Heart and Vessels (2019) 34:557–563
https://doi.org/10.1007/s00380-018-1281-7

ORIGINAL ARTICLE

Immune–inflammatory response after bioresorbable vascular scaffold implantation in patients with acute myocardial infarction with ST elevation in a long-term perspective

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Received: 22 June 2018 / Accepted: 5 October 2018 / Published online: 12 October 2018

Abstract

A higher rate of bioresorbable vascular scaffold (BVS) thrombosis has been observed after device implantation compared to implantation of permanent metallic stents in recently published studies. The mechanism of BVS thrombosis is currently under debate. To assess whether the immune–inflammatory response after BVS implantation is a potential trigger of BVS thrombosis. The PRAGUE-19 study was an academic study that enrolled consecutive patients with ST-segment elevation myocardial infarction (STEMI) with the intention to implant a BVS. A laboratory sub-study included 49 patients with an implanted BVS (of which 38 underwent the complete 2-year follow-up) and 52 patients having an implanted permanent metallic stent as the control group (of which 30 underwent the complete 2-year follow-up). Samples for inflammatory markers [high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)] were taken before BVS or stent implantation, on days 1 and 2 after device implantation and at 1 month and 2 years for a clinical control. The primary combined clinical endpoint of the sub-study (death, reinfarction or target vessel revascularization) occurred in 4.08% of the BVS group and 7.69% of the control group ($p=0.442$) during the 2-year follow-up period, with overall mortality of 2.04% in the BVS group and 1.92% in the control group ($p=0.966$). Definite BVS thrombosis occurred in one patient in the subacute phase; there was no late or very late thrombosis. Two definite stent thromboses were observed in the control group: one in the subacute phase and the other in the late phase. Baseline inflammatory marker levels did not differ between the groups. Lower levels of IL-6 and hs-CRP were observed in the BVS group compared to the control group (12.02 ± 5.94 vs. 15.21 ± 5.33 pg/ml; $p<0.01$; 3952.9 ± 1704.75 ng/ml vs. 4507.49 ± 1190.01 ng/ml; $p=0.037$, respectively) on days 1 and 2 (12.01 ± 6.31 vs. 13.85 ± 6.01 pg/ml; $p=0.089$; 4447.92 ± 1325.31 ng/ml vs. 4637.03 ± 1290.99 ng/ml; $p=0.255$, respectively). No differences in IL-6 or hs-CRP were observed after 1 month or 2 years in the clinical control. Levels of TNF-α did not differ between the groups in the early period after BVS or metallic stent implantation, nor during follow-up. The immune–inflammatory response is lower during the early phase after BVS implantation compared to that after metallic stent implantation, but the responses did not differ in the long term.

Keywords Bioresorbable vascular scaffold · Percutaneous coronary intervention · Myocardial infarction · Thrombosis · Immune–inflammatory reaction

Introduction

Bioresorbable vascular scaffolds (BVS) were widely used during coronary interventions in daily clinical practice, including for patients with ST-segment elevation myocardial infarction (STEMI). Absorb stents are currently not available, because several randomized trials have revealed that the rate of first-generation BVS thrombosis is about twice as high in the mid-term compared to that of second-generation permanent drug-eluting stents [1, 2]. However, the mechanism of coronary device thrombosis is complex. Several

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risk factors that contribute to stent thrombosis have been identified, including procedural-related factors, patient- and lesion-related factors, antiplatelet therapy and stent-related factors (including the inflammatory reaction caused by different device components) [3]. The aim of this study was to compare long-term changes in immune–inflammatory markers [high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)] in patients with STEMI treated with BVS versus a permanent metallic stent, and to assess possible triggers for BVS thrombosis.

Methods

The PRAGUE-19 study was an academic study intending to implant a first-generation Absorb BVS device (Abbott Vascular, Santa Clara, CA, USA) as a default strategy for consecutive patients with STEMI who fulfilled the pre-specified inclusion and exclusion criteria. The protocol was designed by the study authors and approved by the local ethical committee as well as by the national multicentric ethical committee. The study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from all study patients. There was no support from industry [4].

A total of 580 patients with STEMI were screened from December 2012 to March 2015, and BVSs were implanted in 142 patients. All remaining patients were entered into a prospective registry. Dual antiplatelet therapy was recommended for 12 months (strict minimum of 6 months); a combination of prasugrel and aspirin was preferred but not mandated. All other aspects of acute and long-term care were standard and left to the discretion of the attending physicians.

A laboratory sub-study included 49 patients with implanted BVSs and 52 patients having an implanted metallic stent as the control group. Samples were taken for evaluation of immune–inflammatory markers (hs-CRP, IL-6 and TNF-α) before BVS or stent implantation, on days 1 and 2 after device implantation, and at 1 month and 2 years for the clinical control. After centrifugation (3500 rpm, 15 min), the serum was stored at − 70 °C. Commercially available enzyme-linked immunosorbent assays were used to measure serum concentrations of the immune–inflammatory markers of interest. All measurements were performed by staff unaware of the clinical data.

The primary combined clinical endpoint was defined as cardiac death, target vessel-related MI and target vessel revascularization.

Statistics

Categorical parameters were described by absolute and relative frequencies and continuous parameters were described by valid count/median supplemented by 5th and 95th percentile. Normal distribution and homogeneity of variances was assessed using Kolmogorov–Smirnov distribution and *F* test. Statistical significance of difference between groups of patients was tested by ML Chi square test for categorical variables and by Kruskal–Wallis test for continuous variables. The level of statistical significance was set at $p = 0.05$. Microsoft Excel 2016 MSO for Windows software (ver. 17.09) (Microsoft Inc., Redmond, WA, USA) was used for the data analysis.

Results

Baseline characteristics

The BVS group included 49 patients. One patient died of a non-cardiac cause before the end of the 2-year follow-up period, and 10 patients were unable to undergo the complete clinical 2-year follow-up including blood collection. The remaining 38 patients underwent the complete clinical 2-year follow-up. The control group included 52 patients, among whom one died of a non-cardiac cause before the end of the 2-year follow-up period. 21 patients did not undergo the 2-year follow-up as 10 patients were unable to be contacted, the other 11 patients refused to undergo clinical control with blood collection, thus only their current health status and medication were found. Thirty patients underwent the complete clinical 2-year follow-up.

The demographic characteristics of the patients are shown in Table 1. No difference in age was observed between the patients in the BVS and control groups. The BVS patients had a lower body mass index and a lower incidence of diabetes mellitus. There was no significant difference in levels of high sensitivity troponin T on admission or first day. Also, no significant difference was observed in ejection fraction on admission.

The pharmacological therapy is shown in Table 2. Patients in the control group used on admission insignificantly more statins [4 patients (8.2%) in the BVS group vs. 11 patients (21.2%) in the control group; $p = 0.07$] and ASA [3 patients (6.1%) in the BVS group vs. 8 (15.4%) in the control group; $p = 0.14$]. Medication on discharge in both groups was similar. During the 2-year follow-up, it was seen that significantly more patients in the BVS group used statins and ASA. Two patients in the control group did not use any antiplatelet or anticoagulant therapy.

Table 1 Demographic characteristics of patients

	BVS group (N=49)	Control group (N=52)	p=
Men, *n* (%)	33 (67, 3)	42 (80.8)	0.12
Age (years), mean	58.44 (44, 78)	57.52 (41.5,72.9)	0.20
BMI, mean	27.16 (20.8, 33.5)	28.87 (23, 37.2)	0.01
Active smoking, *n* (%)	30 (61.2)	41 (78.8)	0.52
Hyperlipidemia, *n* (%)	9 (18.4)	13 (25.0)	0.41
History of CAD *n* (%)	5 (10.2)	6 (11.5)	0.82
History of CABG, *n* (%)	0 (0.0)	1 (1.9)	0.32
Peripheral vascular disease, *n* (%)	3 (6.1)	6 (11.5)	0.33
Hypertension, *n* (%)	23 (46.9)	28 (53.8)	0.48
Diabetes, *n* (%)	6 (12.2)	14 (26.9)	0.06
Creatinine (µmol/l), mean	78.43 (53.3, 107)	82.58 (53.8, 115.1)	0.16
Level of hs-TnT on admition, ng/l, mean	1535.71 (24.6, 6924)	1821.71 (67.9, 10,000)	0.28
Level of hs-TnT 1st day, ng/l, mean	3197.06 (154.45, 8875)	3246.21 (273.05, 10000)	0.47
EF on admition, %, mean	48.52 (33.5, 63)	46.83 (32.5, 58.6)	0.17

BMI body mass index, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *hs-TnT* high sensitivity troponin T, *EF* ejection fraction

Table 2 Pharmacological therapy of patients

	BVS group (N=49)	Control group (N=52)	p=
On admission, *n* (%)			
ACEi/sartan	17 (34.7)	20 (38.5)	0.69
Betablockers	11 (22.4)	9 (17.3)	0.52
Statins	4 (8.2)	11 (21.2)	0.07
ASA	3 (6.1)	8 (15.4)	0.14
Warfarin	2 (4.1)	1 (1.9)	0.52
On discharge, *n* (%)			
ACEi/sartan	45 (91.8)	44 (84.6)	0.26
Betablockers	43 (87.8)	50 (96.2)	0.11
Statins	49 (100)	51 (98.1)	0.32
DAPT	47 (95.9)	47 (90.4)	0.27
Warfarin + clopidogrel	1 (2)	4 (7.7)	0.19
Warfarin + DAPT	1 (2)	1 (1.9)	0.96
On 2-year follow-up, *n* (%)			
ACEi/sartan	36 (73.5)	35 (67.3)	0.49
Betablockers	38 (77.6)	38 (73.1)	0.60
Statins	43 (87.8)	37 (71.2)	0.04
ASA	42 (85.7)	32 (61.5)	0.006
DAPT	3 (6.1)	2 (3.8)	0.60
Warfarin	3 (6.1)	2 (3.8)	0.60
P2Y12 alone	0 (0)	1 (1.9)	0.33
OAC + ASA or P2Y12	1 (2)	1 (1.9)	0.97
No antiplatelet/ OAC therapy	0 (0)	2 (3.8)	0.17

ACEi angiotensin-converting-enzyme inhibitors, *ASA* acetylsalicylic acid, *DAPT* dual antiplatelet therapy, *OAC* oral anticoagulant

The procedural characteristics of the primary percutaneous coronary intervention are shown in Table 3. The right coronary artery was the most frequently treated vessel in the control group and larger diameter stents were used in this group compared to those used in the BVS group. The length of the devices did not differ between the groups.

Clinical outcome

The primary combined clinical endpoint occurred in 4.08% of the BVS group and 7.69% of the control group ($p=0.442$) during the 2-year follow-up period, with overall mortality of 2.04% in the BVS group and 1.92% in the control group ($p=0.966$). Definite scaffold thrombosis occurred in one patient in the subacute phase (7 days after BVS implantation) due to non-medication use; there was no case of late or very late BVS thrombosis. Two definite stent thromboses were observed in the control group, one in the subacute phase and the other in the late phase.

Evaluation of immune–inflammatory markers

Baseline levels of inflammatory markers did not differ between the groups. Lower levels of IL-6 and hs-CRP were detected in the BVS group compared to those in the control group (12.02 ± 5.94 vs. 15.21 ± 5.33 pg/ml; $p < 0.01$; 3952.9 ± 1704.75 ng/ml vs. 4507.49 ± 1190.01 ng/ml; $p=0.037$, respectively) on day 1, and we did not observe differences on day 2 (12.01 ± 6.31 vs. 13.85 ± 6.01 pg/ml; $p=0.089$; 4447.92 ± 1325.31 ng/ml vs. 4637.03 ± 1290.99 ng/ml; $p=0.255$, respectively). No differences in IL-6 or hs-CRP were observed at the 1 month or 2-year

Table 3 Procedural characteristics of primary PCI

	BVS group ($N=49$)	Control group ($N=52$)	$p=$
Target vessel, *n* (%)			
LAD	22 (44.9)	21 (40.3)	0.64
RCA	16 (32.6)	26 (50)	0.07
LCx	11 (22.4)	6 (11.5)	0.14
Multiple vessels	27 (55.1)	31 (59.6)	0.64
Diameter of stent, mm, mean	3.3 (2.5, 3.5)	3.8 (3, 4.5)	0.000001
Length of stent, mm, mean	20.4 (12, 28)	23.0 (9.6, 38)	0.02
Type of implanted stent, *n* (%)			
BVS	49 (100)	0 (0)	
DES	0 (0)	35 (67.3)	
BMS	0 (0)	17 (32.6)	

PCI percutaneous coronary intervention, *LAD* left anterior descending artery, *RCA* right coronary artery, *LCx* left circumflex artery, *BVS* bioresorbable vascular scaffold, *DES* drug eluting stents, *BMS* bare metal stents

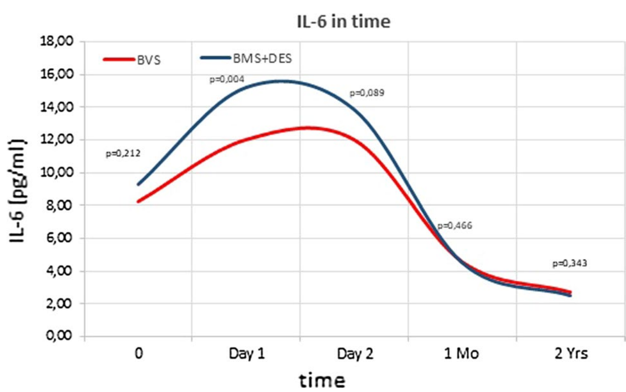

Fig. 1 Changes of IL-6 in time

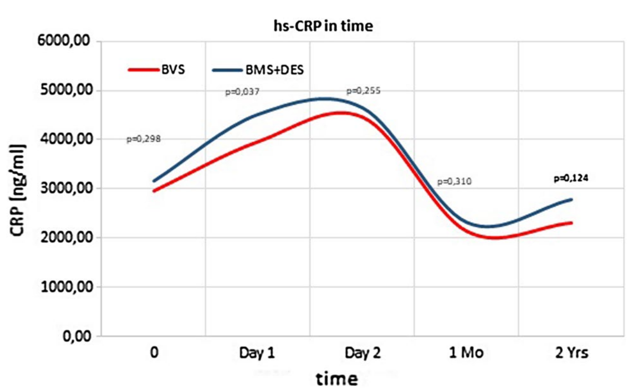

Fig. 2 Changes of hs-CRP in time

follow-up (Figs. 1, 2, Table 4). In both groups, the TNF-α level was elevated above normal values, but the levels did not differ between the groups at any time point (Fig. 3, Table 4).

Table 4 Values of inflamatory markers and changes during 2-year follow-up

	BVS group ($N=49$)	Control group ($N=52$)	$p=$
IL-6 (pg/ml), mean			
Day 0	8.25 (1.20, 20)	9.28 (1.37, 20)	0.21
Day 1	12.02 (3.62, 20)	2.73 (4.86, 20)	0.004
Day 2	12.01 (3.18, 20)	13.85 (3.18, 20)	0.09
1 month	4.58 (0.62, 12.74)	4.51 (1.02, 12.19)	0.47
2 years	2.73 (0.41, 7.96)	2.49 (0.38, 6.24)	0.34
hs-CRP (ng/ml), mean			
Day 0	2952.98 (480.80, 5000)	3153.97 (149.25, 5000)	0.30
Day 1	3952.90 (648.75, 5000)	4507.49 (2065.88, 5000)	0.04
Day 2	4447.92 (915.50, 5000)	4637.03 (196.45, 5000)	0.25
1 month	2131.63 (99.20, 5000)	2310.20 (134.55, 5000)	0.31
2 years	2302.15 (179.0, 5000)	2775.65 (161, 5000)	0.12
TNF-α (pg/ml), mean			
Day 0	0.95 (0.5, 1.87)	1.19 (0.5,2.44)	0.11
Day 1	1.39 (0.5, 2.79)	1.67 (0.56,2.49)	0.20
Day 2	1.49 (0.65, 2.68)	2.48 (0.78,5.87)	0.11
1 month	1.88 (0.71, 3.29)	2.49 (0.80, 3.69)	0.22
2 years	1.09 (0.5, 2.93)	0.88 (0.50, 2.19)	0.17

IL-6 interleukin 6, *hs-CRP* high sensitivity C-reactive protein, *TNF-α* tumor necrosis factor α

Discussion

Our study evaluated inflammation markers after first-generation BVS implantation in patients with acute STEMI. We focused specifically on this potential trigger of scaffold thrombosis due to the ongoing debate regarding the mechanism underlying BVS thrombosis. Several studies have shown that first-generation BVS thrombosis occurs

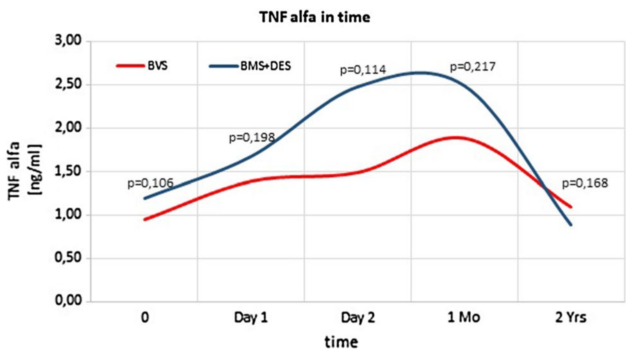

Fig. 3 Changes of TNF-α in time

more frequently compared to second-generation drug-eluting stent (DES) thrombosis in patients with various clinical statuses. A meta-analysis [5] that included the last four randomized studies comparing the Absorb BVS to the Xience metallic DES (Abbott Vascular) showed that MI was more common in the Absorb group than in the Xience group (5.1% vs. 3.3%, $p=0.04$), partly due to more frequent periprocedural MI and partly to the higher rate of stent thrombosis (defined or 'probable') in the Absorb group (1.3% vs. 0.6%, $p=0.08$). This was also confirmed in a trial that compared BVS Absorb with Xience in STEMI [6].

Risk factors for device thrombosis (ST) can be classified as patient- or lesion-related, procedure-related, antiplatelet treatment-related or device-related factors. The most important risk factors for early ST are procedure-related, including stent undersizing, malapposition, residual dissection, impaired TIMI flow and residual disease proximal or distal to the stent lesion [7, 8]. Patient-specific risk factors include reduced cardiac function, diabetes mellitus and impaired response to ADP-antagonist therapy. Early discontinuation of antiplatelet therapy is one of the most important risk factors for stent thrombosis [9]. Device-related risk factors also influence the risk of ST. First-generation DESs are associated with a higher risk of cardiovascular death, due in turn to a higher incidence of ST [10]. Meta-analyses demonstrated that first-generation sirolimus- and paclitaxel-eluting stents were associated with a slightly but significantly increased risk of ST, which persists 4–5 years after implantation of the stent [11–14]. The causes were attributed to delayed arterial healing, a pathophysiological process characterized by impaired endothelial coverage, persistent fibrin deposition, and ongoing vessel wall inflammation [13]. Delayed arterial healing is associated with a number of clinicopathological entities, including not only late ST but also delayed late luminal loss (which may contribute to late re-stenosis) [15], persistent vasomotor dysfunction proximal and distal to the stented segment [16] and de novo in-stent atherosclerosis [17].

For this reason, new generations of permanent metallic DESs with thinner stent struts (which reduce acute vessel injury) and more biocompatible polymer coatings (both nonerodable and biodegradable), have been developed with lower dosages of sirolimus analogue drugs [18, 19]. However, first-generation BVSs represent a different type and design of coronary device, with thick 157 µm polymer struts leading to greater vessel contact with the vessel wall after implantation and potentially different rheological aspects at the level of the implanted BVS. Thus, the immune–inflammatory response after BVS implantation with greater strut thickness could differ compared to that after permanent metallic second-generation DES implantation. Evaluation of this pathophysiological mechanism is important given that the debate about the potential triggering mechanism for BVS thrombosis is ongoing.

The link between inflammatory response and acute coronary syndrome is a very complex and not a fully researched area. As we know, pro-inflammatory risk factors trigger the production of primary inflammatory mediators such as interleukin-1 and TNF-α. TNF-α is not expressed in normal cardiomyocytes, but is largely produced in cardiomyocytes and mononuclear macrophages in infarcted zone and infarction border zone [20]. Interleukin-1 and TNF-α, among other things, trigger the production of secondary mediators of inflammation such as interleukin-6 (IL-6). In the case of acute coronary syndrome, IL-6 is produced by macrophages, mast cells and T-lymphocytes at the site of an inflammatory response in the atherosclerotic plaque or at the site of myocardial necrosis [21]. The source of CRP and complement components is hepatocytes. Up-regulation of CRP after tissue injuries such as acute myocardial infarction is regulated by inflammatory cytokines such as IL-6 [22–26]. And, the plasma concentration of IL-6 and its CRP product reflects the intensity of inflammation in atherosclerotic plaque and indirectly its susceptibility to rupture. The levels of these substances are increased in patients with acute myocardial infarction and unstable angina pectoris. The IL-6 concentration is also elevated after PCI [27].

Our study showed that the levels of inflammatory markers (hs-CRP and IL-6) in patients with STEMI on day 1 after implantation of BVS Absorb were significantly lower than those in patients implanted with a permanent metallic stent, but there was no difference in the long term. In both groups, the TNF-α level was elevated above normal values, but the levels did not differ between the groups at any time point. We think that the increase in TNF-α is due to an ongoing myocardial infarction and is not dependent on PCI, thus the values between the two groups do not differ.

This supports the general hypothesis that the main risk factors of BVS thrombosis are procedural specific, and that the immune–inflammatory response after implantation of the stent has a less important role. The very short duration of elevation of inflammatory markers is attributable to "arterial damage" during PCI. Thus, it is crucial to follow the recommendations for BVS implantation of adequate preparation of the lesion, accurate vessel sizing, and post-dilatation with high pressure non-compliant balloons.

Limitations

Our study had several limitations. First, the systematic evaluation of immune–inflammatory markers did not accurately reflect the local inflammatory reaction after BVS/stent implantation. Changes in plasma levels of immune–inflammatory markers are also caused by myocardial necrosis in STEMI. However, it has been shown previously that changes in systemic levels of inflammatory markers correspond to local changes after stent implantation [28]. Furthermore, the IL-6 level can be used to predict future cardiovascular events, including stent thrombosis [29]. Our aim was to evaluate whether this systemic inflammatory reaction was a risk factor and a trigger for ST in implanted BVS and metallic DES patients. Second, various types of metallic stents were used (DES, BMS). Another limitation of the study was the small number of patients in both groups and the low rate of complete 2-year follow-up.

Conclusion

The immune–inflammatory response was lower during the early phase after BVS implantation compared to that after permanent metallic DES implantation, but there was no difference over the long term. It appears that the risk of BVS thrombosis may be more strongly associated with procedural-related factors than an unexpected inflammatory reaction after BVS implantation. However, larger studies including more patients and more complex scenarios are necessary to confirm these observations.

Funding This study was supported by Charles University Research Program Q38 and Charles University Research Centre Programme UNCE/MED/002.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kang SH, Chae IH, Park JJ, Lee HS, Kang DY, Hwang SS, Youn TJ, Kim HS (2016) Stent thrombosis with drug-eluting stents and bioresorbable scaffolds: evidence from a network meta-analysis of 147 trials. JACC Cardiovasc Interv 9:1203–1212
2. Lipinski MJ, Escarcega RO, Baker NC, Benn HA, Gaglia MA Jr, Torguson R, Waksman R (2016) Scaffold thrombosis after percutaneous coronary intervention with ABSORB bioresorbable vascular scaffold: a systematic review and meta-analysis. JACC Cardiovasc Interv 9:12–24
3. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R (2007) Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 27:1500–1510
4. Kočka V, Malý M, Toušek P, Buděšínský T, Lisa L, Prodanov P, Jarkovský J, Widimský P (2014) Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'. Eur Heart J 35:787–794
5. Stone GW, Gao R, Kimura T, Kereiakes DJ, Ellis SG, Onuma Y, Cheong WF, Jones-McMeans J, Su X, Zhang Z, Serruys PW (2016) 1-year outcomes with the Absorb bioresorbable scaffold in patients with coronary artery disease: a patient-level, pooled meta-analysis. Lancet 387(10025):1277–1289
6. Sabaté M, Brugaletta S, Cequier A (2014) The EXAMINATION trial: 2-year results from a multicenter randomized controlled trial. JACC Cardiovasc Interv 7:64–71
7. Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, Mitsudo K, Miyazaki S, Yamaguchi T, Hiyoshi E, Nishimura E, Isshiki T, RESTART Investigators (2010) Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 122:52–61
8. Toušek P, Kočka V, Malý M, Lisa L, Buděšínský T, Widimský P (2016) Neointimal coverage and late apposition of everolimus-eluting bioresorbable scaffolds implanted in the acute phase of myocardial infarction: OCT data from the PRAGUE-19 study. Heart Vessels 31(6):841–845
9. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A (2005) Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 293:2126–2130
10. Camenzind E, Steg PG, Wijns W (2007) Stent thrombosis late after implantation of first generation drug-eluting stents: a cause for concern. Circulation 115:1440–1455 **(discussion 1455)**
11. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A (2007) Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 356:1030–1039
12. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB (2007) Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 356:998–1008
13. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P (2007) Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 370:937–948
14. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW (2007) Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 369:667–678

15. Byrne RA, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schomig A, Kastrati A (2009) Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. JACC Cardiovasc Interv 2:291–299
16. Togni M, Raber L, Cocchia R, Wenaweser P, Cook S, Windecker S, Meier B, Hess OM (2007) Local vascular dysfunction after coronary paclitaxel-eluting stent implantation. Int J Cardiol 120:212–220
17. Otsuka F, Byrne RA, Yahagi K, Mori H, Ladich E, Fowler DR, Kutys R, Xhepa E, Kastrati A, Virmani R, Joner M (2015) Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 36:2147–2159
18. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A (2013) Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv 6:1267–1274
19. Raber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Juni P, Serruys PW, Windecker S (2012) Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation 125:1110–1121
20. Chen Y, Zhang Q, Liao YH (2011) Effect of tumor necrosis factor-alpha on neutralization of ventricular fibrillation in rats with acute myocardial infarction. Mediat Inflamm. 2011:565238
21. Deliargyris EN, Raymond RJ, Theoharides TC, Boucher WS, Tate DA, Dehmer GJ (2000) Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure. Am J Cardiol 86:913–918
22. Mendall MA, Patel P, Ballam L, Strachan D, Morthfield TC (1996) C-reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ 312(7038):1061–1065
23. Morrow DA, Rifai N, Antman EM, Weiner DL, Mccabe CH, Canno CP, Braunwald E (1998) C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes. J Am Coll Cardiol 31:1460–1465
24. Pietila K, Harmoinen A, Hermens W, Simoons ML, Van de Werf F, Verstraete M (1993) Serum C-reactive protein and infarct size in myocardial infarct in patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. Eur Heart J 14(7):915–919
25. Pietila K, Harmoinen AP, Jokinitty J, Pasternack AI (1996) Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. Eur Heart J 17:1345–1349
26. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340:448–454
27. Ikeda U, Ito T, Shimada K (2001) Interleukin-6 and acute coronary syndrome. Clin Cardiol 24:701–704
28. Kefer JM, Galanti LM, Desmet S, Deneys V, Hanet CE (2005) Time course of release of inflammatory markers after coronary stenting: comparison between bare metal stent and sirolimus-eluting stent. Coron Artery Dis 16(8):505–559
29. Chen SL, Liu Y, Lin L, Ye F, Zhang JJ, Tian NL, Zhang JX, Hu ZY, Xu T, Li L, Xu B, Latif F, Nguyen T (2014) Interleukin-6, but not C-reactive protein, predicts the occurrence of cardiovascular events after drug-eluting stent for unstable angina. J Interv Cardiol 27(2):142–154