Facts and principles learned at the 31st Annual Williamsburg Conference on Heart Disease

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The December 2003 conference on heart disease in Williamsburg, Virginia, was the 31st such conference to be held in that city and has been directed by one of us (WCR) since it began in 1972. The conference usually attracts about 200 enrollees, most of whom are repeat attendees. The conference provides 19.75 hours of continuing medical education credit, and nearly all of the speakers are nationally and/or internationally recognized. It is one of the longest-running cardiology courses sponsored by the American College of Cardiology. Its unique feature is that each presentation is 90 minutes, which allows most speakers to discuss more than one topic and answer questions.

The proceedings of the December 2002 conference were summarized in the April 2003 issue of *Baylor University Medical Center Proceedings*, and this issue attempts to summarize the proceedings of the December 2003 conference. We took extensive notes during the latest conference and met on many occasions to reproduce as accurately as possible what was said by the presenters. This year's summary also provides many references to the topics discussed.

VASCULAR BIOLOGY OF CORONARY RISK FACTORS

Robert A. Vogel, MD

1. *Cardiovascular disease and endothelial function.* Endothelial cell dysfunction, which is reversible, leads to atherosclerosis. It is worsened by hyperlipidemia, hypertension, diabetes mellitus, obesity, and cigarette smoking. Endothelial cell function declines with age unless high levels of physical activity are maintained; physical activity preserves normal endothelial cell function (1–3). High-fat foods acutely decrease endothelial cell function; eating the average fast-food meal reduces endothelial cell function as much as smoking 2 cigarettes. Endothelial cell dysfunction does not occur when an active nonsmoking patient's LDL cholesterol is <80 mg/dL, systolic BP is <120 mm Hg, and BMI is 20 to 25 kg/m². A good marriage, a pet dog, and a good laugh now and then improve endothelial cell function and prolong survival.

2. *Cardiovascular disease and obesity.* Total mortality begins to increase at a BMI of 25 kg/m² in Americans, at 22 kg/m² in Indians, and at 23 kg/m² in Pacific Islanders (4). Obesity causes cardiovascular disease to occur about 10 years earlier than in individuals of the same age who are of normal weight. Levels of C-reactive protein decrease by about 50% if a person loses 30 pounds (14 kg) (5). An overweight but physically fit person, however, is actually healthier than a lean but physically unfit person.

Abbreviations used:

ACE, angiotensin-converting enzyme	ICD, implantable cardiac defibrillator
ACS, acute coronary syndrome	INR, international normalized ratio
AF, atrial fibrillation	LDL, low-density lipoprotein
AMI, acute myocardial infarction	LMWH, low-molecular-weight heparin
AR, aortic regurgitation	MR, mitral regurgitation
ARB, angiotensin receptor blocker	MRI, magnetic resonance imaging
AS, aortic stenosis	MS, mitral stenosis
AVR, aortic valve replacement	PCI, percutaneous coronary intervention
BMI, body mass index	PET, positron emission tomography
BP, blood pressure	SCD, sudden cardiac death
CABG, coronary artery bypass grafting	SPECT, single photon emission computed tomography
CAD, coronary artery disease	UAP, unstable angina pectoris
CT, computed tomography	UFH, unfractionated heparin
HDL, high-density lipoprotein	
HF, heart failure	

3. *Cardiovascular disease and lipids.* Endothelial cell function is normal when the serum LDL cholesterol is ≤60 mg/dL and is clearly abnormal when the LDL cholesterol is >100 mg/dL (6). Atherosclerotic progression can be seen with LDL values as low as 80 mg/dL. Endothelial cell function improves when LDL cholesterol is lowered from 100 to 50 mg/dL. The LDL cholesterol level for a person's last 5 years determines his or her risk of cardiovascular disease. If a 65-year-old person who had a serum LDL cholesterol of 160 mg/dL from age 30 to age 60 lowered it to 100 mg/dL from age 60, he or she would have the same risk as a 65-year-old person who always had an LDL cholesterol of 100 mg/dL! Endothelial cell function is significantly influenced by HDL cholesterol; an HDL cholesterol ≥85 mg/dL is best for reversing endothelial dysfunction (7). Patients with low HDL cholesterol levels benefit the most from statin therapy. Atheroma regression, as determined by intravascular ultrasonic imaging, occurs within 6 weeks in patients receiving infusions of recombinant HDL (8).

4. *Dietary concepts in cardiovascular disease.* The average dress size in France is a 6 and in the USA, 14. The portion sizes in French restaurants are 25% smaller than those in US restaurants. Calories in snacks are mostly fat and sugar; the average American adult eats 150 kcal/day in snacks. Beverages can also be high-

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calorie foods; the average American adult drinks 400 kcal of soft drinks each day. Never eat between meals or drink sugar! One alcoholic drink a day is good for the heart; the type of beverage (wine, beer, or liquor) makes no difference.

5. *Concepts in weight loss.* Decreasing dietary intake by 100 kcal/day results in a 25- to 50-pound weight loss over 5 years. Start meals with a beverage, soup, or salad and eat smaller portions of the main course. Eat more slowly and avoid snacking. Be aware of the glycemic index: pasta and grains are better than potatoes and white bread. Physical activity is important in maintaining ideal weight, endothelial cell function, and overall cardiovascular health. Type 2 diabetes can be prevented, with few exceptions, by maintaining ideal body weight throughout adulthood (9, 10).

6. *Cigarette smoking.* With each cigarette, 7 minutes of life are lost! Thus, 20 cigarettes (1 pack) shorten life span by 140 minutes. One pack daily for a year shortens life span by 35 days, and that amount over a decade shortens life span by 1 year.

SYSTEMIC HYPERTENSION

Daniel Levy, MD

1. No specific peak systolic or end-diastolic BP number separates normotension from hypertension. Beginning around 115/75 mm Hg, the risk of cardiovascular disease doubles for each increase of 20 mm Hg systolic and 10 mm Hg diastolic (11). Thus, BP is a continuum. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (12) proposed the following definitions of systemic BP (in mm Hg): normal BP, <120/80; prehypertension, 120–139/80–89; stage I hypertension, 140–159/90–99; and stage II hypertension, >160/100. Thiazide diuretics are considered the first-line agents (13). Most patients require >2 drugs to reduce their BP to “prehypertensive” levels. Therapy might best begin with 2 agents simultaneously when the systolic BP is >160 mm Hg or the diastolic pressure >100 mm Hg in nondiabetics or when systolic BP is >150 mm Hg or diastolic >90 mm Hg in patients with diabetes mellitus.

2. Systolic BP increases linearly throughout life, regardless of the starting level. Diastolic BP increases to age 50, is level from age 50 to 60, and then declines after age 60 years (14). Isolated diastolic hypertension is most common in patients in their 30s and decreases at age 91. Contrary to older teachings, isolated systolic hypertension is not a normal part of aging and *does* need treatment (14).

3. In patients >60 years of age with isolated systolic hypertension (systolic BP >160 mm Hg and diastolic BP <90 mm Hg), lowering the systolic BP by about 10 mm Hg with medications decreases the incidence of stroke by about 40%, CAD by about 30%, and HF by about 40% (15, 16).

4. The decreased number of cardiovascular events occurring in hypertensive patients on antihypertensive drugs is due to the BP lowering, irrespective of which drugs provided that lowering. In a recent large trial, a diuretic (chlorthalidone), an ACE inhibitor (lisinopril), and a calcium antagonist (amlodipine) produced similar degrees of BP lowering and similar decreases in cardiovascular events (13).

5. Obstacles to BP control include *lack of awareness* (only about 70% of patients are aware of their hypertension), *lack of treatment* (only about 60% are treated), and *lack of adequate treat-*

ment (only about 30% are at BP goal) (17). Despite 5 years of close follow-up in a recent trial, only 67% of patients achieved their BP goal of <140/90 mm Hg (13).

6. Diastolic BP is much easier to control than systolic BP. Only about 70% of patients aged <60, 50% of those aged 61 to 75, and 35% of those aged >75 years have their peak systolic pressures lowered by antihypertensive drugs to <140 mm Hg (17).

7. If systemic hypertension were better controlled or eliminated, the frequency of chronic HF would drop about 50% (18, 19). HF that develops after AMI is of the systolic type; HF that develops in the setting of systemic hypertension not associated with AMI, in contrast, is usually of the diastolic type (20–22). Thus, treating hypertension is one of the best means of preventing chronic HF!

EFFECTIVE LONG-TERM WEIGHT MANAGEMENT AND ITS IMPORTANCE

John P. Foreyt, PhD

1. *Obesity in the USA.* Two thirds of Americans are overweight, and half of them are obese. In 1976, 47% of Americans were overweight or obese; by 1988, 56%; and by 1999, 64%. The average American is 25 pounds (11 kg) heavier than his or her same-sex great-great-grandparent was at the same age. The average Civil War (1861–1865) soldier was 68 inches (172 cm) tall and weighed 146 pounds (66 kg); the average American man today is also 68 inches tall but weighs 171 pounds (77 kg). We all tend to overestimate our height and underestimate our weight. In the past 10 years, the average American adult has increased fat consumption by 26 g/day and now consumes about 3400 kcal/day.

2. *The metabolic syndrome.* Over 50 million and perhaps 75 million Americans meet criteria for the metabolic syndrome, namely three of the following: 1) abdominal obesity (waist size >40 inches in men or >35 inches in women), 2) triglycerides ≥150 mg/dL, 3) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, 4) systemic hypertension (BP >130/85 mm Hg), and 5) fasting blood glucose >110 mg/dL. Weight loss decreases BP and serum LDL cholesterol, triglycerides, insulin, and glucose and increases HDL cholesterol!

3. *Weight loss.* The key factors in the development of obesity are excessive food portion sizes and lack of exercise (23). The chance of developing diabetes mellitus falls nearly 60% with a low-fat diet and 150 minutes per week of exercise. It's not fat, protein, or carbohydrates that make people obese; it's calories! Fad diets work, but the weight usually returns because of a lack of lifestyle modification. One simple strategy for effective weight loss is the 100/100 plan: eat 100 fewer kcal/day (1 cookie or 3 bites of a hamburger) and increase exercise by 100 kcal/day (walk 20 minutes per day). Strength training works as well as aerobics for weight loss, and multiple short bouts of exercise are as good as a long bout for weight loss. Longer bouts of aerobic exercise, however, are better for cardiovascular fitness.

4. *Behavioral strategies for weight loss.* The most important strategy is *self-monitoring*, which includes daily weighing and daily recording of all calories ingested (food diary). The average adult underreports calories consumed by one third and overreports exercise by 50%! The second most important is *stimulus control*: avoid snacking and eating too quickly or too slowly. Third is *cognitive restructuring*: expectations must be realistic, such as 10% weight loss (about 20 pounds) as a first goal. The average person wants

to lose 37% of body weight; this type of goal is unrealistic. The 100/100 plan is a realistic option that should provide a 20-pound weight loss in a year. Fourth is *stress management*: physical activity and relaxation techniques such as meditation can reduce stress and decrease snacking. Fifth is *social support*: eat healthily and exercise together with family or friends.

5. *Medical treatment for obesity*. *Sibutramine* (Meridia), a selective serotonin and norepinephrine reuptake inhibitor, enhances satiety in some patients (24). *Orlistat* (Xenical) blocks fat absorption in the gut by about 30%. Both of these drugs provide a modest (10-pound) weight loss in most patients but are ineffective at achieving more significant weight loss. Gastric bypass is now the treatment of choice for morbid obesity (BMI >40 kg/m²).

6. *Obesity and the environment*. Obesity is a problem of the American “toxic” environment; the problem is fast food, huge portions, and sedentary lifestyle (23). We need to focus on prevention of obesity in the young because once present, obesity is hard to overcome.

DEFINING QUALITY IN MEDICAL TREATMENT

Robert M. Califf, MD

1. *Elements of quality medical care*. Care must be safe, effective, timely, efficient, equitable, and patient-centered. Cardiology presently cannot provide all 6 components.

2. *Life expectancy*. Women born today in the USA have a mean life expectancy of 85 years and men, 80 years. In contrast, the life expectancy of Americans in 1900 was 47 years. With each passing decade, life expectancy in the USA increases by 2 years. Today, only 10% of the population is ≥65 years of age, but that amounts to 30 million people. By 2030, it is predicted that 20%, or 70 million Americans, will be ≥65 years of age (25).

3. *Upcoming shortage of cardiologists*. Because of the increasing number of older persons, cardiovascular disease will be increasing over the next 10 to 20 years. In the meantime, the proportion of cardiologists to population is decreasing despite a continual increase in demand for cardiovascular services (25).

4. *Increasing health care costs*. US health care costs in 2000 were \$1.2 trillion. These costs continue to increase because of expensive technological innovations and increasing demands of patients, despite the efforts of government, employers, and insurance companies to limit costs.

5. *Improving quality decision making*. Decisions are made in the hippocampus, the area of the brain most influenced by images and emotion. Performance indicators of quality care are now being linked to reimbursement by Medicare. Hospitals' mortality rates correlate to the performance of their physicians on these indicators.

RESULTS OF RECENT TRIALS OF PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AFTER ACUTE MYOCARDIAL INFARCTION

Robert M. Califf, MD

1. *Captopril* (50 mg 3 times daily), the most commonly used ACE inhibitor in the world, proved superior to *losartan* (50 mg daily) for patients with left ventricular systolic dysfunction after AMI, probably because of inadequate dosing of *losartan* (OPTIMAAL) (26).

2. *Captopril* (6.25 to 50 mg 3 times daily), *valsartan* (20 to 160 mg twice daily) or *both* (with aggressive dose up-titration in

all groups) were compared prospectively in these patients, and no statistically significant differences in mortality were seen in any of the 3 groups (VALIANT) (27). While cough and angioedema were more common in the captopril group, hypotension and creatinine elevation were more common in the valsartan group. Those in the combination group (captopril and valsartan) had more side effects than either single-drug group without any additional benefits. Surprisingly, only about 50% of patients with decreased left ventricular systolic function after AMI are actually receiving an ACE inhibitor or ARB.

3. The reason the ARB was equivalent to the ACE inhibitor in VALIANT but not in OPTIMAAL is likely to be the aggressive up-titration of the ARB dose in VALIANT. Using the maximal tolerated dose is important in obtaining the maximal clinical benefit for these patients.

4. *Eplerenone* (25–50 mg daily), an aldosterone antagonist similar to *spironolactone* but with fewer side effects, proved superior to placebo in patients with depressed left ventricular ejection fractions after AMI (EPHESUS) (28).

RESULTS OF RECENT TRIALS ON THERAPIES FOR CHRONIC HEART FAILURE

Robert M. Califf, MD

Candesartan proved superior to placebo for patients with chronic HF who could not tolerate ACE inhibitors (CHARM—Alternative) (29). The combination of *candesartan* and an ACE inhibitor was better than an ACE inhibitor alone, with or without a beta-blocker (CHARM—Added). HF patients with a left ventricular ejection fraction >40% tended to do better with *candesartan* than placebo (CHARM—Preserved). The results of these and other trials are now being adapted into quality indicators to measure physicians' and hospitals' abilities to deliver quality medical care, and these indicators soon will determine reimbursement rates.

MANAGEMENT OF ACUTE CORONARY SYNDROMES

William E. Boden, MD

1. *Medical therapy for ACS*. ACS is a term used to refer to UAP and AMI, both ST elevation and non-ST elevation. The ABCDEs of ACS management include the following:

- A: antiplatelet, ACE inhibition, anticoagulation
- B: BP control, beta-blockade
- C: cholesterol control, cigarette cessation
- D: diabetes control, dietary modification
- E: exercise, education

The use of *aspirin* for UAP decreases additional cardiovascular events in 5 years by nearly 50% (30). The 81-mg and 325-mg doses appear to be equally effective. *UFH* added to *aspirin* in ACS may be beneficial, but in a metaanalysis of 6 studies, the difference was statistically insignificant. *Clopidogrel* provided a slightly better risk reduction than did *aspirin* in ACS patients (CAPRIE) (31). *Clopidogrel* added to *aspirin* proved better than *aspirin* alone, and the benefit was not offset by the slight increase in bleeding seen in the combination group (CURE) (32). When given prior to PCI, *clopidogrel* provided a 30% relative risk reduction compared with *aspirin* alone (PCI-CURE) (33). The benefit of *clopidogrel* was greatest when initiated >6 hours before PCI (CREDO) (34).

LMWH for ACS decreases the frequency of death, AMI, and revascularization better than UFH, and the highest-risk patients derive more benefit than the lower-risk patients (ESSENCE and TIMI 11B trials) (35).

Direct thrombin inhibitors provide a 10% better risk reduction for death and AMI than UFH (36). For patients having PCI, *bivalirudin*, another direct thrombin inhibitor, had a slight benefit compared with combined UFH and a *glycoprotein IIB/IIIA inhibitor* (REPLACE II), the benefit resulting entirely from a decrease in major bleeding with bivalirudin.

The “upstream” administration of a glycoprotein IIB/IIIA inhibitor (*tirofiban* or *eptifibatide* but not *abciximab*) combined with UFH early after onset of the ACS, whether or not PCI was planned, is better than UFH alone (PRISM-PLUS, PURSUIT, GUSTO-IV). The higher-risk patients received more benefit than the lower-risk patients, as did diabetics compared with nondiabetics and those who had PCI vs those who did not. For ACS patients undergoing PCI, the benefit of *abciximab* has been established in multiple studies (EPIC, EPILOG, CAPTURE, EPISTENT).

2. *PCI in ACS.* Among men with ST depression or positive troponin during hospitalization for ACS, those allocated to cardiac catheterization early had better outcomes than those treated medically who were later studied in the cardiac catheterization laboratory only if at very high risk or if complications developed. This early invasive strategy was not beneficial in women (FRISC-II, TACTICS/TIMI-18, RITA-3).

3. *Lipids in ACS: “lower is better.”* After coronary bypass, patients treated with lovastatin 20 mg/day whose LDL cholesterol was <90 mg/dL did better than those with LDL cholesterol levels between 100 and 135 mg/dL. A trial comparing 341 patients with stable angina pectoris randomized to atorvastatin 80 mg (46% LDL lowering) vs PCI plus “usual care” (18% LDL lowering) disclosed better outcomes at 6 months in the atorvastatin arm (AVERT). In another trial of patients with ACS comparing atorvastatin 80 mg/day vs placebo, those receiving the atorvastatin had better outcomes at 16 weeks (mean LDL decrease from 124 to 72 mg/dL) (MIRACL). In a study of patients after PCI, those treated with fluvastatin 80 mg daily had a 22% relative risk reduction over placebo-treated patients (LIPS).

In the study comparing simvastatin 40 mg daily to placebo in >20,000 high-risk patients, most of whom had had an atherosclerotic event and nearly a third of whom had diabetes mellitus, those with baseline LDL cholesterol levels <100 mg/dL, 100–130 mg/dL, and >130 mg/dL all had similar outcomes (36% relative risk reduction in 5 years) (Heart Protection Study). A trial combining simvastatin with niacin demonstrated angiographic regression of plaque with therapy (HATS).

NONINVASIVE ASSESSMENT OF MYOCARDIAL VIABILITY IN PATIENTS WITH CORONARY ARTERY DISEASE AND SEVERE LEFT VENTRICULAR DYSFUNCTION

George A. Beller, MD

Left ventricular dysfunction can be due to ischemic causes, namely, scar (healed myocardial infarct), stunning (myocardial dysfunction following transient ischemia), or hibernation (myocardial dysfunction due to chronic ischemia in viable tissue), or to nonischemic causes (e.g., habitual alcoholism, systemic hyper-

tension, cardiac valvular disease). The concept of hibernation was popularized by Rahimtoola et al when they demonstrated improvement in the left ventricular ejection fraction after CABG (37). About 60% of patients with HF from CAD have hibernating myocardium. The purpose of viability assessment is to detect hibernating myocardium in patients with left ventricular dysfunction and identify those who may have improved outcomes after revascularization (38, 39).

Viability can be assessed by radionuclide perfusion imaging/SPECT, PET, dobutamine echocardiography, contrast echocardiography, and MRI (40–60). Of the 2 most common methods, dobutamine echocardiography has a higher specificity while SPECT has a higher sensitivity. SPECT can be performed with thallium-201 or technetium-99m; both have similar positive predictive values (about 0.7) and negative predictive values (about 0.8). MRI has the unique ability to visualize and quantify myocardial scar by detecting “delayed hyperenhancement.” In one study, 55% of patients with myocardial scar by MRI had normal fluorodeoxyglucose PET scans. The extent of myocardial scar present predicts a patient’s response to beta-blockade for HF. Those with larger scars show the least improvement.

Patients with positive viability studies have an 80% lower mortality rate with revascularization compared with medical management. Patients receiving medical therapy with a negative viability study have a 60% lower mortality rate than medically treated patients with positive viability studies due to their extensive myocardium at risk. Patients with lower ejection fractions and viable myocardium derive the most benefit from revascularization. In one study, hospital mortality after CABG was higher in patients with low ejection fractions and poor viability (11%) than in those with low ejection fractions and good viability (0%). Patients with viable myocardium improve their functional class on average from 3 to 1.5 after CABG; patients with nonviable myocardium usually show no improvement in functional class. Adding viability assessment to catheterization and clinical data in deciding whether to pursue revascularization results in improved survival after CABG. Although no large randomized trials exist, current evidence suggests that the extent of viability is the best preoperative predictor of survival after CABG. The STICH trial, currently under way, will provide the first large randomized study on the effect of viability testing on outcomes.

It is important to revascularize hibernating myocardium early. Delays of >1 month increase long-term mortality from 5% to 20% because over time hibernating myocardium undergoes fibrosis and apoptosis.

Reasons for failure to improve function after revascularization despite a preoperative demonstration of viability include poor revascularization, intra- or postoperative reinfarction, graft occlusion, false-positive viability study, or presence of subendocardial scar (scar >25% of the wall’s thickness). MRI is the only reliable method for detecting subendocardial scar.

Radionuclide myocardial perfusion imaging in other settings includes detection of CAD, assessment of risk, and determination of the significance of an intermediate coronary narrowing on cardiac catheterization. Exercise is the best form of stress for nuclear studies. An alternative is the “adenowalk,” the performance of low levels of exercise during an adenosine infusion. Dobutamine is used in those who cannot exercise or have reactive airways.

Nuclear imaging looks for an imbalance in perfusion and requires a normal area to detect an abnormal one; if all areas are abnormal, the study may be falsely negative (balanced ischemia). Transient ischemic dilation is an important marker of myocardial ischemia, even without a discrete abnormality, and usually is indicative of 3-vessel CAD with balanced ischemia.

Most patients (85%) with intermediate Duke's treadmill scores can have their risk clarified with the addition of nuclear imaging. A normal nuclear stress test gives a 1% risk of AMI or death in the next 4 years. Patients who have positive pharmacologic stress tests are at higher risk than those with positive exercise stress tests because inability to exercise is a risk in itself. In dobutamine nuclear stress tests, a positive electrocardiogram with negative images carried the same risk as a negative electrocardiogram with positive images; having both tests positive indicated the highest risk. A normal nuclear stress test is less reliable in diabetic patients, who have a threefold to fourfold increased risk with a normal study than do nondiabetics (0.3% to 1% for men, 0.5% to 2% for women). Statin therapy can reverse a myocardial ischemic defect on nuclear stress test without revascularization!

CONGESTIVE HEART FAILURE

Robert O. Bonow, MD

1. *Concepts.* HF is an increasing problem; 62 million people in the USA have risk factors for HF, and >5 million have symptomatic HF (61). In whites HF is usually (65%) due to CAD, whereas in blacks it is usually due to hypertension. The 2 major goals of HF treatment are to improve hemodynamics and reduce neurohormonal stimulation. Neurohormonal stimulation causes increased oxygen consumption, tachycardia, myocardial hypertrophy, arrhythmias, and myocardial necrosis. The goals in compensated HF are hemodynamic improvement, neurohormonal modulation (beta-blocker, ACE inhibitors, ARBs, and aldosterone antagonists), prevention of left ventricular dilation, and prevention of further coronary narrowing. The goal in decompensated HF is hemodynamic stabilization (avoiding inotropes whenever possible).

2. *Management.* Proper management of HF requires establishing its cause, determining whether it is mainly systolic or diastolic, correcting the precipitating factors (especially myocardial ischemia if present), initiating therapy, and assessing response. General principles of management include 1) control volume (diuretics); 2) slow disease progression (beta-blockers or ACE inhibitors or ARBs); 3) prevent sudden death (beta-blockers or ICDs); and 4) treat symptoms (digoxin or cardiac resynchronization therapy).

ACE inhibition is a cornerstone of HF therapy (62–64). Seven trials have shown these agents to be effective and to decrease the mortality rate (61). Low BP (in the absence of orthostatic symptoms) and elevations of creatinine are *not* contraindications to ACE inhibitors. ARBs are equivalent to ACE inhibitors and, of course, are the drugs of choice in patients who cannot tolerate ACE inhibitors because of symptoms such as cough or angioedema (27, 29, 65). Whether the combination of an ARB and an ACE inhibitor offers additional benefit is still unclear. Aldosterone antagonists (spironolactone, eplerenone) also have been demonstrated to have a 30% relative risk reduction for patients with New York Heart Association class III and IV HF (66, 67). The choice of diuretic depends on renal function: loop diuretics should

be used twice daily if the creatinine clearance is <30 mL/min and thiazides if it is >30 mL/min. Digoxin is useful in both systolic and diastolic HF, but the serum level must be <1.2 mg/dL (68). Beta-blockers can improve ejection fractions in HF patients after 3 to 6 months of therapy (following a small initial decrease). Only metoprolol, carvedilol, and bisoprolol have been approved for use in HF patients (69–71). Doses of these drugs should be titrated slowly over 2-week intervals and usually started in the hospital after the patient has been adequately diuresed. It is not advisable to stop beta-blockers in patients admitted with HF exacerbations, as this may trigger a worsening of symptoms. Low BP (in the absence of orthostasis) and low ejection fraction are *not* contraindications to beta-blockade in HF. Patients with an ejection fraction <35% who are at high risk of SCD should be considered for ICD implantation (72). Patients with class III or IV HF and a wide (>0.12 seconds) QRS complex should be considered for cardiac resynchronization therapy (biventricular pacing).

3. *Principles for management of HF with normal systolic function (diastolic HF).* 1) Control systolic and diastolic BP. 2) Control ventricular rate in patients with AF. 3) Anticoagulate all patients with AF. 4) Restore sinus rhythm in patients with AF. 5) Control edema with diuretics. 6) Revascularize patients with myocardial ischemia. 7) Prescribe beta-blockers, ACE inhibitors, and/or ARBs. 8) Use digoxin to minimize symptoms.

4. *Management of ischemic HF.* CAD has long been considered the initiating factor in ischemic HF but has been ignored as a factor in accelerating the decline of HF patients through ongoing myocyte injury (61, 73–75). Aggressive CAD treatment strategies (aspirin, ACE inhibitor, beta-blocker, statin) must be applied to HF patients if there is *any* chance that CAD may be playing a role in their HF (76). ACE inhibition and beta-blockade are most beneficial to patients with both CAD and HF. Patients with HF from CAD (ischemic cardiomyopathy) have worse outcomes than those with nonischemic HF with the same degree of left ventricular dysfunction. Viability assessment and revascularization are key in the treatment of these patients and may slow progression or reverse their HF (77, 78).

DIASTOLIC HEART FAILURE

A. Jamil Tajik, MD

1. *Definitions.* HF is not a disease but a manifestation of a disease. The etiology of HF always needs to be sought. About 80% of patients ≥75 years of age have some form of left ventricular diastolic dysfunction. Half of patients with HF have diastolic rather than systolic dysfunction, and the survival of patients with these 2 forms of HF is identical (79). Systemic hypertension is by far the leading cause of diastolic HF, with myocardial ischemia a distant second.

2. *HF stages.* Stage A is the presence of risk factors only (e.g., hypertension); treatment should be directed at modifying the risk factors. Stage B is asymptomatic left ventricular dysfunction; identifying and aggressively treating this stage is crucial to preventing symptomatic HF. Stage C is symptomatic left ventricular dysfunction; at this point the process is irreversible and treatment is difficult. Stage D is terminal HF.

3. *Echocardiographic assessment of diastolic HF.* The history, physical examination, electrocardiogram, chest radiograph, and laboratory studies are useful in diagnosing HF, but none of these

can distinguish systolic from diastolic HF; only echocardiography can separate them. Mitral inflow and mitral annular tissue Doppler can be used to assess diastolic dysfunction; the E:E' ratio is the most sensitive marker (80). Assessment of left atrial volume also can be helpful in diagnosing diastolic HF.

Diastolic dysfunction on echocardiogram is graded I through IV: *grade I* is impaired relaxation, *grade II* is pseudonormalization, *grade III* is restrictive filling without maximal medical therapy, and *grade IV* is restrictive filling despite maximal medical therapy. Simultaneous Doppler and catheterization studies have shown that grade I diastolic dysfunction equates to a mean left atrial pressure of about 8 mm Hg and grade III, to a mean of about 28 mm Hg. Grade I diastolic dysfunction increases mortality rates eightfold, and grade II/III diastolic dysfunction increases them 20-fold.

4. *Echocardiographic maneuvers in assessing diastolic HF.* Prognosis and responsiveness to therapy can be predicted in diastolic HF patients by performing echocardiography during a Valsalva maneuver: if the diastolic pattern improves (grade III to grade I or II), then the patient is likely to respond well to volume unloading with diuretics. The contribution of mild (grade I) diastolic HF to a patient's exertional dyspnea can be assessed by performing echocardiography during supine bicycle exercise. If the diastolic pattern worsens (grade I to grade II or III) with exercise, then it is likely that the mean left atrial pressure is increasing to >25 mm Hg, and pulmonary edema is the cause of exertional dyspnea.

5. *Therapy for diastolic HF.* Therapy for diastolic HF is determined primarily by the severity of the dysfunction. Patients with grade I diastolic dysfunction have normal left atrial pressures and are best treated with maintenance of sinus rhythm, slower heart rates, and neurohormonal blockade (beta-blockers, ACE inhibitors, aldosterone antagonists). Patients with grade III diastolic dysfunction have high left atrial pressures and short mitral deceleration times (i.e., left ventricular filling is completed during the first third of ventricular diastole), and decreasing heart rate does not improve left ventricular filling but instead decreases cardiac output. Patients with grade III diastolic dysfunction have tiny a-waves (i.e., minimal atrial contribution to left ventricular filling), and they are not necessarily worse off in AF. These patients need gentle diuresis and neurohormonal blockade.

PERICARDIAL DISEASE

A. Jamil Tajik, MD

1. *Pericardial constriction.* The number one cause of constrictive pericardial disease today is prior cardiac surgery (occurring up to 10 years earlier). Any patient *not* doing well after cardiac surgery should be considered to have pericardial constriction until proven otherwise. The number of cases of constrictive pericardial disease is increasing as awareness and diagnostic tools improve. Thickened pericardia can be seen on CT or MRI, but nearly 20% of cases have pericardia of normal thickness on these studies. Calcified pericardia are indicative of old or chronic disease, and the prognosis in patients with calcified pericardia is worse than in patients with noncalcified pericardia.

2. *Hemodynamic features of constriction.* The 2 hallmark features of pericardial constriction in the catheterization laboratory are dissociation between intracavitary (left ventricular) and intrathoracic (pulmonary artery) pressures. To distinguish restrictive cardiomyopathy from pericardial constriction, the superimposed

left ventricular and pulmonary artery pressure tracings need to be studied during the respiratory cycle. In restrictive cardiomyopathy, the left ventricular and pulmonary arterial pressure tracings move up and down together with respiration (concordance); in pericardial constriction, in contrast, the left ventricular and pulmonary artery pressure tracings move closer together with inspiration and separate with expiration (discordance).

ECHOCARDIOGRAPHY: PAST, PRESENT, AND FUTURE

A. Jamil Tajik, MD

Echocardiography may be the most important breakthrough in cardiology in the past 4 decades! Over 50,000 echocardiograms were done at the Mayo Clinic in 2002. Echocardiography has 2 big advantages over CT and MRI: 1) the ability to image irregular rhythms (no gating) and 2) portability. In the near future, handheld echocardiography will be ubiquitous, the first new bedside diagnostic tool for physicians since the development of noninvasive BP measurement nearly 100 years ago.

ATRIAL FIBRILLATION

Harold L. Kennedy, MD

1. *Definitions.* AF lasting <7 days is considered *paroxysmal* and that lasting >7 days, *persistent*. Cardioversion is more successful in the paroxysmal type than the persistent type. Most patients (70%) with AF are >65 years of age. Risk factors for AF include systemic hypertension, diabetes mellitus, HF, and AMI. AF increases mortality rates twofold and the risk of stroke fivefold (81).

2. *Principles of treatment* (82). 1) Control ventricular rate (with beta-blockade, calcium antagonists, or digoxin). 2) Prevent emboli (aspirin, warfarin, or ximelagatran). 3) Restore sinus rhythm (with antiarrhythmic drugs or direct-current cardioversion). 4) Maintain sinus rhythm (antiarrhythmic drugs, radiofrequency ablation, or pacing). Direct-current cardioversion is more successful with bipolar defibrillators than with unipolar ones. An anteroposterior pad position is preferable to an anterolateral position (83). Use at least 200 J from the beginning rather than lower energies. In patients with HF, treatment with ACE inhibitors results in a near-20% absolute risk reduction for development of AF compared with patients not receiving them.

3. *Rate control vs rhythm control.* Rate control is slightly more beneficial in persistent AF than is rhythm control (84, 85). If patients with persistent AF are >65 years of age or have symptomatic HF, rhythm control may still be useful (AFFIRM). Neither rhythm control nor rate control obviates the need for warfarin in patients with AF.

4. *Devices for treatment.* Because the pulmonary veins may have "sleeves" of muscle that may produce ectopic electrical foci, isolation of the pulmonary veins with radiofrequency ablation decreases the incidence of AF by 80% and improves morbidity rates, mortality rates, and quality of life (86–88). This procedure, however, may cause stricture and/or thrombosis of one or more pulmonary veins, a complication that may limit its application.

5. *Anticoagulation.* The use of aspirin alone is acceptable in low-risk patients, but in high-risk patients warfarin should be used, with a target INR of 2 to 2.5 (SPAF). In a recent trial comparing ximelagatran, a new oral direct thrombin inhibitor, and warfarin, ximelagatran was equivalent to warfarin for stroke prevention and slightly superior for reducing bleeding complica-

tions (SPORTIF-III) (89, 90). Ximelagatran, however, produced increased hepatic transaminase levels in 6% of the patients.

SUDDEN CARDIAC DEATH

Harold L. Kennedy, MD

SCD most commonly is the consequence of atherosclerotic CAD but on occasion is the result of other structural cardiac conditions or a primary electrical system disorder (e.g., long QT syndrome) (91, 92). Some investigators suggest that an ICD should be inserted in all patients with aborted SCD. Current American College of Cardiology/American Heart Association guidelines, however, state that an ICD is indicated only if there is no identifiable reversible cause of the SCD. Patients with healed AMI, HF, low ejection fractions, nonsustained ventricular tachycardia (on Holter monitoring), and inducible ventricular tachyarrhythmia on electrophysiologic study (i.e., those at highest risk) have better survival when randomized to ICD placement (MADIT-I, MUSTT) (93–95). A recent trial of patients with ischemic cardiomyopathy, an ejection fraction <35%, and no electrophysiologic study showed that the patients receiving an ICD had a 30% decrease in mortality rates after 20 months compared with those receiving only medical therapy, mainly amiodarone (MADIT-II) (72). In patients with ICDs, beta-blockers are useful in preventing frequent firings of the ICD. Mortality rates in patients with idiopathic dilated cardiomyopathy are not improved by prophylactic insertion of an ICD (96).

CARDIOVASCULAR DISEASE AND THE SLEEP APNEA SYNDROME

Harold L. Kennedy, MD

Sleep apnea is common in patients who are obese, who habitually snore, who are >65 years of age, who have neck circumference sizes >17 inches (43 cm), and who have an abnormal pharynx. Apneas and hypopneas at night requiring arousal elevate catecholamine levels and result in hypertension (97, 98). Therapy with continuous positive airway pressure can decrease the number of apneas and hypopneas and thus reduce BP. Sleep apnea also increases serum levels of C-reactive protein and interleukin-6, both of which can be lowered by continuous positive airway pressure therapy (99). Sleep apnea affects about 50% of patients with HF (100).

CURRENT AND FUTURE MANAGEMENT OF VALVULAR HEART DISEASE

Jeffrey S. Borer, MD

1. AS. Patients with untreated symptomatic AS have an average survival of 2 years. Survival in asymptomatic patients with AS is good and is not improved by AVR. Exercise testing can help determine which asymptomatic (at rest) AS patients would benefit from AVR. (The risk of mortality on the treadmill is extremely low.) Indications for AVR in asymptomatic patients with AS include aortic valve jet velocity >4.0 m/sec, jet velocity across the aortic valve that has increased by >0.3 m/sec in a year, abnormal exercise stress test, and low ejection fraction at rest. Calcific deposits on aortic valves detected by echocardiography imply worse outcomes. After AVR, maximal improvement in ejection fraction may take up to 3 years.

2. MS. MS is a long, slowly progressive disease. If the patient is asymptomatic or mildly symptomatic, the survival is 80% at 10 years. Patients with moderate to severe symptoms, however,

have a <15% survival at 10 years. Patients with severe pulmonary hypertension have a mean survival of <3 years. Mitral valve area can be improved greatly by balloon valvuloplasty. Percutaneous valvuloplasty has equivalent mortality to open commissurotomy with less morbidity.

3. AR. Patients with asymptomatic AR with depressed left ventricular function require AVR. The worse the preoperative left ventricular ejection fraction in patients with AR, the worse their survival after AVR. Drug therapy for AR is usually successful only in patients with coexisting systemic hypertension. Long-acting nifedipine can reduce the degree of AR and delay AVR. Although both could potentially decrease the degree of AR, ACE inhibitors and amlodipine have not been tested.

4. MR. Severe MR by itself is not an indication for a mitral operation. Indications for surgery for asymptomatic MR include a depressed left ventricular or right ventricular ejection fraction and severe pulmonary hypertension. Medical therapy infrequently provides much benefit. Mitral valve repair is preferred over replacement in patients with purely regurgitant mitral valves.

SURGICAL THERAPY FOR CORONARY AND VALVULAR HEART DISEASES

Charles S. Roberts, MD

1. CABG. Nearly 95% of patients having CABG for angina pectoris are angina-free at 1 year after operation. The mortality risk of CABG is the same as for hip surgery. The patients at highest risk for early mortality after CABG include age >90 years, BMI >40 or <22 kg/m², AMI in the last 48 hours, and emergent CABG. The outcomes of CABG with cardiopulmonary bypass are equivalent to those done “off-pump” (101). Additionally, off-pump CABG requires “stabilization” of the beating heart and allows poor access to the left circumflex coronary artery and its branches. As a consequence, it is utilized in <10% of CABG operations nationwide.

2. *Valvular cardiac surgery.* Mechanical valves, the preferred valve in patients without contraindications to anticoagulation, are gaining increasing competition from bovine pericardial bioprostheses. These bioprostheses have improved longevity over the porcine aortic valves and avoid the risk of bleeding from warfarin and emboli associated with mechanical valves. A significant endorsement comes from cardiothoracic surgeons, who tend to request that these bioprostheses be used when valve replacement is needed. Maintaining low cholesterol levels, low BPs, and low heart rates can prolong the life of bioprostheses. The Ross procedure (moving the pulmonic valve to the aortic position) is recommended only if AVR is indicated in a patient <30 years old. Mitral valve repair is useful for myxomatous or ischemic MR but rarely in valves damaged by infective or rheumatic heart disease (102, 103).

3. *Cardiothoracic surgery training.* The number and quality of applicants for cardiothoracic surgery training positions have been declining for several years. The widespread use of coronary angioplasty and stenting is decreasing the number of CABG operations done, while those that are done now involve higher-risk patients. Trainees are increasingly less experienced as a result of this lower volume of procedures. Therefore, the number of trainees annually needs to be decreased to provide an adequate number of procedures for training.

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