Even the greatest advances in medicine have their drawbacks. Take vascular disease. Interventional cardiologists today are asked to treat far more rigid, resistant plaque than they did three decades ago. Todd Brinton, MD, an interventional cardiologist at Stanford University Medical Center and the Veterans Affairs Palo Alto Healthcare System, says, “These days we don’t see the kind of soft thrombus lesions that Andreas Gruentzig described when he developed angioplasty.” The advent of drugs (such as statins), stenting, and angioplasty are enabling people to live longer lives. But this gives calcified plaque – hard as concrete and as difficult to remove – time to form along vessel walls, making them stiff and immobile. Interventionalists must get in there with devices to drill, sand, or shave off the plaque. Says Brinton, “We are basically using tools from the late 1970s to treat modern-day disease.”

The longer lifespans – coupled with our changing lifestyles – also give rise to metabolic syndrome, type 2 diabetes, and chronic kidney disease, contributing to an increase in the number of patients who have calcified plaque in their arteries. On the coronary side, there were 1.1 million percutaneous coronary interventions in 2012, and 38% of them likely involved moderate to severe levels of calcified plaque, according to “Patterns of Calcification in Coronary Artery Disease,” in the April 1995 journal Circulation.

Unmet needs in peripheral vascular disease are also driving the demand for atherectomy devices, specialized balloons, and other lesion debulking tools, particularly because the peripheral vascular system is even more prone to calcified plaque, in long, diffuse lesions in vessels where stenting should be avoided. Half of patients undergoing peripheral revascularization have calcified arteries, and the proportion of patients with calcified plaque below the knee is even higher. (See Exhibit 1.) Ten to twelve million people in the US suffer from peripheral artery disease. One million of them have critical limb ischemia (CLI), and within one year of diagnosis, 30% of patients with CLI will undergo an amputation and 25% will die. Atherectomy and other calcium ablation modalities have an important role to play in avoiding amputations.

Shockwave Medical is the newest company searching for a trauma-free way to treat calcified vascular plaque, the enemy of durable success following angioplasty and stenting.

Even the greatest advances in medicine have their drawbacks.
valvular leaks after the implantation of transcatheter aortic heart valves. These unmet clinical needs are opening doors for companies with technologies and tools that can prepare the diseased tissue for the best therapy or even become stand-alone therapies.

However, in order for use of calcium debulking tools to grow beyond the levels seen today, the devices will have to be much more benign than most of the existing products, which can cause adverse events such as vessel perforation and trauma to vessels, leading to late loss.

That’s the opportunity that Shockwave Medical Inc. has set its sights on. Co-founded by Daniel Hawkins, John Adams and Brinton, Shockwave Medical has developed a low-pressure lithotripsy-emitting balloon with a mechanism of action that is specific for calcium.

Shockwave hopes to crack open a market that will expand significantly as clinicians working with drug-eluting balloons, bioresorbable scaffolds, and transcatheter heart valves seek to better prepare vessels for therapeutic intervention or take an entirely new direction with a stand-alone therapy for these patients.

MECHANISM MATTERS

Today, clinicians have several options for debulking or scoring calcium — a variety of specialized angioplasty balloons and atherectomy devices — and they all have different mechanisms of action. (See Exhibit 2.)

Standard balloon angioplasty uses high inflation pressures to try to dilate calcified arteries, but runs the risk of dissecting arteries, in which case bail-out stenting is required.

There are several atherectomy devices on the market. Boston Scientific Corp.’s Rotablator, for example, is a rotational atherectomy device, sends calcified plaque circumferentially. Covidien PLC’s TurboHawk is a directional atherectomy device that cuts plaque with rotating blades in a forward fashion. Spectranetics Corp. sells Turbo Elite, an excimer laser that vaporizes plaque. It’s questionable, however, whether any of the existing options for debulking calcified plaque are benign enough to see wider use. Balloons, as noted, can result in vessel dissection and cause injury by overstretching the vessel. Atherectomy devices aren’t used in large volumes because it takes time and expertise for clinicians to use them safely and consistently; inadvertent vessel perforation is one of the risks of such devices.

Many of the devices damage vessels in various ways — they cause thermal injury, or destroy the endothelium or internal elastic lamina — and this damage ultimately leads to high target-lesion revascularization (TLR) rates, which apply to most of the current interventions. Says Brinton, “We seem to be surprised by the fact that the vessel scars and is prone to restenosis, when that is defined by the amount of trauma we cause in the vessel. Then we spend time using stents, drug-eluting stents, and balloons to fix what we did in the first part of the procedure.”

According to a presentation made at the Transcatheter Cardiovascular Therapeutics conference in October 2013 by Jeff Chambers, MD, an interventional cardiologist with the Metropolitan Heart and Vascular Institute in Minneapolis, MN (and a principal investigator for Cardiovascular Systems Inc.), major studies of Rotablator in coronary applications showed restenosis rates of 33% to 49% at six months.

Cardiovascular Systems is one of a next generation of atherectomy companies that seek to make the procedures safer and more benign. Its Diamondback 360° orbital atherectomy device, which has the United States Food and Drug Administration’s approval for both coronary and peripheral applications, has a diamond-coated crown (like a BB), on a wire that spins, sending the crown into an orbit 360 degrees around the vessel wall. The device works by “differential sanding,” according to company CEO David Martin, that is, the crown sands the rock-hard plaque and pushes pliable healthy tissue out of the way. Particles created by the system are generally smaller than red blood cells and are carried away by the bloodstream. In coronary applications, Diamondback 360° received approval just two months ago, but since then, more than 50 physicians have used it to perform over 200 cases at 17 institutions, Martin reports, a measure of the unmet clinical need in coronary arteries.

Other companies seek to make atherectomy more safe and effective. Avinger Inc. has developed an imaged-guided atherectomy device with the goal of treating peripheral artery disease safely. (See “Avinger: Finally, Seeing Through Total Occlusions, But Will Clinical Value Generate Economic Return?” — IN VIVO, March 2013.)

Companies are innovating around angioplasty balloons as well. AngioScore Inc. has developed AngioSculpt, a balloon that bears a framework of metal scoring elements that renders the rigid part of the vessel more flexible and decreases the risk of dissection, but it still creates significant injury to the vessel wall. TríReme Medical Inc.’s solution to the problem is its Chocolate PTA Balloon catheter, which has a nitinol constraining structure mounted on a semi-compliant balloon to create pillows to increase contact surface and minimize trauma.

The founders of Shockwave Medical, however, contend that most of these devices are neither quite as specific to calcium nor as sparing to healthy tissue as they need to be. Furthermore, having to change instruments and guidewires to prepare the vessel with one tool, and then dilate the vessel with a balloon (as is the case with atherectomy devices) is laborious. They believe they have solved both of those sets of disadvantages with a new balloon-based device that is inherently familiar to all interventionalists.

A BENIGN TREATMENT IN A FRONTLINE TOOL

Shockwave Medical has developed an angioplasty balloon containing lithotripsy emitters — the same mechanical energy used to break kidney stones. The device can do the work of disrupting calcium at low inflation pressures, and then be inflated to dilate the vessel without overstretching it, to minimize tissue injury and avoid dissections. The product is early in its development cycle; first-in-man
studies have been completed and it’s now in the early stages of a clinical trial in Europe, but the safety of its concept has been validated by decades of lithotripsy in patients with renal disease.

It took a team of seasoned medical device entrepreneurs with experience across many different clinical segments – founders Daniel Hawkins, John Adams, and Todd Brinton – to connect the dots.

Daniel Hawkins, CEO, is a founder of diabetes company Calibra Medical (acquired by Johnson & Johnson), and has worked at Guidant, Omnicell, Intuitive Surgical, Restore Medical, EnteroMedics, Endologix, and Intellectual Ventures. John Adams is a founder of Stealth Medical, Seattle Medical Technologies, EndoGastric Solutions, Cardiac Dimensions, and InControl. Brinton, as noted, is an interventional cardiologist and is also a member of the Stanford BioDesign group. He serves on the boards of a number of early stage medical device companies and is a founder of BioParadox Inc., the developer of a platelet cell therapy for cardiovascular disease.

Hawkins says he happened to be looking at the IP disclosure for a calcium scoring balloon when he recalled some lithotripsy experiments he’d seen John Adams conduct. He put two and two together and the result was Lithoplasty, a new modality for treating calcifications in vessels.

Lithotripsy has been safely used for 25 years in the treatment of

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### Exhibit 2

#### Selected Devices For Treating Calcified And Fibrotic Arterial Plaque

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>APPROACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>AngioScore</td>
<td>AngioSculpt is a standard PTCA catheter with a scoring balloon near the tip. Scoring element consists of three nitinol spiral struts that wrap around the balloon. Has regulatory clearance for both coronary and peripheral applications. First PMA approval for coronary artery disease was in 2007; now approved for peripheral and renal stenoses. Is now conducting PATENT-C, first-in-human trial on paclitaxel-coated scoring balloon to treat in-stent restenosis.</td>
</tr>
<tr>
<td>AtheroMed</td>
<td>Phoenix atherectomy system for peripheral artery disease is a low-profile device that uses a rotating, front-cutting element with a deflectable tip that can treat several sizes of blood vessels with a single insertion. Shaves material directly into the catheter and debulked material is captured continuously and removed by an Archimedes screw running the length of the catheter. FDA cleared in January 2014 based on the EASE study.</td>
</tr>
<tr>
<td>AtheroMed</td>
<td>Panteris combines directional atherectomy with optical coherence tomography for real-time intravascular visualization. Has CE mark for peripheral applications.</td>
</tr>
<tr>
<td>Bayer (acquired from Pathway Medical)</td>
<td>Jetstream has front-facing rotating cutting tip that debulks calcium, thrombus, and fibrotic lesions and aspirates material out to collection bag located at the console. Expandable cutting surface allows the system to treat several vessel sizes from the tibial to a larger common femoral artery with one insertion. (First-generation Jetstream was approved for atherectomy in the peripheral arteries in 2008.)</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Rotablator rotational atherectomy device is one of the only options for debulking calcified plaque in coronary arteries. BSX also offers Peripheral Rotablator. Rotablator has distal tip with rotating elliptical burr in which diamond crystals are embedded to sand calcified plaque into small particles. (Approved in 1994 for coronary applications.)</td>
</tr>
<tr>
<td>Cardiovascular Systems Inc. (CSI)</td>
<td>Diamondback 360° orbital atherectomy system. Cutting diameter can be controlled by speed; increased speed covers larger diameter; continuous flow of blood and saline minimizes thermal injury and results in no re-flow. Approved for coronary and peripheral applications.</td>
</tr>
<tr>
<td>Covidien (developed by FoxHollow)</td>
<td>TurboHawk and SilverHawk plaque excision systems for peripheral artery disease work by directional atherectomy. The DEFINITIVE-AR and ADCAT ongoing trials are studying atherectomy before treatment with drug-coated balloon.</td>
</tr>
<tr>
<td>Shockwave Medical</td>
<td>Balloon-based Electromechanical Lithoplasty incorporates multiple lithotripsy emitters along the length of an angioplasty balloon to deliver mechanical energy that fractures calcium specifically without harming healthy tissue. Controlled, low-pressure inflation avoids injury to the vessel wall. Has conducted FIM, now (in 2014) conducting multi-center EU study for SFA/popliteal stenosis.</td>
</tr>
<tr>
<td>Spectranetics</td>
<td>Turbo Elite excimer laser atherectomy catheter vaporizes blockages in peripheral arteries. (Received FDA clearance in October 2006.)</td>
</tr>
<tr>
<td>TriReme Medical</td>
<td>Chocolate PTA Balloon catheter has nitinol constraining structure mounted on a semi-compliant balloon to create pillows and increase contact surface. At nominal pressure, the balloon expands beyond the diameter of the nitinol structure, creating pillows and valleys, uniformly increasing contact points, avoiding “dog boning” and minimizing vessel trauma. Received 510(k) in December 2011 for treated occluded peripheral arteries.</td>
</tr>
</tbody>
</table>

**SOURCE:** Company web sites
renal calcifications. “Mechanical waves pass through soft tissue and when they hit something hard, they pound it like a ball peen hammer,” Hawkins says. The beautiful part of this therapy is that it benefits from the laws of physics, he explains. “We don’t have to be selective or directional and pointing.” The mechanical energy of lithotripsy falls off very quickly from the location of its source, so its effects are site-specific. To be effective from within the vessel, mechanical energy only needs to travel a few millimeters, Hawkins says. “We don’t have to worry about transient energy doing something to the body somewhere else.”

To reduce lithotripsy to a catheter-based therapy, Shockwave’s founders not only had to miniaturize lithotripsy emitters, but to also find a way to place multiple sources along the length of a balloon. Hawkins says Shockwave has placed 10 lithotripsy emitters in a 60-mm balloon. “Making them very small and highly deliverable in multiples within a single balloon is not trivial and we have solved that,” he says. One other technical challenge was overcome. “Every manner of lithotripsy probe shoots forward. We figured out a way to make the emitters shoot sideways, and that’s important because we can direct mechanical energy to the vessel walls.”

Shockwave Medical starts with a mechanism of action that is specific to calcium and benign to healthy tissue, but its device avoids trauma in other ways. Lithoplasty devices are built on a standard semi-compliant balloon platform – the conventional frontline tool of revascularization – and are inflated at a pressure low enough to avoid vessel overstretch (+4 atmospheres) while delivering lithotripsy. As noted, high inflation pressures (12 to 18 atmospheres) used by standard balloons to pre-dilate stiff, calcified lesions cause damage that leads to elastic recoil, restenosis, and even dissections. The Shockwave balloon delivers therapy at a very low inflation pressure.

After delivering lithotripsy at 4 atmospheres, the balloon is inflated to the diameter of the healthy vessel on the opposite sides of the lesion (reference vessel diameter) avoiding overstretch. “We believe it provides less of a chance of acute failure in terms of a dissection that would then require a stent, and ultimately there is less injury because it doesn’t disrupt the fundamental components of vascular biology,” says Brinton. “If you minimize injury to the internal elastic lamina, you don’t promote macrophages or other factors that drive smooth muscle migration and the formation of scar tissue.”

Lithoplasty doesn’t actually remove calcium; it forms micro-cracks in the rock-hard surface, rendering the vessel supple so it can more easily be dilated. Hawkins compares it to the shell of a hard-boiled egg, which cracks finely when you roll it on a hard surface with the palm of your hand, but remains attached to its thin membrane (which is analogous to the endothelial lining of the vessel).

Lithoplasty passed its animal testing, in which the company demonstrated that shockwaves pulsed at 70 atmospheres to 80 atmospheres in microsecond bursts didn’t cause meaningful heat changes inside the balloon. Shockwave completed its first-in-man trial in New Zealand and is now conducting its first multi-center clinical trial in Europe in peripheral artery disease.

As an interventional cardiologist, Brinton says his interest is in coronary applications, but peripheral vascular disease represents the best first indication because the degree of calcification is greater in peripheral arteries and there are fewer safe and effective treatment options. “In the periphery, our reference data for calcified lesions show a bail-out rate for stenting as high as 30%. But if an interventionalist can achieve a good result with a single device that avoids the need for a stent, that delivers a lot of value to the health care system and the patients.”

In January 2014, Shockwave Medical raised $12.5 million in its Series A round, led by Sofinnova Partners. Antoine Papiernik, managing partner at Sofinnova Partners, says it was a “good old-fashioned deal. It’s a great technology with people who have done it before,” with a significant first indication before it in peripheral disease, a market he estimates at $400 million to $600 million, an even larger market in coronaries, and several emerging indications, including aortic valve stenosis.

Hawkins says in the near term the company will be looking at preparing aortic valves to receive a transcatheter valve, like a CorvValve (Medtronic Inc.) or a Sapiens (Edwards Lifesciences Corp.) valve. “The goal there is to prepare the valve without going to very high pressure, which might disrupt the annulus.” Calcification may cause gaps around valve stents that lead to aortic regurgitation.

Lithoplasty might also revive balloon aortic valvuloplasty, which is rarely performed today. Brinton says, “A large number of patients are not the right candidates for transcatheter aortic valve replacement [TAVR]and need a better therapy than the failed valvuloplasty of 20 years ago.” The idea would be to disrupt the calcium with Lithoplasty, then dilate under lower pressure to get a much better result. Lithoplasty-enabled valvuloplasty could become a future therapeutic option that delays the need for TAVR, says Brinton.

Brinton still looks to Lithoplasty to provide effective therapy in coronary disease. “Directional atherectomy is not approved for coronary vessels, and the use of Rotablator is reserved for high-grade stenosis in lesions that are highly calcified. We don’t have a lot of tools for treating modern-day disease.”

Hawkins notes that the company is already exploring a drug-eluting version of its balloon.

If it is successful, Lithoplasty might be coming to market as an enabling technology for the newest paradigm in interventional cardiology, biodegradable stents, a market led by Abbott Laboratories Inc., which has approval to market its Absorb BV in Europe. “Vessel preparation continues to become more and more important because ultimately we are not going to leave an implant in. Implants will be going away,” says Hawkins. The balloon is a frontline tool, he says. It’s easy to use, familiar to all interventionalists, and it has a really good opportunity to make an impact on several markets.

Atherectomy was once reserved as a tool of last resort for patients with calcified plaque, principally because of the risk of adverse events with many of the devices. Shockwave Medical might be the first in a new generation of companies developing safe, efficacious, and easy-to-use tools that enable effective intervention in calcified vessels across a broad spectrum of cardiovascular disease.