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SUMMARY

The closure market is growing in Europe but relatively flat in the U.S. All U.S. labs questioned already use at least one mechanical device, and most use more than one. St. Jude/Kensey Nash's AngioSeal and Abbott's Perclose dominate the mechanical market, and that is likely to continue. However, the field is getting more crowded with new entrants in both mechanical devices and topical products (patches). There is some – but not severe – downward pricing pressure, due in part to the additional competitors. Price is the major factor in the choice of a patch.

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CLOSURE DEVICE UPDATE

U.S. and European interventional cardiologists, U.S. cath lab managers, officials of several closure companies, and numerous experts in the field were interviewed to determine the outlook for closure devices in general and patches in particular in the U.S. and Europe. Sources generally agreed that the closure market is likely to continue to expand in Europe, but the prospects are for little growth in the U.S. market. The field is getting crowded and pricing is coming down, but margins are still sufficient to attract new entrants, and doctors and other cath lab personnel are willing to test new products. A European source said, "There are enough cardiologists interested in something less invasive to support growth of closure devices."

THE COMPETITORS

AngioSeal and Perclose dominate the mechanical closure market, but there are at least eight companies vying for a share of the mechanical closure market, with more on the way.

MECHANICAL

- ABBOTT'S Perclose
- ANGIOLINK'S EVS, vascular stapling system
- DATASCOPE'S VasoSeal
- ST. JUDE/KENSEY NASH'S AngioSeal
- SUB-Q'S QuickSeal Arterial Closure System**,** which was FDA approved in March 2002. It uses a sponge-like material called Gelfoam to obtain hemostasis.
- SUTURA'S SuperStitch
- VASCULAR SOLUTIONS' Duett

TOPICAL

There appears to be renewed interest in patches with several new entrants. An industry source said, "I've yet to talk to a cardiologist who hasn't had at least one complication with a mechanical closure device, so patches should be able to do well."

MARINE POLYMER TECHNOLOGIES' Syvek patch, which uses a marine toxin as a hemostatic agent. Most of the use appears to be in the U.S. There is very little visibility for Syvek in Europe, and the company did not have a booth at the 2003 European Society of Cardiology meeting.

MEDTRONIC/SCION CARDIO-VASCULAR'S Clo-Sur PAD. This closure patch doesn't use any gel, enzyme or powder. Instead, it relies on the ionic charge of the polymer in the patch to speed coagulation. Medtronic is the U.S. and European distributor, but it does not appear to be putting much marketing effort behind Clo-Sur PAD. Medtronic did not even have either signage or product displays of Clo-Sur PAD at the European Society of Cardiology meeting in Vienna in September 2003. A Medtronic official said the booth was small, and they had to pick their most important products – and interventional cardiology was not a focus at ESC. However, Medtronic also reportedly did not show Clo-Sur PAD at the premier interventional cardiology meeting in Europe, the EuroPCR meeting in Paris in May 2003. There also was an unconfirmed report that Medtronic has stopped selling Clo-Sur PAD in Germany, though Medtronic reportedly is still supplying existing customers there. Rather, it seems Medtronic European sales reps currently are focusing on the launch of the company's new Driver stent.

ABBOTT'S Chito-Seal. This uses essentially the same agent (a chitosan gel) as Syvek to achieve hemostasis. Chito-Seal has slightly more visibility in Europe than Syvek, but Abbott also did not have a booth at the 2003 European Society of Cardiology meeting. Sources said Abbott is carefully marketing Chito-Seal to avoid taking business away from the company's mechanical device, Perclose.

MEDAFOR'S M-Patch. This new – and very neat – patch gained FDA 510K approval in April 2003 as a wound closure device for vascular access. It is like a circular band-aid, but after it is applied to the skin, a clear strip is pulled out from under it that allows a white powder of extremely tiny, very porous microspheres to reach the wound site under the patch. The powder, which is held in place by the patch (it is in the center only), soaks up water from the blood creating hemostasis.

Medafor, a privately held company started in 1999, was the only patch company to have a booth at the 2003 European Society of Cardiology meeting. However, the booth number was incorrectly listed in the program and the location was very poor (far corner), making it difficult to find. However, doctors who saw the product there described it as interesting. Reportedly, a German clinic that uses lot of Clo-Sur PAD, and is happy with it, has agreed to test M-Patch – because it is cheaper. An M-Patch is priced at about 50 euros, and a Medafor official said Medtronic charges 67 euros for Clo-Sur PAD in Germany.

The manager of a U.S. cath lab that tried M-Patch described the results as "okay but not dramatic." Since then, that lab has not purchased any M-Patches, though it does continue to use some Chito-Seal patches.

Medafor has a CE Mark to sell the powder alone in a vial for surgical applications as Arista. The company also has an IDE for Arista in the U.S. and is beginning a 300-patient, randomized trial of Arista vs. gelfoam (50 cardiac patients, 50 general surgery patients, and 50 orthopedic patients), with hopes of getting FDA approval.

The problem for Medafor is lack of a sales staff. The company only has two people in Europe, and three or four regional managers in the U.S. In the U.S., it is depending on 15 independent distributors to sell the product, though Medafor says it requires those distributors to demonstrate the product with face-to-face visits to new and potential accounts. A Medafor official said, "If you just give someone the product to try without being there and showing him how to use it, it is a prescription for failure."

JOHNSON & JOHNSON. The Ethicon division is working on a patch, but it won't be sold by the cardiology division (Cordis). A senior J&J/Cordis official, asked if J&J/Cordis was looking at offering a closure device, said, "Closure patches are becoming a commodity. Ethicon is working on one, but I told Ethicon them to keep it and sell it to nurses, if they want. We don't want to handle them in Cordis."

TZ MEDICAL'S Neptune Hemostatic Pad, a calcium alginate wound dressing (patch). This product was 510K approved earlier this year. A company official said is more efficient for interventions than for diagnostics.

MANUAL PRESSURE

- SEMLER TECHNOLOGY'S C-Clamp.
- RADI MEDICAL SYSTEMS' FemoStop.

THE CATH LAB PERSPECTIVE

EUROPE

In Europe, sources generally agreed that about 10%-20% of interventional procedures are being done with a closure device today, and the market is expected to expand. AngioSeal definitely is the market leader, and it is unlikely that any mechanical or external (patch) device will unseat it from that position in the next couple of years. AngioSeal sales are expected to continue to expand. On the other hand, Datascope sources said their European sales have flattened, and they did not predict much growth there for the next year.

European cardiologists questioned about closure devices offered these comments:

- A French doctor who runs a large lab said, "We use Perclose and AngioSeal. We tried 10 Clo-Sur PADs, and they didn't work, so we don't use them now."

- A Belgian doctor said his lab is not currently using any closure devices, "We tried AngioSeal, VasoSeal and 10 Perclose patients, plus we recently tried a couple of Syvek patches…But closure devices are not reimbursed, and we can't charge the patient. In our lab, nurses pull sheaths, and we don't believe we would save enough time with closure devices to allow even one additional patient, so there would be no benefit."
- A Polish doctor said his lab is not using closure devices but has tried Perclose, "The advantage was small for the cost."
- A German cardiologist said 70% of the interventional patients in his cath lab get AngioSeal, but none of the diagnostic patients because they use 4F for that, which eliminates the need for a closure device. He plans to test a patch soon, but declined to say which one.
- A very large Dutch lab uses AngioSeal for about 50% of its patients and does not plan to increase the percentage of patients getting a closure device. A doctor there said, "We tried Perclose, but we haven't tried patches."
- A U.K. cardiologist said, "We use closure devices on PTCA cases mainly and some diagnostic cases with aortic regurgitation who are likely to bleed…AngioSeal is the simplest and best in my opinion."

UNITED STATES

Fifteen cardiac cath lab managers and directors were questioned about closure device use. AngioSeal and Perclose are the mechanical closure devices most used in the these labs. AngioSeal's popularity is due to its ease of use and speed of deployment. Closure devices are used in about a third of all diagnostic procedures and nearly half of all interventions, but their use appears to have peaked and is not expected to increase. There is little interest in patches.

On average, these labs use mechanical devices for 37% of all diagnostic procedures and for 48% of all interventions. A New Jersey tech said, "We use them for all the patients we possibly can." A California cath lab tech said, "We're using them for both diagnostic and interventions." An Ohio cath lab manager said, "Mechanical closure products are used on 70% of total patients, with intervention patients being slightly higher. Many of our patients have been referred from the outside and have an extensive cath lab history. These patients are well-informed and often ask whether or not they will 'get a plug' at the end of the procedure." A Florida cath lab director said, "We use Perclose on out-patients who can go home today and Syvek on potential bleeders. This probably won't change." An Ohio cardiologist said, "We use the devices on anything with a larger than 6F sheath." A Pennsylvania doctor said, "We use the devices on patients with 'normal' angiographic studies and on patients with PCI to reduce the time of immobilization."

In most cases, the decision to use a closure device is up to individual physicians. A Kansas cath lab manager said, "It's physician-dependent. Some doctors don't use closure devices at all on their PCIs. It's roughly 80% of diagnostic procedures and about 30-35% of interventions." An Ohio cath lab manager said, "We may use closure devices on any patient undergoing a cardiac or endovascular procedure. The device selection is predominantly physician preference."

Sources agreed that labs rarely, if ever, use closure devices for all their patients – whether interventional or diagnostic. Among the criteria for choosing patients in which to use them are:

- **Procedure**. Some labs use them mostly for interventional procedures, not diagnostics. However, AngioSeal officials said most of their growth in the U.S. has been in diagnostic facilities.
- **Anticoagulation**. Patients on ReoPro (Lilly, abciximab) and other anticoagulants are more likely to get a closure device.
- **Obese patients.** Manual compression is much harder with these patients. A source said, "patients with a high BMI have a higher bleeding risk."
- **Patient intolerance of lying flat.** Some patients have spinal problems that make it too uncomfortable to lie on their back for extended periods, and sources said they will use closure devices for them.
- **Size of introducer.** When a 4F introducer is used, there is no need for a closure device. With a large puncture (6f-7F), a closure device has more utility.
- **Urination.** Patients with problems urinating (frequency).

Sources are familiar with a wide variety of devices, and most have tried several different devices before settling on their current product(s). A California cardiac cath lab tech said, "We've probably tried everything that's come on the market, and how well they do depends a lot on the patient's anatomy and the type of procedure." A Pennsylvania cardiologist said, "They are all very effective in achieving hemostasis with improved patient comfort as compared to manual hemostasis." An Ohio lab manager said, "We've tried all of these products – AngioSeal, VasoSeal, Perclose, Duett, Syvek, and Chito-Seal, with the exception of Sutura and the Clo-Sur PAD, in the past, plus a number of others. Each product has its own pros and cons, and their success or failure can be measured predominantly by operator experience and proper technique." A Maryland cardiologist said, "I've tried most. My impression is that the suture-based devices are the only ones worth using."

All these labs use at least one mechanical (invasive) device, and most use more than one. A New Jersey cath lab tech said, "We mostly use AngioSeal with some Perclose." A Kansas cath lab manager said, "We've used AngioSeal, Perclose and Duett. The first two are more reliable for interventions." A

cardiologist said, "Each of the invasive closure devices has a slightly higher risk of infection than more traditional compression methods." A Virginia cath lab manager had another perspective: "The differences are mostly in ease of use. Perclose is more technically demanding. AngioSeal is easy for the staff to learn to use. VasoSeal was the first one we tried, so they had a harder time with that product. What's best depends on the application. We get generally good results with AngioSeal, which is used for both diagnostic and interventional procedures -- pretty much any time we do something involving the femoral artery or vein. We haven't had many adverse events ourselves, but we've heard about bleeding and hematomas at other places. Early in our experience with Perclose there were rare instances of embolization of collagen, but this hasn't happened lately."

Sources generally consider AngioSeal the best mechanical device. A Kansas cath lab manager said, "AngioSeal is the best. It's easier to deploy and is more comfortable to deploy in the patient." A New Jersey cath lab technologist said, "AngioSeal is the best because it's quick and easy."

Two sources favor Perclose. A Pennsylvania doctor said, "When successfully deployed, Perclose is the best device." Another lab manager said, "For mechanical closure, if I were the patient, I would prefer to have a Perclose device over the other products. I would also prefer that my doctor use the 'pre-close' technique, where the device is deployed at the beginning of the case with sheath insertion. By using this method, there wouldn't be a worry about potential device failure post-procedure. Currently, the Perclose family of products is the only group of hemostasis devices that can take advantage of this technique."

A cardiologist offered these comments on specific devices:

- "The AngioSeal product has an intravascular absorbable anchor; the Perclose and Sutura products percutaneously suture the arterial site closed from the inside out. By design, these products may provide a more secure closure. However, there is a very small risk of the AngioSeal anchor to dislodge and embolize. The Perclose and Sutura products use non-absorbable sutures. The VasoSeal (collagen), Duett (collagen/thrombin) and QuickSeal (gelfoam) are completely extravascular. The vascular seal may be less secure than those of AngioSeal or Perclose.
- Anecdotally, I have seen more hematomas, albeit with limited experience, with the VasoSeal and QuickSeal products. This may be related to experience and technique. The Duett device effectively closes the puncture tract completely, and there is absolutely no oozing at the site. If the Duett collagen/thrombin procoagulant enters the intravascular space, however, there is instantaneous thrombosis that could be potentially life threatening."

Three sources said they preferred manual compression (with or without a patch) to any mechanical device. A California lab manager said, "Our director prefers manual pressure." An Ohio manager said, "My personal preference is manual compression with the Syvek NT or pneumatic compression with the FemoStop. Both products are non-invasive and additionally the FemoStop will effectively control a hematoma if one is present." A Nebraska cath lab supervisor said, "We mostly do half radials here, and we prefer manual compression. No closure devices are in use or are planned for use."

Four sources had no preference among the devices. An Ohio manager said, "There's no real difference between them. They all work pretty much the same."

Only three labs currently use topical patches (one Syvek, one Chito-Seal, and one both Chito-Seal and Syvek). An Ohio cath lab manager said, "For mechanical closure we predominantly use Perclose and AngioSeal, and we also stock the Duett and QuickSeal products. For topical hemostasis accelerators, we currently use the Abbott Chito-Seal or Marine Polymer's Syvek patch, but we have evaluated the Neptune PAD. We also inventory the more traditional manual assist devices, including the Semler Technology C-Clamp and the FemoStop pneumatic compression device from RADI Medical."

Sources all agreed that the patches are safe. The question is whether they work, or whether they work enough to justify even a $50 cost. Among the patches, sources generally perceived little differentiation. One source who is familiar with the various patches available said, "I favor one particular product, the Syvek NT, for overall effectiveness. This is based on personal preference, not a side-by-side comparison. The Syvek NT has a good tactile feel compared to the original Syvek and Abbott Chito-Seal, and, in my opinion, is the quickest topical product to achieve hemostasis."

Few sources were familiar with the Clo-Sur PAD. One cath lab manager said, "I don't have a lot of experience with the Clo-Sur PAD, but I haven't been impressed with what I've seen. I've also been following their issues with the FDA and the warnings they (Scion Cardio-Vascular) received related to product claims. They received a warning letter from the FDA dated July 11, 2003, stating the product is being marketed inappropriately for unapproved indications and for unadulterated use. The warning letter states that the Clo-Sur PAD was classified by the Centers for Devices and Radiological Health (CDRH) as a Hydrophilic Wound Dressing."

Price is the major factor when it comes to choosing among patches, sources said. A Florida cath lab manager said, "It's price for me." A cardiologist said, "Efficacy and price mainly dictate my choice." A Kansas cath lab technologist said, "If we did use them, it would be based on price and sales support." A Midwest cath lab manager said, "We allow the users – our cath lab nurses and techs — to evaluate the product, and we ask for their input as to overall effectiveness.

Price is also a consideration. We switched from the original Syvek patch to Chito-Seal based on feedback from our staff and better pricing. The staff considered the new Syvek NT patch; however, Marine Polymers would not consider lowering the cost of the NT product to be more competitive. We are evaluating the Neptune Pad from TZ Medical, and we will probably trial the D-Stat Dry from Vascular Solutions as well." A Florida cath lab manager said, "We were using a good number of Syvek patches for a time, but when I looked at hematoma and pseudoaneurysm rates over a year's time, the patch didn't make any difference. So now what I say is that even if the patch does work, it doesn't change the patient outcome. I keep them around as a nurse satisfier, but they've stopped asking for it except occasionally."

Sources were mixed as to whether ***external*** devices (patches) can cause adverse events.

- **Yes, they do:** A Midwest tech said, "Maybe some skin irritations." A California tech said, "I'm not aware of external devices causing external events, but we don't use them that much." A New Jersey source said, "Yes, they can cause events such as hematomas and infections, just the same as any other complication." An Ohio cardiologist said, "Yes, any of these devices can cause adverse events such as occlusion of the femoral artery, bleeding and infection."

- **No, they don't:** A Florida cath lab manager said, "I'm not aware of any except perhaps an allergy." An Ohio cath lab manager said, "There have been no reported adverse reactions to these products. Clo-Sur PAD and Chito-Seal use chitin or chitosan as their active ingredient, which is derived from the exoskeletons of crustaceans such as crabs, shrimp and lobsters. There is an incredibly remote change of an allergic reaction in patients with seafood and shellfish allergies; however, chitin and chitosan have been used in cosmetics and health supplements since the 1960s without any adverse reactions linked to them. One limit of the hemostasis patches is compression technique. The product is only as effective if the user is trained and utilizes good technique. Pressure needs to be applied 2 cm above and slightly medial to the skin entry point. If the sheath is removed and compression is applied incorrectly – for example, directly over the puncture hole – the hemostasis patch won't make a difference. Poor technique also increases the likelihood of hematoma formation."

Sources said that use of mechanical closure devices has probably peaked and will remain stable. An Ohio cath lab manager said, "At my facility, I believe the use of mechanical closure devices has peaked at 70%, and I don't see an increase in the future. Other facilities may increase their utilization as patients are more aware of these products and continue to ask." A Maryland cardiologist said, "I think that usage has plateaued. In fact, we use them less than before because we can now do most procedures with smaller catheters. Some patients really benefit from them, though. And I believe that large-hole closure device usage will clearly increase for stent-graft aortic procedures." A Pennsylvania cardiologist said, "Mechanical devices will be used sparingly in the future due to the increased cost of interventional procedures (from IIb/IIIa use and drug-eluting stents, etc.). Also, as more interventions are performed via radial access, the need for closure devices will decrease." A Midwest physician said, "I think that use will increase over the next year by about 5% and maybe 50% over the next five years, but the trend is not to use mechanical devices." An Ohio cath lab manager said, "Our usage of closure devices has more than likely peaked. Any patient may receive a closure device if the cardiologist deems it clinically appropriate. As interventional products, particularly coronary stents, decrease in profile, usage of small 5F access sheaths will become more common. As arterial access continues to downsize and different procedural pharmaceutical regimens are developed and adopted, mechanical closure may slowly decrease or disappear entirely in favor of traditional manual or assisted compress – i.e., topical pads, C-Clamp, FemoStop – methods."

There is no move away from mechanical devices toward pads or patches, sources agreed. An Ohio cath lab manager said, "While many users of these products swear by their results, there is a lack of any randomized clinical data supporting the efficacy of topical pads and patches. Nor is there data suggesting safer early ambulation as compared to manual compression alone. Positive word of mouth may increase their usage, but lack of data will hamper widespread adoption." A cardiologist said, "I don't see any move away from mechanical devices." A Pennsylvania cardiologist said, "Performing more procedures via radial access limits the use of the closure devices." A Florida cath lab manager said, "My physicians won't change their post-procedure bed rest times except for Perclose, and even then, not always. If I can't get the patient up and moving sooner, why bother with it?"

It is already a crowded market, and sources don't see many new or interesting closure devices or procedures on the horizon, though a few sources mentioned Neptune. A New Jersey cath lab technologist commented, "I don't see anything that I'm interested in." A Florida cath lab manager said, "We're evaluating the Neptune pad based solely on price to see if it can replace Syvek." A California lab tech said, "Interventional radiology is very interested in something called Neptune." An Ohio source said, "There are numerous topical agents on the horizon to compete with the likes of the Syvek pad, Chito-Seal, Clo-Sur PAD and Neptune. I find it funny how just a few years ago when Marine Polymer Technologies introduced Syvek, many were calling it snake oil and voodoo. Now, the market is becoming saturated with competitors. Mechanically, the AngioLink percutaneous surgical staple device is somewhat interesting and may have a future as they continue to refine the staple design. I also heard there's a company designing a product that utilizes some form of external radio-frequency energy to instantly achieve hemostasis. That would be very interesting to see and try."

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