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CLINICAL PRACTICE

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Peripheral Artery Disease

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 61-year-old woman presents with a 3-year history of discomfort in the right thigh on exertion. Her symptoms have recently progressed to involve the right calf. She is able to walk no more than 50 m before having to stop because of leg pain. Her medical history is notable for coronary-artery bypass surgery after a myocardial infarction at 55 years of age and for hyperlipidemia, for which she takes atorvastatin at a dose of 40 mg daily. She has a smoking history of 50 pack-years and currently smokes eight cigarettes per day. On examination, the blood pressure is 126/82 mm Hg, there is a bruit over the right femoral artery, and pulses are diminished in the right leg. How would you evaluate and manage this case?

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KEY CLINICAL POINTS

PERIPHERAL ARTERY DISEASE

- Atherosclerotic peripheral artery disease affects more than 200 million persons worldwide, including at least 8.5 million persons in the United States, and is associated with high rates of cardiovascular events and death. Smoking and diabetes are the strongest risk factors.
- Noninvasive vascular testing provides information on the presence, severity, and location of peripheral artery disease. Exercise testing can uncover mild disease and quantify functional capacity.
- In the treatment of peripheral artery disease, the main goals are to reduce cardiovascular risk and improve functional capacity. Supervised exercise increases walking distance. Cilostazol can be used as an adjunct to an exercise program.
- Conventional angiography is typically performed when revascularization is being considered. Computed tomography or magnetic resonance angiography can also be useful in planning for revascularization.
- Revascularization, endovascular or surgical, is indicated for symptoms that persist despite medical management or for limb salvage in the context of critical limb ischemia.

Figure 1. Noninvasive Arterial Testing in the Leg.

Shown are the results of measurement of segmental blood pressures and indexes in the leg and continuous-wave Doppler examination of the patient discussed in the vignette. To obtain segmental blood pressures, cuffs are placed at three or four sites on the legs. The higher of the two arm pressures is used to calculate each segment–brachial index (the ratio of the systolic blood pressure at the segment to the systolic blood pressure in the arm). Peripheral artery disease is considered to be present when the resting ankle–brachial index is 0.90 or less. Generally a drop in the blood pressure of more than 20 mm Hg between two adjacent locations indicates a hemodynamically significant stenosis. Continuous-wave Doppler waveforms can be qualitatively analyzed to assess arterial blood flow (circles indicate sites of Doppler-probe placement). Normally, a triphasic or biphasic response is present, whereas a reduced biphasic or monophasic signal indicates a hemodynamically significant stenosis. DP denotes dorsalis pedis, L left, PT posterior tibial, and R right.

Table 1. Noninvasive Evaluation of Peripheral Artery Disease.*

Diagnosis, as assessed on the basis of resting or postexercise ABIs
Peripheral artery disease is considered to be present when the ABI is ≤0.90 (normal range, 1.00 to 1.30; values of 0.91 to 0.99 are considered borderline low) or when the resting ABI is normal but the postexercise ABI is ≤0.90 or there is a ≥20% decrease in ABI after exercise
A high ABI (>1.40) is suggestive of poorly compressible arteries, and an ABI of 1.30 to 1.40 is borderline high; toe–brachial indexes and toe pressures can be used in such a situation
Disease severity, as assessed by resting or postexercise ABIs
Mild: resting or postexercise ABI, ≤0.90
Moderate: resting ABI, ≤0.70, or postexercise ABI, ≤0.50
Severe: resting ABI, ≤0.50, or postexercise ABI, ≤0.15
Disease location, according to continuous-wave Doppler waveforms and segmental blood pressures
Proximal, involving the aortoiliac and femoropopliteal locations
Distal, involving the infrapopliteal location
Proximal and distal (multilevel disease)
Functional capacity, as assessed by the distance walked during exercise on a treadmill
Pain-free walking distance
Maximal walking distance
Tissue oxygenation, as assessed with the use of transcutaneous oximetry, is useful in assessing the healing potential of ischemic wounds and possible amputation sites, as well as in assessing candidacy for hyperbaric oxygen or intermittent pneumatic compression therapy
Concomitant atherosclerotic vascular disease
Coronary heart disease: electrocardiogram positive for ischemia during exercise
Subclavian artery disease: difference of >12 mm Hg in blood pressures in the arm

* The ankle–brachial index (ABI) is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm.[3]

Antiplatelet Agents

Patients with symptomatic peripheral artery disease should receive antiplatelet therapy in the form of aspirin (at a dose of 75 to 325 mg daily). A meta-analysis of randomized trials of aspirin use in patients with peripheral artery disease showed no significant reduction in the risk of cardiovascular events but a significant reduction in the risk of nonfatal stroke.[29] Aspirin did not improve outcomes among persons with an ankle–brachial index of 0.95 or less who did not have symptoms.[30] In a randomized trial that included persons with symptomatic peripheral artery disease or other manifestations of atherosclerotic vascular disease, clopidogrel (at a dose of 75 mg daily) was slightly more effective than aspirin in reducing the risk of a composite outcome of ischemic stroke, myocardial infarction, or death from vascular causes.[31] Dual antiplatelet therapy can be considered in patients with symptomatic peripheral artery disease who are not at increased risk for bleeding.[32]

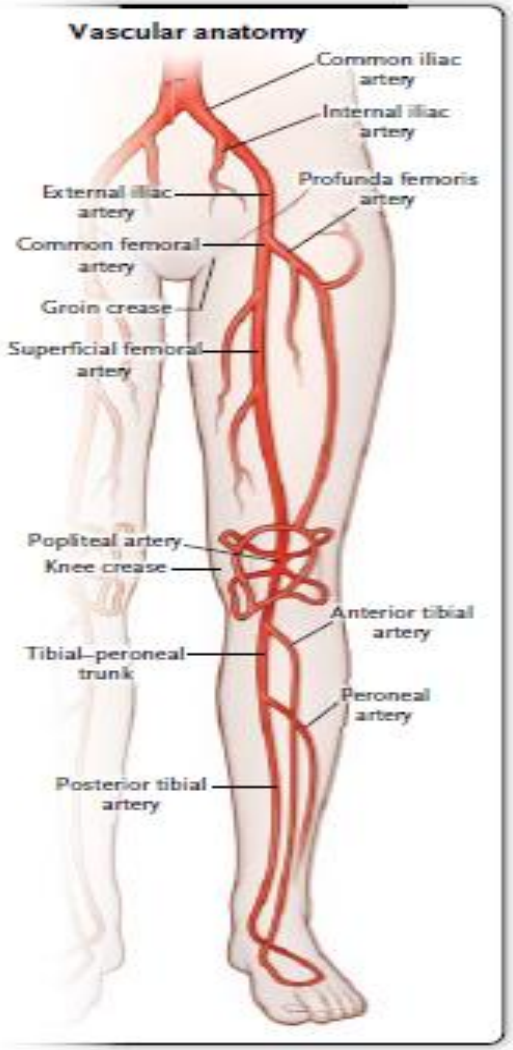
Management of Symptomatic Peripheral Artery Disease

- Reduce cardiovascular risk
  - High-intensity statin
  - Treatment of hypertension and diabetes
  - Smoking cessation
  - Antiplatelet aspirin (75–325 mg/day) or clopidogrel (75 mg/day)
- Improve functional capacity
  - Supervised exercise program
  - Cilostazol (100 mg, orally twice daily)
  - Revascularization if no response to exercise and medication
- Treat coexisting conditions
- Follow-up
  - Assess adherence to lifestyle changes and drugs and functional capacity
  - Monitor for stent or graft patency in patients who have undergone revascularization

Vorapaxar, a new antiplatelet agent that blocks the thrombin protease-activated receptor 1, reduced the risk of cardiovascular death or ischemic events among patients with atherosclerotic vascular disease but increased the risk of bleeding events, including intracranial hemorrhage.[33] In the subgroup of patients with peripheral artery disease, the drug reduced the risk of acute limb ischemia and peripheral-revascularization events,[34] which led to its approval for use in patients with peripheral artery disease who did not have a history of stroke. Warfarin is not recommended, because the combination of warfarin and aspirin did not result in a greater reduction in the risk of cardiovascular events than aspirin alone and was associated with more bleeding.[35]

Medications

Cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilatory properties, increases the maximal walking distance on a treadmill by approximately 25%, as compared with placebo.[39] Side effects include tachycardia, diarrhea, and increased bleeding tendency; it is contraindicated in patients with heart failure or low ejection fraction. Nafronyl, a 5-hydroxytryptamine–receptor blocker that inhibits platelet aggregation, may be more effective than cilostazol and is approved in Europe for claudication.[39] Atorvastatin (at a dose of 80 mg daily for 12 months) was associated with a modestly longer pain-free walking time, but not a longer maximal walking time, than was placebo.[40]



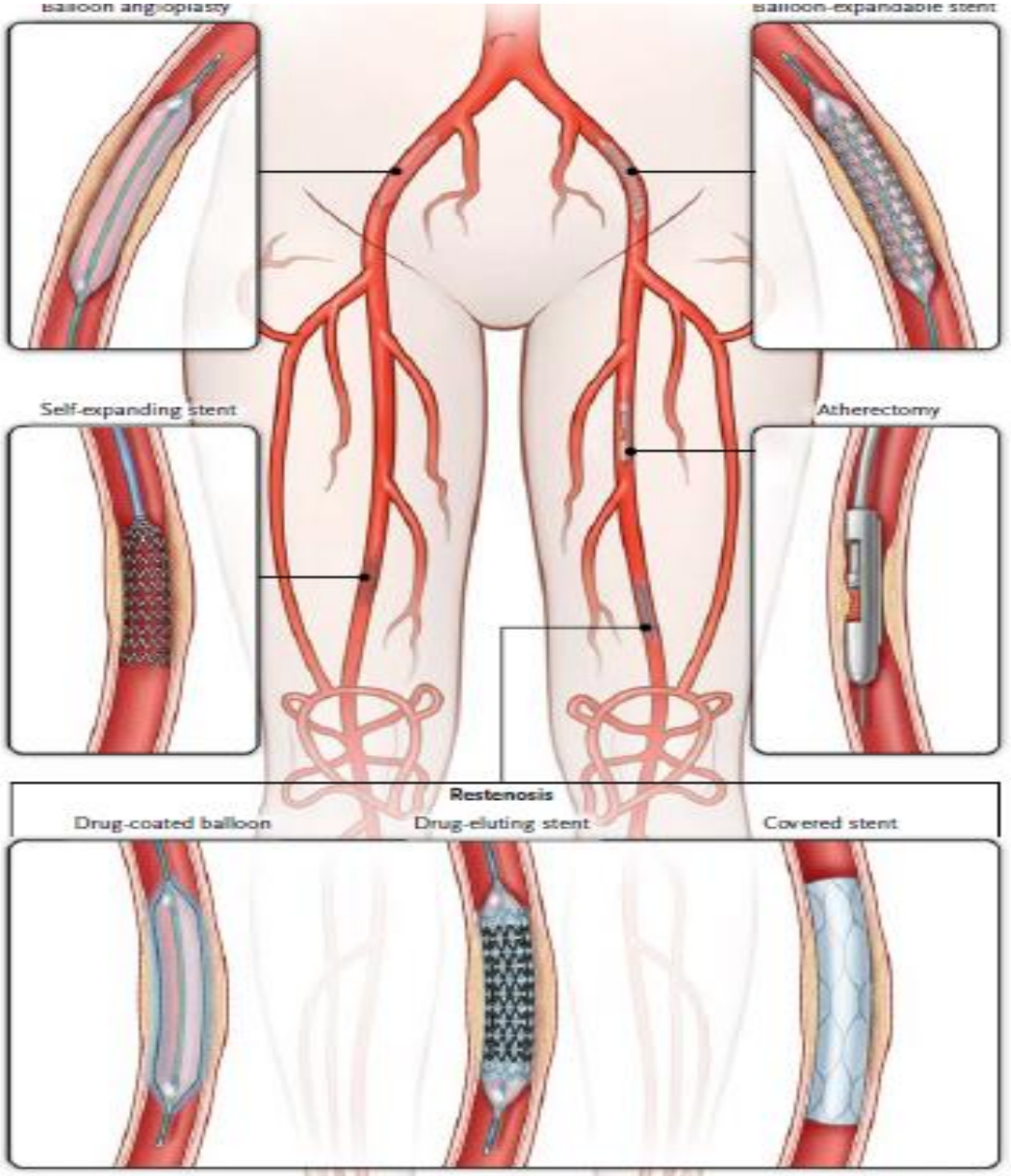


Figure 3. Major Arteries of the Legs and Endovascular Procedures for Treatment of Peripheral Artery Disease.

Balloon angioplasty, stenting (with balloon-expandable or self-expanding stents), and atherectomy are common endovascular procedures. Drug-eluting or covered stents and drug-coated balloons are being evaluated to reduce the rate of restenosis.

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PRACTICE GUIDELINE

2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (Updating the 2005 Guideline)

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery

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Table 4. Recommendations for Antiplatelet and Antithrombotic Drugs

2005 Recommendations	2011 Focused Update Recommendations	Comments
Class I		
Antiplatelet therapy is indicated to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: A)*	1. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (43–45). *(Level of Evidence: A)*	Modified recommendation (wording clarified).
Aspirin, in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: A)*	2. Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (44,45). *(Level of Evidence: B)*	Modified recommendation (wording clarified; and level of evidence changed from A to B).
Clopidogrel (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: B)*	3. Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (43). *(Level of Evidence: B)*	Modified recommendation (wording clarified).

Class IIa		
	1. Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90 (45). *(Level of Evidence: C)*	New recommendation
Class IIb		
	1. The usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with borderline abnormal ABI, defined as 0.91 to 0.99, is not well established (46,47). *(Level of Evidence: A)*	New recommendation
	2. The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk (48,49). *(Level of Evidence: B)*	New recommendation
Class III: No benefit		
Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD. *(Level of Evidence: C)*	1. In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding (50). *(Level of Evidence: B)*	Modified recommendation (level of evidence changed from C to B).

ABI indicates ankle-brachial index; MI, myocardial infarction; and PAD, peripheral artery disease.

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ESC Guidelines on the diagnosis and treatment of peripheral artery diseases

Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries

The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC)

Endorsed by: the European Stroke Organisation (ESO)

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3.4.3 Antiplatelet and antithrombotic drugs

The Antithrombotic Trialists' Collaboration meta-analysis combined data from 42 randomized studies of 9706 patients with intermittent claudication and/or peripheral arterial bypass or angioplasty. The incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke at follow-up was significantly decreased, by 23%, by antiplatelet drugs.[37] Low-dose aspirin (75–150 mg daily) was at least as effective as higher daily doses. The efficacy of clopidogrel compared with aspirin was studied in the randomized Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, including a subgroup of 6452 patients with LEAD.[38] At 1.9-year follow-up, the annual combined incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke in the LEAD group was 3.7% and 4.9%, respectively, in the clopidogrel and aspirin groups, with a significant 23.8% decrease with clopidogrel. These benefits appeared higher than in patients enrolled for CAD or stroke. The small benefits of dual antiplatelet therapy do not justify its recommendation in patients with LEAD due to an increased bleeding risk.[39,40]

Editorial

Comments on the ESC Guidelines on the Diagnosis and Treatment of Peripheral Artery Diseases. A Report of the Task Force of the Clinical Practice Guidelines Committee of the Spanish Society of Cardiology

Comentarios a la guía de práctica clínica de la ESC sobre diagnóstico y tratamiento de las enfermedades arteriales periféricas. Un informe del Grupo de Trabajo del Comité de Guías de Práctica Clínica de la Sociedad Española de Cardiología

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Medical Treatment

The following comments expand upon the details that are partially discussed in the guidelines:

1. In addition to antiplatelet therapy, optimal medical treatment must include high doses of statins[20] (cholesterol bound to low density lipoproteins<100 mg/dl) and angiotensin-converting enzyme inhibitors for controlling hypertension.

2. For symptomatic patients, antiplatelet medication is recommended with low doses of aspirin (75 mg-325 mg).[21] For patients with asymptomatic carotid artery disease, low doses of aspirin reduce the frequency of cardiovascular events, but do not specifically affect the rate of ictus. The efficacy of antiplatelet treatment is similar to that of anticoagulants,[22] and so in the case of needing chronic oral anticoagulant therapy the treatment regimen would only involve dicoumarin with an international normalized ratio of 2.5 (range: 2-3). Double antiplatelet therapy with aspirin and thienopyridines does not provide any added benefit compared to antiplatelet monotherapy, except for following stent implantation (during at least 1 month).

Eur J Vasc Endovasc Surg 33, S1–S75 (2007)
doi:10.1016/j.ejvs.2006.09.024, available online at http://www.sciencedirect.com on ScienceDirect

Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)

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on behalf of the TASC II Working Group

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Recommendation 6. Antiplatelet therapy in peripheral arterial disease (PAD)

- All symptomatic patients with or without a history of other cardiovascular disease should be prescribed an antiplatelet drug long term to reduce the risk of cardiovascular morbidity and mortality [A].
- Aspirin/ASA is effective in patients with PAD who also have clinical evidence of other forms of cardiovascular disease (coronary or carotid) [A].
- The use of aspirin/ASA in patients with PAD who do not have clinical evidence of other forms of cardiovascular disease can be considered [C].
- Clopidogrel is effective in reducing cardiovascular events in a subgroup of patients with symptomatic PAD, with or without other clinical evidence of cardiovascular disease [B].

Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication

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Antiplatelet therapy. The Aspirin for Asymptomatic Atherosclerosis Trial[55] randomized 3350 patients with asymptomatic PAD to treatment with enteric-coated aspirin (100 mg) or placebo. During 8 years of follow-up, no difference in vascular event rates was noted. However, this trial used an epidemiologic method of ABI determination in which the lower of the ankle pressures was used to calculate the ABI. Thus, the individuals in this study might not be fully representative of the universe of PAD patients with a greater burden of disease. At present, the benefit of antiplatelet therapy for patients with asymptomatic PAD and no other clinical cardiovascular disease is unknown.

Antiplatelet and antithrombotic agents. Numerous studies have demonstrated the benefit of antiplatelet therapy, especially aspirin, in doses of 75 to 325 mg/d in reducing rates of myocardial infarction, stroke, and vascular-related deaths in individuals with symptomatic lower extremity atherosclerosis.[81] The American Heart Association practice guidelines for lower extremity ischemia rated this treatment recommendation class I-A.[43] In the 6452 patients with PAD in the Clopidogrel vs Aspirin In Patients At Risk of Ischaemic Events trial, clopidogrel reduced the myocardial infarction, stroke, or vascular death rate by 23.8% more than aspirin alone.[82] Although a single study demonstrated that combination aspirin and clopidogrel therapy was associated with a 20% relative risk reduction for myocardial infarction, cardiovascular death, or stroke,[83] there is no evidence to date that combination therapy is a more effective treatment for PAD than a single agent, and bleeding risks are increased.[84]

Warfarin has been demonstrated to reduce myocardial infarction or stroke in patients with coronary artery disease, although at the cost of a 4.5-fold increase in major bleeding.[85,86] There is no evidence that warfarin decreases the likelihood of adverse events related to PAD alone. Only one prospective trial exists comparing the effect of warfarin vs aspirin on graft patency. A similar number of graft occlusions occurred in both study cohorts, with a twofold increased risk of major bleeding in the warfarin cohort.[85]

Homocysteine-lowering drugs. Approximately 30% of patients with known PAD have elevated serum levels of homocysteine compared with 1% in the general population.[9] Folic acid and cobalamin (vitamin B_{12}) have been found to reduce serum homocysteine levels by 25% and 7%, respectively, in clinical trials. However, there are no data demonstrating that reducing homocysteine serum levels decreases the likelihood of adverse cardiovascular events in patients with PAD,[87] although clinical trials are ongoing.[87-89] Pending the outcomes of prospective trials, treating hyperhomocysteinemia with folic acid to reduce serum levels to <10 μmol/L is generally safe and well tolerated but is of no proven benefit.

Overview of lower extremity peripheral artery disease

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Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Sep 2016. | **This topic last updated:** Jul 29, 2016.

INTRODUCTION — Atherosclerosis results in the accumulation of lipid and fibrous material between the layers of the arterial wall and causes disease of the coronary, cerebral, and peripheral arteries. Atherosclerotic disease often involves the arteries providing flow to the lower extremities, referred to as lower extremity peripheral artery disease (PAD). Atherosclerosis can lead to acute or chronic symptoms due to embolism from more proximal disease, or due to thrombosis of an artery that has been progressively narrowed.

Antithrombotic therapy — Based upon randomized trials showing a reduced risk of myocardial infarction, stroke, and vascular death, we recommend long-term antiplatelet therapy for patients identified with lower extremity PAD. We do not use dual antiplatelet therapy in patients with PAD in the absence of other indications (eg, drug-eluting stent, prosthetic distal lower extremity bypass).

Aspirin is the antiplatelet agent of choice; clopidogrel may be used if aspirin cannot be tolerated. However, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial found that clopidogrel (75 mg/day) had a modest, although significant, advantage over aspirin (325 mg/day) for the prevention of stroke, myocardial infarction (MI), and PAD in 19,185 patients with a recent stroke, MI, or PAD (annual rate of 5.3 versus 5.8 percent) [23]. The Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial randomly assigned 21,162 patients with prior myocardial infarction (MI one to three years prior) to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, all on a background of low-dose aspirin [24]. A history of PAD was obtained at baseline in a total of 1143 patients (5 percent). Among PAD patients with prior MI, compared with placebo, use of ticagrelor reduced the absolute rate of major adverse cardiovascular events (MACE) by 4.1 percent and reduced the risk for peripheral revascularization for limb ischemia (hazard ratio [HR]: 0.63; 95% CI 0.43-0.93). However there was a 0.12 percent absolute excess of major bleeding. A trial is ongoing (EUCLID, NCT01732822) to evaluate the role of antiplatelet monotherapy (clopidogrel, ticagrelor) in patients with PAD.

Original Investigation | June 2016

Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease

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Commentary by Dr. Valentin Fuster

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Objectives This study evaluated the efficacy and safety of ticagrelor on major cardiovascular (CV) events and major adverse limb events in patients with PAD and a prior MI.

Methods PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis In Myocardial Infarction 54) randomized 21,162 patients with prior MI (1 to 3 years) to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, all on a background of low-dose aspirin. History of PAD was obtained at baseline. Occurrences of major adverse cardiovascular events (MACE) (defined as CV death, MI, or stroke) and major adverse limb events (MALE) (defined as acute limb ischemia or peripheral revascularization for ischemia) were recorded in follow-up.

Results A total of 1,143 patients (5%) had known PAD. In the placebo arm, those with PAD (n = 404) had higher rates of MACE at 3 years than those without (n = 6,663; 19.3% vs. 8.4%; $p < 0.001$), which persisted after adjusting for baseline differences (adjusted hazard ratio: 1.60; 95% confidence interval: 1.20 to 2.13; $p = 0.0013$), and higher rates of acute limb ischemia (1.0% vs. 0.1%) and peripheral revascularization procedures (9.15% vs. 0.46%). Whereas the relative risk reduction in MACE with ticagrelor was consistent, regardless of PAD, patients with PAD had a greater absolute risk reduction of 4.1% (number needed to treat: 25) due to their higher absolute risk. The absolute excess of TIMI major bleeding was 0.12% (number needed to harm: 834). The 60-mg dose had particularly favorable outcomes for CV and all-cause mortality. Ticagrelor (pooled doses) reduced the risk of MALE (hazard ratio: 0.65; 95% confidence interval: 0.44 to 0.95; $p = 0.026$).

Conclusions Among stable patients with prior MI, those with concomitant PAD have heightened ischemic risk. In these patients, ticagrelor reduced MACE, with a large absolute risk reduction, and MALE. (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS-TIMI 54]; NCT01225562)

Vorapaxar is a novel antagonist of protease-activated receptor (PAR-1), which is located on platelets, vascular endothelium, and smooth muscle, and is the primary receptor for thrombin on human platelets [25]. In the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50), 3787 patients with symptomatic PAD were included [26,27]. Among patients with symptomatic lower extremity PAD, vorapaxar reduced the rate of first acute limb ischemia events, particularly among those who had undergone revascularization [27,28]. (See "Surgical management of claudication", section on 'Antithrombotic therapy' and "Percutaneous interventional procedures in the patient with lower extremity claudication", section on 'Antiplatelet therapy' and 'Antithrombotic medications to improve patency' below.)

No benefit over aspirin has been established for oral anticoagulation for reducing mortality, and the rate of major bleeding events is increased. A meta-analysis identified nine trials involving 4889 patients with PAD evaluating oral anticoagulation that had conflicting results [29]. A randomized trial is planned to more fully evaluate anticoagulant therapy in patients with PAD, the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial (NCT00125671). The role of oral anticoagulation for preventing graft thrombosis is discussed below. (See 'Antithrombotic medications to improve patency' below.)

Whether or not antiplatelet therapy is beneficial for patients with asymptomatic PAD and no other clinical cardiovascular disease is unknown. (See "Benefits and risks of aspirin in secondary and primary prevention of cardiovascular disease".)

Vorapaxar in Patients With Peripheral Artery Disease
Results From TRA2°P-TIMI 50

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Background—Vorapaxar is a novel antagonist of protease-activated receptor-1, the primary receptor for thrombin on human platelets that is also present on vascular endothelium and smooth muscle. Patients with peripheral artery disease are at risk of systemic atherothrombotic events, as well as acute and chronic limb ischemia and the need for peripheral revascularization.

Methods and Results—The Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) was a randomized, double-blind, placebo-controlled trial of vorapaxar in 26 449 patients with stable atherosclerotic vascular disease (myocardial infarction, stroke, or peripheral artery disease). Patients with qualifying peripheral artery disease (n=3787) had a history of claudication and an ankle-brachial index of <0.85 or prior revascularization for limb ischemia. The primary efficacy end point was cardiovascular death, myocardial infarction, or stroke, and the principal safety end point was Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) bleeding. In the peripheral artery disease cohort, the primary end point did not differ significantly with vorapaxar (11.3% versus 11.9%; hazard ratio, 0.94; 95% confidence interval, 0.78–1.14; *P*=0.53). However, rates of hospitalization for acute limb ischemia (2.3% versus 3.9%; hazard ratio, 0.58; 95% confidence interval, 0.39–0.86; *P*=0.006) and peripheral artery revascularization (18.4% versus 22.2%; hazard ratio, 0.84; 95% confidence interval, 0.73–0.97; *P*=0.017) were significantly lower in patients randomized to vorapaxar. Bleeding occurred more frequently with vorapaxar compared with placebo (7.4% versus 4.5%; hazard ratio, 1.62; 95% confidence interval, 1.21–2.18; *P*=0.001).

Conclusions—Vorapaxar did not reduce the risk of cardiovascular death, myocardial infarction, or stroke in patients with peripheral artery disease; however, vorapaxar significantly reduced acute limb ischemia and peripheral revascularization. The beneficial effects of protease-activated receptor-1 antagonism on limb vascular events were accompanied by an increased risk of bleeding.

Circulation 2013; 127 : 1522-1529

Acute Limb Ischemia and Outcomes With Vorapaxar in Patients With Peripheral Artery Disease

Results From the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50)

Marc P. Bonaca, MD, MPH; J. Antonio Gutierrez, MD, MHS; Mark A. Creager, MD; Benjamin M. Scirica, MD; Jeffrey Olin, MD; Sabina A. Murphy, MPH; Eugene Braunwald, MD; David A. Morrow, MD, MPH

Background—Patients with peripheral artery disease (PAD) are at heightened risk of acute limb ischemia (ALI), a morbid event that may result in limb loss. We investigated the causes, sequelae, and predictors of ALI in a contemporary population with symptomatic PAD and whether protease-activated receptor 1 antagonism with vorapaxar reduced ALI overall and by type.

Methods and Results—The Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50) was a randomized, double-blind, placebo-controlled trial of vorapaxar in stable patients, including 3787 with symptomatic PAD. ALI was a prespecified adjudicated end point using a formal definition. A total of 150 ALI events occurred in 108 patients during follow-up (placebo 3-year rate, 3.9%; 1.3% annualized). For patients with symptomatic PAD, previous peripheral revascularization, smoking, and the ankle-brachial index were predictive of ALI. The majority of ALI events occurred as a result of surgical graft thrombosis (56%), followed by native vessel in situ thrombosis (27%). Stent thrombosis and thromboembolism caused ALI in 13% and 5%, respectively. Amputation occurred in 17.6% presenting with ALI. Vorapaxar reduced first ALI events by 41% (hazard ratio, 0.58; 95% confidence interval, 0.39–0.86; *P*=0.006) and total ALI events by 41% (94 versus 56 events; risk ratio, 0.59; 95% confidence interval, 0.38–0.93; *P*=0.022). The efficacy of vorapaxar was consistent across types of ALI.

Conclusions—In selected patients with symptomatic PAD and without atrial fibrillation, ALI occurs at a rate of 1.3%/y, is most frequently caused by acute bypass graft thrombosis or in situ thrombosis of a diseased vessel, and often results in limb loss. Vorapaxar reduces ALI in patients with symptomatic PAD with consistency across type, including PAD resulting from surgical graft thrombosis and in-situ thrombosis.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00526474.

(*Circulation*. 2016;133:997-1005. 10.1161/CIRCULATIONAHA.115.019355.)

AHJ
American Heart Journal

January 2006 Volume 151, Issue 1, Pages 1–9 Next Article >

The effects of oral anticoagulants in patients with peripheral arterial disease: Rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials

Aims

Patients with peripheral arterial disease (PAD) are at a high risk for cardiovascular (CV) morbidity and mortality even when treated with antiplatelet therapy. We present the rationale (including a meta-analysis of relevant trials), design, and baseline characteristics of the WAVE trial evaluating oral anticoagulants (OAC) in PAD.

Methods and Results

Nine trials involving 4889 patients with PAD evaluating OAC have conflicting results. Combining the data, it appears that OAC may reduce mortality and graft occlusion but increase major bleeding compared with no treatment. Compared with aspirin, OAC do not appear to reduce mortality (odds ratio [OR] = 1.04, 95% CI 0.55-1.29), although the CI are wide, or graft occlusion (OR = 0.91, 95% CI 0.77-1.06), and major bleeding is increased (OR = 1.96, 95% CI 1.43-2.69). Compared with aspirin, OAC used together with aspirin appears to increase mortality (OR = 1.57, 95% CI 1.16-2.12); may reduce graft occlusion (OR = 0.84, 95% CI 0.62-1.12), and major bleeding is increased (OR = 2.13, 95% CI 1.27-3.57). To further clarify the efficacy and safety profile of OAC in patients with PAD, we initiated the WAVE trial in which patients with PAD are randomized to receive OAC (target international normalizing ratio 2-3) plus antiplatelet therapy or antiplatelet therapy alone. Patients are treated for a minimum of 2.5 years and a maximum of 3.5 years. The co–primary efficacy outcomes are (1) CV death, MI, and stroke; and (2) CV death, MI, stroke, and acute limb or coronary ischemia requiring urgent intervention. The baseline characteristics of the study population confirm that patients with PAD represent a high-risk group.

Conclusions

The results of previous randomized trials evaluating OAC in patients with PAD (who represent a group at a high risk for thrombotic events) are inconclusive. WAVE is a large, international, randomized clinical trial designed to determine if moderate levels of oral anticoagulation (international normalizing ratio 2-3) improve upon antiplatelet therapy alone.

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Oral Anticoagulant and Antiplatelet Therapy and Peripheral Arterial Disease

The Warfarin Antiplatelet Vascular Evaluation Trial Investigators*

ABSTRACT

BACKGROUND

Atherosclerotic peripheral arterial disease is associated with an increased risk of myocardial infarction, stroke, and death from cardiovascular causes. Antiplatelet drugs reduce this risk, but the role of oral anticoagulant agents in the prevention of cardiovascular complications in patients with peripheral arterial disease is unclear.

The members of the writing group (Sonia Anand, M.D., Ph.D., F.R.C.P., Salim Yusuf, D.Phil., Changchun Xie, Ph.D., Janice Pogue, M.Sc., and John Eikelboom, M.B., B.S., McMaster University, Hamilton, ON, Canada; Andrzej Budaj, M.D., Ph.D., Cra-

METHODS

We assigned patients with peripheral arterial disease to combination therapy with an antiplatelet agent and an oral anticoagulant agent (target international normalized ratio [INR], 2.0 to 3.0) or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes; the second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes.

RESULTS

A total of 2161 patients were randomly assigned to therapy. The mean follow-up time was 35 months. Myocardial infarction, stroke, or death from cardiovascular causes occurred in 132 of 1080 patients receiving combination therapy (12.2%) and in 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (relative risk, 0.92; 95% confidence interval [CI], 0.73 to 1.16; P=0.48). Myocardial infarction, stroke, severe ischemia, or death from cardiovascular causes occurred in 172 patients receiving combination therapy (15.9%) as compared with 188 patients receiving antiplatelet therapy alone (17.4%) (relative risk, 0.91; 95% CI, 0.74 to 1.12; P=0.37). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared with 13 patients receiving antiplatelet therapy alone (1.2%) (relative risk, 3.41; 95% CI, 1.84 to 6.35; P<0.001).

CONCLUSIONS

In patients with peripheral arterial disease, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding. (ClinicalTrials.gov number, NCT00125671.)

Antithrombotic medications to improve patency — Following percutaneous or surgical intervention, patients should be maintained on antiplatelet therapies prescribed to reduce cardiovascular risk.

Whether dual antiplatelet therapy offers any additional benefit for those who have undergone lower extremity percutaneous revascularization remains debated. (See "Percutaneous interventional procedures in the patient with lower extremity claudication", section on 'Antiplatelet therapy'.)

Definitive data to support the use of antithrombotic therapy to improve the patency of lower extremit surgical revascularization is overall lacking. Antiplatelet therapy may benefit those undergoing prosthetic bypass, and although anticoagulation with vitamin K antagonists is not routinely used following surgical revascularization, it may be useful in the following situations: following vein bypas for those with either a suboptimal conduit or compromised distal runoff, or following prosthetic graft bypass to reduce the ischemic consequences of graft thrombosis. (See "Surgical management of claudication" and "Percutaneous interventional procedures in the patient with lower extremity claudication".)

Review | August 2016

Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease

Advances in Diagnosis and Treatment

Samia Mora, MD, MHS[1,2]; JoAnn E. Manson, MD, DrPH[1,3]

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ABSTRACT

ABSTRACT | INTRODUCTION | METHODS | ADVANCES IN TREATMENT | ADVANCES IN DIAGNOSIS | CONCLUSIONS | ARTICLE INFORMATION | REFERENCES

Importance Clinical decision making regarding the appropriate use of aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) events is complex, and requires an individualized benefit to risk assessment.

Objective To review advances in the individualized assessment for ASCVD and bleeding risk, and to provide an update of the randomized clinical trial evidence that examined the use of aspirin for primary prevention (primarily for ASCVD, and secondarily for colorectal cancer). The recently released 2016 US Preventive Services Task Force recommendations are discussed, as well as the role of ASCVD risk, age, sex, and aspirin dose/formulation in clinical decision making.

Evidence Review We performed a detailed review of peer-reviewed publications that were identified through searches of MEDLINE and the Cochrane Database through 2016 using the literature search terms "aspirin," "primary prevention," "cardiovascular disease," "mortality," "cancer." Bibliographies from these references as well as meta-analyses of these randomized clinical trials were also reviewed.

Findings Evidence from a total of 11 trials involving more than 118 000 patients is available to guide clinical decision making for aspirin use in the primary prevention of ASCVD. Clinicians should balance the benefit to risk ratio and the individual's preferences, calculating the 10-year ASCVD risk and evaluating risk factors for gastrointestinal bleeding, to facilitate a safer and more personalized approach to appropriate selection of candidates for low-dose aspirin (75 to 81 mg/d) for the primary prevention of ASCVD, with secondary considerations for reducing colorectal cancer risk when taken for longer periods (>10 years). Both the net ASCVD benefit and the bleeding risk of aspirin therapy increased as the absolute ASCVD risk increased, but the net benefits generally exceeded the risks at higher baseline ASCVD risk (≥10% ASCVD 10-year risk). The Aspirin-Guide is a clinical decision making support tool (app for mobile devices) with internal risk calculators to help clinicians with this dual assessment by calculating the ASCVD risk and the bleeding risk in the individual patient, and incorporating age- and sex-specific guidance based on randomized trial results.

Conclusions and Relevance Balancing the benefit of ASCVD reduction with the risk of bleeding from low-dose aspirin is difficult but essential for informed decision making and achieving a net clinical benefit from aspirin for primary prevention. This is facilitated by a free and readily available evidence-based clinical decision support tool.

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REVIEW TOPIC OF THE WEEK

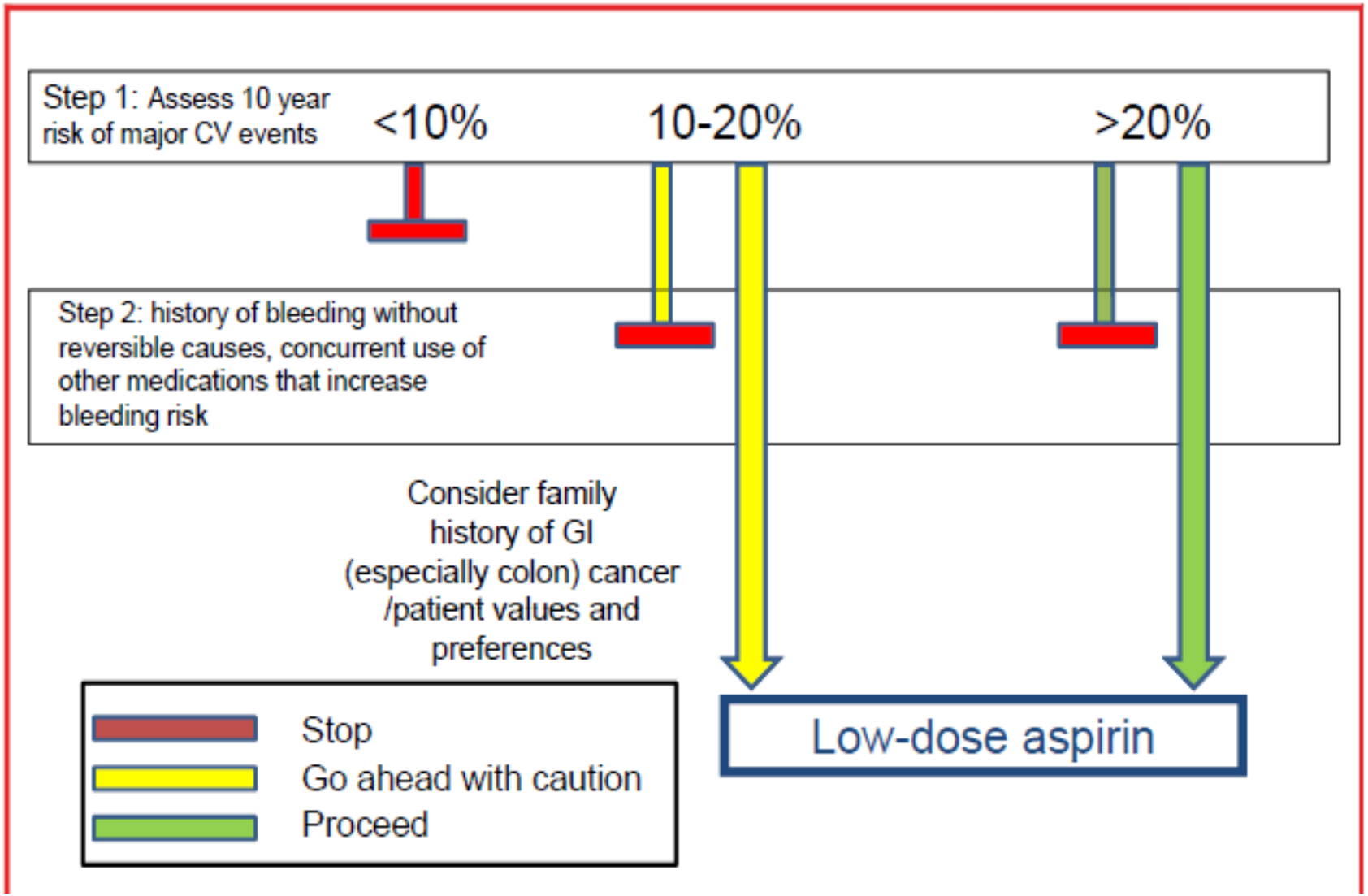
Aspirin Therapy in Primary Cardiovascular Disease Prevention

A Position Paper of the European Society of Cardiology Working Group on Thrombosis

Sigrun Halvorsen, MD,* Felicita Andreotti, MD, PhD,† Jurriën M. ten Berg, MD,‡ Marco Cattaneo, MD,§ Sergio Coccheri, MD,|| Roberto Marchioli, MD,¶ João Morais, MD,# Freek W. A. Verheugt, MD,** Raffaele De Caterina, MD, PhD††

ABSTRACT

Although the use of oral anticoagulants (vitamin K antagonists) has been abandoned in primary cardiovascular prevention due to lack of a favorable benefit-to-risk ratio, the indications for aspirin use in this setting continue to be a source of major debate, with major international guidelines providing conflicting recommendations. Here, we review the evidence in favor and against aspirin therapy in primary prevention based on the evidence accumulated so far, including recent data linking aspirin with cancer protection. While awaiting the results of several ongoing studies, we argue for a pragmatic approach to using low-dose aspirin in primary cardiovascular prevention and suggest its use in patients at high cardiovascular risk, defined as ≥2 major cardiovascular events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding. (J Am Coll Cardiol 2014;64:319-27)


Step 1: Assess 10 year risk of major CV events
<10%
10-20%
>20%
Step 2: history of bleeding without reversible causes, concurrent use of other medications that increase bleeding risk
Consider family history of GI (especially colon) cancer /patient values and preferences
Stop
Go ahead with caution
Proceed
Low-dose aspirin

CENTRAL ILLUSTRATION **A Proposed Practical Stepwise Approach to the Use of Aspirin in Primary CV Prevention**

The first step should be an assessment of patient's eligibility to the treatment, by assessing the 10-year risk of major cardiovascular (CV) events (death, myocardial infarction, and stroke), according to local population risk estimates. Eligible patients will be those with an estimated 10-year risk >20%. Patients with a 10-year risk between 10% and 20% will be deemed as "potentially eligible," and those with a risk <10% will be considered noneligible. The second step will be assessing safety in eligible and potentially-eligible patients, through a history of bleeding without reversible causes, and concurrent use of other medications that increase bleeding risk. In the absence of such conditions, patients with a risk >20% should be given low-dose aspirin, and those with a risk 10% to 20% should be engaged in a case-by-case discussion, factoring family history of gastrointestinal cancer (especially colon cancer) and patient values and preferences; particularly motivated patients can then be prescribed low-dose aspirin.

CONCLUSIONS AND RECOMMENDATIONS

We recommend that aspirin use in the primary prevention of acute MI and other atherothrombotic cardiovascular events in subjects of both sexes is guided by an assessment of the underlying cardiovascular risk (Grade of Recommendation: I, Level of Evidence: B) (Central Illustration). We suggest that aspirin be considered in the primary prevention of CVD in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) >2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding (GI bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk) (Class of Recommendation: IIa, Level of Evidence: B).

Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

Kirsten Bibbins-Domingo, PhD, MD, MAS, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2009 USPSTF recommendation on aspirin use to prevent cardiovascular disease (CVD) events and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug use to prevent colorectal cancer (CRC).

Methods: The USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up data. The USPSTF also relied on commissioned systematic reviews of all-cause mortality and total cancer incidence and mortality and a comprehensive review of harms. The USPSTF then used a microsimulation model to systematically estimate the balance of benefits and harms.

Population: This recommendation applies to adults aged 40 years or older without known CVD and without increased bleeding risk.

Recommendations: The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and 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 recommendation)

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. (C recommendation)

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. (I statement)

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. (I statement)

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For author affiliation, see end of text.

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* For a list of members of the USPSTF, see the **Appendix** (available at www.annals.org).

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

Population	Adults aged 50 to 59 y with a ≥10% 10-y CVD risk	Adults aged 60 to 69 y with a ≥10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommendation	Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Risk Assessment	Primary risk factors for CVD are older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking. Risk factors for GI bleeding with aspirin use include higher aspirin dose and longer duration of use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. The USPSTF used a calculator derived from the ACC/AHA pooled cohort equations to predict 10-y risk for first atherosclerotic CVD event.			
Preventive Medication	Aspirin's anticlotting effect is useful for primary and secondary CVD prevention because it potentially decreases the accumulation of blood clots that form as a result of reduced blood flow at atherosclerotic plaques, thereby reducing hypoxic damage to heart and brain tissue. The mechanisms for inhibition of adenoma or colorectal cancer development are not yet well-understood but may result from aspirin's anti-inflammatory properties.			
Treatment and Dosage	A reasonable approach consistent with the evidence is to prescribe 81 mg/d (the most commonly prescribed dose in the United States), and assess CVD and bleeding risk factors starting at age 50 y and periodically thereafter, as well as when CVD and bleeding risk factors are first detected or change.			
Balance of Benefits and Harms	The benefits of aspirin use outweigh the increased risk for bleeding by a moderate amount.	The benefits of aspirin use outweigh the increased risk for bleeding by a small amount.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on smoking cessation and promoting a healthful diet and physical activity, as well as screening for carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, obesity, diabetes, peripheral artery disease, and colorectal cancer. These recommendations are available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).			

Annals of Internal Medicine

REVIEW

Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force

Evelyn P. Whitlock, MD, MPH; Brittany U. Burda, MPH; Selvi B. Williams, MD, MPH; Janelle M. Guirguis-Blake, MD; and Corinne V. Evans, MPP

Background: The balance between potential aspirin-related risks and benefits is critical in primary prevention.

Purpose: To evaluate the risk for serious bleeding with regular aspirin use in cardiovascular disease (CVD) primary prevention.

Data Sources: PubMed, MEDLINE, Cochrane Central Register of Controlled Trials (2010 through 6 January 2015), and relevant references from other reviews.

Study Selection: Randomized, controlled trials; cohort studies; and meta-analyses comparing aspirin with placebo or no treatment to prevent CVD or cancer in adults.

Data Extraction: One investigator abstracted data, another checked for accuracy, and 2 assessed study quality.

Data Synthesis: In CVD primary prevention studies, very-low-dose aspirin use (≤100 mg daily or every other day) increased major gastrointestinal (GI) bleeding risk by 58% (odds ratio [OR], 1.58 [95% CI, 1.29 to 1.95]) and hemorrhagic stroke risk by 27% (OR, 1.27 [CI, 0.96 to 1.68]). Projected excess bleeding events with aspirin depend on baseline assumptions. Estimated excess major bleeding events were 1.39 (CI, 0.70 to 2.28) for GI bleeding and 0.32 (CI, −0.05 to 0.82) for hemorrhagic stroke per 1000 person-years of aspirin exposure using baseline bleeding rates from a community-based observational sample. Such events could be greater among older persons, men, and those with CVD risk factors that also increase bleeding risk.

Limitations: Power to detect effects on hemorrhagic stroke was limited. Harms other than serious bleeding were not examined.

Conclusion: Consideration of the safety of primary prevention with aspirin requires an individualized assessment of aspirin's effects on bleeding risks and expected benefits because absolute bleeding risk may vary considerably by patient.

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For author affiliations, see end of text.

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outcomes. Measures to reduce intracerebral bleeding attributable to aspirin, such as by detecting and adequately treating hypertension (64), are high priority.

Even at low or very low doses, aspirin increases the risk for bleeding events but absolute excess bleeding events will vary depending on individual baseline bleeding risks. Depending on the bleeding site, age is the strongest common risk factor for increased baseline bleeding, along with male sex, co-medications, and specific CVD risk factors. A history of GI bleeding or ulcers also greatly increases the baseline risk for bleeding, which explains why persons with these risks have been excluded from trials. Because no validated tools for predicting bleeding risk are available in this clinical scenario, pinpointing the balance between the benefits and harms of aspirin use, particularly considering the first 10 years of regular use, will depend on qualitative assessment of the baseline risk for bleeding alongside CVD benefits.

Association of Aspirin Use With Major Bleeding in Patients With and Without Diabetes

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Gianni Tognoni, MD
Antonio Nicolucci, MD

Context The benefit of aspirin for the primary prevention of cardiovascular events is relatively small for individuals with and without diabetes. This benefit could easily be offset by the risk of hemorrhage.

Objective To determine the incidence of major gastrointestinal and intracranial bleeding episodes in individuals with and without diabetes taking aspirin.

Design, Setting, and Participants A population-based cohort study, using administrative data from 4.1 million citizens in 12 local health authorities in Puglia, Italy. Individuals with new prescriptions for low-dose aspirin (≤300 mg) were identified during the index period from January 1, 2003, to December 31, 2008, and were propensity-matched on a 1-to-1 basis with individuals who did not take aspirin during this period.

Main Outcome Measures Hospitalizations for major gastrointestinal bleeding or cerebral hemorrhage occurring after the initiation of antiplatelet therapy.

THERAPY WITH LOW-DOSE ASPIrin is used for the treatment of cardiovascular disease. It is rec-

Results There were 186 425 individuals being treated with low-dose aspirin and 186 425 matched controls without aspirin use. During a median follow-up of 5.7 years, the overall incidence rate of hemorrhagic events was 5.58 (95% CI, 5.39-5.77) per 1000 person-years for aspirin users and 3.60 (95% CI, 3.48-3.72) per 1000 person-years for those without aspirin use (incidence rate ratio [IRR], 1.55; 95% CI, 1.48-1.63). The use of aspirin was associated with a greater risk of major bleeding in most of the subgroups investigated but not in individuals with diabetes (IRR, 1.09; 95% CI, 0.97-1.22). Irrespective of aspirin use, diabetes was independently associated with an increased risk of major bleeding episodes (IRR, 1.36; 95% CI, 1.28-1.44).

Conclusions In a population-based cohort, aspirin use was significantly associated with an increased risk of major gastrointestinal or cerebral bleeding episodes. Patients with diabetes had a high rate of bleeding that was not independently associated with aspirin use.

JAMA 2012; 307 (21) : 2286-2294

In conclusion, weighing the benefits of aspirin therapy against the potential harms is of particular relevance in the primary prevention setting, in which benefits seem to be lower than expected based on results in high-risk populations. In this population-based cohort, aspirin use was significantly associated with an increased risk of major bleeding, but this association was not observed for patients with diabetes. In this respect, diabetes might represent a different population in terms of both expected benefits and risks associated with antiplatelet therapy.

Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies

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Abstract

Background

Low-dose aspirin has proven effectiveness in secondary and primary prevention of cardiovascular events, but is also associated with an increased risk of major bleeding events. For primary prevention, this absolute risk must be carefully weighed against the benefits of aspirin; such assessments are currently limited by a lack of data from general populations.

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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Competing Interests: Drs García Rodríguez and Martín-Pérez work at CEIFE, which has received research grants from Bayer Pharma AG. Dr García

Methods

Systematic searches of Medline and Embase were conducted to identify observational studies published between 1946 and 4 March 2015 that reported the risks of gastrointestinal (GI) bleeding or intracranial hemorrhage (ICH) with long-term, low-dose aspirin (75–325 mg/day). Pooled estimates of the relative risk (RR) for bleeding events with aspirin versus non-use were calculated using random-effects models, based on reported estimates of RR (including odds ratios, hazard ratios, incidence rate ratios and standardized incidence ratios) in 39 articles.

Findings

The incidence of GI bleeding with low-dose aspirin was 0.48–3.64 cases per 1000 person-years, and the overall pooled estimate of the RR with low-dose aspirin was 1.4 (95% confidence interval [CI]: 1.2–1.7). For upper and lower GI bleeding, the RRs with low-dose aspirin were 2.3 (2.0–2.6) and 1.8 (1.1–3.0), respectively. Neither aspirin dose nor duration of use had consistent effects on RRs for upper GI bleeding. The estimated RR for ICH with low-dose aspirin was 1.4 (1.2–1.7) overall. Aspirin was associated with increased bleeding risks when combined with non-steroidal anti-inflammatory drugs, clopidogrel and selective serotonin reuptake inhibitors compared with monotherapy. By contrast, concomitant use of proton pump inhibitors decreased upper GI bleeding risks relative to aspirin monotherapy.

Conclusions

There was an approximately 40% increased risk of all GI bleeding with low-dose aspirin in the observational studies reviewed here, a finding very similar to that reported in randomized trials [6, 20]. When UGIB was studied separately, there was an approximately twofold increased risk of bleeding with low-dose aspirin. Neither aspirin dose nor the duration of treatment had consistent effects on the RR for GI bleeding. The overall risk of ICH was also increased by approximately 40% with long-term low-dose aspirin, which is also similar to the estimates from randomized trials, although an increase in risk was not consistently reported in all studies. In users of low-dose aspirin, the absolute risk of bleeding, but not the RR for bleeding compared with non-use, increased with age.

Ongoing and future studies will provide further information on the benefit–risk profile of low-dose aspirin in the prevention of CV events, particularly in primary prevention of CVD. In the meantime, by providing estimates of bleeding risks in a real-world setting, the data presented in this review should assist clinicians in making individual clinical judgments [72] on whether to prescribe low-dose aspirin for the prevention of CVD events.

Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer

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ABSTRACT

ABSTRACT | INTRODUCTION | METHODS | RESULTS | DISCUSSION | CONCLUSIONS | ARTICLE INFORMATION | REFERENCES

Importance The US Preventive Services Task Force recently recommended the use of aspirin to prevent colorectal cancer and cardiovascular disease among many US adults. However, the association of aspirin use with the risk for other cancer types and the potential population-wide effect of aspirin use on cancer, particularly within the context of screening, remain uncertain.

Objectives To examine the potential benefits of aspirin use for overall and subtype-specific cancer prevention at a range of doses and durations of use and to estimate the absolute benefit of aspirin in the context of screening.

Design, Setting, and Participants Two large US prospective cohort studies, the Nurses' Health Study (1980-2010) and Health Professionals Follow-up Study (1986-2012), followed up 135 965 health care professionals (88 084 women and 47 881 men, respectively) who reported on aspirin use biennially. The women were aged 30 to 55 years at enrollment in 1976; the men, aged 40 to 75 years in 1986. Final follow-up was completed on June 30, 2012, for the Nurses' Health Study cohort and January 31, 2010, for the Health Professionals Follow-up Study cohort, and data were accessed from September 15, 2014, to December 17, 2015.

Main Outcomes and Measures Relative risks (RRs) for incident cancers and population-attributable risk (PAR).

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Results Among the 88 084 women and 47 881 men who underwent follow-up for as long as 32 years, 20 414 cancers among women and 7571 cancers among men were documented. Compared with nonregular use, regular aspirin use was associated with a lower risk for overall cancer (RR, 0.97; 95% CI, 0.94-0.99), which was primarily owing to a lower incidence of gastrointestinal tract cancers (RR, 0.85; 95% CI, 0.80-0.91), especially colorectal cancers (RR, 0.81; 95% CI, 0.75-0.88). The benefit of aspirin on gastrointestinal tract cancers appeared evident with the use of at least 0.5 to 1.5 standard aspirin tablets per week; the minimum duration of regular use associated with a lower risk was 6 years. Among individuals older than 50 years, regular aspirin use could prevent 33 colorectal cancers per 100 000 person-years (PAR, 17.0%) among those who had not undergone a lower endoscopy and 18 colorectal cancers per 100 000 person-years (PAR, 8.5%) among those who had. Regular aspirin use was not associated with the risk for breast, advanced prostate, or lung cancer.

Conclusions and Relevance Long-term aspirin use was associated with a modest but significantly reduced risk for overall cancer, especially gastrointestinal tract tumors. Regular aspirin use may prevent a substantial proportion of colorectal cancers and complement the benefits of screening.

Invited Commentary

Aspirin for Cancer Prevention
One Step Closer

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ing the use of aspirin as a true cancer chemopreventive agent would typically require additional data from dedicated randomized clinical trials regarding the ability of aspirin to protect against cancers with the definition of an effective dose, the frequency and duration of treatment, and the clinical population at risk. In addition, as we have seen with the US Food and Drug Administration's prior consideration of other agents for possible CRC and polyp prevention effects, the impact of such agents in the context of established and effective screening modalities, such as colonoscopy with polypectomy, is also important.

sis, regular aspirin users experienced a statistically significant 15% reduction in the risk for all GI tract cancers, with a significant 19% reduction in the risk for CRC and a nonsignificant 15% reduction in the risk for gastroesophageal cancer. They also demonstrate that protection against GI tract cancers occurs at relatively low doses (0.5-1.5 standard tablets per week) that were used for various other reasons (eg, cardioprotection, headache, arthritis, musculoskeletal pain), with greater risk reduction seen at increasing doses and with longer duration of use and 6 years suggested as the minimum duration of use needed to realize cancer-protective benefits. The associa-

lated the proportion of incident cancers that could have been prevented with regular aspirin use, or the partial population-attributable risk, and found that 8.0% of all GI tract cancers and 10.8% of CRCs could have been prevented with regular aspirin use. In addition, their findings suggest that regular aspirin use could have prevented 33 CRCs per 100 000 person-years (17.0% of CRCs) among those who did not have lower endoscopy, and another 18 CRCs per 100 000 person-years (8.5%) could have been prevented among those who did have lower endoscopy. This finding is important because it suggests that aspirin use may complement CRC screening and may have an absolute benefit regardless of endoscopy status, a critical insight that few other studies have provided

Although the analysis by Cao and colleagues[1] provides more context to the use of aspirin as a CRC-preventive agent, the study provides no assessment of the potential harms of aspirin in these cohorts and does not assess the full range of aspirin's benefits beyond its cancer-preventive effects. Moreover, aspirin's long-term effects, if any, on cancer and overall mortality are not addressed, although earlier observational studies suggest inverse associations with cancer-specific and all-cause mortality.[3,5,6] To reflect accurately the often complex, real-world clinical scenarios in which physicians and patients contemplate the use of aspirin, any truly informative analysis of its use must weigh its cumulative benefits against its cumulative risks. Few studies are capable of such an assessment, but 2 ongoing randomized clinical trials of aspirin in older patient populations[7,8] should provide important additional detail on all of these points. For now, learning that aspirin's preventive effects on GI tract cancer seem to extend even to those individuals who undergo CRC screening provides further support for aspirin's possible future use as a cancer-preventive agent.

Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

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Summary

Background

Daily aspirin reduces the long-term risk of death due to cancer. However, the short-term effect is less certain, especially in women, effects on cancer incidence are largely unknown, and the time course of risk and benefit in primary prevention is unclear. We studied cancer deaths in all trials of daily aspirin versus control and the time course of effects of low-dose aspirin on cancer incidence and other outcomes in trials in primary prevention.

Methods

We studied individual patient data from randomised trials of daily aspirin versus no aspirin in prevention of vascular events. Death due to cancer, all non-vascular death, vascular death, and all deaths were assessed in all eligible trials. In trials of low-dose aspirin in primary prevention, we also established the time course of effects on incident cancer, major vascular events, and major extracranial bleeds, with stratification by age, sex, and smoking status.

Results

Allocation to aspirin reduced cancer deaths (562 *vs* 664 deaths; odds ratio [OR] 0·85, 95% CI 0·76–0·96, p=0·008; 34 trials, 69 224 participants), particularly from 5 years onwards (92 *vs* 145; OR 0·63, 95% CI 0·49–0·82, p=0·0005), resulting in fewer non-vascular deaths overall (1021 *vs* 1173; OR 0·88, 95% CI 0·78–0·96, p=0·003; 51 trials, 77 549 participants). In trials in primary prevention, the reduction in non-vascular deaths accounted for 87 (91%) of 96 deaths prevented. In six trials of daily low-dose aspirin in primary prevention (35 535 participants), aspirin reduced cancer incidence from 3 years onwards (324 *vs* 421 cases; OR 0·76, 95% CI 0·66–0·88, p=0·0003) in women (132 *vs* 176; OR 0·75, 95% CI 0·59–0·94, p=0·01) and in men (192 *vs* 245; OR 0·77, 95% CI 0·63–0·93, p=0·008). The reduced risk of major vascular events on aspirin was initially offset by an increased risk of major bleeding, but effects on both outcomes diminished with increasing follow-up, leaving only the reduced risk of cancer (absolute reduction 3·13 [95% CI 1·44–4·82] per 1000 patients per year) from 3 years onwards. Case-fatality from major extracranial bleeds was also lower on aspirin than on control (8/203 *vs* 15/132; OR 0·32, 95% CI 0·12–0·83, p=0·009).