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Late Thrombosis After Double Versus Single Drug-Eluting Stent in the Treatment of Coronary Bifurcations

A Meta-analysis of Randomized and Observational Studies

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Objectives This study sought to hypothesize that the higher risk of myocardial infarction (MI) documented after a routine double drug-eluting stent (DES) strategy (DDS) compared with a single DES strategy (SDS) with provisional stenting in percutaneous coronary interventions (PCI) of bifurcation lesions is driven by an increased rate of DES thrombosis.

Background The results of currently available randomized, controlled trials (RCTs) were inconclusive in the choice between SDS and DDS. Meta-analyses have shown an increased risk of MI in the DDS group, without identifying the underlying mechanism(s).

Methods We performed a meta-analysis of 12 major (>100 patients) studies of bifurcation DES PCI: 5 RCTs and 7 nonrandomized observational studies, for a total of 6,961 patients. Random-effects models were used to calculate summary risk ratios (RRs). As a primary endpoint, we assessed the RRs and 95% confidence intervals (CIs) of definite DES thrombosis; death, MI, and target vessel revascularization (TVR) were evaluated as secondary endpoints.

Results Compared with SDS, DDS had an increased risk of DES thrombosis (RR: 2.31; 95% CI: 1.33 to 4.03) and MI (RR: 1.86; 95% CI: 1.34 to 2.60). Mortality (RR: 1.18; 95% CI: 0.85 to 1.65) and TVR (RR: 1.02; 95% CI: 0.80 to 1.30) were similar. The RRs of MI and DES thrombosis were associated ($p = 0.040$).

Conclusions In PCI of coronary bifurcations, SDS should be the preferred approach, as DDS is associated with an increased risk of MI, likely driven by DES thrombosis. (J Am Coll Cardiol Intv 2013;■:■–■) © 2013 by the American College of Cardiology Foundation

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Percutaneous coronary interventions (PCI) in the treatment of coronary bifurcation lesions has been associated with worse in-hospital and long-term outcomes compared with nonbifurcation lesions (1,2). In the drug-eluting stent (DES) era, several randomized, controlled trials (RCTs) (3–9) and nonrandomized, observational studies (nROSs) (10–17) tried to identify the optimal strategy for the treatment of bifurcations between a single DES strategy (SDS) (stenting in the main vessel with provisional stenting of the side branch only in bail out) and a double DES strategy (DDS) (deployment of 2 DESs in whatever technique used). Having the vast majority of these studies show no difference among the 2 strategies, several meta-analyses of RCTs were performed (18–25); a significantly higher incidence of myocardial infarction (MI) with the DDS was documented, without identifying the underlying mechanism(s).

We hypothesized that the increase in adverse outcomes reported with DDS would be driven by a significant increase in the rate of DES thrombosis. To test such a hypothesis, we performed a meta-analysis of major available RCTs and nROSs comparing SDS and DDS.

Abbreviations and Acronyms

CI = confidence interval

DDS = double drug-eluting stent strategy

DES = drug-eluting stent(s)

MI = myocardial infarction

nROS = nonrandomized, observational study

PCI = percutaneous coronary intervention

RCT = randomized, controlled trial

RR = relative risk

SDS = single drug-eluting stent strategy

TVR = target vessel revascularization

Methods

Search strategy and selection criteria. We searched PubMed, the Clinical Trials Registry (www.clinicaltrials.gov), as well as abstracts from meetings of major cardiology societies. The search terms used were "coronary," "bifurcat*," and "stent." Websites, including cardiosource.com, TCTMD.com, the-heart.org, and escardio.org, were also searched for relevant materials. References of the articles identified in this manner were also searched to locate additional references not identified by the search strategy that might be useful for the purpose.

Two of the authors (A.C. and F.R.) performed screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. The search was performed for the period January 2001 through December 2011 and was limited to the English-language literature. Reviewers were not blinded to study authors or outcomes. Disagreement was resolved by contact with the corresponding authors or by consensus. We included only studies with >100 patients with a follow-up duration of at least 6 months.

Among 845 identified citations, 815 were considered irrelevant for our purpose; in addition to meta-analyses, papers describing the use of bare-metal stents and 2 small studies, although relevant, were excluded, 1 because of non-English language (26) and 1 (27) because data were reported only as percentages (Fig. 1).

Both RCTs and nROSs comparing SDS and DDS in the treatment of bifurcating lesions were included in the analysis.

Because bifurcation morphology was not systematically reported, we decided to include all studies referring to the treatment of bifurcating lesion, however classified.

Data collection and quality assessment. Relevant information extracted from the studies included the type of study (RCT or nROS), year of publication, treatment allocation, age, sex, acute coronary syndrome, diabetes, length of the implanted stents, use of IIb-IIIa glycoprotein inhibitors, final "kissing" balloon, "true" bifurcation with disease involvement of both main and side branches, defined by Medina et al. (28) as type 1,1,1 or 0,1,1, and 1,0,1, follow-up duration, type of DES, DDS technique, crossover from SDS to DDS, and recommended duration of double antiplatelet therapy.

Absolute numbers were recalculated when percentages were reported.

The quality of each study was assessed by evaluating specific elements of each study design (29), with Jadad (30) and Newcastle-Ottawa (31) scales for RCTs and nROSs, respectively (see Supplementary Tables S1 and S2).

Outcomes. The endpoints of interest in the overall analysis were DES thrombosis as the primary endpoint, and death, MI, and target vessel revascularization (TVR) as secondary endpoints. Stent thrombosis was accepted when the "definite" criteria of the Academic Research Consortium (32) were met, whenever specified. Mortality was accepted as reported. MI was defined by studies as periprocedural or during follow-up: few studies gave precise definitions or how MI was diagnosed, and, when available, MI diagnostic criteria varied widely. TVR was defined according to the study protocols, and, if not reported, we used target lesion revascularization instead. The numbers of events in each study were extracted, when available, on the basis of an intention-to-treat approach.

Outcome data were extracted by one of the authors (F.R.) and checked by another author (A.C.).

Statistical analysis. Categorical variables were reported as number and percentage, and continuous variables were presented as mean ± SD. Normal distribution of variables was assessed, when needed, by the 1-sample Kolmogorov-Smirnov test. From the abstracted data, the relative risk (RR) was calculated using the Mantel-Haenszel method for each study outcome to allow pooling of similar outcomes. The average effects for the outcomes and 95% confidence interval (CI) were obtained using a random-effects model.

Heterogeneity of effect across studies was assessed by Cochrane Q chi-square statistics and I^2 statistics (33). Lack of homogeneity was considered for Cochrane Q chi-square test p values ≤0.10 and for I^2 statistics ≥50%. When heterogeneity was judged significant, the pooled RR was calculated with the DerSimonian-Laird method for random

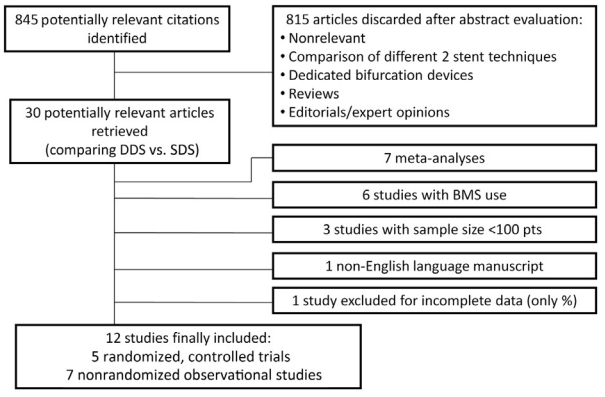

Figure 1. Flow chart Showing the Process of Study Selection

BMS = bare metal stent; DDS = double drug-eluting stent strategy; pts = patients; SDS = single drug-eluting stent strategy.

effects (34). We report the meta-analysis results in classic Forest plots, with point estimates and 95% CIs for each trial and for the studies overall. We also performed a sensitivity analysis to evaluate whether the summary estimate of the effect could have been significantly affected by a single study. To this purpose, pooled estimates were recalculated, using a random-effects model, by omitting 1 study at a time. The likelihood of publication bias was assessed graphically by generating a funnel plot for the endpoints of MI and DES thrombosis and evaluated by Egger's test of intercept (p value for significant asymmetry <0.1).

We also performed an explorative meta-regression analysis using a mixed-effects model to assess the effect of selected variables (type of study, age, sex, diabetes, acute coronary syndrome, "true" bifurcation, use of glycoprotein IIb-IIIa inhibitors, total length of implanted DES, final "kissing" balloon, follow-up duration, and recommended duration of double antiplatelet therapy) on the risk of DES thrombosis. The RRs of DES thrombosis and MI for individual trials were log-transformed before being used as independent variables in the linear meta-regression analysis on MI event. Statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, Texas).

Results

We selected 12 studies (5 RCTs and 7 nROSs) for a total of 6,961 patients, 1,868 treated with DDS and 5,093 with SDS.

The main characteristics of the studies are summarized in Table 1. The mean patient age ranged from 62 to 68 years, and diabetes mellitus prevalence ranged from 12% to 45%. Dual antiplatelet therapy (with both clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily) was recommended for a minimum of 3 to 12 months, depending on the study design.

Table 1. Summary of the Characteristics of the Included Studies

	Nordic	BBK	CACTUS	BBC-ONE	DK-CRUSH-II	Ge et al.	Di Mario et al.	ARTS-II	COBIS Registry	J CYPHER Registry	J-PMS Registry	Assall et al.
Type of study	RCT	RCT	RCT	RCT	RCT	nROS	nROS	nROS	nROS	nROS	nROS	nROS
Year of publication	2006	2008	2009	2010	2011	2005	2007	2007	2010	2011	2011	2012
No. of patients	413	202	350	500	390	174	150	324	1,691	2,122	324	401
Patient treatment (SDS/DDS)	199/196	101/101	173/177	248/249	185/185	117/57	38/109	263/61	1,376/292	1,870/263	263/37	260/141
Follow-up, mo	14	9	6	6	12	9	12	12	22	36	36	24
Type of DES	Sirolimus	Sirolimus	Sirolimus	Paclitaxel	Sirolimus	Sirolimus	Paclitaxel	Sirolimus	Operator discretion	Sirolimus	Sirolimus	Operator discretion
DDS technique	Crush	T stenting	Crush	Crush	Crush	Crush	Crush	Crush	Crush	Crush	Crush	Mini-Crush
	Culotte			Culotte		V stenting	T stenting	V stenting	V stenting	T stenting	T stenting	T stenting
	Other			T stenting		T stenting	Culotte	T stenting	T stenting	Culotte	Culotte	V stenting
				Other		Culotte	Kissing stents	Culotte	Culotte	Kissing stents	Kissing stents	Culotte
True bifurcations*, no. (%)	NA	138 (68)	328 (94)	415 (83)	390 (100)	NA	NA	200 (62)	1,170 (69)	1,181 (56)	NA	NA
Use of glycoprotein IIb/IIIa, no. (%)	211 (51)	0	70 (20)	180 (36)	10 (3)	82 (47)	35 (23)	119 (37)	NA	NA	NA	235 (58)
Final kissing balloon, no. (%)	217 (52)	202 (100)	319 (91)	262 (52)	332 (85)	103 (59)	112 (75)	40 (12)	686 (41)	1,254 (59)	97 (30)	318 (79)
Duration of DAPT, mo	14	6	6	>9	>12	>3	>3	2	3–6 (recommended)	3 (recommended)	3 (recommended)	6 (recommended)
Crossover rate from provisional to double stenting, %	4.30	19	31	—	—	—	—	—	—	—	—	—

*With disease involvement of both main and side branches, as defined by Medina (28) type 1,1,1 or 0,1,1 or 1,0,1.

ARTS-II = Arterial Revascularization Therapies Study Post-Marketing Surveillance; BBC-ONE = British Bifurcation Coronary Study; BBK = Bifurcations Bad Krozingen; CACTUS = Coronary bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents; COBIS = COronary Bifurcation Stenting; DAPT = double antiplatelet therapy; DDS = double-stent strategy; DES = drug-eluting stent; nROS = nonrandomized observational study; DK-CRUSH = Double Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions; J CYPHER = Japan Cypher (TM); J-PMS = J-PMS: Japan Post-Marketing Surveillance; NA = not available; Nordic = Nordic Bifurcation Study; RCT = randomized, controlled trial; SDS = single DES strategy.

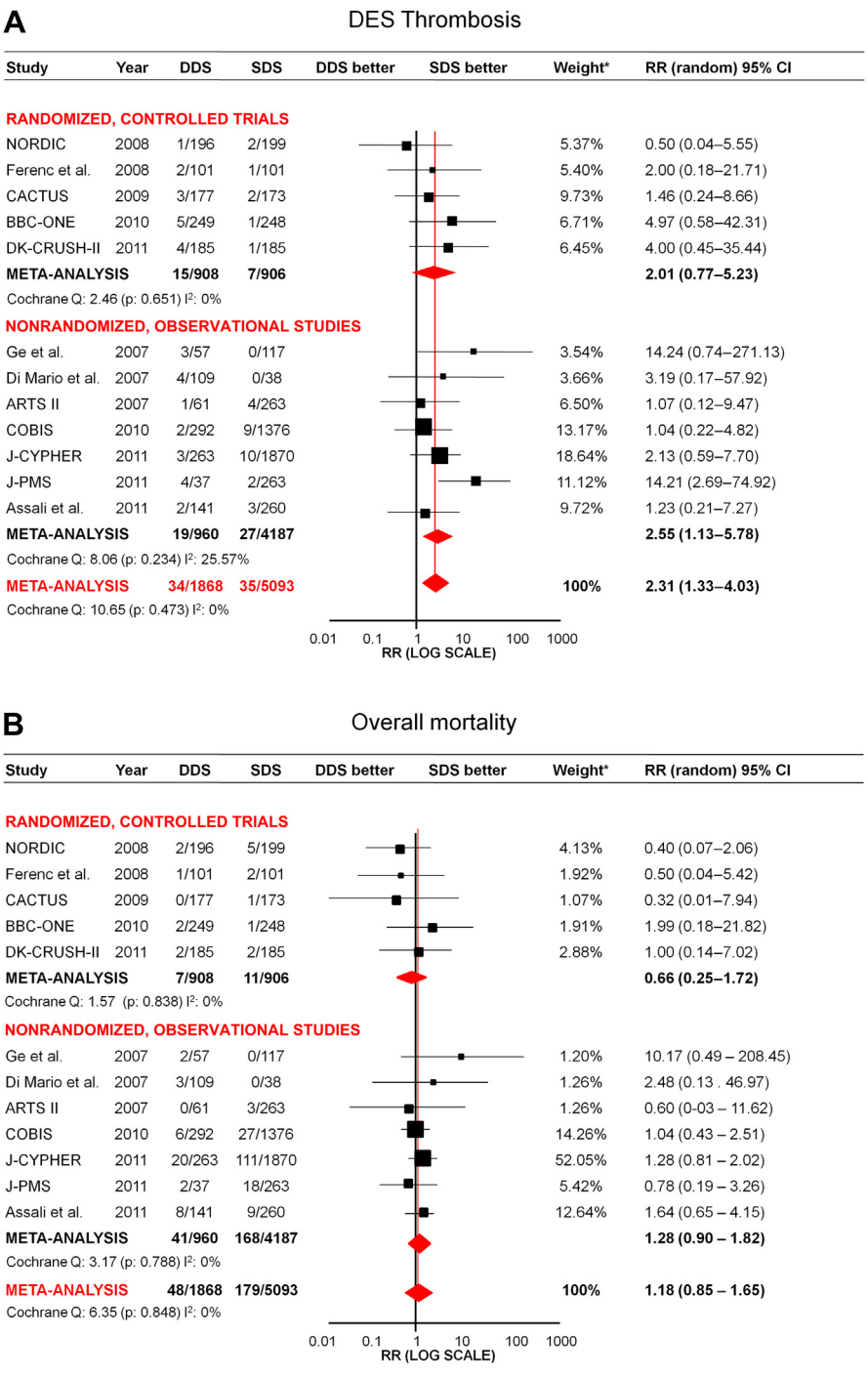

Figure 2. Outcomes in randomized and observational studies

Forest plot with individual and summary estimates of the relative risk (RR) and 95% confidence interval (CI) of drug-eluting stent (DES) thrombosis **(A)**, overall mortality **(B)**

The DDS group had a higher risk of the primary endpoint definite DES thrombosis (RR: 2.31; 95% CI: 1.33 to 4.03) (Fig. 2A), without significant heterogeneity among studies (Cochrane Q p = 0.473; I^2 = 0%). Subgroup analysis, again performed despite the absence of heterogeneity, showed that a significantly increased risk was limited to nROSs (RR: 2.35; 95% CI: 1.13 to 5.78), whereas RCTs showed only

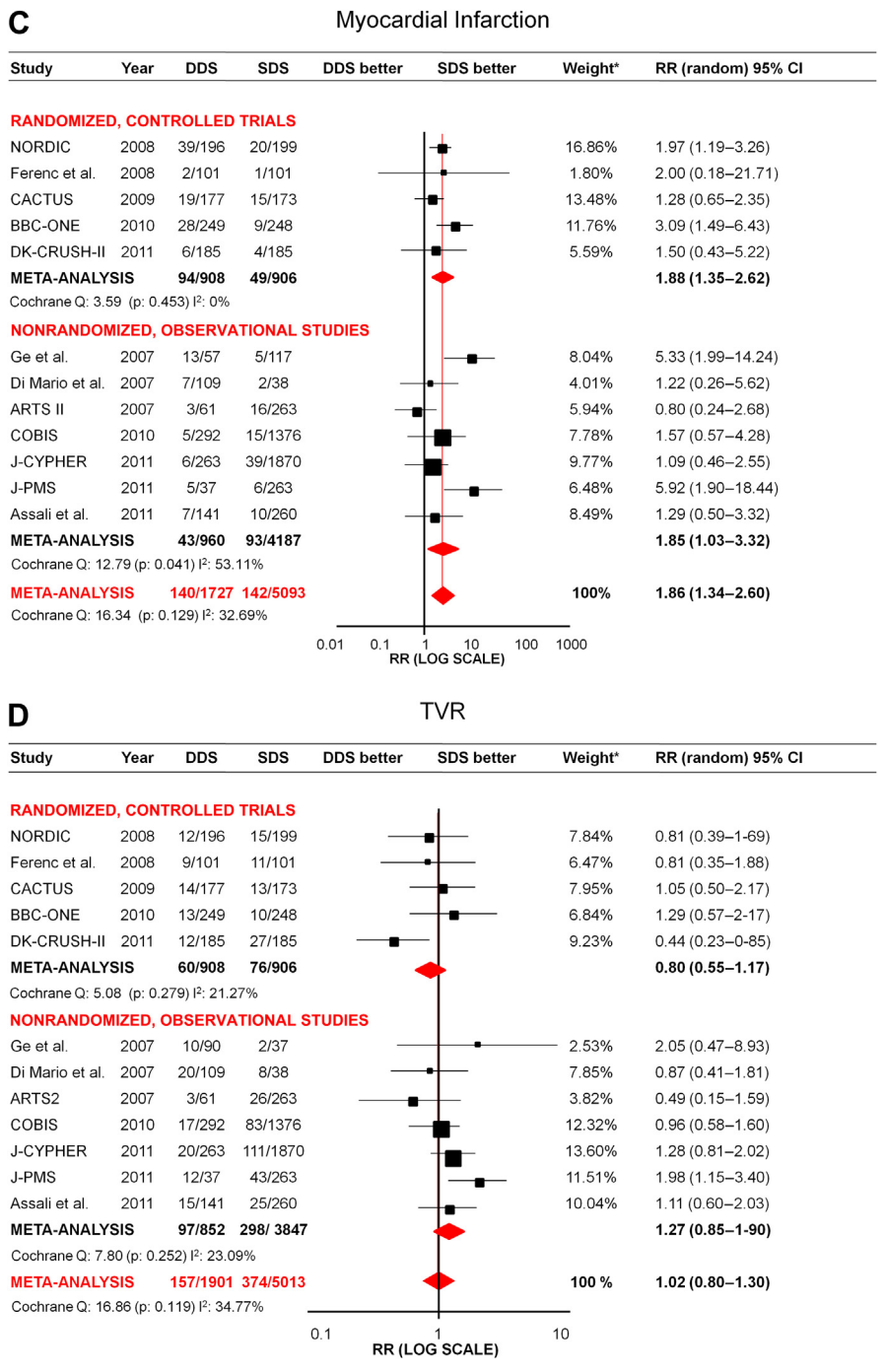

Figure 2. continued

myocardial infarction **(C)**, and target-vessel revascularization (TVR) **(D)** among patients treated with DDS compared with SDS. Diamond size is proportional to study weight in random-effects model. For study acronyms, refer to Table 1. *Weights are from random-effects analysis. Trials' acronyms as in Table 1. Other abbreviations as in Figure 1.

a trend toward this direction (RR: 2.01; 95% CI: 0.77 to 5.23).

All-cause mortality was similar in the 2 treatment groups (RR: 1.18; 95% CI: 0.85 to 1.65) (Fig. 2B).

MI occurred more frequently in the DDS group (RR: 1.86; 95% CI: 1.34 to 2.35) (Fig. 2C). A subgroup analysis, performed despite no significant heterogeneity among studies (Cochrane Q p = 0.129; I^2 = 32.69%), confirmed

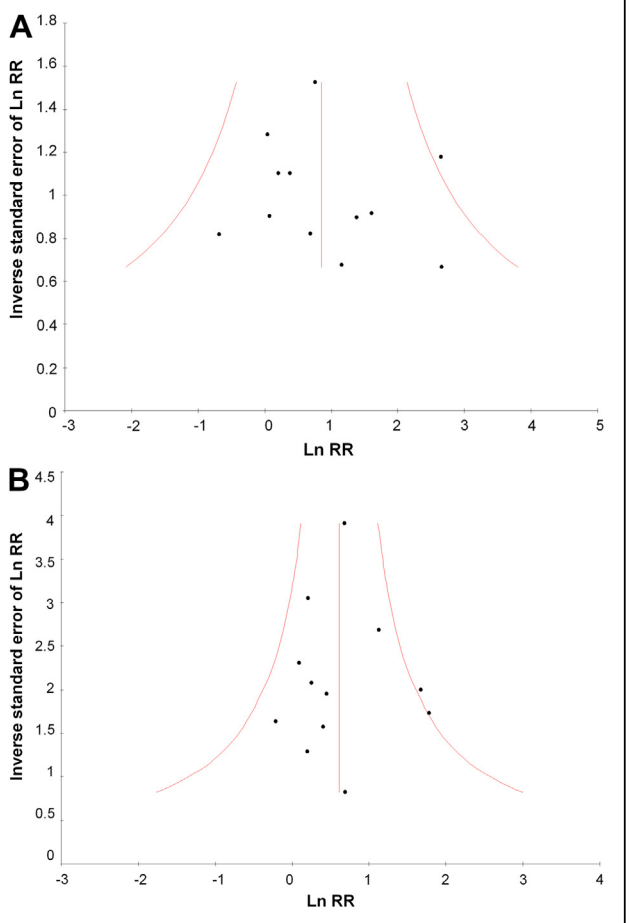

Figure 3. Publication bias

Begg's funnel plot of studies according to the logarithmic relative risk (Ln RR) of drug-eluting stent thrombosis **(A)** and myocardial infarction **(B)** versus SE. Lower SE indicates better precision and larger study size.

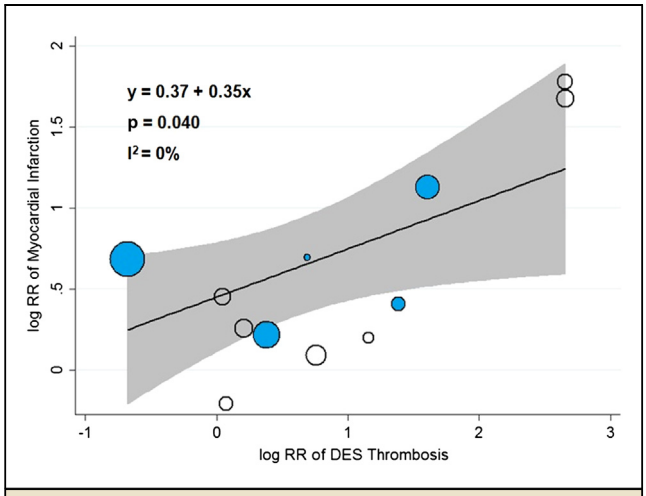

Figure 4. Association Between Log-Transformed Risk of DES Thrombosis and Myocardial Infarction

The size of each circle represents the precision of each estimate (the inverse variance of the log RR in the trial), and the line is the best fit for the meta-regression model. Randomized, controlled trials (**filled circles**); nonrandomized observational studies (**open circles**). Abbreviations as in Figures 2 and 3.

an increased risk of MI after DDS in both RCTs (RR: 1.88; 95% CI: 1.35 to 2.62) and nROSs (RR: 1.85; 95% CI: 1.03 to 3.32).

TVR was similar in the 2 groups (RR: 1.02; 95% CI: 0.80 to 1.30) (Fig. 2D).

The post hoc sensitivity analysis showed that no single study significantly affected the pooled estimates of RR for DES thrombosis and MI (Supplementary Figs. S1 and S2). Moreover, visual inspection of the funnel plot for MI (Fig. 3A) and DES thrombosis (Fig. 3B) did not reveal asymmetry; in support of this finding, publication bias or "small study effect" were likely excluded by Egger's test of intercept (DES thrombosis intercept = 0.34, p = 0.786; MI intercept = 0.63, p = 0.204). The meta-regression analysis failed to show any association between the overall risk of DES thrombosis and the type of study (classified as RCT or nROS) (y = 0.47 + 0.22x; p = 0.733) or any of the other selected variables. We documented a significant association between the RR of DES thrombosis and MI among the various studies (p = 0.040) (Fig. 4).

Discussion

The present meta-analysis of RCTs and nROSs confirms that in patients undergoing PCI for coronary bifurcation lesions, DDS is associated with similar mid-term mortality and TVR, but an increased MI rate compared with SDS. Our data extend previous knowledge by showing that the increased risk of MI is associated with (and, our inference, driven by) a higher risk of DES thrombosis with DDS.

Coronary bifurcations are commonly considered complex lesions, and their optimal interventional treatment may require initial adjunctive debulking, double guidewire placement, recrossing of stent struts toward the side branch, and final "kissing" balloon inflation. Therefore, in the treatment of multivessel disease, bifurcations may become a crucial obstacle to complete revascularization, with a potentially negative impact on long-term outcome (35). However, the technique of stent deployment has not been fully standardized, with a wide range of use of crush, culotte, and T stenting among various reports (Table 1), even for PCI of unprotected left main bifurcation disease, currently investigated as a valuable alternative to bypass surgery (36,37).

The introduction of DES has been thought to improve outcomes by decreasing restenosis and TVR compared with bare-metal stents, even in the bifurcation subset (38). However, DES can exert an optimal effect on vessel wall healing only if the drug is released for the entire lesion length; incomplete coverage of the carina has therefore been

postulated as a possible cause of restenosis in bifurcating lesions (39). To overcome this problem and to obtain full coverage of the bifurcating lesion, different complex techniques with double DES have been developed as dedicated stents (2), but the advantage of routine stenting of the side branch for every anatomic subset has been severely criticized.

Currently available guidelines (40) recommend SDS as the preferred approach when the side branch is not large and has only mild or moderate focal disease at the ostium (class I, level of evidence A); DDS is reasonable in cases of complex bifurcation morphology involving a large side branch, where the risk of side-branch occlusion is high and the likelihood of successful side-branch re-access is low (class IIa, level of evidence B).

Several RCTs (3–9) yielded almost similar outcomes for DDS compared with SDS, but the studies were mainly powered for angiographic or combined clinical endpoints. The most significant results were obtained by the recent DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial (9) that arguably enrolled the most complex patients in the trials, with lesion lengths >3 times longer than those in other trials. Here, SDS showed an increased angiographic restenosis rate in both main and side branches, and this fostered a higher TVR (14.6%) compared with DDS (6.5%, $p = 0.017$); however, the authors reported a 2.2% thrombosis rate after DDS that was dismissed as "similar" because, although being >4 times higher than SDS (0.5%), this difference did not reach statistical significance. Only after combining patient-level data from the Nordic and the British Bifurcation Coronary Study: Old, New, and Evolving strategies (BBC-ONE) studies, Behan et al. (24) documented that SDS was associated with a significantly reduced combined death, MI and TVR (10.1%) compared with DDS (17.3%, $p < 0.001$). However, such results were mainly driven by a higher MI rate in DDS (12.3%) versus SDS (4.8%, $p < 0.001$), being mostly periprocedural MIs, whereas subsequent MIs were only slightly higher in DDS (2.4%) than in SDS (1.3%, p = NS); DES thrombosis occurred in 1.3% of DDS and in 0.7% of SDS (p = NS). Procedure duration, amount of contrast medium used, and x-ray dose all favored SDS over DDS.

Several meta-analyses of RCTs (18–25) documented an increased MI risk in patients undergoing DDS, although authors were not able to discern periprocedural from subsequent events because the definition used to diagnose MI was slightly different among studies and the information on timing was not always specified. Our report confirms this finding, excluding significant heterogeneity among the studies included. Stent thrombosis is an extremely unfavorable event, occurring more frequently and associated with even higher in-hospital and long-term mortality rates when involving bifurcation than nonbifurcation lesions (41). In our meta-analysis, a close association between the increased risk of MI and DES thrombosis was documented (Fig. 4), being a causal relationship consistent in both RCTs and nROSs.

To date, no meta-analysis has clearly identified an increased risk of DES thrombosis after DDS; only a trend toward a higher risk has been documented, without reaching statistical significance (18–25). To disclose whether DDS would be significantly associated with an increased risk of DES thrombosis, we pooled data from both RCTs and nROSs. Obviously, the mechanisms underlying the increased risk of DES thrombosis go beyond the stenting technique, as this may be a surrogate marker for more complex atherosclerotic disease and more advanced bifurcation involvement.

Study limitations. Although nROSs may be affected by different limitations (e.g., selection and publication bias, lack of intention-to-treat data reporting), they reflect, on the other hand, real-world clinical practice in the overall population. Although RCTs may have limited generalizability to everyday practice, nROSs analyze larger populations and provide longer follow-up, although in this case, they yielded mixed results, probably because of the mixed patient selection; nROSs answer crucial questions that are otherwise impossible to answer and can produce results with a relevance comparable to that obtained in RCTs, provided a meticulous quality control of methodology is used. Inclusion of both RCTs and nROSs could represent a source of data heterogeneity, although in our meta-analysis, this possibility was excluded for both MI and DES thrombosis by Cochrane Q chi-square test and I^2 statistics.

The risk of DES thrombosis is approximately 2-fold when patients are treated with DDS, and even higher in another registry that was not included in the present meta-analysis because of the lack of detail (27). The significant RR of DDS for DES thrombosis obtained after merging data derived from nROSs might raise the suspicion of a systematic overestimation of treatment effect in nROSs. However, the RR of DES thrombosis with DDS is similar in both RCTs and nROS (2.17 vs. 2.49, respectively, Fig. 2C); moreover, the funnel plot showed no asymmetry or "lower left-hand corner effect" (42), the bias coming from pooling results of small studies with Egger's test supporting this finding (Fig. 3B). Therefore, the cumulative significantly increased RR of DES thrombosis after DDS must be interpreted as a mere consequence of the higher overall number of events recorded, leading to narrower confidence intervals.

DES PCI of a bifurcation lesion is a known risk factor for coronary thrombosis (43). In the nROSs selected for the present analysis, SDS was used in most cases, but we must acknowledge that selection bias might be a major limitation of this analysis because DDS would have been more likely used in complex anatomic settings, and this choice would account for an increased risk of DES thrombosis in the DDS group. All the studies, both RCTs and nROSs, were included in the present meta-analysis regardless of the

presence or absence of any morphological classification; therefore, we cannot infer whether a differential result can be applied to the treatment of "true" bifurcations. Plaque distribution at bifurcation sites significantly affects stenting outcomes, and the presence of plaque in the whole bifurcation area is associated with enhanced TVR risk, seemingly regardless of stent technique and plaque severity (44). In real-world practice, DDS is sometimes inevitable in the effort to keep the side patent, especially in the case of a true bifurcated lesion with a massive plaque burden and a side branch of considerable size. Most DDS techniques entail the placement of multiple metal layers, double at best when it extends to the main vessel, as in the culotte technique, or is limited to the ostium of the side branch or the carina, as in V/T stenting or in "kissing" stents, and even triple, as in the crush technique or its modifications (45). This complex final stent architecture likely impairs homogeneous metal strut endothelialization (46) and likely increases the risk of DES thrombosis. In such cases, there is no consensus as to whether a final "kissing balloons" with simultaneous baloon inflation in both main and side branches might improve outcome: in general, it seems associated with a reduced TVR rate in DDS and unnecessary and even harmful in SDS (47).

We must acknowledge a second major limitation. Although most RCTs, with the exception of 1 study (4), were based on an intention-to-treat analysis, nROSs showed on-treatment event reporting. This difference may represent a confounding element in the pooled analysis. However, overall crossover rates among RCTs (i.e., the percentage of patients shifting from SDS to DDS) appear to be acceptably low.

We also recognize that we analyzed TVR, not restenosis, which was not systematically reported in all studies or was reported only for the cohort of patients who underwent follow-up angiography.

We also acknowledge that all the studies included describe results of first-generation DESs, which have recently shown an increased tendency toward thrombosis compared with contemporary DESs (48).

A further limitation of the present analysis resides in the antithrombotic therapy: the use of glycoprotein IIb-IIIa inhibitors during PCI and the duration of double antiplatelet therapy (49) in the follow-up differed widely among the studies (Table 1). Newer thienopyridines have documented a significant reduction of DES thrombosis after PCI performed for acute coronary syndrome (50,51); however, to date, no available data exist on the potential implication of this benefit in the treatment of bifurcation lesions.

Conclusions

In PCI of coronary bifurcations, routine DDS, DES implantation in both branches, is associated with an increased mid-term risk of MI compared with SDS—DES deployment in the main branch and provisional stenting of the side branch. The risk of MI is associated with and seems driven by an increased risk of DES thrombosis. Because of this likely causal association, when DDS has to be performed, an aggressive antiplatelet therapy should be recommended, provided that future studies assess whether more potent antiplatelet therapies would reduce the risk of DES thrombosis in the setting of bifurcation lesions.

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Key Words: coronary bifurcation ■ drug-eluting stent thrombosis ■ percutaneous coronary intervention.

APPENDIX

For supplemental material, please see the online version of this article.