Diet and Nutrition in Circulation and the Circulation Subspecialty Journals

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 articles related to diet and nutrition that were published in Circulation and the Circulation subspecialty journals in 2010 and 2011. (Circulation. 2012;125:e551-e568.)

Distribution of 10-Year and Lifetime Predicted Risks for Cardiovascular Disease in US Adults: Findings From the National Health and Nutrition Examination Survey 2003 to 2006

Summary: National guidelines for primary prevention suggest consideration of lifetime risk for cardiovascular disease in addition to 10-year risk, but it is currently unknown how many US adults would be identified as having low short-term but high lifetime predicted risk if stepwise stratification were used. We included 6329 cardiovascular disease–free and nonpregnant individuals ages 20 to 79 years, representing approximately 156 million US adults, from the National Health and Nutrition Examination Survey 2003 to 2004 and 2005 to 2006. We assigned 10-year and lifetime predicted risks to stratify participants into 3 groups: low 10-year (<10%); low lifetime (<39%) predicted risk, low 10-year (<10%)/high lifetime (>39%) predicted risk, and high 10-year (>10%) predicted risk or diagnosed diabetes. The majority of US adults (56%, or 87 million individuals) are at low short-term but high lifetime predicted risk for cardiovascular disease. Twenty-six percent (41 million adults) are at low short-term and low lifetime predicted risk, and only 18% (28 million individuals) are at high short-term predicted risk. The addition of lifetime risk estimation to 10-year risk estimation identifies higher-risk women and younger men in particular.

Conclusions: Whereas 82% of US adults are at low short-term risk, two thirds of this group, or 87 million people, are at high lifetime predicted risk for cardiovascular disease. These results provide support for use of a stepwise stratification system aimed at improving risk communication, and they provide a baseline for public health efforts aimed at increasing the proportion of Americans with low short-term and low lifetime risk for cardiovascular disease.

Endothelial-Specific Deletion of Connexin40 Promotes Atherosclerosis by Increasing CD73-Dependent Leukocyte Adhesion

Summary: Endothelial dysfunction, the initiating event of atherosclerosis, is characterized by increased expression of adhesion molecules and cytokines, which promotes the transmigration of leukocytes into the atherosclerotic lesion. This study provides evidence that connexin40 (Cx40), a gap junction protein expressed in endothelial cells, regulates the activity of the membrane-bound 5′-ecto-nucleotidase (CD73). The activity of endothelial CD73 generates adenosine from the hydrolysis of adenine nucleotides. Adenosine, in turn, activates surface membrane receptors to trigger antiadhesive responses within the endothelium. These findings support the idea of a quiescent nonactivated endothelium by propagating adenosine-evoked anti-inflammatory signals between endothelial cells. Alteration in this mechanism by targeting Cx40 promotes leucocyte adhesion to the endothelium, thus accelerating atherosclerosis.

Use of Evidence-Based Therapies in Short-Term Outcomes of ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Myocardial Infarction in Patients With Chronic Kidney Disease: A Report From the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network Registry

Summary: Chronic kidney disease (CKD) is a risk factor for myocardial infarction (MI) and death. We sought to characterize the association between CKD severity and short-term outcomes and the use of in-hospital evidence-based therapies among patients with ST-segment elevation MI (STEMI) and non–ST-segment elevation MI (NSTEMI) using the Acute Coronary Treatment and Intervention Outcomes Network registry, a nationwide sample of STEMI and NSTEMI patients admitted to hospitals in the United States. Overall, 30.5% and 42.9% of patients with STEMI and NSTEMI, respectively, had CKD. Regardless of MI type, patients with progressively more severe CKD had higher rates of death. In addition, patients with progressively more severe CKD were less likely to receive immedi-
ate evidence-based therapies including aspirin, β-blockers, or clopidogrel, were less likely to undergo any reperfusion (STEMI) or revascularization (NSTEMI), and had higher rates of bleeding. We conclude that a large proportion of patients presenting with STEMI or NSTEMI have CKD and have increased in-hospital mortality rates. These patients receive fewer evidence-based therapies. Additional research to define optimal post-MI care in patients with CKD is warranted.

**Conclusions:** Reports over the past decade have highlighted the importance of CKD among patients with MI. Data from this contemporary cohort suggest that patients with CKD still receive fewer evidence-based therapies and have substantially higher mortality rates.  

**Association of Diet, Exercise, and Smoking Modification With Risk of Early Cardiovascular Events After Acute Coronary Syndromes**

**Summary:** Although preventive drug therapy is a priority after myocardial infarction (MI), less is known about adherence to behavioral recommendations. The aim of this study was to examine the influence of adherence to behavioral recommendations on the risk for repeat MI. The study population included 18,809 patients from 41 countries enrolled in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 randomized clinical trial. One month after presenting with MI, 28.5% reported nonadherence to diet and exercise recommendations, and about one third of smokers persisted in smoking. In models adjusted for known risk factors and medical treatments, quitting smoking was associated with about half the risk of repeat MI compared with persistent smoking (odds ratio, 0.57; 95% confidence interval, 0.36–0.89); and diet and exercise adherence was associated with about half the risk of repeat MI compared with nonadherence (odds ratio, 0.52; 95% confidence interval, 0.4–0.69). Persistent smoking and nonadherence to diet and exercise were associated with a 3.8-fold (95% confidence interval, 2.5–5.9) increased risk of cardiovascular events (MI, stroke, and death) compared with risks in never smokers who modified diet and exercise. These analyses highlight the relatively poor adherence to behavioral advice (diet, exercise, and smoking cessation) after MI and suggest that behavioral modification should be given priority similar to other preventive medications immediately after MI because they are associated with substantial benefits in the prevention of repeat events.

**Conclusions:** Adherence to behavioral advice (diet, exercise, and smoking cessation) after acute coronary syndrome was associated with a substantially lower risk of recurrent cardiovascular events. These findings suggest that behavioral modification should be given priority similar to other preventive medications immediately after acute coronary syndrome.

**Regular Exercise Training Prevents Aortic Valve Disease in Low-Density Lipoprotein-Receptor–Deficient Mice**

**Summary:** Calcified aortic valve (AV) stenosis is a large and growing health problem with no alternatives to costly invasive treatment in Western countries. Thus, the optimum timing of novel therapy for the prevention of calcified AV disease is an active area of investigation. AV sclerosis can develop into AV stenosis in many patients. In addition, severe valve calcification indicates a rapid disease progression and poor prognosis in patients with AV sclerosis. Thus, an effective intervention at an earlier stage of disease before the development of severe valve calcification (eg, AV sclerosis) would have major clinical benefits. The present study demonstrated that regular exercise training but not occasional exercise training prevented AV sclerosis in mice via numerous favorable mechanisms, including preservation of valvular endothelial integrity and a subsequent decrease in recruitment of inflammatory cells, oxidative stress, and the osteogenic process. These novel findings indicate that regular physical activity may be recommended for prevention of the early stage of calcified AV disease. Accumulated evidence suggests that several cardiovascular risk factors are associated with AV sclerosis/stenosis and that the metabolic syndrome is associated with an increased prevalence of AV calcium or progression of AV stenosis. The metabolic syndrome is a potentially preventable and modifiable condition that results primarily from a sedentary lifestyle. Many of the features of the metabolic syndrome are not reversed by the pharmacological treatment of traditional risk factors (eg, statins). Therefore, regular exercise training is warranted and may represent a promising intervention to reduce the incidence and mortality of calcified AV stenosis, particularly at an early stage of disease.

**Conclusions:** In the low-density lipoprotein–receptor–deficient mouse, regular exercise training prevents aortic valve sclerosis by numerous mechanisms, including preservation of endothelial integrity, reduction in inflammation and oxidative stress, and inhibition of the osteogenic pathway.

**Twelve-Year Follow-Up of American Women’s Awareness of Cardiovascular Disease Risk and Barriers to Heart Health**

**Summary:** Awareness of heart disease as the leading cause of death among women is suboptimal and a gap in awareness exists between whites and racial/ethnic minorities. It is well established that delay in seeking emergency services is associated with greater cardiac mortality rates. Clinical trials have demonstrated that some interventions (eg, antioxidant vitamin supplementation) do not prevent heart disease. Environmental factors (such as limited availability of fresh fruits and vegetables, have been cited as barriers to heart-healthy living. Although levels of heart disease awareness have improved since 1997, almost half of women remain unaware that coronary heart disease is the leading cause of death among women, and the gap in awareness among minorities is closing. The present study documents that only about one half of women would call 9–1 if they thought they were having symptoms of a heart attack. A substantial percentage of women perceive that unproven preventive therapies will reduce their risk of heart disease. Women support environmental approaches such as increased access to healthy foods, recreational facilities, and enhanced nutrition labeling to lower risk.

**Conclusions:** Awareness of cardiovascular disease as the leading cause of death among women has nearly doubled since 1997 but is stabilizing and continues to lag in racial/ethnic minorities. Numerous misperceptions and barriers to prevention persist and women strongly favored environmental approaches to facilitate preventive action.

**Prediction of Cardiovascular Death in Racial/Ethnic Minorities Using Framingham Risk Factors**

**Summary:** Few studies have evaluated how well individual cardiovascular risk factors predict cardiovascular mortality in racial/ethnic minorities. In fact, most studies looking at the association between risk factors and cardiovascular disease mortality have used the predominately white Framingham cohorts. Looking at the National Health and Nutrition Examination Survey III, which oversampled non-Hispanic blacks and Mexican Americans, we found that, in aggregate, cardiovascular risk factors predict cardiovascular disease mortality equally well in non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. However, individual risk factors had variable prevalences and associations with cardiovascular disease mortality in each racial/ethnic group. Most notably, age was more strongly associated with cardiovascular disease mortality in non-Hispanic whites than in racial/ethnic minorities.

**Conclusions:** Framingham risk factors predict cardiovascular disease mortality equally well in non-Hispanic white, non-Hispanic black,
and Mexican-American participants, but the strength of the association between individual risk factors and cardiovascular disease mortality differs by race and ethnicity. When other risk factors are held constant, minority individuals are at higher risk of cardiovascular disease mortality at younger ages than non-Hispanic whites.7

Dietary Intervention to Reverse Carotid Atherosclerosis

Summary: The main findings in this study are as follows: (1) Diet-mediated weight loss over a 2-year period can induce a significant regression of carotid vessel wall volume. (2) Low-fat, low-carbohydrate, and Mediterranean diets provide similar degrees of carotid vessel wall volume regression. Thus, a low-carbohydrate diet is an alternative to low-fat and Mediterranean diets in reversing carotid atherosclerosis. (3) Over 2 years, changes in carotid intima-media thickness and 3-dimensional ultrasound are more clearly predicted by diet-induced changes in blood pressure than by changes in lipoprotein levels. For the practicing clinician, this study demonstrates that carotid atherosclerosis is reversible by long-term adherence to dietary strategies to induce weight loss. This effect is more pronounced among mildly obese persons who lose >5.5 kg body weight within 12 months and whose systolic blood pressure decreases by >7 mm Hg within 9 months. Increase in apolipoprotein A1 and decrease in plasma total homocysteine levels are also associated with subsequent success in reversing carotid atherosclerosis.

Conclusions: Two-year weight loss diets can induce a significant regression of measurable carotid vessel wall volume. The effect is similar in low-fat, Mediterranean, or low-carbohydrate strategies and appears to be mediated mainly by the weight loss–induced decline in blood pressure.8

Urinary Creatinine Excretion Rate and Mortality in Persons With Coronary Artery Disease: The Heart and Soul Study

Summary: Recent studies have demonstrated that low body mass index is associated with mortality in individuals with coronary artery disease, whereas higher body mass index is not. Lower body mass index may reflect low muscle mass rather than low fat. When serum creatinine is in steady state, urinary creatinine excretion rate is proportional to muscle mass. In 903 outpatients with stable coronary artery disease, we collected 24-hour urine collections and evaluated the relation of creatinine excretion rate with mortality over 6 years. Individuals within the lowest tertile of creatinine excretion rate were at >2-fold mortality risk compared with the highest tertile independently of body mass index, waist-to-hip ratio, traditional coronary artery disease risk factors, inflammatory biomarkers, and kidney function. Timed urine collection may provide an inexpensive and readily available method to measure muscle mass in outpatients with coronary artery disease and to garner additional information on mortality risk independently of conventional measures of body composition or traditional coronary artery disease risk factors. Future studies are required to determine whether resistive exercise and/or nutritional interventions can improve creatinine excretion rate and whether such improvements in creatinine excretion rate are associated with demonstrable improvements in health outcomes.

Conclusions: Lower creatinine excretion rate is strongly associated with mortality in outpatients with coronary artery disease, independently of conventional measures of body composition, kidney function, and traditional coronary artery disease risk factors. Future studies should determine whether low creatinine excretion rate may be a modifiable risk factor for mortality among persons with coronary artery disease, potentially through resistive exercise training or nutrition interventions.9

Alcohol Intake and Risk of Coronary Heart Disease in Younger, Middle-Aged, and Older Adults

Summary: The association between alcohol consumption and decreased risk of coronary heart disease is well established, but possible age differences are plausible because of potential pathogenic differences in coronary heart disease events occurring in younger compared with middle-aged or older individuals. We studied these relations in a large population of men and women 35 to 89 years of age at baseline. We observed a lower risk of coronary heart disease among men and women with a light to moderate alcohol intake compared with nondrinkers, and this finding was consistent and of similar size in all age groups. However, the absolute risk of coronary heart disease was small in the youngest age group, and risk differences between abstainers and light to moderate alcohol consumers were of negligible size. Therefore, our results provide strong evidence for a lower risk of coronary heart disease among moderate consumers relative to nondrinkers in younger, middle-aged, and older adults; however, considering absolute risks across age groups, younger adults are not likely to benefit from an overall recommendation of moderate alcohol intake.

Conclusion: Alcohol is also associated with a decreased risk of coronary heart disease in younger adults; however, the absolute risk was small compared with middle-aged and older adults.10

Apolipoprotein C-III and the Metabolic Basis for Hypertriglyceridemia and the Dense Low-Density Lipoprotein Phenotype

Summary: Hypertriglyceridemia is a common form of dyslipidemia that is frequently linked to premature coronary artery disease. Hypertriglyceridemic patients often exhibit a small, dense low-density lipoprotein (LDL) phenotype. Our previous investigations demonstrate that apolipoprotein (apo) C-III and E, surface protein components of very low-density lipoprotein (VLDL) and LDL, play a dominant role in regulating the metabolism of these lipoproteins. In this work, we studied VLDL and LDL metabolism by the kinetics of its principal protein component, apoB, in 9 patients with moderate hypertriglyceridemia and 12 normotriglyceridemic control subjects using stable isotope labeling. Our results support a central role for apoC-III in VLDL and LDL metabolic defects leading to hypertriglyceridemia. Triglyceride-rich lipoprotein metabolism shifts from an apoE-dominated system in normolipidemic participants characterized by rapid clearance from the circulation of VLDL to an apoC-III–dominated system in hypertriglyceridemic patients characterized by reduced clearance of triglyceride-rich lipoproteins that are channeled to formation of dense LDL in plasma. In addition, apoC-III contributes to the formation of the dense LDL phenotype through a quartet of kinetic perturbations. These results indicate that the action of apoC-III to retard clearance of triglyceride-rich lipoproteins is a central metabolic feature underlying major changes in VLDL and LDL metabolism in hypertriglyceridemia. These adverse changes in apoB lipoprotein metabolism caused by apoC-III, in addition to the newly established proatherogenic effects of apoC-III itself, directly link moderate hypertriglyceridemia to increased risk for coronary heart disease. Therefore, modulating apoC-III may not only improve lipid profiles but also prevent the development of atherosclerotic plaques and their acute thrombotic complications.

Conclusions: These results support a central role for apoC-III in metabolic defects leading to hypertriglyceridemia. Triglyceride-rich lipoprotein metabolism shifts from an apoE-dominated system in normotriglyceridemic participants characterized by rapid clearance from circulation of VLDL to an apoC-III–dominated system in hypertriglyceridemic patients characterized by reduced clearance of triglyceride-rich lipoproteins and the formation of the dense LDL phenotype.11
Blockade of Interleukin-17A Results in Reduced Atherosclerosis in Apolipoprotein E–Deficient Mice

Summary: Atherosclerotic lesion progression depends on chronic inflammation within the artery wall, and T cells are involved in the immune response that accompanies atherosclerosis. Interleukin (IL)-17A is a recently discovered cytokine that plays a protective role in host defenses against extracellular pathogens and a pathogenic role in several autoimmune diseases, including multiple sclerosis, inflammatory bowel disease, and arthritis. In the present study, we showed that plasma levels of IL-17A and aortic IL-17A–producing γδ T and CD4+ (Th17) T cells were significantly elevated in the atherosclerosis-prone conditions found in apolipoprotein E–deficient (Apoe–/–) mice. We confirmed a proatherogenic role of IL-17A using adenovirus-delivered soluble IL-17 receptor against IL-17A, which caused a significant decrease in plasma levels of IL-6 and granulocyte colony-stimulating factor, diminished aortic macrophage content and CXCL1 expression, and led to a reduction in plaque burden in treated Apoe–/– mice. Conversely, the treatment of isolated Apoe–/– aortas with recombinant IL-17A increased CXCL1 expression and monocyte adhesion to vessel wall. Our findings highlight a proatherogenic role for IL-17A in coronary atherosclerosis and suggest that future therapies targeting IL-17A could potentially reduce vascular wall infiltrates and lesion size and attenuate atherosclerosis and other forms of vascular disease.

Conclusions: These results demonstrate that atherosclerosis-prone conditions induce the differentiation of IL-17A–producing T cells. IL-17A plays a proatherogenic inflammatory role during atherogenesis by promoting monocyte/macrophage recruitment into the aortic wall.

In Vivo Detection of Vulnerable Atherosclerotic Plaque by MRI in a Rabbit Model

Summary: Rupture or erosion of vulnerable atherosclerotic plaque is responsible for a substantial number of deaths and disabilities worldwide. Thus, in situ detection of plaques at high risk of disruption and thrombosis may improve risk prediction and treatment of individuals with atherosclerotic disease. The present study describes the use of MRI to identify characteristics of vulnerable plaques in a rabbit model of controlled plaque disruption. Our findings are promising because they are noninvasive, do not entail the use of ionizing radiation or nephrotoxic contrast agents, and can be performed with clinical MRI scanners. Furthermore, the development and testing of drugs to stabilize vulnerable plaques is a major challenge. Because atherosclerosis progression in humans is slow and large patient numbers are required for pharmacological studies, the rabbit model could be used to test the efficacy of therapeutic strategies on plaque morphology. If future investigations find that arterial remodeling and gadolinium uptake have prognostic and clinical value in identifying vulnerable plaques, then the findings of this study can be expanded to monitor the effectiveness of interventions in humans.

Conclusions: We demonstrate that in vivo MRI at 3.0 T detects features of vulnerable plaques in an animal model of controlled atherothrombosis. These findings suggest that MRI may be used as a noninvasive modality for localization of plaques that are prone to disruption.

Analysis of Metabolic Remodeling in Compensated Left Ventricular Hypertrophy and Heart Failure

Summary: Congestive heart failure (CHF) is associated with a significant change in energy metabolism of the heart, and this alteration has been hypothesized to be important in the progression of CHF. Because treatment that improves the prognosis of patients with CHF, such as with β-adrenergic receptor blockers or angiotensin-converting enzyme inhibitors, is energy-sparing, it is hoped that modulation of cardiac energy metabolism may ameliorate CHF. We analyzed cardiac energy metabolism in Dahl salt-sensitive rats that were fed a high-salt diet, which showed a transition from compensated left ventricular hypertrophy to CHF. Left ventricular hypertrophy or CHF was associated with a distinct change in the metabolic profile of the heart. Glucose uptake increased and fatty acid uptake decreased in CHF. On comprehensive metabolome analysis that simultaneously measured the levels of multiple metabolites in heart tissue, the pentose phosphate pathway that regulates the cellular redox state was found to be activated in CHF. Dichloroacetate, a compound known to enhance glucose oxidation, increased glucose uptake and the energy reserve and improved cardiac function and survival. Dichloroacetate also activated the pentose phosphate pathway, decreased oxidative stress, and prevented cell death of cultured cardiomyocytes. Thus, increased glucose metabolism in CHF is likely to act as a protective mechanism by increasing the energy reserve and decreasing oxidative stress via pentose phosphate pathway activation. In summary, modulating the energy metabolism of the heart is likely to be a promising modality of CHF treatment.

Conclusions: Left ventricular hypertrophy or CHF is associated with a distinct change in the metabolic profile of the heart. Dichloroacetate attenuated the transition associated with increased energy reserves, activation of the pentose phosphate pathway, and reduced oxidative stress.

Tumor Necrosis Factor Receptor–Associated Factor 1 (TRAF1) Deficiency Attenuates Atherosclerosis in Mice by Impairing Monocyte Recruitment to the Vessel Wall

Summary: Tumor necrosis factor receptor–associated factors (TRAFs) mediate inflammatory signaling for important cytokines of the tumor necrosis factor/interleukin-1/Toll-like receptor superfamily such as CD40L, tumor necrosis factor–α, and interleukin-1β. Atherosclerosis is a chronic inflammatory disease governed by a network of such inflammatory cytokines. Although the inflammatory nature of atherosclerosis has been known for some time, cardiology still lacks a causal anti-inflammatory or immunomodulatory treatment option. The potential of such therapies is clearly suggested by the pleiotropic treatment benefits of statins, most recently demonstrated in the JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). Although overall inhibition of cytokines may produce a variety of undesirable side effects, the inhibition of specific signaling intermediates potentially may overcome some of these limitations. The present study presents the novel and somewhat unexpected finding that TRAF1 deficiency potently attenuates murine atherosclerosis, most likely by impairing monocyte recruitment to the vessel wall, which suggests a proatherogenic function of TRAF1. In line with this notion, we found increased expression of TRAF1 in blood of patients who had an acute coronary syndrome. Future studies will be needed to determine whether TRAF1 targeting might indeed represent a novel treatment strategy for chronic inflammatory diseases such as atherosclerosis.

Conclusions: TRAF1 deficiency attenuates atherosclerosis in mice, most likely owing to impaired monocyte recruitment to the vessel wall. These data identify TRAF1 as a potential treatment target for atherosclerosis.

Whole-Grain, Cereal Fiber, Bran, and Germ Intake and the Risks of All-Cause and Cardiovascular Disease–Specific Mortality Among Women With Type 2 Diabetes Mellitus

Summary: Although whole grain consumption has been associated with a lower risk of cardiovascular disease incidence and mortality in
the general population, little is known about the effect of whole grain and its components on cardiovascular risk and mortality in diabetic patients. In this prospective study, we followed 7822 US women with type 2 diabetes mellitus for up to 26 years to investigate intakes of whole grain and its components cereal fiber, bran, and germ in relation to all-cause and cardiovascular disease–specific mortality. Our results indicated that intakes of whole grain, especially its subcomponent bran, were inversely associated with all-cause and cardiovascular disease–specific mortality among women with type 2 diabetes mellitus. Low whole-grain intake may be considered an important modifiable risk factor for decreasing mortality and cardiovascular risk in persons with diabetes mellitus.

**Conclusions:** Whole-grain and bran intakes were associated with reduced all-cause and cardiovascular disease–specific mortality in women with diabetes mellitus. These findings suggest a potential benefit of whole-grain intake in reducing mortality and cardiovascular risk in diabetic patients.16

**Red and Processed Meat Consumption and Risk of Incident Coronary Heart Disease, Stroke, and Diabetes Mellitus: A Systematic Review and Meta-Analysis**

**Summary:** US dietary-guidelines recommend “eating less” red and processed meat. For cardiovascular disease, these recommendations are based largely on expected effects on blood cholesterol of saturated fat and dietary cholesterol in meats. However, relationships of meat intake with cardiometabolic disease outcomes, including coronary heart disease, stroke, and diabetes mellitus, are not well established. Additionally, few studies have separately evaluated unprocessed red versus processed meats, for which nutritional differences could produce different health effects. We systematically reviewed and pooled all available worldwide data on relationships between meat consumption and risk of coronary heart disease, stroke, or diabetes mellitus. Twenty studies were identified including 1,218,380 individuals from the United States, Europe, Australia, and Asia. When all data were pooled, consumption of unprocessed red meat (eg, unprocessed meat from beef, pork, lamb) was not associated with risk of coronary heart disease or diabetes mellitus. In contrast, each daily serving of processed meat (eg, bacon, hot dog, salami) was associated with 42% higher coronary heart disease and 19% higher diabetes mellitus risk. No associations were seen with stroke, but only 3 studies evaluated these relationships. When nationally representative US data on average types of meats consumed were analyzed, unprocessed red and processed meats contained relatively similar saturated fat and dietary cholesterol; processed meats contained much higher salt and nitrate preservatives. Our findings suggest that unprocessed red and processed meats have differing relationships with cardiometabolic outcomes and also suggest that differences in preservative contents, rather than fats, could at least partly account for these findings. Future research should separately consider potential health effects and underlying mechanisms of unprocessed versus processed meats, and current clinical and policy efforts should especially focus on reducing processed meat consumption.

**Conclusions:** Consumption of processed meats, but not red meats, is associated with higher incidence of coronary heart disease and diabetes mellitus. These results highlight the need for better understanding of potential mechanisms of effects and for particular focus on processed meats for dietary and policy recommendations.17

**Reducing Consumption of Sugar-Sweetened Beverages Is Associated With Reduced Blood Pressure: A Prospective Study Among United States Adults**

**Summary:** Consumption of sugar-sweetened beverages (SSBs) has increased dramatically in the United States. Although high SSB consumption has been linked to excess calorie intake and overweight/obesity, SSBs may have other adverse effects. In a prospective study of 810 US adults with prehypertension and stage I hypertension, we found that reducing SSB consumption was associated with significant reductions in blood pressures (BP). On average, a reduction in SSB intake of 1 serving a day (12 oz/d) was associated with a 1.8-mm Hg reduction in systolic BP and 1.1-mm Hg reduction in diastolic BP over 18 months. A positive association was also found for dietary sugar intake and BP. No association was found for diet beverage consumption or caffeine intake and BP. These findings have important clinical and public health implications. It has been estimated that a 3-mm Hg reduction in systolic BP should reduce stroke mortality by 8% and coronary heart disease mortality by 5%. Such reductions in systolic BP would be anticipated by reducing SSB consumption by an average of 2 servings per day. Currently, the average intake of SSBs is 2.3 servings per day for US adults. Nationwide, 72 million US adults (35%) have hypertension, and another 59 million (29%) have prehypertension. Given the high prevalence of both SSB consumption and hypertension in the United States and throughout much of the world, even small reductions in SSB consumption should have a beneficial public health impact. In conclusion, our data suggest that reducing SSB and sugar consumption may be an important dietary strategy to lower BP.

**Conclusions:** Reduced consumption of SSB and sugars was significantly associated with reduced BP. Reducing SSB and sugar consumption may be an important dietary strategy to lower BP.18

**Mediterranean Dietary Pattern Is Associated With Improved Cardiac Autonomic Function Among Middle-Aged Men: A Twin Study**

**Summary:** The Mediterranean diet is associated with lower cardiovascular risk. Lower heart rate variability, reflecting cardiac autonomic dysfunction, is a risk factor for cardiac death. To date, no prior studies have explored the association between a whole diet conforming to the Mediterranean diet and cardiac autonomic function measured as heart rate variability. Using a twin study design, for the first time, to our knowledge, we found that the more an individual’s diet conformed to the Mediterranean diet, the greater the heart rate variability, indicating better cardiac autonomic function. This positive association was independent of genes, shared environmental factors, and known cardiovascular risk factors; this means that whether or not a person has an adverse genetic background or other risk factors for cardiovascular disease, this person would be likely to have better cardiac autonomic function if he or she follows a diet similar to the Mediterranean diet.

**Conclusions:** The Mediterranean dietary pattern is associated with higher heart rate variability.19

**Blood Eicosapentaenoic and Docosahexaenoic Acids Predict All-Cause Mortality in Patients With Stable Coronary Heart Disease: The Heart And Soul Study**

**Summary:** Populations that report higher intakes of long-chain omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) have lower rates of heart disease death than those with lower intakes. Supplementation with omega-3 fatty acids has reduced risk for total mortality in high-risk populations. Blood levels of omega-3 fatty acids are reliable surrogates of tissue levels, but are only moderately correlated with dietary intakes of these fatty acids. Patients with coronary heart disease with above-average blood levels of omega-3 fatty acids are at lower risk for death from any cause than patients with lower levels. A reduced blood omega-3 level is an independent risk marker for death from any cause in patients with stable coronary heart disease.
Conclusions: In these outpatients with stable coronary heart disease, blood n-3 fatty acid levels were inversely associated with total mortality independent of standard and emerging risk factors, suggesting that reduced tissue n-3 fatty acid levels may adversely impact metabolism.\[^{20}\]

**Molecular Imaging of Atherosclerotic Plaques Targeted to Oxidized LDL Receptor LOX-1 by SPECT/CT and Magnetic Resonance**

*Summary: Oxidized low-density lipoprotein plays a critical role in atherosclerosis, and its effects are mediated by activation of its specialized receptor, LOX-1. LOX-1 induces apoptosis, expression of adhesion molecules and matrix metalloproteinases, and in general, activates inflammation. LOX-1 activation not only initiates lesion formation but also contributes to the vulnerability of the plaque to rupture. Thus, a noninvasive molecular imaging approach to identify LOX-1 in the live animal would be advantageous to study the atherosclerotic process early in its natural history to enable optimal therapies to prevent acute coronary syndromes. Imaging probes for both single-photon emission computed tomography/computed tomography and MRI were constructed that consisted of liposomes decorated with anti–LOX-1 antibodies (LOX-1 probe) and either \(^{111}\) indium or gadolinium, as well as fluorescent markers. In vivo imaging was performed 24 hours after intravenous injection of 150 \(\mu\)L LOX-1 probe in mouse models of atherosclerosis. Single-photon emission computed tomography/computed tomography imaging showed aortic arch hot spots, and MRI showed significant contrast enhancement in aortic atherosclerosis. Binding was shown to be specific for LOX-1, and the probe bound preferentially to the plaque shoulder, a region with vulnerable plaque features including extensive LOX-1 expression, macrophage accumulation, apoptosis, and matrix metalloproteinase-9 expression. Thus, this flexible multimodality molecular imaging approach could be used to identify features of vulnerable plaque in vulnerable patients. Moving this approach into the clinic to identify patients at risk for acute coronary syndromes could lead to improved targeting of therapies aimed at reducing inflammation and atherosclerosis to prevent these syndromes.*

*Conclusions: LOX-1 can be used as a target for molecular imaging of atherosclerotic plaque in vivo. Furthermore, the LOX-1 imaging signal is associated with markers of rupture-prone atherosclerotic plaque.*\[^{21}\]

**Mineralocorticoid Accelerates Transition to Heart Failure With Preserved Ejection Fraction via “Nongenomic Effects”**

*Summary: A wealth of data from human systolic heart failure and experimental models of hypertension and heart failure suggests that mineralocorticoid receptor antagonists reduce mortality and attenuate hypertrophy, fibrosis, and diastolic dysfunction. These data have led to the ongoing multicenter randomized Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure (TOPCAT). Although aldosterone levels are elevated in heart failure with preserved ejection fraction, whether aldosterone itself causes adverse cardiac remodeling, which could promote the transition from hypertensive heart disease to overt heart failure with preserved ejection fraction, is controversial. In this study, we show that oxidative stress is induced in the hypertensive heart and sensitizes the heart to exogenous mineralocorticoids. In normal mice, exogenous mineralocorticoid had little effect on cardiac structure or function. Mice with pressure-overload hypertrophy had increased myocardial oxidative stress, and in these mice, exogenous mineralocorticoid accentuated hypertrophy, fibrosis, and diastolic dysfunction, suggesting an interaction between excess mineralocorticoid (inappropriate for salt status) and oxidative stress. Interestingly, this effect was observed without evidence of classic mineralocorticoid receptor–mediated gene transcription in the heart (“nongenomic” effects) and independently of changes in the magnitude of pressure overload. These results suggest that aldosterone excess may promote the transition from compensated hypertensive heart disease to heart failure with preserved ejection fraction via nongenomic effects or alternatively through effects on noncardiac cells. Because the nongenomic effects of aldosterone are exerted both via the mineralocorticoid receptor and independent from the mineralocorticoid receptor, development of novel antagonists that target both genomic and nongenomic effects may have benefit beyond mineralocorticoid receptor antagonists.*

*Conclusions: Pressure-overload hypertrophy sensitizes the heart to mineralocorticoid excess, which promotes the transition to heart failure with preserved ejection fraction independently of classic mineralocorticoid receptor–dependent gene transcription.*\[^{22}\]

**Major Dietary Protein Sources and Risk of Coronary Heart Disease in Women**

*Summary: With the exception of fish, few major dietary protein sources have been studied in relation to the development of coronary heart disease (CHD). Our objective was to examine the relation between foods that are major dietary protein sources and incident CHD. We prospectively followed 84 136 women aged 30 to 55 years in the Nurses’ Health Study with no known cancer, diabetes mellitus, angina, myocardial infarction, stroke, or other cardiovascular disease. During 26 years of follow-up, we documented 2210 incident nonfatal infarctions and 952 deaths from CHD. In multivariate analyses including age, smoking, and other known cardiovascular risk factors, a higher intake of red meat was significantly associated with an elevated risk of CHD. Higher intakes of poultry, fish, and nuts were significantly associated with lower risk. In a model controlling statistically for total energy intake, 1 serving per day of nuts was associated with a 30% (95% confidence interval, 17%–42%) lower risk of CHD compared with 1 serving per day of red meat. Similarly, compared with 1 serving per day of red meat, 1 serving per day of low-fat dairy was associated with a 13% (95% confidence interval, 6%–19%) lower risk, 1 serving per day of poultry was associated with a 19% (95% confidence interval, 3%–33%) lower risk, and 1 serving per day of fish was associated with a 24% (95% confidence interval, 6%–39%) lower risk. These data suggest that high red meat intake increases risk of CHD and that risk of CHD may be reduced importantly by shifting the sources of protein in the US diet.*

*Conclusions: These data suggest that high red meat intake increases risk of CHD and that CHD risk may be reduced importantly by shifting sources of protein in the US diet.*\[^{23}\]

**The Effect of Dietary Patterns on Estimated Coronary Heart Disease Risk: Results From the Dietary Approaches to Stop Hypertension (DASH) Trial**

*Summary: Lifestyle modification, including dietary change, is the initial treatment for hypertension, a major independent risk factor for coronary heart disease (CHD). The Dietary Approaches to Stop Hypertension (DASH) Trial demonstrated that the DASH diet lowers blood pressure and total and LDL cholesterol but decreases HDL cholesterol. The Framingham Heart Study risk equations allow for the calculation of 10-year estimated CHD risk based on both modifiable risk factors (systolic blood pressure, total cholesterol, and HDL cholesterol) and nonmodifiable risk factors (age and sex). Our study demonstrates that adoption of the DASH diet has the potential to decrease estimated 10-year CHD risk by 18% when compared with the control diet, taking into account both its effects on blood pressure and lipids. Given findings that the DASH diet should be especially effective in blacks, future research should explore the potential of the DASH diet as a means to reduce racial disparities in CHD.*
Conclusions: Compared with control and fruits and vegetables, the DASH diet reduced estimated 10-year CHD risk by 18% and 11%, respectively. In addition to reducing blood pressure, the DASH diet should substantially reduce the risk of CHD.

Chocolate Intake and Incidence of Heart Failure: A Population-Based Prospective Study of Middle-Aged and Elderly Women

Summary: Although the association between chocolate intake and heart failure (HF) is not known, there have been observational studies documenting its association with lower incidence of hypertension and cardiovascular and overall mortality. Therefore, we evaluated the association between chocolate consumption and incidence of HF using data from the Swedish Mammography Cohort. The study population included 31,823 women aged 48 to 83 years without baseline diabetes or a history of HF or myocardial infarction. Compared with no regular chocolate intake, the multivariable-adjusted rate ratio of HF was 0.74 (95% CI, 0.58–0.95) for women consuming 1 to 3 servings of chocolate per month, 0.68 (95% CI, 0.50–0.93) for those consuming 1 to 2 servings per week, 1.09 (95% CI, 0.74–1.62) for those consuming 3 to 6 servings per week, and 1.23 (95% CI, 0.73–2.08) for those consuming ≥1 servings per day (P=0.0005 for quadratic trend). On the basis of these results, moderate chocolate consumption appears to be protective against HF incidence among women in the Swedish Mammography Cohort. Definitive proof would require a large-scale randomized clinical trial, which is unlikely to occur in the near future.

Conclusions: In this population, moderate habitual chocolate intake was associated with a lower rate of HF hospitalization or death, but the protective association was not observed with intake of ≥1 servings per day.

C5a Receptor Targeting in Neointima Formation After Arterial Injury in Atherosclerosis-Prone Mice

Summary: Despite the success of antiproliferative therapies, restenosis remains a common problem after vascular intervention. The receptor for complement C5a (C5aR) has been identified in human atherosclerotic tissue, and adverse cardiovascular events have been correlated with C5a plasma levels. Receptor binding of C5a leads to proinflammatory activation of many cell types, but the role of receptor-mediated action during arterial remodeling after injury has not been studied. In the present study, we examined the contribution of the C5aR to neointima formation in apolipoprotein E–deficient mice employing a human peptidomimetic C5aR antagonist and a C5aR-blocking monoclonal antibody. Our results indicate a strong protective effect by short-term (1 week) blockade of C5aR with C5aR antagonist or anti-C5aR monoclonal antibody on neointimal plaque formation, leukocyte recruitment, and vascular cell adhesion molecule-1 expression. In contrast, long-term treatment (3 weeks) reduced inflammatory cell recruitment and vascular cell adhesion molecule-1 expression but also induced plasminogen activator inhibitor-1–dependent smooth muscle cell migration to the neointima, thus stabilizing but not reducing plaques. Further studies confirmed that protective effects of short-term C5aR antagonist treatment persisted over 3 weeks after injury. On the basis of these properties, C5aR targeting can be considered an attractive pharmacological strategy for short-term treatment of vascular injury and inflammation. However, long-term approaches should account for direct or indirect effects of C5aR signaling on adaptive immune responses, cell apoptosis, migration, and tissue regeneration or fibrosis that may affect such treatment. Thus, our study provides the first evidence that intervention of the complement cascade at the level of C5aR may be clinically feasible to limit restenosis after vascular injury.

Conclusions: One-week treatment with C5aRA or anti-C5aR-blocking monoclonal antibody limited neointimal hyperplasia and inflammatory cell content and was associated with reduced vascular cell adhesion molecule-1 expression. However, treatment for 3 weeks failed to reduce but rather stabilized plaques, likely by reducing vascular plasminogen activator inhibitor-1 and increasing vascular smooth muscle cell migration.

Genes Within the MHC Region Have a Dramatic Influence on Radiation-Enhanced Atherosclerosis in Mice

Summary: In this investigation, we report an unexpected finding that genes within the major histocompatibility complex (MHC) have a dramatic influence on radiation-enhanced atherosclerosis in mice. The mouse strain C3H/HeJ (C3H) is extremely resistant to atherosclerosis, with development of much smaller lesions than the strain C57BL/6 (B6) when the mouse is deficient in apolipoprotein E (apoE/−/−) or fed an atherogenic diet. The 2 inbred strains differ in the MHC haplotype, with B6 having H2a and C3H having H2k. C3.SW is a congenic strain of C3H/HeJ in which the H2a haplotype is replaced with the H2k haplotype. C3.SW apoE/−/− mice that underwent bone marrow transplantation after lethal irradiation exhibited a 21-fold increase in atherosclerotic lesion size as compared with C3H apoE/−/− mice receiving the same treatment, demonstrating the huge influence of H2 haplotypes on radiation-enhanced atherosclerosis. Radiation-induced tissue damage depends on radiation dose, tissue volume treated, and an unknown genetic predisposition. The ability to identify which patients are at risk for radiation-induced complications could facilitate the development of patient-specific treatment regimens toward maximizing therapeutic efficacy while minimizing the incidence of side effects.

Conclusions: These results indicate that gene(s) within the H2 region have a dramatic impact on radiation-enhanced atherosclerosis, and their effect is conveyed partially through bone marrow–derived cells.

Apolipoprotein E Polymorphisms and Postprandial Triglyceridemia Before and After Fenofibrate Treatment in the Genetics of Lipid Lowering and Diet Network (GOLDN) Study

Summary: Elevated plasma triglyceride concentrations have been associated with an increased risk of cardiovascular disease. A key mediator of triglyceride metabolism is the apolipoprotein E (APOE) gene. Although much is known about the association of APOE alleles (ε2, ε3, and ε4) with fasting triglyceride concentrations, much less is known about the association of these alleles with postprandial blood triglyceride concentrations. We evaluated the effects of the APOE locus on postprandial triglyceride concentrations as part of the Genetics of Lipid Lowering and Diet Network (GOLDN) study. This population is unique, as participants were evaluated after a high-fat meal challenge before (n=1072) and after 3 weeks of daily treatment with 160 mg of fenofibrate (n=738). We report that APOE polymorphisms are important correlates of triglyceride concentrations. Importantly, APOE ε2 alleles are associated with higher triglycerides in the fasting and postprandial state before and after treatment with fenofibrate. Exposure to elevated triglyceride concentrations is clinically important because growing evidence links excess circulating triglyceride rich lipoprotein remnant particles to oxidative stress and subsequent atherosclerosis. Future studies should determine if the APOE genotype is useful for the early prevention of hypertriglyceridemia, especially among high-risk groups such as those with a family history of cardiovascular disease.

Conclusions: APOE polymorphisms are important determinants of triglyceride concentrations, especially in the fasting state.

Low Hemoglobin A1c and Risk of All-Cause Mortality Among US Adults Without Diabetes

Summary: The widespread use of hemoglobin A1c as a diagnostic test for diabetes may lead to the frequent detection of low hemoglo-
Bin A1c values. The prognostic importance of low hemoglobin A1c values is unknown, but the natural assumption of clinicians may be that low HbA1c is beneficial. Hemoglobin values as low as 2.8% were detected in this nationally representative study. Low hemoglobin A1c (<4.0%) was associated with an increased risk of all-cause mortality. Other biological processes, such as inflammation and liver function, may underlie the association between low hemoglobin A1c (<4.0%) and all-cause mortality.

Conclusions: In this nationally representative cohort, low hemoglobin A1c was associated with increased all-cause mortality among US adults without diabetes. Additional research is needed to confirm these results and identify potential mechanisms that may be underlying this association.29

Early Impairment of Transmural Principal Strains in the Left Ventricular Wall After Short-Term, High-Fat Feeding of Mice Predisposed to Cardiac Steatosis

Summary: Previous MRS data of elevated myocardial lipids in human subjects with impaired glucose tolerance or type-2 diabetes suggest lipid overstorage is an early manifestation of type 2 diabetes, preceding heart failure. This study explored the link between short-term dietary, high fat intake and early changes in left ventricular (LV) wall mechanics in normal and diseased hearts. The approach, in studying transgenic mice, is the first to combine localized MRS of cardiac lipid with transmural resolution of 2-dimensional strains in the LV wall using cardiac tagged MRI at ultrahigh magnetic field (14.1 T). Our earlier work showed these strains to change prior to global impairment of LV function in myopathic hearts. The responses of endocardial and epicardial mechanics, of the in vivo mouse heart, to a two week, high fat diet (HFD) link overstorage of lipid (steatosis) to early impairment in LV wall contractility. We report on normal mice and transgenic mice with low levels of cardiac-specific overexpression of the nuclear receptor hormone, PPARα (MHC-PPARα) that exhibit elevated myocardial triglyceride. Other strains of MHC-PPARα, with greater expression levels, develop cardiomyopathy and have been reported to mimic the metabolic phenotype of the diabetic heart. The negative consequences of short-term HFD on LV wall mechanics were only apparent in MHC-PPARα hearts, and not nontransgenic animals, suggesting an underlying pathophysiologic or genetic requirement for cardiac steatosis in the development of early LV dysfunction. The findings contribute new understanding of the risks associated with elevated myocardial lipid for contractile dysfunction preceding cardiomyopathy.

Conclusions: A short-term HFD elevated myocardial lipid measures as determined by magnetic resonance spectroscopy, which became dissociated from triacylglyceride content in hearts predisposed to cardiac steatosis. The increased lipid was associated with concurrent, transmural reductions in E1 and E2 strains across the left ventricular wall. Strains were attenuated at the highest levels of lipid accumulation, suggesting a threshold response. Thus, 2-dimensional strains are impaired early and without left ventricular diastolic dysfunction, owing to cardiac steatosis.30

Hyperlipidemia-Triggered Neutrophilia Promotes Early Atherosclerosis

Summary: Atherosclerosis is a chronic inflammatory disease of large arteries with prominent roles of various leukocyte subsets that are recruited from the bloodstream into the vessel wall. Although current dogma emphasizes the role of monocyte and lymphocyte subsets, we describe here a pivotal role for neutrophils in the early stages of atherosclerosis. Hypercholesterolemia is an important risk factor, and we find evidence that high levels of cholesterol induce neutrophilia by cranking up granulopoiesis and by disturbing the chemokine axes regulating neutrophil mobilization from the bone marrow. We further found that levels of circulating neutrophils correlate with the degree of atherosclerosis, which may be useful as a simple approach to cardiovascular risk prediction. In addition, neutrophils infiltrate arteries prominently through the involvement of CCR1, CCR2, CCR5, and CXCR2. The use of CCR1 and CCR5 contrasts to peripheral neutrophil recruitment and may be ascribed to endothelial deposition of CCL5 by platelets. Once emigrated, neutrophils promote atherogenesis, as evidenced by reduced plaque sizes in neupenic mice. Thus, the use of CCR1 and CCR5 in arterial but not venous recruitment may emerge as a feasible option for therapeutic targeting. Clearly, the addition of the neutrophil as a previously not fully appreciated player in atherosclerosis increases the complexity of cellular interactions in disease pathogenesis but also harbors valuable strategies for prevention and treatment.

Conclusions: Our data provide evidence that hypercholesterolemia-induced neutrophilia is multifactorial and that neutrophils infiltrate arteries primarily during early stages of atherosclerosis. Collectively, these data suggest an important role of neutrophils in the initiation of atherosclerosis.31

The Alternative Pathway Is Critical for Pathogenic Complement Activation in Endotoxin- and Diet-Induced Atherosclerosis in Low-Density Lipoprotein Receptor–Deficient Mice

Summary: Previous experiments in animals have suggested that the early components of the classical and lectin complement pathways may have protective effects against the development of atherosclerosis. In this study, we have addressed the role of the alternative pathway by crossing the low-density-lipoprotein receptor–deficient mouse model of atherosclerosis (Ldlr−/−) with mice that lack complement factor B (Bf−/−), the initiator of the alternative pathway. Under 2 different proatherogenic conditions, administration of lipopolysaccharide and high-fat diet, Bf−/−/Ldlr−/− mice showed markedly reduced atherosclerotic lesion formation compared with Ldlr−/− mice. The protective effects of factor B deficiency were associated with significant reductions in systemic and lesional complement activation. Overall, our data provide the first direct evidence of the proatherogenic role of the amplification of complement activation by the alternative pathway in response to lipopolysaccharide or high-fat diet. This work lends support for developing therapeutic strategies aiming to inhibit the complement system by blocking the alternative pathway without interfering with the protective effect(s) mediated by the classical and lectin pathways.

Conclusions: These data demonstrate that amplification of complement activation by the alternative pathway in response to lipopolysaccharide or high-fat diet plays a proatherogenic role.32

Inhibition of Hyaluronan Synthesis Accelerates Murine Atherosclerosis: Novel Insights Into the Role of Hyaluronan Synthesis

Summary: Hyaluronan is an integral extracellular matrix component that plays crucial roles in, for example, development and homeostasis of cartilage and skin. However, increased hyaluronan production is associated with tumor progression and vascular disease. Hyaluronan accumulates during neointimal thickening in atherosclerotic plaques and restenotic lesions. In the neointima, it contributes to volume expansion and supports the proliferative and secretory phenotype of vascular smooth muscle cells. Therefore, inhibition of hyaluronan synthesis has been considered as a strategy to limit neointimal thickening and atheropropression. On the other hand, recent research has established hyaluronan on the luminal surface of vascular endothelial cells to be a critical constituent of the endothelial glyocalyx, which has strong vasoprotective functions. In the present study, it is shown in a murine model of atherosclerosis that inhibition of hyaluronan synthesis by an oral hyaluronan synthesis
inhibitor surprisingly enhances inflammatory and thrombotic responses and in the long term increases atherosclerosis. This adverse effect was attributed to a partial loss of the endothelial glyocalyx. Of note, hyaluronan synthesis inhibitors are effective in inhibiting tumor progression in mouse models and may be tested clinically to enhance the response to antitumor strategies. In light of the present results, it may be crucial to avoid adverse effects on the endothelial glyocalyx because damage of the glyocalyx may lead to increased atherothrombotic risk and enhance inflammatory cell recruitment.

Conclusions: The data suggest that systemic inhibition of hyaluronan synthesis by 4-methylumbelliferone interferes with the protective function of the endothelial glyocalyx, thereby facilitating leukocyte adhesion, subsequent inflammation, and progression of atherosclerosis.33

Genome-Wide Linkage and Positional Candidate Gene Study of Blood Pressure Response to Dietary Potassium Intervention: The Genetic Epidemiology Network of Salt Sensitivity Study

Summary: Current understanding of the genetic mechanisms underlying blood pressure (BP) response to dietary potassium intake is limited. Using data from 3142 Han Chinese participants, including 1906 who took part in a 7-day high-sodium diet followed by a 7-day high-sodium plus potassium dietary intervention, we conducted a genome-wide linkage scan and positional candidate gene study of systolic BP, diastolic BP, and mean arterial pressure responses to changes in dietary potassium intake. Our results identified regions on chromosomes 3 and 11 that may harbor important susceptibility loci for dietary potassium sensitivity. In addition, a novel variant in the angiotensin II receptor, type 1, gene was shown to be a strong predictor of BP response to dietary potassium. These findings provide early evidence of a definitive genetic mechanism underlying potassium sensitivity. Elucidating the genetic mechanisms that influence this complex phenotype could provide further insight into the pathophysiology of hypertension. In addition, cataloging variants that influence this trait could potentially lead to the development of targeted dietary interventions among potassium-sensitive subgroups for the primary and the secondary prevention of hypertension.

Conclusions: Genetic regions on chromosomes 3 and 11 may harbor important susceptibility loci for potassium sensitivity. Furthermore, the AGTR1 gene was a significant predictor of BP responses to potassium intake.34

Efficacy and Safety of Carvedilol in Treatment of Heart Failure With Chronic Kidney Disease: A Meta-Analysis of Randomized Trials

Summary: Chronic heart failure is a clinical syndrome associated with increased rates of morbidity, frequent hospitalizations, and increased utilization of health care costs as well as all-cause mortality. Similarly, chronic kidney disease (CKD) increases the risk for adverse cardiovascular outcomes in the general population as well as in those with underlying heart failure. There is a paucity of evidence whether therapeutic interventions that are effective for the treatment of heart failure in the general population are also effective in those heart failure patients with concomitant CKD. Consequently, clinicians may be reluctant to use these evidence-based therapies in those heart failure patients with concomitant CKD. Consequently, clinicians may be reluctant to use these evidence-based therapies in those heart failure patients with concomitant CKD. The data were categorized for the presence or absence of CKD, based on the estimated glomerular filtration rate (<60 or ≥60 mL/min/1.73 m², respectively), using the Modified Diet Renal Disease equation from the serum creatinine values obtained at the time of enrollment. Our study demonstrates that carvedilol therapy leads to similar benefits in the presence of CKD as in those heart failure patients without CKD. However, the effect of carvedilol therapy in heart failure patients with advanced CKD (estimated glomerular filtration rate <45 mL/min/1.73 m²) was not different from placebo. This hypothesis-generating finding that carvedilol may not be efficacious in very advanced stages of CKD must be confirmed by future studies. We also observed that the use of carvedilol therapy in the presence of CKD can lead to transient fluctuations in renal function and increases the risk for orthostatic hypotension and other electrolyte abnormalities. Hence, patients with heart failure with concomitant CKD should have careful dose titration as well as judicious monitoring of kidney function, blood pressure, and electrolytes when treated with carvedilol.

Conclusions: This analysis suggests that the benefits of carvedilol therapy in patients with systolic left ventricular dysfunction with or without symptoms of heart failure are consistent even in the presence of mild to moderate CKD. Whether carvedilol therapy is similarly efficacious in heart failure patients with more advanced kidney disease requires further study.35

Consumption of Added Sugars and Indicators of Cardiovascular Disease Risk Among US Adolescents

Summary: Consumption of added sugars (caloric sweeteners), which contribute calories but no other nutrients to the diet, are the source of more than one fifth of the calories consumed by US adolescents. The results of our study show that higher consumption of these sugars is associated with blood lipid levels that may place adolescents at increased risk of future cardiovascular disease. We also found that the risks associated with added sugar consumption may be higher among overweight or obese adolescents because higher consumption among this group was also associated with increased insulin resistance. Our findings highlight the prominence of added sugars in the diets of adolescents and suggest that reducing this consumption could be a strategy for modifying cardiovascular disease risk factors and helping to prevent cardiovascular disease. The associations demonstrated in our cross-sectional study point to the need for controlled trials to determine if reducing consumption of added sugars can improve cardiovascular disease risk factors in adolescents and prevent future disease.

Conclusion: Consumption of added sugars among US adolescents is positively associated with multiple measures known to increase cardiovascular disease risk.36

Association of Chronic Kidney Disease With Atrial Fibrillation Among Adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

Summary: Atrial fibrillation (AF) is a common cardiac arrhythmia that substantially increases risk for cardiac death and ischemic stroke. Chronic kidney disease (CKD) is also highly prevalent and associated with excess cardiac morbidity and mortality. Although AF and CKD share many risk factors, most studies evaluating the association between CKD and AF have been limited to those with advanced dialysis-dependent CKD. We evaluated the association between ECG-documented AF and non–dialysis-dependent CKD among 26 917 community-dwelling US adults. In this study, the prevalence of AF was significantly higher in those with versus without CKD. Moreover, the prevalence of AF was higher at progressively more advanced renal disease. The association between CKD and AF remained statistically significant across numerous subgroups. We did not detect any important differences in the risk factors for AF among those with versus without CKD. These results may provide important insight on increased thrombotic risk in CKD populations. Screening for AF among those with predialysis CKD may be warranted.
Conclusions: Regardless of severity, CKD is associated with an increased prevalence of AF among US adults.37

Omega-3 Fatty Acids Prevent Pressure Overload–Induced Cardiac Fibrosis Through Activation of Cyclic GMP/Protein Kinase G Signaling in Cardiac Fibroblasts

Summary: Heart failure is the leading reason for hospital admissions and is the most expensive Medicare expenditure. About half of heart failure cases are due to diastolic dysfunction. One of the main causes of diastolic dysfunction is cardiac fibrosis, and no therapies are available to prevent or treat cardiac fibrosis. Transforming growth factor-β–induced cardiac fibroblast transformation and proliferation are the key events leading to cardiac fibrosis. This study shows that ω-3 polyunsaturated fatty acids prevent pressure overload–induced cardiac fibrosis and subsequent cardiac dysfunction. This study also demonstrates that in cardiac fibroblasts, eicosapentaenoic acid and docosahexaenoic acid increase cyclic GMP levels by increasing phosphorylated endothelial nitric oxide synthase and endothelial nitric oxide synthase protein levels and nitric oxide production, and they exert their antifibrotic effect through activation of the cyclic GMP/protein kinase G pathway and subsequent blocking of transforming growth factor-β–induced nuclear translocation of phospho-Smad2 and phospho-Smad3. This study defines the beneficial effects of ω-3 polyunsaturated fatty acids on cardiac fibrosis and cardiac dysfunction and clarifies the underlying mechanisms. In addition, this study provides the basis for extending the application of ω-3 polyunsaturated fatty acids, which appear to be exceptionally safe and well tolerated, to the prevention of cardiac fibrosis.

Conclusion: Omega-3 fatty acids prevent cardiac fibrosis and cardiac dysfunction by blocking transforming growth factor-β–induced phospho-Smad2/3 nuclear translocation through activation of the cyclic GMP/protein kinase G pathway in cardiac fibroblasts.38

Augmented Expression and Activity of Extracellular Matrix–Degrading Enzymes in Regions of Low Endothelial Shear Stress Colocalize With Coronary Atheromata With Thin Fibrous Caps in Pigs

Summary: This study explores the molecular mechanisms that determine the localized formation of thin-capped fibroatheromas in the coronary arteries of diabetic, hyperlipidemic swine. Local endothelial shear stress was calculated in vivo with a combination of intravascular ultrasound, coronary angiography, and computational fluid dynamics in plaque-free subsegments of interest at baseline (week 23). The messenger RNA and protein expression and the elastolytic activity of selected matrix-degrading proteases were assessed in these subsegments at follow-up (week 30), demonstrating that (1) subsegments with low preceding endothelial shear stress at week 23 had reduced endothelial cell coverage and enhanced lipid accumulation and inflammation at week 30; (2) these subsegments showed increased expression of messenger RNAs encoding matrix metalloproteinase-2, -9, and -12 and cathepsins K and S relative to their endogenous inhibitors and increased elastolytic activity; and (3) expression of these enzymes correlated positively with the severity of internal elastic lamina fragmentation. We further showed that thin-capped atheroma developed in regions with lower preceding endothelial shear stress and had reduced endothelial coverage, intense lipid and inflammatory cell accumulation, enhanced messenger RNA expression of matrix metalloproteinases and cathepsins, heightened elastolytic activity, and severe internal elastic lamina fragmentation. Our results provide new insight into the hemodynamic and molecular mechanisms of regional formation of plaques with thin fibrous cap and indicate that the in vivo understanding of local endothelial shear stress may allow identification of a high-risk plaque in its early stages of development. Early identification of a high-risk plaque may provide a rationale for selective local coronary interventions, supplemented by an intensive systemic pharmacological approach, to avert future acute coronary events.

Conclusions: Low endothelial shear stress induces endothelial discontinuity and accumulation of activated inflammatory cells, thereby augmenting the expression and activity of elastases in the intima and shifting the balance with their inhibitors toward matrix breakdown. Our results provide new insight into the mechanisms of regional formation of plaques with thin fibrous caps.39

Chronic Kidney Disease and the Risk of Heart Failure in Men

Summary: Individuals with chronic kidney disease (CKD) have higher prevalence of left ventricular hypertrophy and cardiovascular disease; however, it remains unclear if development of CKD is associated with higher incidence of heart failure, independent from diabetes and hypertension. We analyzed the relations of CKD to incident heart failure and to cardiovascular disease (CVD) death or heart failure (combined end point) in 10 181 Physicians’ Health Study male participants (mean age, 67 years). Kidney function was assessed by estimating the glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation in clinically relevant categories of <60 and ≥60 mL · min⁻¹ · 1.73 m⁻² (referred) and <<45, 45 to 60, 60 to 90, and ≥90 mL · min⁻¹ · 1.73 m⁻² (referred). During follow-up, heart failure developed in 439 participants and 832 had a combined end point of CVD death or heart failure. In multivariable models, men with eGFR 45 to 60 and <45 mL · min⁻¹ · 1.73 m⁻² had nearly 2 to 2.5-fold higher risk for heart failure compared with the referent category. Further, these relations remained robust in the analyses restricted to a subgroup of nondiabetic individuals and normotensive individuals at baseline (n = 7545). In addition, men with eGFR 45 to 60 and <45 mL · min⁻¹ · 1.73 m⁻² had 2 to 2.5-fold risk of CVD death or heart failure compared with referent category. In summary, our results show that moderate level of CKD, even in the absence of diabetes and hypertension, is associated with a higher risk of development of heart failure and CVD death/heart failure in men.

Conclusions: Moderate level of CKD, even in absence of diabetes and hypertension at baseline, is associated with a higher risk of development of heart failure and CVD death/heart failure in men.40

Reversal of Hyperlipidemia With a Genetic Switch Favorably Affects the Content and Inflammatory State of Macrophages in Atherosclerotic Plaques

Summary: The ultimate cure for atherosclerosis would be the regression of arterial plaques. Discovery research toward this goal has been hampered by limited and sometimes cumbersome animal models. The Reversa mouse combines a standard model of human atherosclerosis, the hyperlipidemic low-density lipoprotein receptor-deficient mouse, with a genetic switch that electively shuts off low-density lipoprotein production. In the present study, arterial plaques were allowed to develop in Reversa mice to a stage mimicking advanced human coronary artery disease, and then the elevated low-density lipoprotein level was severely reduced, thereby simulating aggressive lipid management. The major findings after such lipid reduction were decreases in the content and inflammatory state of the central cell of plaques, macrophages, with the change in total plaque size more modest because of compensatory increases in collagen content. The improvement in macrophage inflammatory status was augmented by treatment with pioglitazone, consistent with the effects of peroxisome proliferator-activated receptor-γ agonists on macrophages in vitro. The results may explain why plaque volume decreases have been modest in recent statin trials despite significant reduction in events and may provide one basis for the
cardioprotective effects of pioglitazone in clinical studies. Continued study of this convenient model should lead to an improved understanding of plaque regression at the molecular level.

**Conclusion:** The Reversa mouse is a new model of atherosclerosis regression. After lipid lowering, favorable changes in plaque composition were independent of changes in size. In addition, plaque CD68⁺ cells became less inflammatory, an effect enhanced by treatment with pioglitazone.41

**S100A9 Differentially Modifies Phenotypic States of Neutrophils, Macrophages, and Dendritic Cells: Implications for Atherosclerosis and Adipose Tissue Inflammation**

**Summary:** It has previously been demonstrated that elevated plasma levels of S100A9 (also known as myeloid related protein-14) in complex with its binding partner S100A8 (myeloid related protein-8) predict increased risk of future cardiovascular events in healthy postmenopausal women and recurrent events in patients with acute coronary syndromes. Furthermore, apolipoprotein E–deficient mice that are also deficient in S100A9 exhibit reduced atherosclerosis. These important findings suggest that S100A9 is both a biomarker and a mediator of atherosclerosis and cardiovascular events. Most of the constitutively secreted S100A9 is believed to be derived from myeloid cells. We demonstrate that low-density lipoprotein receptor–deficient mice that lack S100A9 in bone marrow–derived cells, including myeloid cells, are not protected against diet-induced atherosclerosis or insulin resistance. Furthermore, S100A9 deficiency differentially modifies phenotypic states of myeloid cell populations. S100A9-deficient neutrophils exhibit a reduced secretion of cytokines, whereas S100A9-deficient dendritic cells show an exacerbated release of cytokines. The effect of S100A9 deficiency on atherosclerosis and other inflammatory diseases is therefore predicted to depend on the relative contribution of these cell types at different stages of disease progression. Furthermore, S100A9 expression in nonmyeloid cells is likely to contribute to atherosclerosis. Further study is needed to fully understand the functions of S100A8A9 in specific cell populations and disease states before S100A8 and S100A9 are considered therapeutic targets.

**Conclusions:** S100A9 differentially modifies phenotypic states of neutrophils, macrophages, and dendritic cells. The effect of S100A9 deficiency on atherosclerosis and other inflammatory diseases is therefore predicted to depend on the relative contribution of these cell types at different stages of disease progression. Furthermore, S100A9 expression in nonmyeloid cells is likely to contribute to atherosclerosis.42

**Association of DASH Diet With Cardiovascular Risk Factors in Youth With Diabetes Mellitus: The SEARCH for Diabetes in Youth Study**

**Summary:** Since the publication of the landmark findings of the Dietary Approaches to Stop Hypertension (DASH) trial, the DASH diet has become well known as an effective whole-diet approach to hypertension prevention and blood pressure reduction. However, little is known about its impact on other cardiovascular disease risk factors, especially in youth with type 1 and type 2 diabetes mellitus. In this cross-sectional study, we explored the association of DASH diet with blood lipid levels, lipoproteins, adipocytokines, and measures of adiposity and glycemic control in 2130 youth aged 10 to 22 years with physician-diagnosed diabetes mellitus. Dietary intake was assessed by food frequency questionnaire, categorized into the DASH food groups, and assigned an adherence score. In both type 1 and type 2 diabetes mellitus youth, the average DASH diet scores were low, suggesting very poor dietary intake quality in this population. Of the various cardiovascular disease risk factors evaluated, we found that among youth with type 1 diabetes mellitus, higher adherence to the DASH diet was significantly associated with lower levels of low-density lipoprotein/high-density lipoprotein ratio and A1c. In youth with type 2 diabetes mellitus, higher adherence to the DASH diet was significantly associated with higher low-density lipoprotein particle density and lower body mass index Z score. In conclusion, the DASH dietary pattern may prove beneficial in the prevention and management of cardiovascular disease risk in this vulnerable population of youth with diabetes mellitus, among whom there is clearly much room for improvement in the quality of dietary intake.

**Conclusions:** The DASH dietary pattern may be beneficial in the prevention and management of cardiovascular disease risk in youth with diabetes mellitus.43

**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.44


**Summary:** Aspirin use reduces first heart attack and ischemic stroke by about 18% and 14%, respectively, but it also increases rates of intracerebral hemorrhage and gastrointestinal bleeding. Only ~28% of American adults are in the high cardiovascular risk group for whom aspirin for primary prevention is likely to be highly beneficial. For most adult Americans, the potential benefit of aspirin is small, and treatment decisions should depend almost completely on personal preferences. However, most official guidelines do not identify these individuals as candidates for aspirin therapy. Few adults would increase their net risk substantially by using aspirin.

**Conclusions:** The benefits of aspirin therapy depend substantially on an individual’s risk of cardiovascular disease and adverse treatment
Noninvasive Assessment of Atherosclerotic Plaque Progression in ApoE−/− Mice Using Susceptibility Gradient Mapping

Summary: Coronary artery disease remains the leading cause of death in the Western world. The majority of complications result from plaque rupture and subsequent thrombosis. X-ray angiography allows the assessment of the extent of luminal narrowing but provides little information on plaque composition and biology, resulting in the inability to distinguish between stable and unstable lesions. Inflammation is a recognized contributor to atherosclerotic plaque development and complication. Macrophages are thought to play a central role in these processes. Therefore, a noninvasive imaging technique that is able to detect and quantify intraplaque macrophages could be of great clinical value. Using “standard” T2- or T2*-weighted sequences, iron oxide detection can be ambiguous because signal loss can be mimicked by artifacts resulting from cardiac motion, interfaces between tissues, local hemorrhage, or calcification. Susceptibility gradient mapping allows positive contrast visualization of iron oxide on MR gradient echo data sets. Susceptibility gradient mapping utilizes the local shift in k-space caused by local field distortions (susceptibility gradients), resulting from the presence of iron oxide particles and allows deriving information about the local concentration of iron oxide particles. Susceptibility gradient mapping–MRI could be useful for the in vivo detection and quantification of iron oxide uptake into macrophage-rich plaques and to monitor response to treatment in patients with atherosclerotic vessel wall disease.

Conclusions: This study shows an increase in iron oxide uptake (measured by in vivo susceptibility gradient mapping–MRI, histology, and mass spectroscopy) with the progression of plaque development in an apoE−/− mouse model of accelerated atherosclerosis. Positive contrast provided by susceptibility gradient mapping–MRI allowed for a clear visualization of intraplaque iron oxide deposits, and magnitudes (mT/m) of contrast enhancement in susceptibility gradient parameter maps allowed for the quantification of intraplaque iron oxide particles.

Validity of Estimated Glomerular Filtration Rates for Assessment of Baseline and Serial Renal Function in Patients With Atherosclerotic Renal Artery Stenosis: Implications for Clinical Trials of Renal Revascularization

Summary: In clinical practice, renal function is commonly assessed using glomerular filtration rate (GFR) estimates based on serum creatinine. Whereas several observational studies report improvement in GFR estimates in patients with renal artery stenosis after revascularization, randomized clinical trials comparing medical therapy and renal stenting have failed to demonstrate any renal benefit of revascularization. Importantly, GFR estimates have not been validated for evaluating serial changes in renal function after revascularization. Using directly measured GFR as the reference standard, this study evaluated the validity of GFR estimates for assessing serial changes in renal function in patients with renal artery stenosis and demonstrates that GFR estimates are unreliable for detecting a 20% change in measured GFR. Furthermore, correlations between percent changes in measured GFR and GFR estimates as well as the degree of agreement between serial changes in measured GFR and GFR estimates are poor. These observations suggest that conclusions of published randomized trials may be misleading and that GFR estimates should not be used as major end points in clinical trials evaluating the impact of revascularization on renal function in patients with renal artery stenosis.

Conclusions: In patients with renal artery stenosis, GFR estimates demonstrate good sensitivity and modest specificity for identifying (125)I-iothalamate GFR <60 mL/min per 1.73 m² but poor sensitivity and reliability for detecting 20% changes in (125)I-iothalamate GFR. GFR estimates should not be used in clinical trials as major end points to assess serial GFR after renal revascularization.

High-Resolution Identity by Descent Mapping Uncovers the Genetic Basis for Blood Pressure Differences Between Spontaneously Hypertensive Rat Lines

Summary: Blood pressure and essential hypertension are influenced by genetic factors. Identification of the genetic factors influencing blood pressure and hypertension in human populations has had only limited success. This undoubtedly arises from genetic complexity such as interaction between genetic variants to cause changes in blood pressure, the relatively small effects of each genetic factor alone, the possibly large number of genetic factors dispersed in the population, and the effect of environmental variation to obscure underlying genetic effects. For this reason, animal models of hypertension may be useful because environmental variables can be controlled, genetic complexity can be reduced (using inbred strains), and selective breeding can be performed to map genes. In the present study, we examined 2 closely related spontaneously hypertensive rat lines to determine whether the genetic basis for their hypertension was identical. We concluded that it was not. Next, we used single nucleotide polymorphism markers to ask how related are these lines. The 2 lines had inherited ≈87% of their genome from the same ancestors. Genetic difference in blood pressure must be limited to the 13% of the genome that came from different ancestors, further reducing genetic complexity. Our mapping experiments found a single locus containing genetic variation affecting blood pressure. We used gene expression data to identify <10 genes in this region that were expressed at different levels in the kidneys of the 2 spontaneously hypertensive rat lines. Among these genes may be those that are able to influence blood pressure. Sequence analysis of these genes has begun to identify possible genetic variation that may contribute to elevated blood pressure.

Conclusions: Thus hypertension in spontaneously hypertensive rat (SHR)-A3 and -B2 appears to arise from an overlapping set of susceptibility alleles, with SHR-A3 possessing an additional hypertension locus that contributes to further increase blood pressure.

Fish Intake and the Risk of Incident Heart Failure: The Women’s Health Initiative

Summary: The association between fish or the fatty acids they contain and risk for incident heart failure (HF) among postmenopausal women is unclear. Using the Women’s Health Initiative Observation Cohort (93 676 women ages 50–79 years at baseline), we examined the independent association between intakes of baked/broiled fish (total), baked/broiled fish subtypes (white fish: cod, snapper) versus dark fish (salmon, mackerel) versus tuna fish), fried fish, marine omega-3 fatty acids (eicosapentaenoic acid+docosahexaenoic acid), plant-derived fatty acids (ω-linolenic acids), and transfatty acids and risk for incident HF. Consumption of ≥5 servings/wk of baked/broiled fish was associated with a 30% lower risk for incident HF, whereas consumption of ≥1 serving/wk of fried fish was associated with a 48% higher risk for incident HF. Notably, consumption of higher levels of baked/broiled dark fish (salmon, mackerel, bluefish) was associated with a 22% lower risk for incident HF (P-trend across tertiles =0.012), whereas baked/broiled white fish or tuna fish were not significantly associated with HF risk. No significant associations were found between eicosapentaenoic acid+docosahexaenoic acid, ω-linolenic acid, or transfatty acid intake and incident HF. These data suggest that higher baked/broiled fish intake, specifically dark fish such as salmon and mackerel, can lower risk for incident HF, whereas higher fried fish...
intake raises HF risk in postmenopausal women. Future clinical trials examining the impact of these dietary factors on HF risk are paramount to confirm and extend these observations.

**Conclusions:** Increased baked/broiled fish intake may lower HF risk, whereas increased fried fish intake may increase HF risk in postmenopausal women.⁴⁹

**Coffee Consumption and Incidence of Heart Failure in Women**

**Summary:** A previous study raised the concern that heavy coffee consumption (>5 cups per day) may increase risk of heart failure. Subsequent investigations have not replicated the results. This study reports on the relationship between coffee consumption and incidence of heart failure hospitalization or mortality among more than 34,000 women ages 48 to 83 years, living in central Sweden. Coffee consumption was high; 6000 of the women consumed ≥5 cups of coffee per day. The women were followed through administrative records. Over 9 years of follow-up, 602 of the women were hospitalized for or died of heart failure. There was no evidence that coffee consumption was associated with heart failure in this population. Taken together, the studies suggest that intake of coffee is not an important risk factor for development of heart failure.

**Conclusions:** In this population of middle-aged and older women, we did not find an association between coffee consumption and incidence of heart failure events.⁵⁰

**Application of an Exercise Intervention on the Evolution of Diastolic Dysfunction in Patients With Diabetes Mellitus: Efficacy and Effectiveness**

**Summary:** Diastolic dysfunction (DD) is associated with adverse cardiovascular outcomes and is a common finding in patients with type 2 diabetes mellitus (T2DM). However, the evolution and potential therapies for DD are poorly understood, and pharmacological studies have been largely disappointing. Exercise has beneficial effects on glycemic control, lipid levels, weight loss, blood pressure, and other vascular parameters in T2DM. This prospective, randomized study describes the impact of an exercise and lifestyle intervention on DD at 3 years in a group of patients with T2DM. Although confirming that DD is common in patients with T2DM, the intervention program on an intention-to-treat basis did not significantly reduce the progression of subclinical DD. This finding may reflect the recognized difficulty of adherence to prolonged exercise intervention, which also was seen in this trial. These findings reinforce the importance of further investigations to identify potential treatment options for patients with T2DM who have evidence of myocardial dysfunction.

**Conclusions:** Despite being efficacious in the subgroup who completed 3 years of exercise-based lifestyle intervention, randomization to this program was not effective in reducing progression of subclinical DD in patients with T2DM, which may reflect the recognized difficulty of adherence to prolonged exercise intervention.⁵¹

**Secondary Prevention and Mortality in Peripheral Artery Disease: National Health and Nutrition Examination Study, 1999 to 2004**

**Summary:** Cardiovascular disease remains a major cause of morbidity and mortality in the United States. Peripheral artery disease (PAD) is a manifestation of systemic atherosclerosis that confers a significantly increased risk of myocardial infarction, stroke, and death. Whether cardiovascular risk can be reduced by implementation of secondary prevention therapies (such as antiplatelet therapy, statins, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) in individuals with PAD identified by a screening ankle-brachial index measurement is unknown. Using data from the National Health and Nutrition Examination Survey (NHANES), we demonstrate that millions of high-risk US adults with PAD (ankle-brachial index ≤0.90) were not receiving guideline-recommended secondary prevention therapies. All-cause mortality was significantly higher in individuals with PAD, including those without previously recognized cardiovascular disease. Furthermore, treatment with multiple secondary prevention therapies was associated with significantly reduced risk of all-cause mortality in this population. Given the conflicting literature about the use of secondary prevention therapies, aspirin in particular, in patients with PAD, these observational findings underscore the importance of a large-scale clinical trial to determine whether implementation of multiple secondary prevention therapies specifically in high-risk individuals identified by ankle-brachial index screening as having PAD can indeed reduce cardiovascular morbidity and mortality.

**Conclusions:** Millions of US adults with PAD are not receiving secondary prevention therapies. Treatment with multiple therapies is associated with reduced all-cause mortality.⁵²

**Nonmuscle Myosin Light-Chain Kinase Deficiency Attenuates Atherosclerosis in Apolipoprotein E–Deficient Mice via Reduced Endothelial Barrier Dysfunction and Monocyte Migration**

**Summary:** Endothelial dysfunction and monocyte migration have been implicated in the pathogenesis of atherosclerosis. Nonmuscle myosin light chain kinase (nmMLCK) is known to contribute to inflammation-associated endothelial barrier dysfunction by activating the cytoskeletal contractile response via its kinase activity on myosin light chain phosphorylation. The specific contribution of nmMLCK to atherosclerotic injury and its mechanism of action have not been evaluated. In this study, we tested the hypothesis that nmMLCK promoted atherosclerotic lesion development by altering endothelial barrier properties. In the aorta of apolipoprotein E–deficient mice fed an atherogenic diet, nmMLCK deficiency significantly reduced lesion size, intimal hyperplasia, and macrophage deposition in the vascular wall, indicating a pathogenic role of nmMLCK in atherosclerosis. Consistent with the in vivo observations, nmMLCK expression was detected in both AECs and perihedral monocytes, and nmMLCK deficiency attenuated endothelial hyperpermeability and monocyte transendothelial migration caused by atherosclerosis-relevant inflammatory stimuli, including thrombin, oxidized low-density lipoprotein, tumor necrosis factor α, and monocyte chemotactic protein-1. Further mechanistic studies demonstrated that, in addition to myosin light chain phosphorylation, Src signaling contributed to nmMLCK-induced cellular responses. Pharmacological blockade or genetic manipulation of Src inhibited nmMLCK-mediated hyperpermeability and monocyte transmigration. Taken together, the data suggest a novel function of nmMLCK in atherosclerosis that involves a nonconventional signaling pathway independent of myosin light chain phosphorylation. Further characterization of specific cellular responses to isofrom-specific MLCK kinase activity and kinase-independent mechanisms would contribute to the development of new therapeutic targets for treating atherosclerosis.

**Conclusions:** Nonmuscle myosin light-chain kinase contributes to atherosclerosis by regulating endothelial barrier function and monocyte migration via mechanisms involving not only kinase-mediated MLC phosphorylation but also Src activation.⁵³

**Dynamic Changes in Regulatory T Cells Are Linked to Levels of Diet-Induced Hypercholesterolemia**

**Summary:** CD4⁺ effector T cells have multiple proinflammatory properties that contribute to the chronic inflammatory phenotype of
evolving atherosclerotic lesions, as well as to the destabilization of plaques associated with acute coronary events. Regulatory T cells (Treg) actively suppress T cell–mediated immune responses, and reduced Treg function or numbers are associated with immune-mediated inflammatory disease. The influence of Treg in atherosclerosis has become a central area of interest because of potential therapeutic implications. This study demonstrates that in a mouse model of atherosclerosis, a Treg response is induced by hypercholesterolemia, but the response declines while the effector T cell response is maintained when hypercholesterolemia is prolonged. The decline in the Treg response is associated with selective decrease in homing properties and increased apoptosis of Treg but not Teff during prolonged hypercholesterolemia. The Treg response is sustained by dietary reversal of hypercholesterolemia early after the initial response is induced. Our data suggest that an important therapeutic goal in atherosclerotic patients is to reestablish favorable lesional Treg:Teff ratios, and this may be one of the mechanisms of benefit of profound cholesterol lowering.

Conclusions: Prolonged hypercholesterolemia impairs Treg but not effector T cell accumulation in lesions, but reversal of hypercholesterolemia can prevent loss of lesional Treg. Therefore, cholesterol-lowering therapies may induce dynamic and beneficial changes in Treg:effector T cell ratios in atherosclerotic lesions.54

Exploring Determinants of Secular Decreases in Childhood Blood Pressure and Hypertension

Summary: The dramatic reduction in mortality from stroke and coronary heart disease observed over several decades in many countries is due partly to declines in blood pressure (BP) and hypertension. Medical treatment and behavioral changes have contributed to the declines. However, there may be important childhood determinants of the reduction in BP and hypertension, considering reports showing that BP tracks from childhood to later life and high adolescent BP are important risk factors for adulthood cardiovascular diseases. One way to unravel childhood determinants of BP and hypertension is to track secular trends in childhood BP because childhood BP is largely uninfluenced by medical treatment and behavioral changes associated with hypertension diagnosis. In the present analyses, on the basis of 4 waves of the Korean National Health and Nutrition Examination Survey between 1998 and 2008, age- and height-adjusted mean systolic BP decreased by 8.7 to 10.0 mm Hg among boys and girls. Childhood hypertension and prehypertension/hypertension prevalences decreased by 52% to 86%. These remarkable decreases were found among all age and socioeconomic groups and were not explained by concomitant secular changes in childhood obesity, health behaviors, nutritional factors, psychological factors, and sociodemographic factors. These results have public health significance because they suggest that important population determinants of secular declines in BP and associated diseases may lie in early life before 10 years of age. Healthcare providers need to keep in mind that, although medical treatment and behavioral changes among adults are important to reduce the disease burden of elevated BP, prevention of BP-related diseases may begin earlier in childhood.

Conclusions: We observed important population declines in blood pressure in Korea over a 10-year period in children 10 to 19 years of age, but the likely causes for these secular trends remain to be determined.55

Insulin Receptor Substrate 1 Gene Variation Modifies Insulin Resistance Response to Weight-Loss Diets in a 2-Year Randomized Trial: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial

Summary: Although recent data from gene–environment interaction analyses provide support for the notion of a personalized nutrition approach, evidence from clinical trials is scarce. Genome-wide association studies have identified common genetic variants in the IRS1 locus associated with insulin resistance and hyperinsulinemia, as well as type 2 diabetes mellitus and coronary heart disease. In a 2-year randomized weight-loss trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, we genotyped the best associated variant (single nucleotide polymorphism rs2943641) in 738 overweight adults, to examine the modifications of the IRS1 gene variation on the long-term changes in body weight, fasting insulin, and insulin resistance in response to weight-loss diets with different compositions of macronutrients. Our results indicated that participants with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype in response to a high-carbohydrate/low-fat diet. Our data may provide novel information for the development of effective dietary intervention strategies based on genetic background in preventing diseases related to obesity and insulin resistance, such as type 2 diabetes mellitus and cardiovascular disease.

Conclusions: Individuals with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype by choosing a high-carbohydrate and low-fat diet.56

Effect of Dietary Protein Supplementation on Blood Pressure: A Randomized, Controlled Trial

Summary: Observational epidemiological studies have reported an inverse association between dietary protein intake and blood pressure. We compared the effect of soy protein, milk protein, and complex carbohydrate supplementation on blood pressure in a randomized, double-blind crossover trial among 352 adults with prehypertension or stage 1 hypertension. The trial participants were assigned to take 40 g/d of soy protein, milk protein, or complex carbohydrate supplementation each for 8 weeks in a random order. A 3-week washout period was implemented between the interventions. Three blood pressure measurements were obtained at 2 baseline and 2 termination visits during each of the 3 intervention phases by use of a random-zero sphygmomanometer. Compared with carbohydrate controls, soy protein and milk protein supplementations were significantly associated with a $-2.0$ mm Hg (95% confidence interval $-3.2$ to $-0.7$ mm Hg, $P=0.002$) and $-2.3$ mm Hg ($-3.7$ to $-1.0$ mm Hg, $P=0.0007$) net change in systolic blood pressure, respectively. The results from this randomized, controlled trial indicate that both soy and milk protein intake reduce systolic blood pressure compared with carbohydrate intake among patients with prehypertension and stage 1 hypertension. Furthermore, these findings suggest that partially replacing carbohydrate with soy or milk protein might be an important component of nutrition intervention strategies for the prevention and treatment of hypertension.

Conclusions: The results from this randomized, controlled trial indicate that both soy and milk protein intake reduce systolic blood pressure compared with a high-glycemic-index refined carbohydrate among patients with prehypertension and stage 1 hypertension. Furthermore, these findings suggest that partially replacing carbohydrate with soy or milk protein might be an important component of nutrition intervention strategies for the prevention and treatment of hypertension.57

Combined Effects of Ezetimibe and Phytosterols on Cholesterol Metabolism: A Randomized, Controlled Feeding Study in Humans

Summary: The US National Cholesterol Education Program recommends both supplemental phytosterols, categorized as a therapeutic lifestyle change, and drugs, including ezetimibe, for low-density lipoprotein cholesterol reduction. However, relatively little is known
about cotreatment with phytosterols and ezetimibe. Is such a combination helpful because both reduce cholesterol absorption, or could differing mechanisms of action vitiate the effectiveness of each? Answering this question is not straightforward because it requires careful control of dietary phytosterols and concomitant measurement of cholesterol absorption and excretion, as well as low-density lipoprotein cholesterol. In this article, we have used a controlled feeding trial incorporating a baseline diet containing phytosterols in the lower range of current consumption and adding ezetimibe and phytosterols to it. The results show that phytosterols given with ezetimibe further reduce low-density lipoprotein cholesterol and result in a substantial increase in fecal cholesterol excretion and reduction in cholesterol absorption efficiency. The expected rise in plasma phytosterols is blunted by ezetimibe. These results show that phytosterols and ezetimibe can be used together without adverse interaction and that their fundamental effects on whole-body cholesterol metabolism complement one another.

**Conclusion:** The addition of phytosterols to ezetimibe significantly enhanced the effects of ezetimibe on whole-body cholesterol metabolism and plasma low-density lipoprotein cholesterol. The large cumulative action of combined dietary and pharmacological treatment on cholesterol metabolism emphasizes the potential importance of dietary phytosterols as adjunctive therapy for the treatment of hypercholesterolemia.

**Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008**

**Summary:** Defining the characteristics of uncontrolled hypertensive patients may facilitate efforts to improve blood pressure control. Data were analyzed for 13,375 hypertensive adults from the National Health and Nutrition Examination Surveys for 1988 to 1994, 1999 to 2004, and 2005 to 2008. Multivariable logistic regression was used to identify clinical characteristics associated with untreated hypertension, hypertension uncontrolled on 1 to 2 blood pressure medications, and apparent treatment-resistant hypertension on ≥3 blood pressure medications. More than half of uncontrolled hypertensives were untreated, including 52.5% in 2005 to 2008, with about two thirds of them unaware of their hypertension. Untreated hypertensive patients were more often men, infrequent users of primary health care, lean, and without clinical cardiovascular or renal disease. Most treated uncontrolled patients reported taking 1 to 2 blood pressure medications, a proxy for therapeutic inertia. This group, which was older and had higher 10-year coronary heart disease risk than patients controlled on 1 to 2 medications, comprised 34.4% of all uncontrolled and 72.0% of treated uncontrolled patients in 2005 to 2008. Apparent treatment-resistant hypertension increased from 15.9% (1998–2004) to 28.0% (2005–2008) of treated patients (P < 0.001). Clinical characteristics associated with apparent treatment-resistant hypertension included ≥4 visits a year, obesity, chronic kidney disease, and 10-year coronary heart disease risk >20%. Adherence to health lifestyles and medications is important for all patients. Raising hypertension awareness among infrequent users of primary health care and linking them to a medical home could reduce untreated hypertension. Uncontrolled patients on 1 to 2 blood pressure medications could benefit from an additional antihypertensive medication. More effective selection of antihypertensive combination therapy is important for the growing proportion of patients with apparent treatment-resistant hypertension.

**Conclusion:** Untreated, undertreated, and apparent treatment resistant hypertension (aTRH) patients have consistent characteristics that could inform strategies to improve blood pressure control by decreasing untreated hypertension, reducing therapeutic inertia in undertreated patients, and enhancing therapeutic efficiency in aTRH.

**Iron Deficiency in Community-Dwelling US Adults With Self-Reported Heart Failure in the National Health and Nutrition Examination Survey III: Prevalence and Associations With Anemia and Inflammation**

**Summary:** Iron deficiency has been proposed as a potential therapeutic target in heart failure. Recent research has characterized the prevalence of iron deficiency in symptomatic heart failure patients referred to tertiary care centers, but the prevalence in the community-dwelling population of US adults with heart failure remains unclear. Recent research has also demonstrated that iron deficiency may be associated with mortality in symptomatic heart failure patients referred to tertiary care centers; iron supplementation in these patients may be associated with improved exercise tolerance and quality of life. Our study characterizes the prevalence of iron deficiency in ambulatory, community-dwelling US adults with self-reported heart failure and demonstrates cross-sectional associations with both anemia and inflammation. Our study also suggests that iron deficiency is not associated with mortality in this population. Our results suggest that though iron repletion may be a useful strategy in symptomatic patients with advanced heart failure to improve symptoms and quality of life, iron repletion appears less important in patients with less advanced heart failure and milder symptoms. Our study thus adds to the emerging body of literature regarding the management of iron deficiency in heart failure patients, and provides useful data for clinicians caring for ambulatory, community-dwelling patients with heart failure.

**Conclusions:** Iron deficiency is common in heart failure and is associated with decreased hemoglobin and increased C-reactive protein. In multivariate analysis, hemoglobin was associated with cardiovascular mortality while C-reactive protein was associated with both all-cause and cardiovascular mortality. Iron deficiency was not associated with all-cause or cardiovascular mortality in this cohort.

**Marine n-3 Polyunsaturated Fatty Acids in Adipose Tissue and the Risk of Acute Coronary Syndrome**

**Summary:** Previous studies have shown that intake of marine n-3 polyunsaturated fatty acids (PUFAs) has a beneficial effect on coronary mortality, especially among patients already diagnosed with coronary disease. The effects of marine n-3 PUFAs on nonfatal coronary disease and in healthy subjects have, however, been inconsistent. This may be explained by the use of heterogeneous methods to assess the intake of marine n-3 PUFAs. The content of marine n-3 PUFAs in adipose tissue has been reported to be a good and objective marker for long-term dietary intake of n-3 PUFAs. In a cohort study including 57,053 healthy subjects, we investigated the content of n-3 PUFAs in adipose tissue among 1012 cases with incident acute coronary syndrome during the study period of 7.6 years and in a random sample of the cohort (n = 1630). We found negative dose-response associations between the content of marine n-3 PUFAs and the risk of acute coronary syndrome among men, whereas no consistent associations were found among women. These results support the hypothesis that dietary intake of marine n-3 PUFAs may protect against acute coronary syndrome in healthy men and therefore support the recommendation by the American Heart Association and the European Society of Cardiology to eat fish, especially oily fish (the primary source of dietary n-3 PUFAs), at least twice a week.

**Conclusion:** Intake of marine n-3 polyunsaturated fatty acids may protect against acute coronary syndrome in men.
Pharmacological Suppression of Hepatic ATP-Binding Cassette Transporter 1 Activity in Mice Reduces High-Density Lipoprotein Cholesterol Levels but Promotes Reverse Cholesterol Transport

Summary: Plasma levels of high-density lipoprotein cholesterol (HDL-C) do not always reflect the dynamic process of reverse cholesterol transport (RCT) from macrophage to bile and feces and the risk of atherosclerosis. For example, mice lacking the hepatic HDL receptor scavenger receptor class B type I have markedly elevated HDL-C levels but impaired RCT and increased atherosclerosis. The ATP-binding cassette transporter 1 (ABCA1) is expressed in the liver, and by exporting cholesterol out of the liver to the HDL protein, apolipoprotein A-I plays a critical role in maintaining plasma HDL-C levels. However, the relationship of hepatic ABCA1 to RCT and atherosclerosis remains poorly understood. Because hepatic ABCA1 pumps cholesterol from the liver into the blood instead of the bile, it might reduce the rate at which the liver excretes HDL-derived cholesterol. Probucol is a drug that reduces HDL-C levels but also, paradoxically, reduces atherosclerosis and xanthomas. We tested the hypothesis that probucol inhibits hepatic ABCA1 activity, thereby reducing HDL-C levels but promoting RCT from macrophages. In studies in mice lacking the hepatic HDL receptor scavenger receptor class B type I, probucol substantially reduced HDL-C but significantly increased macrophage RCT. Furthermore, probucol significantly enhanced the excretion of HDL-derived cholesterol into the feces. Probucol markedly inhibited ABCA1-dependent cholesterol efflux from mouse primary hepatocytes, and this effect was shown to be responsible for the effect of probucol on increasing the fecal excretion of HDL-derived cholesterol in vivo. These results provide an explanation for the beneficial effects of probucol on atherosclerosis despite its HDL-lowering effects and suggest that inactivation of hepatic ABCA1 leads to increased RCT despite reducing plasma HDL-C levels.

Conclusions: We demonstrate that pharmacological inhibition of hepatic ABCA1 activity with probucol reduced HDL-C levels but promoted RCT through diversion of HDL-derived cholesterol from efflux back into plasma instead of excretion in the bile. These results explain the beneficial effects of probucol on atherosclerosis and xanthomas despite its HDL-lowering effects and suggest that inactivation of hepatic ABCA1 leads to increased RCT despite reducing plasma HDL-C levels.

Racial/Ethnic Variation in the Association of Lipid-Related Genetic Variants With Blood Lipids in the US Adult Population

Summary: The present study describes the independent and combined effects of 57 genetic variants associated with lipid levels among adults of European and non-European ancestry in a unique nationally representative survey of the United States. There is good evidence that some of these loci, which were all identified through genome-wide association studies, may directly contribute to variation in clinical phenotypes, although the clinical and public health implications of many of these variants remain unclear. We report that although allele frequencies varied significantly by race/ethnicity, the patterns of genetic association with lipid levels were generally consistent across racial/ethnic groups, indicating that these common polymorphisms may reflect a shared biological influence on lipid levels. The data also show that the included single-nucleotide polymorphisms account for only a small fraction of the interindividual variability in blood lipid levels, suggesting that a considerable number of additional common variants (probably with modest effects) and rare alleles (probably with large effects) remain to be identified. Nevertheless, we observed that the genetic risk score, which assessed the combined effect of multiple single-nucleotide polymorphisms, was significantly associated with increased lipid measures in all racial/ethnic groups.

Conclusions: Our findings show that the combined association of single-nucleotide polymorphisms, based on a genetic risk score, was strongly associated with increased blood lipid measures in all major race/ethnic groups in the United States, which may help in identifying subgroups with a high risk for an unfavorable lipid profile.

Long-Term Dipeptidyl-Peptidase 4 Inhibition Reduces Atherosclerosis and Inflammation via Effects on Monocyte Recruitment and Chemotaxis

Summary: The incretin hormones glucagon-like peptide and glucose-dependent insulotropic polypeptide play a key role in the regulation of postprandial glycemia and satiety. Incretin hormones are inactivated by the exopeptidase dipeptidyl-peptidase 4 (DPP-4). Both small-molecule inhibitors of DPP-4 and DPP-4-resistant incretin analogs are increasingly common treatments for type II diabetes mellitus, although their effects in reducing long-term cardiovascular complications remain to be established. An expanding list of potential beneficial effects of DPP-4 inhibition on the cardiovascular system includes glucagon-like peptide–mediated effects on cardioprotective pathways, nitric oxide–dependent vasodilation, and non–glucagon-like peptide effects that relate to a pathophysiological role for DPP-4 in regulating inflammation. In this study, we investigated the net effects of long-term DPP-4 inhibition with alogliptin in a model of atherosclerosis and insulin resistance. DPP-4 activity was increased in atherosclerosis with a reduction in response to treatment. DPP-4 inhibition improved insulin resistance, blood pressure, and visceral adiposity with reductions in atherosclerosis and inflammation (evidenced by a reduction in plaque and adipose inflammatory macrophage content) and a shift to an alternately activated macrophage phenotype. DPP-4 inhibition prevented monocyte migration and actin polymerization in vitro via Rac-dependent mechanisms and prevented in vivo migration of labeled monocytes to the aorta in response to exogenously administered tumor necrosis factor–α and DPP-4. These data support a net effect of DPP-4 inhibition in reducing adipose and vascular inflammation with a concomitant reduction in atherosclerosis and support a therapeutic role for these agents in preventing cardiovascular complications in type II diabetes mellitus.

Conclusion: DPP-4i exerts antiatherosclerotic effects and reduces inflammation via inhibition of monocyte activation/chemotaxis. These findings have important implications for the use of this class of drugs in atherosclerosis.

Effects of Weight Loss and Long-Term Weight Maintenance With Diets Varying in Protein and Glycemic Index on Cardiovascular Risk Factors: The Diet, Obesity, and Genes (DiOGenes) Study: A Randomized, Controlled Trial

Summary: Food components are well known to affect cardiovascular risk, for which blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and the inflammatory marker C-reactive protein (CRP) are established biomarkers. In the present randomized, multicenter study, the separate effects of 11 kg weight loss achieved during an 8-week low-calorie diet as well as a subsequent 26-week intake of diets varying in protein and glycemic index on these biomarkers were studied. The choice of food was ad libitum but was strictly controlled by nutritional advice concerning the targeted fat and protein content as well as glycemic index. Expectedly, the initial weight loss significantly reduced systolic and diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and CRP. The subsequent consumption of different low-fat isocaloric diets resulted in moderate increases of blood lipids and blood pressure, which, however, were independent of the protein content and glycemic index of the diet. This clearly indicated that the beneficial effects on...
blood lipids and blood pressure were driven by the weight reduction itself but not by the dietary composition. In explicit contrast to the other biomarkers, consumption of low-glycemic-index diets led to a further decrease of CRP compared with high-glycemic-index diets. A low protein content enhanced the CRP-lowering effect, whereas a high protein content diminished it. Thus, the combination of low glycemic index and low protein intake appears to be most effective to reduce CRP, an established marker of low-grade inflammation and cardiovascular risk.

**Conclusions:** This large-scale intervention study clearly separates weight loss from dietary composition–related effects. Low-glycemic-index carbohydrates and, to a lesser extent, low-protein intake may specifically reduce low-grade inflammation and associated comorbidities in overweight/obese adults.

**References**


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