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Providing Evidence for Plaque Excision

Coprincipal investigators James F. McKinsey, MD, and Lawrence A. Garcia, MD, discuss their new clinical trial to study plaque excision in PAD patients.

Initiated in April 2009 by ev3 Inc. (Minneapolis, MN), DEFINITIVE LE (Determination of Effectiveness of SilverHawk Peripheral Plaque Excision System [SilverHawk Device] for the Treatment of Infrainguinal Vessels/Lower Extremities) is the largest study to date to investigate the utility of minimally invasive plaque excision (atherectomy) for peripheral artery disease (PAD) as a frontline therapy. With an expected enrollment of up to 800 patients at 50 sites in the United States and Europe, this prospective, multicenter, single-arm study will evaluate 1-year patency rates in patients with claudication and limb salvage in patients with critical limb ischemia (CLI) after treatment with ev3's catheter-based SilverHawk® Plaque Excision System. Because of the study's unprecedented large scope and hard endpoint with core-laboratory adjudication, it is expected to generate robust data to support the use of plaque excision in a wide variety of PAD patients.

DEFINITIVE LE Coprincipal Investigators James F. McKinsey, MD, Interim Chief of Vascular Surgery of New York Presbyterian Hospital System and the Universities of Columbia and Cornell in New York, and Lawrence A. Garcia, MD, Chief of Interventional Cardiology and Associate Director of Vascular Medicine at St. Elizabeth's Medical Center in Boston, recently discussed key aspects of the study with Mike Ennen, MD, Chief Scientific Officer of the Peripheral Vascular Division for ev3 Inc.

Mike Ennen: *Atherectomy has been criticized for not having data. Is that a fair criticism?*

Dr. McKinsey: I think this question is really about what kind of data. Although many single-center reports have come out, there has not been a prospective, randomized trial comparing atherectomy to surgical bypass or angioplasty and stenting. The difficulty has been finding (a) patients willing to be randomized into that type of trial and (b) experienced investigators who have expertise in both modalities (ie, angioplasty vs atherectomy or bypass vs atherectomy). That being said, we and others have produced large volumes of single-center data looking at duplex-confirmed patency and functional improvement of patients undergoing atherectomy. In one of our series, which was presented at the American Surgical Association[1] and published in the *Annals of Surgery*,[2] we treated more than 570 lesions with follow-up going up to 30 months. We showed excellent primary and secondary patency rates as well as limb salvage for patients undergoing atherectomy. Furthermore, in a prospective, nonrandomized trial of patients with diabetes undergoing angioplasty with bailout stenting versus atherectomy, we showed a statistically significant advantage for atherectomy in the popliteal and

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infrapopliteal region with a *P* value of .001 to .008 compared to PTA.

Mike Ennen: *How does DEFINITIVE LE build on what we know today?*

Dr. Garcia: I think that DEFINITIVE LE may be the first large-scale study that will demonstrate where plaque excision can be used effectively in a wide series of patients. It is really an all-comers study looking at the simple claudicant with mild, moderate, or severe disease and also gleaning a tremendous amount of data for patients with CLI. DEFINITIVE LE is examining patency rates after atherectomy, which is a standard endpoint in peripheral studies, but limb salvage, wound healing, etc., are all critical when dealing with CLI patients with threatened limbs. The rate of wound healing, in particular, is being looked at in this study.

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Mike Ennen: *Dr. McKinsey, this study has an ambitious scope—up to 800 patients at 50 sites on both sides of the ocean. Can you comment on why this study enrolls so many patients from so many sites?*

Dr. McKinsey: One thing you have to consider is the experience and real-life outcomes from this kind of procedure. Having multiple investigators at varying levels of ability will probably give you a very realistic interpretation of what the technology can do; a large series such as DEFINITIVE LE will allow us to go in and actually look at these patients and perform an overall analysis as well as a subset analysis to more closely evaluate specific issues. We will gain more insight into very specific lesions, such as the degree of calcification, total occlusion versus nontotal occlusion, or length of lesion. Another very interesting area that needs to be studied is the comparison of the diabetic and nondiabetic patient population and their outcomes.

Mike Ennen: *DEFINITIVE LE is part of a series of clinical investments being made in SilverHawk. What are the other components, and what are they intended to show?*

Dr. Garcia: The DEFINITIVE group of protocols will cover a number of very important clinical questions ranging from the treatment of calcified lesions to the core performance of SilverHawk to the role of vessel preparation followed by drug delivery. First, the DEFINITIVE Calcium Investigational Device Exemption study is going to look at the use of RockHawk with distal protection using the SpiderFX™ filter. This will give us a very good idea of how we can treat calcific lesions with a plaque-excision type of device. The second step is DEFINITIVE LE, which we are discussing in great depth here. Finally, one of the biggest Achilles' heels of what we do in the SFA from an endovascular perspective has been the durability of the intervention. If you look at some of the stent data, the first year appears very good compared to PTA. However, beyond 1 year, we're seeing quite a bit of restenosis or catch-up compared to PTA, such that your 2-year benefit is lost when compared to that at 1 year. The DEFINITIVE antirestenosis protocol will evaluate plaque excision with an antirestenosis drug in a surrogate angioplasty arm. It allows us to see if vessel preparation with SilverHawk followed by one-time drug delivery will afford any greater benefit to durability compared with no vessel preparation.

Mike Ennen: *Dr. Garcia, in this single-arm study, as opposed to a randomized protocol, what do you think clinicians are looking to see to potentially reconsider the role of plaque excision in their practice?*

Dr. Garcia: I think the grand picture, if you take a 30,000-foot view, is simply the data. A lot of us have been quoting data from single-center studies with smaller patient cohorts—60 patients here, 120 patients there.[3,4] At the end of the day, for an 800-patient study, whether it is single-arm or a randomized clinical trial is really irrelevant; the size of the data subset and the way we obtain and evaluate those results with core laboratory, etc., becomes very important. I believe clinicians, from those who modestly believe in atherectomy or plaque excision to those who absolutely don't believe in atherectomy, will look to this dataset to answer a variety of questions: Does plaque excision work? Is there a sweet spot, if you will, as to where it works best? Are there subgroups in which it works exceedingly well? Are there subgroups in which it doesn't work exceedingly

well? This is the type of data that many clinicians will be very eager to see.

Mike Ennen: *Dr. McKinsey, the study will use a higher peak systolic velocity ratio (PSVR) cutoff of 3.5 for its primary endpoint but with a mechanism to capture any patients with symptomatic degradation. Can you comment on the rationale for that?*

Dr. McKinsey: There are multiple aspects to the decision for using a higher PSVR for endovascular procedures. The original data were extrapolated from duplex velocity ratios found in vein grafts. The investigators were trying to determine which PSVR correlated with an increased probability of vein graft failure. If a vein graft fails, it will occlude throughout its length, and its long-term patency, even if the thrombus is removed and the vein graft repaired, is dramatically decreased compared with a vein graft that is repaired before it can fail. A vein graft is a very compliant structure that allows scanning throughout its length. In the arteries of patients that have undergone an endovascular procedure—whether it be an angioplasty, a stent, or an atherectomy—you will find varying areas that have irregularities within the arterial wall, as well as changes in compliance, such as with a stent or going through a less calcific vessel.

This means that the PSVRs that we have seen in the past are not really borne out to be accurate for endovascular intervention as they were for vein graft. This was further substantiated by a presentation at the 2008 Society of Vascular Surgery (SVS) national meeting and subsequently published following peer review, showing that a PSVR of 3.5 may be more appropriate. This year at the SVS meeting, we will see another discussion of PSVR and how it may actually be more appropriate to have a higher value. In my opinion, the original ratio that was appropriate for vein grafts may not be appropriate for predicting interventional failure or recurrent symptoms after endovascular intervention.

Finally, you have to decide what you're trying to achieve with reintervention. In looking at the whole patient, it may be most important to say, "We're intervening for symptoms." Patients with elevated velocity ratios but who are asymptomatic may not require reintervention. It's the patient who develops symptoms that you should reintervene on.

Mike Ennen: *Dr. Garcia, at last year's Transcatheter Cardiovascular Therapeutics meeting, you spoke about treating diabetic patients, and how our thinking may need to evolve. How will DEFINITIVE LE advance our understanding here?*

Dr. Garcia: Diabetics have a very high proportion of coronary and peripheral arterial disease, and their risk of limb loss is higher than that of patients who do not have diabetes. That is why the DEFINITIVE study is looking specifically at the diabetic population. There have been several kinds of glimpses into diabetics with directional atherectomy and plaque excision. The original TALON (Treating Peripherals With SilverHawk: Outcomes Collection) study, which confirmed plaque excision with the SilverHawk as an effective treatment for patients with significant blockages above and below the knee, showed a fairly good result with diabetics who did just as well with plaque excision. Subsequent studies, both European and more recently the Columbia dataset, suggested that the TALON data were not outliers, and that plaque excision may have a role with diabetics who may respond just as well as nondiabetic patients with PAD. I believe that DEFINITIVE LE will advance our knowledge of the diabetic patient population and whether or not claudicants or CLI patients benefit by this type of therapy. DEFINITIVE LE will also include a substudy focused on protein and gene analysis of the plaque that has the potential to add new insight on the biology of the disease process and the potential differences between diabetics and nondiabetics.

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Mike Ennen: *One of the small substudies ev3 intends to build into DEFINITIVE LE is a treadmill exercise test for claudicants. How does this complement the primary endpoint, and why was it included?*

Dr. McKinsey: Again, you must obtain a functional assessment as well as an anatomic assessment, as you get with ultrasound. Patients with claudication can have

a normal, or near-normal, ankle brachial index (ABI) at rest. It's only when they have the vasodilatation and increased arterial flow that is associated with exercise that they unmask a more significant stenosis. You may get a high ABI at rest that falls dramatically with exercise, such that the resting ABI gives you a misrepresentation of the extent of the disease. When you get both an anatomic assessment with an ultrasound and a functional, real-life assessment by putting patients on a treadmill to see how far they can walk before they have the onset of pain, you are now looking at both variables of the equation: (1) Functionally, is the intervention staying open? (2) Probably more importantly—can we assess, in an objective way, the impact of our intervention so that, with exercise, we have really improved their walking distance? That's really why we're doing this intervention—to improve our patients' ability to walk.

Mike Ennen: *For CLI patients, DEFINITIVE LE will measure limb salvage, but many modalities—be it balloons, stents, or the SilverHawk directional atherectomy device—have reported good numbers in CLI patients in terms of limb salvage. How might the data generated by DEFINITIVE LE help guide treatment for these patients?*

Dr. McKinsey: This is a very interesting question, when you look at how we measure our success. I think that limb salvage for the claudication group is totally irrelevant because you should have 100% limb salvage. For patients with CLI, obviously that is an important endpoint, but it's only one of many endpoints. Despite limb salvage, some of the patients may no longer be functional, because they are bedbound, wheelchair-bound, living in constant pain, or having progression of their gangrene or ulceration. We need to study not only the endpoint of limb salvage but also at the quality of life for our patients. Have they been able to return to some form of meaningful existence? Have they returned to their activities of daily living? Are they living without pain? These are questions that are sometimes lost in just looking at yes or no questions, such as were any limbs lost or not. This is where DEFINITIVE LE will advance our understanding. The study will ask more extensive questions and provide data as to the quality of life for patients. Are their wounds healing, do they no longer have rest pain, and are they enjoying a meaningful and productive life?

Mike Ennen: *Dr. Garcia, atherectomy is now a category of devices, but unlike stents, for example, each device has a very different mechanism of action. Do you think the data generated in this study will eventually be generalized across the category?*

Dr. Garcia: Regardless of how many devices end up being on the market, the one critical part here is that, of the devices that are currently available, not one is similar in its mode of operation to what the SilverHawk does. Its ability to be directionally controlled and to capture its debris in the nosecone is different than the two rotational devices that are currently on the market. First, by the size of the treated artery, there is no good comparison to these devices, and second, in its mechanism of therapy, neither of the other two devices are similar to the SilverHawk.

Once DEFINITIVE LE is presented and published, the generalizability of what we find in DEFINITIVE LE would not probably translate to the other devices that are currently out there because they debulk atheroma in a different manner. That is not to say that debulking may not be the right answer for many things, and would be one generalizable idea. But to generalize what DEFINITIVE LE shows and then translate it to the other alternative or rotational atherectomy devices, I think, would be a stretch that many would not want to take and would not be scientifically valid. ■

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