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ORIGINAL RESEARCH ARTICLE

Sequential Epidemiological Analyses of Real-World Data: A Tool for Prospective Drug Safety Surveillance from the Rofecoxib Example

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Abstract

Introduction Large administrative healthcare databases can be used for near real-time sequential safety surveillance of drugs as an alternative approach to traditional reporting-based pharmacovigilance. The study aims to build and empirically test a prospective drug safety monitoring setup and perform a sequential safety monitoring of rofecoxib use and risk of cardiovascular outcomes.

Methods We used Danish population-based health registers and performed sequential analysis of rofecoxib use and cardiovascular outcomes using case–time–control and cohort study designs from January 2000 to September 2004. Each monitoring period added 6 months of data until the end of the study period. In the case–time–control study, incident cases of myocardial infarction (MI) and ischemic stroke were identified and matched with up to five time controls on age, sex, and calendar time. Exposure status on the date of diagnosis was assessed using a 60-day focal window, with reference windows 120, 180, and 240 days prior to the diagnoses. In the cohort study, incident users of rofecoxib were matched up to 1:4 with ibuprofen users (active comparators) using high-dimensional disease risk scores and were followed for 60 days.

Results The earliest association between rofecoxib use and the risk of MI was seen in study period 2 for case–time–control design (OR 1.42, 95% CI 1.04–1.93) and in study period 7 for the cohort study design (RR 1.22; 95% CI 1.02–1.47).

Conclusions Our prospective drug safety monitoring setup showed that the risk of MI could have been detected 3.5 years before the ultimate market withdrawal of rofecoxib. However, further research is needed to validate this approach.

1 Introduction

Monitoring the safety of drugs in the postmarketing phase is crucial for identifying uncommon yet serious adverse events that may not have surfaced during premarketing clinical trials [1]. These adverse events can have a significant impact, as was seen in the international Vioxx controversy [2], where a rapid uptake [3] and a 5-year gap between marketing and withdrawal of rofecoxib due to safety concerns [4, 5] caused thousands of adverse cardiovascular events [6]. Undetected safety issues can arise due to the rarity of adverse effects,

Key Points

To test a prospective drug safety monitoring setup, we performed sequential monitoring of rofecoxib use and the risk of cardiovascular outcomes using the case–time–control and cohort study designs.

The study showed that the risk of myocardial infarction (MI) could have been detected 3.5 years before the ultimate market withdrawal of rofecoxib.

The case–time–control design resulted in earlier identification of MI risk compared with a more rigorously controlled active-comparator cohort design. However, further research is needed to validate the broader applicability of this approach.

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which may not occur in sufficient numbers within the limited sample size of a phase 3 clinical trial or because certain subpopulations, such as older individuals, are excluded from the trial in which the adverse effects are more likely to occur [1, 7]. In such cases, epidemiological studies provide the best alternative to trials in generating evidence for clinicians and regulatory bodies.

Conventional postmarketing surveillance has mainly relied on the systematic review of spontaneous reports of adverse drug reactions. This is highly problematic due to several well-established limitations to this system, hindering timely detection of many adverse events or leaving them unrecognized altogether [8, 9]. Still, the cornerstone of drug safety surveillance, the analysis of spontaneous reporting, remains largely unchallenged. Other data sources, such as large administrative healthcare databases, can provide a good demonstration of how the drugs are being used in 'real-world' settings and, thus, can be used for near real-time sequential safety surveillance of drugs as an alternative approach to traditional reporting-based pharmacovigilance. Similar approach has been previously used by Sentinel System [10] and others [11–13]. To build and empirically test this prospective drug safety monitoring setup, we performed sequential monitoring of rofecoxib use, as has previously been done by others [14, 15], and its associated risk of cardiovascular outcomes using the case–time–control and cohort study designs.

2 Methods

We used Danish population-based health registers to examine the association of rofecoxib use with cardiovascular outcomes during the study period from June 1999 to August 2004, using case–time–control and cohort study designs. We included patients who were aged 18 years or above and had no history of cardiovascular disease prior to June 1999. A protocol was registered and made publicly available prior to the commencement of any statistical analysis (https://osf.io/va3yj).

2.1 Data Sources

Danish healthcare registers provide some of the finest sources of data for epidemiological research worldwide [16]. Both the Danish National Prescription Registry [17] and the Danish National Patient Register [18] are known to provide high-quality data recorded since the year 1995 and 1977, respectively. The Danish National Prescription Registry contains all data on prescription drugs redeemed at the community pharmacies in Denmark. The data include the name, dose, and quantity of the drug dispensed as well as the date of dispensing. The registry utilizes the Anatomical Therapeutic Chemical (ATC) classification system developed by World Health Organization [19]. The Danish National Patient Register contains data on all hospital admissions (nonpsychiatric) since 1977 and on all outpatient contacts since 1995. Since 1994, all diagnoses are coded according to International Classification of Diseases, Tenth Revision (ICD-10). Furthermore, we used Central Person registry [20], which has a civil registry number (CPR number), a unique identifier, assigned to the residents of Denmark since 1968. The data linkage was enabled by an encrypted CPR number and was performed by Statistics Denmark [21]. The data availability lag in the Danish context is typically around 1–2 months.

2.2 Case–Time–Control Analysis

This sequential monitoring study was conducted with interim analyses and a final analysis to assess the incremental evidence as the data accumulated. Each interim analysis added 6 months of data from January 2000 until June 2004. The final analysis utilized additional 3 months of data until the withdrawal of rofecoxib in September 2004 (Fig. 1). To evaluate the association of rofecoxib use with MI, ischemic stroke, and all-cause mortality, we used a case–time–control design; a 'self-controlled' study design that utilizes a within-person comparison at different time periods [22]. Like the case–crossover design, the case–time–control design is robust to time-invariant confounders [22, 23]. The case–crossover design was devised to study acute effects with short-term exposure [24] but does not account for exposure time trends [25]. By including a nondiseased control group in a case–time–control design, one can adjust for exposure time trends [25]. Unlike case–control studies, controls in the case–time–control design serve only to adjust for the bias introduced by the temporal trend in the exposure prevalence during a study period. These exposure trends are particularly strong for newly marketed drugs [26]. The target population in the case–time–control design is a subset of those not immune to the outcome. From the study cohort, we identified all the incident cases of MI, ischemic stroke and all-cause death after June 1999 until August 2004. The index date was when the person received an incident diagnosis of MI or ischemic stroke, or the date of death. Each case subject was matched to five control subjects by age, sex, and calendar time, and each control was assigned the same index date as their matched case.

2.2.1 Exposure Ascertainment

Rofecoxib exposure was identified using rofecoxib prescriptions registered in the Danish National Prescription Registry [17]. We assessed exposure status during predefined time

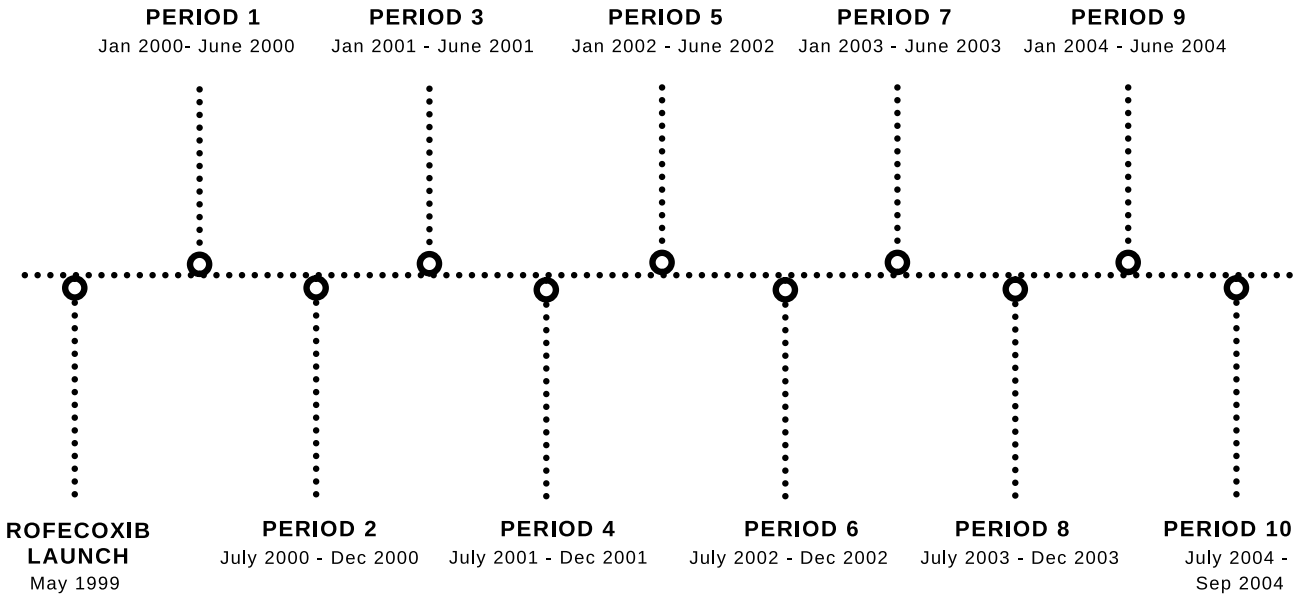

Fig. 1 Distribution of time periods for the sequential analysis of rofecoxib from January 2000 to September 2004

windows prior to the date of the outcome with a width of 60 days. This duration was selected based on the number of dispensed tablets in the redeemed prescriptions, which in most cases was more than 30. We set the focal window to day −1 to −60 relative to the index date. We also applied washout and reference windows, each having the width of 60 days (Fig. 2). A washout window was used to avoid carrying over the effects of prior medication exposures or use of minor stockpiled supplies. Up to three reference windows were used, depending on the calendar time of the case. To allow room for rofecoxib exposure in at least one of the reference windows, we included only outcomes occurring 180 days or more (focal, washout, and one reference window) after the market launch.

2.2.2 Study Outcomes

Cases of MI and ischemic stroke were identified as discharge diagnoses registered in the Danish National Patient Register [18]. The primary outcomes of interest included fatal and nonfatal cardiovascular or cerebrovascular events, including MI and ischemic stroke (see online material, Table 1 for ICD-10 codes). The outcome codes have been previously validated in the Danish cohort [27, 28]. All-cause mortality was included as a secondary endpoint. The composite outcome included all three: MI, stroke, and all-cause mortality. The day of diagnosis or death in the registers was used as the index/outcome date.

2.2.3 Statistical Analyses

We performed sequential analyses adding 6 months of data from each monitoring period throughout the 5-year study period. To avoid bias from exposure autocorrelation within multiple reference windows [29], we used the Mantel–Haenszel (MH) method to calculate odds ratios (ORs) with 95% compatibility intervals (CIs) for the associations between rofecoxib use and MI, ischemic stroke, and all-cause mortality. To reduce variance that can arise from small sample sizes, a weak Bayesian shrinkage was applied throughout [30]. A normal prior distribution was used 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–time–control design for this study is illustrated in Fig. 2.

2.2.4 Sensitivity Analyses

Sensitivity analyses were performed where we changed the width of focal, washout, and reference windows to 30 days for cases and matched controls. A 30-day focal window was chosen on the basis of the observation that some individuals redeemed rofecoxib prescriptions in smaller quantities (fewer than 30 tablets). We also performed a subgroup analysis by stratifying on rofecoxib dose (12.5 mg and 25 mg).

2.3 Cohort Analysis

We further performed a sequential cohort analysis for comparison using the active comparator, new user

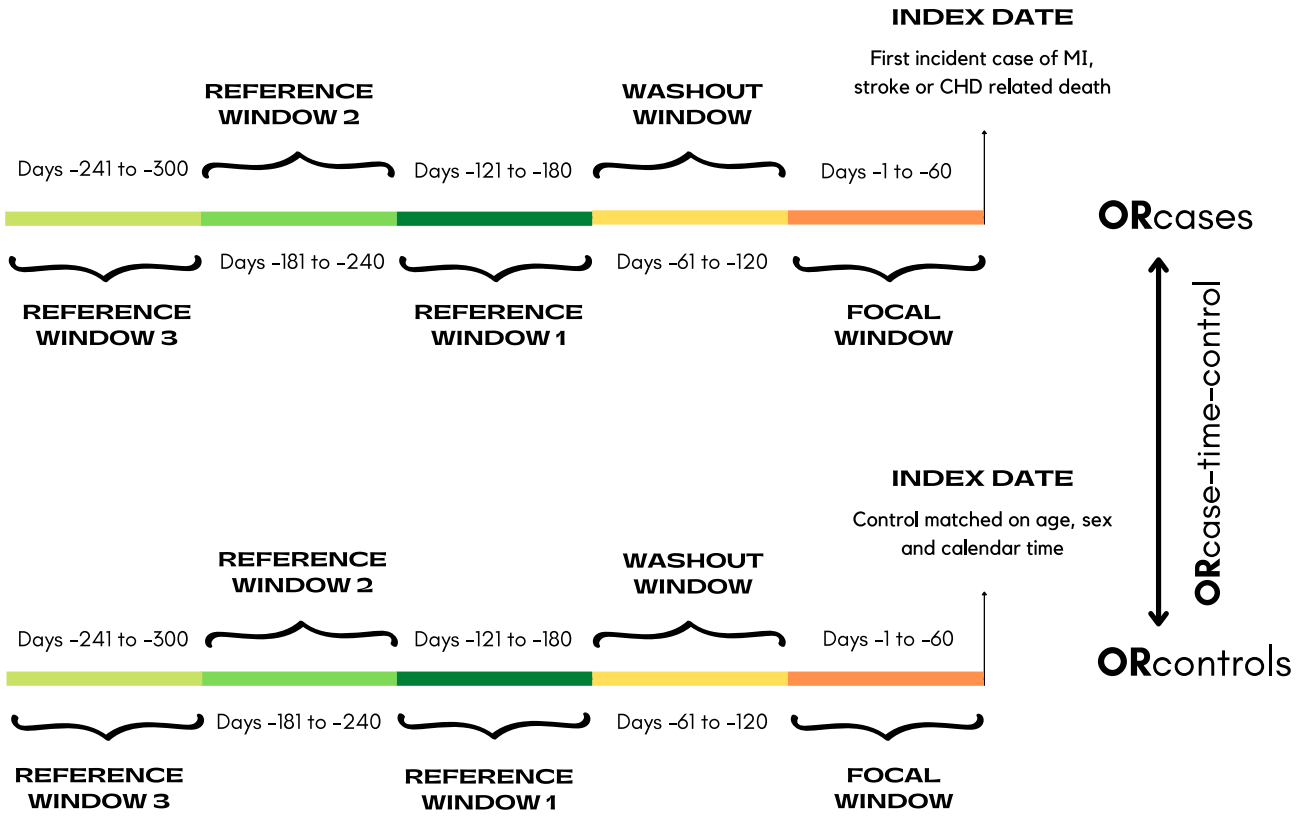

Fig. 2 Illustration of case–time–control study design

(ACNU) cohort design [31]. Ibuprofen was used as an active comparator. This prospective monitoring study was conducted with similar time periods of interim and final analysis as the case–time–control analysis. We used high-dimensional disease risk scores (hdDRS) [32] to adjust for confounding. DRS is a prognostic summary score that summarizes variable associations with outcomes of interest [33]. Unlike propensity scores (PS), which models physicians' behavior or clinical practice (who is prescribed what), DRS models biology (what conditions predispose individuals to the outcome), which is more stable over time. In the case of newly marketed drugs, one would expect clinical practice to change rapidly, hence making a good case for using DRS [34]. The development of the hdDRS model involved empirical covariate identification, covariate prioritization or ranking, and model specification including covariate selection. We used historical cohort data from 1995–1999, i.e., prior to rofecoxib marketing, to estimate DRS on the basis of 60-day follow-up of initiators of ibuprofen. Historical controls are useful for DRS model fitting, particularly in pharmacoepidemiologic studies with newly introduced or evolving treatments [35]. The outcome in the DRS model was a composite of MI and ischemic stroke. We used all available prescription and diagnosis data (including prescriptions used to define existing medical conditions) to obtain a set of variables. Covariate prioritization was performed on the basis of the log-likelihoods from logistic regression, which assessed the association of each variable with the study outcomes (dependent variable). Based on the strength of association, we selected the 50 covariates that were the most likely to be associated with the study outcomes and included these in the hdDRS model. DRS were estimated using multivariable logistic regression. Based on the DRS, we matched each episode of rofecoxib use to up to four episodes of ibuprofen use (1:4), using nearest-neighbor matching with replacement. DRS matching was performed separately for each study period.

2.3.1 Follow-up and Censoring

Incident users of rofecoxib and ibuprofen were followed for 60 days, corresponding to the focal window of the case–time–control design. Cohort entry was the date of first prescription of either rofecoxib or ibuprofen. A washout window prior to the index date was used to ensure no previous use of either drug in the past 365 days. Ibuprofen episodes were censored if a rofecoxib prescription occurred during follow-up (i.e., during days 1–60 after the index

date) and vice versa. Each patient was followed until the first occurrence of the study outcome (MI, ischemic stroke, or death due to any cause), after 60 days of follow-up, or until the end of the study period. Each patient entered the cohort only once.

2.3.2 Statistical Analyses

For the cohort analysis, we estimated the relative risks (RRs) with 95% CIs from the log-binomial regression model for each interim as well as for the final analysis to show the sequential change in effect estimates over time.

2.3.3 Sensitivity Analyses

Similar sensitivity analyses, as in the case–time–control study, were performed by using a 30-day follow-up time and a subgroup analysis by stratifying on dose (12.5 mg and 25 mg).

2.3.4 Post-Hoc Analysis

We performed a post-hoc analysis where we used celecoxib as an active comparator for rofecoxib and performed 1:1 DRS matching with replacement. Due to the anticipated limited availability of celecoxib users compared with ibuprofen, it was initially not considered a primary active comparator for rofecoxib.

2.4 Definition of Signal

The signal threshold was defined ad hoc based on the strength of association. A threshold of OR or RR of 1.20 and a lower limit of 95% compatibility interval above 1.00 was chosen, as it was deemed practical for this study on the basis of the authors' judgment. Following discussion, the authors agreed that 1.20 was an appropriate and meaningful threshold.

2.5 Multiple Comparisons

As this study aimed to evaluate how evidence evolved as data accumulated, we reported the results of each interim analysis to illustrate changes in effect estimates over time. We decided beforehand to continue the monitoring until the study period ended (September 2004) and did not perform sequential testing [36] at each interim analysis to determine if evidence was sufficient to stop monitoring. For routine implementation, however, adjustments for multiple comparisons should be applied, similar to sequential monitoring in randomized controlled trials [37, 38], where the aim is to make statistically defensible decisions about terminating a trial when outcomes can be reliably predicted.

2.6 Other

All analyses were conducted using R (version 4.2.2). In Denmark, studies based solely on register data do not require review or ethical approval.

3 Results

In the case–time–control analysis, a total of 44,077 cases of MI, 26,654 cases of ischemic stroke, and 236,905 cases of all-cause mortality were initially identified from January 2000 to September 2004. After applying inclusion and exclusion criteria, the number of cases was reduced to 43,917 for MI, 26,510 for ischemic stroke, and 236,052 for all-cause mortality. Finally, following the exclusion of patients without discordant exposure status, the analyses included 1213 cases of MI, 679 cases of ischemic stroke, and 10,314 cases of all-cause mortality. There were 6017, 3375, and 51,131 matched time controls, having discordant exposure status, for MI, stroke, and all-cause mortality, respectively. The selection and distribution of cases and their matched time controls in study periods 1–10 are depicted in Fig. 3.

The case–time–control analysis provided an OR of 1.12 (95% CI 0.99–1.27) for MI and 1.25 (95% CI 1.19–1.30) for all-cause mortality. However, no such association with ischemic stroke was observed (OR 1.00, 95% CI 0.85–1.19). For MI, the early estimate from study period 1 (OR 1.21, 95% CI 0.75–1.97) was the least precise, with the precision improving gradually. We observed initial evidence of a potential association during study period 2 (OR 1.42, 95% CI 1.04–1.93), with the subsequent study periods consolidating the evidence (Fig. 4).

In the cohort study, we identified 1,314,272 users of rofecoxib or ibuprofen during the study period from January 2000 to September 2004. After applying inclusion and exclusion criteria, there were 128,117 new users of rofecoxib matched with 505,453 new users of ibuprofen (Table 1). Figure 5 shows the selection and proportion of rofecoxib and ibuprofen users in the study periods 1–10. There was a steady increase in the use of rofecoxib from study periods 1 to 5, and then it decreased sharply in the subsequent study periods.

In the cohort analyses, a RR of 1.31 (95% CI 1.10–1.56) was seen for MI (Fig. 4). The earliest evidence of association was seen in the seventh study period (RR 1.22, 95% CI 1.02–1.47), with later study periods further consolidating the evidence (Fig. 4). The risk estimates showed gradual increase in strength and precision with increasing number of patients in each study period. Rofecoxib use was also associated with higher risk of all-cause mortality (cumulative RR 1.53, 95% CI 1.45–1.61), but no association with ischemic stroke was seen (cumulative RR 1.11, 95% CI 0.97–1.28).

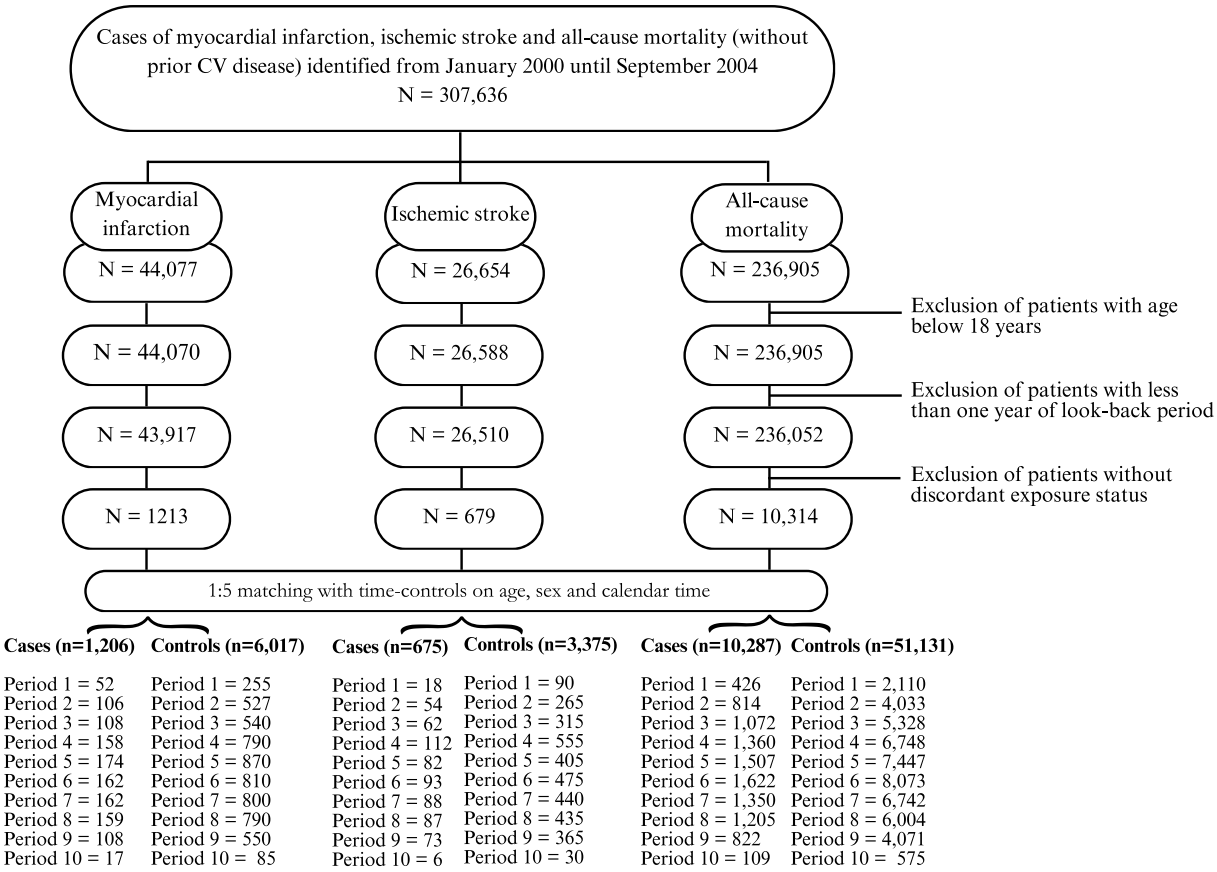

Fig. 3 Selection of cases and time controls for case–time–control study

During the sensitivity analyses, a cumulative OR of 1.29 (95% CI 1.11–1.49) for MI was seen in case–time–control study, where the length of focal, washout, and reference windows was reduced to 30 days (Fig. 6). When the follow-up time was reduced to 30 days in the cohort study design, no noteworthy association between the rofecoxib use and risk of MI was seen, except for study period 8 and 9 (Fig. 6). When stratified on dose, we found an increased risk of MI in patients using rofecoxib at a dose 25 mg or above (Fig. 7) in both case–time–control (RR 1.37, 95% CI 1.17–1.61) and cohort study designs (RR 1.32, 95% CI 1.04–1.67). Use of rofecoxib at 12.5 mg dose demonstrated a protective effect against MI (see online material, S2) in case–time–control design (RR 0.78, 95% CI 0.64–0.95), while no association was seen in the cohort study design (RR 1.27, 95% CI 0.97–1.64; see online material, S3).

In the post-hoc analysis with celecoxib as an active comparator, the cumulative RR of 1.05 (95% CI 0.86–1.28) and 1.20 (95% CI 0.91–1.58) were seen for MI and ischemic stroke, respectively (see online material, S6). Other results for all-cause mortality and composite outcome are provided as a supplementary material (see online material, S1, S4, S5).

4 Discussion

We describe a prospective drug safety monitoring system using a working example of cardiovascular adverse effects of rofecoxib. The monitoring system successfully identified the associations between use of rofecoxib and increased risk of MI and all-cause mortality using two different study designs. This highlights the importance of surveillance approaches beyond traditional spontaneous reporting systems and leveraging healthcare databases and pharmacoepidemiological methodologies to enhance drug safety monitoring. Our results agree with the results of previous observational studies and meta-analyses [39–45]. As expected for the newly marketed drug, such as rofecoxib, the estimates were imprecise and unstable during the earlier study periods in both study designs [26], but the precision improved as sample size increased with each interim analysis.

The main strength of this study lies in the utilization of Danish healthcare registers that provide some of the finest sources of data for the epidemiological research worldwide [16]. The Danish National Prescription Registry [17], Danish National Patient Register [18], and Central Person registry [20] allowed the implementation of both case–time–control

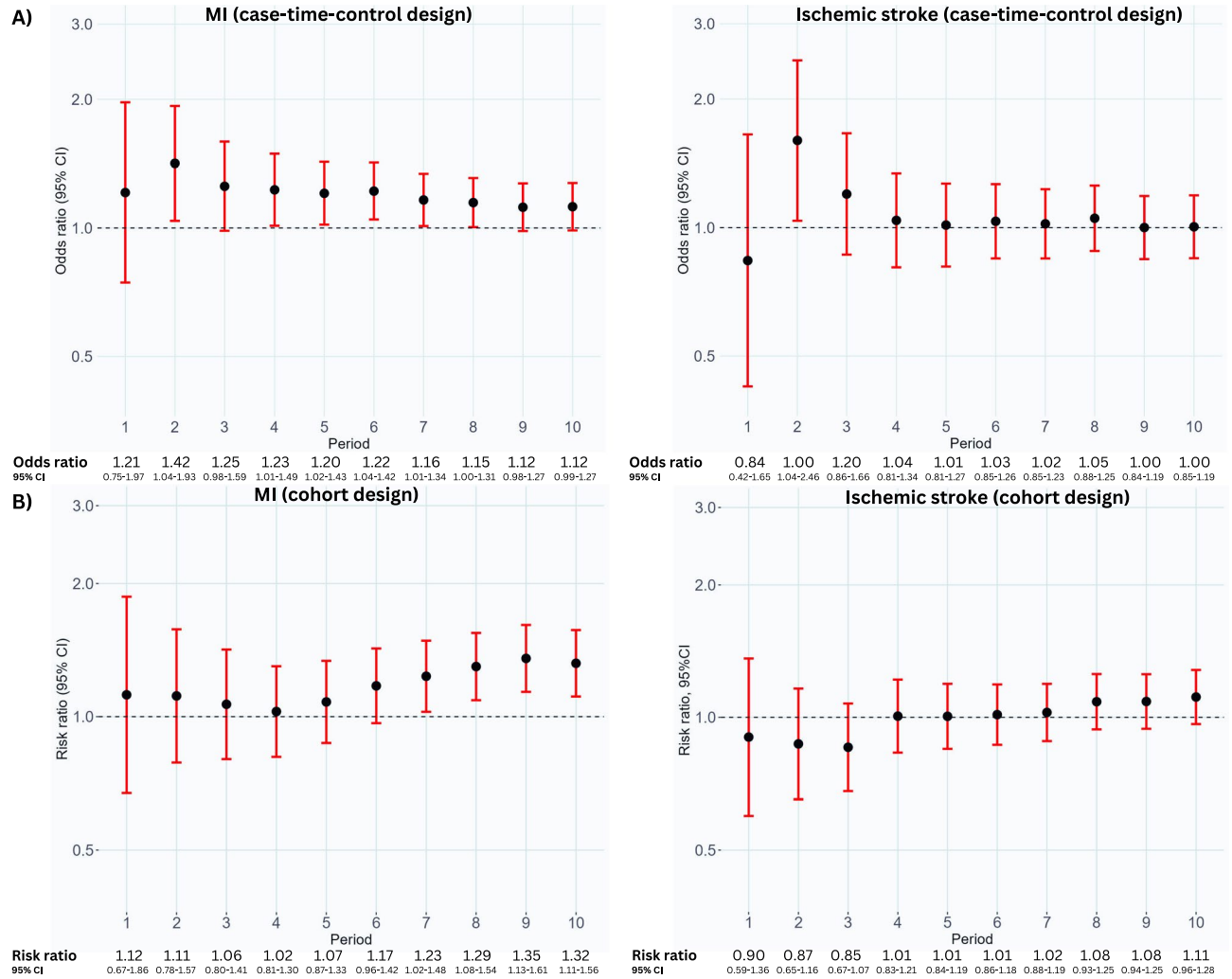

Fig. 4 Sequential monitoring of rofecoxib use for myocardial infarction and ischemic stroke using case–time–control (**A**) and cohort study (**B**) designs. Study periods 1–10 correspond to ten sequential analyses conducted from January 2000 to September 2004. Each analysis adds 6 months of data, except for study period 10, which adds 3 months of data. The effect estimates (odds ratios or risk ratios) are cumulative and estimated at the end of each study period. I, odds ratio (**A**) or risk ratio (**B**) with 95% compatibility interval; - - -, null

and active comparator new user cohort designs, for which nonavailability and selection of suitable controls and active comparators can otherwise be troublesome. Secondly, the study designs used were equipped with better confounder control techniques, such as the use of hdDRS-matched active comparators in the cohort design to reduce the effect of confounding.

The study also has some limitations. Firstly, we lacked the data on many socioeconomic and life-style factors, such as alcohol use, smoking, and body mass index (BMI), that are not available in Danish healthcare registers. We attempted to mitigate such confounding in two ways; in the case–time–control design, confounders that are stable within the focal and reference windows cancel out. For all practical purposes, the mentioned life-style factors (and their health effects) are stable over this short time range. In addition, we used an active comparator about which we could assume that the confounding structure would be largely similar. We therefore believe that our study is not affected by life-style confounding to any material degree. Secondly, the Danish national prescription registry only contains data on prescriptions redeemed at the community pharmacies. It lacks information on inpatient and over-the-counter drug use, which may have resulted in some exposure misclassification. Furthermore, this study essentially addresses sensitivity, indicating that such a system can detect unsuspected safety issues. However, we are unsure about specificity, i.e., whether this setup detects only true positive signals cannot be determined from this study. Additionally, our results are contextual, based on the Danish setup. Using a larger

Table 1 Selected baseline characteristics of the study population before and after hdDRS matching.

	Before hdDRS matching		SMD	After hdDRS matching		SMD
	Rofecoxib use *N* (mean or %)	Ibuprofen use *N* (mean or %)		Rofecoxib use *N* (mean or %)	Ibuprofen use *N* (mean or %)	
Individuals (*N*)	130,096	101,5411		128,117	505,453	
Age, mean (SE)	62.29 (16.84)	46.01 (16.71)	0.971	61.49 (16.72)	61.21 (16.61)	0.01
Female sex	44,379 (34.1)	481,408 (47.4)	0.273	43,476 (33.9)	171,059 (33.8)	0.002
Drug use (past 1 year)						
Sodium picosulfate	2277 (1.8)	2915 (0.3)	0.14	2096 (1.6)	3889 (0.8)	0.08
Metformin	2015 (1.5)	8816 (0.9)	0.06	1882 (1.5)	7988 (1.6)	0.01
Glibenclamide	958 (0.7)	3239 (0.3)	0.05	858 (0.7)	3763 (0.7)	0.01
Tolbutamide	369 (0.3)	1235 (0.1)	0.03	287 (0.2)	1351 (0.3)	0.01
Glipizide	522 (0.4)	1784 (0.2)	0.04	449 (0.4)	1954 (0.4)	0.01
Potassium chloride	13,579 (10.4)	25,700 (2.5)	0.32	12,664 (9.9)	37,967 (7.5)	0.08
Warfarin	2261 (1.7)	4642 (0.5)	0.12	2041 (1.6)	5107 (1.0)	0.05
Acetyl salicylic acid	11,429 (8.8)	30,623 (3.0)	0.24	10,499 (8.2)	41,886 (8.3)	0.003
Digoxin	4975 (3.8)	8566 (0.8)	0.19	4525 (3.5)	13,790 (2.7)	0.04
Glyceryl trinitrate	4755 (3.7)	9364 (0.9)	0.18	4115 (3.2)	11,659 (2.3)	0.05
Isosorbide dinitrate	1918 (1.5)	3203 (0.3)	0.12	1547 (1.2)	3979 (0.8)	0.04
Isosorbide mononitrate	2020 (1.6)	3439 (0.3)	0.12	1649 (1.3)	4132 (0.8)	0.04
Furosemide	14,452 (11.1)	28,146 (2.8)	0.33	13,508 (10.5)	40,046 (7.9)	0.09
Spironolactone	3049 (2.3)	5591 (0.6)	0.15	2807 (2.2)	7535 (1.5)	0.05
Atenolol	2151 (1.7)	7861 (0.8)	0.08	2022 (1.6)	8676 (1.7)	0.01
Amlodipine	6574 (5.1)	22,110 (2.2)	0.15	6234 (4.9)	25,374 (5.0)	0.007
Verapamil	2497 (1.9)	5949 (0.6)	0.12	2353 (1.8)	7801 (1.5)	0.02
Diltiazem	2083 (1.6)	4461 (0.4)	0.11	1731 (1.4)	5260 (1.0)	0.02
Captopril	652 (0.5)	2034 (0.2)	0.05	524 (0.4)	2149 (0.4)	0.003
Enalapril	3448 (2.7)	14,058 (1.4)	0.09	3257 (2.5)	15,339 (3.0)	0.03
Losartan	2913 (2.2)	7954 (0.8)	0.12	2671 (2.1)	8748 (1.7)	0.02
Bendroflumethazide	17,636 (13.6)	54,689 (5.4)	0.28	16,990 (13.3)	68,464 (13.5)	0.008
Finasteride	740 (0.6)	1936 (0.2)	0.06	673 (0.5)	2141 (0.4)	0.01
Desogestrol and ethinylestradiol	979 (0.8)	26,022 (2.6)	0.14	979 (0.8)	4281 (0.8)	0.009
Gestodene and estrogen	1587 (1.2)	46,631 (4.6)	0.20	1584 (1.2)	7726 (1.5)	0.02
Sulfamethizole	9903 (7.6)	44,398 (4.4)	0.13	9478 (7.4)	35,063 (6.9)	0.01
Allopurinol	2785 (2.1)	7797 (0.8)	0.11	2617 (2.0)	7724 (1.5)	0.03
Aspirin	7331 (5.6)	16,404 (1.6)	0.21	6801 (5.3)	23,159 (4.6)	0.03
Acetaminophen	32,234 (24.8)	50,877 (5.0)	0.57	31,320 (24.4)	79,470 (15.7)	0.21
Ketobemidone	5081 (3.9)	8240 (0.8)	0.20	4870 (3.8)	8051 (1.6)	0.13
Diazepam	9797 (7.5)	28,136 (2.8)	0.21	9511 (7.4)	29,233 (5.8)	0.06
Nitrazepam	5525 (4.2)	13,106 (1.3)	0.18	5396 (4.2)	22,025 (4.4)	0.007
Zopiclone	10,866 (8.4)	31,356 (3.1)	0.22	10,561 (8.2)	37,419 (7.4)	0.03
Zolpidem	7631 (5.9)	22,735 (2.2)	0.18	7381 (5.8)	22,095 (4.4)	0.06
Citalopram	7516 (5.8)	25,411 (2.5)	0.16	7230 (5.6)	24,437 (4.8)	0.03
Quinine	4606 (3.5)	8520 (0.8)	0.18	4424 (3.5)	12,997 (2.6)	0.05
Fenoterol and ipratropium bromide	2919 (2.2)	7782 (0.8)	0.12	2731 (2.1)	9117 (1.8)	0.02
Theophylline	1548 (1.2)	3733 (0.4)	0.09	1470 (1.1)	4424 (0.9)	0.02
Comorbidities						
Type 2 diabetes mellitus	1654 (1.3)	5324 (0.5)	0.07	1318 (1.0)	4622 (0.9)	0.01
Transient cerebral ischemic attacks	327 (0.3)	917 (0.1)	0.03	181 (0.1)	643 (0.1)	0.004
Age-related cataract	1949 (1.5)	4381 (0.4)	0.10	1862 (1.5)	8152 (1.6)	0.01
Primary hypertension	2594 (2.0)	8102 (0.8)	0.10	2224 (1.7)	8361 (1.7)	0.006

Table 1 (continued)

	Before hdDRS matching		SMD	After hdDRS matching		SMD
	Rofecoxib use *N* (mean or %)	Ibuprofen use *N* (mean or %)		Rofecoxib use *N* (mean or %)	Ibuprofen use *N* (mean or %)	
Angina pectoris	1693 (1.3)	4878 (0.5)	0.08	1474 (1.2)	4815 (1.0)	0.01
Chronic IHD	1709 (1.3)	3764 (0.4)	0.10	1399 (1.1)	3960 (0.8)	0.03
Atrial fibrillation	1787 (1.4)	3847 (0.4)	0.10	1543 (1.2)	4536 (0.9)	0.03
Heart failure	1417 (1.1)	2569 (0.3)	0.10	1169 (0.9)	3223 (0.6)	0.03
Sequelae of cerebrovascular disease	330 (0.3)	740 (0.1)	0.04	93 (0.1)	211 (0.0)	0.01
Atherosclerosis	797 (0.6)	1774 (0.2)	0.07	558 (0.4)	1549 (0.3)	0.02
Medical observation for suspected diseases	10,938 (8.4)	53,227 (5.2)	0.12	10,349 (8.1)	34,534 (6.8)	0.04

SMD, standardized mean difference; hdDRS, high-dimensional disease risk score; IHD, ischemic heart disease

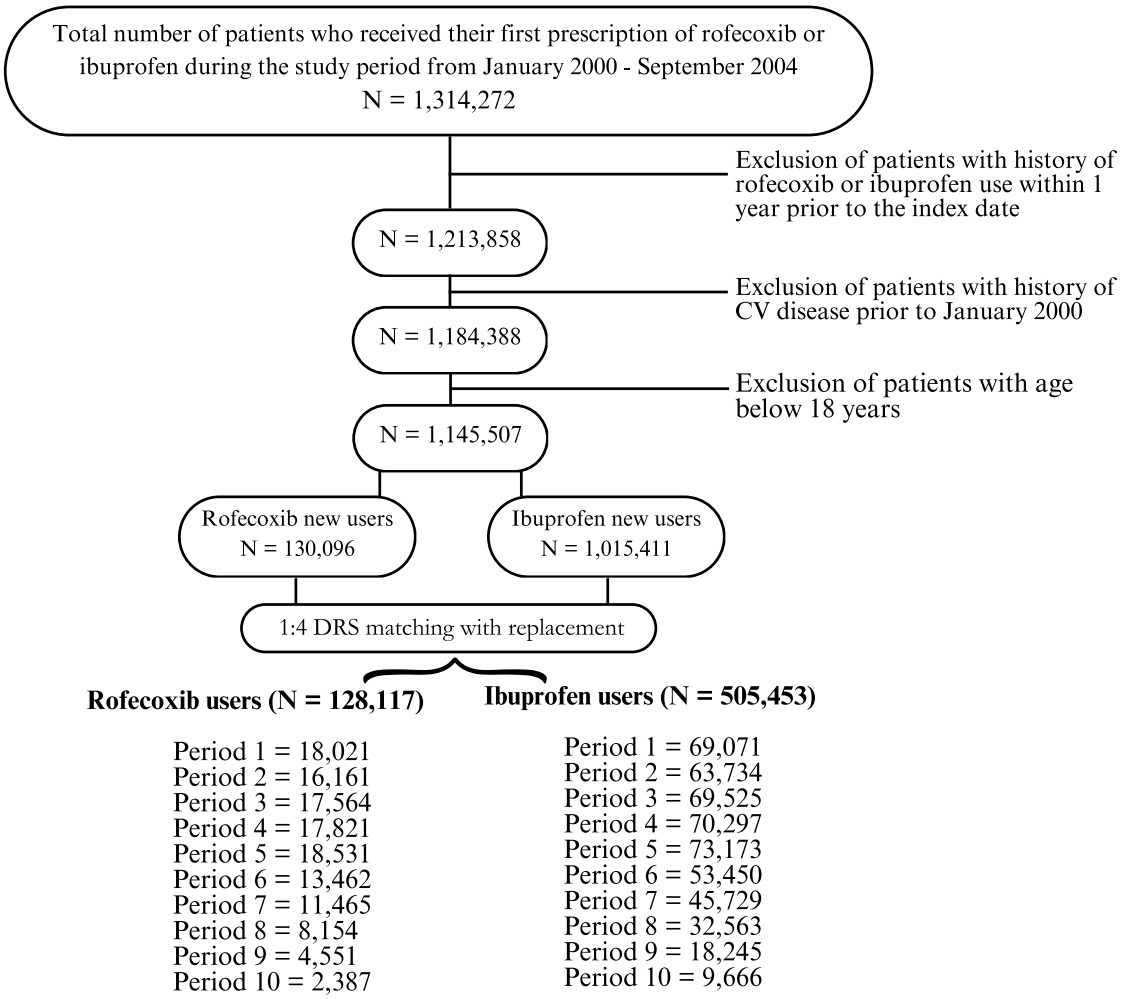

Fig. 5 Selection of rofecoxib and ibuprofen users for cohort study

data source such as Sentinel [46] could fulfill signal criteria earlier, advocating for collaborative efforts in drug safety monitoring. Lastly, the signal threshold used was ad hoc; for routine implementation, a predefined threshold would in most cases have to be established.

In general, the effect estimates were more stable across study periods for the case–time–control study design than

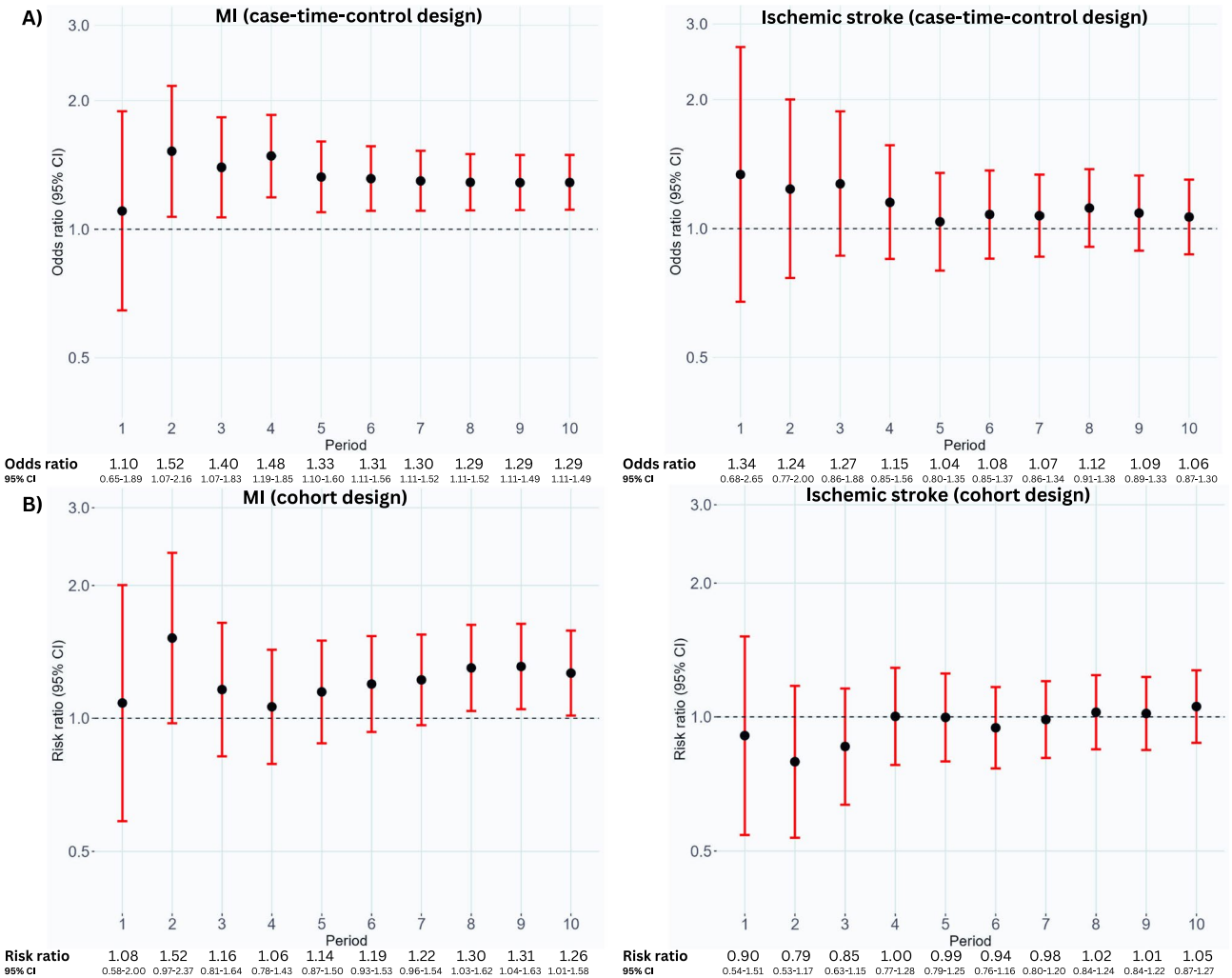

Fig. 6 Sensitivity analyses. Sequential monitoring of rofecoxib use for myocardial infarction and ischemic stroke using a 30-day focal window and follow-up time in case–time–control (**A**) and cohort study (**B**) design, respectively. Study periods 1–10 correspond to ten sequential analyses conducted from January 2000 to September 2004. Each analysis adds 6 months of data, except for study period 10, which adds 3 months of data. The effect estimates (odds ratios or risk ratios) are cumulative and estimated at the end of each study period. ⊢, odds ratio (**A**) or risk ratio (**B**) with 95% compatibility interval. - - -, null

for the cohort design. The earliest evidence of the association between rofecoxib use and risk of MI could be seen at the end of study period 2 for the case–time–control design. Hence, using this monitoring setup, the association could be identified as early as 1.5 years after the rofecoxib launch, corresponding to 3.5 years before its ultimate market withdrawal. For the cohort study design, the earliest association between rofecoxib use and risk of MI was seen in study period 7 (RR 1.22, 95% CI 1.02–1.47). Our monitoring study did not find any association of rofecoxib use with risk of ischemic stroke in both case–time–control (cumulative OR 1.00, 95% CI 0.85–1.19) and cohort (cumulative RR 1.11, 95% CI 0.97–1.28) study designs.

The sensitivity analyses provided a wider picture of the cardiovascular effects of rofecoxib. Firstly, when the length of the focal, washout, and reference windows in case–time–control was reduced to 30 days, a stronger association of rofecoxib use and risk of MI could be seen. Some studies have suggested that the cardiovascular adverse effects occurred after transient rofecoxib use and could appear within the first few weeks of use [47, 48]. Hence, explorations of varying focal windows may help elucidate time periods where risk is elevated. Secondly, use of rofecoxib at 25 mg or above showed increased risk of MI (1.4 times) in case–time–control and use at a dose of 12.5 mg showed no risk in both study designs. The counter argument could be that patients receiving higher doses would be inherently frailer or have underlying health conditions predisposing them to cardiovascular events. This is one of the examples where self-controlled designs, such as case–time–control,

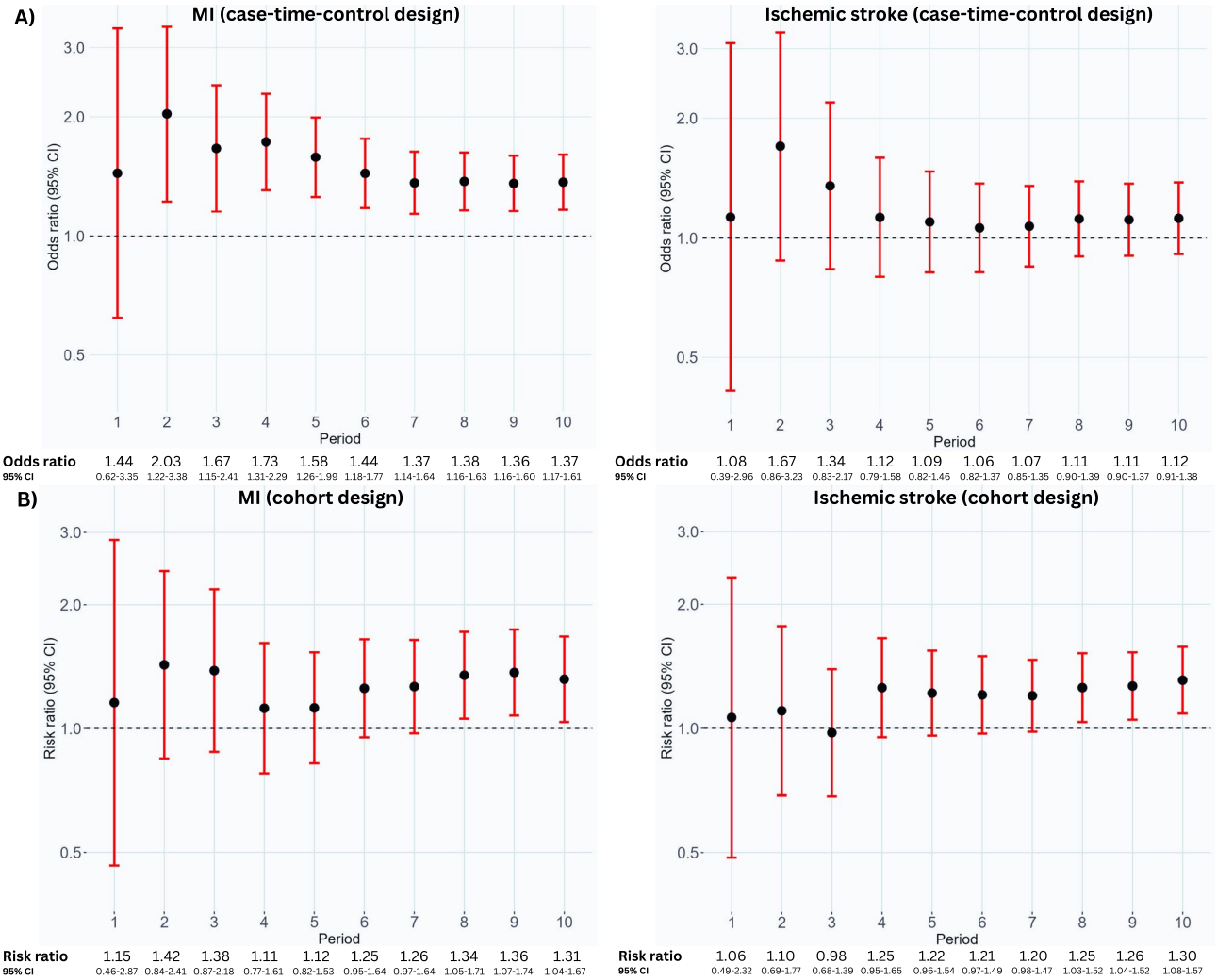

Fig. 7 Sensitivity analyses. Sequential monitoring of rofecoxib use for myocardial infarction and ischemic stroke using case–time–control (**A**) and cohort study (**B**) designs for patients in the dose category of 25 mg or above. Study periods 1–10 correspond to ten sequential analyses conducted from January 2000 to September 2004. Each analysis adds 6 months of data, except for study period 10, which adds 3 months of data. The effect estimates (odds ratios or risk ratios) are cumulative and estimated at the end of each study period. ⊥, odds ratio (**A**) or risk ratio (**B**) with 95% compatibility interval. - - -, null

may provide an advantage over a cohort design. With within-person comparison and shorter duration of focal and reference windows, one would not expect a substantial change in patients' frailty and other subject specific confounders that predispose the outcome.

Compared with the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (RR 2.65, 95% CI 1.21–5.75), our case–time–control (OR 1.12, 95% CI 0.99–1.27) and cohort design (RR 1.32, 95% CI 1.11–1.56) identified a weaker association of rofecoxib use and the risk of MI. However, the RR obtained from the trial had a much larger uncertainty due to small number of events. In addition to statistical uncertainty, the divergence between the results of this study and those of the APPROVe trial can also be explained by differences in the duration of follow-up. The current study had a relatively short follow-up period of only 60 days, whereas the trial follow-up spanned over a year. By focusing on short-term exposure–outcome associations, the case–time–control design may not fully capture the long-term impact and dynamics of the intervention or treatment, thus leading to differing results compared with a study with an extended follow-up period. Furthermore, the trial utilized only a 25 mg dose of rofecoxib, whereas the present study included both the 12.5 mg and 25 mg dose. As seen in the sensitivity analyses, the dose of 12.5 mg was associated with a reduced risk of MI. This could be one of the reasons for the lower estimates in the main analyses.

The cohort study design has been the primary choice for the sequential monitoring of newly marketed drugs [11–13, 49]. This design is unaffected by the bias induced by time trends in exposure but could be affected by other sources of bias. For instance, the cohort study design does not, as the case–time–control design, account for time-stable unmeasured confounders. Moreover, confounding by indication is a concern in any observational study design [50]. We used an active comparator to mitigate the effects of confounding by indication. The inability of the cohort design to identify an association in earlier study periods in this study should not limit its use for prospective safety monitoring of drugs. This design should still be a choice for future monitoring of new drugs that will almost surely have slower uptake, for less commonly observed outcomes, and when the use of a self-controlled design would not be appropriate, e.g., when studying delayed outcomes such as cancer. Although the use of DRS is appropriate in the case of newly marketed drugs, studies suggest that DRS methods yield higher type 1 error rates than PS methods [51]. Also, using DRS for signal detection programs would be impractical, as it would require modeling for each evaluated outcome. Hence, further exploration is required if DRS methods are to be used in routine signal detection.

There are instances in which the conventional cohort study is not feasible, for example, if confounding by indication remains a significant concern and there is a lack of appropriate active comparators available [52]. Therefore, we showed the case–time–control design to be an alternative approach for the sequential safety monitoring of drugs. This design is expected to provide a better control over the temporal trend of exposure than the case–crossover design [26], although it under other circumstances can be more biased than the simple case–crossover [53], which is an important consideration in the safety and effectiveness studies on newly marketed drugs. By focusing on each individual case and their own exposure history, the case–time–control design could be considered as an efficient means of studying rare outcomes that may occur infrequently in the population. The detectable signal for MI after about 2 years of rofecoxib marketing was previously reported [54] on the basis of sequential monitoring using the cohort study design. Similar findings using the case–time–control design in our study suggest that prospective drug safety monitoring using this design, or self-controlled designs in general, may have major public health benefits, given that safety monitoring programs using the cohort analysis may not be employed regularly owing to a lack of efficiency and rare outcomes. Both of these limitations could be addressed using the case–time–control design.

5 Conclusions

Our prospective drug safety monitoring setup using the case–time–control design effectively showed that the risk of MI could have been detected as early as after 1.5 years of rofecoxib launch or 3.5 years before its ultimate market withdrawal. Although the case–time–control design resulted in earlier identification of MI risk compared with a more rigorously controlled active comparator cohort design, these findings are context specific and should not be interpreted as conclusive evidence favoring one design over another. This study demonstrates the potential for the self-controlled design as an alternative for the safety monitoring of newly marketed drugs where the cohort design is not feasible. However, further research is needed to validate the broader applicability of this approach.

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Declarations

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Conflicts of Interest The authors have no conflicts of interest to declare.

Authors' Contributions Saad Hanif Abbasi and Anton Pottegård were responsible for the initial concept and planning of the study. Saad Hanif Abbasi and Lars Christian Lund were responsible for managing and analyzing 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.

Data and Code Availability Due to Danish data protection regulations, individual-level data cannot be shared directly by the authors. Deidentified data from Danish healthcare registries are accessible for researchers after application to the Danish Health Data Authority. The source code can be shared by the authors upon request. A protocol was registered and made publicly available prior to the commencement of any statistical analysis (https://osf.io/va3yj).

Ethics Approval Not applicable.

Consent to participate/consent for publication Not applicable.

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