

2012 Oman Heart Association Simplified Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction

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Abstract: Although current practice guidelines provide an evidence-based approach to the management of acute coronary syndromes, application of the evidence by individual physicians has been suboptimal. This gap between comprehensive guidelines and actual practice stimulated Oman Heart Association to issue a simplified series for the management of the common cardiac abnormalities to be applied by the entire cardiac caregivers all over the country. This simplified approach for the management of non–ST-elevation acute coronary syndrome provides a practical and systematic means to implement evidence-based medicine into clinical practice.

Key Words: acute coronary syndrome, ischemic risk, bleeding risk, anti-ischemic therapy, antiplatelet therapy, anticoagulant agents, anti-remodeling therapy, antilipid agents, coronary revascularization

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“Acute coronary syndromes” represent the spectrum of myocardial ischemia, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UA) (Fig. 1). The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque and is usually *nonocclusive*. Microembolization of platelet aggregates and components of the disrupted plaque are believed to be responsible for the release of myocardial markers in many of these patients. An *occlusive* thrombus/plaque can also cause this syndrome in the presence of an extensive collateral blood supply.

RISK STRATIFICATION

Ischemic Risk

The *early* mortality risk in UA/NSTEMI relates to the extent of myocardial damage and resulting hemodynamic compromise

and is less than in patients with STEMI. In contrast, *long-term* outcome—for both mortality and nonfatal events—is actually worse for patients with UA/NSTEMI compared with STEMI. This finding probably results from the greater likelihood of recurrence of ACS in patients with UA/NSTEMI, as well as their older age, greater extent of coronary disease, prior MI, and comorbidities such as diabetes mellitus and impaired renal function.

Early risk stratification is important to identify patients at high immediate and long-term risk of death and cardiovascular events, and in whom intensive medical therapy and an early invasive strategy may reduce that risk. It is equally important to identify patients at low risk in whom potentially hazardous and costly invasive and medical treatments provide little benefit or in fact may cause harm. In patients with a suspected NSTEMI ACS, diagnosis and short-term ischemic risk stratification should be based on a combination of clinical history, physical findings, electrocardiogram (ECG), and biomarkers.

Although several risk stratification tools are available, one that is frequently used is the Thrombolysis in Myocardial Infarction (TIMI) risk score. This tool combines 7 simple variables in an evenly weighted scale. A more comprehensive approach based on a combination of clinical history, physical findings, ECG, troponin (Tn), and laboratory findings is shown in Table 1, which should be used as a general guidance rather than a rigid rule.

Electrocardiogram

A 12-lead ECG should be obtained within 10 minutes after first medical contact and immediately read by an experienced physician. If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs, initially at 15- to 30-minute intervals, should be performed to detect the potential for development of ST-segment elevation or depression. After admission, ECG should be repeated after 6 and 24 hours in the case of recurrence of symptoms and before hospital discharge.

Troponin

Blood has to be drawn promptly for Tn (cardiac Tn T or I) measurement. The result should be available within 60 minutes. Where available, high-sensitivity Tn assays should be used in preference to conventional assays.

When using high-sensitivity Tn assay, a test should be interpreted as positive if the level is ≥ 99 th centile for the reference population or if there is a change of $\geq 50\%$ above the initial baseline level. Although Tn accurately identifies myocardial necrosis, it does not inform as to the cause or causes of necrosis; these can be multiple and include noncoronary causes. A positive result should be

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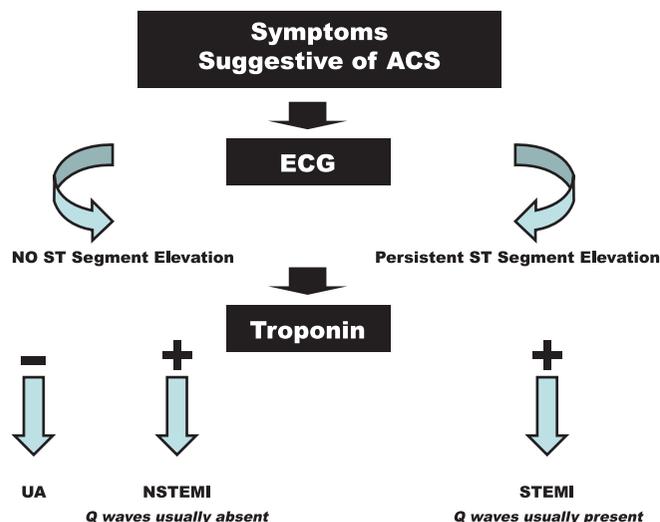


FIGURE 1. The spectrum of ACS.

considered within the entire clinical context (history, examination, ECG findings, and other investigations).

At 3 hours after presentation (with at least 1 assay performed >6 hours from symptom onset), a test using a high-sensitivity Tn assay should be interpreted as negative if the level is <99th percentile or if the change from baseline is <50%. It should be cautioned, however, that Tn should not be used as the sole marker of risk. If the local laboratory cannot provide Tn results within 60 minutes, point-of-care testing should be performed.

Echocardiography

An echocardiogram is recommended for all patients to evaluate regional and global left ventricular (LV) function and to rule in or rule out differential diagnoses.

Bleeding Risk

Although intensive antithrombotic therapy and invasive management reduce recurrent ischemic events, they also increase the risk of bleeding. Major bleeding and the need for transfusion have become the most frequent complication of ACS, and are associated with a 60% higher risk of in-hospital mortality and a 5-fold greater 1-year risk of death or MI.

Clinical Features Associated With Increased Bleeding Risk

1. Age ≥75 years
2. History of stroke or a transient ischemic attack
3. Prior vascular disease
4. History of bleeding
5. Renal insufficiency [creatinine clearance (CrCl) <60 mL/min]
6. Hemodynamic instability
7. Anemia
8. Female sex
9. Body weight ≤60 kg
10. Hypertension
11. Diabetes mellitus
12. Use of glycoprotein IIb/IIIa receptor inhibitors (GPIs)
13. Procedural factors:
 - Femoral artery access
 - Prolonged procedure
 - Intra-aortic balloon pulsation
 - Right heart catheterization

TABLE 1. Indicators of Early Significant Risk in Patients With NSTEMI ACS

| Diagnostic Tool | High or Intermediate Risk Indicators |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| History | <ol style="list-style-type: none"> 1. Prolonged rest angina (>20 min) 2. Accelerating angina in preceding 48 h 3. Nocturnal angina 4. New-onset (<2 months) or progressive CCS class III or IV angina in the past 2 weeks 5. Prior MI or PCI or CABG 6. Prior peripheral or cerebrovascular disease 7. Age 65 years or greater 8. Presence of 3 or more traditional risk factors for coronary disease 9. Use of aspirin within the last 7 days |
| Clinical findings | <p>Signs of HF (Pulmonary edema most likely due to ischemia, new or worsening MR murmur, S3 or new/worsening rales)</p> <p>Signs of shock (The 2 cardinal manifestations of shock are:</p> <ol style="list-style-type: none"> 1. Sustained hypotension: SBP ≤90 mm Hg for ≥30 min 2. Hypoperfusion: Usually diagnosed from 1 or more of the following: <ol style="list-style-type: none"> a. Altered mental status: restlessness, agitation, obtundation b. cool, clammy skin c. reduced urine output [<20 ml/h]) <p>Other shock signs may include:</p> <ol style="list-style-type: none"> 1. Pulses are rapid and faint 2. Jugular venous distension 3. Precordial heave: LV dyskinesia 4. Pulmonary rales 5. Distant heart sounds 6. S3 or S4 or both 7. Systolic murmur of MR or VSD |
| ECG | <ol style="list-style-type: none"> 1. ST-segment depression or transient elevation (persistent >20 min STE suggests STEMI) 2. Deep (≥2 mm), symmetrical inversion of the T waves 3. ST elevation (>0.1 mV) in lead aVR has been associated with a high probability of left main or triple-vessel CAD and worse clinical prognosis 4. Q waves suggesting prior MI 5. Left bundle branch block |
| Troponin | Elevated cardiac TnT or TnI |
| Laboratory | <ol style="list-style-type: none"> 1. Anemia 2. Impaired renal function |

CAD indicates coronary artery disease; CCS, Canadian cardiovascular society; MR, mitral regurgitation; VSD, ventricular septal defect.

How to Prevent Bleeding?

1. Careful patient history and physical examination
2. Appropriate choice of antithrombotic drugs
3. Avoid excessive dosing: titrate antithrombotic agents to optimal dose for age, weight and renal function

4. Avoid upstream GPIs unless there is recurrent ischemia on standard medical therapy
5. Shorten duration of exposure to antithrombotic agents (if early invasive strategy is selected)
6. During percutaneous coronary intervention (PCI):
 - Radial artery access
 - Minimize catheter size
 - Remove sheath as soon as possible
7. Use a proton pump inhibitor for gastric protection in patients at high risk

Management of Bleeding

1. Minor bleeding should preferably be managed without interruption of active treatments.
2. Major bleeding:
 - Discontinue intravenous (IV) antithrombotic agents
 - Maintain volume status
 - Consider protamine for unfractionated heparin (UFH)/enoxaparin
3. Blood transfusions may have deleterious effects on outcome and should therefore be considered individually, but withheld in hemodynamically stable patients without overt bleeding with hematocrit >25% or hemoglobin level >8 g/dL.

MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NSTEMI

Treatment of the patient with primary ACS is aimed at:

1. Preventing thrombus propagation
2. Relieving angina
3. Stabilizing the “vulnerable” plaque
4. Preventing remodeling
5. Identifying those considered to be at high risk for developing recurrent ischemia or infarction that would benefit from coronary revascularization.

ANTI-ISCHEMIC THERAPY

1. Admission to coronary care unit or cardiology ward: Patients with UA/NSTEMI at medium or high risk should be admitted to coronary care unit. If this is not possible, then admission to a monitored bed, preferably in a cardiac step-down unit, is acceptable for patients judged to be at lower risk.
2. Bed rest should be prescribed initially. Ambulation, as tolerated, is permitted if the patient has been stable without recurrent chest discomfort for at least 12 to 24 hours.
3. Supplemental oxygen: The routine use of supplemental oxygen is not recommended. Oxygen therapy is indicated for patients with hypoxia (oxygen saturation <90%) 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.
4. Nitroglycerin (NTG) at a rate of 0.4 mg sublingually every 5 minutes for a total of 3 doses; afterward, assess need for IV NTG.
5. IV NTG for the first 48 hours for treatment of persistent ischemia, heart failure (HF), or hypertension.
6. Oral β -blockers (β Bs) within 24 hours for patients without a contraindication.
7. When β Bs are contraindicated, a nondihydropyridine calcium channel blocker (CCB) (eg, verapamil or diltiazem) should be given as initial therapy in the absence of severe LV dysfunction or other contraindications.
8. Morphine sulfate:

Action: Morphine may act as both an analgesic and an anxiolytic, but its venodilatory effects may produce beneficial

hemodynamic effects by reducing ventricular preload, which is especially useful in the presence of pulmonary congestion.
Dose: initial dose of 2 to 4 mg, with increments of 2 to 4 mg repeated at 5 to 15 minute intervals

Contraindications:

- Allergy for this drug (meperidine can be substituted)
- Hypotension

Cautions:

- Morphine may cause hypotension; if that occurs, supine positioning and intravenous saline should restore blood pressure; pressors are rarely needed.
- If respiratory depression develops, naloxone (0.4–2.0 mg) may be given.

β -Blockers

β Bs competitively block the effects of catecholamines on cell membrane β 1-adrenergic receptors (located primarily in the myocardium), and this will result in reducing myocardial oxygen consumption by lowering the heart rate (HR), systolic blood pressure (SBP), and myocardial contractility.

Early placebo-controlled trials in UA/NSTEMI demonstrated the benefit of β Bs in reducing subsequent MI or recurrent ischemia, although there was no significant effect on mortality. Most of the evidence for the beneficial effects of β Bs is extrapolated from early studies in STEMI and stable angina patients.

Oral β B therapy should be initiated within the first 24 hours for patients who do not have 1 or more of the following:

1. Signs of HF
2. Evidence of a low-output state
3. Increased risk for cardiogenic shock
4. Other contraindications: PR interval >0.24 second, second- or third-degree heart block, active asthma, or reactive airway disease.

β Bs can be administered at low doses to patients with HF once they are stabilized.

Greater caution is now suggested in the early use of IV β Bs, which should be targeted to specific indications and should be avoided with HF, hypotension, and hemodynamic instability. If ischemia and chest pain are ongoing despite IV nitrate therapy, IV β Bs may be used cautiously, followed by oral administration.

The choice of β B can be individualized on the basis of the LV function, drug's pharmacokinetics, cost, and physician familiarity.

RISK FACTORS FOR CARDIOGENIC SHOCK

(The greater the number of risk factors present, the higher the risk of developing cardiogenic shock)

- a. Age >70 years
- b. SBP <120 mm Hg
- c. Sinus tachycardia >110 bpm or HR <60 bpm
- d. Increased time since onset of symptoms

Calcium Channel Blockers

CCBs reduce cell transmembrane inward calcium flux, which inhibits both myocardial and vascular smooth muscle contraction; some also slow atrioventricular conduction and depress sinus node impulse formation.

There are 3 subclasses of CCBs, which are chemically distinct and have different pharmacological effects: dihydropyridines (such as nifedipine), benzothiazepines (such as diltiazem), and phenylethylamines (such as verapamil).

Atrioventricular block may be induced by nondihydropyridines. Nifedipine and amlodipine produce the most marked peripheral

arterial vasodilatation, whereas diltiazem has the least vasodilatory effect. All subclasses cause similar coronary vasodilatation.

CCBs may be used to control ongoing or recurring ischemia-related symptoms in:

1. Patients who are already receiving adequate doses of nitrates and β Bs
2. Patients unable to tolerate adequate doses of 1 or both of these agents
3. Patients with variant angina
4. Management of hypertension in patients with recurrent UA

Definitive evidence for a benefit of CCBs in UA/NSTEMI is predominantly limited to symptom control.

The CCB evidence base in UA/NSTEMI is greatest for verapamil and diltiazem. The risks and benefits in UA/NSTEMI of newer CCBs, such as the dihydropyridines amlodipine and felodipine, remain undefined. For immediate-release nifedipine, an increase in serious events is suggested when administered early without a β B.

Nitrates

Nitrates are endothelium-independent vasodilators that both increase myocardial blood flow by coronary vasodilation and reduce myocardial oxygen demand. By dilating the venous bed, it increases venous pooling to decrease myocardial preload, thereby reducing ventricular wall tension, a determinant of myocardial oxygen demand (MVO₂). More modest effects on the arterial circulation decrease systolic wall stress (afterload), which contributes to further reductions in MVO₂. This decrease in MVO₂ is in part offset by reflex increases in HR and contractility, which counteract the reductions in MVO₂ unless a β B is concurrently administered.

Most studies of nitrate treatment in UA/NSTEMI have been small and uncontrolled, and there are no randomized, placebo-controlled trials that address either symptom relief or reduction in cardiac events. If the patient is experiencing ischemic pain, nitrates should initially be given sublingually or by buccal spray (0.3–0.6 mg). If pain persists after 3 sublingual tablets (or buccal sprays) administered at 5-minute intervals, IV NTG by use of non-absorbing tubing (5–10 μ g/min) is recommended. The rate of the NTG infusion may be increased by 10 μ g/min every 3 to 5 minutes until relief of symptoms occurs or SBP falls to below 100 mm Hg. Although there is no absolute maximum dose, a dose of 200 μ g/min is generally used as a ceiling. The abrupt cessation of IV NTG has been associated with exacerbation of ischemic changes on the ECG, and a graded reduction in the dose of IV NTG is advisable.

ANTITHROMBOTIC AGENTS

Antiplatelet Therapy

Platelet adhesion, activation, and aggregation are stimulated during an ACS. Intimal injury due to plaque rupture exposes collagen and von Willebrand factor to which circulating platelets adhere.

After adhesion, multiple metabolic pathways are stimulated within the platelet, resulting in the production and release of thromboxane A₂, adenosine diphosphate (ADP), and other substances from platelet granules. These platelet products stimulate further platelet recruitment, activation, and vasoconstriction; they also lead to platelet aggregation by activating the glycoprotein IIb/IIIa (GP IIb/IIIa) complex, which binds platelets to one another through linkage with fibrinogen molecules. Aspirin, ADP receptor (P2Y₁₂) antagonists, and the GPIs represent the main antiplatelet agents used in the management of ACS.

Aspirin

By irreversibly inhibiting cyclooxygenase (COX-1) within platelets, aspirin prevents the formation of thromboxane A₂, thereby diminishing platelet aggregation promoted by this pathway but not

by others. Aspirin has been shown to reduce the risk of developing MI by about 50% in at least 4 randomized trials.

Aspirin should be given to all patients without contraindications at an initial loading dose of 300 mg and at a maintenance dose of 75 to 100 mg daily. After PCI, it is reasonable to use aspirin 75 to 100 mg per day in preference to higher maintenance doses.

ADP Receptor (P2Y₁₂) Antagonists

The thienopyridines clopidogrel, ticlopidine, and prasugrel, the cyclopentyltriazolopyrimidine ticagrelor, and cangrelor block the ADP receptor P2Y₁₂ on platelets. Ticagrelor differs from the thienopyridines (clopidogrel and prasugrel) in that it binds reversibly rather than irreversibly with the P2Y₁₂ platelet receptor.

The onset of action of clopidogrel is delayed (2–4 hours) compared to both prasugrel and ticagrelor (30 minutes); in addition, both agents achieve higher degrees of platelet inhibition and this was associated with lower cardiovascular event rates and higher rates of bleeding compared to clopidogrel.

Landmark Trials

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial

Twelve thousand five hundred sixty-two UA/NSTEMI patients were randomized to aspirin alone or aspirin plus clopidogrel. At an average follow-up of 9 months, combination therapy was associated with 20% reduction in the composite end point of cardiovascular death, MI, or stroke, which was largely due to fewer MIs. Evidence of benefit began to emerge within 24 hours. There was no significant excess of late life-threatening bleeding, but there was a small excess of major bleeds (5 per 1000) that was much smaller than the total cardiovascular benefit at 1 year (22 per 1000).

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction 38 (TRITAN-TIMI 38) Trial

Prasugrel was compared directly to clopidogrel in 13,608 moderate- to high-risk ACS patients undergoing PCI; in the majority of cases both drugs were given after coronary angiography.

At 15-month follow-up, the primary efficacy end point (cardiovascular death, MI, and stroke) was reduced significantly by 19%; this was driven primarily by a significant reduction in nonfatal MI. Twelve thousand eight hundred forty-four patients received coronary stents at the time of the PCI. In the prasugrel group, the incidence of stent thromboses was reduced in half compared with clopidogrel.

The greater platelet inhibitory effect of prasugrel was associated with more common serious bleeding. There was a 32% higher relative incidence of serious, including fatal, bleeding. The risk of bleeding was especially higher in the elderly (≥ 75 years), in those with reduced body weight (≤ 60 kg), and in patients with a history of stroke or a transient ischemic attack.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) Trial

PLATO enrolled 18,624 patients, 15,381 (62%) of whom had UA/NSTEMI. The primary end point, a composite of cardiovascular death, MI, and stroke, was reduced significantly by 16%. There were also significant 16% reductions in MI, 21% in cardiovascular death, and 22% relative (1.4% absolute) reduction in total mortality.

The greater clinical efficacy of ticagrelor was observed across a broad array of subgroups, including patients who had previously received clopidogrel, patients treated with a noninvasive strategy, and patients with STEMI. There was no difference with ticagrelor in total major bleeding, but a significantly higher 19% occurrence

of non-coronary artery bypass graft (CABG) major bleeding ($P = 0.03$) and an 11% significant increase in major plus minor bleeding. Episodes of dyspnea and ventricular pauses exceeding 5 seconds occurred more frequently in the ticagrelor-treated patients than in the clopidogrel-treated patients.

Dose

Dosing for P2Y12 antagonists in patients with UA/NSTEMI is given in Table 2.

Important Recommendations

- Patients should be counseled on the need for and risks of dual antiplatelet therapy (DAPT) before placement of intra-coronary stents, especially drug-eluting stent, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of DAPT.
- A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal hemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).
- In patients pretreated with P2Y12 inhibitors who need to undergo nonemergent major surgery (including CABG), postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischemic events, should be considered. Ticagrelor or clopidogrel should be considered to be started (or restarted) after CABG surgery as soon as considered safe.
- A P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

Glycoprotein IIb/IIIa Receptor Inhibitors

The 3 IV GPIs approved for clinical use are abciximab, eptifibatide, and tirofiban. Although certain early randomized controlled trials (RCTs) demonstrated a trend toward reduced mortality, statistically significant mortality reduction for individual GPI RCTs is lacking. However, mild mortality benefit can be derived only from meta-analyses.

Most GPI studies demonstrated consistent and statistically significant reduction in small, generally subclinical procedural MI especially in high-risk patients. Although numerous non-RCTs have claimed that Tn or creatine phosphokinase leaks result in worse patient outcomes, this was not supported by prospective RCTs using multivariate analysis. The price for this significant reduction in small MIs was significant increase in major bleeding. Stenting was not routinely performed in these early studies, and patients were not pretreated with P2Y12.

As opposed to the pivotal GPI trials, studies performed in the current era of routine stenting and thienopyridine therapy have not consistently shown a net clinical benefit with GPI, that is, a benefit on the composite of death, MI, revascularization, and major bleeding.

Recommended Indications for GPIs in NSTEMI/ACS

Upstream Use

1. Patients with ongoing and/or recurrent ischemia despite DAPT and an anticoagulant
2. Patients with HF, serious arrhythmias, or cardiogenic shock who are scheduled for urgent coronary angiography

During PCI

1. Patients having thrombotic complications or large side-branch closure or unsealed dissection

TABLE 2. Dosing Table for P2Y12 Antagonists in Patients With UA/NSTEMI

| Drug | Loading Dose (mg) | After PCI (Bare-Metal or Drug-Eluting Stents) |
|-------------|-------------------|------------------------------------------------------------|
| Clopidogrel | 600 | 150 mg daily for 7 days followed by 75 mg daily for 1 year |
| Ticagrelor | 180 | 90 mg BID/1 year |
| Prasugrel | 60 | 10 mg daily/1 year |

2. Patients undergoing PCI and not adequately preloaded with P2Y12

GPIs and CABG

Use of GPIs before CABG increases bleeding complications and the need for bleeding-related surgical reexploration. Surgery should be delayed for 4 to 6 hours in eptifibatide or tirofiban recipients and ≥ 12 hours, preferably 24 to 48 hours as bleeding risk is greatest within the first 12 hours after drug withdrawal, in abciximab recipients.

Dose

Standard Dose

Abciximab, 0.25 mg/kg IV bolus then 0.125 $\mu\text{g}/\text{kg}/\text{min}$ IV; or eptifibatide, 180 $\mu\text{g}/\text{kg}$ IV bolus then 2.0 $\mu\text{g}/\text{kg}/\text{min}$ IV or tirofiban, 0.4 $\mu\text{g}/\text{kg}/\text{min}$ IV for 30 minutes then 0.1 $\mu\text{g}/\text{kg}/\text{min}$ IV.

Bolus-only Strategy

Double-bolus eptifibatide (180 $\mu\text{g}/\text{kg}$ bolus followed 10 minutes later by a second 180 $\mu\text{g}/\text{kg}$ bolus) and high-bolus dose tirofiban (25 $\mu\text{g}/\text{kg}$) all result in a high degree of platelet inhibition, have been demonstrated to reduce ischemic complications in patients undergoing PCI, and appear to lead to comparable angiographic and clinical outcomes.

ANTICOAGULANT AGENTS

Unfractionated Heparin

UFH exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and factor Xa. It prevents thrombus propagation but does not lyse existing thrombi.

The data on UFH are not definitive. Overall, with appropriate dosing and IV administration, meta-analyses suggest that there may be slight benefits in NSTEMI/ACS at the risk of increased bleeding. In the setting of novel antithrombotics, however, the continued importance of heparin has been questioned. Nevertheless, given the ability to monitor and fully reverse UFH, many continue to use it preferentially during invasive management of ACS.

Monitoring of the anticoagulant response by activated partial thromboplastin time is recommended with titrations made according to a standardized nomogram, aiming for an activated partial thromboplastin time of 50 to 70 seconds or 1.5 to 2.5 times control.

Low-Molecular-Weight Heparin

The advantages of LMWH preparations are the ease of subcutaneous (SC) administration and the absence of a need for monitoring. Furthermore, the LMWHs stimulate platelets less than UFH and are less frequently associated with heparin-induced thrombocytopenia.

LMWH binds less avidly than UFH to plasma proteins and therefore has a more consistent anticoagulant effect. However, in the event of bleeding, the anticoagulant effect of LMWH can be reversed less effectively with protamine than that of UFH. In addition, LMWH administered during PCI does not permit monitoring of the ACT to

titrate the level of anticoagulation. In addition, LMWHs are more affected by renal dysfunction than UFH, and the dose should be reduced in patients with a CrCl <30 mL/min.

Nine randomized trials have directly compared LMWH with UFH. Two trials evaluated dalteparin, another evaluated nadroparin, and 6 evaluated enoxaparin.

Trials with dalteparin and nadroparin reported similar rates of death or nonfatal MI compared with UFH, whereas 5 of 6 trials of enoxaparin found point estimates for death or nonfatal MI that favored enoxaparin over UFH. The benefit of enoxaparin appeared to be driven largely by a reduction in nonfatal MI. Treatment with enoxaparin was associated with an excess of major bleeding compared with UFH. The standard dose of enoxaparin is 1 mg/kg SC every 12 hours, with dosing only once daily for patients with a CrCl <30 mL/min.

Fondaparinux

Fondaparinux is a synthetic polysaccharide composed of the same pentasaccharide sequence found in UFH and LMWH. Similar to LMWH, fondaparinux inhibits factor Xa indirectly by binding to anti-thrombin and inducing a conformational change that allows for factor X inhibition; however, unlike with UFH and LMWH, fondaparinux-bound antithrombin does not have the ability to inhibit thrombin. Fondaparinux is excreted almost entirely unchanged in the urine.

Fondaparinux is 100% bioavailable after SC injection with peak serum concentrations reached after at about 1.7 hours. The half-life of approximately 17 to 21 hours is longer than that of UFH and LMWH, so it can be given once daily. It is not inactivated by protamine and in the case of bleeding no antidotes are known.

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial compared fondaparinux, (2.5 mg SC once daily) with standard-dose enoxaparin in 20,078 patients with high-risk UA/NSTEMI.

The rates of death, MI, or refractory ischemia throughout the first 9 days were similar. Of importance, however, the rate of major bleeding was reduced significantly—almost by half—in the fondaparinux arm.

By 30 days, mortality was significantly lower in the fondaparinux arm. However, in patients undergoing PCI, fondaparinux was associated with more than a 3-fold increased risk of catheter-related thrombi. Supplemental UFH at the time of catheterization appeared to minimize the risk of this problem with fondaparinux.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors have a potential advantage over indirect thrombin inhibitors, such as UFH, LMWH, and fondaparinux, in that they do not require antithrombin and can inhibit clot-bound thrombin. They do not interact with plasma proteins, provide a stable level of anticoagulation, and do not cause thrombocytopenia.

Bivalirudin

Bivalirudin is a synthetic peptide that binds reversibly to thrombin at its catalytic site and at an anion-binding exosite, leading to competitive inhibition. Among the direct thrombin inhibitors, it possesses the shortest elimination half-life (approximately 25 minutes in healthy individuals). The drug is cleared from plasma through a combination of renal excretion and proteolysis, and dosage adjustments are thus necessary in individuals with moderate renal impairment.

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, 13,819 patients with NSTEMI ACS were randomized in an open-label fashion to receive 1 of 3 anticoagulation strategies: heparin (UFH or enoxaparin) plus a GPI, bivalirudin plus a GPI, or bivalirudin alone. PCI was performed in 56% of patients.

With use of a composite ischemia end point of death, MI, or unplanned revascularization for ischemia and major bleeding to determine net clinical benefit, bivalirudin alone, compared with

heparin plus a GPI, showed noninferiority in the composite ischemia end point and significantly reduced rates of major bleeding, resulting in a better net clinical outcome end point.

Choice of Anticoagulant Agents

Currently available agents in Oman are Unfractionated Heparin, enoxaparin, and fondaparinux. Choice of anticoagulant agents depends upon the balance between the ischemic and bleeding risk.

Enoxaparin

Indications:

For patients WITHOUT the following precautions/contraindications:

- 1- Patients with an increased risk for bleeding, mainly :
 - Patients with a history of stroke or a transient ischemic attack
 - Renal insufficiency (CrCl <60 mL/min)
 - Age ≥75 years
 - Hemodynamic instability
- 2- When immediate or urgent coronary angiography is indicated especially if the patient will most likely undergo CABG (diabetic with widespread ST-depression and/or ST-elevation (>0.1 mV) in lead aVR or multiple wall motion abnormalities)

Dose: 1 mg/kg SC every 12h.

Duration: for the duration of hospitalization or until PCI or CABG is performed.

Fondaparinux

Indications:

- 1- Patients most likely will need prolonged anticoagulation (including patients admitted to hospitals without cathLab facilities)
- 2- Patients with an increased risk for bleeding
- 3- Patients with GFR between 30 and 58 ml/min. Avoid using if CrCl <30 ml/min.

Dose: 2.5 mg SC once daily.

Duration: for the duration of hospitalization or until PCI or CABG is performed.

Unfractionated Heparin

Indications:

- 1- Severe renal insufficiency (CrCl ≤ 30 mL/min)
- 2- When immediate or urgent coronary angiography is indicated especially if the patient will most likely undergo CABG
- 3- Patients with an increased risk for bleeding, if fondaparinux not available

Dose: 60 U/kg IV bolus (not to exceed 4000 U), followed by IV infusion of 12 U/kg/h (not to exceed 1000 U/h) to achieve goal aPTT 1.5 to 2.0 times control (approximately 50 to 70 s); check aPTT in 6 h and adjust heparin as indicated

Duration: for 48 hours.

ANTI-REMODELING THERAPY

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been shown to lower mortality in patients with MI and reduced LV function or HF. As for patients without ventricular dysfunction or HF, the evidence of improved survival is limited to stable CAD.

ACE inhibitors should be given—unless contraindicated—within the first day of admission and continued indefinitely for UA/NSTEMI patients with:

1. HF
2. LV dysfunction (LVEF <40%)
3. Hypertension
4. Diabetes mellitus
5. Chronic kidney disease

ACE inhibitors may be given—unless contraindicated—during the course of hospitalization and continued indefinitely for all the other patients with UA/NSTEMI.

An angiotensin receptor blocker should be prescribed at discharge to those UA/NSTEMI patients who are intolerant of an ACE inhibitor.

Aldosterone Receptor Antagonist

Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated CrCl should be >30 mL/min) or hyperkalemia (potassium should be ≤5 meq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF ≤40%, and have either symptomatic HF or diabetes mellitus.

ANTILIPID AGENTS

Lipid management should include assessment of a fasting lipid profile for all patients, within 24 hours of hospitalization. Statins, in the absence of contraindications, should be given to all UA/NSTEMI patients regardless of the baseline low-density lipoprotein cholesterol (LDL-C) and diet modification. Therapy should be initiated or intensified to achieve an LDL-C <100 mg/dL. Further titration to <70 mg/dL is reasonable. If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibric acid derivatives (fenofibrate, gemfibrozil) or niacin before LDL-lowering therapy is recommended. If triglycerides are >200 mg/dL, niacin and fibrate can be useful as therapeutic options after LDL-C-lowering therapy. Achievement of a non-HDL-C <130 mg/dL (ie, 30 mg/dL > LDL-C target) if possible is recommended. Therapeutic options to reduce non-HDL-C (after LDL-C lowering) include niacin or fibrate therapy. Niacin or fibrate therapy can be used (after LDL-C-lowering therapy) for HDL-C <40 mg/dL.

Encouraging consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/d) for risk reduction may be reasonable. For treatment of elevated triglycerides, higher doses (2–4 g/d) may be used for risk reduction.

We recommend therapy with atorvastatin 80 mg/d, which was used in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trials.

CORONARY REVASCULARIZATION

The goals of coronary angiography and revascularization in UA/NSTEMI patients are to reduce the risk of death and MI and provide symptom relief.

Several large randomized, controlled trials performed over the past decade have compared routine early invasive with selective invasive strategies in patients with NSTEMI/ACS, with conflicting results. Comparisons are difficult because the studies included heterogeneous patient populations, and the comparisons cannot account for the rapid advances in PCI technology and medical therapies over time. Integrating the results of these trials presents a clearer but not entirely consistent picture.

First, mortality rates appear to be similar between routine and selective invasive strategies, provided a low threshold for crossover to angiography is used in patients who are initially managed with a conservative strategy. On the other hand, nonfatal recurrent ischemic events are significantly reduced by an early invasive strategy, particularly among patients at high risk for these outcomes.

Early invasive strategy provides rapid, accurate diagnosis and risk stratification (approximately 20% of patients have no angiographically significant coronary artery disease, whereas about 15% will have left main stenosis). Thus, in high-risk patients, a routine invasive strategy is generally preferred if there are no contraindications to coronary angiography.

Among intermediate-risk patients, the benefits of an invasive approach are attenuated but still present; among low-risk patients, no benefit exists for the routine invasive approach.

Urgent coronary angiography: (<2 h)

1. Hemodynamic instability or cardiogenic shock
2. Severe HF
3. Life-threatening ventricular arrhythmias
4. Recurrent or persistent rest angina despite intensive medical therapy
5. New or worsening mitral regurgitation or new ventricular septal defect

Early angiography: (within 24–48 hours of admission)

1. Prior PCI within 6 months or prior CABG
2. New or presumably new ST-segment depression
3. Elevated serum Tns
4. Recurrent angina or ischemia at rest or with low level activity
5. LV ejection fraction <40 %

REFERENCES AND FURTHER READING

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