European Heart Journal (2010) **31**, 1172–1180
doi:10.1093/eurheartj/ehn553

REVIEW

Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis

Ayman K.M. Hassan[1,2], Sandrin C. Bergheanu[1,3,4], Theo Stijnen[5], Bas L. van der Hoeven[1], Jaapjan D. Snoep[3], Josepha W.M. Plevier[6], Martin J. Schalij[1], and J. Wouter Jukema[1]*

[1]Department of Cardiology C5-P, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands; [2]Department of Cardiology, Assiut University, Assiut, Egypt; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [4]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands; [5]Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands; and [6]Information Specialist Walaeus Library, Leiden University Medical Center, Leiden, The Netherlands

Received 13 June 2008; revised 17 September 2008; accepted 19 November 2008; online publish-ahead-of-print 21 January 2009

Aims Late stent malapposition (LSM) may be acquired (LASM) or persistent. LSM may play a role in patients who develop late stent thrombosis (ST). Our objective was to compare the risk of LASM in bare metal stents (BMS) with drug-eluting stents (DES) and to investigate the possible association of both acquired and persistent LSM with (very) late ST.

Methods and results We searched PubMed and relevant sources from January 2002 to December 2007. Inclusion criteria were: (a) intra-vascular ultrasonography (IVUS) at both post-stent implantation and follow-up; (b) 6–9-month-follow-up IVUS; (c) implantation of either BMS or the following DES: sirolimus, paclitaxel, everolimus, or zotarolimus; and (d) follow-up for LSM. Of 33 articles retrieved for detailed evaluation, 17 met the inclusion criteria. The risk of LASM in patients with DES was four times higher compared with BMS (OR = 4.36, CI 95% 1.74–10.94) in randomized clinical trials. The risk of (very) late ST in patients with LSM (five studies) was higher compared with those without LSM (OR = 6.51, CI 95% 1.34–34.91).

Conclusion In our meta-analysis, the risk of LASM is strongly increased after DES implantation compared with BMS. Furthermore, LSM seems to be associated with late and very late ST.

Keywords Meta-analysis • Late stent malapposition • Late stent thrombosis • Drug-eluting stents

Introduction

Late and very late stent thromboses (STs) are rare,[1–5] but potentially lethal complications emerged during the increasing use of stent implantation. It was recently suggested that stent malapposition (SM) as assessed by intra-vascular ultrasonography (IVUS) imaging plays an important role in patients who develop very late ST after drug-eluting stent (DES) implantation.[6] SM (synonymous with incomplete stent apposition) represents a separation of at least one stent strut from the intimal surface of the arterial wall (in the absence of a side branch) with evidence of blood behind the strut.[7] SM can be acute if detected post-procedure or late if detected at follow-up IVUS imaging.[8] Acute SM can resolve or persist during the follow-up period. Late SM (LSM) may be persistent if present both immediately after the procedure and at follow-up, or acquired if present only at follow-up (LASM).[9] Acute SM can generally be controlled by performing an IVUS immediately post-procedure and treated with subsequent balloon angioplasty. However, for LASM, this is not the case as by definition there is no SM at the time of stent placement. Thus far,

* Corresponding author. Tel: +31 71 526 6695, Fax: +31 71 526 6885, Email: j.w.jukema@lumc.nl

no clear conclusion could be drawn with regard to the occurrence of LSM (acquired or persistent) and the risk of (very) late ST as only a small number of studies report on LSM and its possible relation with ST, and the incidence of (very) late ST is relatively low. Therefore, we have conducted a meta-analysis to compare the risk of LASM between bare-metal stents (BMS) and DES and a subanalysis to investigate the possible association of LSM (acquired or persistent) with (very) late ST.

Methods

Selection of studies

We searched PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials between January 2002 and 17 December 2007 with the keywords (IVUS OR intravascular ultrasonography OR interventional ultrasonography OR intravascular ultrasound OR intravascular ultrasonic) AND (Cypher OR SES OR Sirolimus OR Endeavor OR ABT-578 OR Promus OR Everolimus OR Taxus OR Paclitaxel OR DES OR drug-eluting stent OR drug-eluting stents OR drug eluted stent OR drug eluted stents OR BMS OR bare-metal stent OR bare-metal stents) or variants of these terms, adapted to each of the different databases. Relevant websites (http://www.tctmd.com, www.europcr.com, www.acc.org, www.theheart.org, www.escardio.org, and www.clinicaltrialresults.org) were searched for pertinent abstracts and expert slide presentations. No language restriction was applied.

To be selected for this meta-analysis, studies had to meet the following criteria: (a) IVUS analysis in native coronary arteries at both baseline and follow-up; (b) follow-up IVUS performed no sooner than 6 months and not later than 9 months after stent implantation; (c) implantation of either BMS or one of the following DES: sirolimus-, paclitaxel-, everolimus-, or zotarolimus-eluting stents; and (d) recording of LSM. For the analysis of late ST risk in LSM patients, we searched among the included papers those that presented follow-up data for ST in two separate groups: LSM vs. non-LSM.

Data abstraction

Two investigators (A.K.M.H. and S.C.B.) independently extracted all data, and disagreements were solved in consultation with a third investigator (J.W.M.P.). A number of 221 papers were identified from PubMed, 71 papers from Web of Science and EMBASE, and 3 additional clinical trials from relevant websites (total of 295 citations) (*Figure 1*). After reading the titles and abstracts, we identified a

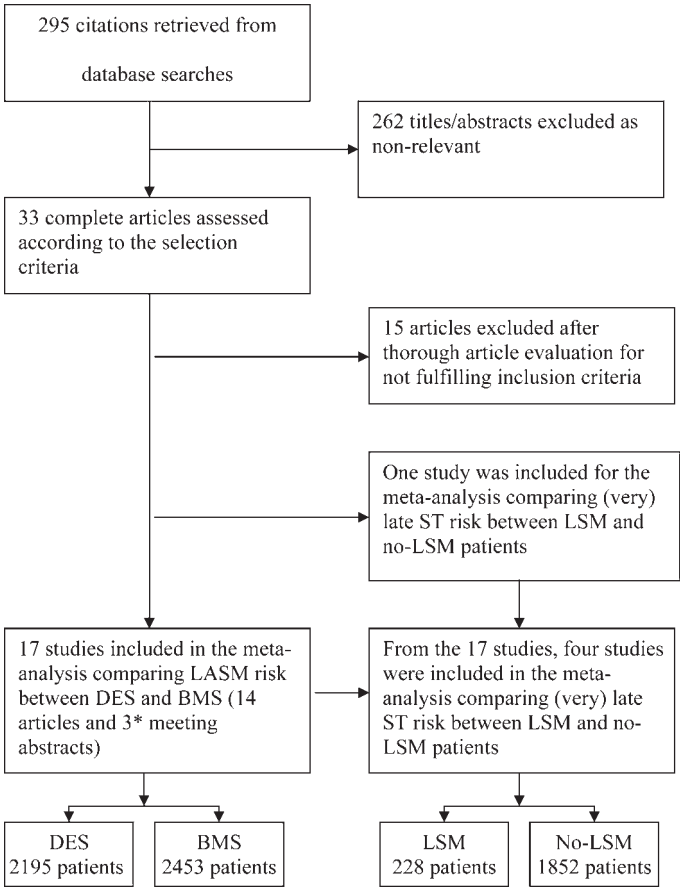

Figure 1 Flow diagram of review process. Process of identification and selection of studies for inclusion in meta-analysis. BMS, bare metal stents; DES, drug-eluting stents; LASM, late-acquired stent malapposition; LSM, late stent malapposition (acquired or persistent); pts, number of patients; ST, stent thrombosis. *Data for the MISSION! Study were initially collected from expert presentation. Before submission, the results were published and we therefore added a reference[35] for an easy access of the reader.

potential number of 33 papers from which 17 studies were eligible for inclusion. Among these, nine papers presented original results from randomized clinical trials (RCTs) that compared DES with BMS. We searched among the references from the identified studies and from most recent review articles on DES for relevant papers, but no further studies were identified. Five papers that provided data on the incidence of ST in patients with LSM (acquired or persistent) were used for the assessment of late ST risk. Data were extracted from studies as they were presented. The authors did not review individual patients' data and therefore special attention was paid to avoid repeated analysis of same data (as this may arise when same core laboratories publish multiple studies).

Drug-eluting stents

Two major categories of DES are described in our study: the '-limus' group comprising sirolimus, everolimus, and zotarolimus and the paclitaxel group.

The -limus group prototype is rapamycin (sirolimus), a macrolide with cytostatic properties that blocks progression from G1 to S in the cell cycle and inhibits thus the vascular smooth muscle cell migration and proliferation.[10,11] The newer generation rapamycin derivative, everolimus,[12,13] is reported to be more lipophilic than sirolimus, whereas zotarolimus[14,15] efficiently suppresses the lymphocyte-mediated local inflammatory reaction. Paclitaxel inhibits vascular smooth muscle cell migration and proliferation mainly as a result of binding to and stabilizing cellular microtubules.[10,16]

The construction of the sirolimus-eluting stent (SES, CYPHER™), paclitaxel-eluting stent (PES, TAXUS EXPRESS™), everolimus-eluting stent (EES, XIENCE V™/PROMUS™), and zotarolimus-eluting stent (ZES, ENDEAVOR™) is described elsewhere.[10–16]

Intra-vascular ultrasonography imaging and analysis

The IVUS acquisition and analysis technique was similar in all studies. After administration of intracoronary nitroglycerin, IVUS images were acquired using commercially available imaging systems with automated transducer (0.5 mm/s). Images were acquired for every millimetre in the stent and for 5 mm proximal and distal of the stent and were analysed with various commercially available software. LASM assessment was performed as follows. First, investigators reviewed all follow-up IVUS recordings to identify cases of SM. Secondly, in identified cases, immediate post-stenting and follow-up IVUS images were reviewed side-by-side to discriminate cases in which SM existed immediately after stent implantation or not.

SM was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches.[7]

Statistical analysis

To compare BMS with DES, two analyses were performed. The first was based on all 17 studies included in the meta-analysis (*Table 1*). The second analysis was restricted to the seven studies that compared BMS with DES in a randomized manner. The first analysis was based on the bivariate random-effects model as described by van Houwelingen *et al.*[17] In this model also, the studies with only one treatment group, BMS or DES, are used. Owing to the small numbers of patients with LASM, the usual normal approximation for the number of events within a treatment group is not reliable, and the exact binomial distribution was used instead, as described by Chu and Cole.[18] The second analysis was based on a standard random-effects model for the log odds ratio. However, due to the small numbers of LASMs, the hypergeometric distribution as described by van Houwelingen *et al.*[19] was used to model the number of events within a study, instead of the usual normal approximation. A third analysis was performed to compare the -limus group of DES with the paclitaxel group. There were only three studies directly comparing a -limus stent with PES. However, six studies compared -limus with BMS and three studies compared PES with BMS. These studies contain indirect evidence on the comparison of -limus with PES. To combine all the evidence on this comparison, a tri-variate meta-analysis was performed as in Arends *et al.*,[20] assuming compound symmetry for the covariance matrix of the random effects. To accommodate the small numbers of LASMs, again the exact binomial distribution was used to model the number of events within a treatment group. A fourth analysis was performed to compare the incidence of late ST between patients with and without LSM. As stated, there were only five studies providing data on this comparison, and the numbers of late ST were very small, prohibiting a random effects meta-analysis. Therefore, we used a fixed-effects analysis using the exact Mantel–Haenszel test. We provide in *Table 2* the expected values of (very) late ST under the assumption of the null hypothesis [LSM is not related to (very) late ST]. All analyses were performed using the SAS statistical package version 9.1.3. The procedure Proc NLMIXED was used for the random-effect meta-analyses.

Study quality assessment

As mentioned earlier, our meta-analysis was especially designed to extract data from various types of available studies: observational studies in which the authors present the incidence of LASM within BMS or DES cohorts; RCTs in which two types of DES are compared; and RCTs in which BMS is compared in a randomized manner with BMS after rotablation and RCTs in which DES are compared with BMS. Only for the latter category, it is of interest to perform an RCT study quality assessment. We have used the Delphi list for the quality assessment of RCTs as described by Verhagen *et al.*[21] In short, the Delphi list allocates 'yes', 'no', or 'do not know' to a total number of nine questions. Quality of RCTs is defined as the likelihood of the trial design to generate unbiased results. When five or more questions are answered 'yes', the RCT is considered to have a low risk of bias. In a respective manner, RCTs may have unclear or high risk to cause bias.

Results

Search results and study characteristics

A total of 17 studies[22–38] with 4648 patients were included in this meta-analysis (*Table 1*).

A total of 2453 patients received BMS and 2195 received DES. The mean age of the participants in individual trials varied from 56 to 67 years. The mean timepoint of IVUS follow-up ranged from 6 to 9 months. Eleven trials[22–24,26,27,30,31,33–35,37] represent data from RCTs. Among these, nine studies[22,24,26,27,30,33–35,37] analysed DES vs. BMS (944 patients with BMS and 1050 patients with DES), one study randomized two types of DES,[23] and one study randomized only BMS with or without prior directional coronary atherectomy (DCA).[31]

Among the whole group analysed, SES appeared in four studies,[22,25,30,35] PES in four studies,[24,27,33,37] EES in one study,[34] and ZES in two studies.[26,36] Three trials compared two different types of DES (SES vs. PES[29,38] and EES vs. PES[23]), whereas the remaining three studies included BMS only.[28,31,32]

Table 1 Characteristics of the source studies

Study	Design	Mean age (years)	Men (%)	Diabetes mellitus (%)	Inclusion criteria	Follow-up (months)	Stent	No. of patients	No. of LASM
Ako *et al.* (SIRIUS)[22]	RCT	62	72	26	SA/UA/signs of myocardial ischaemia	8	SES BMS	80 61	7 0
van der Hoeven *et al.* (MISSION!)[35]	RCT	59	78	10	STEMI	9	SES BMS	104 80	26 4
Jimenez-Quevedo *et al.* (DIABETES)[30]	RCT	67	62	100	Symptoms or objective evidence of ischaemia	9	SES BMS	75 65	11 0
Tanabe *et al.* (TAXUS II)[33]	RCT	62	76	15	SA/UA/SI	6	PES BMS	229 240	20 13
Chechi *et al.* (SELECTION)[24]	RCT	60	82	13	AMI	7	PES BMS	39 37	2 1
Weissman *et al.* (TAXUS IV, V, and VI)[37]	RCT	62[a]	72	28	SA/UA/SI	9	PES BMS	287 260	24 9
Hong *et al.* (ASPECT)[27]	RCT	59	75	14	Symptomatic coronary heart disease	6	PES-NP[b] BMS	56 25	1 0
Bullesfeld *et al.* (SPIRIT III)[23c]	RCT	63	67	29	SA/UA/SI	8	EES PES	90 43	1 1
Tsuchiya *et al.* (FUTURE I, II)[34]	RCT	65	80	12	SA/UA/SI	6	EES BMS	48 58	0 0
Fajadet *et al.* (ENDEAVOR II)[26]	RCT	62	76	20	Symptoms or objective evidence of ischaemia	8	ZES BMS	132 118	0 0
Nakamura *et al.* (DESIRE)[31]	RCT	62	85	NA	NA	6	BMS	412	10
Hong *et al.*[29c]	OS	57	73	23	SA/UA/AMI	6	SES PES	538 167	71 14
Degertekin *et al.*[25]	OS	61	76	4	SA/UA/SI	6	SES BMS	24 10	1 0
Siqueira *et al.*[38]	OS	60	68	46	SA/UA	8	SES PES	175 20	7 3
Hong *et al.*[28]	OS	56	75	21	SA/UA/AMI	6	BMS	881	54
Shah *et al.*[32]	OS	57	100	1	SA/UA/SI	6	BMS	206	9
Waseda *et al.*(ENDEAVOR RESOLUTE)[36]	OS	61	75	18	SA/UA/SI	9	ZES	88	6

AMI, acute myocardial infarction; BMS, bare metal stent; EES, everolimus-eluting stent; LASM, late acquired stent malapposition; NA, not available; OS, observational study; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; SA, stable angina; SI, silent ischaemia; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; ZES, zotarolimus-eluting stent.

[a]Only IVUS groups.

[b]Non-polymer-encapsulated paclitaxel-coated stents.

[c]We considered number of lesions equal to the number of patients.

Table 2 Characteristics of the studies used for the assessment of the risk of (very) late stent thrombosis in patients with and without late stent malapposition

Study	Design	Clinical follow-up (months)	Type of stent	LSM	Patients number	Observed values for (very) late ST		Expected values for (very) late ST	Definition of ST
						Late ST (≤12 months)	Very late ST (>12 months)		
Hoffmann *et al.*[39]	RCT	48	SES+BMS	Yes	57	0	1	0.18	Occurrence of acute symptoms in combination with angiographically documented TIMI flow 0 or 1 or the presence of flow-limiting thrombus (TIMI flow 1 or 2)
				No	268	0	0	0.82	
Tanabe *et al.*[33]	RCT	12	PES+BMS	Yes	46	0	NA	0.20	NA
				No	423	2	NA	1.80	
Hong *et al.*[40]	OS	36	SES+PES	Yes	82	NA	1	0.44	According to the Academic Research Consortium Criteria[48]
				No	475	NA	2	2.56	
Siqueira *et al.*[38]	OS	29[a]	SES+PES	Yes	10	0	2	0.11	Angiographic documentation of partial or total stent occlusion with or without the presence of thrombus and sudden cardiac death or MI that is not clearly attributable to another coronary lesion
				NO	172	0	0	1.89	
Weissman *et al.*[37]	RCT	24	PES+BMS	Yes	33	0	0	0.06	NA
				NO	514	1	0	0.94	

BMS, bare metal stent; LSM, late stent malapposition; MI, myocardial infarction; NA, not available; OS, observational study; RCT, randomized controlled trial; ST, stent thrombosis; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent.
[a]Mean duration of clinical follow-up.

The incidence of LASM in patients treated with DES varied with the type of stent used: the highest incidence was observed in SES (4%,[25,38] 9%,[22] 13%,[29] 15%,[30] and 25%[35]) followed by PES (2%,[23,27] 5%,[24] 8%,[29,37] 9%,[33] and 15%[38]) then ZES (0%[26] to 7%[36]), and the lowest incidence was observed in EES (0%[34] to 1%[23]). LASM was observed in 0–6% of the patients treated with BMS.[28,31,32]

Risk of late-acquired stent malapposition in drug-eluting vs. bare-metal stents

The incidence of LASM varied between DES and BMS: (a) in DES, the highest incidence was 25% at 9 months in the MISSION! Intervention Study,[35] whereas the lowest incidence was 0% at 6[34] and 8 months;[26] (b) in BMS, the highest reported incidence was 6% at 6 months,[28] whereas the lowest incidence was 0% at 6,[25,27,34] 8,[22,26] and 9 months.[30]

In our meta-analysis, the pooled odds ratio varied according to the approach we used. When both randomized trials and all observational studies were included,[22–38] the risk of LASM in patients with DES was 2.5 times higher compared with those with BMS (OR = 2.49, CI 95% 1.15–5.35, $P = 0.02$). When we included in our meta-analysis only the randomized controlled studies comparing DES with BMS (seven randomized control studies[22,24,27,30,33,35,37] were included and two remaining studies[26,34] reported zero cases in both arms), the risk of LASM in patients with DES was four times higher compared with those with BMS (OR = 4.36, CI 95% 1.74–10.94, $P = 0.002$) (*Figure 2*).

Risk of late-acquired stent malapposition in patients with paclitaxel-eluting stents compared with -limus-eluting stents

The meta-analysis comparing paclitaxel- with -limus-eluting stents showed that the risk of LASM was not significantly (OR = 0.84, 95% CI 0.26–2.71, $P = 0.77$) lower after paclitaxel-eluting stent implantation.

Risk of (very) late stent thrombosis in patients with late stent malapposition (acquired or persistent)

In our meta-analysis, we used five studies[33,37–40] to calculate the risk of late ST in patients with LSM ($n = 228$), compared with patients with no LSM ($n = 1852$). We demonstrate that the risk of (very) late ST in patients with LSM was higher compared with those without LSM (OR = 6.51, CI 95% 1.34–34.91, $P = 0.02$) (*Table 2*). Based on the expected numbers of (very) late ST, there are three trials[38–40] in favour of the relation between LSM and ST and two studies[33,37] with a slight tendency not to support this relation.

The recommended length of thienopyridine therapy after stent implantation was highly variable between the studies: 2–3 months in Hoffmann *et al.*,[39] 6 months in Tanabe *et al.*[33] and Weissman *et al.*,[37] 6 months in Hong *et al.*[29,40] (however, 60% of his patients received additional 5 months of treatment after the original 6-month follow-up), 3–6 months in Siqueira *et al.*,[38] and 12 months in van der Hoeven *et al.*[35]

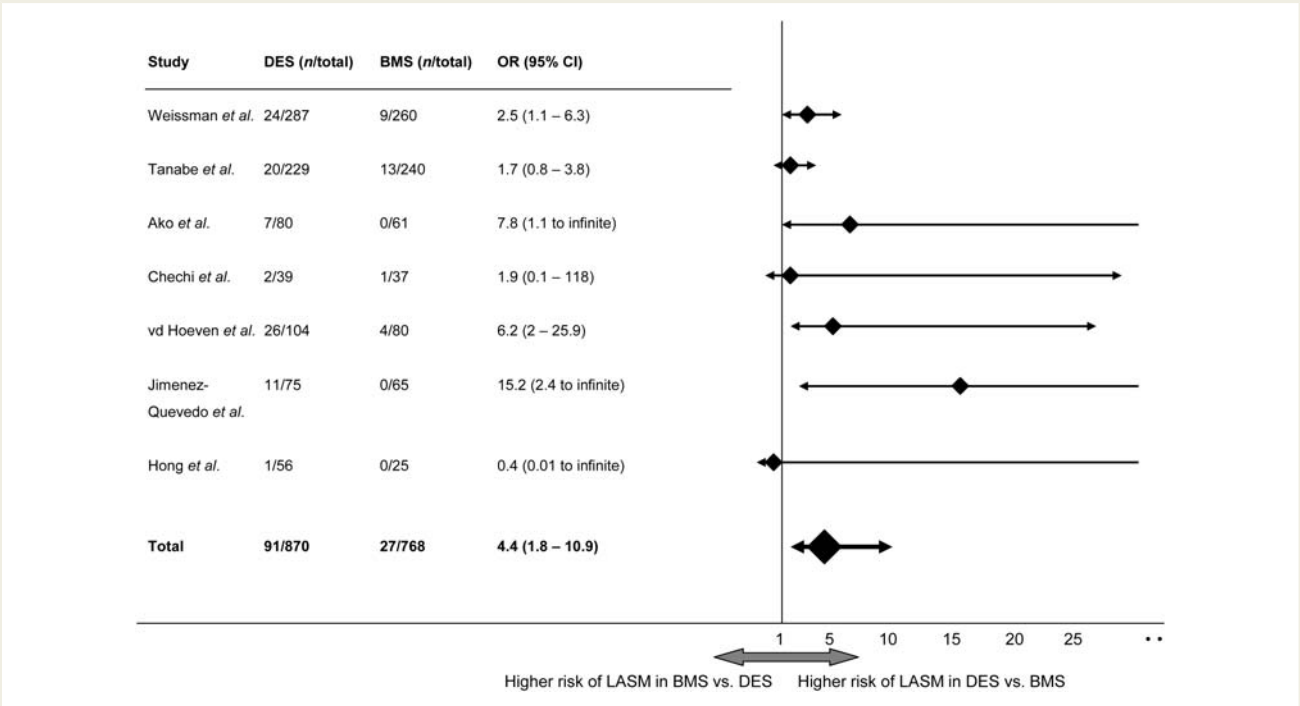

Figure 2 Odds ratio (95% CI) for late-acquired stent malapposition in drug-eluting stent vs. bare metal stent in individual trials; Squares, odds ratios (OR); lines, 95% confidence intervals (95% CI); *n*, number of patients with late-acquired stent malapposition; total, total number of patients in each stent group; BMS, bare metal stents, DES, drug-eluting stents; LASM, late-acquired stent malapposition; ∞, infinite.

Randomized clinical trials quality assessment

Each of the RCTs comparing DES with BMS (seven randomized control studies[22,24,27,30,33,35,37] used in the analysis presented in *Figure 2*) had five or more questions answered with 'yes' when assessed with the Delphi list. Therefore, all seven RCTs were considered to have a low risk of introducing bias in the assessment of LASM in DES vs. BMS.

Discussion

Our key findings were: (a) the risk of LASM was significantly higher after DES vs. BMS implantation; (b) the risk of LASM does not differ significantly between paclitaxel- and -limus-eluting stents; and (c) the presence of late (acquired or persistent) SM at follow-up was significantly associated with the risk of developing (very) late ST.

Late-acquired stent malapposition

In our meta-analysis, the risk of developing LASM in all observational and randomized trials appeared to be slightly lower than in the RCTs only (odds ratio = 2.5 vs. 4.4, respectively). These results may be interpreted from the perspective that each RCT used in the RCT-only analysis was assessed (as described in Methods section) to have low risk of inducing bias in the meta-analysis, in which no similar formal quality assessment may be performed to the rest of the studies included in all observational and randomized trial analyses. The highest incidence of LASM in the DES group was observed in studies including patients with acute myocardial infarction (MI),[35] unstable angina,[38] and diabetic patients.[30] Independent predictors of LASM after BMS implantation were primary stenting in acute MI and DCA before stenting.[28,31] Tanabe *et al.*[33] also identified lesion length, unstable angina, and absence of diabetes as predictive factors of LASM independent of BMS or DES use.

Two mechanisms for LASM were described both for BMS and DES:[6,28,32,35,41] decrease of the plaque volume behind the stent (including clot lysis or plaque regression) and positive remodelling of the vessel wall.

We found a higher risk of LASM in DES when compared with BMS. This difference could be attributable to the adverse effect of the drug on the vessel wall, resulting in positive remodelling.[35] Virmani *et al.*[42] reported that in BMS, hypersensitivity to the metallic stent was mostly associated with restenosis, whereas in DES, the hypersensitivity to the metallic stent, the polymer, or to the drug was associated with positive remodelling and excessive inflammation in the vessel wall. Pires *et al.*[43] suggested that the vascular response to the DES in a murine model differs from the type of the drug used. This is also reported by Hong *et al.*,[29] who compared SES and PES and suggested that the mechanism of SM in SES was a greater suppression of peri-stent neointimal hyperplasia, whereas in PES, a greater amount of peri-stent positive remodelling was observed.

In our meta-analysis, we looked for difference in the risk of LASM between different types of DES. Although there appeared to be a slightly lower risk in the PES group compared with the -limus group, this was far from statistical significance.

Relation between stent thrombosis and malapposition

The present study suggests that the risk of (very) late ST in patients with LSM is higher compared with those without LSM. Our results are consistent with a number of studies,[6,44,45] suggesting LSM to be linked to (very) late ST. Other IVUS studies with BMS[27] and DES[22,29,33] failed thus far to identify LSM as a predictor of clinical adverse events. However, the predictive accuracy of these studies was limited to a small number of patients with LSM (13–90 patients), the limited follow-up period of only 1 year after DES implantation, and the infrequent occurrence of (very) late ST.[6] In our meta-analysis, the real number of patients with late ST due to LSM may possibly be underestimated due to the fact that IVUS imaging was not performed before 6–9 months after implantation.

The mechanism by which LSM may contribute to ST remains unclear. It has been stated that SM may serve as a local nidus for thrombus formation by allowing fibrin and platelet deposition.[46] Moreover, SM may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent.[47] Delayed re-endothelialization, impaired vasomotion, and chronic inflammation may be as well regarded as primary ST mechanisms (SM being just a marker) by allowing platelet adhesion, initiation of the coagulation cascade, and subsequent thrombotic stent occlusion.[6]

To the best of our knowledge, this is the first meta-analysis to assess the risk of LASM in DES compared with BMS. Furthermore, we conducted an analysis on the risk of (very) late ST in patients with LSM. On the basis of the available data, LASM appears to be a problem that cannot be avoided by IVUS immediately after the procedure, that occurs more frequent with DES implantation, and is associated with increased risk of late and very late ST. Our findings demand a careful assessment of the intervention strategy and post-intervention medical treatment as we may trade a benign complication of restenosis in BMS with the serious LASM and the subsequent ST in DES.

For the time being, we do not know whether the presence of LSM should be treated and how. As it is evident that many LSMs may persist for years without leading to (very) late ST, we need to explore the underlying relation between LSM and ST and for how long should patients receive thienopyridine therapy after DES implantation. All these questions are to be clarified in future larger studies.

Limitations

Our results are not a substitute for a large RCT. All studies used in this meta-analysis included a clear definition for LASM, except for one[39] in which the distinction between late-acquired and persistent SM was not clear (the authors used data from the RAVEL trial that did not have a post-procedural IVUS assessment). All analysed studies reported the number of patients with LASM except for two studies[23,29] that reported the number of lesions instead of number of patients. For these studies, we considered the

number of reported lesions to be equivalent to patients. For the (very) late ST subanalysis, the main limitation is the overall small number of patients with events. Another inconvenience is represented by the various definitions of ST. Ideally, an analysis structuring ST as definite, definite and probable, and definite, probable, and possible would grant the most reliable results. The present study does not provide any information on the relation between antiplatelet therapy and ST in the presence or absence of SM. However, we did not intend to perform a meta-analysis on the ST issue, but we rather performed a subanalysis investigating a possible relation between LSM and (very) LST within the studies included in our main analyses. Therefore, we consider that the hypothesis-generating purpose of this subanalysis was accomplished. Consequently, future large and well-designed studies are warranted to replicate these findings.

The aim of the present meta-analysis was to investigate the outcome of stent implantation at a follow-up period no longer than 9 months. However, SM is a dynamic phenomenon and the absence of SM at IVUS follow-up does not warrant a well-apposed stent at later stages as well as it does not warrant a clinically uneventful course. We cannot exclude that these limitations may have influenced our results.

Conclusion

In our meta-analysis, the risk of LASM is strongly increased after DES implantation compared with BMS. Furthermore, LSM seems to be associated with late and very late ST.

Acknowledgements

A.K.M.H. and S.C.B. have equally contributed to this work in conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and supervision. T.S. contributed to analysis and interpretation of data, critical revision, and statistical analysis. B.L.v.d.H., J.D.S., and M.J.S. contributed to conception and design, drafting of the manuscript, and supervision. J.W.M.P. contributed to acquisition of data, critical revision for important intellectual content, and administrative support. J.W.J. contributed to conception and design, drafting of the manuscript, critical revision of the manuscript, statistical analysis, technical support, and supervision. No additional contributors are to be reported for this paper.

Funding

Support for this work was provided by Leiden University Medical Center, Leiden, The Netherlands.

Conflict of interest: none declared.

References

1. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;**356**:1020–1029.
2. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–2130.
3. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;**356**:998–1008.
4. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–1780.
5. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for *de novo* coronary lesions. *Circulation* 2003;**107**:38–42.
6. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;**115**:2426–2434.
7. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;**37**:1478–1492.
8. Arnold JR, van Gaal WJ III, Banning AP. Thrombotic occlusion of a drug-eluting stent—is IVUS mandatory. *J Invasive Cardiol* 2006;**18**:E238–E240.
9. Mintz GS. What to do about late incomplete stent apposition? *Circulation* 2007;**115**:2379–2381.
10. Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, Virmani R. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007;**115**:1051–1058.
11. McKeage K, Murdoch D, Goa KL. The sirolimus-eluting stent: a review of its use in the treatment of coronary artery disease. *Am J Cardiovasc Drugs* 2003;**3**:211–230.
12. Schuler W, Sedrani R, Cottens S, Haberlin B, Schulz M, Schuurman HJ, Zenke G, Zerwes HG, Schreier MH. SDZ RAD, a new rapamycin derivative: pharmacological properties *in vitro* and *in vivo*. *Transplantation* 1997;**64**:36–42.
13. Costa RA, Lansky AJ, Mintz GS, Mehran R, Tsuchiya Y, Negoita M, Gilutz Y, Nikolsky E, Fahy M, Pop R, Cristea E, Carlier S, Dangas G, Stone GW, Leon MB, Muller R, Techen G, Grube E. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). *Am J Cardiol* 2005;**95**:113–116.
14. Miyazawa A, Ako J, Hongo Y, Hur SH, Tsujino I, Courtney BK, Hassan AH, Kandzari DE, Honda Y, Fitzgerald PJ. Comparison of vascular response to zotarolimus-eluting stent vs sirolimus-eluting stent: intravascular ultrasound results from ENDEAVOR III. *Am Heart J* 2008;**155**:108–113.
15. Nakazawa G, Finn AV, John MC, Kolodgie FD, Virmani R. The significance of preclinical evaluation of sirolimus-, paclitaxel-, and zotarolimus-eluting stents. *Am J Cardiol* 2007;**100**:36M–44M.
16. Waugh J, Wagstaff AJ. The paclitaxel (TAXUS)-eluting stent: a review of its use in the management of *de novo* coronary artery lesions. *Am J Cardiovasc Drugs* 2004;**4**:257–268.
17. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;**21**:589–624.
18. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol* 2006;**59**:1331–1332.
19. van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. *Stat Med* 1993;**12**:2273–2284.
20. Arends LR, Voko Z, Stijnen T. Combining multiple outcome measures in a meta-analysis: an application. *Stat Med* 2003;**22**:1335–1353.
21. Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG. The Delphi List: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**:1235–1241.
22. Ako J, Morino Y, Honda Y, Hassan A, Sonoda S, Yock PG, Leon MB, Moses JW, Bonneau HN, Fitzgerald PJ. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. *J Am Coll Cardiol* 2005;**46**:1002–1005.
23. Bullesfeld L. Clinical, angiographic, and IVUS results from the pivotal US randomized SPIRIT III trial of the XIENCE V everolimus eluting coronary stent system (abstract). *Herz* 2007;**32**:248.
24. Chechi T, Vittori G, Biondi Zoccai GG, Vecchio S, Falchetti E, Spaziani G, Baldereschi G, Giglioli C, Valente S, Margheri M. Single-center randomized evaluation of paclitaxel-eluting vs conventional stent in acute myocardial infarction (SELECTION). *J Interv Cardiol* 2007;**20**:282–291.
25. Degertekin M, Regar E, Tanabe K, Lemos P, Lee CH, Smits P, de Feyter P, Bruining N, Sousa E, Abizaid A, Ligthart J, Serruys PW. Evaluation of coronary remodeling after sirolimus-eluting stent implantation by serial three-dimensional intravascular ultrasound. *Am J Cardiol* 2003;**91**:1046–1050.

26. Fajadet J, Wijns W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, Popma JJ, Fitzgerald PJ, Bonan R, Kuntz RE. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;**114**:798–806.
27. Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Weissman NJ, Fearnot NE, Park SW, Park SJ. Paclitaxel coating reduces in-stent intimal hyperplasia in human coronary arteries: a serial volumetric intravascular ultrasound analysis from the Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT). *Circulation* 2003;**107**:517–520.
28. Hong MK, Mintz GS, Lee CW, Kim YH, Lee SW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Park SW, Park SJ. Incidence, mechanism, predictors, and long-term prognosis of late stent malapposition after bare-metal stent implantation. *Circulation* 2004;**109**:881–886.
29. Hong MK, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006;**113**:414–419.
30. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, Costa MA, Alfonso F, Gomez-Hospital JA, Hernandez-Antolin R, Banuelos C, Goicolea J, Fernandez-Aviles F, Bass T, Escaned J, Moreno R, Fernandez C, Macaya C. Vascular effects of sirolimus-eluting vs bare-metal stents in diabetic patients: three-dimensional ultrasound results of the Diabetes and Sirolimus-Eluting Stent (DIABETES) Trial. *J Am Coll Cardiol* 2006;**47**:2172–2179.
31. Nakamura M, Kataoka T, Honda Y, Bonneau HN, Hibi K, Kitamura K, Tamai H, Aizawa T, Yock PG, Fitzgerald PJ. Late incomplete stent apposition and focal vessel expansion after bare metal stenting. *Am J Cardiol* 2003;**92**:1217–1219.
32. Shah VM, Mintz GS, Apple S, Weissman NJ. Background incidence of late malapposition after bare-metal stent implantation. *Circulation* 2002;**106**:1753–1755.
33. Tanabe K, Serruys PW, Degertekin M, Grube E, Guagliumi G, Urbaszek W, Bonnier J, Lablanche JM, Siminiak T, Nordrehaug J, Figulla H, Drzewiecki J, Banning A, Hauptmann K, Dudek D, Bruining N, Hamers R, Hoye A, Ligthart JM, Disco C, Koglin J, Russell ME, Colombo A. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. *Circulation* 2005;**111**:900–905.
34. Tsuchiya Y, Lansky AJ, Costa RA, Mehran R, Pietras C, Shimada Y, Sonoda S, Cristea E, Negoita M, Dangas GD, Moses JW, Leon MB, Fitzgerald PJ, Muller R, Storger H, Hauptmann KE, Grube E. Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials). *Am J Cardiol* 2006;**98**:464–469.
35. van der Hoeven BL, Liem SS, Dijkstra J, Bergheanu SC, Putter H, Antoni ML, Atsma DE, Bootsma M, Zeppenfeld K, Jukema JW, Schalij MJ. Stent malapposition after sirolimus-eluting and bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: acute and 9-month intravascular ultrasound results of the MISSION! Intervention Study. *J Am Coll Cardiol Intv* 2008;**1**:192–201.
36. Waseda K, Yamasaki M, Koizumi T *et al.* Short- and mid-term intravascular ultrasound analysis of the new ENDEAVOR CR zotarolimus-eluting stent: insights from the RESOLUTE trial (abstract). *Am J Cardiol* 2007;**100**:19L–20L.
37. Weissman NJ, Ellis SG, Grube E, Dawkins KD, Greenberg JD, Mann T, Cannon LA, Cambier PA, Fernandez S, Mintz GS, Mandinov L, Koglin J, Stone GW. Effect of the polymer-based, paclitaxel-eluting TAXUS Express stent on vascular tissue responses: a volumetric intravascular ultrasound integrated analysis from the TAXUS IV, V, and VI trials. *Eur Heart J* 2007;**28**:1574–1582.
38. Siqueira DA, Abizaid AA, Costa JR, Feres F, Mattos LA, Staico R, Abizaid AA, Tanajura LF, Chaves A, Centemero M, Sousa AG, Sousa JE. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes. *Eur Heart J* 2007;**28**:1304–1309.
39. Hoffmann R, Morice MC, Moses JW, Fitzgerald P, Mauri L, Breithardt G, Schofer J, Serruys P, Stoll HP, Leon M. Impact of late incomplete stent apposition after sirolimus-eluting stent implantation on 4-year clinical events. Intravascular Ultrasound Analysis from the Multicenter, Randomized, RAVEL, E-SIRIUS and SIRIUS Trials. *Heart*, epub ahead of print 29 August 2007.
40. Hong MK, Mintz GS, Lee CW, Park DW, Lee SW, Kim YH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Impact of late drug-eluting stent malapposition on 3-year clinical events. *J Am Coll Cardiol* 2007;**50**:1515–1516.
41. Mintz GS, Shah VM, Weissman NJ. Regional remodeling as the cause of late stent malapposition. *Circulation* 2003;**107**:2660–2663.
42. Virmani R, Farb A, Guagliumi G, Kolodgie FD. Drug-eluting stents: caution and concerns for long-term outcome. *Coron Artery Dis* 2004;**15**:313–318.
43. Pires NM, Eefting D, de Vries MR, Quax PH, Jukema JW. Sirolimus and paclitaxel provoke different vascular pathological responses after local delivery in a murine model for restenosis on underlying atherosclerotic arteries. *Heart* 2007;**93**:922–927.
44. Feres F, Costa JR, Abizaid A. Very late thrombosis after drug-eluting stents. *Catheter Cardiovasc Interv* 2006;**68**:83–88.
45. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;**109**:701–705.
46. Waksman R. Late Thrombosis after radiation: sitting on a time bomb. *Circulation* 1999;**100**:780–782.
47. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;**48**:193–202.
48. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical endpoints in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.