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# Bioresorbable Coronary Scaffold Thrombosis

## Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors

Serban Puricel, MD,[a] Florim Cuculi, MD,[b] Melissa Weissner, MTA,[c] Axel Schmermund, MD,[d] Peiman Jamshidi, MD,[b] Tobias Nyffenegger, MD,[b] Harald Binder, PhD,[e] Holger Eggebrecht, MD,[d] Thomas Münzel, MD,[c] Stephane Cook, MD,[a] Tommaso Gori, Dott Med Chir, PhD[c]

## ABSTRACT

**BACKGROUND** Recent reports suggest an elevated incidence of bioresorbable vascular scaffold (BVS) thrombosis (scaffold thrombosis [ScT]).

**OBJECTIVES** This study investigated occurrence rates, clinical and angiographic characteristics, and possible mechanisms of ScT in all-comer patients undergoing BVS implantation at 2 German and 2 Swiss hospitals.

**METHODS** A total of 1,305 consecutive patients (mean age 64 years, 78% male) who received 1,870 BVS (mean 1.4 ± 0.8 BVS/patient) were enrolled. Clinical/procedural characteristics, mortality, and ScT data at 485 days (range 312 to 652 days) were examined.

**RESULTS** ScT occurred in 42 patients. The incidence of probable and definite ScT was 1.8% at 30 days and 3.0% at 12 months, without differences among centers ($p = 0.60$). A total of 22 (52%) ScTs presented as ST-segment elevation myocardial infarction and 6 (17%) as sudden cardiac death. In multivariable analysis, ostial lesions ($p = 0.049$) and impaired left ventricular ejection fraction ($p = 0.019$) were independently associated with ScT. Nine (21%) of the ScTs occurred in patients who had suspended dual antiplatelet therapy, in 6 cases prematurely. Lower post-procedural minimum lumen and reference vessel diameters were hallmarks of ScT (all $p < 0.0001$). The risk of ScT appeared to rapidly increase for post-procedural minimum lumen diameters below 2.4 mm (for the 2.5- to 3.0-mm BVS) and 2.8 mm (for the 3.5-mm BVS). When a BVS-specific implantation strategy was implemented, 12-month ScT rates fell from 3.3% to 1.0%, an effect that remained significant when adjusted for multivariable propensity score ($p = 0.012$; hazard ratio: 0.19; 95% confidence interval: 0.05 to 0.70).

**CONCLUSIONS** The 12-month incidence of ScT reached 3% and could be significantly reduced when an optimized implantation strategy was employed. (retrospective multicentric registry and Mainz Intracoronary Database. The Coronary Slow-flow and Microvascular Diseases Registry [MICAT]; NCT02180178) (J Am Coll Cardiol 2016;67:921–31)


From the [a]Department of Cardiology, University & Hospital Fribourg, Fribourg, Switzerland; [b]Department of Cardiology, Luzerner Kantonsspital, Luzern, Switzerland; [c]Zentrum für Kardiologie, University Hospital Mainz, Mainz, Germany, and German Center for Cardiac and Vascular Research (DZHK), Standort Rhein-Main, Mainz, Germany; [d]Cardioangiologisches Centrum Bethanien, Frankfurt am Main, Germany; and the [e]Institute of Medical Biostatistics, Epidemiology and Informatics, University Hospital Mainz, Mainz, Germany. Dr. Cuculi has received lecture fees from Abbott Vascular; and has received unrestricted grants from Abbott Vascular and SIS Medical. Drs. Schmermund has received speakers' fees and travel expenses from Abbott Vascular. Dr. Eggebrecht has received unrestricted research grants from Abbott Vascular. Drs. Münzel and Cook have received speakers' fees from Abbott Vascular. Drs. Münzel and Gori receive funding from the Center for Translational Vascular Biology, Mainz. Dr. Gori has received speakers' honoraria from Abbott Vascular and St. Jude Medical. Abbott Vascular had no role in any phase of this research. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Puricel and Cuculi as well as Drs. Cook and Gori contributed equally to the study.

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**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndromes

**BVS** = bioresorbable vascular scaffolds

**DES** = drug-eluting stents

**LVEF** = left ventricular ejection fraction

**MLD** = minimum lumen diameter

**QCA** = quantitative coronary angiography

**RVD** = reference vessel diameter

**ScT** = scaffold thrombosis

**STEMI** = ST-segment elevation myocardial infarction

Bioresorbable vascular scaffolds (BVS) have been introduced in interventional cardiology to address late-occurring complications of drug-eluting stents (DES) (1). Although the initial ABSORB cohort studies (2,3) and the recently published randomized trials ABSORB II and III (4,5) and EVERBIO-2 (Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents) (6) provided data in support of the safety of BVS, an unexpectedly high incidence of scaffold thrombosis (ScT) has been reported in single-center and multicenter observational studies (7–10) and in a recently published meta-analysis (11).

In particular, the 6-month incidence of ScT was 2% in the GHOST-EU (Gauging coronary Healing with biOresorbable Scaffolding platforms in EUrope) registry (7) and was as high as 3% in the academic medical center single-center registry (8). In the BVS EXAMINATION trial, a propensity score-matched analysis of ST-segment elevation myocardial infarction (STEMI) patients, a tendency toward higher rates of early ScT was observed in patients who received BVS compared with DES or bare-metal stents. Rates at 1 month were 2.1% for BVS, 0.3% for DES, and 1.0% for bare-metal stents ($p = 0.06$ for BVS vs. DES) (12).

The existence of clinical or procedural predictors of ScT, and whether this incidence can be addressed, are unknown. The aim of this study was to describe the incidence and clinical presentation of ScT and to identify its clinical and procedural predictors in a large all-comer population.

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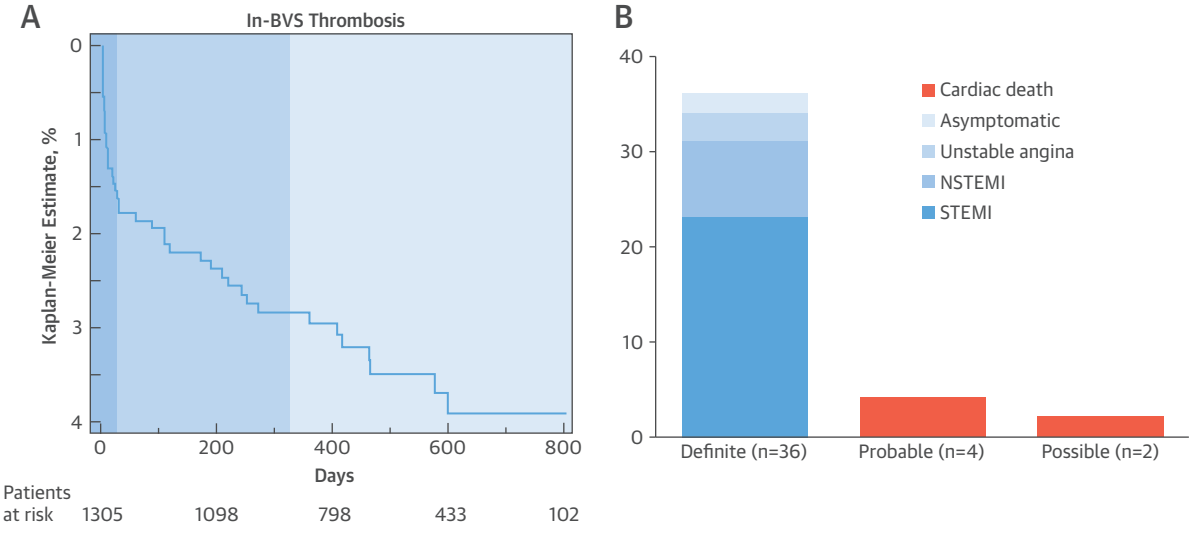
## METHODS

**STRUCTURE OF THE DATABASE.** Patients were treated in each of the participating institutions according to clinical indications and underwent clinical follow-up at regular, pre-scheduled intervals. These data were acquired locally by trained medical staff using standardized questionnaires via clinical visits and through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data were then internally audited in each center by staff who were not involved in data entry (T.G., M.W.), and they were retrospectively entered in the multicentric database in an anonymized way according to national privacy policies and laws and following the requirements of the ethics committee of the University Medical Center Mainz. Data were audited again centrally for consistency and plausibility, and queries were generated when necessary.

**FIGURE 1 Incidence and Clinical Presentation of ScT**




**(A)** Incidence of scaffold thrombosis (ScT). The different **shades of blue** identify early (<30 days from implantation), late (30 to 365 days), and very late (>365 days) thrombosis. **(B)** Clinical presentation and characterization of ScT. BVS = bioresorbable vascular scaffold; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

**TABLE 1 Major Patient, Lesion, and Procedural Characteristics**

| | All Patients (n = 1,305) | Patients Without Thrombosis (n = 1,263) | Patients With ScT (n = 42) | p Value |
|---|---|---|---|---|
| Patient-level analysis | | | | |
| Male | 1,061/1,305 (81) | 1,030/1,263 (82) | 31/42 (74) | 0.528 |
| Age, yrs | 64 (55–73) | 64 (55–73) | 65 (56–74) | 0.779 |
| Hypertension | 906/1,305 (69) | 875/1,243 (70) | 31/42 (74) | 0.881 |
| Hyperlipidemia | 645/1,305 (49) | 627/1,240 (54) | 18/42 (43) | 0.601 |
| Diabetes | 290/1,284 (23) | 285/1,242 (23) | 5/42 (12) | 0.238 |
| Smoking | 469/1,281 (37) | 451/1,239 (36) | 18/42 (43) | 0.285 |
| Previous PCI | 459/1,285 (36) | 444/1,243 (36) | 15/42 (36) | 0.983 |
| Previous CABG | 51/1,285 (4) | 49/1,243 (4) | 2/42 (4) | 0.949 |
| History of stroke | 58/991 (6) | 57/957 (6) | 1/34 (3) | 0.749 |
| Clinical presentation | | | | |
| ACS | 653/1,303 (50) | 628/1,261 (50) | 25/42 (58) | 0.222 |
| STEMI | 243/1,300 (19) | 233/1,258 (19) | 10/42 (24) | 0.507 |
| eGFR, ml/min | 85 (71–101) | 86 (71–101) | 86 (72–97) | 0.619 |
| LVEF, % | 55 (50–59) | 55 (50–59) | 55 (45–58) | 0.177 |
| Number of vessels treated | | | | 0.096 |
| 1 | 1,193/1,305 (91) | 1,158/1,263 (92) | 35/42 (83) | |
| 2 | 104/1,305 (8) | 97/1,263 (8) | 7/42 (17) | |
| 3 | 8/1,305 (<1) | 8/1,263 (<1) | 0/42 (0) | |
| Number of BVS implanted | 1.4 ± 0.8 | 1.4 ± 0.8 | 1.5 ± 0.7 | 0.575 |
| Mean BVS diameter, mm | 3.0 (2.8–3.5) | 3.0 (2.8–3.5) | 3.0 (2.8–3.5) | 0.523 |
| Minimum BVS diameter, mm | 3.0 (2.5–3.5) | 3.0 (2.5–3.5) | 3.0 (2.5–3.5) | 0.665 |
| Mean total BVS length, mm | 20 (18–36) | 18 (18–30) | 28 (18–46) | 0.538 |
| Overlap | 205/1,294 (16) | 198/1,253 (16) | 7/41 (17) | 0.998 |
| Mean total BVS surface, $cm^2$ | 1.97 (1.81–3.32) | 1.97 (1.81–3.32) | 2.76 (1.81–4.57) | 0.159 |
| Total outer BVS surface, $cm^2$ | 0.58 (0.52–0.98) | 0.58 (0.52–0.98) | 0.79 (0.52–1.31) | 0.165 |
| Glycoprotein IIb/IIIa inhibitors | 187/933 (20) | 183/895 (20) | 4/38 (11) | 0.414 |
| DAPT type | | | | 0.498 |
| Clopidogrel | 613/1,305 (47) | 598/1,263 (47) | 15/42 (36) | |
| Prasugrel | 416/1,305 (32) | 404/1,263 (32) | 12/42 (29) | |
| Ticagrelor | 272/1,305 (21) | 259/1,263 (21) | 13/42 (31) | |
| Pre-dilation | 1,295/1,296 (100) | 1,254/1,254 (100) | 41/42 (98) | 0.691 |
| Post-dilation | 656/1,300 (50) | 638/1,259 (51) | 18/41 (44) | 0.487 |
| Lesion-level analysis | | | | |
| Lesion type B2 or C | 547/1,430 (38) | 528/1,388 (38) | 19/42 (45) | 0.433 |
| Bifurcation lesion | 141/1,318 (11) | 136/1,279 (11) | 5/39 (13) | 0.904 |
| Lesion location | | | | |
| Ostial | 78/1,468 (5) | 73/1,424 (5) | 5/42 (12) | 0.332 |
| Proximal | 562/1,468 (38) | 543/1,424 (38) | 20/42 (48) | |
| Mid | 542/1,468 (37) | 530/1,424 (37) | 11/42 (26) | |
| Distal | 164/1,468 (11) | 159/1,424 (11) | 5/42 (12) | |
| Diagonal branch | 51/1,468 (3) | 51/1,424 (4) | 0/42 (0) | |
| Marginal branch | 12/1,468 (1) | 12/1,424 (1) | 0/42 (0) | |
| Ramus intermedius | 15/1,468 (1) | 14/1,424 (1) | 1/42 (2) | |

Values are n/N (%), median (range), or mean ± SD.

ACS = acute coronary syndromes (unstable angina, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction); BVS = bioresorbable vascular scaffold; CABG = coronary artery bypass grafting surgery; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LAD = left anterior descending; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; RCA = right coronary artery; RCX = circumflex; ScT = scaffold thrombosis; STEMI = ST-segment elevation myocardial infarction.

All cases of ScT were also centrally audited against the original anonymized clinical documents by 2 investigators who were not involved in data collection (T.G., M.W.).

**OBJECTIVES.** We investigated the incidence and clinical presentation of ScT in consecutive all-comer patients undergoing BVS implantation. In a separate analysis, we set out to evaluate the existence of clinical

**TABLE 2 Predictors of ScT: Cox Proportional Hazard Analysis**

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| | p Value | HR (95% CI) | p Value | HR (95% CI) |
| Patient-level analysis | | | | |
| Male | 0.428 | 0.76 (0.38–1.50) | | |
| Age | 0.886 | 1.00 (0.98–1.03) | | |
| Hypertension | 0.646 | 1.18 (0.59–2.33) | | |
| Hyperlipidemia | 0.363 | 0.75 (0.41–1.38) | | |
| Diabetes | 0.111 | 0.47 (0.18–1.18) | 0.147 | 0.46 (0.16–1.30) |
| Smoking | 0.402 | 1.30 (0.71–2.39) | | |
| Previous PCI | 0.960 | 1.02 (0.54–1.90) | | |
| Previous CABG | 0.823 | 1.18 (0.29–4.83) | | |
| History of stroke | 0.495 | 0.50 (0.07–3.62) | | |
| Clinical presentation: ACS | 0.204 | 1.49 (0.81–2.73) | | |
| eGFR | 0.763 | 1.13 (0.52–2.45) | | |
| LVEF (5% increase) | 0.079 | 0.86 (0.73–1.00) | 0.019 | 0.82 (0.70–0.97) |
| Number of vessels treated | 0.125 | 1.76 (0.86–3.60) | 0.692 | 1.23 (0.45–3.39) |
| Number of BVS implanted | 0.622 | 1.09 (0.77–1.54) | | |
| Mean BVS diameter | 0.514 | 0.76 (0.34–1.71) | | |
| Minimum BVS diameter | 0.669 | 0.87 (0.45–1.67) | | |
| Total BVS length | 0.178 | 1.01 (0.99–1.02) | | |
| Overlap | 0.635 | 1.22 (0.54–2.74) | | |
| Total BVS surface | 0.136 | 1.10 (0.97–1.26) | 0.304 | 1.10 (0.93–1.29) |
| Total outer BVS surface | 0.141 | 1.40 (0.90–2.19) | | |
| Glycoprotein IIb/IIIa inhibitors | 0.471 | 0.68 (0.24–1.94) | | |
| Prasugrel | 0.823 | 1.07 (0.57–2.03) | | |
| Ticagrelor | 0.032 | 2.02 (1.07–3.83) | 0.400 | 1.37 (0.66–2.86) |
| Pre-dilation | 0.226 | 0.29 (0.04–2.11) | | |
| Post-dilation | 0.921 | 0.97 (0.52–1.80) | | |
| Lesion-level analysis | | | | |
| Lesion location | 0.510 | 0.93 (0.76–1.14) | | |
| Lesion type B2 or C | 0.423 | 1.28 (0.70–2.34) | | |
| Bifurcation lesion | 0.890 | 1.07 (0.42–2.71) | | |
| Ostial lesion | 0.074 | 2.35 (0.93–5.96) | 0.049 | 2.59 (1.01–6.64) |

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

and angiographic predictors of ScT and provide hypothesis-generating data on the effect of a BVS-specific implantation strategy on the incidence of ScT.

**PATIENT POPULATION AND BVS IMPLANTATION.** The present report includes all consecutive patients who received a BVS for the treatment of de novo lesions in the setting of acute or stable coronary syndromes in the 4 participating institutions between May 2012 and December 2014. Following the manufacturer's and experts' recommendations (13), BVS were not used to treat lesions in the left main coronary, in-stent restenoses, degenerated saphenous vein grafts, vessels <2.25 or >4 mm, and bifurcation lesions with side branches >2 mm. Additional exclusion criteria included patients who were taking chronic therapy with anticoagulants, had intolerance to aspirin or thienopyridines, and or had a limited life expectancy. Pre-dilation was recommended; intracoronary imaging, post-dilation, thrombus aspiration, and glycoprotein IIb/IIIa inhibitors were left to the operator's discretion. Aspirin together with clopidogrel, prasugrel, or ticagrelor were administered pre-procedurally or periprocedurally in all patients. Dual antiplatelet therapy was recommended for 12 months. A total of 405 patients were also included in the GHOST-EU, 78 in the EVERBIO-2, and 93 in the EXAMINATION registries. The endpoints tested here were, however, not investigated in any of these studies.

**DEFINITION OF ScT.** ScT was classified as definite, probable, and possible on the basis of the Academic Research Consortium criteria (14). Timing of ScT was categorized as early when occurring during the first 30 days, late between 1 month and 1 year, and very late beyond 1 year after BVS implantation.

**QUANTITATIVE CORONARY ANALYSIS.** Coronary angiograms were digitally recorded at baseline and immediately after the procedure, and were assessed at the Mainz angiographic laboratory (15). Recently published BVS definitions were applied (16). Quantitative measurements included lesion length, minimum lumen diameter (MLD), reference vessel diameter (RVD), TIMI (Thrombolysis In Myocardial Infarction) flow, % residual stenosis, scaled residual stenosis (MLD divided by the nominal BVS diameter) and % maximum footprint (% of the vascular circumference occupied by struts at the level of the MLD). All definitions are detailed in the Online Appendix.

The quantitative coronary angiography (QCA) analysis was performed in all patients with BVS who developed ScT and, for the purpose of angiographic comparison, in a group of control subjects (2 for each ScT patient) consecutively selected from the general database using the criteria identified as predictors of ScT by the multivariable analysis described in the following text.

**EFFECT OF BVS-SPECIFIC IMPLANTATION STRATEGY.** The outcomes of patients treated in 2014 using a BVS-specific implantation protocol designed to specifically address the issue of incomplete BVS expansion ("BVS-specific protocol" group) were compared with those of patients treated in 2012 and 2013 ("early experience"). The analysis was limited to 4 operators who consistently followed these guidelines starting on January 1, 2014 (see a more detailed description in the Online Appendix):

1. Pre-dilation with noncompliant balloon up to the same size as the RVD.
2. BVS implantation only in case of full expansion of the noncompliant percutaneous transcatheter

coronary angioplasty balloon as demonstrated by angiography in 2 orthogonal planes.
3. Implantation of a BVS of the same size as the RVD at 10 to 12 atm.
4. Post-dilation with noncompliant balloons up to a maximum of 0.5 mm larger at 14 to 16 atm.

**STATISTICAL ANALYSIS.** Statistical methods are described in detail in the Online Appendix. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]) and were compared using a parametric or nonparametric test based on the inspection of the Q-Q plots. Categorical variables are presented as counts and percentages. Kaplan-Meier curves were built to derive the event rates and plot time-to-event curves. Analyses were performed at a patient- and lesion-level as appropriate. Univariate and multivariable Cox proportional hazards analysis was performed to identify the clinical and procedural parameters relevant for the endpoint. To remove potential treatment assignment bias in evaluation of the BVS-specific implantation strategy, a propensity score was built from a logistic regression model (with implantation strategy as outcome) and used for adjustment. To assess the effect of QCA parameters on the risk of ScT in a nested case-control design, each ScT patient was matched with 2 corresponding control subjects using the clinical variables that showed $p < 0.05$ in the multivariable analysis. Conditional logistic regression was used. To identify relevant cut-offs for QCA parameters, sensitivities and specificities for different cut-offs were calculated, using observation weights for the nested case-control design, resulting in receiver-operating characteristic (ROC) curves. Positive predictive values were calculated on the basis of a prevalence of 3%.

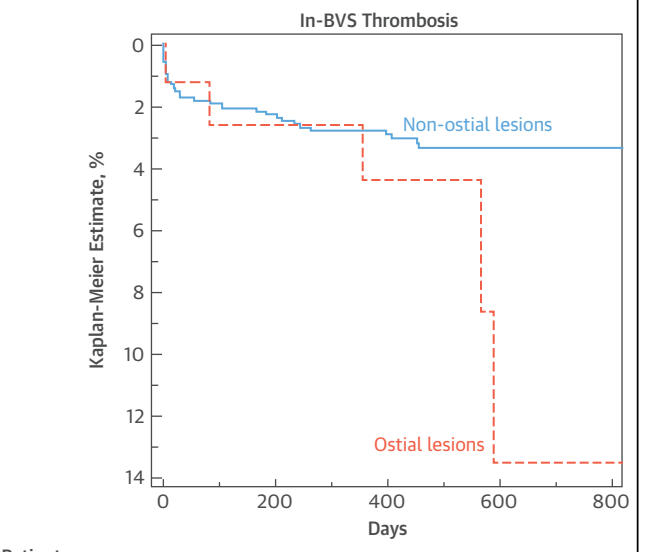
## RESULTS

### INCIDENCE AND CLINICAL PRESENTATION OF ScT.

This multicenter registry included 1,305 patients with a mean age of 63.8 ± 11.5 years who received a total of 1,870 BVS (1.4 ± 0.8/patient). Diabetes was present in 23% of the patients, a clinical presentation as acute coronary syndrome (ACS) was recorded in 50% (19% STEMI), and 40% had a history of revascularization. Figure 1A depicts the Kaplan-Meier curve for the Kaplan-Meier incidence of ScT. The median follow-up was 485 days (IQR: 312 to 652 days).

There were 36 definite, 4 probable, and 2 possible ScT (Figure 1B). A total of 21 ScTs (50%) occurred early, of which 10 (24%) were "acute" or within 1 day, 11 (26%) were "subacute" or within 1 month, 11 (26%)

**FIGURE 2 ScT in Ostial Lesions**




The incidence of ScT as a function of the treated segment (ostial vs. nonostial). The 2 curves appear to diverge with the loss of the radial force of the BVS. Abbreviations as in Figure 1.

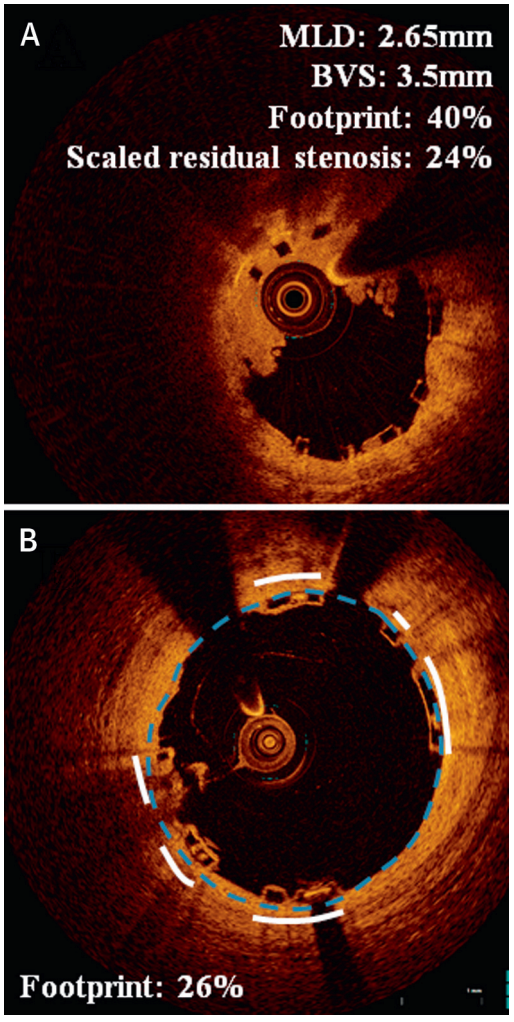
**TABLE 3 Quantitative Coronary Analysis Predictors of ScT**

| | Pre-Procedure | | | | After BVS Implantation | | | |
|---|---|---|---|---|---|---|---|---|
| | BVS Thrombosis (n = 42) | Control (n = 84) | p Value for Risk | HR (95% CI) | BVS Thrombosis (n = 42) | Control (n = 84) | p Value for Risk | HR (95% CI) |
| MLD, mm | 0.66 ± 0.59 | 0.68 ± 0.51 | 0.784 | 0.88 (0.35-2.22) | 2.39 ± 0.58 | 2.85 ± 0.49 | 0.001 | 0.05 (0.01-0.28) |
| RVD, mm | 2.77 ± 0.58 | 3.13 ± 0.66 | 0.014 | 0.27 (0.10-0.77) | 2.93 ± 0.58 | 3.41 ± 0.52 | 0.002 | 0.13 (0.04-0.46) |
| % stenosis | 76 ± 20 | 77 ± 16 | 0.815 | 1.00 (0.97-1.03) | 19 ± 12 | 16 ± 7 | 0.071 | 1.05 (0.10-1.10) |
| Maximum footprint, % | – | – | | | 43 ± 11 | 35 ± 6 | 0.001 | 1.20 (1.08-1.33) |
| Scaled residual stenosis | – | – | | | 0.21 ± 0.18 | 0.07 ± 0.14 | 0.001 | 1,714 (20.07-146,454) |

Values are mean ± SD unless otherwise indicated. Maximum footprint: the scaffold outer surface area divided by actual arterial surface area calculated from the MLD. The p value was adjusted for diabetes, prior percutaneous coronary intervention, overlap, vessel treated, and type of dual antiplatelet therapy in multivariable analysis (details in Online Tables 2 to 10).

MLD = minimum lumen diameter; RVD = reference vessel diameter; other abbreviations as in Tables 1 and 2.

**FIGURE 3 Residual Versus Residual Scaled Stenosis and Footprint**




**(A)** ScT at optical coherence tomography (white thrombus) in a poorly expanded BVS; the residual scaled stenosis expresses the relationship between quantitative coronary angiography–measured minimum lumen diameter (MLD) at the end of the procedure and nominal BVS diameter. **(B)** Proximal segment in the same BVS. The **blue lines** mark the lumen circumference; the **white lines** indicate the fraction covered by struts. The % footprint is the ratio of the 2 and is a function of the MLD and of the BVS outer surface area. Abbreviations as in Figure 1.

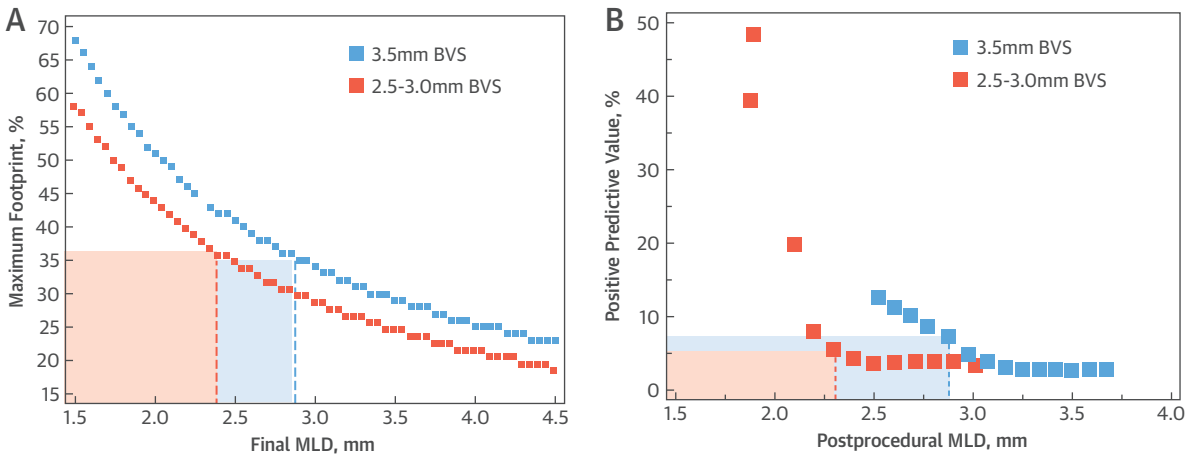
were late, and 10 (24%) were very late. The median duration from implantation to ScT was 26 days (IQR: 4 to 212 days). The curve describing the incidence of ScT showed an initial peak within the first 30 days, followed by a more diffuse distribution in the following months. Overall, the Kaplan-Meier incidence was 1.8% at 30 days, 2.3% at 6 months, and 3.0% at 12 months, without significant differences among centers (hazard ratio: 1.07; 95% confidence interval: 0.83 to 1.38; p = 0.603) (Online Figure 1).

A total of 40 of the 42 ScT patients presented with ACS or sudden cardiac death; 22 presented with STEMI (peak creatine kinase: 1,688 ± 3,219 U/l, 1 died during the immediate follow-up), 9 presented with non-STEMI, and 3 patients presented with unstable angina (Figure 1B). One patient died upon hospital arrival, and ScT was diagnosed at autopsy. One patient reported dyspnea only; in this patient, a complete occlusion of the BVS was observed <30 days after implantation. A total of 9 (21%) patients developed ScT while not on dual antiplatelet therapy (DAPT) (in 2 cases within 1 day of interruption and in another 3 within 1 month). Three of these patients developed very late ScT 14, 32, and 197 days after planned 12-month DAPT interruption. The other 6 patients had interrupted DAPT prematurely (range 2 to 234 days after BVS implantation). ScT occurred in these patients 0 to 227 days after DAPT interruption. All patients with angiographically definite ScT were treated with glycoprotein IIb/IIIa inhibitors and thrombus aspiration. In patients with ScT on day 0 or 1, ScT was treated with balloon-only angioplasty. In all others, a DES was implanted after PTCA. In the patient with dyspnea only, revascularization was unsuccessful. Three of the patients died in-hospital.

**PREDICTORS OF ScT.** Clinical and procedural characteristics are presented in Table 1. The results of the Cox analysis are shown in Table 2. Left ventricular ejection fraction (LVEF) and treatment of ostial lesions (Figure 2) were mildly associated with the incidence of ScT. Interestingly, the association between ScT and treatment of ostial lesions appeared to be particularly evident at later follow-up times. When the analysis was limited to late and very late ScT, univariate analysis resulted in a hazard ratio of 4.18 (95% confidence interval: 1.41 to 12.45; p = 0.011). When ScT patients with premature DAPT interruption were excluded, the results of the univariable and multivariable analysis did not differ substantially.

**QCA ANALYSIS.** The QCA was conducted using a nested case-control design in the 42 ScT patients (42 lesions) and 84 matched control subjects (84 lesions). At baseline, lesion length, pre-PCI TIMI flow rate, MLD, and % stenosis were similar between the groups (Online Table 1). RVD was significantly larger in the control subjects. After implantation, significant differences were found for RVD and MLD, which were lower in the ScT group (Table 3). The residual stenosis was comparable between the groups, but when this parameter was corrected by the nominal BVS diameter ("residual scaled stenosis," expressing the degree of deployment of the BVS

**FIGURE 4 QCA Analysis**




**(A)** The relationship between final MLD (MLD at the end of the index procedure) and maximum footprint in 2.5 to 3.0-mm and 3.5-mm BVS. The **dotted lines** mark values at which the risk of ScT appears to increase (see **B**, corresponding to a value of 36%). **(B)** Positive predictive value for each MLD in the prediction of ScT. Below MLD values of 2.4 mm in a 2.5 to 3.0-mm BVS and 2.8 mm in a 3.5-mm BVS, the risk increases rapidly. QCA = quantitative coronary angiography; other abbreviations as in Figures 1 and 3.

compared with its nominal value), the difference between groups was highly significant. Similarly, the MLD-derived maximum footprint (Figure 3) was significantly larger in the ScT group (Online Table 1).

In multivariable analyses (Table 3, Online Tables 2 to 10), post-procedural MLD, pre- and post-procedural RVD, maximum footprint, and residual scaled stenosis remained strongly associated with ScT.

In the ROC analysis, a value of maximum BVS footprint of 36% (corresponding to MLDs of 2.4 mm for 2.5-/3.0-mm BVS and 2.8 mm for 3.5-mm BVS) was associated with a sensitivity and specificity of 69% and 63%, respectively. Very similar data were obtained when the ROC analysis was applied directly to MLD values. Figure 4 describes the relationship between MLD and footprint (Figure 4A) and the positive predictive value of the final MLD in predicting ScT (Figure 4B). The curve describing the positive predictive values of different post-procedural MLDs showed a steeper increase for values <2.4/2.8 mm. MLD values <2.1 mm (for the 2.5-/3.0-mm BVS) and 2.7 mm (for the 3.5-mm BVS) were associated with ScT with a specificity of ~90% and a sensitivity of ~50%.

**IMPLEMENTATION OF A BVS-SPECIFIC IMPLANTATION PROTOCOL.** Results and patient characteristics are presented in the Online Appendix.

At the time of follow-up, all 369 patients in the "early experience" group had reached the 365-day follow-up. In the "BVS implantation protocol" group, 292 and 175 patients had reached 180- and 365-day follow-up, respectively. The Kaplan-Meier incidence of ScT at 1 and 12 months was 2.7% and 3.3% for patients in the "early experience" group and 1.0% at both 1 and 12 months in the "BVS implantation protocol" group (log-rank p = 0.023) (Central Illustration).

A number of clinical or procedural characteristics showed relevant differences between the 2 groups (Online Tables 11 and 12); however, none of these, except for ostial lesions, was associated with ScT (Table 4). In contrast, the implantation protocol used ("early experience" versus "BVS-specific implantation protocol" group) was independently associated with a significant (~70%) reduction in the incidence of ScT (p = 0.035). This result was confirmed by the propensity score analysis (p = 0.012).

## DISCUSSION

The key findings of this all-comer, multicentric registry study are: 1) similar to DES, ScT is a particularly severe complication whose 12-month incidence was as high as 3% unless meticulous attention was paid at the time of implantation; 2) none of the clinical characteristics was an independent predictor of ScT, although treatment of ostial lesions and reduced LVEF trended in this direction; 3) QCA features of small vessels were a hallmark of ScT; and 4) suboptimal post-procedural angiographic results, with even small deviations from the nominal BVS diameter, were associated with exponential increases in the risk of ScT. ROC analysis applied to MLD data suggest that a

**TABLE 4 Implantation Strategy Substudy: Cox Regression Analysis**

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| | p Value | HR (95% CI) | p Value | HR (95% CI) |
| Patient-level analysis | | | | |
| Male | 0.846 | 1.11 (0.38-3.30) | | |
| Age | 0.417 | 0.99 (0.95-1.02) | | |
| Hypertension | 0.347 | 1.69 (0.57-4.96) | | |
| Hyperlipidemia | 0.880 | 0.94 (0.39-2.25) | | |
| Diabetes | 0.463 | 0.63 (0.19-2.13) | | |
| Smoking | 0.930 | 1.04 (0.44-2.46) | | |
| Previous PCI | 0.803 | 0.87 (0.32-2.43) | | |
| Previous CABG | 0.960 | 0.00 (0.00-29.0) | | |
| History of stroke | 0.964 | 0.00 (0.00-2.85) | | |
| Clinical presentation | | | | |
| ACS | 0.834 | 1.10 (0.46-2.61) | | |
| STEMI | 0.513 | 0.69 (0.24-2.05) | | |
| eGFR | 0.201 | 3.57 (0.51-24.9) | | |
| LVEF (5% increase) | 0.912 | 0.97 (0.77-1.28) | | |
| Number of vessels treated | 0.443 | 1.44 (0.57-3.78) | | |
| Number of BVS implanted | 0.541 | 1.14 (0.74-1.76) | | |
| Mean BVS diameter | 0.720 | 1.24 (0.37-4.19) | | |
| Minimum BVS diameter | 0.750 | 1.19 (0.41-3.44) | | |
| Total BVS length | 0.275 | 1.01 (0.99-1.03) | | |
| Overlap | 0.320 | 1.75 (0.59-5.20) | | |
| Total BVS surface | 0.206 | 1.12 (0.94-1.33) | | |
| Total outer BVS surface | 0.203 | 1.48 (0.81-2.70) | | |
| Glycoprotein IIb/IIIa inhibitors | 0.502 | 0.69 (0.23-2.04) | | |
| Prasugrel | 0.465 | 1.38 (0.58-3.26) | | |
| Ticagrelor | 0.333 | 1.60 (0.62-4.10) | | |
| Pre-dilation | 0.226 | 0.29 (0.04-2.11) | | |
| Post-dilation | 0.670 | 1.22 (0.50-2.97) | | |
| Lesion-level analysis | | | | |
| Implantation strategy | 0.035 | 0.27 (0.08-0.91) | 0.035 | 0.26 (0.08-0.90) |
| Implantation strategy (adjusted for multivariable propensity score model) | 0.012 | 0.19 (0.05-0.70) | | |
| Lesion type (B2 or C) | 0.492 | 1.15 (0.77-1.73) | | |
| Bifurcation lesion | 0.441 | 0.56 (0.13-2.42) | | |
| Ostial lesion | 0.016 | 3.46 (1.27-9.39) | 0.015 | 3.50 (1.28-9.45) |

Abbreviations as in Table 1.

minimum final MLD of 2.4 mm for 2.5-/3.0-mm BVS and 2.8 mm for 3.5-mm BVS should at least be attained.

**INCIDENCE AND CLINICAL PRESENTATION OF BVS THROMBOSIS.** In line with previous registries (7–9), we demonstrate a 30-day thrombosis rate (definite, probable, and possible) of 1.8% and 12-month thrombosis rate of 3.0%. Definite ScT was diagnosed in 36 of 1,305 patients (2.8%). For comparison, recently published randomized all-comers trials using metallic stents with or without a biodegradable polymer (17,18) reported definite thrombosis rates at 12 months between 0.3% and 0.9%. As with metallic stents, ScT is a particularly malignant condition with a very severe presentation.

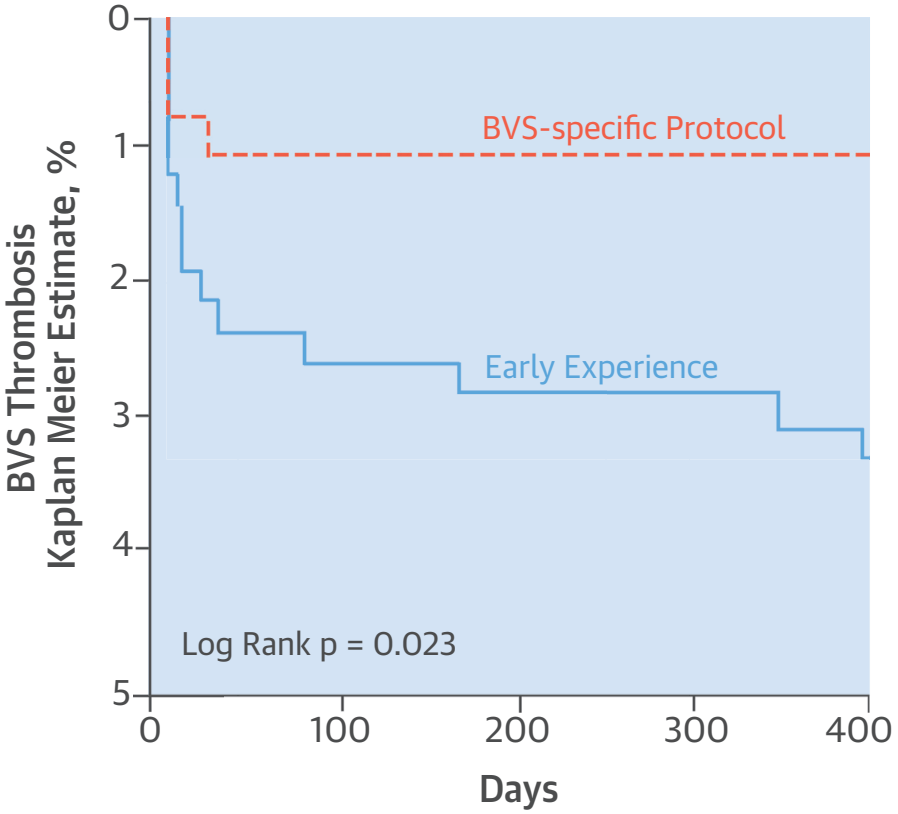
**PREDICTORS OF ScT AND IMPLICATIONS FOR BVS IMPLANTATION.** Stenting in patients with decreased LV function, treatment of ostial and/or type B2/C lesions, and interruption of DAPT have all been previously reported to be associated with stent thrombosis (19–21). In line with this, an association was shown with decreased LVEF and ostial lesions in the present cohort, and 9 of the patients developed ScT after interruption of DAPT. In particular, the implantation of BVS in ostial lesions showed a strong association with late and very late ScT. There are at least 2 possible explanations for this latter observation, particularly at the time of DAPT interruption: first, an insufficient radial strength at implantation resulting in incomplete expansion (22) and/or the loss of radial strength following BVS resorption might represent a specific risk in this subset of often calcific lesions located at hinge points in the coronary vasculature; and second, the limited availability in BVS sizes (maximum diameter 3.5 mm) might have led to malapposition in ostial segments.

The QCA analysis provided further insights into the possible mechanisms of ScT. In line with the DES evidence of increased risk in small(er) vessels (23), both the RVD (before and after implantation) and the MLD post-implantation were smaller in the ScT group. In addition, MLD-derived indexes such as the maximum footprint or the residual scaled stenosis were strongly associated with ScT. In sum, these data appear to suggest that incomplete expansion of BVS (resulting from the implantation of BVS in smaller vessels) was an important factor associated with ScT. These data provide the angiographic correlate of recent optical coherence imaging evidence showing that the incidence of incomplete BVS expansion is relatively high immediately after BVS implantation when a specific technique is not used (24) and that this might be associated with ScT (25,26). Importantly, these data fit well with those of the recently published ABSORB III trial, in which a trend toward more accentuated differences between BVS and DES was shown for smaller vessels (5).

The systematic introduction of a BVS-specific implantation protocol was associated with an ~70% decrease in ScT to rates similar to those reported in DES. These data fit well with the previously mentioned QCA observations and with the optical coherence tomography evidence that systematic use of post-dilation (and particular care in sizing) results in post-procedural area stenosis and minimal lumen area values that are similar to those observed when DES are used (27).

**STUDY LIMITATIONS.** This was a multicentric registry. Although the absence of randomization is a clear

**CENTRAL ILLUSTRATION** **Thrombosis in Bioresorbable Scaffolds: Implantation Strategy**




| Patients | | | | | |
|---|---|---|---|---|---|
| Early Experience | 369 | 369 | 369 | 369 | 369 |
| BVS-specific | 292 | 292 | 281 | 217 | 155 |

Puricel, S. et al. J Am Coll Cardiol. 2016; 67(8):921–31.

Kaplan-Meier curves describing the incidence of scaffold thrombosis (ScT) according to the implantation strategy used. **Orange** indicates bioresorbable vascular scaffold (BVS)–specific technique. The difference among the 2 curves remained significant in multivariable analysis.

limitation, this design allows for gathering real-world information that represent an important complement to randomized studies and provides an interpretation of the different incidence of ScT in randomized trials versus all-comers registries. This study had no formal external monitoring; however, all data were centrally monitored and queries were issued in case of conflicts, and all events were centrally audited and validated against the original source data.

We investigated clinical and angiographic correlates of ScT, and the analyses should be seen as hypothesis generating and exploratory. Given the relatively low incidence of ScT, it is possible that larger cohorts would have allowed the identification of other clinical or procedural parameters. Further, other possible causes of thrombosis exist that are not investigated here. The role of early DAPT discontinuation should be addressed in future randomized studies. Further, although the present data point to the role of incomplete BVS expansion as a possible predictor of ScT (26), the importance of undersizing and malapposition, which is best addressed with intracoronary imaging, cannot be emphasized enough. Given the nonhomogeneous distribution of the struts along the scaffold length, footprint should be assessed only using intracoronary imaging.

Although more complex methods of intracoronary imaging would have provided a better resolution and more detailed information in assessing BVS deployment, QCA remains, however, a simple and widely available technology. The fact that QCA parameters such as MLD and RVD were independent predictors of ScT in our dataset provides easily accessible instruments to help predict post-PCI outcomes with BVS. For the ROC analysis, all patients were pooled together. It is possible that the values identified as a predictor of thrombosis might differ in different subsets of patients.

A number of additional limitations apply to the analysis on the implantation technique. First, this analysis was limited to the patients treated by 4 operators, among which 21 ScTs were observed; residual confounding may exist that the propensity score has not removed. The nonrandomized nature of our approach and the resulting differences in the clinical characteristics of patients are important confounders, even though the prevalence of risk factors was actually higher in the 2014 cohort, and the results were confirmed in the propensity score analysis. The fact that the 2 implantation protocols were applied at different time points is partially addressed by limiting this analysis to a restricted number of operators among which these strategies were applied rigorously. Most importantly, the protocol presented here is only 1 of several strategies to reduce the risk of incomplete expansion, and the role of intracoronary imaging needs to be acknowledged.

## CONCLUSIONS

In a multicentric, all-comer cohort of consecutive patients, ScT is a particularly severe event with a 12-month incidence as high as 3%, but it can be addressed by taking particular precautions at the time of implantation. The implantation protocol used was an independent predictor of ScT, and, in line with results from DES, treatment of ostial lesions and low LVEF were also identified as possible predisposing factors. Finally, angiographic features of relatively smaller vessels, suggestive of incomplete BVS expansion, result in a steeper increase in the risk of ScT. Although it is acknowledged that other possible predictors of ScT (e.g., malapposition) exist, the present data emphasize the importance of vessel sizing and of the implantation techniques in reducing the rate of this complication.

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**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Tommaso Gori, Zentrum für Kardiologie, University Medical Center Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany. E-mail: tommaso.gori@unimedizin-mainz.de.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The incidence of thrombosis of coronary bioresorbable scaffolds is as high as 3% over 12 months, but it can be reduced by ~70% using a specific implantation technique. Ostial locations and reduced left ventricular ejection fraction are independent predictors of scaffold thrombosis.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to confirm the predictive value of measuring minimum lumen diameter as a guide to clinical outcomes following implantation of coronary bioresorbable scaffolds in patients with ischemic heart disease.

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**KEY WORDS** bioresorbable scaffold, stent thrombosis

**APPENDIX** For a supplemental Methods section as well as tables and a figure, please see the online version of this article.