

Facts and principles learned at the 39th Annual Williamsburg Conference on Heart Disease

Mina M. Benjamin, MD, and William C. Roberts, MD

The December 2012 Williamsburg Conference on Heart Disease in Williamsburg, Virginia, was the 39th such annual conference to be held in that city. The conference has been directed by one of the authors (WCR) since 1972. The conference provides 16.5 hours of continuing medical education category one credit, and nearly all of the speakers are nationally and internationally recognized. It is one of the 2 longest-running cardiology courses. Its unique feature is that each presentation is 90 minutes, which allows the speakers time to discuss more than one topic and to answer questions from enrollees. This article summarizes the proceedings of the 2012 conference.

SOME FACTS AND PRINCIPLES LEARNED AFTER SPENDING 50 YEARS INVESTIGATING CORONARY HEART DISEASE

William C. Roberts, MD, Executive Director, Baylor Heart and Vascular Institute; Dean, A. Webb Roberts Center for Continuing Medical Education, Baylor University Medical Center, Dallas, Texas; and Editor in Chief, The American Journal of Cardiology and the Baylor University Medical Center Proceedings

Although the same blood flows through both arteries and veins, atherosclerosis affects only the arteries. The arterial system can be subdivided into various regions—coronary, carotid, cerebral, renal, peripheral (arm and leg), and aorta—and one region may cause symptoms of organ ischemia or discomfort and the other regions may be clinically silent. Nevertheless, when one region contains considerable amounts of atherosclerotic plaque such that it produces symptoms or discomfort in that region, necropsy studies have demonstrated that large quantities of atherosclerotic plaque also are present in the other regions. In other words, atherosclerosis is a systemic disease. To demonstrate this principle, detailed studies of the coronary arteries in patients with large abdominal aneurysms and/or peripheral limb ischemia so severe that amputation was required disclosed atherosclerotic plaque in every 5-mm segment of each of the 4 major epicardial coronary arteries (right, left main, left anterior descending, left circumflex). The quantity was so severe that a large portion (about 33%) of the length of the four major coronary arteries had plaques that narrowed the lumens >75% in cross-sectional area (1, 2).

Multiple necropsy studies have shown that when any particular arterial region produces symptoms of organ ischemia (or discomfort in the case of abdominal aortic aneurysm), the atherosclerotic process in that region is diffuse and severe—i.e., there are no “skip areas” where a 5-mm-long arterial segment does not contain atherosclerotic plaque (3). Multiple necropsy studies of each 5-mm-long segment of the 4 major epicardial coronary arteries in a variety of coronary subsets (those with acute myocardial infarction, stable and unstable angina pectoris, healed myocardial infarction with and without chronic heart failure, and sudden coronary death) have demonstrated that about a third of the entire lengths of the 4 major coronary arteries is narrowed >75% in cross-sectional area by atherosclerotic plaque alone (3, 4).

There appears to be a common belief that atherosclerotic plaques consist mainly of lipid material. Several studies have examined the composition of atherosclerotic coronary plaques at necropsy in patients with fatal coronary heart disease (5–8). The studies traced out the various components of plaques from each 5-mm-long segment of each of the 4 major coronary arteries, and fibrous tissue was by far the dominant component of coronary plaques, comprising about 70%, while lipids comprised about 10%; calcium, about 10%; and miscellaneous, the other 10%. Fibrous tissue also was the dominant component of plaques in saphenous veins used for aortocoronary bypass grafts. That the predominant component of coronary plaques is fibrous tissue is probably advantageous for percutaneous coronary intervention (PCI) because that procedure works simply by cracking plaques and not by compressing them to the side.

Studying atherosclerosis at necropsy or after endarterectomy has convinced Roberts that the only real long-term therapy for the Western world’s number one disease is prevention. Although the Framingham investigators and others have convinced most physicians and the lay public that atherosclerosis is a multifactorial disease, Roberts is convinced that the disease has a

From the Departments of Internal Medicine (Benjamin, Roberts) and Pathology (Roberts), and the Baylor Heart and Vascular Institute (Roberts), Baylor University Medical Center at Dallas.

Corresponding author: William C. Roberts, MD, Baylor Heart and Vascular Institute, 621 North Hall Street, Suite H030, Dallas, TX 75246 (e-mail: wc.roberts@baylorhealth.edu).

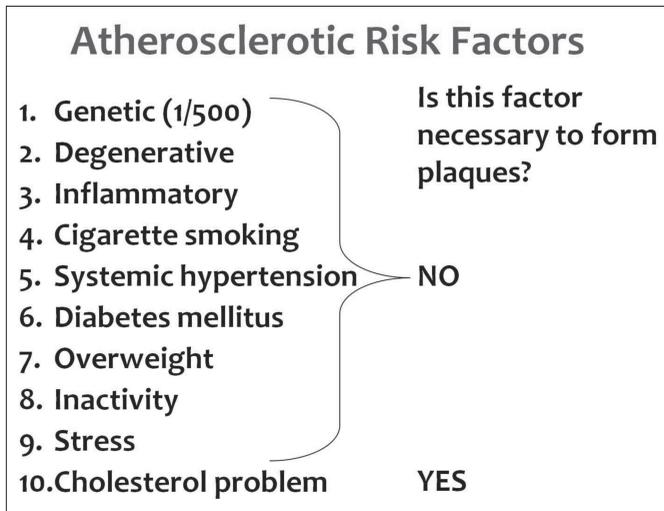


Figure 1. The atherosclerotic risk factors showing that the only factor required to cause atherosclerosis is cholesterol.

single cause, namely cholesterol, and that the other so-called atherosclerotic risk factors are only contributory at most (9–13). As shown in *Figure 1*, most of the risk factors do not in themselves cause atherosclerosis.

There are in Roberts' opinion 4 facts supporting the contention that atherosclerosis is a cholesterol problem: 1) *Atherosclerosis is easily produced experimentally in herbivores (monkeys, rabbits) by giving them diets containing large quantities of cholesterol (egg yolks) or saturated fat (animal fat).* Indeed, atherosclerosis is one of the easiest diseases to produce experimentally, but the recipient must be an herbivore. It is not possible to produce atherosclerosis in carnivores (tigers, lions, dogs, etc.). In contrast, it is not possible to produce atherosclerosis simply by raising a rabbit's blood pressure or blowing cigarette smoke in its face for an entire lifetime. 2) *Atherosclerotic plaques contain cholesterol.* 3) *Societies with high average cholesterol levels have higher event rates (heart attacks, etc.) than societies with much lower average cholesterol levels.* 4) *When serum cholesterol levels (especially the low-density lipoprotein cholesterol [LDL-C] level) are lowered (most readily, of course, by statin drugs), atherosclerotic events fall accordingly and the lower the level, the fewer the events ("less is more").* Although most humans consider themselves carnivores or at least omnivores, basically we humans have characteristics of herbivores (*Table 1*).

The Adult Treatment Panel of the National Cholesterol Education Program has provided guidelines for whom to treat with cholesterol-altering drugs. The latest (2004) guidelines are summarized in *Table 2*. The guidelines are aimed entirely at reducing the risk of atherosclerotic events. Lowering the LDL-C goal from <100 to <70 mg/dL is recommended by the committee only in patients who have already

Table 1. The differences between carnivores and herbivores

Features	Carnivore	Herbivore
Teeth	Sharp	Flat
Intestine	Short (3 × BL)	Long (12 × BL)
Fluids	Lap	Sip
Cooling	Pant	Sweat
Appendages	Claws	Hands or hoofs
Vitamin C	Self-made	Diet

BL indicates body length.

Table 2. Drug treatment guidelines of the Adult Treatment Panel of the National Cholesterol Education Program (2004) to decrease risk

LDL (mg/dL)	Other RF	Goal
>190	≤1	<160
>160	>1	<130
>130	HA	<100 (<70)

HA indicates heart attack; LDL, low-density lipoprotein cholesterol; RF, risk factor.

had an atherosclerotic event, who have diabetes mellitus, or who are at an extremely high risk of developing an atherosclerotic event (e.g., homozygous or heterogeneous familial hypercholesterolemia). Roberts' guidelines, in contrast, are directed at preventing atherosclerotic plaques, and when they are prevented atherosclerotic risk is negated. The only requirement is an LDL-C <50 mg/dL.

Statins, at least in Roberts' view, are the finest cardiovascular drug ever created (released in the USA in 1987) (14). *Table 3* displays the equivalent doses of six statins, their average reductions in total cholesterol and LDL-C, and the additional LDL-C-lowering effect when ezetimibe is added to a statin (15).

Table 3. Dosing of six statin drugs, their relative efficacy and effects on cholesterol, and the effect of adding ezetimibe

	Equivalent dose (mg)						↓ TC	↓ LDL	E (10 mg) ↓ LDL	Total LDL ↓
	R (C)	A (L)	S (Z)	P (P)	L (M)	F (L)				
1.25	5	10	20	20	40	22%	27%	18%	45%	
2.5	10	20	40	40	80	27%	34%	18%	52%	
5	20	40	80	80	–	32%	41%	14%	55%	
10	40	80	–	–	–	37%	48%	12%	60%	
20	80	–	–	–	–	42%	55%	10%	65%	
40	–	–	–	–	–	45%	62%	10%	72%	

R indicates rosuvastatin (C, Crestor); A, atorvastatin (L, Lipitor); S, simvastatin (Z, Zocor); P, pravastatin (P, Prava-chol); L, lovastatin (M, Mevacor); F, fluvastatin (L, Lescol); TC, total cholesterol; LDL, low-density lipoprotein cholesterol; E, ezetimibe.

ASSESSING THE BENEFIT OF THERAPY THAT RAISES HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

William E. Boden, MD, Chief of Medicine, Stratton VA Medical Center, Vice-Chairman of Medicine, Albany Medical Center, and Professor of Medicine, Albany Medical College, Albany, New York

All the major primary and secondary prevention statin studies have shown an average of 25% cardiovascular risk reduction at 5 years, which means that 75% of the cardiovascular events were not prevented during this time period. Statins act mainly on LDL-C, with much less effect on triglycerides or high-density lipoprotein cholesterol (HDL-C). Fibrates act mainly on triglycerides, reducing it 30% to 35% with a slight increase in HDL-C and only a minor effect on LDL-C (16). In the FIELD study (17), fenofibrate did not significantly reduce coronary events in 9775 patients vs placebo. In the ACCORD trial (18), the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction (MI), or nonfatal stroke, compared with simvastatin alone in 5518 high-risk patients with diabetes mellitus. Niacin raises HDL-C by 30% to 35%, has a lesser effect on triglycerides than fibrates, and reduces LDL-C by 15% to 20%. Niacin also increases LDL particle size, from a small, dense pattern B to the larger nonatherogenic pattern A (19). In the Framingham study (20), LDL-C and HDL-C were independent risk factors of coronary heart disease (CHD). A patient with an LDL-C of 220 and HDL-C of 45 mg/dL had a similar risk to a patient with an LDL-C of 100 and HDL-C of 25 mg/dL. Statins had a maximal relative risk reduction in cardiovascular events of about 30% (21), niacin about 20% (22), and fibrates 23% (16). Although the National Cholesterol Education Program Adult Treatment Panel III guidelines (23) stated that low HDL-C is an independent risk factor for coronary artery disease (CAD) morbidity and mortality, the panel concluded that the risk reduction documented by controlled clinical trials is not sufficient to warrant setting a specific HDL-C goal.

Several surrogate marker studies (24–26) demonstrated slowing or even regression of arterial narrowing with niacin. The ARBITER 6-HALTS (26) trial was terminated early on the basis of a prespecified interim analysis showing superiority of niacin over ezetimibe for change in carotid thickness. Major adverse cardiac events occurred at a significantly lower incidence in the niacin (1.2%) vs the ezetimibe group (5.5%). In a metaanalysis of the 14 niacin studies including 2682 patients taking 1 to 3 g/day of niacin and 3934 controls, niacin decreased the rate of progression of atherosclerosis by 41% and decreased carotid intima thickness by 17 $\mu\text{m}/\text{year}$.

In the Coronary Drug Project (27), immediate-release niacin (3 g/day) reduced the incidence of CHD death/MI by 14%, nonfatal MI by 26%, and stroke/transient ischemic attacks by 21% after 5 years. There was also a 50% reduction in the need for coronary bypass surgery. In the VA-HIT study (28), gemfibrozil reduced CHD death/MI by 22% vs placebo after 5 years. These patients did not take statins, and the benefit was attributed to a decrease in triglycerides (–31%) and an increase in HDL-C (+6%), as there was no significant change in LDL-C. It took 2 years in the VA-HIT trial for a considerable benefit

to be evident with treatment, quite different from the time course seen with statins, where event reduction is seen as early as 2 weeks after institution of treatment.

Several single-center trials demonstrated the benefits of adding niacin to other cholesterol-lowering drugs. In the Familial Atherosclerosis Treatment Study (FATS) (29, 30), 126 men with known CHD were randomized to receive conventional therapy or lovastatin plus colestipol or niacin (4 g/day). All patients had a coronary angiogram at baseline. After 2.5 years, coronary narrowing in patients on conventional therapy progressed, while it regressed in the treatment group. Multivariate analysis showed that increasing HDL-C correlated independently with the regression of disease. The HDL Atherosclerosis Treatment Study (HATS) (31) was a 3-year trial of 160 patients with CHD whose HDL-C averaged 31 mg/dL and LDL-C, 125 mg/dL. Patients were administered either niacin (mean dose 2.4 g/day) plus simvastatin (mean dose 13 mg/day) or placebo for 3 years. In the group receiving niacin plus simvastatin, LDL-C levels decreased 42% and HDL-C increased 26%. The combination of niacin and simvastatin reduced CHD events by about 75%. There was a slight regression in coronary narrowing with simvastatin plus niacin but progression in all other groups. Both FATS and HATS were single-center studies with relatively small numbers of patients. Pooled data from 28 different lipid trials (32) showed that there was an aggregation of benefit from adding different cholesterol-altering medicines. Data from the 4S (33), CARE (34), WOSCOPS (35), and LIPID (36) trials demonstrated that a 1% decrease in LDL-C was associated with a 1% decrease in CHD events. A 1% increase in HDL-C was associated with a 3% decrease in events, as seen in HELSINKI (37), AFCAPS/TexCAPS (38), and VA-HIT.

The results from the Coronary Drug Project, VA-HIT, and HATS constituted the base for a large, multicenter trial assessing the outcomes for niacin. The AIM-HIGH (39) study was conducted mainly to investigate whether the residual risk associated with low levels of HDL-C in patients with established CHD (whose LDL-C therapy was optimized with statins \pm ezetimibe) would be mitigated with extended-release niacin vs placebo. The patients were >45 years of age with CHD, cerebrovascular disease, or peripheral arterial disease and dyslipidemia (HDL-C <40 for men, <50 for women; triglycerides 150–400; LDL-C <180 mg/dL). A total of 3414 patients were randomized to receive extended-release niacin (1.5 to 2 g/day) or placebo. All patients received simvastatin (40 to 80 mg/day) plus ezetimibe (10 mg/day) (if needed) to maintain an LDL-C of 40 to 80 mg. (The placebo tablets had a small amount of niacin, 200 mg/2 g, to produce similar side effects as in the treatment group.) Patients on statins (94%) had a mean baseline LDL-C of 71 mg/dL. The trial was stopped after a mean follow-up period of 3 years due to a lack of efficacy. There was also an increased incidence of ischemic strokes in the niacin arm ($n = 29$) vs the placebo arm ($n = 18$). At study termination, HDL-C had increased from 35 to 42 mg/dL, LDL-C had decreased from 74 to 62 mg/dL, and triglycerides had decreased from 164 to 120 mg/dL. In both the Coronary Drug Project and VA-HIT, in the prestatin era, niacin and gemfibrozil increased HDL and lowered triglycerides

and also decreased cardiovascular events, but baseline triglycerides and LDL-C were significantly higher than in AIM-HIGH. It appears that the addition of niacin did not work in this population, possibly because these patients had been well treated with statins and the HDL-C had increased to 38 mg/dL in the placebo arm, changes that might have minimized event rate differences between the treatment and placebo groups.

The HPS 2-THRIVE trial began in 2004 and is expected to be finished by 2013. It enrolled 25,000 patients with CAD or diabetes mellitus from the UK, Scandinavia, and China. Patients were randomized to simvastatin 40 mg or simvastatin plus extended-release niacin/laropiprant. The use of ezetimibe is allowed. There is no target LDL-C level or attempt to equalize LDL-C levels between groups.

COCAINE-ASSOCIATED MYOCARDIAL ISCHEMIA AND INFARCTION

L. David Hillis, MD, Professor and Chair, Department of Medicine, Dan F. Parman Distinguished Chair of Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

Five million Americans use cocaine daily, 1 million are addicted to it, and 5000 use it for the first time each day. Possible mechanisms of cocaine-induced myocardial ischemia include increased myocardial oxygen demand with severe CAD and decreased myocardial oxygen supply due to coronary arterial vasospasm (40) and/or coronary arterial thrombosis. α -Blockers abolish the coronary vasoconstrictor effect of cocaine, while β -blockers augment it (41). Cocaine-induced vasoconstriction is more pronounced in coronary arterial segments narrowed by atherosclerosis (42). The time course of cocaine-induced vasoconstriction parallels the blood concentration of cocaine following intranasal administration, after which a second “wave” of vasoconstriction parallels the increasing blood concentrations of cocaine’s major metabolites and occurs as the blood concentration of cocaine is decreasing (43). The deleterious effects of cocaine on myocardial oxygen supply and demand are exacerbated by concomitant cigarette smoking. This combination substantially increases the metabolic requirement of the heart for oxygen but simultaneously decreases the diameter of diseased coronary arterial segments (44). The combination of intranasal cocaine and intravenous ethanol causes an increase in the determinants of myocardial oxygen demand. The combination also causes a concomitant increase in epicardial coronary arterial diameter (45). Morphine can reverse cocaine-induced coronary arterial vasoconstriction (46). Sublingual nitroglycerin (47) 0.4 to 0.8 mg and intravenous verapamil (48) also reverse the coronary vasoconstrictive effect of cocaine, while intravenous labetalol has no effect (49). The mechanism of cocaine-induced vasospasm and its aggravating and relieving factors are summarized in *Figure 2*.

CORONARY ARTERY BYPASS GRAFTING—2012

L. David Hillis, MD

Coronary artery bypass grafting (CABG) is superior to medical therapy for eliminating angina pectoris (50). CABG,

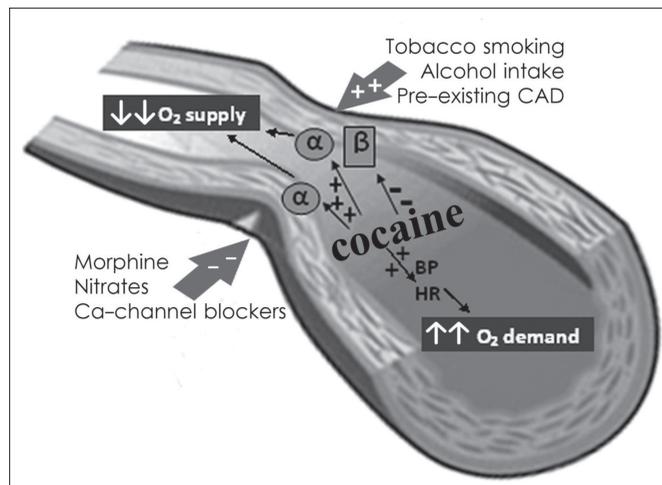


Figure 2. The mechanism of cocaine-induced coronary vasospasm, aggravating factors, and treatment. CAD indicates coronary artery disease; Ca, calcium.

however, does not prevent MIs (51, 52). CABG is superior to medical therapy in improving survival only in patients with left main CAD, in those with 3-vessel CAD and left ventricular (LV) ejection fraction (EF) <50%, and in those with 2- or 3-vessel CAD with significant narrowing of the proximal left anterior descending coronary artery. In the VA COOPERATIVE study (53), the survival of patients with 1, 2, and 3-vessel CAD with a normal LVEF (medical therapy vs CABG) was 87% vs 82%, 82% vs 77%, and 68% vs 61% at 5, 7, and 11 years, respectively, while the survival of patients with 3-vessel CAD and LVEF <50% was (medical therapy [n = 97] vs CABG [n = 71]) 66% vs 83%, 52% vs 78%, and 38% vs 50% at 5, 7, and 11 years, respectively. In the STICH trial (54), a total of 1212 patients with an EF < 35% and CAD amenable to CABG were randomly assigned to medical therapy alone (n = 602) or medical therapy plus CABG (n = 610). At 5 years, death from any cause was 41% in the medical therapy arm and 36% in the CABG group (insignificant), and the rate of hospitalization for heart failure was 54% vs 48%. Patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes. Compared with patients who have CABG, those who have PCI are more likely to require another revascularization procedure in the next 12 months (45), and rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (18% vs 12% for CABG), in large part because of an increased rate of repeat revascularization (13% vs 6%).

The determinants of peri-CABG mortality include age (peri-CABG mortality markedly increases above 70 years) (55), LV systolic function, comorbid conditions (chronic obstructive pulmonary disease, diabetes mellitus, azotemia, obesity), extracardiac vascular disease, left main CAD, previous thoracotomy (mortality of the first sternotomy 3% vs 7% for subsequent sternotomies), and gender (1.9% in men vs 4.5% in women in CASS [n = 6630] and 2.6% in men vs 5.3% in women in the Texas Heart Institute [n = 22,284] registry).

There was no significant difference in 30-day death, MI, stroke, or renal failure requiring dialysis between patients

undergoing CABG off-pump or on-pump in a large trial involving 79 centers in 19 countries randomizing 4752 patients. Off-pump CABG reduced rates of transfusion, reoperation for perioperative bleeding, respiratory complications, and acute kidney injury but also resulted in an increased risk of early revascularization (56).

CARDIOPULMONARY RESUSCITATION AND PUBLIC-ACCESS DEFIBRILLATION

Richard L. Page, MD, George R. and Elaine Love Professor, Chair, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

The 2010 American Heart Association guidelines (57) place a strong emphasis on delivering high-quality chest compressions. Rescuers should push hard to a depth of at least 2 inches (5 cm) at a rate of at least 100 compressions per minute, allow full chest recoil, and minimize interruptions in chest compressions. Rescuers also should provide ventilation using a compression:ventilation ratio of 30:2. Longer periods of resuscitation are associated with better outcomes. Goldberger et al (58) studied 64,339 subjects with cardiac arrest in US hospitals. The median duration of resuscitation was 12 minutes in survivors vs 20 minutes in nonsurvivors. The survival to discharge was related to hospital duration of resuscitation.

The PAD trial (59) evaluated automated external defibrillator (AED) use vs conventional cardiopulmonary resuscitation (CPR) in 1000 US sites. There were more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of AEDs (30 survivors among 128 arrests) than there were in the units assigned to have volunteers trained only in CPR. Weisfeldt et al (60) reported 13,769 out-of-hospital arrests where 32% received CPR but no AED before paramedics arrived and 2.1% had an AED placed before paramedics arrived. The survival to hospital discharge was 9% with CPR only, 24% with AED application, and 38% with AED shock delivery. Page et al reported early results of the first use of the AEDs by a US airline between 1997 and 1999. Of 200 events (mean age 58 years), ventricular fibrillation (VF) was present in 16 patients. All VF episodes were recognized (sensitivity 100%) and shock delivered in 15 of 16. First shock success was 100%. Six of 15 patients receiving shocks for VF survived to hospital discharge (40%). Valenzuela et al (61) published a study where casino officers were trained in the use of AEDs. The first 148 patients were reported: 105 (71%) had VF and 59% survived to hospital discharge. There was a significant difference in survival between defibrillation used before and after 3 minutes of the arrest (26/35 [74%] vs 27/55 [49%]).

MANAGEMENT OF VALVULAR HEART DISEASE

Robert O. Bonow, MD, Goldberg Distinguished Professor of Cardiology, Director, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Only 0.3% of the guidelines for valvular heart disease are at evidence level A, i.e., based on high-quality randomized clinical

trial or metaanalysis, while 70% are at evidence level C, i.e., based on expert consensus (62).

Mitral regurgitation (MR). The current guidelines for treatment of severe chronic primary (degenerative) MR recommend mitral valve surgery in symptomatic patients (class I), patients with LVEF <0.6 and LV end systolic dimension 50 to 55 mm (class I), asymptomatic patients with atrial fibrillation (class Ia), and asymptomatic patients with pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise (class Ia). Management of asymptomatic severe MR with preserved EF remains controversial.

The mortality of severe asymptomatic MR varies markedly among different studies. Maurice et al (63) studied 456 patients with MR (EF 70 ± 8%): the 5-year mortality rate with severe MR was 42%, while that of moderate MR was 33%. In contrast, Rosenhek et al reported 0% 5-year mortality in 132 patients with severe asymptomatic MR (64); Grigioni and coworkers (65) reported 14% 5-year mortality in 394 patients with severe MR who were followed for an average of 3.9 years; and Kang et al (66) reported 5% 7-year mortality among 286 patients with severe MR and preserved EF who were treated medically.

In a retrospective review of outcomes of 13,614 patients having elective surgery for MR between 2000 and 2003 in 575 North American centers (67), the hospital procedural volume was associated with higher frequency of valve repair, higher frequency of prosthetic valve usage in older patients, and lower adjusted operative mortality. There was variation among cardiologists as to the degree of knowledge and adherence to the guidelines about the timing of referral to surgery. In a survey in 2007, among 319 responders, LVEF was rated as extremely important in referral decisions by 71% of those who completed the surveys and moderately important by 26%. In asymptomatic patients, EF of 50% to 60% was correctly identified as a trigger for surgery by 57% of cardiologists, while only 16% of cardiologists correctly referred New York Heart Association (NYHA) class II patients with normal LV function (68).

Ischemic MR is managed differently from primary MR. Detection and quantification of ischemic MR provide major information for risk stratification and clinical decision making in the chronic post-MI phase (69). The mitral annulus clip is an evolving technique for treatment of functional MR. Treatment with the clip device in 51 severely symptomatic cardiac resynchronization therapy (CRT) nonresponders with functional MR was feasible, safe, and demonstrated improved functional class, increased LVEF, and reduced ventricular volumes in about 70% of these study patients (70).

Aortic stenosis (AS). The current guidelines do not recommend aortic valve replacement (AVR) in patients with severe asymptomatic AS. The producibility of symptoms or hypotension with exercise is currently a class IB indication, according to the American College of Cardiology and American Heart Association. In 123 adults with asymptomatic AS, event-free survival—with endpoints defined as death (n = 8) or aortic valve surgery (n = 48)—was 93%, 62%, and 26% at 1, 3, and 5 years, respectively (71). The likelihood of remaining alive without valve replacement at 2 years was only 21% for a jet velocity >4.0 m/s

at entry, compared with 66% for a velocity of 3.0 to 4.0 m/s and 84% for a jet velocity <3.0 m/s. In another series of 128 patients with asymptomatic severe AS (72), event-free survival—with the endpoint defined as death (8 patients) or AVR necessitated by the development of symptoms (59 patients)—was 67%, 56%, and 33% at 1, 2, and 4 years, respectively. Rosenhek et al also reported a series of 116 asymptomatic patients (73) with very severe AS, defined by a peak aortic jet velocity ≥ 5.0 m/s. Event-free survival was 64%, 36%, 25%, 12%, and 3% at 1, 2, 3, 4, and 6 years, respectively. Patients with a peak aortic jet velocity ≥ 5.5 m/s had an event-free survival of 44%, 25%, 11%, and 4% at 1, 2, 3, and 4 years, respectively. Early elective valve replacement surgery should therefore be considered in these patients. The current guidelines recommend AVR in patients with a high likelihood for rapid progression (calcification) and/or very severe AS (maximum velocity > 5 m/s, mean gradient > 60 mm Hg, AV area < 0.6 cm²) (class IB).

Exercise-stress echocardiography is very useful for risk stratification of true asymptomatic patients with AS (74). N-terminal beta natriuretic peptide (75) independently predicts symptom-free survival, and preoperative N-terminal beta natriuretic peptide independently predicts postoperative outcome with regard to survival, symptomatic status, and LV function. The STS score (76) is more suitable than the EuroSCORE (77) for estimating the perioperative mortality associated with AVR.

Transcatheter aortic valve implantation (TAVI) is an emerging technique with enormous potential (78). The PARTNER trial (79) investigators concluded that TAVI is superior to medical therapy in patients who are not fit for AVR and that TAVI is equivalent to surgical AVR in high-risk patients. In patients with severe AS and depressed LV systolic function, TAVI is associated with better LVEF recovery compared with surgical AVR (80). In 200 patients undergoing surgical AVR and 83 patients undergoing TAVI for severe AS (AV area ≤ 1 cm²) with LVEF $\leq 50\%$, patients who underwent TAVI had better recovery of LVEF compared with those who underwent surgical AVR (Δ LVEF, 14% vs 7%). Stroke and paravalvular regurgitation remain concerns with TAVI. The average hospital mortality for TAVI was 9% (13.0% for low-volume centers vs 6% for high-volume centers). The broad application of TAVI presents challenges for patient selection and the need for dedicated expert heart valve centers.

The goal in AS patients is to operate late enough in the natural history to justify the risk of intervention and early enough to prevent irreversible ventricular dysfunction, pulmonary hypertension, and/or chronic arrhythmias and sudden death.

OPERATIVE TREATMENT OF CARDIOVASCULAR DISEASE

Charles S. Roberts, MD, Trident Health, Hospital Corporation of America, Charleston, South Carolina

CABG remains the standard of care for patients with 3-vessel or left main CAD, since the use of CABG, as compared with PCI, results in lower rates of the combined endpoint of major adverse cardiac events or cerebrovascular events at 1 year (81). For patients with less severe CAD, symptom severity and non-invasive test results are used to stratify patients into one of two groups: those who will benefit from immediate revascularization

and those in whom an initial trial of aggressive medical therapy alone may be safely attempted. In patients without the highest-risk CAD who require revascularization because of unacceptable symptoms or because of noninvasive test results indicating a high risk of failure of medical therapy, PCI with drug-eluting stents and CABG appear to result in similar rates of death and MI. Therefore, the choice depends largely upon how effectively the lesions can be treated with PCI and upon the patient's feelings about the temporary disability and the slightly increased stroke risk associated with CABG vs the increased risk of repeat revascularization with PCI (82). Stroke predictors from prospective data collected on 4941 patients undergoing cardiac surgery included history of stroke and hypertension, older age, systolic hypertension, bronchodilator and diuretic use, high serum creatinine, surgical priority, great vessel repair, use of inotropic agents after cardiopulmonary bypass, and total CABG time (83).

Carotid endarterectomy (CEA). CEA currently remains the first choice of revascularization therapy for an asymptomatic carotid lesion in most centers (84). The Society for Vascular Surgery appointed a committee of experts to formulate evidence-based clinical guidelines for the management of carotid stenosis. In formulating clinical practice recommendations, the committee used systematic reviews to summarize the best available evidence and the GRADE scheme to grade the strength of recommendations (GRADE 1 for strong recommendations; GRADE 2 for weak recommendations) and rate the quality of evidence (high, moderate, low, and very low quality) (85). The following therapies had both GRADE 1 recommendation and high quality of evidence:

- Medical therapy for symptomatic patients with $< 50\%$ stenosis
- Medical therapy for asymptomatic patients with $< 60\%$ stenosis
- CEA for symptomatic patients with $\geq 50\%$ stenosis
- CEA for asymptomatic patients with $\geq 60\%$ stenosis

Concomitant carotid and coronary artery surgery is safe and effective, particularly in preventing ipsilateral stroke, and neutralizes the impact of unilateral carotid stenosis on early and late stroke (86). In the US, patients who undergo carotid artery stenting and CABG have significantly decreased in-hospital stroke rates compared with patients undergoing CEA and CABG, but the in-hospital mortality is similar. Carotid artery stenting may provide a safer carotid revascularization option for patients who require CABG (87).

Surgical treatment of peripheral artery disease. Invasive therapy in peripheral artery disease is indicated for critical limb ischemia (ankle brachial index < 0.4), not for claudication, unless it is disabling. The long-term results of the Bypass vs Angioplasty in Severe Ischemia of the Leg (BASIL) trial favor surgery rather than angioplasty if there is a good vein and the patient is fit (88).

THORACIC AORTIC ANEURYSMS: DIAGNOSIS AND TREATMENT

Randolph P. Martin, MD, Medical Director, Cardiovascular Imaging, Chief, Structural and Valvular Heart Disease, Piedmont Heart Institute; Professor Emeritus of Medicine, Emory University School of Medicine, Atlanta, Georgia

Thoracic aortic aneurysms (TAA). Each year, 30,000 to 60,000 deaths occur due to TAA. Thus, in the USA, they are the 18th most common cause of death and the 15th most common cause of death in individuals >65 years of age. TAAs are increasing in incidence. TAA is a virulent condition but an indolent process, growing slowly at ~0.1 cm per year. The use of an imaging technique to estimate true aortic size is confounded by its obliquity and asymmetry; thus, multiple imaging techniques may be required (89). Surgical intervention is indicated before TAAs reach 5.5 cm in diameter. A diameter of 5.0 cm may be the cut-off for patients with Marfan syndrome, a bicuspid aorta, or a family history of aortic dissection.

Aortic dissection occurs in a circadian and diurnal pattern, with predominance in winter months and early morning. Aortic dissections also occur around the time of extreme physical exertion or emotional distress. The frequency of aortic dissection or through-and-through rupture increases sharply when the ascending aortic diameter reaches 6.0 cm (34% lifetime risk of rupture or dissection) and 7.0 cm in descending thoracic aorta.

The Marfan syndrome. Marfan syndrome occurs due to a mutation of the fibrillin-1 gene. Patients with Marfan syndrome have a 50% risk of developing aortic dissection in their lifetime. About 5% of all TAAs are due to Marfan syndrome. TAAs in Marfan syndrome patients grow rapidly (>0.5 cm per year). A family history of aortic dissection may prompt earlier operative intervention at a diameter <5.0 cm. Pregnant patients with Marfan syndrome are at increased risk for aortic dissection if aortic diameter exceeds 4.0 cm.

Loeys-Deitz syndrome. Loeys-Deitz syndrome occurs due to mutations in the *TGFBR1* and *TGFBR2* genes. Patients have skeletal features of Marfan syndrome but with distinct cranial features, including craniosynostosis. Other features include hypertelorism, translucent skin and veins, arterial tortuosity, and aneurysms. Aortic repair should be done at aortic diameters <5.0 cm in patients with Loeys-Deitz syndrome.

Osteoarthritis syndrome. Osteoarthritis syndrome is an autosomal dominant disorder (*SMAD3* mutations) responsible for 2% of familial TAA dissections. The main features of the disease include early onset of osteoarthritis (the usual reason for patients seeking medical attention), mild craniofacial abnormalities, and tortuosities throughout the arterial tree—mostly the intracranial, iliac, abdominal, and thoracic aorta—leading to aneurysms. Patients have a substantial mortality and a high risk of aortic rupture and dissection with mildly dilated aortas.

Penetrating atherosclerotic ulcers. Atherosclerotic lesions may ulcerate (penetrating the internal elastic lamina) and produce hematomas within the media (90% in the descending thoracic aorta). They appear as a mushroom-like outpouching of the aortic lumen with overhanging edges.

Pseudoaneurysm of the thoracic aorta. Pseudoaneurysms occur in the descending thoracic aorta due to deceleration or torsional trauma. They can also occur after aortic root or aortic valve surgery, catheter-based interventions, or penetrating trauma.

Takayasu's aortitis. Takayasu's aortitis (90), a chronic inflammatory vasculitis involving the ascending aorta and carotid, renal, and subclavian arteries, is rare (1–2 cases/million) and

of unknown etiology. It affects women more than men (with a ratio of 9:1) and usually begins in the second or third decade of life. Takayasu's aortitis produces intimal fibroproliferation that results in segmental stenosis, occlusion, dilatation, and aneurysm formation. It is the only aortitis that causes stenosis and occlusion. Takayasu's aortitis is more prevalent in women of Asian descent, and 90% of the cases occur in patients <30 years of age. In its inflammatory stage, patients present with low-grade fever, tachycardia, pain adjacent to the inflamed arteries (carotodynia), and easy fatigability. Carotid and cervical bruits are often present. The systemic stage can be followed in 5 to 20 years by an occlusive stage. Neurologic symptoms are present in 80% of patients.

SEVERE BUT ASYMPTOMATIC AORTIC STENOSIS

Randolph P. Martin, MD

Severe AS is undertreated. More than 50% of patients with echocardiographic findings of severe AS are not referred for further evaluation for AVR. In the Euro Heart Survey (91), 36% of patients already had significant symptoms at the time of evaluation for AVR: 47% were NYHA class III/IV and 8% were NYHA class IV and had LV dysfunction at the time of surgery. Studies of severe asymptomatic AS suggest that a third of the patients will become symptomatic within 2 years. Within 4 to 5 years, two thirds have either had an AVR or died. The risk for sudden death is about 1% per year. Kang et al (92) showed a risk of sudden cardiac death of 1.7% per year in those with aortic velocity >5.0 m/sec.

The assessment of AS severity should be based on valve morphology: calcium, peak jet velocity, mean gradient, aortic valve area, LVEF, LV wall strain, LV wall fibrosis, and beta natriuretic peptide. These parameters should be integrated with presenting symptoms and response to exercise stress testing. The predictors of poor outcome in asymptomatic severe AS are a resting peak transvalvular velocity of 5.0 to 5.5 m/sec (73, 93), densely calcified aortic valve, valve area <0.75 cm² (94), mean gradient >50 mm Hg, abnormal LVEF, beta natriuretic peptide, and abnormal exercise test (defined as failure of systolic blood pressure to rise or a fall in systolic blood pressure, symptoms, or ST-segment depression with exercise). The echocardiographic predictors of poor outcome in AS also include the degree of valve calcium (95). The degree of valve calcium is not influenced by hemodynamic conditions, which is useful in low flow states. A computed tomography calcium score >1650 AU has 80% sensitivity and specificity for severe AS. Exercise stress testing can uncover symptoms in >40% of "asymptomatic severe AS" patients. Only 20% of patients who have positive stress tests are alive, symptom-free, without AVR at 24 months vs 85% with a negative test.

SYSTEMIC HYPERTENSION

William H. Frishman, MD, the Barbara and William Rosenthal Professor and Chairman, Department of Medicine, New York Medical College; Director of Medicine, Westchester Medical Center, Valhalla, New York

In older adults, hypertension is characterized by an elevated systolic blood pressure with normal or low diastolic blood

pressure, due to age-associated stiffening of the large arteries. Hypertension prevalence increases markedly with age; ~60% of the population has hypertension by age 60 and ~65% of men and ~75% of women have hypertension by 70 years (96). In the Framingham Study (97), hypertension eventually developed in >90% of subjects with normal blood pressure at age 55 years. Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg (98). Numerous randomized trials have shown substantial reductions in cardiovascular events in cohorts of patients 60 to 79 years old with antihypertensive drug therapy, though the effect on all-cause mortality has been modest. In HYVET, antihypertensive therapy reduced all-cause mortality in people ≥80 years old by 21% at 1.8-year follow-up. Those randomized to indapamide vs placebo had a 30% nonsignificant decrease in fatal/nonfatal stroke, 39% significant decrease in fatal stroke, 21% significant decrease in all-cause mortality, 23% insignificant decrease in cardiovascular death, and 64% significant decrease in heart failure.

Although the optimal blood pressure treatment goal in the elderly has not been determined, a therapeutic target <140/90 mm Hg in persons aged 65 to 79 years and a systolic blood pressure of 140 to 145 mm Hg, if tolerated, in persons aged ≥80 years is reasonable. The further lowering of diastolic blood pressure below 60 mm Hg may lead to coronary insufficiency and myocardial ischemic manifestations.

ALTERNATIVE MEDICINE FOR THE HEART

William H. Frishman, MD

About 50% of patients seek an alternative sort of medicine, which is defined as any practice that is put forward as having the healing effects of medicine, but is not based on evidence gathered by the scientific method. The placebo effects on blood pressure, arrhythmia (e.g., decrease in premature ventricular complexes), heart failure symptoms (increase in EF of 5% to 20%–30% of patients) and angina pectoris (about 50% of patients) have been noticed in every cardiovascular trial. Patients also develop common adverse effects to placebo drugs (99). No megavitamin, mineral, or nutraceutical has shown an evidence-based effect on cardiovascular disease. Most trials evaluating homeopathy have shown no benefit on cardiovascular diseases (100). Chelation therapy has theoretical benefits but had no effect on CAD in clinical trials (101). Neither masked prayer nor music, imagery, or touch therapy significantly improved clinical outcomes after elective catheterization or PCI (102). There are some conditions in which herbal medicines are used as cardiovascular treatments. Several adverse cardiovascular reactions have been observed with herbal medicines used for other indications. Also, several herbs have potential and documented interactions with warfarin (103).

HYPERTROPHIC CARDIOMYOPATHY AND PREVENTING SUDDEN DEATH IN THE YOUNG

Barry J. Maron, MD, Director, Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota

Age, magnitude of LV hypertrophy, EF, presence of atrial fibrillation, LV obstruction, apical aneurysm, and other cardiovascular risk factors all contribute to the outcome of patients with hypertrophic cardiomyopathy (HC). Morbidity in patients with HC includes sudden death, progressive heart failure, or the development of atrial fibrillation and stroke. The incidence of sudden death is proportional to the LV wall thickness; its incidence is only 0.2%/year in patients diagnosed after the age of 60 years. In a multicenter study of 670 low-risk HC patients, the incidence of sudden death was 0.6%/year. The Bethesda Conference recommended that athletes with an unequivocal diagnosis of HC should not participate in most competitive sports, with the possible exception of those of low intensity. This recommendation includes those athletes with or without symptoms and with or without LV outflow obstruction.

Drugs provide only a modest protection from sudden death in HC. A report of 506 patients showed that the implantable cardioverter defibrillator (ICD) intervened appropriately to abort ventricular tachycardia/fibrillation in 20% of patients over an average follow-up period of only 3.7 years, at a rate of about 4% per year in those patients implanted prophylactically, and often with considerable delays of up to 10 years (104). Appropriate device discharges for ventricular tachycardia/ventricular fibrillation occur with similar frequency in patients with 1, 2, or ≥3 noninvasive risk markers. In a study of 1101 patients with HC, the risk of progression to NYHA class III or IV or death specifically from heart failure or stroke was greater among patients with obstruction (relative risk: 4.4) (105). About 70% of HC patients have LV outflow obstruction either at rest (37%) or with provocation (33%).

Ommen and colleagues (106) evaluated 1337 consecutive HC patients: 289 patients had surgical myectomy; 228 had LV outflow obstruction without operation; and 820 had nonobstructive HC. Mean follow-up duration was 6 ± 6 years. Their 1-, 5-, and 10-year overall survival after myectomy was 98%, 96%, and 83%, respectively, which did not differ from that of patients with nonobstructive HC or from the general US population matched for age and gender. Compared with nonoperated obstructive HC patients, myectomy patients experienced superior survival free from all-cause mortality (98%, 96%, and 83% vs 90%, 79%, and 61%, respectively), HC-related mortality, and sudden cardiac death.

Different cardiology societies in the US and Europe recommend surgical myectomy as the gold standard in HC patients rather than alcohol septal ablation. Several issues remain with alcohol septal ablation: whether the outflow gradient/symptom relief is long-lasting; the relatively high rate of repeat procedures (25%); failure to obliterate the high gradients; and the fact that myectomy after failed ablations is difficult. The infarct/scar produced by ablation also may predispose patients to sudden death.

HEART FAILURE GUIDELINES

Clyde W. Yancy, MD, Professor of Medicine, Chief, Division of Cardiology, Northwestern University Feinberg School of Medicine, and Associate Director, Bluhm Cardiovascular Institute, Northwestern Memorial Hospital, Chicago, Illinois

There is a substantial variation among cardiologists in conformity with quality treatment measures for heart failure patients (107). Fonarow et al (108) reported 15,177 patients with reduced LVEF ($\leq 35\%$) and chronic heart failure or post-MI. The mortality rate at 24 months was 22%. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, β -blocker use, anticoagulant therapy for atrial fibrillation, CRT, ICDs, and heart failure education for eligible patients were each independently associated with improved 24-month survival, whereas aldosterone antagonist use was not. Each 10% improvement in guideline-recommended composite care was associated with a 13% lower odds of 24-month mortality. The adjusted odds for mortality risk for patients with conformity to each measure was 38% lower than for those whose care did not conform for one or more measures.

The 2013 heart failure guidelines are expected to include changes in the areas of CRT, LV assist device, the role of reduced dietary sodium intake, and evidence-proven methods to reduce readmissions.

Cardiac resynchronization therapy. The REVERSE (109) trial was designed to determine if CRT \pm ICD modified disease progression over 12 months in patients with asymptomatic and mildly symptomatic heart failure and ventricular dyssynchrony. Patients were in NYHA class II or I (previously symptomatic), normal sinus rhythm, QRS ≥ 120 ms, LVEF $\leq 40\%$, LV end diastolic diameter ≥ 55 mm, without bradycardia, with or without ICD indication, on optimal medical therapy. All patients received CRT and then were randomized to have the device either on or off. Beginning at 1 year in the US and 2 years in Europe, all patients with CRT ON underwent yearly follow-up over 5 years. The heart failure clinical composite response endpoint indicated 16% worsening with CRT-ON compared with 21% worsening with CRT-OFF. Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (-18.4 mL/m² vs -1.3 mL/m²) and other measures of LV remodeling. Time to first heart failure hospitalization was significantly delayed in CRT-ON (hazard ratio: 0.47). The investigators concluded that CRT produced sustained reverse remodeling accompanied by low mortality and need for heart failure hospitalization. The benefits of CRT persisted, indicating that CRT attenuates disease progression in mildly symptomatic heart failure patients with wide QRS over at least 5 years. REVERSE, however, was underpowered to show mortality benefit and there was no long-term comparator. The RAFT (110) and MADI CRT (111) trials also showed the benefit of CRT in mild to moderate heart failure with short follow-up periods.

Left ventricular assist device. Several clinical studies (112–115) have shown improved survival with LV assist devices compared to medical therapy for advanced heart failure. The LV assist devices have not been shown to be cost effective.

Salt restriction in systolic heart failure. Taylor et al (116) performed a Cochrane database review and identified 7 randomized controlled trials (3 in normotensives, 2 in hypertensives, 1 in a mixed population of normo- and hypertensives, and 1 in heart failure) with follow-up of at least 6 months comparing restricted

dietary salt intake or advice to reduce salt intake to control/no intervention in adults, and reported mortality or cardiovascular disease morbidity data. All-cause mortality and cardiovascular mortality for both normotensives and hypertensives were not reduced compared with the control group. In heart failure patients, salt restriction significantly increased all-cause death. Dinicolantonio and colleagues (117) analyzed 6 randomized controlled trials comparing low-sodium diets (1.8 g/day) with a higher-sodium diet (2.8 g/d) in 2747 patients with systolic heart failure. The low-sodium diet significantly increased all-cause mortality, sudden death, death due to heart failure, and heart failure readmissions.

Heart failure readmission rates. Hernandez et al studied a population that included 30,136 patients from 225 hospitals (118). Patients who were discharged from hospitals with higher early follow-up rates had a lower risk of 30-day readmission. The proper planning for transition of care and early outpatient follow-up was the only evidence-proven method of decreasing readmission rates for heart failure patients.

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