THE CEYLON MEDICAL JOURNAL

Established 1887
The Official Publication of the Sri Lanka Medical Association
Volume 66, No.4, December 2021
Quarterly ISSN 0009–0875

Current management of non ST elevation acute coronary syndrome (NSTE-ACS)

DOI: http://doi.org/10.4038/cmj.v66i4.9505

Ceylon Medical Journal 2021; **66**: 157-161

Acute coronary syndrome is an important cause of morbidity and mortality in Sri Lanka. The pathology of acute coronary syndromes is characterized by disruption of coronary atherosclerotic plaque triggering activation of platelets and the coagulation system and the resulting myocardial ischemia [1]. Acute coronary syndromes comprises of ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). The initial care of patients with NSTE-ACS consists of rapid diagnosis, risk assessment, treatment of ischemic symptoms, initiation of antithrombotic therapies and risk-based decision for the timing of invasive management or conservative management.

At present high sensitive cTn (hs-cTn) is used for diagnosis of myocardial injury. However, chronic stable elevations and fluctuations in cTn concentration is known to occur in healthy individuals. This chronic elevation of troponin may result in absolute cTnc levels similar to those in patients with minor myocardial injury [2]. Therefore, a change in the cTn concentration is an absolute requirement for the diagnosis of myocardial infarction. The European Society of Cardiology (ESC) recommend on admission and 1 or 2 hour measurement of cTn levels, a greater change (≥5 ng/L for hs-cTnT, ≥6 ng/L for hs-cTnI) will rule-in ACS [3]. High hs-Tn level in a patient presenting after 3 hours of onset of pain will rule in ACS. In chronic renal failure and very old age the hs-Tn level can be elevated three times the normal value [4].

The duration and intensity of antiplatelet therapy varies depending on whether the patient is treated with primary intervention, thrombolytic therapy or is already on oral anti-coagulant. A loading dose of 300 mg of aspirin followed by a maintenance dose of 75-100mg/day has been shown to improve mortality and morbidity in patients with ACS. Intravenous aspirin has been shown to produce rapid and more complete inhibition of thromboxane A_2 with similar bleeding risk. Aspirin should be continued indefinitely in patients with ischemic heart disease [5].

Adenosine diphosphate-receptor antagonists include clopidogrel, prasugrel and ticagrelor. Clopidogrel has shown a large variability in platelet response due to its two-step activation process involving a number of cytochrome P450 iso-enzymes which have genetic polymorphisms. However, doubling the dose of clopidogrel has shown a better outcome in the management of ACS by resulting in higher concentration within a short period.

A loading dose of 600 mg of clopidogrel may be a better option than the conventional 300 mg [6,7].

Two new P2Y12 inhibitors, prasugrel and ticagrelor, lead to a faster and more potent ADP-receptor inhibition than clopidogrel. Prasugrel a non-reversible thienopyridine needing only one metabolization step to form the active metabolite. A trial comprising moderate-to-high-risk patients with ACS with scheduled percutaneous coronary intervention comparing prasugrel (60 mg loading dose and 10 mg daily maintenance dose) against clopidogrel (300 mg loading dose and 75 mg daily maintenance dose) demonstrated that prasugrel was superior to clopidogrel in reducing ischaemic events with increased risk of major bleeds [8].

Ticagrelor, a reversible cyclopentyl-triazolo-pyrimidine, is an active drug. In a study on patients presenting with ACS, treatment with ticagrelor significantly reduced death from vascular causes, myocardial infarction, or stroke as compared with clopidogrel [9].

Pretreatment with prasugrel or ticagrelor in NSTE-ACS was not associated with improved ischaemic outcomes, however the risk of bleeding was increased. Therefore, $P2Y_{12}$ inhibitors should be administered only just before percutaneous coronary intervention (PCI) [10,11,12]. However, a study which compared prasugrel and ticagrelor head-to-head in ACS showed that prasugrel was better than ticagrelor in patients undergoing PCI for STEMI and NSTEMI [13]. In patients with ACS with or without ST elevation who are not undergoing PCI, ticagrelor has shown greater reduction of mortality [14]. Prasugrel should not be used in patients with prior cerebro-vascular events, elderly patients (>75 years of age) and patients with lower body weight (<60 kg), as there is lack of benefit and increased risk of bleeding [15].

De-escalation is a strategy to reduce bleeding risk without compromising ischaemic protection in ACS. Various regimes of de-escalation have been tested in trials. This includes switching $P2Y_{12}$ inhibitors after initial treatment with potent agents, stopping aspirin after initial dual anti-platelet therapy (DAPT), and reducing the dose of $P2Y_{12}$ inhibitors. Genetic testing for *CYP2C19* polymorphism and platelet functional testing also have been used to identify poor responders to clopidogrel in some trials [16,17].

The duration of DAPT for NSTE-ACS was established as 12 months by early trials [18]. With new $P2Y_{12}$ inhibitors and improved stent technology the duration of DAPT has come under scrutiny. Recent trials with safer newer-generation stents have shown considerable reduction in early and late stent thrombosis. However, activation of platelets is also a part of the process of atherosclerosis, and prolonged DAPT could prevent non-coronary thrombotic events [19]. The duration of DAPT should be guided by careful evaluation of thrombotic vs. bleeding risk of the individual patient. If the thrombotic risk is low, the duration of DAPT can be shortened to 3 to 6 months followed by monotherapy [20].

In NSTE-ACS, parenteral anticoagulants enoxaparin, bivalirudin, fondaparinux, or unfractionated heparin (UFH) are used for the first 48 hours or till PCI is performed. If early invasive therapy is planned unfractionated heparin or bivalirudin is the choice of anticoagulant. The anticoagulant is discontinued after PCI unless warranted by the clinical condition, such as atrial fibrillation or large akinetic apical segment with clot. If the risk score does not favor an early invasive approach, enoxaparin or fondaparinux will be the anticoagulant of choice [21].

The value of long-term use of anticoagulants in ASC is not well established. Several studies have investigated the long-term use of direct oral anticoagulants (DOACs) after ACS. All these studies have shown reduction in cardiac events and a dose dependent bleeding risk with DOAC. Low dose DOAC with DAPT can be useful in patients with high thrombotic risk. However, warfarin is not recommended for long term use after ACS. A study showing benefit with a very low dose of rivaroxaban (2.5 mg b.i.d.) plus aspirin has raised the possibility of such a regimen being considered as an option for maintenance treatment beyond 12 months in post ACS patients undergoing PCI. Thus, low dose rivaroxaban in addition to aspirin could be considered in patients at high thrombotic risk [22].

Early studies with glycoprotein (GP) II_b/III_a receptor inhibitors (done prior to the use of $P2Y_{12}$ receptor inhibitors) [23, 24] demonstrated the efficacy of GP II_b/III_a inhibitors in the treatment of NSTE-AC. These trials and other studies have shown increased bleeding risk with GP II_b/III_a inhibitors [25]. Thus, the routine use of GP III_a/II_b inhibitors is not recommended in NSTE-ACS, but these can be selectively used in patients with thrombotic complication during PCI.

Approximately 6-8% of patients undergoing PCI have an indication for long-term oral anticoagulants (OACs) due to conditions such as AF, mechanical heart valves, or venous thromboembolism. These patients will need OAC with DAPT after PCI. Several recent trials have shown a reduction in bleeding with DOAC and a $P2Y_{12}$ inhibitor combination, as compared with warfarin-based triple therapy in patients undergoing PCI. In the PIONEER AF-PCI trial, patients were randomly assigned to receive high dose rivaroxaban plus a $P2Y_{12}$ or low dose rivaroxaban and DAPT or warfarin and DAPT. The results showed a lower risk of bleeding with the rivaroxaban treatment strategies compared to warfarin-based treatment [26]. Similar results were observed in trials with dabigatran, apixaban and edoxaban.

At present the evidence favors short duration of triple therapy with DOAC and DAPT followed by dual

antithrombotic therapy with a clopidogrel and a DOAC for at least 12 months [27]. However, AFIRE trial has shown that antithrombotic therapy with rivaroxaban monotherapy was noninferior and safer than combination therapy for longer-term management of atrial fibrillation in patients at least 1 year after PCI or bypass surgery. Hence, rivaroxaban mono-therapy may be a safe alternative for post PCI patients who need long-term anticoagulation [28].

The decision on duration and intensity of anti-thrombotic therapy should be based on assessment of thrombotic and bleeding risk. Increased thrombotic risk can be due to factors that increase risk of ischaemic event or those associated with increased risk of stent thrombosis. Increased ischemic risk is associated with:

- Advanced age
- Acute coronary syndrome
- Past history of ischaemic events
- Extensive atheromatous disease
- Chronic kidney disease
- Diabetes mellitus

Increased risk of stent thrombosis is associated with the number of stents used, complexity of the lesion, the expertise of the operator and some patient related factors such as presence of diabetes.

The DAPT score is an important clinical risk scores that predicts ischemic and bleeding risk in patients on DAPT. Higher scores indicate increasing ischaemic events risk, hence patients with higher score benefit from DAPT being continued for a longer period. The PRECISE-DAPT score was developed to assess the bleeding risk in patients treated with DAPT after PCI. Five items are considered in calculating this score (age, white blood cell count, hemoglobin level, creatinine clearance, and history of spontaneous bleeding). Patients having a score of more than 25 are at a high risk of bleeding [29]. The current guidelines have recommended the use of bleeding and thrombotic risk stratification to determine the duration and intensity of anti-thrombotic therapy [30].

Timing of invasive approach in patients with ACS has been studied in two large trials. These studies have shown that an early invasive approach in unselected NSTE-ACS patients is not superior in reducing the composite clinical endpoints compared to a delayed invasive strategy. However, an invasive approach has been shown to be beneficial in high-risk patients. These studies have not shown benefit with an early invasive strategy based on ST-segment/T-wave changes. Similar observations have been made in several recent meta-analyses [31, 32]. These results of meta-analyses and other recent studies highlight the role of risk stratification in the decision making process in the management of patients with NSTE-ACS.

Invasive strategy can be urgent in patients with very high risk (within 2 hours) or early in patients with high risk (within 24 hours). Very high-risk patients are defined according to the following features:

- Haemodynamic instability or in cardiogenic shock
- Recurrent chest pain despite medical treatment
- Life threatening arrhythmias
- Mechanical complications such as severe mitral regurgitation
- Acute heart failure
- ST depression > 1 mm in 6 leads and ST elevation in a VR or V1

Patients at high risk are defined according to the following features:

- Established NSTE-ACS
- Dynamic new ST/T changes in contiguous leads
- Resuscitated cardiac arrest
- Grace risk score >140

Patients who do not fall into these two categories need further evaluation and should undergo selective invasive approach. Low risk patients may be subjected to non-invasive testing with stress echocardiography, stress CMR or CT coronary angiography to delineate the coronary anatomy [33].

Several prognostic models have been developed from clinical trial databases and other registry data for ACS. Recent studies suggest that the unselected GRACE mortality model is superior to other prognostic models, based on trial data on selected population such the TIMI or the PURSUIT models. The Global Registry of Acute Coronary Events (GRACE) (1999-2009) included a wide spectrum of unselected population with ACS from 30 countries [34].

High-intensity statin therapy should be initiated in NSTE-ACS to reduced the combined endpoint of death, recurrent MI and stroke. Atorvastatin at 80 mg daily dose is recommended for this purpose. The treatment target is to:

- lower LDL-C to <1.4 mmol/L (<55 mg/dL), reduce it by at least 50% if the baseline LDL-C level is 1.8-3.5 mmol/L (70-135 mg/dL)
- addition of ezetimibe is recommended if this level cannot be achieved, especially in patients with diabetes

Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors (e.g. evolocumab and alirocumab) can be used in resistant cases [35].

Beta blockers play an important role in reduction of reinfarction and complex ventricular arrhythmias in ACS.

Beta blockers are recommended to be given orally within the first 24 hours. The preferred drugs are metoprolol, carvedilol, or bisoprolol, Atenolol can be given to stable patients [36].

Angiotensin Converting Enzyme Inhibitors (ACEI) also reduces morbidity and mortality in ACS. Many randomized trials of ACE inhibitors or ARBs started have shown improvement in left ventricular ejection fraction (LVEF) and survival when started within 24 hours to 16 days following ACS [37].

Oral or sublingual nitrates are useful in patients having chest pain. Intra-venous nitrates are used in patients with left ventricular failure and elevated blood pressure. Control of blood sugar, blood pressure and hormonal therapy are also important considerations in the initial stages of NSTE-ACS management.

References

1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med*. 1992; **326**: 242-50.
2. Thomas E Kaier, Bashir Alaour, Michael Marber, Cardiac troponin and defining myocardial infarction, *Cardiovascular Research*, 2021;**117** :2203-15.
3. Collet J P, Thiele H, Barbato E, *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), *European Heart Journal*, 2021; **42**: 1289-367.
4. Mueller C, Giannitsis E, Christ M, *et al*. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med* 2016; **68**: 76-87.
5. Patrono C, Garcia Rodriguez LA, Landolfi R, *et al*. Low dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005; **353**: 2373-83.
6. Montalescot G, Sideris G, Meulemann C, Bal-dit Sollie RC. A randomized comparison of high clopidogrel loading doses in patients with non-ST segment elevation acute coronary syndromes. The ALBION trial. *J Am Coll Cardiol*. 2006; **48**: 931-38.
7. Mehta S, Tanguay J, Eikelboom J, *et al*. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose Aspirin in individuals undergoing percutaneous coronary intervention for acute Coronary syndromes (CURRENT OASIS 7): a randomised factorial trial. *Lancet*. 2010; **376**: 1233-43.
8. Wiviott SD, Braunwald E, McCabe CH, *et al*. Prasugrel vs. clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007; **357**: 2001-15.
9. Wallentin L, Becker R, Budaj A, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009; **361**: 1045-57.
10. Montalescot G, Bolognese L, Dudek D, *et al*. ACCOAST Investigators. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med*. 2013; **369**: 999-1010.
11. Schüpke S, Neumann FJ, Menichelli M, *et al*. ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2019; **381**: 1524-34.
12. Dworeck C, Redfors B, Angerås O, *et al*. Association of pretreatment with P2Y12 receptor antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. *JAMA Netw Open* 2020; **3**: e2018735.
13. Schüpke S, Neumann FJ, Menichelli M, *et al*. on behalf of the ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2019; **381**: 1524-34.
14. Navarese EP, Khan SU, Kolodziejczak M, *et al*. Comparative Efficacy and Safety of Oral P2Y12 Inhibitors in Acute Coronary Syndrome Network Meta-Analysis of 52816 Patients From 12 Randomized Trials. *Circulation*. 2020; **142**: 150-60.
15. Montalescot G, Wiviott S, Braunwald E, *et al*. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009; **373**: 723-31.
16. Angiolillo DJ, Rollini F, Storey RF, *et al*. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. *Circulation* 2017; **136**: 1955-75.
17. Galli M, Benenati S, Capodanno D, *et al*. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta analysis. *Lancet* 2021; **397**: 1470-83.
18. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, *et al*. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2018; **53**: 34-78.
19. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007; **357**: 2482-94.
20. Bittl AJ, Baber U, Bradley SM, Wijesundera DN Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease *J Am Coll Cardiol* 2016; **68**: 1116-39.
21. Amsterdam EA, Wenger NK, Brindis RG, *et al*. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; **64**(24): e139-e228. Erratum in: *J Am Coll Cardiol*. 2014; **64**: 2713-4.
22. Connolly SJ, Eikelboom JW, Bosch J, *et al*. COMPASS

investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018; **391**: 205-18.

23. The PURSUIT Trial Investigators *N Engl J Med.* 1998; **339**: 436-43.
24. Gibson CM, Goel M, Cohen DJ, Piana RN, Deckelbaum LI, Harris KE, King SB. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *J Am Coll Cardiol.* 1998; **32**(1): 28-34.
25. Nuhrenberg TG, Hochholzer W, Mashayekhi K, Ferenc M, Neumann FJ. Efficacy and safety of bivalirudin for percutaneous coronary intervention in acute coronary syndromes: a meta-analysis of randomized-controlled trials. *Clin Res Cardiol* 2018; **107**: 807-15.
26. Gibson CM, Mehran R, Bode C, *et al*. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med.* 2016; **375**: 2423-34.
27. Khan SU, Osman M, Khan MU, Khan MS, Zhao D, *et al.* Dual Versus Triple Therapy for Atrial Fibrillation After Percutaneous Coronary Intervention: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2020; **172**: 474-83.
28. Yasuda S, Kaikita K, Akao M, *et al.* AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med.* 2019; **381**: 1103-13.
29. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient data sets from clinical trials. *Lancet.* 2017; **389**: 1025-34.
30. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS) *Eur. Heart J.* 2018; **39**: 213-60.
31. Kofoed KF, Kelbaek H, Hansen PR, *et al.* Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome *Circulation.* 2018; **138**: 2741-50.
32. Mehta SR, Granger CB, Boden WE, *et al.* Investigators TIMACS. Early versus delayed invasive intervention in acute coronary syndromes *N Engl J Med* 2009; **360**: 2165-75.
33. Siontis GC, Mavridis D, Greenwood JP, *et al.* Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. *BMJ* 2018; **360**: k504.
34. Khalill R, Han L, Jing C, Quan H. The use of risk scores for stratification of non-ST elevation acute coronary syndrome patients. *Exp Clin Cardiol.* 2009; **14**: e25-e30.
35. Amsterdam EA, Wenger NK, Brindis RG, *et al*. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: Executive Summary. *Circulation* 2014; **130**: 2354-94.
36. Ryan TJ. Percutaneous coronary intervention in st-elevation myocardial infarction. *Curr Cardiol Rep.* 2001; **3**: 273-9.
37. Teo KK, Yusuf S, Pfeffer M, *et al.* Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; **360**: 1037.

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