

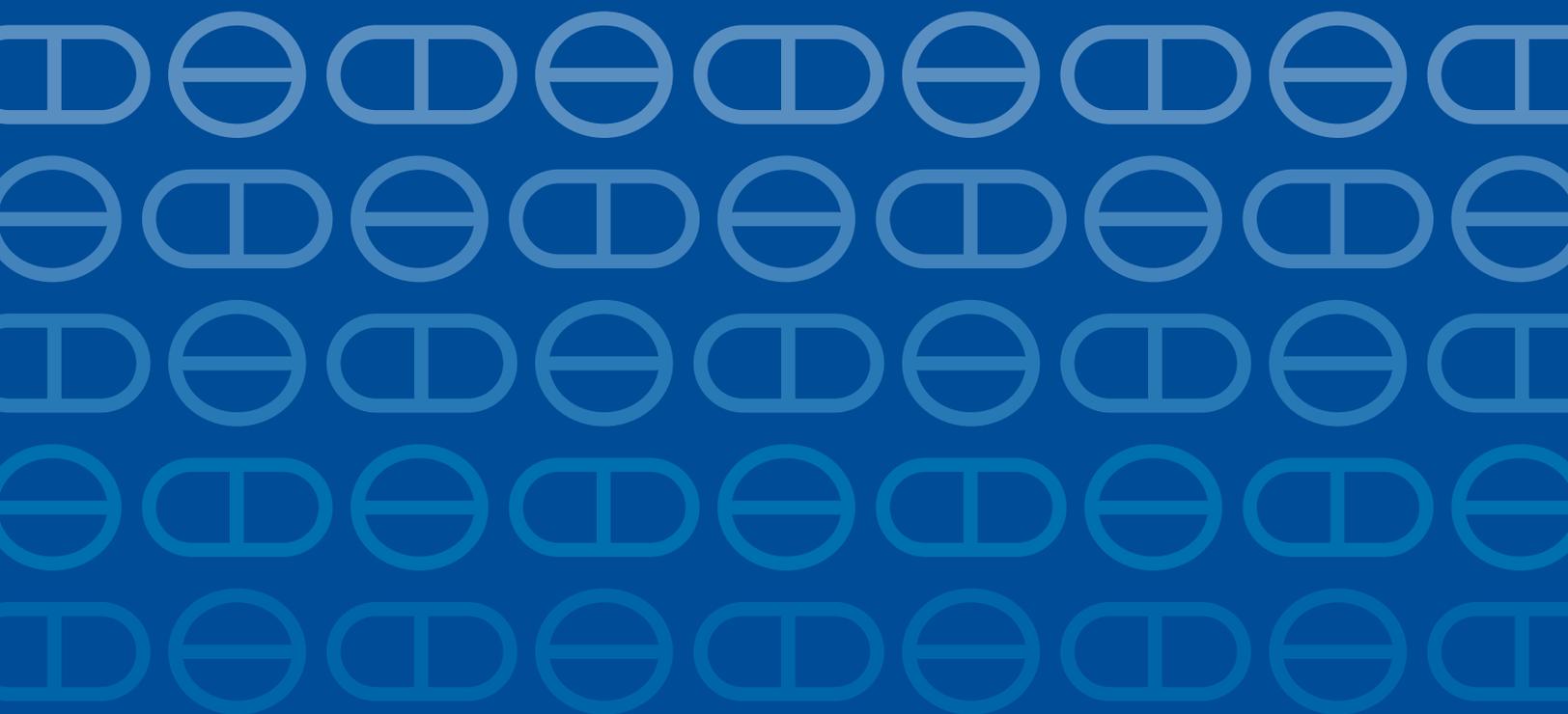


Pharmaceutical Assistance  
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# Aggregating the latest evidence on antiplatelet agents



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## Alosa Health

### Aggregating the latest evidence on antiplatelet agents

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#### Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.0 *AMA PRA* participation in the activity.

#### Activity Overview:

The goal of the educational program is to help practitioners assess the comparative effectiveness and safety of antiplatelet medications; understand the evidence regarding selection and duration of the appropriate therapy; weigh the benefits, risks, and value of treatment options; and improve the quality of prescribing and patient care.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of top 4-5 key messages
- “Academic detailing” educational sessions in physicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear off sheets)

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially-trained clinical educators.

#### Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

#### Learning Objectives:

Upon completion of this activity, participants will be able to:

- Describe the role of aspirin for preventing CV events in patients without prior CV event
- Recommend aspirin for secondary prevention in patients who have had a CV event
- Identify the duration of dual antiplatelet therapy (DAPT) for patients with cardiac indications based on patient and clinical factors.
- Recognize clopidogrel plus aspirin may be used to prevent CV events after stroke, during an acute period, but clopidogrel alone or dipyridamole plus aspirin should be used long-term.

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# Introduction

Antithrombotic drugs, which include antiplatelet and anticoagulant agents, prevent and treat many cardiovascular disorders and are some of the most commonly-prescribed drugs worldwide.<sup>1</sup>

Anticoagulants (e.g., heparin, warfarin, and newer oral anticoagulants) slow clotting by reducing fibrin formation. Antiplatelets (e.g., aspirin, clopidogrel) prevent platelet aggregation, which helps prevent thrombus formation and growth. Anticoagulants and antiplatelets are both used (occasionally together) for a range of cardiovascular indications.

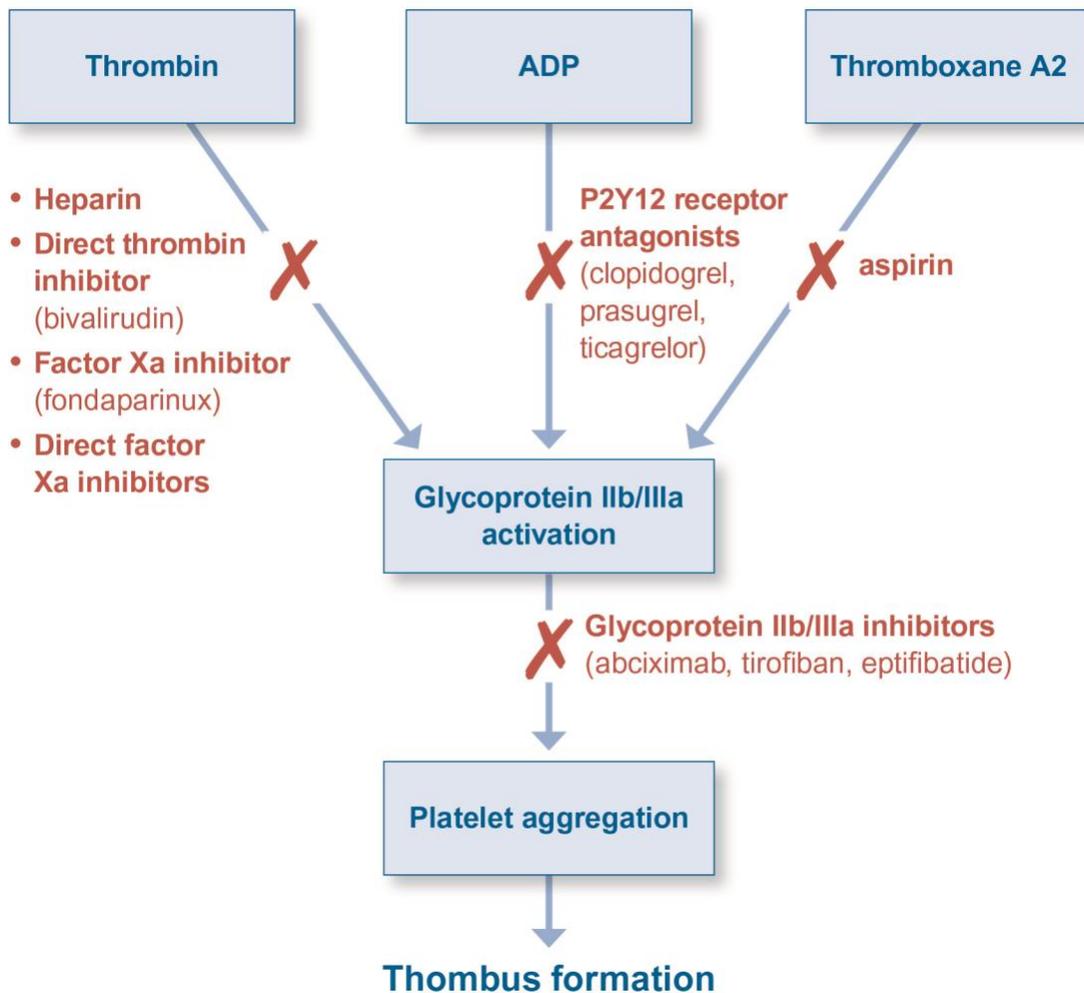
As a general principle, more potent antithrombotic effect is associated with a decreased risk of ischemic events, particularly among patients who are appropriately risk-stratified.<sup>2</sup> This decreased risk, however, must be balanced by the unavoidable increase in bleeding risk associated with more potent antithrombotic effects. Tailoring antithrombotic therapy to find the optimal risk/benefit balance for individual patients remains a major clinical challenge.<sup>2</sup> In addition, greater efforts are needed to improve long-term adherence to antiplatelet therapy given that 13.6% of patients prescribed an antiplatelet following implantation of a drug-eluting stent discontinued treatment within one month,<sup>3</sup> and about 50% of patients prescribed clopidogrel in-hospital after myocardial infarction (MI) discontinued within the first year.<sup>3,4</sup>

This evidence document focuses on antiplatelet medications because the results of recent clinical trials have shifted the clinical calculus used when balancing the potential benefits of these agents against the potential harms in individual patients. In addition, increased knowledge of the mechanisms underlying thrombosis has led to the development of newer antiplatelet agents with fewer interactions, more rapid onset of action, and less interpatient variability in antithrombotic effects than previous antithrombotic drugs.<sup>2</sup>

## Antiplatelet agents

Aspirin is the oldest antiplatelet agent. It irreversibly binds to cyclooxygenase 1 and is the most widely-used antiplatelet drug. Decades of evidence support its efficacy for reducing cardiovascular risk in a variety of clinical settings. Clopidogrel (Plavix, generics), prasugrel (Effient, generics), and ticagrelor (Brilinta) block the P2Y<sub>12</sub> receptor (also called the adenosine diphosphate [ADP] receptor). Both of these mechanisms lie in the physiological cascade that leads to platelet aggregation (anticoagulants, by contrast, act at different parts of this pathway, as illustrated in Figure 1). Dipyridamole (a component of Aggrenox) inhibits the uptake of adenosine into platelets, which inhibits platelet activation and, thus, reduces platelet aggregation.<sup>5</sup> It is sold as a combination product (25 mg aspirin/200 mg extended-release dipyridamole).<sup>5</sup> Ticlopidine (Ticlid), an ADP-receptor antagonist chemically similar to clopidogrel, has been associated with thrombotic thrombocytopenic purpura.<sup>6</sup> Because of this and dose-related neutropenia, ticlopidine is rarely used and will not be covered in this evidence document.

Figure 1: Antithrombotic mechanisms of action<sup>7</sup>



Choosing the right antiplatelet therapy requires understanding the benefits and risks of specific agents and regimens as well as their role in different clinical settings and patient populations. Cost, too, is a factor. Prasugrel, ticagrelor, and combination aspirin and extended-release dipyridamole cost substantially more than aspirin (pennies per day for aspirin vs. approximately \$338 per month for generic prasugrel, \$448 for ticagrelor, and \$427 for generic aspirin/dipyridamole ER).<sup>8,9</sup> Clopidogrel, which prior to losing patent protection in 2011 was the second best-selling prescription drug in the world with approximately \$9 billion in annual sales,<sup>10</sup> is now available generically for about \$9 per month. (For detailed information about costs, see page 25.)

## Assessing cardiovascular risk

Using antiplatelets to help prevent primary cardiovascular events requires an assessment of a patient's risk for atherosclerotic cardiovascular disease (ASCVD). Several validated tools are available for calculating 10-year ASCVD risk (Table 1).<sup>11</sup> Some calculators assess 10-year risk of any adverse cardiovascular event, such as MI, stroke, or cardiovascular death, while some are event-specific.

**Table 1: USPSTF-recommended online risk calculators<sup>11</sup>**

<b>10-year risk of combined cardiovascular event</b>
ACC/AHA ASCVD calculator: <a href="https://tools.acc.org/ASCVD-Risk-Estimator/">tools.acc.org/ASCVD-Risk-Estimator/</a>
Reynolds risk score: <a href="http://www.reynoldsriskscore.org">www.reynoldsriskscore.org</a>
<b>10-year risk of MI</b>
Framingham risk calculator: (evidence review available at: <a href="https://cvdrisk.nhlbi.nih.gov/calculator.asp">cvdrisk.nhlbi.nih.gov/calculator.asp</a> )
<b>Stroke risk calculator</b>
UCLA risk calculator: <a href="https://stroke.ucla.edu/#calculaterisk">stroke.ucla.edu/#calculaterisk</a>

The ASCVD risk estimator may underestimate 10-year risk of clinical events in certain clinical situations (e.g., patients with inflammatory conditions, such as HIV).<sup>12</sup> As will be detailed below, patients in the **ARRIVE trial** who were thought to be at moderate risk for CVD based on a mean 10-year ASCVD score of 17% were found to have an estimated 10-year risk (based on 5 years of data) of only 8.4% to 8.8%.<sup>13</sup>

## Aspirin for primary prevention

For more than a century, aspirin has been one of the most widely-used and widely-studied drugs in the physician's armamentarium. It is an inexpensive, easily-available agent with analgesic, anti-inflammatory, and antipyretic effects. Aspirin also has antiplatelet properties, which is the basis for its use in patients with, or at risk for, cardiovascular disease, the leading causes of death in the U.S.<sup>11</sup>

Prescribing this classic drug, or guiding patients in their over-the-counter use of this drug, is not straightforward, however. Patients vary widely in the benefits they may receive from aspirin therapy, in their inherent vulnerabilities to the risks posed by aspirin, in their use of other medications that may directly or indirectly alter aspirin's risk/benefit profile, and in their comorbidities and past medical histories, all of which complicate decision-making.

Many people currently taking daily aspirin should not be doing so, either because they have contraindications that have not been recognized or revealed, or because they, or their prescribers, are not aware of the latest evidence suggesting that aspirin is not appropriate for primary prevention of ASCVD in most patients. For example, based on data from 14,328 adults in the 2017 National Health Interview Survey, 23.4% of adults aged ≥40 years (about 29 million persons) reported taking aspirin daily for CVD prevention, about 6.6 million of whom were doing so without a physician's recommendation.<sup>14</sup> The rate of aspirin use was much higher in older adults: 44.6% of adults aged 70-79 years, and 46.2% of adults aged ≥80 years used daily aspirin for primary prevention (an estimated 9.5 million adults).<sup>14</sup> Primary care providers (PCPs) can make a difference by identifying such patients and educating them about appropriate use of aspirin.<sup>15</sup>

## New data, new perspectives

As recently as 2016, the preponderance of evidence seemed to suggest that low-dose aspirin (e.g., 81 mg/day) conferred a net benefit for the primary prevention of cardiovascular disease, and a number of guidelines used these data as the basis for their recommendations.<sup>16,17</sup>

In 2018, however, two large, long-term, high-quality randomized trials showed no ASCVD benefits for aspirin in primary prevention, while simultaneously demonstrating small, but significant, increased risk for major bleeding (Table 2).<sup>13,18</sup> A third 2018 trial in patients with diabetes found a modest CVD benefit, but with similarly increased bleeding risks.<sup>19</sup> Together, these trials led the American College of Cardiology/American Heart Association (ACC/AHA) to revise their recommendations for primary prevention with aspirin (detailed below following a summary of the three pivotal trials).<sup>20</sup> It is worth noting that some of the differences in results from the three recent trials compared to older primary prevention trials may be explained by the fact that the older trials were conducted at a time when smoking was common, blood pressure control was suboptimal, and aggressive lipid lowering was rare.<sup>21</sup>

**Table 2: Trials published in 2018 comparing aspirin vs. placebo for primary prevention of ASCVD<sup>13,18,19</sup>**

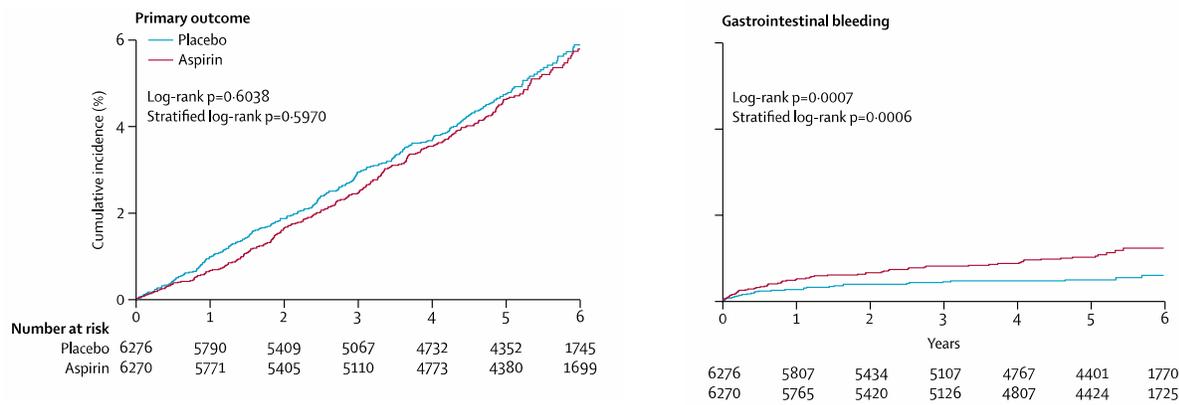
RCT	Patient population	Size	Follow-up	Mean age	CV effect (95% CI)	Major bleeding	
						Relative risk (95% CI)	Actual risk difference
ASPREE	Healthy older adults	19,114	4.7 years (median)	74	No difference	<b>HR 1.38 (1.18-1.62)</b>	2.4 extra events/ 1000 person-years
ARRIVE	“moderate” CV risk	12,546	5 years (median)	64	No difference	<b>HR 2.11 (1.36-3.28)</b>	0.5%
ASCEND	Diabetes	15,480	7.4 years (mean)	63	<b>RR 0.88 (0.79-0.97)</b>	<b>RR 1.29 (1.09-1.52)</b>	0.9%

HR – hazard ratio; RR – rate ratio

The **ASPREE trial** randomized 19,114 community-dwelling older adults (mean age 74 years, 44% male) to aspirin 100 mg/day vs. placebo.<sup>18</sup> No significant difference in CV events was observed after a median follow-up of 4.7 years (HR 0.95; 95% CI: 0.83-1.08), but aspirin was associated with a significantly increased risk of major bleeding (HR 1.38; 95% CI: 1.18-1.20). This trial also showed an increased risk of cancer-related death with aspirin (HR 1.31; 95% CI: 1.10-1.56) although this result should be interpreted cautiously because the outcome was not prespecified nor adjusted for multiple testing for effect sizes.

The **ARRIVE trial** enrolled 12,546 patients (70% male) thought to be at moderate risk for CVD based on a mean 10-year ASCVD risk score of 17%.<sup>13</sup> In fact, after a median follow-up of 5 years, the actual 10-year risk was extrapolated to 8.4% to 8.8% (Figure 2). The trial randomized patients to 100 mg daily aspirin vs. placebo, and, as with ASPREE, no statistically significant difference in the rate of major CV events was observed (HR 0.96; 95% CI: 0.81-1.13). There was, however, a significantly increased risk of gastrointestinal (GI) bleeding (HR 2.11; 95% CI: 1.31-3.28).

**Figure 2: Primary and GI bleeding outcomes in ARRIVE<sup>13</sup>**



The **ASCEND trial** randomized 15,480 patients with diabetes (any diabetes type, 62% male) but no evidence of CVD to aspirin 100 mg/day vs. placebo with mean follow-up of 7.4 years.<sup>19</sup> Serious vascular events occurred less frequently in the aspirin group vs. the placebo group (8.5% vs. 9.6%, P=0.001), but the incidence of major bleeding was also higher with aspirin: 4.1% vs. 3.2%, P=0.003). In subgroup analyses, the CVD benefits of aspirin were only significant in patients aged 60 and younger. The risks of major bleeding, however, were significantly higher for patients older than 60 years, suggesting that the risk/benefit equation in this population favors younger patients.

A 2019 meta-analysis combined data from 13 previous trials, including all those summarized above, and the results essentially confirm the take-away messages of the individual trials: an aggregate benefit associated with aspirin compared to placebo for CVD outcomes (60.2 per 10,000 participant-years with aspirin and 65.2 per 10,000 participant-years with placebo, HR 0.89; 95% CI: 0.84-0.94, NNT 241) and a significantly increased risk of bleeding (23.1 per 10,000 participant-years vs. 16.4 per 10,000 participant years, HR 1.43; 95% CI: 1.30-1.56, NNH 210).<sup>22</sup> The merging of older and newer studies in this meta-analysis (with the differing associated conditions and medications in the respective populations) reduces the clinical relevance of these results, although they are consistent with the outcomes of the individual trials.

In light of these pivotal trials, the 2019 ACC/AHA guidelines for primary prevention of CVD with aspirin state that “aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.”<sup>20</sup> Prescribers can consider discussing the risks and benefits of aspirin for primary prevention with younger patients at high risk for CVD but low risk for bleeding, or patients with diabetes (see Figure 3 for a summary of recommendations about aspirin for primary prevention). A given patient’s risk of ASCVD events can be calculated using the ASCVD Risk Estimator Plus (with “low-borderline risk” defined as <7.5%) available at: [tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/](https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/) When discussing risks and benefits of aspirin with patients, consider posing the following questions:<sup>23</sup>

- How concerned are you about having a heart attack or stroke, or developing cancer?
- Have you ever had problems with bleeding?
- Are you concerned about the risk of bleeding while on aspirin?
- Could you tolerate minor bleeding or bruising as a side effect?
- How do you feel about medication side effects in general?
- How do you feel about taking daily aspirin for years?

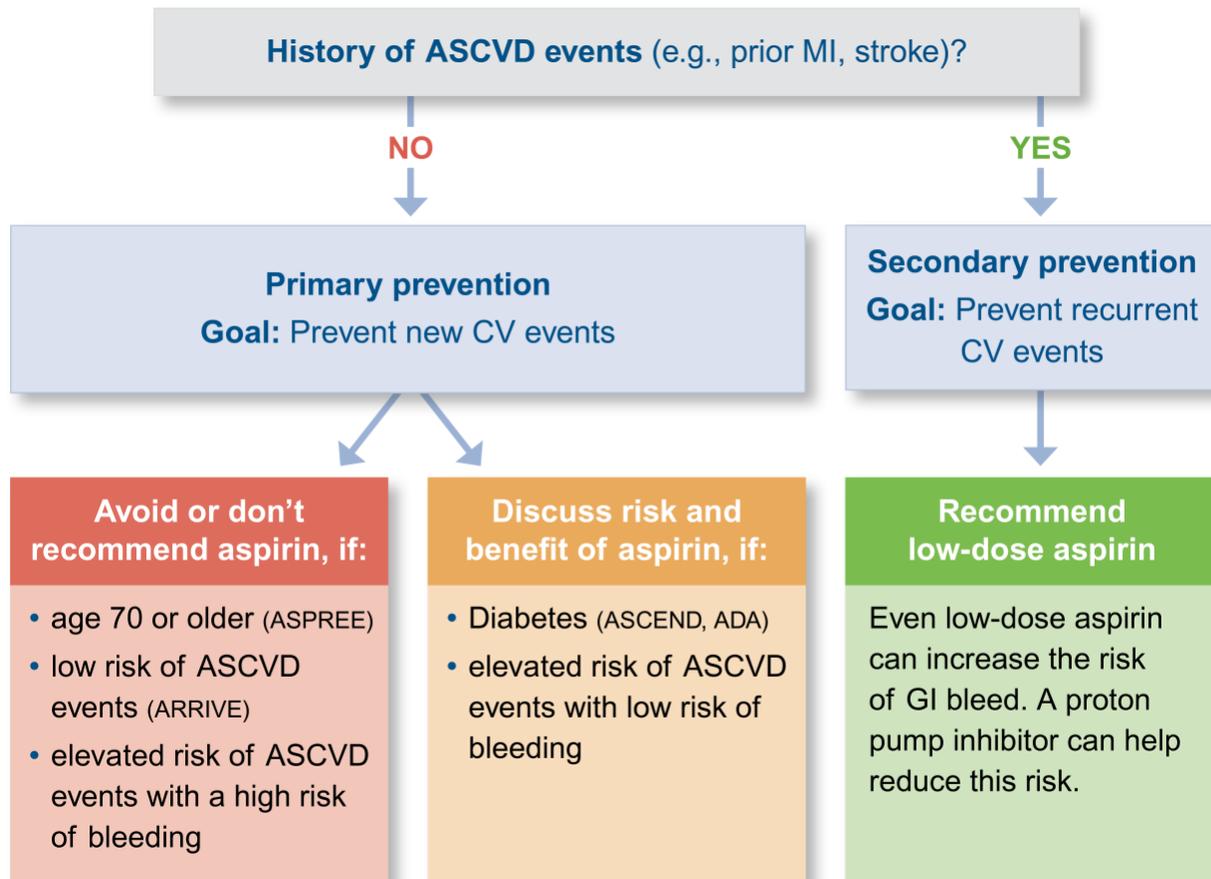
## Assessing patients for aspirin-associated risks

The primary adverse effect of aspirin is gastrointestinal (GI) bleeding, the risk of which is dose dependent. The increased risk of GI bleeding exists even with low doses of aspirin. Doses <100 mg daily increase the risk of GI bleeding approximately 2-fold relative to patients not on aspirin, while doses  $\geq 300$  mg increase the risk 4-fold.<sup>24</sup> In contrast, the benefit of aspirin is less dose-dependent, which is why, in the U.S., low-dose aspirin (81 mg) is usually recommended for antiplatelet indications.

The risk of GI bleeding increases with age, and men have a higher risk of bleeding compared to women.<sup>24</sup> Patients concomitantly taking NSAIDs or other antiplatelet medications and patients with peptic ulcer disease also have a higher risk of GI bleeding.

Prevention of GI bleeding is important in high-risk individuals who would benefit from the CV benefits of aspirin. Buffered or enteric-coated aspirin does not reduce the risk of GI bleeding compared to plain tablets.<sup>25</sup> In patients with healed peptic ulcer disease, restarting aspirin with a proton pump inhibitor (PPI) decreases the risk of recurrent bleeding.<sup>24</sup> Patients treated with aspirin and a PPI have lower bleeding rates than patients treated with clopidogrel alone.<sup>26</sup> A PPI should also be prescribed for patients with a history of GI bleeding, those taking dual antiplatelet therapy (DAPT), and those concomitantly taking anticoagulant medications. Eradication of *Helicobacter pylori* infection also reduces the risk of aspirin-induced bleeding in affected patients.<sup>27</sup>

**Figure 3: Summary of recommendation for aspirin for primary CVD prevention**



## Other (non-antiplatelet) agents for primary prevention

Efforts to reduce the risk of a first-time CV event (i.e., primary prevention) are not limited to aspirin. The evidence for the use of statins in primary prevention is considerably more robust than the evidence for aspirin. For example, three landmark trials demonstrated that statins lower cholesterol levels and reduce the risk of CVD events, including CVD mortality, in patients without pre-existing CVD: the 1995 West of Scotland Coronary Prevention Study (**WOSCOPS**) trial comparing pravastatin 40 mg vs. placebo,<sup>28</sup> the Air Force/Texas Coronary Atherosclerosis Prevention Study (**AFCAPS/TexCAPs**) trial of lovastatin (20-40 mg) vs. placebo,<sup>29</sup> and the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (**ASCOT-LLA**) of atorvastatin 10 mg vs. placebo.<sup>30</sup>

A 2011 Cochrane meta-analysis of 14 studies of statin use for primary prevention found that statins reduced all-cause mortality by 14% (OR 0.86; 95% CI: 0.79-0.94) and reduced combined cardiovascular endpoints by 30% (RR 0.70; 95% CI: 0.61-0.79).<sup>31</sup> Finally, a 2012 patient-level analysis of pooled data from 174,149 participants from 27 trials found a 21% reduction in major CVD events for those on statins (RR 0.79; 95% CI: 0.77-0.81), an association that held true even for the two lowest-risk groups (i.e., patients with 5-year CVD risk <5% or between 5% and 10%).<sup>32</sup>

Taken together, these trials suggest that statins for primary prevention are effective over a wide range of LDL-C levels and provide a similar relative risk reduction as has been observed in secondary prevention trials of statins. The 2019 ACC/AHA guidelines for primary prevention of CVD state that “Statin therapy is first-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels ( $\geq 190$  mg/dL), those with diabetes mellitus who are 40 to 75 years of age, and those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion.”<sup>20</sup> The guideline reserves the possibility of low-dose aspirin for adults aged 40-70 years at higher ASCVD risk but not at increased bleeding risk.

In addition, adequate control of blood pressure and smoking cessation among smokers are two other proven methods of reducing CVD risk among those without prior CVD.<sup>20</sup>

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**BOTTOM LINE: Aspirin should not be routinely prescribed for primary prevention, but should generate a discussion between providers and patients. Prescribers can consider discussing the risks and benefits of aspirin for primary prevention with younger patients at high risk for CVD but low risk for bleeding, or patients with diabetes. For older patients, those with low CVD risk or those with increased bleeding risk but without a history of a CV event, prophylactic use of a statin and/or blood pressure control has a better risk-benefit profile than primary prevention with aspirin.**

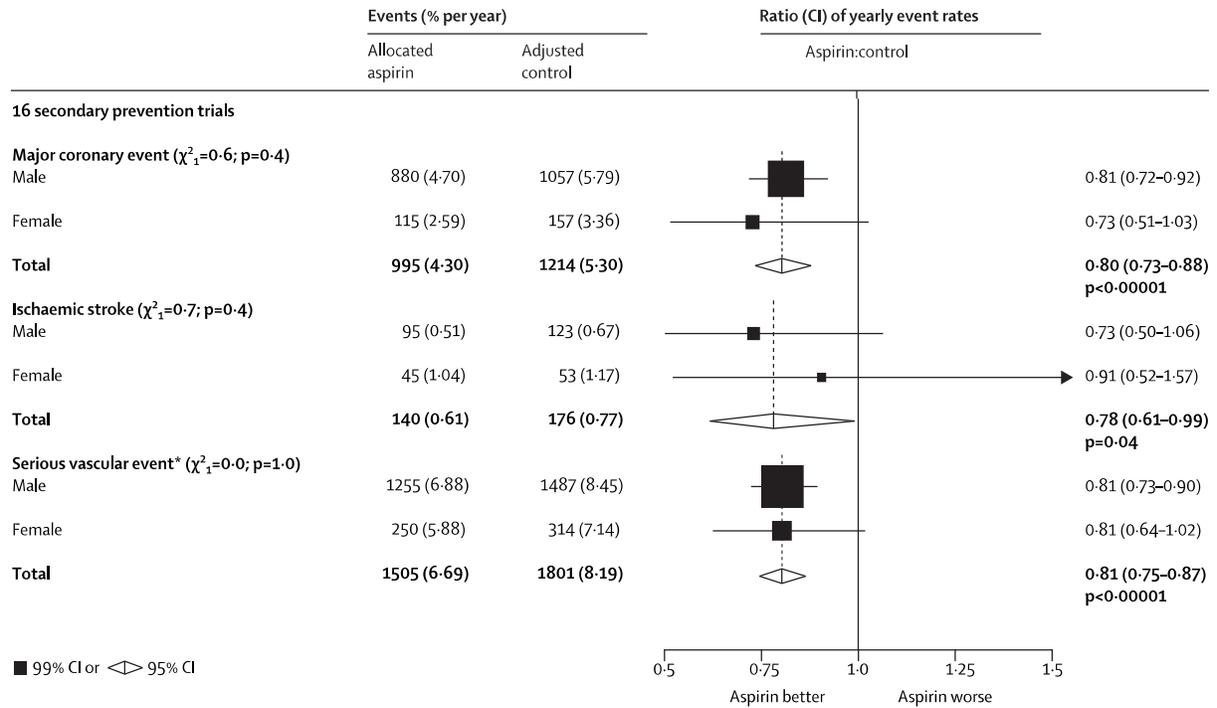
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## Aspirin for secondary prevention

The benefits of aspirin for secondary prevention were made clear by the 2009 Antithrombotic Trialists Collaboration meta-analysis.<sup>33</sup> Among the issues evaluated in this seminal publication was an analysis of 16 trials comparing aspirin vs. placebo for secondary prevention in approximately 17,000 patients with acute or prior vascular disease (Figure 4). It found significant reductions in the rate of major coronary events (RR 0.8; 95% CI: 0.73-0.88) and serious vascular events (MI, stroke, or vascular death) (RR 0.81;

95% CI: 0.75-0.87). The rate of ischemic stroke was lower in the aspirin group (0.61% vs. 0.77%) but the result was marginally significant (P=0.04).

**Figure 4: Meta-analysis of 16 trials of aspirin for secondary prevention<sup>16</sup>**

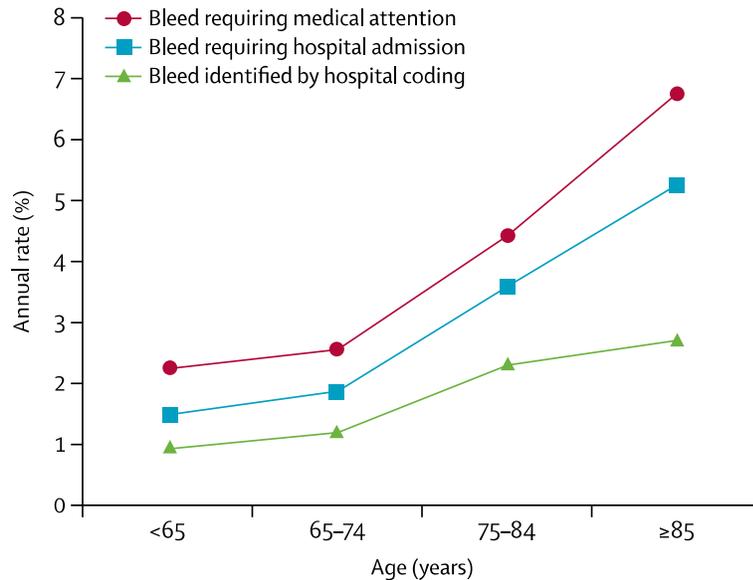


The beneficial effect of aspirin was seen among all sub-categories of high-risk patients, and the rates of outcomes were similar between men and women.<sup>16</sup>

An earlier analysis by the same group concluded that the optimal aspirin dose for secondary prevention was 75-100 mg/day, since pharmacodynamic studies suggest that doses as low as 30 mg/day may provide complete thromboxane inhibition, while doses >100 mg/day do not confer additional cardiovascular benefit, but are associated with greater bleeding risk.<sup>34</sup> Low-dose aspirin for secondary prevention with aspirin is currently recommended to be indefinite (i.e., life-long).<sup>35</sup>

Because the risk of major bleeding rises significantly after age 75 (Figure 5) co-prescription of a PPI with aspirin is recommended for this age group.<sup>35</sup>

**Figure 5: Annual rates of bleeding events requiring medical attention in patients on antiplatelet agents (mostly aspirin)<sup>36</sup>**



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**BOTTOM LINE: Robust evidence supports indefinite use of low-dose aspirin for secondary prevention of adverse cardiac events. Although the rate of major bleeding events is generally low, incidence increases significantly in adults >75 years old, therefore co-prescription of a PPI is generally recommended.**

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## Dual antiplatelet therapy (DAPT)

Although there are several potential combinations of antiplatelet agents, DAPT refers to combining aspirin with a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor). Aspirin and clopidogrel have been studied among patients with stable coronary artery disease and acute coronary syndrome (ACS) whereas the more recent (and more potent) P2Y12 receptor inhibitors have been evaluated primarily in patients with ACS.

DAPT provides more intense platelet inhibition than single antiplatelet therapy resulting in incremental reductions in the risk of thrombotic events after ACS and/or elective percutaneous coronary intervention (PCI), but it is associated with an increased risk of major bleeding.<sup>37</sup> The optimal duration for DAPT remains a matter of some debate. An individualized approach based on the patient clinical presentation (stable CAD or ACS), baseline ischemic and bleeding risk profiles, and management strategy (medical management alone, PCI or coronary artery bypass graft) is currently advocated (see section below on duration of DAPT for more details).<sup>37</sup>

Platelet function testing and genetic testing are generally not recommended to guide treatment decisions with DAPT (for more details refer to section on aspirin and clopidogrel resistance on page 23).<sup>38</sup> In

patients scheduled for surgery, aspirin should be continued until surgery, but P2Y12 inhibitors should be stopped 5-7 days prior to surgery (5 days prior for clopidogrel and ticagrelor, 7 days prior for prasugrel).<sup>38</sup>

## Antiplatelets for cardiac indications

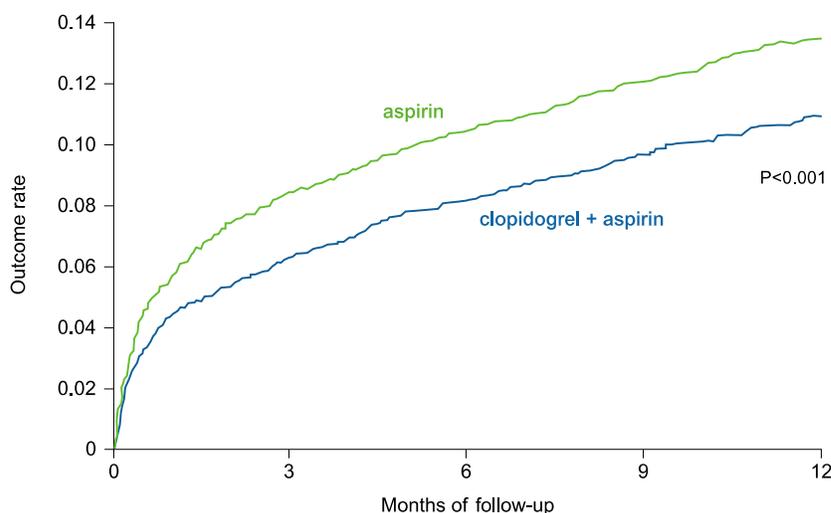
### Acute coronary syndromes

ACS represents a spectrum of clinical conditions including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI or NSTEMI-ACS) and ST-segment elevation MI (STEMI). Many patients with an ACS undergo PCI with stenting. Less commonly, patients with ACS will undergo PCI with balloon angioplasty without stenting or will be medically managed. Several large-scale randomized trials have assessed the role of antiplatelet agents for these patients in preventing adverse cardiovascular events.

### Clopidogrel

The **Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)** trial randomized 12,562 patients with NSTEMI or UA to clopidogrel (300 mg load then 75 mg daily) vs. placebo, with all patients also receiving aspirin (75 mg to 325 mg daily).<sup>39</sup> (36% of patients in the clopidogrel group and 36.9% of patients in the placebo group had coronary revascularization during the study.) The patients continued to receive their assigned therapy for up to one year after discharge (mean 9 months). Patients in the dual antiplatelet group had a significantly lower risk of death from cardiovascular causes, non-fatal MI, and non-fatal stroke (9.3% vs. 11.4%,  $P < 0.001$ ). The rate of major bleeding was higher with clopidogrel: 3.7% vs. 2% (RR 1.38; 95% CI: 1.13-1.67).

**Figure 6: Primary outcome (death from CV causes, nonfatal MI, or stroke) from CURE<sup>39</sup>**



A 2,658 patient sub-study of the CURE trial, (PCI-CURE), compared dual antiplatelet therapy with clopidogrel plus aspirin to aspirin alone for ACS patients undergoing PCI.<sup>40</sup> Patients were pretreated with their assigned regimen for a median of 6 days before PCI and all subjects received open-label clopidogrel

for 4 weeks before returning to their randomized study drug. The group that received clopidogrel and aspirin had a 1.9% absolute, and 30% relative, reduction in cardiovascular events compared to patients given aspirin alone.

Clopidogrel has several clinically relevant limitations, including a modest level of platelet inhibition and considerable inter-individual variability in response, because of genetic variation and drug-drug interactions. To address this, several studies have evaluated intensification of antiplatelet therapy, either with dose escalation of clopidogrel or use of alternative agents that offer more potent and consistent platelet inhibition.

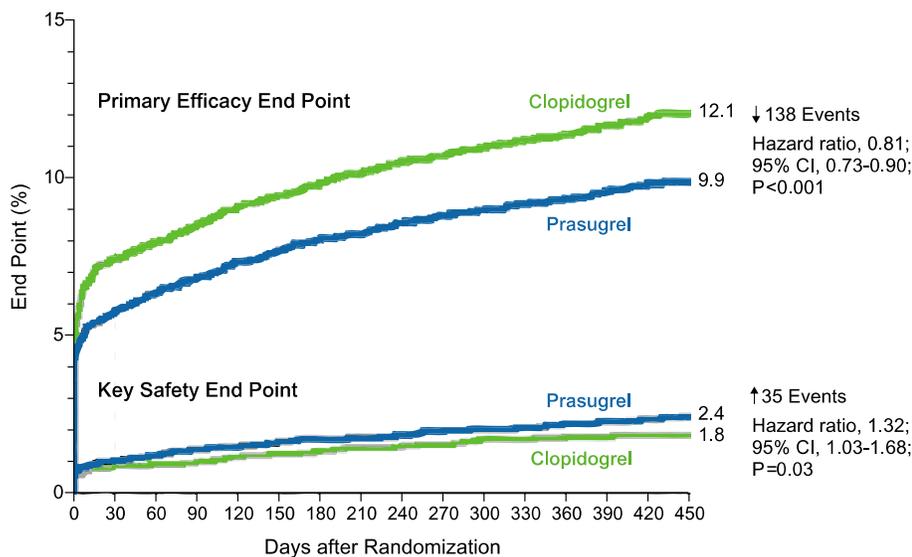
### Double dose clopidogrel vs. standard dose clopidogrel

The **CURRENT-OASIS 7** trial randomized ACS patients referred for angiography to double-dose clopidogrel (600 mg load on day 1, followed by 150 mg daily for six days, and 75 mg daily thereafter) vs. standard dose clopidogrel (300 mg load on day 1 and 75 mg daily thereafter).<sup>41,42</sup> No significant benefit was observed with double-dose clopidogrel compared to standard dose clopidogrel in the rate of the composite outcome of cardiovascular death, MI, or stroke (4.2% vs. 4.4%, P=0.3). However, a prespecified analysis of patients who underwent PCI found that double-dose clopidogrel marginally reduced the rate of cardiovascular death, MI, or stroke (3.9% vs. 4.5%, P=0.04).

### Prasugrel

The **TRITON-TIMI 38** study randomized 13,608 patients with moderate-to-high-risk ACS (99% of whom had PCI as index procedure) to prasugrel (60 mg load then 10 mg/day plus aspirin 75-162 mg daily) vs. clopidogrel (300 mg load then 75 mg/day plus aspirin).<sup>43</sup> After median follow-up of 14.5 months, prasugrel was associated with a significantly lower rate of the composite cardiovascular primary endpoint compared to clopidogrel plus aspirin (9.9% vs. 12.1%, P<0.001) primarily because of a difference in non-fatal MI (7.3% vs. 9.5%, P<0.001), although all-cause mortality did not differ between groups. The rate of major bleeding was higher in the prasugrel group: 2.4% vs. 1.8% with clopidogrel (HR 1.32; 95% CI: 1.03-1.68).

**Figure 7: Primary outcome (death from CV causes, nonfatal MI, or nonfatal stroke) and safety end point (major bleeding not related to coronary-artery bypass grafting) in TRITON-TIMI 38<sup>43</sup>**



In subgroup analyses, no significant differences in the primary outcome were observed between prasugrel and clopidogrel in: patients with a history of stroke or transient ischemic attack (TIA); patients age  $\geq 75$  years; and those with weight  $< 60$  kg. Patients with prior stroke or TIA experienced increased rates of bleeding and overall net harm with prasugrel compared to clopidogrel.

Some patients with ACS do not undergo PCI or other procedures. The relative efficacy of prasugrel compared with clopidogrel in such patients managed medically was evaluated in the **TRILOGY-ACS trial**. In 7,234 patients younger than age 75 who were receiving ongoing aspirin therapy, adding 10 mg/day prasugrel was not superior over 30 months to clopidogrel (75 mg daily) in reducing the rate of cardiovascular death, MI, or stroke (13.9% vs. 16.0%,  $p=0.21$ ).<sup>44</sup>

The FDA required a boxed warning against use of prasugrel in patients with a history of stroke or TIA, and a recommendation against its use in patients  $\geq 75$ , or those whose weight is under 60 kg. Therefore, for these patients, based on the evidence summarized above, prasugrel should only be used after PCI and avoided in adults age 75 and over.

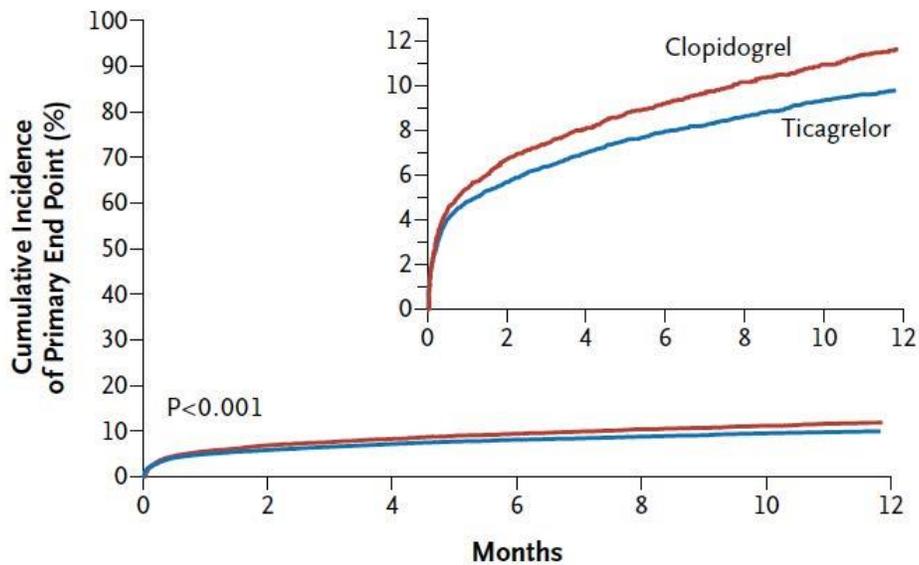
## Ticagrelor

The **PLATO** trial evaluated ticagrelor versus clopidogrel, both given in combination with aspirin, in patients with ACS (38% STEMI, 43% NSTEMI, and 17% UA).<sup>45</sup> (60.9% of the ticagrelor group and 61.1% of the clopidogrel group had PCI during the index hospitalization.) Ticagrelor differs from clopidogrel and prasugrel in that it binds reversibly rather than irreversibly to the P2Y<sub>12</sub> receptor, and may thus result in more potent and rapid platelet inhibition. **PLATO** randomized patients to ticagrelor (180 mg loading dose followed by 90 mg twice daily) vs. clopidogrel (300-600 mg loading dose followed by 75 mg daily). All patients also received aspirin 75-325 mg daily.

The study's primary efficacy endpoint was death from vascular causes, MI, or stroke at 12 months. Those receiving ticagrelor had a significantly lower rate of the primary endpoint compared to those randomized to clopidogrel (9.8% vs. 11.7%,  $P<0.001$ ). No significant differences were observed in the rate of major bleeding 11.6% vs. 11.2% (HR 1.04; 95% CI: 0.95-1.13).

Of note, the efficacy of ticagrelor appeared to differ by geographic region – the primary endpoint occurred more often with ticagrelor among patients enrolled in the U.S. (12.6% vs. 10.1%) compared to patients outside the U.S., although the difference was not statistically significant. The cause of this geographic heterogeneity may have been the higher doses of aspirin ( $>100$  mg/day) in the U.S., which has led to the recommendation that aspirin therapy be limited to 75-100 mg daily in patients receiving ticagrelor.<sup>45</sup>

Figure 8: Cumulative estimates of the time to the first adjudicated occurrence of the primary efficacy end point in PLATO<sup>45</sup>



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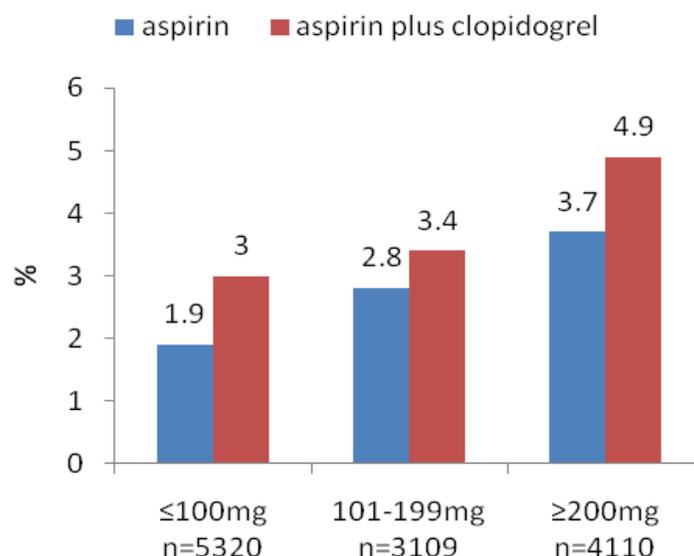
**BOTTOM LINE:** The combinations of prasugrel/aspirin and ticagrelor/aspirin are superior to clopidogrel/aspirin, which, in turn, is superior to aspirin monotherapy for secondary prevention of ischemic heart disease in a limited time period after MI or PCI.

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### Bleeding risks with DAPT

As detailed above, all antiplatelet agents increase the risk of gastrointestinal and intracranial bleeding, even low-dose aspirin, with risk rising in a dose-dependent manner.<sup>24</sup> This was clearly illustrated in **CURE**, with the risk of bleeding from aspirin alone nearly doubling as dose rose from 100 mg to >200 mg, and bleeding risk was amplified with the addition of clopidogrel (Figure 9 next page).<sup>39</sup>

**Figure 9: Rates of major bleeding observed in the CURE trial for patients treated with aspirin alone and aspirin plus clopidogrel<sup>39</sup>**



**Table 3: Summary of main trials of DAPT for ACS<sup>39,43,45</sup>**

	CURE	TRITON-TIMI 34	PLATO
Year published	2001	2007	2009
Study regimen	Clopidogrel + aspirin	Prasugrel + aspirin	Ticagrelor + aspirin
Comparator	Aspirin alone	Clopidogrel + aspirin	Clopidogrel + aspirin
Number of patients enrolled	12,562	13,608	18,624
% women	38%	26%	28%
Follow-up	9 months	14.5 months	9 months
<b>CV Events</b>			
Absolute difference	9.3% vs. 11.4%	9.9% vs. 12.1%	9.8% vs. 11.7%
Relative difference (95% CI)	<b>RR 0.80 (0.72-0.90)</b>	<b>HR 0.81 (0.73-0.90)</b>	<b>HR 0.84 (0.77-0.92)</b>
<b>Major bleeding</b>			
Absolute difference	3.7% vs. 2%	2.4% vs 1.8%	11.6% vs. 11.2%
Relative difference	<b>RR 1.38 (1.13-1.67)</b>	<b>HR 1.32 (1.03-1.68)</b>	HR 1.04 (0.95-1.13)

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**BOTTOM LINE: DAPT confers greater protection from CV events compared to aspirin alone in patients with ACS, but increases risk of bleeding. Prasugrel should be reserved for patients having PCI and avoided in adults  $\geq 75$  years or a history of cerebrovascular disease.**

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## Stable ischemic heart disease

Strong evidence supports low-dose aspirin monotherapy for patients with stable ischemic heart disease. In a meta-analysis of 7 trials with 2,920 patients, aspirin was associated with a 33% reduction in the risk of stroke, MI, or vascular death.<sup>34</sup>

There is no evidence on the comparative value of clopidogrel vs. aspirin in patients with stable ischemic heart disease who have not had a recent MI, stroke, or who do not have PVD. Current AHA/ACC guidelines recommend that stable ischemic heart disease patients be treated with aspirin alone.<sup>46</sup> Clopidogrel monotherapy should be used in patients with a contraindication to aspirin.

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**BOTTOM LINE: Patients with stable ischemic heart disease should be treated with low-dose aspirin unless contraindicated.**

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## Duration of treatment

The duration of treatment for DAPT depends on why it is needed and risk of bleeding. For patients with ACS (regardless of whether a stent is placed) and not at high risk for bleeding, 12 months of DAPT is generally recommended, with 6 months recommended for patients at high risk of bleeding.<sup>38</sup> In patients who have had PCI for stable CAD, duration of treatment depends on the type of stent used. Patients at low bleeding risk with bare metal stents (BMS) should have only one month of DAPT, whereas similar patients with drug-eluting stents (DES) should continue DAPT for 6 months. In patients who have had PCI with high bleeding risk, the duration with BMS is also one month, but the duration with DES is shorter: only 3 months.<sup>38</sup> In all cases of patients at low bleeding risk, DAPT may be continued beyond these recommended durations at clinical discretion.

A meta-analysis of 5 trials (n=12,078 patients having newer-generation drug-eluting stents) comparing DAPT for 3-6 months vs. DAPT for 12 months found no significant difference in a composite endpoint of CV events, stent thrombosis, or MI, and a non-significant trend toward reduced rates of major hemorrhage with shorter-duration DAPT.<sup>47</sup> Meta-analyses by the same authors of five trials comparing 6-12 months of DAPT vs. 18-48 months found that longer treatment was associated with reduced rates of MI (5 trials, OR 0.67; 95% CI: 0.47-0.95) and stent thrombosis (5 trials, OR 0.42; 95% CI: 0.24-0.74, absolute rates 0.003% vs. 0.009%), but also higher rates of major hemorrhage (6 trials, OR 1.58; 95% CI: 1.20-2.09).<sup>47</sup>

The **DAPT Study** randomized 9,961 patients with drug-eluting stents to 12 months of DAPT then an additional 18 months of aspirin alone vs. 30 months of DAPT.<sup>48</sup> Longer duration of DAPT was associated with reduced rates of stent thrombosis (0.4% vs. 1.4%,  $P < 0.001$ ) and major adverse CV and cerebrovascular events (4.3% vs. 5.9%,  $P < 0.001$ ), but an increased risk of moderate or severe bleeding (2.5% vs. 1.6%,  $P = 0.001$ ).

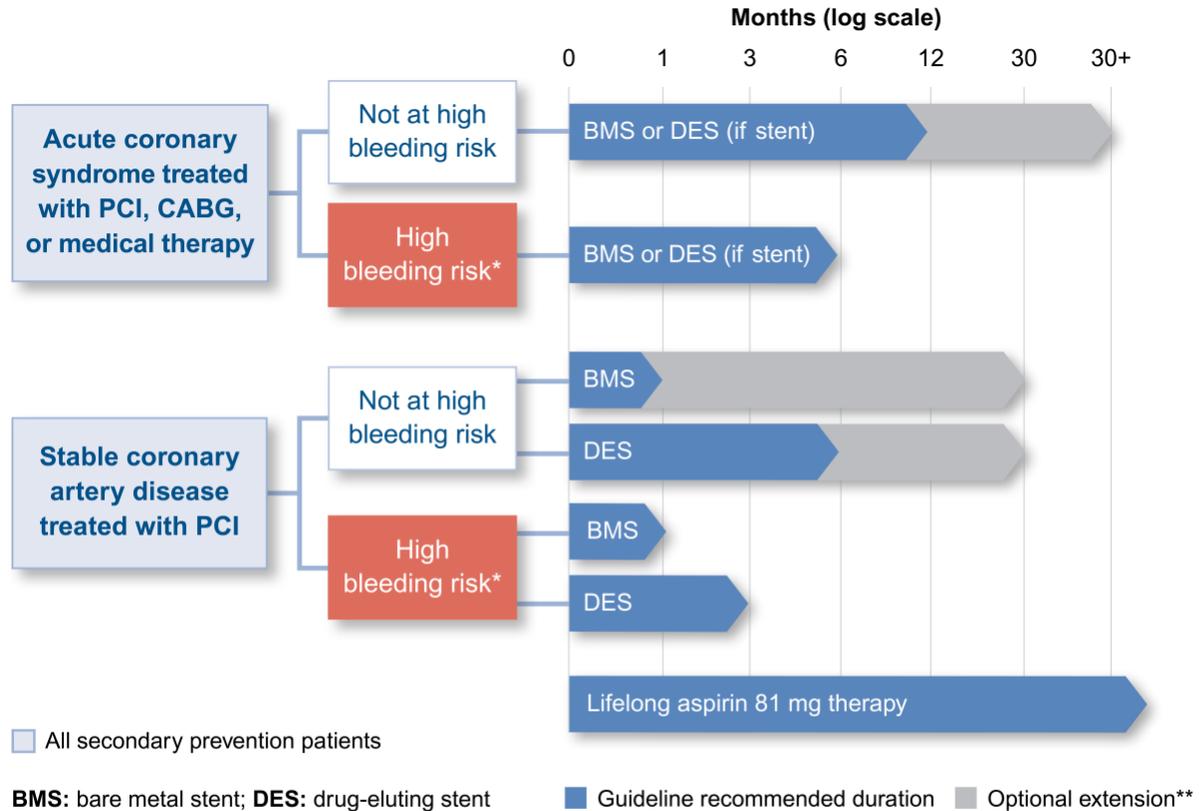
The **PEGASUS-TIMI 54** trial randomized 21,162 patients with prior MI to a median of 33 months of ticagrelor 60 mg twice daily, ticagrelor 90 mg twice daily, or placebo. The two ticagrelor doses each reduced rates of CV death, MI, or stroke compared to placebo (7.85% with 90 mg, 7.77% with 60 mg, and 9.04% with placebo [P=0.008 for each comparison to placebo]), and increased the risk of major bleeding (2.6% with 90 mg, 2.3% with 60 mg, and 1.06% with placebo, [P<0.001]).

In general, the following factors tend to favor shorter durations of DAPT:<sup>35</sup>

- history of prior bleeding
- oral anticoagulant therapy
- female sex
- advanced age
- low body weight
- CKD
- diabetes mellitus
- anemia
- chronic steroid or NSAID therapy

Currently, low-dose aspirin is recommended for secondary prevention on an indefinite (i.e., lifetime) basis. Aspirin sparing regimens such as GLOBAL LEADERS trial, STOPDAPT-2, and SMART-CHOICE require additional data to support use in wider, more diverse populations.

Figure 10: Recommended treatment durations of DAPT by indication<sup>38,48,49</sup>



**\*\*Optional extension in duration of therapy:** In patients without a high risk of bleeding who do not have another ASCVD event or a major bleed during the initial treatment period, the prescriber may opt to extend treatment up to 30 months if a stent was placed and possibly longer in patients after an MI. In patients with a second ASCVD event, the duration for DAPT should reset (i.e., another 12 months after an ACS event).

**BOTTOM LINE:** Aspirin therapy for patients with ACS should be life-long. DAPT is time-limited, with recommended duration driven by indication, bleeding risk, type of stent, and ischemic risk. The risks and benefits of DAPT extended beyond recommended durations should be discussed with patients.

### New data about aspirin's role in DAPT

The results of several recent trials have called into question the appropriate duration of aspirin as a component of DAPT in patients having coronary stenting for ACS or stable CAD.<sup>50</sup>

The **GLOBAL LEADERS trial** randomized 15,968 patients having PCI for stable CAD or ACS and one month of DAPT with aspirin/ticagrelor to continuation with ticagrelor alone for 23 months vs. continuation with DAPT, either with ticagrelor/aspirin or clopidogrel/aspirin for 12 months, then aspirin monotherapy for 12 months.<sup>51</sup> After 23 months of follow-up, in a superiority analysis no significant differences were observed for the primary outcome of mortality or MI, or for risk of serious bleeding, hence this approach is not recommended at this time.

The **STOPDAPT-2** trial randomized 3,045 patients in Japan with drug-eluting stents to 12 months of DAPT vs. 1 month of DAPT followed by a P2Y12 (mostly clopidogrel) monotherapy.<sup>52</sup> At 12-month follow-up, the rates of major adverse cardiovascular events between groups was not significant in a non-inferiority analysis: 2.5% in the 12-month DAPT group vs. 1.96% in the group that got only one month of DAPT with no aspirin thereafter (P2Y12 monotherapy) (P=0.34 for superiority). The rate of major or minor bleeding was significantly lower in the short-DAPT group: 0.4% vs. 1.5% (P=0.004).

The similar **SMART-CHOICE** trial randomized 2,993 patients in Korea with drug-eluting stents to 12 months of DAPT vs. 3 months of DAPT followed by P2Y12 monotherapy.<sup>53</sup> At 12-month follow-up, the rate of major adverse cardiovascular events was 2.5% in the 12-month DAPT group vs. 2.9% in P2Y12 monotherapy group (P=0.007 for noninferiority). The rate of major or minor bleeding was lower in the short-DAPT group: 2% vs. 3.4% (P=0.02).

Given the physiological and genetic differences in the study populations of STOPDAPT-2 AND SMART-CHOICE compared to the U.S. it remains to be seen whether these results can be extrapolated to the U.S. and Europe or whether they will significantly affect clinical practice.<sup>50</sup>

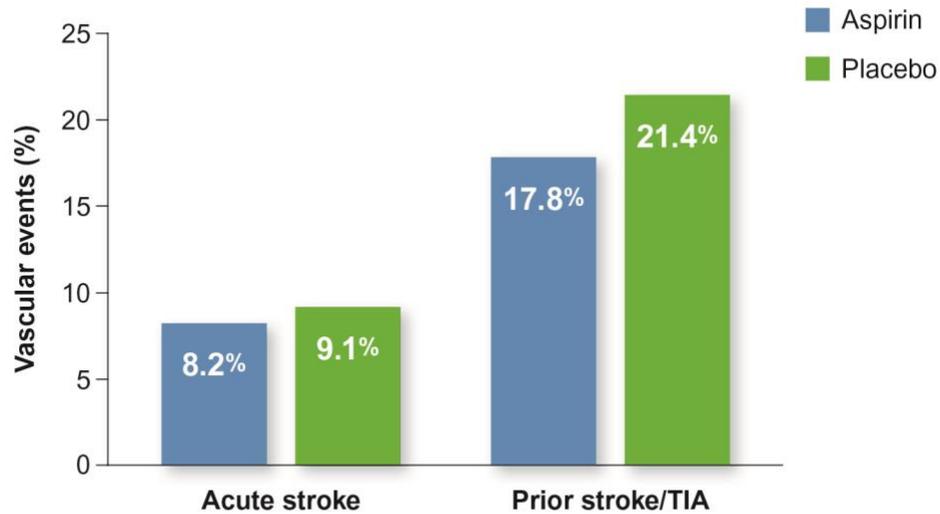
## Antiplatelets for secondary stroke prevention

The use of antiplatelet monotherapy for preventing serious vascular events, arterial occlusion, and venous thromboembolism in patients with a previous ischemic stroke has been well-established for decades.<sup>54-56</sup> More recent trials have evaluated both monotherapy options and DAPT for secondary stroke prevention.

### Monotherapy

Aspirin for the acute management of ischemic stroke was evaluated in a meta-analysis of 7 trials with almost 41,000 patients, which found that aspirin reduced the rate of vascular events compared to control (8.2% vs. 9.1%, for a relative reduction of 11%, P<0.0001).<sup>34</sup> An analysis in the same study of 21 trials including approximately 23,000 patients with a history of stroke or TIA found similarly reduced risk with aspirin (17.8% vs. 21.4%, P<0.0001). Overall, no significant differences in the rate of major extracranial bleeds was observed across comparisons, although there were too few fatal and non-fatal bleed in any particular category to estimate absolute risks directly.

Figure 11: Aspirin monotherapy for acute and prior stroke<sup>33</sup>



The comparative value of clopidogrel vs. aspirin for patients with recent ischemic stroke was evaluated in the **CAPRIE trial** (n=19,185).<sup>57</sup> With a mean follow-up of 1.9 years, there was no significant difference in the rate of ischemic stroke, MI, or vascular death (7.15% in the clopidogrel group vs. 7.71% in the aspirin group). There was no significant difference between groups in the rate of any bleeding disorder (9.27% with clopidogrel vs. 9.28% with aspirin), although the rate of GI bleeding was higher in the aspirin group (1.99% with clopidogrel vs. 2.66% with aspirin, P<0.05).

The **SOCRATES trial** randomized 13,199 patients with acute non-severe ischemic stroke or high-risk TIA to ticagrelor 90 mg/twice daily vs. aspirin 100 mg/day with 90-day follow-up.<sup>58</sup> No significant differences were found for either the primary endpoint rate of stroke, MI, or death (6.7% with ticagrelor vs. 7.5% with aspirin, P=0.07) or in the rate of major bleeding (0.5% vs. 0.6%, P=0.45).

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**BOTTOM LINE:** Aspirin is superior to placebo for reducing risk of new vascular events in patients with either acute or prior stroke, and clopidogrel and ticagrelor are comparable to aspirin for stroke risk reduction. Overall, bleeding risks between antiplatelet agents for secondary stroke prevention appear roughly equivalent, although aspirin may be associated with a slightly higher risk of GI bleeding than other agents in this population.

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## DAPT

DAPT for the immediate post-stroke period (i.e., <21 days after the stroke) is handled during the acute hospitalization period, and the 2018 AHA/ASA guidelines suggest that in the immediate post-stroke period the benefits of combined aspirin/clopidogrel generally outweigh the increased risk of bleeding.<sup>59</sup>

The **POINT trial** randomized 4,881 patients with minor stroke or TIA to clopidogrel 75 mg/day plus aspirin 325 mg/day vs. aspirin alone with follow-up 90 days post-event.<sup>60</sup> The combination was significantly better for reducing the primary outcome of stroke, MI, or death from ischemic vascular disease (5% vs.

6.5%, P=0.02), although the risk of bleeding was also modestly higher (0.9% vs. 0.4%, P=0.02). The **POINT** findings and main conclusions were replicated in a Chinese population through the **CHANCE** trial, which evaluated 5,170 patients within 24 hours of a minor ischemic stroke or high-risk TIA.<sup>61</sup>

Other trials have compared DAPT regimens to either monotherapy or alternative DAPT regimens for secondary stroke prevention for durations beyond the immediate post-stroke period. Three trials used a clopidogrel/aspirin combination, and two used an aspirin/dipyridamole combination. The three trials of clopidogrel/aspirin found no significant differences in CV events with the combination, although all three showed modestly increased rates of bleeding. The two trials evaluating aspirin/dipyridamole showed mixed results for efficacy (reduced rates of CV events in one, but not the other) and non-significant increases in bleeding risk (Table 4). (Note: dipyridamole ER/aspirin may cause headaches, which may not be tolerated by some patients.)<sup>62</sup>

**Table 4: Major trials of DAPT for secondary stroke prevention beyond immediate post-stroke period<sup>62-66</sup>**

	<b>MATCH</b>	<b>CHARISMA</b>	<b>SPS3</b>	<b>ESPIRIT</b>	<b>PRoFESS</b>
Year published	2004	2006	2012	2006	2008
Study regimen	Clopidogrel + aspirin	Clopidogrel + aspirin	Clopidogrel + aspirin	Dipyridamole ER + aspirin	Dipyridamole ER + aspirin
Comparator	Clopidogrel	Aspirin	Aspirin	Aspirin	Clopidogrel
Number of patients enrolled	7,599	15,603	3,020	2,739	20,332
Mean age	66	64	63	63	66
Follow-up	1.5 years	2.3 years	3.4 years	3.5 years	2.5 years
<b>CV Events</b>					
Absolute difference	16% vs 17%	6.8% vs. 7.3%	3.4%/year vs. 3.1%/year	11% vs. 14%	13% vs. 13%
Relative difference (95% CI)	RRR 6.4% (-4.6 to 16.3)	RR 0.93 (0.83-1.05)	HR 0.89 (0.72-1.11)	<b>HR 0.78 (0.63-0.97)</b>	HR 0.99 (0.92-1.07)
<b>Major bleeding</b>					
Absolute difference	2 vs. 1%	2.1% vs. 1.3%	1.1%/year vs. 2%/year	2.6% vs. 3.9%	4.1% vs. 3.6%
Relative difference (95% CI)	<b>Not reported</b>	<b>RR 1.62 (1.27-2.08)</b>	<b>HR 1.97 (1.42-2.71)</b>	HR 0.67 (0.44-1.03)	HR 1.15 (1.00-1.32)

**BOTTOM LINE:** Low-dose (i.e., 81 mg/day) aspirin monotherapy is recommended for patients with a more remote history of stroke (i.e., >21 days). In patients with acute stroke, clopidogrel plus aspirin reduces ischemic events in the short term and may continue to provide benefit for up to 90 days, although with increased bleeding risk.

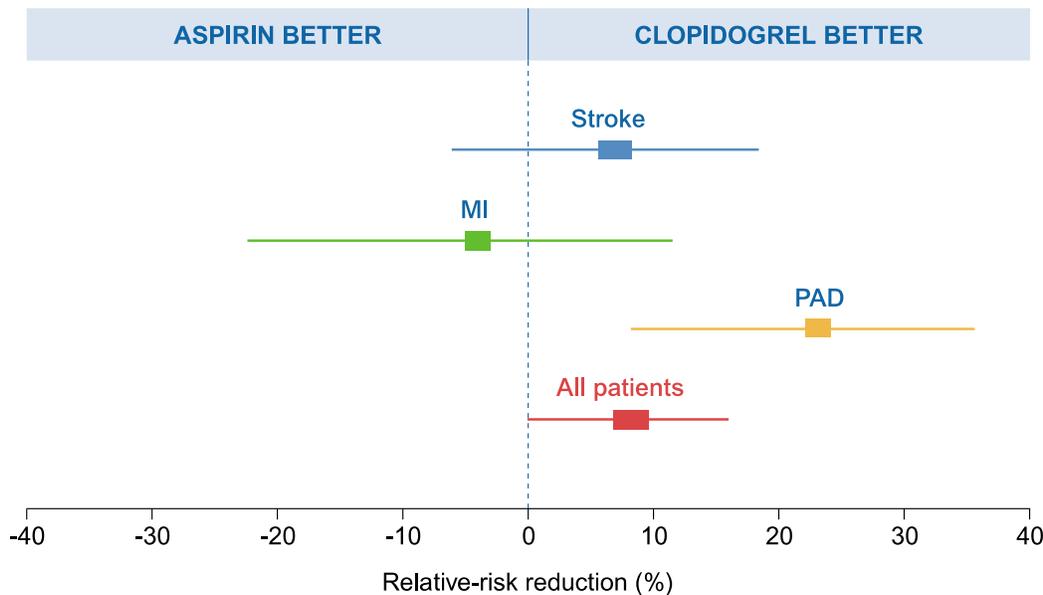
For longer-term prevention, aspirin/clopidogrel should be stopped, with aspirin or clopidogrel monotherapy continued. The combination of aspirin and dipyridamole ER appears more effective than aspirin monotherapy, and equally effective compared to clopidogrel monotherapy.

## Antiplatelets for peripheral artery disease (PAD)

The efficacy of aspirin monotherapy in patients with PAD for preventing CV events was established in the 2002 Antiplatelet Trialists' Collaboration meta-analysis of 42 trials with 9,706 patients, which showed that aspirin reduces the odds of major vascular events by 23% (standard error 8%) compared to control.<sup>34</sup>

The **Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial** evaluated clopidogrel 75 mg/day vs. aspirin (325 mg/day) in a pre-specified subgroup of 6,452 patients with PAD. The total CVD event rate was 3.71% per year in the clopidogrel group vs. 4.86% in the aspirin group, for a relative risk reduction of 23.8% (P=0.0028) (Figure 12).<sup>57</sup> No significant differences were observed in rates of intracranial bleeding between groups, but the rate of any reported GI bleeding was significantly higher in the aspirin group vs. the clopidogrel group (2.7% vs. 2%, P<0.05). (The AHA/ACC currently recommends clopidogrel for PAD management in patients unable to take aspirin due to allergy or GI intolerance.<sup>67</sup>)

Figure 12: Relative reductions in CV events in the CAPRIE trial by subgroup<sup>57</sup>



The use of DAPT (clopidogrel plus aspirin vs. aspirin alone) in patients with PAD was also assessed in the **CHARISMA trial**.<sup>64</sup> No significant difference was observed in the rate of the primary endpoint (a composite of MI, stroke, and CV death): 7.6% in the dual group vs. 8.9% in the aspirin alone group (P=0.183). The lack of benefit from dual therapy was confirmed in a post-hoc subgroup analysis restricted to patients with symptomatic PAD.<sup>68</sup> Current evidence is insufficient for making recommendations about the benefits of antiplatelets in the context of PAD treatment with stents.<sup>69-71</sup>

Vorapaxar (Zontivity) is an oral antagonist of protease-activated receptor 1 and is FDA-approved for reduction of thrombotic events in patients with a history of MI or PAD who do not have a history of stroke or TIA.<sup>72</sup> Approval was based on two trials **TRA 2°P-TIMI 50**<sup>73</sup> (n = 26,499) and **TRACER**<sup>74</sup> (n=12,944), both of which evaluated vorapaxar as a third antithrombotic agent in combination with clopidogrel/ aspirin. Both trials were terminated early due to significantly higher rates of major bleeding in the vorapaxar groups.<sup>72</sup>

In a secondary analysis from TRA 2°P-TIMI 50, patients with PAD who received vorapaxar had decreased hospitalizations for acute limb ischemia (HR 0.58; 95% CI: 0.39-0.86) and decreased need for peripheral artery revascularization (HR 0.84; 95% CI: 0.73-0.97).<sup>75</sup>

The American College of Cardiology, in a report on vorapaxar, notes that no trials have yet evaluated vorapaxar with the more potent antiplatelets prasugrel and ticagrelor, and that the use of vorapaxar is “challenging” due to the heightened risk of bleeding.<sup>72</sup>

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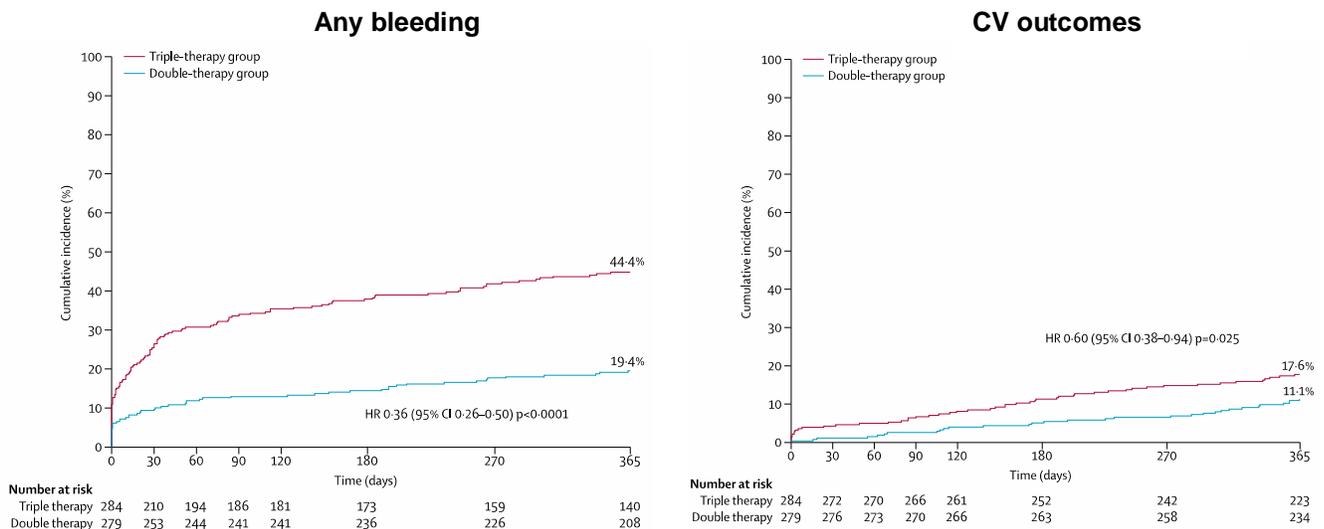
**BOTTOM LINE: Clopidogrel monotherapy for PAD is more effective than aspirin monotherapy. DAPT with aspirin-clopidogrel is not superior to aspirin alone, and causes more bleeding.**

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## Antithrombotic therapy combining an antiplatelet with an anticoagulant

The first randomized trial evaluating the addition of a third agent to DAPT was the **What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial**. This open-label trial randomized 573 patients with atrial fibrillation (AF) to dual therapy with warfarin and clopidogrel (75 mg daily) or to triple therapy with warfarin, clopidogrel 75 mg/day and aspirin 80 mg/day.<sup>76</sup> After one year follow-up, triple therapy was associated with an increased risk of bleeding events (44.4% vs. 19.4%, P<0.0001). The study found that the rates of thrombotic and thromboembolic events were similar in both arms.

**Figure 13: Bleeding and CV outcomes with double vs. triple therapy in WOEST trial<sup>76</sup>**



These results were confirmed in the 2019 **AUGUSTUS trial**, which included 4,614 patients (71% male) with AF who had an ASC or PCI.<sup>77</sup> Patients were randomized to one of 4 trial arms in which all patients received a P2Y12 inhibitor plus:

- apixaban plus aspirin
- apixaban plus placebo
- vitamin K antagonist plus aspirin
- vitamin K antagonist plus placebo

After six-month follow-up patients treated with aspirin had an increased risk of major or clinically relevant bleeding compared to those in the placebo groups (HR 1.89; 95% CI: 1.59-2.24), but the incidence of ischemic events was not significantly lower among patients who did not receive aspirin. This suggests that in patients requiring anticoagulation just adding a P2Y12 inhibitor, without additional aspirin, is sufficient to prevent ischemic events and reduce the risk of bleeding.<sup>77</sup> Patients receiving apixaban had lower incidence of major bleeding, hospitalization, and death compared to patients in the vitamin K antagonist group.

In light of these trials, triple antithrombotic therapy (i.e., an anticoagulant plus DAPT) in patients with AF and ACS or PCI is uncommon. Triple therapy will often be started for a short period of time after an initial event. For example, in the AUGUSTUS trial, the median time from ACS and/or stent placement to randomization was 6 days, during which time all patients were treated with triple therapy. In the relatively rare cases where a patient might benefit from prolonged triple therapy, the 2016 ACC/AHA guidelines recommend the following:<sup>35</sup>

- Assess ischemic risk using a validated predictor tool (e.g., CHA<sub>2</sub>DS<sub>2</sub>-VASc).
- Keep triple therapy duration as short as possible.
- Dual therapy only (oral anticoagulant + clopidogrel) may be considered in select patients.
- Consider a target INR of 2.0-2.5 when warfarin is used.
- Clopidogrel is the P2Y12 inhibitor of choice.
- Use low-dose aspirin.
- PPIs should be used in patients at increased risk of GI bleeding.

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**BOTTOM LINE:** In patients requiring anticoagulation therapy (e.g., those with AF, ACS, or following PCI) adding a single P2Y12 inhibitor appears to confer similar protection from secondary CV events as adding a DAPT regimen to the anticoagulant and reduces bleeding risk.

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## Associated topics

### Aspirin and clopidogrel resistance

Platelet-dependent thrombosis can occur despite treatment with aspirin and clopidogrel.<sup>78,79</sup> These phenomena have been termed “aspirin resistance” and “clopidogrel resistance,” and may result from a variety of causes including genetic factors, poor adherence, inadequate dosage, and coexisting medical conditions.<sup>80</sup>

Clopidogrel is a pro-drug that requires activation by specific hepatic cytochrome P-450 (CYP) enzymes. Carriers of the specific alleles of CYP2C19 and CYP3A4 have a diminished response to the effects of clopidogrel, although there are conflicting data regarding the impact of genotype on the response to clopidogrel and clinical outcomes.<sup>80-86</sup> Several analyses have demonstrated that the presence of at least one reduced function allele (particularly for CYP2C19) is associated with reduced formation of the active drug metabolite, less platelet inhibition, and less protection from adverse ischemic events, particularly stent thrombosis.

The **ELEVATE-TIMI 56** trial showed that in patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in patients heterozygous for the reduced function mutation in the CYP2C19\*2 gene achieved levels of platelet reactivity similar to that seen with the standard 75 mg dose in noncarriers of that mutation.<sup>87</sup> In contrast, for patients homozygous for CYP2C19\*2, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition.

Other data from randomized trials and observational studies, however, suggest that changes in platelet reactivity or other physiological parameters may not translate into clinically important associations between genotype and CV outcomes.<sup>87-89</sup> For example, a systematic review and meta-analysis of genotype, clopidogrel metabolism, platelet function, and cardiovascular events encompassing 32 studies and 42,016 patients concluded that while there was an association between genotype and the pharmacodynamics of clopidogrel, there was no significant association between genotype and the occurrence of cardiovascular events in patients taking the drug.<sup>90</sup>

In 2010, the FDA issued a boxed warning recommending that practitioners consider genotype testing prior to prescribing clopidogrel. However, the AHA and ACC have not recommended routine testing given the insufficient and conflicting evidence.<sup>91</sup> Ongoing trials (e.g., the NHLBI-supported **TAILOR-PCI** trial) are trying to answer the question of whether genotype testing is helpful in patients who require DAPT for ACS.<sup>92</sup>

## Clopidogrel and PPIs

Pharmacokinetic/pharmacodynamic studies, as well as observational and retrospective data, have suggested diminished antiplatelet efficacy and increased rates of adverse clinical outcomes in patients prescribed clopidogrel and a PPI. In 2009, the FDA issued a patient advisory and updated the patient safety information on the package insert for clopidogrel about this interaction, warning that co-administration of omeprazole reduces the antiplatelet inhibition of clopidogrel by approximately 50%. However, other studies have not borne out this concern.<sup>93</sup> Data from the **Clopidogrel and the Optimization of Gastrointestinal Events (COGENT)** trial, the first randomized clinical study evaluating the postulated interaction, found no difference in the rate of CV death, MI, revascularization, or stroke in over 3,700 patients with ACS or recent PCI randomized to receive clopidogrel and placebo vs. clopidogrel with omeprazole (5.7% vs. 4.9%, P=0.96).<sup>94</sup>

## Aspirin and cancer

Although some early observational studies suggested an association between aspirin use and reduced risk of cancer, particularly colorectal cancer,<sup>95</sup> newer trials have not supported this hypothesis. As noted earlier, the **ASPREE trial** of low-dose aspirin vs. placebo in community-dwelling older adults actually found an *increased risk* of cancer-related death with aspirin (HR 1.31; 95% CI: 1.10-1.56).<sup>18</sup>

The **ASCEND trial** found no significant differences in the rate of GI cancer risk between the aspirin and placebo groups after 7.4 years of follow-up (RR 0.99; 95% CI: 0.80-1.24).<sup>19</sup>

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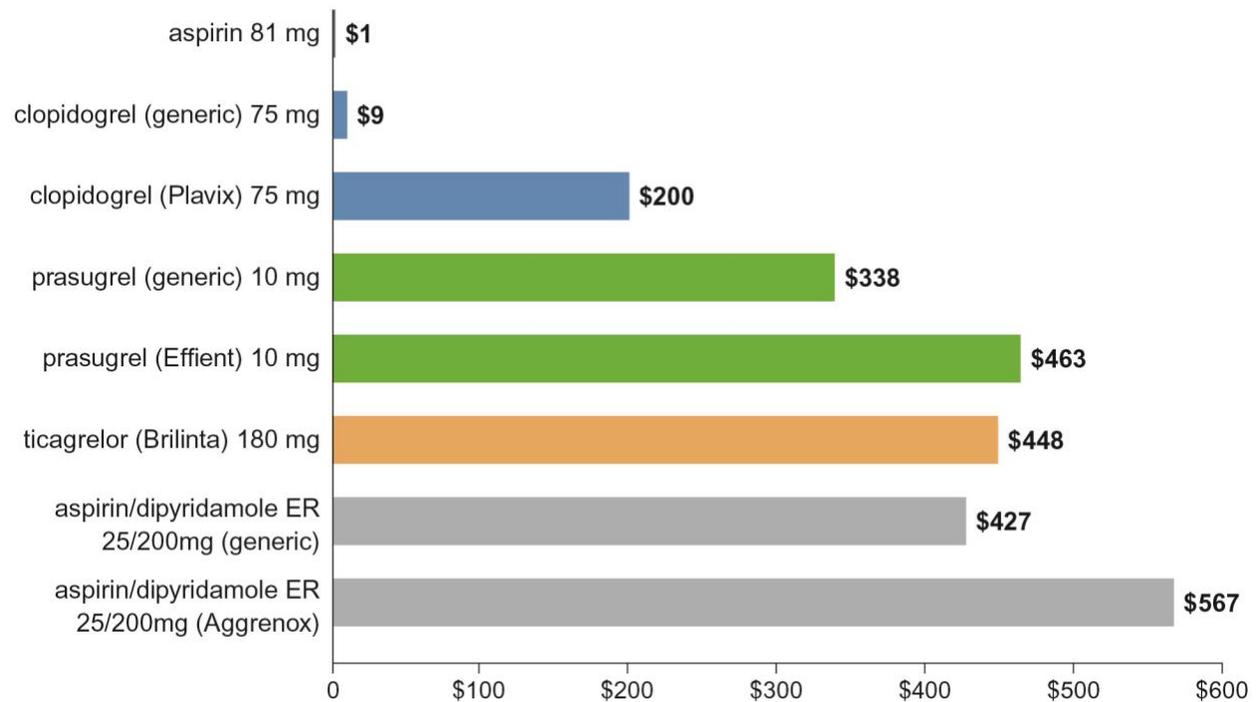
**BOTTOM LINE:** Although older studies suggested concerns about diminished antiplatelet efficacy due to genetic mutations in key liver enzymes and with the combination of clopidogrel and PPIs, more recent evidence does not support these fears. Older studies suggesting a protective effect of aspirin on colon cancer risk have not been supported by newer trials.

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## Costs

While the literature provides relatively clear evidence about the choice of antiplatelet drugs in various clinical situations, there are substantial price differences between these agents. These differences are particularly relevant when choosing between agents that are probably equally effective or safe.

**Figure 14: Cost of 30-day supply of antiplatelet medications**



Prices from goodrx.com, June 2019. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All prices shown are for generics when available, unless otherwise noted. These prices are a guide; patient costs are subject to copays, rebates, and other variables.

## Putting it all together

This evidence document has summarized the latest evidence for the use of antiplatelet agents in both primary and secondary prevention of cardiovascular diseases. The use of these agents must always be tailored to each patient, taking into account the many significant variables involved, including the patient's CV history and risk factors, bleeding risk, age, comorbidities, and the efficacy and safety profiles of the agents being considered as treatment. The following recommendations are based on this evidence review:

- Aspirin is no longer recommended for the primary prevention of cardiovascular disease in patients with low risk or who are over 70 years of age.
- There is good evidence for DAPT (e.g., clopidogrel plus aspirin) following acute coronary syndromes or elective PCI.
- The duration of DAPT depends on indication and patient characteristics, but is not life-long.
- Aspirin should be recommended indefinitely for secondary prevention of cardiovascular events.
- DAPT with anticoagulation should be of minimal duration, continuing the anticoagulant and P2Y12 inhibitor as needed.
- Immediately following stroke (i.e., <21 days), clopidogrel plus aspirin reduces ischemic risk in the short term.
- Clopidogrel alone or aspirin plus dipyridamole are best for long-term prevention of cardiovascular events after stroke.
- Clopidogrel is more effective than aspirin in preventing cardiovascular events in PAD.

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## About this publication

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**These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.**

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