IVUS Use in PAD

Executive Summary and Overview of Medical Literature

Intravascular Ultrasound (IVUS) Use in Peripheral Arterial Disease (PAD)

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Executive Summary

At present, angiography is the only universally accepted method for guiding percutaneous peripheral interventional procedures; however, despite providing an accurate roadmap and planar representation of the vessel lumen, angiography provides very little information about the vessel wall or plaque within the vessel. Furthermore, angiography provides limited information on the interaction of endovascular devices with the arterial wall. Intravascular ultrasound (IVUS) is an adjunctive imaging modality that helps guide peripheral vascular interventions by providing multiple parameters, such as luminal cross-sectional measurements and detailed information about lesion morphology (see Figure 1 and Figure 2). In addition to providing real-time diagnostic information, IVUS also may help guide the choice of the appropriate angioplasty technique, provide information that may assist in the delivery of an endovascular device, and help assess effectiveness of the intervention.[11]

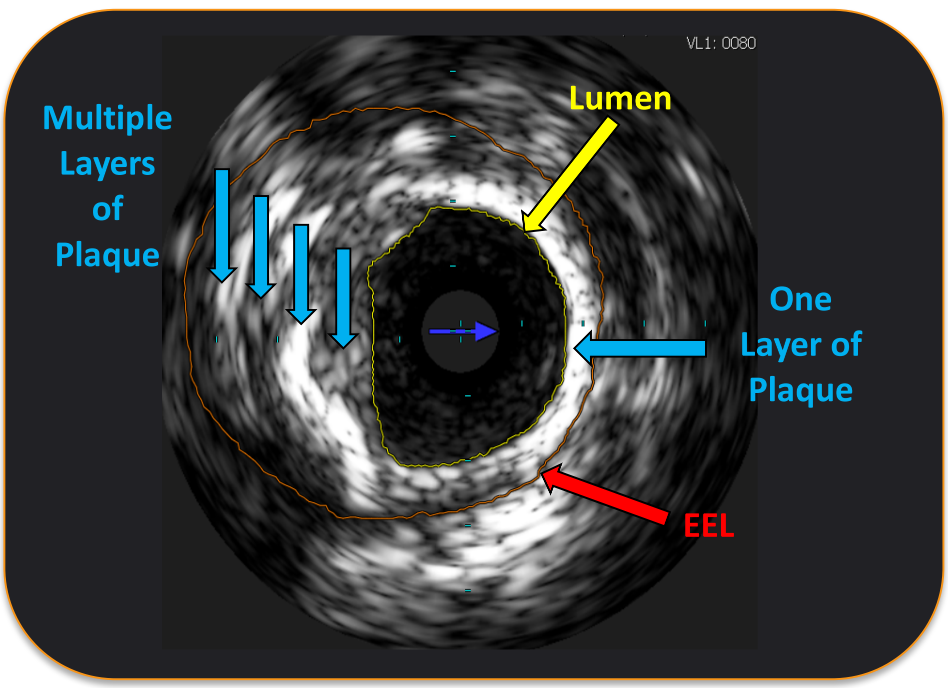

Figure 1. IVUS image of a peripheral artery

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Objective

The intent of this document is to provide background information regarding IVUS imaging in patients with peripheral arterial disease (PAD), to describe outcomes following IVUS-guided percutaneous peripheral interventions compared to those guided by angiography alone, and to present evidence regarding the relationship between PAD vessel sizing and clinical outcomes.

Search Strategy

Publications were identified by searching the MEDLINE database (via PubMed) for articles indexed under the Medical Subject Headings (MeSH) terms "*intravascular ultrasound*, *peripheral arterial disease*, *percutaneous peripheral intervention*, *peripheral vascular disease*" through February 2016. Articles were limited to those published in English that reported on human subjects. The searches were supplemented by manual bibliography review of selected references.

Selection Criteria

All publications were ranked using the Oxford Centre for Evidence Based Medicine method.[1] Clinical trials and case series were included. Several relevant studies were identified based on IVUS use as a diagnostic or therapeutic tool for the evaluation of vessel wall morphology, or for the assessment of adequate stent deployment.

Background: Prevalence, Incidence, and Socioeconomic Impact

Peripheral arterial disease (PAD) encompasses a range of vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiological processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremities. PAD affects ~8.5 million Americans aged ≥40 years and is associated with significant morbidity and mortality. PAD prevalence is higher in older individuals and appears to disproportionately affect African Americans.[2] Lower extremity PAD affects a large proportion of most adult populations worldwide. The prevalence of lower extremity PAD has been defined by a series of epidemiological investigations that have used either claudication as a symptomatic marker of lower extremity PAD, or an abnormal ankle-to-brachial systolic blood pressure ratio to define the population affected.[3]

The clinical manifestations of PAD are a major cause of acute and chronic illness, are associated with decrements in functional capacity and quality of life, cause limb amputation, and increase the risk of death. The systemic nature of the atherosclerotic process also contributes to the development of concomitant disease of the arteries of the heart and the brain. Consequently, patients with PAD often face an associated increased risk of cardiovascular ischemic events such as myocardial infarction (MI), ischemic stroke, and death. Overall, the manifestations of PAD are associated with a substantial personal, social, and economic burden in the United States, Europe, South America, and Asia. PAD is increasingly recognized as a significant health issue worldwide.[3]

Critical limb ischemia (CLI) is defined as limb pain that occurs at rest or impending limb loss that is caused by severe compromise of blood flow to the affected extremity. CLI includes patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity, and is to be distinguished from acute limb ischemia. Unlike individuals with claudication, patients with CLI have resting perfusion that is inadequate to sustain viability in the distal tissue bed. Left untreated, CLI likely will lead to limb amputation within 6 months. Treatment of CLI is dependent on increasing blood flow to the affected extremity to relive pain, heal ischemic ulcerations, and reduce the risk of limb loss. Individuals with minimal or no skin breakdown, or comorbid conditions preventing revascularization, may occasionally be treated with medical therapies in the absence of revascularization. Such therapies are much more likely to be successful when CLI is detected promptly and tissue necrosis is minimal.[3]

Angiography is, at present, the only universally accepted method for guiding percutaneous peripheral interventions. Adjunctive hemodynamic parameters (e.g., pressure gradients and duplex velocity measurements), and complementary imaging modalities (e.g., intravascular ultrasound, angioscopy, and optical coherence tomography) may also help guide procedures.[3]

Traditionally, IVUS imaging has aided in the understanding of coronary artery disease (CAD) and percutaneous coronary intervention. The cross-sectional imaging capabilities of IVUS (adjunctive to contrast angiography) have increased our understanding of the pathophysiology of coronary atherosclerosis, and have facilitated significant refinements in the diagnosis and percutaneous treatment of CAD.[4,5]

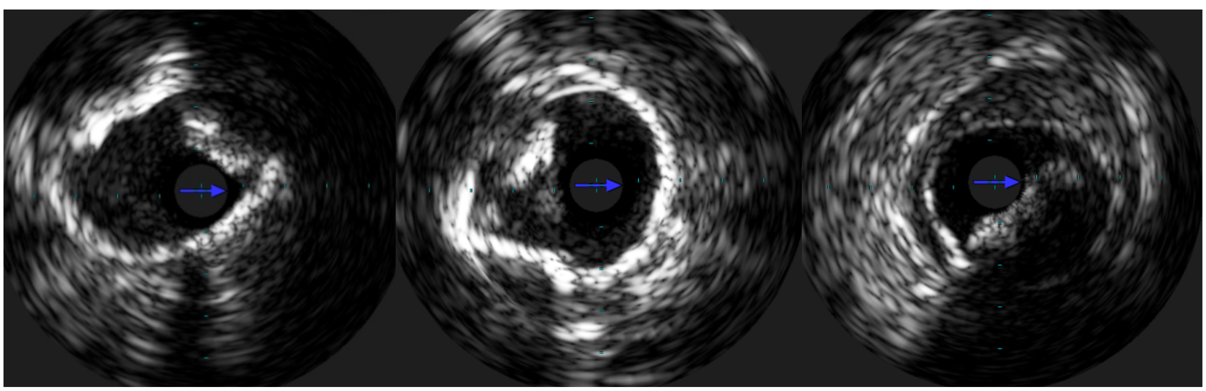

Figure 2. IVUS images of irregular lumens and calcified lesions in peripheral arteries

Despite being the “gold standard” for assessing and quantifying arterial disease, angiography only provides luminography, with little or no information regarding the vessel’s wall, thereby limiting its ability to detect atheroma and determine lesion severity. IVUS provides information about vessel walls and the pathological process taking place in atherosclerosis. Consistently, studies have shown large inter- and intra-observer variability in the assessment of lesion severity based on coronary angiography, even when quantitative coronary angiographic measurements were used.[4] By comparison, IVUS imaging technology has higher spatial resolution (100-200 um compared with 0.15-0.25 mm for angiography), which enables accurate measurement of vessel dimensions and analysis of vessel walls, including plaque burden, calcifications, and fibrotic tissue.[4]

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IVUS is an adjunctive imaging modality that helps guide peripheral vascular interventions because it provides multiple parameters, including luminal cross-sectional measurements and detailed information about lesion morphology. In addition to providing diagnostic information during a procedure, IVUS may also help guide the choice of the appropriate angioplasty technique, provide information that may assist in the delivery of an endovascular device, and help assess effectiveness of the intervention.[11]

Main Results

Successful percutaneous transluminal angioplasty (PTA) of peripheral arterial lesions requires an accurate measurement of the true luminal diameter, assessment of the calcific nature of the plaque, delineation of wall morphology, and the ability to carefully visualize the post-balloon result. IVUS images provide an outline of the luminal and adventitial surfaces of vessel segments and may help discriminate between normal and diseased tissue. In peripheral vessels, studies have shown that angiography-guided stent deployment resulted in incorrect positioning or expansion in as many as 20% to 40% of cases.[11]

Buckley[9] and colleagues reported that utilizing IVUS as an adjunct to iliac angioplasty and stenting improved iliac artery patency rates by defining the appropriate angioplasty diameter endpoint and adequacy of stent deployment. In the group that was treated with both angiographic and IVUS guidance, 20 of 49 patients (41%) were found by IVUS to have underdeployed stents, even though they appeared to be adequately apposed based on angiography. This group (angiography plus IVUS) had a 100% primary patency rate at 3 years, whereas the group of patients treated based on angiography alone had an 82% primary patency rate. There were 4 early failures in the angiography-alone group, and all 4 patients were documented to have underdeployed stents as visualized by IVUS at the time of re-intervention. The authors note that study limitations included retrospective design, fewer observations in the angiography alone group, procedures done with an open femoral artery exposure technique, and that patients in the IVUS plus angiography group were younger. They have been hesitant to pursue a prospective, randomized trial, however, because – in their opinion – "*not using IVUS for angioplasty and stenting procedures would put some of those patients randomized to a non-IVUS evaluation group at a disadvantage.*" Based on this study, the authors concluded that IVUS helped define arterial diameter and adequacy of stent deployment, which was associated with improved long-term patency.[9]

A recently published analysis of the Retrospective Multicenter Analysis for Femoropopliteal stenting (REAL-FP) clinical database by Iida, et al. analyzed data from 1198 limbs (965 patients) with TASC II A-C femoropopliteal lesions (28% CLI) and compared primary patency rates of IVUS vs. non-IVUS guided procedures in 234 propensity score matched pairs. Of the 1198 procedures, IVUS was used in 22% (n=268) and was more likely to be used in cases with more complicated femoropopliteal lesions (e.g., more severe TASC II class, longer lesion length, and narrower reference diameter). Furthermore, analysis of the 234 propensity score-matched pairs (mean follow-up 1.9 ± 1.5 years; 142 events) revealed that IVUS use was associated with higher 5-year primary patency than no IVUS use (65 ± 6% vs 35 ± 6%, p<0.001), and was associated with significantly better assisted primary patency (p<0.001), secondary patency (p=0.004), freedom from any reintervention (p<0.001), freedom from any adverse limb event (p<0.001), and event-free survival (p<0.001).[20]

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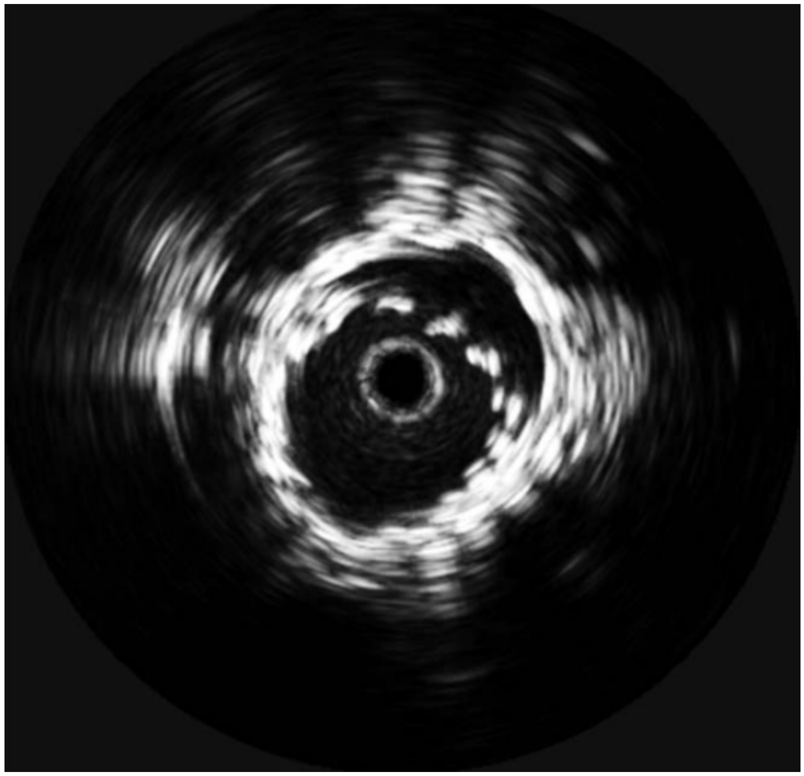

Figure 3. IVUS clearly demonstrates incomplete stent expansion as a separation of the stent from the artery wall[11]

Contrast angiography is essential for the diagnosis and treatment of PAD, but it has significant limitations for evaluating atherosclerotic disease. The disassociation of angiographic findings and histologic analysis has been documented in both coronary and peripheral vascular territories. Autopsy studies in patients who underwent coronary angiography found that 33% had coronary atherosclerosis that was not identified by angiography.[17] A 69 patient study by Kashyap, et al. found that by all parameters, angiographic scoring of atherosclerotic burden underestimated the presence and amount of atherosclerosis in patients with PAD and "normal appearing arteries" on arteriography.[12]

Arthurs, et al. directly compared IVUS measurements to angiography measurements in 93 patients with PAD in a prospective observational analysis. All patients underwent imaging with both angiography and IVUS. When the maximal diameter stenosis from angiography was compared with the maximal area stenosis from IVUS imaging, IVUS-derived data were greater by 10%. Also, when the overall length of plaque stenosis was determined, angiography-derived length of stenoses were 3 mm shorter than IVUS-derived data.[17]

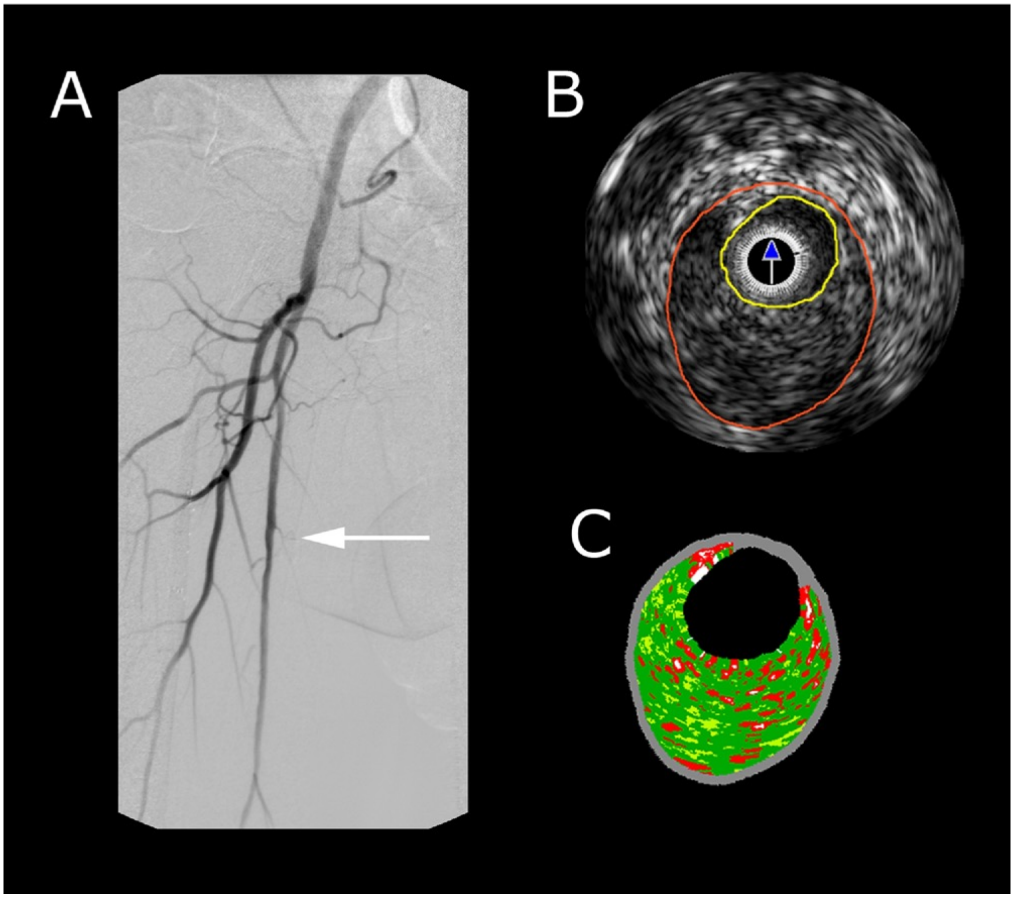

Figure 4. An example of angiographic and intravascular ultrasound (IVUS) analysis is shown. **A**, The *large white arrow* in the angiogram marks the area for analysis. This was interpreted as a 30% stenosis based on the angiogram. **B**, IVUS grey scale imaging through this area is illustrated. The *yellow line* marks the internal elastic lamina, and the *red line* marks the external elastic lamina. By IVUS, this represents a 76% area stenosis. **C**, In this example of Volcano virtual histology (VH) analysis [Note: safety and effectiveness of VH IVUS for use in the characterization of vascular lesions and tissue types has not been established.], the *dark* and *light green shades* denotes fibrous plaque, which accounts for the majority of this lesion, the *red areas* represent necrotic plaque, and *white areas* denote calcium.[17]

Another study by Dangas, et al. of 131 patients evaluated IVUS-guided Palmaz stent implantation in 153 stenotic renal arteries found that, although angiographic success was achieved in all patients, data provided by IVUS suggested the need for additional intervention in 36 cases (23.5%). The data suggested a strong correlation between the angiographic and IVUS measurements of lesion length (r=0.60; p<0.0001) and pre-/post-procedural minimal luminal diameter (r=0.72 and 0.63, respectively; p<0.0001). Based on the results of this study, the authors concluded that IVUS-guided stenting may facilitate safe renal artery revascularization.[8]

A cohort study by Panaich, et al. examined the impact of IVUS utilization during lower limb endovascular interventions in relation to post-procedural complications and amputation in 92,714 patients extracted from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database between the years 2006 and

2011. In total, IVUS was used in 1,299 (1.4%) patients. The authors found that IVUS utilization during lower extremity peripheral vascular procedures was independently predictive of a lower rate of post-procedural complications as well as lower amputation rates without any significant impact on in-hospital mortality. Multivariate analysis also revealed IVUS utilization to be predictive of a non-significant increase in hospitalization costs ($1333, 95% CI -$167 to +$2833, p=0.082).[24]

Kumakura et al. evaluated the 15-year patency and life expectancy in 455 patients who underwent endovascular treatment (EVT) with primary stenting guided by IVUS in 507 iliac artery lesions.[25] Post-procedural mean stent lumen area (MLA), in-stent thrombosis, discontinuation of antiplatelet therapy, and calcified lesions were independent predictors of primary patency. Age, CLI, diabetes mellitus, hemodialysis, and higher D-dimer levels were independent predictors of all-cause mortality after EVT. There were no significant differences among TASC-II categories. The authors concluded that IVUS-guided stenting for the iliac artery had favorable 15-year patency in all TASC categories.[25]

Discussion

IVUS used as an adjunct to angiography has demonstrated enhanced technical outcomes compared to angiography alone in the coronary literature, including use with drug-eluting stents.[4] Several studies have documented an unexpectedly high (approximately 80%) percentage of stents that were incompletely expanded, incompletely apposed, or asymmetrically expanded. These *in vivo* observations lead to high-pressure balloon angioplasty in order to correct these issues during percutaneous coronary interventions. Likewise, IVUS may help facilitate improved technical outcomes in peripheral arterial interventions. Experience in the peripheral arteries highlights the difficulties of determining the extent of disease angiographically, which may lead to incomplete treatment of PAD lesions. Sizing of endovascular devices, balloons, and stents is based upon luminal rather than true vessel diameters and the ability to assess stent expansion, sizing, and apposition is extremely challenging with angiography alone.[6] Results of from the VIPER[22] (Gore Viabahn Endoprosthesis with Heparin Bioactive Surface in the Treatment of Superficial Femoral Artery Obstructive Disease) and SUPERB[23] (Comparison of the Supera® PERipheral System to a Performance Goal Derived From Balloon Angioplasty Clinical Trials in the Superficial Femoral Artery) trials are good examples of inaccurate vessel sizing adversely impacting clinical outcomes during endovascular treatment of PAD. By contrast, recently published[20] retrospective data from a 965 patient clinical registry (REAL-FP) reported statistically significant associations with higher 5-year primary patency, freedom from any reintervention, and event-free survival with IVUS-plus-angiography guided PAD interventions for TASC II A-C femoropopliteal lesions as compared to angiographically guided interventions (without IVUS).

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Conclusion

According to published medical literature, IVUS used as an adjunct to angiography during endovascular peripheral arterial interventions has been associated with better outcomes compared to procedures guided by angiography alone. Angiography provides imaging of the arterial lumen; however, angiographic evaluation of true vessel diameter, luminal area stenosis, plaque concentricity, and calcification may be extremely discordant when compared to IVUS. Additionally – due to its cross-sectional nature – IVUS imaging is capable of more complete visualization of vessel wall and lesion morphology (e.g., dissection, calcium distribution, stent malapposition, medial/adventitial damage) which may identify factors other than luminal narrowing that may affect treatment decisions in real-time. Potential limitations of IVUS use in PAD include acoustic shadowing due to heavily calcified lesions, increased cost and time associated with the use of an additional device, and the training required to become familiar with IVUS image interpretation. Nevertheless, current clinical evidence regarding endovascular treatment of PAD supports a conclusion that IVUS-guided intervention may result in better technical and clinical outcomes than procedures guided by angiography alone.

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Overview of Medical Literature

Peer-reviewed journal articles published between 2000 and February 2016 were identified in MEDLINE (via PubMed). Search terms included: intravascular ultrasound (IVUS), peripheral arterial disease (PAD), percutaneous peripheral intervention, peripheral vascular disease. Articles were restricted to human clinical studies and case series published in English. The searches were supplemented by manual bibliography review of selected references.

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- **2001, Irshad K, et al**: In a report describing early clinical experience with IVUS, 100 peripheral interventions were summarized. The authors concluded that ChromaFlo®-enhanced IVUS shows colorized blood flow inside the vessel lumen, which is helpful in distinguishing echolucent disease from luminal blood flow, and may also be used to perform peripheral interventions in patients with renal failure or contrast allergy while limiting the use of contrast media. When this study was published (2001), it was noted by the authors that IVUS – at the time – was prohibitively expensive for many endovascular specialists, and that evidence from randomized trials on the clinical benefit of IVUS in peripheral interventions would likely be required to prove its cost effectiveness and define its clinical role. [Irshad K, Reid DB, Miller PH, Velu R, Kopchok GE, White RA. Early clinical experience with color three-dimensional intravascular ultrasound in peripheral interventions. *J Endovasc Ther* 2001;8(4):329-38.][7]

- **2001, Dangas G, et al**: In this study, 131 patients underwent IVUS-guided Palmaz stent implantation in 153 stenotic renal arteries at a single center. Angiographic success was achieved in all patients, but IVUS revealed that additional intervention was indicated in 36 (23.5%) cases. There was strong correlation between the angiographic and IVUS measurements of lesion length ($r = 0.60$, $p < 0.0001$) and pre-/post-procedural minimal luminal diameter ($r = 0.72$ and 0.63, respectively; $p < 0.0001$). The authors concluded that IVUS-guided stenting facilitates safe renal artery revascularization, and that IVUS imaging may complement angiography in certain cases, which should be studied further in prospective studies with iodinated or non-iodinated contrast agents. [Dangas G, Laird JR Jr, Mehran R, Lansky AJ, Mintz GS, Leon MB. Intravascular ultrasound-guided renal artery stenting. *J Endovasc Ther* 2001;8(3):238-47.][8]

- **2002, Buckley CJ, et al**: In this study, 71 limbs (52 patients) with symptomatic aortoiliac occlusive disease underwent balloon angioplasty with primary stenting. IVUS and arteriography were used in 49 limbs (36 patients) to evaluate stent deployment. In 40% (20/49) of these limbs, IVUS demonstrated inadequate stent deployment at the time of the index procedure. Kaplan-Meier 3- and 6-year primary patency estimates were 100% and 100% in the IVUS plus angiography group, and 82% and 69%, respectively, in limbs treated without IVUS guidance ($P<0.001$). For all patients (both groups combined), Kaplan-Meier primary patency estimates at 3 and 6 years were 84% and 67%, respectively. They have been hesitant to pursue a prospective, randomized trial, because – in their opinion – "*not using IVUS for angioplasty and stenting procedures would put some of those patients randomized to a non-IVUS evaluation group at a disadvantage.*" Based on this study, they concluded that IVUS helped define arterial diameter and adequacy of stent deployment, which was associated with improved long-term patency. [Buckley CJ, Arko FR, Lee S, Mettauer M, Little D, Atkins M, Manning LG, Patterson DE. Intravascular ultrasound scanning improves long-term patency of iliac lesions treated with balloon angioplasty and primary stenting. *J Vasc Surg* 2002;35(2):316-23.][9]

- **2003, Meissner OA, et al**: In this study of 7 patients with peripheral arterial occlusive disease, 20 femoral arterial segments per patient were examined by high-resolution magnetic resonance imaging (MRI) and IVUS; comparison was possible in 123 of 140 segments. The authors acknowledge that IVUS is the current reference standard for "*quantitative and qualitative evaluation of the vascular wall and lumen in humans*"; hence, IVUS was used as the validation reference in this study. Bland-Altman mean bias in lumen area (LA) was -0.4mm with a precision of ±5.1mm (P=0.062). Vessel area (VA) measurements were moderately correlated (r=0.74; P<0.0001), however a 25% overestimation by MRI relative to IVUS was observed. Vessel wall calcifications were classified with a sensitivity of 91%, a specificity of 93%, and an accuracy of 93%. Study limitations include inability to measure VA with IVUS in almost half of the vessel segments because of extensive vessel wall calcifications leading to dorsal echo extinction; MRI's 25% overestimation of VA may have been related to difficulty in precisely defining the outer vessel boundary with both IVUS and MRI, particularly in atherosclerotic vessel segments. The authors conclude that the MRI protocol used in this study showed high concordance with IVUS, and may have the potential for noninvasive monitoring of femoral arteries. [Meissner OA, Rieger J, Rieber J, Klauss V, Siebert U, Tató F, Pfeifer KJ, Reiser M, Hoffmann U. High-resolution MR imaging of human atherosclerotic femoral arteries in vivo: validation with intravascular ultrasound. *J Vasc Interv Radiol* 2003;14(2 Pt 1):227-31.][10]

- **2006, Lee JT, et al**: In this technological review of IVUS applications in the treatment of peripheral occlusive disease, the authors state that IVUS has been useful in establishing the need for stenting as well as guiding stent deployment for both coronary and peripheral lesions. As vascular interventions become increasingly complex and venture into smaller target vessels, success will be related to the degree of accuracy of the guidance system employed during the procedure. IVUS is an important component of current and future endovascular interventions and should be integrated into training programs and the routine practice of the advanced endovascular surgeon. [Lee JT, Fang TD, White RA. Application of intravascular ultrasound in the treatment of peripheral occlusive disease. *Semin Vasc Surg* 2006;19(3):139-44.][11]

- **2008, Kashyap VS, et al**: In this study, 69 patients with CLI underwent amputation of a lower extremity for severe tissue loss, gangrene, or pedal sepsis precluding limb salvage. Popliteal and tibial vessels were harvested, perfusion-fixed, and analyzed histologically. Thirty-four of these patients had pre-amputation angiography during attempted salvage procedures. Angiograms performed prior to aboveknee (n=9) or below-knee (n=10) amputation revealed 24 stenoses with a mean (±SD) diameter-reducing stenosis of 19.5 ± 15.2%. Corresponding histological cross sections revealed greater linear stenoses measured via boundaries of the internal elastic lamina (IEL stenosis, 28.9 ± 20.2%, p=0.003 versus angiography) or via boundaries of the external elastic membrane (vessel stenosis, 43.1 ± 15.2%, p<0.0001). The authors concluded that angiography provides information on luminal characteristics of peripheral arteries but severely underestimates the extent of atherosclerosis in patients with PAD even in ‘‘normal appearing’’ vessels. [Kashyap VS, Pavkov ML, Bishop PD, Nassoiy SP, Eagleton MJ, Clair DG, Ouriel K. Angiography underestimates peripheral atherosclerosis: lumenography revisited. *J Endovasc Ther* 2008;15(1):117-25.][12]

- **2009, Treitl M, et al**: In this study, thirty patients with untreated superficial femoral artery stenosis underwent digital subtraction angiography (DSA) and IVUS before intervention to determine which angiography-based algorithm delivers the most precise results in comparison with direct measurements with IVUS and evaluate their influence on the resulting balloon size for treatment. They found that mean vessel diameter was 5.7 mm for IVUS, 6.6 mm for caliper calibration, 6.0 mm for calibration of the catheter tip, and 4.7 mm for visual estimation. Selected balloon sizes were 6.0 mm, 7.0 mm, 6.0 mm, and 5.0 mm, respectively. The mean percentage of stenosis was 78.8% for IVUS, 81.6% for caliper calibration, 79.7% for catheter calibration, and 88.8% for visual estimation. This suggests that measurements on DSA equipment calibrated to a catheter tip correlate best with direct IVUS measurements, and that visual estimates may lead to underestimation of the true vessel size and overestimation of stenosis. [Treitl M, Wirth S, Hoffmann U, Korner M, Reiser M, Rieger J. Assessment of the vessel lumen diameter and degree of stenosis in the superficial femoral artery before intervention: comparison of different algorithms. *J Vasc Interv Radiol* 2009;20(2):192-202.][13]

- **2009, Kataoka T, et al**: This study evaluated the relationship between renal arterial structure and vessel remodeling in patients with atherosclerotic renal artery stenosis (RAS), compared with that seen in coronary artery disease (CAD). Gray scale and virtual histology (VH) IVUS was used to assess 23 lesions in 14 consecutive RAS patients and 20 left main trunk lesions in age-matched CAD patients. Remodeling was assessed by means of the remodeling index (RI), which is defined as the vessel area (VA) at the minimum lumen area divided by the reference VA. Positive remodeling was defined as an RI >=1.05, and was present in 15 RAS and 9 CAD lesions. Intermediate/negative remodeling (RI of <1.05) was present in 8 RAS and 11 CAD lesions. The distribution of plaque components (fibrous > fibro-fatty > necrotic core > dense calcium) was similar in both locations. Greater vascular adaptive enlargement was observed in slices with plaque burden <=40% compared with plaque burden >40% (p<0.001 for all). VH analysis showed that the most powerful determinant of adaptive vessel enlargement is dense calcium in RAS (p<0.001), and necrotic core in CAD (p<0.001). Study limitations include small sample size, retrospective analysis, use of manual pullbacks preventing calculation of plaque volumes, and that VH-IVUS lesion types lack histopathological validation in renal arteries. The authors conclude that tissue characterization using VH may provide more insight into the prognosis and natural history of patents with RAS, and into the effect of conventional and emerging treatment modalities for RAS. [Kataoka T, Mathew V, Rubinshtein R, Rihal CS, Lennon R, Lerman LO, Lerman A. Association of plaque composition and vessel remodeling in atherosclerotic renal artery stenosis: a comparison with coronary artery disease. *JACC Cardiovasc Imaging* 2009;2(3):327-38.][14]

- **2009, Leesar MA, et al**: In this study, 62 patients were investigated to compare the accuracy of renal translesional pressure gradients (TPG), intravascular ultrasound (IVUS), and angiographic parameters in predicting hypertension improvement after stenting of renal artery stenosis. TPG (resting and hyperemic systolic gradient [HSG], fractional flow reserve, and mean gradient) were measured by a pressure guidewire; IVUS and angiographic parameters (minimum lumen area and diameter, area stenosis, and diameter stenosis) were measured by quantitative analyses. By odds ratio and receiver-operating characteristic (ROC) curve analyses, TPG and IVUS parameters were superior to angiographic or clinical measures for prediction of blood pressure reduction over 12 months. Study results suggest that an HSG ≥21 mmHg was the best independent predictor of blood pressure improvement after stenting of renal artery stenosis. [Leesar MA, Varma J, Shapira A, Fahsah I, Raza ST, Elghoul Z, Leonard AC, Meganathan K, Ikram S. Prediction of hypertension improvement after stenting of renal artery stenosis: comparative accuracy of translesional pressure gradients, intravascular ultrasound, and angiography. *J Am Coll Cardiol* 2009;53(25):2363-71.][15]

- **2009, Niwamae N, et al**: The objective of this study was to analyze relationships between plaque-morphology classified by IVUS and risk factors in patients with PAD who underwent endovascular treatment between July of 1996 and April of 2004. A total of 203 patients with common (n=98) or external (n=105) iliac artery angiographic stenosis of >=70% were included. Patients with chronic total occlusions and those receiving hemodialysis were excluded. Investigators described 22% of lesions as soft, 18% as fibrous, 32% as calcified, and 28% as mixed; superficial vs. deep calcification was present in 65% and 35%, respectively. The arc of calcium correlated with increasing hemoglobin A1c (HbA1c) and decreasing estimated glomerular filtration rate (eGFR) ($p<0.05$). Associations were found between deep calcification and insulin resistance (odds ratio: 4.4, $p<0.05$); lipid core and hypercholesterolemia (odds ratio: 3.2, $p<0.05$). The odds ratio for an intimal flap was 15.6 times with hypercholesterolemia ($p<0.05$) and 16.9 times with elevated insulin resistance ($p<0.01$). Authors note that a study limitation was use of IVUS technology that did not permit virtual histology (VH). They conclude that iliac arterial calcification was associated with diabetes mellitus, insulin resistance, and eGFR <=60mL/min; also, hypercholesterolemia was associated with detection of soft plaque and intimal flaps. [Niwamae N, Kumakura H, Kanai H, Araki Y, Kasama S, Sumino H, Iehikawa S, Hasegawa A, Kurabayashi M. Intravascular ultrasound analysis of correlation between plaque-morphology and risk factors in peripheral arterial disease. *Ann Vasc Dis* 2009;2(1):27-33.][16]

- **2010, Arthurs ZM, et al**: In this study, 93 patients undergoing angiography for PAD were evaluated in a prospective observational analysis. The authors found that angiographic and IVUS interpretation were similar for luminal diameters, but external vessel diameter was greater by IVUS imaging (7.0 ± 0.7 vs 5.2 ± 0.8 mm, $P<0.05$). The two-dimensional diameter method resulted in a significant correlation for stenosis determination ($r = 0.84$); however, IVUS determination of vessel area stenosis was greater by 10% (95% confidence interval, 0.3 – 21%, $P<0.05$). IVUS imaging indicated that a higher proportion of plaques were concentric. Grading of calcification was moderate to severe in 40% by angiography but in only 7% by IVUS (P<0.05). They concluded that luminal quantitative assessments are very reliable with angiography, but assessment of true vessel diameter, actual area stenosis, plaque concentricity, and calcification are extremely discordant with IVUS imaging. In addition, IVUS imaging offers an objective assessment of plaque morphology. A better understanding of vessel and plaque morphology may identify parameters other than luminal flow-limiting stenoses with which to guide therapeutic approaches to PAD. [Arthurs ZM, Bishop PD, Feiten LE, Eagleton MJ, Clair DG, Kashyap VS. Evaluation of peripheral atherosclerosis: a comparative analysis of angiography and intravascular ultrasound imaging. *J Vasc Surg* 2010;51(4):933-8.][17]

- **2013, Eberhardt KM, et al**: The purpose of this study was to compare optical coherence tomography (OCT) and IVUS imaging in popliteal and infrapopliteal arteries. Patients with non-occlusive femoropopliteal Transatlantic Inter-Society Consensus II (TASC II) A lesions (<10cm in length) and Rutherford category 2 or 3 symptoms were considered for study participation. Enrollment occurred after initial angiography showed patency of all three infrapopliteal vessels. Two hundred forty (240) patients were screened in order to yield 16 study participants in whom 112 arterial segments were evaluated by three observers for image quality, artifact frequency, discriminability of vessel wall layers, and plaque composition. Measurements of lumen, vessel, and plaque areas were compared for both modalities. Intrareader and interreader reproducibility of plaque tissue discrimination (0.88 vs 0.75), overall image quality, and vessel wall layer discriminability were significantly higher for OCT (all P<0.001). Artifact frequency was also higher with OCT, limiting image quality of the tibioperoneal trunk. OCT artifacts decreased with decreasing vessel diameter, and were primarily caused by retrograde blood flow from collateral vessels, which occurs frequently in patients with PAD. Measurements of the lumen and vessel area were comparable for both modalities (correlation >0.9, P<0.001); plaque area measurements differed (correlation 0.8, P<0.01) because OCT underestimated it. OCT scans were more time-consuming than IVUS scans. Fluoroscopy time for placement of the imaging catheter was significantly longer for OCT vs IVUS [404.0 seconds (215-759) vs 237.7 seconds (63-513), P=0.005]; consequently, radiation exposure in terms of dose area product (cGy/cm^2) was significantly higher for OCT vs IVUS [147.8 (46-245) vs 65.1 (43-120), P=0.01]. Low pressure proximal balloon occlusion and 1 mL/s saline flush were used to achieve the bloodlessness required for OCT imaging; as a result, a mean of 305mL (range, 180-510mL) of saline was infused in order to perform OCT. In terms of complications, neither local thrombosis nor distal embolization occurred with either modality; proximal balloon occlusion induced vessel spasm in 2 cases (12.5%) with OCT, but spasm did not occur with IVUS (P=0.09). Study limitations include small sample size and inclusion criteria that restricted the investigation to undiseased vessel segments which limits the clinical utility of these results. [Eberhardt KM, Treitl M, Boesenecker K, Maxien D, Reiser M, Rieger J. Prospective evaluation of optical coherence tomography in lower limb arteries compared with intravascular ultrasound. *J Vasc Interv Radiol* 2013;24(10):1499-508.][18]
- **2013, Kashyap VS, et al**: This was a first-in-man study of endothelial function of the superficial femoral arteries (SFAs) in patients with PAD; it builds upon prior studies of endothelial function in

preclinical models, and in human brachial and coronary arteries. Twenty-five (N=25) patients with PAD requiring lower extremity angiography were enrolled. Endothelial dependent relaxation (EDR) was measured using IVUS and a Doppler Flow wire after the infusion of acetylcholine (Ach). IVUS-derived virtual histology (IVUS-VH) of the same vessel was calculated. Endothelial independent relaxation (EIR) was measured with infusion of nitroglycerin (NTG, 200 ug). Levels of nitric oxide (NOx) and serum metabolites were determined by laboratory analysis. The mean SFA diameter was 5.2 ± 1mm (range, 3.2-6.9mm). EDR increased over baseline for all patients with Ach infusion; diameter and area changes in the diseased SFA were modest and insignificant. Average peak velocity (APV), however, significantly increased 26, 46, and 63% with Ach infusion 10^-6 to 10^-4. Calculations of limb volumetric flow were significantly increased after Ach infusion. Lower extremity NOx levels were slightly lower than systemic venous levels (P=0.04). NTG infusion indicated normal smooth muscle responsiveness (3% diameter, 9% area, and 116% velocity change over baseline). IVUS-VH plaque stratification indicated predominantly fibrous morphology (46%; necrotic core, 29%; calcium, 18%). Atheroma burden was 14.9 ± 5.5 mm^3/cm and did not correlate with endothelial responsiveness. The authors conclude that endothelial function may be measured directly in human lower extremity arteries at sites of vascular disease. Despite extensive atherosclerosis, endothelial function is still intact. These data support the application of regional endothelial-specific biological therapies in patients with PAD. [Kashyap VS, Lakin RO, Feiten LE, Bishop PD, Sarac TP. In vivo assessment of endothelial function in human lower extremity arteries. *J Vasc Surg* 2013;58(5):1259-66.][19]

- **2014, Iida O, et al**: This recently published retrospective study reported on data from 1198 limbs (965 patients) with TASC II A-C femoropopliteal lesions (28% CLI) and compared primary patency rates of IVUS vs. non-IVUS guided procedures in 234 propensity score matched pairs. Of the 1198 procedures, IVUS was used in 22% (n=268) and was more likely to be used in cases with more complicated femoropopliteal lesions (e.g., more severe TASC II class, longer lesion length, and narrower reference diameter). Furthermore, analysis of the 234 propensity score-matched pairs (mean follow-up 1.9±1.5 years; 142 events) revealed that IVUS use was associated with higher 5-year primary patency than without (65 ± 6% vs. 35 ± 6%, p<0.001) and was associated with significantly better assisted primary patency (p<0.001), secondary patency (p=0.004), freedom from any reintervention (p<0.001), freedom from any adverse limb event (p<0.001), and event-free survival (p<0.001). [Iida O, Takahara M, Soga Y, Suzuki K, Hirano K, Kawasaki D, Shintani Y, Suematsu N, Yamaoka T, Nanto S, Uematsu M. Efficacy of intravascular ultrasound in femoropopliteal stenting for peripheral artery disease with TASC II class A to C lesions. *J Endovasc Ther* 2014;21(4):485-92.][20]

- **2015, Hitchner E, et al**: Completion angiography is typically performed to confirm satisfactory outcomes following superficial femoral artery (SFA) angioplasty and/or stenting. Two-dimensional angiography, however, may not accurately reflect the extent of residual stenosis. This prospective study evaluated whether or not IVUS may help with residual disease assessment and procedure outcome. Following endovascular SFA intervention with angioplasty and/or stenting, a completion angiogram was performed to confirm satisfactory results before IVUS evaluation. IVUS-detected maximal residual stenosis, maximal residual lesion volume, and number of non-consecutive post-treatment SFA

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segments with >50% residual stenosis were evaluated. Peri-procedural ankle-brachial indexes (ABIs), SF-36 surveys, and Walking Impairment Questionnaires (WIQs) were also collected. Fifty-nine (N=59) patients with primary SFA disease on diagnostic angiography were included; 33 received angioplasty only, and 26 received angioplasty and stenting. Grayscale IVUS showed that 68% of study patients had >70% residual stenosis after "successful" endovascular interventions were confirmed by angiograms; according to the authors, "*the finding of an overall average residual stenosis of 73.4% following interventions is alarming and underscores the suboptimal device design and treatment modalities currently available.*" The angioplasty only cohort had more non-consecutive areas of >50% residual stenosis (p=0.004), greater residual stenosis (p=0.03), and smaller minimal luminal diameters following treatment (p=0.01) as compared to the angioplasty and stenting cohort. There was no significant difference in ABI between the two groups, and no difference in ABI improvement following intervention. Sixty-four percent (64%) of all patients demonstrated a >0.2 increase in post-intervention ABI. Improvement in ABI at 1 month post-procedure significantly correlated with post-intervention SF-36 survey physical scores (R=0.435, p=0.007). Study limitations include small sample size, limited 6-month follow-up data, inclusion of patients with heterogeneous co-morbidities, nearly half of patients had TASC C or D lesions, 100% male VA study population, and patients were not excluded if they had disease in other arteries (e.g., popliteal or tibial) which may have affected ABI measurements. Despite these limitations, the authors conclude: "*Utilization of IVUS in the SFA is feasible, low-risk, and may provide the operating clinician with information on residual disease of the artery following intervention and further guide intervention. Further investigation is warranted to determine whether IVUS can be used to improve these procedures and predict outcomes.*" [Hitchner E, Zayed M, Varu V, Lee G, Aalami O, Zhou W. A prospective evaluation of using IVUS during percutaneous superficial femoral artery interventions. *Ann Vasc Surg* 2015;29(1):28-33.][21]

- **2015, Panaich SS, et al**: This cohort study examined the impact of intravascular ultrasound (IVUS) utilization during lower limb endovascular interventions as regards post-procedural complications and amputation in 92,714 patients extracted from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database between the years 2006 and 2011. IVUS was used in 1,299 (1.4%) patients. The authors found that IVUS utilization during lower extremity peripheral vascular procedures was independently predictive of a lower rate of post-procedural complications (OR 0.80, 95% CI 0.66 to 0.99, p=0.037) as well as lower amputation rates (OR 0.59, 95% CI 0.45 to 0.77, p<0.001) without any significant impact on in-hospital mortality. Multivariate analysis also revealed IVUS utilization to be predictive of a non-significant increase in hospitalization costs ($1333, 95% CI -$167 to +$2833, p=0.082). [Panaich SS, Arora S, Patel N, Patel NJ, Savani C, Patel A, Thakkar B, Singh V, Patel S, Patel N, Agnihotri K, Bhatt P, Deshmukh A, Gupta V, Attaran RR, Mena CI, Grines CL, Cleman M, Forrest JK, Badheka AO. Intravascular ultrasound in lower extremity peripheral vascular interventions: variation in utilization and impact on in-hospital outcomes from the nationwide inpatient sample (2006-2011). *J Endovasc Ther* 2016;23(1):65-75.][24]

- **2015, Kumakura H, et al**: This study evaluated the 15-year patency and life expectancy after endovascular treatment (EVT) with primary stenting guided by intravascular ultrasound (IVUS) for iliac artery lesions. EVT was performed for 507 lesions in 455 patients with PAD. The 5-, 10-, and 15-year primary and secondary patencies were 89%, 83%, and 75%, respectively, and 92%, 91%, and 91%, respectively. There were no significant differences among TASC-II categories. In Cox multivariate analysis, post-procedural lumen area, in-stent thrombosis, antiplatelet therapy discontinuation, and calcified lesions were independent predictors of primary patency ($p < 0.05$). The overall 5-, 10-, and 15-year survival rates were 82%, 56%, and 40%, respectively. Causes of death were cardiovascular disease (49%), malignancy (23%), and pneumonia (20%). In Cox multivariate analysis, age, critical limb ischemia, diabetes, hemodialysis, and D-dimer level were independent predictors of survival ($p < 0.05$). The 5-, 10-, and 15-year freedom from MACE rates were 71%, 44%, and 25%, respectively. There were no significant differences in overall survival and freedom from MACE or MACLE among TASC-II categories. The authors concluded the 15-year patency was favorable after EVT in patients with PAD. Post-procedural MLA, in-stent thrombosis, discontinuation of antiplatelet therapy, and calcified lesions were independent predictors of primary patency. The 15-year survival rate was more favorable than the reported life expectancy in patients with PAD. Age, CLI, diabetes mellitus, hemodialysis, and higher D-dimer levels were independent predictors of all-cause mortality after EVT. IVUS-guided stenting for the iliac artery had favorable 15-year patency in all TASC categories. Life expectancy after EVT was poor, but stenting is feasible for patients with PAD. [Kumakura H, Kanai H, Araki Y, Hojo Y, Iwasaki T, Ichikawa S. Fifteen-year patency and life expectancy after primary stenting guided by intravascular ultrasound for iliac artery lesions in peripheral arterial disease. *JACC Cardiovasc Interv* 2015;8(14):1893-901][25]

Importance of PAD Vessel Sizing

Although neither trial involved IVUS imaging, the following are examples of how vessel sizing during endovascular treatment of infrainguinal PAD may impact clinical outcomes.

- **2013, Saxon RR, et al**: The VIPER (Gore Viabahn Endoprosthesis with Heparin Bioactive Surface in the Treatment of Superficial Femoral Artery Obstructive Disease) trial was a single-arm, prospective, 11-center study in which 119 limbs (113 patients) underwent femoropopliteal artery (FPA) Viabahn stent graft implantation. Mean lesion length was 19 cm, and 56% of lesions were occlusions. Follow-up evaluations included duplex ultrasonography in all patients, with patency defined as a peak systolic velocity ratio < 2.5. At 12 months, primary and secondary patency rates were 73% and 92%, respectively. The primary patency for devices oversized ≤ 20% at the proximal landing zone was 88%, whereas the primary patency for devices oversized by > 20% was 70% ($P = 0.047$). Primary patency was not significantly affected by device diameter (5 vs 6 vs 7 mm) or lesion length (≤ 20 cm vs > 20 cm). The authors concluded that the Viabahn stent graft provided clinical improvement and a primary patency rate of 73% at 1 year in the treatment of long-segment FPA disease, and that careful sizing of the device relative to vessel landing zones is essential for achieving optimal outcomes.

[Saxon RR, Chervu A, Jones PA, Bajwa TK, Gable DR, Soukas PA, Begg RJ, Adams JG, Ansel GM, Schneider DB, Eichler CM, Rush MJ. Heparin-bonded, expanded polytetrafluoroethylene-lined stent graft in the treatment of femoropopliteal artery disease: 1-year results of the VIPER (Viabahn Endoprosthesis with Heparin Bioactive Surface in the Treatment of Superficial Femoral Artery Obstructive Disease) trial. *J Vasc Interv Radiol* 2013;24(2):165-73.][22]

- **SUPERB Trial** (Comparison of the Supera® PERipheral System to a Performance Goal Derived From Balloon Angioplasty Clinical Trials in the Superficial Femoral Artery): N=264 patients (intention-to-treat) were enrolled in this prospective, multicenter, single arm study. The primary effectiveness endpoint was primary stent patency rate at 12 months. Primary patency was defined as peak systolic velocity ratio (PSVR) < 2.0 at the stented target lesion assessed by duplex ultrasound with no clinically-driven reintervention within the stented segment. Overall, the 12-month primary patency rate was 78.9%. If stents were appropriately sized, however, post-hoc analysis showed that 12-month primary patency was 90.5%. Due to the mechanical properties of the woven Supera stent, oversizing relative to the reference vessel diameter causes elongation. Relative to appropriately sized stents, 12-month primary patency rates were significantly lower if minimal elongation (73.7%, p=0.026), moderate elongation (74.4%, p=0.029), or severe elongation (57.7%, p<0.001) was present. The Supera instructions for use (IFU) includes the statement: "*Physicians should pay careful attention to deploy the stent to the appropriate dimensions to achieve the best possible clinical results*." In addition, an IFU precaution reads: "*The stent should not be oversized > 1mm. The stents are labeled based on the outer stent diameter. Appropriate stent sizing is critical. Choosing a labeled diameter to match the reference vessel diameter, then appropriately preparing the vessel to match that stent's diameter will result in a stent that is properly sized to the vessel.*" [From the Supera® Peripheral Stent System Summary of Safety and Effectiveness Data (SSED), PMA Number P120020, FDA Notice of Approval 28March2014; ClinicalTrials.gov identifier: NCT00933270][23]

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