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ORIGINAL ARTICLE

Acute cardiovascular effects associated with the use of prescription medications: A Danish nationwide screening study

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Abstract

Aim: This study aims to conduct a hypothesis-generating screening for acute cardiovascular effects of prescription medications.

Methods: This Danish nationwide screening study was conducted among incident cases of cardiovascular diseases, including myocardial infarction (MI), ischemic stroke (IS), heart failure (HF), venous thromboembolism (VTE), myocarditis, and atrial fibrillation (AF), between January 2000 and December 2022. Using a case-crossover study design, we examined exposure to individual drugs on the date of the cardiovascular event (focal date) and three reference dates corresponding to days −180, −270 and −360 prior to index date. We calculated odds ratios (ORs) with 95% credible intervals (CIs) for associations between exposure drug and cardiovascular outcomes using the conditional logistic regression with a weak Bayesian shrinkage.

Results: After applying exclusion criteria, we identified 191,979 cases of AF, 145,148 cases of MI, 132,271 cases of IS, 71,821 cases of HF, 16,127 cases of VTE and 10,045 cases of myocarditis. Based on the threshold for the strength of associations (OR ≥ 1.5; lower limit of CI ≥ 1), we identified 222 associations for 104 individual drugs across all six outcomes. Some major drug classes, such as antibiotics, analgesics and corticosteroids, consistently demonstrated associations for most cardiovascular outcomes. Use of pantoprazole, in contrast to other PPIs, was associated with AF (OR 1.83; 95% CI 1.68–2.00) along with MI, HF, myocarditis and VTE. Similarly, oxazepam stood out among other benzodiazepines and demonstrated increased risk of VTE (OR 2.53; 95% CI 1.55–4.13) as well as MI, HF and AF.

Conclusions: The results highlight several potentially important associations across various pharmacological drug classes that warrant further investigation in tailored pharmacoepidemiological analyses.

KEYWORDS
adverse drug reactions, cardiovascular disease, case–crossover design, pharmacoepidemiology, pharmacovigilance

1 | INTRODUCTION

There are established cardiovascular side-effects to numerous prescription drugs, ranging from well-established risks with use of the analgesics rofecoxib[1] and diclofenac[2] over less well-elucidated risks with use of antipsychotics[3,4] to hypotheses of potential risks with use of ephedrine-containing products[5] and stimulants.[6] Such effects are often only recognized after marketing and, as a consequence, one out of 25 new drugs is later withdrawn because of adverse effects.[7] The cornerstone of traditional pharmacovigilance is the reporting of suspected adverse drug reactions (ADRs) by vigilant clinicians or lay people. Unfortunately, this approach has several important limitations: it is prone to underreporting,[8] it is highly sensitive towards media attention,[9] and it is less effective in detecting delayed adverse events, e.g. cancer,[10] as well as events that are common in the background population.[11] The latter was painfully evident for rofecoxib, where a massive uptake[12] and a five-year gap between marketing and withdrawal due to safety concerns[1,13] caused thousands of adverse cardiovascular events.[14]

An alternative approach to traditional pharmacovigilance is the use of large healthcare databases and epidemiological methodology to identify drug–outcome associations. Though still in its infancy, hypothesis-generating epidemiological screening of such databases has previously been used in addressing drug use and risk of cancer,[10,15,16] diabetes[17] and other unsuspected adverse outcomes.[18] The latter utilized a self-controlled design,[19] which is particularly useful to study acute effects after transient medication use[20] and, in most cases, does not require the selection of appropriate comparators, making it useful for large-scale automated screening. Hence, this study aims to conduct a screening of acute cardiovascular effects of prescription medications using the case–crossover design.

What is already known about this subject

- Traditional pharmacovigilance relies on spontaneous reporting of adverse drug reactions, which has considerable limitations, in particular that this system is unable to detect delayed adverse events and adverse events that are common in the background population.
- To overcome these limitations, use of large administrative databases coupled with epidemiological methodology has been proposed as an alternative to traditional pharmacovigilance to detect unsuspected drug–outcome associations.

What this study adds?

- This study applied a hypothesis-generating approach leveraging real-world drug data to investigate whether prescription medications have previously unknown adverse effects on acute cardiovascular outcomes.
- The study highlights the feasibility of proactive screening using epidemiological methods.
- The study has created a repository of drug–outcome associations for cardiovascular outcomes, including specific hypotheses, such as a potential association of pantoprazole and oxazepam use with increased cardiovascular risk.

2 | METHODS

Using a case–crossover study design, this nationwide hypothesis-free screening study was conducted with incident cases of cardiovascular diseases between January 2000 and 31 December 2022. We used the Danish population-based health registers to perform the screening of all prescription drugs for a range of cardiovascular and cerebrovascular outcomes, including myocardial infarction, ischemic stroke, heart failure, venous thromboembolism, myocarditis and atrial fibrillation among patients aged 35 years and above with no previous history of cardiovascular disease. The protocol was pre-registered at https://osf.io/seqpg.

2.1 | Data sources

Free and centrally recorded healthcare services in Denmark allow for high-quality population-based studies, covering the entire Danish population. Danish healthcare registers provide some of the finest sources of data for epidemiological research worldwide.[21] Both the Danish National Prescription Registry[22] and Danish National Patient Register[23] are known to provide high-quality data recorded since the years 1995 and 1977, respectively. The Danish National Prescription Registry contains all data on prescription drugs redeemed at community pharmacies in Denmark. The data include the name, dose and quantity of drug dispensed as well as the date of dispensing. The registry uses the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization.[24] The Danish National Patient Register contains data on all hospital admissions (non-psychiatric) since 1977 and on all outpatient contacts since 1995. Since 1994, all diagnoses are coded using International Classification of Diseases, tenth revision (ICD-10). Data linkage is possible with the help of the Danish civil registration number (CPR number) assigned to all Danish residents and was performed by Statistics Denmark.[25]

2.2 | Study design

We used a case–crossover design, a 'self-controlled' study design which utilizes a within-person comparison at different time periods.[26] In this design, an individual's drug exposure during a time

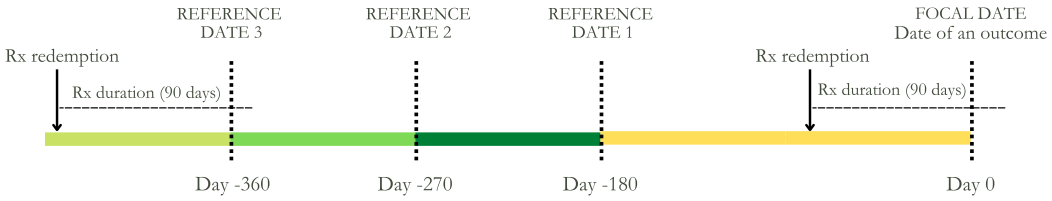

FIGURE 1 Illustration of case–crossover design.

period immediately prior to an event of interest (focal date) is compared with their exposure status prior to one or more reference dates that precede the focal date (Figure 1). The case–crossover design controls for confounders that are stable over time,[19] such as genetics, sex, obesity and smoking behaviour. This design is particularly useful to study acute or abrupt outcomes after intermittent drug exposures,[27] making it useful to study potential drug-triggered cardiovascular events.

2.3 | Analysis

We identified all newly diagnosed cases of myocardial infarction, ischaemic stroke, heart failure, venous thromboembolism, myocarditis and atrial fibrillation from 2000 until 2022 (see Appendix for specific ICD-10 codes). The study period was based on data availability while restricting to the period where ICD-10 was used in Denmark and to ensure sufficient number of cases. To ensure accurate identification of truly incident cases, we included individuals with a minimum run-in of 1 year. The day of diagnosis was used as the index date. We analysed all drugs by assigning a fixed prescription duration of 90 days; except for antibiotics and drugs prescribed in smaller quantities, for which we used a fixed prescription duration of 30 days. We assessed exposure status on a focal date (Day 0) and three reference dates corresponding to Days −180, −270 and −360 prior to index date (Figure 1). A larger gap between a focal and first referent date was intended to mitigate carryover effects of previous drug exposures. Further, for newly marketed drugs, we excluded all cases during the first year after their registration to allow the possibility of drug exposure in at least one of the reference windows.

We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for associations between exposure drug and risk of myocardial infarction, ischaemic stroke, heart failure, venous thromboembolism, myocarditis, and atrial fibrillation using a conditional logistic regression. We applied a weak Bayesian shrinkage[28] to stabilize the low-powered estimates using a normal prior distribution for the log relative risk (log RR), with a mean of 0 and variance of 0.5, corresponding to an OR of 1.0 and a 95% CI of 0.25–4.00. The case–crossover design is vulnerable to bias from time trends in use of the drug under study. To adjust for this, we adopted a new approach, by including calendar time as a standardized covariate in the regression analysis. This method adapts the original case–time–control approach by Suissa,[29] with type of window as a dependent variable and exposure status as an independent variable (clogit (focal ∼ expo + indexdate + strata [id], …)).

2.4 | Multiple comparisons

Standard approaches to adjust for multiple testing, such as Bonferroni correction,[30] can limit false positive signals (type-I error), but they also reduce the number of true positives. In this exploratory screening study, our goal was to avoid premature rejection of true signals prior to rigorous evaluation. Consequently, we did not apply multiple testing adjustments, as others recommend.[31] Instead, we incorporated a weak Bayesian shrinkage method[28] to mitigate concerns about type-I error due to multiple comparisons.[32]

2.5 | Screening process

Drug exposures were defined at the 5th level (e.g. A02BC01, omeprazole) of the ATC classification. For class effects, level 4 (e.g. A02BC, proton pump inhibitors) ATC codes were used. During the screening process, we only analysed drug–outcome associations with more than 25 cases that had a discordant exposure status between the focal and one or more reference windows. This threshold was chosen to ensure sufficient statistical power to detect meaningful associations. We excluded all drugs acting on cardiovascular system (ATC main group: C) as well as all antithrombotic agents (ATC subgroup B01A) to limit confounding by indication.

2.6 | Signal detection and filtering

After screening, a three-step signal detection and filtering process was applied to identify signals that need to be followed up with tailored epidemiological analyses.

Step 1: Strength of association. In the first step, we only selected associations with OR ≥ 1.5 and lower bound of confidence interval ≥ 1 to indicate a noteworthy positive drug–outcome association. We then performed manual assessment of these signals in Steps 2 and 3.

Step 2: Assessment of risk of bias or confounding. In Step 2, a team of pharmacologists and pharmacoepidemiologists performed a manual assessment, using subject-matter knowledge, to rule out signals that might be generated due to protopathic bias or time-varying confounding. For example, in studying the effects of antibiotics on cardiovascular outcomes, a significant association may be observed between antibiotic use and higher risk of these outcomes. However, this apparent relationship could be due to time-varying confounding, as antibiotic use is a marker of acute illness (infection) which again is

associated with cardiovascular outcomes. All reviewers reviewed the signals independently and decisions were made through consensus.

Step 3: Novelty. This step of manual assessment was also based on the subject-matter knowledge where we evaluated each signal's novelty and categorized associations into three groups: those corresponding to known ADRs, those indicative of unknown ADRs or those that were considered to act as proxies. The latter is defined as a drug that represents another drug or a disease condition that has a correlation with the outcome of interest. For example, use of oral anticoagulants can be considered a proxy for the presence of atrial fibrillation because they are commonly prescribed to prevent stroke in atrial fibrillation patients. To discern novel ADRs, we used the SIDER database[33] to search for signals linked to known ADRs. This filtering process enabled us to flag potential novel, idiosyncratic ADRs that may not have been previously documented or understood.

2.7 | Other

All analyses were conducted using R (version 4.3.2). In Denmark, studies based solely on register data do not require review or ethical approval. The project was funded by the Independent Research Fund Denmark—Sapere Aude (grant no. 1052-00035B).

3 | RESULTS

We identified 583 267 eligible new cases of cardiovascular diseases between January 2000 to December 2022. After applying inclusion and exclusion criteria, we ended up with 191 979 cases of atrial fibrillation, 145 148 cases of myocardial infarction, 132 271 cases of ischaemic stroke, 71 821 cases of heart failure, 16 127 cases of venous thromboembolism and 10 045 cases of myocarditis (Figure 2).

The overall analyses consisted of a total of 4998 drug–outcome and drug class–outcome pairs across the six different outcomes. Based on the threshold for the strength of associations (OR ≥ 1.5; lower limit of 95% CI ≥ 1), we identified a total of 222 associations for 104 individual drugs across all six outcomes which further underwent the process of manual assessment. The highest number of associations was seen for heart failure ($n = 67$) followed by atrial fibrillation ($n = 55$) and myocardial infarction ($n = 32$). For drug classes, we identified 151 total associations, with the most number of associations for heart failure ($n = 44$) followed by atrial fibrillation ($n = 33$) and venous thromboembolism ($n = 26$) (Table S1, Figures S1–S6).

We found some major drug classes—analgesics, antibiotics, corticosteroids and laxatives—to constitute the majority of the associations across all cardiovascular outcomes (Figure 3). For instance, for heart failure, use of natural opioids (OR 1.76; CI 1.49–2.09), macrolides (OR 3.29; CI 2.81–3.85), glucocorticoids (OR 1.87; CI 1.60–2.19) and contact laxatives (OR 1.81; CI 1.46–2.24) showed 95% probability of the OR being above 1. Similar associations were seen between these drug classes and other cardiovascular outcomes (Table S2, Figures S7–S11).

Of the 222 associations that underwent manual assessment (Table S1), 130 (58%) were classified as unexplained, 76 (34%) were classified as explained by time-varying confounding, 10 (4.5%) were previously known, while 6 (2.7%) were considered proxies. Some associations were flagged as particularly interesting, e.g. pantoprazole use which, in contrast to use of other proton pump inhibitors (PPIs), showed a strong association with venous thromboembolism (OR 1.98; CI 1.55–2.52), atrial fibrillation (OR 1.83; CI 1.68–2.00), myocarditis (OR 1.81; CI 1.35–2.44) as well as myocardial infarction and heart failure. Similarly, oxazepam stood out among other benzodiazepines and demonstrated increased risk of venous thromboembolism (OR 2.53; CI 1.55–4.13), heart failure (OR 1.93; CI 1.56–2.37), atrial fibrillation (OR 1.73; CI 1.49–2.02) and myocardial infarction (OR 1.57; CI 1.31–1.87). Use of ferrous sulfate, but not ferrous glycine sulfate or ferrous

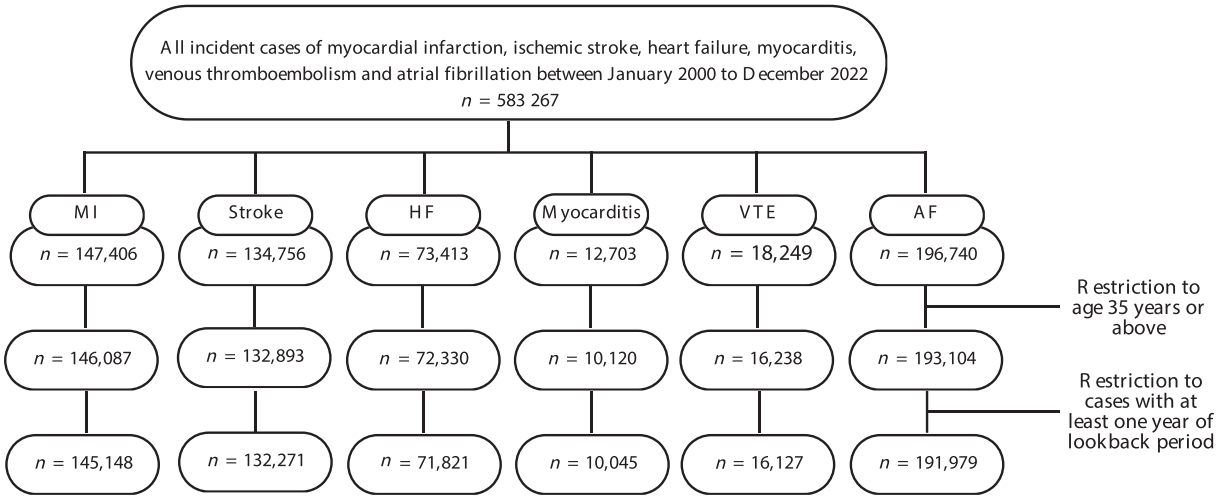

FIGURE 2 Identification of incident cases of cardiovascular diseases between January 2000 and December 2022. MI: myocardial infarction; HF: heart failure; VTE: venous thromboembolism; AF: atrial fibrillation.

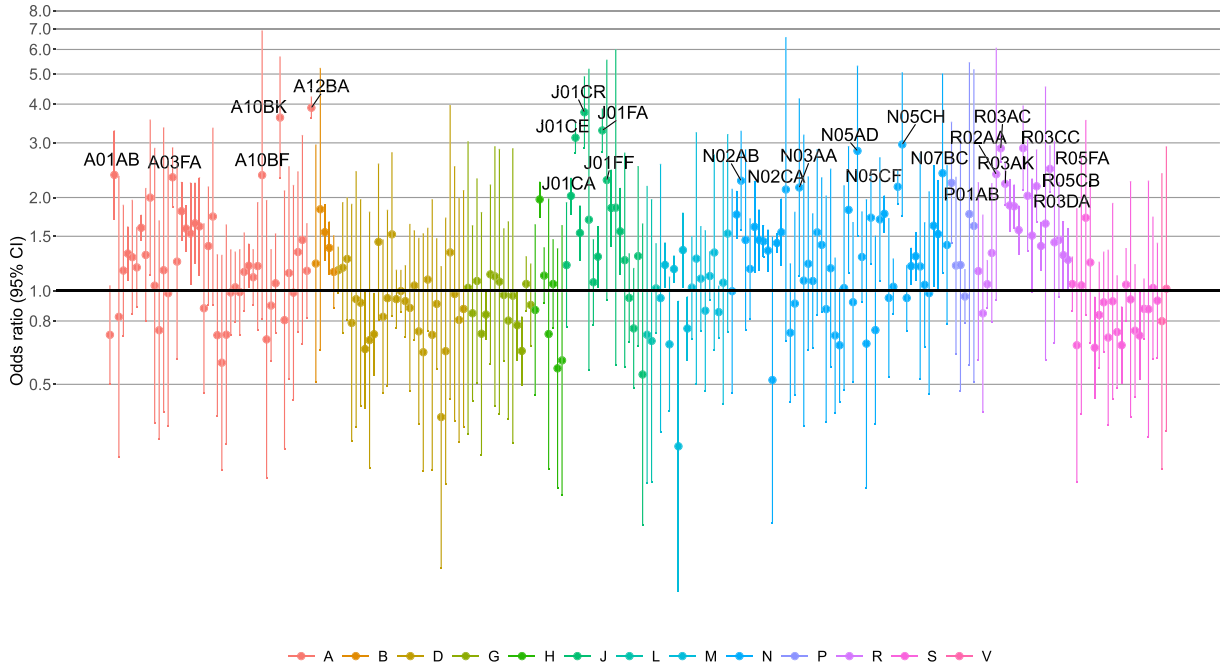

FIGURE 3 Associations of major drug classes (ATC level 4) with heart failure given as odds ratios (OR) with 95% confidence intervals (CI). Only drug classes with an OR of above 2 are labelled. The letters (A, B, D, G, H, J, L, M, N, P, R, S and V) correspond to drug classes based on the Anatomical Therapeutic Chemical (ATC) classification system, where each letter represents a specific anatomical or therapeutic group. A: Alimentary tract and metabolism; B: Blood and blood-forming organs; D: Dermatologicals; G: Genitourinary system and sex hormones; H: Systemic hormonal preparations, excluding sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic and immunomodulating agents; M: Musculo-skeletal system; N: Nervous system; P: Antiparasitic products, insecticides, and repellents; R: Respiratory system; S: Sensory organs; V: Various. A01AB: Anti-infectives and antiseptics for local oral treatment; A03FA: Propulsives; A01AB: Alpha glucosidase inhibitors; A10BK: Sodium-glucose co-transporter 2 (SGLT2) inhibitors; A12BA: Potassium; J01CA: Penicillins with extended spectrum; J01CE: Beta-lactamase sensitive penicillins; J01CR: Combinations of penicillins, incl. beta-lactamase inhibitors; J01FA: Macrolides; J01FF: Lincosamides; N02AB: Phenylpiperidine derivatives; N02CA: Ergot alkaloids; N03AA: Barbiturates and derivatives; N05AD: Butyrophenone derivatives; N05CF: Benzodiazepine related drugs; N05CH: Melatonin receptor agonists; N07BC: Drugs used in opioid dependence; P01AB: Nitroimidazole derivatives; R02AA: Antiseptics; R03AC: Selective beta-2-adrenoreceptor agonists; R03AK: Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics; R03CC: Selective beta-2-adrenoreceptor agonists; R03DA: Xanthines; R05CB: Mucolytics; R05FA: Opium derivatives and expectorants.

tartrate, was associated with atrial fibrillation (OR 1.84; CI 1.50–2.26) and heart failure (OR 1.54; CI 1.25–1.90) (Table 1).

4 | DISCUSSION

Using hypothesis-free screening approach, we investigated the cardiovascular adverse effects of all prescription drugs in Denmark. We identified 222 such associations that underwent manual assessment. A large proportion of these associations were explained by time-varying confounding or constituted previously known associations. However, we also identified several unexplained associations, such as for pantoprazole and oxazepam, warranting deeper inquiry. We acknowledge the limitations of predefined thresholds, which were chosen arbitrarily and might result in the dropping of some important associations. We therefore openly present all these associations, allowing other researchers to explore results and review selected associations based on their personal thresholds. Only few associations, which we deemed important, are presented here and the discussion will focus primarily on these selected drug–outcome associations. Considering the hypothesis-generating nature this study, the reported associations should be interpreted with caution and should not be used to guide clinical practice at present.

The primary strength of this study lies in its utilization of Danish healthcare registers, renowned for providing high-quality data for observational research.[21] These registers have comprehensive nationwide coverage for all Danish residents, which minimizes the risk of selection bias. The use of a case–crossover design constitutes another significant strength. This design is robust towards confounders that are stable over time for the individual,[19] thereby minimizing potential biases and enhancing the internal validity of the study.

The study also has some limitations. The Danish registers does not include data on important lifestyle factors such as body mass index, alcohol use or smoking status, which are important risk factors for cardiovascular diseases. However, the study design precludes confounding by stable personal characteristics, and we expect these factors to be stable over the short time range of this study. Secondly, the case–crossover design is susceptible to persistent user bias,[34]

TABLE 1 Examples of the signals for associations of prescription drugs with cardiovascular diseases for individual drugs (ATC level 5).

Drug name (ATC code)	Myocardial infarction OR (95% CI)	Ischaemic stroke OR (95% CI)	Heart failure OR (95% CI)	Myocarditis OR (95% CI)	Venous thromboembolism OR (95% CI)	Atrial fibrillation OR (95% CI)	Comments
Pantoprazole (A02BC02)	**1.71 (1.53–1.91)**	1.42 (1.27–1.58)	**1.78 (1.55–2.04)**	**1.81 (1.35–2.44)**	**1.98 (1.55–2.52)**	**1.83 (1.68–2.00)**	Similar associations were not seen for other PPIs. There are no immediate explanations for this finding which therefore might warrant further scrutiny. However, SIDER database has reported AF and CHF as adverse effects of pantoprazole (frequency unknown).
Macrogol, combinations (A06AD65)	1.33 (1.05–1.68)	1.33 (1.09–1.61)	**1.69 (1.34–2.13)**	1.29 (0.66–2.53)	**1.64 (1.05–2.56)**	**1.86 (1.55–2.22)**	Similar associations were seen for other laxatives. However, there are no immediate explanations for this finding which therefore might warrant further scrutiny. Further, SIDER database has no information on this drug.
Ferrous sulfate (B03AA07)	1.25 (1.00–1.57)	1.48 (1.17–1.87)	**1.54 (1.25–1.90)**	1.78 (0.89–3.54)	1.50 (0.80–2.80)	**1.84 (1.50–2.26)**	Similar associations were not seen for ferrous glycine sulfate or ferrous tartrate. There are no immediate explanations for this finding which therefore might warrant further scrutiny. However, SIDER database has reported MI and HF as adverse effects of iron supplement (frequency unknown).
Zopiclone (N05CF01)	1.20 (1.05–1.38)	1.22 (1.06–1.40)	**2.33 (1.99–2.71)**	**1.69 (1.09–2.63)**	**1.53 (1.07–2.19)**	**1.55 (1.39–1.74)**	Similar associations were seen for other non-benzodiazepine hypnotics. There are no immediate explanations for this finding which therefore might warrant further scrutiny. However, SIDER database has reported tachycardia (frequency unknown) as an adverse effect of this drug.
Prednisolone (H02AB06)	**1.59 (1.40–1.79)**	**1.58 (1.38–1.81)**	**2.09 (1.81–2.40)**	**1.67 (1.11–2.49)**	**2.01 (1.48–2.73)**	**2.40 (2.17–2.66)**	Prednisolone has known cardiovascular adverse effects. SIDER database has also reported MI, CHF, thromboembolism and arrhythmia as adverse effects of this drug (frequency unknown).
Prednisone (H02AB07)	**1.55 (1.12–2.13)**	1.13 (0.74–1.70)	1.38 (0.96–1.99)	1.09 (0.41–2.91)	0.78 (0.34–1.78)	**1.59 (1.15–2.18)**	Prednisone has known cardiovascular adverse effects. SIDER database has also reported MI, CHF, thromboembolism and arrhythmia as adverse effects of this drug (frequency unknown).
Morphine (N02AA01)	**1.84 (1.51–2.24)**	**1.80 (1.49–2.17)**	**2.08 (1.68–2.57)**	1.65 (0.96–2.83)	**2.77 (1.92–3.99)**	**2.44 (2.09–2.86)**	Similar associations are seen for other opioid analgesics. There are no immediate explanations for this finding which therefore might warrant further scrutiny. However, SIDER database has reported MI, atrial fibrillation and cardiovascular disorder as adverse effects of this drug (frequency unknown).
Dapagliflozin (A10BK01)	0.68 (0.38–1.24)	1.08 (0.62–1.89)	**4.14 (2.22–7.72)**	—	—	1.11 (0.67–1.84)	Similar association was not seen for other antidiabetic drugs. There are no immediate explanations for this finding which therefore might warrant further scrutiny. Further, SIDER database has not reported HF as an adverse effect of this drug.
Levetiracetam (N03AX14)	1.00 (0.43–2.85)	**2.01 (1.11–3.62)**	1.68 (0.71–4.00)	—	0.72 (0.25–2.04)	**2.43 (1.30–4.56)**	Similar associations were seen for some of the other antiepileptic and anticonvulsant drugs. There are no immediate explanations for this finding which therefore might warrant further scrutiny. Further, SIDER database has not reported any of these adverse effects for this drug.

TABLE 1 (Continued)

Drug name (ATC code)	Myocardial infarction OR (95% CI)	Ischaemic stroke OR (95% CI)	Heart failure OR (95% CI)	Myocarditis OR (95% CI)	Venous thromboembolism OR (95% CI)	Atrial fibrillation OR (95% CI)	Comments
Oxazepam (N05BA04)	**1.57 (1.31–1.87)**	1.29 (1.08–1.54)	**1.93 (1.56–2.37)**	**1.45 (0.82–2.55)**	**2.53 (1.55–4.13)**	**1.73 (1.49–2.02)**	Similar associations were not seen for other benzodiazepines, except for associations of alprazolam and chlordiazepoxide with HF. There are no immediate explanations for this finding which therefore might warrant further scrutiny. Further, SIDER database has not reported any of these adverse effects for this drug.

particularly for chronically used medications, which might lead to artificially increased risk estimates. Finally, the Danish national prescription registry does not have data for inpatient and over-the-counter drug use, which may introduce some exposure misclassification.

Of the 222 associations that underwent manual assessment, 76 were classified as drugs with associations due to time-varying confounding. Examples of such drugs include antibiotics, antispasmodics and drugs for nausea and vomiting. For instance, the association of antibiotic use and risk of cardiovascular effects is likely to be confounded by underlying infection, which in turn is a predictor of acute cardiovascular outcomes.[35,36] Similar explanation is valid for other above-mentioned drug classes. Further, four of the 107 drugs showed associations which were previously known, including associations for some non-steroidal anti-inflammatory drugs (such as rofecoxib) and glucocorticoids (such as prednisolone and prednisone). However, these associations could also be explained by confounding due to underlying illnesses (e.g., pain and inflammation), which again are linked to increased cardiovascular risk.[37,38] Finally, 130 associations were included in the unexplained category in Step 3 of signal filtering.

The unexplained associations for individual drugs had some interesting findings, particularly for pantoprazole and oxazepam, which exhibited higher estimates for cardiovascular outcomes within their respective drug classes. While PPI use has been shown to be associated with adverse cardiovascular outcomes,[39–41] the specific associations observed with pantoprazole in this study, distinct from other commonly prescribed PPIs like omeprazole, were unexpected. From a clinical standpoint, pantoprazole and omeprazole are often seen as interchangeable regarding their indication of use. Furthermore, existing data from the SIDER database[33] highlights cardiovascular risks unique to pantoprazole, reinforcing the possibility of true underlying associations. Several systematic reviews and meta-analyses show that increased risk of adverse cardiovascular events with PPI use come from the data pooled from observational studies, but not from randomized controlled trials (RCTs),[42–44] hinting at the potential effect of confounding due to chronic conditions. However, one meta-analysis of RCTs indicated a significant association between PPI use and increased cardiovascular risk.[40]

Another interesting finding was the higher risk of cardiovascular events associated with oxazepam use but not with other benzodiazepines, except alprazolam, which showed increased risk of heart failure (OR 1.90; CI 1.34–2.70). A meta-analysis of observational studies suggested a 60% increase in risk of all-cause mortality among benzodiazepine users.[45] However, studies specifically for cardiovascular mortality showed conflicting results; ranging from decreased,[46] unchanged[47,48] or increased[49,50] mortality due to benzodiazepine use. Benzodiazepines are used for anxiety and sleep disorders which are independent risk factors of increased cardiovascular risk,[51–53] the increased risk of mortality observed with benzodiazepine use is thus likely due to confounding by indication,[45,54] which cannot be ruled out either in our study. However, specific associations with oxazepam and not with other benzodiazepines warrants further investigation.

In conclusion, our study has identified several potentially intriguing associations; however, given the hypothesis-generating nature of

our investigation, these should be interpreted with caution. Due to the limited and conflicting data for some of these associations, further investigation in more focused follow-up studies is warranted.

AUTHOR CONTRIBUTIONS

Saad Hanif Abbasi and Anton Pottegård were responsible for the initial concept and planning of the study. Martin Thomsen Ernst and Saad Hanif Abbasi were responsible for managing and analysing the data. All authors provided significant contributions in the planning and subsequent reporting of the work described in this paper. The manuscript was primarily drafted by Saad Hanif Abbasi. All authors have revised the manuscript for important intellectual content and approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Due to Danish data protection regulations, individual-level data cannot be shared directly by the authors. Deidentified data from Danish healthcare registries is accessible for researchers after application to the Danish Health Data Authority. The study protocol was registered in the Real-World Evidence Registry (https://osf.io/seqpg) before commencement of statistical analyses. The analytical source code can be made available by the authors upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Outcome definitions

Outcomes of interest	ICD-10 code, definition
Myocardial infarction	**I21, acute MI** I21.0, anterior acute MI with Q wave development I21.1, inferior or posterior acute MI with Q wave development I21.3, ST-elevation acute MI I21.4, non-ST elevation acute myocardial infarction I21.9, acute MI, unspecified
Ischemic stroke	**I63, cerebral infarction** I63.0, cerebral infarction caused by thrombosis of precerebral artery I63.1, cerebral infarction caused by embolism in precerebral artery I63.2, cerebral infarction caused by occlusion or stenosis of precerebral artery, unspecified I63.3, cerebral infarction caused by thrombosis in cerebral artery I63.4, cerebral infarction caused by embolism in cerebral artery I63.5, cerebral infarction caused by occlusion or stenosis of cerebral artery, unspecified I63.6, cerebral infarction caused by non-pyogenic cerebral venous thrombosis I63.8, other type of cerebral infarction I63.9, cerebral infarction, unspecified **I64, stroke without information on bleeding or infarction**
Heart failure	**I50, heart failure** I50.0, Chronic heart failure I50.1, Left-sided heart failure I50.9, Heart failure, unspecified
Venous thromboembolism	**I82, Other venous embolism and thrombosis** I82.0, Budd-Chiari syndrome I82.1, Thrombophlebitis migrans I82.2, Embolism or thrombosis in the vena cava I82.3, Embolism or thrombosis in the renal vein I82.8, Embolism or thrombosis in another vein I82.9, Embolism or thrombosis in vein, unspecified
Myocarditis	**I40, acute myocarditis** I40.8, other type of acute myocarditis I40.9, acute myocarditis unspecified I51.4, myocarditis, unspecified
Arrhythmia	**I48, Atrial flutter and atrial fibrillation** I48.0, paroxysmal atrial fibrillation I48.1, persistent atrial fibrillation I48.2, chronic atrial fibrillation I48.3, typical atrial flutter I48.4, atypical atrial flutter I48.9, atrial flutter or atrial fibrillation, unspecified