Distribution of angiographic measures of restenosis after drug-eluting stent implantation

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ABSTRACT

Background: A bimodal distribution of measures of restenosis has been demonstrated at 6–8 months after bare metal stent implantation. Drug-eluting stent (DES) treatment has attenuated the impact of certain factors (eg, diabetes) on restenosis but its effect on the distribution of indices of restenosis is not known.

Objective: To perform a detailed analysis of the metrics of restenosis indices after DES implantation.

Design, settings, patients: Prospective observational study of patients undergoing DES implantation (Cypher, sirolimus-eluting stent; or Taxus, paclitaxel-eluting stent) at two German centres, with repeat angiography scheduled at 6–8 months after coronary stenting.

Main outcome measures: In-stent late luminal loss (LLL) and in-segment percentage diameter stenosis (%DS) as determined by quantitative coronary angiography at recatheterisation.

Results: Paired cineangiograms were available for 2057 patients. Overall mean (SD) LLL was 0.31 (0.50) mm; mean (SD) %DS was 30.3 (15.7)%. Distribution of both LLL and %DS differed significantly from normal (Kolmogorov–Smirnov test; $p < 0.001$ for each). For both parameters a mixed distribution model better described the data (likelihood ratio test with 3df; $p < 0.001$ for each). This consisted of two normally distributed subpopulations with means (SD) of 0.10 (0.25) mm and 0.69 (0.60) mm for LLL, and means (SD) of 22.2 (8.6)% and 40.1 (16.6)% for %DS. The results were consistent across subgroups of DES type, ''on-label'' versus ''off-label'' indication, and presence or absence of diabetes.

Conclusions: LLL and %DS at follow-up angiography after DES implantation have a complex mixed distribution that may be accurately represented by a bimodal distribution model. The introduction of DES treatment has not resulted in elimination of a variable propensity to restenosis among subpopulations of patients with stented lesions.

Restenosis after coronary intervention was initially perceived as the tail end of a universal response to vessel healing after injury related to balloon dilatation and stent implantation.[1–3] As with other biological processes a Gaussian distribution of indices of restenosis would therefore be expected. Subsequent investigation, however, disclosed a complex dispersal pattern of such markers after both balloon angioplasty and Palmaz–Schatz stent implantation—a pattern best represented in both cases by a bimodal distribution model.[4 5] Consequently, it was hypothesised that two different subpopulations exist, comprising subsets of lesions with varying propensity to restenosis. This was in keeping with a series of studies identifying both patient and lesion characteristics portending a higher risk of restenosis at late follow-up after percutaneous coronary intervention.[6–8]

The introduction of drug-eluting stent (DES) treatment has resulted in a levelling of the playing field with respect to the effects of certain characteristics on the likelihood of restenosis after coronary intervention. For example, the influence of diabetes mellitus on the risk of target lesion revascularisation has been largely negated by DES treatment.[9–11] Whether or not this impacts significantly on the distribution of indices of restenosis is not known. At the same time, use of restenotic indices as surrogate end points in clinical trials of new DES platforms has assumed increasing importance in the performance of comparative efficacy studies permitting the continuing refinement of DES technology.[12] An insight into their patterns of distribution may contribute to an improved understanding of the role of these indices in inter-DES efficacy studies. We therefore conducted formal dedicated analysis of the distribution of angiographic indices of restenosis at 6–8 month angiographic follow-up after DES implantation. Late luminal loss (LLL) and percentage diameter stenosis (%DS) are the most well-studied markers of antirestenotic efficacy and were selected as the most appropriate parameters to analyse.

PATIENTS AND METHODS

Study population and protocol

All patients receiving a sirolimus-eluting stent (Cypher, Cordis, Miami Lakes, Florida, USA) or a paclitaxel-eluting stents (Boston Scientific, Natick, Massachusetts, USA) between August 2002 and June 2005 at either of the two participating institutions—the Deutsches Herzzentrum and the 1. Medizinische Klinik, Klinikum rechts der Isar, both in Munich, Germany—were eligible for inclusion in the study. Indications for stenting were ischaemic symptoms or evidence of myocardial ischaemia in the presence of ≥50% stenosis located in native coronary vessels. Patients presenting with acute myocardial infarction, or with malignancies or other comorbid conditions with life expectancy <12 months, known allergy to the study drugs (aspirin, clopidogrel, paclitaxel, rapamycin, stainless steel) or pregnancy were considered ineligible for the study.

Stenting procedure and adjunctive treatment

An oral loading dose of 600 mg clopidogrel was given to all patients at least 2 h before the intervention, regardless of whether the patient

was taking clopidogrel before admission. During the procedure, patients were given intravenous aspirin (if not already receiving oral treatment) and heparin; glycoprotein IIb/IIIa inhibitor usage was at the discretion of the operator. After the intervention, all patients received 200 mg/day aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge), followed by 75 mg/day for at least 6 months. Rehospitalisation for repeat coronary angiography was scheduled for all patients between 6 and 8 months after the intervention.

Data management, end points and quantitative coronary angiography

Relevant data were collected and entered into a computer database by specialised personnel of the Clinical Data Management Centre. Endpoint adjudication and quantitative coronary angiographic analysis was blinded to stent type. When patients required multiple lesion intervention, one lesion was selected at random for inclusion in the analysis. Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed offline in the quantitative angiographic core laboratory (Deutsches Herzzentrum ISAResearch Centre) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, The Netherlands) by two independent experienced operators unaware of the treatment allocation. All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin using the same single worst-view projection at all times. The contrast-filled non-tapered catheter tip was used for calibration. Quantitative analysis was performed on both the "in-stent" and "in-segment" area (including the stented segment, as well as both 5 mm margins proximal and distal to the stent). Qualitative morphological lesion characteristics were characterised by standard criteria. The primary end points of interest were in-stent LLL, defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up angiography; and in-segment %DS at follow-up angiography. Binary angiographic restenosis was defined as diameter stenosis $\geqslant$50% in the in-segment area. The results were also examined for consistency across the subgroups of Cypher versus Taxus, on-label versus off-label and diabetes versus no diabetes. On-label use was defined as stent implantation in a de novo native coronary vessel between 2.5 mm and 3.75 mm reference vessel diameter with a lesion length <30 mm. Lesions not meeting these criteria were classified as off-label. Intervention on ostial, bifurcational, left main stem and chronic total occlusion lesions were also considered off-label.

Statistical analysis

Data are expressed as counts (percentages) for discrete variables and as mean (SD) or median (interquartile range) for continuous variables. The frequency distribution of the angiographic variables was tested for normality by the Kolmogorov–Smirnov goodness-of-fit test. For graphical presentation, histograms, hanging histograms and density curves are used. For distributions with bimodal appearance and a marked deviation from the theoretical normal curve, deconvolution in two best-fitted normally distributed curves was performed with the EM algorithm[13] using the S-Plus statistical package (S-Plus version 2000, StaSci Division, MathSoft Seattle, Washington, USA). As a result, the mean, SD, and proportion of the population belonging to each of the estimated component normal distributions were obtained and used to construct the combined

mixture distribution. The mixture distribution was tested against the respective observed frequency distribution by the Kolmogorov–Smirnov test. Improvement in the fit of the distribution was performed using the likelihood-ratio test R comparing the likelihood function under the assumption of one normal distribution or a mixture of two normal distributions. The hypothesis of a mixture of two distributions was accepted if the value of R exceeded the 95% centile of a χ^2 distribution with three degrees of freedom. The intersection point separating both normal distributions was obtained by crossing between both density functions. The stability of the findings presented was ensured by bootstrapping with 1000 replications of the original data.[14] The bootstrapping technique also allowed calculation of the 95% confidence interval for the intersection point. Statistical significance was accepted for all values of p<0.05.

RESULTS

Of 2523 consecutive patients, 2092 patients (82.9%) had angiographic follow-up data. Thirty-five (1.7%) had a totally reoccluded artery at follow-up and were excluded from analysis. The remaining study group comprised 2057 patients. Tables 1 and 2 present the baseline patient and procedural characteristics. Table 3 shows the overall angiographic follow-up results. Overall late luminal loss was 0.31 (0.50) mm and percentage diameter stenosis was 30.3 (15.7)%. Binary angiographic restenosis was seen in 255 (12.4%) lesions.

Distribution of LLL differed significantly from normal (Kolmogorov–Smirnov test; p<0.001). This can be clearly seen from a frequency distribution histogram (fig 1A) and a hanging histogram (fig 1B). A mixed distribution model better described the data. The Kolmogorov–Smirnov test comparing the observed frequency distribution with the mixed distribution model showed no significant differences (p = 0.51). The likelihood ratio test confirmed this superior goodness-of-fit (with three degrees of freedom, p<0.001). This consisted of two deconvoluted populations with normal distribution (fig 1C), the first with a mean (SD) late loss of 0.10 (0.25) mm; the second with a mean (SD) of 0.69 (0.60) mm. From analysis of the raw data, the weights of the populations were 64.5% and 35.5%,

Table 1 Baseline characteristics

Characteristics	Patients (n = 2057)
Age (years), mean (SD)	65.8 (10.4)
Female	427 (20.8)
Diabetes	560 (27.2)
Insulin-requiring	185 (9.0)
Hypertension	1200 (58.3)
Current smoker	275 (13.4)
Hyperlipidaemia	1528 (74.3)
Coronary disease	
Single vessel	334 (16.2)
Two vessel	566 (27.5)
Three vessel	1157 (56.2)
Multivessel disease	1723 (83.8)
Clinical presentation	
Unstable angina	604 (29.4)
Stable angina	1453 (70.6)
Prior myocardial infarction	751 (36.5)
Prior percutaneous intervention	1287 (62.6)
Prior aortocoronary bypass surgery	213 (10.4)
Left ventricular ejection fraction (%), mean (SD)	55.3 (12.3)

Data are shown as No (%) unless otherwise indicated.

Interventional cardiology

Table 2 Procedural characteristics

Characteristics	Lesions (n = 2057)
Number of lesions treated/patient	1.18 (0.44)
Target vessel	
Left main coronary artery, No (%)	131 (6.4)
Left anterior descending artery, No (%)	884 (43.0)
Left circumflex artery, No (%)	531 (25.8)
Right coronary artery, No (%)	511 (24.8)
Complex (type B2/C) lesions, No (%)	1540 (74.9)
Chronic total occlusion, No (%)	150 (7.3)
Ostial, No (%)	452 (22.0)
Bifurcational, No (%)	533 (25.9)
Restenotic, No (%)	640 (31.1)
Lesion length (mm)	13.2 (7.6)
Vessel size (mm)	2.74 (0.57)
Minimal luminal diameter before procedure (mm)	1.09 (0.50)
Diameter stenosis before procedure (%)	60.2 (15.3)
Balloon-to-vessel ratio	1.15 (0.12)
Max balloon pressure (atm)	14.6 (3.0)
Overlapping stents, No (%)	114 (5.5)
Number of stents/lesion	1.09 (0.31)
Total stented length (mm)	22.7 (9.1)
Minimal luminal diameter after procedure	
In-stent (mm)	2.63 (0.49)
In-segment (mm)	2.23 (0.60)
Diameter stenosis after procedure	
In-stent analysis (%)	8.2 (6.5)
In-segment analysis (%)	22.8 (12.1)
Stent type	
Sirolimus-eluting, No (%)	1166 (56.7)
Paclitaxel-eluting, No (%)	891 (43.3)

Data are shown as means (SD) unless otherwise indicated.

Table 3 Main angiographic outcomes at 6–8 months' follow-up

Angiographic outcomes	Mean (SD) (n = 2057)	Median (IQR) (n = 2057)
MLD, in-stent (mm)	2.33 (0.67)	2.35 (1.94–2.75)
MLD, in-segment (mm)	2.03 (0.63)	2.02 (1.59–2.43)
Stenosis, in-stent (%)	19.7 (16.9)	15.2 (8.8–25.6)
Stenosis, in-segment (%)	30.3 (15.7)	27.8 (19.0–39.1)
Late loss, in-stent (mm)	0.31 (0.50)	0.20 (−0.02–0.53)
Late loss, in-segment (mm)	0.21 (0.54)	0.15 (−0.14–0.50)
Binary restenosis, in-segment, No (%)	255 (12.4)	
Target lesion revascularisation, No (%)	182 (8.8)	

MLD, minimal luminal diameter.

respectively. Bootstrap resampling (1000 samples) generated mean weights of 64.7% (95% CI 58.4% to 70.6%) and 35.3% (95% CI 29.4% to 41.6%), respectively. The intersection of the two curves occurred at 0.45 mm (fig 1C). Bootstrap resampling (1000 samples) generated a mean intersection point at 0.45 mm (95% CI 0.41 to 0.49).

Similarly, distribution of %DS differed from normal (Kolmogorov–Smirnov test; p<0.001; figs 2A and B). In this case a mixed distribution model also better described the data (Kolmogorov–Smirnov test comparing observed data with mixed model, p = 0.99; likelihood ratio test with three degrees of freedom, p<0.001).This consisted of two deconvoluted populations with normal distribution (fig 2C), the first with a mean (SD) %DS of 22.2 (8.6)%; the second with a mean (SD) of 40.1 (16.6)%. From the data, the weights of the populations were 54.4% and 45.6%, respectively. Bootstrap resampling (1000 samples) generated mean weights of 54.8% (95% CI 46.3% to 63.8%) and 45.2% (95% CI 36.2% to 53.8%), respectively. For %DS the intersection of the two curves occurred at 32.7% (fig 2C). Bootstrap resampling (1000 samples) revealed a mean %DS intersection point at 32.8% (95% CI 31.1% to 34.4%).

Comparison of hanging histograms fitted to a normal distribution and to the composite mixed distribution curves graphically illustrates the superior goodness-of-fit of the latter models for both parameters under investigation (figs 1A and D; figs 2A and D).

Additional testing
We also investigated straightforward log and square-root transformations of the data. In both cases the resultant dataset differed significantly from normal (Kolmogorov–Smirnov test for non-normality, p<0.001 for both transformations on both parameters).

Exploratory subgroup analyses for LLL and %DS distributions were also performed for Cypher versus Taxus, on-label versus off-label implantation, and in patients with diabetes versus those without. Overall, a composite mixed distribution model continued to better represent LLL and %DS across all the subgroups (online supplementary tables 1 and 2). The most notable observation was that a slightly larger proportion of patients seemed to belong to the higher LLL and higher %DS subpopulations in patients treated with Taxus, those stented for an off-label indication, and those with diabetes. Mixed distribution (bimodal) models were very similar for both Cypher and Taxus are shown in (fig 3), save for a slight right shift of LLL and %DS subpopulations with Taxus.

We also used the curve deconvolution algorithm to explore whether a three-group model might accurately represent the observed distributions. For LLL a three-group composite distribution curve was associated with some further improvement in fit; whereas for %DS the two-group model continued to be a better fit (supplementary tables 3 and 4).

DISCUSSION
This study is the first to report detailed statistical analysis of the metrics of restenosis at angiographic follow-up after DES implantation. We report that the distribution of late loss and percentage diameter stenosis has a complex mixed distribution pattern that may accurately be represented by a bimodal distribution model. Curve deconvolution discloses two distinct theoretical normally distributed populations for both late loss and percentage diameter stenosis. For both parameters a composite mixed distribution curve, derived from merging these subpopulations, accurately describes the data. Furthermore, such distribution patterns appear to hold when analysed according to the type of DES implanted, on-label versus off-label usage and presence or absence of diabetes.

The delineation of a mixed (bimodal) distribution is in keeping with findings from studies after both balloon angioplasty and bare metal stent implantation. Historically, restenosis after percutaneous coronary intervention was perceived as the tail end of a distribution consequent on a ubiquitous healing response to vessel injury that was expected to affect all treated lesions similarly. The corollary of this assumption—namely, that a Gaussian distribution of markers of restenosis could be expected, appeared to be supported by early investigation in this field.[1–3] Lehmann and colleagues provided the first challenge to this perception and proposed that despite the superficial appearance of a normal distribution of indices of restenosis after balloon angioplasty, a complex pattern of
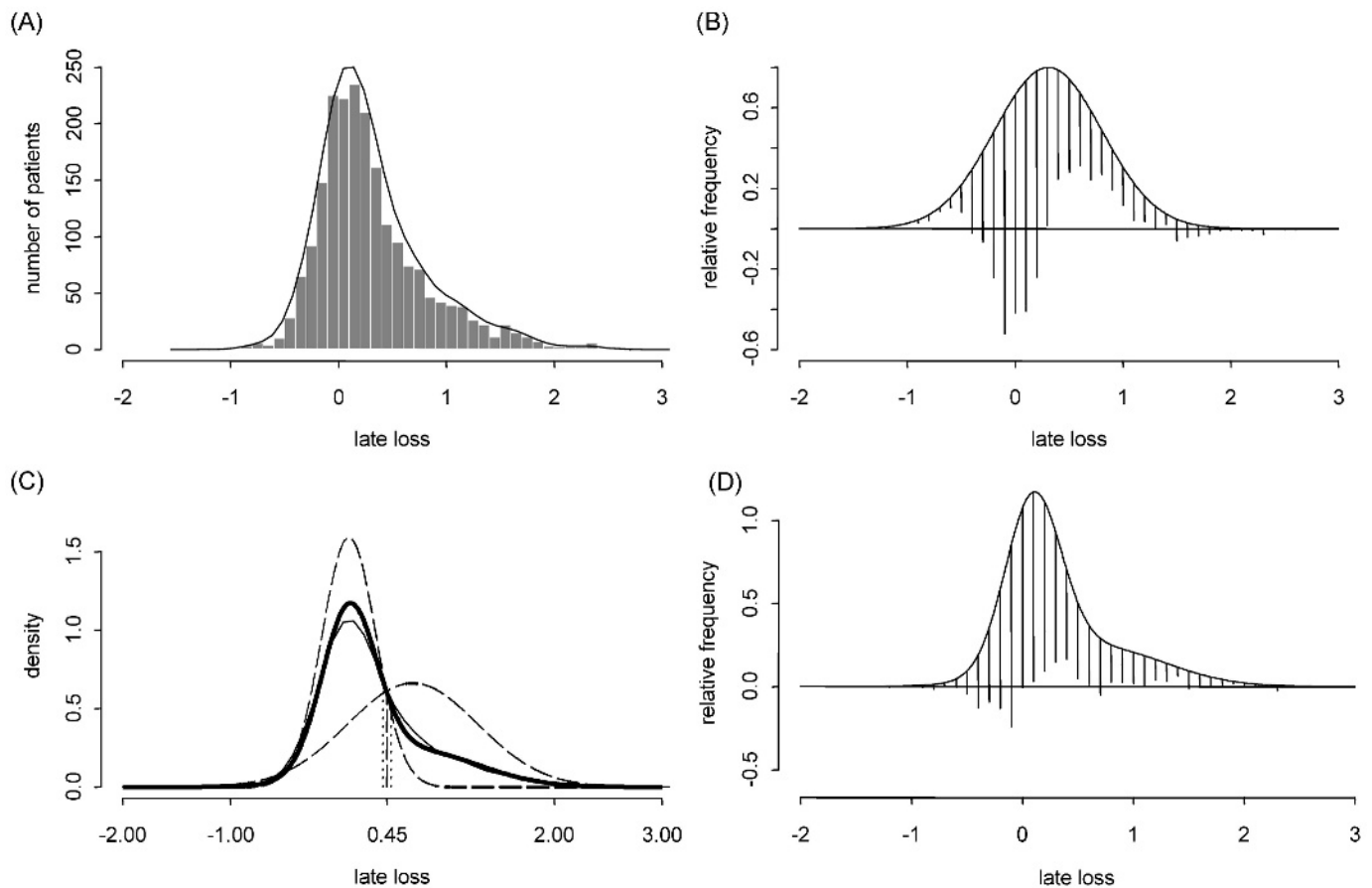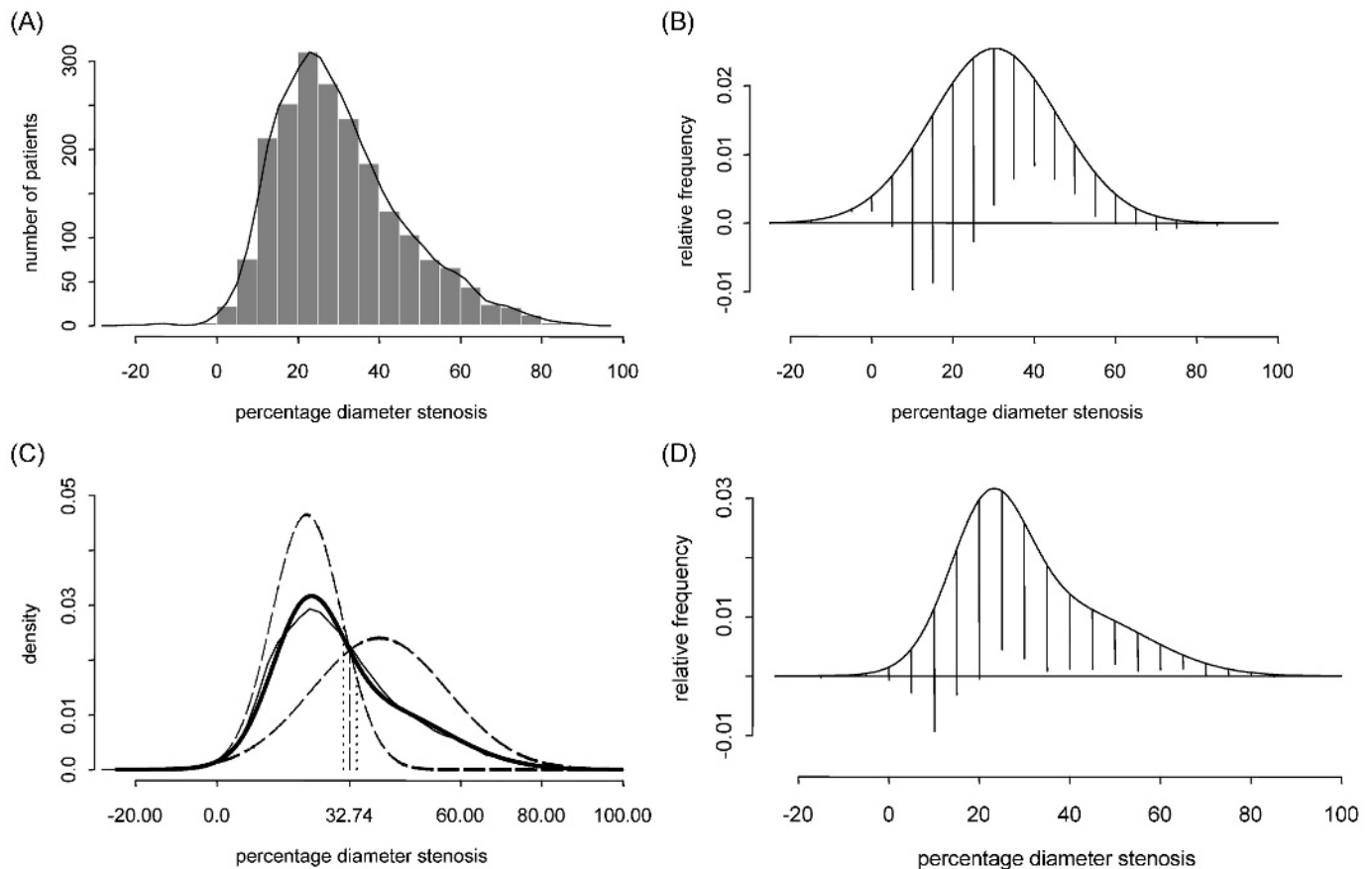
Figure 1 Distribution of late luminal loss for 2057 treated lesions. (A) Frequency distribution histogram with superimposed kernel density estimate; (B) hanging histogram highlighting lack of goodness-of-fit with normal distribution; (C) deconvolution of the observed frequency distribution curves (thin solid line) yields two subpopulations with normal distribution (dashed lines). The weighted sum of these two components yields the composite distribution curve (thick solid line); the vertical dashed line denotes the intersection point between the two subpopulation distribution curves; (D) hanging histograms applied to composite mixed distribution curves for late luminal loss.

distribution existed, probably representative of subpopulations with varying propensity to restenosis.[4] Subsequently, frequency distribution curves of angiographic indices of restenosis after bare metal stent placement were analysed at our centres. Here also a similar pattern was observed.[5] The impact of DES treatment on neointimal hyperplasia—the dominant remaining cause of restenosis—has been so dramatic as to make a re-evaluation of this hypothesis an important undertaking. The superficial appearance of frequency histograms after DES implantation might be perceived as a left-skewed distribution pattern with a long right tail. Despite this, the existence of a bimodal distribution has been postulated based on observations from DES registry data.[15 16]

Specifically, for our results we found that late loss (in-stent) can be accurately represented by two populations—a larger population (comprising two-thirds of patients) with a low mean (0.10 mm), perhaps defined by patient, lesion or procedural characteristics, portending a more favourable antirestenotic outcome; and a second smaller group with a higher mean (0.69 mm), representative of a cohort with higher-risk features. For percentage diameter stenosis, our findings show two more equally divided populations—the first with a peak at about 20% diameter stenosis comprising ~55% of the patients studied; the second with a peak at around 40% stenosis containing the remainder. These findings are strikingly similar to the bimodal distributions observed in the bare metal stent era,[5] with the exception of a significant left shift (from centres

at ~0.5 mm and 1.5 mm for late loss and ~30% and 70% for percentage diameter stenosis). This left shift is illustrative of the significant neointimal inhibitory effect of DES technology. The disconnection between the weights of the subpopulations in the LLL and %DS analyses may occur for a number of reasons, including the influence of vessel size (only a factor in the latter parameter) and the use of *in-segment* (as opposed to *in-stent*) analysis in the measurement of %DS. Our findings have at least two important implications.

First, this analysis serves to confirm that the clear benefits shown by antirestenotic efficacy observed after the introduction of DES technology[17] is not associated with an elimination of the variable propensity to restenosis across all treated lesions. In other words, the "rising tide does not lift all boats to the same level". This runs somewhat counter to the observations of a markedly attenuated impact of diabetes on restenosis, for example, but is in keeping with delineation of ongoing patient and procedural factors predictive of a higher restenotic risk in certain treated lesions.[9–11] The confirmation of subpopulations at increased risk is relevant. Perhaps these patients should be chosen to receive a DES with the highest antirestenotic efficacy? Furthermore, the observation that high-risk subpopulations are found even in traditionally straight-forward lesion types (on-label indications) may imply the existence of additional risk factors not yet fully delineated (eg, drug resistance, polymer hypersensitivity). This may prove to be a target for further improvements in DES treatment.

Figure 2 Distribution of percentage diameter stenosis for 2057 treated lesions. (A) Frequency distribution histogram with superimposed kernel density estimate; (B) hanging histogram highlighting lack of goodness-of-fit with normal distribution; (C) deconvolution of the observed frequency distribution curves (thin solid line) yields two subpopulations with normal distribution (dashed lines). The weighted sum of these two components yields the composite distribution curve (thick solid line); the vertical dashed line denotes the intersection point between the two subpopulation distribution curves; (D) hanging histograms applied to composite mixed distribution curves for percentage diameter stenosis.

Second, this pattern of distribution may assist the clinician in the interpretation of inter-DES efficacy studies, which often include both angiographic and clinical end points. A bimodal distribution pattern may help to explain why the highly significant differences in indices of restenosis sometimes seen in comparative efficacy studies between certain DES platforms do not invariably translate into clear differences in target lesion revascularisation. Mean late loss, for example, is a commonly used surrogate end point in inter-DES comparative efficacy studies. As a continuous variable, it is an attractive end point as it is associated with a stronger discriminatory propensity than a binary variable such as angiographic restenosis. At an *individual patient level*, its relation to both binary angiographic restenosis and clinical restenosis (target lesion revascularisation) may be thought of as a straightforward function of reference vessel size and residual post-intervention stenosis. For vessel sizes of interest in most clinical trials, a sharp inflection in the correlation curve may be expected between late losses of ~1.1–1.4 mm.[12]

Of more significance is the relation between *mean* late loss and the probability of restenosis at a *study population level*. A number of reports have validated mean late loss as a surrogate for target lesion revascularisation,[18–21] though remain somewhat at odds with the realities observed in inter-DES clinical trials and large-scale registries, where significant between-platform differences in late loss have often failed to translate into significant treatment effects for clinical restenosis.[16 22] From this current analysis it can be seen that differences between

competing DES platforms across *low mean late loss populations* (which comprise the bulk of DES-treated patients) are unlikely to have any impact on rates of restenosis and revascularisation, regardless of vessel size or residual stenosis, as even patients at the extreme upper limits of the distribution pattern are unlikely to exceed the threshold late loss (eg, 1.1–1.4 mm) associated with binary restenosis at an individual patient level. On the other hand, it is differences in the smaller number of patients comprising these higher late loss subpopulations which will impact significantly on the comparative number of patients spilling over the theoretical revascularisation threshold and declaring themselves as cases of clinical restenosis.

Limitations

This study is an observational angiographic follow-up study based on quantitative coronary angiographic analysis. Conceivably, such analysis may have introduced systematic error, though we feel that this is unlikely to have accounted for the bimodal distribution observed. Incompleteness of angiographic follow-up is an inherent feature of a study such as this. The handling of multiple lesions for each patient is complex owing to the potential interdependence of lesions treated in the same patient.[23 24] Thus we randomly selected a single lesion for each patient. Comparison of the distribution patterns of markers of restenosis after sirolimus-eluting stent and paclitaxel-eluting stent implantation is limited by the non-randomised nature of the
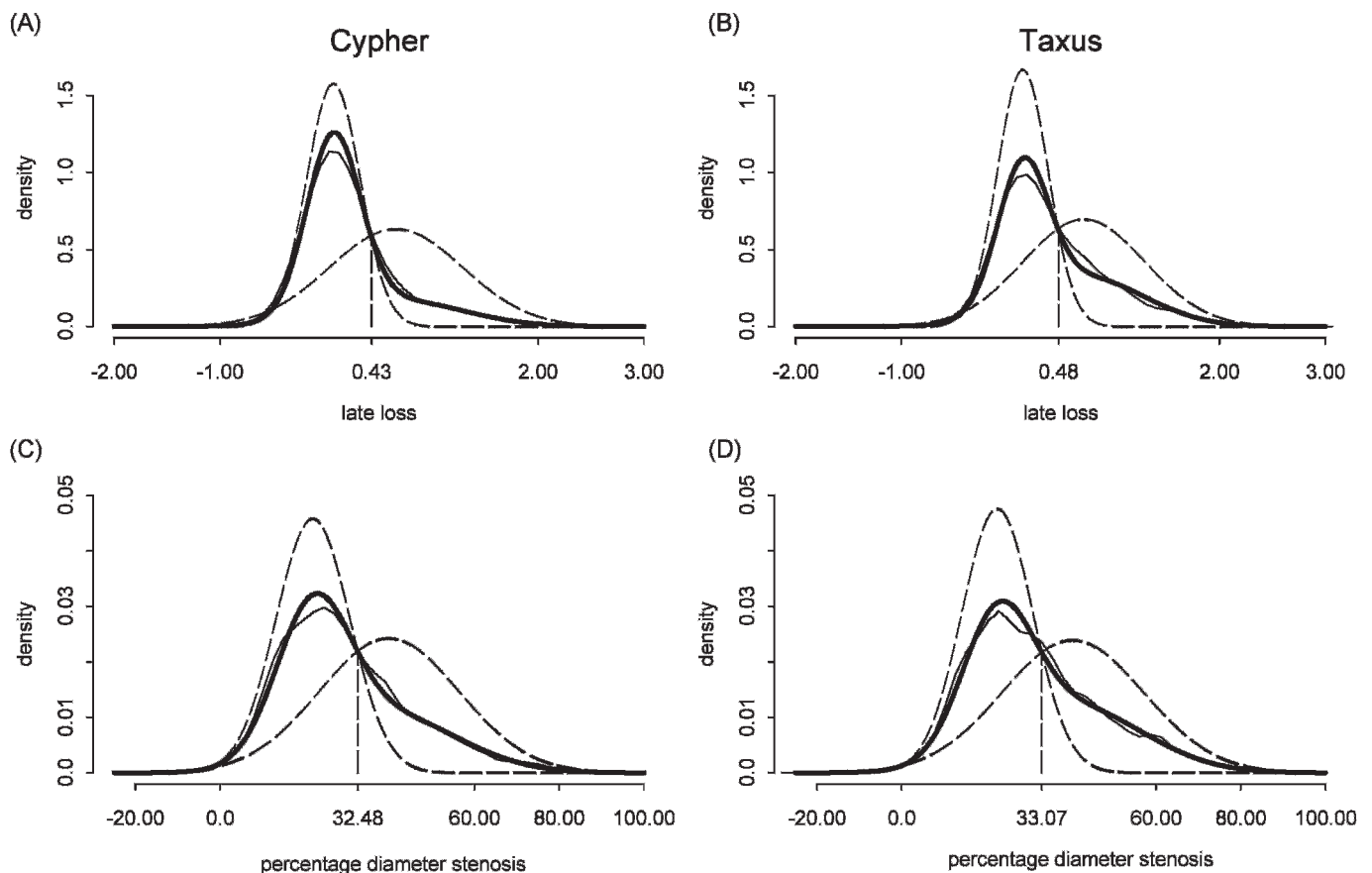
Figure 3 Distribution of late luminal loss and percentage diameter stenosis according to drug-eluting stent type. (A) Late luminal loss for Cypher stent; (B) late luminal loss for Taxus stent; (C) percentage diameter stenosis for Cypher stent; (D) percentage diameter stenosis for Taxus stent. In each panel the observed frequency distribution curve (thin solid line), two subpopulations normal distribution curves (dashed lines) and the composite distribution curve (thick solid line) are displayed; the vertical dashed line denotes the intersection point between the two subpopulation distribution curves.

patient groups. Exploratory analysis to test whether a three-group model might offer further improvements in fit found that some further refinement of a composite model was possible for LLL, though not for %DS. While further division of variable propensity subpopulations is not counter to our hypothesis, this was true only for LLL, and remaining with a bimodal distribution model affords enhanced clarity of description. Finally, while appropriate in the bare metal stent era, the choice of 6–8 months as the time point of efficacy assessment for evaluation of DES treatment effects is arguably not ideal as late loss and percentage diameter stenosis may be continuing dynamic processes at this time point.[25]

In conclusion, dedicated statistical analysis of the distribution of markers of restenosis after DES implantation confirms that such markers are non-normally distributed. A composite model based on two normal distribution curves with differing means accurately describes the data and suggests the presence of a subpopulation of lesions with a significantly higher risk of restenosis. These subpopulations may present targets for further refinements in antirestenotic technology and may also help to explain the sometime observed discordance between angiographic measures of restenosis and rates of clinical restenosis in inter-DES comparative efficacy studies.

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Heart

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Notes