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Use of Aspirin and NSAIDs to Prevent Colorectal Cancer

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the U.S. This report was requested and funded by the Centers for Disease Control and Prevention (CDC). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Structured Abstract

Objectives: The purpose of this report was to systematically review the literature on the effectiveness of aspirin (ASA), non-aspirin nonsteroidal anit-inflammatory drugs (non-ASA NSAIDs), and cyclooxygenase-2 inhibitors (COX-2 inhibitors) for the chemoprevention of colorectal cancer (CRC) and CRC-related mortality in average-risk individuals. The review also assessed the harms associated with the use of these agents and their cost effectiveness.

Data Sources: To review the effectiveness of ASA/NSAIDs, Medline 1966 to week 3, November 2004; Embase 1980 to week 47, 2004, and CENTRAL, the Cochrane Collaboration's registry of clinical trials (Issue 4, 2004) were searched. To identify recent systematic reviews of NSAIDs that address harms, Medline (2003 to week 3, November 2004), the Cochrane Database of Systematic Reviews (CDSR), and DARE (Cochrane Library, 3rd Quarter 2004) were searched. Additional material potentially relevant to the economic analysis question was sought in Medline (1966 to week 3, November 2004), HealthStar (1987 to November 2004), Embase (1980 to 2004 Week 50), NHS EED, and HTA databases of The Cochrane Library (4th Quarter 2004). The TRIP (www.tripdatabase.com) database was also searched (December 14, 2004).

Methods: RCTs, case-control, and cohort studies were sought for the effectiveness of ASA, NSAIDs, and COX-2 inhibitors to prevent colorectal adenomas (CRAs,), CRC, and mortality. Systematic reviews were sought for the harms of these agents, and cost-effectiveness analyses were sought for each of the agents. Multilevel screening by two independent reviewers was conducted to identify studies to be included based on predefined inclusion criteria. Data from included studies were abstracted and their quality assessed. Included studies were grouped based on an *a priori* defined hierarchy, and statistical pooling was conducted only if clinically and statistically appropriate.

Results: Effectiveness for Chemoprevention: Regular use of ASA appears to be effective at reducing the incidence of CRA. Two of the four RCTs demonstrated statistically significant relative risk reductions (RRR) in CRAs (relative risk [RR]=0.44, and 0.58), whereas the remaining two RCTs, including the Physicians Health Study (PHS), showed no benefit. The pooled estimate, however, was statistically significant (RR=0.82; 95% CI: 0.7-0.95). Pooled estimates for the case-control (RR=0.87; 95% CI: 0.77-0.98) and cohort studies (RR=0.72; 95% CI: 0.61-0.85) also showed a statistically significant relative risk reduction in CRAs with ASA. The use of non-ASA NSAIDs appeared to be associated with somewhat higher RRRs (pooled estimate - RR= 0.43; 95% CI: 0.26-0.70), and based on a very limited number of studies, the RRRs are likely higher still for higher-risk individuals than for those at average risk. The regular use of ASA was associated with RRRs of 15% to 40% for CRC incidence. The pooled RR for cohort studies was 0.78 (95% CI: 0.63-0.97). The RCT data of the effect of ASA on CRC incidence was, however, negative, both in the PHS and the newly published Women's Health Study (WHS). The pooled estimates for non-ASA NSAIDs suggest somewhat greater RRRs, on

the order of 30% to 40%, and longer duration of use of ASA/NSAIDs and higher doses also appear to offer greater protection.

Only two observational studies considered the effect of ASA/NSAIDs on CRC mortality. Among the observational studies, one study reported that CRC mortality was reduced by about 40% with ASA use for more than 15 years, whereas, the other found nonsignificant trends towards increased standardized mortality ratios for bowel and rectal cancers with ibuprofen. The recently published WHS found no benefit of ASA on CRC mortality.

Harms: The use of ASA is associated with an increased incidence of important ulcer complications with RRs of 1.5 to 3.0. The annualized incidence of these events for non-ASA NSAIDs, as a group, is approximately 1.5% to 2.0% in average-risk individuals with arthritis. As a "class," COX-2 inhibitors are associated with fewer endoscopic ulcers and clinically important ulcer complications, when compared with non-ASA NSAIDs overall, with pooled RRRs of about 50% for important ulcer complications.

In individuals with low-to-average cardiovascular (CV) risk (i.e., the primary prevention population), ASA significantly reduced the incidence of total CV events, but had no effect on coronary heart disease mortality, fatal and nonfatal stroke events, or all cause mortality. In high-risk CV patients (i.e., secondary prevention), the use of ASA significantly reduces all-cause mortality, and CV mortality. There is a paucity of RCT data on the CV harm of non-ASA NSAIDs, but non-naproxen NSAIDs appear to offer no cardioprotection in observational studies, and may actually increase the risk of CV events. Knowledge regarding the CV harms associated with non-ASA NSAIDs and COX-2 inhibitors is in a rapid state of flux. COX-2 inhibitors appear to be associated with an increased risk of CV events.

Cost-Effectiveness: In average-risk populations, and in the context of regular endoscopic screening for CRC, NSAID chemoprevention is presently not cost-effective because of the relatively large costs associated with their adverse effects, as well as their relative inefficacy compared with colonoscopy. To be cost-effective, daily ASA use would have to decrease the CV mortality by 0.1% or more, and it would have to decrease CRC mortality by at least 30%. Additionally, chemoprevention with COX-2 inhibitors, independent of their newly recognized cardiotoxicity, is expensive and their use as an adjunct to colonoscopy is economically acceptable (i.e. ICER less than $100,000/LY saved) if they can prevent CRC mortality by at least 60% and their cost be reduced by at least 75%. In higher-risk groups, the use of COX-2 inhibitors for chemoprevention of CRC is both less effective and considerably more costly than screening protocols, which are in themselves cost effective by all criteria—their use as an adjunct to screening is economically acceptable if their current cost is considerably reduced and if their efficacy as chemopreventive agents is of at least 50%. These results do not account for any potential CV harms of COX-2 inhibitor use.

Conclusions: ASA and non-ASA NSAIDs appear to be effective at reducing the incidence of CRAs and CRC. However, the data on CRC incidence is inconsistent with observational studies, which tend to be positive, whereas, two large RCTs showed no benefit for low-dose ASA every second day on CRC incidence. The effect of ASA/NSAIDs on CRC mortality is also mixed, with one positive and one negative cohort study, and the negative findings of the WHS. There are well-defined GI risks associated with ASA and NSAIDs when used daily for months. There are no quantitative data on GI or CV risk for chronic multiyear use of daily NSAIDs. We found no information regarding the effectiveness of COX-2 inhibitors on these outcomes in average-risk individuals. Available data on COX-2 inhibitors suggest that an absolute risk increase of over 1% for CV events can be anticipated from only 2 to 3 years use, and higher risks may accrue over longer periods. Further, the results of the economic evaluations consistently reveal that chemoprevention is not cost-effective. In the case of ASA, the costs of complications are significant; in the case of COX-2 inhibitors, independently of the recently reported CV toxicity, drug costs are great. Lastly, in addition to emerging CV toxicity, non-ASA NSAIDs are associated with significant GI harms. Arguments can be made for the use of ASA chemoprevention, particularly if used in populations that may benefit from its CVS harms prevention. However, since observational studies suggest that higher doses and prolonged use improve chemopreventative efficacy, more information is required to clarify the optimal dose, starting age, and duration of use of ASA. In addition, clarification of its effect on CRC incidence and mortality, particularly given the evidence that in patients at average CV risk, all-cause mortality is not reduced with the use of ASA.

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CHAPTER 1. INTRODUCTION

This systematic review examines the evidence for the effectiveness of aspirin (ASA) and non-aspirin nonsteroidal anti-inflammatory drugs (non-ASA NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, for the prevention of colorectal adenomas (CRAs), colorectal cancer (CRC), and mortality in asymptomatic individuals. The review also examines the harms associated with the long-term use of these agents, as well as their cost-effectiveness in the setting of chemoprevention.

Background

Cancer accounts for 23% of all deaths in the U.S. It is the second leading cause of death after heart disease overall, and the leading cause of death in those under the age of 65. CRC is the third most common type of cancer in both men and women, and is also the second leading cause of cancer-related deaths. In 2004, it is estimated that there were 146,940 new cases of CRC, and that 56,730 died of the disease (11% and 10% of all cancers, respectively). The incidence of CRC declined beginning in the early 1980s, but has leveled out since the mid-90's; whereas mortality from CRC has continued to decline.[1]

Age is a major risk factor for CRC, with approximately 90% of cases occurring after 50 years of age.[1] Other risk factors for CRC include: a family history of sporadic CRC or colonic polyps; hereditary polyposis and non-polyposis colon cancer syndromes; inflammatory bowel disease; and, other factors such as cholecystectomy, diabetes mellitus, alcoholism, and smoking. Hereditary CRC syndromes account for less than 5% of CRC cases.

Strategies for the prevention of CRC and CRC-related mortality

Two main strategies exist for the prevention of CRC. First, and currently promoted by most medical societies, is screening-based prevention. This strategy relies on the early detection of premalignant polyps and/or early stage CRC. Since it is widely accepted that adenomatous polyps are the precursors of the vast majority of CRC, the early detection and removal of these precursor lesions is presumed to reduce the incidence of CRC, and its related mortality. Even cancers detected by screening are potentially early stage and curable.

CRC fulfills many of the characteristics of a disorder that would benefit from screening at-risk individuals. The disorder has a long and typically clinically silent premalignant and early malignant stage, which can be detected by relatively safe and commonly performed tests. The treatment of the premalignant (polyp) stage and the early malignant stage is highly effective. Surgical treatment of early stage CRC is typically curative without the need for additional therapy. This subject has recently been reviewed by the USPSTF.[2] Several screening methods are available and have been shown to be effective. However, despite the evidence of

effectiveness, adoption of widespread routine screening of eligible individuals by any method continues to be low in the U.S.[3-6]

An alternate or possibly complementary strategy to screening is a preventive strategy. This can include a variety of lifestyle and dietary changes or, as the focus of this report, chemoprevention. Several basic science, population-based, and experimental studies have suggested a protective effect of aspirin (ASA) and non-ASA non-steroidal anti-inflammatory drugs (non-ASA NSAIDs), including COX-2 inhibitors (COX-2 inhibitors), on CRA and CRC. However, these agents are not without harms. Significant gastrointestinal (GI) hemorrhage can occur with all of these agents, though to a lesser extent with the COX-2 inhibitors. Furthermore, these agents have varying cardiovascular and renal toxicities, and recent interest has focused on a potentially prothrombotic effect of selective COX-2 inhibitors. In fact, during the conduct of the present review, two COX-2 inhibitors (rofecoxib, valdecoxib) were withdrawn from the market because of concerns regarding their cardiovascular toxicity, leaving only celecoxib and meloxicam (the least COX-2 selective agents) remaining, and uncertainty regarding the future of others, such as lumiracoxib and etoricoxib. These developments have thrown our understanding of the safety of COX-2 inhibitors and even non-ASA NSAIDs into a state of uncertainty. This is particularly true because it is apparent that although there is a great deal of clinical trial data regarding the safety of these agents, it is available only to a select few, such as those with contacts with manufacturers or regulatory agencies. These developments also have an impact on this review, not only because of the proprietary nature of some of the harms data derived from recent clinical trials, but also because three of the clinical trials were COX-2 polyp prevention trials (Adenomatous Polyp Prevention on Vioxx [APPROVe] trial, and two celecoxib spontaneous adenomatous polyposis [SAP] prevention trials [APC, and preSAP])[7,8] The results of the efficacy portion of these trials are currently unavailable.

These potential harms also have to be considered in light of the potentially long period of exposure to these agents when used for CRC prevention, and specifically whether the harms with prolonged use of these agents are outweighed by their potential benefits, as judged by more objective clinical outcomes such as overall mortality reductions. Furthermore, reductions in CRC mortality would have to be great enough to compete with the mortality reductions of 21% with simple bi-yearly fecal occult blood testing (FOBT), or the 60% reduction with flexible sigmoidoscopy for lesions within reach of that instrument. Further, there are data to suggest that sigmoidoscopy followed by colonoscopy when polyps are found could decrease CRC incidence by up to 80%.[9] The USPSTF strongly recommends screening of men and women over the age of 50 (A recommendation).[2]

If a preventive strategy with NSAIDs is not as effective as screening, it may still have a role as an adjunct, but the risks and cost-effectiveness would need to be favorable.

The purpose of this report was to systematically review the literature on the effectiveness of ASA, non-ASA-NSAIDs, and COX-2 inhibitors, for the chemoprevention of CRC and CRC-

related mortality in average-risk individuals. The review also assessed the harms associated with the use of these agents and their cost effectiveness.

CHAPTER 2. METHODS

The current University of Ottawa EPC's evidence report on the use of aspirin and NSAIDs to prevent CRC is based on a systematic review of the scientific-medical literature which identified and synthesized the results from studies addressing key questions developed in consultation with the USPSTF. The analytical framework presented in Figure 1 was used to guide the development of the literature search in order to address the key questions related to the value and harms related to the use of ASA and NSAIDs for the prevention of CRA, CRC, and mortality reduction. A more comprehensive description of the methods is provided in Appendix 4.

Key questions

The purpose of this evidence report was to synthesize information from relevant studies to address the following basic questions:

- Does aspirin/NSAID use in healthy adults (> 18 years of age) decrease CRC mortality and/or all-cause mortality? (Question 1A)
- What is the magnitude of decreased CRC incidence due to aspirin/NSAID chemoprevention in healthy adults? (Question 1B)
    a) What is the impact (benefits and harms) of different doses of aspirin and of the different classes of NSAIDs?
    b) What is the impact (benefits and harms) for aspirin/NSAID therapy in persons at different levels of CRC risk?
- What is the magnitude of decreased CRA incidence due to aspirin/NSAID chemoprevention in healthy adults? (Question 2)
- What is the magnitude of decreased CRA on CRC in healthy adults? (Question 3)
- What is the magnitude of harms of aspirin/NSAID use in healthy adults (i.e. increased major GI bleeding, hemorrhagic stroke or nephropathy)? (Question 4)

Literature search and strategy

The strategy was developed in Medline and modified for the other databases. For questions 1 and 2, three main concepts were included: NSAIDs or chemoprevention, CRC or intestinal polyps, and relevant study designs. Study designs sought were randomized controlled trials (RCTs), case-control and cohort studies. A comprehensive retrieval strategy for NSAIDs was derived from indexing both Medline and Embase, using reviewer-nominated terms, and examining previous reviews.[10-14]

Terms were derived from the National Cancer Institute (NCI) Cancer topic searches for "Colorectal Cancer" and "Adenomatous polyps." The search was limited to the English language and non-human studies were excluded (Appendix 1). Databases searched were Medline 1966-November week 3, 2004, Embase 1980-week 47 2004 (publication years 2003-2005 only), CENTRAL, and The Cochrane Library Issue 4, 2004. Pubmed Cancer subset was searched for non-Medline material. This search used the NCI search strategy for CRC with free text terms for NSAIDs and COX-2 inhibitors, and was conducted on December 1, 2004.

Additional material for the economic analysis question was sought in Medline (1966 to November Week 3 2004), HealthStar (1987 to November 2004), Embase (1980 to 2004 Week 50), Cochrane Library 4th Quarter 2004, NHS EED, and HTA. The TRIP (www.tripdatabase.com) database was searched December 14, 2004.

A search strategy to detect recent systematic reviews of NSAIDs that appeared to address harm was developed and run in Medline (2003 to November Week 3 2004). Cochrane Database of Systematic Reviews (CDSR) and DARE (Cochrane Library, 3rd Quarter 2004) were searched without date restrictions for all systematic reviews related to NSAIDS.

We implemented a weekly monitoring strategy to detect emerging information on CV harms associated with COX-2 inhibitors. We also monitored the FDA news digest and Health Canada's Health Product Information mailing list for announcements related to COX-2 inhibitors and CV harms (monitoring dates Jan 14, 2005- May 26, 2005).

Study selection methods

1) Effect of NSAIDs on the risk of CRC and/or CRAs

Screening of articles for inclusion was conducted for each screening level by two members of the review team (Appendix 2). An initial screening level to identify potentially relevant articles was followed by a relevance assessment to identify articles meeting inclusion criteria. Conflicts were resolved by consensus.

A third level of screening was included (for questions 1 and 2) to discriminate the different study designs (Appendix 4). Data abstraction (Appendix 2) was performed by one reviewer and was checked by a second reviewer.

Inclusion/exclusion criteria (efficacy):

Design: RCTs, controlled clinical trials, and observational studies (cohorts and case-control) were considered for inclusion if they fulfilled the population, intervention, and outcome criteria detailed below.

Population: Participants at "average-risk" for CRC (i.e., no known risk factors for CRA or CRC other than age); a personal or family history of CRA; or, a family history of sporadic CRC. Familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer syndromes (Lynch I or II) were excluded since these syndromes account for a small percentage of CRC. Secondary prevention studies of patients with a personal history of CRC were also excluded.

Interventions: Included studies assessed the efficacy or effectiveness of ASA, and non-ASA NSAIDs, including COX-2 inhibitors.

Outcomes: The incidence of CRA and/or CRC; reductions in CRC-related mortality or overall mortality.

2) Harms

The GI, CV, and renal harms associated with the use of ASA, non-ASA NSAIDs, and COX-2 inhibitors were sought through identification of systematic reviews due to the vast amount of reviews already done on these topics (see Appendix 5 for more details).

3) Cost-effectiveness

A specific search was conducted to identify cost-effectiveness analyses of chemoprevention with ASA or non-ASA NSAIDs for the prevention of the above listed endpoints.

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as "good", "fair", or "poor" (Appendix 3). A description of the quantitative analysis can be found in Appendix 4.

Figures and Tables are depicted in Appendix 8.

CHAPTER 3. RESULTS

Our comprehensive literature search yielded 1,788 citations. Screening yielded 362 potentially relevant articles that were obtained in full for further review. Of these, 66 studies met our eligibility criteria and were included in the evidence report. More than half of these articles (n=39) were companion or duplicate articles., and nineteen of these were excluded on that basis,[15-33] (Table 2, Appendix 8) as well as two[34,35] of four[34-37] studies from different authors with overlapping patient populations. Although excluded, the duplicate and companion articles were used to fill in any missing data not reported in the articles that we used. One study was also excluded because the patient population encompassed a significant proportion of subjects with a personal history of CRC.[38] The final study sample included 39 unique studies of effectiveness and five economic evaluations (see Figure 2 [Appendix 8], QUOROM flowchart [Appendix 7], and Table 3 [Appendix 8]). Five[39-43] of the included 44 articles and an additional one[44] addressed the question of the effect of chemoprevention on FOBT.

We identified a great deal of variability in the conduct of the observational studies. These differences centered predominately on the methods of: ascertainment of cases and controls; NSAID exposure measurement and its ascertainment; and, ascertainment of the outcomes of interest. As described in the methods, the presented framework (Figure 1, Appendix 8) was used to divide the studies into appropriate subgroups, based on both clinical and statistical factors.

Key Question 1A.

Does aspirin/NSAID use in healthy adults (>18 years of age) decrease CRC mortality and/or all-cause mortality?

Two cohort studies assessed the effect of ASA and non-ASA NSAIDs on CRC-related mortality. Thun et al.,[45] in a large study of 662,424 patients, found a statistically significant reduction in CRC mortality for men (relative risk [RR]=0.58; 95% CI: 0.36-0.93) and women (RR=0.61; 95% CI: 0.38-0.97) without a history of colon cancer at enrolment (i.e., average risk) and use of ASA for greater than 15 years. The results for ASA use for 1 to 15 years was statistically significant for men (RR=0.72; 95% CI:0.52-0.99), but not women (RR=0.72; 95% CI: 0.51-1.02). Lipworth et al.,[46] in a study of 113,538 participants who filled at least one ibuprofen prescription over a 6-year period, reported increases in all-cause mortality (SMR=1.21; 95% CI: 1.19–1.24) and no reduction in mortality from bowel (SMR=1.05; 95% CI: 0.9–1.2) or rectal cancer (SMR=1.26; 95% CI: 1.0–1.5).

Key Question 1B.

Does aspirin/NSAID use in healthy adults (>18 years of age) decrease CRC incidence?

RCT data

Only one RCT, the Physicians Health Study (PHS), assessed the effect of ASA on CRC incidence.[47] This study failed to demonstrate a benefit of ASA use on invasive CRC prevention (at 5 yrs: RR=1.15; 95% CI: 0.80-1.65; at 12 yrs: RR=1.03; 95% CI: 0.83-1.28).[47] This study also failed to demonstrate a statistically significant difference in stage of CRC at diagnosis, nor differences in rectal bleeding between the ASA and placebo groups.

Observational study data

The effectiveness of ASA/NSAID chemoprevention on CRC incidence was assessed in eight cohort[42,43,48-53] and 12 case-control studies.[36,54-64] A detailed description of the included studies, including their study population and outcome measures, are presented in Evidence Tables 1.2, 1.3, 2.2, and 2.3 (Appendix 8).

Cohort study data: CRC incidence:

Regular use of ASA in average-risk individuals was assessed in five studies.[42,48-50,52] One study demonstrated a non-significant increased risk of CRC with ASA use in men and women separately, and due to its method of reporting, we could not use it in the statistical analysis.[53] Together, the remaining four studies demonstrated a 22% reduction in CRC incidence (RR = 0.78; 95% CI: 0.63-0.97) (Figure 2).

Four studies assessed the effect of duration of ASA use on CRC incidence.[42,48,49,52] Two studies showed no statistically significant reduction of CRC regardless of duration.[48,52] One study demonstrated no benefit of ASA use for less than 5 to 9 years, but a statistically significant reduction in CRC risk with greater than 20 years of use (RR=0.56; 95% CI: 0.36-0.9).[49] Another report demonstrated a statistically significant reduction in the risk of CRC with ASA use of more than twice per week for more than 2 years (RR= 0.54; 95% CI: 0.34-0.83) and for more than 4 years (RR=0.35; 95% CI: 0.16-0.75).[48]

The effect of non ASA-NSAIDs on CRC incidence was assessed in one study which also provided data on duration of use and dose response.[43] Overall, patients with greater than 12 months of non-ASA NSAID use, including use in the preceding year, had a statistically significant reduction in CRC incidence (RR= 0.61; 95% CI: 0.48-0.77). In the dose analyses, only the larger sample "medium" dose endpoint reached statistical significance (RR=0.59; 95% CI: 0.45-0.77).

Use of non-ASA NSAIDs for 1 to 3 years was associated with statistically significant reductions in CRC incidence (RR=0.65; 95% CI: 0.48-0.87), but just failed to reach statistical significance at 4 to 6 years (RR=0.49; 95% CI: 0.24-1.0) (Figure 2).

Case-control data: CRC frequency:

Significant heterogeneity precluded us from combining studies reporting the effect of regular use of ASA on CRC frequency (Figure 3). Four studies reported widely varying statistically significant reductions in the RR of CRC with regular ASA use (RR=0.3 to 0.98),[33,56,57,59] while the other three studies reported non-significant trends in favour of ASA use (RR=0.8-0.9).[36,54,62] These studies differed considerably in the methods for assessment of ASA exposure and outcome assessment.

The effect of duration of ASA use on CRC frequency was assessed in five studies.[23,33,36,54,56] The RRs of CRC with ASA use of 1 to 3 years, and 4 to 6 years were 0.85 (95% CI: 0.72-1.0) and 0.68 (95% CI: 0.54-0.87), respectively. A single study assessed longer durations of use from 7 to 9 years to greater than 14 years, with the individual estimates not reaching statistical significance.[23] Four studies assessed the effect of the recency of use of ASA in this setting.[23,33,36,54] ASA use greater than 1 year from study onset did not reduce the RR of CRC (RR= 0.99; 95%CI: 0.84-1.17),[33,36,54] but its use within 1 year of study onset resulted in a statistically significant reduction in the RR of CRC in two[23,33] of the four studies.[23,33,36,54] (Heterogeneity precluded pooling.)

Dose response was assessed in two studies.[23,36] Rosenberg assessed dosages from 162.5 mg/day to greater than 650 mg/day in a small sample of patients, and found that only the 325 mg/day was associated with reductions in CRC frequency (RR=0.60; 95% CI: 0.5-0.9).[23] Rodriguez assessed dosages of 75 mg to 300 mg/day, and found that only the 300 mg/day dose resulted in a statistically significant reduction in the frequency of CRC (RR=0.60; 95% CI: 0.4-0.9).[36]

Based on four studies, regular use of non-ASA NSAIDs was associated with reductions in CRC frequency.(RR=0.70; 95%: 0.63-0.78).[33,36,57,62] An additional study found a statistically significant reduction in CRC frequency (OR=0.30; 95% CI: 0.08-0.98), but could not be pooled with the others because of the method it used to quantify regular NSAID use.[59] The same analysis for "any NSAID" showed significant statistical heterogeneity. However, five of six studies demonstrated a statistically significant reduction in CRC frequency.[23,55,58,63,64]

Duration of use was assessed in one study for non-ASA NSAIDs,[36] and in four studies for "any NSAID."[23,55,62,63] Some of the subgroups demonstrated significant heterogeneity. The pooled estimates reached statistical significance for "any NSAID" use for the durations of 4 to 6 years (RR=0.38; 95% CI: 0.23-0.620), and for 10 years or greater (RR=0.56; 95% CI: 0.39-0.82).

Dose response was assessed by Peleg using the "calculated cumulative dose" (CCD; defined based on NSAID dosage equivalence and cumulative use). "Any NSAID" use at the moderate (320-700 mg) and high CCDs (>700 mg) was associated with a statistically significant reductions in CRC frequency (RR=0.19; 95% CI: 0.09-0.52, and RR=0.22; 95% CI: 0.09-0.56, respectively). No significant reductions in frequency were observed with use of "any NSAID" at the lowest CCD (RR=0.58; 95% CI: 0.26-1.32).

In this analysis group, regular use of ASA and non-ASA NSAIDs appear to reduce the incidence of CRC. Recent use, and increased dose and duration of use, appear to result in a greater reduction of CRC incidence.

Key Question 2.

What is the magnitude of decreased CRA incidence due to aspirin/NSAID chemoprevention in healthy adults?

RCT data

Four RCTs assessed the effectiveness of chemoprevention on CRA incidence (Figure 4; Appendix 8, Evidence Tables 1.1 and 2.1).[47,65-67] Two of these studies assessed the effect of ASA in patients with a prior history of CRAs,[65,66] and one assessed the effect in average-risk individuals.[47] Overall, the use of ASA in doses of 81-325 mg/day resulted in modest reductions in CRAs. These reductions reached statistical significance in two studies.[65,66] The PHS[47] failed to show a statistically significant reduction in CRAs with ASA (RR=0.86; 95% CI: 0.68-1.1). Baron et al.[65] found a statistically significant benefit when participants took 81 mg of ASA but not 325 mg, for prevention of recurrence of any (RR=0.83; 95% CI: 0.70-0.98 - for 81 mg) or advanced CRAs (RR=0.58; 95% CI: 0.37-0.90 - for 81 mg), respectively. Neither dose was effective at reducing the recurrence of small CRAs (<1.0 cm). In the last study, Benamouzig et al.[66] reported statistically significant reductions in the mean number of CRAs (0.45 vs 0.86 for ASA and placebo, respectively, p=0.01), the recurrence of greater than three CRAs (RR=0.3; 95% CI: 0.1-0.89) or one or more CRAs greater than 1.0 cm (RR=0.44; 95% CI: 0.24-0.82). There were no statistically significant reductions for CRAs greater than 1.0 cm, or for the various categories of advanced adenomas. These authors also reported no statistically significant difference in CRA recurrence between the 160 mg of lysine ASA and 300 mg groups (35% vs 25%, respectively; p=0.23). When these last two studies were combined, a statistically significant reduction in CRA incidence was observed (RR= 0.82; 95% CI: 0.7-0.95) for low-dose ASA.

One RCT assessed the effect of sulindac (non-ASA NSAID) on the regression of CRAs (<1.0 cm) found at flexible sigmoidoscopy.[67] In this short 4-month study, 300 mg of sulindac failed to show a statistically significant regression of the identified CRAs.

The results of this analysis group were mixed. Two RCTs showed a reduction in CRAs with ASA.[68,69] On the other hand, the large PHS did not show a benefit of ASA on CRA incidence. However, participants in this study were relatively young males (mean age 53.2 years) who used a relatively small amount of ASA (325mg of ASA every second day). Participants were also not necessarily free of CRAs at study onset, and outcomes were collected through mailed questionnaires. In contrast, the two positive RCTs were colonoscopy-based studies in populations with a prior history of CRAs, and required an absence of polyps at the start of the study.

Observational study data

The effectiveness of ASA/NSAID chemoprevention on CRA incidence was assessed in four cohort studies[39,42,70,71] and 12 case-control studies.[26,37,41,56,63,72-78] A detailed description of the included studies, including their study population, and outcome measures are presented in Evidence Tables 1.2, and 1.3 (Appendix 8). A summary of the breakdown of the study types, numbers, and outcome measures is presented in Table 1 (Appendix 8). The age and gender distributions of the included studies are presented in Table 6 (Appendix 8).

Cohort study data: CRA incidence:

Regular use of ASA in average-risk individuals was associated with a statistically significant reduction in CRA occurrence (RR=0.72; 95% CI: 0.61-0.85).[39,42] The effect was similar for small and large polyps, and for polyps with advanced histology.[39] A single study of average-risk women assessed the effect of duration of ASA use, and demonstrated a non-significant trend towards a reduction in CRA incidence with increased duration of use from 1 to 3 years to greater than 20 years.[39] This same study also assessed dose response. Taking less than five ASA tablets per week did not significantly reduce the risk of CRA, but taking 6 to 14 or greater than 14 tablets were each associated with a statistically significant reduction in CRA incidence (RR= 0.68; 95% CI: 0.55-0.84; and RR=0.57; 95% CI: 0.42-0.77, respectively) (Figure 5).

In two studies, regular use of ASA by higher-risk patients appeared to reduce the risk of CRAs,[70,71] although this effect reached statistical significance in only one study (RR=0.52; 95% CI: 0.31-0.89).[70] In Tangrea et al.,[71] doses of ASA greater than 325 mg/day were associated with a statistically significant reduction in the risk of CRAs (RR=0.54; 95% CI: 0.3-0.96). The same study also found that regular use of any NSAID in higher-risk patients reduced the incidence of CRAs (RR= 0.64; 95% CI: 0.48-0.85) (Figure 5).

Case-control data: CRA frequency:

Regular use of ASA in average-risk individuals significantly reduced CRA frequency in a pooled analysis of five studies (RR=0.87; 95% CI: 0.77-0.98) (Figure 6).[37,56,72,77,79] The duration and dose response for average-risk individuals was assessed in a single study that reported a non-significant trend in favour of higher ASA dose and longer duration of use.[37]

The regular use of non-ASA NSAIDs[37,72,73,79] or "any NSAID"[41,63,72,74,75] in average-risk individuals was associated with significant reductions in CRA frequency (RR=0.54 [95% CI: 0.4-0.74] and RR= 0.57 [95% CI: 0.46-0.71], respectively). Also with "any NSAID" use, there were statistically significant reductions in CRAs when these agents were used for less than 5 years (RR=0.55 [95% CI: 0.39-0.77]; and even greater reductions with use longer than 5 years (RR= 0.43 [95% CI:0.26-0.70].[41,63,72,74] Dose response was assessed in a single study,[63] which reported a statistically significant reduction in CRA frequency (RR=0.31; 95% CI: 0.11-0.84) for the highest CCD, but not for the lower CCDs (Figure 6).

A single study assessed ASA and non-ASA NSAID use in higher risk individuals, using both population and hospital-based controls.[76] When using the population-based controls, the reduction in CRAs did not reach statistical significance for any endpoint except for the "any NSAID use" for greater than 5 years (RR=0.21; 95% CI: 0.04-0.99). Likewise, using hospital-based controls, only the reduction in CRAs with ASA for greater than 5 years was associated with significant reductions in CRA frequency (RR=0.09; 95% CI: 0.01-0.82) (Figure 6).

Overall, the data suggests that regular use of ASA and non-ASA NSAIDs reduces the risk of CRA. Higher doses, and longer duration of use (trend), appear to be more effective at reducing CRA incidence than low-dose, short-term use. In this analysis group, dose response, duration, and higher-risk patient data was limited.

Key Question 3.

What is the magnitude of decreased CRA incidence on CRC in healthy adults?

Given the wide acceptance of the polyp to cancer pathway (and association), it was felt that there was no need to re-establish this association for the current report.

Key Question 4.

What is the magnitude of harms of aspirin/NSAID use in healthy adults (i.e., increased major GI bleeding, hemorrhagic stroke or nephropathy)?

Twenty-eight systematic reviews were identified for this question. The term review will be equivalent to systematic review in all the descriptions made below. The review characteristics and results are described in the set of Evidence Tables 3 (Appendix 8).

4a. Harms due to aspirin use

There were 11 reviews addressing the magnitude of harms due to ASA use in an adult population (Evidence Table 3.1, Appendix 8),[2,80-89] none of which addressed its nephrotoxocity.

General. Five systematic reviews addressed general ASA harms in the adult population.[2,80-83] The outcomes measured were: all-cause mortality, mortality due to harms, and withdrawal due to harms with the use of ASA.

All-cause mortality. All-cause mortality was measured in all the reviews.[2,80-83] However, mortality and withdrawals due to harms with aspirin use were not reported across the reviews.

For primary prevention, a non-significant reduction in mortality rate was observed for ASA compared with placebo: OR=0.93 (95% CI: 0.84-1.02)[2] and RR=0.94 (95% CI: 0.87-1.01).[81] For secondary prevention, a significantly lower all-cause mortality rate was detected with ASA compared with placebo: RR: 0.82 [95% CI: 0.70-0.99][83]and RR: 0.85 [95% CI: 0.8-0.9][82] The all-cause mortality did not differ between ASA alone, oral anticoagulant drugs (OAD) or a combination of OAD and ASA[80], yet one trial (ASPECT-2) observed a significantly lower mortality rate in the OAD group compared with ASA alone (1.2% vs. 4.5%, $p<0.05$).[90]

CV harms: There were seven reviews addressing the magnitude of CV harms associated with ASA use in an adult population.[2,80-85] The CV events reported were: acute MI, stroke (all, hemorrhagic or ischemic), and death due to CV events.

Three reviews reported the **mortality due to CV events**.[2,81,82] For primary prevention, mortality due to CV events was not significantly different between ASA and placebo [OR: 0.87 (95% CI: 0.70-1.09)[2] and RR: 0.93 [95% CI: 0.83-1.03].[81] For secondary prevention, there was a significant reduction in the mortality due to CV events with ASA (RR: 0.84 [95% CI: 0.79- 0.90]).[82]

Six reviews reported the risk of **acute MI** with ASA use.[2,80-83,85] For primary prevention, a significantly lower risk of MI was reported for ASA compared with placebo in two reviews [OR: 0.72 (95% CI: 0.60- 0.87)[2] and 0.74 (95% CI: 0.68-0.82)][81]. In a third review, although the data was not pooled, a significant absolute risk reduction in MIs was reported in one trial comparing the use of ASA with placebo in patients with arterial hypertension (ARR=0.5%, NNT=200) [85] For secondary prevention, two reviews reported a significant reduction in MI risk with ASA use compared with placebo (RR: 0.68 [95% CI: 0.62-0.74][82] and RR: 0.7 [95% CI: 0.7- 0.9][83]). In one review of ASA use compared with OAD use, one RCT showed a significantly lower incidence of MI (WARIS-II: ASA= 9.7% vs. OAD= 7.4%, $p<0.001$), while the other trials showed no difference.[80]

Six reviews reported on the risk of **acute stroke** (including hemorrhagic and ischemic stroke) with ASA use.[2,81-85] In primary prevention trials, the risk of stroke was no different between ASA and placebo: OR=1.02 [95% CI: 0.85-1.23][2] and RR=1.20 (0.96-1.49)[81] in healthy males; RR=1.02 (95% CI: 0.86-1.21) in patients with vascular risk factors [81]; and, OR=0.94 [95% CI: 0.76-1.17] in patients with hypertension.[85] One review also reported a non-significant OR of 1.4 (95% CI: 0.9-2.0) for hemorrhagic stroke.[2] For secondary prevention, the overall risk of stroke was not statistically different between ASA and placebo (RR 0.88 [95% CI: 0.76-1.02][82] and RR of 0.8 [95% CI: 0.7-1.0],[83] respectively). However, the risk of hemorrhagic stroke was increased by 84% with ASA use (RR: 1.84 [1.24-2.74]).[82] In secondary prevention trials, Serebruany et al. found higher rates of hemorrhagic stroke with higher doses of ASA used (ASA <100 mg/day: 0.3% [95% CI: 0.2-0.4]; ASA 100-325 mg/day: 0.3% [95% CI: 0.2-0.3]; ASA >325 mg/day: 1.1% [95% CI: 0.7-1.5]), while the risk of ischemic stroke was decreased by 18% (RR: 0.82 [0.73-0.92]).[82]

GI harms. GI harms of aspirin (ASA) were considered in seven reviews.[2,83,84,86-89] The included reviews summarized data from RCTs,[2,83,84,86,88,89,91] cohort,[2,87,88] and case-control studies,[87,88] and some considered both low and high doses of ASA.[84,92]

ASA was consistently associated with a statistically significant elevated risk of GI bleeding (Evidence Table 3.1, Appendix 8). In the systematic reviews of RCTs, this increase in RR ranged from 1.6 to 2.5 times that seen with non-ASA users; in the systematic review of cohorts it was 2.2 times, and in the systematic review of case controls it was 3.1 times. The use of ASA was also associated with an increased risk of adverse GI symptoms such as nausea and dyspepsia (OR: 1.7 [95% CI:1.5-1.8]).[89]

A dose effect has been suggested for ASA-induced GI toxicity. One systematic review pooled GI bleeding incidence among large CV studies and found that 2.5% (95% CI: 2.2-2.6) of patients taking >100 mg of ASA/day suffered a GI bleed compared with 1.1% (95% CI: 0.9-1.3) taking less than 100 mg/day.[84] Tramer et al. found that ulcer bleeds or perforation occurred in 0.34% and 0.86% of patients taking low (325 mg q 2 days) and high dose ASA (2.5-5.2 g per day), respectively (difference statistically significant).[88] Similarly, Roderick et al. found a greater risk of GI bleeding with high-dose ASA (1600 mg) (OR: 2.8 [95% CI: 1.3-5.7]), than with a lower dose of 300 mg/day (OR: 1.6 [95% CI: 0.7-4.0).[89] Another systematic review of RCTs demonstrated an increased risk of GI bleeding with low-dose ASA (50-162.5 mg) (RR: 1.59 [95% CI: 1.40-181]), but the rate of GI bleeding with the higher dose (>162 mg) was not statistically different (RR: 1.68 [95% CI: 1.51-1.88]).[86]

Hayden et al.[2] estimated that 3/1000 middle-aged men would suffer a GI bleed over a 5-year period of continuous ASA use, and the rate would be as high as 2/1000 patients per year if older, higher-risk patients were considered. Roderick et al. also suggested that the GI bleeding rate with ASA (300 mg) is 60% higher than with placebo, and represents an attributable rate of 2.5 events/1000 patient-years.[89] The risk of hospitalization because of GI bleeding is also increased (OR: 1.9 [95% CI: 1.1-3.1]), though death from GI bleeding per se is rare.[89] Of the reviews that reported on this latter outcome,[83,88,89] only one death was recorded with ASA use.[88]

4b. Harms due to NSAID use (other than aspirin or COX-2 inhibitors – non-ASA NSAIDs)

CV harms. Only one of the included reviews reported on the CV harms of non-ASA NSAIDs.[93] This cumulative meta-analysis of RCTs of the CV harms of rofecoxib (described below) also reported a systematic review of 11 observational studies of the risk of MI with NSAIDs. Ten of those studies used data from large administrative or clinical databases. The pooled analysis (but not a cumulative one) found a small statistically significant protective effect with naproxen (OR: 0.86; 95% CI: 0.75–0.99). Similar results were obtained when analyses were based on comparisons with non-naproxen NSAIDs (OR: 0.86; 95% CI: 0.75–0.99). These results, particularly the first one, need to be interpreted with caution, especially since there was substantial inter-study heterogeneity in the analyses (I2 = 68%). Unfortunately, this meta-analysis did not report on the risk of CV harms with non-naproxen NSAIDs.

GI harms. The included systematic reviews of the GI harms of NSAIDs summarized data from RCTs,[88,94-97] cohort,[88,94,98] and case-control studies.[88,94,98] Two of the systematic reviews of RCTs focused mainly on prevention of NSAID-induced upper GI toxicity through the use of prophylactic agents or the use of COX-2 inhibitors.[96,97] One of these reported on the rate of GI complications in patients taking NSAIDs.[96]

The doses of NSAIDs described in the included systematic reviews were those generally indicated for that particular NSAID. Dose effects were defined differentially by doses of a given NSAID within a study and/or by comparison to other NSAIDs using dose equivalency tables.

All the included studies reported an increased risk of peptic ulceration and GI hemorrhage with NSAIDs use. Among those taking these medications for greater than 4 weeks, 19% have gastric ulcers,[96] 6% duodenal ulcers,[96] and approximately 20% to 24% have gastroduodenal ulcers greater than 3 mm in size.[88,96] If any ulcers are considered, estimates as high as 40% have been reported, though it is felt that over 80% of these are not clinically significant.[96] The best RCT evidence of the risk with NSAIDs of complicated peptic ulcers, that is, ulcers with perforation, obstruction or bleeding (POB), was derived from the original MUCOSA study,[11,96,99] and collaborated by data from the NSAID arms of the COX-2 inhibitors trials.[96,100,101] These studies demonstrated a POB rate of approximately 1.5% to 2% per year in average-risk individuals taking standard non-ASA NSAIDs. The risk of POBs is considerably higher and can reach 10% in higher-risk individuals, such as those with previous peptic ulcer, older age, and comorbid conditions, such as CV disease.[11,96,100,102]

In a systematic review by Ofman et al.,[94] the risk of perforation or bleeding in NSAID users compared with non-users was elevated in the pooled analyses for RCTs (OR= 5.36; 95% CI: 1.79-16.1), cohort (RR=2.7; 95% CI: 2.1-3.5), and case-control studies (OR=3.0; 95% CI: 2.5-3.7). The same authors assessed the risk of adverse GI symptoms with NSAIDs in a separate publication.[95] Overall, 4.8% of patients reported dyspeptic symptoms. Dyspepsia was greater with higher NSAID doses (RR=2.6; 95% CI: 1.5-4.5) and high dyspepsia NSAIDs (indomethacin, meclofenamate, and piroxicam) (RR=2.2;1.5–3.2), than with low-dose NSAIDs overall (RR=1.3; 95%CI: 0.9-1.8), although these confidence intervals overlapped.

In a study that predominately looked at the risk of NSAID complications in relation to H. pylori status, Huang et al.[98] found that NSAIDs alone were associated with a statistically significant increased risk of endoscopically-detected ulcers (OR: 5.14; 95% CI: 1.35-19.6) and peptic ulcer bleeds (OR:4.79; 95% CI: 3.78-6.06). Tramer et al. reported that peptic ulcer bleeds occurred in 4.8% of patients taking NSAIDs.[88] The results of this systematic review were reported as the absolute risk difference (ARD) for those taking NSAIDs compared with non-NSAID users. The authors found that, among the included RCTs, the ARD for NSAID-induced perforation or bleeding was 0.48%, while it was 0.22% in the included cohort studies. The ARD for death for users of ASA and non-ASA NSAIDs was 0.008% in RCTs and cohort studies. The authors estimated that the RR of death from NSAIDs was 3.4, and suggested that it may be an underestimate (95% CI: 1.3-8.7).[88] Using a biological progression model based on the proportion of patients with NSAID ulcers that subsequently

bleed, Tramer et al. estimated that the increased risk of death among NSAID users was closer to 0.08% (ARD).[88]

The risk of non-ASA-NSAID-induced upper GI toxicity can be reduced through the use of a concomitant prophylactic agent. Only one study of the use of these agents, MUCOSA,[99] considered the reduction of clinically important NSAID ulcer complications such as perforation or bleeding. Here, misoprostol was associated with a 40% RRR (OR: 0.598; 95% CI: 0.364-0.982) in combined clinical ulcer complications.[11,96,99] The remaining agents (H2-receptor antagonists and proton pump inhibitors) have only been evaluated in endoscopic ulcer studies.[11,96] In the systematic review by Rostom et al.,[11,96] double-dose H2-receptor antagonists (equivalent to ranitidine 300 mg twice daily) were associated with statistically significant reductions in the risk of duodenal (RR: 0.26; 95% CI: 0.11-0.65) and gastric ulcers (RR: 0.44; 95% CI: 0.26-0.74). Standard dose H2-receptor antagonists were not effective at reducing the risk of NSAID induced gastric ulcers. Proton pump inhibitors significantly reduced the risk of both endoscopic duodenal (RR: 0.19; 95% CI: 0.09-0.37) and gastric ulcers (RR: 0.40; 95% CI: 0.32-0.51).[11,96]

4c. Harms due to COX-2 inhibitor use (including COX-2 selective)

Fourteen systematic reviews investigated the harms due to COX-2 inh use (Evidence Table 3.3, Appendix 8, and Appendix 4 for full text).

COX-2 inhibitors appear to be better tolerated, and have fewer adverse effects causing withdrawal than standard NSAIDs. These agents cause significantly fewer GI symptoms, endoscopically detected ulcers, and clinically important ulcer complications (perforation, hemorrhage or bleeding) than standard NSAIDs. The coadministration of ASA with a COX-2 inhibitor appears to abolish the GI safety advantage of these agents. COX-2 inhibitors have been suggested to have a greater risk of CV events than placebo. The data on the CV harms are rapidly changing and are detailed further in the discussion and Appendix 4.

Other Considerations

What is the cost and cost effectiveness of aspirin/NSAID use in preventing CRC?

Five economic evaluations of the use of NSAIDs in adenoma and/or CRC prevention were identified (Evidence Table 4).[40,103-106] All the studies used decision analysis and a Markov model within a U.S. economical and clinical practice context.

A. NSAID chemoprophylaxis in average-risk populations

Suleiman et al.[103] simulated a population of 100,000 50-year-old average-risk subjects followed until death. The model included four mutually exclusive interventions: 1) no screening, no chemoprevention; 2) colonoscopy every 10 years (every 3 years if adenomas were identified); 3) ASA 325 mg per day; and, 4) colonoscopy every 10 years along with ASA 325 mg per day.

Key probabilities and assumptions are presented in Evidence Table 4 (Appendix 8). The efficacy of colonoscopy at preventing CRC was 75%; that of ASA was 50%, and that of ASA combined with colonoscopy was 87.5%. The authors also assumed that ASA use affected polyp growth in the same magnitude as it affected CRC growth. Subject compliance with the intervention was assumed to be 100%, and the effect of ASA on CV outcomes was not incorporated into the model.

Costs were in U.S. dollars, discounted at 3% from a third-party payer perspective. The cost of colonoscopy was $696, that of ASA, including both drug cost and that of complications, was $172 per patient per year.

Colonoscopy every 10 years saved 7,951 LYs (life years), at a total cost of $223,780,829; chemoprevention saved 5,301 LYs at a total cost of $386,920,810. Compared with no intervention, the incremental cost-effectiveness ratios (ICERs) were $10,983, $47,249 and $41,929 per LY saved for colonoscopy, chemoprevention and colonoscopy/chemoprevention, respectively. When added to colonoscopy every 10 years, the ICER of ASA 325 mg daily is $227,607/LY saved. Sensitivity analysis showed that the costs of chemoprevention (which includes drug cost and cost of complications) need to fall below $70 per patient per year to become more cost-effective than colonoscopy.

The authors concluded that daily ASA use as chemoprevention for CRC was at present not cost-effective because of the relatively large costs associated with its adverse effects, as well as its relative inefficacy compared with colonoscopy.[103]

In a very similar model, Ladabaum et al.[40] evaluated the cost effectiveness of ASA at 325 mg per day in average-risk U.S. subjects, compared with two different screening strategies: (1) colonoscopy every 10 years (every 5 years if polyps were discovered) ("COLON"); and (2) flexible sigmoidoscopy every 5 years combined with yearly fecal occult blood testing ("FS/FOBT"). In the later strategy, any positive test would be followed by colonoscopy.

The model simulated an infinitely large population of 50-year-old average-risk U.S. subjects followed until the age of 80.

Key probabilities and assumptions are presented in Evidence Table 4 (Appendix 8). It was assumed that the efficacy of ASA at preventing CRC was 30% (lower than in Suleiman et al.'s study[103]), and that the compliance with screening was only 25%. The effect of ASA on CV outcomes was modelled in sensitivity analysis.

Costs were also in U.S. dollars, discounted at 3% and from a third-party payer perspective. The cost of colonoscopy was comparable to Suleiman et al.'s study, that of ASA therapy $4 per patient per

year, with a probability of ASA-related complications of 2-16 per 10,000 patient-years, each event costing $15,000.

Results show that, compared with no screening, FS/FOBT or COLON markedly reduced CRC mortality. When ASA was added to no screening or to screening, the additional decrease in cancer deaths was offset by ASA-related deaths. The ICERs for screening were $16,844 for each life-year ($16,844/LY) saved and $20,172/LY saved for FS/FOBT and COLON, respectively. As an adjunct to FS/FOBT, ASA increased costs and decreased LYs because of related complications. Sensitivity analysis showed that the cost effectiveness of daily ASA use as chemoprevention for CRC was highly dependent on its efficacy, on its complication rate and on the degree of compliance to screening in the population.

The authors also examined the effect of ASA as an adjunct to screening if it decreased CV death as well as CRC incidence. If ASA decreased CV mortality by 0.1% and CRC incidence by 30%, its use as an adjunct to screening would cost $10,039 and $8,976 per LY saved for FS/FOBT and COLON, respectively.

It was concluded that ASA therapy could not be considered a substitute for screening. Although ASA chemoprevention seems cost-effective in an unscreened population, it is much less effective than screening, which is highly cost effective. The use of ASA as an adjunct to screening is cost-effective if it can reduce CRC risk by 40% to 80% and has low complication rates. If, in addition, ASA was modelled to decrease CV mortality by at least 0.1%, its use as an adjunct to screening would remain cost-effective as long as its chemopreventive efficacy is 30% or greater.

Ladabaum et al.[106] also modelled the use of COX-2 inhibitors (celecoxib or rofecoxib) in the same average-risk U.S. population, using similar probabilities and costs for the natural history of the disease as well as the screening tests. The authors restricted the comparison to that of colonoscopy every 10 years. The efficacy of COX-2 inhibitors was assumed to be 30% (similar to that of ASA in their prior report), it was assumed that their effect is similar on polyp and CRC growth, the rate of excess major complications and death with COX-2 inhibitors were assumed to be 0, and the cost of COX-2 inh therapy was estimated at $325 per year. Sensitivity analysis was used to explore the effects of: varying COX-2 inh's chemopreventive efficacy from 0 to 100%; assuming a differential effect on polyp and CRC growth; using a COX-2 inh exclusively in individuals younger than 65; increasing the rate of excess major GI complications to 0.1% per year and of death from COX-2 to 2% to 8% per complication; varying the doses of COX-2 inhibitors, with yearly costs of COX-2 chemoprevention ranging from $81.25 to $1300; and evaluating whether COX-2 inh chemoprevention would allow for less frequent screening. The effect of COX-2 on CV mortality was not modelled.

Compared with no intervention, colonoscopy every 10 years saved 0.065LY/person and its ICER was $20,200/LY saved, whereas COX-2 inh saved 0.027LY/person with an astronomical ICER of $233,300/LY saved. In comparison to screening alone, the addition of a COX-2 inh saved an extra 0.008LY/person and its ICER was of $823,800/LY saved. If, in combination with COX-2 inh

chemoprevention, colonoscopy was decreased to every 20 years, the ICER became $3,313,000/LY saved. In the strategies incorporating chemoprevention, COX-2 use accounted for 66% to 92% of total costs.

In summary, use of a COX-2 inh was both less effective and more costly than screening alone. These results were highly sensitive to the chemopreventive efficacy and the cost of COX-2 inhibitors. COX-2 inh use alone would need to reduce CRC risk by 60% at a cost of $0.25/day to approach the cost effectiveness of colonoscopy every 10 years. Their use as an adjunct to colonoscopy screening incurred ICERs lower than $100,000/LY saved only if their chemopreventive efficacy was greater or equal to 60% and their cost was $0.25/day.

Hur et al. compared the cost effectiveness of ASA 325mg daily with that of celecoxib 400 mg bid in a population of 50-year-old average-risk U.S. men followed for 10 years.[104] It was assumed that both ASA and celecoxib (Celebrex) had the same efficacy for RR of CRC. It was also assumed that ASA reduced the risk of CV events, while celecoxib had no impact on CV morbidity and mortality. The model, not accounting for the impact of screening or that of chemoprevention on cancer incidence, essentially compared the costs, cardioprotective effects, and toxicities of ASA versus celecoxib. The results of the base-case analysis showed comparable efficacies (7.60 and 7.57 QALYs for ASA and celecoxib, respectively), but at an enormous cost difference ($181 and $23,403 for ASA and celecoxib, respectively). Sensitivity analysis showed that coxibs became more effective than ASA if the relative ulcer rate on coxibs (COX-2 inhibitors) was 93% lesser than in the base-case, if the combined relative MI/ulcer rate for coxibs was decreased by 60% and if the relative bleeding rate on ASA was increased by 550%.

B. NSAID chemoprophylaxis in higher-risk populations

Ladabaum et al,[106] using the same Markov model as described in their average-risk analyses, compared the daily use of COX-2 inhibitors (celecoxib or rofecoxib) with either "do nothing," colonoscopy every 5 years, or with the combination of colonoscopy every 5 years with daily COX-2, in an infinitely large U.S. population of 50-year-old subjects with one or two affected first-degree relatives. It was assumed that the risk of CRC was 2.6 and 3.6 times that of the average-risk population (derived from SEER data 1973-1994) for subjects with one and two affected first-degree relatives, respectively. Other assumptions and costs were similar to those described for their COX-2 chemoprevention in the analysis of average-risk subjects; the same sensitivity analyses were also performed, but in addition, it was used to determine if screening and/or chemoprevention should be instituted by the age of 40 instead of 50. The effect of COX-2 inhibitors on CV mortality was not modelled.

The ICERs for the interventions were similar whether screening began at age 40 or at age 50 for these subjects. Screening colonoscopy, either every 5 or 10 years, costs under $6,500/LY saved as compared with no intervention. The ICER of colonoscopy screening every 5 years compared with every 10 years was $19,800 and $10,900/LY saved, for persons with one and two affected first-degree relatives, respectively. As per average-risk subjects, use of a COX-2 inhibitor alone in higher-risk groups was both less effective and more costly than screening alone. Moreover, chemoprevention

combined with colonoscopy every 10 years lost LYs and was more costly than colonoscopy every 5 years. Two-way sensitivity analysis showed that, in persons with two affected first-degree relatives, COX-2 inhibitors alone would need to reduce cancer risk by 70% at $0.50/day to approach the effectiveness and cost effectiveness of colonoscopy every 5 years ($4,800 vs $2,600/LY saved compared with no intervention, respectively). In that same higher-risk group, the ICER of COX-2 inhibitor use as an adjunct to colonoscopy every 5 years, compared with colonoscopy every 5 years alone, would be less than $100,000/LY saved only if they reduced cancer risk by 60% or more at $0.50/day, and would be less than $50,000/LY saved if they reduced cancer risk by 50% or more at $0.25/day.

In summary, colonoscopy every 5 years in subjects with one or two affected first-degree relatives was cost effective, whereas COX-2 inh use alone is both less effective and more expensive than screening. COX-2 inh use as an adjunct to colonoscopy every 5 years could be considered relatively cost effective if COX-2 inhibitors could reduce cancer risk by at least 50% and if their daily cost was of $0.50 or less.

Arguedas et al. compared 1) surveillance colonoscopy 3 years after the initial polypectomy and every 5 years once no polyps were recovered, 2) chemoprevention with celecoxib 200 mg/day, to 3) no surveillance, no chemoprevention[105] in subjects with a prior history of colonic adenoma followed for 10 years.

Key probabilities and assumptions are presented in Evidence Table 4 (Appendix 8). The cancer RR on COX-2 inhibitors was 50% (range 0%-100%); the rate of peptic ulcer disease on celecoxib was 0.02/y (range 0.01-0.15) and the rate of withdrawal from COX-2 inhibitors due to side effects was 0.01/y (range 0-0.02/y). Subjects who withdrew from celecoxib would undergo the surveillance colonoscopy protocol and compliance with any intervention was assumed to be 100%. The cost of celecoxib therapy was $1,766/y (range $25-$1,766). The effect of COX-2 inhibitors on CV mortality was not modelled.

Colonoscopic surveillance was more effective and considerably less costly than chemoprevention, saving 0.01995LY at a cost of $558 compared with 0.00579LY for $9,931 with celecoxib. Compared with no intervention, the ICERs for colonoscopy and chemoprevention were $27,970 and $407,498/LY saved, respectively. Sensitivity analysis showed that the results were not sensitive to the rate of polyp formation (i.e., increasing or decreasing the magnitude of patient risk) but that, as per Suleiman's study, varying the cost and/or the chemopreventive effect of celecoxib would affect the ICERs. For example, celecoxib use could be economically advantageous (ICER less than $50,000/LY saved) if it reduced polyp recurrence by 50% and cost $0.10/day, or reduced recurrence by 75% and cost $0.35/day.

In summary, the use COX-2 inhibitors does not appear to be cost effective either compared with screening or as an adjunct to screening. In higher-risk patients, COX-2 inhibitors would have to reduce polyp recurrence by 50% or more and cost less than $0.50/day.

C. The impact of NSAID chemoprevention on FOBT testing

This section was added at the request of the USPSTF and is located in Appendix 6.

CHAPTER 4. DISCUSSION

CRC is a frequent cause of morbidity and mortality in the United States. Chemoprevention with ASA or NSAIDs is one possible strategy to reduce the burden associated with this disease. The results of this report suggest that such a strategy may be effective, but also that the possible harms of chemoprevention and its cost effectiveness have to be considered. New data regarding the effectiveness of chemoprevention using COX-2 inhibitors are likely to become available in the upcoming year, and our understanding of the CV harms of these agents and of non-ASA NSAIDs is evolving.

The regular use of ASA appears to be effective in reducing the incidence of CRA with RRR, on the order of 13% to 28% in average-risk individuals. The use of non-ASA NSAIDs appears to be associated with somewhat higher RRRs, on the order of 23% to 46%. Based on a limited number of studies, the RRRs for higher risk individuals are likely higher than for those at average risk. Furthermore, it appears that longer use of ASA/NSAIDs, particularly if that use continued to the year prior to the ascertainment of the study outcome, as well as higher doses, is associated with greater RRRs than shorter-term and lower-dose use.

The findings reported above also hold for CRC incidence. Regular use of ASA was associated with RRRs of 10% to 65% for CRC incidence. The analysis for the case-control studies demonstrated significant heterogeneity, but based on a pooled RRR of 22% in the cohort studies and consideration of the included studies, RRRs in CRC incidence of 15% to 40% represents a more realistic range. The pooled estimates for non-ASA NSAIDs suggest somewhat greater RRRs, on the order of 30% to 40%, and longer duration of use of ASA/NSAIDs and higher doses also appear to offer greater protection. Data from two RCTs, however, demonstrated no clear benefit of ASA on CRC incidence.[47,107]

Only two observational studies considered the effect of ASA/NSAIDs on CRC mortality.[45,46] Among the observational studies, CRC mortality was reduced by about 40% with the use of ASA for greater than 15 years in one,[45] while the other found nonsignificant trends towards increased standardized mortality ratios for bowel and rectal cancers with ibuprofen.[46] Table 5 (Appendix 8) summarizes the main results and lists the effects of various screening strategies detailed in the USPSTF recommendation on CRC screening.

Limitations

The body of evidence included in this systematic review was quite consistent in suggesting reductions in CRA and CRC incidence with ASA/NSAIDs. However, the included studies demonstrated important variability in how they were conducted, a circumstance which necessitated careful assessment and grouping of the studies in an effort to minimize this variability. Nonetheless, some variability could not be completely explained. These types of study differences centered around how cases, controls and outcomes were ascertained (i.e., directly, or from hospital records or databases). But perhaps more problematic were differences among the studies in how NSAID exposure was ascertained and measured; for example, through prescriptions databases or from mailed

self-administered questionnaires. Measurement and exposure ascertainment introduces a degree of uncertainty in the interpretation of the dose-response relationship and duration-of-use analyses. These concerns also affected the base analyses of regular use, but were not as problematic. It is possible that the effect of ASA/NSAIDs varies in different populations. These study population differences may also have contributed to the observed heterogeneity in some analyses. We tried to minimize the variability relating to duration and dose effects by defining a priori subgroups and using qualitative descriptions of studies when necessary.

The effect of ASA/NSAIDs on CRC mortality represents another area of uncertainty, due to the limited number of studies and the discordance between the included cohort studies. Furthermore, the observational studies suggest a reduction in CRC incidence with chemoprevention, but the widely cited PHS and the recently published Women's Health Study (WHS) found no benefit of ASA on CRC incidence. The PHS and the WHS were well conducted RCTs that share many similarities. They were conducted in male physicians and female health care workers, respectively. Both used a relatively low dose of ASA (325mg every second day and 100mg every second day, respectively), and both used self reporting of outcomes in mailed questionnaires, as well as mailed medication packs. Both studies followed patients for a long period of time (14 and 10 years, respectively), but in the case of the PHS, the RCT portion was the first 5 years and was followed by an observational phase, where patients chose their intervention; the WHS continued the RCT design for the entire study. The PHS study could be criticized for its observational phase which could have introduced several forms of bias, including contamination by intervention. Additionally, participants in the study had a lower rate of CRC than matched members of the U.S. population (SMR =0.82; 95% CI, 0.75 to 0.90). The strength of their RCT design adds weight to their negative findings regarding the benefit of ASA on CRC incidence. However, participants in both studies were relatively young males (mean age 53.2 years, and 54.6 years, respectively) who used a relatively small amount of ASA (every second day). Participants were also not necessarily CRA free at study onset, and outcomes were collected through mailed questionnaires. It is difficult to entirely reconcile the discrepancy between the negative RCT data, and the overwhelmingly positive observational data, other than to say that low-dose ASA every second day is not effective at reducing CRC incidence, but that higher doses used for longer periods may be effective. The recently published follow-up to the Nurse's Health Study, a prospective cohort study including 82, 911 women, adds support to this conclusion.[108] This study demonstrated a statistically significant RRR in CRC incidence with ASA. The study also demonstrated an important dose and duration effect, with the maximal benefit seen when more than 14 standard ASA tablets were used for more than 10 years. The data regarding CRC-related mortality is also mixed. One cohort study was positive, while another was negative. The recently published WHS also showed no effect of ASA on colorectal cancer mortality.

The current review identified no COX-2 chemoprevention studies in average-risk individuals. The results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, and two celecoxib spontaneous adenomatous polyposis (SAP) prevention trials (APC and preSAP) are not yet available. Furthermore, two of these trials, and an Alzheimer's prevention trial, have caused considerable upheaval in the current state of understanding of the CV safety of COX-2 inhibitors and non-ASA-NSAIDs.[7,8]

Subjects at "high risk" of CRC, such as those with previous CRC or those with hereditary CRC syndromes, represent a distinct group that was not assessed in this review. It is likely that the balance of efficacy and harms for these individuals is different than that presented here for average- and higher-risk individuals.

Harms

The use of ASA, non-ASA NSAIDs, and COX-2 inhibitors are each associated with important harms. ASA and non-ASA NSAIDs are associated with an increased risk of ulcers and clinically important ulcer complications such as hemorrhage, perforation or pyloric obstruction. The annualized incidence of these events for non-ASA NSAIDs, as a group, is approximately 1.5% to 2.0% in average-risk individuals with arthritis.[100,101] As a "class," COX-2 inhibitors are associated with fewer endoscopic ulcers and clinically important ulcer complications when compared with non-ASA NSAIDs overall, with pooled RRRs of about 50% for important ulcer complications. As a class, COX-2 inhibitors are associated with fewer GI symptoms than NSAIDs. However, the use of a COX-2 inhibitor among ASA users was assessed in a subgroup of patients in the CLASS (celecoxib),[100] Target (lumiracoxib)[109] and the Goldstein valdecoxib[102] trials. In this setting, the frequency of clinically important ulcer complications were not different between COX-2 inhibitors and non-ASA NSAID users. ASA added to celecoxib appears to result in a four-fold increase in ulcer complications over celecoxib alone,[96,100] and the combination of valdecoxib and ASA results in a nine-fold increase in ulcer complications over valdecoxib alone.[102]

The use of ASA is associated with an increased incidence of important ulcer complications, with RRs of 1.5 to 3.0 reported in the current evidence report. Furthermore, Henry et al. found that ASA appears to show rates of GI toxicity between those of diclofenac and sulindac.[110] The absolute risk of GI bleeding with less than 100mg ASA/day was 0.97% per year and 2.69% per year for greater than 200 mg/day.[111] The CV outcomes associated with the use of ASA depend on the underlying CV risk of the population under investigation. In low-to-average risk individuals (i.e., primary prevention), ASA significantly reduces the incidence of total CV events (RR=0.72; 95% CI:0.60-0.87), but has no effect on coronary heart disease mortality, fatal and nonfatal stroke events, or all-cause mortality. In low-to-moderate risk individuals, the use of ASA would prevent three to eight fatal or non-fatal coronary heart disease events, but would not prevent an ischemic stroke event, and would cause one hemorrhage stroke and one major GI hemorrhage (based on 1,000 treated patients).[2] In high-risk CV patients in a secondary prevention setting, the use of ASA significantly reduces all-cause mortality and CV mortality, despite the increased incidence of major GI hemorrhage. Weisman et al. suggested that 67 patients would need to be treated to prevent one death, with the cost of one non-fatal GI bleed. They further suggest that two strokes could be prevented for every GI bleed caused.[83,86] In the setting of CRC chemoprevention with ASA, depending on what age the intervention is started, it is possible that most patients would be at low-to-moderate CV risk, and may be exposed more to the harms of ASA rather than to its benefits.

Data on the effectiveness of COX-2 inhibitors for the chemoprevention of CRA and CRC were unavailable to us, and during the conduct of this review rofecoxib was withdrawn from the market based on the results of the polyp prevention APPROVe study,[112] which demonstrate a 16/1,000 excess

risk of CV events, confirming the suspicions brought out by the VIGOR trial.[101] Subsequently, celecoxib was also found to have a 13-21/1,000 excess risk of CV events in another polyp prevention study (APC).[113] Valdecoxib was also withdrawn on the basis of excess CV risk in two short term cardiac surgery pain studies (CABG 1 & 2), and due to rare dermatological toxicity.[7,8] The data are, however, far from clear at present. Celecoxib did not show the same CV risk in a second polyp trial and in an Alzheimer's prevention trial, while based on the Alzheimer's trial it was suggested that naproxen may carry an increased CV risk.[7,8] Also in the Target study, Lumiracoxib appears not to be associated with increased CV risk.[109]

Our report only identified one systematic review of CV harms of non-ASA NSAIDs.[93] This review suggested a small CV protective effect, although the included studies were heterogeneous. Clinical trial data of the quality available for the COX-2 inhibitors are not available for the non-ASA NSAIDs, and is likely forthcoming from analyses of the non-ASA NSAID arms of these COX-2 inh trials. However, we assessed the CV harms of non-ASA NSAIDs in the studies identified in the systematic review by Juni[93] and in a recent publication by Hippisley-Cox.[114-123] Overall, non-ASA NSAIDs, and particularly non-naproxen NSAIDs, appear to offer no cardioprotective effects, and in some studies there appears to be an increased risk of CV harms with non-naproxen NSAIDs.[114,118,123]

The evidence relating to the CV harms of COX-2 inhibitors and NSAIDs is in a state of rapid flux. In addition to the sources used in the systematic review we have included other sources of data in the Discussion. After the FDA advisory panel meeting of Feb 16, 2005, Health Canada also convened an advisory panel of experts on June 9th 2005 in Ottawa, Canada to provide advice to the Department on the safety and efficacy of COX-2. Dr. Alaa Rostom, the clinical lead author of the present evidence report, was a member of this panel. No information obtained as part of the evidence report was released to the panel.

During the public forum portion of the panel meeting a meta-analysis was presented using an extensive set of RCT data provided by manufacturers. It is difficult to determine the completeness of the data set, but it appeared that the manufacturers provided the required CV data from their clinical trials. The results suggested that as a group, COX-2 inhibitors are associated with an increased risk of CV outcomes when compared with placebo or naproxen, but not when compared with non-naproxen NSAIDs. These data also suggest that the increased risk of CV harms with COX-2 inhibitors is shared by the non-naproxen NSAIDs. Furthermore on June 15th 2005, the FDA requested that all sponsors of marketed prescription NSAIDs, including COX-2 inhibitors, revise their labeling to include a boxed warning highlighting the potential for increased risk of CV events, in addition to the well-described GI toxicity associated with these agents.[124]

Cost-effectiveness

In average-risk populations, and in the context of regular endoscopic screening for CRC, NSAID chemoprevention is at present not cost-effective because of the relatively large costs associated with its adverse effects, as well as its relative inefficacy compared with colonoscopy. To be cost-effective, daily ASA use would have to decrease the CV mortality by 0.1% or more, and it would have to

decrease CRC mortality by at least 30%. Additionally, chemoprevention with COX-2 inhibitors, independently of the newly recognized cardiotoxicity, is expensive, and its use as an adjunct to colonoscopy can only be economically acceptable (i.e., ICER less than $100,000/LY saved) if it can prevent CRC mortality by at least 60%, and the cost be reduced by at least 75%.

In higher-risk groups, the use of COX-2 inhibitors for chemoprevention of CRC is both less effective and considerably more costly than screening protocols, which are in themselves cost effective by all criteria; the use of COX-2 inhibitors as an adjunct to screening can only be economically acceptable if their current cost is considerably reduced and if their efficacy as chemopreventive agents is of at least 50%. These results do not account for any potential CV harms of COX-2 use.

Conclusions

ASA and non-ASA NSAIDs appear to be effective at reducing the incidence of CRAs and CRC. However, the data on CRC incidence is inconsistent, with observational studies tending to be positive, and two large RCTs showing no benefit for low-dose ASA every second day on CRC incidence. The effect of ASA/NSAIDs on CRC mortality is also mixed, with one positive and one negative cohort study, and the negative findings of the WHS. There are well-defined GI risks associated with ASA and NSAIDs when used daily for months. There are no quantitative data on GI or CV risk of chronic multiyear use of daily NSAIDs. We found no information regarding the effectiveness of COX-2 inhibitors on these outcomes in average-risk individuals. Available data on COX-2 inhibitors suggest that absolute risk increase of over 1% for CV events can be anticipated from only 2 to 3 years use, and higher risks may accrue over longer periods. Further, the results of the economic evaluations consistently reveal that chemoprevention is not cost effective. In the case of ASA, the costs of complications are significant; in the case of COX-2 inhibitors, independently of the recently reported CV toxicity, the drug costs are great. Lastly, in addition to their emerging CV toxicity, non-ASA NSAIDs, are associated with significant GI harms. Arguments can be made for the use of ASA chemoprevention, particularly in populations that may benefit from its CVS harms preventive effect. However, since observational studies suggest that higher doses and prolonged use improve chemopreventative efficacy, more information is required to clarify the optimal dose, starting age, and duration of use of ASA, as well as clarification of its effect on CRC incidence and mortality, particularly given the evidence that in patients at average CV risk, all-cause mortality is not reduced with the use of ASA.

Future research

COX-2 inhibitors appeared poised due to their GI safety to be the ideal candidates for CRC chemoprevention. However, the recent data regarding the CV harms of COX-2 inhibitors, and possibly of non-naproxen NSAIDs, have put this expectation into question. Nonetheless, data from the Vioxx and Celebrex polyp prevention trials need to be made available so as to at least test the hypothesis that COX-2 inhibition is clinically effective at reducing polyp occurrence.

Furthermore, because of the discrepancy between the RCT data (PHS and WHS), and the observational study data, it would seem prudent to assess the role of standard daily doses of ASA by means of an RCT designed for the sole purpose of assessing its effect on polyp and CRC incidence. Other questions also need to be answered; for example, "What is the effective dose of ASA?" and "At what age should chemoprevention should start?".

There is strikingly little data on the long term (>2-3 years) harms of NSAIDs and COX-2 inhibitors. Studies of pharmacologic therapies in general, and preventive strategies in particular, that use these agents should incorporate outcomes such as overall mortality, hospitalization, and serious adverse effects. It is known that GI bleeding risk with NSAIDs increases with advancing age and underlying CV disease; that is, the risk is heightened in the very same population in which chemoprevention may be utilized. Further study should be undertaken on the balance of harms and benefits in this particular population, with particular emphasis on the cumulative harms over the time period over which chemoprevention is likely to be used.

Reliable estimates of compliance rates with chemoprevention need to be determined and compared with those of current and potential screening-based preventive methods.

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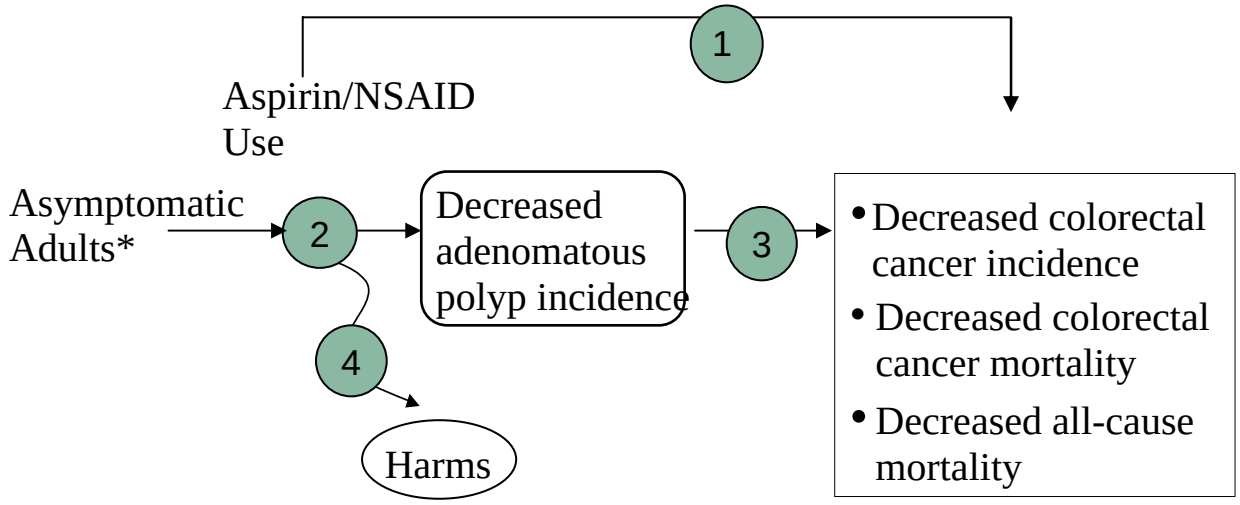
Figure 1. Analytic framework: aspirin/NSAID to prevent colorectal cancer



*Adults without known colorectal cancer

*Excluding FAP and HNPCC (Lynch Syndrome I and II)

Figure 2. Cohort studies—average risk population and CRC incidence

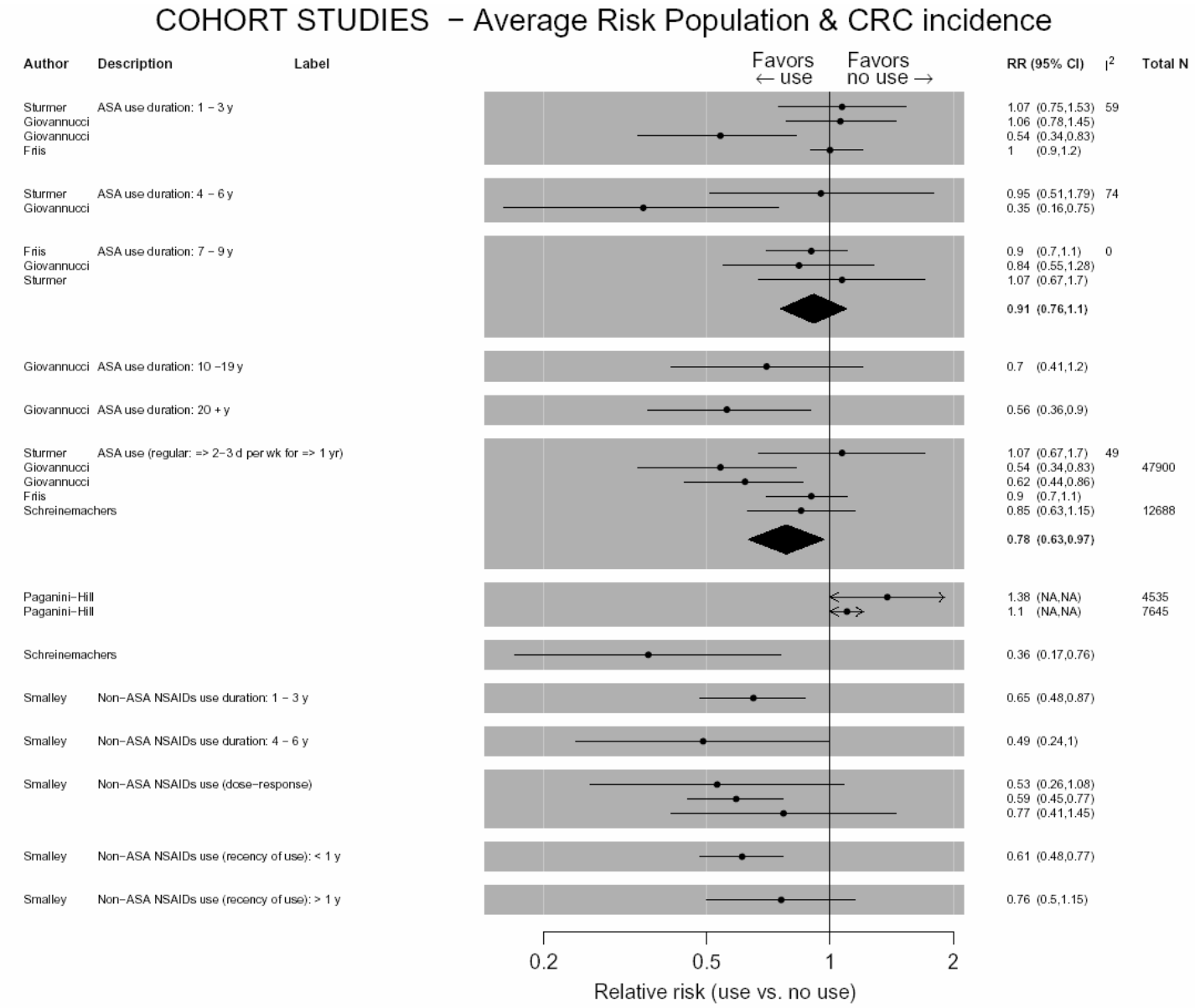


Figure 3. Case-control studies—CRC incidence

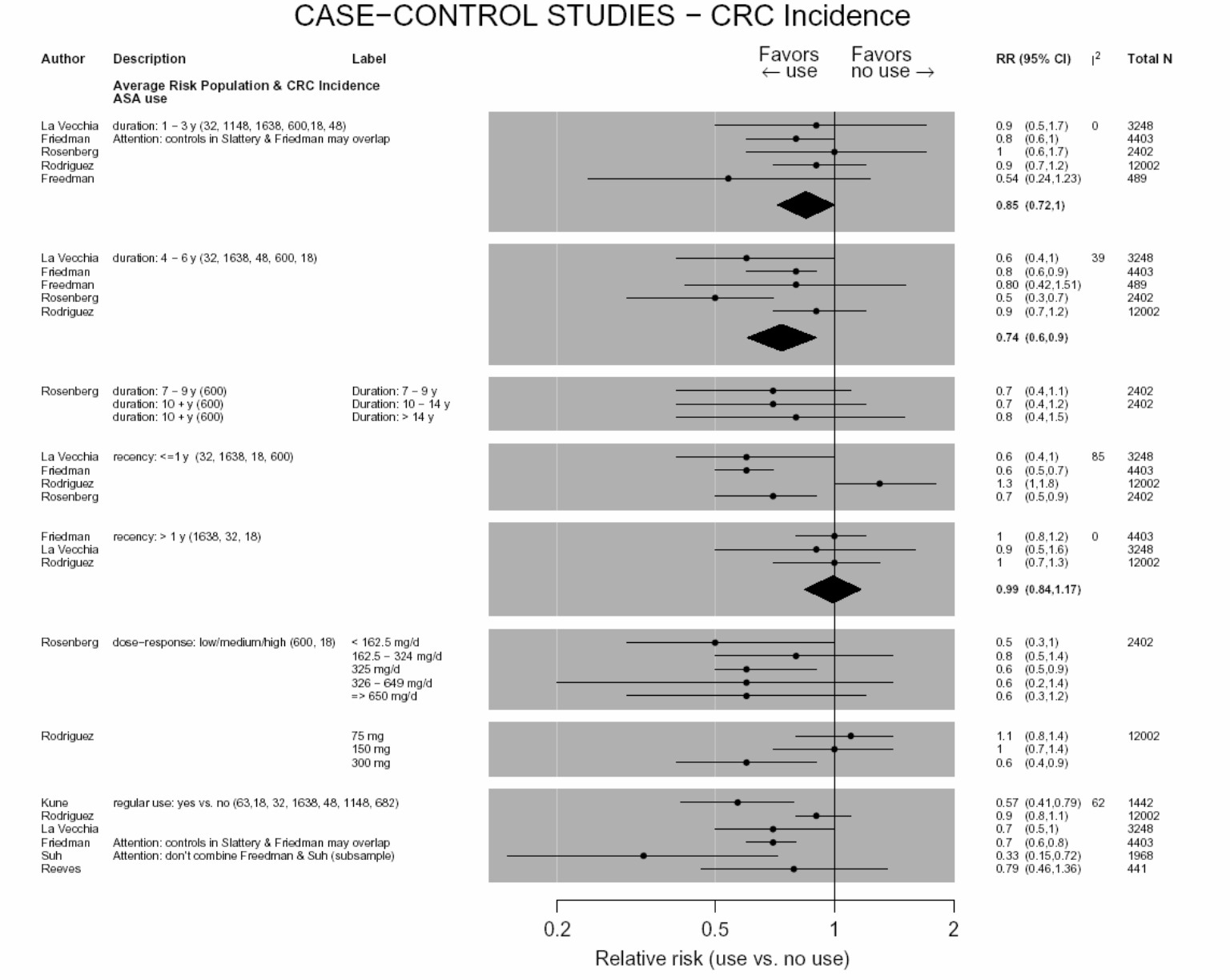


Figure 3 (cont'd)

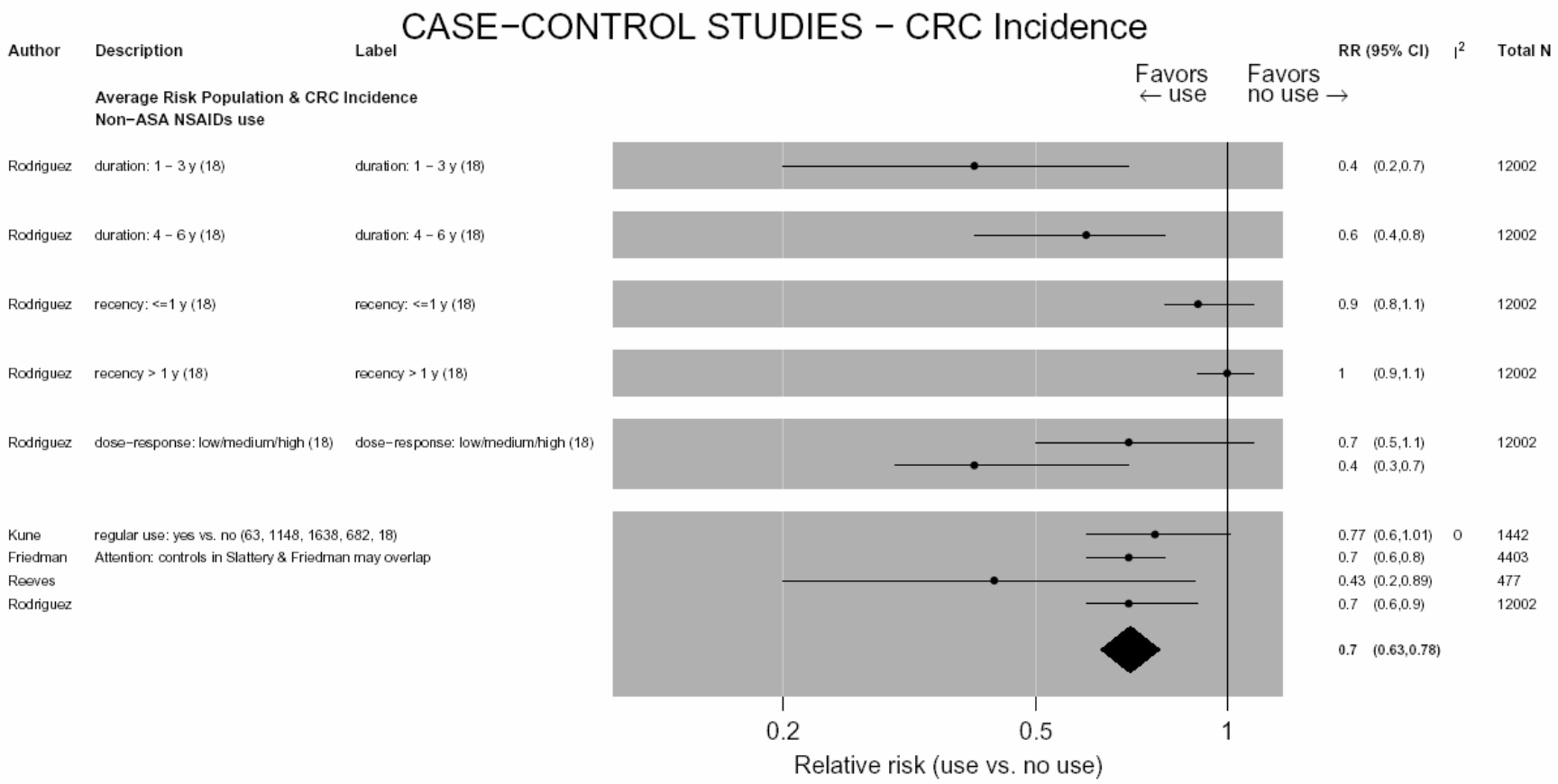


Figure 3 (cont'd)

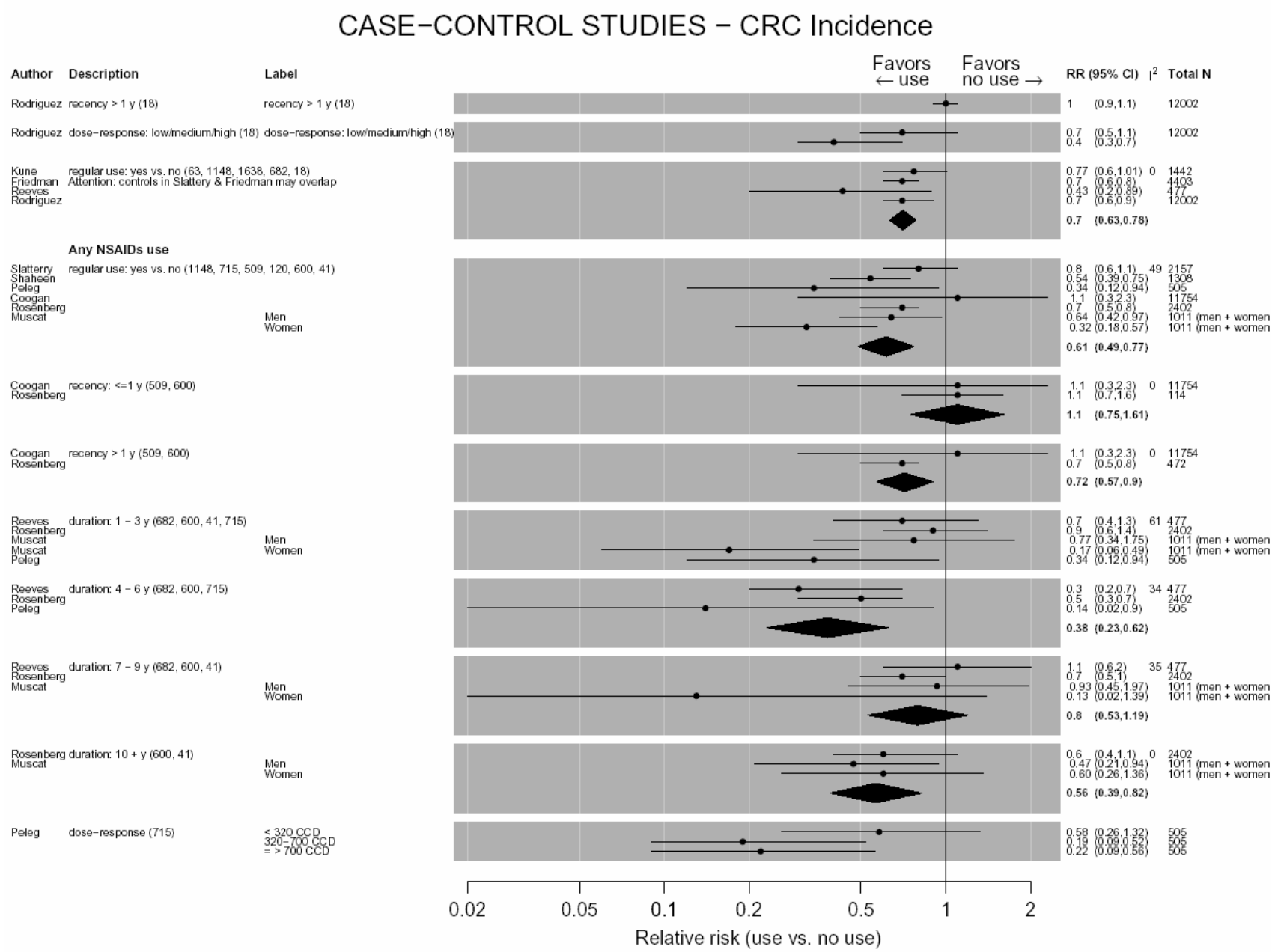


Figure 4. RCT studies—incidence of adenomas

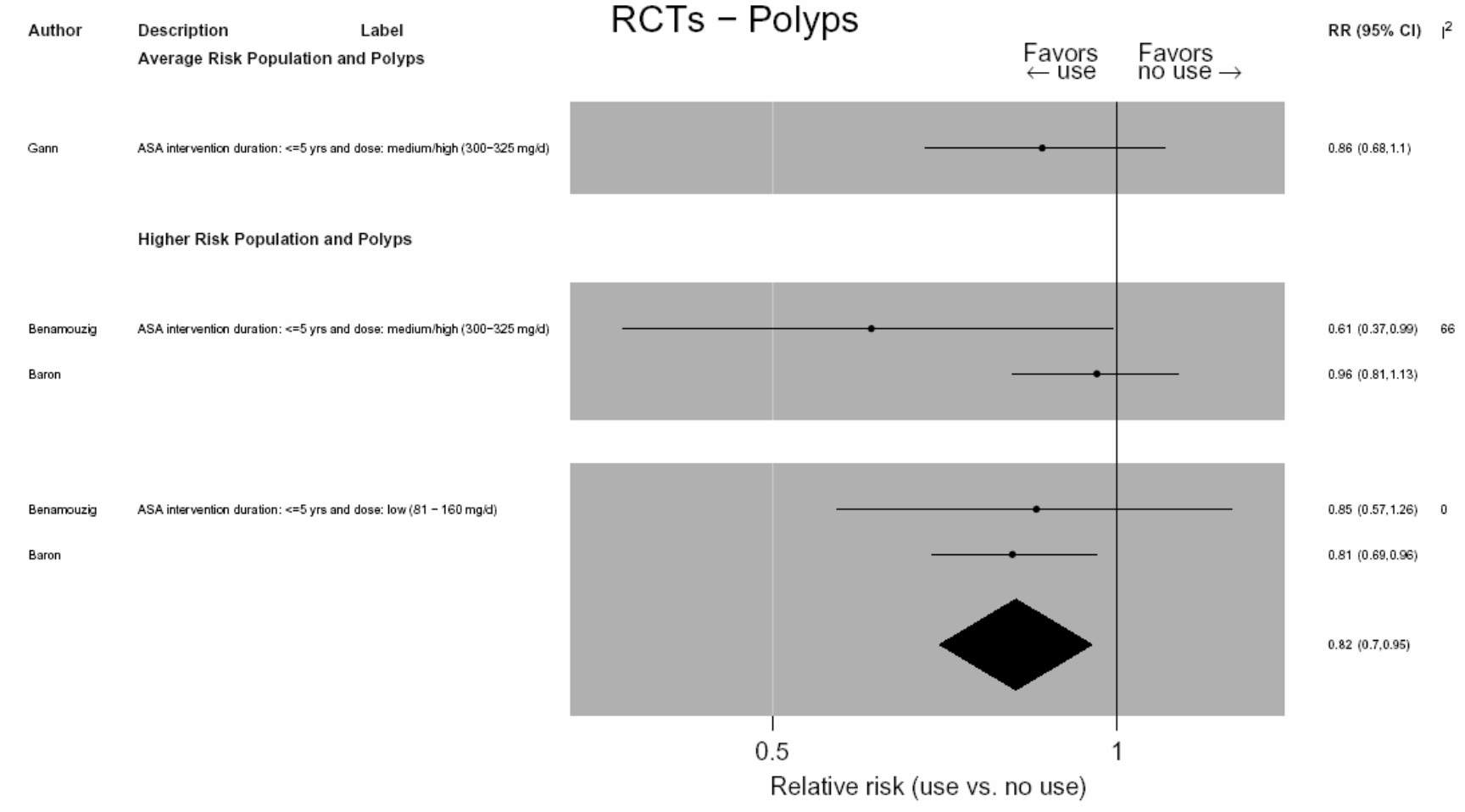


Figure 5. Cohort studies—incidence of adenomas (CRA)

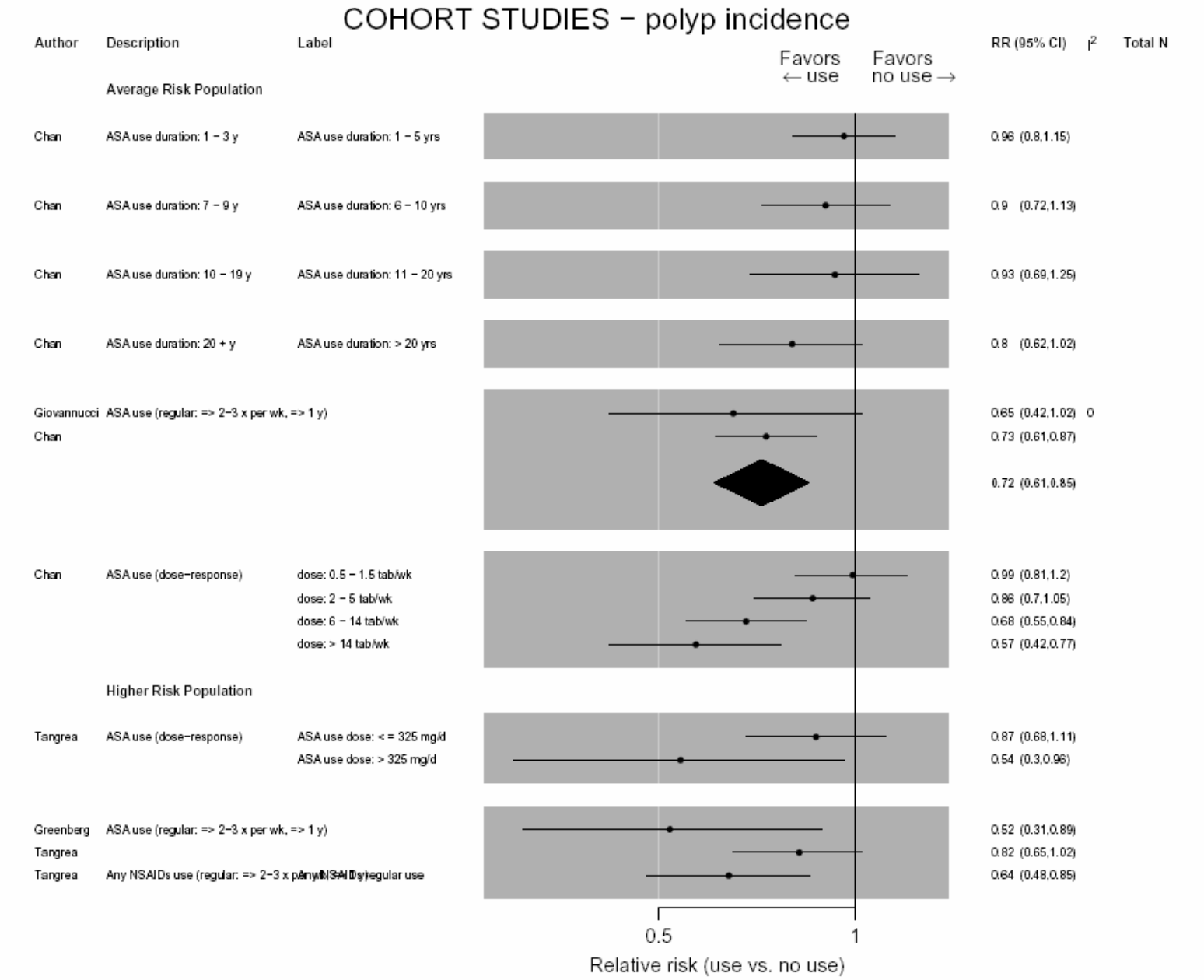


Figure 6. Case-control studies—incidence of adenomas

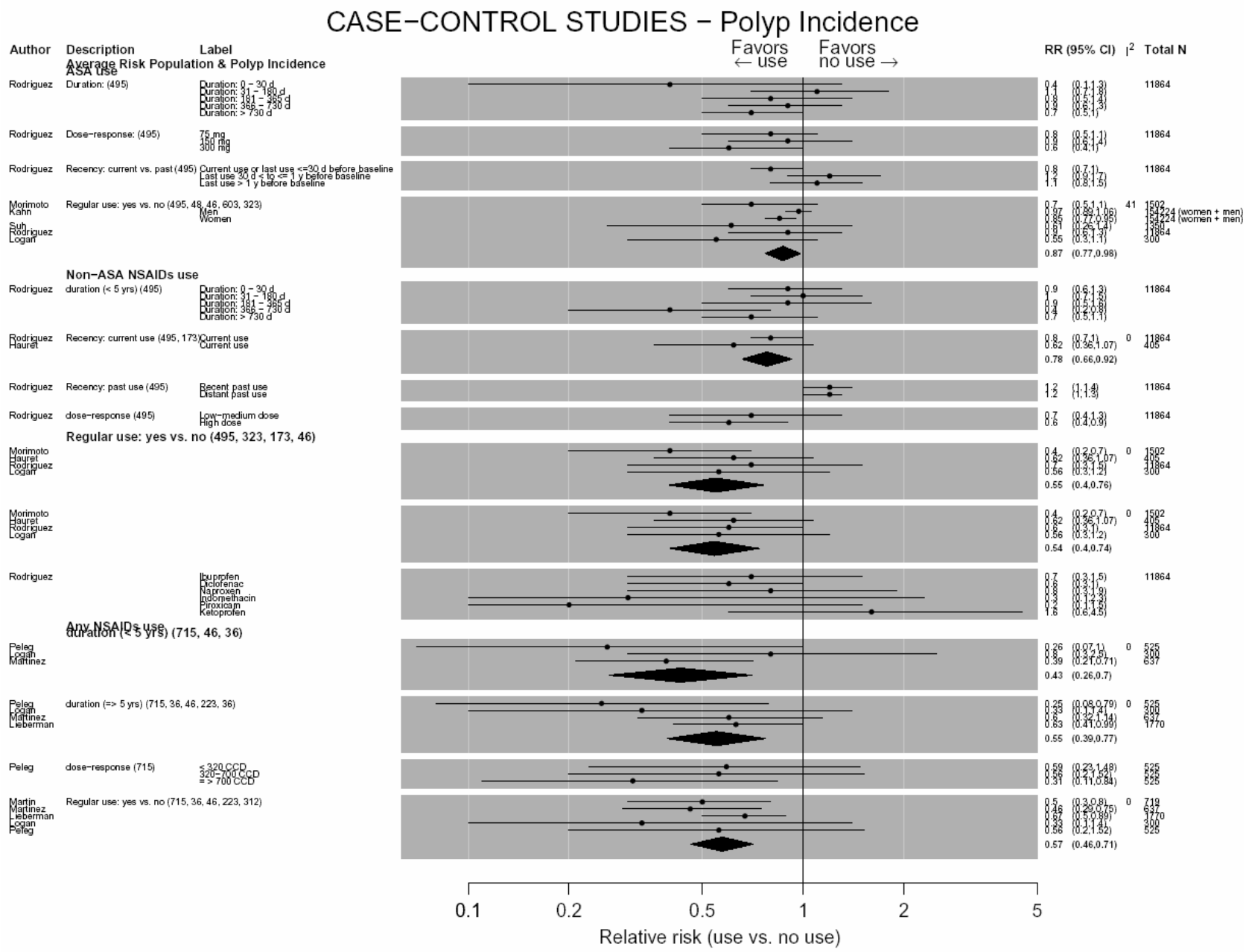
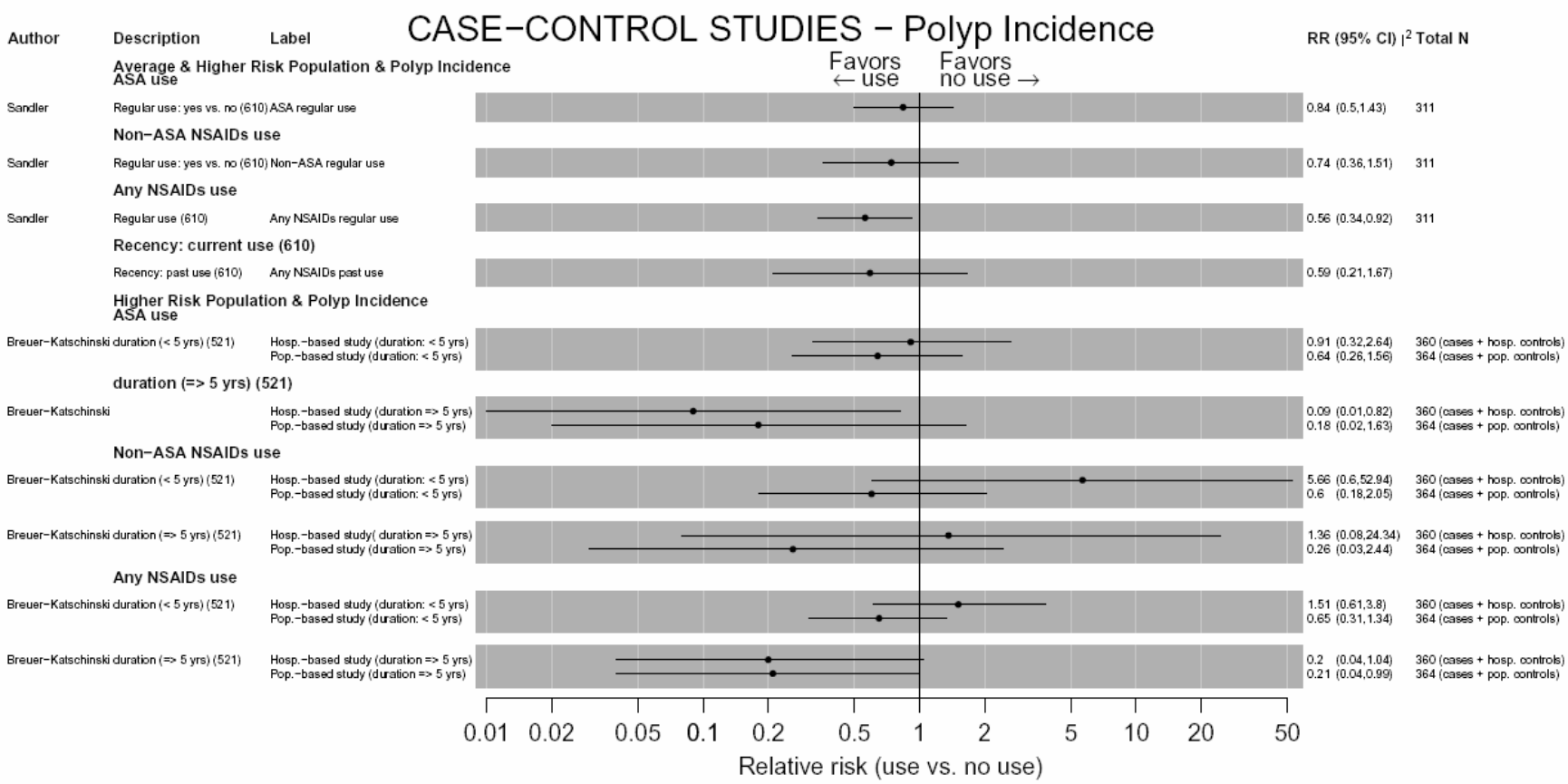


Figure 6 (continued)



Appendix 1. Search strategies

Key questions 1 and 2 (efficacy)

1. exp Anti-Inflammatory Agents, Non-Steroidal/
2. exp Cyclooxygenase Inhibitors/
3. Aminopyrine.ti,ab,rw.
4. Amodiaquine.ti,ab,rw.
5. Ampyrone.ti,ab,rw.
6. Antipyrine.ti,ab,rw.
7. Apazone.ti,ab,rw.
8. Aspirin.ti,ab,rw.
9. Bromelains.ti,ab,rw.
10. BW-755C.ti,ab,rw.
11. Celecoxib.ti,ab,rw.
12. Clofazimine.ti,ab,rw.
13. Clonixin.ti,ab,rw.
14. Curcumin.ti,ab,rw.
15. Dapsone.ti,ab,rw.
16. Diclofenac.ti,ab,rw.
17. Diflunisal.ti,ab,rw.
18. Dipyrone.ti,ab,rw.
19. Epirizole.ti,ab,rw.
20. Etodolac.ti,ab,rw.
21. Etoricoxib.ti,ab,rw.
22. Fenoprofen.ti,ab,rw.
23. Flurbiprofen.ti,ab,rw.
24. Glycyrrhizic Acid.ti,ab,rw.
25. Ibuprofen.ti,ab,rw.
26. Indomethacin.ti,ab,rw.
27. Indoprofen.ti,ab,rw.
28. Ketoprofen.ti,ab,rw.
29. Ketorolac.ti,ab,rw.
30. Lumiracoxib.ti,ab,rw.
31. Meclofenamic Acid.ti,ab,rw.
32. Mefenamic Acid.ti,ab,rw.
33. Mesalamine.ti,ab,rw.
34. Naproxen.ti,ab,rw.
35. Niflumic Acid.ti,ab,rw.
36. Nordihydroguaiaretic Acid.ti,ab,rw.
37. Oxyphenbutazone.ti,ab,rw.
38. Parecoxib.ti,ab,rw.
39. Pentosan Sulfuric Polyester.ti,ab,rw.
40. Phenylbutazone.ti,ab,rw.
41. Piroxicam.ti,ab,rw.
42. Prenazone.ti,ab,rw.

43. Salicylate$.ti,ab,rw.
44. Sulfasalazine.ti,ab,rw.
45. Sulindac.ti,ab,rw.
46. Suprofen.ti,ab,rw.
47. Tolmetin.ti,ab,rw.
48. Valdecoxib.ti,ab,rw.
49. Meloxicam.ti,ab,rw.
50. Nabumetone.ti,ab,rw.
51. Choline magnesium trisalicylate.ti,ab,rw.
52. Rofecoxib.ti,ab,rw.
53. or/1-52
54. Chemoprevention/
55. (prevention or prevent or chemoprevent$ or chemoprophyl$).ti.
56. 54 or 55
57. 53 or 56
58. exp Colorectal Neoplasms/
59. exp Intestinal Polyps/
60. exp Adenomatous Polyps/
61. (colorectal or colon or colonic or rectal or rectum or rectosigmoid or adenomat$).mp.
62. (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplasm$ or polyp$).mp.
63. 61 and 62
64. or/58-60,63
65. 57 and 64
66. exp Case-Control Studies/
67. exp cohort studies/
68. Cross-sectional studies/
69. exp Epidemiologic Studies/
70. ((cohort or incidence or prospective) adj2 (stud$ or analys$)).mp.
71. (case adj (control$ or base or comparison or referent)).mp.
72. ((Follow up or followup) adj (study or studies)).tw.
73. (observational adj (study or studies)).tw.
74. Longitudinal.tw.
75. Retrospective.tw.
76. Cross sectional.tw.
77. or/66-76
78. RANDOMIZED CONTROLLED TRIAL.pt.
79. CONTROLLED CLINICAL TRIAL.pt.
80. RANDOMIZED CONTROLLED TRIALS.sh.
81. RANDOM ALLOCATION.sh.
82. DOUBLE BLIND METHOD.sh.
83. SINGLE-BLIND METHOD.sh.
84. or/78-83
85. (ANIMALS not HUMAN).sh.
86. 84 not 85
87. CLINICAL TRIAL.pt.

88. exp CLINICAL TRIALS/
89. (clin$ adj25 trial$).ti,ab.
90. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
91. PLACEBOS.sh.
92. placebo$.ti,ab.
93. random$.ti,ab.
94. versus.tw.
95. RESEARCH DESIGN.sh.
96. or/87-95
97. 96 not 85
98. 97 not 86
99. 86 or 98
100. 77 or 99
101. 100 and 65
102. limit 101 to english language
103. 102 not (ANIMALS not HUMAN).sh.

#1 (colorectal neoplasms[majr] AND human[mh] AND english[la]) OR ((colorectal[ti] OR colon[ti] OR colonic[ti] OR rectal[ti] OR rectum[ti] OR rectosigmoid[ti]) AND (cancer*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR malignan*[ti] OR tumor*[ti] OR tumour*[ti] OR neoplasm*[ti]))

#2 non-steroidal anti inflammatory drugs or nsaids or nsaid or cox-2 inhibitor or cox 2 inhibitor or cyclooxygenase

#3 #1 AND #2 not (medline[sb] or in process[sb] or pubstatusaheadofprint) Limits: English, Cancer

Harms (Key question 3)

1. (ae or ct or to).fs.
2. (risk$ or harm$).mp.
3. (adverse event$ or (Adverse adj2 reaction$)).mp.
4. (ADR or SAE).mp.
5. safety.mp.
6. (side effect$ or toxic$).mp.
7. or/1-6
8. exp Anti-Inflammatory Agents, Non-Steroidal/
9. exp Cyclooxygenase Inhibitors/
10. Aminopyrine.ti,ab,rw.
11. Amodiaquine.ti,ab,rw.
12. Ampyrone.ti,ab,rw.
13. Antipyrine.ti,ab,rw.
14. Apazone.ti,ab,rw.

15. Aspirin.ti,ab,rw.
16. Bromelains.ti,ab,rw.
17. BW-755C.ti,ab,rw.
18. Celecoxib.ti,ab,rw.
19. Clofazimine.ti,ab,rw.
20. Clonixin.ti,ab,rw.
21. Curcumin.ti,ab,rw.
22. Dapsone.ti,ab,rw.
23. Diclofenac.ti,ab,rw.
24. Diflunisal.ti,ab,rw.
25. Dipyrone.ti,ab,rw.
26. Epirizole.ti,ab,rw.
27. Etodolac.ti,ab,rw.
28. Etoricoxib.ti,ab,rw.
29. Fenoprofen.ti,ab,rw.
30. Flurbiprofen.ti,ab,rw.
31. Glycyrrhizic Acid.ti,ab,rw.
32. Ibuprofen.ti,ab,rw.
33. Indomethacin.ti,ab,rw.
34. Indoprofen.ti,ab,rw.
35. Ketoprofen.ti,ab,rw.
36. Ketorolac.ti,ab,rw.
37. Lumiracoxib.ti,ab,rw.
38. Meclofenamic Acid.ti,ab,rw.
39. Mefenamic Acid.ti,ab,rw.
40. Mesalamine.ti,ab,rw.
41. Naproxen.ti,ab,rw.
42. Niflumic Acid.ti,ab,rw.
43. Nordihydroguaiaretic Acid.ti,ab,rw.
44. Oxyphenbutazone.ti,ab,rw.
45. Parecoxib.ti,ab,rw.
46. Pentosan Sulfuric Polyester.ti,ab,rw.
47. Phenylbutazone.ti,ab,rw.
48. Piroxicam.ti,ab,rw.
49. Prenazone.ti,ab,rw.
50. Salicylate$.ti,ab,rw.
51. Sulfasalazine.ti,ab,rw.
52. Sulindac.ti,ab,rw.
53. Suprofen.ti,ab,rw.
54. Tolmetin.ti,ab,rw.
55. Valdecoxib.ti,ab,rw.
56. Meloxicam.ti,ab,rw.
57. Nabumetone.ti,ab,rw.
58. Choline magnesium trisalicylate.ti,ab,rw.
59. Rofecoxib.ti,ab,rw.
60. or/8-59

61. limit 60 to systematic reviews
62. limit 61 to english language
63. 7 and 62
64. 63 and (2003$ or 2004$).ed.

Cost-effectiveness analysis (Key question 4)

1. exp Anti-Inflammatory Agents, Non-Steroidal/
2. exp Cyclooxygenase Inhibitors/
3. Aminopyrine.ti,ab,rw.
4. Amodiaquine.ti,ab,rw.
5. Ampyrone.ti,ab,rw.
6. Antipyrine.ti,ab,rw.
7. Apazone.ti,ab,rw.
8. Aspirin.ti,ab,rw.
9. Bromelains.ti,ab,rw.
10. BW-755C.ti,ab,rw.
11. Celecoxib.ti,ab,rw.
12. Clofazimine.ti,ab,rw.
13. Clonixin.ti,ab,rw.
14. Curcumin.ti,ab,rw.
15. Dapsone.ti,ab,rw.
16. Diclofenac.ti,ab,rw.
17. Diflunisal.ti,ab,rw.
18. Dipyrone.ti,ab,rw.
19. Epirizole.ti,ab,rw.
20. Etodolac.ti,ab,rw.
21. Etoricoxib.ti,ab,rw.
22. Fenoprofen.ti,ab,rw.
23. Flurbiprofen.ti,ab,rw.
24. Glycyrrhizic Acid.ti,ab,rw.
25. Ibuprofen.ti,ab,rw.
26. Indomethacin.ti,ab,rw.
27. Indoprofen.ti,ab,rw.
28. Ketoprofen.ti,ab,rw.
29. Ketorolac.ti,ab,rw.
30. Lumiracoxib.ti,ab,rw.
31. Meclofenamic Acid.ti,ab,rw.
32. Mefenamic Acid.ti,ab,rw.
33. Mesalamine.ti,ab,rw.
34. Naproxen.ti,ab,rw.
35. Niflumic Acid.ti,ab,rw.
36. Nordihydroguaiaretic Acid.ti,ab,rw.
37. Oxyphenbutazone.ti,ab,rw.
38. Parecoxib.ti,ab,rw.
39. Pentosan Sulfuric Polyester.ti,ab,rw.

40. Phenylbutazone.ti,ab,rw.
41. Piroxicam.ti,ab,rw.
42. Prenazone.ti,ab,rw.
43. Salicylate$.ti,ab,rw.
44. Sulfasalazine.ti,ab,rw.
45. Sulindac.ti,ab,rw.
46. Suprofen.ti,ab,rw.
47. Tolmetin.ti,ab,rw.
48. Valdecoxib.ti,ab,rw.
49. Meloxicam.ti,ab,rw.
50. Nabumetone.ti,ab,rw.
51. Choline magnesium trisalicylate.ti,ab,rw.
52. Rofecoxib.ti,ab,rw.
53. or/1-52
54. Chemoprevention/
55. (prevention or prevent or chemoprevent$ or chemoprophyl$).ti.
56. 54 or 55
57. 53 or 56
58. exp Colorectal Neoplasms/
59. exp Intestinal Polyps/
60. exp Adenomatous Polyps/
61. (colorectal or colon or colonic or rectal or rectum or rectosigmoid or adenomat$).mp.
62. (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or neoplasm$ or polyp$).mp.
63. 61 and 62
64. or/58-60,63
65. 57 and 64
66. exp Case-Control Studies/
67. exp cohort studies/
68. Cross-sectional studies/
69. exp Epidemiologic Studies/
70. ((cohort or incidence or prospective) adj2 (stud$ or analys$)).mp.
71. (case adj (control$ or base or comparison or referent)).mp.
72. ((Follow up or followup) adj (study or studies)).tw.
73. (observational adj (study or studies)).tw.
74. Longitudinal.tw.
75. Retrospective.tw.
76. Cross sectional.tw.
77. or/66-76
78. RANDOMIZED CONTROLLED TRIAL.pt.
79. CONTROLLED CLINICAL TRIAL.pt.
80. RANDOMIZED CONTROLLED TRIALS.sh.
81. RANDOM ALLOCATION.sh.
82. DOUBLE BLIND METHOD.sh.
83. SINGLE-BLIND METHOD.sh.
84. or/78-83

85. (ANIMALS not HUMAN).sh.
86. 84 not 85
87. CLINICAL TRIAL.pt.
88. exp CLINICAL TRIALS/
89. (clin$ adj25 trial$).ti,ab.
90. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
91. PLACEBOS.sh.
92. placebo$.ti,ab.
93. random$.ti,ab.
94. versus.tw.
95. RESEARCH DESIGN.sh.
96. or/87-95
97. 96 not 85
98. 97 not 86
99. 86 or 98
100. 77 or 99
101. 100 and 65
102. limit 101 to english language
103. 102 not (ANIMALS not HUMAN).sh.
104. limit 65 to english language
105. 104 not (ANIMALS not HUMAN).sh.
106. ec.fs.
107. 105 and 106
108. limit 105 to "economics (sensitivity)"
109. 107 or 108
110. 109 not 103

Appendix 2. Study Selection—Screening Forms

Aspirin and NSAIDs for chemoprevention of colorectal cancer (CRC_NSAID)-SRS

Screening questions: LEVEL 1 (Broad screening)

Inclusion Criteria

1. Does this citation refer to a **potentially** relevant study of ASA or any NSAIDs/Cox-2 Inhibitors for the prevention of polyps or colon cancer or related death? (NOTE: we are not interested in animal or tissue culture studies. Include FAP or Lynch or IBD for discussion *only)*
   YES NO CAN'T TELL

2. Please, check all that apply (*non-consequential*)
   a. Refers also to harms (key question 3)
   b. Is a systematic or narrative review
   c. Is a cost-effectiveness analysis
   d. IMPORTANT for Introduction/discussion
   e. None of the above
   f. Can't tell

3. Comment's box

Screening questions: LEVEL 2 (Relevant Assessment)

Inclusion Criteria

1. Does this study include the following population: healthy adults (>18 years of age) with or without family history of sporadic CRC *or* a **personal** history of polyps (exclude: previous CRC, FAP, HNPCC, IBD)?
   YES NO CAN'T TELL

2. Does this study employ Aspirin or any class of NSAIDs (e.g., ibuprofen, diclofenac, naproxen, COX-2 Inh, etc.) as an intervention?
   YES NO CAN'T TELL

3. Does this intervention target the prevention of colorectal cancer *or* incidence of colorectal adenomatous polyps *or* its related mortality?
   YES NO CAN'T TELL

4. What is the study design? *Select one*: (a-e included for Data Abstraction/quality assessment) colorectal cancer
    a. RCT
    b. Non-RCT (controlled trial, non-randomized)
    c. Prospective cohort study
    d. Case-control study
    e. Cost-effectiveness analysis
    f. Systematic review
    g. Narrative Review
    h. Can't tell
    i. None of the Above

5. I want this article for the report (discussion, introduction) *(optional)*
   YES NO

6. Comment's box

Screening questions: LEVEL 3 (Level of evidence)

1. Does this report belong to the following Levels of Evidence (see below)?
   YES NO

2. Level of evidence of this report (select one):
    a. RCT parallel design
    b. RCT crossover design
    c. RCT factorial design
    d. Controlled clinical trial (non-RCT)
    e. Multiple prospective cohorts
    f. At least one prospective cohort and one retrospective cohort
    g. Case-control
    h. Cost-effectiveness analysis/Economic
    i. None of the above

Data abstraction form: General and by level of evidence

Instructions: ***Please answer each question.*** Selecting response options means clicking on them. A box presented with or without a request to select response options is asking you to provide specific information. When it is not reported (= NR), the question does not apply (= N/A), you cannot tell what it is (= CT), or you have no comment (= NC), type the relevant code in the text box. If the research report describes more than one study, answer in this eForm all the questions for the *first reported study* and the companion studies as if it were only one report.

1. Initials of reviewer: BOX
2. Reference identification # (Refid): BOX

3. Author, Year, Location (country(ies): BOX
4. Publication status (*select one*):
    a. Journal publication
    b. Cochrane review
    c. Conference abstract/poster
    d. Book
    e. Book chapter
    f. UpTodate
    g. HTA/technical report
    h. FDA website document
    i. Other Internet document
    j. Thesis
    k. Unpublished document
    l. Study sponsor's internal report
    m. Other: BOX

5. If other included reports refer to this same study, provide the Refid(s): BOX
6. Setting(s) *(select all)*:
    - Number of sites: BOX
    - Setting(s) (e.g., GI department, teaching hospital, etc): BOX

7. Funding source type (*select all that apply*) and specify:
    a. Government
    b. Industry
    c. Private (non-industry)
    d. Hospital
    e. Other
    f. Not reported
    g. Can't tell

8. Population characteristics (*select all*):
    - Total # individuals screened/enrolled/completed (e.g. n=320/298/270): BOX
    - Mean Age (SD/SE; range) of all study participants (eg. 35 (20-55) y): BOX
    - % Males (full sample): BOX
    - Race/ethnicity (White (%), Black (%), etc): BOX
    - Weight (per arm/cohort): BOX

9. Eligibility criteria (*select all):*
    - Inclusion criteria: BOX
    - Exclusion criteria: BOX

10. Study duration (select all):
    - Total study duration: BOX

- Screening/wash out/intervention/follow-up periods (eg. 2 y/NR/1 y/4 y): BOX

11. Number of dropouts/withdrawals with reasons, per study arm/cohort: BOX
12. Comments BOX

1. Please, click the design where is belongs:

-Randomized controlled trial/non-randomized controlled trial
-Prospective Cohort study (multiple or single)
-Case-control study

RCTs/Non-RCTs

2. Identify any problems with the research design (e.g., definition of placebo/control(s); inappropriateness of run-in and washout periods), or its implementation: BOX
3. Comments on notable differences between study arms/cohorts re Age, % males, Race/ethnic composition and/or weight of their participants at baseline (e.g. Arm 1 S > % males than Arm 2 or NS between arms): BOX
4. **Risk Factors for CRC at baseline**, specify proportion of each (*select all that apply*):
    - **a.** Average risk: BOX
    - **b.** Family history of colorectal cancer: BOX
    - **c.** Family history of polyps: BOX
    - **d.** Personal history of polyps: BOX
    - **e.** Other: BOX
    - **f.** None of the above
    - **g.** can't tell
5. Comments, including notable differences between study arms re **each risk factor** at baseline (eg. Arm 1 S > % family history of polyps than Arm 2): BOX
6. Concurrent and/or antecedent conditions **at baseline** (% per arm), including notable differences between arm/cohorts: BOX
7. Pre-study medications/treatments and dose, per arm (including NSAID, aspirin, GI protectors, supplements, vitamins, etc): BOX
8. Participants were enrolled according to which criterion (*select one*)?
    - **a.** Intention-to-treat (all randomized/enrolled)
    - **b.** Those receiving at least one dose
    - **c.** Those completing the study (i.e., with follow-up data)
    - **d.** Can't tell
    - **e.** Other: BOX
9. Was sample size calculated (Beta, alpha, one/two-sided?) (*select one):*
   YES NO CAN'T TELL
10. Comments about the statistical analysis (Power analysis, appropriateness of statistical method, etc): BOX
11. **Cointerventions/other exposures:** describe the medications/treatments/exposures allowed **during** the study period (drug, dose, etc): BOX
12. Describe the diagnosis method(s) of polyps/CRC (e.g., colonoscopy, surgery, etc): BOX
13. How were the intestinal polyps/CRC defined (including size, location and histology)? BOX
14. Describe the outcomes measured in this study (*select all):*

    - **a.** Primary: BOX
    - **b.** Secondary: BOX
15. Timing of outcome assessments and when, relative to start of intervention (eg, week 4): BOX
16. Which method(s) were used to assess the clinical outcomes (e.g., Flexible sigmoidoscopy, colonoscopy, barium enema, combination, other)? BOX
17. Number of arms included in this study (define) **Note**: in a cross-over trial, each different phase is considered an intervention arm): BOX
18. **Study arm number 1** (*select all*):
    - **a.** Intervention type (e.g., drug or placebo): BOX
    - **b.** Brand/ manufacturer (if applicable): BOX
    - **c.** Dose / frequency / timing: BOX
    - **d.** Intervention length: BOX
    - **e.** number of participants enrolled/completed (eg, n=22/16) BOX
19. **Study arm number 2** (*select all)* (<u>if there are no more arms/cohort GO to question 25</u>)
    - **a.** Intervention type (e.g., drug or placebo): BOX
    - **b.** Brand/ manufacturer (if applicable): BOX
    - **c.** Dose / frequency / timing: BOX
    - **d.** Intervention length: BOX
    - **e.** number of participants enrolled/completed (eg, n=22/16) BOX
20. **Study arm number 3** (*select all)* (<u>if there are no more arms/cohort GO to question 25</u>)
    - **a.** Intervention type (e.g., drug or placebo): BOX
    - **b.** Brand/ manufacturer (if applicable): BOX
    - **c.** Dose / frequency / timing: BOX
    - **d.** Intervention length: BOX
    - **e.** number of participants enrolled/completed (eg, n=22/16) BOX
21. **Study arm number 4** (*select all)* (<u>if there are no more arms/cohort GO to question 25</u>)
    - **a.** Intervention type (e.g., drug or placebo): BOX
    - **b.** Brand/ manufacturer (if applicable): BOX
    - **c.** Dose / frequency / timing: BOX
    - **d.** Intervention length: BOX
    - **e.** number of participants enrolled/completed (eg, n=22/16) BOX
22. Adverse events/ side effects reported in the present study, per study arm/cohort (*select all that apply):*
    - **a.** GI toxicity: BOX
    - **b.** Renal: BOX
    - **c.** Hemorrhagic events: BOX
    - **d.** Cardiovascular: stroke BOX
    - **e.** CV: MI BOX
    - **f.** Hepatic: BOX
    - **g.** Death BOX
    - **h.** Hospitalization BOX
    - **i.** Other: BOX
    - **j.** Comments BOX
23. **Outcome results** (statistical significant difference only, e.g., NSAID group did S better than placebo group) (*select all that apply):* NOTE: ROW DATA WILL BE

EXTRACTED IF METAANALYSIS IS FEASIBLE BY OUR STATISTICIAN NS = nonstatistically significant difference; S = statistically significant difference

- **a.** Mortality (Overall) BOX
- **b.** Mortality for CRC: BOX
- **c.** Incidence of CRC: BOX
- **d.** Stage of CRC: BOX
- **e.** Incidence of any polyps: BOX
- **f.** Incidence of advanced polyps: BOX
- **g.** Number of polyps: BOX
- **h.** Size of polyps: BOX
- **i.** Other (defined by the author): BOX

24. Control for potential confounders/ covariates/ effect modifiers (If it was done, how and results): BOX
25. Comments BOX

Prospective cohort studies (multiple or single)

26. **Study population**: (select all)
    -Name of cohort(s): BOX
    -Length of followup: BOX
27. **Risk Factors for CRC at baseline**, specify proportion of each (*select all that apply*):
    - **a.** Average risk: BOX
    - **b.** Family history of colorectal cancer: BOX
    - **c.** Family history of polyps: BOX
    - **d.** Personal history of polyps: BOX
    - **e.** Other: BOX
    - **f.** None of the above
    - **g.** can't tell
28. Comments, including notable differences between exposed vs. non-exposed re **each risk factor** at baseline (eg. exposed 1 S > % family history of polyps than non-exposed): BOX
29. Number and definition of exposures (types of NSAIDs/ASA considered): BOX
30. Ascertainment of exposure (e.g. questionnaire; frequency of data gathering): BOX
31. **Cointerventions/other exposures:** describe the medications/treatments/exposures allowed **during** the study period (drug, dose, etc): BOX
32. Comments on notable differences between exposed vs. non-exposed re Age, % males, Race/ethnic composition, and co-interventions: BOX
33. Describe the outcomes measured in this study (*select all that apply):*
    - **a.** Primary
      -Number of polyps
      -Number of CRCs
      -Mortality from CRC
      -Overall mortality
      -Other: BOX
    - **b.** Secondary
      -Number of polyps

-Number of CRCs
-Mortality from CRC
-Overall mortality
-Other: BOX

~~34.~~ Timing of outcome assessments and when, relative to start of intervention (eg, years of f/u): BOX

35. Describe the data source for outcome measure (e.g., colonoscopy, surgery, pathology records, mortality records): BOX
36. How were the intestinal polyps/CRC defined (including size, location and histology)? BOX
37. How were cases ascertained? (review of case records, pathology slides): BOX
38. Completeness of data (e.g. % subjects with incomplete records): BOX
39. Identify any problems with the research design (e.g., measure of exposure, case ascertainment, follow-up, study population), or its implementation: BOX

40. **Non-exposed (select all that apply)**
    - **a.** exposure type if any: BOX
    - **b.** Cumulative dose or equivalent: BOX
    - **c.** Duration of f/u: BOX
    - **d.** number of participants enrolled/analyzed (eg, n=22/16) BOX
41. **Exposed number 1**
    - **a.** exposure type: BOX
    - **b.** Cumulative dose or equivalent: BOX
    - **c.** Duration of f/u: BOX
    - **d.** number of participants enrolled/analyzed (eg, n=22/16): BOX
42. **Exposed number 2** (<u>if there are no more arms/cohort GO to question 48</u>)
    - **a.** exposure type: BOX
    - **b.** Cumulative dose or equivalent: BOX
    - **c.** Duration of f/u: BOX
    - **d.** number of participants enrolled/analyzed (eg, n=22/16) BOX
43. **Exposed number 3** (<u>if there are no more arms/cohort GO to question 48</u>)
    - **a.** exposure type: BOX
    - **b.** Cumulative dose or equivalent: BOX
    - **c.** Duration of f/u: BOX
    - **d.** number of participants enrolled/analyzed (eg, n=22/16) BOX
44. Adverse events/ side effects reported in the present study, in exposed vs. non exposed (*select all that apply):*
    - **a.** GI toxicity: BOX
    - **b.** Renal: BOX
    - **c.** Hemorrhagic events: BOX
    - **d.** Cardiovascular: stroke BOX
    - **e.** CV: MI BOX
    - **f.** Hepatic: BOX
    - **g.** Death BOX
    - **h.** Hospitalization BOX
    - **i.** Other: BOX

j. Comments BOX

45. **Outcome results** (statistical significant difference only, e.g., exposed group did S better than non-exposed group) (*select all that apply):* NOTE: ROW DATA WILL BE EXTRACTED IF METAANALYSIS IS FEASIBLE BY OUR STATISTICIAN NS = nonstatistically significant difference; S = statistically significant difference
    a. Mortality (Overall) BOX
    b. Mortality for CRC: BOX
    c. Incidence of CRC: BOX
    d. Stage of CRC: BOX
    e. Incidence of any polyps: BOX
    f. Incidence of advanced polyps: BOX
    g. Number of polyps: BOX
    h. Size of polyps: BOX
    i. Other (defined by the author): BOX
46. Control for potential confounders/ covariates/ effect modifiers (If it was done, how and results): BOX
47. Comments about the statistical analysis (Power analysis, appropriateness of statistical method, etc): BOX
48. Comments BOX

Case-control studies

49. Comments on notable differences between **cases and controls** re Age, % males, Race/ethnic composition and/or weight of their participants at baseline (e.g. cases S > % males than controls or NS between groups): BOX
50. Comments on notable differences between **case and controls** re **Risk Factors for CRC (as %in cases and % in controls)** (*select all that apply*): *(if applicable)*
    a. Average risk: BOX
    b. Family history of colorectal cancer: BOX
    c. Family history of polyps: BOX
    d. Personal history of polyps: BOX
    e. Other: BOX
    f. Not reported
    g. Not applicable
51. Comments, including notable differences between **cases and controls** re **each risk factor** at baseline (eg. cases S > % family history of polyps than controls): BOX
52. Concurrent and/or antecedent conditions (% per group), including notable differences between **cases and controls** *(if applicable):* BOX
53. Number and definition of exposures (types of NSAIDs considered): BOX
54. Ascertainment of exposure (e.g. questionnaire, chart review): BOX
55. **Co-interventions/other exposures:** list other exposures that were also measured BOX
56. Comments on notable differences between cases and controls re co-interventions: BOX
57. Describe the diagnosis method(s) of polyps/CRC (e.g., colonoscopy, surgery, etc): BOX
58. How were the intestinal polyps/CRC defined (including size, location and histology)? BOX
59. Describe the outcomes measured in this study (*select all that apply):*
    a. Primary

-number of polyps
-number of CRCs
-mortality from CRC
-overall mortality
-NASID exposure
-Other: BOX

b. Secondary

-number of polyps
-number of CRCs
-mortality from CRC
-overall mortality
-NSAID exposure
-Other: BOX

60. Which method(s) were used to assess the clinical outcomes (e.g., Flexible sigmoidoscopy, colonoscopy, barium enema, combination, other)? BOX
61. **Cases** (*select all*)
    -Source of recruitment of **cases** (eg database, part of a cohort, clinic attendance): BOX
    -Definition of **cases**: (eg. Incident adenomatous polyp, incident CRC etc): BOX
    -Ascertainment of **cases** (eg, Review of pathology, chart review, etc) BOX
    -Number of participants enrolled/analyzed (eg, n=22/16) BOX

62. **Controls 1**
    -Source of recruitment of **controls** (e.g. pts attending a clinic): BOX
    -Definition of **controls** (eg. absence of CRC or polyp, etc): BOX
    -Number of participants enrolled/analyzed (eg, n=22/16) BOX
63. **Controls 2** (if applicable)
    -Source of recruitment of **controls** (e.g. pts attending a clinic): BOX
    -Definition of **controls** (eg. absence of CRC or polyp, etc): BOX
    -Number of participants enrolled/analyzed (eg, n=22/16) BOX
64. Adverse events/ side effects reported in the present study, per study arm/cohort (*select all that apply):*
    a. GI toxicity: BOX
    b. Renal: BOX
    c. Hemorrhagic events: BOX
    d. Cardiovascular: stroke BOX
    e. CV: MI BOX
    f. Hepatic: BOX
    g. Death BOX
    h. Hospitalization BOX
    i. Other: BOX
    j. Comments BOX
65. Identify any problems with the research design (e.g., definition of case/control(s)), or its implementation: BOX
66. **Outcome results** (as OR according to NSAID exposure) (*select all that apply):* NOTE: ROW DATA WILL BE EXTRACTED IF METAANALYSIS IS FEASIBLE BY OUR

STATISTICIAN NS = nonstatistically significant difference; S = statistically significant difference

a. Mortality (Overall) BOX
b. Mortality for CRC: BOX
c. Incidence of CRC: BOX
d. Stage of CRC: BOX
e. Incidence of any polyps: BOX
f. Incidence of advanced polyps: BOX
g. Other (defined by the author): BOX

67. Control for potential confounders/ covariates/ effect modifiers (If it was done, how and results): BOX
68. Comments about the statistical analysis (Power analysis, appropriateness of statistical method, etc): BOX
69. Comments BOX

Screening Questions For Key question 3 (harms): LEVEL 1 (Broad screening)

1. Is this a systematic review (*of RCTs or cohort studies or case-control*) that addresses gastrointestinal and/or cardiovascular and/or renal harms due to the chronic use (at least 4 weeks) of Aspirin or any NSAID (including COX-2 Inhibitors) on any **human** adult (> 18 years old) population? **(only in English)** **(Reviews about efficacy of a drug are also included)**
   YES NO CAN'T TELL

2. I want this article for Introduction-Discussion
   YES NO CAN'T TELL

3. Comments BOX

Screening Questions For Key question 3 (harms): LEVEL 2 (Relevance assessment)

1. Is this a systematic review (of RCTs or cohort studies or case-control) that addresses gastrointestinal and/or cardiovascular and/or renal harms due to the chronic use (at least 4 weeks) of Aspirin or any NSAID (including COX-2 Inhibitors) on any human adult (> 18 years old) population? (only in English (Reviews about efficacy of a drug are also included)
   YES NO CAN'T TELL

2. Does this review report on **at least one** the following endpoints:
   - **GI:** endoscopic ulcers, clinical ulcers (POB & PUB), GI symptoms (i.e., hemorrhage, pain, etc), death
   - **CV:** Hypertension, CHF, edema, MI, stroke, death
   - **Renal:** Renal failure (CFR, ARF), dialysis, increase in creatinine

3. I want this article for Introduction-Discussion
   YES NO CAN'T TELL

4. I want to contact the author for more info
   YES NO

5. Comments BOX

Data abstraction form: Key question 3 (harms)

Instructions: ***Please answer each question.*** Selecting response options means clicking on them. A box presented with or without a request to select response options is asking you to provide specific information. When it is not reported (= NR), the question does not apply (= N/A), you cannot tell what it is (= CT), or you have no comment (= NC), type the relevant code in the text box. If the research report describes more than one study, answer in this eForm all the questions for the *first reported study* while at the same time letting the review manager know that another data abstraction form is required.

1. **All.** Initials of reviewer: **BOX**
2. **All**. Reference identification # (Refid): **BOX**
3. **All**. Author, Year: **BOX**
5. **General.** Publication status (*select one*):
   - Journal publication
   - Cochrane review
   - Conference abstract/poster
   - Book
   - Book chapter
   - UpTodate
   - HTA/technical report
   - FDA website document
   - Other Internet document
   - Thesis
   - Unpublished document
   - Study sponsor's internal report
   - Other **BOX**

6. **All**. If other included reports refer to this same study, provide the Refid(s): **BOX**

7. **Title**: was this report identified as a meta-analysis [or systematic review]? YES NO

8. Funding source type (*select all that apply*), specify: **BOX**
   - Government
   - Industry
   - Private (non-industry)
   - Hospital

Other **BOX**
Not reported
Can't tell

9. Is the objective of the review (select all that apply):
-Efficacy of ASA/NSAID
-Harms of ASA/NSAID
-Both (efficacy and harms)
-Other: BOX

10. Methodology (*select all*):
-Searching method (information sources: databases [number], registers, personal files, gray literature, etc): BOX
-Range of years considered in the search (e.g., 1966-2000): BOX
-Language restriction (e.g., only English): BOX

11. Selection process (*select all*):
-Inclusion criteria: population: BOX
-Inclusion criteria: Intervention: BOX
-Inclusion criteria: Outcomes: BOX
-Inclusion criteria: Study design: BOX
-Exclusion criteria: BOX

12. Comments on the quantitative data synthesis protocol (select all)
-principal measures of effect [RR, OR, etc]: BOX
-method combining results: BOX
-handling missing data (contact authors?): BOX
-how statistical heterogeneity was assessed (sensitivity analysis): BOX
-publication bias assessed: BOX

13. Did the authors use at least 2 independent reviewers during the screening process? YES NO CAN'T TELL

14. Trial Flow (*select all*):
-n citations screened at level 1: BOX
-n reports retrieved for relevance assessment (hard copy): BOX
-n reports included in the SR: BOX
-n unique studies included in SR: BOX
-n unique studies or reports included in meta-analysis (if applicable): BOX

15. Quality assessment (describe which score system was used for each study design, eg, Jadad score, etc): BOX

16. Were the study characteristics of each trial described or tabulated?

YES NO CAN'T TELL

17. Study characteristics (*select all*):
-Countries where trials were conducted: BOX
-Sample size (total, range of sample sizes per study): BOX
-Mean-median age or range of mean ages (all participants): BOX
-Intervention(s) (name of drug, dose): BOX
-Comparators (placebo, other drug): BOX
-Duration of intervention (mean, range): BOX
-Follow-up period (mean, range): BOX

18. Results GI adverse events (*select all that apply*):
-POB (perforation/obstruction bleed): BOX
-PUB (or symptomatic ulcer): BOX
-Endoscopic ulcers: BOX
-Dyspepsia: BOX
-Abdominal pain: BOX
-Nausea: BOX
-Anemia/iron deficiency: BOX
-Occult GI blood loss: BOX
-Death due to GI adverse events: BOX
-Other (defined by authors): BOX
-None of the above

19. Results CV events (*select all that apply*):
-Hypertension: BOX
-CHF: BOX
-Edema: BOX
-MI: BOX
-Stroke/TIA: BOX
-Death due to CV events: BOX
-Other (defined by authors): BOX
-None of the above

20. Results Renal events (*select all that apply*):
-Chronic renal failure (CRF): BOX
-Acute renal failure (ARF): BOX
-Dialysis: BOX
-Increase in creatinine: BOX
-Death due to Renal events: BOX
-Other (defined by authors): BOX
-None of the above

21. Results (*select all that apply*):
-Mortality due to AE (general): BOX

-Other (defined by authors): BOX
-None of the above

22. If meta-analysis was done on harms, please describe the following information (*select all*):
-Outcome 1 analyzed (with result): BOX
-Outcome 2 analyzed (with result): BOX
-Outcome 3 analyzed (with result): BOX
-Outcome 4 analyzed (with result): BOX
-Other outcomes and results: BOX
-None of the above

23. Were the number and/or reasons for dropouts/withdrawals due to harms reported in the Systematic review (across the included studies)? YES NO Can't Tell

24. Was the author contacted by you or other members of the NSAID team re more information (raw data)? YES NO

25. Quality assessment results (mean score, by study design): BOX

26. Comment's BOX

Appendix 3. Quality Rating Criteria

Quality assessment of evidence

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor" based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
  - for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups

(including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Appendix 4. Detailed Report Supporting Sections

Study Identification

Literature search

A highly sensitive electronic search strategy was developed in Medline (Appendix 1) and modified for the other databases. For questions 1 and 2, three main concepts were included: NSAIDs or chemoprevention; CRC or intestinal polyps; and relevant study designs. Study designs sought were randomized controlled trials (RCTs; using the Cochrane highly sensitive search strategy plus "versus")[1] and case-control and cohort studies (using a filter for observational study designs based on the SIGN filter [available at http://www.sign.ac.uk/methodology/filters.html#obs, visited December 1, 2004] and terms suggested in McKibbon).[2] A comprehensive retrieval strategy for NSAIDs was derived from the indexing in both Medline and Embase, reviewer nominated terms, and previous reviews.[3-7] Terms were derived from the National Cancer Institute (NCI) Cancer topic searches (available at http://cancer.gov/search/searchcancertopics.aspx) for "Colorectal Cancer." Adding the term "Adenomatous polyps," increased the sensitivity by removing major emphasis and by retrieving text words in all fields rather than just title. The search was limited to English language reports, and non-human studies were excluded. The search was validated by testing to see if it retrieved included studies from two recent major reviews.[7-9]

Databases searched were Medline 1966-November week 3, 2004, Embase 1980-week 47 2004 (publication years 2003-2005 only) and CENTRAL, The Cochrane Library Issue 4, 2004. Pubmed Cancer subset was searched for non-Medline material. That search used the NCI search strategy for CRC with free text terms for NSAIDs and COX-2 inhibitors (COX-2 inhs) and was also limited to English. The search was conducted on December 1, 2004 and yielded seven items. The strategy is reproduced in Appendix 1.

A supplemental search was made of non-Medline material from the PubMed Cancer subset. This search used the NCI search strategy for CRC with free text terms for NSAIDs and COX-2 inhs and was limited to English. The search was conducted on December 1, 2004 and yielded seven items. The strategy is reproduced in Appendix 1.

Additional material potentially relevant to the economic analysis question (question 4 of the task order) was sought in Medline (1966 to November Week 3 2004), HealthStar (1987 to November 2004), Embase (1980 to 2004 Week 50), Cochrane Library 4th Quarter 2004 NHS EED and HTA. TRIP (www.tripdatabase.com) database was searched December 14, 2004.

A search strategy to detect recent systematic reviews of NSAID that appeared to address harm was developed and run in Medline (2003 to November Week 3 2004). Cochrane Database of Systematic Reviews (CDSR) and DARE (Cochrane Library, 3rd Quarter 2004) were searched for all systematic reviews related to NSAIDS, without date restrictions.

A weekly monitoring strategy was implemented to detect emerging information on CV harms associated with COX-2 inhs. We ran the harms search against new material added to Medline or PreMedline with the exception that a concept restricting the results to CV disease was added and the search was not limited to systematic reviews but included all new reports of NSAIDS and

harms. In addition, any records that related to CV disease matching our search strategy for NSAIDS (Appendix 1) were obtained — these included case reports, comments, consensus development, conference proceedings, editorials or letters, news or newspaper articles, published erratums, as well as retracted publications. We also monitored the FDA news digest and Health Canada's Health Product Information mailing list for announcements related to COX- 2 inhs and CV harms (monitoring dates Jan 14, 2005-May 26, 2005).

Literature Synthesis and Preparation of Systematic Evidence Review

Study selection methods:

1) Effect of NSAIDs on the risk of CRC and/or CRA. A calibration exercise was conducted prior to the initiation of study selection. Screening of articles for inclusion was conducted for each screening level by two members of the review team (see Appendix 2 for screening forms). An initial screening level to identify potentially relevant articles was followed by a relevance assessment to identify articles meeting inclusion criteria. Conflicts were resolved by consensus.

A third level of screening was included (for questions 1 and 2, efficacy) to discriminate the different levels of evidence, as follows: 1) RCT parallel design; 2) RCT crossover design; 3) RCT factorial design; 4) controlled clinical trial (non-RCT), 5) multiple prospective cohort; 6) at least one prospective cohort and one retrospective cohort; 7) case-control study; and, 8) cost-effectiveness analysis.

Data abstraction (see Appendix 2 data abstraction form) was performed by one reviewer using the SRS system and electronic forms and was checked by a second reviewer.

Inclusion/exclusion criteria (efficacy):

Design: RCTs, controlled clinical trials, and observational studies (cohorts and case-control) were considered for inclusion if they fulfilled the population, intervention, and outcome criteria detailed below.

Population: Studies were considered for inclusion if the study population included participants at 'average' risk for CRC (i.e., no known risk factors for CRA or CRC other than age), or a personal or family history of CRA or sporadic CRC. Studies involving participants with familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer syndromes (Lynch I or II) were excluded since these syndromes account for a small percentage of CRC and represent distinct clinical entities with specific management strategies. Secondary prevention studies of patients with a personal history of CRC were also excluded.

Interventions: Included studies assessed the efficacy or effectiveness of ASA, or non-ASA NSAIDs including COX-2 inhs.

Outcomes: The incidence of CRA and/or CRC; reductions in CRC-related mortality or overall mortality.

2) Harms: The GI, CV, and renal harms associated with the use of ASA, non-ASA NSAIDs, and COX-2 inhs were sought through identification of systematic reviews. Authors of systematic reviews were contacted by electronic email in the case that incomplete harms data was provided in the systematic review report. The timeline for response was set a priori by the review team as 2 weeks. If no response was obtained, the review was excluded on the basis of incomplete data.

The GI harms included: incidence of endoscopic ulcers; clinically important ulcers (POB- perforation, obstruction, bleeding, and PUB- perforation, obstruction, bleeding or symptomatic ulcer); and, GI related mortality. The CV harms included: stroke; myocardial infarction (MI); congestive heart failure; hypertension; and, CV related deaths. The renal harms included: acute renal failure; chronic renal failure; need for dialysis; ans, renal related mortality.

3) Cost-effectiveness: A specific search was conducted to identify cost-effectiveness analyses that addressed the question of the cost-effectiveness of chemoprevention with ASA or non-ASA NSAIDs for the prevention of the above listed endpoints.

Quality assessment

We used predefined criteria from the USPSTF to assess the internal validity of included systematic reviews, trials and observational studies, which we rated as "good", "fair", or "poor" (see Appendix 3) (US Preventive Services Task Force Procedure Manual. Revised July 2004).

Meta-analysis

Figure 2 and Table 1 illustrate a hierarchical framework that identifies key characteristics that were expected to be common to all the included studies. This framework was used to facilitate study grouping and subsequent data analysis. Studies were initially grouped by the "disorder" (i.e., adenoma vs. CRC), study design, study population and exposure, as these characteristics were expected to be reliably and consistently reported. Subsequently, studies were subcategorized based on the measures of dose effect and secondary outcomes, such as comparisons of polyp size, histology, morbidity or mortality. Evidence tables based on the illustrated framework were created to aid in subgroup generation (Appendix 8). We anticipated the dose effect measure to be the most heterogeneous outcome reported between studies. Measuring the dose effect depends on the intervention dose, the frequency and duration of use, and potentially, whether the use is current and ongoing or was at some remote time in the past. In RCTs, dose effect was precisely defined, while in observational studies we anticipated variability in the definitions of "regular use" and that the dose, per se, would be rarely reported. When possible, data was reported based on a precise dose or based on defined levels of dose intensity within a study (such as low moderate or high dose). When this was not possible, we defined various levels of dose effect based on the duration of regular use of an intervention (e.g., regular use for: 1-3 years; 4-6 years; 7-9 years; and 10 or more years in the case of CRC). For CRC, studies of regular use of the intervention for <1 year or intermittent use for <5 years were not included in any meta-analytical pooling. This level of exposure was not felt to be "relevant" given the presumed mechanism of chemoprevention of CRC. Intermittent use for >5 years was considered separately, and as a meta-analytical subgroup analysis with the "lower dose"

exposure group. For adenoma incidence outcomes, shorter durations of exposure were considered.

To perform the analysis of regular NSAID use versus nonuse, we compared the risk of outcome (CRC or adenoma according to the case) in the patients exposed to the equivalent of 3 days or more per week for at least a year, with nonexposed patients. When the frequency or duration of use was not reported, we compared the risk of outcome in patients with "any NSAID use" with nonexposed patients.

Ascertainment of NSAID exposure and outcomes in the observational studies were also anticipated to be variable. The method of ascertainment of exposure of each study was abstracted and recorded in evidence tables to facilitate data analysis and interpretation. In cases where statistical pooling was possible, sensitivity analyses were conducted based on the methods of ascertainment used (i.e., questionnaire, database).

We only pooled when I^2 was 50% or less, which Higgins et al.[10] refer to as "moderate" heterogeneity. In the event that pooling was conducted, we used the reported relative risks (RRs) and corresponding 95% confidence intervals (CIs), rather than using cell counts from 2×2 tables. This was because analysis results from observational studies require adjustment for potential confounders, so that unadjusted cell counts are not appropriate. For generating the CIs, we computed the CI width by subtraction and then divided by 2*1.96 to obtain the standard error. Calculations were performed on a log scale because the standard errors of relative risks are most appropriately represented on this scale. In one case, in which no CIs were provided,[11] we chose a CI from two different reported estimates. We then computed the standard error based on that imputed CI. The pooling was conducted using inverse-variance weighting and a random effects model.[12] In all cases, we used study groupings that appeared to be clinically comparable.

Heterogeneity in efficacy data

Included studies were grouped using the methods detailed above in an effort to form logical, usable subgroups and to reduce heterogeneity. In the generated subgroups, heterogeneity was further assessed through the use of Forest plots and through the use of the I squared test for heterogeneity. Statistical pooling of results was only considered if clinically and statistically appropriate.

Analysis of harms and cost-effectiveness data

For the harms and cost-effectiveness data, the results of the included systematic reviews and cost-effectiveness studies were summarized and presented as a qualitative systematic review.

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Appendix 5. Results: Harms Due to COX-2 Inhibitor Use (Including COX-2 Selective)

Fourteen systematic reviews investigated the harms due to COX-2 inh use (Evidence Table 3.3).

General

Six systematic reviews assessed the general harms associated with COX-2 inh use in the adult population.[1-6] All six reviews included exclusively RCTs. The types of harms due COX-2 use relevant for this review were: all-cause of mortality, mortality due to harms and withdrawals due to harms.

All-cause mortality

All-cause mortality was reported in three reviews.[1,2,6] Hooper et al. found no statistically significant difference between COX-2 inh (selective or specific) and other type of NSAIDs.[1] For the less specific COX-2 inhs (etodolac, meloxicam, nabumetone or nimesulide) the RR was 0.68 (95% CI: 0.3-1.6) across 51 RCTs, while the 17 RCTS of COX-2 specific (celecoxib and refocoxib) showed a pooled RR of 1.02 (95% CI: 0.6-1.9).[1] Garner et al. did not observe any death across three RCTs comparing celecoxib with either placebo or other NSAIDs[2] and found no difference in mortality between rofecoxib (0.5%) and naproxen (0.4%) in the VIGOR trial (VIGOR: data from FDA 2001).[6]

Withdrawals due to harms

The withdrawals due to harms were reported in six reviews.[1-6] Hooper et al. observed that there was no significant difference between COX-2 selective inhs and NSAIDs across 51 trials (RR: 0.93 [95% CI: 0.9-1.0]), whereas, the risk was reduced in the 17 RCTS comparing COX-2 specific inhs with NSAIDs, yet the heterogeneity test was significant for this result (pooled RR: 0.82 [95% CI: 0.7-0.9]).[1] Deeks et al. found an increased risk of withdrawal due to harms in the celecoxib group compared with placebo in five RCTs (RR: 1.49 [95% CI: 1.15-1.92]), however, when the celecoxib group is compared with other NSAIDs the risk did not differ significantly (RR: 0.86 [95% CI: 0.72-1.04]) across eight RCTs.[3] Garner et al. showed that there was no difference between celecoxib and placebo for this outcome in one trial.[2] Edwards et al. observed no difference between valdecoxib and placebo (RR: 0.9 [95% CI: 0.7-1.3]), but valdecoxib use was associated with a lower risk of withdrawals due to harms when compared with other NSAIDs (RR: 0.6 [95% CI: 0.5-0.7]).[4]

Garner et al. showed significantly greater withdrawals due to harms with rofecoxib 12.5 mg (RR: 2.18 [95% CI: 1.34-3.55]) and 50 mg/day (RR: 2.04 [95% CI: 1.24-3.36]) when compared

to placebo when used over 6-12 weeks.[5] When rofecoxib (12.5 to 25 mg/day) was compared with diclofenac (150 mg/day), there were fewer withdrawals due to harms in both 12.5 mg and 25 mg/day (RR: 0.71 [0.52-0.97] and RR: 0.70 [0.51-0.95], respectively) in two 1-year trials.[5] Nine trials were pooled comparing the withdrawals due to harms between celecoxib (200 mg/day) versus rofecoxib (25 mg/day), showing no differences (RR: 1.03 [0.77-1.39]).[5]

In another review, Garner et al. showed that there was no statistically significant difference between rofecoxib 5 mg (3%), 25 mg (3.2%), 50 mg (4.7%) and placebo (6.2%) based one trial,[6] and no difference between rofecoxib and naproxen in another(RR: 1.02 [95% CI: 0.92-1.12]).[6]

In general COX-2 inh appear to be better tolerated than NSAIDs, but are associated with some adverse effects when compared with placebo.

CV harms

There were seven systematic reviews addressing the magnitude of CV harms due to COX-2 inh use in an adult population.[2,4-9] Six reviews included exclusively RCTs, while Jüni et al. also included observational studies such as cohort or case-control studies.[9]

The CV events reported across the systematic reviews were: death due to CV events, serious CV events (overall), acute MI, acute stroke, arterial hypertension, congestive heart failure, edema, and thrombotic events.

Three reviews reported the **mortality due to CV events**.[2,6,9] Garner et al. reported that none of the trials had experienced deaths due to CV events in patients taking celecoxib or comparators,[2] and no difference in CV mortality between rofecoxib and naproxen (0.2% both groups)in another trial.[6] Jüni et al. found no significant difference between rofecoxib and other NSAIDs in nine RCTs [RR: 0.79 (95% CI: 0.29-2.19)].[9]

Overall **serious CV events** were reported in two reviews.[8,9] Jüni et al. found that the rofecoxib group had an increased risk of serious CV harms compared with standard NSAIDs (RR: 1.55 [95% CI: 1.05–2.29]).[9] Mukherjee et al. also found an increased risk of events in the VIGOR trial (rofecoxib vs. naproxen) with a RR of 1.89 (95% CI: 1.03-3.45) in low-risk patients (not aspirin takers), while the high CV risk group (aspirin indicated patients) had a RR of 4.89 (95% CI: 1.41-16.88).[8]

Five reviews reported the **risk of acute MI** in patients taking COX-2 inh.[4-6,8,9] Jüni et al. observed an increased risk of MI with rofecoxib versus control groups (RR: 2.24 [95% CI: 1.24-4.02]).[9] Jüni et al. performed a stratified meta-analysis that showed the estimates of RR varied depending on whether rofecoxib had been compared with placebo (RR: 1.04 [0.34-3.12]), NSAIDs other than naproxen (RR: 1.55 [0.55-4.36]) or naproxen (RR: 2.93 [1.36-6.33]). High dose rofecoxib (50 mg/day) (RR: 2.83 [1.24-6.43]), as well as long-term use of at least 6 months (RR: 2.17 [1.03-4.59]) showed a significant increase in the risk of MI.[9] Mukherjee et al. reported that there were 26/99 cases of MI in patients taking rofecoxib and 37/102 cases in patients taking celecoxib in the Adverse Event Reporting System in United States.[8] Garner et al. reported the results of one large RCT (ADVANTAGE study),[10] where 5/2,785 and 1/2,772 patients in the rofecoxib and naproxen groups, respectively, had an episode of MI (RR: 4.98 [95% CI: 0.58-42.57]).[5] The statistically non significant result of this trial and the few events

that occurred make drawing conclusions from this trial difficult. In another review, Garner et al. reported that there was an increased risk of MI with rofecoxib compared with naproxen from one trial (VIGOR), with a RR of 5.0 (95% CI: 1.5-13.2).[6]

Edwards et al. observed that there were 3/2733 (0.1%) cases of MI in the valdecoxib group compared with 11/1846 (0.6%) cases in the NSAID group in nine RCTs.[4] This difference was statistically significant.[4]

Acute stroke was reported in four reviews.[5,6,8,9] Jüni et al. combined 11 RCTs and found no difference between rofecoxib and standard NSAIDs (RR: 1.02 [95% CI: 0.54-1.93]).[9] Garner et al. likewise found no difference between rofecoxib and naproxen (RR: 0.08 [95% CI: 0.00-1.36])[5]in the ADVANTAGE study, or for total cerebrovascular events (RR: 1.37 [0.55-3.41]), ischemic stroke (RR: 1.12 [0.43-2.91]) and TIA (RR: 4.98 [0.24-103.77]) in the VIGOR study.[6] Mukherjee et al. reported that there were 43/99 cases of stroke in patients taking rofecoxib, and 31/102 cases in patients taking celecoxib in the Adverse Event Reporting System in United States.[8]

Arterial hypertension was reported in four reviews.[2,5-7] Garner et al. found that there were similar rates of hypertension between three doses of rofecoxib and placebo in one review[6] and another review reported that hypertension occurred in 4/236 (1%) patients taking celecoxib and 5/329 (2%) patients taking diclofenac in one RCT.[2] Gomez Cerezo et al. reported that the patients included in the VIGOR trial using rofecoxib had an increased risk of withdrawal due to hypertension related adverse events compared with naproxen use (RR: 4.67 [95%CI: 1.93-11.28]).[7] Garner et al. reported that there was no difference between rofecoxib and naproxen in the ADVANTAGE trial (RR: 1.22 [95% CI: 0.89-1.68]),[5] and no difference between rofecoxib and nabumetone in the risk of hypertension (RR: 1.46 [95% CI: 0.53-4.12]) in three 6-week RCTs.[5] There were no differences between rofecoxib and celecoxib in this outcome (RR: 3.51 [0.73-16.84]) in two trials.[5]

Gomez Cerezo et al. also reported that the risk of developing **congestive heart failure** in the rofecoxib group did not differ from the naproxen group in one large trial (VIGOR; RR: 2.11 [95% CI: 0.96-4.67]).[7]

The incidence of **lower extremity edema** was reported in five reviews.[2,4-7] Garner et al. showed that the incidence of peripheral edema was 1% to 2% in the celecoxib groups compared with none in the placebo groups across two trials.[2] However, the incidence of edema in the naproxen group and high dose (400-800 mg/day) celecoxib groups was 2% across two trials.[2] More patients experienced peripheral edema in the celecoxib group (11/236, 3%) compared with the diclofenac group (5/329, 2%) in one trial.[2] Garner et al. (2004) observed a similar incidence of edema among rheumatoid arthritis patients receiving three doses of rofecoxib (5, 25 and 50 mg/day) and those taking placebo at 8 weeks.[6] Gomez Cerezo et al. reported a nonsignificant risk between rofecoxib and naproxen in the incidence of withdrawals due to edema in the VIGOR trial (RR: 1.92 [95% CI: 0.98-3.75]).[7] Garner et al. reported that there was no difference between rofecoxib and nabumetone from three, 6-week RCTs, in the risk of lower extremity edema (RR: 1.41 [95% CI: 0.72-2.77]), as well as from one, 6-week RCT, comparing the use of rofecoxib with diclofenac/misoprostol (RR: 1.39 [95% CI: 0.63-3.08]).[5] However, there was a greater incidence of edema in the rofecoxib (25 mg/day) groups compared with celecoxib (200 mg/day) groups from four RCTs (RR: 1.77 [95% CI: 1.27-2.47]).[5] Lastly, Edwards et al.

reported that edema affected 2% of patients taking valdecoxib and NSAID, and that it occurred significantly more frequently than with placebo (NNH: 57, 39-103) across nine trials.[4]

In summary, knowledge of the CVS harms of COX-2 inh and NSAIDs is in state of flux. There was a signal of increased cardiovascular events with rofecoxib from the VIGOR trial, and suggestion based on the Juni meta-analysis that COX-2 inh may have similar rates of CVS harms as non-naproxen-non-ASA NSAIDs , but higher rates when compared with naproxen for some endpoints. The effect of co-administration of ASA and COX-2 inhs for CVS harms has not been fully studied.

Renal

Edwards et al. observed that valdecoxib had an increased risk of developing clinically significant renal events (defined as verified abnormal renal laboratory test results or clinical findings) compared with placebo (RR: 2.9 [95% CI: 1.4-5.7]), yet not compared with other NSAIDs (ibuprofen, diclofenac or naproxen) (RR: 0.7 [95% CI: 0.5-1.0]).[4]

GI harms

Twelve reviews addressed the GI harms with the COX-2 inh use.[1-7,11-15]

In general, the COX-2 inh harms data is of greater quality than those for ASA and non-ASA NSAIDs as a result of the greater emphasis put on manufacturers by regulatory agencies in recent years to conduct large and longer term RCTs. For the non-ASA NSAIDs, a single large clinical outcome study was conducted.[16] Similarly designed large RCTs of clinically important ulcer complications such as POBs (perforation, obstruction or bleeding) have been conducted for the COX-2 inhs.[17-20] In addition to these trials, combined analyses studies including previously unpublished manufacturer data have also been published.[13,21-23] These combined analyses studies are a cross between a meta-analysis and primary clinical data in that previously unpublished data and published data from very similar trials are pooled. Furthermore, multiple trials of endoscopic ulcer outcomes have also been published for the COX-2 inh compared with placebo, and to various non-ASA NSAIDs.[24]

The included systematic reviews of the GI safety of COX-2, therefore, encompass more or less the same body of evidence described above, with the major differences being the number of included studies (because of the date of publication of the systematic review) and the emphasis of the conclusions. The following COX-2 inhs were assessed in these systematic reviews: celecoxib;[1-3,11,12,25,26] rofecoxib;[1,5-7,11] valdecoxib;[4,13,15] and meloxicam.[1,11,14] Three systematic reviews considered more than one COX-2 inh.[1,7,11]

COX-2 inh compared with placebo. Six Reviews[2-4,6,11,13] found no statistically statistically significant difference in GI bleeding or ulceration between COX-2 inhs and placebo. In a review by Ascroft et al.,[12] those patients taking celecoxib 200 mg/day did not have an increased risk of endoscopic ulcers compared with placebo, but those taking 400 mg/day were at increased risk (RR= 2.35; 95% CI: 1.02-5.38). Garner[5] found a statistically increased risk of total adverse events (RR=1.32; 95% CI: 1.11-1.56) and total GI events (one study, RR=3.39; 95% CI: 1.47-

7.84) with rofecoxib compared with placebo at 6 weeks, but not at longer time periods or for single GI outcomes.

COX-2 inh compared with non-ASA NSAIDs. In general, COX-2 are associated with a significantly lower risk of endoscopically-detected ulcers, clinically significant POBs/PUBs (POB or symptomatic ulcer), and dyspeptic symptoms than with non-ASA NSAIDs when the later group is pooled to include the commonly studied agents (ibuprofen, diclofenac, and naproxen). Furthermore, since the systematic reviews included many of the same studies, the actual risk estimates are fairly consistent.

The RR of endoscopic ulcers with a COX-2 inh versus a non-ASA NSAID is close to 0.25 (i.e., a 75% RR reduction).[1-3,5,6,11,12] The RR of POBs and PUBs each varied somewhat from about 0.40 to 0.60 (40%-60% RR reduction).[1-4,6,7,11,13,14] This latter result is driven by the COX-2 inh clinical outcome studies described above. COX-2 inhs also appear to be associated with a statistically lower RR for GI symptoms, such as dyspepsia.[1,3,5,11,15]

Specific COX-2 and specific Non-ASA NSAIDs. Celecoxib, rofecoxib and valdecoxib individually appear to have greater GI safety than naproxen, and ibuprofen with RRs of endoscopic ulcers and POBs similar to that reported above for the combined analyses.[2,3,5-7,11,12] However, some systematic reviews, particularly those based on the results of the CLASS study,[17] have suggested that celecoxib may not offer any advantage over diclofenac. In the CLASS trial there was no statistically significant difference in POBs between celecoxib and NSAIDs combined or celecoxib versus diclofenac. Celecoxib, however, appeared to be safer than ibuprofen.[3,5,7,11,17] Rostom et al. also found no statistically significance difference in PUBs between COX-2 and diclofenac in a pooled analysis of six trials.[11] Furthermore, the systematic reviews by Rostom[11] and Ashcroft[12] found no difference in endoscopic ulcers between celecoxib and diclofenac, though Ashcroft reports that in one 24-week study the RRR in favor of celecoxib over diclofenac reached statistical significance. Garner et al. reported similar findings for celecoxib versus diclofenac based on the CLASS study.[2] The apparent safety of diclofenac in this setting may be explained by its greater COX-2 selectivity compared with other non-ASA NSAIDS.[27]

The GI safety of meloxicam has been assessed in three of the systematic reviews,[1,11,14] although in the review by Hooper, meloxicam was pooled with etodolac, nabumetone, and nimesulide. If one only considers the two large meloxicam trials,[19,20] then there is no statistically significant difference in POBs or PUBs between meloxicam and the compared NSAIDs (piroxicam and diclofenac), even when these studies are pooled.[1,11,14] However, the addition of data from combined analyses trials, efficacy and tolerability trials allows meloxicam to show a statistically significant reduction in PUBs compared with non-ASA NSAIDs[1,11,14]

Influence of coadministration of ASA with a COX-2 inhs. Three trials allowed assessment of the effects of the co-administration of ASA with a COX-2: the CLASS, and TARGET studies,[17,28] and the valdecoxib combined analysis.[13] The results of all three trials found that among ASA users, the use of a COX-2 offers no GI safety advantage over the use of a standard non-ASA NSAID. In subgroup analyses of the CLASS study, celecoxib was superior to combined NSAIDs in patients not taking ASA, but not for those on celecoxib and ASA. The risk of ulcer complications in patients taking celecoxib and ASA was nearly four times that of those who were not taking ASA. Paradoxically, patients taking ibuprofen and low-dose ASA suffered fewer ulcer complications than patients taking either celecoxib or diclofenac and low-dose

ASA.[11,17] Nearly identical findings were reported by Goldstein et al. in a combined analysis study of the safety of valdecoxib.[13] In that study, valdecoxib users who were also taking ASA had a nine-fold greater risk of GI bleeding than those on valdecoxib alone. Goldstein also found that patients in the non-ASA NSAID arms of these studies who were also taking ASA did not have any further increased risk of GI bleeding.

Dose effect of COX-2 inhs. Rostom et al.[11] analyzed the COX-2 data by dose. In this systematic review, low-dose COX-2 selective NSAIDs were defined as celecoxib 200 mg bid or less, rofecoxib 25 mg daily or less, and meloxicam 7.5 mg daily. There were no statistically significant differences between low dose (seven studies) and high dose (three studies) COX-2 compared with non-ASA NSAIDs for the outcome of endoscopic ulcer,[11] Ashcroft found no difference in the risk of endoscopic ulcers between celecoxib 200 mg and 400 mg per day.[12] Garner, in a combined analysis of two studies, found a greater risk of endoscopic ulcers >5mm with rofecoxib 50 mg/day compared with 25 mg/day (RR=2.48; 95% CI: 1.21-5.11), but not for endoscopic ulcers >3mm or for the more frequent gastric ulcers.[5] Goldstein likewise found no differences in ulcer complications across doses of valedcoxib ranging from 5 mg to 80 mg per day.[13] The apparent GI safety of the COX-2 with higher doses may be in part explained by their relatively flat COX-2 inhibition curve in the range of doses that can be used clinically.[27]

In summary, COX-2 inhs offer greater GI safety than most non-ASA NSAIDs. The safety advantage over non-ASA NSAIDs appears to disappear when COX-2 inh are used with ASA.

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Appendix 6. Results: The Impact of NSAID Chemoprevention on FOBT Testing

The use of NSAIDs (both ASA and non-ASA NSAIDs) could increase GI blood loss, either occult or overt. Subjects on NSAIDs could be more likely to undergo lower GI investigations in the years prior to CRC diagnosis, potentially leading to removal of adenomas during that period and, therefore, reducing the risk of an eventual malignancy. Alternatively, the intake of NSAIDs could induce an underlying malignancy to bleed, increasing the likelihood of cancer detection. This issue was addressed in six studies, four cohort studies,[1-4] one case-control study,[5] and one decision analysis.[6] (Table 4)

In the Nurses' Health study, a prospective cohort of 27,077 average-risk women who underwent lower endoscopy between 1980 and 1998, Chan et al. compared the likelihood of regular ASA use in women with adenomas depending on the presence of manifestations of GI blood loss (either occult or visible blood) as the indication for endoscopy.[1] The multivariate RR of regular ASA use for asymptomatic women with adenoma was 0.74 (0.61-0.90) and 0.71 (0.59-0.86) for symptomatic women with adenoma (NS).

Over a 22-month period, Kahi et al. prospectively assessed 315 consecutive patients referred for a colonoscopy on the basis of a positive FOBT.[4] Patient with overt GI bleeding, those having undergone a colonoscopy within 5 years, and those on anticoagulants were excluded. Finding of lesion that could explain the positive FOBT result was possible in 21% (95% CI 14-28) and 19% (9-29) of regular ASA or NSAID users and non users, respectively (NS). Among regular ASA users, there was no relation between the dose of ASA and the likelihood of colonic findings and is unlikely to explain a positive FOBT result.

In the Health Professionals Follow-up Study, a prospective cohort of 47,900 males throughout the U.S. who underwent lower endoscopy between 1986 and 1992, Giovannucci et al. examined the possibility that subjects with undiagnosed cancers or polyps might have had bleeding, which would have led them to avoid ASA use and artifactually create an inverse association between ASA use and cancer.[2] In fact, men using ASA regularly at the onset of the study had a decreasing risk of CRC over time, negating that potential association.

In a population-based retrospective cohort study of 104,217 subjects aged 65 years or older enrolled in the Tennesse Medicaid Program, Smalley et al. noted that the use of NSAIDs at diagnosis did not affect cancer presentation, with comparable prevalence of anemia, rectal bleeding, abdominal pain, or tumor at stage I or II among NSAID users and nonusers.[3] They also noted that the adjusted RR of CRC was significantly reduced in subjects who had used NSAIDs for more than 5 years prior to diagnosis, and who had not undergone any lower GI investigations, negating the possibility that the observed protective effect of NSAID use was due to an increased likelihood of undergoing lower GI testing.

In a case-control study of 637 average-risk U.S. subjects undergoing lower endoscopy, Martinez reported that occult blood in the stools was an indication for endoscopy in 9.9% and 10.3% of NSAID users and nonusers, respectively (NS), and that the corresponding figures for rectal bleeding were 17.4% and 17.9% (NS).[5]

Ladabaum et al. used decision analysis to examine the effect of increased sensitivity and decreased specificity for FOBT in average-risk U.S. subjects taking ASA.[6] When sensitivities for CRC or CRA were as extreme as 70% and 20%, respectively, and when specificity was as low as 85%, the addition of ASA to a screening strategy of yearly FOBT plus flexible sigmoidoscopy every 5 years slightly decreased CRC mortality rates, slightly increased screening-related mortality rates, and marginally increased costs.

In summary, we could not find any evidence of a detection bias to explain the chemoprotective effect of NSAID.

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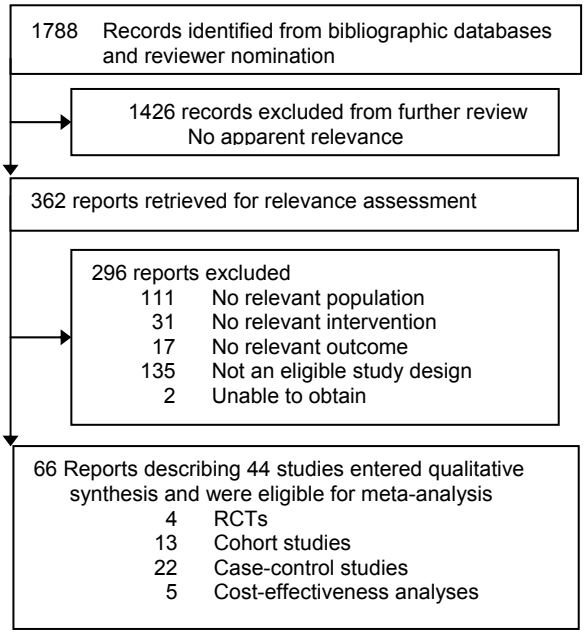
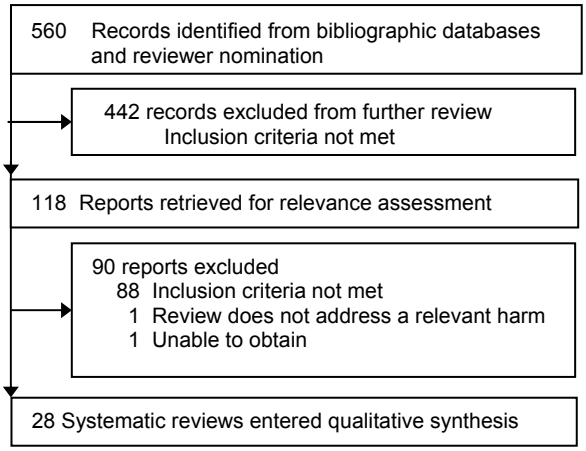
Appendix 7. QUOROM flowchart.

Key Questions 1, 2 and 4 (Efficacy and cost-effectiveness)



Key Question 3 (Harms)



Appendix 8. Figures and Tables

Figure 1. Decision making hierarchy for grouping of included studies

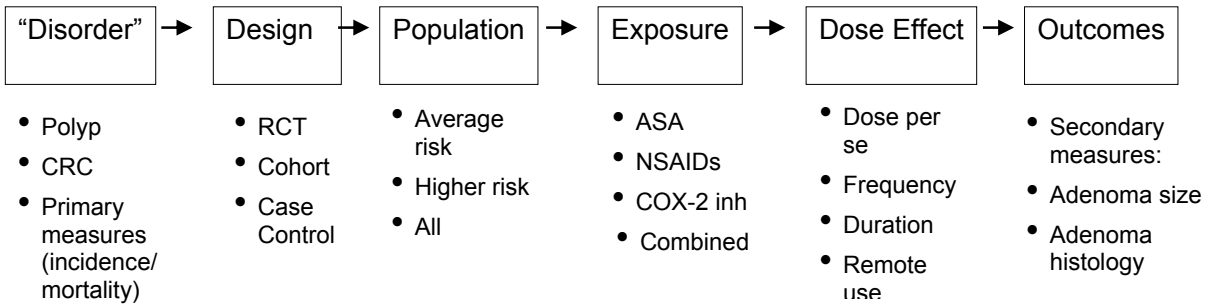
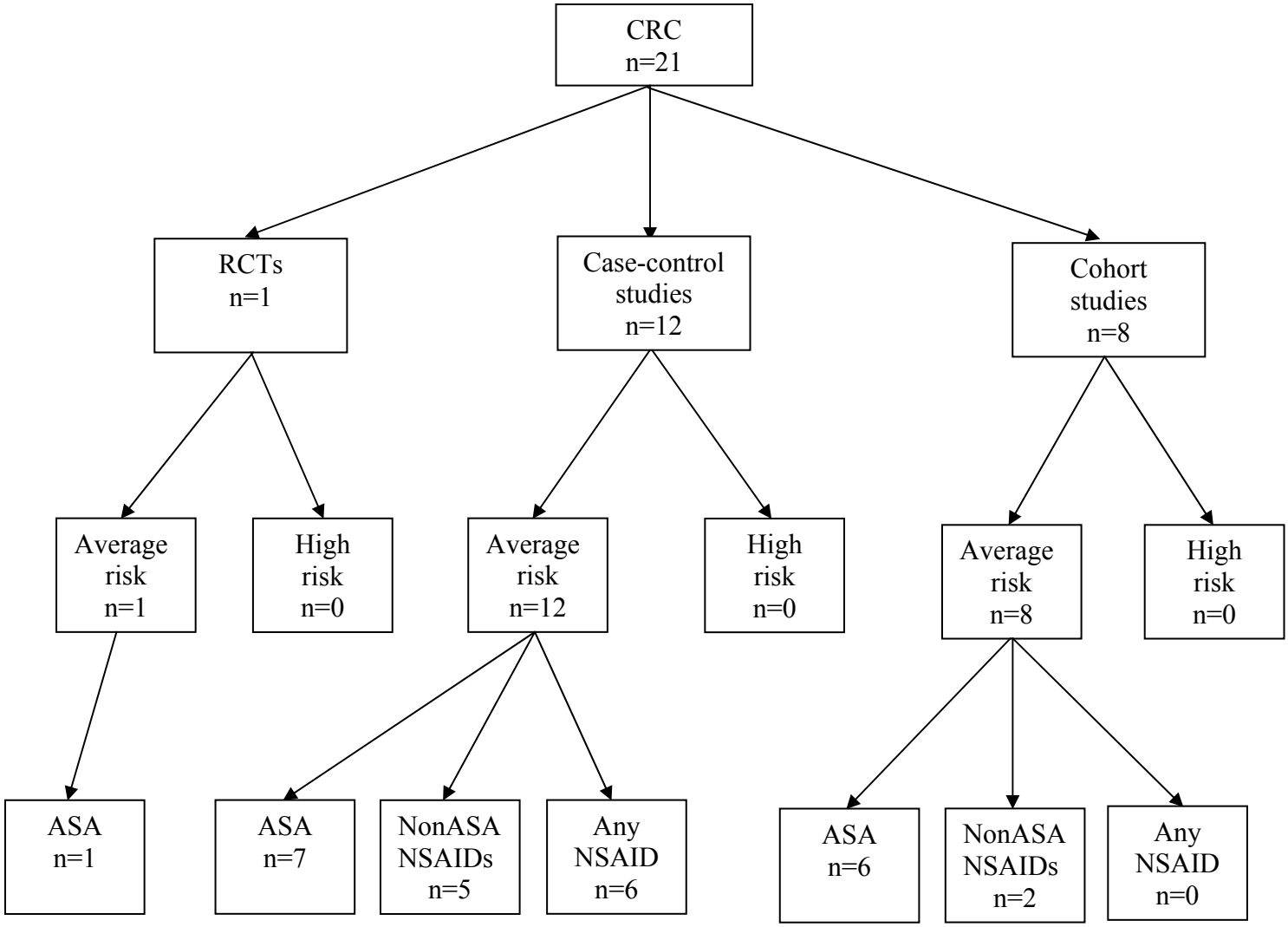
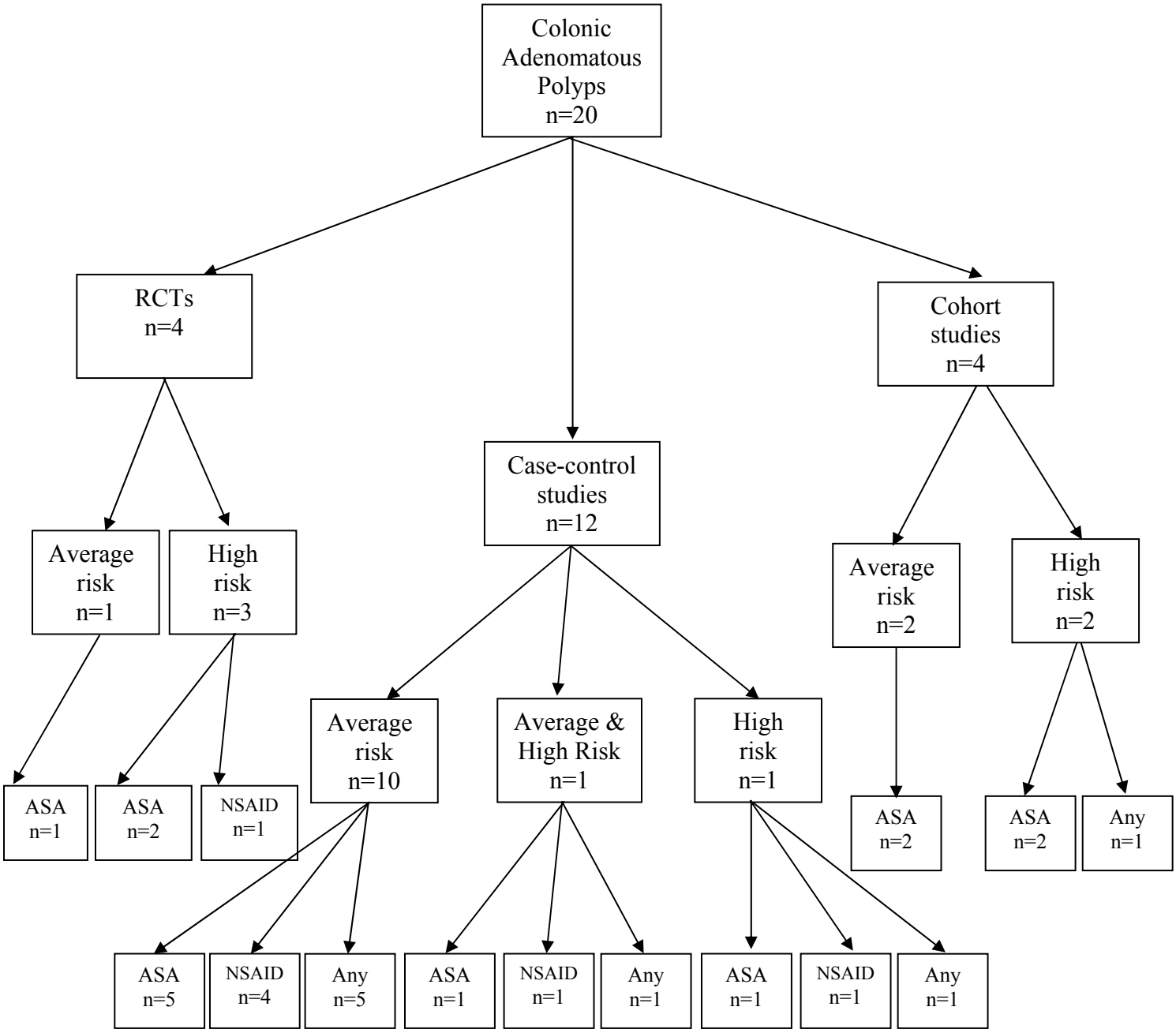


Figure 2.1 Incidence of colorectal cancer



NOTE: There were also two cohort studies on CRC mortality in average-risk subjects{56}{155}

Figure 2.2. Incidence of colonic adenomas



Any=Any NSAID

Table 1. Hierarchical framework for data analysis

NSAID chemoprevention and colonic adenomas				
Study Design	**Interventions**	**Populations**	**Measures of Exposure**	**Outcomes**
Case control studies (n=12)[1-12]	ASA (n=7)[1,3,4,8-11] nonASA NSAIDs (n=6)[1,3,8,9,11,13] Any NSAIDs (n=6)[2,6,7,9,11,12]	Average risk (n=10)[1-8,10,12] Prior adenoma (n=1)[9] Both (n=1)[11]	Duration (cutoffs: 1, 5, 10y) (n=7)[2,3,6,8,9,11,12] Frequency (n=6)[2-4,6,7,10] Dose-response (n=2)[8,12] Recency (n=4)[1,5,8,11]	Histological grade (n=0) Number of polyps (n=0)
Cohorts (n=4)[14-17]	ASA (n=4)[14-17] nonASA NSAIDs (n=0) Any NSAIDs (n=1)[17]	Average risk (n=2)[14,15] Prior adenoma (n=2)[16,17] Both (n=0)	Duration (cutoffs: 1, 4, 5y) (n=2)[14,17] Frequency (n=2)[14,16] Dose-response (n=2)[14,17] Recency (n=0)	Histological grade (n=2)[14,17] Number of polyps (n=1)[17] Proximal vs distal (n=1)[14]
RCTs (n=4)[18-21]	ASA (n=3)[18-20] nonASA NSAIDs (n=1)[21] Any NSAIDs (n=0)	Average risk (n=1)[20] Prior adenoma (n=3)[18,19,21] Both (n=0)	Duration (cutoffs: q1y to 5y) (n=1)[20] Frequency (n=0) Dose-response (n=1)[18] Recency (n=0)	Histological grade (n=3)[18-20] Polyp size (n=3)[18,19,21] Number of polyps (n=3)[18,19,21] Prox vs distal (n=1)[18]

Table 1 (cont'd). Hierarchical framework for data analysis

NSAID chemoprevention and colorectal cancer				
Study Design	**Interventions**	**Populations**	**Measures of Exposure**	**Outcomes**
Case control studies (n=12)[4,12,22-31]	ASA (n=7)[4,22,23,25,27,30,31] nonASA NSAIDs (n=5)[22,25,27,30,31] Any NSAIDs (n=6)[12,24,26,28-30]	Average risk (n=12)[4,12,22-31] Prior adenoma (n=0) Both (n=0)	Duration (cutoffs: 1, 2, 3, 5, 10, 15y) (n=6)[12,22-24,29,30] Frequency (n=4)[4,24,28,30] Dose-response (n=5)[12,22,26,27,29] Recency (n=3)[22,23,28]	Incidence (n=12)[4,12,22-31] Mortality (n=0) Stage (n=0)
Cohorts (n=10)[15,32-40]	ASA (n=7)[15,32-35,38,40] nonASA NSAIDs (n=3)[36,37,39] Any NSAIDs (n=0)	Average risk (n=10)[15,32-40] Prior adenoma (n=0) Both (n=0)	Duration (cutoffs: 1, 2, 4, 6, 5, 10, 20y) (n=8)[15,32,33,35-39] Frequency (n=4)[33,35,39,40] Dose-response (n=1)[39] Recency (n=3)[32,35,39]	Incidence (n=8)[15,32-34,37-40] Mortality (n=2)[35,36] Stage (n=3)[15,32,39]
RCTs (n=1)[20]	ASA	Average risk	Duration (cutoffs: q1y to 5y)	Incidence Stage

Table 2. CRC/NSAIDS review: list of duplicates and related studies grouped by name*

1. NURSES' HEALTH STUDY a. **Chan (#9)** – adenomas (cohort) b. **Giovannucci (#38)** – CRC (cohort) c. Chan (#2145) – adenomas (case control) d. Chan (#2337) – adenomas (case control) *e. (same population, same period, same exposure, different outcome)*
2. PHYSICIANS' HEALTH STUDY a. **Gann (#49)** – CRC (RCT) b. **Sturman (#29)** – CRC (cohort post RCT) *c. (same population, different periods, different exposures, same outcome)*
3. POLYP PREVENTION STUDY a. **Tangrea (#225)** – adenoma (cohort) b. Hartman (#2223) – adenoma (cohort) *c. (same population, same period, same exposure, #225 focuses on NSAIDs, #2223 focuses on Ca/D intake)*
4. CANCER PREVENTION STUDY II a. Thun (#52) – CRC (cohort 1982-88) b. **Thun (#56)** – CRC (cohort 1982-88) c. Thun (#865) – CRC (cohort 1982-88) *d. (similar contents)*
5. MARKERS FOR ADENOMATOUS POLYPS STUDY a. **Hauret (#173)** – adenoma (case control) b. Boyapati (#193) – adenoma (case control) *c. (same population, same period, same exposure, #173 focuses on exercise, #193 focuses on Ca/D intake)*
6. ASSOCIATION POUR LA PREVENTION PAR L'ASPIRINE DU CANCER COLORECTAL a. **Benamouzig (#11)** – adenoma (RCT) b. Benamouzig (#84) – adenoma (RCT, baseline characteristics of subjects)
7. **MASSACHUSETTS CASE-CONTROL STUDY OF CRC AND THE CASE CONTROL SURVEILLANCE STUDY (CCS)** a. Rosenberg (#58) – CRC (case control, CCS 1977-88) b. Rosenberg (#600) – CRC (case control, Mass CC Study 1992-94) c. **Coogan (#509)** – CRC (case control, CCS 1983-96 + Mass CC Study)
8. NORTH CAROLINA COLON CANCER STUDY a. **Shaheen (#120)** – CRC (case control 1996-2000) b. **Sandler (#610)** – adenoma (case control, 1992-95)
9. ROSWELL PARK TUMOR REGISTRY a. Freedman (#27) – CRC (case control) b. **Suh (#48)** – CRC and adenoma (case control)
10. **GRADY MEMORIAL HOSPITAL** a. Peleg (#45) – CRC, adenoma (case control 1988-90) b. **Peleg (#715)** – CRC, adenoma (case control 1987-92)
11. MINNESOTA CANCER PREVENTION RESEARCH UNIT a. Bigler (#17) – adenoma (case control) b. **Murimoto (#323)** – adenoma, hyperplastic polyps (case control) c. Ulrich (#2149) – adenoma (case control)
*reports included in the analysis are in bold

Table 2(cont'd). CRC/NSAIDS review: list of duplicates and related studies grouped by name

12. MULTICENTER NY
- a. **Muscat (#41)** – CRC (case control)
- b. Muscat (#771) - CRC (case control)
- *c. (similar contents)*

13. LEISURE WORLD COHORT
- a. Paganini-Hill (#59) – CRC (cohort, 1981-85)
- b. **Paganini-Hill (#770)** – CRC (cohort, 1981-92)
- c. Paganini-Hill (#885) – CRC (cohort, 1981-90)
- **d.**

14. **NORTH CALIFORNIA KAISER PERMANENTE MEDICAL CARE PROGRAM**
- a. Camp (#310) – CRC (case control, methodology paper)
- b. Murtaugh (#1009) - RC (case control, 1997-2001)
- c. **Slattery (#1148)** - CRC (case control, 1991-94, 1997-2001)
- **d. Friedman (#1638) -** CC (case control 1991-94)

15. UK GENERAL PRACTICE RESEARCH DATABASE
- a. **Garcia Rodriguez (#18)** – CRC (case control 94-97)
- b. **Garcia Rodriguez (#495)** – adenomas (case control, 94-97)
- c. Meier (#368) – CRC (case control, females >60, 92-97)
- d. Langman (#499) – CRC (case control, 93-95)
- e.

16. NORTH JUTLAND POPULATION DATABASE
- a. **Lipworth (#155)** – CRC (cohort, mortality and ibuprofen exposure)
- b. **Sorensen (#264)** – CRC (cohort, CRC incidence and naNSAID exposure)
- c. **Friis (#285)** – CRC (cohort, CRC incidence and low dose ASA exposure)

*reports included in the analysis are in bold

Table 3. CRC/NSAIDS review: list of included studies*

Refid	Author	Outcome(s)	Study type
7	Baron	Adenoma	RCT
9	Chan	Adenoma, FOBT	Cohort
11	Benamouzig	Adenoma	RCT
15	Suleiman	Cost-effectiveness	decision analysis
16	Ladabaum	Cost-effectiveness, FOBT	decision analysis
17	Bigler	adenoma	case control
18	Garcia-Rodriguez	CRC	Case control
29	Sturman	CRC	cohort
32	La vecchia	CRC	case control
36	Martinez	Adenoma, FOBT	case control
38	Giovannucci	CRC	cohort
41	Muscat	CRC	case control
42	Giovannucci	CRC, adenoma, FOBT	cohort
43	Schreinemachers	CRC	cohort
46	Logan	adenoma	case control
48	Suh	CRC, adenoma	case control
49	Gann	CRC, adenoma	RCT
50	Greenberg	adenoma	cohort
56	Thun	CRC	cohort
63	Kune	CRC	case control
91	Ladenheim	adenoma	RCT
120	Shaheen	CRC	case control
155	Lipworth	CRC	cohort
163	Hur	Cost-effectiveness	decision analysis
173	Hauret	adenoma	case control
223	Lieberman	adenoma	case control
225	Tangrea	adenoma	cohort
264	Sorensen	CRC	cohort
285	Friis	CRC	cohort
312	Martin	adenoma	case control
320	Juarraz	CRC	case control
439	Arguedas	Cost-effectiveness	decision analysis
495	Garcia-Rodriguez	adenoma	case control
509	Coogan	CRC	case control
521	Breuer-Katschinski	adenoma	case control
528	Collet	CRC	case control
549	Smalley	CRC, FOBT	cohort
603	Kahn	adenoma	case control
610	Sandler	adenoma	case control
682	Reeves	CRC	case control
715	Peleg	CRC, adenoma	case control
770	Paganini-Hill	CRC	cohort
1148	Slattery	CRC	case control
1541	Ladabaum	Cost-effectiveness	decision analysis
2289	Kahi	FOBT	cohort
*(including source data on the impact of NSAID on FOBT or on protopathic bias)			

Table 4. Impact of NSAID intake on cancer detection

Author	Design	Exposure	Test	Result(s)
Chan	Prospective cohort	ASA	Lower GI endoscopy	multivariate RR of regular ASA use in pts w adenoma: 0.74 (0.61-0.90) aSx 0.71 (0.59-0.86) Sx (NS)
Kahi	Prospective cohort	Any NSAIDs	Colonoscopy	21% (95% CI 14-28) and 19% (9-29) of regular ASA or NSAID users and non users respectively had colonoscopies findings (NS)
Giovannucci	Prospective cohort	ASA	Lower GI endoscopy	Multivariate RR of CRC in ASA users at onset 0.68 (0.52-0.92)
Smalley	Retrospective cohort	naNSAIDs	Colonoscopy, sigmoidoscopy, ACBE	Prevalence of GI Sx's NSAID users vs nonusers at CRC dx: anemia (69% vs 73%; NS), rectal bleeding (54% vs 56%; NS), abdominal pain (56% vs 56%), tumor at stage I or II (56% vs 52%; NS) RR of CRC among NSAID users over 5y without lower GI test 0.63 (0.49-0.81)
Martinez	Case control	Any NSAIDs	Lower GI endoscopy	Indication for test: FOBT + in 9.9 and 10.3% NSAID users vs nonusers; rectal bleeding in 17.4 and 17.9% users vs nonusers
Ladabaum	Decision analysis	ASA	FOBT + FS	Increasing the sensitivity and decreasing the specificity of FOBT if adjunct ASA is given doesn't improve the economical attractiveness of ASA chemoprevention

Sx and aSx refer to the presence or absence of occult or visible blood as the indication for screening
FOBT: fecal occult blood testing
FS: flexible sigmoidoscopy
ACBE: air contrast barium enema

Table 5.1. Regular use of NSAIDs on CRA incidence

Design	Agent	Group	RR
Case Control	ASA	Average risk	**RR=0.87**; 95% CI:0.77-0.98
	Non-ASA NSAID	Average risk	RR=0.54; 95% CI:0.4-0.74
	'any NSAID'	Average risk Higher risk (1 study)	RR=0.57; 95% CI: 0.46-0.71 RR=0.21; 95% CI: 0.04-0.99
Cohort	ASA	Average risk Higher risk (1 study)	**RR=0.72**; 95% CI: 0.61-0.85 RR=0.52; 95% CI: 0.31-0.89
	Non-ASA NSAID	n/a	n/a
	'any NSAID'	Average risk Higher risk (1 study)	RR=0.77; 95% CI:0.63–0.95 RR= 0.69; 95% CI: 0.55-0.88
RCTs	ASA	Low dose – higher risk	**RR=0.82**; 95% CI:0.7-0.95
	Non-ASA NSAID	Higher risk – CRA regression	1.65 (ns)
Nurses's Health Study – Cohort (2005) included > 14 tablets / week RR=0.49 (CI, 0.36 to 0.65)			

Table 5.2. Regular use of NSAIDs on CRC incidence

Design	Agent	Group	RR
Case Control	ASA	Average risk	**Hetero RR=0.3 to 0.9**
	Non-ASA NSAID	Average risk	RR=0.70; 95%: 0.63-0.78
	'any NSAID'	Average risk	Hetero RR=0.13-0.80
Cohort	ASA	Average risk	**RR=0.78**; 95% CI: 0.63-0.97
	Non-ASA NSAID	Average risk (1 study)	RR= 0.61; 95% CI:0.48-0.77
	'any NSAID'	n/a	n/a
RCTs	ASA	Average risk (1 study)	**RR=1.15**; 95% CI:0.80, 1.65
	Non-ASA NSAID	n/a	n/a
Women's Health Study – July 2005 – RCT – no effect of 100mg ASA ever other day **Nurses Healthy Study AUG 2005** – Cohort -14 aspirin/week > 10 years RR= 0.47 (95% CI:0.31-0.71) – effect dose dependant			

Table 5.3. Regular use of NSAIDs on CRC mortality

Design	Agent	Group	RR
Cohort	ASA (1 study–Thun)	average risk men average risk women	RR=0.58; 95% CI:0.36-0.93 RR=0.61; 95% CI:0.38-0.97
	Non-ASA NSAID (1 study–Lipworth)	Average risk – bowel ca Rectal ca	SMR=1.05; 95% CI: 0.9–1.2 SMR=1.26; 95% CI:1.0–1.5
Women's Health Study – July 2005 – RCT – no effect of 100mg ASA ever other day			

Table 5.4. USPSTF—Screening Average risk on CRC mortality

Method	RR	RRR	ARR (per 1000)
FOBT	67%-75%	15%-33%	0.8-4.6
FOBT+Sigmoidoscopy	56%	44%	0.27
Sigmoidoscopy*	41%	59%	
Colonoscopy*	57%	43%	
Sigmoidoscopy followed by colonoscopy	20% (incidence)	80% (incidence)	
* limited data			

Table 6. Summary of study populations

#studies	Range of Mean age	% male	% FHx CRC	% PHx polyps
CRC				
RCTs (n=1)	53	100	Not reported	Not reported
Cohorts (n=10)	46-73	100 in 3; 0 in 1; 24-51% others	Not reported	Not reported
Case controls (n=12)	64-70	50-63	1-20% (reported in 2/12)	Not reported
ADENOMAS				
RCTs (n=4)	52-64	63-100	28-35 (reported in 2/4)	25-100 (reported in 2/4)
Cohorts (n=4)	57-61	100 in 1; 0 in 1; 64-80 others	23 (reported in 1/4)	Not reported
Case controls (n=12)	55-68	40-97	18-36 (reported in 3/12)	Not reported

Evidence Table 1.1. ASA-NSAIDs and CRC/adenoma: Incidence—Randomized Controlled Trials

Author, Year, Location,	N	Duration	Population	Intervention	Outcomes assessed	Quality
Baron, 2003, US[18]	1,121/1,084	7 y	**Inclusion criteria:** Healthy 21-80 y old; with 1 or + histologically confirmed CRA removed within 3 mo, or within16 mo with hx of two or more confirmed CRA, or a histologically confirmed adenoma ≥ 1 cm in diam. removed within 16 mo; complete CC within 3 mo with no colorectal polyps remaining **Exclusion criteria:** Hx of familial CRC syndrome; invasive large-bowel cancer; malabsorption syndromes; CI to aspirin, NSAIDS, or folate	ASA 81mg/d vs. ASA 325mg vs. placebo	**Primary:** -% of pts with 1 or > adenomatous polyp 1 y post randomization or later **Secondary:** -n of adenomatous or more advanced lesions -n of right-sided vs. left-sided lesions	Good
Benamouzig, 2003, France[19]	272/238	> 8 y	**Inclusion criteria:** Pts 18-75 y, with ≥ 3 CRA of any size, or 1 ≥6 mm; no regular use of ASA or other NSAIDs (7 consecutive d >3 wk/y or > 21 d/y); removed polyps < 3 mo upon consultation; with a clean colon/ rectum at entry; eligible women: menopausal or with efficient contraception **Exclusion criteria:** Hx of CRC; FAP, bowel resection excluding appendectomy, IBD, or debilitating or life threatening dx	Lysine acetylsalicylate (Sanofi-Synthelabo) 160mg/d (n=73) vs. 300mg/d (n= 67) vs. placebo	**Primary:** -Recurrence of adenoma at 1y & 4 y (NR) **Secondary:** -Toxicity & tolerability of ASA (NR)	Good
Gann, 1993, US[20]	22071/NR	6 y	**Inclusion criteria:** US male physicians, age 40-84 y **Exclusion criteria:** hx of CVD, cancer, liver or renal disease, gout, peptic ulcer, CI to ASA, or current use of NSAIDs or vitamin A	ASA vs. placebo	**Primary:** -OR CRC **Secondary:** -OR polyps	Fair
Ladenheim, 1995, US[21]	44/40	4 mo	**Inclusion criteria:** Adults > 50 y, with routine screening flexible sigmoidoscopy, polyps ≤ 1 cm **Exclusion criteria:** Hx of GI bleeding, CRF, PUD, underlying malignancy, long-term over-the-counter or prescription NSAIDs use (except ASA); decompensated pulmonary or cardiac disease; polyp(s) > 1 cm	Sulindac for 4 mo (n= 22) vs. placebo	**Primary:** -Polyp disappeared or regressed (>2 mm reduction in size)	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wks = week(s); d = day(s); CI = contraindication; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = no steroid anti-inflammatory drugs; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; CRF = chronic renal failure; CVD = cardiovascular disease; GI = gastrointestinal; ASA = acetylsalicylic acid; PUD = peptic ulcer disease

Evidence Table 1.2. ASA-NSAID and adenomas/CRC: Incidence and Mortality—Cohort studies

Author, Year, Location,	N	Study Duration	Population	Exposure(s)	Outcomes assessed	USPSTF Quality Rating
Chan, 2004, US[14]	27,077/27,077	21 y	**Inclusion criteria:** Women (registered US nurses), age 30-55 y, who completed baseline dietary questionnaire, & underwent CC or sigmoidoscopy during study period **Exclusion criteria:** Incomplete questionnaires; no data/implausible dietary/ASA data; hx of cancer (except nonmelanoma skin cancer), CRA, IBD, or FAP	ASA: 0.5-1.5 tabs/wk (n=6,340); ASA: 2-5 tabs/wk (n=4,172); ASA: 6-14 tabs/wk (n=4,352); ASA: >14 tabs/wk (n=1,634); -non exposed: (n=10,579);	**Primary:** -Incidence of adenoma: (RR) **Secondary:** -Proximal adenomas in absence of distal synchronous adenoma (RR)	Good
Friis, 2003, Denmark[38]	29,470/29,470	9 y	**Inclusion criteria:** Pts with prescribed low-dose ASA max doses of 150 mg, Danish Cancer registry, controlled for age, gender, county **Exclusion criteria:** Residency outside country of North Jutland; invalid civil registry number; death prior to/at date of prescription; parent (of patient) registered as customer.	Low-dose ASA (follow up: 6 y) (n=29,470)	**Primary:** -Incidence all cancers	Fair
Giovannucci, 1995, US[33]	89,446/85,868	12 y	**Inclusion criteria:** Female nurses who completed the sections on medication use & food-frequency questionnaire in 1980 **Exclusion criteria:** Hx of cancer (excluding nonmelanoma skin cancer), FAP, or ulcerative colitis	ASA use in all 3 questionnaires (n=95,258 PYs); nonexposed (n=456,393 PYs)	**Primary:** -Incidence of CRC	Good

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; CRF = chronic renal failure; ASA = acetysalicylic acid; RR = relative risk; GP = general practitioner; CC = colonscopy;

Evidence Table 1.2 (continued). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Cohort studies

Author, Year, Location	N	Study Duration	Population	Exposure(s)	Outcome assessed	Quality Rating
Giovannucci, 1994, US[15]	47,900/45,505	7 y	**Inclusion criteria:** Male health professionals respondents to mailed questionnaire in 1986, age 40-75 y **Exclusion criteria:** NR	ASA: in all 3 questionnaires (n=11,260 Pys) in CRC study; ASA: in 1986 survey only (n=1,242); Non-exposed: (n=30,020 PYs in CRC study); non-exposed: (n= 2,472 in adenoma study)	**Primary:** -Incidence of CRC (RR) **Secondary:** -Distal adenomatous polyp (RR)	Good
Greenberg, 1993, US[16]	864/793	Approx. 4 y	**Inclusion criteria:** Pts with at least one histologically confirmed ademoma removed within 3 mo pre-study entry, free of further polyps, age < 80 y, otherwise healthy **Exclusion criteria:** Invasive large-bowel cancer, infalammatory bowel dx, malabsorption, syndrome, or any contraindication to betacarotene, vitamin C, E (hx of kidney stones or thrombophlebitis)	ASA: consistent use (n = 102); ASA: Intermittent use (n = 98); non-exposed (n = 593)	**Primary:** -Incidence of adenoma (RR)	Fair
Lipworth, 2004, Denmark[36]	113,538/102,566	7 y	**Inclusion criteria:** Pts with at least 1 ibuprofen prescription between 1989-1995 **Exclusion criteria:** NR	Ibuprofen (n=113,538)	**Primary:** -Overall mortality **Secondary:** -Mortality from GI bleeding, CVD & cancer	Fair
Paganini-Hill, 1995, USA[40]	13979 /12180	11 y	**Inclusion criteria** Community residents with returned questionnaire on medical hx, use of drugs, laxatives & supplements, smoking, alcohol consumption, & exercise habits, health care utilization, & females: menstrual hx, i.e. estrogen tx **Exclusion criteria:** NR	ASA: <daily; ASA: daily	**Primary:** -n of CRC	Poor

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; CRF = chronic renal failure; ASA = acetysalicylic acid; RR = relative risk; PYs = person-years;

Evidence Table 1.2 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Cohort studies

Author, Year, Location	N	Study Duration	Population	Exposure(s)	Outcome assessed	Quality Rating
Schreinemachers, 1994, US[34]	14,407/12,668	16 y	**Inclusion criteria:** Pts with medical examination & were 25-74 y at the time of NHANES I (National Health & Nutrition Examination Survey I) **Exclusion criteria:** Cases: dx occuring =/> 2 y NHANES I; Ctrls: incomplete surverys/aspirin use data	ASA: within 30 d of baseline interview (n=7438); Non-ASA: within 30 d of baseline interview (n=5250)	**Primary:** -Incidence of all cancers	Fair
Smalley, 1999, US[39]	104217/NR	13 y	**Inclusion criteria:** Enrollees of the Tennessee Medicaid program, 65 y or older, with 5 or more y continuous enrollment (5 y medical hx available) **Exclusion criteria:** End point: dx with incident colorectal cancer, death, loss of eligibility, or the end of the study (Dec 1992)	non-ASA NSAID cumulative dose <3 mo (n = 93,392 PYs); 3-11 mo (n = 82,247 PYs); 12-23 mo (n = 47,326 PYs); 24-35 mo (n = 24,919 PYs); 36-47 mo (n = 22,450 PYs); <48 mo (n = 9,962 PYs); non-exposed (n = 166,769 PYs)	**Primary:** -Incidence of CRC	Fair
Sorensen, 2003, Denmark & US/Sweden[37]	183693/ 172057	9 y	**Inclusion criteria:** Pts with prescribed non-aspirin NSAIDs **Exclusion criteria:** Occurence of cancer excluding nonmelanoma skin cancer proir to the date of first recorded perscription; end of follow-up: cancer dx, death, emigration or reaching study end date (Dec 1, 1997)	ASA: 1 prescription (n=71603); 2-4 prescriptions (n=59964); 5-9 prescriptions (n=21398); ≥ 10 prescriptions (n=19092)	**Primary:** -incidence of CRC	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; tx = treatment; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; CRF = chronic renal failure; ASA = acetysalicylic acid; RR = relative risk; PYs = person-years;

Evidence Table 1.2 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Cohort studies

Author, Year, Location	N	Study Duration	Population	Exposure(s)	Outcome assessed	Quality Rating
Sturmer, 1998, US[32]	22071/22071	12 y (RCT X 5 y; cohort X 7 y)	**Inclusion criteria:** US male physicians, 40-84 y in 1982 **Exclusion criteria:** Regular use of aspirin or other NSAIDs; hx of myocardial infarction, stroke, cancer, liver or renal dx, gout, peptic ulcer, or contraindications to aspirin	Randomized to ASA/ regular ASA use thereafter (n = 41869 PYs); Randomized to Placebo/ irregular ASA use thereafter (n = 18342 PYs)	**Primary:** -RR CRC	Poor
Tangrea, 2003, US[17]	NR/1905	4 y	**Inclusion criteria:** Enrolees of the Polyp Preventin Trial ,1991, at least 35 y old with one or more histologically confirmed colorectal adenomas identified by complete colonoscopy within 6 mo prior to randomization. **Exclusion criteria:** Hx of colorectal cancer, surgical resection of adenomas, inflammatory bowel syndrome, or the familial polyposis syndrome	ASA:, any use (n = 431); up to 325mg/day (n = 369); >325mg/day (n = 62); unexposed (n =1474); NSAID: any use (n = 629); unexposed (n = 1276); Use reported at all 5 visits (n = 253); no use reported at all 5 visits (n =1462)	**Primary:** -n of polyps	Good
Thun, 1991, US[35]	1083531/ 662424	6y	**Inclusion criteria:** White adults (friends/family of volunteers for Cancer Prevention Study II in 1982) who provided information in 1982 on the frequency & duration of aspirin use **Exclusion criteria:** Non-white (due to small # of death in this grp); aspirin use < 1 y	ASA: <1 a mo (n = 486,620 PYs men & n = 671,927 PYs women); 1-15 times a mo (389,083 PYs men & 505,854 PYs women); ≥ 16 times a mo (n = 201,638 PYs men & n = 265,424 PYs women); non-exposed: (n = 646,346 PYs men & n = 705,064 women)	**Primary:** -Mortality from CRC	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; CRF = chronic renal failure; ASA = acetysalicylic acid; RR = relative risk; PYs = person-years;

Evidence Table 1.3. ASA-NSAID and adenomas/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Bigler, 2001, US[1]	1037/1037	3y	Cases: incident of adenomatous polyp (n = 474)	Controls: colonoscopy negatives (n = 563)	ASA; non-ASA NSAID (questionnaire)	**Primary:** -n of polyps	Fair
Hauret, 2004, US[5,13]	669/405	2 y	Cases: colonoscopy positives (n = 177)	Controls: Subjects free of adenomas (n = 228)	Non-ASA NSAID (questionnaire)	**Primary:** -n of polyps	Poor
Breuer-Katschinski, 2000, Germany[9]	1265/550	3.5 y	Cases: pts with histoligically proven & endoscopy removed adenoma of colon or rectum (n = 182);	Hospital Controls: matched for age & sex free of adenomatous polyps at colonoscopy (n = 178); Non-hospital (community) Controls: selected pts of the same age and sex from the inhabitants list of the City of Essen (n = 182);	NSAID (questionnaire)	**Primary:** -n of polyps	Fair
Collet, 1999, Canada[29]	Colon Cancer Study NR/19217 Rectal Cancer Study NR/9853	NR	Cases: pts with histologically proven adenocarcinoma of colon or rectum & reported to SCA (n = 3844 colon; n = 1971 rectal)	Controls: matched in age, gender with cases, and alive, > 35 y at entry; free of CRC & other cancer except non-melanoma & carcinoma in situ of cervix (n = 15,373 matched to colon cancer cases; n = 7,882 matched to rectal cancer cases)	NSAID (prescription drug database)	**Primary:** -n of CRC	Good

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk; SCA: Saskatchewan Cancer Agency

Evidence Table 1.3 (cont'd). ASA-NSAID and adenoma/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Coogan, 2000, US[28,41,42]	11754/ 11754	13 y	Cases: primary CRC (n = 1032 colon; n = 494 rectum) dx < 6 mo	Cancer Controls: dx of lung, or other respiratory, malignant melanoma, prostate bladder, kidney, ovary, uterus, and other cancers dx < 6 mo (n = 4192) Non-Cancer Controls: pts admitted for trauma, or acute infection with no hx of cancer (n = 6036)	NSAID (tumor registry of hospitals; Sate Cancer registry)	**Primary:** -n of CRC	Fair
Garcia Rodriguez, 2000, Spain[8,22]	943903/NR	5 y , 8 mo	Adenoma Cases: adenoma on medical records database with biopsy (n = 1864); CRC Cases: incident of CRC (n = 2002)	Controls: randomly selected age, sex matched persons from database; absence of adenoma (n = 10,000)	Non-ASA NSAID, ASA, Ibuprofen, Diclofenac, Naproxen, Indomethacin, Piroxicam, Ketoprofen (prescription database)	**Primary:** -n of polyps -Incidence of CRC (by sex & age-groups)	Good

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk

Evidence Table 1.3 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Juarranz, 2002, Spain[27]	502/424	NR	Cases: subjects with laboratory-confirmed colon cancer between January 1995 - December 1996, residing in Madrid (n=196)	Controls: subjects free of neoplasm or severe digestive disease (Crohn's or ulcerative colitis) at enrollment, randomly chosen, from electoral lists from same area as cases & age-sex matched to cases	ASA & NSAIDs (questionnaire)	**Primary:** -n of colon cancer cases	Fair
Kahn, 1998, US[10]	177939/ 154224	10 y	Cases: self reported polyps on mailed questionnaire (n = 7504 men; n = 5111 women)	Controls: subjects who did not report the polyp (n = 65,364 men; n = 76,245 women)	ASA (questionnaire)	**Primary:** -n of polyps	Poor
Kune, 1988, Australia[25]	1442/ 1367	1 y	Cases: newly dx CRC between Apr 1980-Apr 1981(n = 715)	Controls: randomly selected pts matched for age, sex, & geographic area	ASA, NSAID (questionnaire)	**Primary:** -RR CRC, RR colon cancer, RR rectal cancer	Fair
La Vecchia, 1997, Italy[23]	3248/ 3248	4.5 y	Cases: histologically confirmed CRC (n = 860 colon; n = 497 rectum)	Controls: pts in the same residing area/hospital of cases, identified for acute conditions unrelated to known or likely risk factors for CRC (n = 1891)	ASA (questionnaire)	**Primary:** -OR CRC	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk; OR = odds ratio

Evidence Table 1.3 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Lieberman, 2003, US[6]	3121/ 1770	3 y	Cases: advanced neoplasia ≥ 10mm; villous adenoma at least 25% villous; high grade dysplasia included carcinoma in situ & intramucosal cancer; invasive cancer (malignant cells beyond muscularis mucosa) (n = 329)	Controls: Pts free of lower tract GI symptoms & polyps (n = 1441)	NSAID (questionnaire)	**Primary:** -n of polyps -n of CRC	Fair
Logan, 1993, United Kingdom[3]	476/NR	7 y	Cases: pts with positive results in faecal occult blood tests with CRA (n = 147)	Contols: matched for age & sex; pts tested negative on occult blood test (negative controls), and pts with positive results on screening but found to be free of adenomas and carcinomas or sigmoidoscopy and barium enema (positive controls) (n = 153)	ASA, NSAIDS, non-ASA NSAIDS (questionnaire)	**Primary:** -n of polyps	Fair
Martin, 2002, US[7]	719/504	2 y	Cases: First incident of adenoma (n = 226)	Controls: free of adenomatous polyps (n = 493)	NSAIDS (questionnaire)	**Primary:** -OR adenoma	Good

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk; OR = odds ratio

Evidence Table 1.3 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Martinez, 1995, US[2]	919/637	Approx. 19 mo	Cases: first pathological dx of villous, tubular or tubulovillous adenomatous polyps (adenomas and hyperplastic polyps were both included) (n = 157)	Controls: negative for colorectal polyps (n = 480)	NSAID (questionnaire)	**Primary:** -OR adenoma	Good
Muscat, 1994, US[24]	1011/ 1011	3 y	Cases: histologically confirmed colorectal cancer pts (n = 346 colon; n = 165 rectum)	Controls: matched pts by sex, race, hospital, age (+/-5 y), & mo of interview; conditions unrelated to NSAID use (n = 500)	NSAID (questionnaire)	**Primary:** -OR CRC	Poor
Peleg, 1996, US[12]	**Study 1:** 279/279 **Study 2:** 339/339	**Study 1:** 5.5 y **Study 2:** 2.5 y	**Study 1:** Cases: incident CRC (n = 93) **Study 2:** Cases: incident adenoma (n = 113)	Controls: hospital pt free of cancer, born 1948, with regular follow ups at GMH for the same duration as the case at the time **Study 1:** (n = 186); **Study 2:** (n = 226)	NSAID (prescription database)	**Primary:** -n of CRC **Secondary:** -n of polyps	Poor
Reeves, 1996, US[30]	845/400	1 y	Cases: women 40-74 y, local residents with new dx of invasive cancer of the colon or rectum, with listed telephone number (n = 184)	Controls: pts with listed telephone number, & either a current Wisconsin driver's license (< 65 y), or a Medicare card (>65 y) (n = 293)	ASA, NSAID, non-ASA NSAID (questionnaire)	**Primary:** -n of CRC	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk; OR = odds ratio; GMH = Grand Memorial Hospital

Evidence Table 1.3 (cont'd). ASA-NSAID and adenomas/CRC: Incidence and Mortality—Case-Control Studies

Author, Year, Location	N	Duration	Cases	Controls	Exposure (Ascertainment)	Outcomes assessed	USPTF Quality Rating
Sandler, 1998, US[11]	492/379	3 y	Cases: incident of adenoma (n = 142)	Controls: free of adenomatous polyps or having hyperplastic (n = 169)	ASA, NSAID, non-ASA NSAID (questionnaire)	**Primary:** -n of polyps	Fair
Shaheen, 2003, US[26]	1308/ 1308	4 y	Cases: pts 40-79 y; residing in 33-county area, with first time dx of colon cancer (enrolled within 22-63 d, median 34 d from dx date) between Oct. 1996-Oct. 2000 (n = 475)	Controls: sampled from same geographic area age > 65 y; & driver's licence age < 65 y (n = 833)	NSAID (questionnaire)	**Primary:** -OR CRC	Fair
Slattery, 2004, US[31]	3051/ 2157	5 y, 2 mo	Cases: English speaking, mentally competent to complete the interview, 30-79 y; first primary tumor in the rectosigmoid junction or rectum, May 1997- May 2001 (n = 952)	Controls: matched by sex & by 5-y age group, pts> 65 randomly selected from Health Care Financing Administration lists, pts < 65 y selected from driver's license lists (n = 1205)	ASA, NSAID (questionnaire)	**Primary:** -n of CRC	Fair
Suh, 1993, US[4]	2704/NR	9 y	Cases 1: first primary colon cancers (n = 490) Cases 2: first primary rectum cancers (n = 340)	Controls 1: Prevention health care healthy visitors (n = 1138) Controls 2: healthy pts without cancer (n = 524)	ASA (questionnaire)	**Primary:** -n of polyps -n of CRC	Fair

N = number of participants enrolled/completed; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; dx = diagnosis; NR = not reported; CRC = colorectal cancer; CRA = colorectal adenoma; NSAID = non steroid anti-inflammatory drug; ASA = acetysalicylic acid; RR = relative risk, OR = Odds Ratio

Evidence Table 2.1. RCTs of incidence of CRC with aspirin use

Author, Year, Location	Population Risk	Experimental Intervention (dose & duration)	Sample Size (n experimental arm/n control arm)	OR (95% CI)*
Gann, 1993, U.S.[20]	Average	325 mg every other d for 5 y	11,037/11,034	1.15 (0.80, 1.65)

* Reference group = placebo arm; RR = relative risk; CI = confidence interval; y = year(s); n = number; RCT = randomized controlled trial; CRC = colorectal cancer; d = day(s)

Evidence Table 2.1 (cont'd). RCTs of incidence of adenomas with aspirin use

Author, Year, Location	Population Risk	Experimental Intervention (dose & duration)	Sample Size (n experimental arm/n control arm)	OR (95% CI)*
Gann, 1993, U.S.[20]	Average	325 mg every other d for 5 y	11,037/11,034	0.86 (0.68, 1.1)
Benamouzig, 2003, U.S., France[19]	Higher	160 mg/d for 4 y	73/132	0.85 (0.57, 1.26)
		300 mg/d for 4 y	67/132	0.61 (0.37, 0.99)
Baron, 2003, U.S.[18]	Higher	81 mg/d for 3 y	377/372	0.81 (0.69, 0.96)
		325 mg/d for 3 y	372/372	0.96 (0.81, 1.13)

* Reference group = placebo arm; RR = relative risk; CI = confidence interval; y = year(s); n = number; RCT = randomized controlled trial; d = day(s)

Evidence Table 2.1 (cont'd). RCTs of incidence of adenomas with non-aspirin NSAIDs use

Author, Year, Location	Population Risk	Experimental Intervention (dose & duration)	Sample Size (n experimental arm/n control arm)	OR (95% CI)*
Ladenheim, 1995, U.S.[21]	Higher	Sulindac 300 mg/d for 4 mo	22/22	1.65 (NS; 95% CI = NR)

* Reference group = placebo arm; NS = not significant; NR = not reported; RR = relative risk; CI = confidence interval; mo = month(s); n = number; RCT = randomized controlled trial; NSAID = non-steroidal anti-inflammatory drug

Evidence Table 2.2. Cohort studies of incidence or mortality of CRC with aspirin use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n exposed/n non-exposed)	OR (95% CI)
Sturmer, 1998, U.S.[32]	Average	≥ 1 y	34,983 p-y/18,342 p-y	1.02 (0.64, 1.65)
		≥ 5 y	11,563 p-y/18,342 p-y	0.95 (0.51, 1.79)
		≥ 6 y	41,869 p-y/18,342 p-y	1.07 (0.67, 1.70)
		regular use	41,869 p-y/18,342 p-y	1.07 (0.67, 1.70)
Giovannucci, 1995, U.S.[33]	Average	1 – 4 y	70,860 p-y/357,905 p-y	1.06 (0.78, 1.45)
		5 – 9 y	42,306 p-y/357,905 p-y	0.84 (0.55, 1.28)
		10 – 19 y	28,709 p-y/357,905 p-y	0.70 (0.41, 1.20)
		≥ 20 y	52,259 p-y/357,905 p-y	0.56 (0.36, 0.90)
		regular use	95,258 p-y/456,393 p-y	0.62 (0.44, 0.86)
Giovannucci, 1994, U.S.[15]	Average	≥ 2 y	33,661 p-y/75,637 p-y	0.54 (0.34, 0.83)
		≥ 4 y	11,260 p-y/30,020 p-y	0.35 (0.16, 0.75)
		regular use	33,661 p-y/75,637 p-y	0.54 (0.34, 0.83)
Friis, 2003, Denmark, U.S.[38]	Average	1 – 4 y	NR/NA	SIR = 1.0 (0.9, 1.2)
		5 – 9 y	NR/NA	SIR = 0.9 (0.7, 1.1)
		regular use	29,470/NA	SIR = 0.9 (0.7, 1.1)
Paganini-Hill, 1995, U.S.[40]	Average	regular use	**Men:** 4,535 (total sample) **Women:** 7,645 (total sample)	**Men:** 1.38 (p ≥ 0.05) **Women:** 1.1 (p ≥ 0.05)
Schreinemachers, 1994, U.S.[34]	Average	regular use	**Total sample:** 7,438/5,250 **Men** (< 65 y): NR	**Total sample:** 0.85 (0.63, 1.15) **Men** (< 65 yrs): 0.36 (0.17, 0.76)
Thun, 1991, US [35]	Average	regular use (16 + doses/month)	411,188p-y/1,325,822 p-y	**Colon** 0.63 (0.44-0.89) **Rectum** 0.79 (0.41-1.53)

y = year(s); p-y = person-years; wk = week(s); regular use = 2-3 x per/wk for ≥ 1 y; RR = relative risk; CI = confidence interval; SIR = standardized incidence ratio; NR = not reported; NA = not applicable; CRC = colorectal cancer

Evidence Table 2.2 (cont'd). Cohort studies of incidence or mortality of CRC with non-aspirin NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n exposed/n non-exposed)	OR (95% CI)
Smalley, 1999, U.S.[39]	Average	1 – 2 y	47,326 p-y/166,769 p-y	0.65 (0.48, 0.87)
		4 y	9,962 p-y/166,769 p-y	0.49 (0.24, 1.00)
		low dose	9,058 p-y/164,052 p-y	0.53 (0.26, 1.08)
		medium dose	68,615 p-y/164,052 p-y	0.59 (0.45, 0.77)
		high dose	7,796 p-y/164,052 p-y	0.77 (0.41, 1.45)
		recency of use (< 1 y before Dx)	86,105 p-y/164,052 p-y	0.61 (0.48, 0.77)
		recency of use (≥ 1 y before Dx)	18,552 p-y/164,052 p-y	0.76 (0.50, 1.15)
		regular use	24,919 p-y/164,052 p-y	0.70 (0.48, 1.02)
Sorensen, 2003, Denmark[37]	Average	regular use	19,092/NA	SIR = 0.7 (0.6, 0.9)
Lipworth, 2004, Denmark[36]	Average	regular use	484,369 p-y/NA	SMR colon=1.05 (0.9–1.2) SMR rectal=1.26 (1.0–1.5)

NSAID = non-steroidal anti-inflammatory drug; p-y = person-years; wk = week(s); regular use = 2-3 x per/wk for ≥ 1 y; RR = relative risk; CI = confidence interval; y = year(s); SIR = standardized incidence ratio; NA = not applicable; CRC = colorectal cancer; Dx = diagnosis

Evidence Table 2.2 (cont'd). Cohort studies of incidence of adenomas with aspirin use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n exposed/n non-exposed)	OR (95% CI)
Chan, 2004, U.S.[14]	Average	1 – 5 y	4,016/16,919	0.96 (0.80, 1.15)
		6 – 10 y	2,429/16,919	0.90 (0.72, 1.13)
		11 – 20 y	1,392/16,919	0.93 (0.69, 1.25)
		>20 y	2,321/16,919	0.80 (0.62, 1.02)
		0.5 – 1.5 tab/wk dose	6,340/10,579	0.99 (0.81, 1.20)
		2 – 5 tab/wk dose	4,172/10,579	0.86 (0.70, 1.50)
		6 – 14 tab/wk dose	4,352/10,579	0.68 (0.55, 0.84)
		> 14 tab/wk dose	1,634/10,579	0.57 (0.42, 0.77)
		regular use	10,158/16,919	0.73 (0.61, 0.87)
Giovannucci, 1994, U.S.[15]	Average	regular use	1,242/2,472	OR = 0.65 (0.42, 1.02)
Tangrea, 2003, U.S.[17]	Higher	≤ 325 mg/d dose	369/1,474	0.87 (0.68, 1.11)
		> 325 mg/d dose	62/1,474	0.54 (0.30, 0.96)
		regular use	431/1,474	0.82 (0.65, 1.02)
Greenberg, 1993, U.S.[16]	Higher	regular use	102/593	0.52 (0.31, 0.89)

regular use = 2-3 x per/wk for ≥ 1 y; RR = relative risk; CI = confidence interval; y = year(s); tab = tablets; OR = odds ratio; wk = week(s); d = day(s)

Evidence Table 2.2 (cont'd). Cohort studies in incidence of adenomas with any NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n exposed/n non-exposed)	OR (95% CI)
Tangrea, 2003, U.S.[17]	Higher	regular use	253/1,462	0.64 (0.48, 0.85)
NSAID = non-steroidal anti-inflammatory drug; wk = week(s); regular use = 2-3 x per/wk for ≥ 1 y; RR = relative risk; CI = confidence interval				

Evidence Table 2.3. Case-control studies of incidence of CRC with aspirin use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
La Vecchia, 1997, Italy[23]	Average	< 2 y	1,357/1,891	0.9 (0.5, 1.7)
		≥ 2 y		0.6 (0.4, 1.0)
		recency of use (< 1 y before Dx)		0.6 (0.4, 1.0)
		recency of use (≥ 1 y before Dx)		0.9 (0.5, 1.6)
		regular use		0.7 (0.5, 1.0)
Slattery, 2004, U.S.[31]	Average	≥ 1 mo (current)	952/1,205	0.8 (0.6, 1.0)
		regular use		0.8 (0.5, 1.2)
Friedman, 1998, U.S.[43]	Average	1 - ≤ 5 y	1,993/2,410	0.8 (0.6, 1.0)
		>5 y		0.8 (0.6, 0.9)
		recency of use (< 1 y before Dx)		0.6 (0.5, 0.7)
		recency of use (≥ 1 y before Dx)		1.0 (0.8, 1.2)
		regular use		0.7 (0.6, 0.8)
Garcia-Rodriguez, 2001, Spain[22]	Average	1 – 2 y	2,002/10,000	0.9 (0.7, 1.2)
		> 2 y		0.9 (0.7, 1.2)
		75 mg dose		1.1 (0.8, 1.4)
		150 mg dose		1.0 (0.7, 1.4)
		300 mg dose		0.6 (0.4, 0.9)
		recency of use (< 1 y before Dx)		1.3 (1.0, 1.8)
		recency of use (≥ 1 y before Dx)		1.0 (0.7, 1.3)
		regular use		0.9 (0.8, 1.1)

regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); CRC = colorectal cancer; OR = odds ratio; Dx = diagnosis; y = year(s)

Evidence Table 2.3 (cont'd). Case-control studies of incidence of CRC with aspirin use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Suh, 1993, U.S.[4]	Average	regular use	830/1,138	0.33 (0.15, 0.72)
Reeves, 1996, U.S.[30]	Average	regular use	184/293	0.79 (0.46, 1.36)
Kune, 1988, Australia[25]	Average	regular use	85/147	0.53 (0.40, 0.71)
Juarranz, 2002, Spain[27]	Average	mg/week	196/228	0.98 (0.89, 0.99)

regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); CRC = colorectal cancer; OR = odds ratio; Dx = diagnosis; y = year(s)

Evidence Table 2.3 (cont'd). Case-control studies of incidence of CRC with non-aspirin NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Garcia-Rodriguez, 2001, Spain[22]	Average	1 – 2 y	2,002/10,000	0.4 (0.2, 0.7)
		> 2 y		0.6 (0.4, 0.8)
		low-medium dose		0.7 (0.5, 1.1)
		high dose		0.4 (0.3, 0.7)
		recency of use (< 1 y before Dx)		0.9 (0.8, 1.1)
		recency of use (≥ 1 y before Dx)		1.0 (0.9, 1.1)
		regular use		0.7 (0.6, 0.9)
Kune, 1988, Australia[25]	Average	regular use	715/727	0.77 (0.60, 1.01)
Slattery, 2004, U.S.[31]	Average	regular use	952/1,205	0.8 (0.5, 1.1)
Friedman, 1998, U.S.[43]	Average	regular use	1,993/2,410	0.7 (0.6, 0.8)
Reeves, 1996, U.S.[30]	Average	regular use	184/293	0.43 (0.20, 0.89)
Juarranz, 2002, Spain[27]	Average	mg/week	196/228	0.30 (0.08, 0.98)

regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); CRC = colorectal cancer; OR = odds ratio; Dx = diagnosis; y = year(s); NSAID = non-steroidal anti-inflammatory drug

Evidence Table 2.3 (cont'd). Case-control studies of incidence of CRC with any NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Peleg, 1996, U.S.[12]	Average	1 y	93/412	0.34 (0.12, 0.94)
		4 y		0.14 (0.02, 0.90)
		≥ 5 y		0.12 (0.04, 0.39)
		< 320 CC dose		0.58 (0.26, 1.32)
		320 – 700 CC dose		0.19 (0.09, 0.52)
		> 700 CC dose		0.22 (0.09, 0.56)
		regular use		0.13 (0.33, 0.55)

NSAID = non-steroidal anti-inflammatory drug; regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); CRC = colorectal cancer; OR = odds ratio; Dx = diagnosis; y = year(s)

Evidence Table 2.3 (cont'd). Case-control studies of incidence of CRC with any NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Shaheen, 2003, U.S.[26]	Average	regular use	475/833	0.54 (0.39, 0.75)
Coogan, 2000, U.S.[28]	Average	regular use	1,211/8,535	1.1 (0.3, 2.3)
Muscat, 1994, U.S.[24]	Average	regular use 1 – 4 y 5 – 9 y > 9 regular use 1 – 4 y 5 – 9 y > 9	283/276 (men) 228/224 (women)	**Men** 0.64 (0.42, 0.97) 0.77 (0.34, 1.75) 0.93 (0.45, 1.97) 0.47 (0.21, 0.94) **Women** 0.32 (0.18, 0.57) 0.17 (0.06, 0.49) 0.13 (0.02, 1.39) 0.60 (0.26, 1.36)
Reeves, 1996, U.S.[30]	Average	0 – 2 y 2 – 5 y > 5 y	184/293	0.7 (0.4, 1.3) 0.3 (0.2, 0.7) 1.1 (0.6, 2.0)
Collet, 1999, Canada[29]	Average	0 - ≤ 0.1 mg/d dose 0.1 < - ≤ 0.3 mg/d dose > 0.3 mg/d dose regular use	3,844/15,373	1.01 (0.88, 1.15) 0.73 (0.55, 0.96) 0.57 (0.36, 0.89) 1.00 (0.92, 1.09)

NSAID = non-steroidal anti-inflammatory drug; regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); CRC = colorectal cancer; OR = odds ratio; Dx = diagnosis; y = year(s)

Evidence Table 2.3 (cont'd). Case-control studies of incidence of adenomas with aspirin use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Garcia-Rodriguez, 2000, Spain[8]	Average	1 – 2 y	1,864/10,000	0.9 (0.6, 1.3)
		> 2 y		0.7 (0.5, 1.0)
		75 mg dose		0.8 (0.5, 1.1)
		150 mg dose		0.9 (0.6, 1.4)
		300 mg dose		0.6 (0.4,1.0)
		recency of use (< 1 y before Dx)		1.2 (0.9, 1.7)
		recency of use (≥ 1 y before Dx)		1.1 (0.8, 1.5)
		regular use		0.9 (0.6, 1.3)
Morimoto, 2002, U.S.[44]	Average	regular use	794/708	0.7 (0.5, 1.1)
Kahn, 1998, U.S.[10]	Average	regular use	7,504/65,364 (men) 5,111/76,245 (women)	Men: 0.97 (0.89, 1.06) Women: 0.85 (0.77, 0.95)
Suh, 1993, U.S.[4]	Average	regular use	212/1,138	0.61 (0.26, 1.4)
Logan, 1993, UK[3]	Average	regular use	147/153 (test-negative controls screened with occult blood test for adenomas)	0.55 (0.3, 1.1)
Sandler, 1998, U.S.[11]	Average and higher	regular use	142/169	0.84 (0.50, 1.43)
Breuer-Katschinski, 2000, Germany[9]	Higher	< 5 y	182/182 (population-based)	0.64 (0.26, 1.56)
		≥ 5 y		0.18 (0.02, 1.63)

regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); OR = odds ratio; Dx = diagnosis; y = year(s)

Evidence Table 2.3 (cont'd). Case-control studies of incidence of adenomas with non-aspirin NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Garcia-Rodriguez, 2000, Spain[8]	Average	1 – 2 y	1,864/10,000	0.4 (0.2, 0.8)
		> 2 y		0.7 (0.5, 1.1)
		low-medium dose		0.7 (0.4, 1.3)
		high dose		0.6 (0.4, 0.9)
		recency of use (< 1 y before Dx)		1.2 (1.0, 1.4)
		recency of use (≥ 1 y before Dx)		1.2 (1.0, 1.3)
		regular use (Ibuprofen)		0.7 (0.3, 1.5)
		regular use (Diclofenac)		0.6 (0.3, 1.0)
		regular use (Indomethacin)		0.2 (0.1, 2.3)
		regular use (Naproxen)		0.8 (0.3, 1.9)
Hauret, 2004, U.S.[13]	Average	regular (current) use	177/228	0.62 (0.36, 1.07)
Morimoto, 2002, U.S.[44]	Average	regular use	794/708	0.4 (0.2, 0.7)
Logan, 1993, UK[3]	Average	regular use	147/153 (test-negative controls screened with occult blood test for adenomas)	0.56 (0.30, 1.20)
Sandler, 1998, U.S.[11]	Average and higher	regular use	142/169	0.74 (0.36, 1.51)
Breuer-Katschinski, 2000, Germany[9]	Higher	< 5 y	182/182 (population-based)	0.60 (0.18, 2.05)
		≥ 5 y		0.26 (0.03, 2.44)

regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); OR = odds ratio; Dx = diagnosis; y = year(s); NSAID = non-steroidal anti-inflammatory drug

Evidence Table 2.3 (cont'd). Case-control studies of incidence of adenomas with any NSAIDs use

Author, Year, Location	Population Risk	Exposure Group(s) (duration, dose, recency, & regular use)	Sample Size (n cases/n controls)	OR (95% CI)
Peleg, 1996, U.S.[12]	Average	1 y	113/412	0.59 (0.22, 1.63)
		2 y		0.24 (0.07, 0.83)
		3 y		0.26 (0.07, 1.00)
		4 y		0.24 (0.06, 0.95)
		≥ 5 y		0.25 (0.08, 0.79)
		< 320 CC dose		0.59 (0.23, 1.48)
		320 – 700 CC dose		0.56 (0.20, 1.52)
		> 700 CC dose		0.31 (0.11, 0.84)
		regular use		0.56 (0.20, 1.52)
Martinez, 1995, U.S.[2]	Average	< 5 y	157/480	0.39 (0.21, 0.71)
		≥ 5 y		0.60 (0.32, 1.14)
Lieberman, 2003, U.S.[6]	Average	< 10 y 10 – 19 y > 19 y regular use	329/1,441	0.71 (0.52, 0.96) 0.63 (0.41, 0.99) 0.49 (0.30, 0.80) 0.67 (0.50, 0.89)
Martin, 2002, U.S.[7]	Average	regular use	226/493	0.5 (0.3, 0.8)
Sandler, 1998, U.S.[11]	Average and higher	recency of use (≥ 1 y before Dx)	142/169	0.59 (0.21, 1.67)
		regular use		0.56 (0.34, 0.92)
Breuer-Katschinski, 2000, Germany[9]	Higher	< 5 y	182/182 (population-based)	0.65 (0.31, 1.34)
		≥ 5 y		0.21 (0.04, 0.99)

NSAID = non-steroidal anti-inflammatory drug; regular use = 2-3 x per/wk for ≥ 1 y; CI = confidence interval; y = year(s); OR = odds ratio; Dx = diagnosis; y = year(s); mo = month(s)

Evidence Table 3.1. Harms due to aspirin use—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Gibbs, 2004[45]	18,626	**Included studies** RCTs: n = 5 **e-databases** n = 3 **Range years** 1966 – 2003 **Quality of SR** Good	**Inclusion** • Pts with previous MI • RCTs (ASA vs. oral anticoagulation [OAD] vs. ASA + OAD or ASA + OAD vs. ASA) • Incidence of recurrent MI, all-cause mortality, & safety/harms • ASA dose (75 - 325 mg/d) • Follow-up length: ≥ 1 y **Exclusion** • Studies involving pts who underwent CABG or PTCA without being diagnosed MI • Abstracts		**All-cause mortality:** (1 RCT) OAD (1.2%) vs. ASA (4.5%), p<0.05 **Acute MI:** (1 RCT) OAD (9.7%) vs. ASA (7.4%), p<0.001
Hart, 2000[46]	52,251	**Included studies** RCTs: n = 5 Cohorts: n = 4 **e-databases** n = NR **Range years** 1980 – 1998 **Quality of SR** Fair	**Inclusion** • Subjects without clinically manifest CVD • Major CV risk factors • RCTs + prospective cohort studies • Stroke incidence • ASA vs. pb **Exclusion** • >20% pts with CVD • NR stroke outcomes	ASA (75 to 650 mg/d) vs. pb	**All-cause mortality:** (5 RCTs) RR: 0.94 (0.87, 1.01), NS **CV –mortality:** RR: 0.93 (0.83, 1.03), NS **Acute MI:** RR: 0.74 [(0.68, 0.82), S **Acute stroke:** RR: 1.02 (0.86, 1.21), NS

N = number of participants ; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; MI = myocardial infarction; OAD = oral coagulation drug; INR = international odds ratio; CABG = coronary artery bypass graft; PTCA =percutaneous coronary angioplasty; NS = nonstatistically significant difference; S = statistically significant difference; CVD = cardiovascular disease; SR = systematic review

Evidence Table 3.1 (cont'd). Harms due to aspirin use—Systematic reviews (cont'd)

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Hayden, 2002[47]	50,035	**Included studies** RCTs: n = 5 **e-databases** n = 1 **Range years** 1966-2001 **Quality of SR**	**Inclusion** • Pts with no hx of CVD disease • ASA vs. placebo or vs. no treatment; harms - ASA use • MI, stroke, mortality, harms • RCTs of at least 1 y duration; Harms - case-control, RCTs **Exclusion** • > 10% pts with CVD	ASA (162-500 mg/d) vs. pb	**All-cause mortality:** (5 RCTs) OR: 0.93 (0.84, 1.02), NS **CV-mortality:** OR: 0.87 (0.70, 1.09), NS **Acute MI:** OR: 0.72 (0.60, 0.87), S **Acute stroke:** OR: 1.02 (0.85, 1.23), NS **Hemorrhagic stroke:** OR: 1.4 (0.9, 2.0), NS **Major GI bleeding:** RR: 1.7 (1.4, 2.1), S **GI events (total):** 0.7/1,000 pts 2/1,000 pts / y in older pts
He, 1998[48]	55,462	**Included studies** RCTs: n = 16 **e-databases** n = 1 **Range years** 1966 – 1997 **Quality of SR** Fair	**Inclusion** • Human subjects • RCTs • No intervention difference other than ASA, intervention ≥ 1 mo **Exclusion** • Non-RCTs, comparison arm other than pb or no treatment, pts with acute complete stroke, study duration < 1 mo, no info on the occurrence of stroke subtypes	ASA (NR) vs. pb	**All-cause mortality:** (16 RCTs) RR: 0.85 (0.8, 0.9), S **CV-mortality:** RR: 0.84 (0.79, 0.90), S **Acute MI:** RR: 0.68 (0.62, 0.74), S **All acute stroke:** RR: 0.88 (0.76, 1.02), S **Hemorrhagic stroke:** RR: 1.84 (1.24, 2.74), S **Ischemic stroke:** RR: 0.82 (0.73, 0.92), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; OR = odds ratio; MI = myocardial infarction; CVD = cardiovascular disease; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review

Evidence Table 3.1 (cont'd). Harms due to aspirin use—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Weisman, 2002[49]	6,300	**Included studies** RCTs: n = 6 **e-databases** n = 3 **Range years** 1970 – 2002 **Quality of SR** Good	**Inclusion** • Pts with hx of stroke/TIA, MI or angina • RCTs **Exclusion** • ASA used for < 3 mo, used for nonprevention indications, coadministration with other agents, primary prevention	ASA (50-325 mg) vs. pb	**All-cause mortality**: (6 RCTs) RR: 0.82 (0.7, 0.99), S **Acute MI:** RR: 0.7 (0.6, 0.8), S **Acute stroke:** RR: 0.8 (0.7, 1.0), NS **GI bleed:** RR: 2.5 (1.4, 4.7)
Serebruany, 2003[50]	338,191	**Included studies** RCTs: n = 23 **e-databases** n = 3 **Range years** 1988 – 2002 **Quality of SR** Fair	**Inclusion** • Risk of hemorrhagic events with antiplatelet agents • Follow-up length: ≥ 1 mo **Exclusion** • NR	ASA (30 to 1.3 g/d) vs. pb	**Acute stroke:** < 100 mg/d (4 RCTs): 0.3% (0.2, 0.4) 100-325 mg/d (15 RCTs): 0.3% (0.2, 0.3) > 325 mg/d: 1.1% (0.7, 1.5) **GI bleed (%):** < 100 mg/d: 1.1% (0.9, 1.3) 100-325 mg/d: 2.5% (2.2, 2.6) > 325 mg/d: 2.50% (1.8, 3.1)

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; OR = odds ratio; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review

Evidence Table 3.1 (cont'd). Harms due to aspirin use—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Lip, 2004[51]	24,827	**Included studies** RCTs: n = 5 **e-databases** n = 4 **Range years** 1998 – 2001 **Quality of SR** Good	**Inclusion** • RCTs • Pts mild increases in BP or HTN • Antiplatelet agents > 3 mo • All-cause mortality, CV death, stroke, MI, thomboembolic events **Exclusion** • Atrial fibrillation, CHF, preeclampsia, eclampsia, pulmonary hypertension • Cohort, nonRCTs, open-label studies	ASA 75 mg vs. pb	**Acute MI:** (1 RCT) AAR: 0.5%; NNT: 200 **Ischemic stroke**: (2 RCTs) OR: 0.94 (0.76, 1.17), NS
Derry, 2000[52]	65,987	**Included studies** RCTs: n = 24 **e-databases** n = 3 **Range years** NR **Quality of SR** Fair	**Inclusion** • Oral ASA as antiplatelet agent with duration ≥ 12 mo • Trials providing numerical data on GI hemorrhage events in both ASA & pb/control arms • RCTs **Exclusion** • Abstracts, review articles, non-randomized trials, cross-over trials, case reports, clinical observations, unpublished data, trials with < 50 pts per each arm, special populations (pregnant women, children, & pts with pre-existing platelet disorders)	ASA (0.5-1.5 g) vs. pb	**GI bleed:** >162.5 mg/d: RR: 1.68 (1.51, 1.88), S 50-162.5 mg/d: RR: 1.59 (1.40, 1.81), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); RR = relative risk; OR = odds ratio; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review; AAR = absolute risk reduction; NNT = number needed to treat; BP = blood pressure; HTN = hypertension; CV = cardiovascular; CHF = congestive heart failure;

Evidence Table 3.1 (cont'd). Harms due to aspirin use—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Garcia Rodriguez, 2001[53]	67,722	**Included studies** Cohorts: n= 3 Case-controls: n = 14 **e-databases** n = 1 **Range years** 1990 – 2001 **Quality of SR** Fair	**Inclusion** • Adults • ASA use vs. No ASA use • Serious UGIC resulting in hospitalization or visit to specialist • Case-control or cohort studies **Exclusion** • No specific data on ASA or UGIC, studies reporting non-serious GI, studies combining upper & lower GI bleedings, studies with flawed methodology (selection & analysis)	ASA use vs. no use	**GI bleed:** Cohorts: RR: 2.2 (2.1, 2.4), S Case-control: RR: 3.1 (2.8, 3.3), S
Tramer, 2000[54]	**RCT:** 19,364 **Cohorts**: 215,076 **Case-control:** 2,957 cases	**Included studies** RCTs = 15 Cohorts = 3 Case-controls = 6 **e-databases** n = 2 **Range years** NR – 1996 **Quality of SR** Fair	**Inclusion** • Gastric or duodenal ulcer, ulcer hemorrhage or perforation, death due to these events • Oral NSAID or ASA exposure > 2 mo • Any level of evidence **Exclusion** • Abstracts & reports of NSAID-induced complications other than Upper GI	ASA (325 mg -5.2 g/d) or NSAID vs. pb	**Symptomatic ulcer incidence:** (RCT & cohorts) 1.48% **Bleed or perforation incidence**: Low dose (325 mg q 2 d): 0.34% 1 g/d: 0.57% 2.5 to 5.2 g/d: 0.86%

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review; UGIC = upper gastrointestinal complications

Evidence Table 3.1 (cont'd). Harms due to aspirin use—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Roderick, 1993[55]	39,646	**Included studies** RCTs = 21 **e-databases** n = 1 **Range years** NR-1990 **Quality of SR** Fair	**Inclusion** • GI toxicity reported in a form allowing events & symptoms to be defined in a reasonably standard manner • ASA vs. pb • Follow-up at least 1 y • RCTs **Exclusion** • NR	ASA (0.5-1.5 g/d) vs. pb	**All GI bleed**: (11 RCTs) OR: 2.0 (99% CI: 1.5, 2.8), S 300 mg/d (1 RCT): OR: 1.6 (0.7, 4.0), NS > 1,200 mg/d (1 RCT): OR: 2.8 (1.3, 5.7), S **Hospitalization for GI Bleed**: (3 RCTs) OR: 1.9 (99% CI: 1.1, 3.1), S **GI symptoms*:** (7 RCTs) OR: 1.7 (99% CI: 1.5, 1.8), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); RR = relative risk; OR = odds ratio; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; *GI symptoms: nausea, vomiting, heartburn, indigestion; SR = systematic review

Evidence Table 3.2. Harms due to non-aspirin NSAID (other than COX-2 inhibitors)—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Tramer, 2000[54]	**RCT:** 19,364 **Cohorts**: 215,076 **Case-control:** 2,957 cases	**Included studies** RCTs = 15 Cohorts = 3 Case-controls = 6 **e-databases** n = 2 **Range years** NR – 1996 **Quality of SR** Fair	**Inclusion** • Gastric or duodenal ulcer, ulcer hemorrhage or perforation, death due to these events • Oral NSAID or ASA exposure > 2 mo • Any level of evidence **Exclusion** • Abstracts & reports of NSAID-induced complications other than Upper GI	NSAID vs. pb or non users	**Average GI bleeding rate**: 4.8% **GI ulcer bleed or perforation:** (3 RCTs) Absolute Risk Difference: 0.48% (1 Cohort): Absolute Risk Difference: 0.22% **Mortality due to GI events:** (RCT & cohort) 0.008% NNT: 16,932
Huang, 2002[56]	734	**Included studies** Cohort = 1 Case-control = 7 **e-databases** n = 3 **Range years** 1984 – 2000 **Quality of SR** Fair	**Inclusion** • Harms of ASA/NSAID • Roles of helicobacter pylori infection & NSAID drugs in the occurrence of peptic ulcer disease, GI harms • Incidence/prevalence of PUD in NSAIDs adult users or prevalence of H pylori infection & NSAID use amongst pts with PUB; influence of H pylori & NSAID use on the rate of PUD • Cross-sectional, case-control, or cohort **Exclusion** • Abstracts • Antibiotic &/or anti-ulcer drug use 3-4 wks before study entry • Hx gastric surgery • Non-ulcer GI bleeding, gastric tumors • Pts taking corticosteroids or anticoagulants	NSAIDs users vs. no users	**PUB:** OR: 4.79 (3.78, 6.06), S **Endoscopic GI ulcers >5mm:** OR: 5.14 (1.35, 19.6), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID; = non steroid anti-inflammatory drug; ARR = absolute risk reduction; OR = odds ratio; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review; NNT = number needed to treat; PUD = peptic ulcer disease; H pylori = Helicobacter pylori; PUB = perforation ulcer bleed

Evidence Table 3.2 (cont'd). Harms due to non-aspirin NSAID (other than COX-2 inhibitors)—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Ofman, 2002[57]	**RCTs:** 4,431 **Cohorts:** 758,776 pt-y **Case-controls:** 25,732	**Included studies** RCTs: n = 92 Cohorts: n = 24 Case-controls: n = 57 **e-databases** n = 4 **Range years** 1966 – 1998 **Quality of SR** Good	**Inclusion** • Subjects ≥ 18 y • Oral NSAIDs ≥ 5 d • Serious upper GI complications: PUB (perforation, ulcer, & bleeding) • RCTs, cohort & case-control studies **Exclusion** • Studies not reporting PUB, animal studies, studies reporting the use of non-oral NSAIDs or ASA alone, studies not reporting inclusion criteria, reviews, editorials, letters, clinical practice guidelines, case-reports, case-series, or consensus statements, studies reporting the duration of NSAIDs use < 5 d	NSAIDs vs. pb (RCTs) NSAIDs users vs. non users (cohorts)	**PUB:** (16 RCTs): OR: 5.36 (1.79, 16.1), S (9 Cohorts): RR: 2.7 (2.1, 3.5), S (23 case-controls): OR: 3.0 (2.5, 3.7), S
Ofman, 2003[58]	12,000	**Included studies** RCTs: n = 48 **e-databases** n = 4 **Range years** 1966 – 1998 **Quality of SR** Good	**Inclusion** • Subjects > 18 y • NSAID use > 5 d • Dyspepsia • RCT, case-control, cohort, exposure **Exclusion** • Animal studies, studies reporting the use of non-oral NSAIDs or ASA alone, reviews, editorials, letters, clinical practice guidelines, case-reports, case-series, or consensus statements • NSAID < 5 d	NSAIDs v. pb	**NSAID vs. control** **Dyspepsia rate**: 4.8% (3.8, 5.8), S **High dose - Dyspepsia**: Risk ratio: 2.6 (1.5, 4.5), S **Low Dose – Dyspepsia**: Risk ratio: 1.3 (0.9, 1.8), NS **Indomethacin, meclofenamate & piroxicam** **Dyspepsia:** Risk ratio: 2.2 (1.5, 3.2), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; OR = odds ratio; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; PUB = perforation ulcer bleed

Evidence Table 3.2 (cont'd). Harms due to non-aspirin NSAID (other than COX-2 inhibitors)—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Rostom, 2003[59]	4,675	**Included studies** RCTs: n = 37 **e-databases** n = 8 **Range years** 1966 – 2002 **Quality of SR** Good	**Inclusion** • OA pts, RA > 18 y, chronic use (> 4 wks) NSAID **Exclusion** • NR	Celecoxib vs. NSAID (naproxen, diclofenac, ibuprofen) Rofecoxib vs. NSAID All Cox-2 vs. NSAID	**% pts with endoscopic ulcers** (NSAIDs): 19% gastric; 6% duodenal **Clinically important ulcers:** 1.5% / y - average OA, RA pt; up to 9%/y high risk of GI complications

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID; = non steroid anti-inflammatory drug; GI = gastrointestinal; SR = systematic review; Cox-2 = Cox-2 inhibitors; OA = osteoarthritis; RA = rheumatoid arthritis

Evidence Table 3.3. Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Hooper, 2004[60]	74,666	**Included studies** RCTs: n = 68 **e-databases** n = 3 **Range years** 1966 – 2002 **Quality of SR** Good	**Inclusion** • COX-2 vs. NSAID, misoprostol, PPI and H2 • GI, CV, renal, other harms • RCTs **Exclusion** • Non-RCTs • No treatment • Children • < 21 d study period	COX 2- selective (etodolac, meloxicam, nabumetone, nimesulide) vs. NSAIDs COX-2 specific (celecoxib, rofecoxib) vs. NSAIDs	**All-cause mortality:** Cox-2 selective (51 RCTs): RR: 0.68 (0.3, 1.6), NS Cox-2 specific (17 RCTs): RR: 1.02 (0.6, 1.9), NS **Withdrawals due to harms:** Cox-2 selective (51 RCTs): RR: 0.93 (0.9, 1.0), NS Cox-2 specific (17 RCTs): RR: 0.82 (0.7, 0.9)^ **Endoscopic GI ulcers:** Cox-2 selective (51 RCTs): RR: 0.41 (0.2, 1.1), NS Cox-2 specific (17 RCTs): RR: 0.25 (0.2, 0.3), S **Symptomatic ulcers:** Cox-2 selective (51 RCTs): RR: 0.41 (0.3, 0.7), S Cox-2 specific (17 RCTs): RR: 0.49 (0.38, 0.62), S **POB:** Cox-2 selective (51 RCTs): RR: 0.61 (0.34, 1.10), NS Cox-2 specific (17 RCTs): RR: 0.55 (0.38, 0.80), S **GI symptoms:** Cox-2 selective (51 RCTs): RR: 0.73 (0.7, 0.8), S Cox-2 specific (17 RCTs): RR: 0.81 (0.7, 0.9), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; OR = odds ratio; NS = nonstatistically significant difference; S = statistically significant difference; ^ high heterogeneity; GI = gastrointestinal; SR = systematic review; Cox-2 = Cox-2 inhibitors; PPI = proton pump inhibitors; H2 = H2 blockers; CV = cardiovascular

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Garner, 2002[61]	4,465	**Included studies** RCTs: n = 5 **e-databases** n = 3 **Range years** 1966 – 2002 **Quality of SR** Good	**Inclusion** • RA pts (some with OA) • RCTs • Published • celecoxib vs. pb • celecoxib vs. other NSAID **Exclusion** • <50 pts in each arm • <1mo treatment	Celecoxib vs. pb Celecoxib vs. NSAIDs Used FDA CLASS study description	**Celecoxib vs. pb:** **All-cause mortality:** (3 RCTs) None • **Withdrawals due to harms:** (1 RCT) Cel 40mg (4%) vs. 200 mg (5%) vs. 400 mg (5%) vs. pb (6%), NS • **Edema:** (2 RCTs) Cel 1-2% vs. pb 0% • **Endoscopic ulcers:** NS **Celecoxib vs. NSAIDs**: • **Arterial hypertension**: (1 RCT) Cel 4/236 (1%) vs. diclofenac 5/329 (2%) • **Edema:** (3 RCTs) Cel (400-800 mg/d) & naproxen 2% Cel 11/236 (3%) vs. diclofenac 5/329 (2%) • **Endoscopic ulcers:** (2 RCTs) RR: 0.22 (0.15-0.32), S **Used FDA CLASS study description** • **Endoscopic ulcers:** (52 wks) Celecoxib (22/3105) was S lower than for the NSAID's pooled (39/ 3,124; p=0.02) & for ibuprofen alone (29/ 1,573; p=0.001) but not for diclofenac alone (29/1,573)

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; OA = osteoarthritis; RA = rheumatoid arthritis; FDA = food and drug administration; Cel = celecoxib

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Deeks, 2002[62]	15,187	**Included studies** RCTs: n = 9 **e-databases** n = 3 **Range years** 1998 – 2001 **Quality of SR** Fair	**Inclusion** • OA/ RA **Exclusion** • NR	Celecoxib vs. pb Celecoxib vs. NSAIDs	**Celecoxib vs. pb** • **Withdrawals due to harms:** (5 RCTs) RR: 1.49 (1.15, 1.92), S • **Endoscopic GI ulcers:** RR: 1.53 (0.73, 3.21), NS **Celecoxib vs. NSAIDs** • **Withdrawals due to harms:** (8 RCTs) RR: 0.86 (0.72, 1.04), NS • **Endoscopic GI ulcers:** (vs. naproxen, diclofenac): RR: 0.25 (0.12, 0.53) • **POB:** (vs. ibuprofen, diclofenac) RR: 0.55 (0.26, 1.14), NS • **PUB:** (vs. ibuprofen, diclofenac) RR: 0.61 (0.39, 0.96), S
Edwards, 2004[63]	5,726	**Included studies** RCTs: n = 9 **e-databases** NR **Range years** 2002 – 2003 **Quality of SR** Good	**Inclusion** • Pts: OA or RA • Double-blind RCTs • Valdecoxib vs. pb or NSAIDs **Exclusion** • NR	Valdecoxib 10 –20 mg/d vs. pb Valdecoxib 10 –20 mg/d vs. NSAIDs (ibuprofen, diclofenac, naproxen)	**Valdecoxib vs. pb:** • **Withdrawals due to harms**: RR: 0.9 (0.7, 1.3), NS • **Significant renal events:** RR: 2.9 (1.4, 5.7), S • **Endoscopic GI ulcers:** RR: 0.9 (0.5, 1.6), NS **Valdecoxib vs. NSAIDs:** (9 RCTs) • **Withdrawals due to harms**: RR: 0.6 (0.5, 0.7), S • **Acute MI:** Valdecoxib 3/2,733 (0.1%) vs. NSAID 11/1,846 (0.6%), S • **Edema:** 2% each group, NS • **Significant renal events:** RR: 0.7 (0.5, 1.0), NS • **Endoscopic GI ulcers:** RR: 0.4 (0.3, 0.5), S **POB:** RR: 0.4 (0.2, 1.2), NS

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID; = non steroid anti-inflammatory drug; RR = relative risk; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review; OA = osteoarthritis; RA = rheumatoid arthritis; POB = perforation obstruction, bleed; PUB = perforation ulcer bleed

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Garner, 2005[64]	NR	**Included studies** RCTs: n = 26 **e-databases** n = 3 **Range years** 1966 - 2004 **Quality of SR** Good	**Inclusion** • Pts with OA any age or sex • Published RCTs • Rofecoxib vs. pb or active comparators • Efficacy & safety outcomes **Exclusion** • Unpublished RCTs	Rofecoxib vs. pb Rofecoxib vs. NSAIDs (diclofenac, naproxen, ibuprofen, nimesulide, nabumetone, paracetamol, celecoxib)	**Rofecoxib vs. pb:** • **Withdrawals due to harms:** (6 RCTs) 12.5 mg/d: RR: 2.18 (1.34-3.55), S 25 mg/d: RR: 1.56 (0.94, 2.59) 50 mg/d: RR: 2.04 (1.24, 3.36), S • **All symptoms and endoscopic ulcers**: NS • **Total adverse events**: RR: 1.32 (1.11, 1.56) @ 6 wks; longer durations, NS **Rofecoxib vs. diclofenac (150 mg/d):** • **Withdrawals due to harms:** (2 RCTs) 12.5 mg/d: RR: 0.71 (0.52-0.97) 25 mg/d: RR: 0.70 (0.51-0.95) • **PUB**: RR: 0.25 (0.03, 2.25), NS **Rofecoxib vs. naproxen:** (1 RCT) • **Acute MI:** RR: 4.98 (0.58, 42.57), NS • **Acute stroke:** RR: 0.08 (0.00, 1.36), NS • **Arterial hypertension:** RR: 1.22 (0.89, 1.68), NS • **PUB:** RR: 0.14 (0.01, 2.77), NS **Rofecoxib vs. nabumetone:** (3 RCTs) • **Arterial hypertension:** RR: 1.46 (0.53, 4.12), NS • **Edema:** RR: 1.41 (0.72, 2.77), NS **Rofecoxib vs. ibuprofen:** • **Endoscopic GI ulcers**: RR: 0.28 (0.19, 0.42), S • **PUB**: RR: 0.25 (0.03, 2.26), NS **Rofecoxib (25 mg) vs. celecoxib (200 mg)**: • **Withdrawals due to harms:** (9 RCTs) RR: 1.03 (0.77, 1.39), NS • **Arterial hypertension:** (2 RCTs) RR: 3.51 (0.73, 16.84), NS • **Edema:** RR: 1.39 (0.63, 3.08), NS

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; OA = osteoarthritis; PUB = perforation ulcer bleed

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Garner, 2005[65]	NR	**Included studies** RCTs: n = 2 **e-databases** n = 5 **Range years** 1966 - 2000 **Quality of SR** Good	**Inclusion** • Pts with RA any age or sex • RCTs • Rofecoxib vs. pb or active comparators • Efficacy & safety outcomes **Exclusion** • < 50 pts included in RCT • Duration treatment < 4 wks • Used concomitant intra-articular corticosteroid therapy	Rofecoxib (12.5-50 mg/d) vs. pb Rofecoxib (12.5-50 mg/d) vs. naproxen (1 g/d)	**Rofecoxib vs. pb:** • **Withdrawals due to harms:** Rofe 5 mg (3%) vs. 25 mg (3.2%) vs. 50 mg (4.7%) vs. pb (6.2%), NS • **GI outcomes**: NS • **Edema & hypertension:** NS between 3 doses of rofecoxib & pb. **Rofecoxib vs. naproxen (VIGOR):** • **All-cause mortality:** 0.5% vs. 0.4%, NS • **CV-mortality:** both 0.2%, NS • **Withdrawals due to harms:** (1 RCT) RR: 1.02 (0.92, 1.12), NS • **Acute MI:** (1 RCT) RR: 5.0 (1.5, 13.2), S • **All-acute stroke:** (1 RCT) RR: 1.37 (0.55, 3.41), NS • **Ischemic stroke:** RR: 1.12 (0.43, 2.91), NS • **TIA:** RR: 4.98 (0.24, 103.77), NS • **POB:** RR: 0.43 (0.24, 0.77), S
Gomez Cerezo, 2003[66]	45,761	**Included Studies** RCTs: n = 3 **e-databases** n = 1 **Range years** 1998 – 2002 **Quality of SR** Poor	**Inclusion** • Cox 2 specific • RCTs **Exclusion** • non-English	Rofecoxib (12.5-50 mg/d) or celecoxib (50-800 mg/d) vs. NSAIDs (naproxen 1g/d, ibuprofen 2.4 g/d, diclofenac 100-150 mg/d) or pb	**Rofecoxib vs. naproxen** • **HTN (withdrawals):** (1 RCT) RR: 4.67 (1.93, 11.28), S • **CHF:** (1 RCT): RR: 2.11 (0.96, 4.67), NS • **Edema (withdrawals)**: (1 RCT) RR: 1.92 (0.98, 3.75), NS • **PUB:** RR: 0.46 (0.34, 0.63), S • **POB**: RR: 0.43 (0.24, 0.77), S rofecoxib vs. Ibuprofen & diclofenac: • **PUB:** RR: 0.51 (0.26, 1), NS **Celecoxib vs. NSAID** • **POB:** RR: 0.10 (0.01, 0.81), S celecoxib vs. Ibuprofen & diclofenac: • **POB:** RR: 0.60 (0.25, 1.40), NS • **PUB:** RR: 0.61 (0.39, 0.96), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; CHF = congestive heart failure; PUB = perforation ulcer bleed; POB = perforation obstruction bleed; Cox-2 = Conx-2 inhibitors; RA = rheumatoid arthritis; TIA = transitory ischemic attack; HTN = arterial hypertension

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Mukherjee, 2001[67]	18,064	**Included studies** RCTs: n = 4 **e-databases** n = 1 **Range years** 1998 – 2001 **Quality of SR** Fair	**Inclusion** • Pts without previous CV event • COX-2 (rofecoxib, celecoxib) • Double-blind RCT **Exclusion** • Non-RCTs, RCTs reporting non-CV adverse events	Rofecoxib (50 mg/d) vs. naproxen (1 g/d)	**Rofecoxib vs. naproxen:** (1 RCT) • **Serious CV events:** Low CV risk: RR: 1.89 (1.03, 3.45), S High risk (ASA indicated): RR: 4.89 (1.41, 16.88), S
Juni, 2004[68]	25,273	**Included studies** RCTs: n = 18 Case-control: n = 8 **e-databases** n = 4 **Range years** 1966 – 2004 **Quality of SR** Good	**Inclusion** • RCTs & observational studies • Rofecoxib vs. NSAID or pb • Pts with chronic musculoskeletal disorders • Fatal or nonfatal MI, stroke, CV mortality, serious CV events **Exclusion** • NR	Rofecoxib vs. pb or NSAIDs	**Rofecoxib vs. NSAIDS**: (9-17 RCTs) • **Acute MI:** RR: 2.24 (1.24, 4.02), S • **Stroke/TIA:** RR: 1.02 (0.54, 1.93), NS • **Death due to CV harms:** RR: 0.79 (0.29, 2.19), NS • **Serious CV events:** RR: 1.55 (1.05, 2.29), S **Rofecoxib vs. pb:** • **Acute MI**: RR: 1.04 (0.34, 3.12), NS **Rofecoxib vs. no naproxen NSAID:** • **Acute MI**: RR: 1.55 (0.55, 4.36), NS **Rofecoxib vs. naproxen:** • **Acute MI:** RR: 2.93 (1.36, 6.33), S 12.5 mg/d RR: 2.71 (0.99, 7.44), NS 25 mg/d RR: 1.37 (0.52, 3.61), NS 50 mg/d RR: 2.83 (1.24, 6.43), S

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID = non steroid anti-inflammatory drug; RR = relative risk; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; TIA = transitory ischemic attack; CV = cardiovascular

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Rostom, 2003[59]	86,702	**Included studies** RCTs: n = 37 **e-databases** n = 8 **Range years** 1966 – 2002 **Quality of SR** Good	**Inclusion** • OA pts, RA > 18 y, chronic use (> 4 wks) NSAID **Exclusion** • NR	Celecoxib vs. NSAID (naproxen, diclofenac, ibuprofen) Rofecoxib vs. NSAID All Cox-2 vs. NSAID	**Celecoxib vs. NSAID:** • **Endoscopic ulcers:** RR: 0.28 (0.23, 0.35), S **Celecoxib vs. diclofenac:** • **Endoscopic ulcers:** RR: 0.45 (0.15, 1.29), NS **Rofecoxib vs. NSAIDs:** • **Endoscopic ulcers**: RR: 0.25 (0.20, 0.32), S **Meloxicam vs. NSAIDs:** • **POB**: RR: 0.50 (0.22 -1.17), NS **All Cox 2 vs. NSAIDs:** • **POB:** RR: 0.45 (0.32, 0.63), S • **Endoscopic ulcers:** RR: 0.27 (0.23, 0.32), S
Ashcroft, 2001[69]	4,632	**Included studies** RCTs: n = 5 **e-databases** n = 3 **Range years** 1988 – 2000 **Quality of SR** Fair	**Inclusion** • Pts with RA & OA who had scheduled endoscopies • Celecoxib • RCTs **Exclusion** • Healthy population not undergone by endoscopy	Celecoxib vs. NSAIDs (ibuprofen, diclofenac, naproxen) or pb	• **Endoscopic ulcers:** Celecoxib vs. naproxen: 200 mg/d: RR: 0.22 (0.13, 0.37), S 400 mg/d: RR: 0.24 (0.17, 0.33), S Celecoxib vs. diclofenac: 12 wks: RR: 0.73 (0.45, 1.2), NS 24 wks: RR: 0.24 (0.11, 0.52), S Celecoxib vs. Ibuprofen: RR: 0.30 (0.20, 0.46), S Celecoxib vs pb: 200 mg/d: RR:1.96 (0.85, 4.55) 400 mg/d: RR:2.35 (1.02, 5.38)

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID; = non steroid anti-inflammatory drug; RR = relative risk; NS = nonstatistically significant difference; S = statistically significant difference; SR = systematic review; OA = osteoarthritis; RA = rheumatoid arthritis

Evidence Table 3.3 (cont'd). Harms due to COX-2 inhibitors—Systematic reviews

Author, year	N	Review characteristics/ quality	Eligibility criteria	Intervention(s) (dose range)	Results
Goldstein, 2004[70]	10,305	**Included studies** RCT: n=8 Cohorts: n = 3 **e-databases** NR **Range years** NR **Quality of SR** Fair	**Inclusion** • Pts with RA and/or OA • RCTs (long-term, open-label) **Exclusion** • NR	Valdecoxib vs. pb or NSAIDs	**Valdecoxib vs. pb:** • **PUB**: RR :3.8 (0.22-65.70), NS **Valdecoxib vs. NSAIDs:** • **POB** (8 RCTs): (Valdecoxib 0.69%; NSAIDs 1.96%) RR: 0.14 (0.04-0.51), S Non - ASA users: (Valdecoxib 0.29%; NSAIDs 2.08%): RR: 0.35 (0.14-0.87), S **Valdecoxib + ASA** = 9-fold increase risk of bleeding **NSAIDS + ASA** = did not increase risk further **Open-label:** dose-reponse not seen with valdecoxib
Schoenfeld, 1999[71]	20,374	**Included studies** RCTs: n = 10 **e-databases** n = 1 **Range years** 1990 – 1998 **Quality of SR** Fair	**Inclusion** • Adult pts • Meloxicam vs. other non-COX 2 NSAID • GI events: dyspepsia, nausea/vomiting, abdominal pain, diarrhea, perforations, ulcers, bleeds, & withdrawals due to GI events • RCTs (including crossover with washout period) **Exclusion** • NR	Meloxicam (7.5 to 15 mg) vs. NSAID	• **Overall GI harms: OR: 0.64 (0.59, 0.69), S** • **PUB: OR: 0.52 (0.28, 0.96), S** • **Dyspepsia: OR: 0.73 (0.64, 0.84), S** • **Withdrawals due to GI harms:** OR: 0.59 (0.52, 0.67), S
Eisen, 2005[72]	4,394	**Included studies** RCTs: n = 5 **e-databases** NR **Range years** NR **Quality of SR** Fair	**Inclusion** • Adult pts ≥ 18 y withOA or RA • Phase III RCTs • Valdecoxib use **Exclusion** • Pts with concomitant GI, renal, hepatic or coagulation disorder or malignancy	Valdecoxib (10-20 mg/d) vs. pb or other NSAIDs (ibuprofen, diclofenac, naproxen)	• **Dyspepsia**: Valdecoxib vs. NSAIDs: HR =1.0 Valdecoxib vs. pb: Valdecoxib: HR = 0.56 (0.45–0.69) Pb: HR= 0.59 (0.45–0.79)

N = number of participants; y = year(s); mo = month(s); wk = week(s); d = day(s); n = number; pts = patients; hx = history; NR = not reported; vs. = versus; pb = placebo; ASA = acetylsalicylic acid/aspirin; RCT(s) = randomized control trial(s); NSAID; = non steroid anti-inflammatory drug; RR = relative risk; OR = odds ratio; MI = myocardial infarction; NS = nonstatistically significant difference; S = statistically significant difference; GI = gastrointestinal; SR = systematic review; HR = hazard ratio; PUB = perforation ulcer bleed; OA = osteoarthritis; RA = rheumatoid arthritis

Evidence Table 4.1. Cost-effectiveness analysis—Suleiman 2002[73]

Study type	Decision analysis using a Markov model
Interventions	1) Do nothing 2) Colonoscopy q10 y; q3 y if polyp(s) found 3) ASA 325mg po daily 4) Colonoscopy q10 y + ASA 325mg po daily
Study population	100 000 average-risk subjects age 50 followed until death
Economical context	Third-party payer perspective in U.S. dollars discounted at 3% per year
Probabilities (range used in sensitivity analysis)	Incidence polyps: 0.01/yr Age-specific incidence CRC: from SEER data 1973-94 Efficacy of colonoscopy at preventing CRC: 75% (50-75%) Efficacy of ASA at preventing CRC: 50% (25-75%) Efficacy of ASA+colonoscopy at preventing CRC: 87.5% (50-100%) Mortality from CRC: 40% Effect of ASA on cardiovascular outcomes: not modeled Compliance to interventions: 100%
Costs (range used in sensitivity analysis)	ASA: $172/PY ($20-200) (includes costs of complications) Colonoscopy: $696 Colonoscopy with polypectomy: $1004 Care for CRC: $45 228 (up to $60 000)
Outcomes	Screening vs do nothing: • saves 7,951 LYs for $223,780,829 • ICER $10,983/LY saved ASA vs do nothing: • Saves 5,301 LYs for $386,920,810 • ICER $47,249/LY saved ASA + screening vs do nothing • ICER $41,929/LY saved ASA+screening vs screening alone • ICER $227,607/LY saved
Sensitivity Analyses	Cost of ASA (including drug cost and cost of complications) needs to fall below $70/patient/y for ASA to be more cost-effective than screening

Evidence Table 4.2. Cost-effectiveness analysis—Ladabaum 2001[74]

Study type	Decision analysis using a Markov model
Interventions	1) Do nothing 2) Flexible sigmoidoscopy q5 y + FOBT q1y (FS/FOBT) 3) Colonoscopy q10 y; q5 y if polyp(s) found (COLON) 4) ASA 325mg po daily 5) FS/FOBT + ASA 325mg po daily 6) Colonoscopy q10 y + ASA 325mg po daily
Study population	Average-risk subjects age 50 followed for 30 years
Economical context	Third-party payer perspective in U.S. dollars discounted at 3% per year
Probabilities (range used in sensitivity analysis)	Incidence polyps: 0.011/yr at age 50-60 to 0.019/y age 70+ Baseline prevalence polyps: 15% Age-specific incidence CRC: from SEER data 1973-94 FOBT: sensitivity CRC 40% (30-60%); polyps 10% (5-15%) FS: sensitivity Lt-sided CRC 90% (80-95%) % Lt-sided CRC: 50% COLON: sensitivity CRC 95% (90-97%); polyps 90% (85-95%) Efficacy of ASA at preventing CRC: 30% (5-55%) Incidence ASA-related morbidity: <65y: 2 (0.5-5)/10 000PYs; >/= 65y: 16 (4-40)/10 000PYs Incidence ASA-related mortality: 5% (2-8%) Compliance w interventions: 25%
Costs (range used in sensitivity analysis)	ASA: $4/PY ($20-200) Major ASA-related complication: $15 000 ($10 000-$20 000) FOBT: $10 ($5-15) FS: $206 ($76-336) Colonoscopy: $623 ($288-958) Care for advanced CRC: $40 000 ($30 000-50 000)
Outcomes	Screening vs do nothing • ICER FS/FOBT $16,844/LY saved • ICER COLO $20,172/LY saved ASA + screening vs screening alone • increased costs and decreased LYs If ASA decreased cardiovascular mortality by 0.1% and CRC incidence by 30%: • ICER ASA + FS/FOBT vs FS/FOBT alone $10,039/LY saved • ICER ASA + COLO vs COLO alone $8,976/LY saved
Sensitivity Analyses	ASA use affects both polyp and CRC growth vs only CRC growth Effect of ASA on cardiovascular outcomes: nil vs reduction Effect of ASA on FOBT: nil vs increased sensitivity and decreased specificity

Evidence Table 4.3. Cost-effectiveness analysis—Ladabaum 2003[75]

Study type	Decision analysis using a Markov model
Interventions	1) Do nothing 2) Colonoscopy q10 y in avrg risk; q5 y in at-risk subjects 3) Daily COX-2 inhibitors 4) Colonoscopy q10 y in avrg risk/q5 y in at-risk + daily COX-2 inhibitors
Study populations	1) Average-risk subjects age 50 followed for 30 years 2) At-risk subjects age 50 followed for 30 years a. With 1 1st degree rel w CRC (RR 2.6avrg) b. With 2 1st degree rel w CRC (RR 3.6avrg)
Economical context	Third-party payer perspective in U.S. dollars discounted at 3% per year
Probabilities (range used in sensitivity analysis)	Incidence polyps in avrg risk: 0.011/yr at age 50-60 to 0.019/y age 70+ Baseline prevalence polyps: 15% Age-specific incidence CRC: from SEER data 1973-94 Colonoscopy: sensitivity CRC 95% (90-97%); polyps 90% (85-95%) Efficacy of COX-2 at preventing CRC: 30% (0-100%) Incidence COX-2-related morbidity: Nil (0-0.1%/y) Incidence COX-2-related mortality: nil (2-8%)
Costs (range used in sensitivity analysis)	COX-2: $365/PY ($91.25-$1 460/PY) Major COX-2-related complication: $15 000 ($10 000-$20 000) Colonoscopy: $623 ($288-958) Care for advanced CRC: $40 000 ($30 000-50 000)
Sensitivity Analyses	Varying COX-2's chemopreventive efficacy from 0 to 100% Assuming a differential effect on polyp and CRC growth Using a COX-2 inhibitor in individuals younger than 65 Increasing the rate of excess major GI complications to 0.1%/year Varying rate of death from COX-2 from 2 to 8% per complication Varying the doses of COX-2's, with yearly costs of COX-2 chemoprevention ranging from $81.25 to $1300 Evaluating whether COX-2 chemoprevention would allow for less frequent screening
Outcome	Colonoscopy vs do nothing • saves 0.065LY/person; ICER $20,200/LY saved COX-2 vs do nothing • saves 0.027LY/person; ICER of $233,300/LY saved COX-2 + colon vs colon alone • saves 0.008LY/person; ICER $823,800/LY saved COX-2 use alone would need to reduce CRC risk by 60% at a cost of $0.25/day to approach the cost effectiveness of colonoscopy every 10 years

Evidence Table 4.4. Cost-effectiveness analysis—Arguedas 2001[76]

Study type	Decision analysis using a Markov model
Interventions	1) Do nothing 2) Colonoscopy every 3 years; every 5 years if no polyp found 3) Celecoxib 200mg po daily
Study population	50 yo subjects with colonic adenomas followed for 10 years
Economical context	Third-party payer perspective in U.S. dollars discounted at 3% per year
Probabilities (range used in sensitivity analysis)	Incidence polyps: 0-3 yrs: 0.106/y (0.05-0.20); after 3 yrs: 0.05/y (0.02-0.15) Incidence CRC: 0.10/y (0.05-0.20) Efficacy of celecoxib at preventing CRC: 50% (0-100%) Incidence of celecoxib-induced PUD: 0.02/y (0.01-0015) Incidence withdrawal re celecoxib SE: 0.01/y (0-0.02) Compliance w intervention: 100% Effect of celecoxib on cardiovascular outcomes: not modeled
Costs (range used in sensitivity analysis)	ASA: $172/pt/yr ($20-200) Colonoscopy: $514 ($300-750) Colonoscopy with polypectomy: $658 ($500-1000) Care for CRC: $100 000/case ($10,000-250,000)
Outcomes	Colonoscopy vs do nothing • 0.01995LY saved at a cost of $558 • ICER $27, 970/LY saved Celecoxib vs do nothing • 0.00579LY saved for $9,931 • ICER $407,498/LY saved Celecoxib use could be economically advantageous (ICER less than $50,000/LY saved) if 50% effective for polyp prevention at a cost of $0.10/day or if 75% effective at a cost of $0.35/day Results not sensitive to the rate of polyp formation (i.e. increasing or decreasing the magnitude of patient risk)

Evidence Table 4.5. Cost-effectiveness analysis—Hur 2003[77]

Study type	Decision analysis using a Markov model
Interventions	1) ASA 325mg po daily 2) Celecoxib 200mg po bid
Study population	Average-risk men age 50 followed for 10 years
Economical context	Societal perspective in U.S. dollars discounted at 3% per year
Probabilities (range used in sensitivity analysis)	Incidence polyps: 0.01/yr Age-specific incidence CRC: from SEER data 1973-94 Efficacy of ASA at preventing CRC: 50% (25-75%) Efficacy of ASA+colonoscopy at preventing CRC: 87.5% (50-100%) Mortality from CRC: 40% Effect of ASA on cardiovascular outcomes: not modeled
Costs (range used in sensitivity analysis)	ASA: $172/pt/yr ($20-200) Colonoscopy: $696 Colonoscopy with polypectomy: $1004 Care for CRC: $45 228 (up to $60 000)
Outcomes	ASA • 7.60 QALY saved for $181 Celecoxib • 7.57 QALY saved for $23,403
Sensitivity Analyses	Coxibs become more effective than ASA if • the relative ulcer rate on coxibs is 93% lesser than in the base-case • the combined relative MI/ulcer rate for coxibs is decreased by 60% • the relative bleeding rate on ASA is increased 550%

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