Recent Advances in Preventive Cardiology and Lifestyle Medicine

A Themed Series

Barry A. Franklin, PhD; Mary Cushman, MD, MSc

Multifactorial risk factor modification and control, especially interventions designed to reduce total cholesterol, systolic blood pressure, smoking prevalence, overweight/obesity, diabetes mellitus, and physical inactivity, can have a profound and favorable impact on decreasing the incidence of initial and recurrent cardiovascular events. Between 1980 and 2000, mortality rates from coronary heart disease (CHD) fell by >40%. Using a previously validated statistical model (IMPACT), researchers attempted to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in risk factors among US adults aged 25 to 84 years. Approximately half of the decline in cardiovascular deaths was attributed to reductions in major risk factors (obesity and diabetes mellitus were notable exceptions), and approximately half was attributed to evidence-based medical therapies (eg, secondary prevention medications, rehabilitation, and initial treatments for acute myocardial infarction [AMI]). In contrast, emergent and elective revascularization accounted for only 7% of the overall decline in deaths from CHD. Recently, similar results were reported in a Canadian study that evaluated the decrease in CHD mortality between 1994 and 2005.

Over the past decade, mortality rates from CHD and stroke in the United States decreased by >25% (Figure 1). Although there were also impressive reductions in the prevalence of uncontrolled high blood pressure, elevated blood cholesterol, and, to a lesser extent, cigarette smoking, there was only limited impact on other risk factors, including increases in the prevalence of obesity and diabetes mellitus, and a small reduction in those not engaged in moderate or vigorous physical activity. These indicators represent major challenges to achieving future goals for cardiovascular health promotion and disease reduction.

In 2009, a task force representing numerous professional organizations/associations developed a Competence and Training Statement on the Prevention of Cardiovascular Disease. More recently, the American Heart Association (AHA) released its bold new impact goal for the next 10 years, the 2020 Impact Goal: “to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%.” This 2020 goal has an innovative new element to improve clinically relevant health and behavioral factors. Cardiovascular health is defined in 3 categories of ideal, intermediate, and poor on the basis of 7 simple health factors and modifiable behaviors, as detailed in the My Life Check assessment tool at http://www.mylifecheck.heart.org.

This review provides a compendium of important advances in preventive and lifestyle medicine during the past decade, including discussion of some emerging but unproven interventions (ie, the polypill) as well as the value of conducting large-scale randomized clinical trials rather than relying on biological hypotheses and observational data (ie, the homocysteine story). We also provide a call to action to support the AHA’s 2020 goals, summarize the impact of preventive interventions as a first-line strategy to combat stable cardiovascular disease (CVD), and discuss the potential impact of behavioral and complementary interventions in reducing the burden of CVD. Finally, we detail the goals of a new Circulation series of publications on Preventive Cardiology and Lifestyle Medicine.

A Decade of Discovery: Implications for Primordial, Primary, and Secondary Prevention

Prevention can be divided into 3 types: primordial (prevention of risk factors); primary (treatment of risk factors); and secondary (prevention of recurrent cardiovascular events) (Figure 2). Much of the success in reducing CVD in recent years has been through the latter 2 methods; however, additional emphasis on primordial prevention is needed to meet the AHA 2020 Impact Goal of improving cardiovascular health and achieving an additional 20% reduction in death from CVD and stroke.

From the Departments of Medicine and Cardiology, Cardiac Rehabilitation and Exercise Laboratories, William Beaumont Hospital, Royal Oak, MI (B.A.F.); and Departments of Medicine and Pathology, University of Vermont College of Medicine, Burlington (M.C.). Dr Franklin is Immediate Past Chair, American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Dr Cushman is Immediate Past Chair, American Heart Association Council on Epidemiology and Prevention.

Correspondence to Barry A. Franklin, PhD, Cardiac Rehabilitation and Exercise Laboratories, William Beaumont Hospital, Beaumont Health Center, 4949 Coolidge Hwy, Royal Oak, MI 48073. E-mail bfranklin@beaumont.edu

(Circulation. 2011;123:2274-2283.)

© 2011 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.981613

2274
The importance of risk factors in the development of CVD has received increased attention over the past decade. In addition, along with cardioprotective medications, the roles of lifestyle interventions, psychosocial factors, air pollution, dietary patterns, physical inactivity, low cardiorespiratory fitness, obesity, cardiac rehabilitation, and inflammation have been better elucidated as modulators of CVD and as targets for education, behavioral interventions, and policy approaches to improving health. Newer statin drugs, in particular, which markedly decrease and increase low-density lipoprotein and high-density lipoprotein cholesterol, respectively, have been heralded as a potential breakthrough to prevent initial and recurrent atherosclerotic events. Consider the following key reports of the 2000s.

Risk Factors as Antecedents of Cardiovascular Disease: Debunking the Only 50% Myth

The INTERHEART study examined the risk factors associated with first AMI in 52 countries, including 15 152 cases and 14 820 controls. Collectively, 9 risk factors (abnormal lipids, smoking, hypertension, diabetes mellitus, abdominal obesity, psychosocial variables, consumption of fruits and vegetables, regular alcohol consumption, regular physical activity) accounted for 90% of the population attributable risk in men and 94% in women. Similarly, Khot et al and Greenland et al examined data from 14 randomized clinical trials (n = 122 458) and 3 prospective cohort studies (n = 386 915), reporting that >80% of patients who developed CHD and ≥87% of patients who experienced a fatal coronary event had antecedent exposure to ≥1 of the 4 conventional cardiovascular risk factors (cigarette smoking, dyslipidemia, hypertension, diabetes mellitus). People with optimal levels of cardiovascular risk factors and lifestyle behaviors at 50 years of age demonstrate a marked survival advantage and only a 5% and 8% lifetime risk of developing CVD for men and women, respectively. Collectively, these data and other recent reports discount the longstanding claim that only 50% of CHD is attributable to conventional risk factors, and suggest that a more rigorous focus on these and the lifestyle behaviors that promote them has great potential to reduce the burden of atherosclerotic heart disease.

Lifestyle and Mortality in Coronary Patients

One review of prospective cohort studies and randomized, controlled trials among patients with established CHD sought to provide evidence for a prognostic benefit of lifestyle and dietary recommendations. Effect estimates for smoking cessation, higher levels of physical activity, and moderate alcohol consumption varied from a 20% to 35% lower risk of all-cause mortality. For individual dietary goals, data were too limited to provide reliable effect size estimates. If these estimates reflect the true value, they compare favorably with mortality reductions reported for low-dose aspirin, statins, β-blockers, and angiotensin-converting enzyme inhibitors after AMI. On the other hand, there are no randomized trials showing that alcohol consumption improves health, and the overall harms are well known: addiction, social dysfunction, and motor vehicle accidents. One large-scale study showed that low to moderate alcohol consumption may be associated with an increased risk of cancer in women.

Cigarette Smoking, Mortality, and Effects of Secondhand Smoke

A landmark study of 50 years of observation of 34 439 male British physicians found that, on average, cigarette smokers die sooner than non-smokers from ischemic heart disease, stroke, and all-cause mortality.

Figure 1. Mortality rates from coronary heart disease and stroke, rate of uncontrolled blood pressure, and prevalence of high cholesterol from 2004 to 2008. Reproduced from Lloyd-Jones et al.
and \( \approx 10 \) years younger than nonsmokers.\textsuperscript{15} For someone who has smoked since adulthood, cessation at age 50 years halved the hazard, and cessation at age 30 years avoided almost all of it. Quitting smoking at age 60 or 40 years increased life expectancy by \( \approx \) 3 and 9 years, respectively. More recently, using data from the Survival and Ventricular Enlargement trial, investigators reported that in selected patients with left ventricular dysfunction after AMI, smoking cessation is associated with a 40% lower hazard of all-cause mortality compared with persistent smokers over an average follow-up of 42 months.\textsuperscript{16}

A moderate-sized randomized clinical trial, involving a 10-week smoking cessation program that included strong physician counseling and 12 group sessions using behavior modification and nicotine gum, plus either ipratropium or a placebo inhaler, found that over a 14.5-year follow-up, the intervention reduced the risk of death by 18% compared with a usual-care control group.\textsuperscript{17} It should be noted, however, that these findings applied to a special group of heavy smokers who had preexisting airway obstruction. Because the relative risk for lung cancer is so high among smokers, the need for randomized trials is less compelling. On the other hand, nearly all risk factors associated with CHD have effect sizes that are much smaller, making them seriously vulnerable to confounding variables and selection biases when evaluated in observational studies.

Although it is tempting to believe that the tobacco war has been won because of the important strides that have been made in tobacco control, in terms of both interventions and outcomes, the prevalence of smoking in the United States hovers at 20%, >8 million people are sick or disabled as a result of tobacco use, and smoking kills an estimated 450,000 Americans annually.\textsuperscript{18} Even a very short period of passive smoke exposure has persistent vascular consequences, such as the mobilization of dysfunctional endothelial progenitor cells with blocked nitric oxide production.\textsuperscript{19} Secondhand smoke is responsible for an estimated 603,000 deaths worldwide each year, and more than half of the deaths (379,000) are due to CVD.\textsuperscript{20} Accordingly, despite the current emphasis on healthcare reform, escalating medical costs, and childhood obesity, cigarette smoking remains by far the most common cause of preventable death and disability in the United States.\textsuperscript{18} Unless legal challenges delay or defeat government plans, in 2012 each cigarette pack sold in the United States will carry powerful graphic label warnings of the dangers of smoking, which may serve to reduce smoking rates among younger people.

### Prevention of Type 2 Diabetes Mellitus With Lifestyle Intervention

Considerable data now strongly support the role of lifestyle intervention to improve glucose and insulin homeostasis. The Finnish Diabetes Prevention Study reported that a lifestyle intervention (reducing body weight by \( \geq 5\% \); decreasing fat and saturated fat intake to \( <30\% \) and \( <10\% \) of energy intake, respectively; increasing fiber intake to \( \geq 15 \) g/1000 kcal; and an increase in exercise to \( \geq 30 \) min/d) resulted in a 58% reduction in the development of diabetes mellitus in high-risk overweight subjects with impaired glucose tolerance compared with a usual-care control group over 3.2 years.\textsuperscript{21} Similarly, the Diabetes Prevention Program Research Group demonstrated that a lifestyle modification program with goals of \( \geq 7\% \) weight loss and \( \geq 150 \) minutes of physical activity per week in overweight patients with impaired fasting glucose resulted in a 58% reduction in the incidence of diabetes mellitus, whereas there was a 31% reduction with metformin (850 mg twice daily) compared with placebo.\textsuperscript{22} The Diabetes Prevention Program (http://www.ClinicalTrials.gov; NCT00004992) and its long-term outcome study (NCT00387277) will determine whether the lifestyle-induced reduction in diabetes mellitus translates into a reduction in major coronary events.\textsuperscript{23,24}

### Impact of Psychosocial Risk Factors on Cardiovascular Disease

An escalating body of research provides compelling evidence for an association of psychosocial factors with risk of CVD and prognosis of patients with CHD.\textsuperscript{25} Psychological risk factors such as depressive symptoms, anxiety, and vital exhaustion may worsen or exacerbate the development of CVD through associated unhealthy behaviors and physiological responses (Table) that may lead to clinical consequences, including myocardial ischemia, threatening ventricular arrhythmias, vulnerable plaque, and increased thrombosis potential and inflammation.\textsuperscript{26–29} Recognizing this relationship offers an important potential target for cardiovascular risk reduction that requires testing in appropriately designed trials.\textsuperscript{30} This may maximize the potential for cardiovascular risk reduction by addressing at least a portion of the 10% to 25% incidence of CHD that is unexplained by traditional risk factors.\textsuperscript{11,31}

Patients with clinical depression are at least 3 times more likely to die during the first year after AMI than are patients without depression.\textsuperscript{32} Although the reasons for this are unclear, it appears that patients with depression after AMI are less likely to take prescribed medications and adhere to recommended behavior and lifestyle changes intended to reduce the risk of recurrent cardiovascular events.\textsuperscript{33} Moreover, investigators recently reported that depression is associated with a decrement in composite health score that is significantly greater than that associated with other chronic
diseases, including angina, arthritis, asthma, and diabetes mellitus. When depression occurred in conjunction with other chronic diseases, it was associated with significantly greater decrements in overall health than the medical condition alone, particularly in persons with diabetes mellitus. Although a recent AHA Science Advisory recommended screening for depression in patients with CVD, there have been no large-scale randomized trials showing that screening prevents major cardiovascular events.

Ineffectiveness of Homocysteine Lowering on the Incidence of Cardiovascular Events

Although homocysteine levels have been directly associated with cardiovascular risk in many observational studies, several randomized, double-blind, placebo-controlled clinical trials have discounted the hypothesis that supplementation with folic acid and other B vitamins that lower homocysteine would prevent acute cardiovascular events. After 7.3 years of treatment and follow-up, Albert and associates found that a combination pill of folic acid, vitamin B₆, and vitamin B₁₂ did not reduce the incidence of cardiovascular events among 5542 women with prior CVD or ≥3 coronary risk factors, despite significant homocysteine lowering. In the Heart Outcomes Prevention Evaluation Trial (HOPE 2), the same homocysteine-lowering treatment did not reduce the risk of major cardiovascular events among 5522 patients aged ≥55 years with vascular disease or diabetes mellitus over an average of 5 years. These results are consistent with a prior meta-analysis of randomized, controlled trials performed primarily among men with known vascular disease and do not support the use of B vitamins as preventive interventions for CVD in at-risk populations. The homocysteine story is an excellent example of why prevention enthusiasts must insist on large-scale randomized trials and not rely on biological hypotheses and observational data.

A Cardioprotective Polypill: Need for a Fully Powered Trial?

Wald and Law proposed a theoretical cardioprotective polypill, on the basis of a review of the scientific literature (including >750 trials with ≈400 000 participants), as a population strategy to combat CVD. The daily formulation would include a statin, 3 blood pressure–lowering drugs, folic acid, and aspirin, and could theoretically reduce coronary events by 88% and stroke by 80%. Others have reported that a similar polypill (Polycap formulation) effectively reduces events by 88% and stroke by 80%. Others have reported that a similar polypill (Polycap formulation) effectively reduces events by 88% and stroke by 80%. Others have reported that a similar polypill (Polycap formulation) effectively reduces events by 88% and stroke by 80%. Others have reported that a similar polypill (Polycap formulation) effectively reduces events by 88% and stroke by 80%.

Lifestyle Factors Associated With Lower Cardiovascular Risk

According to 2 recent studies, favorable lifestyle factors are associated with dramatically reduced risks of hypertension and heart failure. In the first study, an analysis of data from the longitudinal Nurses’ Health Study II, adherence to 6 lifestyle factors—normal body mass index (<25 kg/m²); a low-sodium diet high in fruits, vegetables, and low-fat dairy products; a daily average of 30 minutes of vigorous exercise; modest alcohol intake (up to 10 g/d); infrequent use of nonnarcotic analgesics (less than once per week); and folic acid supplementation (≥400 μg/d)—was associated with a significantly lower incidence of self-reported hypertension. The authors acknowledged that if these associations were causal and independent, then lifestyle modification could have the potential to prevent a large proportion of new-onset hypertension occurring in young women. Similarly, the PREMIER randomized clinical trial reported that individuals with above optimal blood pressure, including stage 1 hypertension (120 to 159 mm Hg systolic and 80 to 95 mm Hg diastolic), who were not taking antihypertensive medications, can make multiple lifestyle changes that lower blood pressure and reduce cardiovascular risk. In another report, data were analyzed from 20 900 apparently healthy men (mean age at baseline, 53.6 years) in the Physicians’ Health Study who were followed for 22.4 years, during which time 1200 developed heart failure. Men who adhered to ≥4 of 6 healthy lifestyle habits (normal body weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereals, and a diet high in fruits and vegetables) had a 10% risk of developing heart failure. Men who did not adhere to any of these factors had a 21% risk of developing heart failure.

Because the healthy adherer effect is well known, these reports from observational studies should be interpreted with caution. The Coronary Drug Project showed that individuals who adhere to placebo therapy generally have better health outcomes. Accordingly, people who adhere to healthy lifestyle practices often do better, but it remains unclear whether it is due to the intervention per se.

Air Pollution and Cardiovascular Risk

Numerous epidemiological studies have demonstrated consistent associations between short-term elevations in particular matter (air pollution) and increases in nonfatal and fatal cardiovascular events, including myocardial ischemia and infarction, ventricular arrhythmia, heart failure exacerbation, and stroke. The pathways linking air pollution exposure to the onset of acute cardiovascular events may be explained by the direct effects from agents that cross the pulmonary epithelium into the circulation, including gases and the soluble constituents of particles (eg, transition metals). Al-
though the increase in relative risk for CVD due to air pollution for an individual may be small compared with the impact of conventional risk factors, this omnipresent exposure likely translates into a substantial increase in total mortality within the population.\(^5\) The potential to substantially decrease cardiovascular morbidity and mortality by lowering particulate matter levels to current Environmental Protection Agency standards is apparent.\(^5\)

**Dietary Pattern and Risk of Cardiovascular Disease**

A substantial and expanding body of evidence has now associated a healthy dietary pattern with lower rates of major coronary events and diabetes mellitus.\(^5\) One systematic review found strong evidence of a causal relationship for cardioprotective dietary practices, including vegetables, nuts, and Mediterranean eating patterns, as well as associations for harmful factors, including intake of trans fatty acids and foods with a high glycemic index or load, and CHD.\(^5\) Modest reductions in dietary salt may also substantially reduce cardiovascular events and associated medical costs.\(^5\) Epidemiological and controlled interventional studies have consistently demonstrated the beneficial effects of omega-3 fatty acid consumption, especially the longer-chain fatty acids (≥20 carbons) from marine sources, on cardiovascular end points.\(^5\) Moreover, a 2-year study of weight loss diets, using either low-fat, Mediterranean, or low-carbohydrate strategies, reported a significant regression of carotid atherosclerosis, irrespective of the dietary intervention.\(^5\) On the other hand, the Women’s Health Initiative Dietary Modification Trial, the largest long-term randomized, controlled trial of a dietary intervention conducted to date, including 48 835 postmenopausal women aged 50 to 79 years who were followed over a mean of 8.1 years, showed that a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD, and achieved only modest effects on CVD risk factors.\(^5\) Nevertheless, subgroup analyses showed positive trends toward greater reductions in low-density lipoprotein cholesterol levels and rates of CHD in women with the lowest intakes of saturated fat or trans fat or highest intakes of vegetables/fruits. Because the trial was designed to test the hypothesis that a dietary intervention could lower rates of breast and colorectal cancer rather than CVD, the investigators suggested that more focused diet and lifestyle interventions may be needed to reduce CVD risk.

**Mortality Benefits of Cardiac Rehabilitation in Modern Cardiology**

Among older patients with documented CHD who undergo cardiac rehabilitation, mortality rates are generally 21\% to 34\% lower than among nonusers,\(^6\) and a significant dose-response relationship exists between the number of cardiac rehabilitation sessions attended and cardiovascular outcomes at 4 years.\(^6\) It has been suggested that contemporary thrombolytic and emergent revascularization procedures, which markedly diminish early postinfarction mortality, and newer cardioprotective drug therapies may serve to attenuate the impact of adjunctive exercise-based cardiac rehabilitation. Although a recent review of 48 randomized trials concluded that the mortality benefits of cardiac rehabilitation persist in modern cardiology,\(^6\) meta-analyses like these are suggestive but cannot be considered definitive.\(^6\) Despite the potential survival advantage and related beneficial outcomes, cardiac rehabilitation services remain vastly underutilized among Medicare beneficiaries.\(^6\)

**Pharmacotherapies and Lifestyle Modification in Patients With Acute Coronary Syndrome**

Although individual drug therapies, such as antiplatelet medications, \(\beta\)-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering agents, are effective in reducing mortality in patients with acute coronary syndrome, it appears that the combination of these agents may have incremental and even synergistic benefits. Researchers created a composite appropriateness score for 6-month mortality based on the number of drugs used divided by the number of drugs potentially indicated for each patient, as follows: 0, none of the indicated medications used; I, 1 medication used if 3 or 4 medications indicated; II, 2 medications used if 3 or 4 medications indicated or 1 medication used if 2 medications indicated; III, 3 medications used if 4 medications indicated; and IV, all indicated medications used. The odds ratio for death for appropriate levels IV, III, II, and I were 0.10, 0.17, 0.18, and 0.36, respectively.\(^6\) A more recent study reported that adherence to behavioral advice (modify diet, exercise, and quit smoking) after acute coronary syndrome was associated with a substantially lower risk of recurrent cardiovascular events.\(^6\) Collectively, these data suggest that a combination of evidence-based medical therapies and behavioral recommendations in the immediate postevent care of patients with acute coronary syndrome should be given a high priority by physicians and adjunctive healthcare providers.

**Physical Activity, Cardiorespiratory Fitness, and Mortality**

A recent systematic review and meta-analysis of 33 physical activity studies (\(n=883\) 372 participants) reported risk reductions of 30\% to 50\% for cardiovascular mortality and of 20\% to 50\% for all-cause mortality, with pooled risk reductions of 35\% and 33\%, respectively.\(^6\) There are multiple mechanisms by which moderate to vigorous physical activity may decrease mortality rates associated with CVD (Figure 3), including antithrombotic, anti-ischemic, antiarrhythmic, and psychological effects. Numerous studies also suggest that cardiorespiratory fitness, expressed as metabolic equivalents (1 metabolic equivalent=3.5 mL \(\text{O}_2\) per kilogram per minute) is 1 of the strongest prognostic markers in persons with and without CHD.\(^7\) In healthy men and women, each 1-metabolic equivalent increase in exercise capacity confers a 13\% and 15\% reduction in all-cause mortality and cardiovascular events, respectively. Participants with an aerobic capacity ≥7.9 metabolic equivalents had the most favorable health outcomes.\(^7\) Dutcher et al\(^7\) reported that cardiorespiratory fitness more accurately predicts 5-year mortality than left ventricular ejection fraction in patients with ST-segment elevation MI treated with percutaneous coronary intervention (PCI). On the other hand, a

---

\(^{5}\) Dutcher et al. 2017

\(^{6}\) Dutcher et al. 2011

\(^{7}\) Dutcher et al. 2017

\(^{8}\) Dutcher et al. 2011

\(^{9}\) Dutcher et al. 2012

\(^{10}\) Dutcher et al. 2013

\(^{11}\) Dutcher et al. 2014

\(^{12}\) Dutcher et al. 2015

\(^{13}\) Dutcher et al. 2016
disproportionate number of acute cardiovascular events occur in habitually sedentary individuals with known or occult CHD performing unaccustomed vigorous physical activity. Collectively, these data suggest that the least active, least fit, “high-risk” patient cohort (bottom 20%) may especially benefit from structured exercise, increased lifestyle activity, or both to improve survival. Future large-scale event-driven trials of moderate to vigorous physical activity, in varied populations, would be helpful in further clarifying the cardioprotective benefits and risks of this widely recommended intervention.

Obesity Is Strongly Associated With Acute Coronary Events Occurring Prematurely

In 1998, in response to an emerging body of scientific evidence, the AHA reclassified obesity as a major modifiable risk factor for CHD. Subsequently, numerous studies have substantiated that obesity confers an independent and additive risk of all-cause and cardiovascular mortality, even in the absence of metabolic syndrome. Other reports suggest that excess adiposity is strongly associated with the premature occurrence of AMI. Although some obese patients with CVD have lower adverse events and mortality than their metabolically leaner counterparts (ie, the “obesity paradox”), numerous studies now support purposeful weight reduction in this escalating patient subset.

With the use of serial data and appropriate follow-up from the National Health and Nutrition Examination Surveys (I, II, III), the Centers for Disease Control and Prevention found that underweight and obesity, particularly high levels of obesity, were associated with increased mortality relative to the normal weight category. On the other hand, overweight individuals with CVD have lower adverse events and mortality than their metabolically leaner counterparts (ie, the “obesity paradox”). Numerous studies now support purposeful weight reduction in this escalating patient subset.

Potential Cardioprotective Effects of Regular Physical Activity

Figure 3. Mechanisms by which moderate to vigorous exercise training may reduce the risk of nonfatal and fatal cardiovascular events. The cardioprotective vascular conditioning effect may include enhanced nitric oxide vasodilator function, improved vascular reactivity, altered vascular structure, or combinations thereof. BP indicates blood pressure; EPCs, endothelial progenitor cells; CACs, cultured/circulating angiogenic cells; and HR, heart rate. Adapted from Franklin BA, McCullough PA.

Inflammation, Low-Density Lipoprotein Cholesterol, and Statin Therapy: Implications for Primary Prevention?

Although numerous studies have highlighted the potential role of inflammation in the genesis of CVD and atherothrombosis and there is mounting evidence supported by guidelines of the clinical utility of inflammation assessment with biomarkers such as C-reactive protein, some investigators remain unconvinced that measurement of inflammation markers in practice is useful in risk prediction. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial enrolled 17,802 men and women without documented CVD or diabetes mellitus with low-density lipoprotein cholesterol levels ≤130 mg/dL and C-reactive protein levels ≥2 mg/L and randomly assigned them to rosuvastatin 20 mg daily or placebo. The investigation was designed to test the hypothesis that statin therapy, in people with levels of low-density lipoprotein cholesterol below currently recommended thresholds for treatment, would decrease the rate of first major cardiovascular events by virtue of the inflammation- and lipid-lowering potential of this treatment. The trial was stopped prematurely after a median follow-up of 1.9 years, demonstrating a 44% reduction in incident cardiovascular events and a 20% reduction in all-cause mortality. These data have potential implications for primary prevention by providing treatment to a large segment of the population that would not normally be prescribed a statin. Others contend that a significant proportion of the JUPITER subjects were not healthy, and warranted aggressive management, regardless of the concentration of C-reactive protein. Their analyses suggested that failure to adhere to currently accepted guidelines for care probably resulted in a spuriously high event rate that was conducive to the demonstration of benefit from statin therapy. Optimally designed trials to test the hypothesis of risk reduction with inflammation lowering would require a trial of a specific inflammation-lowering agent or a trial randomizing participants to usual care or to C-reactive protein testing as a guide to treatment.

Value of Percutaneous Coronary Intervention in Stable Coronary Heart Disease? Prevention as a First-Line Strategy to Combat Cardiovascular Disease

Primary PCI, with mechanical revascularization, reduces mortality in patients presenting with AMI. However, in patients with symptomatic or asymptomatic myocardial ischemia, the benefits of elective PCI are not as robust. In 2003, investigators evaluated the 7-year outcome of angioplasty versus medical therapy as the initial treatment strategy for chronic angina. Although symptoms were improved and use of antianginal medications decreased, the incidence of death or MI was slightly higher in the angioplasty cohort than in the medically treated patients, at 7.3% versus 4.1%, respectively.

The Atorvastatin Versus Revascularization Treatment (AVERT) study rekindled the debate concerning the pre-
ferred therapeutic strategy in patients with stable single- or double-vessel coronary artery disease.93 After 18 months’ follow-up, 22 of the 164 patients (13%) receiving atorvastatin had an ischemic event compared with 37 of 177 (21%) assigned to angioplasty and usual care, signifying a 36% reduction (P<0.05) in the group that received aggressive lipid-lowering therapy. In another clinical trial, men with single-vessel coronary disease were randomized to PCI versus a 12-month exercise program.94 Significantly higher event-free survival occurred with exercise training (88% versus 70%). Increased exercise capacity, reduced need for hospitalization, and decreased numbers of repeat revascularizations were also noted in patients randomized to the exercise intervention. Accordingly, Green et al95 suggested the following: “Coronary interventions treat a very short segment of the diseased coronary tree, whereas exercise exerts beneficial effects on endothelial function and disease progression in the entire arterial bed.”

In 2005, Katritsis and Ioannidis96 performed a meta-analysis of 11 randomized trials, including a total of 2950 patients, comparing PCI with conservative medical management in patients with stable coronary artery disease. In the absence of a recent MI, there was no significant difference between the 2 treatment strategies in terms of death, MI, or the need for subsequent revascularization. The COURAGE trial randomized 2287 patients with objective evidence of myocardial ischemia and stable coronary disease to PCI with optimal medical therapy versus optimal medical therapy alone. Again, lack of mortality benefit from PCI was observed.97 Similarly, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study Group reported no significant difference in the rates of death and major cardiovascular events among patients with type 2 diabetes mellitus and stable ischemic heart disease undergoing prompt revascularization versus medical therapy alone.98 Despite these sobering reports, in 2006, 1.3 million coronary angioplasty procedures were performed at a cost approximating $60 billion, and 448 000 coronary bypass operations were performed the same year throughout the United States, at an estimated cost of >$44 billion.99 Total healthcare spending in 2006 exceeded $2 trillion or $6700 per person, representing 16% of the gross domestic product. This trend is expected to increase at similar levels over the next few years, reaching $4 trillion in 2015 or 20% of the gross domestic product.100 Thus, in the near future, according to current projections, healthcare will account for $1 of every $5 spent in the United States. Currently, costs associated with chronic diseases (eg, obesity, diabetes mellitus, hypertension, coronary artery disease) account for ≈75% of the nation’s annual healthcare costs. Accordingly, we must find ways to implement effective preventive interventions (eg, medications, weight reduction, healthier eating practices, regular physical activity) as a first-line strategy to combat CVD.100

**Goals of the Prevention Series**

The science volunteers of the AHA have become energized early toward the achievement of the AHA 2020 Impact Goal and the role that prevention will have in improving cardiovascular health. Accordingly, this special Prevention series will review new insights in preventive cardiology, lifestyle interventions, and cardiac rehabilitation, with a focus on emerging clinical and psychosocial risk factors, cardioprotective drug and dietary recommendations, smoking cessation, cardiorespiratory fitness/physical activity, and counseling of patients regarding cardioprotective lifestyle changes. The series will explore the independent and additive benefits that may result when aggressive lifestyle modification is superimposed on optimal medical therapy (eg, cardioprotective medications). Interest in this area spans multiple dimensions involving traditional prevention strategies, improving compliance, lifestyle medicine, methods of education of healthcare providers, the built environment (where people live), strategies for health promotion in underserved ethnic groups, including the economically disadvantaged, childhood inter-
ventions, complementary and alternative therapies, and public policy interventions. Figure 2 illustrates a general framework for integration of these activities.

In summary, we hope that the new Circulation series will serve as a stimulus for leaders in preventive cardiology and lifestyle medicine to reflect on current knowledge and propose concepts for well-designed, large-scale randomized clinical trials and quasi-experimental studies that are needed to prove or disprove the many hypotheses listed herein. Equally, we hope that the reader will be stimulated to pursue changing paradigms and perceptions of these important topics. New studies should serve to complement the armamentarium of clinical, public health, and advocacy initiatives that will be needed to achieve further reductions in death from CVD and stroke. The challenge is yours!

Disclosures

None.

References


2282  Circulation  May 24, 2011


50. Hennekens CH, DeMets D. The need for large-scale randomized evidence without undue emphasis on small trials, meta-analyses, or subgroup analyses. JAMA. 2009;302:2361–2362.


61. Hennekens CH, DeMets D. The need for large-scale randomized evidence without undue emphasis on small trials, meta-analyses, or subgroup analyses. JAMA. 2009;302:2361–2362.


65. Nocn M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and...
Franklin and Cushman

Preventive Cardiology and Lifestyle Medicine

2283


91. Keeley EC, Boura JA, Grimes CL. Primary angioplasty versus intrave-
nous thrombolytic therapy for acute myocardial infarction: a quantitative

92. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KAA, Julian
DG, Chamberlain DA; for the Second Randomized Intervention
Treatment of Angina (RITA-2) Trial Participants. Seven-year outcome in
the RITA-2 trial: coronary angioplasty versus medical therapy. J Am

Eisenberg D, Shurrizinke L, McCormick LS; for the Atovarstatin versus
Revascularization Treatment Investigators. Aggressive lipid-lowering
therapy compared with angioplasty in stable coronary artery disease.

94. Hambrecht R, Walther C, Möbius-Winkler S, Glien S, Linke A, Con-
G. Percutaneous coronary angioplasty compared with exercise
training in patients with stable coronary artery disease: a randomized

95. Green DJ, O’Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovas-
cular risk reduction: time to update the rationale for exercise? J Appl

96. Katrisis DG, Ioannidis JPA. Percutaneous coronary intervention versus
conservative therapy in nonacute coronary artery disease: a meta-

97. Bonow RO, Lee W-M, Teo KK, Hartigan L, Maron DJ, Kostuk
WJ, Knudson M, Dada M, Casperson P, Harris CL, Chaitman BR,
DC, Bates ER, Speruta JA, Berman DS, Mancini GB, Weintraub WS;
for the COURAGE Trial Research Group. Optimal medical therapy with
or without PCI for stable coronary disease. N Engl J Med. 2007;356:
1503–1516.

98. The BARI 2D Study Group. A randomized trial of therapies for type 2
2503–2515.

99. Chopra D, Ornish D, Roy R, Weil A. ‘Alternative’ medicine is main-

100. Franklin BA. Physical activity to combat chronic diseases and escalating
7:122–125.

101. Schroeder ST. We can do better: improving the health of the American

102. Murray CJL, Frenk J. Ranking 37th: measuring the performance of the

103. Reeves MJ, Rafferty AP. Healthy lifestyle characteristics among adults

104. Anz J, Butsch M, Vartiainen E, Michael M, Cott JJ, Howard G.
The national prevalence of healthy lifestyles is low and varies by race and

DL, McCullough PA. Reduction in predicted coronary heart disease risk
after substantial weight reduction after bariatric surgery. Am J Cardiol.
2007;99:222–226.

106. Sjöström L, Narbro K, Sjöström D, Karason K, Larsson B, Wulked H,
Lystig T, Schachtler LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustuble gastric banding and
conventional therapy for type 2 diabetes: a randomized trial. JAMA.

RO, Bartelson BB, Krautz MJ. Reduction in the incidence of acute
myocardial infarction associated with a citywide smoking ordinance.

Mommaiche A, Pringle S, Murdoch D, Dunn F, Oldroyd K, MacIntyre
P, O’Rourke B, Borland W. Smoke-free legislation and hospitalizations

KEY WORDS: lifestyle medicine ■ preventive cardiology
Recent Advances in Preventive Cardiology and Lifestyle Medicine: A Themed Series
Barry A. Franklin and Mary Cushman

Circulation. 2011;123:2274-2283
doi: 10.1161/CIRCULATIONAHA.110.981613
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/123/20/2274

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/