Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results

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ABSTRACT

Background: Drug-eluting stent (DES) platforms devoid of durable polymer have potential to enhance long-term safety outcomes. The ISAR-TEST-3 study was a randomised trial comparing three rapamycin-eluting stents with different coating strategies. The present study examined 2-year outcomes of these patients and is the first large-scale trial to report longer-term outcomes with biodegradable polymer and polymer-free DES.

Methods: Patients with de novo coronary lesions in native vessels were randomly assigned to receive biodegradable polymer (BP; n = 202), permanent polymer (PP; Cypher; n = 202) and polymer-free (PF; n = 201) stents. The 2-year endpoints of interest were target lesion revascularisation (TLR), death/myocardial infarction (MI), stent thrombosis and delayed angiographic late luminal loss (LLL) between 6–8 months and 2 years.

Results: There were no significant differences in TLR (8.4%, 10.4% and 13.4% for BP, PP and PF stents, respectively; p = 0.19), death/MI (5.9%, 6.4% and 6.5% with BP, PP and PF respectively; p = 0.97) or stent thrombosis (definite/probable 0.5%, 1.0% and 1.0% with BP, PP and PF, respectively; p = 0.82). Paired angiographic follow-up at 6–8 months and 2 years was available for 302 patients (69.0% of eligible patients). Delayed LLL was significantly different across the treatment groups: 0.17 (0.42) mm, 0.16 (0.41) mm and −0.01 (0.36) mm for BP, PP and PF stents, respectively (p<0.001).

Conclusion: Clinical antirestenotic efficacy was maintained with all three platforms between 1 and 2 years, although angiographic surveillance showed ongoing delayed LLL with both BP and PP stent platforms. At 2 years there was no signal of a differential safety profile between the three stent platforms.

Concern exists regarding a possible excess of late thrombotic stent occlusion following drug-eluting stent (DES) implantation.[1] Such safety concerns may be linked to delayed vascular healing which has been observed following DES implantation in both animal and human studies.[2–4] While the aetiology of delayed healing is multifactorial, the persistence of polymer in the coronary milieu, beyond a time point at which its useful function has been served, may be an important factor.[5 6] This has led a number of investigators to pursue novel DES platforms that can optimise antirestenotic efficacy without recourse to permanent polymer.[7–11]

The Intracoronary Stenting and Angiographic Restenosis–Test Efficacy of Rapamycin-Eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3) study was a two-centre assessor-blinded randomised study examining the safety and efficacy of both novel polymer-free (PF) and biodegradable polymer (BP) rapamycin-eluting stents in comparison with the commercially available permanent polymer rapamycin-eluting stent (PP).[8] Results up to 1 year indicated that, whereas the antirestenotic efficacy of the PF stent was inferior to that of the PP platform, the BP stent achieved a similar antirestenotic efficacy to the PP stent. Potential benefits of DES platforms devoid of permanent polymer may be expected to appear only with longer-term follow-up.[12 13] The current analysis is the first large-scale study to report 2-year outcomes with a stent platform free from durable polymer.

METHODS

Study population and protocol

The methods of the ISAR-TEST-3 trial have been previously reported.[8] In brief, eligible patients were older than age 18 with ischaemic symptoms or evidence of myocardial ischaemia in the presence of ⩾50% de novo stenosis located in native coronary vessels. Key exclusion criteria included patients with target lesion located in the left main stem, acute myocardial infarction, cardiogenic shock, malignancies or other co-morbid conditions with life expectancy less than 12 months, known allergy to the study medications (aspirin, clopidogrel, rapamycin, stainless steel), pregnancy or positive pregnancy test.

Full details of treatment allocation, study devices and adjunctive antithrombotic therapy have been previously reported.[8] An oral loading dose of 600 mg clopidogrel was administered to all patients at least 2 hours before the intervention, regardless of whether the patient was taking clopidogrel before admission. 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 12 months and other cardiac medications according to the judgment of patient's physician (for example, β-blockers, ACE-inhibitors, statins, etc).

Data management and follow-up

Patients were followed up either by physician office visit or by telephone at 30 days, 6–8 months, 1 year and 2 years. Relevant clinical data were collected and entered into a computer database by specialised personnel of the Clinical Data Management Centre. Clinical events were adjudicated upon by an independent clinical event adjudication committee. Endpoint adjudication was fully blinded to randomly assigned stent type. Angiographic follow-up was scheduled at two time points following coronary intervention—namely, 6–8 months and 2 years. Baseline, post-procedural and follow-up coronary angiograms were digitally recorded and assessed offline in the independent quantitative angiographic core laboratory (Deutsches Herzzentrum ISAResearch Centre) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems) by two experienced operators unaware of the treatment allocation. All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerine 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).

Endpoints and definitions

The primary endpoint of interest to this current report was the need for target lesion revascularisation (TLR) at 2 years. Secondary endpoints were defined as the composite of death or myocardial infarction (MI); stent thrombosis; and delayed in-stent late luminal loss (LLL), defined as the difference between the minimal luminal diameter at 6–8-month and 2-year surveillance angiography. Patients undergoing TLR before 12 months were excluded from this angiographic analysis. The diagnosis of myocardial infarction required the presence of new Q waves on the ECG and/or elevation of creatine kinase or its MB isoform to at least three times the upper limit of normal in no fewer than two blood samples. Stent thrombosis was classified according to Academic Research Consortium criteria.[14]

Statistical analysis

The results of the primary analysis have already been published and this additional analysis is exploratory in nature. Baseline descriptive statistics are presented as frequencies and percentages for categorical variables and means (SD) or median (interquartile range) for continuous variables. Differences across groups were checked for significance with analysis of variance (continuous data) or contingency table analysis (categorical variables). Intergroup outcome comparisons were assessed using the Student t test (continuous data) and χ^2 or Fisher's exact test (where expected cell value was <5) for categorical variables. Survival and event-free status were assessed using the methods of Kaplan-Meier. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, WA, USA) was used for all analyses.

RESULTS

As previously reported a total of 605 patients were enrolled in this study: 202 patients received the BP stent, 202 were treated with the PP stent and 201 received the PF stent. Baseline clinical, angiographic and procedural characteristics were similar across all three treatment groups (table 1).

Two-year clinical outcomes

Clinical follow-up data at 2 years was available for all 605 enrolled patients (table 2). TLR was required in 17 (8.4%), 21 (10.4%) and 28 (13.9%) cases in BP, PP and PF groups, respectively (p = 0.19); these trends mirrored those observed at 1 year though in comparison with the PF stent, both polymer-based platforms showed a slightly larger number of incident cases between 1 and 2 years (fig 1). The composite of death or MI at 2 years had occurred in 14 cases (6.9%) with BP stent, 14 cases (6.4%) with PP stent and 13 cases (7.0%) with PF stent (p = 0.97) (fig 2). Overall, stent thrombosis was an infrequent event after 12 months and did not differ significantly across the treatment groups (fig 3). Definite/probable stent thrombosis occurred in one case with the BP stent, two cases (1.0%) with the PP stent and two cases (1.0%) with the PF stent (p = 0.82).

Table 1 Key baseline patient characteristics

	Overall (n = 605)	Biodegradable polymer (n = 202)	Permanent polymer (n = 202)	Polymer-free (n = 201)
Male	480 (79.3)	158 (78.2)	165 (81.7)	157 (78.1)
Age (years)	66.1 (10.7	66.5 (11.6	65.0 (10.7	66.8 (9.70
Diabetes	166 (27.4)	58 (28.7)	53 (26.4)	55 (27.2)
Insulin-requiring	63	20	18	25
Tablet-controlled	78	28	29	21
Hypertension	410 (67.8)	145 (71.8)	130 (64.4)	135 (67.2)
Current smoker	99 (16.4)	33 (16.3)	30 (14.9)	36 (17.8)
Hyperlipidaemia	416 (68.8)	144 (71.3)	129 (63.9)	143 (71.1)
Coronary disease				
Single vessel	105 (17.4)	35 (17.3)	27 (13.4)	43 (21.4)
Two vessel	169 (27.9)	54 (26.7)	63 (31.2)	52 (25.9)
Three vessel	331 (54.7)	113 (56.0)	112 (55.4)	106 (52.7)
Multivessel disease	500 (82.6)	167 (82.7)	175 (86.6)	158 (78.6)
Unstable angina	187 (30.9)	64 (31.7)	59 (29.2)	64 (31.8)
Previous myocardial infarction	199 (32.9)	65 (32.2)	68 (33.7)	66 (32.9)
Prior bypass surgery	69 (11.4)	21 (10.4)	21 (10.4)	27 (13.4)

Data shown as mean (SD) or number (percentage).

Table 2 Clinical events at 1 year and 2 years

	Biodegradable polymer (n = 202)	Permanent polymer (n = 202)	Polymer-free (n = 201)	p Value
1 year				
Myocardial infarction	3 (1.5)	4 (2.0)	5 (2.5)	0.77
Death	4 (2.0)	4 (2.0)	4 (2.0)	0.91
Death/myocardial infarction	5 (2.5)	7 (3.5)	8 (4.0)	0.69
Target lesion revascularisation	12 (5.9)	16 (7.9)	26 (12.9)	0.04
Coronary bypass surgery	1 (0.5)	3 (1.5)	3 (1.5)	0.56
Re-PCI	11 (5.4)	14 (7.0)	23 (11.4)	0.07
2 years				
Myocardial infarction	5 (2.5)	4 (2.0)	7 (3.5)	0.63
Death	7 (3.5)	10 (5.0)	8 (4.0)	0.75
Death/myocardial infarction	14 (6.9)	13 (6.4)	14 (7.0)	0.97
Target lesion revascularisation	17 (8.4)	21 (10.4)	27 (13.4)	0.26
Coronary bypass surgery	1 (0.5)	3 (1.5)	3 (1.5)	0.56
Repeat PCI	16 (7.9)	19 (9.4)	25 (12.4)	0.30

Data shown as number (percentage); PCI, percutaneous coronary intervention.

Angiographic follow-up

As previously reported angiographic follow-up at 6–8 months was available for 492 (81.3%) patients. Mean late lumen loss at 6–8-month angiographic follow-up was 0.17 (0.45) mm in the group who received a BP stent, 0.23 (0.46) mm in those receiving a PP stent and 0.47 (0.56) mm in patients treated using a PF stent ($p<0.001$). Whereas there was no significant difference between the BP and PP stent ($p = 0.17$), the PF stent was associated with a significantly higher late loss in comparison with the PP stent ($p<0.001$).

Paired angiographic follow-up at 6–8 months and 2 years was available for 302 of 438 eligible patients (69.0%; 113 excluded due to no initial 6–8 months angiogram; 54 excluded due to TLR at ⩽12 months; no significant differences in angiographic surveillance rates across the three groups, $p = 0.60$). Restricting analysis to this group only, initial mean late loss at 6–8 months was 0.10 (0.29) mm in the BP stent group, 0.14 (0.32) mm in the PP group and 0.30 (0.31) mm in the PF stent group ($p<0.001$). At second angiographic follow-up delayed late loss was also significantly different across the treatment groups: 0.17 (0.42) mm in the BP stent group, 0.16 (0.41) mm in the PP group and −0.01 (0.36) mm in the PF stent group ($p<0.001$) (table 3, fig 4).

Overall, late luminal loss at 2 years (based on latest angiographic follow-up available for the entire study population) was 0.27 (0.52) mm in the BP stent group, 0.35 (0.55) mm in the PP group and 0.46 (0.58) mm in the PF stent group ($p = 0.003$).

DISCUSSION

This ISAR TEST-3 study was a two-centre randomised trial comparing the safety and efficacy of three rapamycin-eluting stents with different coating strategies—namely, novel polymer-free and biodegradable polymer rapamycin-eluting stents and the commercially available permanent polymer rapamycin-eluting stent (Cypher). Two-year results of the ISAR-TEST-3 study are noteworthy for two reasons: (1) the occurrence of safety events beyond 12 months was rare; there was no signal of a differential safety profile across the groups out to 2 years; (2) while the prevention of clinical restenosis (TLR) was maintained with all three platforms, angiographic surveillance suggests sustained inhibition of neointimal suppression with the polymer-free platform, whereas both biodegradable polymer and durable polymer platforms were associated with a degree of ongoing late luminal loss beyond 6–8 months.

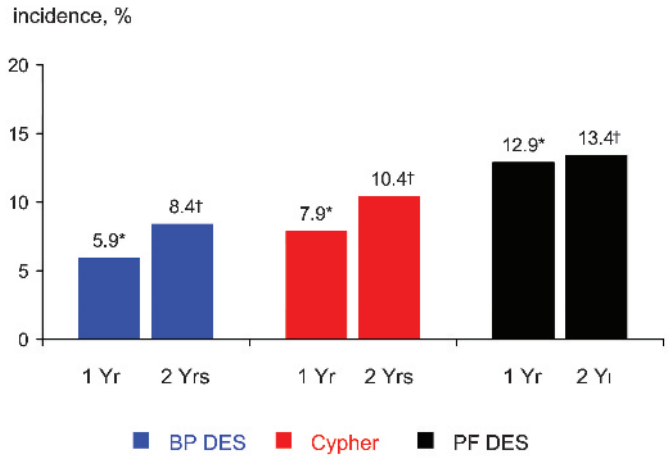

Figure 1 Clinical restenosis. Target lesion revascularisation at 1 and 2 years. *p = 0.04 for comparison across groups; †p = 0.26 for comparison across groups. BP DES = biodegradable polymer rapamycin-eluting stent; PF DES = polymer-free rapamycin-eluting stent.

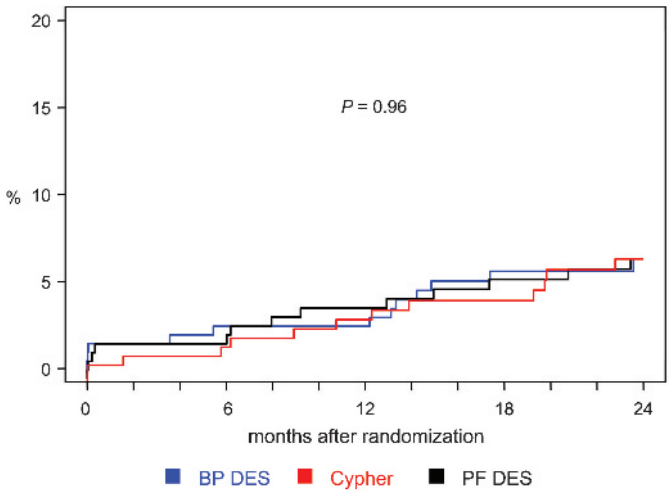

Figure 2 Kaplan-Meier estimates of death/myocardial infarction out to 2 years. BP DES = biodegradable polymer rapamycin-eluting stent; PF DES = polymer-free rapamycin-eluting stent.

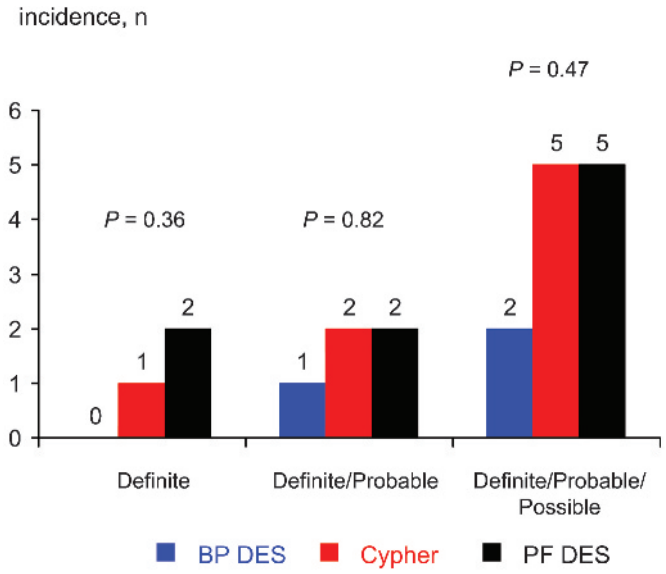

Figure 3 Rates of stent thrombosis at 2 years. Events defined according to academic research consortium criteria. BP DES = biodegradable polymer rapamycin-eluting stent; PF DES = polymer-free rapamycin-eluting stent.

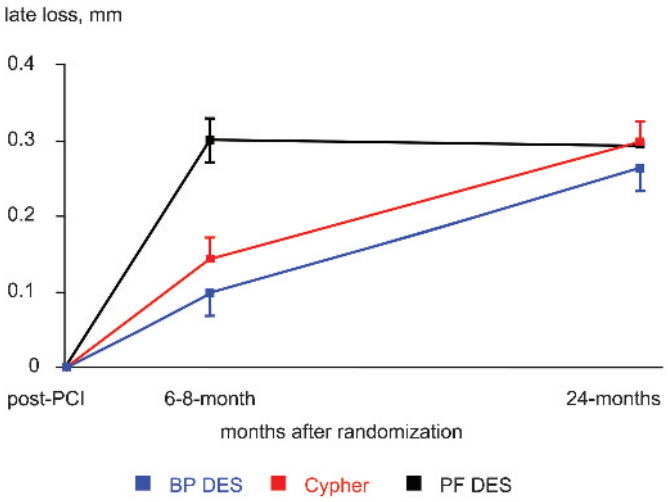

Figure 4 Temporal course of late luminal loss in subgroup of patients with paired angiographic surveillance data. Data shown as mean (SEM). Patients undergoing target lesion revascularisation at ⩽12 months were excluded. BP DES, biodegradable polymer rapamycin-eluting stent; PCI , percutaneous coronary intervention; PF DES, polymer-free rapamycin-eluting stent.

Delayed vascular healing after DES implantation has been demonstrated in animal models and in human autopsy studies[2–4] and intuitively it may be expected to have a significant aetiological role in adverse events late (>1 year) after coronary stenting. While a number of factors contribute to delayed healing, a persistent inflammatory response to durable polymer seems likely to be contributory.[5 6] Safety concerns regarding late stent thrombosis have been the main motivation behind the development of DES that can optimise antirestenotic efficacy without recourse to durable polymer. In this respect the 1-year efficacy and safety results reported with DES utilising biodegradable polymer in the ISAR-TEST-3[8] and LEADERS (Limus Eluted from A Durable versus ERodable Stent coating)[9] trials were certainly encouraging. However, the real interest lies in the longer-term safety outcomes with these stents.[12 13] The 2-year clinical results of this study are therefore noteworthy as the first available data in this field. At the current time point we have observed no signal of safety difference between the platforms with and without durable polymer. In view of the lesion and patient complexity (complex lesion morphology 74.1%; bifurcational 26.0%; mean lesion length 14.3 (6.5; diabetes 27.4%) in fact rates of stent thrombosis were very low across all three study groups. At 2 years, the rates of definite/probable stent thrombosis for BP, PP and PF stents were 0.5%, 1.0% and 1.0%, respectively.

The observation of differential delayed late loss beyond 6–8 months ("late luminal creep") across the three study arms is a noteworthy finding. The demonstration of additional late loss beyond 6–8 months with the permanent polymer DES is in keeping with previous studies such as the 2-year angiographic surveillance data from the everolimus-eluting stent arm of the SPIRIT-II trial[15] and with registry data from our institutions.[16] Long-term follow-up of the original First-in-Man (Cypher) study also showed a modest progressive reduction in luminal calibre with the permanent polymer DES (n = 26; mean late loss

Table 3 Paired angiographic follow-up data at 6–8 months and 2 years

	Biodegradable polymer (n = 126)	Permanent polymer (n = 127)	Polymer-free (n = 100)	p Value
6–8 months				
MLD, in-stent (mm)	2.42 (0.50)	2.41 (0.50)	2.30 (0.47)	0.11
MLD, in-segment (mm)	2.10 (0.51)	2.03 (0.55)	2.06 (0.53)	0.55
Diameter stenosis, in-stent (%)	14.6 (9.1)	15.8 (11.3)	17.8 (9.9)	0.07
Diameter stenosis, in-segment (%)	26.1 (11.2)	29.7 (13.0)	27.1 (11.1)	0.05
Late luminal loss, in-stent (mm)	0.10 (0.29)	0.14 (0.32)	0.30 (0.31)	<0.001
Binary angiographic restenosis	4 (3.2)	8 (6.3)	5 (5.0)	0.51
2 years				
MLD, in-stent (mm)	2.25 (0.59)	2.25 (0.59)	2.31 (0.57)	0.67
MLD, in-segment (mm)	2.10 (0.56)	2.02 (0.55)	2.06 (0.55)	0.55
Diameter stenosis, in-stent (%)	20.1 (14.5)	21.0 (16.8)	18.0 (13.0)	0.30
Diameter stenosis, in-segment (%)	25.5 (14.2)	29.5 (15.1)	27.2 (12.7)	0.08
Delayed late luminal loss, in-stent (mm)	0.17 (0.42)	0.16 (0.41)	−0.01 (0.36)	<0.001
Binary angiographic restenosis	8 (6.3)	11 (8.7)	4 (4.0)	0.37

Data shown as mean (SD) or number (percentage). Lesion-based analysis. Patients undergoing target lesion revascularisation at ⩽12 months were excluded.
MLD, minimal luminal diameter.

between 12 months and 4 years was 0.17 mm), though in fact this was driven predominantly by delayed late loss in the fast-release subgroup (which interestingly had early release-kinetics approaching those of a polymer-free platform).[17] Despite significant performance differences between "limus" drugs and paclitaxel,[18–20] a similar catch-up effect has also been noted with the permanent polymer Taxus stent.[21] On the other hand the observation of ongoing late loss beyond 6–8 months with the biodegradable polymer stent is novel and perhaps somewhat surprising. Bench testing suggests that the biopolymer is completely degraded at 6–9 weeks and it might be expected that its late antirestenotic performance would resemble that of a polymer-free DES or a bare-metal stent (that is, no further late loss or even a small late increase in luminal calibre due to neointimal contraction).[22 23] One possible explanation is that inflammatory reaction associated with biodegradable polymer breakdown is significant and may be biologically persistent.[24]

It might also be proposed that the absence of delayed late loss with the polymer-free stent is directly related to the more rapid initial drug-release (~75% in the first 10 days), and consequently relatively higher initial late loss at 6–8 months (compared to the other two stent arms), perhaps reflective of a more complete and earlier vessel healing. This would be in keeping with the low rate of late TLR seen with the Endeavor stent, for example, which has a very rapid drug-release profile (~95% in the first 14 days) and a high initial late loss (~0.65 mm).[25 26] However, early antirestenotic performance alone cannot fully account for subsequent differences in delayed late loss, as despite a baseline 6–8 month LLL very similar to that of the polymer-free platform, the Taxus stent also demonstrates a significant delayed late loss.[21]

Limitations

The primary design of the ISAR-TEST-3 trial was a non-inferiority comparison of BP and PF stents against the commercially available PP stent in terms of the endpoint of late loss at 6–8 months. Additional comparisons at 2 years may be regarded as post hoc. Regarding safety outcomes this study was not powered to detect a difference in rarely occurring clinical events such as stent thrombosis. Longer follow-up with larger patient numbers should be the subject of future investigation. Similarly, the study was not designed to detect a difference in late angiographic endpoints such as delayed late loss. Furthermore, inherent in the analysis of delayed late loss, is the exclusion of patients who require TLR at initial 6–8-month follow-up because at this time point, time zero is considered to be reset. As a result, when we consider data on the subset of patients with paired follow-up angiographic data, patients with higher initial late loss at 6–8 months tend to be excluded as they are likely to have undergone initial TLR. Conclusions based on angiographic follow-up data are based on incomplete observations—though in this respect it is notable that the trends in delayed late loss were similar to those in delayed TLR (for which data was available for the entire cohort).

CONCLUSION

The 2-year results of ISAR-TEST-3 provide reassurance regarding maintained antirestenotic efficacy of stent platforms devoid of permanent polymer. Angiographic surveillance however suggests that a biodegradable polymer stent is associated with a similar degree of "late luminal creep" to that of a permanent polymer DES, something not observed with a polymer-free platform. In terms of safety outcomes, there were no significant differences across stent groups regarding rates of stent thrombosis or death/myocardial infarction. Longer-term follow-up with larger patient numbers should be the subject of future investigation.

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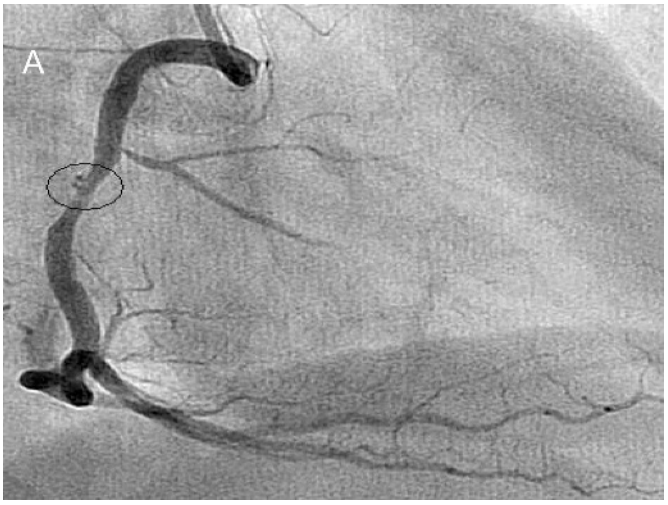
Images in cardiology

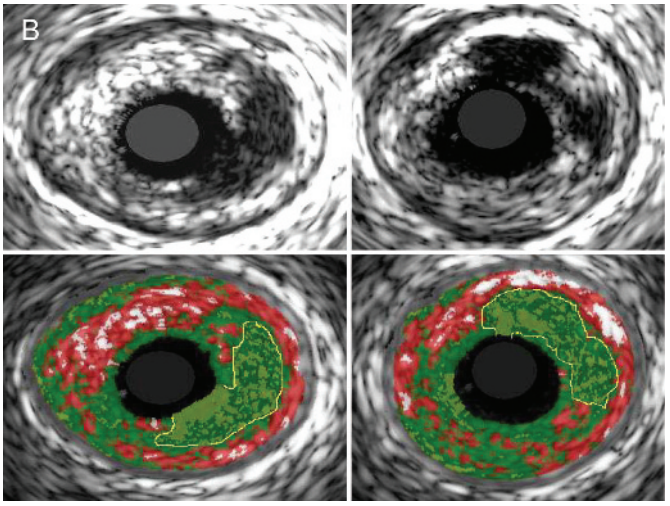
Intravascular ultrasound and virtual histology interpretation of plaque rupture and thrombus in acute coronary syndromes

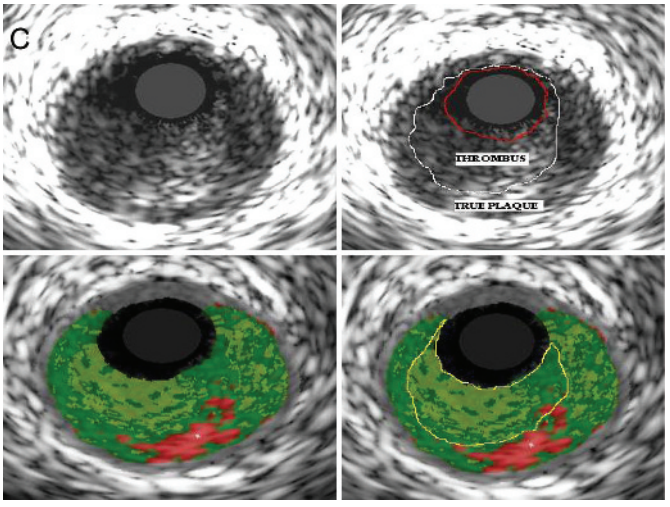
A 62-year-old woman with a history of a thrombolysed inferior ST elevation myocardial infarction was referred to our tertiary cardiac centre for urgent interventional treatment of a right coronary artery lesion. Initial angiographic shots of the culprit lesion (panel A) showed an appearance consistent with an ulcerated lesion and also some distal lesion haziness.

Subsequent in-house study with intravascular ultrasound (IVUS) and IVUS-VH analysis showed extensive evidence of plaque rupture at the region of maximum plaque burden (panel B). The corresponding virtual histology frames show that the residual plaque burden at this site is of a ''high-risk'' nature with abundant necrotic core (red) and speckled calcification (white), in keeping with a previous thin-cap fibroatheroma. Fibrous stable plaque is shown as dark green and fibrofatty plaque (light green) is erroneously classified here within the plaque rupture/lumen extension, as outlined in yellow.

For the intraluminal thrombus at the distal lesion edge; if close attention is not paid to the moving grey-scale IVUS images, then the slowing of intraluminal blood speckling to the ''squirming'' composition of thrombus can easily be mistaken later for plaque. Panel C shows that if the echo reflection from the thrombus is included as plaque burden, then again classification as fibrofatty plaque occurs. Usually there is evidence of a ''double lumen'' sign, indicating where the thrombus meets the true luminal surface as highlighted in this example.







The current generation of the Volcano IVUS-VH algorithm cannot recognise or trace ruptured plaque or thrombosis. These images are an excellent illustration of the ability of IVUS and IVUS-VH to show plaque rupture and associated high-risk plaque. It also highlights potential pitfalls for researchers or clinicians, who may not have been aware of this limitation, to ensure they do not erroneously misclassify thrombus or plaque rupture as fibrofatty plaque. A consensus statement on IVUS-VH acquisition and interpretation is expected soon.

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Heart

Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results

R A Byrne, S Kufner, K Tiroch, S Massberg, K-L Laugwitz, A Birkmeier, S Schulz, J Mehilli and for the Intracoronary Stenting and Angiographic Restenosis-Test Efficacy of Rapamycin-Eluting STents with Different Polymer Coating Strategies (ISAR-TEST-3) Investigators

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