

Q: Should patients stop taking aspirin for primary prevention?

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A: In view of current evidence, we do not recommend routinely using aspirin for primary prevention of cardiovascular disease, even in patients with diabetes mellitus. The decision must be individualized on the basis of the patient's risks of cardiovascular disease and bleeding, especially the risk of serious bleeding events such as gastrointestinal and intracranial hemorrhage.

For example, patients with a family history of myocardial infarction at an early age and patients who smoke or have multiple cardiovascular risk factors may be most likely to benefit, whereas those with risk factors for gastrointestinal bleeding such as dyspepsia or ulcer would not be good candidates. Of note, current recommendations are mixed and confusing and will need to be reevaluated as new trial data become available.

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TRIALS THAT SET THE STAGE FOR CURRENT PRACTICE

Routine use of aspirin for primary prevention of cardiovascular disease remains controversial.^{1,2} Aspirin's safety and efficacy for this indication was studied in six major trials (TABLE 1).³⁻⁸ In the late 1980s, the first two primary prevention trials of aspirin enrolled healthy male physicians who had minimal cardiovascular risk factors^{3,4}:

The British Doctors' Trial³ observed no significant differences between aspirin (300–500 mg/day) and no aspirin in the rates of the primary end point of cardiovascular death or in the individual secondary end points of nonfatal myocardial infarction, nonfatal stroke, or bleeding.³

The Physicians' Health Study⁴ found no differences in the rates of cardiovascular mortality or ischemic stroke between aspirin (325 mg every other day) and placebo. The rate of nonfatal myocardial infarction was significantly lower with aspirin than with placebo, but with a higher risk of bleeding. Relative risks and 95% confidence intervals with aspirin vs placebo:

- Nonfatal myocardial infarction
0.59 (0.47–0.74), $P < .00001$
- Bleeding
1.32 (1.25–1.40), $P < .00001$
- Blood transfusions
1.71 (1.09–2.69), $P = .02$
- Hemorrhagic stroke
2.14 (0.96–4.77), $P = .06$.

A subgroup analysis revealed that the benefit of aspirin for myocardial infarction in the Physicians' Health Study was predominantly in those age 50 and older.⁴ This finding established the common clinical practice of routinely using aspirin for primary prevention in men age 50 and older.¹

Current evidence for aspirin as primary prevention in diabetic patients does not clearly show a net clinical benefit

TABLE 1

Six trials of aspirin for primary prevention of cardiovascular disease

	Mean follow-up (years)	Cardiovascular mortality	Myocardial infarction	Stroke	Bleeding	Hemorrhagic stroke
British Doctors' Trial ³ (1988)	5.6	NS	Nonfatal: NS	Ischemic: NS	All except cerebral: NS	NS
Physicians' Health Study ⁴ (1989)	5.0	NS	Nonfatal: NNT: 111	Ischemic: NS	All: NNH: 14	NS
Thrombosis Prevention Trial ⁵ (1998)	6.7	NS	Nonfatal: NNT: 37	Ischemic: NS	Major: NS	NNH: 200
Hypertension Optimal Treatment ⁶ (1998)	3.8	NS	Nonfatal and fatal: NNT: 200	Any: NS	Nonfatal major: NNH: 143	NS
Primary Prevention Project ⁷ (2001)	3.7	NNT: 167	Nonfatal: NS	Any: NS	All: NNH: 125	NS
Women's' Health Study ⁸ (2005)	10.0	NS	Nonfatal: NS	Ischemic: NNH: 500	Any gastrointestinal, hematuria, epistaxis: NNH: 25	NS

NNH = number needed to harm; NNT = number needed to treat; NS = not significant

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Later, aspirin for primary prevention was studied in four trials,⁵⁻⁸ three of which enrolled patients at higher cardiovascular risk⁵⁻⁷:

The Thrombosis Prevention Trial⁵ was conducted in men in the highest quintile of cardiovascular risk. The aspirin dosage was 75 mg/day.

The Hypertension Optimal Treatment⁶ trial included men and women ages 50 to 80 with hypertension. Aspirin dosage: 75 mg/day.

The Primary Prevention Project⁷ involved men and women age 50 and older with at least one risk factor for cardiovascular disease.^{1,5-7} The aspirin dosage was 100 mg/day.

In these trials (TABLE 1), aspirin significantly lowered the rate of ischemic events compared with placebo or control: nonfatal myocardial infarction in the Thrombosis Prevention Trial; myocardial infarction and major adverse cardiac event (ie, cardiovascular death, myocardial infarction, or stroke) in the Hypertension Optimal Treatment trial; and cardiovascular mortality and major cardiovascular events

(cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, angina pectoris, transient ischemic attack, peripheral artery disease, or revascularization procedures) in the Primary Prevention Project. However, aspirin's benefit in each trial was largely offset by a higher rate of various bleeding end points.⁵⁻⁷

The Women's Health Study

A subgroup analysis of the Hypertension Optimal Treatment trial suggested that sex may influence the efficacy of aspirin—specifically, aspirin did not prevent nonfatal myocardial infarction in women.⁹ Given the paucity of female participants in the previous primary prevention trials, the Women's Health Study⁸ was designed to determine the efficacy and safety of aspirin (100 mg every other day) in women age 45 and older with very few cardiovascular risk factors.⁸

Aspirin did not significantly reduce the rate of the primary end point of cardiovascular death, myocardial infarction, or stroke,

TABLE 2

Ongoing trials of aspirin in primary prevention of cardiovascular disease

	ARRIVE (NCT00501059)	ASPREE (NCT01038583)	ASCEND (NCT00135226)	ACCEPT-D (ISRCTN48110081)
Planned enrollment	12,551	19,000	15,480	5,170
Design	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter, 2-by-2 factorial: omega-3 fatty acids	Randomized, blinded (outcome), open-label
Aspirin dosage	100 mg daily	100 mg daily	100 mg daily	100 mg daily (all patients will also be on simvastatin 20 mg daily)
Study population	Men age \geq 55 or women age \geq 60 years with an estimated 10-year risk \geq 10% for coronary heart disease	Age \geq 65 with no prior cardiovascular event	Patients with type 1 or 2 diabetes mellitus, age \geq 40, with no history of vascular disease	Patients with type 1 or 2 diabetes mellitus, age \geq 50, with no prior major vascular event, but with a need for statin therapy
Primary efficacy end point	Cardiovascular death, myocardial infarction, stroke, unstable angina, transient ischemic attack	All-cause mortality, dementia, persistent physical disability	Vascular death, myocardial infarction, stroke, transient ischemic attack	Cardiovascular death, myocardial infarction, stroke, unplanned cardiovascular hospitalization
Implications	One of the first primary prevention trials to use coronary heart disease risk as an entry criterion; could clarify whether patients with moderate risk or higher risk benefit from aspirin	Designed to assess the efficacy and safety of aspirin in an elderly population	Assessing if aspirin prevents cardiovascular events in patients with diabetes without established cardiovascular disease	Will clarify whether aspirin has an incremental benefit in patients who are already on statin therapy

ACCEPT-D = Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; ARRIVE = A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly

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though a significant effect was observed in the subgroup of women age 65 and older. Although overall the Women's Health Study found no benefit in the rate of myocardial infarction, there was a significant reduction in the rate of ischemic stroke (which needs to be interpreted cautiously in an overall neutral trial) and a nonsignificant increase in the rate of hemorrhagic stroke. As in other trials, rates

of bleeding, including gastrointestinal bleeding, were higher with aspirin.

A meta-analysis of six trials of aspirin for primary prevention

In 2009, the Antithrombotic Trialists' Collaboration¹⁰ published a meta-analysis of six trials of aspirin for primary prevention. In this analysis, aspirin did not reduce the rate of cardiovas-

TABLE 3

Current guidelines on aspirin for primary prevention of cardiovascular disease**American College of Chest Physicians,¹⁵ 2012**

Suggested for people ages 50 and older without symptomatic cardiovascular disease (CVD)

American Diabetes Association,¹⁶ 2013

Reasonable in diabetic patients at increased 10-year risk of CVD (ie, > 10%; typically men over age 50 or women over age 60 with one or more CVD risk factors) and who are not at increased risk of bleeding
 May be considered in diabetic patients with an intermediate 10-year risk of CVD risk (ie, 5–10%; typically patients under age 50 with one or more CVD risk factors, or older patients with no risk factors) and who are not at an increased risk of bleeding
 Not recommended in diabetic patients with a low 10-year risk of CVD (ie, < 5%; typically men under age 50 and women under age 60 with no additional CVD risk factors)

American Heart Association,¹⁷ 2002

May be considered in patients at higher risk of coronary heart disease (CHD), especially if the 10-year risk is > 10%
 Do not use in patients with an increased risk of gastrointestinal (GI) bleeding or hemorrhagic stroke

American Heart Association,¹⁸ 2011

Routine use to prevent myocardial infarction (MI) in healthy women under age 65 is not recommended
 Can be useful in women ages 65 and older if blood pressure is controlled and benefit for ischemic stroke and MI prevention outweighs risk of GI bleeding or hemorrhagic stroke
 May be reasonable in women under age 65 for prevention of ischemic stroke

Canadian Cardiovascular Society,¹⁹ 2011

Not recommended for routine use
 May consider only in special circumstances where CHD risk is high and bleeding risk is low

European Society of Cardiology,²⁰ 2012

Not recommended in patients without overt evidence of cardiovascular or cerebrovascular disease

US Preventive Services Task Force,²¹ 2009

Men: Recommended if potential benefit for reduction in risk of MI outweighs the risk of GI bleeding:
 Age 45–59: use if 10-year CHD risk \geq 4%^a
 Age 60–69: use if 10-year CHD risk \geq 9%^a
 Age 70–79: use if 10-year CHD risk \geq 12%^a
 Women: Recommended if potential benefit for reduction in ischemic stroke outweighs the risk of harm from GI bleeding:
 Age 55–59: use if 10-year stroke risk \geq 3%^a
 Age 60–69: use if 10-year stroke risk \geq 8%^a
 Age 70–79: use if 10-year stroke risk \geq 11%^a
 Not recommended in any patient age 80 or older
 Not recommended in men under age 45
 Not recommended in women under age 55

^a The US Preventive Services Task Force recommends calculating the 10-year risk with a tool such as that available at www.mcw.edu/calculators/Coronary-Heart-Disease-Risk.htm or www.westernstroke.org/index.php?header_name=stroke_tools.gif&main=stroke_tools.php.

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cular death, but it did reduce the yearly risk of:

- Death from coronary heart disease or nonfatal myocardial infarction (0.28% vs 0.34%, $P < .0001$)
- Nonfatal myocardial infarction (0.18% vs 0.23%, $P < .0001$)
- Ischemic stroke (0.11% vs 0.12%, $P = .05$).¹⁰

Despite aspirin's apparent efficacy, the absolute yearly risk for major extracranial bleeding and hemorrhagic stroke was also significantly increased with aspirin use by 0.3% and 0.1%, respectively. The efficacy of aspirin for preventing all serious vascular events (vascular death, myocardial infarction, or stroke) was similar in men and women.¹⁰ The authors concluded that the net benefit of aspirin did not outweigh the increased risks of bleeding.

■ WHAT ABOUT PATIENTS WITH DIABETES?

When considering whether to prescribe aspirin for primary prevention, the individual patient's risks of cardiovascular disease and bleeding must be carefully assessed. Those at highest risk of cardiovascular disease and at low risk of bleeding may still benefit, but current evidence does not clearly support this strategy.

For example, diabetes mellitus has traditionally been considered a coronary heart disease equivalent, and aspirin was routinely prescribed as "secondary prevention."¹¹ In the six trials of aspirin for primary prevention, the prevalence of diabetic patients ranged from 1% to 17%, the efficacy of aspirin in this subgroup was inconsistent among the trials, and aspirin did not confer a net clinical benefit according to the 2009 Antithrombotic Trialists' Collaboration meta-analysis.^{1,3-8,10}

Additionally, two trials of aspirin for pri-

mary prevention in diabetes^{12,13} failed to demonstrate significant efficacy for aspirin compared with no aspirin, either in Japanese patients with type 2 diabetes and no history of cardiovascular disease¹² or in patients with asymptomatic peripheral artery disease.¹³

Thus, the current evidence for aspirin for primary prevention in diabetes does not demonstrate a net clinical benefit, but ongoing trials (TABLE 2) may provide evidence for the use of aspirin in this important subgroup.

An important finding from the 2009 Antithrombotic Trialists' Collaboration was that traditional risk factors for cardiovascular disease also increase the risk of major bleeding, thus making it difficult to determine who will receive the maximum net clinical benefit.¹⁰ Additionally, many of the aspirin primary prevention trials predated the widespread use of statins and the current lower prevalence of smoking, which may further limit the generalizability of the positive signals seen in earlier trials.

■ THE DATA ARE MIXED, BUT ONE MESSAGE IS CLEAR

Based on the current available evidence, the US Food and Drug Administration recently issued a Consumer Update that does not support aspirin for primary prevention and warns patients about the risk of serious bleeding complications.¹⁴ Moreover, current guidelines and consensus panels (TABLE 3) for aspirin in primary prevention differ from one another,¹⁵⁻²¹ making it challenging for clinicians to determine which patients would benefit. One message is clear in the most current clinical guidelines, namely, that routine use of aspirin for primary prevention is not recommended.¹⁵⁻²¹ Several ongoing trials may resolve this important clinical dilemma. ■

One message is clear for now: the routine use of aspirin for primary prevention of cardiovascular disease is not recommended

■ REFERENCES

1. Depta JP, Bhatt DL. Current uses of aspirin in cardiovascular disease. *Hot Topics Cardiol* 2013; 32:7-21.
2. Nemerovski CW, Salintri FD, Morbitzer KA, Moser LR. Aspirin for primary prevention of cardiovascular disease events. *Pharmacotherapy* 2012; 32:1020-1035.
3. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988; 296:313-316.
4. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989; 321:129-135.
5. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998; 351:233-241.
6. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351:1755-1762.
7. de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet* 2001; 357:89-95.
8. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; 352:1293-1304.
9. Kjeldsen SE, Kolloch RE, Leonetti G, et al. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. *Hypertension Optimal*

- Treatment. *J Hypertens* 2000; 18:629–642.
10. **Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, Collins R, et al.** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373:1849–1860.
 11. **Buse JB, Ginsberg HN, Bakris GL, et al; American Heart Association; American Diabetes Association.** Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007; 115:114–126.
 12. **Ogawa H, Nakayama M, Morimoto T, et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators.** Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008; 300:2134–2141.
 13. **Belch J, MacCuish A, Campbell I, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh.** The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; 337:a1840.
 14. **US Food and Drug Administration (FDA).** Use of aspirin for primary prevention of heart attack and stroke. <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm390574.htm>. Accessed January 9, 2015.
 15. **Vandvik PO, Lincoff AM, Gore JM, et al; American College of Chest Physicians.** 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. *Chest* 2012; 141(suppl 2):e637S–e668S.
 16. **American Diabetes Association.** Standards of medical care in diabetes—2013. *Diabetes Care* 2013; 36(suppl 1):S11–S66.
 17. **Pearson TA, Blair SN, Daniels SR, et al.** AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002; 106:388–391.
 18. **Mosca L, Benjamin EJ, Berra K, et al.** Effectiveness-based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update: a Guideline from the American Heart Association. *Circulation* 2011; 123:1243–1262.
 19. **Bell AD, Roussin A, Cartier R, et al; Canadian Cardiovascular Society.** The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines. *Can J Cardiol* 2011; 27(suppl A):S1–S59.
 20. **Perk J, De Backer G, Gohlke H, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG).** European guidelines on cardiovascular disease prevention in clinical practice (version 2012). 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). *Eur Heart J* 2012; 33:1635–1701.
 21. **US Preventive Services Task Force.** Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; 150:396–404.

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