The Resolute Zotarolimus-eluting stent and diabetes mellitus

Patients with diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI) often present with more complex coronary artery disease, leading to increased risks for restenosis and adverse events. While drug-eluting stents (DES) have been recommended for PCI in DM patients, no DES prior to the Resolute has been specifically indicated by the US Food and Drug Administration (FDA) for use in this high-risk population.

1. The Resolute Global Clinical Program

The Resolute zotarolimus-eluting stent (ZES) (Medtronic Inc., Santa Rosa, California, USA) is a new-generation DES consisting of a thin-strut cobalt alloy bare metal stent coated with a durable biostable polymer and the cell-cycle inhibitor zotarolimus. The polymer architecture was engineered to allow for prolonged elution of zotarolimus for more effective inhibition of neointimal proliferation.

The safety and effectiveness of the Resolute ZES have been established in the RESOLUTE Global Clinical Program, which includes 2 large international trials (1 randomized and 1 single-arm) with minimal exclusion criteria and 3 single-arm trials with identical on-label inclusion and exclusion criteria. All 5 Resolute trials were designed with similar endpoints and statistical methodologies, and all required the same regimen of dual antiplatelet therapy. An ad hoc analysis has pooled outcomes for the 5130 recipients of the Resolute ZES in these 5 clinical trials.

2. Achievement of the FDA indication for diabetes

To obtain an indication for DM patients for the Resolute ZES, discussions with the FDA were initiated over five years ago. A statistical analysis plan was developed prospectively with the FDA to compare 1-year target-vessel-failure (TVF) outcomes.

![Fig. 1 – The cumulative incidence of target lesion revascularization at 2 years in the pooled analysis from the RESOLUTE Global Clinical Program.](http://dx.doi.org/10.1016/j.ihj.2012.10.011)
for on-label noncomplex Resolute DM patients against a performance goal derived from a meta-analysis of published literature (which included 6 trials with Cypher SES and Taxus PES), and pooled data for the Endeavor ZES.

The composite TVF endpoint included cardiac death, myocardial infarction, and target vessel revascularization (TVR). At 1 year, the rate of TVF for the 878 noncomplex diabetic Resolute patients was 7.8% (upper 95% CI 9.51%), significantly lower than the performance goal of 14.5% ($p = 0.001$), thus supporting the new FDA indication for DM.

3. Two-year pooled outcomes encouraging for diabetics

For the total population of DM patients, 2-year outcomes were compared with those for 3595 non-DM patients from the pooled cohort. As expected, rates of major adverse cardiac events were significantly higher in DM patients than in non-DM patients. However, the 2-year incidence of ARC-defined definite or probable stent thrombosis was very low regardless of the presence or severity of diabetes (0.82% for non-DM patients, 0.93% for non-insulin-treated DM patients, and 1.79% for insulin-treated DM patients).

When outcomes were analyzed by treatment with insulin, the incidence of target lesion failure was nearly the same for non-insulin-treated DM patients versus non-DM patients but was significantly higher for insulin-treated DM patients (8.4% for nondiabetics, 8.9% for non-insulin-treated DM patients, and 16.7% for insulin-treated DM patients).

The accompanying figure (Fig. 1) breaks out the cumulative incidence for target lesion revascularization by diabetes status. The event rates on this important index of DES effectiveness are low out to 2 years, despite the higher risks and more complex disease presented by DM patients.6

REFERENCES