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CARDIOVASCULAR DISEASE

(«INTERNAL MEDICINE» MODULE 2)

PART 3

The executive task force for students of medical faculty of 5th cource

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The executive task force is provided for students of 5th courses of medical faculties for helping to study of some topics in the fields of cardiovascular diseases incorporated into the discipline «Internal Medicine». There is the information about the most important topics regarding diagnosis of cardiac diseases.

CONTENT

Index of acronyms

ACE	angiotensin-converting enzyme
ACEI	ACE inhibitors
ACEI	angiotensin-converting enzyme inhibitor
ACM	alcoholic cardiomyopathy
ACS	acute coronary syndrome
AHA	American Heart Association
AHF	acute heart failure
AHMD	alcoholic heart muscle disease
ANP	atrial natriuretic peptide
APA	aldosterone-producing adenomas
APAH	associated pulmonary arterial hypertension
APCs	atrial premature complexes
ARB	angiotensin receptor blockers
ARVC	arrhythmogenic right ventricular cardiomyopathy
ARVD	arrhythmogenic right ventricular dysplasia
ASD	atrial septal defect
AV	atrioventricular
AVNRT	Atrioventricular Nodal Reentrant Tachycardia
BAS	balloon atrial septostomy
BB	beta-adrenoblockers
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute;
BSAC	British Society for Antimicrobial Chemotherapy
CA	calcium antagonists
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
CCSC	Canadian Cardiovascular Society Classification
CHD	coronary heart disease
CHF	chronic heart failure
CI	cardiac index
CK	creatine kinase
CMR	cardiac magnetic resonance imaging
CNS	central nervous system
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CRP	C-reactive protein
CT	computed tomography
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CV	cardiovascular diseases

CVP	central venous pressure
CVVH	continuous veno-venous hemofiltration
DAD	delayed after-depolarization
DCM	dilated cardiomyopathy
IDC	implantable defibrillator-cardioverter
IE	infective endocarditis
IGF	insulin-like growth factor
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
ISH	isolated systolic hypertension
IVDU	Intravenous drug use
IVUS	intravascular ultrasound
JET	functional ectopic tachycardia
LA	left arm
LAFB	left anterior fascicular block
LBBB	left bundle branch block
LL	left leg
LMWH	low molecular weight heparin
LMWH	low molecular weight heparin
LQTS	long-QT syndrome
LV	left ventricle / ventricular
LVH	left ventricular hypertrophy
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
MAC	mitral annular calcification
MBC	minimum bactericidal concentration
MHC	myosin heavy chain
MI	myocardial infarction
MIC	minimal inhibitory concentration
MR	mitral regurgitation
MRI	magnetic resonance imaging
MVP	mitral valve prolapsed
NBTE	nonbacterial thrombotic endocarditis
NCCLS	USA National Commmittee for Clinical Laboratory Standards
NIPPV	non-invasive positive pressure ventilation
NO	nitric oxide
NOS	nitric oxide synthase
NSTEMI	non ST-elevation MI
NT-proBNP	N-terminal fragment of pro- brain natriuretic peptide
PA	pulmonary artery
PAC	pulmonary artery catheter
PAP	pulmonary arterial pressure
PCI	Percutaneous Coronary Intervention
PDEIs	phosphodiesterase inhibitors
PDGF	platelet-derived growth factor

PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PHIRST	Pulmonary arterial Hypertension and ReSponse to Tadalafil
PJT	paroxysmal functional tachycardia
PK	pharmacokinetics
PK	pharmacokinetics
PNS	peripheral nervous system
PP	pulse pressure
PPCM	peripartum cardiomyopathy
PSVTs	paroxysmal supraventricular tachycardia's
PVCs	premature ventricular complexes
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PVT	prosthetic valve thrombosis
PWP	pulmonary wedge pressure
RA	right arm
RAAS	rennin-angiotensin-aldosterone system
RAP	right atrial pressure
RBBB	right bundle branch block
RCM	restricted cardiomyopathy
RCT	randomized controlled trial
RHC	right heart catheterization
RV	right ventricle/ventricular
SAECG	signal-averaging electrocardiography
SERCA^2	sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase pump
6MWT	6-minute walking test
SNP	sodium nitroprusside
SNS	sympathetic nervous system
SVC	superior vena cava
SVT	supraventricular tachycardia
t.i.d.	three times a day
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TTE	transthoraxic echography
VA	ventriculoatrial
VF	ventricular fibrillation
VPC	ventricular premature complexes
VSR	ventricular septal rupture
VT	ventricular tachycardia
WHO	World Health Organization
WHO-FC	World Health Organization functional class
WPW	Wolff-Parkinson-White syndrome

PREFACE

The task force is addressed to students of 5th course of medical university for helping to study of some parts of internal medicine in field of cardiovascsular diseases. It includes the use of contemporary tools for identification of congenital and acquired heart diseases, coronary artery disease, arterial hypertension, heart failure, arrhythmias, pericardial diseases etc., including objectives, laboratory studies, genetic investigations, biopsy materials, X-ray, multidetector CT, angiography, MRI procedures. Etiology and pathophisiology are discussed also separately for each of cardiovascular disorders. Diagnostic algorithm and procedures choosing are considered obligatory with an elucidation of contemporary management and prevention of cardiovascular diseases. This book has been written in a concise and easy assimilable style to enable rapid understanding of the cardiovascular diseases. It has been structured in a format that incorporates information for quickly reminding and squeezes are applied also. Hopefully, in some way, all of the effort and expertise brought together here will help advance this field.

Authors.

CHAPTER 1
ATHEROSCLEROSIS. DIAGNOSIS AND MANAGEMENT

Foreword

Atherosclerosis is, for the most part, a rather benign condition that affects, to some degree, virtually all the adult population both in developed countries and in many developing countries. Many adults will die from other causes before atherosclerosis causes overt problems. If the plaque is big enough and sitting in a coronary artery, it may impede blood flow and cause symptoms of angina. But if it is small, the plaque will usually be asymptomatic until the moment it supports thrombosis. The central role of thrombosis in the evolution of atherosclerotic plaque and the denouement in an acute cardiovascular event are well reflected in the title of this impressive book, and the interplay between plaque and thrombus is one of its central themes.

Atherosclerosis: Theories of genesis

The encrustation theory

This theory, proposed by Rokitansky in 1851, suggested that atherosclerosis begins in the intima with deposition of thrombus and its subsequent organization by the infiltration of fibroblasts and secondary lipid deposition.

The lipid theory

In 1856, Virchow proposed that atherosclerosis starts with lipid transudation into the arterial wall and its interaction with cellular and extracellular elements, causing "intimal proliferation."

The response-to-endothelial injury theory

Ross proposed this more unifying theory. Termed the response-to-injury hypothesis, it postulates that atherosclerosis begins with endothelial injury, making the endothelium susceptible to the accumulation of lipids and the deposition of thrombus.

The currently accepted response-to-vascular injury theory

Over the past decade, it has been proposed that vascular injury starts the atherosclerotic process. The effect of such vascular injury can be classified as follows:

Type I - Vascular injury involving functional changes in the endothelium with minimal structural changes, (ie, increased lipoprotein permeability and white blood cell adhesion)

Type II - Vascular injury involving endothelial disruption with minimal thrombosis

Type III - Vascular injury involving damage to media, which may stimulate severe thrombosis, resulting in unstable coronary syndromes

According to the response-to-vascular injury theory, injury to the endothelium by local disturbances of blood flow at angulated or branch points, along with systemic risk factors (eg, hyperglycemia, dyslipidemia, cigarette smoking, possibly infection) perpetuates a series of events that culminate in the development of atherosclerotic plaque.

Role of endothelium

Endothelium is the monolayered inner lining of the vascular system. It covers almost 700 m^2 and weighs 1.5 kg.

Functions of endothelium

• Providing a nonthrombogenic surface: This is achieved by producing prostaglandin derivatives such as prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, and by its surface covering of heparan sulfate.

• Secreting the most potent vasodilator, EDRF, a thiolated form of nitric oxide: EDRF formation by endothelium is critical in maintaining a balance between vasoconstriction and vasodilation in the process of arterial homeostasis.

• Secreting agents effective in lysing fibrin clots: These agents include plasminogen and procoagulant materials such as von Willebrand factor and type 1 plasminogen activator inhibitor.

• Secreting various cytokines and adhesion molecules, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1

• Secreting a number of vasoactive agents, such as endothelin, angiotensin II (A-II), serotonin, and platelet-derived growth factor, which may be important in vasoconstriction

Endothelium, through the above mechanisms, regulates the following:

• Vascular tone

- Platelet activation
- Monocyte adhesion and inflammation
- Thrombus generation
- Lipid metabolism
- Cellular growth and vascular remodeling

Endothelial damage occurs in many clinical settings and can be demonstrated in individuals with dyslipidemia, hypertension, diabetes, advanced age, nicotine exposure, and products of infective organisms (ie, *Chlamydia pneumoniae*). Experimental studies have shown that endothelial damage may be reversed if the underlying cause is attenuated. Endothelial damage may cause changes that are localized or generalized and transient or persistent, as follows:

- Increased permeability to lipoproteins
- Decreased nitric oxide production
- Increased leukocyte migration and adhesion
- Prothrombotic dominance
- Vascular growth stimulation
- Vasoactive substance release

Endothelial dysfunction is the initial step that allows diffusion of lipids and inflammatory cells (ie, monocytes, T lymphocytes) into the endothelial and subendothelial spaces. Secretion of cytokines and growth factors promotes intimal migration; SMC proliferation; and accumulation of collagen matrix, monocytes, and other white blood cells, forming an atheroma. More advanced atheromas, even though nonocclusive, may rupture, thus leading to thrombosis and the development of ACS and MI.

Multiple studies have demonstrated that risk-factor modification through therapeutic lifestyle change (TLC), reduction of low-density lipoprotein cholesterol (LDL-C) levels, and smoking cessation rapidly improves endothelial function.

Role of LDL - Oxidative stress

The most atherogenic type of lipid is the low-density lipoprotein (LDL) component of total serum cholesterol. The endothelium's ability to modify lipoproteins may be particularly important in atherogenesis. LDLs appear to be modified by a process of low-level oxidation when bound to the LDL receptor, internalized, and transported through the endothelium. LDLs initially accrue in the subendothelial space and sti-

mulate vascular cells to produce cytokines for recruiting monocytes, which causes further LDL oxidation. Extensively oxidized LDL (oxLDL) is picked up by the scavenger receptors on macrophages, which absorb the LDL and turn into foam cells. oxLDL is exceedingly atherogenic and is responsible for the following:

- Promoting cholesterol accumulation in macrophages, which then become foam cells: All macrophages are derived from circulating monocytes. When the monocyte enters a tissue, it appears to take on characteristics peculiar to the host tissue. In most inflammatory sites, the macrophage acts as a scavenger cell to remove foreign substances by phagocytosis and intracellular hydrolysis. As a scavenger cell, the macrophage attempts to remove injurious materials (eg, oxLDL) via scavenger receptors and can oxidize LDL by such means as lipoxygenase enzymes (eg, 15-lipoxygenase) forming the foam cells.

- Enhancing endothelial production of leukocyte adhesion molecules, ie, cytokines and growth factors that regulate SMC proliferation, collagen degradation, and thrombosis (eg, vascular cell adhesion molecule-1, intercellular cell adhesion molecule-1)

- Inhibiting nitric oxide synthase activity and increasing reactive oxygen species generation (eg, superoxide, hydrogen peroxide), thus reducing endothelium-dependent vasodilation

- Altering the SMC response to A-II stimulation and increasing vascular A-II concentrations: The SMCs that proliferate in the intima to form advanced atheromas are originally derived from the media. The theory that accumulation of SMCs in the intima represents the sine qua non of the lesions of advanced atherosclerosis is now widely accepted.

Substantial evidence suggests that oxLDL is the prominent component of atheromas. Antibodies against oxLDL react with atherosclerotic plaques, and plasma levels of immunoreactive altered LDL are greater in persons with AMI than in controls. Oxidative stress has therefore been recognized as the most significant contributor to atherosclerosis by causing LDL oxidation and increasing nitric oxide breakdown.

Histopathology of atherosclerotic lesions

Stary I lesion: The endothelium also expresses surface adhesion molecules E selectin and P selectin, attracting more polymorphonuclear cells and monocytes in the subendothelial space.

Stary II lesion: Macrophages begin to take up large amounts of LDL (fatty streak).

Stary III lesion: As the process continues, macrophages eventually become foam cells.

Stary IV lesion: Lipid exudes into the extracellular space and begins to coalesce to form the lipid core.

Stary V lesion: SMCs and fibroblasts move in, forming fibroatheromas with soft inner lipid cores and outer fibrous caps.

Stary VI lesion: Rupture of the fibrous cap with resultant thrombosis causes ACS.

Stary VII and VIII lesions: As lesions stabilize, they become fibrocalcific (Stary VII lesion) and, ultimately, fibrotic with extensive collagen content (Stary VIII lesion).

Atherosclerotic plaque may require 10-15 years for full development. Further growth is determined by the local activity of regulatory substances (ie, interleukin (IL)–1, IL-6, transforming growth factor-beta) and by thrombin, leukotriene, prostaglandin, fibrin, and fibrinogen.

Although a logical conclusion is that the most severely stenotic lesions are the ones at the greatest risk of sudden occlusion, this is not the case. As previously described, ACS has been shown to more often develop because of rupture and thrombosis of mild (<60%) coronary stenoses. This occurs because of the relatively higher lipid content of the lipid core, the thinner fibrous cap, and the increased leukocyte activity at the shoulder regions of the plaque. These characteristics make such plaques, called the vulnerable plaques, much more prone to rupture.

Mechanisms of the effects of risk factors

The presence of risk factors accelerates the rate of development of atherosclerosis. Smoking increases platelet activity and catecholamine levels, alters prostaglandins, and decreases high-density lipoprotein (HDL) levels. Arterial hypertension

causes endothelial dysfunction and increases collagen, elastin, and endothelial permeability and platelet and monocyte accumulation. Diabetes causes endothelial dysfunction, decreases endothelial thrombo-resistance, and increases platelet activity, thus accelerating atherosclerosis.

Plaque growth and vascular remodeling

As endothelial injury and inflammation progress, fibroatheromas grow and form the plaque. As the plaque grows, 2 types of remodeling occur, positive remodeling and negative remodeling.

Positive remodeling is an outward compensatory remodeling (the Glagov phenomenon) in which the arterial wall bulges outward and the lumen remains uncompromised. Such plaques grow further, although they usually do not cause angina because they do not become hemodynamically significant for a long time. In fact, the plaque does not begin to encroach on the lumen until it occupies 40% of the cross-sectional area. The encroachment must be 70% or greater to cause flow limitation. Such positively remodeled lesions thus form the bulk of the vulnerable plaques, grow for years, and are more prone to result in plaque rupture and ACS than stable angina, as documented by intravascular ultrasound (IVUS) studies.

Negative remodeling

Many fewer lesions exhibit almost no compensatory vascular dilation, and the atheroma steadily grows inward, causing gradual luminal narrowing. Many of the plaques with initial positive remodeling eventually progress to the negative remodeling stage, causing narrowing of the vascular lumen. Such plaques usually lead to the development of stable angina. They are also vulnerable to plaque rupture and thrombosis.

Plaque rupture - The main event causing acute presentations
Eruption of the vulnerable plaque

Tight coronary atheromas rarely cause ACS and MI. In fact, most of the atheromas that cause ACS are less than 50% occlusive as demonstrated by coronary arteriography. Atheromas (plaques) with smaller obstruction experience greater wall tension, which changes in direct proportion to their radii.

Most plaque ruptures occur because of disruption of the fibrous cap, which allows contact between the highly thrombogenic lipid core and the blood. These modestly obstructive plaques, which have a greater burden of soft lipid core and thinner fibrous caps with chemoactive cellular infiltration near the shoulder region, are called vulnerable plaques. The amount of collagen in the fibrous cap depends on the balance between synthesis and destruction of intercellular matrix and inflammatory cell activation.

T cells that accumulate at sites of plaque rupture and thrombosis produce the cytokine interferon gamma, which inhibits collagen synthesis. Already formed collagen is degraded by macrophages that produce proteolytic enzymes and by matrix metalloproteinases (MMPs), particularly MMP-1, MMP-13, MMP-3, and MMP-9. The MMPs are induced by macrophage- and SMC-derived cytokines such as IL-1, tumor necrosis factor (TNF), and CD154 or TNF-alpha. Authorities postulate that lipid lowering stabilizes the vulnerable plaques by modulating the activity of the macrophage-derived MMPs.

Inflammatory markers in atherosclerosis

In recent years, the role of inflammatory cells and signaling in the development, rupture, and thrombosis of an atheromatous plaque has been extensively studied. Infection or inflammation, which may be local or distant, generates potent proinflammatory cytokines (eg, IL-1B, TNF-alpha) that stimulate production of adhesion molecules, procoagulants, and messenger cytokine, ie, IL-6. IL-6 induces hepatic production of acute phase reactants such as C-reactive protein (CRP) and serum amyloid-A.

C-reactive protein appears to provide prognostic information for CAD. In the Physicians' Health Study, men with CRP levels in the highest quartile had a 3-times greater risk of MI. Use of aspirin resulted in a significant (55.7%) reduction in the risk of MI in men in the highest CRP quartile, suggesting that the aspirin-related reduction in the risk of first MI was clearly related to the level of CRP. CRP levels tended to increase over time in the placebo group, whereas levels remained lower in the treatment group at 5 years. Additionally, the efficacy of statin therapy was greater in subjects with higher levels of CRP.

The role of infection

Traditional risk factors, such as dyslipidemia, tobacco abuse, hypertension, and diabetes, often do not account for atherosclerosis in many patients. Certain nontraditional risk factors, including hyperhomocystinemia, are sometimes blamed. However, accumulating evidence suggests that atherosclerosis is an inflammatory disease; therefore, a great deal of attention has recently been focused on the possibility that infectious agents play a role in the etiology of CAD. Certain infectious agents have been implicated based on their isolation from the atheromatous plaques or on the presence of positive serology findings for organisms such as *C pneumoniae, Helicobacter pylori,* herpes simplex virus, and cytomegalovirus.

Even though prospective studies have fallen short of providing definitive evidence, *C pneumoniae* appears to exhibit the strongest association. *C pneumoniae* has been isolated from autopsy and arthrectomy specimens and in both early and well-developed lesions. When studied by means of immunologic cytochemistry and tissue staining, the association has been found in 70-100% of cases. Possible mechanisms by which infectious agents exert their effect may include local effects on the endothelium, SMCs, or macrophages or systemic effects by generating cytokines, stimulating monocytes, and promoting hypercoagulability.

Some of the completed studies have shown variable results. In the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infarction with Chlamydia (ACADEMIC) trial, markers of inflammation improved at 6 months in the subjects with positive serologic evidence of chlamydial infection, but no difference in clinical events was observed. In another trial, the Randomization Trial of Roxithromycin in Non–Q-Wave Coronary Syndromes (ROXIS), a reduction in CRP level was observed at 1 month and was associated with a significant decrease in triple clinical endpoint. The effect, however, dissipated by 3-6 months.

Several multicenter trials have evaluated the effect of antibiotic therapy on recurrent cardiac events when used as secondary prevention. The London study, Argentinian study, ACADEMIC trial, Azithromycin in Acute Coronary Syndrome (AZACS) study, and the South Thames Trial of Antibiotics in Myocardial Infarction

and Unstable Angina (STAMINA) trial all returned negative results in terms of any significant benefit from antibiotic therapy. However, these trials were not powered to detect the difference in the rate of composite events to begin with, while 3 of the recently presented trials were powered to detect such a difference.

First of these, the Weekly Intervention with Zithromax (Azithromycin) Against Atherosclerosis-Related Disorders (WIZARD) trial, enrolled 7700 subjects with a prior history of MI and positive *C pneumoniae* antibody findings and treated them with azithromycin. The follow-up period averaged 2.5 years. No significant difference in the rate of composite events (ie, death, MI, revascularization) was found.

The second trial, the results of which were presented at the 2004 European Society of Cardiology meeting held in Munich, Germany (sponsored by the US National Heart, Lung, and Blood Institute [NHLBI]), called the Azithromycin Coronary Events (ACES) study, randomized 4000 subjects with a history of stable CAD with 1- to 4-year follow-up to azithromycin at 600 mg once per week for 1 year versus placebo. The occurrence rate of composite events (ie, death, MI, revascularization) was 22.3% in the azithromycin cohort and 22.4% in the placebo cohort. The difference was not significant.

A new antibiotic, gatifloxacin, was tested in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, which enrolled 4162 subjects with ACS. The results of the lipid arm of the PROVE-IT trial already indicated more aggressive LDL-C lowering in high-risk patients with CAD. The results of the antibiotic portion of the trial were presented at the 2004 European Society of Cardiology meeting in Munich, Germany. Again, the rates of composite events for the gatifloxacin and placebo groups were 23.7% and 25.1%, respectively, and the difference was not statistically significant.

All the above trials used different patient populations and types and doses of antibiotics, but antibiotic therapy does not appear to have a significant role in secondary prevention. However, the role of inflammation in the pathogenesis of coronary atherosclerosis; its assessment via measurement of the CRP level or other molecules; and therapy with statins, ACE inhibitors, and, possibly, yet-to-be-discovered agents, re-

main very active areas of research with a strong possibility of significant improvement in therapy.

Frequency

The international incidence of ACS and AMI, especially in developed countries, is similar to that observed in the United States. Despite consumption of rich foods, inhabitants of France and the Mediterranean region appear to have a lower incidence of CAD. This phenomenon (sometimes called the French paradox) is partly explained by greater use of alcohol, with its possible HDL-raising benefit, and by consumption of the so-called Mediterranean diet, which includes predominant use of monounsaturated fatty acids, such as olive oil or canola oil, which are less atherogenic. Eskimos have been found to have a lower prevalence of CAD as a result of consuming fish oils containing omega-3 fatty acids. The incidence, prevalence, and manifestations of CAD vary significantly with race, as does the response to therapy. Men traditionally have a higher prevalence of CAD. Women, however, follow men by 10 years, especially after menopause. Nevertheless, the value of estrogen supplementation has been discredited by the Heart and Estrogen/Progestin Replacement Study (HERS). The presence of diabetes eliminates the protection associated with female sex.

- Even in women, the most common cause of death is CAD, which accounts for more deaths than those related to breast and uterine diseases combined.

- Women with AMI present later than average, are less often subjected to invasive strategies, and experience greater overall mortality. Similar statistics can also be cited for the presentation and treatment of patients with stable CAD.

Mortality/Morbidity

In the United States, approximately 14 million persons experience CAD and its various complications. Congestive heart failure (CHF) that develops because of ischemic cardiomyopathy in hypertensive MI survivors has become the most common discharge diagnosis for medical patients in American hospitals.

- Annually, approximately 1.5 million Americans have an AMI, a third of whom die.

- The survivors of MI have a poor prognosis, carrying a 1.5- to 15-fold higher risk of mortality and morbidity than the rest of the population.

- For example, historically within 1 year of MI, 25% of men and 38% of women die. These rates may overstate the 1-year mortality rate today, given advances in the treatment of CHF and sudden cardiac death. Among survivors, 18% of men and 34% of women have a second MI within 6 years, 7% of men and 6% of women die suddenly, 22% of men and 46% of women are disabled with CHF, and 8% of men and 11% of women have a stroke.

Age is the strongest risk factor for the development of CAD. Elderly persons still experience higher mortality and morbidity rates from CAD. Complication rates of multiple therapeutic interventions tend to be higher; however, the magnitude of benefit from the same interventions is greater because these patients form the high-risk subgroup.

History

Coronary artery atherosclerosis manifests in a broad spectrum of presentations. Most individuals remain asymptomatic. The condition is a progressive disease process that generally begins in childhood and manifests clinically in mid-to-late adulthood.

- The spectrum of presentation includes symptoms and signs consistent with the following conditions:
    - Asymptomatic state (subclinical phase)
    - Stable angina pectoris
    - Unstable angina (ie, ACS)
    - Acute MI
    - Chronic ischemic cardiomyopathy
    - Congestive heart failure
    - Sudden cardiac arrest

- History may include the following:
    - Chest pain
    - Shortness of breath
    - Weakness, tiredness, reduced exertional capacity

- o Dizziness, palpitations
- o Leg swelling, weight gain
- o Symptoms related to risk factors

Physical examination may reveal the following findings in various combinations:

- Pulse volume, rate, and regularity: Tachycardia is common in persons with ACS and AMI. Heart rate irregularity may signal the presence of atrial fibrillation or frequent supraventricular or ventricular ectopic beats. Ventricular tachycardia is the most common cause of death for persons with AMI.

- High or low blood pressure: Hypotension often reflects hemodynamic compromise and is a predictor of poor outcome in the setting of AMI.

- Diaphoresis: This is a common finding.

- Tachypnea: Patients often have rapid breathing.

- Shock

- Syncope

- Leg edema

- Congestive heart failure: Signs and symptoms of CHF may indicate cardiogenic shock or a mechanical complication of AMI such as ischemic mitral valve regurgitation.

- Heart sounds and gallop: An S_4 gallop is a common early finding. The presence of an S_3 is an indication of reduced left ventricular function.

- Heart murmurs: These, particularly those of mitral regurgitation and ventricular septal defect, may be found after the initial presentation; their presence indicates a grave prognosis. The murmur of aortic insufficiency may signal the presence of aortic dissection as a primary etiology, with or without the complication of AMI.

- Pulmonary congestion, rales

- Stigmata of risk factors: Patients may develop xanthelasmas, livedo reticularis, or both.

- Body habitus: Central obesity is often seen.

- Diagonal ear crease, short stature, baldness, thoracic hairiness

- Findings consistent with previous CAD: These patients may have scarring from coronary artery bypass graft or similar surgeries.

Causes. To varying degrees, coronary artery atherosclerosis results from the interplay of multiple risk factors, as follows:

- Family history of premature CAD
- Hypercholesterolemia (high LDL syndrome)
- Hypertension
- Cigarette smoking
- Diabetes mellitus
- Hypoalphalipoproteinemia
- Dysmetabolic syndrome
- Obesity
- Physical inactivity
- Nontraditional risk factors
  - Hyperhomocystinemia
  - High lipoprotein(a) levels
  - High iron levels
- Syndromes of accelerated atherosclerosis - Graft atherosclerosis, CAD after cardiac transplantation
- Restenosis
- Infection
  - *C pneumoniae*
  - *H pylori*
  - Herpes simplex virus

Lab Studies

- Routine blood tests
  - CBC count
  - Chemistry panel
  - Thyroid function tests - To exclude thyroid disorders
- Fasting lipid profile
  - Total cholesterol level

- LDL-C level
    - HDL cholesterol (HDL-C) level
    - Triglyceride level
- Special tests
    - Specific lipid studies (if necessary)
        - Small, dense LDL-C level
        - Lipoprotein(a) level
        - Apoprotein profile
    - Miscellaneous tests
        - Homocysteine level
        - Inflammatory markers (eg, CRP)
- Tests specific to the presentation of ACS
    - Serum markers
        - Creatine kinase with MB isozymes
        - Troponins (I or T)
        - Lactate dehydrogenase and lactate dehydrogenase isozymes
        - Serum aspartate aminotransferase
    - Inflammatory markers - CRP

Imaging Studies

- Echocardiography
    - Transthoracic echocardiography helps assess left ventricular function, wall motion abnormalities in the setting of ACS or AMI, and mechanical complications of AMI.
    - Transesophageal echocardiography is most often used for assessing possible aortic dissection in the setting of AMI.
    - Stress echocardiography can be used to evaluate hemodynamically significant stenoses in stable patients who are thought to have CAD.
    - Treadmill echocardiography stress testing and dobutamine echocardiography stress testing provide equivalent predictive values.

- Nuclear imaging studies (myocardial perfusion imaging): These studies are also useful in assessing patients for hemodynamically significant coronary artery stenoses.
  - Stress and rest nuclear scintigraphic studies using thallium, sestamibi, or teboroxime are sometimes helpful.
  - Radionuclide stress myocardial perfusion imaging can be used to quantify coronary flow reserve (CFR).
    - Thallium Tl^{201} or sestamibi are widely used to quantify CFR. Flow reserve is typically assessed by these techniques during exercise or with pharmacological coronary vasodilators. In contrast to invasive techniques that measure an index of absolute flow reserve (an index related to the quotient of maximal and basal flow), cardiac imaging techniques assess relative CFR (rCFR) by comparing the perfusion of ischemic regions of the left ventricle with presumably normally perfused reference regions.
    - Imaging techniques yield a less quantitative index of flow reserve than catheter-based techniques. In addition, results can be misleading in the setting of diffuse coronary disease when a normal reference region is not available. However, unlike most measures of absolute flow reserve, relative flow reserve is independent of the loading conditions because these affect all regions of the left ventricle equally.
    - Taken together, absolute flow reserve and rCFR provide a more complete description of the severity of physiological stenosis than either method alone.
  - Types of nuclear imaging include a treadmill nuclear stress test, a dipyridamole (Persantine) or adenosine nuclear stress test, and a dobutamine nuclear stress test.
  - MI avid scintigraphy may be indicated.
- Magnetic resonance angiography
- Electron beam CT scanning

- Electron beam computed tomography (EBCT) scanning is a noninvasive method of evaluating calcium content in the coronary arteries. Healthy coronary arteries lack calcium. As atherosclerotic plaques grow, calcium accumulates because of a perpetuating inflammatory process or the healing and scarring induced by this process. EBCT is currently used as a screening test in asymptomatic patients and as a diagnostic test for obstructive CAD in symptomatic patients, although experts in the field have reached no consensus regarding indications for its use.

- The American College of Cardiology/American Heart Association Expert Consensus Document indicates the following:
  - EBCT scanning has been demonstrated to have high sensitivity.
  - Overall predictive accuracy is 70%.
  - EBCT has low specificity, ie, a substantial false-positive rate, which raises the index of suspicion for CAD and leads to expensive and unwarranted additional testing to exclude CAD. Consequently, O'Rourke and colleagues do not recommend EBCT scanning to help diagnose obstructive CAD.

- Whether EBCT scanning is a worthwhile tool for screening of CAD is still unclear. Well-established clinical indicators, such as the Framingham risk score and the National Cholesterol Education Program (NCEP) risk calculator, already accurately predict the likelihood of CAD. Whether EBCT scanning adds to these indicators has yet to be shown. The Multi-Ethnic Study of Atherosclerosis (MESA), sponsored by the US National Institutes of Health, is now assessing prospective evaluation of EBCT scanning in asymptomatic subjects to answer this question.

- EBCT scanning may have niche uses, including (1) determining whether individuals who appear to be at intermediate risk are really at a higher risk (eg, asymptomatic elderly patients who have high calcium scores) and (2) determining a low likelihood of significant CAD if EBCT scanning demonstrates a low or absent calcium score.

Other Tests

- Twelve-lead ECG

- Treadmill ECG stress test

- Holter monitoring for silent ischemia

- Angioscopy

Procedures

- Coronary angiography: Coronary arterial luminography remains the criterion standard for defining significant flow-limiting stenoses that must be revascularized through percutaneous or surgical intervention to improve prognosis. Quantitative coronary angiography (QCA) is used to perform computerized quantitative analysis of the entire coronary tree. It introduces a correction factor for the presence of diffuse disease. QCA has been widely used in many trials of atherosclerotic progression and regression.

- The role of QCA in regression studies is as follows:

  - The Familial Atherosclerosis Treatment Study (FATS) analyzed 9 angiographic trials of lipid-reducing therapy. Approximately 50% of subjects in the control group exhibited progression, but only 25% of the subjects in the treatment group did so. Regression was observed in 8% of the control group and in 28% of the treatment group. Subjects with mild-to-moderate lesions showed the most benefit.

  - The reduction in the number of clinical coronary events was much more pronounced (disproportionately greater), although the effect on lesion progression was only modest. For example, in the FATS, only 12% of subjects showed regression. The mean regression in the stenosis was less than 1%; however, this resulted in a 70% reduction in coronary events. ACS is known to develop in nonocclusive (<50%) plaques in most patients. The luminographic images obtained by coronary arteriograms miss mild-to-moderate vulnerable plaques, which cause most of the acute events.

- Limitations of coronary arteriography are as follows:

- Severity of stenosis is generally estimated visually, but estimation is limited by the fact that interobserver variability may range from 30-60%.
- The presence of diffuse disease also may lead to underestimation of stenoses because the stenosed areas are expressed as a percent of luminal diameter compared with adjacent normal coronary segments, and, in diffuse disease, no such segments exist. This usually occurs in diabetic patients, in whom coronary arteries are traditionally described as small-caliber vessels, when that appearance is actually due to the presence of diffuse symmetrical involvement of the entire vessel, as elucidated by recent IVUS studies.

- Coronary blood flow determinations: Because of the inherent limitations of coronary angiography, attention has been directed to using physiological approaches for determining the severity of coronary stenoses. The 5 methods of measuring human coronary blood flow in the cardiac catheterization laboratory are (1) thermodilution, (2) digital subtraction angiography, (3) electromagnetic flowmeters, (4) Doppler velocity probes (for measuring CFR), and (5) pressure wires (for measuring fractional flow reserve [FFR]). Although most current methods measure relative changes in coronary blood flow, useful information about the physiological significance of stenosis, cardiac hypertrophy, and pharmacological interventions can be obtained from these measurements.

- Doppler velocity probes use a Doppler flow meter, which is based on the principle of the Doppler effect. This is the most widely applied technique for measuring coronary flow in humans. High-frequency sound waves are reflected from moving red blood cells and undergo a shift in sound frequency proportional to the velocity of the blood flow.

  In pulsed-wave Doppler methods, a single piezoelectric crystal can both transmit and receive high-frequency sound waves. These methods have been successfully applied in humans by using miniaturized crystals fixed to the tip of catheters. Technological developments have further miniaturized steerable 12-MHz Doppler guidewires to a diameter of 0.014 inches.

Flow to a stenosis can therefore be assessed distally and proximally. The Doppler guidewire measures phasic flow velocity patterns and tracks linearly with flow rates in small, straight coronary arteries.

- Indications for Doppler velocity probe use include determining the severity of intermediate stenosis (40-60%) and for evaluating whether normal blood flow has been restored after PTCA.

  The use of smaller Doppler catheters allows measurement of selective coronary artery flow velocity. By noting the increase in flow velocity following administration of a strong coronary vasodilator, such as papaverine or adenosine, the CFR can be defined. CFR provides an index of the functional significance of coronary lesions that obviates some of the ambiguity of anatomical description. The current Doppler probe method has limitations. Limitations include (1) only changes in flow velocity, rather than absolute velocity or volumetric flow, are measurable; (2) the change in flow velocity is directly proportional to changes in volumetric flow only when vessel dimensions are constant at the site of the sample volume; (3) other factors, including left ventricular hypertrophy and myocardial scarring, can also affect CFR; and (4) changes in luminal diameter and arterial cross-sectional area during interventions are not reflected in measurements of flow velocity, thus potentially causing underestimation of the true volume flow.

- In summary, Doppler wires have a miniaturized Doppler crystal placed at the tip of an angioplasty guidewire, permitting measurement of phasic and mean coronary blood flow velocities. Because this technique does not measure absolute coronary blood flow, several indices of flow velocity have been used for assessing the physiological significance of coronary stenoses. Coronary flow velocity reserve is the ratio of maximum flow velocity to baseline flow velocity.

  Patients with a coronary flow velocity ratio of less than 2 typically have other corroborating evidence of myocardial ischemia and improve symptomatically with revascularization. Conversely, patients with a ratio of more than 2 usually

lack other objective evidence of myocardial ischemia and have a favorable outcome with conservative management; therefore, flow velocity measurements can be helpful in the treatment of patients with coronary lesions of intermediate severity. The diastolic-to-systolic velocity ratio has also been used to evaluate stenosis severity. In normal arteries, diastolic flow velocity far exceeds systolic velocity; however, the two are more equal distal to significant stenoses. A ratio of less than 1.7 has been used to define significant coronary lesions.

During coronary interventions, the Doppler guidewire can be used to judge the adequacy with which stenosis severity has been reduced. Patients with higher CFRs at completion of the procedure have a lower prevalence of abrupt reocclusion and restenosis.

- rCFR is calculated as follows: ([rCFR] = CFR target/CFR reference). rCFR involves Doppler coronary flow measurements of target and reference vessel CFR with a Doppler-tipped guidewire. Compared with patients who have negative stress imaging study findings, patients who have positive stress study findings showed more angiographically severe stenoses (74% +/- 13% vs 44% +/- 24%; P = .0005) with lower target CFRs (1.68 +/- 0.55 vs 2.46 +/- 0.74; P = .002) and lower rCFRs (0.72 +/- 0.22 vs 1 +/- 0.26; P <.003).

  - Based on cut points (CFR >1.9; rCFR >0.75), compared with CFR, rCFR had similar agreement (kappa 0.54 vs 0.5), sensitivity (63% vs 71%), specificity (88% vs 83%), and positive predictive value (83% vs 81%) with myocardial perfusion tomography.

  - Although rCFR, as with CFR, correlates with stress myocardial perfusion imaging results, rCFR did not have significant incremental prognostic value over CFR alone for myocardial perfusion imaging. However, rCFR does provide additional information regarding the status of the microcirculation in patients with CAD and complements the CFR for lesion assessment.

- With regard to FFR, the measurement of pressure gradients across coronary stenoses was originally advocated to assess the results of coronary angioplasty. Ow-

ing to the large profile of catheters used, this technique was never widely applied. However, new technology using 0.018-inch guidewires to assess pressure gradients across stenoses has been introduced.

Myocardial FFR has been used as an index of functional severity of coronary artery stenosis.

Pressure gradients are determined by measuring the ratio of the mean pressure distal to a coronary stenosis compared with that proximal to the stenosis. The proximal stenosis is measured through the tip of the guiding catheter, and the distal pressure is measured through the tip of the guidewire. Maximal vasodilation is induced by intracoronary administration of either adenosine or papaverine.

FFR is calculated from the ratio of the mean pressure distal to a coronary stenosis to the mean aortic pressure during maximal hyperemia. If the FFR is less than 0.75, sensitivity is at least 80% and specificity is at least 85% for an abnormal exercise test result.

Pressure wire measurement has been less well validated than Doppler flow reserve measurement; however, early studies indicate improved clinical utility owing to the ease of use and the reproducibility of results.

In summary, myocardial FFR is a recently developed index of the functional severity of coronary stenoses that is calculated only from simultaneous pressure measurements proximally and distally to a stenosis obtained with a pressure monitoring guidewire.

FFR represents the fraction of the normal maximal coronary flow that can be achieved in an artery in which flow is restricted by a coronary stenosis. The concept of FFR is founded in the previously noted observation that myocardial perfusion is entirely pressure dependent during maximal hyperemia.

Maximal blood flow in the presence of a stenosis is therefore determined by the driving pressure distal (Pd) to the stenosis, whereas the theoretical normal maximal blood flow is determined by the pressure proximal (Pp) to the stenosis. FFR is calculated during maximal hyperemia (obtained with adenosine or papaverine) as FFR =

Pd/Pp. FFR less than 0.75 is typically associated with other objective evidence of myocardial ischemia.

Measurement of FFR in patients with coronary stenoses of moderate severity has been shown to be a useful index of the functional severity of the stenoses and the need for coronary revascularization. Measurement of FFR can also guide the adequacy of reducing coronary stenosis severity with balloon angioplasty or stenting.

- Intravascular ultrasound
    o IVUS demonstrates the luminal dimensions and, more importantly, the tissue composition of the vascular wall in tomographic subsegments that can be summated to create a 3-dimensional picture showing arterial remodeling and the diffuseness of atherosclerosis with clarity unobtainable by angiography (luminography).
    o IVUS delineates vascular remodeling—both positive (Glagov phenomenon) and negative. Positive remodeling shows adaptive outward expansion of the external elastic membrane to accommodate growing plaques. Negative remodeling exhibits discrete areas of vascular luminal encroachment by the ingrowing plaques.
    o In a 2000 IVUS study of 85 subjects, Schoenhagen and colleagues demonstrated that positive remodeling is more commonly associated with unstable angina, whereas negative remodeling is associated with stable angina.
    o The apparently paradoxical findings of angiographic studies suggesting that AMI most often occurs in less than 50% of stenosed arterial segments, and those of autopsy studies showing AMI to be associated with large plaques, are reconciled by IVUS findings. IVUS shows the responsible lesions to be large plaques that have positively remodeled, thus causing minimal luminal encroachment and exhibiting echolucency suggesting a lipid-rich pool in the plaque center.
    o The ability of IVUS to identify positively remodeled plaques and the presence of diffuse disease in some ways makes it better than angiography, the less-than-perfect criterion standard. IVUS can much more clearly demonstrate the

presence or absence of fibrosis, calcium, and ulceration, as well as eccentricity of the plaques.

- o Ostial lesions can also be better defined by IVUS.

- Stenosis severity and clinical events

  - o The severity of stenoses and their propensity to cause MI, unstable angina, or sudden coronary death are poorly correlated.

  - o Pathologic and angiographic studies have revealed that MIs and unstable angina are most often caused by rupture of atherosclerotic plaques with formation of a superimposed occlusive thrombus.

  - o Most atherosclerotic lesions responsible for these serious events are mild stenoses of inconsequential hemodynamic significance and are characterized by an abundance of lipid, numerous inflammatory cells, and a thin, fragile fibrous cap.

  - o These observations suggest that although measurements of CFR may be useful in the assessment of the severity of stenoses and in the identification of lesions responsible for effort angina, they are not likely to identify the more dangerous plaques responsible for unstable angina, AMI, and sudden ischemic death.

Medical Care

The treatment goals for patients with coronary artery atherosclerosis are to relieve symptoms and to prevent future cardiac events such as unstable angina, AMI, and death. This clinical approach will be considered in appropriate chapters.

Prevention of future cardiac events

Pharmacotherapeutic strategies that affect the risk factor profile, such as the administration of statins for LDL reduction or the administration of agents that alter the atherosclerotic plaque, are of paramount importance in this regard.

LDL cholesterol: the primary target of therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-

lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cut points for initiating treatment are stated in terms of LDL.

Risk assessment: first step in risk management

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants. In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total cholesterol and HDL cholesterol will be usable. In such a case, if total cholesterol is >200 mg/dL or HDL is <40 mg/dL, a follow-up lipoprotein profile is needed for appropriate management based on LDL. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL levels from low to high. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in Table 1.1, which also shows the classification of total and HDL cholesterol levels.

Table 1.1

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL cholesterol

<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high

Total cholesterol

<200	Desirable
200-239	Borderline high
≥240	High

HDL cholesterol

<40   Low
≤60   High

Risk determinants in addition to LDL cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (Table 1.2). LDL is not counted among the risk factors in Table 1.2 because the purpose of counting those risk factors is to modify the treatment of LDL.

Table 1.2

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (blood pressure ≥140/90mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

Based on these other risk determinants, ATP III identifies 3 categories of risk that modify the goals and modalities of LDL-lowering therapy. Table 3 defines these categories of risk and shows corresponding LDL cholesterol goals. The category of highest risk consists of CHD and CHD risk equivalents. The latter carry a risk for major coronary events equal to that of established CHD, ie,.20% per 10 years (ie, more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years).

CHD risk equivalents comprise:

• Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)

• Diabetes

• Multiple risk factors that confer a 10-year risk for CHD >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial in-

farction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with CHD or CHD risk equivalents have the lowest LDL cholesterol goal (<100 mg/dL). The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for CHD is ≤20%. Risk is estimated from Framingham risk scores. The major risk factors, exclusive of elevated LDL cholesterol, are used to define the presence of multiple risk factors that modify the goals and cut-points for LDL lowering treatment, and these are listed in Table 3.3. The LDL cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL. The third category consists of persons having 0-1 risk factor; with few exceptions, persons in this category have a 10-year risk <10%. Their LDL cholesterol goal is <160 mg/dL.

Method of Risk Assessment: Counting Major Risk Factors and Estimating 10-Year CHD Risk

Risk status in persons without clinically manifest CHD or other clinical forms of atherosclerotic disease is determined by a 2-step procedure. First, the number of risk factors is counted (Table 1.3). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring to identify individuals whose short-term (10- year) risk warrants consideration of intensive treatment.

Table 1.3

Three Categories of Risk That Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors	<130
0-1 risk factor	<160

Estimation of the 10-year CHD risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high LDL level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure, and

cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for LDL cholesterol, but LDL cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for CHD of .20%, 10%-20%, and 10%. It should be noted that this 2-step sequence can be reversed with essentially the same results. (If Framingham scoring is carried out before risk factor counting, persons with 10% risk are then divided into those with 2+ risk factors and 0-1 risk factor by risk factor counting to determine the appropriate LDL goal [Table 3].) Initial risk assessment in ATP III uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

Role of Other Risk Factors in Risk Assessment

ATP III recognizes that risk for CHD is influenced by other factors not included among the major, independent risk factors (Table 3.3). Among these are life-habit risk factors and emerging risk factors. The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein(a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The lifehabit risk factors are direct targets for clinical intervention but are not used to set a lower LDL cholesterol goal of therapy. The emerging risk factors do not categorically modify LDL cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of riskreduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic Syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the metabolic syndrome. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syn-

drome as a secondary target of risk-reduction therapy, after the primary target - LDL cholesterol. Diagnosis and treatment of the metabolic syndrome is described below under "Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy."

The Link Between Risk Assessment and Cost-effectiveness

In ATP III, a primary aim is to match intensity of LDL-lowering therapy with absolute risk. Everyone with elevated LDL cholesterol is treated with lifestyle changes that are effective in lowering LDL levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cut-points for drug treatment are based primarily on risk benefit considerations: those at higher risk are likely to get greater benefit. However, cut-points for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost - effectiveness. Lifestyle changes are the most cost-effective means to reduce risk for CHD. Even so, to achieve maximal benefit, many persons will require LDL-lowering drugs. Drug therapy is the major expense of LDL lowering therapy and it dominates cost-effectiveness analysis. However, the costs of LDL-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower-risk persons and still be cost-effective. In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL-lowering drugs even though use of drugs may not be cost-effective by current standards.

Primary Prevention with LDL-Lowering Therapy

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher-risk persons. One aim of primary prevention is to reduce long term risk (>10 years) as well as short-term risk (<10 years). LDL goals in primary prevention depend on a person's abso-

lute risk for CHD (ie, the probability of having a CHD event in the short term or the long term) - the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Secondary prevention with LDL-lowering therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 1, an LDL cholesterol level of <100 mg/dL is optimal; therefore, ATP III specifies an LDL cholesterol level of <100 mg/dL as the goal of therapy in secondary prevention.

This goal is supported by clinical trials with both clinical and angiographic end points and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-lowering therapy in 3 risk categories

The 2 major modalities of LDL lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 1.4 defines LDL cholesterol goals and cut points for initiation of TLC and for drug consideration for persons with 3 categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10%-20% and <10%); and 0-1 risk factor.

Table 1.4

LDL Cholesterol Goals and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)
2+ Risk factors (10-year risk 10%-20%)	<130	≥130	10-year risk 10%-20%: $130
			10-year risk ,10%: ≥160
0-1 Risk factor	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

CHD and CHD Risk Equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cut-points for initiating lifestyle and drug therapies are shown in Table 4. *If baseline LDL cholesterol is .130 mg/dL*, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol level of ,100 mg/dL; thus an LDL cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy. *If LDL cholesterol levels are 100-129 mg/dL*, either at baseline or on LDL lowering therapy, several therapeutic approaches are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.

- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.

- Delay use or intensification of LDL lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid modifying drugs (eg, nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol.

If baseline LDL cholesterol is <100 mg/dL, further LDL-lowering therapy is not required. Patients should nonetheless be advised to follow the TLC Diet on their own

to help keep the LDL level optimal. Several clinical trials are currently under way to assess benefit of lowering LDL cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) Risk Factors and 10-Year Risk of ≤20%

For persons with multiple (2+) risk factors and 10-year risk ≤20%, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each category is summarized in Table 4. *Multiple (2+) Risk Factors and a 10-Year Risk of 10%-20%.* In this category, the goal for LDL cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, TLC is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL after 3 months of TLC, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of <130 mg/dL. Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost effective. If the LDL falls to less than 130 mg/dL on TLC alone, TLC can be continued without adding drugs. In older persons (>65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues, may influence treatment decisions and may suggest a more conservative approach.

Multiple (2+) Risk Factors and a 10-Year Risk of <10%. In this category, the goal for LDL cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, the TLC Diet is initiated to reduce LDL cholesterol. If LDL is <160 mg/dL on TLC alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol level of <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

0-1 Risk Factor

Most persons with 0-1 risk factor have a 10-year risk <10%. They are managed according to Table 4. The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is TLC. If after 3 months of TLC the LDL cholesterol is <160 mg/dL, TLC is continued. However, if LDL cholesterol is 160-189 mg/dL after an adequate trial of TLC, drug therapy is optional depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol)
- Multiple life-habit risk factors and emerging risk factors (if measured)
- 10-year risk approaching 10%. If LDL cholesterol is ≥190 mg/dL despite TLC, drug therapy should be considered to achieve the LDL goal of <160 mg/dL.

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol (≥160 mg/ dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥190 mg/dL after TLC. For persons whose LDL cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic follow-up, and control of other risk factors are needed.
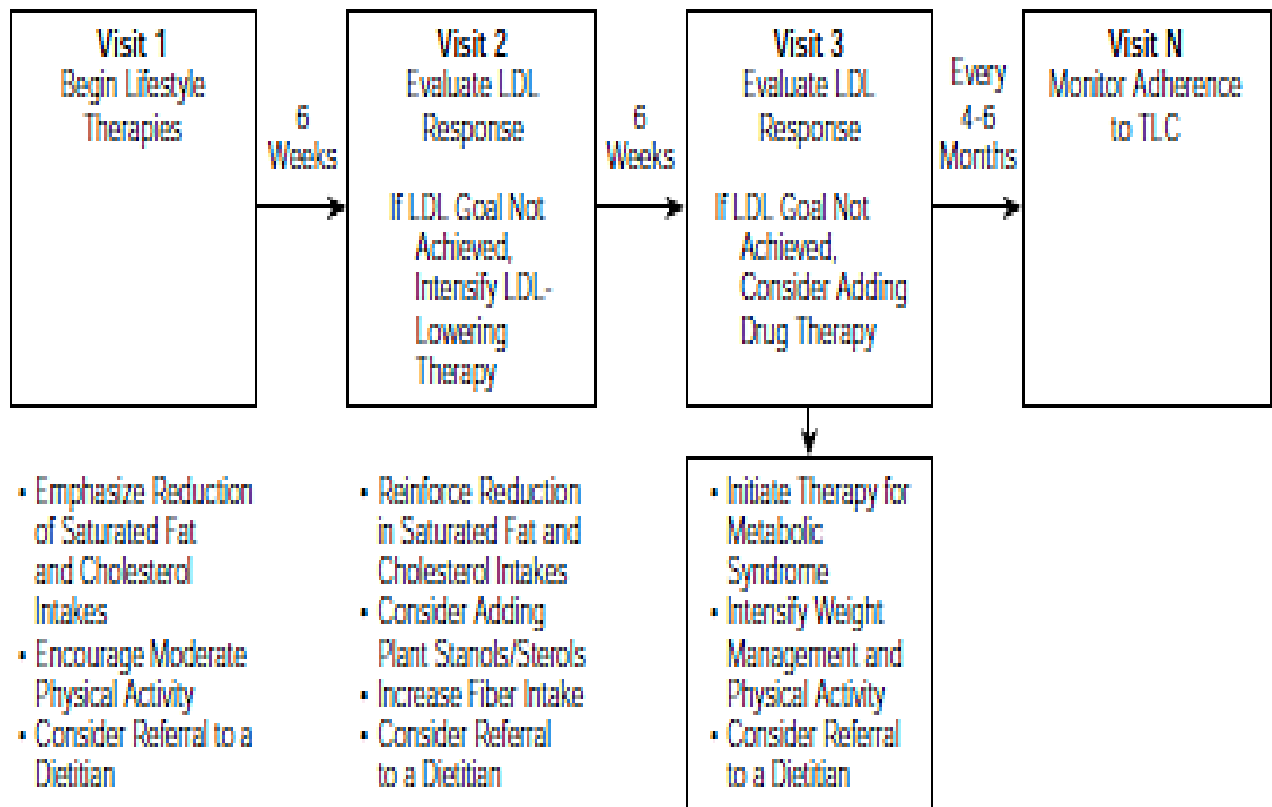
Therapeutic lifestyle changes in LDL-lowering therapy

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated therapeutic lifestyle changes (TLC). Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/d)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d)
- Weight reduction
- Increased physical activity.

A model of steps in TLC is shown in Figure 1.1.

Figure 1.1

Model of Steps in Therapeutic Lifestyle Changes (TLC)

Visit 1		Visit 2		Visit 3		Visit N
Begin Lifestyle Therapies	6 Weeks	Evaluate LDL Response If LDL Goal Not Achieved, Intensify LDL-Lowering Therapy	6 Weeks	Evaluate LDL Response If LDL Goal Not Achieved, Consider Adding Drug Therapy	Every 4-6 Months	Monitor Adherence to TLC
• Emphasize Reduction of Saturated Fat and Cholesterol Intakes • Encourage Moderate Physical Activity • Consider Referral to a Dietitian		• Reinforce Reduction in Saturated Fat and Cholesterol Intakes • Consider Adding Plant Stanols/Sterols • Increase Fiber Intake • Consider Referral to a Dietitian		• Initiate Therapy for Metabolic Syndrome • Intensify Weight Management and Physical Activity • Consider Referral to a Dietitian		

To initiate TLC, intakes of saturated fats and cholesterol are reduced first to lower LDL cholesterol. To improve overall health, ATP III's TLC Diet generally contains the recommendations embodied in the Dietary Guidelines for Americans 2000. One exception is that total fat is allowed to range from 25%-35% of total calories provided saturated fats and *trans* fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise HDL cholesterol in persons with the metabolic syndrome. In accord with the Dietary Guidelines, moderate physical activity is encouraged. After 6 weeks, the LDL response is determined; if the LDL cholesterol goal has not been achieved, other therapeutic options for LDL lowering such as plant stanol/sterols and viscous fiber can be added. After maximum reduction of LDL cholesterol with dietary therapy, emphasis shifts to management of the metabolic syndrome and associated lipid risk factors.

The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance LDL lowering and will provide other health benefits including modifying other

lipid and nonlipid risk factors. Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative (1998). Additional risk reduction can be achieved by simultaneously increasing physical activity. At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy*, which is the term for the nutritional intervention and guidance provided by a nutrition professional.

Drug therapy to achieve LDL cholesterol goals

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol. When drugs are prescribed, attention to TLC should always be maintained and reinforced. Some cholesterol-lowering agents are currently available over-the-counter (OTC) (eg, nicotinic acid), and manufacturers of several classes of LDL lowering drugs (eg, statins, bile acid sequestrants) have applied to the Food and Drug Administration (FDA)to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responsesandside effects.

Secondary Prevention: Drug Therapy for CHD and CHD Risk Equivalents

For persons with CHD and CHD risk equivalents, the goal is to attain an LDL cholesterol level of <100 mg/dL. The cut-points for initiating lifestyle and drug therapies are shown in Table 4. Most patients with CHD will need LDL lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification. In patients admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coro-

nary event or procedure should be discharged on drug therapy if the LDL cholesterol is ≥130 mg/dL. If the LDL is 100-129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that LDL cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24 to 48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold that drug therapy should be initiated whenever a patient hospitalized for a CHD-related illness is found to have an LDL cholesterol <100 mg/dL. Initiation of drug therapy at the time of hospital discharge has 2 advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient follow-up is often less consistent and more fragmented.

LDL-Lowering Drug Therapy for Primary Prevention

Table 4 shows the cut-points for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in Figure 1.2. When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (Figure 1) will typically be the visit to initiate drug treatment. Even if drug treatment is started, TLC should be continued. As with TLC, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason, an LDL lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be evaluated about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid. After 12 weeks of drug therapy, the response to therapy should again be assessed. If the LDL cholesterol goal is still not achieved, consideration can be given to further intensifica-

tion of drug therapy. If the LDL goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for LDL cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

Figure 1.2.

Progression of Drug Therapy in Primary Prevention
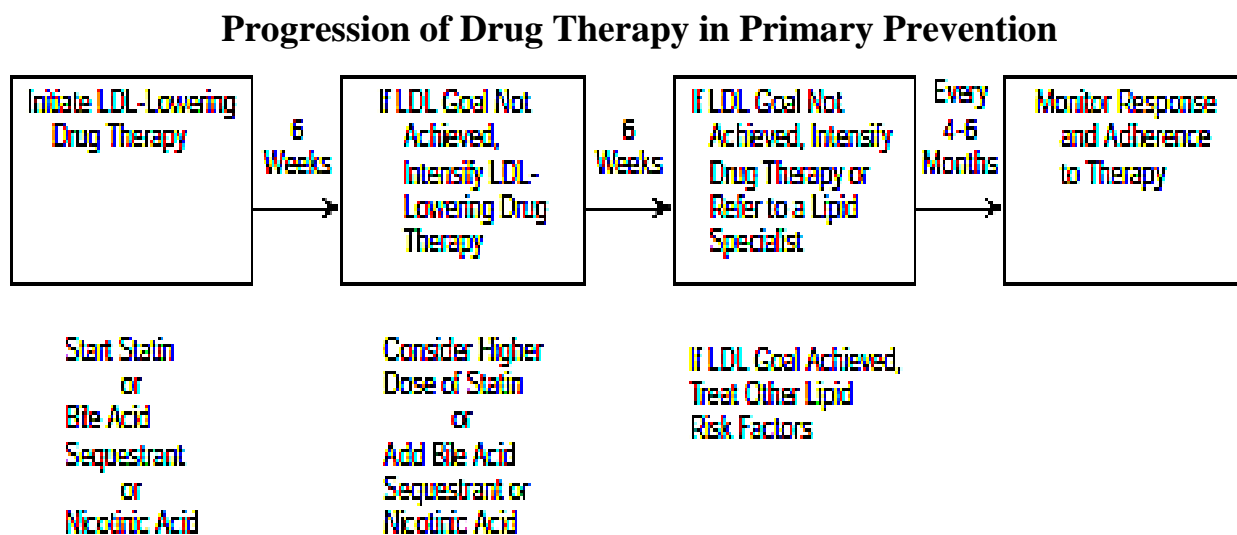
Benefit beyond LDL lowering: the metabolic syndrome as a secondary target of therapy

Evidence is accumulating that risk for CHD can be reduced beyond LDL lowering therapy by modification of other risk factors. One potential secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance. The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for CHD at any given LDL cholesterol level. For purposes of ATP III, the diagnosis of the metabolic syndrome is made when 3 or more of the risk determinants shown in Table 1.5 are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice. Management of the metabolic syndrome has

a 2-fold objective: (1) to reduce underlying causes (ie, obesity and physical inactivity) and (2) to treat associated nonlipid and lipid risk factors.

Clinical Identification of the Metabolic Syndrome

Risk factor	Defining level
Abdominal obesity (waist circumference)	Men >102 cm (>40 in) Women >88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	Men >40 mg/dL Women >50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

Management of Underlying Causes of the Metabolic Syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, which will effectively reduce all of these risk factors. Therefore, after appropriate control of LDL cholesterol, TLC should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight Control. In ATP III overweight and obesity are recognized as major, underlying risk factors for CHD and identified as direct targets of intervention. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the clinical guidelines of the Obesity Education Initiative.

Physical Activity. Physical inactivity is likewise a major, underlying risk factor for CHD. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low-density lipoprotein (VLDL) levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the US Surgeon General's Report on Physical Activity.

Specific Treatment of Lipid and Nonlipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and non-lipid risk factors of the metabolic syndrome will reduce CHD risk. These include treatment of hypertension, use of aspirin in patients with CHD to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low HDL cholesterol as discussed below under "Management of Specific Dyslipidemias."

Management of Specific Dyslipidemias

Very High LDL Cholesterol (>190 mg/dL). Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy.

Elevated Serum Triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD. Factors contributing to elevated (higher than normal)triglycerides in the general population include obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high-carbohydrate diets (<60% of energy intake), several diseases (eg, type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (eg, corticosteroids, estrogens, retinoids, higher doses β-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia). In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150-199 mg/dL
- High triglycerides: 200-499 mg/dL

• Very high triglycerides: ≥500 mg/dL (To convert triglyceride values to mmol/L, divide by 88.6.)

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called *remnant lipoproteins*. In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL+VLDL cholesterol (termed *non-HDL cholesterol* [total cholesterol−HDL cholesterol]) as a secondary target of therapy in persons with high triglycerides (≥200 mg/dL). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for LDL cholesterol (Table 1.6) on the premise that a VLDL cholesterol level ≤30 mg/dL is normal.

Table 1.6

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for 3 Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) risk factors and 10-year risk ≤20%	<130	<160
0-1 Risk factor	<160	<190

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with borderline high or high triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are borderline high (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For high triglycerides (200-499 mg/dL), non-HDL cholesterol becomes a secondary target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL cholesterol goal. There are 2 approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; second, nicotinic acid or fibrate can be added, if

used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering VLDL cholesterol.

In rare cases in which triglycerides are very high (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low-fat diets (<15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to, 500mg/dL should attention turn to LDL lowering to reduce risk for CHD.

Low HDL Cholesterol. Low HDL cholesterol is a strong independent predictor of CHD. In ATP III, low HDL cholesterol is defined categorically as a level <40 mg/dL, a change from the level of <35 mg/dL in ATP II. In the present guidelines, low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD. Low HDL cholesterol levels have several causes, many of which are associated with insulin resistance, i.e., elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette smoking, very high carbohydrate intakes (.60% of calories), and certain drugs (eg, β-blockers, anabolic steroids, progestational agents).

ATPIII does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined earlier. Also, if triglycerides are ,200 mg/dL (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be

considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

Diabetic Dyslipidemia. This disorder is essentially atherogenic dyslipidemia in persons with type 2 diabetes. Although elevated triglycerides, low HDL cholesterol, or both are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when LDL cholesterol is $130 mg/dL, most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with TLC to achieve the LDL goal. When LDL cholesterol levels are in the range of 100-129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥200 mg/dL, non-HDL cholesterol becomes a secondary target of cholesterol lowering therapy. A variety of factors, including concomitant illnesses, general health status, and social issues, may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-Aged Men (35-65 Years). In general, men have a higher risk for CHD than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

Women Aged 45-75 Years. In women, onset of CHD generally is delayed by some 10 to 15 years compared with that in men; thus, most CHD in women occurs after age 65 years. All risk factors contribute to CHD in women, and most premature CHD in women (>65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the sex difference in risk for CHD

reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce CHD risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, ATP III's general approach is similarly applicable for women and men. However, the later on- set of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older Adults (Men 65 Years and Women .5 Years). Overall, most new CHD events and most coronary deaths occur in older persons (≥65 years). A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention, TLC is the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger Adults (Men 20-35 Years;Women 20-45 Years). In this age group, CHD is rare except in those with severe risk factors, eg, familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age. Thus, risk factor identification in young adults is an important aim for

long-term prevention. The combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL cholesterol levels of ≥130 mg/dL, TLC should be instituted and emphasized. Particular attention should be given to young men who smoke and have a high LDL cholesterol (160-189 mg/dL); they may be candidates for LDL-lowering drugs. When young adults have very high LDL cholesterol levels (≥190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require LDL-lowering drugs in combination (eg, statin+bile acid sequestrant).

Racial and Ethnic Groups. African Americans have the highest overall CHD mortality rate and the highest out of hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for CHD, this evidence did not appear sufficient to lead the ATP III panel to modify general recommendations for cholesterol management in these populations.

Adherence to LDL-lowering therapy

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed to attain the highest possible levels of CHD risk reduction.

Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, clinicians, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention.

CHAPTER 2
STABLE CORONARY ARTERY DISEASE: RECOGNITION, CLINICAL ASSESSMENT, DIFFERENTIAL DIAGNOSIS, PREVENTION AND CONTAMPORARY MANAGEMENT

Foreword

The prevalence of occult atheromatous coronary disease among industrialized communities is so high that the incidental finding of coronary disease on pathologic examination is the norm rather than the exception. Thus, most individuals with non-obstructive coronary arterial disease are asymptomatic and manifest no clinical signs nor symptoms of the disease process. This guideline focuses on chronic stable coronary disease manifest through symptoms, clinical signs, or cardiac complications.

Chronic stable angina is the most common symptomatic manifestation of obstructive coronary artery disease. Although myocardial oxygen supply "on demand" imbalance may result in angina in the absence of detectable atheromatous coronary artery disease, the vast majority of angina occurs in the presence of obstructive coronary artery plaques. However, the threshold for provoking angina and the severity of symptoms depend on a variety of factors that influence loading conditions, oxygen demand, and cellular cytoprotective pathways because myocardial ischemia is more prevalent than symptomatic angina and the threshold for provoking symptoms varies within and between patients. Rather than an isolated condition, chronic stable angina should be regarded as a symptomatic manifestation of predominantly obstructive coronary artery disease and a relatively stable interlude in the pathophysiology of progression of atheromatous coronary artery disease.

Despite the absence of symptoms and clinical manifestations early in the progression of coronary disease, markers of the disease process intermediate phenotypes may be detectable biochemically and by noninvasive and invasive testing and prognosis may be altered by interventions that aim to mitigate the progression of atheroma.

Prevalence and Incidence of Angina

The elegant description by William Heberden in 1768 captures the key features of angina: a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, the sense of

strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris. Those who are afflicted with it are seized while they are walking (more especially if it be uphill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes. Angina is not extremely rare: it affects approximately 3.1 million men and 3.3 million women in the United States (overall, 3.8% of the population) and there are an additional 400,000 new cases each year. The prevalence of angina rises markedly with age (21.1% in men, 13.7% in women 65 to 69 and 27.3% and 24.7%, respectively, for men and women 80 to 84 years of age). Thus, angina is highly prevalent especially in the elderly, has a major impact on lifestyle and quality of life, and imposes a major financial burden on the individual and a huge socioeconomic impact on the community.

Pathophysiology of Angina

Cardiac ischemic pain is transmitted via sensory afferents located in the coronary vessels and myocardium. These afferents are sensitive to both stretch and by local expression of specific chemical stimuli. It has been categorized cardiac ischemic pain into three components: (a) a diffuse visceral component, (b) a better defined somatic component conforming to a distribution by dermatomes, and (c) an interpretive component modulated by psychological factors. Pain-producing stimuli traveling through afferent nerve endings converge with others from the same dermatome on the same dorsal horn spinal neurons. Cardiac afferents distributed from the first to the fourth thoracic spinal neurons interact with other afferents and descending signals from supraspinal sources, then ascend to the thalamus and from thence to the cortex, where the decoding is processed by a complex collage of physical, emotional, and other factors.

The symptomatic discomfort that represents angina pectoris usually reflects underlying coronary atherosclerosis sufficient to reduce maximal blood flow during exercise (Table 2.1). Whereas fixed segmental coronary stenosis (e.g., >50% diameter stenosis) may prevent sufficient myocardial blood flow to meet the increased oxygen

requirements imposed by physical exercise; changes in vascular tone also modulate the threshold for ischemia. Failure of flow mediated dilation is due to deficient endothelial-dependent relaxation and is associated with the diffuse nature of coronary artery disease, even in the absence of stenotic atheromatous lesions. Thus, angina may result from exercise-induced coronary vasoconstriction of noncritically narrowed coronary arteries and imbalance between oxygen supply and demand.

Table 2.1.

Causes of Anginal Chest Pain

Coronary arterial disease	Vascular disorders	Other cardiac and systemic disorders	Precipitating angina
Fixed obstructive coronary disease	Variant angina	Aortic stenosis	Anaemia
Coronary disease with dynamic flow limitation	Coronary vasospasm (Printzmetal angina)	Hypertrophic cardiomyopathy	Thyrotoxicosis
Microvascular angina (Syndrome X)	Syndrome X (without obstructive vascular disease)	Hypertensive heart disease and left ventricular hypertrophy	High-output states (e.g., arterio-venous shunts)
		Severe pulmonary hypertension and right ventricular hypertrophy	
		Mitral valve prolapse	

Mental or physical stress can precipitate angina pectoris and ischemia; mental stress is mediated by sympathetic activation, with a commensurate increase in myocardial oxygen requirements resulting from tachycardia, hypertension, and increased contractility. This exerts a double jeopardy on the ischemic myocardium by also reducing regional coronary flow. Failure of endothelial-dependent epicardial coronary vasodilatation is evident during mental stress in patients with stable angina, and, vasoconstriction of coronary resistance vessels may be present. Several neurohumoral factors contribute including serotonin, neuropeptide Y, norepinephrine, angiotensin II, thromboxane A_2, endothelin, and arginine vasopressin. As many as one of five stable angina patients have features of recent injury and/or repair in their culprit coronary lesions. Aggregation and activation of platelets can contribute to the alterations in vascular tone.

Stable Angina: A Symptom Complex

Most patients with stable angina describe retrosternal chest discomfort or distress, rather than pain. Anginal discomfort is sometimes characterized as heaviness, burning, tightness, or a choking sensation. It is commonly felt in the center of the chest, characteristically gestured with a clenched-fist or the flat of the hand across the sternum. In some patients, it is exclusively located outside the chest, in the arms, shoulders, back, jaw, or epigastrium. Patterns of anginal radiation are associated with severe ischemia and can spread from the chest to the neck, shoulders, arms (usually left), and jaw. Anginal equivalents characterized by dyspnea, profound fatigue, weakness, or syncope may occur in the absence of any discomfort. Ischemic symptoms during stable angina are usually of brief duration, persisting for 3 to 5 minutes, and are typically relieved by rest, dissipation of emotional distress, or the administration of nitroglycerin. Typically, the symptoms are produced by vigorous physical activity or emotional distress, and the threshold at which they occur may be lowered by exposure to cold weather, by smoking a cigarette, or after ingestion of a meal. Some patients experience warm-up angina (possibly a form of ischemic preconditioning) such that they experience angina much more readily on initiating exercise, than after the episode of angina. After pausing for the initial episode of angina to dissipate, they are able to continue for a sustained time at the same or even an accelerated pace. Warm-up angina is evident in approximately 20% of patients; hence, the second exertional effort is predictably better than the first if there is separation of at least 2 to 5 minutes between them. However, if the second effort is initiated later than 30 to 60 minutes after the first, the improvement disappears. It has been suggested a patho-physiologic link triggered by favorable adaptive myocardial metabolic changes that result in less of a decline in high-energy phosphate and less lactate production despite recurrent ischemia. Experimental insights into the phenomenon of ischemic preconditioning have demonstrated changes in mitochondrial K_{ATP} channel function, leading to reduced requirement for oxygenated substrate and attendant reduction in myocardial oxygen consumption.

Angina is traditionally categorized into four grades based on the Canadian Cardiovascular Society grading scale. In class I, patients experience angina only with strenuous or protracted physical activity; those in class II experience only slight limitation with vigorous physical activity such as walking up a hill briskly. Patients in class III have marked limitation, with symptoms during the activities of everyday living, and those in class IV have the inability to perform the activities of daily living because of symptoms as well as angina that may occur at rest. This classification does not address changes in the pattern or frequency of angina (including the development of unstable angina) or take into account the warm-up effect or the self-imposed alteration in activities of daily living that may subtly modify symptomatic status.

Silent Ischemia

The chronologic sequence of events during ischemia begins with diminished myocardial perfusion and is followed by diminished diastolic and systolic left ventricular function, abnormal myocardial lactate metabolism, electrocardiographic (ECG) changes, and then finally symptoms of angina pectoris. Most ischemic episodes in patients with stable angina (>75%) are clinically silent, and despite symptomatic control of angina, a substantial proportion (40% of patients with stable angina) continue to demonstrate ischemia on ambulatory monitoring.

Impairment of contractile function may persist for an extended period of time (60-120 minutes after exercise-induced angina) despite abrupt normalization of hemodynamic and ECG parameters. It has been demonstrated the delay in return of contractile performance despite normal perfusion after the development and relief of exertional angina (myocardial stunning), in the context of severely obstructive coronary artery disease.

Syndrome X

Cardiac syndrome X represents a heterogeneous group of disorders best characterized by a reduced capacity of the coronary circulation to augment flow in the face of an increase in oxygen demand. Abnormalities of coronary vasomotor tone and angina, or angina-like chest pain may occur in the presence of angiographically normal coronary arteries. In addition, about 25% of patients with stable angina have coronary

lesions on angiography that do not alter exercise-induced coronary flow. Evidence for myocardial ischemia in such patients has been demonstrated by reversible perfusion defects with thallium scintigraphy and transient impairment of global and regional left ventricular function by radionuclide ventriculography. Survival in patients with syndrome X is not significantly impaired in comparison with age- and gender-matched controls.

Prinzmetal's Variant Angina

Focal coronary spasm has been demonstrated as a mechanism for variant angina based on the association of transient ST elevation concurrent with symptoms and localized myocardial perfusion and functional abnormalities. This uncommon but well-recognized syndrome is evident in up to 2% of patients presenting with chest pain undergoing invasive study. It is usually associated with underlying fixed coronary obstruction, but a substantial cohort may have angiographically normal coronary arteries or minimally evident disease.

Demographics and Outcome of Patients with Angina

Evaluation of a general outpatient population of 5,125 patients with stable angina enrolled by 1,266 primary care physicians in the United States demonstrates approximately equal gender distribution (mean age of women of 71 years and that of men of 67 years). In the Coronary Artery Surgery Study, 62% of women with definite angina had coronary disease compared with a much higher proportion (89%) of men. Most patients had more than one cardiovascular-related illness, usually systemic hypertension, hypercholesterolemia, prior infarction, heart failure, or diabetes. The majority perceived their health to be either poor or fair and had experienced at least two episodes of angina per week, and although more than 90% had angina with activity, nearly half also experienced angina at rest, highlighting the commonality of mixed angina. Recently, the 5-year outcome and risk characteristics of a trial population of patients with chronic ischemic heart disease was defined. The rate of death, nonfatal myocardial infarction (MI), or stroke varied almost 10-fold according to baseline risk characteristics (from 1% to 9%) (Table 2.2). Thus, estimating baseline

risk is critically important in weighing up the balance between risk and benefit of therapeutic interventions.

Risk Factors for Adverse Prognosis in Patients with Chronic Coronary Artery Disease

- Age: the likelihood of death or nonfatal ischemic event increases with age
- Smoking status
- Diabetes/glucose intolerance
- Previous myocardial infarction or stroke
- Recent episode of unstable angina or new-onset stable angina
- Coexisting heart failure or evidence of left ventricular dysfunction
- Coexisting risk factors for coronary artery disease, such as hypertension
- Frequent anginal symptoms: quiescent angina is associated with a reduced risk of death and cardiac ischemic events
- Renal dysfunction/creatinine elevation
- Elevated white cell count
- Male gender

New-onset angina, defined as occurring within 2 to 3 months of presentation, is associated with at least a doubling of the risk of nonfatal MI within the first year after onset. This accentuated risk over patients with chronic coronary disease appears in spite of a lesser extent of triple-vessel disease and a greater frequency of single-vessel disease than in patients with chronic stable angina.

African Americans, especially those born in the southern United States, have an excess of cardiovascular mortality compared with American whites. Less aggressive use of diagnostic procedures has been recorded in African Americans. Asian Indians living outside of India have an excess risk of MI (range, 2.5 to 5.0) and mortality for coronary artery disease (range, 1.5 to 3.0) compared with indigenous populations. Their disease is characterized by premature onset and a severe and diffuse nature such that it is less amenable to coronary artery bypass grafting (CABG) and more likely to lead to permanent disability. Factors promoting this more malignant course include increased triglycerides and lipoprotein(a) levels, low high-density lipoprotein (HDL) cholesterol levels, insulin resistance, and more prevalent diabetes occurring earlier in life. A consistent inverse relationship exists between indicators of socioeco-

nomic status and coronary artery disease. Although socioeconomic status is strongly and inversely linked to conventional risk factors such as cigarette smoking, hypertension, cholesterol, and obesity, it is likely to be an independent risk factor for cardiovascular disease.

Principles of Management

The clinical assessment of patients with angina pectoris should involve a systematic review of cardiac and extracardiac factors that might contribute to the genesis of symptoms. Hence, cardiovascular factors such as hypertension, left ventricular hypertrophy, aortic and other valvular disease, and arteritis must be considered. Important contributory systemic illnesses such as anemia, thyrotoxicosis, renal disease, chronic volume overload, and high-output states need identification. Homocysteinuria (estimated prevalence of 1% to 2% of the population in a heterozygous state) has been found to be associated with symptomatic coronary artery disease. However, correction of elevated homocysteine with folic acid does not appear to improve outcome.

Identification is required of cardiac and systemic factors that support the clinical suspicion of coronary disease (lipid profiles; hypertension with signs of target organ damage; microalbuminuria; concomitant vascular disease in extracranial neck vessels, abdominal aorta, or peripheral arteries). Left ventricular dysfunction and elevated left ventricular filling pressure may, uncommonly, be accompanied by a presystolic fourth heart sound, cardiomegaly, mitral regurgitation, or paradoxical splitting of the second sound. However, most commonly findings on physical examination of a patient with chronic stable angina are normal unless signs of the contributory illnesses or cardiac complications are present.
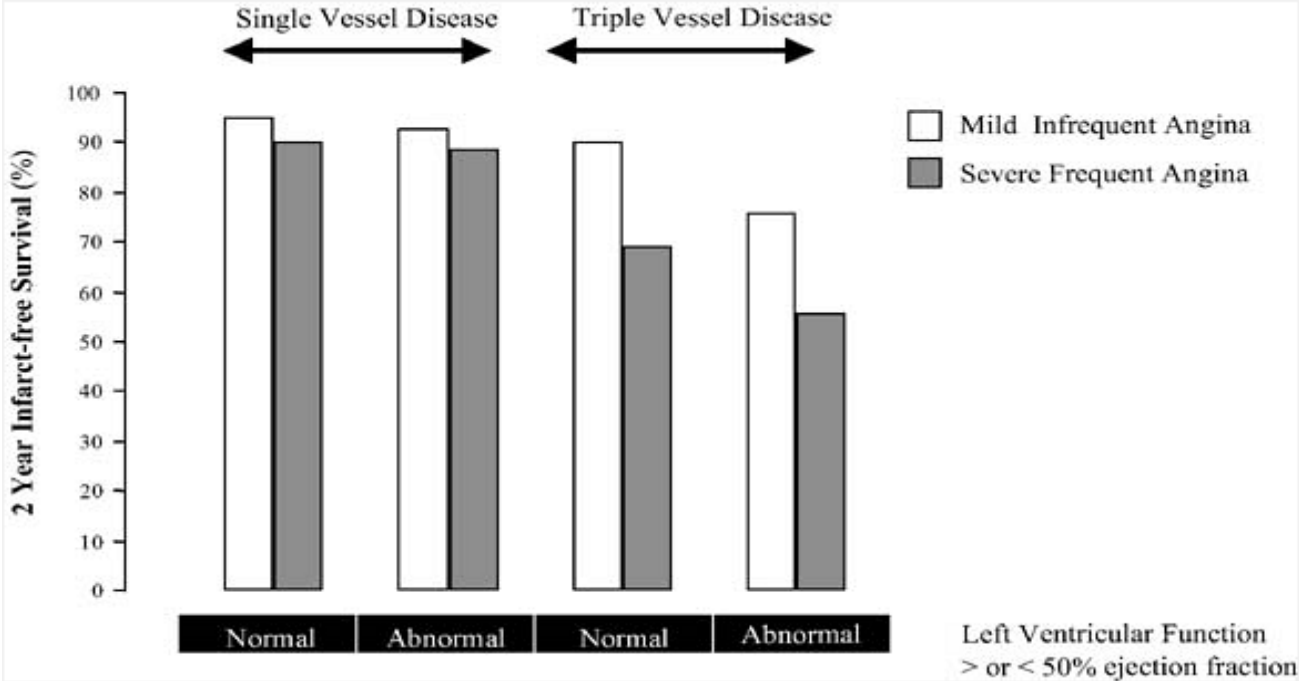
Diagnostic Tests

The ECG at rest is commonly normal in patients with angina pectoris, but it can demonstrate evidence of prior infarction or with persisting ST-segment elevation, aneurysm, T-wave change, intraventricular conduction defects, and atrial abnormalities may also be evident. ECG observations captured during an episode of angina permit evaluation of the location and extent of ECG changes. When the total amount of ST-segment change is extensive (>12 mm), there is a high positive predictive ac-

curacy for the detection of three-vessel or left main coronary disease. Frequency of angina, especially with dysfunction, predicts three-vessel coronary disease (*Figure 2.1*).

Figure 2.1.
Infarction-free survival (2 year) of patients with angina pectoris according to angina frequency, extent of coronary artery disease, and left ventricular function

The graded exercise stress test forms the cornerstone of diagnostic testing in patients with known or suspected stable angina pectoris. It should be performed in all such patients before undertaking more detailed or invasive procedures. At least four important potential objectives may be achieved by conducting this test:

- Correlation of patient symptoms with the presence of ischemia. When angina occurs with ischemic ECG changes, the prediction of coronary disease is more reliable but the predictive accuracy is lower in women.

- Definition of risk of future events. Those patients who are unable to exercise for more than 6 minutes on the Bruce protocol or demonstrate significant ischemia within this temporal window are at increased risk and merit further investigation. A summary of high-risk variables associated with unfavorable prognosis during exercise testing is shown in Table 3. A recent addition to this profile is the observation that a delay in the decrease in heart rate during the first minute after a graded exercise test was strongly predictive of mortality at 6 years.

- To assess the level of activity and heart rate / blood pressure product at which ischemia develops.

- To evaluate the efficacy of pharmacologic and/or revascularization therapy by assessing subjective and objective manifestations of ischemia.

Deriving an index or score from information relating to the duration of exercise, the extent of ST-segment deviation, and the reproduction of limiting or nonlimiting angina can provide a more precise estimation of prognosis. In various circumstances, more specialized noninvasive assessment is warranted. When an adequate exercise test is coupled with either myocardial nuclear imaging or two-dimensional echocardiography, it is a highly effective and diagnostically accurate test. Both exercise and the infusion of dobutamine induce ischemia through an increase in myocardial oxygen consumption mediated by augmented heart rate, systolic blood pressure, and contractility. However, exercise results in a 50% greater increment in heart rate systolic blood pressure product versus dobutamine in direct comparisons, probably accounting for its greater sensitivity in detecting coronary artery disease in some series.

Given that a high proportion of patients with stable angina have prior infarction and/or wall motion abnormalities at rest detected by two-dimensional echocardiography or resting perfusion defects, the question of whether such wall motion abnormalities possess residual myocardial perfusion and viability becomes highly relevant in therapeutic planning. Dobutamine enhancement of left ventricular dysfunction or inotropic stimulation evident after a ventricular premature beat is predictive of improvement in function with revascularization of the affected segment. Delayed imaging, 18 to 24 hours after thallium exercise scintigraphy, reveals that 50% or more of segments with apparently irreversible thallium defects on delayed imaging demonstrate isotope redistribution thought to be indicative of severe ischemia and predictive of favorable response to revascularization. Thallium reinjection at rest, 3 to 4 hours after stress imaging, has been demonstrated to provide similar information to delayed imaging in a more time-efficient and practical fashion. The use of thallium in this fashion to detect myocardial viability has been validated by concomitant metabolic im-

aging using positron emission tomography with oxygen-15 labeled water and exogenous glucose use with fluorine-18 labeled fluorodeoxyglucose.

By contrast, dipyridamole- and adenosine-induced hyperemia results in maldistribution of coronary flow by maximally dilating normal vascular segments, whereas those with fixed coronary stenosis already have near-maximal dilatation, resulting in image defects. Adenosine's rapid onset of action and extremely short half-life, as opposed to that of dipyramidole, circumvents the need for theophylline reversal of troublesome side effects such as bronchial constriction. Two-dimensional echocardiography performed before and immediately after exercise testing and continuously before, during, and after dobutamine infusion is used to detect new or worsening preexisting wall motion abnormalities. These findings show excellent concordance with the territory of the affected coronary vessel; they demonstrate prognostic value in patients with known or suspected coronary artery disease.

Perfusion imaging with thallium-201m or technetium-99m labeled radiopharmaceuticals (either sestamibi [MIBI] or tetrofosmin) provides visualization of myocardial blood flow. Injected immediately before cessation of exercise or pharmacologic stress, these agents can delineate relative differences in myocardial blood flow conforming to areas of myocardial ischemia. With thallium-201, a late image associated with redistribution of blood flow 3 to 4 hours after exercise can be obtained to assess reversibility of defects observed during exercise. By contrast, with the technetium-99m labeled MIBI, myocardial distribution is relatively fixed without significant redistribution; hence, imaging can be conducted for a few hours after the time of injection during pharmacologic or exercise stress. A second injection is necessary to characterize blood flow at rest. Perfusion is also useful in assessing ischemia in specific vascular segments when coronary disease has been established. Substantial data are available to support the role of myocardial perfusion imaging in more precisely defining prognosis; in this regard, a high-risk scan may be especially useful, and the characteristics of this finding are depicted in Table 2.3.

Table 2.3.

Features Associated with a Poor Prognosis and Indicative of Severe Disease

a. *Exercise ECG:*
- Inability to perform exercise ECG on account of limiting symptoms
- Poor maximal exercise capacity (less than stage 3 of the Bruce protocol)
- Early positive test (<3 min) or strongly positive test:
  - >1-mm ST-segment depression during stage 2 or less (Bruce protocol)
  - >2-mm ST-segment depression at any time
  - Downsloping ST depression
- Flat or lowered blood pressure response (fall or no rise from baseline)
- Delayed recovery or delayed decrease in heart rate on cessation of exercise
- Ventricular arrhythmia on exercise (rate >120/min)

b. *Radionuclide imaging:*
- Reversible radionuclide perfusion defect in more than one territory
- Large perfusion defect (>15% of ventricle)
- Presence of fixed and reversible perfusion defects
- Reduced radionuclide ejection fraction with exercise
- Increased lung uptake of radionuclide after exercise

Although coronary calcification has long been recognized as a marker of atherosclerosis, its clinical utility has been limited. The availability of electron beam (ultrafast) tomography has dramatically increased the sensitivity of coronary calcium detection. However, there may be marked intrapatient variability on repeat testing and its role remains controversial. An American College of Cardiology/American Heart Association consensus document concluded that in the test has proven to have a predictive accuracy approximately equivalent to alternative methods for diagnosing coronary artery disease but has not been found to be superior to alternative non-invasive tests.

Intravascular Imaging

Fiber-Optic Imaging (Angioscopy) Visualization of the physical appearance of atheromatous lesions, and in particular the detection of unsuspected plaque rupture events, has provided new information on the diffuse nature of coronary arterial disease. In particular, the detection of multiple vulnerable plaques in segments of coronary artery without detectable abnormality on angiography has led to key insights into the mechanisms of progression of acute coronary arterial disease. These findings suggest multiple sites of plaque disruption with associated platelet aggregation and

thrombosis. However, angioscopy remains a research tool and its focus is mainly in the field of acute coronary artery disease rather than stable ischemic syndromes.

Intravascular Ultrasound . High-resolution intravascular ultrasound (IVUS) has provided critically important observations that demonstrate the extent and distribution coronary artery disease and reveal the severity and eccentric nature of plaque lesions. These may be underestimated on angiography (Figure 2.2). Vascular remodeling results in extensive atheroma but relative preservation of the coronary arterial lumen until late in the disease process. IVUS has also provided insights into plaque composition, including the distribution and extent of lipid-rich plaques, extent of calcification, and thickness of the fibrous cap. All of these features provide evidence of susceptibility of atheromatous plaques to rupture, but validated outcome studies are required to demonstrate that interventions on such nonstenotic lesions alter clinical outcome.

Figure 2.2

Coronary angiography and IVUS: segment of vessel with dissection (see arrows on angiogram) and flow within the dissection cavity. IVUS showing stent struts (A) and dissection (B).
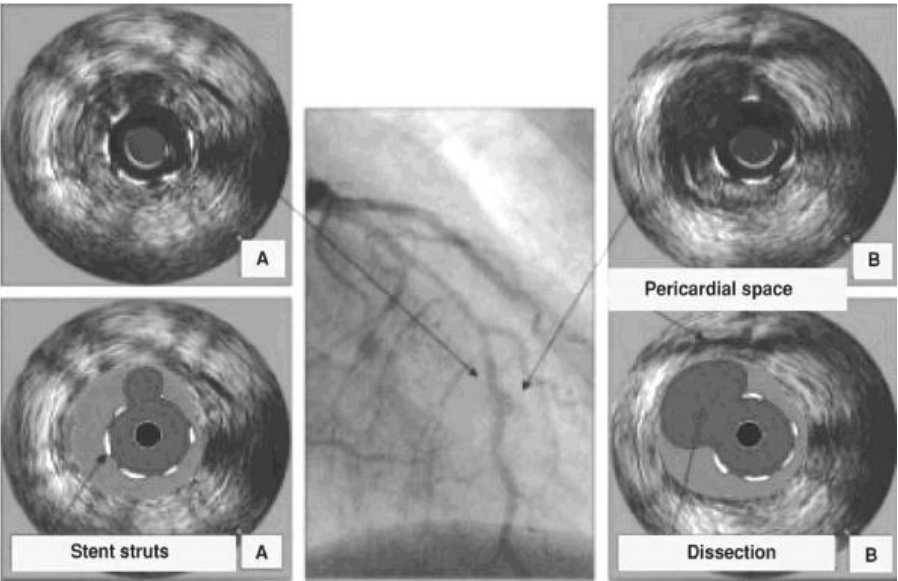
Optical Coherence Tomography Using light from an intravascular device, and having cleared red cells from the field of view, it is possible to obtain exquisite resolution of structures in the vascular wall. This technique has great potential as an experimental tool, but it may have limited clinical application on account of the need for a blood-free field and the fact that only limited segments of the coronary arterial tree are currently accessible with this device.

Magnetic Resonance Imaging ng (MRI) is emerging as the reference standard for clinical assessment of ischemia and for evaluation of myocardial viability. The exquisite structural information provided by either MRI or multislice CT. In addition to such structural information, MRI in conjunction with administration of a contrast agent (e.g., gadolinium chelate) can be used to detect perfusion abnormalities and viability. Perfusion measurements were first investigated based on tissue water content detected by MRI and evaluation of T_1 and T_2 signals. However, such assessment is not sufficiently reliable without the administration of MRI contrast material. First-pass imaging in the presence of a contrast agent allows the detection of impaired perfusion and can provide assessment of the physiologic significance of stenoses in different vascular beds.

An alternative approach involves the detection of reversible left ventricular contractile dysfunction using multiphasic MRI. Such regional dysfunction is associated with reversible ischemia (e.g., with dipyridamole stress). Sensitivity, specificity, and accuracy of 91%, 80%, and 90%, respectively, have been reported, and dobutamine stress MRI avoids the problems of poor acoustic windows in patients assessed with dobutamine stress echo.

In addition to assessing the volume of myocardial flow affected by decreased perfusion, late enhancement of gadolinium chelate allows the detection of reperfused but viable myocardium and the potential for distinguishing such zones from myocardium with impaired perfusion but without the potential for function recovery.

Thus, MRI imaging with the aid of MRI contrast agents can detect abnormalities in structure and function of the ventricle, estimate the volume of myocardium with reduced perfusion, and demonstrate potentially viable segments. For these reasons, MRI is emerging as the reference standard for the assessment of the impact of functional stenoses in coronary arteries.

Coronary Angiography . Selective coronary angiography is the most widely used diagnostic investigation to define the extent and severity of intrinsic coronary narrowing. In general, it should be performed in patients (a) when the diagnosis of coronary disease is important to establish yet remains in doubt after noninvasive assessment,

(b) when high-risk coronary disease is suspected based on the results of clinical and noninvasive evaluation, and (c) in non high-risk patients when significant symptoms persist despite adequate medical therapy or medical therapy is poorly tolerated. Coronary angiography is widely applied, but significant limitations need to be considered:

- Angiographically apparently normal vessels may have extensive nonstenotic coronary disease, as demonstrated histopathologically or with high-resolution IVUS.
- The physiologic importance of moderate and apparently similar stenoses may differ markedly (as demonstrated by measurements of coronary flow reserve).
- Standard coronary angiography does not assess the impact of changes in vascular tone.
- As a result of collateral development, angiographic appearances may underestimate or overestimate the impact of stenosis on myocardial perfusion.
- The angiogram does not provide insights into the histologic structure of stenotic lesions or the likelihood of plaque rupture.
- Disrupted endothelium or minor plaque fissures may precipitate signs and symptoms of non ST-elevation acute coronary syndrome and yet may be difficult to detect on coronary angiography.

Despite these limitations, coronary angiography provides key information on the extent and distribution of coronary stenoses and long-term survival. It may be combined with provocative testing with ergonovine maleate in patients with known or suspected Prinzmetal variant angina and may identify the location and extent of provokable coronary spasm. In patients without major anatomic narrowing and in the absence of Prinzmetal variant angina, vasoreactivity of lesions may be provoked by intravenous ergonovine in almost 20% of patients. Combined with IVUS to provide precise definition of not only the extent of coronary narrowing and the thickness and extent of atheroma in the coronary arterial wall.

Multislice CT (64 slice) can provide accurate detection of coronary stenosis with high negative predictive accuracy. It may facilitate rapid triage of patients with suspected cardiac pain.

Therapeutic Interventions

In chronic stable coronary disease, the goals of treatment are to relieve symptoms and reduce the risk of future cardiac events (including acute coronary syndrome,

heart failure, and death). Simultaneous rather than alternative approaches are required: these include lifestyle modification, management of risk factors, pharmacologic therapy, and coronary revascularization. All forms of intervention present some hazard and hence they should be instituted when the perceived benefits, in terms of improved symptoms and prognosis, outweigh the associated risks. The clinician, and the informed patient, need to institute an overall treatment strategy to minimize the impact of the disease throughout the remainder of the patient's life. Accurate assessment of prognostic risk is critically important in this regard.

Lifestyle and Risk Factor Modification are integral to treatment of patients with chronic stable coronary disease. They may provide both symptomatic and prognostic benefits and their impact may enhance mechanical or pharmacologic treatment and their lack of impact may substantially diminish potential benefits.

Smoking accounts for about one third of the excess risk of MI, and this is observed consistently across all geographic regions. Cessation of smoking is associated with major benefits and repeated brief and supportive advice should be given to all patients. Short-term nicotine replacement therapy should be offered to those individuals with a heavy consumption of tobacco (>10 cigarettes/d), because it is associated with up to a ninefold increased likelihood of success. The antidepressants bupropion and nortriptyline may aid long-term smoking cessation, but selective serotonin reuptake inhibitors such as fluoxetine do not. This suggests that these agents produce their beneficial effects independent of an antidepressant effect. Recent studies of a CB_1 cannabinoid receptor antagonist (rimonabant) suggest that smoking cessation may be enhanced by this approach. Challenges remain to avoid relapse in smokers who have successfully quit for a short time; supportive groups and counseling may enhance longer term abstention.

Dietary Interventions complements the use of lipid-lowering therapy, but on average a low-fat diet reduces serum cholesterol concentrations by only 5%, even in motivated individuals. Nevertheless, dietary modification may provide additional preventative benefits, such as those obtained from a Mediterranean-type diet or those high in (ω-3) polyunsaturated fatty acids of fish oils. It has been suggested that the

consumption of fruits and vegetables containing high levels of antioxidant vitamins or supplementation with vitamin E is protective against the development of coronary events. However, three large-scale multicenter randomized controlled trials demonstrated that low- or high-dose vitamin E supplementation has no effect on cardiovascular outcomes. Finally, modest alcohol consumption is associated with a reduced risk of coronary heart disease and should be limited to 21 to 28 units per week (1 U = 8 g of absolute alcohol) for a man and 14 to 21 units a week for a woman. Neither folic acid nor vitamin B_6 supplementation improves outcome and the combination may be associated with increased hazards of fatal or nonfatal stroke or MI.

Obesity. There are escalating levels of obesity, not only in Western societies, but also in other societies undergoing industrialization. These demographic changes have the potential for a major adverse impact on the incidence and prevalence of cardiovascular disease in the future. Obesity, and particularly abdominal obesity (increased waist-to-hip ratio), is associated with increased risk of MI. Abdominal obesity, and to a lesser extent increased BMI, is associated with the development of the metabolic syndrome characterized by obesity, insulin resistance, hypertension, and dyslipidemia. Novel therapeutic strategies may be able to reduce obesity and the metabolic syndrome. For example, cannabinoid type-1 receptor antagonism, when combined with a low-calorie diet, markedly enhances weight loss and improves many of the associated cardiovascular risk factors. Its role in obese patients with coronary heart disease has yet to be established. Despite the high prevalence of obesity, there have been no interventional trials to show that weight reduction in obese patients with chronic stable angina or coronary artery disease improves symptoms or outcome. However, it is reasonable to assume that weight reduction would reduce the frequency of anginal episodes and potentially improve prognosis.

Diabetes Mellitus. Good glycemic control is essential in all patients with diabetes mellitus because of the reduced risk of long-term complications, including coronary artery disease. Although there are no specific trials of diabetic control in patients with chronic stable angina, primary prevention trials and secondary prevention trials in patients after MI indicate that cardiovascular morbidity and mortality rates

are reduced with intensive hypoglycemic therapy regimens. Moreover, poor glycemic control at the time of presentation with MI is a poor prognostic sign. It has been suggested that metformin should be the first-line agent of choice in overweight patients with diabetes mellitus because it is associated with a decreased risk of diabetes-related end points, less weight gain, and fewer hypoglycemic episodes.

Symptomatic Therapy

Pharmacologic Therapy. No single class of antianginal drug has been shown to be superior to another in the reduction of anginal episodes, nor in reducing outcome events. However, because of the inferred secondary preventative benefits of β-blockers, they should be the first-line agents (Figure 2.3).

Figure 2.3

Flow diagram for the initial assessment and investigation of patients with chronic stable angina: differentiation of lower and higher risk.
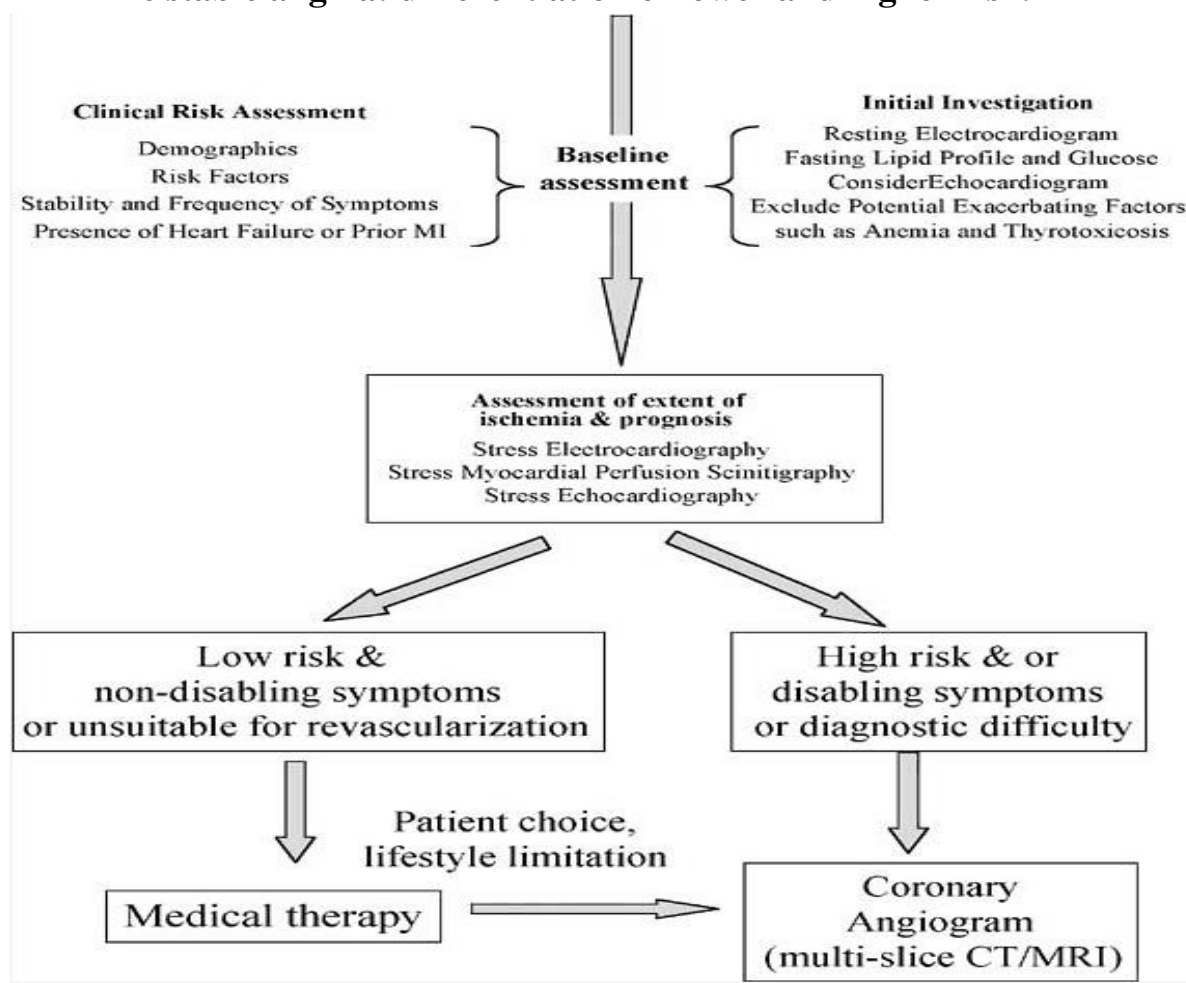
A meta-analysis suggests that β-blockers are better tolerated and may be more efficacious than calcium antagonists in the treatment of chronic stable angina.

If monotherapy does not control anginal symptoms, the introduction of a second antianginal agent provides significant but modest additional benefits. The combination of β-blockade and rate-limiting calcium antagonism may cause excessive bradycardia or heart block. However, this interaction is uncommon, and if there is concern, a long-acting dihydropyridine-type calcium antagonist should be coprescribed. There is no definitive evidence that triple or quadruple antianginal therapy produces further benefit beyond dual therapy.

β-Blockers

It had demonstrated that β-blocker therapy is efficacious in reducing symptoms of angina and episodes of ischemia and in improving exercise capacity. β-Blockers inhibit the β-adrenergic receptors of the myocardium to produce negative chronotropism and negative inotropism of the heart. The attenuation of the heart rate response to exercise and stress reduces the myocardial oxygen demand and severity of ischemia. They also prolong diastole, a major determinant of myocardial perfusion time.

There is no evidence to support the suggestion that one type of β-blocker is superior to another. However, the secondary preventive benefits of β-blockers may be lost where agents have intrinsic sympathomimetic action and the use of such agents should therefore be avoided.

True side effects from β-blocker therapy are not common (<10%), but include symptoms such as fatigue and lethargy. Because such symptoms are encountered in patients with stable coronary disease, a causative association should be established before permanent discontinuation of β-blocker therapy. Because of β-adrenergic receptor up-regulation in the presence of β-blockade, patients should not be rapidly withdrawn from therapy. This can cause an acute withdrawal syndrome and may even precipitate acute MI.

Calcium Antagonists

Patients who are intolerant of a β-blocker should be prescribed a rate-limiting calcium channel antagonist such as diltiazem or verapamil. However, other calcium channel antagonists and classes of antianginal agents are equally effective in relieving symptoms. It had been suggested that long-acting nifedipine has a neutral effect on

survival, MI, and stroke, but it reduces angina and the need for coronary angiography and revascularization. There is controversy as to whether calcium channel blockers can be used safely in patients with heart failure, but amlodipine has been shown to have a neutral effect on mortality rates in patients with heart failure.

Nitrates

Nitrates were the first form of antianginal drug and their mechanism of action is through the release of nitric oxide either indirectly (glyceryl trinitrate) by reactions with sulfhydryl groups, such as methionine or cysteine, or by interaction with plasma or cell membranes. The liberated nitric oxide causes endothelium-independent relaxation of vascular smooth muscle by increasing intracellular cyclic guanidine monophosphate. However, as with calcium antagonists, their use in severe aortic stenosis and hypertrophic obstructive cardiomyopathy should be avoided because of the potential to compromise coronary perfusion through peripheral vasodilatation and systemic arterial hypotension.

Acute Relief of Angina. Sublingual or buccal nitrates produce rapid and effective relief of acute anginal episodes. All patients should be provided with a sublingual nitrate preparation. Buccal preparations provide a more protracted release of nitrate, which is appropriate for prolonged activities that may provoke episodes of angina. Prevention of Anginal Episodes Long-acting nitrates, either oral or transdermal, provide effective relief of angina. Nitrates undergo extensive first-pass metabolism through hepatic glutathione reductases. Topical and transdermal nitrate preparations are able to bypass such metabolism, and some nitrate preparations, such as isosorbide mononitrate, undergo less extensive hepatic metabolism and have better bioavailability and more prolonged action. One of the main limitations of prophylactic nitrate use is the development of tolerance and this phenomenon requires a daily nitrate-free period.

Potassium Channel Agonists. This class of antianginal agents has nitrate like vasodilatory propetics and potential cardioprotective actions. Potassium channel openers act on the ion channels of vascular smooth muscle cells and cardiac myocytes. Consequently, they may enhance ischemic preconditioning and improve the myocardial response to an ischemic insult. Nicorandil is the only preparation of this class in

clinical use. It is effective in the treatment of angina and has both nitrate and potassium channel-opening properties. However, there is no evidence that potassium channel openers are superior to other classes of antianginal agents.

If-blockers. If-blockers (ivabradine) is reserved as all clinical situation when control for heart rate is not adequate or β-blockers are contraindicated. Ivabradine can be use as monotherapy and as adding to combined therapy.

Coronary Revascularization. Although periprocedural risks have diminished, both CABG and percutaneous coronary intervention (PCI) carry a measurable early morbidity and mortality risk that exceeds the early risks of medical therapy in patients with chronic stable ischemic disease. These risks have diminished over time. Revascularization should be instituted if the perceived benefits, in terms of improved symptoms and prognosis, are likely to outweigh the associated risks. This is particularly important when the therapy is for symptomatic rather than prognostic benefits, such as with PCI or CABG for one-vessel disease. Selection of the appropriateness and the type of revascularization procedure is heavily influenced by technical aspects of the coronary anatomy, as well as by factors such as comorbidity and patient preference. Patients vary greatly in what is considered an acceptable level of symptoms, optimal medical therapy, and tolerable drug side effects. Thus, the need for, and type of, coronary revascularization should take into account both objective clinical criteria and the patient's symptoms and informed choices.

Several factors must also be considered when evaluating the applicability and evidence of the clinical usefulness of coronary revascularization strategies. The major randomized trials are based on highly selected patient groups and may not reflect the broad mix of patients who present to the clinic. Many datasets reported in the literature are outdated; medical therapy and surgical techniques (e.g., use of arterial conduits) have improved substantially. In addition, the early failure and restenosis rates in PCI have been reduced with coronary stents, drug-eluting stents, and adjuvant antiplatelet agents.

Percutaneous Coronary Intervention. The success and complication rates of PCI are influenced by factors including age, gender, clinical presentation, left ventricular

function, comorbidity (e.g., diabetes mellitus), and the experience of the operator. The nature of the target lesion is a key determinant of outcome. For example, short discrete lesions on straight segments of artery that do not compromise major branches are ideal for PCI. Lesions that are less suitable include chronic total occlusions, long lesions, calcifications, those on complex tortuous segments, flexures, or complex branching vessels.

Complications. The most common serious complication of PCI is acute occlusion of the dilated vessel owing to dissection or thrombosis. Other complications include vascular damage, thromboembolism (including stroke), and hemorrhage due to anticoagulant therapy. Elective PCI is associated with overall angiographic success rates of 96% to 99%; transmural MI rates of 1% to 3%, emergency coronary bypass surgery rates of 0.2% to 3.0%, and unadjusted in-hospital mortality rates of 0.5% to 1.4%. The reported risk of angiographic restenosis for isolated balloon angioplasty (without stenting) is 25% to 40. Restenosis occurs predominantly within the first 3 to 6 months does not always lead to recurrent symptoms, and has been dramatically reduced by the widespread use of intracoronary stents, particularly drug-eluting stents. Current rates of restenosis with drug-eluting stents are 5% to 10%.

Feasibility of PCI has been established in multivessel angioplasty (>2 vessels), but no definitive outcome data are available comparing PCI and CABG with current technology in multivessel disease. The absence of definitive outcome data for multivessel PCI versus surgery leads to the following recommendation: PCI is an appropriate alternative to CABG in patients with symptom-limiting angina despite medical treatment who have suitable one- or two-vessel disease without a significant proximal LAD stenosis.

Culprit Lesion Percutaneous Coronary Intervention. When the purpose of revascularization is relief of angina, PCI of the lesion that is thought to be responsible for the patient's symptoms may be undertaken, even with multivessel disease. This strategy, culprit lesion PCI, may be appropriate in symptomatic patients with multivessel coronary artery disease who have an exceptionally severe stenosis and many minor lesions or in patients unsuitable for CABG because of comorbid conditions.

Culprit lesion PCI is also a reasonable option if surgical revascularization with CABG would be incomplete and therefore may not confer prognostic benefit.

Percutaneous Coronary Intervention After Coronary Artery Bypass Grafting

Five years after undergoing CABG, 50% of patients will have redeveloped angina, and by 12 years, 30% will have undergone repeat revascularization . However, these data do not reflect the current high use and improved patency of arterial conduits. Repeat CABG is associated with a higher risk and a lower likelihood of benefit than the initial intervention. However, complications were significantly lower with PCI, and survival was similar at 1 and 6 years of follow-up. In patients with limiting angina despite previous CABG and medical therapy when technically feasible, an initial strategy of PCI may be preferred to repeat CABG.

Stents. Intracoronary stents were employed initially to minimize the risk of acute or threatened vessel occlusion. They enhanced vessel patency and led to a reduction in the need for emergency CABG after PCI. It has been suggested that elective stent-in*g* being associated with improved procedural and clinical outcomes and a reduction in the need for subsequent revascularization procedures. The clearest evidence has come from PCI procedures for higher risk lesions, namely chronically occluded arteries, saphenous vein grafts, proximal LAD stenosis, and restenosis after prior PCI, and when conventional PCI has produced a suboptimal result.

Importantly, after stent implantation, patients have less restenosis and greater MI-free survival and reduced needs for repeated coronary intervention. To reduce the incidence of stent thrombosis and restenosis, coated stents have been developed (e.g., with heparin), but these stents had limited benefits over bare metal stents. In contrast, a major development involves drug-eluting stents that contain antiproliferative agents. Sirolimus is a macrolide antibiotic with antifungal, immunosuppressive, and antimitotic properties that has been used in the prevention of renal transplant rejection. Sirolimus-coated stents were associated with a dramatic reduction in the incidence of in-stent restenosis, with failure of target vessel revascularization falling. Paclitaxel is a microtubule-stabilizing agent with potent antitumor activity that has also been successfully used in stent coatings with similar reductions in in-stent restenosis.

Antiplatelet Therapy for Percutaneous Coronary Intervention

Aspirin therapy is associated with a 50% reduction in the rate of vascular occlusion after PCI and compared with conventional anticoagulant therapy, the combination of clopidogrel (75 mg OD) and aspirin (100 mg BID) was superior to aspirin alone or aspirin in combination with warfarin. Clopidogrel avoids the adverse hematologic risks of ticlopidine and observational data indicate that it is as efficacious as ticlopidine in the prevention of stent thrombosis; it is currently the thienopyridine of choice in this setting.

Secondary Prevention. Certain lifestyle interventions (e.g., smoking cessation) and risk factor modifications have been shown to improve the prognosis of patients with ischemic heart disease, but others remain unproven or have neutral effects. The major secondary prevention therapies are associated with very modest rates for hazard (e.g., bleeding risk with aspirin) and side effects, (e.g., with statin therapy) and the hazards are outweighed by benefits in outcome (Figure 2.4).

Figure 2.4

Secondary prevention of stable CAD

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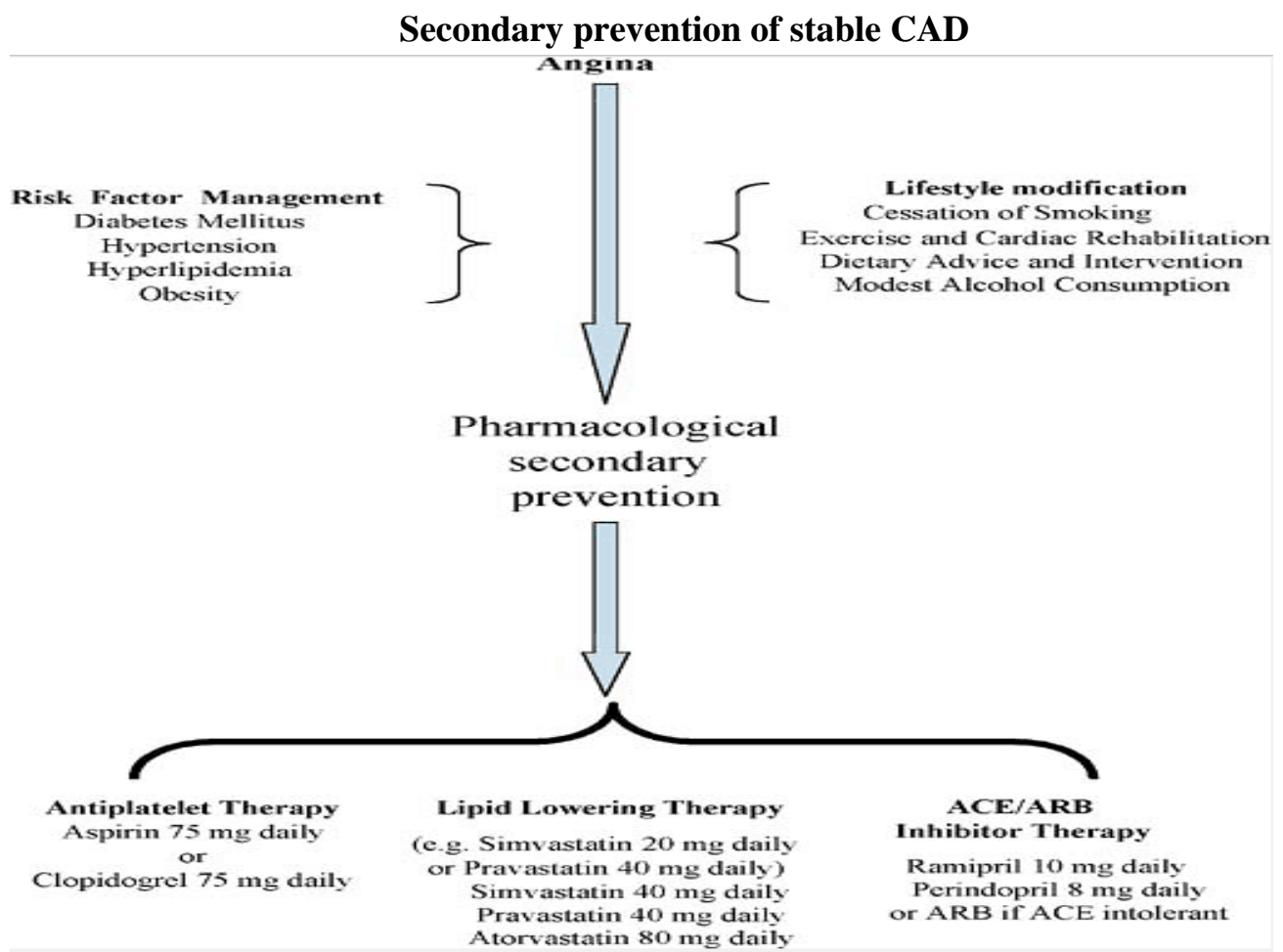
Antiplatelet Therapy. Aspirin has been described as a weak inhibitor of platelet aggregation, based on in vitro responses to specific agonists. However, it substantially reduces cardiovascular events across the spectrum of vascular risk. It is a simple and effective treatment in patients with chronic stable angina. Long-term aspirin (<100 mg/d) is recommended to reduce the risk of death and MI in all patients with chronic ischemic heart disease. Clopidogrel is indicated as an alternative to aspirin in patients with aspirin intolerance. There is no outcome evidence to support the practice of clopidogrel treatment when administered at the time of PCI. Clopidogrel is beneficial when used in combination with aspirin, in patients with acute non ST-elevation ACS. Combination aspirin and clopidogrel did not show significant improvement in the risk of death or MI or stroke, although there were trends for better outcome in those with pre-existing vascular disease.

Lipid-Lowering Therapy. Serum cholesterol concentrations should be assessed in all patients with chronic stable angina, but the summation of evidence suggests that cholesterol-lowering therapy confers benefit to almost all patients (at least for total cholesterol >136 mg/dL; see below). Thus, all patients with chronic ischemic heart disease should be treated with an hydroxy-3-methyl glutaryl coenzyme A reductase inhibitor or statin, irrespective of the serum cholesterol concentration. Other classes of drugs, such as fibrates, also lower serum lipid concentrations, but the benefits on mortality are inferred rather than demonstrated directly. An exception is the Veterans Affairs trial of gemfibrozil, which demonstrated significant secondary preventive benefits of elevating reduced HDL cholesterol concentrations. Fibrates should therefore be considered in patients with normal LDL but low HDL cholesterol concentrations.

β-Blockers for Secondary Prevention. There have been no randomized controlled trials to demonstrate that β-blocker therapy improves survival in patients with chronic stable angina. However, post-MI, in hypertension, and in case-control studies patients maintained on β-blockers are less likely to have a vascular event and have a reduced mortality rate if they subsequently experience an MI. For these reasons, it is reasonable that β-blockers should be the first-line agents of choice for patients with chronic stable angina. Concerns that β-blocker therapy is associated with reduced peripheral

perfusion owing to unopposed β±-adrenergic vasoconstriction and blockade of β_2 vascular receptors, are unfounded, even in patients with peripheral vascular disease. Because of the common risk factor of smoking, many patients with angina have chronic obstructive pulmonary disease and are denied β-blocker therapy because of the concern of provoking bronchospasm. However, there is a large body of observational data demonstrating that patients with obstructive pulmonary disease derive similar mortality benefits (40% relative risk reduction) after MI with β-blocker therapy.

Patients with chronic stable angina and coexistent heart failure are particularly at risk and should be given β_I-blocker therapy as the agent of choice. Several large randomized controlled trials have demonstrated major mortality and morbidity benefits in patients with mild to severe heart failure who were maintained on β_I-blocker therapy. Although cautious dose up-titration and close clinical observation for cardiac decompensation are necessary, the withdrawal rates of patients with heart failure from βI-blocker therapy are modest (15%) and equivalent to those for placebo. Moreover, rates of rehospitalization are reduced and symptoms of heart failure are improved with βI-blocker therapy

Angiotensin-Converting Enzyme Inhibition. The major morbidity and mortality benefits of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockers (and ARB) therapy were first demonstrated in patients with heart failure. Patients with chronic stable angina and a predicted 10-year event rate below 15% should receive ACE inhibitor therapy on account of the major secondary preventive benefits.

Coronary Revascularization. There have been no randomized controlled trials to test whether PCI improves long-term survival in patients with chronic stable angina. In the short to medium term, the hazards of PCI exceed those of medical therapy. In contrast, in selected groups, CABG is associated with significant reductions in mortality rates compared with medical therapy. Comparisons of the prognostic benefits of PCI and CABG demonstrated no statistically significant differences between the two approaches, but this does not establish equivalence. Thus, in patients with chronic stable angina, PCI is an important treatment to relieve symptoms, but is associated with a small excess early risk.

In comparison with medical therapy, CABG improves long-term (10-year) survival in patients with stable angina. Subgroup analysis demonstrates that patients with greater than 50% left main stem stenosis had the greatest survival benefit with CABG. Survival benefits are also seen in patients with three-vessel disease or two-vessel disease that includes proximal LAD stenosis, especially in the context of LV dysfunction. However, for patients with two-vessel disease without proximal LAD stenosis or one-vessel disease, there is no evidence of a survival advantage from CABG. It has not yet been established in these patient populations whether PCI with current stent technology has a similar impact on survival. Patients with abnormal left ventricular function, high-risk anatomy (e.g., left main or proximal LAD stenosis), or strongly positive exercise tests derive greater absolute survival benefit from CABG than from medical therapy.

It is important to note that in the trials a significant number of patients with three-vessel disease who were initially randomized to medical therapy crossed over to surgery (41% at 10 years). These studies compared strategies rather than surgery per se, and may underestimate the benefits of surgery. Thus, randomized controlled trials may underestimate the benefits of modern CABG techniques with arterial conduits and do not take into account improvements in secondary preventive therapy

Cardiac Rehabilitation. Cardiac rehabilitation involves a multidisciplinary approach addressing medical and psychosocial care, exercise, education, secondary prevention, and vocational advice. Although predominantly applied to the immediate post-MI or post-CABG period, it is also applicable to patients with chronic stable angina. The rehabilitation process encompasses three main components:

- Explanation and understanding.
- Specific interventions: secondary prevention, exercise training, and psychological support.
- Long-term adaptation and education.

Patients with stable angina who attend a regular exercise and rehabilitation program have less angina and may have fewer recurrent MIs, as well as better cardiorespiratory fitness and vocational status. Exercise programs improve patient confidence and functional capacity, and although they are labor intensive, are potentially cost ef-

fective. Benefits appear to be most prominent in the first 2 years; secondary preventive effects appear to be sustained over 10 years. Although these benefits have not been definitively demonstrated in populations of patients with chronic stable angina in the absence of MI, the referral of such patients to a cardiac rehabilitation program can improve symptoms and enhance measures of quality of life.

Controversies and Personal Perspectives. The vast majority of individuals with chronic stable coronary disease are asymptomatic and exhibit no clinical manifestations of the disease process. Individuals only become patients relatively late in the time course of coronary atherogenesis. Our current diagnostic and therapeutic interventions are targeted at those who develop complications of the disease (angina, MI, heart failure) rather than individuals at particular risk of atheroma progression and plaque rupture. Smarter primary prevention strategies would allow higher risk individuals to be targeted. Based on clinical risk factors, family history, and phenotypic and genetic markers of susceptibility, such approaches have greater potential for benefit, and greater cost effectiveness, than blanket strategies in primary prevention.

In patients with symptomatic chronic stable coronary disease, the syndrome describes a relatively quiescent interval between symptomatic episodes of plaque rupture or between cardiac complications. Nevertheless, the disease process involves atheroma progression and thrombotic complications and is potentially amenable to intervention. Novel approaches may allow identification of vulnerable plaques and both mechanical interventions and pharmacologic interventions may modify the balance between inflammation and plaque rupture versus stabilization and repair.

Until such approaches are developed, the main focus in patients with chronic stable coronary disease is the control of symptoms and improvement in prognosis with current therapeutic interventions. These approaches would be enhanced by systematic and careful risk stratification, not only to provide insights into prognosis, but also to guide therapeutic decisions. Currently, a major gap exists between evidence of benefit and the systematic application of evidence-based therapy. Redressing this gap is an urgent clinical imperative.

The Future

Diagnostic Tools. Developments in several imaging modalities now provide insights into the extent, and limited information on the structure of coronary atheromatous plaque (e.g., high-resolution IVUS, positron emission tomography with labeling of plaque metabolic activity, optical coherence tomography). As yet, none of the these techniques has demonstrated that the enhanced anatomic and biological information translates into therapeutic decisions and altered patient outcome. However, such techniques provide major advances over the current reference standard in chronic ischemic heart disease, coronary angiography. Although angiography provides critical information to guide revascularization, it is limited to assessing the extent of encroachment of plaque into the arterial lumen (stenosis severity).

A critical goal for novel diagnostic techniques is to distinguish biologically active plaques, with enhanced risks of rupture and thrombotic events, from quiescent plaques with stable anatomic and biological features. Such differentiation would allow targeted therapy of nonstenotic but vulnerable plaques and avoid unnecessary treatment of stable quiescent and nonobstructive lesions. This goal is yet to be realized.

Risk Assessment in Chronic Stable Angina. In contrast to the settings of acute coronary syndrome or heart failure, limited risk stratification information has been available to guide therapeutic choices in chronic stable angina. Indeed, recent long-term trials have demonstrated the relatively low risk of cardiovascular events in patients with chronic stable ischemic heart disease annual mortality in the range of 1.5%. However, these overall figures obscure a substantial range of almost 10-fold in risk depending on baseline characteristics. Such risk stratification is based on clinical characteristics (many of which are nonmodifiable, like age or prior myocardial injury) and includes commonly available biochemical or hematologic, measurements (e.g., creatinine, glucose, white blood cell count). It is critically important to determine whether markers of upregulation of the inflammatory and coagulation systems may provide additional and more accurate prognostic information (e.g., hsCRP, CD40, IL1, serum amyloid A, markers of platelet activation).

A longer term goal is to establish the extent to which environmental factors modify the expression and the impact of specific genetic characteristics (rather than

single gene polymorphisms). Unraveling the influence of many different genetic influences on phenotype expression may provide more accurate prognostic information, guide therapeutic choices, and avoid adverse drug effects in specific individuals.

Therapeutic Interventions

The role of percutaneous revascularization has evolved remarkably rapidly and it is critical that PCI with modern technology be tested against best currently available surgical revascularization in the context with secondary prevention. Until this is done, it is uncertain whether the current displacement of CABG surgery by PCI procedures in patients with multivessel lesions is appropriate in terms of outcome complications and cost effectiveness.

Smart technologies have already altered proliferative responses to stent implantation with cell-cycle inhibitors. Whether more sophisticated drug-eluting stents may alter the behavior and susceptibility of other plaques to rupture (by achieving higher local concentrations of agents to modify plaque inflammation) remains to be determined.

Angiogenesis has great potential and promised much as a method of improving coronary revascularization. Much of this promise is yet to be fulfilled and the clinical importance of blood flow changes induced by angiogenesis requires further development. Nevertheless, in conjunction with major developments in gene transfer therapy, it may provide highly innovative future methods of improving myocardial perfusion.

Cytoprotection mechanisms, including pre- and postconditioning, have been demonstrated in experimental studies to have a major impact on cell survival in tissues subject to ischemia and reperfusion. As yet, these approaches have not translated into therapeutic interventions, but they have the potential to do so.

Thus, a series of approaches will allow more accurate diagnostic, risk prediction, and therapeutic interventions and a move from blanket approaches to treatment to smarter and more individualized therapies.

CHAPTER 3
MYOCARDIAL INFARCTION:
DEFINITION, ETHIOLOGY, PATHOGENSIS, DIAGNOSIS AND CONTEMPORARY MANAGEMENT

Preface.

Myocardial infarction (MI) is a major cause of death and disability worldwide. Coronary atherosclerosis is a chronic disease with stable and unstable periods. During unstable periods with activated inflammation in the vascular wall, patients may develop a myocardial infarction. Myocardial infarction may be a minor event in a lifelong chronic disease, it may even go undetected, but it may also be a major catastrophic event leading to sudden death or severe hemodynamic deterioration. A myocardial infarction may be the first manifestation of coronary artery disease, or it may occur, repeatedly, in patients with established disease. Information on myocardial infarction attack rates can provide useful data regarding the burden of coronary artery disease within and across populations, especially if standardized data are collected in a manner that demonstrates the distinction between incident and recurrent events. From the epidemiological point of view, the incidence of myocardial infarction in a population can be used as a proxy for the prevalence of coronary artery disease in that population. Furthermore, the term myocardial infarction has major psychological and legal implications for the individual and society. It is an indicator of one of the leading health problems in the world, and it is an outcome measure in clinical trials and observational studies. With these perspectives, myocardial infarction may be defined from a number of different clinical, electrocardiographic, biochemical, imaging, and pathological characteristics.

Definition of myocardial infarction.

In the past, a general consensus existed for the clinical syndrome designated as myocardial infarction. In studies of disease prevalence, the World Health Organization (WHO) defined myocardial infarction from symptoms, ECG abnormalities, and enzymes. However, the development of more sensitive and specific serological biomarkers and precise imaging techniques allows detection of ever smaller amounts of

myocardial necrosis. Accordingly, current clinical practice, health care delivery systems, as well as epidemiology and clinical trials all require a more precise definition of myocardial infarction and a re-evaluation of previous definitions of this condition.

It should be appreciated that over the years, while more specific biomarkers of myocardial necrosis became available, the accuracy of detecting myocardial infarction has changed. Such changes occurred when glutamine-oxaloacetic transaminase (GOT) was replaced by lactate dehydrogenase (LDH) and later by creatine kinase (CK) and the MB fraction of CK, i.e. CKMB activity and CKMB mass. Current, more specific, and sensitive biomarkers and imaging methods to detect myocardial infarction are further refinements in this evolution.

In response to the issues posed by an alteration in our ability to identify myocardial infarction, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) convened a consensus conference in 1999 in order to re-examine jointly the definition of myocardial infarction (published in the year 2010 in the *European Heart Journal* and *Journal of the American College of Cardiology*). The scientific and societal implications of an altered definition for myocardial infarction were examined from seven points of view: pathological, biochemical, electrocardiographic, imaging, clinical trials, epidemiological, and public policy. It became apparent from the deliberations of the former consensus committee that the term myocardial infarction should not be used without further qualifications, whether in clinical practice, in the description of patient cohorts, or in population studies. Such qualifications should refer to the amount of myocardial cell loss (infarct size), to the circumstances leading to the infarct (e.g. spontaneous or procedure related), and to the timing of the myocardial necrosis relative to the time of the observation (evolving, healing, or healed myocardial infarction).

Following the 2009 ESC/ACC consensus conference, a group of cardiovascular epidemiologists met to address the specific needs of population surveillance. This international meeting, representing several national and international organizations. These recommendations addressed the needs of researchers engaged in long-term population trend analysis in the context of changing diagnostic tools using retrospec-

tive medical record abstraction. Also considered was surveillance in developing countries and out-of-hospital death, both situations with limited and/or missing data. These recommendations continue to form the basis for epidemiological research.

Given the considerable advances in the diagnosis and management of myocardial infarction since the original document was published, the leadership of the ESC, the ACC, and the American Heart Association (AHA) convened, together with the World Heart Federation (WHF), a Global Task Force to update the 2012 consensus document. As with the previous consensus committee, the Global Task Force was composed of a number of working groups in order to refine the ESC/ACC criteria for the diagnosis of myocardial infarction from various perspectives. With this goal in mind, the working groups were composed of experts within the field of biomarkers, ECG, imaging, interventions, clinical investigations, global perspectives, and implications. During several Task Force meetings, the recommendations of the working groups were coordinated, resulting in the present updated consensus document.

The Task Force recognizes that the definition of myocardial infarction will be subject to a variety of changes in the future as a result of scientific advance. Therefore, this document is not the final word on this issue for all time. Further refinement of the present definition will doubtless occur in the future.

Clinical Features of Ischemia

The term myocardial infarction reflects cell death of cardiac myocytes caused by ischemia, which is the result of a perfusion imbalance between supply and demand. Ischemia in a clinical setting most often can be identified from the patient's history and from the ECG. Possible ischemic symptoms include various combinations of chest, upper extremity, jaw, or epigastric discomfort with exertion or at rest. The discomfort associated with acute myocardial infarction usually lasts at least 20 min. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnea, diaphoresis, nausea, or syncope.

These symptoms are not specific to myocardial ischemia and can be misdiagnosed and thus attributed to gastrointestinal, neurological, pulmonary, or musculoskeletal disorders. Myocardial infarction may occur with atypical symptoms, or even

without symptoms, being detected only by ECG, biomarker elevations, or cardiac imaging.

Pathology

Myocardial infarction is defined by pathology as myocardial cell death due to prolonged ischemia. Cell death is categorized pathologically as coagulation and/or contraction band necrosis, which usually evolves through oncosis, but can result to a lesser degree from apoptosis. Careful analysis of histological sections by an experienced observer is essential to distinguish these entities.

After the onset of myocardial ischemia, cell death is not immediate but takes a finite period to develop (as little as 20 min or less in some animal models). It takes several hours before myocardial necrosis can be identified by macroscopic or microscopic post-mortem examination. Complete necrosis of all myocardial cells at risk requires at least 2–4 h or longer depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, pre-conditioning, and/or, finally, individual demand for myocardial oxygen and nutrients. Myocardial infarctions are usually classified by size: microscopic (focal necrosis), small [10% of the left ventricular (LV) myocardium], moderate (10–30% of the LV myocardium), and large (<30% of the LV myocardium), and by location. The pathological identification of myocardial necrosis is made without reference to morphological changes in the coronary arterial tree or to the clinical history.

Myocardial infarction can be defined pathologically as acute, healing, or healed. Acute myocardial infarction is characterized by the presence of polymorphonuclear leukocytes. If the time interval between the onset of the infarction and death is quite brief, e.g. 6 h, minimal or no polymorphonuclear leukocytes may be seen. The presence of mononuclear cells and fibroblasts, and the absence of polymorphonuclear leukocytes characterize healing infarction. Healed infarction is manifested as scar tissue without cellular infiltration. The entire process leading to a healed infarction usually takes at least 5–6 weeks. Reperfusion may alter the macroscopic and microscopic appearance of the necrotic zone by producing myocytes with contraction bands and large quantities of extravasated erythrocytes. Myocardial infarctions can be clas-

sified temporally from clinical and other features, as well as according to the pathological appearance, as evolving (<6 h), acute (6 h–7 days), healing (7–28 days), and healed (29 days and beyond). It should be emphasized that the clinical and electrocardiographic timing of the onset of an acute infarction may not correspond exactly with the pathological timing. For example, the ECG may still demonstrate evolving ST-T changes and cardiac biomarkers may still be elevated (implying a recent infarct) at a time when pathologically the infarction is in the healing phase.

Patients who suffer sudden cardiac death with or without ECG changes suggestive of ischemia represent a challenging diagnostic group. Since these individuals die before pathological changes can develop in the myocardium, it is difficult to say with certainty whether these patients succumbed to a myocardial infarction or to an ischemic event that led to a fatal arrhythmia. The mode of death in these cases is sudden, but the etiology remains uncertain unless the individual reported previous symptoms of ischemic heart disease prior to the cardiac arrest. Some patients with or without a history of coronary disease may develop clinical evidence of ischemia, including prolonged and profound chest pain, diaphoresis and/or shortness of breath, and sudden collapse. These individuals may die before blood samples for biomarkers can be obtained, or these individuals may be in the lag phase before cardiac biomarkers can be identified in the blood. These patients may have suffered an evolving, fatal, acute myocardial infarction. If these patients present with presumably new ECG changes, for example ST elevation, and often with symptoms of ischemia, they should be classified as having had a fatal myocardial infarction even if cardiac biomarker evidence of infarction is lacking. Also, patients with evidence of fresh thrombus by coronary angiography (if performed) and/or at autopsy should be classified as having undergone sudden death as a result of myocardial infarction.

Clinical Classification of Myocardial Infarction

Clinically the various types of myocardial infarction can be classified as shown in table 3.1.

Table 3.1

Clinical classification of myocardial imfarction.

Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary

	coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

On occasion, patients may manifest more than one type of myocardial infarction simultaneously or sequentially. It should also be noted that the term myocardial infarction does not include myocardial cell death associated with mechanical injury from coronary artery bypass grafting (CABG), for example ventricular venting, or manipulation of the heart; nor does it include myocardial necrosis due to miscellaneous causes, e.g. renal failure, heart failure, cardioversion, electrophysiological ablation, sepsis, myocarditis, cardiac toxins, or infiltrative diseases.

Biomarker Evaluation

Myocardial cell death can be recognized by the appearance in the blood of different proteins released into the circulation from the damaged myocytes: myoglobin, cardiac troponin T and I, CK, LDH, as well as many others. Myocardial infarction is diagnosed when blood levels of sensitive and specific biomarkers such as cardiac troponin or CKMB are increased in the clinical setting of acute myocardial ischemia. Although elevations in these biomarkers reflect myocardial necrosis, they do not indicate its mechanism. Thus, an elevated value of cardiac troponin in the absence of clinical evidence of ischemia should prompt a search for other etiologies of myocardial necrosis, such as myocarditis, aortic dissection, pulmonary embolism, congestive heart failure, renal failure, and other examples indicated in table 3.2.

Table 3.2

Elevations of troponin in the absence of overt ischemic heart disease

- Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
- Congestive heart failure—acute and chronic
- Aortic dissection
- Aortic valve disease
- Hypertrophic cardiomyopathy
- Tachy- or bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke or subarachnoid haemorrhage
- Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure or sepsis
- Burns, especially if affecting .30% of body surface area
- Extreme exertion

The preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has nearly absolute myocardial tissue specificity as well as high clinical sensitivity, thereby reflecting even microscopic zones of myocardial necrosis. An increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population (URL = upper reference limit). Detection of a rise and/or fall of the measurements is essential to the diagnosis of acute myocardial infarction.

Blood samples for the measurement of troponin should be drawn on first assessment (often some hours after the onset of symptoms) and 6–9 h later. An occasional patient may require an additional sample between 12 and 24 h if the earlier measurements were not elevated and the clinical suspicion of myocardial infarction is high. To establish the diagnosis of myocardial infarction, one elevated value above the decision level is required. The demonstration of a rising and/or falling pattern is needed to distinguish background elevated troponin levels, e.g. patients with chronic renal failure (Table 3.2), from elevations in the same patients which are indicative of myocardial infarction. However, this pattern is not absolutely required to make the diag-

nosis of myocardial infarction if the patient presents >24 h after the onset of symptoms. Troponin values may remain elevated for 7–14 days following the onset of infarction.

If troponin assays are not available, the best alternative is CKMB (measured by mass assay). As with troponin, an increased CKMB value is defined as a measurement above the 99th percentile URL, which is designated as the decision level for the diagnosis of myocardial infarction. Gender-specific values should be employed. The CKMB measurements should be recorded at the time of the first assessment of the patient and 6–9 h later in order to demonstrate the rise and/or fall exceeding the 99th percentile URL for the diagnosis of myocardial infarction. An occasional patient may require an additional diagnostic sample between 12 and 24 h if the earlier CKMB measurements were not elevated and the clinical suspicion of myocardial infarction is high.

Measurement of total CK is not recommended for the diagnosis of myocardial infarction, because of the large skeletal muscle distribution and the lack of specificity of this enzyme.

Reinfarction

Traditionally, CKMB has been used to detect reinfarction. However, recent data suggest that troponin values provide similar information. In patients where recurrent myocardial infarction is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of the employed cardiac marker is recommended. A second sample should be obtained 3–6 h later. Recurrent infarction is diagnosed if there is a >20% increase of the value in the second sample. Analytical values are considered to be different if they are different by >3 SDs of the variance of the measures. For troponin, this value is 5–7% for most assays at the levels involved with reinfarction. Thus, a 20% change should be considered significant, i.e. over that expected from analytical variability itself.

Electrocardiographic Detection of Myocardial Infarction

The ECG is an integral part of the diagnostic work-up of patients with suspected myocardial infarction. The acute or evolving changes in the ST-T waveforms and the Q-waves when present potentially allow the clinician to date the event, to suggest the infarct-related artery, and to estimate the amount of myocardium at risk. Coronary ar-

tery dominance, size and distribution of arterial segments, collateral vessels, and location, extent, and severity of coronary stenoses can also impact ECG manifestations of myocardial ischemia. The ECG by itself is often insufficient to diagnose acute myocardial ischemia or infarction since ST deviation may be observed in other conditions such as acute pericarditis, LV hypertrophy, LBBB, Brugada syndrome, and early repolarization patterns. Also Q-waves may occur due to myocardial fibrosis in the absence of coronary artery disease, as in, for example, cardiomyopathy.

ECG Abnormalities of Myocardial Ischemia That May Evolve to Myocardial Infarction

ECG abnormalities of myocardial ischemia or infarction may be inscribed in the PR segment, the QRS complex, and the ST segment or T-waves. The earliest manifestations of myocardial ischemia are typical T-waves and ST segment changes. Increased hyper-acute T-wave amplitude with prominent symmetrical T-waves in at least two contiguous leads is an early sign that may precede the elevation of the ST segment. Increased R-wave amplitude and width (giant R-wave with S-wave diminution) are often seen in leads exhibiting ST elevation, and tall T-waves reflecting conduction delay in the ischemic myocardium. Transient Q-waves may be observed during an episode of acute ischemia or rarely during acute myocardial infarction with successful reperfusion.

Table 3.3 lists ECG criteria for the diagnosis of acute myocardial ischemia that may lead to infarction. The J-point is used to determine the magnitude of the ST elevation. J-point elevation in men decreases with increasing age; however, that is not observed in women, in whom J-point elevation is less than in men.

Table 3.3.

ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)

ST elevation	New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1mV in other leads
ST depression and T-wave changes	New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

Contiguous leads means lead groups such as anterior leads (V_1-V_6), inferior leads (II, III, and aVF), or lateral/apical leads (I and aVL). More accurate spatial contiguity in the frontal plane can be established by the Cabrera display: aVL, I, aVR, II, aVF, and III. Supplemental leads such as V_3R and V_4R reflect the free wall of the right ventricle.

Although the criteria in Table 5.3 require that the ST shift be present in two or more contiguous leads, it should be noted that occasionally acute myocardial ischemia may create sufficient ST segment shift to meet the criteria in one lead but have slightly less than the required ST shift in an adjacent contiguous lead. Lesser degrees of ST displacement or T-wave inversion in leads without prominent R-wave amplitude do not exclude acute myocardial ischemia or evolving myocardial infarction.

ST elevation or diagnostic Q-waves in regional lead groups are more specific than ST depression in localizing the site of myocardial ischemia or necrosis. However, ST depression in leads V_1-V_3 suggests myocardial ischemia, especially when the terminal T-wave is positive (ST elevation equivalent), and may be confirmed by concomitant ST elevation >0.1 mV recorded in leads V_7-V_9. The term 'posterior' to reflect the basal part of the LV wall that lies on the diaphragm is no longer recommended. It is preferable to refer to this territory as inferobasal. In patients with inferior myocardial infarction it is advisable to record right precordial leads (V_3R and V_4R) seeking ST elevation in order to identify concomitant right ventricular infarction.

During an acute episode of chest discomfort, pseudo-normalization of previously inverted T-waves may indicate acute myocardial ischemia. Pulmonary embolism, intracranial processes, or peri-/myocarditis may also result in ST-T abnormalities and should be considered (false positives) in the differential diagnosis.

The diagnosis of myocardial infarction is difficult in the presence of LBBB even when marked ST-T abnormalities or ST elevation are present that exceed standard criteria. A previous ECG may be helpful to determine the presence of acute myocardial infarction in this setting. In patients with right bundle branch block (RBBB), ST-T abnormalities in leads V_1-V_3 are common, making it difficult to assess the presence of ischemia in these leads; however, when ST elevation or Q-waves are found, myo-

cardial ischemia or infarction should be considered. Some patients present with ST elevation or new LBBB, and suffer sudden cardiac death before cardiac biomarkers become abnormal or pathological signs of myocardial necrosis become evident at autopsy. These patients should be classified as having had a fatal myocardial infarction.

Prior Myocardial Infarction

As shown in Table 3.4, Q-waves or QS complexes in the absence of QRS confounders are usually pathognomonic of a prior myocardial infarction. The specificity of the ECG diagnosis for myocardial infarction is greatest when Q-waves occur in several leads or lead groupings. ST deviations or T-waves alone are non-specific findings for myocardial necrosis. However, when these abnormalities occur in the same leads as the Q-waves, the likelihood of myocardial infarction is increased. For example, minor Q-waves >0.02 and <0.03 s that are >0.1 mV deep are suggestive of prior infarction if accompanied by inverted T-waves in the same lead group.

Table 3.4

ECG changes associated with prior myocardial infarction

- Any Q-wave in leads V_2–V_3 ≥0.02 s or QS complex in leads V_2 and V_3
- Q-wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4–V_6 in any two leads of a contiguous lead grouping (I, aVL, V_6; V_4–V_6; II, III, and aVF)
- R-wave ≥0.04 s in V_1–V_2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

Other validated myocardial infarction-coding algorithm, define Q-wave depth on the basis of depth, width, and ratio of R-wave amplitude, such as Q-wave depth at least one-third or one-fifth of R-wave amplitude, and have been used extensively in epidemiological studies and clinical trials

Conditions That Confound the ECG Diagnosis of Myocardial Infarction

A QS complex in lead V_1 is normal. A Q-wave ≥0.03 s and ≥1/4 of the R-wave amplitude in lead III is normal if the frontal QRS axis is between 30 and 0°. The Q-wave may also be normal in aVL if the frontal QRS axis is between 60 and 90°. Septal Q-waves are small non-pathological Q-waves <0.03 s and <1/4 of the R-wave amplitude in leads I, aVL, aVF, and V_4-V_6. Pre-excitation, obstructive or dilated cardi-

omyopathy, LBBB, RBBB, left anterior hemi-block, left and right ventricular hypertrophy, myocarditis, acute cor pulmonale, or hyperkaliemia may be associated with Q/QS complexes in the absence of myocardial infarction.

Reinfarction

The ECG diagnosis of reinfarction following the initial infarction may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when ST elevation >0.1 mV reoccurs in a patient having a lesser degree of ST elevation or new pathognomonic Q waves, in at least two contiguous leads, particularly when associated with ischemic symptoms for 20 min or longer. The re-elevation of the ST segment can, however, also be seen in threatening myocardial rupture and should lead to additional diagnostic work-up. ST depression or LBBB on their own should not be considered valid criteria for myocardial infarction.

Coronary Revascularization

ECG abnormalities during or after percutaneous coronary intervention (PCI) are similar to those seen during spontaneous myocardial infarction. In patients who have undergone CABG, new ST-T abnormalities are common but not necessarily diagnostic of myocardial ischemia. However, when new pathological Q waves (Table 3.4) appear in territories other than those identified before surgery, myocardial infarction should be considered, particularly if associated with elevated biomarkers, new wall motion abnormalities, or hemodynamic instability.

Imaging Techniques

Non-invasive imaging plays many roles in patients with known or suspected myocardial infarction, but this section concerns only its role in the diagnosis and characterization of infarction. The underlying rationale is that regional myocardial hypoperfusion and ischemia lead to a cascade of events including myocardial dysfunction, cell death, and healing by fibrosis. Important imaging parameters are therefore perfusion, myocyte viability, myocardial thickness, thickening, and motion, and the effects of fibrosis on the kinetics of radiolabeled and paramagnetic contrast agents.

Commonly used imaging techniques in acute and chronic infarction are echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy (MPS),

and magnetic resonance imaging (MRI). Positron emission tomography (PET) and X-ray computed tomography (CT) are less common. There is considerable overlap in their capabilities, but only the radionuclide techniques provide a direct assessment of myocardial viability because of the properties of the tracers used. Other techniques provide indirect assessments of myocardial viability, such as myocardial function from echocardiography or myocardial fibrosis from MRI.

Echocardiography

Echocardiography is an excellent real-time imaging technique with moderate spatial and temporal resolution. Its strength is the assessment of myocardial thickness, thickening, and motion at rest. This can be aided by tissue Doppler imaging. Echocardiographic contrast agents can improve endocardial visualization, but contrast studies are not yet fully validated for the detection of myocardial necrosis, although early work is encouraging.

Radionuclide Imaging

Several radionuclide tracers allow viable myocytes to be imaged directly, including thallium-201, technetium-99m MIBI, tetrofosmin, and [18F]2-fluorodeoxyglucose (FDG). The strength of the techniques are that they are the only commonly available direct methods of assessing viability, although the relatively low resolution of the images disadvantages them for detecting small areas of infarction. The common single photon-emitting radio-pharmaceuticals are also tracers of myocardial perfusion and so the techniques readily detect areas of infarction and inducible perfusion abnormalities. ECG-gated imaging provides a reliable assessment of myocardial motion, thickening, and global function

Magnetic Resonance Imaging

Cardiovascular MRI has high spatial resolution and moderate temporal resolution. It is a well-validated standard for the assessment of myocardial function and has, in theory, similar capability to echocardiography in suspected acute infarction. It is, however, more cumbersome in an acute setting and is not commonly used. Paramagnetic contrast agents can be used to assess myocardial perfusion and the increase in extracellular space associated with the fibrosis of chronic infarction. The former is not

yet fully validated in clinical practice, but the latter is well validated and can play an important role in the detection of infarction

X-Ray Computed Tomography

Infarcted myocardium is initially visible to CT as a focal area of decreased LV enhancement, but later imaging shows hyperenhancement as with late gadolinium imaging by MRI. This finding is clinically relevant because contrast-enhanced CT may be performed for suspected embolism and aortic dissection, conditions with clinical features that overlap with those of acute myocardial infarction.

Application in the Acute Phase of Myocardial Infarction

Imaging techniques can be useful in the diagnosis of myocardial infarction because of the ability to detect wall motion abnormalities in the presence of elevated cardiac bio-markers. If for some reason biomarkers have not been measured or may have normalized, demonstration of new loss of myocardial viability alone in the absence of non-ischemic causes meets the criteria for myocardial infarction. However, if biomarkers have been measured at appropriate times and are normal, the determinations of these take precedence over the imaging criteria.

Echocardiography provides assessment of many non-ischemic causes of acute chest pain such as peri-myocarditis, valvular heart disease, cardiomyopathy, pulmonary embolism, or aortic dissection. Echocardiography is the imaging technique of choice for detecting complications of acute infarction including myocardial free wall rupture, acute ventricular septal defect, and mitral regurgitation secondary to papillary muscle rupture or ischemia. However, echocardiography cannot distinguish regional wall motion abnormalities due to myocardial ischemia from infarction.

Radionuclide assessment of perfusion at the time of patient presentation can be performed with immediate tracer injection and imaging that can be delayed for up to several hours. The technique is interpreter dependent, although objective quantitative analysis is available. ECG gating provides simultaneous information on LV function.

An important role of acute echocardiography or radionuclide imaging is in patients with suspected myocardial infarction and a non-diagnostic ECG. A normal echocardiogram or resting ECG-gated scintigram has a 95–98% negative predictive

value for excluding acute infarction. Thus, imaging techniques are useful for early triage and discharge of patients with suspected myocardial infarction.

A regional myocardial wall motion abnormality or loss of normal thickening may be caused by acute myocardial infarction or by one or more of several other ischemic conditions including old infarction, acute ischemia, stunning, or hibernation. Non-ischemic conditions such as cardiomyopathy and inflammatory or infiltrative diseases can also lead to regional loss of viable myocardium or functional abnormality, and so the positive predictive value of imaging techniques is not high unless these conditions can be excluded and unless a new abnormality is detected or can be presumed to have arisen in the setting of other features of acute myocardial infarction.

Application in the Healing or Healed Phase of Myocardial Infarction

Imaging techniques are useful in myocardial infarction for analysis of LV function, both at rest and during dynamic exercise or pharmacological stress, to provide an assessment of remote inducible ischemia. Echocardiography and radio-nuclide techniques, in conjunction with exercise or pharmacological stress, can identify ischemia and myocardial viability. Non-invasive imaging techniques can diagnose healing or healed infarction by demonstrating regional wall motion, thinning, or scar in the absence of other causes.

The high resolution of contrast-enhanced MRI means that areas of late enhancement correlate well with areas of fibrosis and thereby enable differentiation between transmural and subendocardial scarring. The technique is therefore potentially valuable in assessing LV function and areas of viable and hence potentially hibernating myocardium.

Myocardial Infarction Associated With Revascularization Procedures

Peri-procedural myocardial infarction is different from spontaneous infarction, because the former is associated with the instrumentation of the heart that is required during mechanical revascularization procedures by either PCI or CABG. Multiple events that can lead to myocardial necrosis are taking place, often in combination, during both types of intervention. While some loss of myocardial tissue may be un-

avoidable during procedures, it is likely that limitation of such damage is beneficial to the patient and their prognosis.

During PCI, myocardial necrosis may result from recognizable peri-procedural events, alone or in combination, such as side-branch occlusion, disruption of collateral flow, distal embolization, coronary dissection, slow flow or no-reflow phenomenon, and microvascular plugging. Embolization of intracoronary thrombus or atherosclerotic particulate debris cannot be entirely prevented despite current antithrombotic and antiplatelet adjunctive therapy or protection devices. Such events induce extensive inflammation of non-infarcted myocardium surrounding small islets of myocardium necrosis. New areas of myocardial necrosis have been demonstrated by MRI following PCI. A separate subcategory of myocardial infarction is related to stent thrombosis as documented by angiography and/or autopsy.

During CABG, numerous additional factors can lead to peri-procedural necrosis. These include direct myocardial trauma from sewing needles or manipulation of the heart, coronary dissection, global or regional ischemia related to inadequate cardiac protection, microvascular events related to reperfusion, myocardial damage induced by oxygen free radical generation, or failure to reperfuse areas of the myocardium that are not subtended by graftable vessels. MRI studies suggest that most necrosis in this setting is not focal, but diffuse and localized to the sub-endocardium. Some clinicians and clinical investigators have preferred using CKMB for the diagnosis of peri-procedural infarction because of a substantial amount of data relating CKMB elevations to prognosis. However, an increasing number of studies using troponins in that respect have emerged.

Diagnostic Criteria for Myocardial Infarction With PCI

In the setting of PCI, the balloon inflation during a procedure almost always results in ischemia whether or not accompanied by ST-T changes. The occurrence of procedure-related cell necrosis can be detected by measurement of cardiac biomarkers before or immediately after the procedure, and again at 6–12 and 18–24 h. Elevations of biomarkers above the 99th percentile URL after PCI, assuming a normal baseline troponin value, are indicative of post-procedural myocardial necrosis. There is cur-

rently no solid scientific basis for defining a biomarker threshold for the diagnosis of peri-procedural myocardial infarction. Pending further data, and by arbitrary convention, it is suggested to designate increases more than three times the 99th percentile URL as PCI-related myocardial infarction (type 4a).

If cardiac troponin is elevated before the procedure and not stable for at least two samples 6 h apart, there are insufficient data to recommend biomarker criteria for the diagnosis of peri-procedural myocardial infarction. If the values are stable or falling, criteria for reinfarction by further measurement of biomarkers together with the features of the ECG or imaging can be applied.

A separate subcategory of myocardial infarction (type 4b) is related to stent thrombosis as documented by angiography and/or autopsy. Although iatrogenic, myocardial infarction type 4b with verified stent thrombosis must meet the criteria for spontaneous myocardial infarction as well.

Diagnostic Criteria for Myocardial Infarction With CABG

Any increase of cardiac biomarkers after CABG indicates myocyte necrosis, implying that an increasing magnitude of biomarker is likely to be related to an impaired outcome. This has been demonstrated in clinical studies employing CKMB where elevations five, 10 and 20 times the upper limit of normal after CABG were associated with worsened prognosis. Likewise, the increase of troponin levels after CABG indicates necrosis of myocardial cells, which predicts a poor outcome, in particular when elevated to the highest quartile or quintile of the troponin measurements.

Unlike the prognosis, scant literature exists concerning the use of biomarkers for defining myocardial infarction in the setting of CABG. Therefore, biomarkers cannot stand alone in diagnosing myocardial infarction (type 5). In view of the adverse impact on survival observed in patients with significant biomarker elevations, this Task Force suggests, by arbitrary convention, that biomarker values more than five times the 99th percentile of the normal reference range during the first 72 h following CABG, when associated with the appearance of new pathological Q-waves or new LBBB, or angiographically documented new graft or native coronary artery occlu-

sion, or imaging evidence of new loss of viable myocardium, should be considered as diagnostic of a CABG-related myocardial infarction (type 5 myocardial infarction).

Conclusion.

Cardiovascular disease is a global health problem. Approximately one-third of persons in the world die of cardiovascular disease, largely coronary artery disease and stroke, and 80% of these deaths from cardiovascular disease occur in developing countries. The greater proportion of deaths is due to heart disease and specifically coronary heart disease, of which myocardial infarction is a major manifestation. Since it is difficult to measure the prevalence of coronary artery disease in a population, the incidence of myocardial infarction may be used as a proxy, provided that a consistent definition is used when different populations, countries, or continents are being compared.

The changes in the definition of myocardial infarction have critical consequences for less developed and developing countries. In many countries, the resources to apply the new definition may not be available in all hospitals. However, many developing countries already do have medical facilities capable of or currently employing the proposed definition of myocardial infarction. In the context of the overall cost for a patient with myocardial infarction, the expense associated with a troponin assay would not be excessive and should be economically affordable in many hospitals in developing countries, particularly those where infarcts are frequent events. The necessary equipment, staff training, and running costs may be lacking in some regions, but certainly not in others. In less advantaged hospitals, the diagnosis of myocardial infarction may depend mostly on clinical signs and symptoms coupled with less sophisticated biomarker analyses. Some of these institutions may only have access to CK and its isoenzymes at the present time. The redefinition arises from and is compatible with the latest scientific knowledge and with advances in technology, particularly with regard to the use of bio-markers, high quality electrocardiography, and imaging techniques. The definition can and should be used by developed countries immediately, and by developing countries as quickly as resources become available.

The change in the definition of myocardial infarction will have a substantial impact on the identification, prevention, and treatment of cardiovascular disease throughout the world. The new definition will impact epidemiological data from developing countries relating to prevalence and incidence. The simultaneous and continuing use of the older WHO definition for some years would allow a comparison between data obtained in the past and data to be acquired in the future employing the newer biomarker approach. Cultural, financial, structural, and organizational problems in the different countries of the world in diagnosis and therapy of acute myocardial infarction will require ongoing investigation. It is essential that the gap between therapeutic and diagnostic advances be addressed in this expanding area of cardiovascular disease.

Management of Patients With ST-Elevation Myocardial Infarction

Analgesia

Use of morphine remains for patients with STEMI, however, because STEMI patients should either have received reperfusion or are not candidates for reperfusion, and continuing pain requires relief in either case. Because of the known increased risk of cardiovascular events among patients taking cyclooxygenase-2 (COX-2) inhibitors and other nonsteroidal anti-inflammatory drugs (NSAIDs), these drugs should be discontinued immediately at the time of STEMI

Beta Blockers

It has been recommended both fibrinolytic therapy and intravenous (IV) beta blockers for reduce incidence of subsequent reinfarction and recurrent ischemia in patients with MI.

There is a potential risk of administering i.v beta blockers to patients with severe heart failure or cardiogenic shock. There are several circumstances in which it can be useful to administer an i.v beta blocker acutely to a STEMI patient, and these situations are discussed below. It is reasonable to administer i.v. beta-blocker therapy on Days 0 to 1 of hospitalization for STEMI when hypertension is present and the patient is not at an increased risk of cardiogenic shock on the basis of the risk factors defined above. Patients with sinus tachycardia or atrial fibrillation should have left ventricular

(LV) function rapidly evaluated before administration of i.v. beta blockers (or other negative inotropes, such as non-dihydropyridine calcium channel blockers). From Day 2 onward, when beneficial effects on reinfarction and ventricular fibrillation are seen, administration of 200 mg of controlled-release oral metoprolol daily appears to be safe in hemodynamically stable patients with STEMI who are free of contraindications. It is prudent to initiate a dose of 50 mg of metoprolol orally every 6 hours, transitioning to a dose equivalent to 200 mg per day orally or the maximum tolerated dose. It should be noted that long-term use of oral beta blockers is strongly recommended for secondary prevention in patients at highest risk, such as those with low ejection fraction, heart failure, or postshock, once they have stabilized, with gradual dose titration

Reperfusion

1. If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 minutes of arrival of EMS on the scene.
2. If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a *non*–PCI-capable hospital, the **door-to-needle** time should be within 30 minutes for patients for whom fibrinolysis is indicated.
3. If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the **EMS arrival-to-balloon** time should be within 90 minutes.
4. If EMS takes the patient to a *non*–PCI-capable hospital, it is appropriate to consider emergency *interhospital transfer* of the patient to a PCI-capable hospital for mechanical revascularization if
   - There is a contraindication to fibrinolysis.
   - PCI can be initiated promptly within 90 minutes **from EMS arrival-to-balloon time at the PCI-capable hospital**.
   - Fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI").

It is important to note that the door-to-balloon goal is a systems goal that may not be possible to achieve for an individual patient because of patient variables (uncertainty about diagnosis, evaluation and treatment of other life-threatening conditions, obtaining informed consent, etc.) that delay the patient's arrival in the interventional cardiology laboratory or anatomical challenges (issues of arterial, coronary, or lesion access) that prolong the PCI procedure. In the absence of such circumstances,

however, reperfusion should be achieved as soon as possible within this time, and many hospitals with refined systems are approaching median door-to-balloon times of 60 to 70 minutes. Discussions about measurement, particularly with respect to inclusion criteria and the appropriate time to end measurement, are beyond the scope of this document and are being considered by groups that are focusing on how to improve the alignment between what is measured and patient outcomes. The focus on measurement should not displace the emphasis on improving processes that will facilitate more rapid treatment that is delivered safely and appropriately.

This committee continues to endorse the concept that faster times to reperfusion and better systems of care are associated with important reductions in morbidity and mortality rates in patients with STEMI. An underutilized but effective strategy for improving systems of care for STEMI patients is to expand the use of pre-hospital 12-lead electrocardiography programs by emergency medical systems (EMS) that provide advanced life support.

The emphasis on primary PCI should not obscure the importance of fibrinolytic therapy. Many hospital systems in North America do not have the capability of meeting the time goal for primary PCI. Therefore, because of the critical importance of time to treatment from onset of symptoms of STEMI in reducing morbidity and mortality, fibrinolytic therapy is preferred. In these settings, transfer protocols need to be in place for arranging rescue PCI when clinically indicated.

For fibrinolytic therapy, the system goal is to deliver the drug within 30 minutes of the time that the patient presents to the hospital. The focus for primary PCI is from first medical contact because in regionalization strategies, extra time may be taken to transport patients to a center that performs the procedure. Consequently, it is important to consider the time from first medical contact. The writing group does believe that every effort should be made to reduce the time from first medical contact to fibrinolytic therapy when that is considered the appropriate reperfusion strategy.

Facilitated PCI

Facilitated PCI refers to a strategy of planned immediate PCI after administration of an initial pharmacological regimen intended to improve coronary patency before

the procedure. These regimens have included high-dose heparin, platelet glycoprotein (GP) IIb/IIIa inhibitors, full-dose or reduced-dose fibrinolytic therapy, and the combination of a GP IIb/IIIa inhibitor with a reduced-dose fibrinolytic agent (e.g., fibrinolytic dose typically reduced 50%). Facilitated PCI should be differentiated from primary PCI without fibrinolytic therapy, from primary PCI with a GP IIb/IIIa inhibitor started at the time of PCI, from early or delayed PCI after successful fibrinolytic therapy, and from rescue PCI after unsuccessful fibrinolytic therapy. Potential advantages of facilitated PCI include earlier time to reperfusion, smaller infarct size, improved patient stability, lower infarct artery thrombus burden, greater procedural success rates, higher TIMI (Thrombolysis in Myocardial Infarction trial) flow rates, and improved survival rates. Potential risks include increased bleeding complications, especially in older patients. Potential limitations include additional cost.

Despite the potential advantages, clinical trials of facilitated PCI have not demonstrated any benefit in reducing infarct size or improving outcomes.Defenders of the facilitated PCI strategy point out that the absence of an infusion of heparin after bolus administration and the absence of a loading dose of clopidogrel, plus prohibition of GP IIb/IIIa inhibitors except in bail-out situations, made adjunctive antithrombotic therapy suboptimal for the facilitated PCI group. Moreover, the median treatment delay between administration of tenecteplase and PCI was only 104 minutes, and mortality rates were higher in PCI centers. The evidence on whether earlier (prehospital) administration of fibrinolytic therapy, better antithrombotic therapy, longer delays to PCI, or selective use of PCI as a rescue strategy would make the facilitated PCI strategy beneficial is unclear. These issues require further study. On the basis of these data, however, facilitated PCI offered no clinical benefit.

Immediate or Emergency Invasive Strategy and Rescue PCI

Pharmacological reperfusion with full-dose fibrinolysis is not uniformly successful in restoring antegrade flow in the infarct artery. In such situations, a strategy of prompt coronary angiography with intent to perform PCI is frequently contemplated. In certain patients, such as those with cardiogenic shock (especially those less than 75 years of age), severe congestive heart failure/pulmonary edema, or hemodynamically

compromising ventricular arrhythmias (regardless of age), a strategy of coronary angiography with intent to perform PCI is a useful approach regardless of the time since initiation of fibrinolytic therapy, provided further invasive management is not considered futile or unsuitable given the clinical circumstances.

In other patients who do not exhibit the clinical instability noted above, PCI may also be reasonable if there is clinical suspicion of failure of fibrinolysis. This is referred to as rescue PCI. Critical to the success of rescue PCI is the initial clinical identification of patients who are suspected of having failed reperfusion with full-dose fibrinolysis. Because the presence or absence of ischemic discomfort may be unreliable for identifying failed reperfusion, clinicians should search for evidence of inadequate ST-segment resolution on the 12-lead electrocardiogram (ECG). Operationally, the 12-lead ECG should be scrutinized after adequate time has elapsed before it is decided that fibrinolytic therapy has not been effective. Although earlier times have been used in some studies, the writing committee believed that 90 minutes after initiation of fibrinolysis was the best time point for evaluating the need for rescue PCI; hence, if there is less than 50% ST resolution in the lead showing the greatest degree of ST-segment elevation at presentation, fibrinolytic therapy has likely failed to produce reperfusion.

Given the association between bleeding events and subsequent ischemic events, it might be reasonable to select moderate- and high-risk patients for PCI after fibrinolysis and to treat low-risk patients with medical therapy. As noted above, patients with cardiogenic shock, severe heart failure, or hemodynamically compromising ventricular arrhythmias are excellent candidates. An ECG estimate of potential infarct size in patients with persistent ST-segment elevation (less than 50% resolution at 90 minutes following initiation of fibrinolytic therapy in the lead showing the worst initial evaluation) and ongoing ischemic pain is useful for selecting other patients for rescue PCI. Anterior MI or inferior MI with right ventricular involvement or precordial ST-segment depression usually predicts increased risk. Conversely, patients with symptom resolution, improving ST-segment elevation (less than 50% resolution), or inferior MI localized to 3 ECG leads probably should not be referred for angiography.

Likewise, it is doubtful that PCI of a branch artery (diagonal or obtuse marginal branch) will change prognosis in the absence of high-risk criteria noted above.

PCI After Fibrinolysis or for Patients Not Undergoing Primary Reperfusion.

PCI has been performed immediately after successful fibrinolytic therapy, hours to days after successful fibrinolytic therapy, and days to weeks after successful fibrinolytic therapy. With the increase in use of an invasive strategy, consideration is now also given to PCI in patients who did not undergo fibrinolysis, and this concept is reflected in the decision of the writing committee to rename this section to reflect considerations for PCI both after fibrinolytic therapy and in STEMI patients who do not undergo primary reperfusion.

The open artery hypothesis suggested that late patency of an infarct artery is associated with improved LV function, increased electrical stability, and provision of collateral vessels to other coronary beds for protection against future events. It has been demonstrated that elective PCI of an occluded infarct artery 1 to 28 days after MI in stable patients had no incremental benefit beyond optimal medical therapy with aspirin, beta blockers, ACE inhibitors, and statins in preserving LV function and preventing subsequent cardiovascular events.

Ancillary Therapy

Anticoagulant therapy is beneficial in patients with STEMI, and there is benefit in more prolonged anticoagulant therapy (duration of index hospitalization) in patients receiving fibrinolytics, fondaparinux, and enoxaparin. The mechanism of benefit from a more prolonged anticoagulant regimen is probably multifactorial and includes a longer exposure to anticoagulants to prevent rethrombosis of the infarct artery and prevention of the rebound increase in events seen after abrupt discontinuation of UFH infusions. Concern was raised about a rebound increase in events after abrupt discontinuation of UFH infusions in patients with UA/NSTEMI, but this also appears to occur in patients with STEMI. The optimum method of terminating treatment with UFH has not been rigorously established for patients with either UA/NSTEMI or STEMI, but it is common clinical practice to simply discontinue UFH infusions. Finally, when the new anticoagulant regimens are compared with

UFH as an active control, the greater degree of inhibition of the proximal portion of the coagulation cascade may lead to a greater reduction in thrombin generation.

Of note, reviparin, enoxaparin, and fondaparinux all involve, at least in part, clearance via the renal route. Hence, the potential exists for accumulation of anti-Xa activity with increasing degrees of renal failure. On the basis of available data, recommendations have been formulated for baseline creatinine cut points when a patient is considered for one of the new regimens. Also, estimation of creatinine clearance should be calculated via the Cockcroft-Gault formula rather than the Modification of Diet and Renal Disease (MDRD) equation, because the former has been used to modify dosing in clinical trials. It is also recommends head-to-head comparative studies to evaluate newer anticoagulant drugs (e.g., fondaparinux, enoxaparin, bivalirudin) to assess optimal anticoagulant therapy in patients with STEMI; such studies could provide more clinically useful information than comparisons against UFH or no anticoagulant. When added to previous data, the benefits of anticoagulation therapy started concurrently with non–fibrin-specific fibrinolytic agents (e.g., streptokinase) seen with all 3 of the new anticoagulation regimens led the writing group to recommend the use of an anticoagulant across the spectrum of fibrinolytic agents in common clinical use. When moving to PCI after fibrinolytic therapy, those patients who received upstream UFH or enoxaparin can continue to receive those anticoagulants in a seamless fashion (i.e., without crossover to another agent) using the dosing regimens listed in the recommendations.

Clopidogrel.

Adding clopidogrel to aspirin in patients undergoing fibrinolytic therapy is recomended. It has also supported the use of clopidogrel in patients who were not receiving reperfusion therapy. Although the available data suggest that the oral maintenance dose should be 75 mg daily, uncertainty exists about the efficacy and safety of adding a loading dose to elderly patients (more than 75 years of age), especially when they receive a fibrinolytic. Thus, it does not recommend a loading dose in the elderly who receive a fibrinolytic and endorses further research to define the optimum clopidogrel regimen in the elderly.It appears that the administration of clopidogrel at

the time of initial fibrinolytic therapy is of benefit when PCI is performed subsequently. No data are available from clinical trials regarding long-term clopidogrel treatment in STEMI patients. Extrapolating from experience in patients with UA/NSTEMI, as well as those patients undergoing coronary stenting, the writing committee felt that long-term therapy with clopidogrel (e.g., 1 year) can be useful in patients with STEMI.

Anticoagulants.

Anticoagulant therapy with UFH is recommended for patients not receiving reperfusion with the goal of reducing mortality and reinfarction rates. In patients with UA/NSTEMI, treatment with LMWH is recommended with a similar goal, as well as for prevention of episodes of recurrent ischemia.

Conclusion.

In summary, choice of revascularisation method rests on weighing the more invasive nature of CABG against the increased need of additional revascularization after PCI / stenting or some thrombolytic procedures should be provided aggressively. This clinical approach can improve outcomes of the patients with documented MI and ACS.

CHAPTER 4
ACUTE CORONARY SYNDROME WITHOUT ST-SEGMENT ELEVATION.

Foreword.

Worldwide, cardiovascular diseases are now the most common cause of death and a substantial source of chronic disability and health costs. Ischemic heart disease includes a wide spectrum of conditions, ranging from silent ischemia and exertion-induced angina, through unstable angina, to acute MI.

The syndromes of unstable angina, non ST-elevation MI (NSTEMI) and ST-elevation MI (STEMI) are a continuum, and the pathophysiology is heterogeneous and dynamic. Clinical presentation depends on the severity of the arterial injury, the size and type of thrombus formed, the extent and duration of ischemia, and the amount of previous myocardial necrosis. The extent of ischemia depends on the myocardial distribution of the ischemia-producing artery, the severity of the ischemia-producing stenosis, the absence or presence of collateral circulation, and factors that affect the supply of oxygenated blood or that increase myocardial demands, such as the heart rate, blood pressure, and contractility. Patients may die or may develop MI, recurrent ischemia, heart failure, arrhythmia, or a stroke.

Unstable angina is classically described as a heterogeneous disease, referring to a wide spectrum of clinical manifestations from stable angina to MI, of disease processes from coronary vasospasm to thrombus formation, and of extent of CAD from no significant stenosis to severe three-vessel disease. Not surprisingly, therefore, the prognosis of unstable angina is quite variable. Despite all these heterogeneous features, the recent progress made in knowledge and management of unstable angina and acute MI has driven the acute coronary syndromes to the forefront of modern cardiology, helping shape future research and development. The new concepts are active coronary plaque and triggers and promoters of inflammation and of thrombus formation. The new therapeutic goals are plaque stabilization and prevention of accelerated atherosclerosis.

Unstable angina occupies the center of this spectrum, causing disability and risk greater than that of chronic stable angina but less than that of acute MI. Although

non–Q-wave MI for many years was considered prognostically similar to unstable angina, recent longitudinal studies indicate that it is similar to Q-wave infarction.

The concept of unstable angina has emerged from observations of frequent symptoms preceding acute MI, followed by prospective documentation that unstable symptoms frequently culminated in acute MI. The syndrome was rapidly accepted as a well-defined clinical entity as specific clinical manifestations, pathophysiological mechanisms, laboratory findings, and treatment became better characterized. Unstable angina is currently one of the leading causes of hospital admission for CAD, and non–Q-wave MI accounts for >30% of admissions for acute MI.

Yet, the diagnosis of unstable angina remains clinical, based on symptom recognition. The physician caring for patients with unstable angina is in a privileged position of recognizing rapidly evolving CAD and being able to intervene to prevent irreversible left ventricular damage and progression of CAD.

Definition of acute coronary syndrome.

Acute coronary syndromes describes a spectrum of clinical syndromes ranging from unstable angina to NSTEMI and STEMI. Patients presenting with ACS are divided into those with ST elevation or new left bundle branch block, and those with NSTEACS which includes transient ST elevation (lasting <20 minutes), unstable angina, and NSTEMI.

Unstable angina is a syndrome intermediate between chronic stable angina and MI. It is a clinical diagnosis based on a history of chest pain and exclusion of the diagnosis of MI by electrocardiography (ECG) and biomarker testing for myocardial necrosis. The chest pain may be prolonged at rest or of new onset, may represent accelerating symptoms of previously stable angina, or may occur after MI. Patients presenting without ST elevation on the ECG are diagnosed as having either NSTEMI or unstable angina based on whether or not their troponin or creatine kinase (CK)-MB levels are elevated. Between 2% and 15% of patients diagnosed with unstable angina subsequently develop Q-wave MI.

The unstable angina classification developed by Braunwald E. is based on the severity of symptoms, their clinical context, and the intensity of medical treatment.

The classification has been validated clinically, has been shown to correlate with coronary angiographic findings, and has now been updated to include troponin levels. Prinzmetal angina (recurrent rest angina accompanied by ST elevation on the ECG owing to coronary artery spasm) is considered a separate entity.

Clinical Presentations and Pathophysiology

In 1994, the Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute published a practice guideline: "Unstable Angina: Diagnosis and Management." This guideline defined unstable angina as follows: "... as having three possible presentations: symptoms of angina at rest (usually prolonged >20 minutes), new-onset (<2 months) exertional angina of at least Canadian Cardiovascular Society Classification (CCSC) class III in severity, or recent (<2 months) acceleration of angina as reflected by an increase in severity of at least one CCSC class to at least CCSC class III. In most, but not all, of these patients, symptoms will be caused by significant coronary artery disease (CAD). Variant angina, non–Q-wave myocardial infarction (MI), and post-MI (>24 hours) angina are part of the spectrum of unstable angina".

Thus, the diagnosis of unstable angina implies recognition of aggravating symptoms of myocardial ischemia of new onset or departing from the usual pattern of chest pain, the reference baseline being the patient's previous status. By definition, symptoms of unstable angina may have atypical features compared with classic angina. The diagnosis requires discriminative clinical judgment to integrate clinical and laboratory elements orienting to the likelihood of CAD and to the ischemic nature of the chest pain and its severity. Patients with a previous history of CAD are more likely to experience an ischemic pain; presence of risk factors and older age increase the likelihood of disease, and ST-T ischemic changes magnify the specificity of the diagnosis. Elevation of plasma levels of CK with presence of CK-MB is diagnostic of myocardial necrosis; troponin I and troponin T are sensitive markers of myocardial cell ischemia and necrosis, and elevated levels are associated with a more serious prognosis. Studies have also documented that systemic markers of an inflammatory state, such as C-reactive protein, can provide independent prognostic information.

Because angina is the clinical manifestation of an imbalance between oxygen demand and supply, extracardiac or cardiac factors that lead to excess demand must be ruled out when instability is recognized. These are an inappropriate tachycardia (anemia, fever, hypoxia, tachyarrhythmias, thyrotoxicosis), a high afterload (aortic valve stenosis, left ventricular hypertrophy) or preload (cardiac chamber dilatation, high cardiac output), or inotropic state (sympathomimetic drugs, cocaine intoxication). When no precipitating factors are identified, a primary intracoronary disease process limiting coronary blood flow is the likely cause of unstable angina.

Non–Q-wave MI is often diagnosed a posteriori when the results of the cardiac enzymes become available. The clinical presentation, however, is often suggestive of the diagnosis; the chest pain is prolonged, sometimes accompanied by symptoms originating from the autonomic nervous system, and frequently by ST-segment depression persisting well after the resolution of pain. Prinzmetal's variant angina is diagnosed when transient ST-segment elevation is documented during an episode of chest pain; coronary angiography is required to determine the severity of the underlying stenosis. Diagnostic clinical clues are intermittent episodes of chest pain, often repetitive, usually at rest, typically in the early morning hours, and rapidly relieved by nitroglycerin; syncope during pain is infrequent but highly suggestive of the diagnosis, as are other manifestations of spastic disease, such as migraine headache and Raynaud's phenomenon. Postinfarction angina, recognized by recurrent pain 24 hours to 4 weeks after MI, denotes impaired prognosis; the ischemia can be located at a distance or at the site of infarction. The former is more frequent in inferior MI and is associated with multivessel disease; the latter occurs mainly in anterior MI. Inclusion of these patients within the diagnosis of unstable angina has helped management.

Evaluation of Risk and Prognosis

Various classifications of unstable angina have been proposed, accounting for clinical presentation, pathophysiological mechanisms, and, most importantly, risk or prognosis. The classification proposed by Braunwald has become frequently used. This classification considers pathophysiology and clinical background and the severity of manifestations.

The pathophysiological clinical situations are

(A) a condition extrinsic to the coronary vascular bed intensifying myocardial ischemia,

(B) primary unstable angina with no extrinsic condition to intensify ischemia,

(C) unstable angina within 2 weeks after MI.

The severity grading is as follows:

I, new onset of severe angina or significative aggravation of previous angina, without rest pain;

II, angina at rest within the past month but not within 48 hours; and

III, angina at rest within 48 hours. Subclassifications address the intensity of previous treatment from 1, none; to 2, standard treatment for chronic stable angina; and to 3, maximal anti-ischemic drug therapy.

This classification is based on a large, diverse number of observations on the natural history of unstable angina. Collectively, these have demonstrated that patients with new-onset, severe angina (class I) have a better prognosis than those with rest pain (classes II and III); among the latter, patients who have experienced ischemia at rest in the immediate past (class III) are at higher risk than those who have "cooled off" (class II). Similarly, patients with secondary unstable angina, in whom a clearly identifiable precipitating cause of unstable angina can be identified (class A), have a better prognosis (insofar as unstable angina is concerned) than do patients in whom intrinsic CAD is responsible (class B), because in the former, simple removal of the precipitating cause usually returns them to their preexisting state. Patients who develop unstable angina early in their recovery from acute MI (class C) are at high risk of developing additional myocardial damage.

According to this understanding, there is an unstable angina risk score of 1 to 9, with 1 being the mildest and 9 being the most severe, but certain variants have also been examined. For example, the classification described above has been correlated with the underlying coronary anatomy in patients with unstable angina and with chronic stable angina. An "unstable angina score" was established by denoting the severity of unstable angina (class I=1, class II=2, and class III=3) and the clinical circumstances in which it occurs (class A=1, class B=2, and class C=3). Thus, patients

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with unstable angina received scores of 2 to 6; patients with chronic stable angina were assigned a score of 0. In this and other subsequent prospective studies, multivariate analysis identified the unstable angina score to be the most important predictor of coronary lesion complexity and intracoronary thrombus.

A further stratification of risk is suggested, based on absence or presence of ST-T–wave changes during pain and on absence or presence of elevation of troponin levels and CK-MB levels and of the magnitude of changes when present. Hemodynamic deterioration during pain with pulmonary edema, new mitral regurgitation or third heart sound, or hypotension also predicts a more serious prognosis. Other predictors are factors relevant to prognosis at any stage in the evolution of CAD, such as left ventricular dysfunction and extensive CAD, age, and comorbid conditions such as diabetes mellitus, obstructive pulmonary disease, renal failure, and malignancy.

Pathogenesis

The five major causes of ACS are thrombus, mechanical obstruction, dynamic obstruction, inflammation, and increased oxygen demand. The major pathophysiologic mechanism is rupture or fissuring of an atheromatous plaque with superimposed thrombus. Other mechanisms include superficial erosion (which is more common in women), intraplaque hemorrhage, and erosion of a calcified nodule. Patients with ACS often have more than one ulcerated plaque, as shown by angiography, intravascular ultrasound, angioscopy, and release of inflammatory markers such as myeloperoxidase across nonculprit coronary vascular beds. Multiple plaque ruptures are more common in patients with increased C-reactive protein (CRP) levels.

In some patients, thrombogenicity of the blood (sometimes referred to as vulnerable blood leading to the concept of vulnerable patients) is implicated, with alterations in circulatory prothrombotic or antifibrinolytic mechanisms. Levels of plasminogen activator inhibitor-1 are increased in patients with obesity or diabetes

Superficial fissuring of a plaque usually results in platelet deposition. There is less superimposed thrombus formation in patients with NSTEACS than in those with STEMI, which is usually associated with deep arterial injury and occlusive thrombus. Angioscopic findings show that the thrombus associated with unstable angina is

white or gray and consists mostly of platelets, whereas the thrombus associated with STEMI consists mostly of red blood cells.

Inflammation plays a major role in atherosclerosis, and activation of macrophages triggers inflammatory processes that lead to plaque instability, procoagulation, and clinical events. Plaque rupture or fissuring can be triggered by increased shear forces with sudden changes in pressure or tone. Rupture most often occurs on minor plaques that are eccentric and have a large lipid core with a thin fibrous cap, increased concentrations of macrophages, and local expression of tissue factor. Macrophages produce metalloproteases such as collagenase, elastases, and stromelysins, which digest extracellular matrix. Macrophage-rich areas are more commonly found in atherectomy specimens from patients with unstable angina than from those with stable angina. Activated T lymphocytes are present at sites of plaque rupture and they release various cytokines which activate macrophages and promote smooth muscle cell proliferation. Mast cells are found on plaque edges at sites that are likely to rupture. Increased levels of CRP and its major inducer, interleukin-6, have been found in patients with unstable angina, and are associated with higher rates of death/MI at hospital discharge and at 1 year.

The inflammatory stimulus for triggering expression of soluble cell adhesion molecules has been shown to persist for 6 months after presentation with NSTEACS. The inflammatory nature of the cells at the site of plaque rupture and shared T-cell receptor sequences in clonotypes from different patients have led to speculation that chronic stimulation by a common antigen or certain bacterial infections, such as Chlamydia pneumoniae or Helicobacter pylori, may be associated with an increased risk of plaque rupture.

The T-cell response in patients with unstable angina is antigen-driven and directed toward antigens carried in culprit coronary atherosclerotic plaques. Cytomegalovirus has been found in atheromatous plaque specimens, but active replication of the virus is not thought to be a major cause of plaque instability.
After plaque rupture or fissuring, subendothelial adhesive proteins, collagen tissue factor, and von Willebrand factor are exposed, and tissue factor is released. Platelets

adhere to GP Ia and Ib, change their shape, and release serotonin, thromboxane A_2, and adenosine diphosphate (ADP). In animal models, episodic platelet aggregation at sites of coronary stenosis has been shown to cause cyclic coronary blood flow. Platelet emboli have been found downstream from atheromatous plaques in small intramyocardial vessels from patients who have died suddenly. Platelet activation may manifest in anginal episodes associated with increased urinary levels of thromboxane B2.

Released tissue factor combines with factor VII, stimulating the extrinsic coagulation cascade to form thrombin, a very potent stimulus of platelet aggregation. At the platelet surface, factors V and X are activated to form the prothrombinase complex, which generates more thrombin. Damage to endothelium without plaque rupture may also result in thrombus formation. Evidence of a hypercoagulable state has been found in patients with unstable angina. During anginal episodes, increases occur in the plasma concentrations of prothrombin fragments 1 and 2 (signifying increased activity of factor Xa and thrombin formation) and fibrinopeptide A (a sign of increased thrombin activity and fibrin formation). These markers remain elevated for at least 6 months after ACS, and platelets remain activated for at least 28 days. Intracoronary thrombus is visualized in 35% to 52% of patients having coronary angiography for unstable angina; the detection rate rises to 70% to 93% when angioscopy is performed. The presence of thrombus at angiography denotes an increased risk of recurrent ischemia and MI. Another potential mechanism of ACS is increased narrowing of a coronary artery due to progression of atherosclerosis or plaque rupture.

Cocaine is toxic to the heart, and its use may be associated with ACS, even in patients with angiographically normal coronary arteries. There is a circadian variation in the onset of ACS. Platelet aggregation increases in the morning, elevating the risk of MI or sudden death. Activities such as heavy exertion, which produces acute physiologic effects, may also trigger ischemic events.

Coronary Artery Spasm
In 1959, Prinzmetal et al. described a variant form of angina characterized by chest pain predominantly at rest and usually associated with ST elevation on the ECG. Rarely, variant angina is associated with other vasospastic disorders (such as

migraine or Raynaud syndrome) in patients with angiographically normal coronary arteries. In Prinzmetal's variant angina, there is a transient, abrupt, marked reduction in the diameter of a proximal epicardial coronary artery, resulting in myocardial ischemia in the absence of any preceding increases in myocardial oxygen demand (reflected in elevations of heart rate or blood pressure). This reduction in diameter can usually be reversed by nitroglycerin and can occur in either normal or diseased coronary arteries. The striking reduction in luminal diameter is usually focal and involves one site or occasionally more than one. Sites of spasm in Prinzmetal's angina are often adjacent to atheromatous plaques. Potential mechanisms include endothelial injury (which reverses the dilator response to a variety of stimuli, eg, acetylcholine) and hypercontractility of vascular smooth muscle due to vasoconstrictor mitogens, leukotrienes, serotonin, and higher local concentrations of blood-borne vasoconstrictors in areas of neovascularized atherosclerotic plaques. Moreover, several studies suggest that magnesium ions play a role in the pathogenesis of attacks of variant angina. In patients with variant angina, magnesium sulfate has been shown to terminate stressor-induced variant anginal attacks.

Although many episodes of unstable angina and acute MI are caused by the disruption or erosion of plaque with superimposed thrombosis, other mechanisms that alter myocardial oxygen supply and demand must be considered. Original studies have suggested that coronary vasoconstriction plays an important role. In the acute coronary syndromes, vasoconstriction either may occur as a response to a mildly dysfunctional endothelium near the culprit lesion or, more likely, may be a response to deep arterial damage or plaque disruption of the culprit lesion itself. Thus, in regard to this second type of vasoconstriction, it appears that a predisposition exists for platelet-dependent and thrombin-dependent vasoconstriction at the site of plaque disruption and thrombosis that may be very significant but transient. Thus, platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A_2, and thrombin-dependent vasoconstriction occur if the vascular wall has been significantly damaged with de-endothelialization, suggesting the direct interaction of these substances with the vascular smooth muscle cells.

Plaque Disruption

The process of atherogenesis, lipid accumulation, cell proliferation, and extracellular matrix synthesis is neither linear nor predictable. New high-grade lesions often appear in segments of artery that were normal only months earlier at angiographic examination. Indeed, mild coronary lesions may be associated with significant progression to severe stenosis or total occlusion; these lesions may account for as many as two thirds of the patients in whom unstable angina or other acute coronary syndromes develop. This unpredictable and episodic progression is most likely caused by plaque disruption with subsequent thrombus, which changes the plaque geometry, leading to intermittent plaque growth and acute occlusive coronary syndromes.

Pathological studies have revealed that such atherosclerotic plaques prone to rupture are commonly composed of a crescentic mass of lipids separated from the vessel lumen by a fibrous cap. Plaques that undergo disruption tend to be relatively soft and have a high concentration of cholesteryl esters rather than of free cholesterol monohydrate crystals. In addition, plaques rich in extracellular matrix and smooth muscle cells, not necessarily considered vulnerable or lipid rich, may have a superficial erosion with complicated thrombosis also leading to unstable angina and other acute coronary syndromes. Moreover, in addition to this rather "passive" phenomenon of plaque disruption, a better understanding of an "active" phenomenon related to macrophage activity is evolving.

Passive Plaque Disruption

Related to physical forces, passive plaque disruption occurs most frequently where the fibrous cap is thinnest, most heavily infiltrated by foam cells, and therefore weakest. For eccentric plaques, this is often the shoulder or between the plaque and the adjacent vessel wall. Pathoanatomic examination of intact and disrupted plaques and in vitro mechanical testing of isolated fibrous caps from aorta indicate that vulnerability to rupture depends on three factors: circumferential wall stress or cap "fatigue"; location, size, and consistency of the atheromatous core; and blood flow characteristics, particularly the impact of flow on the proximal aspect of the plaque (ie, configuration and angulation of the plaque).

Active Plaque Disruption

An active phenomenon of plaque disruption is probably important. Thus, atherectomy specimens from patients with acute coronary syndromes revealed macrophage-rich areas. Macrophages can degrade extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and a family of matrix metalloproteinases (collagenases, gelatinases, and stromelysins) that may weaken the fibrous cap, predisposing it to rupture.

Acute Thrombosis

Disruption of a vulnerable or unstable plaque with a subsequent change in plaque geometry and thrombosis results in a complicated lesion. Such a rapid change in the atherosclerotic plaque geometry may result in acute occlusion or subocclusion with clinical manifestations of unstable angina or other acute coronary syndromes. More frequently, however, the rapid changes appear to result in mural thrombus without evident clinical symptoms, which, by self-organization, may be a main contributor to the progression of atherosclerosis. More specifically, at the time of coronary plaque disruption, a number of local and thrombogenic factors may influence the degree and the duration of thrombus deposition. Such a thrombus may then either be partially lysed or become replaced in the process of organization by the vascular repair response

Vulnerable Plaque Substrate and TF-Dependent Thrombus

Various human atherosclerotic plaques (by American Heart Association classification) were exposed to flowing blood at high shear rate, and their thrombogenicity was evaluated. In a disrupted vulnerable plaque with ulceration, as occurs in approximately two thirds of acute coronary syndrome, the lipid-rich core abundant in cholesteryl ester displayed the highest thrombogenicity and the most intense TF staining compared with other arterial components. Colocalization analysis of coronary atherectomy specimens (culprit lesions) from patients with unstable angina demonstrated a strong relationship between TF and macrophages.

Systemic Hypercoagulable State–Dependent Thrombosis

It was also investigated whether systemic factors, such as the circulating monocyte, may be involved in TF expression and thrombogenicity, triggered by infection, hypercholesterolemia, or other systemic factors. Thus far, preliminary evidence confirms that in a disrupted plaque with only an erosion, as occurs in approximately one third of acute coronary syndromes (exposing collagen or smooth muscle cells), thrombosis may occur only in the presence of some of the circulating or systemic factors mentioned above.

Integrated Pathogenesis of the Various Coronary Syndromes and of Unstable Angina

Having discussed plaque disruption and thrombus formation, we will summarize the current views on the pathophysiology of acute coronary syndromes. In patients with stable CAD, angina or silent ischemia commonly results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increase its delivery. In contrast, unstable angina or ischemia, non–Q-wave MI, and Q-wave MI (on occasion these acute syndromes may also be silent) present a continuum of the disease process and are usually characterized by an abrupt reduction in coronary flow. Thus, the presence of local and systemic thrombogenic risk factors at the time of plaque disruption may modify the extent and duration of thrombus deposition and account for the variety of pathological and acute clinical manifestations.

In unstable angina, a relatively small erosion or fissuring of an atherosclerotic plaque may lead to an acute change in plaque structure and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque injury may occur, leading to angina at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10 to 20 minutes. In addition, release of vasoactive substances by platelets and vasoconstriction secondary to endothelial vasodilator dysfunction may contribute to a reduction in coronary flow. Overall, alterations in perfusion and myocardial oxygen supply probably account for two thirds of episodes of unstable angina; the rest may be caused by transient increases in myocardial oxygen demand.

In non–Q-wave MI, more severe plaque damage would result in more persistent thrombotic occlusion, perhaps lasting up to 1 hour. Approximately one fourth of patients with non–Q-wave MI may have an infarct-related vessel occluded for >1 hour, but the distal myocardial territory is usually supplied by collaterals. ST-segment elevation in the ECG, an early peak in plasma CK concentration, and a high rate of angiographic patency of the involved vessel in early angiograms support these speculations. Resolution of vasoconstriction may be also pathogenically important in non–Q-wave MI. Therefore, spontaneous thrombolysis, vasoconstriction resolution, and presence of collateral circulation are important in preventing the formation of Q-wave MI by limiting the duration of myocardial ischemia.

In Q-wave MI, larger plaque fissures may result in the formation of a fixed and persistent thrombus. This leads to an abrupt cessation of myocardial perfusion for >1 hour, resulting in transmural necrosis of the involved myocardium. The coronary lesion responsible for the infarction and the other acute coronary syndromes is frequently only mildly to moderately stenotic, which suggests that plaque rupture with superimposed thrombus rather than the severity of the underlying lesion is the primary determinant of acute occlusion. Some cases of sudden coronary death probably involve a rapidly progressive coronary lesion in which plaque rupture and resultant thrombosis lead to ischemic and fatal ventricular arrhythmias in the absence of collateral flow. Platelet microemboli may contribute to the development of sudden ischemic death.

Pathophysiologic Implications for Clinical Management

The management of patients with NSTEACS should focus on the pathophysiology. The primary aims of treatment are to reduce initial symptoms and ischemia, prevent MI, minimize necrosis in the event of MI, and reduce mortality. In individual patients, the mechanisms of plaque rupture or fissuring, platelet aggregation, thrombus formation, and increased vasomotor tone may play different roles at different times. A variety of therapeutic approaches are needed to modify these processes.

The mainstays of medical management are intensive antithrombotic therapy with aspirin and heparin (either UFH or low-molecular-weight heparin [LMWH]), and an-

tiplatelet therapy with clopidogrel and/or GP IIb/IIIa antagonists. OI-Blockers, nitrates, and calcium channel antagonists should be used for relief of symptoms. Early angiography and revascularization are recommended for patients at high risk or with recurrent symptoms. Risk profiling is pivotal to triage, and the results determine whether patients should be discharged early, admitted and monitored closely, or have early angiography and revascularization.

Patients with an increased oxygen demand or a decreased oxygen supply (e.g., those with anemia or thyrotoxicosis) need to be managed appropriately. Patients with vasospasm require therapies such as nitrates and calcium channel antagonists. It has not yet been established how patients with evidence of inflammation should be managed, although falls in CRP levels have been noted with aspirin and with statins, which improve outcomes independently of their effect on LDL-C

Approach to Early Management

Initial Orientation

Guidelines have been published for the management of patients with unstable angina. Patients at low risk with new-onset exertion angina or minor exacerbation of chest pain during exercise, which is promptly relieved by nitroglycerin, can be safely managed as outpatients, assuming close follow-up and rapid investigation. Patients with prolonged pain and a ruled-out diagnosis of MI are observed in the emergency room or in a chest pain unit, where clinical status, ECG, cardiac enzymes, and whenever possible, troponin T or troponin I plasma levels are monitored. Blood tests are obtained at admission and repeated 8 to 12 hours after the onset of chest pain to rule out myocardial damage. Patients with a more definite diagnosis and one or more features of high risk, including repetitive pain, hemodynamic compromise, ST-segment shift, or elevation in cardiac enzymes or troponin T or I levels are best monitored in a coronary care unit setting. Management of patients with an intermediary risk is directed by the physician's judgment, often dictated by local facilities and pattern of practice.

Clinical Profile

History and Physical Examination

The physical findings and the site, character, and radiation of the discomfort are similar to those seen in patients with MI. The physical examination is usually normal unless ischemia causes signs of poor tissue perfusion, with sweating, tachycardia, cool extremities, third or fourth heart sounds, and signs of heart failure or cardiogenic shock.

Electrocardiography

The ECG is a very important investigative tool; prognosis and management critical depend on ECG findings. An ECG should be performed at admission, daily throughout hospitalization, and during episodes of ischemia. If there are symptoms lasting longer than 20 minutes with ST elevation or new left bundle branch block, administration of fibrinolytic therapy or primary PCI should be considered. A normal ECG does not exclude the possibility of an ACS. Transient ST depression (or, less frequently, elevation) and T-wave inversion occur commonly only during ischemia.

Continuous Electrocardiographic Monitoring

Ischemic ST-segment changes are detected on continuous ECG monitoring in 85% to 90% of patients with unstable angina, but the changes are often silent. Silent ischemia during Holter monitoring has been shown to correlate with reduced myocardial perfusion and impaired ventricular function, and patients with silent ischemia are more likely to die, develop MI, or require revascularization. The European Society of Cardiology (ESC) guidelines for the management of NSTEACS recommend that patients should have multilead continuous ST-segment monitoring if it is available or, failing that, frequent ECGs.

Chest X-Ray

Unless MI has occurred previously, heart size is usually normal. Transient pulmonary edema may occur with global ischemia, and suggests the possibility of a left main coronary stenosis.

Troponins

The cardiac troponins are sensitive and specific markers of myocyte necrosis and are the markers of choice for the diagnosis of MI. Short- and long-term studies have shown that troponin levels correlate with the risk of death and the combined risk of death/MI, with a clear gradient of risk as troponin levels increase. Troponin levels

have been shown to be more powerful prognosticators than CK-MB levels. Thirty percent of patients who present with NSTEACS and normal CK-MB levels have elevated troponin levels, and these patients have poor outcomes. The combination of troponin T testing and exercise testing further defines patients at low, intermediate, and high risk.

Elevated troponin levels correlate with the pathophysiology of ACS (the presence of thrombus in the coronary artery), and reflect the thrombogenic activity of ruptured or fissured plaques with embolism downstream and resultant myocyte necrosis. The prognostic value of troponins is greater than would be expected from the extent of myocyte necrosis and left ventricular impairment, perhaps reflecting preceding episodes of embolic episodes). Angiographic studies have shown that evidence of thrombus, complex lesions, and a reduced TIMI flow grade were more common in patients with elevated troponin levels than in those with normal levels.

Troponin levels identify patients who are most likely to benefit from LMWH, GP IIb/IIIa antagonists, and revascularization. Troponin testing may be the only biomarker assay needed if utilized in a chest pain pathway. Point-of-care testing is recommended in institutions that cannot consistently deliver laboratory results within 1 hour for logistical reasons. Baseline point-of-care use of a multimarker assay including myoglobin (which is released earlier than troponins) has been shown to be a more effective means of risk profiling than single-marker, laboratory-based testing.

Troponins are very sensitive markers of myocyte necrosis, and elevated levels may be detected in contexts other than spontaneous myocardial ischemia or PCI. Apart from ACS, the most common causes of elevated troponin levels are atrial or ventricular tachycardia (often with hypotension and an increased myocardial oxygen demand), pulmonary emboli with right ventricular MI, cardiac failure, cardiac surgery, myocarditis, and renal failure. Other tests such as myosin light-chain assays are not currently recommended as standard practice.

White Blood Cell Count

The white blood cell count is usually normal. An elevated count is associated with higher risks of mortality and MI.

Renal Function

Impaired renal function is associated with a poor prognosis and requires modification of the dosing regimen if LMWH is used.

Inflammatory Markers

There has been extensive research into the roles of inflammation and inflammatory markers in NSTEACS. The levels of high-sensitivity CRP, interleukin-6 and, more recently, CD-40 ligand (which has prothrombotic effects) have been shown to provide independent prognostic information. Elevated levels of other inflammatory markers such as adhesion molecules, interleukin-7, and matrix-metalloproteinases (including pregnancy-associated plasma protein A) have also been observed in patients with NSTEACS.

C-Reactive Protein is an acute-phase protein produced by the liver when there is tissue injury, infection, or inflammation. High-sensitivity CRP levels are elevated in 50% to 70% of patients with Braunwald class IIIB angina. Patients with elevated CRP levels at admission have been shown to have worse in-hospital and 1-year outcomes, and elevated levels at discharge have been associated with recurrent instability in the long term.

CD40 Ligand is expressed on activated platelets, and is prothrombotic and proinflammatory. Elevated levels are associated with increased rates of death, MI, and recurrent ischemia.

Amyloid A is an acute-phase protein produced by the liver. Its predictive value appears to be similar to that of CRP.

Fibrinopeptide A is a polypeptide cleaved from fibrinogen by thrombin. It is a sensitive marker of thrombin activity and fibrin generation. Elevated urinary fibrinopeptide A levels are associated with the presence of intracoronary thrombus and signify an increased risk of death, MI, or revascularization. Persistently elevated levels denote an increased risk of coronary events.

B-Type Natriuretic Peptide (BNP) and the N-terminal fragment of the BNP prohormone (NT-proBNP) are synthesized in the ventricles, and are important markers of neurohormonal activity. BNP levels correlate with left ventricular pressure, and in-

crease in response to myocardial stretching in the event of myocardial ischemia. Several studies have shown that BNP and NT-proBNP levels have powerful prognostic value for death and MI in patients with NSTEACS, independent of markers of myocardial necrosis or inflammation. Patients with normal troponin levels and low BNP levels are at very low risk of cardiovascular events.

Other Markers

A number of other markers are currently under investigation, including interleukin-6, intercellular adhesion molecule-1, lipoprotein-associated phospholipase A_2, and various tissue inhibitors of metalloproteinases. Current guidelines do not recommend routine assessment of inflammatory markers.

Other Laboratory Tests

Primary risk factors, such as cholesterol and glucose levels, should be assessed at admission. Possible secondary causes of unstable angina should be investigated depending on the clinical circumstances, namely anemia, thyrotoxicosis, pulmonary embolism, and aortic dissection.

Risk Profiling is critical because it determines the choice of treatment strategy and provides prognostic information for the patient and relatives. It also enhances the cost effectiveness of patient care by allowing evidence-based treatments to be targeted at patients most likely to benefit from them. Risk profiling should take into account clinical factors, ECG features, cardiac marker levels, evidence of spontaneous or inducible ischemia, measures of left ventricular function, and coronary anatomy. Certain clinical features are not included in risk profiling models, and the clinical assessment should always be regarded as paramount. For instance, a patient who is gray, sweating, and anxious is likely to be at higher risk than one who is relaxed and appears well. Patients should be assessed fully at presentation and then reviewed at 6 to 8 hours for recurrence of ischemia, response to treatment, and the results of cardiac marker tests, particularly the troponins. Further risk profiling should be done at 12 and 24 hours and again before discharge.

Low-risk patients should be discharged early, advised to report any changes in symptoms (e.g., recurring discomfort at rest or at night), and reviewed subsequently

at an outpatient clinic. Intermediate-risk patients should receive intensive antithrombotic therapy and close monitoring. If recurrent ischemia occurs or troponin levels rise, early angiography should be performed with a view to revascularization. If symptoms settle and troponin levels do not rise, tests for inducible ischemia should be performed. If the tests show ischemia at a low workload, angiography should be performed with revascularization as appropriate; otherwise, the patient can be managed medically. High-risk patients should receive intensive antithrombotic therapy and have early angiography and revascularization if their coronary anatomy is suitable.

Noninvasive Investigations

Stress Testing. Exercise or pharmacologic testing (with or without imaging) can be performed as part of a chest pain unit assessment or when patients have been asymptomatic on antithrombotic therapy for 24 to 48 hours. Ischemia occurring at a low workload (<6 metabolic equivalents) is associated with a poor prognosis. When exercise testing for ischemia is negative in patients with a normal baseline ECG, the 5-year survival rate is 95%. Exercise thallium imaging can be used to assess the severity of CAD and the risk of subsequent cardiac events in patients with unstable angina.

Some patients have physical limitations that preclude exercise testing and others have ECG changes that are difficult to interpret because of baseline abnormalities such as left ventricular hypertrophy, left bundle branch block, preexcitation, or the effects of digoxin. Pharmacologic stress testing is of particular value in these patients. Although stress testing can indicate the presence of severe coronary stenoses and the likelihood of multivessel disease, it cannot detect instability of coronary artery plaques.

Echocardiography. Two-dimensional echocardiography can provide anatomic and functional information, which is helpful in determining the diagnosis and prognosis. Transient wall motion abnormalities and changes in ventricular volumes can be detected during ischemia. These findings may be helpful if symptoms are atypical or if ECG findings are nondiagnostic. Echocardiographic changes may precede chest pain or ischemic ST-segment changes. Transesophageal echocardiography is particularly valuable for evaluating the possibility of aortic dissection and structural abnor-

malities of the mitral valve. Dobutamine stress echocardiography is very useful for assessing ischemia and the viability of myocardium.

Cardiac Magnetic Resonance Imaging (MRI) has been shown to accurately predict the presence of significant CAD in patients with NSTEACS. It can also be used to assess global and regional cardiac function, myocardial perfusion, and myocardial viability.

Coronary Angiography. The findings at coronary angiography depend on the population studied. Angiography outlines only the arterial lumen, and may not detect large plaques within the arterial wall. It was predisposed that 19% of patients had no coronary stenoses of more than 60% narrowing, and 4% had a left main coronary stenosis of more than 50%. Single-vessel disease was found in 38%, double-vessel disease in 29%, and triple-vessel disease in 15%. Eccentric plaques and complex plaques are more common in patients with unstable angina than in those with chronic stable angina. Coronary artery thrombi may be detected in 40% of patients having angiography soon after an episode of rest pain. Impaired coronary flow is common.

Left Ventriculography may detect abnormalities of regional wall motion caused by previous MI or hibernation owing to prolonged or recurrent ischemia. Wall motion abnormalities and changes in ventricular volumes may occur during episodes of acute ischemia. The presence of mitral regurgitation can be detected and its severity assessed.

Prognosis. The prognosis is worse in patients with NSTEACS than in patients with STEMI. Within 1 month, 2% to 5% die and 5% to 16% have an MI. Within 1 year, 26% to 35% require readmission to hospital for recurrent symptoms and 4% to 15% die. Patients with unstable angina and a normal coronary angiogram have good short- and long-term prognoses. Some patients may have had elevated troponin levels for another reason, or they may have had coronary atherothrombosis undetected by angiography. Coronary artery spasm may also have played a role.

Clinical Variables. The most important prognostic variables are age, left ventricular function, coronary anatomy, diabetes, and comorbid conditions such as chronic obstructive pulmonary disease, renal failure, cerebrovascular disease, peripheral vascular disease, and malignancy. Rest pain at admission and recurrent ischemic epi-

sodes are high-risk features. Patients who have recurrent rest pain within 48 hours after admission have a 20% lower survival rate. MI occurs in approximately 3% of patients who have accelerating angina without ECG changes and in approximately 18% of those who have rest pain with ECG changes. Ischemic ST-segment changes on the admission ECG are high-risk features. Patients who have myocardial ischemia on continuous ST-segment monitoring have a significantly increased risk of death/MI. Mortality at 1 year can be predicted by the depth of ST depression on the admission ECG. ST depression of more than 1 mm after admission has 89% sensitivity for predicting MI, further angina, or the need for revascularization. The number of ischemic episodes correlates with outcomes. ST-segment shifts increase the risk of death or MI. Patients with ischemia during continuous ST-segment monitoring have an increased risk of death/MI at 1 year.

The medicines that patients are receiving at the time of presentation can be an important indicator of risk. Patients who develop an ACS while on aspirin are at high risk, and thus current aspirin therapy is listed as a risk factor in the TIMI risk score.

Principles of Management

Aims of Treatment

The immediate aims of treatment are to relieve pain with morphine and antianginal therapy, and to prevent MI and death by stabilizing the thrombotic process with antithrombotic therapy. If MI develops, treatments to preserve myocardium should be used, such as fibrinolytic therapy or primary PCI in the event of ST elevation or new-onset left bundle branch block. Longer term goals include identification and treatment of cardiac risk factors such as hypertension, dyslipidemia, smoking, obesity, and lack of exercise. Patients should be assessed for anxiety and depression, and treated appropriately. They should also be enrolled in a cardiac rehabilitation program. It is incumbent upon physicians to use the most cost-effective strategy available.

General Measures

Patients with rest pain and ECG changes within the previous 48 hours should be admitted to hospital. Antithrombotic and antiischemic therapy should be commenced without delay when the patient is first seen in the emergency department, chest pain

unit, or coronary care unit. Patients should be placed on bed rest, ideally with continuous ECG monitoring for arrhythmias and ischemia. Failing that, 12-lead ECGs should be performed at baseline, at 30 minutes, and at 1 hour, and repeated if further pain occurs.

Oxygen is commonly administered to all patients with acute chest pain. The Agency for Health Care Policy and Research guidelines recommend more selective use of oxygen in patients with obvious cyanosis, respiratory distress, or high-risk features.

Morphine is effective for relieving pain and anxiety. It may also reduce cardiac workload and oxygen consumption by causing venodilation and slightly decreasing the heart rate and blood pressure. Morphine should be administered in IV doses of 2 to 5 mg if angina has not been relieved by nitroglycerin tablets or spray, provided there are no contraindications. The dose can be repeated every 5 to 30 minutes.

Antiplatelet Agents

Aspirin potently inhibits thromboxane A_2-dependent platelet aggregation by irreversibly inhibiting the platelet enzyme, cyclooxygenase, and consequently reducing platelet synthesis of thromboxane A_2. Platelet adhesion to damaged endothelium is not affected. Aspirin does not prevent platelet degranulation and does not inhibit platelet aggregation in response to stimuli such as thrombin, ADP, collagen, catecholamines, and shear-induced platelet aggregation. Aspirin resistance occurs in up to 40% of patients and is more common in women and the elderly. However, patients with PIA2 polymorphism of the GP IIb/IIIa receptor have been shown to be more responsive to aspirin. Some patients cannot tolerate aspirin because of gastrointestinal side effects, bleeding, or allergy, and these patients should receive clopidogrel instead.

Aspirin has a number of nonplatelet effects. It inhibits prostaglandin, interleukin-6 synthesis in leukocytes, and the activity of endothelial nitric oxide inhibitors. These features may explain why aspirin appears to have greater effects than would be expected from inhibition of thromboxane A_2-dependent platelet aggregation alone. At high doses, aspirin reduces endothelial production of the vasodilating prostaglandin, prostacyclin.

Despite these limitations, aspirin has been shown to reduce the risk of death or MI by approximately 50% in patients with NSTEACS. The doses used in these studies varied from 75 mg/d to 325 mg four times daily. The effect of aspirin is rapid. In a study of normal volunteers, 162.5 mg of aspirin inhibited 91% of arachidonic acid induced platelet aggregation ex vivo within 15 minutes.

All patients with NSTEACS should receive aspirin as soon as possible unless there is active bleeding or documented hypersensitivity. The initial dose should be 150 to 325 mg to allow for the possibility of reduced intestinal blood flow during ischemia and ensure complete inhibition of thromboxane A_2 production. In the long term, a dose of 75 to 162 mg should be used.

Ticlopidine and Clopidogrel are thienopyridine derivatives, and both are prodrugs. They are selective antagonists of ADP-induced aggregation and reduce responses to other agonists that require ADP. Because of its side effects and delayed onset of action (2-3 days for maximal antiplatelet effect), ticlopidine is not recommended as initial therapy for patients with unstable angina. The American College of Cardiology/American Heart Association (ACC/AHA) and ESC guidelines recommend that a loading dose of 300 mg of clopidogrel be given at the time of PCI.

There are a number of different approaches to prescribing clopidogrel in patients with NSTEACS. One approach is to treat all patients except those likely to have CABG (patients with ECG changes suggestive of left main CAD, multiple regional wall motion abnormalities on echocardiography, hemodynamic instability, or left ventricular failure). An alternative approach is to use clopidogrel at the time of angiography after the coronary anatomy is known.

Clopidogrel is indicated for acute and long-term treatment (for >1 month and ideally for >9 months) in addition to aspirin in all patients with NSTEACS. It is particularly useful for patients who cannot tolerate aspirin. In high-risk patients, use of clopidogrel should be considered in addition to GP IIb/IIIa antagonists.

Platelet Glycoprotein IIb/IIIa Antagonists

The final common pathway to platelet aggregation is the binding of fibrinogen to GP IIb/IIIa receptors on platelet surfaces, with cross-linking and formation of a plate-

let thrombus. The surface of each platelet has 50,000 to 80,000 of these receptors, but they are usually unactivated unless conformational changes are induced by disruption of endothelium. Inhibition of these receptors blocks the final common pathway to platelet aggregation. The effects of multiple antagonists inducing thrombin, thromboxane A_2, collagen, ADP, catecholamine, and shear-induced platelet aggregation can be prevented by blocking these receptors.

Abciximab is a monoclonal antibody to the GP IIb/IIIa receptor, and binds for the life of the platelet. It can cause thrombocytopenia in approximately 1% of patients. Abciximab (0.25 mg/kg IV bolus and 0.125 Bμg/kg/min infusion) should be administered for 24 hours prior to PCI in high-risk patients with known coronary anatomy or for 12 hours starting at the time of PCI.

Tirofiban is a small nonpeptide antagonist of the GP IIb/IIIa receptor, and mimics the tripeptide arginine-glycine-aspartate sequence in fibrinogen. It is nonimmunogenic and highly selective for the platelet fibrinogen receptor, producing an acute effect within 5 minutes of administration. The effects are reversible in 4 to 6 hours.

Heparin

A number of trials have compared UFH with a placebo or control aspirin therapy in patients with unstable angina. A pooled analysis showed that there was a trend for UFH to reduce death/MI at 30 days.

Low-Molecular-Weight Heparins

Although LMWHs lack the minimum 18 saccharides that are required for simultaneous binding of thrombin and antithrombin III, and bind to and inhibit factor X_a more effectively than UFH does. Because the different LMWHs have different chemical structures and different molecular weights, they have different biological properties, different antifactor X_a to antifactor II_a ratios, and different effects on the release of tissue factor pathway inhibitor. The antifactor X_a effects of LMWHs can be partially reversed (by approximately 60%) by administration of protamine sulfate.

LMWHs have a number of advantages over UFH, including greater bioavailability, a more predictable dose response owing to minimal protein binding, higher antifactor X_a to antifactor II_a ratios, greater ability to inhibit thrombin generation, inhibi-

tion of von Willebrand factor release, resistance to inactivation by platelet factor 4, lack of heparin resistance, and lack of platelet activation. LMWHs are more convenient to use than UFH because they require no monitoring of the activated partial thromboplastin time (APTT) and no IV lines. Use of LMWHs has been shown to save money in some healthcare systems. Thrombocytopenia and osteoporosis are less common with LMWHs than with UFH, and rebound ischemia may be less common after cessation of LMWHs. When used for prolonged treatment, however, LMWHs have not been shown to be superior to UFH.

Recommendations for Heparin Use

Patients with intermediate- or high-risk NSTEACS should receive either enoxaparin (1 mg/kg twice daily) or weight-adjusted IV UFH immediately, provided they have no contraindications. The initial dose of UFH should be a weight-adjusted bolus (60 IU/kg) followed by an infusion of 12 IU/kg per hour to maintain the APTT at 50 to 70 seconds. The infusion should be continued for 2 days or until revascularization.

Enoxaparin is the preferred antithrombotic agent in low-risk patients and in intermediate- or high-risk patients who are being managed conservatively for reasons such as multiple comorbidities. For other intermediate- and high-risk patients, UFH and enoxaparin offer similar benefits, although enoxaparin is associated with increased bleeding. Patients should not be switched from one antithrombotic therapy to another.

Direct Antithrombins

Heparin has a number of limitations. It requires monitoring, has a limited effect on fibrin and platelet-bound thrombin, requires antithrombin III as a cofactor, is inactivated by platelet secretion products such as platelet factor 4 and thrombospondin, and carries a risk of thrombocytopenia. Conversely, direct antithrombins have a more predictable and consistent effect on the APTT, are able to inactivate clot-bound thrombin, do not require antithrombin III, and are only minimally affected by plasma proteins or platelet factor 4.

Bivalirudin (formerly known as Hirulog) is a synthetic 20-amino-acid peptide. Its half-life is shorter than that of hirudin (25 minutes versus 2.3 hours) and its action

is reversible. By inhibiting both fibrin-bound and circulating thrombin directly, bivalirudin blocks the powerful effect of thrombin on platelet aggregation. In the Hirulog Angioplasty study, 4,098 patients undergoing PCI for unstable or postinfarction angina were randomized to receive either heparin or bivalirudin. Bivalirudin reduced the combined incidence of death/MI/abrupt vessel closure/CABG/intraaortic balloon pumping [IABP]/repeat PCI from 14.2% to 9.1% (P < 0.05) in patients with postinfarction angina, and overall was associated with lower bleeding rates than heparin. Transfusions were required in 3.7% of patients receiving bivalirudin versus 8.6% of those receiving heparin (P < 0.001).

β-Adrenoreceptor Blockers. β-Blockers are effective when used singly in unstable angina and in combination with nitrate to reduce recurrent ischemia. In a review of 4,700 randomized patients, β-blockers reduced the percentage of those developing MI by 13%. Patients should be started on a β-blocker or have their existing dose adjusted to maintain the resting heart rate at 50 to 60 beats per minute. IV β -blockers should be considered in high-risk patients with rest pain and widespread ST-segment changes or tachycardia. Standard contraindications include marked first- (>0.24 s), second-, or third-degree atrioventricular block, asthma, and severe left ventricular dysfunction. Therapy should be continued in the long term.

Nitrates. No large randomized trials of nitrates in unstable angina have been performed, and there is no compelling evidence that they reduce the risk of death/MI. They do, however, relieve angina. Nitrates are of particular value in patients with vasospasm or a physiologic increase in coronary artery tone. Although they reduce ischemia very effectively, tolerance can develop within 24 hours. Small doses or concomitant administration of the sulfhydryl donor, N-acetylcysteine, may augment the effect of nitroglycerin and decrease tolerance. Nitrates should not be used within 24 hours of sildenafil (Viagra) because of the risk of severe hypotension.

Nitroglycerin should be given immediately, either as a sublingual tablet or spray, to relieve angina. If this does not relieve the symptoms, IV nitroglycerin can be infused to relieve pain and to optimize hemodynamics, starting at an infusion rate of 5

to 10 Bμg/min, with increases every 5 to 10 minutes depending on symptoms and side effects such as headache or hypotension.

Calcium Channel Antagonists dilate coronary arteries by reducing the cellular membrane influx of calcium. They have variable vasodilatory effects in peripheral arteries and have negative inotropic, chronotropic, and atrioventricular conduction-slowing effects. They may enhance diastolic relaxation and left ventricular compliance. When used without a β -blocker, agents that increase the heart rate (e.g., short-acting nifedipine) may result in worse outcomes than agents that reduce the heart rate (e.g., verapamil or diltiazem). Calcium channel antagonists should be used in patients who have refractory ischemia in the presence of β -blocker and nitrate therapy, or in combination with a β -blocker if hypertension is present. Calcium channel antagonists should be avoided in patients with pulmonary edema or left ventricular dysfunction, but are the agents of choice in individuals with variant angina.

Other Agents

Nicorandil has nitrate and potassium channel-opening effects. When compared with a placebo in 188 patients with unstable angina, nicorandil was found to reduce the incidence of recurrent ischemia but not death or MI. Ranolazine increases the efficacy of energy production by decreasing fatty acid oxidation and promoting glucose utilization. It is currently being tested in large clinical trials.

Oral Anticoagulants. Because of their delayed onset of action, oral anticoagulants are not appropriate for acute treatment, but can be considered for long-term use if aspirin is contraindicated.

New Agents. There are a number of new antiplatelet drugs in development. Some block the $P2Y_{12}$ ADP receptor inhibiting platelet secretion and sustained aggregation; others block the $P2Y_1$ ADP receptor on platelets inhibiting shape change and transient aggregation.

Tissue factor is an integral protein of vascular endothelium, and an essential cofactor for the proteolytic activity of factor VII toward its substrates, factors IX and X. Human plasma contains a tissue factor inhibitor that inhibits coagulation. A recombi-

nant tissue factor pathway inhibitor, targeted at exposed subendothelium, is currently in development.

Ximelagatran is an oral direct thrombin inhibitor that requires no coagulation monitoring and can be given in a fixed dose. In a pilot trial of patients with NSTEACS, it reduced the combined incidence of death/MI/severe recurrent ischemia from 11.2% to 7.4%. Pentasaccharides, which are indirect inhibitors of factor Xa, are currently being tested in clinical trials.

Thrombolytic Therapy is not recommended for routine use in patients with unstable angina because it has been shown to increase the risk of MI.

Intra aortic Balloon Pumping (IABP) stabilizes patients and relieves symptoms very effectively. By increasing aortic diastolic pressure, coronary blood flow is improved distal to critical stenoses, and there is a decrease in myocardial oxygen demands owing to reduction of afterload. No randomized trials of IABP have been done in patients with unstable angina. IABP should be considered in patients with refractory symptoms or hemodynamic instability to stabilize patients during angiography or prior to CABG.

Indications for Angiography. Coronary angiography determines the extent and severity of CAD, and may detect thrombus. Assessment of valvular and left ventricular function can be performed at the same time. Indications for angiography (other than as part of an invasive treatment strategy) are listed below.

Indications for Angiography with a conservative strategy

- Suspicion of left main CAD
- Two ischemic episodes lasting >5 min
- Chest pain lasting >20 min >1 mm of ST depression or T-wave inversion while on heparin with a therapeutic APTT
- >2 mm of ST depression or T-wave inversion with or without pain
- Ischemia with development of pulmonary edema, mitral regurgitation, or hypotension
- PCI within previous 6 months
- Previous CABG
- Significant ventricular arrhythmias
- Impaired left ventricular function
- Abnormal stress testing at the nonacute stage

- Diagnosis of CAD in a patient with atypical symptoms

Revascularisation. It is recommended that high-risk patients have early revascularization accompanied by aspirin, clopidogrel, UFH or enoxaparin, and a small-molecule GP IIb/IIIa antagonist for 4 to 48 hours prior to angiography. An alternative approach is to withhold GP IIb/IIIa antagonists, clopidogrel, or both until the coronary anatomy has been defined.

Percutaneous Coronary Intervention. PCI techniques have evolved rapidly over the past several years with the advent of drug-eluting stents. Although PCI improves coronary flow, it may be associated with periprocedural MI owing to obstruction of branch vessels or distal embolization of thrombus or plaque material. In the past, acute thrombotic closure and MI associated with PCI were more common in patients with NSTEACS than in those having elective interventions. Revascularization is not recommended unless the benefits are likely to outweigh the risks.

Coronary Artery Bypass Grafting. CABG is an excellent treatment for relieving angina, and grafts protect against proximal minor plaque instability.

Unstable Angina after Percutaneous Coronary Intervention. If angina develops within the first 7 months after PCI, it is likely that restenosis has occurred at the PCI site. Another possibility is acute thrombotic closure, which may occur late after implantation of a drug-eluting stent. In the event of angina occurring after revascularization, angiography should be performed expeditiously with repeat revascularization if indicated. IV nitroglycerin has been shown to be superior to antithrombotic therapy in preventing recurrent or refractory angina after balloon angioplasty.

Unstable Angina after Coronary Artery Bypass Grafting. Within the first 12 months after CABG using venous conduits, 10% to 15% of grafts occlude owing to technical reasons and fibroproliferation with or without superimposed thrombus formation. Internal mammary artery grafts have better long-term patency rates (approximately 92%), but are vulnerable to early stenosis. In the long term, late graft disease occurs as a result of atherosclerosis and superimposed thrombosis. Progression of atherosclerosis also occurs in the native coronary arteries. Patients with NSTEACS after CABG should have expeditious angiography. Stenting may prevent occlusion of

a severely stenosed vein graft, thereby avoiding reoperation and its associated risks. Unfortunately, disease progression commonly occurs in nonstented segments of the vein graft within 2 years.

The Case for Conservative Management in Intermediate- and Low-Risk Patients. The favorable prognosis of low-risk patients justifies a conservative approach because they are unlikely to require revascularization. These patients can be managed initially with antithrombotic and antianginal therapy to passivate the ruptured or fissured plaque. Subsequent management depends on the severity of recurrent or inducible ischemia. Stress testing can be performed to assess the hemodynamic significance of CAD, and should be delayed until 24 to 48 hours after the last episode of angina. It should be noted, however, that noninvasive stress testing does not predict plaque instability or the risk of future MI; thus, it is important that these patients be reviewed and instructed to report any continuing symptoms.

Early Lipid Lowering. The concept that lipid lowering may stabilize plaques is supported by numerous trials showing that statin therapy reduces the risk of clinical events despite only modest angiographic reductions in the severity of coronary stenoses. The pleiotrophic effects of statins may improve clinical outcomes independently of lipid changes in patients with ACS. Statins may also suppress inflammatory cell activity and reduce thrombus formation. Statin trials have reported rapid improvements in endothelial function and reduced levels of inflammatory markers such as CRP. A major rationale for early commencement of lipid lowering therapy is that it emphasizes to patients that this treatment is important and needs to be continued in the long term. Also patients may be more likely to comply with therapy and achieve their target lipid levels if therapy is commenced and dietary advice is provided during hospitalization.

Anti-Inflammatory and Anti-Infectious Therapy. A small randomized trial compared 48 hours of methylprednisolone therapy with a placebo in 166 patients with unstable angina, and reported a reduction in CRP levels, but no effect on short-term outcomes. A study of long-term therapy with antichlamydial antibiotics found that there was no reduction in the risk of ischemic events after ACS.

Control of the inflammatory process may prevent plaque activation and thrombus formation. Potentially useful interventions are inhibitors of leukotrienes, cyclooxygenase-2, metalloproteinases, monocyte/macrophages, cytokines and adhesive molecules, and modulation of promoters of gene transcription such as nuclear factor-B. There is also a large potential for correcting the triggers to inflammation and the biological offenders, such as oxidized LDL, free radicals, and viruses and bacteria. Candidates for an infectious process are *Helicobacter pylori*, *Chlamydia pneumoniae*, cytomegalovirus, and other herpesviruses. Compelling evidence exists for a role of *Chlamydia pneumoniae*, such as high titers of antibodies in patients with CAD and an acute manifestation, and the presence of elementary bodies, DNA, and antigens in atherosclerotic arterial wall. The infectious process can be a distant infection that induces immune activation, cross-reactive antibodies, cytokine release, endothelial damage and thrombogenesis, or a local infection of endothelial cells, smooth muscle cells, or macrophages and lymphocytes resulting in endothelial injury, cell proliferation, and inflammation. Alternatively, the bacteria can be an innocent bystander. Two pilot studies, however, have suggested that antibiotic therapy with a macrolide could improve prognosis after an acute coronary syndrome.

Prevention of Cell Necrosis. Left ventricular damage is the strongest independent predictor of short- and long-term prognosis after an acute coronary syndrome. Attempts to reduce left ventricular damage in humans have been few in the past because of lack of an effective therapy but are now reviving with the availability of new agents. Ischemic myocardial injury initiates an acute inflammatory response, with neutrophil activation and release of cytokines, leukotrienes, proteases, and free radicals. The interruption of these processes with free radical scavengers and inhibitors of cytokines, lipooxygenase, cyclooxygenase, and various adhesive proteins may be effective in limiting the size of infarction. It is also now possible to prevent the calcium overload associated with myocardial cell ischemia and reperfusion, leading to cell contracture, rupture of sarcolemmas, and cell death by inhibiting the sodium-hydrogen antiport system. Such a potent and relatively selective inhibitor of the Na^+-H^+ exchange system is presently being investigated in clinical situations with risk of

necrosis.

Secondary Prevention. Smoking cessation and treatment of dyslipidemia and hypertension are important secondary preventative measures in all patients with CAD. Other measures that should be instituted include achievement of ideal weight, a regular exercise program, an appropriate low cardiovascular-risk diet, and achievement of optimal diabetic control where necessary. If facilities are available, patients should be referred to a cardiac rehabilitation program. Aspirin, β-blockers, statins, and ACE inhibitors should be prescribed in all patients without contraindications.

Atherosclerosis. The importance of an aggressive program of control of risk factors needs to be stressed with each patient. Discontinuation of smoking, control of hypertension, aggressive lowering of LDL cholesterol values, and physical fitness prevent death, MI, and the need for coronary angiography in later years, suggesting modification in plaque constitution and decreased thrombogenicity. New risk factors are emerging; their independent contributing roles in atherosclerosis and in acute coronary syndrome, as well as the potential benefit associated with their control, need better definition. Some of these are associated with endothelial dysfunction, such as estrogen deficiency, and high homocystein, P-selectin, and von Willebrand factor plasma levels. Others, such as fibrinogen, TF, and factor VII, mark a thrombogenic state. Levels of tissue plasminogen activator inhibitor and of lipoprotein(a) can also be elevated. Markers of an inflammatory state, such as C-reactive protein, interleukin, P-selectin and other cell adhesion molecules, activated circulating leukocytes, and platelet-leukocyte aggregates, are found in unstable angina. The value of these markers to identify the high-risk patients and to evaluate response to treatment needs further investigation. Of interest, the protective effect of aspirin against occurrence of a first MI in the Physicians' Health Study appears to be related to baseline levels of C-reactive protein, raising the possibility that anti-inflammatory agents may have clinical benefits in preventing cardiovascular disease. The doses of aspirin in the study were 325 mg on alternate days.

Guidelines. There is strong evidence that better outcomes are achieved by institutions with higher usage rates of evidence-based therapies. The uptake of treatment

guidelines has been variable. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines investigators (CRUSADE) reported that an early invasive strategy was utilized in only 44.89% of high-risk patients with NSTEACS. Predictors of early invasive treatment included younger age, male gender, lack of comorbidities, and management by cardiologists. When an early invasive strategy was used, there was a lower risk of in-hospital mortality after adjustment for differences in clinical characteristics.

Controversies and Personal Perspectives

Optimal Timing of Revascularization

The optimal timing of revascularization has not been defined. There is increasing evidence that the earlier intervention is undertaken, the better the outcomes are. The optimal timing of intervention may depend on the patient's risk status. Very high-risk patients, such as those with hemodynamic instability or important ventricular arrhythmias, should have angiography as soon as possible. Patients with dynamic ST-segment changes are also likely to benefit from very early intervention, whereas patients with elevated troponin levels may benefit from upstream treatment with GP IIb/IIIa antagonists before angiography within the first 24 to 48 hours. The only way to determine whether early angiography (e.g., within 4 hours) is preferable to delayed angiography (e.g., at 12-24 hours) is to conduct prospective trials in which the timing of planned angiography is randomized.

Upstream Versus In-Laboratory Administration of Glycoprotein IIb/IIIa Antagonists

A distinct advantage of starting a GP IIb/IIIa antagonist prior to intervention is that it extends the benefit of this therapy to patients not having PCI (i.e., those having CABG or no intervention). Conversely, if GP IIb/IIIa antagonist use is limited to the catheterization laboratory, only 40% to 60% of all patients presenting with NSTEACS receive its benefits, and overall the treatment is less beneficial than if it had been administered upstream.

Benefits of Upstream Combination Antithrombotic Therapy

The concept of upstream treatment can also be applied to clopidogrel and enoxaparin. When administered upstream, clopidogrel reduces event rates prior to intervention. In a systematic overview of five trials comparing enoxaparin with UFH in a total of 9,835 patients receiving no antithrombotic therapy prior to randomization, enoxaparin reduced death/MI by 19% at 30 days. This benefit may be applicable to patients receiving upstream enoxaparin prior to revascularization. For every 1,000 patients with elevated troponin levels who receive clopidregrel, enoxaparin and IIb/IIIa antagonists upstream, there may be a 60% relative reduction in event rates and 12 fewer cardiovascular events based on the following calculations: if the event rate is 2% in the first 24 hours, clopidogrel may prevent four cardiovascular deaths, MIs, or strokes; GP IIb/IIIa antagonists may prevent four deaths or MIs; and enoxaparin may prevent four deaths or MIs. If these benefits are additive, 12 major cardiovascular events per 1,000 patients treated may be prevented by upstream administration of intensive antithrombotic therapy. These benefits will need to be balanced with increased bleeding rates.

The Future

Despite considerable advances in treatment, patients with NSTEACS continue to have high morbidity and mortality rates. The number of patients with NSTEACS is likely to increase as the current epidemic of obesity and the metabolic syndrome impact on the prevalence of CAD. There are now six evidence-based treatments available for the treatment of NSTEACS (aspirin, clopidogrel, GP IIb/IIa antagonists, enoxaparin, bivalirudin, and revascularization) and the challenge now facing clinicians is to use them in suitable combinations. New biomarkers such as BNP and inflammatory markers such as interleukin-6 and CRP need to be integrated into risk algorithms.

Dynamic multimarker risk profiling needs to be integrated into routine clinical management, perhaps with the use of computer algorithms. New biomarkers for risk profiling including markers of ischemia, inflammation, thrombosis, myocyte necrosis, and plaque instability will enable targeting of therapies for efficacy and safety.

High-resolution, three-dimensional MRI can distinguish intact thick and fibrous plaque caps from intact thin and disrupted caps in human carotid arteries. This technology may allow examination of the association between fibrous cap changes and clinical outcomes, enabling the development of therapies to stabilize plaques. Innovative research is currently being done on noninvasive assessment of plaque temperature. Warmer plaques have increased numbers of macrophages and a greater propensity for rupture.

Further developments in noninvasive imaging may enable detection of coronary thrombi composed mostly of platelets, at which agents such as GP IIb/IIIa antagonists could be targeted. If imaging showed that a thrombus consisted mostly of red blood cells, a direct antithrombin might be more effective, whereas if the thrombus was a mixture of platelets and red blood cells, combination therapy might be more suitable. If an elevated plaque with little thrombus was detected, PCI without adjunctive drug therapy might be the most appropriate first-line treatment.

Our knowledge of the mechanisms that lead to plaque instability will continue to expand. Predictors of plaque instability need to be identified so that high-risk patients can be targeted with specific therapies. Apoptotic macrophages can be detected in recently disrupted plaques by scintigraphy using radiolabeled antiannexin antibodies. Treatments that may reduce the vulnerability of plaques to rupture include matrix metalloproteinase inhibitors and locally delivered growth factor inhibitors. Modulation of the ability of the myocardium to survive ischemia, including angiogenesis and metabolic manipulation, will be the focus of active research. Diagnostic modalities such as single-photon emission with radiolabeled B-methyl iodophenyl pentadecanoic acid can detect myocardium that has been ischemic in the last 24 to 36 hours. It may be possible to combine this technology with high-resolution computed tomography for noninvasive detection of thrombogenic coronary plaques. Rapid genomic profiling tests may be developed for bedside use so that therapies can be targeted at patients who are most likely to benefit and least likely to experience side effects. Clinical outcomes may be improved by combinations of current therapies with different dosing regimens. Nevertheless, there is still a need for safer, more effective, cost-effective,

and easily administered treatments, including oral medications. In the long term, greater emphasis must be placed on primary prevention.

Conclusions.

In summary, the pathophysiology of ACS involves numerous pathways building up to result in intravascular thrombosis, ischemia, and cell death. The multifactorial etiology requires a multifactorial approach. The road to effective control has been marked by definition of the cellular mechanisms; development of effective antithrombotic therapy with aspirin, heparin, and the GP IIb/IIIa inhibitors; and progress in revascularization procedures. The road to future progress is rich in new working hypotheses and therapeutic strategies.

SQUEEZES

SQUEEZE FOR ATHROSCLEROSIS

1. What kind of value of fixed coronary atherosclerotic lesion shows myocardial ischemia during increased myocardial metabolic demand? Choose one corrected answer only.
   a. More 50%
   b. More 60%
   c. More 70%
   d. More 80%
   e. More 90% or oclusion

2. What kind of value of fixed atherosclerotic lesions of coronary artery abolishes completely the blood flow reserve? Choose one corrected answer only.
   a. at least 90%
   b. at least 80%
   c. at least 70%
   d. at least 60%
   e. at least 50%

3. Coronary X-syndrome is referred as combination some sings. Choose one uncorrected answer only.
   a. severe left and / or right main stenosis
   b. normal or minimal atherosclerosis of epicardial coronary arteries
   c. stable angina pectoris
   d. reduced coronary flow reserve
   e. structural alterations of small coronary arteries and arterioles

4. What kinds of factors may be responsible as multiple mechanisms for coronary X-syndrome? Choose one uncorrected answer only.
   a. decreased release of local vasoconstrictors,
   b. impaired endothelial dysfunction,
   c. fibrosis and medial hypertrophy of the microcirculation,
   d. abnormal cardiac adrenergic nerve function,
   e. estrogen deficiency

5. To improve prognosis by preventing myocardial infarction in patients with CAD some directions are available. Choose one uncorrected answer only.
   a. Eradicating symptoms of angina
   b. Reverse endothelial dysfunction
   c. Reduced plaque progression
   d. Stabilize plaque
   e. Prevention thrombosis

6. Determine clinical settings that occur with endothelial dysfunction. Choose all correct answers.
   a. Dyslipidemia
   b. Arterial hypertension
   c. Diabetes\mellitus
   d. Nicotine exposure
   e. All answers are correct

7. Determine causes that can be occur with endothelial dysfunction appierence. Choose all correct answers.
   a. Increased permeability to lipoproteins
   b. Decreased nitric oxide production
   c. Prothrombotic dominance
   d. Vascular growth stimulation
   e. All answers are correct

8. Determine causes that can be occur with endothelial dysfunction appierence. Choose all correct answers.
   a. Increased permeability to lipoproteins
   b. Decreased nitric oxide production
   c. Prothrombotic dominance
   d. Vascular growth stimulation
   e. All answers are correct

9. Determine causes associated with arterial hypertension that can induce an endothelial damage. Choose all correct answers.
   a. increases collagen and elastin,
   b. induce endothelial permeability
   c. modulate monocyte accumulation
   d. decreased nitric oxide production
   e. All answers are correct

10. Determine methods of measuring human coronary blood flow in the cardiac catheterization laboratory. Choose all correct answers.
   a. thermodilution,
   b. digital subtraction angiography,
   c. electromagnetic flowmeters,
   d. Doppler velocity probes for measuring coronary flow reserve
   e. All answers are correct

SQUEEZE FOR STABLE CORONARY ARTERY DISEASE
1. The initial treatment of the patient with stable angina pectoris should include all the elements. Choose one uncorrected answer only.

a. Antioxidants and Vitamins Supplementation
b. Diet and Diabetes Mellitus treatment
c. Cigarette smoking and Cholesterol Lowering
d. Beta-blocker and Blood pressure lowering
e. Aspirin and Antianginal therapy
f. Education and Exercise performing

2. To minimize or abolish symptoms of angina pectoris some approaches are available. Choose one uncorrected answer only.
   a. Education and Exercise
   b. Life-style modification
   c. Drug therapy
   d. Opening of coronary artery
   e. Revascularization procedures

3. What kind of fixed segmental coronary stenosis value may prevent sufficient myocardial blood flow? Choose one corrected answer only.
   a. <50%
   b. <40%
   c. <30%
   d. <60%
   e. <70%

4. Determine risk factors associated with stable coronary artery disease. Choose all correct answers.
   a. Diabetes mellitus
   b. Smoking status
   c. Arterial hypertension
   d. Previous myocardial infarction or stroke
   e. All answers are correct

5. Determine non-cardiovascular risk factors associated with stable coronary artery disease. Choose all correct answers.
   a. anemia,
   b. thyrotoxicosis,
   c. chronic renal disease,
   d. chronic volume overload,
   e. All answers are correct

6. Determine non-cardiovascular risk factors associated with stable coronary artery disease. Choose all correct answers.
   a. anemia,
   b. thyrotoxicosis,
   c. chronic renal disease,

d. chronic volume overload,

e. All answers are correct

7. Determine reason of vascular remodeling associated with stable coronary artery disease. Choose all correct answers.

a. extensive atheroma,

b. intima-media thickness,

c. lipids compositions,

d. microvasculatory damage,

e. All answers are correct

8. Determine indications for selective coronary angiography in suspected stable coronary artery disease paatients. Choose all correct answers.

a. when the diagnosis of coronary disease is important to establish yet remains in doubt after noninvasive assessment,

b. when high-risk coronary disease is suspected based on the results of clinical and noninvasive evaluation,

c. in non high-risk patients when significant symptoms persist despite adequate medical therapy

d. when medical therapy is poorly tolerated,

e. All answers are correct

9. Determine diagnostic limitations for selective coronary angiography in suspected stable coronary artery disease paatients. Choose all correct answers.

a. Angiographically apparently normal vessels and stable angina are present

b. Angiographic appearances may underestimate or overestimate the impact of stenosis on myocardial perfusion

c. Angiogram does not provide insights into the histologic structure of stenotic lesions or the likelihood of plaque rupture

d. Standard coronary angiography does not assess the impact of changes in vascular tone

e. all answers are correct

10. Determine indications for CABG in documented stable coronary artery disease paatients. Choose all correct answers.

a. three-vessel disease or two-vessel disease

b. left main stenosis

c. right main stenosis

d. proximal coronary artery stenosis with multiple lesions

e. all answers are correct

SQUEEZE FOR MYOCARDIAL INFARCTION

1. Determine type 1 of myocardial infarction according follow graduations. Choose 1 correct answer.
   a. Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
   b. Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply
   c. Sudden unexpected cardiac death
   d. Myocardial infarction associated with PCI
   e. Myocardial infarction associated with stent thrombosis
   f. Myocardial infarction associated with CABG

2. Determine biological markers that can increase sensitivity and specifity of myocardial infarction identification. Choose all correct answers.
   a. tropinins
   b. MB-CK
   c. myoglobin
   d. trasaminase
   e. free fatty acide-binded protein

3. Determine type 2 of myocardial infarction according follow graduations. Choose 1 correct answer.
   a. Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply
   b. Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
   c. Sudden unexpected cardiac death
   d. Myocardial infarction associated with PCI
   e. Myocardial infarction associated with stent thrombosis
   f. Myocardial infarction associated with CABG

4. Determine biological markers that can use for reinfarction identification. Choose all correct answers.
   a. MB-CK
   b. myoglobin
   c. tropinins
   d. trasaminase
   e. free fatty acide-binded protein

5. Determine biological markers that can use for identification of myocardial infarction after revascularization procedures or CABG. Choose all correct answers.

    a. free fatty acide-binded protein

    b. MB-CK

    c. myoglobin

    d. tropinins

    e. trasaminase

6. Determine all corrected sentences that can be occure in acute myocardial infarction.

    a. ST elevation or diagnostic Q-waves in regional lead groups are more specific than ST depression

    b. In order to identify concomitant right ventricular infarction right precordial leads (V_3R and V_4R) seeking ST elevation are recomended

    c. During an acute episode of chest discomfort, pseudo-normalization of previously inverted T-waves may indicate acute myocardial ischemia

    d. Acute right bundle branch block is considered as equivalent of acute myocardial infarction

    e. Pulmonary embolism, intracranial processes, pancreatitis, or peri-/myocarditis may not result in ST-T abnormalities

7. Determine corrected door-to-needle time for adequate reperfusion procedure in acute myocardial infarction.

    a. within 30 minutes for patients for whom fibrinolysis is indicated

    b. within 30 minutes of arrival of emergency department

    c. within 60 minutes for all patients with ST-segment elevation on ECG

    d. within 90 minutes for all patients with ST-segment elevation on ECG

    e. no corrected answer

8. Determine corrected arrival-to-balloon time for adequate reperfusion procedure in acute myocardial infarction.

    a. within 90 minutes for all enrollement patients for whom PCI is indicated

    b. within 60 minutes of arrival of emergency department

    c. within 30 minutes for all patients with ST-segment elevation on ECG

    d. within 1200 minutes for all patients with ST-segment elevation on ECG

    e. no corrected answer

9. Determine potential advantages of early PCI in acute myocardial infarction.

    a. To minimize infarct size,

    b. To improve patient stability,

    c. To lowe infarct artery thrombus burden,

    d. To increase procedural success rates

e. All answeres are correct

10. Determine more optimal time window for successful thrombolisis in acute myocardial infarction.
    a. 2-16 HRs,
    b. 0-2 HRs
    c. 2-8 HRs
    d. 4-10 HRs
    e. All answeres are correct

SQUEEZE FOR ACUTE CORONARY SYNDROME

1. Determine performances of unstable angina IA type accordingly classification proposed by Braunwald.
    a. new onset of severe angina related to the coronary vascular bed intensifying myocardial ischemia
    b. primary unstable angina with no extrinsic condition to intensify ischemia
    c. significative aggravation angina within 2 weeks after myocardial infarction
    d. angina at rest within the past month but not within 48 hours after myocardial infarction
    e. All answeres are correct

2. Determine performances of unstable angina IIB type accordingly classification proposed by Braunwald.
    a. Primary angina at rest within the past month but not within 48 hours
    b. new onset of severe angina related to the coronary vascular bed intensifying myocardial ischemia
    c. primary unstable angina with no extrinsic condition to intensify ischemia
    d. significative aggravation angina within 2 weeks after myocardial infarction
    e. no correct answere

3. Determine patients of unstable angina with better prognosis.
    a. patients with new-onset, severe angina
    b. patients with primary rest pain
    c. patients who develop unstable angina early in their recovery from acute myocardial infarction
    d. patients with secondary unstable angina
    e. all answeres are correct

4. Determine major causes of unstable angina.
    a. acute thrombus,
    b. mechanical obstruction,

c. dynamic obstruction,

d. inflammation

e. all answeres are correct

5. Determine performances that clarify vulnerable plaque apierence.

    a. intraplaque hemorrhage,

    b. superficial erosion of a cap

    c. calcified cap

    d. rupture of plaque

    e. all answeres are correct

6. Determine the leading cause of superficial fissuring of a plaque.

    a. platelet deposition,

    b. mechanical reasons

    c. calcified cap

    d. deep arterial injury

    e. occlusive thrombus

7. Determine the leading cause of inflammatory stimulus for triggering of plaque fissuring.

    a. Macrophage activation,

    b. mechanical reasons

    c. T-cell-activation

    d. bacterial infections

    e. platelet adgesia

8. Determine all corrected sentences for diagnostic power of cardiac biomarkers in acute coronary syndromes.

    a. cardiac troponins are sensitive and specific markers of myocyte necrosis

    b. Troponin levels have more powerful prognosticators than CK-MB levels

    c. The combination of troponin T testing and exercise testing defines patients at low, intermediate, and high risk

    d. Elevated troponin levels don't reflect the thrombogenic activity of ruptured or fissured plaques

    e. MB-CK levels has higher diagnostic power for myocardial necrosis when compared with troponin T

9. Determine all corrected sentences for diagnostic power of troponin T in acute coronary syndromes.

    a. Troponin levels identify patients who are most likely to benefit from LMWH, GP IIb/IIIa antagonists, and revascularization

    b. Troponin testing may be the only biomarker assay needed if utilized in a chest pain pathway

    c. Troponins may not be detected in contexts other than spontaneous myocardial ischemia or PCI

    d. Multimarker assay including myoglobin (which is released earlier than troponins) is more effective for risk profiling than single-marker

    e. No correted answered

10. Determine indications for angiography in acute coronary syndromes paatients required a conservative strategy

    a. Two ischemic episodes lasting >5 min

    b. Chest pain lasting >20 min >1 mm of ST depression

    c. Suspicion of left main stenosis

    d. Ischemia with development of pulmonary edema, mitral regurgitation, or hypotension

    e. All answeres are correct

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