Regarding “Withdrawal of article by the FDA after objection from Medtronic”

As one of the authors of the paper “Aneurysm-related mortality rates in the US AneuRx clinical trial,” which was accepted for publication and then withdrawn by the FDA under threat of legal action from Medtronic, I write to respond to the issues raised by the Cronenwett and Seeger editorial (J Vasc Surg 2004;40:209-10). In a letter to the FDA, Medtronic claimed that the outcomes data used were “proprietary information” protected as confidential. In fact, the data were used in the FDA’s AneuRx Public Health Notice dated December 17, 2003, making the information public, and the manuscript had been cleared by the FDA’s Freedom of Information Office as containing neither proprietary nor protected health information. Medtronic was also concerned that we had used the predicted mortality rate of 1% to 2% from open repair to show that the cumulative aneurysm-related death rate following use of the AneuRx graft would exceed that of open repair after the second year of follow-up. In fact, the evidence supports this conclusion, showing that the rate of mortality in the AneuRx patients does not decline with time. Previous published studies justifying the 2% open mortality rate for high-volume institutions for comparison, especially since the AneuRx cohort excluded patients with serious comorbidities such as renal failure, obesity, ASA above level IV, and aortoiliac occlusive disease. The question of whether the mortality rate in AneuRx patients actually increases with time is a valid concern since the trend in the data was not statistically significant. This could be answered by additional data held by the company since the information submitted to the FDA did not go beyond October, 2002.

Of most concern is the response of FDA administration, which failed to support its own investigators after evidence that there was no merit in the company’s complaints. This study belongs in the leading vascular journal so that it can be debated nationally and internationally. Just as patients still die from pulmonary embolism after placement of a Greenfield filter, patients are dying from aneurysm rupture after placement of stent grafts. It does not mean that either technology is inappropriate treatment. Instead, users of these devices and their patients should be fully informed of their associated risks. Inability to publish this manuscript will have a chilling effect on further critical investigation at the FDA, and could undermine the confidence of physicians and the public in its objectivity.

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Inappropriate industry influence on FDA processes

The recent withdrawal by the FDA of a peer-reviewed manuscript concerning the AneuRx stent graft as a result of legal pressure from industry is an alarming episode that should trouble all health care providers as well as the public at large. As reported in the 9 July 2004 Wall Street Journal, the FDA made this request under direct threat of litigation by Medtronic after the accepted article, which included publicly available information, had initially appeared on the Journal of Vascular Surgery Web site. The mission statement of the FDA notes that it performs “. . .high quality, science-based work that results in maximizing consumer protection.” For the past 15 years, I have voluntarily served as a consultant to the Circulatory Devices Panel of the FDA and have had the privilege of working with many FDA employees who are incredibly dedicated, hard-working public servants of unquestioned ethics, who strive to carry out that mission every day of their professional lives. I continue to have nothing but the utmost respect for their service. My concern is with the political leadership of the FDA. It is unacceptable that this mission should be compromised by extraneous pressure to impede the dissemination of information. What is particularly disconcerting is that the episode depicted in the Wall Street Journal article is strikingly similar to an experience I have had recently with the FDA.

I had been invited to participate in the FDA Circulatory Devices Carotid stent panel meeting in April 2004 concerning the SAPPHIRE carotid stent trial. I felt well qualified to participate in this deliberation in light of my long-standing interest in carotid artery disease. Although I believe that carotid endarterectomy is the best treatment for the majority of patients with carotid disease, I believe carotid stenting is appropriate for truly high-risk patients and have recommended this in my practice. My public position on these issues, including the SAPPHIRE trial, was well known to the leadership of the Circulatory Devices panel prior to my inclusion on the carotid stent panel. Over the last 15 years of service that I have provided to the FDA, there never has been a question of my commitment to a fair, ethical, and unbiased assessment of the data presented to our panel meetings. However, somewhat inexplicably, just a few weeks prior to the carotid stent panel meeting, I was called by the leadership of the Circulatory Devices section and informed that I was being dropped from the panel because of my public commentary concerning carotid stenting. After I wrote a strongly worded letter of protest, and emphasized that my public statements on the issue were well known to the FDA prior to my selection for the panel, I was explicitly told by an individual at the highest level of leadership in the Devices Section that “if I were allowed to participate, and if the carotid stent device under consideration were not approved, the FDA would be sued by the industry sponsor.” It was clear that I had been eliminated on the basis of pressure from industry, in this case Cordis, Inc. I was, needless to say, dumbfounded, but in light of the recent AneuRx manuscript withdrawal, perhaps I should not have been. The FDA had apparently reacted on the basis of a fear of litigation, as subsequently was the case with the AneuRx article. It appeared to me that the FDA leadership had caved to pressure from those it was supposed to regulate, and this is absolutely unacceptable.

While FDA personnel have always and must continue to work closely with industry in the design and evaluation of device trials, it appears that the leadership of the FDA has recently yielded excessive control of that regulatory process to the industry that it is supposed to regulate, and this is wrong. Suppression of the publication of trial data, positive or negative; preventing the communication of information that consumers and health care providers need to make informed judgments; and undue control, including veto power, over who can most effectively support the regulatory function of our government in assessing medical device and pharmaceutical scientific studies is intolerable, and will ultimately be detrimental to all stakeholders in the system, and most importantly our patients. The public interest should be our moral compass.

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Misperceptions regarding the long-term safety of the AneuRx stent graft

On July 9, 2004, the Wall Street Journal reported that an article posted on the Journal of Vascular Surgery Web site was
withdrawn from publication by the FDA as a result of lobbying by Medtronic. According to the Wall Street Journal, this article “raised concerns about the long term safety record of a device” which was the subject of a Public Health Notification (PHN) by the FDA in December 2003. We regret that the article will not be published for it would provide an opportunity to examine evidence upon which clinical practice decisions may be based. We hope that this letter will provide information on the long-term safety of the AneuRx stent graft that can be weighed against the FDA PHN and media interpretations.

In the PHN, the FDA reported its analysis of 942 patients treated with the AneuRx stent graft and found a 30-day abdominal aortic aneurysm (AAA) death rate of 1.5%, with 8 late AAA deaths during 8 follow-up years. The cumulative AAA death rate was 2.7% at 3 years, which was lower than the 3.1% AAA death rate reported for all 1193 patients treated during the AneuRx clinical trial, due to exclusion of high-risk patients from the FDA analysis. It was also lower than the 5% to 5% operative mortality for surgery, which the FDA found in the literature. However, rather than reassuring patients with these good results, the FDA suggested that the risk of late AAA-related mortality associated with AneuRx may exceed that associated with open surgery and the overall AAA-associated mortality from open surgery at some point in time. How could the FDA arrive at this remarkable conclusion? Perhaps the supporting data appear in the “squelched” article, and these needs to be published.

From our reading of the PHN, it appears the FDA assumed that operative mortality for surgery is 1% to 2%, that late AAA death rate is 0.18% per year (as opposed to 0.4% per year for AneuRx), and that late adverse events for both increase linearly with time. We find little data to support these assumptions. There is, however, actual data with Kaplan-Meier analysis extending to 5 years for all 1193 AneuRx clinical trial patients. How do the FDA’s projections compare to these actual data? Since the FDA excluded high-risk patients, we excluded the 262 high-risk patients in the trial, leaving 931 patients, very similar to the 942 patients studied by the FDA. The AAA death rates for these 931 patients at 30 days and 1 to 5 years are as follows: 1.5%, 1.5%, 1.8%, 1.9%, 2.5%, and 2.5% (Kaplan-Meier analysis). Thus far, there have been no AAA deaths beyond 4 years, suggesting that AAA death for AneuRx patients does not increase linearly with time. Using the FDA’s estimate of 0.18% per year, and assuming operative mortality rates of 2% and 5% at 5 years, the AAA death rate for surgery would be 2.9% and 5.9%, both higher than the actual 2.5% 5-year AAA death rate for AneuRx. Thus, evidence for a late “cross-over” of results is lacking.

We call for publication of the article containing the evidence upon which the FDA has made practice-based recommendations in its PHN so that patients and physicians can judge the evidence and select the best treatment option.

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REFERENCES


Regarding “Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: Implications for selecting patients for carotid angioplasty and stenting”

A recent article by Mozes and associates (J Vasc Surg 2004; 39:958-965) seeks to compare 2 groups of patients who underwent carotid endarterectomy at a single institution over a 5-year period. These 2 groups were defined as high risk and low risk, ostensibly on the basis of the eligibility criteria of the high-risk SAPIR randomized trial of stenting versus endarterectomy. The reference that the authors quote, however, is not from the SAPIR trial. Rather, the high-risk criteria were extracted from an article by Jordan and colleagues.

That aside, the authors aptly concluded that endarterectomy can be performed in high-risk patients with acceptable risks of stroke and death. The question of whether carotid stenting should be considered in such high-risk patients, however, cannot be resolved by a comparison of outcome in high- and low-risk patients. Rather, this question is best answered through a randomized comparison of stenting and endarterectomy, either in lower-risk patients (eg, the CREST trial) or higher-risk patients (eg, SAPIR).

The authors reasoned that similar results with endarterectomy in high-risk versus lower-risk patients raise questions about the appropriateness of stenting as an alternative to endarterectomy. But the authors’ own data document a mortality rate of 0.6% in high-risk patients versus 0.0% in low-risk patients (P = .11, calculated with the χ² test and from their data). When the high-risk subgroups were compared with lower-risk subgroups, the stroke rate was 1.9% versus 1.1% (P = .45), the frequency of perioperative myocardial infarction was 3.1% versus 0.9% (P = .05), and the rate of the composite stroke and death myocardial infarction was 9.3% versus 1.6% (P = .000001). For each end point, the point estimates were higher in the high-risk patients. While some end points did not achieve statistical superiority, the failure to detect statistical superiority does not exclude an end point with conviction. Said another way, the P value of .11 suggests that we are “only” 89% certain that the mortality rate was greater in the high-risk patients. Although the SAPIR data have not yet appeared in the literature, the data presented to the Food and Drug Administration panel this April suggested that the results of stenting were equivalent or superior to endarterectomy. The demonstration of non-inferiority of stenting is all that will be required for patients to preferentially choose a procedure that avoids a neck incision.

Vascular surgeons appear best-equipped to care for patients with carotid disease: they understand the anatomy, the indications for intervention, and the necessity for long-term follow-up. We can choose to become proficient at carotid stenting and be able to offer it as one potential treatment option. Alternatively, we can discount this new modality, but we will risk relinquishing the responsibility for carotid diagnosis and treatment to other specialty groups who may be unaccustomed to caring for patients with cerebrovascular disease.

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