Web Appendix 2 – Characteristics of included studies

Risk of acute MI with NSAIDs in real-world use: a Bayesian IPD MA

Web Table 1: Overview and design of the four healthcare database studies included in the one-stage Bayesian IPD MA of NSAIDs and acute MI – Dataset supplied by Investigator

	RAMQ (N=233 816)	**Finland** (N=172 219)	**GPRD** (N=17 561)	**Saskatchewan** (N=23 167)
Jurisdiction	Province of Québec, Canada	Finland	United Kingdom (UK)	Province of Saskatchewan, Canada
Design	Cohort with nested case-control analysis	Population-based case-control study	Cohort with nested case-control analysis	Cohort with nested case-control analysis
Matching of controls to cases on time	Individual matching on: 1) year and month of cohort entry 2) duration of follow-up in cohort	Individual matching on index date	Individual matching on: 1) year of cohort entry 2) duration of follow-up in cohort	Frequency matching on distribution of cases on index date (± 3 months) of non-cases within their person-time of follow-up
Matching of controls to cases on demographic or healthcare variables	Age (± 1 year) and sex	Age at end of calendar year, sex, and hospital catchment area	Age (± 2 year), sex, medical practice	None
Case:control ratio	1:10	1: up to 5	1: up to 4	1:up to 7
Number of cases in study	21 256	33 309	3643	3252
Proportion of total cases in IPD MA, %	34.6	54.2	5.9	5.3
Number of controls in study	212 560	138 910	13 918	19 915
Size of case-control study	233 816	172 219	17 561	23 167
Size of underlying cohort	364 840	Not applicable	486 378	364 658
Study period	1 January 1993 to 30 September 2004	1 January 2000 to 31 December 2003	1 June 2000 to 31 October 2004	15 November 1999 to 31 December 2001
Recruitment dates	1 January 1993 to 31 March 2004	1 January 2000 to 31 December 2003	1 June 2000 to 13 August 2004	15 November 1999 to 22 December 2001
Target population *	Quebec ≥ 65 years	Finland General	United Kingdom ≥ 45 years	Saskatchewan covered population eligible for outpatient prescription drug benefits and 40-84 years

	RAMQ (N=233 816)	**Finland** (N=172 219)	**GPRD** (N=17 561)	**Saskatchewan** (N=23 167)
Target population size (year) †	1 511 600 (1996) 1 704 910 (2001)	5 181 000 (2000)	20 706 897 (2001)	431 739 (June 30, 2001)
Data sources ‡	Régie de l'assurance maladie du Québec (RAMQ) Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO – hospital discharge summary) Institut de la statistique du Québec	Finnish National Prescription Register Special Reimbursement Register of the Finnish Social Insurance Institution Finnish Hospital Discharge Register	Clinical system software (Vision) used by general practitioners on a voluntary basis throughout the UK Data collected: medical practice, demographics, lifestyle factors, diagnoses, laboratory tests and pathology, referral to hospitals or specialists, consultations, therapies, treatment outcomes	Saskatchewan's health services databases: population registry, prescription drug, hospital separation, medical services, vital statistics
Extent of coverage of the target population in data sources, after data linkage (during study years) §	Quebec residents living in the community 1993-1996: individuals aged ≥ 65 years and recipients of last-resort financial assistance 1997-2004: individuals not eligible for private group insurance plan covering prescription drugs, aged ≥ 65 years, and recipients of last-resort financial assistance	Permanent Finnish residents living in the community	3 million patients in 380 general medical practices throughout the United Kingdom	Saskatchewan Ministry of Health's covered population eligible for outpatient prescription drug benefits (primarily excludes registered Indians whose prescription drug benefits are covered under a federal health plan)
Proportion of coverage of the target population in linked data sources (during study years) ‖	About 80% of individuals aged 55-64 years (2002) About 90% of individuals aged ≥ 65 years (2002)	Not available	Not available	About 91%
Study population age	≥ 65 years (1.4% aged 54-64 years upon cohort entry)	All ages	≥ 40 years	40-84 years

	RAMQ (N=233 816)	**Finland** (N=172 219)	**GPRD** (N=17 561)	**Saskatchewan** (N=23 167)
Cohort entry	Date of first dispensing of single NSAID prescription after 1 January 1993 in individuals without NSAID prescriptions for ≥ 1 year	Not applicable	Date of NSAID first prescription after 1 June 2000	15 November 1999
NSAID use at study entry	New use	Use in the last 2 years before index day	New or prevalent use	New or prevalent use
Cohort/study exclusion	NSAID use within the year preceding cohort entry Enrolment in the health plan for < 1 year	≥ 90 days in institutionalized care at any time during the 2 years preceding the index day ≥ 1 prescription for warfarin in the year preceding the index day	Age < 40 years Registration with a practice without ensured quality standards of data recording for ≥ 1 year	Cancer, HIV/AIDS, liver injury, alcohol-related disease, or organ transplant
Cohort exit	Earliest of the following dates: first hospital admission for acute MI, death, termination of health system coverage, or end of the study (30 Sep 2004)	Not applicable	Earliest of the following dates: date of acute MI, death, end of registration with the practice, or end of the study (31 Oct 2004)	Earliest of the following dates: first hospital admission for acute MI, diagnosis of one of the exclusion criteria, 85th birthday, death, termination of health system coverage, or end of the study (31 Dec 2001)
Cross-reference to dataset used in published paper	None (new dataset)	Investigators shared published study cases and re-sampled controls (138 910 in supplied dataset and 138 949 in published paper) Investigators created the categorical 'recency-dose-duration' NSAID exposure variable	Investigators shared dataset with same number of cases and controls as study publication	Investigators shared dataset with same number of cases and controls as study publication
Reference study publication	Not applicable	Helin-Salmivaara A, et al. Eur Heart J. 2006;27(14):1657-63.	Andersohn F, et al. Circulation. 2006;113(16):1950-7.	Varas-Lorenzo C, et al. Pharmacoepidemiol Drug Saf. 2009;18(11):1016-25.

	RAMQ (N=233 816)	Finland (N=172 219)	GPRD (N=17 561)	Saskatchewan (N=23 167)

* Based on age inclusion/exclusion criteria for study population

† *Québec (RAMQ):* Statistics Canada. 1996 Census Technical Reports. Age, sex, marital status and common-law status. Table A1 (Quebec). Catalogue No. 92-353-XIE. 1999. Available at: http://www.statcan.gc.ca/pub/92-353-x/92-353-x1996000-eng.pdf. Last accessed February 12, 2017.
and Statistics Canada. 2001 Census Technical Reports. Age, sex, marital status and common-law status. Available at: http://www12.statcan.gc.ca/english/census01/Products/Reference/tech_rep/age_sex/table_c1.cfm. Last accessed February 12, 2017.
Finland: Statistics Finland. Population. Available at: http://www.stat.fi/tup/suoluk/suoluk_vaesto_en.html#byage. Last accessed February 12, 2017.
United Kingdom (GPRD): Office for National Statistics. Census 2001 Key Statistics - Local Authorities KS02 Age structure. Local Authorities in England and Wales. Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-211026. Last accessed February 27, 2016.
Saskatchewan: Saskatchewan Health. Corporate Information and Technology Branch Covered Population 2001. ISSN 0139-5988 Available at http://www.ehealthsask.ca/HealthRegistries/Covered%20Population/covered-population-2001.pdf. Last accessed February 27, 2016.

‡ *United Kingdom (GPRD*): Wood L, Martinez C. The General Practice Research Database: role in pharmacovigilance. Drug Saf. 2004;27(12):871-81
Saskatchewan: Downey W, Stang MR, Beck P, Osei W, Nichol JL. Health Services Databases in Saskatchewan. Chapter 19. In: Strom BL. Pharmacoepidemiology. 4th edition. John Wiley & Sons Ltd. Chichester, West Sussex, UK. 2005. pp 295-301.

§ *Québec (RAMQ):* In August 1996, RAMQ introduced a cost-sharing drug insurance plan. Implementation of this plan had an impact on individuals aged 65 years and older, as co-payment changed from a flat $2 fee per prescription to yearly costs of $200 to $750, scaled by income.
Source: Currie GR, Nielson NL. Models for Funding Prescription Drug Programs. Institute of Health Economics Working Paper 99-5. 1999. ISSN 1481-3823. Available at: https://www.researchgate.net/publication/239753417_MODELS_FOR_FUNDING_PRESCRIPTION_DRUG_PROGRAMS Last accessed February 12, 2017.
Régie de l'assurance-maladie du Québec. Prescription drug insurance. Available at: http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/description.aspx. Last accessed February 12, 2017.

‖ Régie de l'assurance maladie du Québec (RAMQ). Portrait évolutif du régime public d'assurance médicaments. 1998-1999-2000. Juin 2002. Available at: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/citoyens/fr/rapports/rappetu-evolution-assurance-medicaments-fr.pdf. Last accessed February 12, 2017.

Web Table 2: Definition and ascertainment of cases and controls in dataset supplied by Investigator in the four healthcare database studies included in the one-stage Bayesian IPD MA of NSAIDs and acute MI

	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Index day for cases	Date of hospital admission with acute MI	Date of hospital admission with acute MI	Earliest date of the recorded acute MI, symptoms, hospitalization with acute MI, or coronary heart disease (CHD) death	Date of hospital admission with acute MI or CHD death
Index day for matched controls	Date resulting in same follow-up time in cohort	Index date of the case	Date resulting in same follow-up time in cohort	Each cohort member was assigned a randomly generated date between November 15, 1999 and December 31, 2001 regardless of start date, exposure or outcome. Patients whose random date fell within their individual person-time of follow-up were eligible as controls. Controls were randomly selected from all eligible controls, frequency-matched to the distribution of cases on index date (±3 months). Index date for study controls was their random date
Case definition and ascertainment	First hospitalization with ICD-9 code 410.x following cohort entry (fatal and non-fatal acute MI) Length of hospital stay ≥ 3 days, unless transfer to or from another institution or percutaneous coronary intervention (non-fatal acute MI)	First hospitalization with ICD-9 code 410.x and ICD-10 codes I21 and I22 in a patient without MI in the 7 years preceding the current MI	Diagnosis of acute MI, death from acute MI, sudden or unexpected death from coronary heart disease confirmed by codes indicating acuteness (e.g., hospitalization, fibrinolysis, chest pain, coronary intervention, testing for troponin T) Length of hospital stay ≥ 3 days	First hospitalization for acute MI or out-of-hospital coronary heart disease (OOH-CHD)-related death All hospitalizations with a primary discharge code of ICD-9 410 or 411, and all OOH deaths with CHD as underlying cause of death (ICD-9 codes: 410-414, 427.5, 798 and ICD-10 codes: I20-I22; I23.3; I24-I25; I46; R96.0; R96.1, and R98) were ascertained

	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Reasons for excluding cases	Acute MI on cohort entry date (first NSAID prescription dispensing after study start)	Receipt of ≥ 1 prescription for warfarin during the 365 days preceding the index date (also exclusion in Table 1)	Acute MI in hospitalized surgical patients Deaths after acute MI in patients with a possibly fatal disease	Failure to confirm case status based on American Heart Association / European Society of Cardiology and Braunwald criteria
Reasons for under-ascertainment of cases	Out-of-hospital fatal acute MI Non-fatal MI cared for outside a hospital Silent MI and sudden death	Out-of-hospital fatal acute MI Non-fatal MI cared for outside a hospital Silent MI and sudden death	Silent MI	Silent MI

[*] Levy AR, Tamblyn RM, Fitchett D, et al. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Can J Cardiol 1999;15:1277-82.
Lambert L, Blais C, Hamel D, et al. Evaluation of care and surveillance of cardiovascular disease: can we trust medico-administrative hospital data? Can J Cardiol 2012;28:162-8.
Kiyota Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99-104.

[†] Pajunen P, Koukkunen H, Ketonen M, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2005;12(2):132-7

[‡] Hammad TA, McAdams MA, Feight A, et al. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2008; 17(12): 1197–1201 and Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60(572):e128-36.

[§] Varas-Lorenzo C, Castellsague J, Stang MR, et al. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. Pharmacoepidemiol Drug Saf. 2008;17(8):842-52.

Web Table 3: Definition and ascertainment of exposure in dataset supplied by Investigator in the four healthcare database studies included in the one-stage Bayesian IPD MA of NSAIDs and acute MI

	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Commonly used NSAIDs	Celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib	Celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib	Celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib	Celecoxib, diclofenac, ibuprofen, naproxen, rofecoxib
Other NSAIDs	Diflunisal, etodolac, fenoprofen, flurbiprofen, ketoprofen, indomethacin, mefenamic acid, meloxicam, nabumetone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolmetin sodium	Aceclofenac, etodolac, etoricoxib, indomethacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, nimesulide, piroxicam, tenoxicam, tiaprofenic acid, tolfenamic acid	Etoricoxib, valdecoxib Other non-selective and semi-selective NSAIDs available in the UK (details not available from data sources)	Diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, phenylbutazone, piroxicam, sulindac, tiaprofenic acid, tolmetin
Proxy for NSAID exposure	Pharmacy dispensing	Pharmacy dispensing	Physician prescription	Pharmacy dispensing
Marketing approval date of coxibs in jurisdiction	Celecoxib: Apr 1999 Rofecoxib: Oct 1999	Launch dates Celecoxib: Apr 2000 Rofecoxib: Oct 1999	Celecoxib: Apr 1999 Rofecoxib: Apr1999	Celecoxib: Apr 1999 Rofecoxib: Oct 1999
Public formulary listing date of coxibs in jurisdiction	Celecoxib: Oct 1999 Rofecoxib: Apr 2000	Celecoxib: Oct 2001 Rofecoxib: Oct 2001	Celecoxib: May 2000 Rofecoxib: Jun 1999	Celecoxib: 15 Nov 1999 Rofecoxib: 1 Feb 2000
Restriction on coxib reimbursement during study	No	No	No	Yes
NSAIDs with OTC status during study	Ibuprofen	Ibuprofen Ketoprofen	Ibuprofen	Ibuprofen
Main reasons for under-ascertainment of NSAID exposure (aside from proxy)	Use of OTC ibuprofen	Use of OTC ibuprofen or ketoprofen	Use of OTC ibuprofen	Use of OTC ibuprofen Database may incompletely capture celecoxib and rofecoxib use in patients < 65 years during the entire study period and in patients ≥ 65 years before 21 June 2000 if these patients did not request or were denied coverage under the Exception Drug Status program

	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Ascertainment sources for descriptors of NSAID exposure	Computer-recorded drug substance, dosage form, strength, number of drug units (quantity), dispensing date, and number of days supplied (duration of prescription)	Computer-recorded drug substance, dosage form, strength, number of drug units (quantity), and dispensing date	Computerized medical records documenting prescription	Computer-recorded drug substance, dosage form, strength, number of drug units (quantity), and dispensing date
Descriptors of NSAID exposure with greatest potential for measurement error (over and above 'as needed' use)	--	Duration of single prescription and, consequently, daily dose	--	Duration of single prescription and, consequently, daily dose
Ascertainment of NSAID daily dose	Calculated as: daily dose= strength × quantity dispensed / duration of supply using computer-recorded information for 'strength', 'quantity' and 'duration'	Inferred from each NSAID Defined Daily Dose (DDD) Sensitivity analyses allowed for actual daily NSAID dose being larger (× 2 DDD) or smaller (× 0.5 DDD)	Calculated as: daily dose= strength × prescribed number of units (e.g. tablets) per day	Inferred from computer-recorded information for 'strength', 'quantity', and 'dosage form' and a usual supply of 34 days
Form of 'daily dose' variable	Discrete (dose in mg corresponding to available dosage forms)	Dataset supplied as 'recency-dose-duration' variable pre-defined for the IPD MA	Discrete (dose in mg corresponding to available dosage forms) Last daily dose in current user only	Continuous (calculated dose may not correspond to an available dosage form)
Ascertainment of duration of single NSAID prescription	Computer-recorded duration of prescription (number of days supplied)	Variable 'duration' does not exist in the computerized prescription database Estimated from dispensing dates and from DDD for each NSAID Sensitivity analyses on duration allowed for actual daily NSAID dose being larger (× 2 DDD) or smaller (× 0.5 DDD)	Calculated by dividing the quantity of prescribed units (e.g. tablets) by the number of units to be taken daily	Variable 'duration' does not exist in the computerized prescription database During study period, pharmacists were allowed to charge a dispensing fee for each 34 day supply Duration was estimated from time elapsed between prescriptions and a pre-defined gap based on NSAID drug product

	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Ascertainment of duration of continuous episode of NSAID use at a given daily dose	Calculated by adding the duration, in days, of consecutive prescriptions Use classified as continuous if interval between 2 prescriptions ≤ 14 days	Calculated by adding the duration, in DDDs equivalent, of consecutive prescriptions Use classified as continuous if interval between 2 prescriptions ≤ 14 days	Calculated by adding the duration of consecutive prescriptions	Calculated by counting the number of days between dispensing date of the first consecutive prescription and earlier of the index date or the dispensing date of the last consecutive prescription plus 41 days. Prescriptions considered consecutive if the number of days between dispensing dates was < 102 days, therefore use classified as continuous if interval between 2 prescriptions < 60 days
Form of 'duration' variable	Continuous, in days	Dataset supplied as 'recency-dose-duration' variable pre-defined for the IPD MA	Continuous, in days Available for last continuous duration of use	Continuous, in days
Ascertainment of recency of NSAID exposure	Calculated from computer-recorded dispensing date and duration of prescription	Inferred from computer-recorded dispensing date and estimated duration of prescription	Calculated from computerized medical records documenting prescription	Inferred from computer-recorded dispensing date and estimated duration of prescription
'Recency' of exposure variable definitions	Current use: duration of prescription supply overlapped with the index date Recent use: duration of prescription supply ended 1-30 days before index date Past use: duration of prescription supply ended in the 31-365 days before index date	Current use: duration of prescription supply overlapped with the index date Recent use: duration of prescription supply ended 1-30 days before index date Past use: duration of prescription supply ended in the 31-365 days before index date	Current use: duration of prescription supply lasted into the 14-day period before index date Recent use: duration of prescription supply ended in the 15-183 days before index date Past use: duration of prescription supply ended in the 184-365 days before index date	Current use: duration of prescription supply overlapped with the index date or ended within 7 days before index date Recent use: duration of prescription supply ended 8-60 days before index date Recent use: duration of prescription supply ended 61-365 days before index date

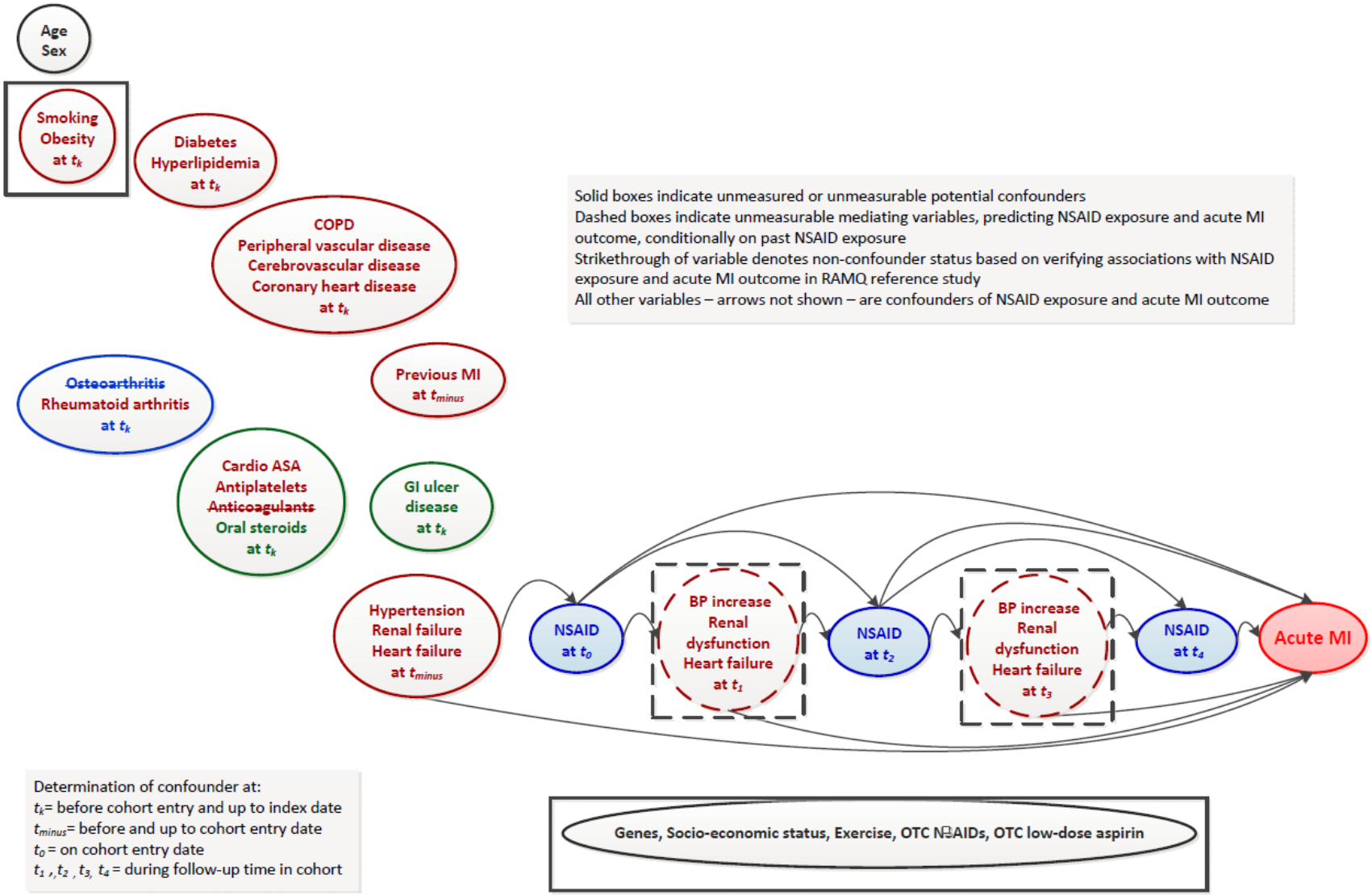
	RAMQ [*] (N=233 816)	**Finland** [†] (N=172 219)	**GPRD** [‡] (N=17 561)	**Saskatchewan** [§] (N=23 167)
Definition of 'non-use'	No NSAID prescriptions in the 365 days before the index date	No NSAID prescriptions in the 365 days before the index date	No NSAID prescriptions in the 365 days before the index date	No NSAID prescriptions in the 365 days before the index date
Study allowed for NSAID switching	Yes	No	Yes	Yes

[*] *Québec (RAMQ):*
Celecoxib was approved in Canada April 1999 and listed on Quebec *Liste de médicaments du régime général* October 1999. Available at: (http://www.inesss.qc.ca/fileadmin/doc/CDM/Inscription_medicaments/Capsules_Pharmaco%C3%A9conomiques/CCP-Capsules-pharmacotherapeutiques-19991001.pdf). Last accessed October 18, 2013. Rofecoxib was approved in Canada October 1999 and listed on Quebec *Liste de médicaments du régime général* April 2000. Available at: http://www.inesss.qc.ca/fileadmin/doc/CDM/Inscription_medicaments/Capsules_Pharmaco%C3%A9conomiques/CCP-Capsules-pharmacotherapeutiques-20000401.pdf. Last accessed October 18, 2013.
Canada Gazette. Regulations Amending the Food and Drug Regulations (1584 — Schedule F). Naproxen and its salts. Vol. 143, No. 10. May 13, 2009. Available at: http://www.gazette.gc.ca/rp-pr/p2/2009/2009-05-13/html/sor-dors119-eng.html. Last accessed February 27, 2016.

[†] *Finland:*
DDD defined as the standard dose per 24 hours for an adult taking the drug for its main indication as suggested by WHO (WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD system. Available at: http://www.whocc.no/atcddd/). Last accessed February 12, 2017.
Celecoxib (200 mg), diclofenac (100 mg), ibuprofen (1 200 mg) naproxen (500 mg), rofecoxib (25 mg)

[‡] *United Kingdom (GPRD)*:
United Kingdom Medicines and Healthcare Products Regulatory Agency. Public consultation ARM 41: Request to re-classify Naproxen 250 mg tablets from prescription only medicine (POM) to pharmacy availability (P). May 2007. Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/publication/con014817.pdf. Last accessed January 14, 2015.
UK National Health Services. National Prescribing Centre. New drugs in clinical development. November 2001. Available at: http://www.ukmi.nhs.uk/NewMaterial/secure/10120102.pdf. Last accessed January 14, 2015.
National Institute for Clinical Excellence. Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. Technology Appraisal No. 27. July 2001. Available at: http://www.spitjudms.ro/_files/protocoale_terapeutice/reumatologie/protocol%20de%20tratament%20al%20par.pdf. Last accessed February 12, 2017.

[§] *Saskatchewan:*
The pharmacist may charge one dispensing fee for each prescription for most drugs listed in the Formulary. If a prescription is for a duration of one month or more, the pharmacist is entitled to charge a dispensing fee for each 34 day supply, however the Agreement does not prohibit the pharmacist from dispensing more than a 34 day supply for one fee (Government of Saskatchewan. Saskatchewan Health Drug Plan and Extended Benefits Branch. Annual Statistical Report 2000-01.)



Web Figure 1: Identification of confounders of NSAID exposures and acute MI outcome showing occurrence of time-dependent confounding affected by previous exposure

Web Table 4: List of confounders available in the dataset supplied by the Investigator and included (X) or not included (N) in the one-stage Bayesian IPD MA of NSAIDs and acute MI

Variable	RAMQ (N=233 816)	Finland (N=172 219)	GPRD (N=17 561)	Saskatchewan (N=23 167)
Demographic characteristics				
Age	X	X	X	X
Sex	X	X	X	X
Comorbidities				
Diabetes	X	X	X	X
Hyperlipidemia	X	X	X	X
Hypertension	X	X	X	X
Previous myocardial infarction	X	--	--	X
Coronary heart disease	X	X	X	X
Congestive heart failure	X	--	--	X
Cerebrovascular disease	X	--	X	X
Peripheral vascular disease	X	--	--	X
Chronic obstructive pulmonary disease	X	--	--	X
Gastrointestinal ulcer disease	X	--	--	X
Gastrointestinal bleed	X	--	--	X
Acute or chronic renal failure	X	--	--	X
Rheumatoid arthritis	X	X	X	X
Osteoarthritis	N [a]	--	N [b]	N [b]
Smoking	--	--	N [c]	--
Obesity or body mass index	--	--	N [c]	N [d]
Concomitant drug treatment				
Use of oral corticosteroids	X	--	--	N [e]
Use of clopidogrel	X	X	--	--
Use of cardioprotective aspirin	X	--	--	-- [f]
Use of anticoagulants	N [a]	--	--	N [b]
Use of nitrates	N [g]	--	--	N [e]
Use of beta-blockers	N [g]	N [e]	--	N [e]
Use of hormonal replacement therapy	N [b]	N [e]	--	N [b]
Other health status indices				
Hospitalizations history	-- [h]	--	--	N [h]
Socio economic status indicator	-- [h]	--	--	N [h]
Formulary calendar period	--	--	--	N [h]

--: systematically missing from dataset supplied by Investigator

[a] Potential confounder based on a directed acyclic graph of the relations among the variables relevant to NSAID exposure and acute MI outcome. Confounder status not substantiated by odds ratio (OR) of association between this covariate and exposure to NSAIDs among controls and OR of association between this covariate and acute MI outcome in unexposed subjects in the RAMQ study (reference standard)

[b] On the basis of analysis of confounding in the RAMQ study (reference standard) not included in the study dataset created for the IPD MA

[c] Not included in the study dataset created for the IPD MA. Complete information was available on smoking and body mass index for 78.7% of patients (Andersohn F, et al. Circulation. 2006;113(16):1950-7); methods that would appropriately allow accounting for missingness cannot be implemented

[d] Defined in the original study as any history of hospital discharge for obesity (ICD-9 278.x) or any history of physician

Variable	RAMQ (N=233 816)	Finland (N=172 219)	GPRD (N=17 561)	Saskatchewan (N=23 167)

service for obesity prior to (ICD-9 278). Obesity not included in the study dataset created for the IPD MA due to potential underascertainment in administrative databases

[e] Not used for adjustment in the IPD MA as variable was not considered separately of related comorbidities in the RAMQ study (reference standard)

[f] Capture of aspirin (ASA) use in the Saskatchewan outpatient prescription drug database is incomplete. The 80 mg ASA tablet formulation is not listed in the formulary. The 325 mg formulation is listed, but due to the current cost-sharing arrangement of the Saskatchewan Drug Plan it is more financially sensible for most beneficiaries to buy 325 mg ASA over-the-counter than by prescription (Varas-Lorenzo C, et al. Pharmacoepidemiol Drug Saf. 2009;18(11):1016-25)

[g] Included in drug algorithms used for ascertaining comorbidities

h The original RAMQ study adjusted MI risk estimates for 3 measures of health care utilization (the number of hospitalizations, medical outpatient visits, and visits to a cardiologist), and 3 measures of comorbidity (the chronic disease score, the number of distinct drugs dispensed, and the Charlson index assessed in the year preceding the index date for the reason that no gain in precision was shown with the use of a parsimonious model. (Lévesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. Ann Intern Med. 2005;142(7):481-9.) Because of this and the lack of harmonizability of healthcare utilization between studies comprised in the IPD MA, this was not assessed in the RAMQ study