Innovations in Cardiovascular Devices Will Offer Potential Benefits as Well as Challenges

Written by Lori Alexander

Innovative cardiovascular (CV) devices are poised to offer substantial benefit. Despite the potential to substantially reduce the morbidity and mortality that are associated with CV diseases, these products also raise a variety of challenges in research as well as clinical practice. David R. Holmes, Jr., MD, Mayo Clinic, Rochester, Minnesota, USA, addressed the challenges that are associated with some devices that have been evaluated in clinical trials.

The LAA Closure Device

The PROTECT-AF trial compared the WATCHMAN Left Atrial Appendage (LAA) Closure Technology with anticoagulation in patients with atrial fibrillation (AF) and found the device to be noninferior for the primary composite endpoint of stroke, CV death, or systemic embolization and associated with a significant reduction in the risk of hemorrhagic stroke. There was an increased risk in the primary safety endpoint (composite of major bleeding, pericardial effusion, or device embolization) with the device; however, 87% of successfully implanted subjects were able to cease warfarin therapy in 45 days, and the rate increased over time [Holmes DR et al. *Lancet* 2009].

Despite these benefits, the research identified treatment-related safety issues with the new medical device. In the case of the LAA closure device, the procedure-related risks must be balanced against the long-term risk of bleeding with warfarin. The device is not yet approved for use in the United States but is available in other countries.

Trial design is another issue with studies on new technology. In PROTECT-AF, as well as other stroke prevention trials, patients are randomly assigned to the device or medical therapy with an anticoagulant. Only approximately 50% of patients who are eligible for long-term warfarin therapy are treated with it, which presents a challenge in the assessment of new therapies for AF. Other medications to prevent clots, such as clopidogrel and prasugrel, are not as effective as anticoagulants, such as warfarin, for this indication.

Imaging to Identify Vulnerable Plaque

Vulnerable plaque accounts for as many as 1.9 million hospitalizations per year for associated clinical syndromes, such as acute coronary syndrome (ACS). Vulnerable atherosclerotic plaque often leads to acute ischemic syndromes with little or no warning. Early identification of individuals with vulnerable plaque who are at an increased risk of ACS could reduce morbidity and mortality.

Results of A Prospective Natural History Study of Coronary Atherosclerosis showed that in patients who presented with ACS and received percutaneous coronary intervention, major adverse events during follow-up were equally due to recurrence at the site of culprit and nonculprit lesions [Stone GW et al. *NEJM* 2011]. Intravascular imaging has the potential to identify the nonculprit lesions that are vulnerable and may lead to recurrent

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events. Although the development of radiofrequency intravascular ultrasonography makes it possible to characterize the vessel wall with the use of an imaging technique that correlates well with histological findings, the limitations and risks that are associated with use of the technology remain to be addressed.

Early Warning Systems

One early warning system that is currently in clinical trials is the Guardian System. The implantable medical device sends a vibratory alarm when it senses an ST-segment change. As such, it has the potential to improve outcomes through the early warning and diagnosis of ischemia and arrhythmias. But, it may also create a need to refine disease-related definitions and terminology. For example, endocardial leads (as used in the device) show acute injury current as ST-segment depression, not elevation, conflicting with the current designation of STEMI. Another issue is how to classify disease if treatment is given before the expected cardiac event.

TAVI

Initial data from the PARTNER trial showed a significant improvement in clinical outcomes, including rates of death from any cause, with the use of transcatheter aortic valve replacement implantation (TAVI) for patients who are not candidates for surgical aortic valve replacement [Leon MB et al. *NEJM* 2010] (See pages 14 and 15 of this report). Dr. Holmes said that many crucial questions must be answered before TAVI can move into clinical practice. For example, how will the procedure be regulated and by whom? Will the procedure be available only at regional centers or at all "qualified centers?" How will training of physicians be done and who will develop the curriculum? Lastly, how will the technology migrate to other patient groups? Answering these questions will require the collaborative efforts of several professional heart associations, as well as regulatory agencies and policymakers.

Other Issues

Many additional factors must be considered when evaluating new devices, such as the selection of appropriate endpoints, comparative effectiveness, and cost effectiveness. These issues were discussed later in the symposium by David J. Cohen, MD, MSc, Director of Cardiovascular Research, Saint Luke's Mid America Heart Institute, Kansas City, Kansas, USA. Dr. Cohen noted that given the current economic pressures in health care, the focus of research on devices should be on novel technologies that address unmet needs. In addition, study designs should emphasize clinical benefits, and outcome-based studies should be done early in the development of devices to demonstrate their economic value.