Web Appendix 1 – Systematic review

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

Web Table 1: Search strategies for the systematic review of observational studies of NSAIDs and risk of acute MI

Individual observational studies
PubMed

#	Keywords
1	(((case-control studies [mh] OR cohort studies [mh] OR cross-over studies [mh] OR epidemiologic studies [mh:noexp] OR cross-sectional studies [mh] OR evaluation studies as topic [mh] OR meta-analysis as topic [mh] OR practice guidelines as topic [mh] OR case control [tw] OR case controlled [tw] OR case controls [tw] OR cohort [tw]OR cohorts [tw] OR follow-up [tw] OR followup [tw] OR longitudinal [tw] OR matched-pair analysis [mh] OR observational studies [tw] OR observational study [tw] OR multicenter study [pt]) AND ((comparative study [pt] OR compare [tw] OR compares [tw] OR compared [tw] OR compared [tw] OR comparing [tw] OR comparison [tw] OR comparative [tw] OR effective [tw] OR effectiveness [tw] OR versus [ti] OR vs [ti]) AND (activities of daily living [mh] OR benefit [tw] OR benefits [tw] OR budgets [mh] OR chronic disease [mh] OR clinical trials data monitoring committees [mh] OR cognitive function [tw] OR ec [sh] OR death [mh] OR diffusion of innovation [mh] OR discharge [tw] OR economics, pharmaceutical [mh] OR evidence based practice [mh] OR functional status [tw] OR guideline adherence [mh] OR harm [tw] OR harms [tw] OR health services research [mh] OR health status [mh] OR hospitalization [mh] OR interventions [tw] OR life expectancy [mh] OR longevity [mh] OR models, statistical [mh] OR models, theoretical [mh:noexp] OR morbidity [mh] OR mortality [mh] OR noninferior [tw] OR noninferiority [tw] OR outcome and process assessment [mh] OR outcome [tw] OR outcomes [tw] OR patient compliance [mh] OR postoperative care [mh] OR postoperative complications [mh] OR product surveillance, postmarketing [mh] OR propensity score [tw] OR quality-adjusted life years [mh] OR quality of life [mh] OR recovery of function [mh] OR recurrence [mh] OR relapse [tw] OR remission [tw] OR reoperation [mh] OR risk [tw] OR risk management [mh] OR survival analysis [mh] OR survival rate [mh] OR technology assessment, biomedical [mh])))) OR (((administrative data [tw] OR administrative database [tw] OR administrative databases [tw] OR chart review [tw] OR data registry [tw] OR data registries [tw] OR databases, factual [mh] OR hospital claims [tw] OR insurance claim review [mh] OR medical record linkage [mh] OR medical record review [tw] OR medical records systems, computerized [mh] OR national database [tw] OR observational analysis [tw] OR patient-reported outcomes measurement information system [tw] OR promis [tw] OR patient registry [tw] OR patient registries [tw] OR practice based research network [tw] OR practice based research networks [tw] OR pbrn [tw] OR pbrns [tw] OR registries [mh]) OR (national hospital discharge survey [tw] AND sn [sh]) OR (OSCAR AND nursing homes [tw]) OR Hospitalization/sn [majr] OR (hospitalization/td [majr] AND sn [sh])) AND (comparative study [pt] OR (activities of daily living [mh] OR benefit [tw] OR benefits [tw] OR budgets [mh] OR chronic disease [mh] OR clinical trials data monitoring committees [mh] OR cognitive function [tw] OR ec [sh] OR death [mh] OR diffusion of innovation [mh] OR discharge [tw] OR economics, pharmaceutical [mh] OR evidence based practice [mh] OR functional status [tw] OR guideline adherence [mh] OR harm [tw] OR harms [tw] OR health services research [mh] OR health status [mh] OR hospitalization [mh] OR interventions [tw] OR life expectancy [mh] OR longevity [mh] OR models, statistical [mh] OR models, theoretical [mh:noexp] OR morbidity [mh] OR mortality [mh] OR noninferior [tw] OR noninferiority [tw] OR outcome and process assessment [mh] OR outcome [tw] OR outcomes [tw] OR patient compliance [mh] OR postoperative care [mh] OR postoperative complications [mh] OR product surveillance, postmarketing [mh] OR propensity score [tw] OR quality-adjusted life years [mh] OR quality of life [mh] OR recovery of function [mh] OR recurrence [mh] OR relapse [tw] OR remission [tw] OR reoperation [mh] OR risk [tw] OR risk management [mh] OR survival analysis [mh] OR survival rate [mh] OR technology assessment, biomedical [mh])))) OR (registries/es [mh] OR registries/st [mh] OR registries/sn [mh] OR (registries [mh] AND (medicare [mh] OR practice guidelines as topic [mh])))) NOT randomized controlled trial [pt] NOT systematic [sb])
2	"Anti-Inflammatory Agents, Non-Steroidal"[mh] OR "Cyclooxygenase 2 Inhibitors"[mh] OR "Naproxen"[mh] OR "Ibuprofen"[mh] OR "Diclofenac"[mh] OR "celecoxib "[Substance Name] OR "rofecoxib"[Substance Name] NOT "Aspirin"[mh]
3	"Myocardial Infarction"[mh] OR "Myocardial Ischemia"[mh] OR "Acute Coronary Syndrome"[mh] OR "Angina Pectoris"[mh] OR "Coronary Disease"[mh] OR "Stroke"[mh] OR "Heart Failure"[mh]
4	1 and 2 and 3

Strategy 1 is from PubMed, HSRProj, and ClinicalTrials.gov Search Strategies for Informing Comparative Effectiveness Research. CER Observational Studies search strategy. http://www.nlm.nih.gov/nichsr/cer/CER_search_strategies.html#CER_Observational_Studies
Search dates: June 2010 to November 2013 (weekly updates)

MEDLINE via Ovid

#	Keywords
1	epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or case control.tw. or (cohort adj (study or studies)).tw. or cohort analy$.tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or longitudinal.tw. or retrospective.tw. or cross sectional.tw. or cross-sectional studies/
2	cohort.ti,ab. or exp cohort studies/ or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
3	exp case-control studies/ or control groups/ or (case-control or (case* adj5 control*) or (case adj3 comparison) or case-comparison).ti,ab.
4	exp cohort studies/ OR cohort$.tw. OR controlled clinical trial.pt. OR epidemiologic methods/ OR exp case-control studies/ OR (case$ and control$).tw.
5	1 or 2 or 3 or 4
6[a]	exp anti-inflammatory agents, non-steroidal/
7	exp Aspirin/
8	6 not 7
9	(meloxicam or nabumetone or tenoxicam or tiaprofenic acid).mp.
10	(celecoxib or etoricoxib or lumiracoxib or rofecoxib or valdecoxib).mp.
11	8 or 9 or 10
12[b]	exp Myocardial Infarction/ or exp myocardial ischemia/ or exp acute coronary syndrome/ or exp angina pectoris/ or exp coronary disease/
13	exp Stroke/
14	exp Heart Failure/
15	12 or 13 or 14
16	5 and 11 and 15

Strategy 1 is from Scottish Intercollegiate Group Network (SIGN).Observational Studies search filter http://www.sign.ac.uk/methodology/filters.html#obs

Strategies 2 and 3 are from University of Texas Health Science Center at Houston - School of Public Health – Search filter for cohort studies and search filter for case control studies. http://www.sph.uth.tmc.edu/library/default.aspx?id=7200#pubmed.

Strategy 4 is from BMJ Clinical Evidence - MEDLINE cohort and case-control filter. http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp. Cyclooxygenase inhibitors[mh], cyclooxygenase 2 inhibitors[mh], diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam, sulindac, and tolmetin part of tree

Anterior wall myocardial infarction[mh], inferior wall myocardial infarction[mh], myocardial stunning[mh], shock and cardiogenic[mh] part of tree

Search dates: June 2010 to November 2013 (weekly updates)

EMBASE via Ovid

#	Keywords
1	clinical study/ or case control study or family study/ or longitudinal study/ or retrospective study/ or prospective study/ or cohort analysis/ or (cohort adj (study or studies)).mp. or (case control adj (study or studies)).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or (epidemiologic$ adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. not randomized controlled trials/
2	exp cohort analysis/ or exp longitudinal study/ or exp prospective study/ or exp follow up/ or cohort$.tw. or exp case control study/ or (case$ and control$).tw.
3	1 or 2
4[a]	exp nonsteroid antiinflammatory agent/
5	exp acetylsalicylic acid/
6	4 not 5
7	exp rofecoxib/ or exp celecoxib/ or exp naproxen/or exp ibuprofen/or exp diclofenac/ or exp diflunisal/ or exp etodolac/ or exp etoricoxib/ or exp fenoprofen/ or exp flurbiprofen/ or exp indomethacin/ or exp ketoprofen/ or exp lumiracoxib/ or exp meloxicam/ or exp nabumetone/ or exp piroxicam/ or exp sulindac/ or exp tenoxicam/ or exp tiaprofenic acid/ or exp tolmetin/ or exp valdecoxib
8	6 or 7
9[b]	exp ischemic heart disease/or exp coronary artery disease/
10	exp stroke/ or exp cerebrovascular accident/
11[c]	exp heart failure/
12	9 or 10 or 11
13	3 and 8 and 12

Strategy 1 is from Scottish Intercollegiate Group Network (SIGN).Observational Studies search filter. Available at: http://www.sign.ac.uk/methodology/filters.html#obs. Strategy 2 is from BMJ Clinical Evidence - EMBASE cohort and case-control filter. http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp.

Includes cyclooxygenase 2 inhibitors

Includes heart infarction/, which is used for myocardial infarction

Includes congestive heart failure

Search dates: June 2010 to November 2013 (weekly updates)

Systematic reviews

MEDLINE via Ovid

#	Keywords
1	Cochrane database of systematic reviews.jn. or search.tw. or meta-analysis.pt. or Medline.tw. or systematic review.tw.
2	meta-analysis as topic/ or meta analy$.tw. or metaanaly$.tw. or meta-analysis/ or (systematic adj (review$1 or overview$1)).tw. or exp review literature as topic/ or cochrane.ab. or embase.ab. or (psychlit or psyclit).ab. or (psychinfo or psycinfo).ab. or (cinahl or cinhal).ab. or science citation index.ab. or bids.ab. or cancerlit.ab. or reference list$.ab. or bibliograph$.ab. or hand-search$.ab. or relevant journals.ab. or manual search$.ab.
3	(selection criteria or data extraction).ab. AND review/
4	2 OR 3
5	("review" or "review academic" or "review tutorial").pt.
6	(medline or medlars or embase or pubmed or (scisearch or psychinfo or psycinfo) or (psychlit or psyclit) or cinahl or ((hand adj2 search$) or (manual$ adj2 search$)) or (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$) or (pooling or pooled or mantel haenszel)).tw,sh. or (retraction of publication or retracted publication).pt. or (peto or dersimonian or der simonian or fixed effect).tw,sh.
7	5 and 6
8	meta-analysis.pt. or meta-analysis.sh. or (meta-analys$ or meta analys$ or metaanalys$).tw,sh. or (systematic$ adj5 review$).tw,sh. or (systematic$ adj5 overview$).tw,sh. or (quantitativ$ adj5 review$).tw,sh. or (quantitativ$ adj5 overview$).tw,sh. or (quantitativ$ adj5 synthesis$).tw,sh. or (methodologic$ adj5 review$).tw,sh. or (methodologic$ adj5 overview$).tw,sh. or (integrative research review$ or research integration).tw.
9	7 or 8
10	1 or 4 or 9
11	comment/ or letter/ or editorial/
12	animal/ not (animal/ and human/)
13	11 or 12
14	10 not 13
15[a]	exp anti-inflammatory agents, non-steroidal/
16	exp Aspirin/
17	15 not 16
18	(meloxicam or nabumetone or tenoxicam or tiaprofenic acid).mp.
19	(celecoxib or etoricoxib or lumiracoxib or rofecoxib or valdecoxib).mp.
20	17 or 18 or 19
21	exp Myocardial Infarction/ or exp myocardial ischemia/ or exp acute coronary syndrome/ or exp angina pectoris/ or exp coronary disease/
22	exp Stroke/
23	exp Heart Failure/
24	21 or 22 or 23
25	14 and 20 and 24

Strategy 1 is from Montori VM, Wilczynski NL, Morgan D, Haynes RB; Hedges Team. Optimal search strategies for retrieving systematic reviews from Medline: analytical survey.BMJ. 2005 Jan 8;330(7482):68.
Strategies 2-4 and 11-13 are from Scottish Intercollegiate Group Network. (emphasis on specificity).
http://www.sign.ac.uk/methodology/filters.html#systematic.
Strategies 5-9 are from BMJ Clinical Evidence - Medline systematic review filter. http://www.york.ac.uk/inst/crd/intertasc/rct.htm.
Search dates: June 2010 to November 2013 (weekly updates)

EMBASE via Ovid

#	Keywords
1	meta-analysis or systematic review).tw.
2	exp meta analysis/ or ((meta adj analy$) or metaanalys$).tw. or (systematic adj (review$1 or overview$1)).tw. or cancerlit.ab. or cochrane.ab. or embase.ab. or (psychlit or psyclit).ab. or (psychinfo or psycinfo).ab. or (cinahl or cinhal).ab. or science citation index.ab. or bids.ab. or reference lists.ab. or bibliograph$.ab. or hand-search$.ab. or manual search$.ab. or relevant journals.ab.
3	(data extraction or selection criteria).ab. and review.pt.
4	2 or 3
5	exp review/
6	(medline or medlars or embase or pubmed or (scisearch or psychlit or psyclit) or (psycinfo or psychinfo) or cinahl).ti,ab,sh. or ((hand adj2 search$) or (manual$ adj search$)).tw. or ((electronic adj database$) or (bibliographic adj database$)).tw. or ((pooled adj analys$) or pooling).tw. or (peto or dersimonian or (fixed adj effect) or mantel haenszel).tw. or RETRACTED ARTICLE/
7	5 and 6
8	exp meta analysis/ or meta?analys$.tw,sh. or (systematic$ adj5 review$).tw,sh. or (systematic$ adj5 overview$).tw,sh. or (quantitativ$ adj5 review$).tw,sh. or (quantitativ$ adj5 overview$).tw,sh. or (methodologic$ adj5 review$).tw,sh. or (methodologic$ adj5 overview$).tw,sh. or ((integrative adj5 research adj5 review$) or (research adj5 integration)).tw. or (quantitativ$ adj5 synthesi$).tw,sh.
9	7 or 8
10	1 or 4 or 9
11	(letter or editorial).pt.
12	animal/not (animal/ and human/)
13	11 or 12
14	10 not 13
15[a]	exp nonsteroid antiinflammatory agent/
16	exp acetylsalicylic acid/
17	15 not 16
18	exp rofecoxib/ or exp celecoxib/ or exp naproxen/or exp ibuprofen/or exp diclofenac/ or exp diflunisal/ or exp etodolac/ or exp etoricoxib/ or exp fenoprofen/ or exp flurbiprofen/ or exp indomethacin/ or exp ketoprofen/ or exp lumiracoxib/ or exp meloxicam/ or exp nabumetone/ or exp piroxicam/ or exp sulindac/ or exp tenoxicam/ or exp tiaprofenic acid/ or exp tolmetin/ or exp valdecoxib
19	17 or 18
20[b]	exp ischemic heart disease/or exp coronary artery disease/
21	exp stroke/ or exp cerebrovascular accident/
22[c]	exp heart failure/
23	20 or 21or 22
24	14 and 19 and 23

Strategy 1 is from Wilczynski NL, Hayne RB, for the Hedges Team. EMBASE search strategies achieved high sensitivity and specificity for retrieving methodologically sound systematic reviews. J Clin Epidemiol 2007;60:29-33.
Strategies 2-4 and 11-13 are from Scottish Intercollegiate Group Network. (emphasis on specificity).
http://www.sign.ac.uk/methodology/filters.html#systematic.
Strategies 5-9 are from BMJ Clinical Evidence – EMBASE systematic review filter. http://www.york.ac.uk/inst/crd/intertasc/rct.htm.
Search dates: June 2010 to November 2013 (weekly updates)
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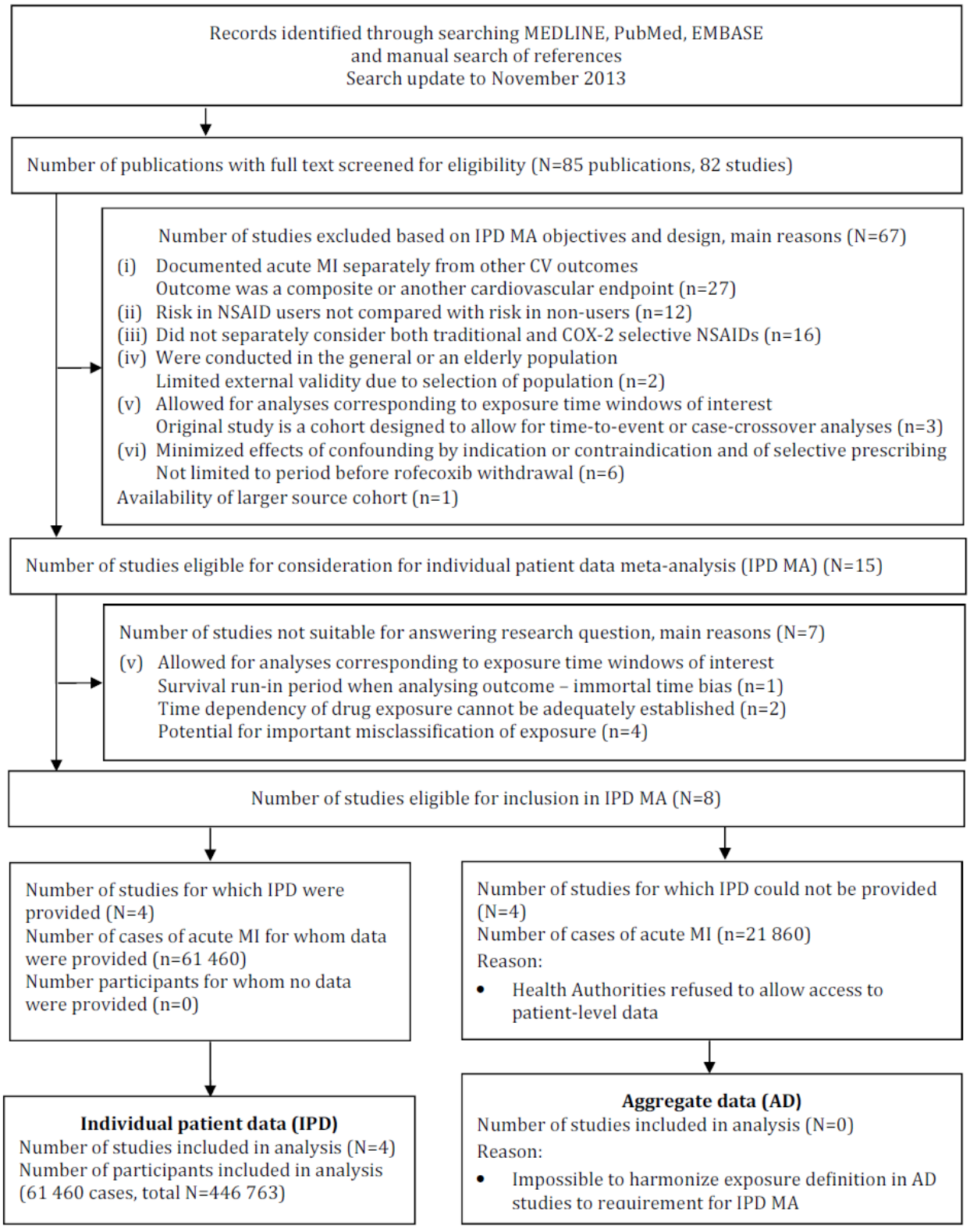


Web Figure 1: Study flow in the one-stage Bayesian IPD MA of NSAIDs and risk of acute MI

Web Table 2: Systematic review of healthcare database studies of NSAIDs and acute MI – Studies excluded based on IPD MA objectives and design

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
1. Jick SS. The risk of gastrointestinal bleed, myocardial infarction, and newly diagnosed hypertension in users of meloxicam, diclofenac, naproxen, and piroxicam. Pharmacotherapy 2000;20:741-4.	Risk in users not compared with non-users (reference group was diclofenac users) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were diclofenac, meloxicam, naproxen, piroxicam)
2. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000;160:777-84.	Outcome was not myocardial infarction (congestive heart failure)
3. Ko D, Wang Y, Berger AK, Radford MJ, Krumholz HM. Nonsteroidal antiinflammatory drugs after acute myocardial infarction. Am Heart J 2002;143:475-81.	Outcome was not myocardial infarction (all-cause mortality) Did not separately consider both traditional and COX-2 selective NSAIDs (exposure was use of NSAIDs as a group)
4. Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. Arch Intern Med 2002;162:1111-5.	Risk in users not compared with non-users (reference group was naproxen users) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were naproxen and 'other nonaspirin NSAIDs' as a group)
5. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: An observational cohort study. Lancet 2002;359:118-23.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were 'nonaspirin NSAIDs' as a group)
6. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-3.	Study is a cohort designed to allow for time-to-event analysis
7. Schlienger RG, Jick H, Meier CR. Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction. Br J Clin Pharmacol 2002;54:327-32.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were fenbufen, flurbiprofen ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam) Limited external validity due to selection of population (study excluded subjects with preexisting diagnosed cardiovascular or metabolic diseases)
8. Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002;162:1099-104.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were 'any NSAID', ibuprofen, naproxen)
9. Watson DJ, Rhodes T, Cai B, Guess HA. Lower risk of thromboembolic	Outcome was acute thromboembolic cardiovascular events defined as a

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med 2002;162:1105-10.	composite of myocardial infarction, sudden death, or cerebrovascular event Did not separately consider both traditional and COX-2 selective NSAIDs (exposure was naproxen) Limited external validity due to selection of population (limited to patients with rheumatoid arthritis)
10. Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM. Aspirin, ibuprofen, and mortality after myocardial infarction: Retrospective cohort study. BMJ 2003;327:1322-23.	Outcome was not myocardial infarction (mortality) Risk in users not compared with non-users (reference group was aspirin users) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were aspirin, aspirin and ibuprofen, aspirin and other NSAIDs)
11. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361:573-4.	Outcome was not myocardial infarction (all-cause mortality, cardiovascular mortality) Risk in users not compared with non-users (reference group was aspirin users) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were aspirin, aspirin and ibuprofen)
12. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Discontinuation of nonsteroidal anti-inflammatory drug therapy and risk of acute myocardial infarction. Arch Intern Med 2004;164:2472-6.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were NSAIDs as a group and comprised acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid)
13. Garcia Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004;109:3000-6.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were diclofenac, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, piroxicam, 'other NSAIDs') *
14. Kimmel SE, Berlin JA, Reilly M, et al. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. J Am Coll Cardiol 2004;43:985-90.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were aspirin, nonselective NSAIDs as a group, ibuprofen, naproxen) †
15. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-	Outcome was not myocardial infarction (congestive heart failure)

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
based cohort study. Lancet 2004;363:1751-6.	
16. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. Ann Intern Med 2004;164:852-6.	Risk in users not compared with non-users (reference group was aspirin) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were aspirin, aspirin and ibuprofen)
17. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004;109:2068-73.	Risk in users not compared with non-users (exposures were celecoxib or rofecoxib and reference groups were alternative coxib or no current use of that coxib or ibuprofen or naproxen or other NSAID)
18. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR. Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction. Pharmacotherapy 2005;25:503-10.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid)
19. Garcia Rodriguez LA, Gonzalez-Perez A. Long-term use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. BMC Med 2005;3.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were NSAIDs as a group, diclofenac, ibuprofen, naproxen) *
20. Hudson M, Baron M, Rahme E, Pilote L. Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. J Rheumatol 2005;32:1589-93.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were NSAIDs as a group, diclofenac, ibuprofen, naproxen, 'other NSAIDs')
21. Hudson M, Richard H, Pilote L. Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: population based study. BMJ 2005;330:1370.	Outcome was not myocardial infarction (congestive heart failure, congestive heart failure and mortality) Risk in users not compared with non-users (exposures were celecoxib, rofecoxib, NSAIDs as a group and reference groups were alternative coxib users or NSAID users as a group)
22. 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;142:481-9. (Lévesque LE, Brophy JM, Zhang B. Time variations in the risk of myocardial infarction among elderly users of COX-2 inhibitors. CMAJ 2006;174:1563-9. Brophy JM, Levesque LE, Zhang B. The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction. Heart 2007;93:189-94.)	Availability of a larger source cohort (superseded by RAMQ study included in this IPD MA)
23. Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective	Outcome was not myocardial infarction (ischemic stroke)

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: A nested case-control study. Stroke 2006;37:1725-30.	
24. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation 2006;113:1578-87.	Outcome was major cardiovascular events, a composite of nonfatal myocardial infarction, fatal coronary heart disease or nonfatal and fatal stroke
25. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation 2006;113:2906-13.	Study is a cohort designed to allow for time-to-event and case-crossover analyses ‡
26. Hawkey CJ, Hawkey GM, Everitt S, Skelly MM, Stack WA, Gray D. Increased risk of myocardial infarction as first manifestation of ischaemic heart disease and nonselective nonsteroidal anti-inflammatory drugs. Br J Clin Pharmacol 2006;61:730-7.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were aspirin, non-aspirin non-naproxen NSAID, aspirin and naproxen) §
27. Huang WF, Hsiao FY, Tsai YW, Wen YW, Shih YT. Cardiovascular events associated with long-term use of celecoxib, rofecoxib and meloxicam in Taiwan: an observational study. Drug Saf 2006;29:261-72.	Risk in users not compared with non-users (exposures were meloxicam, celecoxib, rofecoxib; reference group was meloxicam users)
28. Huang WF, Hsiao FY, Wen YW, Tsai YW. Cardiovascular events associated with the use of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) versus a cyclooxygenase-2 inhibitor (celecoxib): A population-based analysis in Taiwanese adults. Clin Ther 2006;28:1827-36.	Risk in users not compared with non-users (exposures were celecoxib, etodolac, nabumetone, ibuprofen, naproxen; reference group was celecoxib users)
29. Jick H, Kaye JA, Russmann S, Jick SS. Nonsteroidal antiinflammatory drugs and acute myocardial infarction in patients with no major risk factors. Pharmacotherapy 2006;26:1379-87.	Limited external validity due to selection of population (limited to patients without major cardiovascular risk factors) ‖
30. McGettigan P, Han P, Henry D. Cyclooxygenase-2 inhibitors and coronary occlusion--exploring dose-response relationships. Br J Clin Pharmacol 2006;62:358-65.	Outcome was acute coronary syndrome defined as unstable angina or acute myocardial infarction Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were celecoxib, rofecoxib, other NSAIDs as a group)
31. Motsko SP, Rascati KL, Busti AJ, et al. Temporal relationship between use of NSAIDs, including selective COX-2 inhibitors, and cardiovascular risk. Drug Saf 2006;29:621-32.	Outcome was a composite of acute myocardial infarction, death from coronary heart disease, or cerebrovascular event Risk in users not compared with non-users (exposures were etodolac, ibuprofen, naproxen, celecoxib, rofecoxib; reference group was ibuprofen users)

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
32. Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55:531-6.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were traditional NSAIDs as a group, COX-2 inhibitors as a group) Limited external validity due to selection of population (limited to patients with rheumatoid arthritis)
33. Velentgas P, West W, Cannuscio CC, Watson DJ, Walker AM. Cardiovascular risk of selective cyclooxygenase-2 inhibitors and other non-aspirin non-steroidal anti-inflammatory medications. Pharmacoepidemiol Drug Saf 2006;15:641-52.	Outcome was a composite of acute coronary syndrome, acute myocardial infarction, and sudden cardiac death Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, naproxen, celecoxib, rofecoxib; reference group was ibuprofen/diclofenac users)
34. Jick SS, Kaye JA, Jick H. Diclofenac and acute myocardial infarction in patients with no major risk factors. Br J Clin Pharmacol 2007;64:662-7.	Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, naproxen) Limited external validity due to selection of population (limited to patients without major cardiovascular risk factors)
35. Lee TA, Bartle B, Weiss KB. Impact of NSAIDS on mortality and the effect of preexisting coronary artery disease in US veterans. Am J Med 2007;120.	Outcome was a composite of cardiovascular events Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were NSAIDs as a group, COX-2 selective NSAIDs as a group)
36. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology 2007;46:435-8.	Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, naproxen, celecoxib, rofecoxib; reference group was acetaminophen)
37. Rahme E, Watson DJ, Kong SX, Toubouti Y, LeLorier J. Association between nonnaproxen NSAIDs, COX-2 inhibitors and hospitalization for acute myocardial infarction among the elderly: a retrospective cohort study. Pharmacoepidemiol Drug Saf 2007;16:493-503.	Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, celecoxib, rofecoxib; reference groups were one of these exposures or diclofenac/ibuprofen)
38. Spalding WM, Reeves MJ, Whelton A. Thromboembolic cardiovascular risk among arthritis patients using cyclooxygenase-2-selective inhibitor or nonselective cyclooxygenase inhibitor nonsteroidal anti-inflammatory drugs. Am J Ther 2007;14:3-12.	Outcome was a composite of acute myocardial infarction or stroke Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were non-selective NSAIDs as a group, celecoxib, rofecoxib)
39. Abraham NS, Castillo DL, Hartman C. National mortality following upper gastrointestinal or cardiovascular events in older veterans with recent nonsteroidal anti-inflammatory drug use. Aliment Pharmacol Ther 2008;28:97-106.	Outcome was not myocardial infarction (all-cause mortality after gastrointestinal or cardiovascular events) Did not separately consider both traditional and COX-2 selective NSAIDs (exposure was NSAIDs as a group)

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
40. Cunnington M, Webb D, Qizilbash N, et al. Risk of ischaemic cardiovascular events from selective cyclooxygenase-2 inhibitors in osteoarthritis. Pharmacoepidemiol Drug Saf 2008;17:601-8.	Outcome was a composite of acute myocardial infarction or ischemic stroke Risk in users not compared with non-users (exposures were chronic users of naproxen, celecoxib, rofecoxib - defined as at least 90 days continuous use with at least two prescriptions; reference group was non-chronic users)
41. Haag MD, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Cyclooxygenase selectivity of nonsteroidal anti-inflammatory drugs and risk of stroke. Arch Intern Med 2008;168:1219-24.	Outcome was not myocardial infarction (stroke)
42. Hammad TA, Graham DJ, Staffa JA, Kornegay CJ, Dal Pan GJ. Onset of acute myocardial infarction after use of non-steroidal anti-inflammatory drugs. Pharmacoepidemiol Drug Saf 2008;17:315-21.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were traditional NSAIDs as a group, COX-2 selective NSAIDs as a group) Limited external validity due to selection of population (limited to patients without major cardiovascular risk factors)
43. Roumie CL, Mitchel EF, Jr., Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke 2008;39:2037-45.	Outcome was not myocardial infarction (stroke)
44. Solomon DH, Glynn RJ, Rothman KJ, et al. Subgroup analyses to determine cardiovascular risk associated with nonsteroidal antiinflammatory drugs and coxibs in specific patient groups. Arthritis Rheum 2008;59:1097-104.	Outcome was a composite of cardiovascular events (myocardial infarction, stroke, congestive heart failure, and cardiovascular death)
45. Sorensen R, Abildstrom SZ, Torp-Pedersen C, Gislason GH. Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs in high doses increases mortality and risk of reinfarction in patients with prior myocardial infarction. J Cardiovasc Nurs 2008;23:14-9.	Study is a cohort designed to allow for time-to-event and case-crossover analyses
46. van Staa TP, Rietbrock S, Setakis E, Leufkens HG. Does the varied use of NSAIDs explain the differences in the risk of myocardial infarction? J Intern Med 2008;264:481-92.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were ibuprofen, diclofenac, naproxen, meloxicam, indomethacin, piroxicam, mefenamic acid)
47. Warner JJ, Weideman RA, Kelly KC, et al. The risk of acute myocardial infarction with etodolac is not increased compared to naproxen: a historical cohort analysis of a generic COX-2 selective inhibitor. J Cardiovasc Pharmacol Ther 2008;13:252-60.	Risk in users not compared with non-users (exposures were etodolac, naproxen, celecoxib, or rofecoxib; reference group was naproxen)

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
48. Fosbol EL, Gislason GH, Jacobsen S, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. Clin Pharmacol Ther 2009;85:190-7.	Outcome was a composite of myocardial infarction and all-cause death Limited external validity due to selection of population (limited to healthy individuals)
49. Haara M, Heliovaara M, Arokoski JPA, et al. Regular use of traditional analgesics predicts major coronary events: A cohort study. Ther Clin Risk Manag 2009;5:9-15.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposure was analgesics as a group)
50. Roumie CL, Choma NN, Kaltenbach L, Mitchel EF, Jr., Arbogast PG, Griffin MR. Non-aspirin NSAIDs, cyclooxygenase-2 inhibitors and risk for cardiovascular events-stroke, acute myocardial infarction, and death from coronary heart disease. Pharmacoepidemiol Drug Saf 2009;18:1053-63.	Outcome was a composite of cardiovascular events (acute myocardial infarction, stroke, or out of hospital CHD death)
51. Bueno H, Bardaji A, Patrignani P, Martin-Merino E, Garcia-Rodriguez LA. Use of non-steroidal antiinflammatory drugs and type-specific risk of acute coronary syndrome. Am J Cardiol 2010;105:1102-6.	Outcome was acute coronary syndrome defined as unstable angina or acute myocardial infarction
52. Chang CH, Shau WY, Kuo CW, Chen ST, Lai MS. Increased risk of stroke associated with nonsteroidal anti-inflammatory drugs: A nationwide case-crossover study. Stroke 2010;41 (9):1884-90.	Outcome was not myocardial infarction (stroke)
53. De Vries F, Setakis E, Van Staa TP. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. Br J Clin Pharmacol 2010;70 (3):429-38.	Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were paracetamol, ibuprofen, paracetamol and ibuprofen)
54. Fosbol EL, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes 2010;3 (4):395-405.	Limited external validity due to selection of population (limited to healthy individuals)
55. Gudbjornsson B, Thorsteinsson SB, Sigvaldason H, et al. Rofecoxib, but not celecoxib, increases the risk of thromboembolic cardiovascular events in young adults-a nationwide registry-based study. Eur J Clin Pharmacol 2010;66:619-25.	Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, naproxen, celecoxib, rofecoxib; reference group was diclofenac) [¶]
56. Mangoni AA, Woodman RJ, Gaganis P, Gilbert AL, Knights KM. Use of non-steroidal anti-inflammatory drugs and risk of incident myocardial infarction and heart failure, and all-cause mortality in the Australian veteran community. Br J Clin Pharmacol 2010;69:689-700.	Risk in users not compared with non-users (exposures were diclofenac, ibuprofen, naproxen, meloxicam) [a]
57. Pratt N, Roughead EE, Ryan P, Gilbert AL. Differential impact of NSAIDs	Did not separately consider both traditional and COX-2 selective NSAIDs

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
on rate of adverse events that require hospitalization in high-risk and general veteran populations: a retrospective cohort study. Drugs Aging 2010;27:63-71.	(exposure was NSAIDs as a group)
58. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf 2011;20:754-62.	Not limited to period before rofecoxib withdrawal (inclusion years 2003-2005) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were opioids, rofecoxib, celecoxib, valdecoxib)
59. Caughey GE, Roughead EE, Pratt N, Killer G, Gilbert AL. Stroke risk and NSAIDs: an Australian population-based study. Med J Aust 2011;195:525-9.	Outcome was not myocardial infarction (stroke) Not limited to period before rofecoxib withdrawal (inclusion years 2001-2008)
60. Grimaldi-Bensouda L, Rossignol M, Danchin N, et al. Risk of ST versus non-ST elevation myocardial infarction associated with non-steroidal anti-inflammatory drugs. Heart 2011;97:1834-40.	Not limited to period before rofecoxib withdrawal (inclusion years 2007-2009) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were diclofenac, ibuprofen, naproxen)
61. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation 2011;123:2226-35. (Schjerning-Olsen AM, Fosbol EL, Lindhardsen J, et al. Long-term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: a nationwide cohort study. Circulation 2012;126:1955-63.)	Outcome was a composite of all-cause death and reinfarction Not limited to period before rofecoxib withdrawal (inclusion years 1997-2006)
62. Schmidt M, Pedersen L, Maeng M, et al. Nonsteroidal antiinflammatory drug use and cardiovascular risks after coronary stent implantation. Pharmacotherapy 2011;31 (5):458-68.	Not limited to period before rofecoxib withdrawal (inclusion years 2002-2005) Limited external validity due to selection of population (limited to patients undergoing coronary stent implantation)
63. Back M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of rofecoxib. Eur Heart J 2012;33 (15):1928-33.	Not limited to period before rofecoxib withdrawal (inclusion years 2005-2008) Did not separately consider both traditional and COX-2 selective NSAIDs (exposures were celecoxib, etoricoxib)
64. Chao TF, Liu CJ, Chen SJ, et al. The association between the use of non-steroidal anti-inflammatory drugs and atrial fibrillation: A nationwide	Outcome was not myocardial infarction (atrial fibrillation) Not limited to period before rofecoxib withdrawal (inclusion years 2000-

Study (additional references)	Reasons for non-eligibility (First reason listed cross-referenced to study flow chart as main reason)
case-control study. Int J Cardiol 2012.	2009)
65. Lamberts M, Fosbol EL, Olsen AM, et al. Ongoing treatment with non-steroidal anti-inflammatory drugs at time of admission is associated with poorer prognosis in patients with first-time acute myocardial infarction. Int J Cardiol 2012.	Outcome was a composite of all-cause death and reinfarction Not limited to period before rofecoxib withdrawal (inclusion years 1997-2006)
66. Liu SS, Bae JJ, Bieltz M, Ma Y, Memtsoudis S. Association of perioperative use of nonsteroidal anti-inflammatory drugs with postoperative myocardial infarction after total joint replacement. Reg Anesth Pain Med 2012;37:45-50.	Not limited to period before rofecoxib withdrawal (inclusion years 2009-2010) Limited external validity due to selection of population (limited to patients undergoing total joint replacement)
67. Shau WY, Chen HC, Chen ST, et al. Risk of new acute myocardial infarction hospitalization associated with use of oral and parenteral non-steroidal anti-inflammation drugs (NSAIDs): A case-crossover study of Taiwan's National Health Insurance claims database and review of current evidence. BMC Cardiovascular Disorders 2012;12.	Not limited to period before rofecoxib withdrawal (inclusion year 2006)

* Use was considered 'current' when the supply of the most recent prescription lasted until index date or ended in the 30 days before the index date

† Case-control study in which exposure ascertainment was by structured telephone interview in the participants' homes (definition of non-use not given); cases were interviewed only if they could be reached within four months of their MI

‡ In case-crossover study, case period 0–30 days before event and control periods 60-90 and 90-120 days before event

§ Case-control study in which current exposure was ascertained as any exposure to any non-aspirin NSAID during the week prior to the first onset of symptoms (cases and hospital controls) or interview (community controls)

‖ A subject was considered exposed if they had received two or more prescriptions for the study NSAID of interest before the index date but after January 1, 1999. Those with receipt of only one prescription of the study NSAID before their index date composed the reference group.

¶ Only those individuals who received the same NSAID or coxib on at least two occasions were included in the risk analysis

[a] Exposure was total prescription supplies to each of the different NSAIDs in the last 2 years

Web Table 3: Systematic review of healthcare database studies of NSAIDs and acute MI – Studies found not suitable for answering research question

Study	Reasons for exclusion
1. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163:481-6.	Survival run-in period when analysing outcome (immortal time bias) "To exclude sporadic users of NSAID therapy, we included only individuals who were dispensed at least 2 successive prescriptions and who received enough drug for at least 30 days of observation." Access to IPD not requested
2. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005;142:157-64.	Potential for important misclassification of exposure (due to possible recall bias) "We collected exposure and covariate data for all case-patients and controls by using the same structured telephone interview. " "To maximize the validity of drug exposure information, case-patients were interviewed only if they could be reached within 4 months of their MI. Controls were interviewed within 4 months of their initial identification to prevent selection bias. " "The a priori definition of exposure was any nonselective NSAID, COX-2 inhibitor, or aspirin use within 1 week before the index date (the date of first onset of symptoms of MI for case-patients and the date of the telephone interview for controls)." Permission to access IPD requested but denied
3. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365:475-81.	Potential for important misclassification of exposure (based on definition of 'current' and 'past' use in the IPD MA, this study compared current use to past use) "Remote users were those whose drug supply ended more than 60 days before the index date … We used conditional logistic regression to compare current exposure to a specific NSAID with remote exposure to any NSAID." Permission to access IPD requested but denied
4. van der Linden MW, van der Bij S, Welsing P, Kuipers EJ, Herings RM. The balance between severe cardiovascular and gastrointestinal events among users of selective and non-selective non-steroidal anti-inflammatory drugs. Ann Rheum Dis 2009;68:668-73.	Potential for important misclassification of exposure (based on definition of 'current' and 'past' use in the IPD MA, this study compared current use to past use) "Subjects were defined as current users if the duration of the COX-2 inhibitor or t-NSAID prescription closest to and preceding the event date overlapped with that date. Remote users were those whose drug supply ended more than 60 days prior to that date."

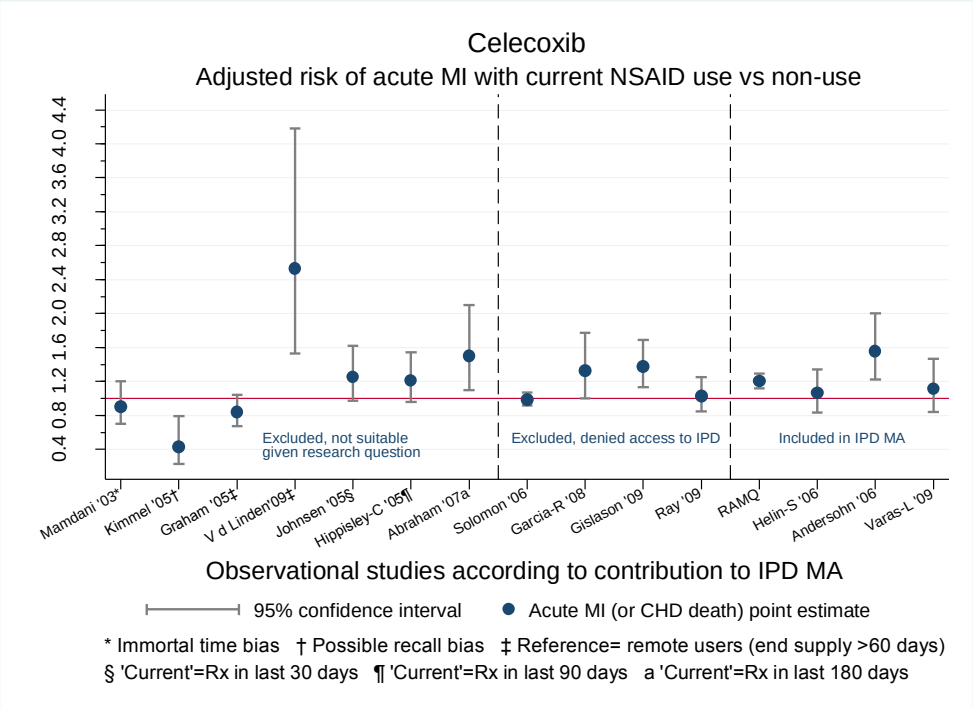
Study	Reasons for exclusion
	"Risk of first hospitalisation for acute myocardial infarction … with current use of cyclo-oxygenase 2 (COX-2) inhibitors and traditional non-steroidal anti-inflammatory drugs (tNSAIDs), compared to remote use" Access to IPD not requested
5. Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. Arch Intern Med 2005;165:978-84.	Potential for important misclassification of exposure (based on exposure definitions in the IPD MA, current use in this study may correspond to either 'current' or 'recent' use in the IPD MA) "We classified individuals according to their most recent use: current users (having filled a prescription within 0-30 days) ... or nonusers (no recorded prescriptions for any nonaspirin NSAID before index date)." Permission to access IPD requested but denied
6. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;330:1366.	Time dependency of drug exposure not adequately established (based on exposure definitions in the IPD MA, current use in this study may correspond to 'current', 'recent' or 'past' use in the IPD MA) "We coded the time since last prescription as not prescribed within the past three years, prescribed within 90 days (defined as current use) ..." Permission to access IPD requested but denied
7. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. Aliment Pharmacol Ther 2007;25:913-24.	Time dependency of drug exposure not adequately established (based on exposure definitions in the IPD MA, current use in this study may correspond to 'current', 'recent' or 'past' use in the IPD MA) "The incidence density (number of events/person-years of follow-up) of MI and CVA was calculated for the 180 days following index prescription." Access to IPD not requested

Web Table 4: Systematic review of healthcare database studies of NSAIDs and acute MI – Studies excluded due to denied access to patient-level data

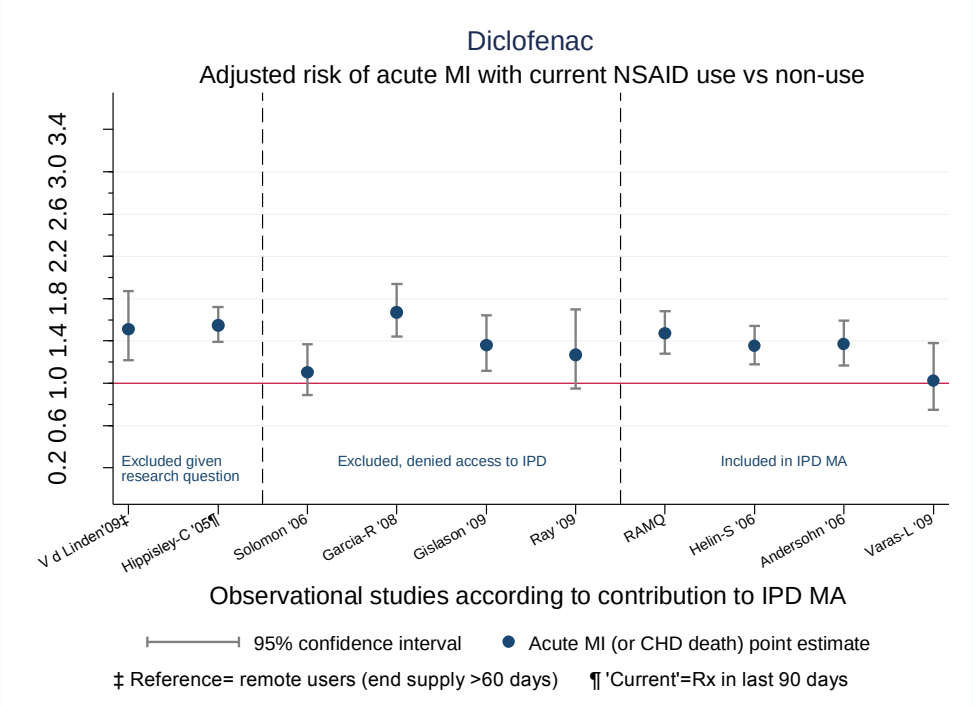
Study	Risk of acute myocardial infarction (MI) with NSAIDs estimated by
1. Solomon DH, Avorn J, Sturmer T, Glynn RJ, Mogun H, Schneeweiss S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: High-risk subgroups and time course of risk. Arthritis Rheum 2006;54:1378-89.	Incidence rate ratio for current use of NSAID (based on pharmacy dispensing records) compared with non-use "Longitudinal exposure was assessed on a daily basis starting with the index date."
2. Garcia Rodriguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. J Am Coll Cardiol 2008;52:1628-36.	Incidence rate ratio for current use of NSAID (based on prescription writing) compared with nonuse (defined as no recorded use in the year before the index date) "We categorized exposure to NSAIDs into mutually exclusive time windows... Duration of use was computed summing the days included in the time frame of "consecutive" prescriptions…"
3. Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 2009;169:141-9.	Hazard ratio for current use (based on pharmacy dispensing records) compared with non-use
4. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes 2009;2:155-63.	Incidence rate ratio for current use of NSAID (based on pharmacy dispensing records) compared with non-use of any NSAIDs in the past 365 days "Each person-day of follow-up was classified according to current use of individual NSAIDs."

Web Table 5: Systematic review of healthcare database studies of NSAIDs and acute MI – Studies included in the IPD MA

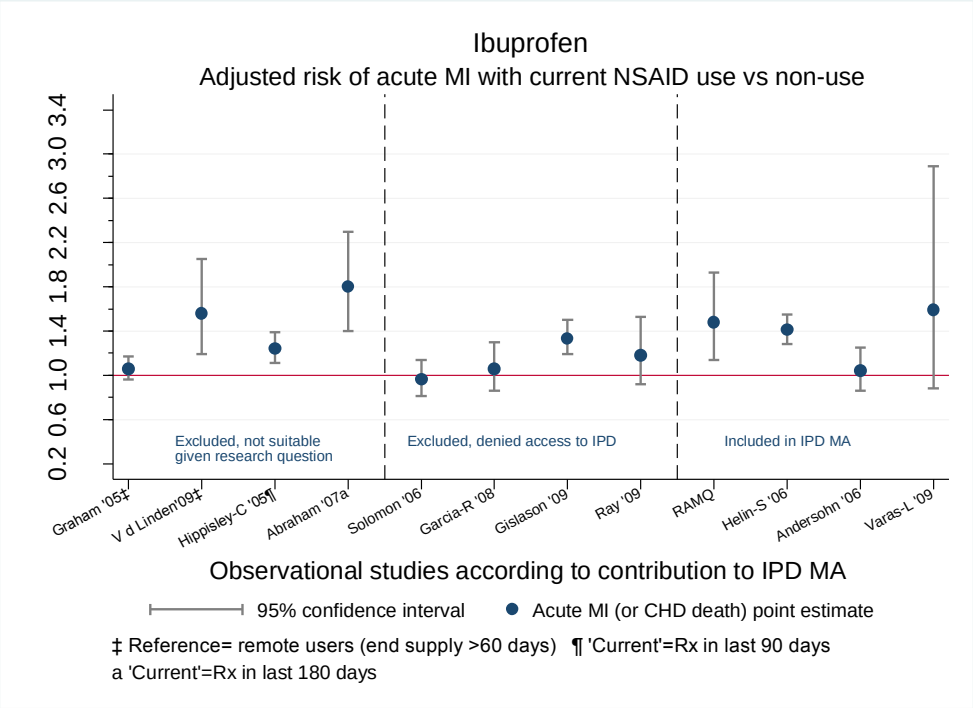
Study	**Risk of acute myocardial infarction with NSAIDs estimated by**
1. RAMQ study. Dataset created for this IPD MA	Rate ratio with current use of NSAID (defined as duration of prescription supply that overlapped with the index date – based on pharmacy dispensing) compared with non-use in the year preceding the index date
2. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J. 2006 Jul;27(14):1657-63.	Odds ratio with current use of NSAID (defined as duration of prescription supply that overlapped with the index date – based on pharmacy dispensing) compared with non-use in the 2 years preceding the index date
3. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial infarction. Circulation. 2006;113(16):1950-7.	Rate ratio with current use of NSAID (defined as duration of prescription supply that overlapped with the index date or ended in the 14-day period before the index date – based on medical scripts) compared with non-use in the year preceding the index date
4. Varas-Lorenzo C, Castellsague J, Stang MR, et al. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. Pharmacoepidemiol Drug Saf. 2009;18(11):1016-25.	Odds ratio with current use of NSAID (defined as duration of prescription supply that overlapped with the index date or ended in the 7-day period before the index date – based on pharmacy dispensing) compared with non-use in the year preceding the index date



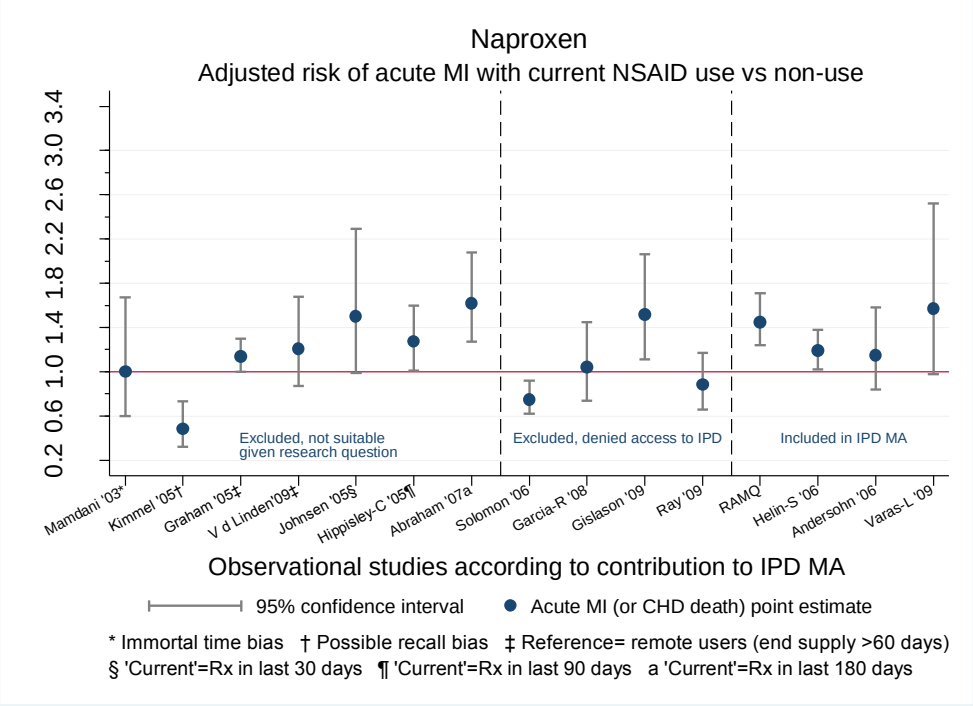
Web Figure 2: Acute MI risks with Celecoxib according to study contribution to IPD MA: 1) excluded, not suitable given research question; 2) excluded, denied access to IPD; 3) included



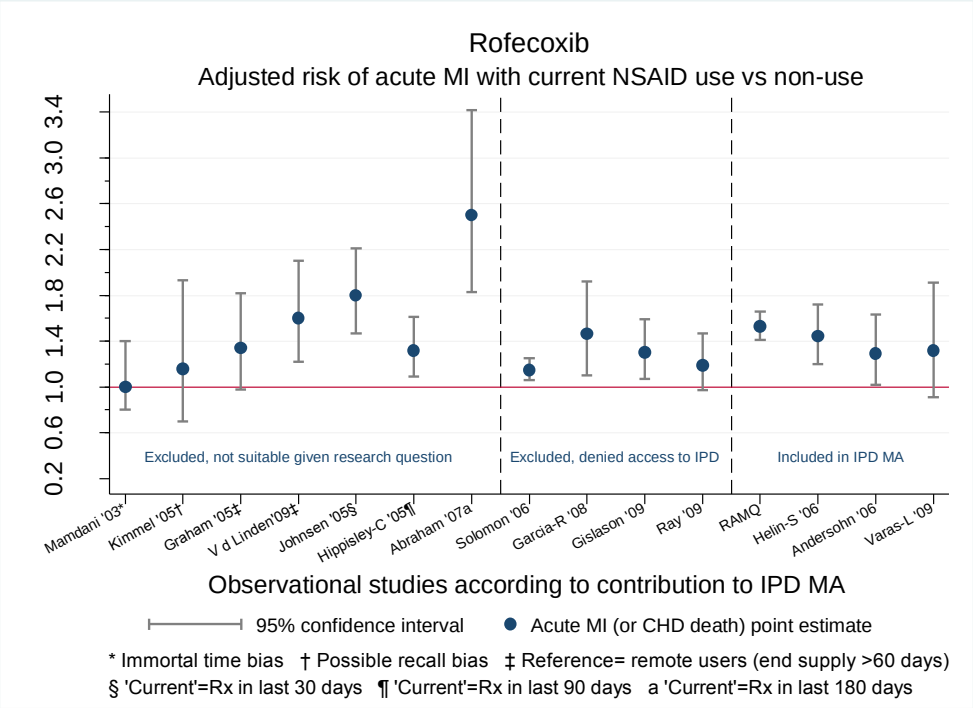
Web Figure 3: Acute MI risks with Diclofenac according to study contribution to IPD MA: 1) excluded, not suitable given research question; 2) excluded, denied access to IPD; 3) included



Web Figure 4: Acute MI risks with Ibuprofen according to study contribution to IPD MA: 1) excluded, not suitable given research question; 2) excluded, denied access to IPD; 3) included



Web Figure 5: Acute MI risks with Naproxen according to study contribution to IPD MA: 1) excluded, not suitable given research question; 2) excluded, denied access to IPD; 3) included



Web Figure 6: Acute MI risks with Rofecoxib according to study contribution to IPD MA:
1) excluded, not suitable given research question; 2) excluded, denied access to IPD; 3) included