12 – Which therapy for which condition?

BERNARD J. GERSH,
LIONEL. H. OPIE

> *"Stop it at the start, 'tis late for medicine to be prepared when disease has grown strong through long delays."*
>
> *Ovid, Remedia Amoris*

Angina pectoris

The general approach to angina or any other manifestation of coronary disease has become both more interventional (with increasing use of stents) and more preventional, in that lifestyle modification and aggressive risk factor reduction are now regarded as crucial. Every patient with coronary artery disease requires an assessment of predisposing factors such as diet, smoking, obesity, and lack of exercise, with a search for the metabolic syndrome and diabetes. In exertional angina pectoris, the long-term objectives of treatment are first to improve survival primarily by the prevention of myocardial infarction (MI) and death, and second to improve the quality of life by relief of symptoms.[1] Initial examination requires attention to any precipitating factors (hypertension, anemia, congestive heart failure [CHF], and valve disease). A cornerstone of the management of patients with established coronary artery disease who comprise a population at high risk of subsequent cardiovascular events is aggressive risk-factor reduction.[2-4] The key risk factors are hypertension, hyperlipidemia, smoking, obesity, lack of exercise, and diabetes; more recently, chronic kidney disease has been considered as a coronary heart disease risk equivalent.[5]

Although depression is not established as a major risk factor for the *development* of coronary heart disease, it frequently coexists in patients with symptomatic disease and its recognition and treatment may improve the quality of life.

Role of education in risk-factor modification

Risk-factor modification is a critical component of the integrative management of chronic stable angina as emphasized by the following mnemonic modified from the American College of Cardiology (ACC)–American Heart Association (AHA) guidelines:

A = Aspirin and angiotensin-converting enzyme (ACE) inhibitor
B = β-blocker and blood pressure (BP)
C = Cigarette smoking and cholesterol
D = Diet and diabetes
E = Education and exercise

Therapeutic targets

Lipids.

Regarding a low *high-density lipoprotein (HDL) cholesterol,* our previous advice was to add niacin, but in patients with stable coronary disease and a well-controlled low-density lipoprotein (LDL) cholesterol, the current AIM/HIGH trial found no change in cardiovascular and mortality outcomes even though niacin both increased HDL and decreased triglyceride levels.[6] Furthermore, a large genetic study on more than 100,000 persons found that those with genetically high HDL levels were at the same risk of MI as those with lower HDL values.[7] On the other hand, hereditary factors had no influence on the very strong ($p < 10^{-9}$) relationship between LDL levels and MI.[7] Thus strong evidence suggests concentrating on lowering the

LDL cholesterol.

LDL cholesterol.

In regard to the goal LDL cholesterol, the 2007 ACC-AHA guidelines concluded that a goal of less than 70 mg/dL (1.8 mmol/L) was reasonable in patients with non–ST-elevation acute coronary syndromes (ACS), but there is no reason that this should not apply to all patients with established coronary disease.[8] In patients with an LDL cholesterol of less than 40 mg/dL (1.03 mmol/L) the role of exercise, smoking cessation, and weight loss in obese subjects makes sense and requires further study

Goal blood pressures.

Goal BPs are more controversial, but the recent ACCORD trial demonstrated no compelling reason to support a goal of less than 130/80 mm Hg in patients with established cardiovascular disease and in any event irrespective of the goal, BP reduction should be gradual.[9] ACE inhibitors or angiotensin receptor blockers (ARBs) are indicated in patients with cardiovascular disease who need antihypertensive therapy.[10] In all patients with chronic stable angina, β-blockers are an established therapy. In diabetics, strict glycemic control is recommended, but “how low one should go” is also controversial, as discussed elsewhere in Chapter 11, p. 454).

Diet and supplements

We do not recommend supplemental vitamin E or other antioxidants. The trial data in regard to vitamin E are largely neutral or even negative in two large studies in high-risk or postinfarct patients.[2] Long-term follow-up in the HOPE trial showed an increased risk of heart failure with vitamin E. Rather, we recommend the Mediterranean diet, rich in ω-3 fatty acids.[11] Testosterone improved angina in only one trial.[12] Side effects and lack of data limit its use.

Aspirin is strongly indicated in patients without contraindications, and its efficacy in reducing cardiovascular events in stable angina has been confirmed by a metaanalysis of 287 randomized trials.[13] Clopidogrel is the recommended alternative in patients intolerant to aspirin, although never tested in patients with chronic stable angina. Moreover, for chronic angina its combination with aspirin is unlikely to be more effective than aspirin alone.[14] Low-intensity anticoagulation with warfarin may give benefit similar to that obtained with aspirin,[15] but this approach is rarely employed. Despite the established links between inflammatory markers and coronary artery disease, there is as yet no role for antibiotic therapy.[16] Of note, both statins and aspirin have antiinflammatory properties.

Antianginal drugs

Sublingual nitroglycerin.

Of the various agents that give pain relief (see Fig. 2-2), nitrates are among the most effective, although there is no evidence that nitrates reduce mortality in patients with chronic coronary artery disease. Nonetheless, their efficacy in relieving symptoms and improving exercise tolerance justifies their use as standard therapy in conjunction with a β-blocker or calcium channel blocker (CCB). The prophylactic use of sublingual nitroglycerin prior to activity may be very effective and is probably underused. Thereafter, the addition of long-acting nitrates is indicated. Nitrate tolerance remains a major problem, although the precise mechanisms remain unclear. Eccentric dosage schedules with 8- to 12-hour nitrate-free intervals are the most practical method of avoiding tolerance. Alternatively, a long-acting mononitrate may be given once a day in the morning; its duration of action is supposedly long enough to see the patient through the day, yet short enough to provide a nitrate-free interval at night. All long-acting nitrates appear to be equally effective provided that an adequate nitrate-free interval is provided.

β-blockers versus calcium channel blockers.

Deciding whether to choose a β-blocker or CCB for first-line treatment of angina pectoris is not always easy. Each is combined with nitrates. The metaanalysis of 90 randomized or crossover studies comparing β-blockers, CCBs, and long-acting nitrates demonstrated no significant difference in the rates of cardiac death and MI between β-blockers and CCBs.[17] Nevertheless, there are groups of patients for whom, on the whole, one of these agents might be preferable. First, in the presence of left ventricular (LV) dysfunction,

β-blockers are much preferred because of their capacity to confer postinfarction protection and their favorable effects on outcomes in trials of patients with heart failure.[18] Specifically, there are strong data favoring carvedilol, metoprolol *(Toprol XL)*, and bisoprolol in heart failure. All β-blockers appear to be effective in chronic stable angina irrespective of their pharmacologic properties, and the best advice is to become familiar with one or two drugs (e.g., atenolol, metoprolol, propanolol, and carvedilol, and although rarely used pindolol and acebutolol) that have sympathomimetic activity that may be helpful in patients with a resting sinus bradycardia. Of the β-blockers, only atenolol, metoprolol, nadolol, and propranolol are approved by the US Food and Drug Administration (FDA) for chronic stable angina, leaving metoprolol as the common denominator. Second, in those at risk of acute myocardial infarction (AMI), β-blockers protect in the acute and chronic phases. Third, in patients with angina associated with a relatively high heart rate (anxiety), β-blockade is more logical, or if CCBs are used they should be of the nondihydropyridine variety (heart rate–lowering agents). β-Blocker downsides include quality-of-life problems such as impaired exercise capacity, erectile dysfunction, and weight gain, besides risk of glucose intolerance (see Fig. 11-3), the latter being less likely with carvedilol, nebivolol, and especially the CCBs.

Absolute contraindications to β-blockers.

Absolute contraindications are severe bradycardia, preexisting high-grade or second-degree atrioventricular (AV) block, sick sinus syndrome, asthma that is at least moderate in severity, or class IV heart failure. In patients with chronic obstructive pulmonary disease without frank bronchospasm, cardioselective β-blockers should be used.[19] Most diabetics will tolerate β-blockers, but particular care is needed in patients with insulin-dependent diabetes mellitus with symptomatic hypoglycemia. CCBs may be more effective in hypertensives; in the large ASCOT study, amlodipine combined with an ACE inhibitor reduced the development of unstable angina, MI, and heart failure.[20] When coronary spasm is the established cause of the angina, as in Prinzmetal's variant angina, β-blockers are ineffective and probably contraindicated, whereas CCBs work well.

Which drug and when?

Despite such guidelines, the choice between these two types of agents often cannot readily be resolved. β-Blockers are logical initial therapy in the absence of contraindications in those with prior MI or LV dysfunction. Then, if needed, CCBs should be combined with β-blockers and long-acting nitrates. In the ACTION study, combination of long-acting nifedipine with prior β-blockade reduced major endpoints, particularly in patients with persisting modest hypertension.[21] If side effects from β-blockers are substantial, CCBs in combination with nitrates are the substitute, and long-acting nondihydropyridine CCBs should be used preferentially. "Triple therapy" with nitrates, CCBs, and β-blockers should not be automatically equated with maximal therapy because of new metabolic modulators such as ranolazine (see next section). Furthermore, patients' reactions vary. In particular, excess hypotension should be avoided.

Other antianginal agents.

Nicorandil, a combined nitrate and adenosine triphosphate–dependent potassium channel activator, reduced major coronary events in patients with stable angina in the IONA trial, but there has been no application for its use in the United States.[22] *Ranolazine,* a metabolic agent that is thought to inhibit fatty acid oxidation and the slow sodium channel, improves exercise tolerance and is currently approved for chronic effort angina in the United States (see Fig. 2-8).[23] The drug is effective in reducing symptoms and improving exercise capacity and its role as an antiarrhythmic and glycometabolic agent is currently under investigation.[24] *Trimetazidine* is another metabolic agent, also free of hemodynamic effects, widely used as an antianginal in Europe. *Ivabradine,* approved for use in Europe, acts specifically on the pacemaking hyperpolarization-activated current (I_f) in the sinoatrial node to cause bradycardia. It gives a dose-dependent improvement in exercise tolerance with a lower side effect profile than atenolol.[25],[26] The efficacy of ivabradine in regard to the composite endpoint of cardiovascular death, MI, and hospitalization for heart failure was evaluated in the BEAUTIFUL trial of 10,000 patients with stable coronary artery disease and an ejection fraction of less than 40%, and there was no difference between ivabradine and placebo except in a specific subgroup of patients with heart failure and a rate of 70 beats per minute.[27] However, in the subsequent trial of patients with symptomatic heart failure who are in sinus rhythm with heart rates of 70 beats or higher, ivabradine was associated with a reduction in the composite of cardiovascular death or hospital admission for worsening heart failure.[28] *Allopurinol* decreases myocardial oxygen demand per unit of cardiac output in patients with heart failure, and in a small study of patients with documented coronary

disease high-dose allopurinol showed promise as antianginal agent but needs to be tested further.[29] In patients with stable coronary disease treated with conventional antiischemic and vasculoprotective agents, high-dose allopurinol creates vascular oxidative stress and improved endothelial-dependent vasodilatation.[30] *Perhexiline* was shown to be effective in older trials but is little used to hepatotoxicity and peripheral neuropathy. It has however been used in Australia and Europe in patients with refractory angina.[31]

Revascularization or optimal medical therapy for chronic stable angina?

In stable effort angina, even with multivessel disease, two important trials have not demonstrated any benefit with regard to death or MI of percutaneous coronary intervention (PCI) over medical therapy in patients with preserved LV function in the main, and symptoms of mild to moderate severity.[32],[33] In addition, the BARI IID trial in patients with type 2 diabetes and stable coronary disease demonstrated no benefit for a strategy of revascularization over medical therapy, although in patients with severe coronary artery disease there was a benefit from coronary bypass surgery (but not PCI) on major cardiac events, driven mainly by a reduction in nonfatal MI.[34] In summary, based on the COURAGE and BARI IID trials, in *angiographically selected patients with chronic stable angina and preserved LV function, there is no benefit from coronary revascularization on death and MI.* Unresolved questions are how to extrapolate this to the population at large and the role of stress testing. Another key question is the role of revascularization in patients with moderate to severe ischemia and mild to moderate angina, and this is the objective of the recently initiated National Institutes of Health Heart, Lung, and Blood Institute (NHLBI) ISCHEMIA trial (David Maron, personal communication, 2011). These results are consistent with almost 3 decades of trials and emphasize that current mortality rates in patients with chronic stable angina on intensive medical therapy receiving aggressive secondary prevention are low and unlikely to be improved by revascularization. Thus decisions about the indications for, timing, and type of intervention must be tailored to the individual and need to take into account all these complex cardiac factors and, in addition, the patient's lifestyle, occupation, other medical conditions, and tolerance of optimal medical therapy. In general the concept of "the greater the risk, the greater the benefit from revascularization over medical therapy" applies to patients with left main coronary artery disease, multivessel disease, and in particular in conjunction with LV dysfunction, severe angina, and proximal left anterior descending coronary disease in conjunction with multivessel disease.[35]

Percutaneous coronary intervention.

Major advances have occurred in the use of drug-eluting stents, new antiplatelet agents, new anticoagulants including low-molecular-weight heparin (LMWH) and bivalirudin, and the concept of physiologically directed PCI using measurements of fractional flow reserve as demonstrated by the FAME trial.[36] The introduction of drug-eluting stents (Fig. 12-1) has further decreased the rate of in-stent restenosis and the need for target lesion revascularization by 30%-70% compared with bare-metal stents (BMS), but a metaanalysis of 14 randomized clinical trials failed to demonstrate any differences in rates of death or MI.[37] Several studies have demonstrated the slight increase in very late (greater than 1 year) stent thrombosis, but this has not been associated with any increase in mortality.[38] Despite registry reports demonstrating both increased and decreased late mortality with drug-eluting stents,[39] a randomized trial demonstrated no difference in mortality at all in patients with AMI, suggesting that baseline differences may have played a role in the impact of the registry studies.[40],[41] There were four articles in the *Journal of the American College of Cardiology* in 2007, and five in *Circulation*. The *Lancet* focused on cost-effectiveness of BMS versus drug-eluting stents (if results are the same for some categories of patients, chose the cheaper option). *Reasonable conclusions* to be drawn at present are that the major risk of drug-eluting stents is late thrombosis and that of BMS is restenosis needing revascularization.[40] *Thus drug-eluting stents reduce the need for repeat PCI and improve the quality of life, at the cost of late stent thrombosis that, although infrequent, is unpredictable and has catastrophic consequences.* For on-label indications, there is no increase in death or MI with drug-eluting stents, and for off-label indications where drug-eluting stents are generally used for more complex lesions, several but not all registry studies show no increase in mortality.[42] Crucial to the decision to implant a drug-eluting stent is an assessment of the patient's compliance and ability to tolerate prolonged dual antiplatelet therapy. In the event that a subsequent noncardiac surgical procedure may be likely, it is best to use BMS if at all possible, particularly in patients with larger vessels and shorter, less complex lesions. Third-generation stents are under development and may further change the landscape.

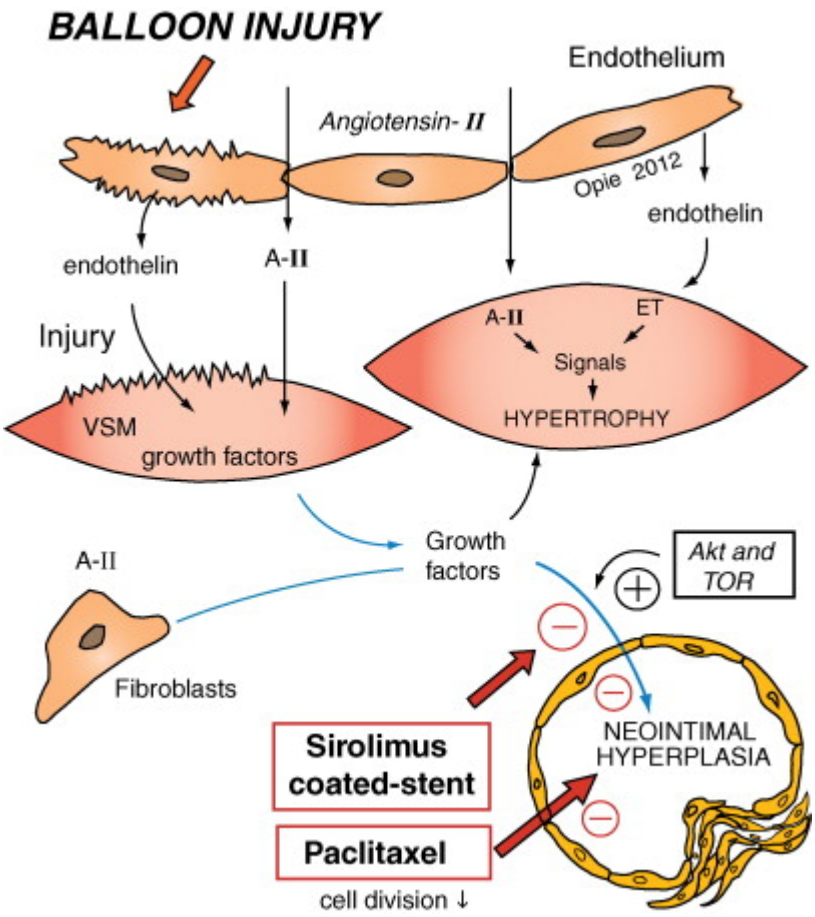

Figure 12-1 Molecular events in restenosis and prevention by drug-eluting stents. The balloon-induced injury damages both endothelium and vascular smooth muscle (VSM) with release of endothelin (ET) and penetration of angiotensin II (A-II). These act to promote growth of both VSM cells and fibroblasts. Growth signals include protein kinase B (Akt) and target of rapamycin (TOR). The result is neointimal hyperplasia that predisposes to restenosis. Drug-eluting stents diminish restenosis. Sirolimus (rapamycin) inhibits growth pathways at the site of TOR, whereas paclitaxel inhibits neointimal hyperplasia.
(Figure © L.H. Opie, 2012.)

Role of coronary artery bypass surgery.

Techniques for surgical and nonsurgical intervention as well as optimal medical therapy are all constantly improving, with off-pump surgery, drug-eluting stents, statins, and tighter BP and glycemic control all giving tangible improvements.[43] For high-risk patients, especially those with complex coronary anatomy, surgery remains a very good option with better results than medical therapy.[44],[45] High risk includes some patients with ACS, recalcitrant effort angina, left mainstem disease whether symptomatic or not, triple-vessel disease, diabetes, and LV dysfunction. In a somewhat lower risk group that excluded left mainstem lesions and poor LV function, stenting was more cost-effective than off-pump surgery with equal improvement in angina and a better quality of life after 1 year.[46] *Off-pump bypass surgery* is an attractive option, particularly in older adult patients, in those with peripheral vascular disease and aortic atherosclerosis, and in the presence of impaired renal function, but it is technically more difficult and randomized trials have not demonstrated its superiority over standard “on-pump” surgery. This is an area of continued investigation and evaluation,[47] with special reference to cognitive function,[48] graft patency,[49] and mortality.[50] Currently in the United States approximately 20% to 25% of all coronary bypass operations are off-pump.

Randomized trials of PCI versus bypass surgery.

The key to selecting the appropriate revascularization strategy, whether bypass surgery or PCI, is based on a careful assessment of the coronary anatomy and the extent of myocardial jeopardy, the need for “complete” revascularization, LV function, the technical suitability of the lesions for a transcatheter

technique, and realistic expectations from the patient of what can be achieved by each procedure. Worldwide, the trend is toward PCI for revascularization.[51] In an older patient population, it is particularly important to screen for comorbid conditions, which can have a crucial effect on procedural success and complications, but also on the long-term outcome. Furthermore, stent insertion has become more adventurous; for example, multiple stent insertion is common and selected stenting for unprotected left mainstem disease is under study.[52] *The ability of coronary artery bypass grafting to bypass the entire vessel as opposed to a single culprit lesion treated by stenting is probably an important predictor of prognosis in the intermediate term* (Fig. 12-2).[53] In clinical practice, it appears that physician judgment and patient preference result in the appropriate bias toward referral of the more complex forms of multivessel disease to surgery as opposed to PCI. Ongoing trials such as FREEDOM in diabetics and the long-term follow-up data from the SYNTAX trial will provide important information regarding the efficacy of drug-eluting stents versus coronary bypass surgery in patients with complex three-vessel and left main coronary disease but against a backdrop of aggressive risk factor reduction. Data from the SYNTAX trial using an angiographic grading tool, namely the SYNTAX score, emphasized the superiority of bypass surgery in patients with more complex and diffuse disease, but approximately one third of patients with three-vessel and left main disease may be appropriately treated with PCI with outcomes that are at least equivalent to coronary artery bypass grafting (CABG). Additional trials in patients with left main coronary disease are needed.[54] It is important in interpreting the results of registry and randomized trials to understand the strengths and limitations of each as the data may be complimentary if used in the correct context.

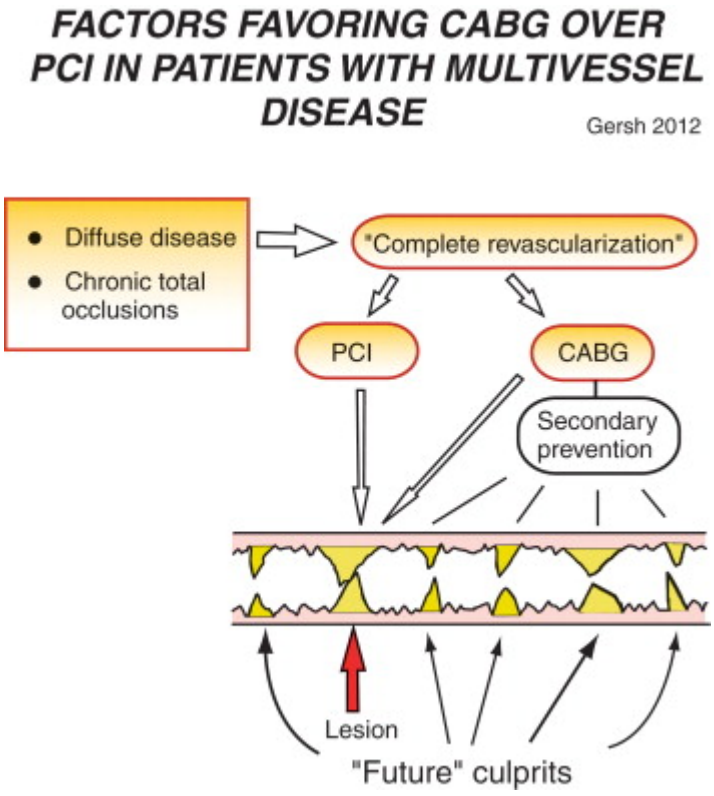

Figure 12-2 Advantages of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in severe multivessel coronary artery disease. CABG gives added protection by bypassing future "culprit lesions." Whereas PCI is directed to the culprit lesion or lesions that are considered responsible for the patient's symptoms, CABG and secondary prevention are directed toward the entire epicardial vessel, including potential "future culprits," defined by nonobstructive lesions that may be the sites of future plaque rupture.
(Figure © B.J. Gersh, 2012.)

Mechanical therapies for refractory angina.

Revascularization is the key when the effort angina is more than mild, especially if symptoms are escalating. The patient population with refractory angina not amenable to revascularization is growing and constitutes a difficult clinical problem. Alternative therapies such as chelation and acupuncture, ineffective in

controlled trials, should be avoided. Of the promising mechanical therapies, the best studied is enhanced external counterpulsation.[55] The multicenter study MUST-EECP trial[56] and several registries have demonstrated both efficacy and tolerability, although the mechanisms of benefit are unclear.[55],[57-59] Spinal cord stimulation in which an electrode is inserted into the epidural space at C7-T1 level is thought to function via the "gate theory" and has been shown to be effective in reducing symptoms and improving the quality of life.[60] Other techniques include transcutaneous electrical nerve stimulation and the intramyocardial implementation of stem cells.[61],[62] All of these modalities require the rigorous scrutiny of large placebo-controlled trials[55]; translaser myocardial revascularization failed this test.[63]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Acute coronary syndromes

MI as redefined by cardiac troponin elevation has become much more common in patients with chest pain.[64],[65] Further classification of ACS is based on the presence or absence of electrocardiographic ST-segment elevation at presentation, giving two clear divisions. ST-elevation ACS requires urgent revascularization by early fibrinolysis or PCI. The sooner revascularization takes place, the better. In non–ST-elevation myocardial infarction (NSTEMI) and unstable angina, management is determined by the degree of risk (Fig. 12-3), with the emphasis in the low-risk groups on prevention of complete thrombosis by antiplatelet and antithrombotic agents, with symptomatic management followed in medium and higher-risk groups by rapid revascularization by PCI.[66] In the current era of new and more powerful antithrombotic agents in conjunction with older and sicker patients, the risk of bleeding is of increasing importance.[67],[68] *General measures* include bed rest and immediate relief of ischemia by nitroglycerin (sublingual, spray, or intravenously) with added β-blockers to reduce the myocardial oxygen demand (Table 12-1). Morphine sulfate is given intravenously if the pain persists or if the patient is agitated or pulmonary congestion is present. Supplemental oxygen is required for hypoxemia or respiratory distress (class IB in the ACC-AHA guidelines),[8] and although in practice it is given routinely to all patients, only three randomized controlled clinical trials have been performed in just 387 patients and no benefit in terms of mortality or pain relief has been demonstrated. In fact, a recent systematic review suggested a trend toward harm from the administration of oxygen, but this could be due to chance.[69]

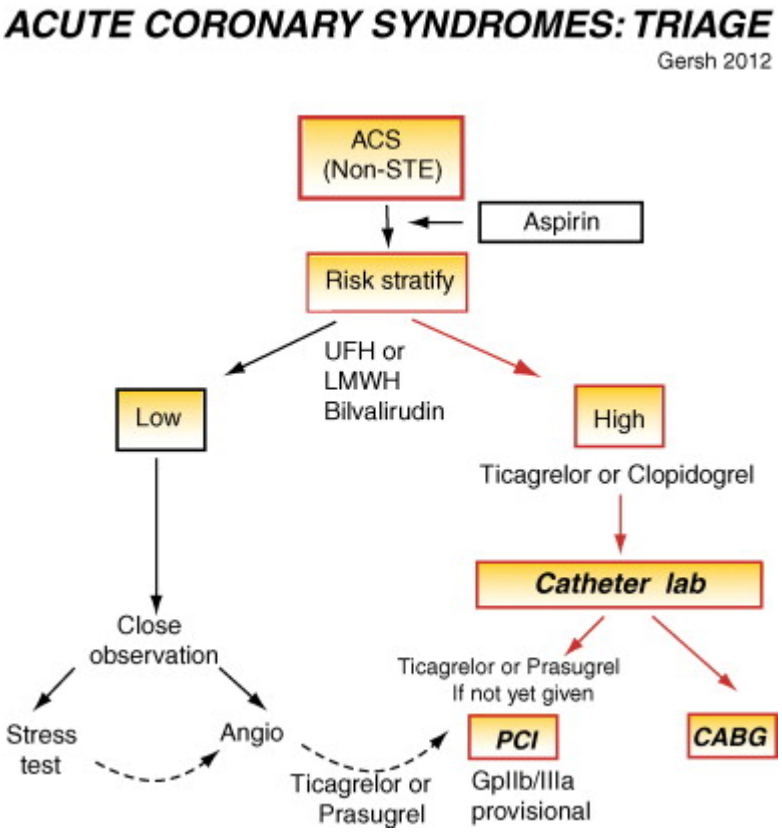

Figure 12-3 Principles of triage for acute coronary syndromes (ACS) with non–ST elevation (non-STE). All receive aspirin. Patients are stratified according to the risk are given unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and bivalirudin (no glycoprotein [Gp] IIb/IIIa, as below). Those *at high risk* are given ticagrelor or clopidogrel, and taken to the catheter laboratory. Then they either undergo coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Those undergoing PCI are given ticagrelor (or prasugrel), if not yet given, and some are selected to be given GpIIb/IIIa inhibitors (see text, Chapter 9, p. 352). Those *at low risk* are closely observed and if requiring an angiogram (angio) given ticagrelor or

prasugrel to be followed by PCI. Those at lower risk and stable are subject to an effort stress test.
(Figure © B.J. Gersh, 2012.)

Table 12-1 -- ACCF-AHA Guidelines for Management of Unstable Angina and Non–ST-Elevation Myocardial Infarction[589]

Early Antiischemic and Analgesic Therapy
1. Oxygen if low arterial saturation (<90%) or respiratory distress (class 1B).*
2. IV nitroglycerin if persistent ischemia, heart failure, or hypertension (class 1B). (Oral nitroglycerin 0.4 mg every 5 min.)
3. Oral β-blockade if no C/I (class 1B).
4. If β-blockade C/I, nondihydropyridine CCB (class 1B).
5. Oral ACE inhibitor within 24 h if LV failure if BP > 100 mm Hg or not >30 mm Hg less than baseline (class 1A); oral ARB if ACE intolerant (class 1A).
Antiplatelet Therapy
1. Aspirin on arrival or before, continue indefinitely (class 1A), nonenteric 162-325 mg; long-term 75-162 mg daily, higher disease after stenting.
2. If aspirin intolerant, clopidogrel loading dose 300 mg, then 75 mg daily (class 1A).
3. Proton pump inhibition if gastric intolerance to aspirin or clopidogrel (class 1B).
4. Initial invasive strategy: upstream clopidogrel or GpIIb/IIIa blocker (class 1A). Abciximab only if rapid PCI likely, otherwise eptifibatide or tirofiban (class 1B).
5. Initial conservative strategy: upstream before urgent diagnostic angiography, clopidogrel loading dose or GpIIb/IIIa (eptifibatide or tirofiban) (class 1A).
Anticoagulant Therapy
1. Initial invasive strategy: enoxaparin or UFH (class 1A) as soon as possible; fondaparinux or bivalirudin (class 1B).
2. Initial conservative strategy: enoxaparin or UFH (class 1A); fondaparinux (class 1B) especially if increased risk of bleeding (1B).

ACCF, American College of Cardiology Foundation; *ACE,* angiotensin-converting enzyme; *AHA,* American Heart Association; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *C/I,* contraindication; *Gp,* glycoprotein; *IV,* intravenous; *LV,* left ventricular; *PCI,* percutaneous coronary intervention; *UFH,* unfractionated heparin.

* Classes of Recommendations (1-3) and levels of evidence (A-C).

Non–ST-segment elevation ACS

Aspirin and clopidogrel.

Evidence for the efficacy of combined aspirin and heparin is strong.[70] Aspirin should be started immediately and continued indefinitely. The key to effective therapy is to institute all other components in the emergency room as rapidly as possible. In patients who are unable to take aspirin, the case for clopidogrel is self-evident. In addition, there is now compelling evidence for combining clopidogrel and aspirin on admission, irrespective of whether catheterization and PCI is planned. Clopidogrel 75 mg daily should be added (class IA in guidelines)[71] for at least 7 days.[72] In centers in which bypass surgery is performed soon after angiography, it is reasonable to withhold clopidogrel until the coronary anatomy and the revascularization strategy have been determined. Before PCI, a loading dose of clopidogrel (class IA) 300 or 600 mg should be given at least 6 hours before the procedure and continued thereafter for at least 1 month, and ideally up to 12 months for drug-eluting stents depending on the type of stent used (see Table 12-3 later), while checking for the bleeding risk, which is increased by combining with aspirin. The ACC-AHA guidelines recommend that troponin-positive high-risk ACS patients needing PCI should be

covered both by upstream clopidogrel and by glycoprotein (Gp) IIb/IIIa inhibition besides aspirin and an anticoagulant.[4] Although there appears to be an interaction between clopidogrel and proton pump inhibitors (PPIs), the clinical significance of this is uncertain.[73] Furthermore, in regard to clopidogrel there is considerable controversy over the effect of CYP2C19 loss-of-function carrier status. In regard to clinical responses and outcomes, in one recent study of patients with ACS and also atrial fibrillation (AF), the effect of clopidogrel over placebo was consistent, irrespective of CYP2C19 status.[74]

Moreover, the recent GRAVITAS trial demonstrated no benefit from double-dose clopidogrel in patients with higher on-treatment platelet reactivity after PCI, suggesting that clinical, procedural, and genetic predictors of the early resolution of high-on-treatment platelet reactivity after PCI requires further investigation. Current evidence suggests that clopidogrel responsiveness is a clinically relevant factor, but we are not sure how to deal with this therapeutically.[75]

Limitations of clopidogrel include its delayed onset of action; marked patient variability; the drug responsiveness, which may be genetically mediated; and the irreversibility of its inhibitory effect. This has led to the development of growth that has higher efficacy but more bleeding.[76] Ticagrelor binds reversibility with $P2Y_{12}$ platelet receptor and has a more rapid onset of action than clopidogrel. Its antiplatelet inhibiting effects appear greater than with clopidogrel, but it is not yet approved for clinical use.[77] In the PLATO trials, ticagrelor was superior overall to clopidogrel in patients treated both invasively and noninvasively.[78] The new European Society of Cardiology (ESC) guidelines recommend *ticagrelor* 180 mg loading dose and 90 mg twice daily in all patients at moderate to high risk of ischemic events (e.g., elevated troponins) regardless of initial treatment strategy. Clopidogrel should be discontinued at the time of *ticagrelor* initiation. In patients in whom the coronary anatomy is known and who are proceeding directly to PCI, *prasugrel* is recommended depending on the risk of bleeding. If fondaparinux is used and the patient proceeds to PCI, a single bolus of unfractionated heparin (UFH) should be added at the time of PCI (and the dose depends on the concomitant use of IIB/IIIA inhibitor.[79]

Cangrelor.

Cangrelor is an intravenous nonthiepyridine $P2Y_{12}$ receptor blocker. It has a rapid onset of action and a short half-life, but has not been shown to be superior to clopidogrel in the CHAMPION trials and is still under evaluation.[80] *Atopaxar* (E555) is a reversible protease-activated receptor-1 thrombin receptor antagonist that interferes with platelet signaling and was shown in a recent trial of patients treated with clopidogrel to reduce early ischemia on Holter monitoring without any increase in bleeding. The drug is not available for clinical use.[81] Clearly, the therapeutic armamentarium in regard to platelet inhibitor therapy is expanding, but it remains to be seen how this plays out depending on the trade-off between efficacy and bleeding.

Heparin versus low-molecular-weight heparin.

The optimum dose of UFH is not established, but a weight-adjusted regimen with frequent monitoring to maintain the activated partial thromboplastin time (aPTT) between 1.5 and 2 times controlled is probably the most reasonable.[82] Although the optimal duration of anticoagulant therapy remains undefined, in the majority of trials, UFH was continued for 2 to 5 days. There is a lower incidence of heparin-associated thrombocytopenia with LMWH. The introduction of LMWH has been an advance given the ease of subcutaneous administration and the absence of a need for aPTT monitoring. This allows for a longer period of treatment and consequently offers some protection against the “rebound” phenomenon seen soon after heparin withdrawal. Theoretically, LMWH offers other potential benefits by acting on both thrombin generation and thrombin activity (see Chapter 9, p. 369).

Which lmwh should be used?

Because there are no direct head-to-head comparative trials, definitive conclusions cannot be drawn. Two trials with enoxaparin, ESSENCE and TIMI IIB, have demonstrated a moderate benefit over UFH,[83],[84] one trial with dalteparin[85] was neutral, and the FRAXIS trial with nadroparin showed an unfavorable trend.[86] Hence enoxaparin is preferred in guidelines.

Lmwh and PCI.

Because the level of anticoagulant activity cannot easily be measured in patients receiving LMWH, concern

has been expressed regarding its use in patients undergoing coronary angiography. Three studies have shown, however, that PCI can be performed safely in this setting,[87-89] as now confirmed in the large SYNERGY study, although at the cost of a modest increase in bleeding.[90] A subsequent comprehensive review of seven relevant trials found no difference between the two treatments in regard to mortality, recurrent angina, and bleeding, although LMWH significantly reduced the risk of MI, revascularization, and thrombocytopenia.[91] Thus LMWH is safe and effective with PCI and GpIIb/IIIa inhibitors, but in many institutions, particularly in the United States, is used less frequently than UFH, with which clinical experience is greater.

Direct thrombin and factor Xa inhibitors.

Bivalirudin, a direct thrombin inhibitor, is approved in the United States for clinical use in patients with unstable angina undergoing PCI, as summarized in Chapter 9 (see Fig. 9-11). In patients with moderate- to high-risk ACS and planned early catheterization, bivalirudin infusion with upstream aspirin is superior to UFH or enoxaparin plus GpIIb/IIIa antagonists, with less bleeding and similar clinical outcomes.[92]

Fondaparinux (see Chapter 9, p. 374) is a synthetic pentasaccharide that is an antithrombin-dependent indirect inhibitor of activated factor X (Xa) without inhibition of the thrombin molecule itself (see Fig. 9-10). The specific anti-Xa activity is approximately sevenfold higher that that of LMWHs. It has a longer half-life (approximately 17 hours) than UFH or LMWH, and needs no monitoring. Fondaparinux is superior to placebo but not to UFH in ST-elevation myocardial infarction (STEMI) (treated with thrombolytic agent or without reperfusion) and is superior to LMWH in non–ST-elevation ACS (lower bleeding and fewer deaths). The ESC guidelines favor fondaparinux in non–ST-elevation ACS unless the patient is planned for early intervention.[93] ACC-AHA guidelines, however, support fondaparinux for both invasive and conservative strategies as class IB, below class IA for UFH or enoxaparin.[8] Before PCI, adjunctive UFH is added to lessen the risk of catheter thrombosis.

Platelet GpIIb/IIIa receptor antagonists.

Smith et al. state, “A challenge for current guidelines is the integration of GpIIb/IIIa studies from the 1990s with more recent studies using preangiography clopidogrel loading and newer anticoagulants.”[4] As shown in Fig. 12-3, GpIIb/IIIa blockers combined with aspirin and clopidogrel and heparin (UFH/LMWH) benefit patients who have ACS without ST-segment elevation but are also at high risk (high risk score or elevated troponin levels), in whom intervention by PCI is likely or indicated. The ACC-AHA guidelines recommend that troponin-positive high-risk ACS patients needing PCI should be covered both by upstream clopidogrel and by GpIIb/IIIa inhibition besides aspirin and an anticoagulant (class I).[4] For such use “upstream” of PCI, the “small-molecule” agents eptifibatide or tirofiban are FDA approved in the United States, whereas abciximab is not. In low-risk patients, the guidelines suggest that either a GpIIb/IIIa blocker *or* clopidogrel should be added to aspirin and anticoagulation before angiography.[4] However, the more recent results of the ACUITY study show that bivalirudin monotherapy can replace heparin plus GpIIb/IIIa inhibitors with less bleeding[94] and similar outcomes at 1 year.[94],[95]

The window of opportunity for new anticoagulants in the acute syndromes is narrow, particularly because many patients are on dual antiplatelet therapy and the risk of bleeding with a third drug is higher. In the ACS2-TIMI 51 trial rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. It did, however, reduce the risk of the composite endpoint of death from cardiovascular causes, MI, or stroke.[96] A previous trial on the ACS with apixaban was stopped prematurely because of a lack of benefit and an increased risk of bleeding.[97]

In a nonrandomized subgroup analysis of the PLATO trial, the use of PPI was independently associated with a higher rate of cardiovascular events in ACS patients receiving clopidogrel and also during ticagrelor treatments. The conclusion is that the association between PPI use and adverse events may be confounding with PPI use more of marker for than a cause of a higher rate of cardiovascular events.[98]

Thrombolytic therapy to be avoided.

Despite its beneficial role in patients with AMI presenting with ST-segment elevation, thrombolytic therapy is absolutely contraindicated in patients with unstable angina or NSTEMI. Not only is the complication rate increased, but in some studies, overall mortality was higher.

Antiischemic drugs for ACS

Intravenous nitroglycerin.

Intravenous nitroglycerin (Fig. 12-4) is part of the standard therapy, although sometimes it is held in reserve for patients with recurrent pain despite oral nitrates.

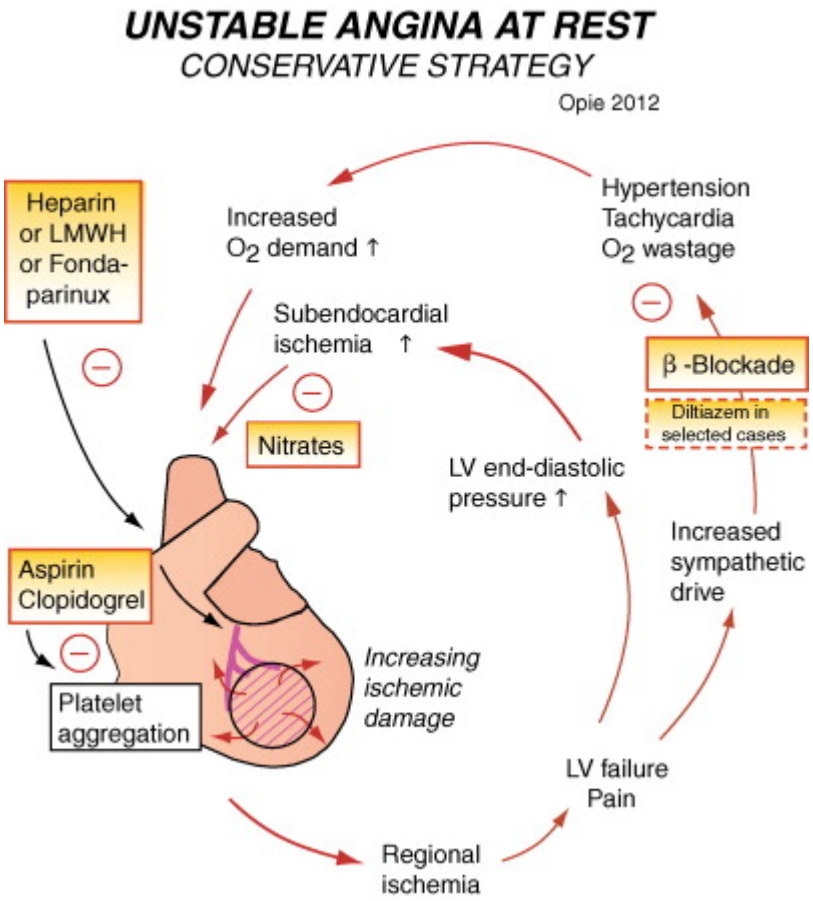

Figure 12-4 Hypothetical mechanisms in acute coronary syndrome presenting as unstable angina at rest, and for proposed conservative therapy. Note major role of anticoagulants, including fondaparinux and antiplatelet agents (aspirin plus clopidogrel). Nitrates and β-blockade are standard. β-Blockade should be particularly effective against sympathetic activation with increased heart rate and blood pressure. Calcium channel blockers such as diltiazem (heart-rate lowering) may be used intravenously or orally if β-blockade is contraindicated or fails or with care added to β-blockade. Dihydropyridines such as amlodipine and nifedipine should generally not be used unless vasospastic angina is strongly suspected. *LMWH,* Low-molecular-weight heparin; *LV,* left ventricular; *O2*, oxygen.
(Figure © L.H. Opie, 2012.)

β-blockers.

β-Blockers, even though lacking good prospective trial data, are standard therapy, and should be started early in the absence of contraindications. Arguments for β-blockade largely rest on first principles (reduced myocardial demand). For higher-risk patients or those with ongoing rest pain, intravenous β-blockers are followed by oral administration, whereas oral β-blockers will suffice for patients at lower risk. In hemodynamically unstable patients, ultra-short-acting esmolol may be used.[99]

Calcium channel blockers and other drugs.

Nondihydropyridine CCBs (diltiazem or verapamil) are used when β-blockers are contraindicated or are inadequate; contraindications include clinically significant LV dysfunction. Diltiazem compared well with nitrates during the acute phase of unstable angina, with better event-free survival at 1 year.[100] An *ACE*

inhibitor should be administered orally within 24 hours in patients with pulmonary congestion or an LV ejection fraction of 40% in the absence of hypotension or other contraindications.[8] Although not available in the United States, *nicorandil,* a K_{ATP} channel opener, could be useful (see Chapter 2). *Ranolazine* (see Fig. 2-9; p. 55) was tested in the large MERLIN-TIMI 36 randomized trial in 6560 patients with non–ST-elevation ACS.[101] The primary endpoint (composite of cardiovascular death, MI, or recurrent ischemia) was not achieved, yet recurrent ischemia was reduced. In patients with refractory angina on maximal medical therapy, the potential antiarrhythmic effects of ranolazine are currently under investigation.[102] Ranolazine has also been shown to significantly improve hemoglobin A1c (HbA1c) and recurrent ischemia in patients with diabetes and reduce the incidence of increased HbA1c in those without evidence of previous hyperglycemia in the MERLIN-TIMI 36 randomized controlled trial of patients with ACS. The mechanisms of these glycometabolic effects are under investigation.[103] Intraaortic balloon counterpulsation may be helpful in hemodynamically unstable patients pending angiography and PCI.

Invasive versus conservative strategy in ACS

Although there is general agreement that the first step is to stabilize the patient, there has been considerable debate as to whether the subsequent strategy should be invasive or conservative (see Fig. 12-3). The former involves coronary angiography with a view toward coronary revascularization based on the anatomy, whereas the more conservative approach advocates angiography only for patients with recurrent ischemia, either spontaneous or induced by stress testing. Recent metaanalyses strongly favor an invasive approach, particularly in patients at higher risk and in centers in which facilities for early angiography and PCI are available.[104-108]

Risk stratification.

Risk stratification is the key to balancing both approaches (see Fig. 12-3).[109] Subgroups at higher risk who will probably benefit from an early aggressive strategy include patients with elevated serum levels of troponins, ST-segment depression, or steep symmetric anterior precordial T-wave inversion; older patients; patients with prior long-standing angina or MI; and diabetics.[110-112]

Long-term prophylaxis of coronary disease

Overall management of both stable and unstable angina includes a vigorous attack on coronary artery disease. "Antiplatelet agents for all" (provided that the BP is well controlled) is now joined by "statins for all," irrespective of cholesterol level (see Chapter 10, p. 402). Clopidogrel is chosen in those who are intolerant to aspirin, and in some patients is added to aspirin. ACE inhibitors or ARBs are essential for all post–coronary syndrome patients with LV dysfunction, diabetes, or hypertension. Should an ACE inhibitor be given to all with established coronary artery disease? This controversy is discussed in Chapter 5 (see p.136). Taking together the results of three major trials, the answer is a qualified yes.[10] They should certainly be considered in all patients but their use is not mandatory. *The Mediterranean diet* has strong support, especially because it reduced total mortality (see p. 488). Combined laboratory, epidemiologic, and clinical trial data strongly suggest that increased dietary ω-3–rich fish oils help to protect from sudden cardiac death (SCD).[113] Tight BP and glycemia control is logical although not evidence based. Other risk factors also need optimizing, including weight loss, increased exercise, and smoking cessation. Long-term β-blockade is generally recommended, although without firm supporting contemporary trial data, and with potential side effects of fatigue, erectile dysfunction, and weight gain that mitigate against an optimal lifestyle.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Prinzmetal's vasospastic angina

Prinzmetal's vasospastic angina is a relatively rare condition, which is much more common in Japan, that often manifests as acute ischemic pain with ST-segment elevation but without MI, although MI and malignant arrhythmias may occur.[114] It requires relief of coronary spasm rather than thrombolytic therapy. *β-Blockers are inferior to CCBs* and may theoretically aggravate the spasm. However, in one study of active cocaine users, β-blockers were associated with a reduced risk of MI.[115] Coronary spasm is usually responsive to nitroglycerin, long-acting nitrates, and CCBs, all of which are considered first-line therapies. Short-acting nifedipine, diltiazem, and verapamil all completely abolish the recurrence of angina in approximately 70% of patients, with a substantial improvement in another 20%. Starting doses of CCBs are high (e.g., 240 to 480 mg/day of verapamil, 120 to 360 mg/day of diltiazem, and 60 to 120 mg/day of nifedipine). The relatively vasoselective long-acting dihydropyridine amlodipine is also effective. The next step is to add a CCB from another class or a long-acting nitrate.[116] Smoking cessation is imperative. β-Blockers may be tried, particularly in patients not responding to CCBs and nitrates. In refractory cases of Prinzmetal's angina associated with coronary artery disease, bypass grafting may be combined with cardiac sympathetic denervation (plexectomy).

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Early phase acute myocardial infarction

Management of AMI encompasses two different strategies. *The early phase* of evolving MI is dominated by the need for prompt reperfusion therapy because the time for possible salvage is so limited, possibly only up to 3 hours at the most (Fig. 12-5), whereas the *chronic phase* is a multipronged attack on the extent and progression of coronary artery disease, ventricular remodeling, and arrhythmias.

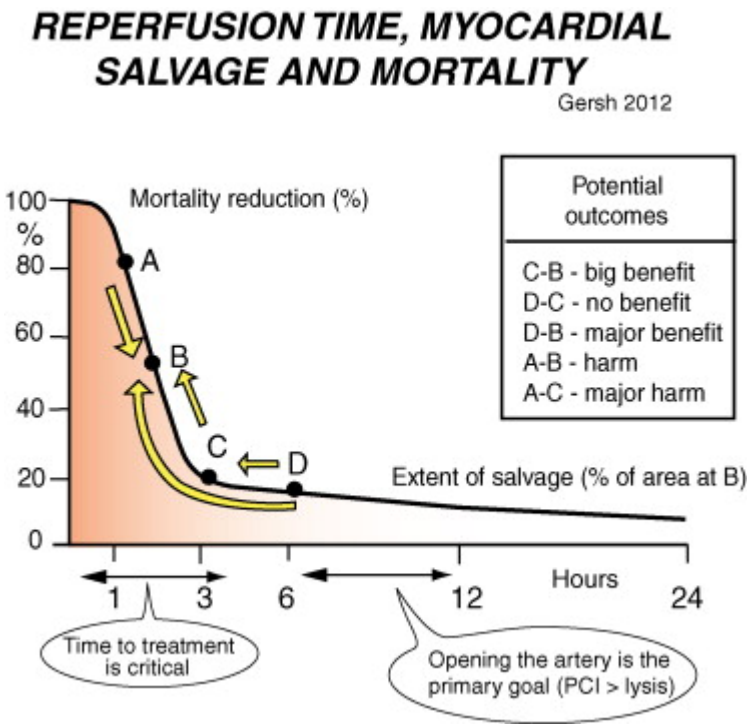

Figure 12-5 Relationship between mortality reduction and extent of salvage. Schematic illustrating the relationship between duration of ischemia prior to reperfusion, reduction in mortality *(thick black line)*, and myocardial salvage *(area under the curve)*. During the first 2 to 3 hours *(shaded in pale red)*, potential benefits are large and time to treatment is critical. *The shorter the time, the greater the benefit*. Later, on the "flat" part of the curve, time is less of a factor and the priority is to open the infarct-related artery; in this setting a mechanical approach is preferable. *A-D* illustrates potential outcomes from strategies that alter times to achieve reperfusion. A key issue relates to delays incurred on the steep part of the curve in which transfer to receive a more effective strategy (primary percutaneous coronary intervention [PCI]) might be offset by achieving earlier reperfusion with fibrinolytic agents *(D-C)*. These relationships might be modified by other factors such as myocardial oxygen uptake, collaterals, and preconditioning.

General care.

General care is nonetheless also crucial (Table 12-2). Aspirin needs to be given as early as possible, and pain relieved. *Morphine* (4-8 mg IV by slow intravenous push followed by 2-8 mg at 5- to 15-min intervals) combines a potent analgesic effect with hemodynamic actions that are particularly beneficial in reducing myocardial oxygen demand (mixed venous oxygen [MVO_2]), namely a marked venodilator action reducing ventricular preload, a decrease in heart rate, a mild arterial vasodilator action that may reduce afterload, and a decrease in sympathetic outflow. A "hidden" benefit of morphine may be its capacity, shown experimentally, to precondition the heart, thereby protecting against further ischemia. In the presence of hypovolemia, morphine may cause profound hypotension. The administration of *oxygen* by nasal prongs is almost universal practice in AMI, although whether it does any good is not established. Oxygen should be

administered to those patients with overt pulmonary congestion or arterial oxygen desaturation (SaO_2 < 90%).[8]

Table 12-2 -- Early Phase Acute Myocardial Infarction: Principles of Management[589]

1. Minimize pain-to-needle time, urgent hospitalization. Relieve pain by morphine.
2. Aspirin upon suspicion. Add clopidogrel 75 mg daily (class 1A),* continue for at least 14 days (class 1B).[71]
3. Anticoagulation: Minimum 48 h, prefer up to 8 days; if beyond 48 h, avoid UFH (class 1A).[71]
4. Duration of pain: If >3 h, rapid transfer for PPCI. If <2-3 h, or if delay to balloon inflation is greater than 90 min, urgent thrombolysis with anticoagulation by UFH or low-molecular-weight heparin or bivalirudin (see Fig. 12-3).
5. Acute angioplasty and stenting in selected patients at centers with documented expertise and good results. (See previous discussion of delay times.)
6. Continuing pain: Check BP. Intravenous nitrates or β-blockers. Consider added diltiazem (see Chapter 3, page 81) or ranolazine. Urgent angiography and IABP if the patient is a potential candidate for PCI.
7. Consider indications for early β-blockade, ACE inhibition. Diabetes argues for ACE inhibition or ARB.
8. Management of complications:
   a. LVF: Treat aggressively; diuretics, nitrates, ACE inhibitors, or ARBs (consider Swan-Ganz catheterization).
   b. Symptomatic ventricular arrhythmias: Lidocaine; if refractory, amiodarone.
   c. Supraventricular arrhythmias: Adenosine; consider esmolol; avoid verapamil or diltiazem if LVF.
   d. Cardiogenic shock: Acute angioplasty, IABP, bypass surgery.
   e. RV infarction: Fluids, inotropic support. Avoid nitrates.
   f. Rupture of free wall, mitral valve, ventricular septum: Cardiac surgery.
   g. Hyperglycemia: Use insulin whether or not patient is diabetic.
   h. Strongly consider ACE inhibition or ARB for all diabetics.

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *IABP,* intraaortic balloon pump; *LVF,* left ventricular failure; *PCI,* percutaneous coronary intervention; *PPCI,* primary percutaneous coronary intervention; *RV,* right ventricular; *UFH,* unfractionated heparin.

* Classes of Recommendations (1-3) and levels of evidence (A-C)

Bradyarrhythmias.

Atropine (0.3-0.5 mg IV aliquots to a maximum of 2 mg) has a vagolytic effect that is useful for the management of bradyarrhythmias with AV block (particularly with inferior infarction), sinus or nodal bradycardia with hypotension, or bradycardia-related ventricular ectopy. Small doses and careful monitoring are essential because the elimination of vagal inhibition may unmask latent sympathetic overactivity, thereby producing sinus tachycardia and rarely even ventricular tachycardia (VT) or ventricular fibrillation (VF). The role of prophylactic atropine for uncomplicated bradycardia remains questionable.

Sinus tachycardia.

Sinus tachycardia is a common manifestation of early phase sympathetic overactivity, which increases MVO_2 and predisposes to tachyarrhythmias. The first step is to treat the underlying cause—pain, anxiety, hypovolemia, or pump failure—and then to use a β-blocker, which is safe and effective provided that there are no contraindications and the patient is carefully observed. If the hemodynamic status is borderline, the

very-short-acting esmolol (see next section) may be selected.

Acute hypertension.

Acute hypertension must be tightly controlled in all patients in whom thrombolytic therapy is under consideration because elevated BPs increase the risk of bleeding and, in particular, cerebral hemorrhage.[72] Target BPs are in the range of less than 130/80 mm Hg, but without hard data to support these goals. The BP should be lowered gradually, particularly in older patients. In STEMI, the principles of hypertension management are similar to those for the non–ST-elevation ACS.[117] Short-acting β-blockers, usually intravenous, in conjunction with intravenous nitrates, are given to hemodynamically stable patients. ACE inhibitors are indicated in stable patients with persistent hypertension, particularly in the presence of large infarcts, anterior MIs, and LV dysfunction. In patients intolerant to ACE inhibitors, ARBs are a proven alternative. CCBs are untested in the setting of AMI.

Acute reperfusion therapy for AMI

How urgent?

Reperfusion therapy has revolutionized the management and prognosis of STEMI.[118] The benefit is that more cardiomyocytes are saved from ischemic death than are killed by reperfusion injury.[119] There is a steep relationship during the first 3 hours between the duration of ischemia, mortality reduction, and myocardial salvage (see Fig. 12-5). Thus the window of opportunity is narrow and time to treatment is critical. This relationship between time and salvage may be modified by factors such as myocardial oxygen demands, ischemic preconditioning, the extent of collaterals, age, and infarct location.[120] Thereafter, on the "flat" part of the curve, time dependence of therapy is less urgent in comparison to the primary objective of achieving patency of the infarct-related artery. It is likely that the efficacy of lysis decreases as clots become increasingly resistant with time, whereas the ability of PCI to open arteries probably remains unimpaired, supporting a mechanical approach at this stage in the time course of MI.[121],[122] In approximately 60% of hospitals in the United States with facilities for primary percutaneous coronary intervention (PPCI), the mechanical approach is unequivocally the preferred form of therapy, providing this can be carried out 24 hours a day, 7 days a week.

Community management.

The approach to the patient presenting in a community hospital without a catheterization laboratory but within 2 to 3 hours of symptoms (Fig. 12-6) is controversial. The crucial question now is whether such patients should receive routine fibrinolytic therapy as opposed to the delay incurred in transferring to a hospital with PPCI facilities. The degree of delay that is acceptable remains controversial. After 2-3 hours, when time to treatment is less of an issue, transfer for PPCI is logical and widely used.[123-125]

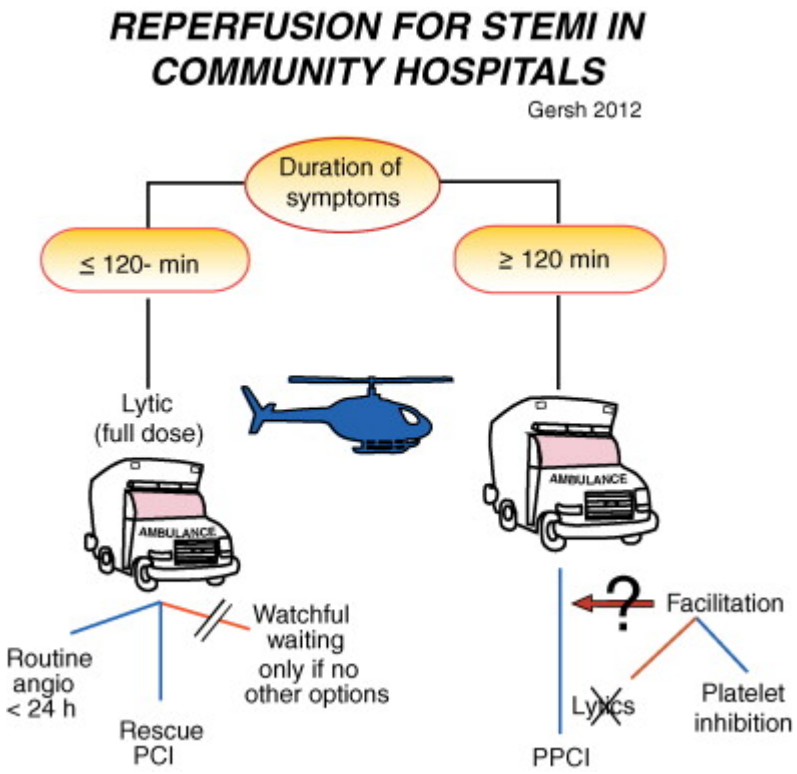

Figure 12-6 Reperfusion therapy for ST-elevation myocardial infarction in community hospitals, according to duration of symptoms. If less than 120 to 180 minutes have passed, lytic therapy is started and the patient transferred to a percutaneous coronary intervention (PCI) center by ambulance or helicopter, followed by routine angiography (angio) and, if needed, rescue PCI. If more than 120 to 180 minutes have passed, the patient is transported to a PCI center for primary percutaneous coronary intervention (PPCI). Facilitation by thrombolytic therapy en route gives no benefit. In the long term, one solution is the development of PCI facilities at peripheral hospitals even without on-site surgery.
(Figure © B.J. Gersh, 2012.)

Mechanical revascularization in AMI.

Despite the undisputed success of early fibrinolysis, especially in the first 2 to 3 hours, there are considerable limitations to the ability of currently available thrombolytics in achieving “optimal” reperfusion. This provides a strong rationale for the mechanical approaches using PPCI with angioplasty and stents. Several metaanalyses comparing PPCI with thrombolytic therapy have demonstrated 30-day and 1-year benefits for PPCI in terms of death and particularly reinfarction and stroke. This was noted in each period after symptom onset, but these analyses do not address the effect of incremental delay prior to transport for PPCI.[126] Thus there is now consensus that PPCI is the preferred form of reperfusion therapy providing the time delay between balloon inflation versus administration of lytic drug is less than 90 minutes. Stents lessen the high rates of restenosis and reocclusion after balloon angioplasty but without any overall difference in mortality.[127] For any program using PPCI, constant auditing of individual and institutional outcomes is mandatory. It is not good enough to rely on the results of randomized trials in large registries, composed of individuals with expertise and enthusiasm for this particular approach.[128] In the HORIZONS trial, patients receiving a paclitaxel-eluting stent had a slightly but statistically significantly lower rate of ischemia-driven revascularization at 3 years with no differences in rates of death, MI, and stroke.[129] Given the drive to shorten door-to-balloon times, many patients will present for PPCI without crucial information on comorbidities, the ability to continue platelet inhibitors for at least 1 year, and the need for noncardiac surgical procedures in the future, and in this situation, BMS may be a better option depending on lesion length, complexity, and vessel diameter.[128],[130-132] Intracoronary thrombectomy and distal protection devices, although logical and at times clinically useful, have not had any beneficial effects on outcomes, and their routine use is not recommended.[133] Intracoronary β-blockade may be a simple procedure to protect the distal myocardium during PCI.[134]

How to do it faster.

The quicker the better, whether the reperfusion is by fibrinolysis or by PCI: a delay of only 30 minutes increases 1-year mortality by 7.5%.[94] Three major time delays are (1) onset of patient's pain to first medical contact; (2) home-to-hospital time; and (3) door-to-needle or door-to-balloon time in the hospital. The greatest delay is from symptom onset to emergency room, and this has changed little over the last decade, being in the range of 85 minutes.[135] The next delay is the door-to-balloon time, with the benchmark being less than 90 minutes.[136] There have been marked improvements in door-to-balloon times in the United States and elsewhere, but the Achilles heel of reperfusion therapy remains the delay between symptom onset and first medical contact and prolonged delays incurred in transferring patients to PCI-capable facilities.[137-141] The major advances in the delivery of reperfusion therapy will arise from steps taken outside the PCI-capable hospitals, which already have streamlined systems in place.[142-144] In large cities, the optimal approach is achieved by having paramedics available to triage and transport patients directly to designated PPCI centers.

cf septic shock and antibiotics = 7.5%/hr

Regional systems of care.

To rapidly reperfuse patients who present to hospitals without PCI capability, rapid transfer to sites with PPCI can be streamlined.[128] To reduce the overall "ischemic time" (symptom onset to reperfusion), effective and integrated prehospital systems (including paramedic ambulance with telemetry of the electrocardiogram and rapid coordination with the PCI center) can substantially reduce prehospital delays.[128],[141],[144] Another approach to early reperfusion, which has been effective in some countries, particularly in Europe, is prehospital thrombolytic therapy, which requires intense community organization to get the paramedic team trained and on site in time.[145],[146] The key to the establishment of successful STEMI networks is to understand that "one size does not fit all" and that factors such as weather, distance (rural or urban), resources, and the organization of ambulance services play a determining role.[128],[147] As recently pointed out in a French registry, the key is to keep it simple and avoid the involvement of too many people.[148],[149]

Facilitated PCI or pharmacoinvasive approach.

Facilitated PCI is defined by the initial use of fibrinolytic drugs followed by routine immediate PCI after transfer to a PCI-capable institution.[124],[130],[150]

The "pharmacoinvasive approach" is characterized by full-dose fibrinolytic therapy followed by transfer either for rescue PCI or, if the patient is stable with evidence of successful reperfusion, there is a general consensus that angiography with a view to PCI should be performed within 3 to 24 hours of admission (the so called "drip and ship" approach).[128],[151],[152] Facilitated PCI is now not recommended following the results of the FINESSE[153] and ASSENT–4 studies.[154],[155] Although the pharmacoinvasive strategy is currently the objective of an ongoing trial, this approach is widely practiced and recommended by the ESC guidelines for systems in which transfer times result in door-to-balloon times of greater than 90 minutes.[72]

Which thrombolytic agent?

Worldwide, most patients with AMI are given fibrinolytic therapy. The first GUSTO trial[156] demonstrated the superiority of the accelerated regimen of tissue plasminogen activator (tPA; *Alteplase*) over streptokinase. Nonetheless, this came at two prices: increased cost (see Table 9-8) and a slightly but significantly greater risk of intracranial hemorrhage (see Table 9-9), especially in women older than 75 years.[157] Single-bolus *tenecteplase* (TNK) is now the most widely used thrombolytic agent in North America and Europe because of its efficacy and ease of administration. TNK and alteplase are equivalent in regard to 30-day mortality, but noncerebral bleeding and blood transfusions were less with TNK.[158] The dose of TNK is weight adjusted and administered as a single bolus over 5 seconds (versus 90 minutes of variable-rate infusion with tPA). *Reteplase* (rPA) is a more fibrin-specific agent administered as two 10-unit boluses given 30 minutes apart. Alteplase and rPA are equivalent in both mortality and hemorrhage.[159] Overall, we appear to have reached a plateau in that the new fibrinolytics do not result in increased reperfusion rates or reduced mortality. The major strength of the bolus agents (TNK, rPA) lies in their ease of administration, resulting in fewer dosing errors.

Limited benefit of GpIIb/IIIA inhibitors plus reperfusion therapy.

The initial promise of GpIIb/IIIa inhibitors for acute STEMI has not been translated into a major long-term clinical benefit. In the early trials totaling more than 22,000 patients, there was a modest benefit on rates of

reinfarction, no mortality benefit, and a significant increase in bleeding that is especially marked in the case of abciximab.[160] In the setting of PPCI, a metaanalysis of six randomized trials suggested that the early administration of the GpIIb/IIIa inhibitors abciximab or tirofiban in patients receiving UFH was associated with a nonsignificant 28% reduction in mortality and significant improvements compared with placebo in TIMI flow grades.[161] However, no bivalirudin was used and two of the four studies refer only to abstracts. The largest study,[162] not included in this metaanalysis, did not show any benefit from abciximab and stenting. In HORIZON's AMI trial, bivalirudin with provisional GpIIb/IIIA use was equivalent in efficacy to heparin plus Gp IIab/IIIa use prior to PPCI, but major non–CABG-related bleeding was less.[163] Despite the lack of decisive data, in current practice GpIIb/IIIa inhibitors are usually administered on arrival in the catheterization laboratory or during transfer unless bivalirudin is used.

Reperfusion injury and microvascular dysfunction.

Considerable experimental evidence points to a spectrum of reperfusion events, including ventricular arrhythmias, mechanical stunning, and microvascular injury. Reperfusion-induced apoptosis has now been added to this list.[119] Reperfusion injury occurs on reperfusion, not later. Microvascular dysfunction, however, may precede or follow arterial reperfusion. There is now increasing realization that, despite restoration of flow to the epicardial infarct-related artery, there remains a persistent impairment of myocardial reperfusion and microvascular dysfunction[164],[165] that has stimulated multiple trials of widely diverse agents aimed at modifying these pathophysiologic consequences of coronary occlusion and reperfusion. Initially optimistic expectations that myocardial cooling, the use of aqueous oxygen, erythropoietin, delta protein kinase C inhibition, antiinflammatory agents, and compliment inhibitors, among many others, would be effective adjuncts to reperfusion therapy by enhancing myocardial salvage have not been met.[166-170] Although distal mechanical protection devices have been shown to be ineffective, the use of adjunctive manual thrombectomy devices is associated with better epicardial and myocardial perfusion, less distal embolization, and a lower mortality.[171] More recently, a number of novel strategies such as ischemic preconditioning,[172-174] human atrial natriuretic peptide,[175] cyclosporine A,[176] and remote ischemic preconditioning[177] have been shown to reduce infarct size in smaller trials that illustrate proof of the concept that reperfusion injury can be modified. A recent addition to the list of promising agents is exenatide, which is a drug initially used for glycemic control.[178],[179] Whether this drug that appears to enhance myocardial salvage can also improve clinical outcomes remains to be determined. This has been an area of considerable frustration and the failure to translate the animal models into the clinical setting could be due to multiple factors including inappropriate animal models, species differences, the different natural history between experimental occlusion and reperfusion versus the dynamic nature of an evolving MI, and poorly designed clinical studies. The problem is that, even if these approaches were effective, they are often given too late to make a difference. Conversely, if used very early in the course of MI, the preexisting low mortality rates and high rates of salvage would make it difficult to "demonstrate" a difference—a real "Catch-22" situation.

Aspirin and clopidogrel.

All patients with AMI need both aspirin and clopidogrel. For the initial aspirin dose, 160 mg was used in the first large AMI trial in 1988[180] and also favored by a recent retrospective analysis,[181] although some guidelines recommend 160-325 mg for the initial dose.[182] The first tablet should be chewed or crushed and as indefinite maintenance therapy, the dose should be 75-162 mg per day. Clopidogrel is given whether AMI is treated by fibrinolysis or PPCI, provided that the added risk of bleeding is acceptable (see Tables 12-1 and 12-2; see also Chapter 9, p. 348). In patients receiving fibrinolytic drugs, the 2007 focus update of the 2004 ACC-AHA guidelines advocate 300 mg of clopidogrel followed by 75 mg per day for 14 days and no loading dose in patients older than the age of 75.[183] Although there are no trials specifically addressing the efficacy of clopidogrel plus aspirin versus aspirin alone in STEMI patients treated with PPCI, subset analyses from other trials strongly favor the use of clopidogrel and most would advocate a loading dose of 600 mg.[184] The first perspective randomized trial to compare a 600-mg loading dose of clopidogrel with a 300-mg dose in patients with STEMI undergoing PPCI demonstrated a reduction in infarct size and in clinical events at 30 days[185] and support the recommendations of the latest European guidelines in the context of primary PCI for STEMI.[186]

Prasugrel and ticagrelor.

Depending on the risk bleeding, prasugrel 60 mg given as early as possible after presentation may be superior to clopidogrel, particularly in patients with diabetes as shown in the Triton-TIMI 38 trial.[187],[188] The

role of ticagrelor in STEMI remains to be determined.

Heparin prophylaxis.

Reocclusion, which occurs both early and late (weeks or months) after thrombolysis, remains the "Achilles heel" of reperfusion therapy. In a metaanalysis of more than 20,000 patients, the frequency of symptomatic recurrent MI during the index hospitalization was 4.2%, together with a two- to threefold increase in 30-day mortality.[189] Irrespective of the timing, reocclusion has markedly deleterious effects on LV function and long-term outcomes. There are many contributory factors, including the severity of the underlying residual stenosis, the persistence of the initial thrombogenic substrate (plaque fissure), and activation of platelets and of the clotting cascade. *Intravenous UFH* has an established place in fibrinolysis alongside tPA, TNK, or rPA, and should be used in the initial 24 to 48 hours to prevent further thrombin generation and reduce the risk of reocclusion. The dose should be adjusted to keep the aPTT between 60 and 80 seconds, taking care to avoid wide swings in the aPTT values. The aPTT should be evaluated 4 to 6 hours following a heparin bolus and then checked every 6 to 8 hours thereafter.

Duration of heparin therapy.

Appropriate duration of heparin therapy is uncertain, but up to 48 hours has a class I recommendation, the limit existing because of increasing risk of heparin-induced thrombocytopenia (see Chapter 9 p. 368); thereafter other anticoagulant regimens are recommended.[72] In patients presenting with AMI and already on chronic warfarin therapy, the use of intravenous heparin should be similar to that in those not on warfarin. In patients receiving streptokinase, added intravenous heparin is controversial. (For our positive recommendations, see section on streptokinase, Chapter 9, p. 394).

Low-molecular-weight heparins.

Enoxaparin is increasingly used because of the heparin deficiencies as an antithrombotic agent. In fibrinolytic therapy of AMI, dose-adjusted enoxaparin continued up to 8 days has class IA evidence.[72] Reduce doses for those aged 75 years or older or for renal impairment (see Table 9-5). For PCI, a single dose of enoxaparin gave less bleeding than heparin (see Chapter 9).

In the randomized ATOLL trial intravenous enoxaparin compared with UFH significantly reduced clinical ischemic outcomes without differences in bleeding and procedural success in 910 patients undergoing primary PCI.[190]

Direct thrombin and factor Xa inhibitors.

Fondaparinux and bivalirudin (see Fig. 9-10 for sites of action) both cause less bleeding than heparin, with fondaparinux best tested for fibrinolytic therapy and bivalirudin for early invasive PCI (see Table 9-5). Bivalirudin has excellent data for use in an invasive strategy (PCI), especially when bleeding should be avoided (see Chapter 9, p. 371). For thrombolytic or no reperfusion therapy for STEMI, fondaparinux was superior to placebo and to UFH in the OASIS-6 trial.[191] However, when primary PCI was chosen, there was an increase in guiding catheter thrombosis with no overall benefit. Thus we do not recommend fondaparinux for STEMI treated by primary PCI.

Protecting the ischemic myocardium

Prophylactic early β-blockade.

Pooled data on trials of β-blockers given early to approximately 29,000 patients with AMI showed a 13% reduction in acute-phase mortality.[192] Yet almost all of these studies were gathered in the prethrombolytic era. With thrombolysis, there is no hard evidence on the benefits of β-blockers on early mortality in patients receiving reperfusion therapy. Moreover, the COMMIT trial on almost 46,000 patients, half of whom had received thrombolytics, raised serious questions about the routine use of intravenous β-blockers; mortality increased in patients with hemodynamic instability with a balancing trend in the other direction in stable patients.[193] Furthermore, in the only study comparing early intravenous β-blockade with delayed oral β-blockade (6 days later), early reinfarction decreased with early therapy but mortality was unchanged at 1 year.[194] Overall, *early intravenous β-blockade should be used only selectively* for sinus tachycardia, tachyarrhythmias such as AF, hypertension, and recurrent ischemia. Despite the lack of definitive clinical

trial evidence, several studies from a variety of databases suggested the mortality benefit of β-blockers persists during the reperfusion era[195-197] and that the benefit is similar or greater in older patients.[198] For patients undergoing primary PCI, observational analyses (but no prospective studies) suggest that early intravenous β-blocker therapy may be beneficial and may reduce 6-month mortality.[199-201] Although there have been no randomized trials of β-blockers specifically in patients with NSTEMI, nonetheless, based on pathophysiologic considerations and evidence of efficacy in unselected patients with ACS and chronic coronary disease, the 2011 ACC-AHA focus update on the management of patients with unstable angina and non–ST-elevation ACS do recommend use of β-blockers in all patients with ACS who do not have contraindications.[202] β-blockers are particularly indicated in patients with ongoing chest pain, hypertension, or tachycardia.[117] Ideally β-blockade can more easily be introduced later, when there is hemodynamic stabilization (late intervention, 25 studies, 24,000 patients) to bring about a 23% reduction in late-phase mortality.[192] The drugs with US licenses are metoprolol and atenolol, whereas the short-acting esmolol is preferred when the hemodynamic situation is potentially unstable.

Early use of ACE inhibitors or ARBs in AMI.

Early oral ACE inhibitors in patients at high risk (hypertension, diabetes, chronic renal disease, clinical LV failure or LV ejection fraction less than 40%) followed by treatment continued indefinitely is strongly advised (class IA).[72] A logical policy would be to start the ACE inhibitor as soon as the patient is hemodynamically stable and to watch for hypotension or new renal impairment. An ARB is the therapy of choice if there is ACE inhibitor intolerance. Intravenous ACE inhibitors are not recommended because of the risk of hypotension.

Limitation of infarct size.

Because MI is ultimately the consequence of a serious imbalance between myocardial oxygen supply and demand, it is logical and prudent to employ measures aimed at redressing this imbalance. These measures include the treatment of arrhythmias, hypoxia, heart failure, hypertension, and tachycardia. Hypokalemia should be sought and treated. Despite much laboratory evidence that numerous pharmacologic agents such as β-blockers, nitrates, metabolic agents, and free radical scavengers will reduce infarct size, clinical evidence of benefit has been difficult to prove, perhaps because such therapy has inevitably been started after the first 2 to 3 hours, whereafter the infarct size is relatively fixed (see Fig. 12-5).

Early intervention before PCI.

Logically timing is important and the earlier the better as shown experimentally[203] and in patients by the benefits of early metabolic intervention by exenatide or glucose-insulin-potassium (GIK). Exenatide, a glucagon-like peptide–1 agonist (see Fig. 11-6), reduced infarct size by 30%.[204] In the IMMEDIATE trial, 871 patients with suspected ACS were given GIK in the ambulance, which reduced rates of the composite outcome of cardiac arrest or in-hospital mortality, although the primary endpoint was not achieved.[205] That timing is crucial was shown as follows. Exenatide reduced reperfusion infarct size by 30% when given within 132 minutes or less of the time delay from first medical contact to first balloon.[204] In another early study in the ambulance, intervention by remote conditioning (pumping up and down a BP cuff), increased the myocardial reperfusion salvage index by approximately one-third from 0.55 to 0.75 ($p = 0.33$).[206] Thus in the future there will be more emphasis on ideal management in the ambulance whether by metabolic therapy or by conditioning.

Timing of metabolic therapy is critical. A recent metaanalysis of nine randomized trials that involved more than 28,000 patients did not reveal any mortality benefit for GIK given for ST-segment elevation AMI.[207] However, all the studies were on AMI 3 or more hours after the onset of symptoms except for GIPS-1, which accounted for only 3% of the total and had a relative risk (RR) of 0.83, whereas more than 20,000 of the patients were in one large trial, CREATE-ECLA, which accounted for 70% of the patients and in which the mean delay time was 4.7 hrs.[207]

Intravenous magnesium.

Intravenous magnesium, otherwise discredited, remains indicated for patients with a torsades de pointes type of VT and in patients who have low serum magnesium or potassium levels frequently associated with chronic diuretic therapy.

Intravenous erythropoietin.

Experimental data suggesting a variety of potentially cardioprotective mechanisms from the use of erythropoietin led to the REVEAL trial of 222 patients in which there was no difference in infarct size at 10-14 weeks, but there was a significantly increased risk of death, recurrent MI, stroke, or stent thrombosis in erythropoietin-treated patients.[208]

Arrhythmias in AMI

Therapy of ventricular arrhythmias in AMI.

Primary VF and VT are associated with a sixfold increased mortality.[209] Although infrequent, recurrent ventricular arrhythmias pose a difficult management problem. *Lidocaine* (lignocaine) should not be given prophylactically but only against documented serious ventricular arrhythmias. A metaanalysis of 14 trials showed that prophylactic lidocaine reduces VF by approximately one-third, but may increase mortality by approximately the same percentage.[210] *Amiodarone* is now the preferred intravenous antiarrhythmic agent for life-threatening VTs when lidocaine fails. *Interventional techniques* such as atrial or ventricular pacing, stellate ganglion blockade, or radiofrequency catheter ablation may occasionally be life saving. Treatment of LV failure is an essential adjunct to antiarrhythmic therapy. The possibility of drug-induced VT or of hypokalemia should always be borne in mind.

Supraventricular tachyarrhythmias in AMI.

AF, atrial flutter, or paroxysmal supraventricular tachycardia (PSVT) is usually transient, yet may be recurrent and troublesome.[211] Such arrhythmias may increase myocardial oxygen demands with an adverse prognosis. Precipitating factors requiring treatment include heart failure with atrial distention, hypoxia, acidosis, and pericarditis. Recurrent AF is best treated with intravenous amiodarone, particularly in the face of hemodynamic compromise, but in some patients the careful use of β-blockers may achieve adequate rate slowing. In the presence of hemodynamic instability, the ultra-short-acting β-blocker esmolol may be chosen. Intravenous digoxin may have a role especially in patients with heart failure. Class IC antiarrhythmic drugs should be avoided in place of supraventricular tachycardia. Initial therapy should be carotid sinus massage or other vagal maneuvers, and intravenous adenosine. If this fails, try intravenous metoprolol, amiodarone, or cardioversion depending on hemodynamic instability. In the case of supraventricular tachycardia, initial therapy should be carotid sinus massage or other vagal maneuvers. In the absence of LV failure, intravenous diltiazem or verapamil is effective in controlling the ventricular rate. Although intravenous diltiazem is licensed in the United States for acute conversion of supraventricular tachycardia, experience in AMI is limited and concurrent use of intravenous β-blockade is a contraindication. In the presence of LV failure, intravenous adenosine (*Adenocard*) or the careful use of esmolol may be tried. Adenosine cannot be used for AF or atrial flutter because of its ultrashort action. *Cardioversion* may be required in the face of compromised hemodynamics or severe ischemia, starting with a low threshold. To avoid systemic embolization after cardioversion for AF, heparin should be restarted or continued.

LV failure and shock in AMI

The first step is to exclude a reversible cause such as volume depletion, papillary muscle or ventricular septal rupture, or transient LV apical ballooning. Acute emotional stress can precipitate acute LV failure.[211],[212] Swan-Ganz catheterization to measure LV filling pressure and cardiac output allows a rational choice between various IV agents that reduce both preload and afterload or chiefly the preload. Although for diverse reasons the use of the Swan-Ganz catheterization has declined, the concepts of pre- and afterload reduction remain important.

Load-reducing agents in AMI.

In the intensive care unit setting, intravenous nitroglycerin is the most appropriate preload-reducing agent, particularly in the early hours of acute infarction when ischemia may contribute to LV dysfunction. For pulmonary edema, excess diuresis with excess preload reduction and relative volume depletion must be avoided, because reduced ventricular compliance requires higher filling pressures to maintain cardiac output. Where there are no intensive care facilities, intravenous unloading agents such as nitroprusside and nitrates are best avoided. Sublingual agents that reduce the preload (short-acting nitrates) should be useful.

The diuretic furosemide, although standard therapy and acting by rapid vasodilation as well as by diuresis, may sometimes paradoxically induce vasoconstriction.

Nitrates in AMI.

Current indications for nitrate therapy in AMI include recurrent or ongoing angina or ischemia, hypertension, and load reduction in patients with CHF and mitral regurgitation. Nitrates should not be administered to patients with a systolic BP of less than 90 mm Hg, patients with right ventricular infarction, or those who received sildenafil (or its equivalent) in the last 24 hours.

Low cardiac output in AMI.

Monitoring the hemodynamic response invasively is indispensable. When cardiac output is low in the absence of an elevated wedge pressure or clinical and radiographic evidence of LV failure, it is crucial to exclude hypovolemia (possibly drug induced) or right ventricular infarction. In the absence of these conditions, acute positive inotropes such as norepinephrine, dopamine, or dobutamine (see Fig. 6-3) are used to bring the systolic BP up to 80 mm Hg. However, it is often forgotten that dobutamine, by stimulating peripheral β_2-receptors, can drop the diastolic BP. Nitrates are usually contraindicated because their main effect is reduction of the preload. Intraaortic balloon counterpulsation may be extremely helpful in the temporary stabilization of the patient, particularly if angiography and revascularization are being considered.[213] The benefit-to-harm ratio of digoxin in AMI is doubtful, so that its use is restricted to patients with atrial tachyarrhythmias in whom diltiazem or verapamil or esmolol fails or is contraindicated.

Cardiogenic shock.

Cardiogenic shock is the leading cause of death in AMI. A crucial aspect of the management of cardiogenic shock is the diagnosis and prompt treatment of potentially *reversible mechanical complications* such as rupture (free wall, septum, or papillary muscle), tamponade, and mitral regurgitation. Underlying hypovolemia or dominant right ventricular infarction also needs to be excluded.[214] Another paradigm postulates that activation of inflammatory cytokines leads to increased activity of inducible nitric oxide (NO) synthase with excess production of NO and toxic peroxynitrite.[215],[216] Unfortunately, the large TRIUMPH trial testing the NO synthase inhibitor tilarginine did not reduce mortality despite the presence of an open infarct artery.[217] Probably the best strategy in cardiogenic shock is *intraaortic balloon counterpulsation* followed by prompt revascularization. With either PCI or in some patients CABG, one of the few indications for acute multivessel primary PCI is in the hemodynamically compromised or shocked patient without significant improvement after PCI of the culprit vessel.[218] Inotropes and vasopressors are frequently required, and the choice of agent may be modified by hemodynamic parameters measured by pulmonary artery (PA) catheterization.[72] Occasionally LV and biventricular assist devices and percutaneous cardiopulmonary bypass support are used. Although hemodynamic and metabolic parameters were reversed more effectively by ventricular assist than by standard treatment with intraaortic balloon counterpulsation in a small trial, there was no difference in mortality or bleeding, and limb ischemic events were more frequent after use of a ventricular assist device.[219]

Recurrent chest pain after STEMI.

Distinguishing between recurrent ischemic pain and pericarditis depends on the clinical history, the electrocardiogram, and, often, angiography. Pericarditis may be extremely distressing, and initial recommendations are to use aspirin and discontinue anticoagulation if pericardial effusion develops; if aspirin is ineffective, it is reasonable to try colchicine or acetaminophen. Nonsteroidal antiinflammatory drugs (NSAIDs) as a single dose may be extremely effective, but should not be administered if possible because their use may precipitate cardiac rupture and infarct expansion. *Cardiac tamponade* is an infrequent but life-threatening complication of AMI. Subacute rupture amenable to surgery should be suspected in all patients with recurrent pericardial-like pain and a pericardial effusion.[220]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Long-term therapy after AMI

General management.

As the early acute-phase MI merges into the chronic phase (Table 12-3), so does the therapeutic approach evolve (Fig. 12-7). Long-term prognosis depends chiefly on the postinfarct LV function, the LV volume, the absence of ischemia, coronary anatomy, and electrical stability.[1] A major aim is to minimize adverse remodeling, specifically by load reduction and renin-angiotensin-aldosterone system (RAAS) inhibitors (Fig. 12-8). On this background, control of risk factors, including lipids and BP, remains essential. Careful choice of long-term protective drugs, giving full reasons, also reassures. For example, those patients receiving statins feel (and do) better.[221] There is increasing realization that psychosocial factors such as depression, social isolation, anger, and marital stress commonly present after MI can carry an adverse prognosis.[222],[223] Although psychosocial interventions in drug therapy improve depressive symptoms and their use is logical, the cardiovascular benefits are less clear. Sertraline is at least safe,[224] unlike the tricyclic antidepressants, which may cause orthostatic hypotension in addition to potential proarrhythmia.[225] A heightened awareness of the frequency and prognostic implication of psychosocial factors is a key component of cardiac rehabilitation and post MI care.

Table 12-3 -- Postinfarct Follow-up: Principles of Management[589]

1. Risk factor modification.
   - No smoking, full lipogram, control of hypertension, aerobic exercise, psychological support.
   - Diabetics: Control of weight, blood pressure, glycemia, lipids.
   - For all: Strongly consider statin therapy, aggressive, to LDL ≤70–100 mg/dL (1.8-2.6 mmol/L); if triglycerides ≥200 mg/dL: lifestyle modification, more intense LDL reduction (class 1B),*[71] then consider fibrate or niacin.

2. Assess extent of coronary disease.
   - Residual ischemia (symptoms, exercise test): Revascularize depending on extent and estimated viability of ischemic tissue.

3. Assess LV function and size. Avoid LV dilation.
   - If LV dysfunction (low EF) or anterior MI or diabetes: ACE inhibitor or ARB. Consider aldosterone antagonists (watch serum K^+).

4. Prevention of reinfarction.
   - Aspirin indefinitely.
   - Clopidogrel added for 14 days (no stent), 1 month or more (BMS), 12 months or longer (DES) (all class 1B).[71]
   - β-Blockade also to prevent SCD, if not contraindicated (e.g., severe respiratory disease). If contraindicated, verapamil or diltiazem if no clinical LV failure.
   - ACE inhibition or ARB (consider for all, especially if high risk).
   - Oral anticoagulation for selected patients.

5. Complications that may need revascularization.
   - *Postinfarct angina:* Cardiac catheterization; nitrates, add CCB to β-blocker, consider revascularization.

- *Severe LV dysfunction: Identify hibernating myocardium*—assess viability; consider revascularization after dobutamine echocardiography or stress scintigraphy or positron emission tomography.

6. Complex ventricular arrhythmias (VA).
- Exclude significant coronary disease; assess LV function.
- LV preserved: Effort stress test, exercise rehabilitation.
- Complex symptomatic VA: Consider ICD (covered by amiodarone and β-blockade); data for EF <35%.[381]

7. Advanced heart failure.
- Maximal medical therapy (see Fig. 6-8).
- Primary prevention of SCD: For NYHA classes II & III—EF <35%, strongly consider ICD, must wait for 40 days post-MI; add CRT if QRS prolongation >120 msec (CRT, defibrillator).

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BMS,* bare metal stent; *CCB,* calcium channel blocker; *CRT,* cardiac resynchronization therapy; *DES,* drug-eluting stent; *EF,* ejection fraction; *ICD,* implantable cardioverter defibrillator; *LDL,* low-density lipoprotein; *LV,* left ventricular; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *SCD,* sudden cardiac death; *VA,* ventricular arrhythmia.

Classes of Recommendations (1-3) and levels of evidence (A-C).

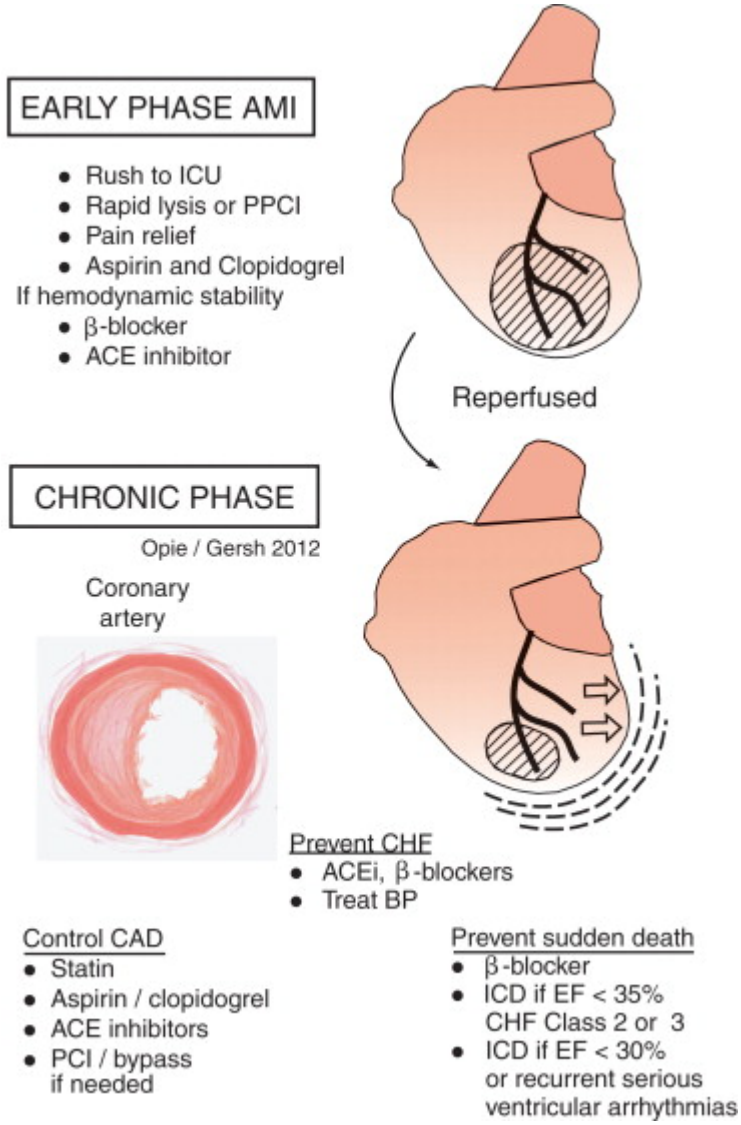

Figure 12-7 Contrasting management of early and chronic phases of acute myocardial infarction (AMI). In the early phase, the major aim is to achieve reperfusion either by rapid thrombolysis or by primary percutaneous coronary intervention (PPCI), while protecting from pain and starting cardioprotective drugs such as aspirin plus clopidogrel and, when hemodynamically stable, β-blockers and angiotensin-converting enzyme inhibitors (ACEi). In the chronic phase, for secondary prevention, three major aims are to control coronary artery disease, to inhibit adverse remodeling with congestive heart failure (CHF), and to prevent sudden cardiac death. ACEi may be indicated for all or selected for higher-risk patients (controversial). (For implantable cardioverter defibrillator [ICD] management, see Chapter 8 and Fig. 8-16.) *BP,* Blood pressure; *EF,* ejection fraction; *ICU,* intensive care unit; *PCI,* percutaneous coronary intervention.

(Figure © L.H. Opie & B.J. Gersh, 2012.)

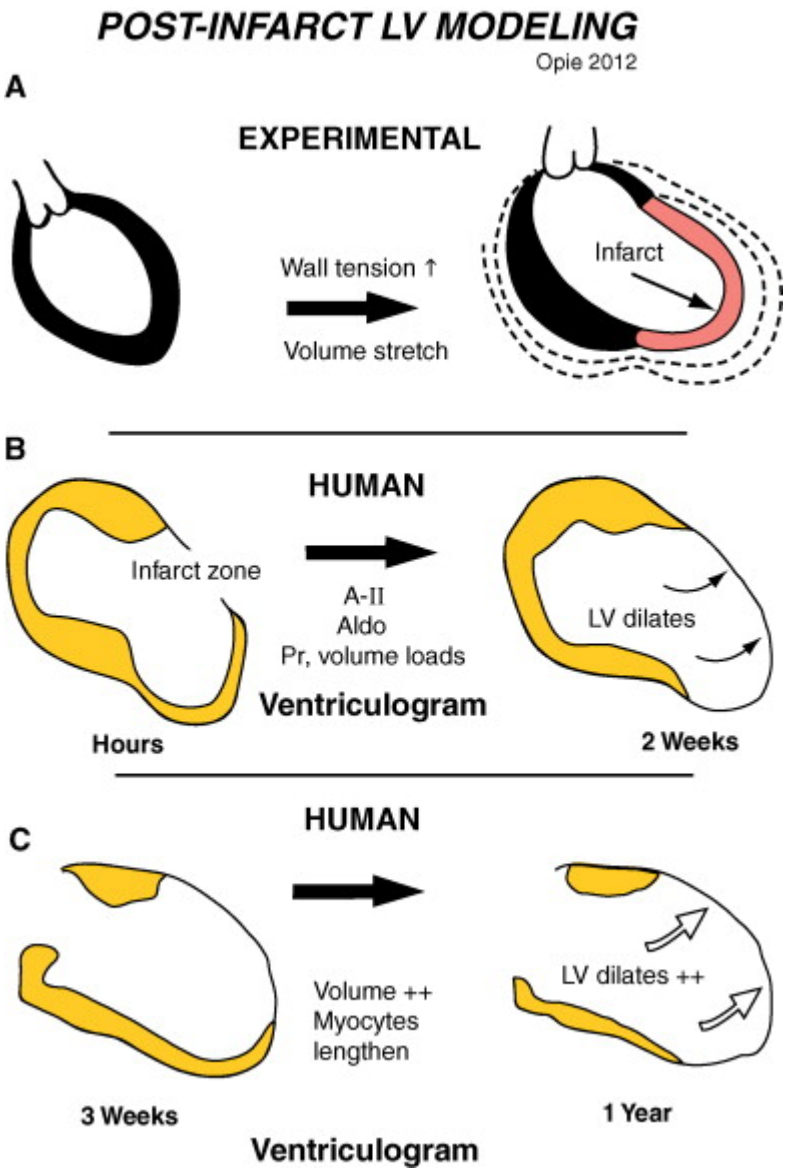

Figure 12-8 Postinfarct remodeling patterns. **A,** Simplified overall patterns (cartoon style) based on animal models, where *solid black* represents the noninfarcted and *red zones* the infarcted myocardium of the left ventricle (LV). Note potential for considerable remodeling of the infarct zone, thereby increasing the volume of the noninfarcted zone. **B,** Endocardial wall motion outlines of two separate human hearts in the early postinfarct phase with adverse effects of pressure (Pr) or volume loads, angiotensin II (A-II) and aldosterone (aldo). **C,** The late postinfarct phase, derived from contrast ventriculography. Note considerable remodeling in accord with the animal models, with emphasis on progressively increased LV volume.
(Modified from Opie LH, et al. Controversies in ventricular remodeling. Lancet 2006;367:356–367.)

Lifestyle changes.

Lifestyle changes are often much needed. A rehabilitation exercise program combines social support with the specific benefits of exercise. To stop smoking, patients need enough education and encouragement to become determined in their efforts. Then, if needed, the antidepressant drug bupropion (Wellbutrin) helps them to stop.[226] Even better is varenicline tartrate (Chantix in the United States), newly approved by the FDA. Multifactorial cardiac rehabilitation, which addresses the medical and psychosocial complications of MI, exercise training, and risk-factor modification, is a proven value but for a variety of reasons remains underused.[227-229]

Mediterranean diet, wine, and cocoa.

Epidemiologically, Mediterranean countries have a low incidence of coronary heart disease. In the Lyon Diet Heart Study of Infarct Survivors, a Mediterranean-type diet with a high intake of linolenic acid (the precursor of ω-3 long-chain fatty acids found in fish oils), vegetables, fruits, and oils (olive and canola) but with reduced butter and red meat, gave striking protection. Total mortality, cardiac death, and non-fatal MI fell for up to 4 years of follow-up.[230] In a population-based study in Greece, the closer the adherence to the traditional Mediterranean diet, the greater the longevity.[231] In postinfarct survivors, 1 g daily of fish oil gave cardiovascular protection over 3.5 years.[232],[233] In line with the *evidence for ω-3 fatty acids,* the Nutrition Committee of the AHA now recommends two fatty fish meals per week or dietary fish oil capsules.[234] A Mediterranean diet supplemented with olive oil or nuts has better effects on cardiovascular risk factors than does a low-fat diet.[235] The benefits of red wine have probably been overdramatized, but modest intake of wine with meals, part of the Mediterranean culture, is beneficial.[236] The current dietary rage is cocoa, as found in certain bitter chocolates that contain protective flavonoids; ordinary dark chocolates do not contain these.[237] However, there are no dose-response data, and hard cardiovascular benefits still have to be proven.

No to b-carotene and vitamin E.

β-Carotene and vitamin E have not stood the test of time. After 7 years of follow-up in the HOPE study, there was no cardiovascular benefit from vitamin E but rather increased heart failure.[238] Despite indirect evidence associating elevated plasma homocysteine levels to cardiovascular disease, several recent trials have failed to show any benefit from supplementation with folic acid, vitamin B_6, or vitamin B_{12}.[239]

Hormone replacement therapy: Harmful.

Large landmark clinical trials have provided firm evidence that combination estrogen and progestin replacement therapy should not be used as either the primary or secondary prevention of cardiovascular disease in women. Postmenopausal women who are already taking hormone replacement therapy at the time of MI should not continue taking the drugs; neither should hormone replacement therapy be given de novo. *Raloxifene,* a selective estrogen receptor modulator, when given to postmenopausal women with coronary artery disease or multiple risk factors for it, did not decrease primary coronary events compared with placebo. There was a reduction in the risk of estrogen receptor–positive invasive breast cancer and vertebral fractures, but an increased risk of fatal stroke and venous thromboembolism. Thus raloxifene, similar to estrogen and progestin replacement therapy, should not be used as either primary or secondary prevention of cardiovascular disease in women.[240]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Postinfarct cardioprotective drugs

Postinfarct statins.

There no longer is any doubt that statins reduce hard endpoints in patients with coronary disease. Starting statins during the period of acute hospitalization may enhance the continued use of these drugs after discharge. The only remaining issue is how far to reduce LDL cholesterol, with a strong trend favoring aggressive lowering (see Tables 10-2, 10-3, and 12-3; see also Chapter 10). An elegant study with intravascular ultrasound suggests that 75 mg/dL (1.95 mmol/L) is the equilibrium LDL level at which progression and regression of the plaque are, on average, similar.[241]

Postinfarct β-blockade.

Solid evidence shows that postinfarct β-blockade provides benefit. In a very large survey on more than 200,000 patients, late mortality fell by approximately 40%.[18],[196] The present trend is to continue β-blockers indefinitely, together with aspirin, a statin, and, whenever there is LV dysfunction or diabetes, ACE inhibition, or an ARB. β-Blockers protect from the adverse effects of surges of catecholamines, which may explain their effects on SCD.[242] In a pooled analysis of four intravascular ultrasonography trials, β-blockers slowed the progression of coronary atherosclerosis.[243] In the presence of severe respiratory problems but in the absence of heart failure, verapamil is a viable alternative to β-blockade (see next section). Which subsets of patients are most likely to benefit? Paradoxically, those patients who appear to be at higher risk also benefit most. For example, β-blockade may have its best effects in the presence of heart failure, with all-cause mortality reduced by 23%.[244] The mortality reduction also extends to co-therapy with ACE inhibitors, ARBs, and aspirin.[196] Obvious contraindications to β-blockade remain grade IV heart failure, severe bradycardia, hypotension, overt asthma, and heart block greater than first degree.

ACE inhibitors for all with coronary disease?

As already argued in Chapter 5 (see p. 135), prophylactic ACE inhibitors should be considered for all patients with coronary disease even with preserved LV function, and are positively indicated for those with angina pectoris with hypertension, peripheral vascular disease, diabetes, or LV dysfunction.[10]

Aldosterone antagonists.

Aldosterone antagonists should be prescribed to all STEMI patients who are receiving an ACE inhibitor, have an ejection fraction of less than 40%, a serum creatinine of less than or equal to 2.5 mg/dL, and a serum potassium of less than 5 mEq/L or have either symptomatic heart failure or diabetes depending on baseline serum potassium levels and renal function (see Chapter 5, p. 161). The risk of hyperkalemia is substantial, and patients need to be monitored carefully.[245] These initial recommendations in the guidelines in 2006 were not changed in the focused updates in 2009.[246]

When to use calcium channel blockers.

As a group, CCBs do not give postinfarct protection.[247] No CCB has been shown to reduce mortality in STEMI and they may be harmful in patients with heart failure, significant LV dysfunction, or conduction disease. The major use is for the management of recurrent ischemia despite β-blockers and in patients who are not revascularizable. A case can also be made for the use of verapamil or diltiazem in the absence of LV failure, especially when β-blockade is contraindicated. In the large Danish postinfarct trial (DAVIT-2) in which overt LV failure was prospectively excluded, verapamil 120 mg three times daily decreased reinfarction in cardiac mortality.[247] For BP control, long-acting nifedipine (or amlodipine) added to β-blockade and ACE inhibitors may be helpful.

Aspirin and clopidogrel.

Aspirin, the simplest and safest agent, is now established therapy, starting with an oral dose as soon as possible after the onset of symptoms of AMI and continuing indefinitely thereafter (provided that the BP is adequately controlled). It prevents reinfarction, stroke, and vascular mortality as shown in numerous trials. The dose for long-term indefinite aspirin is 75 to162 mg daily. The updated ACC-AHA recommendations are that, for all post-PCI STEMI stented patients without aspirin resistance, allergy, or increased risk of bleeding, aspirin 162 to 325 mg daily should be given for at least 1 month after BMS, 3 months after sirolimus-eluting stent, and 6 months after paclitaxel-eluting stent implantation, after which the dose is 75 to 325 mg daily (class IB).[72] The lower doses have fewer side effects. Clopidogrel should be used for aspirin intolerance or resistance, and added to aspirin for 14 days (no stent), 1 month or more (BMS), or at least for 12 months (drug-eluting stent) (all class IB).[72] In regard to long-term co-therapy with clopidogrel and aspirin, there are no trials that specifically address this in patients with prior STEMI, other than in patients undergoing PCI and stenting. Many theoretical benefits have to be offset against the risk of bleeding.

Aspirin plus ACE inhibitors.

Combined with aspirin, ACE inhibition has an odds ratio for risk reduction of 0.80 versus 0.71 without aspirin.[248]

Nonsteroidal antiinflammatory drugs.

Both the cyclooxygenase-2–selective inhibitors and the traditional NSAIDs have been associated with an increase in cardiovascular events. In a metaanalysis and systematic review, low-dose naproxen and ibuprofen appear to be the safest NSAIDS.[249],[250] Diclofenac and indomethacin appear to cause the most harm. Celecoxib in doses of 200 mg or more daily is associated with an increase in cardiovascular events. Patients with or at risk of cardiovascular disease are particularly at risk. The combination of aspirin and an NSAID may reduce aspirin's efficacy. Two ex vivo studies have demonstrated a potential interaction of ibuprofen and possibly naproxen, but not diclofenac or rofecoxib, when combined with aspirin.[251],[252] The FDA currently recommends that ibuprofen be given 30 minutes after aspirin or at least 8 hours before aspirin to negate this potential interaction.[167] Choice of agent requires a detailed risk evaluation of the potential underlying gastrointestinal and cardiovascular risk profile in the individual patient. The AHA has recommended a stepped-care approach to prescribing these agents.[253]

Warfarin anticoagulation.

Warfarin is usually given for 3 to 6 months after an infarct to patients with prior emboli; in those with LV thrombus (echocardiographically proven), or large anterior infarcts (threatened thrombus), or with established AF; and in those with contraindications or hypersensitivity to aspirin. Medium-intensity anticoagulation with an international normalized ratio (INR) of approximately 2.5 seemed effective, albeit in two relatively small studies,[254],[255] whereas low-intensity anticoagulation with an INR of 1.8 in the largest study was not.[256] In another large study, mean INR values of approximately 2.2 to 2.8 reduced nonfatal MI and nonfatal embolic stroke.[257] These modest returns need to be balanced against increased bleeding, greater cost, and added inconvenience to the patient. Patients older than 75 years have not been adequately studied. There is some evidence that chronic anticoagulation can reduce the number of adverse cardiovascular events after ACS, but these trials generally antedated the widespread use of clopidogrel and early revascularization for both ST-segment elevation and non–ST-segment elevation AMI.[258] It has been previously widely recommended that either UFH or LMWH should be administered to reduce the risk of deep vein thrombosis until patients become ambulatory. Nonetheless, based on the 2008 American College of Chest Physicians guideline, it is considered that venus thromboembolism prophylaxis is not necessary (unless indicated for some other reason) for complicated STEMI patients who are likely to be on bed rest for less than 24 hours. If longer periods of bed rest are required, than prophylaxis with UFH, LMWH, or fondaparinux is indicated.

Postinfarct antiarrhythmic agents.

Complex ventricular ectopy and VT in the late hospital phase of MI are predictors of subsequent sudden death after discharge, independently of their frequent association with LV dysfunction. Nonetheless, the hoped-for benefit of antiarrhythmic therapy on postinfarct mortality is still elusive, with β-blockers the only agents showing clear-cut mortality reduction.[192] The momentum has swung away from amiodarone, given

its side effect profile and lack of a consistent mortality benefit in clinical trials, to implantable cardioverter defibrillators (ICDs; see next section).[259] Nonetheless, amiodarone can relieve highly symptomatic premature ventricular extrasystoles or runs of nonsustained VT.

Implantable cardioverter defibrillators.

The role of ICDs in the primary prevention of postinfarct SCD in patients with heart failure is well established (see section on Interventions for Severe Stable LV Dysfunction later; see also Fig. 8-16). The use of Holter monitoring and invasive electrophysiologic testing has declined, and the major inclusion criterion is the ejection fraction, albeit an imprecise measurement.

The future.

There is an urgent need for new methods of arrhythmia risk stratification. Microvolt T-wave alternans appears the most promising of the new approaches, but its ultimate role requires further clarification.[260],[261]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Other supraventricular arrhythmias

Atrial flutter.

Satisfactory control of the ventricular rate may be extremely difficult to achieve, but flutter is easily converted by a low-energy countershock. Although the left atrium still contracts, the potential for embolism does occur and the same rules as those for AF apply for anticoagulation both in relation to cardioversion and for prevention of thromboembolism and chronic atrial flutter. Moreover, AF and atrial flutter may coexist in the same patient. For resistant or recurrent cases, catheter ablation of the AV node with pacemaker implantation is increasingly used. Patients with “typical atrial flutter” enjoy a very high success rate with radiofrequency ablation of the flutter circuit. In some patients with atrial flutter with documented AF at other times, successful flutter ablation may nonetheless result in recurrences of AF. The combination of AF and atrial flutter either can be treated by drugs or, if refractory, may respond to radiofrequency procedures isolating the pulmonary veins from the left atrium[329] (for details, see Chapter 8, p. 314).

Multifocal atrial tachycardia.

Multifocal atrial tachycardia is an uncommon but not rare arrhythmia frequently associated with significant lung disease, respiratory failure, and pulmonary hypertension. It may respond to verapamil or β-blockers, but there appear to be no formal drug trials, and the clinical impression is that this is a very difficult arrhythmia to control. Exclude underlying theophylline toxicity. Intravenous magnesium may be effective for rate control and helps in restoration of sinus rhythm in patients with and without serum magnesium levels.[330]

Supraventricular tachycardia.

In the standard paroxysmal type (PSVT) with nodal reentry, vagotonic procedures (Valsalva maneuver, facial immersion in cold water, or carotid sinus massage) may terminate the tachycardia (Table 12-5). Always auscultate the carotid arteries before performing carotid sinus massage. If these measures fail, the next step is to use intravenous adenosine followed by intravenous diltiazem, verapamil, or esmolol (see Chapter 8, p. 303). Adenosine with its ultrashort duration of action is safest, especially if there is a diagnostic uncertainty between PSVT with aberrant conduction and wide-complex VT. If these steps fail, vagotonic maneuvers are worth repeating. Thereafter the choice lies between intravenous digitalization or intravenous amiodarone or direct-current cardioversion, and the decision needs to be tempered by the clinical condition of the patient. (Also, in countries outside the United States, intravenous flecainide is approved and may be a choice in the absence of structural heart disease.)

Table 12-5 -- PSVT: Principles of Management[590]

Entry Point
• Narrow QRS complex tachycardia; either AV nodal reentry or WPW (see Fig. 8-14). If *atrial flutter,* proceed straight to DC cardioversion (may consider ibutilide but torsades risk).
Acute Therapy: Hemodynamically Stable
• Vagal maneuvers. • Intravenous AV nodal blockers (adenosine,* verapamil, diltiazem, esmolol; high success rate). • Occasionally intravenous propafenone. • Synchronized DC cardioversion. • Burst pacing in selected cases (e.g., postbypass surgery).
Acute Therapy: Hemodynamically Unstable

• Intravenous adenosine (not other AV nodal blockers—negative inotropes). • Must cardiovert if adenosine unsuccessful.
Follow-up: PSVT with AV Nodal Reentry
• Self-therapy by vagal procedures. • Prevention by long-acting AV nodal blockers (verapamil, diltiazem, standard β-blockers, digoxin). • If repetitive attacks, perinodal ablation to inhibit reentry through reentry pathways. Small risk of AV nodal damage requiring permanent pacemaker.
Follow-up: Preexcitation (WPW, Delta Wave during Sinus Rhythm)
• RF catheter ablation of bypass tract. • Rarely, surgery is performed for associated conditions (young children with associated anomalies; multiple paths). • Occasionally drug therapy: Class IC or class III agents.[†] Digoxin contraindicated, avoid other AV nodal blockers.
Follow-up: Atrial Flutter
• Prevent by sotalol, amiodarone, dofetilide, or RF ablation of flutter circuits. • Rate control by AV nodal inhibitors (verapamil, diltiazem, β-blocker, digoxin, or combinations). • Consider RF AV nodal ablation and permanent pacemaker.
Catheter Ablation
• Treatment of choice for recurrent PVST.

Flecainide, propafenone (=Ic) or Amiodarone, ibutilide (=III agents)

AV, Atrioventricular; *DC,* direct-current; *PSVT,* paroxysmal supraventricular tachycardia; *RF,* radiofrequency; *WPW,* Wolff-Parkinson-White syndrome.

* Adenosine preferred (ultra-short-acting); esmolol action wears off more slowly but fast enough to allow subsequent safer use of verapamil or diltiazem if needed.

† *Class* refers to class of antiarrhythmic drug (see Fig. 8-1), not to American Heart Association–American College of Cardiology class of recommendation.

Refractory PSVT.

Patients with supraventricular arrhythmias that are very rapid or refractory to standard drugs, or associated with a wide QRS complex on the standard electrocardiogram (implying either aberration, antegrade preexcitation, or VT), warrant an invasive electrophysiologic study. In the majority of other patients, drug management is successful. Nonetheless, the ease of radiofrequency ablation coupled with its very high success rates and low rates of complications have increasingly led to its use as first-line therapy, particularly in younger patients reluctant to commit to lifelong drug therapy, even if the latter is effective.

Prevention of PSVT.

The best measure is often catheter ablation. Otherwise initiating ectopic beats may be inhibited by β-blockade, verapamil, diltiazem, or amiodarone. The latter is highly effective for supraventricular arrhythmias, including paroxysmal AF and arrhythmias involving accessory pathways; potentially severe side effects may be limited by a low dose (see Chapter 8, p. 319). The class IC drugs (propafenone and flecainide) are viable alternatives but should not be used in the presence of structural heart disease.

Wolff-parkinson-white syndrome.

The acute treatment of choice or Wolff-Parkinson-White syndrome is cardioversion if the patient is hemodynamically compromised. If presenting with narrow-complex PSVT, the same intravenous therapy as for standard PVST may be followed (see Table 12-5). For follow-up, because of the risk of antegrade preexcitation via the bypass tract, *digoxin is absolutely contraindicated* (because it shortens the refractory period of the tract). Verapamil, diltiazem, and β-blockade may also be dangerous by blocking the AV node and redirecting impulses down the bypass tract. In the prevention of PSVT, including AF, radiofrequency catheter ablation of the accessory pathway is usually highly successful and is now standard treatment.

Otherwise, low-dose amiodarone is probably best, followed by sotalol or propafenone. Prophylactic ablation in asymptomatic individuals at high risk may be the best approach—for example, in those age 35 years or younger, patients with evidence of rapidly conducting pathways with short refractory periods, or patients with rapid arrhythmias inducible at the time of an electrophysiologic study, or on the basis of occupational or other lifestyle circumstances. This is, however, still controversial.[331]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Bradyarrhythmias

Asymptomatic sinus bradycardia does not require therapy and may be normal, especially in athletes. For *symptomatic sinus bradycardia, sick sinus syndrome, and sinoatrial disease,* probanthine and chronic atropine are unsatisfactory so that pacing is usually required. First, however, the adverse effects of drugs such as β-blockers, digitalis, verapamil, diltiazem, quinidine, procainamide, amiodarone, lidocaine, methyldopa, clonidine, and lithium carbonate should be excluded. AV block that was "truly caused by drugs" was found in only 15% of patients during therapy with β-blockers, verapamil, or diltiazem.[332] In this study 56% of patients for whom drug discontinuation led to resolution of AV block had recurrence of AV block in the absence of therapy during follow-up.[332] In this respect, drugs such as β-blockers and verapamil constituted a "pharmacologic stress test." Second- or third-degree AV block, which resolved following discontinuation of β-blockers, verapamil, or diltiazem, 56% had a subsequent recurrence of AV block in the absence of therapy. In the *tachycardia/bradycardia syndrome,* intrinsic sinus node dysfunction is difficult to treat and once again may require permanent pacing. β-Blockers aggravate the bradycardiac component of the syndrome. Patients usually end up with a combination of a permanent pacemaker and antiarrhythmic agents. However, in many patients the combination of radiofrequency ablation of the AV node followed by permanent pacemaker implantation is a highly effective method of controlling refractory tachycardia. For *AV block with syncope* or with excessively slow rates, atropine or isoproterenol or transthoracic pacing is used as an emergency measure, pending pacemaker implantation. In asymptomatic patients with congenital heart block, the role of permanent pacing is debatable, with current trends favoring an aggressive approach at an earlier age.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Ventricular arrhythmias and proarrhythmic problems

The criteria for instituting drug therapy for ventricular arrhythmias are not clear cut, although patients with sustained VT (Table 12-6), survivors of previous arrhythmia-related cardiac arrest, and those with severely symptomatic arrhythmias all require treatment. A full cardiologic assessment is required. An essential adjunct to antiarrhythmic therapy lies in the management of underlying disease such as LV failure, ischemia, anemia, thyrotoxicosis, or electrolyte imbalance. The potential hazards of antiarrhythmic therapy were emphasized by the CAST study, which warned that the proarrhythmic effects of some class I agents can actually increase mortality in patients with ischemic heart disease. In patients with ICDs, concomitant drug therapy by β-blockade and amiodarone to reduce inappropriate discharges is often administered and the ICD provides "backup" in the event of proarrhythmia. The most effective way to prevent SCD in patients with coronary disease is to eliminate ischemia and to improve LV function, often by coronary revascularization. In the patient who has already survived an episode of cardiac arrest or hemodynamically unstable VT, coronary revascularization alone will usually not suffice, and an ICD is indicated.

Table 12-6 -- Acute Sustained Ventricular Tachycardia[591]

Entry Point: Wide QRS Complex Tachycardia

• Approximately 90% will be wide-complex ventricular tachycardia; the others will include PSVT with aberration or WPW with anterograde conduction.
• DC cardioversion—procedure of choice (ACC/AHA/ESC class 1C*),usually effective.
• If DC cardioversion fails or if patient hemodynamically stable:
  • IV amiodarone often used (class IIA/B).
  • IV procainamide (more effective but less safe) (class IIA/C).
  • IV lidocaine (safe but will revert only a minority) (class IIB/C).
  • If torsades de pointes, IV magnesium sulfate; consider atrial pacing; isoproterenol in an emergency.
  • If VT recurs soon after cardioversion, repeat the latter under cover of lidocaine or other IV drug.
• (Only if PSVT presents as suspected VT, use IV adenosine for diagnosis but *never* verapamil or diltiazem.)

Follow-up of Acute Attack

• If PSVT, see Table 12-5.
• If VT (majority):
  • Requires thorough cardiologic evaluation.
  • Need accurate diagnosis of rhythm, structural heart disease, and LV function (long QT syndrome); arrhythmogenic RV dysplasia.
• Empirical drug approach (amiodarone) if patient not candidate for ICD.
• Various trials have left unresolved the best way to select antiarrhythmic drugs for patients with ventricular arrhythmias.
• Strong trend toward ICD, away from EPS-guided drug choice.
• Sometimes surgery (LV aneurysm).
• If idiopathic refractory VT, especially RVOT in origin, radiofrequency catheter ablation but verapamil may be effective in RVOT VT and exercise-induced VT in patients without structural heart disease.
• ICD as first-line therapy if high risk of sudden death: in survivors of cardiac arrest, in symptomatic VT, or in asymptomatic VT with a low ejection fraction.

- In patients with recurrent ICD shocks caused by VT, consider amiodarone plus β-blockade—if needed, radiofrequency ablation.

ACC, American College of Cardiology; *AHA,* American Heart Association; *DC,* direct current; *EPS,* electrophysiologic stimulation; *ESC,* European Society of Cardiology; *ICD,* implantable cardioverter defibrillator; *IV,* intravenous; *LV,* left ventricular; *PSVT,* paroxysmal supraventricular tachycardia; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White preexcitation syndrome.

* Classes of Recommendations (1-3) and levels of evidence (A-C).

Drug choice for ventricular arrhythmias.

The choice of drug for chronic use is ideally based on prior demonstration during acute and chronic Holter or electrophysiologic testing that the drug actually works and on its potential for toxicity in the patient under study. Unfortunately, neither the Holter nor the electrophysiologic study is a reliable guide to long-term efficacy of therapy. Class I agents, including quinidine, disopyramide, and mexiletine, are used less and less. Propafenone is possibly the most effective and least harmful of the class IC agents, although not as good as β-blockade or amiodarone in the CASH study,[333] in which the propafenone arm was discontinued. In patients without structural heart disease, the risk of proarrhythmia with both propafenone and flecainide is low. The antiarrhythmic effect of *empirical β-blockade monotherapy* for VT is impressive and reportedly as good as electrophysiologic-guided drug choice. In comparison with other drugs, amiodarone appears to be the most effective antiarrhythmic agent, despite its considerable side effects. Sotalol, a β-blocker with antiarrhythmic class III activity (see Table 1-3), is an alternative, with a reduced dose in renal insufficiency; it should only be given in the hospital under monitoring conditions because QT prolongation and torsades des pointes occur in 1% to 4% of patients.

β-Blockers are among the few antiarrhythmic agents with positive long-term beneficial effects in postinfarct patients.[192] In those not responding to β-blockade, or in whom β-blockade is contraindicated, *low-dose amiodarone* is increasingly used, despite potentially serious side effects. Like β-blockade, amiodarone appears to give postinfarct protection. Deciding between these agents is somewhat of a personal choice and not entirely evidence based. Yet, in comparison with others, amiodarone is the most effective antiarrhythmic agent despite its considerable side effects that are, however, lower at reduced doses.

Implantable cardioverter defibrillators.

The treatment of recurrent sustained VT and VF is difficult, and pharmacologic therapy has, in the main, been very disappointing. This failure has stimulated alternative approaches such as surgical or catheter ablation of the VT foci and use of the ICD, which is now mandated for all survivors of SCD, for intractable ventricular arrhythmias, and increasingly for primary prevention of SCD in postinfarct heart failure (for details see section on p. 320). The advent of the ICD has virtually eliminated surgical procedures such as endocardial resection. Prophylactic antiarrhythmic drug therapy is contraindicated except for β-blockade, which can be very helpful, especially in those with coronary-related CHF receiving an ICD, for whom β-blockade is standard therapy, often with amiodarone, to reduce the effect of unpleasant shocks on the patient. Radiofrequency catheter ablation may be very successful in idiopathic or right-ventricular outflow tract VTs. For the vast majority of patients who have VT secondary to coronary artery disease and LV dysfunction, catheter ablation remains an option as newer mapping techniques are improving success rates.

In patients with ICDs, *recurrent discharges* are a major source of morbidity, depression, and anxiety. With the backup of an ICD in place, there is a new role for the use of antiarrhythmic drugs, despite LV dysfunction, whereas these might be contraindicated in patients without devices.[334] Common causes of inappropriate device discharges include supraventricular arrhythmias including AF, electrical noise, inappropriate sensing, and device or lead malfunction. The frequency can be reduced by additional reprogramming, the use of dual-chamber devices, and antitachycardia pacing.[335] Appropriate discharges caused by recurrent VT can be treated with antiarrhythmic drugs to prevent the arrhythmia or slow the rate such that it is more responsive to antitachycardia pacing.[336] Radiofrequency may be effective in reducing

the frequency of discharges,[337] and prophylactic ablation of a ventricular arrhythmic substrate was found to reduce the frequency of subsequent ICD discharges in two trials.[338],[339]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Congestive heart failure

General policy.

Despite powerful protective agents (ACE inhibitors, ARBs, β-blockers, spironolactone, eplerenone), the long-term prognosis of CHF remains poor, unless a reversible cause is found. The initial steps in a patient with heart failure include investigation and specific treatment for a cause, including ischemia, hypertension, valvular heart disease, uncontrolled diabetes, thyrotoxicosis, alcohol abuse, cocaine, obstructive sleep apnea, and anemia. It is important to exclude the use of other *drugs that could exacerbate heart failure,* that is, NSAIDs, CCBs, thiazolidinediones, and antiarrhythmic drugs, many of which are negatively inotropic. It is also important to obtain a careful family history as the familial and genetic components of idiopathic dilated cardiomyopathy are increasingly recognized.[340] The effect of lifestyle modification in CHF has not been tested in randomized trials, but makes sense and includes smoking cessation, restriction of salt and alcohol, weight reduction in obese subjects, and regular monitoring to detect fluid build-up.[341-343] Pneumococcal vaccination and an annual influenza vaccination are strongly recommended. The previous policy was to initiate treatment with loop diuretics, salt restriction, and then digoxin before proceeding to conventional vasodilators, but *ACE inhibitors and β-blockers are now the cornerstone of therapy,* increasingly given from the start of symptoms (with diuretics), or even before an asymptomatic LV dysfunction (without diuretics). The key to maximizing the dose of both ACE inhibitors and β-blockers is gradual titration. Although *digoxin* for AF patients with heart failure is less used, meticulous attention must be paid to the new safer blood ranges (see Fig. 6-12); older "therapeutic" ranges were also potentially lethal. As digoxin does not improve mortality, the current trend is to emphasize the agents that do improve mortality (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists) and then to consider digoxin among other options such as nitrate-hydralazine (see Fig. 6-10) for patients remaining symptomatic. Previous combination "triple therapy" with diuretics, ACE inhibition, and digoxin is now replaced by *modern quadruple therapy* (ACE inhibitors or ARBs, β-blockade, diuretics, and spironolactone or eplerenone). How can clinical judgment be aided? Plasma B-type (brain) natriuretic peptide (BNP) is a rapid and sensitive guide that reflects elevated LV filling pressures and is useful in the diagnosis of heart failure in the patient presenting with dyspnea. Studies evaluating the role of BNP measurements in guiding management in both symptomatic and asymptomatic patients are ongoing.

ACE inhibitors versus ARBs.

The vast experience gained with ACE inhibitors makes them the "gold standard" for renin-angiotensin inhibition (see Table 5-5). When ACE inhibitors cannot be tolerated (cough), ARBs become a logical replacement, but the combination of these is also being advocated for heart failure.[344] Although the CHARM-Added trial suggested that adding an ARB to an ACE inhibitor may be helpful from a symptomatic standpoint, this was not in patients taking aldosterone antagonists, and the combination of an aldosterone antagonist, ACE inhibitor, and an ARB is not recommended.[345]

β-blockers.

When cautiously added to ACE inhibitors and diuretics in hemodynamically stable patients, β-blockers consistently decrease mortality by approximately 30% or even more. The patient should be closely supervised during this initial titration because there is the risk of transient deterioration. Trial data favor the use of carvedilol, metoprolol, and bisoprolol (see Chapter 1, p. 16). Of these, only carvedilol and long-acting metoprolol XL are licensed for use in the United States (see Chapter 6 for evaluation of these drugs). Only carvedilol is approved for class IV heart failure.[346] Metoprolol XL is only licensed for class II and III heart failure but has an angina license in the United States, which carvedilol does not. β-Blockers are typically initiated after the patient is stabilized on ACE inhibitors, when the watchword is to use low doses and titrate slowly as tolerated. However, the CIBIS-3 trial showed that β-blockade could be instituted *before* ACE inhibition.[347] In practice, many start with a low dose of an ACE inhibitor increasing at 1-2 week intervals followed by the initiation of a β-blocker at very low doses and gradual titration over a period of

weeks.

Congestive heart failure.

A metaanalysis of double-blind, placebo-controlled trials of β-blockers in heart failure demonstrated a lower magnitude of survival benefit among patients enrolled in the United States versus the rest of the world. Whether this is due to population differences, genetics, cultural or social differences, and disease management or simply chance is uncertain.[348]

Diuretic therapy.

Doses and drugs should not be fixed, but loop diuretics are usually the drugs of choice for the treatment of pulmonary or peripheral edema. Diuretics may need to be reduced when the ACE inhibitor is introduced or the dose increased, or diuretic therapy may have to be stepped up in cases of refractory edema. Especially in severe right ventricular failure, the absorption of drugs given orally is impaired and a short course of intravenous furosemide can be very helpful. *Posture* can influence diuretic efficacy. To improve renal perfusion and to increase diuresis, the patient may have to return to bed for 1 to 2 hours of supine rest after taking a diuretic. The principle of *sequential nephron blockade* (see Figs. 4-2 and 4-5) states that different types of diuretics can synergistically be added, such as a thiazide to a loop diuretic.

Aldosterone antagonists.

The adverse neurohumoral qualities of diuretic therapy, often forgotten, need to be balanced by an ACE inhibitor or ARB, often with spironolactone. Yet especially in patients with poor renal function, these combinations can precipitate hyperkalemia.

Nonetheless, the RALES study[349] showed that the addition of spironolactone at an average dose of 25 mg daily while watching K can give substantial clinical improvement and save lives in patients with class III or IV heart failure. RALES is complemented by the EPHESUS study that used eplerenone, a selective aldosterone blocker, in post-MI patients with transient heart failure or, in the case of diabetics, an ejection fraction of less than 40%.[245] This too was strongly positive. Subsequently, the EPHESUS-HF trial in sessions with milder symptoms (New York Heart Association [NYHA] class II heart failure) and an ejection fraction of no more than 35% was also resoundingly positive, and aldosterone antagonists are now considered standard therapy.[350] It remains essential to monitor the serum potassium carefully, particularly when ACE inhibitors or ARBs are also part of the therapeutic attack. In patients treated by both an ACE inhibitor and an ARB, ACC-AHA guidelines warn that aldosterone antagonists should not be used.[351] The remarkable story of aldosterone antagonists for heart failure is backed by experimental evidence suggesting that aldosterone may mediate myocardial fibrosis in remodeling, whereas clinical data suggest that aldosterone antagonism may improve LV function, mass, and volumes (reverse remodeling).[352]

Vasodilators.

High-dose nitrates (on-off patches) improve exercise tolerance and LV size and function when added to ACE inhibitors, diuretics, and digoxin.[353] In patients with pulmonary congestion, nitrates given at night can decisively improve sleep. For long-term use, the old combination of nitrates plus hydralazine is logical because the hydralazine appears to counteract nitrate tolerance (see Chapter 2, p. 53), although it is still prudent to maintain a nitrate-free window of 8 to 10 hours depending on whether symptoms occur primarily at night or with exertion during the day. Because black patients appeared to be less responsive to ACE inhibitors in earlier trials, the African-American Heart Failure trial tested the addition of isosorbide dinitrate plus hydralazine to standard therapy, finding increased survival.[354] This trial sparked a controversy about the role of race and ethnicity in clinical trials,[354],[355] although settling the issue of how to prevent nitrate tolerance in heart failure. Another byproduct of the African American Heart Failure trial has been a series of investigations aimed at untangling the pharmacogenomic issues underlying the differences between black and white heart failure patients.[356]

Atrial fibrillation in congestive heart failure.

AF both contributes to mortality[357] and is a marker for severe disease.[358] Both the AF and the heart failure must be treated as vigorously as possible. In selected patients cardioversion under anticoagulation or new atrial pacing techniques or internal cardioversion may be appropriate, but for most, strict rate control

over 24 hours and anticoagulation with warfarin “remain the mainstays of therapy.”[358] Failing rate control, the next option is conversion and maintenance of sinus rhythm with amiodarone, which is well tested in CHF although not approved for AF in the United States. Sotalol is an alternative. Dofetilide, approved for highly symptomatic AF, converts to sinus rhythm in CHF but in only approximately 12% of patients.[359] Once sinus rhythm was restored, dofetilide reduced recurrences by 65%. Careful dose adjustment is needed in renal failure. Another major downside is the risk of early torsades de pointes (3.3%). Although dronedarone was associated with reduced heart failure and hospitalization in the ATHENA trial, the results of the ANDROMEDA trial, which compared dronedarone to placebo in patients with symptomatic heart failure and severe LV systolic dysfunction, demonstrated an increased mortality in the dronedarone group. The drug should not be used in patients with NYHA class III-IV heart failure, and great caution should be exercised if the drug is to be given to patients with less severe degrees of heart failure.[291],[292]

Rate versus rhythm control.

Controversies in patients with LV systolic dysfunction and heart failure will hopefully soon be resolved. The AF-CHF trial found no outcome differences between these policies over 2 years.[360] Although pulmonary vein isolation and wide atrial circumferential ablation can be successful in patients with heart failure, the success rates are reduced, and the option of AV nodal ablation with single or often biventricular pacing is frequently used. One advantage of AV nodal ablation in patients undergoing biventricular pacing is that it ensures 100% paced rhythm and therefore theoretically increases the efficacy of cardiac resynchronization therapy (CRT).[361] In regard to the indications for warfarin therapy in patients with AF and heart failure there are limited data, and the American College of Chest Physicians’ guidelines recommend against the routine use of warfarin or aspirin in patients with heart failure resulting from a nonischemic cause.[362] Nonetheless, many believe that warfarin is indicated in this situation, and it is mandatory in any patients with a history of systemic or pulmonary emboli. In the WATCH trial of 1587 patients in sinus rhythm with symptomatic heart failure there was no benefit from aspirin in regard to the primary endpoint of death, nonfatal MI, or nonfatal stroke.[363] In the WARCEF trial of patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The choice between warfarin and aspirin should be individualized.[364]

Ventricular arrhythmias in CHF.

The incidence of sudden death seems to be falling since the widespread introduction of ACE inhibitors and now β-blockers. For those who still have severe *significantly symptomatic ventricular arrhythmias,* it is first essential to pinpoint precipitating factors such as hypokalemia, hypomagnesemia, or use of sympathomimetics, phosphodiesterase inhibitors, or digoxin. The hemodynamic status of the myocardium must be made optimal because increased LV wall stress is arrhythmogenic. Amiodarone is the most effective drug for preventing AF and complex ventricular ectopy or nonsustained VT, but there was no benefit on SCD or total mortality.[365],[366] Patients with class IV symptoms are likely to die of CHF, and an ICD is not indicated unless the patient is a candidate for CRT. *Increasingly, ICDs are considered* for selected high-risk patients with life-threatening arrhythmias, and especially those with an ejection fraction of less than 30% (see Fig. 8-16). Prophylactic class I antiarrhythmic drug therapy is contraindicated. In contrast, prophylactic β-blockade can be very helpful, especially in patients with coronary-related CHF.

Severe intractable CHF.

The first steps are to ensure support of oxygenation and ventilation; assess volume status and hemodynamic stability, which may often require the use of a PA catheter; address precipitating factors such as infection, dietary indiscretion, and the administration of nonsteroidal antiinflammatory agents; and to relieve symptoms. In patients with “flash” pulmonary edema, one should be aware of acute hypertension and underlying renal artery stenosis. The next steps are to administer intravenous diuretics (depending on volume status); optimize intravenous vasodilator therapy with nitroprusside, nitroglycerin, or nesiritide; and institute inotropic agents (usually milrinone or dobutamine) for the objective of optimizing hemodynamics. In the DOSE trial, there was no significant difference in efficacy or safety endpoints for bolus versus continuous infusion of furosemide, and high-dose furosemide (2.5 times the previous oral dose) compared with low-dose furosemide produced greater fluid loss, weight loss, and relief from dyspnea, but also more frequent transient worsening of renal function.[367] In this setting, dobutamine has three potential hazards: further β-receptor downgrading, increased arrhythmias,[368] and hypotension. In the current era when most patients are on β-blockers, milrinone may be a better choice. Dopamine remains a useful drug (see Fig.

6-4), although the idea of the renal dose is now discredited.

Nesiritide.

Nesiritide is a recombinant human BNP that reduces pulmonary capillary wedge pressure and improves symptoms.[369] In a very large recent trial of more than 7000 patients with acute decompensated heart failure, nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization and had a small, nonsignificant effect on dyspnea when used in combination with other therapies. Renal function was unchanged, but it was associated with an increase in rates of hypotension, and on the basis of these results nesiritide should not be recommended for routine use in a broad population of patients with acute heart failure.[370] When compared with dobutamine, nesiritide was required for a shorter period and gave a lower 6-month mortality, so that there was an overall saving in health costs.[371] A metaanalysis of five studies in 2005 raised the risk of worsening renal function,[372] which has, however, been discounted by two more recent studies.[373],[374]

Other new agents for CHF.

The list of promising drugs and therapies for CHF that have failed the rigorous scrutiny of randomized controlled trials makes for lengthy reading and includes *levosimendan* (a calcium sensitizer), *rolofylline* (an adenosine A1 receptor antagonist), *tolvaptan,* endothelin receptor blockers, central sympatholytics, phosphodiasterase-3 inhibitors, immune modulators, erythropoietin, darbepoetin, and vasopeptidase inhibitors. Immune modulators, erythropoietin, and darbepoetin, vasopeptidase inhibitors, and surgical LV reconstruction were studied in the STITCH trial, although better results with this procedure have been reported in nonrandomized studies.[375-377] Ivabradine, which is a selective I_F -channel inhibitor that slows the heart rate (see Fig. 8-4), appears to be of significant benefit based on the randomized SHIFT trial, but the drug is not yet available in the United States.[28] Ongoing studies include trials of direct renin inhibition, combined neutral endopeptidase inhibitor-angiotensin II receptor blocker, the reduction of uric acid with allopurinol, and warfarin versus aspirin in patients with a reduced ejection fraction.[377] Neuregulin-1, which is expressed in the heart and plays a role in the maintenance of adult heart functional integrity, appears to be promising in a recent phase 2 randomized double-blind trial with recombinant neuregulin, but larger trials will be needed.[378]

Omecamtiv mecarbil is a novel investigational myosin-activator given intravenously.[379] Cardiac output is increased not by strengthening contractile force but by prolonging systole, thereby enhancing the efficiency of contraction. The idea of improving cardiac output in a safe way is appealing but further evaluation is needed, and it should be remembered that the field of heart-failure drug development is strewn with casualties.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Interventions for severe stable LV dysfunction

Implantable cardioverter defibrillators.

The role of the ICD in the primary prevention of SCD is now well established. In patients with prior MI and nonischemic dilated cardiomyopathy, major trials and current recommendations (reviewed in Chapter 8, p. 320) taken in concert support the use of ICDs in those with class II and III CHF with an ejection fraction of less than 35%, and class I if less than 30%.[259],[380],[381] Patients with class IV symptoms are likely to die of CHF, and an ICD is not indicated unless the patient is a candidate for CRT. The DINAMIT and IRIS trials confined to high-risk patients 6-40 days postinfarction were completely neutral and supported the recommendation to *delay ICD implantation for primary prevention after MI*.[382],[383] Additionally, in our opinion, in patients who have hemodynamically significant sustained ventricular arrhythmias within 24-48 hours of an MI, this is indicative of an arrhythmic substrate and an indication for ICD implantation or an invasive electrophysiologic study, provided that reversible causes such as ischemia have been excluded. Because the ejection fraction may change and improve or deteriorate during the first few weeks post-MI, the current recommendations are to wait at least 40 days before making a definite decision to implant an ICD for primary prevention in post-MI patients. The role of the automatic external defibrillator (AED) during this waiting period has been disappointing.[357] The major cause of the death in the first 18 months postinfarction is probably recurrent MI and ischemic events or heart failure, and during this period, although the device may be effective in terminating arrhythmias, it is unlikely to affect long-term prognosis.[384] The role of Holter monitoring and invasive electrophysiologic testing in identifying candidates for the primary prevention of SCD has declined, and the major inclusion criterion is the ejection fraction, albeit an imprecise measurement. Risk stratification needs to be repeated because interim events such as recurrent ischemia or heart failure are independent risk factors for late SCD.[385]

Cardiac resynchronization therapy.

CRT should be considered for patients who have either ischemic or nonischemic cardiomyopathy, an LV ejection fraction EF of 35% or less, class III or IV symptoms, and a QRS duration of greater than 120 msec.[386],[387] Recently, the resynchronization R-Defibrillation for Ambulatory Heart Failure Trial (RAFT) has extended the benefits of CRT to patients with minimally symptomatic heart failure, an LV ejection fraction of less than or equal to 30% (mean 22%), and a QRS with equal to or greater than 120 msec (mean 158 msec).[262] The greatest benefit obtained is in patients with a QRS complex of 150 msec or greater (not due to right bundle branch block), and the magnitude of benefit in those with narrower QRS complexes (120-149 msec) is controversial.[388],[389] A frustrating aspect of CRT therapy is the relative inability to predict which patients will respond ahead of time and despite a number of echocardiographic and other indices, the magnitude of QRS width still appears to be the best predictors.

Viability testing and revascularization.

In moderate to severe ischemic cardiomyopathy, substantial segments of myocardium may be nonfunctioning but hibernating and thus metabolically viable, a state that revascularization could potentially improve.[390],[391] Using a variety of modern imaging techniques, including dobutamine magnetic resonance imaging and positron emission tomography, myocardial viability can be recognized and revascularization considered. The recent STITCH trial of coronary bypass surgery versus medical therapy in patients with heart failure and coronary artery disease but without a clear cut indication for CABG is modestly positive, and a viability substudy from this trial is somewhat confusing in that patients with viability appear to do better than those without viability, but the benefit of surgery actually appeared to be greater than those without viability.[392]

Other invasive options.

Patients with severe heart failure who are refractory to conventional medical therapy may benefit from

extracorporeal ultrafiltration via hemofiltration for the removal of intravascular fluid.[393] An *LV or biventricular assist device* may "bridge" the gap to transplantation, or may even initiate "reverse remodeling" by myocyte unloading.[394] The development of a range of devices for supporting the failing heart has improved outcomes and expanded the use of mechanically assisted circulatory support as both "bridge" and destination therapy.[395],[396] A recent randomized trial of treatment with a continuous-flow Heart Mate II device in comparison to the pulsatile flow Heart Mate XVE device demonstrated a significant improvement in the probability of survival free from stroke and device failure at two years, but both devices significantly improved the quality of life and functional capacity.[397] This is a dynamic and evolving field, but despite the improving results the incidence of complications such as infection, bleeding, peripheral emboli, and device failure remain formidable. Most surgical mitral valve repair in patients with heart failure and functional mitral regurgitation does not appear to be beneficial.[398] There is nonetheless understandable interest in the use of percutaneous techniques such as the Mitra Clip system.[399]

General management of CHF.

Sodium restriction and, in severe cases, water limitation are important ancillary measures. It is often forgotten that in severe CHF there is delayed water diuresis. Weight loss and exercise rehabilitation, as well as psychological support, are all positive procedures. Home nursing helps patients with severe limitation of exercise. A short-term high-carbohydrate diet, by allowing muscle glycogen to break down more slowly, can increase endurance exercise, of potential interest to CHF patients who need extra energy for a special occasion.[398] A major advance in the management of CHF is an *extensive, nurse-based outpatient program* that relies on patient education and regular communication between patient and health care provider.[400],[401] *Anemia* and its potential as a therapeutic target is increasingly recognized.[402],[403] Relatively small-scale studies have shown promising results with the correction of anemia using erythropoietin and darbepoetin, but the final verdict will await the ongoing RED-HF study.[404] As to therapy with intravenous iron, more studies are needed, but the FAIR-HF trial did show an improvement in symptoms and New York Heart Class, quality of life, and exercise capacity.[405]

Summary.

In asymptomatic LV dysfunction, initial therapy is by ACE inhibition or ARB. Added β-blockade started in very low doses and titrated upward adds decisive benefit. In patients with symptomatic CHF, a diuretic is required. Spironolactone or eplerenone is being added earlier than before. Of these agents, ACE inhibitors, β-blockers, and spironolactone and eplerenone all improve longevity. Digoxin may be added for AF or to control symptoms, with careful control of the blood levels and without expecting any effect on mortality. The combination of ACE inhibitors or ARBs, β-blockers, diuretics, and spironolactone is now increasingly common, followed by addition of vasodilators such as hydralazine and nitrates. An important advance is the concept of primary prevention of sudden death by prophylactic implantation of an ICD, selected for those with ejection fractions of less than 35% and class II or III heart failure, or below 30% for class I (see Chapter 8, Fig. 8-16). The lot of the individual patient with severe CHF can be improved by searching out underlying causes, by diuretic synergism, by ensuring that there is maximal RAAS inhibition, by checking on serum potassium and magnesium, and by general management including salt restriction, exercise rehabilitation, psychological support ("keep going, you are doing better than you think"), and intensive nurse-based outpatient care of CHF. Team management results in fewer hospital admissions and improved outcomes.[406],[407]

Future directions.

A recent NHLBI workshop identified challenges and research opportunities in regard to the emergency department management of cardiac failure, including the development of methods of early detection and hemodynamic and biomarker.[408] The last two decades have been characterized as the era of hemodynamic improvement in neurohormonal modulation. Adjunctive nonpharmacologic approaches included the ICD, cardiac resynchronization, therapy, ventricular assist devices, and the recognition and treatment of sleep apnea. Cardiac transplantation has continued but is limited by donor supply. Future approaches will depend on unraveling the molecular web, underlying altered sarcomeric function, myocardial energetics, signaling, and calcium transport in CHF, and we hope will identify new therapeutic targets. Pharmacogenomic profiling is a field that becomes increasingly complex but is evolving rapidly. Other nonpharmacologic areas under development include biomarker and wireless hemodynamic monitoring, the miniaturization and improvements in the design of ventricular assist devices and the total

artificial heart, and in the distant future perhaps a role for xenotransplantation and cardiac cell repair therapy (a field that has captured the imagination of many investigators around the world).

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Diastolic heart failure

Preserved systolic function and diastolic dysfunction.

Differences between proven diastolic heart failure and preserved systolic function (simplistically and variably diagnosed by systolic ejection fractions of less than 40%-50%) are outlined in Chapter 6 (see p. 207), together with definitions.[409] Major causes are increasing age and left ventricular hypertrophy (LVH). Prognosis is serious, similar to that of systolic failure.[410] Therapy trials are scant. Logically, the aim is regression of LVH, which is often the underlying cause. Vigorous therapy of underlying hypertension or aortic stenosis is essential. In clinical heart failure with hypertension, tight 24-hour BP control is mandatory. Other measures are a reduction in central blood volume by diuretics, countering tachycardia, aggressive treatment of AF, and management of concomitant coronary artery disease and ischemic diastolic dysfunction, including revascularization.

Does RAAS blockade give specific benefit?

Angiotensin II has powerful profibrotic and proapoptotic properties in the hypertrophic heart.[44] Regarding ARBs, candesartan gave only modest benefit in one arm of the CHARM studies, in which there was heart failure with relatively preserved LV function.[344] The ACE inhibitor perindopril also gave only modest benefits in clinical heart failure in older adults, of whom 79% were hypertensive; therapy decreased the BP and hospitalization.[411] Whether CCBs exert a "lusitropic" effect by enhancing ventricular relaxation is difficult to distinguish from potential benefits from slowing the heart rate. Aldosterone is linked to the development of cardiac hypertrophy and fibrosis, and a large National Institutes of Health–sponsored study (TOPCAT) is currently evaluating the hypothesis that spironolactone could be beneficial in patients with CHF and preserved systolic function (Clinical Trials.gov/ct2/show/NCT00094302). Other treatments of suggestive but unproven benefit include statins and exercise conditioning.

At present we accept that specific therapies for diastolic heart failure are lacking and that the management is similar to that for CHF with systolic dysfunction. Moreover, in patients with systolic dysfunction, diastolic dysfunction frequently coexists. Specific therapies await a better understanding of the pathophysiologic findings and, in particular, the extent to which this is a cardiac disease versus an imbalance between the heart and the vasculature.[412]

Diastolic dysfunction without clinical heart failure.

Here too RAAS inhibition has been studied. In younger hypertensive patients with diastolic dysfunction but without LVH or heart failure, lowering BP by an ARB with an aim of less than 135/80 mm Hg improved diastolic dysfunction, without any specific clinical benefit.[413] In early hypertensive heart disease and diastolic dysfunction but with a mean ejection fraction of 67% and without exercise limitation, aldosterone antagonism improved diastolic function, and modestly decreased LV posterior wall thickness without altering LV mass.[414] Clinically, these studies, albeit imperfect, suggest vigorous BP lowering in hypertensives with diastolic dysfunction even in the absence of clinical heart failure.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Acute pulmonary edema

In acute pulmonary edema of cardiac origin, the initial management requires positioning the patient in an upright posture and administering oxygen. The standard triple-drug regimen is morphine, furosemide, and nitrates, to which ACE inhibitors must now be added. If the underlying cause is a tachyarrhythmia, restoration of sinus rhythm takes priority. Morphine sulfate, with both venodilator and central sedative actions, is highly effective in relieving symptoms. Intravenous furosemide, both diuretic and vasodilator, is the other basic therapy. *Acute digoxin* is undesirable in view of the prevailing arrhythmogenic environment, unless there is uncontrolled AF. β-Blockers are contraindicated in the acute phase, but should be initiated before discharge.

Nitrates.

Nitrates are excellent for unloading of the left heart and relief of pulmonary congestion. Which is better, repetitive furosemide or repetitive intravenous nitrates? Repeated intravenous boluses of high-dose isosorbide (3 mg every 5 minutes) after a single low dose (40 mg) of furosemide were better than repeated high-dose furosemide with low-dose isosorbide,[415] the former treatment reducing the need for mechanical ventilation and the frequency of MI.

ACE inhibitors.

ACE inhibitors such as sublingual captopril or intravenous enalaprilat (1 mg over 2 hours) are logical and achieve load reduction when added to the standard regimen of oxygen, nitrates, morphine, and furosemide.[416],[417] In practice, these agents (or ARBs) are rather started orally as soon as the hyperacute phase is over.

Other vasodilators.

In patients with pulmonary edema secondary to severe acute or chronic mitral or aortic regurgitation, *intravenous nitroprusside* (see Chapter 6, p. 186) is probably the agent of choice. Whenever vasodilators are contemplated, particular caution is necessary in the patient with a systolic BP of less than 90 mm Hg. In AMI, compounds such as aminophylline and milrinone are best avoided because of their proarrhythmic potential. *Nesiritide* was better than nitroglycerin in small trials, but its effects in renal function were controversial.[418],[419] A large recent trial of more than 7000 patients alleviated concerns about nesiritide safety, but its effects on dyspnea were only marginally beneficial, and there was no effect on 30-day mortality or hospitalization.[370] It seems that nesiritide is a second-line agent to fall back on when standard therapies are ineffective in improving symptoms.

Severe hypertension.

Use carefully titrated intravenous nicardipine or sodium nitroprusside or nitrates or enalaprilat, together with pressure monitoring. Oral ACE inhibitors are started as soon as feasible, taking care to prevent hypotension. *Bronchospasm* usually responds to diuresis or load reduction. *β-Blockers* should be withheld until hemodynamic stabilization is achieved.

Intravenous positive inotropic agents.

The majority of patients will not require positive inotropic agents in the absence of persistent hypotension, cardiogenic shock, severe end-organ dysfunction, or failure to respond to standard therapy.

Refractory cases.

In refractory cases, intubate with mechanical ventilation: “When in doubt, intubate.” A modest amount of

evidence supports the use of continuous positive airway pressure given via a face mask to patients with cardiogenic pulmonary edema.[420] Although noninvasive ventilation resulted in more rapid improvement in respiratory distress and metabolic disturbance, there was no effect on overall mortality.[421] Further studies are needed before general use of increased airway pressures can be recommended.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy, together with bicuspid aortic valve disease, is one of the commonest forms of inherited cardiac disease and the first ACC-AHA Guidelines for the management of this condition were published in 2011.[422] The principles of management are to screen first-degree relatives for HCM, avoid competitive sport, volume depletion, and isometric exercise, to control symptoms primarily with the use of β-blockers and if necessary the addition of a nondihydropyridine CCB (usually verapamil), and in the event that medical therapy fails septal reduction therapy with surgical myectomy or alcohol septal ablation is indicated. Risk stratification for SCD and prevention with ICD is also the cornerstone of management. Older asymptomatic patients need reassurance, regular surveillance, and exclusion of hypertension.

Principles of pharmacologic therapy.

The principles of pharmacologic therapy are (1) to lessen the hypercontractile state by a negative inotrope such as a β-blocker or nondihydropyridine CCB with the combination, and (2) to relieve the outflow tract obstruction with negative inotropes or with septal reduction therapy. The role of ACE inhibitors in aldosterone antagonists is unproven and currently under evaluation. One way to improve diastolic function is to slow the heart rate by prolonging the diastolic filling period. This also serves to reduce myocardial oxygen demands and improve the balance between supply and demand. In patients without outflow tract obstruction, the role of ACE inhibitors, ARB, and aldosterone antagonists is unproven but worth trying in patients with severe symptoms. A new therapeutic approach using metabolic modulation was demonstrated by a small trial of perhexiline maleate, which improved exercise capacity and myocardial energetics in 46 patients with nonobstructive hypertrophic cardiomyopathy.[423]

Is prevention possible?

Can the development of hypertrophic cardiomyopathy be prevented? After all, all patients with the genotype have a genetic substrate for the disease, but penetrance is varied and very often the manifestations of hypertrophic cardiomyopathy may be delayed until adolescence or much later in life, or in some patients the phenotype may never become manifested. This does suggest that perhaps the disease could be prevented, and the finding that a statin improves cardiac hypertrophy and fibrosis in an animal model is fascinating and unexpected, but is also far from translation into clinical practice.[424] Likewise are the impressive data with the CCB diltiazem in an animal model,[425] and prospective trials are in the planning phase.

Negative inotropes.

Negative inotropes are β-blockers, nondihydropyridine CCBs, and disopyramide. The postulated mechanism of benefit is via a reduction in LV ejection acceleration, which reduces the hydrodynamic force on the protruding mitral leaflet, delaying mitral-septal contact and reducing the outflow tract gradient. Furthermore, the reduction in ventricular afterload and outflow tract gradient may result in a secondary improvement in diastolic function.[426] *High-dose β-blockers,* such as 200-400 mg of propranolol per day or its equivalent, are effective in relieving symptoms such as dyspnea, fatigue, or angina in approximately 50% to 70% of patients. The high doses required may in turn result in dose-limiting side effects. *Calcium channel blockade,* usually verapamil at a dose of 240-320 mg/day, is advocated particularly in patients with asthma and other contraindications to β-blockers or else in combination with β-blockers in patients with continued symptoms. Although CCBs are usually well tolerated, caution needs to be exercised because the peripheral vasodilatory effects can lead to increased hemodynamic obstruction and clinical deterioration. This effect is unpredictable, and the consequences may be rapid and serious. In general, maximum symptomatic benefits are obtained by using β-blockers in combination with verapamil. Nifedipine and other dihydropyridines are contraindicated in patients with resting obstruction. Logically, verapamil and diltiazem may be helpful in relieving the diastolic relaxation problems found in the nonobstructive variety, but clinical evidence is sparse.[427] *Disopyramide,* a class I antiarrhythmic with negative inotropic properties, can be used in patients with significant outflow tract obstruction. Anticholinergic side effects, especially urinary retention,

glaucoma, and dry mouth, are frequent.[428]

Relief of outflow tract obstruction.

Drug efficacy may decline over the long term, or side effects become a major problem, and in such patients the remaining treatment options are invasive, such as surgical myectomy, *dual-chamber pacing,* or alcohol septal ablation. *Dual-chamber pacing,* programmed with a short AV delay, initially gave encouraging results, but the perceived functional improvement is largely a placebo effect apart from a small subset of patients who might benefit. Nonetheless, a logical application of dual-chamber pacing is with AV nodal ablation for refractory AF. *Alcohol septal ablation* is a very promising technique that needs to stand the test of time. Results may be operator dependent, and there appears to be a steep learning curve. The indications are the same as those for surgery, namely, severe symptoms unresponsive to medical therapy. Alcohol is injected into the first septal perforator branch of the left anterior descending coronary artery, producing a "controlled infarction." Acute and intermediate-term hemodynamic studies show a marked but variable reduction in outflow tract gradients and excellent improvement in symptoms. Short-term results are very similar to surgical myectomy.[428] The most frequent complication is complete heart block requiring a permanent pacemaker. Caution is advocated until the long-term results are available and the potential arrhythmic consequences of creating an MI with an area of transmural necrosis are better understood.[429],[430]

Surgery for obstructive cardiomyopathy.

When standard therapy fails, surgical myotomy or myectomy is the best choice. Surgery is associated with relief of symptoms and a substantial decrease in gradient and in the degree of mitral regurgitation, but should be reserved for patients with significant obstruction and symptoms. Although there are no trial data to suggest that surgery prolongs life, overall survival is excellent and consistent with that expected in the general population, matched for age and sex. Moreover, rates of SCD and ICD discharge are strikingly reduced. A key, however, to excellent surgical outcomes is a center with documented experience and expertise and a mortality rate approximately less than 1% in patients younger than age 60.[431],[432] *Systolic anterior motion of the mitral valve* is an important component of dynamic LV outflow tract obstruction, and mitral regurgitation is common. Thus mitral valve repair and rarely replacement may be combined with surgery. Mitral valve repair is chosen for markedly elongated mitral valve leaflets.[433] A novel repair procedure is grafting a pericardial patch over the center of the anterior leaflet.[434] A subset of patients with markedly hypertrophied and displaced papillary muscles that contribute to the obstruction may require papillary muscle relocation as part of the surgical procedure.

Alcohol septal ablation or surgery?

Alcohol ablation avoids the complications of cardiopulmonary bypass and is associated with less expense and a shorter hospital stay. Conversely, surgery appears to provide more immediate and complete relief of outflow tract obstruction, there is a lower incidence of heart block requiring pacemaker insertion, surgery provides the ability to deal with associated abnormalities of the mitral valve apparatus, and it is a procedure of proven durability with a follow-up of up to 20 years. For patients who are not good surgical candidates because of comorbidities or older patients in whom implantation of a pacemaker may be less of an issue, alcohol septal ablation is preferred, but surgery remains the gold standard. This was reaffirmed in the recent ACC-AHA guidelines that recommend surgical septal myectomy as the initial step unless surgery is contraindicated or the risk is considered unacceptable as a result of serious comorbidities.[422] The essence of optimal decision making in hypertrophic cardiomyopathy is a thorough discussion of the risks and benefits with the patient and the performance of either procedure by operators with expertise working within a comprehensive hypertrophic cardiomyopathy clinical program. Randomized trials are needed but for many reasons unlikely to ever be performed.[429]

Management of arrhythmias in hypertrophic cardiomyopathy.

Patients at high risk for SCD, usually from VT or VF,[435] include those with documented ventricular arrhythmias, young patients with a history of syncope, a strong family history of SCD,[436] or, highly controversially, certain specific genotypes. The most effective procedure for patients with documented VT or out-of-hospital cardiac arrest is the ICD. Its indications have expanded to asymptomatic patients with a strong family history of SCD.[435] Coexisting coronary artery disease seriously impairs the prognosis.[437] The major complications of ICD implantation are a high rate of inappropriate discharges with their attendant

psychological morbidity, particularly in younger patients and patients with AF.[438] *AF* can be a devastating complication in patients with hypertrophic cardiomyopathy. Treatment options include amiodarone, disopyramide, β-blockers, and CCBs for rate control, and AV nodal ablation plus permanent pacemaker implantation. Anticoagulation with warfarin is essential.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Other cardiomyopathies

Dilated cardiomyopathy.

The basic management of CHF in patients with idiopathic dilated cardiomyopathy in regard to drugs, devices, and transplantation is the same as in patients with ischemic cardiomyopathy (see prior discussion). Patients with idiopathic dilated cardiomyopathy and complete left bundle branch block may respond dramatically to CRT.

Inflammatory and immunologic factors.

Specific therapies for inflammatory and immunologic types of myocarditis and dilated cardiomyopathy have not met with clinical success. Ribavarin and interferon have been used in experimental models but clinical data are very limited. A trial of beta-interferon in the clinical setting is ongoing.[439],[440] Randomized trials of immunosuppressive therapy for myocarditis have not demonstrated efficacy,[441],[442] other than one trial of 84 patients with dilated cardiomyopathy of greater than 6 months' duration and chronic inflammation on biopsy in which 3 months of immunosuppressive therapy had a beneficial effect on ejection fraction and clinical symptoms at 2 years.[443] In a trial of patients with recent-onset dilated cardiomyopathy and an ejection fraction of less than 40%, intravenous immune globulin was no better than placebo.[444] Cytokine inhibitors such as tumor necrosis factor–alpha have also been a disappointment. Unlike the case in dilated cardiomyopathy and lymphocytic myocarditis, *giant cell myocarditis* may respond to immunosuppressive therapy.[445],[446] For patients who fail immunosuppressive therapy, cardiac transplantation is a reasonable option,[447] and long-term survival without recurrence has been reported. Another role for immunosuppressive therapy may be for specific disorders such as sarcoid and celiac disease, which may be associated with a dilated cardiomyopathy picture.

Chagas heart disease.

The World Health Organization suggests that 15 to 20 million people, primarily in Latin America, are affected by Chagas disease (a *Trypanosoma cruzi* infection). In the acute phase, antitrypanosomal agents (nifurtimox and benznidazole) are helpful in controlling symptoms, in addition to supportive therapy for CHF, arrhythmias, and conduction disturbances. Approximately 20% to 30% of those infected go on to develop the chronic stage of the disease, of which the cardiac form composes 40%.[448] Does acute therapy prevent chronic organ damage? One small trial of benznidazole suggested that specific therapy may have a favorable effect on the chronic phase of Chagas disease. A large, unblinded, nonrandomized trial suggested that benznidazole might reduce the development of progressive disease and deterioration in LV function.[448] Thus the management of Chagas disease remains supportive. Cardiac transplantation may be required in selected cases.[449]

Restrictive cardiomyopathy.

Restrictive heart disease is not well understood. It may be idiopathic or associated with other diseases such as amyloidosis or endomyocardial disease with or without hypereosinophilia. First exclude constrictive pericarditis, the treatment of which may be curative, whereas the therapy of the restrictive cardiomyopathy is both difficult and highly unsatisfactory.[450],[451] In older adults, restriction may reflect increased myocardial fibrosis, and the latter can perhaps be countered by ACE inhibitors, ARBs, or aldosterone blockers (see Fig. 5-5). Once fibrosis has developed, the most important aspect of treatment is to avoid dehydration and overdiuresis, which impairs the left atrial filling pressure, and to control the heart rate in AF. Pharmacologic therapy of restrictive heart disease is extremely difficult. The fact that amyloid fibrils may bind to both digitalis and nifedipine may lead to increased susceptibility to digitalis toxicity and hemodynamic deterioration after nifedipine, but this can also occur with verapamil. ACE inhibitors may lead to hypotension. Amiodarone is reasonably well tolerated in patients who develop AF. Intracardiac thrombosis and embolism is extremely common in patients with cardiac amyloidosis, but there are also an

increased risk of bleeding on anticoagulants.[452] Conduction disease may require a permanent pacemaker. Cardiac transplantation with and without bone marrow transplantation is currently under investigation, as is the role of chemotherapy for some patients with cardiac involvement caused by primary amyloidosis. High-dose melphalan and autologous stem-cell transplantation in patients with amyloid light-chain amyloidosis appears to have a significant benefit on survival in patients without cardiac amyloid.[453] Although long-term follow-up data are not available, cardiac transplantation followed by high-dose chemotherapy and autologous hemopoietic cell transplantation has been associated with symptomatic improvement, although there appears to be a high rate of occurrence.[454],[455] Despite the many treatment strategies, none is based on randomized controlled data, nor are randomized trials likely.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Valvular heart disease

Rheumatic fever prophylaxis.

Treatment should start as soon as a definitive diagnosis of streptococcal infection has been made; the treatment is either a single dose of benzathine penicillin (1,200,000 units for adults and half this dose for children) or a full 10-day course of oral penicillin V (for children, 250 mg two or three times daily[456]; empirically double this for adults). Thereafter, in selected patients in whom recurrences are feared, the penicillin injection is repeated monthly, or penicillin V is given as 125 to 250 mg twice daily continuously. The best route is by injection, which is used for 5 years, followed by oral prophylaxis possibly for life. For *penicillin allergy,* use sulfadiazine,[456] erythromycin, or the cephalosporins.[457]

General approach to valvular heart disease.

As surgical techniques for valve repair and the performance of prosthetic valves have improved, so have the surgical indications become less stringent.[458] Now most patients with LV dysfunction are operated on even if asymptomatic. Thus the tendency is to become more aggressive, particularly in the case of mitral regurgitation, where a strong case can be made for surgical repair in asymptomatic patients with severe mitral regurgitation, even in the face of well-preserved LV function. An essential component of this strategy is the local results in regard to mitral valve repair versus mitral valve replacement. Concomitant therapy in patients with valvular heart disease is not based on trial data but may include diuretics, ACE inhibitors, and, especially for certain nonstenotic lesions, vasodilators. Attention to arrhythmias, particularly AF, is essential, and rate control with anticoagulation must be considered.

Aortic stenosis

In valvular stenosis, the basic problem is obstructive and requires surgical relief. Four advances in understanding are as follows:

1. Increased LV pressure sets in motion a series of signaling pathways that lead not only to myocyte hypertrophy but to fibrosis and progressive myocyte death. The latter promotes deterioration from compensated hypertrophy to failure, arguing for valve replacement while LV function is still relatively preserved.[459]
2. Improved surgical techniques allow valve replacement even in patients with heart failure of such severity that the aortic valve gradient is low.[460] Pseudo–aortic stenosis, in which calculated aortic valve area falsely overestimates the severity of aortic stenosis at low flow rates, must be excluded.[461]
3. Peripheral vasoconstriction can contribute to critically severe heart failure, when careful vasodilator therapy improves the hemodynamic status,[418] so that aortic valve replacement becomes feasible.
4. The potential but unproven role of medical therapy by statins and other drugs is based on the hypothesis that aortic stenosis in older adults has risk factors similar to coronary artery disease[462] and that hypercholesterolemia is associated with disease progression. In the SEAS trial of patients with mild to moderate aortic stenosis, the combination of simvastatin and ezetimibe was no better than placebo in regard to progression to aortic valve replacement.[463]

Afterload reduction remains generally contraindicated, except in highly selected patients,[418] because it increases the pressure gradient across the stenosed valve. Thus CCBs should not be used to treat any accompanying hypertension except in mild degrees of stenosis. In patients with decompensated heart failure caused by systolic dysfunction and severe aortic stenosis, intravenous nitroprusside may play a role as a bridge to valve replacement, but meticulous monitoring is mandatory.[418]

Asymptomatic aortic stenosis.

In truly asymptomatic aortic stenosis, which is nonetheless hemodynamically significant, the key to management is careful and regular supervision, with intervention as soon as symptoms appear. Nonetheless, a strong case can be made for surgery for asymptomatic patients with severe aortic stenosis who have LV systolic dysfunction without any evidence of symptomatic cardiac failure and in patients who manifest an abnormal response to exercise (e.g., hypotension). A case, albeit a weaker one, can be made for surgery in asymptomatic patients with documented VT, a valve area of 0.6 cm, or very marked or excessive LVH of 15 mm or greater.[458] Progression of aortic stenosis is unpredictable and may be rapid, so that careful monitoring of a patient on medical therapy is essential. Exercise testing should help to identify asymptomatic patients likely to develop symptoms in the near future.[464]

Aortic valve replacement.

Surgical therapy is required for patients with angina, exertional syncope, or symptoms of LV failure (even if early). Surgery can relieve the hypertrophy, improve the coronary perfusion pressure, and often also correct any accompanying coronary artery disease. The combination of aortic stenosis and gastrointestinal bleeding suggests type 2A von Willebrand disease, which improves with aortic valve replacement.[465] Results following aortic valve replacement are excellent in both older and younger patients and in the absence of perioperative CHF, although the latter is not a contraindication to aortic valve replacement.[466] Percutaneous valve replacement, currently generating interest, may be an alternative to conventional open-heart surgery in selected high-risk patients with severe symptomatic aortic stenosis in whom surgical risks are considered excessive.[467]

Transcatheter aortic valve implantation.

Transcatheter aortic valve implantation (TAVI) is an exciting and evolving approach that is holding up well in randomized trials.[468] This is the largest consecutively enrolled registry for transcatheter aortic valve procedures and demonstrates excellent 1-year survival in high-risk and inoperable patients. It provides a benchmark against which future TAVI cohorts and devices can be measured.[469] In the PARTNER trial, TAVI with the Edwards-Sapien valve improved survival and functional status in comparison with medical therapy.[470] In 699 high-risk patients, TAVI (either transfemoral or transapical) and surgical aortic valve replacement resulted in similar rates of mortality and major stroke at 30 days and 1 year and 1-year symptomatic improvement was the same.[471] Periprocedural complications including vascular access problems, stroke, subclinical brain injury, and heart block are frequent, but techniques continue to evolve and hopefully will result in improvements.[472-474] The recently published 2-year data from the PARTNER trials are also encouraging.[475],[476]

Valvuloplasty for aortic stenosis.

The initial enthusiasm for percutaneous aortic balloon valvuloplasty has been tempered by the long-term results, which are disappointing, but it does offer an alternative for patients in whom surgery is contraindicated and in some patients as a bridge to aortic valve replacement, if for one reason or another immediate surgery is inadvisable. Experience with percutaneous balloon valvotomy prior to TAVI is limited. There are also subsets of patients with low gradients and poor ventricular function in whom the symptomatic response to balloon valvuloplasty may provide a guide to the success of surgery in the future.[477] The discouraging results of balloon valvuloplasty in older adults contrast with more positive outcomes in young patients with congenital aortic stenosis.[478]

Bicuspid aortic valve.

It has been increasingly recognized that bicuspid aortic valve is a manifestation of an inherited aortopathy and that first-degree relatives should be screened with comprehensive transthoracic echocardiography.[479]

Mitral stenosis

In mitral stenosis with sinus rhythm, β-blockade improves exercise capacity to lessen possible pulmonary symptoms. This may be particularly helpful in patients with symptomatic mitral stenosis during pregnancy. Prophylactic digitalization is still sometimes used supposedly to avoid a high ventricular rate during intermittent AF; this practice is not supported by the available data. Percutaneous balloon mitral commissurotomy is now well established for relief of symptoms. Excellent long-term results for up to 15 years have been reported, and predictors of event-free survival are the valve echocardiographic score and

age.[480] In severely symptomatic patients during pregnancy, balloon valvuloplasty may be extremely effective with minimal or maternal or fetal morbidity. Paroxysmal AF precipitating left-sided failure may require carefully titrated intravenous diltiazem, verapamil, or esmolol, particularly in the presence of LV dysfunction as may be present in patients with associated mitral regurgitation. In established AF, digitalization is usually not enough to prevent an excessive ventricular rate during exercise, so that digoxin, if used, should be augmented by diltiazem, verapamil, or β-blockade. Anticoagulation is essential for patients with AF and merits consideration for those in sinus rhythm thought to be at high risk for AF (marked left atrial enlargement or frequent atrial extrasystoles).

Balloon mitral valvuloplasty gives excellent early and late results in rheumatic mitral stenosis. All patients with symptomatic mitral stenosis should be considered for this procedure. The degree of commissural opening resulting in the larger mitral valve area, the better the patient outcome after balloon valvuloplasty. This can be assessed by use of three-dimensional echocardiography.[481],[482] Contraindications include the presence of left atrial thrombus, severe subvalvular fibrosis or valve calcification, and a significant mitral regurgitation, but this can be determined ahead of time by TEE. The surgical alternatives are open mitral commissurotomy or mitral valve replacement. The percutaneous technique is comparable to the more invasive surgical approach.[483]

Aortic regurgitation

In aortic regurgitation, indications for operation are the development of symptoms or, in the absence of symptoms, evidence of progressive or impending LV dysfunction based on impaired indices of contractility, a LV ejection fraction of less than 55%, or increased LV end-diastolic dimensions.[484] However, “agreement is greatest where data are fewest”[484] because there are no rigorous trials to support any improved survival using such indicators. What is controversial in patients with chronic aortic regurgitation is the degree of severity of LV dysfunction that contraindicates surgery. Substantial long-term improvements in ejection fraction, volumes, and symptoms have been described in patients with both mild (ejection fraction 45% to 50%) degrees of LV dysfunction and in those with ejection fractions of less than 45%.[485] Although aortic valve replacement remains the standard of care, aortic valve repair is increasingly being performed at some centers.[486],[487] In patients with systolic hypertension, chronic afterload reduction by long-acting nifedipine is logical[488] and benefits those with asymptomatic aortic regurgitation. Experimental data show that afterload reduction by ACE inhibitors or ARBs, despite increasing the LV ejection fraction, may adversely influence myocardial contractility so that there is no mandate for their use.[484] In asymptomatic patients treated with ACE inhibitors, nifedipine, or placebo, there were no differences in outcomes at 7 years.[489],[490] Nonetheless, the guidelines state that there remains a role for vasodilator therapy for symptom relief in patients for whom surgery is not recommended because of additional cardiac or noncardiac factors.[458] β-Blockers are relatively contraindicated in patients in sinus rhythm in that rate slowing could increase regurgitant volume.

Marfan syndrome

In Marfan syndrome with aortic root dilatation the trend is to be increasingly aggressive with aortic surgery including aortic valve-sparing techniques.[491]

Prosthetic paravalvular regurgitation.

Paravalvular leaks, particularly in patients with prosthetic valves, are increasingly being treated by percutaneous transcatheter closure.[492]

Mitral regurgitation

In mitral regurgitation, the disease is more serious because it affects three primary organs: the left ventricle, the left atrium, and the right ventricle.[484] Hence the criteria for surgery are more stringent, with an LV ejection fraction of less than 60% the best validated predictor of prognosis.[484] Other criteria are persistent AF, a subnormal right ventricular ejection fraction, and an increased LV internal diameter. The current trend is to operate even earlier both to prevent ventricular dilation and to “preserve the atrium,” hopefully avoiding AF. Obviously, the development of symptoms is a mandatory indication for surgery, but the best results even in asymptomatic patients are obtained prior to the development of even mild degrees of LV systolic dysfunction.[493] Thus the approach to surgery has become increasingly aggressive, especially if the likelihood of a repair versus valve replacement is high. The ability to perform a mitral valve repair is based

on the skill and the experience of the surgeon and on the location and type of mitral valve disease that caused mitral regurgitation. Repair is more likely with degenerative as opposed to rheumatic or ischemic involvement of the mitral valves, and TEE is a critical aspect of pre- and intraoperative strategies. In the United States, for isolated mitral regurgitation the rate of repair is increased steadily, and this has been accompanied by a decline of operative mortality rates.[494] In skilled hands reoperation rates are low but not neglible.[495],[496] The EVEREST trial demonstrated that in patients with severe mitral regurgitation percutaneous repair using a clip that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet was less effective at reducing mitral regurgitation than conventional surgery, but safety was said to be superior and clinical outcomes were similar.[497] In the right hands surgical mitral valve repair is a superb operation, and it may be difficult to equal the results percutaneously, but one potential application for the percutaneous device will be in patients with severe heart failure and functional mitral regurgitation, and future trials in this area will be interesting. Currently direct annuloplasty by retrograde catheterization of the left ventricle from the aorta is under test with the aim of reducing the regurgitant orifice.[498]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Cor pulmonale

The initial step in management is to exclude potentially reversible causes of cor pulmonale and pulmonary hypertension (i.e., obstructive sleep apnea). Many clinical trials attest that ischemic heart disease is a leading but underrecognized cause of death in chronic obstructive pulmonary disease.[499] Retrospective analysis suggests that even low-risk patients receiving ACE inhibitor or ARB plus statin therapy have a major reduction in death or MI and death. Thus prospective studies are now required to test this combination.[500] Therapy of right heart failure is similar to that of left heart failure, except that digoxin appears to be even less effective because of a combination of hypoxemia, electrolyte disturbances, and enhanced adrenergic discharge. Thus when AF develops, cautious verapamil or diltiazem is preferred to reduce the ventricular rate. Multifocal atrial tachycardia is associated with chronic lung disease and is a difficult arrhythmia to treat, although success with verapamil has been reported. In general, all β-blockers should be avoided because of the risk of bronchospasm. Bronchodilators should be β2-selective. For example, albuterol (salbutamol) has relatively little effect on the heart rate while unloading the left heart by peripheral vasodilation. The administration of oxygen has been shown to result in modest reductions in PA pressure and pulmonary vascular resistance in patients with chronic obstructive pulmonary disease complicated by cor pulmonale.[501]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Idiopathic pulmonary arterial hypertension*

Among all subsets of pulmonary arterial hypertension (PAH), idiopathic PAH, familial PAH, and anorectic drug-induced PAH are considered the classical disease manifestations, because patients are commonly young without comorbid conditions and very similar in their clinical disease presentation.

The term *primary pulmonary hypertension* has been replaced by *idiopathic PAH,* both sporadic and familial, and includes pulmonary hypertension secondary to chronic pulmonary disease, congenital heart disease, or left heart disease.[502] Mutations involving the transforming growth factor–β cell signaling family are implicated in the genesis. The three major pathogenetic mechanisms that may influence therapy are an imbalance between vasodilation and vasoconstriction in the pulmonary circulation; vascular smooth muscle and endothelial cell proliferation; and coagulation abnormalities, which may lead to thrombosis in situ.[503] The hallmark of pulmonary hypertension is the histopathologic similarity shared by the different clinical types, and even on lung biopsy the exact pathogenesis may not be apparent. Long-term anticoagulants are frequently used on the assumption that there is thromboembolism or thrombosis in situ. A number of studies, but no randomized trials, suggest a better survival in patients treated with warfarin.[504] Oxygen supplementation should be used as necessary to maintain saturations of 90% at all times, with diuretics for fluid retention and digoxin if the right ventricle begins to fail.

PAH treatment should be initiated exclusively in expert centers. Current treatments are based on the concept of a primarily vasoconstrictive pathophysiologic finding and use three classes of vasodilated drugs: prostacyclins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors (see Fig. 6-14). Randomized trials with these agents have primarily involved patients with idiopathic PAH but also patients with other forms of PAH and improved quality of life and survival.[505] However, it has become increasingly clear that PAH treatments do not systematically benefit patients with so-called non-PAH pulmonary hypertension (i.e., PAH associated with left heart disease, interstitial lung disease, chronic obstructive pulmonary disease, and chronic thromboembolic pulmonary hypertension [CTEPH]). It is imperative to exclude CTEPH, which is amenable to surgical pulmonary thromboendartectomy, potentially yielding a complete and sustained normalization of pulmonary hemodynamics.[506]

Calcium channel blockers.

CCBs are targeted to patients who are hemodynamic responders; in other words, they display a robust drop of at least 10 mm Hg; a drop in mean artery pressure on the acute administration of inhaled NO, intravenous prostacyclin, or adenosine, resulting in a mean PA pressure of less than 40 mm Hg and the presence of a stable cardiac output. Approximately 10%-15% of patients will have a similarly positive response to high-dose CCBs, and only half of these will have a sustained clinical and hemodynamic benefit,[507] but if they do respond, they have an excellent 3-year survival.[508] Systemic hypotension may limit adequate dosing.

Prostacyclin and prostacyclin analogues.

A continuous infusion of prostacyclin (epoprostenol sodium) improved hemodynamics, symptoms, and survival in NYHA functional class IV patients.[509] Nonetheless, its use is limited by side effects, the need for continuous intravenous infusion, tachyphylaxis, and rebound pulmonary hypertension on withdrawal. Treprostinol is a prostacyclin analogue that is approved in the United States for both subcutaneous and intravenous use,[510] and its use in Europe is limited to a few centers.[511] Strict evidence for a survival benefit is lacking. Alternatives include oral analogues and inhaled iloprost, neither of which have data for long-term benefit.

Endothelin receptor antagonists.

Endothelin-1 levels are elevated in patients with PAH and cause vasoconstriction and myocyte hypertrophy

via two receptor subtypes. The orally administered dual endothelin receptor antagonist bosentan improves hemodynamics, clinical status, and echocardiographic variables and is currently approved for patients in NYHA classes III and IV in the United States and for classes II and III in Europe. The major side effect is liver toxicity (i.e., aminotransferase elevations greater than three times the upper limit of normal), which appears in approximately 12% of patients.[512] *Sitaxsentan* is more selective for the ETA receptor, and was recently withdrawn from the market because of liver toxicity.[513] *Ambrisentan*, a nonsulfanimide class endothelin-receptor antagonist has been approved in the United States and Europe after successful phase 3 trials.[503]

Phosphodiesterase-5 inhibitors.

Logically, an agent that increases intravascular levels of cyclic guanosine monophosphate (cGMP) should vasodilate in primary pulmonary hypertension. Sildenafil, a selective inhibitor of cGMP-specific phosphodiesterase-5, given as 50 mg every 8 hours, attenuates pulmonary hypertension in animals and improves clinical status over 3 months.[514] Sildenafil is much cheaper than iloprost or bosentan. The largest randomized controlled trial to date demonstrated an improvement in 6-minute walk and lean PA pressure after 12 months of treatment.[515] *Tadalafil,* a longer-acting drug, improved exercise and quality of life[516] and has been approved in the United States and Europe.

Novel emerging therapies.

The emerging paradigm shift is addressing the vascular remodeling process with the aim of "reverse remodeling."[517] A host of novel emerging therapies include *imatinib*, a platelet-derived growth factor receptor antagonist, and *fasudil,* a Rho-kinase inhibitor involved in calcium sensitization and vasoconstriction. The data of the large randomized *imatinib* trial are pending. Trials of *simvastatin,* which could enhance endothelial function by actions on the bone morphogenic protein receptive pathway, and endogenous and intestinal vasoactive peptides have been negative.

Among the new vasodilators, *riociguat,* an activator of soluble guanylate cyclase, and the direct prostaglandin receptor antagonist *selexipag* deserve attention. Both drugs are currently undergoing phase 3 clinical randomized evaluations. *Terguride,* a dopamine agonist, and *cicletanine,* an endothelial NO synthase coupling agent, are recruiting.

Bilateral lung transplantation and other surgical interventions.

Heart-lung and lung transplantation have been performed for primary pulmonary hypertension for more than 20 years, but this has been hampered by the lack of centers with expertise, shortage of donors, and long waiting times. A more recent trend is clearly toward double- or even single-lung transplantation for PAH. Waiting times remain long and complications such as organ rejection and infections pose formidable obstacles, with survival times with the first transplant of approximately 5 years in approximately 50% of patients. The use of assist devices for the right ventricle (extracorporeal membrane oxygenation [ECMO], Novaloung) is growing. First experience on a wait ECMO and minute-size right-ventricular assist devices has been gained.

* Section cowritten with Irene M Lang, MD

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Infective endocarditis*

Infective endocarditis remains potentially fatal if not aggressively treated by antibiotics, with or without surgery.[518] New risk factors have replaced the old. Rheumatic valve disease, long the major predisposing cause, has given way to more modern risk factors such as intravenous drug use; degenerative valve diseases of older adults; prosthetic valves' and healthcare-associated factors, particularly indwelling vascular catheters.[518] In addition, increasing numbers of patients are immunologically compromised by human immunodeficiency virus or acquired immune deficiency syndrome or because they are undergoing therapeutic immune suppression. Drug-resistant endocarditis is increasing, whether caused by "old pathogens" outwitting the standard antibiotics or by the more new "exotic organisms" that include fungi. To diagnose infective endocarditis, echocardiography and TEE are very helpful but a negative result does not rule out the diagnosis. Blood cultures remain the key to the diagnosis and treatment of endocarditis. Optimal therapy requires identification of the causative organism, so that appropriate therapy is initiated even though this may delay the start of therapy for a short period. Definitive antibiotic therapy is based on pathogen identification and susceptibility testing and requires the advice of an expert in infectious diseases. In culture-negative endocarditis, therapy is empirical and requires an evaluation of the epidemiologic findings of infection to attempt to define the optimal therapeutic regimen.

Streptococcus viridans and streptococcus bovis.

Streptococcus viridans and *Streptococcus bovis* are sensitive to penicillin and are still often the causative organisms in community-acquired endocarditis in nonaddicts. Gentamicin may be added to shorten the duration of therapy. If a highly penicillin-resistant streptococcus is suspected, even if not proven, a combination of ampicillin or ceftriaxone with gentamicin is suggested. For highly resistant streptococci[518] or for penicillin allergy, vancomycin is used. In general, the duration of therapy in current responders is 4 weeks for native valve endocarditis and 6 weeks for prosthetic valve endocarditis.

Staphylococcus aureus.

Staphylococcus aureus is also a common cause of endocarditis, moving up to first place in intravenous drug users, who are also at increased risk of gram-negative bacilli, fungal, and polymicrobial infections, some of which carry a high mortality. *Staphylococcus aureus* is usually penicillin resistant; use naxoline or cefazolin if the infecting strain is methicillin susceptible. Vancomycin is used for methicillin-resistant *S. aureus* infection. If the isolator is vancomycin resistant or the patient is intolerant of vancomycin, then there are few options, including daptomycin or linezolid and co-trimoxazole.[518] Despite optimal diagnostic techniques and appropriate antimicrobial therapy, the mortality in patients infected with the most virulent organisms, such as *S. aureus,* remains high.

Coagulase-negative staphylococci.

Coagulase-negative *staphylococci* are an important cause of prosthetic valve endocarditis, particularly within the first 2 months of valve placement. Many of these strains are methicillin resistant and require vancomycin, in combination with rifampin, for at least 6 weeks of treatment and 2 weeks of gentamicin. *Enterococcus species, even when fully susceptible to penicillin,* require the addition of a minor glycoside such as gentamicin to achieve an attempted cure. Increasing numbers of enterococci have acquired resistance to vancomycin and penicillin.

The hacek organisms.

Gram-negative bacilli *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* (HACEK organisms) can cause culture-negative endocarditis, which requires empirical therapy for both gram-positive and gram-negative organisms. The AHA recommends treatment with an ampicillin-sulbactam plus gentamicin or with vancomycin plus gentamicin plus ciprofloxacin for 4 to 6 weeks.[519] The ESC

recommends combination therapy with vancomycin for 4 to 6 weeks with gentamicin added for the initial 2 weeks of treatment.[520]

Indications for surgery in endocarditis.

An increasingly aggressive approach to early cardiac surgery has favorably influenced the outcome of infective endocarditis. In patients with native valve endocarditis, the indications for surgery are CHF resulting from valve dysfunction, new valve regurgitation, systemic embolization to vital organs, refractory infection, and a vegetation on echocardiography.[521] This policy reduces 6-month mortality versus medical therapy alone.[521],[522] This policy reduces short-and long-term mortality versus medical therapy alone[521],[523] and may improve survival. There is a greater risk of relapses and prosthetic valve dysfunction.[524] EASE, with 134 patients with confirmed endocarditis, is the first prospective trial to demonstrate that early surgery produces better outcomes than conventional therapy in these patients. Surgery outperformed conventional therapy for the primary endpoint of in-hospital death plus embolic events within 6 weeks of randomization (3% versus 23%, P = 0.014).[525] The approach to prosthetic valve endocarditis, particularly within 3 months of the initial operation, is even more aggressive, with surgery for any signs of prosthetic valve dysfunction or any of the indications for surgery in native valves. Infection of a prosthetic valve by *S. aureus*, gram-negative bacilli, or fungi provides an additional indication for early surgery. In the face of hemodynamic decompensation, surgery should not be delayed pending completion of antibiotic therapy. Relative indications for early surgical intervention include apparent failure of medical therapy as evidenced by persistent bacteremia or fever, or an increase in the size of vegetation during treatment. TEE is extremely helpful in the detection of intracardiac vegetations and other complications such as perivalvular extension.

Anticoagulant and antiplatelet therapy.

The issues regarding anticoagulant and antiplatelet therapy are complex and characterized by a lack of hard data. The decision to initiate or continue anticoagulant therapy in patients with infective endocarditis is often difficult. In those patients already on anticoagulants (e.g., patients with mechanical prostheses or those in whom there are other indications for anticoagulation, such as thrombophlebitis), anticoagulant therapy should be continued or initiated. In the event of a cerebral thromboembolic complication, the risk of anticoagulant-induced hemorrhage must be balanced against the alternate risk of recurrent embolism. In general, aspirin has not been indicated in the early management of infective endocarditis, being without effect on vegetation resolution and valvular dysfunction.[142] However, one large retrospective study found fewer embolic complications after prior continuous daily antiplatelet therapy (aspirin, dipyridamole, clopidogrel, ticlopidine, or any of combination of these agents).[526]

Antibiotic prophylaxis against infective endocarditis.

The AHA recommendations underwent major and controversial revisions in 2007 and were updated in 2008 (Table 12-7) with new underlying pathophysiologic principles very similar to those of the British Society for Antimicrobial Chemotherapy.[527] The changed AHA recommendations reflect the principle that, even if antibiotic prophylaxis were completely effective, of which there is no proof, only a very small number of cases would be prevented. Furthermore, unnecessary antibiotics have possible side effects. Rather, the stress is on sustained prophylactic maintenance of strict oral hygiene. Antibiotic prophylaxis is only indicated for patients with those serious underlying cardiac conditions that are associated with the highest risk of adverse outcomes, such as prosthetic valves, severe congenital heart disease, or cardiac transplantation (Table 12-8). For dental procedures in these individuals, only those procedures that involve manipulation of gingival tissue or perforation of the oral mucosa should be covered by antibiotics. Recommended antibiotics reflect changed organism sensitivities (Tables 12-8 and 12-9).[528] *Updated American recommendations* suggest that, for high-risk patients, only one amoxicillin dose of 2 g be given orally 1 hour before the dental procedure, with specified antibiotic regimens for those unable to take oral medication or allergic to penicillins or amoxicillin (see Table 12-8). *Overall, note that there are no recommendations with Class I and Level of Evidence A.*

Table 12-7 -- Cardiac Conditions with the Highest Risk of Infectious Endocarditis[592]

Antibiotic prophylaxis during dental procedures recommended by American Heart Association.
1. Prosthetic cardiac valve or prosthetic material used for cardiac valve repair (class 1C).

2. Previous infectious endocarditis (class 1C).
3. Congenital heart disease* (class 1C):
   - Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits.
   - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure.[†]
   - Repaired coronary heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization).
4. Hypertrophic cardiomyopathy, latent or resting obstruction (class 1C).
5. Mitral valve prolapse without mitral regurgitation or thickened leaflets (class 1C).

Dental procedures for which endocarditis prophylaxis is reasonable in these groups of patients: *All dental procedures* that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

* Except for the conditions listed previously, antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease.

† Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure, per the American Heart Association recommendations (2007).[528]

Table 12-8 -- Revised American Regimens for Antibiotics for Dental Procedures[592]*

		Regimen: Single Dose 30-60 min before Procedure	
Situation	**Agent**	**Adults**	**Children**
OralUnable to take oral medication	AmoxicillinAmpicillin or Cefazolin or ceftriaxone	2 g2 g IM or IV 1 g IM or IV	50 mg/kg50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[†‡] *or*Clindamycin or Azithromycin or clarithromycin	2 g600 mg 500 mg	50 mg/kg20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[‡] *or*	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM, Intramuscular; *IV,* intravenous.

* Only for those at risk (see Table 12-7).

† Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

‡ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Table 12-9 -- European Recommended Prophylaxis for Adults for Dental Procedures at Risk[593]

		Single Dose 30-60 Minutes Before Procedure	
Situation	**Antibiotic**	**Adults**	**Children**
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin*	2 g PO or IV	50 mg/kg PO or IV
Allergy to penicillin or ampicillin	Clindamycin	600 mg PO or IV	20 mg/kg PO or IV

IV, Intravenous; *PO,* by mouth.

Cephalosporins should not be used in patients with anaphylaxis, antiooedema, or urticaria after intake of

penicillin and ampicillin.

* Alternatively cephalexin 2 g IV, cefazolin or ceftriaxone 1 g IV.

Prophylaxis is recommended for procedures on infected respiratory tract or skin, on skin structures, or on musculocutaneous tissue. The new guidelines also simplify antibiotic prophylaxis for patients undergoing gastrointestinal or genitourinary procedures. No antibiotic coverage is suggested even for high-risk patients, but for those with existing gastrointestinal or genitourinary infections, an antienteroccocal agent is "reasonable" without, however, supporting trial data.

Primary prevention.

Despite common perceptions, most infectious endocarditis is not preceded by medicosurgical or dental interventions, so the real answer lies in primary prevention.[518] Thus conditions predisposing to infective endocarditis, such as poor dental hygiene or genitourinary tract pathologic conditions, must be eliminated.

* Section cowritten with Larry M Baddour, MD

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Peripheral vascular disease

Burns et al. write, “Peripheral vascular disease is a marker for systemic atherosclerosis; the risk to limb is low, but the risk to life is high.”[529] The basis of therapy is medical treatment focused on aggressive risk-factor modification, including control of lipids, diabetes, and BP; smoking cessation; and exercise. Revascularization, either percutaneous or surgical, is indicated for patients with refractory symptoms causing significant disability or the presence of limb-threatening ischemia.[522],[529],[530] Large vessel disease is usually treated surgically but catheter-based therapy using stents and endovascular grafts are increasingly used alternatives.[531],[532] In the area of critical limb ischemia, both endovascular and surgical revascularization (with a vein conduit) are reasonable initial procedures for critical limb ischemia —Class IIA.

Prophylaxis of cardiovascular complications.

The basis of medical therapy lies in risk-factor modification, exercise training, and aspirin.[529] A supervised exercise program can result in a major improvement in motivated patients, but the benefits are lost if the patient stops exercising. Class I recommendations include a statement that all smokers or former smokers should be asked about their smoking status at every visit, and smokers should be assisted with counseling and the development of a quit-smoking treatment plan that includes pharmacologic therapy with varenicline, bupropion, or nicotine-replacement therapy.[533] To what extent smoking cessation improves symptoms is unclear, but its effect on the progression of disease and amputation rates is well documented.[534] Decreased amputation and rest ischemia are well documented, and in any event, the logic is irrefutable. In addition, ACE inhibitors, clopidogrel, and a statin can all be given with large trial justification.[535-537] Although without formal proof that clopidogrel, aspirin, statin, and an ACE inhibitor give additive protection and do not adversely interfere with each other, each agent acts by a different mechanism so that we recommend this combination. In the CHARISMA trial, a subset of patients with prior MI, stroke, or symptomatic peripheral arterial disease appeared to benefit from clopidogrel added to aspirin.[530] Antiplatelet therapy may be useful in patients with an abnormal ankle-brachial index who are currently asymptomatic with a level of evidence C. Ongoing major trials of statins, antiplatelet agents, recombinant growth factors, and immune modulators may result in clinically relevant new advances in the medical management of peripheral vascular disease in the future, but trials of gene therapy for therapeutic angiogenesis have been disappointing.[538] A randomized placebo-controlled trial of more than 500 patients with critical ischemia demonstrated no difference between fibroblastic growth factor (NV1FGF) on amputation and death.[539] On the other hand, autologous bone-marrow mononuclear stem cells appear to be safe and promising in preliminary trials.[540],[541]

Cilostazol.

Cilostazol, a phosphodiesterase-3 inhibitor, was approved in 2000 in the United States for intermittent claudication. It suppresses platelet aggregation and is a direct vasodilator. Increased walking distance was shown in a metaanalysis of 2702 patients.[542] The usual dose is 100 mg twice daily. It is metabolized by the cytochrome P-450 3A4 system, and hence open to interaction with ketoconazole, erythromycin, and diltiazem, as well as grapefruit juice, which should all be avoided.

Pentoxifylline.

Pentoxifylline (*Trental*) decreases blood viscosity and maintains red cell flexibility of the erythrocytes as they are squeezed through the capillary bed. It is licensed for use in intermittent claudication in the United States. Yet in a randomized trial of pentoxifylline and cilostazol, only cilostazol improved both functional status and the walking impairment questionnaire.[543] ACC-AHA guidelines conclude that any benefits of pentoxifylline are marginal and not well established.[544]

Naftidrofuryl.

Naftidrofuryl is a 5-hydroxytriptamine-2 receptor antagonist available in Europe. Mechanisms of action are unclear, but a recent consensus statement recommended its addition to cilostazol.[545] In a Cochrane metaanalysis of four trials an improvement in time to initial pain on treadmill walking over a 3- to 6-month period was noted.[546]

Other agents.

Levocarnitine and l-propionyl-carnitine favorably improve the metabolic status of skeletal muscle to lengthen the walking distance. Neither preparation is licensed in the United States. Gingko biloba gives modest success but the mechanisms are unclear.[547] Buflomedil is an α-adrenergic blocker with vasoactive and rheologic properties licensed in Europe but not in the United States.

Ineffective therapies that should be discouraged include estrogen replacement, chelation therapy, and vitamin E supplementation. Ginkgo biloba has been shown to be moderately successful but problems with the studies have been identified and ACC-AHA guidelines concluded that benefit has not been established.[544] Other agents under investigation include verapamil, ACE inhibitors, anticlamydophila therapy, L-propionyl-carntine, prostaglandins, defibrotide (an agent stimulating fibrinolysis), and glutathione, among others.[548] Other potentially effective agents include prostaglandin, indirect vasodilators such as serotonin uptake inhibitors, phosphodiesterase inhibitors, sympatholytic agents, and toxofilin.

Claudication plus hypertension or angina.

β-Blockers are still generally held to be relatively contraindicated in the presence of active peripheral vascular disease, although a metaanalysis of 11 pooled trials showed no adverse effects on the walking distance in mild to moderate disease.[549] Verapamil increases pain-free walking time[550] and is preferred to β-blockers, although without strict comparative studies.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Raynaud's phenomenon

Once a secondary cause has been excluded (e.g., vasculitis, scleroderma, or lupus erythematosus), then calcium channel antagonists are logical. Nifedipine is best tested, and one 10-mg capsule may be taken intermittently at the start of an attack. β-Blockers are traditionally contraindicated, although the evidence is not good. Sustained-release glycerol trinitrate patches may be effective in Raynaud's phenomenon, but are limited by the frequency of headaches. Several reports attest to the efficacy of topical glycerol trinitrate in this condition.[551] Common-sense measures such as avoidance of exposure to cold and rapidly changing temperatures; keeping the digits warm; avoidance of sympathomimetic drugs such as decongestants, amphetamines, and over-the-counter drugs containing ephedrine; and, above all, smoking cessation are extremely important.[552] For intractable disease, spinal cord stimulation or thoracic or localized digital sympathectomy may provide relief.[553],[554]

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Beriberi heart disease

Beriberi heart disease is characterized by high-output CHF caused by thiamine deficiency. Common in Africa and Asia, in Western countries it is underdiagnosed especially in alcoholics and in those on "fad diets" or occasionally in patients receiving parenteral nutrition.[555] The basis of treatment is thiamine 100 mg parenterally followed by 50 to 100 mg daily with vitamin supplements, a balanced diet, and abstinence from alcohol. Even in Shoshin beriberi with peripheral circulatory shock and severe metabolic acidosis, thiamine remains the mainstay of treatment because the acidosis responds poorly to treatment. Diuretics are needed when diuresis is delayed beyond 48 hours of thiamine therapy (Professor DP Naidoo, University of Natal, South Africa, personal communication).

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Cardiovascular drugs in pregnancy

Most cardiovascular drugs are not well studied for safety in pregnancy. ACE inhibitors, ARBs, warfarin, and the statins are all clearly contraindicated (Table 12-10). For pregnancy hypertension, methyldopa is best validated, and the diuretics are not as bad as often thought.

Table 12-10 -- Cardiovascular Drugs in Pregnancy

Drug Category	Potential Adverse Effect on Fetus	Safety in Pregnancy (Classification)*	Trimester Risk (1, 2, 3)
β-Blockers	Intrauterine growth retardation; neonatal hypoglycemia, bradycardia	C or D	1, 3
Nitrates	None; may benefit by delaying premature labor	C	None
CCBs	None; may delay labor; experimentally embryopathic	C	None
Diuretics			
Thiazides	May impair uterine blood flow; usually regarded as C/I, yet metaanalysis suggests safety[†]	B or C	3
Furosemide	Experimentally embryopathic	C	(1)
Torsemide	None	B	None
Indapamide	None	B	None
ACE inhibitors; ARBs	Embryopathic in all semesters[†]; may be lethal	D or X	1, 2, 3
Digoxin	None	C	None
Antihypertensives			
Methyldopa	Well tested in pregnancy	B	None
Others as shown	Generally no adverse effects	C	None
Antiarrhythmics			
Amiodarone	Altered thyroid function	D	2, 3
Sotalol	None	B	None
Statins	Serious	X	1,2,3
Antithrombotics			
Warfarin	Embryopathic; crosses placenta with risk of fetal hemorrhage	X	1, 3
Heparin	None; does not cross placental barrier	C[‡]	None
Enoxaparin	No trials in humans	B	Not known
GpIIa/IIIb blockers			
Abciximab	No data in humans	C	? None
Eptifibatide	No data in humans	B	? None
Tirofiban	No data in humans	B	? None
Aspirin	High dose: risk of premature closure of patent ductus	None	3

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CCB,* calcium channel blocker; *C/I,* contraindication; *Gp,* glycoprotein.

* US Food and Drug Administration Pregnancy Categories range from A (completely safe) to D (considerable risk) and X (contraindicated).

† Data from Cooper et al. *N Engl J Med* 2006;354:2443.

‡ For heparin, see p. 369.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Cardiopulmonary resuscitation*

In 2010 the AHA published new guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (Fig. 12-10).[556] The key issues and major changes addressed include:

- A simplified universal adult basic life support algorithm
- A change in sequence from airway-breathing-compression to compression-airway-breathing for *lone rescuers,* and use of compression-only rescue for rescuers untrained in CPR
- Continued emphasis on teaching rescuers to deliver chest compressions of adequate rate (at least 100 per minute) and depth to at least 2 inches (5 cm).[556]

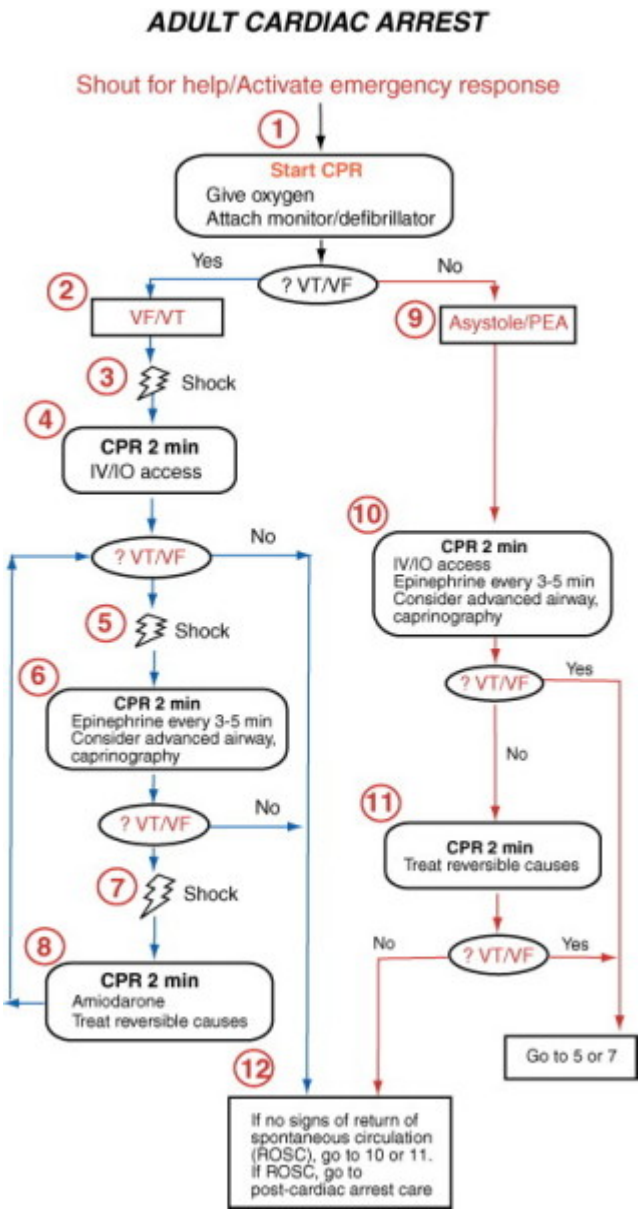

Figure 12-10 Algorithm for cardiopulmonary resuscitation (CPR) for adult cardiac arrest, when there is ventricular tachycardia (VT) or ventricular fibrillation (VF) or pulseless electrical activity (PEA), based on the recommendations of the American Heart Association.[556],[588] *IO,* Intraoral; *IV,* intravenous; *ROSC,* return of spontaneous circulation.

It is important to emphasize that the 2010 guidelines recommend omission of mouth-to-mouth "rescue" breathing for lay rescuers and witnessed cardiac arrest, based on evidence that adequate oxygenation can be provided by chest compressions only for several minutes following cardiac arrest. In addition, lay rescuers typically have difficulty attempting to establish an airway and ventilation of the lungs, consuming needed time to establish blood flow with chest compressions. Thus CPR, although still valid for trained healthcare providers, should for bystanders be replaced by continuous chest compression. The phrase "push hard and push fast" encourages rescuers to compress at a rate of at least 100 compressions per minute and at a depth of at least 2 inches.

The first step.

The first step is to shout for help and to start chest compressions urgently. As soon as an AED is available, it should be attached and a shock delivered if a shockable rhythm is detected. Following a shock, chest compressions are immediately resumed unless the victim quickly regains consciousness following the shock. If monomorphic wave form defibrillators are used, 360-Joule shocks are recommended. For biphasic wave forms, this is device specific ranging from 120-200 Joules with subsequent shocks at the same or higher energy levels (see Fig. 12-10). A recent trial compared 2 minutes of CPR performed by emergency medical service (EMS) personnel before the first analysis of cardiac rhythm with a strategy of a longer period of CPR with delayed analysis of cardiac rhythm. In more than 9000 patients without a hospital cardiac arrest, the trial identified no difference in outcomes with a brief period as opposed to a longer period of EMS-administered CPR for the first analysis of cardiac rhythm, which emphasizes the strategy of push first and push hard.[557]

Role of ventilation.

The best ratio of chest compression to ventilation is not clear and, as stated, ventilation is not recommended for bystanders.[558] The guidelines recommend a compression-to-ventilation ratio of 30:2 prompted by observations that rescue breaths can result in excessively long interruptions during chest compressions. The controversial area relates to observational and experimental studies that support the recommendation that cardiac-only resuscitation is as effective for several minutes in witnessed cardiac arrest as standard CPR given the disadvantages of mouth-to-mouth ventilation such as bystander distaste, reduced ventricular filling with positive pressure ventilation, the potentially deleterious effects of pressure recoil on gas exchange, and interruption of chest compression caused by delays and intubation.[559] This does not negate the value of a clear airway or rapid intubation if achievable, or the benefit of rescue breathing in an unwitnessed arrest and of course during prolonged CPR (beyond 15 minutes). All healthcare providers are expected to be able to perform rescue breathing effectively during CPR.[560] A recent consensus document from the 2009 AHA Cardiac Arrest Survival Summit addressed a number of issues and strategies for implementing optimized systems of out-of-hospital cardiac arrest care in the United States, but obviously these have international implications as well.[561]

Update: New Content Added *Date Added: 21 February 2013*

Chest compression only resuscitation for out-of- hospital sudden cardiac arrest

Lionel H. Opie, MD, DPhil, Professor of Medicine Em., Hatter Insitute for Cardiovascular Research in Africa, University of Cape Town Medical School, and Groote Schuur Hospital, Observatory, Cape Town, South Africa

Summary

Background: Out-of-hospital cardiac arrest (OHCA) is a common cause of death. Following approved guidelines survival rates of patients with OHCA were extremely variable, with only a few areas having good results. An alternative approach to improving survival is to use continuous quality improvement (CQI), a process often used to address public health problems. Continuous quality improvement advocates that baseline data are obtained and, if not optimal, make changes and continuously re-evaluate the results

Methods & results: Using CQI, the authors instituted cardiocerebral resuscitation as the preferred approach and found significant improvement in survival of patients with OHCA (1). The basic choice was based primarily on extensive experimental laboratory data. By using continuous quality improvement they found that passive ventilation was much better than bag-valve-mask ventilation by paramedics at 8 breaths per min. Thus they advocate chest compression only CPR (CO-CPR) given bystanders of patients with primary OHCA and encouraging the use of cardiocerebral resuscitation by emergency medical systems, survival of patients with primary cardiac arrest in Arizona increased over a 5-year period from 17.7% to 33.7%. They recommend that all emergency medical systems determine their baseline survival rates of patients with OHCA and a shockable rhythm, and consider implementing the CQI approach if the community does not have a neurologically intact survival rate of at least 30%.

Comment: In an accompanying Editorial (2) two aspects are stressed. First, "successful resuscitation is a team sport" and a community effort. Secondly, well-performed cardiocerebral resuscitation (CCR) by by-passers is at least as good as standard CPR because of the similar results with the simpler CCR and performance is easier.

References

1. Ewy GA, Sanders AB: Alternative approach to improving survival of patients with out-of-hospital primary cardiac arrest. *J Am Coll Cardiol* 2013; 61:113-118.

2. Rea TD: Protocol or performance. *J Am Coll Cardiol* 2013; 61:119-120.

Ongoing studies.

Reversed CPR uses intermittent back pressure in the prone patient.[562] Another approach uses rhythmic abdominal compression instead of compression of the rib cage and potentially increases blood flow to the heart and avoids fractured ribs, but this has not been widely accepted.[563] A major advance has been the use of AEDs for out-of-hospital cardiac arrest with an impressive increase in survival discharge.[564],[565] Lay persons and first responders can be trained to operate these devices and the key is community education. CPR programs focusing on early defibrillation have improved the rate of survival to discharge in many locations, and in patients with out-of-hospital cardiac arrest treated by early defibrillation, 46% were discharged neurologically intact.[566] These data serve as a benchmark for what can be achieved, particularly in smaller communities with rapid and easy access to trained life-support personnel.[567] Other areas of ongoing investigation include whether to proceed shock delivery in VF arrest with a period of CPR or to shock immediately, and whether chest compressions delivered immediately after a shock can induce resumption of VF. The role of automated electronic analysis of the cardiac rhythm as a determinant as to whether to shock first or provide CPR first is under active investigation.[568-571]

Adjunctive pharmacotherapy.

In patients with shockable rhythms (see Fig. 12-10), if the second shock fails to restore a hemodynamically effective spontaneous rhythm, either epinephrine 1 mg every 3 to 5 minutes or vasopressin 40 IU to replace the second dose of epinephrine should be administered, either intravenously or intraosseously in the event that venous access, either peripheral or via a central venous line (jugular, femoral, or subclavian) is not obtained. Comparisons of epinephrine versus vasopressin have not shown any differences in regard to survival to discharge.[572] Do not interrupt CPR to administer medications. After the third shock, amiodarone should be considered. The efficacy of amiodarone has been established by two clinical trials in patients with out-of-hospital cardiac arrest.[573],[574] Lidocaine is logical but without evidence to support its efficacy and should not be used as the sole first-line antiarrhythmic drug. For polymorphic VT associated with a long QT interval (torsades de pointes), magnesium in a 1- to 2-g loading dose should be given.[575] Sodium bicarbonate is only used in prolonged resuscitation when respiration is controlled because carbon dioxide formed from bicarbonate permeates into cells to increase intracellular acidosis.

Asystole or pulseless electrical activity.

Asystole and pulseless electrical activity account for up to 70% of all out-of-hospital cardiac arrests

encountered by EMS[576],[577] and has a dreadful prognosis.[578] A decline in the incidence of VF in out-of-hospital cardiac arrest has been accompanied by an increase in the incidence of asystole and pulseless electrical activity.[579] The focus is to perform resuscitation with CPR while attempting to identify reversible causes or complicating factors. AHA guidelines recommend epinephrine every 3 to 5 minutes with a single dose of vasopressin substituted for the first or second epinephrine dose.[580] No study has demonstrated that atropine administered in 1-mg doses every 3 to 5 minutes for asystole or slow pulseless electrical activity has had any effect on outcomes. CPR should not be discontinued during the administration of medications. During CPR the rhythm should be checked and shocks delivered for persistent or recurrent VF or VT followed by resumption of CPR after each shock.

Other interventions.

Interventions not supported by outcome evidence include routine use of fibrinolysis, attempted pacing for asystole, administration of procainamide for VF or pulseless VT, and routine fluid loading. No recommendations for or against precordial thumps have been made, which in some studies led to a deterioration in cardiac rhythm.

When to call it off.

The ethics of when to stop the “loops” and when not to resuscitate are becoming increasingly complex. The 2010 guidelines address the situation in detail. The increasing use of capnography during cardiac arrest provides readily measurable and objective data to guide decision making.[581]

Self-help by coughing.

Those persons who are alone when having a heart attack and begin to feel faint should cough repeatedly and very vigorously, which might save them from fatal VF.[582]

Care of cardiac arrest survivors.

The patient will have been urgently hospitalized and central nervous injury and cardiogenic shock are the major risks. Amiodarone is the most commonly used antiarrhythmic drug following a VF arrest or for ongoing ventricular arrhythmias. In unconscious patients with spontaneous circulation after recovery from cardiac arrest caused by VF, mild therapeutic hypothermia of 32° C to 34° C improves the neurologic outcome and long-term survival.[583-586] In a retrospective analysis of cardiac arrest survivors at the Mayo Clinic, survival was 64% in those treated with induced hypothermia versus 24% in patients not treated with hypotheramia.[587] Once the patient is stabilized, a full cardiac evaluation is required, including echocardiography and coronary angiography.

Long-term care.

The substrate for sustained monomorphic VT is seldom abolished by bypass grafting, so that the indications for cardiac surgery must be decided in their own right. Nevertheless, it makes sense to consider an ischemic cause in such patients, and aggressively to treat coronary heart disease and LV failure aggressively both medically and, where indicated, surgically. Empirical β-blockade is the prime long-term antiarrhythmic treatment unless contraindicated, whereupon empirical amiodarone is the next choice. The ICD is widely regarded as the ultimate treatment, and it undoubtedly reduces SCD. The ICD has irrevocably altered the landscape for patients with malignant ventricular tachyarrhythmias, yet there are reservations. In patients with a cardiac arrest in the setting of decompensated heart failure, an ICD may simply replace SCD by delayed death resulting from heart failure. Thus ICDs should be selectively applied, specifically to patients at serious risk of SCD yet otherwise having a reasonable expected overall cardiac prognosis.

* Section cowritten with Roger D. White, MD.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com

References*

1.. Fraker Jr TD, et al: 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina. a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines writing group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina*Circulation* 2007; 116:2762-2772.

2.. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002; 106:3143-3421.

3.. Association AD: Standards of medical care in diabetes—2007. *Diabetes Care* 2007; 30:S4-S41.

4.. Smith Jr SC, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention-summary article. a report of the American College Of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines For Percutaneous Coronary Intervention)*J Am Coll Cardiol* 2006; 47:216-235.

5.. Foundation NK: K/doqi clinical practice guidelines for chronic kidney disease. evaluation, classification, and stratification*Am J Kidney Dis* 2002; 39:S1-S266.

6.. Boden WE: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. AIM-HIGH Investigators. *N Engl J Med* 2011; 365:2255-2267.

7.. Voight BF, et al: Plasma HDL cholesterol and risk of myocardial infarction. a mendelian randomisation study*Lancet* 2012; 380:572-580.

8.. Anderson JL, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine*J Am Coll Cardiol* 2007; 50:e1-e157.

9.. Cushman WC, et al: Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575-1585.

10.. Dagenais GR, et al: Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure. a combined analysis of three trials*Lancet* 2006; 368:581-588.

11.. Kris-Etherton P, et al: AHA Science Advisory. Lyon diet heart study. Benefits of a Mediterranean-style, national cholesterol education program/American Heart Association Step I dietary pattern on cardiovascular disease*Circulation* 2001; 103:1823-1825.

12.. English KM, et al: Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. a randomized, double-blind, placebo-controlled study*Circulation* 2000; 102:1906-1911.

13.. Collaboration AT: Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high-risk patients. *Brit Med J* 2002; 324:71-86.

14.. Bhatt DL, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354:1706-1717.

15.. Thrombosis prevention trial. Randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's general practice research framework. *Lancet* 1998; 351:233-241.

16.. O'Connor CM, et al: Azithromycin for the secondary prevention of coronary heart disease events. the WIZARD studya randomized controlled trial*JAMA* 2003; 290:1459-1466.

17.. Heidenreich PA, et al: Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA* 1999; 281:1927-1936.

18.. Bangalore S, et al: Cardiovascular protection using beta-blockers. a critical review of the evidence*J Am Coll Cardiol* 2007; 50:563-572.

19.. Salpeter S, et al: *Cardioselective beta-blockers for chronic obstructive pulmonary disease*. Cochrane Database Syst Rev, 2005. CD003566

20.. Dahlof B, et al: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo-scandinavian cardiac outcomes trial-blood pressure lowering arm (ascot-bpla). a multicentre randomised controlled trial*Lancet* 2005; 366:895-906.

21.. Lubsen J, et al: Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension. the action trial*J Hypertens* 2005; 23:641-648.

22.. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina. the impact of nicorandil in angina (IONA) randomised trial. *Lancet* 2002; 359:1269-1275.

23.. Chaitman BR, et al: Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. a randomized controlled trial*JAMA* 2004; 291:309-316.

24.. Scirica BM, et al: Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome. results from the metabolic efficiency with ranolazine for less ischemia in non ST-elevation acute coronary syndrome thrombolysis in myocardial infarction 36 (merlin-timi 36) randomized controlled trial*Circulation* 2007; 116:1647-1652.

25.. Borer JS, et al: Antianginal and antiischemic effects of ivabradine, an i(f) inhibitor, in stable angina. a randomized, double-blind, multicentered, placebo-controlled trial*Circulation* 2003; 107:817-823.

26.. Tardif JC, et al: Efficacy of ivabradine, a new selective i(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005; 26:2529-2536.

27.. Fox K, et al: Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (beautiful). a randomised, double-blind, placebo-controlled trial*Lancet* 2008; 372:807-816.

28.. Swedberg K, et al: Ivabradine and outcomes in chronic heart failure (shift). a randomised placebo-controlled study*Lancet* 2010; 376:875-885.

29.. Noman A, et al: Effect of high-dose allopurinol on exercise in patients with chronic stable angina. a randomised, placebo controlled crossover trial*Lancet* 2010; 375:2161-2167.

30.. Rajendra NS, et al: Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. *J Am Coll Cardiol* 2011; 58:820-828.

31.. Lee L, et al: Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. *Eur Heart J* 2004; 25:634-641.

32.. Boden WE, et al: Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J*

Med 2007; 356:1503-1516.

33.. Hueb W, et al: Five-year follow-up of the medicine, angioplasty, or surgery study (mass II). a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease*Circulation* 2007; 115:1082-1089.

34.. Frye RL, et al: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009; 360:2503-2515.

35.. Cassar A, et al: Chronic coronary artery disease. diagnosis and management*Mayo Clin Proc* 2009; 84:1130-1146.

36.. Tonino PA, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360:213-224.

37.. Kastrati A, et al: Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356:1030-1039.

38.. Morice MC, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346:1773-1780.

39.. Mauri L, et al: Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med* 2008; 359:1330-1342.

40.. Curfman GD, et al: Drug-eluting coronary stents—promise and uncertainty. *N Engl J Med* 2007; 356:1059-1060.

41.. Stone GW, et al: Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 2009; 360:1946-1959.

42.. Marroquin OC, et al: A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med* 2008; 358:342-352.

43.. Corpus RA, et al: Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated Type II diabetic patients undergoing elective percutaneous coronary intervention. *J Am Coll Cardiol* 2004; 43:8-14.

44.. Opie LH, et al: Controversies in ventricular remodelling. *Lancet* 2006; 367:356-367.

45.. Rihal CS, et al: Indications for coronary artery bypass surgery and percutaneous coronary intervention in chronic stable angina. review of the evidence and methodological considerations*Circulation* 2003; 108:2439-2445.

46.. Eefting F, et al: Randomized comparison between stenting and off-pump bypass surgery in patients referred for angioplasty. *Circulation* 2003; 108:2870-2876.

47.. Khan NE, et al: A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med* 2004; 350:21-28.

48.. van Dijk D, et al: Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA* 2007; 297:701-708.

49.. Lim E, et al: A systematic review of randomized trials comparing revascularization rate and graft patency of off-pump and conventional coronary surgery. *J Thorac Cardiovasc Surg* 2006; 132:1409-1413.

50.. Hannan EL, et al: Off-pump versus on-pump coronary artery bypass graft surgery. differences in short-term outcomes and in long-term mortality and need for subsequent revascularization*Circulation* 2007; 116:1145-1152.

51.. Schofield PM: Indications for percutaneous and surgical revascularisation. how far does the evidence base guide us*Heart* 2003; 89:565-570.

52.. Brener SJ, et al: Comparison of percutaneous versus surgical revascularization of severe unprotected

left main coronary stenosis in matched patients. *Am J Cardiol* 2008; 101:169-172.

53.. Gersh BJ, et al: Methods of coronary revascularization—things may not be as they seem. *N Engl J Med* 2005; 352:2235-2237.

54.. Serruys PW, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360:961-972.

55.. Yang EH, et al: Current and future treatment strategies for refractory angina. *Mayo Clin Proc* 2004; 79:1284-1292.

56.. Arora RR, et al: The multicenter study of enhanced external counterpulsation (must-EECP). effect of EECP on exercise-induced myocardial ischemia and anginal episodes*J Am Coll Cardiol* 1999; 33:1833-1840.

57.. Akhtar M, et al: Effect of external counterpulsation on plasma nitric oxide and endothelin-1 levels. *Am J Cardiol* 2006; 98:28-30.

58.. Nichols WW, et al: Enhanced external counterpulsation treatment improves arterial wall properties and wave reflection characteristics in patients with refractory angina. *J Am Coll Cardiol* 2006; 48:1208-1214.

59.. Soran O, et al: Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the international EECP patient registry). *Am J Cardiol* 2006; 97:17-20.

60.. McNab D, et al: An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris. the SPIRIT trial*Eur Heart J* 2006; 27:1048-1053.

61.. Losordo DW, et al: Intramyocardial, autologous cd34+ cell therapy for refractory angina. *Circ Res* 2011; 109:428-436.

62.. Losordo DW, et al: Intramyocardial transplantation of autologous cd34+ stem cells for intractable angina. a phase i/iia double-blind, randomized controlled trial*Circulation* 2007; 115:3165-3172.

63.. Leon MB, et al: A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. *J Am Coll Cardiol* 2005; 46:1812-1819.

64.. Alpert JS, et al: Myocardial infarction redefined—a consensus document of the joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000; 36:959-969.

65.. Roger VL, et al: Redefinition of myocardial infarction. prospective evaluation in the community*Circulation* 2006; 114:790-797.

66.. Anderson JL, et al: 2011 ACCF/AHA FOCUSED UPDATE incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*Circulation* 2011; 123:e426-579.

67.. Mehran R, et al: Standardized bleeding definitions for cardiovascular clinical trials. a consensus report from the bleeding academic research consortium*Circulation* 2011; 123:2736-2747.

68.. Steg PG, et al: Bleeding in acute coronary syndromes and percutaneous coronary interventions. position paper by the working group on thrombosis of the European Society of Cardiology*Eur Heart J* 2011; 32:1854-1864.

69.. Burls A, et al: Oxygen therapy for acute myocardial infarction. a systematic review and meta-analysis*Emerg Med J* 2011; 28:917-923.

70.. Oler A, et al: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in

patients with unstable angina. A meta-analysis. *JAMA* 1996; 276:811-815.

71.. Smith Jr SC, et al: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease. 2006 updateendorsed by the National Heart, Lung, and Blood Institute*Circulation* 2006; 113:2363-2372.

72.. Antman EM, et al: focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction, writing on behalf of the 2004 Writing Committee. *Circulation* 2008; 117:296-329.

73.. Bhatt DL, et al: Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; 363:1909-1917.

74.. Pare G, et al: Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 2010; 363:1704-1714.

75.. Price MJ, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. the gravitas randomized trial*JAMA* 2011; 305:1097-1105.

76.. Wiviott SD, et al: Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the triton-timi 38 trial. a subanalysis of a randomised trial*Lancet* 2008; 371:1353-1363.

77.. Schomig A: Ticagrelor—is there need for a new player in the antiplatelet-therapy field. *N Engl J Med* 2009; 361:1108-1111.

78.. James SK, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management. substudy from prospective randomised platelet inhibition and patient outcomes (PLATO) trial*Brit Med J* 2011; 342:d3527.

79.. Hamm CW, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)*Eur Heart J* 2011; 32:2999-3054.

80.. Bhatt DL, et al: Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 2009; 361:2330-2341.

81.. O'Donoghue ML, et al: Safety and tolerability of atopaxar in the treatment of patients with acute coronary syndromes. the lessons from antagonizing the cellular effects of thrombin-acute coronary syndromes trial*Circulation* 2011; 123:1843-1853.

82.. Cannon CP: Diagnosis and management of patients with unstable angina. *Curr Probl Cardiol* 1999; 24:681-744.

83.. Antman EM, et al: Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11b trial. *Circulation* 1999; 100:1593-1601.

84.. Cohen M, et al: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. *N Engl J Med* 1997; 337:447-452.

85.. Klein W, et al: Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997; 96:61-68.

86.. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a

6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction. Frax.I.S. (fraxiparine in ischaemic syndrome). *Eur Heart J* 1999; 20:1553-1562.

87.. Collet JP, et al: Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. *Circulation* 2001; 103:658-663.

88.. Fox KA, et al: Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction. the British heart foundation RITA 3 randomised trial. Randomized intervention trial of unstable angina*Lancet* 2002; 360:743-751.

89.. Kereiakes DJ, et al: Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J Invasive Cardiol* 2001; 13:272-278.

90.. Ferguson JJ, et al: Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. SYNERGY Trial Investigators. *JAMA* 2004; 292:45-54.

91.. Magee KD, et al: *Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes*. Cochrane Database Syst Rev, 2003. CD002132

92.. Stone GW, et al: Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. a subgroup analysis from the acute catheterization and urgent intervention triage strategy (ACUITY) trial*Lancet* 2007; 369:907-919.

93.. Bassand JP, et al: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007; 28:1598-1660.

94.. Stone GW, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355:2203-2216.

95.. Stone GW, et al: Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management. one-year results from the acuity trial*JAMA* 2007; 298:2497-2506.

96.. Mega JL, et al: Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366:9-19.

97.. Alexander JH, et al: Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; 365:699-708.

98.. Goodman SG, et al: Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor. insights from the platelet inhibition and patient outcomes trial*Circulation* 2012; 125:978-986.

99.. Hohnloser SH, et al: Usefulness of esmolol in unstable angina pectoris. European esmolol study group. *Am J Cardiol* 1991; 67:1319-1323.

100.. Gobel EJ, et al: Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris. *Eur Heart J* 1998; 19:1208-1213.

101.. Scirica BM, et al: Relationship between nonsustained ventricular tachycardia after non-ST-elevation acute coronary syndrome and sudden cardiac death. observations from the metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndrome-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36) randomized controlled trial*Circulation* 2010; 122:455-462.

102.. Morrow DA, et al: Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes. the MERLIN-TIMI 36 randomized trial*JAMA* 2007; 297:1775-1783.

103.. Morrow DA, et al: Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009; 119:2032-2039.

104.. Bavry AA, et al: Benefit of early invasive therapy in acute coronary syndromes. a meta-analysis of contemporary randomized clinical trials*J Am Coll Cardiol* 2006; 48:1319-1325.

105.. Fox KA, et al: Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010; 55:2435-2445.

106.. Hoenig MR, et al: *Early invasive versus conservative strategies for unstable angina & non-ST-elevation myocardial infarction in the stent era*. Cochrane Database Syst Rev, 2006. CD004815

107.. Lagerqvist B, et al: 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome. a follow-up study*Lancet* 2006; 368:998-1004.

108.. Mehta SR, et al: Routine vs selective invasive strategies in patients with acute coronary syndromes. a collaborative meta-analysis of randomized trials*JAMA* 2005; 293:2908-2917.

109.. Fox KA, et al: Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome. prospective multinational observational study (grace)*Brit Med J* 2006; 333:1091.

110.. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina. the capture study. *Lancet* 1997; 349:1429-1435.

111.. Cannon CP, et al: The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction. results of the TIMI III registry ECG ancillary study. Thrombolysis in myocardial ischemia*J Am Coll Cardiol* 1997; 30:133-140.

112.. Heeschen C, et al: Angiographic findings in patients with refractory unstable angina according to troponin T status. *Circulation* 1999; 100:1509-1514.

113.. Albert CM, et al: Blood levels of long-chain 3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; 346:1113-1118.

114.. Rezkalla SH, et al: Cocaine-induced acute myocardial infarction. *Clin Med Res* 2007; 5:172-176.

115.. Dattilo PB, et al: Beta-blockers are associated with reduced risk of myocardial infarction after cocaine use. *Ann Emerg Med* 2008; 51:117-125.

116.. Braunwald E, et al: ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina)*J Am Coll Cardiol* 2002; 40:1366-1374.

117.. Rosendorff C, et al: Treatment of hypertension in the prevention and management of ischemic heart disease. a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention*Circulation* 2007; 115:2761-2788.

118.. Jernberg T, et al: Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011; 305:1677-1684.

119.. Minners J, et al: Diazoxide-induced respiratory inhibition—a putative mitochondrial K(ATP) channel independent mechanism of pharmacological preconditioning. *Mol Cell Biochem* 2007; 294:11-18.

120.. Pinto DS, et al: Hospital delays in reperfusion for ST-elevation myocardial infarction. implications when selecting a reperfusion strategy*Circulation* 2006; 114:2019-2025.

121.. Schomig A, et al: Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. *Circulation* 2003; 108:1084-1088.

122.. Silvain J, et al: Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol* 2011; 57:1359-1367.

123.. Gersh BJ, et al: Selection of the optimal reperfusion strategy for STEMI. does time matter*Eur Heart J* 2006; 27:761-763.

124.. Gersh BJ, et al: Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. is the slope of the curve the shape of the future*JAMA* 2005; 293:979-986.

125.. Nallamothu BK, et al: Time to treatment in primary percutaneous coronary intervention. *N Engl J Med* 2007; 357:1631-1638.

126.. Timmer JR, et al: Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus. results from the primary coronary angioplasty vs thrombolysis-2 trial*Arch Intern Med* 2007; 167:1353-1359.

127.. Grines CL, et al: Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent primary angioplasty in myocardial infarction study group. *N Engl J Med* 1999; 341:1949-1956.

128.. Ting HH, et al: Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction. the Mayo Clinic STEMI protocol*Circulation* 2007; 116:729-736.

129.. Stone GW, et al: Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI). final 3-year results from a multicentre, randomised controlled trial*Lancet* 2011; 377:2193-2204.

130.. Laarman GJ, et al: Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006; 355:1105-1113.

131.. Spaulding C, et al: Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006; 355:1093-1104.

132.. Valgimigli M, et al: Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction. a randomized trial*JAMA* 2005; 293:2109-2117.

133.. Kaltoft A, et al: Routine thrombectomy in percutaneous coronary intervention for acute ST-segment-elevation myocardial infarction. a randomized, controlled trial*Circulation* 2006; 114:40-47.

134.. Wang CH, et al: C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation* 2003; 107:1783-1790.

135.. Welsh RC, et al: Prehospital management of acute ST-elevation myocardial infarction. a time for reappraisal in North America*Am Heart J* 2003; 145:1-8.

136.. Le May MR, et al: A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2008; 358:231-240.

137.. Flynn A, et al: Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med* 2010; 170:1842-1849.

138.. Glickman SW, et al: Care processes associated with quicker door-in-door-out times for patients with ST-elevation-myocardial infarction requiring transfer. results from a statewide regionalization program*Circ Cardiovasc Qual Outcomes* 2011; 4:382-388.

139.. Jollis JG, et al: Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. *JAMA* 2007; 298:2371-2380.

140.. Terkelsen CJ, et al: System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010; 304:763-771.

141.. Wang TY, et al: Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA* 2011; 305:2540-2547.

142.. Holmes Jr DR, et al: Systems of care to improve timeliness of reperfusion therapy for ST-segment

elevation myocardial infarction during off hours. the Mayo Clinic STEMI protocol*JACC Cardiovasc Interv* 2008; 1:88-96.

143.. Jollis JG: Moving care forward. prehospital emergency cardiac systems*Circulation* 2010; 122:1443-1445.

144.. Kalla K, et al: Implementation of guidelines improves the standard of care. the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI Registry)*Circulation* 2006; 113:2398-2405.

145.. Danchin N: Systems of care for ST-segment elevation myocardial infarction. impact of different models on clinical outcomes*JACC Cardiovasc Interv* 2009; 2:901-908.

146.. Qasim A, et al: Safety and efficacy of nurse initiated thrombolysis in patients with acute myocardial infarction. *Brit Med J* 2002; 324:1328-1331.

147.. Henry TD, et al: The ideal reperfusion strategy for the ST-segment elevation myocardial infarction patient with expected delay to percutaneous coronary intervention. paradise lost or paradise renamed*JACC Cardiovasc Interv* 2009; 2:931-933.

148.. Danchin N, et al: Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction. data from the French registry on acute ST-elevation myocardial infarction (FAST-MI)*Circulation* 2008; 118:268-276.

149.. McMullan JT, et al: Reperfusion is delayed beyond guideline recommendations in patients requiring interhospital helicopter transfer for treatment of ST-segment elevation myocardial infarction. *Ann Emerg Med* 2011; 57:213-220.e211

150.. Kiernan TJ, et al: Facilitated percutaneous coronary intervention. current concepts, promises, and pitfalls*Eur Heart J* 2007; 28:1545-1553.

151.. Beygui F, et al: High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. *Circulation* 2006; 114:2604-2610.

152.. Van de Werf F, et al: Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology*Eur Heart J* 2008; 29:2909-2945.

153.. Ellis SG, et al: Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008; 358:2205-2217.

154.. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI). randomised trial. *Lancet* 2006; 367:569-578.

155.. Gersh BJ, et al: Pharmacological facilitation of coronary intervention in ST-segment elevation myocardial infarction. time is of the essence*JACC Cardiovasc Interv* 2010; 3:1292-1294.

156.. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO angiographic investigators. *N Engl J Med* 1993; 329:1615-1622.

157.. Gibbons RJ, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on management of patients with chronic stable angina)*J Am Coll Cardiol* 1999; 33:2092-2197.

158.. Van De Werf F, et al: Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction. the ASSENT-2 double-blind randomised trial*Lancet* 1999; 354:716-722.

159.. A comparison of reteplase with alteplase for acute myocardial infarction. The global use of strategies to open occluded coronary arteries (GUSTO III) investigators. *N Engl J Med* 1997; 337:1118-1123.

160.. Eisenberg MJ, et al: Glycoprotein IIb/IIIa inhibition in the setting of acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2003; 42:1-6.

161.. Montalescot G, et al: Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction. a meta-analysis*JAMA* 2004; 292:362-366.

162.. Stone GW, et al: Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002; 346:957-966.

163.. Stone GW, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; 358:2218-2230.

164.. Lerman A, et al: Microcirculatory dysfunction in ST-elevation myocardial infarction. cause, consequence, or both*Eur Heart J* 2007; 28:788-797.

165.. Sorajja P, et al: Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J* 2005; 26:667-674.

166.. De Luca G, et al: Adjunctive mechanical devices to prevent distal embolization in patients undergoing mechanical revascularization for acute myocardial infarction. a meta-analysis of randomized trials*Am Heart J* 2007; 153:343-353.

167.. Granger CB, et al: The search for myocardial protection. is there still hope*J Am Coll Cardiol* 2007; 50:406-408.

168.. O'Neill WW, et al: Acute myocardial infarction with hyperoxemic therapy (AMIHOT). a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention*J Am Coll Cardiol* 2007; 50:397-405.

169.. Stone PH, et al: Effect of intensive lipid lowering, with or without antioxidant vitamins, compared with moderate lipid lowering on myocardial ischemia in patients with stable coronary artery disease. the vascular basis for the treatment of myocardial ischemia study*Circulation* 2005; 111:1747-1755.

170.. Yellon DM, et al: Myocardial reperfusion injury. *N Engl J Med* 2007; 357:1121-1135.

171.. Burzotta F, et al: Clinical impact of thrombectomy in acute ST-elevation myocardial infarction. an individual patient-data pooled analysis of 11 trials*Eur Heart J* 2009; 30:2193-2203.

172.. Staat P, et al: Postconditioning the human heart. *Circulation* 2005; 112:2143-2148.

173.. Thibault H, et al: Long-term benefit of postconditioning. *Circulation* 2008; 117:1037-1044.

174.. Vinten-Johansen J, et al: Postconditioning. a simple, clinically applicable procedure to improve revascularization in acute myocardial infarction*Circulation* 2005; 112:2085-2088.

175.. Kitakaze M, et al: Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND). two randomised trials*Lancet* 2007; 370:1483-1493.

176.. Piot C, et al: Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 2008; 359:473-481.

177.. Botker HE, et al: Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction. a randomised trial*Lancet* 2010; 375:727-734.

178.. Hausenloy DJ, et al: GLP-1 therapy. beyond glucose control*Circ Heart Fail* 2008; 1:147-149.

179.. Lonborg J, et al: Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012; 33:1491-1499.

180.. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. ISIS-2. ISIS-2 (second international study of infarct survival) collaborative group. *Lancet* 1988; 2:349-360.

181.. Berger JS, et al: Initial aspirin dose and outcome among ST-elevation myocardial infarction patients treated with fibrinolytic therapy. *Circulation* 2008; 117:192-199.

182.. Goodman SG, et al: Acute ST-segment elevation myocardial infarction. American College of Chest Physicians evidence-based clinical practice guidelines (8th ed.)*Chest* 2008; 133:708S-775S.

183.. Antman EM, et al: 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. a report of the American College of Cardiology/American Heart Association task force on practice guidelines*J Am Coll Cardiol* 2008; 51:210-247.

184.. Dangas G, et al: Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty. results from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial*J Am Coll Cardiol* 2009; 54:1438-1446.

185.. Patti G, et al: Outcome comparison of 600- and 300-mg loading doses of clopidogrel in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. results from the ARMYDA-6 MI (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Myocardial Infarction) randomized study*J Am Coll Cardiol* 2011; 58:1592-1599.

186.. Wijns W, et al: Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31:2501-2555.

187.. Montalescot G, et al: Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38). double-blind, randomised controlled trial*Lancet* 2009; 373:723-731.

188.. Wiviott SD, et al: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. *Circulation* 2008; 118:1626-1636.

189.. Gibson CM, et al: Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the thrombolysis in myocardial infarction trials. *J Am Coll Cardiol* 2003; 42:7-16.

190.. Montalescot G, et al: Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction. the international randomised open-label ATOLL trial*Lancet* 2011; 378:693-703.

191.. Yusuf S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction. the OASIS-6 randomized trial*JAMA* 2006; 295:1519-1530.

192.. Teo KK, et al: Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. an overview of results from randomized controlled trials. *JAMA* 1993; 270:1589-1595.

193.. Chen ZM, et al: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction. randomised placebo-controlled trial*Lancet* 2005; 366:1622-1632.

194.. Roberts R, et al: Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) II-b study. *Circulation* 1991; 83:422-437.

195.. Freemantle N, et al: Beta blockade after myocardial infarction. systematic review and meta regression analysis*Brit Med J* 1999; 318:1730-1737.

196.. Gottlieb SS, et al: Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; 339:489-497.

197.. Wienbergen H, et al: Prognostic impact of acute beta-blocker therapy on top of aspirin and angiotensin-converting enzyme inhibitor therapy in consecutive patients with ST-elevation acute myocardial

infarction. *Am J Cardiol* 2007; 99:1208-1211.

198.. Alexander KP, et al: Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; 115:2570-2589.

199.. Faxon DP: Beta-blocker therapy and primary angioplasty. what is the controversy*J Am Coll Cardiol* 2004; 43:1788-1790.

200.. Halkin A, et al: Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol* 2004; 43:1780-1787.

201.. Kernis SJ, et al: Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty. *J Am Coll Cardiol* 2004; 43:1773-1779.

202.. Wright RS, et al: 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoraxic Surgeons*J Am Coll Cardiol* 2011; 57:e215-367.

203.. Jonassen AK, et al: Myocardial protection by insulin at reperfusion requires early administration and is mediated via AKT and p70s6 kinase cell-survival signaling. *Circ Res* 2001; 89:1191-1198.

204.. Lønborg J, et al: Exenatide reduces final infarct size in patients with ST-segment-elevation myocardial infarction and short-duration of ischemia. *Circ Cardiovasc Interv* 2012; 5:288-295.

205.. Selker HP, et al: Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes. the IMMEDIATE randomized controlled trial*JAMA* 2012; 307:1925-1933.

206.. Bøtker HE, et al: Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction. a randomised trial*Lancet* 2010; 375:727-734.

207.. Zhao YT, et al: Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction. a contemporary meta-analysis of randomised controlled trials*Heart* 2010; 96:1622-1626.

208.. Najjar SS, et al: Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction. REVEAL: a randomized controlled trial*JAMA* 2011; 305:1863-1872.

209.. Henkel DM, et al: Ventricular arrhythmias after acute myocardial infarction. a 20-year community study*Am Heart J* 2006; 151:806-812.

210.. MacMahon S, et al: Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA* 1988; 260:1910-1916.

211.. Schmitt J, et al: Atrial fibrillation in acute myocardial infarction. a systematic review of the incidence, clinical features and prognostic implications*Eur Heart J* 2009; 30:1038-1045.

212.. Sharkey SW, et al: Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005; 111:472-479.

213.. De Luca G, et al: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. every minute of delay counts*Circulation* 2004; 109:1223-1225.

214.. Holmes Jr DR, et al: Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. *Circulation* 1999; 100:2067-2073.

215.. Cotter G, et al: L-NMMA (a nitric oxide synthase inhibitor) is effective in the treatment of cardiogenic shock. *Circulation* 2000; 101:1358-1361.

216.. Hochman JS: Cardiogenic shock complicating acute myocardial infarction. expanding the paradigm*Circulation* 2003; 107:2998-3002.

217.. Alexander JH, et al: Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock. the TRIUMPH randomized controlled trial*JAMA* 2007; 297:1657-1666.

218.. Vlaar PJ, et al: Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction. a pairwise and network meta-analysis*J Am Coll Cardiol* 2011; 58:692-703.

219.. Thiele H, et al: Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 2005; 26:1276-1283.

220.. Patel MR, et al: Cardiac tamponade in the fibrinolytic era. analysis of .100,000 patients with ST-segment elevation myocardial infarction*Am Heart J* 2006; 151:316-322.

221.. Young-Xu Y, et al: Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003; 42:690-697.

222.. Lesperance F, et al: Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 2002; 105:1049-1053.

223.. Ziegelstein RC: Depression in patients recovering from a myocardial infarction. *JAMA* 2001; 286:1621-1627.

224.. Glassman AH, et al: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288:701-709.

225.. Jiang W, et al: Antidepressant therapy in patients with ischemic heart disease. *Am Heart J* 2005; 150:871-881.

226.. Hurt RD, et al: A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997; 337:1195-1202.

227.. Lavie CJ, et al: Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clin Proc* 2009; 84:373-383.

228.. Suaya JA, et al: Use of cardiac rehabilitation by medicare beneficiaries after myocardial infarction or coronary bypass surgery. *Circulation* 2007; 116:1653-1662.

229.. Thomas RJ, et al: AACVPR/ACC/AHA 2007 performance measures on cardiac rehabilitation for referral to and delivery of cardiac rehabilitation/secondary prevention services endorsed by the American College of Chest Physicians, American College of Sports Medicine, American Physical Therapy Association, Canadian Association of Cardiac Rehabilitation, European Association for Cardiovascular Prevention and Rehabilitation, Inter-American Heart Foundation, National Association of Clinical Nurse Specialists, Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2007; 50:1400-1433.

230.. de Lorgeril M, et al: Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction. final report of the Lyon diet heart study*Circulation* 1999; 99:779-785.

231.. Trichopoulou A, et al: Adherence to a mediterranean diet and survival in a Greek population. *N Engl J Med* 2003; 348:2599-2608.

232.. Dietary supplementation with ω-3 polyunsaturated fatty acids and vitamin E after myocardial infarction. Results of the gissi-prevenzione trial. Gruppo italiano per lo studio della sopravvivenza nell'infarto miocardico. *Lancet* 1999; 354:447-455.

233.. Burr ML, et al: Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction. Diet and Reinfarction trial (DART)*Lancet* 1989; 2:757-761.

234.. Welty FK: Optimal management of non-ST segment elevation myocardial infarction remains unclear. *J Am Coll Cardiol* 2000; 35:903-906.

235.. Estruch R, et al: Effects of a Mediterranean-style diet on cardiovascular risk factors. a randomized trial*Ann Intern Med* 2006; 145:1-11.

236.. Boucher F, et al: Preconditioning increases ischemic contracture in isolated rat hearts. substrate-dependent effects*J Mol Cell Cardiol* 1992; 24:S82.

237.. Hollenberg NK, et al: Is it the dark in dark chocolate. *Circulation* 2007; 116:2360-2362.

238.. Lip GY, et al: More evidence on blocking the renin-angiotensin-aldosterone system in cardiovascular disease and the long-term treatment of hypertension. data from recent clinical trials (CHARM, EUROPA, VALHEFT, HOPE-TOO and SYST-EUR2)*J Hum Hypertens* 2003; 17:747-750.

239.. Baigent C, et al: B vitamins for the prevention of vascular disease. insufficient evidence to justify treatment*JAMA* 2007; 298:1212-1214.

240.. Barrett-Connor E, et al: Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 2006; 355:125-137.

241.. von Birgelen C, et al: Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (> or =512 months) follow-up intravascular ultrasound. *Circulation* 2003; 108:2757-2762.

242.. Huikuri HV, et al: Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. *J Am Coll Cardiol* 2003; 42:652-658.

243.. Sipahi I, et al: Beta-blockers and progression of coronary atherosclerosis. pooled analysis of 4 intravascular ultrasonography trials*Ann Intern Med* 2007; 147:10-18.

244.. Dargie HJ: Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction. the CAPRICORN randomised trial*Lancet* 2001; 357:1385-1390.

245.. Pitt B, et al: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348:1309-1321.

246.. Kushner FG, et al: 2009 focused updates. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update)a report of the American College of Cardiology Foundation/American Heart Association Task Force On Practice Guidelines*Circulation* 2009; 120:2271-2306.

247.. Opie LH, et al: Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases. a critical analysis based on 100 studies*Prog Cardiovasc Dis* 2000; 43:171-196.

248.. Teo KK, et al: Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin. a systematic review*Lancet* 2002; 360:1037-1043.

249.. Kearney PM, et al: Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *Brit Med J* 2006; 332:1302-1308.

250.. McGettigan P, et al: Cardiovascular risk and inhibition of cyclooxygenase. a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2*JAMA* 2006; 296:1633-1644.

251.. Capone ML, et al: Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol* 2005; 45:1295-1301.

252.. Catella-Lawson F, et al: Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345:1809-1817.

253.. Antman EM, et al: Use of nonsteroidal antiinflammatory drugs. an update for cliniciansa scientific statement from the American Heart Association*Circulation* 2007; 115:1634-1642.

254.. Brouwer MA, et al: Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction. results of the antithrombotics in the prevention of reocclusion in coronary thrombolysis (APRICOT)-2 trial*Circulation* 2002; 106:659-665.

255.. van Es RF, et al: Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study). a randomised controlled trial*Lancet* 2002; 360:109-113.

256.. Fiore LD, et al: Department of Veterans Affairs Cooperative Studies Program clinical trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction. primary results of the CHAMP study*Circulation* 2002; 105:557-563.

257.. Hurlen M, et al: Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; 347:969-974.

258.. Andreotti F, et al: Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes. an updated and comprehensive meta-analysis of 25,307 patients*Eur Heart J* 2006; 27:519-526.

259.. Bardy GH, et al: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352:225-237.

260.. Cantillon DJ, et al: Predictive value of microvolt T-wave alternans in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2007; 50:166-173.

261.. Klingenheben T: Microvolt T-wave alternans for arrhythmia risk stratification in left ventricular dysfunction. which patients benefit*J Am Coll Cardiol* 2007; 50:174-175.

262.. Tsang TS, et al: The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota. changes over three decades*J Am Coll Cardiol* 2003; 42:93-100.

263.. Cotter G, et al: Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm. the effect of no treatment and high-dose amiodarone. A randomized, placebo-controlled study*Eur Heart J* 1999; 20:1833-1842.

264.. Podrid PJ: Redefining the role of antiarrhythmic drugs. *N Engl J Med* 1999; 340:1910-1912.

265.. Azpitarte J, et al: Value of single oral loading dose of propafenone in converting recent-onset atrial fibrillation. Results of a randomized, double-blind, controlled study. *Eur Heart J* 1997; 18:1649-1654.

266.. Camm AJ, et al: A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011; 57:313-321.

267.. Camm AJ, et al: Guidelines for the management of atrial fibrillation. the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) identifying patients at high risk for stroke despite anticoagulationa comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort*Eur Heart J* 2010; 31:2369-2429.

268.. Kowey PR, et al: Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery. a randomized, double-blind, placebo-controlled trial*Circ Arrhythm Electrophysiol* 2009; 2:652-659.

269.. Gurevitz OT, et al: Comparative efficacy of monophasic and biphasic waveforms for transthoracic cardioversion of atrial fibrillation and atrial flutter. *Am Heart J* 2005; 149:316-321.

270.. Fuster V, et al: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with

Atrial Fibrillation)developed in collaboration with the North American Society of Pacing and Electrophysiology*J Am Coll Cardiol* 2001; 38:1231-1266.

271.. Kahn HS, et al: Metabolic risks identified by the combination of enlarged waist and elevated triacylglycerol concentration. *Am J Clin Nutr* 2003; 78:928-934.

272.. De Simone A, et al: Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. *J Am Coll Cardiol* 1999; 34:810-814.

273.. Klein AL, et al: Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation. *J Am Coll Cardiol* 2001; 37:691-704.

274.. Malouf JF, et al: Critical appraisal of transesophageal echocardiography in cardioversion of atrial fibrillation. *Am J Med* 2002; 113:587-595.

275.. Imazio M, et al: Colchicine reduces postoperative atrial fibrillation. results of the colchicine for the prevention of the postpericardiotomy syndrome (COPPS) atrial fibrillation substudy*Circulation* 2011; 124:2290-2295.

276.. Chung MK, et al: Functional status in rate- versus rhythm-control strategies for atrial fibrillation. Results of the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) functional status substudy*J Am Coll Cardiol* 2005; 46:1891-1899.

277.. Singh SN, et al: Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation. a veterans affairs cooperative studies program substudy*J Am Coll Cardiol* 2006; 48:721-730.

278.. Wyse DG, et al: A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347:1825-1833.

279.. Hohnloser SH, et al: Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (PIAF). a randomised trial*Lancet* 2000; 356:1789-1794.

280.. Van Gelder IC, et al: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; 347:1834-1840.

281.. Falk RH: Management of atrial fibrillation—radical reform or modest modification. *N Engl J Med* 2002; 347:1883-1884.

282.. Van Gelder IC, et al: Rate control efficacy in permanent atrial fibrillation. a comparison between lenient versus strict rate control in patients with and without heart failure. Background, aims, and design of RACE II*Am Heart J* 2006; 152:420-426.

283.. Van Gelder IC, et al: Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010; 362:1363-1373.

284.. Brignole M: Ablate and pace. a pragmatic approach to paroxysmal atrial fibrillation not controlled by antiarrhythmic drugs*Heart* 1998; 79:531-533.

285.. Dries DL, et al: Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction. a retrospective analysis of the SOLVD trials. Studies of left ventricular dysfunction*J Am Coll Cardiol* 1998; 32:695-703.

286.. Li H, et al: Usefulness of ibutilide in facilitating successful external cardioversion of refractory atrial fibrillation. *Am J Cardiol* 1999; 84:1096-1098.A1010

287.. Oral H, et al: Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med* 1999; 340:1849-1854.

288.. Kumar S, et al: Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm* 2012; 9:483-491.

289.. Nodari S, et al: ω-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion. a prospective, randomized study*Circulation* 2011; 124:1100-1106.

290.. Le Heuzey JY, et al: A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation. the DIONYSOS study*J Cardiovasc Electrophysiol* 2010; 21:597-605.

291.. Hohnloser SH, et al: Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360:668-678.

292.. Kober L, et al: Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358:2678-2687.

293.. *Administration FDA*. FDA drug safety communication. Multaq (dronedarone): an increased risk of death and serious cardiovascular adverse events. European Medicines Agency updates on ongoing benefit-risk review of multaq, 2011.

294.. Anand K, et al: Meta-analysis. inhibition of renin-angiotensin system prevents new-onset atrial fibrillation*Am Heart J* 2006; 152:217-222.

295.. Slavik RS, et al: Pharmacologic conversion of atrial fibrillation. a systematic review of available evidence*Prog Cardiovasc Dis* 2001; 44:121-152.

296.. Dobrev D, et al: New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 2010; 375:1212-1223.

297.. Fuster V, et al: ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation —executive summary. a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation)*J Am Coll Cardiol* 2006; 48:854-906.

298.. Lip GY, et al: Identifying patients at high risk for stroke despite anticoagulation. a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort*Stroke* 2010; 41:2731-2738.

299.. Mant J, et al: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged study, BAFTA). a randomised controlled trial*Lancet* 2007; 370:493-503.

300.. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2008; 39:1901-1910.

301.. Lip GY: Identifying patients at high risk for stroke despite anticoagulation. a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort*Stroke* 2010; 41:2731-2738.

302.. Lip GY, et al: Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation. the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score*J Am Coll Cardiol* 2011; 57:173-180.

303.. Broderick JP, et al: Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. *Stroke* 2011; 42:2509-2514.

304.. Connolly SJ, et al: Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009; 360:2066-2078.

305.. Hart RG, et al: Meta-analysis. antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation*Ann Intern Med* 2007; 146:857-867.

306.. Connolly S, et al: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial

fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE W). a randomised controlled trial*Lancet* 2006; 367:1903-1912.

307.. Gersh BJ, et al: Antiplatelet and anticoagulant therapy for stroke prevention in patients with non-valvular atrial fibrillation. evidence based strategies and new developments*Rev ESP Cardiol* 2011; 64:260-268.

308.. Connolly SJ, et al: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139-1151.

309.. Eikelboom JW, et al: Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial*Circulation* 2011; 123:2363-2372.

310.. Patel MR, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883-891.

311.. Garcia-Fernandez MA, et al: Role of left atrial appendage obliteration in stroke reduction in patients with mitral valve prosthesis. a transesophageal echocardiographic study*J Am Coll Cardiol* 2003; 42:1253-1258.

312.. Holmes DR, et al: Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation. a randomised non-inferiority trial*Lancet* 2009; 374:534-542.

313.. Ostermayer SH, et al: Percutaneous left atrial appendage transcatheter occlusion (plaato system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation. results from the international multi-center feasibility trials*J Am Coll Cardiol* 2005; 46:9-14.

314.. Holmes Jr DR, et al: Left atrial appendage occlusion eliminates the need for warfarin. *Circulation* 2009; 120:1919-1926.discussion 1926

315.. Whitlock RP, et al: Left atrial appendage occlusion does not eliminate the need for warfarin. *Circulation* 2009; 120:1927-1932.discussion 1932

316.. Sundt TM, et al: Making sense of the maze. which patients with atrial fibrillation will benefit*JAMA* 2005; 294:2357-2359.

317.. Herrera Siklody C, et al: Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation. comparison of different atrial fibrillation ablation technologies in a multicenter study*J Am Coll Cardiol* 2011; 58:681-688.

318.. Calkins H, et al: Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation. two systematic literature reviews and meta-analyses*Circ Arrhythm Electrophysiol* 2009; 2:349-361.

319.. Jais P, et al: Catheter ablation versus antiarrhythmic drugs for atrial fibrillation. the A4 study*Circulation* 2008; 118:2498-2505.

320.. Wazni OM, et al: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation. a randomized trial*JAMA* 2005; 293:2634-2640.

321.. ClinicalTrials.gov Identifier: NCT00911508 Catheter Ablation vs. Anti-arrhythmic Drug therapy for Atrial Fibrillation Trial (CABANA) is ongoing.

322.. Weerasooriya R, et al: Catheter ablation for atrial fibrillation. are results maintained at 5 years of follow-up*J Am Coll Cardiol* 2011; 57:160-166.

323.. Wokhlu A, et al: Long-term outcome of atrial fibrillation ablation. impact and predictors of very late recurrence*J Cardiovasc Electrophysiol* 2010; 21:1071-1078.

324.. Cappato R, et al: Worldwide survey on the methods, efficacy, and safety of catheter ablation for

human atrial fibrillation. *Circulation* 2005; 111:1100-1105.

325.. Cha YM, et al: Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction. a comparison to systolic dysfunction and normal ventricular function*Circ Arrhythm Electrophysiol* 2011; 4:724-732.

326.. Oral H, et al: Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006; 354:934-941.

327.. Pappone C, et al: A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation. the APAF study*J Am Coll Cardiol* 2006; 48:2340-2347.

328.. Stabile G, et al: Catheter ablation treatment in patients with drug-refractory atrial fibrillation. a prospective, multi-centre, randomized, controlled study (catheter ablation for the cure of atrial fibrillation study)*Eur Heart J* 2006; 27:216-221.

329.. Wazni O, et al: Randomized study comparing combined pulmonary vein-left atrial junction disconnection and cavotricuspid isthmus ablation versus pulmonary vein-left atrial junction disconnection alone in patients presenting with typical atrial flutter and atrial fibrillation. *Circulation* 2003; 108:2479-2483.

330.. McCord JK, et al: Usefulness of intravenous magnesium for multifocal atrial tachycardia in patients with chronic obstructive pulmonary disease. *Am J Cardiol* 1998; 81:91-93.

331.. Pappone C, et al: A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med* 2003; 349:1803-1811.

332.. Zeltser D, et al: Drug-induced atrioventricular block. prognosis after discontinuation of the culprit drug*J Am Coll Cardiol* 2004; 44:105-108.

333.. Siebels J, et al: Preliminary results of the cardiac arrest study hamburg (CASH). CASH investigators. *Am J Cardiol* 1993; 72:109F-113F.

334.. Singer I, et al: Azimilide decreases recurrent ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2004; 43:39-43.

335.. Friedman PA, et al: Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis. the detect supraventricular tachycardia study*Circulation* 2006; 113:2871-2879.

336.. Connolly SJ, et al: Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators. the Optic studya randomized trial*JAMA* 2006; 295:165-171.

337.. Stevenson WG, et al: Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction. the multicenter thermocool ventricular tachycardia ablation trial*Circulation* 2008; 118:2773-2782.

338.. Kuck KH, et al: Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (vtach). a multicentre randomised controlled trial*Lancet* 2010; 375:31-40.

339.. Reddy VY, et al: Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007; 357:2657-2665.

340.. Matsumura Y, et al: Familial dilated cardiomyopathy. assessment of left ventricular systolic and diastolic function using doppler tissue imaging in asymptomatic relatives with left ventricular enlargement*Heart* 2006; 92:405-406.

341.. Dickstein K, et al: ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the heart failure association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)*Eur Heart*

J 2008; 29:2388-2442.

342.. Hunt SA, et al: 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelinesdeveloped in collaboration with the International Society for Heart and Lung Transplantation*Circulation* 2009; 119:e391-479.

343.. Lindenfeld J, et al: HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail* 2010; 16:e1-194.

344.. Yusuf S, et al: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction. the CHARM-PRESERVED trial*Lancet* 2003; 362:777-781.

345.. McMurray JJ, et al: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors. the CHARM-ADDED trial*Lancet* 2003; 362:767-771.

346.. Packer M, et al: Effect of carvedilol on the morbidity of patients with severe chronic heart failure. results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study*Circulation* 2002; 106:2194-2199.

347.. Willenheimer R, et al: Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence. results of the randomized cardiac insufficiency bisoprolol study (CIBIS) III*Circulation* 2005; 112:2426-2435.

348.. O'Connor CM, et al: Influence of global region on outcomes in heart failure beta-blocker trials. *J Am Coll Cardiol* 2011; 58:915-922.

349.. Pitt B, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999; 341:709-717.

350.. Zannad F, et al: Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364:11-21.

351.. Hunt SA, et al: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; 112:e154-235.

352.. Chan AK, et al: Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. *J Am Coll Cardiol* 2007; 50:591-596.

353.. Elkayam U, et al: Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. *Circulation* 1999; 99:2652-2657.

354.. Taylor AL, et al: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351:2049-2057.

355.. Cooper RS, et al: Should ethnicity serve as the basis for clinical trial design? Diversity and inclusiveness should remain the guiding principles for clinical trials. *Circulation* 2005; 112:3660-3665.discussion 3665–3666

356.. McNamara DM: Emerging role of pharmacogenomics in heart failure. *Curr Opin Cardiol* 2008; 23:261-268.

357.. Bardy GH, et al: Home use of automated external defibrillators for sudden cardiac arrest. *N Engl J Med* 2008; 358:1793-1804.

358.. Stevenson WG, et al: Atrial fibrillation in heart failure. *N Engl J Med* 1999; 341:910-911.

359.. Torp-Pedersen C, et al: Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med* 1999; 341:857-865.

360.. Roy D, et al: Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; 358:2667-2677.

361.. Wilton SB, et al: Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation. a systematic review and meta-analysis*Heart Rhythm* 2011; 8:1088-1094.

362.. Becker RC, et al: The primary and secondary prevention of coronary artery disease. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition)*Chest* 2008; 133:776S-814S.

363.. Massie BM, et al: Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure. the warfarin and antiplatelet therapy in chronic heart failure (WATCH) trial*Circulation* 2009; 119:1616-1624.

364.. Homma S, et al: Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012; 366:1859-1869.

365.. Julian DG, et al: Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction. EMIAT. European Myocardial Infarct Amiodarone Trial Investigators*Lancet* 1997; 349:667-674.

366.. Cairns JA: Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations. CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators*Lancet* 1997; 349:675-682.

367.. Felker GM, et al: Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; 364:797-805.

368.. Burger AJ, et al: Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure. the precedent study*Am Heart J* 2002; 144:1102-1108.

369.. Abraham WT, et al: In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications. an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE)*J Am Coll Cardiol* 2005; 46:57-64.

370.. O'Connor CM, et al: Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011; 365:32-43.

371.. Silver MA, et al: Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. *J Am Coll Cardiol* 2002; 39:798-803.

372.. Sackner-Bernstein JD, et al: Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111:1487-1491.

373.. Mentzer Jr RM, et al: Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery. the NAPA trial*J Am Coll Cardiol* 2007; 49:716-726.

374.. Witteles RM, et al: Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction; a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007; 50:1835-1840.

375.. Jones RH, et al: Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009; 360:1705-1717.

376.. Mebazaa A, et al: Levosimendan vs dobutamine for patients with acute decompensated heart failure. the SURVIVE randomized trial*JAMA* 2007; 297:1883-1891.

377.. Rouleau JL: New and emerging drugs and device therapies for chronic heart failure in patients with systolic ventricular dysfunction. *Can J Cardiol* 2011; 27:296-301.

378.. Gao R, et al: A phase II, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in patients with chronic heart failure. *J Am Coll Cardiol* 2010; 55:1907-1914.

379.. Cleland JG, et al: The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure. a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial*Lancet* 2011; 378:676-683.

380.. Buxton AE, et al: Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter unsustained tachycardia trial investigators. *N Engl J Med* 2000; 342:1937-1945.

381.. Moss AJ, et al: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346:877-883.

382.. Hohnloser SH, et al: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; 351:2481-2488.

383.. Steinbeck G, et al: Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009; 361:1427-1436.

384.. Bunch TJ, et al: Mechanisms of sudden cardiac death in myocardial infarction survivors. insights from the randomized trials of implantable cardioverter-defibrillators*Circulation* 2007; 115:2451-2457.

385.. Adabag AS, et al: Sudden death after myocardial infarction. *JAMA* 2008; 300:2022-2029.

386.. Cleland JG, et al: The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352:1539-1549.

387.. Strickberger SA, et al: Patient selection for cardiac resynchronization therapy. from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working group, in collaboration with the Heart Rhythm Society*Circulation* 2005; 111:2146-2150.

388.. Sipahi I, et al: Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy. meta-analysis of randomized controlled trials*Arch Intern Med* 2011; 171:1454-1462.

389.. Stevenson LW: A little learning is a dangerous thing. *Arch Intern Med* 2011; 171:1494-1495.

390.. Camici PG, et al: Stunning, hibernation, and assessment of myocardial viability. *Circulation* 2008; 117:103-114.

391.. Chareonthaitawee P, et al: Revascularization in severe left ventricular dysfunction. the role of viability testing*J Am Coll Cardiol* 2005; 46:567-574.

392.. Velazquez EJ, et al: Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011; 364:1607-1616.

393.. Marenzi G, et al: Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol* 2001; 38:963-968.

394.. Katz AM: Regression of left ventricular hypertrophy. new hope for dying hearts*Circulation* 1998; 98:623-624.

395.. Baughman KL, et al: Bridge to life—cardiac mechanical support. *N Engl J Med* 2007; 357:846-849.

396.. Miller LW, et al: Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007; 357:885-896.

397.. Slaughter MS, et al: Advanced heart failure treated with continuous-flow left ventricular assist

device. *N Engl J Med* 2009; 361:2241-2251.

398.. Acker MA, et al: Mitral valve repair in heart failure. five-year follow-up from the mitral valve replacement stratum of the acorn randomized trial*J Thorac Cardiovasc Surg* 2011; 142:569-574.e561

399.. Siegel RJ, et al: The acute hemodynamic effects of mitraclip therapy. *J Am Coll Cardiol* 2011; 57:1658-1665.

400.. Powell LH, et al: Self-management counseling in patients with heart failure. the heart failure adherence and retention randomized behavioral trial*JAMA* 2010; 304:1331-1338.

401.. Stevenson LW: Counting performance with therapies for heart failure. aiming for quality or quantity*Circulation* 2010; 122:561-566.

402.. Francis GS, et al: Anemia and heart failure a new pathway. *J Am Coll Cardiol* 2007; 50:1666-1667.

403.. Salisbury AC, et al: Low-to-moderate alcohol intake and health status in heart failure patients. *J Card Fail* 2005; 11:323-328.

404.. McMurray JJ, et al: Design of the reduction of events with darbepoetin alpha in heart failure (RED-HF). a phase III, anaemia correction, morbidity-mortality trial*Eur J Heart Fail* 2009; 11:795-801.

405.. Anker SD, et al: Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361:2436-2448.

406.. Cleland JG, et al: Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death. the Trans-European Network-Home-Care Management System (TEN-HMS) study*J Am Coll Cardiol* 2005; 45:1654-1664.

407.. Sisk JE, et al: Effects of nurse management on the quality of heart failure care in minority communities. a randomized trial*Ann Intern Med* 2006; 145:273-283.

408.. Peacock WF, et al: National Heart, Lung, and Blood Institute Working Group on Emergency Department Management of Acute Heart Failure. research challenges and opportunities*J Am Coll Cardiol* 2010; 56:343-351.

409.. Borlaug BA, et al: Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation* 2011; 123:2006-2013.discussion 2014

410.. Bhatia RS, et al: Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; 355:260-269.

411.. Cleland JG, et al: The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; 27:2338-2345.

412.. Mak GJ, et al: Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J Am Coll Cardiol* 2009; 54:1674-1682.

413.. Solomon SD, et al: Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction. a randomised trial*Lancet* 2007; 369:2079-2087.

414.. Mottram PM, et al: Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004; 110:558-565.

415.. Cotter G, et al: Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998; 351:389-393.

416.. Annane D, et al: Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. *Circulation* 1996; 94:1316-1324.

417.. Hamilton RJ, et al: Rapid improvement of acute pulmonary edema with sublingual captopril. *Acad*

Emerg Med 1996; 3:205-212.

418.. Khot UN, et al: Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003; 348:1756-1763.

419.. Sackner-Bernstein JD, et al: Short-term risk of death after treatment with nesiritide for decompensated heart failure. a pooled analysis of randomized controlled trials*JAMA* 2005; 293:1900-1905.

420.. Moritz F, et al: Boussignac continuous positive airway pressure device in the emergency care of acute cardiogenic pulmonary oedema. a randomized pilot study*Eur J Emerg Med* 2003; 10:204-208.

421.. Gray A, et al: Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008; 359:142-151.

422.. Gersh BJ, et al: 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons*J Am Coll Cardiol* 2011; 58:e212-260.

423.. Abozguia K, et al: Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* 2010; 122:1562-1569.

424.. Patel R, et al: Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation* 2001; 104:317-324.

425.. Semsarian C, et al: The l-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. *J Clin Invest* 2002; 109:1013-1020.

426.. Matsubara H, et al: Salutary effect of disopyramide on left ventricular diastolic function in hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 1995; 26:768-775.

427.. Sherrid MV, et al: Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. *Circulation* 1998; 97:41-47.

428.. Sorajja P, et al: Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation* 2008; 118:131-139.

429.. Olivotto I, et al: Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial. *J Am Coll Cardiol* 2007; 50:831-834.

430.. Valeti US, et al: Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 2007; 49:350-357.

431.. McLeod CJ, et al: Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J* 2007; 28:2583-2588.

432.. Ommen SR, et al: Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005; 46:470-476.

433.. Stetson SJ, et al: Cardiac hypertrophy after transplantation is associated with persistent expression of tumor necrosis factor-alpha. *Circulation* 2001; 104:676-681.

434.. van der Lee C, et al: Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. *Circulation* 2003; 108:2088-2092.

435.. Maron BJ, et al: Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000; 342:365-373.

436.. Bos JM, et al: Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. *Am J Cardiol* 2010; 106:1481-1486.

437.. Sorajja P, et al: Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. *Circulation* 2003; 108:2342-2348.

438.. Maron BJ, et al: Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007; 298:405-412.

439.. Kishimoto C, et al: Ribavirin treatment of murine coxsackievirus b3 myocarditis with analyses of lymphocyte subsets. *J Am Coll Cardiol* 1988; 12:1334-1341.

440.. Kishimoto C, et al: Prevention of murine coxsackie b3 viral myocarditis and associated lymphoid organ atrophy with recombinant human leucocyte interferon alpha a/d. *Cardiovasc Res* 1988; 22:732-738.

441.. Cooper Jr LT: *Clinical manifestations and diagnosis of myocarditis in adults*. In: Rose BD, ed. *UpToDate*, Waltham, MA; 2007.

442.. Mason JW, et al: A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. *N Engl J Med* 1995; 333:269-275.

443.. Frustaci A, et al: Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy. the TIMIC study*Eur Heart J* 2009; 30:1995-2002.

444.. Chagas' disease—an epidemic that can no longer be ignored. *Lancet* 2006; 368:619.

445.. Cooper Jr LT, et al: Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter giant cell myocarditis study group investigators. *N Engl J Med* 1997; 336:1860-1866.

446.. Cooper Jr LT, et al: Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol* 2008; 102:1535-1539.

447.. Moloney ED, et al: Transplantation for myocarditis. a controversy revisited*J Heart Lung Transplant* 2005; 24:1103-1110.

448.. Viotti R, et al: Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment. a nonrandomized trial*Ann Intern Med* 2006; 144:724-734.

449.. Bocchi EA: Heart transplants for patients with Chagas heart disease. *Sao Paulo Med J* 1995; 113:873-879.

450.. Ammash NM, et al: Clinical profile and outcome of idiopathic restrictive cardiomyopathy. *Circulation* 2000; 101:2490-2496.

451.. Ha JW, et al: Differentiation of constrictive pericarditis from restrictive cardiomyopathy using mitral annular velocity by tissue doppler echocardiography. *Am J Cardiol* 2004; 94:316-319.

452.. Feng D, et al: Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation* 2007; 116:2420-2426.

453.. Skinner M, et al: High-dose melphalan and autologous stem-cell transplantation in patients with al amyloidosis. an 8-year study*Ann Intern Med* 2004; 140:85-93.

454.. Dubrey SW, et al: Cardiac transplantation for amyloid heart disease. the United Kingdom experience*J Heart Lung Transplant* 2004; 23:1142-1153.

455.. Kpodonu J, et al: Outcome of heart transplantation in patients with amyloid cardiomyopathy. *J Heart Lung Transplant* 2005; 24:1763-1765.

456.. Dajani A, et al: Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever. a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association*Pediatrics* 1995; 96:758-764.

457.. Shapera RM, et al: Erythromycin therapy twice daily for streptococcal pharyngitis. Controlled comparison with erythromycin or penicillin phenoxymethyl four times daily or penicillin g benzathine. *JAMA* 1973; 226:531-535.

458.. Bonow RO, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons*J Am Coll Cardiol* 2006; 48:e1-148.

459.. Hein S, et al: Progression from compensated hypertrophy to failure in the pressure-overloaded human heart. structural deterioration and compensatory mechanisms*Circulation* 2003; 107:984-991.

460.. Pereira JJ, et al: Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 2002; 39:1356-1363.

461.. Carabello BA: Aortic stenosis. two steps forward, one step back*Circulation* 2007; 115:2799-2800.

462.. Rajamannan NM, et al: Calcific aortic stenosis. from bench to the bedside—emerging clinical and cellular concepts*Heart* 2003; 89:801-805.

463.. Rossebo AB, et al: Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359:1343-1356.

464.. Das S, et al: Resveratrol-mediated activation of cAMP response element-binding protein through adenosine A3 receptor by AKT-dependent and -independent pathways. *J Pharmacol Exp Ther* 2005; 314:762-769.

465.. Vincentelli A, et al: Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med* 2003; 349:343-349.

466.. Hannan EL, et al: Aortic valve replacement for patients with severe aortic stenosis. risk factors and their impact on 30-month mortality*Ann Thorac Surg* 2009; 87:1741-1749.

467.. Webb JG, et al: Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007; 116:755-763.

468.. Vahanian A, et al: Transcatheter valve implantation for patients with aortic stenosis. a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)*Eur Heart J* 2008; 29:1463-1470.

469.. Thomas M, et al: One-year outcomes of cohort 1 in the Edwards Sapien Aortic Bioprosthesis European Outcome (SOURCE) registry. the European registry of transcatheter aortic valve implantation using the Edwards Sapien valve*Circulation* 2011; 124:425-433.

470.. Leon MB, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; 363:1597-1607.

471.. Smith CR, et al: Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011; 364:2187-2198.

472.. Bauer F, et al: Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis. the Cribier-Edwards/Edwards-Sapien valve experience*J Am Soc Echocardiogr* 2010; 23:370-376.

473.. Kahlert P, et al: Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation. a diffusion-weighted magnetic resonance imaging study*Circulation* 2010; 121:870-878.

474.. Piazza N, et al: Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 fr) Corevalve Revalving System. results from the multicentre, expanded

evaluation registry 1-year following ce mark approval*EuroIntervention* 2008; 4:242-249.

475.. Kodali SK, et al: Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012; 366:1686-1695.

476.. Makkar RR, et al: Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012; 366:1696-1704.

477.. Prendergast BD, et al: Valvular heart disease. recommendations for investigation and management. Summary of guidelines produced by a working group of the British Cardiac Society and the research unit of the Royal College of Physicians*J R Coll Physicians Lond* 1996; 30:309-315.

478.. Galal O, et al: Follow-up results of balloon aortic valvuloplasty in children with special reference to causes of late aortic insufficiency. *Am Heart J* 1997; 133:418-427.

479.. Rahimtoola SH: The year in valvular heart disease. *J Am Coll Cardiol* 2010; 55:1729-1742.

480.. Fawzy ME, et al: Long-term clinical and echocardiographic results after successful mitral balloon valvotomy and predictors of long-term outcome. *Eur Heart J* 2005; 26:1647-1652.

481.. Hilliard AA, et al: The interventional cardiologist and structural heart disease. the need for a team approach*JACC Cardiovasc Imaging* 2009; 2:8-10.

482.. Messika-Zeitoun D, et al: Impact of degree of commissural opening after percutaneous mitral commissurotomy on long-term outcome. *JACC Cardiovasc Imaging* 2009; 2:1-7.

483.. Iung B, et al: Late results of percutaneous mitral commissurotomy in a series of 1024 patients. Analysis of late clinical deterioration. frequency, anatomic findings, and predictive factors*Circulation* 1999; 99:3272-3278.

484.. Borer JS, et al: Contemporary approach to aortic and mitral regurgitation. *Circulation* 2003; 108:2432-2438.

485.. Tornos P, et al: Long-term outcome of surgically treated aortic regurgitation. influence of guideline adherence toward early surgery*J Am Coll Cardiol* 2006; 47:1012-1017.

486.. le Polain de Waroux JB, et al: Functional anatomy of aortic regurgitation. accuracy, prediction of surgical repairability, and outcome implications of transesophageal echocardiography*Circulation* 2007; 116:I264-1269.

487.. Minakata K, et al: Is repair of aortic valve regurgitation a safe alternative to valve replacement. *J Thorac Cardiovasc Surg* 2004; 127:645-653.

488.. Scognamiglio R, et al: Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994; 331:689-694.

489.. Evangelista A, et al: Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med* 2005; 353:1342-1349.

490.. Rahimtoola SH: Vasodilators in aortic regurgitation. *N Engl J Med* 2006; 354:300-303.author reply 300–303

491.. Kallenbach K, et al: Decade of aortic valve sparing reimplantation. are we pushing the limits too far*Circulation* 2005; 112:I253-1259.

492.. Bhindi R, et al: Surgery insight. percutaneous treatment of prosthetic paravalvular leaks*Nat Clin Pract Cardiovasc Med* 2008; 5:140-147.

493.. Enriquez-Sarano M, et al: Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005; 352:875-883.

494.. Gammie JS, et al: Trends in mitral valve surgery in the United States. results from the Society of Thoracic Surgeons adult cardiac surgery database*Ann Thorac Surg* 2009; 87:1431-1437.discussion

1437–1439

495.. Flameng W, et al: Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. *J Thorac Cardiovasc Surg* 2008; 135:274-282.

496.. Gillinov AM, et al: Valve repair versus valve replacement for degenerative mitral valve disease. *J Thorac Cardiovasc Surg* 2008; 135:885-893.

497.. Feldman T, et al: Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; 364:1395-1406.

498.. Feldman T, et al: Prospects for percutaneous valve therapies. *Circulation* 2007; 116:2866-2877.

499.. Han MK, et al: Pulmonary diseases and the heart. *Circulation* 2007; 116:2992-3005.

500.. Mancini GB, et al: Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006; 47:2554-2560.

501.. Klings E: *Cor pulmonale*. In: Rose B, ed. *Uptodate*, Waltham, Mass; 2011.

502.. Galie N, et al: Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25:2243-2278.

503.. Puri A, et al: Pulmonary arterial hypertension. current therapeutic strategies*Nat Clin Pract Cardiovasc Med* 2007; 4:319-329.

504.. Fuster V, et al: Primary pulmonary hypertension. natural history and the importance of thrombosis*Circulation* 1984; 70:580-587.

505.. Galie N, et al: A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J* 2009; 30:394-403.

506.. Mayer E, et al: Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension. results from an international prospective registry*J Thorac Cardiovasc Surg* 2011; 141:702-710.

507.. Sitbon O, et al: Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111:3105-3111.

508.. Rich S, et al: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327:76-81.

509.. Barst RJ, et al: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334:296-302.

510.. Runo JR, et al: Primary pulmonary hypertension. *Lancet* 2003; 361:1533-1544.

511.. Lang I, et al: Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest* 2006; 129:1636-1643.

512.. Rubin LJ, et al: Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346:896-903.

513.. Barst RJ, et al: Treatment of pulmonary arterial hypertension with the selective endothelin-a receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006; 47:2049-2056.

514.. Michelakis ED, et al: Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. *Circulation* 2003; 108:2066-2069.

515.. Galie N, et al: Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J*

Med 2005; 353:2148-2157.

516.. Affuso F, et al: Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension. *Int J Cardiol* 2006; 108:429-431.

517.. Sakao S, et al: Reversible or irreversible remodeling in pulmonary arterial hypertension. *Am J Respir Cell Mol Biol* 2010; 43:629-634.

518.. Moreillon P, et al: Infective endocarditis. *Lancet* 2004; 363:139-149.

519.. Baddour LM, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111:e394-434.

520.. Horstkotte D, et al: Guidelines on prevention, diagnosis and treatment of infective endocarditis, executive summary. the Task Force on Infective Endocarditis of the European Society of Cardiology*Eur Heart J* 2004; 25:267-276.

521.. Vikram HR, et al: Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis. a propensity analysis*JAMA* 2003; 290:3207-3214.

522.. Steg PG, et al: One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; 297:1197-1206.

523.. Bannay A, et al: The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis. do differences in methodological approaches explain previous conflicting results*Eur Heart J* 2011; 32:2003-2015.

524.. Thuny F, et al: The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis. a propensity analysis*Eur Heart J* 2011; 32:2027-2033.

525.. Kim DH, et al: Impact of early surgery on embolic events in patients with infective endocarditis. *Circulation* 2010; 122:S17-22.

526.. Anavekar NS, et al: Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. *Clin Infect Dis* 2007; 44:1180-1186.

527.. Gould FK, et al: Guidelines for the prevention of endocarditis. report of the working party of the British Society for Antimicrobial Chemotherapy*J Antimicrob Chemother* 2006; 57:1035-1042.

528.. Wilson W, et al: Prevention of infective endocarditis. guidelines from the American Heart Associationa guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia,and the Quality of Care and Outcomes Research Interdisciplinary Working Group*Circulation* 2007; 116:1736-1754.

529.. Burns P, et al: Management of peripheral arterial disease in primary care. *Brit Med J* 2003; 326:584-588.

530.. Bhatt DL, et al: Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the charisma trial. *J Am Coll Cardiol* 2007; 49:1982-1988.

531.. Adam DJ, et al: Bypass versus angioplasty in severe ischaemia of the leg (BASIL). multicentre, randomised controlled trial*Lancet* 2005; 366:1925-1934.

532.. Wain RA, et al: Analysis of endovascular graft treatment for aortoiliac occlusive disease. what is its role based on midterm results*Ann Surg* 1999; 230:145-151.

533.. Rooke TW, et al: 2011 ACCF/AHA focused update of the Guideline for the Management of Patients with Peripheral Artery Disease (updating the 2005 guideline). a report of the American College of

Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*J Am Coll Cardiol* 2011; 58:2020-2045.

534.. Girolami B, et al: Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl. a meta-analysis*Arch Intern Med* 1999; 159:337-345.

535.. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Caprie steering committee. Caprie steering committee. *Lancet* 1996; 348:1329-1339.

536.. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7-22.

537.. Yusuf S, et al: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000; 342:145-153.

538.. Rajagopalan S, et al: Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease. a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication*Circulation* 2003; 108:1933-1938.

539.. Belch J, et al: Effect of fibroblast growth factor NV1FGF on amputation and death. a randomised placebo-controlled trial of gene therapy in critical limb ischaemia*Lancet* 2011; 377:1929-1937.

540.. Gupta R, et al: Cell therapy for critical limb ischemia. moving forward one step at a time*Circ Cardiovasc Interv* 2011; 4:2-5.

541.. Idei N, et al: Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in patients with critical limb ischemia. a comparison of atherosclerotic peripheral arterial disease and buerger disease*Circ Cardiovasc Interv* 2011; 4:15-25.

542.. Thompson PD, et al: Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. *Am J Cardiol* 2002; 90:1314-1319.

543.. Dawson DL, et al: A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med* 2000; 109:523-530.

544.. Hirsch AT, et al: ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). a collaborative report from the American Association For Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Transatlantic Inter-Society Consensus; and Vascular Disease Foundation*Circulation* 2006; 113:e463-654.

545.. Norgren L, et al: Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45(Suppl S):S5-67.

546.. De Backer T, et al: Naftidrofuryl for intermittent claudication. meta-analysis based on individual patient data*Brit Med J* 2009; 338:b603.

547.. Pittler MH, et al: Ginkgo biloba extract for the treatment of intermittent claudication. a meta-analysis of randomized trials*Am J Med* 2000; 108:276-281.

548.. Mohler E: *Medical management of claudication*. In: Rose B, ed. *Uptodate*, Waltham, Mass; 2011.

549.. Radack K, et al: Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1991; 151:1769-1776.

550.. Bagger JP, et al: Effect of verapamil in intermittent claudication; a randomized, double-blind, placebo-controlled, cross-over study after individual dose-response assessment. *Circulation* 1997; 95:411-414.

551.. Coppock JS, et al: Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; 62:15-18.

552.. Wigley F: *Pharmacologic and surgical treatment of the Raynaud's phenomenon*. In: Rose B, ed. *Uptodate*, Waltham, Mass; 2011.

553.. Maga P, et al: Long-term effects of thoracic sympathectomy on microcirculation in the hands of patients with primary Raynaud's disease. *J Thorac Cardiovasc Surg* 2007; 133:1428-1433.

554.. Ting JC, et al: Treatment of refractory ischemic pain from chemotherapy-induced Raynaud's syndrome with spinal cord stimulation. *Pain Pract* 2007; 7:143-146.

555.. Wooley JA: Characteristics of thiamin and its relevance to the management of heart failure. *Nutr Clin Pract* 2008; 23:487-493.

556.. Field JM, et al: Part 1. Executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*Circulation* 2010; 122:S640-656.

557.. Stiell IG, et al: Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med* 2011; 365:787-797.

558.. Ewy GA: Continuous-chest-compression cardiopulmonary resuscitation for cardiac arrest. *Circulation* 2007; 116:2894-2896.

559.. SOS-KANTO study group. Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO). an observational study*Lancet* 2007; 369:920-926.

560.. Iwami T, et al: Effectiveness of bystander-initiated cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation* 2007; 116:2900-2907.

561.. Neumar RW, et al: Implementation strategies for improving survival after out-of-hospital cardiac arrest in the United States. consensus recommendations from the 2009 American Heart Association Cardiac Arrest Survival Summit*Circulation* 2011; 123:2898-2910.

562.. Mazer SP, et al: Reverse CPR. a pilot study of CPR in the prone position*Resuscitation* 2003; 57:279-285.

563.. Geddes LA, et al: A new cardiopulmonary resuscitation method using only rhythmic abdominal compression. a preliminary report*Am J Emerg Med* 2007; 25:786-790.

564.. de Vries W, et al: Trained first-responders with an automated external defibrillator. how do they perform in real resuscitation attempts*Resuscitation* 2005; 64:157-161.

565.. Hallstrom AP, et al: Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med* 2004; 351:637-646.

566.. Agarwal DA, et al: Ventricular fibrillation in Rochester, Minnesota. experience over 18 years*Resuscitation* 2009; 80:1253-1258.

567.. Bunch TJ, et al: Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med* 2003; 348:2626-2633.

568.. Berdowski J, et al: Chest compressions cause recurrence of ventricular fibrillation after the first successful conversion by defibrillation in out-of-hospital cardiac arrest. *Circ Arrhythm Electrophysiol* 2010; 3:72-78.

569.. Eftestol T, et al: Predicting outcome of defibrillation by spectral characterization and nonparametric classification of ventricular fibrillation in patients with out-of-hospital cardiac arrest. *Circulation* 2000; 102:1523-1529.

570.. Simpson PM, et al: Delayed versus immediate defibrillation for out-of-hospital cardiac arrest due to ventricular fibrillation. a systematic review and meta-analysis of randomised controlled trials*Resuscitation* 2010; 81:925-931.

571.. Young C, et al: Amplitude spectrum area. measuring the probability of successful defibrillation as applied to human data*Crit Care Med* 2004; 32:S356-358.

572.. Ali B, et al: Narrative review. cardiopulmonary resuscitation and emergency cardiovascular carereview of the current guidelines*Ann Intern Med* 2007; 147:171-179.

573.. Dorian P, et al: Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; 346:884-890.

574.. Kudenchuk PJ, et al: Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341:871-878.

575.. Tzivoni D, et al: Treatment of torsade de pointes with magnesium sulfate. *Circulation* 1988; 77:392-397.

576.. Lloyd-Jones D, et al: Executive summary. heart disease and stroke statistics—2010 updatea report from the American Heart Association*Circulation* 2010; 121:948-954.

577.. Nichol G, et al: Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; 300:1423-1431.

578.. McIntyre KM: Vasopressin in asystolic cardiac arrest. *N Engl J Med* 2004; 350:179-181.

579.. Bunch TJ, et al: Trends in treated ventricular fibrillation out-of-hospital cardiac arrest. a 17-year population-based study*Heart Rhythm* 2004; 1:255-259.

580.. Management of cardiac arrest. AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005; 112:IV-58-IV-66.

581.. Bakris GL: Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. *Mayo Clin Proc* 2011; 86:444-456.

582.. Criley JM, et al: Cough-induced cardiac compression. Self-administered from of cardiopulmonary resuscitation. *JAMA* 1976; 236:1246-1250.

583.. Dumas F, et al: Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients? Insights from a large registry. *Circulation* 2011; 123:877-886.

584.. Lampe JW, et al: State of the art in therapeutic hypothermia. *Annu Rev Med* 2011; 62:79-93.

586.. Sunde K, et al: Therapeutic hypothermia after cardiac arrest. where are we now*Curr Opin Crit Care* 2011; 17:247-253.

587.. Fugate JE, et al: Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors. *Neurology* 2011; 77:1346-1350.

588.. Sayre MR, et al: On behalf of the Adult Basic Life Support Chapter Collaborators. Part 5. adult basic life support2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations*Circulation* 2010; 122(Suppl. 2):S298-S324.

589.. Anderson JL, et al: 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*Circulation* 2011; 123:e426-579.

590.. Blomström-Lundqvist C, et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of

Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Supraventricular Arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol* 2003; 42:1493-1531.

591.. Zipes DP, et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death)developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society*Circulation* 2006; 114:e385-484.

592.. Nishimura RA, et al: ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; 118:887-896.

593.. Habib G, et al: ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; 30:2369-2413.

594.. Wittstein IS, et al: Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; 352:539-548.

595.. You JJ, et al: Antithrombotic therapy for atrial fibrillation. antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines*Chest* 2012; 141(Suppl. 2):e531S-575S.

596.. Granger CB, et al: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981-992.

597.. Westheim AS, et al: Hemodynamic and neuroendocrine effects for candoxatril and frusemide in mild stable chronic heart failure. *J Am Coll Cardiol* 1999; 34:1794-1801.

Copyright © 2013 Elsevier Inc. All rights reserved. Read our Terms and Conditions of Use and our Privacy Policy.
For problems or suggestions concerning this service, please contact: online.help@elsevier.com