Overview of Vascular Closure

The *Endovascular Today* annual review.

BY ZOLTAN G. TURI, MD

The past year saw the effect of the recession in endovascular procedures trickle down to vascular closure devices (VCDs): fewer catheterizations and fewer interventions led to at least a slowing—if not a reversal—of the persistent growth seen in VCDs in the past decade. Despite the economic realities of a maturing market, diminishing growth, and increased competition, a number of new devices made their appearance. Several devices had significant changes in platform, and at least one important new technological concept was introduced. As in the previous 6 years, I will review the status of the existing technologies, introduce technologies in the works, discuss some of the practical and theoretical issues affecting vascular closure, and comment on a few of the more important articles in the medical literature. I will take the liberty of using my annual soapbox on safety, discuss VCD complications in general, and revisit the issue of retroperitoneal hemorrhage and VCDs. Finally, the classification system first introduced in this review 2 years ago has now been adopted in an increasing number of settings but is included as Table 1 for those who are unfamiliar.

EXISTING TECHNOLOGY

Angio-Seal (St. Jude Medical, Inc., St. Paul, MN), a "belts-and-suspenders" device because it incorporates active approximation of the arteriotomy along with a thrombosing agent in the tissue track, continues to dominate the vascular closure market. It is favored with a short learning curve, a high success rate even in the setting of full anticoagulation, and a modest (but very important) complication rate. It is handicapped by two properties inherent to the technology. First, the anchor placed inside the vessel produces a transiently visible filling defect in the arterial lumen and is occasionally obstructive, either at the puncture site or with embolization. Second, it leaves a mass of collagen inside the tissue track and a suture that extends from the arteriotomy to near the skin surface, providing both a nidus and a wick for potential infection. Repuncture should be done with caution during the first 3 months, although a small published series demonstrated no complications.[1]

Perclose (Abbott Vascular, Santa Clara, CA) remains popular among those who prefer the well-established surgical approach of suturing arteriotomies. It leaves less foreign body inside either the artery or tissue track, but unlike Angio-Seal, does not resorb. StarClose (Abbott Vascular) deploys a nitinol clip rather than suture, is simpler to use than Perclose, and is designed not to leave behind any intraluminal foreign body. In general classification terms, it is similar to Perclose, featuring active approximation, a permanent foreign body, and no thrombosing agent; thus, it has less of a nidus for infection but more of a predisposition to oozing after the procedure in fully anticoagulated patients. The latter may be exacerbated by the diameter of the StarClose deployment shaft. Both Perclose and StarClose lend themselves well to immediate repuncture. There is no restriction on reaccess after Perclose; the evidence base for repuncture after StarClose is modest but has worked well in our experience.

The Boomerang ClosureWire (Cardiva Medical, Mountain View, CA) has a unique niche in vascular closure. Unlike Angio-Seal, Perclose, or StarClose, it is a passive approximator, relying on a nitinol disk inside the artery, with a spring mechanism to maintain traction at the arteriotomy inside the vessel until hemostasis occurs. A theoretical drawback is the need to withdraw the relatively low-profile collapsed assembly through the freshly formed plug, requiring additional compression. Its appeal includes the lack of any foreign body left behind (reducing the risk of infection), ability to repuncture with the same considerations as if manual compression had been used, and deployment through the original procedural sheath. A new version, the Boomerang Catalyst, is designed to provide facilitated thrombosis in the tissue track by exposing two agents on the shaft of the device to stimulate coagulation, platelet adhesion, and platelet aggregation when tension is applied to the disk inside the

TABLE 1. VASCULAR CLOSURE TECHNOLOGY

	Invasive/Noninvasive	Active/Passive Approximation	Intraluminal/ Extraluminal	Thrombosing/Sealing	Temporary/Permanent Foreign Body
Angio-Seal	Invasive	Active	Intraluminal	Thrombosing	Temporary
Perclose	Invasive	Active	Intraluminal	No	Permanent
StarClose	Invasive	Active	Extraluminal	No	Permanent
Boomerang	Invasive	Passive		No	No
Mynx	Invasive	Passive		Sealing	Temporary
Patches	Noninvasive	Passive		Thrombosing	No
Compression	Noninvasive	Passive		No	No
		Investigational			
Arstasis	Invasive	Active	Intraluminal	No	No
EpiClose Plus	Invasive	Active	Extraluminal	No	No
ExoSeal	Invasive	Passive		Sealing	Temporary
Therus	Noninvasive	Active	Extraluminal	No	No
		FDA Approved; Limited Release or Not Marketed			
AngioLink	Invasive	Active	Extraluminal	No	Permanent
FISH	Invasive	Active	Intraluminal	Sealing	Temporary
SuperStitch	Invasive	Active	Intraluminal	No	Permanent
Duett*	Invasive	Passive		Thrombosing	Temporary
VasoSeal*	Invasive	Passive		Thrombosing	Temporary

Invasive devices are listed before noninvasive, active before passive approximators, and intraluminal before extraluminal in each category. AngioLink (Medtronic CardioVascular, Santa Rosa, CA), EpiClose Plus (Cardiodex, Tirat-Hacarmel, Israel), SuperStitch (Sutura, Inc., Fountain Valley, CA), Therus (Therus, Seattle, WA). Manufacturers of the other devices are noted in the text.
**Available from the manufacturer.*

vessel. As with other passive approximators, the litmus test for this device will be its success and complication rate in the setting of the vigorous anticoagulation environment of interventional cases. A more extensive list of devices is included in Table 1.

NEW TECHNOLOGY

The Thresholds for Successful New VCDs

Most laboratories cannot afford the shelf space or inventory management issues raised by stocking more than two or three closure devices. A successful new device in the increasingly crowded VCD marketplace has to meet one or more of the following standards:

- A high enough success rate in both diagnostic and interventional procedures to be the primary, go-to device in the lab
- Favorable features (ease of use, short learning curve, slick deployment mechanism)
- A niche that is perceived valuable
  - Perceived low risk of associated infection
  - Favorable features for use in peripheral vascular disease or puncture outside the common femoral artery
  - Favorable features for use in nonfemoral access
- Manufacturing costs that allow a sustainable profit

The last item, manufacturing costs, may seem tangential to the other considerations, but I suspect this has been the primary cause of some otherwise novel technologies never making it to market. The original VCD, VasoSeal (Datascope

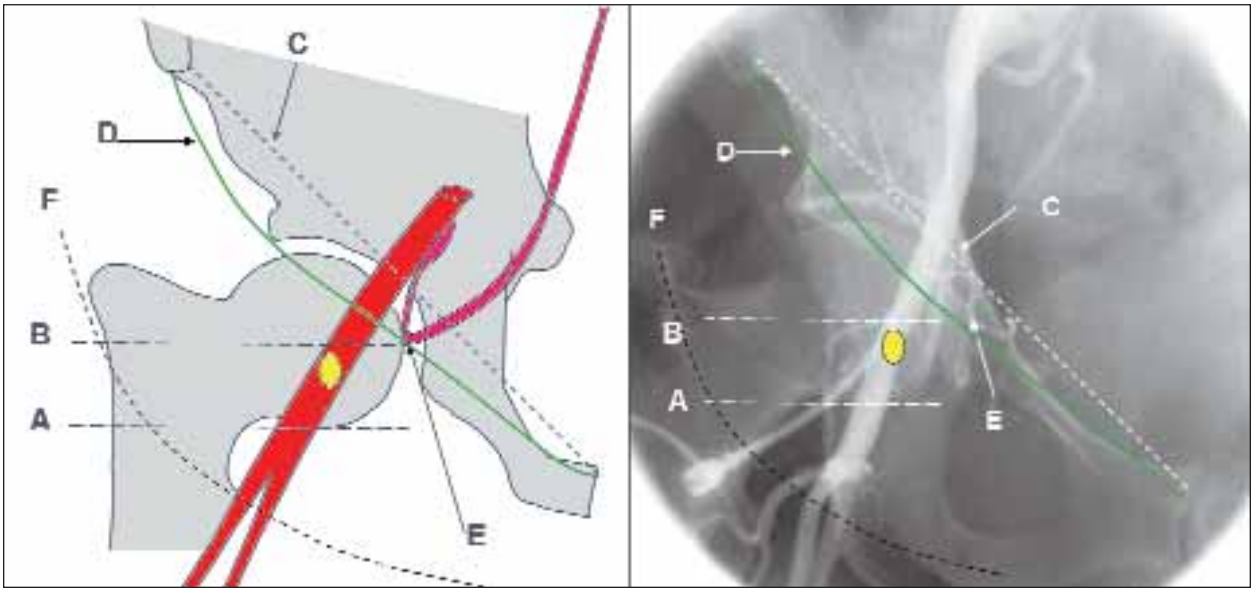

Figure 1. Anatomic features for femoral arterial puncture. The bottom of the femoral head (A), center line of the femoral head (B), and the approximate location of the inguinal ligament estimated from a line drawn between the anterior superior iliac crest and symphysis pubis (C) are all visible on plain fluoroscopy before puncture. The actual location of the inguinal ligament (D) can be more accurately assessed with angiography showing the point of lowest excursion of the inferior epigastric artery (E). The inguinal crease (F) is an overutilized and potentially misleading landmark. The ideal target for puncture (yellow oval) is a point below the center line of the femoral head.

Corp., Montvale, NJ), consisted of a few molded plastic parts and one or two collagen plugs. More complex technologies, with finely milled pieces made of expensive metals and multiple moving parts can be prohibitively expensive to manufacture. Device failure, not just failure to achieve hemostasis but failure to function perfectly, is not acceptable to clinicians, patients, or their lawyers, thus the technical demands in this crowded intellectual property space require substantial creativity.

Return of the Unanchored Plugs

After the demise of both the Duett (Vascular Solutions, Inc., Minneapolis, MN) and VasoSeal (both available from the manufacturer but no longer actively marketed), it appeared that the potential drawbacks of passive closure were proving to be a significant factor in VCD success rates and acceptability. Although both devices had secular issues (VasoSeal had a high failure rate, particularly in fully anticoagulated patients, whereas the Duett was associated with occasional intra-arterial injection, sometimes with catastrophic results), the lack of active approximation was perceived to be a drawback for use in the interventional environment. Failure of devices in anticoagulated patients is at best messy, requiring prolonged compression with or without adjunctive use of other devices and is associated with a significant complication rate. The greater success rates of active approximators, such as Angio-Seal and Perclose, relegated the unanchored plugs to small shares in the VCD market.

Thus, it is something of a surprise that the most prominent new VCD marketed in 2007 and the next important device likely to be released are both unanchored plugs. Both devices, the Mynx (AccessClosure, Mountain View, CA) and ExoSeal (Cordis Corporation, Warren, NJ), also share several other characteristics: they utilize biopolymers that are sealing rather than thrombosing agents, both deploy through the existing vascular sheath, and both feature streamlined, short learning curve delivery mechanisms. The Mynx (polyethylene glycol) is being actively marketed, and the ExoSeal (polyglycolic acid) has finished its pivotal trial but is not yet FDA approved. Although both devices appear to have high success rates, yet to be determined are the failure rates in the real-world interventional environment and how well sealing agents stack up against thrombosing agents (ie, biopolymers vs collagen) with regard to tissue track oozing in fully anticoagulated patients.

Given the low single-digit failure rates that operators expect with closure devices in interventional cases, the challenge for these unanchored plugs will be to match that standard in the full anticoagulation/antiplatelet agent environment. If they do, these devices will benefit from their ease of use; if they do not, they will be relegat-

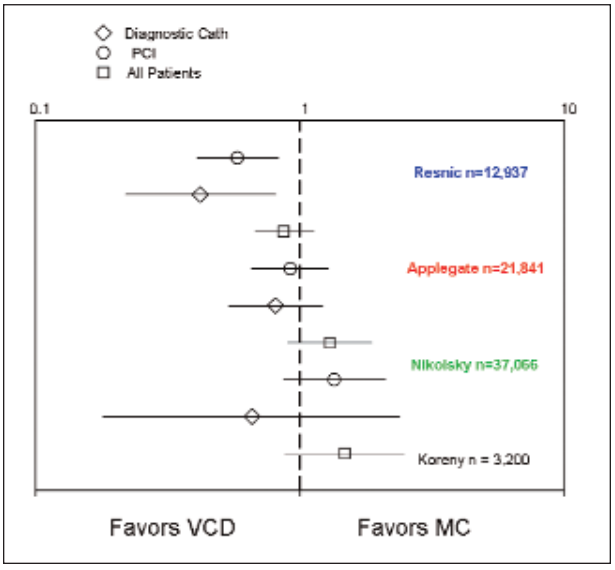

Figure 2. Meta-analyses by Koreny et al,[11] Nikolsky et al,[12] and propensity analyses by Applegate et al[13] and Resnic et al[7] comparing VCDs and manual compression. The meta-analyses suffer from weak underlying studies. The propensity analyses may not fully compensate for variables that may have influenced patient selection for VCDs. In general, the data suggest parity or superiority with VCDs, with the exception of the Koreny et al study, which had a strong trend in favor of manual compression. The trends in favor of manual compression in the Nikolsky et al study were not seen when the VasoSeal data were excluded. Only Resnic et al shows statistical significance in favor of VCDs.

ed to that second tier reserved for VCDs used primarily for diagnostic catheterizations.

TECHNOLOGY IN THE WORKS

A new class of devices has entered the VCD world, best described as "closure begins with access," or CBA. This should be distinguished from "preclosure," typically the deployment of Perclose at the time of initial access and before upsizing the sheath from 6 F or so to very large sizes (up to 24 F in some cases). Preclosure has been around for at least a decade and has had considerable success in settings such as percutaneous stent graft placement for abdominal aortic aneurysms.[2] Now, two true CBA devices have appeared. The FISH (Femoral Introducer Sheath and Hemostasis) device (Morris Innovative Research, Bloomington, IN) uses small intestinal submucosa wrapped around the access sheath, which is deployed as the sheath is withdrawn at the end of the case. This device is FDA approved. Considerable interest has been provoked by the initial presentation of data on the Arstasis device (Modesitt, San Carlos, CA).

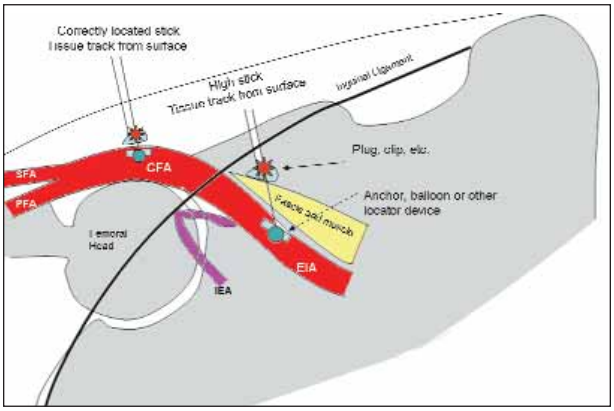

Figure 3. Cartoon depicting vascular closure device deployment in correctly located and high sticks. Note that with puncture above the inguinal ligament, the external iliac artery moves away from the skin surface, and the track passes through layers of muscle and fascia en route to the artery. Various closure devices deploy anchors, balloons, or metal locators inside the artery through a sheath already in the blood vessel. However, the passage of plugs, clips, or other devices onto the surface of the artery through the tissue track may be impeded by the fascial and muscle layers, resulting in failure to achieve closure. CFA=common femoral artery, IEA=inferior epigastric artery, PFA=profunda femoris, SFA=superficial femoral artery, EIA=external iliac artery. (Based on description by Ellis et al.[4])

This technology creates a dissection plane in the femoral artery at the time of access to create a self-sealing mechanism as the sheath is withdrawn at the end of the case. Unlike FISH, the Arstasis concept leaves no foreign body behind. A small, first-in-man pilot study presented at the TCT 2007 meeting was reasonably successful. Several important issues need to be answered before it will be possible to meaningfully comment on the long-term future of the Arstasis concept:

- The applicability of devices based on this technology to interventional cases
- The applicability to femoral arteries with atherosclerosis and particularly calcification
- The potential implications of high or low femoral access
- The ability to use these devices in patients with perivascular fibrosis, such as is seen after multiple femoral access procedures
- The nature of postprocedure healing as compared with manual compression or current VCDs

Both of these devices raise the issue of a need to evaluate the femoral artery before access so as to avoid small or diseased arteries. The need to enter a healthy segment of the common femoral artery may help speed up an

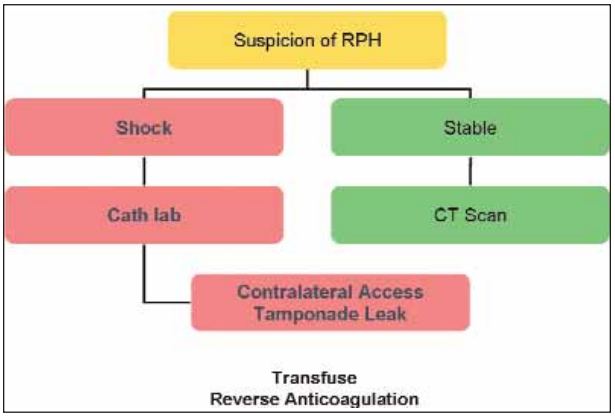

Figure 4. An algorithm for addressing possible retroperitoneal hemorrhage after catheterization. A particular conundrum exists after carotid stenting because sustained hypotension, which should always raise concern about possible bleeding, can result from pressure on the carotid body caused by stent placement.

evolution of two approaches I have advocated in *Endovascular Today* in the past. First, there will be benefit from performance of better and more comprehensive evaluation of the common femoral artery for disease and level of bifurcation *before* access is obtained. Second, use of fluoroscopic and ultrasound techniques can ensure entry into the ideal target zone (Figure 1) in the common femoral artery rather than in one of the bifurcation vessels or above the inguinal ligament.

VCDs FOR OTHER APPLICATIONS

Several VCDs are being adapted for applications other than vessel closure. A logical consideration for suture technologies has been expansion to closure of patent foramen ovale (PFO). Sutura, Inc. has had a recent first-in-man series with the SuperStitch EL, a modification designed for percutaneous PFO closure. At least one PFO was sealed in 2006 with Perclose,[3] and a spin-off from Abbott (Ovalis, Mountain View, CA) has been developing a percutaneous device for this indication. Cardica Medical (Redwood City, CA), which is developing a VCD, is also developing a PFO closure device, although the nature of their technology is not in the public domain.

THE DARK SIDE

All enthusiasm for VCDs needs to be tempered by the dark side of all medical devices: complications. In the VCD world, this issue is exacerbated by the continuing unresolved issue of the risk/benefit ratio of VCDs versus manual compression. Figure 2 shows the relative risk of VCDs versus manual compression in a number of meta-analyses and propensity analyses. There is tremendous noise in these data and, as discussed in several of our previous reviews in *Endovascular Today*, the results are muddled by learning curve issues, changing device platforms, changing clinical practices, and the inclusion of devices or generations of devices that have been supplanted by better technology.

Retroperitoneal Hemorrhage Revisited

Nevertheless, it is clear that some complications are additive to manual compression. These include infection (discussed in detail in last year's review), vascular obstruction, retroperitoneal hemorrhage (RPH), and possibly nerve entrapment. RPH has been discussed in previous years in this article, but in lecturing on this subject, I am reminded that awareness of the potential additional risk of deploying VCDs in high sticks has not been adequately disseminated to the interventional community.

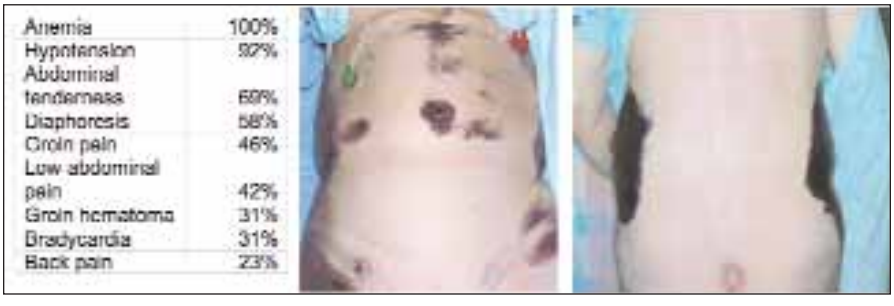

Figure 5. Sensitivity of various symptoms and signs for diagnosis of retroperitonal hemorrhage, based on data from Farouque et al.[10] Although a decrease in hemoglobin is universal, hypotension is usually the earliest finding. Images at right demonstrate the Cullen's and Grey Turner signs, respectively. It is important to note that findings on physical examination such as these are frequently late and, in the case of acute RPH, may occur long after life-saving treatment needs to be instituted. (Images on right reprinted with permission from Mookadam and Cikes.[14] Copyright 2005, Massachusetts Medical Society.)

The salient factors are as follows: high sticks, those above the inferior epigastric artery's lowest point of excursion (Figure 1), are associated with an odds ratio as high as 17:1 of RPH.[4] The mechanism has obvious and somewhat more subtle features. The obvious is the potential for free bleeding into the retroperitoneal space once the inguinal ligament has been crossed. The less obvious is

TABLE 2. AN ALGORITHM FOR PREVENTING AND MANAGING RETROPERITONEAL HEMORRHAGE

1. Access using the iterative fluoroscopic technique described at length in our previous annual articles, with emphasis on puncture over the lower half of the femoral head (Figure 1).

2. Femoral angiography *before* anticoagulation will reveal a high stick and allow the operator to postpone elective interventions. The postponement is an inconvenience to patients and families and problematic to catheterization lab administrators and insurers. Nevertheless, delaying a procedure for 24 hours is far preferable to RPH and its associated 5% mortality rate. RPH in unanticoagulated patients is rare.

3. In the setting of high stick in a patient who is already anticoagulated, use of VCDs may have significant additive risk. In the study by Ellis and colleagues,[4] the odds ratio was 2.8:1, and although it was apparent only for Angio-Seal, it may well be a class effect. In an earlier study from the same institution,[9] RPH despite IIb/IIIa use occurred in <0.2% of patients when manual compression was used and >1% when VCDs were used. I have interpreted that study to suggest that not only is VCD use a potential culprit but also anticoagulation, because VCDs are deployed in fully anticoagulated patients on the catheterization table, whereas manual compression is performed with the ACTs at or near normal levels.

4. Institutions should consider a set algorithm for treating possible RPH after catheterization (Figure 4). Hypotension should always raise the possibility of RPH. The potential for missing the diagnosis is simply too high, and mortality continues to occur too frequently to leave this to ad hoc diagnosis and treatment. Figure 5 shows the relative sensitivity of various findings for RPH after catheterization, based on data from Farouque and colleagues.[10] Note that the most sensitive and specific marker of hemorrhage is, of course, anemia, but because of the equilibration time required for the blood count to fall to diagnostic levels, the confounding effect of dilution typical after catheterization, and the time frame in which diagnosis needs to be made, it is best to make the diagnosis before the blood count becomes diagnostic. Note that the algorithm in Figure 4 features two pathways: one for relatively stable patients and one for patients in obvious trouble—those who are in shock and have not responded to the usual measures, such as fluid bolusing. The CT scanner, although providing the best tool for diagnosis of a stable patient, may not be a suitable location for one who is exsanguinating. We believe that when the facilities and staff are available, unstable patients should be brought emergently to the catheterization lab, and a catheterizer trained in peripheral intervention should obtain contralateral access and be prepared to tamponade a bleeding external iliac artery. If this does not succeed in resolving the hemorrhage after balloon release, a covered stent can be considered depending on anatomy.

5. A *sine qua non* while these maneuvers are being performed is transfusion at the earliest possible opportunity. Two sources of error frequently confound diagnosis and treatment. An ultrasound at the puncture site may be of little use in making the diagnosis of RPH. Chest pain and ischemia on EKG can be a reflection not just of acute occlusion of the freshly intervened upon coronary artery but can instead reflect a combination of decreased oxygen-carrying capacity and decreased perfusion pressure, thereby causing ischemia in unrevascularized areas of myocardium.

the mechanism of failure when a closure device is utilized. Figure 3 shows why a plug (and possibly a stitch, clip, or other element in a closure device approaching through the tissue track) would fail to land on the arterial surface: the presence of layers of tissue, notably the transversus abdominis muscle, obstructs passage down to the artery.

Although still lacking a solid evidence base, several straightforward recommendations for postprocedure management deserve to be emphasized (Table 2). Ultimately, RPH continues to challenge excellent institutions and interventionists. It is unfortunate, because it remains a cause of mortality in every hospital. In my opinion, if the routine steps in Table 2 are followed, the

rate of RPH and its consequences can be decreased substantially, although unfortunately not eliminated.

The FDA Database

Although suffering from grossly incomplete reporting, the FDA Manufacturer and User Facility Device Experience (MAUDE) database remains a treasure trove for assessing the complications associated with technology including VCDs. I reviewed the reports for 2007 available as of February 2008. It is important to point out that a minority of complications are reported, that the details of individual cases are notoriously incomplete, that the data are replete with noise, and there is some duplication. No Clinical Events Committee adjudicates these reports, and thus assignment of causality is hazardous. Further, different institutions, and for that matter, different vendors have disparate reporting standards.

> "... the FDA MAUDE database remains a treasure trove for assessing the complications associated with technology including VCDs."

The five closure devices with a significant footprint in the database (Angio-Seal, Perclose, StarClose, Mynx, and Boomerang) had a total of 1,499 adverse event reports in 2007, including 22 deaths, of which several may not have been device related. Of these 22, 15 were due to bleeding, almost all retroperitoneal hemorrhage, four were due to infection, and three were complications of vascular obstruction. The devices had various propensities for mechanical failure, obstruction of the artery, need for surgical removal, infection, pseudoaneurysm formation, and most importantly, blood loss. It is important to point out that there is no MAUDE database for manual compression, and despite Figure 2, the verdict may never be in on a clear risk-benefit ratio.

THE MEDICAL LITERATURE

Four articles deserve particular mention from the past year. The overall complication rate of vascular access and closure is decreasing, as shown in an analysis of more than 36,000 PCI patients from the Northern New England Cardiovascular Disease Study Group. In the interval between 2002 and 2006, the rate of major vascular complications decreased from 3.4% to 2%.[5] The extent to which this resulted from better access techniques, better adjunctive sheath and pharmacological management, or better VCDs and better VCD deployment techniques is unknown. For a surgeon's perspective on VCD complications, including a suggested algorithm for complication management, the latest article on this subject by Eidt and colleagues[6] is enlightening.

A cost-minimization analysis of VCD versus manual compression by Resnic and colleagues[7] suggests potential cost savings with VCD use, despite the cost of these devices, largely based on a lower complication rate with VCDs—a finding that will not apply universally to all hospitals, operators, or types of VCDs. Finally, a carefully conducted propensity analysis[8] of nearly 13,000 patients undergoing diagnostic catheterization and PCI showed statistically significant lowering of complications with VCD use (Figure 2). This study is part of an overall trend suggesting improving VCD results and hopefully reflects the increasing attention being paid to vascular access and closure in general. ■

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