New advancement of Drug Eluting Stent (DES): focusing on in-stent thrombosis

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Drug eluting stent (DES) had been proved to reduce in-stent restenosis at 6-9 months in several large scale randomized studies, and Cypher had been approved for clinical use (Sirolimsus-coated Cypher stent, Cordis, J & J Corp.) in CE-market since 2002 & Taxus (Paclitaxel-coated Taxus, Boston Scientific Corp.) since 2003. Subsequently, these 2 DES were also available for clinical use in Taiwan since 2003. Earlier Cypher experience in U.S., had been reported relatively higher incidence of in-stent subacute thrombosis, the risk of stent thrombosis (ST) may be increased by delayed arterial healing associated with DES, however it improved overtime after improving DES deployment technique. The FDA requested both manufacturers (Cordis & Boston) to follow patients in their original clinical trials (SIRIUS & Taxus-IV) for 5 years after implantation, and to conduct registry studies of consecutively enrolled new patients to collect data on "real-world" use.

The adverse effects after DES implantation had been reported by BASKET-late trial in Switzerland, with 746 patients and 1,133 stented lesions, after discontinuation of Clopidogrel at 6-month after stent implantation, between 7 to 18 months, death & myocardial infarction (MI) rate were 4.9% for DES versus 1.3% for bare-metal stenting (BMS). The higher incidence of late events maybe due to higher rate of late ST. Later on, in World Congress of Cardiology Meeting September 2006 (Barcelona), four Cypher randomized trials meta-analysis was analysed & reported by Dr. Carmenzind which revealed a small increase but significant higher death/MI rate at 3-year follow-up, the incidence of ST occurred

at a rate of 0.6% per year between 30 days and 3 years after implantation. Original FDA label use recommendation for Clopidogrel were 3 months for Cypher and 6 months for Taxus stent, but after these reports, prolong course of Clopidogrel use up to 12 months had been suggested by consensus expert Meeting (Academic Research Consortium, ARC) in December 2006. During the Meeting, expert panel also agreed to use the same definition of ST in the future DES clinical trials and every publications regarding this issue. The following were definitions of ST:

Definite/Confirmed

- **Coronary symptoms and**
- **Angiographic confirmation of thrombus or occlusion or**
- **Pathologic confirmation of acute thrombosis**

Probable

- **Unexplained death within 30 days**
- **Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion**

Possible

- **Unexplained death after 30 days**

SCAAR registry from national database of Sweden, published in New England Journal of Medicine 2007, a 3-year follow-up of DES versus BMS patients, death/MI rate were higher in DES group (adjusted relative risk, 1.20; 95% confidence interval [CI], 1.05 to 1.37). However, European Society Congress ESC-2007 in Vienna, study period extended to 4-year for SCAAR patients, the adjusted mortality rate between DES and BMS became no difference. Similar registry studies from Denmark and Ontario/Canada, revealed no difference of MI incidence in DES versus BMS patients, contrary as SCAAR study, mortality rate was lower in DES group. Although, the solid end point of DES (death/MI) showed discrepancy in different studies, but cumulated

incidence of ST for DES were consistently higher. Recent report in ESC-2007 from Bern-Rotterdam registry, the cumulated incidence of ST between 30 days and 4 years was 0.6% per year for DES patients.

The most common etiology for DES-ST had been reported as early discontinuation of Clopidogrel, but current guideline endorsed by the General health Bureau of Taiwan, was only 3 months after stent implantation which was quite appropriate for BMS, but 3-month clopidogrel usage for DES implantation, obviously is an unsafe management. Other etiologies of increasing incidence of ST were: diabetes mellitus, chronic renal failure, low ejection fraction, bifurcation lesions, longer/complex lesions, over-lapping stents, stent mal-apposition, stent fracture and thrombus containing ST-elevation MI. Although the incidence of ST was higher in DES, but target vessel revascularization (TVR) rate was significantly lower as compared with BMS, death/MI may presented at restenosis or occurred during TVR for BMS patients, which was represented as a trade off for both groups. The long-term (2-5 years) follow-up major adverse cardiac events (death, MI, TVR) between DES versus BMS for different clinical trials, were still favoring DES contributing dominantly by lower TVR rate.

Conclusions: 1) Incidence of ST especially > 30 days after stenting, were consistently higher for DES, but Aspirin/clopidogrel combine use for longer period (up to 12 months according to the ARC recommendation), or even longer (> 12-month) at no obvious side effects, may reduce the incidence of late (30 – 365 days) or very late (> 365 days) ST. 2) Inform our patients and other non-cardiovascular Physicians, try not to stop Clopidogrel prematurely after DES, is quite important. 3) Technical point of views, good apposition of DES by intra-vascular ultrasound guide and non-compliant balloon in-stent high pressure inflation, may play another role for preventing future ST.