

## Have we been misled by the ESC DES firestorm?

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On September 3, 2006, a giant eruption burst out from the European Society of Cardiology Annual Meeting/World Congress of Cardiology Meeting in Barcelona: drug-eluting stent (DES) may kill!

Let us turn back the hands-of-time to a couple of months before this event. Interventional cardiologists had embraced DES with a growing enthusiasm since 2002, and dreamed about conquering even more of the remaining surgical strongholds. Suddenly at the beginning of the year 2006 there emerged a general recognition of a logical, unavoidable, anticipated<sup>1</sup> – and yet snubbed – bane of DES: very late stent thrombosis.

Although the spectre of late DES thrombosis had been hovering over PCI since 2003 with repeated warnings issued by opinion leaders, it was not until this moment that a first cooling of the DES hype was felt. At the March 2006 American College of Cardiology Scientific Session in Atlanta, doubts were cast on the 1-year benefit of DES in acute myocardial infarction. More importantly, an increased incidence of very late stent thrombosis was put back on the agenda to explain the results of the BASKET-LATE trial in which the mortality and myocardial infarction rate one year after discontinuation of clopidogrel was higher in the group assigned to DES than in the group treated with bare metal stents (BMS). The heat continued to grow in May 2006 at EuroPCR held that year in Paris. In a large necropsy study, Joner et al documented a persistent delayed arterial healing and incomplete endothelialisation in patients treated with DES in comparison with patients treated with BMS<sup>2</sup>. Although, this is exactly what DES are designed for, an uproar ensued and DES had lost their magic of infallibility. They had become “human”.

Finally, on September 3, 2006, during the annual European Society of Cardiology and World Congress of Cardiology meeting in Barcelona, two independent meta-analyses presented during the hotline session invoked the idea that first generation DES increase mortality. Nordmann suggested that sirolimus- (but not paclitaxel-) eluting stents were associated with a small but significant increase in non-

cardiac mortality at two and three years of follow-up. Camenzind insinuated that the mortality rate of patients treated with DES was higher than that of those treated with BMS. The (small) increase in the rate of death and myocardial infarction was observed in patients followed 18 months to three years after stent implantation. The results were in keeping with reports on disparate very late stent thrombosis in DES and BMS, like the Bern-Rotterdam Registry. The red flag was thrown in. Not only was “King” DES dethroned, it also was accused of being one of the most active serial killers in industrialised countries. Without regurgitating the details of these results, which remain controversial, it has to be noted that the mass media and some cardiology leaders (most of them critical of PCI) literally jumped on the information and spread it like it was the apocalypse.

Responsible cardiologists refused to fall for this sensationalism and sat down to assess the problem. In an attempt at returning to reason, first a session at Transcatheter Cardiovascular Therapeutics 2006 was devoted to the ESC firestorm. Secondly, in December 2006, the indicted killer – DES – appeared before the high court, i.e., an extraordinary session of the FDA. Opinion leaders were heard and DES was acquitted, but still put on probation. Research groups feverishly gathered more evidence concerning the safety of DES.

While the February 2007 edition of the *New England Journal of Medicine* contained some evidence bound to rehabilitate DES, there was also a report published in this same issue of the SCAAR registry reiterating that DES probably kills.

While some considered this the final nail in the DES coffin, most were aware of the lack of balance between the patient characteristics of those registries in countries considering DES as a treatment to be reserved for only the “difficult cases”.

Now, the truth has prevailed. DES are indeed slightly more prone to very late stent thrombosis in comparison with BMS. Yet, DES improve the quality of life without increasing mortality (and the trend is rather pointing to the fact that they save lives). The explanation is straightforward. DES prevent neointimal formation, restenosis, and target lesion

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revascularisation and this is more instrumental than the small increase of late stent thrombosis. The body of evidence currently consists of several “real-world” registries, with adjustments for the DES versus BMS patient characteristics, registries with Propensity Score Matched Pairs, and finally results of meta-analyses from randomised control trials (RCTs). Moreover, the final version of the SCAAR registry including 35,266 patients (BMS 21,480 patients, DES 13,786 patients) showed no significant difference in either mortality (RR 1.03, CI 95% 0.94-1.14) or the combined outcome “death or myocardial infarction” (RR 1.01, CI 95% 0.94-1.09) between DES and BMS. Other “real-world” registries – including a total of 49,052 patients – showed either a comparable mortality between the two groups, such as seen in the study of the National Heart, Lung, and Blood Institute (NIH)<sup>3</sup> (DES 1,460 patients, BMS 1,763 patients), or even a lower mortality rate in patients assigned to DES, e.g., the DESCover Registry (DES 397 patients, BMS 6,509 patients), the REAL<sup>4</sup> (DES 3,064 patients, BMS 7,565 patients), the Wake Forest University<sup>5</sup> (DES 1,164 patients, BMS 1,285 patients), the Western-Denmark (DES 3,548 patients, BMS 8,847 patients), the STENT Registry (DES 1,377 patients, BMS 5,631 patients) or the study of Thoraxcenter (SES 976 patients, PES 2,776 patients, BMS 2,287 patients). These last registries have results very similar to the two registries with Propensity Score Matched Pairs adding 17,484 patients: Ontario<sup>6</sup> demonstrated a reduction in the absolute mortality from 2.3% at 3-year follow-up, and Massachusetts<sup>7</sup> showed a absolute reduction of 2.5% in 2-year mortality, both in favour of DES-patients.

Two meta-analyses compared the clinical follow-up of the two leading first generation DES (Cypher eluting sirolimus and Taxus eluting paclitaxel) and BMS<sup>8,9</sup>. One network meta-analysis finally compared all the RCTs of the first generation published up to now<sup>10</sup>. These three individual studies, encompassing a total of 18,023 patients treated in 38 RCTs, do not show any difference in mortality between DES and BMS up to four years for Taxus and five years for Cypher. The only difference consisted of a smaller rate of myocardial infarction in patients treated with Cypher than BMS or Taxus stents. Many were misled by the ESC 2006 firestorm. Notwithstanding some good came out of it. Most changed their practice to fewer and shorter stents, likely something which will be a benefit for our patients. The same holds true for increased emphasis on prolonged dual antiplatelet therapy. The industry got even busier developing the ideal DES, with all the benefits and less of the blemishes. DES, even those of the first generation, are not dangerous. They protect. Late stent thrombosis (incontestably slightly more germane to DES) is a serious, but rare event. Its effect on overall prognostic endpoints is more than offset by the beneficial effects of DES, mainly its obviating the need for further interventions, which engender a certain percentage of complications often censured in comparative analyses between DES and BMS.

The polymer covering DES as a drug repository remains under scrutiny for a causal role in late stent thrombosis. However, early on, when it is still fully exposed, it appears to prevent thrombosis rather than causing it.

On the positive side, the inappropriately fabricated panic about DES thrombosis stimulated powerful research leading to significant improvement, not only in patient care (better selection, better

follow-up), but also in research tools (Academic Research Consortium consensus)<sup>11</sup>. It also created a tighter collaboration between the various research centres (data sharing) and finally carved some peep-holes into the DES industry firewalls.

The dent in DES sales curves will forever mark this storm in a teacup, but it will not seriously challenge their unstoppable evolution towards supremacy.

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