Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study

Previous studies have suggested that low total cholesterol levels are associated with an increased risk of intraparenchymal hemorrhage. The present study extends the evidence of an association between low total cholesterol levels and hemorrhage risk. We showed an association between low low-density lipoprotein cholesterol (<80 mg/dL [<2.06 mmol/L]) and increased risk of death due to intraparenchymal hemorrhage in the general population. The basic pathology of intraparenchymal hemorrhage is arteriolarosclerosis, characterized by angioneurosis (destruction) of smooth muscle cells in intracerebral small arteries, as opposed to atherosclerosis (plaque formation) in medium to large arteries. Low-density lipoprotein cholesterol may have an opposite effect on development of intraparenchymal hemorrhage in the general population. The basic pathology of intraparenchymal hemorrhage is arteriolarosclerosis, characterized by angioneurosis (destruction) of smooth muscle cells in intracerebral small arteries, as opposed to atherosclerosis (plaque formation) in medium to large arteries. Low-density lipoprotein cholesterol may have an opposite effect on development of intraparenchymal hemorrhage than on coronary heart disease. The present finding suggests that low low-density lipoprotein cholesterol may be an independent risk factor for intraparenchymal hemorrhage. See p 2136.

Influence of Systolic and Diastolic Blood Pressure on the Risk of Incident Atrial Fibrillation in Women

Prior studies have clearly established the independent role of arterial hypertension in the pathogenesis of atrial fibrillation, but optimal blood pressure levels for atrial fibrillation prevention have not been defined. We therefore assessed in detail the relationship of systolic and diastolic blood pressure levels and the risk of incident atrial fibrillation among 34,221 middle-aged, initially healthy women. During a median follow-up of 12.4 years, we confirmed 644 events. Our findings show that both systolic (P for trend <0.0001) and diastolic (P for trend=0.004) blood pressures were independently associated with incident atrial fibrillation. We also found that women with nonhypertensive systolic (130 to 139 mm Hg) or diastolic (85 to 89 mm Hg) blood pressure levels had a 28% and 53% increased risk of incident atrial fibrillation compared with women with systolic blood pressure <120 mm Hg or diastolic blood pressure <65 mm Hg, respectively. These results were similar when we took into account blood pressure changes over time. Taken together, the tight association between blood pressure, incident atrial fibrillation, and subsequent cardiovascular events suggests that future hypertension guidelines may assign a more important role to atrial fibrillation for cardiovascular risk stratification in patients with hypertension. Our findings also indicate that tight blood pressure control may help to reduce the growing burden of atrial fibrillation in the community. See p 2146.

Dietary Intake of Fruits and Vegetables Improves Microvascular Function in Hypertensive Subjects in a Dose-Dependent Manner

Observational evidence has consistently linked increased fruit and vegetable consumption with reduced rates of cardiovascular morbidity. Although health promotion literature and clinical guidelines suggest that eating 5 or more portions of fruit and vegetables daily may have beneficial vascular effects, this specific hypothesis has rarely been addressed in intervention studies in free-living participants. We conducted a randomized, controlled trial among 117 volunteers with mild hypertension to examine the dose-dependent effects of altered fruit and vegetable consumption on microvascular function. A significant relationship between increased fruit and vegetable consumption and improvements in forearm blood flow responses to intra-arterial acetylcholine was observed. Such findings link a potentially achievable dietary goal with favorable changes in an established predictor of cardiovascular morbidity. This study was conducted among free-living volunteers rather than under controlled feeding conditions, and many of the participants were taking anti-hypertensive and/or lipid-lowering therapies. These details allow application of our findings within a broader patient population and should encourage further trials to assess the impact of nutrition and lifestyle intervention on cardiovascular health. Such work is vital both in providing physicians with a sound evidence base for nonpharmacological prescription and in scientifically informing future public health advice. See p 2153.

Vascular Smooth Muscle Cell–Selective Peroxisome Proliferator–Activated Receptor-γ Deletion Leads to Hypotension

Hypertension control is one of the major goals in the management of cardiovascular disease. The occurrence of hypertension in diabetic patients further aggravates their cardiovascular outcomes. In clinical practice, thiazolidinediones, agonists of peroxisome proliferator–activated receptor-γ (PPARγ), stand out as therapeutic drugs for diabetes control. They act as insulin sensitizers but also improve hypertension in diabetic patients. Experimental models have been developed to elucidate the molecular mechanisms by which PPARγ mediates these processes. Endothelium-, cardiac-, and smooth muscle tissue–specific gain- and loss-of-PPARγ-function animal models display a considerable range of effects on various aspects of the cardiovascular pathophysiology such as pulmonary hypertension, cardiac remodeling, or high-fat diet–induced atherosclerosis. Here, we describe that vascular smooth muscle cell–selective PPARγ deletion leads to systemic hypotension with a circadian component, and we specifically identify the β2-adrenergic receptor as a novel gene subjected to PPARγ-dependent repression in the vasculature, which will undoubtedly open new paradigms in the regulation of blood pressure and vascular tone. See p 2161.

Neuropilin-1 Identifies Endothelial Precursors in Human and Murine Embryonic Stem Cells Before CD34 Expression

Our understanding of the manner in which endothelial cells develop from embryonic stem cells is still incomplete. An important question is whether endothelial precursor cells have common identifying features that serve as “biomarkers” for tracking their development into mature endothelial cells. Here we report that expressions of 3 markers—(1) neuropilin-1 (a vascular endothelial growth factor coreceptor); (2) Brachyury; and (3) vascular endothelial growth factor receptor 2—identify human and mouse embryonic stem cells that developmentally become endothelial cells. Neuropilin-1 expression occurs very early and defines the origin of a single population of human and mouse stem cells that progress toward endothelial cells. Use of these biomarkers may facilitate marking and tracking of embryonic stem cells that may eventually be used for therapeutic purposes. See p 2170.
Mineralocorticoid Modulation of Cardiac Ryanodine Receptor Activity Is Associated With Downregulation of FK506-Binding Proteins

Defective calcium handling is a key contributor to the pathophysiology of heart failure, not only in the weakening of the heart’s ability to pump blood but also in the erratic heart beats that cause sudden death. Research conducted to understand the molecular mechanisms underlying those fatal arrhythmias has focused mainly on downstream mechanisms (the defective calcium-handling processes) rather than the causes. The present study highlights the role of the cardiac aldosterone pathway as an upstream primary molecular event that leads to defective calcium handling. Combining ex vivo and in vivo (transgenic mice) approaches and using state-of-the-art Ca²⁺ imaging, electrophysiology, and biochemistry methods, we provide the first evidence that downregulation of FK506 binding proteins (also known as calstabin) through the aldosterone pathway causes defectiveness of ryanodine receptor activity, which has been associated with the common pathogenic mechanism of sudden cardiac death and heart failure. In addition, these findings underline the potential of mineralocorticoid receptor antagonists as antiarrhythmic therapy. See p 2179.

Macrophage-Specific Expression of Mannose-Binding Lectin Controls Atherosclerosis in Low-Density Lipoprotein Receptor–Deficient Mice

Since an initial publication in 1998, population-based studies identified mannose-binding lectin (MBL) as a modifier of atherosclerosis development; both proatherogenic and antiatherogenic roles of MBL were demonstrated. However, as stated by G.K. Hansson in his 2006 Arteriosclerosis, Thrombosis, and Vascular Biology editorial, “confusion prevails.” The mechanisms by which MBL influences atherosclerosis development are unknown, and epidemiological data are conflicting, emphasizing the need for additional experimental studies. MBL is considered to be an important initiating complement component with immune regulatory properties and considerable variation in plasma levels between individuals. Its function ranges from complement activation to the MBL-mediated uptake of late apoptotic cells, cellular debris, and foreign organisms by macrophages. In the present study, local MBL-A and MBL-C gene expressions were demonstrated in murine atherosclerotic lesions. Interestingly, mice carrying MBL-A and -C double deficient macrophages had increased (30%) atherosclerotic lesions compared with wild-type controls. Furthermore, the MBL-A and -C distribution pattern observed in the present study suggests that MBL may play a differential role in the atherogenic process. Low MBL levels, although possibly disadvantageous during early atherosclerosis development because of a defect in removal, may well be able to reduce inflammation and subsequent atherosclerosis development in advanced stages of atherosclerosis. This hypothesis would support in large part the previous and often conflicting studies on the role of MBL in atherosclerosis development. See p 2188.

Physician Alerts to Prevent Symptomatic Venous Thromboembolism in Hospitalized Patients

Despite published guidelines for venous thromboembolism (VTE) prevention, underuse of prophylaxis in hospitalized patients remains problematic. We previously described a novel system using electronic alerts to prevent symptomatic VTE in hospitalized patients. We created a computer program linked to the patient database to identify hospitalized patients at high risk for VTE who were not receiving prophylaxis and randomize notification (versus no notification) of physicians caring for these patients. The physicians in the intervention group received electronic alerts urging them to order prophylaxis. This resulted in a 41% reduction in symptomatic VTE at 90 days compared with the control group. Because it required an intricate electronic notification system and medical informatics support, this strategy could not be easily implemented by most hospitals. Therefore, we devised a clinical trial that used a human rather than an electronic alerting system. We randomized 2493 patients to the intervention group, in which the attending physician was alerted by another hospital staff member by direct page, or the control group, in which no alert was issued. Patients whose physicians were alerted were more than twice as likely to receive VTE prophylaxis. Although a human alerting system more than doubled VTE prophylaxis use, the ensuing 21% reduction in symptomatic VTE at 90 days did not achieve statistical significance (P = 0.31). Increasing resources for computer-based decision-support strategies may enhance the effectiveness of VTE prevention measures. See p 2196.


Abdominal aortic aneurysms (AAAs) have no or few symptoms until a possible rupture. In rupture, the mortality rate is 65% to 85%. Death due to ruptured AAA accounts for ~1% of all deaths in the Western world. Screening of risk groups has been suggested to reduce the frequency of ruptured AAAs. In this population-based study, 4345 persons with normal-sized abdominal aortas in 1994/1995 were rescanned by ultrasound 7 years later. The aim was to identify risk factors for developing an AAA. There were 119 incident cases of AAA, which yielded an incidence of 0.4% per year. Risk factors for developing an AAA were increasing age, male sex, smoking, high serum total cholesterol, low serum high-density lipoprotein cholesterol, and hypertension. Smoking, both the number of years and the number of daily cigarettes, influenced the risk for AAA strongly. Thus, the risk factors for AAA are the same as those for developing atherosclerosis. These results may be helpful both to identify patients at risk for developing an AAA (eg, smokers with low high-density lipoprotein cholesterol) and to clarify which groups should be offered a possible screening program. Both smoking reduction and (ideally) complete smoking cessation for reducing the risk for AAA are supported by the present results. See p 2202.

Clinical Trial of Doxycycline for Matrix Metalloproteinase-9 Inhibition in Patients With an Abdominal Aneurysm: Doxycycline Selectively Depletes Aortic Wall Neutrophils and Cytotoxic T Cells

Pharmaceutical stabilization of abdominal aneurysms, thereby reducing the need for aneurysm repair, holds many promises. Matrix metalloproteinase-9 is considered pivotal to the process of aneurysm formation. Because of its ability to reduce matrix metalloproteinase-9 expression and activity, the tetracycline analogue doxycycline has been brought forward as a promising lead candidate. Although animal studies have convincingly shown that doxycycline inhibits both aneurysm formation and growth, the effects of doxycycline on matrix metalloproteinase-9 are controversial in human studies. In this study, we confirm that doxycycline lowers aneurysmal wall matrix metalloproteinase-9 protein levels but also show that this reduction may be secondary and related to an effect on neutrophils, a cell type loaded with preformed matrix metalloproteinase-9 protein. We demonstrate that doxycycline has a profound but selective suppressive effect on inflammation in abdominal aortic aneurysms; doxycycline specifically lowers aortic wall neutrophil (~76%) and cytotoxic T-cell (~96%) content, 2 types considered crucial for aneurysm formation. Moreover, it is shown that treatment reduces interleukin-6 and -8 hyperexpression, a key feature of abdominal aortic aneurysm. Results of this study are relevant for pharmaceutical stabilization of the abdominal aneurysm and possibly for other (vascular) inflammatory conditions involving neutrophils and/or cytotoxic T cells such as Kawasaki disease and Behçet syndrome. See p 2209.