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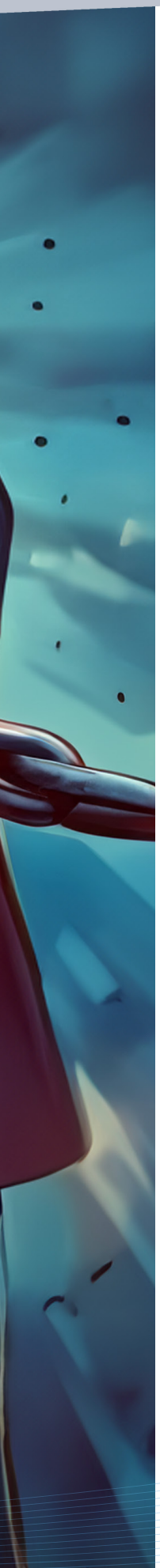
IS BETTER IVUS THE MISSING LINK IN PERIPHERAL VASCULAR DISEASE?

Intravascular ultrasound has been proven to make endovascular interventions safer, and good outcomes more durable, but only a minority of clinicians use it. Two device imaging start-ups—Provisio Medical and Evident Vascular—are innovating to address barriers to the use of IVUS, with an initial focus on peripheral vascular disease, the largest potential endovascular market, and the one most in need because of the complexity of the anatomy and disease.

▶ MARY STUART



In early January 2024, the *Journal of the Society for Cardiovascular Angiography & Interventions* (JSCAI) published a report advocating for the use of intravascular ultrasound (IVUS) in peripheral arterial and deep venous interventions, the work of a multidisciplinary expert round table. Across interventional cardiology, interventional radiology, and vascular surgery, 15 physicians representing six professional societies weighed in on the value of IVUS. This was in recognition of both two decades of evidence that IVUS helps reduce adverse events during percutaneous coronary interventions (PCIs) and contributes to better outcomes, and the significant underutilization of this valuable tool in coronary and peripheral endovascular procedures.

IVUS yields far more information about vessels than conventional angiography, and two-dimensional C-arm fluoroscopy. With a cross-sectional view of the vessel, IVUS is excellent at showing stenosis, plaque burden, plaque morphology, reference vessel diameter, lesion length and eccentricity, dissections, and extrinsic and dynamic compression. It helps clinicians properly size vessels for the correct choice of pre-therapy vessel dilation strategies, stents and angioplasty balloons, to identify suitable landing zones and the presence of calcium that might need removal before stenting, to confirm the apposition of those devices to the vessel walls, and to reveal the not uncommon dissections that encourage restenosis and doom interventions to failure.

In addition, because the use of IVUS cuts down on the need to use angiography and fluoroscopy for vessel sizing, it reduces radiation exposure and minimizes iodinated contrast media, the latter an important benefit for patients with renal impairment.

Speaking with *MedTech Strategist*, the study's lead author, interventional cardiologist Eric A. Secemsky, MD (Beth Israel Deaconess Medical Center and Harvard Medical School) noted, "In the coronary space, with the advent of drug-eluting stents, we see good outcomes for years after our procedures. But we haven't gotten there yet in the peripheral space." Indeed, peripheral vascular disease is a challenging space where vessels vary in diameter and mechanical stresses, and diseased segments are prone to be longer and more calcified. "We have gotten much better at acute technical success, but even with all the amazing technology that has come out, we are still looking for answers to give patients durable outcomes." That's why Secemsky believes IVUS is so important. "We are looking for more tools to augment what we can do for the patient, because we haven't seen the same evolution here as in the coronary space."

In deep venous disease, particularly in the iliofemoral region, where stents are placed to relieve extrinsic compression, IVUS also plays a valuable role in increasing the safety of procedures. "The risks of poor stent placement are much higher in the venous system," says Secemsky, noting that the potential consequences of stent misplacement—embolization to the heart and lungs, and open surgery to address that event—are even less tolerable in younger, otherwise healthy patients with venous disease.

Vascular surgeon Paul Gagne, MD (Vascular Care Connecticut) was among the first investigators to validate the role of IVUS in improving the outcomes of endovascular venous interventions, as lead author on the VIDIO trial published in 2017. The study demonstrated that venous stenting was more successful when IVUS was used to evaluate patients and guide the procedure as compared to venography. Yet, Gagne says, "We still see stents embolizing to the heart and lungs, which means interventionalists aren't getting the information they need from IVUS, because stents are undersized."

According to Gagne, he has often said from the podium, "You can't fix what you can't see." IVUS, he adds, gives clinicians vision that they don't get with angiography.

A preponderance of data, largely on the coronary side, suggests that the advantages associated with using IVUS to guide interventional therapies result in lower rates of periprocedural adverse events and superior long-term clinical outcomes, in part because clinicians have enough information to choose the right treatment for the patient. At the ESC Congress in August 2023, interventional cardiologist Gregg Stone, MD (Icahn School of Medicine at Mount Sinai, New York) presented a meta-analysis of 20 randomized clinical trials to compare results of percutaneous coronary interventions guided by angiography to those guided by intravascular imaging. The study arms were randomized across angiography (5,390 patients), IVUS (3,120 patients), optical coherence tomography (OCT; 2,826 patients), and either IVUS or OCT (1,092

patients). The procedures guided by intravascular imaging benefitted from significant reductions in all the following negative outcomes: target lesion failure (31% reduction), cardiac death (cut by 46%), target lesion revascularization (down by 29%), and stent thrombosis (down by 52%).

From a slightly different perspective another study measured the extent to which IVUS led clinicians to change their pre-procedure treatment plans. A recent randomized, prospective single-center trial (published in the *Journal of the American College of Cardiology* in March 2022, by lead authors R.B. Allan and P.J. Puckridge) studied 150 patients undergoing endovascular intervention in the femoropopliteal artery. Investigators found that the use of IVUS led clinicians to change their pre-procedure treatment plan in 78.9% of cases.

It's clear that when armed with more information about the vessel and disease they're working on, clinicians can achieve better outcomes. There is perhaps an even more compelling need for clarity during peripheral interventions, where both complex anatomy and disease require more insight to provide a precise match between the device therapy and the vessel disease causing the occlusion.

The Valuable Solution Nobody Uses

Despite the fact that IVUS provides rich and relevant information to endovascular clinicians (interventional cardiologists, interventional radiologists, and vascular surgeons), IVUS is used in only 15-17% of endovascular (both coronary and peripheral) procedures in the US.

Moreover, that 15% penetration rate in coronary interventions belies the fact that most coronary or peripheral interventionalists aren't using IVUS. It seems that procedures are concentrated in the hands of a select group of expert clinicians operating at high-volume hospitals, at least according to a statewide (Michigan) registry called BMC2 and a published analysis of usage patterns of intracoronary imaging (which included both IVUS and OCT, although the latter is done to a lesser extent).

The study (by R. Madder, et al., which was published in *Circulation: Cardiovascular Interventions* in March 2022) found that out of 48,872 percutaneous coronary interventions, intracoronary imaging was used in 16.6% of cases. But across the various hospitals in the study, usage varied from none to 75%, and at the physician level, the median rate of IVUS/OCT usage was only 6%. That low penetration rate accords with the SCAI report's findings that median IVUS use across all groups of interventional clinicians is only 5.4%.

That level of intracoronary imaging adoption contrasts strongly with Japan, where IVUS guides 85% of PCI procedures. Is it simply the financial framework of US-based healthcare? Yes, and no. It's true that in the office-based laboratory setting, where there is dedicated reimbursement for IVUS imaging, it is used more. There is a perception that it's not as cost-effective for hospital inpatient procedures reimbursed under the DRG model, but Gagne disagrees. In the inpatient setting, he says, "It is not directly covered, but the payment for the large bundled code is high. The money is there, if there is motivation and dedication to the concept that better patient outcomes are served by having this extra imaging. Cost should not be a barrier."

When Gagne queries surgeons who are new to sites of care that have IVUS and who didn't use it before, they cite lack of timely access to the equipment and knowledgeable staff to run the equipment as reasons why they hadn't used it regularly before. "If it was locked in a closet somewhere and it would take 35-40 minutes to get it, or if nobody knew how to run it, they were just trying to get their work done and move on."

But the previously mentioned SCAI report identifies several other hurdles to adoption, chief among them image quality and difficulty in interpreting the information. Reports Secemsky, "Many physicians say they just don't know what they are looking at." The perception that IVUS increases procedural time is also often mentioned as a barrier to adoption, but the report acknowledges that this is largely a training and workflow issue.

The cost of the current capital-equipment-based systems from market leaders **Boston Scientific** and **Philips** might be a hurdle that prevents IVUS from being available in every cath lab, angiography suite, or operating room that needs it. (In addition to the two large companies that dominate the market, at least three other have hybrid systems that combine IVUS with other modalities—ultrasound, high-resolution optical coherence tomography [OCT], or near infrared spectroscopy, for example—to enable better plaque characterization, including **Terumo Medical**, **Conavi Medical**, and **Nipro**. **Abbott** has placed its intracoronary imaging bet on OCT and machine learning to automate interpretation.)

It is in this context of clinical need and market opportunity that two companies have taken up the charge to create next-generation IVUS systems to finally address the technology's usability. **Provisio Medical**, which was founded by a medtech veteran experienced in intracoronary imaging, has developed a platform called *SLT-IVUS* (*Sonic Lumen Tomography-IVUS*), which, with the ability to be incorporated into a standard support crossing catheter, rapidly and automatically gives clinicians the one of the important metrics for evaluating a diseased vessel: a vessel's flow lumen size.

Evident Vascular has gone back to the drawing board to develop a system designed for the clinical needs of the peripheral vascular interventionalist, with streamlined workflow

and AI/machine learning-enabled image interpretation, to address all the above-stated barriers to adoption.

There is room for both approaches. Notes Gagne, "Provisio is not looking to replace conventional IVUS. It is providing another way of looking at the vasculature with ultrasound to meet the goals of ease-of-use and proper device sizing." Provisio is working hard to take on the barriers to adoption and reach the 80-90% of interventional clinicians who aren't using any IVUS. The start-up aims to make it quick and easy for clinicians to get the information they need.

Others will turn to Evident Vascular's workflow improvements for conventional IVUS, for additional information about the disease. Says Gagne, "If you look at the same interventions with angiography and IVUS, there is a significant incidence of finding flow-limiting disease with IVUS that wasn't obvious on the angiogram." Some of the decision-making revolves around the size of the lumen, and both technologies will be able to determine that. "And for doctors who feel like they want to know what the arterial wall composition is, and you can get some idea of that from conventional IVUS today, Evident will provide that additional information potentially faster and more easily."

While beginning with the greatest medical need in the peripheral space, the platforms of the two companies will also serve coronary and peripheral procedures. The mission that both companies share comes down to democratizing IVUS so that it can be easily adopted by all interventionalists to improve the outcomes of intravascular therapies. As they step into the gap, Provisio's founder and CEO, S. Eric Ryan, MD, notes, "Our largest competitor is non-use."

Evident Vascular: IVUS, Tailor-Made for PVD

Evident Vascular was founded in 2021 by Vensana Capital, which has committed $35 million to the start-up. In its ongoing successful strategy of supporting interventions for the peripheral vascular market, the medtech investor decided this time to create a company from scratch, to fill an unmet diagnostic need in the space.

In the peripheral arterial disease space, the Vensana investment team previously backed TriVascular, which developed a percutaneous endovascular stent graft for abdominal aortic aneurysms (acquired by Endologix); CV Ingenuity and Lutonix, developers of drug-coated balloons for peripheral arterial disease (acquired by Covidien/**Medtronic** and **CR Bard,** respectively); and Intact Vascular, which developed the *Tack* device for the treatment of dissections, with a rare approval for below-the-knee indications (acquired by Philips). In deep venous disease, Vensana's portfolio companies include Vesper Medical, a venous stent that recently presented best-in-class clinical data, which supported FDA approval (acquired by Philips) and **Inari Medical**, a venous thrombectomy that transformed the treatment of venous thrombosis and pulmonary embolism, now publicly-traded with a multi-billion dollar market cap.

Peripheral vascular disease still represents a serious and enormous unmet clinical need. In the US, 8-12 million people suffer from peripheral arterial disease and 900,000 are affected by venous thromboembolisms each year. Justin Klein, MD, JD, managing partner at Vensana, says, "Over a decade ago, we identified peripheral vascular as one of the highest growing segments in the cardiovascular space, and we made a concerted effort to invest in this sector. In doing that, we realized that a lot of dollars were going into therapeutic interventions, but not into the diagnostics necessary to guide appropriate treatment for these procedures."

Vensana identified intravascular ultrasound as a key area of interest in 2019, after talking to key opinion leaders to understand the disconnect between what was clinically necessary to drive good treatment decisions and the actual adoption of IVUS. According to Vensana partner and Evident Vascular board member Cynthia Yee, "We didn't understand why IVUS wasn't more widely adopted," but it came down to the fact that available IVUS systems were created over 25 years ago for coronary use. "From clinicians we heard that those legacy technologies have sub-optimal image quality and workflow for peripheral use," says Yee. "Moreover, those platforms lack the systems hardware and software necessary to take advantage of the growing number of artificial intelligence and machine learning breakthroughs that we believe could transform this category."

Vensana evaluated potential investments in multiple existing private start-ups before ultimately deciding in 2021 to build

a comprehensive next generation IVUS imaging platform that would address the usability equation to bridge the gap.

Going forward with a plan to create a product that meets the needs of peripheral vascular disease, the Vensana team recruited Howard Rosen to run Evident Vascular as its CEO. Rosen was well known to the team as the former VP of marketing and business development for Intact Vascular, the same role he had fulfilled at Vesper Medical.

Figure 2

Major Barriers to Increased Use of IVUS

Limitations of the technology (i.e., imaging quality)
Operator comfort with use and interpretation
Access/cost (i.e., capital needed for technology in catheterization labs/angiography suites/operating rooms)
Additional time required for the integration of IVUS into standard procedures
Further need of evidence supporting its use

Source: "Intravascular Ultrasound Use in Peripheral Arterial and Deep Venous Interventions," E. Secemsky, et al., JSCAI, January 9, 2024

Following a pattern that's typical for device development in the peripheral vascular space, IVUS began with coronary interventions. "Its use in peripheral was originally an afterthought. Yet in terms of the number of cases today, the peripheral market is twice as large as the coronary market," Rosen says.

Looking at an existing but underpenetrated market dominated by just two players, Philips and Boston Scientific, the team saw that one held the greater share of the market with an easier-to use "plug and play" approach, whereas the other competed on the basis of superior image quality. Says Rosen, "Physicians have told our third-party research firm that they don't use IVUS, even though they know it helps patients, because they inherently don't know what they are looking at. Image interpretation is a challenge." Evident Vascular's founders believed it wasn't necessary to sacrifice one advantage for the other.

The company has attracted the right talent to address the imaging and workflow challenges. Technical co-founders include Danielo Piazza, chief product officer, who, among many experiences over a 25-year career in the design and development of software-driven diagnostics and therapy delivery, was VP of software engineering at VytronUS, the developer of an ultrasound-based catheter system for the treatment of atrial fibrillation. He previously led the development of automated diagnostic systems based on OCT at Carl Zeiss Meditec, and earlier had developed ultrasound transducers for Acuson (which became part of **Siemens Ultrasound**). Co-founder Patrick Philips, PhD, chief technology officer, is also steeped in diagnostic imaging for interventional therapies, as the former SVP of engineering and manufacturing at VytronUS, having formerly directed R&D for an IVUS start-up acquired by Volcano (now Philips) and been director of systems engineering and a technical fellow for Acuson.

The thesis for Evident Vascular became, says Rosen, "How do you integrate the strengths of both systems, prioritizing peripheral and then coronary, and effectively address the various workflow challenges encountered by physicians and support staff?" By doing so, the founders of Evident Vascular aim to introduce an innovative solution that will increase adoption, enabling physicians to use IVUS for the benefit of more patients.

Rebuilding From the Ground Up

With the benefit of hindsight and timing, the Evident Vascular team is creating a fundamentally different offering, by "building the data collection and processing power for AI from the start and not as an afterthought, which is a big piece of our strategy," says Rosen. This systems architecture will allow not only real-time processing for streamlined and consistent image interpretation, but also data collection capabilities to inform all future improvements in the platform and medical care itself. Notes Yee, "Imaging informatics is the next chapter of innovation in medicine, catapulting diagnostics into the position of not only informing treatment decisions, but also driving improved clinical outcomes. A lot of the existing systems aren't equipped with the ability to capture large volumes of image data. We are building in the computing power to enable innovation in image interpretation, procedure documentation, and more."

The company also set to work on optimizing catheter performance and all the usability aspects of how interventionalists and their support staff use intravascular imaging. For example, notes Yee, Evident Vascular is optimizing the size, working length and overall handling and deliverability characteristics of a catheter that can potentially reach all the way to the lower third of the ankle, to address below-the-knee lesions. "We address all aspects across the workflow and imaging process, and we feel confident that the solution we are building will provide best-in-class imaging and workflow, contributing to the expansion of the IVUS market," says Rosen.

The company isn't ready to speak about specific solutions for workflow issues, but at a high level, Rosen shares, "We have addressed many of the challenges that exist in the workflow between the physician and the support staff." Today, the workflow is cumbersome, he says. "Clinicians have to stop to use IVUS. To be most effective, the technology must be seamlessly incorporated into the workflow of the procedure." The start-up is proposing some innovative solutions to its scientific advisory board, and, according to Rosen, "they have been well received." And the SAB includes many luminaries in the field, including the previously quoted Eric Secemsky and Paul Gagne.

Currently, clinicians have a number of tools in the peripheral interventional toolbox—atherectomy, drug-coated balloons, cutting/scoring balloons, and intravascular lithotripsy. Decision support around the choice of therapy needs to include knowledge of vessel sizing and of the disease itself—the length, the depth, and the morphology of the plaque. Then it's important to be able to confirm that the therapy has been successful. And in today's financial and legal environments, it is increasingly necessary to support one's interventional choices, notes Rosen. Finally, there will also be cost savings, he says, when, after being educated as to what is going on inside the vessel, clinicians don't have to try out a variety of options before hitting on the most effective one.

Improving the Standard of Care

Rosen anticipates that the company will be able to test its system in animal studies this year. "We are well into our journey." Once it passes that hurdle, the rest of the steps are less challenging than for some other medtech categories. Says Yee, "We were excited about IVUS as an investment opportunity, not only because we saw the clinical need, but also because there is a well-established regulatory pathway and reimbursement, and there are significant clinical tailwinds supporting IVUS in more expanded indications." In terms of regulation, IVUS benefits from a well-established 510(k) pathway. The team has done a great job in the last two years developing the catheters and systems hardware and software, and now we are in the second stage of product development to advance us toward regulatory clearance," Yee explains.

"In light of technology innovations that exist today and advances in imaging capabilities, we recognize the need for improvement. Our aim is to significantly enhance adoption rates by streamlining workflow, improving imaging quality for better interpretation, and integrating AI to simplify the process," says Rosen. "The driving force of Evident Vascular is to address the existing shortcomings and obstacles that are preventing clinicians from utilizing IVUS to its full potential for the benefit of patients." MTS

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