

Should ultrathin strut drug eluting stents be considered the new benchmark for novel coronary stents approval? The complex interplay between stent strut thickness, polymeric carriers and antiproliferative drugs

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New generation drug eluting stents (DES), differ mainly from first generation DES due to their metallic scaffolds, with thinner struts (<100 µm). These DES have shown excellent safety and efficacy profiles for the treatment of coronary artery disease (CAD) (1-5), with a consequent widespread diffusion in the daily clinical practice. The biomechanical characteristics of cobalt- and platinum-chromium alloys has allowed the production of even thinner stent struts, with further improvement of DES mechanical performances (6). However besides the stent strut thickness, the employ of sirolimus as anti-proliferative drug and of bio-resorbable polymers as drug-eluting carriers represent important features of new generation DES. Each of these characteristics was demonstrated to be associated with a reduced late lumen loss (LLL) and minimal hazard of thrombus formation, in both clinical studies (7-9) and meta-analyses (10).

The strut thickness is a crucial parameter, as it is associated with local inflammation at the lesion site and, when excessive, is a formidable obstacle to stent strut coverage with neo-intima (11,12). Several studies have confirmed that the rate of restenosis was reduced according to strut thickness (8,9) and LLL showed a significant positive correlation with strut thickness in a meta-regression

study (10).

The safety and efficacy of “limus family” DES have been confirmed in several clinical studies (1,3,5,13) and in particular sirolimus is associated with the best outcomes in terms of LLL, binary restenosis and late stent thrombosis (10). In fact the ancestor of “limus” drugs still represents an ideal choice considering that it acts on the common final pathway of cell division cycle without excessive risks of necrosis induction. It is a macrolide with cytostatic rather than cytotoxic properties that impedes advancement from G1 to S in the cell cycle and inhibits the vascular smooth muscle cell migration and proliferation (14).

Finally, the bio-resorbable polymer influence the rate and completeness of vessel healing limiting the anti-proliferative drug elution to the time frame in which restenosis occurs, without excessive delay in stent endothelialization (14).

In a recent report in *The Lancet* (15) the Orsiro™ stent (Biotronik, Buelach, Switzerland), a second generation DES with an ultrathin cobalt-chromium platform (60 µm strut thickness) and a bioresorbable carrier made of poly-L-lactic acid loaded with sirolimus (1.4 µg/mm²), demonstrated better clinical outcomes in comparison with the Xience™ stent (Abbott Vascular, Santa Clara, CA, USA), an everolimus-eluting stent with a non-resorbable

polymer carrier and a thin cobalt-chromium platform (80 µm strut thickness), currently considered the benchmark for DES comparisons due to the huge number of patients included in its study programme and the excellent clinical results reported (16). In detail, the BIOFLOW V study recruited 1,334 patients with stable and unstable CAD scheduled for elective or urgent percutaneous coronary intervention in 90 hospitals from 13 countries. These patients were randomized (2:1 ratio) to treatment with the Orsiro™ (n=884) or the Xience™ stent (n=450). The primary endpoint was 12-month target lesion failure, defined as the composite of cardiovascular death, target vessel-related myocardial infarction or ischemia-driven target lesion revascularization. The primary non-inferiority comparison was performed with Bayesian methods, pooling data from the BIOFLOW V study with two additional randomised controlled trials (RCT) comparing bioresorbable polymer sirolimus-eluting stents and durable polymer everolimus-eluting stents, the BIOFLOW II (13) and BIOFLOW IV (17) studies.

Primary endpoint was met in 6% of patients treated with the Orsiro™ stent and in 10% of those treated with the Xience™ stent (P=0.04). These results were mainly driven by the reduction in target vessel myocardial infarction observed in the Orsiro™ stent group (5% *vs.* 8%, P=0.016).

According to the Bayesian analysis of the pooled data from BIOFLOW II, IV and V studies, the reported posterior probability that the Orsiro™ stent was non-inferior to the Xience™ stent was 100%.

BIOFLOW V investigators concluded that the excellent performance of the Orsiro™ stent over the Xience™ stent should be principally attributed to the reduction of stent strut thickness, suggesting a new direction in improving next generation drug-eluting stent technology and design.

Several previous studies demonstrated excellent clinical results in patients treated with Orsiro™ stent (13,18-21). However the BIOFLOW V study first demonstrated a clear superiority, rather than non-inferiority, of the Orsiro™ stent in comparison with the Xience™ DES. BIOFLOW V investigators attributed most of the study results to the difference in the stent strut thickness of the compared devices and claimed that after the publication of the BIOFLOW V study the Orsiro™ stent should have been considered the new benchmark against which novel generation stents should be tested in future RCTs. We have a little concern about these statements. First, the superiority of Orsiro™ was tested pooling the results of BIOFLOW II, IV and V studies with a complex Bayesian

method. This approach is not exactly equivalent to classical randomization, and cannot completely exclude selection bias. However, several reports validated Bayesian analyses in RCTs and often the value of Bayesian tools was demonstrated to be complementary to classical statistical methods to enhance interpretation of RCT results (22). Second, Orsiro™ has ultrathin struts, sirolimus elution and bio-resorbable polymer carrier and each of these features was associated with improved LLL and late thrombosis in previous studies (10). It is hard to extrapolate which technical feature mostly contributed to the excellent device performance, as the comparator Xience™ has a permanent polymer carrier, thicker stent struts and elutes a different “limus”. Third, we should not forget that an excessive reduction of stent strut thickness might weaken the stent platforms making them vulnerable to longitudinal stent deformation (23,24), a problem that only in part can be mitigated by improvements in stent platform design.

However these considerations do not change the substance of the matter: the new generation Orsiro™ sirolimus-eluting stent, equipped with the latest technological advances in coronary stent bio-engineering, did yield better clinical outcomes in comparison with the older and less advanced Xience™ everolimus-eluting stent. Robert Norton Noyce said “*Innovation is everything. When you’re on the forefront, you can see what the next innovation needs to be. When you’re behind, you have to spend your energy catching up.*” The efforts of the BIOFLOW V investigators dramatically confirmed this point of view.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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