New South Wales Therapeutic Advisory Group Inc.

ANTIPLATELET THERAPIES: CURRENT ISSUES

Targeted Literature Review

November 2009

Updated 26th November 2009
Incorporating 2009 American College of Cardiology / American Heart Association Guidelines
(*Circulation* published online November 18 2009)

This version supercedes all previous versions of this document

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About this document

This document updates "Antiplatelet therapies: A Position Statement of the [then] NSW Therapeutic Assessment Group Inc. December 2000".

During early 2009 TAG and TAGNet members were asked which current issues related to use of antiplatelet agents were of most importance to them in daily clinical practice. This document deals with the majority of those issues in a question and answer format as they relate to cardiovascular and cerebrovascular disease. A further document is planned to address the outstanding issues regarding drug interactions involving antiplatelet agents.

The data were collated after reviewing published clinical practice guidelines, systematic reviews and meta-analyses from 2005 onwards. Websites searched for freely available information included:

International websites
- Agency for Healthcare Research and Quality Guideline Clearing House
- American Heart Association
- British Committee for Standards in Haematology
- Canadian Agency for Drugs and Technologies in Health
- Centers for Disease Control and Prevention
- Cochrane Database of Systematic Reviews
- European Society of Cardiology
- National Health Service Health Technology Assessment Programme
- National Health Service Evidence
- National Institute for Health and Clinical Excellence
- Scottish Intercollegiate Guidelines Network

Australian websites
- Australian Prescriber
- Cardiac Society of Australia and New Zealand
- Medical Journal of Australia
- National Health and Medical Research Council
- National Heart Foundation

The Internet was also searched for appropriate guidelines/systematic reviews/meta-analyses for inclusion. Australian prescribing information was reviewed and the Adverse Drug Reaction Advisory Committee provided information regarding reports involving patients taking multiple antiplatelet agents. Additional relevant information (not guideline, systematic review or meta-analyses) have also been presented where appropriate.

This Targeted Literature Review is not a Position Statement and does not represent recommendations from the NSW Therapeutic Advisory Group. The document has been derived from key points from the reviews, guidelines and articles identified. These key points are presented verbatim from the source document along with reference and web address. Some abbreviations have been modified for uniformity e.g. STEMI, STE MI, STE-MI are all presented as STEMI and some abbreviations have been expanded for clarity e.g. /d or /day has been expanded to daily.

In general, guidelines presented here describe method of development, author involvement and provide grading for recommendations. In some cases, grading has not been performed and this is noted where relevant. Systematic reviews and meta-analyses all describe the search strategy undertaken and describe author involvement. Grades of evidence are presented as per the system used in each document. These are not easily reconcilable and readers are referred to the original publications for details of each grading system.

Key points summarised here are not necessarily presented immediately following each other in the source documents – they may be separated by considerable amounts of other information. Readers are advised to refer to the source documents for further information. Key points from each section are summarised in a tabular format at the end of each section. Information in each section is presented chronologically according to publication date, commencing with the most recent.

Abbreviations

ACC = American College of Cardiology
ACCF = American College of Cardiology Foundation
ACG = American College of Gastroenterology
ACCP = American College of Chest Physicians
ACS = Acute coronary syndromes
ADRAC = Adverse Drug Reactions Advisory Committe
AF = Atrial fibrillation
AHA = American Heart Association
AMH = Australian Medicines Handbook
ASA = Acetylsalicylic acid (Aspirin)
BMS = Bare metal stent
CABG = Coronary artery bypass grafting
CADTH = Canadian Agency for Drugs and Technologies in Health
CIAP = Clinical Information Access Program http://www.ciap.health.nsw.gov.au/
CSANZ = Cardiac Society of Australia and New Zealand
CT = Computed tomography
DAP = Dual antiplatelet therapy
DES = Drug eluting stent
ESC = European Society of Cardiology
GI = Gastrointestinal
GP = Glycoprotein
HF = Heart failure
HIT = Heparin induced thrombocytopenia
HTA = Health technology assessment
INR = International normalised ratio
IV = Intravenous
LMWH = Low molecular weight heparin
MI = Myocardial infarction
MRI = Magnetic resonance imaging
NHF = National Heart Foundation
NHMRC = National Health and Medical Research Council
NIHR = National Institute for Health Research
NSAID = Non-steroidal anti-inflammatory drug
NSTEACS = Non-ST-segment elevation acute coronary syndromes
NSTEMI = Non-ST-segment elevation myocardial infarction
NZGG = New Zealand Guideline Group
PCI = Percutaneous coronary intervention
PTCA = Percutaneous transluminal coronary angioplasty
RR = Relative risk
SCAI = Society for Cardiovascular Angiography and Interventions
SIGN = Scottish Intercollegiate Guideline Network
STEACS = ST-segment elevation acute coronary syndromes
STEMI = ST-segment Elevation Myocardial Infarction
TG = Therapeutic Guidelines
TIA = Transient ischaemic attack
TURP = Transurethral resection of prostate
UA = Unstable angina
UFH = Unfractionated heparin
UGIE = Upper gastrointestinal event
VKA = Vitamin K antagonist

Question 1: What is the appropriate duration of clopidogrel therapy?

AUSTRALIAN PRESCRIBING RECOMMENDATIONS

Australian Medicines Handbook[1]
Key points:
- Acute coronary syndrome: Loading dose 300 mg, then 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.
- Placement of coronary stent: Loading dose 300–600 mg at least 6 hours before the procedure, then 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.amh.net.au/

2009 RECOMMENDATIONS

ACC/AHA: 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)[2]
Key Points:
- Class I recommendation: In patients receiving a stent (BMS or drug-eluting stent [DES]) during PCI for ACS, clopidogrel 75 mg daily (Level of Evidence: B) or prasugrel 10 mg daily (Level of Evidence: B) should be given for at least 12 months
- Class I recommendation: If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. (Level of Evidence: C)
- Class IIb recommendation: Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing DES placement (Level of Evidence: C)

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192663v1

HTA: The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis[3]
Key points:
- The optimal duration of clopidogrel treatment in patients with NSTEACS is uncertain and requires further research.
- The results of the updated decision model suggest that durations of clopidogrel treatment beyond 3 months do not appear to be cost effective in patients at lower risk. However, for an average-risk patient (and in higher risk patients), 12 months of treatment with clopidogrel appear to be cost-effective.

http://www.hta.ac.uk/fullmono/mon1331.pdf

2008 RECOMMENDATIONS

ACCP: The Primary and Secondary Prevention of Coronary Artery Disease[4]
Key points:
- For patients with STEACS, with or without fibrinolytic therapy, we recommend clopidogrel as a 300mg oral loading dose for patients < 75 years of age and 75mg starting dose for those > 75 years of age, and continued at a daily dose of 75 mg for 2–4 weeks (Grade 1A). We suggest continuing clopidogrel for up to 12 months following hospital discharge (Grade 2B).
- For patients with NSTEACS, we recommend combination therapy with aspirin (75–100 mg daily) and clopidogrel (75 mg daily) for 12 months (Grade 1A).
- For patients undergoing PCI with a DES, we recommend aspirin (75–100 mg daily) plus clopidogrel (75 mg daily for at least 12 months) [Grade 1A for 3 to 4 months; Grade 1B for 4 to 12 months]. Beyond 1 year, we suggest continued treatment with aspirin plus clopidogrel indefinitely if no bleeding or other tolerability issues (Grade 2C).

- For patients undergoing stent placement with a strong concomitant indication for VKA, we suggest triple antithrombotic therapy (Grade 2C). We suggest 4 weeks of clopidogrel following BMS and 1 year following DES (Grade 2C).
- In patients who undergo CABG following NSTEACS, we suggest clopidogrel, 75 mg daily, for 9 to 12 months following the procedure in addition to treatment with aspirin (Grade 2B).

http://www.chestjournal.org/content/133/6_suppl/776S.full.pdf+html

ACCP: Acute ST-Segment Elevation Myocardial Infarction[5]
Key points:
- For patients with acute STEMI, we recommend clopidogrel in addition to aspirin (Grade 1A). The recommended dosing for clopidogrel is 300 mg po for patients < 75 years old and 75 mg po for patients > 75 years old if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg daily po for up to 28 days (Grade 1A).
- For patients with acute STEMI who have not received a coronary stent, we suggest that clopidogrel, 75 mg daily, could be continued beyond 28 days and up to 1 year (Grade 2B).

http://www.chestjournal.org/content/133/6_suppl/708S.full.pdf+html

ACC/AHA: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction[6]
Key points:
- Clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. (Level of Evidence: A) Treatment with clopidogrel should continue for at least 14 days. (Level of Evidence: B).
- Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. (Level of Evidence: C)
- For all STEMI patients not undergoing stenting (medical therapy alone or PTCA without stenting), treatment with clopidogrel should continue for at least 14 days. I (B)
- Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. IIa (C)

http://circ.ahajournals.org/cgi/reprint/117/2/296.pdf

2007 RECOMMENDATIONS

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes[7]
Key points:
- For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

ACC/AHA: Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction[8]
Key points:
- For UA/NSTEMI patients in whom an initial conservative (i.e.noninvasive) strategy is selected (see Section IV.C), clopidogrel (loading dose followed by daily maintenance dose) should be added to ASA [aspirin] and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (Level of Evidence: A) and ideally up to 1 year. (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/116/7/803.pdf

SIGN: Acute coronary syndromes: A national clinical guideline[9]
Key points:
- In addition to long term aspirin, clopidogrel therapy should be continued for three months in patients with non-ST elevation acute coronary syndromes. (Grade B recommendation)
- In addition to long term aspirin, clopidogrel therapy should be continued for up to four weeks in patients with ST elevation acute coronary syndromes. (Grade A recommendation)

http://www.sign.ac.uk/pdf/sign93.pdf

SIGN: Management of stable angina: A national clinical guideline[10]
Key points:
- Drug eluting stents delay re-endothelialisation and dual antiplatelet therapy (aspirin plus clopidogrel) must be continued for at least 3 months after sirolimus stents and six months after paclitaxel stents. Thereafter, clopidogrel can be discontinued. (Level 3 evidence).

http://www.sign.ac.uk/pdf/sign96.pdf

2006 RECOMMENDATIONS

NHF/CSANZ: Guidelines for the management of acute coronary syndromes 2006[11]
Key points:
- Management of patients with ST-segment-elevation myocardial infarction: Clopidogrel (75 mg daily) should be continued for at least a month after fibrinolytic therapy, and for up to 12 months after stent implantation, depending on the type of stent and circumstances of implantation (Level II evidence; grade B recommendation).

http://www.mja.com.au/public/issues/184_08_170406/suppl_170406_fm.pdf

2005 RECOMMENDATIONS

ESC: Guidelines for Percutaneous Coronary Interventions[12]
Key points:
- After all bare metal stent procedures: 3-4 weeks (1A)
- After vascular brachytherapy: 12 months (1C)
- After drug-eluting stents: 6-12 months (1C)
- After NSTEACS: Prolonged for 9-12 months (1B)

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf

Summary of recommendations for question 1 according to indication*

Indication	Recommendation for clopidogrel duration	Class/ Grade	Year & organisation
NSTEMI/ NSTEACS:	Optimal duration unknown	--	2009 HTA UK[3]
	12 months therapy for average and higher risk patients appears cost-effective	--	2009 HTA UK[3]
	1-12 months	-- A/B	2009 AMH[1] 2007 ACC/AHA[8]
	12 months	IA IA	2008 ACCP[4] 2007 ESC[7]
	3 months	B	2007 SIGN[9]
STEMI/ STEACS:	Up to 12 months	-- 2B IIA C	2009 AMH[1] 2008 ACCP[4] 2008 ACC/AHA[6]
	Up to 1 month	IA A	2008 ACCP[5] 2007 SIGN[9]
	1-12 months (if no stents)	2B	2008 ACCP[5]
	14 days (if no stents)	IB	2008 ACC/AHA[6]
	1 month after fibrinolysis	IIB	2006 NHF/CSANZ[11]
	Up to 4 weeks	A	2007 SIGN[9]
	Up to 12 months after stent (depending on type)	IIB	2006 NHF/CSANZ[11]
Drug Eluting Stent	At least 12 months	IB	2009 ACC/AHA[2]
	Consider discontinuation if risk of bleeding outweighs benefit	IC	2009 ACC/AHA[2]
	Continuation beyond 15 months may be considered	IIB C	2009 ACC/AHA[2]
	3-4 months	IA	2008 ACCP[4]
	4-12 months	IB	2008 ACCP[4]
	Continue indefinitely if no bleeding or other tolerability issues	2C IIB C	2008 ACCP[4] 2008 ACC/AHA/SCAI[13]
	At least 3 months after sirolimus stents and 6 months after paclitaxel stents.	3	2007 SIGN[10]
	6-12 months	IC	2005 ESC[12]
Bare Metal Stent	At least 12 months	IB	2009 ACC/AHA[2]
	Consider discontinuation if risk of bleeding outweighs benefit	IC	2009 ACC/AHA[2]
	1-12 months	--	2009 AMH[1]
	2 weeks if risk of bleeding	IB	2008 ACC/AHA[6]
	3-4 weeks	IA	2005 ESC[12]
Stent plus VKA indication	1 month after BMS	2C	2008 ACCP[4]
	12 months after DES	2C	2008 ACCP[4]
CABG following NSTEMI:	9-12 months	2B	2008 ACCP[4]

*Recommendations presented in order of publication within each indication

Question 2: What is the role of high dose vs. low dose aspirin?

AUSTRALIAN PRESCRIBING INFORMATION

Australian Medicines Handbook[1]
Key points:
- 75–150 mg daily is effective for long term use; Dose of 150–300 mg daily may be required in acute conditions (MI, acute ischaemic stroke, unstable angina, placement of intracoronary stent).

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.amh.net.au/

Therapeutic Guidelines[14]
Key points:
- It is important to distinguish between the effects of a single dose of aspirin and repeated daily dosing. When given as a single dose, soluble aspirin 300 mg is more than sufficient to maximally inhibit platelet function within 30 minutes. Thus, when an immediate antiplatelet effect is required, such as for acute myocardial infarction, unstable angina or acute ischaemic stroke, a loading dose of 150 to 300 mg of aspirin is recommended, as this dose produces rapid and complete inhibition of thromboxane A2–mediated platelet aggregation. Crushing, sucking or chewing a tablet can give more rapid absorption.
- Soluble aspirin at a dose of 40 to 80 mg daily has a cumulative effect, such that it maximally inhibits platelet thromboxane formation (by more than 95%) after 4 to 5 days. Enteric-coated aspirin 80 to 100 mg daily also produces cumulative and near complete inhibition of platelet aggregation and thromboxane formation in 3 to 5 days.
- Aspirin in doses between 75 mg and 325 mg per day is antithrombotic. Adverse effects such as gastrointestinal or cerebral haemorrhage are dose related. Aspirin in a dose of 75 to 150 mg per day is effective for long-term use, and this dose minimises (but doesn't eliminate) the risk of adverse effects. Aspirin at doses above 300 mg daily does not offer further therapeutic benefit, and increases the risk of clinically significant adverse effects.
- Maintenance therapy of stable angina: 75 to 300 mg orally, daily
- Cardiovascular disease risk reduction: Aspirin is beneficial if the absolute risk of a major cardiovascular event in the next five years is greater than 15%. Use aspirin 100 to 325 mg orally, daily.
- If an acute coronary syndrome is suspected, give: aspirin 300 mg chewed or dissolved before swallowing (providing aspirin has not already been taken)
- Aspirin should be used routinely in acute ischemic stroke, unless thrombolysis or anticoagulation is used, or there is a contraindication to aspirin. Use aspirin 100 to 300 mg orally, daily (initial CT scan is required to exclude cerebral haemorrhage).

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.tg.org.au/

2009 RECOMMENDATIONS

NZGG: New Zealand Cardiovascular Guidelines Handbook: A summary resource for primary care practitioners. 2nd ed.[15] [NB: Recommendations not graded]
Key points:
- After myocardial infarction or angina: Aspirin 75–150 mg should be given routinely and continued for life. These doses are at least as effective as higher doses
- Aspirin 150 to 300 mg should be given as soon as possible after the onset of a stroke in most patients if intracerebral haemorrhage has been excluded with brain imaging. If brain imaging will be delayed, then treatment may be initiated safely prior to imaging and discontinued if intracerebral haemorrhage detected subsequently.
- Aspirin 75–150 mg should be given routinely, long-term after ischaemic stroke or TIA, unless there is an indication for anticoagulation with warfarin. These doses are at least as effective as higher doses

http://www.nzgg.org.nz/guidelines/0154/CVD_handbook_june_2009_update.pdf

Cochrane: Antiplatelet therapy for acute ischaemic stroke – systematic review[16]
Key Points:
- Antiplatelet therapy with aspirin 160 mg to 300 mg daily, given orally (or by nasogastric tube or per rectum in patients who cannot swallow), and started within 48 hours of onset of presumed ischaemic stroke reduces the risk of early recurrent ischaemic stroke without a major risk of early haemorrhagic complications and improves long-term outcome.

http://www.cochrane.org/reviews/en/ab000029.html

2008 RECOMMENDATIONS

SIGN: Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention[17]
Key points:
- Aspirin 300 mg daily should be commenced within 48 hours of ischaemic stroke and continued for at least 14 days. (Grade A)
- Low dose aspirin (75 mg daily), and dipyridamole (200 mg modified release twice daily) should be prescribed after ischaemic stroke or transient ischaemic attack for secondary prevention of vascular events. (Grade A)

http://www.sign.ac.uk/pdf/sign108.pdf

ACCP: Antiplatelet Drugs[18] **[NB: Recommendations not graded]**
Key points:
- Bleeding risks increased with increasing aspirin dose with or without clopidogrel
- Use of the lowest effective dose of aspirin (50 to 100 mg daily for long-term treatment) is currently the most appropriate strategy to maximize its efficacy and minimize its toxicity.
- For patients with different manifestations of ischemic heart or brain disease, a widespread consensus exists in defining a rather narrow range of recommended daily doses (ie 75 to 160 mg) for the prevention of MI, stroke, or vascular death.

http://www.chestjournal.org/content/133/6_suppl/199S.full.pdf+html

ACCP: Antithrombotic and thrombolytic therapy for ischaemic stroke[19]
Key points:
- For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (initial dose of 150–325 mg) [Grade 1A].
- In patients who have experienced a noncardioembolic stroke or TIA (ie, atherothrombotic, lacunar, or cryptogenic), we recommend treatment with an antiplatelet drug (Grade 1A) … We recommend an aspirin dose of 50–100 mg daily over higher aspirin doses (Grade 1B).
- For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin at a dose of 75–325 mg daily (Grade 1B)

http://www.chestjournal.org/content/133/6_suppl/630S.full.pdf+html

ACCP: Antithrombotic Therapy for Non–ST-Segment Elevation Acute Coronary Syndromes[20]
Key points:
- For all patients presenting with NSTEACS, without a clear allergy to aspirin, we recommend immediate aspirin (162 to 325 mg po) and then daily oral aspirin (75 to 100 mg) [Grade 1A].

http://www.chestjournal.org/content/133/6_suppl/670S.full.pdf+html

ACCF/ACG/AHA: 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use[21] **[NB: Recommendations not graded]**
Key points:
- The use of low-dose ASA for cardioprophylaxis is associated with a 2- to 4-fold increase in UGIE risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of adverse events, gastroprotection should be prescribed. The risk of UGIE increases with ASA dose escalation; thus, for the chronic phase of therapy, doses greater than 81 mg should not be routinely prescribed.

http://content.onlinejacc.org/cgi/reprint/52/18/1502.pdf

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ESC: Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation[22]

Key points:

- Aspirin should be started at a dose of 150–325 mg in a chewable form (enteric-coated aspirin should not be given because of slow onset of action). An alternative approach, especially if oral ingestion is not possible, is i.v. administration of aspirin at a dose of 250–500 mg, although no specific data are available on the relative merits of this strategy.
- A lower dose (75–160 mg) is given orally daily thereafter for life. (Class 1, level A)

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-AMI-FT.pdf

2007 RECOMMENDATIONS

ACC/AHA/SCAI: 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention[13]

Key points:

- Patients already taking daily long-term aspirin therapy should take 75 mg to 325 mg of aspirin before PCI is performed. (Level of Evidence: A)
- Patients not already taking daily long-term aspirin therapy should be given 300 mg to 325 mg of aspirin at least 2 hours and preferably 24 hours before PCI is performed. (Level of Evidence: C)
- After PCI, in patients without allergy or increased risk of bleeding, aspirin 162 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily long-term aspirin use should be continued indefinitely at a dose of 75 mg to 162 mg. (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.188208v1.pdf

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes[7]

Key points:

- Aspirin is recommended for all patients presenting with NSTEACS without contraindication at an initial loading dose of 160–325 mg (non-enteric) (I-A), and at a maintenance dose of 75–100 mg long-term (I-A).

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

SIGN: Acute coronary syndromes: A national clinical guideline[9]

Key points:

- Patients with acute coronary syndrome should be treated immediately with 300mg aspirin (grade A)
- Following acute coronary syndrome, all patients should be maintained on long term aspirin therapy (grade A). A dose of 75-150 mg aspirin per day is recommended in patients with acute coronary syndrome.

http://www.sign.ac.uk/pdf/sign93.pdf

NHMRC: Clinical Guidelines for Acute Stroke Management: National Stroke Foundation 2007[23]

Key points:

- Aspirin (150-300mg) should be given as soon as possible after the onset of stroke symptoms (i.e. within 48 hours) if CT/MRI scan excludes haemorrhage. (Grade A; Level I)
- Aspirin at lower doses (75-150mg) is just as effective as higher doses (300-1300mg) and is associated with a lower risk of gastrointestinal adverse effects. The lowest therapeutic dose of aspirin remains unclear, but the DUTCH TIA trial showed that in more than 3,000 patients with TIA, 30 mg was as effective as 283 mg in preventing serious vascular events.

http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp109.pdf

2006 RECOMMENDATIONS

NHF/CSANZ: Guidelines for the management of acute coronary syndromes 2006. Acute Coronary Syndrome Guidelines Working Group[11]
Key points:
- Aspirin (300mg) should be given unless already taken or contraindicated (grade A recommendation).
- Aspirin (300 mg) should be given to all patients with STEMI unless contraindicated and, in the absence of significant side effects, low-dose therapy should be continued in the long term (grade A recommendation)
- Discharge medications: All patients should take 75–150 mg daily unless contraindicated (level I evidence, grade A recommendation).

http://www.mja.com.au/public/issues/184_08_170406/suppl_170406_fm.pdf

2005 RECOMMENDATIONS

ESC: Guidelines for Percutaneous Coronary Interventions[12]
Key points:
- Today, ASA continues to play an important role in reducing ischaemic complications related to PCI. If patients are not chronically pre-treated or when there is doubt about medication compliance, a loading dose of 500 mg orally should be given more than 3 hours prior or at least 300 mg intravenously directly prior to the procedure. Only in patients with known allergy against ASA, should it be omitted. As pointed out in the ESC consensus document, for chronic use, there is no need for doses higher than 100 mg daily (1B)

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf

OTHER INFORMATION

Analysis of bleeding complications after different doses of aspirin in 192000 patients enrolled in 31 randomized controlled trials[24]
Key points:
- We sought to compare the risk of hemorrhage due to the low (<100 mg), moderate (100 to 200 mg), and high (>200 mg) doses of aspirin (acetylsalicylic acid [ASA]) in 192,036 patients enrolled in 31 clinical trials. Despite substantial differences in the reporting patterns of bleeding complications, low-dose ASA was associated with the lowest risk, and moderate doses caused a relatively high hemorrhagic event rate, especially with regard to minor, gastrointestinal, and total bleeding, and stroke. These findings should be considered when using combination antiplatelets, anticoagulant therapy, or both, with ASA, especially with the daily dose of >100 mg.

http://www.ajconline.org/article/S0002-9149(05)00294-8/abstract

Summary of recommendations for question 2 according to indication*

Indication	Recommendation for aspirin dosing	Class/ Grade	Year & Organisation
General	150-300mg may be required in acute conditions	--	2009 AMH[1]
	75-150 mg (maintenance dosing)	--	2009 AMH[1]
		--	2008 TG[25]
		--	2007 SIGN[9]
		IA	2006 NHF/CSANZ[11]
	Doses over 300 mg does not offer additional therapeutic benefit	--	2008 TG[25]
	Lowest effective dose usually 50-100 mg	--	2008 ACCP[18]
	Recommended daily doses usually 75-160 mg	--	2008 ACCP[18]
	Maximum 81 mg for chronic therapy	--	2008 ACCF/ACG/AHA[21]
	Aspirin at 75-150 mg as effective as 300-1300mg	--	2007 NHMRC[23]
ACS (unspecified)	300mg for ACS (acute)	--	2008 TG[25]
		A	2007 SIGN[9]
		A	2006 NHF/CSANZ[11]
	75-150 mg	--	2009 NZGG[15]
NSTEMI	162 to 325 mg (acute)	IA	2008 ACCP[20]
	75 to 100 mg (maintenance)	IA	2008 ACCP[20]
	160–325 mg (non-enteric) (acute)	IA	2007 ESC[7]
	75–100 mg (maintenance)	IA	2007 ESC[7]
STEMI	150–325 mg chewable initially / 250–500 mg IV	--	2008 ESC[22]
	75–160 mg (maintenance)	IA	2008 ESC[22]
	300 mg (acute)	--	2008 TG[25]
		A	2006 NHF/CSANZ[11]
PCI	75-325 mg (loading dose) if already on aspirin	A	2008 ACC/AHA/SCAI[13]
	300-325 mg (loading dose) if not already on aspirin	C	2008 ACC/AHA/SCAI[13]
	162-325 mg for 1 month after BMS / 3 months after sirolimus DES / 6 months after paclitaxel DES	B	2008 ACC/AHA/SCAI[13]
	75-162 mg (maintenance)	B	2008 ACC/AHA[13]
	500 mg (loading dose) orally OR 300 mg IV	--	2005 ESC[12]
	No need for doses higher than 100 mg daily	IB	2005 ESC[12]
Stroke/TIA -general	150-300 mg (acute)	--	2009 NZGG[15]
	75-150 mg (maintenance)	--	2009 NZGG[15]
	300 mg (acute) for at least 14 days	A	2008 SIGN[17]
	75 mg (maintenance)	A	2008 SIGN[17]
	150-300 mg (acute)	1A	2007 NHMRC[23]
Ischaemic Stroke	160-300 mg within 48 hours of onset	--	2009 Cochrane[16]
	100-300 mg orally (acute)	--	2008 TG[25]
	150–325 mg (acute)	1A	2008 ACCP[19]
	300 mg for 14 days (acute)	A	2008 SIGN[17]
	75 mg (maintenance)	A	2008 SIGN[17]
Non-embolic stroke/TIA	50-100 mg (maintenance)	1B	2008 ACCP[19]
Embolic stroke	75–325 mg (maintenance) if anticoagulants contraindicated	1B	2008 ACCP[19]

*Recommendations presented according to year of publication within each indication

Question 3: What is the comparative efficacy of glycoprotein IIb/IIIa antagonists agents – abciximab, eptifibatide, tirofiban?

AUSTRALIAN PRESCRIBING RECOMMENDATIONS

Australian Medicines Handbook[1]
Key points:
- Abciximab has a longer duration of action than tirofiban and eptifibatide and is less suitable for patients likely to need coronary artery bypass graft surgery.

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.amh.net.au/

2009 RECOMMENDATIONS

ACC/AHA: 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)[2]
Key Points:
- Class IIa recommendation: It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab [Level of Evidence: A], tirofiban [Level of Evidence: B] or eptifibatide [Level of Evidence: B]) at the time of primary PCI (with or without stenting) in selected patients with STEMI.
- Class IIb recommendation: The usefulness of glycoprotein IIb/IIIa receptor antagonists (as part of a preparatory pharmacological strategy for patients with STEMI before their arrival in the cardiac catheterization laboratory for angiography and PCI) is uncertain. (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192663v1

2007 RECOMMENDATIONS

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes[7]
Key points:
- In high-risk patients not pre-treated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography (I-A). The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).
- When anatomy is known and PCI planned to be performed within 24 hours with GP IIb/IIIa inhibitors, most secure evidence is for abciximab (IIa-B).

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

ACC/AHA: Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction[8]
Key points:
- The question of how best to integrate thienopyridine [e.g. clopidogrel] use with parenteral glycoprotein (GP) IIb/IIIa antagonists to provide optimal antiplatelet therapy early in the course of UA/NSTEMI therapy, including cardiac catheterization, is an evolving subject and continues to present a challenge.
- CLASS I recommendations for antiplatelet therapy (procedure/treatment should be performed/administered)
    - For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose) or an IV GP IIb/IIIa inhibitor. (Level of Evidence: A) Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. (Level of Evidence: B)
    - For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF, or serious arrhythmias subsequently

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appear, then diagnostic angiography should be performed (Level of Evidence: A). Either an IV GP IIb/IIIa inhibitor (eptifibatide or tirofiban; Level of Evidence: A) or clopidogrel (loading dose followed by daily maintenance dose; Level of Evidence: A) should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). (Level of Evidence:C)

- Class IIa recommendations for antiplatelet therapy (it is reasonable to perform procedure/administer treatment)
    – For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel (loading dose followed by daily maintenance dose) and an IV GP IIb/IIIa inhibitor (Level of Evidence: B). Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor (Level of Evidence: B)
- CLASS IIb recommendations for antiplatelet therapy (procedure/treatment may be considered)
    – For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. (Level of Evidence:B)
- CLASS III recommendations for antiplatelet therapy (procedure/treatment should not be performed/administered since it is not helpful and may be harmful)
    – Abciximab should not be administered to patients in whom PCI is not planned. (Level of Evidence: A)

http://circ.ahajournals.org/cgi/reprint/116/7/803.pdf

2006 RECOMMENDATIONS

NHF/CSANZ: Guidelines for the management of acute coronary syndromes 2006[11]
Key points:
- Management of patients with ST-segment-elevation myocardial infarction: It is reasonable to use abciximab with primary PCI, although there are conflicting data (grade B recommendation).
- Management of patients with non-ST-segment-elevation acute coronary syndromes: Intravenous tirofiban or eptifibatide is particularly recommended in high-risk patients in whom an invasive strategy is planned (level I evidence, grade A recommendation).
- Intravenous tirofiban or eptifibatide are also recommended if [NSTEACS] patients continue to have ischaemia while receiving enoxaparin or unfractionated heparin (level III evidence, grade B recommendation).
- Concomitant tirofiban is particularly beneficial and recommended in patients with diabetes (level I evidence, grade A recommendation).

http://www.mja.com.au/public/issues/184_08_170406/suppl_170406_fm.pdf

2005 RECOMMENDATIONS

CADTH: Glycoprotein IIb/IIIa antagonists: a systematic review of randomized clinical trials in patients undergoing percutaneous coronary intervention[26]
Key points:
- Eptifibatide and tirofiban are not found to be superior to abciximab.
- The death rate with abciximab treatment is reduced. The reduction is only significant at 30 days after a PCI. Eptifibatide and tirofiban are not associated with any significant reduction in the risk of death.
- Use of eptifibatide is not associated with a statistically significant reduction in the risk of death or revascularization at 30 days, six months or one year. It is associated, however, with a statistically significant reduction in the risk of MI at seven days and six months
- Use of tirofiban is not associated with a statistically significant reduction in the risk of death or MI. It significantly reduces the need for revascularization at seven days.

http://www.cadth.ca/index.php/en/publication/503

OTHER INFORMATION

A Comparison of Abciximab and Small-Molecule Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Primary Percutaneous Coronary Intervention: A Meta-Analysis of Contemporary Randomized Controlled Trials[27]
Key points:
- Our data suggest that the use of tirofiban or eptifibatide is associated with a clinical outcome similar to that associated with the more widely evaluated agent abciximab in patients undergoing primary PCI.
- No difference in outcome of patients treated with the 2 classes of drugs could be identified in the early or medium-term outcome with respect to mortality, reinfarction, or bleeding.

http://circinterventions.ahajournals.org/cgi/reprint/2/3/230?cookietest=yes

The Relative Safety and Efficacy of Abciximab and Eptifibatide in Patients Undergoing Primary Percutaneous Coronary Intervention: Insights From a Large Regional Registry of Contemporary Percutaneous Coronary Intervention[28]
Key points:
- There is no apparent difference in early outcomes of patients treated with eptifibatide compared with patients treated with abciximab.

http://content.onlinejacc.org/cgi/reprint/51/5/529.pdf

Summary of recommendations for question 3*

	Recommendation	Class/ Grade	Year & Organisation
Comparative efficacy	Abciximab less suitable for patients likely to need coronary artery bypass graft surgery.	--	2009 AMH[1]
	Tirofiban and eptifibatide similar efficacy to abciximab for primary PCI	--	2009 Gurm et al[27]
	No difference in outcomes between abciximab and eptifibatide	--	2008 Gurm et al[28]
	Eptifibatide and tirofiban are not found to be superior to abciximab	--	2005 CADTH[26]
	The death rate with abciximab treatment is reduced at 30 days – not for eptifibatide or tirofiban	--	2005 CADTH[26]
	Eptifibatide associated with a statistically significant reduction in the risk of MI at seven days and six months	--	2005 CADTH[26]
	Tirofiban significantly reduces the need for revascularization at seven days	--	2005 CADTH[26]
Recommendations	It is reasonable to start abciximab at time of primary PCI in patients with STEMI	IIA A	2009 ACC/AHA[2]
	It is reasonable to start tirofiban at time of primary PCI in patients with STEMI	IIA B	2009 ACC/AHA[2]
	It is reasonable to start eptifibatide at time of primary PCI in patients with STEMI	IIA B	2009 ACC/AHA[2]
	The useful of GP IIB/IIIA antacgonists before arrival in cardiac catheter laboratory is uncertain	IIB B	2009 ACC/AHA[2]
	Abciximab is recommended following angiography in patients with NSTEMI proceeding to PCI	IA	2007 ESC[7]
	The use of eptifibatide or tirofiban is less well established than abciximab following angiography in patients with NSTEMI proceeding to PCI	IIA B	2007 ESC[7]
	Eptifibatide or tirofiban are preferred prior to diagnostic angiography in patients with NSTEMI	IB	2007 ACC/AHA[8]
	Abciximab is only recommended if no delay to angiography and PCI likely to be performed in patients with NSTEMI	IB	2007 ACC/AHA[8]
	Abciximab may be used with primary PCI for STEMI	B	2006 NHF/CSANZ[11]
	Tirofiban or eptifibatide are recommended for high-risk NSTEACS if invasive strategy planned	IA	2006 NHF/CSANZ[11]
	Tirofiban or eptifibatide recommended in NSTEACS if ischaemia continues with anticoagulation	IIIB	2006 NHF/CSANZ[11]
	Tirofiban beneficial in patients with diabetes	IA	2006 NHF/CSANZ[11]

*Recommendations presented according year of publication within each indication

Question 4: What is the role of bivalirudin?

AUSTRALIAN PRESCRIBING RECOMMENDATIONS

Australian Medicines Handbook[1]
Key points:
- In percutaneous coronary intervention bivalirudin (with optional glycoprotein IIb/IIIa inhibitor) is similar to heparin (with a glycoprotein IIb/IIIa inhibitor) in terms of mortality and ischaemic events.
- Bivalirudin may be used instead of heparin (or LMWH) and a glycoprotein IIb/IIIa inhibitor in patients with non–ST-segment elevation acute coronary syndromes where there is a high risk of bleeding and an early invasive intervention is planned.

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.amh.net.au/

2009 RECOMMENDATIONS

ACC/AHA: 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)[2]
Key Points:
- Class I recommendation: Bivalirudin is useful as a supportive measure for primary PCI with or without prior treatment with UFH (Level of Evidence: B)
- Class IIa recommendation: In STEMI patients undergoing PCI who are at high risk of bleeding, bivalirudin anticoagulation is reasonable (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192663v1

2007 RECOMMENDATIONS

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes [7]
Key points:
- In an urgent invasive strategy, UFH (I-C), enoxaparin (IIa-B), or bivalirudin (I-B) should be immediately started.
- Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH (IIa-B).

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

ACC/AHA: Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation Myocardial Infarction[8]
Key points:
- Class IIa recommendations: For patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an IV GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier than planned catheterization or PCI. (Level of Evidence: B)
- Class I recommendations: Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation. For patients in whom an invasive strategy is selected, regimens with established efficacy at a Level of Evidence: A include enoxaparin and UFH (Fig. 6; Box B1), and those with established efficacy at a Level of Evidence: B include bivalirudin and fondaparinux (Fig. 7; Box B1).
- Class IIa recommendations: For UA/NSTEMI patients in whom PCI is selected as a postangiography management strategy, it is reasonable to omit administration of an IV GP IIb/IIIa antagonist if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 hours earlier. (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/116/7/803.pdf

NHF/CSANZ: 2007 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006[29] [NB: Recommendations not graded]
Key points:

- Fondaparinux and bivalirudin, both currently not licensed for upstream therapy of NSTEACS, may be preferable alternatives to standard therapy with unfractionated heparin or low molecular weight heparin with a GP IIb/IIIa inhibitor for patients with high-risk NSTEACS, particularly where there is an increased risk of bleeding. The selection of the most appropriate upstream therapy may best be determined for any individual patient from their risk of ischaemia versus bleeding.
- Bivalirudin has the advantage of monotherapy for both upstream and procedural administration at the time of PCI, and therefore may be particularly useful in patients planning to have an early invasive intervention.

http://www.mja.com.au/public/issues/188_05_030308/aro11283_fm.pdf

2005 RECOMMENDATIONS

ESC: Guidelines for Percutaneous Coronary Interventions[12]
Key points:

- Recommendations for bivalirudin as adjunctive medications for PCI
    - Bivalirudin - Replacement for UFH or LMWHs (+GP IIb/IIIa inhibitors) to reduce bleeding complications (IIa C)
    - Bivalirudin - Replacement for UFH in HIT (I C)
- In STEMI, stenting plus abciximab seems to be a more evidence based reperfusion strategy. Bivalirudin is suggested today as a replacement for UFH (or LMWHs) because of significantly less bleeding compared with UFH alone or UFH + GP IIb/IIIa inhibitors. Bivalirudin is unanimously recommended for PCI as a replacement for UFH (and LMWHs) in patients with HIT.

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf

*Summary of recommendations for question 4**

Clinical situation	Recommendation for bivalirudin	Class/ Grade	Year & Organisation
NSTEMI / NSTEACS	Bivalirudin can be used instead of heparin or LMWH + GP IIb/IIIa inhibitor if high risk of bleeding and early invasive intervention is planned	-- -- IIA B	2009 AMH[1] 2008 NHF/CSANZ[29] 2007 ESC[7]
	Bivalirudin is an alternative to GP IIb/IIIa inhibitors for diagnostic angiography +/- PCI if clopidogrel adminsitered at least 6 hours befre procedure	IIA B	2007 ACC/AHA[8]
	Bivalirudin may be started immediately	IB	2007 ESC[7]
	Bivalirudin can be used as anticoagulation in an invasive strategy	IB	2007 ACC/AHA[8]
STEMI treated with streptokinase	Do not use bivalirudin as alternative to heparin	2B	2008 ACCP[5]
PCI	Useful as supportive measure +/- UFH	IB	
	Bivalirudin is reasonable if high risk of bleeding	IIA C	2009 ACC/AHA[2]
	In PCI, bivalirudin is similar to heparin + GP IIb/IIIa inhibitor in terms of mortality and ischaemic events	--	2009 AMH[1]
	Bivalirudin may be particularly useful in patients planned for an early invasive intervention	--	2008 NHF/CSANZ[29]
	Replacement for UFH or LMWHs (+GP IIb/IIIa inhibitors)	IIA C	2005 ESC[12]
	Replacement for UFH in HIT	IC	2005 ESC[12]

*Recommendations presented according to year of publication within each indication

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Question 5: What is the evidence for warfarin + aspirin + clopidogrel combination therapy?

<u>**2009 RECOMMENDATIONS**</u>

Journal of the American College of Cardiology White Paper: Combining antiplatelet and anticoagulant therapies[30]
Key points:
- A major clinical issue that is currently unresolved centers around the management of patients who have a firm indication for warfarin therapy and who have received stents and thus also have an indication for dual antiplatelet therapy. This question is particularly vexing among patients who have received DES and who, with the indication for long-term treatment with dual antiplatelet therapy, have both a need for as well as prolonged exposure to the risk of triple therapy.
- Unfortunately, there is very limited information regarding patients treated with triple therapy, who present significant clinical challenges because of the imperative to balance bleeding risks against risks entailed in stopping 1 of the 3 therapies.
- The principal concern associated with triple therapy is risk of bleeding or transfusion. The frequency of such events in reported series varies, with up to 21% of patients needing a transfusion; bleeding events typically involve the GI tract. This frequency might increase with longer durations of triple therapy, which directly correlate with bleeding risk and might influence mortality in follow-up after PCI. In particular, the RR of major bleeding in patients receiving triple therapy is 3- to 5-fold higher than that observed in patients receiving dual antiplatelet therapy alone.
- It also seems that patients receiving dual antiplatelet therapy only after PCI (prolonged warfarin interruption) have a 3-fold increase in incidence of stroke or thromboembolic events, compared with patients receiving triple therapy or warfarin plus a single antiplatelet agent.
- The combined use of antiplatelet and anticoagulant drugs for the treatment and prevention of complications of 2 or more coexisting conditions, such as AF, mechanical valve prosthesis, and/or a DES, is associated with an increase in bleeding complications that might range from mild or moderate to severe or life-threatening. This risk increases with the duration of therapy, which should therefore be limited to the time necessary for stent endothelialization in patients at high risk for bleeding events. Before committing a patient to triple therapy for an indefinite period, the physician should carefully consider approaches that might not require prolonged dual antiplatelet therapy in conjunction with warfarin. For patients who require triple therapy, careful follow-up is indicated, with low-dose (<100 mg) ASA, conventional dose (75 mg) clopidogrel, a lower target INR (approximately 2.0), and consideration of prophylactic proton-pump inhibition.

http://content.onlinejacc.org/cgi/content/short/54/2/95

<u>**2008 RECOMMENDATIONS**</u>

ACCP: The Primary and Secondary Prevention of Coronary Artery Disease[4]
Key points:
- For patients undergoing stent placement with a strong concomitant indication for VKA, we suggest triple antithrombotic therapy (Grade 2C). We suggest 4 weeks of clopidogrel following BMS and 1 year following DES (Grade 2C).

http://www.chestjournal.org/content/133/6_suppl/776S.full.pdf+html

2008 Expert consensus document
ACCF/ACG/AHA: 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use[21]
Key points:
- Use of combination antiplatelet and anticoagulant therapy should be considered only in cases in which the benefits are likely to outweigh the risks. When warfarin is added to ASA plus clopidogrel, an INR of 2.0 to 2.5 is recommended

http://content.onlinejacc.org/cgi/reprint/52/18/1502.pdf

2007 RECOMMENDATIONS

ACC/AHA: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction[6]

Key points:
- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. I (B)
- In patients requiring warfarin, clopidogrel, and aspirin therapy, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75 mg dose of clopidogrel. I (C)

http://circ.ahajournals.org/cgi/reprint/117/2/296.pdf

ACC/AHA/SCAI: 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention[13]

Key points:
- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. (Class 1B recommendation)
- In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel. (Class 1C recommendation)

http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.188208v1.pdf

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes[7]

Key points:
- The triple association of aspirin, clopidogrel, and a VKA should only be given if a compelling indication exists, in which case, the lowest efficacious INR and shortest duration for the triple association should be targeted (IIa-C).

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

OTHER RELEVANT INFORMATION

Aspirin, Clopidogrel, and Warfarin: Is the Combination Appropriate and Effective or Inappropriate and Too Dangerous?[31]

Key points:
- Available guidelines pertaining to the concomitant administration of aspirin, a thienopyridine, and warfarin are based on limited trial data and consensus judgment. Overall, selection of triple antithrombotic therapy for patients with vascular disease is considered a matter of clinical judgment for an individual patient based on the prescriber's perceived balance between the patient's risk for recurrent ischemic events, expected duration of treatment, and patient's risk for bleeding.

http://www.theannals.com/cgi/reprint/42/6/790

ADRAC reports involving
combination antiplatelet agents plus warfarin

The following table summarises reports to ADRAC as at May 2009 involving combination of antiplatelet and anticoagulant agents. Bruising (including ecchymoses, haematoma) or laboratory changes (e.g. anaemia, thrombocytopenia, INR changes) are not included in the table. If two types of haemorrhage are reported only the first type mentioned is included in the table. Other haemorrhages includes miscellaneous problems such as haematuria, epistaxis, wound, post-procedural or injection site haemorrhage, vitreous haemorrhage

Drug combination	Death	Neurological Haemorrhage	Pulmonary Haemorrhage	Gastrointestinal Haemorrhage	Intra-abdominal or Retroperitoneal Haemorrhage	Other Haemorrhage
Aspirin Clopidogrel Warfarin	0	3	0	1	0	5
Aspirin Clopidogrel Warfarin + other antiplatelet agent	2	0	4	0	0	0
Aspirin Clopidogrel or Warfarin Clopidogrel or Warfarin aspirin	12	19	2	63	1	30
Other combinations involving 1 or more antiplatelet agents* plus 1 or more anticoagulant**	22	4	7	35	9	17
Other combinations of 2 or more antiplatelet agents	3	0	1	8	0	6
Combinations of antiplatelet agent and/or anticoagulant with thrombolytic agent	9	2	2	2	0	2
Total	48	28	16	109	10	60

*Antiplatelet agents include the following:
- Group IIb, IIIa inhibitors
- NSAIDs including aspirin, selective and non-selective COX-2 inhibitors
- Others including clopidogrel, dipyridamole, ticlopidine

**Anticoagulant agents include the following:
- Warfarin
- Unfractionated heparin
- Low molecular weight heparin

Summary of recommendations for question 5 according to indication*

Indication	Recommendation	Class/ Grade	Year & Organisation
Balancing risks	The RR of major bleeding is 3-5x higher in patients on triple therapy compared to dual antiplatelet therapy	--	2009 Holmes et al[30]
	The RR of stroke or thromboembolic events is 3x higher in patient on dual antiplatelet therapy after PCI compared to those on triple therapy or warfarin plus a single antiplatelet agent	--	2009 Holmes et al[30]
	Warfarin with aspirin and/or clopidogrel should be monitored closely	1B	2007 ACC/AHA[6]
Dosing recommendations for triple therapy	Aspirin <100 mg / Clopidogrel 75 mg / Target INR 2.0	--	2009 Holmes et al[30]
	Target INR 2.0 - 2.5	--	2008 ACCF/ACG/AHA[21]
	Aspirin 75-81 mg / Clopidogrel 75 mg / Target INR 2.0-2.5	IC IC	2007 AHH/ACA[6] 2007 ACC/AHA/SCAI[13]
	Lowest efficacious INR and shortest duration for the triple association should be targeted	IIA C	2007 ESC[7]
Stent + warfarin indication	Triple therapy is recommended	2C	2008 ACCP[4]
	BMS – clopidogrel for 4 weeks	2C	2008 ACCP[4]
	DES – clopidogrel for 1 year	2C	2008 ACCP[4]

*Recommendations presented according to year of publication within each indication

Question 6: How should patients on antiplatelet therapy be managed perioperatively?

AUSTRALIAN PRESCRIBING INFORMATION

Australian Medicines Handbook[1]
Key points:
- Aspirin may be stopped 7 days before surgery to decrease risk of bleeding; however, aspirin withdrawal may increase risk of cardiac events.
- Low dose aspirin may be beneficial if taken before coronary artery bypass surgery.
- Stop [clopidogrel] at least 5 days before planned surgery or dental procedures if an antiplatelet effect is not desired; stop at least 5 days before coronary artery bypass.
- Stent patients: assess bleeding risk if clopidogrel continued versus risk of stent thrombosis if it is stopped prematurely; consider delaying elective surgery until dual antiplatelet therapy is no longer required.

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.amh.net.au/

Therapeutic Guidelines[14]
- Aspirin and clopidogrel increase the risk of bleeding but are probably protective against coronary thrombosis in the perioperative period. The decision regarding continuation of antiplatelet drugs is a balance of risk and benefits, and should be made after discussion with the surgeon concerned. If they are to be discontinued, they should be ceased five days before surgery.
- Patients with recent coronary angioplasty and stenting are at high risk of stent thrombosis in the first 30 days, with potentially serious consequences. Any interruption of dual antiplatelet therapy during this time should be discussed with a specialist

Available through CIAP for NSW Health employees. Otherwise available through subscription at http://www.tg.org.au/

2009 RECOMMENDATIONS

CSANZ: Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery[32]
Key points:
- Elective non-cardiac surgery should be deferred for at least 6 weeks and ideally 3 months following PCI with bare metal stenting (Level of evidence III-3, GRADE of recommendation A).
- Elective non-cardiac surgery should be deferred for 12 months following DES (Level of evidence IV, GRADE of recommendation B).
- Wherever possible, continuation of antiplatelet therapy is recommended in patients with prior coronary artery stenting undergoing non-cardiac surgery (Level of evidence III-3, GRADE of recommendation B).
- Exceptions to this include patients undergoing spinal, intracranial, extraocular, TURP or major plastic reconstructive procedures. For these patients antiplatelet therapy should be ceased perioperatively (Level of evidence IV, GRADE of recommendation A).
- Patients at high risk of stent thrombosis in whom antiplatelet therapy is ceased perioperatively should have their procedures performed at facilities with capacity for 24/7 PCI, and should be monitored in a high dependency area in the peri-operative period (Level of evidence IV, GRADE of recommendation B).
- In selected cases, in patients receiving DAP prior to surgery, consideration may be given to receive bridging therapy with heparin/tirofiban or heparin/eptifibitide although there are limited data in support of such treatments (Level of evidence IV, GRADE of recommendation B).

http://www.csanz.edu.au/Portals/0/Guidelines/Practice/Use%20of%20antiplatelet%20therapy%20in%20patients%20with%20coronary%20stents%20undergoing%20non-cardiac%20surgery.pdf

ESC: Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery[33]

Key points:
- Continuation of aspirin in patients previously treated with aspirin should be considered in the perioperative period. IIa B
- Discontinuation of aspirin therapy in patients previously treated with aspirin should be considered only in those in whom haemostasis is difficult to control during surgery. IIa B

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-perioperative-cardiac-care-FT.pdf

2008 RECOMMENDATIONS

ACCP: The Perioperative Management of Antithrombotic Therapy[34]

Key points:
- In patients who require temporary interruption of aspirin- or clopidogrel-containing drugs before surgery or a procedure, we suggest stopping this treatment 7 to 10 days before the procedure over stopping this treatment closer to surgery (Grade 2C).
- In patients who have had temporary interruption of aspirin therapy because of surgery or a procedure, we suggest resuming aspirin approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming aspirin closer to surgery (Grade 2C). In patients who have had temporary interruption of clopidogrel because of surgery or a procedure, we suggest resuming clopidogrel approximately 24 h (or the next morning) after surgery when there is adequate hemostasis instead of resuming clopidogrel closer to surgery (Grade 2C).
- For patients who are not at high risk for cardiac events, we recommend interruption of antiplatelet drugs (Grade 1C). For patients at high risk of cardiac events (exclusive of coronary stents) scheduled for noncardiac surgery, we suggest continuing aspirin up to and beyond the time of surgery (Grade 2C); if patients are receiving clopidogrel, we suggest interrupting clopidogrel at least 5 days and, preferably, within 10 days prior to surgery (Grade 2C). In patients scheduled for CABG, we recommend continuing aspirin up to and beyond the time of CABG (Grade 1C); if aspirin is interrupted, we recommend it be reinitiated between 6 h and 48 h after CABG (Grade 1C). In patients scheduled for CABG, we recommend interrupting clopidogrel at least 5 days and, preferably, 10 days prior to surgery (Grade 1C). In patients scheduled for PCI, we suggest continuing aspirin up to and beyond the time of the procedure; if clopidogrel is interrupted prior to PCI, we suggest resuming clopidogrel after PCI with a loading dose of 300 to 600 mg (Grade 2C).
- In patients with a bare metal coronary stent who require surgery within 6 weeks of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C). In patients with a drug-eluting coronary stent who require surgery within 12 months of stent placement, we recommend continuing aspirin and clopidogrel in the perioperative period (Grade 1C). In patients with a coronary stent who have interruption of antiplatelet therapy before surgery, we suggest against the routine use of bridging therapy with UFH, LMWH, direct thrombin inhibitors, or glycoprotein IIb/IIIa inhibitors (Grade 2C).
- Values and preferences: These recommendations reflect a relatively high value placed on preventing stent related coronary thrombosis, a consideration of complexity and costs of administering bridging therapy in the absence of efficacy and safety data in this clinical setting, and a relatively low value on avoiding the unknown but potentially large increase in bleeding risk associated with the concomitant administration of aspirin and clopidogrel during surgery.

http://www.chestjournal.org/content/133/6_suppl/299S.abstract

ACCP: Antithrombotic Therapy for Non–ST-Segment Elevation Acute Coronary Syndromes[20]

Key points:
- For NSTEACS patients who have received clopidogrel and are scheduled for coronary bypass surgery, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).

http://www.chestjournal.org/content/133/6_suppl/670S.full.pdf+html

2007 RECOMMENDATIONS

ACC/AHA: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction[6]
Key Points:

- In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days and preferably for 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. (Level of Evidence: B)

http://circ.ahajournals.org/cgi/reprint/117/2/296.pdf

ESC: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes[7]
Key points:

- Overall, the benefit of clopidogrel treatment outweighs the risk in all patients with NSTEACS, including those submitted to CABG. The excess bleeding risk in patients submitted to surgery may be attenuated or eliminated by stopping clopidogrel for 5 days before surgery. However, it has not been investigated whether this results in increased complication rates during washout.
- In patients pre-treated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible (IIa-C).
- However, surgery in patients receiving GP IIb/IIIa inhibitors has been shown to be safe when appropriate measures are taken to ensure adequate haemostasis. GP IIb/IIIa inhibitors should be discontinued at the time of cardiac surgery.
- If interruption of dual antiplatelet therapy becomes mandatory, such as need for urgent surgery or major bleeding that cannot be controlled by local treatment, no proven efficacy alternative therapy can be proposed as a substitute.
- Temporary interruption for major or life-threatening bleeding or for surgical procedures where even minor bleeding may result in severe consequences (brain or spinal surgery) is mandatory (IIa-C).
- If CABG is planned, clopidogrel should be stopped and surgery deferred for 5 days, if the clinical condition and the angiographic findings permit this.

http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-NSTE-ACS-FT.pdf

Summary of recommendations for question 6 according to indication*

Indication	Recommendations	Class/ Grade	Year & Organisation
Non-cardiac surgery	Aspirin can be discontinued 7 days prior to surgery to reduce bleeding (may increase cardiovascular events)	--	2009 AMH[1]
	Stop clopidogrel 5 days before surgery if antiplatelet effect is not desired. Consider delaying surgery until clopidogrel no longer required.	--	2009 AMH[1]
	Defer elective non-cardiac surgery for at least 6 weeks and ideally 3 months after PCI with BMS	III-3 A	2009 CSANZ[32]
	Defer elective non-cardiac surgery for 12 months following DES	IV B	2009 CSANZ[32]
	Continue antiplatelet therapy in patients with prior coronary artery stenting (see exceptions below)	III-3 B	2009 CSANZ[32]
	Cease antiplatelet therapy perioperatively in patients undergoing spinal, intracranial, extraocular, TURP or major plastic reconstructive procedures.	IV A	2009 CSANZ[32]
	Cease antiplatelet therapy perioperatively in patients at high risk of stent thrombosis if capacity for 24/7 PCI and high dependency monitoring	IV B	2009 CSANZ[32]
	Consider bridging therapy with heparin/tirofiban or heparin/eptifibatide although there are limited data in support of such treatments	IV B	2009 CSANZ[32]
	Continuation of aspirin should be considered. Discontinue aspirin if potential haemostasis problems.	IIA B	2009 ESC[33]
	If high risk of cardiac events stop clopidogrel 5-10 days prior to surgery.	2C	2008 ACCP[34]
	Stop antiplatelet 7-10 days prior to procedure.	2C	2008 ACCP[34]
	Resume antiplatelet agent 24 hours after procedure if adequate haemostasis.	2C	2008 ACCP[34]
	If high risk of cardiac events (exclusive of stents), continue aspirin.	2C	2008 ACCP[34]
	In patients with a BMS who require surgery within 6 weeks of stent placement, continue aspirin and clopidogrel in the perioperative period.	IC	2008 ACCP[34]
	In patients with a DES who require surgery within 12 months of stent placement, continue aspirin and clopidogrel in the perioperative period.	IC	2008 ACCP[34]
	Decision to stop antiplatelet agent should be made in conjunction with specialist	--	2008 TG[14]
Cardiac surgery	Low dose aspirin may be beneficial prior to CABG	--	2009 AMH[1]
	Stop clopidogrel at least 5-10 days prior to surgery	-- / IC / B / --	2009 AMH[1] / 2008 ACCP[20, 34] / 2007 ACC/AHA[6] / 2007 ESC[7]
	Continue aspirin up to and beyond CABG	IC	2008 ACCP[34]
	If aspirin is stopped, reinitiate 6-48h after CABG	IC	2008 ACCP[34]
	GP IIb/IIIa inhibitors should be discontinued at the time of cardiac surgery.	--	2007 ESC[7]
	Clopidogrel should be stopped and surgery deferred for 5 days, if the clinical condition and the angiographic findings permit this.	--	2007 ESC[7]
PCI	Continue aspirin up to and beyond procedure	2C	2008 ACCP[34]
	If clopidogrel is interrupted, resume clopidogrel with a loading dose of 300-600 mg	2C	2008 ACCP[34]

*Results presented according to year of publication within each indication

Acknowledgements

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