Most Important Papers in Peripheral Arterial Disease

The Editors

The following are highlights from the series, Circulation: Cardiovascular Interventions Topic Review. This series summarizes the most important manuscripts, as selected by the editors that have published in the Circulation portfolio. The studies included in this article represent the most noteworthy research in the area of peripheral arterial disease. (Circ Cardiovasc Interv. 2012;5:e39-e44.)

Risk Factors and Prevention

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 antplatelet 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), the authors demonstrate that millions of high risk United States adults with PAD (ankle-brachial index \( \leq 0.90 \)) 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 a 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 United States adults with PAD are not receiving secondary prevention therapies. Treatment with multiple therapies is associated with reduced all-cause mortality.

High-Molecular-Weight and Total Adiponectin Levels and Incident Symptomatic Peripheral Artery Disease in Women: A Prospective Investigation

Summary: Lower-extremity 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 also may 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 \( \geq 45 \) 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 that may reflect a more prominent role of adipokines in peripheral atherosclerosis.

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

Intrinsic Coagulation Activation and the Risk of Arterial Thrombosis in Young Women: Results From the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) Case-Control Study

Summary: Arterial forms of thrombosis are leading causes of death and disability in the Western world. The Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study is a population-based case control study that focuses on arterial thrombosis in young women (18–50 years of age), and has a unique opportunity to identify risk factors that are difficult to identify in older patients because they could be obscured by age-related comorbidities. The identification of these new risk factors could aid in the prevention and treatment of arterial thrombosis in all age groups. This study investigated whether proteins of the intrinsic coagulation pathways are risk factors for arterial thrombosis. Historically, the role of some of these factors was thought to be minor. However, both animal and clinical studies have implicated these proteins in pathophysiological thrombus formation. Furthermore, these proteins also play a role in other relevant biological systems, such as inflammation. Inhibitor complexes of coagulation factors XIIa, Xa, and kallikrein were determined as a measure of protein activation. It was found that these complexes were higher in ischemic stroke cases, but were not higher in myocardial infarction cases when compared with matched controls. The risk of stroke was further increased (up to 23-fold) among

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users of oral contraceptives. However, because of the low incidence of arterial thrombosis in young women, screening for these factors before the start of arterial thrombosis does not seem to be warranted. Further studies should be performed to investigate the exact pathophysiological mechanism and whether these mechanisms are different for the subtypes of arterial thrombosis, especially for subtypes of ischemic stroke.

**Conclusions:** High levels of activated proteins of the intrinsic coagulation system are associated with arterial thrombosis, whereas the strength of these associations differs for myocardial infarction and ischemic stroke. This contradicts similar analyses among men in the Northwick Park Heart Study. Together with the finding that oral contraceptive use further increases the risks, the question of whether the role of intrinsic coagulation proteins in the pathogenesis of arterial thrombosis is sex-specific is raised.³

**Association of Colony-Forming Units With Coronary Artery and Abdominal Aortic Calcification**

**Summary:** Endothelial progenitor cells are made up of circulating cells that originate from the bone marrow and are believed to contribute to arterial homeostasis. Although experimental studies suggest that decreased endothelial progenitor cell quantity may promote atherosclerosis, data in humans are limited. Therefore, among 889 participants of the Framingham Heart Study, the authors examined the association of endothelial progenitor cell-related cell types with the presence of subclinical atherosclerosis as evidenced by coronary artery calcification or abdominal aortic calcification detected by multidetector computed tomography. The authors observed that a lower quantity of colony-forming units was associated significantly with greater coronary artery calcification and abdominal aortic calcification, even after adjustment for cardiovascular risk factors. In contrast, neither the CD34+/KDR⁺ nor CD34⁺ cell type was associated with differences in coronary artery calcification or abdominal aortic calcification. These results are consistent with the theory that colony-forming units and CD34⁺-related cells represent different functional types of endothelial progenitor cells, with likely distinct roles in mediating the vascular response to atherogenic exposures. Overall, these findings suggest that decreased angiogenic potential, as represented by colony-forming unit quantity, could contribute to the development of atherosclerosis in humans.

**Conclusions:** In this large, community-based sample of men and women, a lower colony-forming unit number was associated with a higher burden of subclinical atherosclerosis in the coronary arteries and aorta. Decreased angiogenic potential could contribute to the development of atherosclerosis in humans.⁴

**Renal Microvascular Disease Determines the Responses to Revascularization in Experimental Renovascular Disease**

**Summary:** Percutaneous transluminal renal angioplasty with stenting is technically effective for treating renal artery stenosis; however, the ischemic kidney does not improve or deteriorate in 60% to 70% of patients undergoing these treatments. The reasons behind these relatively poor outcomes are still unknown, but the authors have shown previously that the stenotic kidney undergoes a progressive deterioration of its function paralleled by an evolving intrarenal microvascular damage and loss. Using a well-established swine model of chronic renal artery stenosis, the authors tested the hypothesis that preserving the renal microcirculation in the stenotic kidney will improve the responses to revascularization. They observed that preservation of the renal microvascular architecture and function improved the outcomes of percutaneous transluminal renal angiography, supporting a crucial role of renal microvascular integrity in determining the progression of renal injury in renal artery stenosis and the responses to revascularization.

**Conclusions:** Preservation of the MV architecture and function in the stenotic kidney improved the responses to percutaneous transluminal renal angioplasty, indicating that renal MV integrity plays a role in determining the responses to percutaneous transluminal renal angioplasty. This study indicates that damage and early loss of renal MV is an important determinant of the progression of renal injury in renal artery stenosis and instigates often irreversible damage.⁵

**Periaortic Fat Deposition Is Associated With Peripheral Arterial Disease: The Framingham Heart Study**

**Summary:** Central obesity is associated with peripheral arterial disease, suggesting that ectopic fat depots may be associated with localized diseases of the aorta and lower extremity arteries. The authors hypothesized that persons with greater amounts of periaortic fat are more likely to have clinical peripheral arterial disease and a low ankle-brachial index (ABI). They found that periaortic fat is associated with peripheral arterial disease and low ABI, whereas no association with body mass index, waist circumference, or visceral abdominal fat was observed.

**Conclusions:** Periaortic fat is associated with low ABI and intermittent claudication.⁶

**Superficial Femoral Artery Plaque, the Ankle-Brachial Index, and Leg Symptoms in Peripheral Arterial Disease: The Walking and Leg Circulation Study (WALCS) III**

**Summary:** Among 427 participants with and without lower-extremity PAD, the authors found that lower ankle-brachial index values were associated with greater atherosclerotic plaque and smaller lumen area in the proximal segment of the superficial femoral artery (SFA). Associations remained in the subset of participants with PAD and were independent of age, sex, race, and atherosclerotic disease risk factors. PAD participants who had no exertional leg symptoms (that is, were asymptomatic) had less atherosclerotic plaque and a larger lumen area in the proximal region of the SFA. These findings suggest that SFA plaque and lumen area in the initial segment of the SFA may be surrogates for atherosclerotic disease burden in the lower extremities as measured by the ankle-brachial index.

**Conclusions:** Lower ABI values are associated with greater magnetic resonance imaging (MRI)-measured plaque burden and smaller lumen area in the first 30 mm of the SFA. Compared with PAD participants with claudication, asymptomatic PAD participants have smaller plaque area and larger lumen area in the SFA.⁷

**Abdominal Aortic Aneurysm Growth Predicted by Uptake of Ultrasmall Superparamagnetic Particles of Iron Oxide: A Pilot Study**

**Summary:** Abdominal aortic aneurysm (AAA) rupture is a catastrophic event associated with a very high mortality rate. Patients with known AAA, therefore, are enrolled in a surveillance program involving serial ultrasound scanning to monitor changes in aneurysm diameter, taken as a surrogate for risk of rupture. Patients with an aneurysm >5.5 cm in diameter are perceived to be at high risk and are offered surgical or endovascular aneurysm repair. Although AAA diameter is the best predictor of rupture currently available, up to 20% of ruptured AAA are <5.5 cm. Large studies have shown no mortality benefit for early surgery over continued surveillance in this group of patients. Conversely, many patients have AAA considerably larger than 5.5 cm without rupture. We therefore need an improved method of predicting rupture for individual patients. Rupture is thought to occur in regions of the aortic wall featuring intense inflammation and proteolytic activity. The authors used MRI
with a novel contrast agent consisting of ultrasmall superparamagnetic particles of iron oxide (USPIO) to identify focal inflammation within the aortic wall. The key finding is that USPIO uptake within the aortic wall was associated with a rate of aneurysm expansion (0.66 cm/year) three-fold higher than AAA with no mural USPIO uptake. If confirmed in larger longitudinal studies, these results suggest that USPIO-enhanced MRI may be a more accurate way to predict disease progression than diameter alone in patients with AAA, facilitating selection of patients for preventative surgery.

Conclusions: Uptake of USPIO in abdominal aortic aneurysms identifies cellular inflammation and appears to distinguish those patients with more rapidly progressive abdominal aortic aneurysm expansion. This technique holds major promise as a new method of risk-stratifying patients with abdominal aortic aneurysms that extends beyond the simple anatomic measure of aneurysm diameter.8

Effects of Peripheral Arterial Disease on Outcomes in Advanced Chronic Systolic Heart Failure: A Propensity-Matched Study

Summary: Peripheral arterial disease is a manifestation of systemic atherosclerosis and is associated with poor outcomes. However, little is known about the effect of PAD in patients with heart failure (HF). In this study, the authors demonstrate that the prevalence and the burden of coronary artery disease were high among patients with advanced chronic systolic HF with a history of PAD, and that a history of PAD was associated significantly with an increased risk of mortality and hospitalization in these patients. To determine an independent effect of PAD, they used propensity scores methods to assemble a cohort of patients with HF in which those with and without PAD had similar baseline characteristics, so that any differences in outcomes could be attributed to the presence of PAD. Strong bivariate associations of PAD with major natural history end points suggest that the presence of PAD may be useful as an inexpensive clinical tool to risk-stratify patients with HF who might be at an increased risk for poor outcomes. Strong independent associations of PAD with poor outcomes highlight the importance of prevention and timely detection of PAD, and aggressive treatment of atherothrombotic risk factors in patients with HF.

Conclusions: In a well-balanced propensity-matched population of chronic systolic HF patients, a history of PAD was associated independently with increased mortality and hospitalization.9

Outcomes

Late Outcomes of a Single-Center Experience of 400 Consecutive Thoracic Endovascular Aortic Repairs

Summary: Operative repair of thoracic aortic pathologies is accompanied by significant morbidity and mortality. Thoracic endovascular aortic repair has become a minimally invasive alternative to open repair in anatomically suitable patients. Although the therapy remains indicated primarily for aneurysms and penetrating ulcers, other pathologies, such as traumatic transections and dissections, have been treated successfully after commercial availability of devices and increasing collective experience of endovascular operators. Early outcomes after thoracic endovascular aortic repair have been promising, but to date most published reports involve limited numbers of patients and are restricted to perioperative outcomes with relatively short-term follow-up. This study represents one of the largest single-center, real-world thoracic endovascular aortic repair experiences, spanning nearly a decade of practice. The results showed an overall 30 day/in-hospital mortality of 6.5%, an elective mortality of 2.6%, a stroke rate of 3.0%, and a rate of permanent paraparesis/paraplegia of 4.5%. Survival at 3 years was 60%. The risk of intraoperative surgical conversion was extremely low. The importance of careful case planning and a core multidisciplinary approach cannot be overemphasized. The high rate of late mortality suggests that patients with thoracic aortic diseases may represent a subset whose underlying comorbidities may pose a greater threat to their lives than the aortic disease itself. Perhaps the greatest challenge is not the search for a better widget, but improved patient selection to identify those who will truly benefit from this therapy and those for whom the therapy may represent a futility of care.

Conclusions: Thoracic endovascular aortic repair may be used to treat a variety of thoracic aortic pathologies with a very low risk of intraoperative conversion. Overall rates of mortality and neurological complications were relatively low but significantly increased in emergent repairs. There appeared to be a substantial number of late deaths, which may represent a combination of poor patient selection and treatment failures.10

Incidence and Predictors of Plaque Rupture in the Peripheral Arteries

Summary: This study investigated the incidence and clinical significance of the plaque rupture in the iliofemoral arteries detected by intravascular ultrasound in 101 patients with peripheral artery disease. Overall, plaque rupture of the iliofemoral arteries was detected in 42 of 101 arteries (42%), and a history of acute coronary syndrome and male gender were independent predictors of the plaque rupture. Importantly, major adverse cardiac or cerebrovascular events (death, myocardial infarction, and ischemic stroke) plus peripheral vascular event-free (unplanned vascular intervention and amputation) survival rate was significantly higher in patients with plaque rupture than in patients without plaque rupture (46% versus 21%, P=0.008). By multivariable analysis, plaque rupture and Fontaine stage IV were independent predictors of major adverse cardiac or cerebrovascular events plus peripheral vascular events. Therefore, even in the peripheral arterial territory, plaque rupture in the peripheral arteries is not a rare finding. Furthermore, the presence of plaque rupture in the peripheral arteries may suggest the presence of the coronary and peripheral vascular vulnerability. According to the results, clinicians should consider patients with peripheral arterial disease and plaque rupture as patients at a higher risk, and therefore, aggressive risk factor management may be indicated.

Conclusions: Ruptured plaque of the iliofemoral arteries is a common finding. Patients with plaque rupture had a higher prevalence of history of acute coronary syndrome and lower major adverse cardiac or cerebrovascular events plus peripheral vascular event free survival.11

Vascular Hospitalization Rates and Costs in Patients With Peripheral Artery Disease in the United States

Summary: Patients with PAD constitute a high-risk population with higher rates of polyvascular disease, higher annual cardiovascular event and hospitalization rates, and greater associated costs relative to coronary artery disease or cerebrovascular disease. This study provides an in-depth examination of long-term rates of vascular events, hospitalizations, and revascularization procedures in different PAD subgroups categorized according to symptomatic status and prior diagnostic/treatment history. The study also documents the existence of an iterative pattern of cost accrual related to high rates of recurrent rehospitalizations and repeat revascularization procedures in patients with symptomatic PAD. The high rates of recurring rehospitalizations and revascularization procedures suggest that neither patients, physicians, nor health care systems should assume that an initial lower extremity PAD procedure serves as a permanent resolution of the underlying condition. Cost estimates provided by this study are potential inputs into health economic models aimed at examining the long-term cost implications and cost effectiveness of different treatment options, including secondary cardiovascular risk prevention strategies.
Conclusions: The economic burden of PAD is high. Recurring hospitalizations and repeat revascularization procedures suggest that neither patients, physicians, nor health care systems should assume that a first admission for a lower extremity PAD procedure serves as a permanent resolution of this costly and debilitating condition.\textsuperscript{12}

Medical and Interventional Therapy

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 an exercise program transported to the community setting (ie, home-based walking). However, home exercise has been studied poorly. This prospective, randomized, controlled clinical trial compared changes in claudication onset time, peak walking time, and daily ambulatory activity in peripheral artery disease patients with intermittent claudication after home-based exercise, supervised exercise, and usual-care control. Both exercise programs consisted of intermittent walking to near maximal claudication pain for 12 weeks. The authors used a step activity monitor to address the primary flaw of previous home exercise programs by objectively measuring ambulatory cadence during home exercise sessions. Patients in home-based exercise completed 83\% of their exercise sessions, averaging 42 minutes per session at a cadence of 37 strides per minute, and they increased claudication onset time, peak walking time, and daily ambulatory cadences apart from 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 was greater. The clinical implication is that a home-based exercise program consisting of ambulatory monitoring, biweekly 15-minute meetings with staff, and feedback motivated patients to adhere to the program and may serve as a new model for improving claudication measures in more patients with less effort and fewer resources than a traditional supervised exercise program.

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.\textsuperscript{13}

Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease: Twelve-Month Zilver PTX Randomized Study Results

Summary: Restenosis and loss of patency remain limitations of percutaneous transluminal balloon angioplasty (PTA) and bare metal stents (BMS) in the endovascular management of patients with symptomatic femoropopliteal peripheral artery disease. Data are limited regarding successful use of drug-eluting stents (DES) in the treatment of femoropopliteal artery disease. The Zilver PTX is a randomized study of a paclitaxel-coated, self-expanding nitinol stent (DES) versus PTA and provisional stenting (BMS versus DES) for lesions up to 14 cm long in the above-the-knee femoropopliteal artery. DES in moderate length femoropopliteal lesions resulted in superior outcomes at 12 months compared with PTA and BMS, supporting use in this lesion subset. The results with DES in a broader population of patients with femoropopliteal disease, including lesions longer than 14 cm, could complement the present study.

Conclusions: Femoropopliteal peripheral artery disease treatment with the paclitaxel-eluting stent was associated with superior 12 month outcomes compared with PTA and provisional BMS placement.\textsuperscript{14}

Nitinol Stent Implantation Versus Balloon Angioplasty for Lesions in the Superficial Femoral Artery and Proximal Popliteal Artery: Twelve-Month Results From the RESILIENT Randomized Trial

Summary: There is uncertainty regarding the optimal endovascular treatment strategy for patients with lifestyle-limiting claudication and disease in the superficial femoral artery. Previous clinical trials have demonstrated conflicting data regarding the benefits of stenting compared with balloon angioplasty for lesions in this location. There continue to be concerns about the potential for superficial femoral artery stent fracture. The RESILIENT (Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone In Lesions INVolving The SFA or Proximal Popliteal Artery) trial compared the safety and efficacy of a self-expanding nitinol stent with balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery. In RESILIENT, 206 patients were assigned randomly to stent implantation versus balloon angioplasty (2:1 randomization). Stenoses or occlusions up to 15 cm in length could be treated. The acute angiographic results were better after stenting, and at 12 months, primary patency rate was significantly higher in the stent group. There was a reduced need for target lesion revascularization after stenting. The rate of stent fracture was low (3.1\%), and none of these stent fractures were associated with adverse clinical consequences. In this multicenter, randomized trial, stenting with a self-expanding nitinol stent was superior to balloon angioplasty for moderate-length lesions in the superficial femoral artery and proximal popliteal artery.

Conclusions: In this multicenter trial, primary implantation of a self-expanding nitinol stent for moderate length lesions in the superficial femoral artery and proximal popliteal artery was associated with better acute angiographic results and improved patency compared with balloon angioplasty alone.\textsuperscript{15}

Defining the Optimal Degree of Heparin Anticoagulation for Peripheral Vascular Interventions: Insight From a Large, Regional, Multicenter Registry

Summary: The optimal degree of heparin anticoagulation for peripheral vascular interventions (PVI) has not been defined. Current recommendations have been based empirically on data from the coronary literature. The authors sought to correlate heparin dose and peak procedural activated clotting time with post procedural outcomes in patients undergoing PVI in a regional, multicenter registry. Total heparin dose \( \geq 60 \text{ U/kg} \) and peak activated clotting time \( \geq 250 \text{ seconds} \) were associated with significantly higher rates of post PVI drop in hemoglobin \( \geq 3 \text{ g/DL} \) or transfusion, with no differences in technical or procedural success or thromboembolic complications. These findings suggest that weight-based heparin dosing (initially up to 60 U/kg) with a target activated clotting time of 250 seconds or less may improve outcomes in PVI, with the caveat that an acceptable lower activated clotting time (ACT) threshold is unknown. Our study is important because it establishes an evidence base for the optimal degree of heparin anticoagulation for PVI.

Conclusions: During PVI, higher total heparin dose (\( \geq 60 \text{ U/kg} \)) and peak ACT \( \geq 250 \text{ seconds} \) were predictors of postprocedural transfusion. The high technical and procedural success in all groups suggests that use of weight-based heparin dosing with a target ACT <250 seconds in PVI may minimize the bleeding risk without compromising procedural success or increasing thromboembolic complications.\textsuperscript{16}
**Novel Therapy**

**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 and walking distance, 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.

**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 vascular surgery; 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 degraded rapidly by proteases expressed in ischemic tissues. Therefore, the authors designed novel variants of SDF-1 that are protease resistant. In the present study, they 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 angiogenesis when delivered in a hydrogel of self-assembling peptides, indicating that slow release is necessary for functional improvement. On the basis of this study, the authors 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.

**Autologous Bone-Marrow Mononuclear Cell Implantation Reduces Long-Term Major Amputation Risk in Patients With Critical Limb Ischemia: A Comparison of Atherosclerotic Peripheral Arterial Disease and Buerger Disease**

**Summary:** Preclinical studies and clinical trials have shown that cell therapy, including autologous bone-marrow mononuclear cell (BM-MNC) implantation, improves clinical symptoms and increases collateral vessel formation in patients with PAD. Unfortunately, there have been few studies on the long-term follow-up of clinical symptoms and events, such as major amputation and mortality, and there has been no information on predictors of major amputation with BM-MNC implantation. The authors found that autologous BM-MNC implantation decreased the rate of major amputation in patients with critical limb ischemia (CLI), both patients with atherosclerotic PAD and patients with Buerger disease, compared with that in control patients. After BM-MNC implantation, the amputation-free rate was markedly worse in patients with atherosclerotic PAD than in patients with Buerger disease. Overall, the survival rate was also markedly worse in patients with atherosclerotic PAD than in patients with Buerger disease. The results of this study showed that BM-MNC implantation was an independent predictor of prevention of major amputation and that hemodialysis and diabetes mellitus were independent predictors of major amputation. In the present study, the authors confirmed that BM-MNC implantation is safe and effective in patients with CLI during long follow-up periods. Patients with Buerger disease, but not PAD patients who have diabetes mellitus and are undergoing hemodialysis, are eligible for treatment with BM-MNC implantation. Future large-scale studies with a randomized, double-blinded, and placebo-controlled design are needed to confirm the effects of cell therapy on the clinical symptoms and cardiovascular outcomes in patients with CLI.

**Conclusions:** These findings suggest that BM-MNC implantation is safe and effective in patients with CLI, especially in patients with Buerger disease.

**Intraarterial Administration of Bone Marrow Mononuclear Cells in Patients With Critical Limb Ischemia: A Randomized-Start, Placebo-Controlled Pilot Trial (PROVASA)**

**Summary:** Injection of autologous BM-MNC is a promising therapeutic option in patients with critical limb ischemia, but double-blind, randomized trials are lacking. The present study is the first randomized, placebo-controlled trial showing that intra-arterial BM-MNC administration accelerates wound healing and induces pain reduction until 3 months in patients with critical limb ischemia with stable ulcers, but not in patients with extensive gangrene. Ulcer healing induced by repeated BM-MNC administration significantly correlated with limb salvage. Successful ulcer healing required repeated applications of functionally competent BM-MNC. These exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with critical limb ischemia and stable ulcers.

**Conclusions:** Intra-arterial administration of BM-MNC is safe and feasible and accelerates wound healing in patients without extensive gangrene and impending amputation. These exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with critical limb ischemia and stable ulcers.

**References**

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