Drug-Eluting Stents Frequently Used Off Label

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NEW ORLEANS — More than a third of the drug-eluting stents placed in the first 9 months following marketing approval of the Cypher stent were for off-label indications, according to data from the American College of Cardiology–National Cardiovascular Data Registry.

The use of drug-eluting stents rose rapidly during this period, and growth in the off-label uses kept pace with the increase for the approved indication, Sunil V. Rao, M.D., said at the annual scientific sessions of the American Heart Association.

Dr. Rao presented a unique picture of the clinical adoption of a major new medical technology as reflected in a large national registry experience. The American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) is an ACC-initiated quality improvement project that to date includes more than 2 million admissions and 800,000 percutaneous coronary interventions (PCIs) at 528 participating U.S. sites.

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The registry data are reassuring in that off-label use of drug-eluting stents (DESs) appeared to be safe, at least in terms of the very low associated periprocedural adverse event rate, said Dr. Rao of the Duke Clinical Research Institute, Durham, N.C. "However, long-term safety and efficacy of drug-eluting stent use in off-label situations really should be evaluated in appropriately powered, randomized controlled trials," he said.

For purposes of his study, Dr. Rao focused on PCIs involving only the Cypher stent, the first DES to reach the U.S. market between the device's April 2003 approval through the end of that year. PCIs involving placement of both a Cypher stent and one or more bare metal stents were excluded from consideration. Cypher-only procedures comprised 30% of the nearly 163,000 PCIs entered into the registry during the study period.

The official Food and Drug Administration–approved indication for the Cypher DES is for use in improving coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo coronary lesions less than 30 mm long in native arteries having a reference vessel diameter of 2.5-3.5 mm, Dr. Rao said.

Dr. Rao focused on four specific off-label applications: ST-segment elevation MI, in-stent restenosis, saphenous vein grafts, and chronic total occlusions. These four off-label uses accounted for 33% of all DES procedures during the study period. This figure is actually an underestimate of the true proportion of DES procedures that were off label, since it doesn't include other possible off-label indications, such as long lesions or bifurcations.

The fastest growth in off-label use of the DES during the 9-month study period was in cases of ST-segment elevation MI, followed by in-stent restenosis.

The incidences of in-hospital mortality and unplanned coronary artery bypass surgery in connection with off-label use of the Cypher stent were both well below 1%. Moreover, the postprocedural acute MI rate was similar to that seen with bare metal stents, Dr. Rao said.

Several audience members took issue with his call for randomized trials designed to expand the approved indications for DEs. Some observed that companies have little incentive to conduct such trials, since business is already booming. Others argued that at this point it would be unethical to randomize patients to bare metal stents for most off-label uses and said that the FDA should rely on registry data to evaluate possible expanded indications for drug-eluting stents.

Dr. Rao replied that it's highly unlikely the FDA would expand the indications on the basis of registry data, which after all are inferior to information gained from randomized trials. "The registry data have a tremendous amount of residual confounding that cannot be accounted for regardless of the statistical analyses used. I think registries are highly valuable for safety data. I don't think, however, we can accept efficacy data as reliable," he said. ■