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A meta-analysis of randomised controlled trials assessing drug-eluting stents and vascular brachytherapy in the treatment of coronary artery in-stent restenosis

Lisa N Oliver¹, Petra G Buttner², Helen Hobson¹, and Jonathan Golledge¹

¹The Vascular Biology Unit, James Cook University, Townsville, Queensland. 4811. Australia.

²School of Public Health and Tropical Medicine James Cook University Townsville, Queensland. 4811. Australia.

Abstract

Objective—We undertook a meta-analysis of randomised trials assessing the outcome of vascular brachytherapy (VBT) or DES for the treatment of coronary artery ISR.

Methods and results—Studies utilising DES or VBT for ISR were identified by a systematic search. Data was pooled and combined overall effect measures were calculated for a random effect model in terms of deaths, myocardial infarctions, revascularisation, binary restenosis, mean late luminal loss and major adverse cardiac events (MACE). Fourteen eligible studies (3103 patients) were included. Neither therapy had any effect on mortality or myocardial infarction rate. VBT reduced the rate of revascularisation (RR 0.59, 95% CI 0.50–0.68), MACE (RR 0.58, 95% CI 0.51–0.67), binary restenosis (RR 0.51, 95% CI 0.44–0.59) and late loss (–0.73 mm, 95% CI –0.91 to –0.55 mm) compared to balloon angioplasty and selective bare metal stents (BMS) alone at intermediate follow-up and MACE (RR 0.72, 95% CI 0.61–0.85) at long term follow-up. DES reduced the rate of revascularisation (OR 0.51, 95% CI 0.36–0.71), MACE (OR 0.55, 95% CI 0.36–0.71) and binary restenosis (OR 0.57, 95% CI 0.40–0.81) compared to VBT but follow-up was limited to 9 months.

Conclusions—VBT improves the long-term outcome of angioplasty compared with BMS alone in the treatment of ISR. DES appears to provide similar results to that of VBT.

Keywords

In-stent restenosis; Vascular brachytherapy; Drug-eluting stent

Introduction

Catheter based percutaneous interventions have become the primary invasive treatment for coronary artery disease. [1] A significant problem associated with this therapy has been the high recurrence rate. The introduction of drug eluting stents (DES) has dramatically reduced the incidence of in-stent restenosis (ISR) following percutaneous coronary interventions. [2] However, ISR continues to be a problem in the treatment of some patients such as those with small vessels or diabetes mellitus where rates over 10% have been reported. [3,4] Historically

Correspondence to: Professor Jonathan Golledge, Director, The Vascular Biology Unit, James Cook University, Townsville. Queensland. 4811. Australia. Fax +61 7 4796 1401 Telephone +61 7 4796 1417 Email Jonathan.Golledge@jcu.edu.au.

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the treatment of ISR has been disappointing with techniques such as cutting balloons, atherectomy devices and bare metal stents failing to improve the outcome over angioplasty alone. [5–7] Vascular brachytherapy (VBT) was introduced to reduce recurrence following coronary interventions and present guidelines advocate its use for the treatment of ISR with level I evidence. [8] The restricted availability, need for specific licensing, and more cumbersome treatment delivery have all limited the use of VBT to specialist centres. [9] Given the success of DES in primary coronary lesions their use has recently been advocated for ISR. [10] We carried out a meta-analysis to examine the outcome of VBT and DES in the treatment of coronary artery ISR.

Methods

Search Strategy

This meta-analysis was carried out in accordance with the standard protocol recommended by the Quality of Reporting of Meta-analyses group. [11] An extensive literature search for randomised controlled trials addressing the management of ISR was conducted from August 10, 2005 to April 26, 2006 (see supplemental data available on-line). In all 17 trials were considered potentially appropriate for inclusion in this meta-analysis.

Study Selection

Eligible studies were randomised controlled trials assessing the use of VBT or DES in patients with native coronary artery ISR. Mixed studies in which a subset of the participants only had ISR (others having primary lesions or non-stent restenosis) were allowable although sensitivity analyses were planned to assess the effect of including such studies. At least one treatment group needed to use VBT or DES. Trials were also considered if they referred either to intravascular or intracoronary instead of 'vascular', and radiotherapy or radiation instead of 'brachytherapy' when describing the VBT treatment. We required that outcome should have been assessed for a minimum of six months following treatment of ISR by clinical and angiographic measures.

Data Extraction and Validity Assessment

Two authors (LO & HH) independently extracted the data from the identified studies. Any discrepancies were resolved with discussion until agreement was met. In the event of missing or difficult to interpret data, the chief investigator of the study concerned was contacted directly for further information. The quality of the studies was assessed independently by two authors (JG and PB). These assessors were blinded to names, affiliations and addresses of the investigators as well as to the journals in which the trials were published. Quality assessment was based on three scales: 1) the 17 checklist items required in the methods and results of randomised controlled trials according to the CONSORT statement; 2) a scale of six criteria devised by our group in order to assess hypothesis setting, outcome assessment, randomisation, blinding, reporting of patient numbers and analysis (score ranging from 0 to 8); and 3) the previously validated scale by Jadad et al. (score ranging from 0 to 5). [12,13] Agreement between the two assessors was judged using the concordance correlation coefficient. [14] For each scale the scores from the two assessors was added and ranked to determine the trials of high and low quality.

Study Characteristics and Definitions

The study design, patient characteristics, target lesion characteristics, procedural details, outcomes measures, and follow-up periods were reviewed to assess clinical heterogeneity. The components of the study design that were noted included the blinding of the studies as well as the number of centres involved in recruiting patients. The trials were noted to be unblinded,

single-blinded or double-blinded based on whether treatment allocation was concealed from the patient, treating physician and/ or outcome assessor. Characteristics of the study participants that were noted included age, gender, the presence of diabetes mellitus and multi-vessel disease. Lesion characteristics recorded included the classification of stenosis (primary, non-stent restenosis (NSR), and ISR), lesion length and the initial minimal lumen diameter (MLD). The trial intervention details recorded included the application and source (beta or gamma radiation) of VBT, the type of DES (sirolimus or paclitaxel stents), and the frequency of balloon angioplasty, bare-metal stent placement, atherectomy (direct or rotational) or excimer laser angioplasty.

Outcome assessment

The outcome measures considered included the angiographic endpoints of binary restenosis and late lumen loss, as well as the clinical outcome of major adverse cardiac events (MACE), a composite of the number of deaths, myocardial infarctions (MI), and either target vessel revascularisation (TVR) or target lesion revascularisation (TLR), as defined by each study. A breakdown of MACE into the individual components also provided additional outcome measures. While all studies reported outcome at the same period after intervention for treatment and control patients the exact time points varied from study to study. Therefore clinical measures were recorded as short-term (in-hospital or 30-day events), intermediate (6–24 months), and long-term follow-up (3 years or more). Short-term results were preferentially taken from the 30-day event rates, intermediate outcomes were preferentially taken from the 12-month assessment and long-term results were preferentially taken from the 3-year findings. For definitions of outcome measures see supplemental data (available on-line).

Quantitative Data Synthesis

For categorical outcome characteristics relative risks were chosen as treatment effect measures. For late loss standardised differences in means were calculated. Combined overall effect measures were calculated for a random effect model and are presented with 95% confidence intervals (95%CI). Statistical heterogeneity was assessed using the chi-square distributed Q-statistic. Sensitivity analyses were carried out differentiating between (1) studies in which participants all had ISR and those with mixed patients including some with primary lesions or NSR in addition to ISR; (2) trials using gamma and those using beta radiation; (3) studies with a follow-up time of one year or more and those with a shorter observation period; (4) trials utilising DES and those using VBT; and (5) studies that were judged to be of lower quality against all other studies. Publication bias was assessed graphically using funnel plots and statistically using the classic fail-safe N. Statistical analysis was conducted using the software program Comprehensive Meta Analysis, Version 2 (Englewood, NJ 07631, USA).

Results

Study characteristics

Fourteen randomized controlled trials (3103 participants) were identified for inclusion in this meta-analysis (Supplemental Figure 1 available on-line). [15–35] Three additional trials (ARREST, ARTISTIC, BRITE) were unable to be included as there was incomplete reporting of the results. [36, 37] The chief investigators for each of these trials were contacted for further information but were unable to provide any assistance. Two trials (TAXUS V ISR, SISR) evaluated the use of VBT compared to DES in the treatment of ISR. [34, 35] One study (ISAR-DESIRE) addressed the use of DES compared to a control group and eleven trials addressed the use of VBT compared to control groups. [15–33] The design of the trials is shown in Supplemental Table I (available on-line) and the patient and lesion characteristics in Table I. Agreement between the assessors of study quality was low for Jadad's scale (Concordance correlation coefficient $r = 0.31$, 95%CI = [0.23, 0.39]) but good to very good for the other two

scales (CONSORT with 17 items: $r = 0.69$, 95% CI = [0.61, 0.76]; our scale: $r = 0.79$, 95% CI = [0.73, 0.84]). Both independent and blinded assessors of the studies agreed on judging two of the 14 studies of lower quality. [18, 23]

Trial outcomes

The clinical outcomes in the trials are reported in Table II. The angiographic follow-up and outcome of the trials are shown in Supplemental Table II (available on-line).

Outcome of brachytherapy compared to other treatment options

Thirteen of the studies compared VBT with another treatment, either PTCA plus selective BMS ($n=11$) or DES ($n=2$). By comparison with all other treatments VBT reduced the odds of MACE, TVR, TLR, restenosis and late loss at intermediate follow-up and MACE at long-term follow-up (Table III, Supplemental Figure available on-line). Heterogeneity was significant for TVR, TLR, MACE after 1 year, restenosis and late loss ($p < 0.001$, respectively). Exclusion of the two studies TAXUS and SISR which compared DES with VBT reduced heterogeneity to in-significance in all analyses except for late loss (Table III). Heterogeneity for the late loss results persisted even after further exclusion of the two studies that were considered of less quality (Schuhlen et al. and PREVENT) which showed comparably large effects for late loss. A sensitivity analysis was conducted removing the two studies considered of less quality, which resulted in findings almost identical to the initial results. Differences between results generated by fixed and random effect models were minimal. The studies were stratified into those studying “pure” in-stent restenosis lesions ($n=9$) and those including “mixed” lesions ($n=4$). Results for the two groups were very similar except that VBT had no effect on TVR or TLR in the pure ISR studies. These effects disappeared when the two DES studies (TAXUS and SISR) were excluded from the analyses (Table III). Further sensitivity analyses are available in the supplemental data (available on-line).

Outcome of DES compared to other treatment options

Combined numerical results of all studies with DES as one treatment arm ($n=3$) showed significant reductions of TVR, MACE assessed after 1 year follow up, and restenosis for the intervention compared with control group ($p < 0.001$, respectively) (Table IV). Similar results were found when analysis was restricted to the two studies that compared DES against VBT (Table IV, Supplemental Figure 3–5 available on-line). In addition, the combined results of the two DES studies that compared against VBT also showed a significant reduction in TLR. For these analyses heterogeneity was not significant. Further sub-group analyses were not conducted because of the small sample size.

Discussion

Vascular brachytherapy (VBT) has been the principal scientifically investigated local therapy for coronary artery ISR. In the course of this meta-analysis we identified 17 randomised controlled trials assessing the efficacy of VBT for ISR of which 14 met our inclusion criteria. [15–35] This represents a total of 3103 patients randomised. Around one-third of patients treated had diabetes mellitus, mean TLL and MLD were over 15 mm and less than 9 mm respectively in the majority of studies (Table I). VBT followed balloon angioplasty plus selective placement of bare-metal stents (BMS) and/or atherectomy in the majority of studies with comparable interventional treatment being used in the control patients except in two studies where VBT was compared with DES. [34,35] Thus in 11 studies the addition of VBT to standard treatment of ISR was assessed. While in 2 studies VBT following balloon angioplasty plus selective BMS (in approximately 16%) was compared with DES placement. A total of three studies were identified comparing DES with other treatments for ISR. [33–

35] Two of these studies compared DES with VBT (mentioned above) and one with balloon angioplasty plus selective BMS placement (mean 4%).

Our overall findings demonstrate that VBT improves intermediate term outcome in terms of binary restenosis, late lumen loss, need for revascularisation and MACE in the treatment of ISR by comparison to balloon angioplasty and selective BMS placement (Table II–Table IV). This finding is only apparent in the 11 studies comparing VBT with similar treatment in the control patients and is unaffected by radiation source, removal of lower quality studies and those with shorter follow-up. Analysis of the three studies comparing DES with other treatments for ISR demonstrated reduced need for revascularisation, MACE and binary restenosis in patients receiving DES. This finding included benefit of DES over VBT in all these three outcome measures. Although it should be noted that DES have not been compared with VBT following obligate placement of BMS i.e. the difference in outcome identified may result from an effect of the stent in addition to the eluted drug. Neither VBT nor DES was shown to reduce mortality, myocardial infarction or improve short-term outcome. In addition DES was not shown to reduce late lumen loss, which is believed to be the most robust measure of restenosis [38]. Long term assessment is limited in most of these studies, with only 5 studies having follow-up over 2 years. Analysis of these studies demonstrated superiority of VBT over standard treatments (all the DES studies had 12 months or less follow-up) in terms of reduced need for revascularisation and MACE.

The benefit of coronary interventions which do not reduce the clinical end-points of death and myocardial infarction have been questioned since restenosis has not been linked to these more significant events in some studies [39]. Coronary intervention studies have been criticised for focusing too much on restenosis which when identified by the protocol-driven angiogram defines the need for revascularisation. In this regard most investigators left decisions regarding re-intervention to the local treating physician. However, TAXUS V ISR which compared paclitaxel-eluting stents and VBT attempted to isolate ischaemia driven revascularisation [35]. This was defined as at least 50% binary restenosis associated with electrocardiographic changes at rest or a positive functional study in the distribution of the vessel or at least 70% stenosis associated with recurrent symptoms. The investigators reported a small but significant reduction in the rate of ischaemia driven revascularisation in favour of the DES treated patients (Supplemental Figure 2 available on-line).

The results of this meta-analysis suggest that DES produce results at least as good as VBT in the treatment of ISR during the first year of treatment. Larger studies with longer follow-up would have been preferred to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Patient and Lesion Characteristics

Study	Age - yrs		Male - %		DM - %		MVD - %		ISR - %		TLL - mm		MLD - mm	
	VBT	C	VBT	C	VBT	C	VBT	C	VBT	C	VBT	C	VBT	C
SCRIPPS15-17	69.8 (9.7)	68.8 (10.8)	73	76	27	41	n/r	n/r	62	62	12.89 (7.05)	11.86 (6.77)	1.10 (0.46)	1.03 (0.46)
PREVENT18	63 (11)	63 (8)	64	76	20	24	35	28	24	24	n/r	n/r	n/r	n/r
WRIST19-21	63.2 (10.9)	62.3 (10.2)	66	72	39	45	65	56	100	100	28.8 (12.4)	26.7 (11.3)	0.94 (0.42)	0.81 (0.42)
GAMMA-ONE22	58 (12)	61 (11)	75	74	31	31	40	43	100	100	19	20.3	0.98	0.96
Schühlen et al.23	65 (13)	66 (10)	73	60	18	40	n/r	n/r	100	100	13.3 (7.3)	14.6 (7.4)	0.35 (0.26)	0.36 (0.30)
INHIBIT24	62 (11)	61 (11)	70	73	33	27	37	44	100	100	16.9 (8.9)	17.9 (8)	1.01 (0.47)	0.95 (0.47)
START25,26	61.5 (11.5)	61.1 (10.4)	68	63	31	32	37	44	100	100	16.3 (7.2)	16	0.98 (0.38)	0.98 (0.37)
SVG-WRIST27,28	67 (8)	66 (9)	82	77	45	35	79	73	100	100	17.6 (10.2)	14.9 (10)	0.73 (0.47)	0.91 (0.60)
ECRIS29	62.5 (10.5)	64.5 (10.1)	75	79	24	25	n/r	n/r	21	19	9.3 (3.9)	9.7 (5.4)	0.84 (0.40)	0.74 (0.39)
Long-WRIST30,31	63 (10)	61 (10)	67	62	42	37	45	48	100	100	29.2 (12.1)	29.1 (12.4)	0.80 (0.40)	0.70 (0.43)
SPARE32	61.9 (8.79)	61.9 (9.32)	68	63	28.8	26.5	55.8	61.4	23	10.8	12.93 (3.92)	13.06 (4.12)	0.78 (0.35)	0.73 (0.37)
Weighted mean	62.1	62.2	70.4	70.1	31.2	31.2	44.7	48.5	77.4	79.8	17.2	19.0	0.92	0.88
DES vs. Control	DES	C	DES	C	DES	C	DES	C	DES	C	DES	C	DES	C
ISAR-DESIRE33*	64.3 (57.1-72.9)	63.2 (55.5-70.8) ^S	78	78.5	25	29	n/r	n/r	100	100	12.3 (9.0-16.7)	12.4 (7.9-18.3) ^S	0.95 (0.72-1.21)	0.91 (0.73-1.17) ^S
VBT vs. DES	VBT	DES	VBT	DES	VBT	DES	VBT	DES	VBT	DES	VBT	DES	VBT	DES
SISR34	63.5 (11.7)	62.7 (10.7)	65.6 (70.1)	68.2 (62.1)	29.6 (30.3)	33.3 (40.0)	50.4 (n/r)	43.4 (n/r)	100 (100)	100 (100)	16.76 (8.55)	17.22 (7.97)	0.86 (0.35)	0.78 (0.51)
TAXUS V	63 (54-73)	63 (54-70)	70.1	62.1	30.3	36.2	n/r	n/r	100	100	15.0 (10.0-23.3)	15.9 (11.8-22.8)	0.83 (0.61-1.01)	0.90 (0.55-1.04)
Weighted mean	63.2	62.8	68.4	65.6	30.0	36.2	50.4	43.4	100	100	15.7	16.7	0.84	0.83

VBT – Vascular brachytherapy group, DES – Drug-eluting stent group, C – Control group, () denotes standard deviation values (unless study is marked with a *, indicating interquartile range), DM – diabetes mellitus, MVD – multivessel disease, TLL – target lesion length, MLD – minimum luminal diameter, S – sirolimus stent group, P – paclitaxel stent group, n/r – not reported

Table II
Clinical outcome in randomised trials of VBT and DES for ISR

Study	MACE - %		Death - %		MI - %		TVR - %		TLR - %	
	VBT	Control	VBT	Control	VBT	Control	VBT	Control	VBT	Control
VBT vs. Control										
SCRIPPS15-17	3.8	3.4	0	0	3.8	0	0	0	0	3.4
PREVENT18	1.3	4	0	0	1.3	4	0	0	0	0
WRIST 19-21	10.8	7.7	0	0	10.8	7.7	0	0	0	0
GAMMA-ONE22	2.3	3.3	0.8	0	2.3	2.5	n/r	n/r	n/r	n/r
Schühlen et al.23	0	0	0	0	0	0	0	0	0	0
INHIBIT24	2.4	2.4	0	1.2	3.0	1.8	n/r	n/r	1.8	1.8
START25,26	2.5	2.2	0	0	1.6	1.7	0.8	0.4	n/r	n/r
SVG-WRIST27,28	8.3	18.3	0	1.7	8.3	13.3	0	3.3	n/r	n/r
ECRIS29	1.8	2.7	0	0	1.8	2.7	0	0	0	0
Long-WRIST30,31	16.3	16.7	0	0	16.7	16.7	n/r	n/r	n/r	n/r
SPARE32	0	0	0	0	0	0	0	0	0	0
Weighted mean	3.7	4.6	0.1	0.3	3.6	3.8	0.3	0.5	0.6	0.8
DES vs. Control	DES	Control	DES	Control	DES	Control	DES	Control	DES	Control
ISAR-DESIRE33	0	0	0	0	0	0	0	0	0	0
VBT vs. DES										
SISR34	0	1.5	0	0	0	1.5	0	0	0	0
TAXUS V ISR35	2.5	2.1	0	0	1.5	1.5	1.5	1.0	n/r	n/r
Weighted mean	1.5	1.8	0	0	0.9	1.5	0.9	0.4	0	0
INTERMEDIATE										
VBT vs. Control										
SCRIPPS15-17	15	48	0	3	4	0	n/r	n/r	12	45
PREVENT18	16	24	1	0	10	4	21	32	6	24
WRIST19-21	38.5	78.5	4	4	6	6	22	44	15	41
GAMMA-ONE22	28.2	43.8	3.1	0.8	9.9	4.1	31.3	46.3	24.4	42.1
Schühlen et al.23	27.3	80	0	0	0	0	27.3	80	n/r	n/r
INHIBIT24	12	28	3	3	8	5	19	30	8	26
START25,26	31.1	40	2.9	4.7	4.1	5.6	27.5	36.6	23.4	32.8
SVG-WRIST27,28	32	63	7	7	12	15	28	62	17	57
ECRIS29	14.2	21.4	0	0.9	6.2	4.5	8.0	16.1	1.8	15.2
Long-WRIST30,31	42.4	63.3	6.8	1.7	23.7	18.3	n/r	n/r	39.0	61.7
SPARE32	15.4	22.9	1	0.8	0	0	14.4	21.7	n/r	n/r
Weighted mean	24.0	40.5	2.7	2.8	7.3	5.8	22.0	35.3	16.5	35.0
DES vs. Control	DES	Control	DES	Control	DES	Control	DES	Control	DES	Control
ISAR-DESIRE33	16.5	36	1.5	3	1.5	0	13.5	33	n/r	n/r
VBT vs. DES										
SISR34	19.2	10.0	0	0	0	2.7	21.6	10.8	19.2	8.5
TAXUS V ISR35	20.1	11.5	0.5	0	4.6	3.7	23.7	12.0	20.1	7.9
Weighted mean	19.8	10.6	0.3	0	2.8	3.1	22.9	11.3	19.8	8.2
LONG-TERM										
VBT vs. Control										
SCRIPPS15-17	23.1	55.2	11.5	10.3	3.9	10.3	30.8	58.7	25.4	48.3
WRIST19-21	39	65	11	9	20	14	43	69	31	63
SVG-WRIST27,28	63	77	22	11	26	20	59	71	43	66
Long-WRIST30,31	48	68	13.3	3.4	24.7	18	47	65	41	65
SPARE32	24.5	34.2	1.2	2.5	2.4	2.4	22.4	30.4	n/r	n/r
Weighted mean	39.2	58.5	10.3	6.6	14.9	12.4	39.0	56.8	36.6	62.4

VBT – Vascular brachytherapy group, DES – Drug-eluting stent group, Control – Control group (PTCA), MACE – major adverse cardiac event, MI – myocardial infarction defined as either Q wave or non-Q wave infarction, TLR – target lesion revascularisation, TVR – target vessel revascularisation, Short-term: in-hospital complications or 30-day MACE, Intermediate: 6-24mth MACE, Long-term: 36mth MACE, n/r – not reported

Table III

Quantitative summary of randomised controlled trials comparing brachytherapy (intervention) with any other treatment (control) for coronary ISR.

Follow-up	Included studies	Number of studies	Effect size [95% Confidence interval]		p-value (Heterogeneity statistics if significant)	“Pure” in-stent restenosis studies		“Mixed” studies
			All studies	“Pure” in-stent restenosis studies				
Short-term	All	11 [*]	0.87 [0.58, 1.3] p = 0.478	0.90 [0.59, 1.4] p = 0.601		0.63 [0.17, 2.3] p = 0.485	0.63 [0.17, 2.3] p = 0.485	
	Excluding TAXUS V ISR & SISR	9 [*]	0.86 [0.57, 1.3] p = 0.480	0.89 [0.57, 1.4] p = 0.610		0.63 [0.17, 2.3] p = 0.485	0.63 [0.17, 2.3] p = 0.485	
intermediate	All	11 [*]	1.3 [0.73, 2.4] p = 0.349	1.6 [0.84, 3.1] p = 0.147		0.40 [0.09, 2.1] p = 0.287	0.40 [0.09, 2.1] p = 0.287	
	Excluding TAXUS V ISR & SISR	10 [*]	1.3 [0.70, 2.4] p = 0.410	1.6 [0.81, 3.1] p = 0.179		0.42 [0.09, 2.1] p = 0.287	0.42 [0.09, 2.1] p = 0.287	
Intermediate	All	11 [*]	1.2 [0.86, 1.7] p = 0.286	1.1 [0.80, 1.6] p = 0.473		1.7 [0.67, 4.3] p = 0.267	1.7 [0.67, 4.3] p = 0.267	
	Excluding TAXUS V ISR & SISR	9 [*]	1.2 [0.86, 1.8] p = 0.254	1.2 [0.79, 1.7] p = 0.440		1.7 [0.67, 4.3] p = 0.267	1.7 [0.67, 4.3] p = 0.267	
Intermediate	All	11 [†]	0.72 [0.53, 0.99] p = 0.041 (Q=47.1; p<0.001)	0.76 [0.52, 1.1] p = 0.140 (Q=46.0; p<0.001)		0.61 [0.31, 1.2] p = 0.144	0.61 [0.31, 1.2] p = 0.144	
	Excluding TAXUS V ISR & SISR	9 [†]	0.59 [0.50, 0.68] p < 0.001 (Q=4.5; p=0.813)	0.58 [0.49, 0.69] p < 0.001 (Q=4.0; p=0.552)		0.61 [0.41, 0.91] p = 0.016	0.61 [0.41, 0.91] p = 0.016	
Intermediate	All	11 [‡]	0.54 [0.34, 0.85] p = 0.007 (Q=72.4; p<0.001)	0.67 [0.41, 1.1] p = 0.101 (Q=62.4; p<0.001)		0.21 [0.08, 0.57] p = 0.002	0.21 [0.08, 0.57] p = 0.002	
	Excluding TAXUS V ISR & SISR	9 [‡]	0.42 [0.33, 0.55] p < 0.001 (Q=14.8; p=0.063)	0.47 [0.37, 0.59] p < 0.001 (Q=8.9; p=0.113)		0.21 [0.10, 0.44] p < 0.001	0.21 [0.10, 0.44] p < 0.001	
Intermediate	All	13	0.68 [0.52, 0.87] p = 0.002 (Q=42.4; p<0.001)	0.71 [0.53, 0.96] p = 0.027 (Q=39.0; p<0.001)		0.57 [0.34, 0.96] p = 0.034	0.57 [0.34, 0.96] p = 0.034	
	Excluding TAXUS V ISR & SISR	11	0.58 [0.51, 0.67] p < 0.001 (Q=6.9; p=0.732)	0.58 [0.50, 0.67] p < 0.001 (Q=4.2; p=0.647)		0.59 [0.42, 0.83] p = 0.002	0.59 [0.42, 0.83] p = 0.002	
Intermediate	All	13	0.57 [0.42, 0.78] p < 0.001 (Q=69.8; p<0.001)	0.67 [0.48, 0.91] p = 0.025 (Q=56.9; p<0.001)		0.38 [0.22, 0.67] p = 0.001	0.38 [0.22, 0.67] p = 0.001	
	Excluding TAXUS V ISR & SISR	11	0.51 [0.44, 0.59] p < 0.001 (Q=11.9; p=0.292)	0.55 [0.48, 0.64] p < 0.001 (Q=6.6; p=0.361)		0.38 [0.28, 0.53] p < 0.001	0.38 [0.28, 0.53] p < 0.001	
Intermediate	All	13	-0.63 [-0.84, -0.41] p < 0.001 (Q=68.7; p<0.001) §	-0.54 [-0.78, -0.30] p < 0.001 (Q=50.7; p<0.001)		-0.82 [-1.20, -0.44] p < 0.001	-0.82 [-1.20, -0.44] p < 0.001	
	Excluding TAXUS V ISR & SISR	11	-0.73 [-0.91, -0.55] p < 0.001 (Q=30.3; p=0.001) §	-0.69 [-0.92, -0.46] p < 0.001 (Q=20.6; p=0.002) §		-0.81 [-1.1, -0.49] p < 0.001	-0.81 [-1.1, -0.49] p < 0.001	
Long-term	All	5/1	0.72 [0.61, 0.85] p < 0.001	0.74 [0.61, 0.89] p = 0.001		0.61 [0.40, 0.94] p = 0.024	0.61 [0.40, 0.94] p = 0.024	

recorded no deaths (Schühlen & SISR), no myocardial infarctions (Schühlen & SPARE), and no MACE after 30 days (SPARE & Schühlen) in both intervention and control group,

in TVR after one year of follow-up was missing for two studies (long-WRIST & SCRIPPS). Both studies had presented results for a three years follow-up period showing less TVR in the compared to the control group (28 versus 39, 8 versus 17, respectively).

recorded no TLR in both intervention and control groups (Schühlen et al) and one study did not record TLR (SPARE).

persisted after exclusion of TAXUS and SISR mainly caused by the large effects of the two studies that were considered of less quality (Schühlen et al and PREVENT). However, even of those studies heterogeneity was significant (Q=17.5; p=0.025 including 9 studies).

TAXUS V ISR and SISR had no long-term follow-up. Only five studies (3 pure ISR studies; see Table 1) had long-term follow-up.

Table IV

Quantitative summary of randomised controlled trials comparing DES (intervention) with any other treatment (control) for coronary ISR.

Outcome	Effect size [95% confidence interval] p value	
	DES vs. VBT/Control (n=3)	DES vs.VBT (n=2)
Death [*]	0.46 [0.11, 1.9] p = 0.289	0.34 [0.01, 8.4] p = 0.512
Myocardial infarction	1.5 [0.41, 5.6] p = 0.540	1.6 [0.22, 11.6] p = 0.654
TVR	0.47 [0.36, 0.62] p < 0.001	0.51 [0.36, 0.71] p < 0.001
TLR [†]	/	0.42 [0.29, 0.62] p < 0.001
MACE intermediate	0.51 [0.39, 0.67] p < 0.001	0.55 [0.39, 0.79] p = 0.001
MACE after 30 days [‡]	/	1.1 [0.31, 3.9] p = 0.868
Restenosis	0.50 [0.37, 0.68] p < 0.001	0.57 [0.40, 0.81] p = 0.002
Late loss [‡]	/	-0.08 [-0.23, 0.08] p = 0.338

Comparisons of intervention with control groups were considered for number of deaths, myocardial infarction, TVR, TLR, and major adverse cardiac events (MACE) after one year of follow-up (intermediate) and of restenosis and late loss after six months of follow-up and of MACE after 30 days (short-term). Effect sizes presented are risk ratios for all categorical variables and standardised differences in mean values for late loss estimated from random effect models. Results are given separately for all trials (n=3) and for studies comparing DES with brachytherapy (control)(n=2).

^{*} One study (SISR) recorded no deaths in both intervention and control groups.

[†] ISAR-DESIRE did not report on TLR and on late loss.

[‡] ISAR-DESIRE recorded zero MACE after 30 days for both intervention and control group.