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EDITORIAL COMMENT

Arteriotomy Closure Devices—The FDA Perspective*

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In this issue of the *Journal*, Dangas et al. (1) assessed the incidence of vascular complications at the Washington Hospital Center following percutaneous coronary interventions (PCI) when arteriotomy closure devices (ACD) were used to achieve hemostasis of the femoral artery versus when manual compression was used. Their main finding was that three vascular complications—hematoma, hematocrit drop of >15%, and the need for surgical repair of the access site—were approximately twice as frequent in patients in the ACD group than in the manual compression group.

First and foremost, Dangas et al. (1) are to be commended for their effort, which represents important and useful information not only to clinicians but also to other stakeholders, including patients, regulated industry and the

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Food and Drug Administration (FDA). All of us share in a mutual responsibility to continue to assure the safety and effectiveness of marketed medical devices. Studies like this help achieve that goal.

To put their study by Dangas et al. (1) in perspective, we reviewed several previous studies that compared the incidence of serious complications associated with ACDs with those from manual compression (2–13). Most of these studies found no significantly greater incidence with the use of ACDs (2–10). Besides the lack of power to detect small-to-moderate differences in most of these studies, use factors must be taken into account. These factors include improper patient selection, insufficient or inadequate training of the device operator, and poor recognition of postprocedure patient problems. Improper patient selection might include patients that are obese, very slight of build, or have a history of high blood pressure and peripheral vascular disease. Improper training might occur when a user has less than optimal training or experience or attempts to use the device with no training. Adverse events due to these problems may involve postprocedure patient problems that are not recognized until the patient's status is severely compromised. Some institutions, however, might be more proficient in the use of these devices (especially those that participate in clinical trials) and, therefore, experience lower complication rates than other institutions.

Conversely, some studies have found significantly greater complication rates with ACDs (specifically, collagen plug-type devices) than with manual compression (11–13). In addition, the study by Shrake (13), like the Dangas et al. (1) study, found statistically significant higher rates of vascular complication with one brand (Angio-Seal) compared to others. The study by Dangas et al. (1), however, shows a tendency to higher rates, with all but one of the other devices as well (although not so statistically significantly).

One of the potential problems with this study, as with any epidemiologic study, concerns the manner in which subject (i.e., those who had ACDs used on them) and control status (i.e., those who had manual compression applied to them) was determined. In this study, as the investigators state, determining subject and control status was by the preference of the individual physicians. This raises the possibility that subjects and controls may have differed in substantial ways, and that these differences might have contributed to some or all of the differences in clinical outcomes.

The investigators (1) attempted to deal with this potential problem by identifying several potential confounding variables and then statistically controlling for them in the multivariate analysis. It is unclear to us why some of the baseline characteristics and procedural variables identified by the researchers in Tables 1 and 2 of their study were apparently not included in the multivariate analysis. In particular, previous myocardial infarction, history of PCI and use of debulking devices were all significantly more frequent in the control group than in the subject group, and yet they were apparently not considered in the multivariate analysis. Nevertheless, given the small differences in these variables between the two groups it does not seem at all likely that failure to control for them would have substantially influenced the final results.

In addition, it would have been useful to know something about how physicians made the determination of whether or not to use an ACD—in particular, did they preferentially, but unknowingly, choose patients who were at high risk for complications for ACD use? If so, that could have accounted for some or all of the differences in clinical outcomes between the two groups. However, we can think of no reason to believe that that was the case.

A final point on the issue of confounding concerns activated clotting times (ACTs). Although Table 2 in the Dangas et al. (1) report notes the average final ACT values (presumably at the end of the PCI procedure) for both the subjects and controls, the more clinically, likely and signif-

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icant difference in ACTs would be the difference noted at the time either the ACD or manual compression was applied. Because ACDs are applied right after the procedure, ACTs for the subjects would approximate the final procedural value (i.e., on average 277 s), whereas ACTs for the controls would be <150 s (per hospital protocol). The investigators rightly stress in their Discussion section that this could have been a reason for the higher complication rate in the ACD group. If ACT values at the time of manual compression are available for the control group, then entering the subject and control values into their regression equations could reveal to what extent this variable was responsible for the observed differences in complication rates.

One aspect of the multivariate analysis was somewhat confusing. The ACDs were found to be associated with major hematoma (as they were in the univariate analysis) with an odds ratio (OR) of 4.28 and a p value of <0.001, yet ACDs were not noted to be significantly associated with "any vascular complication." This is very hard to understand, for hematoma accounted for almost half of the vascular complications noted in this study, and ACDs were also significantly associated in the univariate analysis with hematocrit drop, "major hematoma" and surgical repair. Thus, ACDs were significantly associated with vascular complications in the Dangas et al. (1) study, with a relative risk (RR) of approximately 2, which together accounted for 99 of 111 (89%) vascular complications identified in this study, and yet ACDs were not associated with "any vascular complication" in the multivariate analysis when controlled for age, body surface area and gender. We believe that identification of the reason for this perplexing finding could be very interesting.

A couple of points should be made with regard to ascertainment of complications. Given the retrospective nature of the study, it is unclear to what extent there was any differential recording of complications (e.g., hematoma) in the medical or other record by subject or control status. One could argue that this could more likely occur with "softer" findings (such as hematoma) than with "harder" outcomes (such as surgical repair). But the differential recording would have to be systematic to bias the results, and no evidence or likely scenario suggests that. In addition, it should be noted that this study is limited to in-hospital complications and does not capture postdischarge events. Both overall and complication-specific risk estimates would be affected to the extent that postdischarge complications are more likely to occur in subjects or controls.

The investigators rightly note in the first paragraph of their Discussion section that ACDs may result in rapid hemostasis, early ambulation, and "*ideally* achieve *potentially* fewer complications." Yet their study suggests just the opposite—that ACDs result in more, not fewer, complications. This issue is obviously of importance to the FDA. The question: "Do ACDs cause an excess of serious complications and deaths as compared with manual compression?" is critical to the FDA and must be assessed given the totality of evidence and the benefits of the device.

In their Limitations section the investigators note, among other things, two issues that would appear to make the results of their study of limited usefulness. One is their statement that: there was no uniform, laboratory-initiated, standardized training for ACD selection and application. We believe that this fact, from a practical standpoint, may actually make these study results more, rather than less, important. Clinical trials that avoid the above-noted problem may sometimes demonstrate greater device safety and effectiveness than will later be seen for a given device "in the real world" after it is marketed. This would tend to occur if the clinical investigators are better trained in the use of complicated and difficult-to-use medical devices than most practitioners, who will actually use the device after it is marketed. A related problem, which applies both to clinical trials and to this type of study, is that the results of these studies apply to specific clinical setting(s) and may not be generalizable to the larger universe of clinical settings. One way to address this problem is to design a population-based study to examine these issues. To date, none have been conducted.

The investigators note at the end of their report that their results may not be applicable to newer "generations" of ACDs. This type of statement is probably applicable in greater or lesser degree to most studies of medical devices, as changes that presumably result in improvements are continually made during the life cycles of most of them. Nevertheless, we believe that the evidence of serious and potentially fatal complications noted in the Dangas et al. (1) study warrants continued research and monitoring. It is important to learn about these problems because they may be applicable to subsequent generations.

Finally, the Dangas et al. (1) study must be viewed in the broader context of postmarket surveillance. Once a product is marketed, the FDA routinely receives reports of device-related adverse events and product problems through its nationwide voluntary and mandatory Medical Device Reporting (MDR) system (14). Indeed, by the end of year 2000, a total of 1,879 reports of serious injuries (mostly hemorrhage, hematoma and infection) and 36 reports of deaths associated with the use of ACDs had been received (15). The reports are reviewed individually from a variety of perspectives (i.e., the device, the user and the patient) that might signal problems—for instance, with manufacturing, labeling (including instructions and training), device design (e.g., one that induces human error) or biocompatibility. Although reports of the type received (e.g., hematoma) are expected given the nature of the device, the relative novelty of the technology, and the fact that a variety of less experienced clinicians will use the device in a wider array of patients, the severity of some of the events and the shear number do arouse concern.

Although the MDR system serves a vital "signaling" function of potential product problems, its limitations

preclude us from making risk assessments that studies of the kind discussed here can. The important limitations in this regard are: 1) significant underreporting of actual incidents; 2) lack of use data to derive actual incident rates; and most germane to the Dangas et al. (1) study, 3) similar complications following PCI—where manual compression rather that an ACD is used for hemostasis—are not reportable. Therefore, we are not able to conclude from the MDR reports alone that hemorrhagic complications following PCI are any more frequent when ACDs are used than when they are not used. We rely on observational studies in the postmarket period to assess further the risk/benefit ratio as product development and improvement occurs.

To be most effective, however, these studies need to: 1) address specific public health questions, 2) be timely, and 3) be considered important by not only the clinical community but also by the regulated industry and the FDA. Depending upon the specific public health question, various study approaches and designs may be pursued to address the issue most efficiently and effectively. Although the FDA has the statutory authority to mandate manufacturers to conduct postmarket studies (either as a condition of approval for marketing or "for cause" later in the postmarket period), the agency prefers to work collaboratively with clinicians and the regulated industry to enhance and continue to develop a postmarket framework that provides early signals of potential problems and that addresses new and ongoing concerns with effective postmarket tools. To that end, the FDA has been recently working with the clinical community and regulated industry to foster the development and use of cardiovascular registries. It is tools such as these, and the continuing applied research by the clinical community as evidenced by the report by Dangas et al. (1), that will provide the postmarket surveillance needed to protect the public health.

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