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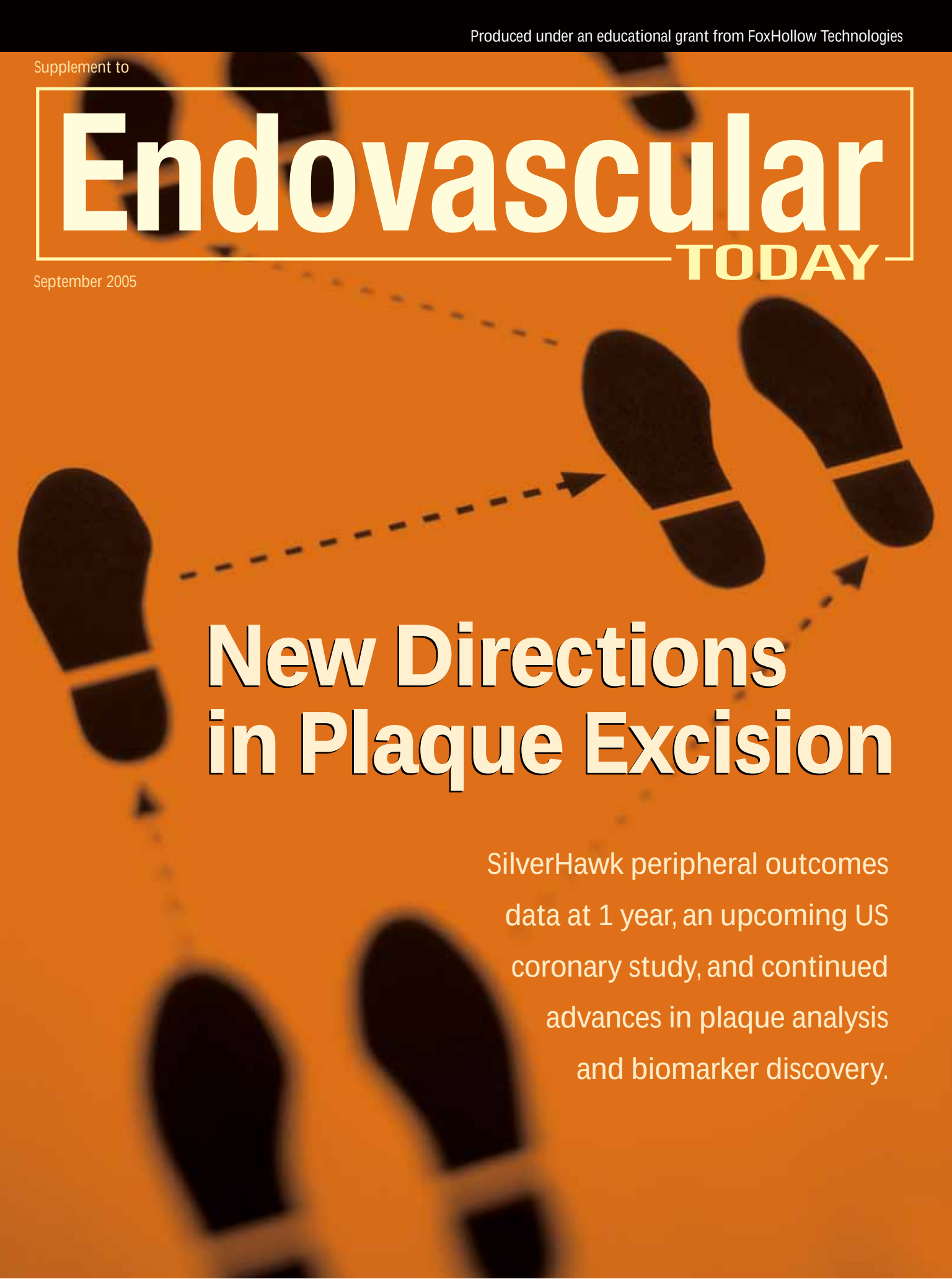

New Directions in Plaque Excision

SilverHawk peripheral outcomes data at 1 year, an upcoming US coronary study, and continued advances in plaque analysis and biomarker discovery.

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In July 2005, the most experienced users of the SilverHawk Plaque Excision System (FoxHollow Technologies, Redwood City, CA) gathered for the second annual SilverHawk Summit. The multi-specialty group shared their clinical experiences and provided insight into real world experiences and the future of plaque excision.

Several physicians presented mid- and long-term single-center outcomes data, as well as an update on the results of the multicenter TALON Registry. The treatment of coronary bifurcation lesions was another focus of discussion, with participants presenting data indicating that this clinical need has yet to be adequately addressed using currently approved devices and techniques. Encouraging case studies and results from a European feasibility study of plaque excision in this setting were shared, as were early US investigational experiences and plans for an upcoming US IDE study called ECLIPSE. Breakout sessions also focused on the ideal designs of next-generation devices intended for possible future applications.

Finally, scientific presentations were given on pharmacogenomic research currently underway using plaque excised with the SilverHawk System. Identifying predictive markers in plaque may help us better understand exactly how an individual patient's genomic and proteomic profile affects how and why cardiovascular disease progresses. This newfound ability to biopsy atherosclerosis real-time offers the possibility of new biomarker discovery that may help accelerate the development of biologically-based drugs and diagnostics.

2005 SILVERHAWK SUMMIT PARTICIPANTS

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Tom Davis, MD	St. John's Medical Center	St. Clair Shores, MI
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Roger Gammon, MD	Heart Hospital of Austin	Austin, TX
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Monica Hunter, MD	The Christ Hospital	Cincinnati, OH
Patricio Ilabaca, MD	Thoracic & Cardiovascular Surgery Association	Memphis, TN
David Joffe, MD	Dayton Heart Hospital	Dayton, OH
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Venkatesh Ramaiah, MD	Arizona Heart Hospital	Phoenix, AZ
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Barry Weinstock, MD	Florida Hospital	Orlando, FL

SilverHawk Outcomes Data

As patients enrolled in single-center studies and the multicenter TALON Registry reach 12-month follow-up, results continue to be consistently favorable.

SINGLE-CENTER OUTCOMES

Beth Israel Deaconess Medical Center
Boston, Massachusetts
Presented by Lawrence A. Garcia, MD

Between August 2003 and December 2004, 103 patients (142 lesions) underwent infrainguinal revascularization using the SilverHawk Plaque Excision System. Ninety-three of the lesions treated were located in the SFA, 40 were infrapopliteal, and nine were in the common femoral artery. Ninety-three of the patients presented with claudication, and 10 had limb-threatening disease and/or ulceration. Standalone plaque excision was performed on 121 of the treated lesions, and adjunctive therapy (PTA and/or stenting, or cryoplasty) was performed on 21 lesions.

One hundred twenty lesions were *de novo*, 22 were restenotic, six were in-stent restenosis cases, and 27 (19%) were total occlusions. The average lesion length was 5.3 cm (SFA, 7.4 cm; infrapopliteal, 3.4 cm). Prior to therapy, the average lesion stenosis was 87%. The average baseline ABI was .67±.02.

The median follow-up period is currently 363 days (range, 6 months to 2 years). Angiographic restenosis was noted in 16 patients (11%) and clinical restenosis (TVR) was noted in 25 patients (17%). Postprocedure, the average ankle-brachial index (ABI) is .84±.03; the average change in ABI is 18%±3.3. The average postprocedural percent stenosis is 9.8% with standalone SilverHawk of 11% and SilverHawk with additional adjunctive therapy of 5.5% ($P<.05$). Minor complications that occurred were two embolizations and two perforations. Deep cut plaque excision not leading to perforation or clear dissection occurred in 16 patients. One of the 10 patients at risk for limb loss has undergone amputation.

The conclusions thus far are (1) plaque excision using the SilverHawk System is reliable and durable for the treatment of infrainguinal atherosclerotic disease; (2) standalone plaque excision appears to limit postprocedure stenosis; and (3) plaque excision may be the default therapy for infrainguinal revascularization.

Memphis Heart Clinic
Memphis, Tennessee
Presented by Stevan I. Himmelstein, MD

Between December 2003 and April 2004, 73 consecutive patients presenting for lower-extremity percutaneous revascularization were treated with the SilverHawk Plaque Excision System. Of this community-based population, 71 patients were claudicants, and multiple vascular disease risk factors were present. One hundred eight lesions in 99 limbs were treated. Most of these lesions (78) were located in the SFA; 11 were popliteal, nine were located in the tibial-peroneal trunk, nine were in the anterior or posterior tibial segments, and one was in the CFA. The average lesion lengths were 7.3 cm in the SFA, 3.0 cm in the popliteal, and 1.9 cm in the infrapopliteal arteries. Lesion characteristics included 67 moderate-to-severe calcifications and 16 total occlusions.

The majority of lesions (95) were treated with SilverHawk alone; nine were treated with and SilverHawk plus PTA, and three were treated with SilverHawk plus PTA and stenting. Postprocedural ABIs improved to .96±.10 (baseline, .72±.13), and percent diameter stenosis improved from 94% preprocedure to 6% postprocedure. Nine complications occurred: one embolization was subsequently treated via surgical bypass; two perforations were treated with prolonged balloon inflations; three out of five dissections were treated with PTA alone, whereas the remaining two were also stented; and one hemorrhage required repair of the puncture site.

Seventy-one patients have been followed to 7.6±4.2 months, and the TLR rate at 12 months is 12%. Dr.

Himmelstein concluded by noting that the majority of patients were treated with SilverHawk plaque excision as a standalone procedure with excellent acute results, 12-month TLR, and a low complication rate.

Cardiovascular Institute of the South
Lafayette, Louisiana
Presented by David E. Allie, MD

From September 2003 to May 2005, 251 limbs and 324 lower-extremity lesions were treated using the SilverHawk Plaque Excision System. The majority of the lesions treated were located in the SFA (252/324); 36 were popliteal lesions, 20 were in the tibial-peroneal trunk or peroneal artery, and 16 were in either the posterior or anterior tibial arteries. Of the 251 limbs treated, 201 were categorized as Rutherford Class 5; Class 3, 4, and 6 disease was noted in 10, 24, and 16 limbs, respectively. Plaque excision was the sole therapy used in 277 of the lesions treated (85%).

A subset of 89 limbs with 102 SFA lesions has reached 12-month follow-up. These cases have been evaluated using either 16- or 64-slice multidetector computed tomography angiography (CTA). The mean lesion length in this subset was 17.6 cm (range, 4-39 cm). At 12 months, the overall SFA primary patency rate is 80%, and the primary assisted patency rate is 94%. The limb salvage rate is 92%. The overall TLR is 13%. In 24 lesions treated for in-stent restenosis, the primary patency rate at 12 months is 83%, and the primary assisted patency rate is 88%.

Dr. Allie emphasized the importance of addressing the large number of amputations being performed on critical limb ischemia patients, many of whom continue to undergo amputation without having an angiographic or ABI evaluation. With current technology such as the SilverHawk system and a multidisciplinary approach—including podiatry and other referring physicians—to treat critical limb ischemia, the majority of these patients can be revascularized and have their limbs salvaged.

Arizona Heart Institute
Phoenix, Arizona
Presented By Venkatesh G. Ramaiah, MD

From June 2003 to January 2005, 386 lesions in 220 patients were treated using the SilverHawk Plaque Excision System. One-year follow-up has been completed in 102 patients with 154 treated lesions. Of the lesions treated and evaluated at 1-year follow-up, 61 were exclusively in the SFA; 43 involved the SFA and at least one additional vessel; 19 were below the knee; 16 were in-stent restenosis cases; and 15 were in either the iliac, renal, profunda, or subclavian arteries.

Of the 104 SFA subset lesions who have completed 1-year follow-up, 65 were associated with claudication (Rutherford-Becker categories 1, 2, and 3), and 39 were associated symptoms of rest pain and tissue loss (Rutherford-Becker categories 4, 5, and 6). Lesion characteristics varied, with 24 categorized as TASC A, 41 as TASC B, 29 as TASC C, and 10 as TASC D. Single-vessel runoff was observed in 44 of the patients, two-vessel runoff in 35, and three-vessel runoff in 25.

Patients were evaluated using Duplex ultrasound, ABIs, and clinical evaluation at 1 month, 3 months, 6 months, and 1 year. Technical success was achieved in 92% of these cases. Standalone plaque excision was performed on 81 of the lesions, with adjunctive treatments administered in 23 (14 PTA alone, nine PTA plus stent placement). The average tissue collected was 140 mg (range, 30-410 mg), and the average length of stay was 1.2 days.

The primary patency of SFA lesions at 1 year was 86% (89/104). Assisted primary patency was 96% (100/104), and secondary patency was 100%. The mean ABI was .68±.01 (baseline, .57±.18). Fifteen patients had restenosis/occlusion at 1 year; two underwent plaque excision with adjunctive PTA, four underwent bypass surgery, and nine were treated with PTA and stenting. There were no incidences of major complications, and six minor complications occurred: two groin hematomas, two cases of renal failure, one pseudoaneurysm, and one perforation.

Dr. Ramaiah concluded that SilverHawk plaque excision can be successfully used to maintain a high degree of patency in the SFA with acceptable durability.

SIX- AND 12-MONTH RESULTS FROM THE TALON REGISTRY

Presented by Roger Gammon, MD
Austin Heart, Austin, Texas

The TALON (Treating PeripherAls with SiLverHawk: Outcomes CollectioN) is a prospective, multicenter, nonrandomized, observational outcomes registry that enrolled consecutive patients undergoing plaque excision for lower-extremity PAD. In addition to demographics, risk factors, and procedure results, TALON collects acute, mid-term (6-month), and long-term (12-month) outcomes data. Tissue and blood samples were also collected from consenting participants.

The endpoints of the TALON Registry are 6- and 12-month TLR. TLR was determined by office visit, chart

review, or telephone call. Investigators reported any percutaneous or surgical procedure that affected the SilverHawk treated lesion as a TLR. As of July 2005, the registry has enrolled more than 700 patients at 21 sites. The results of 601 patients with 882 procedures and 1,258 lesions enrolled before February 28, 2005, are summarized here. The patient population was 59% male and had a mean age of 70 years. Sixty-seven percent had a history of smoking. More than half were diabetics (52%), and 53% had a history of heart disease. Nearly 15% of the treated limbs had CLI (defined as Rutherford Becker score ≥5).

Two or more lesions were treated in 42% of the procedures with a mean SilverHawk time of 28 minutes. Of the lesions treated, 75% were located above the knee, and 25% were below the knee. Moderate-to-severe calcification was present in 65% of treated lesions. Chronic total occlusions comprised 27% of the lesions. Mean lesion length was 7.6 cm for SFA lesions. More than 73% of lesions received standalone SilverHawk treatment. Only 6% of all treated lesions required adjunctive stent placement. In standalone SilverHawk plaque excision cases, a reduction in stenosis of 75% occurred, from a mean of 86% to 11%.

Complications were reported by each TALON investigator. Dissections were classified according to NHLBI (National Heart Lung and Blood Institute) standards. Post-SilverHawk complications were site adjudicated and reported, and included 0.8% major dissection (type C or greater), 0.8% perforation, 0.1% occlusion, and 0.1% embolism.

At 6 months, freedom from TLR was 90%. Mean ABI was .85±.23 (baseline, .70±.23). At 12 months, freedom from TLR was 80%, and mean ABI remained .85±.20.

FUTURE CLINICAL STUDIES DISCUSSION

After presentation of the outcomes data generated to date, the Summit participants engaged in a healthy, comprehensive discussion about the ideal directions and goals of future clinical research. The participants agreed that as with any new technology, continued research is of benefit to both physicians electing to utilize plaque excision and to the patients they treat. The merits and challenges of numerous lower-extremity study designs, most notably randomized studies, were debated at length. Some of the challenges to conducting a randomized study were discussed as follows.

Bypass surgery is considered by some to be the "gold standard" for treating PAD. However, it would be impractical to perform a randomized trial due to the difficulty in getting patients to agree to randomization between open versus endovascular procedures because of the differences in invasiveness between the two procedures. Further, there is no "gold standard" endovascular treatment for the SFA and popliteal arteries. Advocates of stenting in this anatomy have called for randomizing SilverHawk plaque excision against stenting, but this would prove problematic for several reasons. First, there are only two stents with FDA approval for this indication, and neither is routinely used by interventionists who place stents in this anatomy; most elect to use other stents off-label. Were plaque excision to show superiority to either of the approved stents in a randomized study, criticisms would undoubtedly be heard that the reason for this outcome was the inferior stent choice. It is also highly unlikely that regulatory or ethical committees would approve a study comparing an approved therapy to an option that is not approved for the indication being studied. Additionally, recent data on stent fractures questions the utility of this technology to treat patients in an appropriate manner. Finally, similar to plaque excision, stenting itself has not been shown to be a superior treatment in this anatomy by means of a randomized clinical trial. For these reasons, randomization against PTA plus stenting would be of limited evaluative benefit.

Similarly, some interventionists consider standalone PTA to be the gold standard therapy for femoropopliteal disease. However, most physicians would not advocate the use of PTA alone in anything but short, focal lesions, which do not comprise the majority of lesions encountered in the everyday clinical setting.

Because PTA alone or PTA plus stenting in the femoropopliteal arteries have yet to be proven, and most interventionists would not agree to randomize patients against surgical bypass for this indication, the consensus of the Summit participants was that a study randomizing SilverHawk plaque excision against any other available and approved therapeutic option would be extremely limited in its ability to yield conclusive results.

The group did, however, agree on the merits of incorporating additional quantifiable follow-up measures into future studies. Most participants felt that enhancing observational data with duplex ultrasound and/or angiography would be extremely useful in further demonstrating the long-term efficacy of SilverHawk, but that these results could be aptly produced in a nonrandomized setting. Subsequent prospective studies would also include the use of an independent core lab for patency and safety review.

Case Study: Limb-Salvage

Plaque excision from the superficial femoral and tibial-peroneal trunk arteries.

JOHN PAUL RUNYON, MD, FACC
CHRIST HOSPITAL, CINCINNATI, OHIO

CLINICAL HISTORY

An 80-year-old male, former smoker, with a history of CAD, hypercholesterolemia, previous CABG procedure, and previous aortic valve replacement presented with a nonhealing wound and tissue loss on his left great toenail (Figure 1A). His left ankle-brachial index (ABI) was measured as 0.61, and he was classified as Rutherford Becker 5.

PROCEDURE

Angiography in the left lower extremity revealed long, diffuse disease and a 90% stenosis in the distal SFA (Figure 1B), an occluded left anterior tibial artery just distal to the takeoff, and a subtotal occlusion of the left tibial-peroneal trunk artery. Plaque excision with the SilverHawk device was planned for the SFA and tibial-peroneal trunk.

Contralateral access was obtained with a 7-F Pinnacle Destination sheath (Terumo Medical Corporation, Somerset, NJ). A Mailman guidewire (Boston Scientific Corporation, Natick, MA) was passed to lesion areas in the SFA, and a SilverHawk LS catheter was used to excise plaque. Subsequently, plaque was excised from the left tibial-peroneal trunk artery with several passes of the SilverHawk SS catheter.

RESULTS

Immediately after the SilverHawk plaque excision procedure, brisk flow was observed through the left superficial femoral (Figure 1C) and tibial-peroneal trunk arteries. Sixty days after the procedure, the patient's left foot was warm, and regrowth of the great toenail was observed (Figure 1D). The patient is walking daily without leg pain.

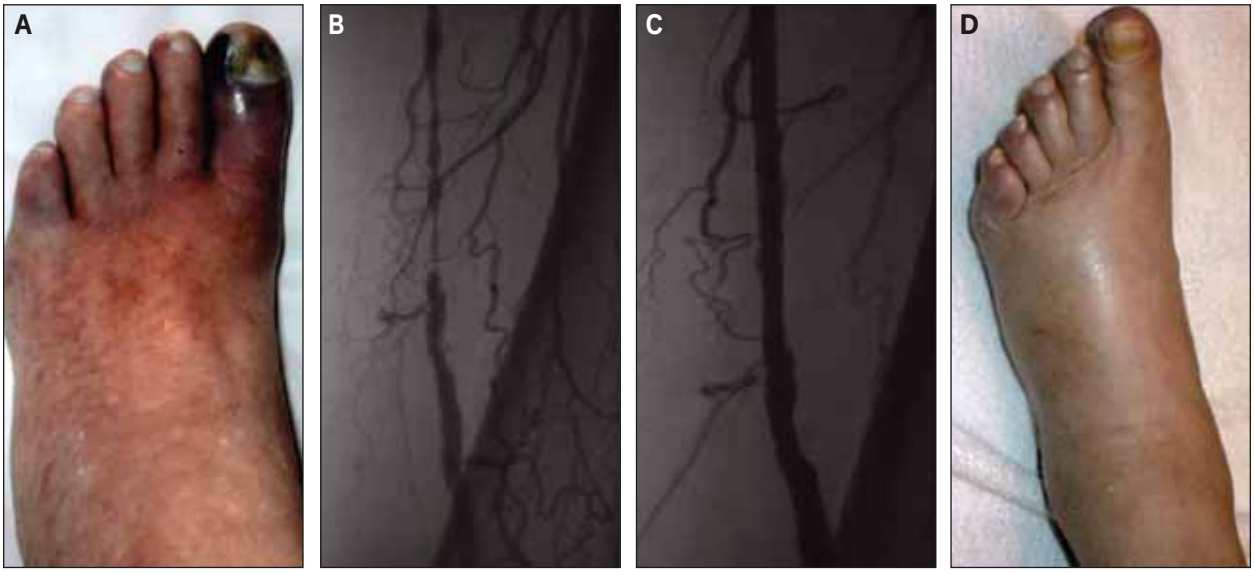

Figure 1. The patient presented with a nonhealing wound and tissue loss on his left great toenail (A). Preprocedural angiography revealed long, diffuse disease and a 90% stenosis in the distal SFA (B). Postprocedurally, brisk flow was observed through the left SFA (C). At 60 days, the patient's left foot was warm, and his great toenail had regrown (D).

Coronary Bifurcation Disease:

An Unmet Clinical Need

A nonstenting option may provide the favorable results that continue to be elusive for stenting in these challenging lesions.

BASED ON PRESENTATIONS BY
DRS. BARRY WEINSTOCK, DAVID KANDZARI, BRUCE CHAMBERS, AND EZIO BRAMUCCI

For most coronary artery lesions, stenting with modern devices—most notably drug-eluting stents (DESs)—has yielded consistently favorable results. Minimal late loss, very low restenosis rates, and single-digit TLR rates have been seen in almost all patient and lesion subsets, including patients with diabetes, *de novo* lesions, long lesions, and small vessels. However, poor results have consistently been seen in one subset—bifurcation lesions.

Bifurcations are most often found on the left anterior descending coronary artery, but they are also common in the left circumflex and right coronary. Proximal segments generally have larger plaque volume than distal segments, but a similar percentage of plaque burden. Plaque accumulates opposite the flow divider in distal segments, and the angle of takeoff of the side branch influences plaque distribution.

Bifurcation disease comprises an estimated 15% to 18% of all coronary lesions.[1] Numerous studies, including the National Heart, Lung, and Blood Institute (NHLBI) Bifurcation Lesion Registry, have shown that currently available treatments yield results that are inferior to those achieved in other coronary lesions.[2] Percutaneous transluminal coronary angioplasty (PTCA) and stenting procedures have also been linked to an increased incidence of adverse events, such as plaque shift and its associated sequelae.[1] PTCA can cause plaque to shift proximally, distally, circumferentially, and longitudinally, and stenting exaggerates this effect. Plaque can shift from the main branch to the side branch and vice versa. This shift can result in severe stenosis of the untreated vessel, which may then be difficult or impossible to rescue.

From July 1997 to February 1998, 2,436 coronary lesion treatments were attempted, 321 (13.2%) of which were bifurcation lesions according to the NHLBI Bifurcation Lesion Registry. The results of this registry, which accepted and evaluated cases using one or more of several different devices (PTCA, rotational atherectomy, and stenting), showed poorer results across several outcome categories for bifurcation lesions versus nonbifurcation lesions: the angiographic success rates 86% and 93%, respectively; the periprocedural myocardial infarction rates were 3.7% and 2.6%, respectively; and the 1-year major adverse cardiac event rates were 32.1% and 25.7%, respectively. The investigators concluded that the treatment of bifurcation lesions remains difficult and is associated with decreased success and increased complication rates compared with nonbifurcation lesions.

In stark contrast to the results seen in treating most coronary artery disease, off-label stenting in bifurcation lesions has been shown to be particularly problematic in the literature. Several of the problems encountered occur regardless of whether the device being placed is a bare-metal stent or a DES; examples include inadequate coverage of the ostium or overlap into the parent vessel during side-branch stenting; stent deformation at the true bifurcation; double layers of metal in the artery after some techniques (eg, stent-crush, culotte); and trauma to the vessel wall(s).

Results from a recent study comparing bare-metal stenting in one branch of a bifurcation lesion versus stenting in both branches favor a single-stent approach, leaving the side branch device-free.[3] Despite lower initial "optimal angiographic success" (87% for single-stent procedures versus 100% for two-stent procedures), at 6-month follow-up, the two-stent group showed higher clinically driven TLR (37.6% vs 5.6%) and more angiographic restenosis (40.6% vs 11%).

CORONARY BIFURCATION LESION CASE STUDY

Performed by Stefan Kiesz, MD, and Pawel Buszman, MD, at the American Heart of Poland

Presentation

A 48-year-old male, former smoker, with a history of diabetes, dyslipidemia, hypertension, a myocardial infarction in 1999, and prior cardiac revascularization presented with stable angina and Canadian Cardiac Society Class II. Preprocedure angiography revealed a *de novo* type III coronary bifurcation lesion involving the mid-left anterior descending (LAD) artery and the second diagonal (Figure 1A).

Procedure and Results

SilverHawk device insertions and cutting passes were made in the mid-left anterior descending (LAD), with the CL catheter decreasing the percent diameter stenosis from 50% to 28%. A CS catheter was then used to treat the second diagonal, reducing the percent diameter stenosis from 78% to 7%. Postprocedure angiography revealed brisk flow within the lesion (Figure 1B). Intravascular ultrasound was performed pre- and postprocedure and confirmed angiographic findings. No complications were reported.

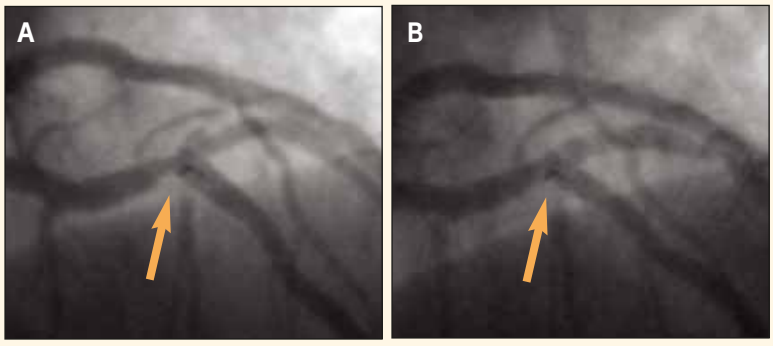

Figure 1. Preprocedure angiography reveals a *de novo* type III coronary bifurcation lesion involving the mid-LAD artery and the second diagonal (A). Postprocedure angiography reveals brisk flow within the lesion (B).

Another recent study randomized patients to undergo either stenting of both branches or stenting of the main branch with provisional stenting of the side branch (note: most side branches were stented due to suboptimal results).[4] The stents used were sirolimus-eluting Cypher stents (Cordis Corporation, a Johnson & Johnson company, Miami, FL). Acute results from this study also showed better angiographic success for lesions treated with two stents (93.6%) versus those treated with one (77.3%). At 6 months, four patients (4.6%) had experienced subacute stent thrombosis, one of whom died suddenly at 4.5 months; all four patients received two stents. Additionally, there was a trend toward higher restenosis rates in patients treated with two stents (28%) versus one (18.7%), although not statistically significant. Most restenoses (14/18) occurred at the ostium of the side branch. The overall TLR at 6 months was 8.2%, and the rate of target vessel failure was 17.6%.

From these and other studies of stenting in coronary bifurcation lesions, it is clear that restenosis and negative outcomes after treatment of bifurcation lesions continue to be a problem unresolved by stenting. There are multiple types of bifurcation lesion anatomies, and many stenting techniques are currently being used to treat them, but none has emerged as clearly the best means of doing so. Compared to nonbifurcation lesions, stenting in bifurcation lesions has been shown to result in increased periprocedural and long-term MACE and higher restenosis rates.

PLAQUE EXCISION OF BIFURCATION LESIONS

Considering the results of these studies, the Summit participants agreed that a new option for treating bifurcation disease is needed, and that a nonstenting option such as plaque excision could play a role in the treatment of these problematic but not uncommon lesions. Drs. Kandzari and Chambers presented the outlines of a new US Investigational Device Exemption study called ECLIPSE, which will examine the safety and efficacy of the SilverHawk plaque excision system in treating Type II and Type III *de novo* or first-time restenotic bifurcation lesions.

The prospective, multicenter, nonrandomized study will be conducted at several US sites. ECLIPSE's endpoints will include angiographic binary restenosis (≥50% diameter stenosis) of the parent vessel or side branch at 6 months after the index procedure, and 30-day and 6-month MACE.

In preparation for ECLIPSE, a five-site European feasibility study using new SilverHawk devices optimized specifically for the challenges of treating bifurcation lesions was conducted. One of the investigators, Dr. Bramucci, presented a number of cases from the feasibility study. Cases at other European sites were also conducted.

1. Lefevre T, Louvard Y, Morice MC, et al. Stenting of bifurcation lesions: a rational approach. J Interv Cardiol. 2001;14:573-585.
2. Al Suwaidi J, Yeh W, Cohen HA, et al. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). Am J Cardiol. 2001;87:1139-1144.
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The Future:

Genomic and Proteomic Research in Plaque

Novel biomarker discovery in plaque may transform the way cardiovascular drugs are developed and prescribed.

BASED ON PRESENTATIONS BY

DRS. EUAN ASHLEY, DAVID KANDZARI, AND BRUCE MURPHY

The paradigm of atherosclerosis pathology and treatment has changed significantly in recent years. Until recently, cholesterol was generally considered the single biggest risk factor, and the medical community placed its focus and that of its patients on lowering cholesterol to reduce risk. Our understanding has incrementally become more sophisticated, with a current emphasis on inflammation, which is in part triggered by cholesterol. The inflammation process can vary significantly in perceived healthy and high-cardiovascular-risk individuals; consequently, the fibrous plaque that results from inflammation can exist in a broad spectrum of varying compositions, ranging from stable to highly unstable.

Many factors cause these variations; some are biological, and others are behavioral or environmental. The nature and degree of influence each has on the disease process remains our biggest unknown, and for this reason has become the current focus of our research. We have come to learn that it is not necessarily the largest plaques that cause infarctions. In fact, some postmortem studies have shown that greater size may cause plaque to be somewhat more stable. Smaller plaques that are soft and fatty, which may not even be seen on angiography, are often those that are more likely to rupture and cause infarction.

It has yet to be determined exactly why one person may be at greater risk for developing a more serious condition than another. Plaques that look the same can have vastly different gene expressions. To compound this uncertainty, approximately half of the people who present with high-risk disease do so by dying suddenly or experiencing a nonfatal myocardial infarction (MI). Many of these patients have stable angina and do not have an elevated low-density lipoprotein level, which according to the old paradigm would indicate they are not at high risk for a fatal MI. Some also exhibit lifestyle factors that clearly put them at higher risk for a cardiac event, such as habitual tobacco use, obesity, and lack of exercise, yet they live into old age without ever requiring cardiac or vascular treatment; other less fortunate individuals, however, live healthy lifestyles characterized by regular exercise and proper diet but die in their early 50s of an MI.

ATTEMPTING TO ADDRESS UNKNOWN NEEDS

The current approach to preventing cardiac events is primarily based on symptom relief and prevention, rather than disease process interruption. The interventional procedures in use today have been developed to treat stable disease, which has successfully saved the lives and limbs of countless individuals. However, although successful in reducing the risk of those patients who have "predictable" risk factors, the current medications and interventional procedures are of little to no benefit to those with hidden risks. For patients who suffer sudden fatal or serious events, this approach to disease management does not address the problem early enough, because for them, the event is the first warning sign.

Based on these unpredictable phenomena and the likely existence of as yet unknown cardiovascular risk factors, some researchers have shifted their focus to determining possible genetic determinants and biomarkers for athero-

sclerotic disease. At present, little is known regarding the genomic and proteomic differences among individuals and their effects on cardiovascular health and response to treatment. Research has shown that the potential influence of possible inflammatory markers such as C-reactive protein (CRP), and this work is a significant step in the right direction. However, CRP research requires large cohorts to demonstrate small effects. The goal of recent and ongoing study is to identify biomarkers that are sensitive and specific in their ability to indicate which individuals are truly at risk. It is believed that this discovery could help to meet the urgent need for therapeutics that will act with immediacy to halt the disease process (as it is currently understood) in the vessel wall.

RECENT RESEARCH

Part of the reason these biomarkers have not been identified previously has been the inability to access real-time atherosclerosis, such as has been done in researching the nature of cancer via tumor biopsies. Recent research conducted with explanted hearts has shown a great deal. Researchers at Stanford University worked on-call with a heart transplant team, and within 1 hour of harvest would dissect the coronary arteries microscopically. The arteries were then inspected under a light microscope and removed for histology. Material was flash-frozen in liquid nitrogen with patient data recorded. Micro-array experiments were then conducted, with their results illustrated in the form of heat maps, which show much data in a single place that is easy to view and interpret (Figure 1). These heat maps can identify differences in gene expression patterns across multiple genes and samples. In simple terms, low gene expression is indicated as green, and high expression is indicated as red.

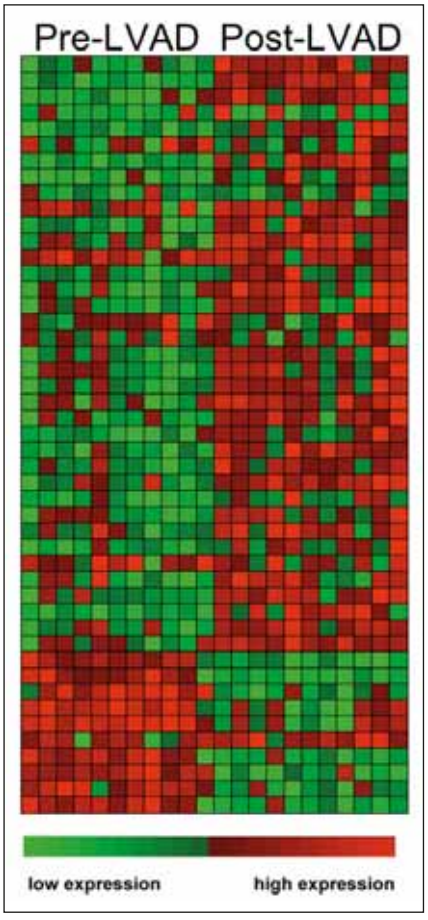

Figure 1. Heat map example showing differential gene expression patterns in pre-LVAD versus post-LVAD subjects.

Current research has shown differences between diabetic and nondiabetic groups and within patients on various medications. Although further research is needed and is ongoing, it is evident from these studies that genetics plays a fundamental role in determining the nature of an individual's specific disease. Hypertension is commonly treated using ACE-inhibitors, although the exact means by which these drugs are effective is not known. However, similar studies evaluating the inflammatory profiles of patients on ACE-inhibitors indicate that these drugs are also working by interrupting the inflammatory process at the molecular level, a process that had previously not been shown and that may indicate a possible reason for their efficacy. These and other findings have been accepted for upcoming publication in peer-reviewed journals.

OBTAINING REAL-TIME SAMPLES

Although of substantial value, heart explant studies have been limited by the presence of end-stage heart failure and high levels of circulating inflammatory markers. Also, the research is essentially frozen in time because there is no possibility for patient follow-up and future analysis. In order to conduct continuing studies, a system for extracting cardiovascular tissue in intact vessels and living patients is necessary. Using samples gathered with the SilverHawk Plaque Excision System, this research has recently become possible and is already underway at Duke University and Stanford University. In addition to its immediate therapeutic benefit, plaque excision can also serve as a method for generating a molecular phenotype for disease, independent of environment. This will likely enable the identification of genes possessing discriminatory capabilities that strongly indicate potential roles in atherosclerosis.

It is believed that working with these real-time samples from living patients can open an entirely new realm of possibilities for transforming discovery and development pathways for drugs that are more patient-specific, based on genomic and proteomic phenotypes. The ability to obtain and analyze the biomarkers found in the plaque of a living patient and observe outcomes with ongoing follow-up will likely prove to be of unparalleled benefit.

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