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Editorial Comment

Long-Term Follow-Up of the First in Man Experience With Everolimus-Eluting Stents

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The introduction of drug-eluting stents (DES) into clinical practice has ushered in an era of expanded indications of percutaneous coronary intervention with the routine expectation of low repeat revascularization rates. Following preclinical evaluation, initial experience with stents and other cardiac devices normally undergo clinical evaluation in ''First In Man'' (FIM) testing, typically in a low-risk population. FIM programs, although normally focused on small numbers of patients, rigorously evaluate enrolled subjects with serial follow-up, often using angiography and intravascular ultrasound (IVUS) in an effort to more fully elucidate the vascular biological response to an arterial prosthesis, which elutes a drug from a polymer-coated metallic stent [1,2]. The small number of evaluated patients in FIM programs typically precludes evaluation of clinical endpoints.

In this issue of the Journal, Wiemer et al. [3] describe 5-year clinical follow-up in patients randomized into the initial clinical experience evaluating the XIENCE V everolimus-eluting coronary stent (EES). Over 5-year follow-up, they document an approximate halving of major adverse cardiac event (MACE)/target vessel failure (TVF) rates when compared with the control arm in this single-blinded study. Importantly, in the group receiving the EES, there were no significant cardiac endpoints observed over the last 4 years of patient observation. Following the initial dissemination of FIM data, the EES has been initially documented to have diminished late loss when compared with paclitaxel-eluting stents within the SPIRIT clinical trial program [4,5], although in one long-term follow-up, the two devices appear noninferior over longer term follow-up [4]. The initial differences in event-free survival in this program with the use of an EES can generally be viewed, at least partially, as a validation of the cost borne by stent manufacturers for research and development of newer generation DES.

The currently reported study describes low clinical event rates and more significantly describe a physiologic construct concerning how larger clinical trials might be interpreted in light of the 6-month and 1-year follow-up angiographic and IVUS data from the FIM experience. Taking into consideration the presented data, several general points concerning patient outcomes can be made. The 5-year MACE/TVF rates in the EES arm was 16.7%—this underscores the importance of aggressive medical therapy targeting coronary risk reduction especially when considering the population of patients encountered in usual clinical practice is likely to be at higher overall risk than those patients reported in the current study.

More than any other group of medical practitioners, interventional cardiologists have a plethora of data to guide clinical decision making. General adherence to guideline recommendations and trial results in general can be expected to improve patient outcomes. Several caveats regarding the application of clinical trial results to patient care decisions regarding coronary stenting should be mentioned. In general, whether considering clinical or angiographic characteristics, DES trials enroll lower risk and more rigorously followed populations than those typically encountered by clinicians or those reported on in postmarketing registries. Consequently, 1-year MACE rates of nearly 20% have been reported in general populations treated with DES [6]. A recent pharmacologic trial of thienopyridines in relatively high-risk patients has documented a stent thrombosis rate of 2.4% in clopidogrel-treated patients [7]. In light of these data, one could surmise that clinical trial results may not adequately reflect potential treatment benefit.

Virtually all seminal stenting trials leading to clinical approval involve angiographic restudy within the first year following coronary intervention. Such prac-

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tices can lead to repeat revascularization which outside of enrollment in a clinical trial would likely not occur—the so-called oculostenotic reflex. Stenting trials have reported target lesion revascularization rates of 23% [8] in the bare metal population, while in an unselected elderly population, not routinely restudied, the repeat revascularization rate has been documented to be almost half [9]. In light of these data, one could postulate that clinical trial results may overestimate treatment benefit by overestimating the reduction in restenosis.

Wiemer et al. have made an important contribution, documenting the long-term FIM experience with the XIENCE V EES. Future such work will continue to be important given the importance of a variety of factors—stent composition and design, type of polymer, dose and characteristics of specific eluted drug, etc. on patient outcomes following coronary stenting.

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