Postmarket Surveillance of Vascular Closure Devices

The FDA perspective on VCDs and the importance of continued surveillance.

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Bleeding and vascular complications were the most common noncardiac, procedure-related adverse outcomes of the estimated 1,178,000 percutaneous coronary interventions (PCI) performed in 2007.[1,2] While it is not surprising that adverse vascular events are associated with a procedure that begins with puncture of an artery, the number and type of local vascular complications, and the clinical outcomes associated with them (increased morbidity, mortality, and length of stay in the hospital), underscore the importance of continuing surveillance by the Food and Drug Administration (FDA).

Clinicians who performed PCIs in the early years of the procedure achieved hemostasis after femoral sheath removal via manual and/or mechanical compression approaches. These hemostasis strategies required that patients remain immobilized for extended periods of time (up to 8 hours after a procedure). This approach created substantial discomfort and extended hospital stays. Alternative methods of achieving hemostasis were introduced into cardiac catheterization laboratories more than 20 years ago. Loosely termed *vascular closure devices* (VCDs), these alternatives typically included sutures, sealants, clips, and arterial compression mechanisms, and offered clinicians an alternative to manual and mechanical compression. Since the inception of these devices, the federal government has required that they receive premarketing approval from the FDA, as well as undergo postmarketing surveillance and safety assessments. The FDA has approved these devices for the purpose of decreasing the amount of time to achieve hemostasis, which thereby allows patients to ambulate earlier.[3]

Between 1996 and 2000, nearly 2,000 reports of serious adverse events and 36 deaths associated with the use of VCDs were received by the FDA through its routine surveillance system, with a large proportion of these events occurring in women.[4] Because of its concern about these reports, the FDA collaborated with the American College of Cardiology (ACC) and its National Cardiovascular Data Registry (NCDR) to analyze closure device-related adverse events. Analysis indicated that a higher rate of bleeding or vascular complications was associated with one particular device (Vasoseal, St. Jude Medical, Inc., St. Paul, MN; OR = 2.38; 95% CI = 1.47-3.85; P = .0004),[5] which was subsequently and voluntarily removed from the market by its manufacturer. This experience underscored the value of investigating real-world methods of hemostasis via analysis of data collected in observational registries, such as those within the NCDR.

Since that study, the FDA has approved more closure devices, and again collaborated with the NCDR to evaluate safety profiles of the most frequently used closure devices, and compare their safety profiles to manual and mechani-

TABLE 1. MULTIVARIATE ANALYSIS OF COMPLICATION RATES BY DEVICE GROUP FOR PATIENTS WITH FEMORAL ACCESS SITES

	Odds Ratio [95% CI] *P* Value					
	Bleeding OR [95% CI]	***P***	**Vascular OR [95% CI]**	***P***	**Either OR [95% CI]**	***P***
Device group						
Manual compression	--		--		--	
Mechanical compression	1.09 [1.03-1.16]	.002	1.162 [1.09-1.24]	< .001	1.15 [1.10-1.20]	< .001
Angio-Seal	0.84 [0.80-0.87]	< .001	0.458 [0.43-0.48]	< .001	0.68 [0.65-0.70]	< .001
Perclose	0.69 [0.65-0.74]	< .001	0.343 [0.31-0.38]	< .001	0.54 [0.51-0.57]	< .001
StarClose	1.05 [0.98-1.13]	NS	0.385 [0.34-0.43]	< .001	0.77 [0.72-0.82]	< .001
Boomerang	0.98 [0.78-1.22]	NS	0.399 [0.31-0.51]	< .001	0.63 [0.53-0.75]	< .001
Mynx	1.32 [1.16-1.50]	< .001	0.478 [0.39-0.58]	< .001	0.91 [0.82-1.02]	NS
Patches	0.92 [0.86-0.98]	.013	0.527 [0.49-0.57]	< .001	0.70 [0.67-0.74]	< .001

Abbreviations: OR, odds ratio; CI, confidence interval; NS, not significant.

cal compression. This latest study used data obtained from the NCDR CathPCI Registry.[6] Although it is voluntary, several states and health plans require participation in the NCDR CathPCI Registry to fulfill state or performance recognition reporting requirements. As of June 2009, more than 1,200 institutions had joined the CathPCI Registry.

THE NCDR CATHPCI REGISTRY STUDY

This study, by far the largest one ever conducted to evaluate the safety profiles of VCDs, included data from 1,089 sites and 1,861,566 patients who underwent PCI and were discharged between January 1, 2005 and June 30, 2009.[7]

Eight types of hemostasis strategies were evaluated in that study, including manual and mechanical compression, the five major VCDs then in use (Angio-Seal [St. Jude Medical, Inc.] , Perclose [Abbott Vascular, Santa Clara, CA], Boomerang [Cardiva Medical, Inc., Sunnyvale, CA], StarClose [Abbott Vascular], and the original Mynx [AccessClosure, Inc., Mountain View, CA]), and hemostatic patches. Assessed outcomes included bleeding complications (entry site bleed and retroperitoneal bleed), vascular complications (arterial occlusion, embolization, arterial dissection, pseudoaneurysm, and arteriovenous fistula), and "bleeding and vascular complications" (bleeding complications plus vascular complications).

The overall frequency of bleeding and vascular complications was 1.08% and 0.76%, respectively. The most frequent vascular complication, pseudoaneurysm, occurred in 0.41% of patients. Multivariate analyses assessed adjusted odds ratios (with manual compression as the reference group) for each of the other types of hemostasis strategies, for bleeding complications, vascular complications, and bleeding or vascular complications (Table 1).

All of the hemostasis strategies performed significantly better compared to manual compression, except for mechanical compression devices and the original Mynx. The other types of hemostasis all demonstrated significantly lower odds of bleeding or vascular complications compared to manual compression. Every VCD was associated with lower bleeding or vascular complication rates than manual compression for every clinical outcome except for retroperitoneal bleed. Decreasing rates of bleeding and vascular complications were demonstrated over time for each hemostasis strategy assessed.

HISTORICAL CONTEXT

Our findings in the CathPCI Registry study are consistent with the body of literature that examines VCD use specifically associated with PCI, although a majority of this literature consists of small, uncontrolled studies that report a wide range of safety and efficacy endpoints according to varied clinical definitions.

Most recent studies show evidence that VCDs are associated with safety profiles that are not significantly different than manual compression,[8-11] including several randomized controlled trials that compare specific brands to each other and against manual compression controls.[12-16] Several other studies present evidence that VCDs are associated with decreased risk of bleeding and/or vascular

complications,[17-20] including an analysis by Marso et al who used data from the CathPCI Registry to examine periprocedural bleeding complications in 1,522,935 patients.[21] That study used data from the same registry as the FDA-ACC studies, and assessed patients who underwent PCI from January 1, 2004 through September 30, 2008. It found that VCD use was associated with a significant reduction in bleeding events compared to manual compression (OR = 0.77 [0.73-0.80]). Another large registry capturing 45,987 patients undergoing PCI from 2002 to 2007 found VCD use to be associated with a significant reduction in bleeding and vascular complications for both men and women compared to non-VCD use (OR = 0.75; $P < .007$ and OR = 0.72; $P = .0002$, respectively).[22] Although these large, representative registries did not report their findings by device type, the results regarding local vascular complications of VCDs as a whole are very similar to the FDA-ACC findings noted previously.

An investigation of predictors of retroperitoneal hemorrhage after PCI in 112,430 patients in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) Registry found that VCDs, and in particular Angio-Seal (St. Jude Medical, Inc.), were more frequently used in patients who developed retroperitoneal hemorrhage than in those who did not. The association was significant for Angio-Seal (OR = 1.68; $P < .0001$), whereas it was nonsignificant for Perclose (OR = 1.29; $P = .13$).[23] Our study found that retroperitoneal bleed occurred in 0.38% of patients who received Angio-Seal, compared to 0.22% who received Perclose, and 0.26% of the manual compression controls; thus confirming the BMC2 study with regard to the relatively high risk of Angio-Seal (and some other VCDs) for retroperitoneal bleed.

Four separate meta-analyses evaluated trials related to the early generations of VCDs and demonstrated a considerable amount of overlap with each other.[24-27] Two of these meta-analyses evaluated outcomes from the initial clinical trials of VCDs,[25,26] and another one was also influenced by the results of these trials.[27] The major finding from these meta-analyses was that VCDs generally performed as well or better than manual compression controls, but that there was strong evidence to show that Vasoseal performed substantially worse than either Perclose or Angio-Seal with respect to the three most frequently reported outcomes—hematoma, bleeding, and pseudoaneurysm.

A meta-analysis by Koreny et al,[25] which included almost 4,000 patients across 30 clinical trials, suggested that when results were limited to trials that used intention-to-treat analysis, VCDs were associated with a higher risk of hematoma and pseudoaneurysm. However, there was no separate analysis of diagnostic and interventional procedures, and the results must be interpreted with caution due to the variability of study reporting and endpoint definitions.

For example, Nikolsky et al[26] catalogued the wide range of hematoma definitions described in study methodologies and noted at least a dozen different descriptions in the 30 trials included in their analysis. That study attempted to address the heterogeneity of study results by performing separate analyses of diagnostic and PCI procedures, as well as by device type. With respect to major vascular complications, the authors found that Angio-Seal and Perclose were similar to manual compression for complications associated with PCI.

A meta-analysis by Biancari et al reflected relatively more recent randomized studies (about a third of the included studies were published after the previous three meta-analyses), but is generally consistent with the other three meta-analyses.[27] That study found some evidence for an increased risk of groin infection, arterial complications resulting in arterial stenosis, and lower limb ischemia, as well as the need for vascular surgery for repair of arterial complications after the use of VCDs. These findings appear to be more evident in patients undergoing PCI than diagnostic procedures, although the authors note that they may be significantly biased by the poor methodological quality of available studies.

CONCLUSIONS

Overall, the medical literature on this issue has been highly consistent, with large studies and meta-analyses demonstrating good safety profiles for VCDs compared to manual compression controls across a wide range of treatment groups and clinical outcomes. Most studies were very small compared to the FDA-NCDR Cath-PCI registry study, and consequently many of them demonstrated no statistically significant clinical differences between manual compression and VCDs.

It is, however, possible that unknown and unmeasured variables could have exerted a confounding effect that was undetected by the medical literature. For example, physicians may have been reluctant to use VCDs in certain high-risk situations, such as when an injury occurred to the vessel wall during the procedure, when a groin hematoma occurred during the catheterization, or when a predeployment femoral angiogram demonstrated the puncture site to present a risk that was thought to contraindicate the use of a VCD. If so, these considerations would have biased the study results against manual compression. This type of situation probably accounts, at least in part, for the apparent protective effect of VCDs. On the other hand, a very high puncture (with consequent high risk of retroperitoneal bleed) may have encouraged the use of a VCD because of the difficulty of manual compression in those

cases. Another unmeasured confounding variable could have been sheath size, which is known to be associated with a high risk of local vascular complications,[5] and which could also have been correlated with a decision not to use a VCD, thus biasing the study results in favor of VCDs.

The one clinical endpoint for which the medical literature demonstrates worse outcomes for VCDs compared to manual compression is retroperitoneal bleed. With retroperitoneal hemorrhage, the back wall of the femoral artery has been punctured, meaning that the femoral artery has been punctured completely through. VCDs are only capable of controlling bleeding from the puncture site, whereas manual compression controls bleeding from both the original puncture site and the back wall puncture site, by compressing the femoral artery.

Studies in the medical literature that demonstrated superior safety profiles for the VCDs compared to manual compression controls tended to analyze data accrued over more recent time periods. There are three possible explanations for these improving safety profiles over time: (1) over time, the VCDs have become smaller and less cumbersome and easier to use; (2) health care professionals using the devices have become more adept at using them as they gain more experience with them; and (3) case selection may have improved over time.

Finally, it should be emphasized that our experience has shown that large and high-quality registries have the potential to play a vital role in the FDA's surveillance efforts. Compared to most or all research studies reported in the medical literature, studies using large registries have several important advantages: (1) they usually contain sample sizes that are orders of magnitude larger, thus providing more power to detect differences in low frequency adverse events; (2) by virtue of the fact that they assess experience from a large variety of geographically separated medical institutions and providers throughout the United States, rather than a single or small number of institutions, they tend to reflect outcomes that are more representative of national experience; (3) the use of uniform methodologies across institutions enhances the ability to interpret results, compared to meta-analyses, which almost always assess numerous institutions that use disparate methodologies; (4) they are much more likely than single-site studies to allow for comparison of multiple hemostasis strategies; (5) large numbers of subjects and sites is conducive to greater efficiency of resource use, which thereby reduces cost compared to studies that use a single or a small number of sites; and (6) once a large registry is established, it can be used to answer many different research questions that arise over time. ■

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Editor's Note: In the original printing of this article, MynxGrip was incorrectly listed as one of the eight devices in the CathPCI registry study. The correct device is the original Mynx (AccessClosure, Inc., Mountain View, CA).

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