

Taglieri et al., Network Meta-analysis¹

Frequently Asked Questions

Statistics

1. What is a network meta-analysis and what is the difference to a conventional meta-analysis²?

A network meta-analysis is a statistical technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials (RCTs). In contrast, the conventional meta-analysis approach can only compare two interventions at a time, and only those evaluated directly in head-to-head trials.

2. What is the difference between direct and indirect comparison/evidence²?

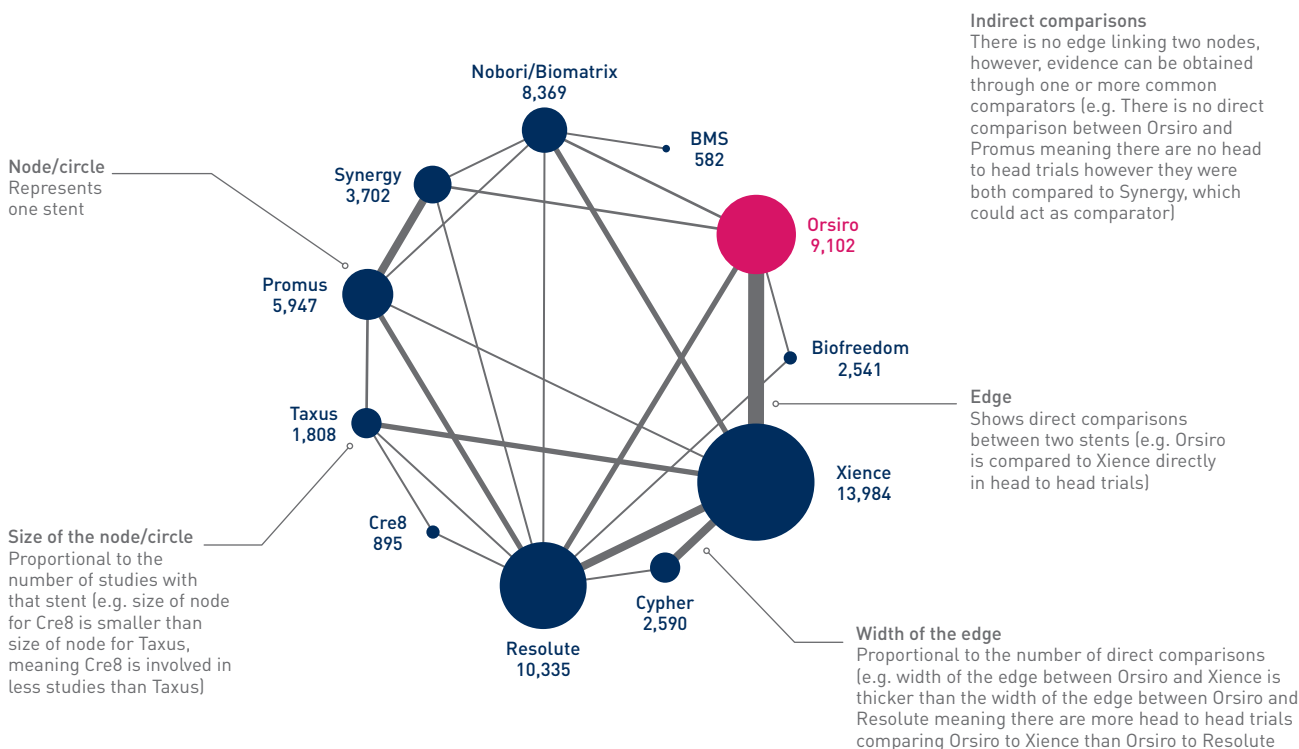
Direct evidence: Refers to evidence obtained from head to head comparisons in RCTs.

Indirect evidence: Refers to the evidence obtained through one or more common comparators (e.g. interventions A and B can be compared indirectly if both have been compared to C in studies).

The direct and indirect comparisons can be seen in the geometry network. In Taglieri et al. meta-analysis the geometry network can be seen in figure 1 and shows which interventions have been compared directly in RCTs, and which can only be compared indirectly. The width of the edges and the size of the nodes are proportional to the amount of information available.

In this schematic approach we can see that our ultrathin strut Orsiro[®] is one of the most studied DES with a large volume of information available.

Figure 1: Evidence Network for 1-year Target Lesion Failure



Taglieri et al., Network Meta-analysis¹

Frequently Asked Questions

Statistics

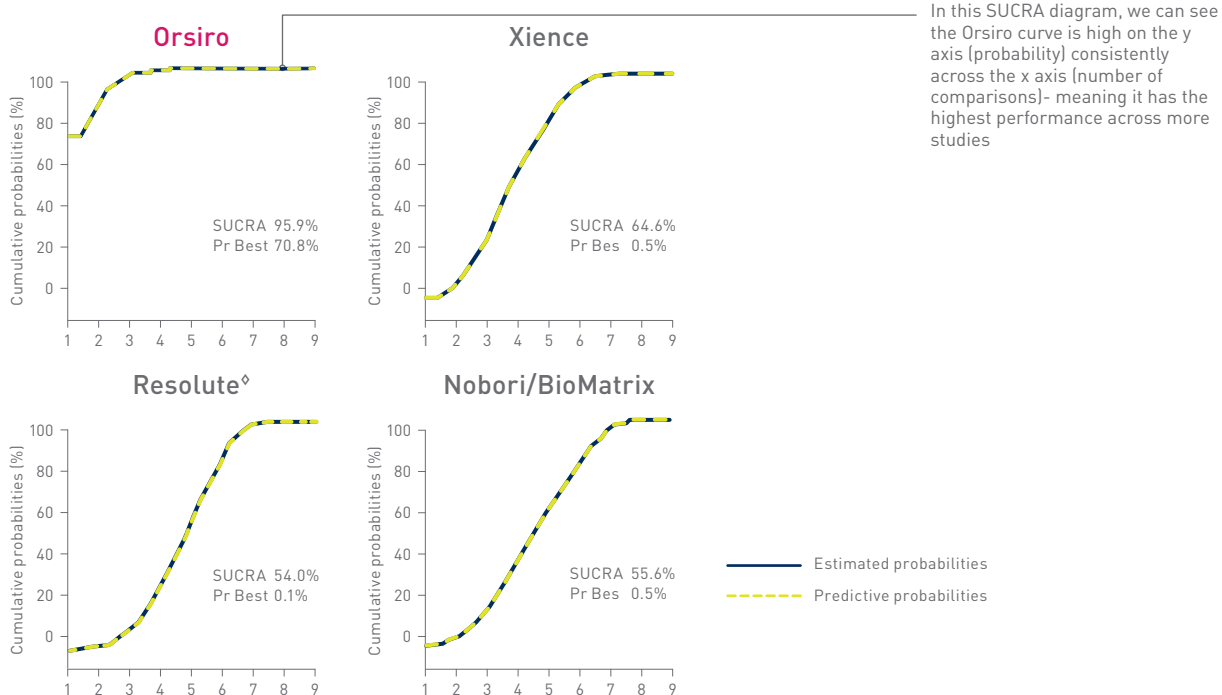
3. What is the SUCRA value and how it is linked to the probability to be the best²?

The Surface Under the Cumulative Ranking Curve (SUCRA) value is the probability each treatment has of being among the best of those in the network, with larger values representing higher ranking probabilities. A SUCRA value of 100% indicates the treatment is certain to be the most effective in the network, while a value of 0% indicates it is certain to be the least effective. The larger the SUCRA value, the better the rank of an intervention in the analysis.

Figure 4 in the supplemental material in the Taglieri et al. network meta-analysis shows the cumulative ranking probability curves for each DES included in analysis. From the curves we see the SUCRA value of Orsiro being the highest among all major competitors and thus having the highest probability to be the best.

Figure 2: SUCRA probability curves

Cumulative ranking probabilities (SUCRA) – TLF at 1 year



4. Which were the criteria used to qualify for trials to be included the in the meta-analysis?

In the meta-analysis only trials including second-generation or later currently used DES were selected. Trials comparing first-generation DES with each other or BMS were not included. In the network meta-analysis only DES that were investigated in at least 3 RCTs were included. In addition, trials with sample sizes <100 patients, trials with follow-up duration <12 months, and trials using biodegradable scaffolds were excluded from the analysis.

The full list of RCTs included in the network meta-analysis are available in the table 1 of the supplemental material.

Taglieri et al., Network Meta-analysis¹

Frequently Asked Questions

Statistics

5. How were the authors able to compare studies in the network meta-analysis with different patient populations?

As the Network Meta-Analysis compared RCTs with different patient populations enrolled, the authors performed so call meta-regression analysis to test the potential influence of the most common risk factors in the Network Meta-Analysis – diabetes and STEMI – on the outcome of TLF. By this means they could show that there was no correlation between diabetes or STEMI and the treatment effect observed for the primary endpoint.

6. How was the power of the trial determined for TLF at 1 year and what was the power for long-term FUP?

Inclusion of 39 trials and 59,855 randomized patients provided sufficient statistical power to show that Orsiro was associated with 1-year lower rates of TLF compared with the most widely evaluated XIENCE. For long-term follow-up, only 23 trials with 42,127 patients contributed to the analysis. Therefore, the power of the trial was reduced to detect differences in long-term risk of TLF.

7. Why was Synergy DES not among the 4 DES that received extensive research?

In figure 1 “Evidence network for 1-year Target Lesion Failure”, each circle represents 1 stent: the size is proportional to the number of trials with that stent and the number above is the total of patients randomized. The edges represent direct comparisons between 2 stents and their width is proportional to the number of comparisons. We see that for Synergy the number of patients enrolled in RCTs, (a pre-requisite for inclusion in the meta-analysis), is 3,702 which is not among the 4 DES with the highest patient numbers enrolled in RCTs and thus not among those extensively investigated.

8. What other similar network meta-analyses investigating competitor devices are available?

Over the course of the last 10 years several large network meta-analyses have been reported, comparing safety and/or efficacy of the most recent at any given time DES including major competitor devices (e.g. Xience). You may find selected publications listed below:

- Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; 379:1393–402.
- Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with bioabsorbable polymer-versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2014; 63:299–307.
- Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015; 65:2496–507.
- Philip F, et al. Very late stent thrombosis with second generation drug eluting stents compared to bare metal stents: Network meta-analysis of randomized primary percutaneous coronary intervention trials. *Catheter Cardiovasc Interv* 2016 Jul;88(1):38-48
- Forrestal B, et al. A Network Meta-analysis comparing clinical outcomes of thick- and thin-strut biodegradable polymer stents with second generation drug-eluting stents. *JACC: Cardiovascular Interventions*.2018

Taglieri et al. network meta-analysis is the most updated and comprehensive meta-analysis including 77 RCTs and 99,039 patients comparing 1-year and long-term efficacy and safety of currently used DES.

Taglieri et al., Network Meta-analysis¹

Frequently Asked Questions

Results/ Objection Handling

9. How can we interpret the results and what is the driver behind the differences we see with Orsiro vs. other major competitors?

The Taglieri et al. network meta-analysis confirms a similar signal with previous meta-analyses comparing newer generation DES with thinner vs. thicker struts and other large RCTs and highlights the potential role of several design aspects such as strut thickness, polymer type and drug distribution contributing to the excellent clinical performance of Orsiro.

The authors in the publication state a polymer degradation time of 9 m for Orsiro, which is incorrect. However, the assumption that polymer degradation is unlikely to play a role in 1 yr efficacy is reasonable due to enduring polymer presence beyond 1 yr. Overall, the results are consistent with the large body of evidence for Orsiro, confirmed as one of the most studied DES with currently more than 55,000 patients enrolled in more than 70 studies, and the best in class among newer generation DES.

10. Why do we see an attenuation of the efficacy signal with Orsiro vs. other DES comparators at long-term follow-up?

At long-term follow-up (a median duration of 50 months) fewer studies with smaller numbers of patients were available compared with 1-year follow-up. Thus, the lack of statistical significance at long-term follow-up between Orsiro and the other DES comparators might be related to a reduced statistical power of the study. However, at long term follow-up Orsiro still ranked as the best DES.

11. The editorial from George Dangas "Stent Technology reaches maturity"³ suggests that there are minimal differences between DES these days, and improvements might come from factors outside of the stent. How would you respond?

The study results confirm data from individual RCTs that the DES type and platform characteristics such as stent design, strut thickness, polymer type and drug distribution play a major role in reducing event rates within the first year of stent implantation. However, the potential lack of impact of stent technology on very late outcomes underscores the importance of further trials which are adequately powered to see if there will be an impact on reducing long term events.

References

1. Taglieri N., et al. Target lesion failure with current drug-eluting stents. Evidence from a comprehensive network meta-analysis. J Am Coll Cardiol Interv. 2020;13(24):2868–78.
2. Rouse B., et al. Network Meta-analysis: An introduction for clinicians. Intern Emerg Med. 2017Feb;12(1):103–111.
3. Dangas G., Claessen B. Stent technology reaches maturity? JACC: Cardiovascular Interventions. 2020:2879– 81.

Orsiro, is a trademark or registered trademark of the BIOTRONIK Group of Companies. Resolute Integrity and Resolute Onyx are trademarks or registered trademarks of the Medtronic Group of Companies. Xience is a trademark or registered trademark of the Abbott Group of Companies. Synergy and Promus are trademarks or registered trademarks of the Boston Scientific Group of Companies. Nobori is a trademark or registered trademark of the Terumo Group of Companies. Biofreedom and BioMatrix are trademarks or registered trademarks of the Biosensors International Group. Cre8 is a trademark or registered trademark of the Alvimedica Group of Companies. Clinical data conducted with Orsiro, Orsiro Mission's predecessor device can be used to illustrate Orsiro Mission clinical outcomes.

Clinical data conducted with Orsiro, Orsiro Mission's predecessor device can be used to illustrate Orsiro Mission clinical outcomes.