Clin Res Cardiol (2016) 105:744–754
DOI 10.1007/s00392-016-0983-z

ORIGINAL PAPER

External validity of the "all-comers" design: insights from the BIOSCIENCE trial

Anna Franzone[1] · Dik Heg[2,5] · Lorenz Räber[1] · Marco Valgimigli[1] · Raffaele Piccolo[1] · Thomas Zanchin[1] · Kyohei Yamaji[1] · Stefan Stortecky[1] · Stefan Blöchlinger[1] · Lukas Hunziker[1] · Fabien Praz[1] · Peter Jüni[3,4] · Stephan Windecker[1] · Thomas Pilgrim[1]

Received: 11 January 2016 / Accepted: 22 March 2016 / Published online: 1 April 2016

Abstract
Objectives We sought to systematically evaluate the external validity of a contemporary randomized controlled stent trial (BIOSCIENCE).
Methods Baseline characteristics and clinical outcomes of patients enrolled into the BIOSCIENCE trial at Bern University Hospital ($n = 1216$) were compared to those of patients included in the CARDIOBASE Bern PCI Registry at the same institution ($n = 1045$). The primary study endpoint was the rate of target lesion failure (TLF), defined as a composite of cardiac death, target vessel-myocardial infarction (MI) or target lesion revascularization (TLR), at 1 year.
Results Women were underrepresented in the RCT compared to the registry (25 vs. 29.4 %, $p = 0.020$). Non-participants were older compared to study participants (69.2 ± 12.4 vs. 67.0 ± 11.6, $p < 0.001$), and had a higher prevalence of previous cerebrovascular events (10.8 vs. 5.2 %, $p < 0.001$), and chronic renal failure (35.5 vs. 15.6 %, $p < 0.001$). ST-segment elevation myocardial infarction (STEMI) and Killip class IV at presentation were more common among non-participants than participants (30.7 vs. 21.1 %, $p < 0.001$ and 7.8 vs. 0.4 %, $p < 0.001$, respectively). At 1 year, non-participants experienced a significantly higher rate of TLF, (15.0 vs. 6.5 %, $p < 0.001$), and patient-oriented composite endpoint (POCE), including death, MI or any repeat revascularization (21.6 vs. 11.2 %, $p < 0.001$). There was a significant interaction between POCE and presence or absence of an acute coronary syndrome in participants versus non-participants, respectively ($p = 0.009$).
Conclusions Non-participants of this all-comers trial had a higher risk profile and adverse prognosis compared to study participants. Further efforts are needed to improve the external validity of contemporary RCTs.

Keywords Generalizability · Interventional trial · Drug-eluting stents

Electronic supplementary material The online version of this article (doi:10.1007/s00392-016-0983-z) contains supplementary material, which is available to authorized users.

✉ Stephan Windecker
stephan.windecker@insel.ch

Anna Franzone
Anna.Franzone@insel.ch

[1] Department of Cardiology, Swiss Cardiovascular Center, Bern University Hospital, 3010 Bern, Switzerland

[2] Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

[3] Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada

[4] Department of Medicine, University of Toronto, Toronto, Canada

[5] Clinical Trials Unit, Department of Clinical Research, University of Bern, Bern, Switzerland

Introduction

Drug-eluting stents (DES) represent the standard of care for percutaneous coronary revascularization [1] and transformed the field of interventional cardiology conferring higher efficacy as compared to bare-metal stents (BMS) [2–4]. Moreover, new generation DES featuring reduced strut thickness, ameliorated design, biocompatible polymers and reduced dosages of anti-proliferative drugs surpassed first generation DES in terms of efficacy and safety [5].

Randomized controlled trials (RCTs) are the cornerstone of treatment recommendations and clinical guidelines. During the past decade, the evolution of stent technology was paralleled by the refinement of design and accuracy of randomized trials assessing their performance. Ensuring internal validity of RCTs by reducing the risk of chance, confounding and potential bias has been strongly recommended and adopted by a growing number of researchers [6]. The need to provide generalizable evidence prompted the design of trials with minimal exclusion criteria, generally referred to as all-comer design [7, 8]. However, the adequacy of contemporary interventional trials to reflect routine clinical practice outside of study protocols needs to be delineated. Indeed, inadequate consideration of issues affecting the external validity is one of the most common criticisms of RCTs [9].

The BIOSCIENCE trial was a randomized controlled multicenter study showing non-inferiority of the biodegradable polymer-sirolimus eluting Orsiro stent (BP-SES) to the durable polymer-everolimus eluting Xience stent (DP-EES) in a population with minimal exclusion criteria [10]. The objective of the present analysis was to compare clinical features and outcomes of study participants at Bern University Hospital versus subjects undergoing percutaneous coronary intervention (PCI) at the same institution but not included in the trial.

Methods

Study population

The study population included participants of the BIOSCIENCE trial (NCT01443104) who were enrolled at the Bern university Hospital and non-participants included in the CARDIOBASE Bern PCI registry during the same study period (between February 2012 and May 2013).

The BIOSCIENCE was an investigator-initiated, multicenter, single-blind, randomized trial assessing the non-inferiority of the Orsiro BP-SES (Biotronik AG, Bülach, Switzerland) relative to the Xience DP-EES (Abbott Vascular, Abbott Park, IL, USA) [11].

Eligibility was defined by: age above 18 years, presence of stable coronary artery disease (CAD) or acute coronary syndromes (ACS), de novo or restenotic lesions in native coronary arteries or bypass grafts. Patients were excluded in case of pregnancy, inability to provide consent, participation in another trial, intolerance to aspirin, clopidogrel, or components of DES, and surgery planned within 6 months after the index PCI that would require discontinuation of dual antiplatelet therapy (DAPT) [10]. The CARDIOBASE Bern PCI Registry (NCT02241291) collects clinical, procedural and outcome data of patients undergoing PCI in the setting of stable CAD or ACS at Bern University Hospital. For the purpose of the present analysis, patients included in the registry during the enrollment time of the BIOSCIENCE trial were used. The trial and the registry were managed in accordance with the Declaration of Helsinki and patients provided written informed consent.

Procedures and follow-up

Participants of the BIOSCIENCE trial were randomly allocated in a 1:1 ratio to the treatment with BP-SES or DP-EES, respectively. Details of the study devices have previously been reported [10]. Clinical follow-up was performed at 30 days and 1 year after PCI. Regardless of patient allocation, PCI was performed according to international recommendations [1]. As for study protocol, all patients in the trial received new generation DES (BP-SES or DP-EES). Non-participants also received new generation DES in the vast majority of cases, including zotarolimus-eluting stents (Resolute, Medtronic Cardiovascular), biodegradable polymer DES (BioMatrix, Biosensors Europe; Synergy, Boston Scientific Corporation), and bioresorbable vascular scaffold (Absorb, Abbott Vascular). The Clinical Trials Unit and the Department of Cardiology at Bern University Hospital had the responsibility of data monitoring and storing for both the trial and the registry. Adverse events were adjudicated by a dedicated clinical events committee in both study participants and non-participants, respectively.

Study endpoints

The primary endpoint of this study was the rate of target lesion failure (TLF), defined as a composite of cardiac death, target vessel-myocardial infarction (MI) or target lesion revascularization (TLR), at 1 year. Secondary endpoints were a patient-oriented composite endpoint (POCE), including all-cause death, MI or any repeat revascularization; all-cause death; cardiac death; MI; repeat revascularization; and definite or probable stent thrombosis (ST). Definitions of study endpoints have been reported in detail elsewhere [10]. Briefly, cardiac death was considered as any death of immediate cardiac cause, death related to the procedure, unwitnessed death, and death of unknown cause. Myocardial infarction was defined as Q wave and non-Q wave according to the electrocardiographic criteria of the Minnesota code manual [12]. The definition of MI included: spontaneous MI, peri-procedural MI and reinfarction. TLR was considered as any repeat percutaneous or surgical intervention because of a stenosis within the stent or within the 5-mm borders proximal or distal to the stent. ST was defined on the basis of the Academic Research Consortium criteria [13].

Statistical analysis

Continuous variables were expressed as mean ± standard deviations (SD, groups compared with *t* tests); categorical variables were summarized as frequencies (%, groups compared with Fisher's or Chi-square tests). *p* values derived from general or generalized linear mixed models for the per-lesion analyses, accounting for lesions nested within patients. A Mantel–Cox method was used to compare the outcomes between participants and non-participants.

In case of zero events in any comparator group, we reported continuity corrected risk ratios with *p* values from Fisher's exact tests. Risk ratio (RR) with their 95 % confidence intervals (CI) were provided. *p* values for interactions were obtained with approximate χ^2 tests for unequal RRs in the subgroups. Survival curves up to 1-year follow-up were constructed for time-to-event variables with Kaplan–Meier estimates and compared by the log-rank test. A landmark analysis with a landmark set at 30 days to provide insights into the differences in early and late event rates through the different study cohorts was also performed. Stratified analyses were pre-defined: acute coronary syndrome, ST-elevation myocardial infarction, diabetes, gender, age ≥65 years, BMI ≥30 kg/m^2, renal failure, multivessel treatment, in-stent restenosis (any lesion), long lesions (total stent length in any lesion >20 mm), small vessels (stent diameter in any lesion <3.0 mm), stent used (BP-SES only vs DP-EES only). We also re-analyzed the primary endpoint after excluding cardiogenic shock patients. A *p* value of <0.05 was considered significant, and all tests were 2-tailed. All analyses were carried out with Stata 14 (College Station, TX: StataCorp LP).

Results

Study population

Between February 2012 and May 2013, 2261 patients underwent PCI in our institution. 1216 patients participated in the BIOSCIENCE trial (57.3 % of the overall trial population); the remaining 1045 patients not participating in the trial were included into the CARDIOBASE Bern PCI Registry (Fig. 1).

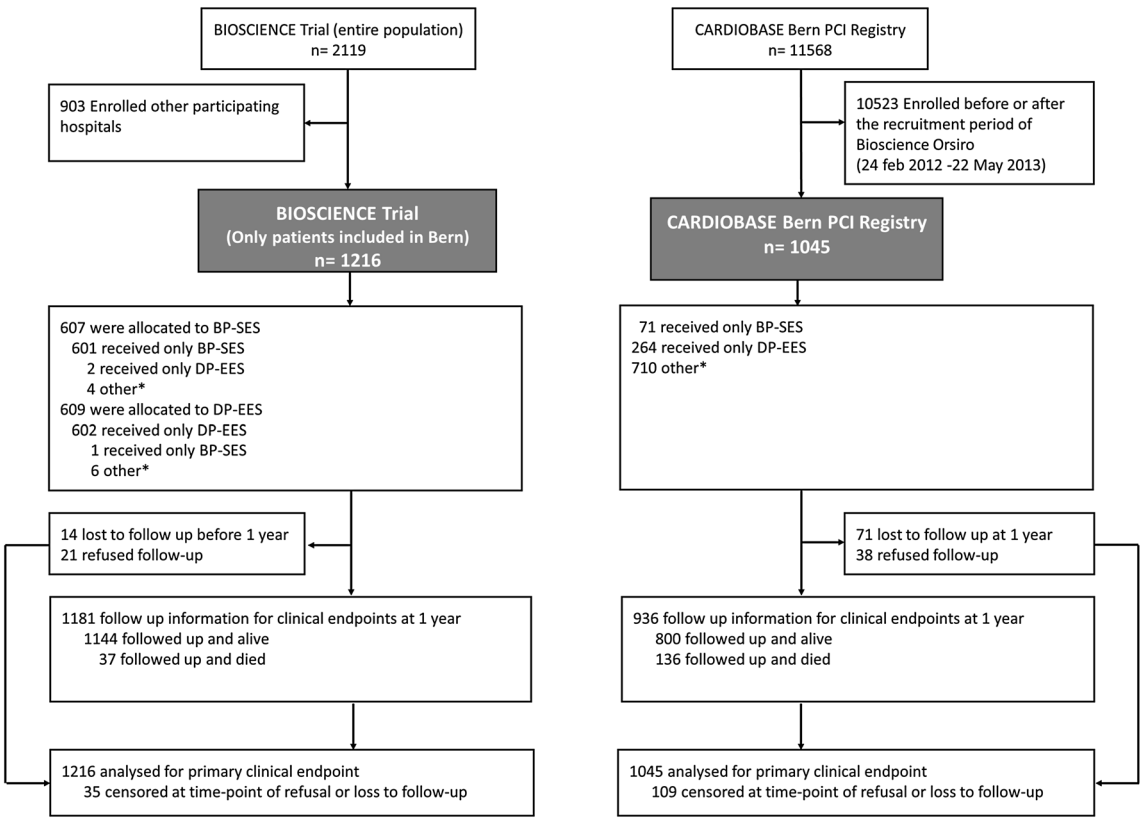

Fig. 1 Study flow diagram for comparison between participants in the BIOSCIENCE trial and non-participants entered in the CARDIOBASE Bern PCI Registry. *BP-SES* biodegradable polymer-sirolimus eluting stent, *DP-EES* durable polymer-everolimus eluting stent

Baseline clinical characteristics

Table 1 shows baseline clinical characteristics of participants in the BIOSCIENCE trial as compared to non-participants. Women were underrepresented in the RCT compared to the registry (25 vs. 29.4 %, $p = 0.020$). Patients included into the registry were older (69.2 ± 12.4 vs. 67.0 ± 11.6 years, $p < 0.001$), and had a significantly higher prevalence of previous cerebrovascular events (10.8 vs. 5.2 %, $p < 0.001$), and chronic renal failure (35.5 vs. 15.6 %, $p < 0.001$).

Moreover, non-participants presented with lower left ventricular ejection fraction (51.2 ± 15.5 vs. 54.6 ± 12.3 %, $p < 0.001$).

Conversely, a family history of CAD (25.9 vs. 18.0 %, $p < 0.001$) and previous PCI (30.2 vs. 22.1 %, $p < 0.001$) were more common among study participants.

Regarding clinical presentation, the registry included a significantly higher number of patients with ST-segment elevation myocardial infarction (STEMI) (30.7 vs. 21.1 %, $p < 0.001$) and patients with Killip class IV at presentation (7.8 vs. 0.4 %) compared with patients included into the RCT. Study arms also differed with respect to medical treatment at baseline: patients in the trial were more likely to be on DAPT (20.1 % vs. registry 9.9 %, $p < 0.001$), statins (54.3 vs. 46.3 %, $p < 0.001$) and beta-blockers (48.6 vs. 42.0 %, $p = 0.003$). In contrast, oral anticoagulation (OAC) was more frequent among patients in the registry (8.4 vs. 12.9 %, $p = 0.001$). Similarly, at discharge, 98.1 versus 92.4 % of patients were on DAPT in the trial and registry, respectively ($p < 0.001$); higher use of ticagrelor and statins was reported among patients included in the trial (Online Resource 1).

Procedural characteristics

Angiographic and procedural characteristics are summarized in Online Resource 2. There were no significant differences in the number of treated lesions and target vessel location between the two cohorts. In addition, the number of complex lesions was comparable between study participants and non-participants. As per study protocol, participants of the trial received BP-SES or DP-EES, and only three patients received bare-metal stents (BMS). The vast majority of subjects included in the registry were treated with DES, and only 5.9 % received BMS. Significantly higher use of intra-aortic balloon pump counterpulsation (2.9 vs. 0.3 %) and vasopressors (8.0 vs. 0.9 %) was reported in the registry compared to the RCT.

Clinical outcomes

Table 2 and Fig. 2 show clinical outcomes of participants relative to non-participants after 1 year from the index procedure.

The rate of the primary endpoint, TLF, amounted to 6.5 % in the RCT versus 15.0 % in the registry, respectively (RR 0.40, 95 % CI 0.30–0.53, $p < 0.001$).

The patient-oriented composite endpoint (POCE) occurred in 11.2 % of RCT compared to 21.6 % of registry patients (RR 0.47, 95 % CI 0.38–0.59, $p < 0.001$).

RCT participants experienced significantly lower rates of all-cause death (3.1 vs. 14.1 %, RR 0.20, 95 % CI 0.14–0.29, $p < 0.001$), cardiac death (2.0 vs. 10.5 %, RR 0.18, 95 % CI 0.11–0.28, $p < 0.001$), MI (4.0 vs. 5.8 %, RR 0.66, 95 % CI 0.45–0.98, $p = 0.038$) and definite or probable ST (2.7 vs. 10.4 %, RR 0.25, 95 % CI 0.17–0.37, $p < 0.001$) compared to registry participants. Rates of repeat revascularization (including target lesion and target vessel revascularization) were not significantly different between the two study cohorts (7.4 vs. 7.8 %, RR 0.92, 95 % CI 0.67–1.27, $p = 0.614$). The rate of POCE was not affected by the type of stent used, in both the registry and the trial (Online Resource 3).

In a landmark analysis of all-cause death, MI, repeat revascularization and POCE with the landmark set at 30 days, registry participants experienced significantly higher rates of adverse events compared to RCT participants within the first month after PCI (Fig. 3). The difference in outcome was preserved up to 1 year for the rate of all-cause death and POCE, whereas a reversal of the trend for repeat revascularizations, disfavoring patients in the registry, was observed beyond 30 days. Moreover, after the first month, rates of MI did not significantly differ between the two cohorts.

Figure 4 shows the risk of POCE among RCT versus registry patients across pre-specified subgroups. The lower risk of POCE in RCT patients was particularly pronounced among patients presenting with ACS (RR 0.38, 95 % CI 0.28–0.51) compared to patients presenting with stable coronary artery disease (RR 0.70, 95 % CI 0.49–0.99), with a statistically significant interaction for presence or absence of ACS ($p = 0.009$).

Discussion

The present analysis comparing all-comer study RCT participants with registry participants with regard to clinical characteristics, presentation and outcome recruited during the same time period at a single tertiary care center provided the following findings:

1. RCT participants were younger, more commonly male, and had a lower clinical risk profile as compared to registry participants; along the same line, patients presenting with STEMI and cardiogenic shock were underrepresented in the RCT.

Table 1 Baseline clinical characteristics of participants and non-participants of the BIOSCIENCE trial

	RCT participants ($n = 1216$)	Registry participants ($n = 1045$)	Difference (95 % CI)	p value
Age, years (SD)	67.0 ± 11.6	69.2 ± 12.4	−2.3 (−3.3; −1.3)	<0.001
Male gender, no. (%)	912 (75.0 %)	738 (70.6 %)	−4.4 % (−8.0 %; −0.7 %)	0.020
Body mass index, kg/m^2	27.7 ± 4.6	27.0 ± 5.0	0.6 (0.2; 1.0)	0.003
Diabetes mellitus, no. (%)	276 (22.7 %)	250 (24.1 %)	1.4 % (−2.1 %; 4.9 %)	0.454
Oral-treated	192 (15.8 %)	149 (14.5 %)	−1.3 % (−4.3 %; 1.7 %)	0.409
Insulin-treated	99 (8.1 %)	102 (9.9 %)	1.8 % (−0.6 %; 4.2 %)	0.159
Hypertension, no. (%)	840 (69.2 %)	715 (69.7 %)	0.5 % (−3.3 %; 4.3 %)	0.818
Hypercholesterolemia, no. (%)	811 (66.7 %)	689 (67.3 %)	0.5 % (−3.4 %; 4.4 %)	0.822
Current smoker, no. (%)	339 (27.9 %)	278 (27.8 %)	0.1 % (−3.7 %; 3.9 %)	0.962
Family history of CAD, no. (%)	313 (25.9 %)	185 (18.0 %)	−7.9 % (−11.3 %; −4.4 %)	<0.001
Previous MI, no. (%)	238 (19.6 %)	188 (18.2 %)	−1.4 % (−4.7 %; 1.8 %)	0.418
Previous PCI, no. (%)	367 (30.2 %)	228 (22.1 %)	−8.1 % (−11.8 %; −4.5 %)	<0.001
Previous CABG, no. (%)	136 (11.2 %)	132 (12.8 %)	1.6 % (−1.1 %; 4.3 %)	0.267
Atrial fibrillation, no. (%)	125 (10.3 %)	122 (11.9 %)	1.6 % (−1.0 %; 4.2 %)	0.250
Previous stroke or TIA, no. (%)	63 (5.2 %)	112 (10.8 %)	5.6 % (3.4 %; 7.8 %)	<0.001
Peripheral vascular disease, no. (%)	101 (8.3 %)	111 (10.7 %)	2.4 % (−0.0 %; 4.8 %)	0.051
Renal failure (GFR <60 ml/min), no. (%)	178 (15.6 %)	299 (35.5 %)	−19.9 % (−23.6 %; −16.2 %)	<0.001
Clinical presentation				
Congestive heart failure, no. (%)	$n = 1209$	$n = 1045$		<0.001
Killip I	1037 (85.8 %)	737 (70.5 %)	15.2 % (11.9 %; 18.6 %)	
Killip II	144 (11.9 %)	154 (14.7 %)	−2.8 % (−5.6 %; −0.0 %)	
Killip III	23 (1.9 %)	72 (6.9 %)	−5.0 % (−6.6 %; −3.3 %)	
Killip IV	5 (0.4 %)	82 (7.8 %)	−7.4 % (−9.0 %; −5.9 %)	
Left ventricular ejection fraction (%)	54.6 ± 12.3	51.2 ± 15.5	3.3 (2.1; 4.5)	<0.001
Acute coronary syndrome or other indication, no. (%)	$n = 1216$	$n = 977$		<0.001
Unstable angina	74 (6.1 %)	41 (4.2 %)	1.9 % (0.0 %; 3.8 %)	0.054
NSTEMI	307 (25.2 %)	270 (27.6 %)	−2.4 % (−6.1 %; 1.3 %)	0.223
STEMI	256 (21.1 %)	300 (30.7 %)	−9.7 % (−13.3 %; −6.0 %)	<0.001
Stable angina, no. (%)	404 (33.2 %)	283 (29.0 %)	4.3 % (0.4 %; 8.2 %)	0.033
Silent ischemia, no. (%)	175 (14.4 %)	83 (8.5 %)	5.9 % (3.2 %; 8.6 %)	<0.001
Baseline medications, no. (%)				
Aspirin	711 (59.8 %)	497 (53.4 %)	−6.4 % (−10.7 %; −2.2 %)	0.004
Clopidogrel	176 (14.8 %)	105 (11.3 %)	−3.5 % (−6.4 %; −0.6 %)	0.020
Prasugrel	44 (3.7 %)	7 (0.8 %)	−3.0 % (−4.3 %; −1.6 %)	<0.001
Ticagrelor	58 (4.9 %)	17 (2.2 %)	−2.7 % (−4.4 %; −1.0 %)	0.002
Any dual antiplatelet treatment	239 (20.1 %)	92 (9.9 %)	10.2 % (7.1 %; 13.3 %)	<0.001
Oral anticoagulants—vitamin K antagonists	100 (8.4 %)	120 (12.9 %)	4.5 % (1.9 %; 7.1 %)	0.001
Novel oral anticoagulants	4 (0.3 %)	1 (0.1 %)	−0.2 % (−0.7 %; 0.2 %)	0.654
Any antithrombotic treatment	104 (8.8 %)	121 (13.0 %)	−4.2 % (−6.9 %; −1.6 %)	0.002
Statins	644 (54.3 %)	431 (46.3 %)	−8.0 % (−12.2 %; −3.7 %)	<0.001
ACE-inhibitors or receptor blockers	320 (27.0 %)	246 (26.5 %)	−0.5 % (−4.3 %; 3.3 %)	0.843
Betablockers	576 (48.6 %)	390 (42.0 %)	−6.5 % (−10.8 %; −2.3 %)	0.003

Data expressed as n (%) or means ± standard deviations

ACE angiotensin converting enzyme, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *GFR* glomerular filtration rate, *MI* myocardial infarction, *NSTEMI* non-ST segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction, *TIA* transient ischemic attack

Table 2 1-year clinical outcomes in participants and non-participants of the BIOSCIENCE trial

	RCT participants ($n = 1216$)	Registry participants ($n = 1045$)	Risk difference (95 % CI)	Risk ratio (95 % CI)	p value
All-cause death	37 (3.1)	136 (14.1)	−9.97 (−12.23 to −7.71)	0.20 (0.14 to 0.29)	<0.001
Cardiac death	24 (2.0)	101 (10.5)	−7.69 (−9.65 to −5.74)	0.18 (0.11 to 0.28)	<0.001
Myocardial infarction (any)	47 (4.0)	54 (5.8)	−1.30 (−3.03 to 0.42)	0.66 (0.45 to 0.98)	0.038
Q-wave	10 (0.8)	8 (0.9)	0.06 (−0.68 to 0.79)	0.94 (0.37−2.38)	0.904
Non-Q-wave	38 (3.2)	47 (5.1)	−1.37 (−2.96 to 0.22)	0.61 (0.40− 0.94)	0.024
Target vessel-myocardial infarction	31 (2.6)	32 (3.4)	−0.51 (−1.88 to 0.86)	0.76 (0.46− 1.25)	0.279
Q-wave	8 (0.7)	3 (0.3)	0.37 (−0.19 to 0.93)	2.09 (0.55 to 7.92)	0.265
Non-Q-wave	23 (1.9)	29 (3.0)	−0.88 (−2.14 to 0.37)	0.62 (0.36 to 1.08)	0.088
Cardiac death or MI	69 (5.8)	147 (15.2)	−8.39 (−10.87 to −5.92)	0.35 (0.26 to 0.47)	<0.001
Repeat revascularization (any)	87 (7.4)	69 (7.8)	0.55 (−1.54 to 2.64)	0.92 (0.67 to 1.27)	0.614
Percutaneous repeat revascularization (any)	84 (7.1)	67 (7.5)	0.50 (−1.56 to 2.55)	0.91 (0.66 to 1.26)	0.586
Surgical repeat revascularization (any)	6 (0.5)	5 (0.6)	0.01 (-0.56 to 0.59)	0.87 (0.27 to 2.81)	0.817
Any target lesion revascularization	38 (3.2)	37 (4.1)	−0.42 (−1.90 to 1.07)	0.75 (0.48 to 1.19)	0.226
Percutaneous TLR	35 (3.0)	36 (4.0)	−0.57 (−2.02 to 0.88)	0.71 (0.44 to 1.14)	0.156
Surgical TLR	4 (0.3)	2 (0.2)	0.14 (−0.28 to 0.55)	1.45 (0.27 to 7.69)	0.661
Any target vessel revascularization	50 (4.2)	48 (5.4)	−0.48 (−2.17 to 1.21)	0.76 (0.51 to 1.14)	0.180
Any percutaneous TVR	48 (4.1)	46 (5.1)	−0.45 (−2.11 to 1.20)	0.76 (0.51 to 1.15)	0.190
Any surgical TVR	4 (0.3)	3 (0.4)	0.04 (−0.42 to 0.50)	0.97 (0.22 to 4.25)	0.969
Cerebrovascular event CVE	15 (1.3)	19 (2.1)	−0.58 (−1.60 to 0.44)	0.58 (0.29 to 1.14)	0.111
Stroke[a]	12 (1.0)	17 (1.9)	−0.64 (−1.59 to 0.31)	0.52 (0.24 to 1.09)	0.076
Ischemic stroke	11 (0.9)	14 (1.6)	−0.44 (−1.31 to 0.44)	0.58 (0.26 to 1.28)	0.170
Transient ischemic attack	4 (0.3)	2 (0.2)	0.14 (−0.28 to 0.55)	1.48 (0.27 to 8.02)	0.650
Cardiac death, TV-MI or TLR[b]	78 (6.5)	145 (15.0)	−7.46 (−9.97 to −4.95)	0.40 (0.30 to 0.53)	<0.001
Death, MI, or any repeat revascularization[c]	134 (11.2)	209 (21.6)	−8.98 (−11.98 to −5.98)	0.47 (0.38 to 0.59)	<0.001
Definite stent thrombosis	9 (0.8)	16 (1.7)	−0.79 (−1.68 to 0.10)	0.43 (0.19 to 0.99)	0.041
Definite or probable stent thrombosis	33 (2.7)	102 (10.4)	−7.05 (−9.06 to −5.03)	0.25 (0.17-0.37)	<0.001

Number of first events and percentages are reported. Rate ratios RR (95 % CI) are estimated using the Mantel–Cox method with two-sided p values from log-rank test (Bioscience/Registry). All events were censored beyond 365 days. Continuity corrected RR with Fisher's exact test for zero outcomes

CVE cerebrovascular events, *MI* myocardial infarction, *TLR* target lesion revascularization, *TV* target vessel, *TVR* target vessel revascularization

[a] Includes ischemic stroke, intracerebral hemorrhage and unclear etiology CVE

[b] Target lesion failure (TLF)—device-oriented composite endpoint

[c] Patient-oriented composite endpoint (POCE)

2. The risk of death, patient-oriented adverse events and ST was more than doubled in registry participants compared to RCT participants up to 1 year after PCI. While the effect on all-cause mortality was consistent within the first 30 days and beyond, the difference with regard to MI and repeat revascularization was limited to the first 30 days after intervention.
3. The difference in the risk of POCE between RCT participants and registry participants was accentuated in patients presenting with ACS.

RCTs are considered to generate the most reliable evidence, and provide the robust basis of treatment recommendations, expert consensus, and clinical guidelines. The use of new generation DES is currently recommended in all patient and lesion subsets among patients undergoing PCI, on the basis of head-to-head comparisons of different devices [1, 14–16]. The development of novel stent designs bearing the potential to refine the performance of new generation DES and scaffolds is paralleled by a progressive evolution of trial designs. Sample size calculations are

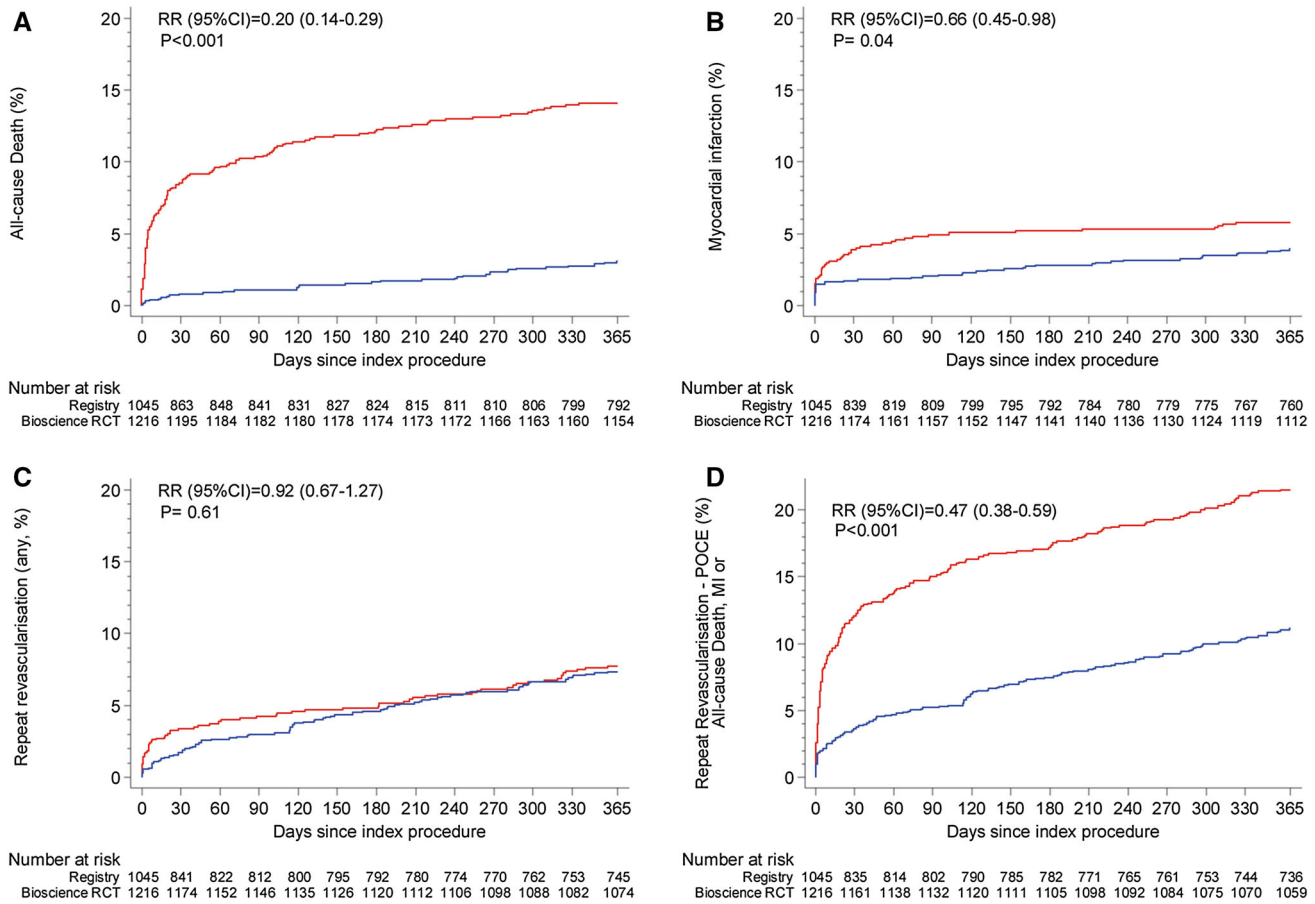

Fig. 2 Kaplan–Meier graphs of all-cause death (**a**), myocardial infarction (**b**), any repeat revascularization (**c**) and POCE (**d**) at 1-year follow-up. BIOSCIENCE *blue line*; CARDIOBASE Bern PCI Registry *red line*. *MI* myocardial infarction, *POCE* patient-oriented composite endpoint

performed to reduce the risk of chance, and randomization and stratification are used to minimize the risk of confounding factors. At the same time, broad inclusion criteria are applied to minimize selection and entry bias, and study subjects and event adjudication committees are blinded to treatment in order to avoid information bias [6].

Consistently, contemporary trials aim for the recruitment of large numbers of patients with minimal exclusion criteria to generate robust findings translatable into routine clinical practice.

Overall, these features attest to the internal validity of RCTs, but proved to be not sufficient to ensure the generalizability of their results [17, 18].

The systematic appraisal of external validity of relevant RCTs could help to identify factors still affecting their effectiveness in representing the real world outside of study protocols.

Significant differences in baseline characteristics and outcomes, for instance, were described for RCT participants and non-participants of the LEADERS and RESOLUTE III trials, two large "all-comers" PCI trials [19].

Furthermore, marked differences with regard to hospital characteristics between participating and non-participating sites of the recent DAPT trial were reported; a lower cardiovascular disease burden and younger age were also described for participants as compared to non-participants in the trial [20].

Along the same line, we found that trial participants had a lower risk profile and higher probability of mid-term survival than non-participants. Even though the rationale for non-inclusion of individual subjects had not been prospectively recorded, the important differences in baseline characteristics suggest a tendency to systematically exclude patients with specific features. Female gender continued to be an important determinant of non-participation in the trial. Sex-specific aspects of clinical presentation of CAD and inadequate awareness of the burden of the disease prevent an adequate proportion of women to be enrolled in interventional trials [21]. This underrepresentation hampers our knowledge about the typical aspects of the disease in female compared with male patients and aggravates a gender gap. Several previous reports, indeed,

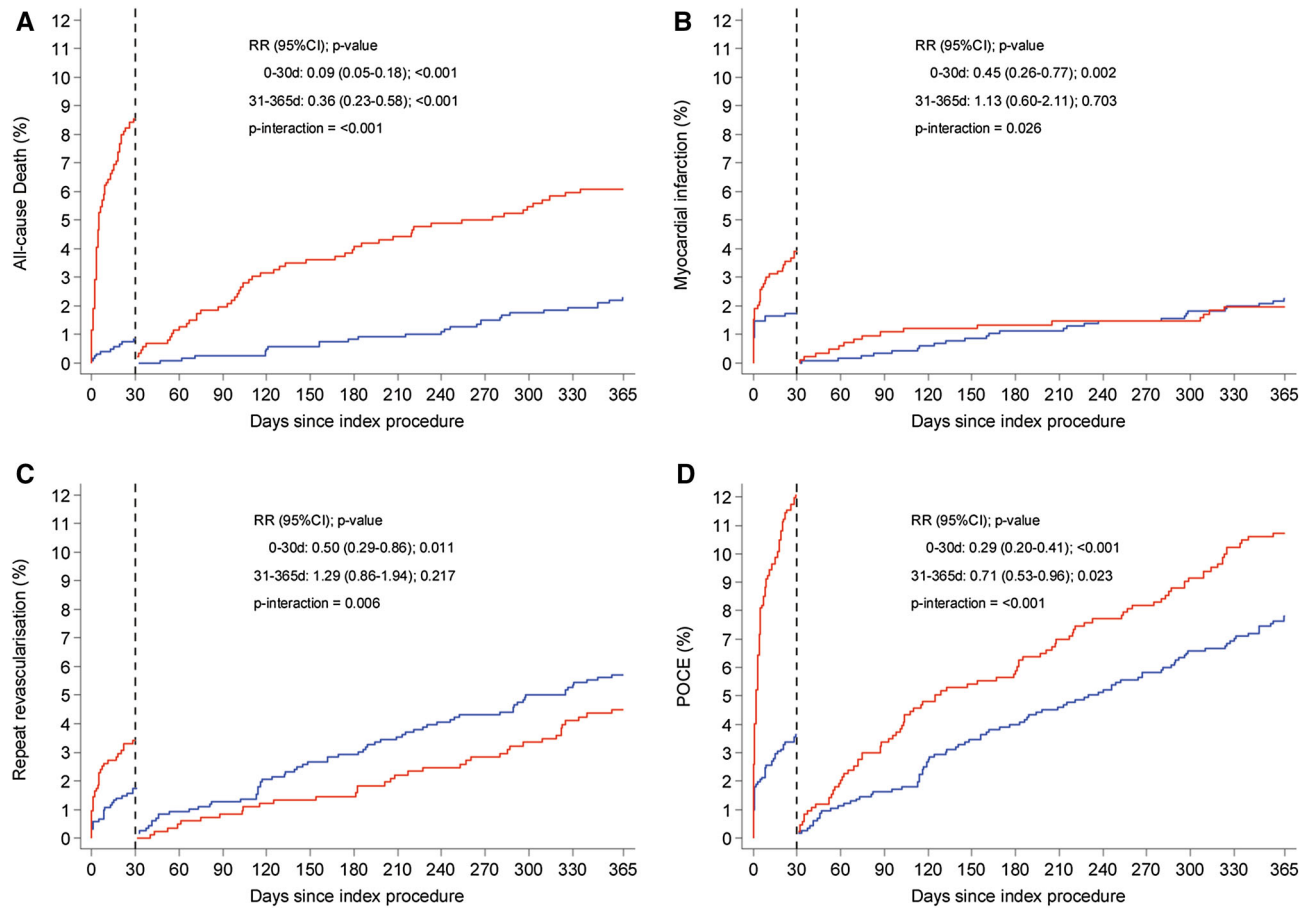

Fig. 3 Landmark at 30 days analyses of all-cause death (**a**), myocardial infarction (**b**), any repeat revascularization (**c**) and POCE (**d**) at 1-year follow-up. BIOSCIENCE *blue line*; CARDIOBASE Bern PCI Registry *red line*. *MI* myocardial infarction, *POCE* patient-oriented composite endpoint

described disparity in the provision of medical care in female population with cardiac diseases [22–24].

Advanced age, multiple comorbidities, need for long-term OAC and a more compromised status at presentation also increased the probability to be not included into the trial. These baseline differences translated into worse clinical outcomes of non-participants, especially in the early period after PCI.

All-cause and cardiac death were the stronger determinants of higher risk of the composite endpoints whilst rates of ischemic events (MI and repeat revascularization) were not significantly different between groups.

This finding has two main implications: (1) it reinforces the notion that critically ill patients, with pre-procedural higher probability to die, were preferentially not included in the trial; (2) the widespread use of new generation DES has the potential to mitigate the effects of higher baseline risk profiles on the risk of restenosis.

Indeed, rates of repeat revascularization were higher among registry participants during the early period after PCI (probably driven by higher occurrence of ST), but they were not different between the groups up to 1 year.

As an additional finding, we observed that the imbalance in terms of risk of adverse events between RCT and registry participants was prominent in the setting of ACS. The tendency to enroll lower risk patients was mirrored by a higher proportion of subjects with STEMI and/or cardiogenic shock at time of presentation in the registry. In emergency conditions, patients are less prone or unable to voluntarily accept the participation in studies. Inability to provide informed consent, indeed, was one of the main reasons for exclusion of subjects from two large "all-comers" trials and was reported mainly among patients with acute MI [19]. However, other factors hindering the participation in the trials in case of acute MI are still largely unrecognized because of an inadequate use of screening logs.

Overall, our results raise important concerns about the generalizability of current interventional trials: particularly, the persistent underrepresentation of higher risk patients limits our knowledge on how to optimize care among patients at highest risk [15, 25, 26]. A number of

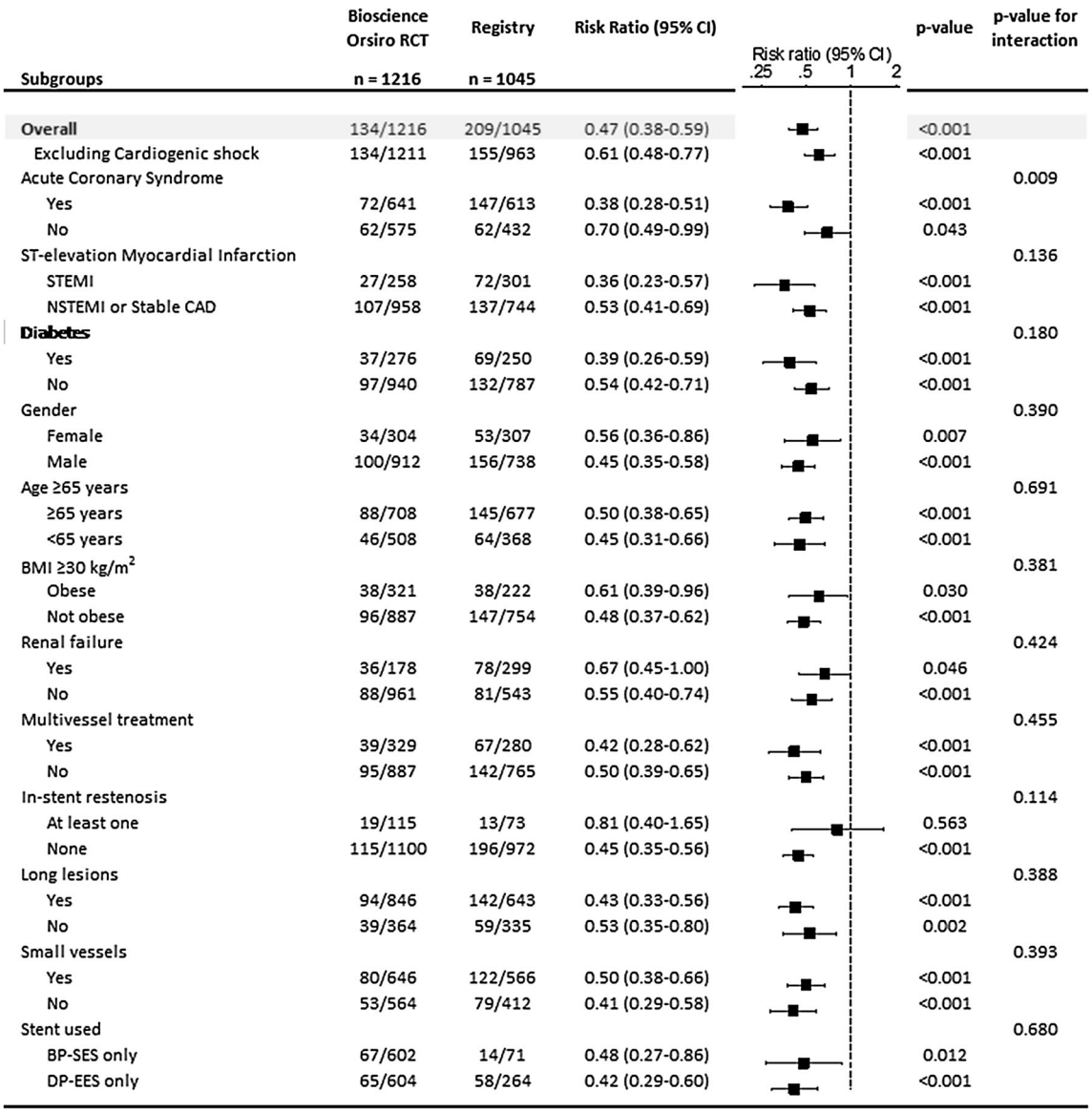

Fig. 4 Stratified analyses of POCE at 1-year in pre-specified subgroups. *BMI* body mass index, *BP-SES* biodegradable polymer-sirolimus eluting stent, *CAD* coronary artery disease, *MI* myocardial infarction, *DP-EES* durable polymer-everolimus eluting stent, *POCE* patient-oriented composite endpoint

tools have been proposed to overcome this issue: simplified acquisition of informed consent to facilitate the enrollment of patients, especially in emergency situations [19]; use of dedicated checklists inspired to the CONSORT flow diagram [9]; systematic collection of screening logs [19]; identification of a dedicated space within journals to report the information about external validity of published RCTs [27]; embedding of clinical trials in registries [28].

Their implementation in routine clinical practice could help to enhance the relevance of scientific research in several settings.

Our study has the following limitations: (1) although the BIOSCIENCE trial recruited patients at nine hospitals, the present analysis was limited to patients enrolled at a single institution. We acknowledge that considering the experience of a single site disregards the multicenter design of the trial; however, the ability to compare participants with patients included, during the same period, in a dedicated PCI registry with active follow-up and uniform adjudications of adverse events represents a major strength of our work; (2) we did not prospectively record reasons for non-inclusion into the BIOSCIENCE trial precluding an accurate estimate of actual reasons for non-inclusion; (3) selection of registry participants is only one of the numerous categories of external validity; (4) this was a post hoc analysis open to all the limitations of such investigations.

Conclusions

Several factors still affect the generalizability of contemporary interventional RCTs. Our study shows important differences between study participants and non-participants with regard to baseline characteristics and clinical outcomes in an unselected patient population referred for PCI. Disparities were not accounted for by study exclusion criteria, and were particularly pronounced among patients presenting with ACS. Major efforts are needed to ensure adequate representativeness of real-world patients and the consequent wide application of the study results.

Compliance with ethical standards

Conflict of interest AF has received a grant from Fondazione Umberto Veronesi. LR is on the advisory board of Abott Vascular; and received speaker fees from St. Jude Medical. RP has received a grant from Fondazione Umberto Veronesi. PJ is an unpaid steering committee or statistical executive committee member of trials funded by Abbott Vascular, Biosensors, Medtronic, and Johnson & Johnson. CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees. SW has received research contracts to the institution from Biotronik and St Jude. TP has received travel expenses and payment for lectures from Biotronik. All other authors have no relationships relevant to the contents of this article to disclose.

References

1. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A (2014) 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35(37):2541–2619. doi:10.1093/eurheartj/ehu278
2. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig 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(9591):937–948. doi:10.1016/S0140-6736(07)61444-5
3. Akin I, Nienaber CA, Richardt G, Tolg R, Hochadel M, Schneider S, Senges J, Tebbe U, Zeymer U, Sabin G, Kuck KH, Bergmann MW (2014) Risk factors for clinical events at 1-year follow-up after drug-eluting stent implantation: results from the prospective multicenter German DES.DE registry. Clin Res Cardiol 103(5):363–372. doi:10.1007/s00392-014-0662-x
4. De Luca G, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, Thuesen L, van der Hoeven B, Vink MA, Kaiser C, Musto C, Chechi T, Spaziani G, de la Llera LS, Pasceri V, Di Lorenzo E, Violini R, Suryapranata H, Stone GW (2014) Drug-eluting stents in patients with anterior STEMI undergoing primary angioplasty: a substudy of the DESERT cooperation. Clin Res Cardiol 103(9):685–699. doi:10.1007/s00392-014-0702-6
5. Stefanini GG, Holmes DR Jr (2013) Drug-eluting coronary-artery stents. N Engl J Med 368(3):254–265. doi:10.1056/NEJMra1210816
6. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T, Consort G (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 134(8):663–694
7. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P (2008) Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 372(9644):1163–1173. doi:10.1016/S0140-6736(08)61244-1
8. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B (2005) Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 353(7):653–662. doi:10.1056/NEJMoa051175
9. Rothwell PM (2005) External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 365(9453):82–93. doi:10.1016/S0140-6736(04)17670-8
10. Pilgrim T, Heg D, Roffi M, Tuller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Juni P, Windecker S (2014) Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet 384(9960):2111–2122. doi:10.1016/S0140-6736(14)61038-2
11. Pilgrim T, Roffi M, Tuller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Heg D, Juni P, Windecker S (2014) Randomized comparison of biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for percutaneous coronary revascularization: rationale and design of the BIOSCIENCE trial. Am Heart J 168(3):256–261. doi:10.1016/j.ahj.2014.06.004
12. Prineas RCRBH (1982) Minnesota code manual of electrocardiographic findings. John Wright-PSG, Littleton, p 1982
13. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research C (2007) Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 115(17):2344–2351. doi:10.1161/CIRCULATIONAHA.106.685313
14. Planer D, Smits PC, Kereiakes DJ, Kedhi E, Fahy M, Xu K, Serruys PW, Stone GW (2011) Comparison of everolimus- and paclitaxel-eluting stents in patients with acute and stable coronary syndromes: pooled results from the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) Trials. JACC Cardiovasc Interv 4(10):1104–1115. doi:10.1016/j.jcin.2011.06.018
15. Stefanini GG, Baber U, Windecker S, Morice MC, Sartori S, Leon MB, Stone GW, Serruys PW, Wijns W, Weisz G, Camenzind E, Steg PG, Smits PC, Kandzari D, Von Birgelen C, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Valgimigli M, Kastrati A, Chieffo

A, Mehran R (2013) Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. Lancet 382(9908):1879–1888. doi:10.1016/S0140-6736(13)61782-1

16. Harle T, Zeymer U, Schwarz AK, Luers C, Hochadel M, Darius H, Kasper W, Hauptmann KE, Andresen D, Elsasser A (2014) Use of drug-eluting stents in acute myocardial infarction with persistent ST-segment elevation: results of the ALKK PCI-registry. Clin Res Cardiol 103(5):373–380. doi:10.1007/s00392-014-0664-8
17. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR (1999) Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 282(15):1458–1465
18. Hordijk-Trion M, Lenzen M, Wijns W, de Jaegere P, Simoons ML, Scholte op Reimer WJ, Bertrand ME, Mercado N, Boersma E, Investigators E-C (2006) Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. Eur Heart J 27(6):671–678. doi:10.1093/eurheartj/ehi731
19. de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E (2011) Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. Eur Heart J 32(17):2161–2167. doi:10.1093/eurheartj/ehr126
20. Yeh RW, Czarny MJ, Normand SL, Kereiakes DJ, Holmes DR Jr, Brindis RG, Weaver WD, Rumsfeld JS, Roe MT, Kim S, Driscoll-Shempp P, Mauri L (2015) Evaluating the generalizability of a large streamlined cardiovascular trial: comparing hospitals and patients in the dual antiplatelet therapy study versus the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes 8(1):96–102. doi:10.1161/CIRCOUTCOMES.114.001239
21. Chieffo A, Hoye A, Mauri F, Mikhail GW, Ammerer M, Grines C, Grinfeld L, Madan M, Presbitero P, Skelding KA, Weiner BH, Mehran R, Group WIN, Women in Innovations I (2010) Gender-based issues in interventional cardiology: a consensus statement from the Women in Innovations (WIN) Initiative. Catheter Cardiovasc Interv 75(2):145–152. doi:10.1002/ccd.22327
22. Clarke KW, Gray D, Keating NA, Hampton JR (1994) Do women with acute myocardial infarction receive the same treatment as men? BMJ 309(6954):563–566
23. Milcent C, Dormont B, Durand-Zaleski I, Steg PG (2007) Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. Circulation 115(7):833–839. doi:10.1161/CIRCULATIONAHA.106.664979
24. Pilgrim T, Heg D, Tal K, Erne P, Radovanovic D, Windecker S, Juni P, Investigators AP (2015) Age- and gender-related disparities in primary percutaneous coronary interventions for acute ST-segment elevation myocardial infarction. PLoS One 10(9):e0137047. doi:10.1371/journal.pone.0137047
25. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L, Get With the Guidelines Steering C, Investigators (2008) Sex differences in medical care and early death after acute myocardial infarction. Circulation 118(25):2803–2810. doi:10.1161/CIRCULATIONAHA.108.789800
26. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM, American Heart Association Council on Clinical C, Society of Geriatric C (2007) Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 115(19):2549–2569. doi:10.1161/CIRCULATIONAHA.107.182615
27. Patrick K, Scutchfield FD, Woolf SH (2008) External validity reporting in prevention research. Am J Prev Med 34(3):260–262. doi:10.1016/j.amepre.2007.11.011
28. Lauer MS, D'Agostino RB Sr (2013) The randomized registry trial–the next disruptive technology in clinical research? N Engl J Med 369(17):1579–1581. doi:10.1056/NEJMp1310102