

## Circulation Editors' Picks

### Most Read Articles on the Topic of Primary Prevention

The Editors

The following articles are being highlighted as part of *Circulation's* Topic Review series. This series will summarize the most important manuscripts, as selected by the editors, published in *Circulation* and the *Circulation* subspecialty journals. The studies included in this article represent the most read manuscripts published on the topic of primary prevention within the two years. (*Circulation*. 2013;128:e126-e134.)

#### Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension: One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

**Summary**—Patients with uncontrolled hypertension are at significant risk for cardiovascular events, and a subset of these patients who do not respond to aggressive pharmacological treatment ( $\geq 3$  antihypertensive drugs including a diuretic) are considered to have treatment-resistant hypertension. It has been shown that activation of the sympathetic nervous system is involved in the pathogenesis and maintenance of hypertension. Renal denervation with the Symplicity catheter is a minimally invasive procedure based on the premise that interruption of renal afferent and efferent nerves with resultant decreased sympathetic outflow to the kidneys will reduce renin release and sodium retention, increase renal blood flow, and lower blood pressure. The Symplicity HTN-2 trial demonstrates that radiofrequency ablation of renal nerves can significantly lower blood pressure in patients with systolic blood pressures  $>160$  mm Hg with no loss of treatment effect through 1 year and thus may provide a safe and effective adjunctive therapy for treatment-resistant hypertensive patients.

**Conclusions**—Control patients who crossed over to renal denervation with the Symplicity system had a significant drop in blood pressure similar to that observed in patients receiving immediate denervation. Renal denervation provides safe and sustained reduction of blood pressure to 1 year.<sup>1</sup>

#### Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

**Summary**—Stroke is a feared complication of carotid endarterectomy (CEA) and carotid stenting (CAS). The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and European trials have shown that CAS is associated with a greater risk of stroke than CEA. CREST also showed that CEA was associated with a greater risk of myocardial infarction (MI) than CAS. The greater risk of MI numerically balanced the greater risk of stroke, so that the composite primary outcome (periprocedural stroke, MI, or death and ipsilateral stroke at up to 4 years) was similar for CEA and CAS. This result has invited criticism because of the differing directions of stroke and MI within the composite outcome. To understand further, we examined the strokes

that occurred as a complication of the procedure. Stroke was still more common after CAS, but overall the risk of severe stroke was  $<1\%$  and was similar for CEA and CAS. The delayed timing of some major strokes, particularly intracerebral hemorrhage that occurred a few days postoperatively, makes it plausible that these postoperative strokes are preventable, perhaps with careful attention to blood pressure control. Minor stroke occurred most commonly on the same day as CAS, which suggests that the technical aspects of the procedure could be improved to minimize stroke as a complication. Previously, we reported that MI, including biomarker-only MI, was associated with an increased risk in long-term mortality. Here we report that stroke, including minor stroke, was also associated with an increased risk in long-term mortality. Carotid intervention with CEA or CAS is safe. Periprocedural stroke incurred significant morbidity and mortality.

**Conclusions**—Stroke, particularly severe stroke, was uncommon after carotid intervention in CREST, but stroke was associated with significant morbidity and was independently associated with a nearly 3-fold increased future mortality. The delayed timing of major and hemorrhagic stroke after revascularization suggests that these strokes may be preventable.<sup>2</sup>

#### Important Differences in Mode of Death Between Men and Women With Heart Failure Who Would Qualify for a Primary Prevention Implantable Cardioverter-Defibrillator

**Summary**—Multiple randomized clinical trials have demonstrated that ambulatory heart failure with moderate heart failure symptoms and an ejection fraction of  $<35\%$  derive a survival benefit from an implanted cardiac defibrillator for primary prevention of sudden death. The implantable cardioverter-defibrillator (ICD) can be life-saving to patients at risk for sudden death attributable to ventricular arrhythmias. Recently published meta-analysis have raised the possibility that women may not benefit as much from ICDs and have less appropriate ICD shocks compared with men with heart failure. The possibility that women may not derive as much benefit from an ICD is plausible, as it is well understood that men and women differ significantly in the epidemiology, pathophysiology, and natural history of heart failure. Further, randomized studies evaluating the role of the ICD for primary prevention of sudden death are not unlike most studies in heart failure in that there is a significant underrepresentation of women in these studies. Relevant to this question, we evaluated the sex differences in mode of death in 8337 ambulatory heart failure patients, including 1685 (20%) women,

who would qualify for a primary prevention ICD. Although age-adjusted total mortality was 24% lower in women compared with men, the annual mortality for women in this study was significant (9.1%). When compared with men, women were 31% less likely to die of sudden death. These findings provide a plausible reason for potential differences in ICD benefit between men and women and lend further support for the need for randomized studies aimed at defining the role of the ICD in the primary prevention of sudden death in women.

**Conclusions**—Women with heart failure have a lower mortality than men, and fewer of those deaths are sudden throughout a spectrum of all-cause mortality risk. These data provide a plausible reason for and thus support the possibility that sex differences in ICD benefit may exist.<sup>3</sup>

### **Apolipoprotein B Synthesis Inhibition With Mipomersen in Heterozygous Familial Hypercholesterolemia: Results of a Randomized, Double-Blind, Placebo-Controlled Trial to Assess Efficacy and Safety as Add-On Therapy in Patients With Coronary Artery Disease**

**Summary**—Heterozygous familial hypercholesterolemia is a common genetic disorder that leads to premature coronary artery disease. Despite aggressive lipid-lowering therapy, many patients with heterozygous familial hypercholesterolemia fail to achieve optimal low-density lipoprotein cholesterol (LDL-C) goals. We evaluated mipomersen, an apolipoprotein B synthesis inhibitor, to further lower LDL-C in patients with heterozygous familial hypercholesterolemia with coronary artery disease who were already on maximally tolerated lipid-lowering therapy and had LDL-C >2.6 mmol/L (100 mg/dL). The phase 2, double-blind, placebo-controlled trial randomized 124 patients (41 placebo, 83 mipomersen) to weekly subcutaneous mipomersen 200 mg or placebo (2:1) for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28. Safety assessments included adverse events, laboratory tests, and MRI assessment of hepatic fat. Mean LDL-C decreased 28.0% with mipomersen compared with a 5.2% increase with placebo ( $P < 0.001$ ), and 45.1% compared with 4.9% achieved LDL-C <2.6 mmol/L (100 mg/dL), respectively. Mipomersen significantly ( $P < 0.001$ ) reduced apolipoprotein B (−26.3%) and lipoprotein(a) (−21.1%) compared with placebo. More frequent and severe injection site reactions occurred with mipomersen, and 5 mipomersen-treated patients (6%) had 2 consecutive alanine aminotransferase levels  $\geq 3$  times the upper limit of normal at least 7 days apart; none were associated with significant bilirubin increases. Hepatic fat content increased a median of 4.9% with mipomersen versus 0.4% with placebo ( $P < 0.001$ ). The clinical implications of such increases in hepatic fat and transaminase elevations are unclear and must be elucidated in longer-term studies. We conclude that mipomersen is effective to further reduce apolipoprotein B-containing lipoproteins, including LDL and lipoprotein(a), in patients with heterozygous familial hypercholesterolemia with coronary artery disease on statins and other lipid-lowering therapy.

**Conclusions**—Mipomersen is an effective therapy to further reduce apolipoprotein B-containing lipoproteins, including LDL and lipoprotein(a), in hypercholesterolemia patients with coronary artery disease on statins and other lipid-lowering therapy. The significance of hepatic fat and transaminase increases remains uncertain at this time.<sup>4</sup>

### **Variation in Warfarin Dose Adjustment Practice Is Responsible for Differences in the Quality of Anticoagulation Control Between Centers and Countries: An Analysis of Patients Receiving Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial**

**Summary**—The outcome of atrial fibrillation patients on warfarin partially depends on maintaining adequate time in therapeutic International Normalized Ratio (INR) range (TTR). Large differences in TTR have been reported between centers and countries, but the reasons are unclear. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, a warfarin dosing algorithm provided to participating centers recommended no change for in-range and 10% to 15% weekly dose changes for out-of-range INR values. We determined whether algorithm-consistent warfarin dosing could predict patient TTR and the composite outcome of stroke, systemic embolism, or major hemorrhage. Among 6022 nonvalvular atrial fibrillation patients from 44 countries, we found a strong association between the proportion of algorithm-consistent warfarin doses and mean country TTR ( $R^2 = 0.65$ ). The degree of algorithm-consistent warfarin dosing accounted for a majority of the TTR variation between centers and countries. Each 10% increase in center algorithm-consistent dosing independently predicted a 6.12% increase in TTR (95% confidence interval, 5.65–6.59), and an 8% decrease in rate of the composite clinical outcome (hazard ratio, 0.92; 95% confidence interval, 0.85–1.00). In summary, warfarin dosing practice that does not change the dose when the INR is in range, and that makes relatively small (10% to 15%) weekly dose adjustments when the INR is out of range, is associated with improved TTR and clinical outcomes. Systems that implement algorithm-based dosing for patients with atrial fibrillation on warfarin could potentially improve outcomes on a global scale, especially in centers and countries with suboptimal INR control.

**Conclusions**—Adherence, intentional or not, to a simple warfarin dosing algorithm predicts improved TTR and accounts for considerable TTR variation between centers and countries. Systems facilitating algorithm-based warfarin dosing could optimize anticoagulation quality and improve clinical outcomes in atrial fibrillation on a global scale.<sup>5</sup>

### **Trends in Antihypertensive Medication Use and Blood Pressure Control Among United States Adults With Hypertension: The National Health and Nutrition Examination Survey, 2001 to 2010**

**Summary**—Trends in antihypertensive medication use and blood pressure control for US adults were examined at a population level during the decade 2001 to 2010 with the use of National Health and Nutrition Examination Survey data. The decade showed significant increases in the percentage of people with hypertension who are treated with medication (from 64% to 77%). Blood pressure control rates have improved from 29% to 47%, and treated control rates have improved from 45% to 60%. Consistent with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, significantly more patients with hypertension are on combination therapy now than a decade ago. In addition, the current data indicate that those receiving antihypertensive polytherapy were significantly more likely to meet their blood pressure goals than those who were on monotherapy regimens. Increased usage of multiple antihypertensive drugs has made substantial contributions

to the overall control of blood pressure in the general population. This underscores the important role of antihypertensive polytherapy for achieving blood pressure control previously demonstrated in clinical drug trials. Patients whose hypertension is not controlled with monotherapy could benefit from more effective polytherapy regimens. The data also identify key population subgroups that apparently continue to lag behind. Younger adults and Mexican-American people appeared to be undertreated, as did those without health insurance. Older adults and non-Hispanic black people were more likely to be treated, but their hypertension was less likely to be controlled once they were on treatment. The same was true for those with chronic kidney disease and diabetes mellitus. Continued efforts are needed to close these gaps in treatment and to control rates and maximize the public health and clinical benefits of hypertensive therapy.

**Conclusions**—Antihypertensive medication use and blood pressure control among US adults with hypertension significantly increased over the past 10 years. Combination therapy regimens can facilitate achievement of blood pressure goals.<sup>6</sup>

## Dietary Nitrate Supplementation Improves Revascularization in Chronic Ischemia

**Summary**—With the worldwide increase in cardiovascular diseases in recent decades, the need for novel preventive and noninvasive therapeutic strategies has grown tremendously. In this context, there is accumulating evidence that inorganic nitrate from dietary sources is able to influence the hallmarks of cardiovascular functions, including blood pressure regulation. The bioactivation of nitrate from dietary or endogenous sources is carried out mainly by commensal bacteria that express effective nitrate reductase enzymes and are located in the gastrointestinal tract and on body surfaces. Under conditions of low oxygen tensions, nitrate and nitrite are physiologically recycled in blood and tissues to form nitric oxide and other bioactive nitrogen oxides that mediate cytoprotective signaling in the setting of pathological ischemia. The present study provides the first evidence that dietary nitrate supplementation improves revascularization in chronic ischemia. This study identified that dietary nitrate supplementation increases mobilization and migration of regenerative cells, improves the regenerative capacities of chronically ischemic tissue, and decreases apoptosis at the site of ischemia. Eradicating the commensal bacteria in the oral cavity and thus interrupting the bioactivation of the ingested nitrate decreased circulating levels of bioactive nitrogen oxides and reversed all of these beneficial effects. These data underscore the potential therapeutic value of inorganic nitrate and suggest the possible application of a nutritional approach in the prevention and treatment of cardiovascular diseases.

**Conclusions**—Long-term dietary nitrate supplementation may represent a novel nutrition-based strategy to enhance ischemia-induced revascularization.<sup>7</sup>

## Childhood Physical, Environmental, and Genetic Predictors of Adult Hypertension: The Cardiovascular Risk in Young Finns Study

**Summary**—Hypertension is a major cardiovascular risk factor influenced by genetic propensity and various environmental stimuli. The present longitudinal study aimed to examine the best combination of childhood physical and environmental factors to predict adult hypertension. Furthermore, we examined whether newly identified genetic variants for blood pressure enhance the prediction of adult hypertension. In this longitudinal study, 2625 individuals who participated in the Cardiovascular Risk in Young Finns Study in

the baseline year 1980 (when 3–18 years of age) were followed up 21 to 27 years (then 24–45 years of age). Youth risk factors independently associated with adult hypertension were the individual's own systolic and diastolic blood pressures, parental hypertension, youth overweight/obesity, low parental occupational status, and high genetic risk score. We also found that both parental hypertension history and the genetic risk score enhanced the prediction of adult hypertension when added separately to the prediction model compared with the model consisting of only childhood blood pressure. Furthermore, the prediction power was significantly stronger when both of these variables were added to the same model. From these findings, it seems that the genetic risk score and parental hypertension provide complementary information. Present data suggest that a multifactorial approach, if implemented, could improve the identification of children with a high risk of adult hypertension. Moreover, these data demonstrate that the prediction of adult hypertension was enhanced when the novel genetic variants were taken into account. In terms of the care of individual patients with elevated blood pressure, our data emphasize the importance of overweight as a potential modifiable risk factor.

**Conclusions**—Prediction of adult hypertension was enhanced by taking into account known physical and environmental childhood risk factors, family history of hypertension, and novel genetic variants. A multifactorial approach may be useful in identifying children at high risk for adult hypertension.<sup>8</sup>

## Racial Differences in Risks for First Cardiovascular Events and Noncardiovascular Death: The Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Multi-Ethnic Study of Atherosclerosis

**Summary**—In this article, we used 3 multicenter, ethnically diverse, Heart, Lung, and Blood Institute–sponsored cohort studies to compare differences between black and white study participants in competing risks for specific first cardiovascular disease (CVD) events relative to each other and to non-CVD death. The competing risks framework is distinct from approaches used in typical survival analyses, which consider only a single event at a time (eg, stroke alone or CHD alone) and assume that each event is independent of the others when, in reality, these events are not independent of one another because of common underlying risk factors. We found that CVD was the most likely first event rather than non-CVD death in black and white adults and that middle-aged blacks were significantly more likely than whites to experience any CVD as a first event, although this disparity disappeared by older adulthood and after adjustment for CVD risk factors. A sensitivity analysis of the identical data with use of traditional Cox modeling rather than the competing risks methodology yielded different results for CHD risk. Competing risks models estimate which specific events are more likely to occur first for various populations; this ability to understand risks for multiple different outcomes at a given point in time may be clinically useful, because it affords patients and clinicians a more accurate sense of real-life risks for first events.

**Conclusions**—CVD affects blacks at an earlier age than whites; this may be attributable in part to elevated CVD risk factor levels among blacks. Racial disparities in first CVD incidence disappear by older adulthood. Competing risks analyses may yield somewhat different results than traditional Cox models and provide a complementary approach to examining risks for first CVD events.<sup>9</sup>

## Maternal Use of Hydroxychloroquine Is Associated With a Reduced Risk of Recurrent Anti-SSA/Ro-Antibody–Associated Cardiac Manifestations of Neonatal Lupus

**Summary**—A recent case-control study suggested a benefit of hydroxychloroquine (HCQ) in lowering the risk of cardiac manifestations of neonatal lupus (cardiac-NL) in pregnancies of anti-SSA/Ro-positive patients with systemic lupus erythematosus. In this study, we examined whether HCQ reduces the  $\approx 10$ -fold higher recurrence rate in cardiac-NL by identifying 257 pregnancies of anti-SSA/Ro-positive mothers (40 exposed and 217 unexposed to HCQ) after the birth of a child with cardiac-NL from 3 international databases. Exposure was defined as the sustained use of HCQ throughout pregnancy with initiation before 10 weeks of gestation. The recurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3 of 40) compared with 21.2% (46 of 217) in the unexposed group ( $P=0.050$ ). There were no deaths in the HCQ-exposed group, whereas the overall case fatality rate of the cardiac-NL fetuses in the unexposed group was 21.7%. In a multivariable analysis, HCQ use remained significantly associated with a decreased risk of cardiac-NL (odds ratio, 0.23;  $P=0.037$ ). Similar results (odds ratio, 0.18;  $P=0.011$ ) were obtained with propensity score analysis, an alternative approach to adjust for possible confounding by indication. Data obtained from this multinational historical cohort study suggest that HCQ use in a mother with anti-SSA/Ro antibodies and a previous child with cardiac-NL may reduce the risk of cardiac-NL recurrence in a subsequent offspring. Further prospective studies are needed to confirm these findings.

**Conclusions**—Aggregate data from a multinational effort show that in mothers at high risk of having a child with cardiac-NL, the use of HCQ may protect against recurrence of disease in a subsequent pregnancy.<sup>10</sup>

## Duration of QRS Complex in Resting ECG Is a Predictor of Sudden Cardiac Death in Men

**Summary**—Sudden cardiac arrest accounts for one half of all deaths related to coronary heart disease and presents as the first manifestation of coronary heart disease in  $\approx 20\%$  to  $30\%$  of the deaths. Large epidemiological studies have not been able to identify specific ECG markers for sudden cardiac death (SCD), and little is known about the relationship between the duration of the QRS complex and the risk of SCD among the general population. Our study shows that prolonged QRS duration is an independent predictor of SCD, with risk levels comparable to those for established clinical risk factors such as smoking, lipids, hypertension, history of myocardial infarction or coronary heart disease, and type 2 diabetes mellitus. Each 10-ms increment in QRS duration was associated with a 27% higher SCD risk. Thus, the measurement of QRS duration may have utility in evaluation of SCD risk in the general population.

**Conclusions**—QRS duration is an independent predictor of the risk of SCD and may have utility in estimating SCD risk in the general population.<sup>11</sup>

## Cardiovascular Health Behavior and Health Factor Changes (1988–2008) and Projections to 2020: Results From the National Health and Nutrition Examination Surveys

**Summary**—The American Heart Association's Strategic Planning Task Force set forth the goal of improving the cardiovascular

health of all Americans by 20% by 2020. To assess progress toward this goal, 7 health metrics were defined: smoking, diet, physical activity, body weight, blood glucose, blood pressure, and cholesterol. In this investigation, we asked, "If current trends in these metrics continue, will this goal be reached?" We evaluated past trends by using data from the 1998 to 2008 National Health and Nutrition Examination Survey (NHANES) examination cycles and created best-fit linear regression models and linear forward projections to 2020. We also created an individual-level Cardiovascular Health Score to evaluate individual-level changes in cardiovascular health amid larger population trends. Our results suggest that if current trends continue, changes in the individual-level Cardiovascular Health Score will be minimal and that the overall cardiovascular health of the US population will improve by only 6% by 2020; this progress is far short of the American Heart Association's target of 20% improvement. This projection reflects modest further declines in tobacco use and improved control of high cholesterol and high blood pressure that are offset by increases in obesity and dysglycemia prevalence. In conclusion, continued individual-level primary and secondary preventive measures should be complemented by an increased national commitment to policies promoting prevention of the development of abnormal risk factor levels from childhood onward. If the American Heart Association target of 20% improvement in overall cardiovascular health were achieved, the potential reductions in cardiovascular disease burden could be substantial, rapid, and associated with substantial cost savings.

**Conclusions**—The American Heart Association 2020 target of improving cardiovascular health by 20% by 2020 will not be reached if current trends continue.<sup>12</sup>

## The Age Associations of Blood Pressure, Cholesterol, and Glucose: Analysis of Health Examination Surveys From International Populations

**Summary**—Cardiovascular disease (CVD) risk factors, such as systolic blood pressure, total cholesterol, and fasting plasma glucose, tend to increase with age and these age trends are generally believed to be inevitable. However, it is unclear how much of these age trends are truly physiological and not due to environment or lifestyle factors. Studies on a few rural populations in developing countries have reported very little elevation in CVD risk factors with age, suggesting that lifestyle and environmental factors may play an important part in creating age trends. However, there are no comparative multicountry studies that cover all or large parts of national populations and address multiple risk factors simultaneously. The present analysis uses data from 83 national and subnational surveys from high- and low/middle-income countries to consistently estimate the age trends of 3 major CVD risk factors. The results showed that age trends in total cholesterol, fasting plasma glucose, and systolic blood pressure varied substantially across populations. Total cholesterol increased more rapidly with age in Western high-income countries, especially before 2000, possibly because total cholesterol slope is affected by animal fat intake. The largest fasting plasma glucose slopes were in Oceania, the Middle East, and, more recently, the United States, which also have high body mass index levels. Age trends in systolic blood pressure had no specific income or geographical pattern, possibly because salt intake is determined more by cultural factors. These cross-population variations indicate that environmental and lifestyle factors play a large role in determining age trends in metabolic risk factors of CVD and emphasize

the importance of life-long prevention to attenuate and delay the age-related increases in CVD risk.

**Conclusions**—The rise with age of major metabolic cardiovascular disease risk factors varied substantially across populations, especially for fasting plasma glucose (FPG) and total cholesterol TC rose more steeply in high-income countries and FPG in the Oceania countries, the Middle East, and the United States. The systolic blood pressure age association had no specific income or geographical pattern.<sup>13</sup>

## Triggers of Hospitalization for Venous Thromboembolism

**Summary**—There are >330 000 hospital admissions for venous thromboembolism annually in the United States. The objective of this study was to evaluate triggers, or acute transitory exposures, of such hospitalizations that potentially are amenable to change. We designed a case-crossover study using the databases of the Health and Retirement Study, a longitudinal study of a nationally representative sample of older Americans, linked to Medicare files. This design incorporates a within-person comparison (90 days before the hospitalization versus other time periods) and is particularly useful in controlling for factors such as hereditary conditions, sex, race, and past comorbidities. We found that over half (52%) of all hospitalizations for venous thromboembolism were preceded by an infection and that the risk of such hospitalizations was 2.9-fold greater within 90 days of an infection than at other times. Both respiratory and non-respiratory tract infections were associated with greater risk. Individuals were at 9.3-fold greater risk of hospitalization for venous thromboembolism within 90 days of receiving erythropoiesis-stimulating agents than at other times. In addition, the results suggest that blood transfusion is a significant trigger of hospitalization for venous thromboembolism, independent of major surgeries, infection, injuries, and immobility. We recommend that clinical prediction rules and patient informational sources be updated to include infection, erythropoiesis-stimulating agents, and blood transfusion as risk factors for venous thromboembolism.

**Conclusions**—Risk prediction algorithms for venous thromboembolism should be reevaluated to include infection, erythropoiesis-stimulating agents, and blood transfusion.<sup>14</sup>

## Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women's Health Initiative

**Summary**—Both the Framingham Adult Treatment Panel III (ATP-III) and the Reynolds scores are commonly used in North America and have received Class I recommendations from the American College of Cardiology and the American Heart Association. Little direct comparison of these scores has been conducted in an independent validation cohort. This article directly compares Framingham-based and Reynolds Risk Scores for cardiovascular disease prediction in the Women's Health Initiative Observational Cohort (WHI-OS). Predicted 10-year risk varied widely between models, with  $\geq 10\%$  risk in 6%, 10%, and 41% of women with the use of the ATP-III, Reynolds, and newer Framingham cardiovascular disease models, respectively, which has implications for statin therapy. The Reynolds Risk Score was better calibrated than the ATP-III score and showed improved discrimination over either Framingham-based model. Furthermore, the lack of effect modification in our data by ethnicity suggests that these findings

are clinically relevant in ethnically diverse populations. Within the WHI-OS, the greatest impact of the Reynolds Risk Score appeared to be among those women with 5% to 10% estimated 10-year risk according to ATP-III. This group includes a large number of women destined to suffer myocardial infarction or stroke and in whom trial data indicate efficacy of statin therapy in reducing cardiovascular events.

**Conclusions**—The Reynolds Risk Score was better calibrated than the Framingham-based models in this large external validation cohort. The Reynolds score also showed improved discrimination overall and in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy.<sup>15</sup>

## Association of Plasma Phospholipid Long-Chain Omega-3 Fatty Acids With Incident Atrial Fibrillation in Older Adults: The Cardiovascular Health Study

**Summary**—Atrial fibrillation (AF) is the most common chronic arrhythmia in adults, and risk increases markedly with age. Experimental studies suggest that long-chain n-3 polyunsaturated fatty acids (n-3 PUFA) from seafood may reduce onset of AF, but most prior studies of n-3 PUFA and new-onset AF in ambulatory populations have used estimates based on dietary questionnaires and were not focused on older adults, the general population at highest risk. We prospectively investigated the associations of circulating blood levels of the n-3 PUFA eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) with incidence of AF among 3,326 older men and women ( $\geq 65$ y) from 4 US communities over a 14-year period. We excluded study subjects taking fish oil supplements. After adjustment for other risk factors, participants in the top quartile of total n-3 PUFA (EPA+DPA+DHA) levels had 29% lower risk of AF, compared with the lowest quartile ( $P$  trend  $< 0.004$ ). Among the individual n-3 fatty acids, only DHA was significantly associated with AF, with a 23% lower risk among participants in the highest versus lowest quartile ( $P=0.01$ ). These associations were consistent among different subgroups, including men and women as well as whites and blacks. Although the observational nature of this study does not prove a causal relationship, these findings suggest that increased dietary intake of total n-3 PUFA or DHA from seafood may reduce incidence of AF in older adults.

**Conclusions**—In older adults, higher circulating total long-chain n-3 PUFA and docosahexaenoic acid levels were associated with lower risk of incident AF. These results highlight the need to evaluate whether increased dietary intake of these fatty acids could be effective for the primary prevention of AF.<sup>16</sup>

## Ideal Cardiovascular Health and Mortality From All Causes and Diseases of the Circulatory System Among Adults in the United States

**Summary**—In 2010, the American Heart Association presented a set of 7 metrics that were designed to promote cardiovascular health: smoking status, body mass index, physical activity, healthy dietary score, total cholesterol, blood pressure, and fasting plasma glucose. For each metric, 3 levels of health were defined (poor, intermediate, and ideal health). The state of ideal health for each metric emphasizes the concept of primordial prevention. Using data from a nationally representative cohort of US adults, we found that about half of adults had 3 or 4 ideal health metrics (only  $\approx 1\%$  met the ideal health criteria for all 7 metrics). Furthermore, we observed a strong dose-response relationship between the number of ideal health metrics and mortality from all

causes and diseases of the circulatory system. Clinicians can reduce cardiovascular morbidity and mortality in their patient populations not only by helping their patients maximize the number of attained ideal cardiovascular health metrics but also by helping patients with poor health for some metrics transition to intermediate health. Optimizing cardiovascular health involves addressing key lifestyle behaviors of smoking, diet, and physical activity. Besides the resources in their practices, clinicians can opt to draw on available institutional, clinical, and community resources. An implication of the AHA goals and our findings is that the cardiovascular health of patients should be monitored from an early age. Clinicians should strive to maximize the numbers of patients with hypercholesterolemia, hypertension, and hyperglycemia who require pharmacological management who are on treatment and under control.

**Conclusions**—The number of ideal cardiovascular health metrics is a strong predictor of mortality from all causes and diseases of the circulatory system.<sup>17</sup>

### Associations Between Lipoprotein(a) Levels and Cardiovascular Outcomes in Black and White Subjects: The Atherosclerosis Risk in Communities (ARIC) Study

**Summary**—On the basis of observational and prospective studies with limited statistical power, lipoprotein(a) [Lp(a)] is not considered a risk factor for cardiovascular disease in blacks. The Adult Treatment Panel III guidelines also note that “although Lp(a) levels are higher in African Americans than in Caucasians, an increased risk for coronary heart disease associated with higher Lp(a) levels in African Americans has not been documented.” This is despite the fact that Lp(a) levels in blacks are 2 to 4 times higher than those in whites. In these analyses, we evaluated the association between plasma Lp(a) levels and the risk of incident cardiovascular disease events (incident coronary heart disease and incident ischemic strokes) in 3467 black and 9851 white participants in the Atherosclerosis Risk in Communities (ARIC) study over a 20-year follow-up period. Our analyses show that Lp(a) levels were positively associated with cardiovascular disease events in both races. Associations were at least as strong in blacks, with a larger range of relevant Lp(a) concentrations in blacks than in whites. Elevated Lp(a) levels should therefore be considered to be associated with an increased cardiovascular disease risk in blacks.

**Conclusions**—Lp(a) levels were positively associated with CVD events. Associations were at least as strong, with a larger range of Lp(a) concentrations, in blacks compared with whites.<sup>18</sup>

### Using Stress Testing to Guide Primary Prevention of Coronary Heart Disease Among Intermediate-Risk Patients: A Cost-Effectiveness Analysis

**Summary**—In an era of low-cost statin therapy, universal statin therapy for patients at intermediate risk of coronary heart disease may be more cost effective than using noninvasive testing to select which patients should receive statins and aspirin. Our analyses show that, under a wide variety of assumptions, asymptomatic intermediate-risk adults should not be screened with stress electrocardiography, stress ECG, or stress nuclear scanning to make decisions on statin treatment (in men and women) and aspirin treatment (in men). Rather, all such intermediate-risk patients should be treated. However, if adherence with universal statin treatment is <21% and if a positive stress test would raise adherence to 75%, stress ECG

would save costs because of the increased adherence. Alternatively, if stress ECG testing were reserved for individuals who are non-adherent to statin and aspirin therapy, such testing would be cost effective if it raised adherence to  $\geq 5\%$  and cost saving if it raised adherence to 13% in those who were previously nonadherent. The potential virtue of this approach to increasing adherence requires further study and comparison with alternative interventions to increase adherence. Regardless, routine statin (men and women) and aspirin (men) treatment is warranted without prior stress test screening in all intermediate-risk men and women.

**Conclusions**—When generic high-potency statins are available, non-invasive cardiac stress testing to target preventive medications is not cost effective unless it substantially improves adherence.<sup>19</sup>

### Combined Lifestyle Factors and Cardiovascular Disease Mortality in Chinese Men and Women: The Singapore Chinese Health Study

**Summary**—Lifestyle factors directly affect established and novel pathways of cardiovascular risk. Despite this evidence, few studies have examined the combined association of multiple lifestyle factors with cardiovascular disease (CVD) mortality. Furthermore, there has been little ethnic variation in the populations studied or examination of this topic in patients with a history of diabetes mellitus and/or CVD. Therefore, this study examined the combined association of lifestyle factors with CVD mortality and its major subgroups in healthy Chinese men and women and a high-risk subcohort with a history of diabetes mellitus and CVD during study enrollment in the Singapore Chinese Health Study (1993–98) and followed up through 2009. In 50 466 healthy and high-risk Chinese men and women, protective lifestyle factors were represented by a diet plentiful in vegetables, fruit, and soy; higher relative levels of physical activity; light to moderate alcohol consumption; average usual sleep of 6 to 8 h/d; no history of smoking, and normal weight (ie, not underweight or overweight). In combination, a marked decrease in rate and risk of dying as a result of CVD was observed with each additional protective lifestyle factor in healthy and high-risk participants. Overall, data from this large cohort of Chinese adults highlight that multiple modifiable lifestyle factors are of paramount importance in improving population-wide cardiovascular risk reduction in both primary and secondary prevention. Efforts to increase the prevalence of protective lifestyle factors in healthy and high-risk populations should significantly influence CVD mortality.

**Conclusions**—An increasing number of protective lifestyle factors is associated with a marked decreased risk of coronary heart disease, cerebrovascular disease, and overall CVD mortality in Chinese men and women.<sup>20</sup>

### Colchicine Reduces Postoperative Atrial Fibrillation: Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy

**Summary**—Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases. POAF increases patient morbidity, length of hospital stay, and management costs. Its prevention is an important management goal. Systemic and local inflammatory responses are believed to contribute to the pathogenesis of POAF. Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are decreased by corticosteroids. Because of its anti-inflammatory effects for the treatment and prevention of pericarditis, colchicine has the potentiality to prevent

POAF. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) POAF substudy is the first trial designed to assess the efficacy and safety of colchicine for POAF prevention. It is a substudy of the COPPS trial, in which colchicine halved the occurrence of the postpericardiotomy syndrome. On the third postoperative day, consecutive adult patients undergoing cardiac surgery and without contraindications to colchicine were randomized to receive placebo or colchicine on top of standard therapy. The substudy primary efficacy end point was the incidence of POAF on placebo/colchicine treatment at 1 month. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively;  $P=0.021$ ; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay ( $9.4\pm 3.7$  versus  $10.3\pm 4.3$  days;  $P=0.040$ ) and rehabilitation stay ( $12.1\pm 6.1$  versus  $13.9\pm 6.5$  days;  $P=0.009$ ). Side effects were similar in the study groups. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both the postpericardiotomy syndrome and POAF, 2 common and troublesome complications of cardiac surgery.

**Conclusions**—Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.<sup>21</sup>

## Cost-Effectiveness of Statin Therapy for Primary Prevention in a Low-Cost Statin Era

**Summary**—This cost-effectiveness analysis sought to identify whether expanded use of statins for primary prevention would be cost-effective or even cost-saving in an era of generic, low-cost statins. Assuming that statins are universally available at a cost of \$4/mo and efficacious in all persons >35 years of age, treatment thresholds of low-density lipoprotein cholesterol >160 mg/dL for low-risk persons (0–1 risk factor), >130 mg/dL for moderate-risk persons ( $\geq 2$  risk factors and 10-year risk <10%), and >100 mg/dL for moderately high-risk persons ( $\geq 2$  risk factors and 10-year risk >10%) would reduce annual healthcare costs by \$430 million compared with Adult Treatment Panel III guidelines. Lowering thresholds to >130 mg/dL for persons with 0 risk factors and >100 mg/dL for persons with 1 risk factor and treating all moderate- and moderately high-risk persons would further lower CHD burden for \$9900 per quality-adjusted life-year compared with Adult Treatment Panel III guidelines. These findings were insensitive to known and hypothetical side effects, but were sensitive to large reductions in efficacy of statins or a long-term disutility burden for which a patient would trade 30 to 80 days of life to avoid 30 years of statins. Low-cost statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart disease risk factors if they do not mind taking a pill daily.

**Conclusions**—Low-cost statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart disease risk factors if they do not mind taking a pill daily. Adverse effects are unlikely to outweigh benefits in any subgroup in which statins are found to be efficacious.<sup>22</sup>

## Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose: Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials

**Summary**—Most guidelines for treatment of hypertension, including the seventh report of the Joint National Committee, recommend an

aggressive blood pressure goal of <130/80 mmHg for patients with diabetes mellitus. However, the evidence on which the guidelines are based is limited. In our analyses of 13 randomized trials with 37736 participants, we noted that in patients with type 2 diabetes mellitus, a systolic blood pressure treatment goal of 130 to 135 mmHg is acceptable. However, with more aggressive goals (<130 mmHg), we observed target organ heterogeneity in that the risk of stroke continued to fall, but there was no benefit regarding the risk of other macrovascular or microvascular (cardiac, renal, and retinal) events, and the risk of serious adverse events even increased.

**Conclusions**—The present body of evidence suggests that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, a systolic BP treatment goal of 130 to 135 mmHg is acceptable. However, with more aggressive goals (<130 mmHg), we observed target organ heterogeneity in that the risk of stroke continued to fall, but there was no benefit regarding the risk of other macrovascular or microvascular (cardiac, renal and retinal) events, and the risk of serious adverse events even increased.<sup>23</sup>

## Lapaquistat Acetate: Development of a Squalene Synthase Inhibitor for the Treatment of Hypercholesterolemia

**Summary**—Elevated low-density lipoprotein cholesterol is the cornerstone of coronary artery disease prevention, and although statins have provided enormous advances, there remains an unmet need for new effective, well-tolerated, safe low-density lipoprotein cholesterol-lowering drugs. This report summarizes the phase 2 and 3 results from the lapaquistat clinical program, which was halted at an advanced stage as a result of potential hepatic safety issues. Lapaquistat acetate is a squalene synthase inhibitor, a step after the statins, investigated for the treatment of hypercholesterolemia. Data were pooled from 12 studies ( $n=6151$ ) lasting 6 to 96 weeks. Trials were randomized, double-blind, parallel, and placebo or active controlled with lapaquistat monotherapy or coadministration with other lipid-altering drugs. All studies included lapaquistat 100 mg daily; 5 included 50 mg; and 1 included 25 mg. The main outcome measure was low-density lipoprotein cholesterol, secondary lipid/metabolic parameters, and overall safety. Lapaquistat 100 mg significantly decreased low-density lipoprotein cholesterol by 21.6% in monotherapy and 18.0% in combination with a statin. It also significantly reduced C-reactive protein. Total adverse events were higher for lapaquistat than placebo, although individual events were similar. At 100 mg, alanine aminotransferase values  $\geq 3$  times the upper limit of normal on  $\geq 2$  consecutive visits increased (2.0% to 2.7% versus 0.3% to 0.7% for placebo or low-dose atorvastatin). Two patients receiving lapaquistat 100 mg met the Hy Law criteria of alanine aminotransferase elevation plus increased total bilirubin. Squalene synthase inhibition with lapaquistat, alone or in combination with statins, effectively lowered low-density lipoprotein cholesterol and C-reactive protein. Elevations in alanine aminotransferase combined with a rare increase in bilirubin presented potential hepatic safety issues, resulting in termination of development. The lapaquistat experience illustrates the current challenges in lipid-altering drug development.

**Conclusions**—Squalene synthase inhibition with lapaquistat acetate, alone or in combination with statins, effectively lowered low-density lipoprotein cholesterol in a dose-dependent manner. Elevations in alanine aminotransferase, combined with a rare increase in bilirubin, presented potential hepatic safety issues, resulting in termination of development. The lapaquistat experience illustrates the current challenges in lipid-altering drug development.<sup>24</sup>

## Particle Traps Prevent Adverse Vascular and Prothrombotic Effects of Diesel Engine Exhaust Inhalation in Men

**Summary**—There is a robust and consistent association between air pollution and cardiovascular morbidity and mortality. These harmful effects are most strongly associated with exposure to traffic-derived fine particles that predominantly originate from diesel engine exhaust emissions. Using a purpose-built exposure chamber, we have demonstrated previously the adverse vascular and prothrombotic effects of exposure to diesel exhaust in healthy men. In the present study, using complementary and relevant measures of cardiovascular health, we have reconfirmed the adverse effects of exposure to diesel engine exhaust on endothelial function and ex vivo thrombosis. In addition, for the first time, we demonstrate that reducing the particulate component of diesel exhaust with a commercially available particle trap can prevent these detrimental cardiovascular effects. Our study provides support for the application of particle traps to diesel-powered vehicles to reduce urban particulate concentrations and limit a range of adverse cardiovascular effects related to exposure to traffic-derived air pollution.

**Conclusions**—Exhaust particle traps are a highly efficient method of reducing particle emissions from diesel engines. With a range of surrogate measures, the use of a particle trap prevents several adverse cardiovascular effects of exhaust inhalation in men. Given these beneficial effects on biomarkers of cardiovascular health, the widespread use of particle traps on diesel-powered vehicles may have substantial public health benefits and reduce the burden of cardiovascular disease.<sup>25</sup>

## Trends in Mortality From All Causes and Cardiovascular Disease Among Hypertensive and Nonhypertensive Adults in the United States

**Summary**—In the period from 2007 to 2008, 29% of adults in the United States had hypertension, a major modifiable risk factor for cardiovascular disease. The control of hypertension is critical to reducing its excess morbidity and mortality. Although important advances in increasing awareness of hypertension and its treatment and control have been achieved, information about the direction of the mortality rate in hypertensive adults is scarce. The current study's results show that the age-adjusted mortality rate from all causes decreased by 4.6 per 1000 person-years in 2 national cohorts of hypertensive adults who were recruited from 1971 to 1975 and from 1988 to 1994. However, this decrease was comparable to the decrease of 4.2 per 1000 person-years among nonhypertensive adults. The reduction among hypertensive men (7.7 per 1000 person-years) significantly exceeded the reduction among hypertensive women (1.9 per 1000 person-years). The reduction among hypertensive blacks (5.4 per 1000 person-years) exceeded the reduction among hypertensive whites by a nonsignificant amount (4.4 per 1000 person-years). Besides having higher mean levels of systolic and diastolic blood pressure, hypertensive adults had a higher mean concentration of total cholesterol, mean body mass index, and prevalence of diabetes mellitus than nonhypertensive adults. Optimizing the control of hypertension and aggressively managing coexisting cardiovascular risk factors in adults with hypertension are key approaches to further reducing the mortality rate among hypertensive adults. Increased clinical and public health efforts are needed to lower the high mortality rate among blacks and to accelerate the tepid decline in the mortality rate among women.

**Conclusions**—The mortality rate decreased among hypertensive adults, but the mortality gap between adults with and without hypertension remained relatively constant. Efforts are needed to accelerate the decrease in the mortality rate among hypertensive adults.<sup>26</sup>

## Incidence of Sudden Cardiac Death in National Collegiate Athletic Association Athletes

**Summary**—This report more accurately estimates the incidence of sudden cardiac death (SCD) in athletes using improved methodology compared with previous studies. It demonstrates an overall rate of SCD of 1:43 000, with some subpopulations showing a risk of SCD as high as 1:3000. The rate of SCD has been commonly cited as 1:200 000. From a clinical perspective, this is critically important information. The preparticipation examination, or sports physical, is a core part of the practice of sports medicine and primary care physicians alike. The purpose of the preparticipation examination, according to the latest AHA scientific statement, is to identify conditions that may lead to SCD. The current recommendation of the AHA is that this is best done, in the United States, by the use of a directed history and physical examination. There is increasing evidence that this strategy is neither effective nor cost-effective. In other countries, an ECG is a routine part of a sports physical, or in some cases a well-child visit. The information presented in this report will inform the ongoing discussion about SCD in young people and how best to prevent it. There may be subpopulations of athletes or young people in which screening with an ECG by use of modern interpretation criteria would be highly cost-effective, and others in which it would not. This report will have significant ramifications for clinical practice as we strive to understand how to best use our resources, fulfill the primary objective of the sports physical, prepare for sudden cardiac arrest, and ultimately prevent SCD.

**Conclusions**—SCD is the leading medical cause of death and death during exercise in NCAA student-athletes. Current methods of data collection underestimate the risk of SCD. Accurate assessment of SCD incidence is necessary to shape appropriate health policy decisions and develop effective strategies for prevention.<sup>27</sup>

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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