**Circulation Editors’ Picks**

**Peripheral Vascular Disease**

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 manuscripts published on the topic of peripheral vascular disease. (*Circulation. 2013;128:e453-e460.)*

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**Direct Quantitative Assessment of the Peripheral Artery Collateral Circulation in Patients Undergoing Angiography**

**Summary**—Peripheral artery disease of the lower extremities is a common disease and present in 15% to 20% of persons older than 65 years. Endovascular or surgical therapy fails or is not applicable in approximately one fourth of patients who would need revascularization therapies, which makes alternative approaches such as arteriogenesis (the positive remodeling of preformed collateral arterioles) necessary. Despite the fact that numerous studies have pursued the important therapeutic strategy of improving collateral function, there is no method available to quantify collateral arterial function of the lower limb and thus to determine therapeutic effects. The present study demonstrates for the first time a quantitatively assessed functional and clinically relevant collateral circulation in the lower limb. Using direct invasive pressure measurements in humans, we show that collateral flow index of the superficial femoral artery in the absence of any significant stenosis amounts to more than half the normal antegrade flow at rest (45±17% after 1 minute, 55±17% after 3 minutes). The amount of collateral flow observed in the present study is remarkably high, especially compared with what has been described previously for normal (18±8%) and stenotic (22±15%) coronary arteries. Importantly, this preexistent collateral blood supply in the absence of significant stenoses is sufficient to completely prevent symptoms during 5 minutes of acute ischemia at rest. Because only indirect and weak end points have been used in past studies to evaluate collateral growth, we propose that the method described in the present study may possibly be used as a gold standard in future clinical studies.

**Conclusions**—Quantitatively assessed collateral arterial function at rest determined in the nonstenotic superficial femoral artery is sufficient to prevent ischemic symptoms during a total occlusion of 5 minutes. During exercise, there is a decline in CFIp that indicates a supply-demand mismatch via collaterals or, alternatively, a steal phenomenon.

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**Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty (DEBATE-BTK): A Randomized Trial in Diabetic Patients With Critical Limb Ischemia**

**Summary**—Critical limb ischemia, characterized by ischemic rest pain or tissue loss, represents the most advanced state of peripheral artery disease, burdened by extremely high morbidity and mortality. Critical limb ischemia generally occurs in diabetics with extensive atherosclerotic disease of the below-the-knee vessels. The optimal strategy for treating critical limb ischemia patients, however, has not been clearly defined, and the 1-year restenosis rate after balloon angioplasty (percutaneous transluminal angioplasty) of long lesions in below-the-knee arteries may be as high as 70%. The Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) is the first randomized study evaluating the efficacy, in terms of 12-month restenosis and target lesion revascularization, of drug-eluting balloons compared with standard percutaneous transluminal angioplasty in diabetic patients with de novo long atherosclerotic lesions and critical limb ischemia undergoing revascularization of below-the-knee arteries. Our study demonstrates that the drug-eluting balloons significantly reduced 12-month restenosis, regardless of lesion length, revascularization technique, and baseline vessel conditions. The advantage conferred by drug-eluting balloons on restenosis resulted in a significant decrease in clinically driven target lesion revascularization, and this benefit is further compounded by the more favorable distribution of Rutherford classes at follow-up and faster index ulcer healing in the drug-eluting balloon group.

**Conclusions**—Drug-eluting balloons compared with PTA strikingly reduce 1-year restenosis, target lesion revascularization, and target vessel occlusion in the treatment of below-the-knee lesions in diabetic patients with critical limb ischemia.

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**Cilostazol Reduces Angiographic Restenosis After Endovascular Therapy for Femoropopliteal Lesions in the Sufficient Treatment of Peripheral Intervention by Cilostazol Study**

**Summary**—Femoropopliteal (FP) lesions are found in 60% to 70% of patients with symptomatic peripheral artery disease. Although implantation of nitinol stents has improved the long-term outcome of endovascular therapy for FP lesions, there remains a 20% to 50% incidence of restenosis at 1 year as an important challenge for endovascular intervention. Current guidelines do not recommend any specific medical intervention to reduce the incidence of restenosis after endovascular therapy for FP disease. The Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) study investigated whether cilostazol reduces the 12-month angiographic restenosis rate.
after percutaneous transluminal angioplasty with provisional nitinol stenting for FP lesions. The angiographic patency rate at 1 year after endovascular therapy was 80% in patients receiving cilostazol treatment in comparison with 51% in patients not receiving it, and cilostazol significantly reduced angiographic restenosis after endovascular therapy for FP disease. The cilostazol group also had a significantly higher event-free survival rate at 12 months, although the rate of cardiovascular events was similar in the 2 groups (83% versus 71%; P=0.02). Cilostazol reduced angiographic restenosis after percutaneous transluminal angioplasty with provisional nitinol stenting for FP lesions.

Conclusions—Cilostazol reduced angiographic restenosis after percutaneous transluminal angioplasty with provisional nitinol stenting for femoropopliteal lesions.

Vorapaxar in Patients With Peripheral Artery Disease: Results From TRA2°P-TIMI 50

Summary—Patients with symptomatic peripheral artery disease are at risk of systemic atherothrombotic events, including cardiovascular death, myocardial infarction, and stroke. In addition, these patients are at a heightened risk of limb vascular events, including acute and chronic limb ischemia and the need for peripheral revascularization. Vorapaxar is a novel antagonist of protease-activated receptor-1, the primary receptor for thrombin on human platelets that is also present on vascular endothelium and smooth muscle. The peripheral artery disease cohort of the Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) trial evaluated the efficacy and safety of vorapaxar in addition to standard antiplatelet therapy in patients with symptomatic peripheral artery disease. Overall, treatment with vorapaxar resulted in a numeric reduction in cardiovascular death, myocardial infarction, or stroke that did not reach statistical significance. Rates of limb vascular events were frequent in this cohort, including a placebo rate of 3.9% for acute limb ischemia and 22.2% for peripheral revascularization over 3 years. Vorapaxar significantly lowered the rates of hospitalization for acute limb ischemia (2.3% versus 3.9%; hazard ratio, 0.58; 95% confidence interval, 0.39–0.86; P=0.006) and peripheral artery revascularization (18.4% versus 22.2%; hazard ratio, 0.84; 95% confidence interval, 0.73–0.97; P=0.017). Bleeding occurred more frequently with vorapaxar compared with placebo.

Conclusions—Vorapaxar did not reduce the risk of cardiovascular death, myocardial infarction, or stroke in patients with peripheral artery disease; however, vorapaxar significantly reduced acute limb ischemia and peripheral revascularization. The beneficial effects of protease-activated receptor-1 antagonism on limb vascular events were accompanied by an increased risk of bleeding.

Association Between 2 Angiographic Subtypes of Renal Artery Fibromuscular Dysplasia and Clinical Characteristics

Summary—Fibromuscular dysplasia is a heterogeneous group of idiopathic, noninflammatory, and nonatherosclerotic stenosing vascular diseases mostly involving renal and cervical arteries. It is the second most frequent cause of renovascular hypertension. Its historical classification based on histology is no longer relevant now that percutaneous revascularization has replaced surgery in most cases. In this study, we describe an angiographic classification of renal artery fibromuscular dysplasia lesions into a unifocal and a multifocal subtype. Fewer patients have unifocal lesions (18% of all patients with renal artery fibromuscular dysplasia), and their characteristics contrast with those of patients with multifocal lesions: They are younger at diagnosis (30 versus 49 years); the proportion of women is lower (69% versus 83%); they are more often current smokers (50% versus 26%) with higher blood pressure levels (157/97 versus 146/88 mm Hg); the disease is more often unilateral (79% versus 38%); they are more amenable to revascularization (90% versus 35%); and have a higher cure rate when revascularization is performed (54% versus 26%).

Conclusions—A binary angiographic classification into unifocal or multifocal renal artery FMD is straightforward and discriminates 2 groups of patients with different clinical phenotypes.

Missed Opportunities: Despite Improvement in Use of Cardioprotective Medications Among Patients With Lower-Extremity Peripheral Artery Disease, Underuse Remains

Summary—One of the main goals for treatment of peripheral artery disease (PAD) is risk factor modification and secondary prevention of vascular events by initiating cardioprotective pharmacotherapies. Studies investigating temporal trends and longitudinal use of cardioprotective agents after incident diagnosis of PAD have been limited. With the use of Danish nationwide administrative registries, which capture medication adherence, we demonstrate a significant temporal improvement from 2000 to 2007 in the use of any antiplatelet and statin therapy after incident diagnosis of PAD. However, the use of these medications is modest, such that by 18 months after incident diagnosis, nearly half of patients with PAD alone are not taking any antiplatelet or statin therapy. After adjustment, patients with incident PAD and a history of coronary artery disease are more likely to take cardioprotective medications than patients with incident coronary artery disease alone (no history of PAD). Meanwhile, patients with PAD alone have nearly half the adjusted odds of taking any antiplatelet in comparison with patients with coronary artery disease alone. Although use of cardioprotective medications improved after publication of the American College of Cardiology/American Heart Association PAD guidelines in 2005, the adjusted odds of any antiplatelet use among patients with PAD alone, compared with patients with coronary artery disease alone, was nearly 35% less, and statin use was 20% less in a more contemporary period (2005–2007). The present analysis underscores the need for systemwide improvements to improve adherence to secondary prevention in this population.

Conclusions—Despite improvement in the use of cardioprotective medications over time, patients with PAD alone remain less likely than those with CAD alone to use these agents.

Nucleotide Excision DNA Repair Is Associated With Age-Related Vascular Dysfunction

Summary—Aging strongly contributes to cardiovascular disease. It prolongs exposure to classic cardiovascular risk factors such as hypertension and diabetes mellitus but also acts as an independent risk factor. Recent evidence suggests that gradually accumulating DNA damage, leading to genomic instability, is a main cause of aging. This study is the first to show that mice with a defective DNA repair mechanism have a significant reduction in vascular relaxation, and cellular aging. Of interest, phosphodiesterase inhibition acutely improved the diminished relaxation in vitro, suggesting that enhanced breakdown of cGMP may underlie this phenomenon.
Furthermore, in humans, variations in DNA repair genes were associated with markers for vascular aging. Taken together, these results indicate that genomic instability plays a central role in vascular aging. Genomic instability may also explain the high prevalence of cardiovascular death in Hutchinson-Gilford progeria and Werner progeroid syndrome, both of which feature genomic instability. Because oxidative stress is an important inducer of DNA damage, future aging-suppressor agents may involve drugs that improve genomic integrity (eg, statins and rapamycin) and drugs that prevent oxidative stress (eg, renin-angiotensin system blockers and antioxidants). In addition, drugs facilitating the nitric oxide–soluble guanylate cyclase–cGMP–phosphodiesterase pathway might be of value. The successful application of such treatments requires proper risk stratification, preferably at younger ages. This might include analyses of genetic variations in DNA repair genes and the identification of all possible sources of cardiovascular DNA damage.

Conclusions—Mice with genomic instability recapitulate age-dependent vascular dysfunction as observed in animal models and in humans but with an accelerated progression compared with wild-type mice. In addition, we found associations between variations in human DNA repair genes and markers for vascular stiffness, which is associated with aging. Our study supports the concept that genomic instability contributes importantly to the development of cardiovascular disease.

The United States Registry for Fibromuscular Dysplasia: Results in the First 447 Patients

Summary—Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women in the prime of their life. There is an average delay of 5 years from the onset of symptoms until the diagnosis of FMD is made. FMD most commonly affects the renal, carotid, and vertebral arteries but may occur in virtually every artery of the body. Multivessel involvement is common. The most common clinical manifestations of FMD are hypertension, headaches, pulsatile tinnitus, and dizziness. However, 1 in 5 patients experience a dissection, and 17% have one or more aneurysms. A cerebrovascular event including transient ischemic attack, stroke, and/or amaurosis fugax occur in 1 of every 4 patients with FMD. The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of FMD. Earlier diagnosis may prevent the consequences of poorly controlled hypertension, and allow for the identification of aneurysms and dissections and their appropriate treatment.

Conclusions—In this registry, FMD occurred primarily in middle-aged women, although it presents across the lifespan. Cerebrovascular FMD occurred as frequently as renal FMD. Although a significant proportion of FMD patients may present with a serious vascular event, many present with nonspecific symptoms and a subsequent delay in diagnosis.

Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies

Summary—Assisted reproductive technology (ART) has been used for 3 decades, and the children born after ART now make up for 1% to 4% of the births in developed countries. ART involves the manipulation of early embryos at a time when they may be particularly vulnerable to external disturbances. Environmental influences during the embryonic and fetal development influence the individual’s susceptibility to cardiovascular disease, raising concerns about the potential consequences of ART on the long-term health of the offspring. Here, we show for the very first time that apparently healthy children born after ART show systemic and pulmonary vascular dysfunction, as evidenced by endothelial dysfunction, increased arterial stiffness, and carotid intima-media thickness in the systemic circulation and exaggerated hypoxic pulmonary hypertension during short-term high-altitude exposure. This vascular dysfunction does not appear to be related to parental factors or hormonal stimulation of the ovulation in the mother but to the ART procedure itself. For the practicing physician, this study indicates that ART children who live at high altitude or suffer from diseases associated with chronic hypoxia are at risk for exaggerated pulmonary hypertension and need to be monitored for this problem. In the systemic circulation, it is not known yet how this vascular dysfunction, which is similar in magnitude to that in children suffering from type 1 diabetes mellitus, will evolve. Although future mechanistic studies in ART mice may reveal possibilities for targeted intervention to improve or prevent ART-induced vascular dysfunction in humans, avoiding additional cardiovascular risk factors in this population appears to be important now.

Conclusions—Healthy children conceived by ART display generalized vascular dysfunction. This problem does not appear to be related to parental factors but to the ART procedure itself.

Supervised Exercise Versus Primary Stenting for Claudication Resulting From Aortoiliac Peripheral Artery Disease: Six-Month Outcomes From the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Study

Summary—Claudication is the most common ischemic symptom of peripheral artery disease (PAD), affecting approximately 30% of these patients and limiting pain-free walking in over 2 million Americans. There are 3 treatments available to improve these symptoms, including claudication pharmacotherapy (cilostazol), supervised exercise, and endovascular revascularization, but little data comparing their relative efficacy, harm, and cost-effectiveness. There has been a marked rise in use of invasive (percutaneous) angioplasty and stenting, while PAD exercise programs remain mostly unavailable. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study is an NHLBI-sponsored comparative effectiveness clinical investigation that randomly assigned 111 patients with aortoiliac PAD (the optimal anatomic site for stenting) to receive 1 of 3 treatments: optimal medical care (OMC, using home exercise and cilostazol), OMC plus supervised exercise (SE), or OMC plus stent revascularization (ST). At 6 months of follow-up (the primary end point), the improvement in peak walking time was greatest for SE, intermediate for ST, and least with OMC (mean change versus baseline =0.04 for SE versus ST). Disease-specific quality of life improved with both SE and ST compared with OMC, but the improvement was greater with ST than SE. This study demonstrates that supervised exercise treatment results in superior treadmill walking performance than stent placement for patients with aortoiliac PAD. The longer-term impact of SE and ST on functional status and health economic outcomes in individuals with aortoiliac PAD will be assessed at 18 months.

Conclusions—SE results in superior treadmill walking performance than ST, even for those with aortoiliac peripheral artery disease. The contrast between better walking performance for SE and better patient-reported quality of life for ST warrants further study.
High-Molecular-Weight and Total Adiponectin Levels and Incident Symptomatic Peripheral Artery Disease in Women: A Prospective Investigation

Summary—Lower-extremity peripheral artery disease (PAD) is a manifestation of atherosclerosis that has received considerably less clinical and research attention than coronary or cerebrovascular disease. PAD shares many risk factors with other cardiovascular diseases, including smoking, diabetes mellitus, hypertension, and hyperlipidemia; however, less is known about how PAD differs from atherosclerosis of other vascular territories. Studies of biomarkers and future disease risk can improve our ability to detect patients at heightened risk and our understanding of disease pathogenesis and, by extension, may identify potential novel modalities for treatment. Adiponectin is secreted from adipose tissue and is known to be inversely correlated with future diabetes mellitus risk. It may also be antiatherogenic. This study is the first to examine the relationship between adiponectin and PAD as a specific vascular end point. A large population of initially healthy women aged ≥45 years without existing cardiovascular disease was studied. After traditional cardiovascular risk factors were taken into account, women with high-molecular-weight or total adiponectin levels in the highest tertile had a 59% (high-molecular-weight) or 63% (total) reduced risk for future symptomatic PAD (intermittent claudication or lower-extremity revascularization) compared with women with levels in the lowest tertile. Given the lack of a consistently demonstrated relationship between adiponectin and other cardiovascular end points, this striking result, if confirmed, suggests a unique relationship of adiponectin in PAD development which may reflect a more prominent role of adipokines in peripheral atherosclerosis.

Conclusions—Total and HMW adiponectin are inversely associated with incident PAD among initially healthy women. These prospective data support a protective role for this adipokine in peripheral atherosclerosis development.

Disruption of Na\(^+\),HCO\(_3\)\(^-\) Cotransporter NBCn1 (slc4a7) Inhibits NO-Mediated Vasorelaxation, Smooth Muscle Ca\(^{2+}\) Sensitivity, and Hypertension Development in Mice

Summary—It has long been speculated that disturbed intracellular pH (pHi) regulation could be important for development of artery dysfunction and cardiovascular disease. The lack of experimental techniques allowing for selective changes in pHi without affecting other conditions has, however, precluded direct studies into the effects of pHi disturbances in the artery wall. In the present study, we used a functional genetics approach to abolish expression of the Na\(^+\),HCO\(_3\)\(^-\) cotransporter NBCn1, which is responsible for pHi control in both vascular smooth muscle and endothelial cells. The cardiovascular function was greatly disturbed by the low intracellular pH resulting from lack of NBCn1 expression. Our findings for the first time directly demonstrate the potential of pHi disturbances in the artery wall and add to the existing complexity of signaling pathways involved in control of artery contractile function and blood pressure. NBCn1 knockout mice were mildly hypertensive at rest but protected against angiotensin-II–induced hypertension. The molecular basis for the altered artery function originated from reduced endothelial NO production and inhibited rho-kinase signaling. Hence, disturbed pHi in the artery wall affects key signaling pathways and may prove particularly important for development of artery dysfunction during conditions of local ischemia or possibly in patients with genetic mutations in NBCn1. These new mechanisms implicated in blood pressure regulation and cardiovascular control provide a potential new target to consider in the treatment of artery dysfunction and blood pressure disturbances.

Conclusions—Intracellular acidification of smooth muscle and endothelial cells after knockout of NBCn1 inhibits NO-mediated rho-kinase–dependent signaling in isolated arteries and perturbs blood pressure regulation.

Effect of Hypoxia-Inducible Factor-1α Gene Therapy on Walking Performance in Patients With Intermittent Claudication

Summary—There are few medical therapies for patients with peripheral artery disease and intermittent claudication. Therapeutic angiogenesis has the potential to improve symptoms of claudication by forming new blood vessels and improving blood flow to affected limbs. Hypoxia-inducible factor 1α (HIF-1α) is an inducible transcriptional regulatory factor that plays a principal role in the cellular response to changes in oxygen tension and regulates genes involved in angiogenesis. This study tested the efficacy of intramuscular administration of Ad2/HIF-1α/VP16, an engineered recombinant type 2 adenovirus vector encoding constitutively active HIF-1α, in improving walking time in patients with intermittent claudication. Compared with placebo, Ad2/HIF-1α/VP16 treatment did not improve peak walking time, claudication onset time, ankle-brachial index, or walking ability assessed by questionnaire. There are multiple reasons that should be considered to explain why this trial failed to improve walking time in patients with intermittent claudication. These include the biological activity of HIF-1α, the efficacy of gene transfer, the ability of intramuscular injection of HIF-1α at multiple sites to establish contiguous collateral vessels, the duration of effect after treatment on just 1 occasion, and the confounding effects of mechanisms other than blood supply that limit walking distance. To date, placebo-controlled clinical trials of angiogenic gene therapy have failed to demonstrate efficacy in patients with peripheral artery disease despite encouraging signals in preclinical models and preliminary human studies. These findings underscore the need to increase our understanding of the biology of angiogenesis and to develop effective and safe means to deliver gene therapy to patients with peripheral artery disease.

Conclusions—Gene therapy with intramuscular administration of Ad2/HIF-1α/VP16 is not an effective treatment for patients with intermittent claudication.

Association of Incident Cardiovascular Disease With Periodic Limb Movements During Sleep in Older Men: Outcomes of Sleep Disorders in Older Men (MrOS) Study

Summary—Periodic limb movements during sleep (PLMS) are a frequent finding of overnight polysomnography, especially in the elderly; however, the clinical significance of these movements is not clear. In this article, when data from the Outcomes of Sleep Disorders in Older Men (MrOS) sleep cohort were analyzed, PLMS were associated with an increased risk of incident cardiovascular disease in elderly men. In this analysis, PLMS preceded the development of cardiovascular disease, which suggests but does not prove a causal role for PLMS in vascular disease. The mechanism behind this increased cardiovascular risk may be associated with the known...
sympathetic hyperactivity associated with PLMS. The association between incident arterial disease and PLMS was particularly robust, suggesting that arterial disease may result from PLMS. In the not too distant future, PLMS frequency noted on the polysomnography report, like the apnea-hypopnea index, may become a useful metric on how to judge a patient’s cardiovascular risk. Additional study is needed to clarify this relationship between PLMS and cardiovascular risk and furthermore to see whether treating PLMS decreases this risk.

Conclusion—These findings provide evidence that PLMS frequency is associated with incident cardiovascular disease in community-dwelling elderly men.14

Downregulation of Kv7.4 Channel Activity in Primary and Secondary Hypertension

Summary—Hypertension is a major risk factor for a number of cardiovascular diseases and is the leading cause of mortality worldwide. Hypertension is characterized by an increase in peripheral resistance and is associated with remodeling of the blood vessel architecture, which contributes to the maintenance of elevated blood pressure in the longer term. Recently, voltage-dependent potassium channels encoded by the KCNQ gene family (Kv7.1 through Kv7.5) have been identified in rodent and human vascular smooth muscle, in which they are important regulators of the membrane potential and hence vascular contractility. The present study shows that in normotensive rats and mice, structurally different Kv7 activators relaxed mesenteric resistance vessels and thoracic aorta and improved coronary perfusion considerably. Strikingly, the vasorelaxant effects of these agents were markedly attenuated in tissues from spontaneously hypertensive rats and angiotensin II–infused hypertensive mice, and the effect on coronary perfusion was negligible. These impaired functional responses were associated with a downregulation of KCNQ4 gene expression and reduced production of Kv7.4 protein. Downregulation of KCNQ4 and the loss of this antispasmodic mechanism appear to be a common feature of hypertensive blood vessels, which provides considerable new insight into the pathogenesis of hypertension. Strategies for restoring KCNQ4 could be therapeutically beneficial.

Conclusions—In 2 different rat and mouse models of hypertension, the functional impact of Kv7 channels was dramatically downregulated.15

Rapid, Direct Effects of Statin Treatment on Arterial Redox State and Nitric Oxide Bioavailability in Human Atherosclerosis via Tetrahydrobiopterin-Mediated Endothelial Nitric Oxide Synthase Coupling

Summary—Statin treatment reduces cardiovascular risk. Although statins exert their antiatherogenic effects mainly by reducing low-density lipoprotein, experimental studies demonstrated a number of pleiotropic effects directly on the vascular cells. However, mechanistic studies examining the pleiotropic effect of statins on endothelial nitric oxide (NO) bioavailability and the vascular redox state in human arteries are remarkably limited. In the present study, we first demonstrate that in a real-life population of 492 patients undergoing coronary artery bypass graft surgery, we demonstrated that 3 days of treatment with atorvastatin 40 mg/d before coronary artery bypass graft surgery improved endothelial function and reduced vascular O2·− in internal mammary arteries of these patients by improving endothelial NO synthase coupling with increased vascular levels of the endothelial NO synthase cofactor tetrahydrobiopterin. We then performed a number of mechanistic ex vivo experiments in which atorvastatin rapidly upregulated GTP-cyclohydrolase I gene expression in the arterial wall, increased GTP cyclohydrolase I activity, and stimulated the synthesis of vascular biopertins, resulting in an improvement of endothelial NO synthase coupling, a reduction of endothelium-derived vascular O2·−, and an improvement in endothelial function in a low-density lipoprotein–free environment. These effects were due to a direct inhibition of hydroxymethylglutaryl-coenzyme A reductase in the vascular wall. Therefore, our study demonstrates for the first time in humans that high-dose treatment with atorvastatin rapidly modifies the vascular redox state and endothelial function via tetrahydrobiopterin-mediated endothelial NO synthase coupling, providing one of the first direct reports of a pleiotropic effect of statins on the human arterial endothelium.

Conclusions—This study demonstrates for the first time in humans the direct effects of statin treatment on the vascular wall, supporting the notion that this effect is independent of low-density lipoprotein lowering. Atorvastatin directly improves vascular NO bioavailability and reduces vascular O2·− through tetrahydrobiopterin-mediated endothelial NO synthase coupling. These findings provide new insights into the mechanisms mediating the beneficial vascular effects of statins in humans.16

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.17
Protease-Resistant Stromal Cell–Derived Factor-1 for the Treatment of Experimental Peripheral Artery Disease

Summary—Peripheral artery disease is a common disorder that is associated with significant morbidity. Peripheral artery disease can present as chronic ischemia with claudication or as critical limb ischemia. Traditional treatment of peripheral artery disease includes surgical revascularization; however, few patients can be treated successfully with surgery only. There is a need for new drugs and delivery systems because few drug therapies for peripheral artery disease currently exist. A potential candidate treatment for treatment of peripheral artery disease would be injection of stromal cell–derived factor-1 (SDF-1), a protein that attracts angiogenic progenitor cells. However, SDF-1 is rapidly degraded by proteases expressed in ischemic tissues. Therefore, we designed novel variants of SDF-1 that are protease resistant. In the present study, we show that protease-resistant SDF-1, called SSDF-1(S4V), induces formation of new blood vessels in a mouse model of peripheral artery disease, SSDF-1(S4V) only induces arteriogenesis when delivered in a hydrogel of self-assembling peptides, indicating that slow release is necessary for functional improvement. On the basis of this study, we believe that SSDF-1(S4V), when injected locally in patients with peripheral artery disease, can result in formation of new vessels and increased tissue perfusion. Local delivery of SSDF-1(S4V) might improve quality of life in patients with peripheral artery disease.

Conclusions—SDF-1 engineered to be resistant to dipeptidylpeptidase IV/CD26 and matrix metalloproteinase-2 cleavage and delivered by nanofibers improves blood flow in a model of peripheral artery disease.18

Efficacy of Quantified Home-Based Exercise and Supervised Exercise in Patients With Intermittent Claudication: A Randomized Controlled Trial

Summary—A primary therapeutic goal for patients with peripheral artery disease and intermittent claudication is to regain lost ambulatory function through exercise rehabilitation. Medically supervised exercise programs are efficacious for improving claudication onset time and peak walking time, but more patients could benefit from exercise programs transported to the community setting (ie, home-based walking). However, home exercise has been poorly studied. This prospective, randomized, controlled clinical trial compared changes in claudication onset time, peak walking time, and daily ambulatory activity in the community setting than the exercise sessions. The changes in claudication onset time and peak walking time after home-based exercise were similar to those after supervised exercise, whereas the change in daily ambulatory cadences apart from the exercise sessions. Therefore, we designed novel variants of SDF-1 that are protease resistant. In the present study, we show that protease-resistant SDF-1, called SSDF-1(S4V), induces formation of new blood vessels in a mouse model of peripheral artery disease, SSDF-1(S4V) only induces arteriogenesis when delivered in a hydrogel of self-assembling peptides, indicating that slow release is necessary for functional improvement. On the basis of this study, we believe that SSDF-1(S4V), when injected locally in patients with peripheral artery disease, can result in formation of new vessels and increased tissue perfusion. Local delivery of SSDF-1(S4V) might improve quality of life in patients with peripheral artery disease.

Conclusions—A home-based exercise program, quantified with a step activity monitor, has high adherence and is efficacious in improving claudication measures similar to a standard supervised exercise program. Furthermore, home-based exercise appears more efficacious in increasing daily ambulatory activity in the community setting than supervised exercise.19

Deregulation of microRNA-503 Contributes to Diabetes Mellitus–Induced Impairment of Endothelial Function and Reparative Angiogenesis After Limb Ischemia

Summary—MicroRNAs (miRNAs) are post-transcriptional inhibitors of gene expression that bind to complementary messenger RNA transcripts. After initial studies in developmental biology and cancer, miRNAs have recently come into focus of cardiovascular diagnostics and therapeutics. Because each miRNA can repress many target miRNAs, it is possible that dysregulation of a single miRNA might account, at least in part, for complex pathological situations. Here, we report for the first time the importance of miR-503 in diabetes mellitus–associated ischemic disease, which currently represents a major cause of morbidity and mortality in diabetic patients. In vitro, the combination of high glucose and starvation remarkably enhances the expression of miR-503 in human endothelial cells, and so does diabetes mellitus in endothelial cells extracted from murine ischemic limb muscles. In vitro experiments showed that forced expression of miR-503 inhibits endothelial cell proliferation and endothelial network formation. Because miR-503 represses cell cycle–associated genes, we investigated whether miR-503 activation may impinge on posts ischemic reparative angiogenesis. In a diabetic mouse model of limb ischemia, local inhibition of miR-503 activity accelerated vascular healing and blood flow recovery. Importantly, miR-503 was found up-regulated in muscular biopsies and peripheral blood–derived plasma of diabetic patients with critical limb ischemia. From a therapeutic perspective, manipulation of miR-503 may represent a novel molecular means to foster reparative angiogenesis in diabetic patients. In the diagnostic context, more studies are necessary to determine if miR-503 could be exploited as a biomarker of progressive vascular disease.

Conclusions—Our data suggest miR-503 as a possible therapeutic target in diabetic patients with critical limb ischemia.20

Mechanisms of Tissue Uptake and Retention in Zotarolimus-Coated Balloon Therapy

Summary—Local drug delivery from endovascular balloons investigated decades ago has been rejuvenated with the expectation that issues like thrombosis with drug-eluting stents and late lumen loss with bare metal stents could be avoided. Early failures of heparin-eluting catheters and balloons were attributed to poor retention of hydrophilic drugs, and, indeed, hydrophobic paclitaxel is retained, because it associates with hydrophilic carriers to enhance the transfer from blood to the artery wall and retains when dissociated. It remained unclear, however, whether sirolimus derivatives such as zotarolimus that are efficacious when released from drug-eluting stent but may not use the same transport-enhancing mechanisms as paclitaxel, could demonstrate comparable efficacy when coated on balloons. Our work is the first to describe the mechanisms of zotarolimus-coated balloon therapy by the use of an integrative approach coupling in
Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

Summary—Transcatheter aortic valve implantation has been associated with a higher rate of cerebrovascular events (CVEs) compared with medical treatment or surgical aortic valve replacement. This multicenter study evaluated in a large cohort of consecutive patients (n=1061) the timing, predictors, and clinical impact of CVEs after transcatheter aortic valve implantation. The incidence of 30-day CVEs was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (<24 hours) CVEs were mechanical factors such as further stretching of the valve prosthesis with balloon postdilation (odds ratio, 2.46; \( P = 0.034 \)) and valve dislodgment/embolization (odds ratio, 4.36; \( P = 0.024 \)), whereas subacute (1–30 days) CVEs were determined mainly by the occurrence of atrial arrhythmias (new-onset atrial fibrillation; odds ratio, 2.76; \( P = 0.028 \)). There were no differences in 30-day CVE rate between different types of valves (balloon expandable, self-expandable) or access routes (transfemoral, transapical). The rate of late (>30 days) CVEs was 3.3% (stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (hazard ratio, 2.84; \( P = 0.002 \)), peripheral vascular disease (hazard ratio, 2.02; \( P = 0.043 \)), and prior cerebrovascular disease (hazard ratio, 2.04; \( P = 0.047 \)). The impact of CVEs on mortality was determined mainly by the severity of the event, and only the occurrence of major stroke was independently associated with an increased 30-day (hazard ratio, 7.43; \( P = 0.001 \)) and late cumulative (hazard ratio, 1.75; \( P = 0.034 \)) mortality. These results provide important insights into the pathophysiology and prognosis value of CVEs after transcatheter aortic valve implantation procedures should help to determine the most appropriate therapeutic measures to reduce the high incidence of CVEs associated with transcatheter aortic valve implantation.

Conclusions—In a large cohort of patients undergoing transcatheter aortic valve implantation, the rates of acute and subacute CVEs were 2.7% and 2.4%, respectively. While balloon postdilation and valve dislodgment/embolization were the predictors of acute CVEs, new-onset atrial fibrillation determined a higher risk for subacute events. Late events were determined mainly by a history of chronic atrial fibrillation and peripheral and cerebrovascular disease. The occurrence of major stroke was associated with increased early and late mortality. These results provide important insights for the implementation of preventive measures for CVEs after transcatheter aortic valve implantation.

References


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