Pocket Guide
Antiplatelet Therapy in the Outpatient Setting
2011 Recommendations

For more information, please visit the Canadian Cardiovascular Society (CCS) Antiplatelet Guidelines at www.ccsguidelineprograms.ca.
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Introduction and Rationale

Antiplatelet therapy is underused in clinical practice. Canadian physicians require guidance that is:
- Clear.
- Easily accessible.
- Evidence-based.

2011 Canadian Antiplatelet Therapy Guidelines
Development Methodology

- Identify relevant clinical guidelines for antiplatelet therapy.
- Develop recommendations via consideration of:
  - Existing guidelines and their associated AGREE score.
  - Literature published subsequent to existing guidelines.
  - Expert opinion.
- Create graded recommendations using a system set forth by the Canadian Cardiovascular Society (CCS).
- Conduct an external review by Canadian experts in their respective fields who were not involved in the writing process.
Antiplatelet Therapy (APT)

Platelets play a pivotal role in cardiovascular pathophysiology.

Rupture or erosion of atherosclerotic coronary artery plaque → Platelet activation and aggregation → Intraarterial thrombosis and adverse cardiovascular events

Available Agents

- ASA
- Clopidogrel
- Dipyridamole
- Ticlopidine
- Prasugrel
- Ticagrelor

Antiplatelet agents are cornerstone therapy in patients with atherosclerotic vascular disease including CAD, cerebrovascular disease, and PAD.

ASA: acetylsalicylic acid; CAD: coronary artery disease; PAD: peripheral artery disease.
Contemporary Classification of ACS

Based on:
- Appearance of presenting ECG.
- Subsequent measurement of cardiac biomarkers (e.g. troponin).

**STEMI**
- ST-segment elevation on surface ECG → typically indicates complete occlusion of a coronary artery.
- Biochemical evidence of myocardial necrosis.

**NSTEACS**
- No ST-segment elevation on surface ECG → typically indicates non-occlusive intracoronary thrombosis.
- Biochemical evidence of myocardial necrosis
- Negative biomarkers

In general, the ADP P2Y$_{12}$ receptor antagonist added to ASA in the acute setting should be maintained for the duration of the therapy (Class I, Level C).

ADP: adenosine diphosphate; ASA: acetylsalicylic acid; CABG: coronary artery bypass graft; STEMI: ST-elevation myocardial infarction.
In general, the ADP P2Y₁₂ receptor antagonist added to ASA in the acute setting should be maintained for the duration of the therapy (Class I, Level C).

ADP: adenosine diphosphate; ASA: acetylsalicylic acid; CABG: coronary artery bypass graft; NSTEACS: non-ST-elevation acute coronary syndrome.
**APT for Secondary Prevention in First Year Post-PCI**

<table>
<thead>
<tr>
<th>PCI is thrombogenic due to:</th>
<th>Secondary prevention with DAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mechanically induced plaque rupture and vessel injury.</td>
<td>• Use for 1 year post PCI.</td>
</tr>
<tr>
<td>PLUS</td>
<td>• <strong>BMS</strong>: early discontinuation may be considered if there is a high risk of bleeding (e.g. major surgery).</td>
</tr>
<tr>
<td>• Implantation of metallic stent scaffolding.</td>
<td>• <strong>DES</strong>: do not discontinue prior to 1 year.</td>
</tr>
<tr>
<td></td>
<td>• Continuation beyond 1 year may be considered if there is a high risk of thrombosis and a low risk of bleeding.</td>
</tr>
<tr>
<td></td>
<td>Allows for:</td>
</tr>
<tr>
<td></td>
<td>• Vessel healing.</td>
</tr>
<tr>
<td></td>
<td>• Plaque stabilization.</td>
</tr>
<tr>
<td></td>
<td>• Reendothelialization.</td>
</tr>
</tbody>
</table>

Discontinuation of DAPT post-PCI is associated with ↑ risks of subacute (1-30 days) and late (30 days-1 year) stent thrombosis.*

*Optimal duration of long-term DAPT currently under investigation.

Post-discharge Management of Patients Undergoing PCI

ASA: acetylsalicylic acid; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.
ACS: acute coronary syndrome; ASA: acetylsalicylic acid; CAD: coronary artery disease.

**Management of Stable CAD**

- **ASA 75-162 mg OD**
  - Indefinite Therapy (Class I, Level A)
  - If ASA intolerant

- **ACS >1 year post event**
  - If high risk of thrombosis and low risk of bleeding
  - **Clopidogrel 75 mg OD**
    - Indefinite Therapy (Class IIa, Level B)
  - **ASA 75-162 mg OD**
    - Indefinite Therapy (Class IIa, Level B)

**Dual-antiplatelet therapy**
- with ASA 75-162 mg OD and clopidogrel 75 mg OD may be considered (Class IIb, Level C).
### Key Considerations: APT Post-ACS/PCI

**DO**
- Provide lifetime APT to all patients post-ACS with or without PCI.
- Provide DAPT with ASA + P2Y$_{12}$ inhibitor to all ACS patients.
- Know the type of stent your patient has inserted.
- Consider DAPT beyond 1 year in patients with high risk of thrombosis and low risk of bleeding.

**DON’T**
- Use doses of ASA above 75-162 mg.
- Discontinue DAPT prior to 1 year without good reason.
- Discontinue DAPT in a patient with a DES prior to 1 year.

ACS: acute coronary syndrome; APT: antiplatelet therapy; ASA: acetylsalicylic acid; DAPT: dual-antiplatelet therapy; DES: drug-eluting stent; PCI: percutaneous coronary intervention.
APT for Secondary Prevention Post-CABG

APT is the gold standard in preventing saphenous vein graft closure after CABG.

**ASA**
- Given indefinitely → may prevent adverse clinical events post-CABG.
- No evidence of improved arterial graft patency.

**Clopidogrel**
- Recommended for patients allergic or intolerant to ASA.
- Safer than other available therapies (e.g. ticlopidine).
- No randomized trial has specifically studied the efficacy of clopidogrel in the prevention of post-CABG vein graft closure.

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Warfarin appears to be as effective as antiplatelet therapy in preventing saphenous graft closure post-CABG, but it is associated with a higher risk of bleeding complications.

APT: antiplatelet therapy; ASA: acetylsalicylic acid; CABG: coronary artery bypass graft.
The outpatient management of patients after CABG is outlined in this figure and may include dual-antiplatelet therapy when a recently stented vessel is not adequately bypassed.

ASA: acetylsalicylic acid; ATP: antiplatelet therapy; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.
APT for Secondary Prevention of Cerebrovascular Disease

Patients with TIA or ischemic stroke are at increased risk of recurrent stroke and other vascular events → require lifetime APT.

Risks of TIA or ischemic stroke
- Highest in the initial 2 days after the event and may remain high for the subsequent 90 days.
- Overall risk at 90 days: ~17%.*
- Risk of combined vascular complications:† ~44%‡ at 10 years.

Any of the following are recommended:
- ASA 75-162 mg OD.
- Clopidogrel 75 mg OD.
- ASA 25 mg + ER-dipyridamole 200 mg BID.
- DAPT with ASA + clopidogrel may be considered for 30 days following high risk TIA or minor stroke, if the risk of bleeding is low.
- DAPT should not be used beyond 30 days for secondary stroke prevention.

Expedited evaluation and early treatment may lower the risk of stroke recurrence.

*95% CI: 9%-25% when the outcome is actively ascertained; †MI, stroke, and vascular death; ‡95% CI: 42%-46%.
APT: antiplatelet therapy; ASA: acetylsalicylic acid; CI: confidence interval; DAPT: dual-antiplatelet therapy; ER: extended-release; MI: myocardial infarction; TIA: transient ischemic attack.
Management of TIA and Ischemic Stroke

The outpatient management of TIA or ischemic stroke of non-cardiac origin can include dual-antiplatelet therapy for the first month. ASA: acetylsalicylic acid; ER: extended-release; TIA: transient ischemic attack.

The combination of ASA 75-162 mg daily plus clopidogrel 75 mg daily should not be used for secondary stroke prevention beyond 1 month unless otherwise indicated and the risk of bleeding is low (Class III, Level B).

The combination of ASA 75-162 mg daily plus clopidogrel 75 mg daily in the first month after TIA or minor ischemic stroke may be superior to ASA alone in patients not at a high risk of bleeding (Class IIb, Level C).

The combination of ASA 75-162 mg daily plus clopidogrel 75 mg daily in the first month after TIA or minor ischemic stroke may be superior to ASA alone in patients not at a high risk of bleeding (Class IIb, Level C).

- ER-dipyridamole 200 mg twice daily plus ASA 25 mg twice daily (Class I, Level A)
- Clopidogrel 75 mg once daily (Class I, Level A)
- ASA 75-162 mg once daily (Class I, Level A)
**Key Considerations: APT for Cerebrovascular Disease**

<table>
<thead>
<tr>
<th><strong>DO</strong></th>
<th><strong>DON’T</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide lifetime antiplatelet therapy to all patients post-ischemic stroke or -TIA.</td>
<td>• Use DAPT with ASA + clopidogrel for long-term secondary stroke prevention.</td>
</tr>
<tr>
<td>• Consider DAPT with ASA + clopidogrel in patients with a high risk of TIA or minor stroke for 30 days.</td>
<td></td>
</tr>
</tbody>
</table>

**APT:** antiplatelet therapy; **ASA:** acetylsalicylic acid; **DAPT:** dual-antiplatelet therapy; **TIA:** transient ischemic attack.
# APT for Vascular Prevention in Patients with PAD

**Peripheral Arterial Disease**

- Bruit found along major vessels, peripheral pulsations reduced or absent.
- Abnormally enlarged artery (possible aneurysm).

**Vascular Risk**

- Usually harbour traditional risk factors.
- Evidence shows patients with ABI <0.9 present a cardiovascular morbidity and mortality rate approx. halfway between that of a patient with a normal ABI and that of a patient with claudication.
- High risk of cardiovascular events and total mortality, even when taking into account usual risk factors.

**Asymptomatic PAD**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>• Bruit found along major vessels, peripheral pulsations reduced or absent.</td>
</tr>
<tr>
<td>• Abnormally enlarged artery (possible aneurysm).</td>
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</table>

**Symptomatic PAD**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>• Claudication.</td>
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<tr>
<td>• Rest pain.</td>
</tr>
<tr>
<td>• Ischemic lesions.</td>
</tr>
</tbody>
</table>

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*ABI <0.9.*

ABI: ankle-brachial index; APT: antiplatelet therapy; PAD: peripheral arterial disease.
Management of Peripheral Arterial Disease

ASA*: 75-162 mg OD may be considered for those at high risk because of associated atherosclerotic risk factors in the absence of risk factors for bleeding (Class IIB, Level C).

ASA*: 75-162 mg OD or clopidogrel 75 mg daily is recommended providing the risk for bleeding is low (Class IIb, Level B).

Antiplatelet therapy* as indicated for the CAD and/or cerebrovascular status is recommended (Class I, Level A).

ASA*: 75-162 mg OD or clopidogrel 75 mg daily is recommended providing the risk for bleeding is low (Class IIb, Level B).

*Asymptomatic PAD is defined by an ankle-brachial index <0.9 in the absence of claudication or other manifestations such as obstructive vascular disease in the extremities; †For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B); ‡For patients with PAD with an indication for oral anticoagulation such as atrial fibrillation, venous thromboembolism, heart failure, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (Class III, Level A).

ASA: acetylsalicylic acid; CAD: coronary artery disease; PAD: peripheral arterial disease.
Management Post-peripheral Artery Surgery

*For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B).

The outpatient management of patients after peripheral arterial surgery or percutaneous revascularization or presenting an abdominal aortic aneurysm AAA.

AAA: abdominal aortic aneurysm; ASA: acetylsalicylic acid; PAD: peripheral arterial disease.

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ASA* 75-162 mg OD may be considered for all patients with an AAA, particularly those with clinical or subclinical PAD (Class IIb, Level C).

ASA* 75-162 mg OD should be given to patients who undergo lower-extremity balloon angioplasty with or without stenting for chronic symptomatic PAD (Class IIa, Level C).

In those with infrainguinal grafts and a high risk of thrombosis or limb loss, combination therapy with a vitamin K antagonist and ASA* 75-162 mg OD may be of benefit (Class IIB, Level C).

ASA*: acetylsalicylic acid

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*For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B).
Primary Prevention of Vascular Events

- May be defined as antiplatelet strategies, administered to individuals free of any evidence of manifest atherosclerotic disease in any vascular bed, to prevent clinical vascular events or manifestations thereof.

- Atherosclerotic disease may include, but is not limited to:
  - Syndromes of angina pectoris.
  - MI.
  - Ischemic stroke.
  - TIA.
  - Intermittent claudication.
  - Critical limb ischemia.

The benefits of ASA and APT for primary prevention have not been demonstrated.

ASA: acetylsalicylic acid; APT: antiplatelet therapy; MI: myocardial infarction; TIA: transient ischemic attack.
For the purpose of this guideline, primary prevention is defined as antiplatelet strategies, administered to individuals free of any evidence of manifest atherosclerotic disease in any vascular bed, to prevent clinical vascular events or manifestations thereof. ASA: acetylsalicylic acid.
### Key Considerations: APT for Primary Prevention

<table>
<thead>
<tr>
<th>DO</th>
<th>DON’T</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider ASA only where there is clear evidence of high risk:</td>
<td>• Use APT for <strong>primary prevention</strong>.</td>
</tr>
<tr>
<td>• Asymptomatic carotid stenosis.</td>
<td></td>
</tr>
<tr>
<td>• Asymptomatic coronary atherosclerosis.</td>
<td></td>
</tr>
<tr>
<td>• Reduced ABI.</td>
<td></td>
</tr>
<tr>
<td>• End-stage renal disease.</td>
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</tbody>
</table>

ABI: ankle-brachial index; APT: antiplatelet therapy; ASA: acetylsalicylic acid.
Patients with diabetes have a variety of risk factors and alterations to platelet function that predispose them to platelet activation and thrombosis.

Platelet alterations may include:
- Increased platelet turnover.
- Enhanced platelet aggregation.
- Increased thromboxane synthesis.

Despite clear evidence of a procoagulant state in patients with diabetes, the balance between benefits and potential harm of antiplatelet treatment appears less favourable in patients with diabetes compared with those in other high cardiovascular risk groups.

The absence of clear primary prevention benefits for antiplatelet therapy in patients with diabetes may indicate that patients with diabetes are a specific subgroup of patients in whom mechanisms such as ASA resistance are manifest.

APT: antiplatelet therapy; ASA: acetylsalicylic acid.
Management of Patients with Diabetes

**ASA** 75-162 mg OD may be considered for secondary prevention in patients with diabetes and **manifest vascular disease for which its benefits are established** (Class I, Level A).

Diabetes

**Patients >40 years and at low risk for major bleeding, low-dose ASA** 75-162 mg OD may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class IIb, Level B).

**Routine use of ASA** at any dose is not recommended for the primary prevention of vascular ischemic events in patients with diabetes (Class III, Level A).

*For patients allergic or intolerant to ASA, use of clopidogrel 75 mg OD is suggested (Class IIa, Level B). ASA: acetylsalicylic acid.*
Largely due to reduced cardiac output, HF is associated with increased risk of thromboembolic events and other ischemic cardiovascular events.

**HF aetiology:**
- Ischemic: 70% of patients.
- Hypertension and idiopathic causes: 30% of patients.

Despite HF being associated with a prothrombotic state, antiplatelet therapy is not recommended in the absence of coronary ischemia.

Antiplatelet therapy should be used in all patients with ischemic HF.*
Limited evidence suggests ASA may ↑ secondary risk of hospitalization for HF.

*No evidence of benefit for patients with nonischemic HF (other than for secondary prevention of HF due to CAD).

APT: antiplatelet therapy; ASA: acetylsalicylic acid; CAD: coronary artery disease; HF: heart failure.
Management of Heart Failure

Heart Failure

Nonischemic

Routine use of antiplatelet agents is not recommended (Class III, Level C).

Ischemic

Antiplatelet therapy should be dictated by the underlying CAD (Class IIa, Level A).

CAD: coronary artery disease.
Management of Chronic Kidney Disease

Chronic kidney disease is defined as estimated glomerular filtration rate (eGFR) or creatinine clearance <60 mL/min/1.73 m² (for purposes of this guideline, obtained using either Cockcroft-Gault formula or Modification of Diet in Renal Disease [MDRD] equation); *For patients allergic or intolerant to ASA, use of clopidogrel 75 mg OD is suggested (Class IIa, Level B). ASA: acetylsalicylic acid; CKD: chronic kidney disease; ESRD: end-stage renal disease.

Antiplatelet therapy should be considered for secondary prevention in patients with CKD and manifest vascular disease for which its benefits are established (Class IIa, Level C).

ASA* 75-162 mg OD may be considered for primary prevention of ischemic vascular events in patients with ESRD and a low risk of bleeding (Class IIb, Level C).
Management in Pregnancy and Lactation

ASA* 75-162 mg OD may be considered for use in breastfeeding women (Class I, Level C).

ASA* 75-162 mg OD is likely safe for use during the first trimester of pregnancy (Class IIa, Level A).

ASA* can be used safely during the second and third trimester of pregnancy (Class I, Level A).

For cardio- or cerebrovascular disease in which antiplatelet therapy would be indicated in nonpregnant women, there should be similar considerations for its use in pregnancy (Class IIa, Level A).

*Use of antiplatelet agents other than low-dose ASA for cardio- or cerebrovascular indications during pregnancy and lactation should only be considered if maternal benefits clearly outweigh potential fetal/infant risks (Class IIb, Level C).

ASA: acetylsalicylic acid.
## Perioperative Management of Patients on APT

### Relative risk of bleeding associated with common surgical and non-surgical procedures.

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>• Neurosurgery (intracranial or spinal surgery)</td>
</tr>
<tr>
<td></td>
<td>• Cardiac surgery (coronary artery bypass or heart valve replacement)</td>
</tr>
<tr>
<td>High Risk</td>
<td>• Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)</td>
</tr>
<tr>
<td></td>
<td>• Major urologic surgery (prostatectomy, bladder tumour resection)</td>
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<tr>
<td></td>
<td>• Major lower limb orthopaedic surgery (hip/knee joint replacement)</td>
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<tr>
<td></td>
<td>• Lung resection surgery</td>
</tr>
<tr>
<td></td>
<td>• Intestinal anastomosis surgery</td>
</tr>
<tr>
<td></td>
<td>• Permanent pacemaker insertion or internal defibrillator placement</td>
</tr>
<tr>
<td></td>
<td>• Selected procedures (kidney biopsy, pericardiocentesis, colonic polypectomy)</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>• Other intra-abdominal surgery</td>
</tr>
<tr>
<td></td>
<td>• Other intrathoracic surgery</td>
</tr>
<tr>
<td></td>
<td>• Other orthopaedic surgery</td>
</tr>
<tr>
<td></td>
<td>• Other vascular surgery</td>
</tr>
<tr>
<td></td>
<td>• Selected procedures (prostate or cervical biopsy)</td>
</tr>
<tr>
<td>Low Risk</td>
<td>• Laprososcopic cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>• Laprososcopic inguinal hernia repair</td>
</tr>
<tr>
<td></td>
<td>• Dental procedures</td>
</tr>
<tr>
<td></td>
<td>• Dermatologic procedures</td>
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<tr>
<td></td>
<td>• Ophthalmologic procedures</td>
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<tr>
<td></td>
<td>• Coronary angiography</td>
</tr>
<tr>
<td></td>
<td>• Gastroscopy or colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Selected procedures (bone marrow or lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)</td>
</tr>
<tr>
<td>Very Low Risk</td>
<td>• Single tooth extraction or teeth cleaning</td>
</tr>
<tr>
<td></td>
<td>• Skin biopsy or selected skin cancer removal</td>
</tr>
<tr>
<td></td>
<td>• Cataract removal</td>
</tr>
</tbody>
</table>

APT: antiplatelet therapy.
The perioperative antiplatelet management will vary depending on the risk of bleeding related to the diagnostic or surgical procedure and the risk of cardiovascular ischemic event.

ASA: acetylsalicylic acid; CAbG: coronary artery bypass graft.
The perioperative antiplatelet management of patients receiving dual-antiplatelet therapy after a coronary stent will vary depending on the type of stent and the urgency of the surgery.

ASA: acetylsalicylic acid; BMS: bare-metal stent; CABG: coronary artery bypass graft; DES: drug-eluting stent.
### Key Considerations: Perioperative APT Management

<table>
<thead>
<tr>
<th>DO</th>
<th>DON’T</th>
</tr>
</thead>
</table>
| • Delay procedures in patients taking DAPT.  
• Stop clopidogrel for 7-10 days prior if it can be done so safely.  
• Stop ASA for 7-10 days for high-risk surgical procedures. | • Discontinue DAPT prior to 1 year in patients with a DES.  
• Discontinue DAPT prior to 6 weeks in patient with a BMS.  
• Stop ASA for minor procedures including:  
  • Arthrocentesis.  
  • Dental procedures.  
  • Cataract surgery.  
  • Skin excisions. |

ASA: acetylsalicylic acid; APT: antiplatelet therapy; BMS: bare-metal stent; DAPT: dual-antiplatelet therapy; DES: drug-eluting stent.
Management of Minor Bleeding

The management of patients on antiplatelet therapy with minor bleeding is outlined and may include further investigation for patients who develop ecchymosis or petechiae.

ASA: acetylsalicylic acid.

In the absence of superimposed abnormalities in hemostatic function, antiplatelet drugs can be continued with clinical observation, whereas in patients with thrombocytopenia or a coagulopathy, ASA (or clopidogrel) should be stopped pending further investigations (Class IIa, Level C).

Patients in whom there is excessive bleeding after a dental procedure should receive application of local pressure and/or use of tranexamic acid mouthwash 2-4 times daily for 1-2 days (Class IIa, Level C).

Patients who develop ecchymosis and petechiae should undergo testing with a complete blood count and international normalized ratio (INR) and activated partial thromboplastin time (aPTT) (Class IIa, Level C).

Patients in whom subconjunctival bleeding develops should continue treatment and be monitored for bleeding (Class IIa, Level C).

Patients in whom there is excessive bleeding after a dental procedure should receive application of local pressure and/or use of tranexamic acid mouthwash 2-4 times daily for 1-2 days (Class IIa, Level C).
Key Considerations: Management of APT in Association with Minor Bleeding

<table>
<thead>
<tr>
<th>DO</th>
<th>DON’T</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If persistent, check:</td>
<td>• Stop antiplatelet therapy for:</td>
</tr>
<tr>
<td>• Complete blood count.</td>
<td>• Ecchymosis.</td>
</tr>
<tr>
<td>• INR and aPTT.</td>
<td>• Petechiae.</td>
</tr>
<tr>
<td></td>
<td>• Subconjunctival hemorrhage.</td>
</tr>
<tr>
<td></td>
<td>• Epistaxis.</td>
</tr>
<tr>
<td></td>
<td>• Dental/gingival bleeding (tranexamic acid mouthwash).</td>
</tr>
</tbody>
</table>

APT: antiplatelet therapy; aPTT: activated partial thromboplastin time; INR: international normalized ratio.
Combination Therapy with Warfarin and ASA

Possible clinical scenarios for combination therapy:
1. Both coagulation- and platelet-mediated pathways involved in 1 disease (e.g. ACS).
2. Patient has 2 diseases, 1 treated with an anticoagulant and 1 with APT (e.g. patients with both atrial fibrillation and CAD, or those with both VTE and CAD).

ACS: acute coronary syndrome; APT: antiplatelet therapy; ASA: acetylsalicylic acid; CAD: coronary artery disease; VTE: venous thromboembolism.
Management of Patients Requiring Warfarin

The management of patients requiring warfarin therapy requires an assessment of the risk of bleeding and the medical conditions for which combination therapy may be reasonable.

ACS: acute coronary syndrome; ASA: acetylsalicylic acid; BMS: bare-metal stent; CABG: coronary artery bypass graft; DES: drug-eluting stent; INR: international normalized ratio.
Interaction Between Clopidogrel and PPIs

Clopidogrel requires activation by cytochrome P450 isozyme CYP2C19 in the liver.

Interaction with PPIs

- May inhibit CYP2C19
  - Lansoprazole
  - Omeprazole
  - Esomeprazole
  - Pantoprazole

PPI: proton-pump inhibitor.

The management of patients on dual antiplatelet therapy may include the use of proton-pump inhibitors with minimal inhibition of cytochrome P2C19 in patients considered at increased risk of upper gastrointestinal bleeding.

PPI: proton-pump inhibitor.
Use of proton-pump inhibitors in patients taking clopidogrel

Patient at risk of upper gastrointestinal bleeding

The pharmacodynamic interaction between clopidogrel and PPIs and the initial findings from observational studies suggested an increased risk of cardiovascular events in concomitant users of clopidogrel and PPIs. Recently published data from a randomized clinical trial suggest that this risk is likely clinically insignificant. Nevertheless, because of potential limitations with study design and patients recruited, PPIs that minimally inhibit CYP2C19 are preferred for patients taking clopidogrel who are considered to be at increased risk of upper gastrointestinal bleeding (Class IIb, Level B).

PPI: proton-pump inhibitor.
Interaction Between ASA and NSAIDs

ASA binds irreversibly to serine residue at position 529 of platelet COX-1, preventing platelet aggregation.

Interaction with NSAIDs*

- Traditional NSAIDs form a reversible complex with COX-1, dependent on serum concentrations of the drug, with dissociation, platelets assume normal function.
- May inhibit binding of ASA to COX-1.

*In patients on ASA, the use of traditional NSAIDs should be avoided and if an anti-inflammatory drug is required, a specific cyclooxygenase-2 inhibitor should be considered.

ASA: acetylsalicylic acid; COX-1: cyclooxygenase-1; NSAID: non-steroidal anti-inflammatory drug.
Use of NSAIDs in Patients on ASA

Individuals taking ASA for vascular protection should avoid the concomitant use of traditional (non-coxib) NSAIDs (Class III, Level C).

All NSAIDs and coxibs should be avoided in patients at increased cardiovascular risk (Class III, Level A).

If a patient taking ASA for vascular protection requires an anti-inflammatory drug, specific coxibs should be chosen over traditional NSAIDs (Class III, Level C).

### APT: Drug-Drug Interactions

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<tr>
<th><strong>DO</strong></th>
<th><strong>DON’T</strong></th>
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<tr>
<td>• Use PPIs with minimal effect on CYP2C19 in patients at increased risk of UGI bleeding taking clopidogrel.</td>
<td>• Use PPIs that inhibit CYP2C19 in patients taking clopidogrel or prasugrel.</td>
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<tr>
<td>• Use coxibs over traditional NSAIDs in patients taking ASA for CV prevention but only if absolutely necessary.</td>
<td>• Use NSAIDs or coxibs in patients at increased risk of vascular events.</td>
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