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New Zealand 2012 guidelines for the management of non ST-elevation acute coronary syndromes

Non ST-Elevation Acute Coronary Syndrome Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand

(see Appendix 1 for author names)

Glossary

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndromes
ACUITY	Acute Catheterisation and Urgent Intervention Triage strategY
AHA	American Heart Association
ARB	angiotensin-receptor blocker
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CREDO	Clopidogrel for the Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ECG	Electrocardiogram
ESC	European Society of Cardiology
FRISC-II	Fragmin and fast Revascularisation during In Stability in Coronary artery disease
hsCRP	High sensitivity C-reactive protein
hsTNT	High sensitivity Troponin T
HPS	Heart Protection Study
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes
IHD	Ischaemic heart disease
ISAR	Intracoronary Stenting and Antithrombotic Regimen trials
LDL_C	Low Density Lipoprotein Cholesterol
LMWH	Low-molecular weight-heparin
LV	Left ventricular
MI	Myocardial infarction
NNT	Number needed to treat
NSTEACS	Non ST-elevation acute coronary syndromes
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCI	Percutaneous coronary intervention
OASIS-5	Fifth Organisation to Assess Strategies in Acute Ischemic Syndromes
RITA	Randomised Intervention Trial of Unstable Angina (RITA-3)
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularisation and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial
TACTICS	Treat Angina With Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction
TNI	Troponin I
TNT	Troponin T
UFH	Unfractionated heparin

Purpose

These guidelines apply to the management of patients with non-ST elevation acute coronary syndromes (NSTEACS). The purpose is to provide a summary of the most up to date New Zealand and overseas evidence and to make recommendations based on the evidence that will lead to the best practice for patients with NSTEACS in New Zealand. The guideline is aimed at all health providers who care for patients with NSTEACS.

These guidelines are based on the New Zealand branch of the Cardiac Society of Australia and New Zealand (2005) Guidelines on the Non ST-elevation acute coronary syndromes: New Zealand management guidelines,[2] the 2011 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines for the management of ACS,[3] and consensus of doctors, recommended by the Head of Department from every major New Zealand hospital.

For a detailed description of the levels of evidence cited in this guideline please see Appendix 2.[4] These guidelines are intended for best clinical practice and include some drugs which are not approved yet for funding by PHARMAC. Where physicians or hospitals are not able to meet the guidelines it is recommended that there is documentation that there have been communications between clinicians and managers clearly defining the clinical implications of any resource shortages.

Early risk assessment

Introduction—Risk assessment of patients with NSTEACS for both ischaemia and bleeding, plays an important role in predicting patient prognosis and determining treatments. This also enhances the cost-effectiveness of patient care by enabling evidence-based treatments including antiplatelet, antithrombotic, and revascularisation therapies to be targeted at the patients who are most likely to benefit and not to be harmed from their use.

Ischaemic risk assessment—The clinical history, examination findings, electrocardiographic changes, and blood levels of cardiac marker and troponins are all critical factors in determining risk.[5–11]

Risk assessment should be considered as a dynamic process and patients should be assessed when first seen, after several hours, 6–8 hours, 24 hours and prior to discharge.**1B** The presence of continuing symptoms and response to therapy are important in risk assessment. Refractory ischaemia or evidence of ongoing (including silent) ischaemia (ST elevation see STEMI guidelines, ST depression ≥0.5 mm) on the electrocardiogram (ECG) or monitoring, haemodynamic instability or life-threatening ventricular arrhythmias should mandate early angiography. Risk assessment may be enhanced by determining the number and severity of flow-limiting coronary artery stenoses and the presence or absence of left ventricular impairment. Risk assessment in patients with NSTEACS allows prediction of low, intermediate or high risk of death or nonfatal myocardial infarction (MI) and particularly the risk of events occurring in the short term.

The important features contributing to ischaemic risk assessment are shown in Table 1. Various risk scores can be used—e.g. the Global Registry of Acute Coronary

Events (GRACE) score [Table 1][4,12] or the Thrombolysis In Myocardial Infarction TIMI risk score.[13]

The Global Registry of Acute Coronary Events (GRACE) score is recommended as it has been shown to correlate the best with risk related to the inclusion of heart rate, blood pressure and renal function which are not included in the TIMI risk score. **1B**[1] It is available on IPODs (www.outcomes.org/GRACE).

Table 1a. GRACE risk score [12]

Variables	Points	Total points	Probability of in-hospital death (%)
Age (years)			
<40	0	≤60	≤0.2
40–49	18	70	0.3
50–59	36	80	0.4
60–69	55	90	0.6
70–79	73	100	0.8
≥80	91	110	1.1
Heart rate (beats per min)		120	1.6
<70	0	130	2.1
70–89	7	140	2.9
90–109	13	150	3.9
110–149	23	160	5.4
150–199	36	170	7.3
>200	46	180	9.8
Systolic blood pressure (mmHg)			
<80	63	190	13
80–99	58	200	18
100–119	47	210	23
120–139	37	220	29
140–159	26	230	36
160–199	11	240	44
>200	0	≥250	≥52
Creatinine (μmol/L)		**This score should be recorded in all ACS patients to aid medical management to determine whether an invasive strategy is appropriate and its timing taking into account co-morbidities, including frailty and renal failure, risk of an invasive procedure, likelihood to benefit and patient preferences. A score >140 is high risk.**	
0–34	2		
35–70	5		
71–105	8		
106–140	11		
141–176	14		
177–353	23		
≥354	31		
Killip class			
Class I	0		
Class II	21		
Class III	43		
Class IV	64		

Other risk factors	
Cardiac arrest at admission	43
Elevated cardiac markers	15
ST segment deviation	30

Table 1b. GRACE risk score and mortality[28](White & Chew, Table 1, Adapted with permission)

Mortality	**GRACE risk score**			
	<96	**96–112**	**113–133**	**>133**
30-day death	3·1%	5·3%	5·9%	11·2%
12-month death	4·2%	9·6%	11·9%	27·2%

Bleeding risk assessment—Major bleeding occurs in approximately 4.7% of patients with non-STEMI and 2.3% with unstable angina.[14] Major bleeding is associated with increased in-hospital mortality; 5.3–15.3% in non-STEMI and 3.0–16.1% in unstable angina. Major bleeding[15,16] and transfusions[17] are strong predictors of mortality in non-STEACS and the increased risk is comparable to that of a recurrent MI.[15] Reducing bleeding improves outcomes and reduces costs. A consensus definition of bleeding has recently been defined [Table 2].[18]

A patients' risk of bleeding should be assessed with risk scores [Table 3].**1B**[19] The CRUSADE risk score[20] includes creatinine clearance, anaemia, female sex, tachycardia, hypotension, severe hypertension, heart failure, diabetes and peripheral vascular disease. Other risk factors associated with bleeding are; age >75 years; history of bleeding; history of stroke or TIA; creatinine clearance rate <60 mL/min; blood pressure <120 mmHg or ≥180 mmHg; concomitant use of a GP IIb/IIIa inhibitor; administration of enoxaparin 48 hours prior to intervention; switching between UF heparin and enoxaparin; procedural factors associated with increased risk (femoral artery versus radial artery access, prolonged procedure, intra-aortic balloon pulsation, right heart catheterisation).

Not all of these factors are also risks for ischaemic events. Bleeding may be reduced by using the radial approach[21] for angiography and PCI, bivalirudin instead of UFH and IIb/IIIa antagonists,[22] avoiding upstream IIb/IIIa antagonists[23,24] and avoiding switching between UFH and enoxaparin.**IIa A**[25] Patients can be switched from UFH or enoxaparin to bivalirudin.**IIa B**[26]

Table 2. Bleeding Academic Research Consortium definition for bleeding[18]

Type 0: no bleeding
Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2: any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
(1) requiring nonsurgical, medical intervention by a healthcare professional,
(2) leading to hospitalisation or increased level of care, or
(3) prompting evaluation

Type 3:
Type 3a
Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
Bleeding requiring intravenous vasoactive agents
Type 3c
Intracranial haemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
Chest tube output ≥2 L within a 24-h period
Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL haemoglobin).

†Cell saver products are not counted.

Adapted with permission: Mehran et al. Circulation. 2011;123(23):2736 – Table 3.[18]

Table 3a. Assessment of bleeding risk[19]

Variables	Add to score
Gender	
Male	0
Female	8
Age (years)	
<50	0
50–59	3
60–69	6
70–79	9
≥80	12
Serum creatinine (µmol/L)	
<88	0
88	2
106	3
124	5
141	6
159	8
177	10
<10	0
10–	2

12–	3
14–	5
16–	6
18–	8
≥20	10
No	0
Yes	6
STEMI	+6
NSTEMI – raised biomarkers	+2
NSTEMI – normal biomarkers	0
Heparin plus a GPI*	0
Bivalirudin monotherapy	–5

*If patient is on bivalirudin alone rather than heparin plus glycoprotein IIb/IIIa inhibitor (GPI), the total score should be reduced by 5.

Adapted with permission: Mehran et al. J Am Coll Cardiol. 2010;55(23):2556 – Table 4.[19]

Table 3b. Probability of bleeding according to risk score[19]

Total Score	Non-CABG major bleeding within 30 days (%)
0	0.9
5	1.6
10	2.8
15	4.7
20	7.9
25	12.9
30	20.4
35	30.7
40	43.5

Choice of antiplatelet regimens with lower bleeding risk (clopidogrel in preference to prasugrel or ticagrelor) and optimal dosing of antithrombotic therapy in relation to age; sex; weight and renal function[27] (enoxaparin, integrillin) may also reduce bleeding risk.

Measurement of troponins

In patients presenting with symptoms within the last 24 hours suggestive of acute myocardial ischaemia cardiac troponins T or I have the best sensitivity and specificity for the diagnosis of MI and these are the markers of choice.[29,30] In both short- and long-term follow-up studies, the magnitude of troponin elevations has correlated consistently with the risk of death and the composite risk of death or nonfatal MI[5,10,31,32,34] and troponin levels have been shown to be more powerful prognostic indicators than CKMB levels.[33] It is recommended that CKMB no longer be measured.**III C**

Troponin point of care testing is recommended when hospital logistics cannot consistently deliver laboratory-assayed results within 1 hour. **IIa C** [35]

Troponins are very sensitive markers of myocyte necrosis, and elevated levels can occur in settings other than with myocardial ischaemia. Apart from acute coronary syndromes (ACS), the most frequent causes of elevated troponin levels are

myocarditis, atrial or ventricular tachycardia (often with hypotension and an increased myocardial oxygen demand), pulmonary emboli with right ventricular infarction, and cardiac failure[37] where troponins may be elevated due to myocardial stretch. Other causes of elevated troponin levels include cardiac surgery, Takotsubo cardiomyopathy, and renal failure. There are 6 mechanisms causing troponin elevations. Table 4.[36] Decreased renal excretion is not considered a cause of troponin elevation.[36]

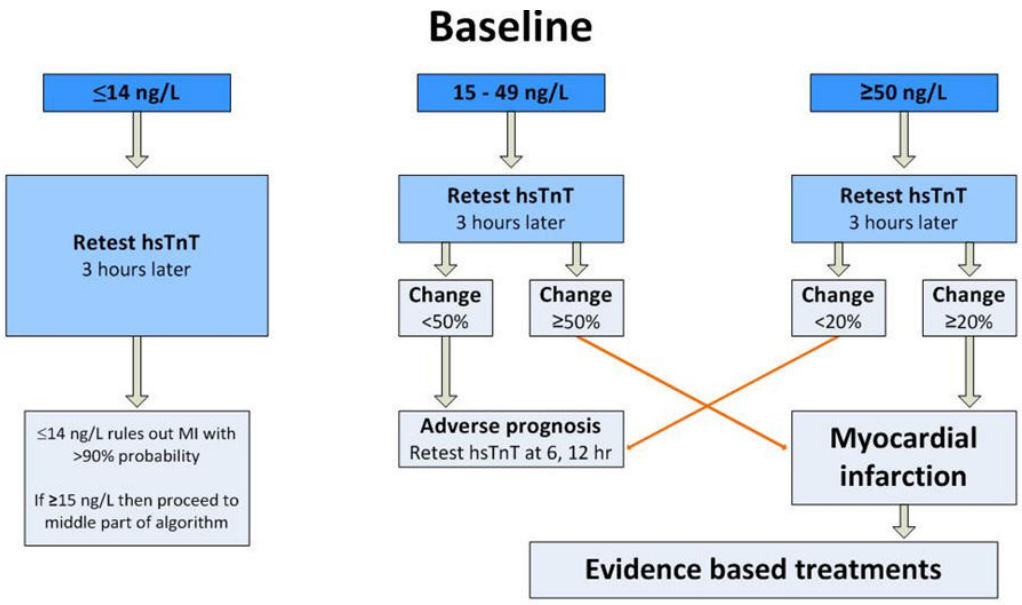
Table 4. Pathobiology of troponin elevations[36]

Type 1	Myocyte necrosis
Type 2	Apoptosis
Type 3	Normal myocyte turnover
Type 4	Cellular release of proteolytic troponin degradation products
Type 5	Increased cellular wall permeability
Type 6	Formation and release of membranous blebs

Adapted with permission: White HD. J Am Coll Cardiol. 2011;57(24):2406 – Table 1.

The diagnostic criteria for MI for high sensitivity troponin T is a discrimination level of ≥15 ng/L, with a rise and or fall of ≥50% over 3–6 hours (Figure 1.[90] There are different cutpoints for troponin I.[38]

Figure 1. Use of hsTnT to diagnose MI in a clinical setting consistent with myocardial ischemia.[89]



Adapted with permission: White HD. Biomarkers in acute coronary syndromes. In: White HD, editor. Advances in acute coronary syndrome management. Future Science Group. Future Medicine Ltd; 2012. p. 18-29.

MI can be ruled out with high sensitivity troponins[39] if there is a level below the 99th percentile 6 hrs after the onset of ischaemic symptoms[3] in the absence of ongoing ischaemic symptoms.

The levels of troponins predict the benefits of therapy with low molecular weight heparins (LMWH),[40] glycoprotein IIb/IIIa antagonists,[41] and of an early invasive/revascularisation strategy.**IIa B**[42] Troponins are also recommended to diagnose reinfarction.**IIa B**[38]

Initial medical management

A 12-lead ECG should be obtained within 10 minutes of patient presentation.**1B** If there is persistent (≥20 minutes) ST elevation patients should be considered for reperfusion therapy (See STEMI guidelines). Abnormalities may involve ST depression (≥0.5 mm)[8] transient ST elevation and or T wave changes.

If the initial ECG is normal or non-diagnostic additional recordings should be made if there are further symptoms and repeated at 3 and 6 hours after presentation.**1B**

A completely normal ECG does not exclude non-STEACS and recordings should be performed for detecting ischaemia in the circumflex territory (V_7–V_9) and the right ventricle (V_3R and V_4R). **1C**[43]

Blood samples for troponins, full blood count, glucose and lipids should be obtained within 10 minutes of presentation. **1C** If a chest pain unit pathway is used patients should be observed and have repeat measurements of troponins at 3-6 hours after symptom onset. **1A** A second high sensitivity troponin sample within 3 hours of presentation increases the sensitivity for the diagnosis of MI to nearly 100%.**1B**[44,45]

Early discharge decisions can then be made based on clinical features, including the presence or absence of recurrence of ischaemia, troponin levels, electrocardiographic changes, and testing for inducible ischaemia as appropriate, usually with exercise testing. CT angiography has the potential to exclude significant fixed coronary artery stenoses.**1B**[46,47] An echocardiogram is recommended in all patients with elevated troponins and those with ECG abnormalities to assess global and regional left ventricular function, assess the valves for defining differential diagnoses.**1C**

Where to manage patients is an important consideration. It is recommended that all high risk patients should be managed in a CCU or CCU step-down until further risk stratification shows them to be at lower risk or revascularisation is performed.**1C**

The very important role of nurses in the management of these patients is acknowledged and highly valued.

Analgesia

Sub-lingual nitroglycerine is recommended for symptoms of ischaemia.**1C** Morphine together with an antiemetic should be used to relieve severe pain.**1C** Intravenous nitroglycerine can also achieve symptomatic relief and be used for blood pressure lowering.**1C**

Oxygen therapy

A recent Cochrane meta-analysis[48] identified three trials with a total of 387 patients evaluating the value of oxygen therapy in whom 14 deaths occurred. The relative risk of death for those receiving oxygen therapy was 2.88 (95%CI 0.88–9.39) by intention-to-treat analysis and 3.03 (95%CI 0.93–9.83) amongst patients with confirmed acute MI. Although these analyses lacked adequate power the findings suggest increased hazard and the routine use of supplemental oxygen is not recommended. **IIa A** Oxygen therapy is indicated for patients with hypoxia (oxygen saturation <93%) and those with evidence of shock, to correct tissue hypoxia. In the absence of hypoxia, the benefit of oxygen therapy is uncertain, and in some cases oxygen therapy may be harmful. **IIa C**

Antiplatelet agents

Table 5 summarises the recommended dosage regimens for various antiplatelet therapies.

Aspirin—Aspirin reduces progression to MI and cardiac mortality by about 50%[49] and all patients without contraindication should immediately receive aspirin 150–300 mg,**1A** which should be chewed if enteric coated. Long-term, lower doses of 75-100 mg in enteric coated formulations to maintain efficacy and to minimise bleeding risk should be given indefinitely. **1C**[49,50]

Clopidogrel—The CURE trial[51] and the separately reported PCI-CURE[52] results provide important evidence for the use of clopidogrel in patients with NSTEACS regardless of whether they are managed conservatively or invasively. In the CURE trial which randomised 12,562 patients (77% managed conservatively), clopidogrel reduced the incidence of death, non-fatal MI and stroke by 20% over an average 9-month follow-up period (9.3% with clopidogrel vs 11.5% with placebo, P<0.001). There were also reductions in the rates of revascularisation, as well as need for thrombolytic therapy and intravenous glycoprotein IIb/IIIa inhibitors in the clopidogrel group.

There was an excess of major bleeding with clopidogrel (3.7% vs 2.7%, P=0.003) but life-threatening bleeding was not increased. In patients undergoing CABG within 5 days of receiving clopidogrel, there was an increase in major bleeding from 6.3% to 9.6%, p=0.05. This compares with 7 major events per 1 000 patients (cardiovascular death, MI or stroke) prevented within the first 24 hours with clopidogrel. Clopidogrel should be stopped 5 days prior to surgery.**1A**

In the PCI-CURE trial with 2658 patients, pre-treatment with clopidogrel for 10 days prior to PCI reduced 30-day composite of death, non-fatal MI and urgent target vessel revascularisation by 30% after PCI (4.5% vs 6.4%, P=0.03).[52] Long-term administration of clopidogrel after PCI for 12 months was associated with a lower rate of cardiovascular death, MI, or any revascularisation (p=0.03), and of cardiovascular death or MI (p=0.047).

Overall (including events before and after PCI) there was a 31% reduction in cardiovascular death or MI (p=0.002). Long-term benefit of clopidogrel plus aspirin after PCI in patients with chronic stable angina was also shown in the CREDO trial.[53] At 1 year, the composite endpoint of death, myocardial infarction or stroke was

reduced by 27% in the clopidogrel group. Greater benefit was achieved in patients receiving clopidogrel >6 hours prior to PCI.

In the CAPRIE trial[54] in patients with previous MI, stroke or peripheral vascular disease clopidogrel had an 8.7% greater benefit than aspirin on reducing vascular death, MI and ischaemic stroke. Clopidogrel is therefore a useful alternative to aspirin when there is intolerance to aspirin.**1A**

The CURRENT trial compared, in patients with ischaemic ECGs or elevated biomarkers, clopidogrel with 600 mg loading followed by 150 mg daily for 7 days and then 75 mg/day compared with 300 mg followed by 75 mg/day. There was no difference between the groups for the primary endpoint of CV death, MI or stroke at 30 days.[55] In a prespecified post randomisation subgroup analysis of patients undergoing PCI (63.1% with non-STEACS) the primary endpoint was reduced with the higher dose clopidogrel regimen; 3.9% vs 4.5%, HR 0.86; 95%CI 0.74–0.99, p=0.039). Stent thrombosis (ARC definition for definite or probable)[56] was also reduced; HR 0.69; 95%CI 0.56–0.87, p=0.001. CURRENT defined major bleeding was increased but TIMI major bleeding was not; 1.0% high dose vs 0.7% standard dose clopidogrel, p=0.07.

The efficacy of clopidogrel is affected by a number of factors including age; diabetes; and genetic polymorphisms.[57,58] High levels of platelet reactivity after clopidogrel are associated with increased risks of ischaemic events and stent thrombosis.[59] However in a trial targeting higher doses of clopidogrel (150 mg vs 75 mg) in patients with high platelet reactivity there was no advantage of the higher dose regimen.[60]

There are two approaches, one is to give clopidogrel only at the time of PCI after the coronary anatomy is known and the other is to give it to all patients prior to angiography, except those in whom urgent CABG is likely as there is increased bleeding if clopidogrel has been given within 5 days of surgery.[51] These patients include those with ECG changes suggestive of ≥50% left main stenosis (i.e. ST deviation in ≥2 coronary artery territories), known coronary anatomy from a previous angiogram which is inappropriate for PCI, the presence of multiple regional wall motion abnormalities on echocardiography, haemodynamic instability or heart failure. All of these patients should be considered for expeditious angiography.

Clopidogrel (600 mg loading dose, 150 mg for 7 days and then 75 mg daily in patients undergoing an invasive strategy; 75 mg daily after the loading dose in patients managed with a conservative strategy) is recommended in addition to aspirin or as an alternative to aspirin **IIa B** and continued for 12 months **1A** if ticagrelor and prasugrel are not available.

Prasugrel—Prasugrel produces more rapid and consistent platelet inhibition than clopidogrel[61] and is not affected by polymorphisms that affect clopidogrel. In the TRITON trial, prasugrel (60 mg loading and 10 mg daily) was compared with clopidogrel 300g loading and then 75 mg/day.[62]

The composite primary endpoint (cardiovascular death, non-fatal MI, or stroke) occurred in 11.2% of clopidogrel-treated patients and in 9.3% of prasugrel-treated patients (HR 0.82; 95%CI 0.73–0.93; P = 0.002), mostly driven by a significant risk reduction for MI (from 9.2% to 7.1%; RRR 23.9%; 95%CI 12.7–33.7; P < 0.001). Definite or probable stent thrombosis was reduced from 2.4% to 1.1%; HR 0.48,

95%CI 0.36–0.64. There was a significant increase in the rate of non-CABG-related TIMI major bleeding (2.4% vs. 1.8%; HR 1.32; 95%CI 1.03–1.68; P = 0.03). Life-threatening bleeding was significantly increased with prasugrel; 1.4% vs. 0.9% (HR 1.52; 95%CI 1.08–2.13; P = 0.01), as well as fatal bleeding, with 0.4% vs. 0.1% (HR 4.19; 95%CI 1.58–11.11; P = 0.002). There was net harm with prasugrel in patients with a history of TIA or stroke. There was no apparent net clinical benefit in patients >75 years of age and in patients with low body weight (<60 kg). Greater benefit without increased risk of bleeding was observed in diabetic patients.

Prasugrel (60 mg loading dose, 10 mg daily) is an alternative (not funded at present) when the coronary anatomy is known and the bleeding risk is low.**1B** Prasugrel should be stopped 7 days prior to surgery. **1C**

Ticagrelor—Ticagrelor is a rapid acting reversible (triazolopyrimidine) P2Y12 inhibitor which achieves greater platelet inhibition at 2 hours (as assessed with light transmittance aggregometry) than after clopidogrel with a 600 mg loading dose (88% vs 38%, p<0.001)[63]

In the PLATO trial which randomized 18,624 patients with an ACS with or without ST elevation received ticagrelor or clopidogrel (300 mg loading dose was recommended unless patients were pre-treated; ≥600 mg was given in 19.6% of patients in the clopidogrel arm) for a mean duration of 277 days. The composite of CV death, MI or stroke was reduced with ticagrelor from 11.7% to 9.8%; HR 0.84, 95%CI 0.77–0.92, p<.001. Definite stent thrombosis was reduced from 1.9% to 1.3%, p<0.01 and total mortality from 5.9% to 4.5%, p<0.001. Overall bleeding was not increased but major bleeding unrelated to CABG was increased; 4.5% ticagrelor, 3.8% clopidogrel, HR 1.19; 95%CI 1.02–1.38, p=0.03.

Ticagrelor (180 mg loading dose, 90 mg bid) is recommended (not currently funded) as the preferred P2Y12 inhibitor.**1B** Ticagrelor should be stopped 5 days prior to surgery. **1C**

Ticagrelor, prasugrel and clopidogrel should be continued for 12 months after ACS including recommencement after CABG.

Glycoprotein IIb/IIIa antagonists—In the EARLY ACS trial in patients with high risk non-ST elevation ACS the routine use of eptifibatide did not lower ischaemic risk on background therapy of aspirin and clopidogrel but was associated with increased risk of bleeding.[23] Similar results were seen in the ACUITY trial.[24]

Routine upstream administration of IIb/IIIa antagonists (tirofiban or eptifibatide) is not recommended in the absence of continuing ischaemia prior to angiography.**III A** They may be administered at the time of PCI (eptifibatide or abxicimab IV or intracoronary) if there is thrombus present or poor coronary flow.**IIb C**

Table 5. Clinical use of antithrombotic therapies

Oral antiplatelet therapies	
Aspirin	Initial dose of 150-300 mg followed by 75-150 mg/day of an enteric formulation
Clopidogrel (Plavix)	A loading dose of 600 mg followed by 150 mg/day for 7 days and then 75 mg daily for 12 months.
Prasugrel (efficient)	A loading dose of 60 mg followed by 10 mg bid for 12 months
Ticagrelor (Brilinta)	180 mg followed by 90 mg bid for 12 months
Heparins	
Heparin (UFH)	Bolus 60U/kg (maximum 4000 U) IV followed by infusion of 12U/kg/h (modified to achieve an aPTT of 50-75s) with laboratory measurements and 60-85 seconds with bedside measurements.
Enoxaparin (Lovenox)	1 mg/kg subcutaneously 12 hourly; preceded by a 30 mg IV bolus.‡ In patients aged ≥75 years no bolus and 0.75 mg/kg subcutaneous 12 hourly. If creatinine clearance <30 mL/min give 1 mg/kg daily
Glycoprotein IIb/IIIa antagonists	
Tirofiban (Aggrastat)	0.4 µg/kg/min for 30 minutes followed by infusion of 0.1 mcg/kg/h for 48 to 96 h and for 12–24 hours post PCI
Eptifibatide (Integrilin)	Double bolus 180 mcg/kg separated by 10 minutes followed by infusion of 2.0 µg/kg/min for 72 to 96 h and for 12-24 hours post PCI. (If creatinine clearance <50mL/min give 1 mg/kg/min)
Abxicimab (ReoPro)	0.25 mg/kg bolus followed by infusion of 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 to 24 hours post PCI. Abxicimab should not be used as upstream treatment unless coronary anatomy is known and the patient is scheduled for PCI

‡ Adjustment required for age ≥75 years and renal dysfunction – see pharmacy guidelines.

Antithrombotic agents

Table 5 summarises the recommended dosage regimens for various antithrombotic therapies.

Enoxaparin—Low molecular weight heparins have several advantages over UFH including less platelet activation, a more predictable dose-effect relationship and a low rate of heparin induced thrombocytopenia (HIT). A meta-analysis of all enoxaparin trials shows a 16% reduction in death and MI at 30 days compared to therapy with UFH.[91]

The SYNERGY trial in 10,027 high risk patients, showed similar outcomes with UFH compared with enoxaparin on a background of high usage of clopidogrel and glycoprotein IIb/IIIa antagonists and an invasive strategy with a modest increase in bleeding.[25] There was no significant increase in transfusions but there was an increase in TIMI major bleeding (See Appendix 3) (non CABG related) in all patients 1.7% UFH, 2.4% enoxaparin; p=0.025. In patients undergoing PCI there were similar TIMI major bleeding rates of 2.8% in patients receiving UFH vs 2.7% in patients receiving enoxaparin on a background of aspirin, clopidogrel, and GP IIb/IIIa inhibitors. Either enoxaparin or UFH should be continued until catheterisation or for 48 hours with the preferred therapy being enoxaparin. **1B**

If patients have been pre-treated with enoxaparin no additional enoxaparin is necessary if PCI is performed within 8 hours of the previous dose. If the previous dose of enoxaparin was >8 hours an additional 0.3 mg/kg IV is required. In view of increased bleeding and events if patients are switched from one antithrombotic agent to another,[25] patients should continue on the initial antithrombotic agent.**III B**

Fondaparinux—Fondaparinux was shown in the OASIS-5 study[65] to be non-inferior to enoxaparin and to be associated with a reduction in major bleeding and 6 months mortality. It is particularly useful in patients not planned to have early invasive management. It is not is not approved for ACS in New Zealand.

Bivalirudin—Bivalirudin is a direct thrombin inhibitor which inactivates fibrin-bound as well as fluid-phase thrombin. In the ACUITY trial 13,819 moderate and high-risk patients with non-STEACS planned for an invasive strategy were randomized to bivalirudin alone, bivalirudin plus a GP IIb/IIIa antagonist, or UFH or enoxaparin with a GP IIb/IIIa antagonist.[22] There was no difference between the first two groups for a composite ischaemic endpoint of death, MI or unplanned revascularisation for ischaemia. Bivalirudin alone was non-inferior (upper 95%CI did not exceed a relative margin of 25%) to the UFH/enoxaparin plus GP IIb/IIIa group; 7.8% vs 7.3% RR 1.08, 95%CI 0.93–1.24, p=0.32. And there was less major bleeding; 3.0% vs 5.7%, RR 0.53, 95%CI 0.43–0.65, p<0.0001. Crossing over from UFH or enoxaparin to bivalirudin maintained the benefit of reduced bleeding with bivalirudin. [26]

Bivalirudin is recommended instead of UFH or enoxaparin with a IIb/IIIa antagonist and use should be considered when the time to angiography is short (<12 hours) or there is a high risk of bleeding and switching is appropriate.**1B**

β-blockers

Oral β-blockers are recommended if there are no contraindications (asthma, systolic BP <110 mmHg, heart rate <50 min or AV block > Mobitz Type I or Killip class ≥3). 1B

Oral B Blockade should be continued for at least 3 years and can be continued indefinitely in the absence of side effects. Class I 1C

Calcium channel blockers

If β-blockers are contraindicated, diltiazem should be given.**1B** Calcium channel blockers are recommended in patients with coronary artery spasm. **1C** Calcium channel blockers that increase heart rate should not be used without concomitant β-blockers therapy.**III C**

Lipid modifying therapy

Use of a fixed dose of simvastatin (40 mg) has been shown to reduce events by over 20% in HPS in non ACS patients.[66] Achievement of an LDL level of 1.6 mmol/L with atorvastatin (80 mg) has been shown to reduce by 16% a composite endpoint of death, MI, readmission with unstable angina, revascularisation and stroke compared to an LDL level of 2.5 mmol/L achieved with pravastatin therapy (40 mg).[67]

Initiation of high dose statin therapy should be commenced in hospital in all ACS patients in order to enhance adherence and to reduce events.**1B** Administration of a high dose statin is reasonable before PCI to reduce the risk of periprocedural MI.**IIa**[68]

ACE inhibitors

All patients with evidence of heart failure, should receive oral ACE inhibitors (or ARB if intolerant of ACE inhibitors) beginning 1 - 2 hours after admission if the systolic BP is >100 mmHg using (e.g. Inhibace 0.5 mg bid, 6.25 mg tds, or equivalent medication) and then increasing over several days to maximally tolerated doses.**1A**[69,70] ACE inhibitors or ARBs are recommended in all other patients to prevent recurrent ischemia events. Drugs used in trials showing benefit and in doses of proven efficacy are recommended.**1B** ACE inhibitors should be continued indefinitely.[69] **1C**

Aldosterone antagonists

Aldosterone antagonists are recommended in patients who have an ejection fraction ≤35%. **IIb**

Aldosterone antagonists should also be considered in all patients with a history of heart failure and impaired LV systolic function treated with a loop diuretic. **IIb**

Caution is needed in patients with impaired renal function because of an increased risk of hyperkalaemia. **1C**

Early angiography and revascularisation

Early angiography and revascularisation improves symptoms, improves prognosis, and shortens hospital stay.[71–75]

The FRISC-II trial demonstrated superiority in higher risk patients of an invasive approach with PCI or CABG after initial medical treatment with the low molecular weight heparin dalteparin and aspirin for 4-7 days with a reduction in mortality at 1 year from 3.9% to 2.2% p=0.01612.[92] The TACTICS trial[42] randomised 2220 high risk patients with aspirin, UFH and tirofiban to an early invasive strategy with angiography within 4–48 hours followed by revascularisation if the anatomy was suitable, or to a more conservative strategy with catheterisation only for recurrent ischaemia or a positive stress test. Death, non-fatal MI and rehospitalisation for ACS at 6 months occurred in 15.9% of patients in the invasive arm and 19.4% in the conservative arm (P=0.025). The benefit of an invasive approach was confined to medium and high-risk patients who had elevated troponins, ST segment changes or diabetes.

RITA 3[71] also showed benefit of an invasive strategy in high risk patients treated with enoxaparin for 3 days prior to intervention. The ISAR Cool study[72] showed that an immediate invasive approach in 410 patients with either ST depression or elevated troponins (time to angiography of 2.4 hours) together with aspirin, clopidogrel, UFH and tirofiban resulted in lower rates of MI (5.9% vs 10.1%) compared with delaying PCI while on the same therapy for 72 hours.

In the ICTUS study in 12000 patients all patients had elevated troponins and a strategy of early invasive therapy was compared with a selective invasive approach.[73]

All patients were recommended to receive aspirin, clopidogrel 300 mg as a loading dose, enoxaparin and atorvastatin 80 mg. The invasive group was also given abxicimab. In the routine invasive group 76% had revascularisation in hospital compared to 40% in the selective invasive group. In this latter group a further 14% crossed over to the invasive arm by 12 months. At 1 year the composite of death, MI or rehospitalisation for anginal symptoms was similar in both groups; 22.7% invasive, 21.2% selective, RR 1.09, 95%CI 0.87–1.33, p=0.33.

A meta-analysis of seven trials comparing a routine invasive vs a conservative or selective approach with contemporary adjunctive therapy showed a reduction with an early routine invasive strategy at 2 years in mortality 4.9% vs 6.3% RR 0.75, 95%CI 0.63–0.90, p=0.001 and non-fatal MI 7.6% vs 9.1% RR 0.83, 95%CI 0.72–0.96, p=0.012.[74]

A recent meta-analysis of 8 trials showed a significant reduction in death, MI or rehospitalisation at 1 year with comparable benefit in men and high-risk women.[75] A more recent meta-analysis of the FRISC-2, ICTUS and RITA 3 studies with 5-year follow-up showed a significant reduction in death and MI with the invasive strategy.[76,77] There was an 11.1% absolute benefit (NNT nine) in the highest risk patients and 2–3.8% absolute benefit (NNT 26–50) in the low and immediate risk patients.

Timing of intervention

The optimal timing for angiography and PCI with an invasive strategy has been evaluated in a number of trials. In a meta-analysis of 4 trials[78] intervention on the first hospital day was shown to be safe, associated with 41% lower risk of recent ischaemia and a shorter hospital stay.

In patients at higher risk [Table 6] there is strong evidence to suggest a benefit of an invasive strategy. In the TIMACS trial at 6 months there was a 38% lower risk of death MI or stroke in patients with a GRACE risk score >140 with no increase in safety concerns.[79] Also in the ACUITY trial delay to PCI >24 hours was an independent predictor of 30-day and 1-year mortality. [81]

Patients at **very high risk** should go to the cath lab emergently ≤2 hours if they have refractory angina, with associated heart failure, life threatening ventricular arrhythmias, hemodynamic instability or recurrent marked (≥1 mm) dynamic ECG changes or ≥1 mm ST depression V2–V4 indicative of circumflex occlusion. **1B** [4,80]

- Immediate arrangement must be made for immediate transfer from a non-PCI hospital to a PCI capable Hospital. **1C**
- Advanced age, frailty, co-morbidities, procedural risk, ability to benefit, and patient preferences must be taken into account. **1C**

Table 6. Criteria for high risk with indication for invasive management [4]

Primary
• Relevant rise or fall in troponin*
• Dynamic ST- or T-wave changes (symptomatic or silent)
Secondary
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m²)
• Reduced LV function (ejection fraction <40%)
• Early post infarction angina
• Recent PCI
• Prior CABG
• Intermediate to high GRACE risk score (*Table 2*)

*Rise/fall of troponin relevant according to precision of assay

CABG = coronary artery bypass graft

eGFR = estimated glomerular filtration rate

GRACE = Global Registry of Acute Coronary Events

LV = left ventricular

PCI = percutaneous coronary intervention.

Adapted with permission: Hamm et al. EHJ. 2011;32:2999 – Table 9.

In patients at **high risk** with both raised troponins, and ischaemic ECG changes (elevation or depression ≥1 mm or T wave inversion ≥ 2 mm V2–V3), and especially if the patient has a GRACE score >140, angiography should optimally be performed in ≤24 hours in a PCI capable hospital. **1B** [78,79]

- Immediate arrangement must be made for transfer within 24 hours from a non-PCI hospital. **1C**

In other patients angiography should be performed within 72 hours. **1A** [80]

- Advanced age, frailty, co-morbidities, procedural risk, ability to benefit, and patient preferences must be taken into account. **Class 1C**
- It is recognised that this is the optimal goal and may not be possible over weekends and public holidays and where resources are limited.

For **low risk** patients in whom a conservative strategy is selected and recurrent ischaemia has not occurred, a non-invasive test for inducible ischaemia should be performed in hospital with management based on the results of the test. **1A** [4,80,82,83]

Renal failure is a relative contraindication for angiography and revascularisation because of the hazard of contrast induced nephropathy. **1C** Randomised data on the advantage of an invasive strategy are not available.

Advanced age is not an absolute contraindication for angiography and PCI, and because of data[42] showing reduced readmissions and reduced costs in the elderly,[84] PCI should be considered in all patients without frailty or significant co-morbidity with appropriate consideration to patient preferences. **1B**

Patients on warfarin or dabigatran

Decisions as to whether patients should undergo an invasive strategy when the INR with warfarin is therapeutic or the patient is on dabigatran should be the same as when

patients are not on these therapies. Treatment should be continued until angiography and adjunctive anticoagulant therapy withheld (unless the INR is subtherapeutic).

Treatment with aspirin and P2Y12 inhibitors and their duration needs to be individualised according to whether a stent is inserted (bare metal preferred) and the individualised risk of stent thrombosis and bleeding.

Triple therapy (aspirin, a P2Y12 inhibitor (prasugrel should not be used), and warfarin (INR 2.0–2.5) or dabigatran) should be used for as short a period as appropriate e.g.: with bare metal stent 1 month, drug eluting stent 6 months. There is currently no evidence base for the use of the combination of the dabigatran (lower bleeding with 110 mg bid as compared with warfarin) and ticagrelor.

Smoking cessation

Smokers should be advised to quit and be given nicotine patches and lozenges as appropriate on day 1. **1C**

Secondary prevention

All patients should be referred to rehabilitation services. All patients without contraindication should be on aspirin, a β-blocker, a statin with optimisation of LDL cholesterol below 1.6mmol/L, and an ACE inhibitor or ARB indefinitely and a P2Y12 inhibitor for 12 months. Patients should stop smoking, have a cardioprotective diet to achieve ideal weight, and exercise 30 minutes on most days. **1A**

Measurement of performance indicators

Reduction of the delay between onset of symptoms and presentation to hospital and time to an invasive strategy is recognized as an important clinical goal. Clinical networks with predefined protocols for transport from hospitals without capacity for early catheterisation to hospitals with the capacity must be further developed.**1C** Appropriate evidence-based treatments should be given to all eligible patients without contraindications. Routine audit should be integrated into all clinical services that provide care to patients with ACS. This should include prescribing and adherence with aspirin, P2Y12 inhibitor, B-blockers, ACE inhibitors or ARBS, aldosterone antagonists, statins, cardiac rehabilitation and smoking cessation. Metrics including percentages of patients undergoing angiography, PCI and CABG, and time to angiography should also be monitored with feedback. **1C**

Resource availability

It is recognised that in New Zealand that providing expensive pharmaceuticals and equitable provision of an invasive strategy for Maori and rural populations is challenging. However, it is recognised that an invasive approach has been shown to be cost effective[85,86] and it is expensive to keep patients in hospital for long periods awaiting diagnostic testing. If these patients are discharged without angiography there is a high risk of reinfarction or readmission to hospital.

In New Zealand, cost-effective and readily available therapies such as aspirin, beta-blockers and ACE inhibitors are still under-prescribed.[87,88] It is important that these

treatments are used in as many patients without contraindications as possible and that PCI is equitably available to all New Zealanders.

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Appendix 1. Non ST-Elevation Acute Coronary Syndromes Guidelines Group

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Appendix 2. Classes of recommendation and grading levels of evidence

Classes of recommendation	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Levels of evidence	
Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomised clinical trial or large non-randomised studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Adapted with permission: Hamm CW. EHJ. 2011; 32(23): 2999- Table 1 and 2).

Appendix 3. TIMI Major Bleeding Criteria

Bleeding is associated with ≥5 g/dL decrease in hemoglobin (each unit of packed rid blood cells or whole blood transfused counting as 1g of hemoglobin) or a ≥15% absolute decrease in hematocrit (each unit of packed red blood cells or whole blood transfused will count as 3% points) or it is intracranial (confirmed by magnetic resonance imaging or computer tomography).