Coronary Artery Disease

2

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2.1 Atherosclerosis

2.1.1 Cardiovascular Disease: Background

Environmental and patient-related risk factors cause atherosclerosis, a diffuse disease affecting virtually all the arterial territories (the noncardiac impact is reviewed in Chap. 11); atherosclerosis may cause ischemia; ischemia may manifest either as stable angina pectoris, or as acute coronary syndrome (ACS); ACS may manifest either as unstable angina, or as acute MI; and finally, acute MI may show ST-elevations (STEMI) or not (NSTEMI). Atherosclerosis will be discussed first, and clinical ischemic syndromes (ACS, stable angina) will be dealt with subsequently. As atherosclerosis and ischemia are strongly linked, there is substantial overlap in regard to diagnosis and therapy. To avoid redundancies while preserving a systematic approach, diagnosis of atherosclerosis and of ischemia will be presented together. In regard to therapy, atherosclerosis treatment (tantamount to risk factor management, assuming revascularization is only carried out in the presence of ischemia) will be presented in Sect. 2.1, while the management of ischemia will be discussed in Sects. 2.1and 2.3.

2.1.2 Atherosclerosis: Definition and Mechanisms

Atherosclerosis is a continuum of lesions resulting from the deposition of cholesterol in the arterial wall, favored by circulating oxidized LDL cholesterol. In turn, cholesterol deposition triggers an inflammatory reaction resulting in arterial wall thickening and decrease in the vessel

G.A. Adelmann, *Cardiology Essentials in Clinical Practice*,
DOI: 10.1007/978-1-84996-305-3_2, © Springer-Verlag London Limited 2011

internal diameter (lumen narrowing or total occlusion). The latter may be chronic, by gradually increasing cholesterol and inflammatory cells deposits, smooth muscle proliferation, and fibrosis, or acute (thrombosis on the surface of a fissured or ruptured plaque, the most significant complication of atherosclerosis). Atherosclerosis tends to involve a multitude of sites, and is thus a "diffuse" disease; however, in a given artery, it often presents as spotty involvement (although "even" atherosclerotic "lining" of the endothelium is also possible). Veins are usually spared, unless surgically transposed into an arterial bed (e.g., saphenous vein grafts in CABG surgery). Macroscopically, the affected vessels (visualized at surgery or autopsy, or indirectly, by invasive or noninvasive imaging) usually display *atherosclerotic plaques* of different shapes and contours, protruding into the vessel lumen to different degrees. Atherosclerotic plaque starts evolving in the first years of life (Table 2.1). The initial lesion consists of infiltration with macrophages replete with oxidized LDL ("foam cells"), alongside minimal extracellular lipid deposits. The exact trigger of cholesterol deposition is debated; endothelial lesions produced by tobacco smoke or unidentified infective agents might play a role. Atherosclerosis involves a cycle of oxidized LDL cholesterol deposition (partly countered by cholesterol removal as HDL), vessel inflammation, and further endothelial injury. Occasionally, these phenomenons are very rapid, causing the so-called *accelerated atherosclerosis* (substantial plaque growth and smooth muscle proliferation).

The healing process involves fibrosis and calcification, increasing vessel wall rigidity and encroaching on the lumen. By the same token, these plaques are "stable," i.e., not prone to fissure/rupture. It is precisely the less obstructive plaques that tend to rupture and expose the thrombogenic core to blood flow, with platelet activation and platelet thrombus, then fibrin thrombus formation.

In the 1980s, at the onset of the modern era of atherosclerosis science, the degree of vascular lumen decrease was considered to simply reflect the plaque burden: the larger the plaque, the greater the degree of vessel obstruction, it was assumed, with the relationship being a linear one. Later work, however, has disproven this. In the acute setting (ACS), vascular occlusion is due not to the physical burden of the plaque, but to an occluding thrombus, while in the chronic setting, the relationship between plaque burden and percent stenosis is not linear. The blood vessel is a living structure, reacting to the atherosclerotic lesions by *vascular remodeling*, classified as (a) *positive*, i.e., vascular dilatation accommodating the plaque: the lumen is unchanged for a plaque burden ≤40%, i.e., an amount of plaque that would obstruct 40% of the lumen, were the vessel an inert conduit. Thus, wall thickness and *outer* vessel diameter increase, but the *inner* diameter remains unchanged; (b) *negative* (significant lumen decrease despite relatively modest plaque burden).

- Positive remodeling – positive effect (lumen larger than expected, given the plaque burden)
- Negative remodeling – negative effect (lumen smaller than expected, given the plaque burden)

Table 2.1 The phases of atherosclerosis: a clinical perspective

Stage	Approximate patient age	Microscopic structure	Macroscopic aspect	Clinical relevance
Initial lesion	Childhood	Isolated macrophages replete with oxidized LDL ("foam cells")	"Normal" endothelium	Clinically inapparent; ideal time for healthy lifestyle choices
Fatty streak	Teens to early adulthood	More foam cells, minimal extracellular lipid deposits.	Endothelial streak	
Intermediate lesion	>20	Extracellular lipid deposits increase[a]	Atherosclerotic plaque	Clinically inapparent or evident[b] (stable angina); primary or secondary prevention
Atheroma	>30	Core of extracellular lipids[a]	Atherosclerotic plaque	
Fibroatheroma	>30	Core of extracellular lipids,[a] smooth muscle proliferation, fibrosis, calcification	Atherosclerotic plaque	
Fissured plaque	>30	As above; ruptured or fissured fibrous cap	Fissured plaque, occlusive thrombus	ACS or self-limiting event

[a]Alongside intracellular lipids

[b]The first sign of disease is an acute ischemic event or SCD in up to two-thirds of males and in up to half of the females

The impact of atherosclerosis is far more complex than simple physical bulk, as the plaque causes a host of functional processes, globally known as *endothelial dysfunction.* These processes include, but are not limited to, a decrease in NO secretion and an increased release of serotonin, thromboxane A_2, and thrombin, causing vasoconstriction or abnormal vasodilatation under vasoactive substances, at the site of the plaque. The prototype of vasospastic angina is Prinzmetal's angina. Atherosclerotic plaques vary widely not only in regard to their bulk, but also in their proneness to rupture and cause thrombosis and MI. In a potentially groundbreaking discovery, Hydrogen Sulfide was found to act as a major physiologic vasodilator and regulator of BP, alongside NO.

Accelerated atherosclerosis consists in substantial plaque growth (smooth muscle proliferation), as a result of initial platelet activation. *Vulnerable plaque*, i.e., fissure- (rupture-) and thrombosis-prone plaque has certain characteristics, discussed under "ACS."

Stable plaque causes stable angina; unstable (vulnerable) plaque causes unstable angina or MI. Many vulnerable plaques are shallow (non-obstructive).

The clinical impact of atherosclerosis: The main cause of ischemia, potentially affecting any organ system, atherosclerosis is also the main cause of morbidity and mortality worldwide. Some organs are more affected than others, mainly the heart (ischemic heart disease), brain (stroke), and lower limbs (PVD). Ischemic injury in other organs (mesenteric arteries, kidneys, etc.) is common as well.

2.1.3 Risk Factors for Atherosclerosis

Hypertension: see Ch. 3

Lipids: *Cholesterol* is a lipid essential for life. It is a component of cell membranes and a precursor of adrenal and sex hormones, liposoluble vitamins, and bile salts. The main source of cholesterol is endogenous secretion, but alimentary intake is also important. The main dietary sources include cheese, egg yolks, beef, pork, poultry and shrimp. Serum cholesterol levels are more strongly correlated with the total intake of saturated and trans-fats than with the intake of cholesterol as such (The trans-fats occur in trace amounts in natural products, but are much more plentiful in some brands of margarine, shortening, fast food, snacks, and commercial baked goods. They increase LDL and decrease HDL levels). In the circulating blood, cholesterol occurs as the lipid moiety of a lipoprotein compound, which, unlike cholesterol itself, is soluble in the serum. In increasing order of density, the types of lipoproteins include: chylomicrons, very low, intermediate, low and high density lipoprotein (VLDL, IDL, LDL, HDL), all atherogenic, with the exception of HDL, which is antiatherogenic. The strongest focus has been on oxidized *LDL* ("bad cholesterol"), which initiates and maintains the atherosclerotic plaque. The desirable levels of total and LDL cholesterol depend on the past medical history (Table 2.2). LDL is usually calculated based on the formula: LDL = total cholesterol − total HDL − VLDL, with VLDL approximated as 20% of the TG value. This assessment is based on three different measured values, each with their own coefficient of error, and thus itself subject to error. The calculations are not accurate if the TG level is >400 mg/dL (4.5 mmol/L). Therefore, direct LDL

Table 2.2 Total and LDL cholesterol: targets[a]

Medical history	LDL	HDL	Total cholestrol
Primary prevention of atherosclerosis			
≤1 risk factor, not including diabetes	<115 (<3)	Low: ♂, <40 (<1); ♀, <45 (<1.2); satisfactory 40–60 (1–1.5); high >60 (>1.5)	<190 (<5)
≥2 risk factors; diabetes	<100 (<2.5); if feasible[b], <80 (<2)		<175 (<4.5); if feasible, <155 (<4)
Secondary prevention of atherosclerosis			
All patients	<100 (<2.5); in severe cases, consider <80 (<2)[b]	As for primary prevention	<175 (<4.5)

[a]Milligram per deciliter (mmol/L)

[b]The AHA advocates decreases to <70 mg/dL <1.8 mmol/L)

measurement is gaining popularity. It is recommended to test cholesterol every 5 years for people ≥20 years of age. While LDL remains pivotal for risk assessment and setting therapeutical goals, patients with the same LDL level can have a significantly different risk of atherosclerosis, even after adjusting for other factors (e.g., TG level, HDL level). The atherogenic effect of LDL is strongest for small, dense LDL particles, sdLDL; sdLDL increases are more common in CAD patients than increased LDL levels as such.

Serum levels of sdLDL are reflected by the level of *apolipoprotein B*, a ligand enabling LDL uptake by the cells (there is only one apoB molecule per LDL particle, which accounts for the good correlation). Apolipoprotein B is not "dedicated" to LDL, but is present in all the lipoproteins (VLDL, IDL, LDL, chylomicrons). As all of the apoB is in atherogenic lipids, and all atherogenic lipids include apoB, apoB indicates the total atherogenic burden in the circulating blood. It is a better predictor of CAD than LDL, in patients with both normal and increased LDL levels. In the general population, values >150 mg/dL are considered increased, while in high-risk patients (additional risk factors or already present atherosclerosis), levels <90 mg/dL or even <80 mg/dL are optimal. Unfortunately, these measurements are still not part of the standard clinical practice. *Apolipoprotein A* and *the ratio apoB/apoA1* are also better risk indicators than LDL, but they, too, are of restricted availability.

HDL ("good cholesterol") is a protective factor only in cultures where unhealthy lifestyles promote a high prevalence of atherosclerosis. This suggests that smoking, obesity, sedentary life style, and diabetes exert their deleterious influence at least partly by decreasing HDL levels. Moderate hypertriglyceridemia is also frequently associated with low HDL levels and with high levels of sdLDL. The protective action of HDL has been traditionally ascribed to mobilization of cholesterol from the vessel wall (and delivery to the liver, for metabolization), but antiinflammatory, antithrombotic, and anti-apoptotic mechanisms are also probable. The desirable levels of HDL cholesterol are >45 mg/dL, and the optimal ratio of total cholesterol to HDL is <5/L (the lower, the better). The higher the HDL levels, the more effective the cardiovascular protection (Table 2.2). The size of HDL particles is also important, large particles being the most protective.

Lp(a) ("lipoprotein little a") is another component of the LDL spectrum; values >30 mg/dL are high-risk for atherosclerosis. Niacin may be effective in decreasing Lp(a) levels.

Non-HDL cholesterol (the sum of the atherogenic cholesterol fractions, i.e., LDL, IDL, and VLDL) is calculated as the difference between total cholesterol and HDL and may be a better risk indicator than LDL; however, the desirable levels are not clear.

The Importance of LDL and HDL: Comments While several landmark studies and meta-analyses have clearly shown a reduction in cardiovascular morbidity and mortality in both primary (WOSCOPS, AFCAPS/TexCAPS, HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, CARDS) and secondary prevention (4S, CARE, LIPID, PROVE-IT-TIMI22, TNT, IDEAL), and while there was a strong relationship between event lowering and decreased LDL levels, recent data has raised some

LDL: Is It the Chief Villain?

The age-honored affirmative answer to this question may have been influenced by several factors.

- The technology bias: initial focus on LDL and HDL was mainly motivated by the then-available technology, and not because of some scientific proof of their prominence as the most harmful lipids. We might be continuing to follow, in the 2000s, technological limitations of the 1960s.
- Besides, LDL assessment itself is subject to error (LDL is not directly measured, but calculated, with unreliable results at high TG concentrations). Additionally, there appears to exist a seasonal variation to LDL levels (lower levels in the summer).
- LDL reduction reduces the risk of clinical events by 40–50%; thus, in more than half of the patients, some other (possibly also lipid-related) mechanism is operative in atherogenesis.
- The ENHANCE study has not found any significant IMT regression (admittedly a surrogate end-point), despite effective LDL lowering.
- Conversely, the JUPITER trial has shown that substantial benefit is to be gained from statins in people with "normal" LDL levels (but elevated CRP levels).
- Despite a great reduction in cardiovascular events, there is little evidence that LDL level reduction prolongs life expectation in any patients but males <70 with already established CAD.

intriguing questions regarding the true prominence of LDL as the main event-driving factor.

Triglycerides: Unto themselves, TG are not taken up into plaque; however, they are hydrolyzed into atherogenic cholesterol-rich remnant particles. Hypertyriglyceridemia is atherogenic by direct toxicity (IDL, small VLDL particles) and by its associated thrombogenic and HDL-decreasing effects. It is frequently associated with other risk factors, (diabetes mellitus, the metabolic syndrome). Levels >150 mg/dL (>1.7 mmol/L) are considered high-risk, but lowering TG is not a primary goal in atherosclerosis management, as TG increase covariates with other risk factors and may not be an independent risk factor. Despite the yet unclear role of TG in the pathogenesis of cardiovascular disease, many clinicians start a second agent (niacin or a fibrate) beside statins, in patients with high TG or very low HDL levels. Moderate, rather than high TG levels are the most hazardous, as very high levels (a significant risk for pancreatitis) tend to involve larger, less toxic particles. If TG are 200–499 mg/dL, non-HDL-cholesterol (total cholesterol-HDL cholesterol) should be <130 mg/dL, and, if feasible, <100 mg/dL.

Therapy of hyperlipidemia: Underlying conditions such as hypothyroidism or nephrotic syndrome must be corrected, as in these patients treatment for dyslipidemia alone will not be successful. The treatment of hyperlipidemia includes dietary and pharmacological measures, and, exceptionally, plasmapheresis. The duration of therapy is usually lifelong.

Diet: Daily cholesterol intake should not exceed 300 mg in healthy subjects, and 200 mg in those with atherosclerosis or multiple risk factors. Saturated fat (*meat or dairy* products such as fatty meats, butter, fat cheese, cream, etc.) should be avoided. *Seafood* is rich in cholesterol and should be eaten in moderation. *Wholegrain cereal, vegetables and fruit*, as well as ≥1 weekly serving of fish (especially the fatty varieties) should be encouraged. Lean meat and low-fat dairy products are also recommended. An egg daily is allowed, as eggs are an excellent source of nutrients and have a low absolute cholesterol content. *Margarine* does not contain cholesterol, but most of the abundant saturated fat it contains is turned into cholesterol in the patient's body. Generally, the harder (less fluid) a margarine, the higher the amount of saturated fat (highest in baking margarine). *Vegetables and fruit* are lipid-poor and may have several additional beneficial actions. *Sterols and stanols* from corn, wheat, and soybeans and *sulfites* from onions, leeks, garlic, cabbage, cauliflower, lettuce, broccoli, radishes might decrease LDL; *lignans*, phytoestrogens found in linseed oil, vegetables, sesame seeds, and pumpkin seeds might decrease LDL and TG. *Dietary fiber* is found in vegetables, mainly grain and cereal. Fiber reduces LDL synthesis (and thus the risk of CAD) and decreases the risk of developing the metabolic syndrome or full-blown diabetes. *Tannin* is an antioxidant from cocoa, chocolate, tea, wine, grapes, and pomegranates; it may inhibit, among others, the oxidation of LDL. As different vegetables contain different phytochemicals, it might be advisable to eat vegetables having a variety of colors. At least five three daily servings (handfuls) of vegetables and two pieces of fruit are recommended. Fresh or frozen vegetables are the best source of nutrients, but canned vegetables are also acceptable (provided they do not contain excessive amounts of salt); vegetable or fruit juice does not provide bulk (unless the pulp is also eaten). Overcooking may destroy some of the nutrients, but normal cooking may actually increase nutrient bioavailability, by breaking the cell walls in the vegetable or fruit; thus, cooking may increase threefold the bioavailability of antioxydants. The much-publicized Mediterranean diet is based on reduced intake of saturated fats, moderate alcohol intake, and high intake of fish, vegetables, and fruit. In lower-risk hypercholesterolemic patients, as well as in case of non-severe LDL elevations, an attempt at dietary correction may be made, with repeat assessment after 3 months. In case of insufficient cholesterol lowering, drug therapy is started, generally with a statin.

Pharmacologic treatment: Therapy of hyperlipiodemia currently revolves around LDL management. TG elevations despite LDL control may justify a further attempt at non-HDL choleserol correction, occasionally with Niacin or fibrates. HDL levels are not a therapeutic target, but may mandate better control, to optimize the ratio of total cholesterol to HDL to <5/L. Antihypercholesterolemic drugs include statins, Ezetimibe, fibrates, Niacin, and bile acid resins. Rarely, plasmapheresis is required. *Statins* are first-choice in hypercholesterolemic patients. They reduce cholesterol levels by 30–50%, usually allowing to reach the recommended levels. If necessary, other agents may be added, or the surrogate aim of cholesterol lowering to ≤50% of the initial level may be chosen. Statins inhibit

hepatic synthesis of cholesterol and TG, by interfering with the activity of HMG-CoA reductase. The most important *adverse effects* (albeit not the most common ones) include headache, LFT derangement (usually reversible), and rhabdomyolysis. Other adverse effects include URTI-like symptoms; GI upset; rash; dizziness, insomnia; joint and muscle pain; albuminuria, hematuria; edema; chest pain; and anaphylaxis or angioneurotic edema. Statins are *contraindicated* in patients with active liver disease, as well as in pregnant or lactating women. Patients under statin treatment require periodic LFT monitoring (discontinuation considered if transaminase levels exceed three times the upper normal limit). In patients with severe myalgia, statins should be discontinued. If myalgia is non-severe, immediate CK measurement is indicated, and statins should be discontinued if CK is elevated. Cholesterol and TG are measured at one month after treatment onset, then annually. The main statins include Atorvastatin (10–80 mg q.d.); Fluvastatin (20–80 mg q.d.); Pravastatin (10–40 mg q.d.); Simvastatin 10–80 mg q.d.); Rosuvastatin (5–40 mg q.d.); and Lovastatin (10–80 mg q.d.). Statins have significant drug interactions, most importantly with fibrates (the risk of rhabdmomyolysis is relatively increased, but remains low). Grapefruit or its juice may increase the levels of Atorvastatin, Lovastatin, and Simvastatin to dangerous levels. Grapefruit should be avoided or be eaten hours apart from statin administration. A class of drugs typically administered chronically, statins actually start exerting their beneficial activity very quickly. Thus, a high loading dose of statin (Atorvastatin 80 mg), given in the 24 h preceding PCI in the statin-naïve patient may provide protection against periprocedural MI.

The practical use of statins first involves establishing a therapeutic aim (Table 2.2), and starting the drug at a routine dosage, with or without a preliminary waiting period of up to 3 months, for maximum effect of dietary changes (Certainly, the use of statins does not obviate the need for a strict diet.). Statin doses are increased according to LDL follow-up results, obtained every 1–3 months. Generally, dosage is doubled up to the maximum allowed dosage. If this is still not sufficient, Ezetimibe may be added, or a more potent statin may be chosen (e.g., Rosuvastatin instead of Simvastatin).

The groundbreaking Jupiter trial has demonstrated that statins reduce cardiovascular morbidity and mortality even in the presence of apparently normal lipid levels, if hsCRP is high. While this trial used Rosuvastatin, the protection is believed to be a class-effect of statins.

LDL Is at Target Levels. Is Lipid Management Successfully Concluded?

Not necessarily. Besides awaiting further data regarding the utility and modality of increasing HDL, it is reasonable to

- Measure CRP, and if high, increase statin dosage
- Measure Lp(a) and if high, start niacin
- Measure apoB levels and consider statin dosage increase, to bring apoB to a target level of <90 mg/dl

Antihyperlipemic therapy in children: The issue of antihyperlipemic therapy in children has been much debated; while early atherosclerosis is the ideal time to initiate primary prevention, there is no experience with life-long anticholesterol therapy. The targets in children are the same as in adults, and dosages depend on age and body weight. Optimal LDL levels are <100 mg/dL (<130 mg/dL acceptable). Therapy (dietary, and, if needed, pharmacologic) is recommended for LDL >190 mg/dL, or, in presence of ≥2 additional risk factors, for LDL >160 mg/dL. In boys, therapy is delayed until age 10, and in girls, until menarche. Healthy life styles should be taught from the earliest age.

Statins: *beyond LDL*: Statins (mostly the newer-generation agents) also lower TG. Rosuvastatin, for instance, decreases TG levels by up to 30%. Statins also increase HDL, but less than fibrates or Niacin. Non-lipid effects of statins include improvement in the endothelial function; antiinflammatory activity; plaque stabilization; and antithrombotic action. In addition to their cardiological use, statins may reduce the incidence of colon and rectal cancer by up to 50%.

Other agents effective in dyslipidemic patients: *Ezetimibe* (10–20 mg q.d.) inhibits intestinal cholesterol absorbtion (cholesterol secreted into the intestine as biliary salts is normally recycled by reabsorbtion). Ezetimibe is usually recommended as a supplement to statins, when a full dose is not effective or not tolerated. If statins are not tolerated at all, Ezetimibe may be used on its own, but results are generally suboptimal. Similarly to statins, it may cause muscle ache or LFT

disturbances, and, additionally, headache and GI upset. Despite an up to 20% LDL level reduction, Ezetimibe does not increase the action of statins in lowering the carotid IMT, a surrogate marker of atherosclerosis evolution. As the results of large trials with this drug will not be available for several years, Ezetimibe use is currently at the physician's discretion. *Bile resins* prevent intestinal recycling of LDL, by increaseing fecal elimination. They have practically no contraindications. The adverse reactions include constipation, diarrhea, flatulence, and inhibition of the intestinal absorbtion of drugs and liposoluble vitamins. Infrequently used since the advent of statins, resins are occasionally required in statin-resistant or -intolerant patients. The main agents include Cholestyramine (2–4 g b.i.d.), Colesevelam (2.5–5 mg b.i.d.), and Cholestypol (1–8 g b.i.d.). *Fibric acid derivatives* activate the peroxisome proliferator-activated receptors (PPARs), to decrease LDL, VLDL and remnant particle levels, decrease hepatic secretion of TG, and increase HDL production. Adverse effects include abdominal pain, nausea, diarrhea, LFT disturbances, eczema, muscular pain and occasional rhabdomyolysis (especially in combination with statins). Gemfibrosil may also cause AF and vision disturbances, and Fenofibrate may cause pancytopenia. Representatives include Bezafibrate (200 mg t.i.d. for the short-acting compound, 400 mg q.d. for the long-acting one); Ciprofibrate (100–200 mg q.d.); Gemfibrosil (600 mg b.i.d., 30 min before meals); and Fenofibrate (200 mg q.d.). The addition of a fibric acid derivative to a statin potentiates the LDL-lowering effect, and has a favorable impact on HDL and TG levels. However, there is increased risk of toxicity, especially to the muscle. The ACCORD study is currently evaluating CVD outcomes in a double-blind manner, comparing Simvastatin + Fenofibrate vs. Simvastatin + placebo. ABT-335 is a derivative of the fibric acid is currently being evaluated as adjunctive antihyperlipemic therapy.

Niacin (vitamin B3, nicotinic acid) blocks fat breakdown in adipose tissue, increasing HDL and reducing total cholesterol, TG, VLDL and LDL levels. It might also be antiinflammatory and inhibit the secretion of leptin (with a major role in atherosclerosis). The dosage is 1–2 g b.i.d. or t.i.d. These doses cause severe flushing and occasional pruritus, rash, dizziness, diarrhea, and abdominal pain. The prostaglandin-mediated flushing can be countered by NSAID or food administration prior to Niacin ingestion, or by a prostaglandin inhibitor (laropiprant) added to niacin. The niacin/laropiprant combination has recently been approved for use in Europe. Niacin is contraindicated in severe hepatic disease, ulcer, hypotension, and in those with bleeding tendency. ω-*3 fatty acid* (eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA) intake should be derived mainly from fatty fish. In high-risk patients, these agents may decrease risk of lethal arrhythmias, decrease TG levels, decrease plaque growth rate and slightly lower BP. The recommendation for fatty acid replacement therapy should be individualized, with 1 g q.d. recommended in patients with documented CAD, and 2–4 g q.d. in patients in whom TG decrease is desired, although, as mentioned, this is not a formally recognized therapeutic target.

There have been conflicting reports in the literature regarding the effect of fatty oils on atherosclerosis. The differences may stem from the study design and populations or from the type and/or potential dietary source of the compound under study. Thus, beside fish-derived ω-fatty acids, research has also focused on the vegetable-derived α-linolenic acid. While the OMEGA study has found no benefit to ω-3 fatty acid therapy in optimally treated post-MI patients, there are still no definitive conclusions to date.

Plasmapheresis is occasionally necessary in congenital dyslipidemia. It consists in replacement of part of the patient's own plasma with donor plasma (with normal cholesterol levels).

Future therapies for dyslipidemia will probably include a genetic approach, using viral vectors to deliver normal genes to the patient's cells, to compete with, and functionally inactivate, the defective ("hyperlipidemic") genes. In preliminary studies, the cholesteryl ester transfer protein (CETP) inhibitor Anacetrapib was found to reduce LDL and increase HDL levels. Darapladib, an inhibitor of the lipoprotein-associated phospholipase A2 (lp-PLA2), has not been found effective in improving the surrogate-endpoint of IVUS-assessed plaque morphology.

Smoking, a major atherosclerosis risk factor, is the main cause of preventible death worldwide. More than 4,000 compounds have been identified in cigarette smoke (60 being oncogenic). About 30% of CAD-related fatalities are attributable to smoking. Active and passive smoking are equally dangerous and affect all age groups, starting in intrauterine life. Smoking decreases HDL and increases LDL levels. Additionally, nicotine and carbon monoxide cause endothelial damage, setting the stage for

atherosclerosis; CO also decreases RBC O_2 transport capacity. In HTN patients, smoking increases the risk of malignant crises. Smoking causes tachycardia, increases myocardial O_2 demand, and may precipitate ischemia. The effect of smoking is cumulative, often over many decades. Lifelong exposure is assessed by multiplying the number of years of smoking by the average number of daily packs; <12 pack-years is considered light smoking, while ≥20 pack-years represent heavy smoking. Cardiovascular morbidity and mortality increase proportionally with exposure to smoke; however, even "light" smoking is a severe hazard. *Smoking cessation*, even after decades-long addiction, significantly reduces cardiovascular risk. One year after smoking cessation, the risk decreases by half, and after 15 years, it equals that of non-smokers. Quitting smoking before the age of 40 prolongs life by an average of 4–5 years. Smoking cessation is feasible, but, unfortunately, rarely achieved, for several reasons: nicotine and certain additives are highly addictive; peer pressure in many age groups and cultures also plays an important role. Unfortunately, defeatism and time shortage preclude proper anti-smoking counseling by the medical personnel (smoking cessation should be discussed at every single encounter with the patient). The main strategies for smoking cessation are reviewed in Table 2.3. About one-third of people who earnestly attempt to quit smoking are able to achieve this and persist in not smoking on the long run.

The so-called "light" *brands* of cigarettes are generally just as dangerous as the regular ones, as the lower nicotine content is compensated by deeper inhalation and more frequent "puffing," resulting in the same net toxic intake. The smoking simulators used for brand testing detect less smoke intake due to the ventilation orifices at the base of the cigarette; however, these orifices are generally sealed by the smoker's lips, precluding any real advantage. *Non-cigarette smoking*: Classically, *cigar or pipe smoking* was believed less noxious than cigarette smoking, as the inhalation patterns were different. However, most current cigar or pipe smokers are ex-cigarette smokers, carrying over the cigarette-smoking inhalation patterns, and thus the risk is the same. *Hookah* (*shisha, nargileh*) smoking is at least as dangerous as cigarette smoking, as the water filtering typical to this technique removes only some of the toxic compunds. A typical 1-h session of hookah smoking exposes the user to volumes of inhaled smoke many times larger than those from a single cigarette. *Tobacco chewing* mainly causes palate malignancies;

Table 2.3 Strategies for smoking cessation

Method	Remarks
Behavioral approaches	
Abrupt ("cold turkey") cessation	Requires tremendous willpower, but has the best results; up to 90% of patients able to refrain from smoking on the long run use this method
Workshops for smoking cessation	Effective if the patient's motivation is high
Pharmacological approaches	
Nicotine replacement therapy	Commonly used, but only modestly effective
Varenicline,[a] a nicotine receptor blocker	Better than nicotine replacement, but may cause neuropsychiatric disturbances and suicidal behavior
Bupropion,[b] an antidepressant	C/I in diabetics, epilepsy, anorexia nervosa, bulimia, or active brain tumors; may cause suicidal behavior in the young
Anti-nicotine vaccine	Under study
Clonidine	Occasionally used to blunt sympathetic activation associated to smoke cessation.
Hypnosis, acupuncture, self-help approaches, plant extracts (chamomile, kava-kava, etc.)	Inconclusive results

[a]0.5 mg q.d. for 3 days and b.i.d. for an additional 3 days; and 1 mg b.i.d. thereafter, for 3 months

[b]150 mg q.d., then b.i.d. for 2–3 months, while the patient continues to smoke; 10–14 days into the treatment, the craving for smoking should abate, enabling smoking cessation. The second dose is taken a few hours before bed time, as it might cause insomnia. Success rates are up to 25% (around 50%, in some studies).

however, it does create addiction to nicotine, likely to be satisfied at some point by cigarette smoking. *Cigarette holders* are probably as effective as the filter and the ventilation system they contain. The latter might be occluded by the smoker's lips, just like with "light" cigarettes. *Passive smoking* associates a 30% increase in CAD risk. Low weight at birth, SIDS, early-onset atherosclerosis, learning difficulties, and tobacco addiction in adulthood are all more frequent in children exposed to cigarette smoke. Additionally, there is a higher risk of spontaneous abortion in mothers who are smokers.

Diabetes (fasting glucose >125 mg/dL) is a major risk factor for CAD. Hyperglycemia causes endothelial dysfunction (decreased levels of NO); increases production of thromboxane and of free O_2 radicals; stimulates smooth muscle cell proliferation and migration and platelet aggregation; increases LDL and TG levels, and decreases HDL levels; increases coagulability; damages the vasa vasorum and vasa nervorum; and inhibits the development of collateral circulation. These effects cause CAD to be more frequent and more severe (three vessel-disease, diffuse atherosclerosis, increased prevalence of MI, increased MI mortality, increased coronary restenosis rate). Cardiovascular risk increases with the severity of diabetes and decreases with adequate diabetes control, best quantified by the HbA1c levels. Overt diabetes increases the risk of cardiovascular disease two to threefold in men and three to fivefold in women. Additionally, diabetes causes non-atherosclerotic cardiac damage, including CMP and cardiac autonomic system dysfunction. Diabetes may occur either *overtly* or as *pre-diabetes* (fasting glucose 100–125 mg/dL and/or abnormal oral glucose challenge test), both conditions associating insulin resistance, itself a risk factor for atherosclerosis. Diabetes may occur in conjunction with the other components of the metabolic syndrome. Maintenance of euglycemia is key in the treatment of the diabetic patient. The American Diabetes Association recommends a target of HbA1c ≤7%, and of 6.7 mmol/L (120 mg/dL) for fasting glucose levels; the (European) International Diabetes Federation recommends ≤6.5%, and 6.0 mmol/L (108 mg/dL), respectively, with postprandial glucose levels ≤7.5 mmol/L (135 mg/dL). However, strict glucose control increases the risk of hypoglycemia, especially deleterious to the heart.

Increased body weight (Table 2.4) is a major risk factor for atherosclerosis, both *directly* (the adipose tissue is an endocrine organ, secreting a vast array of peptide and non-peptide substances, a key compound being adiponectin), and *indirectly,* by increasing LDL and TG, and decreasing HDL levels; causing insulin resistance or frank diabetes; and stimulating inflammation. Multivariate adjustment for other risk factors shows that overweight is not an individual risk factor for atherosclerosis, but acts by increasing the prevalence of dyslipidemia and of glucose metabolism disturbances. Management is based on reduced caloric intake and physical exercise. Fat intake must be reduced to less than or equal to one-third of total caloric intake, with saturated and trans-fatty acids ≤7%. These recommendations are not attenuated by the widely-publicized "obesity paradox," a decreased risk for cardiovascular complications in the obese, possibly due to lower systemic vascular resistance and plasma renin activity.

The pharmacological approach to weight loss is reviewed in Table 2.5. Use of these medications remains at the physician's discretion.

Sedentary lifestyle causes weight gain and cardiorespiratory deconditioning. Physical exercise including ≥30 min of moderately vigorous activity daily, ≥5 days weekly is recommended. "Moderately vigorous" exercise is defined as reaching 60–75% of maximal HR in a Bruce protocol, or as "moderate exertion" on a Borg scale.

Homocystein is an essential aminoacid; congenital hyperhomocysteinemia is associated to extensive, severe and premature atherosclerosis. Milder elevations also increase risk, but correction of elevated homocysteine levels seems not to influence cardiovascular endpoints. Therefore, correction of elevated homocysteine levels remains optional, and should be mainly considered in high-risk patients. Levels of 5–15, 16–100,

Table 2.4 Assessment of excess body weight

Condition	Body mass index (kg/m^2)	Waist circumference (cm)	
	Men/women	Men	Women
Overweight	25–29.9	≥94	≥80
Obesity	≥30	≥102	≥88

Table 2.5 The pharmacological approach to weight loss

Agent	Mechanism	Dose	C/I and adverse effects
Orlistat	Inhibits intestinal lipases, and thus digestion and absorbtion of fats	60–120 mg b.i.d.	GI upset, flatulence, steatorrhea
Sibutramine	Metabolized to compouds that induce early satiety	10 mg q.d., may increase to 15 mg q.d. after 4 weeks	GI upset, dry mouth, dysgueusia, paradoxical hunger, joint or muscle pain, headache, dizziness, seizures, insomnia, flushing, arrhythmia, melena, hematemesis, jaundice, fever and rigors, chest pain, HTN
Rimonabant	Endocannabinoid inverse agonist, reduces hunger	Suspended due to serious side-effects, including severe depression and suicidal ideation	

and >100 μmol/L are considered normal, moderately, and, respectively, severely increased. Homocystein can be decreased by dietary or pharmacological measures. The former include especially leafy vegetables (lettuce, spinach, etc.), folic acid-fortified cereals, and chicken, beef and beef consumption. Effective drugs include folic acid 5 mg q.d., vitamin B6 250 mg q.d., and vitamin B12 0.5 mg q.d (however, see Table 2.19).

Genetic factors (family history): At-risk individuals have a first-degree relative with early-onset CAD (<55 for male, <65 for female relatives); the correlation is less strong, but still present, for second-degree relatives. The earlier the onset and the greater the number of affected relatives, the higher the risk. Family history is as an independent risk factor for atherosclerosis. Several genetic loci have been investigated, for instance, variants in the chromosomal region 9p21. While the exact role of this variant remains to be defined, the magnitude of risk may be comparable to that imparted by hypercholesterolemia. Additionally, the ACE polymorphism may predict, among others, the rate of restenosis after angioplasty. The ability to individually predict the response to given therapies by genetic makeup analysis ("pharmacogenetics") holds promise for the future.

Other factors: *Hypercoagulability* is rarely the sole cause for complicated atherosclerosis, but mutations in factor V (Leyden) or factor II (prothrombin) do cause a somewhat increased risk. *Inflammation* (increased CRP levels) increases the risk of stroke, of CAD, and of severe CAD (ACS). Chronic inflammatory diseases, such as psoriasis, rheumatoid arthritis, periodontitis**,** or recent respiratory infection have been shown to be independent risk predictors for cardiovascular events (However, patients with rheumatoid arthritis may have an uncommonly *good* prognosis for CAD, a fact recently attributed to methotrexate therapy). In younger men, the risk of CAD or its complications is proportional with *HR*. Chronic tachycardia has been postulated to promote atherosclerosis, but in women and in the elderly, this is not an independent risk factor. The impact of routine administration of β-blockers or CCB on morbidity and mortality is unclear. While Ivabradine has not been found to improve prognosis in patients with stable angina and LV dysfunction, some benefit was observed in those with HR ≥70 bpm, thus somewhat clarifying the threshold definition for a "fast" HR. *Psychosocial factors* (stress, depression, social isolation) are independent risk factors for atherosclerosis and CAD. These patients also tend to have unhealthier life styles and lower compliance to medical therapy. The risk of atherosclerosis is independently increased in patients with *renal dysfunction,* especially end-stage renal failure. The association is most likely explained by coexisting diffuse severe atherosclerosis and HTN. *Female gender*: Hormonal protection before menopause defers the risk of complicated atherosclerosis, but overall, more women than men succumb to atherosclerosis. Women are underrepresented in most major trials, and thus the treatment is extrapolated from that used in men. Chest pain is often "atypical" in women, precluding timely treatment. *Other possible risk factors* include: elevated myeloperoxidase levels; micro- or macroalbuminuria, defined by the urinary-albumin-to-creatinine ratio (UACR); fibrinogen levels (which tend to covariate with other risk factors, and are reduced mainly by lifestyle changes); pollution (possibly by triggering a systemic inflammatory response); increased PTH levels (studied in elderly males); and low serum levels of vitamin D (associated with more

Table 2.6 The metabolic syndrome

Component[a]	Severity
Central obesity	Waist circumference >102 cm (♂), >88 cm (♀)
Elevated TG	≥1.7 mmol/L (150 mg/dL)
Low HDL	<1.03 mmol/L (40 mg/dL) (♂), <1.29 mmol/L (50 mg/dL) (♀)
HTN[b]	BP ≥135 mmHg (syst.) and/or ≥85 mmHg (diast.)
Increased fasting plasma glucose levels	>5.6 mmol/L (100 mg/dL)

[a]Metabolic syndrome diagnosed in the presence of ≥3 components
[b]Or previously diagnosed, currently treated BP

classic risk factors, such as HTN, diabetes, or obesity, and with high TG levels).

The metabolic syndrome is a combination of atherosclerosis risk factors, including: central obesity (adipose accumulation in the abdomen, rather than in the limbs), HTN, low HDL, raised TG and high blood glucose levels, resulting from insulin resistance (the combination of the two latter characteristics has earned this syndrome the alternative designation of "insulin resistance syndrome".) The metabolic syndrome substantially increases the risk of atherosclerosis and of full-blown diabetes. The concern that the "metabolic syndrome" is not a true entity, but simply reflects the coexistence of highly prevalent individual conditions, appears unfounded, as the presence of one component dramatically raises the probability of finding others. There are several formal definitions of this syndrome. The NCEP-ATP III (National Cholestrol Education Program Adult Treatment Panel III, Table 2.6) definition is the most predictive of cardiovascular complications. The concept of " metabolic syndrome" (for which there is yet no specific therapy as such) advocates active investigation for additional risk factors, in the presence of one such factor. The treament addresses individual risk factors.

Global cardiovascular risk: While established CAD, type 2 diabetes, type 1 diabetes with microalbuminuria, or very severe individual risk factors entail high risk for (further) manifestations of CAD, the prognostic importance of risk factor coexistence or of lesser risk profiles is not immediately apparent. In these patients, CAD risk is best assessed using a prognostic score called, intuitively, "SCORE." This assesses 10-year cardiovascular mortality (fatal atherosclerotic event). Ten-year risks of <1, 1–4, 5–9, and ≥10% are considered low, moderate, increased, and very increased, respectively. The score is calculated based on age, gender, cholesterol levels, BP, and smoking status; there are separate tables for different country groups (high- and low-risk), according to the prevalence of healthy lifestyles. As many countries transition to healthier lifestyles, the SCORE may overestimate the risk in those populations. Additional tables exist, taking into account the cholesterol: HDL ratio. The SCORE is read off a table. In low-risk patients (10-year risk <5%), the only necessary action is periodic risk reassessment. The risk appears lower in women, but is in fact merely deferred, post-menopausal women having risks similar to those of men. Cardiovascular risk can also be estimated using the Framingham data, by calculating either the Framingham, or the ATP score. The Framingham risk score is calculated based on sex, age (not validated for <35 or >74), total cholesterol, HDL, BP, diabetes, and cigarette smoking. The ATP score differs in that it only refers to systolic BP, and takes into account the presence or absence of antihypertensive therapy. In addition, the Framingham score automatically classifies patients with diabetes and/or PVD as high-risk. The short-term (10-year) risk for developing CAD is considered low at <10% (<5%, according to other authors); intermediate at 10–20%; and high, at ≥20%). The database for total cholesterol being larger than that for LDL, the predictions are more robust than those using LDL. The latter, however, currently remains the primary target of therapy.

Risk Assessment, A Matter of Definition

The widely divergent definitions of "severe risk" as assessed by the Framingham (AHA/ACC) and the SCORE (ESC) scales based on very similar risk factors underscores the need for harmonization of the language and definitions used in the medical community when dealing with a medical condition.

2.1.4 Atherosclerosis: Diagnosis

The diagnosis of atherosclerosis coincides with that of its main complication, ischemia, and is reviewed in the next section.

2.1.5 Atherosclerosis: Treatment

Primary prevention of atherosclerosis consists in risk factor management. The treatment of atherosclerosis as such (secondary prevention, coronary revascularization) is integral part of the treatment of coronary ischemia, and is reviewed in the next section. A "polypill" containing low doses of Atenolol, HCTZ, Ramipril, Simvastatin, and Aspirin has been introduced in some countries, to facilitate compliance and ensure implementation of proven prophylactic therapy in patients at risk for cardiovascular events. Novel drug delivery systems are being actively investigated as well. For instance, recent research has shown the feasibility of drug delivery to the myocardium using drug-laden microspheres, injected directly into the myocardium.

2.2 Ischemia: Overview

2.2.1 Definition and Mechanisms

The main cardiac impact of atherosclerosis is myocardial ischemia, i.e., an absolute or relative decrease in myocardial perfusion. This can be due either to increased metabolic requirements (during stress), or to decreased blood flow through the coronary arteries; occasionally, the two components coexist. Rarely, ischemia is due to decreased O_2 delivery (anemia, methemoglobinemia, etc.), or to coronary compression (*bridging,* a congenital malformation where a portion of the coronary artery has an intramyocardial, rather than subepicardial course, with compression of the artery on each ventricular systole; *congenital coronary anomalies,* where the coronary artery courses between the aorta and the PA, with coronary compression between these two vessels).

The risk factors for ischemia can be classified into: *risk factors for atherosclerosis*, i.e., the histopathological substrate of ischemia; and *risk factors for thrombosis* upon the preexisting support of atherosclerosis. With stable angina, only the first class of risk is operational, whereas the genesis of ACS requires the presence of both classes. The risk factors for thrombosis mainly pertain to *plaque composition* (lipid-rich plaque with a thin fibrous cap is the most prone to rupture); *factors leading to plaque erosion or rupture* (inflammation, hemodynamic trauma, etc.); and, less frequently, *hypercoagulability syndromes*.

Coronary flow can decrease gradually or abruptly. The former scenario involves a gradual increase in plaque dimensions, ultimately increasing coronary resistance to flow; the clinical correlate is *stable angina pectoris.* Acute flow decrease occurs as a result of intracoronary thrombosis, and causes *ACS.* The two mechanisms (obstruction by gradual plaque growth vs. acute thrombotic occlusion) may also coexist, as clots may form on already prominent plaques; however, the less protruding plaques are often the most vulnerable. A comparison of stable angina and ACS is presented at the beginning of Sect. 2.3. Briefly, stable angina is due to increased resistance to flow (due to the mechanical bulk of the plaque or to endothelial dysfunction), while ACS is due to thrombotic occlusion of the coronary artery, with different degrees of distal embolization into the microcirculation, with fragments of thrombus.

The supply/demand imbalance inherent to ischemia is counteracted by several mechanisms, aimed either at increasing blood flow, or at decreasing myocardial consumption. *In the acute setting,* the operative mechanisms include vasodilation and the activation of the endogenous thrombolytic system, while in the *chronic setting,* adaptive mechanisms include: vasodilation (which may increase flow up to fivefold as compared to baseline, but is decreased by the endothelial dysfunction associated to atherosclerosis); vascular remodeling; and the development of collateral circulation. Reduction of O_2 consumption occasionally achieves complete correction of the demand/supply imbalance; however, this comes at the cost of LV dysfunction (Table 2.7).

The main clinical, diagnostic, and therapeutic aspects of myocardial ischemia are reviewed in the present section, while the clinical syndromes (ACS and stable angina) will be reviewed in Sect. 2.3.

2.2.2 Clinical Manifestations

The typical symptom of CAD is retrosternal heaviness (chest discomfort), described as a crushing, squeezing, or constricting sensation in the precordial and substernal areas, often associated with a sense of impending doom. Pain onset may occur at rest or after physical or psychological stress. Pain may be mild or absent, especially in the young (<40), the elderly (>75), and in diabetic or postoperative patients. The pain typically radiates to the left arm, neck, jaw, shoulder, right arm,

Table 2.7 Ischemia-related conditions

Entity	Correction achieved by	Practical importance
Hibernation	Severe hypokinesis[a] (to decrease O_2 requirements)	Myocardial contractility may be regained by revascularization
Preconditioning	Adaptation of myocardium to ischemic conditions	Reduced functional impact of future ischemic episodes
Scarring	Replacement of myocardium with metabolically inert scar tissue	Irreversible functional loss; revascularization is pointless

[a]Hibernation is a chronic state, only reversible by revascularization (PCI or CABG), while stunning is an acute, short-lived condition, reversible spontaneously or under drug therapy. Classification of hibernation as an adaptive mechanism and of stunning as a complication of ischemia might appear arbitrary, as both consist in LV dysfunction resulting from decreased myocardial flow. However, hibernation more appropriately qualifies as an adaptive mechanism and has a different molecular base than stunning.

and epigastrium, often causing confusion with rheumatic or GI problems. Additional symptoms include profuse sweating, dyspnea (occasionally, pulmonary edema), palpitations, confusional state, nausea, vomiting, etc. GI symptoms are especially frequent in patients with inferior MI. The pain may last for a few minutes or more; longer duration (>20 min) is usually, but not always, a sign of ACS, usually MI. The chest discomfort subsides spontaneously or under Nitroglycerin; lack of response to Nitroglycerin of otherwise typical pain pleads in favor of the diagnosis of acute MI. The *physical examination* reveals nonspecific findings, including pallor, tachypnea, tachycardia, evidence of atherosclerosis in other territories (e.g., carotid bruits), evidence of pulmonary congestion (rhales), functional MR, etc. ACS (Sect. 2.3) may present with rhythm and conduction disturbances.

2.2.3 Ischemia Workup

2.2.3.1 Electrocardiography

Electrocardiography (EKG) is the cornerstone of CAD diagnosis, although both false-negative and false-positive diagnoses are frequent. EKG may reflect myocardial ischemia or its complications (rhythm or conduction disturbances, post-MI pericarditis, etc.). EKG signs of ischemia include ST elevations or depressions and T wave inversion, conformational changes, or pseudonormalization. EKG allows localization of the ischemic segment, of the responsible artery and even of the approximate point of stenosis (Table 2.8). EKG is relatively poor at examining the posterobasal and lateral LV walls, leading to underdiagnosis of ischemia in the LCx distribution.

A provocative recent study has found little incremental value to EKG on top of sound clinical assessment for risk stratification of patients with suspected angina. Both resting and stress EKG appeared of no value in this study. This finding, if validated, will serve as a strong reminder that it is mostly the superficial (non-flow limiting) plaques, i.e., the ones usually missed by EKG, that are responsible for acute MI.

EKG stress test: *General remarks*: The EKG stress detects pathologic changes under increased metabolic demands (controlled physical exercise), in patients with a normal rest tracing. Preexisting resting EKG abnormalities (WPW, LVH, or pacemaker rhythm) may render the stress test impossible to interpret, while other conditions (digitalis treatment, electrolyte abnormalities, intraventricular conduction disturbance) reduce the sensitivity and specificity of the test. The average sensitivity and specificity of the EKG stress test are 68 and 77%, respectively (less, in women). While reduced physical capacity is one of the main reasons for obtaining an inconclusive exercise stress test, it is by itself associated to an increased incidence of cardiac and non-cardiac events. *Indications*: The indications for EKG stress testing are reviewed in Table 2.9.

Practical aspects: Preliminary interruption of β-blockers and non-dihydropyridine CCB (used for CAD, HTN or arrhythmia) is required for primary diagnosis of ischemia; however, for functional status evaluation (i.e., assessment of the protection provided by medication), discontinuation is not recommended. Exercise follows different protocols, all using a gradual increase in physical stress, but differing in the duration and workload of each stage (Table 2.10). Protocols can be achieved on a bicycle or on a treadmill. In the US, the treadmill is preferred, as large segments of the population do not regularly ride a bike,

Table 2.8 Ischemia location by EKG

Limb leads	Chest leads: V								MI localization	Responsible artery
	1	2	3	4	5	6	7–9	3–4R		
LAD-dependent MI										
I, aVL									High lateral[a]	LCx or RCA
	■	■							Anteroseptal	Distal LAD or diagonal
	■	■	■	■					Anterior	Midlad or diagonal
	■	■	■	■	■	■			Anterolat.[b]	Proximal or midLAD[c]
					■	■			Lateral	Distal LAD or diagonal
RCA or LCx –dependent MI[d]										
II, III, aVF									"Small" inferior	Distal RCA or LCx
	■	■	[e]				[f]		True post. MI[g]	Proximal RCA or LCx
								■	RV MI[g]	Proximal RCA or LCx

[a]L1 and aVL can be involved alone or in combination
[b]Also termed "extensive anterior MI"
[c]If stenosis is proximal to first septal perforator (proximal LAD), fascicular or BBB is typically associated
[d]The culprit artery in these territories depends on coronary dominance (i.e., the artery supplying the PDA); this is the RCA, the LCx, or both in right, left, or co-dominant circulation respectively, accounting for 70, 10, and 20% of the population, respectively.
[e]Mirror-image: increased R wave amplitude and duration and a R/S ratio in V_1 or V_2 >1 (mirroring posterior wall Q waves); ST depression and large, inverted T waves in V_1–V_3 (mirroring posterior wall ST elevations and hyperacute T waves)
[f]Direct image of the posterior MI
[g]Often associated to inferior MI (infero-posterior MI ± RV MI). The LV segment lying on the diaphragm is currently designated as "inferobasal," rather than "posterior".

and the estimated peak O_2 (i.e., the maximum achieved exertion) is spuriously low.

Interpretation and comments: The main EKG-related data provided by stress test are reviewed in Table 2.11. The intrinsic advantages of the test (availability, safety, physiological, rather than drug-induced exertion) are undermined by the low sensitivity and specificity of ST segment depressions for ischemia; in addition, the 1-mm cutoff value is arbitrary. Additional EKG-related or EKG-independent factors increasing the diagnostic and prognostic yield are briefly reviewed in Table 2.11. The table also reviews findings pertaining to the severity and prognosis of ischemia (rather than its mere presence); in patients with "very positive" tests, an early invasive therapy might be justified. As classical exercise stress test does not individualize the target HR, beyond age and gender, a subjective rate of perceived exertion (RPE) has been introduced. In both its variants (the Borg scale, ranging from 6 to 20, or the modified Borg scale, ranging from 1 to 10), the patient rates effort severity from "nothing at all" to "very, very hard"; a score >18 (Borg scale) or >9 (modified Borg scale) defines "maximal exertion."

Stress test is interrupted if definitely positive or negative (>80% of THR or 110 bpm under β-blocker therapy; recovery completed, in the absence of diagnostic EKG or clinical changes); if the patient cannot carry on (mostly, due to orthopedic problems or fatigue); and in case of a complication. In case of symptoms or ST depressions <1 mm, the test may be cautiously continued. The test can be continued beyond 100% THR, for assessment of functional status; any EKG changes are interpreted in the clinical context. An inconclusive stress test should be followed by another noninvasive test, such as stress echo or nuclear scan.

Table 2.9 Indications and Contraindications of EKG stress testing

Indications	Contraindications[a,b]	Remarks
Diagnosis of obstructive[c] CAD		
Intermediate pretest probability of obstructive or vasospastic disease, based on symptoms, or (Class II indication) on risk factors, especially diabetes. Test also indicated in patients with occupations potentially affecting public safety (pilots, etc.)	WPW, paced rhythm, LBBB, >1 mm resting ST depression	Complete RBBB, resting ST depression <1 mm (with or without LVH), digitalis effect acceptable, but decrease sensitivity and specificity
Risk assessment and prognosis of known CAD (excluding early post-MI patients)		
Recent marked change in clinical status; unstable angina (low-risk, if asymptomatic for ≥8–12 h; intermediate risk, if asymptomatic for ≥2–3 days[d])	High-risk unstable angina; severe co-morbidity limiting candidacy for revascularization or ability to exercise; periodic follow-up in asymptomatic patients[e]	WPW, paced rhythm, LBBB, <1 mm resting ST depression acceptable, mainly for non-EKG-related endpoints aiding prognosis assessment
Early post-MI patients		
Submaximal test at 4–6 days; symptom-limited test early (2–3 weeks) or late (3–6 weeks) post-MI for risk stratification,[f] evaluation of medical therapy and prescription/evaluation of cardiac rehabilitation	Severe co-morbidity limiting candidacy for revascularization or ability to exercise; periodic follow-up in asymptomatic patients; to assess physiological significance of stenoses detected at catheterization	As above

[a]Situations posing an unacceptable risk, or making the stress test uninterpretable
[b]Additional *absolute contraindications*: severe arrhythmia, HF, or aortic stenosis; aortic dissection; PE; myo-, peri- or endocarditis; significant non-cardiac disease; *Relative contraindications*: milder degrees of arrhythmia or other cardiac or non-cardiac disease; electrolyte disturbance; HTN (resting systolic BP >200 mmHg and/or resting diastolic BP >110 mmHg); HOCM; LMCA stenosis or equivalent; AV block; ventricular ectopy or aneurysm; advanced or complicated pregnancy
[c]EKG stress test does not identify non-flow-limiting plaques, the most prone to cause MI
[d]Possibly 12 h, if asymptomatic and repeat troponin negative
[e]A non-Class I, yet very popular indication
[f]In an era of aggressive early revascularization, this population should decrease dramatically; practically, availability issues make it most relevant to current practice

Table 2.10 Stress test protocols

Protocol	Characteristics[a]	Required fitness[b]	Remarks
Bruce	Large workload increments between stages	High	Widely used, enables cross-center comparisons. Disadvantages: stage IV can be either walked or run, which influences O_2 consumption
Modified Bruce	Lower workload increments	Moderate	May still be excessively demanding for unfit persons
Cornell	Adaptable according to the fitness level	Variable	
Balke	Large workload increments between stages	High	
Naughton	Lower workload increments	Low	
Ramp protocol	Continuous, computer-generated, individualized increases in workload	Average	Individualized workload increase avoids early termination of test

[a]The Bruce protocol stages are 3 min long; with the other protocols, the stages are 2 min long
[b]For successful completion of test protocol

Table 2.11 Exercise stress test EKG data

	EKG data[a]	Non-EKG data
Presence	Positive[b] test: horizontal or downsloping ST segment depression ≥1 mm in ≥2 contiguous leads[c]; ST elevation in ≥2 contiguous leads; ST elevation ≥2 mm not associated with post-MI Q waves.[d] Probability of ischemia increases when changes involve a larger number of leads and/or appear at a lower workload; with ST depressions that are downsloping (as opposed to horizontal) and/or persist >1 min into recovery; with a disturbed ST/HR curve[e]; and possibly, with the magnitude of ST depression	Reproduction of typical symptoms on exercise; BP decrease or failure to rise on exercise
Location	ST depressions generally do not localize ischemia; ST elevations do (ischemia in the territory corresponding to the involved leads)	–
Severity/prognosis	ST elevation not associated with post-MI Q waves indicate severe transmural ischemia; the magnitude of ST depressions correlates not only with the probability, but possibly also with the severity of CAD	Systolic BP decrease or failure to rise on exercise[f]; functional capacity <3–5 METs of workload[g]; HR decrease ≤12 bpm after 1-min recovery (18 bpm, if supine); exercise-induced LBBB; ventricular ectopy[h]; chronotropic insufficiency[i]

[a]T wave dynamics are nonspecific; in the absence of LVH and of VHD, U wave inversion is very suggestive of ischemia
[b]Stress test is positive regardless of the time of exercise-induced changes onset. Normal EKG only represents a negative test if ≥80% of the age-predicted maximum HR has been attained, and recovery was uneventful
[c]ST segment is measured from the isoelectric baseline (PR interval), at 80 ms. past the J point; a cutoff of ≥2 mm depression increases specificity, but decreases sensitivit
[d]If associated to Q waves, ST elevations likely reflect segmental dyskinesia (pathogenesis similar to that of ST elevations in patients with an MI-related LV aneurysm)
[e]Computerized quantitation of ST depression at the end of each stage, to increase the diagnostic yield
[f]Normally, SBP increases >10 mmHg, but is <230 mmHg at peak exercise, and DBP either decreases or increases, but not >120 mmHg. A hypertensive response under exercise may reflect poor control of known underlying HTN or predict HTN onset in the future
[g]That is, patients unable to complete stage II of a standard age- and gender-adjusted Bruce protocol
[h]At stress or on recovery; additionally, >7 PVCs/min. On recovery; PVCs in the recovery stage of the exercise have been found to have a potentially higher predictive value than even exercise-induced arrhythmia, and may warrant further work-up for coronary ischemia
[i]That is, the inability to adequately increase HR on exercise, assessed by the "chronothropic response index": CRI = (peak HR-resting HR)/age-predicted maximum HR- resting HR); normal >0.8 (0.62, under β-blockers)

Integrating the Prognostic Data of the Stress Test: the Duke Score (DTS)

The most popular exercise test-based score, (Duke) grades exercise-induced anginal pain (0 = none, 1 = non-exercise limiting (assuming the test was not discontinued at the appearance of anginal pain in the first place; 2 = exercise-limiting), then calculates (manually, or using a nomogram) an index, DTS = exercise duration (min) – 5× maximal ST deviation – 4× anginal score.

The risk of cardiovascular morbidity and mortality is low, intermediate, or high, for a DTS ≥5, 4 to −10, or ≤10, respectively.

Complications (arrhythmia and acute ischemic events) are infrequent, assuming most high-risk patients are excluded using clinical and laboratory indicators (according to Bayes' principle, stress test should be carried out in intermediate-risk individuals).

2.2.3.2 Echo

Echo demonstrates ischemia-related segmental hypokinesia, identifying the affected artery and assessing the extent of the damage. The degree of LVEF decrease is the main prognostic factor after MI, and is routinely measured. Occasionally, segmental dysfunction is used for diagnosis of MI (Sect. 2.3). Contrast echo serves to

better delineate the LV endocardial border, in patients with technically difficult studies. However, myocardial contrast echo, suggested as a potential "one-stop shop" method displaying both perfusion defects and the resulting LV dysfunction is still not widely applied in clinical practice. The 17-segment schematic of the LV, as used in all imaging modalities, is reviewed in Chap. 1.

Stress Echo

Principles: Stress echo (SE) assesses stress-induced myocardial ischemia manifesting as stunning in the territories depending on the involved arteries. Stunning is generally short-lived (thus, SE is safe), and can be identified and quantified as new-onset or exacerbated segmental hypokinesis.

Technique: SE uses either physical exercise on a treadmill or stress bicycle, or Dobutamine-induced tachycardia, based on stepwise increases in the dosage of the IV-administered sympathomimetic agent. The test compares resting and stress regional LV function, imaged from the standard windows (parasternal long- and short axis; apical two- and four-chamber views). A representative resting cardiac cycle (not an extrasystole or a postextrasystolic beat, and not a foreshortened image) is chosen, digitized, and displayed in endless-loop format, side by side with a corresponding stress cycle. Clips must only include ventricular systole, as "snippets" of diastole may be read as false-positive (spurious hypokinesia). Abnormalities must be identified in ≥2 adjacent segments, and, if possible, confirmed from two different views. The basal inferior and basal septal segments are most prone to false-positive readings. With bicycle stress test, images are obtained at rest, before peak and at peak stress, and at recovery; the treadmill protocol uses two sets of images, one at rest, and one immediately (<90 s) after stress, both with the patient in left lateral decubitus. Using a bicycle offers the advantage of recording images at the time of peak effort, avoiding false-negative reads (rapid recovery from stunning); however, accurate imaging may be difficult due to motion artifact (attenuated by having the patient lean forward on the bicycle).

Interpretation: *Table 2.12*

Stress echo tends to be less sensitive than stress scintigraphy, most probably reflecting underdiagnosis of relatively small ischemic myocardial areas. While this may affect the ability of stress echo to establish *the presence* of CAD, *the prognosis* of such localized changes is generally benign, and missing candidates for interventional therapy is highly unlikely.

Table 2.12 Stress echo

Contractility		
Rest	Peak exercise or high-dose[a] Dobutamine; recovery	
	Improved contractility[a]	WMA[b]
Normal	No ischemia	Inducible ischemia[c]
WMA	Stunning or hibernation[d]	Scar

[a]Low doses of Dobutamine (or low-intensity physical exercise, imaged during a bicycle stress test) may also increase contractility; if this increase is followed by recurrent WMA, the territory is hibernating. Such segments also benefit from revascularization

[b]Akinetic or dyskinetic segments (especially if thinned out and brightly lucent) usually correspond to scar

[c]Paradoxically, both normalization of a previous WMA and WMA onset in a previously normal segment signify myocardial ischemia; however, the clinical settings differ. In a patient with normal resting LV function, the test is performed for the diagnosis of ischemia, whereas in patients with a resting WMA, it is performed to assess the reversibility of the abnormality (i.e., its capacity to recover after revascularization)

[d]That is, less hypokinetic or frankly normalized, if there was a baseline WMA, or hyperkinetic, if baseline contractility was normal

Indications: SE is used (a) *for diagnostic purposes:* when baseline EKG precludes an EKG stress test, or when the suspicion of CAD remains, despite an inconclusive EKG stress test; (b) *for prognostic and management purposes (risk stratification),* to assess the severity (magnitude of LV dysfunction, size of the affected area, reversibility of segmental dysfunction) and localization of ischemic involvement. Stress echo can be used in asymptomatic patients with risk factors for CAD; with suspected stable angina, to establish the diagnosis, prognosis, and optimal management; with low-risk unstable angina; or for post-MI risk stratification if PCI was not performed; (c) *for assessing the functional significance of angiographically documented stenoses.*

The possible *complications* when using physical exercise are those discussed for EKG stress test. The complications of Dobutamine stress test include: *hypotension* (due to activation of the Bezold–Jarisch reflex, i.e., vagal triggering by the myocardial C fibers, activated by increased LV contractility in face of a relatively underfilled LV); and arrhythmia, angina exacerbation, headache, dizziness, nausea, shortness of breath, tremor, or flushing. Of note, the hypotension associated to the Dobutamine stress test does not carry

Table 2.13 Capabilities and shortcomings of rest (R) and stress (S) echo in the diagnosis of MI

Clinical Question									Echo helpful
No damage	vs.	Myocardial damage							yes (R)
		Nonischemic	vs.	Ischemic					yes[a](R)
				Irreversible	vs.	Reversible			yes (S)
						Nonacute	vs.	Acute	no[b]

[a]Ischemic damage usually follows a coronary distribution pattern. This criterion is not 100% specific, as non-ischemic damage, e.g., myocarditis, can occasionally also follow a segmental pattern
[b]Except if a recent normal echo is available, and there was no intervening ischemic episode

the same severe prognosis as with exercise stress test; Dobutamine discontinuation is usually sufficient to abort the symptoms. The capabilities and shortcomings of echo for diagnosis of ischemia are summarized in Table 2.13.

2.2.3.3 Nuclear Scan

Principles: Using a gamma camera, the test detects myocardial uptake of a nuclear tracer injected IV. Uptake depends on the coronary blood flow (affected by atherosclerosis) and on myocardial integrity (affected by ischemia). Ischemia manifests as decreased segmental myocardial radiotracer uptake on a perfusion scan, and as segmental WMA on gated SPECT. Correlating decreases of perfusion and regional function improves the sensitivity and specificity of the nuclear scan. The changes may be obvious at rest or under stress, and their magnitude, location, and temporal evolution offer important diagnostic clues. Stress may be elicited by exercise on a treadmill or a bicycle, or by administration of pharmacological agents, mainly including vasodilator agents (Dobutamine nuclear scan is possible, but rarely used). The action mechanism of vasodilators differs from that of exercise or Dobutamine (Table 2.14).

Technology: *Radiotracers:* Nuclear scan can be performed using thallium (Tl), technetium (Tc), or both. *Thallium* has a long half-life (approximately 3 days), precluding administration of large doses. This decreases spatial resolution and makes Tl suboptimal for gated SPECT, which requires good endocardial border delineation (segmental LV function is assessed based on the systolic inward progression of the endocardial border). On the positive side, the long half-life of Tl makes possible the phenomenon of *redistribution* (hypo- or non-captating segments "fill in" a number of hours after the initial stress images). The standard waiting period for redistribution is 4 h; this *early redistribution* is indicative of ischemia (perfusion of the ischemic segment is

Table 2.14 Stressor mechanisms in nuclear perfusion scans

	Exercise, Dobutamine	Dipyridamole, Adenosine
Mechanism	Exerting the myocardium supplied by stenotic arteries disturbs the local O_2 supply/demand balance	Selective vasodilatation of the healthy coronaries, as the stenotic ones are already maximally vasodilated
Tracer uptake in the affected segment is less than in the neighboring segments[a]	Yes	Yes
Tracer uptake in the affected segment is less than the local metabolic needs	Yes	Not as a main mechanism[b]
Remarks	"Absolute" ischemia	"Relative" ischemia

[a]The ischemic segment(s) "stand out" as showing low uptake, since the degree of tracer uptake is compared to that of the non-ischemic segments. *All* the segments being ischemic may cause a false-negative read, a hazard substantially diminished by correlation with LV function and with "high-risk findings"
[b]Some degree of steal phenomenon (diversion of blood from the affected territories to the healthy ones) does occur, as demonstrated by the feasibility of vasodilator stress echo (rarely used)

"slow," but not absent). However, up to 40% of segments with absent early redistribution may improve functionally after revascularization – an unacceptable rate of "missed opportunities" for interventional therapy. These patients may be singled out by checking for *late redistribution,* at 24 h. Late redistribution is diagnostic of myocardial hibernation. The logistical burden of next-day imaging may be solved by rest reinjection of Tl later the same day, to boost fill-in of the initially non-captating segments. With Tl imaging, the stress images are obtained first; if they are normal, there is no need for resting imaging. *Technetium* has a much shorter half-life than Tl, i.e., 6 h. This allows injection of higher doses of tracer (since the decay is fast and the total exposure to radiation is still low), ensuring better spatial resolution and making EKG gating possible. Unfortunately, Tc does not redistribute. While this allows to diagnose ischemia (a second radiotracer dose is injected a few hours after the first, followed by repeat imaging), Tc is not ideal for assessment of myocardial hibernation (viability). Segments retaining at stress >60% of the count recorded at rest tend to improve after revascularization. Tc protocols generally use the "rest first" approach, since the higher tracer dosage given with stress would require a longer waiting time for adequate decay before the second dose is given. *Dual isotope imaging* uses resting Tl and stress Tc imaging significantly shortens the protocol (no waiting between rest and stress), while keeping the advantages of gated SPECT (Tc imaging). As Tl and Tc have different energy levels, stress imaging with Tc is not influenced by the still strong Tl-related radiation.

Imaging technology: Unlike echo, where each and every cardiac cycle is individually imaged, with nuclear scan several hundred cycles are summed up electronically (temporal summation), as the radiation emitted per cycle is very faint. The camera continuously records the emitted radiation, and "allocates" each count to the different phases of systole and diastole, based on a simultaneous EKG tracing. Proper count allocation to a specific slot within either systole or diastole requires a regular heart rhythm. These images are displayed either in a static, or (with gated SPECT) in a dynamic, endless-loop format. The sections are either *transversal* (apex-to-base short-axis sections) or *longitudinal*, running from the septum to the lateral wall (vertical long axis, corresponding to the echocardiographic two-chamber view), or from the inferior to the anterior wall (horizontal long axis, corresponding to the four-chamber view; of note, the RV is normally not visualized by nuclear scan). The LV segmentation and its correspondence to coronary anatomy are discussed in Sect. 2.1.

The radiotracer is injected approximately 1 min before peak stress, so its distribution indeed reflects cardiac function under stress (even if the patient is "resting" in the scanning machine during the actual readings). *Dipyridamole*, if used, is injected at doses of 0.14 mg/kg/min, over 4 min, followed by radiotracer injection after an additional 4 min. Headache, nausea, hypotension, dizziness, flushing, and AV block may ensue, occasionally requiring neutralization with an IV bolus of 50–100 mg Aminophylline. Dipyridamole acts by stimulating *adenosine* release. The latter is also available for IV administration as such (140 μg/kg/min over 4 min). It has the same adverse effects as Dipyridamole, but, due to its very short half-life, adverse effects usually disappear with infusion interruption. *Interpretation*: Ischemic segments may have decreased, absent, or abnormally delayed tracer uptake. The responsible artery or arteries can be inferred from the involved segments. As with echo, two questions are answered: whether ischemia is present, and whether it is reversible (Table 2.15).

High-risk findings (probable severe coronary disease) include increased pulmonary uptake (ischemia-related increased LVEDP) and transient ischemic dilatation (TID) of the LV after stress. The latter may represent true LV ischemic dilatation or diffuse subendocardial ischemia, falsely displacing the perceived endocardial border inward, i.e., increasing the LV diameter. The degree and extent of LV dysfunction are assessed on SPECT scan, by the same semi-quantitative method used for echo assessment. Corroboration of information relative to perfusion and to regional LV function improves diagnostic accuracy. LVEF can be calculated with greater precision than with echo, although, for most clinical applications, the two methods are similarly appropriate. An exception, however, is LV function evaluation in patients before and between courses of cardiotoxic chemotherapy (most commonly, Adriamycin), where scintigraphic evaluation is the norm.

The indications for perfusion scan are, by and large, the same as those for stress echo. A special indication for pharmacologic (rather than exercise) stress test is the presence of LBBB or of pacemaker rhythm, which may create imaging artifacts under exercise.

Table 2.15 Nuclear perfusion scan

Uptake at rest[a]	Uptake after stress[a]	Interpretation	Reversibility after revascularization
Normal	Normal	No ischemia	N/A
Normal	Decreased	Inducible ischemia	Yes
Normal	Decreased at 4 h[b], improved at 24 h[c]	Hibernating myocardium	Yes
Decreased	Decreased	Scar	No
Decreased	Improved	Reverse redistribution, mainly[d] seen in post- MI patients[e]	Occasionally

[a]The terms "decreased" and "improved" are preferred to "normal" or "abnormal," as radiotracer uptake follows a continuum. The highest uptake in the image (brightest spot) is considered "normal" and serves for comparison to the other segments
[b]Myocardial uptake in viable segments generally retains ≥50–60% uptake – the only indicator of viability when using Tc
[c]Can also be checked by Tl reinjection, at rest
[d]Reverse redistribution has been reported (rarely) in normals or in patients with non-ischemic heart disease (e.g., sarcoidosis)
[e]The significance is debated. Explanations include hyperemia in the peri-MI area or myocardial salvage by therapeutic or spontaneous thrombolysis

The complications are those of any stress test. The adverse effects of pharmacological agents and the recommended management were discussed above.

2.2.3.4 Positron Emission Tomography

Positron emission tomography (PET) is based on the phenomenon of positron annihilation, whereby the radiotracer emits protons, a process that can be imaged, to obtain (a) an absolute quantitation of capillary blood flow to the myocardium, using perfusion agents. This is different from the relative quantitation achieved by SPECT, where the brightest spot on the image is considered "normal," and the rest of the image is calibrated accordingly; (b) imaging of the myocardial metabolism, using FDG, a "fake" glucose that is absorbed, but cannot be processed, by the myocytes; (c) identification of fragile atherosclerotic plaque, an application currently of research interest only. Viable myocardium is characterized by preserved myocardial metabolism despite decreased blood flow. PET is the gold standard for demonstration of myocardial viability. Due to the relatively burdensome logistics and to the higher cost, this procedure is used relatively infrequently. A combined approach, using SPECT for myocardial blood flow, solves the main logistical problem, as it is precisely the PET-specific flow tracers that (unlike FDG) have a short shelf-life. Metabolism is then investigated with PET, in this *hybrid SPECT/PET* approach.

2.2.3.5 Cardiac CT

MDCT (multidetector, also called multislice CT) is the gold standard of noninvasive coronary angiography. It has a high negative predictive value, allowing to rule out CAD. Due to its high cost and reduced availability, MDCT cannot yet be recommended as an initial screening agent, but is ideal in patients with ambiguous symptoms and a nonspecific stress test. Of note, the test is radiation-intensive, and concern has been raised about its potential oncogenicity. *Detection of coronary calcification,* a marker of atherosclerosis, using *EBCT (electron-beam CT)* has high sensitivity (90%) but low specificity (54%) for prediction of future CAD and stroke, and is best used as a screening tool. Abnormal results require confirmation by angiography (classic or angio-CT). EBCT is strongly supported by some, but considered by others as not conclusively providing additional information in patients in whom an accurate risk profile has been calculated by simpler methods. The amount of coronary calcium is usually expressed by the Agatston score: a score of zero, <100, 100–399, 400–999, and >1,000 corresponds to absent, mild, moderate, severe, and extensive calcification, respectively. *CT imaging of the myocardium* may be used for assessment of LV aneurysm, thrombus, etc. The "triple scan" approach, i.e., CT to rule out ACS, aortic dissection, and PE, has recently made significant progress both in the image quality and in the amount of administered radiation, which has been significantly diminished with the current techniques.

2.2.3.6 Cardiac MRI

Cardiac MRI can be used in several manners in the diagnosis of CAD: *MRI angiography* is mainly indicated for the diagnosis of congenital coronary anomalies; in the field of atherosclerosis, it currently serves as a research tool, able to define not only myocardial perfusion and coronary anatomy, but plaque morphology as well. This enables angiography, classically a luminogram (delineating the inner vessel border) to assess not only the *extent,* but also the *type* of plaque. Identification of vulnerable plaques may justify aggressive risk factor control. *MRI stress test* is an emerging technique, able to demonstrate both perfusion and regional wall motion abnormalities. Due to its increased cost and limited availability, it is especially recommended in patients with technically difficult echo studies; *MRI myocardial imaging* may demonstrate LV aneurysm, thrombus, etc.

2.2.3.7 Coronary Angiography

Coronary angiography is the current gold standard for coronary anatomy definition, also allowing PCI, if needed. Coronary angiography generally represents the last step of workup (clinical and EKG evaluation, stress testing). Occasionally, however (very high suspicion of coronary disease, ACS, recent cardiac arrest) there is neither time nor justification for preliminary noninvasive testing. Invasive coronarography is a *luminogram*, demonstrating the severity of stenosis, but not the stable or vulnerable nature of the plaque. Even as a luminogram, contrast coronarography is suboptimal, as it represents a summation image, i.e., a 2-D representation of 3-D structures; despite imaging from different angles (standard or nonstandard views), the degree of stenosis occasionally remains ambiguous. In these patients, intravascular ultrasound *(IVUS)* may help assess stenosis severity, plaque anatomy, and coronary remodeling. IVUS is invaluable for detecting diffuse disease (atherosclerosis, transplant vasculopathy), evenly narrowing the coronary bed and often undetected by classical angiography. The functional significance of "borderline" (50–70%) stenoses is occasionally not clear, i.e., it is not obvious to what extent the perfusion of the dependent myocardium is decreased (Table 2.16). This may be clarified by assessment of vasodilator-induced flow increase, which is impaired by atherosclerosis (endothelial dysfunction).

2.2.3.8 Biological markers

The use of *biological markers* in the diagnosis of CAD is reviewed in Table 2.17.

2.2.3.9 Other Diagnostic Methods

Assessment of the intima-media thickness: (IMT), defined as the span between the intima/lumen and the media/adventitia boders is measured bilaterally by B-mode ultrasound, at the distal 1 cm of the common carotid, at the bifurcation, and at the proximal 1 cm of the internal carotid artery. Values >1.3 mm are an independent risk factor for stroke and (a fact questioned by some) coronary atherosclerosis. High-resolution ultrasound allows plaque characterization (ulceration, thrombosis, etc.), with prognostic relevance for future CVA. IMT is strongly associated with atherosclerosis, and serves as a surrogate endpoint for evaluating the regression or progression of atherosclerotic disease. However, not all the processes of thickening of the intima-media are due to atherosclerosis. *The ankle-brachial index (ABI)* is the ratio between the systolic BP in the brachial and the posterior tibial or dorsalis pedis arteries, measured with a Doppler probe, after release of compression with a sphygmomanometer

Table 2.16 Assessing the functional impact of coronary stenosis

Parameter	Definition	Determinants	Normal Values
Vasodilator reserve	Ratio between baseline and maximally enhanced flow	Epicardial stenosis and microvascular impairment	>3[a]
Fractional flow reserve (FFR)	The ratio between flow velocity immediately distal to the stenosis in the aorta	Epicardial coronary stenosis	1[b]; <0.75 distinctly abnormal

[a]There is substantial individual variability. Normal tissue flow is >2 mL/min × g

[b]Aortic flow propagates to the distal coronary bed "as if the stenosis weren't there." FFR-guided PCI has been recently proven to carry substantial clinical benefits, by reducing the risk of death, MI, or repeat revascularization by 30%, as compared to patients in whom stenting decisions were based on QCA assessment alone

cuff. A ratio <0.9 is an independent risk factor for PVD and for coronary and cerebral complications. The procedure is time- and skill-intensive. It is not sensitive to lower degrees of atherosclerosis, and can yield false-negative results in patients with severe atherosclerosis, due to spuriously increased arterial pressure resulting from increased vessel rigidity. *Opthalmoscopy* has been suggested as a screening tool in asymptomatic patients, as there is a good correlation between retinal and global atherosclerosis. Several *novel technologies* hold promise to revolutionize the diagnosis of coronary ischemia and to improve its timeliness, a critical point overall, but especially relevant in STEMI patients. These include ST-segment shift detection by an intracardiac electrogram monitoring system built into the latest generation of ICD, as well as systems entirely dedicated ST-shift detection, similar to an implantable Holter device, and providing a sound alert in case of significant ST segment shifts.

2.2.4 Evaluation for Cardiovascular Risk Before Noncardiac Surgery

Evaluation for cardiovascular risk before non-cardiac surgery is recommended depending on the severity of risk factors or of preexisting atherosclerosis, as well as according to the type of surgery being contemplated. Patients in need of emergency, life-saving surgery should be operated on as needed, under optimal perioperative surveillance. As a rule of thumb, the indication for preoperative evaluation is stronger if the patient- and surgery-related risk are higher (Table 2.18). In patients with no known heart disease, but present risk factors and a low (or unknown) functional capacity, preoperative evaluation is also reasonable.

The tests to be performed are adapted to the patient's specific problem. An EKG is almost universally obtained, and EKG monitoring is indicated in patients with known CAD. An echo should be obtained in patients with LV

Table 2.17 Biomarkers in the diagnosis of CAD[a]

Marker	Diagnostic value	Prognostic value	Remarks
Troponin	Distinguishes NSTEMI-ACS from UA	NSTEMI-ACS has a poorer prognosis than UA	Mild increases occasionally first detected at 48–72 h, leading to an initial classification as UA[b]
hsCRP[c]	None	Portends poorer prognosis[d]	Reflects the systemic inflammation that triggered ACS and/or inflammation in the vulnerable plaque
BNP	None	As above[d]; prognostic value preserved after adjustment for LVEF or Killip class	Reflects LV dysfunction; useful for differential diagnosis of dyspnea
RFT	None	Portends poorer prognosis[d]	Creatinin[e], CrCl, cystatin C[f]

[a]Novel markers, investigating oxidative stress, coagulation cascade activation, vascular-specific inflammation, etc., are under study
[b]This underscores the importance of clinical diagnosis for management decisions. There are multiple non-ACS (cardiac or non-cardiac) causes for troponin elevation, some of great clinical concern (PE, aortic dissection, etc.). Non-cardiac troponin elevations are frequent with creatinine levels >2.5 mg/dL (μ mol/L). For other comments, see under "STEMI"
[c]High-sensitivity CRP assay
[d]May help management decisions in areas where PCI is not universally available
[e]Creatinin varies with age, gender, muscle mass, and race
[f]Less dependent on the factors that influence creatinine levels; as yet unclear clinical relevance (not superior to formula-adjusted CrCl); normal 0.5 – 1.0 mg/L (may vary among laboratories)

Table 2.18 Patient- and surgery-related risk before non-cardiac surgery

Risk	Surgery-related	Patient-related
High	Vascular surgery	Active heart disease (unstable or severe angina; worsening, decompensated, or new-onset HF; significant arrhythmia; severe AS or severe MS)
Moderate	All procedures not considered either high or low	Established atherosclerosis, including coronary (inactive), as well as patients with ≥3 risk factors for atherosclerosis
Low	Endoscopic procedures; breast; cataract; ambulatory; or superficial surgery	All other patients

dysfunction, overt HF, or VHD. An EKG, TTE or TEE, and an imaging stress test are indicated in accordance with the principles exposed above. Preoperative revascularization (by CABG or by PCI) is recommended in patients with ACS; three-vessel disease; LMCA disease; and two-vessel disease with significant proximal LAD stenosis and decreased LV function. PCI has been shown inferior to CABG in patients with complex coronary lesions (SYNTAX trial), and to optimal medical therapy, in patients with stable CAD (COURAGE trial) or with an occluded infarct-related artery (OAT study). However, according to newly published registry data, LMCA artery stenting appears effective and safe. Bare-metal stents are indicated if the contemplated surgery cannot be deferred >12 months, as this is the minimal duration of dual antiplatelet therapy after DES deployment. Pre-operative revascularization is mostly warranted in patients with significant wall motion abnormalities (≥5 abnormal segments), but this indication, too, is relative, and individualization is required. The recommended treatment is similar to that which would be chosen were it not for the surgical event. Invasive (Swan–Ganz) hemodynamic monitoring requires individual tailoring; by no means is it routinely indicated. The same holds true for prophylactic IV Nitroglycerin. Body temperature and glucose concentration must be maintained normal.

Despite these precautions, *perioperative MI* still occurs in 2–6% of all surgical patients; the actual incidence is strongly influenced by comorbidity and the type and duration of surgery. Up to 50% of cases may go undiagnosed, a very important aspect, as perioperative MI is an independent predictor of 6-month mortality. The clinical manifestations may be obscured by those of the underlying disease, as well as by sedation and analgesia. Diagnosis follows the usual procedures. There are no randomized data regarding therapy, which follows the general rules observed in any MI, with the important caveat that thrombolysis is contraindicated and anticoagulation must be used cautiously, if at all.

2.2.5 Ischemia: Therapy

Myocardial ischemia consists in the imbalance between myocardial demands and coronary flow; thus, therapy will seek to decrease the former and to increase the latter. Myocardial demands are mainly decreased by slowing the HR (other mechanisms are operational with some newer-generation agents used in stable angina; see Sect. 2.3). The bulk of the available therapeutic measures address restoration of decreased blood flow, involving relief of coronary stenosis, spasm, and/or thrombosis. The aims and modalities of CAD treatment are reviewed in Table 2.19. Properly speaking, management of the patient with risk factors only does not belong to the spectrum of ischemia therapy, since what is being prevented is in fact ischemia *onset*. However, as the ultimate purpose of this prevention does refer to myocardial ischemia, these patients are also included in the table.

Myocardial revascularization may be achieved pharmacologically, interventionally (PCI or CABG), or by a combination of the two approaches. The main therapeutic agents and modalities are reviewed below, while the specific indications in the ACS and in the stable angina patient are discussed in Sect. 2.3.

Table 2.19 Therapy of myocardial ischemia: aims and modalities

Condition	Treatment – aims	Treatment – modalities
Risk factors	*Prevent* plaque formation *(primary prevention)*	Risk factor management, including (where appropriate) drug therapy for hyperlipidemia, smoking cessation, weight loss, increased homocystein levels[a]
Stable angina	*Prevent* plaque growth and artery occlusion; *treat* ischemic symptoms	As above, + nitrates, β-/calcium-blockers, Aspirin, elective revascularization, and newer dugs (Sect. 2.3)
ACS	*Prevent* further plaque fissure/rupture and coronary thrombosis; *treat* thrombosis, its symptoms and complications; *Prevent* ACS recurrence and coronary restenosis *(secondary prevention)*, *rehabilitate* patient after ACS	As above, but revascularization or IV thrombolysis are urgent or emergent; oxygen; morphine; IABP

[a]Use of Aspirin in primary prevention is not warranted, even in the presence of risk factors, due to an unfavorable risk/efficacy balance in this setting; however, other data indicate that women aged ≥65 may still benefit from primary prevention with Aspirin 81 mg to 100 mg q.d. Lowering homocystein with folic acid and vitamin B_{12} was not proven beneficial

2.2.5.1 Pharmacological Therapy

General therapeutic agents are reviewed in Table 2.20. *Antiplatelet agents* are reviewed in Table 2.21, followed by a discussion of resistance to Aspirin and Clopidogrel. Newer agents are briefly discussed.

Aspirin resistance manifests as the inability to inhibit platelet aggregation (as assessed by various tests). However, as the target degree of platelet activation is still unclear, assessment of platelet (in)activation for clinical purposes is not recommended. When Aspirin resistance is suspected, Clopidogrel is empirically substituted. Aspirin resistance was believed to be in part due to COX-2 receptor activation (Aspirin is only effective on COX-1 receptors); however, COX-2 inhibitors have been proven deleterious in CAD patients. Aspirin can be ineffective when used concurrently with other NSAID agents, which block its binding site. *Aspirin hypersensitivity* mainly manifests as bronchospasm or skin rash; true anaphylaxis is rare. Aspirin desensitization may be an option, especially in settings where the alternative drug, Clopidogrel, is not available. *Clopidogrel resistance* has also been reported, but is difficult to assess clinically; furthermore, there is no proven correlation between lab test results and clinical outcomes. The association of PPIs with Clopidogrel has recently been proved to not significantly decrease the antiplatelet activity of the latter agent, despite initial reports to the contrary.

In case of significant bleeding under platelet inhibitors, or when emergency major surgery is required, the action of Aspirin or Clopidogrel must be neutralized. This is achieved as shown in Table 2.22.

Agents under development: SCH 530348, the first thrombin receptor antagonist, is being evaluated by the TRACER trial; it is a candidate as an adjunct therapy, to be used together with Clopidogrel.

Antithrombin agents are reviewed in Table 2.23, followed by a brief review of some important issues related to Heparin and LMWH.

Gradual discontinuation of Heparin treatment is empirically recommended, to avoid the rebound phenomenon (a high-risk period for recurrent thrombosis). The main caveat of Heparin is an occasionally very serious syndrome, Heparin-induced thrombocytopenia, seen in 3–5% of patients exposed to UFH, and in <1% of those exposed to LMWH. This syndrome is classified as reviewed in Table 2.24. Platelet counts should be monitored daily in patients treated with UFH. Pseudo-HIT can be caused by platelet aggregation in vitro, in EDTA-containing vials. Repeat platelet counts should be obtained using citrate-containing vials, to avoid false reads.

LMWH: It was noted early on that the anticoagulant potency of UFH is variable from batch to batch, due to the difference in molecular weight and in pharmacological activity between the many component molecules. There arose the question whether isolating some of the molecular components of UFH would make the therapeutic action more predictable. The low-molecular weight fraction of UFH was shown to possess unique pharmacological abilities. Unlike UFH, which binds to both antithrombin III (AT III) and to several coagulation factors (factors IIa (thrombin), Xa, IXa, XIa, and XIIa), very small fragments containing the binding site for factor Xa sequence more or less selectively inhibit the latter. All LMWH have a Factor Xa/thrombin activity ratio >1.5:1 (most commonly, 2–4:1); Fondaparinux does not act on thrombin at all. LMWH have revolutionized anticoagulation: (1) *safety-wise,* as they have a lower incidence of adverse effects and a more predictable anticoagulant activity as compared to Heparin, making over- and under-dosage less likely. The more predictable dose-effect relationship that that of UFH is due to the almost complete absorbtion by the S.C. route; less protein binding; and to the lesser degree of platelet activation; (2) *efficacy-wise*, as they are superior to UFH for several crucial indications: Fondaparinux is preferred to Heparin in STEMI patients not undergoing thrombolysis; Fondaparinux and Enoxaparin are as good as Heparin in patients undergoing thrombolysis; and, although not indicated for primary PCI, they are highly effective in patients being prepared for rescue PCI or for routine post-thrombolysis PCI; and (3) *logistics-wise,* as they may be self-administered in many conditions (not related to ACS), and generally do not require lab monitoring (although the latter is available, as anti-factor Xa level assessment, target: 0.5–1.5 U/mL). On the negative side, LMWH are significantly more expensive than UFH.

In case of significant bleeding under UFH or LMWH, or when emergency major surgery is required, the anticoagulant drugs must be neutralized. For UFH, this is achieved by administration of Protamin (see under "Treatment of hemorrhagic stroke"). With LMWH, Protamin is less active than with UFH, and activated factor VII may be used, but caution is recommended, as this may cause thrombosis.

Table 2.20 The pharmacological treatment of CAD[a]

Agent	Mechanism	Clinical effect	Indications	C/I; adverse effects and their treatment
Agents reserved to ACS therapy				
Oxygen	Ventilation-perfusion mismatch and excessive lung water may cause modest early hypoxemia even in uncomplicated ACS. O_2 may limit ischemic injury and reduce ST elevations	Symptom relief	Absolute: SaO_2 <90%; relative: in all ACS patients[b]	Excess O_2 can cause systemic vasoconstriction or, in COPD patients, respiratory depression
Morphine	Relieves pain, which increases sympathetic activity, favoring plaque fissuring and thrombus propagation; Peripheral vasodilation and the reduction in the work of breathing are helpful in pulmonary edema	Symptom relief, sedation	All patients complaining of chest pain	Vagomimetic effects (countered with IV atropine 0.5–1.5 mg); low HR and BP (countered with IV Dopamine or Dobutamine, or with Naloxone, IV 0.1–0.2 mg, may repeat after 15 min)
Antithrombin agents	Inhibit thrombus growth	Symptom relief	All patients	See Sect. 2.3
Thrombolytics	Dissolve occluding clot	See STEMI		
Agents reserved to stable angina therapy				
Ivabradine[c]	Slows HR by inhibition of the sinus node	Symptom relief	Second-line agent	luminous phenomena (sensations of enhanced brightness); bradycardia, headaches first-degree AV block, VPBs, dizziness, blurred vision
Trimetazidine	Improves myocardial glucose utilization by depressing fatty acid metabolism	Symptom relief	Second-line agent	None notable
Ranolazine	Indirectly prevents the calcium overload contributing to cardiac ischemia	Symptom relief	Second-line agent	May prolong QT and cause LFT alterations
Nicorandil	Peripheral venous dilatation; may reduce death and hospitalization for angina	Symptom relief	The only newer agent with a Class I indication	Flushing, palpitation, weakness, headache, mouth and perianalulcers, nausea and vomiting
Agents used in all CAD patients[d]				
Nitrates	Vasodiation (a) peripheral (arterial and venous dilation reduces pre- and afterload reduction); (b) epicardial and collateral vessels; (c) of the atherosclerotic coronaries	Symptom relief	Ischemic discomfort; IV in ACS patients with ongoing discomfort; HTN; pulmonary congestion; coronary spasm	BP <90 mmHg or decrease ≥30 mmHg below baseline, HR <50 or >100 bpm), or suspected RV MI; phosphodiesterase inhibitor for erectile dysfunction <24 h[e]

(*continued*)

Table 2.20 (continued)

Agent	Mechanism	Clinical effect	Indications	C/I; adverse effects and their treatment
β-blockers[f]	Decrease myocardial O_2 demand by reducing HR, BP, and myocardial contractility. Prolong diastole (by reducing HR), increasing myocardial perfusion. Reduce the frequency, severity and duration of stable angina episodes; the risk for myocardial necrosis, in unstable angina; MI size, complications and recurrence rate; and the risk of lethal ventricular tachyarrhythmias.	Symptom relief	All patients	HR <60 bpm; systolic BP <100 mmHg, ≥moderate LV failure; PR >0.24 s; 2-d or 3-d degree AV block; active asthma; cocaine-related MI (may exacerbate coronary spasm). Antidote: IV β-adrenergic agonists (i.e., Isoproterenol 1–5 μg/min).
Antiplatelet agents	Inhibit formation of platelet clot	See Table 2.21	All patients	See text
ACE inhibitors	Reduce oxidative stress, improve endothelial function, favorable effect on adhesion molecules and cytokines, inhibit LDL uptake by macrophages, prevent myocardial and perivascular fibrosis and LVH	Reduce mortality, MI, stroke, and HF in patients with cardiovascular disease or high-risk diabetes		See Chap. 3
ARB	As above	Suboptimal results	in ACEI-intolerant high-risk patients ≥55[g]	See Chap. 3
Statins	See text		All patients	See text

[a]The dosages are discussed in the text
[b]In patients with severe HF or a mechanical complication of STEMI, continuous positive-pressure (C-PAP) breathing or mechanical ventilation may be required
[c]Preliminary data seem to demonstrate the feasibility of Ivabradine treatment as an alternative to Metoprolol in STEMI patients
[d]ACEI or ARB are indicated in patients with HF, diabetes, or HTN. In patients with LV dysfunction (EF <40%) and diabetes or HF, aldosterone antagonists are used on top of ACEI CCB are generally used in stable angina. Their use in ACS is reserved for the occasional patient with Prinzmetal's angina, where they help release coronary spasm
[e]Most of the randomized data date from the pre-thrombolytic era. The utility of IV administration is uncertain; if this route is chosen, IV Atenolol 5–10 mg, followed by PO Atenolol, 100 mg q.d
[f]Forty-eight hours for tadalafil
[g]The ONTARGET trial has found an important decrease of hard cardiovascular endpoint incidence in patients with high-risk cardiovascular disease or diabetes treated with either ACEI or ARB, but combining the two classes increases the rate of adverse events, without added benefit

Table 2.21 Antiplatelet agents

	Mechanism	Adverse effects[a]	Remarks
NSAIDs			
Aspirin[b]	Irreversible inhibition of platelet cyclo-oxygenase, decreasing formation of thromboxane A2 (a stimulant of platelet aggregation)	Gastric irritation	Other NSAID drugs, especially COX-2 inhibitors, are C/I in CAD[c]
Thienopyridines			
Clopidogrel (Plavix)	Inhibit ADP-induced platelet aggregation	GI upset, rash, neutropenia, purpura, dyspnea	Has replaced Ticlopidine
Prasugrel (Ef(f)ient)			Higher efficacy and bleeding rates than with Clopidogrel[d]
Ticlopidine (Ticlid)			Rarely used today
Ticagrelor			Superior to, safer than Clopidogrel in reducing MACE; twice-daily dosing; the only reversible antiplatelet agent
IIb/IIIa inhibitors			
Abciximab (ReoPro)	Binding to the IIb/IIIa platelet receptor, instrumental in platelet aggregation. Blockade of the final pathway of platelet aggregation and, under high shear forces, of the von Willebrand factor as well	Thrombocytopenia, hypersensitivity reactions	An expensive monoclonal antibody
Eptifibatide (Integrilin)		Thrombocytopenia	
Tirofiban (Aggrastat)		Thrombocytopenia	
Phosphodiesterase inhibitors			
Dipyridamole (Persantine)	Countering of platelet aggregation driven by Phosphodiesterase and by other mechanisms; coronary vasodilatation by inhibition of Adenosine degradation	Angina (coronary "steal"); dizziness, hypotension, headache, rash, GI upset, dyspnea, palpitations	No longer used in CAD; diagnostic use in nuclear cardiology
Cilostazol (Pletal)	Countering of platelet aggregation driven by Phosphodiesterase	headache, palpitations, diarrhea, peripheral edema	Unlabeled use as adjunct to Aspirin after coronary stenting[e]

[a]In addition to bleeding, which can be seen with all these agents
[b]Aspirin is the only agent routinely used in stable angina. Triflusal is an antiaggregant related to the salicylate group, with an as yet unclear place in the antiplatelet armamentarium; Clopidogrel is recommended in patients with Aspirin intolerance or resistance
[c]Recent studies suggest that the safest NSAID agent in CHD patients is Naproxen. However, definitive data are still pending
[d]Early Prasugrel treatment might be switched to Clopidogrel after 30 days, as the advantage with Prasugrel is highest early on
[e]This might reduce in-stent restenosis rates

Oral direct thrombin inhibitors have recently reached clinical applicability. Dabigatran, Rivaroxaban and a host of other compounds (Table 2.23) are being assessed in patients with coronary disease. A new agent, provisionally called SCH 530348, the first thrombin *receptor* antagonist, holds the promise of reducing ischemic events without increasing bleeding, in elective PCI patients.

Vitamin K antagonists (VKA) have a relatively modest place in the treatment of CAD. They are to be continued, in addition to antiplatelet therapy, in patients with another indication for their use. In case of LV thrombus, VKA are indicated on a long-time basis (target INR 2–3), as the cause of LV thrombosis is most frequently LV aneurysm, a chronic condition. In high-risk patients in whom Clopidogrel is not

Table 2.22 Reversal of antithrombotic therapy

Agent	Reversal	Remarks
Aspirin, Clopidogrel	Platelet transfusions[a]	Effect persists for 5–10 days, the normal lifespan of platelets; 10–20% of platelets are naturally renewed daily
IIb/IIIa inhibitors[b]	Platelet transfusions	Abciximab: platelet infusion effective, optimal duration not clear; Tirofiban or eptifibatide eliminated renally, effects last 4–8 h. Immediate neutralization more problematic; FFP or plasma cryoprecipitate supplementation useful, as it acts on fibrinogen-dependent platelet aggregation

[a]Recommended dose, $5–7 \times 10^{11}$ platelets in a 70-kg adult; for reference, a typical platelet unit contains $0.6–0.8 \times 10^{11}$ platelets (random platelets), and thus $1–1^1/_2$ units are required for each 10 kg of body weight

[b]IIb/III a inhibitors can also decrease platelet counts without actual hemorrhage; close follow-up is mandatory. Drug discontinuation and platelet supplementation are recommended for platelet counts <10,000/μL. No clear guidelines exist for lesser platelet decreases. Bivalirudin may be equally effective as the IIb/IIIa inhibitor + heparin combination, and can be used in case of uncertainty regarding the origin of the platelet decrease

available and/or not tolerated, Warfarin is added, with a target INR of 2–2.5. The same target is used for Aspirin-resistant patients, in whom Clopidogrel is unavailable or ineffective.

Fibrinolytic Therapy: See Sect. 2.3

2.2.5.2 Interventional Therapy

Interventional therapy includes PCI or CABG. Revascularization may represent (a) *in ACS patients:* an alternative to IV thrombolysis; a rescue procedure after failed IV thrombolysis; or a routine procedure after IV thrombolysis; (b) *in patients with stable angina,* an elective procedure. These different scenarios are discussed in Sect. 2.3.

PCI; Most PCI procedures are performed with stent deployment, to avoid the high restenosis rate of simple PTCA (up to 40% at 6 months). As opposed to the default transfemoral approach, transradial PCI shows significantly fewer bleeding complications and equivalent procedural success. In certain European nations, the transradial approach has become the preferred approach. Simple (stentless) PTCA is reserved as a bridge to subsequent, definitive therapy (e.g., subsequent CABG, in patients presenting with ACS, and in whom rapid restoration of flow of the culprit artery is sought). However, restenosis still occurs in up to 30% of bare-metal stents, especially in small vessels, in patients with suboptimal post-intervention results, long lesions, diabetes, LAD lesions, or untreated stent edge dissection. Drug-eluting stents (DES) have dramatically decreased restenosis rates (by inhibiting neointimal proliferation), but late thrombosis is increased, mandating at least 1 year of dual antiplatelet therapy (Aspirin + Clopidogrel). The possibility that the lower restenosis rate achieved by DES might be compromised by a higher incidence of late stent thrombosis has polarized the cardiologic community. While these concerns appear to have been alleviated by the substantial amount of data accumulated since the initial reports regarding this issue, some DES may pose more risk than others. Figure 2.1 shows pre-and post-PCI images in the RCA and the LCx arteries.

Other percutaneous techniques: *Covered stents* are approved for coronary perforation and, on a case-by-case basis, for coronary aneurysm therapy. *Atherectomy devices* capitalize on the concept that, while classic PCI procedures simply flatten out and "redistribute" the atherosclerotic plaque, it may be possible to actually remove the latter from the vessel. *Cutting balloon devices* consist of several atherotomy blades, and are currently used in ostial and bifurcation lesions, as well as for in-stent restenosis. *Rotational atherectomy* uses a burr-like device that shaves off the plaque. Despite ensuring a higher procedural success, this approach does not improve outcomes; it is, however, useful before stenting of arteries that are severely calcified, undilatable, chronically totally occluded, as well as with bifurcation lesions. *Directional coronary atherectomy (DCA)* is rarely used today, except for the case of some debulking procedures. *Excimer laser*, at one time thought to improve outcomes due to the effective tissue section and to the minute size of the debris it creates, has not been found to improve outcomes and is rarely used today. *Mechanical thrombectomy devices*, creating a number of high-pressure fluid jets to macerate the thrombus, and able to subsequently absorb the debris, have actually been found to be deleterious in ACS, but newer generations of devices may improve ST segment resolution

Table 2.23 Antithrombin agents

	Mechanism	Adverse effects[a]	Remarks	Advantages	Disadvantages[b]
Indirect thrombin inhibitors					
Unfractioned Heparin (UFH)[c]	Activates AT III, which inactivates coagulation factors, (crucially, factors II = thrombin and X)	HIT, HITT, elevated AST/ALT, osteoporosis, hyperkalemia	Thrombin and Factor Xa inhibition are equally potent	Widely available; monitored by aPTT	Unpredictable anticoagulant potency, due to the non-homogenous molecular mix; risk of HIT
Low-molecular weight Heparin (LMWH)[c,d]	Mostly activates the site of AT III responsible for factor Xa inhibition	HIT, HITT, rash, fever, hematoma at injection site	Factor Xa inhibition 2–4[e] times more potent than thrombin inhibition	Less frequent adverse events, more predictable anticoagulant potency	More expensive than UFH; not optimal for primary PCI; risk of HIT lower than with UFH
Danaparoid	Factor X/factor II inhibition >22: 1	Fever, nausea, constipation	Similar action, different structure than LMWH	Chemically unrelated to Heparin, thus an option in HIT(T)	monitoring in patients with extremes of weight or renal failure; no longer available in the US
Direct thrombin inhibitors					
Argatroban[f]	Reversible binding to active site of thrombin	Hypotension, dyspnea, nausea, vomiting, fever	Alternative to Heparin in HIT or HIT-prone patients	Monitored by aPTT; no dose adjustment in renal failure; effect quickly reversed on discontinuation; relatively cheap	Prolongs INR (monitoring necessary in patients transitioned to Warfarin); adjust dosage in liver failure (hepatic metabolism)
Bivalirudin	Reversible binding to active site of thrombin	Hypotension, nausea, headache, back pain	Class I recommendation in primary PCI	Same efficacy, less bleeding than with Heparin + IIb/IIIa inhibitors, in ≤moderate-risk PCI patients	Adjust dosage in renal failure
Lepirudin	Irreversible binding to active site of thrombin	Abnormal LFT, rash, cough, bronchospasm, dyspnea, fever, anaphylaxis[g]	Reduce dosage in renal failure	monitored by aPTT	Slower action reversal on discontinuation; INR prolongation; dose adjustments in renal failure
Dabigatran	Reversible binding to active site of thrombin	Nausea, GI upset, fever, hypotension, insomnia, peripheral edema, anemia, dizziness, DVT, headache, LFT elevation	The first oral direct thrombin inhibitor	Monitoring possible, but generally not necessary[h]	

[a]All agents can cause bleeding
[b]Other than the specific adverse effects
[c]UFH and LMWH also induce endothelial secretion of tissue factor inhibitor, reducing factor VIIa complex activity
[d]Different brand names; use cautiously, if at all
[e]The exact ratio varies with the different preparations; Fondaparinux has no antithrombin action
[f]Rivaroxaban, an oral factor Xa inhibitor approved for DVT prophylaxis after orthopedic surgery, is being evaluated in ACS patients by the ATLAS ACS TIMI 51 trial. Additional factor Xa antagonists under study include apixaban, edoxaban, and otamixaban
[g]Several lethal cases of anaphylaxis have been reported
[h]INR can be prolonged, but is not useful for monitoring. aPTT relates to drug levels, but is not sufficiently precise for monitoring purposes. Ecarin clotting time (ECT) offers accurate monitoring, but is not widely available; and Thrombin Time (TT offers accurate monitoring, but is not standardized; the therapeutic target: TT/control ratio = 10–20)

Table 2.24 Heparin-induced thrombocytopenia

Characteristic	Type I (HIT)	Type II (HITT[a])
Mechanism	Nonimmunologic: direct interaction between heparin and circulating platelets causes platelet aggregation	Immunologic: antibodies to heparin-platelet factor 4 complexes stimulate platelet aggregation and thrombin generation, partly by direct endothelial activation
Incidence[b]	10–20%	1–3%
Onset[c]	First 48–72 h	5–10 days[d]
Diagnosis	Clinical; no lab tests necessary	Several assays available
Clinical course	Benign; Plt count usually does not fall <100,000/mm^3, and often normalizes within 4 days despite continued Heparin use	Severe, occasionally fatal[e]; Plt count usually falls to <100,000/mm^3 (but usually not <10–20,000/mm^3), or by up to 50% of initial level
Complications	Generally absent	Arterial or venous thrombosis in 30–80% of patients: DVT, PE, MI, skin necrosis, limb gangrene
Management	Frequent Plt counts	Immediately discontinue heparin; start anticoagulation with a direct thrombin inhibitor[f]

[a]The last letter in the acronym stands for "thrombosis"
[b]From all Heparin-treated patients
[c]After Heparin therapy onset
[d]The offending antibodies persist up to several months, and on re-exposure to Heparin platelet levels may drop within hours
[e]Ten percent mortality with early recognition, up to 30% otherwise
[f]Both for the treatment of HIT, and for that of the underlying condition requiring anticoagulation

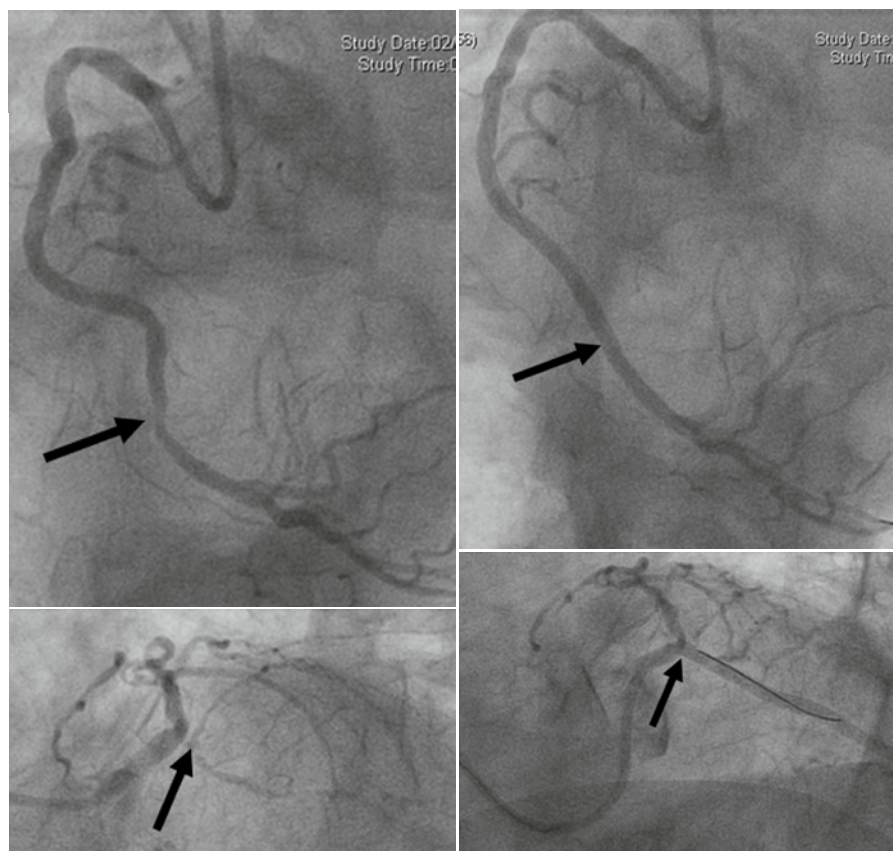


Fig. 2.1 Stenotic and post-PCI coronary arteries. The *arrows* indicate the coronary stenosis in the *left panels,* and the aspect of the same area after dilatation. As, in the illustrated cases, PCI was highly successful, the post-dilatation aspect is virtually undistinguishable from normal anatomy. This illustrates both the utility, and the limitations of the classic luminogram, which demonstrates both stenosis and procedural success, but does not image the endothelial damage caused by either the atherosclerotic plaque, or by the controlled trauma which is PCI. *Upper row:* distal RCA stenosis. *Lower row:* ostial LCx occlusion. Note the apparent absence of the LCx (*left panel*) and the wide patency of the artery after dilation (*right panel*)

and post-procedural myocardial blush. *Brachytherapy* consists in endothelial irradiation, to prevent neointimal proliferation, the main cause of in-stent restenosis. Long-time dual antiplatelet therapy is required subsequently. Brachytherapy is rarely used today.

Not surprisingly, percutaneous technology is in the focus of intense research. There is hope that biodegradable stents, currently under study, might decrease the rate of late stent thrombosis. *Other stents* being developed are designed, among others, to capture circulating endothelial precursor cells that promote vascular healing. *Distal protection devices* (the PercuSurge device, different filters, etc.) are mainly used in degenerated saphenous vein grafts, although newer generations may prove useful in ACS. These devices are all the more important since, to date, there is no medical therapy to counter reperfusion injury (Cyclosporine has been recently suggested to reduce reperfusion injury, a finding requiring further validation).

The success of PCI can be assessed in several ways. The following parameters are assessed post-dilatation: the vessel diameter; the epicardial blood flow; and the coronary capillary flow. *The postintervention vessel diameter* is assessed by the QCA method (quantitative coronary angiography), using a software that detects the luminal border of the vessel and expresses the stenosis as a percentage of the diameter of the healthy adjacent segment (Fig. 2.2).

The postintervention vessel diameter is assessed semiquantitatively using the TIMI flow score, as shown it Table 2.25; finally, *the postintervention capillary flow* is assessed using the TIMI blush score (a whitish coloration reflecting the presence of the contrast material in the microvasculature; Table 2.26).

The complications of PCI are reviewed in Table 2.27.

In-Stent Complications

- In-stent restenosis with bare-metal stents
- In-stent thrombosis with DES

CABG There are several *CABG techniques,* both in regard to the conduits being used (arterial vs. venous grafts), and in regard to the surgical approach (on- or off-pump CABG). Overall, arterial grafts are preferable, having a >90% 20-year patency, as compared to a 60–70% 10–year patency for SVGs. Interestingly, however, arterial graft patency depends not only on the harvesting technique (not surprisingly, in situ grafts have higher patency rates than free grafts), but also on the target vessel (for instance, the 10-year patency of LIMA grafts is of 95% when used on the LAD, but of 76% only, when used on the RCA). The preferred artery used for CABG is the LIMA, but the RIMA, the radial, and the gastroepiploic artery are also used. A hybrid arterial and venous approach can also be used.

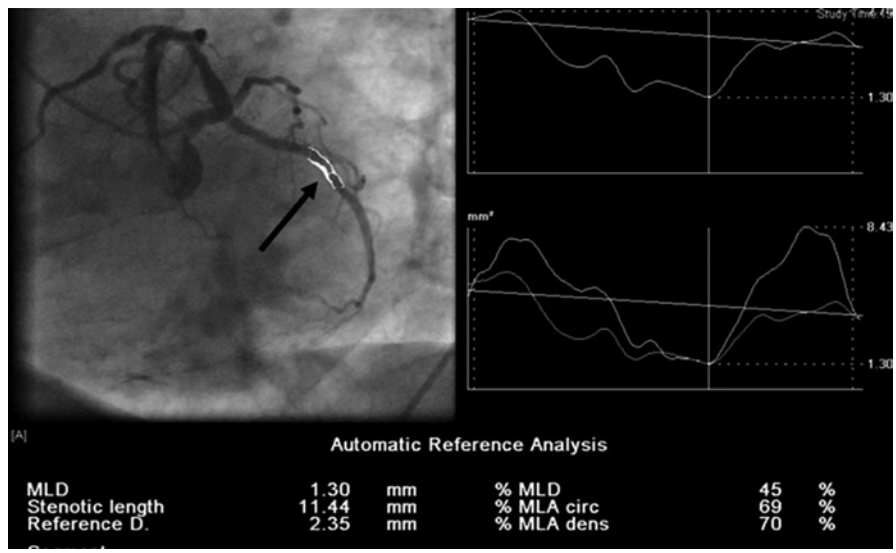


Fig. 2.2 Quantitative coronary analysis (QCA) of a lesion in the LAD

Table 2.25 The TIMI flow score

TIMI grade	Antegrade flow			Alternative designation
	Intensity	Completeness	Speed[a]	
0	Nil	N/A	N/A	Coronary occlusion
1	Faint	No	Slow	Penetration without reperfusion
2	Delayed or sluggish	Yes	Slow	Partial reperfusion
3	Normal	Yes	Rapid	Complete reperfusion

[a]Assessed subjectively, or objectively, by the TIMI frame count, i.e., the number of frames it takes the contrast material to reach the distal vasculature. TIMI frame count is of research interest only

Table 2.26 The TIMI Blush Classes

Grade	Blush		
	Intensity	Persistence by next injection	Appearance
0	0 (absent blush)	–	–
1	Present	Yes, strongly	Stain
2	Moderate	Yes, moderately	Stain
3	Intense	Mild or absent	Ground-glass

Bleeding complications in the therapy of ischemia: The main complication of antithrombotic and fibrinolytic therapy is bleeding. Therefore, assessment of the bleeding risk and (where appropriate) of bleeding severity is an essential component of management, both in STEMI and in NSTEMI/UA patients. Risk factors for bleeding include age, female sex, a past history of bleeding, renal failure, and iatrogenic factors, such as the use of IIb/IIIa inhibitors, combined antithrombotic therapy, and the length of antithrombotic therapy.

Table 2.27 Complications of PCI

Complication	Incidence	Remarks
Peri-procedural MI	0.5–1.4%	Defined as enzyme elevation greater than threefold upper limit of normal
Abrupt vessel closure	<1%	Most frequent in acute MI, complex lesions, and poor post-PCI flow in the culprit artery
Athero- and thromboembolism	Variable	Most frequent with ACS, degenerated vein grafts, and rotational atherectomy; may cause no-reflow and MI. may be prevented by distal protection devices and is treated with vasodilators (Adenosine, Nitroprusside, Verapamil)
Coronary perforation	0.1–1.1%	More frequent with atherectomy and excimer laser
Vascular access site complications	Up to 5%	Include requirement for transfusion; pseudoaneurysm; artery occlusion; infection; retroperitoneal bleeding
Contrast-induced nephropathy	3–7%	Diabetes mellitus is a risk factor; prevented with Acetylcysteine, hydration and low-osmolar agents[a]
Allergy to contrast material	1–2%	Anaphylaxis in 0.1–0.2%. Prevented by low-osmolar agents, cortisone on the evening before and on the morning of the procedure, associated with antihistamines
In-stent thrombosis	<1%[b]	With bare metal stents, endothelization at 2–4 weeks avoids this; long-term double antiplatelet therapy is required with DES
In-stent restenosis	Variable[c]	Use DES instead of bare-metal stents

[a]The efficacy of low-osmolar agents has been questioned. IV bicarbonate has been used for prevention of contrast nephropathy, based on relatively scant data. A recent retrospective analysis has found no benefit to this approach.
[b]Under dual antiplatelet therapy; depending on the, length, and complexity of the stenosis, the vessel diameter, the initial procedural success, and the patient's risk factors (age, diabetes, etc.)
[c]<5% at 2 years with DES

Table 2.28 Assessing bleeding severity in patients treated with fibrinolytic and/or antithrombotic therapy

Manifestation			Severity		Manifestation		
			TIMI	GUSTO			
ICH					ICH		
Overt bleeding[a]	*and*	Hb drop >5 mg/dL	Major	Severe or life-threat.	Causes hemodynamic compromise	*and*	Requires intervention[b]
	and	Hb drop 3–5 mg/dL	*Minor*	*Moderate*	No hemodynamic compromise	*and*	Requires blood transfusion
	and	Hb drop <3 mg/dL	Minimal	Mild	No hemodynamic compromise	*and*	No blood transfusion required

[a]Including internal bleeding demonstrated by imaging, e.g., CT-detected retroperitoneal hemorrhage
[b]Intervention is virtually always required

Assessment of bleeding severity is reviewed in Table 2.28. A striking divergence between the GUSTO and the TIMI assessments is outlined in italics. Non-TIMI major bleeding (i.e., bleeding clinically judged as significant, but not covered by the TIMI criteria) was recently shown to be just as important as TIMI major bleeding in predicting mortality.

The management of bleeding complications depends on their severity. Thus, minor bleeding requires minimal local measures, while major bleeding requires interruption and neutralization of antiplatelet and anticoagulant therapy, unless manageable by local measures alone (e.g., profuse bleeding localized at the puncture site). ICH may require surgical drainage. The management of intermediate-grade bleeding is individualized.

Hemorrhagic stroke is the most severe manifestation of bleeding. The risk factors for this potentially devastating complication include: age >65, or, in other analyses, >75; low body weight (cutoff value differs in different analyses; weight <65 kg is universally considered a risk factor; in some analyses, the cutoff value in male patients is of 80 kg); HTN (cutoff value differs in different analyses; BP >170/95 mmHg is universally considered a risk factor); using a non-Streptokinase (SK) agent; black race, female gender, prior stroke or Nifedipine use, or excessive anticoagulation (INR ≥4, aPTT ≥24 s). Each element is graded with one point, to establish a score, which is then checked against nomograms, to establish the absolute risk. A 2–3% risk of ICH implies "equipoise" (equal risk/benefit ratio) between IV thrombolysis and primary PCI, while a risk >4% (corresponding to ≥5 risk factors) is considered high, and favors primary PCI. *Diagnosis*: Clinically, ICH presents with the usual signs of stroke (Chap. 11), including changes in the level of consciousness, focal neurological signs, headache, nausea, vomiting, seizures, (occasionally, with acute HTN) and, in severe cases, coma and death. While these signs may be seen with either ischemic or hemorrhagic stroke, the latter must be considered present until proven otherwise. A fulminant course, especially in the first 24 h after initiation of treatment, is especially suggestive of hemorrhagic stroke. *Management* of stroke during thrombolytic therapy includes (1) *immediate pre-emptive measures*: discontinuation of fibrinolytic, anticoagulant, and antiplatelet therapy; (2) *CT diagnosis* (hemorrhagic vs. ischemic stroke); (3) *Therapy*: Ischemic stroke – see Chap. 11. Thrombolytic therapy appears safe and effective in catheterization-related stroke. The management *of hemorrhagic stroke* consists in administration of FFP, 2 units; Protamine (1 mg for every 100 U of UFH given in the preceding 4 h); cryoprecipitate 10 units; and platelets 6–8 units. In patients with incipient cerebral herniation, reduction of intracranial pressure is recommended (Chap. 11). HTN control is of the essence. If BP is ≤160/90 mmHg, only follow-up is recommended; for systolic BP 160–180, treatment is individually tailored; and if systolic BP is >180, treatment is required, and should be more aggressive if there is a suspicion of increased intracranial pressure. Control of hyperglycemia (with insulin) and of fever (with Paracetamol) are important in stroke patients. *Prognosis*: the most important predictors of mortality include the Glasgow Coma Scale score, the time from thrombolysis to ICH onset, the ICH volume, and advanced age.

2.3 Ischemia: Clinical Syndromes

2.3.1 Overview

As mentioned, myocardial ischemia can be due either to increased myocardial demands or to decreased perfusion. The latter can be caused by a gradual decrease in the vascular lumen (with a corresponding increase in the resistance to flow, up until complete occlusion and total flow cessation), or to acute lumen occlusion, caused by coronary thrombus. Table 2.29 shows schematically a comparison between the two scenarios. The rest of the present section is dedicated to the discussion of these two scenarios (The reader is also referred to the beginning of Sect. 2.2.).

The Canadian classification of angina pectoris includes four grades of severity (Table 2.30). While grade I usually corresponds to stable angina, and grade IV to NSTEMI/UA, grades II and III can correspond to either.

2.3.2 Acute Coronary Syndrome

2.3.2.1 Background

The concept of ACS revolves around another concept, that of *vulnerable plaque*, with a large lipid core, low density of smooth muscle cells, high concentration of inflammatory cells and a thin fibrous cap. Such plaques are prone to fissuring (superficial damage) or rupture (involving deeper layers), under the impact of flow-dependent factors (circumferential wall stress) and of macrophage-secreted enzymes that lyse collagen. Exposure of the lipid core to the blood flow results in clot formation. The first to appear is a platelet-rich, not fully occlusive thrombus. This manifests with typical anginal pain and EKG changes, with or without myocardial necrosis (enzyme increase); however, at this stage there are no ST elevations on the EKG. In the absence of myocardial necrosis, the resulting syndrome is termed *unstable angina,* while if the enzyme levels increase, the condition is termed "non-ST elevation MI" (NSTEMI). Despite the similar pathogenesis, NSTEMI has a worse prognosis than unstable angina, justifying separate classification. If thrombus growth is countered by the patient's

Table 2.30 The Canadian Classification of Angina Pectoris

Grade	Angina occurs with	Limitation of everyday activity
I	Strenuous activity only	None
II	Walking or climbing stairs rapidly, in the cold, or under stress; walking >2 blocks on the level, climbing >1 flight of stairs at normal pace	Slight
III	Walking 1–2 blocks on the level, climbing 1 flight of stairs at normal pace	Marked
IV	The slightest activity or at rest	Extreme

Table 2.29 ACS and stable angina: a comparison

	Stable angina	ACS
Timeframe of lumen narrowing	Gradual (decades)	Sudden (minutes)
Pathogenesis	Vessel occlusion by increasing plaque volume	Flow cessation due to clot formation; distal embolization to the microcirculation
Disease mechanism	Ischemia at times of increased O_2 demand[a]	Ischemia typically not related to increased O_2 demand[b]
Adaptive mechanisms	Vasodilation[c]; vascular remodeling, collateral circulation	Vasodilation; spontaneous thrombolysis
Clinical manifestations	Chest pain of various intensities	Severe chest pain
EKG changes	ST and T wave changes; no ST elevations	ST and T wave changes; ST elevations, with STEMI
Enzyme elevation	No	Yes or no

[a]The relationship between O_2 demand and ischemia onset is not linear. Occasionally, certain types of activity are more prone than others to cause ischemia and chest pain, despite no apparent excessive O_2 consumption

[b]Occasionally, physical or psychological stress cause sympathetic discharge increasing O_2 consumption at the same time as plaque destabilization, with thrombus formation

[c]Normal vasodilation can increase blood flow up to fivefold. The vasodilator capacity is decreased by endothelial dysfunction

Table 2.31 Acute coronary syndromes

Acute chest pain and		ST elevation		
		Yes		No
Biomarker elevation	Yes	STEMI	Usually, with Q wave	NSTEMI
			Rarely, no Q wave	
	No	Aborted STEMI or non-MI ST elevation		UA

own thrombolytic system or by timely administration of antithrombotic therapy or of spontaneous thrombolysis, blood flow is reestablished, and the acute episode remits. In the contrary case, a fibrin-rich, completely occlusive thrombus forms, and the resulting condition is termed "ST elevation MI" (STEMI). These distinctions are reviewed in Table 2.31.

Differentiating the Ischemic Syndromes

- Stable angina and ACS are differentiated clinically.
- Unstable angina and MI are differentiated by laboratory tests (biomarker level).
- STEMI and NSTEMI are differentiated by EKG.

The diagnosis and treatment of ACS are discussed under "MI," below.

2.3.2.2 Myocardial Infarction (MI)

Definition and Diagnosis

MI consists in necrosis of one or several segments of the cardiac muscle, due to acute coronary ischemia. Necrosis is defined as an increase and subsequent fall in cardiac biological markers (troponin is preferred for diagnosis), in the setting of symptoms and EKG changes suggestive of ischemia. MI can span the spectrum between microscopic and extensive, with vast prognostic differences. The largest MIs involve the proximal LAD; however, with preexisting LV dysfunction, even a small MI can have catastrophic consequences. *Diagnosis*: For clinical use, the definition of MI requires the adoption of quantitative criteria. While pain is notoriously difficult to quantitate, the degree of ST segment deviation and biomarker elevation follow a continuum, and require establishing a threshold value beyond which they are considered "positive." The threshold values for ST deviation are reviewed in this section. In regard to biomarkers, even minute elevations can be detected by current assays. Technically, such elevations correspond to "true" MI s, but their clinical relevance is unclear. Therefore, a threshold for significance has been arbitrarily established, as follows:

- For non-procedure related MI: above the 99th percentile of the upper reference limit (URL) in that population.
- For PCI-related MI: >3× the 99th percentile URL.
- For CABG-related MI: >5× the 99th percentile URL, within ≤72 h of procedure, when associated with new Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new hypokinetic segments.

Occasionally, MI is diagnosed even in the absence of definitive evidence of myocardial necrosis. In victims of *SCD* occurring before there was time to obtain blood samples, or before the biomarker levels could rise, the diagnosis of MI is based on symptoms of ischemia, typical EKG manifestations, or on autopsy findings (fresh coronary thrombus and/or of pathological findings typical for MI). In patients with *angiographic or angioscopic evidence of fresh thrombus*, MI is diagnosed before the biomarker levels had time to rise (short time lag between symptom onset and angiography, or thrombus formation at the time of angiography or angioscopy). MI is often diagnosed retrospectively, by chance or as a result of workup in a patient raising the suspicion of CAD. In clinical practice, it is often necessary to diagnose MI in retrospect. Old MI is diagnosed based on EKG (pathologic Q waves), imaging tests (thin, non-contractile myocardium, lack of radionuclide uptake), or typical pathological findings, at autopsy.

Pathogenesis

MI is caused by acutely decreased coronary blood flow, most frequently due to coronary thrombosis. The other main mechanism is embolism, either (frequently) with fragments from an in situ thrombus, or (less commonly) with fragments from an intracardiac thrombus,

a valvular vegetation, tumor, etc (see Table 2.32). Thrombus forms on plaques with a fissured or ruptured fibrous cap, exposing the subendothelial tissue to the blood flow. This exposure triggers platelet and coagulation system activation and formation of platelet, then fibrin clot. Occlusion mainly occurs in coronary segments with minimal (10–40%) stenosis, generally corresponding to vulnerable plaques (large lipid core, inflammation). Vessel occlusion is dynamic, with recurrent obstruction and spontaneous reperfusion, and various degrees of vasospasm. Distal embolization with clot fragments may cause microvascular occlusion and prevent reperfusion despite flow restoration in the infarct-related artery. The amount of myocardial necrosis depends on the size of the vessel involved, but also on the presence or absence of collateral circulation and on the time lag to treatment. Necrosis starts within approximately 20 min of ischemia onset (see MI classification by stage, below) and progresses from the subendocardial to the subepicardial layer, as the former has greater metabolic demands and lower direct and collateral perfusion. In animal models, the onset of ischemic necrosis requires ≥20 min, and complete necrosis of all the myocytes at risk requires ≥2–4 h, while pathological evidence of healed MI (i.e., scar tissue) requires ≥5–6 weeks.

Prevalence and Importance

Acute MI is the leading cause of death in United States and Western Europe, with an overall mortality of >30% (including out-of-hospital fatalities). These high mortality rates are not likely to abate in the foreseeable future, as therapeutic progress is being offset by a worldwide increase in the prevalence of risk factors. Progress in MI therapy has dramatically increased the prevalence of severe HF (as a sequella of extensive MI, previously universally fatal), a key contemporary cause of morbidity. *Classification*: Based on the clinical circumstances, there are several types of MI (Table 2.32); one and the same MI can belong to more than just one "category."

Additional classifications are used: (1) *STEMI vs. NSTEMI* (see above); (2) *Q-wave (transmural) vs. non-Q wave (non-transmural) MI.* Spontaneous non-Q wave MI (Q wave absence not a result of therapy) has a better short-term prognosis (better collateral circulation), but an increased risk for long-term morbidity and mortality (due to the very reason of collateral formation, i.e., more advanced atherosclerosis). The incidence of non-Q wave MI has dramatically increased in the thrombolytic era, with an improved long-term prognosis; (3) *by size,* i.e., by the percentage of the necrosed myocardium: microscopic (focal necrosis), small (1–10%), moderate

Table 2.32 Clinical classification of MI

Type	Operative criterion	Definition: mechanism	Definition: pathogenesis
1	Pathogenesis	Decreased O_2 supply by in situ occlusive thrombosis	Plaque erosion, rupture, fissuring, or dissection
2	Pathogenesis	(1) Increased O_2 demand; (2) Decreased supply not related to occlusive thrombus	(1) Anemia, arrhythmia, HTN; (2) coronary spasm or embolism; hypotension
3	Conjecture based on limited clinical evidence	SCD, presumed to be of cardiac origin[a]	As with types I or II
4a	Iatrogenic	MI related to PCI	Disruption of flow in the artery under treatment, in side branches or in collaterals, by dissection, distal embolization, slow flow or no-reflow phenomenon, and/or microvascular plugging
4b	Iatrogenic	MI related to stent thrombosis	See text
5	Iatrogenic	MI related to CABG[b]	As with PCI

[a]The supporting evidence does not include biomarker elevation

[b]In addition to the mechanisms operational with PCI, CABG may cause myocyte necrosis by trauma from suture needles or manipulation of the heart, reperfusion injury, O_2 free radical toxicity, or the non-reperfusion phenomenon. This injury tends to be diffuse, subendocardial (rather than focal), and is not included in the definition of MI. The corresponding troponin increase is usually below the fivefold threshold required for CABG-related MI. Moreover, new ST–T abnormalities are frequently seen in patients after CABG, even in the absence of myocardial ischemia. In these patients, demonstration of new segmental LV dysfunction is essential in establishing the diagnosis of MI

(10–30%), and large (>30%); (4) *by location*; (5) *by time of diagnosis*: evolving (hours), acute (hours to days), healing (up to 5–6 weeks), and healed MI (>5–6 weeks).

Non-Q Wave vs. Q-Wave MI Prognosis: A Comparison

Prognosis depends on whether the non-Q status is attained spontaneously, or as a result of thrombolysis. Spontaneous non-Q wave MI has a better short-term, and a worse long-term prognosis, whereas thrombolysis-related non-Q wave MI has a better prognosis all around. Improvement in symptom-to-intervention time may diminish the short-term prognosis disparity between Q wave and non-Q wave MI.

Two Classifications of MI, Two Different Implications

- STEMI vs. NSTEMI: therapeutic implication (only STEMI benefits from acute thrombolysis)
- Q-wave vs. non-Q wave MI: prognostic implication (see above)

Diagnosis

Clinical manifestations – The typical *symptom* of MI is severe anginal pain, as reviewed in Sect. 2.2. The pain is similar to that of angina pectoris, but more severe and of longer duration (typically, >20 min), and is not relieved by either rest or Nitroglycerine. Unlike the pain of PE or aortic dissection, which is maximal from the start, MI-related pain increases gradually. Acute severe pain in the back may be caused by either MI or aortic dissection, or, occasionally, by coexistence of the two. Dyspnea (occasionally, pulmonary edema), palpitations, confusional state, nausea, vomiting, and profuse sweating are typical in the MI patient. GI symptoms are especially frequent in patients with inferior MI. Severe MI may present as cardiogenic shock or SCD. *Physical examination* is important for prognosis and to rule out conditions that might masquerade as MI (Table 2.33).

The degree of pulmonary congestion at presentation is classified according to the Killip class system (Table 2.34). The Killip class is influenced by compensatory hyperkinesia in the healthy myocardium; thus,

Table 2.33 Clinical[a] Differential Diagnosis of MI

	Pain	EKG	Troponin	Regional[b] WMA
(Myo)pericarditis	Worse when supine, better when leaning forward[c]	Diffuse ST elevation (no mirror-image, except for aVR and V_1)[d]; PR depressions, peaked T waves, concave (rather than convex) ST elevations	Elevation persists >1 week[e]	Absent in non-MI-related pericarditis
Aortic dissection (not complicated with MI)	Maximal from the beginning, can be migratory	no EKG changes	Elevated in ≤10% of patients with Type A dissection	No
PE	Maximal from the beginning	Sinus tachycardia; ST/T changes mimicking MI[f]	Increased troponin in cases of severe RV strain	WMA mainly involve the RV[g]
GI disorders (reflux, spasm, inflammation, etc.)[h]	Pain does not radiate	Usually normal; EKG manifestations of inferior MI may be seen in acute cholecystitis	No troponin elevation	No

[a]The EKG differential diagnosis is reviewed in a separate table
[b]Wall motion abnormalities
[c]Pericarditis and MI may coexist
[d]Large, "wrap-around" LAD may cause similar changes
[e]Patients with greater cTnI elevations (>1.5 μg/L) tend to have more severe ST elevations, and potentially be more prone to be misdiagnosed as MI
[f]In addition to the S1Q3T3 pattern (S wave in LI, Q wave in LIII, T wave inversion in L III), sinus tachycardia, RBBB, right axis deviation
[g]In massive PE, there may exist a leftward shift in the IVS, with LV compression
[h]Specific tests may be useful esophageal manometry, HIDA scan to rule out cholecystitis); response to antiacids, spasmolytics, etc.

Table 2.34 The Killip classification[a]

Class	Definition	Characteristics	Patients (%)	Mortality rate (%)
I	No HF	No rhales	85	5
II	HF, no pulmonary edema	Rhales <50% of lung fields	13	14
III	Pulmonary edema	Rhales >50% of lung fields	1	32
IV	Cardiogenic shock	Hypotension, peripheral hypoperfusion	1	58

[a]The data are based on the GUSTO-I trial

Table 2.35 The inadequacies of classical EKG terminology In MI

	Terminology	Why the terminology is confusing
Q wave	"Necrosis"	Necrosis is currently defined as biomarker elevation, and not all biomarker elevation associates a Q wave. Moreover, unlike necrosis, Q waves can be transient
ST changes	"Injury current"	The term was coined to suggest a myocardial involvement severity less than with necrosis, but more than with "lesion". However, many MI patients with "injury currents" actually have myocardial necrosis
T wave changes	"Ischemic current"	The term "ischemia" encompasses the notions of "injury" and "necrosis". Patients with T wave abnormalities can span the spectrum from normal to acute (or old) MI

while an advanced class portends a poor prognosis (in the early thrombolytic era, the mortality in cardiogenic shock, i.e., Killip Class IV, was ≥50%), a lower class does not necessarily correspond to a small infarct-related area. Assuming optimal therapy, the Killip score on admission is the best prognostic predictor in MI patients, as it reflects not merely MI size, but also the impact of MI on the specific patient. Even a small MI may lead to advanced Killip classes, in presence of significant previous myocardial compromise.

EKG manifestations reflect ischemia and its complications (arrhythmia, conduction disturbances, reviewed below and in Chap. 6). EKG also provides a gross estimate of MI size (large MI generally involves a greater number of leads or causes LBBB or RBBB). MI affects ventricular depolarization and repolarization, i.e., the QRS complex, the ST segment, and the T wave. While EKG has preserved its central role in MI diagnosis, the classical terminology, coined decades before the biomarker assay era, has become inadequate and confusing (Table 2.35).

The EKG manifestations of acute MI are reviewed in Table 2.36. *EKG monitoring* is mandatory during the patient's stay in the ICU, and especially at the time of thrombolysis and early thereafter.

While any component of the EKG may be permanently affected by previous MI (e.g., "frozen" ST elevations with LV aneurysm, permanently inverted T waves, etc.), the formal diagnosis of old MI is established based on Q waves and/or the amputation of R waves. The changes must be present in ≥2 contiguous leads, and include any of the findings below:

- Q waves ≥30 ms and ≥0.1 mV, in any two contiguous leads (including RV leads), except for V_1–V_3.
- Q waves or QS complexes ≥30 ms and ≥0.2 mV, in leads V_2–V_3.
- R waves ≥40 ms *and* R/S >1, *and* a concordant positive T wave *and no* conduction defect, all in leads V_1–V_2.

Equally important the diagnosis of reinfarction during recovery from the initial MI, before the ST–T changes have entirely normalized. Reinfarction is diagnosed in presence of new ST elevations ≥0.1 mV, in any two contiguous leads, especially in a suggestive clinical setting. New Q waves must be carefully assessed, to establish if they correspond to the initial event or to the recurrent one.

The evolution of the EKG in acute MI is shown in Fig. 2.3.

Table 2.36 EKG manifestations of acute MI

	Finding	Significance	Remarks
Ventricular depolarization			
Q wave	*Pathologic Q waves* are larger than 25% of the corresponding R wave and/or have a width of ≥40 ms[a]	In MI, Q waves represent a "see-through" image of the myocardial depolarization in the opposite wall of the heart	Classically the hallmark of old MI, Q waves may actually appear within minutes of ischemia onset and can be transient.
R wave	*R wave amputation* = a decrease in the expected (or previously documented) R wave amplitude, e.g., poor progression of R waves in the anterior chest walls	Decrease in the depolarizing myocardial mass of the affected segment	Occasionally, the R wave is completely obliterated, and the QRS complex becomes a QS complex
S wave	May become obliterated by ST segment elevation	EKG is a summation picture; "smaller" events may be obscured by temporally contiguous "larger" events	S waves have secondary importance in the EKG diagnosis of acute MI
The interval between completion of depolarization and the beginning of repolarization			
STsegment	Elevation[b]/depression	Ischemic subendocardium or subepicardium fail to depolarize normally, and there is a transmyocardial ionic gradient; the normal "electrically inert" (isoelectric) ST segment now records an electrical current	
	Elevation ≥1 mm (for leads V_2–V_4, ≥2 mm in men and ≥1.5 mm in women) in ≥2 contiguous leads,[c] i.e., in groups	Transmural or subepicardial injury[d]: the electrical ST vector points toward the area of subepicardial ischemia	Identification of ST segment elevations as described is an indication for thrombolysis
	Horizontal or downsloping *depression* >0.5 mm[e] in ≥2 contiguous leads	Subendocardial injury: the electrical ST vector points toward the area of subendocardial ischemia	ST depressions can be the direct image of subendocardial ischemia or a mirror-image of subepicardial ischemia (occasionally invisible as such, i.e., in posterior wall MI)
Ventricular repolarization			
T wave	Upright or inverted	As for the ST segment	
	Upright; (a) increased amplitude and width; (b) normal	(a) Subepicardial ischemia (hyperacute stage of MI); (b) old MI	(a) Same mechanism as for ST elevation; (b) restoration of normal repolarization vector
	Inverted >0.1mV, in ≥2 contiguous leads	(a) Subepicardial ischemia	

(*continued*)

Table 2.36 (continued)

	Finding	Significance	Remarks
Intraventricular conduction[f]			
	New LBBB	Involvement of a large myocardial mass in the anterior LV wall	LBBB unto itself, in a setting suggestive of MI should lead to thrombolysis in adequate candidates[b]
	New RBBB	May represent involvement of a large portion of the anterior LV wall[g]	Complicates interpretations of ST changes in V_1–V_3[g]

[a]As opposed to normal Q waves, occasionally visible in leads I, aVL, V_5 and V_6, and corresponding to septal depolarization
[b]Measured from the J-point, i.e., where QRS ends and ST begins
[c]Often with reciprocal ST depressions in the contralateral leads. A 1- or 2-mm threshold increases specificity, but decreases sensitivity
[d]Abnormalities of the subepicardial action potential and transmural conduction (among other mechanisms) are believed to be involved
[e]Occasionally, the ST shift is slightly less than the required magnitude, in one of the leads
[f]The Sgarbossa score for MI diagnosis in LBBB patients increases specificity but decreases sensitivity, leading to significant underuse of thrombolysis in extensive anterior MI. Criteria for MI include: concordant ST elevation ≥1 mm in ≥1 lateral (V_5–V_6) or inferior (LII, III, aVF) lead; ST depression ≥1 mm in ≥1 anterior (V_1–V_3) lead; or discordant ST elevation ≥5 mm in ≥2 contiguous leads
[g]RBBB associated to independently diagnosed acute anterior MI carries a poorer prognosis. In MI patients, RBBB at presentation carries poorer prognosis than LBBB; however, RBBB is not an *independent* indication for thrombolysis. RBBB may obscure ST–T changes in V_1–V_3; positive (pseudonormalized) T waves in these leads strengthen the suspicion of ischemia

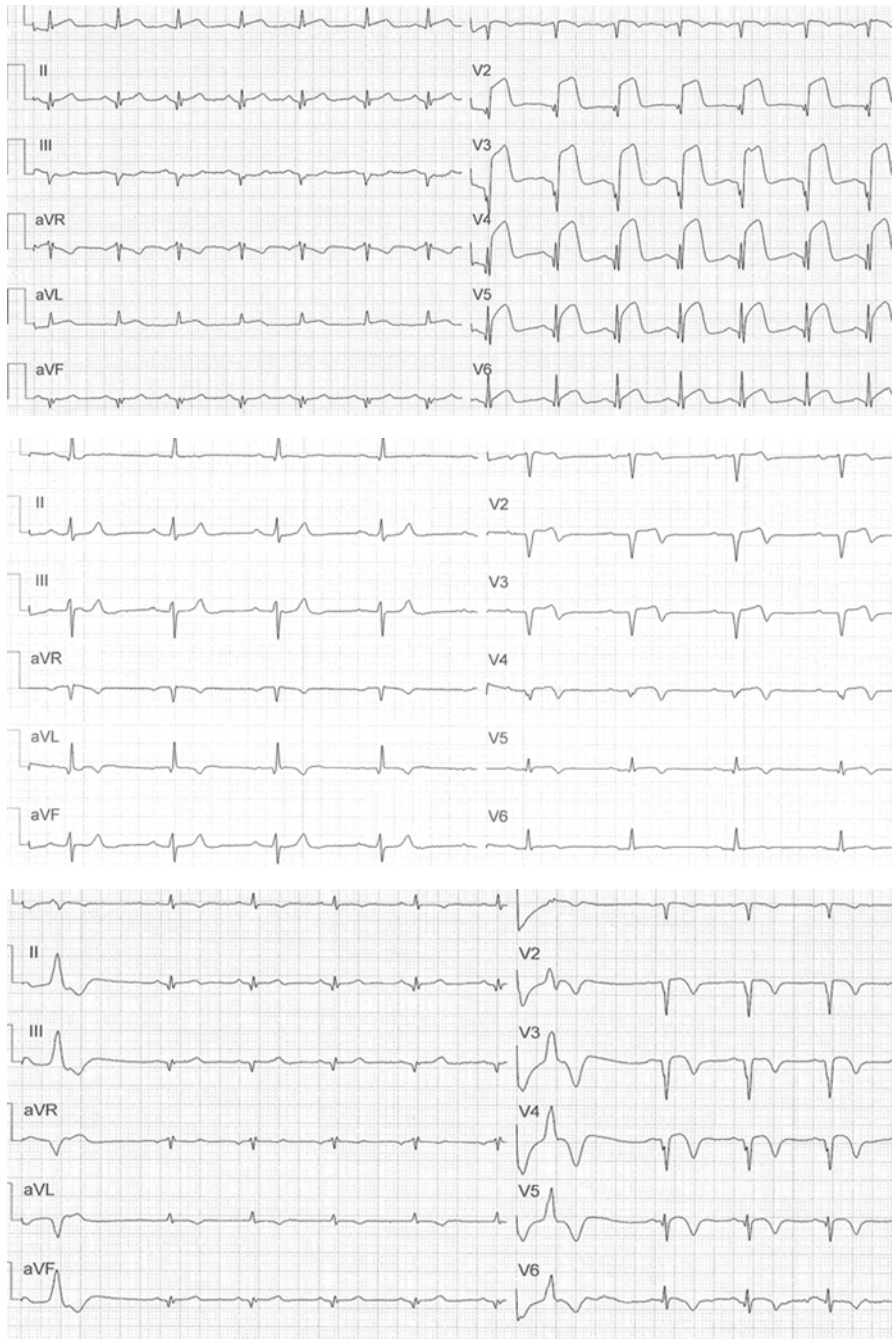


Fig. 2.3 Anterior wall MI. *Top panel* – acute phase (first few hours after onset); *Middle panel* – subacute phase (first few days); *Bottom panel:* chronic phase (beyond the first few days). Note the gradual descent of the ST segments and the appearance of Q waves. In this patient, there is still some residual ST elevation, possibly indicative of LV aneurysm formation. In this case, the T waves have taken a permanent negative configuration, but they may also become isoelectric or revert to the normal positive configuration

Biomarkers: The clinically useful necrosis markers are troponins T and I, and CK-MB; myoglobin is used less frequently. The dynamic of these markers is reviewed in Table 2.37.

The preferred biomarker is troponin, a complex of proteins important for striated muscle contraction. Both types of troponin can be used for diagnosis, but cTnI is more widely available than cTnT. Troponin may be elevated in a variety of non-MI disorders, either cardiac (CMP; cardiac trauma, occasionally iatrogenic, such as after CPR; arrhythmia and AVB; the Takotsubo syndrome; myocarditis; drug cardiotoxicity); or non-cardiac (aortic dissection, PE, stroke, subarachnoid hemorrhage; renal failure; respiratory failure, sepsis, extreme exertion, rhabdomyolysis, etc.).

Table 2.37 Biomarkers in the diagnosis of MI

Marker	Troponin T[a]	Troponin I[a]	CK-MB	Myoglobin
Initial elevation (hours from occlusion)	3–12	3–12	3–12	1–4
Peak elevation (hours from occlusion)	12–48	24	24	6–7
Normalization (days)	5–14	5–10	2–3	1
Blood samples (initial MI)	At initial evaluation; 6–9 h later; and at 12–24 h, if the initial results are negative, but the suspicion of MI is high[b]			
Blood samples (reinfarction)	On initial suspicion, and 3–6 h later[b]			
Blood samples (PCI[c])	Before or immediately after the procedure; at 6–12 h; and at 18–24 h			

[a]A rising and falling pattern is necessary to distinguish MI-related elevations from background elevations; with presentation >24 h after symptom onset, this pattern is not necessary

[b]The preferred biomarker is troponin. When troponin is used, recurrent MI is diagnosed if there is a ≥20% increase of the value in the second sample

[c]PCI virtually always causes ischemia, but patients with associated biomarker elevation have a worse prognosis

An *imaging test* (most frequently, an *echo*) is routinely obtained, as the degree of LVEF decrease is the main prognostic factor after MI. Additionally, if for whatever reason biomarkers have not been obtained or have already normalized, demonstration of new segmental hypokinesia or akinesia or loss of normal systolic thickening, in a suggestive clinical context, meets the definition for MI. Echo is ideal for triaging in chest pain units, as a normal test has a negative predictive value >95% for acute MI. If acute MI has been ruled out, echo often establishes the correct diagnosis (e.g., PE). Contrast echo improves LV endocardial border delineation in technically difficult studies. Myocardial contrast echo, suggested as a "one-stop shop" method allowing to identify perfusion defects at the same time as the resulting segmental LV dysfunction has not reached the threshold of clinical applicability.

To summarize, in the MI patient, resting echo is useful for: (a) *demonstration of new segmental dysfunction* in a suggestive, but not clear-cut clinical context (anginal pain and EKG changes present, biomarker results not, or not yet available); in the occasional patient in whom the EKG is nondiagnostic (e.g., preexisting BBB), echo allows localization of the affected segments and identification of the culprit artery. Echo also allows to classify ST depressions in V_1–V_2 as direct or mirror-images (anterior vs. posterior hypokinesis); (b) *assessing the impact of MI* and/or thrombolytic therapy on LV function. This initial assessment tends to overestimate the damage, as, in addition to necrosis, it includes areas of stunned myocardium. Re-assessment at 4–6 weeks after discharge is essential, to avoid chronic overmedication and undue psychological trauma to the patient; (c) *assessing MI-related damage reversibility*; thin, non-thickening, dyskinetic areas are irreversibly damaged (scarred); akinetic areas are usually irreversibly damaged, but can occasionally be viable; and hypokinetic areas are often viable. Hibernating myocardium can be distinguished from myocardial scar by means of Dobutamine echo; (d) *assessing the effect of chronic medication* on myocardial remodeling, a chronic sequella of MI.

Radionuclide imaging may diagnose MI even in the absence of biomarker elevations, but can only be performed in a hospital setting, where the much simpler biomarker assays are also available. Moreover, diagnostic data only become available a few hours after radiotracer injection, making nuclear scan useless in patients with suspected MI, in whom therapeutic decisions (including thrombolysis, if appropriate) are urgent. Therefore, in the MI patient, radionuclide imaging is mainly used for the diagnosis of myocardial hibernation. If acute STEMI has been ruled out, and the clinical question regards the presence or absence of ischemia, radionuclide tracer can be injected at presentation, with imaging after few hours. A normal perfusion scan has a very high (>95%) negative predictive value for coronary ischemia. Just like echo, radionuclide imaging provides localization of the ischemic segments; in addition, it demonstrates coronary flow impairment and, by means of SPECT imaging, segmental contractile dysfunction. *MRI* can assess myocardial perfusion, contraction, and viability. However, due to the availability of cheaper and less cumbersome methods, the current role of MRI in the diagnosis of MI or of myocardial viability is restricted. Acute MI reflects on MRI as delayed gadolinium hyperenhancement, i.e., over-captation in the infarcted area approximately 20 min after injection

(well within the acceptable window for thrombolysis). In real life, the one important indication for MRI in the diagnosis of coronary ischemia is demonstration of occasional underlying coronary malformations. *CT* scan has capabilities and limitations similar to those of MRI. CT demonstrates fresh MI as a focal area of hypoenhancement (decreased contrast uptake), followed, later on, by focal hyperenhancement. As mentioned, angio-CT is widely used for the diagnosis of coronary atherosclerosis. *Diagnostic coronary angiography* is by definition performed in all patients undergoing PCI or CABG. Routine cardiac catheterization has been proposed as an anatomic risk stratification tool, in all post-MI patients. Thus, the CARESS-in-AMI study has showed substantial advantage for routine early PCI in all high-risk STEMI patients (even if successfully treated with fibrinolytics). If this study receives further confirmation, routine PCI in all non-low risk STEMI patients (just as is undertaken in NSTEMI patients) may become the rule.

Assessment of the Extent of Myocardial Involvement in Acute MI

At comparable levels of collateral circulation, ischemic preconditioning, and preexisting myocardial damage, the size of the involved myocardial segment is proportional with the caliber of the infarct-related artery. *In the acute stage*, the extent of myocardial damage is assessed: (1) *clinically,* by the Killip class; (2) *by EKG, in STEMI* (number of involved leads, severity of ST elevations); (3) *by echo* (magnitude and extension of segmental LV dysfunction; however, necrosis and stunning cannot be distinguished); (4) *using biomarkers,* to obtain a more accurate estimate of the MI size. *In the late stage*, echo, radionuclide studies, or cardiac MRI allow to assess the extent of myocardial involvement, which is the major prognostic factor after MI. The key issue of post-MI damage assessment is discussed under Sect. "2.3.12," below; (5) *Novel approaches:* Eighty-lead EKG mapping, using a special vest and a computer to display the data as color maps permits better visualization of classical EKG "blind spots" (posterior, inferior, right-sided, or high lateral walls).

STEMI

A subgroup of MI patients displays a set of characteristics that merit separate discussion. *The pathogenesis* involves a fully occlusive thrombus; *the prognosis* is generally worse than with non-complete vessel occlusion; *the EKG* displays ST elevations, satisfying certain criteria; and *the treatment* includes IV thrombolysis in appropriate candidates (discussed below). This type of MI is termed "ST-elevation MI" (STEMI). New-onset LBBB has similar clinical characteristics, and is discussed together with STEMI. Occasionally, STEMI is diagnosed retrospectively, based on development of new pathological Q waves. The EKG stages of STEMI evolution are outlined in Table 2.38. Of note, acute MI is *not* the most frequent cause of ST elevation in patients with chest pain (unrelated LVH is more frequent, and unrelated LBBB is just as frequent as acute MI). Additionally, >90% of healthy males have ≥1 mm ST elevations in ≥1 precordial lead.

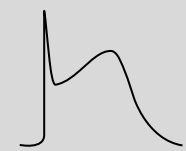
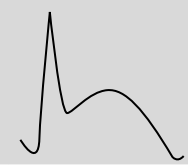
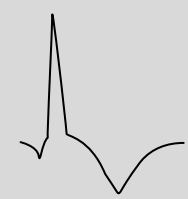
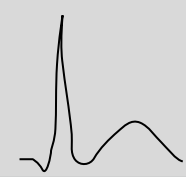
Conditions that may mimic STEMI on the EKG are reviewed in Table 2.39.

The EKG differential diagnosis between acute MI and acute pericarditis is illustrated in Fig. 2.4.

MI Treatment

Background: MI treatment involves different measures in the acute phase (when the accent falls on early restoration of the coronary blood flow, to minimize necrosis, and in treatment of complications) and in the post-MI patient (where the aim is to prevent late complications and recurrences of the MI). In either setting, the treatment may be pharmacological or interventional, as discussed above. The treatment of STEMI is characterized by the option of IV thrombolysis, which has not been proven beneficial in other types of ACS (NSTEMI, unstable angina); however, an early interventional therapy is the preferred approach in all types of ACS, including STEMI. If this approach is implemented, there is virtually no distinction between the therapies of the different types of ACS, although the actual guidelines may differ in the strength of recommendation of the different approaches. This is justified by the evidence-based approach, i.e., on the available data derived from large-scale trials or metaanalyses; however, the practical impact of these occasional finer points is generally modest. STEMI treatment will be reviewed first, to be followed by a table summarizing the particularities of NSTEMI therapy. Therefore, while in the following discussion, the term STEMI is used, most comments also apply to NSTEMI. Importantly, this

Table 2.38 The EKG Evolution of STEMI

Stage	Q	ST	T	EKG
Hyperacute	No	May be elevated	Increased amplitude and width	
Transmural injury	No	Markedly elevated	Increased amplitude and width	
Necrosis	Yes	Starts normalizing	Inverted[a]	
Necrosis and fibrosis	Yes	No	Inverted[a]	
Fibrosis	Yes	No	Upright	

[a]Previously negative T waves may become positive – "pseudonormalization". R waves may be amputated or altogether obliterated, turning the QRS complex into a QS wave

does not include IV thrombolysis, an approach reserved to STEMI patients.

MI Treatment : General Measures *Oxygen* is routinely used, although there are no clear efficacy data, and future placebo-controlled trials are improbable. While O_2 administration in dyspneic patients (especially if hypoxemic) is clearly indicated (occasionally, by orotracheal intubation and mechanical ventilation), the grounds for routine administration in all-comers are less clear; at any rate, O_2 administration in uncomplicated cases should not exceed 6 h. The idea of intracoronary administration of hyperbaric O_2 in STEMI patients undergoing PCI was tested in a small study, with unconvincing results and a higher incidence of bleeding in the treated arm (due to the cumbersome technique involved). *Nitrates*: Both the GISSI-3 and the ISIS-4 trials have failed to demonstrate a mortality benefit for nitrate therapy in asymptomatic patients (an infrequent occurrence in STEMI patients presenting to the ER). After long term use, tolerance may develop, reducing nitrate effectiveness. Several mechanisms have been proposed. Clinically, the problem is dealt with by avoiding continuous use of nitrates; discontinuous use makes it possible to recover sensitivity to these agents. Patients with endothelial dysfunction are more prone to develop nitrate tolerance; thus, nitrates

Table 2.39 EKG differential diagnosis of MI

Condition	Similarity to MI	Difference from MI
Pseudo-anterior wall MI (changes in V_1–V_3[a])		
LV aneurysm	ST elevations	"Frozen" changes, do not have the usual MI dynamic
LVH	Poor R progression	S (V_1) + R (V_5 or V_6, whichever is larger) ≥35 mm; R (aVL) ≥11 mm
LBBB	QS or poor R progression	QRS ≥120 ms; QS or rS in V_1; monophasic R in L I, V6
Pulmonary emphysema and cor pulmonale	Loss of R waves[b]	Right axis deviation; microvoltage
Left anterior fascicular block	Occasionally, q waves	Left axis deviation; q waves are small
Type B WPW	Negative QRS[a]	Presence of the delta wave
Pneumothorax	Loss of R waves	Microvoltage, clinical context
Brugada syndrome	ST elevations	"Coved" (Type I) or "saddle back" (Types II, III) pattern ST elevation
Pseudo-lateral wall MI (changes in L I, aVF, V5–V6)		
HOCM	Deep Q waves	Associated LVH
Pseudo- posterior wall MI (changes in V_1–V_2)		
Type A WPW	Tall R waves	Presence of the delta wave
RVH	Tall R waves	Associated incomplete RBBB, RV "strain"
Diffuse ST–T changes		
Acute pericarditis	ST elevations	Lack of mirror image changes, morphology of ST elevations[c]
CNS disease	Diffuse ST–T wave changes	Often, associated bradycardia; clinical context
Early repolarization[d]	ST elevations	The "J wave," a slurring or notching preceding the ST segment
Hyperkalemia	Peaked T waves (mimic hyper-acute phase of MI); in more severe cases, widened QRS	Reduction of the size of the P waves
Myocardial fibrosis	Q waves	Clinical context

[a]With WPW, the changes are often restricted to V_1
[b]May associate inferior Q waves
[c]Chap. 7
[d]Changes may also be localized in anterior or inferior leads; there is some concern that this latter location may be associated to life-threatening arrhythmia

appear least effective in the patients who need them most. Nitrates can cause severe headaches, hypotension, and occasional paradoxical bradycardia. *Morphine* is not to be viewed merely as a "pain-killer," as it also helps control sympathetic activation (and is thus effective in reducing the size and complication incidence of STEMI); additionally, it helps improve hemodynamic conditions in patients with pulmonary edema. In the pre-reperfusion era, *β-blockers* were shown to significantly reduce STEMI mortality; in light of the sound rationale behind their use, the Class I indication is maintained in the current thrombolytic era. Smaller studies have suggested a higher efficacy with IV administration, but the large-scale COMIT CCS-2 trial has found no reduction in mortality, as reduced incidence of VF and of early reinfarction was offset by a higher

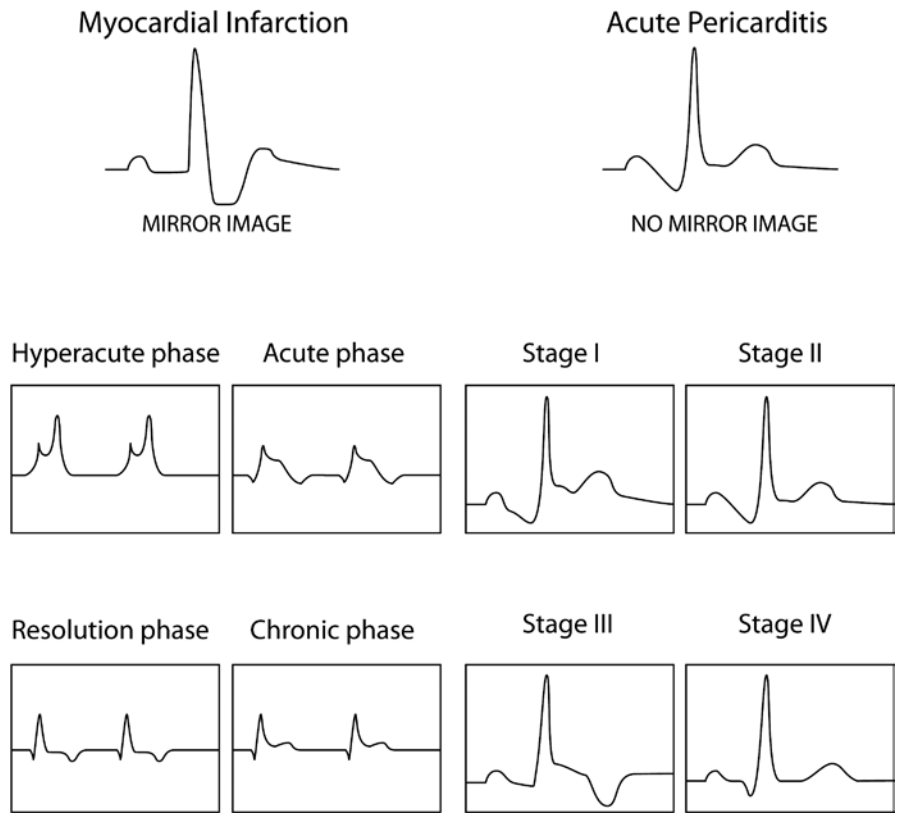


Fig. 2.4 The evolution phases of acute MI vs. those of acute pericarditis (explanations in the text)

prevalence of cardiogenic shock. Therefore, while early IV β-blockade may be considered (Class IIb indication) in case of excessive adrenergic discharge (tachycardia, HTN), the preferred approach is oral therapy, started as soon as the patient has recovered from the acute phase of STEMI. The dosages are similar to the ones used in HTN. Some popular regimens include: *Atenolol (Tenormin)* 100 mg q.d. or 50 mg b.i.d., continued indefinitely (of note, the available data only refer to the first 6–9 days post-MI; the extension of this treatment is empirical). If a choice has been made to administer Atenolol in the early post-MI phase, this is given (in the absence of HF or hypotension) as a slow IV dose of 5 mg over 5 min, with another 5 mg 10 min after uneventful completion of the first dose; oral Atenolol is subsequently started; *Metoprolol (Lopressor)*: start at PO 50 mg q.i.d. for 48 h then switch to 100 mg b.i.d.; continue indefinitely. If administered early post-MI, three sequential IV doses of 5 mg at 2-min intervals are used, with oral therapy started at 15 min after the eventless administration of the IV therapy. The oral dosage may be reduced if the IV administration was not well tolerated and in the elderly. In the event of HF (whether MI-related or not), indefinite β-blocker therapy is mandatory, in the absence of contraindications. Preliminary data seem to demonstrate the feasibility of *Ivabradine* treatment as an alternative to Metoprolol in STEMI patients.

β-Blockade and HF: A Double Standard

β-Blockers are an integral part of *chronic* HF treatment; however, in *acute* HF (such as with acute MI), these agents are contraindicated.

ACEI, started within 24 h of STEMI onset in the absence of contraindications, produce a small but significant decrease in mortality. ACE-inhibitors appear to possess an antiatherogenic effect, irrespectively of LV function and of the presence of HTN. Such an effect has not been proven for ARB drugs. It is not clear whether these agents benefit all STEMI patients (Class IIa recommendation), or if they should be

reserved for high-risk patients (Class I recommendation). High-risk patients have LVEF <40% or clinical HF; the benefit is smallest in patients with small inferior MI. Some popular regimens include: *Captopril*: PO initial dose of 6.25 mg, followed by 12.5 mg t.i.d., and increased to 25, then 50 mg t.i.d.; *Ramipril*: PO initial dose 2.5 mg q.d. for 1 week, then 5 mg q.d. for the next 3 weeks, then increase as tolerated to 10 mg q.d. (or 5 mg b.i.d.); *Lisinopril* 5 mg q.d., increase to 10 mg q.d.; *Trandolapril*, test dose of 0.5 mg, target dose 4 mg q.d.; *Quinapril*: PO 5 mg q.d. or b.i.d., titrated at weekly intervals to 20–40 mg daily in two divided doses. In HF, the target dose is 20 mg b.i.d. These doses may be increased as discussed in Chap. 4, in patients with overt HF. The duration of post-MI ACEI treatment is a matter of debate. While these agents should be continued indefinitely in patients with LV dysfunction or with overt HF, chronic use is not justified in asymptomatic patients with intact LV function. Patients unable to tolerate an ACEI should be treated with an *ARB agent*. The agent of choice is Valsartan 160 mg q.d., started at low doses (20 mg) and uptitrated slowly. Losartan 50 mg q.d. failed to replicate the protection offered by Captopril 50 mg t.i.d. In patients with LV dysfunction (EF <40%) and diabetes or HF *aldosterone antagonists* are used on top of ACEI or ARB agents, under close monitoring of the serum potassium levels. The main agents include *Spironolactone* 25–50 mg q.d. and *Eplerenone*, also dosed at 25–50 mg q.d. Eplerenone has been proven (EPHESUS trial) to reduce mortality as compared to placebo in post-MI patients, and represents an alternative in patients with LVEF <40% and creatinine <2.5 mg/dL in men (2.0 mg/dL in women). As hyperkalemia is common, potassium levels should be monitored, and the drug should not be started at potassium levels >5 mEq/L. Eplerenone has a much lower incidence of gynecomastia than Spironolactone.

Contraindicated or nonindicated therapies, suggested along the decades but proven ineffective or even deleterious include: *CCB*, which, as as a class, are associated with a (nonsignificant) trend towards adverse clinical outcomes; Diltiazem and Verapamil are contraindicated in STEMI patients with associated systolic LV dysfunction and CHF. Immediate-release Nifedipine is contraindicated, as it causes reflex sympathetic activation, tachycardia, and hypotension. *Prophylactic antiarrhythmic therapy*: while prophylactic Lidocaine may decrease the incidence of malignant ventricular arrhythmia, there is no decrease in mortality, as the incidence of asystole increases; therefore, prophylactic Lidocaine in MI patients is contraindicated; *Prophylactic IV magnesium supplements* were found, in some smaller, open-labeled trials, to reduce MI mortality; however, the ISIS-4 trial and the specially-designed, optimally-dosed MAGIC trial have disproven this hypothesis; *glucose–insulin–potassium (GIK) therapy* was postulated to improve myocardial energy production and ventricular function and to decrease the incidence of serious ventricular arrhythmias in MI patients. Unfortunately, the CREATE-ECLA study has disproven this hypothesis as well; *COX-2 inhibitors* were suggested to complement the action of Aspirin and to overcome resistance to the latter, as Aspirin is only effective on the COX-1 receptors. However, COX-2 inhibitors were actually proven to increase mortality in CAD patients, as they reduce production of prostacyclin, a vasodilatory agent; enhance atherogenesis and thrombogenesis; and cause HTN (In fact, NSAIDs, are contraindicated in CAD, as they, too, may increase mortality. However, Naproxen and possibly Diclofenac appear relatively safe.); *HRT*: it was hoped that an *estrogen/progestin* combination would replicate the protective action of natural estrogens, but this was found ineffective in secondary prevention, and actually deleterious (increased risk of CAD and of breast cancer), if used in primary prevention. *Torcetrapib* was developed to raise HDL, but was abandoned due to increased mortality; *Antioxidant therapy,* especially as vitamins E, C and A (β-carotene) have not been proven effective and are not recommended. Nevertheless, due to their intuitive appeal and their over-the-counter availability, they are frequently self-administrated in the population.

Special therapeutic considerations: *RV MI* is usually associated to inferior MI, but occasionally presents in isolation, causing hypotension in a patient with clear lung fields and enhanced jugular veins. Patients with RV MI are especially preload-sensitive, and IV saline infusions (initially, given rapidly) are the mainstay of therapy, while the use of vasodilators (including nitrates, opiates, ACEI, ARB) must be minimized. This is in stark contrast to the aggressive vasodilator and diuretic therapy used in LV MI-related shock. Additional frequent features include *AF* (which must be rapidly converted to NSR, as the atrial kick is especially important in these preload-sensitive patients)

and *AV block*, which requires dual AV pacing, to restore physiologic AV activation sequence and optimize CO. Primary PCI is especially effective; the second-choice alternative, IV thrombolysis, may have suboptimal results. *MI in diabetics*: The mortality of STEMI is double than in non-diabetics, due to an often atypical presentation, with HF onset or exacerbation, rather than anginal symptoms; more diffuse and more severe coronary atherosclerosis; and frequent glucose imbalances in the acute stage. Glycemic control is of paramount importance in these patients (as, indeed, in any MI patient), but the optimal treatment for acute hyperglycemia is unclear (notably, the DIGAMI-2 trial has failed to show any advantage for Insulin, administered in isolation or in the first 24 h of presentation, as opposed to conventional therapy alone). In critically ill patients, insulin therapy should be used to decrease glucose levels to a range of 140–180 mg/dL (7.8–10.0 mmol/L), under frequent monitoring, to avoid hypoglycemia. The previous target levels of 90–140 mg/dL (5–7.8 mmol/L) were only attainable at the cost of a significant increase in poorly-tolerated hypoglycemia episodes, and are no longer recommended. However, tight *chronic* glycemic control does bring about a reduction in the incidence of macrovascular complications, and the recommendation to aim at a HbA1C level <7% has not changed.

MI in patients with renal failure is associated to increased mortality, partly due to underuse of invasive strategy, for fear of renal failure exacerbation under contrast material; on the other hand, if this complication does occur, the mortality is also increased.

MI Treatment : Acute Reperfusion Therapy
General remarks: Reperfusion restores blood flow to ischemic tissues, and is achieved by IV thrombolysis (STEMI only), or by primary PCI. In MI, CABG serves for rescue after failed PCI (due to time constraints and tissue friability after MI). Acute reperfusion improves survival by reducing MI size, myocardial remodeling, and arrhythmic potential. The absolute benefit from acute reperfusion is highest with new LBBB, anterior MI, and large at-risk myocardial areas, and lowest with inferior STEMI (except for the subgroup with associated RV MI or anterior ST-segment depression). However, benefit may be obtained regardless of MI location, patient age, and clinical presentation. Whatever the approach, the main concern is for speediness. The main cause for underuse of acute reperfusion therapy in MI patients remains the delay between symptom onset and presentation to the medical caregiver. In this respect, the education of the public regarding the warning symptoms of a possible "heart attack" cannot be overstressed. The greatest benefit occurs within the first 2 h (when MI can actually be aborted or significantly limited in size); conversely, most of the damage is accomplished by 12 h, and only select patients are candidates for acute reperfusion therapy after this point. After presentation, prompt diagnosis and treatment are just as important. While the target "door-to-needle" and "door-to-balloon" times are of 30 and 90 min, respectively, shorter delays can often be attained, further improving prognosis. These demanding time frames partly compensate for the between symptom onset and presentation.

The absolute benefit from acute reperfusion therapy is highest in patients with new LBBB, anterior MI, and a large at-risk myocardial area (highest number of ECG leads affected, greatest total ST deviation) and lowest with inferior STEMI (except for the subgroup with associated RV MI or anterior ST-segment depression). However, benefit may be obtained regardless of MI location, patient age, and clinical presentation.

Fibrinolytics: Pharmacological reperfusion is indicated in patients presenting within 12 h of chest pain and ST elevation or LBBB onset.

Thrombolysis is indicated despite the absence of the ST elevations

- In postero-basal STEMI, manifesting with ST depressions in V_1–V_3 (posterior leads and echo are helpful for diagnosis)
- In the very early phase of STEMI, with giant hyperacute T waves preceding ST elevation
- In acute LBBB (in a suggestive setting)

Occasionally, STEMI is asymptomatic or associates atypical discomfort; if, by chance, the diagnosis is established in a timely manner, reperfusion therapy is recommended as usual. Coronary occlusion is a dynamic process, involving multiple phases of artery occlusion (occasionally, complete) and spontaneous thrombolysis; thus, some patients actually suffer a series of *successive infarcts*, obscuring the definition of

Table 2.40 Contraindications to IV fibrinolytic therapy

Condition	Absolute contraindications	Relative contraindications
CNS conditions	Any past stroke of hemorrhagic or unknown origin; ischemic stroke in the past 6 months; brain neoplasms	TIA within the past 6 months
Trauma	Major trauma, surgery, or head injury within the past 3 weeks	Traumatic resuscitation
High risk of hemorrhage[a]	Bleeding disorders (predisposition to bleeding) or active bleeding	Oral anticoagulant therapy; advanced liver disease; non-compressible vascular punctures
GI disorders	GI bleeding within the past month	Active peptic ulcer
Other	Aortic dissection	IE; refractory HTN; pregnancy or within 1 week postpartum

[a]Not including menses

the 12-h window of opportunity for reperfusion therapy. If there is evidence of such successive episodes (e.g., sudden significant chest pain worsening), the most recent episode should be taken into account. IV fibrinolytics restore coronary TIMI II or III flow at 90 min in 50–85% of patients with STEMI. However, the pooling of TIMI flow II and III cases has been criticized, due to the significant differences in prognosis between the two populations. Pooled data indicate that TIMI III flow is achieved in only 50–60% of cases, as contrasted with a >90% rate for primary PCI.

The choice of the specific thrombolytic agent depends, besides availability and cost issues, on several factors. SK, by far the cheapest and the most available in developing countries, is *dispreferred* in patients presenting >4–6 h after symptom onset (more fibrin-specific agents, such as alteplase (tPA) or tenecteplase (TNK-tPA) are indicated); in allergic patients (SK is allergenic); and when, in the absence of the PCI option, an initial failed attempt at thrombolysis is followed by a second attempt. The contraindications to pharmacological thrombolysis are reviewed in Table 2.40.

The available IV thrombolytic agents include: SK; tPA; r-PA; and TNK-tPA. All of these agents bind to plasminogen, which is the precursor of the natural fibrinolytic, plasmin. The most important characteristics of these agents are reviewed in Table 2.41.

Hemorrhage, the main complication of thrombolysis and of antithrombotic therapy, is discussed in Sect. 2.2.

Glycoprotein IIb/IIIa inhibitors have been empirically found to occasionally achieve reperfusion by themselves, i.e., without being associated with either IV fibrinolytics or primary PCI. However, restoration of TIMI III flow by these agents alone was not seen in a sufficient number of patients to warrant relying on this approach in acute MI. *Combination therapy with IV thrombolytics and GP IIb/IIIa inhibitors* uses half a dose of a fibrinolytic agent (r-PA or TNK-tPA) associated to Abciximab (to overcome the initial platelet activation induced by thrombolysis). This combination regimen was assessed in the GUSTO-V and ASSENT-III trials; while 1- and 12-month mortality was not reduced as compared to full-dose thrombolytic alone, the rate of non-fatal reinfarction was significantly reduced. Unfortunately, as ICH was found to be twice as frequent in the combination therapy group, this approach is reserved for high-risk STEMI patients (large anterior MI), <75 years of age, and not at high risk for bleeding.

Interventional reperfusion in MI: *Primary PCI* has the same theoretical indications as fibrinolytic therapy, and is especially important in patients with large MI, shock, RV MI, or when fibrinolytic therapy is contraindicated or has failed. In patients with large MI, the main benefit consists in lower rates of nonfatal recurrent MI. Importantly however, PCI is not limited to these groups, and is in fact suitable for ≥90% of patients with acute MI. If expertly performed within 90 min of presentation, primary PCI generally has better results (as to overall prognosis and TIMI-3 flow in the infarct-related artery) than IV fibrinolytics. TIMI 3 flow is obtained in 70–90% of patients receiving primary PCI, with a 15% reocclusion rate after simple balloon angioplasty (5% if a coronary stent is used). In the real world, however, the logistic burden limits the general

Table 2.41 The commonly used fibrinolytics

	Dosage (all IV)	T1/2 (min[a])	Activated plasminogen	Complications (besides bleeding[b])	Heparin treatment[c]	Comments
Streptokinase	1.5mil.u. in 100 mL dextrose 5 or 0.9% saline, over 30–60 min.	20	Systemic	Allergy[d]; hypotension, fever	Optional[e], for 24–48 h	Re-treatment with SK is most hazardous between 5 days and 4 years of initial use
Alteplase (tPA)	15 mg bolus, then 0.75 mg/kg over 30 min, and then 0.5 mg/kg over 60 min.; total dose ≤100 mg.	4	Clot-bound	May cause hypotension, nausea, vomiting	mandatory, for 24–48 h	
Reteplase (r-tPA)	2 boluses of 10 mg each, at a 30-min interval.	15	Clot-bound	May cause hypotension	mandatory, for 24–48 h	
Tenecteplase (TNK-tPA)	One 30 mg bolus for a patient <60 kg; increase bolus by 5 mg for every 10 kg over 60 kg; maximum dose 50 mg (≥90 kg)	60–90	Clot-bound	May cause hypotension	mandatory, for 24–48 h	

[a]This is relevant in case of hemorrhagic complications, when reversal of fibrinolysis is contemplated; for alteplase, for instance, by the time FFP is obtained, most of the fibrinolytic activity may have spontaneously abated[b]. Generally, the risk of intra-cranial hemorrhage is lowest with SK; with the other agents, risk is greatest in patients aged >65 and weighing <70 kg

[c]IV bolus of 60 U/kg, maximum 4,000 U, followed by a continuous infusion of 12 U/kg for 24–28 h, not to exceed 1,000 U/h. aPTT is monitored (target 1.5–2.0 times control) at 3, 6, 12, 24 h in the first day, and with similar frequency if a second day of treatment is necessary. With SK, if Heparin is used, it is started 3–4 h after infusion completion 1,000 units/h, after PTT measurement

[d]Bronchospasm, angioedema, rash, urticaria, up to anaphylaxis

[e]SK produces fibrin and fibrinogen degradation products, themselves anticoagulants, possibly obviating the need for Heparin; on the other hand, SK induces extensive plasmin-mediated thrombin activity, an argument in favor of ancillary antithrombotic therapy. No difference was found between the patients with and without adjunct *subcutaneous* Heparin therapy in the GUSTO-I trial

Table 2.42 Time Constraints in Primary PCI

90 min of presentation	12 h of symptom onset[b]	18 h of symptom onset	20 h of symptom onset
Primary PCI better than IV fibrinolytics	Ideal time frame for primary PCI in STEMI	Acceptable time frame for primary PCI in cardiogenic shock[a]	Acceptable time frame for primary[b] PCI in patients with Killip III HF, hemodynamic or electrical instability, or persistent ischemic symptoms

[a]Provided shock onset was ≤36 h from STEMI onset
[b]*Any* PCI aiming at acute revascularization is "primary." Within the first 12 h, this means PCI was chosen over IV fibrinolysis; beyond 12 h, PCI is chosen over CABG or over no reperfusion therapy whatsoever

applicability of primary PCI. Primary PCI is almost universally carried out with stent deployment, to reduce the incidence of late restenosis. However, stenting does not significantly affect the mortality (3.0%) or reinfarction (2%) rates. PCI complications include problems with the arterial access site; technical complications of angioplasty; pulmonary congestion due to volume overload; CIN; excess bleeding due to antithrombotic medications; and early reocclusion or late restenosis. Of note, primary PCI can be performed up to 24 h of symptom onset in patients with severe HF (but no cardiogenic shock), hemodynamic or electrical instability, or persistent ischemic symptoms. The culprit lesion is often eccentric and has irregular, "shaggy," ulcerated borders, and may demonstrate haziness associated with intracoronary thrombus. Vasoconstriction may increase the apparent severity of the stenosis, and is countered by intracoronary administration of Nitroglycerin. In patients with either widespread or angiographically unapparent coronary atherosclerosis, identification of the culprit lesion requires correlation with the EKG and echo findings. Angiographically non-significant (<50%) culprit plaques should not be intervened upon, as "plaque sealing" with a stent does not improve outcomes. (Of note, however, the concept of "plaque sealing" may still prove valid, by using a specially designed stent, which is flexible and self-expanding, rather than balloon expandable. This device exerts a mild "push" on the vessel wall, to prevent plaque rupture.) Most PCI procedures in the current era involve the use of stents. DES cause an increased incidence of acute or subacute thrombosis; the exact clinical impact is heatedly debated. If the patient is scheduled to undergo surgery which will require interruption of dual antiplatelet therapy, a bare-metal stent (BMS) is preferable. By and large, most patients are amenable to PCI, the rest being referred for surgery. PCI and surgery are not mutually exclusive, as either may offer "rescue" from failure of the other procedure. A staged approach may also be considered, involving first PCI of the culprit lesion, and later full revascularization by elective CABG (at >12 months after PCI, as CABG requires discontinuation of antiplatelet therapy). The somewhat complex time constraints regarding primary PCI are summarized in Table 2.42.

"Facilitated PCI" (PCI following different combinations of fibrinolytics, and/or GP IIb/IIIa inhibitors, generally in reduced dosages, meant to "clear the field" for PCI) was assessed by the FINESSE and the ASSENT IV trials. No advantage was found for this approach, while the risk of peri-procedure adverse events might actually increase. However, this approach may have a role in STEMI patients facing delays in proceeding to the cath lab.

Occasionally, STEMI presents with angiographically normal coronary arteries, as may do patients with NSTEMI or UA. These cases are discussed in Table 2.43.

Angioplasty in Acute STEMI: Beyond Primary PCI

Primary PCI is, by and large, superior to IV thrombolysis, but the two modalities are not mutually exclusive. Thus, PCI can be used after failed thrombolysis (rescue PCI) or after successful thrombolysis, to provide definitive treatment of the culprit plaque. *Rescue angioplasty* is an important option after failed thrombolysis. The REACT trial demonstrated an up to 50% reduction in the composite end-point of death, reinfarction, stroke, and severe HF at 6 months, in patients

Table 2.43 ACS with angiographically normal coronary arteries

Entity	Mechanism	Clinical manifestations	Therapy
Coronary spasm (Prinzmetal's angina)	Spasm at the site of plaque, or in an apparently normal segment, due to ED[a]	Transient ST segment elevations, occasionally syncope, mainly at night, in younger, heavy-smoking patients	Risk factor management, CCB
Intramural plaque with thrombosis	Pseudonormal coronaries; diffuse atherosclerosis, with positive remodeling (vessel expansion)	General ACS presentation	As for any CAD, but revascularization is not an option
Coronary embolism	Normal coronaries, embolus formed at a distance, (e.g., AF)	General ACS presentation	Therapy of the underlying disorder
Syndrome X	ED,[a] increased sensitivity to pain and to sympathetic stimulation	Typical chest pain, on exercise or at rest; positive stress test (ST depressions); excellent prognosis	Nitrates, β-blockers, or CCB
Apical ballooning syndrome[b]	Not clear; high circulating levels of catecholamines may cause microvascular spasm	Apical and mid-ventricular akinesis (Mimicking anterior MI), mainly in post-menopausal women after severe emotional stress. Occasional HF. Usually fully reversible	Supportive; treatment of HF (Occasionally, inotropic agents or IABP are necessary)

[a]Endothelial dysfunction

[b]Alternative names include: Takotsubo syndrome (Japanese for turtle trap, alluding to the shape of the heart during the attack); broken-heart-syndrome (severe emotional stress, usually the loss of a loved one); and stress CMP

undergoing rescue PCI after failed IV thrombolysis. However, even rescue PCI may fail to restore epicardial blood flow in up to 10% of patients, with a variable number of additional patients undergoing reocclusion. The decision in favor of rescue PCI (as opposed to conservative therapy or to CABG) is based on the importance of the myocardium at jeopardy, as judged by the Killip class; the ischemic symptoms; electrical instability; and the results of post-MI risk stratification (There is a Class IIb recommendation for rescue PCI in all patients after failed thrombolysis. If a policy of routine PCI after IV thrombolysis is implemented regardless of the initial success rates, the notion of "rescue PCI" becomes redundant). In occasional patients a relatively small area of jeopardized myocardium may cause electrical instability (with potentially lethal ventricular arrhythmia), justifying rescue PCI. *PCI after successful thrombolysis* has been assessed in the acute setting (within 24 h) and in the late setting. The CARESS-in AMI study, carried out in *high-risk* STEMI patients initially treated with IV thrombolysis (primary PCI unavailable), and then immediately transported to another hospital for elective PCI (regardless of the initial success of IV thrombolysis) has demonstrated improved outcomes in the intervention group. Whether this policy can be extended to *all* post-thrombolysis patients (regardless of MI size and clinical status) is unclear. The TRANSFER-AMI study has confirmed the advantages of the "pharmacoinvasive" strategy as compared with standard treatment, without excess bleeding: post-thrombolysis patients transferred for PCI within 6 h of fibrinolysis fared better than patients treated conservatively (with PCI used for rescue only). *PCI late after IV thrombolysis* has been extensively studied, in light of the *late open artery hypothesis*, proposing that coronary patency may improve prognosis despite lack of myocardial salvage (in older trials, LV dilatation and arrhythmia were more frequent and the overall prognosis was poorer, in patients with a persistently occluded infarct-related artery). Several prospective trials have reached diverging conclusions in this respect, possibly due to the different study populations. Thus, the Occluded Artery Trial (OAT) trial, carried out in *asymptomatic* patients with an occluded epicardial coronary artery, but without three-vessel or left main CAD and with no demonstrable residual ischemia, found no benefit for routine PCI. However, the BRAVE-2 trial, evaluating *symptomatic* elderly patients early after MI, did find both mortality and quality-of-life benefit for PCI at >12 h. These findings suggest that the "late artery hypothesis" is just another way of stating the obvious, i.e., that

patients with residual ischemia fare worse than those without it, and consequently may benefit from intervention. These findings must be extrapolated cautiously to patients with severe LV dysfunction, as 98% of patients in the BRAVE-2 trial were in NYHA Classes I or II. These patients may present symptoms of HF, rather than of ischemia, or can be asymptomatic; hibernation may play an important role.

Surgical reperfusion is an impractical *primary* option in STEMI. If available in patients with a *coronary anatomy unsuited for PCI,* presenting within 12 h of STEMI onset, emergency CABG is an option, especially in presence of hemodynamic or electrical instability, or of severe HF. Left main stenosis ≥50% and/or triple-vessel disease have classically been considered "unsuitable for PCI," an example of conventional wisdom challenged by contemporary PCI techniques. Primary CABG is also indicated in *mechanical complications of MI* (post-MI VSD or MR). By and large, however, the main use of CABG in MI that of a *rescue procedure* after failed PCI (persistent or recurrent pain or hemodynamic instability). The best results are obtained with arterial revascularization, using LIMA, RIMA, or both. CABG is a major surgical procedure, with a 3–4% overall mortality (higher in the elderly, in diabetics, in patients with decreased LV function, renal failure, COPD, or left main artery disease). The main complications include periprocedural MI, stroke, bleeding, distal embolism, and a systemic pro-inflammatory response.

Acute Reperfusion Strategies: A Comparison

Primary PCI preferred to IV Thrombolysis

- In patients without cardiogenic shock, STEMI prognosis is better with primary PCI than with IV fibrinolytics, only if performed (1) *expertly* (i.e., the operator performs ≥75 cases yearly, and the catheterization laboratory performs ≥36 cases yearly); (2) *promptly* (door-to-balloon time <90 min[#]); (3) *safely*: i.e., the risk of PCI is smaller than that of thrombolysis (risk of intracranial bleeding under thrombolysis >4%, as assessed clinically).
- In patients with cardiogenic shock, if performed within 18 h of shock onset and shock has developed ≤36 h after STEMI and the patient age is <75 years[§].
- When symptom onset was >3 h, and not over the admissible maximum delay for the specific type of clinical presentation (i.e., "later" presentation, but still within the window of opportunity).
- When the diagnosis of STEMI is not certain (if the patient suffers from NSTEMI, the indicated therapy is PCI).

While in select centers primary PCI is the default option for all eligible patients, the highest benefit (justifying transport to a hospital with primary PCI capabilities) is seen with larger MI, and when IV thrombolysis is contraindicated.

[#]In itself, primary PCI is *effective* in this group within 12 h of symptom onset, just like IV thrombolytics. PCI is *more effective* than IV thrombolysis if logistics allow artery opening within 90 min of presentation; otherwise the better vascular patency rates are offset by the greater amount of myocardial necrosis. Of note, the ideal door-to-needle time, in case of IV thrombolysis, is *shorter*, i.e., 30 min; however, due to the much simpler logistics, this is often easier to achieve than the more "lenient" 90-min window for primary PCI. If the preparations for primary PCI would take more than 1 h beyond the point when thrombolysis can be administered ("door-to-balloon" – "door-to-needle" = 90–30 = 60 min), then IV thrombolysis is preferred.

[§]In the absence of these characteristics, the decision of IV fibrinolysis vs. no revascularization therapy is individually based. A useful milestone is a ≥4% risk of ICH, as a reason to withhold IV thrombolysis.

The intraaortic counterpulsation balloon pump (IABP) is a device used to decrease myocardial O_2 demand and increase CO. The balloon is introduced by catheter into the descending aorta, after the take-off of the left subclavian artery. The device is inflated in diastole (increasing blood flow to the coronary arteries) and deflated in systole (reducing afterload and increasing forward blood flow). The inflation/deflation are computer-controlled, under EKG or intracardiac pressure gating. IABP is used in patients with *intractable angina*, as a bridge to revascularization or transplant; *after angioplasty,* to support recovery of the ischemic segments; *after CABG*, for gradual weaning from cardiopulmonary bypass; *in case of myocardial rupture after MI* (acute MR, VSD, free wall rupture), as a bridge to surgery; *cardiogenic shock,* as a bridge to heart transplant; *in preoperative patients with unstable angina with a ≥70% LMCA stenosis and LVEF <35%.* Aortic dissection, AI, and severe aortoiliac atherosclerosis are *absolute contraindications*, while aortic aneurysm or

aortic/aortofemoral grafts represent relative contraindications. The main complications include lower limb ischemia and compartment syndrome; renal artery occlusion and renal failure; cerebral embolism during insertion or removal; infection, aortic or iliac dissection or perforation (occasionally, with mediastinal hemorrhage); and thrombocytopenia. Due to these complications, the use of IABP must be restricted to a few days at most.

Assessment of Reperfusion in MI

At first glance, this topic is only relevant in patients undergoing IV thrombolysis, as coronary patency is readily assessed with primary PCI. However, "reperfusion" refers to restoration of *microvascular* circulation; while optimal tissue perfusion requires epicardial TIMI grade III flow, the latter does not guarantee that myocardial perfusion is optimal (or indeed present). The "no-reflow" phenomenon is explained by two strongly interrelated events: *microvascular damage*, (mainly due to distal embolization of atherothrombotic debris) and *reperfusion injury,* due to active mediator release from the microemboli. These mediators cause tissue edema and microvascular spasm, free radical formation, cytokine activation (the first step of an intense inflammatory reaction), calcium overload, and apoptosis.

At the time of primary PCI, reperfusion is assessed in patients with postprocedure TIMI III flow, by the myocardial blush score. Myocardial blush assessment is only possible at the time of coronary angiography. It was hoped that contrast echo would allow bedside evaluation of myocardial perfusion, but this promise it yet unfulfilled. On the other hand, other perfusion-detecting methods (nuclear scan, perfusion MRI) are logistically impractical in acute MI patients. Therefore, evaluation of reperfusion is based on remission of pain and on a greater than or equal to ≥50% reduction in the initial ST elevations 60–90 min after initiation of therapy. Unfortunately, the clinical parameters have low predictive value for the *cause* of lack of reperfusion (failed epicardial reperfusion/subacute thrombosis after PCI vs. no-reflow phenomenon). If the findings persist after IV thrombolysis, or if they recur after an initially successful primary PCI procedure, rescue, respectively "redo" PCI is an option. *Reperfusion arrhythmias* are bursts of ventricular ectopy associated to epicardial vessel recanalization, and as such have long been regarded as a favorable prognostic factor. On the other hand, reperfusion arrhythmias are also a sign of reperfusion injury. These rhythms appear within 6 h after start of thrombolysis and include, most typically, accelerated idioventricular rhythm (AIVR), but also frequent PVCs >8/h, nonsustained VT, sinus bradycardia and possibly high-degree AVB. Reperfusion arrhythmia has a high specificity, but a low sensitivity for the diagnosis of arterial recanalization.

Antithrombotic Therapy

Antithrombotic therapy (a) facilitates and maintains co-ronary reperfusion, (b) limits the consequences of myocardial ischemia, enhances myocardial healing, and (c) reduces the likelihood of recurrent events. Strategies to counter arterial thrombosis include: *measures addressing the atherosclerotic plaque* (primary prevention, i.e., preventing plaque formation or progression; secondary prevention, i.e., preventing recurrent thrombosis on a plaque formerly involved in STEMI occurrence) and *measures addressing the coronary thrombus*, i.e., preventing platelet activation and aggregation; if a platelet clot does form, stopping it from activating the coagulation cascade, either by decreasing the hepatic synthesis of coagulation factors or by preventing the activation of these factors (mainly thrombin); and, if thrombin has not been adequately counteracted, i.e., if a fibrin clot has formed, dismantling the clot. These aims are reached using antiplatelet agents, vitamin K inhibitors, thrombin inhibitors, fibrinolytics, and PCI (primary PCI combines clot lysis and plaque therapy). Of these approaches, antiplatelet and antithrombin therapy are universally used, whether revascularization is undertaken or not. Ideally, percutaneous revascularization should be routine, as primary PCI, or, at the very least, within the first day of STEMI symptoms. In patients with large MI, early PCI is indicated regardless of IV thrombolysis results. *Measures addressing the atherosclerotic plaque* include antihyperlipemic therapy (Sect. 2.1) and PCI, whether primary or early after STEMI. *Measures addressing the coronary thrombus* include antiplatelet therapy; antithrombin therapy;

and fibrinolytic therapy, reviewed above. VKA (oral anticoagulants) are reviewed in Chap. 6. Their role in the management of CAD in general, and of ACS in particular, is relatively modest (they serve as an alternative to Clopidogrel in intolerant patients, and for treatment of intraventricular thrombus, most often formed in a LV aneurysm, itself a consequence of acute MI).

Antiplatelet Therapy

The main antiplatelet agents are reviewed in Sect. 2.2. Antiplatelet therapy in STEMI patients is reviewed in Table 2.44.

Aspirin: Aspirin, started as early as possible, is effective in MI patients, whether they did or did not receive

Table 2.44 Antiplatelet agents in STEMI patients

	No reperfusion therapy	Thrombolysis	PCI[a]
NSAID[b]			
Aspirin	PO[c] 150–325 mg q.d., continue indefinitely	PO[c] 150–325 mg q.d., continue indefinitely	PO 150–325 mg q.d., continue indefinitely
Thienopyridines			
Clopidogrel	PO 75 mg q.d., continue for up to 1 year[d]	PO loading 300 mg[e]; continue for up to 1 year[d]	PO loading dose of 600 mg, then 75 mg q.d., for ≥1 mo. with bare metal stents, ≥12 months (or indefinitely) with DES
Prasugrel	No data to date[f]	No data to date[f]	PO 60 mg loading dose, then 10 mg q.d., for 6–15 months[g]
Ticlopidine	N/A[h]	250 mg b.i.d. for up to 1 year[i]	250 mg b.i.d. for up to 1 year[i]
IIb/IIIa inhibitors			
Abciximab	–	–	IV bolus 0.25 mg/kg, then infusion of 0.125 μg/kg/min over 12 h, not to exceed 10 μg/min
Eptifibatide	–	–	180 μg/kg over 1–2 min at diagnosis, then infusion of 2 μg/kg/min, until PCI, not to exceed 72 h
Tirofiban	–	–	IV infusion 0.4 μg/kg/min, for 30 min, then 0.1 μg/kg/min for ≥12 h, not to exceed 24 h after angioplasty

[a]Primary, rescue, or routine PCI after IV thrombolysis
[b]Other NSAID drugs, including COX-2 inhibitors are contraindicated in ACS; NSAIDS (with the exception of COX-2 inhibitors) may be given for post-MI pericarditis, but the onset of this condition is generally well outside the acute phase of MI
[c]In patients with severe nausea or vomiting, Aspirin can be given IV, in doses of 250–500 mg; older guidelines also suggest Aspirin suppositories of 300 mg; non–enteric-coated formulations are recommended; In patients already on Aspirin, the acute dose may in principle be omitted, but in practice it is frequently administered nonetheless
[d]The risk/benefit ratio must be carefully assessed. The recommendation is based mainly on extrapolation of the data regarding non-STEMI ACS (the CURE trial); A daily dose of 150 mg of Clopidogrel in the week following PCI might improve outcomes, while not increasing bleeding rates
[e]No loading dose in the elderly, except if routine PCI is planned regardless of IV fibrinolytic therapy results (consider lower loading doses); Many advocate a loading dose of 600 mg, even if the patient is already on Clopidogrel (Clopidogrel "reload")
[f]The pivotal study regarding Prasugrel, TRITON-TIMI 38, was carried out in patients with moderate-to-high-risk ACS scheduled for PCI; a 60 mg loading dose was followed by administration of 10 mg q.d., for 6–15 months
[g]This regimen was used in the TRITON TIMI-28 trial, but was not incorporated in the 2008 ESC Guidelines
[h]By extrapolation of data regarding Clopidogrel, 250 mg q 12 h for a total duration similar to that with Clopidogrel appears reasonable. Of note, the current European Guidelines for the treatment of STEMI (2008) do not mention Ticlopidine at all; the recommended alternative in Clopidogrel-intolerant patients is Warfarin
[i]No longer included in the 2009 ESC guidelines

fibrinolytic therapy. It confers as high a benefit as SK, and the combination shows additive benefit. Immediate Aspirin administration is mandatory in all MI patients, with the sole exception of those truly allergic (and not simply intolerant) to the drug. The dose is of 300–325 mg (four chewable tablets of 81 mg, for rapid absorbtion; or one nonchewable tablet of 325 mg). IV Aspirin 250–500 mg, or one suppository (300 mg) are used in case of nausea and vomiting. Technically, the standing recommendation in case of Aspirin allergy is to "replace" this drug with Clopidogrel. Practically, however, as there is a Class I indication for Clopidogrel administration at presentation *in addition* to Aspirin, this amounts to simply omitting Aspirin in these patients. Aspirin 75–162 mg q.d. is continued indefinitely. *Thienopyridines*: Since the landmark CLARITY-TIMI 28 and COMIT/CCS-2 trials, *Clopidogrel* (Plavix) administration at presentation of all STEMI patients (irrespective of subsequent therapeutic strategies) has become routine. Clopidogrel decreases the incidence of hard endpoints such as all-cause mortality, cardiovascular death, reinfarction, or revascularization, without an increased risk of bleeding. A loading dose of 300 mg (600 mg before primary PCI) is followed by 75 mg q.d.; the optimal duration of combined therapy is unknown. If CABG is planned, a 5–7 day waiting period after initial Clopidogrel loading is recommended, if clinically acceptable. Older guidelines notwithstanding, Clopidogrel should be continued for at least 12 months after stent implantation, and possibly indefinitely in DES stents. Therefore, a high risk of bleeding is a relative contraindication to DES implantation. *Prasugrel* (Effient), the latest thienopyridine developed to date, has been shown by the TRITON-TIMI 38 trial to be superior to Clopidogrel in moderate-to-high risk ACS patients, a conclusion also valid in the STEMI subgroup of the patient cohort. Prasugrel significantly reduced the risk for the combined endpoint of cardiovascular death, non-fatal heart attack or non-fatal stroke at both 30 days and 15 months. In the STEMI subgroup, there was no excess bleeding with Prasugrel, unlike the main cohort, where Prasugrel decreased cardiovascular mortality, but increased mortality due to major bleeding, with no difference in mortality between the Clopidogrel and Prasugrel groups. The multiple side effects of *Ticlopidine,* the first clinically available thienopyridine, have lead to its almost universal replacement by Clopidogrel. Ticlopidine can cause neutropenia (1%) and thrombotic thrombocytopenic purpura (TTP; 3%), which mandate CBC follow-up q 2 weeks for the first 3 months of use. Additionally, up to 20% of patients experience nausea, diarrhea, and rash, mandating therapy discontinuation. There are no direct data as to the optimal duration of therapy after DES use, but it is reasonable to follow the guidelines for Clopidogrel. *IIb/IIIa antagonists*: *Abciximab* (ReoPro) can be used (a) *in combination with half-dose reteplase or TNK-tPA* for prevention of reinfarction and other complications of STEMI in patients <75 years with an anterior MI, and no increased risk for bleeding. If an early invasive strategy is planned (transportation to a PCI-capable facility), this strategy is no longer recommended (see "facilitated PCI," above); (b) *in patients undergoing primary PCI*, Abciximab (IV bolus of 0.25 mg/kg, followed by an infusion of 0.125 μg/kg/min over 12 h), started immediately after diagnosis, reduces by 50% the incidence of death, MI, or urgent total revascularization at 30 days. *Eptifibatide* (Integrilin) is effective in unstable angina and NSTEMI; in STEMI, it is used by extrapolation, and also based on a smaller-scale trial, EVA-AMI, which found it non-inferior to Abciximab. As Eptifibatidide is several-fold cheaper than Abciximab, the issue is of great importance. The recommended doses are of 180 μg/kg over 1–2 min at diagnosis, followed by continuous IV infusion of 2 μg/kg/min, until hospital discharge, initiation of coronary revascularization, or the completion of a 72-h course, whichever occurs first. *Tirofiban* (Aggrastat) is administered as an IV infusion of 0.4 μg/kg/min, for 30 min, followed by a continuous infusion, at 0.1 μg/kg/min. The ON-TIME 2 study showed that Tirofiban significantly improved ST-segment resolution at 1 h after primary PCI. The drug is continued for ≥12 h, but not more than 24 h after angioplasty.

Antithrombin Therapy in MI Thrombin inhibition can be achieved indirectly (by AT III activation), or indirectly (by direct binding to thrombin and inactivation of its active site). The main antithrombin agents are reviewed in Sect. 2.2, and their use in STEMI patients is presented in Table 2.45. *Heparin* is recommended in all MI patients, with the possible exception of those treated with SK. In STEMI patients not undergoing fibrinolysis, Heparin is believed to confer a mortality benefit, based on a metaanalysis of pre-reperfusion era studies. While there is no indication for or against Heparin use in the current guidelines, this agent is routinely used, but only if Fondaparinux is not available (Table 2.43).

VKA have a relatively modest place in the treatment of CAD. They are to be continued, in addition to

Table 2.45 Antithrombin therapy in STEMI patients[a]

	No reperf. Tx	Thrombolysis			Primary PCI
Indirect thrombin inhibitors					
UFH	Alternative to Fondaparinux; adjust by weight	IV bolus 60 U/kg, ≤4,000 U, followed by IV 12 U/kg, ≤1,000 U/h for 24–48 h[b]; target aPTT 50–50 s, monitored at 3, 6, 12, 24 h			Loading dose IV 100 U/kg[c], then infusion, for the duration of the procedure only, at an ACT[d] of 250–350 s[e]
Low-molecular weight heparin (LMWH)					
Fondaparinux	As for thrombolysis; it is the preferred agent in this setting	IV bolus 2.5 mg the following day, start S.C. 2.5 mg q.d. ≤8 days			No; OASIS-6 trial: higher rate of catheter thrombosis and coronary complications (abrupt closure, thrombosis, no reflow, dissection, or perforation) with Fondaparinux[f]
Enoxaparin[g]	As for thrombolysis	RFT	Age		Insufficient data; a suggested strategy involves one S.C. dose of 1 mg/kg, supplemented by an IV dose 0.3–0.5 mg/kg, ideally under anti-factor Xa monitoring (target: 0.5–1.5 U/mL; risk of bleeding increases at >1. U/mL)
			≤75	>75	
		Creat. <2.5 g/L (♂), <2 g/L (♀)	IV bolus 30 mg; 15 min. later, start S.C. 1 mg/kg q 12 h ≤8 days[h]	No IV bolus; first S.C. dose 0.75 mg/kg[i]	
		CRCL <30	S.C. doses repeated at 24 h		
Direct thrombin inhibitors					
Argatroban[j]	In HIT or HIT-prone patients; not approved for general STEMI patients	In HIT or HIT-prone patients; not approved for general STEMI patients			In HIT or HIT-prone patients only
Bivalirudin	Insufficient data	HERO-2 study: Bivalirudin does not improve mortality, but may decrease reinfarction, and increases ≤moderate bleeding as compared to UFH			Loading dose IV 0.75 mg/kg, then infusion, usually for the duration of the procedure only, at 1.75 mg/kg/h (based on the HORIZONS trial[k])
Lepirudin	HIT or HIT-prone patients only	HIT or HIT-prone patients only			HIT or HIT-prone patients only
Dabigatran	Under study (RE-DEEM trial)				

[a]Comments about non-indicated regimens are in italics
[b]Optional after SK; recent data suggests post-thrombolysis anticoagulation should be maintained for ≥48 h, and preferably throughout the entire hospitalization, in which case a non-UFH agent (Enoxaparin, Bivalirudin, or Fondaparinux) is indicated beyond the first 24 h
[c]If a IIb/IIIa agent is being used, the loading dose is decreased to 60 mg/kg
[d]Activated clotting time, measured with the HemoTec device; (300–350 s with the Hemochron device)
[e]UFH loading dose reduced to 50–70 U/kg, target ACT 200 s (measured with either the HemoTec or Hemochron device) if a IIb/IIIa agent is being used
[f]This has led the ESC, but not the ACC/AHA to withhold recommendation in patients undergoing PCI. However, the same study has shown the efficacy of Fondaparinux for non-primary PCI, e.g., rescue PCI or routine transportation to a PCI-capable center after initial IV thrombolytic therapy
[g]The EXTRACT-TIMI-25, comparing Enoxaparin to UFH in STEMI patients eligible for IV fibrinolysis, found a higher efficacy, but also a higher rate of major bleeding, in the Enoxaparin group
[h]The first two doses should not exceed 100 mg in total
[i]The first two doses should not exceed 76 mg in total
[j]Argatroban falsely increases INR
[k]The HORIZONS trial has shown a lower rate of major bleeding and adverse events at 30 days with Bivalirudin compared with UFH + a GP IIb/IIIa blocker in STEMI patients undergoing primary PCI

antiplatelet therapy, in patients in with another indication for their use. VKA are indicated in case of LV thrombus (target INR 2–3), on a long-time basis, as the cause of LV thrombosis is most frequently LV aneurysm, a chronic condition. In high-risk patients allergic in whom Clopidogrel is not available (or there is resistance to it as well), Warfarin is added, with a target INR of 2–2.5. The same target is used for Aspirin-resistant patients, in whom Clopidogrel is unavailable or ineffective.

V - Novel Therapies in MI

Beside the quest for newer and safer percutaneous devices and antithrombotic agents, a few novel directions are being explored. Thus, anti-inflammatory compounds are being tested in patients with ACS, under the hypothesis that their addition to a standard optimal regimen will improve clinical outcomes. A fluid bioresorbable material injected percutaneously into the infarcted myocardium may limit MI expansion and improve LV function, by replacing destroyed extracellular matrix, and leading to formation of a smaller and thicker scar.

Post-STEMI Risk Stratification

Post-STEMI risk stratification (all the considerations below also apply to ACS as a whole): Successful ACS therapy implies not only resolution of the acute episode, but also avoidance of recurrent ischemia in the culprit artery and avoidance of late complications (HF and/or arrhythmia). The risk for these events is in the center of attention even as the patient is being treated for the acute disease, and splits the ACS population in several risk strata, hence the term, risk stratification (Table 2.46). Due to its profound influence on therapy, risk assessment is actually carried out, formally and informally, from the time of the patient's presentation. In this respect, it ought to be discussed immediately following the "Diagnosis" section; however, for the sake of fluency, it is discussed in the current section.

Risk stratification is accomplished formally or informally, by using clinical, EKG, and imaging data (obtained at rest or under stress). These individual assessments are used as such, or grouped in more complex, multifactorial risk scores. Some indicators are specific for a group of entities (e.g., enzyme elevation in all MI patients), while others refer to a single entity (e.g., ST segment elevation in STEMI patients only). Assessment methods and scores will be reviewed next. The practical implication of a positive result of risk stratification is that angiography should be carried out, if not already performed; that an ICD device should be implanted as discussed in Chap. 4; and that appropriate medical therapy should be adopted for ventricular dysfunction or HF. Importantly, risk stratification preserves its importance even in affluent countries, where PCI is readily available. Indeed, routine PCI has not been proven to improve prognosis in ACS all-comers. The OAT trial has found no advantage to routine PCI in asymptomatic post-MI patients without three-vessel or left main CAD and with no demonstrable residual ischemia. Similarly, the ICTUS trial has found no advantage to routine invasive therapy in all NSTEMI patients.

Clinical assessment is based on the presence (or absence) of the following elements: Killip class at

Table 2.46 Risk stratification after ACS: aims and means

What risk is being assessed	Method of assessment	Therapeutic implications (acute phase)	Therapeutic implications (long-term)
Of myocardial necrosis, should the culprit artery reocclude	Stress imaging to detect myocardium at jeopardy[a]	Primary, rescue, or post-fibrinolysis PCI[b] improve prognosis as compared to IV thrombolysis (where applicable) or to conservative therapy only	Early PCI decreases late cardiovascular morbidity and mortality
Of late cardiovascular morbidity and mortality	Echo, to detect LV dysfunction; EKG,[c] to detect the risk of arrhythmia	None	Early PCI decreases late cardiovascular morbidity and mortality

[a]The larger the area at risk, the higher the risk, and the stronger the indication for PCI
[b]If routine primary or post-fibrinolysis PCI is undertaken, this aspect of risk stratification is implicitly accomplished
[c]Including Holter, SAECG, and other newer modalities outlined in Sect. 2.2

presentation; clinical signs of reperfusion; recurrent ischemia; arrhythmia beyond the first 24 h; and mechanical complications of MI.

EKG assessment includes: *a resting tracing,* indicating the type and extent of ischemia. The greater the number of involved leads, the larger the ischemic myocardial area, and consequently, the higher the risk. With STEMI, the number of involved EKG leads and the sum elevation of ST segments allow calculation of different severity scores. While the practical utility of scores is questionable, a larger number of involved EKG leads remains correlated to more severe MI. EKG data from the early thrombolytic era have suggested a prognostically important MI classification as large (extensive anterior MI, culprit artery: proximal LAD; extensive posterior MI, culprit artery: proximal dominant or RCA proximal dominant LCx), small (mainly inferior MI, culprit artery: distal RCA or distal LCx), or intermediate-size (all other MI). An additional EKG negative prognostic factor is the presence of Q waves. The resting tracing is also prognostically useful in regard to the risk of late lethal ventricular arrhythmia. Ventricular arrhythmia >24–48 h is an indicator of high risk for SCD. In the past, this was an indication for *EP study* (considered positive if sustained monomorphic VT is inducible). Current guidelines recommend ICD implantation in post-MI patients with decreased EF (see Chap. 4), occasionally making EPS redundant in this setting (assuming ICD devices are readily available). *Additional EKG techniques* to evaluate the late risk of SCD include: SAECG, T wave alternans, HR variability and turbulence, QT dispersion, and baroreceptor sensitivity. The place of these methods in clinical practice remains to be defined. *An EKG stress test* (submaximal or pharmacological test at 4–5 days; symptom-limited test at 2 weeks; or pharmacological test at 4–6 weeks) is integral part of risk stratification.

Echo is occasionally used for MI diagnosis; otherwise, the first echo examination is carried out within 24–48 h of the acute event, to evaluate LV function and identify a possible LV thrombus. An LVEF EF <40% justifies an invasive approach, as it is a strong predictor of cardiovascular morbidity and mortality (late ventricular arrhythmia, HF). A follow-up echo is carried out at some point >2 weeks from the acute event; in the absence of recurrent acute ischemia or of hibernation, systolic LV dysfunction generally reflects myocardial necrosis. An *echo stress test* can be used for risk stratification, in place of an EKG stress test.

Biomarker-based risk assessment: The area under the curve of *CK or its isoform CK-MB* levels plotted against time is proportional to MI size. However, this method is cumbersome, as serial CK levels need to be measured; a surrogate assessment is that of peak CK, which correlates fairly well with MI size. However, there are several problems with this measurement as well: (a) CK increases normalize shortly after the acute phase of MI, and frequent blood sampling is necessary to avoid missing the true peak value; (b) CK elevations are strongly influenced by the reperfusion status. Thus, a high (but short-lived) CK peak may simply correspond to good reperfusion, with "in bulk" spillage of biomarker; conversely, low (but protracted) elevations may reflect non-reperfusion. In practice, it is often difficult to correlate the pattern of CK increase to one or another of these possible causes. *Troponin* can also be used to assess MI size. Only early troponin release is influenced by the reperfusion status; troponin values at 72 h are not substantially influenced. One study has found that toponin T levels >2.98 μg/L predicted a LVEF <40% at 3 months with a sensitivity and specificity in excess of 80%. *Novel biomarkers for MI*, currently under development, aim at very early detection of myocardial necrosis, some as early as a few minutes after the beginning of the ischemic injury.

There are several risk scores, integrating the available clinical, enzymatic, and imaging information (Table 2.47). All scores are used for STEMI and NSTEMI patients alike. For NSTEMI, the most favored risk score is GRACE, using an online calculator to classify the risk as low, intermediate, or high. This classification is established at admission (risk of in-hospital death) and reassessed at discharge (risk of death at 6 months postdischarge).

Even patients without a high-risk score require urgent therapy

ACS requires immediate treatment. Emergency PCI may be required despite the absence of a formally calculated high risk score. High-risk prognostic factors not included in the scores above include: ventricular arrhythmia (other than cardiac arrest, which is included in the GRACE score), hemodynamic instability, LV dysfunction (LVEF <40% or HF); refractory or recurrent ischemia; previous CAD and/or interventions.

Table 2.47 Risk scores in ACS

The score	Common elements	Additional elements	What it predicts	Comments
GRACE	Age, BP,[a] creatinine levels, ST deviation, and elevated cardiac biomarkers	Killip class, the presence of cardiac arrest at admission, HR	Death in hospital and at 6 months	Uses computerized calculator[b]
TIMI	Age, BP,[a] creatinine levels, ST deviation, and elevated cardiac biomarkers	Other risk factors beside systolic BP and creatinine; known CAD (stenosis ≥50%); Aspirin use in the past week; severity of angina (≥2 episodes within 24 hrs = severe)	Death at 14 days	Easily calculated, thus very popular; based on a point sytem[c]
FRISC	Age, BP,[a] creatinine levels, ST deviation, and elevated cardiac biomarkers	Male sex, previous MI, diabetes, markers of inflammation; invasive	Will early invasive strategy decrease death at 1 year?	Easily calculated, based on a point sytem[d]
PURSUIT	Age, BP,[a] creatinine levels, ST deviation, and elevated cardiac biomarkers	HR, HF	Death at 30 days	Difficult to calculate

[a]Systolic BP only, with the GRACE score
[b]http://www.outcomes.org/grace; a PDA- downloadable version allows bedside use
[c]Maximum score – 7 points; ≤2 is low risk, ≥4 points is high risk of death or MI
[d]Maximum score – 6 points; a score of 0–2 corresponds to a low risk, ≥4 points corresponds to a very increased risk of death or MI
With scores ≥2, an early invasive strategy reduces mortality; the higher the score, the greater the gain of the early invasive therapy

Even patients without a high-risk score may have a severe prognosis

Importantly, the risk scores above refer to the *outcome of NSTE-ACS*; however, *the outcome of the hospitalization* also critically depends on the complications of therapy, mainly bleeding or CIN.

Management of Uncomplicated STEMI Beyond the Acute Stage

All patients should be confined to bed for the first 12–24 h, for initial stabilization. In the absence of complications, self-care, including the use of a bedside commode, is allowed by the end of the first day, and ambulation is allowed by the second day, with a total hospitalization of a few days; in complicated cases, clinical judgment is necessary. In case of recurrent ischemia (whether clinical or by EKG) after initial symptom relief, repeat revascularization therapy is indicated. In patients initially treated with IV fibrinolytics, angiography and, according to the results, PCI or CABG are strongly indicated, whether at the original medical facility, or by transportation to another facility. If this option is unavailable, repeat IV thrombolysis should be given (if SK was initially used, strong consideration should be given to a thrombus-specific agent; if this is unavailable, repeat SK is only acceptable within the first 5 days after initial administration, in patients in whom the first dose was well tolerated). In patients initially treated with PCI or CABG, repeat coronarography and repeat angioplasty or redo CABG are indicated.

Table 2.48 reviews the main issues related to the social reinsertion of a post-MI patient.

Secondary prevention after MI. Risk factor control: Primary prevention principles are carried forth for secondary prevention as well, but with more drastic targets. *Smoking cessation* (including passive smoking) must be advocated at every single meeting with the patient; if necessary, Bupropion or Nicotine replacement therapy is indicated. *Physical activity* is recommended as moderate-intensity (as defined by a preliminary exercise stress test) aerobic exercise five times a week; in high-risk patients, exercise is performed in dedicated facilities, capable of medical supervision and treatment, if necessary. Rehabilitation programs often also function as informal support groups. *Diabetes* should be treated and monitored (target HbA1C <6.5%). ACEI or ARB drugs are especially indicated, as they benefit both CAD and renal function; additionally, HTN is frequent in diabetics. *Weight reduction* is indicated in patients with BMI >30 kg/m^2 and in men with a waist circumference >102 cm (88 cm in women). A high intake of vegetables, fruit, and fish (especially "oily fish," rich in ω-3 fatty acids), with a

Table 2.48 Work and leisure after discharge in the NSTE-ACS patient

LVEF (%)		Inducible ischemia	Work[a]		Leisure and sexual activity
			Office	Manual	
>40	*and*	No	May resume normal work, 8 h a day, after discharge	At 50% of maximum capacity achieved in a stress test, 4 h a day, for 1 month, increase by 2 h daily every month	Mild effort (<3 METs): sex, slow walking, desk activities; moderate effort (3–6 METs): calisthenics, slow bicycling. Intense effort: >6 METs; personalize recommendations according to stress test results
30–40	*or*	Mild	As above	Only static manual work allowed	
<30	*or*	Significant, but no symptoms at a stress ≤5 METs[b]	As above; otherwise, work contraindicated	Work contraindicated, regardless of degree of stress eliciting inducible ischemia	

[a]There are no guidelines regarding the duration of sick leave after NSTE-ACS
[c]On a Bruce stress test, this corresponds to very mild physical exertion. For orientation, Bruce protocol starts at 4.7 METs (Stage I), and increases demands by 2–3 METs per stage

low intake of saturated fats and of salt are indicated. Recent data show that even a small reduction in daily salt intake would have a huge public-health impact.

Alcohol consumption (especially red wine) is not discouraged; however, due to concerns about possible abuse, the guidelines do not actually recommend it. Moderate consumption may decrease cardiac mortality due to atherosclerosis, while abstainers and heavy drinkers are at higher risk (J curve). The beneficial effects are attributable to flavonoids present in red wine and purple grape juice and several fruits and vegetables. The mechanisms include antiplatelet actions, increased HDL levels, an antioxidant effect, reduced endothelin-1 production, and increased endothelial NO production. *BP control* is indicated, with target values <130/80 mmHg. If (as is often the case) this is not achieved with β-blockers alone, the second drug of choice is an ACEI or an ARB, which are indicated in any event, in post-MI patients. *Lipid management* is indicated in all patients. Despite past concern that immediate post-MI values may not accurately reflect chronic lipid levels, it appears that, by the end of the fourth day, the levels stabilize sufficiently to establish a therapeutic strategy, allowing patient discharge with this cornerstone issue already addressed. The survival benefit of early, aggressive statin therapy (started within 1–4 days of admission, with rapid uptitration to attain target) is partly due to mechanisms such as plaque stabilization and anti-inflammatory activity. Statins reduce hsCRP levels, but the meaning of this decrease (direct antiinflammatory effect of statins vs. plaque stabilization, with secondary hsCRP decrease) is not clear. The target LDL is <100 mg/dL (<2.5 mmol/L) or, in high-risk patients, <80 or even <70 mg/dL (2, respectively 1.8 mmol/L). LDL lowering to <70 mg/dL was shown by the prospective PROVE-IT study to offer an additional benefit. The target TG level is <150 mg/dL (1.7 mmol/L), and the desirable HDL level (not considered a "target," as there is no specific therapy for low HDL) is >40 mg/L (1.0 mmol/L). HDL decrease often covaries with TG increase; mild abnormalities are treated by emphasizing life style changes, while more severe ones are addressed by newer-generation statins. In statin-intolerant patients, fibrates and ω-3 unsaturated fatty acid supplements are indicated. The value of Ezetimibe as a routine addition to statins (i.e., even if the latter do achieve the LDL targets) is being explored by the IMPROVE-IT study. The impact of HDL increase using a combination of niacin and Simvastatin is being tested in the AIM-HIGH study, while another study (HPS2-THRIVE) is testing niacin in association with a prostaglandin inhibitor, to prevent the main adverse effect of niacin, i.e., flushing.

Medical therapy includes *antithrombotic therapy* (Aspirin, Clopidogrel, or – in patients intolerant to both – Warfarin to a target INR of 2–3); *β-blockers* in all patients, *ACEI or ARB* in all patients, or, at the very least, in those with LVEF <40%; *statins and/or fibrates* as discussed above (practically, a majority of post-STEMI patients require them); and *influenza immunization,* indicated in all patients.

Device therapy includes biventricular pacing and ICD therapy in suitable candidates; these are reviewed under "STEMI complications."

STEMI management: *beyond medicine:* STEMI mandates optimal patient-caregiver communication. Depression, poor self-image, etc., are common after STEMI, and must be addressed, to achieve optimal long-term results and compliance. A typical example is sexual

dysfunction in males receiving β-blockers and diuretics, often ascribed by the patient to the supposedly crippling effects of the "heart attack." In other patients, the omission to perform a late postdischarge echo (a few weeks after the acute event) may result in unrealistic assessment of the myocardial necrosis extent. The patient must understand that part of the damage identified by an early echo may have been salvaged by reperfusion therapy – a fact confirmed by the late echo. A few sentences may clarify this issue and dispel unnecessary worry or the misperception of a discordance between the diagnoses established "by the different doctors." The patient must also be made aware that atherosclerosis is a chronic disease, and that the acute ischemic event has brought not so much a *new disease*, as *new awareness* regarding a long-standing condition. Health-issue awareness must be presented as an important gain in the otherwise negative experience of disease, and this gain must now be used as leverage to obtain optimal compliance to therapy. Conversely, patients overly concerned regarding their disease must be reassured. Except for terminal cases, some truthful but artfully phrased positive insight can almost always be given to the patient. Thus, in the presence of intact or only mildly affected ventricular function, it is fully justified to tell the patient that, far from being crippled by their heart attack, they are in fact (after successful revascularization and with optimal therapy in place), "safer" than they have been in many years (yet, at the same time, they are at increased risk for a subsequent MI, especially in the first year). Conversely, in the patient with extensive myocardial necrosis, the crucial distinction between LV dysfunction and HF must be explained: many patients live (near-) normal lives despite a severely decreased LVEF. Having the patient function as a "goodwill medical ambassador" and promoting primary prevention measures among their siblings or children is also important. Finally, like any chronic disease, atherosclerosis and its complications affect not only the patient, but also his/her significant others. This, too, must be put to use; the spouse's input is often invaluable in ensuring compliance with life style changes and medical therapy on the long run, when compliance tends to decrease.

Complications of STEMI

The complications of STEMI reflect the impact of necrosis on the myocardial function, including: a *negative inotropic effect*, both direct (decreased myocardial function due to ischemia) and indirect (e.g., MI-related RV dysfunction causing suboptimal LV filling and contraction); *myocardial rupture* (decreased resistance of the necrosed tissue); *arrhythmia*, due to altered myocardial excitability and conduction; and *pericardial complications* (pericarditis, tamponade). *Iatrogenic* complications include bleeding, complications of PCI, etc. *Hypotension* may result from cardiogenic shock in extensive MI; suboptimal LV filling due to RV MI; the Bezold–Jarisch effect, in inferior MI; arrhythmia; tamponade; or hypovolemia due to bleeding or excessive diuresis.

Arrhythmia: *Supraventricular tachyarrhythmia* mainly includes paroxysmal AF, which may precipitate HF, by depriving the preload-dependent ischemic LV of the atrial kick. AF is especially common in the elderly and in those with extensive LV dysfunction or RV MI. STEMI-associated AF is associated to higher rates of mortality and stroke. However, many episodes are brief and do not require therapy. In case of rapid AF, which increases O_2 consumption MI size, HR is controlled with an IV β-blocker, a non-dihydropyridine CCB, or Amiodarone, while electrical cardioversion is the procedure of choice in case of hemodynamic compromise. AF therapy includes anticoagulation, often already in place for MI-related indications. *Supraventricular bradyarrhythmia* is mainly seen in inferior MI, due to excessive vagal activation (there is preferential distribution of the vagal nerve in the inferior wall); this is termed *the Bezold–Jarisch reflex*. Occasionally, bradycardia results from opioid therapy or from β-blockade. *Peri-MI AV block* is reviewed in Table 2.49.

Table 2.49 STEMI-associated heart block

MI location	Mechanism	Manifestations	Prognostic significance	Therapy
Inferior	Bezold–Jarisch reflex or AV node artery ischemia	HR >40 bpm, narrow escape rhythm	Benign	IV Atropine, occasionally transvenous pacing
Anterior	extensive myocardial damage	HR <40 bpm, wide-QRS escape rhythm	Severe	Transvenous pacing[a] (atropine not effective)

[a]Even, prophylactically, in cases of MI-associated BBB, with a high probability of later evolution to complete AV block

The significance and impact of *ventricular arrhythmia* (Table 2.50) strongly depend on the time of occurrence in the post-MI evolution (Table 2.48) and on the setting of occurrence (in- vs. out-of-hospital)

The risk for SCD is highest in the first month(s) after MI. SCD is discussed in Chap. 6. In the hospitalized STEMI patient, asymptomatic PVCs (even of the "R-on-T" variety) and hemodynamically stable, non-sustained VT do not require therapy, as their value as predictors of impending VF is poor, and prophylactic Lidocaine is associated to an increased risk of asystole. The only antiarrhythmic therapy indicated in post-MI patients is β-blockade. Hemodynamically unstable ventricular arrhythmia and sustained VT are treated as usual (Chap. 6). Occasionally, the arrhythmia is refractory to therapy. Assuming electrolyte derangements or drug (e.g., digitalis) toxicity are absent, ongoing ischemia should be ruled out by emergency angiography. Transvenous overdrive pacing is often useful for refractory ventricular arrhythmia.

Ventricular dysfunction may be due to irreversible or reversible myocardial damage; to arrhythmia; or to mechanical complications of MI. It manifests by the usual clinical complaints and physical findings, and its severity is quantified by the Killip score. The treatment is the same as that for any HF, as discussed in Chap. 4. In addition to the usual measures, prompt revascularization and/or rupture repair are recommended, especially in case of advanced ventricular dysfunction. The most severe form of HF, cardiogenic shock, may occasionally be due to RV dysfunction, rather than to extensive LV damage. In these patients, volemic support and prompt revascularization are crucial.

Mechanical complications of MI are most frequent within the first 24 h or at 3–5 days and involve myocardial rupture. These frequently fatal events are reviewed in Table 2.51. A case of ruptured papillary muscle is shown in Fig. 2.5.

STEMI in Special Populations

The elderly: Age >75 doubles mortality, due to the characteristics of both ACS as such, and of ACS therapy. Thus, ACS is underdiagnosed in the elderly, as the symptoms are often non-specific. Invasive strategy is often withheld, despite its proven benefit in the elderly; on the other hand, the elderly are also at increased risk for bleeding. Unfortunately, as clinical trials usually enroll healthier-than-average subpopulations, the validity of result extrapolation to the general population is unclear. *Female gender*:

Table 2.50 MI-related ventricular arrhythmia

Time of occurrence	Direct consequences	Long-term prognostic signification	Remarks
Out of hospital			
As the first manifestation of MI	SCD	Fatal/severe	Patients found in VT have the least severe prognosis, followed by those found in VF; asystole is almost universally fatal
In hospital			
At the time of IV thrombolysis	Possible bleeding complications, if CPR is required[a]	None	Reperfusion vs. malignant ventricular arrhythmia
During primary PCI	Minimized by prompt treatment[a]	None	As above
Early (≤48 h after MI onset)	Minimized by prompt treatment[b]	None	Frequency decreased by thrombolytics and β-blockers
Either in hospital or out of hospital			
Late (>48 h)		Severe	In the absence of recurrent acute ischemia, this is an indication for ICD implantation[c]

[a]Reperfusion arrhythmia is generally benign. However, patients with successful reperfusion and *absent* reperfusion arrhythmias have a better prognosis
[b]As for reperfusion arrhythmia
[c]See Chap. 4

Table 2.51 Mechanical complications of MI

Manifestation	IVS rupture	LV free wall rupture	Papillary muscle rupture or dysfunction
Incidence	Up to 3% without, 0.3% with reperfusion therapy	Up to 6%; PCI, but not IV thrombolysis, might reduce its incidence	About 1%; incidence reduced by thrombolytic therapy
Manifestations	Chest pain, pulmonary edema, shock; loud new pansystolic murmur, precordial thrill; S_3; RV failure	Tamponade, presenting as SCD (EMD) in 75% of cases; in 25%, a sealing clot provides opportunity for intervention. Subacute cases may mimic reinfarction, (recurrent ST elevation).	Acute MR[a]; chest pain, pulmonary edema, shock; occasionally soft murmur, no thrill; RV failure
Echo	VSD flow; RV overload	Tamponade; pericardial sealing clot; occasionally, visualization of the site of rupture	Ruptured papillary muscle, with a flail leaflet; severe MR, eccentric jet
Right heart cathterization	Oxygen step-up from RA to RV; large V waves on RA pressure tracing	Non-specific findings	Large V waves, no O_2 step-up, severely elevated PCWP
Treatment[b]	Surgery (problematic, due to friable necrotic tissue) or percutaneous closure; Nitroprusside may decrease the shunt volume, but in occasional patients it may cause pulmonary vasodilatation in excess of the systemic one and actually increases the shunt[c]	Immediate surgery	Surgery, after initial stabilization (MV replacement, occasionally repair). Nitroprusside improves hemodynamics by decreasing the regurgitant volume.
Prognosis[d]	Mortality 20–50%	Untreated, 100% mortality (50%, in presence of a sealing clot)	Mortality 20–40%

[a]Acute MR (Chap. 5) is usually due to papillary muscle dysfunction, rather than rupture. The posteromedial papillary muscle is more frequently affected than the anterolateral one
[c]For the treatment of pulmonary edema and of cardiogenic shock, see Chap. 4
[c]Used as a bridge to intervention.
[d]Mortality is significantly increased in presence of cardiogenic shock

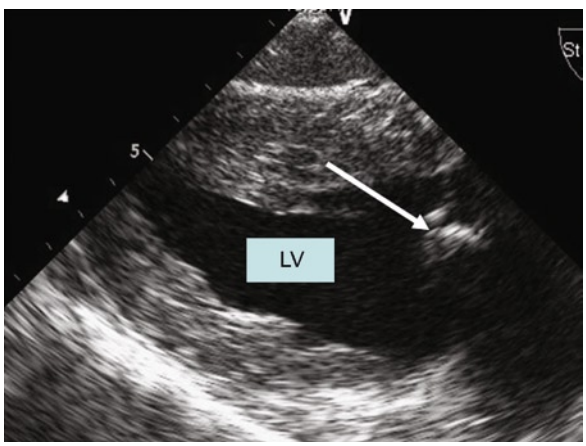


Fig. 2.5 Ruptured papillary muscle in a patient with acute inferior wall MI. Color Doppler demonstrated severe MR

Different studies have found a protective, deleterious, or absent impact of female gender on ACS outcome; therefore, the current guidelines do not recommend gender-based treatment distinction. Of note, European registries show significantly lower aggressive interventional and antithrombotic treatment rates in women, as compared to men. *Diabetes mellitus*: Up to two-third of ACS patients have glucose regulation abnormalities, and one-third have clinically apparent diabetes. These abnormalities increase the risk for CAD and aggravate prognosis; the risk is highest in patients with clinically apparent diabetes. Glycemic control is important in both the chronic and the acute setting, yet tight control increases the risk of hypoglycemia and significantly affects ACS prognosis. Diabetics benefit from early aggressive interventional

and antithrombotic therapy. The risk of CIN is higher in diabetics; contrast material may cause renal failure and lactic acidosis in Metformin-treated diabetics. Metformin must be stopped 24 h before angiography, or at least on the same day, to be resumed after 48 h of uneventful recovery. *Anemia* (of any cause) portends a worse prognosis in ACS patients. However, blood transfusions must be used only if absolutely necessary (generally, with Hb levels <8g/L), as (somewhat counterintuitively) they may increase mortality, especially in NSTE-ACS patients. *Chronic kidney disease (CKD)* is associated with a higher prevalence and severity of ACS, due to coexisting diabetes, HTN, hyperhomocysteinemia, as well as to the prothrombotic state and general inflammation prevalent in CKD patients. The risk is higher in severe renal failure, but the correlation is not linear, with the highest risk seen with CrCl decreases <60 mL/min/1.73 m^2 BSA (normal ≥90). In other words, any patient with more than mild renal dysfunction is at increased risk. Patients with CKD are underrepresented in clinical trials (CKD usually represents an exclusion criterion). CKD also influences ACS treatment, as renally excreted drugs must be either adjusted in dosage, or altogether avoided. An especially important population is that of hemodialysis patients, with a vastly increased risk of cardiovascular morbidity and mortality, due to several mechanisms, pertaining to the dialysis mechanism as such, in addition to the inherent risk represented by the underlying renal failure. Hemodialysis patients are more prone to develop myocardial ischemia, hibernation, and stunning; HF; arrhythmia and SCD; LV hypertrophy; microvascular damage, dependent and independent of the frequently associated severe atherosclerosis; increased peripheral artery stiffness; defective BP control; and myocardial injury, expressed as cardiac troponin elevation. The deleterious effects of hemodialysis are countered by different technical interventions, which are beyond the scope of this text.

The restrictions in the type and dosage of pharmacological therapy in CKD patients are outlined in Table 2.52.

Table 2.52 Dose adjustments and contraindications in ACS patients with CKD

Medication	Dose adjustment
General medication[a]	
Statins	Caution at CrCl <30 mL/min
ACEI	Dose reduction at CrCl <30 mL/min
ARB	Dose reduction at CrCl <30 mL/min
β-blockers	Metoprolol: halve/quarter the dose at CrCl <30, respectively, <15 mL/min
Nitrates	No (poor correlation between nitrate blood levels and clinical action)
Antithrombotic medication	
NSAIDs	
Aspirin	No, but Aspirin (especially in analgesic dosages, i.e., much higher than cardiological dosages) may decrease renal function
Thienopyridines	
Clopidogrel	No[b]
Prasugrel	Insufficient data[c]
Ticlopidine	Probably not; insufficient data[c]
IIb/IIIa inhibitors	
Abciximab	No
Eptifibatide	At CrCl <50 mL/min, keep bolus unchanged, reduce infusion to 1 μg/kg/min; contraindicated at CrCl <30 mL/min
Tirofiban	Reduce dosage to 1 μg/kg/min at CrCl <60 mL/min

(*continued*)

Table 2.52 (continued)

Medication	Dose adjustment
Indirect thrombin inhibitors	
UFH	
LMWH	*Enoxaparin, Fondaparinux, Dalteparin, Tinzaparin:* reduce dosage at CrCl <60 mL/min, consider withholding at CrCl <30 mL/min[d]
Direct thrombin inhibitors	
Argatroban	No
Bivalirudin	At CrCl <30 mL/min, keep bolus unchanged, reduce infusion to 1 μg/kg/min
Lepirudin	At CrCl <60 mL/min or serum creatinine >1.5 mg/dL, adjust dosage
Dabigatran	At CrCl <60 mL/min or serum creatinine >1.5 mg/dL, adjust dosage; contraindicated at CrCl <30 mL/min
VKA	
Warfarin, Acenocoumarol	No, but exercise caution in severe CKD, as this may affect coagulation by other mechanisms

[a]Data extrapolated from specific agents
[b]Clopidogrel metabolite level appears to be in fact *lower* in patients with more severe renal function, but this finding does not seem clinically relevant
[c]Concerns have been raised about the use in patients with CKD
[d]Due to an abundance of caution, Fondaparinux is contraindicated at CrCl <30 mL/min, but it might in fact be safer in this setting than Enoxaparin, which, in CKD patients, is contraindicated in certain countries only

Preexisting CKD carries a high risk of contrast-induced nephropathy (CIN), occurring up to 3 days after angiography. The main risk factors include diabetes, old age, dehydration, and the use of high-osmolality (as opposed to low-osmolality, nonionic) agents, especially in large amounts. Proper hydration and minimizing the number of angiographic injections are crucial. Some studies (but not others) have found *N*-acetylcysteine effective in preventing CIN. A typical regimen involves two daily oral doses of 600 mg, on the day of angiography and one day before.

2.3.2.3 Non-ST-Elevation MI and Unstable Angina (NSTEMI/UA)

Unsurprisingly, the discussion of UA/NSTEMI is very similar to that of STEMI. There are some differences, however, as reviewed in Sect. 2.3.2.2. Similarly, the therapy of NSTEMI/UA generally follows the same lines as that of STEMI; beside the issue of IV thrombolytic therapy (indicated in STEMI only), there are a few additional differences, as reviewed in Table 2.53. Some of these differences may simply reflect the design of the existing trials, while others may genuinely mirror the differences between STEMI and NSTEMI-ACS.

NSTEMI vs. UA: These two entities represent a continuum, differentiated by the presence or absence of biomarker level elevation (in part dependent on the available measuring technology), and by the prognosis, which is worse with NSTEMI. *Clinically,* NSTEMI/UA presents with at least two of the following three criteria: *resting angina* (can also occur with minimal exertion, and usually lasts >10 min); *new-onset angina* (onset within the prior 4–6 weeks); and crescendo angina (more severe, prolonged, or frequent than previously). *The Braunwald classification* was proposed in order to better quantify the severity and prognosis of NSTEMI/UA. The classification is based on the severity of UA (rated between I and III) and the clinical setting of its appearance (the presence or absence of extracardiac conditions or of recent MI), marked as A, B, or C. Thus, each individual case is designated by a numeral and a letter. Good as a descriptive tool, this classification boils down to the conclusion that patients with resting angina <48 h in duration are at increased risk, especially if they are troponin-positive. *The EKG* presents with ST depressions ≥0.5 mm; the more severe the depression, the worse the prognosis; prompt intervention is mandatory with depressions ≥2 mm. ST depressions in V_1–V_3 may be the mirror image of a posterior MI; the posterior EKG leads (V7–V9) clarify this issue (The LCx and the distal RCA

Table 2.53 STEMI and NSTEMI/UA: a comparison

	STEMI	NSTEMI/UA
Pathogenesis	Fully occlusive thrombus	Less than fully occlusive thrombus
Incidence		Higher than that of STEMI
Patient profile		Older; higher co-morbidity (diabetes, renal failure) than STEMI patients
Time course	Minutes to hours	Up to a few days
Clinical manifestations		Similar to STEMI
Imaging studies		Similar to STEMI
EKG	ST elevations	No ST elevations[a]
Biomarkers	Elevated	Elevated
Therapy	See Table 2.54	See Table 2.54
Rehabilitation		Similar to STEMI
Complications		Similar to STEMI
Prognosis		Mortality lower in-hospital, higher at 6 months and 4 years than with STEMI

[a]ST elevations may be seen in Prinzmetal's angina

Table 2.54 NSTEMI vs. STEMI therapy[a]

Agent	STEMI	NSTEMI	NSTEMI-remarks
β-blockers	√	√	Might decrease progression to STEMI; however, the current guidelines call for β-blockers only in NSTE-ACS patients with LV dysfunction; optional, in all patients, but there is no evidence of long-term benefit
Nitrates	√	√	
ACEI	√	√	In NSTE-ACS patients with LV dysfunction (EF <40%), or with other indications for ACEI; optional, in all patients, but there is no evidence of long-term benefit. Only Ramipril and Perindopril have been proven effective
ARB	√	√	In patients with intolerance to ACEI
Aldosterone antagonists	√	√	
CCB	C/I	Non-dihydropyridine agents (Diltiazem) may be considered if symptomatic despite β-blockers and nitrates; agents of choice in vasospastic angina.	In patients symptomatic despite polytherapy, PCI should be strongly considered
Newer agents, useful in stable angina[b]			
Ivabradine	Insufficient data[c]	May be used (off-label) in patients with a C/I to β-blockers	
Trimetazidine	Insufficient data	Insufficient data	Trimetazidine might decrease the MI size in PCI-treated NSTEMI-ACS patients

(*continued*)

Table 2.54 (continued)

Agent	STEMI	NSTEMI	NSTEMI-remarks
Ranolazine	Probably, no role[d]	No role	Ranolazine was proved ineffective in ACS patients by the Merlin- TIMI 36 trial
Nicorandil	Insufficient data[e]	May reduce the post-PCI slow-flow phenomenon	May improve microvascular circulation and epicardial coronary vasodilatation; the clinical impact is yet unclear.
Anticoagulation[f]			
Indirect thrombin inhibitors			
UFH	√	√ (In all patients, regardless of invasive vs. non-invasive strategy)	In NSTEMI-ACS patients, UFH reduces by roughly 1/3 the incidence of death and MI (no similar data available for STEMI)
LMWH	√	√ (In all patients, regardless of invasive vs. non-invasive strategy)	The SYNERGY trial has not confirmed the superiority of LMWH over UFH in the setting of aggressive antithrombotic and invasive therapy. As with primary PCI in STEMI, Fondaparinux causes more catheter thrombosis than Enoxaparin, and, in PCI patients, should only be used in association with UFH (50–100 IU/kg bolus); in non-urgent situations, Fondaparinux is the preferred agent, as it causes less bleeding than other LMWH or UFH
Direct thrombin inhibitors			
Argatroban	√ (HIT)	√ (HIT)	
Bivalirudin	√	√ (As an alternative to UFH)	The ACUITY trial has suggested that Bivalirudin may be non-inferior to Heparin + IIb/IIIa inhibitors, while causing less bleeding; however, several aspects of the study design have been criticized
Lepirudin	√ (HIT)	√ (HIT)	
Dabigatran	Insufficient data	Insufficient data	Under study (RE-DEEM trial)
Vitamin K antagonists			
Warfarin, Acenocoumarol	No role[g]	No role[g]	
Antiplatelet agents			
NSAIDs			
Aspirin	√	√	
Thienopyridines			
Clopidogrel	√	√	
Prasugrel	Insufficient data	Insufficient data	
Ticlopidine	√[h]	√[h]	
IIb/IIIa inhibitors[i]			
Abciximab	√	√	Same dosage as in STEMI, but over 12–24 h
Eptifibatide	√	√	Same dosage as in STEMI, but over 72–96 h
Tirofiban	√	√	Same dosage as in STEMI, but over 48–96 h[j]

Table 2.54 (continued)

Agent	STEMI	NSTEMI	NSTEMI-remarks
Phosphodiesterase inhibitors			
Dipyridamole	No role	No role	
Cilostazol	No clear role	No clear role	Cilostazol may reduce restenosis rates after non-DES implantation; however, the results are inferior to those of DES

[a]For the therapy of STEMI. see text
[b]See discussion in the text
[c]Ivabradine may be useful in STEMI patients as a substitute to Metoprolol
[d]By extrapolation of the MERLIN-TIMI36 trial results
[e]Might be cardioprotective
[f]In the absence of complications or of recurrent ischemia, anticoagulation can be discontinued after 24–48 h, but extension up to discharge may be considered
[g]Unless otherwise indicated. In post-stenting patients with a Warfarin indication, dual antiplatelet therapy + Warfarin are recommended, under consideration of the individual bleeding risk
[h]Rarely used, due to its adverse effects; has been largely replaced by Clopidogrel
[i]In STEMI, glycoprotein IIb/IIIa inhibitors are only used in the setting of primary PCI, while in NSTE-ACS, they may also be used in patients not undergoing revascularization. They are especially effective in patients at moderate or high risk, in addition to dual oral antiplatelet therapy (Aspirin and Clopidogrel) *and* an anticoagulant (UFH/LMWH or Lepirudin)
[j]A higher-dose regimen is being tested (bolus 25 μg, followed by 0.15 μg/kg/min for 18 h)

territories are the most frequently misdiagnosed territories on the 12-lead EKG). T wave flattening, inversion (>1 mm), or pseudonormalization are also seen in NSTEMI/UA. A normal EKG is seen in up to 5% of NSTEMI/UA patients. An initially normal EKG tracing must be repeated at 6 and 24 h, as well as in case of symptom recurrence. *EKG stress testing* has no place in the diagnosis of NSTEMI/UA, which must be diagnosed based on clinical, resting EKG, and biomarker criteria. However, in low-risk patients admitted to the chest pain unit with an initial diagnosis of presumptive NSTEMI/UA, final pre-discharge confirmation or exclusion of ischemia is of the essence. In this setting, EKG stress test is very useful, as a negative test reliably excludes ischemia. *EKG monitoring* is indicated for 24–48 h, in uncomplicated cases. *Other diagnostic methods* (imaging tests, biological markers) are used as discussed in the setting of STEMI. An initially normal troponin sample must be repeated at 6–12 h after presentation, unless the presentation occurred at >12 h after symptom onset.

Exercise Stress Testing and ACS: A Paradoxical Association

In principle (Bayes' theorem), exercise stress testing should only be carried out in presence of an intermediate probability of ACS. However, this would carry a high risk of complications, if ACS is indeed present. Therefore, stress testing is undertaken in patients with *low* pre-test probability of disease – a deviation from Bayes' principle justified by the importance of "teasing out" even the most atypical cases of ACS.

NSTEMI/UA: *medical therapy* – All NSTEMI/UA patients are treated with Aspirin, Clopidogrel, and UFH/LMWH. The doses are: Clopidogrel 300 or 600, then 75 mg daily; Aspirin (non-enteric) 160–325 mg, followed by 75–100 mg q.d.; UFH bolus 60–70 U/kg, maximum 5,000 IU, followed by infusion 12–15 IU/kg/h, maximum 1,000 IU/h; Fondaparinux SC 2.5 mg q.d. Enoxaparin 1 mg/kg b.i.d., Dalteparin 120 IU b.i.d., Nadroparin 86 IU/kg b.i.d., Bivalirudin 0.1 mg/kg bolus, followed by 0.25 mg/kg/h; Fondaparinux is first-choice for conservative therapy; subsequent PCI requires a bolus supplement of UFH or, in HIT- or HIT-prone patients, of Argatroban, Lepirudin, or Bivalirudin. In patients at moderate or high risk, a IIb/IIIa inhibitor is recommended, on top of dual oral antiplatelet therapy and of the thrombin inhibitor. Bivalirudin has been suggested to replace the UFH/LMWH + IIb/IIIa component of therapy. In these high-risk patients, the therapy would include three, rather than four antithrombotic agents, i.e., Lepirudin, Aspirin, and Clopidogrel. Interruption of

antiplatelet therapy in patients after ACS, especially if they underwent stent implantation, is strongly discouraged, but may be mandatory, especially with surgical procedures where even light bleeding may be life-threatening, such as CNS surgery. Emergency surgery is performed as indicated; however, if a few days' delay is admissible, LMWH can be used empirically, while awaiting the washout of antiplatelet drugs. *NSTEMI/UA*: *Interventional therapy* – Several metaanalyses have concluded that a routine invasive strategy in all NSTE-ACS patients improves long-term prognosis, but at the cost of an increased early mortality. However, when investigated prospectively (the ICTUS trial), there was no advantage to routine invasive therapy in all ACS patients. All low-risk patients require early risk stratification, and, in the absence of significant inducible ischemia, can be managed conservatively. Conversely, up to two-third of NSTE-ACS patients with moderate or severe clinical manifestations (severe arrhythmia, hemodynamic instability, refractory or recurrent ischemia, dynamic ST segment changes, or HF) have multivessel disease, requiring invasive therapy, usually avoiding left ventriculography; IABP is also frequently used. The optimal timing of non-emergent PCI in NSTE-ACS patients is unclear, as some of the studies have not found early intervention beneficial (For instance, the ICTUS trial found an increased incidence of MI in patients intervened upon within the first 48 h). However, it is not recommended to delay intervention beyond 72 h from presentation.

Prinzmetal's (variant/vasospastic) angina is a distinct entity, akin to UA. It manifests as anginal pain, mainly at night or in the early morning, typically with ST elevations (but occasionally, with ST depressions or even with a normal EKG); nitrates and CCB relieve pain within a few minutes. Most patients have severe atherosclerosis. The etiology appears to be multifactorial, involving endothelial dysfunction; smooth muscle hyperreactivity; autonomic system hyperactivation; and excess endothelin. There is some overlap with syndrome X, as the latter occasionally involves vasospasm as well. Typically, vasospasm occurs at rest, with no symptoms present on exertion. Factors leading to vasospasm include, among others, cocaine abuse, smoking, electrolyte disturbances, cold stimulation, autoimmune disease, hyperventilation, and insulin resistance. The diagnosis involves demonstration of the typical EKG changes, occasionally by Holter monitoring or by loop recorder implantation. Focal or diffuse coronary spasm, demonstrated angiographically (lumen reduction >75% under intracoronary acetylcholine or Ergonovine as compared to maximum diameter under Nitroglycerin) confirms the diagnosis. Prognosis depends on the extent of atherosclerosis. The treatment is based on CCB and nitrates, in the usual doses.

2.3.3 Stable Angina Pectoris

The pathogenesis of stable angina differs from that of ACS in that the coronary flow is decreased not by a thrombus, but by a gradual decrease of the lumen, caused by increasing atherosclerotic plaque dimensions. A comparison between stable angina and ACS is reviewed in Table 2.55.

The severity of stable angina is quantified by the degree in which it impairs everyday life. This is evaluated by different scores, important for establishing therapy and for assessing its efficacy. *The Canadian Cardiovascular Society score* is the most widely used. Class IV corresponds to resting angina, in principle a type of unstable angina. In some extreme cases, however, a severe anginal score can be otherwise "stable," insofar the severity or frequency of the attacks is unchanged. The *Duke Activity Status Index* is a questionnaire applying a number of points for the ability to perform certain tasks (from self-care to competitive sports); the final score is incorporated in a formula, yielding an estimate of peak O_2 consumption, an important prognostic predictor. VO_2 max is approximately 3.5 L/min (45 mL/kg/min) and

Table 2.55 O_2 supply and demand in stable angina and ACS: a comparison

	Stable angina	ACS
Supply	May be decreased by changes of coronary vascular tone or of platelet activation	Is decreased by coronary thrombosis and distal micro-embolization
Demand	May be increased by physical or emotional stress	Is not necessarily increased; however, ACS may be triggered in a patient previously suffering from stable angina by plaque destabilization caused, among others, by increased sympathetic discharge

2.0 L/min (38 mL/kg/min) in the average young untrained male and female, respectively. The 19-item *Seattle Angina Questionnaire* explores physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. This questionnaire is sensitive to both small and important changes in anginal status. Of note, stable angina may be mimicked by DCM, HOCM, or AS, esophageal, pulmonary, or thoracic disease.

Workup for stable angina follows the general rules reviewed in Sect. 2.2. Non-invasive assessment plays an important role. The EKG manifestations are similar to those of ACS. The various diagnostic tests are reviewed in Table 2.56. *Coronarography* is indicated *for diagnosis* in patients with severe angina or severe ventricular arrhythmia; with nonsevere manifestations and non-diagnostic non-invasive test results; and in survivors of cardiac arrest; and *for follow-up* in patients with known coronary disease (recurrent angina after PCI or CABG) or in asymptomatic patients after complex intervention on a large coronary artery (long lesion, multiple stents, suboptimal stent deployment, etc.)

Prognosis: Stable angina has an annual mortality of 0.9–1.4%, with a 0.5–2.6% incidence of non-fatal MI. The risk of cardiovascular mortality is considered high, intermediate, or low, if it is >2, 1–2, or <1%, respectively. The prognosis varies widely, according to the degree of LV dysfunction (LVEF <40%); the severity and distribution of CAD (three-vessel disease, LMCA artery or proximal LAD involvement have the worst prognosis); the presence of risk factors or of full-blown atherosclerosis; and the angina score, calculated based on 16 variables (age, gender, risk factors, existing atherosclerosis, as well as additional clinical and EKG parameters).

Table 2.56 Tests used in the diagnosis of stable angina

Test	Sensitivity	Specificity
Exercise EKG	68	77
Exercise echo	80–85	84–86
Exercise nuclear scan	85–90	70–75
Vasodilator stress myocardial perfusion	83–94	64–90
Dobutamine stress echo	40–100	62–100
Vasodilator stress echo	56–92	97–100

Stable angina – treatment: As with the other ischemic syndromes, the treatment of stable angina can be pharmacological or interventional. Risk factor management follows the usual principles. The main *pharmacological agents* are reviewed in Sect. 2.2. These include most of the agents already discussed regarding ACS, as well as some agents dedicated to the therapy of stable angina. *Aspirin* 81–325 mg PO q.d. (replace with *Clopidogrel* 75 mg q.d. in case of intolerance) is indicated in all patients, in the usual dosages, as are *β-blockers* (Metoprolol 50–200 mg PO b.i.d., Atenolol 50–200 mg PO q.d.). If the latter are not sufficient to prevent the anginal attacks, they are supplemented with *CCB*. *Amlodipine* 5–10 mg PO q.d. has been shown to reduce progression to unstable angina, the need for revascularization, and the degree of carotid atherosclerosis measured by ultrasound; whether this can be extrapolated to the other CCB is not clear. Popular agents include *Diltiazem* (120–480 mg PO q.d. for the slow-release preparation; 120–360 mg PO divided t.i.d./q.i.d. with the immediate-release preparation); *Verapamil* (120–240 mg PO q.d./b.i.d. for the slow-release preparation; 80–120 mg PO divided t.i.d./q.i.d. with the immediate-release preparation). *Nitrates* may be used either on a daily basis, or reserved for the anginal attacks. *Nitroglycerin* (0.3–0.6 mg SL PRN; 0.4 mg metered-dose spray, PRN; 0.1–0.8 mg/h patch TD q.d.); *Isosorbide dinitrate:* 2.5–10 mg SL PRN; 80–120 mg PO q.d. slow release, 10–30 mg PO b.i.d./t.i.d., immediate-release. Occasionally, angina can be anticipated by the patient, and nitrates may be taken preventively. *ACEI* were shown to reduce rates of death, MI, stroke, and need for revascularization in patients with CAD or diabetes mellitus and at least one other cardiovascular risk factor, irrespective of the presence of HTN or HF. An example is Ramipril, 2.5–5 mg PO q.d., not to exceed 20 mg/d; *Other agents* include *Ranolazine* 500 mg PO b.i.d. initially; if necessary, may increase to 1,000 mg PO b.i.d.; *Nicorandil,* starting at 10 mg b.i.d. (5 mg b.i.d., in patients particularly susceptible to headache), titrated upward, usually to 10–20 mg b.i.d., and up to 30 mg b.i.d.; *Ivabradine* 5 mg b.i.d., increased to 7.5 mg b.i.d. In the elderly, the starting dose is 2.5 mg b.i.d.; *Trimetazidine* 20 mg t.i.d. *Enhanced external counterpulsation* (EECP) is a therapeutic option in stable angina, capitalizing on the same principle as IABP. Briefly, balloons wrapped around the lower limbs are inflated at the beginning of diastole, and deflated before atrial systole, under EKG gating. Subjective and

objective (perfusion scan) improvement in stable angina patients has been demonstrated.

Investigational approaches in stable angina involve injection of vascular growth factor (e.g., VEGF), or gene therapy, to determine overexpression of these factors. *Spinal cord stimulation* has been recently proven effective in patients with refractory angina pectoris due to end-stage CAD.

The decision regarding *pharmacological vs. interventional therapy* in stable angina has been addressed by the COURAGE trial, which has not found any reduction in the incidence of death or MI in stable angina patients initially treated with PCI, as compared to those treated with optimal medical therapy alone. Thus, initial conservative therapy appears appropriate in all patients with stable angina, as well as in asymptomatic CAD patients. On the other hand, there was substantial symptomatic improvement in PCI-treated patients, and a substantial rate of cross-over to PCI from the group initially managed by conservative therapy alone, making the interventional community interpret the study as actually encouraging an early interventional approach. Importantly, Class IV angina patients were not included in the study, neither were patients with refractory CHF, EF <30%, or LMCA artery stenosis >50%, and the results cannot be extrapolated to these populations. In patients in whom medical management alone is not sufficient, an additional decision refers to the type of revascularization therapy to be implemented: PCI vs. CABG. Older data suggest that CABG is the procedure of choice with LM stenosis >50%; LM disease equivalent (combined proximal LAD and proximal LCx stenosis); proximal 3VD (>70%); significant 2VD if one of the involved vessels is the proximal LAD; for significant CAD with impaired LV function; in diabetics; and after severe arrhythmia. However, the tremendous progress in PCI techniques allows to solve many of the above-mentioned problems by PCI. Unsurprisingly, the "CABG-vs.-PCI" debate is just as lively as the "conservative-vs.-interventional" debate, as shown by the SYNTAX trial, comparing the safety and efficacy of CABG vs. PCI with TAXUS DES in patients with 3VD or LMCA disease, who were eligible for either procedure. PCI was found inferior for the primary composite end point of major adverse cardiac or cerebrovascular events (MACCE); however, when the actual results are examined, it turns out that the differences are actually small (numerous CABG procedures needed, to avoid just one repeat PCI), with a fourfold increase in the number of strokes in the CABG group. This has prompted the interventional community to interpret SYNTAX as proof of the appropriateness of PCI in this population. This debate illustrates the necessity of individual decision tailoring. Despite widespread use, there is no evidence that adding a GP IIb/IIIa inhibitor to an optimal dual antiplatelet regimen is of benefit in low-risk patients with uncomplicated lesions.

Syndrome X is a particular instance of stable angina, where typical chest pain, usually in a female patient, is associated to a positive stress test; this prompts coronary angiography, which, however, fails to demonstrate significant atherosclerosis. Occasionally, angiography demonstrates vasospasm (on intracoronary acetylcholine administration). The pathogenesis of this syndrome is unclear, a classic explanation being that of microvascular dysfunction ("microvascular angina"), possibly associated to epicardial coronary endothelial dysfunction. Many patients are hypertensive and suffer from LVH with relative ischemia, as well as perivascular fibrosis with structural changes of both the myocardium and the coronaries. The prognosis is very good, with the possible exception of patients with angiographically demonstrated coronary vasospasm. The treatment follows the general lines of stable angina therapy. Therapy is usually started with slow-release CCB s; if the angiogram reveals epicardial coronary disease, nitrates are added. Aminophylline 400 mg/day, divided t.i.d. or q.i.d.; and Imipramine 50 mg/d may be tried if other measures fail.

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