

# MetaAnalysis – Systematic Review Potential PURL Review Form PURL Jam Version

PURLs Surveillance System  
Family Physicians Inquiries Network

## SECTION 1: Identifying Information for Nominated Potential PURL [to be completed by PURLs Project Manager]

- A. Citation: 1: Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. Eur Heart J. 2019 Feb 14;40(7):607-617. doi: 10.1093/eurheartj/ehy813. PubMed PMID: 30561620.
- B. Link to PubMed Abstract:  
<https://www.ncbi.nlm.nih.gov/pubmed/30561620?report=docsum&format=text>
- C. First date published study available to readers:01/14/19
- D. PubMed ID: 30561620
- E. Nominated By: Jim Stevermer
- F. Institutional Affiliation of Nominator: University of Missouri
- G. Date Nominated: 1/13/2019
- H. Identified Through: Evidence Updates
- I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
- J. Nomination Decision Date: 1/15/19
- K. Potential PURL Review Form (PPRF) Type: Systematic Review
- L. Assigned Potential PURL Reviewer: John Scott Earwood
- M. Reviewer Affiliation: CA – Eisenhower

### A. Abstract:

#### **AIMS:**

**THE ROLE OF ASPIRIN IN THE PRIMARY PREVENTION SETTING IS CONTINUOUSLY EVOLVING. RECENT RANDOMIZED TRIALS HAVE CHALLENGED THE ROLE OF ASPIRIN IN THE PRIMARY PREVENTION SETTING.**

#### **METHODS AND RESULTS:**

**ELECTRONIC DATABASES WERE SEARCHED FOR RANDOMIZED TRIALS THAT COMPARED ASPIRIN VS. PLACEBO (OR CONTROL) IN SUBJECTS WITHOUT ESTABLISHED ATHEROSCLEROTIC DISEASE. THE PRIMARY EFFICACY OUTCOME WAS ALL-CAUSE MORTALITY, WHILE THE PRIMARY SAFETY OUTCOME WAS MAJOR BLEEDING. SUMMARY ESTIMATES WERE REPORTED USING A DERSIMONIAN AND LAIRD RANDOM EFFECTS MODEL. A TOTAL OF 11 TRIALS WITH 157 248 SUBJECTS WERE INCLUDED. AT A MEAN FOLLOW-UP OF 6.6 YEARS, ASPIRIN WAS NOT ASSOCIATED WITH A LOWER INCIDENCE OF ALL-CAUSE MORTALITY [RISK RATIO (RR) 0.98, 95% CONFIDENCE INTERVAL (CI) 0.93-1.02; P = 0.30]; HOWEVER, ASPIRIN WAS ASSOCIATED WITH AN INCREASED INCIDENCE OF MAJOR BLEEDING (RR 1.47, 95% CI 1.31-1.65; P < 0.0001) AND INTRACRANIAL HAEMORRHAGE (RR 1.33, 95% CI 1.13-1.58; P = 0.001). A SIMILAR EFFECT ON ALL-CAUSE MORTALITY AND MAJOR BLEEDING WAS DEMONSTRATED IN DIABETIC AND HIGH CARDIOVASCULAR RISK PATIENTS (I.E. 10-YEAR RISK >7.5%). ASPIRIN WAS ASSOCIATED WITH A LOWER INCIDENCE OF MYOCARDIAL INFARCTION (RR 0.82, 95% CI 0.71-0.94; P = 0.006); HOWEVER, THIS OUTCOME WAS CHARACTERIZED BY CONSIDERABLE HETEROGENEITY (I<sup>2</sup> = 67%), AND THIS EFFECT WAS NO LONGER EVIDENT UPON LIMITING THE ANALYSIS TO THE MORE RECENT TRIALS. TRIAL SEQUENTIAL ANALYSIS CONFIRMED THE LACK OF BENEFIT OF ASPIRIN FOR ALL-CAUSE**

**MORTALITY UP TO A RELATIVE RISK REDUCTION OF 5%.**

**CONCLUSION:**

**AMONG ADULTS WITHOUT ESTABLISHED CARDIOVASCULAR DISEASE, ASPIRIN WAS NOT ASSOCIATED WITH A REDUCTION IN THE INCIDENCE OF ALL-CAUSE MORTALITY; HOWEVER, IT WAS ASSOCIATED WITH AN INCREASED INCIDENCE OF MAJOR BLEEDING. THE ROUTINE USE OF ASPIRIN FOR PRIMARY PREVENTION NEEDS TO BE RECONSIDERED.**

B. Pending PURL Review Date: 9/9/2019

**SECTION 2: Critical Appraisal of Validity  
[to be completed by the Potential PURL Reviewer]**

A. What types of studies are included in this review?  
**RTC's**

B. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.

**Question: Should aspirin be used in primary prevention of cardiovascular disease (CVD)/all-cause mortality in patients without known CVD?**

**Conclusion: Aspirin should NOT be used in healthy individuals – increased harm and lack of mortality benefit (in patients without known CVD/atherosclerosis). No improvement with diabetics.**

**Strength: meta-analysis of 11 RCTs with low heterogeneity of the outcome measured**

**Weakness: not much subgroup analysis**

C. Study addresses an appropriate and clearly focused question. **Well covered**  
Comments: none

D. A description of the methodology used is included. **Well covered**  
Comments: none

E. The literature is sufficiently rigorous to identify all the relevant studies. **Well covered**  
Comments: none

F. Study quality is assessed and taken into account. **Well covered**  
Comments: none

G. There are enough similarities between selected studies to make combining them reasonable.  
**Well covered**  
Comments: none

H. Are patient oriented outcomes included? If yes, what are they?

**Yes. All-cause mortality (primary outcome), cardiovascular mortality, fatal and non-fatal MI, fatal and non-fatal stroke.**

- I. Are adverse effects addressed? If so, how would they affect recommendations?

**Major bleeding (primary adverse outcome), intracranial hemorrhage**

- J. Is funding a potential source of bias? If yes, what measures (if any) were taken to ensure scientific integrity? **No**

- K. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.

**Adults without known CVD**

- L. In what care settings might the findings apply, or not apply?

**Outpatient**

- M. To which clinicians or policy makers might the findings be relevant?

**Primary care, cardiology**

**SECTION 3: Review of Secondary Literature**

**[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer as needed]**

**Citation Instructions:**

For up-to-date citations, use style modified from [http://www.uptodate.com/home/help/faq/using\\_UTD/index.html#cite](http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite) & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert date modified if given.} Accessed February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:

Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

- A. DynaMed excerpts  
**NONE**

- B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date [www.DynamicMedical.com](http://www.DynamicMedical.com) Last Updated: . Accessed **NOT APPLICABLE**

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

**NOT APPLICABLE**

**D. UpToDate excerpts**

- Although aspirin produces important reductions in cardiovascular disease (CVD) mortality and morbidity among survivors of a wide range of atherosclerotic cardiovascular events (secondary prevention), the benefits and harms are closely balanced in apparently healthy people (primary prevention).

- In patients without prior CVD events, aspirin decreases the risk of nonfatal myocardial infarction (MI) but increases the risk of major bleeding. Aspirin possibly reduces the risk of colorectal cancer over long-term follow-up (with >10 years of treatment).

- Factors to be considered in the discussion regarding aspirin use for primary prevention include assessment of the individual's risk for each outcome (cardiovascular events, colorectal cancer, bleeding, and total mortality), assessment of the relative value the individual places on preventing specific outcomes, assessment of the patient's attitude to inconvenience of long-term daily therapy, and value placed on immediate increase in risk of bleeding versus delayed potential benefit on CVD and cancer.

- In some adults, the benefits of aspirin for primary prevention may exceed the harms (principally bleeding), while in others the harms may exceed the benefits. For most patients, the benefits and harms are likely to be closely balanced. As a consequence, we have chosen not to make a recommendation for or against. The decision regarding aspirin for primary prevention must involve a discussion between patients and their clinicians.

- The balance between benefits and harms may weigh more heavily for harms over benefits in those over 70 years of age.

**E. UpToDate citation**

Access date: 09/12/2019. Title: Aspirin in the primary prevention of cardiovascular disease and cancer. Authors: Frederick A Spencer, MD Gordon Guyatt, MD Malavika Tampi, MPH Breanne Golemic, BScH. In: UpToDate [database online]. Available at: <https://www.uptodate.com/contents/aspirin-in-the-primary-prevention-of-cardiovascular-disease-and-cancer>. Last updated: Apr 19, 2019 .

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

**Aspirin for primary prevention of cardiovascular disease is a balance between benefits and risks, with newest studies showing no net benefit overall. There should be a discussion between patient and physician about the benefits vs risks of starting the medication for this purpose, if at all.**

Other excerpts (USPSTF; other guidelines; etc.)

## USPTF Recommendations

### Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a $\geq 10\%$ 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	<b>B</b>
Adults aged 60 to 69 years with a $\geq 10\%$ 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	<b>C</b>
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	<b>I</b>
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	<b>I</b>

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### 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

For decades, low-dose aspirin (75-100 mg with US 81 mg/day) has been widely administered for ASCVD prevention. By irreversibly inhibiting platelet function, aspirin reduces risk of atherothrombosis but at the risk of bleeding, particularly in the gastrointestinal (GI) tract. Aspirin is well established for secondary prevention of ASCVD and is widely recommended for this indication, but recent studies have shown that in the modern era, aspirin should not be used in the routine primary prevention of ASCVD due to lack of net benefit. Most important is to avoid aspirin in persons with increased risk of bleeding including a history of GI bleeding or peptic ulcer disease, bleeding from other sites, age  $>70$  years, thrombocytopenia, coagulopathy, chronic kidney disease, and concurrent use of nonsteroidal anti-inflammatory drugs, steroids, and anticoagulants. The following are recommendations based on meta-analysis and three recent trials:

- Low-dose aspirin might be considered for primary prevention of ASCVD in select higher ASCVD adults aged 40-70 years who are not at increased bleeding risk.
- Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults  $>70$  years.
- Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk.

G. Citations for other excerpts

USPTF 2016 Guidelines: ACCESSED 09/12/2019.

<https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer>. AUTHORS: Kirsten Bibbins-Domingo, et al. PUBLISHED: April 12, 2016.

ACC/AHA 2019 Guidelines: ACCESSED 09/12/2019. <https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/03/07/16/00/2019-acc-aha-guideline-on-primary-prevention-qi-prevention>. AUTHORS: Arnett DK, Blumenthal RS, Albert MA, et al. PUBLISHED: Mar 17, 2019.

H. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

**Aspirin for primary prevention of cardiovascular disease is a balance between benefits and risks, with newest studies showing no net benefit overall. There should be a discussion between patient and physician about the benefits vs risks of starting the medication for this purpose, if at all.**

**SECTION 4: Conclusions**

**[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer as needed]**

- A. **Validity:** Are the findings scientifically valid? **Yes**
- B. If **A** was coded “Other, explain or No”, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?  
**Yes**
- D. If **C** was coded “Other, explain or No”, please provide an explanation.
- E. **Practice changing potential:** If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?  
**Yes**
- F. If **E** was coded as “Yes”, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

**Aspirin should not be used for primary prevention of CVD because it has no effect on all-cause mortality and carries a significantly increased risk of major bleeding. There is no overall benefit – only net harm -- to prescribing aspirin for this purpose.**

**G. Applicability to a Family Medical Care Setting:**

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? **Yes**

H. Please explain your answer to **G**.

**Recommending that physicians do not prescribe aspirin for primary prevention of CVD is a major shift in primary care and should be reinforced given the above study findings.**

**I. Immediacy of Implementation:**

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? **No**

J. If **I** was coded “Other, explain or No”, please explain why.

**No major intervention needed other than re-education of patients and providers in this case.**

**K. Clinically meaningful outcomes or patient oriented outcomes:**

Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

**Yes**

L. If **K** was coded “Other, explain or No”, please explain why.

M. In your opinion, is this a pending PURL? **Yes**

1. Valid: Strong internal scientific validity; the findings appear to be true. **Yes**

2. Relevant: Relevant to the practice of family medicine. **Yes**

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. **Yes**

4. Applicability in medical setting. **Yes**

5. Immediacy of implementation **Yes**

N. Comments on your response for question M.

**There is strong evidence that the common practice of prescribing aspirin for primary prevention of CVD should be discontinued.**