When Should We Start Randomized Trials for New Devices?*
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This year marks the 20th anniversary of the publication of Gruentzig’s landmark work in development of percutaneous transluminal coronary angioplasty (PTCA) (1). In the 20 years since its inception, angioplasty has evolved from a crude, often unsuccessful, often dangerous intervention to a mainstream in the treatment of symptomatic coronary artery disease (2). As an early observer and investigator of this technique, I marvel at the extraordinary advances that have occurred over the last two decades. At its inception, angioplasty was performed by skilled but inexperienced operators, working with crude fluoroscopic images, no replay capability and crude, bulky, rigid, nonsteerable catheters. It is little wonder that even with stringent selection of soft, short, concentric lesions in proximal vessels, only a 64% success rate was achieved (3).

I can clearly recall performing angioplasty on a patient in 1983 and observing a major non–flow-limiting dissection in the dilated vessel. I called numerous colleagues (including Dr. Hartzler and Dr. Gruentzig) to seek advice on whether the patient would require an urgent operation and whether coronary aneurysm or rupture would occur in the convalescent phase. No one had definitive answers on how to treat this patient. In the early 1980s these types of questions often arose. The early operators were not only hampered by inadequate equipment but also by a dearth of data with which to make important decisions. Despite these shortcomings, the field of angioplasty rapidly evolved. A few committed, intrepid investigators pushed the field of angioplasty and carefully documented their results (4). Information was informally exchanged at small demonstration courses and prospective registries were published (5).

The late 1980s saw an explosion in popularity of PTCA. Formal interventional fellowship programs were formed, and dramatic advances in imaging equipment and dramatic improvements in flexibility and steerability of catheters occurred. By 1990, 500,000 patients a year were being treated with PTCA. These accomplishments occurred without the benefit of randomized clinical trials (RCTs). The first RCT of angioplasty therapy validated its use in acute infarction (6). The predominant indication for angioplasty in the 1980s was for treatment of symptomatic angina. A RCT of angioplasty for symptomatic angina was not published until 1992, or 15 years after the inception of the technique (7). Shortly after this study, comparisons of angioplasty to coronary artery bypass graft surgery for treatment of multivessel disease occurred (8). By the time balloon angioplasty was subjected to formal, randomized comparison, it was a mature discipline with large numbers of trained operators, excellent refined equipment and a large data base for intelligent patient selection and periprocedural management. A simple question must be asked: Was society harmed or benefitted by the way in which coronary balloon angioplasty was developed and validated? The reason this fundamental question must be asked is because this proved, successful method for new device development may never be repeated.

Imagine a young Andreas Gruentzig trying to introduce coronary angioplasty in 1999 rather than 1979. Two major hurdles would assuredly thwart his efforts. First, federal regulations would place enormous road blocks. Extensive animal testing would be required. Not only would acute animal safety experiments be required but long-term healing data would also be needed. The expense of this extensive preclinical testing data would mandate venture capital funding. This in turn would place enormous time pressures for start and completion of RCTs. Today the RCT completion is imperative because without it, no insurance coverage for hospital stay or reimbursement for catheter costs would occur. Thus, in 1999, a young Gruentzig would quickly lose control of his idea and be totally stymied by regulatory road blocks. In addition, his new idea would be forced into immediate randomized comparisons. Imagine using the original Gruentzig balloon catheter today in comparison to single-vessel bypass! Balloon angioplasty would never have been validated and developed; atherectomy would never have existed; and coronary stent implantation would not have its delivery platform. Again, the fundamental question must be asked: Was society harmed or benefitted by the way in which coronary balloon angioplasty was developed?

In this issue of the Journal, Tsuchikane et al. (9) report the final results of the STent versus Directional Coronary Atherectomy Randomized Trial (START). The operators use an aggressive debulking technique guided by intravascular ultrasound to obtain results superior to elective stent implantation. The START investigators have proceeded with a line of investigation that has formally tested directional atherectomy in three previous RCTs. These RCTs were conducted only after a large experience base of clinical

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use of this device occurred (10). The superb initial and long-term results from START are not only a testament to the excellent skills of the START investigators, but also show a maturation of the directional atherectomy technique. With each subsequent RCT, lumen stenosis has decreased and target lesion revascularization rates have fallen (Fig. 1). At the time of the original RCT (Coronary Angioplasty Versus Excisional Atherectomy Trial [CAVEAT]), controversy existed about how aggressive one should be with atherectomy. Concern had been voiced based on animal (11) and clinical (12) series that deep, subintimal resection would accelerate restenosis. Thus in the CAVEAT study, a conservative strategy was used with 5F and 6F catheters in 53% of cases, and a final residual stenosis of 29% was achieved. Careful analysis of atherectomy biopsy samples from the CAVEAT I and II trials in fact refuted the relation between depth of tissue resection and restenosis (13). On the basis of the unimpressive results of CAVEAT I and armed with the superb CAVEAT histologic data, the Balloon vs. Optimal Atherectomy Trial (BOAT) investigators (14) later clearly demonstrated that an aggressive debulking technique could result in lower residual stenosis and lower restenosis rates as compared with balloon angioplasty. In the BOAT trial, 7F cutters were used in 95% of cases and balloon postdilation was used in 81% of cases. As a result, final lumen stenosis was 15%. As a consequence of this aggressive debulking, angiographic restenosis was significantly lower for atherectomy than for balloon angioplasty. Further armed with these encouraging BOAT results, the START investigators used an even more aggressive debulking strategy. Seven French cutters were used in 65% of cases and 7F graft cutters were used in 35% of cases. High pressure balloon inflations were used to obtain a 1.1:1 balloon to artery ratio. In fact, 27% of cases had 4.0-mm balloons used after dilation. Presumably because of the use of intravascular ultrasound guidance, no coronary perforations occurred. A final residual stenosis of 13% was achieved, and this was associated with lower angiographic and clinical restenosis rates than with routine stent implantation. Since the completion of START, a mature discipline of directional atherectomy exists. Indications are well established for lesions not well suited for stent implantation such as ostial left anterior descending coronary artery or true bifurcation lesions. Directional atherectomy may be the procedure of choice for these lesions. The major scientific underpinning for directional atherectomy, including all the randomized trials, was obtained after federal approval and commercial availability. Was society harmed by this method of device development?

Imagine a young John Simpson attempting to develop directional atherectomy today. Again, animal testing requirements would be exhaustive. Even more daunting would be that the entire cost of the hospital stay for a patient treated with directional atherectomy would need to be borne by the device company. Assuming an average procedural cost of $10,000, and assuming that 512 patients would be randomized to atherectomy (the number in CAVEAT), a minimum of $5 to $10 million would be required for hospital costs alone. The fact that the CAVEAT results are viewed as largely disappointing, with marginal restenosis benefit and higher one-year mortality occurring for the atherectomy group is even more disturbing (15). On the basis of these results, it is certain that directional atherectomy would have been abandoned. Thus, a useful, safe medical device would never have been available for clinical use.

In retrospect, the development of coronary balloon angioplasty and coronary atherectomy has taught us invaluable lessons on how medical devices can be safely and fruitfully developed. A sequence of initial operator experience, device refinement, large practice experience and ultimately timely conduct of randomized trials is mandatory. Premature conduct of randomized trials before devices are refined, before operators are proficient or before optimal techniques are established can jeopardize development of safe, useful products. Imagine forcing the conduct of an RCT for the original unsheathed Palmaz–Shatz stent (Johnson & Johnson, Warren, New Jersey). The device was rigid, fraught with risk of embolization and associated with the exorbitant risk of subacute thrombosis. Had such a premature RCT been conducted, it is likely that the study would have been stopped prematurely on ethical safety concerns. Thus, the
mainstay of today’s interventional armamentarium would not have been developed.

This risk of premature conduct of randomized trials is in fact occurring today for innovative revascularization techniques. Percutaneous direct myocardial revascularization was forced into early trials before sufficient operators were trained, before large experience on optimal technique occurred and with crude clinical “model A” devices. Randomized trials of beta radiation are occurring before dosing protocols and catheter placement protocols are refined. If these initial randomized trials are negative, will these potentially promising devices be abandoned? Unfortunately, government approval and insurance reimbursement are now directly tied to completion of randomized trials. As a consequence, it is likely that the pace of medical device invention will dramatically slow or even cease in the U.S. At the time that Gruentzig and Simpson attempted to develop their initial devices, all that was required for approval was documentation of successful treatment of 75 cases with six months of clinical follow up. Is society really better off today with the extraordinarily complex and cumbersome regulations that exist for medical device evaluation?

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