ANTIPLATELET GUIDELINES

2012 UPDATE

Canadian Cardiovascular Society

Leadership. Knowledge. Community.

Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

For more information, please visit the Canadian Cardiovascular Society (CCS) Antiplatelet Guidelines at

www.ccsguidelineprograms.ca

Pocket Guide Version: November 2013

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About This Pocket Guide

This pocket guide is a quick-reference tool that features essential diagnostic and treatment recommendations based on the 2012 CCS Antiplatelet Therapy Guidelines.

These recommendations are intended to provide a reasonable and practical approach to care for specialists and allied health professionals with the duty of bestowing optimal care to patients and families. They are subject to change as scientific knowledge and technology advance and practice patterns evolve. The guidelines are not intended to be a substitute for physicians using their judgment in managing clinical care in consultation with the patient, with appropriate regard to the individual circumstances of the patient, diagnostic and treatment options and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

For the complete CCS Guidelines on Antiplatelet Therapy, or for additional resources, please visit our guidelines website at www.ccsguidelineprograms.ca.

Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

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Introduction and Rationale

- The CCS 2012 Focused Update on the use of antiplatelet drugs is intended as an update, not a replacement for the 2010 document
- Updated topics are focused on coronary artery disease and include
    1. Antiplatelet therapy for secondary prevention in the first year after:
        - » Acute coronary syndrome (ACS)
        - » Percutaneous coronary intervention (PCI)
        - » Coronary artery bypass grafting (CABG)
    2. Use of novel oral anticoagulants for secondary prevention after ACS
    3. Interaction between clopidogrel and proton pump inhibitors (PPIs)
- Recommendations from the 2010 documents not addressed in the update continue to apply

Optimal acetylsalicylic acid dose after ACS

- Many well conducted studies have failed to demonstrate additional benefit of high dose ASA (>100 mg/day) for secondary vascular prevention
- However, high dose ASA has been clearly demonstrated to increase the risk of bleeding over low dose
- When used in combination with ticagrelor, there is some suggestion that high dose ASA may reduce efficacy in secondary prevention
- Overall, both short-term and long-term studies suggest that **low-dose ASA (81 mg/day in Canada) is optimal following ACS and PCI**

Clopidogrel

- Studies comparing clopidogrel to newer $P2Y_{12}$ antagonists have demonstrated benefit in cardiovascular outcomes for the new agents, at a cost of slight but significant increased major bleeding
- Compared to standard dose, double dose clopidogrel for the first 6 days following ACS demonstrated no overall vascular benefit, and increased major bleeding. However, in those who underwent PCI, double dose clopidogrel demonstrated additional significant benefit in reducing major vascular events.

Prasugrel

- In combination with ASA, prasugrel, compared with clopidogrel, reduced the risk of vascular events in NSTEACS patients treated by PCI, when administered after coronary anatomy has been defined
- The risk of major, life-threatening, and fatal bleeding was increased by prasugrel at a dose of 10 mg, particularly in those with:
  - Age ≥ 75 years
  - Body weight < 60 kg
- Prasugrel is contraindicated in patients with a prior history of cerebrovascular disease
- STEMI patients treated with PCI had similar benefits in reducing vascular events without increasing major bleeding
- No benefit for prasugrel over clopidogrel was demonstrated in patients managed medically following NSTEACS

Ticagrelor

- In combination with ASA, ticagrelor, compared with clopidogrel, reduced the risk of vascular events including total mortality, in NSTEACS patients treated medically, surgically or with PCI
- STEMI patients treated with primary PCI had similar, but not statistically significant benefits
- Non-CABG related major bleeding was increased with ticagrelor
- Increased rates of transient dyspnea and ventricular pauses are observed with use of ticagrelor
- Ticagrelor is contraindicated in patients with history of intracerebral bleeding and should be used with caution in patients with severe bradycardia

Platelet $P2Y_{12}$ Receptor Antagonists

	Clopidogrel	Prasugrel	Ticagrelor
Dosing	150 – 600 mg loading 75 mg OD	10 mg OD 5 mg OD if: Age ≥ 75 Weight ≤ 60 kg	180 mg loading 90 mg BID
Required Metabolic Activation	Yes sensitive to CYP2C19 polymorphisms	Yes less sensitive to CYP2C19 polymorphisms	No
Indications	ACS, PCI, PAD, CVD	ACS treated with PCI	ACS, PCI or medical treatment
Reversible Inhibition	No	No	Yes
Efficacy	++ • Further 2% ARR over ASA monotherapy	+++ • Further 2% ARR over clopidogrel + ASA	+++ • Further 2% ARR over clopidogrel + ASA • Reduced total mortality over clopidogrel + ASA
Bleeding Risk	+	+++	++
Issues	• Rash	• Bleeding risk in: Age ≥ 75 Weight < 60 kg Increased fatal bleeding contraindicated with history of stroke or TIA	• Dyspnea • Ventricular pause • Hyperuricemia • Slight increased Cr

New Recommendations for NSTEACS

- ✓ We recommend ASA 81 mg daily indefinitely in all patients with NSTEACS
  Strong Recommendation, High-Quality Evidence
- ✓ We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS
  Strong Recommendation, High-Quality Evidence
- ✓ We recommend prasugrel 10 mg daily over clopidogrel 75mg daily for 12 months in addition to ASA 81mg daily in $P2Y_{12}$ inhibitor-naive patients with NSTEACS after their coronary anatomy has been defined and PCI planned
  Strong Recommendation, High-Quality Evidence
- ✓ We recommend avoiding prasugrel in patients with previous TIA or stroke or in patients who are not treated with PCI. Except in patients with a high probability of undergoing PCI, we recommend avoiding prasugrel before the coronary anatomy has been defined
  Strong Recommendation, Moderate-Quality Evidence
- ✓ We recommend clopidogrel 75 mg once daily for 12 months in addition to ASA 81 mg daily in patients with NSTEACS managed with either PCI, CABG, or medical therapy and who are not eligible for ticagrelor or prasugrel
  Strong Recommendation, High-Quality Evidence
- ✓ We recommend that in patients in whom clopidogrel is to be used, a higher maintenance dose of 150 mg daily be considered for the first 6 days in patients with NSTEACS treated with PCI
  Strong Recommendation, Moderate-Quality Evidence

Values and preferences

- These recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis versus an increase in bleeding complications.
- They also take into account the clinical setting under which each of the antiplatelet drugs were evaluated and the more reliable bioavailability of prasugrel and ticagrelor compared with clopidogrel.

Practical tips

- In patients receiving dual antiplatelet therapy (DAPT), we suggest using ASA 81 mg daily.
- Ticagrelor can be used in patients managed with either PCI, CABG, or medical therapy alone, whereas prasugrel should be used only in patients undergoing PCI.
- In patients 75 years of age or older or weight less than or equal to 60 kg prasugrel 5 mg daily could be considered.

CCS Antiplatelet Therapy Guidelines

Recommendations for NSTEACS 1

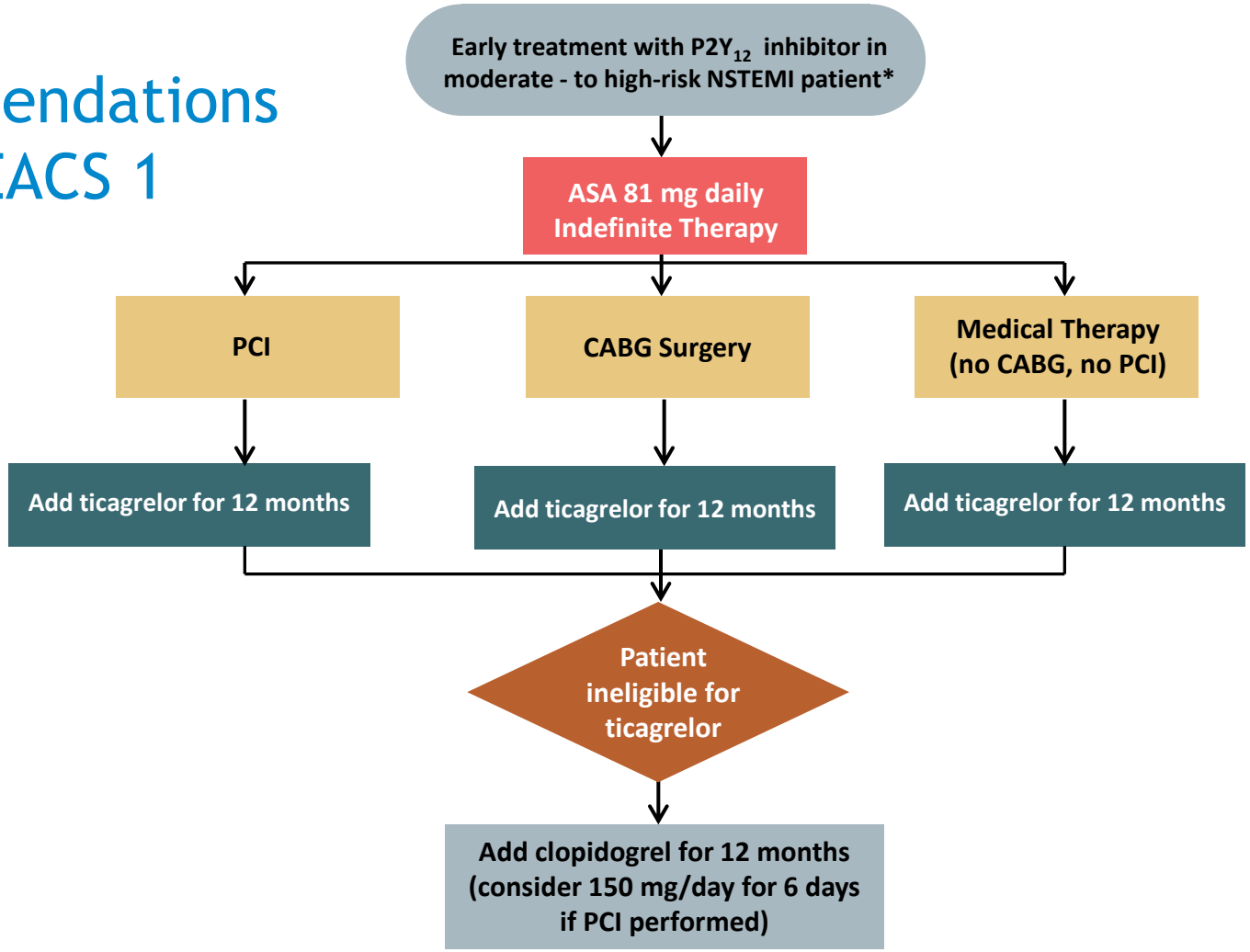

Figure 1. *Recommendations for non-ST-elevation acute coronary syndrome (NSTEACS) 1. ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PLATO. Platelet Inhibition and Patient Outcomes. *Moderate to high-risk NSTEACS as defined in PLATO16 : ≥ 2 of: (1) ischemic ST changes on electrocardiogram; (2) positive biomarkers; and (3) 1 of the following: 60 years of age or greater, previous MI or CABG, CAD > 50% stenosis in 2 vessels, previous ischemic stroke, diabetes, peripheral arterial disease, or chronic renal dysfunction.*

Recommendations for NSTEACS 2

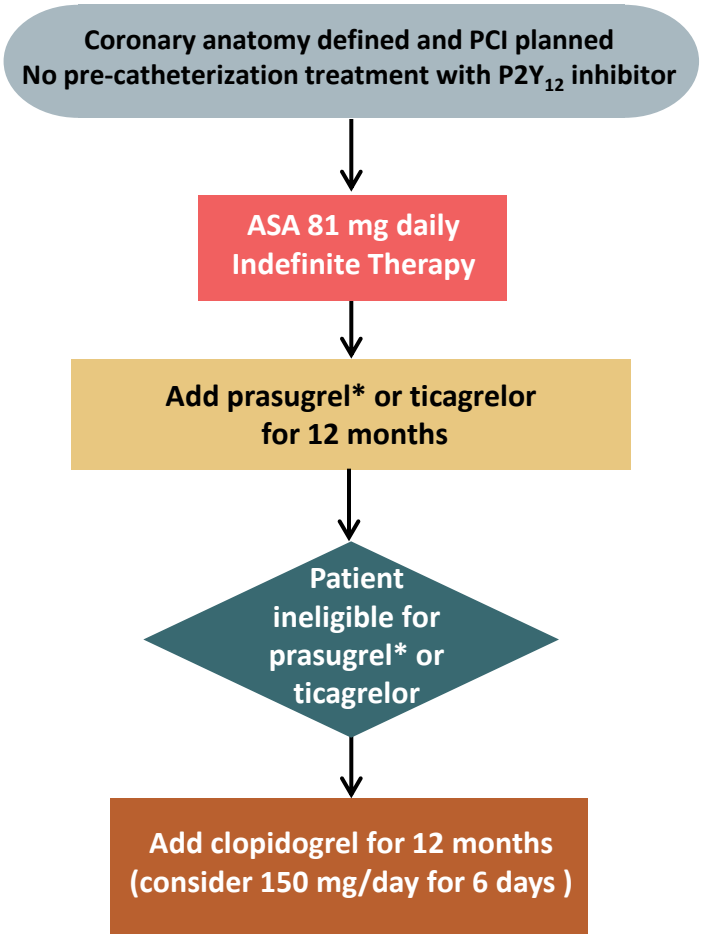

Figure 2. *Recommendations for non-ST-elevation acute coronary syndrome (NSTEACS) 2. ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. * Prasugrel should be avoided in patients with previous TIA or stroke. In patients aged 75 years and older, or body weight ≤ 60 kg, prasgurel should be used with caution and a 5 mg dose considered*

New Recommendations for STEMI

- ✓ We recommend clopidogrel 75 mg daily for at least 1 month in addition to ASA 81 mg daily in patients with STEMI who were managed with either fibrinolytic therapy or no reperfusion therapy
  Strong Recommendation, High-Quality Evidence
- ✓ We suggest that clopidogrel can be continued for 12 months
  Conditional Recommendation, Low-Quality Evidence
- ✓ We recommend either prasugrel 10 mg daily or ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily after primary PCI.
  Strong Recommendation, Moderate-Quality Evidence
- ✓ We recommend clopidogrel 75mg daily for 12 months in addition to ASA 81 mg daily after primary PCI in patients who are not eligible for prasugrel or ticagrelor
  Strong Recommendation, Moderate-Quality Evidence
- ✓ We recommend that in patients in whom clopidogrel is to be used, a higher maintenance dose of 150 mg daily be considered for the first 6 days in patients with STEMI treated with PCI
  Strong Recommendation, Moderate-Quality Evidence
- ✓ We recommend avoiding prasugrel in patients with previous TIA or stroke and using a 5-mg dose if required in patients aged 75 years or older or weight less than or equal to 60 kg
  Strong Recommendation, Low-Quality Evidence

Values and preferences

- These recommendations place greater emphasis on reduction of major cardiovascular events vs an increase in bleeding.
- These also account for the clinical setting where each of the antiplatelet drugs were evaluated and the more reliable bioavailability of prasugrel and ticagrelor compared with clopidogrel.

Practical tips

- In patients receiving dual antiplatelet therapy (DAPT), we suggest using ASA 81 mg daily.
- Ticagrelor can be used in patients managed with either PCI, CABG, or medical therapy alone, whereas prasugrel should be used only in patients undergoing PCI.
- In patients 75 years of age or older or weight less than or equal to 60 kg prasugrel 5 mg daily could be considered.

Recommendations for STEMI

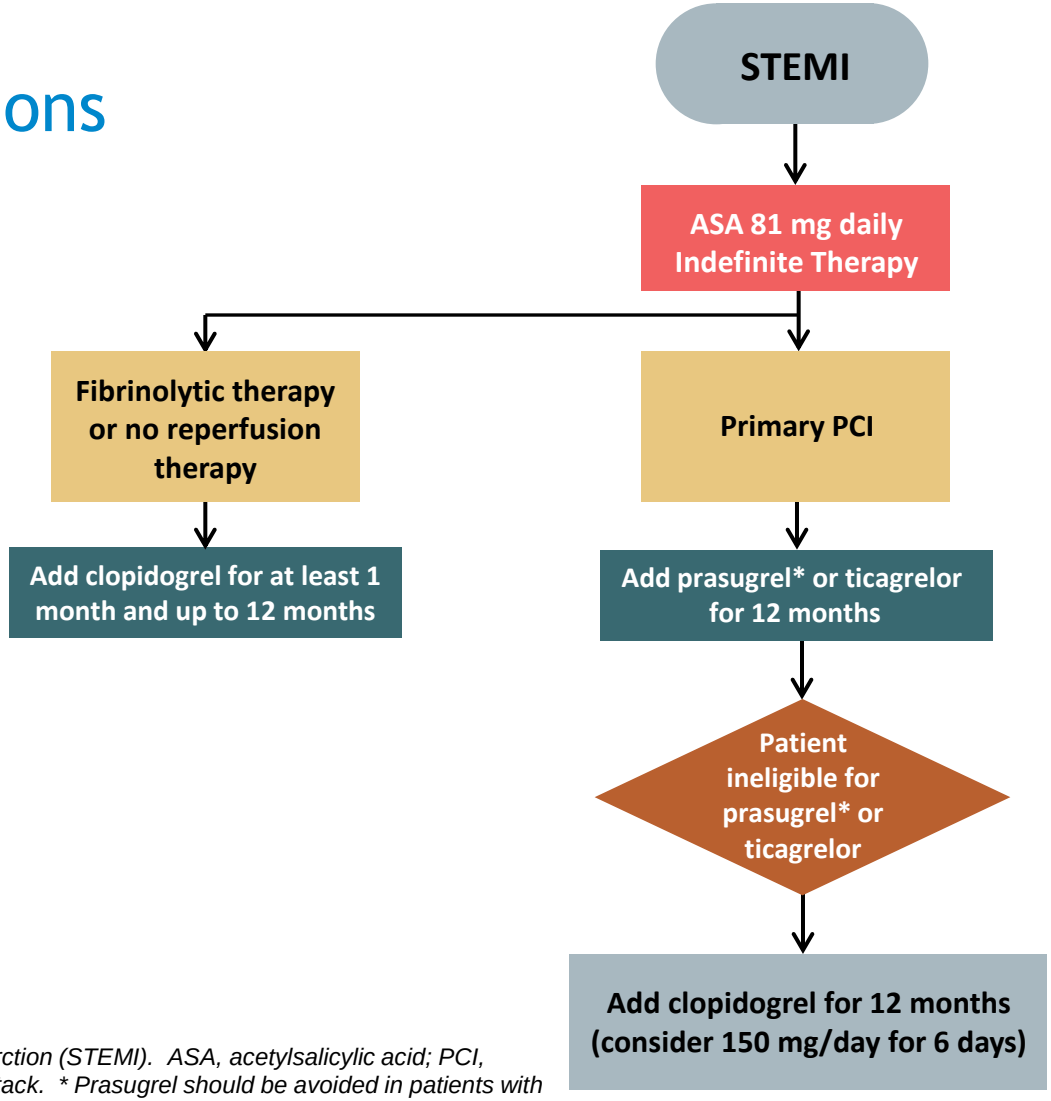

Figure 3. *Recommendations for ST-elevation myocardial infarction (STEMI). ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. * Prasugrel should be avoided in patients with previous TIA or stroke. In patients aged 75 years and older, or body weight ≤ 60 kg, prasgurel should be used with caution and a 5 mg dose considered.*

New general recommendations for ACS and PCI

✓ We recommend that for patients who are compliant with clopidogrel and have experienced stent thrombosis, prasugrel 10 mg daily or ticagrelor 90 mg twice daily may be considered in addition to ASA 81 mg daily. *Strong Recommendation, Low-Quality Evidence*
✓ We suggest continuation of a $P2Y_{12}$ inhibitor with ASA beyond 12 months be considered in patients with a high thrombosis risk and a low bleeding risk *Conditional Recommendation, Low-Quality Evidence*
✓ We suggest that if patients require surgery (CABG or non-CABG), the $P2Y_{12}$ inhibitor be withheld, if possible, as follows: clopidogrel 5 days before, ticagrelor 5 days before, and prasugrel 7 days before to the date of surgery. *Conditional Recommendation, Low-Quality Evidence*
✓ We suggest against switching the $P2Y_{12}$ inhibitor initially selected at discharge unless there is a compelling clinical reason (eg, stent thrombosis, bleeding, or cardiovascular event) *Conditional Recommendation, Very Low-Quality Evidence*

Optimal duration of dual antiplatelet therapy after stent implantation in Non ACS patient

- DAPT duration after drug-eluting stent (DES) placement remains controversial.
- Studies examining outcomes after 3, 6, 12 and 24 months of dual vs single antiplatelet therapy following DES implantation demonstrate differing results
- Overall, our recommendations for DAPT duration after stent implantation remain the same as in the initial guidance, generally for 1 year
- For patients at increased risk for stent thrombosis or in whom stent thrombosis could be related to dire consequences, DAPT continuation beyond 1 year might be considered after accounting for the perceived bleeding risk
- Newer generation DES might require a shorter DAPT duration, thus minimizing bleeding risk

New recommendations for PCI for a non-ACS indication

✓ We recommend that in patients receiving a bare-metal stent who are unable to tolerate clopidogrel for 12 months (eg, increased risk of bleeding or scheduled non cardiac surgery), the minimum duration of therapy should be 1 month *Strong Recommendation, High-Quality Evidence*
✓ We suggest in patients at very high risk of bleeding, the minimum duration of treatment may be 2 weeks *Conditional Recommendation, Low-Quality Evidence*
✓ We suggest that in patients receiving a second generation DES who are unable to tolerate clopidogrel for 12 months (eg, increased risk of bleeding or scheduled noncardiac surgery), the minimum duration of therapy may be 3 months *Conditional Recommendation, Low-Quality Evidence*

Antiplatelet Therapy Management of Patients after Coronary Artery Bypass Surgery (CABG)

- Low dose ASA is long considered the standard of care post CABG
- Studies of dual antiplatelet therapy following CABG have had conflicting results regarding graft related outcomes
- Regardless of its effect on graft-related outcomes, DAPT likely reduces overall thrombotic complications in patients with ACS who undergo CABG
- Large trials of DAPT with clopidogrel, prasugrel and ticagrelor have demonstrated similar outcome benefits in patients undergoing CABG
- Because of the greater potency of these newer antiplatelet therapies, cardiac surgeons must balance bleeding and efficacy in determining the timing of CABG after ACS. In stable patients with non-life-threatening coronary anatomy, therapy should ideally be withheld for 5 days for clopidogrel or ticagrelor and 7 days for prasugrel.
- In unstable and emergent patients, surgeons must weigh the potential risk of excess bleeding.

New recommendations for CABG

✓ We recommend that in patients with ACS requiring CABG, the risk of bleeding vs the benefit of continuing DAPT be weighed in deciding the appropriate timing of intervention

Strong Recommendation, Low-Quality Evidence

✓ We suggest that, if possible, in patients scheduled for CABG, clopidogrel and ticagrelor be discontinued for 5 days and prasugrel for 7 days before surgery

Conditional Recommendation, Low-Quality Evidence

✓ We recommend that DAPT be continued for 12 months in patients with ACS after CABG

Strong Recommendation, Moderate-Quality Evidence

Values and preferences

- These recommendations recognize the advantage of antiplatelet therapy after CABG to prevent early graft occlusion and cardiovascular events, and the importance of weighing the benefits and risks of DAPT when deciding the timing of surgery.

Practical tip

- In stable patients with ACS without critical coronary anatomy who are clinically stable, clopidogrel and ticagrelor should be withheld for 5 days and prasugrel for 7 days before CABG. In patients with ACS, DAPT should be restarted at maintenance dose within 48-72 hours after surgery when deemed safe by the cardiac surgical team.

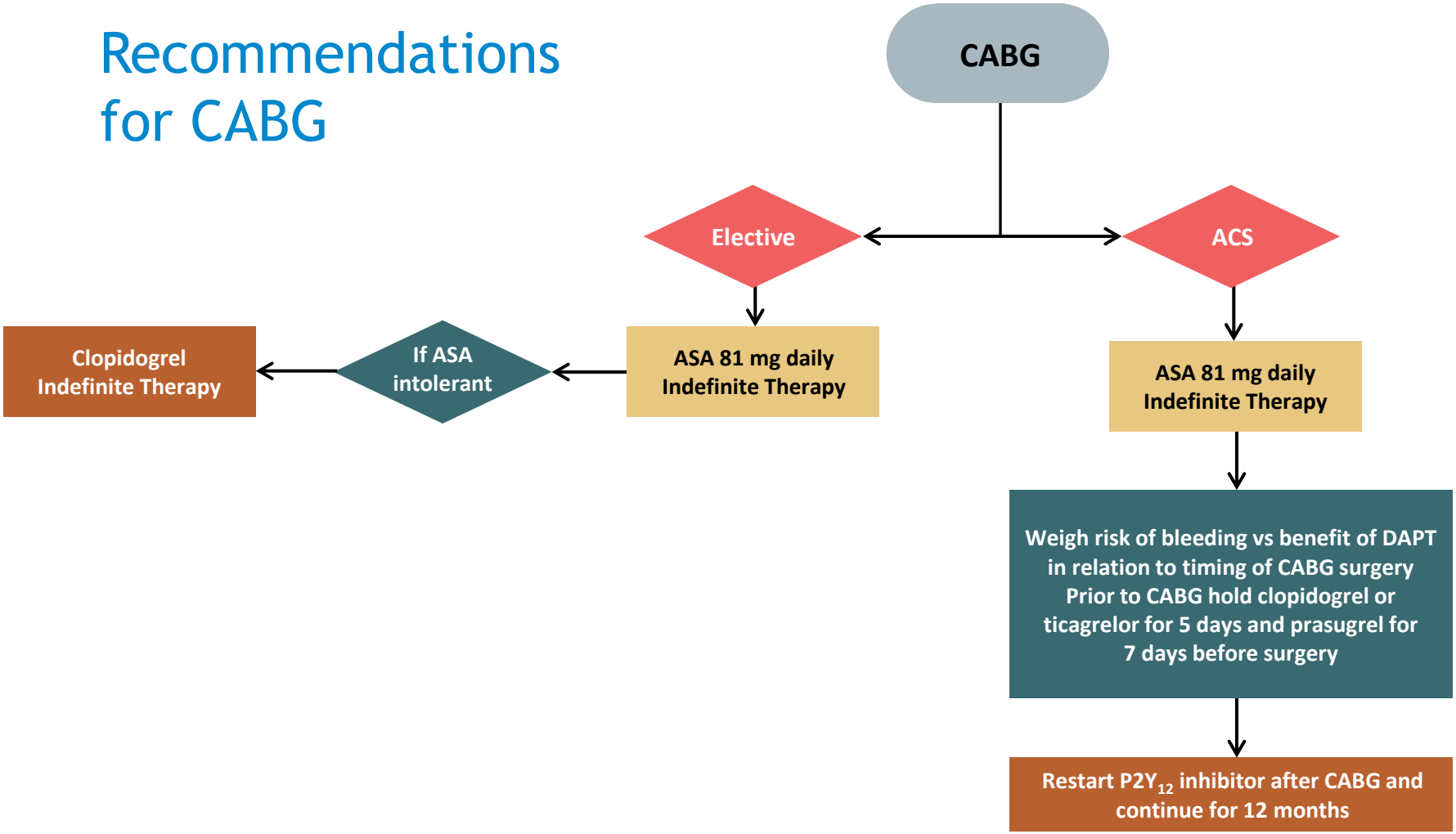

Figure 4. *Recommendations after CABG. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy.*

Use of novel oral anticoagulants for secondary prevention after ACS

- Platelet and coagulation factors are both involved in atherothrombosis
- Evidence for acute ACS management supports combination of both classes to reduce acute thrombosis, but data for long term combination of antiplatelet and anticoagulant are less convincing
- Apixaban plus DAPT (clopidogrel) did not reduce vascular events and was associated with increased major, intracranial and fatal bleeding
- Dabigatran plus DAPT (clopidogrel) also increased major bleeding in a small trial not powered to assess reduction in vascular events
- Rivaroxaban at very low dose plus DAPT (clopidogrel) demonstrated a significant vascular and mortality outcome benefit, but increased the risk of major and intracranial bleeding

New recommendations for NOAC plus DAPT for secondary prevention after ACS

✓ We suggest against the use of triple therapy with rivaroxaban, clopidogrel, and ASA over the use of dual therapy with ticagrelor or prasugrel plus ASA for secondary prevention of ACS
Conditional Recommendation, Very Low-Quality Evidence

✓ We recommend against the use of dabigatran and apixaban at any dose in combination with antiplatelet therapy for secondary prevention of ACS
Strong Recommendation, High-Quality Evidence

Values and preferences

- This recommendation recognizes the significant absolute benefit of triple therapy with rivaroxaban, clopidogrel, and ASA over dual therapy with clopidogrel and ASA for the composite outcome of cardiovascular death, MI, or stroke, and total mortality. However, we remain concerned about increased risk of bleeding complications.
- A similar ischemic benefit has been observed over clopidogrel plus ASA by using DAPT with ASA plus ticagrelor or prasugrel with an apparent lesser increased risk of bleeding over triple therapy with rivaroxaban, clopidogrel, and ASA.
- Our recommendation further recognizes the increased complexity and cost of taking 3 medications over 2.

Practical tip

- There might be patients in whom combining an oral anticoagulant with DAPT is warranted, such as patients with atrial fibrillation or a mechanical heart valve who develop ACS. Attention is needed to monitor and minimize the duration of “triple antithrombotic therapy” considering the high risk for bleeding associated with such treatment.

Use of PPI in patients taking clopidogrel

- Clopidogrel requires metabolic conversion to its active form through the action of CYP2C19
- Some PPIs, notably omeprazole and esomeprazole, are powerful inhibitors of CYP2C19 and reduce the antiplatelet efficacy of clopidogrel
- Results from 2 meta-analyses and a large randomized clinical trial show that PPIs significantly reduce the risk of upper gastrointestinal bleeding in patients on DAPT
- Randomized and population based studies have conflicting results on the significance of this drug interaction on vascular events. However all are limited by methodology and other biases
- Pantoprazole has minimal effect on CYP2C19 and is a preferred agent when a PPI is used in a patient on clopidogrel

New recommendations for the use of PPI in patients taking clopidogrel

✓ We recommend selective use of PPIs in patients receiving DAPT at high risk of upper gastrointestinal bleeding

Strong Recommendation, Moderate-Quality Evidence

Values and preferences

- This recommendation recognizes the risk and consequences of gastrointestinal bleeding and the benefit demonstrated to prevent these events.
- This recommendation recognizes that CYP2C19 inhibition reduces the action of clopidogrel on platelet inhibition. Although the physiological effect has not been clearly demonstrated to have a clinical effect on thrombotic events, it has also not been eliminated.
- Because PPIs with minimal effect on CYP2C19 are widely available, use of such agents is advisable

Practical tip

- PPIs should not be used routinely in all patients taking DAPT but should be considered in patients at higher risk of gastrointestinal bleeding.

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