Should I be on aspirin (ASA: acetylsalicylic acid)?

Craig Williams, PharmD., BCPS, FNLA
Clinical Professor, OSU/OHSU College of Pharmacy
OHSU Division of Family Medicine
A brief history of aspirin

In 1758: Reverend Edward Stone found “bark of the English willow tree” to relieve “common aches” in what is regarded as the first ever clinical trial.

In 1862: Edwin Smith realized that British were beaten to the discovery of willow bark by about 3000 years. Egyptian papyrus described use of willow bark ~ 1500 BC. Also, it did not need to be “English willow bark” to be effective; salicylic acid was purified from many different willow species.

In 1894: young chemist Felix Hoffman, working at the German coal-dye company Friedrich Bayer & Company trying to create a more palatable form of salicylic acid for his ailing father creates acetylsalicylic acid.

In 1966, *NYTimes* calls aspirin “the wonder drug that nobody understands.”
Should I be on aspirin (ASA: acetylsalicylic acid)?

Craig Williams, PharmD., BCPS, FNLA
Clinical Professor, OSU/OHSU College of Pharmacy
OHSU Division of Family Medicine
The easy answer first:

Yes*

*If you’ve had a heart attack or an ischemic stroke
Secondary prevention is treating those who have already had a heart attack or stroke but primary prevention accounts for 2x more events.

<table>
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<th>Myocardial Infarction Incidence and Recurrence (US, Annual)</th>
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So, what if I have not had that first heart attack or ischemic stroke? Should I be on aspirin?
Many of us have decided “yes”

Aspirin Use Among Adults in the U.S.
Results of a National Survey

Craig D. Williams, PharmD, Andrew T. Chan, MD, MPH, Miriam R. Elman, MPH, Alyson H. Kristensen, MPH, W. Fred Miser, MD, Michael P. Pignone, MD, MPH, Randall S. Stafford, MD, PhD, Jessina C. McGregor, PhD

Results: Among 2,509 respondents, 52% reported current aspirin use. Among 2,039 respondents without a history of cardiovascular disease, current use of aspirin was 47%. Regular use of aspirin for primary

Conclusions: Approximately half of the nationwide survey of U.S. adults reported regular aspirin use. Among those with a primary prevention indication, having discussed aspirin with a provider was the strongest predictor of regular use.

At NPR.org......

Search: aspirin

**morning edition**

**Maybe You Should Rethink That Daily Aspirin**

by MAANVI SINGH

April 27, 2015 • A small dose of aspirin taken regularly can help prevent a second heart attack or stroke. But too many healthy people are taking the drug for prevention, and for them, the risks may outweigh benefits.
So, many of us are doing it but is it a good idea i.e. if your friends jumped off a bridge?........
The difficulty of primary prevention (preventing that first event) is who to target?

Gary Larson: The Far Side

“Bummer of a birthmark, Hal”
But, the ~800,000 Americans who will suffer a first heart attack this year don’t have targets on their chest.

So……..
Who is Hal?

Look to the person to your left……look to the person to your right….and consider yourself

Which of the 3 of you should be on aspirin?
The benefit of aspirin therapy is greater in higher risk patients and quite low in low risk patients

Carlo Patrono, Barry Coller, Garret A. FitzGerald, Jack Hirsh, and Gerald Roth
CHEST 2008;133: 1994S-233S.

Key principle to prevention: greater risk = greater benefit (i.e. we can’t prevent events that are not occurring)

5% Absolute risk reduction
Meaning: for every 100 patients treated for one year, 5 patients avoid a recurrent heart attack

2 Events prevented per 1000 treated in healthy population

Diagram: Graph showing the relationship between the annual risk of a vascular event on placebo and the number of subjects in whom a vascular event is prevented by aspirin per 1,000 treated per year.
How do I decide when and where I should use a drug when the benefit is small?

Got to do the clinical trials
The clinical trials with aspirin for primary prevention leave room for interpretation (beauty is in eye of the beholder)

- **Vascular events**: CV death, ACS, stroke
- **Major Bleeding**: Fatal bleed, ICH*, bleed requiring hospitalization or transfusion

*Intracranial hemorrhage

**Figure 4. Benefits and Risks of Low-Dose Aspirin in Primary-Prevention Trials.**

NEJM 2005;353:2373-83
The debate in primary prevention: FDA in 2014

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Use of Aspirin for Primary Prevention of Heart Attack and Stroke

[05/02/2014] Cardiovascular disease, including heart disease and stroke, affects tens of millions of people in the United States. Consumers and patients who do not suffer from cardiovascular disease sometimes consider taking aspirin to reduce the possibility of having a heart attack or stroke. Reducing the possibility of having a first heart attack or stroke is called primary prevention. The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain, in situations where the benefit of aspirin for primary prevention has not been established.

“does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke…”
So, any use of aspirin for primary prevention is “off-label”
The Europeans agree with the FDA


The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Recommendations on antithrombotic therapy

4.10 Antithrombotics

4.10.1 Antiplatelet therapy in individuals without overt cardiovascular disease

4.10.2 Antiplatelet therapy in individuals with overt cardiovascular or cerebrovascular disease

4.10.3 Antithrombotic therapy in atrial fibrillation

Aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding.

“…cannot be recommended in individual without cardiovascular…”
But the American College of Chest Physicians (‘CHEST’ guidelines) disagree

Primary and Secondary Prevention of Cardiovascular Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines

2.1. For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).
And the ADA gives a qualified yes for patients with diabetes, 2016

“Consider aspirin therapy….in those who are at increased cardiovascular risk…”
What about the cardiology societies (AHA/ACC)?

Also a qualified (and outdated – 2003) yes…

“People at high risk of heart attack should take a daily low-dose of aspirin (if told to by their healthcare provider)….”
An important question to be answered:

What is the full magnitude of the benefits and risks of aspirin and how does it vary across populations of patients?
Using clinical trial data to find Hal….
Ten trials met inclusion criteria for USPSTF analysis; all trials excluded patients with prior GI bleed with three* being new since their 2009 guidance

*AAA trial: JAMA. 2010 Mar 3;303(9):841–8
JPAD: JAMA.2008 Nov 12;300(18):2134–41
POPADAD: BMJ.2008;337:a1840
Some key findings:

1. Hal is between 50-70 years of age
2. He/she has no history of a major clinical bleed
3. Has a moderate risk of a CVD event of at least 10% over the next 10 years
Balancing benefits and harms

Lifetime Events per 1,000 persons in Men Taking Aspirin

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A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer (CRC)

Robert S. Sandler, M.D., M.P.H., Susan Halabi, Ph.D., John A. Baron, M.D., Susan Budinger, B.S., Electra Paskett, Ph.D., Roger Keresztes, M.D., Nicholas Petrelli, M.D., J. Marc Pipas, M.D., Daniel D. Karp, M.D., Charles L. Loprinzi, M.D., Gideon Steinbach, M.D., Ph.D., and Richard Schilsky, M.D.

METHODS
We conducted a randomized, double-blind trial to determine the effect of aspirin on the incidence of colorectal adenomas. We randomly assigned 635 patients with previous colorectal cancer to receive either 325 mg of aspirin per day or placebo. We deter-

RESULTS
A total of 517 randomized patients had at least one colonoscopic examination a median of 12.8 months after randomization. One or more adenomas were found in 17 percent of patients in the aspirin group and 27 percent of patients in the placebo group (P = 0.004). The mean (±SD) number of adenomas was lower in the aspirin group than the
Since 2003, interest and research into aspirin and colorectal cancer has grown tremendously.
Collaborative work in this area is ongoing at OHSU

RESEARCH ARTICLE

Aspirin therapy reduces the ability of platelets to promote colon and pancreatic cancer cell proliferation: Implications for the oncoprotein c-MYC

Annachiara Mitrugno,1,2,3 Joanna L. Sylman,1 Anh T. P. Ngo,1 Jiaqing Pang,1 Rosalie C. Sears,2,4 Craig D. Williams,2,5 and Owen J. T. McCarty1,2,3

Conclusion: Inhibition of platelets by aspirin can affect their ability to induce cancer cell proliferation through the modulation of an oncoprotein, c-MYC

Am J Physiol Cell Physiol, Jan 2017
## Balancing benefits and harms

### Lifetime Events per 1,000 persons in Women Taking Aspirin

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Should I be on aspirin if I have NOT had a heart attack or stroke?
The answer is ambiguous and individual

- The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 50 to 69 years who have a greater than 10% 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 use low-dose aspirin.
So, how do we operationalize decision making for our patients or for ourselves?

Our best data in 2017 says you should NOT consider aspirin UNLESS:

1. If you are 50-70 years of age with 
2. no history of a major bleed……..and then you should 

3. Determine if your 10-year risk for CVD is at least 10%

So, I google AHA/ACC risk estimator…..
I am 48 years old with no major risk factors and have a 10-year risk of heart attack or stroke of \(~ 2\%\)
Let’s take a higher risk patient who may be seeking our advice:

A 60 year old female patient who has treated hypertension, an elevated cholesterol of 240 mg/dL and a smoking history…

<table>
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<th>ASCVD Risk Estimator*</th>
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<td><strong>10-Year ASCVD Risk</strong></td>
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<td>16.9% calculated risk</td>
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<td>2.3% risk with optimal risk factors*</td>
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Balancing benefits and harms

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If you have no history of major bleeding and your CVD risk is sufficiently high (google the risk estimator); your risk of a major bleed on aspirin is about equivalent to your benefit of reducing the risk of a heart attack or stroke and you will have a slightly reduced lifetime risk of being diagnosed with colon cancer (~1%).

What would you like to do?

And if they say they just want a simple ‘yes’ or ‘no’ answer, I say “you should go see my colleague in cardiology down the hall.”
Thank you
Draft RS:
For Adults 60-69 years old at increased risk of CVD

• The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 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 use low-dose aspirin.

• Grade C recommendation
A patient walks into your office and says they just turned 60 years of age and wants your opinion on whether or not to start taking a daily ASA. What would you like to recommend?

If you have never had a GI bleeding event, let’s calculate your 10-year ASCVD risk and:

1. If your 10-year risk of a vascular event is low (<10%), then you should probably not take aspirin
2. If your 10-year risk of a vascular event is > 10% then it is reasonable to take aspirin IF you value the CVD benefit over the risk of a major bleed.
What about benefit in average adults without a personal history of cancer?

Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

Peter M Rothwell, Michelle Wilson, Carl-Eric Elwin, Bo Norrving, Ale Algra, Charles P Warlow, Tom W Meade
What percent of patients who die within 30 days of an MI die before reaching the hospital?

1. 10%
2. 20%
3. 40%
4. 50%
5. 75%

Draft RS:
For Adults 50-59 years old at increased risk of CVD

• The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 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.

• Grade B recommendation
A patient without ASCVD presents to our office/hospital or pharmacy and says they just turned 60 years of age and wants your opinion on whether or not to start taking a daily ASA.

What would you like to recommend?
Many patients are deciding to take aspirin or at least tell us they’re taking aspirin.

Aspirin Use Among Adults in the U.S.
Results of a National Survey

Craig D. Williams, PharmD, Andrew T. Chan, MD, MPH, Miriam R. Elman, MPH, Alyson H. Kristensen, MPH, W. Fred Miser, MD, Michael P. Pignone, MD, MPH, Randall S. Stafford, MD, PhD, Jessina C. McGregor, PhD

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Conclusions: Approximately half of the nationwide survey of U.S. adults reported regular aspirin use. Among those with a primary prevention indication, having discussed aspirin with a provider was the strongest predictor of regular use.

FDA committee votes not to approve aspirin for the primary prevention of MI

Tue, 09 Dec 2003 21:00:00 Michael O’Riordan

Gaithersburg, MD - The evidence supporting the use of aspirin for the primary prevention of MI failed to hold up to the scrutiny of the FDA's Cardiovascular and Renal Drugs Advisory Committee at its most recent December 8, 2003 meeting.

The committee voted overwhelmingly 11 votes against and three votes for approval of the petition sought by Bayer Corp to approve aspirin for the reduction of the risk of a first MI in moderate-risk patients, those with a 10-year coronary heart disease risk of > 10% (annual risk ~ 1%)

Despite the existing data, which consisted of five major clinical trials, the committee felt the evidence supporting the extended label for aspirin was inconsistent at best or lacking at worst.
Pre-existing 2007/2009 USPSTF Aspirin Recommendations

• The USPSTF recommends the use of aspirin for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage. (A Recommendation)

• The USPSTF recommends the use of aspirin for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage. (A Recommendation)

• The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older. (I Statement)

• The USPSTF recommends against the use of aspirin for stroke prevention in women younger than 55 years and for myocardial infarction prevention in men younger than 45 years. (D recommendation)

• The USPSTF recommends against the routine use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS) to prevent colorectal cancer in individuals at average risk for colorectal cancer. (D recommendation 2007)
## Balancing benefits and harms

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<td><strong>Age range</strong></td>
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<td>50-69 (&quot;B&quot; rating for 50-59 and &quot;C&quot; rating for 60-69)</td>
</tr>
<tr>
<td></td>
<td>Women: 55-79</td>
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<td><strong>Sex</strong></td>
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<td>No differentiation</td>
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<td><strong>CHD/CVD risk</strong></td>
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<td>10% or greater 10 year CVD risk for 50-69 y/o</td>
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<tr>
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<td>60-69: &gt; 9%</td>
<td></td>
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<tr>
<td></td>
<td>70-79: &gt; 12%</td>
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<tr>
<td></td>
<td>Women: 10 year stroke risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-59: &gt;3 %</td>
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<tr>
<td></td>
<td>60-69: &gt;8 %</td>
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<tr>
<td></td>
<td>70-79: &gt;11 %</td>
<td></td>
</tr>
<tr>
<td><strong>Younger populations</strong></td>
<td>D rec: Men &lt; 45, Women &lt; 55</td>
<td>I rec: Persons &lt; 50</td>
</tr>
<tr>
<td><strong>Older populations</strong></td>
<td>I rec: Persons &gt; 80</td>
<td>I rec: Persons &gt; 70</td>
</tr>
<tr>
<td><strong>CRC</strong></td>
<td>Against use of ASA/NSAIDs</td>
<td>Integrated into benefit</td>
</tr>
</tbody>
</table>

**Sex-specific recommendations**

**CHD – Framingham**

**Stroke – Western Stroke**

**CVD – ACC/AHA**
A 60-year old patient asking about starting a daily ASA……

1. The FDA has evaluated the data and declined to give an indication for primary prevention so I’m generally going to recommend against

2. Americans who reach age 60 with another major risk factor (diabetes, HTN, hyperlipidemia, smoking) generally have adequate risk to consider aspirin with the understanding that initiation confers about the same bleeding risk as vascular benefit and the choice should be individual
Patients who are adherent with chronic medications are different from patients who are not and poor adherence is a common problem.

Take your aspirin if you have clinical atherosclerosis or when you and your informed provider decide benefit outweighs risk. And definitely....

Take your apixaban if you have cancer-associated VTE.

Take your blood pressure medications if you are prone to hypertensive emergencies.
Guidance on Implementation

• The decision to start or continue taking aspirin is complex

• Key considerations:
  • **Age** – related to both benefits and harms, life expectancy needed to gain CRC benefit
  • **Baseline CVD risk** – higher CVD risk increases benefits, aided by using ACC/AHA risk calculator (despite its shortcomings)
  • **Risk for bleeding** – bleeding risk assessment based on patient history
  • **Preference for taking daily aspirin** – very preference sensitive choice
Once clinical atherosclerosis is established, recurrent events are higher in the real world than in the clinical trials.

N = 68,236 outpatients with established CVD* or ≥3 atherothrombotic risk factors


*CAD, PAD, or cerebrovascular disease

REACH = Reduction of Atherothrombosis for Continued Health
What is the role of the platelet in vasculature?

Platelet Activation and Atherothrombosis

Giovanni Davi, M.D., and Carlo Patrono, M.D.

Platelets are essential for...
What is the role of the platelet in vasculature?

Platelet Activation and Atherothrombosis

Giovanni Davi, M.D., and Carlo Patrono, M.D.

Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the development of acute coro-
The initial platelet ‘plug’ is important to facilitate endothelial repair and happens through a diverse array of both vascular and platelet receptors.
So, while still not fully understood, it makes sense that antiplatelet therapies may alter the formation of atherothrombosis in the long-term.