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EDITORIAL COMMENT

Revisiting the Network of Drug-Eluting Stent Trials

Bioresorbable Scaffolds Enter the Arena*

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Ten years ago, during the annual European Society of Cardiology meeting in Barcelona, 2 independent meta-analyses suggested that drug-eluting stents (DES), despite being more effective than bare-metal stents (BMS) in reducing restenosis, increase mortality due to very late thrombosis (1). However, this was no longer confirmed by a plethora of randomized controlled trials (RCTs) and network meta-analyses (NMAs), demonstrating contemporary DES to be not only safe, but even safer than BMS (2). Unquestionably, advancements in DES technology have been instrumental to this newfound perception of safety. The quest for the ideal stent has now culminated with the introduction of bioresorbable scaffolds, in the hope that eliminating inert metal from the coronary arteries will further diminish the onset of late events.

When DES and bioresorbable scaffolds are confronted on infrequent outcomes such as stent thrombosis, RCTs are usually underpowered to provide definite estimates of an effect. Standard frequentist meta-analyses may also have limitations, in that they rely on the availability of RCTs for a given comparison, and cannot compare more than 2 devices simultaneously. In a NMA, multiple treatments are compared using both direct comparisons within RCTs and indirect comparisons across RCTs based on a common comparator. As such, NMAs optimize the use of existing data, particularly in areas compounded with competitors where RCTs cannot be envisioned for any potential comparison.

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In previous NMAs, the durable-polymer XIENCE (Abbott Vascular, Santa Clara, California) everolimus-eluting stent has been repeatedly flagged as the safest DES (3–5). The thin-strut structure of the XIENCE platform and the thromboresistant properties of its fluoropolymer coating have been advocated to justify the low risk of thrombosis. In this issue of the *JACC: Cardiovascular Interventions*, Kang et al. (6) elegantly revisited the topic to reflect the availability of the latest RCTs in the field, and the introduction of new devices. A previously published Bayesian NMA from the same authors encompassed 113 RCTs and 90,584 patients, investigating a total of 8 treatments (the durable-polymer CYPHER (Cordis, a former Johnson & Johnson company, Warren, New Jersey), TAXUS (Boston Scientific Corporation, Marlborough, Massachusetts), ENDEAVOR (Medtronic, Santa Rosa, California), RESOLUTE (Medtronic), XIENCE, and PROMUS (Boston Scientific Corporation) DES; the biodegradable polymer BIOMATRIX (Biosensors Interventional Technologies Pte Ltd., Singapore)/NOBORI (Terumo, Tokyo, Japan) DES; and BMS) (5). The updated NMA now incorporates data from 147 RCTs and 126,526 patients, with 4 new treatments, including the biodegradable-polymer SYNERGY (Boston Scientific Corporation) and ORSIRO (Orsiro, Biotronik, Bülach, Switzerland) DES, the polymer-free YUKON (Translumina GmbH, Hechingen, Germany) DES, and the fully bioresorbable ABSORB (Abbott Vascular) scaffold. When analyzing the expanded geometry of the network and the number of randomized patients in each node, it becomes clear that the information size vehicled by these newly added devices is limited, which

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recommends refraining from over-interpretation when considering how they position themselves in the ranking. Conversely, the number of randomized patients in other nodes is so high (>10,000) that one may legitimately suspect some statistically significant differences to be the reflection of overpowering rather than the signal of a truly remarkable effect. When interpreting the results, the reader should also consider that a NMA assumes all patients to come from RCTs with a very low degree of variability, which is obviously not true.

These limitations taken into account, the DES that more frequently (n = 6) were found to significantly decrease the risk of 1-year definite or probable stent thrombosis compared with other devices were XIENCE and ORSIRO, but 4 of these victories were versus BMS or devices no longer in the market (CYPHER, TAXUS, ENDEAVOR). It is commendable that the authors attempted to detach BMS and nonmarketed DES from the network—thus reducing the number of noncontemporary nodes—but this sensitivity analysis was unfortunately inconclusive due to a marked drop in statistical power. More interestingly, in the full network, both XIENCE and ORSIRO proved better than BIOMATRIX/NOBORI and ABSORB. The conclusion of fluorinated durable-polymer XIENCE DES to be less thrombogenic than biodegradable-polymer BIOMATRIX/NOBORI DES at 1 year is consistent with previous NMAs (5,7). However, a note of caution applies because the authors report that direct and indirect estimates for this comparison trended in opposite directions (6). The claim for the superiority of ORSIRO over BIOMATRIX/NOBORI appears more convincing, being consistent in direct and indirect estimates. Though, very few RCTs of ORSIRO contributed to the NMA, and only 1 directly compared ORSIRO and NOBORI in a study where stent thrombosis was not the primary endpoint. Of note, both ORSIRO and BIOMATRIX/NOBORI have biodegradable polymers, but ORSIRO features a conformal hybrid coating that combines biodegradable and passive components, and its struts are half-thin.

Overall, scrutinizing the rankograms of the NMA invokes the idea of a similar low risk of 1-year definite or probable stent thrombosis across contemporary DES (i.e., SYNERGY, PROMUS, ORSIRO, YUKON, and XIENCE). While these devices features sophisticated combinations of stent alloy, design, strut thickness, polymer, and drug, it is difficult to disentangle which of these characteristics is the most responsible for the observed benefit compared with other DES. On the other side of the ranking, BMS lost all the contrasts, with the only exception of the comparisons versus TAXUS (no longer in use) and ABSORB. BMS have been perceived as the benchmark of safety for years, but latest comparative data versus DES in selected populations makes it more and more difficult to find even a niche indication for these devices (8,9).

Intriguingly, this is the first NMA to include bioresorbable scaffolds. The ABSORB scaffold holds a number of promises, but promises are not enough when comparisons versus metallic DES initiate. While the list of competitors enriches and new iterations of the device appear at the horizon, it is interesting to realize how the first generation ABSORB positions itself in the ranking. Overlapping meta-analyses have recently explored the issue of ≤1-year stent thrombosis with ABSORB and XIENCE, with mixed results due to their disparate design, search range, and pooled sample size (10–12). In the NMA by Kang et al. (6), ABSORB lost 3 comparisons (vs. XIENCE, ORSIRO, and PROMUS) but only the comparison with XIENCE relied on direct evidence. In terms of 1-year definite or probable thrombosis, the ABSORB scaffold was not proven superior even to BMS and TAXUS, and other numerically unfavorable comparisons versus other DES were statistically negative possibly as the reflection of a lack of power rather than the lack of a true difference. While these results may sound disappointing, more RCTs with meaningful control arms are clearly needed to increase the information size of the ABSORB device for the purpose of cross-comparisons in future NMAs.

Finally, because the primary focus of this study was on definite or probable stent thrombosis at 1 year, one may expect future NMAs to focus on longer periods of follow-up once >1-year data from newer RCTs become available. The ultimate goal behind the introduction of novel coronary devices is that of decreasing the rate of very late thrombosis due to local inflammatory reactions and neoatherosclerosis, the original question raised 10 years ago in Barcelona, which has not been tackled by this NMA. For the meantime, the study by Kang et al. demonstrates that contemporary DES have successfully hit the sweet spot of 1-year safety and efficacy, and should represent the benchmark for future investigations of emerging technologies in the field. While novel stents and scaffolds enter the arena, it is becoming increasingly evident that the real competition—in a landscape of similarly effective devices—will be played on the ground of patient safety between 1 year and the long run.

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