International Journal of Cardiology 209 (2016) 206–209

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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Scaffold thrombosis: Exaggerated illusion, or when statistics rules

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ARTICLE INFO

Article history:
Received 20 January 2016
Accepted 2 February 2016
Available online 4 February 2016

Keywords:
Bioresorbable scaffold
Scaffold thrombosis

For some, bioresorbable vascular scaffolds (BVS) represent one of the most promising technologies in interventional cardiology, but in recent months, multiple reports examining the performance of the leading BVS suggest that while the device performs as well as a permanent metallic stent clinically, it carries an increased risk of stent/scaffold thrombosis (ST) which appears to be a signal of the awareness for interventionalists. The most recent meta-analysis of Lipinski MJ et al. (2016) [1] demonstrated that patients who received a BVS were at a higher risk of myocardial infarction (MI) (odds ratio (OR): 2.06, 95% CI: 1.31 to 3.22, p = 0.002) and definite/probable ST (OR: 2.06, 95% CI: 1.07 to 3.98, p = 0.03) compared with patients who received drug-eluting stents (DES) amid the fact that a target lesion failure (TLF) rate of BVS is recognized as “acceptable” in real-world population underscoring the importance of the adequate lesion selection and preparation with the post-implantation optimization. Moreover, the utilized statistical approaches and drawn conclusions raise the certain criticism even within the author-mentioned limitations. A similar situation is revealed in another review of the most recent trials from Cassese S et al. (2015) [2]. Patients treated with BVS had a higher risk of definite or probable ST than those treated with a metallic DES (29/2309 vs 7/1382; OR 1.99, 95% CI: 1.00–3.98, p = 0.05), with the highest risk between 1 and 30 days after implantation (3.11, 1.24–7.82, p = 0.02) [2].

We have extensively statistically analyzed both meta-analyses of Lipinski MJ, et al. (2016) [1], and Cassese S et al. (2015) [2] (see Table 1) with 13 trials and 7,177 patients attempting to shed a light on safety outcomes. Importantly, definite or probable ST was significantly increased after placement of a BVS compared with DES (27/1948 vs 15/2150; OR: 2.06, 95% CI: 1.07 to 3.98; p = 0.03) with a trend toward an increase in definite ST (OR: 1.91, 95% CI: 0.82 to 4.46; p = 0.13) and ST at 1 month (OR: 2.02, 95% CI: 0.69 to 5.93; p = 0.20) [1]. However, in case of definite or probable ST if estimate separately randomized clinical trials (two CRT: ABSORB II, and EVERBIO II) vs non-RCT (7 studies) p value was insignificant in both cases (0.17 vs 0.07 respectively) above the margin of significance (p > 0.05) which was equal to 25/1948 patients (a 1.28% of BVS) vs 15/2150 (a 0.69% of DES). Actually, it means that we need at least 1,744-1,948 patients (mostly non-randomized trials) [1], and 2,309 patients (randomized trials) [2] as a sample size to achieve statistical power evaluating the input of BVS to the ST burden. The recent smaller meta-analysis of *Stone G, et al* (2016) [3] documented non-significant increases in peri-procedural myocardial infarction and device thrombosis with BVS (RR 2.09, 0.92–4.75, p = 0.08) which is relevant to the previous findings, but the sample size achieved 2,161 patients that was below the necessary threshold to get statistical power. Moreover, in case of each clinical trial there was no significance in rates of neither definite nor probable ST which brings us to the conclusion that we face a kind of the unintentional bias.

We consider a phenomenon of any unintentional bias mostly from the point of view of the ‘positive’ trials (usually in favor of a new treatment or against a well-established one) that are more likely to be printed. In our case we tackle the series of the ‘negative’ results of ST (on a small number of trials) with obvious asymmetry on Funnel plot (see Fig. 1; right top plot) if compare for instance with those of myocardial infarction (left top plot which is mostly symmetrical for both meta-analyses, but asymmetrical for each of them) affirming the specific type of the unintentional bias when the whole meta-analysis was built on the matrix of insignificant results whereas a potential of the so called small study effects. Few trials such as ABSORB EXTEND and a study of Mattesini et al. could be excluded from meta-analysis [1] merely because p value and some data are not available which makes infeasible to properly evaluate this information. It looks be honest as an attempt of industry to depreciation of the findings which is disserving the manufacturer due to misleading lack of data from DES in order to ultimately judge the phenomenon. Importantly, all the ST findings in favor of either DES or BVS were not supported by the statistical tests (p value between groups was in 100% cases above 0.05) with the absence of any proofs of the BVS inferiority if compare with DES in the previous pre-clinical and clinical studies.

These 53 cases (a rate of 1.37%) of ST in BVS patients in 13 trials with 3,844 patients (vs a 0.67% rate for 3,305 DES patients in meta-analyses [1-4] and up to a 1.6% incidence in general population of patients [5-9] with the second-generation DES placement) require the special examination to evaluate details of the histological and clinical manifestation of

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http://dx.doi.org/10.1016/j.ijcard.2016.02.054

Table 1
Odds ratio and p *value* of multiple comparisons of the clinical outcomes for BVS and DES.

Trial (years), doi	BVS	DES	ACM	CVD	MACE	MI	TLR	TVR	DST or PST	DST	AST or SAST	TLF
Meta-analysis of Lipinski MJ, et al (2016)												
ABSORB II (RCT, 2011–2015), 10.1016/S0140-6736(14)61455-0	329	164	**0.17** (0.01, 4.08) *P = 0.33*	**0.17** (0.01, 4.08) *P = 1.00*	**0.78** (0.40, 1.53) *P = 0.28*	**3.87** (0.87, 17.13) *P = 0.06*	**0.66** (0.15, 2.99) *P = 0.69*	**0.49** (0.18, 1.32) *P = 0.15*	**3.53** (0.18, 68.68) *P = 0.55*	**2.51** (0.12, 52.61) *P = 1.00*	**2.51** (0.12, 52.61) *P = 1.00*	NP
ABSORB EXTEND (2010–2015), 10.4244/EIJV10I12A243	812	812	NE	**1.20** (0.37, 3.95) *P = NA*	**1.05** (0.67, 1.65) *P = NA*	**2.29** (1.15, 4.56) *P = NA*	**0.79** (0.43, 1.45) *P = NA*	NE	**4.03** (0.85, 19.04) *P = NA*	NE	NE	NP
BVS-EXAMINATION (2012–2015), 10.1016/j.jcin.2014.10.005	290	290	NE	**1.00** (0.32, 3.14) *P = 0.53*	NE	**1.51** (0.42, 5.41) *P = 0.20*	**1.25** (0.33, 4.72) *P = 0.96*	NE	**1.77** (0.51, 6.11) *P = 0.85*	**2.53** (0.49, 13.13) *P = 0.90*	**6.11** (0.73, 51.04) *P = NA*	NP
BVS-RAI (2012-2015), 10.1016/j.amjcard.2015.05.049	122	441	**0.40** (0.05, 3.16) *P = 0.38*	**0.24** (0.01, 4.17) *P = 0.16*	**0.66** (0.27, 1.62) *P = 0.37*	**2.05** (0.67, 6.24) *P = 0.15*	**0.90** (0.33, 2.45) *P = 0.84*	**0.78** (0.29, 2.09) *P = 0.62*	**1.83** (0.45, 7.42) *P = 0.39*	**1.83** (0.45, 7.42) *P = 0.39*	NE	NP
EVERBIO II (RCT, 2012–2015), 10.1016/j.jacc.2014.12.017	78	160	**0.68** (0.07, 6.64) *P = 0.62*	**6.21** (0.25, 154.27) *P = 0.49*	**1.26** (0.53, 3.02) *P = 0.44*	**2.06** (0.13, 33.46) *P = 1.00*	**1.40** (0.48, 4.08) *P = 0.50*	**1.29** (0.51, 3.26) *P = 0.56*	**6.21** (0.25, 154.27) *P = 0.49*	NE	NE	NP
PRAGUE-19 (2012-2014), 10.1093/eurheartj/eht545	40	57	**0.47** (0.02, 11.71) *P > 0.67*	**0.47** (0.02, 11.71) *P > 0.67*	**0.70** (0.12, 4.00) *P > 0.67*	**2.95** (0.26, 33.66) *P > 0.67*	**0.71** (0.06, 8.05) *P > 0.67*	**0.71** (0.06, 8.05) *P > 0.67*	**4.37** (0.17, 109.97) *P > 0.67*	**4.37** (0.17, 109.97) *P > 0.67*	**4.37** (0.17, 109.97) *P > 0.67*	NP
Costopoulos et al. (2007–2015), 10.1002/ccd.25569	92	92	**0.20** (0.01, 4.13) *P = 0.15*	**0.33** (0.01, 8.20) *P = 0.15*	**0.41** (0.10, 1.63) *P = 0.19*	NE	**0.59** (0.14, 2.53) *P = 0.47*	**0.48** (0.12, 1.99) *P = 0.31*	NE	NE	NE	NP
Gori et al. (2012-2014), 10.1016/j.jcin.2014.12.244, 10.4244/EIJV9I9A176	150	103	**0.45** (0.07, 2.74) *P > 0.66*	**0.45** (0.07, 2.74) *P > 0.9*	**0.65** (0.31, 1.37) *P = 0.26*	**1.03** (0.28, 3.75) *P > 0.63*	**1.03** (0.17, 6.28) *P > 0.9*	**1.03** (0.17, 6.28) *P > 0.9*	**0.91** (0.20, 4.17) *P = 1.00*	**1.03** (0.17, 6.28) *P > 0.77*	**0.91** (0.20, 4.17) *P = 1.00*	NP
Mattesini et al. (2012–2014), 10.1016/j.jcin.2014.01.165	35	31	NE	NE	**4.70** (0.22, 101.79) *P = NA*	**2.74** (0.11, 69.72) *P = NA*	**0.43** (0.04, 4.95) *P = NA*	**0.88** (0.12, 6.64) *P = NA*	NE	NE	NE	NP
TOTAL for meta-analysis of Lipinski MJ, et al (2016)	**1948**	**2150**	**0.40** (0.15, 1.06) *P = 0.06*	**0.81** (0.42, 1.58) *P = 0.54*	**0.87** (0.66, 1.16) *P = 0.35*	**2.06** (1.31, 3.22) *P = 0.002*	**0.87** (0.59, 1.28) *P = 0.47*	**0.77** (0.48, 1.25) *P = 0.29*	**2.06** (1.07, 3.98) *P = 0.03*	**1.91** (0.82, 4.46) *P = 0.13*	**2.02** (0.69, 5.93) *P = 0.20*	**NP**
Meta-analysis of Cassese,et al (2015)–fixed-effects odds ratio												
ABSORB II (RCT, 2011–2015), 10.1016/S0140-6736(14)61455-0	329	164	**0.05** (0.00, 3.15) *P = 0.33*	NP	NP	**2.71** (0.97, 7.56) *P = 0.06*	**0.64** (0.13, 3.12) *P = 0.69*	NP	**4.49** (0.04, 49.92) *P = 0.55*	NP	NP	**1.55** (0.61, 3.92) *P = 0.35*
EVERBIO II (RCT, 2012–2015), 10.1016/j.jacc.2014.12.017	78	160	**0.37** (0.05, 2.68) *P = 0.62*	NP	NP	**1.03** (0.06, 16.55) *P = 1.00*	**0.72** (0.28, 1.87) *P = 0.50*	NP	NE	NP	NP	**0.82** (0.32, 2.09) *P = 0.68*
ABSORB III (RCT, 2012–2015), 10.1056/NEJMoa1509038	1322	686	**2.18** (0.82, 5.81) *P = 0.12*	NP	NP	**1.23** (0.84, 1.79) *P = 0.28*	**1.14** (0.67, 1.95) *P = 0.61*	NP	**1.89** (0.82, 4.34) *P = 0.13*	NP	NP	**1.29** (0.09, 1.85) *P = 0.16*
ABSORB China (2013–2015), 10.1016/j.jacc.2015.09.054	241	239	**0.13** (0.02, 0.77) *P = 0.03*	NP	NP	**1.25** (0.33, 4.66) *P = 1.00*	**1.00** (0.34, 2.88) *P = 0.99*	NP	**7.21** (0.14, 363.23) *P = 1.00*	NP	NP	**0.79** (0.31, 2.03) *P = 0.40*
ABSORB Japan (2013–2015), 10.1093/eurheartj/ehv435	266	134	**4.51** (0.24, 85.41) *P = 0.55*	NP	NP	**1.48** (0.44, 4.98) *P = 0.76*	**0.68** (0.20, 2.31) *P = 0.55*	NP	**1.02** (0.18, 5.58) *P = 1.00*	NP	NP	**1.11** (0.38, 3.19) *P = 0.85*
TROFI II(RCT, 2014–2015), 10.1093/eurheartj/ehv500	95	96	NE	NP	NP	**7.47** (0.15, 376.35) *P > 0.05*	**1.98** (0.20, 19.29) *P > 0.05*	NP	**7.47** (0.15, 376.35) *P > 0.05*	NP	NP	**7.47** (0.15, 376.35) *P > 0.05*
TOTAL for meta-analysis of Cassese, et al (2015)	**2331**	**1479**	**0.95** (0.45, 2.00) *P = 0.89*	**NP**	**NP**	**1.36** (0.98, 1.89) *P = 0.06*	**0.97** (0.66, 1.43) *P = 0.87*	**NP**	**1.99** (1.00, 3.98) *P = 0.05*	**NP**	**NP**	**1.20** (0.90, 1.60) *P = 0.21*

The odds ratio below 1 is in favor of BVS; NE — not estimable, NA — not available, NP — not provided. Total data presented with p *value* estimated by the test for overall effect (Z). The purple cells indicate the clinical outcomes which wouldn't be trusted due to *p* value below 0.05 (statistically insignificant). Cells with statistically significant results marked with green. Abbreviations: BVS — bioresorbable vascular scaffold, DES — drug-eluting stent, ACM — all-cause mortality, CVD — cardiovascular death, MACE — major adverse cardiovascular events, MI — myocardial infarction, TLR — target lesion revascularization, TVR — target vessel revascularization, DST — definite stent thrombosis, PST — probable stent thrombosis, AST — acute stent thrombosis, SAST — sub-acute stent thrombosis, RCT — randomized clinical trial, TLF — target lesion failure.

the phenomenon in order to ultimately judge a contribution of BVS to the risk of (sub-)acute and/or late scaffold-related thrombosis. Meanwhile, Lipinski [1] underlines that among patients after BVS implantation in which acute and subacute ST was reported, the risk of acute ST was 0.27% and the risk of subacute ST was 0.57%. Early discontinuation of dual antiplatelet therapy was associated only with 22% of ST. Thus, the scaffold thrombosis rates were similar to the anticipated incidences typically reported in contemporary all-comers registries and trials of the