Bioresorbable Scaffold Thrombosis: Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms and Predictors

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Supplemental material

Methods

Devices

Absorb BVS were available in Mainz starting from May 2012, in Frankfurt in March 2013, in Fribourg in June 2012 and in Luzern in Juli 2013. The database includes all patients treated with BVS until January 2015.

Quantitative coronary angiography

Digital angiograms were analysed with the use of an automated edge-detection system (Xcelera, Philips, the Netherlands). Quantitative measurements included lesion length, MLD (minimum lumen diameter), RVD (reference vessel diameter) and TIMI (thrombolysis in myocardial infarction) flow before and after BVS implantation using standardized definitions. Repeatability and reproducibility data are reported elsewhere(1). The % stenosis before implantation and % residual stenosis after BVS implantation were calculated as

$$\frac{100 * (RVD - MLD)}{RVD}$$

The maximum "footprint", i.e. the maximum % of the vascular circumference occupied by struts, was calculated as:

$$\frac{100 * Outer\ BVS\ surface}{BVS\ length * (\pi MLD)}$$

That is, the outer BVS surface per mm divided by the lumen circumference at the level of the MLD.

As such, the maximum footprint reflects the ratio of the outer surface of the BVS struts to the vascular circumference at the level of the MLD. In a OCT cross-section, this would be the ratio of the white to the blue line.
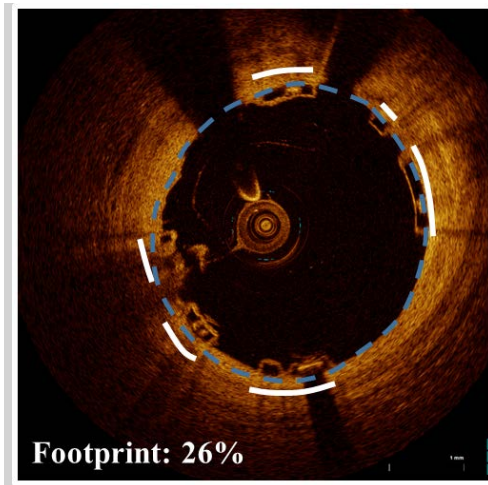
Data on the outer BVS surface were kindly provided by Dr Rapoza of Abbott Vascular.

The scaled residual stenosis was calculated as

$$\frac{100 * (nominal\ BVS\ diameter\ -\ MLD)}{(nominal\ BVS\ diameter)}$$

and reflects the degree of deployment of the BVS as compared to the theoretical nominal value. Of note, in cases where the BVS is implanted or postdilated to a diameter larger than the nominal (MLD larger than nominal BVS diameter), this value becomes negative. The scaled residual stenosis reflects the expansion of the BVS

rather than that of the vessel and therefore provides information that is slightly different from % residual stenosis: a negative scaled stenosis, for instance, reflects the expansion of the BVS above its nominal value, independently of the whether the RVD was reached or not.

"Undersizing" was defined as the implantation of a BVS with a nominal diameter 20% or more smaller than the RVD, and calculated as the ratio of

$$\frac{nominal\ BVS\ diameter}{RVD} < 0.8$$

Correspondingly, oversizing was

$$\frac{nominal\ BVS\ diameter}{RVD} > 1.2$$

Further definitions and reproducibility data are presented in a recent publication(1).

Selection of the control group and matching

For the selection of the control group, 2 patients with BVS implantation and no ScT were matched for each ScT patient. For matching, the clinical variables which showed a P<0.05 in the multivariable analysis were used. As well, patients were matched using the following criteria which clearly interfere with QCA measurements: BVS diameter and length, acute coronary syndrome and complete occlusion at the index procedure. Patients and controls were identical for these variables. Analyses were performed treating the two groups as independent samples. For the assessment of stent implantation, standardized definitions were used(2). While intracoronary imaging

methods allow acquisition at a higher resolution and are in principle better suited for this analysis, definitions are as yet less standardized and these methods are less suited for large databases such as the present one.

The impact of a BVS-specific implantation protocol

Triggered by the initial observations of an unexpectedly high incidence of ScT(3), and based on preliminary findings of incomplete BVS expansion in cases of ScT(4) and improved acute results using 1:1 ballon:vessel predilation and postdilation(5), a major focus was put internationally on strenghtening BVS implantation recommendations. By review of the internal mortality and morbidity conferences, a precise timepoint (January 2014) was identified, in which these recommendations were put into place in our Institutions. The outcome of patients treated during 2012 and 2013 ("early experience") was compared to that of patients treated in 2014 ("BVS-specific protocol"). In order to limit the effect of confounders, this analysis was restricted to a subgroup of 4 expert operators who consistently applied the same implantation techniques.

 Description of implantation procedures:

   During 2012 and 2013 ("early experience"), BVS were implanted using traditional "metal DES" methods, consisting of predilation using undersized semicompliant balloons and no systematic use of postdilation.

   Starting January 2014, the following set of recommendations, which was later partially included in the 2015 experts review(6), was implemented:

1- Predilation using a noncompliant balloon of the same size as the RVD (several dilations were allowed until a 1:1 ratio angiographically was achieved).

2- BVS implantation only in case of full expansion of the PTCA balloon as demonstrated by angiography in two orthogonal planes (i.e. absence of any indentation >10%).

3- Implantation of a BVS with pressures of the same size as the RVD (1:1:1 ratio RVD:predilation ballon:BVS) at a pressure comprised between 10 and 12 ATM.

4- Postdilation with NC Balloons of the same size or, when necessary based on reassessment of RVD, up to a maximum of 0.5mm larger at a pressure of 14-16ATM.

The implantation strategy did not mandate the use of imaging techniques, which was left to the operator´s discretion. Even though not systematically used, it needs to be acknowledged here that optical coherence tomography allows detecting stent underexpansion, malapposition, and, at later time points, the presence of evaginations, uncovered struts, and neoatherosclerosis as risk factors for stent thrombosis(7) and might therefore be of further help. Further, intracoronary imaging provides information on the nature of coronary lesion, the presence of calcifications and the need of postdilation(6).

Statistical analysis

Continuous variables are presented as mean±SD or median[interquartile range - IQR] and were compared using a Student's unpaired t-test, Mann-Whitney, Kruskall-Wallis or analysis of variance based on the inspection of the Q-Q plots. Categorical

variables are presented as counts and percentages, and were compared using chi-square or Fisher's exact tests, as appropriate. Kaplan-Meier curves were built to derive the event rates and plot time-to-event curves. Cox proportional hazards analysis was performed to identify the clinical and procedural parameters relevant for the endpoint (the covariates screened in univariate models are listed in Tables 1, 2, 4, 5). A multivariable analysis of parameters selected at P<0.20 by univariate analysis was performed to identify the independent predictors of ScT and to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Similar uni- and multivariable analysis was repeated to address the hypothesis that the introduction of a BVS-specific implantation strategy would be associated with a reduction in the incidence of ScT. To address potential bias due to non-random assignment to implantation strategies, a propensity score model was built from a logistic regression model, using the implantation strategy as an outcome. Covariates were first screened at P<0.20, and the covariates meeting this criterion were jointly entered into a multivariable model, subjected to backward elimination, using the Akaike information criterion as a selection and stopping criterion. The resulting propensity score was subsequently used for adjustment in the Cox models.

The impact of QCA parameters was assessed using a nested case-control design. Two control patients were matched for each ScT patient as described above. Apart from these criteria, the patients were randomly chosen from the overall database. Conditional logistic regression models were used for univariate screening with P<0.20, to obtain covariates for subsequent adjustment when evaluating QCA parameters in multivariable models. Since these parameters are mathematically correlated with each other, separate analyses

were performed for MLD, RVD, and % scaled residual stenosis. To investigate potentially promising cutoffs, we dichotomized QCA parameters, and for each a grid of values of sensitivity and specificity were calculated using ROC analysis, using observation weights proportional to the number of potential controls available for each case to accommodate the nested case-control design. The positive predicted value was calculated based on the prevalence of 3% observed in the general database. Statistical tests and analyses were performed with Medcalc (Mariakerke, Belgium), SPSS22 (IBM, USA), and using the R statistical environment (R version 3.1.3).

Results

QCA analysis

Uni- and multivariable Cox regression analyses were conducted to assess the association of QCA parameters with ScT (Tables 2-10S). These analyses confirmed that MLD post-PCI, RVD, residual scaled stenosis, and maximum footprint are independently associated with the risk of ScT, the largest effect being associated with footprint. In contrast, the % residual stenosis was not significantly associated with ScT.

Implantation protocol analysis

Prior to enactment of BVS-specific implantation recommendations ("early experience" group), 369 patients were treated with 542 BVS. This represented 20% of the patients undergoing PCI and 19% of the stents implanted during the same period. Following the implementation of the BVS-specific implantation protocol, 415 BVS were implanted in

292 patients, i.e. 24% of the patients undergoing PCI and 26% of the stents used (both P=0.01).

A number of clinical or procedural characteristics showed relevant differences between the two periods (Tables 6 and 7S): the prevalence of hypertension, hyperlipidemia and diabetes, as well as the prevalence of lesions requiring overlapping scaffolds were higher in the patients treated in 2014. In contrast, the LVEF of patients treated in 2014 was lower. Prasugrel was prescribed more frequently and ticagrelor less frequently in 2014. Most importantly, postdilation was performed more systematically in 2014. In multivariable analysis, while none of the clinical and procedural characteristics (except for treatment of ostial lesions) was associated with differences in the incidence of ScT, the implementation of a BVS-specific implantation strategy was associated with ~ 70% reduced incidence of events, corresponding to a HR of 0.26[0.08-0.90] (Table 4).

Table 1. Quantitative coronary analysis – descriptive statistics. All in-BVS analysis.

	Pre-procedure			After BVS implantation		
	BVS Thrombosis (n=42)	Control (n=84)	P between groups	BVS Thrombosis (n=42)	Control (n=84)	P between groups
Stenosis length, mm	15.8±7.3	13.4±0.1	0.111			
MLD, mm	0.66±0.59	0.68±0.51	0.849	2.39±0.58	2.85±0.49	0.000006
RVD, mm	2.77±0.58	3.13±0.66	0.003	2.93±0.58	3.41±0.52	0.000015
TIMI, n of pts (0,1,2,3)	15,2,19,48	7,6,11,18	0.057	0,0,20,64	0,0,2,40	0.016
% Stenosis	76±20	77±16	0.660	19±12	16±7	0.157
Maximum footprint, %	-	-		43±11	35±6	0.0000004
Scaled residual stenosis	-	-		0.21±0.18	0.07±0.14	0.000002
Undersizing, n(%)				2(5%)	18(21%)	0.019
Oversizing, n(%)				10(24%)	3(4%)	0.0009

Table 2. Analysis of the predictors of ScT in the QCA population.

Covariate	P	HR	95%CI
Male	0.644	0.81	0.33-1.99
Age years	0.237	1.02	0.99-1.06
Diabetes	0.061	0.33	0.11-1.05
Family History	0.732	0.84	0.3-2.34
GPIIbIIIA	0.268	0.54	0.19-1.6
Hyperlipidemia	0.793	1.11	0.51-2.39
Hypertension	0.357	0.66	0.27-1.61
Smoking	0.472	1.37	0.58-3.19
Prior stroke TIA	0.726	0.67	0.07-6.41
Prior CABG	0.488	2.00	0.28-14.2
Prior PCI	0.189	1.78	0.75-4.21
eGFR	0.83	1.00	0.99-1.01
N of vessels treated	0.79	0.89	0.39-2.02
Vessel treated	0.011	0.58	0.37-0.88
Lesion type B2 or C	0.312	0.68	0.32-1.44
Bifurcation	0.910	1.07	0.32-3.59
Proximal	0.545	1.25	0.61-2.54
Mid-coronary	0.454	0.75	0.37-1.59
Distal	0.850	0.90	0.29-2.75

ACS	0.868	0.92	0.35-2.45
Overlap	0.054	3.93	0.98-15.77
Prasugrel	0.04	0.39	0.16-0.96
Ticagrelor	0.147	1.89	0.8-4.48
MLD	0.826	0.92	0.41-2.02
RVD	0.001	0.22	0.08-0.55
% Stenosis before PCI	0.618	0.99	0.97-1.02
MLD after PCI	0.000	0.09	0.03-0.28
RVD after PCI	0.000	0.1	0.03-0.31
Residual stenosis	0.182	1.03	0.991.07
Scaled residual stenosis	0.000	462.92	20.15-10634.73
Maximum footprint	0.000	1.16	1.08-1.25

Table 3. Multivariable analysis including MLD before PCI.

Covariate	P	HR	95% CI
Diabetes	0.094	0.33	0.09-1.21
Prior PCI	0.190	1.96	0.72-5.36
Overlap	0.084	4.00	0.83-19.20
Vessel treated	0.062	0.64	0.41-1.02
Prasugrel	0.06	0.33	0.11-1.05
Ticagrelor	0.919	0.95	0.33-2.74
MLD	0.784	0.88	0.35-2.22

Table 4. Multivariable analysis including RVD before PCI

Covariate	P	HR	95% CI
Diabetes	0.215	0.43	0.12-1.63

Prior PCI	0.198	1.94	0.71-5.35
Overlap	0.064	4.86	0.91-25.81
Vessel treated	0.167	0.70	0.42-1.16
Prasugrel	0.208	0.48	0.15-1.51
Ticagrelor	0.797	1.16	0.37-3.67
RVD	0.014	0.27	0.1-0.77

Table 5. Multivariable analysis including the % stenosis before PCI

Covariate	P	HR	95% CI
Diabetes	0.086	0.32	0.09-1.18
Prior PCI	0.229	1.85	0.68-5.05
Overlap	0.078	4.19	0.85-20.64
Vessel treated	0.061	0.64	0.41-1.02
Prasugrel	0.061	0.33	0.11-1.05
Ticagrelor	0.883	0.92	0.32-2.66
% Stenosis	0.815	1.00	0.97-1.03

Table 6. Multivariable analysis including the MLD after PCI

Covariate	P	HR	95% CI
Diabetes	0.157	0.35	0.08-1.51
Prior PCI	0.162	2.40	0.70-8.19
Overlap	0.106	4.31	0.74-25.32
Vessel treated	0.247	0.72	0.41-1.26
Prasugrel	0.354	0.55	0.15-1.97
Ticagrelor	0.33	2.06	0.49-8.65
POST MLD	0.001	0.05	0.01-0.28

Table 7. Multivariable analysis including the RVD after PCI

Covariate	P	HR	95% CI
Diabetes	0.184	0.41	0.11-1.53
Prior PCI	0.453	1.51	0.52-4.42
Overlap	0.183	3.19	0.58-17.64

Vessel treated	0.459	0.82	0.48-1.39
Prasugrel	0.315	0.53	0.15-1.83
Ticagrelor	0.542	1.48	0.42-5.26
POST RVD	0.002	0.13	0.04-0.46

Table 8. Multivariable analysis including the residual stenosis after PCI

Covariate	P	HR	95% CI
Diabetes	0.106	0.34	0.09-1.26
Prior PCI	0.131	2.20	0.79-6.14
Overlap	0.078	4.13	0.85-20.02
Vessel treated	0.038	0.60	0.37-0.97
Prasugrel	0.066	0.33	0.10-1.08
Ticagrelor	0.956	0.97	0.32-2.92
Residual stenosis	0.071	1.05	0.1-1.10

Table 9. Multivariable analysis including the scaled residual stenosis after PCI

Covariate	P	HR	95% CI
Diabetes	0.192	0.39	0.09-1.61
Prior PCI	0.146	2.36	0.74-7.49
Overlap	0.072	5.40	0.86-33.93
Vessel treated	0.179	0.69	0.4-1.19
Prasugrel	0.255	0.48	0.14-1.69
Ticagrelor	0.401	1.81	0.45-7.23
Scaled residual stenosis	0.001	1714.38	20.07-146454.09

Talble 10. Multivariable analysis including the maximum footprint

Covariate	P	HR	95% CI
Diabetes	0.136	0.30	0.06-1.47
Prior PCI	0.152	2.43	0.72-8.2
Overlap	0.149	3.81	0.62-23.47
Vessel treated	0.176	0.68	0.39-1.19
Prasugrel	0.371	0.54	0.14-2.06
Ticagrelor	0.393	1.85	0.45-7.65
Maximum footprint	0.001	1.20	1.08-1.33

Table 11. Implantation protocol analysis – patient and lesion characteristics divided by the presence or absence of ScT during follow-up.

	All patients	Patients without thrombosis (n=640)	In BVS Thrombosis (n=21)	P
Patient-level analysis				
Male sex	526/661(80%)	506/640(79%)	17/21(81%)	0.939
Age, years	62(54-73)	62(54 – 73)	61(54.5 - 69.3)	0.464
Hypertension	478/661(72%)	461/640(72%)	17/21(81%)	0.662
Hyperlipidemia	268/660(41%)	260/639(41%)	8/21(38%)	0.954
Diabetes	140/661(21%)	137/640(21%)	3/21(14%)	0.72
Smoking	272/658(41%)	263/637(41%)	9/21(43%)	0.993
Previous PCI	186/659(28%)	181/638(28%)	5/21(24%)	0.886
Previous CABG	14/661(2%)	14/640(2%)	0/21(0%)	0.777
History of stroke	27/661(4%)	27/640(4%)	0/21(0%)	0.618
ACS STEMI	392/661(59%) 164/661(25%)	379/640(59%) 160/640(25%)	13/21(62%) 4/21(19%)	0.956 0.715
eGFR, ml/min	82±23	82±22	92±33	0.064
LVEF, %	52±8	52±8	52±8	0.994
Number of vessels treated	1.1±0.4	1.1±0.4	1.2±0.4	0.397
Number of BVS implanted	1.4±0.9	1.4±0.9	1.6±0.9	0.5000
Mean BVS diameter, mm	3.0±0.4	3.0±0.4	3.0±0.3	0.733
Minimum BVS diameter, mm	3.0±0.4	3.0±0.4	3.0±0.4	0.775
Total BVS length, mm	18(18-30)	18(18-30)	28(18- 46)	0.255

Overlap	86/650(13%)	82/630	4/20	0.567
Total BVS surface, cm^2	1.97(1.81-3.08)	1.97(1.81-3.08)	2.76(1.81 - 4.69)	0.066
Total outer BVS surface, cm^2	0.58(0.52-0.91)	0.58(0.52-0.91)	0.79(0.52 - 1.36)	0.067
IIbIIIa inhibitors	176/660(27%)	172/640	4/20	0.666
DAPT Type				0.548
Clopidogrel	200/661(30%)	197/640	3/21	0.168
Prasugrel	331/661(50%)	319/640	12/21	0.663
Ticagrelor	128/661(19%)	122/640	6/21	0.421
Predilation	656/661(99%)	636/640	20/21	0.2869
Postdilation	365/656(56%)	354/636	11/20	0.865
Lesion-level analysis		**N=764**	**N=21**	
Lesion type B2 or C	327/785(42%)	315/764	12/21	0.217
Bifurcation lesion	96/673(14%)	94/655	2/18	0.926
Ostial lesion	60/785(8%)	55/764	5/21	0.016

Table 12. Implantation protocol – patient and lesion characteristics divided by treatment group.

	Early experience group (n=369)	BVS implantation protocol (n=292)	P
Patient-level analysis			
Male sex	293/369(80%)	230/292(79%)	0.788
Age, years	62(54–73)	62(54-72)	0.775
Hypertension	252/369(68%)	226/291(78%)	0.008
Hyperlipidemia	135/369(37%)	133/290(46%)	0.020
Diabetes	68/369(18%)	72/291(25%)	0.061
Smoking	161/369(44%)	111/290(38%)	0.182
Previous PCI	101/368(27%)	85/291(29%)	0.168
Previous CABG	11/368(3%)	3/291(1%)	0.146
History of stroke	16/367(4%)	11/291(4%)	0.86
ACS STEMI	215/369(58%) 100/369(27%)	177/292(61%) 64/292(22%)	0.572 0.150
eGFR, ml/min	84±24	81±22	0.116
LVEF, %	54±8	51±9	0.001
Number of vessels treated	1.1±0.4	1.1±0.4	0.182
Number of BVS implanted	1.5±0.9	1.4±0.9	0.493
Mean BVS diameter, mm	3.0±0.4	3.0±0.4	0.172
Minimum BVS diameter, mm	2.90.4	3.0±0.4	0.193
Total BVS length, mm	27.8±18.5	27.7±19.3	0.944
Overlap	35/365(10%)	51/285(18%)	0.003

Total BVS surface, cm^2	1.97(1.81 – 3.08)	1.81(1.35 – 2.76)	0.637
Total outer BVS surface, cm^2	0.58(0.52 – 0.91)	0.58(0.40 – 0.79)	0.647
IIbIIIa inhibitors	99/368(27%)	77/291(26%)	0.485
Clopidogrel	112/369(30%)	88/292(30%)	0.511
Prasugrel	169/369(46%)	162/292(55%)	0.017
Ticagrelor	87/369(24%)	41/292(14%)	0.003
Predilation	367/368(100%)	289/292(99%)	0.330‡
Postdilation	111/364(30%)	254/292(87%)	$4*10^{-51}$
Lesion-level analysis			
Lesion type B2 or C	193/430(45%)	137/355(39%)	0.089
Bifurcation lesion	74/343(21%)	22/330(7%)	0.001
Ostial lesion	31/430(7%)	29/354(8%)	0.712

‡Fisher´s test

Figures

Figure 1. Incidence of ScT in the four centers. No difference was observed.
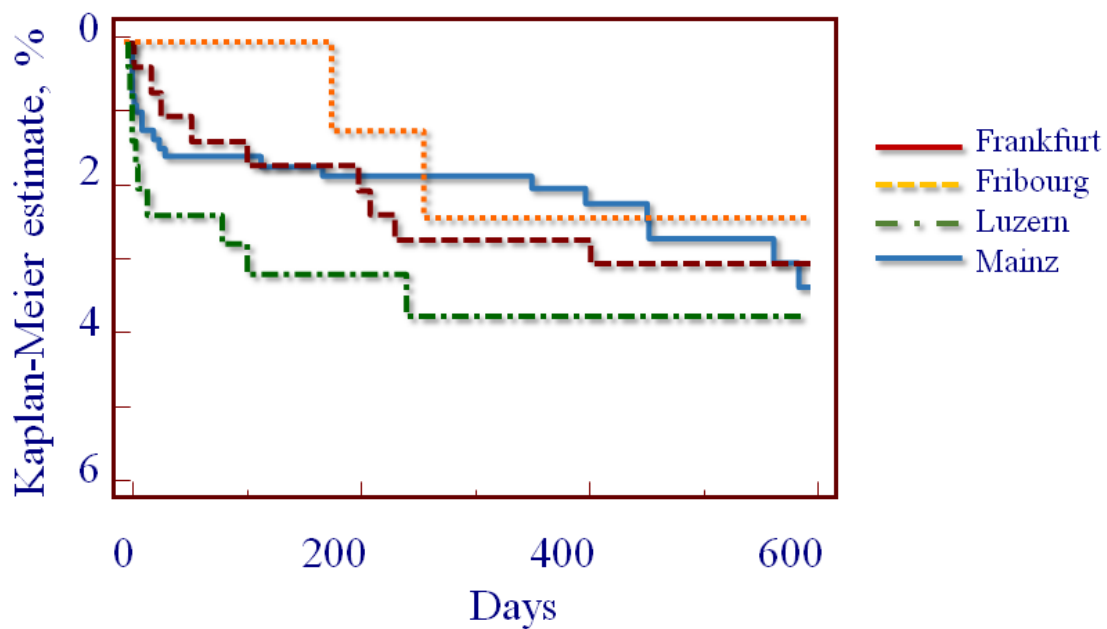
1. Gori TS, E; Hink, U; Kress, M; Weiers, N; Weissner, M; Jabs, A; Wenzel, P; Capodanno, D; Münzel, T. Clinical, Angiographic, Functional and Imaging Outcomes 12 Months after Implantation of Drug-Eluting Bioresorbable Vascular Scaffolds in Acute Coronary Syndromes. JACC Cardiovascular interventions 2015.
2. Garcia-Garcia HM, Serruys PW, Campos CM et al. Assessing bioresorbable coronary devices: methods and parameters. JACC Cardiovascular imaging 2014;7:1130-48.
3. Gori T, Schulz E, Hink U et al. Early outcome after implantation of Absorb bioresorbable drug-eluting scaffolds in patients with acute coronary syndromes. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2014;9:1036-41.
4. Gori T, Schulz E, Munzel T. Immediate, acute, and subacute thrombosis due to incomplete expansion of bioresorbable scaffolds. JACC Cardiovascular interventions 2014;7:1194-5.

5.   Brown AJ, McCormick LM, Braganza DM, Bennett MR, Hoole SP, West NE. Expansion and malapposition characteristics after bioresorbable vascular scaffold implantation. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2014;84:37-45.

6.   Tamburino C, Latib A, van Geuns RJ et al. Contemporary practice and technical aspects in coronary intervention with bioresorbable scaffolds: a European perspective. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2015;10.

7.   Ong DS, Jang IK. Causes, assessment, and treatment of stent thrombosis-intravascular imaging insights. Nature reviews Cardiology 2015.