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Drug Class Update: Platelet Inhibitors

Date of Review: June 2021

Date of Last Review: September 2017
Dates of Literature Search: 07/01/2017 – 04/02/2021

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose the class update is to evaluate new evidence on platelet inhibitors since the last review performed in 2017 and to ensure the preferred drug list (PDL) aligns with current evidence.

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?
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:
- A literature search up to April 2021 identified the following new evidence: 9 systematic reviews and meta-analyses, 6 guidelines, 1 randomized controlled trial (RCT), 1 safety alert and 2 new indications. The use of platelet inhibitors spans several different disease states, which includes multiple indications as outlined below.

<u>VENOUS THROMBOEMBOLISM</u>

- A high quality systematic review and meta-analysis in adult patients undergoing total hip replacement (THR) or total knee replacement (TKR) found moderate quality evidence that aspirin (ASA) was similar to other anticoagulants in venous thromboembolism (VTE) prevention (relative risk [RR] 1.12; 95% confidence interval [CI], 0.78 to 1.62).[1] These findings were supported by results of a recent Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response Review.[2]

STROKE (Secondary prevention)

- A Cochrane review compared the efficacy and safety of multiple antiplatelets compared to fewer antiplatelets or multiple antiplatelets to one antiplatelet on prevention of recurrence in patients with recent ischemic stroke (type not specified) or transient ischemic attack (TIA) when treated for 3 months or longer.[3] The comparisons included the same trials except for one additional trial was included in the "multiple antiplatelet group" which studied ASA + clopidogrel + dipyridamole compared to ASA + dipyridamole or clopidogrel alone. All other trials studied two drug regimens compared to monotherapy.
    - For the comparison of multiple antiplatelets compared to fewer antiplatelets there was moderate to high quality evidence for the outcomes of stroke, ischemic stroke, myocardial infarction [MI], and the composite endpoint (e.g., stroke, vascular death or MI) that multiple antiplatelets were more effective.
    - For the comparison of dual antiplatelets to a single antiplatelet there was moderate to high quality of evidence that the use of dual antiplatelet therapy decreased the risk of stroke, ischemic stroke, and the composite endpoint (e.g., stroke, vascular death or MI).
    - There was high quality evidence that there was an increased risk of extracranial hemorrhage in patients treated with multiple antiplatelet therapies, treated for at least 3 months, compared to fewer antiplatelet therapies, 6.38% versus 2.81%, and for the comparison of dual antiplatelet therapies compared to single antiplatelet regimens, 1.24% versus 0.40%.[3]
- A high-quality systematic review and meta-analysis found that dual antiplatelet therapy with clopidogrel and ASA (75 mg to 300 mg), for up to 90 days, was more effective than ASA alone at reducing the risk of recurrent non-fatal stroke in patients with acute minor ischemic stroke or high risk TIA with an absolute risk reduction (ARR) of 1.9% (RR 0.70; 95% CI, 0.61 to 0.80) (high-quality of evidence).[4]

CARDIOVASCULAR EVENTS

- A 2019 CADTH review found moderate quality evidence that extended (treatment beyond 12 months) dual antiplatelet therapy (DAPT) treatment post-percutaneous coronary intervention (PCI) with stent placement (mostly drug eluting stents [DES]) was associated with a decreased risk of MI (number needed to treat [NNT] 174) and probable or definite stent thrombosis (NNT 348) compared to DAPT use of 6 to 12 months (standard of care). [5] There was an increase in non-CV death in participants treated with extended DAPT RR 2.15 (95% CI, 1.30 to 3.55) and no differences in major bleeding rates.
- A Cochrane review found moderate quality evidence of a reduced risk of fatal and non-fatal MI with ASA (75 mg to 325 mg) plus clopidogrel compared to ASA monotherapy (RR 0.78; 95% CI, 0.69 to 0.90) and fatal and non-fatal ischemic stroke (RR 0.73; 95% CI, 0.59 to 0.91) in patients with established cardiovascular (CV) disease (with or without MI) and without coronary stent.[6] Combination therapy was associated with an increased risk of major bleeding (RR 1.44; 95% CI, 1.25 to 1.64) and minor bleeding (RR 2.03; 95% CI, 1.75 to 2.36). Current data does not support routine use of the addition of clopidogrel to aspirin therapy in patients without coronary stents.
- A National Institute for Health and Care Excellence (NICE) guideline on acute coronary syndromes (ACS) are consistent with our current policy with a few exceptions.[7] NICE recommends the use of prasugrel for patients with acute STEMI. Patients with STEMI not treated with PCI should receive ticagrelor, with ASA. Patients with unstable angina or NSTEMI who are having coronary angiography, dual therapy with aspirin and either prasugrel or ticagrelor should be offered. Ticagrelor is indicated for patients, with aspirin, with unstable angina or NSTEMI when PCI is not recommended.
- A high-quality systematic review and meta-analysis in patients with a median baseline risk of a CV outcome of 10.2%, found ASA (75 mg to 100 mg) to reduce the risk of the primary composite CV outcome (CV mortality, nonfatal MI, and nonfatal stroke) more than no treatment (hazard ratio [HR] 0.89; 95% CI, 0.84 to 0.94; ARR 0.41%/NNT 241); however, ASA was also associated with an increased risk of major bleeding compared to no ASA (HR 1.43; 95% CI, 1.30 to 1.56; ARI 0.47%/NNH 210) and increased risk of intracranial hemorrhage was with ASA compared to no treatment (absolute risk increase [ARI] 0.11%/number needed to harm [NNH] 927) and major gastrointestinal [GI] bleeding (ARI 0.30%/NNH 334).[8]

PRE-ECLAMPSIA

- A Cochrane review found that the use of antiplatelet agents (aspirin 50-150 mg) reduced the risk of pre-eclampsia (number needed to benefit [NNTB] 61), preterm birth (NNTB 61), infant death (NNTB 197) and a reduction in infants small for gestational age (NNTB 146) compared to placebo in women at high risk of pre-eclampsia (mostly primary prevention trials started at different times of gestation).[9]
- There was insufficient high-quality evidence to make recommendations for the optimal use of platelet inhibitors in subgroup populations.

Recommendations:

- Update PA criteria to include new indications for ticagrelor.
- No changes to the PDL are warranted based on the evidence identified since the last review.
- After evaluation of costs in executive session, prasugrel was made PDL preferred and removed from PA criteria.

Summary of Prior Reviews and Current Policy:

- There were no changes made to the PDL as a result of the antiplatelet literature scan in 2017. Previous recommendations were to make clopidogrel, ASA and cilostazol preferred on the PDL.
- Evidence from previous reviews outline the importance of using DAPT following ACS, with evidence of decreased ischemic events with use beyond 12 months but with an increased risk of bleeding.
- Additional evidence was presented for prasugrel and ticagrelor that demonstrated a reduction in ischemic events compared to clopidogrel. A comparison between ticagrelor and clopidogrel found similar efficacy for prevention of CV outcomes and major bleeding.
- The risk of major adverse cardiovascular events (MACEs) was reduced more with prasugrel compared to clopidogrel but with a higher risk of bleeding.

Current Policy:

- Aspirin, ASA/dipyridamole, cilostazol, clopidogrel, and dipyridamole are preferred therapies. Non-preferred therapies require prior authorization (PA) to ensure platelet inhibitors are used for an approved diagnosis and patients are without contraindications.
- Ninety-nine percent of the utilization for this class is for 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 which inhibits prostaglandin synthesis and platelet aggregation. The $P2Y_{12}$ 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).[10] 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. Vorapaxar is the newest platelet inhibitor exerting its antiplatelet effect by selectively antagonizing the protease-activated receptor-1 (PAR-1).[11]

Platelet inhibitors are used for a several indications, including ACS (e.g., unstable angina, STEMI, and NSTEMI), peripheral arterial disease (PAD), stroke prevention, and less commonly as VTE prophylaxis. Both vorapaxar and prasugrel are contraindicated in patients with a history of stroke, TIA or intracranial

hemorrhage (ICH). The FDA approved indications 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, minor bleeding and major bleeding.

Table 1. Antiplatelet FDA Approved Indications

Drug	Dose	Indication
Aspirin/extended-release dipyridamole[12]	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[13]	300 mg single loading dose (if indicated) 75 mg daily (maintenance dose)	- ACS 1. Non-ST segment elevation ACS (unstable angina /NSTEMI). Reduction in the rate of MI and stroke 2. STEMI. Reduction has been shown to reduce the rate of MI and stroke. - Recent MI, recent stroke or established PAD with reduction in the risk of MI and stroke.
Cilostazol[14]	50 – 100 mg twice daily	Reduction of symptoms of intermittent claudication as demonstrated by an increased walking distance
Dypyridamole[15]	75 – 100 mg four times daily	Adjunct to coumarin anticoagulants in prevention of postoperative thromboembolic complications of cardiac valve replacement
Prasugrel[16]	5 – 10 mg once daily (aspirin 75-325 mg daily recommended)	- Reduction of thrombotic CV events (including stent thrombosis) in patients with ACS who are to be managed with PCI as follows: 1. Unstable angina or NSTEMI 2. STEMI when managed with either primary or delayed PCI
Ticagrelor[17]	60 – 90 mg twice daily (indication dependent maintenance dose)	- Reduction in the risk of CV death, MI and stroke in patients with ACS or history of MI - Reduction in the risk of stent thrombosis in patients who have been stented for the treatment of ACS - Reduction in the risk of first MI or stroke in patients with CAD at high risk for such events - Reduction in the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale $\leq$5) or high-risk TIA
Vorapaxar[11]	2.08 mg daily (with aspirin and clopidogrel)	Reduction of thrombotic CV events in patients with a history of MI or PAD. Reduction in the rate of the combined endpoint of CV death, MI, stroke, and urgent coronary revascularization.
Abbreviations: ACS – acute coronary syndrome; CAD – coronary artery disease; CV – cardiovascular; MI – myocardial infarction; NSTEMI - non-ST elevation MI; PAD – peripheral arterial disease; STEMI - ST-elevation MI; TIA – transient ischemic attack		

Guidelines recommend DAPT ($P2Y_{12}$ inhibitors in combination with ASA) for the management of ACS (for both STEMI and NSTEMI).[18,19] Platelet inhibition therapy is chosen for patients with STEMI based on reperfusion strategy. Prasugrel and ticagrelor are often preferred over clopidogrel for patients receiving PCI.[5] Clopidogrel has incomplete platelet inhibition resulting in a variable patient response. The American College of Cardiology/American Heart Association guidelines recommend duration of therapy to be determined by presence of stable coronary artery disease (CAD) in which 6 months is recommended or 12 months for patients with ACS. Use beyond 12 months is reserved for patients at high thrombotic risk and low risk for bleeding.[20] Aspirin use is often recommended to be continued indefinitely in patients with ACS. Guidelines no longer recommend ASA universally for primary prevention of cardiovascular disease but may be considered for patients with specific risk factors, such as diabetes.[21]

Atrial fibrillation (AF) without valvular heart disease is associated with a fivefold increase in incidence in stroke and subject to other underlying risk factors.[22] While AF is traditionally managed with anticoagulants, the use of a platelet inhibitor may occur when patients have comorbidities (e.g., ACS, stents, etc.) and require dual or triple therapy.[23] Clopidogrel, ASA or ASA/extended release (ER) dipyridamole are recommended for secondary prevention of non-cardioembolic ischemic stroke. Combination therapy with clopidogrel and ASA is used for patients with acute ischemic stroke and TIA as initial therapy, usually for 21 days; however, some studies continue treatment out to 90 days. Antiplatelets are also recommended in a subset of patients with valvular heart disease, in combination or in place of anticoagulants. In general, ASA 75 mg to 100 mg is recommended for this patient population.[24]

Symptomatic PAD patients can be managed with cilostazol. Aspirin or clopidogrel are recommended in patients with PAD who are at risk for CAD or stroke.

Methods:
A Medline literature search for new systematic reviews and RCT 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, 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:

<u>VENOUS THROMBOEMBOLISM</u>
<u>CADTH – Acetylsalicylic Acid (Aspirin) for Venous Thromboembolism Prophylaxis in Hip and Knee Replacement</u>
A CADTH Rapid Response Report reviewed the evidence for the use of ASA as a prophylactic therapy in patients undergoing THR or TKR.[2] A literature search ranged from January 1, 2017 to July 22, 2020. Results of findings were reported independently and there was no meta-analysis of data due to heterogeneity of the trials. Five systematic reviews of randomized trials, fourteen non-randomized retrospective studies and one prospective study were included. Three guidelines were also included in the evidence recommendations. ASA was compared to LMWH (enoxaparin [40 mg once daily to 30 mg twice daily] and dalteparin [5000 units once daily]), Factor Xa inhibitors (rivaroxaban [10 mg daily], apixaban [2.5 mg]), direct thrombin inhibitor (dabigatran [220 mg]), warfarin

[initiated at 7.5 mg to 10 mg], or other anticoagulants. Treatment durations ranged from 9 days to 3 months and follow-up varied from 48 hours to one year. Patients were a mean range of 63-71 years and 18% to 44% were male. ASA doses ranged from 81 mg to 650 mg twice daily.[2]

Evidence for the use of ASA after THR or TKR found no significant differences in efficacy and safety between ASA and LMWH, Factor Xa inhibitors, direct thrombin inhibitors and warfarin.[2] Guidelines recommend the use of ASA for prophylaxis based on low quality of evidence. Additional high quality evidence is needed to recommend ASA over other anticoagulants for prophylaxis of VTE for most patients undergoing THR or TKR.

Matharu, et al – Clinical Effectiveness and Safety of Aspirin for VTE Prophylaxis after Total Hip and Total Knee Replacement

A 2020 systematic review and meta-analysis evaluated randomized controlled trial (RCTs) for evidence of efficacy and safety of using ASA (81 mg daily to 1500 mg twice daily) for prophylaxis in patients after they undergo a THR or TKR.[1] Thirteen RCTs (n=6060) with active treatment comparisons were included. Comparators were rivaroxaban (10 mg) with or without LMWH (4000 U daily), dalteparin (4000-50000 U daily), enoxaparin (40 mg daily warfarin (7.5 mg to 10 mg daily and titrated to target INR), LMW dextran (500 ml daily) and dipyridamole (400 mg daily). Treatment lengths ranged from 5 to 42 days. Participants were adults (18 years and older), 57.2% were women, and the mean age was 60.0 years. Of the 13 trials, 11 were open-label and 2 were double-blind.[1] Two studies had low risk of bias and 11 had a high risk of bias due to detection and performance bias. The primary outcome was the incidence of postoperative VTE (asymptomatic or symptomatic) and risk of bleeding.

Pooled results from 13 trials found the risk of ASA as a prophylactic therapy after THR and TKR to be similar to other anticoagulants (RR 1.12; 95% CI, 0.78 to 1.62) based on moderate quality evidence.[1] For the comparison of risk of DVT with ASA to other anticoagulants the results were similar (RR 1.04; 95% CI, 0.72 to 1.51) and for PE (RR 1.01; 95% CI, 0.68 to 1.48), based on moderate and high quality evidence, respectively. The risk of any bleeding was not different between ASA and other anticoagulants (RR 1.35; 95% CI, 0.73 to 2.49) or major bleeding (RR 1.11; 95% CI, 0.47 to 2.59). Evidence for the risk of adverse events was based on 2 trials and was considered low quality evidence.[1]

The review was limited by high heterogeneity across the studies; however, subgroup analyses suggested that the findings were consistent even with differing surgeries, comparative therapy and trial design. There was a high risk of bias found in many of the included studies which lowers the confidence in the findings. The authors had minor conflicts of interest resulting in a risk of bias. Additional, well-designed RCTs would further define the role of ASA as a prophylactic therapy in patients undergoing TKR and THR.

CARDIOVASCULAR EVENTS

Cochrane – Clopidogrel plus Aspirin versus Aspirin Alone for Preventing Cardiovascular Events

Cochrane updated a 2011 review on the benefits and risks of ASA therapy for preventing CV events in patients with established coronary disease, ischemic cerebrovascular disease, PAD or at high risk of atherothrombotic disease but did not have a coronary stent.[6] The updated search was up to July 4, 2017, which identified 13 new studies, bringing the study inclusion total to 15 (n=33,970). All but one study used clopidogrel 75 mg and ASA doses ranged from 70 mg to 325 mg. Treatment durations ranged from 6 weeks to 3.4 years. For most domains, studies were at low risk of bias.[6]

There was no difference between ASA alone and the combination of ASA and clopidogrel for the outcome of CV mortality (RR 0.98; 95% CI, 0.88 to 1.10) based on moderate quality of evidence (7 trials).[6] Based on a median follow-up of 12 months, the risk of fatal and non-fatal MI (6 trials) occurred in 58 per 1000 patients treated with ASA compared to 45 per 1000 patients treated with combination therapy (RR 0.78; 95% CI, 0.69 to 0.90) (moderate quality of evidence). There was moderate evidence that the risk of fatal and non-fatal ischemic stroke (5 trials) was less with combination therapy compared to ASA alone (RR 0.73;

95% CI, 0.59 to 0.91).[6] Evidence for all-cause mortality (9trials) was of low quality and found no difference between treatments. The risk of major bleeding (10 trials) was higher in patients treated with combination therapy compared to ASA alone (RR 1.44; 95% CI, 1.25 to 1.64) (moderate quality of evidence). Moderate evidence also found an increased risk of minor bleeding (8 trials) with combination therapy, 32 per 1000 patients treated compared to 65 per 1000 patients treated with ASA alone (RR 2.03; 95% CI, 1.75 to 2.36).[6]

Zheng, et al – Association of Aspirin Use for Primary Prevention with Cardiovascular Events and Bleeding Events

A high-quality systematic review and meta-analysis was published in 2019 on the use of aspirin and the corresponding benefits and risks when used for primary prevention in patients with a median baseline risk of a CV outcome of 10.2%,.[8] Aspirin was compared to placebo in 9 trials and no ASA in 4 studies. The ASA dose was 75 mg to 100 mg daily in 9 of the RCTS. A search up to November 1, 2018 identified 13 RCTs involving 164,225 participants.[8] The mean duration of follow-up was 5 years and 47.2% of participants were men. Studies enrolling just patients with diabetes were identified in 3 trials comprising 18.5% of patients. Four studies were at high risk of bias (open-label) with the remaining 9 being at low risk of bias (double-blind). The primary outcome was a composite of CV mortality, nonfatal MI, and nonfatal stroke. All-cause mortality, CV-related mortality, MI, total stroke (ischemic, hemorrhagic and unknown), and ischemic stroke were secondary outcomes. Major bleeding was the primary safety outcome, with secondary outcomes being intracranial bleeding and major GI bleeding.

The results for the primary composite CV outcome demonstrated a reduction with the use of ASA, 60 events per 10,000 participant-years, compared to no aspirin, 65.2 events per 10,000 participant-years (HR 0.89; 95% CI, 0.84 to 0.94; ARR 0.41%/NNT 241).[8] The incidence of all-cause mortality was not reduced with ASA compared to no therapy (HR 0.94; 95% CI, 0.88 to 1.01; ARR 0.13%).[8] The incidence of MI was reduced with ASA compared to no therapy by an ARR of 0.28% and NNT of 361. Aspirin reduced the risk of ischemic stroke by an ARR of 0.19% and NNT of 540.[8] Total stroke risk was not reduced by ASA therapy compared to no therapy (HR 0.93; 95% CI, 0.86 to 1.02). In a subgroup analysis of patients where CV risk was low, ASA reduced risks more than no treatment (ARR 0.63%/NNT 160). Results were the same for the risk in patients with a high risk of the CV outcome (ARR 0.63%/NNT 160).[8] The largest reduction in risk was in patients with diabetes where ASA reduced the primary composite CV outcome more than no treatment (HR 0.90; 95% CI, 0.82 to 1.00; ARR 0.65%/NNT 153).[8]

Major bleeding was increased with ASA, 23.1 events per 10,000 participant-years, compared to no treatment, 16.4 events per 10,000 participant-years (HR 1.43; 95% CI, 1.30 to 1.56; ARI 0.47%/NNH 210).[8] The incidence of intracranial hemorrhage was higher with ASA compared to no treatment (ARI 0.11%/NNH 927) and major GI bleeding (ARI 0.30%/NNH 334).[8]

The use of ASA in patients without CV disease was associated with less CV outcomes but higher rates of major bleeding, intracranial hemorrhage and major GI bleeds. The quality of the systematic review was limited by no list of studies that were excluded, omission of funding source and lack of inclusion of grey literature.

CADTH – Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration

A 2019 clinical effectiveness review done by CADTH evaluated the safety and efficacy of using DAPT (combination of $P2Y_{12}$ inhibitor [e.g., clopidogrel, prasugrel or ticagrelor] and aspirin), after PCI with stent insertion, as extended therapy (beyond 12 months) compared to the standard of practice duration of 6-12 months.[5] There were 8 RCTs (n=11,648) that met inclusion criteria and 7 were open-label. Additionally, evidence to guide the use of a particular $P2Y_{12}$ inhibitor was sought, but there was insufficient evidence to inform conclusions since most of the trials studied clopidogrel or a combination of $P2Y_{12}$ inhibitors. The mean patient age was 60 years A majority of patients had DES with only limited data on patients with bare-metal stent (BMS). All-cause, CV and non-cardiovascular death were all primary outcomes. Secondary outcomes of the review were MI, stroke, stent thrombosis, urgent target vessel revascularization, major adverse

cardiac and cerebrovascular event (MACCE), and bleeding. Trials were considered to be at low risk of bias. Trial bias was not downgraded for being open-label because outcomes were objective.[5]

Results for the primary and secondary outcomes are presented in **Table 2**.[5] Of interest was that the incidence of non-cardiovascular death was higher with patients treated with extended DAPT. Analysis of subgroup populations found that those patients with a history of MI had a reduced risk of subsequent MI, probable or definite stent thrombosis and MACCE when treated with extended therapy. Patients presenting with ACS also demonstrated a reduced risk of MI and probable or definite stent thrombosis with extended therapy. Those patients with diabetes were not found to have benefit with extended DAPT and may have an increased risk of bleeding. There was an increased risk of death among patients with no MI history and an increased risk of stroke in those over the age of 75 with extended DAPT therapy.[5] Smokers and non-smokers were found to have a reduced risk of MI and definite or probable stent thrombosis with extended duration of therapy. No trials studied used ticagrelor and only a few studies evaluated the use of prasugrel. Limitations to the evidence include different times of randomization from stenting to trial extended DAPT trial enrollment, and different definitions of MACCE and major bleeding.

Table 2. CADTH Review on the Use of Extended Duration DAPT versus Standard of Care[5]

Outcomes	Result	Comments
Myocardial Infarction (6 trials, N= 24,534)	RR 0.58 (95% CI, 0.48 to 0.70) NNT 174	Extended duration DAPT reduced the risk of MI compared to standard of care*
Probable or Definite Stent Thrombosis (5 trials, N = 19,489)	RR 0.38 (95% CI, 0.21 to 0.67) NNT 348	Extended duration DAPT reduced the risk of stent thrombosis compared to standard of care*
All-cause Death (7 trials, N = 25,982)	RR 1.07 (95% CI, 0.80 to 1.42)	No difference in risk of death between standard of care and extended DAPT therapy
Cardiovascular Death (5 trials, N = 21,561)	RR 0.98 (95% CI, 0.74 to 1.30)	No difference in risk of CV death between standard of care and extended DAPT therapy
Non-cardiovascular Death (3 trials, N = 14,666)	RR 2.15 (95% CI, 1.30 to 3.55)	Higher risk of death with extended DAPT compared to standard of care
Stroke (6 trials, N = 24,534)	RR 0.94 (95% CI, 0.70 to 1.25)	No difference in risk of stroke between standard of care and extended DAPT therapy
Urgent Revascularization (2 trials, N = 3,136)	RR 0.60 (95% CI, 0.24 to 1.54)	No difference in risk of urgent revascularization between standard of care and extended DAPT therapy
MACCE (5 trials, N = 21,227)	RR 0.95 (95% CI, 0.76 to 1.19)	No difference in risk of MACCE between standard of care and extended DAPT therapy
Major Bleeding† (4 trials, N = 9,579)	RR 1.42 (95% CI, 0.88 to 2.29)	No difference in the risk of major bleeding between standard of care and extended DAPT
Abbreviations: CV – cardiovascular death; DAPT – dual antiplatelet therapy; MACCE – major adverse cardiac and cerebrovascular event; NNT- number needed to treat; RR – relative risk; Key: * DAPT for 6-12 months; † As defined by thrombolysis in myocardial infarction (TIMI)		

STROKE

Cochrane – Multiple Versus Fewer Antiplatelet Agents for Preventing Early Recurrence After Ischemic Stroke or Transient Ischemic Attack

A 2020 Cochrane review evaluated the safety and efficacy of using fewer versus multiple antiplatelet therapies within 72 hours after a stroke or TIA, with continued treatment of 30 days to 3.5 years.[3] Fifteen studies (n=17,091) met inclusion criteria. Therapies included combinations of the following oral therapies: aspirin, clopidogrel, dipyridamole, cilostazol, thienopyridine, triflusal, buflomedil and sarpogrelate (the last four products are not available in the US). The most common combinations studied were clopidogrel plus aspirin and dipyridamole plus aspirin. Comparisons were considered to be "multiple antiplatelets" versus "fewer antiplatelets" was the combination of A+B+C versus C or A+B. "Multiple antiplatelets" versus "single antiplatelets" was the combination of the following A+B versus A or B. The primary outcome was stroke or vascular death 3 or more months after initiation of treatment.[3] Two trials were at high risk of bias and performance bias was high in 6 of the 15 trials, due to blinding issues. Results of findings for the comparison of "multiple antiplatelets" compared to "fewer antiplatelets" are presented in **Table 3**. Results for "multiple antiplatelets" compared to "single antiplatelet" are presented in **Table 4**.

Table 3. Multiple Antiplatelets Compared to Fewer Antiplatelets for Recurrence Prevention in Patients with Ischemic Stroke and Transient Ischemic Attacks[3]

Outcome at ≥3 months	Result	Quality of Evidence	Comments
Stroke	RR 0.73 (95% CI, 0.66 to 0.82)	Moderate	There were 22 *fewer* strokes per 1000 patients treated in patients receiving multiple agents versus fewer agents
Vascular Death	RR 0.98 (95% CI, 0.67 to 1.45)	Moderate	There was no difference between treatments
Myocardial Infarction (MI)	RR 1.38 (95% CI, 0.63 to 2.99)	High	There was no difference between treatments
Stroke, vascular death or MI	RR 0.72 (95% CI, 0.64 to 0.82)	Moderate	There were 25 *fewer* strokes, vascular deaths or MIs per 1000 patients treated in patients receiving multiple agents versus fewer agents
Intracranial hemorrhage	RR 1.92 (95% CI, 1.05 to 3.50)	Low	Low quality evidence prevents strong conclusions
Extracranial hemorrhage	RR 2.14 (95% CI, 1.79 to 2.57)	High	There were 36 *more* extracranial hemorrhages per 1000 patients treated in patients receiving multiple agents versus fewer agents
Ischemic Stroke	RR 0.73 (95% CI, 0.64 to 0.83)	High	There were 21 *fewer* ischemic strokes per 1000 patients treated in patients receiving multiple agents versus fewer agents
Abbreviations: CI – confidence interval; RR – relative risk			

Table 4. Multiple Antiplatelets Compared to One Antiplatelet for Recurrence Prevention in Patients with Ischemic Stroke and Transient Ischemic Attacks[3]

Outcome at ≥3 months	Result	Quality of Evidence	Comments
Stroke	RR 0.71 (95% CI, 0.62 to 0.80)	Moderate	There were 23 *fewer* strokes per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Vascular Death	RR 0.84 (95% CI, 0.54 to 1.30)	Moderate	There was no difference between treatments
Myocardial Infarction (MI)	RR 1.38 (95% CI, 0.63 to 2.99)	High	There was no difference between treatments
Stroke, vascular death or MI	RR 0.72 (95% CI, 0.64 to 0.82)	Moderate	There were 25 *fewer* strokes, vascular deaths or MIs per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Intracranial hemorrhage	RR 1.53 (95% CI, 0.76 to 3.06)	Low	Low quality evidence prevents strong conclusions
Extracranial hemorrhage	RR 3.08 (95% CI, 1.74 to 5.46)	High	There were *more* extracranial hemorrhages in patients receiving dual antiplatelets versus one antiplatelet
Ischemic Stroke	RR 0.70 (95% CI, 0.61 to 0.81)	High	There were 27 *fewer* ischemic strokes per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Abbreviations: CI – confidence interval; RR – relative risk			

Hao, et al – Clopidogrel Plus Aspirin Versus Aspirin Alone for Acute Minor Ischemic Stroke or High Risk Transient Ischemic Attack

In a high-quality systematic review and meta-analysis the efficacy and safety of dual therapy with clopidogrel and aspirin compared to ASA alone was compared for the prevention of recurrent thrombotic and bleeding events in patients with minor ischemic stroke (National Institute of Health Stroke Scale [NIHSS] of 3 or less) or high risk TIA ($ABCD^2$ score of 4 or greater).[4] Literature search ranged from January 2012 to July 2018. Three trials met inclusion criteria including 1,447 participants which were enrolled within 12 or 24 hours of symptom onset. All trials used a loading dose of clopidogrel (300-600 mg) plus aspirin (75 mg to 300mg) compared to ASA (50 mg to 325 mg daily).[4] Trials were studied out to 90 days. Fifty-eight percent of participants were men and the average age was 65 years. All trials were found to be at an overall low risk of bias. Outcomes were non-fatal recurrent stroke (both ischemic and hemorrhagic), all-cause mortality, major or moderate non-fatal extracranial hemorrhage.

The risk of non-fatal recurrent stroke was reduced with dual antiplatelet therapy, compared to ASA alone, with an ARR of 1.9% (RR 0.70; 95% CI, 0.61 to 0.80) (high-quality of evidence).[4] The risk of non-fatal ischemic stroke was reduced more with dual therapy compared to ASA alone (RR 0.69; 95% CI, 0.60 to 0.79/ARR 2.0%) based on high-quality of evidence.[4] The incidence of non-fatal intracranial hemorrhage was increased with dual therapy compared to ASA (RR 1.27; 95% CI, 0.55 to 2.89) (moderate quality of evidence). Moderate quality evidence found no differences between treatment for the outcome of all-cause mortality (RR 1.27; 95% CI, 0.73 to 2.23).[4] The risk of moderate or major extracranial hemorrhage was increased with dual antiplatelet therapy with a RR of 1.71 (95% CI, 0.92 to 3.20), with an incidence of 3 per 1000 patient years with ASA compared to 5 per 1000 for patients treated with DAPT (ARR 0.2%) based on moderate quality of evidence.[4]

Study results were limited by differing loading doses of both clopidogrel and ASA. Only three trials met inclusion criteria and therefore, additional evidence would strengthen the conclusions. The quality of the systematic review and meta-analysis had appropriate methods with no funding conflicts or authors with conflicts of interest.

PRE-ECLAMPSIA

Cochrane – Antiplatelet Agents for Preventing Pre-eclampsia and Its Complications

A 2019 Cochrane review evaluated the evidence for antiplatelet (e.g., aspirin and dipyridamole) use on the risk of development of pre-eclampsia.[9] Seventy-seven trials were included, although most of the data was contributed from 9 larger trials. The use of ASA, in doses ranging from 50 mg to 150 mg, was the most common treatment studied. Women included in the study were considered to be at high risk of developing preeclampsia and most trials were primary prevention trials. Gestational age varied at time of antiplatelet initiation. The incidence of pre-eclampsia in the trials varied substantially from 2% to 60%. Overall quality of the trials was considered to be good, with most trials having a low risk of bias.

High quality evidence found reduced proteinuric pre-eclampsia in women taking antiplatelets compared to placebo, 16 fewer per 1000 versus 92 per 1000 (RR 0.82; 95% CI, 0.77 to 0.88: NNTB 61).[9] Infant death was 27per 1000 in the antiplatelet group compared to 33 per 1000 in the placebo group (RR 0.85; 95% CI, 0.76 to 0.95) (high quality evidence). Preterm birth, defined as birth before 37-weeks gestation, was less in women taking antiplatelets with a RR 0.91 (95% CI, 0.87 to 0.95; NNTB 61) based on high quality of evidence.[9] There was high quality evidence that women given antiplatelets had a risk of infants that were small for gestational age, 40 per 1000, compared to placebo risk, 47 per 1000 (RR 0.84; 95% CI, 0.76 to 0.92; NNTB 146).[9] The risk of postpartum hemorrhage was not statistically different in women treated with antiplatelets compared to placebo (RR 1.06; 95% CI, 1.00 to 1.12). Moderate quality evidence found trials reporting individual patient data evaluated serious adverse events outcome (composite of material death, baby death, pre-eclampsia, small-for-gestational age, preterm birth) found 177 per 1000 in women treated with antiplatelets compared to 197 per 1000 for placebo (NNTB 54) (high quality evidence).[9] There was moderate evidence that the risk of postpartum hemorrhage (>500 ml) was slightly increased with antiplatelet therapy (RR 1.06; 95% CI, 1.00 to 1.12).

There was small to moderate benefit for the use of aspirin in women at risk of pre-eclampsia. Outcomes that saw the most benefit were a reduction in risk for proteinuric pre-eclampsia, preterm birth, and infant death.

After review, 70 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).[25–34, 35–44, 45–54, 31,55–63, 64–73, 74–83, 46,84–93]

New Guidelines:

High Quality Guidelines:

NICE – Acute Coronary Syndromes

In November 2020 NICE updated guidance on the use of antiplatelets in coronary syndromes.[7] Early management of acute STEMI or NSTEMI and unstable angina includes administration of 300 mg aspirin unless there is a clear allergy. Patients with acute STEMI who are having a primary PCI should be offered prasugrel, in addition to aspirin, if no other anticoagulant is being taken. Patients already taking an anticoagulant should be offered clopidogrel.[7] Patients with STEMI not treated with PCI should be offered ticagrelor, in combination with ASA. Clopidogrel should be used if there is a high risk of bleeding.

For patients with unstable angina and NSTEMI intended for PCI, ticagrelor has the most evidence for use.[7] NICE also recommends the use of ticagrelor in patients not having coronary revascularization or coronary artery surgery. For patients at high risk of bleeding, clopidogrel may be a better option. For patients with unstable angina or NSTEMI who are having coronary angiography, dual therapy with aspirin and either prasugrel or ticagrelor should be offered. Clopidogrel

should be given if the patient has an indication for ongoing oral anticoagulation. Ticagrelor is indicated for patients, with aspirin, with unstable angina or NSTEMI when PCI is not recommended. If there is a high risk of bleeding clopidogrel is recommended with ASA, or ASA use alone.[7]

Patients that have had a MI, dual antiplatelet therapy with ASA and one other antiplatelet is recommended for secondary prevention for at least 12 months. Aspirin is recommended indefinitely unless there is a contraindication. If the patient cannot take ASA or if they have clinical vascular disease, clopidogrel monotherapy is an alternative option. If the patient has a separate indication for anticoagulation continue clopidogrel for up to 12 months.[7]

NICE – Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing

A 2020 guidance from NICE included recommended anticoagulant therapy for the management of VTE.[94] Antiplatelet therapy (e.g., ASA), as it pertains to this update, will be the reported. Additional anticoagulant recommendations will be included in that designated update. The role of ASA (75 mg to 150 mg daily) is recommended by the guidance for use in patients who require long-term anticoagulation for secondary prevention in patients who decline anticoagulation.[94] No other recommendations pertaining to ASA were included in the guidance.

Additional Guidelines for Clinical Context:

AHA/ACC/HRS Focused Update of the 2014 Guideline on the Management of Patients with Atrial Fibrillation

In 2019 the American Heart Association (AHA)/American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) updated guidance on AF management.[22] A significant portion of the professional practice committee members had conflicts with industry and associations themselves funded by industry. The guideline will be included for clinical context. Pharmacologic recommendations, pertaining to antiplatelet therapy, will be discussed. Recommendations are given a class (strength) of recommendation and level (quality) of evidence recommendation. The class of recommendation range from weak to strong (**Table 5**) and level of evidence description in **Table 6**.

The management of patients with AF is often complicated by the presence of comorbidities. The recommendations for ACS are for dual antiplatelet therapy (DAPT), with the addition of warfarin or novel oral anticoagulants (NOAC) for triple therapy in patients with AF at increased risk of stroke (**Table 7**).[22] The recommendations for the use of ASA have been updated from findings of recent trials showing less benefit of ASA for primary prevention than originally thought. Evidence still strongly supports the use of ASA for secondary prevention of atherosclerotic cardiovascular disease (ASCVD).

Table 5. Description of Class of Recommendation Description[22]

Class of Recommendation	Description
Class I (Strong)	Benefit >>> Risk
Class IIa (Moderate)	Benefit >> Risk
Class IIb (Weak)	Benefit ≥ Risk
Class III: No Benefit (Moderate)	Benefit = Risk
Class III: Harm (Strong)	Risk > Benefit

Table 6. Level of Evidence Description[22]

Level of Evidence	Description
Level A	High quality evidence from more than one RCT Meta-analysis of high quality RCTs One or more RCT corroborated by high-quality registry studies
Level B-R (Randomized)	Moderate quality evidence from 1 or more RCTs Meta-analyses of moderate-quality RCTs
Level B-NR (Nonrandomized)	Moderate quality evidence from 1 or more well-designed nonrandomized studies, observational, or registry studies Meta-analyses of such studies
Level C-LD (Limited data)	Randomized or nonrandomized trials with limitations Meta-analyses of such studies Physiological or mechanistic studies in human subjects
Level C-EO (Expert opinion)	Consensus of expert opinion based on clinical experience

Table 7. Recommendations for the Use of Antiplatelet Therapy in Patients with Atrial Fibrillation[22]

Recommendation	Class of Recommendation	Level of Evidence
AF Complicating ACS		
Clopidogrel is recommended over prasugrel in patients who are prescribed triple therapy with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-NR
Dose-adjusted vitamin K antagonist with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) is a reasonable option in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
Low-dose rivaroxaban (15 mg) daily with a $P2Y_{12}$ inhibitor (clopidogrel) is a reasonable option to reduce the risk of bleeding in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
Double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding compared to triple therapy in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
If triple therapy (oral anticoagulant, $P2Y_{12,}$ and aspirin) is prescribed in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at 4-6 weeks may be considered.	IIb	B-R
Aspirin Use		
Low-dose aspirin (75 mg to 100 mg) may be considered for primary preventions of ASCVD among certain adults 40-70 years old or at higher ASCVD risk but not at increased bleeding risk	IIb	A
For patients 70 years and older, low-dose aspirin (75 mg to 100 mg) should not be administered on a regular basis for the primary prevention of ASCVD	III: Harm	B-R
For adults at increased risk of bleeding the daily administration of low-dose aspirin (75 mg to 100 mg) should not be administered for the primary prevention of ASCVD	III: Harm	C-LD
Abbreviations: ACS - acute coronary syndrome; AF – atrial fibrillation; ASCVD – atherosclerotic cardiovascular disease		

ACC/AHA – Guideline on the Primary Prevention of Cardiovascular Disease

General guidelines for the primary prevention of CV disease in adults was published in 2019 by ACC/AHA.[21] See limitations to the guidelines as discussed above. The class of recommendation and level of evidence description are described above (**Tables 5 and 6**). Recommendations pertaining to management of diabetes, hypertension and lipids will be reviewed in another class update. Aspirin for primary prevention was recommended for a select group of patients as described in the AF Guideline above in **Table 7**.

ACC/AHA – Guideline for the Management of Patient with Valvular Heart Disease

The ACC/AHA updated guidance in 2020 for the management of patients with valvular heart disease.[24] This guideline also had the same class of recommendation and level of evidence designation as the previous 2 guidelines with detailed descriptions in **Tables 5 and 6**, as well as the same limitations as discussed above. The literature was searched from January 1, 2010 to March 1, 2020. Anticoagulation with a vitamin K antagonist (VKA) is most often recommended to patients with prosthetic valves. The use of antiplatelet therapy is an option as described below in **Table 9**.

Table 9. Antiplatelet Use in the Management of Patients with Prosthetic Valves[24]

Recommendation	Class of Recommendation*	Level of Evidence
Aspirin 75 mg to 100 mg daily is reasonable for patients with bioprosthetic TAVI and the absence of other indications for oral anticoagulants	2a	B-R
Aspirin 75 mg to 100 mg daily is reasonable for patients with bioprosthetic SAVR or mitral valve replacement and in the absence of other indications for oral anticoagulants	2a	B-NR
Aspirin 75 mg to 100 mg daily, in addition to a VKA, may be considered for patients with a mechanical SAVR or mitral valve replacement who have an indication for antiplatelet therapy when the bleeding risk is low	2b	B-R
Patients should be continued on ASA 75 mg to 100 mg and may have consider a VKA targeted to a lower INR (1.5 – 2.0) 3 or more months after surgery that have a mechanical On-X AVR and no thrombotic risk factors	2b	B-NR
Aspirin 75 mg to 100 mg and clopidogrel 75 mg may be reasonable 3-6 months after valve implementation for patients with bioprosthetic TAVI who are at low risk of bleeding	2b	B-NR
Low-dose rivaroxaban (10 mg daily) and aspirin 75 mg to 100 mg is contraindicated in the absence of other indications for oral anticoagulants for patients with bioprosthetic TAVI	3: Harm	B-R
Abbreviations: ASA – aspirin; AVR – aortic valve replacement; INR - international normalized ratio; TAVI – transcatheter aortic valve implantation; SAVR – surgical aortic valve replacement; VKA – vitamin K antagonist Key: * The class of recommendation designations were changed from Roman Numeral to numbers in 2020 guidelines but are identically defined.		

In patients who have had thromboembolic events with prosthetic valves (mechanical and bioprosthetic), the addition of antiplatelet therapy is recommended. In patients who have had a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation with a mechanical AVR or mechanical mitral valve replacement, it is reasonable to increase the INR goal from 2.5 (range 2.0 to 3.0) to 3.0 (range 2.5 to 3.5) or to add daily low-dose ASA (75 mg to 100 mg) with assessment of bleeding.[24] Patients who experience a thromboembolic event or stroke while on antiplatelet therapy with a bioprosthetic surgical or transcatheter

aortic valve or bioprosthetic mitral valve should be considered for VKA anticoagulation after assessment of bleeding risk. ASA 75 mg to 100 mg daily may be considered for pregnant women with mechanical valve prostheses, in addition to other anticoagulation, if needed for other indications.[24]

CHEST – Antithrombotic Therapy for Atrial Fibrillation

In 2018, CHEST updated guidance on the management of patients with AF.[23] Guidelines met criteria for inclusion with the limitations of having a majority of authors with conflicts with industry, including the chair. CHEST receives industry support which could bias clinical recommendations. The guideline will be included for context but not relied on for making policy decisions. The literature was searched from January 1, 2007 through October 2017. The quality of evidence was assessed using the GRADE approach, designations of strong to weak, and risk of bias was evaluated for randomized and nonrandomized trials. Anticoagulants are the mainstay of treatment in patients with AF; however, antiplatelets have a role in certain patient populations as described in **Table 10**.[23] Recommendations pertaining to anticoagulants were included in the corresponding class update.

Table 10. CHEST Guidance of the Use of Antiplatelet Therapies in Patients with Atrial Fibrillation[23]

Recommendation	Strength of Recommendation	Quality of Evidence
Antiplatelet therapy alone (monotherapy or ASA in combination with clopidogrel) is not recommended for patients with AF for stroke prevention alone, regardless of stroke risk	Strong	Moderate
Triple therapy for 1-3 months followed by dual therapy with an OAC plus a single antiplatelet (preferably clopidogrel) for 6 months, followed by OAC monotherapy is recommended for patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk is low (HAS -BLED 0-2) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
Triple therapy for 1 month, followed by dual therapy with OAC plus an antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy is recommended for patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk is high (HAS -BLED $\geq$3) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
OAC plus a single antiplatelet (preferably clopidogrel) for 6 months, followed by OAC monotherapy is recommended in patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk unusually high and thrombotic risk is unusually low	Weak	Low
Triple therapy for 6 months followed by dual therapy with OAC plus a single antiplatelet (preferably clopidogrel) until 12 months following which OAC monotherapy is recommended with patients with AF requiring OAC presenting with ACS, undergoing PCI/stenting where bleeding risk is low (HAS -BLED 0-2) compared to risk for recurrent ACS or stent thrombosis	Weak	Low
Triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, in which OAC monotherapy can be used for patients with AF requiring OAC presenting with ACS, undergoing PCI/stenting where bleeding risk is high (HAS -BLED $\geq$3) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
OAC plus a single antiplatelet (preferably clopidogrel) for 6-9 months, followed by OAC monotherapy is recommended for patients with AF requiring OAC presenting with ACS, undergoing elective PCI/stenting where bleeding risk is unusually high and thrombotic risk is low	Weak	Low

If ASA is used with OAC in patients with AF, a dose of 75 mg to 100 mg daily is recommended with concomitant use of a PPI to minimize GI bleeding	Weak	Low
If a $P2Y_{12}$ inhibitor is used with an OAC in patients with AF then clopidogrel is recommended	Weak	Low
Abbreviations: ACS – acute coronary syndrome; AF – atrial fibrillation; ASA – aspirin; HAS – BLED – hypertension, abnormal renal/liver function (1 point), stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly (1 point each); OAC – oral anticoagulant therapy; PCI – percutaneous coronary intervention; PPI – proton pump inhibitor		

AHA/ASA – Guidelines for the Early Management of Patients with Acute Ischemic Stroke

In 2018 the AHA/ASA updated 2013 guidance on the management of patients with acute ischemic stroke.[95] This guideline had minimal authors with connection to industry. See **Table 5** and **6** for descriptions on the level of evidence grading and types of recommendations. A majority of the guideline pertained to non-pharmacologic management of stroke or use of pharmacotherapy not classified as antiplatelets. For the purpose of this update, just platelet inhibitors will be discussed in **Table 11**.

Table 11. Recommendations for the Use of Platelet Inhibitors for Acute Management of Ischemic Stroke[95]

Recommendation	Class of Recommendation	Level of Evidence
ASA should be administered with AIS within 24-48 hours after stroke onset. Delay administration 24 hours if patient received IV alteplase	I	A
ASA should not be used as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy	III: No benefit	B-R
In patients with minor stroke, DAPT (ASA + clopidogrel) for 21 days begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset	IIa	B-R
Ticagrelor is not recommended over ASA for the acute treatment of patients with minor stroke	III: No benefit	B-R

After review, 5 guidelines were excluded due to poor quality.[88,95–98]

New Indications:

Brilinta® (Ticagrelor) – Obtained 2 new indications in 2020.

- The FDA approved ticagrelor (in combination with ASA) in May of 2020 for the indication of reducing the risk of first MI or stroke in patients with coronary artery disease at high risk for such event. Efficacy for use was established in patients with type 2 diabetes mellitus (T2DM), but is not limited to this patient population.[17]
- In November of 2020 the FDA approved ticagrelor to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score of 5 or less) or high-risk transient ischemic attack (TIA).[17]

New FDA Safety Alerts:

Table 1. 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)
Ticagrelor[17]	Brilinta®	10/2019	Warnings and Precautions	Reported to cause false negative test results in platelet functional tests (to include, but not limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT)

Randomized Controlled Trials:

A total of 559 citations were manually reviewed from the initial literature search. After further review, 558 RCT citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Abstracts are presented for included trials in Appendix 2.

Table 12. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
ACEND Study Collaborative Group[99]	1. Aspirin 100 mg daily 2. Placebo daily Mean follow-up of 7.4 years	Adult patients with diabetes (94% type 2) but no evidence of CV disease	First serious vascular event (i.e., MI, stroke, TIA or death from any vascular cause, excluding any confirmed intracranial hemorrhage)	Aspirin: 658 (8.5%) Placebo: 743 (9.6%) RR 0.88 (95% CI, 0.79 to 0.97) P=0.01 *Aspirin use reduced vascular events in participants with diabetes but increased major bleeding (benefits counterbalanced by bleeding hazard)*

Abbreviations: CV – cardiovascular; MI – myocardial infarction; RCT - randomized clinical trial, RR – rate ratio; TIA – transient ischemic attack

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
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	TABLET DR	Y
aspirin	ADULT ASPIRIN REGIMEN	TABLET DR	Y
aspirin	ASPIR 81	TABLET DR	Y
aspirin	ASPIRIN	TABLET DR	Y
aspirin	ASPIRIN EC	TABLET DR	Y
aspirin	ASPIRIN EC	TABLET DR	Y
aspirin	ASPIR-LOW	TABLET DR	Y
aspirin	ECPIRIN	TABLET DR	Y
aspirin/dipyridamole	AGGRENOX	CPMP 12HR	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
aspirin/omeprazole	YOSPRALA	TAB IR DR	N
prasugrel HCl	EFFIENT	TABLET	N
prasugrel HCl	PRASUGREL HCL	TABLET	N
ticagrelor	BRILINTA	TABLET	N
ticlopidine HCl	TICLOPIDINE HCL	TABLET	N
vorapaxar sulfate	ZONTIVITY	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASCEND Study Collaborative Group; Louise Bowman, Marion Mafham, Karl Wallendszus, Will Stevens, Georgina Buck, Jill Barton, Kevin Murphy, Theingi Aung, Richard Haynes, Jolyon Cox, Aleksandra Murawska, Allen Young, Michael Lay, Fang Chen, Emily Sammons, Emma Waters, Amanda Adler, Jonathan Bodansky, Andrew Farmer, Roger McPherson, Andrew Neil, David Simpson, Richard Peto, Colin Baigent, Rory Collins, Sarah Parish, Jane Armitage

Abstract

Background: Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.

Methods: We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer.

Results: A total of 15,480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

Conclusions: Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard. (Funded by the British Heart Foundation and others; ASCEND Current Controlled Trials number, ISRCTN60635500 ; ClinicalTrials.gov number, NCT00135226 .).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 02, 2021
Search Strategy:

#	Searches	Results
1	aspirin.mp. or Aspirin/	68958
2	dipyridamole.mp.	10529
3	cilostazol.mp. or Cilostazol/	1942
4	clopidogrel.mp. or Clopidogrel/	15022
5	prasugrel.mp. or Prasugrel Hydrochloride/	2617
6	ticagrelor.mp. or Ticagrelor/	3174
7	ticlopidine.mp. or Ticlopidine/	11094
8	vorapaxar.mp.	339
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	88006
10	limit 9 to (english language and humans and yr="2017 -Current")	7623
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	559

Appendix 4: Key Inclusion Criteria

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

Appendix 5: Prior Authorization Criteria

Platelet Inhibitors

Goal:

- Approve antiplatelet drugs for funded diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is this new therapy for a patient who was hospitalized and had an antiplatelet initiated in the hospital?	**Yes:** Approve for 30 days only and request a PA from the provider for continuation of therapy.	**No:** Go to #5

Approval Criteria		
5. Is this a request for continuation of therapy for a patient that already received 30 days of therapy that was initiated in the hospital?	**Yes:** Approve for FDA-approved indication for up to 1 year.	**No:** Go to #6
6. Is the request for ticagrelor?	**Yes:** Go to #7	**No:** Got to #8
7. Does the patient have a history of intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indication for up to 1 year.
8. Is the request for vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

FDA Approved Indications (April 2021)

	1° Stroke	2° Stroke	2° PAD	1° MI	2° MI	ACS	
						No PCI	PCI
ASA/DP ER		x					
clopidogrel		x	x		x	x	x
ticagrelor	x	x		x	x	x	x
vorapaxar		CI	x		x		

Abbreviations: 1 ^{o} = prevention, 2^{o} = secondary prevention; ACS=Acute Coronary Syndrome; ASA/DP ER = aspirin/dipyridamole; CI=contraindication; PCI=Percutaneous Intervention; X = FDA-approved indication.

P&T / DUR Review: *6/21 (KS), 9/17 (MH); 7/15; 11/11*
Implementation: *7/1/21; 10/15, 8/15; 7/31/14; 4/9/12*