Management of unstable angina

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Unstable angina is a common condition that presents a challenge to physicians because of its complex pathophysiology, and because of the high incidence of associated death and myocardial infarction. This article summarizes key strategies that can be employed in managing unstable angina and describes their interaction with the mechanisms that underpin the condition.

Unstable angina is an acute coronary syndrome that can be defined by its clinical and pathophysiological features. Clinically, it presents as de novo effort-limiting angina, acceleration of previously stable chronic angina, or as angina at rest. Its pathophysiology consists of a complex sequence of plaque disruption, platelet activation, thrombus formation, vasoconstriction, and partial or complete coronary occlusion (*Figure 1*). Unstable angina is common, and accounts for more hospital admissions than does acute myocardial infarction (MI) — 46% *vs* 39% of chest pain admissions in the ENACT study (Fox, 2000). It is clinically important because the condition can lead to MI and death (7-day incidence approximately 5% and 1.5% respectively for treated patients). Although current pharmacological treatments can substantially reduce mortality, it is not clear which regimen is best. Also, the role of early cardiac catheterization and intervention is currently poorly defined in terms of evidence of mortality reduction from randomized trials.

Obstructive coronary artery disease is found in more than 80% of patients with suspected unstable angina (Thrombolysis in Myocardial Infarction (TIMI) IIIB study; Anderson et al, 1994). Myocardial ischaemia results from an oxygen supply–demand mismatch. Oxygen supply falls because of reduced coronary blood flow, caused by plaque rupture, platelet aggregation, thrombus formation and vasoconstriction.

Oxygen demand can increase because of hypertension or tachycardia. Collectively, these elements form the key therapeutic targets in unstable angina. Additional factors can also lower the threshold for myocardial ischaemia, such as aortic stenosis, pyrexia, hypoxaemia or thyrotoxicosis.

PATHOPHYSIOLOGY

In unstable angina, plaque rupture exposes subendothelial material to the circulation, initiating platelet aggregation and thrombus formation (*Figure 2*). Plaque rupture may result from an inflammatory process in which macrophages and mast cells release proteolytic enzymes that destabilize the collagenous cap that overlies the plaque core. Factors that lead to plaque destabilization may include mechanical forces, circadian variations in platelet aggregation and fibrinogen concentration, and infective agents (e.g. *Chlamydia*) may play a role in the upregulation of the inflammatory response.

Platelets are activated through membrane glycoprotein receptors (integrins). Platelets can interact via these receptors with the subendothelial matrix. Activated platelets initiate a cascade of humoral factors leading to the for-

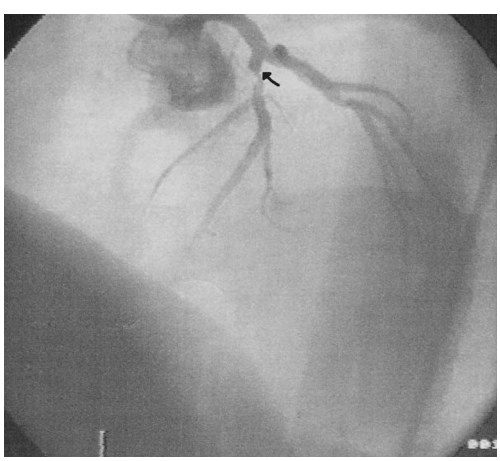

Figure 1. Subtotal occlusion of a stenosed left anterior descending coronary artery from left anterior oblique cranio-caudal view. This patient presented with unstable angina because of atheromatous plaque rupture (arrow).

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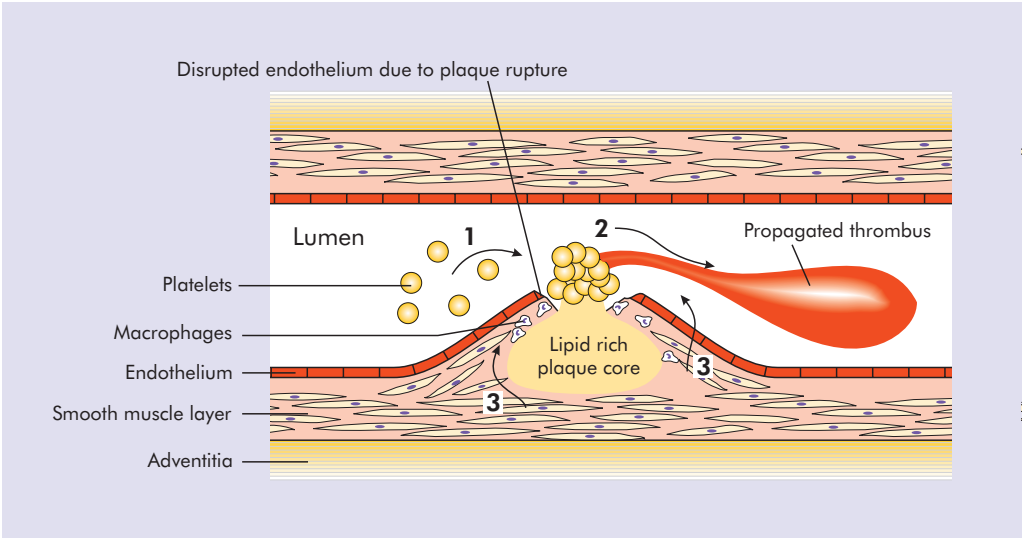

Figure 2. Pathophysiological mechanisms in unstable angina form the therapeutic targets of contemporary drug therapy. Plaque rupture leads to platelet adherence and aggregation (1), which then triggers thrombus formation and propagation (2). Platelet-derived mediators and impaired endothelial function lead to coronary vasoconstriction (3). These mechanisms are addressed using antiplatelet agents, e.g. aspirin (1), antithrombotics, e.g. enoxaparin (2), and vasodilators, e.g. glyceryl trinitrate (GTN) (3).

mation of a platelet aggregate. This process is potentiated by catecholamines and activated thrombin. Platelet activation and aggregation are normally prevented by the endothelium, which provides a physical barrier and produces prostacyclin, an inhibitor of platelet aggregation. Activated platelets release thromboxane A_2, serotonin and adenosine diphosphate (ADP), which promote aggregation.

TABLE 1.
Risk stratification in suspected unstable angina

Clinical high risk indicators	Hypotension		
	(New) cardiac failure		
	Ventricular arrhythmias		
	Recurrent or persistent ischaemic chest discomfort		
Electrocardiographic risk stratification	Low risk	Normal ECG (present initially in 25% of cases)	
		T-wave flattening, or inversion <1 mm	
	Medium risk	ST segment depression 1 mm or less	
		T-wave inversion >1 mm	
	High risk	Transient ST segment elevation	
		ST segment depression > 1 mm	
		Deep symmetrical T-wave inversion	
Troponins and risk stratification			
	Maximum TnT	5-month risk of death or MI	
Low risk	<0.06 μg/litre	4.3%	
Medium risk	0.06–0.18 μg/litre	10.5%	
High risk	>0.18 μg/litre	16.1%	

ECG = electrocardiogram; MI = myocardial infarction; TnT = troponin T

Inhibition of platelet aggregation via reduction in thromboxane A_2 production, ADP receptor antagonism, thrombin inhibition, and blockade of glycoprotein receptors forms the basis of antiplatelet therapy in unstable angina.

Exposure of subendothelial material also activates the coagulation pathways. The intrinsic pathway is triggered by activation of factor XII, and, through a series of enzymatic interactions, activation of factor X. The extrinsic pathway is also activated by endothelial injury. Tissue factor complexes with factor VII and calcium, which enzymatically activates factor X. Thus, factor X stands at the start of the common pathway of coagulation. Factor Xa promotes the conversion of prothrombin to thrombin, which in turn cleaves fibrinogen to form fibrin. An important component of clot propagation is the positive feedback of thrombin on itself; thrombin activates coagulation factors higher up in the cascade (principally factors V, VIII and thrombomodulin). Direct or indirect inhibition of thrombin activity forms a therapeutic target for limitation of clot propagation in unstable angina.

Coronary vasoconstriction in unstable angina is triggered by local changes in the concentrations of vasoconstrictor and vasodilator substances. Endothelial disruption reduces the production of nitric oxide (a potent vasodilator), and prostacyclin (a vasodilator and an inhibitor of platelet activation). Vasoconstrictors such as thromboxane A_2 are released from activated platelets, and endothelin-1 synthesis may be induced by factors such as thrombin and catecholamines.

DIAGNOSIS AND RISK ASSESSMENT

The initial diagnosis of unstable angina is based on clinical assessment. Unstable angina usually presents with ischaemic-type chest discomfort, although the quality and site of the discomfort varies between patients. The symptoms can be difficult to distinguish from those of MI. Other serious pathologies, such as aortic dissection or pulmonary embolism, can present with similar symptoms.

Risk assessment of patients with suspected unstable angina encompasses clinical factors, the electrocardiogram (ECG), and biochemical markers of cardiomyocyte injury (*Table 1*). Estimation of serum troponin T or troponin I concentration is especially helpful, since this allows identification of a subgroup in which the risk of subsequent death or MI is very low. In this group, prolonged hospitalization is not necessary and further investigation can safely be carried out on an outpatient basis (Antman et al, 1996; Lindahl et al, 1996).

BASIC MANAGEMENT

Contemporary guidelines for management of unstable angina are increasingly based on evidence from clinical trials. Basic management consists of risk assessment, admission to an appropriate clinical unit, and consideration of treatment with antiplatelet and antithrombotic agents, vasodilators and β-adrenoceptor antagonists.

Most patients require admission to a hospital with facilities for continuous cardiac monitoring, and should be rested in bed initially. Opiate analgesia should only be given if discomfort persists despite antiplatelet therapy, antithrombotic therapy and β-blockade, since failure to respond to these treatments identifies a high-risk subgroup. Inhaled oxygen should be given if there are high-risk features, or if the patient is hypoxaemic or in respiratory distress.

Continuous ST segment monitoring can help detect early signs of worsening ischaemia or infarction, but is no substitute for repeating the 12-lead ECG and comparison with previous recordings. This should be done if there is a change in clinical status, and at least every 30 minutes if there is continuing chest discomfort.

PHARMACOLOGICAL MANAGEMENT

Antiplatelet therapy

Aspirin: Aspirin is currently the most widely used antiplatelet agent in unstable angina. Aspirin inhibits the enzyme cyclo-oxygenase, which is responsible for the synthesis of thromboxane A_2 in platelets, and of prostacyclin in the endothelium. Thromboxane A_2 promotes platelet aggregation and prostacyclin inhibits it. In practice the antiaggregatory effects predominate, but can be over-ridden by agents that act independently of the cyclo-oxygenase pathway (e.g. catecholamines, thrombin and tissue factor). In the Veterans Administration (VA) Cooperative Study Group, aspirin conferred a 51% reduction in the rate of death and non-fatal MI in patients with unstable angina compared with placebo (Lewis et al, 1983).

The Research Group on Instability in Coronary Disease (RISC, 1990) trial showed that aspirin 75 mg daily reduces the risk of death and MI by 60% compared with placebo. For every 1000 patients treated, 26 lives were saved in the first 90 days of treatment with aspirin. The only absolute contraindications are true aspirin allergy, which is rare, and clear evidence of or risk of major haemorrhage. Thus, an initial oral dose of aspirin 300 mg (soluble or chewed) should be given, followed by 75–300 mg daily, to all patients without contraindications.

ADP receptor antagonists: An alternative to cyclo-oxygenase inhibition is the blockade of ADP-mediated platelet aggregation. Ticlopidine is an ADP receptor antagonist which was shown to reduce the risk of death and MI in patients with unstable angina in the STAI (Studio della Ticlopidina nell' Angina Instabile) trial (Balsano et al, 1990). However, this drug can cause neutropenia and is not licensed for use in unstable angina in the UK.

Clopidogrel is a newer analogue which shows promise in atherosclerotic disease. In the Clopidogrel *vs* Aspirin in Patients at Risk of Ischaemic Events (CAPRIE, 1996) trial, clopidogrel (75 mg daily) was compared with aspirin (325 mg daily) for secondary prevention in patients with confirmed atherosclerotic vascular disease. Clopidogrel conferred a relative risk reduction of 8.7% for ischaemic stroke, MI or vascular death compared with aspirin. It is not clear whether this benefit is realized in patients with unstable angina, and clopidogrel is not currently licensed for this indication.

Glycoprotein IIb/IIIa receptor antagonists: More recently, attention has been focussed on agents which inhibit the final common pathway of platelet aggregation — the glycoprotein (Gp) IIb/IIIa receptor (the integrin which mediates platelet–platelet adhesion via fibrinogen). Administration of intravenous abciximab (a monoclonal FAB fragment that binds this receptor complex) markedly reduces complication rates after high risk coronary angioplasty, and could be helpful in high risk patients with unsta-

ble angina (The EPIC Investigators, 1994; Lefkovits and Topol, 1996).

In the PRISM-PLUS trial (1998), oral tirofiban (a non-peptide GpIIb/IIIa receptor antagonist), heparin, or both were administered for 72 hours to patients with unstable angina already receiving oral aspirin. Combined tirofiban and heparin therapy was associated with a lower incidence of the combined endpoint of death, MI and refractory ischaemia (relative risk 0.68) than heparin alone at 7 days. Benefit continued for at least 60 days after presentation. In contrast, results from trials of long-term orally administered GpIIb/IIIa receptor antagonists have not provided evidence of benefit over that seen with aspirin. Indeed, concern has been raised that long-term administration of these agents may confer additional risk compared with aspirin therapy (SYMPHONY Trial Investigators, 2000).

Antithrombotic therapy

Unfractionated heparin consists of mucopolysaccharide chains of variable lengths. It acts by augmenting the action of antithrombin III, and also augments the action of factors Xa, IXa and XIa. It is usually administered intravenously to maintain an activated partial thromboplastin time (aPTT) between 1.5 and 2.5 times control. In the presence of aspirin, unfractionated heparin appears to reduce the risk of death and MI, compared with aspirin alone (based on trends from individual studies and one meta-analysis) (Oler et al, 1996). Heparin is normally continued for at least 48 hours and either:

1. Cardiac catheterization has been performed, and further management planned or
2. The patient has remained free of angina for at least 24 hours.

In the absence of aspirin treatment, discontinuation of heparin can be associated with 'rebound' angina, possibly because of increased thrombin activity. Concurrent use of aspirin, and gradual rather than sudden cessation of treatment, may ameliorate this.

Low molecular weight heparins provide a theoretical advantage over unfractionated heparin, by inhibiting factors higher in the coagulation cascade. These agents exhibit proportionately greater factor X inhibition than unfractionated heparin. Data from both the ESSENCE and TIMI 11b trials indicate that administration of weight-adjusted subcutaneous enoxaparin is at least as effective as intravenous unfractionated heparin at preventing MI and refractory angina (Cohen et al, 1997; Antman et al, 1999). Since the different low molecular weight heparins have different anti-factor Xa:antithrombin III activity, this benefit may not be realized by all low molecular weight heparins. Low molecular weight heparins have other advantages — the dose response is predictable (so coagulation monitoring is not normally required), subcutaneous injection abolishes the need for infusion pumps and disposables, and although the drug itself is more expensive than unfractionated heparin, an overall cost saving may be realized through its use (Fox and Bosanquet, 1998).

Beta-blockers

Beta-blockers competitively inhibit the neuronally mediated and systemic actions of catecholamines. This reduces myocardial oxygen demand by slowing heart rate and reducing myocardial contractility; blood pressure is also reduced, and catecholamine driven arrhythmias may be prevented (Hohnloser et al, 1991). Patients with unstable angina should be treated with beta blockers unless there are contraindications. These are marked sinus bradycardia, second or third degree atrioventricular block, asthma, acute heart failure, or hypotension with reduced cardiac output (e.g. systolic blood pressure less than 90 mmHg).

Low or intermediate risk patients can be treated with oral β-blockers. Symptom relief can be rapidly achieved in high risk patients through prompt treatment with intravenous β-blockers, (e.g. metoprolol 5 mg over 2 minutes, repeated every 5 minutes, maximum dose 15 mg). If there is concern about possible adverse effects, an intravenous infusion of esmolol, an ultra short-acting β-blocker, can be used (initial dose 0.1 mg/kg/min, increased by 0.05 mg/kg/min every 10 minutes until either a therapeutic response is achieved or a dose of 0.2 mg/kg/min is reached). Oral therapy can usually be initiated 1 hour after the intravenous dose. The maintenance dose should be titrated to the patient's symptoms and heart rate, aiming for a resting heart rate of 50–60 beats per minute. This is typically achieved by oral metoprolol 50–100 mg twice daily, or atenolol 50–100 mg once daily.

Vasodilators

Currently there is no evidence that vasodilator treatment for unstable angina reduces the incidence of death or MI. Vasodilators are effective at relieving ischaemic symptoms, and can confer haemodynamic benefits in hypertensive patients. Nitrates help in acute left ventricular failure by improving myocardial perfusion and by reducing preload and afterload. Intravenous glyceryl trini-

trate (GTN) is most commonly used in the early stages of treatment, titrated according to symptoms (starting at 5 μg/min, increasing every 10 minutes in steps of 5 μg/min). Buccal GTN 2–10 mg may be equally effective. The infusion rate should be reduced if hypotension or headache develop.

Nitrate tolerance can develop after 24 hours of continuous use, reducing the effectiveness of treatment. Nitrate treatment can be stopped once the patient has stabilized on aspirin, heparin and oral antianginal therapy. After stabilization, a long-acting oral nitrate (e.g. sustained release isosorbide mononitrate 30–240 mg daily) can be used for angina prophylaxis, allowing an 8-hour daily nitrate-free period to avoid tolerance.

Alternatively nicorandil, a potassium channel opener and coronary vasodilator, can be used (dose 10–20 mg twice daily) without the need for a drug-free interval. There is some experimental evidence that this agent may afford some myocardial protection by potentiating the ischaemic preconditioning response (Patel et al, 1999).

Calcium channel antagonists are also effective at relieving symptoms. Although one meta-analysis of trials of calcium channel antagonists in stable angina raised concern about the potential for inducing adverse coronary events, this effect related predominantly to the use of short-acting dihydropyridine preparations in MI (Furberg et al, 1995). These agents can cause hypotension and reflex tachycardia, and should therefore be avoided in unstable angina. Amlodipine has a slower onset of action, which causes little reflex tachycardia, and can be useful for symptom control in resistant unstable angina (dose 5–10 mg daily), in combination with a β-blocker. Diltiazem (120–480 mg daily) and verapamil (120–360 mg daily) both have a negative chronotropic action that renders them suitable for patients who are intolerant of β-blockers. Since both depress sinuatrial and atrioventricular node function, they should be introduced cautiously in patients already receiving β-blockers. Intravenous verapamil should not be given to patients already taking an oral β-blocker. Both diltiazem and verapamil depress myocardial contractility, and should be avoided in left ventricular failure.

NON-PHARMACOLOGICAL TREATMENTS

Intra-aortic balloon counterpulsation

Intra-aortic balloon pump (IABP) counterpulsation is a mechanical method of augmenting coronary perfusion pressure and reducing afterload, using a balloon catheter placed percutaneously in the descending thoracic aorta. The balloon is inflated with helium during diastole and rapidly deflated at end diastole. In unstable angina, this treatment is helpful as a bridge to coronary artery bypass surgery or angioplasty in high-risk patients for whom pharmacological treatment has failed. To date there has been no randomized trial showing mortality or morbidity reduction with IABP counterpulsation.

Early conservative *vs* early invasive management strategies

The exact role of and optimal timing of cardiac catheterization in unstable angina is not yet clearly defined. The frequency of angiography and intervention is usually determined by the available facilities, and the level and mechanism of local health-care funding. Both early conservative and early invasive management strategies are appropriate approaches.

Early conservative management: In this strategy, patients are stabilized with aspirin, heparin, β-blockers and vasodilators. Early cardiac catheterization is performed only in patients for whom medical therapy fails to settle ischaemic symptoms and electrocardiographic features within 48 hours. In these patients medical therapy has failed, and revascularization has to be considered. The presence of high-risk clinical indicators (*Table 1*) is also an indication for early angiography. Patients whose symptoms resolve, and who are considered low risk for MI based on risk assessment may be further assessed with a low intensity stress test (e.g. stress ECG, myocardial perfusion scan, or stress echocardiogram). This helps to further determine the risk of subsequent coronary events, and directs these patients towards medical management or elective cardiac catheterization.

Early invasive management: The role of early cardiac catheterization and intervention for patients with unstable angina is currently under investigation. Typically, an early invasive strategy submits patients to cardiac catheterization within 72 hours of admission, followed by revascularization when coronary anatomy permits. In the TIMI IIIB study, outcomes were compared in patients randomized to early conservative and invasive strategies (Anderson et al, 1994). Although the invasive strategy did not confer early benefit in terms of reduction in death or MI, it did reduce episodes of late ischaemia, antianginal drug usage and rehospitalization. In addition, results from the FRISC-II study have indicated that an

early invasive strategy may confer more benefit in the era of contemporary intervention strategies (Wallentin et al, 1997).

Currently a larger scale study (the Third Randomized Intervention Treatment of Angina Trial; RITA-3), is ongoing. This trial aims to clarify, in the setting of current day practice (e.g. intracoronary stents, GpIIb/IIIa receptor antagonists), whether an early invasive strategy reduces cardiovascular risk and improves symptoms. Meanwhile, an early invasive strategy can be considered valid in centres that can offer facilities for high quality angioplasty and coronary artery bypass surgery.

CONCLUSIONS

Unstable angina is the most common acute coronary syndrome encountered by hospital physicians. It is mediated by a complex pathophysiology which forms the targets for current drug therapies. Risk stratification helps target treatment towards patients at greatest risk of death and MI. Early medical management with antiplatelet and antithrombotic therapy significantly reduces the risk of these events. Beta blockade confers additional benefit in terms of oxygen supply–demand balance, and should be used wherever possible. Vasodilator therapy with nitrates, long-acting calcium channel antagonists, or potassium channel openers helps ameliorate symptoms.

Early cardiac catheterization, with a view to revascularization, is appropriate for high risk patients and for patients who fail to respond to medical therapy. The role of an early invasive strategy for all patients is the subject of current clinical trials. HM

Conflict of interest: none.

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KEY POINTS

- Unstable angina is the most common acute coronary syndrome seen by hospital physicians.
- Unstable angina is caused by plaque rupture, platelet aggregation, thrombosis and vasoconstriction.
- The risk of death and myocardial infarction in untreated patients is significant.
- These risks can be minimized by treatment with antiplatelet and antithrombotic agents.
- The role of early cardiac catheterization and revascularization is the subject of ongoing randomized clinical trials.