The cohort study design

A cohort

(not the same as a cohort study!)

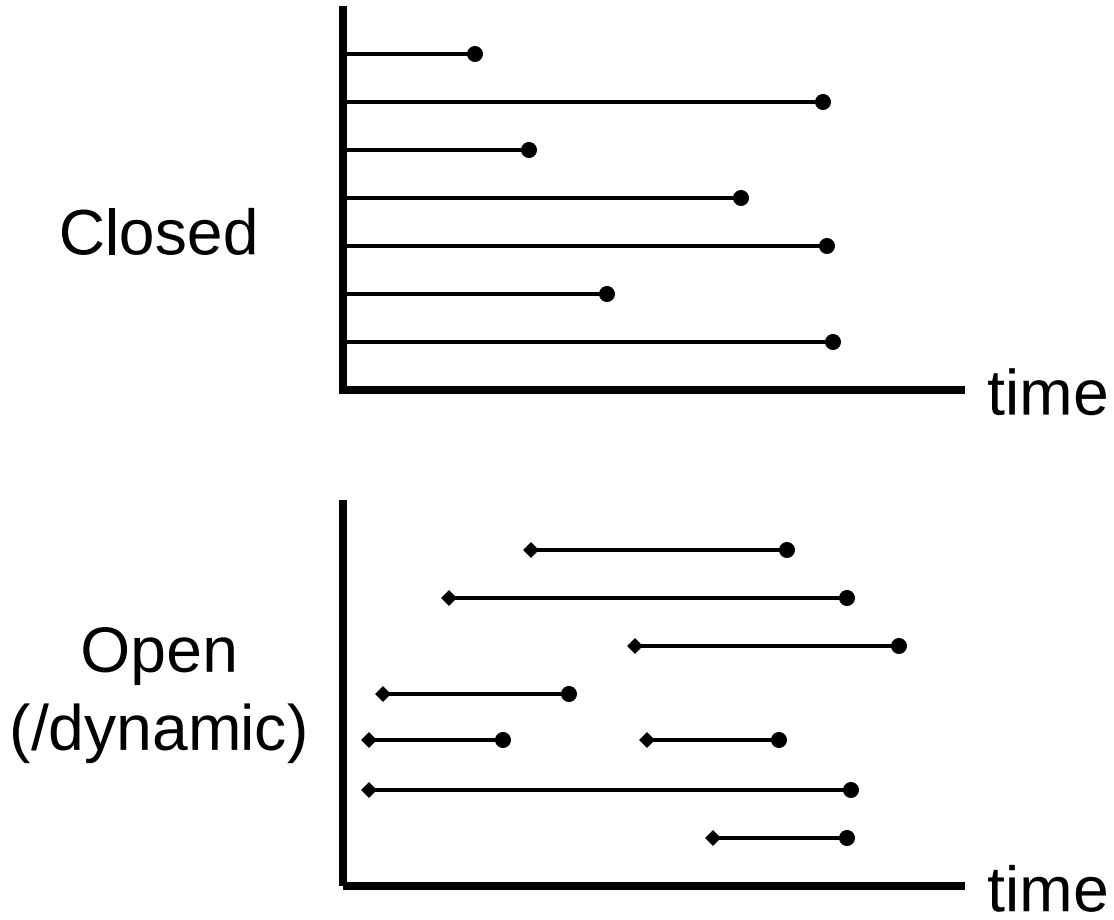
A population followed over time for the occurence of a given outcome

Closed cohort

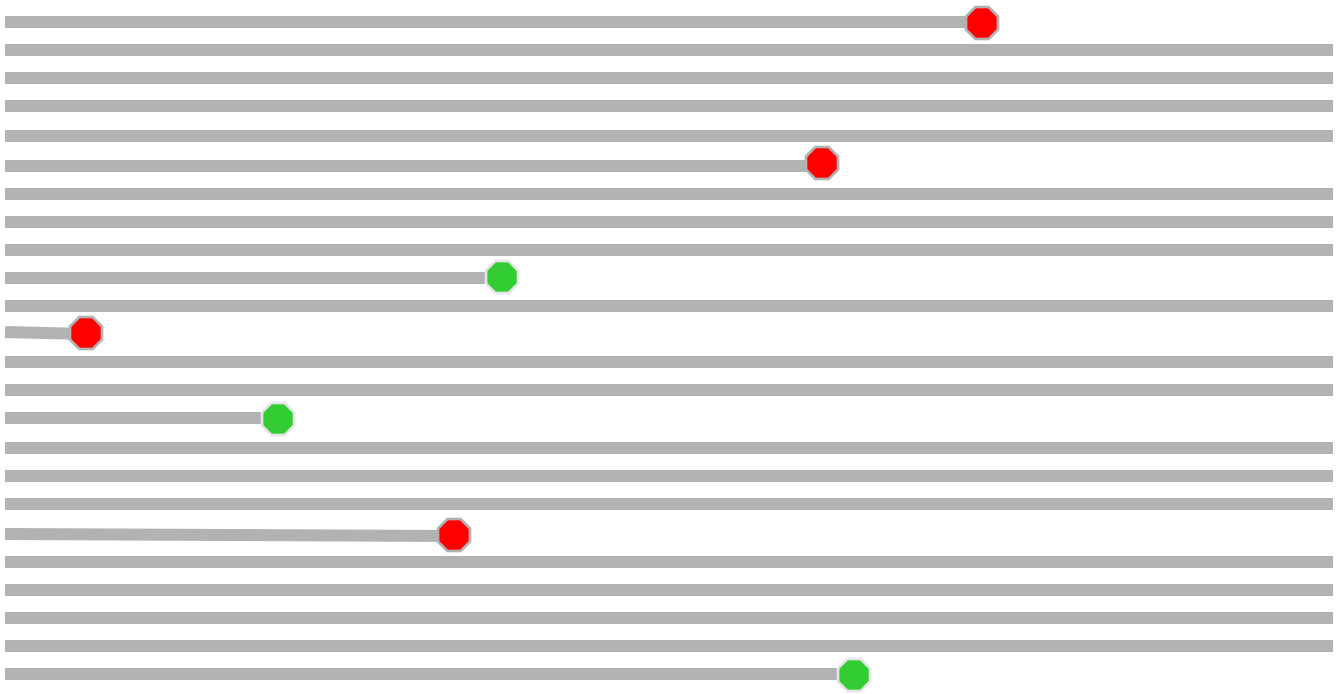
A group of individuals are followed form a given point in time, with no later addition of later individuals. All individuals are followed until the event of interest occur or the study period ends.

Open cohort

A population that is changing over time. Individuals can freely enter and exit the cohort during the observation period.

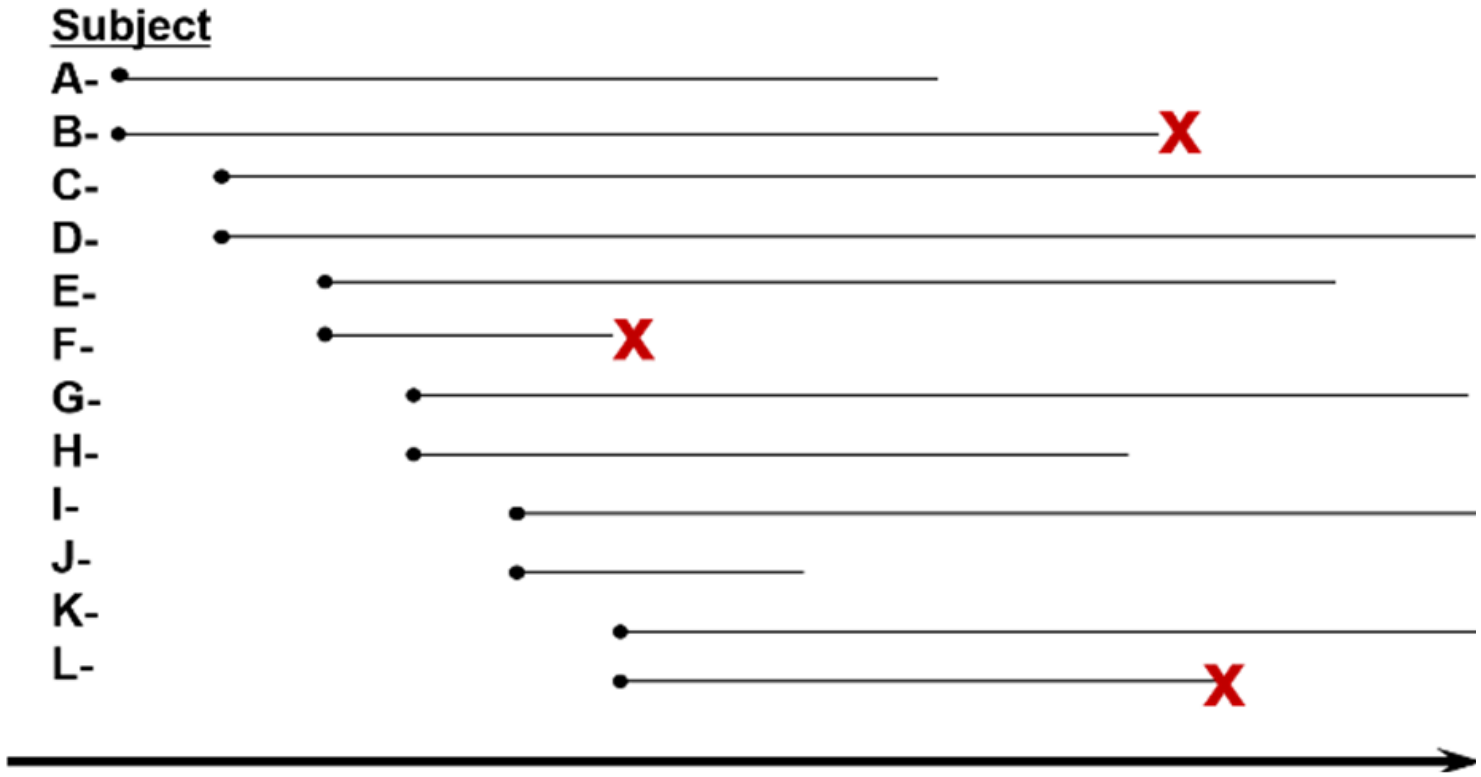

Closed
time
Open
(/dynamic)
time

Cohort design



107.7 person-years

3 events



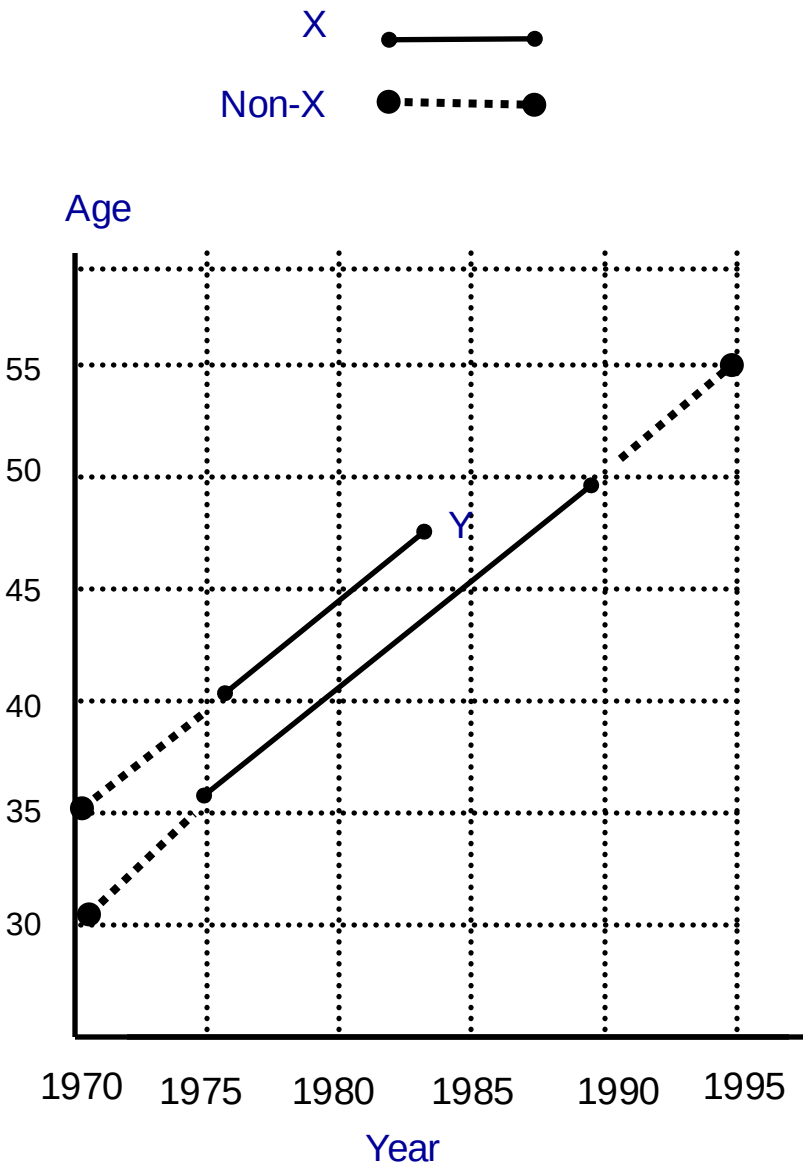
IR = 0.028/py

= 28/1000py

$$IR(\text{exposed}) = 28/1000\text{py}$$

$$IR(\text{unexposed}) = 20/1000\text{py}$$

$$IRR = 28/20 = 1.4$$


X
Non-X
Age
55
50
45
40
35
30
Y
1970
1975
1980
1985
1990
1995
Year

	Exp. to X		Unexp. to X	
Age	**Person years**	**Disease Y**	**Person years**	**Disease Y**
30-34 y	0	0	5	0
35-39 y	5	0	5	0
40-44 y	10	0	0	0
45-49 y	8	1	0	0
50-54 y	0	0	5	0

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005
With ASA										
Person ID	Entry	Exit	ASA_tvc	Outcome						
3245	Jan 1 2001	Feb 22 2003	N	N						
3245	Feb 23 2003	Feb 12 2004	Y	N						
3245	Feb 13 2004	Dec 31 2014	N	N						

Time slicer

Person ID	Entry	Exit	Outcome				PersonID	Exposure	Start	End
3245	Jan 1 2001	Dec 31 2014	N				3245	ASA	Feb 23 2003	Feb 12 2004
							3245	NSAID	Jul 14 2003	Sep 28 2005
With ASA										
Person ID	Entry	Exit	ASA_tvc	Outcome						
3245	Jan 1 2001	Feb 22 2003	N	N						
3245	Feb 23 2003	Feb 12 2004	Y	N						
3245	Feb 13 2004	Dec 31 2014	N	N						
With ASA and NSAID										
Person ID	Entry	Exit	ASA_tvc	NSAID_tvc	Outcome					
3245	Jan 1 2001	Feb 22 2003	N	N	N					
3245	Feb 23 2003	Jul 13 2003	Y	N	N					
3245	Jul 14 2003	Feb 12 2004	Y	Y	N					
3245	Feb 13 2004	Sep 28 2005	N	Y	N					
3245	Sep 29 2005	Dec 31 2014	N	N	N					

First-Trimester Exposure to Methylphenidate: A Population-Based Cohort Study

Anton Pottegård, MScPharm; Jesper Hallas, MD, PhD; Jon T. Andersen, MD, PhD; Ellen C. L. Løkkegaard, MD, PhD; Dorthe Dideriksen, MScPharm; Lise Aagaard, MScPharm, PhD; and Per Damkier, MD, PhD

ABSTRACT

Objective: The use of methylphenidate to treat attention-deficit/hyperactivity disorder has risen dramatically in Western countries, and it is increasingly used by adults, including women of childbearing age. Very little is known about potential hazards of in utero exposure to methylphenidate. We conducted this study to estimate the risk of major congenital malformations following first-trimester in utero exposure to methylphenidate.

Method: Data from 2005 to 2012 were extracted from the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry, and the Danish Civil Registration System. Exposure was defined as having redeemed 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. Each exposed subject was propensity score–matched to 10 unexposed subjects with respect to maternal age, smoking status, body mass index, length of education, calendar year of completion of pregnancy, and concomitant use of antipsychotics,

The issue of methylphenidate use during pregnancy has become increasingly relevant as the prevalence of attention-deficit/hyperactivity disorder (ADHD) among adults has risen over the last decade.[1,2] It is estimated that between 30% and 70% of children with ADHD will experience symptoms as adults.[3] Estimates of the prevalence of adult ADHD have been reported to be around 3%–4%, ranging from 1% to 7% in different countries, with the highest prevalence among developed countries.[4,5] Methylphenidate was approved for use in adults by the US Food and Drug Administration in 2008, but it does not yet hold this indication in Europe.[6,7] Some guidelines recommend the use of methylphenidate in adults suffering from ADHD,[8] including a recommendation on off-label use from the National Institute for Health and Clinical Excellence in the United Kingdom.[9] A recent study[10] showed that in Denmark many women in the fertile age range are prescribed methylphenidate: Among women aged 18–40 years, 4 to 8 per 1,000 persons use methylphenidate (Figure 1).

Safety data on the use of methylphenidate during pregnancy are scarce and give little guidance for the prescribing physician. Labeling for use during pregnancy is "C" ("animal data have shown adverse effect on the fetus") in the United States,[6] while the UK Summary of Product Characteristics[7] states that "there is a limited amount of data from the use of methylphenidate in pregnant women" and that "methylphenidate is not recommended for use during pregnancy unless a clinical decision is

Table 2. Fetal Outcomes and Point Prevalence Ratios (PPRs) Comparing the Exposed to the Unexposed Cohort, Overall, and by Subgroup

Subgroup	Events/No. of Pregnancies		PPR (95% CI)
	Exposed	Unexposed	
All			
Major malformations	7/222	86/2,220	0.8 (0.3–1.8)
Cardiac malformations	3/222	32/2,220	0.9 (0.2–3.0)
Maternal age < 30 y			
Major malformations	6/161	63/1,637	1.0 (0.3–2.2)
Cardiac malformations	2/161	19/1,637	1.1 (0.1–4.4)
Maternal age ≥ 30 y			
Major malformations	1/61	23/583	0.4 (0.0–2.6)
Cardiac malformations	1/61	13/583	0.7 (0.0–4.9)
No use of confounding drugs[a]			
Major malformations	5/125	53/1,346	1.0 (0.3–2.5)
Cardiac malformations	3/125	17/1,346	1.9 (0.4–6.6)

NSAID and UGB Saskatchewan

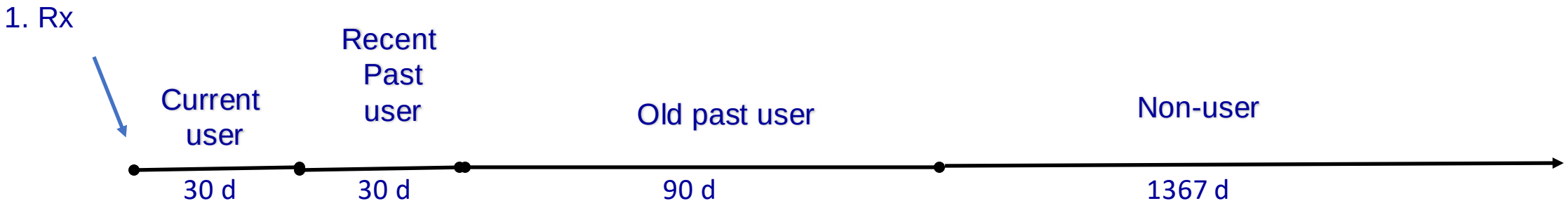
”… entered our cohort upon the first receipt of a prescription for diclofenac, indomethacin, naproxen, piroxicam or sulindac. Person-time contributed by this person continued until the earliest of: 1) hospitalization due to UGB 2) death 3) departure from Saskatchewan or 4) end of study.”

No control group!

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

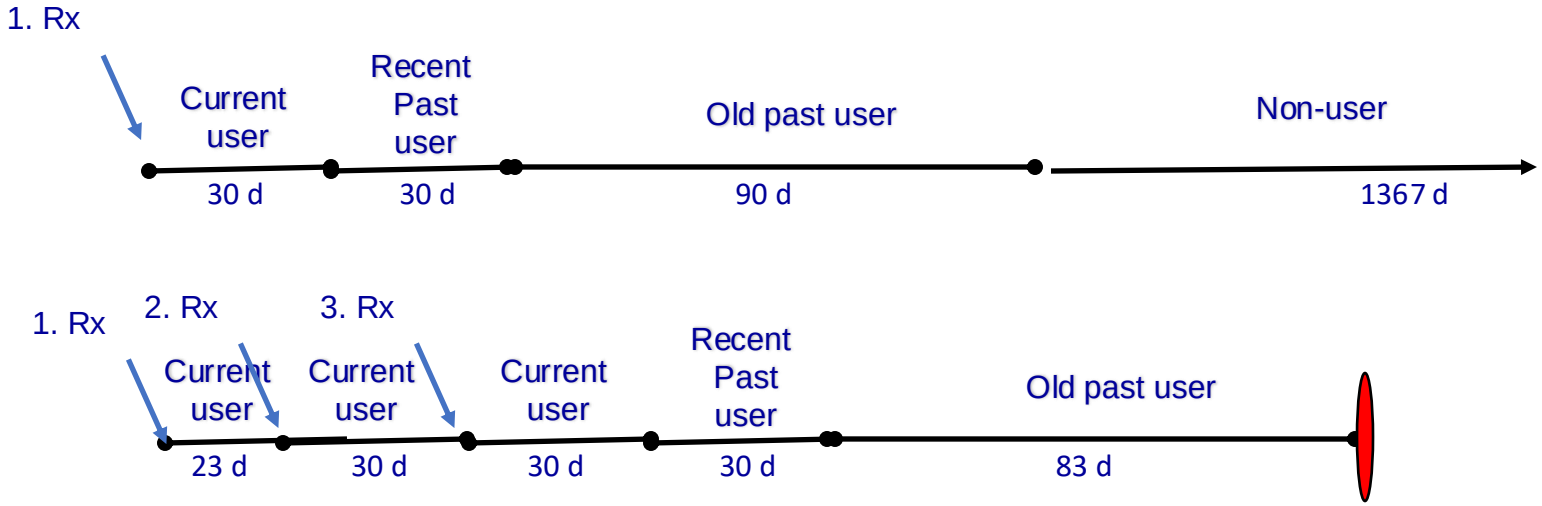
NSAID and UGB Saskatchewan

Current use	<31 d
Recent past use	31-60 d
Old past use	61-150 d
Nonuse	>150 d



García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

NSAID and UGB Saskatchewan



	Current user	Recent past user	Old past user		Nonuser
Person 1	30	30	90		1367
Person 2	83	30	83	1	-
Ialt	113	60	173	1	1367

Total

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.

NSAID and UGB Saskatchewan

Incidence rate ratios of GI-hospitalisations of NSAID users

	Current users (0-30 days)	Recent past users (30-60 days)	Old past users (60-150 days)
Diclofenac	3.9	2.2	1.3
Indomethacin	4.0	1.7	1.4
Naproxen	3.8	2.3	1.4
Nonusers		1.0	

García Rodríguez et al. Epidemiology . 1992 Jul;3(4):337-42.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ORIGINAL REPORT

Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study†

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ABSTRACT

Purpose Generic switching of warfarin was recently repealed in Denmark, as adverse drug reaction (ADR) reports suggested risk of excessive anticoagulation following switches from branded to generic warfarin. We investigated this putative association in a formalized pharmacoepidemiological analysis.

Methods We conducted a nationwide cohort study based on Danish healthcare registries, including data from the introduction of generic warfarin until the repeal (January 2011–April 2015). We followed Danish warfarin users over time and compared the rate of incident hospitalizations due to excessive anticoagulation (i.e. increased INR or any bleeding requiring hospitalization) in periods following a recent switch to generic warfarin to the rate in periods without a recent switch.

Results We included 105 751 warfarin users, filling a total of 1 539 640 prescriptions for warfarin (2.5% for generic warfarin). This constituted 89.0% of all warfarin prescriptions in Denmark during the study period. We observed 19 362 switches to generic warfarin during the study period. The adjusted hazard ratio for excessive anticoagulation following a recent switch from branded to generic warfarin was 1.1 (95%CI, 0.8–1.4). The result was robust within subgroups and several sensitivity analyses.

Conclusion Switching from branded to generic warfarin is not associated with an increased risk of hospitalization with excessive anticoagulation. However, a minor excess risk of transient INR increase cannot be excluded. Pharmacoepidemiological studies provide an effective method for swift evaluation of hypotheses generated by ADR-reports.

KEY WORDS—oral anticoagulants; warfarin; generic drugs; adverse drug reaction reports; excessive anticoagulation; pharmacoepidemiology; Denmark

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(1) Continuous use of branded warfarin (from the date of filling a second prescription for branded warfarin in a row until the time of filling the next prescription)
(2) Continuous use of generic warfarin (from the date of filling a second prescription for generic warfarin in a row until the time of filling the next prescription)
(3) Recent switch TO generic warfarin (the first 60 days from the day of filling a prescription for generic warfarin and having filled branded warfarin as the last prior prescription)
(4) Recent switch FROM generic warfarin (the first 60 days from the day of filling a prescription for branded warfarin and having filled generic warfarin as the last prior prescription)

Outcome measure	Events	Follow-up (PY)	Rate (/1000 PY)	Adjusted HR (95%CI)
Excessive anticoagulation[‡]				
Cont. use of branded	5665	224 282	25	1.0 (ref.)
Cont. use of generic	36	1349	27	1.1 (0.8–1.5)
Switch TO generic	53	1940	27	1.1 (0.8–1.4)
Switch FROM generic	11	375	29	1.2 (0.7–2.2)