Short Communication

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The Reduction in Total Mortality with Drug-Eluting Stents: Does Emperor has New Clothes?

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Short Communication

Over last 3 decades, percutaneous coronary interventions (PCI) has transformed management of obstructive coronary artery disease (CAD). Commenced with balloon dilation i.e. plain old balloon angioplasty (POBA) of severe obstructive CAD lesions, gradually evolved into stenting started with bare-metal stents (BMS), initially first-generation (stain-less steel) [1] and now contemporary second-generation BMS (cobalt-chromium with thinner struts). BMS was rapidly superseded by drug-eluting stents (DES); at first with first-generation (paclitaxel-eluting, taxus; and sirolimus-eluting, cypher) now with second-generation (zotarolimus-eluting, endeavor; and everolimus-eluting, xience) and with ongoing refinements third-generation drug-eluting stents (with biodegradable polymers, polymer-free and biodegradable stents on the basis of poly-L-lactide or magnesium) are undergoing trials and many are available for use in contemporary practice.

Interestingly, each time improvement in the technology was need-driven with genuine intent to reduce the shortcomings like restenosis [1] (concern with POBA and BMS) and stent thrombosis [2,3] (concern with first-generation DES).

Over the years, the practice of interventional cardiology evolved. At first practiced solely, now POBA has very restricted indications in contemporary practice, like dilation of the distal anastomotic stenosis of left internal mammary artery with left anterior descending artery (LAD), very focal tandem stenotic-aneurysmal lesions (to relieve stenosis, stent is best avoided to prevent stent thrombosis in the adjacent aneurysmal segment), in diabetic patients with acute coronary syndromes with triple-vessel disease (planned for coronary artery bypass, POBA to relieve the obstruction to achieve TIMI 3 flow, if possible) etc. Stenting (with/without pre-dilation) is invariable preferred to treat hemodynamic-significant (FFR<0.80) obstructed coronary artery/arteries. First-generation BMS (having stain-less steel) had high restenosis up to 40% over initial six to nine months, the second-generation BMS (having cobalt-chromium with rather thinner struts) are in contemporary use with possibly improved restenosis rates. First-generation DES even though having less restenosis rates, had life-threatening stent thrombosis around 1% per year. To overcome this issue, second-generation DES were invented with thinner struts, increased biocompatibility, and reduced thickness of durable or biodegradable polymers, with different limus (everolimus or zotarolimus) than do first-generation DES. These properties translate into reduced stent thrombogenicity in experimental models and clinically with improved stent thrombosis (possibly <0.5% per year) [4,5]. However, improved technology came with higher cost, unaffordable by most self-paying patients in the resource-constrained countries; and in many government-supported health-care systems even in resource-rich countries.

Decrease in All-Cause Mortality with DES: A Sensational News

Despite frequent attempts to explore any reduction in all-cause mortality (despite proven benefits with clinical and angiographic restenosis rates) with use of DES since its popular use in contemporary practice over last 15 years. No study convincingly proved it. The publication of 5-years follow-up results of EXAMINATION [6,7] trial curiously showed reduction in all-cause mortality with DES. EXAMINATION trial, a rather all-comer multicentric European trial recruited 1504 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. The trial compared BMS with everolimus-eluting stent (EES), a commonly used second-generation DES in many centers around the world. Though it did not show any difference in the mortality at 1-year, [6] upon extending the follow-up for 5 years, the study did show definite difference: the primary endpoint (all-cause mortality and nonfatal myocardial infarction) was significantly lower in patients receiving EES than in those receiving BMS, a benefit that was driven mainly by a lower rate of non-cardiac deaths. Sensational result with thought-provoking message, the only study so far (contrary to all earlier studies conducted with DES) to document reduction in all-cause mortality using DES.

Astutely, investigators in the Norwegian coronary stent trial (NORSTENT), 8 were aware that the findings for BMS have improved, with new stent designs, different metal

composition, and thinner struts. So, they decided to examine outcomes by comparing second-generation DES with newer-generation BMS in a randomized trial that was pragmatic, inclusive, optimally powered, and non-industry-driven. At the end of 6 years, in patients undergoing PCI, there were no significant differences between those receiving DES and those receiving BMS in the composite outcome of death from any cause and nonfatal spontaneous myocardial infarction. However as expected, the rates of repeat revascularization were lower in the group receiving drug-eluting stents. NORSTENT trial was rather inclusive (72% of patients were enrolled), enrolling patients with all spectrum of patients with CAD (both unstable and stable CAD, unlike EXAMINATION trial having patients with STEMI only). It had much larger number of patients (9013 patients) almost six-folds higher, had 100% follow-up over 6 years and used all commonly used second-generation DES (95% patients received EES or zotarolimus-eluting stents, ZES) and second-generation BMS. Both trials included patients with diabetes mellitus (around 20%).

The Reduction in All-Cause Cause mortality in EXAMINATION trial: Genuine or Hype?

In EXAMINATION [6] the primary hypothesis was unproven at 1 year; hence all subsequent analyses, including the new 5-year analysis [7] must be viewed as hypothesis-generating. On analysis, the long-term results of EXAMINATION suggest no signals of late attrition in the revascularization benefit in the EES group at 1-year, and no accrued safety hazards compared with BMS, including reassuringly low rates of very late stent thrombosis and target vessel reinfarction, despite dual antiplatelet therapy being discontinued by most patients at 1-year. These results are comforting as there is no late increase in dreaded thrombotic events with newer durable polymer drug-eluting stents in patients with STEMI, in contrast with earlier-generation stents [8-10]. Newer drug-eluting stents with thromboresistance properties are perfectly safe in patients with STEMI undergoing percutaneous coronary intervention [11,12].

Curiously, when we look at individual contributions to the mortality endpoint, cardiac causes had only a partial, non-significant role (3.3% *vs* 4.9%; p=0.11 for EES versus BMS between 1 year and 5 years, respectively), most of the reduction was attributable to non-cardiovascular causes (1.9% *vs* 3.8%; p=0.03), a surprise and thought-provoking finding. Upon further scrutiny of non-cardiovascular mortality in EXAMINATION [7] an excess of cancer-related and sepsis-related deaths was noted in the BMS group. An observation hard to explain, at present we may at best guess it as play of chance? Imbalances in subclinical cancer at randomization (despite best efforts at randomization) had been known to affect the mortality results as shown in a recent large randomized trial addressing duration of dual antiplatelet therapy following coronary stenting [13].

Up on further extending follow-up of EXAMINATION trial or NORSTENT trial different pattern may emerge. But with the evidences available today, there is no evidence to prove superiority of DES over BMS with regard to all-cause mortality: the emperor has no new clothes.

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