

Chapter 40

Antianginal and Other Anti-ischaemic Drugs

ANTIANGINAL DRUGS

Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

Angina pectoris It is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium. Metabolites that accumulate due to myocardial ischaemia elicit the pain. Two principal forms of angina are recognized:

(a) **Classical angina** (common form) Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. The underlying pathology is—severe arteriosclerotic affliction of larger coronary arteries (conducting vessels) which run epicardially and send perforating branches to supply the deeper tissue (Fig. 40.1). The coronary obstruction is 'fixed'; blood flow fails to increase during

increased demand despite local factors mediated dilatation of resistance vessels (Fig. 40.2) and ischaemic pain is felt. Due to inadequacy of ischaemic left ventricle, the end diastolic left ventricular pressure rises from 5 to about 25 mm Hg—produces subendocardial 'crunch' during diastole (blood flow to the subendocardial region occurs only during diastole) and aggravates the ischaemia in this region. Thus, a form of acutely developing and rapidly reversible left ventricular failure results which is relieved by taking rest and reducing the myocardial workload.

Drugs that are useful, primarily reduce cardiac work (directly by acting on heart or indirectly by reducing preload hence end diastolic pressure, and afterload). They may also cause favourable redistribution of blood flow to the ischaemic areas.

(b) **Variant/Prinzmetal/Vasospastic angina** (uncommon form) Attacks occur at rest or during sleep and are unpredictable. They are due to recurrent localized (occasionally diffuse) coronary vasospasm (Fig. 40.2) which may be superimposed on arteriosclerotic coronary artery disease. Abnormally reactive and hypertrophied segments in the coronary arteries have been demonstrated. Drugs are aimed at preventing and relieving the coronary vasospasm.

Unstable angina (UA) with rapid increase in duration and severity of attacks which may occur even during rest, is mostly due to rupture of an atheromatous plaque attracting platelet

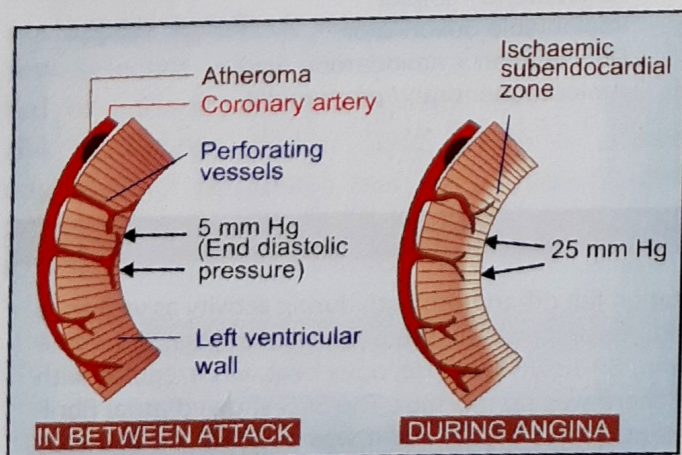


Fig. 40.1: Diagrammatic representation of subendocardial 'crunch' during an attack of angina

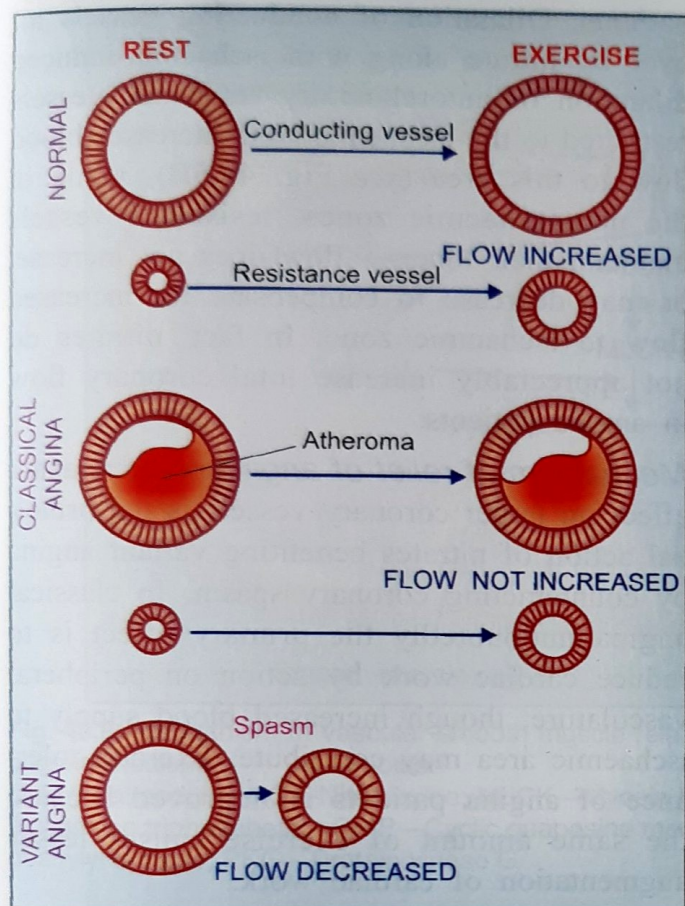


Fig. 40.2: Diagrammatic representation of coronary artery calibre changes in classical and variant angina

deposition and progressive occlusion of the coronary artery; occasionally with associated coronary vasospasm. Patients with UA are at high risk of myocardial infarction (MI).

Chronically reduced blood supply causes atrophy of cardiac muscle with fibrous replacement (reduced myocardial work capacity → CHF) and may damage conducting tissue to produce unstable cardiac rhythms. Antianginal drugs relieve cardiac ischaemia but do not alter the course of coronary artery disease (CAD); no permanent benefit is afforded. On the other hand, aspirin, ACE inhibitors and statins (hypocholesterolaemic) can modify coronary artery disease and improve prognosis.

Glyceryl trinitrate, the drug unsurpassed in its ability to abort and terminate anginal attack, was introduced by Murrell in 1879. Other organic nitrates were added later, but a breakthrough was achieved in 1963 when propranolol was used for chronic prophylaxis. The calcium channel blockers have been a major contribution of the 1970s. A number of vasodilator and other drugs have been promoted from time to time, but none is uniformly effective. Some potassium channel openers (nicorandil), metabolic modulator (trimetazidine), late Na^+ current inhibitor (ranolazine) and heart rate lowering (ivabradine) have been introduced lately.

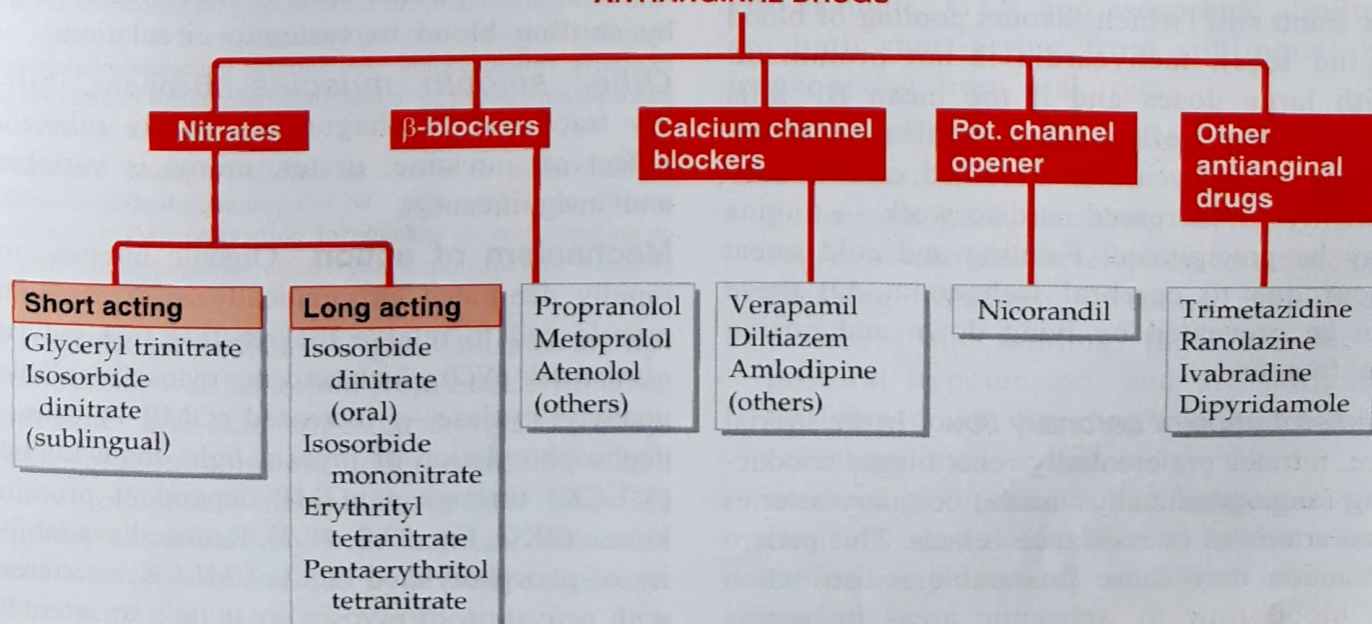
Clinical classification

- Used to abort or terminate attack GTN, Isosorbide dinitrate (sublingually).
- Used for chronic prophylaxis All other drugs.

NITRATES (GTN as prototype)

All organic nitrates share the same action; differ only in time course. The only major action is

ANTIANGINAL DRUGS



direct nonspecific smooth muscle relaxation, particularly vascular smooth muscle.

Preload reduction Nitrates dilate veins more than arteries → peripheral pooling of blood → decreased venous return, i.e. preload on heart is reduced → end diastolic size and pressure are reduced. This decreases cardiac work according to *Laplace relationship* (see p. 561).

Reduction in ventricular radius decreases the tension that must be generated in the ventricular wall—hence decreased O_2 consumption. Reduction in cardiac output (c.o.) occurs at rest but is less marked during angina due to better ventricular emptying. The decrease in end diastolic pressure abolishes the subendocardial crunch by restoring the pressure gradient across ventricular wall due to which subendocardial perfusion occurs during diastole. It is through their action on peripheral veins that nitrates exert major beneficial effects in classical angina.

Afterload reduction Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls somewhat; systolic more than diastolic (reflex sympathetic activity tends to maintain diastolic BP). This action contributes to the reduction in cardiac work which is directly proportional to aortic impedance.

With usual doses, and if the patient does not stand still (which favours pooling of blood in the legs), tachycardia is not prominent. With large doses and if the mean BP falls significantly, reflex sympathetic stimulation occurs → tachycardia, increased cardiac contractility → increased cardiac work → angina may be precipitated. Fainting and cold sweat occur due to cerebral ischaemia. All these can be prevented by lying down and raising the foot end.

Redistribution of coronary flow In the arterial tree, nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels. This pattern of action may cause favourable redistribution of blood flow to ischaemic areas in angina

patients. Dilatation of conducting vessels all over by nitrate along with ischaemia-induced dilatation of autoregulatory resistance vessels restricted to the ischaemic zone increases blood flow to this area (see Fig. 40.5B), while in the non-ischaemic zones, resistance vessels maintain their tone → flow does not increase, or may decrease to compensate for increased flow to ischaemic zone. In fact, nitrates do not appreciably increase total coronary flow in angina patients.

Mechanism of relief of angina The relaxant effect on larger coronary vessels is the principal action of nitrates benefiting variant angina by counteracting coronary spasm. In classical angina undoubtedly the primary effect is to reduce cardiac work by action on peripheral vasculature, though increased blood supply to ischaemic area may contribute. Exercise tolerance of angina patients is improved because the same amount of exercise causes lesser augmentation of cardiac work.

Heart and peripheral blood flow Nitrates have no direct stimulant or depressant action on the heart. They dilate cutaneous vessels (especially over face and neck responsible for flushing) and meningeal vessels causing headache. Splanchnic and renal blood flow decreases to compensate for vasodilatation in other areas. Nitrates tend to decongest lungs by shifting blood to systemic circulation.

Other smooth muscles Bronchi, biliary tract and esophagus are mildly relaxed. Effect on intestine, ureter, uterus is variable and insignificant.

Mechanism of action Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical *nitric oxide* (NO) which activates cytosolic soluble guanylyl cyclase → increased cGMP → causes dephosphorylation of myosin light chain kinase (MLCK) through a cGMP dependent protein kinase (PKG, Fig. 37.2, 40.3). Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin → it fails to interact

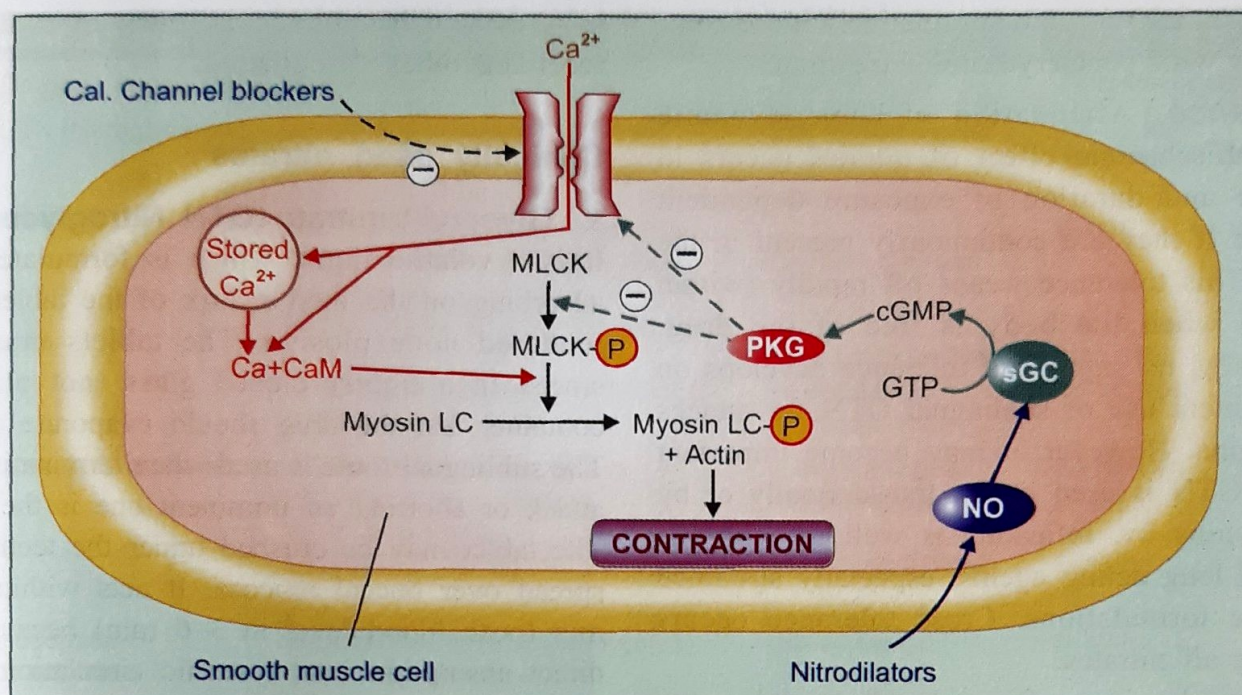


Fig. 40.3: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (---→) Inhibition

CaM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate; Myosin LC—Myosin light chain; sGC—Soluble guanylyl cyclase; PKG—Protein kinase G

with actin to cause contraction. Consequently, relaxation occurs. Raised intracellular cGMP may also reduce Ca^{2+} entry—contributing to relaxation.

Veins express greater amount of mitochondrial aldehyde dehydrogenase, the enzyme that generates NO from GTN, than arteries. This may account for the predominant venodilator action. It has been suggested that preferential dilatation of epicardial conducting arteries over autoregulatory arterioles is also due to differential distribution of nitrate metabolizing enzymes in these vessels.

Platelets Though platelets are poor in mitochondrial aldehyde dehydrogenase, the NO generated from nitrates activates cGMP production in platelets as well, leading to a mild antiaggregatory effect. This action may be valuable in unstable angina.

Pharmacokinetics Organic nitrates are lipid-soluble: well absorbed from buccal mucosa, intestines and skin. Ingested orally, all except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase. The partly denitrated metabolites are less

active, but have longer $t_{1/2}$. Though nitrates have been traditionally classified into short-acting and long-acting, it is the rate of absorption from the site of administration and the rate of metabolism that govern the duration of action of a particular nitrate. For example, GTN and isosorbide dinitrate are both short-acting from sublingual but longer-acting from oral route.

Adverse effects These are mostly due to vasodilatation.

- Fullness in head, throbbing headache; some degree of tolerance develops on continued use.
- Flushing, weakness, sweating, palpitation, dizziness and fainting; these are due to postural hypotension, and are mitigated by lying down. Standing still and alcohol accentuate these symptoms.
- Methemoglobinemia is not noticeable with clinically used doses; but can further reduce O_2 carrying capacity of blood in severe anaemia.

- Rashes are rare, though relatively more common with pentaerythritol tetranitrate.

Tolerance Attenuation of haemodynamic and antiischaemic effect of nitrates occurs in a dose and duration of exposure dependent manner if they are continuously present in the body. This tolerance weans off rapidly (within hours) when the body is free of the drug. Clinically, no significant tolerance develops on intermittent use of sublingual GTN for attacks of angina. However, it may become important when GTN is used orally, transdermally or by continuous i.v. infusion, as well as with the use of long acting agents, especially sustained release formulations. Cross tolerance occurs among all nitrates.

The mechanism of rapid nitrate tolerance is not well understood. It appears that the reactive oxygen species which are produced during denitration of organic nitrates themselves inhibit mitochondrial aldehyde dehydrogenase and related enzymes, so that further NO generation is interfered. Activation of compensatory mechanisms including volume expansion, sympathetic and renin-angiotensin system stimulation or other humoral pathways may contribute to nitrate tolerance.

The most practical way to prevent nitrate tolerance is to provide nitrate free intervals everyday.

Dependence On organic nitrates is now well recognized. Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. MI and sudden deaths have been recorded. Angina threshold is lowered during the nitrate free interval in some patients: episodes of angina may increase. In such patients an antianginal drug of another class should be added. Withdrawal of nitrates should be gradual.

Interactions Sildenafil and other PDE-5 inhibitors cause dangerous potentiation of nitrate action: severe hypotension, MI and deaths are on record (see p. 328). Additive hypotension

is possible when nitrate is given to a patient receiving other vasodilators.

Clinically used nitrates

1. Glyceryl trinitrate (GTN, Nitroglycerine)

It is a volatile liquid which is formulated by adsorbing on the inert matrix of the tablet and rendered nonexplosive. The tablets must be stored in a tightly closed glass (not plastic) container lest the drug should evaporate away. The sublingual route is used when terminating an attack or aborting an imminent one is the aim. The tablet may be crushed under the teeth and spread over buccal mucosa. It acts within 1–2 min (peak blood level in 3–6 min) because of direct absorption into systemic circulation (bypassing liver where almost 90% is metabolized).

Plasma $t_{1/2}$ is 2 min, duration of action depends on the period it remains available for absorption from buccal mucosa. When anginal pain is relieved, the remaining part of tablet may be spit or swallowed. A sublingual spray formulation has been recently marketed—acts more rapidly and is more stable than sublingual tablet. Hepatic metabolizing capacity can be overwhelmed by administering a large dose (5–15 mg) orally. Sustained release oral capsules containing much larger amounts of GTN can be used for chronic prophylaxis.

Nitroglycerine is readily absorbed from the skin. A transdermal patch has been developed which provides steady delivery for 24 hours. The patch starts working within 60 min and has a bioavailability of 70–90%. However, tolerance to the haemodynamic effects develops. The effects start fading after 8–10 hours. It is advised that the patch be taken off for 8–10 hours daily. A transmucosal dosage form which has to be stuck to the gums under the upper lip has also been produced. It acts in 5 min and releases the drug for 4–6 hours.

Intravenous infusion of GTN provides rapid, steady, titratable plasma concentration for as long as desired. It has been successfully used

Table 40.1: Organic nitrates available for angina pectoris

Drug	Preparations	Dose & route	Duration of action
1. GTN (Nitroglycerine)	ANGISED 0.5 mg tab	0.5 mg sublingual	10–30 min
	NITROLINGUAL, GTN SPRAY	0.4–0.8 mg s.l. spray	10–30 min
	ANGISPAN-TR 2.5, 6.5 mg SR cap.		4–8 hr
	NITROCONTIN, CORODIL 2.6, 6.4 mg tabs.	5–15 mg SR oral	
2. Isosorbide dinitrate	NITRODERM-TTS 5 or 10 mg patch		Till applied, max 24 hr.
	MYOVIN, MILLISROL, NITROJECT 5 mg/ml inj	One patch for 14–16 hr per day 5–20 µg/min i.v.	Till infused
	SORBITRATE 5, 10 mg tab, ISORDIL 5 mg sublingual & 10 mg oral tab.	5 mg sublingual 10–20 mg oral	20–40 min 2–4 hr
3. Isosorbide-5-mononitrate	DITRATE 5, 10 mg tab; 20, 40 mg SR tab	10–40 mg SR oral	6–10 hr
	MONOTRATE 10, 20, 40 mg tab, 25, 50 mg SR tabs	10–40 mg oral	6–10 hr
	5-MONO, MONOSORBITRATE 10, 20, 40 mg tab.	10–40 mg SR oral	
4. Erythrityl-tetranitrate	CARDILATE 5, 15 mg tab	15–60 mg oral	4–6 hr
5. Pentaerythritol-tetranitrate	PERITRATE 10 mg tab	10–40 mg oral	3–5 hr
	PERITRATE-SA 80 mg SR tab	80 mg SR oral	8–12 hr

for unstable angina, coronary vasospasm, LVF accompanying MI, hypertension during cardiac surgery, etc. Begin with 5 µg/min, adjust according to need. Early institution of infusion may limit the size of infarct in MI.

2. Isosorbide dinitrate It is a solid but similar in properties to GTN; can be used sublingually at the time of attack (slightly slower in action than GTN, peak in 5–8 min) as well as orally for chronic prophylaxis. Presystemic metabolism on oral administration is pronounced and variable. The $t_{1/2}$ is 40 min, but sustained release formulation may afford protection for 6–10 hours. Last dose should not be taken later than 6 PM to allow nitrate level to fall during sleep at night.

3. Isosorbide mononitrate This is an active metabolite of isosorbide dinitrate. When administered orally it undergoes little first pass metabolism: bioavailability is high, interindividual differences are minimal and it is longer acting ($t_{1/2}$ 4–6 hr). Last dose is to

be taken in the afternoon; SR tablet once a day in the morning.

4. Erythrityl tetranitrate and pentaerythritol tetranitrate These are longer-acting nitrates used only for chronic prophylaxis. Sustained release oral preparations are now available for 2–3 times a day dosing.

There has been considerable scepticism in the past about the efficacy of orally administered long-acting nitrates. Studies with high doses have shown that firstpass metabolism in liver can be saturated and haemodynamic effects lasting 4–6 hours do occur.

USES

1. Angina pectoris Nitrates are effective in classical as well as variant angina. For aborting or terminating an attack, sublingual GTN tablet or spray, or isosorbide dinitrate is taken on 'as and when required' basis. GTN produces relief within 3 min in 75% patients, the rest may require another dose

or take longer (upto 9 min). Nitrates increase exercise tolerance and postpone ECG changes of ischaemia. Longer-acting formulations (oral, transdermal) of GTN or other nitrates are used on regular schedule for chronic prophylaxis. However, development of tolerance and dependence may limit the usefulness of this approach: 6–8 drug free hours daily are advisable. Moreover, chronic nitrate therapy in angina does not decrease cardiac mortality. In terms of prognostic benefit chronic prophylactic therapy with CCBs is superior to long-acting nitrates in variant angina.

2. Acute coronary syndromes (ACS) These are characterized by rapid worsening of anginal status of the patient: include unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI). Aggressive therapy with a combination of drugs intended to prevent further coronary occlusion, increase coronary blood flow and decrease myocardial stress (oxygen demand) is needed. Nitrates are useful by decreasing preload (myocardial work) as well as by increasing coronary flow (dilatation and antagonism of coronary spasm, if present). Initially GTN is given sublingually, but if pain persists after 3 tablets 5 min apart, i.v. infusion of GTN is started. The role of nitrates appears to be limited to relief of pain, because no mortality benefit has been demonstrated in large randomized clinical trials such as GISSI-3 (1994) and ISIS-4 (1995).

Antiplatelet drugs like aspirin, clopidogrel, GPII_b/III_a antagonists, with or without heparin are the primary measures in UA/NSTEMI. The weak antiaggregatory action of GTN is insufficient by itself, but may contribute to the benefit. The β blockers are indicated in all patients (if there are no contraindications) to reduce myocardial oxygen demand. A CCB is indicated only when coronary spasm is not effectively counteracted by the nitrate. Revascularization by thrombolytics/coronary angioplasty with stents/coronary bypass surgery is considered in high risk patients.

3. Myocardial infarction (MI) Administered by carefully titrated i.v. infusion to avoid hypotension and tachycardia, GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting

the area of necrosis by favourably altering O₂ balance in the marginal partially ischaemic zone (a consequence of preload reduction). However, evidence that it decreases mortality is not robust; prognostic benefits appear marginal. Proper patient selection is important. GTN should not be administered if:

- Systolic BP is < 90 mm Hg
- Heart rate is < 50 or > 100 beats/min
- Right ventricular infarction is suspected
- Hypotension caused by nitrate limits the administration of β blockers which have more powerful salutary effects.
- Patient has taken sildenafil in the past 24 hours.

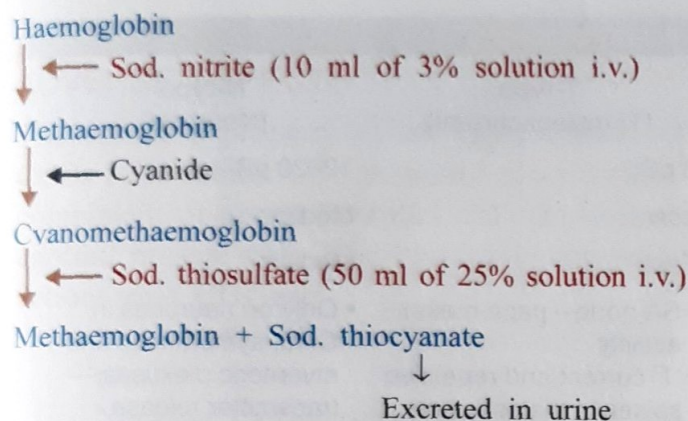
4. CHF and acute LVF The role of vasodilators in CHF is described in Ch. 38. Nitrates afford relief by venous pooling of blood (which can be aided by sitting posture while managing acute LVF or severe chronic CHF) → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function by *Laplace law* and regression of pulmonary congestion. Intravenous GTN is the preparation of choice for emergency use. Rate of infusion must be guided by continuous haemodynamic monitoring.

5. Biliary colic due to gall stone or morphine—responds to sublingual GTN or isosorbide dinitrate.

6. Esophageal spasm Sublingual GTN promptly relieves pain. Nitrates taken before a meal facilitate feeding in esophageal achalasia by reducing esophageal tone.

7. Cyanide poisoning Nitrates and nitrites generate methaemoglobin which has high affinity for cyanide radical (CN) and forms cyanomethaemoglobin. However, this may again dissociate to release cyanide. Therefore, sodium thiosulfate is given to form Sod. thiocyanate which is poorly dissociable and is excreted in urine.

Cytochrome and other oxidative enzymes are thus protected from cyanide; even the enzyme which has complexed CN is reactivated. However, early treatment is critical. The antidotes should be repeated as required.



Sodium nitrite is used for this purpose because it is a very weak vasodilator; large doses (>300 mg) sufficient to generate enough methaemoglobin can be injected i.v. without producing hypotension.

Alternative and probably safer antidotes that are being used in UK and USA are:

- *Hydroxocobalamin*: A form of vit B₁₂ which has high affinity for CN, is injected i.v. in massive dose (5 g for adult or 70 mg/kg). It combines with CN to form cyanocobalamin (another form of vit B₁₂). It is particularly indicated in smoke inhalation during fire accidents (such smoke contains HCN).
- *Dicobalt edetate*: This cobalt compound also has high affinity for CN, and is indicated only in confirmed cases, because it can itself be toxic in non CN-poisoning cases. A dose of 300 mg (in 15 ml) is injected i.v. over 1 min, followed by 50 ml of 50% glucose solution.

β BLOCKERS (see Ch. 10)

These are very valuable antianginal drugs, but do not dilate coronaries or other blood vessels; total coronary flow is rather reduced due to blockade of dilator β₂ receptors. However, flow to the ischaemic subendocardial region is not reduced because of favourable redistribution and decrease in ventricular wall tension. β blockers act by reducing cardiac work and O₂ consumption as a consequence of decreased heart rate, inotropic state and mean BP. While these effects are marginal at rest, β blockers limit the increase in cardiac work that occurs during exercise or anxiety by their antiadrenergic action on heart. Reduction in heart rate indirectly improves coronary perfusion by prolonging diastole during which subendocardial perfusion occurs.

All β blockers, except those with intrinsic sympathomimetic activity (e.g. pindolol), are

nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, but the cardioselective agents (atenolol, metoprolol) are preferred over nonselective β₁ + β₂ blockers (e.g. propranolol). The latter are particularly prone to worsen variant angina due to unopposed α receptor mediated coronary constriction that may accentuate the coronary spasm. Long term β blocker therapy clearly lowers risk of sudden cardiac death among ischaemic heart disease patients. β blockers are the only antianginal drugs which prolong the life-expectancy of CAD patients. As per current guidelines, they should be the first line drugs in all stable angina patients, unless contraindicated.

The dose of β blockers has to be individualized. Abrupt discontinuation after chronic use may precipitate severe attacks, even MI.

Unstable angina (UA)/Non-ST-elevation MI (NSTEMI) Unless contraindicated, β blockers are routinely used in UA/NSTEMI. However, they should be given only after starting nitrate ± calcium channel blocker to counteract coronary vasospasm, if present (β blockers carry the risk of worsening coronary vasospasm). β blockers reduce myocardial O₂ demand and afford additional benefit by reducing risk of impending MI/sudden cardiac death.

CALCIUM CHANNEL BLOCKERS

Verapamil was developed in Germany in 1962 as a coronary dilator. It had additional cardiodepressant property, but its mechanism of action was not known. Fleckenstein (1967) showed that it interfered with Ca²⁺ movement into the cell. In the subsequent years, a large number of chemically diverse Ca²⁺ channel blockers have been produced.

The calcium channel blockers (CCBs) have been grouped into three chemical classes which have distinct pharmacodynamic profiles.

The dihydropyridines (DHPs) are lipophilic and are the most potent CCBs, while verapamil and diltiazem are relatively hydrophilic and less potent.

Calcium channels

Three types of Ca²⁺ channels have been described in smooth muscles (other excitable cells as well):

Voltage sensitive calcium channels

	L-type (Long lasting current)	T-type (Transient current)	N-type (Neuronal)
1. Conductance	25 pS	8 pS	12–20 pS
2. Activation threshold	High	Low	Medium
3. Inactivation rate	Slow	Fast	Medium
4. Location and function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pace-maker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—constriction	• Only on neurones in CNS, sympathetic and myenteric plexuses—transmitter release
5. Blocker	Nifedipine, diltiazem, verapamil	Mibefradil, flunarizine, ethosuximide	ω -Conotoxin

(a) **Voltage sensitive channel** Activated when membrane potential drops to around -40 mV or lower.

(b) **Receptor operated channel** Activated by A α r and other agonists—-independent of membrane depolarization (NA contracts even depolarized aortic smooth muscle by promoting influx of Ca^{2+} through this channel and releasing Ca^{2+} from sarcoplasmic reticulum).

(c) **Leak channel** Small amounts of Ca^{2+} leak into the resting cell and are pumped out by Ca^{2+} ATPase. Mechanical stretch promotes inward movement of Ca^{2+} , through the leak channel or through separate *stretch sensitive channel*. The *voltage sensitive Ca^{2+} channels* are heterogeneous: three major types have been identified (see box):

All voltage sensitive Ca^{2+} channels are membrane spanning funnel shaped glycoproteins that function as ion selective valves. They are composed of a major α_1 subunit which encloses the ion channel and other modulatory subunits like α_2 , β , γ and δ . In L-type Ca^{2+} channels each subunit exists in multiple isoforms which may be site specific, e.g.

Skeletal muscle L-channels are: $\alpha_{1s} \cdot \alpha_2/\delta_a \cdot \beta_1 \cdot \gamma$

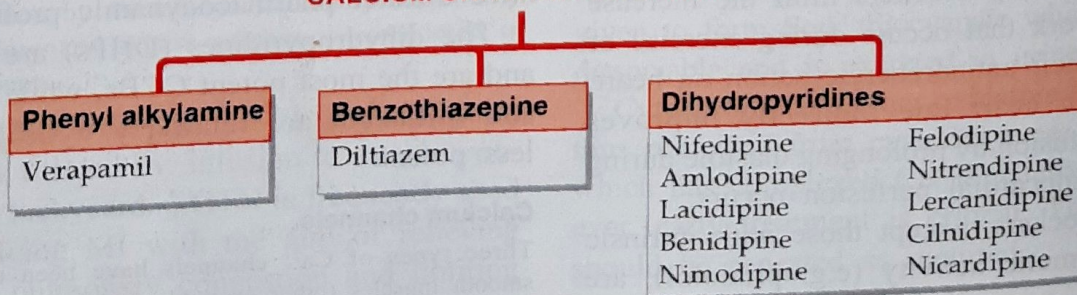
Cardiac muscle L-channels are: $\alpha_{1ca} \cdot \alpha_2/\delta_c \cdot \beta_2$

Smooth muscle L-channels are: $\alpha_{1cb} \cdot \alpha_2/\delta \cdot \beta_3$

Even smooth muscle L-channels differ between vascular and nonvascular. Moreover, distribution may be heterogeneous in different parts of the vascular bed.

Only the voltage sensitive L-type channels are blocked by the CCBs. All CCBs bind primarily to the open and inactivated states of the channel, and minimally to the resting state. The 3 groups of CCBs viz. phenylalkylamines (verapamil), benzothiazepine (diltiazem) and dihydropyridines (nifedipine) bind to their own specific binding sites on the α_1 subunit; all restricting Ca^{2+} entry, though characteristics of channel blockade differ. Further, different drugs may have differing affinities for various site specific isoforms of the L-channels. This may account for the differences in action exhibited by various CCBs. The vascular smooth muscle has a more depolarized membrane (RMP about -40 mV) than heart. This may contribute to the vascular selectivity of certain CCBs.

CALCIUM CHANNEL BLOCKERS



PHARMACOLOGICAL ACTIONS AND ADVERSE EFFECTS

The common property of all three classes of CCBs is to inhibit Ca^{2+} mediated slow channel component of action potential (AP) in smooth/cardiac muscle cell. The two most important actions of CCBs are:

- (i) Smooth muscle (especially vascular) relaxation.
- (ii) Negative chronotropic, inotropic and dromotropic action on heart.

Smooth muscle Smooth muscles depolarize primarily by inward Ca^{2+} movement through voltage sensitive L-type channel. These Ca^{2+} ions trigger release of more Ca^{2+} ions from intracellular stores and together bring about excitation-contraction coupling through phosphorylation of myosin light chain as depicted in Fig. 40.3. The CCBs cause relaxation by decreasing intracellular availability of Ca^{2+} . They markedly relax arterioles but have mild effect on veins. Extravascular smooth muscle (bronchial, biliary, intestinal, vesical, uterine) is also relaxed.

The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.

Nitrendipine and few other DHPs have been shown to release NO from endothelium and inhibit cAMP-phosphodiesterase resulting in raised smooth muscle cAMP. These additional mechanisms may account for their predominant smooth muscle relaxant action. Released endothelial NO may exert antiatherosclerotic action as well.

Heart In the working atrial and ventricular fibres, Ca^{2+} moves in during the plateau phase of AP and releases more Ca^{2+} from sarcoplasmic reticulum. This Ca^{2+} surge causes contraction through binding to troponin—allowing interaction of myosin with actin (see Fig. 38.3). The CCBs would thus have negative inotropic action.

The 0 phase depolarization in SA and A-V nodes is largely Ca^{2+} mediated. Automaticity and conductivity of these cells appear to be dependent on the rate of recovery of the Ca^{2+} channel.

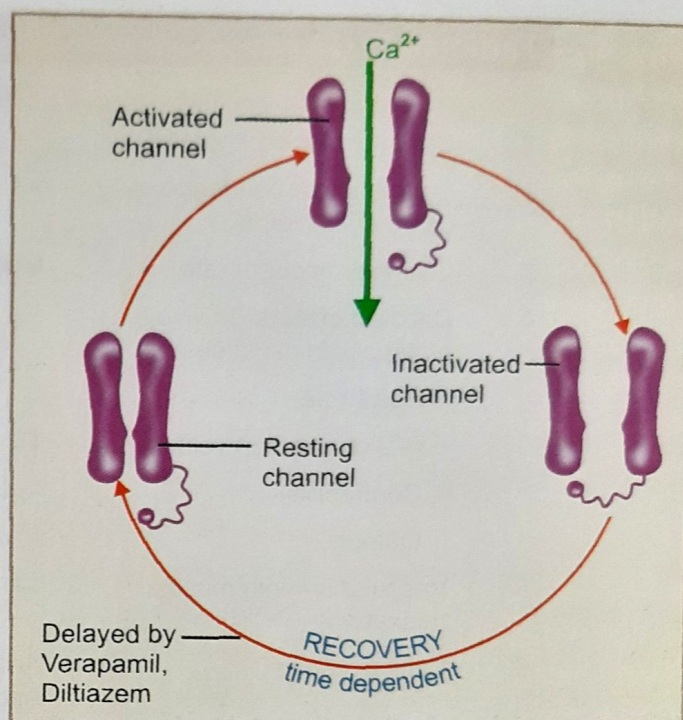


Fig. 40.4: Activation–inactivation–recovery cycle of cardiac Ca^{2+} channels

The L-type Ca^{2+} channels activate as well as inactivate at a slow rate. Consequently, Ca^{2+} depolarized cells (SA and A-V nodal) have a considerably less steep 0 phase and longer refractory period. The recovery process which restores the channel to the state from which it can again be activated (Fig. 40.4) by membrane depolarization is delayed by verapamil and diltiazem (resulting in depression of pacemaker activity and conduction), but not by DHPs (they have no negative chronotropic/dromotropic action). Moreover, channel blockade by verapamil is enhanced at higher rates of stimulation, that by nifedipine is independent of frequency, while diltiazem is intermediate. Thus, verapamil slows sinus rate and A-V conduction, but nifedipine does not. Effect of diltiazem on sinus node automaticity and A-V conduction is similar to that of verapamil.

The relative potencies to block slow channels in smooth muscle do not parallel those in the heart. The DHPs are more selective for smooth muscle L channels. At concentrations which cause vasodilatation they have negligible negative inotropic action which is most prominent

Table 40.2: Comparative properties of representative calcium channel blockers

		Verapamil	Nifedipine	Diltiazem
1.	Channel blocking potency	++	+++	+
2.	Frequency dependence of channel blockade	++	—	+
3.	Channel recovery rate	Much delayed	No effect	Delayed
4.	Cardiac effects (In vivo at usual clinical doses)			
	Heart rate	↓	↑	↓, —
	A-V conduction velocity	↓↓	—	↓↓
	Contractility	—, ↓	↑	↓, ↑
	Output	—, ↓	↑	—, ↑
5.	Vascular smooth muscle relaxation	++	+++	+
6.	Clinical use in	Arrhythmia Angina (Hypertension)	Angina Hypertension Raynaud's	Angina Hypertension Arrhythmia

↑ increase; ↓ decrease; — no change

in verapamil. Diltiazem causes less depression of contractility than verapamil. Important differences between the three representative CCBs are summarized in Table 40.2. Their cardiac electrophysiological effects are compared in Table 39.1.

Verapamil It dilates arterioles and has some α adrenergic blocking activity, thereby decreases t.p.r. but BP is only modestly lowered. The pronounced direct cardiodepressant effect is partially offset *in vivo* by reflex effects of peripheral vasodilatation. The HR generally decreases, A-V conduction is slowed, but c.o. is maintained by reflex sympathetic stimulation and reduction in aortic impedance. However, ventricular contractility may be markedly impaired in CHF patients. Coronary flow is increased.

Dose: 40–160 mg TDS oral, 5 mg by slow i.v. injection. **CALAPTIN** 40, 80 mg tabs, 120, 240 mg SR tabs, 5 mg/2 ml inj. **VASOPTEN** 40, 80, 120 mg tab.

Adverse effects Constipation is the most common side effect. Bradycardia and nausea are more common than with DHPs, while flushing, headache and ankle edema are less common.

Hypotension is occasional. It can accentuate conduction defects (contraindicated in 2nd and 3rd degree A-V block) and precipitate CHF in patients with preexisting disease. Cardiac arrest has occurred on i.v. injection and when it is given to patients with sick sinus.

Interactions Verapamil should not be given with β blockers—additive sinus depression, conduction defects or asystole may occur.

It increases plasma digoxin level by decreasing its excretion: toxicity can develop.

It should not be used along with other cardiac depressants like quinidine and disopyramide.

Diltiazem It is somewhat less potent vasodilator than nifedipine and verapamil, and has modest direct negative inotropic action, but direct depression of SA node and A-V conduction are equivalent to verapamil. A nonspecific antiadrenergic action has also been demonstrated. Usual clinical doses produce consistent fall in BP with little change or decrease in HR. Large dose or i.v. injection decreases t.p.r. markedly which may elicit reflex cardiac effects. Diltiazem dilates coronaries.

Dose: 30–60 mg TDS–QID oral; **DILZEM**, 30, 60 mg tabs, 90 mg SR tab; 25 mg/5 ml inj; **ANGIZEM** 30, 60, 90, 120, 180 mg tab, **DILTIME** 30, 60 mg tab; 90, 120 mg SR tab.

Adverse effects Side effects are milder, but the profile is similar to verapamil. Like verapamil, it increases plasma digoxin level.

Diltiazem should not be given to patients with preexisting sinus, A-V nodal or myocardial disease. Only low doses should be given to patients on β blockers.

Dihydropyridines (DHPs)

All DHPs have similar pharmacodynamic profile, but minor differences in organ selectivity and major differences in pharmacokinetic characteristics exist (Table 40.3). The slower and longer acting ones induce less reflex sympathetic stimulation. Tachycardia, propensity to increase cardiac work, flushing, headache, dizziness are subdued. They are the favoured DHPs because of milder side effects and because increased mortality among post-MI patients is reported with the regular short-acting nifedipine formulation.

Nifedipine It is the first and the prototype DHP, but infrequently used now. The overriding action is arteriolar dilatation $\rightarrow$ t.p.r. decreases, BP falls. The direct depressant action on heart is significant. As described above, it does not depress SA node or A-V conduction. Nifedipine acts rapidly, due to which reflex sympathetic stimulation of heart predominates producing tachycardia, increased contractility and c.o. No decrease in venous return along with lowering of afterload aids increase in c.o. Coronary flow is increased. The duration of action is short (3–6 hours).

Dose: 5–20 mg BD–TDS oral.

CALCIGARD, **DEPIN**, **NIFELAT** 5, 10 mg cap, also 10 mg, 20 mg S.R. (RETARD) tab; **ADALAT RETARD** 10, 20 mg SR tab.

Adverse effects Due to rapidly developing vasodilatation. Frequent side effects are palpitation, flushing, ankle edema, hypotension, headache, drowsiness and nausea. These are related to peaks of drug level in blood: can be minimized by low starting dose or use of

retard formulation. Ankle edema is not due to fluid retention, but because of greater dilatation of precapillary than postcapillary vessels. Nifedipine has paradoxically increased the frequency of angina in some patients. Higher mortality among post MI patients has been confirmed. However, it has been safely administered with β blockers and digoxin.

By its relaxant effect on bladder nifedipine can increase urine voiding difficulty in elderly males. Gastroesophageal reflux may be worsened by all DHPs due to relaxation of lower esophageal sphincter.

Amlodipine Pharmacokinetically it is the most distinct DHP and the most popular. Oral absorption is slow, but complete; peak blood level occurs after 6 to 9 hr—the early vasodilator side effects (palpitation, flushing, headache, postural dizziness) are largely avoided. Because of less extensive and less variable first pass metabolism, its oral bioavailability is higher and more consistent. Volume of distribution and $t_{1/2}$ are exceptionally long: diurnal fluctuation in blood level is small and action extends over the next morning.

Dose: 5–10 mg OD; **AMLOPRES**, **AMCARD**, **AMLOPIN**, **MYODURA** 2.5, 5, 10 mg tabs.

S(–)Amlodipine The single enantiomer preparation is effective at half the dose and is claimed to cause less ankle edema.

Dose: 2.5–5 mg OD;

S-NUMLO, **S-AMCARD**, **ASOMEX**, **ESAM** 2.5, 5 mg tabs.

Felodipine It differs from nifedipine in having greater vascular selectivity, larger tissue distribution and longer $t_{1/2}$. It is approved for symptomatic treatment of Raynaud's disease. The extended release preparation is suitable for once daily administration.

Dose: 5–10 mg OD, max. 10 mg BD.

FELOGARD, **PLENDIL**, **RENDIL** 2.5, 5, 10 mg ER tab.

Nitrendipine This DHP has an oral bioavailability of 10–30% and elimination $t_{1/2}$ of 4–12 hours. Nitrendipine has been shown to release NO from the endothelium and inhibit cAMP phosphodiesterase. These may be the additional mechanisms of

vasodilator action. The endothelial NO may retard atherosclerosis. Ventricular contractility and A-V conduction are not depressed. Nitrendipine is indicated in hypertension and angina pectoris.

Dose: 5–20 mg OD; **NITREPIN, CARDIF 10, 20 mg tabs.**

Lacidipine A highly vasoselective DHP suitable for once daily administration. It is claimed to attain higher concentration in vascular smooth muscle membrane, and is approved only for use as antihypertensive.

Dose: 4 mg OD, increase to 6 mg OD if required.

LACIVAS, SINOPIL 2, 4 mg tabs.

Cilnidipine This DHP has been shown to inhibit N-type (neuronal) calcium channels in addition to the L-type channels, because of which it is claimed not to cause reflex tachycardia that occurs with other DHPs. Cilnidipine is approved for use in angina and in hypertension.

Dose: 5–20 mg OD; **CILACAR, CILAGARD 5, 10 mg tabs.**

Nimodipine It is a short-acting DHP which penetrates blood-brain barrier very efficiently due to high lipid solubility and has high affinity for the cerebral blood vessels. It is believed to selectively relax cerebral vasculature and is approved for prevention and treatment of neurological deficit due to cerebral vasospasm following subarachnoid haemorrhage or ruptured congenital intracranial aneurysms. Side effects are headache, flushing, dizziness, palpitation and nausea.

Dose: 30–60 mg 4–6 hourly for 3 weeks following subarachnoid haemorrhage; **VASOTOP, NIMODIP, NIMOTIDE 30 mg tab; 10 mg/50 ml inj.**

Nicardipine It is a highly vasoselective short acting DHP with more pronounced action on coronary and cerebral vessels. Direct effect on cardiac contractility and HR is minimal. Bioavailability of oral nicardipine is 35%; metabolism by CYP2C8, CYP2D6 and CYP3A4 is extensive and elimination $t_{1/2}$ is 2–4 hours. The metabolites are excreted in both urine and faeces.

Nicardipine is water soluble, and is available as aqueous solution for i.v. use in hypertensive emergencies (see p. 618). Orally it is approved for use in chronic stable angina and Raynaud's disease.

Dose: 20–40 mg TDS or 30–60 mg BD as ER tab.

NICARDIPINE 25 mg/10 ml inj. 5–15 mg/hour i.v. infusion.

Lercanidipine Another DHP similar to nifedipine, but with longer duration of action. Peak plasma concentrations occur at 1.5–3 hrs; $t_{1/2}$ is 5–10 hours. It is indicated in hypertension at a dose of 10–20 mg OD.

LEREZ, LERKA 10, 20 mg tabs.

Benidipine A long-acting DHP that owes its long duration of action to slow dissociation from the DHP receptor on the smooth muscle cell. Marketed only in India and Japan, it is indicated in hypertension and angina pectoris.

Dose: 4–8 mg OD; **CARITEC 4, 8 mg tab.**

PHARMACOKINETICS

The pharmacokinetic parameters of representative Ca^{2+} channel blockers are presented in Table 40.3. All CCBs are well absorbed orally, peak occurring at 1–3 hr (except amlodipine 6–9 hr), but the oral bioavailability is incomplete with marked inter- and intra-individual variations. This is due to high first pass metabolism (modest and less variable in case of amlodipine). All are highly plasma protein bound (min.: diltiazem 80%, max.: felodipine 99%).

The CCBs are high clearance drugs with extensive tissue distribution. All are > 90% metabolized in liver and excreted in urine. Some metabolites are active. The elimination $t_{1/2}$ are in the range of 2–6 hr, but that of amlodipine is exceptionally long; followed by lacidipine, nitrendipine and felodipine.

On chronic use verapamil inhibits its own metabolism so that oral bioavailability is nearly doubled and $t_{1/2}$ is prolonged.

Table 40.3: Pharmacokinetic characteristics of selected calcium channel blockers

	Drug	Bioavailability	Vd (L/Kg)	CL (L/hr/Kg)	Active metabolite	Elimin. $t_{1/2}$ (hr)
1.	Verapamil	15–30%	5.0	0.9	Yes	4–6
2.	Diltiazem	40–60%	3.0	0.7	Yes	3–6
3.	Nifedipine	30–60%	0.8	0.42	Minor	2–5
4.	Felodipine	15–25%	10.0	1.0	None	12–18
5.	Amlodipine	60–75%	21.0	0.42	None	35–45

USES

Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease in whom β blockers are contraindicated. The problem of rebound worsening of angina on withdrawal after chronic use is less marked with CCBs than with β blockers.

1. Angina pectoris All CCBs are effective in reducing frequency and severity of *classical as well as variant angina*. Benefit in classical angina appears to be primarily due to reduction in cardiac work, as a result of reduced afterload and the $BP \times HR$ product. Though, they can increase coronary flow in normal individuals, this is unlikely to be significant in patients with fixed arterial obstruction. Exercise tolerance is increased.

Many controlled studies and metaanalysis have concluded that myocardial ischaemia may be aggravated by short-acting DHPs. This may be due to decreased coronary flow secondary to fall in mean arterial pressure, reflex tachycardia and coronary steal. Trials using high dose regular short-acting nifedipine formulation have reported increased mortality among MI patients. The sudden rush of sympathetic activity evoked by each dose has been held responsible for the deleterious effect. The slow and long-acting DHPs do not share this disadvantage.

On the other hand, verapamil and diltiazem have a direct cardiodepressant effect which tends to reduce the O_2 demand. Vasodilatation and reflex sympathetic stimulation is also less marked. Thus, these CCBs are unlikely to aggravate myocardial ischaemia. However, they must be avoided in patients with heart failure or low EF. Amlodipine is the only CCB shown to be safe (not increase mortality) in CHF patients (PRAISE-2 trial, 2013).

Myocardial infarction: The consensus opinion is against use of CCBs in evolving MI as well as to prevent further attacks, but verapamil/diltiazem may be employed for the latter purpose when β blockers are contraindicated. There is no evidence that CCBs reduce mortality or improve outcome in post-MI patients.

The ability of CCBs to prevent arterial spasm is undoubtedly responsible for the beneficial effect in *variant angina*. Reduction of cardiac O_2 demand would also work in the same direction. No significant difference in efficacy among different CCBs has been noted in angina pectoris.

CCBs are not a first line treatment of *unstable angina*, but may be used as add-on therapy to nitrates when coronary vasospasm is prominent and is not counteracted by nitrate alone. Antiplatelet drugs and β blockers + a nitrate are the primary drugs which reduce infarction and mortality in UA. Use of DHPs in non- β blocked patients is to be avoided.

2. Hypertension The long acting DHPs, diltiazem and verapamil are among the first line drugs for hypertension (*see* Ch. 41).

3. Cardiac arrhythmias Verapamil and diltiazem are highly effective in PSVT and for control of ventricular rate in supraventricular arrhythmias (*see* Ch. 39).

4. Hypertrophic cardiomyopathy The negative inotropic action of verapamil can be salutary in this condition.

5. Other uses Nifedipine is an alternative drug for premature labour (*see* p. 359). The DHPs reduce severity of Raynaud's episodes by blocking vasospasm.

DRUG COMBINATIONS IN ANGINA

Along with any of the drugs used for chronic prophylaxis of angina, sublingual short-acting nitrate is allowed on 'as and when' required basis to abort and terminate anginal attacks when they occur. In addition to the symptomatic treatment with antianginal drugs, therapy aimed at modifying the course of coronary artery disease (CAD), and at cardioprotection with antiplatelet drugs, statins and ACE inhibitors is advised by professional guidelines. The β blockers ward-off attacks of angina as well as afford cardioprotection.

Of the three major classes of antianginal drugs described above, generally one agent is used initially; choice depends on the stage and severity of disease, associated cardiac/other medical conditions and individual acceptability of side effects. The antianginal efficacy and tolerability of long-acting nitrates (including transdermal GTN), β blockers and long-acting CCBs is similar. However, direct comparative studies have found β blockers to achieve greater reduction in the number of anginal attacks than CCBs. Moreover, they afford survival benefit. When monotherapy is unable to provide adequate relief in tolerated doses, concurrent use of 2 or 3 drugs may be required.

I. β blocker + long-acting nitrate combination is rational in classical angina because:

- (a) Tachycardia due to nitrate is blocked by β blocker.
- (b) The tendency of β blocker to cause ventricular dilatation is counteracted by nitrate.
- (c) The tendency of β blocker to reduce total coronary flow is opposed by nitrate.

II. The above advantages may also be obtained by combining a slow acting DHP (in place of nitrate) with β blocker. The DHPs are particularly suitable if there is an element of coronary vasospasm in classical angina. However, verapamil or diltiazem should not be used with β blocker since their depressant effects on SA and A-V node may add up.

III. Nitrates primarily decrease preload, while CCBs have a greater effect on afterload and on coronary flow. Their concurrent use may decrease cardiac work and improve coronary perfusion to an extent not possible with either drug alone. This combination may be especially valuable in severe vasospastic angina, and when β blockers are contraindicated.

IV. In the more severe and resistant cases of classical angina, combined use of all the three classes is indicated. Since their primary mechanism of benefit is different, supraadditive results may be obtained.

- Nitrates primarily decrease preload.
- CCBs mainly reduce afterload + increase coronary flow.

- β blockers decrease cardiac work primarily by direct action on heart.

Verapamil/diltiazem should be avoided in such combinations.

POTASSIUM CHANNEL OPENER

Minoxidil and diazoxide are K^+ channel openers which were used earlier in severe hypertension and hypertensive emergencies. *Nicorandil* is a K^+ channel opener which was introduced as an antianginal drug in the 1990s, and is sporadically used as alternative to nitrates/CCBs. Multiple types of K^+ channels regulate movement of this ion across the cell membrane, out of which nicorandil opens the ATP-sensitive K^+ channels.

Nicorandil This dual mechanism antianginal drug activates ATP sensitive K^+ channels (K_{ATP}) in smooth muscle membrane thereby hyperpolarizing and relaxing it. The vasodilator action is partly antagonized by the K^+ channel blocker glibenclamide. Like nitrates it also acts as a NO donor—relaxes blood vessels by increasing cGMP. Thus, arterial dilatation is coupled with venodilatation, and both cardiac preload as well as afterload are reduced. Coronary flow is increased. No significant effects on cardiac contractility and conduction have been noted.

Beneficial effects on angina frequency and exercise tolerance comparable to nitrates and CCBs have been obtained in stable as well as vasospastic angina. Nicorandil is believed to exert cardioprotective action by simulating 'ischaemic preconditioning' as a result of activation of mitochondrial K_{ATP} channels. Ischaemic preconditioning is a phenomenon in which brief periods of ischaemia and reperfusion exert a cardioprotective effect on subsequent total vascular occlusion, and involves opening of mito. K_{ATP} channels.

A large 'Impact of nicorandil in angina' (IONA, 2002) randomized trial found nicorandil to reduce acute coronary events in high risk stable angina patients.

Nicorandil is well absorbed orally, nearly completely metabolized in liver and is excreted in urine. It exhibits biphasic elimination; the

initial rapid phase $t_{1/2}$ is 1 hour and later slow phase $t_{1/2}$ is 12 hours.

Side effects of nicorandil are flushing, palpitation, weakness, headache, dizziness, nausea and vomiting. Large painful aphthous ulcers in the mouth, which heal on stopping nicorandil have been reported. Nitrate like tolerance does not occur with nicorandil, but it has the potential to interact with sildenafil.

Dose: 5–20 mg BD; **NIKORAN**, 5, 10 mg tabs, 2 mg/vial, 48 mg/vial inj; **KORANDIL** 5, 10 mg tabs.

Nicorandil is a 2nd line antianginal drug, whose efficacy and long term effects are less well established. It has failed to acquire wide acceptance, but may be useful in resistant angina when combined with other drugs. Administered i.v. during angioplasty for acute MI, it is claimed to improve outcome.

OTHER ANTIANGINAL DRUGS

1. Dipyridamole It is a powerful coronary dilator; increases total coronary flow by preventing uptake and degradation of adenosine which is a local mediator involved in autoregulation of coronary flow in response to ischaemia. It dilates resistance vessels and abolishes autoregulation, but has no effect on larger conducting coronary vessels. Cardiac work is not decreased because venous return is not reduced. Accordingly, it fails to relieve anginal symptoms or avert ECG changes.

The pharmacological success but therapeutic failure of dipyridamole has been explained on the basis of 'coronary steal' phenomenon (Fig. 40.5C). By dilating resistance

vessels in nonischaemic zone as well, it diverts the already reduced blood flow away from the ischaemic zone.

Dipyridamole inhibits platelet aggregation. By potentiating PGI_2 and increasing cAMP in platelets, it enhances antiaggregatory influences. Though not useful as an antianginal drug, it is being employed as an adjuvant antiplatelet drug (see Ch. 45)

2. Trimetazidine This antianginal drug acts by nonhaemodynamic mechanisms. There is no effect on determinants of myocardial O_2 consumption, such as HR and BP, both at rest as well as during exercise, but angina frequency is reduced and exercise capacity is increased. In patients not adequately controlled by long-acting nitrate or β blocker or CCB, addition of trimetazidine further reduced anginal attacks and increased exercise duration.

The mechanism of action of trimetazidine is uncertain, but it may improve cellular tolerance to ischaemia by modulating myocardial metabolism. It has been shown to inhibit the mitochondrial *long chain 3-ketoacyl-CoA thiolase (LC3-KAT)*, a key enzyme in fatty acid oxidation. It thus reduces fatty acid oxidation and promotes glucose oxidation in myocardium. Ischaemic myocardium shifts to utilizing fatty acid as substrate, thereby increasing requirement of O_2 for the same amount of ATP generated. Since oxidation of fatty acid requires more O_2 , shift back of substrate to glucose would reduce O_2 demand. Trimetazidine has been labelled as pFOX (fatty acid oxidation pathway) inhibitor.

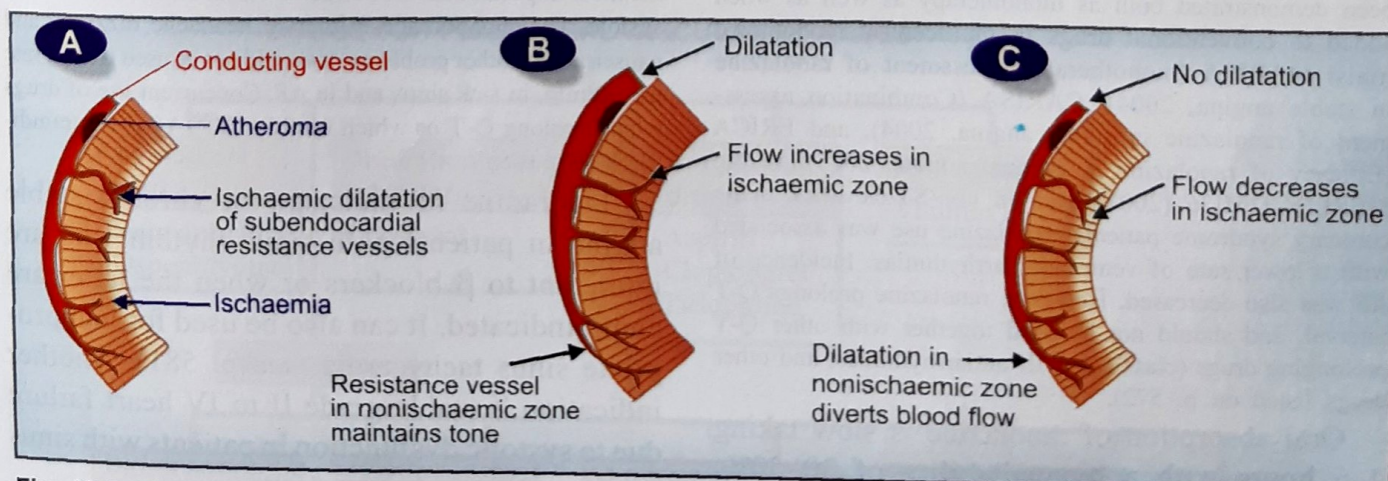


Fig. 40.5: Diagrammatic representation of coronary haemodynamics. A—in classical angina, B — Selective nitrate action on conducting vessels, which along with ischaemic dilatation of resistance vessels, increases flow to the subendocardial region → relief of angina. C—Dipyridamole action on all resistance vessels increases blood flow to nonischaemic zone to the detriment of ischaemic zone → coronary steal

Trimetazidine is absorbed orally, partly metabolized and largely excreted unchanged in urine; $t_{1/2}$ is 6 hr. It is generally well tolerated; side effects are—gastric burning, dizziness, fatigue and muscle cramps. Reversible parkinsonism has been reported in the elderly.

For ischaemic heart disease, trimetazidine has been used in France, Spain, some other European countries and in India, but not in the UK or USA. It is mostly an add-on medication to conventional therapy in angina and post-MI patients.

Dose: 20 mg TDS.

FLAVEDON, CARVIDON, TRIVEDON 20 mg tabs, 35 mg modified release tab.

3. Ranolazine This novel antianginal drug primarily acts by inhibiting a late Na^+ current (late I_{Na}) in the myocardium which indirectly facilitates Ca^{2+} entry through $\text{Na}^+/\text{Ca}^{2+}$ exchanger. Reduction in Ca^{2+} overload in the myocardium during ischaemia decreases contractility and has a cardioprotective effect. Sparing of fatty acid oxidation during ischaemia in favour of more O_2 efficient carbohydrate oxidation by inhibiting LC3KAT has also been demonstrated. This was earlier believed to be the main mechanism of antianginal action of ranolazine, but is now considered secondary. Ranolazine has no effect on HR and BP, but prolongs exercise duration in angina patient.

The efficacy of ranolazine in decreasing frequency of anginal attacks and in prolonging exercise duration has been demonstrated both as monotherapy as well as when added to conventional drugs in multicentric randomized trials: MARISA (monotherapy assessment of ranolazine in stable angina, 2004), CARISA (Combination assessment of ranolazine in stable angina, 2004), and ERICA (Efficacy of ranolazine in chronic angina, 2005). In the MERLIN-TIMI36 (2007) trial on non-ST-elevation acute coronary syndrome patients, ranolazine use was associated with a lower rate of ventricular arrhythmias. Incidence of AF was also decreased. However, ranolazine prolongs Q-T interval, and should not be used together with other Q-T prolonging drugs (class I and III antiarrhythmics, and other drugs listed on p. 572).

Oral absorption of ranolazine is slow taking 4–6 hours with a bioavailability of 30–50%. It is metabolized in liver mainly by CYP3A4 and excreted in urine, with an average $t_{1/2}$ of 7 hours. Side effects reported are dizziness,

weakness, constipation, postural hypotension, headache and dyspepsia. It should not be given to patients taking CYP3A4 inhibitors, but can be given to patients taking sildenafil.

Dose: 0.5–1.0 g BD as SR tab; **RANOZEX, RANX, CARTINEX, REVULANT, RANOLAZ** 0.5 g SR tab.

4. Ivabradine This 'pure' heart rate lowering antianginal drug has been introduced recently as an alternative to β blockers. The only significant action of ivabradine is blockade of cardiac pacemaker (sino-atrial) cell 'f' channels, which are 'funny' cation channels that open during early part of slow diastolic (phase 4) depolarization. The 'f' channels are expressed primarily on the sino-atrial cells, and in some measure on retinal cells. The inward current (I_f) resulting from opening of 'f' channels determines the slope of phase 4 depolarization. Selective blockade of I_f current by ivabradine results in heart rate reduction without any other electro-physiological or negative inotropic or negative lusitropic (slowing of myocardial relaxation) effect. Heart rate reduction decreases cardiac O_2 demand and prolongation of diastole tends to improve myocardial perfusion (O_2 supply). Accordingly, in clinical trials, ivabradine has been found to improve exercise tolerance in stable angina and reduce angina frequency.

Ivabradine is well absorbed orally, 40% bioavailable due to first pass metabolism; degraded by CYP3A4 and excreted in urine with a $t_{1/2}$ of 2 hours. Apart from excess bradycardia, the most important adverse effect is visual disturbance. Extrasystoles, prolongation of P-R interval, headache, dizziness and nausea are the other problems. It should not be used if heart rate is $<60/\text{min}$, in sick sinus and in AF. Concurrent use of drugs which prolong Q-T or which inhibit CYP3A4 is contraindicated.

Ivabradine is indicated in chronic stable angina in patients with sinus rhythm who are intolerant to β blockers or when the latter are contraindicated. It can also be used for inappropriate sinus tachycardia (*see* p. 581). Another indication is stable grade II to IV heart failure due to systolic dysfunction in patients with sinus rhythm $>70/\text{min}$ (*see* p. 568).

Dose: Initially 5 mg BD, increase if needed to 7.5 mg BD. Elderly 2.5 mg BD.

IVABRAD, BRADIA, IVABEAT 5, 7.5 mg tab.

DRUGS FOR PERIPHERAL VASCULAR DISEASES

Peripheral vascular diseases (PVDs) are either primarily occlusive (Buerger's disease with intermittent claudication of legs), or mainly vasospastic (Raynaud's phenomenon with episodic blanching $\pm$ cyanosis of fingers followed by hyperaemia), or both as in arteriosclerotic/diabetic vascular insufficiency, ischaemic leg ulcers, frost bite, gangrene, cerebrovascular inadequacy, etc. Increased cardiovascular risk is associated with all PVDs. Measures that reduce cardiovascular risk (smoking cessation, BP normalization, antiplatelet drugs, diabetes control, statins, weight management, exercise training) have salutary effect on PVDs as well. In addition, vasodilators and many other types of drugs are used (*see* Chart). Most of these drugs have other primary indications and are described elsewhere in the book. The remaining are briefly considered below.

1. Cycandelate It is a papaverine like general smooth muscle relaxant which increases cutaneous, skeletal muscle and cranial blood flow in normal individuals. However, benefits in PVD are minor and restricted to conditions with vasospasm. Side effects are flushing, palpitation and headache.

Dose: 200–400 mg TDS; **CYCLOSPASMOL**, **CYCLASYN** 200, 400 mg tab/cap.

2. Xanthinol nicotinate (Nicotinyl xanthinate) It is a compound of xanthine and nicotinic acid, both of which are vasodilators. It increases blood flow in many vascular beds and has been promoted for cerebrovascular disorders and PVDs, but therapeutic benefits are insignificant.

Dose: 300–600 mg TDS oral; 300 mg by i.m. or slow i.v. injection; **COMPLAMINA** 150 mg tab, 500 mg retard tab, 300 mg/2 ml inj.

3. Pentoxifylline (Oxpentifylline) An analogue of theophylline and a weak phospho-

diesterase (PDE) inhibitor, which has been shown to increase blood flow in ischaemic areas by reducing whole blood viscosity and by improving flexibility of RBCs. The *rheological* (dealing with property of flow) action rather than vasodilatation is said to be responsible for improving passage of blood through microcirculation. Oral doses do not affect heart rate, t.p.r. or BP.

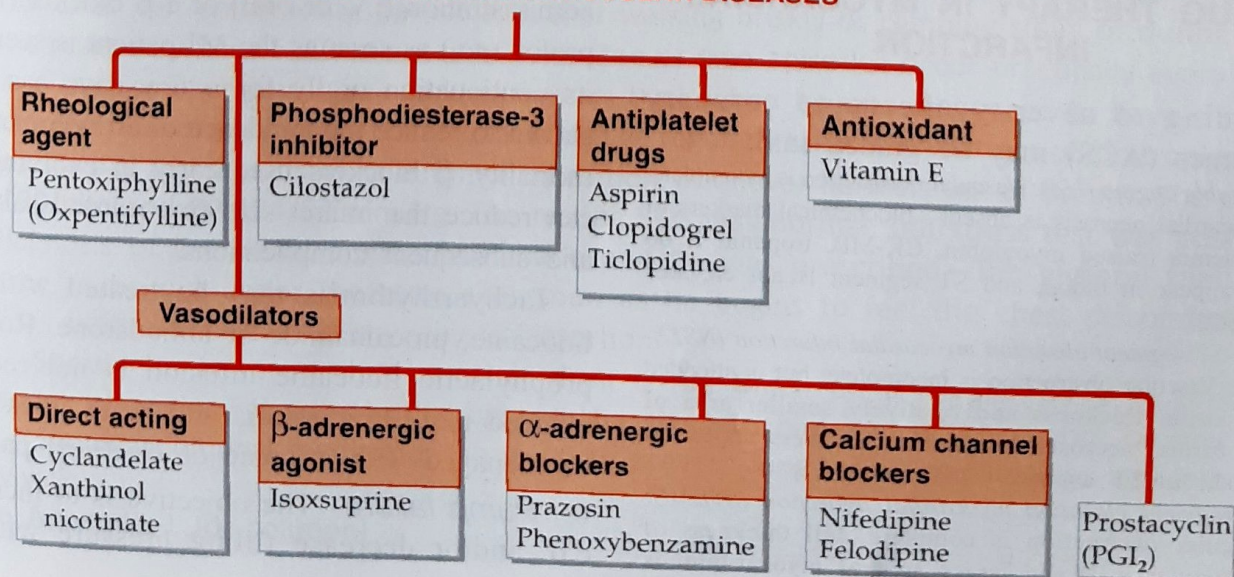
Pentoxifylline is usually well tolerated: side effects are nausea, vomiting, dyspepsia and bloating which can be minimized by taking the drug after meals.

Dose: 400 mg BD-TDS; **TRENTAL-400**, **FLEXITAL** 400 mg SR tab, 300 mg/15 ml for slow i.v. injection.

Pentoxifylline is mainly used in intermittent claudication (calf pain on walking) due to occlusive vascular disease (Buerger's disease). Other conditions claimed to be improved are: trophic leg ulcers, transient ischaemic attacks (TIAs), and chronic cerebrovascular insufficiency. However, overall benefits are minimal.

4. Cilostazol This is a PDE-3 inhibitor (like the inodilator inamrinone and milrinone, (*see* p. 568) which increases intracellular cAMP in platelets and vascular smooth muscle resulting in antiaggregatory and vasodilator effects. In clinical trials it has increased walking distance in patients with intermittent claudication and appears to be more effective than pentoxifylline. Since long-term oral milrinone therapy for heart failure has increased cardiac mortality and has been discontinued, concern is expressed

DRUGS FOR PERIPHERAL VASCULAR DISEASES



about long-term safety of cilostazol. However, no increase in cardiovascular mortality has so far been observed with cilostazol, but a warning has been issued not to use it in patients with heart failure. It is also not to be used in patients who have pain even at rest, or in those with tissue necrosis.

The most common side effect is headache. Others are palpitation, dizziness, nausea, vomiting, weakness and increase in ventricular ectopics or nonsustained VT. Cilostazol is extensively metabolized by CYP3A4 and CYP2C19 into active and inactive metabolites, together having elimination $t_{1/2}$ of ~ 12 hours. It should not be administered along with inhibitors of CYP3A4 and CYP2C19, which increase its toxicity.

Cilostazol is indicated exclusively for intermittent claudication in patients with no rest pain or heart failure.

Dose: 100 mg BD, 30 min before or 2 hours after food.

PLETOZ, CILODOC, STILOZ, ZILAST 50, 100 mg tabs.

Comment It is to be noted that no vasodilator can overcome organic obstruction. Because ischaemia itself is a potent vasodilator stimulus in skeletal muscle and cerebral beds, vasodilators can even divert the blood to nonischaemic areas (steal phenomenon). They obviously are more useful when vasospasm is wholly or partly involved, e.g. in Raynaud's phenomenon. Intravenous PGI₂ has been employed in severe cases with rest pain (p. 207).

DRUG THERAPY IN MYOCARDIAL INFARCTION

According to severity, the acute coronary syndromes (ACS) may be graded into:

- *Unstable angina (UA):* Vascular obstruction is incomplete, myocardial necrosis is absent—biochemical markers of ischaemia (raised myoglobin, CK-MB, troponin I) do not appear in blood, and ST segment is not elevated in ECG.
- *Non-ST segment elevation myocardial infarction (NSTEMI):* Vascular obstruction is incomplete, but is attended by partial thickness and relatively smaller area of myocardial necrosis; biochemical markers appear in blood, but ST segment is not elevated.
- *ST segment elevation myocardial infarction (STEMI):* Vascular obstruction is complete, full thickness of ventricular wall and larger area of myocardium is

necrosed, biochemical markers are prominent and ST segment in ECG is elevated.

However, UA and NSTEMI may progress to STEMI.

Myocardial infarction (MI) is ischaemic necrosis of a portion of the myocardium due to sudden occlusion of a branch of coronary artery. An acute thrombus at the site of atherosclerotic obstruction is the usual cause. About ¼ patients die before therapy can be instituted. The remaining are best treated in specialized coronary care units with continuous monitoring of the haemodynamic parameters, biochemical markers and ECG to guide the selection of drugs and dosage. Those who receive such facility can be greatly benefitted by drug therapy, which according to needs of individual patients is directed to:

1. **Pain, anxiety and apprehension** After pain is not relieved by 3 doses of GTN given 5 min apart, an opioid analgesic (morphine) or diazepam is administered parenterally.
2. **Oxygenation** By O₂ inhalation and assisted respiration, if needed.
3. **Maintenance of blood volume, tissue perfusion and microcirculation** Slow i.v. infusion of saline/dextrose (avoid volume overload).
4. **Correction of acidosis** Acidosis occurs due to lactic acid production; can be corrected by i.v. sod. bicarbonate infusion.
5. **Prevention and treatment of arrhythmias** If there are no contraindications, prophylactic administration (i.v. or oral) of a β blocker (metoprolol, etc.) as soon as the MI patient is seen and its continuation orally for a few days has been shown to reduce the incidence of arrhythmias and mortality. β blockers used early in evolving MI can reduce the infarct size (myocardial salvage) and subsequent complications.

Tachyarrhythmias may be treated with i.v. lidocaine, procainamide or amiodarone. Routine prophylactic lidocaine infusion is not recommended now. Bradycardia and heart block may be managed with atropine or electrical pacing.

6. **Pump failure** The objective is to increase c.o. and/or decrease filling pressure without

unduly increasing cardiac work or lowering BP. Drugs used for this purpose are:

(a) *Furosemide*: indicated if pulmonary wedge pressure is > 20 mm Hg. It decreases cardiac preload.

(b) *Vasodilators*: Venodilator (GTN slow i.v. infusion) is mainly used. It may be supplemented by i.v. esmolol or labetalol.

(c) *Inotropic agents*: dopamine or dobutamine i.v. infusion may be needed to augment the pumping action of heart and tide over the crisis.

7. Prevention of thrombus extension, embolism, venous thrombosis Aspirin (162–325 mg) should be given for chewing and swallowing as soon as MI is suspected (if not already being taken on a regular basis). This is continued at 80–160 mg/day. Clopidogrel/prasugrel/ticagrelor may be given as alternative add-on antiplatelet drugs. Anticoagulants (heparin/fondaparinux followed by oral anticoagulants) are used primarily to prevent deep vein thrombosis (risk is increased due to bed rest) and pulmonary/systemic arterial embolism. The value of anticoagulants in checking coronary artery thrombus extension is uncertain. Any benefit is short-term; anticoagulants are not prescribed on long-term basis now (see Ch. 45).

8. Thrombolysis and reperfusion Fibrinolytic agents, i.e. plasminogen activators—alteplase/tenecteplase to achieve reperfusion of the infarcted area (see Ch. 45) are indicated only in STEMI or high risk NSTEMI. Unless thrombolysis can be started within 1–2 hours of MI symptom onset, primary percutaneous coronary intervention (PCI) with stenting is now the preferred revascularization procedure, wherever available.

9. Prevention of remodeling and subsequent CHF ACE inhibitors/ARBs are of proven efficacy and afford long-term survival benefit (see Ch. 36). They should be started as soon as the patient is haemodynamically stable.

10. Prevention of future attacks

(a) Platelet inhibitors—aspirin or clopidogrel or similar drug given on long-term basis is routinely prescribed (see Ch. 45).

(b) β blockers—These drugs reduce risk of reinfarction, CHF and mortality. All patients not having any contraindication are put on a suitable β blocker for at least 2 years.

(c) Control of hyperlipidaemia—dietary substitution with unsaturated fats, hypolipidemic drugs especially statins are routinely prescribed, irrespective of blood cholesterol level. They have been shown to reduce risk of cardiovascular events (see Ch. 46).

PROBLEM DIRECTED STUDY

40.1 A 55-year-old man presented with complaints of tightness and discomfort over middle part of chest felt episodically, particularly after walking briskly or climbing stairs or during sex. This is relieved within 5–10 minutes of rest. One or two episodes occur practically every day. He is a past smoker who quit smoking 5 years back when he was diagnosed to have chronic obstructive pulmonary disease (COPD), for which he regularly takes 2 inhalations of Ipratropium Br. 3 times a day and 2 puffs of salbutamol inhalation whenever he feels out of breath. The pulse was 90/min and BP 124/82 mm Hg. The resting ECG was normal, but stress test was positive. A diagnosis of exertional angina was made and he was prescribed—Tab glyceryl trinitrate 0.5 mg to be put under the tongue as soon as he begins to feel the chest discomfort, as well as before undertaking any physical exertion.

(a) Should he be prescribed another drug to be taken on a regular basis to prevent episodes of angina? If so, which drugs can be given to him and which cannot be given?

(b) Should additional medication be given to prevent long-term complications and improve survival?

(see Appendix-1 for solution)