooth muscle cells in blood vessels, correspondingly relieving angina pectoris and erectile dysfunction. The effects of nitrates and PDE5 inhibitors are mediated by 2 different molecular pathways, augmenting the effect on blood pressure while inhibiting the body's own mitigation response (1, 2). Accordingly, small, randomized, pharmacologic studies have reported an amplified decrease in blood pressure during controlled coexposure with nitrates and PDE5 inhibitors, both in healthy participants and in participants with ischemic heart disease (IHD) (1, 3, 4). Potentially, this increases the risk for vascular ischemic events including myocardial infarction (MI) and stroke. Product information for prescribers and patients from the European Medicines Agency for the PDE5 inhibitor specifically contraindicates concomitant treatment with nitrates (5–8).

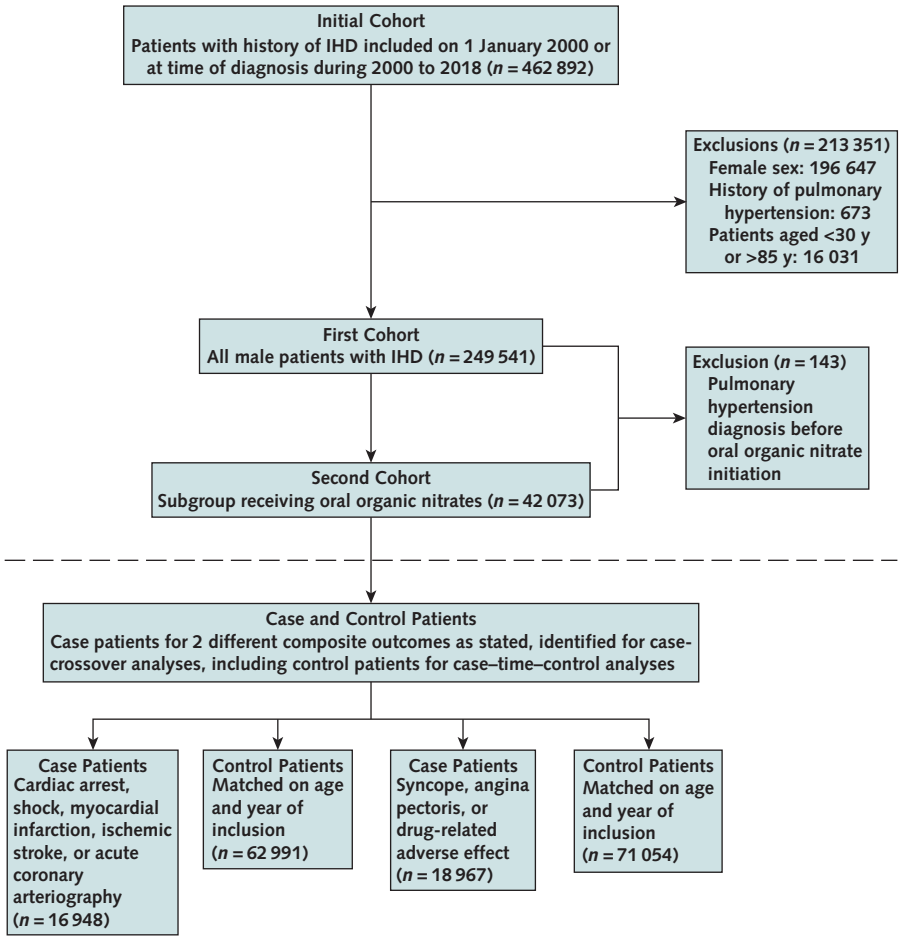
Although indications for nitrates have been expanded, they are primarily used to treat heart failure and chronic angina pain (9, 10), both commonly associated with erectile dysfunction (11). Notably, the prevalence of erectile dysfunction has increased (12, 13) with varying though consistently noticeable prevalence of 22% to 46%, 14%, 10% to 77%, 49%, 8% to 65%, and 54%, respectively, in Europe, North America, South America, Asia, Africa, and Oceania (13). This could translate to a possible growing coprescribing practice and a public health concern. Even though knowledge of this interaction has existed since the introduction of PDE5 inhibitors, the effect in a real-life setting needs further investigation.

See also:

Summary for Patients

Web-Only
Supplement

Figure 1. Flowchart of the study cohort.



The dashed line represents the separation of the 2 study cohorts (above) and the matched data set (below).

We hypothesized that coprescription of nitrates and PDE5 inhibitors was prevalent and has increased in recent years among patients with IHD. Furthermore, we sought to investigate whether coprescription yielded an elevated risk for cardiovascular events.

METHODS

Data Sources

This study was based on nationwide Danish health registers. These are well described and have been previously used by this research group (14–17) (see page 2 of the **Supplement** [available at Annals.org] for details).

Population

We included all male patients aged 30 to 85 years with history of IHD on 1 January 2000 or a first-time diagnosis of IHD during 2000 to 2018 without prior nitrate use; both primary and secondary diagnoses linked to admissions or outpatient visits were included. Furthermore, we identified patients claiming 2 consecutive prescriptions of nitrates within 180 days from each other to define nitrate use. Thus, 2 cohorts were defined: 1 cohort containing all patients with IHD and a second cohort composed of a subgroup of patients treated with nitrates from the first cohort. Both cohorts contributed to the temporal trends analyses of PDE5 inhibitor use among patients with IHD. Only the second cohort was used to assess the potential risk for coprescribing nitrates and PDE5 inhibitors. The index date for the first cohort was 1 January 2000 or the date of first-time diagnosis of IHD if it came afterward. The index date for the second cohort and start of follow-up were the date of the second nitrate prescription. For the second cohort, follow-up was halted if no nitrate prescription was filled for 180 days; however, patients could reenter the cohort if a new nitrate prescription was filled later during the follow-up. In practice, this means that to become a case patient, a filled prescription of nitrates within 180 days from the date of event was required. Patients with a history of pulmonary hypertension–for whom PDE5 inhibitors may be prescribed–were excluded if the condition was developed before the inclusion in either cohort (**Figure 1**). Patients in both cohorts were followed until death, emigration, 31 December 2018, or a diagnosis of pulmonary hypertension.

Characteristics of the Cohort

The following characteristics were defined binarily as present if any of the following diagnoses were given up to 5 years before index date (to capture any diagnosis of relevance to the patients' health): heart failure, acute coronary syndrome, ischemic stroke, peripheral vascular disease, chronic obstructive pulmonary disease, chronic renal disease, and cancer. Likewise, medication was defined as a filled prescription up to 6 months before the index date of the following medications: diuretics, antihypertensive drugs, antiplatelet agents, statins, anticoagulants, and sublingual nitrates. To characterize patients being treated for hypertension and diabetes mellitus outside of hospitals–for example, in general practice–we defined both conditions as either a diagnosis or as a combination of filled prescriptions with at least 2 antihypertensive drugs or treatment with a glucose-lowering drug, respectively (Supplement Table 1, available at Annals.org). The Table shows patient characteristics at baseline for the first cohort (all patients with IHD) and for the second cohort (subgroup receiving nitrates).

PDE5 Inhibitor Use

We investigated temporal trends of PDE5 inhibitor use among all patients with IHD and among the subgroup receiving nitrates, that is, the first and second cohort. To assess temporal trends during 2000 to 2018, the average number of PDE5 inhibitor prescriptions filled within a year per 100 persons was calculated. All included patients alive on 1 January of the relevant calendar year were followed, either from this date or when they entered the cohort (whichever happened last), until the end of said calendar year, death, or end of follow-up. Any PDE5 inhibitor prescription filled during follow-up contributed to the analysis.

To further describe the use of PDE5 inhibitors, the proportion of patients claiming at least 1, 2, … or 8 prescriptions within the first 3 years from the index date was also estimated. Proportions in both cohorts were presented for comparison according to calendar year groups.

Outcomes and Exposure

To assess associations between coprescription of nitrates and PDE5 inhibitors, we used a case-crossover design. Only the second cohort, the subgroup of patients with IHD receiving nitrates, was investigated, and follow-up began at the index date on the date of a second filled nitrate prescription. Two composite outcomes were defined with the first event of interest during follow-up defining each case patient: 1) a composite outcome of cardiac arrest, shock (unspecified, hypovolemic, or cardiogenic), MI, ischemic stroke, and acute coronary angiography and 2) a composite outcome of angina pectoris, syncope, and the diagnosis "drug-related adverse event" (Supplement Table 1). All diagnoses were primary or secondary and were linked to an overnight hospitalization, except coronary angiography, angina pectoris, syncope, and drug-related adverse event for which acute outpatient visits were also counted.

For the main analysis, patients were considered exposed on a given day if they had a filled prescription of a PDE5 inhibitor within 14 days before that day. Periods of 7, 21, and 28 days were used for supplementary analyses, acknowledging that the exact time of PDE5 inhibitor use after a filled prescription could vary. Only exposure windows dividable by 7 were chosen to make certain that compared periods consisted of similar weekdays (18).

Table. Baseline Characteristics for All Patients With IHD, Including Separate Characteristics for the Subgroup Receiving Oral Organic Nitrates

Characteristics	Patients With IHD (*n* = 249 541)	
	All Patients (*n* = 249 541)	Subgroup Receiving Oral Organic Nitrates (*n* = 42 073)
Median age (IQR), *y*	65 (68–82)	70 (62–77)
Comorbidities, *n* (%)		
Hypertension	204 073 (81.8)	40 074 (95.2)
Diabetes mellitus	38 440 (15.4)	9137 (21.7)
Heart failure	38 870 (15.6)	9344 (22.2)
Acute coronary syndrome	101 941 (40.9)	16 986 (40.4)
Ischemic stroke	17 704 (7.1)	4068 (9.7)
COPD	17 034 (6.8)	4662 (11.1)
Chronic kidney disease	9317 (3.7)	2605 (6.2)
Peripheral artery disease	10 884 (4.4)	3106 (7.4)
Cancer	16 531 (6.6)	3530 (8.3)
Concomitant medication, *n* (%)		
β-blockers	141 607 (56.7)	27 839 (66.2)
RASi	105 911 (42.4)	20 716 (49.2)
Thiazides	30 456 (12.2)	6809 (16.2)
Loop diuretics	52 898 (21.2)	14 083 (33.5)
Statins	149 293 (59.8)	26 026 (61.9)
Acetylsalicylic acid	166 185 (66.6)	32 055 (76.2)
ADPi	76 447 (30.6)	9850 (23.4)
Anticoagulants	27 985 (11.2)	5077 (12.1)
Sublingual nitrates	44 628 (17.9)	17 403 (41.4)
Educational level, *n* (%)		
Basic or high school	94 921 (38.0)	18 631 (44.3)
Vocational education	98 106 (39.3)	15 000 (35.7)
Higher education	40 255 (16.1)	4538 (10.8)
Unknown	16 259 (6.5)	3904 (9.3)

ADPi = adenosine diphosphate inhibitor; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; IQR = interquartile range; RASi = renin-angiotensin-system inhibitor.

Ethical Considerations

Retrospective studies using administrative health databases do not need ethical approval in Denmark. The study was approved by the data protection organization of the Capital Region of Denmark (approval number P-2019-348).

Supplementary Analyses

We conducted 4 supplementary analyses. First, to assess associations between PDE5 inhibitor exposure and incidence of any of the individual components in the 2 composite outcomes, we conducted secondary analyses for each outcome separately using 14-day exposure windows. Second, as shown in Supplement Table 2 (available at Annals.org), we identified the characteristics of each case patient at the beginning of the index period for each outcome to compare with characteristics at the beginning

of follow-up. Third, to account for potential differences in temporal prescribing patterns skewing our results, we also performed case–time–control analyses (19, 20). Fourth, to further test our assumptions, we performed analyses that required just 1 filled nitrate prescription as well as analyses in which maximum follow-up was restricted to 1 year (see page 15 of the Supplement for details).

Statistical Analysis

Baseline characteristics are presented with percentages and continuous variables as median with interquartile range.

Average numbers of prescriptions filled within a year and proportions of patients claiming at least 1, 2, . . ., or 8 prescriptions within the first 3 years from the index date were estimated using appropriate methods to analyze recurrent events in the presence of censoring and competing risk for death. Specifically, the Ghosh and Lin method (21) was used to compute the mean with 95% CI and the Aalen–Johansen method (22) to compute proportions with 95% CI, as implemented in the "mets" package for R (23).

The main analyses investigating associations between coprescription of nitrates and PDE5 inhibitors and the composite outcomes were based on a case-crossover design using conditional logistic regression models to obtain odds ratios (ORs). The design compares a person's exposure status in an index period preceding the event against a reference period earlier in time. We used 14-day periods separated by a 7-day-washout period to avoid lagged effects. In supplementary analyses, we also investigated 7-, 21-, and 28-day periods. Taking the 14-day analysis as an example, the index period would be 0 to 14 days before the event and the reference period would be 21 to 35 days before the event. By using each person as his or her control, the method adjusts for unmeasured confounders that remain stable within the 2 periods, for example, lifestyle factors, treatment indications, comorbidities, and other coprescribed medications. This makes this method suitable for studying the effects of transient exposure on abrupt outcomes (24, 25). Notably, only persons with a different exposure status in the index and reference periods (discordant exposure) are included, meaning that case patients exposed only in the index period support an OR of greater than 1 and vice versa for case patients exposed only in the reference period. Therefore, case patients with a concordant exposure history, either exposed or not exposed in both periods, did not contribute to the analyses (24, 25).

We used R (version 3.5.0 for Windows; R Foundation for Statistical Computing) (26) for data management, statistics, and illustrations.

Role of the Funding Source

None of the funding sources has had any influence on the conduct or the reporting of this study.

RESULTS

Cohort Characteristics

We identified 249 541 male patients with IHD (median age, 65 years [interquartile range, 56 to 73 years]). Within this cohort, 42 073 patients received nitrates during follow-up (Figure 1). At the point at which they received nitrates (isosorbide mononitrate, 21%; isosorbide dinitrate, 78%; and nicorandil, 1%), patients had a median age of 70 years (interquartile range, 62 to 77 years) as well as a larger burden of comorbidity and concomitant treatment (Table).

PDE5 Inhibitor Exposure

From 2000 to 2018, the average yearly prescription rate of PDE5 inhibitors increased 10-fold among all patients with IHD from an average of 3.1 (95% CI, 2.8 to 3.3) to 30.9 (CI, 30.3 to 31.6) prescriptions per 100 persons per year. Likewise, in the subgroup receiving nitrates, a 20-fold increase was observed from 0.9 (CI, 0.5 to 1.2) to 19.7 (CI, 18.0 to 21.1) prescriptions (Figure 2). Figure 3 also shows the temporal trend of increasing use of PDE5 inhibitors among both cohorts. In the most recent years, 2014 to 2018, 15.1% of patients with IHD filled at least 1 prescription of nitrates within 3 years of diagnosis, whereas 5.9% filled at least 5. Likewise, in the subgroup receiving nitrates, 9.0% filled at least 1 PDE5 inhibitor prescription with 2.7% claiming at least 5 prescriptions within the first 3 years from nitrate initiation (Figure 3). Of every filled prescription of PDE5 inhibitors during follow-up in the subgroup receiving nitrates (n = 91 838), sildenafil accounted for 69%, tadalafil 27%, vardenafil 4%, and avanafil less than 0.1%. Comparable prescribing patterns were found for filled prescriptions in all patients with IHD (total n = 795 617; sildenafil, 69%; tadalafil, 28%; vardenafil, 3%; and avanafil, <0.1%). Please see Supplement Table 3 (available at Annals.org) for distribution of formulations and strengths.

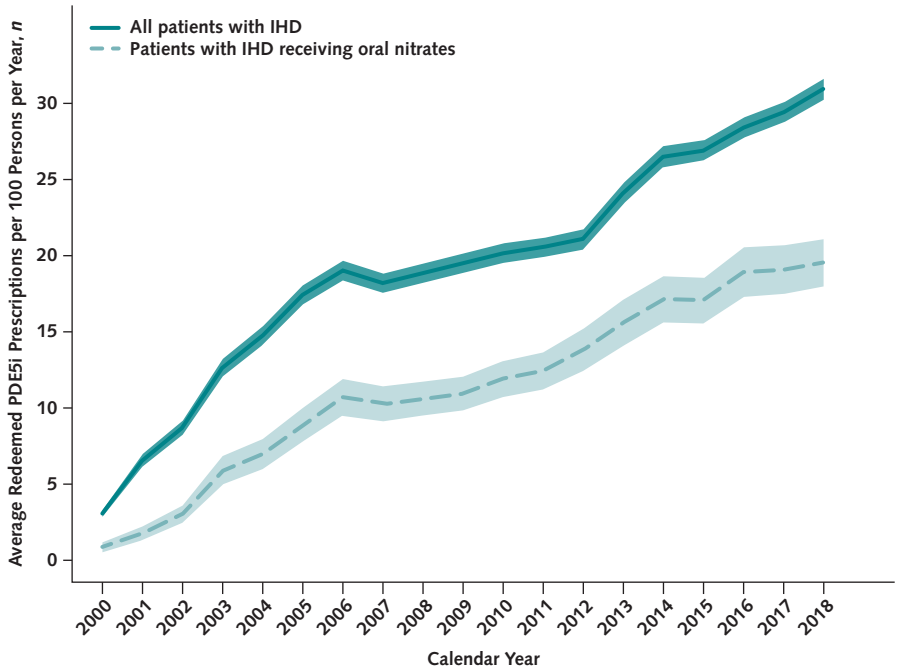
Risk Pertaining to Coexposure

In the subgroup receiving nitrates, we identified 16 948 cases of cardiac arrest, shock, MI, ischemic stroke, or acute coronary arteriography during follow-up. Associating these events to PDE5 inhibitor exposure varying the length of index and reference periods in case-crossover analyses did not show any evidence of an increased risk after coexposure with a case-crossover OR of 0.58 (CI, 0.28 to 1.13) for a 14-day exposure window (Figure 4). In addition, when assessing the second composite outcome of syncope, angina pectoris, and drug-related adverse event (n = 18 967), no increased risk associated with PDE5 inhibitor exposure was found with a case-crossover OR of 0.73 (CI, 0.40 to 1.32) for a 14-day exposure window (Figure 4).

Supplementary Analyses

Characteristics at the time of event were comparable to characteristics at the beginning of follow-up (Table and Supplement Table 2). Assessing each component of the 2 outcomes separately yielded similar results with no evidence of an increased risk after coexposure to nitrates and PDE5 inhibitors. Assessing shock, cardiac arrest, and drug-related adverse event as individual outcomes yielded no meaningful results due to too few cases with discordant exposure history (Supplement Table 4, available at Annals.org). Using a case–time–control design (Supplement Table 5, available at Annals.org), including patients after just 1 filled nitrate

Figure 2. Yearly average use of PDE5i among all male patients with IHD, including a subgroup receiving oral organic nitrates.



Average number of prescriptions was calculated as a marginal mean with 95% CIs, taking the competing risk for death and censoring into account. For each calendar year, all patients included and alive on 1 January of the year in question contributed to the analysis. IHD = ischemic heart disease; PDE5i = phosphodiesterase type 5 inhibitor.

prescription (**Supplement Table 6**, available at Annals.org), or restricting follow-up to a maximum of 1 year (**Supplement Table 7**, available at Annals.org) yielded similar results as the main analyses.

Discussion

In male patients with IHD, use of PDE5 inhibitors has risen markedly from 2000 to 2018; among patients receiving nitrates, a 20-fold increase was observed. Despite this change of practice, no risk increase after a filled prescription of PDE5 inhibitors among male patients with IHD receiving nitrates was found.

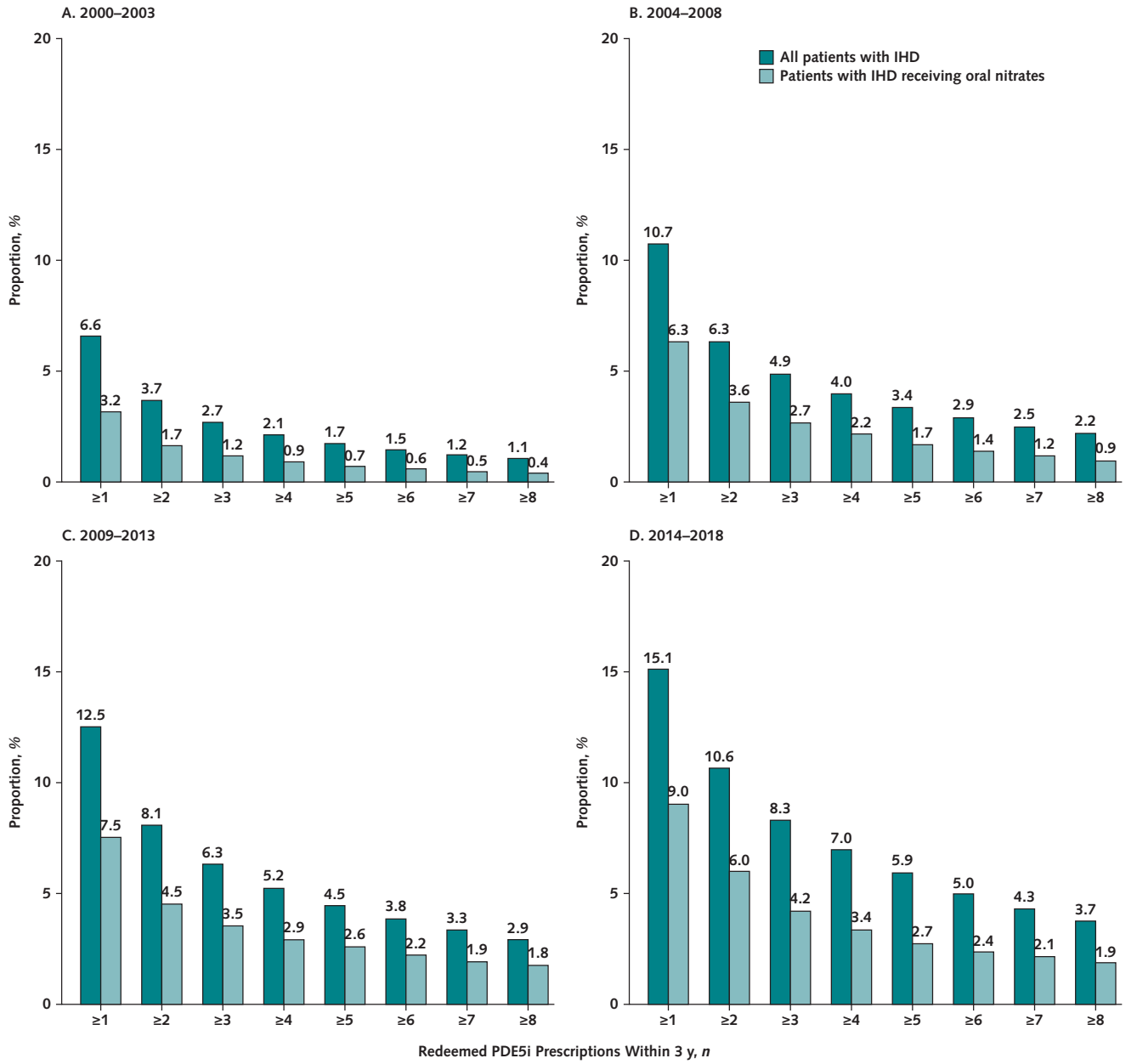
Concomitant treatment with nitrates and PDE5 inhibitors is contraindicated (5–8, 27); however, patient groups who benefit from both drugs are growing (9, 12, 13), possibly prompting a demand for coprescription (1). Our data show that PDE5 inhibitor use has increased among all patients with IHD, but especially among patients receiving nitrates. This result is concerning. Guidelines with a specific recommendation for concomitant use have been debated, but widely accepted recommendations have not materialized due to lack of scientific evidence (1). One exception may be a statement from the American Heart Association that PDE5 inhibitors should not be given to patients receiving nitrates, and nitrates can only be taken safely at least 24 and 48 hours after use of fast- and slow-acting PDE5 inhibitors, respectively (class III; level of evidence B) (27). As a result, imperative unanswered questions remain: for example, which patients receiving nitrates can be treated safely with PED5 inhibitors? And how long should nitrates be withdrawn before a PDE5 inhibitor is taken? Our results underscore the importance and relevance of these questions.

The effect on blood pressure after coadministration of different nitrates and PDE5 inhibitors is well documented with pharmacologic, placebo-controlled trials both in healthy men (28, 29), and men with angina pectoris (3, 28) or coronary artery disease (4). Results across different agents and administrative methods showing that combinations of nitrates and PDE5 inhibitors lead to a substantial drop in blood pressure were consistent. In Denmark, the recommendation is that coprescription should be avoided, but proper guidelines do not exist. If coprescription is chosen deliberately, and not through an oversight, then we would expect patients to be adequately warned not to take the medication within 24 to 48 hours of each other (1).

A recent study based on an American database from 2012 to 2016 compared periods of copossession of nitrates and PDE5 inhibitors with periods in which only 1 or the other medication was prescribed. This study found no increased rates of cardiovascular outcomes associated with expected copossession (30).

We propose several explanations regarding the apparent safety of coprescribing. First, the observed drop in blood pressure may not cause a condition for which patients seek a hospital. A drop in blood pressure has been shown in pharmacologic trials, but it might not translate to a real-life risk for cardiovascular outcomes.

Figure 3. Number of filled PDE5i prescriptions within 3 years of inclusion among all patients with IHD and a subgroup receiving oral organic nitrates, according to calendar year groups.

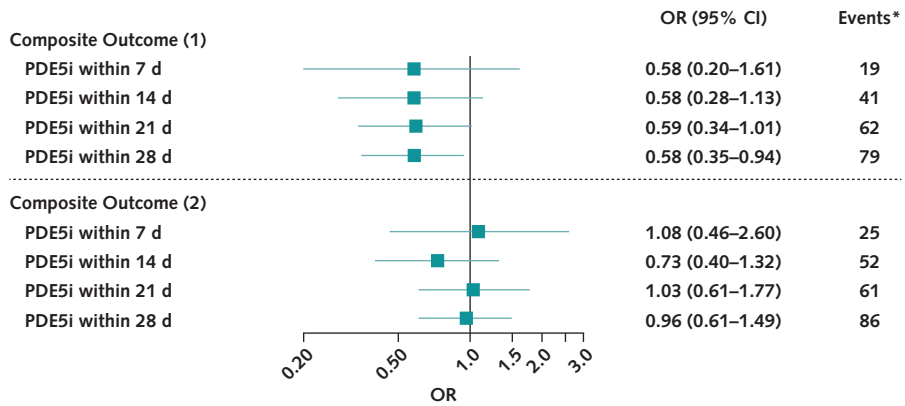


IHD = ischemic heart disease; PDE5i = phosphodiesterase inhibitor. A-D. The proportion among all patients with IHD and in the subgroup receiving oral organic nitrates who filled a minimum of 1, 2, . . ., or 8 prescriptions of PDE5i within the first 3 years after inclusion.

Second, patients could be well informed and adherent to guidance that the prescribing physician has provided: for example, patients are aware of the recommended pause in nitrate treatment before PDE5 inhibitor use and follow these recommendations. One study found that 69 of 252 patients (27%) were adequately warned of coadministration at the time of coprescription (30). This is surprisingly few and underscores that there could be more answers as to why no increased risk was found.

Third, nitrates are often taken in the morning, and we think it is a reasonable assumption that most PDE5 inhibitors are taken in the evening (31). Therefore, for patients who meet these assumptions, the nitrates could be metabolized to a degree such that the synergistic interaction is negligible. Isosorbide dinitrate and isosorbide mononitrate accounted for 78% and 21% of the nitrates in our study and have plasma half-lives of 4.5 and 5 hours, respectively (32), conceivably allowing for a sufficient reduction in plasma levels.

Figure 4. PDE5i exposure and cardiovascular risk according to case-crossover analyses in a subgroup of male patients with ischemic heart disease receiving oral organic nitrates.



OR = odds ratio; PDE5i = phosphodiesterase type 5 inhibitor. Composite outcome (1): cardiac arrest, shock (unspecified, hypovolemic, or cardiogenic), myocardial infarction, ischemic stroke, and acute coronary angiography. Composite outcome (2): angina pectoris, syncope, and the diagnosis drug-related adverse event.

* Case patients contributing to the analyses were those having a discordant drug exposure history in the index and reference periods.

Last, coprescription may not be accurately captured due to our assumptions regarding nitrate treatment and our assumption regarding when PDE5 inhibitors are used. We assumed that patients claiming 2 consecutive prescriptions of nitrates within 180 days from each other would remain on the treatment throughout follow-up. To rely less on this assumption, we also halted follow-up if no prescription of nitrates was filled for 180 days during follow-up. However, we cannot be certain that patients were receiving nitrates at the time of event. Likewise, we assumed that patients planned to take the PDE5 inhibitor relatively close to the date of the filled prescription. These are both important limitations to consider when interpreting these observational data. It is, however, reassuring that we found similar results using varying exposure windows. Both assumptions skewing our results cannot be ruled out with certainty and unmet assumptions would draw our results toward "no association."

A combination of these explanations may explain the seemingly safe coprescription of nitrates and PDE5 inhibitors. A qualitative study involving both prescribers and patients would be needed to elaborate on motivations for coprescribing and possible safety measures undertaken. Our findings and interpretations are only applicable in an outpatient setting where patients fill the prescriptions for use at home. Thus, our data cannot answer the equally important clinical question of nitrate administration for a patient with angina pectoris who recently took PDE5 inhibitor, especially a long-acting agent.

Furthermore, it is likely that our findings could apply primarily to a highly selective group of patients with IHD. Patients receiving nitrates who are coprescribed PDE5 inhibitors by their physician plausibly consist of the healthier and more resourceful proportion of the cohort. Finally, in Denmark, PDE5 inhibitors are only available legally by prescription, but PDE5 inhibitors are readily available on the counterfeit medication market (33). In this study, only data on prescribed PDE5 inhibitors were available. The possibility of patients obtaining PDE5 inhibitors without prior consultation with a physician could still pose a health concern.

The primary strength of this study was the nationwide inclusion of all patients with IHD, some receiving nitrates, in a 19-year period using validated registers, thus limiting selection and inclusion bias. The case-crossover design allows investigators to assess acute events after temporary effects while mitigating time-invariant unmeasured confounding, which seems applicable for this study (24). However, the case-crossover analysis does not account for time-dependent confounding changing between the reference and index period, thus limiting the ability to adjust for patients possibly being healthier when wanting to use PDE5 inhibitors.

The PDE5 inhibitors are primarily administered as performance-enhancing drugs for erectile dysfunction and nitrates have never been shown to improve cardiovascular prognosis (34). Furthermore, as co-use is clearly contraindicated (5–8, 27), refraining from use of the combination would be expected. However, improvement of quality of life may change both physician and patient perspectives of potential benefits and perceived harm. Indeed, our data show that these drugs were coprescribed with a large and growing frequency. Yet, despite noticeable coprescribing, we could not find a statistically significant association with increased risk. This finding raises the possibility that in carefully selected patients, coprescription might be safe. A qualitative study involving both patients and prescribers could be needed to better understand this finding.

Use of PDE5 inhibitors has increased 20-fold among male patients with IHD receiving nitrates from 2000 to 2018, despite an established contraindication. In this carefully conducted study of concomitant use in a nationwide population, we could not find a statistically significant association with an increased cardiovascular risk

after a filled prescription of PDE5 inhibitors among patients receiving nitrates.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Holt (e-mail, anders.holt.03@regionh.dk). *Statistical code* and *data set:* Not available.

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References

1. **Kloner RA, Goggin P, Goldstein I, et al.** A new perspective on the nitrate-phosphodiesterase type 5 inhibitor interaction. J Cardiovasc Pharmacol Ther. 2018;23:375-386. [PMID: 29739235] doi:10.1177/1074248418771896
2. **Schwartz BG, Kloner RA.** Drug interactions with phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. Circulation. 2010;122:88-95. [PMID: 20606131] doi:10.1161/CIRCULATIONAHA.110.944603
3. **Webb DJ, Muirhead GJ, Wulff M, et al.** Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol. 2000;36:25-31. [PMID: 10898408] doi:10.1016/s0735-1097(00)00705-1
4. **Parker JD, Bart BA, Webb DJ, et al.** Safety of intravenous nitroglycerin after administration of sildenafil citrate to men with coronary artery disease: a double-blind, placebo-controlled, randomized, crossover trial. Crit Care Med. 2007;35:1863-8. [PMID: 17522570] doi:10.1097/01.CCM.0000269371.70738.30
5. **European Medicines Agency.** European public assessment report: Viagra. 2021. Accessed at www.ema.europa.eu/en/medicines/human/EPAR/viagra on 7 June 2021.
6. **European Medicines Agency.** European public assessment report: Spedra. 2021. Accessed at www.ema.europa.eu/en/medicines/human/EPAR/spedra on 7 June 2021.
7. **European Medicines Agency.** European public assessment report: Cialis. 2021. Accessed at www.ema.europa.eu/en/medicines/human/EPAR/cialis on 7 June 2021.
8. **European Medicines Agency.** European public assessment report: Levitra. 2021. Accessed at www.ema.europa.eu/en/medicines/human/EPAR/levitra on 7 June 2021.
9. **França-Silva MS, Balarini CM, Cruz JC, et al.** Organic nitrates: past, present and future. Molecules. 2014;19:15314-23. [PMID: 25255247] doi:10.3390/molecules190915314
10. **Meng Z, Gai W, Song D.** Postconditioning with nitrates protects against myocardial reperfusion injury: a new use for an old pharmacological agent. Med Sci Monit. 2020;26:e923129. [PMID: 32516304] doi:10.12659/MSM.923129
11. **Gandaglia G, Briganti A, Jackson G, et al.** A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65:968-78. [PMID: 24011423] doi:10.1016/j.eururo.2013.08.023
12. **Rastrelli G, Maggi M.** Erectile dysfunction in fit and healthy young men: psychological or pathological. Transl Androl Urol. 2017;6:79-90. [PMID: 28217453] doi:10.21037/tau.2016.09.06
13. **Kessler A, Sollie S, Challacombe B, et al.** The global prevalence of erectile dysfunction: a review. BJU Int. 2019. [PMID: 31267639] doi:10.1111/bju.14813
14. **Schmidt M, Pedersen L, Sørensen HT.** The Danish civil registration system as a tool in epidemiology. Eur J Epidemiol. 2014;29:541-9. [PMID: 24965263] doi:10.1007/s10654-014-9930-3
15. **Schmidt M, Schmidt SA, Sandegaard JL, et al.** The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90. [PMID: 26604824] doi:10.2147/CLEP.S91125
16. **Kildemoes HW, Sørensen HT, Hallas J.** The Danish national prescription registry. Scand J Public Health. 2011;39:38-41. [PMID: 21775349] doi:10.1177/1403494810394717
17. **Holt A, Blanche P, Zareini B, et al.** Effect of long-term beta-blocker treatment following myocardial infarction among stable, optimally treated patients without heart failure in the reperfusion era: a Danish, nationwide cohort study. Eur Heart J. 2021;42:907-914. [PMID: 33428707] doi:10.1093/eurheartj/ehaa1058
18. **Redelmeier DA, Tibshirani RJ.** Association between cellular-telephone calls and motor vehicle collisions. N Engl J Med. 1997;336:453-8. [PMID: 9017937] doi:10.1056/NEJM199702133360701
19. **Suissa S.** The case-time-control design. Epidemiology. 1995;6:248-53. [PMID: 7619931] doi:10.1097/00001648-199505000-00010
20. **Jensen AK, Gerds TA, Weeke P, et al.** On the validity of the case-time-control design for autocorrelated exposure histories. Epidemiology. 2014;25:110-3. [PMID: 24257508] doi:10.1097/EDE.0000000000000001
21. **Ghosh D, Lin DY.** Nonparametric analysis of recurrent events and death. Biometrics. 2000;56:554-62. [PMID: 10877316] doi:10.1111/j.0006-341x.2000.00554.x
22. **Putter H, Fiocco M, Geskus RB.** Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389-430. [PMID: 17031868] doi:10.1002/sim.2712
23. **Scheike TH, Eriksson F, Tribler S.** The mean, variance and correlation for bivariate recurrent event data with a terminal event. J R Stat Soc Ser C Appl Stat. 2019;68:1029-49. doi:10.1111/rssc.12350
24. **Cadarette SM, Maclure M, Delaney JAC, et al.** Control yourself: ISPE-endorsed guidance in the application of self-controlled study designs in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2021;30:671-684. [PMID: 33715267] doi:10.1002/pds.5227

25. **Maclure M.** The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991;133:144-53. [PMID: 1985444] doi:10.1093/oxfordjournals.aje.a115853
26. **R Core Team.** R: a language and environment for statistical computing. R Foundation for Statistical Computing; 2018.
27. **Levine GN, Steinke EE, Bakaeen FG, et al; American Heart Association Council on Clinical Cardiology.** Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2012;125:1058-72. [PMID: 22267844] doi:10.1161/CIR.0b013e3182447787
28. **Oliver JJ, Kerr DM, Webb DJ.** Time-dependent interactions of the hypotensive effects of sildenafil citrate and sublingual glyceryl trinitrate. Br J Clin Pharmacol. 2009;67:403-12. [PMID: 19371313] doi:10.1111/j.1365-2125.2009.03375.x
29. **Kloner RA, Hutter AM, Emmick JT, et al.** Time course of the interaction between tadalafil and nitrates. J Am Coll Cardiol. 2003;42:1855-60. [PMID: 14642699] doi:10.1016/j.jacc.2003.09.023
30. **Nunes AP, Seeger JD, Stewart A, et al.** Cardiovascular outcome risks in patients with erectile dysfunction co-prescribed a phosphodiesterase type 5 inhibitor (PDE5i) and a nitrate: a retrospective observational study using electronic health record data in the United States. J Sex Med. 2021;18:1511-1523. [PMID: 34389264] doi:10.1016/j.jsxm.2021.06.010
31. **Refinetti R.** Time for sex: nycthemeral distribution of human sexual behavior. J Circadian Rhythms. 2005;3:4. [PMID: 15790406] doi:10.1186/1740-3391-3-4
32. **Prescribers' Digital Reference.** Accessed at www.pdr.net on 7 June 2021.
33. **Jackson G, Arver S, Banks I, et al.** Counterfeit phosphodiesterase type 5 inhibitors pose significant safety risks. Int J Clin Pract. 2010;64:497-504. [PMID: 20088883] doi:10.1111/j.1742-1241.2009.02328.x
34. **Belsey J, Savelieva I, Mugelli A, et al.** Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. Eur J Prev Cardiol. 2015;22:837-48. [PMID: 24776376] doi:10.1177/2047487314533217

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