Title

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Letters to the Editor

Data That May Shed Some Light On: "Arguments Against Insisting on Randomized Trials for PFO Closure"

TO THE EDITOR

A recent article in CCI [1] argues that the FDA should adopt a different approach than insisting on a randomized clinical trial (RCT) and permit the use of PFO closure devices to treat patients with cryptogenic stroke from a presumed paradoxical embolus.

The author acknowledges that randomized trials comparing a device with medical therapy would result in powerful evidence that would support broad physician and patient consensus. Nonetheless, he opposes RCTs on practical, not theoretical grounds, arguing that, due to slow enrollment, "...trial completion can be anticipated no sooner than the year 2017."

This argument is not valid. Perhaps this reasoning is based on his experience with the CLOSURE Trial using the CardioSEAL (NMT Medical) device. However, the RESPECT trial using the Amplatzer device (AGA Medical) is recruiting patients at an acceptable rate of >100/year and is on target to achieve a sufficient number of enrolled patients by 2009 with publication of results in 2010. Although this may not be as fast as we all would like, the time frame is not unreasonable and it certainly argues against the gloomy prediction that these trials do not "...enroll at a rate that would encourage any optimism that they will proceed to completion."

The rate of enrolling patients into the RESPECT Trial is shown in Fig. 1. These data have not been presented before because the trial is not finished, but we felt it was important to speak out because the propagation of the concept that the trials will never be completed will only lead to discouragement among physicians and patients and make it more difficult to enroll appropriate candidates.

If the randomized trials are not completed, there will always be nagging questions about the relative benefit and safety of these devices. Only a well-designed RCT will convince all practitioners, patients, and payors that device closure is appropriate therapy for PFO and cryptogenic stroke. The RESPECT Trial is designed to demonstrate a statistically significant difference for recurrent stroke between medical and device therapy to close a PFO. All physicians should be encouraged by the information that trial completion is achievable in an acceptable time frame so that they will enroll all appropriate patients in the randomized trials. Interventional cardiologists should recognize that they perform a significant disservice to patients if they circumvent the RCTs and close a PFO "off label." National treatment guidelines from the American Heart Association and the American Academy of Neurology do not recognize device closure as a therapy of proven benefit for cryptogenic stroke patients with PFOs and support the referral of patients for enrollment in RCTs [2,3].

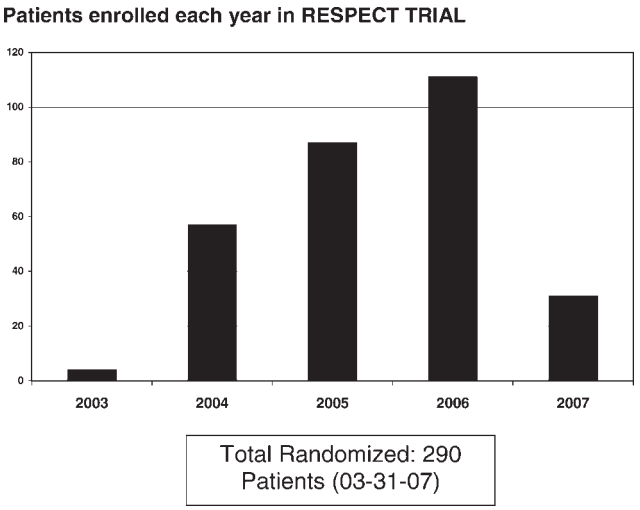

Fig. 1. Patients enrolled each year in RESPECT TRIAL.

The accompanying articles in the same issue of CCI [4,5] emphasize the many problems that will persist if an RCT is not accomplished in the field of PFO and cryptogenic stroke. Cryptogenic stroke is a disease state which is incompletely understood and diagnosed by variable means. Recurrent event rates under medical treatment are highly variable across different studies. Nonrandomized comparisons are vulnerable to

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health cohort bias, outcome observer bias, and other confounders. The risks and efficacy of different devices appears nonequal. Specifically, the rate of thrombosis on the devices and risk of embolization of thrombus from the device within the left atrium is different between the devices [6]. In addition, the incidence of complete closure is different between devices. Therefore it is necessary for each device to demonstrate its benefit by the only means that scientific inquiry has proven to be acceptable: an RCT. This conclusion was unanimously reaffirmed by the Circulatory System Devices Panel at an open meeting of the FDA on March 2, 2007. The clinical and research community can be reassured that with a little perseverance and cooperation from referring physicians, true RCT data will soon be available.

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