Gaining clarity on the question of stent thrombosis: insights from PROTECT

The safety of drug-eluting stents (DES) is clearly a primary concern to both physicians and patients. While there is good evidence that DES reduce restenosis rates compared with bare-metal stents,[1] the incidence of late stent thrombosis remains a concern. Indeed, until recently there have been limited long-term safety data for different DES types when used to manage different lesions in a diverse patient population.

The Patient Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT) was a randomized, open-label trial that compared the long-term safety of zotarolimus-eluting (E-ZES; Endeavor, Medtronic Inc.) and sirolimus-eluting (C-SES; Cypher, Cordis, Johnson & Johnson) stents, which have different vessel healing characteristics and anti-proliferative potencies.[2] The study was designed to ensure wide acceptance of the trial findings. Enrolling patients from across the globe, the broad eligibility criteria included patients with stable and acute coronary syndrome, single or multivessel disease and simple and/or complex lesions. Furthermore, trial procedures were representative of current clinical practice and were carried out in accordance with local or national guidelines.

Clinically relevant endpoints were also critical to ensure the validity of the study. The primary outcome of PROTECT was the composite rate of definite and probable stent thrombosis (as defined by the Academic Research Consortium) at three years after implantation. Main secondary endpoints included assessment of the following combinations of death and myocardial infarction (MI) at three years: total death and large non-fatal MI; total death and non-fatal MI; cardiac death and large non-fatal MI; and cardiac death and non-fatal MI.

PROTECT was the largest of its kind and the only such trial with a global scope, having randomized 8,791 patients across 196 centres in 36 countries. Of these, 8,340 patients (95.8%) completed three years of follow-up. Baseline clinical characteristics and use of antiplatelet therapy were similar between the two treatment groups, with 8,402 patients (96%) receiving dual antiplatelet therapy (DAPT) at discharge and 2,364 (30%) receiving DAPT at three years.[3] Overall characteristics of the patient population, including lesion-related and patient-related pro-thrombotic characteristics, did not differ from those reported in registries worldwide. Analysis of the primary outcome showed no significant difference between rates of definite or probable stent thrombosis between the two stent devices at three years (1.4% vs 1.8% for E-ZES and C-SES, respectively; hazard ratio 0.81; 95% confidence interval 0.58–1.14, P=0.22).[3] In addition, no difference in any of the main secondary endpoints was observed between the two treatment groups.[3] Whereas use of E-ZES was associated with a reduced risk of definite stent thrombosis compared with C-SES, and C-SES reduced the risk of target vessel revascularization compared with E-ZES, low rates of definite or probable stent thrombosis, adverse clinical outcomes and revascularization were reported with both stent devices up to three years.[3] It remains to be established whether factors such as differences in clinical practice or regional variation in ST rates may have contributed to the study results.

To summarize, PROTECT has shown that after three years, the incidence of stent thrombosis was low and similar with the E-ZES and C-SES stent devices when assessed in a broad patient population. Importantly, in its study design and completion, PROTECT has set a new standard as the first large-scale randomized trial designed and powered to assess long-term differences in a stent thrombosis endpoint.

REFERENCES:
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2. Camenzind E, et al. *Am Heart J* 2009;158(6):902-9.
3. Camenzind E, et al. *Lancet* 2012.