Chapter 17

Therapy-related issues: cardiovascular system

Angina

Definition

Angina is defined and diagnosed by clinical criteria. Cardiac pain is retrosternal, intense and gripping, constricting or suffocating, and diffuse rather than sharp.

Pain can radiate to one or both arms, neck, jaw, or teeth. However, it can be difficult to distinguish angina from severe dyspepsia, so other signs need to be considered to help differential diagnosis, such as whether pain comes on acutely following exertion and is relieved within a few minutes by resting or sublingual nitrates.

The underlying pathology is usually, but not always, coronary atherosclerosis. Smoking, hyperlipidaemia, hypertension, obesity, and diabetes mellitus are risk factors that accelerate coronary atherosclerosis.

Types of angina

- Stable angina is induced by effort and relieved by rest.
- Unstable angina (crescendo) is angina of ↑ frequency or severity, which occurs at minimal exertion and ↑ with ↑ risk of MI.
- Decubitus angina is precipitated by lying flat.
- Variant (Prinzmetal) angina is caused by coronary artery spasm.

In stable angina, the problem is chronic atherosclerotic obstruction which is slowly progressive, although the onset of symptoms is often sudden. Severe obstructive coronary atherosclerosis restricts myocardial blood flow, whereas exercise or emotional stress creates a demand for more blood flow, which cannot be achieved because of the obstruction.

Anginal pain signals temporary myocardial ischaemia, which subsides promptly with rest because the ↑ demand subsides.

Not all patients experience typical chest pain. Some experience atypical pain, shortness of breath, or light-headedness.

Aims of treatment

- To relieve or prevent pain.
- To slow progression of atherosclerosis.
- To improve prognosis.

Assess the occurrence of pain in relation to the patient's lifestyle. Drug therapy should be initiated immediately, and risk factors should be assessed.

Attention to good drug adherence/concordance is important, and potential obstacles to this should be considered.

Advice should be given regarding regular moderate exercise and avoidance of heavy, sudden, and unaccustomed exertion and acute emotional stress, if practicable.

Acute attack

The patient should stop activities as soon as pain is felt. To shorten the attack, use one of the following regimens.

- Glyceryl trinitrate (GTN) spray 400micrograms metered-dose sublingually—repeat the dose once after 5min if pain persists (maximum of two metered doses).
- GTN tablet 500micrograms sublingually—repeat every 3–5min up to a maximum of 1500micrograms. (It is important that patients are made aware of the limited 8wk shelf-life of opened containers.)

Note: avoid nitrates if the patient has used sildenafil (Viagra®) in the previous 24h, or tadalafil (Cialis®) or vardenafil (Levitra®) in the previous 5 days.

The patient should sit or lie down, particularly when first using GTN, because of the possibility of hypotension.

If pain persists after three tablets taken over 15min or two sprays at 5min intervals, the patient should be advised to call an ambulance for transfer to the nearest hospital.

Continuing therapy

The aims of continuing therapy are to ↓ myocardial ischaemia, hence ↑ effort tolerance, and to prevent the development of acute coronary syndrome, arrhythmia, and death. Antiplatelet therapy ↓ the incidence of ischaemia at rest and the risk of MI or death. β-blockers enhance effort tolerance by ↓ the onset of myocardial ischaemia. Either of the following regimens can be used for continuing therapy:

- aspirin 75–300mg oral daily
- clopidogrel 75mg daily (if intolerant of aspirin).

The therapies described are given in addition to one of the following regimens:

- Atenolol 25–100mg oral daily.
- Metoprolol 25–100mg oral twice daily.

Nitrates can be used prophylactically before exertion that is likely to provoke angina.

For patients in whom a β-blocker alone does not prevent angina, add a dihydropyridine calcium-channel blocker and/or a nitrate and/or nicorandil, as follows

- Amlodipine 2.5–10mg oral daily or nifedipine controlled-release 30–60mg oral daily.
- Isosorbide mononitrate 30–120mg oral daily in divided doses or GTN 5–15mg transdermally (apply for a maximum of 16h in a 24h period).
- Nicorandil 5mg oral twice daily, ↑ after a week to 10–20mg twice daily.

For patients in whom there is a contraindication to a β-blocker, substitute a calcium-channel blocker, preferably a long-acting non-dihydropyridine and/or a nitrate and/or nicorandil, as follows.

- Diltiazem 30–120mg oral three times daily; diltiazem controlled-release 180–360mg oral daily; verapamil 40–120mg oral twice or three times daily; verapamil sustained-release 160–480mg oral daily; or amlodipine 5–10mg oral daily.
- Isosorbide mononitrate 30–120mg oral daily in divided doses or GTN 5–15 mg transdermally (apply for a maximum of 16h in a 24h period).
- Nicorandil 5mg oral twice daily, ↑ after a week to 10–20mg twice daily.

Choice of calcium-channel blockers

When calcium-channel blockers are used without a β-blocker, the agents of choice are verapamil or diltiazem which slow the heart rate. In general, verapamil should not be administered in combination with β-blockers because of the risk of severe bradycardia, and diltiazem should be administered with caution in combination with a β-blocker for the same reason. Dihydropyridine calcium-channel blockers can be administered in combination with β-blockers.

Amlodipine, which has a very long half-life, and the once-daily form of nifedipine can be used alone for angina, but caution should be exercised because of the possibility of ↑ sympathetic tone and heart rate secondary to arteriolar dilatation.

Tolerance to nitrate therapy

Tolerance to all forms of nitrate therapy develops rapidly. Sustained-release isosorbide mononitrate administered once daily and a GTN patch worn for <16h/day avoid this complication by allowing a nitrate-free period. The commonly used regimen of isosorbide dinitrate three or four times daily results in rapid development of tolerance.

In patients who have a low ischaemic threshold, rebound ischaemia can develop during the drug-free interval when the GTN patch is not worn. This problem might be less common during the low-drug-concentration period with sustained-release isosorbide mononitrate. Therefore this might be useful for patients with a very low ischaemic threshold.

It should be noted that a combination of long-acting nitrate regimens (e.g. sustained-release isosorbide mononitrate plus transdermal GTN) results in the rapid development of tolerance and should be avoided.

Heart failure

Heart failure is mainly a disease of the elderly. It can be predominantly left ventricular, with pulmonary congestion and dyspnoea, or predominantly right ventricular, with ↑ venous pressure, peripheral oedema, and hepatic congestion. Usually both forms coexist in the classical syndrome of congestive or biventricular heart failure.

Heart failure is generally a consequence of myocardial damage, leading to ↓ systolic function. Underlying causes and/or precipitating factors include the following.

- Hypertension.
- Coronary artery disease.
- Valvular heart disease.
- Hypertrophic cardiomyopathy.
- Hyperthyroidism can cause heart failure, particularly in association with rapid atrial fibrillation (AF).
- Alcohol abuse.
- Pericardial effusion.
- Obstructive sleep apnoea.

Non-drug interventions

Physical activity

Patients should be encouraged to be active if symptoms are absent or mild. However, bed rest might have a marked diuretic effect and, in general, patients should be rested if symptoms are severe. When confined to bed, they should receive heparin prophylaxis.

Weight reduction

Obesity is a risk factor for heart failure and left ventricular hypertrophy. Weight reduction should be advised for obese patients.

Sodium restriction

The use of diuretics avoids the need for strict sodium restriction in many patients with heart failure. However, excessive salt ingestion can precipitate or exacerbate heart failure and a no-added-salt diet (60–100mmol/ day) should be recommended. More severe salt restriction might be necessary in patients with severe heart failure.

Water restriction

In patients with severe heart failure the ability to excrete a free water load is diminished. The combination of ↓ sodium intake, potent diuretics, and continued water intake often leads to dilutional hyponatraemia. Liberalizing salt intake or ↓ diuretic dosage is usually inappropriate, because these patients are often still oedematous. Water intake should be limited to ≤1.5L/day in patients with hyponatraemia, particularly those in whom serum sodium concentration falls below 130mmol/L.

Oxygen

Patients with acute pulmonary oedema are hypoxaemic and require O_2. Carbon dioxide (CO_2) retention is not usually a problem, except in patients with cor pulmonale or very severe pulmonary oedema.

Pleurocentesis and pericardiocentesis

Occasionally, patients with heart failure have significant pleural effusions which might require pleural aspiration. Pericardial aspiration should be performed in patients who have compromised circulatory function resulting from pericardial effusion and cardiac tamponade.

Drug interventions for mild to moderate heart failure

Optimization of therapy can take several months and requires close monitoring of symptoms, fluid status, renal function, and electrolyte levels.

ACE inhibitors improve prognosis in all grades of heart failure and should be used as initial therapy in all patients.

Angiotensin II receptor antagonists offer a potential alternative therapy in patients who are intolerant of ACE inhibitors, except if there are contraindications to either class of drug.

ACE inhibitor therapy

Virtually all patients with clinical heart failure should receive an ACE inhibitor as initial therapy (Table 17.1). Asymptomatic patients should also receive an ACE inhibitor if there is significant left ventricular dysfunction (i.e. left ventricular ejection fraction is <40%).

Most symptoms and signs of heart failure are caused by retention of salt and water and the consequent ↑ in cardiac filling pressures. Diuretics should be added to ACE inhibitor therapy to help control congestive symptoms and signs. If the patient's response to ACE inhibitor monotherapy is inadequate, add a diuretic and/or ↑ the dose of ACE inhibitors. Virtually all patients with clinical heart failure require combination therapy with an ACE inhibitor and a diuretic.

Table 17.1 Dosing regimens for ACE inhibitors in heart failure

Drug	Initial dose	Maintenance range
Captopril	6.25mg twice daily	50mg 3 times daily
Enalapril	2.5mg daily	20mg daily in 1–2 doses, maximum 40mg
Lisinopril	2.5mg daily	20–40mg daily
Perindopril	2mg daily	4–8mg daily
Ramipril	1.25mg daily	5–10mg daily

Angiotensin II receptor antagonists

Some patients are unable to tolerate ACE inhibitors because of adverse effects, such as cough or skin rashes. In these patients, angiotensin II receptor antagonists should be used to provide an alternative mechanism of inhibiting the renin–angiotensin system. However, if a patient has experienced angioedema with an ACE inhibitors, angiotensin II receptor antagonists are also contraindicated. They probably provide the same benefits as ACE inhibitors with regard to control of heart failure and improvement in prognosis.

If progressive worsening of renal function is the principal reason for stopping an ACE inhibitor, angiotensin II receptor inhibitors are likely to produce the same effect on renal function.

Diuretic therapy

- Diuretics should be added to ACE inhibitor therapy to control congestive symptoms and signs. Close monitoring of weight, renal function, and electrolytes is required.
- Loop diuretics are commonly used, particularly for heart failure of moderate severity; thiazides produce a gradual diuresis and are effective for mild heart failure. Caution: if thiazide and loop diuretics are combined, there is a considerable synergistic effect and the combination should be reserved for severe heart failure.
- In patients with normal renal function, the combination of ACE inhibitor, diuretic, and a K^+-sparing diuretic or K^+ supplement is occasionally needed.
- In patients with renal impairment, if diuretics are used with an ACE inhibitor, K^+-sparing diuretic or K^+-supplementation is usually not necessary and could cause life-threatening hyperkalaemia.
- If hypokalaemia proves difficult to correct, hypomagnesaemia may be present.

Spironolactone

Has been shown to decrease mortality in patients with NYHA III–IV at doses of 25mg daily who are already receiving standard therapy. As spirolactone is an aldosterone antagonist, it prevents this hormone's mechanism which causes sodium and water retention.

β-blocker therapy

Recent clinical trials have demonstrated beneficial effects of β-blockers in patients with systolic heart failure and low ejection fraction, with improvement of heart failure, left ventricular ejection fraction, and prognosis. The benefits of β-blockade, proven in clinical trials, included ↓ in all-cause mortality, sudden death, and hospitalization rates for heart failure and reversal of some degree of heart damage. Carvedilol and bisoprolol are currently licensed in the UK for chronic heart failure.[1,2,3]

There are two clinical situations in which β-blockers have been used for some time.

- After stabilization of acute heart failure in patients with AF, to control rapid ventricular rate.
- In patients with primarily diastolic heart failure, to improve diastolic filling.

1 CIBIS-II Investigators (1999). The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* **353**: 9–13.

2 MERIT-HF Study Group (1999). Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* **353**: 2001–7.

3 Krum H *et al.* (2003). Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: Results from the COPERNICUS Study. *JAMA* **289**: 712–18.

β-blocker therapy in patients with heart failure can be extremely difficult to manage. Initiation and up-titration should be undertaken in consultation with a specialist.

Patients with systolic heart failure are often very sensitive to β-blockers. Major complications include worsening of heart failure, severe hypotension, and bradyarrhythmias. These complications are caused by β-blockade, leading to withdrawal of sympathetic nervous system support for the failing heart. These complications may be minimized by the following strategies.

- Starting therapy with extremely low doses.
- ↑ the dose very gradually.
- Monitoring the patient frequently, by weighing daily.
- Adjusting the dose of other medications, such as diuretics and ACE inhibitors, to compensate for any tendency to ↑ heart failure.
- Avoiding simultaneous addition of vasodilator drugs.
- Excluding patients with extremely severe heart failure and those whose heart failure is not well controlled on other therapy.

The best advice is 'start low and go slow'. Use one of the following regimens.

- Bisoprolol 1.25mg once daily (the dose can be doubled every 2–4 weeks, provided that the patient is stable, with the aim of ↑ the dose to 10mg once daily).
- Carvedilol 3.125mg twice daily (the dose can be doubled every 2–4wks, provided that the patient is stable, with the aim of ↑ the dose to 25mg oral twice daily).
- Metoprolol 12.5mg twice daily (the dose can be doubled every 2–4wks, provided that the patient is stable, with the aim of ↑ the dose to 100mg oral twice daily).

It seems probable that standard β_1-blockers, such as metoprolol, provide similar benefits to the newer β-blockers, such as bisoprolol and carvedilol, and therefore might be much more cost-effective. However, both bisoprolol and carvedilol offer the advantage of lower-strength tablets for initiation of therapy. Moreover, they are the only β-blockers explicitly approved for use in heart failure.

Digoxin therapy

There are two indications for the use of digoxin in patients with heart failure:

- in patients with AF, to control rapid ventricular rate.
- in patients with sinus rhythm (SR), if heart failure is not adequately controlled by optimal doses of ACE inhibitors and loop diuretics.

If the patient has not been taking digoxin, give the following dose regimen.

- Digoxin 62.5–500micrograms oral daily, according to age, plasma creatinine, and plasma digoxin level.

In patients with normal renal function, the half-life of digoxin is ≥24h. Following initiation of therapy or change in the digoxin dose, the patient will require ≥5 days (five half-lives) to achieve a steady state. In patients with impaired renal function, the half-life of digoxin might be greatly prolonged.

Patients take much longer to reach steady state, and require ↓ in the maintenance dose. Monitoring of digoxin plasma level is recommended.

If the patient requires more rapid digitalization (e.g. AF with rapid ventricular rate), give the following dose regimen.

- Digoxin 500micrograms–1mg oral immediately, followed by 250–500micrograms oral every 4–6h (up to 1.5–2mg in the first 24h) followed by digoxin 62.5–500micrograms oral daily, according to age, plasma creatinine level, and plasma digoxin level.

Caution: elderly patients are susceptible to digoxin toxicity, partly because of ↓ renal clearance and partly because their cardiac tissue is more sensitive to the drug's action. Therefore loading and maintenance doses generally need to be lower.

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Drug interventions for severe heart failure

Patients with severe symptomatic heart failure should be hospitalized, and require bed rest. Therapy will include all of the following drug regimens:

- maximum tolerated dose of an ACE inhibitor orally
- ↑ dose of furosemide, up to a maximum of 500mg/daily
- low-dose spironolactone, 25mg/daily (range 12.5–50mg/daily).

Low-dose spironolactone (25mg/daily) when added to therapy with a loop diuretic and an ACE inhibitor, improves prognosis in patients with severe heart failure, without a major risk of hyperkalaemia or dehydration.

In patients with severe refractory oedema due to severe heart failure, K^+-sparing diuretics, such as amiloride and spironolactone (which are weak diuretics), can facilitate diuresis when used in combination with loop diuretics. They are also much more effective than K^+ supplements in maintaining the serum K^+ level.

All K^+-sparing diuretics can cause severe life-threatening hyperkalaemia, particularly in patients with renal impairment or those taking K^+ supplements or an ACE inhibitor.

The combination of an ACE inhibitor, loop diuretics, and spironolactone can cause severe dehydration and/or hyperkalaemia.

If heart failure is poorly controlled, consider adding one of the following regimens.

- Bendroflumethiazide 2.5mg oral (use a single dose initially and repeat in 2–7 days, depending on diuretic effect).
- Spironolactone—↑ doses to 100–200mg daily.
- One of the following three (only when the patient is stable on optimal doses of ACE inhibitor and combination diuretic therapy).
  - Bisoprolol 1.25mg oral once daily (the dose can be doubled every 2–4 weeks, provided that the patient is stable, with the aim of ↑ the dose to 10mg oral once daily).
  - Carvedilol 3.125mg oral once daily (the dose can be doubled every 2–4wks, provided that the patient is stable, with the aim of ↑ the dose to 25mg oral twice daily).
  - Metoprolol 12.5mg oral once daily (the dose can be doubled every 2–4 weeks, provided that the patient is stable, with the aim of ↑ the dose to 100mg oral twice daily).
- If the patient has not been taking digoxin, add digoxin.
- If the patient has been taking digoxin, check the trough plasma digoxin level not less than 6h after the latest dose and consider ↑ the maintenance dose to achieve a plasma level in the high therapeutic range, provided that there are no symptoms or signs of toxicity.)
- If the patient is confined to bed, give prophylactic heparin as well.

Useful additional therapies in severe heart failure

Nitrates/GTN

Nitrates cause prompt, but temporary, lowering of pulmonary venous pressure. Patients with heart failure associated with hypertension or ischaemia are particularly likely to benefit.

GTN is the preferred IV vasodilator therapy, usually in the setting of an intensive care or coronary care unit. Normally, IV therapy is required for only a short period; prolonged infusion rapidly induces tolerance. Use GTN 10micrograms/min IV and ↑ the dose according to the clinical response, but maintain the systolic BP (SBP) >90mmHg.

Warfarin

Warfarin is recommended for patients who have heart failure with AF and in those with previous systemic embolism and severe left ventricular systolic dysfunction. The INR should be maintained between 2 and 3. It might be less stable in the presence of heart failure, making warfarin therapy more difficult to control.

Patients who have underlying ischaemic or hypertensive heart disease and who are not on warfarin should take low-dose aspirin.

Patients with very severe heart failure might benefit temporarily from further intensive measures. These should only be employed if there is some transient exacerbating factor (e.g. myocardial ischaemia, infection, or surgery) or if some remedial measure (e.g. cardiac transplantation) is planned.

Sodium nitroprusside

Sodium nitroprusside can also be used. It is generally administered with BP monitoring using an arterial line. It is particularly effective for patients with heart failure associated with severe hypertension. If treatment is continued for >24h, monitor thiocyanate and cyanide levels to avoid toxicity. Use sodium nitroprusside 0.3micrograms/kg body weight/min IV initially and ↑ by 0.3micrograms/kg body weight/min every 5–10min to maintain SBP at <90mmHg. Do not use for >3 days.

Other therapies

Short-term catecholamine inotrope administration can cause temporary improvement. However, therapy with positive inotropic drugs has been associated with ↑ mortality. Use dobutamine 2.5–10micrograms/kg body weight/min IV.

Increasingly, patients presenting with severe heart failure are taking a β-blocker. In these patients, the dose of β-blocker should be ↓ or the drug should be completely withdrawn. If temporary IV inotropic support is required, the phosphodiesterase inhibitor milrinone can be used and is effective in ↑ contractility even in the presence of β-receptor blockade.

Finally, an intra-aortic balloon pump might occasionally be required, and cardiac transplantation should be considered in younger patients with severe refractory heart failure. Ventricular-assist devices can provide a bridge to transplantation and, perhaps, even a long-term alternative.

Acute cardiogenic pulmonary oedema

- A medical emergency requiring urgent treatment in hospital. Initially, the patient should receive O_2 4–6L/min through a mask and furosemide 20–80mg IV (repeated 20min later, if necessary).
- Larger doses might be required, particularly in patients on pre-existing diuretic therapy or with impaired renal function. If the response to IV furosemide is inadequate, consider morphine with or without nitrates.
- Morphine 2.5–10mg IV (use the lower end of the range in the elderly).
- If pulmonary oedema is severe, not responding, or associated with ischaemia or significant hypertension, add GTN 10micrograms/min IV and ↑ according to clinical response, but maintain SBP >100mmHg.
- If the patient is in AF with a rapid ventricular rate and has not been taking digoxin, add digoxin 500micrograms oral or IV and repeat at 4h and 8h, if necessary. Administer digoxin 500micrograms oral the following day, followed by digoxin 62.5–500micrograms oral daily, according to age, plasma creatinine level, and plasma digoxin level.
- If the patient is not in AF, withhold digoxin until acute pulmonary oedema is controlled, when a maintenance dose of digoxin can be commenced or restarted.
- If pulmonary oedema remains severe and does not respond to treatment, add continuous positive airway pressure ventilation (CPAP) to improve oxygenation.
- If pulmonary oedema is severe and not responding to diuretics and vasodilator therapy, consider adding either of the following regimens.
  - Dobutamine 2.5–10micrograms/kg body weight/min IV.
  - Milrinone 50micrograms/kg body weight IV slowly over 10min, followed by 0.375–0.75micrograms/kg body weight/min IV, adjusting the dose according to clinical and haemodynamic responses up to a maximum of 1.13mg/kg body weight daily.
- See Table 17.2.

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Treatment of hypertension

High BP is characterized by elevated arterial BP and ↑ risk of stroke, MI, renal failure, heart failure, or other vascular complications.

High BP is one of many risk factors for cardiovascular disease. Currently, there is a shift from consideration of individual risk factors, such as BP, to overall cardiovascular risk. Normal BP is defined as <130/85mmHg. BP is ↑ by drugs such as the following:

- NSAIDs (including cyclo-oxygenase-2 (COX-2) inhibitors)
- corticosteroids
- oral contraceptives
- topical or oral decongestants
- excessive liquorice or salt intake.

Assessment and management of other cardiovascular risk factors, particularly smoking and diabetes mellitus, is an important part of management. These factors can modify the overall cardiovascular risk substantially. Lipids and blood glucose might need checking after changes of therapy (e.g. initiation of diuretics).

Non-pharmacological measures to reduce both BP and cardiovascular risk should be introduced in all patients with hypertension. These might be the only interventions necessary in some patients. Effective measures include the following.

- Weight reduction in overweight patients.
- ↓ of heavy chronic or intermittent alcohol intake (defined as >3units/day in ♀ or >5 units/day in ♂).
- Regular physical activity.
- Moderate sodium restriction (e.g. no-added-salt diet).
- Management of sleep apnoea.
- Stress reduction.

Obstructive sleep apnoea is a strong independent risk factor for stroke and cardiovascular events. Effective management ↓ BP and can reverse these risks, but this has not been formally demonstrated.

Patients should be vigorously encouraged to stop smoking, and hyperlipidaemia should be managed. Management of cardiovascular risk factors, in addition to good glycaemic control, is particularly important in hypertensive patients with diabetes mellitus.

Drug treatment

If the non-pharmacological measures described do not achieve risk factor and BP goals, drug treatment should be commenced (Table 17.2).

In patients with no other risk factors, treatment should be commenced at systolic BP levels >160mmHg and at diastolic BP levels ≥100mmHg. Patients at raised CVD risk (10-year risk of CVD ≥20%, or existing CVD or target organ damage) with persistent BP >140/90 mmHg.

See NICE Clinical Guideline 127[1] and refer to British Hypertension Society guidelines[2] for when to initiate antihypertensives when risk factors (e.g. risk of coronary events, diabetes or end-organ damage) are present.

The six major drug groups used at present are diuretics, β-blockers, ACE inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, and α-blockers. The major objective is to achieve satisfactory control of BP and overall cardiovascular risk. In many patients, this requires a combination of antihypertensive medications to achieve therapeutic targets. Overall, the major drug groups have similar efficacy in ↓ BP in most groups of patients (African patients excluded) with mild to moderate hypertension.

β-blockers are no longer preferred as first-line therapy as, according to a recently published update by NICE (www.nice.org.uk), they raise a patient's risk of developing diabetes.

Target BP

Target BP is <130/85mmHg, but some patients, especially the elderly, might not achieve or tolerate these levels. The achievement of target levels in patients with diabetes mellitus is particularly important.

The optimal outcome is to attain target levels of BP using only one preparation and once-daily dosing. If the initial drug chosen does not achieve target levels, one worthwhile strategy is to consider ↑ the dose or changing to an acceptable substitute until monotherapy is successful or clearly fails. If possible, allow at least 1 month before changing therapy to allow steady-state effects to occur at each dose level. Alternatively, use an appropriate drug in combination.

Further reading

NICE (2006). *Clinical Guideline CG34. Hypertension: Management of Hypertension in Adults: in Primary Care.* http://guidance.nice.org.uk/CG127

1 NICE (2006). *Clinical Guideline CG34. Hypertension: Management of Hypertension in Adults: in Primary Care.* http://guidance.nice.org.uk/CG127
2 British Hypertension Society: http://www.bhsoc.org

Table 17.2 Guidance on selecting antihypertensive therapy with concomitant disease

Drug	Compelling indications	Possible indications	Compelling contraindications	Possible contraindications
Hypertensive patients aged ≥55 years or Black patients of all ages: first-choice initial therapy should be either a calcium-channel blocker or a thiazide-type diuretic (Black patients—does not include patients of mixed race or Asian patients)				
Low-dose thiazides Thiazide-like drugs	Heart failure Elderly patients Systolic hypertension	Diabetes mellitus	Gout	Dyslipidaemia Symptomatic orthostatic hypertension
Calcium-channel blockers	Angina Elderly patients Systolic hypertension	PVD	Heart block	Congestive heart failure
Hypertensive patients aged <55 years: first-choice initial therapy should be an ACE inhibitor (or an angiotensin reseptor blocker if an ACE inhibitor is not tolerated)				
ACE inhibitor	Heart failure Left ventricular dysfunction Acute myocardial infarct Diabetes mellitus		Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Angiotensin II receptor blockers	ACE inhibitor cough Type 2 diabetes	Heart failure	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	

If initial therapy was with a calcium-channel blocker or thiazide-type diuretic and a second drug is required, add an ACE inhibitor (or an angiotensin receptor blocker if an ACE inhibitor is not tolerated). If initial therapy was with an ACE inhibitor, add a calcium-channel blocker or a thiazide-type diuretic				
Triple therapy: ACE inhibitor, thiazide-type diuretic, calcium-channel blocker				
If a fourth drug is required, one of the following should be considered: • a higher dose of a thiazide-type diuretic or the addition of another diuretic (careful monitoring is recommended) or • β-blockers or • selective α-blockers				
β-blockers	Angina Acute myocardial infarct Tachyarrhythmias Heart failure	Pregnancy Diabetes mellitus	Asthma and COPD Heart block	Dyslipidaemia Athletes and physically active patients PVD
α-blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidaemia	Orthostatic hypotension	

Understanding anticoagulation

After injury, three separate mechanisms are activated to ↓/halt bleeding: vasoconstriction, gap plugging by platelets, and the coagulation cascade. These mechanisms can be activated inappropriately and predispose patients to stroke.

The endothethial surface cells of blood vessels are involved in the balance between clotting and bleeding by secreting compounds such as von Willebrand factor, tissue plasminogen activator (t-PA), and prostaglandins (e.g. prostacyclin). The surface cells are also involved in the balance between fibrinolysis and fibrin formation.

Platelet response

- Adhesion
- Secretion
- Aggregation
- Propagation of procoagulant activity.

Regulation of coagulation and fibrinolysis

The coagulation factors consist of 12 plasma proteins that circulate in their inactive form. Coagulation of blood causes a cascading series of proteolytic reactions that result in an active protease which activates (in an enzymatic way) the next clotting factor until a fibrin clot is formed.

Coagulation factors

- Vitamin-K-dependent factors (II, VII, IX and X).
- Contact activation factors (XI, XII, prekallikrein, and high molecular weight kininogen).
- Thrombin-sensitive factors (V, VIII, XIII and fibrinogen).
- Clotting begins at either an intrinsic or an extrinsic pathway, with activation cascading to the common pathway.
- Tissue injury releases either of the following factors (see Fig. 17.1).
  - Tissue factor (extrinsic to blood), which activates the extrinsic pathway through factor VII.
  - Subendothelial membrane contact with factor XII initiates intrinsic pathway (intrinsic—all necessary coagulation factors are present in blood).

Fibrinolysis

Formation of a fibrin clot occurs as a result of the coagulation system. The fibrinolytic system opposes coagulation, dissolving the developing clot and restoring blood flow. The process starts by the release of t-PA from endothelial cells. In response to thrombin or venous stasis, t-PA is incorporated into the forming clot by binding to fibrin. t-PA converts inactive plasminogen into plasmin, which digests fibrin and dissolves the clot.

Laboratory tests

Bleeding time

Bleeding time measures the length of time to the cessation of bleeding following a standardized skin cut.

Factors that prolong bleeding time include the following:

- thrombocytopenia.
- platelet dysfunction.
- aspirin/NSAIDs.
- SSRIs.

Prothrombin time (PT)

Thromboplastin is added to test the extrinsic system. PT is expressed as a ratio compared with control (INR) and has a normal range or 0.9–1.2. The INR is prolonged by warfarin, vitamin K deficiency, and liver disease.

Thrombin time

Thrombin is added to plasma to convert fibrinogen to fibrin (normal range, 10–15s). The thrombin time is ↑ by heparin therapy, disseminated intravascular coagulation (DIC), and fibrinogen deficiency.

Kaolin cephalin clotting time (KCCT) APTT = PTT (partial thromboplastin time)

Kaolin activates the intrinsic system (normal range, 26–34s). KCCT is prolonged by heparin therapy or haemophilia.

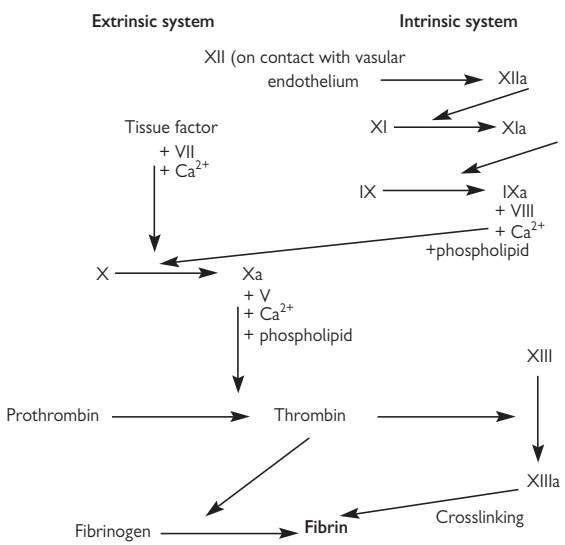

Fig. 17.1 The intrinsic and extrinsic pathways of blood coagulation. Reproduced with permission from Longmore M, Wilkinson IB, and Rajagopalan S (2004). *Oxford Handbook of Clinical Medicine* (6th edn). Oxford: Oxford University Press.

Clinical use of anticoagulants

Prevention of venous thromboembolism (VTE)

VTE is the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a common complication of hospital admission, causing an estimated 25 000 deaths in the UK each year. All patients must be assessed for their risk of VTE on admission to hospital, 24h after admission and again whenever the clinical situation changes. Each risk assessment needs to be documented in the patient's medical notes. The risk of developing VTE during hospitalization, immobilization at home, or in a nursing home depends on factors related to the individual patient and the features of any predisposing medical illness or surgical procedure performed. Patients must also be assessed for their risk of bleeding (Tables 17.3 and 17.4).

Types of thromboprophylaxis

Pharmacological and non-pharmacological methods of prophylaxis are both effective in preventing VTE, and their use in combination is additive.

Pharmacological prophylaxis

- Unfractionated heparin (UFH) was the first pharmacological agent to be used for thromboprophylaxis. Because of its presentation as a high-strength heparin product (25 000units/mL), it is generally reserved for second- or third-line choice for those patients unable to use low molecular weight heparin (LMWH) or fondaparinux.
- LMWH has been shown to be clearly superior to UFH in preventing DVT in patients undergoing orthopaedic surgery and should be used in that situation. Its efficacy in other high- and moderate-risk situations is at least that of UFH, and it is considered a reasonable alternative first-line choice.
- Fondaparinux is a selective anti-Xa inhibitor which, unlike UFH and LMWH, has no antithrombin activity. Fondaparinux is more effective at DVT prevention than LMWH in patients undergoing hip and knee arthroplasty and hip fracture surgery, and is a suitable option for those procedures. Fondaparinux is also a treatment option for many patients who have a history of heparin-induced thrombocytopenia (HIT), although it is not licensed for all patient groups—check product literature.
- Aspirin has only a weak effect in preventing venous thrombosis and should not be considered adequate as sole prophylaxis.
- DVT prophylaxis should continue until the patient is fully ambulant and fit for hospital discharge. In particularly high-risk clinical situations, including hip and knee arthroplasty and oncology surgery, prolonged prophylaxis of 28 days duration should be strongly considered.
- In situations where the slightest risk of local bleeding is unacceptable (e.g. after neurosurgery, ophthalmic surgery, some plastic surgery, head injury, or haemorrhagic stroke), anticoagulant therapy should be avoided and mechanical preventive methods should be used.

Table 17.3 Risk factors for VTE

Medical patients	Surgical patients and patients with trauma
• If mobility significantly reduced for ˜3 days **or** • If expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor	• If total anaesthetic + surgical time >90 min **or** • If surgery involves pelvis or lower limb and total anaesthetic + surgical time >60min **or** • If acute surgical admission with inflammatory or intra-abdominal condition **or** • If expected to have significant reduction in mobility **or** • If any VTE risk factor present

VTE risk factors

- Active cancer or cancer treatment
- Age >60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI >30kg/m^2)
- One or more significant medical comorbidities (e.g. heart disease, metabolic, endocrine, or respiratory pathologies, acute infectious diseases, inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of HRT
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

Table 17.4 Risk factors for bleeding

All patients who have any of the following

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2.0)
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4h or expected within the next 12h
- Acute stroke
- Thrombocytopenia (platelets <75 x 10^9/L)
- Uncontrolled systolic hypertension (˜230/120mmHg)
- Untreated inherited bleeding disorders (such as haemophilia or von Willebrand's disease)
- Neurosurgery, spinal surgery, or eye surgery
- Other procedures with high bleeding risk

Mechanical prophylaxis

Methods of mechanical prophylaxis include graduated compression stockings providing 16–20mmHg pressure at the ankle, sequential pneumatic compression devices, and pneumatic foot compression. These should be applied the evening before surgery and continued until the patient is fully ambulant.

Prophylaxis treatment

The type of prophylaxis recommended depends on the patient's risk category. However, in all patients it is advisable to avoid dehydration and to commence mobilization as soon as possible.

Effective regimens for prophylaxis include the following.

- UFH 5000units SC every 8–12h.
- Enoxaparin 40mg or dalteparin 5000units SC daily, or other LMWH (commencing ≥6h postoperatively in surgical patients) for high- and moderate-risk surgical and medical patients.
- Enoxaparin 20mg or dalteparin 2500units SC daily, commencing ≥6h postoperatively, for low-risk surgical patients (or for patients with a very low body weight or if significant renal impairment is present).
- Fondaparinux 2.5mg SC daily (commencing ≥6h postoperatively in surgical patients).

Treatment of acute DVT

The aim of treatment for established venous thrombosis is to prevent thrombus extension, pulmonary embolism, the post-thrombotic syndrome and recurrent VTE. The type of therapy employed depends on the anatomical extent of the thrombus (Table 17.5).

Anticoagulation

Before anticoagulant therapy is instituted, blood should be collected for determination of APTT, PT, and platelet count. A thrombophilia screen should be considered if there is a family history of VTE, recurrent VTE, and possibly if there is spontaneous VTE. This should include activated protein C resistance, fasting plasma homocysteine, prothrombin, protein C, protein S, antithrombin III, lupus anticoagulant, blood count, and anticardiolipin antibody tests. More specialized testing is occasionally indicated.

LMWH has been shown to be at least as effective and safe as an IV UFH infusion in the initial management of DVT. LMWH has the advantages of not requiring routine laboratory monitoring and enabling management in a hospital out-patient or general practice setting in selected cases, and is now the treatment of choice.

Any of the following regimens are recommended:

- Enoxaparin 1.5mg/kg body weight SC daily (up to a maximum dose of 150mg daily).
- Dalteparin once-daily dose graduated to weight (see *BNF*) or 100units/kg body weight SC twice daily (for patients at higher risk of bleeding or obese patients).
- Tinzaparin 175units/kg body weight SC daily.

- In the presence of renal impairment LMWH requires factor Xa monitoring and possible dose adjustment (calculated creatinine clearance ≤30mL/min).
  - Oral anticoagulation can be commenced as soon as the diagnosis is confirmed.
  - A normal loading dose of warfarin is 15–30mg, divided between 3 days (it is vital to follow local protocol as determination of the first INR will differ for different loading regimes).
- The INR should be monitored daily and the dose adjusted according to the INR until a therapeutic level is achieved. The initial dose of warfarin should be ↓ in the elderly.
- LMWH should be given for a minimum of 5 days or until the INR has been >2 on two consecutive days, whichever is the longer.
- An infusion of UFH or treatment-dose fondaparinux are suitable alternatives for patients who cannot be treated with LMWH.
- Warfarin should not be commenced alone (i.e. without a LMWH) because this is associated with a high rate of DVT recurrence.
- The duration of anticoagulation depends on the risk of both recurrent VTE and bleeding.
- Graduated compression stockings ↓ the incidence and severity of the post-thrombotic syndrome and should be used in all cases. Stockings should provide 30–40mmHg pressure at the ankle and extend to the level of the knee. Graduated compression stockings should be worn for 18 months and indefinitely if the post-thrombotic syndrome is present. This important therapy is often overlooked. Patients should be encouraged to mobilize as soon as possible.

Table 17.5 Overview of the treatment of deep vein thrombosis

Extent of DVT	Therapy
Proximal veins (the popliteal or more proximal veins	Anticoagulation and graduated compression stockings
Distal veins	Anticoagulation or ultrasound surveillance programme and graduated compression stockings

Warfarin dosing

Loading dose

A normal loading dose of warfarin is 15–30mg, divided over 3 days—see Table 17.6 for a suggested loading regime. The individual response is unpredictable and factors that particularly influence first doses should be considered.

- Age and weight—consider ↓ loading dose if patient >60 years old or weight <60kg.
- Pathophysiological changes—consider ↓ loading dose in the following conditions:
  - liver disease
  - cardiac failure
  - nutritional deficiency.
- Drug interactions—check *BNF* (Appendix 1). Remember over-the-counter medicines and complementary therapies.

Maintenance dose

The response to the loading dose can be used to predict the maintenance dose. Aim for an INR of 2–4, depending on the indication (Table 17.7). If the loading regime has been followed and INRs are determined at the correct intervals, the dose for Day 4 in Table 17.6 is a good predictor of maintenance dose in the majority of patients. For those patients who are particularly sensitive or resistant to the effects of warfarin, your local anticoagulation service can be contacted for advice.

Monitoring therapy

It is important to take account of trends rather than single results. If a patient has an unusual individual result, consider whether recent changes in behaviour (e.g. diet, alcohol consumption) could have affected it. If so, these changes should be 'corrected' rather than correcting the warfarin dose.

Factors that can affect response to warfarin include the following.

- Compliance—including timing of dose.
- Changes in kinetic parameters—e.g. weight change and fluid balance.
- Diseases—e.g. infection, congestive cardiac failure, malabsorption, liver disease, renal impairment, and GI disturbances.
- Changes in social behaviour—e.g. smoking and, alcohol.
- Diet (green vegetables contain significant amounts of vitamin K).
- Stress.
- Drug interactions—consult *BNF* (Appendix 1) or Stockley.[1]

1 Baxter K (ed) (2010). *Stockley's Drug Interactions* (9th edn). London: Pharmaceutical Press.

Table 17.6 Suggested loading regime for warfarin

Days 1 and 2	Day 3		Day4	
	INR	Dose (mg)	INR	Dose
Give 5mg each evening if baseline INR is ≤1.3 (PT <17s)	<1.5	10	<1.6	10
	1.5–2.0	5	1.6–1.7	7
	2.1–2.5	3	1.8–1.9	6
	2.6–3.0	1	2.0–2.3	5
	>3.0	0	2.4–2.7	4
			2.8–3.0	3
			3.1–3.5	2
			3.6–4.0	1
			>4.0	0

Table 17.7 INR targets and durations for anticoagulant therapy

Indication	Target INR (range)	Duration
Antiphospholipid syndrome syndrome (arterial thrombosis)	3.5 (3.0–4.0)	Consider long term
Antiphospholipid syndrome (venous thrombosis)	2.5 (2.0–3.0)	Consider long term
Arterial thromboembolism	3.5 (3.0–4.0)	Discuss with haematologist
AF	2.5 (2.0–3.0)	Long term
Calf DVT	2.5 (2.0–3.0)	3 months
Cardiomyopathy	2.5 (2.0–3.0)	Long term
Cardioversion	2.5 (2.0–3.0)	3 weeks before and 4 weeks after
Mechanical prosthetic heart valve (MHV)	3.5 (3.0–4.0)	Long term
Mural thrombosis	2.5 (2.0–3.0)	3 months
Proximal DVT	2.5 (2.0–3.0)	6 months
Pulmonary embolus	2.5 (2.0–3.0)	6 months
Recurrence of VTE (if no longer on oral anticoagulants)	2.5 (2.0–3.0)	Consider long term
Recurrence of VTE (while on oral anticoagulants)	3.5 (3.0–4.0)	Consider long term

Counselling patients treated with warfarin

After the decision had been made to initiate anticoagulation therapy, the ward pharmacist should counsel the patient about the risks associated with warfarin.

Counselling

All patients, whether initiated within the hospital setting or in the community should ideally be given written information on anticoagulants. The following points should be covered.

- Dose—how much, how often, and how long?
- The colour of tablets corresponds to strength. (Imperative to check the patient's understanding on how to work out which tablet(s) to take to allow for the correct dose. This can be done by getting them to explain what they would take for a selection of doses.)
- Missed doses—what to do?
- Importance of compliance.
- How warfarin works—might need to be simplistic for certain patients (i.e. makes the blood take longer than usual to clot; ↓ the risk of clot extending).
- Need for blood tests.
- Importance of telling or reminding healthcare professionals (dentist, community pharmacist, and practice nurse) about their warfarin treatment.
- Signs of overdose/underdose and what to do.
- Recognition of drug interactions, including over-the-counter medicines and herbal preparations.
- Alcohol and diet.
- Pregnancy (if appropriate).
- Record detail of dose and INR result.
- Follow-up and duration of therapy, including arrangements for further monitoring (e.g. need to attend GP practice or out-patient clinic).

Patients should be informed that the dose of warfarin might need to be changed from time to time, and that monitoring their blood is necessary for as long as the therapy is administered. The therapeutic range is narrow and varies according to the indication. It is measured as the ratio to the standard PT.

Each patient should have an explanation of intended duration of therapy, indication for therapy, concurrent medical problems, other medication that must be continued, and target coagulation laboratory values for the patient's condition. This information also needs to be communicated to the patient's primary care team.

Thereafter, there should be a mechanism to ensure that the patient's therapy is monitored in terms of efficacy and risk during the duration of anticoagulation therapy.

Ideally, discharged patients should be reviewed within 48h of discharge (for new patients), but certainly no later than 1wk (new AF patients or existing stable patients). Each condition requires a specific range of

INR values. Therefore adjusting the oral anticoagulant loading dose and maintenance doses is very necessary. Some patients could be particularly sensitive to warfarin–e.g. the elderly, those with high-risk factors, such as liver disease, heart failure, or diabetes mellitus, those who regularly consume alcohol, those on drug therapy that is known to ↑ or ↓ the effect of oral anticoagulation, and those with poor compliance. Knowledge of concomitant medical problems and medication is essential for the safe management of anticoagulation.

Reversing the effects of warfarin (or other vitamin K antagonists)

Because of the unpredictable nature of warfarin dosing, or when an anticoagulated patient needs to go for an invasive procedure, it may be necessary to reverse the anticoagulant effects of warfarin.

Reversal of over-anticoagulation

In all cases of over anticoagulation proceed as follows.

- Identify the precipitating cause.
- Establish whether it is temporary (e.g. other medications) or permanent (e.g. liver failure).
- Review the need for ongoing anticoagulation.
- If the patient is to continue with anticoagulation therapy, the degree of reversal must be decided. For example, patients with metallic heart valves will need to continue their anticoagulation after the event, so complete reversal may not be indicated (except in the case of severe bleeding).

The risk of bleeding on warfarin increases significantly when the INR is ≥5.0. Therapeutic decisions regarding reversal depend on the INR level and the degree of bleeding.

Major/life-threatening bleeding requiring immediate/complete reversal

This relates to patients with intracranial or rapid-onset neurological signs, intra-ocular (not conjunctival) bleeds, compartment syndrome, pericardial bleeds, or active bleeding and shock. These patients need urgent assessment of clotting.

Patients on warfarin may be haemorrhagic for reasons other than the effect of the anticoagulant, such as DIC or factor VIII inhibitor. An urgent full blood count should be requested as well as APTT and INR.

- Stop warfarin and reverse anticoagulation with prothrombin complex concentrate (PCC) *and* IV phytomenadione (vitamin K)
- Anticoagulation can be effectively reversed with approximately 50units/kg of PCC (maximum 3000units) *and* 5–10mg phytomenadione
- As soon as PCC has been given, another clotting screen should be performed to assess the degree of correction of INR. If not corrected, advice should be sought from a haematologist
- All patients with bleeding should be evaluated to see if there is a local anatomical reason for bleeding.

Minor bleeding

INR ≥5.0

- Omit warfarin.
- Give IV phytomenadione 0.5-1mg (or 5–10mg if anticoagulation is to be stopped).

INR <5.0

- A clinical decision needs to be made as to whether lowering the INR is required. If this is the case, consider giving IV phytomenadione 0.5–1mg and modifying the warfarin dose.

No bleeding

INR 5.0–7.9

- Omit warfarin.
- Restart at a lower dose when INR <5.0.

INR 8.0–12.0

- Omit warfarin.
- Give 1–5mg oral phytomenadione.

INR >12.0

- Omit warfarin.
- Give 5mg oral phytomenadione.

Product details

Phytomenadione

- For administration guidelines, see local or national injectables monographs.
- Oral phytomenadione will work within 16–24h of administration; IV phytomenadione will work within 6–8h.

Prothrombin complex concentrate

- Examples of PCCs are Beriplex® and Octaplex®.
- PCCs are derived from human plasma which has been virally inactivated, and they contain coagulation factors II, VII, IX and X.
- The dose should be rounded to the nearest complete vial.
- Doses stated are based on factor IX content.
- Administration of PCC more rapidly than is stated in the product literature is a clinical decision based on risk versus benefit.

Safe medication practice

- Fresh frozen plasma (FFP) is not recommended for warfarin reversal. In non-urgent situations, phytomenadione is sufficient, and in urgent situations PCC is more effective
- Anticoagulated patients should not be given IM injections
- Oral phytomenadione should generally be measured in multiples of 1mg so that doses can be accurately measured using the oral syringes provided with the licensed preparation
- The effects of PCC will wear off relatively quickly, so IV phytomenadione must be given as well if the reversal is to be sustained.

Out-patient anticoagulation clinics

Anticoagulation management is a good example of an area in which patient care is undertaken by a multidisciplinary team of physicians, nurses, and pharmacists. Although warfarin is an effective anticoagulant, its use is complicated in clinical practice by its narrow therapeutic index, with a relatively small margin between safety and toxicity, dietary fluctuations in vitamin K, the effects of certain disease states, and physiological, genetic, and patient-specific factors (e.g. compliance with therapy).

The major implications of long-term therapy with anticoagulants are a tendency to bleeding, haemorrhage, and other factors, such as interaction between warfarin and other drugs, which make it difficult to maintain anticoagulant control in the therapeutic range.

The anticoagulation clinic provides ongoing monitoring of the INR and continual recommendations for warfarin dose adjustment, including management of drug interactions involving warfarin and out-of-range INRs. The goal is to provide follow-up and dose adjustment adequate to maintain the INR within designated therapeutic ranges specific to the conditions for which the anticoagulation is indicated.

Hospital-based clinics

Oral anticoagulation monitoring has traditionally taken place in secondary care because of the need for laboratory testing. The need for frequent monitoring and close patient follow-up introduced the need for coordinated warfarin management by means of an organized system of clinical follow-up. Anticoagulation clinics have historically fulfilled this role. The patients attend the hospital for venepuncture; blood is then sent to the laboratory for testing. The pharmacist, doctor, or nurse is informed of the results and can then discuss dosage adjustment and arrange a further appointment for blood test and review. The healthcare professional also discusses whether any changes in the patient's diet or recent change in alcohol consumption, for example, might have been the reason for the INR being outside the patient's therapeutic range.

GP-surgery-based clinics

The development of reliable near-patient testing systems for INR estimation has facilitated the ability to manage patients within primary care. With the introduction of finger-prick testing services, there is no longer a reliance on the hospital pathology laboratory for INR measurement. The GP discusses compliance with patients and recommends dose and the follow-up date for INR recheck.

Outreach DVT service

In some cases, coordination between primary and secondary care is established. Patients attend their local surgery for blood sampling, the samples for laboratory analysis are collected, and subsequent dosing and patient management are undertaken within the secondary-care anti-coagulation clinic.

Domiciliary service

This service is only suitable for patients who are on the telephone and whose anticoagulation is reasonably well controlled. The patient's GP sends a district nurse to the patient's home to collect blood samples.

Future of services

- The emergence of novel anticoagulant therapies might have dramatic implications not only for patient management, but also for anti-coagulation clinics. Oral direct thrombin inhibitors (DTIs) and direct factor Xa inhibitors show promise as future agents to improve the field of oral anticoagulation management.
- Dabigatran (oral DTI) and rivaroxaban (oral direct factor Xa inhibitor) are in the most advanced phases of clinical development.
- Both of the aforementioned newer agents are currently licensed for thromboprophylaxis post elective hip or knee arthroplasty, and both are seeking marketing authorization for many other indications including stroke prevention in AF and secondary prevention of VTE following standard treatment.
- In theory, both agents have several advantages over warfarin. They have a wider therapeutic index, a predictable dose–response profile (i.e. they do not require dosing adjustments and monitoring), they are not metabolized through known hepatic microsomal enzymes and they seem to lack CYP450-related drug and food interactions. These advantages make them easier and more convenient to administer than warfarin therapy.
- The introduction of the newer agents could lead to a significant drop in the volume of warfarin patients referred to anticoagulation clinics for monitoring. However, because they are relatively expensive compared with warfarin (including the costs associated with ongoing monitoring of warfarin therapy) and clinicians have limited clinical experience of its use (especially with respect to bleeding complications), anticoagulation services will remain a necessary service for the foreseeable future.

Further reading

NICE (2010) Clinical Guideline CG92. Venous Thromboembolism—Reducing the Risk. http://guidance.nice.org.uk/CG92/NICEGuidance/pdf/English.

National Patient Safety Agency (2007). *Safety Alert 18. Actions That Can Make Anticoagulation Therapy Safer*. London: NPSA.

Baglin TP *et al.* (2006). Guidelines on oral anticoagulation (warfarin): third edition – 2005 update. *British Journal of Haematology* **132**: 277–85.

Baglin TP *et al.* (2006). Guidelines on the use and monitoring of heparin. *British Journal of Haematology* **133**: 19–34.

BJH Guideline on Treatment of VTE (due late 2010).

NICE Guidelines on Treatment of VTE (due late 2011/early 2012).

Acute coronary syndrome

- These syndromes are attributable to myocardial ischaemia secondary to coronary obstruction. The syndromes cover a spectrum of conditions ranging from unstable angina to STEMI.
- Unstable angina is a syndrome of chest pain caused by myocardial ischaemia; MI is heart muscle damage caused by prolonged ischaemia. The two conditions share the same pathophysiology, similar symptoms, and the same early management.
- The syndrome depends on the extent of thrombosis, distal platelet and thrombus embolization, and resultant myocardial necrosis.
- The acute coronary syndromes are differentiated according to the extent and duration of chest pain, electrocardiogram (ECG) changes, and biochemical markers.
- Acute coronary syndromes are differentiated into syndromes associated with the following.
  - ST-segment elevation on the ECG (ST-segment elevation MI (STEMI))
  - Without ST-segment elevation (non-ST-segment elevation MI (NSTEMI)), which is associated with ST-segment depression, T-wave inversion, or no changes on the ECG.
- NSTEMI is differentiated from unstable angina by biochemical evidence of myocardial necrosis. The diagnosis of myocardial necrosis is indicated by an ↑ troponin I level. Troponin I is detectible in serum 3–6h after an MI (peaks at 12–24h; elevated for 14 days). If troponin is normal >6h after the onset of pain and the ECG is normal, the risk of MI is small.
- Unstable angina and NSTEMI represent a continuum, and their management is similar.
- Patients presenting with pain at rest or severe exacerbation of stable angina are differentiated into high, low, or intermediate risk, depending on various factors.
- Patients with unstable angina are classified according to the highest-risk category of which they exhibit at least one feature.
- High-risk features.
  - Prolonged (>10min) ongoing chest pain/discomfort.
  - ST-segment elevation or depression (>0.5mm) or deep T-wave inversion in three or more ECG leads.
  - ↑ serum markers of myocardial injury (especially cardiac troponin I or T) (Fig. 17.2).
  - Diabetes mellitus.
  - Associated syncope.
  - Associated heart failure, mitral regurgitation, or gallop rhythm.
  - Associated haemodynamic instability (SBP <90mmHg, cool peripheries, and diaphoresis).
- Intermediate-risk features.
  - Prolonged, but resolved, chest pain/discomfort.
  - Nocturnal pain.
  - Age >65 years.
  - History of MI or revascularization.

  - ECG normal or pathological Q-waves.
  - No significant (<0.5mm) ST-segment deviation, or minor T-wave inversion in <3 ECG leads.
- Low-risk features.
  - ↑ angina frequency or severity.
  - Angina provoked at a lower threshold.
  - New-onset angina >2 weeks before presentation.
  - Normal ECG and negative serum troponin.
  - No high-risk or intermediate-risk features.

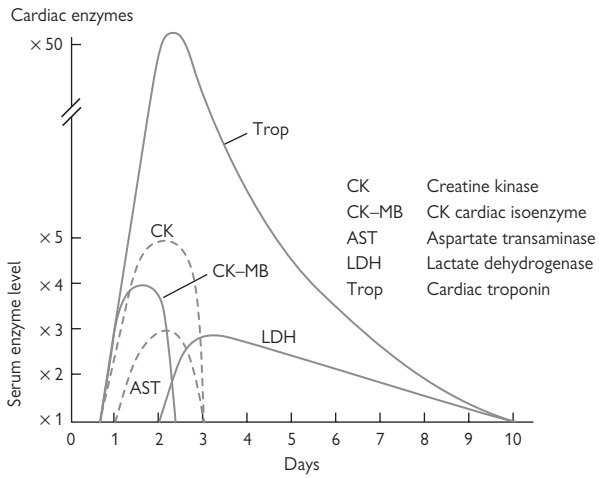

Fig. 17.2 Enzyme changes following acute MI. Reproduced with permission from Longmore M, Wilkinson IB, Rajagopalan S (2004). *Oxford Handbook of Clinical Medicine*, 6th edn. Oxford: Oxford University Press.

ST-segment elevation myocardial infarction (STEMI)

- If the thrombus that occurs on a ruptured plaque completely occludes the coronary artery so that there is no flow beyond it, the result is severe transmural myocardial ischaemia with ST-segment elevation on the ECG.
- This can cause sudden death from ventricular fibrillation.
- If the coronary occlusion is not relieved, MI develops progressively over the next 6–12h.
- The aim of emergency treatment of STEMI is as follows:
  - prevent and treat cardiac arrest
  - relieve pain
  - reperfuse the myocardium urgently to minimize infarct size.
- In STEMI it is important to reopen the artery and re-establish flow as soon as possible. This can be achieved by the administration of thrombolytic therapy or primary percutaneous coronary intervention (PCI).
- Thrombolytic therapy consists of a combination of a fibrinolytic agent, an antiplatelet agent, and antithrombin therapy.
- Reperfusion therapy should be delivered as soon as feasible. Current standards indicate that if thrombolytic therapy is chosen, it should be given within 30min of arrival in hospital.
- If primary PCI is the selected therapy, the aim should be to have the artery reopened within 60min of arrival at hospital.
- Early risk assessment allows categorization in terms of prognosis and choice of treatment. Initial indicators of high risk are ECG evidence of a large infarct, clinical and radiographic evidence of circulatory congestion, hypotension and shock, and serious arrhythmias.

STEMI: prehospital management

- The patient should be advised to call the ambulance directly, rest until it arrives, and immediately take aspirin 300mg (chewed or dissolved before swallowing), if available.
- The patient should also be advised to take a short-acting nitrate, if available.
  - GTN spray 400micrograms sublingually. Repeat after 5min if pain persists (up to a maximum of two metered doses).
  - GTN tablet 500micrograms sublingually. Repeat every 3–5min (up to a maximum dose of 1500micrograms, three tablets).
  - administer supplemental oxygen.
- If a doctor is present, add the following for pain relief, if required.
  - Morphine 2.5–5mg IV. Repeat as necessary.

STEMI: immediate and early hospital management

- An ECG should be performed immediately. If on the basis of clinical assessment and ECG, a diagnosis or presumptive diagnosis of STEMI can be made, give the following treatment.
  - Aspirin 300mg chewed or dissolved before swallowing (if aspirin has not been given) plus O_2 therapy.
- Patients known to have severe obstructive airway disease could underventilate with O_2 therapy and retain CO_2, becoming drowsy.
- For chest pain, use the following treatment:
  - GTN 500micrograms sublingually. Repeat after 5min if pain persists, provided that SBP >95mmHg.
- For persisting chest pain, add the following treatment.
  - Morphine 2.5–5mg IV (repeat as necessary) plus reperfusion therapy.

STEMI: reperfusion therapy

Patient selection for reperfusion therapy

Reperfusion therapy is indicated in the following circumstances.

- Ischaemic/infarction symptoms >20min. This includes not only chest pain, but also other symptoms of MI such as chest discomfort or pressure, shortness of breath, pulmonary oedema, sweating, dizziness, and light-headedness.
- Patient's symptoms commenced within 12h.
- ST-segement elevation or left bundle branch block on the ECG.
- No contraindications to reperfusion therapy.

Percutaneous coronary intervention (PCI)

PCI is the therapy of choice if it is available in a timely manner. Adjuvant therapy for PCI includes aspirin/clopidogrel and heparin. Some patients need a glycoprotein IIb/IIIa inhibitor. The timing of delivery of the agents is determined by the individual interventionalist.

Fibrinolytic therapy

Fibrinolytic therapy is indicated in the following situation: prolonged ischaemic chest pain that has begun within the previous 12h in the presence of significant ST-segment elevation or left bundle branch block (presumed new).

The decision whether or not to give fibrinolysis requires analysis of risk versus benefit. Patients likely to gain most benefit from fibrinolytic therapy present early with large MI, usually anterior, especially if there is any evidence of heart failure. Those with small MI, often inferior, benefit less. After 24h, the chances of benefit are very small and there is ↑ risk of cardiac rupture.

Contraindications to fibrinolytic therapy can be absolute or relative.

Absolute contraindications

- Risk of bleeding:
  - active bleeding
  - recent (<1 month) major surgery or trauma.

- Risk of intracranial haemorrhage:
  - any history of haemorrhagic stroke or history: ischaemic stroke within the past 2–6 months
  - anatomical abnormalities, intracerebral neoplasms, and arteriovenous malformation.

Relative contraindications

- Risk of bleeding:
  - previous use of anticoagulants or INR >2.0
  - non-compressible vascular punctures
  - prolonged cardiopulmonary resuscitation (>10min)
- Risk of intracranial haemorrhage:
  - previous stroke at any time
  - previous transient ischaemic attack (TIA).
- Other:
  - pregnancy
  - severe hypertension that cannot be controlled (>180mmHg SBP and/or >110mmHg DBP).

Patients with absolute contraindications should be transferred for a PCI. With relative contraindication, the risks and benefits of treatment must be weighed up.

Use one of the following thrombolytic agents.

- Alteplase 15mg bolus IV, followed by an IV infusion of 0.75mg/kg body weight over a period of 30min (up to a maximum of 50mg); then 0.5mg/kg body weight over a period of 60min up to 35mg (the total dose should not exceed 100mg).
- Reteplase 10IU bolus IV, followed by 10IU 30min later.
- Streptokinase 1.5 million IU by IV infusion over a period of 20–30min. If SBP <80mmHg, the infusion rate should be halved. If SBP <70mmHg, stop the infusion until BP >70mmHg and then restart at half the previous rate.
- Tenecteplase 500micrograms/kg body weight over a period of 30s (up to a maximum dose of 50 mg).

The plasminogen activators alteplase, reteplase, and tenecteplase are superior to streptokinase but considerably more expensive. Thus streptokinase is the drug of choice. Because antibodies are produced against streptokinase, there is ↑ risk of allergic reactions if the patient is re-treated within 1 year. Prolonged exposure of antibodies to streptokinase can ↓ the effectiveness of subsequent treatment, and streptokinase should not be used again beyond 4 days of the first administration.

The bolus agents reteplase (double bolus) and tenecteplase (single bolus) have major advantages in terms of convenience and can be used in the pre-hospital setting, usually by suitably trained paramedic staff.

Recurrence of chest pain with ST-segment elevation is evidence of re-occlusion, and therefore further thombolysis or urgent angioplasty might be indicated. Hypotension can occur, particularly with streptokinase, and should be treated by raising the foot of the bed and adjusting the infusion rate.

Allergic reactions are common with streptokinase and include bronchospasm, periorbital swelling, angio-oedema, urticaria, itching, flushing, nausea, headache, and musculoskeletal pain. Delayed hypersensitivity reactions, such as vasculitis and interstitial nephritis, have also been observed. Anaphylactic shock is rare.

For mild or moderate allergic reactions and fever, use promethazine 25mg IV and/or hydrocortisone 100mg IV. For severe allergic reactions, immediately discontinue streptokinase and give adrenaline 1:10 000 solution, 1mL IV, over a period of 5min.

Antithrombin therapy

- There is still debate about the use of IV heparin with streptokinase.
- However, there seems to be a small, but significant, benefit. IV UFH is usually given routinely in conjunction with alteplase, reteplase, or tenecteplase. Use UFH 60IU/kg body weight initially (up to a maximum of 4000IU), followed by 12IU/kg body weight adjusted according to the APTT.
- The initial APTT should be taken in 3h and adjusted according to local protocol.
- LMWH has been used in conjunction with fibrinolytic agents. It seems to ↓ reinfarction, but at the cost of ↑ bleeding. It is currently under-going assessment in a large clinical trial. LMWH is not formally approved for use in combination with fibrinolytic agents. Particular care is needed in patients >75 years old; excess bleeding, including intra-cranial haemorrhage, has been reported.
- Occasionally, bleeding can occur following treatment with fibrinolytic therapy and heparin. Intracranial haemorrhages are devastating and life-threatening. Systemic bleeding and GI bleeding can occur, in which case the following treatments are advised:
  - Reverse heparin with protamine. Protamine dosage depends on the level of anticoagulation. Use 1mg of protamine for every 100IU of UFH or 1mg of protamine sulphate for every 100IU (anti-Xa) of dalteparin. The usual maximum dose is 50mg given by slow IV injection (rate not exceeding 5mg/min).
  - Replace fibrinogen using cryoprecipitate (two bags) or fresh frozen plasma (as required).
  - Give blood, as necessary.

Other therapy

- An IV β-blocker should be considered for patients with persistent pain and tachycardia that is not related to heart failure, those with hypertension, and those with a large MI:
  - atenolol 5–10mg IV infusion at a rate of 1mg/min or metoprolol 5–15mg IV infusion at a rate of 1–2mg/min.
- Titrate doses to the maximum dose of the recommended range, provided that SBP does not fall below 95mmHg and heart rate does not fall below 55bpm.
- β-blockers are contraindicated in patients with a significant history of bronchospasm or symptomatic bradycardia.

- The routine use of magnesium in the management of patients with acute MI is not recommended. Electrolyte abnormalities should be corrected appropriately.

Subsequent management of STEMI

On the basis of the probable contribution to clinical decision-making, further investigation should be considered. Many patients will undergo coronary angiography. Provided that there are no contraindications, continue with following treatment regimen:

- aspirin 75–300mg oral daily or (if intolerant of aspirin) clopidogrel 75mg oral daily.

β-*blocker therapy*

- β-blockers offer prognostic benefit following MI, especially in high-risk patients such as those with significant left ventricular dysfunction and/or ongoing ischaemia, and should be commenced during hospital admission unless contraindicated. Any of the following regimens is recommended:
  - atenolol 25–100mg oral daily
  - metoprolol 25–100mg oral twice daily
  - timolol 5–10mg twice daily
  - propranolol 40–80mg four times daily.
- Titrate doses to the maximum dose in the recommended range, provided that SBP does not fall below 95mmHg and heart rate does not fall below 55bpm.
- The benefit of β-blocker therapy persists long term, and it should be continued indefinitely in high-risk patients.
- The usual contraindications to the use of β-blockers apply. Patients with significant left ventricular dysfunction should be observed closely for the development of congestive heart failure.

ACE inhibitor therapy

- ACE inhibitors improve outcome after acute MI. Start ACE inhibitor therapy within 24–48h of acute MI in patients with previous MI, diabetes mellitus, hypertension, anterior location of infarct on ECG, elevated heart rate (>80bpm), and clinical or radiographic evidence of left ventricular failure or significant dysfunction (ejection fraction <45%).
- ACE inhibitors should be continued long term in patients with a low ejection fraction.
- Contraindications to early ACE inhibitor use include haemodynamic instability and hypotension (SBP <100mmHg). Complications of early ACE inhibitor therapy include persistent hypotension and renal dysfunction.

- BP should be closely monitored, and renal function and plasma electrolytes should be monitored on alternate days while the patient is in hospital. If the maintenance dose has not been achieved at discharge, the dose must be ↑ more slowly as an out-patient (e.g. weekly), with renal function and plasma electrolytes determined before each increase in dose.
- Angiotensin II receptor antagonists should be reserved (for this indication) for patients who develop a persistent cough with ACE inhibitor therapy.

Statin therapy

Statin therapy reduces premature death, MI, and other adverse outcomes, such as stroke and revascularization post-MI. Statin therapy should be continued, or initiated, during hospital admission, no matter what the underlying cholesterol level.

Calcium-channel blocker therapy

The use of calcium-channel blockers should be reserved for patients who have post-MI angina and a contraindication to a β-blocker.

Drug treatment in acute coronary syndromes

Drug treatment of high-risk unstable angina/NSTEMI

- Initial therapy for high-risk patients is hospitalization, with subsequent ECG monitoring and platelet inhibition, antithrombin therapy, use of a β-blocker and, potentially, glycoprotein IIb/IIIa inhibitors, and revascularization.
- For pain relief in patients requiring hospital admission, give GTN 10micrograms/min by IV infusion; ↑ by 10micrograms/min every 3min until pain is controlled provided that SBP >95mmHg (dose range for GTN is 10–200micrograms/min).
- Normally, IV GTN is required for only a short period; prolonged infusion rapidly induces tolerance.
- For patients in whom there is a contraindication to β-blockers, a non-dihydropyridine calcium-channel blocker can be substituted. For example, use one of the following regimens:
  - diltiazem 30–120mg oral, three times daily
  - diltiazem controlled release 180–360mg oral, daily
  - verapamil 40–120mg oral, twice to three times daily
  - verapamil sustained release 160–480mg oral, daily.
- For patients in whom angina has not been controlled with a β-blocker alone, a dihydropyridine calcium-channel blocker can be added—e.g. nifedipine sustained release or amlodipine.
- When the pain is nocturnal, long-acting nitrates might best be given at night rather than during the day.
- Isosorbide mononitrate 20–120mg oral, daily in divided doses.
- Avoid nitrates if the patient has used sildenafil (Viagra®) in the previous 24h or tadalafil (Cialis®) in the previous 5 days.
- Pain nearly always settles promptly.
- After initial assessment and management, patients gradually return to the same risk as patients with stable angina.
- Patients who have undergone revascularization procedures involving a coronary stent must be on aspirin and clopidogrel for at least 1 month, and for those receiving drug-eluting stents, this should be for a minimum of 3 months.

Platelet inhibition

Aspirin 75–300mg oral, daily, and clopidogrel 75mg oral, daily (initial loading dose of 300mg).

Antithrombin therapy

- UFH or LMWH should be given in addition to aspirin. One of the following regimens is advised.
  - enoxaparin 1mg/kg body weight SC, twice daily
  - dalteparin, 120units/kg body weight SC, twice daily (up to a maximum of 10 000units).
  - UFH 5000units bolus IV, followed by 1000units/h by IV infusion and then dose adjustment according to the APTT.

- UFH or LMWH should be administered for a minimum of 3days and possibly longer, depending on the clinical response.
- The advantages of LMWH are that it can be given subcutaneously and it has a more predictable effect, so constant monitoring is not required. However, the fact that its effect cannot easily be reversed is a disadvantage for the high-risk patient who might require urgent intervention. Care should be taken in the elderly and in those with impaired renal function, in whom the dose should be decreased in accordance with the drug's SPC or with renal dosing guidelines.
- For patients on IV UFH, the APTT should be checked initially every 6h, with a target range of 60–80s, and should be checked daily after therapy has been stabilized.

β-blocker

- All patients without contraindications to β-blockade should be commenced on a β-blocker. Either of the following regimens is recommended:
  - atenolol 25–100mg oral, once daily
  - metoprolol 25–100mg oral, twice daily.

Glycoprotein IIb/IIIa inhibitors

These agents prevent the binding of fibrinogen, thereby blocking platelet aggregation.

- Some glycoprotein IIb/IIIa inhibitors are beneficial in ↓ MI and death in patients with NSTEMI or high-risk unstable angina. They are of particular benefit in patients who have an elevated troponin level and/or who are undergoing PCI. They are recommended for patients who are at high risk and have abnormal ECGs or a positive troponin test.
- Treatment with glycoprotein IIb/IIIa inhibitors occurs in two different clinical situations.
  - Patients might be treated in the coronary care unit (with tirofiban only) for a number of hours (up to 9h) before undergoing investigation and PCI, if appropriate.
  - Patients might be treated (with abciximab only) at the time of the procedure.

Tirofiban (non-peptide antagonist of glycoprotein IIb/IIIc receptors)

- Approved for use in combination with heparin for patients with unstable angina who are being treated medically and for those undergoing PCI.
- When administered IV, more than 90% of platelet aggregation is inhibited.
- A loading dose of tirofiban 400ng/kg body weight/min is administered over 30min, followed by a maintenance infusion of 100ng/kg body weight/min for up to 108h.

Abciximab (chimeric human–murine monoclonal antibody)

- Approved for use in elective/urgent/emergent PCI.
- Binds to receptor with high affinity and reduces platelet aggregation by 80%. Persists for up to 48h after end of infusion.
- Loading dose of abciximab 250micrograms/kg body weight bolus before the intervention, followed by a maintenance infusion dose of 125ng/kg body weight/min (up to a maximum of 10micrograms/min) administered over the 12h following the PCI.

Eptifibatide

- Antagonist of the platelet glycoprotein IIb/IIIc receptor, which reversibly prevents von Willebrand factor, fibrinogen, and other adhesion ligands from binding to the receptor.
- Prevention of early MI in patients with unstable angina or NSTEMI with last episode of chest pain within 24h.
  - Unstable angina—180micrograms/kg IV bolus, followed by continuous infusion until discharge or surgery.
  - PCI—135micrograms/kg IV bolus administered before PCI, followed by a continuous infusion of 0.5micrograms/kg/min.

Prasugrel

Used in combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndromes undergoing PCI only when immediate primary PCI is necessary for STEMI, or stent thrombosis occurred during treatment with clopidogrel, or the patient has diabetes mellitus.

- 60mg as a single dose, then 10mg daily in patients >60kg, or 5mg daily in patients <60kg or aged >75 years.

Revascularization

Revascularization should be considered in all patients who are at high risk. Clinical trials have demonstrated the benefit of an early invasive strategy.

Drug treatment of intermediate-risk unstable angina/NSTEMI

Patients who are deemed to be at intermediate risk are admitted for monitoring and reassessment of clinical status, ECG, and biochemical markers. They are then reclassified, depending on the results of these investigations, into high or low risk. If it is thought probable that the patient has coronary artery disease, treatment while undergoing assessment should include aspirin (or clopidogrel) and heparin.

Drug treatment of low-risk unstable angina/NSTEMI

Patients who are low risk need cardiac assessment to rule out coronary disease. This involves stress testing, which could be exercise testing with an ECG, stress echocardiography, or nuclear stress study. Patients proved to have coronary disease should proceed to further investigation and management. Patients should be treated with platelet inhibitors (usually aspirin) while being assessed.

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Cardiopulmonary resuscitation

Cardiac arrest in adults: what the pharmacist needs to know

The management of cardiopulmonary arrest can be divided into two categories: basic and advanced life support. Note that this advice applies to **adults only.**

Basic life support

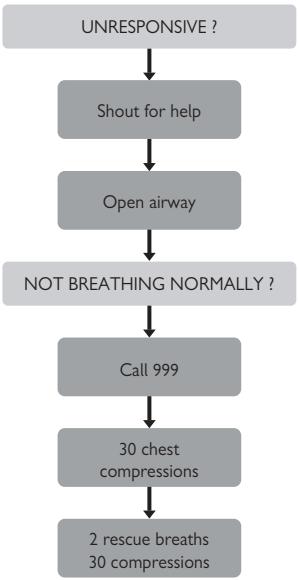
Basic life support is the 'first-responder' phase of the chain of survival. It can be carried out by anyone who has the relevant knowledge or training (Fig. 17.3).

Shout for help. Ask someone to call the arrest team and to bring the defibrillator. Note the time.

Before approaching the patient, the first responder should always check that it is safe to do so. The patient should then be assessed (e.g. check consciousness by calling the patient's name or shaking (if no response) to confirm that an arrest has occurred. This is done by checking the airway, breathing, and circulation (ABC).

- Airway
  - Tilt head (if no spine injury) and lift chin/jaw thrust. Clear the mouth. If this does not restore breathing then:
- Breathing
  - Pinch the patient's nose shut and give two breaths (each inflation should be 2s long), ideally using the Ambu system. Otherwise give mouth-to-mouth resuscitation (unless poisoning is suspected).
- Chest compressions
- Check for pulse, taking no longer than 10s. If no pulse found, then:
  - Give 30 compressions to 2 breaths (30:2). Cardiopulmonary resuscitation (CPR) should not be interrupted, except to give shocks or intubate. Use the heel of the hand with the other hand placed on top and straight elbows. in the middle of the lower half of the sternum, which should be depressed by ~5cm. Compressions should be fairly fast (~100/min). Chest compressions work to promote the forward flow of blood. (Allow the chest to recoil completely between each compression.)
  - Do not start chest compressions if you do not think that you can continue until the cardiac arrest team arrives, as compressions may lead to asystole whereas prior to compressions there may have been some (although inefficient) activity. Alternatively the person providing chest compressions should change about every 2min.

The most common cause of cardiac arrest is an arrhythmia—ventricular fibrillation. Ventricular fibrillation is known as a 'shockable rhythm' because it responds to defibrillation.



Managing the airway

- You open the airway by tilting the head and lifting the chin—but only do this if there is no question of spinal trauma.
- Use a close-fitting mask if available, held in place by thumbs pressing downwards either side of the mouthpiece; palms against cheeks.

Chest compressions

- Cardiopulmonary resuscitation (CPR) involves compressive force over the lower sternum with the heal of the hands placed one on top of the other, directing the weight of your body through your vertical, straight, arms.
- Depth of compression: ~4cm.
- Rate of compressions: 100/min.

Fig. 17.3 UK adult basic life support algorithm. Reproduced with permission from the Resuscitation Council (UK).

Advanced life support

Advanced life support starts when medical personnel arrive, and is nominally provided by the cardiac arrest team (Fig. 17.4).

- Basic life support maintained.
- The patient's airway is secured and O_2 is administered.
- IV access is obtained (in hospital, blood is taken for urgent blood gas analysis and determination of electrolyte levels).

The patient is attached to the cardiac monitor on the defibrillator to allow diagnosis of the arrhythmia. Further management depends on whether or not the type of arrhythmia present responds to defibrillation. In addition to ventricular fibrillation, pulseless ventricular tachycardia responds to defibrillation.

Treat ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) with a single shock, followed by immediate resumption of CPR (30 compressions to 2 ventilations). Do not reassess the rhythm or feel for a pulse. After 2min of CPR, check the rhythm and give another shock (if indicated).

- The recommended initial energy for biphasic defibrillators is 150–200J. Give second and subsequent shocks at 150–360J.
- The recommended energy when using a monophasic defibrillator is 360J for both the initial and subsequent shocks.

Asystole and electromechanical disturbance cannot be corrected using defibrillation. Asystole is the absence of any heart rhythm. Electromechanical disturbance (also known as pulseless electrical activity) is the presence of organized electrical activity that fails to result in mechanical contraction of the heart.

Pharmaceutical aspects of cardiopulmonary resuscitation

Basic CPR and early defibrillation are the only interventions proved to benefit survival in cardiac arrest. However, drugs have a role and should always be considered.

In hospital, an 'arrest box', containing a variety of drugs, is usually kept with the arrest trolley. Drugs in the arrest box commonly tend to be pre-assembled syringes.

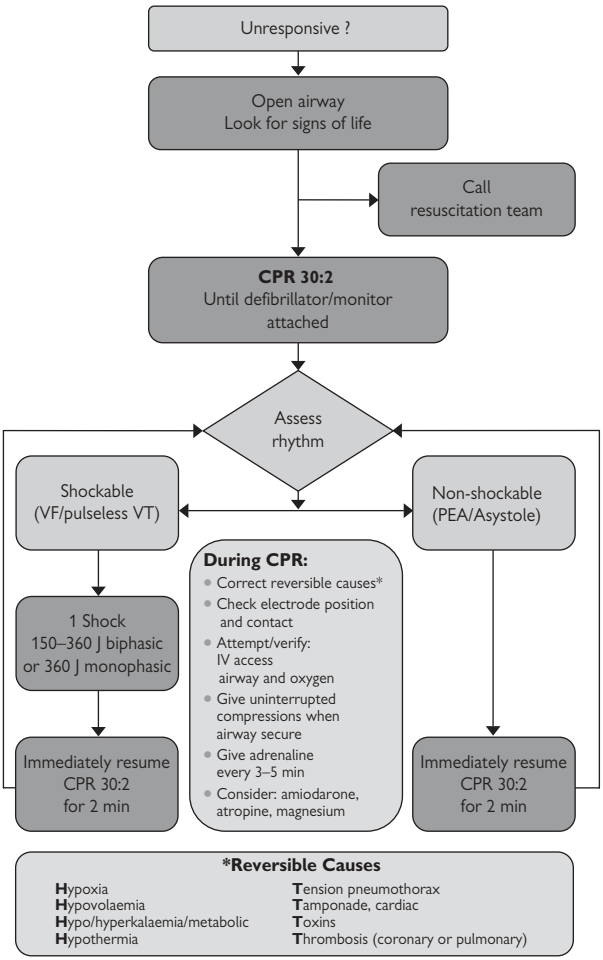


Fig. 17.4 UK adult advanced life support algorithm. Reproduced with permission from the Resuscitation Council (UK).

Drug administration

- *Adrenaline*
  - When treating VF/VT cardiac arrest, current guidelines recommend the administration of 1mg of adrenaline IV (i.e. 10mL of 1 in 10 000 pre-filled syringe) is given after the third shock once chest compressions have restarted and then every 3–5min during resuscitation. IV doses >1mg are no longer considered to be of benefit and should not be used.
  - For IV administration, a flush of 20mL of sodium chloride 0.9% solution should be administered after each drug dose to enhance its passage from the peripheral circulation to the central circulation. Alternatively, the dose can be given in tandem with a fast-flowing IV fluid.
  - If IV access is unattainable, giving drugs via a tracheal tube is no longer recommended. Drugs should be given by the intraosseous (IO) route (tibial and humeral sites preferred).
- *Atropine* was often used in the management of asystole or bradycardia to block any excessive vagal activity that might be contributing to a ↓ in heart rate. Atropine is no longer recommended for asystole and slow pulseless electrical activity (<60/min). Smaller doses (0.5–1mg IV) can be given in bradycardia, up to a maximum total of 3mg.
- *Amiodarone* is the anti-arrhythmic of choice in resistant ventricular fibrillation or pulseless ventricular tachycardia. If VF/VT persists after three shocks, a dose of 300mg in 20mL glucose 5% solution is given as a slow bolus over a period of at least 3min before delivery of the fourth shock. Remember that amiodarone is incompatible with normal saline, and bags of glucose 5% solution should be available to enable prompt setting up of the infusion and for flushing after dose(s). A further 150mg can be given, followed by an infusion of 1mg/min for 6h, and then 0.5mg/min for 6h. It is recommended that, if possible, amiodarone is administered using a volumetric control infusion pump rather than drip-counting technique because of the drug's affect on drip size. If amiodarone is not available, lidocaine 1mg/kg can be used as an alternative, but do not give lidocaine if amiodarone has already been given. Do not exceed a total dose of 3mg/kg during the first hour.
- *Magnesium sulphate* is the agent of choice in torsades de pointes, a type of arrhythmia that is often drug-induced. It can also be useful in resistant arrhythmias, especially if they are associated with hypo-magnesaemia (more common in patients taking diuretics). A bolus of 8mmol (4mL of a 50% w/v) is usually given.
- *Sodium bicarbonate* Giving sodium bicarbonate routinely during cardiac arrest and CPR is not recommended. Give sodium bicarbonate (50mmol) if cardiac arrest is associated with hyperkalaemia or tricyclic antidepressant overdose. Repeat the dose according to the clinical condition of the patient and the results of repeated blood gas analysis. Should only be administered after arterial blood gas analysis where pH has fallen below 7.1. A 50mmol dose (50mL of the 8.4%solution) would normally be given as a slow IV bolus.

- ***Oxygen*** Once return of spontaneous circulation is achieved and oxygen saturation of arterial blood can be monitored (by pulse oximetry and/or arterial blood gas analysis), inspired oxygen should be titrated to achieve SaO_2 of 94–98%.
- ***Calcium chloride*** 10mL of the 10% preparation (equivalent to 6.8mmol of calcium ions) is administered in suspected or actual calcium-channel blocker overdose or in magnesium-induced heart block. Calcium can slow the heart rate and precipitate arrhythmias. ► Do not give calcium solutions and sodium bicarbonate simultaneously by the same route.

Resuscitation is generally stopped after 20min if there is refractory asystole or electromechanical dissociation.

After successful resuscitation, perform the following:

- 12-lead ECG, CXR, U&Es, glucose, blood gases, FBC, creatinine kinase/troponin levels.
- Transfer to coronary care unit.
- Monitor vital signs.
- Communicate to relatives.

Suggested contents of the adult emergency drug box used in pre-arrest and arrest situations

- 5x adrenaline 1:10 000 solution, 1mg in 10mL pre-filled syringe (pre-assembled syringe).
- 1x atropine 3mg in 10mL pre-filled syringe (pre-assembled syringe).
- 1x amiodarone 300mg in 10mL pre-filled syringe (pre-assembled syringe).
- 1x 5% glucose, 50mL to flush amiodarone.

Suggested contents of back-up emergency box, containing the following drugs

- 6x adenosine, 6mg in 2mL vial.
- 5x adrenaline 1:1000 solution, 1mg in 1mL ampoule.
- 2x amiodarone 150mg in 3mL ampoule.
- 6x atropine 500mg in pre-filled syringe (pre-assembled syringe).
- 1x calcium chloride 6.8mmol in 10mL (10%) pre-filled syringe (pre-assembled syringe).
- 1x 50% glucose solution in 50mL vial.
- 1x magnesium sulphate 10mmol in 5mL (50% solution) pre-filled syringe (pre-assembled syringe).
- 1x sodium bicarbonate 8.4% in 50mL pre-filled syringe (pre-assembled syringe).

It is envisaged that back-up emergency boxes are normally issued to the wards and departments with manual defibrillators.

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Chapter 18

Therapy-related issues: respiratory system

Asthma management in adults: British Thoracic Society and SIGN guidelines

Aims

- Minimize symptoms during the day and night.
- Minimize need for reliever medication.
- No exacerbations.
- No limitation on physical activity.
- Achieve best possible pulmonary function.

Treatment

- Initiate treatment at the level most appropriate to the severity of asthma (Table 18.1).
- Step up treatment as necessary.
- Before initiating new therapy re-check compliance and inhaler technique, and eliminate trigger factors.
  - If trials of add-on therapies are ineffective, stop.
  - If trials of ↑ steroids are ineffective, return to original dose.
- Step down treatment levels if control is good:
- Review regularly while treatment is stepped down.

Table 18.1 Management of chronic asthma in adults

Level	Reliever therapy	Additional therapies	Further advice/therapy considerations
Step 1			
Mild Intermittent asthma	Inhaled short-acting β_2-agonist PRN		Review patients with high usage of reliever (>10 puffs/day is a marker of poorly controlled asthma)
Step 2			
Regular preventer therapy	Inhaled short-acting β_2-agonist PRN	Add inhaled steroid (200–800 micrograms daily)	Start at a dose appropriate to the severity and titrate to lowest effective dose. Usual dose is 400micrograms/daily Initially, divide dose twice daily; use once daily if good response is established

Table 18.1 (*Contd.*)

Level	Reliever therapy	Additional therapies	Further advice/therapy considerations
Step 3			
Add-on therapy	Inhaled short-acting β_2-agonist PRN	Add inhaled steroid (200–800 micrograms daily) Add inhaled long-acting β_2-agonist (LABA)	Good response to LABA—continue Improvement with LABA but poor response—continue and ↑ inhaled steroid to 800micrograms daily If control is still inadequate, go to step 4 No response to LABA—discontinue LABA and ↑ inhaled steroid dose to 800micrograms daily. If control still inadequate, trial other therapies—e.g. leukotriene receptor antagonists, theophylline, and slow-release oral β_2-agonists If control still inadequate, go to step 4
Step 4			
Persistent poor control	Inhaled short-acting β_2-agonist PRN	Add inhaled steroid (800micrograms daily) Inhaled LABA (unless discontinued because of poor response)	Consider trials of ↑ inhaled steroids, up to 2000micrograms daily. Consider trials of fourth drug—e.g. leukotriene receptor antagonists, theophylline, and slow-release oral β_2 agonists
Step 5			
Continuous or frequent use of oral steroids	Inhaled short-acting β_2-agonist PRN	High-dose inhaled steroid (2000 micrograms daily) Use oral steroids at lowest dose for adequate control	Consider other treatments to minimize use of oral steroids Refer to a specialist

Inhaler techniques

Metered-dose inhalers

The checklist steps for using a pressurized MDI are as follows.

- Sit or stand upright.
- Remove cap and shake the inhaler vigorously.
- Breathe out slowly and completely.
- Hold the inhaler in the upright position.
- Insert mouthpiece into mouth, between closed lips.
- Depress the canister once . . .
- . . . and at this time, begin slow, deep inhalation.
- Remove inhaler, with lips closed.
- Hold breath for 10–15s.
- Wait for 20–30s before starting the second puff.

Emphasize that coordination of the commencement of breathing with the release of medicament is very important and can require practice to maximize benefit.

The pharmacist may need to consider the use of a spacer or Haleraid® device for specific patients.

Points for the pharmacist/technician

- Demonstrate the correct method of use with a placebo inhaler, and ask the patient to show you how they use it. Most patients are on long-term therapy and many might have developed bad habits.
- The degree of benefit can be demonstrated to the patient by determining peak expiratory flow rates before dosing and 30min afterwards.
- Patients with anything other than mild occasional attacks derive considerable benefit from learning about their disease and how to manage it. They should measure peak expiratory flow rates regularly and keep a diary of the results.

Advice to the patient

- Keep the device clean and replace the mouthpiece cap after use.
- The plastic housing can be cleaned with warm mild detergent solution. Ensure that it is dried before use.

Dry-powder inhalers

Several devices are now available to deliver the medicament in a dry-powder inhaler. Because the medicines are dry powder, they must be inhaled fast enough so that the medicine is released. The basic technique for using a dry-powder medication is as follows.

- Exhale.
- Put the mouthpiece in your mouth.
- Breathe in quickly and deeply.

Diskhaler®

A Diskhaler® is a dry-powder inhaler that holds small pouches (or blisters), each containing a dose of medication, on a disk. The Diskhaler® punctures each blister so that its medication can be inhaled.

The basic technique for using the Diskhaler® is as follows.

- Remove the cover and check that the device and mouthpiece are clean.
- If a new medication disk is needed, pull the corners of the white cartridge out as far as they will go and then press the ridges on the sides inwards to remove the cartridge.
- Place the medication disk with its numbers facing upwards on the white rotating wheel. Then slide the cartridge all the way back in.
- Pull the cartridge all the way out, and then push it all the way in until the highest number on the medication disk can be seen in the indicator window.
- With the cartridge fully inserted and the device kept flat, raise the lid as far as it will go to pierce both sides of the medication blister.
- Move the Diskhaler® away from your mouth and breathe out.
- Place the mouthpiece between teeth and lips, making sure that you do not cover the air holes on the mouthpiece. Inhale quickly and deeply. Do not breathe out.
- Move the Diskhaler® away from your mouth and continue holding your breath for 10s.
- Breathe out slowly.
- If you need another dose, pull the cartridge out all the way and then push it back in all the way. This will move the next blister into place. Repeat procedure.
- After you have finished using the Diskhaler®, put the mouthpiece cap back on.

Turbohaler®

The basic technique for using the Turbohaler® dry-powder inhaler is as follows.

- Remove the cap from the Turbohaler® by unscrewing it.
- Hold the Turbohaler® with the mouthpiece up.
- Turn the bottom of the Turbohaler® all the way to the right and back to the left. You will hear it click.
- Hold the Turbohaler® away from your mouth and gently breathe out.
- Seal your lips around the mouthpiece.
- Inhale rapidly and deeply. Continue to take a full deep breath.
- Resume normal breathing.
- Repeat procedure if more than one puff is prescribed.
- Keep the Turbohaler® cap on when not in use.

Other points to tell patients include the following.

- When the red dot appears at the top of the window, there are 20 doses left. Plan to get a new Turbohaler® when you see the red dot.
- When the red dot is at the bottom of the window, the Turbohaler® is empty. Start using a new Turbohaler®.

Accuhaler®

The basic technique for using the Accuhaler® dry-powder inhaler is as follows.

- Open the Accuhaler® by holding the outer case in one hand and putting the thumb of the other hand on the thumb grip. Push your thumb away as far as it will go until a click is heard.
- Prime the dose by sliding the lever at the right of the mouthpiece away from you until a click is heard. Every time the lever is pushed back, a blister is opened and the powder is made available for inhaling. This is shown by the counter.
- Hold the Accuhaler® away from your mouth and breathe out as far as comfortable. Remember—never breathe into the Accuhaler®.
- Put the mouthpiece to your lips, and breathe in quickly and deeply.
- Remove the Accuhaler® from your mouth. Hold your breath for about 10s or for as long as is comfortable.
- Close the Accuhaler® by sliding the thumb grip back towards you. It should click shut.