Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Antiplatelet Agents for Acute Coronary Syndrome: A Review of the Guidelines and Recommendations

DATE: 4 August 2011

CONTEXT AND POLICY ISSUES

Acute coronary syndrome (ACS) is a spectrum of symptoms associated with a sudden interruption of blood flow to the heart. ACS commonly occurs when a coronary artery is partially or completely blocked due to rupture of an atherosclerotic plaque.[1] The unstable collection of lipids and white blood cells blocks the blood supply to the heart muscle resulting in myocardial infarction (MI). Damaged myocardium can be detected using an electrocardiogram (ECG), echocardiography, blood tests, creatinine kinase-MB fraction and tropnin levels. MIs are classified as ST segment elevation myocardial infarctions (STEMI), non-ST elevation myocardial infarctions (NSTEMI) or unstable angina (UA) based on ECG results. Patients may be managed with medication to stabilize plaque, thrombolysis or percutaneous coronary intervention (PCI) to remove an occlusion, and stenting or coronary artery bypass grafting (CABG) to improve revascularization.[1]

Antiplatelet therapy involving aspirin (ASA) and/or clopidogrel, prasugrel or ticagrelor may be given to reduce the risk of MI recurrence.[1] Clopidogrel is used to prevent ischemic events in NSTEMI and STEMI patients and is given with aspirin to prevent stent thrombosis. In March 2010, the FDA issued a warning stating that 2% to 14% of the US population could be susceptible to an event because they have insufficient levels of the CYP2C19 liver enzyme needed to convert clopidogrel to its active form.[2] Tests are available to identify genetic differences in CYP2C19 function. In addition, omeprazole reduces the effectiveness of clopidogrel. Approved by the FDA in 2009, prasugrel is co-administered with aspirin to prevent ischemic events and stent thrombosis in patients undergoing PCI.[3] A newer antiplatelet, tricagrelor is also used to reduce the risk of thrombotic events in ACS patients.[4]

The purpose of this report is to review evidence-based guidelines and recommendations on the use of antiplatelet agents for ACS.

RESEARCH QUESTION

What are the guidelines and recommendations on the use of antiplatelet agents for acute coronary syndrome?

KEY MESSAGE

While clopidogrel is used to prevent ischemic events in NSTEMI and STEMI patients and prasugrel is given with ASA to prevent stent thrombosis, there is insufficient evidence to determine ticagrelors' place in therapy in relation to these agents.

METHODS

Literature search strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and May 30, 2011.

Selection criteria and method

One reviewer screened citations to identify evidence-based guidelines regarding the use of antiplatelet agents for ACS. Potentially relevant articles were ordered based on titles and abstracts, where available. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adults (≥18 years of age) with either STEMI ACS or NSTEMI ACS
Intervention	Clopidogrel, prasugrel, ticagrelor (with or without ASA)
Comparator	Placebo, ASA, clopidogrel, prasugrel, ticagrelor
Outcomes	Guidelines and recommendations on how these drugs are used in patients with ACS
Study designs	Evidence based guidelines

Exclusion criteria

Articles were excluded if they did not satisfy the selection criteria, provided incomplete methods, were superseded by a more recent guideline, were reviews, or were published prior to January 2006.

Critical appraisal of individual studies

Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument (Appendix 1).[5] The domains evaluated were scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. Instead of calculating numeric scores, the strengths and limitations of each guideline were described.

SUMMARY OF EVIDENCE

Quantity of research available

The literature search yielded 207 citations. Upon screening titles and abstracts, 195 citations were excluded and 12 potentially relevant articles were retrieved for full-text review. An additional 26 potentially relevant reports were retrieved from grey literature and hand searching. Of the 38 potentially relevant reports 25 were excluded; eight did not meet the selection criteria, three had incomplete methods, five were superseded by a more recent guideline and nine were reviews. Thirteen reports related to eleven guidelines were included in the review.[6-18] The process of study selection is outlined in the PRISMA flowchart (Appendix 2).

Summary of study characteristics

The guidelines selected for review ranged in date from 2006[11] to 2011.[6-8,10,15,17] Detailed characteristics on the grading of evidence, guideline recommendations and quality assessment can be found in Appendices 3, 4 and 5 , respectively.

Country of origin

Of the eleven guidelines included in this review, one was Canadian,[6,7] seven were American[8-15] and three were European.[16-18] The recommendations are from the Canadian Cardiovascular Society (CCS),[6,7] the American Heart Association (AHA),[8] the American College of Cardiology (ACC),[9-11] the American College of Chest Physicians (ACCP),[12,13] the Institute for Clinical Systems Improvement (ICSI),[14] the European Society of Cardiology (ESC),[16] the National Institute for Health and Clinical Excellence (NICE),[17] and the Scottish Intercollegiate Guidelines Network (SIGN).[18]

Population

Two guidelines provided recommendations on the use of antiplatelets for primary and secondary prevention,[6,7,12] and one guideline reported on secondary prevention only.[11] Of the remaining seven guidelines on the use of antiplatelets in specific patient groups, three reported on ACS,[8,14,15,18] one on STEMI and PCI,[9] two on UA and NSTEMI,[10,17] and two on NSTEMI.[13,16]

Interventions

All guidelines provided recommendations on the use of aspirin and clopidogrel in ACS patients. The recommendations regarding prasugrel were reported by the CCS,[6,7] AHA,[8,9] and ICSI, [14,15] while ticagrelor was also reported by the CCS.[6,7] ICSI and CCS provide additional guidance regarding the reduced efficacy of clopidogrel with concomitant PPIs[6,7,14,15] and CYP2C19 function.[14,15]

Grading of recommendations and levels of evidence

All guidelines developed their recommendations by reviewing the literature, and ten graded the strength of their recommendations based on the quality of the evidence.[6-13,16,17] Five grading systems were used based on accompanying levels of evidence for each one. The recommendations were generally graded as I when the treatment was effective, IIa when evidence was conflicting but favored treatment, IIb when efficacy was uncertain, and III when treatment was not effective.[6-11] The evidence from randomized controlled trials (RCTs) or meta-analyses (MA) was graded as level A, data from large non-randomized studies was graded as B, and consensus of opinion and small studies were regarded as C.[6-11] While NICE and SIGN used the same grading system, only SIGN graded recommendations.

Summary of critical appraisal

All guidelines clearly specified overall objectives, clinical questions and the population for whom guidance was intended. Guideline development groups were generally representative of their relevant professional groups and recommendations were often peer reviewed.[6-13,16] Patients' views and preferences were seldom sought in the development of guidelines.[6,7,9,10,18] In contrast, the ACCP guidelines on primary and secondary prevention state that grade II recommendations consider that individual patient values may lead to different therapeutic choices.[12] While all guidelines are evidence-based, the methods,[8] literature search,[8,12,13] and selection criteria were seldom reported,[6-8,11-15] but the recommendations are specific and management options were clearly presented. The implementation tools are available for guidance by the CCS, ECS and NICE,[6,7,16,18] but most guidelines failed to provide an implementation strategy.[6,7,12,13,16] ACC/AHA plan to review their guidance annually[10] and SIGN provides plans for implementation and audit.[18]

Summary of findings

Eleven guidelines, represented by thirteen reports, provided recommendations on the use of antiplatelet agents for ACS.[6-18] An overview of recommendations is provided in Table 2.

The AHA recommends that high risk NSTEMI and STEMI patients initially receive a loading dose of clopidogrel (300-600 mg).[8] Medically managed STEMI and NSTEMI patients should be given clopidogrel (75 mg/d) with ASA (75-162 mg/d) for at least 14 days and for one to 12 months, respectively.[6,7] Prasugrel (60 mg) may be used in STEMI patients prior to angiography and as a substitute for clopidogrel in NSTEMI and STEMI patients undergoing PCI following angiography.[8,8] UA and NSTEMI patients selected for an invasive approach should receive ASA on presentation and clopidogrel or prasugrel at the time of PCI.[9,16]

UA and NSTEMI patients selected for CABG should discontinue clopidogrel five days before surgery.[10,16] CABG patients should receive ASA (100-325 mg/d) within 48 hours of surgery and continue therapy up to one year.[11] NSTEMI patients managed by CABG should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for one to 12 months.[6,7] ACS patients undergoing stenting should receive prasugrel (10 mg/d) with ASA (75-162 mg/d) for 12 months.[6,7] Similarly, the ACC/AHA recommends that bare metal stent (BMS) and drug eluting stent (DES) recipients receive clopidogrel (75 mg/d) or prasugrel (20 mg/d) for at least 12 months.[9] According to the CCS, ACS patients may receive ticagrelor (90 mg twice/day) with ASA (75-162 mg/d) for 12 months.[6,7]

The new CCS guidelines provide recommendations on the duration of time individuals should take dual antiplatelet therapy.[7] Following PCI with a BMS, the guideline recommends ASA indefinitely (75-162 mg/d) and clopidogrel (75 mg/d) for at least one month and up to 12 months in the absence of bleeding.[6,7] DES patients should receive clopidogrel (75 mg/d) for 12 months and ASA indefinitely. Dual antiplatelet therapy, with ASA and clopidogrel, can be continued beyond a year in patients with high thrombotic risk and low risk of bleeding.[6,7] Prasugrel (10 mg/d) is recommended in addition to ASA in patients with ACS, but should be avoided in elderly patients with an increased risk of bleeding and those with a history of stroke.[6,7]

Patients taking clopidogrel who are at increased risk of gastrointestinal bleeding should take PPIs that minimally inhibit cytochrome P450 2C19 [IIb,B].[6,7] Other antiplatelet medications and alternative dosing strategies for clopidogrel may be considered for patients who are poor metabolizers.[6,7]

Table 2: Summary of Recommendations by Antiplatelet Agent

Antiplatelet	Recommendations
ASA	1. ACS patients should receive ASA (75 mg/d) indefinitely [IA].[6,7,10,11,11-18] 2. Post-PCI patients should receive ASA (75-162 mg/d) indefinitely regardless of stent type [IA].[6,7,12] 3. Post-CABG patients should receive ASA (75 mg/d) within 24 h of surgery [IIaB] and indefinitely [IA].[6,7,11,12]
Clopidogrel	1. ASA intolerant patients should receive clopidogrel (75 mg/d) indefinitely [IA].[6,7,12,13,16,17] 2. High risk NSTEMI and STEMI patients should receive a loading dose of clopidogrel (300-600 mg) [IA].[8-10,12,13,16,18] 3. STEMI patients should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for at least 14 days [IIb,C].[6,7] 4. STEMI patients undergoing PCI should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) at least 12 months [IB] or more in patients at high risk of thrombosis and low risk of bleeding [IIb,C].[6,7] 5. NSTEMI patients undergoing PCI should receive a loading dose of clopidogrel (600 mg) followed by 150 mg/d for 6 days, then 75 mg/d for those not at high risk of bleeding [IIb, B]NSTEACS patients should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for 1 month [IA] and up to 12 months [IB] or beyond [IIb,C].[6,7,17,18] 6. NSTEACS undergoing CABG should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for 1-12 months [IB].[6,7] 7. NSTEAC patients undergoing PCI should receive clopidogrel and an IV GPIIb/IIa inhibitor [1A].[13] 8. Combination ASA and clopidogrel may be considered beyond 1 year in patients with a BMS or DES provided bleeding risk is low [IIb,C].[6,7,11,12] 9. Patients undergoing CABG after PCI should use ASA (75-162 mg/d) with clopidogrel (75 mg/d) for 9-12 months unless bypassed [IIb,C].[6,7] 10. UA/STEMI patients with history of gastrointestinal bleeding should receive concomitant PPIs when ASA and clopidogrel are given alone or in combination [IB].[6,7] 11. Other antiplatelet medications or alternative dosing strategies for clopidogrel could be considered in patients that are poor metabolizers.[14,15]
Prasugrel	1. ACS at risk of stent thrombosis may receive prasugrel (10 mg/d) with ASA (52-162 mg/d) for 12 months [IIa,B].[6,7]

Antiplatelet	Recommendations
	2. NSTEMI and STEMI patients undergoing PCI may receive prasugrel (60 mg loading dose) as a substitute for clopidogrel [IIAB; IB].[8-10,14,15]
Ticagrelor	1. ACS patients may receive ticagrelor (90 mg twice/d) with ASA (75-162 mg/d) for 12 months [IB].[6,7]

ACS: acute coronary syndrome; ASA: aspirin; BMS: bare metal stent; CABG: coronary artery bypass graft; d: day; DES: drug eluting stent; IV GPIIb/IIIa: intravenous glycoprotein IIb/IIIa; NSTEACS: non-ST elevated acute coronary syndrome; NSTEMI: non-ST elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: protein pump inhibitor; STEMI: ST segment elevation myocardial infarctions; UA: unstable angina

Limitations

Of the eleven guidelines included in this review, one is published by a Canadian professional society.[6,7] While the evidence base is similar across countries, guidelines from other countries may not address some issues faced by Canadian professionals. The CCS guideline provides little guidance on ticagrelors' place in therapy in relation to other antiplatelets for ACS, nor is this issue addressed by other guidelines. While up to 14% of the population may be poor metabolizers of clopidogrel, leaving them at risk of having an event, only two guideline recommended testing[10,14,15] and alternative dosing strategies for poor metabolizers.[14,15] Similarly, two of eleven guidelines recommend patients taking clopidogrel who are at risk of gastrointestinal bleeding should take PPIs that minimally inhibit cytochrome P450 2CY19.[6,7,14,15]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence-guidelines reviewed in this report provide similar recommendations regarding the use of antiplatelets for treating and preventing MI in ACS patients. Clopidogrel is used to prevent ischemic events in NSTEMI and STEMI patients and given with ASA to prevent stent thrombosis. Patients with a history of gastrointestinal bleeding should receive concomitant PPIs that minimally inhibit cytochrome P450 2CY19. Other antiplatelet medications or alternative dosing strategies for clopidogrel should be considered in patients who are poor metabolizers.[14,15] Prasugrel is co-administered with ASA to prevent stent thrombosis in patients undergoing PCI. While ticagrelor may also be used to reduce the risk of thrombotic events in ACS patients its place in therapy with respect to other antiplatelet agents is not clear. Some guidelines provided tools for implementation that decision makers may find useful in everyday practice.

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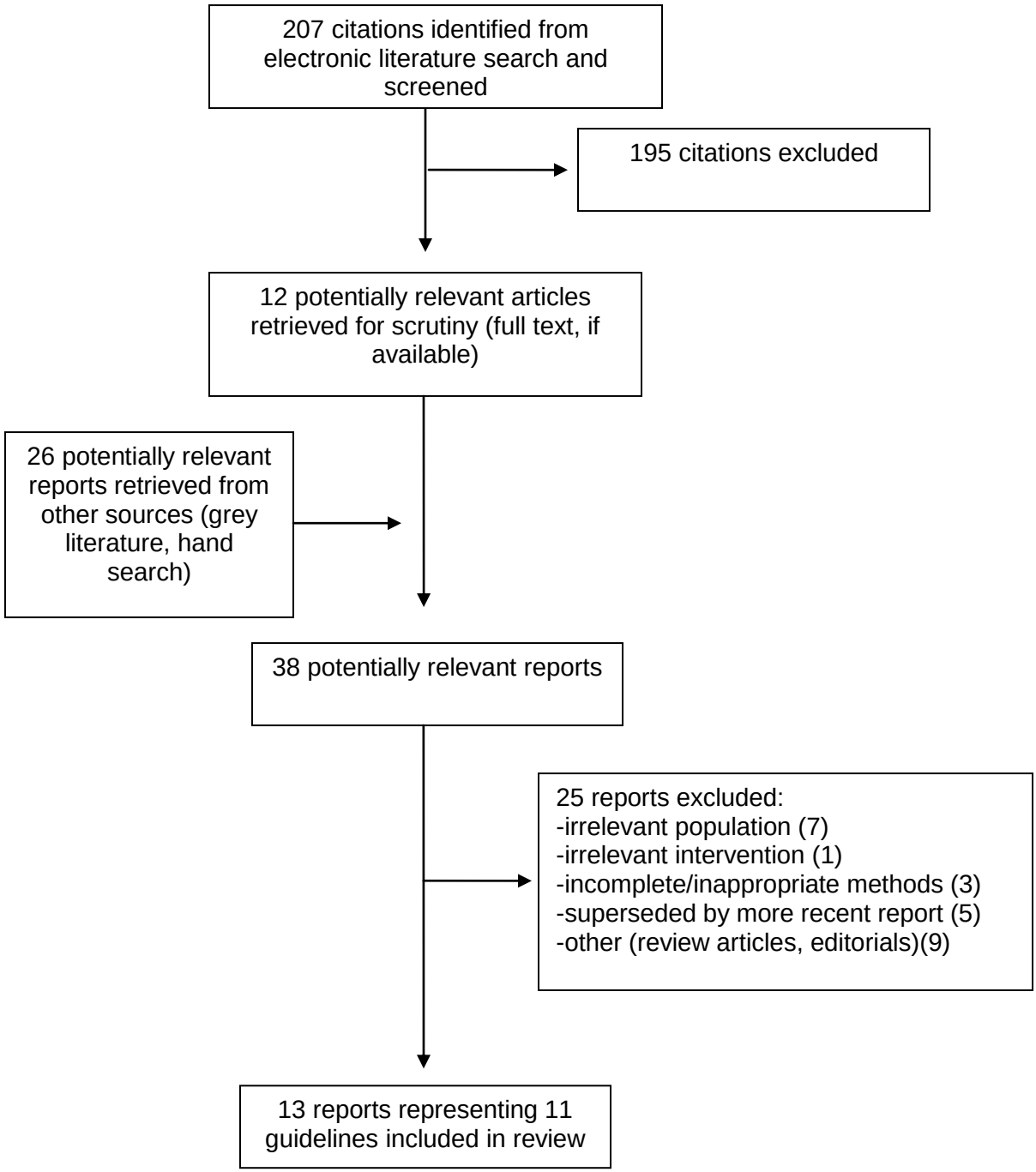
APPENDIX 1: Quality Assessment of Guidelines

APPRAISAL OF GUIDELINES FOR RESEARCH AND EVALUATION (AGREE)[5]		
SCOPE AND PURPOSE	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
1. The overall objective of the guideline is specifically described.		
2. The clinical question(s) covered by the guideline is(are) specifically described.		
3. The patients to whom the guideline is meant to apply are specifically described.		
STAKEHOLDER INVOLVEMENT	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
4. The guideline development group includes individuals from all the relevant professional groups.		
5. The patients' views and preferences have been sought.		
6. The target users of the guideline are clearly defined.		
7. The guideline has been piloted among target users.		
RIGOUR OF DEVELOPMENT	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
8. Systematic methods were used to search for evidence.		
9. The criteria for selecting the evidence are clearly described.		
10. The methods used for formulating the recommendations are clearly described.		
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.		
12. There is an explicit link between the recommendations and the supporting evidence.		
13. The guideline has been externally reviewed by experts prior to its publication.		
14. A procedure for updating the guideline is provided		
CLARITY AND PRESENTATION	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
15. The recommendations are specific and unambiguous.		
16. The different options for management of the condition are clearly presented.		
17. Key recommendations are easily identifiable.		
18. The guideline is supported with tools for application.		
APPLICABILITY	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
19. The potential organizational barriers in applying the recommendations have been discussed.		
20. The potential cost implications of applying the recommendations have been considered.		
21. The guideline presents key review criteria for monitoring and/audit purposes.		
EDITORIAL INDEPENDENCE	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
22. The guideline is editorially independent from the funding source.		
23. Conflicts of interest of guideline development members have		

been reported.		
OVERALL ASSESSMENT	4=Strong agree; 3=agree; 2=disagree; 1=strongly disagree	**Score**
24. Would you recommend these guidelines for use in practice?		

APPENDIX 2: Selection of Included Studies



APPENDIX 3: Grading of Recommendations and Levels of Evidence

Guideline society or institute	Recommendation	Level of evidence
CCS[6,7] and AHA/ACC[8-11]	I: Evidence or general agreement a treatment is effective IIa: Conflicting evidence or divergence of opinion about efficacy in favor IIb: Conflicting evidence or a divergence of opinion about efficacy with uncertain efficacy III: Evidence that treatment is not useful and may harm	A: Data from RCTs or MAs B: Data from single randomized clinical trial or large nonrandomized studies C: Consensus of opinion of the experts and/or small studies, retrospective studies.
ACCP[12,13]	1A: Strong recommendation, high-quality evidence from RCTs without limitations 1B: Strong recommendation, moderate-quality evidence from RCTs with limitations or observational studies 1C: strong recommendation, low quality evidence for at least one critical outcome from observational studies 2A: Weak recommendation, high-quality evidence from RCTs without limitations 2B: Weak recommendation, moderate quality evidence from RCTs with limitations or strong observational studies 2C: Weak recommendation, low quality evidence for at least one critical outcome from observational studies	
ICSI[14,15]	A: RCT B: Cohort study C: Nonrandomized trial with concurrent or historical controls D: Cross sectional study M: meta-analysis R: Consensus document X: Medical opinion	
ESC[16]	I: Evidence and/or agreement a treatment is beneficial II: Conflicting evidence and/or divergence of opinion about the efficacy of a treatment IIa: Weight of evidence/opinion in favor of efficacy IIb: Efficacy is less well established by evidence/opinion III Evidence or agreement a given treatment is not effective	A: Data from multiple RCTs or MAs B: Data from a single RCT or large non-randomized studies C: Consensus of opinion of the experts and/or small studies, retrospective studies and registries
NICE[17] and SIGN[18]	A: At least one MA, SR of RCTs, or RCT rated as 1++ and directly applicable to the large population, or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results B: A body of evidence including studies rated as 2++, directly applicable to the	1++ High quality MA, SRs of RCTs or RCTs with low risk of bias 1+ Well conducted MA, SRs of RCTs or RCTs with a low risk of bias 1 MA, SRs of RCTs or RCTs with a high risk of bias 2++ High quality SRs of case control or cohort studies; high quality case control or cohort studies with low risk of confounding

Guideline society or institute	Recommendation	Level of evidence
	target population, and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1++ or 1+ C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++ D: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+	or bias and a high probability the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal 2 Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 Non-analytic studies (case reports, case series) 4. Expert opinion

ACC: American College of Cardiology; ACCP: American College of Chest Physicians; AHA: American Heart Association; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; ICSI: Institute for Clinical Systems Improvement; MA: meta-analysis; NICE: National Institute for Clinical Excellence; RCT: randomized controlled trial; SIGN: Scottish Intercollegiate Guidelines Network; SR: systematic review.

APPENDIX 4: Guidelines and Recommendations on Antiplatelets for ACS

Guideline society, country, author, year, and indication	Recommendations
ACC/AHA, US Wright et al. 2011[10] UA and NSTEMI	**Antiplatelet Therapy** 1. "UA/NSTEMI patients should receive ASA (162-325 mg) on presentation at hospital and continue ASA (75-162 mg) indefinitely [Class I, Level A]." (pg. 6) 2. "UA/NSTEMI patients who are ASA intolerant should receive clopidogrel (300-600 mg loading dose, 75 mg/day maintenance dose) [Class I, Level B]." (pg. 6) 3. "UA/NSTEMI patients at medium or high risk and in whom initial invasive strategy is selected should receive dual-antiplatelet therapy on presentation [Class I, Level A]. ASA should be initiated on presentation [Class I, Level A]. The choice of second antiplatelet therapy to be added to ASA on presentation includes 1 of the following: Before PCI: Clopidogrel [Class I, Level B]; or An IV GP IIb/IIIa inhibitor [Class I, Level A] IV eptifibatide or tirofiban At the time of PCI: Clopidogrel if not started before PCI [Class I, Level A]; or Prasugrel [Class I, Level B]; or An IV GP IIb/IIIa inhibitor [Class I, Level of Evidence A]." (pg. 6) 4. "UA/NSTEMI patients selected for conservative management should receive clopidogrel (300-600 mg loading dose followed by 75 mg/d maintenance dose) with ASA and anticoagulant therapy on admission and for at least 1 month and ideally up to 1 year [Class I, Level B]." (pg. 6) 5. "UA/NSTEMI patients selected for conservative management who experience recurrent symptoms, ischemia, heart failure or arrhythmias should undergo diagnostic angiography [Class I, Level A]. Either an intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban; [Class I, Level A], or clopidogrel (300-600 mg loading dose followed by 75 mg/d maintenance dose) [Class I, Level A] should be added to ASA and anticoagulant therapy before diagnostic angiography [Class I, Level C]." (pg. 6) 6. "For UA/NSTEMI patients for whom PCI is planned a loading dose of thienopyridine is recommended. Regimens should be 1 of the following: a. Clopidogrel 300-600 mg as early as possible before or at time of PCI [Class I, Level A]; or b. Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI [Class I, Level B]" (pg. 6) 7. "The duration and maintenance dose of thienopyridine therapy should be as follows: a. UA/NSTEMI patients undergoing PCI should receive clopidogrel 75 mg/day or prasugrel 10 mg/day for at least 12 months [Class I, Level B] b. If the risk of morbidity due to bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered [Class I, Level C]" (pg. 6) 8. "For UA/NSTEMI patients selected for conservative management who have recurrent ischemic discomfort with clopidogrel, ASA, and

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	anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography [Class IIa, Level C].” (pg. 7) 9. “For UA/NSTEMI patients selected for invasive interventions, it is reasonable to omit administration of an intravenous GP IIa/IIIb inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI [Class IIa, Level B].” (pg. 7) 10. “For UA/NSTEMI patients in whom an initial conservative strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy [Class IIb, Level B].” (pg. 7) 11. “For UA/NSTEMI patients for whom PCI is planned, prasugrel 60 g may be considered for administration promptly upon presentation, before definition of coronary anatomy if both the risk for bleeding is low and the need for CABG is considered unlikely [Class IIb, Level C].” (pg. 7) 12. “For high-risk UA/NSTEMI patients already receiving ASA and a thienopyridine who are selected for invasive intervention, the use of upstream GP IIb/IIIa inhibitors may be considered for those with elevated troponin levels, diabetes, or significant ST-segment depression, and who are not otherwise at high risk of bleeding [Class IIb, Level B].” (pg. 7) 13. “UA/NSTEMI patients undergoing PCI, should receive a loading dose of clopidogrel (600 mg) followed by a higher maintenance dose of 150 mg/d for 6 days, then 75 mg/d for those not considered at high risk of bleeding. [Class IIb, Level B].” (pg. 7) 14. “Abciximab should not be administered to patients in whom PCI is not planned [Class III, Level A].” (pg. 7) 15. “UA/NSTEMI patients at low risk for ischemic events (TIMI risk score ≤2) or at high risk of bleeding and who are already receiving ASA and clopidogrel, upstream GP IIb/IIIa inhibitors are not recommended [Class III, Level B].” (pg. 7) 16. “In UA/NSTEMI patients with prior history of stroke and/or TIA for whom PCI is planned, prasugrel is potentially harmful as part of a dual-antiplatelet therapy regimen [Class III, Level B].” (pg. 7) **Additional Management Considerations for Antiplatelets** “UA/NSTEMI patients selected for conservative strategy with no subsequent features that necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), a stress test should be performed [Class I, Level B]. a. If after testing the patient is classified as not at low risk, diagnostic angiography should be performed [Class I, Level A]. b. If after testing the patient is classified as being at low risk, the following should be done for discharge: i. Continue ASA indefinitely [Class I, Level A] ii. Continue clopidogrel for at least 1 month and ideally up to 1 year [Class I, Level B] iii. Discontinue IB GP IIb/IIIa inhibitor if started [Class I, Level A] iv. Continue UFH for 48 hours [Class I, Level A] or

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	fondaparinux [Class I, Level B] for duration of hospitalization, up to 8 days, and then discontinue anticoagulant therapy." (pg. 8) "UA/NSTEMI patients selected for CABG should: a. Continue ASA [Class I, Level A]. b. See Class I, #3 in this section. c. Discontinue intravenous GP IIa/IIIb inhibitor (eptifibate or tirofiban) 4 h before CABG [Class I, Level B]. d. Anticoagulant therapy should be managed as follows: 1. Continue UFH [Class I, Level B]; 2. Discontinue enoxaparin 12-24 h before CABG and dose with UFH per institutional practice [Class I, Level B]; 3. Discontinue fondaparinux 24 h before CABG and dose with UFH per institutional practice [Class I, Level B]; 4. Discontinue bivalirudin 3 h before CABG and dose with UFH per institutional practice [Class I, Level B]." (pg. 8) "UA/NSTEMI patients planning to undergo CABG, it is recommended that the drug be discontinued to allow dissipation of the antiplatelet effect [Class I, Level B]. The period of withdrawal should be at least 5 days in patients receiving clopidogrel [Class I, Level B] and at least 7 days in patients receiving prasugrel [Class I, Level C] unless need for revascularization and/or net benefit of thienopyridine outweighs potential risks of bleeding [Class I, Level C]." (pg. 8) "UA/NSTEMI patients undergoing PCI should: a. Continue ASA [Class I, Level A]. b. Administer a loading dose of clopidogrel 9300-600 mg) if not started before diagnostic angiography[Class I, Level A]. c. See Class IIa, #1 in this section. d. Discontinue anticoagulant therapy after PCI [Class I, Level B]." (pg. 8) "UA/NSTEMI patients undergoing medical therapy in whom no significant obstructive CAD on angiography is found should receive antiplatelet and anticoagulant therapy at the discretion of the clinician [Class I, Level C]. For patients in whom evidence of coronary atherosclerosis is present, long-term treatment with ASA and other secondary prevention measures should be prescribed [Class I, Level C]." (pg. 8) "UA/NSTEMI patients undergoing medical therapy and in whom CAD was found on angiography should: a. Continue ASA [Class I, Level A] b. Clopidogrel loading dose if not given before angiography [Class I, Level B] c. Discontinue IV GP IIa/IIIb inhibitor if started previously [Class I, Level B] d. Anticoagulant therapy as follows: i. Continue IV UFH for at least 48 hours or until discharge if given before angiography [Class I, Level A] ii. Continue enoxaparim during hospitalization, up to 8 days if given before diagnostic angiography [Class I, Level A] iii. Continue fondaparinux for duration of hospitalization, up to 8

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	days, if given before angiography [Class I, Level B] iv. Either discontinue bivarlirudin or continue at dose of 0.25 mg/kg/h for up to 72 hours at physician's discretion if given before angiography [Class I, Level B]." (pg. 9) "UA/NSTEMI patients selected for conservative strategy and without angiography or stress testing should: a. Continue ASA indefinitely [Class I, Level A] b. Continue clopidogrel for at least 1 month and up to 1 year [Class I, Level B] c. Discontinue IV GP IIb/IIIa inhibitor [Class I, Level A] d. Continue UFH for 48 hours [Class I, Level A], or administer enoxaparin [Class I, Level A] or fondaparinux [Class I, Level B] for the duration of hospitalization up to 8 days and then discontinue anticoagulant therapy" (pg. 9) e. "UA/NSTEMI patients undergoing PCI should be administered an IV GP IIIb/IIIa inhibitor if not started before diagnostic angiography [Class IIa, Level A]." (pg. 9) "UA/NSTEMI patients on thienopyridine therapy may consider undergoing platelet function testing to determine platelet inhibitory response if results of testing may alter management [Class IIb, Level B]." (pg. 9) UA/NSTEMI patients on clopidogrel therapy might be considered for genotyping for CYP2C19 loss of function variant if results of testing may alter management [Class IIb, Level C]." (pg. 9)
CCS, Canada Bell et al. 2011[6] Primary and secondary prevention	**Secondary Prevention Year 1 after ACS:** 1. "ACS patients should receive ASA (75-162 mg/d) [Class I, Level A]. Patients allergic or intolerant to ASA should receive clopidogrel (75 mg/d) indefinitely [Class IIa, Level B]." (pg. 210) 2. "STEMI patients who are medically managed should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for at least 14 d [Class IIb, Level C]." (pg. 210) 3. "STEMI patients managed by PCI should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for 12 months [Class I, Level B]. Combination therapy beyond 12 months may be considered in patients at high risk of thrombosis and low risk of bleeding [Class IIb, Level C]." (pg. 210) 4. "NSTEACS patients who are medically managed should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for 1 month [Class I, Level A] and up to 12 months in the absence of excessive bleeding [Class I, Level B]. Combined therapy beyond 12 months may be considered in patients at high risk of thrombosis and low risk of bleeding [Class IIb, Level C]." (pg. 210) 5. "NSTEACS patients managed by CABG should receive clopidogrel (75 mg/d) with ASA (75-162 mg/d) for 1 month and up to 12 months [Class I, Level B]." (pg. 210) 6. "ACS patients undergoing stenting with risk of stent thrombosis may receive prasugrel (10 mg/d) with ASA (75-162 mg/d) for 12 months [Class

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	IIa, Level B]. Prasugrel should be avoided in patients with increased bleeding risk, likely to undergo CABG, with history of stroke, ≥75 years of age, or weighing <60 kg [Class III, Level B]" (pg. 210) 7. "ACS patients may receive ticagrelor (90 mg twice/d) with ASA (75-162 mg/d) for 12 months [Class I, Level B]." (pg. 210) **Secondary Prevention beyond 1 Year:** 1. "ACS patients should receive ASA (75-162 mg/d) indefinitely [Class I, Level A] Patients who are allergic or intolerant to ASA should receive clopidogrel (75 mg/d) [Class IIa, Level B] Combination therapy may be considered beyond 1 year in patients with ACS who are medically managed, provided bleeding risk is low [Class IIb, Level C]." (pg. 211) 2. "Post-PCI patients should receive ASA (75-162 mg/d) indefinitely regardless of stent type [Class I, Level A] Combination therapy may be considered beyond 1 year in ACS patients with a BMS or DES provided bleeding risk is low [Class IIb, Level C]." (pg. 211) 3. "CABG patients should receive ASA (75-162 mg/d) within 24 h of surgery [Class IIa, Level B] and for the remainder of their life unless contraindicated [Class I, Level A]. Patients with contraindications to ASA should use clopidogrel (75 mg/d) instead of ticlopidine (250 mg twice/d) because of superior safety profile [Class IIa, Level C] Patients undergoing CABG after PCI should use ASA (75-162 mg/d) with clopidogrel (75 mg/d) for 9-12 months unless stented vessel is adequately bypassed [Class IIb, Level C]." (pg. 212) **Interaction Between Clopidogrel and Proton Pump Inhibitors:** 1. "Patients taking clopidogrel who are at increased risk of upper gastrointestinal bleeding should take PPIs that minimally inhibit cytochrome P450 2C19 [Class IIb, Level B]." (pg. 217)
AHA, US O'Conner et al. 2010[8] ED management of ACS	**Clopidogrel:** 1. "Moderate to high risk NSTEMI and STEMI patients < 75 years of age should receive a loading dose of clopidogrel (300-600 mg) [Class I, Level A]." (pg. S800) 2. "Patients with suspected ACS who are ASA intolerant should receive clopidogrel (300 mg) [Class IIa, Level B]." (pg. S800) 3. "STEMI patients <75 years of age who receive ASA, heparin and fibrinolysis should receive clopidogrel (300 mg) [Class I, Level B]." (pg. S800) **Prasugrel:** 1. "NSTEMI and STEMI patients who are more than 12 hours post symptom onset prior to planned PCI may receive prasugrel (60 mg loading dose) as a substitute for clopidogrel after angiography [Class IIA, Level B]."(pg. S801" 2. "STEMI patients with <12 hours of symptoms may use prasugrel (60 mg oral loading dose) prior to angiography if they are not high risk for bleeding [Class IIa, Level B]." (pg. S801)
ICSI, 2010[14] US	1. "All patients should receive chewable ASA as soon as possible and continue indefinitely. A loading dose of thienopyridine is recommended for

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ACS Evidence Grading:	patients for whom PCI is planned. Regimens for patients undergoing PCI include clopidogrel (300-600 mg) or prasugrel (60 mg) given prior to the procedure. STEMI patients undergoing non-primary PCI should follow the following regimens: a. Patients that received fibrinolytic therapy and have been given clopidogrel should continue clopidogrel as thienopyridine of choice b. Patients that receive fibrinolytic therapy without a thienopyridine should receive clopidogrel (300 mg-600 mg loading dose c. Patients that did not receive fibrinolytic therapy should receive either clopidogrel (300-600 mg loading dose) once coronary anatomy is known and PCI is planned, or prasugrel (60 mg) promptly and no later than 1 h post PCI." (pg. 19) In November 2009, the FDA issued a statement advising prescribers that patients taking clopidogrel should avoid using selected PPIs that inhibit CYP2C19. "ICSI recommends: a. Risks and benefits of concomitant clopidogrel and PPI use be evaluated b. Discontinue PPI if there is no strong indication for use c. Consider H2 blockers d. Patoprazole does not inhibit CYP2C19 and is a reasonable option. However, this has not been shown to be significant in clinical trials (O'Donoghue, 2009 [A])." (pg. 33) In March 2010, the FDA issued a boxed warning to the product label of clopidogrel bisulfate to warn about patients who do not effectively metabolized the drug and therefore may not receive the full benefits of the drug. "Specifically, the purpose is to: a. Warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel – poor metabolizers do not effectively convert clopidogrel to its active form b. Inform health care professionals that tests are available to identify genetic differences in CYP2C19 function; and c. Advise health care professionals to consider the use of other anti-platelet medications or alternative dosing strategies for clopidogrel in patients that are poor metabolizers. Antman, 2004 [R]; ISIS-4 Collaborative Group, 1995 [A]; Lau, 1992 [M]; Sakethou, 1997 [C]" (pg. 19)
ACC/AHA, US Kushner et al. 2009[9] STEMI and PCI	**Recommendations on Thienopyridines** 2. "STEMI patients undergoing PCI should receive a loading dose of thienopyridine. Regimens should be one of the following: a. Clopidogrel (300-600 mg) should be given as early as possible before primary and non-primary PCI [Class I, Level C]. b. Prasugrel (60 mg) should be given as soon as possible for primary PCI [Class I, Level B]. c. STEMI patients undergoing non-primary PCI should receive: i. clopidogrel as the thienopyridine of choice if they were given fibrinolytic therapy and clopidogrel [Class I, Level C];

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	ii. clopidogrel (300-600 mg loading dose) as the thienopyridine of choice if they received fibrinolytic therapy without a thienopyridine [Class I, Level C]; iii. clopidogrel (300-600 mg loading dose) or clopidogrel (300-600 mg) promptly or within 1 hour of PCI if the patient did not receive fibrinolytic therapy [Class I, Level B].” (pg. 2278) 3. “The duration of thienopyridine therapy should be as follows: a. During PI for ACS, BMS and DES recipients should receive clopidogrel (75 mg/d) or prasugrel (20 mg/d) for at least 12 months [Class I, Level B]. b. If the risk of morbidity due to bleeding outweighs benefit, earlier discontinuation should be considered [Class I, Level C].” (pg. 2278) 4. “Thienopyridines should be discontinued in patients in whom CABG is planned and can be delayed to allow dissipation of the antiplatelet effect [Level C]. Withdrawal should be at least 5 days in patients receiving clopidogrel [Level B] and at least 7 days in patients receiving prasugrel [Class I, Level C] unless earlier discontinuation should be considered [Class I, Level C].” (pg. 2278) 5. “DES patients may consider continuing clopidogrel or prasugrel beyond 15 months [Class IIb, Level C].” (pg. 2278) 6. “STEMI patients with prior stroke or TIA for whom primary PCI is planned should not use prasugrel as part of a dual antiplatelet therapy [Class III, Level C].” (pg. 2279) **Timing of Angiography and Antiplatelets** 1. “UA/NSTEMI patients selected for invasive approach should receive ASA on presentation [Class I, Level A] and clopidogrel (before or at the time of PCI) [Class I, Level A] or prasugrel at the time of PCI [Class I, Level B].” (pg. 2278)
ACCP, US Becker et al., 2008[12] Primary and secondary prevention	1. “ACS patients with and without STE should receive ASA (75-162 mg loading dose, 75-100 mg maintenance dose) indefinitely [Grade 1A].” (pg. 777S) 2. “STE-ACS patients with or without fibrinolytic therapy should receive clopidogrel (300 mg loading dose for patients ≤75 years of age; 75 mg for those > 75 years of age, 72 mg/d for 2-4 weeks [Grade 1A] and up to 12 months following discharge [Grade 2B].” (pg. 777S) 3. “NSTE-ACS patients should receive combination therapy with ASA (75-100 mg/d) and clopidogrel (75 mg/d) for 12 months [Grade 1A].” (pg. 777S) 4. “ASA intolerant patients should receive clopidogrel monotherapy (75 mg) [Grade 1A].” (pg. 777S) 5. “Patients with symptomatic CAD should receive ASA (75-100 mg/d) in combination with clopidogrel (75 mg/d) [Grade 2B]. a. PCI patients are recommended to take ASA (75-100 mg/d) indefinitely [Grade 1A]. b. Patients undergoing PCI with BMS should receive ASA (75-100

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	mg/d) with clopidogrel in preference to ASA alone [Grade 1A]. c. Patients undergoing PCI with BMS should receive 12 months of ASA (75-100 mg/d) with clopidogrel (75 mg/d) over ASA alone [Grade 1A]. d. Patients undergoing PCI with DES should receive ASA (75-100 mg/d) with clopidogrel (75 mg/d) for at least 12 months [Grade 1A]. for 3-4 months [Grade 1B] for 4-12 months, and indefinitely should there be no bleeding or tolerability issues [Grade 2C]. e. Patients undergoing stenting with strong concomitant need for VKA should receive triple antithrombotic therapy [Grade 2C]. Four weeks of clopidogrel following BMS and 1 year following DES is recommended [Grade 2C]. f. After stenting, patients should receive clopidogrel [Grade 1A] or ticlopidine [Grade 2B] over cilostazole. Clopidine is recommended over ticlopidine [Grade 1A]. g. ASA intolerant patients undergoing PCI should receive a thienopyridine derivative rather than dipyridamole [Grade 1B]." (pg. 777S) 6. "CAD patients undergoing CABG should receive ASA (75-100 mg/d) indefinitely [Grade 1A]. ASA should start post-operatively.[Grade 2A]. a. Patients undergoing CABG should not receive dipyridamole in addition to ASA [Grade 1A]. b. CAD patients undergoing CABG who are allergic to ASA should receive clopidogrel (300 mg as a loading dose 6 h after surgery followed by 75 mg/d po indefinitely [Grade 1B]. c. Patients undergoing CABG following NSTE-ACS should receive clopidogrel 75 mg/d for 9-12 months following the procedure in addition to ASA [Grade 2B]. d. Patients who received clopidorel for ACS and are scheduled for CABG should discontinue clopidogrel for 5 days prior to surgery [Grade 2A]." (pg. 778S) 7. "For all patients, it is recommended against the routine addition of clopidogrel to aspirin therapy in primary prevention [Grade 1A]. Monotherapy with clopidogrel is recommended for patients who are intolerant to ASA [Grade 1B]." (pg. 778S)
ACCP, US Harrington et al., 2008[13] NSTEMI	1. "NSTE ACS patients should receive ASA (162-325 mg) immediately and 75-100 mg/d thereafter [Grade 1A]." (pg. 671S) 2. "NSTE ACS patients with ASA allergy should receive clopidogrel (300 mg) immediately followed by 75 mg/d indefinitely [Grade 1A]." (pg. 671S) 3. "NSTE patients at moderate risk (e.g. chest pain, hemodynamic instability, positive troponin, or dynamic ECG changes) for an ischemic event and who will undergo early invasive management (i.e. diagnostic catheterization followed by revascularization): a. Should receive "upstream" treatment with either clopidogrel (300 mg bolus, followed by 75 mg/d) or small molecule IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban) [Grade 1A]. b. Should receive upstream use of both clopidogrel and a small-molecule IV GP IIb/IIIa inhibitor [Grade 2]. Scrupulous attention to weight and renal-based dosing algorithms must be part of eptifibatide

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	or tirofiban administration. c. Patients presenting with NSTE ACS should not be given abciximab as initial treatment except when coronary anatomy is known and PCI is planned within 24 h [Grade 1A].” (pg. 671S) 4. “NSTE ACS patients who are at moderate risk for an ischemic event and for whom conservative or delayed invasive management will be used: a. Should receive upstream treatment with clopidogrel (300 mg bolus, followed by 75 mg/d) [Grade 1A]. b. Should receive upstream use of both clopidogrel and a small molecule IV GP IIb/IIIa inhibitor [Grade 2B].” (pg. 671S) 5. “NSTE ACS patients undergoing PCI should receive both clopidogrel and an IV GPIIb/IIIa inhibitor [Grade 1A]. a. A loading dose of 600 mg should be given at least 2 h prior to planned PCI follwed by 75 mg/d [Grade 1B]. b. If ticlopidine is given, a loading dose of 500 mg should be given at least 6 h before planned PCI [Grade 2C]. c. PCI patients who cannot tolerate ASA should receive a loading dose of clopidogrel 9600 mg) or ticlopidine (500 mg) at least 24 h prior to PCI. d. All NSTE ACS patients with moderate risk features undergoing PCI in whom a BP IIb/IIIa inhibitor has not been started “upstream” should receive a GP IIb/IIIa antagonist (abciximab or eptifibatide)[Grade 1A]. Administration of abciximab (0.25 mg/kg bolus, followed by a 12 h infusion at a rate of 10 μg/kg, given 10 minutes apart) followed by an 18 h infusion of 2.0 μg/kg/min [Grade 1A]. Appropriate dose reduction of eptifibatide must be based on renal function. e. Patients undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream should not use tirofiban as an alternative to abciximab [Grade 1B].” (671S). 6. “NSTE ACS patients who have received clopidogrel and are scheduled for CABG should discontinue clopidogrel for at least 5 days prior to the scheduled surgery [Grade 2A].” (671S)
ESC, Europe Bassand et al.,2007[16] NSTEMI	1. “NSTE ACS patients should receive ASA (160-325 mg loading dose, non-enteric) [I-A] and a long term maintenance dose (75-100 mg/d) [I-A].”(pg. 1618) 2. “Clopidogrel (300 mg loading dose, followed by 75 mg/d) is recommended for all patients [I-A]. Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding [I-A].” (pg. 1618) 3. “Clopidogrel should be given to patients with contraindications to ASA [I-B].” (pg. 1618) 4. “Patients considered for an invasive procedure or PCI should receive clopidogrel (600 mg loading dose) to achieve a more rapid inhibition of platelet function [IIa-B].” (pg. 1618) 5. “Patients pre-treated with clopidogrel who need to undergo CABG should be postponed for 5 days for clopidogrel withdrawal if clinically feasible [IIa-C].” (pg. 1618)
SIGN,[18] Scotland, 2007	**Combination ASA and Clopidogrel Therapy** 1. “In the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with ACS should be treated immediately with

Guideline society, country, author, year, and indication	Recommendations
ACS	both ASA (300 mg) and clopidogrel (300 mg) therapy [Level 1+, Grade A]." (pg. 7) **Antiplatelet Therapy** 1. "ACS patients should be maintained on long term ASA (75-150 mg/d) therapy. [Level 1++, Grade A]." (pg. 21) 2. "NSTE ACS patients should receive clopidogrel therapy for 3 months in addition to long term ASA. [Level 1++, Grade B]." (pg. 21) 3. "STE ACS patients should receive clopidogrel for up to 4 weeks in addition to long term ASA. [Level 1+, Grade A]." (pg. 21)
ACC/AHA, US Smith et al. 2006[11] Secondary prevention	1. "Start ASA (75-162 mg/d) and continue indefinitely unless contraindicated [Class I, Level A] Patients undergoing CABG should receive ASA (100-325) mg/d within 48 h after surgery to reduce saphenous vein graft closure. ASA (>162 mg/d) can be continued up to 1 year [Class I, Level A]." (pg. 2365) 2. "Start and continue clopidogrel (75 mg/d) with ASA for up to 12 months in patients after ACS or PCI with stent placement (≥1 month for BMS, ≥3 months for SES, and ≥6 months for PES [Class I, Level B]." (pg. 2365) 3. "PCI patients with stent placement should receive higher dose ASA at 325 mg/d for 1 month for BMS, 3 months for SES, and 6 months for PES [Class I, Level B]." (pg. 2365) 4. "Use of warfarin in conjunction with ASA and/or clopidogrel is associated with increased risk of bleeding and should be monitored [Class I, Level B]." (pg. 2365)

ACC: American College of Cardiology, ACS: acute coronary syndrome; AHA: American Heart Association; ASA: aspirin; BMS: bare metal stent; CABG: coronary artery bypass graft; CAD; coronary artery disease; CCS: Canadian Cardiovascular Society; d: day; ECG: electrocardiogram; ED: emergency department; DES; drug eluting stent; ESC: European Society of Cardiology; GP IIa/IIIb: glycoprotein IIa/IIIb; ICSI: Institute for Clinical Systems Improvement; MA: meta analyses; NHS: National Health Service; NICE: National Institute for Health and Clinical Excellence; NSTE: non-ST elevation; NSTEACS: non-ST elevation acute coronary syndrome; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel eluting stent; PI: percutaneous intervention; RCGP: Royal College of General Practitioners; RCT: randomized controlled trials; SES: sirolimus eluting stent; STE: ST elevation; STEMI: ST segment elevation myocardial infarction; TIA: transient ischemic attack; UA: unstable angina; UFH: unfractionated heparin; UK: United Kingdom; US: United States.

APPENDIX 5: Summary of Critical Appraisal Using AGREE

Guideline society, country author, year, and indication	Strengths	Limitations
ACC/AHA, US Wright et al. 2011[10] UA and NSTEMI	• Clearly defined objectives, scope and target populations • Recommendations overlap previously published ACC/AHA guidelines on STEMI, PCI, secondary prevention, and angina and are evidence-based • Guideline reviewed annually	• Patients views and preferences not considered
CCS, Canada Bell et al. 2011[6,7] Primary and secondary prevention	• Recommendations are evidence based • Comprehensive literature search • Appraisal using AGREE • Executive summary tool	• Inclusion/exclusion criteria NR • Patients perspective unaccounted for • Barriers to implementation NR
AHA, US O'Conner et al. 2010[8] ED management of ACS	• Recommendations are evidence based	• Methods NR in publication, reference to previous guidelines • Literature search strategy and inclusion/exclusion criteria NR
ICSI, 2010[14,15] US ACS	• Recommendations are directly linked to the evidence and grading is by hierarchy • Recommendations for implementations are included	• Selection criteria NR • Unclear whether guideline was externally reviewed or tested
NHS, NICE, 2010,[17] UK UA and NSTEMI	• Implementation tools have been developed	• Supporting evidence is NR for each recommendation
ACC/AHA, US Kushner et al. 2009[9] STEMI and PCI	• Recommendation are directly linked to evidence • Stakeholders involved in drafting and review	• Recommendations based on B and C levels of evidence • Patients views and preferences not considered
ACCP, US Becker et al., 2008[12] Primary and secondary prevention	• Recommendations are based mostly on Grade 1 evidence • Grade 2 recommendations consider that individual patient values may lead to different choices	• Literature search and selection criteria were NR in this article • Potential barriers to implementation were NR • No tools for dissemination were reported
ACCP, US Harrington et al., 2008[13]	• Recommendations are based on mostly Grade 1A evidence	• Literature search and selection criteria were NR in this article • Potential barriers to

Guideline society, country author, year, and indication	Strengths	Limitations
NSTEMI		implementation were NR • No tools for dissemination were reported
ESC, Europe Bassand et al., 2007[16] NSTEMI	• Peer-reviewed recommendations based mostly on class I evidence • Guidelines developed without industry involvement • Implementation tools available (PDA downloadable and picket-sized versions, slide presentation and clinical algorithm)	• Implementation strategy and barriers to implementation were NR
SIGN,[18] Scotland, 2007 ACS	• Recommendations base mostly on Level 1++ or 1+evidence • Peer review by independent experts • Plans for implementation and audit	• Patients perspectives may not have been accounted for • Tools for implementation NR
ACC/AHA, US Smith et al. 2006[11] Secondary prevention	• Recommendations are based on existing ACC/AHA guidelines and supplemental searching.	• Number of source documents NR • Implementation strategy was not provided

ACC: American College of Cardiology, ACCP: American College of Chest Physicians; ACS: acute coronary syndrome; AGREE: Appraisal of Guidelines for Research and Evaluation; AHA: American Heart Association; ASA: aspirin; CCS: Canadian Cardiovascular Society; ED: emergency department; ESC: European Society of Cardiology; ICSI: Institute for Clinical Systems Improvement; NHS: National Health Service; NICE: National Institute for Health and Clinical Excellence; NSTEMI: non-ST segment elevation myocardial infarction; NR: not reported; PCI: percutaneous coronary intervention; PDA: personal digital assistant; SIGN: Scottish Intercollegiate Guideline Network; STEMI: ST segment elevation myocardial infarction; UA: unstable angina; UK: United Kingdom; US: United States.