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## Drug Class Update: Platelet Inhibitors

**Date of Review:** December 2024

**Date of Last Review:** June 2021

**Dates of Literature Search:** 04/01/2021 - 08/14/2024

### Current Status of PDL Class:

See **Appendix 2**.

### Purpose for Class Update:

The purpose of this update is to review the evidence on platelet inhibitors, also commonly called antiplatelets, since the last review done in 2021 and to ensure the preferred drug list (PDL) aligns with current evidence.

### Plain Language Summary:

- This review looks at a class of drugs called platelet inhibitors, also called antiplatelets, which makes the blood thin so it doesn't clot.
- Antiplatelets are used for stroke prevention, heart problems, preventing blood clots and other conditions.
- In this review there is new evidence for the treatment of preeclampsia (a condition in people that are pregnant that causes high blood pressure and can lead to problems with the kidneys, liver, or other organs), stroke, COVID-19, heart disease, chronic kidney disease and peripheral artery disease (condition where the arteries that carry blood to your legs, arms, and other parts of your body get narrowed or blocked).
- The use of antiplatelets in people with chronic kidney disease may help to reduce the risk of heart attacks but also increases the risk of bleeding.
- The risk of stroke is reduced with aspirin therapy in people who have had a stroke.
- Guidelines do not recommend aspirin for most people to prevent heart disease if there is no history of heart disease.
- Antiplatelets are recommended by the guidelines for people with peripheral arterial disease that have symptoms to improve the distance they are able to walk and decrease symptoms.
- In people who are pregnant and are at risk of developing preeclampsia, aspirin should be used to decrease the risk of preeclampsia and dying during pregnancy.
- There was no evidence that the use of antiplatelets help reduce blood clots in people infected with COVID-19.
- The Drug Use and Management Group recommends that ticagrelor be available without a prior authorization. All other antiplatelets are already available without prior authorization.

### Research Questions:

1. Is there any new high-quality comparative evidence on the effectiveness of platelet inhibitors when used for stroke prevention, cardiovascular syndromes, prophylaxis for venous thromboembolism (VTE) or other indications?

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2. Is there new high-quality comparative evidence on the harms of platelet inhibitors when used for stroke prevention, cardiovascular syndromes, prophylaxis for VTE or other indications?
3. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which a specific platelet inhibitor is more effective or associated with fewer harms than another platelet inhibitor?

### Conclusions:

- New literature included in this guideline are 9 systematic reviews and meta-analyses, 8 guidelines, 3 guidelines for clinical context, and 3 updated safety alerts.
- Chronic Kidney Disease:
  - A Cochrane review evaluated the use of antiplatelets for people with chronic kidney disease (CKD) and the use of antiplatelets in patients with CKD may reduce the risk of myocardial infarction (MI) and increase the risk of major bleeding (moderate-quality evidence for both).<sup>1</sup>
- COVID-19:
  - There is moderate-quality evidence that thrombotic events may be decreased in those with COVID-19 treated with antiplatelets compared to placebo; however, results were not statistically significant (relative risk [RR] 0.90; 95% confidence interval [CI], 0.80 to 1.02) (follow-up up to 28 days).<sup>2</sup> There was no benefit of antiplatelet therapies in patients with mild COVID-19, based on low-quality evidence.
- Stroke:
  - The efficacy and harms of antithrombotic treatment, including antiplatelets, after intracerebral hemorrhage was reviewed by Cochrane authors. There was moderate-quality evidence that the use of antiplatelets did not statistically significantly improve outcomes in intracerebral hemorrhage (e.g., major adverse cardiovascular events [MACE], death, major occlusive vascular events).<sup>3</sup> Minor and major bleeding events were not reported in the trials.
  - A Cochrane review found that aspirin used after an acute ischemic stroke (IS) decreased death and dependency (disabling intracranial hemorrhage) and risk of recurrent IS.<sup>4</sup>
  - Guidelines from the American Heart Association (AHA)/American Stroke Association (ASA) recommend the use of antiplatelets, predominately aspirin (81 to 325 mg/day), in certain patients for the secondary prevention of stroke in patients with stroke and transient ischemic attack (TIA).<sup>5</sup>
- Cardiovascular Disease:
  - The National Institute for Health and Care Excellence (NICE) does not routinely recommend the use of aspirin for primary prevention of cardiovascular disease (CVD).<sup>6</sup>
  - In patients with hypertension, Cochrane found low-quality evidence that aspirin reduced non-fatal cardiovascular (CV) events more than placebo (odds ratio [OR] 0.63; 95% CI, 0.45 to 0.87; low-quality evidence) and all CV events (OR 0.86; 95% CI, 0.77 to 0.96; low-quality evidence) but increased the risk of major bleeding (OR 1.77; 95% CI, 1.34 to 2.32; high-quality evidence).<sup>7</sup>
  - The United States (US) Preventative Services Task Force (USPSTF) performed a systematic review and meta-analysis evaluating aspirin use to prevent cardiovascular disease (CVD) and colorectal cancer (CRC).<sup>8</sup> The use of low-dose aspirin for primary CVD prevention was associated with a reduction in odds of experiencing a CVD event (e.g., major CVD event, total MI, ischemic stroke). No reduction in mortality or all-cause mortality was demonstrated. The effects of aspirin on CRC risk were inconclusive as the evidence was limited and primarily from long-term observational data. The risk of major bleeding was increased significantly with aspirin use (OR 1.44; 95% CI, 1.32 to 1.57).<sup>8</sup> Evidence from this systematic review and meta-analysis provided updated recommendations for aspirin use in people at risk for CVD. Based on moderate-quality evidence, USPSTF recommends that adults ages 40-59 years who are at a 10% or greater risk of CVD should consider low-dose aspirin for primary CVD prevention if not at an

increased risk for bleeding.<sup>9</sup> In patients 60 years and older, the USPSTF recommends against initiating aspirin for primary CVD prevention, based on moderate evidence.<sup>9</sup>

- A systematic review and meta-analysis found moderate quality evidence that the use of an abbreviated dual antiplatelet therapy (DAPT) regimen (4-6 weeks) compared to prolonged treatment (three months or greater) in patients undergoing percutaneous intervention (PCI) with an additional indication for anticoagulation demonstrated a reduced incidence of major bleeding and clinically relevant non-major bleeding without an increase in ischemic events.<sup>10</sup>
- The use of antiplatelets in people with chronic coronary disease (CCD) was outlined in a 2023 guideline by the American Heart Association (AHA)/American College of Cardiology (ACC) Joint Committee. The strongest recommendations with the highest level of evidence include the use of aspirin for secondary prevention in patients with CCD and not taking oral anticoagulant (OAC) for another indication and for DAPT in patients with CCD treated with PCI.<sup>11</sup>
- A 2021 update published by ACC/AHA/ Society of Cardiovascular Angiography and Interventions (SCAI) on the management of coronary artery revascularization recommends the use of antiplatelets in patient undergoing PCI and coronary artery bypass graft (CABG).<sup>12</sup> Ticagrelor or prasugrel is recommended in preference to clopidogrel in patients with acute coronary syndrome (ACS) undergoing PCI to reduce ischemic events, including stent thrombosis (moderate recommendation based on randomized controlled trials [RCTs]).
- Peripheral Arterial Disease
  - A 2024 American College of Cardiology (ACC), et al guideline recommends antiplatelets as a mainstay of therapy for peripheral arterial disease (PAD). The use of aspirin or clopidogrel have the most evidence for use in patients with symptomatic PAD.<sup>13</sup>
  - The Canadian Cardiovascular Society (CCS) guidance on the use of antiplatelets for PAD strongly recommends the use of anticoagulants (e.g., rivaroxaban) and aspirin in people with symptomatic lower extremity PAD at high risk (high-quality evidence).<sup>14</sup> Additional recommendations, including use of other antiplatelets, are provided for people at high risk of bleeding and with complications of PAD.
  - A Cochrane review evaluated the use of cilostazol in patients with intermittent claudication and found low-quality evidence that it was more effective than placebo at increasing the initial claudication distance (e.g., maximum distance walked on a treadmill) (mean difference [MD] 26.49; 95% CI, 18.93 to 34.05) but was associated with an increase in headaches (OR 2.83; 95% CI, 2.26 to 3.55).<sup>15</sup>
- Preeclampsia
  - The USPSTF evaluated the use of aspirin in preventing preeclampsia which demonstrated a 21% reduction in the risk of perinatal mortality, compared to placebo, (RR 0.79; 95% CI, 0.66 to 0.96).<sup>16</sup> The risk of preeclampsia was reduced with aspirin (RR 0.85; 95% CI, 0.75 to 0.95). The use of aspirin was not associated with a significant increase in risk of postpartum hemorrhage. Based on the systematic review and meta-analysis the USPSTF recommends that pregnant persons at high-risk of preeclampsia should use aspirin (81 mg/day) as preventative medication after 12 weeks gestation (moderate quality of evidence).<sup>17</sup>

### **Recommendations:**

- Recommend changing ticagrelor to preferred on the PDL due to evidence of superior ticagrelor efficacy compared to other antiplatelets for some indications.
- Retire Platelet Inhibitors PA and default to general non-preferred product PA criteria.

### Summary of Prior Reviews and Current Policy:

- In June of 2021 the PA criteria for platelet inhibitors was updated to include the recently expanded indication for ticagrelor to reduce the risk of first MI or stroke in patients with coronary artery disease (CAD) at high risk for such event and to reduce the risk of stroke in patients with acute ischemic stroke (National Institutes of Health [NIH] Stroke Scale score of 5 or less) or high-risk transient ischemic attack (TIA) for ticagrelor.
- There were no changes made to the PDL as a result of the antiplatelet drug class update in June 2021.
- Additional evidence was presented for prasugrel and ticagrelor that demonstrated a reduction in ischemic events compared to clopidogrel when used in patients with ACS but not in stroke prevention.
- Prasugrel and ticagrelor provide better platelet inhibition with less intersubject variability compared to clopidogrel. Prasugrel is contraindicated in patients with prior history of TIA or stroke.

### Current Policy:

- Aspirin, aspirin/dipyridamole, cilostazol, clopidogrel, dipyridamole and prasugrel are preferred therapies. Non-preferred therapies require PA to ensure platelet inhibitors are used for an approved diagnosis and patients do not have contraindications to therapy.
- In quarter 2 of 2024 there were over 1000 claims for antiplatelets. Utilization for aspirin accounted for 90% of claims and 10% of claims were for clopidogrel. Both therapies are preferred therapies. The overall spend for the antiplatelet class is not a significant source of resource allotment for the Oregon Health Authority (OHA).

### Background:

The platelet inhibitor class is comprised of therapies that exert their effect via different mechanisms of action. Aspirin is the most commonly used antiplatelet medication. Aspirin inhibits prostaglandin synthesis and platelet aggregation. The P2Y<sub>12</sub> inhibitors (e.g., clopidogrel, prasugrel, ticagrelor, ticlopidine) irreversibly block receptors which prevent adenosine diphosphate from activating platelets. Ticlopidine is not commonly used due to risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia, and is no longer available in the United States (US).<sup>18</sup> Less commonly used antiplatelets are cilostazol and dipyridamole. Cilostazol inhibits phosphodiesterase activity and subsequently suppresses cyclic adenosine monophosphate (cAMP) degradation leading to prevention of platelet aggregation, while dipyridamole exerts its effect by inhibiting adenosine uptake.

Platelet inhibitors are used for a several indications, including ACS (e.g., unstable angina, ST- elevation myocardial infarction [STEMI], and non-ST- elevation myocardial infarction [NSTEMI]), PAD, stroke prevention, and less commonly as VTE prophylaxis. Prasugrel is contraindicated in patients with a history of stroke, TIA or intracranial hemorrhage (ICH). The FDA approved indications for this medication class are presented in **Table 1**. Outcomes used to determine efficacy and safety of platelet inhibitors include mortality, MI, stroke or TIA, VTE, CV death, stent thrombosis, intermittent claudication, amputation, minor bleeding and major bleeding. Common adverse reaction associated with antiplatelets are upper gastrointestinal bleeding, ecchymosis, hematuria, epistaxis, thrombocytopenia, nasal polyps, and renal dysfunction.

**Table 1. Antiplatelet FDA Approved Indications**

Drug	Dose	Indication
Aspirin/extended-release dipyridamole <sup>19</sup>	25 mg aspirin/200 mg dipyridamole ER capsule twice daily	Reduction in stroke risk in patients who have had a TIA of the brain or completed ischemic stroke due to thrombosis

Clopidogrel <sup>20</sup>	300 mg single loading dose (if indicated) 75 mg daily (maintenance dose)	<ul style="list-style-type: none"> <li>- ACS               <ol style="list-style-type: none"> <li>1. Non-ST segment elevation ACS (unstable angina/NSTEMI). Reduction in the rate of MI and stroke</li> <li>2. STEMI. Reduction has been shown to reduce the rate of MI and stroke.</li> </ol> </li> <li>- Recent MI, recent stroke or established PAD with reduction in the risk of MI and stroke.</li> </ul>
Cilostazol <sup>21</sup>	50 – 100 mg twice daily	Reduction of symptoms of intermittent claudication as demonstrated by an increased walking distance
Dipyridamole <sup>22</sup>	75 – 100 mg four times daily	Adjunct to coumarin anticoagulants in prevention of postoperative thromboembolic complications of cardiac valve replacement
Prasugrel <sup>23</sup>	5 – 10 mg once daily (aspirin 75-325 mg daily recommended)	<ul style="list-style-type: none"> <li>- Reduction of thrombotic CV events (including stent thrombosis) in patients with ACS who are to be managed with PCI as follows:               <ol style="list-style-type: none"> <li>1. Unstable angina or NSTEMI</li> <li>2. STEMI when managed with either primary or delayed PCI</li> </ol> </li> </ul>
Ticagrelor <sup>24</sup>	60 – 90 mg twice daily (indication dependent maintenance dose)	<ul style="list-style-type: none"> <li>- Reduction in the risk of CV death, MI and stroke in patients with ACS or history of MI</li> <li>- Reduction in the risk of stent thrombosis in patients who have been stented for the treatment of ACS</li> <li>- Reduction in the risk of first MI or stroke in patients with CAD at high risk for such events</li> <li>- Reduction in the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale <math>\leq 5</math>) or high-risk TIA</li> </ul>
Abbreviations: ACS – acute coronary syndrome; CAD – coronary artery disease; CV – cardiovascular; MI – myocardial infarction; NIH – National Institutes of Health; NSTEMI - non-ST elevation MI; PAD – peripheral arterial disease; PCI – percutaneous coronary intervention; STEMI - ST-elevation MI; TIA – transient ischemic attack		

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

## **New Systematic Reviews:**

### Cochrane – Antiplatelet Agents for Chronic Kidney Disease

In 2022 Cochrane evaluated the evidence for the use of antiplatelets in people with CKD.<sup>1</sup> This systematic review updates the 2021 review. One hundred and thirteen studies were identified. Ninety studies were placebo comparisons with the remaining studies being active treatment comparisons. Patients had any form of CKD, including people not receiving renal replacement therapy, patients receiving any form of dialysis, and kidney transplant recipients. Follow-up ranged from 3 to 88.2 months.<sup>1</sup> The antiplatelets studied were: aspirin, dipyridamole, clopidogrel, ticlopidine (no longer available), pentoxifylline, vorapaxar (no longer available), cilostazol, beraprost sodium (not available in the US), ticagrelor, abciximab, tirofiban (not available in the US), eptifibatide, defibrotide, picotamide (not available in the US), sarpogrelate (not available in the US), sulfinpyrazone, sulphonamide derivative (not available in the US), and thromboxane synthetase inhibitor. Disease states included: people with CKD not yet requiring dialysis, people with hemodialysis (HD), people with peritoneal dialysis (PD), kidney transplant recipients, people with earlier stages of CKD and those treated with HD, and people with earlier stages of CKD transplant recipients and participants treated with dialysis (both HD and PD).<sup>1</sup> The risk of bias was low for sequence generation in 16 studies and allocation concealment in 22 studies. Low attrition bias found in 41 studies. Selective reporting bias was reported in 50 studies and 57 studies were at low risk of bias for other potential sources of bias.<sup>1</sup>

Patients with CKD taking antiplatelet therapies compared to those taking control were found to have less fatal or nonfatal MI based on moderate-quality of evidence (RR 0.88; 95% CI 0.79 to 0.99: 18 RCTs).<sup>1</sup> Those patients with an estimated glomerular filtration rate (eGFR) of 15-60 mL/min/1.73m<sup>2</sup> also had less fatal and nonfatal MI when treated with antiplatelet therapies compared to control with a RR 0.85 (95% CI, 0.74 to 0.99: 11 RCTs) (moderate quality of evidence). There was moderate quality of evidence for the same outcome in patients with CKD who were receiving HD that the MI risk was not statistically significantly different from placebo (RR 0.83; 95% CI, 0.49 to 1.41; 6 RCTs).<sup>1</sup> In patients with CKD the incidence of fatal or nonfatal stroke in patients treated with antiplatelets compared to control was not significantly different based on low quality evidence. Death from any cause was not statistically significant different between groups (RR 0.94; 95 % CI, 0.84 to 1.06: 35 RCTs) (low quality of evidence). There was very low-quality evidence that treatment with antiplatelets compared to control did not change the risk of CV death (RR 0.87; 95% CI 0.65 to 1.15).<sup>1</sup> There was more major bleeding in patients taking antiplatelets compared to placebo in all patients with CKD (RR 1.35; 95% CI, 1.10 to 1.65), patients with an eGFR of 15-60 mL/min/1.73m<sup>2</sup> (RR 1.51; 95% CI, 1.15 to 1.98) but not in those with HD (RR 0.90; 95% CI, 0.53 to 1.55) (moderate-quality evidence for all). Results were similar for minor bleeding in those treated with antiplatelets compared to control: all patients (RR 1.55; 95% CI, 1.27 to 1.90) and patients with an eGFR of 15-60 mL/min/1.73m<sup>2</sup> (RR 1.48; 95% CI, 1.20 to 1.83).<sup>1</sup> In patients with HD there was not a difference in minor bleeding based on low-quality evidence (RR 1.87; 95% CI, 0.65 to 5.40). Thrombosis occurring before 8 weeks in patients with HD was statistically lower in those treated with antiplatelets compared to placebo (RR 0.52; 95% CI, 0.38 to 0.70) (low-quality evidence).<sup>1</sup>

There was insufficient evidence for active treatment comparisons between antiplatelet therapies. Overall, the use of antiplatelets in patients with CKD may reduce the risk of MI and increase the risk of major bleeding compared to control. The risk of all-cause death and CV death between antiplatelets and control did not demonstrate any differences in those outcomes.

### Cochrane – Antiplatelet Agents for the Treatment of Adults with COVID-19

A 2023 Cochrane review evaluated the use of antiplatelets for thrombosis prevention, in addition to standard of care, in adult hospitalized and non-hospitalized patients with confirmed diagnosis of COVID-19.<sup>2</sup> Four studies were identified for inclusion (n=17,541). Most participants were over 50 years old and had a comorbid condition such as diabetes or hypertension. Patients were treated with a cyclooxygenase inhibitor or P2Y12 inhibitor.<sup>2</sup>

In hospitalized patients, antiplatelets compared to placebo were not found to be more effective in preventing 28-day mortality based on 3 RCTs and moderate-quality evidence (RR 0.95; 95% CI, 0.85 to 1.05).<sup>2</sup> Thrombotic events, up to 28 days follow-up if reported, may be decreased in those treated with antiplatelets

compared to placebo; however, results were not statistically significant (RR 0.90; 95% CI, 0.80 to 1.02) (moderate-quality evidence). Serious adverse events were higher in those treated with antiplatelets compared to placebo, 7 per 1000 patients treated compared to 5 per 1000 patients treated, respectively (low-quality evidence: 1 RCT).<sup>2</sup> For the outcome of major bleeding (reported 14 to 28 day of follow-up), antiplatelets are associated with higher rates compared to placebo with an OR of 1.68 (95% CI, 1.29 to 2.19) based on moderate-quality evidence (4 RCTs). There was moderate-quality evidence that there was no difference between antiplatelets and placebo for the outcomes of worsening up to day 28 (requirement for mechanical ventilation or death) or improvement up to day 28 (patient discharged).<sup>2</sup>

In non-hospitalized patients with COVID-19, antiplatelets (with standard of care) were compared to standard of care and placebo. All-cause mortality, at 45 days, was the same for both groups (OR 1.00; 95% CI, 0.45 to 2.22; 2 RCTs; low-quality of evidence).<sup>2</sup> There was very low-quality evidence that hospital admissions or death up to day 45 was not statistically significant between groups (OR 0.79; 95% CI, 0.57 to 1.10; 2 RCTs). Thrombotic events, up to day 45, was reduced with antiplatelets compared to placebo based on low-quality evidence but results were not statistically significant (OR 0.37; 95% CI, 0.09 to 1.46).<sup>2</sup> Serious adverse events were the same between groups (OR 1.0; 95% CI, 0.60 to 1.64) (low-quality evidence). There were no cases of major bleeding in either group.

Overall, in hospitalized patients with COVID-19, evidence did not find a short-term mortality benefit but there may be a decrease in thrombotic events. In non-hospitalized patients the evidence was of low quality and found no benefit of antiplatelets with mild COVID-19.

#### Cochrane – Antithrombotic Treatment after Stroke due to Intracerebral Hemorrhage

A 2023 review by Cochrane evaluated the efficacy and harms of antithrombotic treatment, including antiplatelets, after intracerebral hemorrhage.<sup>3</sup> People that experience a stroke are at increased risk of MACE, including ICH. This review updates the previous 2017 systematic review and meta-analysis in this population. Literature was searched up till October 2021. Antiplatelets and antithrombotic therapies were analyzed separately.

In patients who were trying to avoid anticoagulation, long-term antiplatelet therapy was initiated in patients surviving an ICH (one RCT).<sup>3</sup> In studies with a median follow-up of 2 years, the risk of MACE was not significantly different between no anticoagulants compared to antiplatelet therapy (RR 0.89; 95% CI, 0.64 to 1.22) (moderate-quality evidence). There was moderate-quality evidence that death between groups was also not statistically different (RR 1.08; 95% CI, 0.76 to 1.53).<sup>3</sup> Major occlusive vascular events were not different between antiplatelets and avoiding anticoagulants (RR 1.03; 95% CI, 0.68 to 1.55; moderate-quality of evidence). The risk of ICH was 86 per 1000 patients who were avoiding anticoagulants compared to 45 per 1000 in patients taking antiplatelets (RR 0.52; 95% CI, 0.27 to 1.03; moderate-quality evidence).<sup>3</sup> There was no statistically significant difference between the two groups for the outcome of functional status, measured at 1 year (type of measurement tool was not stated) (RR 0.95; 95% CI, 0.77 to 1.18; moderate-quality evidence).<sup>3</sup>

One RCT, with a median follow-up of 1.8 years, compared cilostazol (100 mg twice daily) to aspirin (100 mg daily) in patients with a history of ICH within 180 days of non-cardioembolic ischemic stroke or TIA with a history of cerebral hemorrhage.<sup>3</sup> Low quality evidence showed no difference in the risk of MACE between cilostazol and aspirin (RR 1.33; 95% CI, 0.74 to 2.40).<sup>3</sup> The risk of death was not statistically different between groups with a risk of 34 per 1000 people treated with aspirin compared to 57 per 1000 people treated with cilostazol ( $P>0.05$ ) (low-quality evidence). There was low-quality evidence that the risk of ICH was higher, but not significantly different, with patients treated with cilostazol compared to aspirin (RR 1.29; 95% CI, 0.35 to 4.69).<sup>3</sup>

There was no evidence of substantial benefit for important outcomes in patients with ICH treated with antiplatelets.

### Cochrane – Oral Antiplatelet Therapy for Acute Ischemic Stroke

A 2022 Cochrane review evaluated the safety and efficacy of oral antiplatelets within 14 days of assumed acute IS. Eleven trials were included (n= 42,226).<sup>4</sup> The majority of patients were aged 70 years and older. Aspirin 160 mg to 300 mg, ticlopidine, clopidogrel, and aspirin plus dipyridamole were antiplatelets included in the review.<sup>4</sup> Ninety-six percent of the data came from studies comparing aspirin to control (no treatment). Patients were randomized to treatment within 6 hours to 4 weeks of stroke onset. Treatment duration ranged from 5 days to 3 months. Patients were followed from 10 days to 6 months.<sup>4</sup> Main outcomes were death and dependency (disabling intracranial hemorrhage).

Moderate-quality evidence from 7 RCTs found antiplatelets reduced the incidence of death or dependence (OR 0.95; 95% CI, 0.91 to 0.99).<sup>4</sup> Results translate into 13 fewer events per 1000 people treated with antiplatelets compared to control. Small confidence intervals demonstrate confidence in the findings. For the outcome of death from any cause, there was very low-quality of evidence that antiplatelets reduced death more than placebo (OR 0.93; 95% CI, 0.87 to 0.98; 10 RCTs; 8 fewer per 1000 people treated).<sup>4</sup> There was very low-quality of evidence that the incidence of pulmonary embolism and recurrent IS/unknown stroke was reduced with antiplatelets compared to control, 1 fewer per 1000 people treated and 7 fewer per 1000 people treated, respectively.<sup>4</sup> Symptomatic intercranial hemorrhage was higher in patients treated with antiplatelets compared to control (OR 1.18; 95% CI, 0.97 to 1.44; 9 RCTs; very low-quality evidence). There was very low-quality evidence that the use of antiplatelets increased the incidence of major extracranial hemorrhage compared to control, OR 1.69 (95% CI, 1.35 to 2.11; 7 RCTs).<sup>4</sup>

Limitations for this review include over 50% of participants included in the meta-analysis were Chinese, limiting external validity to fee-for-service (FFS) patients in Oregon. Studies showed variable results for death due to any cause, reducing confidence in the findings. Results are primarily based on aspirin therapy as the was the primary medication used in the meta-analysis.

### Cochrane – Antiplatelet Agents and Anticoagulants for Hypertension

The use of antiplatelet and anticoagulation therapy in people with hypertension was the focus of a 2022 systematic review and meta-analysis by Cochrane.<sup>7</sup> Six trials, lasting at least 3 months or longer, were included. Two trials were active comparison trials and 4 were placebo controlled. Sixty-seven percent were primary prevention trials and 33% were secondary prevention. All included patients had a diagnosis of hypertension. Patients with atrial fibrillation, CHF, pre-eclampsia, or pulmonary hypertension were excluded. The dose of aspirin was 75 mg, 81 mg or 100 mg once daily.<sup>7</sup>

In placebo-controlled trials with a follow-up of a mean of 3.8 years the use of aspirin did not demonstrate a mortality benefit compared to placebo based on low-quality evidence (OR 0.97; 95% CI, 0.87 to 1.08; 3 studies).<sup>7</sup> For the outcome of CV mortality, aspirin was not statistically significantly superior to placebo in patients followed for a mean of 3.8 years (OR 0.98; 95% CI, 0.82 to 1.17; 3 studies) (low-quality evidence). There was low-quality evidence that non-fatal CV events were reduced with aspirin compared to placebo in trials lasting a mean of 4.4 years with an OR of 0.63 (95% CI, 0.45 to 0.87; 1 study) (low-quality evidence).<sup>7</sup> Major bleeding was increased in patients treated with aspirin compared to placebo with an incidence of 13.4 per 1000 patients-years compared to 7.7 per 1000 patients-years (OR 1.77; 1.34 to 2.32) (high-quality evidence).<sup>7</sup> For the outcome of all CV events, aspirin reduced the risk more than placebo (OR 0.77 to 0.96) (low-quality evidence).

In one active treatment study comparing aspirin to clopidogrel there was high-quality evidence that there was no difference in all-cause mortality (OR 1.02; 95% CI, 0.91 to 1.15) and CV mortality (OR 1.08; 95% CI, 0.94 to 1.26).<sup>7</sup> Aspirin may decrease non-fatal CV events with an OR of 1.10 (95% CI, 1.00 to 1.22; p=0.06) and the risk of all CV events (OR 1.08; 95% CI, 1.00 to 1.17; p=0.05) compared to clopidogrel; however, results were not statistically significant (high-quality evidence for both). The risk of major bleeding was increased with clopidogrel compared to aspirin (OR 1.35; 95% CI, 1.14 to 1.61) based on high-quality evidence.<sup>7</sup>

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There was low-quality evidence that there was no difference in aspirin and warfarin from one small study (n=91) in all-cause mortality in patients with unstable angina or NSTEMI in MI (OR 0.98; 95% CI, 0.06 to 16.12). Incidence of major bleeding was not different between aspirin and warfarin (low-quality evidence).

#### Cochrane – Cilostazol for Intermittent Claudication

A 2021 Cochrane systematic review and meta-analysis assessed the benefit of cilostazol in patients with stable intermittent claudication. Outcomes included b initial and absolute claudication distances (e.g., the maximum distance walked on a treadmill), mortality and vascular events.<sup>15</sup> Cilostazol is thought to cause vasodilation, inhibit platelet aggregation and have beneficial effects on decreasing triglycerides and increasing high-density lipoproteins. Sixteen studies met inclusion criteria. Cilostazol was compared to placebo and pentoxifylline. Doses of cilostazol ranged from 100 to 300 mg and pentoxifylline was dosed from 800 to 1200 mg.<sup>15</sup> All study participants had intermittent claudication secondary to peripheral vascular disease.

There was a moderate to high level of bias in the included studies, predominately due to publication bias. In 5 RCTs cilostazol was compared to placebo with 12-24 weeks of follow-up. Initial claudication distance, measured by change in meters, was higher with cilostazol compared to placebo (mean difference [MD] 26.49; 95% CI, 18.93 to 34.05) (low-quality of evidence).<sup>15</sup> Low-quality evidence found the quality of life to be improved with cilostazol compared to placebo based on 4 studies that evaluated this outcome by measurement with short-form (SF)-36. Absolute claudication distance was higher with cilostazol compared to placebo (MD 39.57; 95% CI, 21.8 to 57.33; 8 RCTs); however, evidence was of very low-quality.<sup>15</sup> One study found the same results for arterial revascularization and amputation, which was less with cilostazol compared to placebo, (OR 0.16; 95% CI, 0.01 to 4.07) and (OR 0.16; 95% CI, 0.01 to 4.07), respectively (very low-quality evidence). There was moderate quality of evidence that headache was more common with cilostazol compared to placebo, 105 per 100 people treated with placebo compared to 250 per 1000 people treated with cilostazol.<sup>15</sup> There were more CV events with cilostazol compared to placebo based on low-quality of evidence (OR 1.50; 95% CI, 0.51 to 4.47).

Cilostazol 100 mg twice daily was compared to pentoxifylline 400 mg twice daily in one RCT which demonstrated a mean difference in initial claudication distance at 24 weeks follow-up of 20.00 meters higher with cilostazol (low-quality of evidence).<sup>15</sup> Absolute claudication was higher with cilostazol compared to pentoxifylline (MD 13.43; 95% CI, 43.50 lower to 70.36 higher; p>0.05) (very low-quality of evidence). Low-quality of evidence found higher rates of headache in the cilostazol group (OR 2.20; 95% CI, 1.16 to 4.17).<sup>15</sup>

#### US Preventative Services Task Force – Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer

The UPSTF updated recommendations for the use of aspirin in 2022 in people with CVD and CRC for the use of primary CVD prevention based upon evidence identified in a systematic review.<sup>8</sup> The literature was searched from January 20214 through January 2021. Eleven RCTs were included (n=134,470). Sixty-three percent of participants were women and in overall mean age was 63 years (range: 55 to 74 years). In the 4 trials where race was reported, in which 90% of participants were White. Aspirin dosing ranged from 100 mg every other day, 75 mg daily, 81 mg daily, or 100 mg daily and was compared to placebo or no intervention.<sup>8</sup> Trial durations lasted from 3.6 years to 10.1 years. The primary outcomes were CVD events (e.g., a composite of nonfatal MI, nonfatal stroke, and CVD mortality), total MI, total stroke, total ischemic stroke, CRC incidence and CRC mortality. The risk of cancer of any type was studied in 3 of the low-dose aspirin RCTs.<sup>8</sup>

The risk of major CVD events, MI or stroke was significantly reduced with aspirin, compared to placebo, in patients treated for primary prevention OR 0.90 (95% CI, 0.85 to 0.95).<sup>8</sup> When compared to placebo, the risk of total and nonfatal MI were also reduced, (OR 0.89; 95% CI, 0.82 to 0.96) and (OR 0.88; 95% CI, 0.80 to

0.96), respectively. The incidence of stroke and ischemic stroke were significantly reduced with aspirin use (OR 0.91; 95% CI, 0.84 to 0.99) and (OR 0.82; 95% CI, 0.72 to 0.92), respectively.<sup>8</sup>

The risk of CRC was reduced with aspirin (OR 0.82; 95% CI, 0.69 to 0.98) based on evidence from 1 RCT and observational follow-up of 20 years, which is considered low-quality evidence. Observational data from 10 to 20 years of follow-up found a reduction in CRC risk with aspirin use (OR 0.63; 95% CI, 0.47 to 0.83).<sup>8</sup> Mortality due to CRC was decreased with aspirin use (OR 0.77; 95% CI, 0.61 to 0.98) based on observational data and 1 RCT with 18 years of follow-up. In trials studying shorter follow-up periods, 5-10 years, aspirin did not show a reduction in CRC (OR 1.07; 95% CI, 0.92 to 1.24). Follow-up durations from baseline to 26 years of aspirin use demonstrated no benefit of a reduced CRC risk (OR 0.87; 95% CI, 0.74 to 1.02).<sup>8</sup> The overall incidence of CRC mortality was low and studies were probably not powered to detect a difference in the effect of aspirin on mortality.

The risk of bleeding was increased with aspirin therapy compared to placebo. Total major bleeds were increased with aspirin (OR 1.44; 95% CI, 1.32 to 1.57) and major GI bleeds (OR 1.58; 95% CI, 1.38 to 1.80).<sup>8</sup> Extracranial and intracranial bleeds were increased with patients taking aspirin (OR 1.53; 95% CI, 1.39 to 1.70) and (OR 1.31; 95% CI, 1.11 to 1.54), respectively.

There was insufficient evidence to determine if specific populations (e.g., people with diabetes, gender, baseline CVD risk, race or ethnicity) received more benefits or harms from aspirin use.

#### US Preventative Task Force – Aspirin Use to Prevent Preeclampsia

The USPSTF conducted a systematic review and meta-analysis on the use of aspirin in preventing preeclampsia in those who are deemed to be at increased risk.<sup>16</sup> Literature was searched from January 2013 to May 2020. The aspirin dose used in trials ranged from 50 to 150 mg daily and all efficacy trials compared aspirin to placebo. The majority of trials initiated aspirin therapy at 11-12 weeks of gestation while 5 trials allowed initiation as late as 36-38 weeks. Eight trials stopped aspirin before delivery, as early as 34 weeks, or upon delivery.<sup>16</sup> The most common patient characteristic for trial eligibility included a history of hypertensive disorders, alone or in combination with other risk factors. The risk of preeclampsia in the trial participants ranged from 4% to 30%.<sup>16</sup> Main outcomes were diagnosis of preeclampsia, adverse pregnancy health outcomes and complications (e.g., eclampsia, perinatal mortality, preterm birth, small for gestational age and bleeding harms).

Twenty-three RCTs were included that were determined to be fair- to good-quality.<sup>16</sup> Quality was primarily downgraded due to lack of details on baseline characteristics, including risk factors for preeclampsia. Results are presented in **Table 3**. Results demonstrated that aspirin reduced the risk of perinatal mortality and preeclampsia. The risk of postpartum hemorrhage was not significantly increased with aspirin use compared to placebo.<sup>16</sup>

**Table 3. Health Outcomes with the Use of Aspirin for the Prevention of Preeclampsia<sup>16</sup>**

Outcome	Studies Analyzed	Results
Perinatal mortality	11 (n=13,860)	RR 0.79 (95% CI, 0.66 to 0.96)
Preterm birth	13 (n=13,619)	RR 0.80 (95% CI, 0.67 to 0.95)
Small for gestation age/intrauterine growth restriction	16 (n=14,385)	RR 0.82 (95% CI, 0.68 to 0.99)
Preeclampsia	16 (n=14,093)	RR 0.85 (95% CI, 0.75 to 0.95)
Postpartum hemorrhage	9 (n=23,133)	RR 1.03 (95% CI, 0.94 to 1.12)

Placental abruption	10 (n=24,970)	RR 1.15 (95% CI, 0.76 to 1.72)
Fetal intracranial bleeding	6 (n=23,719)	RR 0.90 (95% CI, 0.51 to 1.57)

### Dual Antiplatelet Therapy after PCI in Patients on Oral Anticoagulants

A systematic review and meta-analysis was performed to assess the use of DAPT in patients after PCI and with an indication for oral anticoagulation (OAC) therapy to determine optimal duration.<sup>10</sup> Randomized clinical trials were included comparing an abbreviated duration or prolonged duration (three months or greater) of DAPT. A literature search from January 2000 to September 2021 identified five trials (n=7,665) for inclusion. Patients with ACS and undergoing PCI with an indication for long-term OAC were included. Trial evaluating triple antithrombotic therapy were excluded. The mean duration of treatment of prolonged DAPT was 6 months (range: 3-12 months). The abbreviated duration DAPT lasted a maximum of 6 weeks. After discontinuation of DAPT patients were continued on a single antiplatelet agent.<sup>10</sup> The most common indication for OAC was atrial fibrillation (AF) and the mean age of participants was 72 years of age. The most common OACs were direct acting oral anticoagulants (DOACs), most often apixaban (81.5%), and vitamin K antagonists (VKAs). Clopidogrel was the most used single antiplatelet in the abbreviated duration group after DAPT discontinuation. The coprimary endpoints were major or clinically relevant non-major bleeding events. Major cardiac events (MACE) were the primary safety endpoint.

The included studies were graded as overall risk of bias as being low and no publication bias was detected.<sup>10</sup> The abbreviated DAPT regimen was associated with less clinically relevant non-major bleeding compared to prolonged duration (RR 0.69; 95% CI 0.52 to 0.91; P=0.01) and major bleeding (RR 0.70; 95% CI, 0.52 to 0.95; P=0.01).<sup>10</sup> The risk of MACE was not statistically different between the groups (RR 0.96; 95% CI, 0.70 to 1.33).

Limitations include the lack of data on type of stent implanted and heterogeneity between the included trials. In summary, abbreviated DAPT may be an alternative for patients with ACS requiring PCI who also have an additional indication for anticoagulation based on moderate quality evidence.

After review, 76 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

### **New Guidelines:**

High Quality Guidelines:

#### NICE – Cardiovascular Disease Risk Assessment and Reduction

In 2023 NICE updated guidance in 2023 on the risk assessment and reduction in patients who have CVD. Recommendations related to lifestyle changes, lipid-lowering treatment, primary prevention of CVD, and recommendations for people who have diabetes or CKD were included. Recommendations as they relate to antiplatelets will be presented.

Aspirin is not routinely recommended by NICE for primary prevention of CVD due to an increased risk of bleeding that may not outweigh the benefit of the protective effects of aspirin.<sup>6</sup> This recommendation was based on a review of the evidence completed in February 2023 that included results from the ARRIVE, ASCEND, and ASPREE trials. No recommendations regarding aspirin use for secondary prevention were provided.

## 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease

A joint guideline was published on the management of patients with lower extremity PAD that updates the 2016 guidance.<sup>13</sup> Evidence was searched from October 2020 to June 2022. Recommendations and level of evidence ratings were based on the American College of Cardiology/American Heart Association methodology. See **Appendix 1** for grading of the evidence.

Antiplatelets are commonly used in patients with PAD, who are at higher risk of MI, ischemic stroke, and vascular death.<sup>13</sup> The guidelines recommend aspirin 81 mg daily in people with PAD to prevent major adverse CV events and major limb events in patients with PAD who are not at increased risk of bleeding. The benefit of antiplatelets in people with asymptomatic PAD are less certain due to a higher risk of bleeding.<sup>13</sup> Dual antiplatelet therapy, in the absence of revascularization, is associated with an increased risk of bleeding and harms may negate the benefits.

Recommends for the use of antiplatelets in patients with PAD are the following<sup>13</sup>:

- To reduce the risk of MACE, single antiplatelet therapy is recommended in patients with symptomatic PAD (Class 1; level A).
- In patients with symptomatic PAD, aspirin (75-325 mg daily) monotherapy is recommended to reduce the risk of MACE (Class 1; level C-LD)
- In patients with symptomatic PAD, clopidogrel (75 mg daily) monotherapy is recommended to reduce the risk of MACE (Class 1; level B-R)
- To reduce the risk of MACE and major amputation and endovascular or surgical lower-extremity revascularization (MALE), low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended in patients with symptomatic PAD (Class 1; level A).
- Antiplatelet therapy is recommended after endovascular or surgical revascularization for PAD (Class 1; level B-R).
- The combination of low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended after endovascular or surgical revascularization for PAD to reduce the risk of MACE and MALE (Class I; level A).
- After endovascular revascularization for PAD, dual antiplatelet treatment with a P2Y<sub>12</sub> antagonist and low-dose aspirin is reasonable for at least 1-6 months (Class 2a; level C-LD).
- In patients requiring full-intensity anticoagulation for another indication and are not at high risk of bleeding after endovascular or surgical revascularization in patients with PAD adding single antiplatelet therapy is reasonable (Class 2a; level C-LD).
- Single antiplatelet therapy is reasonable in patients with asymptomatic PAD to reduce the risk of MACE (Class 2a; level C-EO).
- The benefits of dual antiplatelet therapy are uncertain in patients with symptomatic PAD without recent revascularization (Class 2b; level B-R).
- In patients with symptomatic PAD the benefit of vorapaxar added to existing antiplatelet therapy is uncertain (Class 2b; level B-R).
- Dual antiplatelet therapy with a P2Y<sub>12</sub> antagonist and low-dose aspirin may be reasonable for at least 1 month in patients with PAD after surgical revascularization (Class 2b; level B-R).
- In patients with PAD without another indication (e.g. atrial fibrillation), full intensity oral anticoagulation should not be used to reduce the risk of MACE and MALE (Class 3 harm; level A).

## US Preventative Services Task Force – Aspirin Use to Prevent Cardiovascular Disease Recommendation Statement

The USPSTF updated 2016 recommendations on the use of aspirin for primary CVD prevention in 2022. Recommendations were based on a systematic review and meta-analysis presented above.<sup>9</sup> Recommendations pertain to adult patients who are 40 years or older with no known CVD, symptoms or diagnosis, who did not have risk factors for bleeding (e.g., GI ulcers, recent bleeding, use of medication that may increase risk of bleeding, medical conditions known to cause bleeding). Recommendations are provided in **Table 2** below.

**Table 2. Recommendations for the Use of Aspirin for Primary Prevention to Prevent CVD<sup>9</sup>**

Population	Recommendation	Strength of Evidence	Evidence Grade
Adults ages 40-59 years with a 10% or greater 10-year CVD risk	Initiation of low-dose aspirin* use should be individualized. The net benefit of aspirin use is small. Those that are not at increased risk of bleeding and are willing to take a low-dose aspirin are more likely to benefit.	Moderate	C
Adults 60 years and older	It is not recommended to initiate low-dose* aspirin for primary CVD prevention in this age group.	Moderate	D
Key: * low-dose aspirin = 100 mg daily or less Abbreviations: CVD = cardiovascular disease			

Canadian Cardiovascular Society – Guidelines for Peripheral Arterial Disease

In 2022 the Canadian Cardiovascular Society (CCS) updated guidance for the use of antiplatelets for people with PAD.<sup>14</sup> Recommendations for diagnosing and management in this population were provided. Evidence was searched from 2016 to 2021 and graded based on the GRADE methodology. Recommendations and quality of evidence on the use of antiplatelets in PAD will be presented in Table 5.

**Table 5. Recommendations for the Use of Antiplatelets for PAD<sup>14</sup>**

Patient Population	Recommendation	Strength of Recommendation	Quality of Evidence
Asymptomatic lower extremity PAD	Routine antithrombotic treatments are not recommended for patients with isolated asymptomatic lower extremity PAD	Strong	High
Symptomatic lower extremity PAD	Treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for those who are high risk for ischemic events (e.g., high-risk comorbidities*) and/or high-risk limb presentation post peripheral revascularization, limb amputation, rest pain, ischemic ulcers and at low bleeding risk	Strong	High
	Combination treatment with rivaroxaban 2.5 mg twice daily and aspirin or single antiplatelet therapy for people at low bleeding risk in the absence of high-risk limb presentation or high-risk comorbidities	Strong	High
	Single antiplatelet therapy with either aspirin (75-325 mg) or clopidogrel (75 mg) should be considered for patients at high bleeding risk who remain eligible for antithrombotic therapy	Strong	High
Stable symptomatic lower extremity PAD	Clopidogrel (75 mg daily) is suggested for those people who single antiplatelet therapy is the optimal antithrombotic choice	Weak	Moderate
Symptomatic lower extremity PAD at high-risk for vascular events	DAPT (aspirin and clopidogrel OR aspirin and ticagrelor) for those at low bleeding risk and who have contraindications to rivaroxaban	Weak	Moderate

Stable lower extremity PAD	Full-dose anticoagulation with antiplatelet therapy for the purpose of decreasing MACE and MALE events is recommended against	Strong	High
Lower extremity PAD after endovascular revascularization	Rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) with or without short-term clopidogrel use	Strong	Moderate
Lower extremity PAD after elective open revascularization	Rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily)	Strong	High
Lower extremity PAD after elective endovascular revascularization	DAPT with aspirin (75-325 mg) and clopidogrel (75 mg) for at least 1 month for patients with lower extremity PAD in patient who are unable to receive low-dose rivaroxaban	Weak	Very low
Lower extremity PAD after elective open revascularization	VKA or single antiplatelet therapy for patients who are unable to receive low dose rivaroxaban	Weak	Very low
Lower extremity PAD after urgent or emergent revascularization	Full-dose anticoagulation in combination with single antiplatelet therapy or rivaroxaban (2.5 mg twice daily) in combination with aspirin with or without short-term use of clopidogrel or DAPT	Strong	High
Key: * Polyvascular disease, diabetes, history of heart failure, or renal insufficiency Abbreviations: DAPT = dual antiplatelet therapy; PAD = peripheral arterial disease; VKA = vitamin k antagonist			

#### NICE – Heart Valve Disease

In 2021 NICE updated guidance on the management of heart valve disease in adults.<sup>25</sup> Recommendations for the use of antiplatelets were to consider aspirin, or clopidogrel if aspirin is not tolerated, after transcatheter aortic valve implantation (TAVI). Other anticoagulation should not be offered after surgical biological valve replacement unless other indications for anticoagulation exist.

#### AHA/ACC/ACCP/ASPC/NLA/PCNA – Guideline for the Management of Patients with Chronic Coronary Disease

Management of people with CCD was outlined in a 2023 guideline by the American Heart Association/American College of Cardiology Joint Committee.<sup>11</sup> Recommendations apply to a heterogeneous conditions including: obstructive and nonobstructive CAD with or without previous MI or revascularization, ischemic heart disease diagnosed only by noninvasive testing, and chronic angina syndromes with varying underlying causes. Guidelines were based on a literature search and review that was conducted from September 2021 to May 2022.<sup>11</sup> Additional studies published through November 2022 were also considered. Recommendations were assigned a Class recommendation; Class I = strong, Class 2a = moderate, Class 2b = weak, Class 3 = moderate for no benefit, Class 3 = strong for harm. Levels of evidence were also assigned to the quality of evidence identified, ranging from Level A to Level C-EO (Appendix 1). Recommendations pertaining to antiplatelet therapy are summarized below.

Recommendations for the use of antiplatelets in patients with CCD are presented in **Table 6**. One of the main points in the updated guidance was for the use of shorter durations of dual antiplatelet therapy in many scenarios, especially if the risk of bleeding is high and the ischemic risk is low to moderate, as these short-term regimens have been proven to be safe and effective.<sup>11</sup>

**Table 6. Recommendations for Antiplatelet Use in Patients with Chronic Coronary Disease<sup>11</sup>**

Recommendations	Class of Recommendation	Level of Evidence
<b>Antiplatelet Therapy without OACs</b>		
Low-dose aspirin 81 mg (75-100 mg) is recommended to reduce atherosclerotic events in patients with CCD and no indication for OAC	1	A
DAPT with aspirin and clopidogrel for 6 months post PCI followed by SAPT is indicated for the reduction in MACE events and bleeding events in patients with CCD treated with PCI	1	A
To reduce bleeding risk, select patients with CCD treated with PCI and DES who have completed 1-3 months of DAPT the use of a single P2Y <sub>12</sub> inhibitor for at least 12 months is reasonable	2a	A
In patients with CCD who have a history of MI and are at low bleeding risk, extended DAPT beyond 12 months for up to 3 years may be reasonable to reduce MACE	2b	A
The use of DAPT after CABG may be useful to reduce the incidence of saphenous vein graft occlusion in patients with CCD	2b	B-R
In patients with CCD without recent ACS or a PCI-related indication for the use of DAPT, the addition of clopidogrel to aspirin therapy is not indicated to reduce the risk of MACE	3: no benefit	A
In patients with CCD and previous stroke, TIA or ICH, prasugrel should not be used because of the risk of significant or fatal bleeding	3: harm	B-R
<b>Antiplatelet Therapy with DOACs</b>		
In patients who require OAC and have CCD who have undergone elective PCI, DAPT for 1-4 weeks followed by clopidogrel alone for 6 months should be administered in addition to DOAC	1	B-R
In patients who require OAC and have CCD who have undergone PCI, continuing aspirin in addition to clopidogrel for up to 1 month is reasonable if the patient has a high thrombotic risk and low bleeding risk	2a	B-R
In patients who require OAC and have CCD with a low atherothrombotic risk, discontinuing aspirin while continuing DOAC alone may be considered 1 year after PCI to reduce bleeding risk	2b	B-R
DOAC monotherapy may be considered in patient with CCD who require OAC if there is no acute indication for concomitant antiplatelet therapy	2b	C-LD
In patients with CCD without an indication for DOAC or DAPT who are at high risk for recurrent ischemic events but low-to-moderate risk of bleeding may add rivaroxaban 2.5 mg twice daily to aspirin 81 mg for long-term reduction in the risk of MACE	2a	B-R
GI bleeding risk can be reduced in patients with CCD on DAPT with the use of a PPI	2a	B-R
Abbreviations: ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CCD = chronic coronary disease; DAPT = dual antiplatelet therapy; DES = drug eluting stents; DOAC = direct acting oral anticoagulant; GI = gastrointestinal; ICH = intracerebral hemorrhage; MACE = major adverse cardiovascular event; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; SAPT= single antiplatelet therapy; TIA = transient ischemic attack.		

**ACC/AHA/SCAI – Management of Coronary Artery Revascularization**

Updated guidance to the 2011 version of coronary artery revascularization management was published in 2021.<sup>12</sup> The methods are the same as other AHA guidelines presented in this document and class of recommendation and levels of evidence are provided in **Appendix 1**. The literature for this update was

searched from May 2019 to September 2019. Additional relevant studies published through May 2021 were also included. Recommendations for the use of oral antiplatelets will be presented.<sup>12</sup>

Updated recommendations include the use of short duration DAPT after percutaneous revascularization in patients with stable ischemic heart disease (SIHD) to reduce the risk of bleeding. Select patients may be able to transition to P2Y<sub>12</sub> inhibitor monotherapy and discontinue aspirin after 1-3 months of DAPT.<sup>12</sup> Additional recommendations are presented in Table 7 and antiplatelet dosing in **Table 8**.

**Table 7. Recommendations for Antiplatelet Use in Patients with Coronary Artery Revascularization<sup>12</sup>**

Recommendations	Class of Recommendation	Level of Evidence
<b>Patients undergoing PCI</b>		
A loading dose of P2Y <sub>12</sub> inhibitor, followed by a daily dose is recommended in patients with ACS undergoing PCI for reduced ischemic events	1	B-R
In patients with SIHD undergoing PCI, a loading dose of clopidogrel, followed by daily dosing is recommended to reduce ischemic events	1	C-LD
Clopidogrel 300 mg as a loading dose, followed by daily dosing, is recommended to reduce ischemic events in patients undergoing PCI within 24 hours of fibrinolytic therapy	1	C-LD
Ticagrelor or prasugrel is recommended in preference to clopidogrel in patients with ACS undergoing PCI to reduce ischemic events, including stent thrombosis	2a	B-R
In patients less than 75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events	2b	B-R
Prasugrel should not be given to patients with a history of stroke or TIAs	3: harm	B-R
<b>Patients undergoing CABG</b>		
Patients already taking a daily aspirin should continue taking it until the time of surgery to reduce ischemic events in patients undergoing CABG	1	B-R
In patients referred for urgent CABG that are already taking clopidogrel or ticagrelor, these treatments should be discontinued at least 24 hours before surgery to reduce major bleeding complications	1	B-R
In patients undergoing elective CABG who receive P2Y <sub>12</sub> inhibitors before surgery, it is reasonable to discontinue clopidogrel for 5 days, ticagrelor for 3 days and prasugrel for 7 days before surgery to reduce the risk of major bleeding and blood product transfusion	2a	B-NR
Initiating aspirin in the immediate pre-operative period (less than 24 hours prior to surgery) in patients undergoing elective CABG is not recommended	3: no benefit	B-R
In patients undergoing PCI, shorter duration of DAPT (1-3 months) is reasonable in select patients with subsequent transition to P2Y <sub>12</sub> inhibitor monotherapy to reduce the risk of bleeding events	2a	A
<b>Patients after CABG</b>		
Aspirin (100-325 mg daily) should be given within 6 hours postoperatively and continued indefinitely to reduce the occurrence of SVG closure and adverse CV events in patients after CABG	1	A

DAPT with aspirin and clopidogrel for 1 year may be reasonable to improve vein graft patency compared with aspirin alone in select patients undergoing CABG	2b	B-R
Patients with AF on OAC after PCI		
In patients with AF on OAC who are undergoing PCI, it is recommended to discontinue aspirin treatment after 1-4 weeks while maintaining P2Y <sub>12</sub> inhibitors in addition to a DOAC or warfarin to reduce the risk of bleeding	1	B-R
A DOAC may be chosen in preference to warfarin in patients with AF who are undergoing PCI and treated with OAC and DAPT, or P2Y <sub>12</sub> monotherapy, to reduce the risk of bleeding	2a	B-R
Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; CABG = coronary artery bypass graft; CV – cardiovascular; DAPT = dual antiplatelet therapy; DOAC = direct acting oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; SVG = saphenous vein graft; TIA – transient ischemic attack.		

**Table 8. Antiplatelet Dosage Recommendations for Patients undergoing PCI**

Medication	Dosage
Aspirin	Loading dose of 162-325 mg orally. Maintenance dose should be 75-100 mg once daily.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg daily. Fibrinolysis: initial dose of 300 mg should be considered in patients after fibrinolytic therapy
Prasugrel	Loading dose of 60 mg orally followed by a maintenance dose of 10 mg daily. If patient has a body weight of <60 kg, a maintenance dose of 5 mg daily is recommended. In patients 75 or older a dose of 5 mg daily is recommended.
Ticagrelor	Loading dose of 180 mg daily. Maintenance dose 90 mg twice daily.

AHA/ASA – Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack

The AHA/ASA published guidance in 2021 on stroke and TIA prevention in patients that have a history of stroke.<sup>5</sup> All evidence was searched from July 2019 to February 2020, with additional RCTs published from February 2020 to June 2020. The methods are the same as other AHA guidelines presented in this document and class of recommendation and levels of evidence are provided in **Appendix 1**.<sup>5</sup> Recommendations pertaining to antiplatelet therapy will be presented.

The guideline emphasizes several points pertaining to the use of antiplatelet therapy. Antithrombotic therapy (e.g., antiplatelet or anticoagulants) is recommended for almost all patients without contraindications.<sup>5</sup> The combination of antiplatelets and anticoagulants is typically not indicated for secondary stroke prevention, with few exceptions. The use of DAPT is not recommended long term. Short term antiplatelet therapy and DAPT is recommended only in specific patients (e.g., early arriving minor stroke and high-risk TIAs or severe symptomatic intracranial stenosis).<sup>5</sup> Aggressive medical management of risk factors and short-term DAPT are preferred for patients with severe intracranial stenosis in the vascular territory of ischemic stroke or TIA.<sup>5</sup> Patients with embolic stroke of uncertain source should not be treated with anticoagulants or ticagrelor due to no evidence of benefit. Additional recommendations regarding the use of antiplatelets are outlined in **Table 9**.

**Table 9. Recommendations for the Use of Antiplatelets for Patients with Stroke and TIA<sup>5</sup>**

Recommendations	Class of Recommendation	Level of Evidence
Extracranial Carotid Stenosis		

Intensive medical therapy with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension is recommended to reduce stroke risk in patients with extracranial carotid stenosis	1	A
Extracranial Vertebral Artery Stenosis		
Intensive medical therapy with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension is recommended in patients with recently symptomatic extracranial vertebral artery stenosis to reduce stroke risk	1	A
Aortic Arch Atherosclerosis		
Patients with stroke or TIA and evidence of aortic arch atherosclerosis antiplatelet therapy is recommended to prevent recurrent stroke	1	C-LD
Patients with Small Vessel Disease		
Evidence for the use of cilostazol for secondary stroke prevention is uncertain in patients with ischemic stroke related to small vessel disease	2b	B-R
Valvular Disease		
Aspirin (75-100 mg daily) is recommended in addition to warfarin with an INR of target of 3.0 (range 2.5-3.5) in patients with a mechanical mitral valve and a history of ischemic stroke or TIA before valve replacement to reduce the risk of thrombosis and recurrent stroke or TIA	1	C-LD
In patients with ischemic stroke or TIA and native aortic nonrheumatic mitral valve disease who do not have AF or another indication for OAC, antiplatelet therapy is recommended to reduce the risk of thrombosis and recurrent stroke or TIA	1	C-EO
Long-term aspirin therapy is recommended in preference to long-term OAC to reduce the risk of thrombosis and recurrent stroke or TIA in patients with bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before valve replacement and no other indication for OAC	1	C-EO
In patients with a history of ischemic stroke and TIA and a mechanical aortic valve, anticoagulation with higher-intensity warfarin to achieve an INR of 3.0 (range, 2.5-3.0) or the addition of aspirin (75-100 mg daily) can be helpful to reduce the risk of thromboembolic events.	2a	B-NR
Cardiomyopathy		
In patients with a history of ischemic stroke and TIA with a mechanical assist device, the use of warfarin or aspirin can be beneficial to reduce the risk of recurrent stroke or TIA	2a	C-LD
The effectiveness of anticoagulation compared with antiplatelet therapy is uncertain in patients with a history of ischemic stroke and TIA in sinus rhythm with ischemic or nonischemic cardiomyopathy and reduced EF without evidence of left atrial or LV thrombus, and the choice should be individualized	2b	B-R
Patent Foramen Ovale		
Closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for patients 18-60 years of age with nonlacunar ischemic stroke of undetermined cause despite thorough evaluation and a PFO with high-risk anatomic features is recommended to prevent recurrent stroke	2a	B-R
In patients 18-60 years of age with nonlacunar ischemic stroke of undetermined cause despite thorough evaluation and a PFO without high-risk anatomic features the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established	2b	C-LD
Dissection		

Aspirin or warfarin for prevention of recurrent stroke or TIA is reasonable for patients with ischemic stroke or TIA who are <3 months after an extracranial carotid or vertebral arterial dissection	2a	B-R
<b>Antiphospholipid Syndrome</b>		
Antiplatelet therapy alone is recommended for patients with ischemic stroke or TIA who have an isolated antiphospholipid antibody but do not fulfill the criteria for antiphospholipid syndrome, to reduce the risk of recurrent stroke	1	B-NR
<b>Carotid Web</b>		
Antiplatelet therapy is recommended to prevent recurrent ischemic stroke or TIA in patients with carotid web in the distribution of ischemic stroke and TIA, without other attributable causes of stroke	1	B-NR
<b>Fibromuscular Dysplasia</b>		
In patients with FMD and a history of ischemic stroke or TIA without other known causes, treatment with antiplatelets, BP control, and lifestyle modifications are recommended to prevent further events	1	C-LD
In patients with FMD due to dissection and history of ischemic stroke or TIA with no evidence of intraluminal thrombus, it is reasonable to administer antiplatelet therapy for the prevention of future ischemic events	2a	C-EO
<b>Dolichoectasia</b>		
Antiplatelets or anticoagulation therapy is a reasonable choice in patients with vertebrobasilar dolichoectasia and a history of ischemic stroke or TIA without other attributable causes to prevent the recurrence of ischemic events	2a	C-LD
<b>Embolic Stroke of Undetermined Source</b>		
Patients with embolic stroke of undetermined source it is not recommended that treatment with ticagrelor be used to reduce the risk of secondary stroke	3: no benefit	B-NR
<b>Antithrombotic Medications in Secondary Stroke Prevention</b>		
In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is recommended in preference to OAC to reduce the risk of recurrent ischemic stroke and other CV events while minimizing the risk of bleeding	1	A
Aspirin 50 to 325 mg daily, clopidogrel 75 mg or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated for secondary stroke prevention for patients with noncardioembolic ischemic stroke or TIA	1	A
DAPT (aspirin plus clopidogrel) should be given early (e.g., with 12-24 hours of symptom onset if possible and at least within 7 days of onset) and continued for 21 to 90 days, followed by SAPT in patients with recent minor (NIHSS score of 3 or less) noncardioembolic ischemic stroke or high-risk TIA, to reduce the risk of recurrent ischemic stroke	1	A
For patients with recent (<24 hours) minor or moderate stroke (NIHSS score of 5 or less), high-risk TIA (ABCD score of 6 or more), or symptomatic intracranial or extracranial (30% or more) stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH	2b	B-R
For patients taking aspirin at the time of a noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established	2b	B-NR
The continuous use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage in patients with noncardioembolic ischemic stroke or TIA	3: harm	A

Abbreviations: AF = atrial fibrillation; BP = blood pressure; CV = cardiovascular; DAPT = dual antiplatelet therapy; EF = ejection fraction; FMD = fibromuscular dysplasia; ICH = intracerebral hemorrhage; INR = international normalized ratio; LV = left ventricle; NIHSS = National Institutes of Health Stroke Scale; OAC = oral anticoagulant therapy; PFO = patent foramen ovale; SAPT = single antiplatelet therapy; TIA = transient ischemic attack; VKA = vitamin K antagonist.

#### US Preventative Services Task Force – Aspirin Use to Prevent Preeclampsia Recommendation Statement

The USPSTF updated recommendations on the use of aspirin for preeclampsia prevention in 2021. Recommendations were based on a systematic review and meta-analysis presented above, also done in 2021.<sup>17</sup> Recommendations pertain to pregnant persons at high risk for preeclampsia who have no contraindications to low-dose aspirin. The task force determined that there is substantial net benefit of aspirin to reduce the risk of preeclampsia, preterm birth, small for gestational age/intrauterine growth restriction, and perinatal mortality in pregnant persons at high risk. Risk factors that considered high-risk are: history of preeclampsia, multifetal gestation, chronic hypertension, pregestational type 1 or type 2 diabetes, kidney disease, autoimmune disease and combination of multiple moderate-risk factors.<sup>17</sup> A patient is considered to be at moderate-risk if they have the following: nulliparity, obesity, family history of preeclampsia, black persons, lower income, age 35 years or older, personal history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, greater than 10-year pregnancy interval) or *in vitro* conception. Recommendations are presented in **Table 4**.

**Table 4. USPSTF Recommendations for the Use of Aspirin for Preeclampsia Prevention<sup>17</sup>**

Population	Recommendation	Strength of Evidence	Evidence Grade
Pregnant persons at high-risk for preeclampsia	The use of aspirin (81 mg/day) is recommended as preventative medication after 12 weeks gestation in persons who are at high risk for preeclampsia	Moderate	B
Pregnant persons at moderate risk for preeclampsia	Low-dose aspirin (81 mg/day) is recommended if the patient has 2 or more moderate-risk factors.  Low-dose aspirin may be considered if the patient has 1 moderate-risk factors.	NR	NR
Pregnant persons at low risk for preeclampsia	Low-dose aspirin is not recommended for pregnant persons with prior uncomplicated term delivery and absence of risk factors.	NR	NR
Abbreviations: NR = not reported			

#### Additional Guidelines for Clinical Context:

##### ESC – 2021 Guidelines on Cardiovascular Disease Prevention

The 2013 European Society of Cardiology (ESC) guidelines were updated in 2021 and provided new recommendation for the use of aspirin and other antiplatelets.<sup>26</sup> Recommendations were graded based on evidence. Evidence was designated a Class I, II, IIa, IIb, or III, with Class I being recommended and Class III being not recommended. The levels of evidence were graded A-C, dependent upon quality of evidence. Level of evidence A is high-quality, B is a mix of RCTs and non-randomized study types and C is consensus opinion and/or low quality sources. Lack of detail on methodology, such as literature search strategy and grading, led to down grading of the quality of the guideline.

Several new recommendations were included in the guidance. Low-dose aspirin for primary prevention *should* be considered for individuals with diabetes at high or very high CVD risk who do not have clear contraindications (level IIb recommendation).<sup>26</sup> In individuals with a high-risk of ischemic events, without high

risk of bleeding, should be considered for an addition of a second antithrombotic drug (a P2Y<sub>12</sub> inhibitor or low-dose rivaroxaban) in addition to aspirin for long-term secondary prevention (level IIa).<sup>26</sup> For people with diabetes and chronic symptomatic lower extremity artery disease (LEAD), without high risk of bleeding, combining low-dose rivaroxaban (2.5 mg twice daily) with aspirin (100 mg daily) may be considered (level IIb).<sup>26</sup> Long-term secondary prevention may be considered in people with moderate risk of ischemic events, without a high bleeding risk, by adding a second antithrombotic drug to aspirin (level IIb). Additional recommendations for the use of antithrombotic therapies, that are not new or revised since the last guidance, are presented in **Table 10**.

**Table 10. ESC Guideline Recommendations for Antithrombotic Therapy<sup>26</sup>**

Recommendation	Class of Recommendation	Level of Evidence
Aspirin 75-100 mg daily is recommended for secondary prevention of CVD	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin for secondary prevention of CVD in case of aspirin intolerance	I	B
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to increased risk of major bleeding	III	A
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD	IIb	A
Concomitant use of a PPI is recommended in patients taking antiplatelet therapy who are at high risk of GI bleeding	I	A
Patients with diabetes at high or very high risk of CVD risk, may be considered for low-dose aspirin for primary prevention in the absence of clear contraindications	IIb	A
Antiplatelet medications are not recommended in patients with low or moderate CV risk due to risk of major bleeding	III	A
<b>Cardiovascular Indications for Antiplatelets</b>		
Patients with previous MI or revascularization aspirin 75-100 mg daily is recommended	I	A
In patients with definitive evidence of CAD on imaging, without a history of MI or revascularization, may be considered for aspirin 75 -100 mg daily	IIb	C
In patients with ACS, DAPT with a P2Y <sub>12</sub> inhibitor in addition to aspirin is recommended for 12 months, unless contraindicated, such as an excessive risk of bleeding	I	A
Clopidogrel 75 mg daily is recommended, with aspirin, for 6 months following coronary stenting, irrespective of stent type in patients with CCS, unless a shorter duration (1-3 months) is indicated due to risk or occurrence of life-threatening bleeding	I	A
Adding a second antithrombotic drug (e.g., P2Y <sub>12</sub> inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention <i>should</i> be considered in patients with a <i>high risk</i> of ischemic events and without bleeding risk	IIa	A
For patients at <i>moderate risk</i> of ischemic events, and without high risk of bleeding risk, adding a second antithrombotic drug to aspirin for long-term secondary prevention <i>may</i> be considered	IIb	A
<b>Cerebrovascular disease</b>		
Prevention with aspirin only, or dipyridamole plus aspirin, or clopidogrel alone is recommended in patients with non-cardioembolic ischemic stroke or TIA	I	A
DAPT with aspirin and clopidogrel or with aspirin and ticagrelor <i>should</i> be considered in patients with minor ischemic stroke or TIA for 3 weeks following an acute event	IIa	A
Lower extremity artery disease		

In patients with diabetes and chronic symptomatic LEAD without high risk of bleeding, the combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin (100 mg daily) <i>may</i> be considered	IIb	B
Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; GI = gastrointestinal; LEAD = lower extremity artery disease; MI = myocardial infarction; TIA = transient ischemic attack		

### ESC – 2023 Guidelines on Acute Coronary Syndromes

The management and drug treatment of patients with acute coronary syndromes (ACS) was recently published by the European Society of Cardiology. Guideline methodology was the same as described above. Significant conflicts of interest were also reported by the guideline task force. Recommendations for the use of antiplatelets will be presented.

Recommendations for antiplatelet therapies in ACS are presented in **Table 11**. The default recommendation for patients with ACS following PCI, regardless of stent type, is DAPT with aspirin and a potent P2Y<sub>12</sub> receptor inhibitor (e.g., prasugrel, or ticagrelor), usually for 12 months. Beyond the first 12 months after ACS, aspirin is recommended. Clopidogrel is considered less effective and should only be used in patients considered high bleeding risk (HBR) or when prasugrel or ticagrelor are contraindicated. Clopidogrel may also be considered in patients 70 years old and older. Prasugrel is recommended in patients with ACS that proceed to PCI. Switching between P2Y<sub>12</sub> may be considered in select cases due to bleeding complications, adverse events or socioeconomic considerations. P2Y<sub>12</sub> de-escalation may be considered in patients with ACS who are high risk of bleeding. De-escalation is not recommended within the first 30 day after an ACS event. Strategies to decrease the risk of bleeding in the first 12 month after ACS include shortening the DAPT duration to 1 or 3-6 months (abbreviated DAPT) or de-escalating the DAPT from prasugrel/ticagrelor DAPT to clopidogrel-based DAPT. Evidence on ischemic outcomes using alternative DAPT therapies is limited.

The bleeding risk of the patient should be considered when selecting an antiplatelet. Bleeding risk is estimated by the Academic Research Consortium on High Bleeding Risk (ARC-HBR). If the patient has one major or two minor ARC-HBR risk factors they are considered HBR. Recommendations are presented in **Table 11** and dosing is provided in **Table 12**.

**Table 11. New ESC Recommendations for Antiplatelet Therapy Use in Acute Coronary Syndrome†**

New Recommendations	Class of Recommendation	Level of Evidence
Stop DAPT therapy in patients presenting with ACS that are undergoing coronary artery bypass grafting. Resuming DAPT after surgery for at least 12 months is recommended after surgery.	I	C
In patients that are older, especially if HBR, and are with ACS it is recommended that the clopidogrel as the P2Y <sub>12</sub> receptor inhibitor may be considered.	IIb	B
Single antiplatelet inhibitor therapy, preferably with a P2Y <sub>12</sub> inhibitor, should be considered in patients who are event-free after 3-6 months of DAPT and who are not at high ischemic risk.	IIa	A
Long-term treatment with a P2Y <sub>12</sub> receptor inhibitor may be considered as an alternative to aspirin monotherapy.	IIb	A
In patients who are HRB, aspirin or P2Y <sub>12</sub> receptor inhibitor monotherapy after one month of DAPT may be considered.	IIb	B
Withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered in patients requiring OAC	IIb	B

De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended	III	B
Prasugrel or ticagrelor are not recommended in patients with ACS patients with cancer and <50,000/microliter platelet count	III	C
Revised Recommendations		
In patients undergoing a primary PCI strategy, pre-treatment with a P2Y <sub>12</sub> receptor inhibitor may be considered in patients undergoing a primary PCI strategy	IIb	B
SAPT (preferably with a P2Y <sub>12</sub> receptor inhibitor) should be considered in patients who are event-free after 3-6 months of DAPT and who are not high ischemic risk	IIa	A
Unchanged Recommendations		
Aspirin is recommended for all patients without contraindications.*	I	A
P2Y <sub>12</sub> receptor inhibitor is recommended in addition to aspirin in all ACS patients. An initial loading dose should be given followed by a maintenance dose for 12 months	I	A
A PPI should be given with DAPT in patients at high risk of GI bleeding	I	A
Prasugrel is recommended in P2Y <sub>12</sub> receptor inhibitor-naïve patients before PCI*	I	B
Ticagrelor is recommended for invasive and conservative treatment strategies*	I	B
Clopidogrel is recommended for patients who cannot tolerate, therapy is contraindicated or not tolerated with prasugrel or ticagrelor	I	C
If DAPT is stopped in patients presenting with ACS undergoing CABG, DAPT should be resumed after surgery for at least 12 months	I	C
In ACS patients proceeding to PCI, prasugrel is preferred over ticagrelor	IIa	B
Cangrelor may be considered in P2Y <sub>12</sub> receptor inhibitor-naïve patient	IIb	A
Clopidogrel may be considered for older patients with ACS, especially if they are at HRB	IIb	B
Antiplatelet use with oral anticoagulants		
In patients with AF and CHA <sub>2</sub> DS <sub>2</sub> -VAS score of 1 or more in men and 2 or more in women, after up to a week of triple antithrombotic therapy following an ACS event, dual antithrombotic therapy using a NOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel) for up to 12 months is recommended	I	A
For patients with an indication for OAC with VKA in combination with aspirin and/or clopidogrel, target INR with the VKA should be 2.0-2.5 and time in therapeutic range of >70% should be considered	IIa	B
In patients who are treated medically and require anticoagulation, a single antiplatelet in addition to an OAC should be considered for up to 1 year	IIa	B
In patients treated with an OAC, aspirin plus clopidogrel for longer than 1 week and up to 1 month should be considered in those with high ischemic risk or with other anatomical/procedural characteristics that are judged to outweigh the bleeding risk	IIa	C
Patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing the OAC may be considered	IIb	B
When a patient requires triple therapy the use of ticagrelor or prasugrel as part of triple therapy is not recommended	III	C
Alternative Therapeutic Regimens		
After 3-6 months of DAPT if the patient remains event-free and are not at high ischemic risk, single antiplatelet therapy (preferably with a P2Y <sub>12</sub> inhibitor) should be considered	IIa	A

P2Y <sub>12</sub> de-escalation treatment (e.g., switching from prasugrel or ticagrelor to clopidogrel) may be considered as an alternate DAPT strategy to reduce bleeding risk	IIb	A
In the first 30 days after an ACS event it is not recommended to de-escalate antiplatelet therapy	III	B
In patients treated with OAC discontinuation of antiplatelets is recommended after 12 months	I	B
In patients at high ischemic risk and without HBR, adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderate ischemic risk and without HBR	IIb	A
P2Y <sub>12</sub> inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment	IIb	A
<p>Key: * Dosage recommendations in <b>Table 12</b> below; † Antiplatelet therapy recommendations for use outside the surgical setting are presented.  Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; CABG = coronary artery bypass graft; CHA<sub>2</sub>DS<sub>2</sub>-VAS = Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease; DAPT = dual antiplatelet therapy; GI = gastrointestinal; HRB = high-risk of bleeding; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PPI= proton pump inhibitor; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.</p>		

**Table 12. Antiplatelet Dosage Recommendations for Patients with ACS**

Medication	Dosage
Aspirin	Loading dose of 150-300 mg orally or 75-250 mg IV (if oral ingestion is not possible). Maintenance dose should be 75-100 mg once daily. No adjustment for CKD.
Clopidogrel	Loading dose of 300-600 mg orally, followed by a maintenance dose of 75 mg daily. No adjustment for CKD. Fibrinolysis: initial dose of 300 mg (75 mg for patients older than 75 years of age).
Prasugrel	Loading dose of 60 mg orally followed by a maintenance dose of 10 mg daily. If patient has a body weight of <60 kg, a maintenance dose of 5 mg daily is recommended. In patients 75 or older, prasugrel should be used with caution. If treatment is used then 5 mg daily should be given. No adjustment for CKD. Prior stroke is a contraindication.
Ticagrelor	Loading dose of 180 mg daily. Maintenance dose 90 mg twice daily. No adjustment for CKD.
Cangrelor	Bolus of 30 mcg/kg IV., followed by 4 mcg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer).
Abbreviations: CKD – chronic kidney disease; IV - intravenous	

#### ESC – 2024 Guidelines on Atrial Fibrillation

The European Society of Cardiology in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) published guidance on the management of patients with AF. The diagnosis and management of AF is multifactorial. Anticoagulants are one of the cornerstones of AF treatment. The use of antiplatelets alone is not recommended for stroke prevention in patients with AF, and is not an alternative to anticoagulation (Class III, level A). Antiplatelet treatment, in addition to anticoagulants, is not recommended in patients with AF for the goal of ischemic stroke prevention or thromboembolism (Class III, level B). In patients with AF, adding antiplatelet treatment should not be added to anticoagulation for the prevention of recurrent embolic stroke (Class III, level B). In patients with chronic coronary vascular disease, do not use antiplatelets beyond 12 months in stable oral anticoagulant (OAC)-treated patients (Class III, level not specified).

Recommendations for patients with AF and an indication for combination antiplatelet treatment, a preference for direct acting oral anticoagulation (DOAC) therapy over a VKA to prevent thromboembolism and mitigate bleeding risk (Class I, level A). If rivaroxaban is used with an antiplatelet, rivaroxaban 15 mg should be used over rivaroxaban 20 mg daily if there are concerns about bleeding risk more than stent thrombosis or ischemic stroke (Class IIa, level B). Similarly, dabigatran 110 mg twice daily should be used over dabigatran 150 mg twice daily, if combined with an antiplatelet and bleeding risk is more of a concern than risk of stent thrombosis or stroke (Class IIa, level B). If the use of a VKA is combined with an antiplatelet, an international normalized ratio (INR) goal of 2.0-2.5, with time in therapeutic (TTR) of >70%, should be considered in patients with AF (Class IIa, level C).

In patients with AF and ACS and undergoing uncomplicated PCI, it is recommended that aspirin be stopped early (one week or less) and continuation of an oral anticoagulant (preferably a DOAC) with a P2Y<sub>12</sub> inhibitor (preferably clopidogrel) for up to 12 months to avoid major bleeding if thrombosis risk is low and bleeding risk is high (Class I, level A). If ischemic risk outweighs the bleeding risk in patients with AF and ACS triple therapy with aspirin, clopidogrel and oral anticoagulation for longer than 1 week after an acute ACS event should be considered with a total duration (one month or less) decided by assessment of risks and clear documentation of discharge treatment plan (class IIa, level C). If ischemic risk is low after undergoing an uncomplicated PCI, early cessation (1 week or less) of aspirin and continuation of a P2Y<sub>12</sub> inhibitor (preferably clopidogrel) and an oral anticoagulant for up to 6 months is recommended to avoid major bleeding (Class I, level A). Triple therapy with aspirin, clopidogrel and an oral anticoagulant for longer than 1 week should be considered in patients with AF and after PCI when the risk of stent thrombosis outweighs the bleeding risk with the total duration of therapy (1 month or less) should be determined by assessment of risks and clear documentation (Class IIa, level B). Use of antiplatelets beyond 12 months in stable patients with AF and chronic coronary or vascular disease treated with oral anticoagulants is not recommended due to lack of efficacy and to avoid major bleeding (Class III, level B).

**New Formulations or Indications:**

None identified.

**New FDA Safety Alerts:**

**Table 13. Description of new FDA Safety Alerts**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Clopidogrel <sup>20</sup>	Plavix®	March 2021	Drug Interactions	Rifampin strongly induces CYP219 resulting in an increase level of clopidogrel active metabolites and platelet inhibition, which may increase risk of bleeding. Avoid concomitant use.
Ticagrelor <sup>24</sup>	Brilinta®	August 2021	Warnings and Precautions	Central sleep apnea (CSA) including Cheyne-Stokes respiration (CSR) has been reported in the post-marketing setting in patients taking ticagrelor, including recurrence or worsening of CSA/CSR following rechallenge. If central sleep apnea is suspected, consider further clinical assessment.
Ticagrelor <sup>24</sup>	Brilinta®	March 2024	Labeling Changes	Guidance for providers was added regarding discontinuation of concomitant aspirin in patients with coronary artery disease undergoing PCI, due to evolving risk of thrombotic versus bleeding events. Labeling recommends not exceeding 100 mg of maintenance dose of aspirin when used in combination with ticagrelor.

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### Randomized Controlled Trials:

A total of 589 citations were manually reviewed from the initial literature search. After further review, all RCTs were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: American College of Cardiology/American Heart Association Evidence Grading Criteria

**TABLE 3** Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated May 2019)

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS 1 (STRONG)</b> <span style="float: right;"><b>Benefit &gt;&gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is recommended</li> <li>• Is indicated/useful/effective/beneficial</li> <li>• Should be performed/administered/other</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>– Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>– Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<b>LEVEL A</b> <ul style="list-style-type: none"> <li>• High-quality evidence‡ from more than 1 RCT</li> <li>• Meta-analyses of high-quality RCTs</li> <li>• One or more RCTs corroborated by high-quality registry studies</li> </ul>
<b>CLASS 2a (MODERATE)</b> <span style="float: right;"><b>Benefit &gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is reasonable</li> <li>• Can be useful/effective/beneficial</li> <li>• Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>– Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>– It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more RCTs</li> <li>• Meta-analyses of moderate-quality RCTs</li> </ul>
<b>CLASS 2b (WEAK)</b> <span style="float: right;"><b>Benefit ≥ Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• May/might be reasonable</li> <li>• May/might be considered</li> <li>• Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li> </ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"> <li>• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>• Meta-analyses of such studies</li> </ul>
<b>CLASS 3: No Benefit (MODERATE)</b> <span style="float: right;"><b>Benefit = Risk</b></span> <b>(Generally, LOE A or B use only)</b> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Is not recommended</li> <li>• Is not indicated/useful/effective/beneficial</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"> <li>• Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>• Meta-analyses of such studies</li> <li>• Physiological or mechanistic studies in human subjects</li> </ul>
<b>Class 3: Harm (STRONG)</b> <span style="float: right;"><b>Risk &gt; Benefit</b></span> <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"> <li>• Potentially harmful</li> <li>• Causes harm</li> <li>• Associated with excess morbidity/mortality</li> <li>• Should not be performed/administered/other</li> </ul>	<b>LEVEL C-EO (Expert Opinion)</b> <ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>

COR and LOE are determined independently (any COR may be paired with any LOE).  
 A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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**Appendix 2: Current Preferred Drug List**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
aspirin	ASPIRIN	TAB CHEW	Y
aspirin	CHILDREN'S ASPIRIN	TAB CHEW	Y
aspirin	ASPIRIN	TABLET	Y
aspirin	LITE COAT ASPIRIN	TABLET	Y
aspirin	ADULT ASPIRIN REGIMEN	TABLET DR	Y
aspirin	ASPIRIN	TABLET DR	Y
aspirin	ASPIRIN EC	TABLET DR	Y
aspirin	ASPIRIN REGIMEN	TABLET DR	Y
aspirin/dipyridamole	ASPIRIN-DIPYRIDAMOLE ER	CPMP 12HR	Y
cilostazol	CILOSTAZOL	TABLET	Y
clopidogrel bisulfate	CLOPIDOGREL	TABLET	Y
clopidogrel bisulfate	PLAVIX	TABLET	Y
dipyridamole	DIPYRIDAMOLE	TABLET	Y
prasugrel HCl	EFFIENT	TABLET	Y
prasugrel HCl	PRASUGREL HCL	TABLET	Y
aspirin/omeprazole	ASPIRIN-OMEPRAZOLE	TAB IR DR	N
ticagrelor	BRILINTA	TABLET	N

### Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 14, 2024

Search Strategy:

#	Searches	Results
1	aspirin.mp. or Aspirin/	75886
2	Dipyridamole/ or dipyridamole.mp.	10780
3	cilostazol.mp. or Cilostazol/	2257
4	clopidogrel.mp. or Clopidogrel/	17283
5	prasugrel.mp. or Prasugrel Hydrochloride/	3154
6	ticagrelor.mp. or Ticagrelor/	4438
7	1 or 2 or 3 or 4 or 5 or 6	95519
8	limit 7 to (english language and humans and yr="2021 -Current")	6454
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	589

### Appendix 4: Key Inclusion Criteria

<b>Population</b>	Patients with an indication for treatment with a platelet inhibitor
<b>Intervention</b>	Platelet inhibitors
<b>Comparator</b>	Placebo or active treatment comparison
<b>Outcomes</b>	Mortality, stroke, myocardial infarction, cardiovascular death, stent thrombosis, and thrombotic cardiovascular events
<b>Timing</b>	Treatment or prophylaxis (primary or secondary)
<b>Setting</b>	Outpatient