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Trial sequential analysis of studies comparing the frequency of target-vessel revascularization with drug-coated balloons as compared with second-generation drug-eluting stents in coronary in-stent restenosis: Have we generated enough evidence in the field?

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Treatment of in-stent restenosis (ISR) in patients remains a challenge.[1] Neointimal proliferation has drastically reduced following the introduction of drug-eluting stents (DESs),[2] which is hypnotized as the dominant mechanism in ISR. The burden of ISR remains high even in the present era of second-generation DES.[3] ISR was treated previously with methods such as conventional balloon angioplasty, cutting and scoring balloon therapy, debulking technique, and vascular brachytherapy. However, the present standard of treatment is resenting with second-generation DES or drug-coated balloon (DCB). Treatment of ISR with DCBs and second-generation DESs have been studied extensively using well-designed randomized control trials. The studies have shown comparable advantages in both angiographic and clinical aspect.[4–10] The studies have been summarized in Table 1.

A recent well-performed meta-analysis studied second-generation DES as compared with DCB in ISR (ISR of both bare-metal stent and DES).[13] The authors of the meta-analysis concluded that DCB was associated with an increased risk of target lesion revascularization (TLR) (risk ratio [RR] 1.83, 95% confidence interval 1.07–3.13, $p = 0.03$) at a mean follow-up period of 27 months. The increased risk was also noted on the analysis limited to only DES-ISR too (RR 1.88, 95% confidence interval 1.08–3.20, $p = 0.02$). There was no difference noted in terms of target vessel revascularization, major adverse cardiac events, myocardial infarction, stent thrombosis, all-cause mortality, and the angiographic outcomes (i.e., in segment minimum luminal diameter, diameter stenosis, and late lumen loss).

Most meta-analysis included very few participants to completely justify the intervention effect, usually resulting in spurious overestimation (type 1 error) or underestimation (type 2) of the effect.

We performed a trial sequential analysis (TSA) on all included trials comparing DCB with DES in ISR and the outcome of interest being TLR. Meta-analysis may result in type 1 error due to an increased risk of random error due to repeated significance testing. To access the risk of type 1 error, we used TSA. TSA combines information size estimation for meta-analysis with adjusted boundary for statistical significance in the cumulative meta-analysis.[14] An adjusted information size is calculated based on a specified intervention effect, pre-fixed alpha and beta error, control event proportion, and an estimation of heterogeneity.

The trial sequential analysis was performed for five studies reporting TLR in their outcome,[4–8,11,12] including a total of 929 patients for a relative risk reduction of −83% (pooled estimate) by the use of DCB instead of DES in patients with ISR, with TLR as the outcome of interest. A required diversity-adjusted information size of 1425 was calculated based on a control event proportion of 5.6%, permissible type 1 error of 5% two-sided, type 2 error of 20%, relative risk reduction of TLR following DCB as compared with DES in ISR to be −83% (suggested by pooled effect of included trails) and diversity of 26%. The cumulative Z-curve (blue) crosses the conventional test boundary ($p = 0.05$) but fails to cross the trial sequential monitoring boundary indicating lack of firm evidence yet (Fig. 1), for the superiority of DES over DCB in the treatment

Table 1
Baseline characteristic of included studies comparing drug-coated balloons versus second-generation drug eluting stents in in-stent restenosis.

Study	Year	Country	Number of participants	Mean age	Male%	Mean follow-up	Diabetes	Hypertension
SEDUCE[4]	2014	Belgium	25/25	68/64	72/100	12 months	24/4	64/60
RIBS V[5,6]	2014	Spain	95/94	67/64	86/87	36 months	32/20	72/72
RIBS IV[7,8]	2015	Spain	154/155	66/66	82/84	12 months	49/43	71/78
TIS[9]	2016	Czech Republic	68/68	66/66	63/68	12 months	25/26	–
DARE[10]	2017	The Netherlands	137/141	66/65	72/84	12 months	31/33	64/67
RESTORE[11]	2018	Multicenter	86/86	67/66	61/62	12 months	43/38	60/65
BIOLUX[12]	2018	Germany	157/72	67/69	78/69	18 months	30/33	144/70

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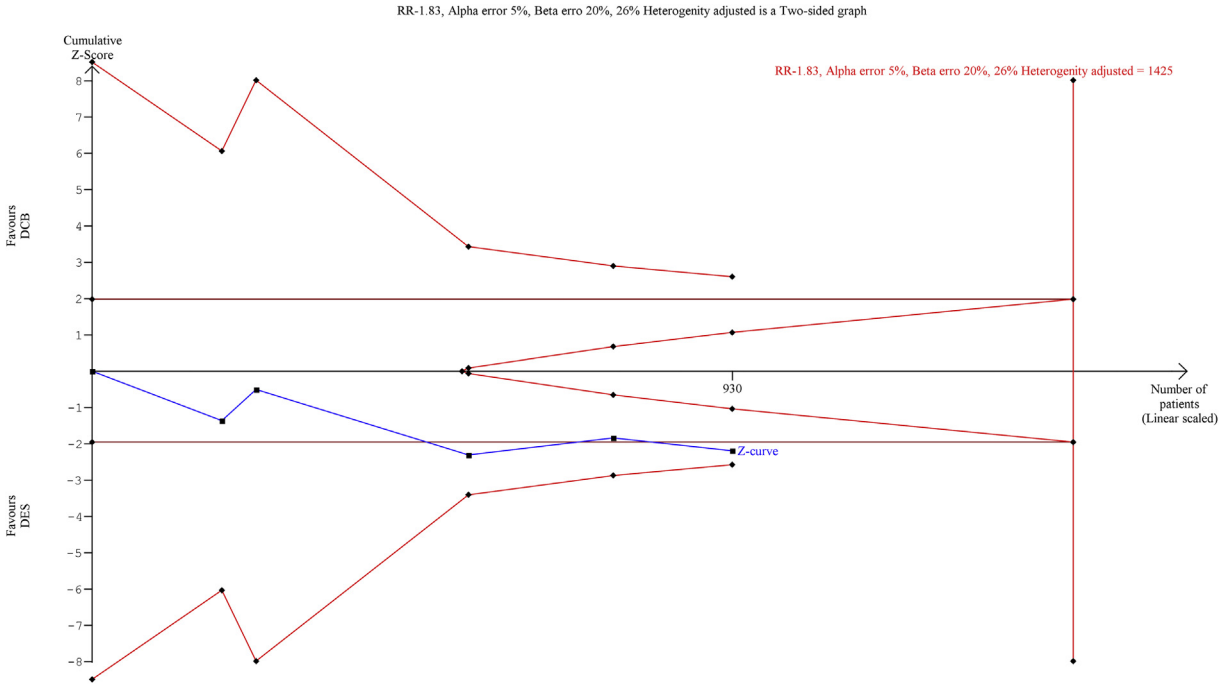

Fig. 1. Trial sequential analysis plot with cumulative Z cure, conventional boundary, and trial sequential boundary. DCB, drug-coated balloon; DES, drug-eluting stent; RR, risk ratio.

of ISR. The adjusted confidence interval of relative risk for target lesion revascularization when ISR is treated with DCB as compared with DES is 0.9–3.71 (as compared with 1.07–3.13 reported in the meta-analysis).

In conclusion, though DES has better outcome numbers, the present available evidence has not reached the level of statistical significance yet. And hence, the question, is DES superior to DCB for the treatment of ISR still needs to be answered.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.06.001.

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