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Society Guidelines

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

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ABSTRACT

The initial 2010 Canadian Cardiovascular Society (CCS) Guidelines for the Use of Antiplatelet Therapy in the Outpatient Setting were published in May 2011. As part of a planned re-evaluation within 2 years, we conducted an extensive literature search encompassing all topics included in the 2010 CCS Guidelines, and concluded that there were sufficient new data to merit revisiting the guidance on antiplatelet therapy for secondary prevention in the first year after acute coronary syndrome (ACS), percutaneous coronary intervention, or coronary

RÉSUMÉ

Les Lignes directrices de la Société canadienne de cardiologie (SCC) 2010 pour le traitement antiplaquettaire en milieu extrahospitalier furent publiées en mai 2011. Avec une réévaluation planifiée en dedans de 2 ans, nous avons effectué une recherche exhaustive de la littérature couvrant tous les sujets inclus dans les lignes directrices de la SCC 2010 et conclu qu'il y avait suffisamment de nouvelles données probantes publiées qui justifiaient une mise à jour ciblée des lignes directrices pour l'utilisation des thérapies antiplaquettaires pour la prévention

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The disclosure information of the authors and reviewers is available from the CCS on the following websites: www.ccs.ca and/or www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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artery bypass grafting, and the interaction between clopidogrel and proton pump inhibitors. In addition, new clinical trials information about the efficacy and safety of combining novel oral anticoagulants with antiplatelet therapy in ACS justified the addition of a new section of recommendations to the Guidelines. In this focused update, we provide recommendations for the use of clopidogrel, ticagrelor, and prasugrel in non-ST elevation ACS, avoidance of prasugrel in patients with previous stroke/transient ischemic attack, higher doses of clopidogrel (j) /day) for the first 6 days after ACS, and the preferential use of prasugrel or ticagrelor after percutaneous coronary intervention in ACS. For non-ACS stented patients, we recommend acetylsalicylic acid/clopidogrel for 1 year, with at least 1 month of therapy for bare-metal stent patients and 3 months for drug-eluting stent patients unable to tolerate year-long double therapy. We also consider therapy for patients with a history of stent thrombosis, the indications for longer-term treatment, discontinuation timing preoperatively, indications for changing agents, the management of antiplatelet therapy before and after bypass surgery, and use/selection of proton pump inhibitors along with antiplatelet agents.

secondaire durant la première année après un syndrome coronarien aigu (SCA), une intervention coronarienne percutanée, ou une revascularisation chirurgicale par pontages et les interactions entre le clopidogrel et les inhibiteurs de la pompe à protons (IPP). De plus, le comité a estimé que la publication d'essais cliniques pivots évaluant l'efficacité et la sécurité d'ajouter un nouvel anticoagulant oral à la thérapie antiplaquettaire chez un patient avec SCA exigeait l'addition d'une nouvelle section de recommandations pour ces lignes directrices. Dans cette mise à jour ciblée, nous présentons des recommandations pour l'utilisation du clopidogrel, du ticagrelor et du prasugrel pour les SCA sans élévation du segment ST, d'éviter le prasugrel chez les patients avec antécédents d'accident vasculaire cérébral/ischémie cérébrale transitoire, de doses plus élevées de clopidogrel (150 mg/jour) pour les premiers 6 jours post-SCA, et l'utilisation préférentielle du prasugrel ou du ticagrelor après l'angioplastie lors d'un SCA. Pour les patients stables, nous recommandons acide acétylsalicylique/clopidogrel pour 1 an, avec un minimum d'un mois post-tuteur non médicamenté et 3 mois après tuteur médicamenté chez les patients ne pouvant tolérer la thérapie antiplaquettaire double pour une année complète. Nous avons considéré le traitement des patients avec thrombose de tuteur, les indications pour le traitement à plus long terme, l'interruption en peri-opératoire, les indications pour changer d'agents, l'utilisation pré et post-pontages, et la sélection des patients pour thérapie concomitante avec les IPP.

The initial Canadian Cardiovascular Society (CCS) Guidelines on the Use of Antiplatelet Therapy Writing Committee was committed to reconvene within 2 years to evaluate the need for updating the Guidelines.[1] After an extensive literature search, this Committee recommended updating the following guidelines: antiplatelet therapy for secondary prevention in the first year after acute coronary syndrome (ACS); percutaneous coronary intervention (PCI); coronary artery bypass grafting (CABG); and the interaction between clopidogrel and proton pump inhibitors (PPIs). There was additional guidance on the use of novel oral anticoagulants for secondary prevention after an ACS.

The updated guideline was developed using the same methodology as the original guideline[1] but for this iteration, we adopted the **G**rading of **R**ecommendations **A**ssessment, **D**evelopment, and **E**valuation (GRADE) system to evaluate evidence and determine the strength of recommendations.[2] The primary panel assembled included family physicians, vascular medicine specialists, cardiologists, interventional cardiologists, pharmacists, and cardiovascular surgeons. To maintain continuity, some members of the 2010 panel were retained in the current panel. Additional panelists included individuals without significant conflicts of interest.

Updated Evidence for Antiplatelet Therapy After ACS in Patients Treated With PCI, CABG, or Medical Therapy Alone

Optimal acetylsalicylic acid dose after ACS

An analysis of **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents (CURE) provides insight into the optimal acetylsalicylic acid (ASA) dose after an ACS.[3] There did not appear to be additional benefit for high-dose ASA in either the ASA alone group (highest dose [$\geq$ 200 mg daily] vs lowest dose [$\leq$ 100 mg daily]) or the ASA plus clopidogrel group.[4] Conversely, major bleeding increased in a dose-dependent fashion in the ASA alone (1.9% low-dose, 2.8% medium-dose [>100 to < 200 mg daily], 3.7% high-dose) and ASA plus clopidogrel (3.0%, 3.4%, 4.9%, respectively) groups. Analysis of **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents in Patients Undergoing **P**ercutaneous **C**oronary **I**ntervention (PCI-CURE) showed no additional benefit with high- vs low-dose ASA, but high-dose ASA increased bleeding risk. Net adverse clinical events (death, myocardial infarction [MI], stroke, and major bleeding) favoured low-dose ASA in PCI.[5]

Clopidogrel and Aspirin Optimal Dose **U**sage to **R**educe **R**ecurrent **Ev**e**n**t**s**-**O**rganization to **A**ssess **S**trategies in **I**schemic **S**yndromes 7 (CURRENT-OASIS 7) was the first large-scale randomized study to assess the optimal ASA dose in patients with ACS scheduled to undergo an early invasive strategy.[6] Overall, there was no significant difference between high-dose (300-325 mg/day) and low-dose (75-100 mg/day) ASA for the primary outcome of cardiovascular death, MI, or stroke at 30 days.[6] In the PCI population, there was no difference between high- and low-dose ASA for the primary outcome or stent thrombosis.[7] Major bleeding did not differ between high- and low-dose ASA. There was a nominally significant increase in minor bleeding (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.00-1.26; $P = 0.043$) and a small excess in major gastrointestinal bleeds (0.4% vs 0.2%; $P = 0.039$) with high-dose ASA. There were 6 intracranial bleeds in both ASA dose groups.

Overall, both short-term (CURRENT-OASIS 7) and long-term (CURE) studies suggest that low-dose ASA (81 mg/day in Canada) is the optimal dose after an ACS.

Platelet $P2Y_{12}$ receptor antagonists

Clopidogrel. Since the initial CCS guidance,[1] limited data on clopidogrel safety and efficacy after ACS have been

published. As summarized in the previous guidance, overall results of CURRENT-OASIS 7 showed no significant difference in the 30-day rate of cardiovascular death, MI, or stroke (primary outcome) between double-dose and standard-dose clopidogrel.[6] In the PCI population, a significant 14% relative risk reduction in the primary outcome was observed with the double-dose regimen (3.9% vs 4.5%; HR, 0.86; 95% CI, 0.74-0.99; $P = 0.039$).[7] There was also a 46% relative reduction in definite stent thrombosis (academic research consortium definition[8]) with double-dose clopidogrel (0.7% vs 1.3%; adjusted HR, 0.54; 95% CI, 0.39-0.74). In the PCI population, double-dose clopidogrel increased trial-defined major bleeding (2.5% vs 2.0%; $P = 0.01$), but not **T**hrombosis **i**n **M**yocardial **I**nfarction (TIMI) major or fatal, intracranial, or CABG-related major bleeding.[7]

Prasugrel. The primary evidence supporting prasugrel in ACS remains the **Tr**ial to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n** With Prasugrel-**T**hrombolysis **i**n **M**yocardial **I**nfarction 38 (TRITON-TIMI 38).[9] As summarized in the initial CCS guidance,[1] prasugrel significantly reduced the relative risk of the primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel; both prasugrel and clopidogrel were given with ASA after confirmation of coronary anatomy without pretreatment.[9] Cardiovascular death did not significantly differ between groups. Prasugrel was associated with significant increases in TIMI-defined major, life-threatening, and fatal bleeding in the total population and increased intracranial bleeding in those with a history of cerebrovascular disease. In patients with ST-elevation MI (STEMI) and planned primary or secondary PCI, in whom the study drug could be initiated before angiography, prasugrel significantly reduced the primary end point without increasing risks of major, life-threatening, or fatal bleeding; this benefit with prasugrel was observed for primary and secondary PCI, although it was more pronounced for secondary PCI.[10]

Based on TRITON-TIMI 38, prasugrel is contraindicated in patients with a known history of transient ischemic attack (TIA) or stroke, and the product monograph includes a boxed warning that highlights the bleeding risks and recommends avoidance in patients aged 75 years or older or with body weight < 60 kg.[11] A post hoc analysis of TRITON-TIMI 38 supports the regulatory product label, because net clinical benefit was maximized in patients aged younger than 75 years who weighed ≥ 60 kg without a history of stroke or TIA.[12] The recently completed **Ta**r**g**eted Platelet **I**nhibition to **C**l**a**rify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY ACS) study of prasugrel vs clopidogrel in patients with non-ST−elevation ACS (NSTEACS) managed medically did not demonstrate added benefit for prasugrel and does not alter our recommendations.[13] However, patients aged 75 years and older or weighing < 60 kg received prasugrel 5 mg/day instead of 10 mg/day and experienced similar rates of bleeding as clopidogrel recipients. Emerging data will provide information on the efficacy and safety of prasugrel in patients pretreated before coronary angiography (**A** **C**omparison of Prasugrel at the Time of Percutaneous **C**oronary Intervention **o**r as Pretreatment **a**t the Time of Diagnosis in Patients With Non-**ST**-Elevation Myocardial Infarction [ACCOAST] study[14]), of high vs low body weight (A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Low Body Weight vs Higher Body Weight Aspirin-Treated Subjects With Stable Coronary Artery Disease [FEATHER]; NCT01107925), and pretreated with a clopidogrel loading dose (LD) (**Tr**ansferring From Clop**i**dogrel Loading Dose to **P**rasugrel **L**oading Dose in Acute Coronary Syndrome Pati**en**t**s** [TRIPLET]; NCT01115738).

Ticagrelor. Ticagrelor is an oral, reversibly binding, direct-acting $P2Y_{12}$ receptor antagonist. Compared with a 600-mg clopidogrel LD, a 180-mg ticagrelor LD achieves a more rapid, significantly greater antiplatelet effect.[15] When ticagrelor is discontinued, antiplatelet effect offset is faster than with clopidogrel. However, because ticagrelor achieves a much greater antiplatelet effect, platelet inhibition 24-48 hours after discontinuation of the last dose is similar in ticagrelor- and clopidogrel-treated patients.[15]

As summarized in the initial CCS guidance,[1] **Plat**elet Inhibition and Patient **O**utcomes (PLATO) compared the efficacy and safety of ticagrelor plus ASA with that of clopidogrel plus ASA, started before cardiac catheterization.[16] Compared with clopidogrel, ticagrelor significantly reduced the primary end point of cardiovascular death, MI, or stroke at 12 months, and MI, cardiovascular mortality, and all-cause mortality risks; primary outcome results were similar in patients managed invasively and noninvasively.[16] The ticagrelor benefit was not accompanied by an increase in major bleeding, although non−CABG-related bleeding was significantly increased. Data published since the original CCS guidance show that in the 7544 patients undergoing primary PCI for STEMI in PLATO, there was a consistent, but not statistically significant, reduction in the primary end point with ticagrelor (9.4% vs 10.8%; HR, 0.87; 95% CI, 0.75-1.01; $P = 0.07$) without increased major bleeding risk.[17] Ticagrelor significantly reduced mortality (9.8% vs 11.3%; HR, 0.87; 95% CI, 0.75-1.00) and reinfarction (4.7% vs 5.8%; HR, 0.80; 95% CI, 0.65-0.98) but significantly increased stroke risk (1.7% vs 1.0%; HR, 1.63; 95% CI, 1.07-2.48). Mahaffey et al. demonstrated that a significant proportion of the regional interaction observed in PLATO was explained by the ASA dose alone and using ASA < 100 mg/day favoured the use of ticagrelor over clopidogrel (HR, 0.77; 95% CI, 0.69-0.86).[18]

In a more detailed analysis of dyspnoea and ventricular pauses in PLATO, ticagrelor was associated with an increased risk of mild-to-moderate and usually transient dyspnoea (13.8% vs 7.8%; HR, 1.84; 95% CI, 1.68-2.02).[19] Dyspnea rarely resulted in treatment discontinuation (0.9% vs 0.1%). Ventricular pauses ≥ 3 seconds were more common with ticagrelor than clopidogrel in the first week of treatment.[19]

Updated Data for Antiplatelet Therapy for Secondary Prevention in the First Year After PCI

Optimal duration of dual antiplatelet therapy after stent implantation

The optimal dual antiplatelet therapy (DAPT) duration after drug-eluting stent (DES) placement remains

controversial. A pooled analysis of randomized trials of patients free of major adverse cardiovascular events (MACEs) and major bleeding for $\geq$ 12 months after DES placement failed to show a significant benefit for an additional 12 months of DAPT with ASA and clopidogrel over ASA alone.[20] In **Pro**longing **D**ual Antiplatelet Treatment After Grading Stent-Induced **I**ntimal Hyperplasia Stud**y** (PRODIGY), 2013 patients undergoing PCI (74% with ACS) were randomized to bare-metal, zotarolimus-eluting (ZES), everolimus-eluting, or paclitaxel-eluting stent implantation. Thirty days later 1970 of these patients underwent a second randomization to either 6 or 24 months of DAPT with ASA 80-160 mg/day and clopidogrel 75 mg/day. At 2 years, there was no significant difference in the risk of the primary end point (death, MI, or cerebrovascular accident) between those who received DAPT for 6 and 24 months or any of the secondary end points, including stent thrombosis, but a 2-fold greater risk of BleedScore type 5, 3, or 2 bleeding (HR, 2.17; 95% CI, 1.44-3.22).[21] A retrospective analysis of 7689 stent recipients in an administrative database (73% with ACS) demonstrated significantly higher bleeding rates but significantly lower MI rates among patients receiving vs not receiving DAPT from 0 to 6 months, 7 to 12 months, and 13 to 18 months after coronary intervention.[22] These findings underscore the need to carefully evaluate and balance ischemic risk reduction with the potential for increased bleeding.

Newer generation DES might require a shorter DAPT duration, thus minimizing bleeding risk. In a large meta-analysis, the everolimus-eluting stent treatment effect was consistent in patients who received 6 and 12 months of DAPT.[23] In another meta-analysis of 5 clinical trials of ZES recipients, risk-adjusted death, MI, and definite/probable stent thrombosis rates were not significantly different over 3 years between DAPT durations of 6 and $\geq$ 12 months and 6 and $\geq$ 24 months.[24] Similarly, in a prospective, multicentre registry of 823 ZES recipients, DAPT discontinuation at 3 months did not increase the risk of cardiac death, MI, or stent thrombosis at 1 year[25]; this registry might have been underpowered because the primary end point rate was only 0.6%, reflecting a low-risk population. The DAPT study, a large, multicentre, randomized trial comparing the efficacy and safety of 1 vs 2 years of DAPT with ASA and either clopidogrel or prasugrel after successful DES placement (NCT00977938),[26] is expected to provide more information on the optimal duration of DAPT.

Overall, our recommendations for DAPT duration after stent implantation remain the same as in the initial guidance.[1] 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, with the ideal duration remaining unknown.

The following are changed recommendations for NSTEACS (Figs. 1 and 2).

RECOMMENDATION

1. We recommend ASA 81 mg daily indefinitely in all patients with NSTEACS (Strong Recommendation, High-Quality Evidence).
2. 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 (as defined in PLATO[16]: $\geq$2 or more of (1) ischemic ST changes on electrocardiogram; (2) positive biomarkers; or (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), managed with either PCI, CABG surgery, or medical therapy alone (Strong Recommendation, High-Quality Evidence).
3. We recommend prasugrel 10 mg daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in $P2Y_{12}$ inhibitor-naive patients with NSTEACS after their coronary anatomy has been defined and PCI planned (Strong Recommendation, High-Quality Evidence).
4. 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).
5. 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).
6. 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 vs 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 tip. In patients receiving 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 $\leq$ 60 kg, when available, prasugrel 5 mg daily could be considered.

The following are changed recommendations for STEMI (Fig. 3).

RECOMMENDATION

1. 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).
2. 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).
3. We recommend clopidogrel 75 mg 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).
4. 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).
5. We recommend avoiding prasugrel in patients with previous TIA or stroke and using a 5-mg dose if required in patients aged years or older or weight $\leq$ 60 kg (Strong Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis vs 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.

The following are changed recommendations for PCI for a non-ACS indication.

RECOMMENDATION

1. 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 noncardiac 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).
2. 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).

The following are general recommendations for ACS and PCI.

RECOMMENDATION

1. 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).
2. 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).
3. 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).
4. 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).

What Is the Optimal Antiplatelet Therapy Regimen After CABG?

Considered the gold standard for preventing saphenous vein graft closure after CABG, ASA is generally continued indefinitely because of its benefit in preventing subsequent clinical events.[27-29] However, there is no published evidence suggesting antiplatelet therapy improves arterial graft patency. As summarized in the initial CCS guidance,[1] low-dose ASA initiated 6 hours after surgery appears to maximize prevention of graft occlusion and minimize bleeding risk.[30]

The initial CCS guidance highlighted conflicting evidence on the benefit of DAPT with ASA and clopidogrel on graft-related outcomes after CABG.[1] Observational evidence suggests DAPT might be beneficial in the first month after off-pump CABG but not beyond.[31] Results of direct comparisons showed that neither angiographic patency 1 and 12 months after surgery nor intravascular ultrasound-determined intimal hyperplasia differed in stable patients treated with clopidogrel vs DAPT, suggesting no benefit for adding ASA to clopidogrel after CABG.[32,33] In another randomized trial, the addition of clopidogrel was superior for preventing graft failure (occlusion and string sign) in radial artery grafts.[34]

Regardless of its effect on graft-related outcomes, DAPT might reduce overall thrombotic complications in subsets of patients with ACS who undergo CABG.[35] Data from the CURE and **C**lopidogrel for the **R**eduction of **E**vents **D**uring **O**bservation (CREDO) randomized trials provide evidence on the benefits and risks of DAPT with ASA and clopidogrel in CABG.[36,37] More recent data provide evidence for DAPT with ASA and prasugrel or ticagrelor in patients with ACS who undergo CABG.[12,16,38,39] In PLATO, 1899 patients underwent CABG.[16,37] Preoperatively, ticagrelor and clopidogrel were to be withheld for 1-3 days and 5 days, respectively. In a retrospective analysis, the 1261 patients who underwent CABG and received study treatment in the 7 days before surgery showed a relative risk reduction with ticagrelor similar to that observed in the overall patient population; total mortality was reduced from 9.7% with

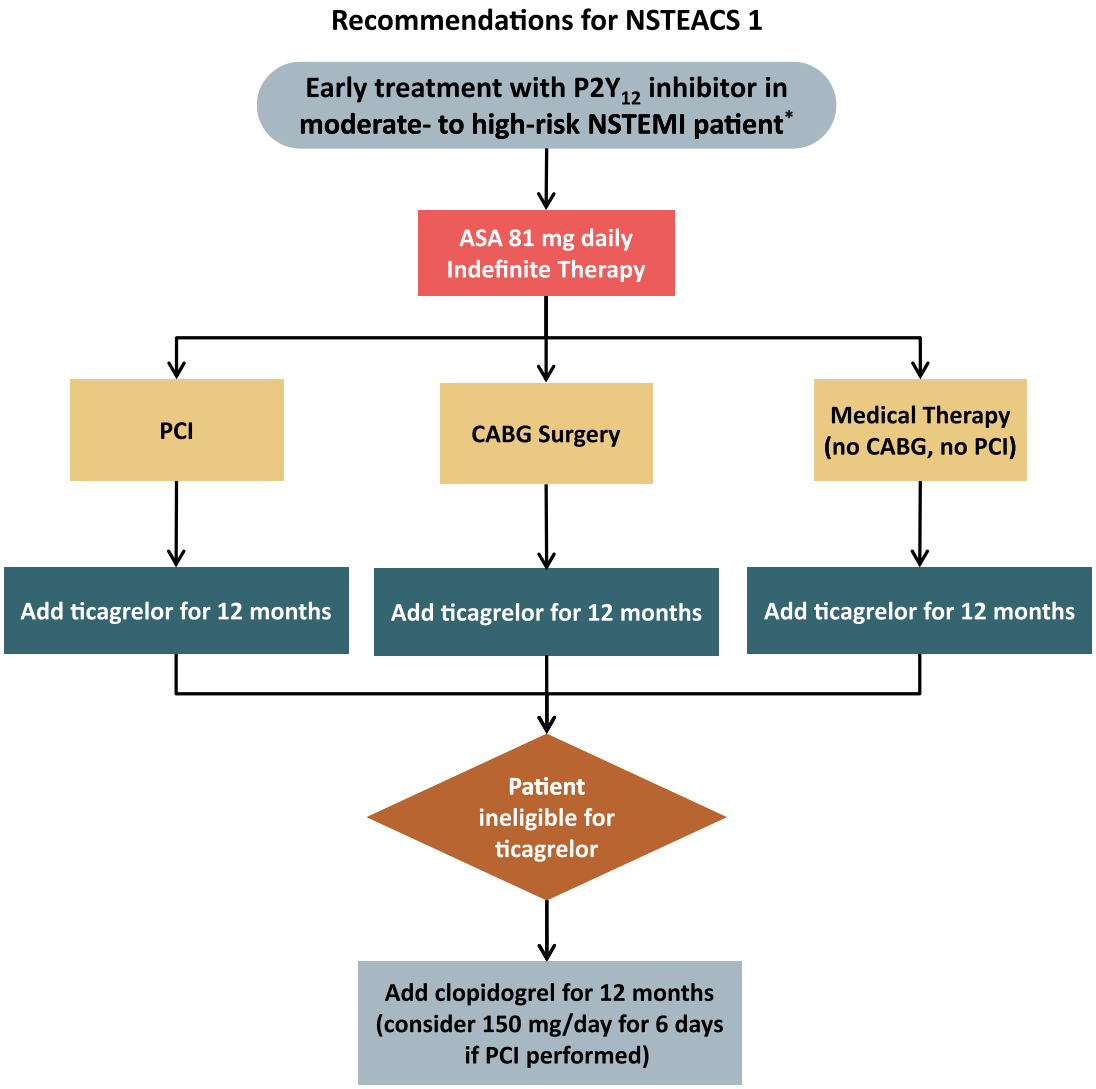

Figure 1. Recommendations for non-ST—elevation acute coronary syndrome (NSTEACS) 1. ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes. * Moderate to high-risk NSTEACS as defined in PLATO[16]: ≥ 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.

clopidogrel to 4.7% with ticagrelor (HR, 0.49; 95% CI, 0.32-0.77), cardiovascular death from 7.9% to 4.1% (HR, 0.52; 95% CI, 0.32-0.85), and noncardiovascular death from 2.0% to 0.7%.[38] There was no significant difference in CABG-related major bleeding between the treatment arms. Of note, 70% of ticagrelor recipients stopped therapy 3-7 days before surgery, suggesting that the protocol recommendation to stop ticagrelor 1-3 days before surgery was upheld in only a minority of patients. Approximately 2/3 of patients restarted antiplatelet therapy after CABG, of which approximately half restarted within the first 14 days after CABG. In the 422 patients who required CABG after randomization in TRITON-TIMI 38, prasugrel significantly reduced all-cause mortality (2.31% vs 8.67% with clopidogrel; adjusted odds ratio, 0.26; $P = 0.025$) and increased 12-hour chest tube blood loss (655 ± 580 mL vs 503 ± 378 mL; $P = 0.050$) without significantly increasing red blood cell transfusion.[39]

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. Although there is no clear recommendation in the literature, bridging with a glycoprotein IIb/IIIa inhibitor in the 5-7 days before surgery or transfusing platelets at the time of surgery might be considered.[35] Considering data suggesting that the rate of stent thrombosis could be as high as 20% in patients undergoing CABG shortly after PCI,[40] patients requiring CABG after PCI should continue taking DAPT as recommended in the post-PCI guidelines, particularly if the stented vessel is not bypassed during surgery.

The following are changed recommendations for antiplatelet therapy (Fig. 4).

RECOMMENDATION

1. 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).
2. 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).
3. 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 importance of the advantage of antiplatelet therapy in patients who have received CABG to prevent early graft occlusion and long-term 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.

Should Novel Oral Anticoagulants Be Used With Antiplatelet Agents for Secondary Prevention After ACS?

Patients with ACS remain at high risk for recurrent ischemic events despite significant advances in management. Considering the key role of platelet and coagulation factors in atherothrombosis, modern ACS treatment algorithms combine antithrombin and antiplatelet agents. Although an abundance of evidence demonstrates that prolonged antiplatelet therapy reduces recurrent events after ACS, data supporting long-term antiplatelet plus anticoagulant combination therapy are less convincing. Prolonged subcutaneous dalteparin use reduces recurrent events among troponin T-positive patients,[41] and warfarin alone and in combination with antiplatelet agents reduces the risk of post-ACS events.[42,43] However, the most recent guidelines from the American College of Cardiology Foundation/American Heart Association and the Focused 2012 Update of the CCS Atrial Fibrillation Guidelines note that concomitant use of warfarin with ASA or DAPT is associated with a greater bleeding risk and should be monitored closely.[44,45] Although a recent meta-analysis[46] suggested a significant increase in major bleeding with triple therapy, the stroke and bleeding risks assessment might help select which PCI patient should continue taking triple therapy.[47,48]

Novel oral anticoagulants targeting factors IIa and Xa are now available for preventing venous thromboembolism and strokes in atrial fibrillation. In the phase III **A**nti-Xa **T**herapy to **L**ower Cardiovascular Events in **A**ddition to **S**tandard **T**herapy in Subjects with **A**cute **C**oronary **S**yndrome-**T**hrombolysis **I**n **M**yocardial **I**nfarction 51 (ATLAS ACS2-TIMI 51) trial, 15,526 patients were randomized within 7 days of ACS to rivaroxaban 2.5 mg or 5 mg twice daily or placebo for a mean of 13 months.[49,50] Background therapy included a thienopyridine, mainly clopidogrel and ASA in more than 90% of patients. Rivaroxaban at either dose significantly reduced the primary end point of cardiovascular death, MI, or stroke vs placebo (8.9% vs 10.7%; HR, 0.84; 95% CI, 0.74-0.96). Rivaroxaban 2.5 mg twice daily significantly reduced death from cardiovascular (2.7% vs 4.1%) and any (2.9% vs 4.5%) cause, benefits not seen with 5 mg twice daily. Rivaroxaban increased rates of non-CABG-related TIMI major bleeding (2.1% vs 0.6%; $P < 0.001$) and intracranial hemorrhage (0.6% vs 0.2%; $P = 0.009$) Rivaroxaban 2.5 mg twice daily resulted in fewer fatal bleeding events than 5 mg twice-daily (0.1% vs 0.4%; $P = 0.04$).

In the phase III **Ap**ixaban for **Pr**evention of **A**cute **I**schemic **S**afety **E**vents (APPRAISE-2) trial, subjects with ACS in the previous 7 days were randomized to apixaban 5 mg twice daily or placebo.[51,52] Among enroled patients, 97% and 81% were taking ASA, and a $P2Y_{12}$ inhibitor, predominantly clopidogrel, respectively. APPRAISE-2 was terminated prematurely after the recruitment of 7392 patients because of increased major bleeding with apixaban without a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the primary outcome of cardiovascular death, MI, or ischemic stroke occurred in 7.5% of apixaban and 7.9% of placebo recipients (HR, 0.95; 95% CI, 0.80-1.11). Major TIMI bleeding occurred in 1.3% of patients who received ≥ 1

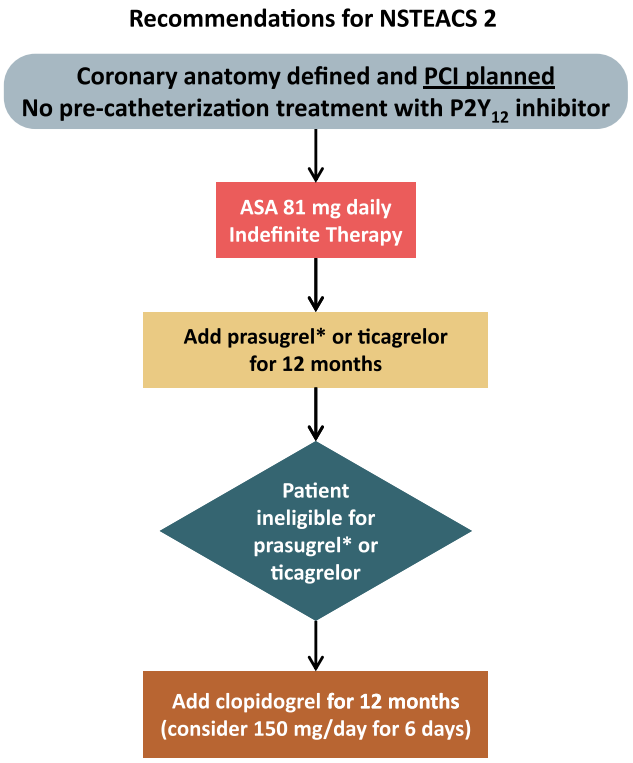

Figure 2. Recommendations for non-ST–elevation acute coronary syndrome (NSTEACS) 2. ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. * Prasugrel should be avoided in patients with previous TIA or stroke. In patients aged 75 years and older, or body weight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

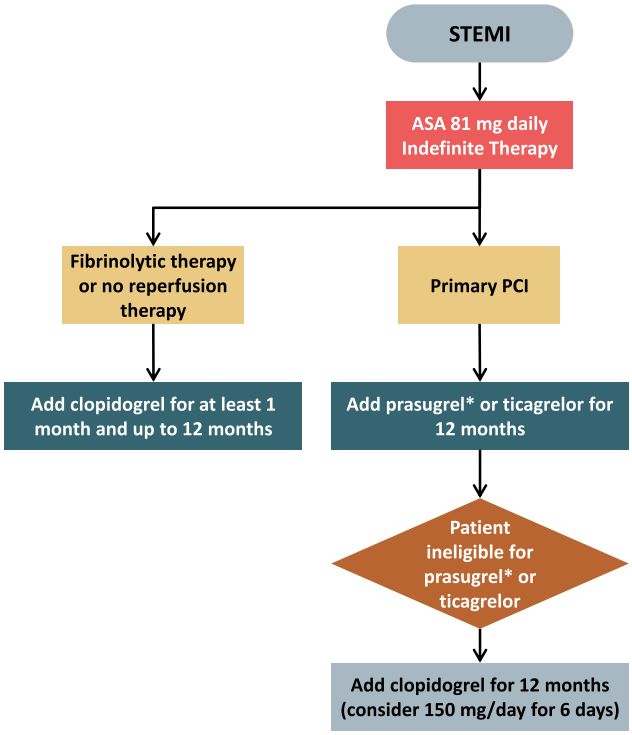

Figure 3. Recommendations for ST-elevation myocardial infarction (STEMI). ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. * Prasugrel should be avoided in patients with previous TIA or stroke. In patients aged 75 years and older, or body weight $\leq$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

apixaban dose and 0.5% of patients who received $\geq$ 1 placebo dose (HR, 2.59; 95% CI, 1.50-4.46). A greater number of intracranial and fatal bleeding events occurred with apixaban.

The phase II **R**andomize**d** **D**abigatran **E**texilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index **E**vent With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: **M**ulti-centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study (RE-DEEM) trial randomized 1861 subjects within 14 days of ACS, who were receiving treatment with ASA and clopidogrel, to placebo or dabigatran 50 mg, 75 mg, 110 mg, or 150 mg twice daily.[53] Compared with placebo, a dose-dependent increase in the primary outcome of major or clinically relevant minor bleeding during the 6-month treatment period was observed with dabigatran: HR, 1.77 (95% CI, 0.70-4.50) for 50 mg; HR, 2.17 (95% CI, 0.88-5.31) for 75 mg; HR, 3.92 (95% CI, 1.72-8.95) for 110 mg; and HR, 4.27 (95% CI, 1.86-9.81) for 150 mg. A phase III trial of dabigatran in patients with ACS has, to date, not been conducted.

RECOMMENDATION

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).

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 the 4-fold increased risk of major bleeding and > 3-fold increase in intracranial hemorrhage. The recommendation further acknowledges the loss to follow-up of a significant number of patients in ATLAS ACS2-TIMI 51, which has precluded approval of this combination by the US Food and Drug Administration pending additional supporting documentation.

A similar ischemic benefit has been observed over clopidogrel plus ASA by using DAPT with ASA plus ticagrelor[16] or prasugrel[12] 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. However, significant differences exist in the design of studies examining these strategies, and the lack of validity in cross-study comparisons is acknowledged by the very low level of evidence assigned to this recommendation.

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.

RECOMMENDATION

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 that existing evidence does not demonstrate benefit for the use of apixaban and suggests harm associated with the use of dabigatran in the setting of ACS treated with DAPT.

Should PPIs Be Used in Patients Taking DAPT That Includes Clopidogrel?

Patients receiving clopidogrel, particularly as part of DAPT, are often prescribed PPIs for gastroprotection or acid suppression. Results from 2 meta-analyses and a large randomized clinical trial show that PPIs reduce the risk of upper gastrointestinal bleeding by $\geq$ 50% in this population.[54-56] The effect of PPI and clopidogrel coadministration on ischemic events is less clear. Reports from several observational studies suggest concomitant PPI use might mitigate the beneficial effect of clopidogrel.[57,58] In a large Canadian case-control study of patients prescribed clopidogrel after an acute MI, current PPI users had an increased risk of

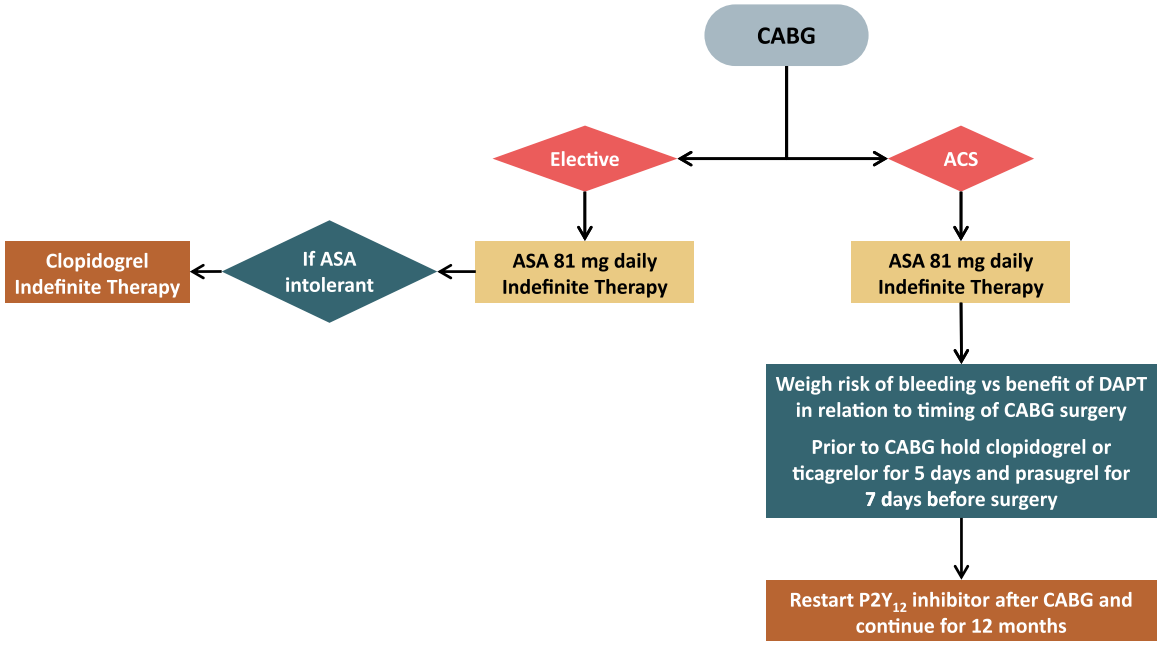

Figure 4. Recommendations after CABG. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy.

reinfarction compared with nonusers (odds ratio, 1.27; 95% CI, 1.03-1.57).[57]

The biological plausibility for a clopidogrel/PPI interaction stems from the 2-step metabolism of clopidogrel mediated by the hepatic cytochrome system, specifically CYP2C19. CYP2C19 is known to be inhibited by certain PPIs, including omeprazole. Of note, in the Canadian case-control study, pantoprazole, a PPI with minimal inhibitory effect on CYP2C19, was not associated with increased reinfarction risk.[58] The potentially significant drug-drug interaction between clopidogrel and PPIs, mainly omeprazole, is supported by platelet function studies.[59,60]

Several cohort studies have been recently published in this area.[61-66] One of these studies suggests PPI and clopidogrel coadministration is associated with an increased MACE risk,[61] while another does not.[62] Emerging evidence from other studies suggests that "channeling bias" (a tendency of clinicians to prescribe treatment based on prognosis, ie, a patient who is perceived to be more "high risk" with multiple comorbidities would be more likely to be prescribed PPIs) plays a major role in the observed MACE risk observed with PPI and clopidogrel coadministration.[63-66] A reanalysis of PLATO demonstrated that PPI use was independently associated with a higher rate of cardiovascular death, MI, and stroke at 12 months in clopidogrel and ticagrelor recipients even though ticagrelor is not dependent on CYP2C19 conversion.[67] A higher rate of cardiovascular events was also observed with non-PPI gastrointestinal treatments. In a Danish cohort study of 13,001 patients who underwent coronary stenting, there was a nonsignificant interaction effect for the use of PPIs modifying the cardioprotective effect of clopidogrel (HR, 1.20; 95% CI, 0.91-1.58).[63] Interestingly, before PCI and independent of clopidogrel use, PPI users had a 25% increased MACE compared with PPI nonusers. In another study using a Danish administrative registry, MACE risk was increased in patients receiving PPIs with ASA alone and without clopidogrel (HR, 1.46; 95% CI, 1.33-1.61; $P < 0.001$).[64] In a separate study, the authors further confirmed that PPI use itself was associated with an increased MACE risk independent of clopidogrel.[65]

In a retrospective analysis of a randomized clinical trial that compared 2 types of DES, all patients who underwent PCI and received clopidogrel were analyzed for PPI use.[61] Compared with PPI nonusers, users had a higher risk of MACE (30.3% vs 20.8%; $P = 0.027$) and MI (14.7% vs 7.4%; $P = 0.01$). After regression analysis, PPI use remained an independent predictor of MACE. Results from the **F**rench Registry of **A**cute **ST**-Elevation and Non-ST−Elevation **M**yocardial **I**nfarction (FAST-MI) registry of 3670 patients with MI revealed that cardiovascular events were not increased in patients who received both clopidogrel and PPIs.[62] In another cohort study that investigated post-PCI clinical outcomes, the authors reported that with propensity-adjusted analyses, MACEs were not increased with PPI and DAPT coadministration even though PPI users were older and had more comorbidities than nonusers.[66]

Notably, results from 2 randomized clinical trials do not support a clinically significant interaction between PPIs and clopidogrel.[56,68] The **C**lopidogrel and the **O**ptimization of **G**astrointestinal Ev**ent**s Trial (COGENT) showed no difference in the MACE risk between patients who received DAPT with or without omeprazole (4.9% vs 5.7%), whereas the risk of upper gastrointestinal bleeding was reduced by > 50% in the PPI-treated group.[56] However, the COGENT population was at low MACE risk: < 50% of patients had a history of ACS. In a small study, 165 patients with atherosclerotic disease and increased risk of peptic ulcer disease were randomized to esomeprazole plus clopidogrel or clopidogrel alone.[68] There was no observed increase in platelet activity in esomeprazole recipients. Both of these trials are limited by potential type II error. Since our initial guidance, several meta-analyses have been published.[54,55,69,70] These

meta-analyses found significant heterogeneity among studies. When results of these, mostly observational studies, were pooled, increased MACE risk was noted with PPI/clopidogrel coadministration.

RECOMMENDATION

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 in this population.

This recommendation recognizes that CYP2C19 inhibition significantly reduces the pharmacologic action of clopidogrel on platelet inhibition. We also recognize that 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 might be most prudent. Specific PPIs that inhibit CYP2C19 can interact with clopidogrel, resulting in reduced efficacy and consequently, increased risk of cardiovascular events; this might be particularly undesirable in patients deemed at "high risk" of rethrombosis. Point-of-care genotyping might provide an alternative approach when broader experience has been achieved.[71]

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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