Methodology and Challenges of Network Meta-Analysis in Health Technology Assessment of Medical Devices:

A Case Study of Drug Eluting Stents

Canolfan ar gyfer Gwerthuso, Asesu Dyfeisiau ac Ymchwil Gofal Iechyd
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Background

- Network meta-analysis (NMA) is a well-established technique and has become a core methodology in health technology assessments (HTA) with increasing applications. It is useful in determining the comparative effectiveness of interventions that have not been directly compared.[1,2]
- However, its use and interpretation remain challenging, particularly in the presence of heterogeneity, inconsistency and methodological complexities (e.g. network sparsity).[3]
- A Bayesian network meta-analysis (NMA) was undertaken in the National Institute of Health and Care Excellence (NICE) multi-technologies late-stage assessment (LSA) of drug-eluting stents (DES).[4] Several methodological challenges were encountered, leading to imprecise results.

Objectives

- We aimed to report and compare methods used for NMAs of drug-eluting-stents (DES), including key challenges.

Methods

- The targeted literature searches of 8 bibliographic databases conducted in NICE LSA of DES were used to identify any NMAs of DES in any population
- The data including NMA model, model specification, sensitivity analyses, results and key limitations were extracted from a total of 3 studies and quality assurance was performed for this data extraction by a second reviewer.

Findings

- 3 NMAs were identified from the search. The population included a mixed patient population treated with DES in three studies, and patients with high bleeding risk in one study. These NMAs found from the literature were compared with the NMA undertaken for the NICE LSA.
- Among NMAs comparing at least 10 devices, the LSA NMA had the fewest RCTs (n=14) with 25,974. Conversely, the NMA by Kang et al. (2016) included 147 RCTs with 126,526 participants. Network plots are illustrated in Figure 1.

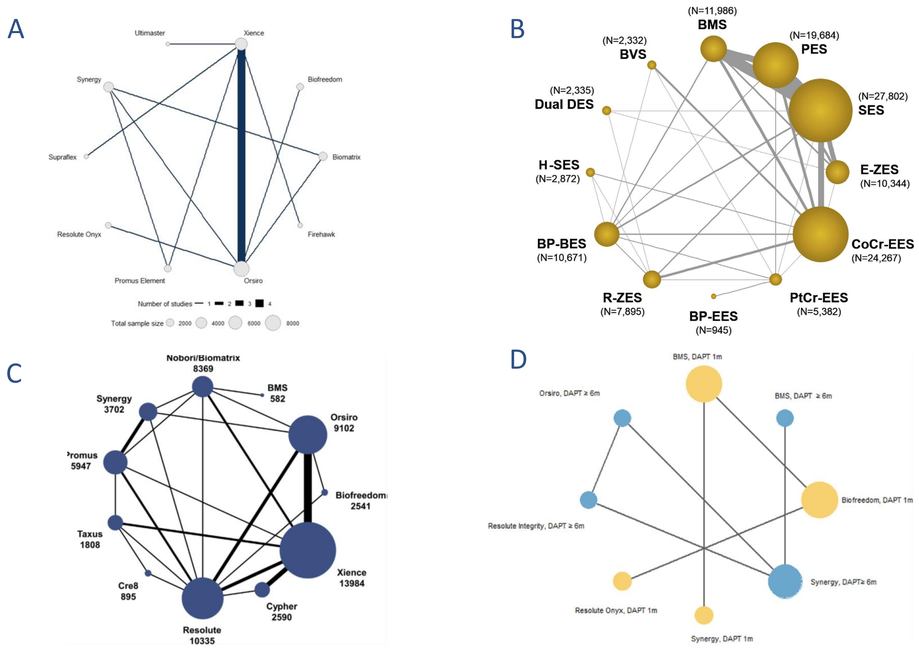

Figure 1: 4 Network plots. **A** – LSA NMA[4]. **B** – Kang et al.[5], **C** – Taglieri et al.[6], **D** – Giacobbe et al.[7]

Findings, continued

- A Bayesian framework was used in 2 studies, however the specifications of the prior distributions used were not reported.
- When using sparser data where the number of studies were reduced, NMA results became unstable or produced even wider 95% credible intervals (CrIs).

Challenges faced

- **Data sparsity** – Due to the presence of very few studies and rare events, between-study heterogeneity cannot be estimated reliably.
- **Lack of prior information –** Due to the lack of meta-analyses (MA) in medical devices, a suitable prior was unable to be chosen for the NMA. This influences the NMA estimate precision.
- **Focus on single-armed studies** - The current evidence base for medical devices tends to focus on single-arm studies rather than comparative multiple arm studies. This limits the ability to perform meta-analyses.
- **Wide 95% credible intervals** – This is evident when comparing with unequal sample sizes as in the NMA conducted for the LSA and the published studies that were identified.
- **Underpowered data in the NMA model** – Non-inferiority trials are common in medical devices; however, these studies are not powered to demonstrate differences in effectiveness. Using data from non-inferiority trials and studies that were not powered for the NMA outcome would affect the robustness of the NMA.

Conclusions

- Conducting NMA in medical devices is challenging when data are sparse, leading to uncertainty.
- While RCTs are gold standard for evaluating efficacy, the incentive for conducting RCTs in some medical devices is limited given their rapidly evolving nature and the high costs associated with conducting these trials.
- Generating comparative real-world data is also challenging, however it may offer an alternative to bridge this evidence gap if this can be used in a NMA to address data sparsity.

Table 1 – Comparison of LSA NMA with other DES NMAs

	LSA NMA[4]	Kang et al. 2016[5]	Taglieri et al. 2020[6]	Giacobbe et al. 2023[7]
Population	Mixed patient population treated with DES	Mixed patient population treated with DES	Mixed patient population treated with DES	Patients with high bleeding risk and treated with DES
Devices compared	10	12	11	6
RCTs included / participants	14 / 25,974	147 / 126,526	77 / 99,039	4 / 6,637
Framework used	Bayesian	Bayesian	Frequentist	Bayesian
Outcome	Target lesion revascularisation at 1 year	Stent thrombosis at 1 year	Target lesion failure at 1 year	Major Adverse Cardiovascular Events
NMA estimate(95%CrI/CI) between devices with the largest sample size	Orsiro (n=8,222) vs Xience (n=5,278): 1.25 (0.84-1.81)	SES (n=27,802) vs CoCr-EES (n=24,267): 1.63 (1.23-2.26)	Xience (n=13,984) vs Resolute (n=10,335): 0.96 (0.83-1.12)	Biofreedom (n=2,214) vs BMS (n=1,815): 1.40 (1.11-1.76)
NMA estimate(95%CrI/CI) between devices with the smallest sample size and the largest sample size	Supraflex (n=720) vs Xience (n=5,278): 0.94 (0.46-1.73)	SES (n=27,802) vs BP-EES (n=945): 4.24 (0.70-27.6)	Xience (n=13,984) vs Cre8 (n=895): 0.80 (0.52-1.24)	Biofreedom (n=2,214) Resolute Integrity (n=336) : 0.93 (0.50-1.75)
Sensitivity analysis	Using higher prior heterogeneity	One of the sensitivity analyses: excluding studies <100 participants	Meta-regression	Meta-regression, including studies on DCB
Results of sensitivity analysis using smaller sample size or an alternative prior distribution	Orsiro vs Xience: 1.26 (0.74-2.06) Supraflex vs Xience: 0.74 (0.27-1.64)	SES vs CoCr-EES: 1.65 (1.22-2.27) SES vs BP-EES: 3.99 (0.59-35.6)	NA	NA

BMS: Bare metal stent, CrI: Credible interval, CI: Confidence interval, DCB: Drug coated balloon, DES: drug-eluting stent

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