# Novel insights in reperfusion therapy and stent thrombosis in the drug eluting stent era

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# Chapter 6

## The risk of late acquired stent malapposition is higher after drug-eluting stent compared to bare-metal stent implantation and is associated with late stent thrombosis: Meta-analysis and systematic review

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## ABSTRACT

**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 till December 2007. Inclusion criteria were: (1) Intra-vascular ultrasonography (IVUS) at both post-stent implantation and follow-up; (2) 6 to 9 months follow-up IVUS; (3) Implantation of either BMS or the following DES: sirolimus, paclitaxel, everolimus or zotarolimus and (4) 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 4 times higher compared to BMS (OR = 4.36, CI 95% 1.74-10.94) in randomized control trials. The risk of (very) late ST in patients with LSM (5 studies) was higher compared to the patients without LSM (OR= 6.51, CI 95% 1.34-34.91).

**Conclusion:** The risk of late acquired stent malapposition is significantly higher after drug-eluting stent compared to bare-metal stent implantation. Late stent malapposition seems to be associated with (very) late stent thrombosis.

## INTRODUCTION

Late and very late stent thrombosis are rare[1-5] but potentially lethal complications that emerged during the increasing use of stent implantation. It was recently suggested that stent malapposition (SM) as assessed by IVUS imaging, plays an important role in patients who develop very late stent thrombosis after drug-eluting stent 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-procedural, or late if detected at follow-up IVUS imaging.[8] Acute SM can resolve or persist during the follow-up period. Late stent malapposition (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 since by definition there is no stent malapposition at the time of stent placement. Thus far, no clear conclusion could be drawn with regard to the occurrence of LSM (acquired or persistent) and the risk of (very) late ST since 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 drug-eluting stents (DES) and a sub-analysis to investigate the possible association of LSM (acquired or persistent) with (very) late ST.

## METHODS

### Selection of studies

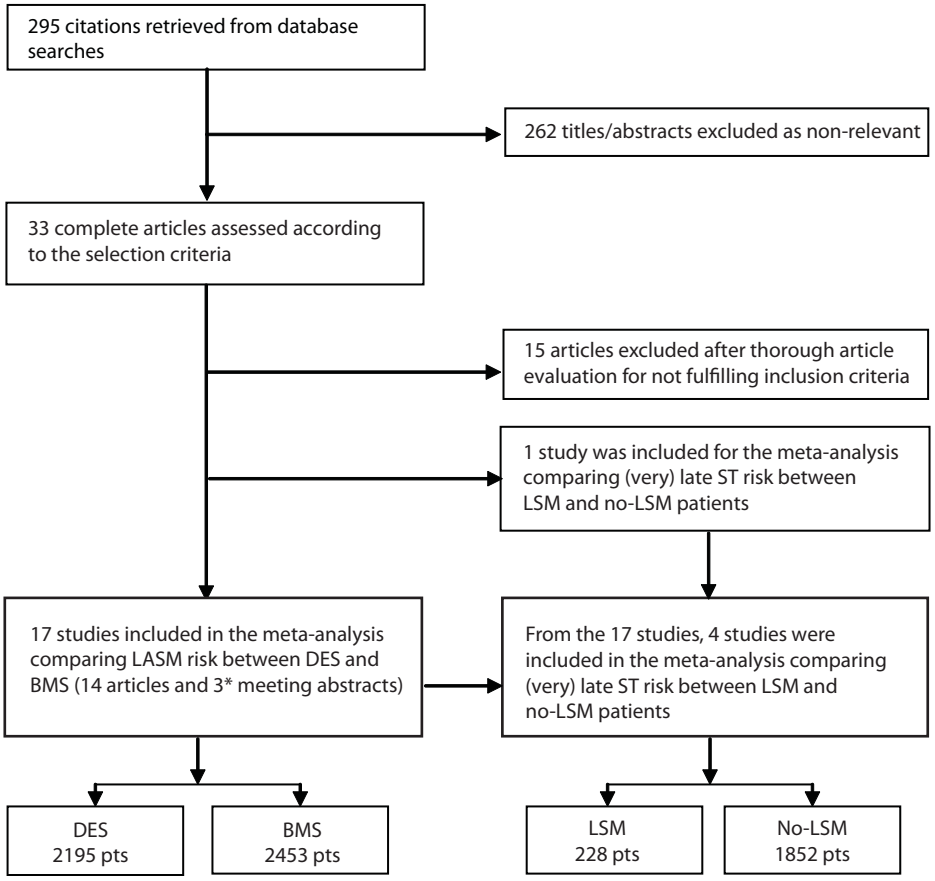
We searched PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials between January 2002 and December 17, 2007 with the keywords (IVUS OR intravascular ultrasonography OR interventional ultrasonography OR intravascular ultrasound OR intravascular ultrasonic) AND (Cypher 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 slides presentations. No language restriction was applied.

To be selected for this meta-analysis, studies had to meet the following criteria: (1) IVUS analysis in native coronary arteries at both baseline and follow-up; (2) Follow-up IVUS performed no sooner than 6 months and not later than 9 months after stent implantation; (3) Implantation of either BMS or one of the following DES: sirolimus-, paclitaxel-, everolimus- or zotarolimus-eluting stents; (4) Recording of late stent malapposition. For the analysis of late ST risk in LSM patients we searched among the included papers those that presented follow-up data for stent thrombosis in two separate groups: LSM versus non-LSM.

**Figure 1** Flow diagram of the 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 was initially collected from expert presentation. Before submission, the results were published and we therefore added a reference[34] for an easy access of the reader.






## Data abstraction

Two investigators (A.H. and S.B.) independently extracted all data, and disagreements were solved in consultation with a third investigator (J.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). After reading the titles and abstracts we identified a potential number of 33 papers from which 17 studies were eligible for inclusion. Among these, 9 papers presented original results from randomised clinical trials that compared drug-eluting stents (DES) with bare metal stents (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. 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 drug-eluting stents 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 where 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]

### IVUS 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 mm in the stent and for 5 mm proximal and distal of the stent and were analyzed with various commercially available software. LSM assessment was performed as follows. First, investigators reviewed all follow-up IVUS recordings to identify cases of stent malapposition. Second, in identified cases, immediate post-stenting and follow-up IVUS images were reviewed side-by-side to discriminate cases in which stent malapposition existed immediately after stent implantation or not.

Stent malapposition 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 done. The first was based on all 17 studies included in the meta-analysis. The second analysis was restricted to the 7 studies that compared BMS with DES in a randomised 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. Due to the small numbers of patients with LSM, 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 et al.[18] The second analysis was based on a standard random effects model for the log odds ratio. However, due to the small numbers of LSMs, 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 done to compare the '-limus' group of drug eluting stents with the paclitxel group. There were only three studies directly comparing a '-limus' stent with PES. However, 6 studies compared '-limus' with BMS and 3 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 done as in Arends et al.,[20] assuming compound symmetry for the covariance matrix of the random effects. To accommodate the small numbers of LSMs, again the exact binomial distribution was used to model the number of events within a treatment group. A fourth analysis was done to compare the incidence of late ST between patients with and without LSM. As stated, there were only 5 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 above, our meta-analysis was especially designed to extract data from various types of available studies: observational studies where the authors present the incidence of LASM within BMS or DES cohorts; RCTs where 2 types of DES are compared; RCTs where BMS is compared in a randomized manner to BMS after rotablation and RCTs where DES are compared to BMS. Only for the latter category it is of interest to perform an RCT study quality assessment. We have used the Delphi list for quality assessment of randomized clinical trials as described by Verhagen et al.[21]. In short, the Delphi list allocates "yes", "no" or "do not know" to a total number of 9 questions. Quality of RCTs is defined as the likelihood of the trial design to generate unbiased results. When 5 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[22-37] with 4648 patients were included in this meta-analysis (table 1).

A number 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 randomized control trials (RCT). Among these, 9 studies[22,24,26,27,30,33-35,37] analyzed DES versus BMS (944 patients with BMS and 1050 patients with DES), one study randomized 2 types of DES[23] and one study randomized only BMS with or without prior directional coronary atherectomy.[31]

**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 , 2005 (SIRIUS)[22] | RCT | 62 | 72 | 26 | SA/UA/signs of myocardial ischemia | 8 | SES | 80 | 7 |
| | | | | | | | BMS | 61 | 0 |
| Van der Hoeven et al, 2007 (MISSION!)[35] | RCT | 59 | 78 | 10 | STEMI | 9 | SES | 104 | 26 |
| | | | | | | | BMS | 80 | 4 |
| Jiménez-Quevedo et al, 2006 (DIABETES)[30] | RCT | 67 | 62 | 100 | Symptoms or objective evidence of ischemia | 9 | SES | 75 | 11 |
| | | | | | | | BMS | 65 | 0 |
| Tanabe et al, 2005 (TAXUS II)[33] | RCT | 62 | 76 | 15 | SA/UA/SI | 6 | PES | 229 | 20 |
| | | | | | | | BMS | 240 | 13 |
| Chechi et al, 2007 (SELECTION)[24] | RCT | 60 | 82 | 13 | AMI | 7 | PES | 39 | 2 |
| | | | | | | | BMS | 37 | 1 |
| Weissman et al, 2007 (TAXUS IV, V, and VI)[37] | RCT | 62[§] | 72 | 28 | SA/UA/SI | 9 | PES | 287 | 24 |
| | | | | | | | BMS | 260 | 9 |
| Hong et al, 2003 (ASPECT)[27] | RCT | 59 | 75 | 14 | Symptomatic coronary heart disease | 6 | PES-NP* | 56 | 1 |
| | | | | | | | BMS | 25 | 0 |
| Bullesfeld et al , 2007 (SPIRIT III)[23†] | RCT | 63 | 67 | 29 | SA/UA/SI | 8 | EES | 90 | 1 |
| | | | | | | | PES | 43 | 1 |
| Tsuchiya et al, 2006 (FUTURE I ,II)[34] | RCT | 65 | 80 | 12 | SA/UA/SI | 6 | EES | 48 | 0 |
| | | | | | | | BMS | 58 | 0 |
| Fajadet et al, 2006 (ENDEAVOR II)[26] | RCT | 62 | 76 | 20 | Symptoms or objective evidence of ischemia | 8 | ZES | 132 | 0 |
| | | | | | | | BMS | 118 | 0 |
| Nakamura et al, 2003 (DESIRE)[31] | RCT | 62 | 85 | NA | NA | 6 | BMS | 412 | 10 |

| Study | Design | Mean age (years) | Men (%) | Diabetes mellitus (%) | Inclusion criteria | Follow-up (months) | Stent | No. of patients | No. of LASM |
|---|---|---|---|---|---|---|---|---|---|
| Hong et al, 2006 [29†] | OS | 57 | 73 | 23 | SA/UA/AMI | 6 | SES | 538 | 71 |
| | | | | | | | PES | 167 | 14 |
| Degertekin et al, 2003[25] | OS | 61 | 76 | 4 | SA/UA/SI | 6 | SES | 24 | 1 |
| | | | | | | | BMS | 10 | 0 |
| Siqueira et al, 2007[38] | OS | 60 | 68 | 46 | SA/UA | 8 | SES | 175 | 7 |
| | | | | | | | PES | 20 | 3 |
| Hong et al, 2004[28] | OS | 56 | 75 | 21 | SA/UA/AMI | 6 | BMS | 881 | 54 |
| Shah et al, 2002[32] | OS | 57 | 100 | 1 | SA/UA/SI | 6 | BMS | 206 | 9 |
| Waseda et al, 2007 (ENDEAVOR RESOLUTE)[36] | OS | 61 | 75 | 18 | SA/UA/SI | 9 | ZES | 88 | 6 |

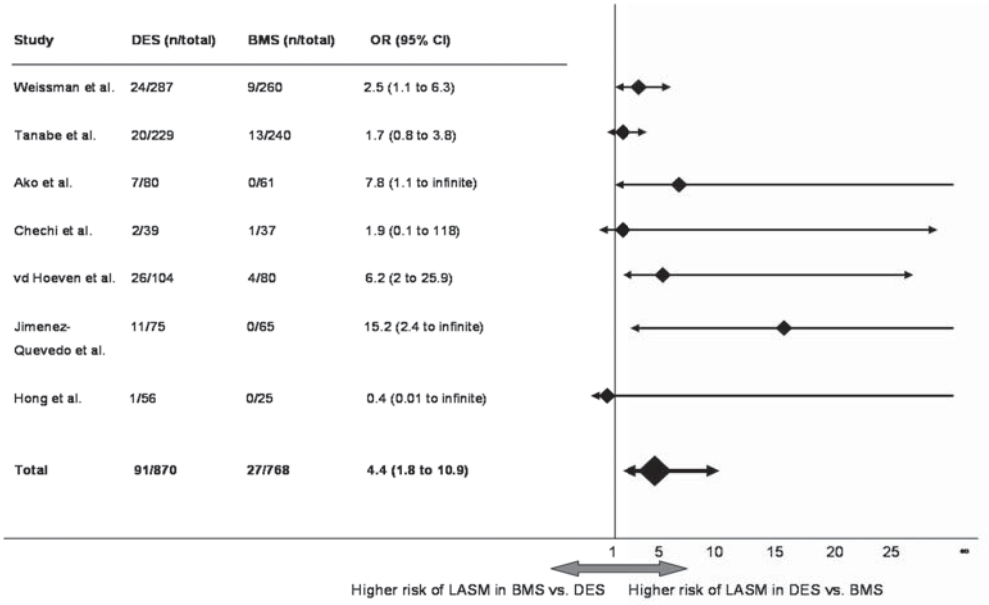
*AMI=acute myocardial infarction; BMS= bare Metal stent; EES= everolimus eluting stent; LSM= late stent malapposition; NA=not available; OS = observational study; PES= paclitaxel eluting stent; RCT= randomized control trial; SES= sirolimus eluting stent; SA=stable angina; SI=silent ischemia; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina; ZES= zotarolimus eluting stent. *non-polymer-encapsulated paclitaxel-coated stents, [†]we considered number of lesions as the number of patients, [§]Only IVUS groups.*

### Risk of LASM in DES versus BMS

The incidence of LASM varied between DES and BMS: (1) in DES, the highest incidence was 25% at 9 months in the MISSION! Intervention Study[35] while the lowest incidence was 0% at 6 months[34] and 8 month;[26] (2) in BMS, the highest reported incidence was 6% at 6 months[28] while the lowest incidence was 0 % at 6 months,[25,27,34] 8 months[22,26] and 9 months.[30]

**Figure 2** Odds ratio (95% CI) for late-acquired stent malapposition in drug eluting stents versus bare metal stents

Odds ratio (95% CI) for late-acquired stent malapposition in DES versus BMS 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.




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,[22-37] the risk of late acquired stent malapposition in patients with DES was 2.5 times higher compared to those with BMS (OR = 2.49, CI 95% 1.15-5.35, P= 0.02). When we included in our meta-analysis only the randomised controlled studies comparing DES with BMS ( 7 randomized control studies[22,24,27,30,33,35,37] were included and 2 remaining studies[26,34] reported zero cases in both arms) (table 3), the risk of late acquired stent malapposition in patients with DES was 4 times higher compared to those with BMS (OR= 4.36, CI 95% 1.74-10.94, P = 0.002).(figure 2).

### Risk of LASM 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.

**Table 2** Characteristics of the studies used for 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† | 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 stents; LSM= late stent malapposition; MI= myocardial infarction; NA=not available; OS = observational study; RCT= randomized control trial; ST= stent thrombosis; SES= sirolimus eluting stent; PES= paclitaxel eluting stent.† Mean duration of clinical follow-up.*

### Risk of (very) late ST in patients with LSM (acquired or persistent)

In our meta-analysis we used 5 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 to patients 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 3 trials[38-40] in favour of the relation between LSM and ST , and 2 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 to 3 months in Hoffman et al.,[39] 6 months in Tanabe et al., and Weissman et al.,[33,37] 6 months in Hong et al.[29,40] (however 60% of his patients received additional five-month of treatment after the original six-month follow-up), 3 to 6 months in Siqueira et al.[38] and 12 months in van der Hoeven et al.[35]

### RCTs quality assessment

Each of the RCTs comparing DES with BMS ( 7 randomized control studies[22,24,27,30,33,35,37] used in the analysis presented in Figure 2) had 5 or more questions answered with "yes" when assessed with the Delphi list. Therefore all 7 RCTs were considered to have a low risk of introducing bias in the assessment of LASM in DES versus BMS.

## DISCUSSION

Our key findings were: (1) The risk of late-acquired stent malapposition was significantly higher after drug-eluting stents versus bare-metal stents implantation; (2) The risk of late-acquired stent malapposition does not differ significantly between paclitaxel- and "-limus"-eluting stents and (3) The presence of late (acquired or persistent) stent malapposition at follow-up was significantly associated with the risk of developing (very) late stent thrombosis.

### 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 RCTs only analysis was assessed (as described in methods section) to have low risk of inducing bias in the meta-analysis where no similar formal quality assessment may be performed to the rest of the studies included in all observational and randomized trials analysis. The highest incidence of LASM in the DES group was observed in studies including patients with acute myocardial infarction, [35] unstable angina[38] and diabetic patients.[30] Independent predictors of LASM after BMS implantation, were primary stenting in acute MI and directional coronary atherectomy (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 bare-metal stents and drug-eluting stents[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 to BMS. This difference could be attributable to the adverse effect of the drug on the vessel wall resulting in positive remodeling.[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 drug eluting stents in murine model differ with the type of drug used . This is also reported by Hong et al.[29] who compared sirolimus- and paclitaxel-eluting stents and suggested that the mechanism of stent malapposition in sirolimus eluting stents was a greater suppression of peri-stent neointimal hyperplasia whereas in paclitaxel eluting stents a greater amount of peri-stent positive remodeling was observed.

In our meta-analysis we looked for difference in the risk of LASM between different types of drug eluting stents. Although there appeared to be a slightly lower risk in the PES group compared to '-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 to patients 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 this far to identify LSM as a predictor of clinical adverse events. However, the predictive accuracy of these studies was limited by the small number of patients with LSM (13 to 90 patients), the limited follow-up period of only one 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 to 9 months after implantation.

The mechanism by which LSM may contribute to stent thrombosis 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 stent thrombosis mechanisms (stent malapposition being just a marker) by allowing the platelet adhesion, initiation of the coagulation cascade, and subsequent thrombotic stent occlusion.[6]

To our knowledge, this is the first meta-analysis to assess the risk of LASM in DES compared to 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 stent thrombosis. Our findings demand a careful assessment of the intervention strategy and post intervention medical treatment since we may trade a benign complication of restenosis in bare-metal stents with the serious late acquired stent malapposition and the subsequent stent thrombosis in drug-eluting stents.

For the time being we do not know whether the presence of LSM should be treated and how. Since it is evident that many LSMs may persist for years without leading to (very) late stent thrombosis, we need to explore the underlying relation between LSM and stent

thrombosis and for how long should patients receive thienopyridine therapy after drug-eluting stent implantation. All these questions are to be clarified in future larger studies.

## LIMITATIONS

Our results are not a substitute for a large randomised controlled trial. All studies used in this meta-analysis included a clear definition for late acquired stent malapposition except for one[39] where the distinction between late acquired and persistent stent malapposition was not clear (the authors used data from the RAVEL trial which did not have a post-procedural IVUS assessment). All analyzed studies reported the number of patients with LASM except for 2 studies[23,29] that reported the number of lesions instead of number of patients. For these studies we considered number of reported lesions to be equivalent to patients. For the (very) late ST sub-analysis, the main limitation is the the overall small number of patients with events. Another inconvenience is represented by the various definitions of stent thrombosis. Ideally, an analysis structuring stent thrombosis 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 stent thrombosis in the presence or absence of stent malapposition. However, we did not intend to perform a meta-analysis on the stent thrombosis issue but we rather performed a sub-analysis 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 sub-analysis 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, stent malapposition is a dynamic phenomenon and the absence of stent malapposition 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 late acquired stent malapposition is strongly increased after drug-eluting stent compared to bare-metal stent implantation. Furthermore, late stent malapposition seems to be associated with late and very stent thrombosis.

## ACKNOWLEDGMENTS

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. vd H., J.D.S. and M.J.S. contributed in conception and design, drafting of the manuscript and supervision. J.W.M.P. contributed with acquisition of data, critical

revision for important intellectual content and administrative support. J.W.J. contributed with 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.

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