International Journal of Cardiology 276 (2019) 61–65

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Predictors of strut coverage of drug eluting stent implantation in diabetic patients

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ARTICLE INFO

Article history:
Received 31 July 2018
Received in revised form 15 October 2018
Accepted 8 November 2018
Available online 9 November 2018

Keywords:
Diabetes mellitus
Clopidogrel resistance
Drug eluting stent
Optical coherence tomography

ABSTRACT

Background: Incomplete re-endothelialization of drug eluting stent (DES) segments has been associated with the occurrence of major adverse cardiac events after DES implantation. It is unknown whether on-clopidogrel platelet reactivity (OPR) and/or circulating endothelial progenitor cells (EPC) levels may predict uncovered strut rate in diabetic patients treated by DES implantation.
Methods: One-hundred and five diabetic patients undergoing elective DES implantation were included into the study. EPC levels and OPR were assessed at 24 h (baseline) and 3 months. EPC were evaluated by flow cytometric analysis and defined by the co-expression of the markers CD34 and KDR. OPR was assessed using the impedance aggregometer. The degree of DES re-endothelialization was assessed at 3 months by optical coherence tomography.
Results: A direct correlation was observed between the uncovered strut rate and OPR both at baseline ($r = 0.47$: $p < 0.001$) and at the 3 months ($r = 0.25$: $p = 0.015$). On the contrary, we found no significant correlation between EPC level and uncovered strut rate either at baseline ($r = -0.02$; $p = 0.85$) or at 3 months ($r = -0.06$; $p = 0.13$). By multivariable regression analysis, independent predictors of uncovered strut rate > 5% were complex lesions (OR = 5.35; 95% confidence interval 1.32–17.57; $p = 0.027$) and OPR at baseline (OR = 4.73; 95% confidence interval 1.04–8.14; $p = 0.039$).
Conclusions: In diabetic patients treated with DES implantation OPR at baseline and complex lesions are independent predictors of uncovered strut rate at 3 months.

1. Introduction

A delayed or poor endothelial coverage over the stent struts has been associated with an increased rate of stent thrombosis [1–5]. The pathophysiological determinants of the impairment in stent struts coverage have not completely elucidated. Diabetes mellitus is an independent predictor of uncovered strut rate [6]. High on clopidogrel platelet reactivity (OPR) is an independent predictor of stent thrombosis and myocardial infarction after drug-eluting stent (DES) placement [7–12]. Furthermore, a low number of circulating endothelial progenitor cells (EPC) [13,14] has been associated with the occurrence of major adverse cardiac events after DES implantation.

In the Rosuvastatin For Reduction Of Myocardial Damage And Systemic Inflammation During Coronary Angioplasty EPC (REMEDY-EPC) trial we failed to demonstrate a correlation between EPC level and uncovered strut rate in diabetic patients treated by DES [15]. Purpose of the present analysis of the REMEDY-EPC trial was to identify the independent predictors of uncovered strut rate in diabetic patients treated by DES implantation.

2. Methods

The REMEDY-EPC study was conducted between 21 February 2012 and 15 December 2014 at the Clinica Mediterranea (Naples, Italy). The design of the REMEDY-EPC study has been previously reported (EudraCT Number: 2009-013622-17) [15,16]. In brief, 130 consecutive diabetic patients, statin näive or on chronic low intensity statin therapy, scheduled for elective DES implantation, were included. In the current study, all patients with the availability of OPR, EPC levels and optical coherence tomography (OCT) examination at 3 months follow-up were included. Written informed consent for participation was obtained in each patient. The study was funded through the Programma Operativo Nazionale (PON) Ricerca e Competitività 2007–2013 (PON01_02342), and was approved by our Ethic Committee.

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https://doi.org/10.1016/j.ijcard.2018.11.025
0167-5273/

2.1. Percutaneous coronary intervention

All patients were treated with the Cre8™ stent, a polymer-free sirolimus eluting formulation (Amphilimus) stent (Alvimedica, Istanbul, Turkey). All patients received daily aspirin (100 mg/day) and clopidogrel (75 mg/day if on chronic treatment, or 600 mg loading dose at least 6 h before the procedure). The complexity of coronary artery disease was quantified using the SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score. Lesions were classified according to the modified ACC/AHA grading system as type A, B1, B2, or C [17]. B2 and C lesions were considered complex.

2.2. Postprocedure management and follow-up

Aspirin (100 mg/day), and clopidogrel (75 mg daily for 12 months) were prescribed. Enrolled patients were scheduled for re-hospitalization at 3 months in order 1) to assess OPR and EPC levels, and 2) to perform OCT examination. We chose the 3 months interval of therapy and follow-up assessment in order to focus on the potential pathophysiologic correlation between the number of circulating EPC and the struts coverage and neointimal growth in the early phase after DES implantation, when the anti-proliferative effect of the eluted drug may interfere with the re-endothelialization process [15]. Clinical follow-up at one, 6 and 12 months was obtained by office visit in all patients to assess the occurrence of major adverse events (MACE), including death, non-fatal myocardial infarction, and the need for additional revascularization. Target lesion revascularization and stent thrombosis were defined according to the Academic Research Consortium criteria. All events were adjudicated by a Clinical Events Committee, blinded to treatment assignment.

2.3. Biochemical parameters

Blood samples were taken to assay total cholesterol, low and high-density lipoprotein cholesterol (LDL-C, HDL-C), triglycerides, high-sensitivity C-reactive protein (CRP), aspartate and alanine transaminases, serum creatinine, glycemia and glycosylated hemoglobin (HbA_1c). Optimal glycemic and lipid control were defined as $HbA_1c < 7\%$ and LDL-C < 70 mg/dL, respectively. The glomerular filtration rate (GFR) was calculated by applying the Modification of Diet in Renal Disease formula.

2.4. On-clopidogrel platelet reactivity

The ADP-induced platelet aggregation in whole blood was assessed with multiple electrode platelet aggregometry (MEA) using the impedance aggregometer (Multiplate analyzer, Dynabyte) [10]. The test was performed in the morning, within 3 h from the last maintenance dose of clopidogrel. Impedance with MEA was transformed to arbitrary aggregation units (AU) that were plotted against time (AU·min) [10]. According to the AU·min value, the following groups were identified: normal OPR (responders; ≤467 AU·min) and high OPR (non-responders; ≥468 AU·min) [10,18].

2.5. EPC assessment

Details on the experimental procedures of the flow cytometric analysis have been previously reported [15,16]. Peripheral blood samples were collected in ethylenediaminetetraacetic acid-treated tubes (4 tubes/patient) at the time of randomization, at 24-hour and at 3-month after procedure [16]. Peripheral mononuclear cells (PMNC) were isolated from 12 mL of peripheral blood by gradient centrifugation using Ficoll-Paque PLUS (GE Healthcare Life science, Milan Italy). EPC were evaluated by flow cytometric analysis which was performed on a FACSCanto II flow cytometer (BD Biosciences). EPC were defined by the co-expression of the markers CD34 and CD309 (VEGFR-2/KDR) [19,20].

2.6. Quantitative coronary angiography (QCA) and OCT

A Fourier-domain OCT system (Ilumien imaging system, LightLab Imaging, Inc., St. Jude Medical, St. Paul, MN) and the corresponding 6F guide catheter compatible Dragonfly Intravascular Imaging Catheter were used. All QCA and OCT analysis were performed by an independent Core laboratory (Euroimage Research s.r.l.). All assessments were performed off-line by personnel blinded to procedural data and clinical outcome. In particular, lesion and vessel parameters were obtained by means of QCA measurements using an automated edge detection algorithm (Medis 7 Cardiovascular angiography Analysis System II, The Netherlands). Similarly, all OCT frames were digitally stored and analyzed using an off-line software (LightLab Consolle, Westford, Massachusetts, USA) applying a 0.50-mm intervals, on all available frames. Assessment of strut tissue coverage, malapposition and neointimal thickness was done at stent level (per-stent analysis) [6,21]. Stent with suboptimal strut visualization (i.e. inability of OCT to address all stent struts in a specific cross-section) in >10% of total stent struts was excluded from final analysis. Details on OCT analysis have been previously reported [15,16]. Uncovered struts were defined as having a neointimal thickness of 0 μm [22]. In analyzing the degree of stent coverage at a patient-level, we identified a rate > 5% as cutoff value for the ratio of uncovered struts which might be considered clinically relevant [23]. For totally occluded vessels not associated with stent thrombosis, it was estimated that the entire length of the stent was filled with neointima. A malapposed strut was defined as a strut that had detached from the vessel wall by ≥ 100 μm (that is, strut thickness 80 μm + OCT resolution limit 20 μm). Cross-sections with major side branches (diameter ≥ 2 mm) and overlapping stents were excluded from this analysis.

2.7. Study objective

The objective of the present study was to identify the independent predictors of uncovered strut rate > 5% at 3 months follow-up.

2.8. Statistical analysis

Continuous variables are given as mean ± 1 standard deviation or median (interquartile range), as appropriate. The Student's *t*-test and the nonparametric Mann-Whitney tests were used to determine differences between mean values for normally and, respectively, non-normally distributed variables. Categorical variables are reported as percentage and were analyzed by either the Chi-square or the Fisher's exact test, as appropriate. Changes of EPC levels and OPR from baseline to the 3-month follow-up were assessed by a two repeated-measures analysis of variance ANOVA model, after transforming EPC levels into a natural logarithm (to overcome the problem of non-normal distribution). The correlation coefficients between OPR, EPC levels and uncovered strut rate were estimated using the Sperman's rho test. Interaction between OPR and EPC and uncovered strut rate was assessed with Generalized Linear Model. Logistic regression model was used to identify independent predictors of uncovered strut rate > 5%: variables entered into the model were selected according to the study hypothesis, literature and significance [p ≤ 0.10] at univariable analysis. Probability level < 0.05 was considered significant. Data were analyzed with SPSS 20 (Chicago, Illinois).

3. Results

3.1. Clinical and procedural characteristics

One-hundred and thirty patients were included into the REMEDY-EPC study. However, OCT data were available in 105 (81%) patients that represents the population of the current study. The remaining 25 (19%) patients refused OCT evaluation at 3 months. The most relevant clinical and angiographic characteristics are summarized in the Tables 1 and 2. The majority of the patients had stable coronary artery disease. We observed an improvement of clopidogrel responsiveness as well as an increase in the EPC levels from baseline to 3-month follow-up (Supplementary Fig. 1). OPR was not different between insulin-treated and oral-treated patients both at baseline (282 ± 175 versus 254 ± 196 AU·min; p = 0.44) and at 3 months (243 ± 165 versus 193 ± 130 AU·min; p = 0.10).

3.2. OCT evaluation at 3 months

Uncovered struts rate was 2.34 ± 2.40%. Uncovered strut rate > 5% occurred in 14 (13%) of patients. A significant direct correlation was observed between the uncovered strut rate and OPR both at baseline and at 3 months (Fig. 2). Patients with baseline high OPR showed higher uncovered strut rate than patients with normal OPR (4.41% [0−12] versus 1.32% [0–9.37]; p < 0.001). On the contrary, no significant correlation was observed between EPC level and uncovered strut rate either at baseline (r = −0.02; p = 0.85) or at 3 months (r = −0.06; p = 0.13). No interaction was observed between OPR, EPC level and uncovered strut rate. By multivariable logistic regression analysis, independent predictors of uncovered strut rate > 5% were complex lesions (OR = 5.35; 95% confidence interval 1.32–17.57; p = 0.027).and OPR at baseline (OR = 4.73; 95% confidence interval 1.04–8.14; p = 0.039) (Table 3).

3.3. Clinical outcome

At 1 year, MACE occurred in 22 (21%) patients. Although not statistically different, MACE rate was numerically higher in patients with uncovered strut rate > 5% at 3 months (5/14 [35.7%] versus 17/91 [18.7%]; p = 0.16). No case of definite or probable stent thrombosis occurred. Two patients (both with uncovered strut rate > 5%) experienced possible stent thrombosis (2/14 [14%] versus 0/91; OR = 13.25; 95% confidence intervals 5.05–14.70; p = 0.016).

Table 1
Clinical and biochemical characteristics of the patients.

	Patients (n = 105)
Age	67 ± 7
Male	74 (70%)
Symptoms	
Silent ischemia	26 (25%)
Stable angina	70 (67%)
Unstable angina	8 (8%)
Body mass index (kg/m^2)	29 ± 4
Left ventricular ejection fraction (%)	52 ± 8
Previous myocardial infarction	19 (18%)
Hypercholesterolemia	75 (72%)
Systemic hypertension	93 (88.5%)
Active smokers	28 (26.5%)
Treatment for diabetes mellitus	
Oral hypoglicemic drugs	67 (64%)
Insulin	38 (36%)
Concomitant therapy	
Beta blockers	57 (55%)
Calcium antagonists	21 (20%)
ACE inhibitors	26 (25%)
Angiotensin receptor blockers	18 (17%)
Diuretics	27 (26%)
Serum creatinine, median (IQR)	
Baseline	1.01 (0.90–1.30)
3 months	1.10 (0.85–1.20)
GFR (ml/min/1.73 m^2)	
Baseline	71 ± 22
3 months	71 ± 20
Microalbuminuria (mg/dL)	27 (5–105)
CRP, mg/dL	
Baseline	3.0 (3.0–3.6)
3 months	3.0 (3.0–5.5)
On-treatment platelet reactivity (AU·min)	
Baseline	264 ± 189
3 months	212 ± 145
HbA_1c (%)	
Baseline	7.5 ± 1.8
<7%	38 (36%)
3 months	7.4 ± 1.1
<7%	38 (36%)
Lipid profile (mg/dL)	
Baseline	
Total cholesterol	152 ± 41
LDL-C	88 ± 30
HDL-C	41 ± 10
Triglycerides	113 ± 80
3 months	
Total cholesterol	134 ± 41
LDL-C	65 ± 29
HDL-C	42 ± 14
Triglycerides	111 ± 80

ACE = angiotensin-converting-enzyme; GFR = glomerular filtration rate; CRP = C reactive protein; HbA_1c = glycosylated hemoglobin; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol.

Table 2
Angiographic characteristics of the patients.

	Patients (n = 105
Distribution of coronary artery disease	
Single vessel	9 (8.5%)
Double vessel	32 (30.5%)
Triple vessel	64 (61%)
Syntax score	17 ± 98
Low (0−22)	82 (78%)
Intermediate (23−32)	17 (16%)
High (≥33)	6 (6%)
Vessel treated	221
Left main	17 (7.5%)
Left anterior descending artery	70 (31.5%)
Diagonal branch	8 (3.5%)
Circumflex artery	44 (20%)
Obtuse marginal branch	13 (6%)
Right coronary artery	54 (24.5%)
Posterolateral branch	10 (4.5%)
Posterior descending artery	2 (1%)
Ramus	3 (1.5%)
Lesion site	295
Ostial	37 (12.5%)
Proximal	109 (37%)
Midvessel	118 (40%)
Distal	31 (10.5%)
Number of treated vessel/patient	2.17 ± 0.63
Number of treated lesion/patient	2.80 ± 1.16
Complex lesions (B2/C)	43 (41.5%)
Bifurcation lesions	24 (23%)
Diameter stenosis, %	
Pre	83 ± 11
Post	5 ± 8
Follow-up	12 ± 18
Reference vessel diameter, mm	
Pre	2.93 ± 0.78
Post	3.16 ± 0.52
Follow-up	3.18 ± 0.55
Minimal lumen diameter, mm	
Pre	0.74 ± 0.44
Post	3.00 ± 0.58
Follow-up	2.82 ± 0.76
Lesion length, mm	18 ± 10
Stent/patient	3.128 ± 1.24
Stent length (mm)	30 ± 16
Balloon-to-artery ratio	1.04 ± 0.10
Maximum pressure inflation (atmospheres)	15 ± 4

4. Discussion

The main result of the present study is that in diabetic patients, affected by stable coronary artery disease and treated with DES implantation, OPR and complex lesions are independent predictors of uncovered strut rate at 3 months.

4.1. On clopidogrel platelet reactivity and uncovered strut rate

High OPR is an independent predictor of 1-year stent thrombosis and myocardial infarction after DES placement [9], even though its overall diagnostic accuracy is quite fair [7,24]. Furthermore, in both autopsy and OCT studies, delayed and poor endothelial coverage over the stent struts have been associated with an increased rate of stent thrombosis [1–4].

Our finding of the association between OPR and uncovered strut rate might give insights on the potential mechanism linking OPR to cardiovascular events. Indeed, although previous studies reported that the occurrence of stent thrombosis in DES-treated patients was significantly associated with a poor response of the platelets to clopidogrel [10,25,26], our result demonstrates for the first time the association between OPR and uncovered strut rate. Circulating activated platelets affect endothelial inflammation, by releasing proinflammatory cytokines, such as CD40 and interleukin 1β [27,28] and leukocyte-endothelial interactions [27,29]. Inflammation profoundly impairs endothelial function in human microvascular circulation [30]. In addition, activated platelets are important sources of reactive oxygen species such as superoxide anions known to inactivate endothelium-derived nitric oxide. Future studies should test whether the administration of ticagrelor (instead of clopidogrel) in diabetic patients treated by DES implantation may reduce uncovered strut rate. The lack of correlation between EPC level and uncovered strut rate supports the concept that the majority of repopulating endothelial cells derives from outsides the stented vessel segment, whereas the contribution of circulating EPC may be minimal [31].

4.2. Complex lesions and uncovered strut rate

Although conflicting results exist on the correlation between lesion complexity and uncovered strut rate [6,21,32], our finding supports the role of lesion complexity in predicting uncovered strut rate [6]. The use of a single DES in the present study may explain the disagreement with

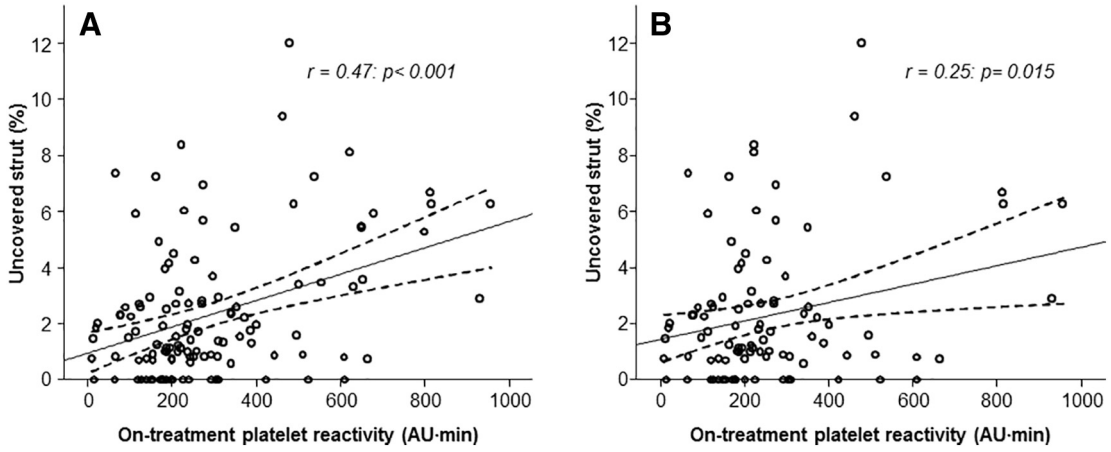

Fig. 2. Correlation between on clopidogrel platelet reactivity at 24 h (Panel A) and 3-month (Panel B) and uncovered strut rate assessed at 3 months after DES implantation.

previous investigations suggesting the lack of significant relevance of lesion complexity on strut coverage. Those studies, indeed, have been conducted in patients treated by different DES types, with different polymers, stent design, and strut thickness. It has been clearly showed that DES type may be a factor more powerful than plaque characteristics in determining strut coverage [21,32]. Previous studies suggested a higher rate (ranging from 8.6% to 21.3%) of incomplete strut coverage at 3 months after first generation DES implantation. We may speculate that the systematic implantation of the Cre8™ stent, a polymer-free sirolimus eluting formulation (which has been shown to perform quite well in diabetic patients [33]) may have had a role in our results.

4.3. Study limitations

We acknowledge some limitations of the present study: 1) while the results are encouraging, caution is warranted given the relative small size; 2) the present analysis was not a pre-specified endpoint of the REMEDY trial and, therefore, no a-priori power calculation was defined; 3) the results of the present study should be limited to the boundaries of the functional assay used (i.e. the Multiplate analyzer) and cannot be directly extended to other clinical assays proposed to assess OTR. At present, indeed, there is no standardized procedure, due to significant variability among the methods and the absence of uniform cutoff values for identifying patients at higher risk; 4) our findings, also should be interpreted into the boundaries of 3 months follow-up and cannot be extended to a longer follow-up; 5) different arbitrary cutoff values for the ratio of uncovered struts which might be considered clinically relevant have been reported. Due to the distribution of the uncovered strut rate in our population, we selected the cutoff of >5%. No data, however, exist on the superiority of this cutoff versus others (that is, >10% or >30%); and 6) preprocedural OCT was not performed; therefore we cannot evaluate the relationship between the baseline plaque characteristics (that is, fibrous, lipid, large lipid pool covered with a thin fibrous cap [thin-cap fibroatheroma], and large calcification) and stent strut coverage. Therefore, the findings of the present study should be interpreted as hypothesis generating.

Table 3
Predictors of uncovered strut rate > 5% by univariable and multivariable analysis.

Variable	Univariable model	Multivariable model		
		OR	95% CI	p
High on clopidogrel platelet reactivity				
At 24 h	0.020	4.73	1.04–8.54	0.039
At 3 months	0.045			
Complex lesions	0.020	5.35	1.32–17.57	0.027
Intensive statin therapy	0.90			
HbA1c < 7%				
At baseline	0.20	1.14	0.29–4.61	0.84
At 3 months	0.34			
LDL < 70 mg/dL				
At baseline	0.044	0.45	0.07–2.84	0.39
At 3 months	0.33			
EPC level				
At 24 h	0.55			
At 3 months	0.30			
High CRP level				
At baseline	0.14			
At 3 months	0.29			
Sex (male)	0.35			
Age	0.32			
LVEF	0.66			
BMI	0.25			
Insulin therapy	0.17			
CKD	0.76			
SYNTAX score	0.20			
Total stent length	0.30			
Complete revascularization	0.56			

OR = odds ratio; CI = confidence interval; EPC = endothelial progenitor cell; LVEF = left ventricular ejection fraction; BMI = body mass index; CKD = chronic kidney disease.

4.4. Conclusions

In diabetic patients, with stable coronary artery disease, treated with DES implantation OPR and complex lesions are an independent predictors of uncovered strut rate at 3 months. Future studies should evaluate whether the administration of ticagrelor (instead of clopidogrel) may reduce the uncovered strut rate and therefore improve the outcome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.025.

Acknowledgements

The study was funded through the Programma Operativo Nazionale (PON) Ricerca e Competitività 2007-2013 (PON01_02342) granted by the italian Ministry of Education, University and Research.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] A.V. Finn, M. Joner, G. Nakazawa, F. Kolodgie, J. Newell, M.C. John, H.K. Gold, R. Virmani, Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization, Circulation 115 (18) (8 2007) 2435–2441.

[2] G. Guagliumi, V. Sirbu, G. Musumeci, R. Gerber, G. Biondi-Zoccai, H. Ikejima, E. Ladich, N. Lortkipanidze, A. Matiashvili, O. Valsecchi, R. Virmani, G.W. Stone, Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging, J. Am. Coll. Cardiol. Intv. 5 (1) (2012) 12–20.
[3] J.S. Kim, M.K. Hong, C. Fan, T.H. Kim, J.M. Shim, S.M. Park, Y.G. Ko, D. Choi, Y. Jang, Intracoronary thrombus formation after drug-eluting stents implantation: optical coherence tomographic study, Am. Heart J. 159 (2) (2010) 278–283.
[4] J. Park, D.H. Shin, B.K. Kim, A.Y. Her, Y.H. Kim, H.H. Choi, J.S. Kim, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, Relationship between aspirin/clopidogrel resistance and intra-stent thrombi assessed by follow-up optical coherence tomography after drug-eluting stent implantation, Eur. Heart J. Cardiovasc. Imaging 14 (12) (2013) 1181–1186.
[5] Y. Ozaki, M. Okumura, T.F. Ismail, H. Naruse, K. Hattori, S. Kan, M. Ishikawa, T. Kawai, Y. Takagi, J. Ishii, F. Prati, P.W. Serruys, The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study, Eur. Heart J. 31 (12) (2010) 1470–1476.
[6] F. Prati, G. Guagliumi, G.S. Mintz, M. Costa, E. Regar, T. Akasaka, P. Barlis, G.J. Tearney, I.K. Jang, E. Arbustini, H.G. Bezerra, Y. Ozaki, N. Bruining, D. Dudek, M. Radu, A. Erglis, P. Motreff, F. Alfonso, K. Toutouzas, N. Gonzalo, C. Tamburino, T. Adriaenssens, F. Pinto, P.W. Serruys, C. Di Mario, Expert's OCTRD, Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures, Eur. Heart J. 33 (20) (2012) 2513–2520.
[7] N.J. Breet, J.W. van Werkum, H.J. Bouman, J.C. Kelder, H.J. Ruven, E.T. Bal, V.H. Deneer, A.M. Harmsze, J.A. van der Heyden, B.J. Rensing, M.J. Suttorp, C.M. Hackeng, J.M. ten Berg, Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation, JAMA 303 (8) (2010) 754–762.
[8] G. Parodi, R. Marcucci, R. Valenti, A.M. Gori, A. Migliorini, B. Giusti, P. Buonamici, G.F. Gensini, R. Abbate, D. Antoniucci, High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI, JAMA 306 (11) (2011) 1215–1223.
[9] G.W. Stone, B. Witzenbichler, G. Weisz, M.J. Rinaldi, F.J. Neumann, D.C. Metzger, T.D. Henry, D.A. Cox, P.L. Duffy, E. Mazzaferri, P.A. Gurbel, K. Xu, H. Parise, A.J. Kirtane, B.R. Brodie, R. Mehran, T.D. Stuckey, Investigators A-D, Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study, Lancet 382 (9892) (Aug 17 2013) 614–623.
[10] D. Sibbing, S. Braun, T. Morath, J. Mehilli, W. Vogt, A. Schomig, A. Kastrati, N. von Beckerath, Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis, J. Am. Coll. Cardiol. 53 (10) (2009) 849–856.
[11] M.J. Price, D.J. Angiolillo, P.S. Teirstein, E. Lillie, S.V. Manoukian, P.B. Berger, J.F. Tanguay, C.P. Cannon, E.J. Topol, Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial, Circulation 124 (10) (2011) 1132–1137.
[12] J.L. Mega, S.L. Close, S.D. Wiviott, L. Shen, R.D. Hockett, J.T. Brandt, J.R. Walker, E.M. Antman, W. Macias, E. Braunwald, M.S. Sabatine, Cytochrome p-450 polymorphisms and response to clopidogrel, N. Engl. J. Med. 360 (4) (2009) 354–362.
[13] N. Werner, S. Kosiol, T. Schiegl, P. Ahlers, K. Walenta, A. Link, M. Bohm, G. Nickenig, Circulating endothelial progenitor cells and cardiovascular outcomes, N. Engl. J. Med. 353 (10) (2005) 999–1007.
[14] C. Briguori, U. Testa, R. Riccioni, A. Colombo, E. Petrucci, G. Condorelli, G. Mariani, D. D'Andrea, F. De Micco, N.V. Rivera, A.A. Puca, C. Peschle, G. Condorelli, Correlations between progression of coronary artery disease and circulating endothelial progenitor cells, FASEB J. 24 (6) (2010) 1981–1988.
[15] C. Briguori, C. Quintavalle, F. D'Alessio, M. Donahue, G. Roscigno, F. De Micco, A. Focaccio, G. Visconti, L. Del Vecchio, R. Madonna, R. De Caterina, G. Condorelli, Impact of statin therapy intensity on endothelial progenitor cells after percutaneous coronary intervention in diabetic patients. The REMEDY-EPC late study, Int. J. Cardiol. 244 (2017) 112–118.
[16] C. Briguori, R. Madonna, M. Zimarino, P. Calabro, C. Quintavalle, M. Salomone, G. Condorelli, R. De Caterina, Rosuvastatin for reduction of myocardial damage during coronary angioplasty - the remedy trial, Cardiovasc. Drugs Ther. 30 (5) (2016) 465–472.
[17] S.G. Ellis, M.G. Vandormael, M.J. Cowley, G. DiSciascio, U. Deligonul, E.J. Topol, T.M. Bulle, Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group, Circulation 82 (4) (1990) 1193–1202.
[18] D. Sibbing, S. Braun, S. Jawansky, W. Vogt, J. Mehilli, A. Schomig, A. Kastrati, N. von Beckerath, Assessment of ADP-induced platelet aggregation with light transmission aggregometry and multiple electrode platelet aggregometry before and after clopidogrel treatment, Thromb. Haemost. 99 (1) (2008) 121–126.
[19] M. Peichev, A.J. Naiyer, D. Pereira, Z. Zhu, W.J. Lane, M. Williams, M.C. Oz, D.J. Hicklin, L. Witte, M.A. Moore, S. Rafii, Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors, Blood 95 (3) (2000) 952–958.
[20] M. Hristov, C. Weber, Endothelial progenitor cells: characterization, pathophysiology, and possible clinical relevance, J. Cell. Mol. Med. 8 (4) (2004) 498–508.
[21] F. Prati, E. Romagnoli, M. Valgimigli, F. Burzotta, M. De Benedictis, A. Ramondo, R. Mehran, P.R. Stella, Randomized comparison between 3-month Cre8 DES vs. 1-month Vision/Multilink8 BMS neointimal coverage assessed by OCT evaluation: the DEMONSTRATE study, Int. J. Cardiol. 176 (3) (2014) 904–909.
[22] M. Takano, S. Inami, I.K. Jang, M. Yamamoto, D. Murakami, K. Seimiya, T. Ohba, K. Mizuno, Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation, Am. J. Cardiol. 99 (8) (2007) 1033–1038.
[23] P. Barlis, E. Regar, P.W. Serruys, K. Dimopoulos, W.J. van der Giessen, R.J. van Geuns, G. Ferrante, S. Wandel, S. Windecker, G.A. van Es, P. Eerdmans, P. Juni, C. di Mario, An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study, Eur. Heart J. 31 (2) (2010) 165–176.
[24] C.V. Anselmi, C. Briguori, R. Roncarati, L. Papa, G. Visconti, A. Focaccio, F. De Micco, M.V. Latronico, P. Pagnotta, G. Condorelli, Reply: platelet reactivity is preferred over genotyping in monitoring efficacy of antiplatelet therapy, J. Am. Coll. Cardiol. Intv. 7 (4) (2014) 448–449.
[25] M.J. Price, S. Endemann, R.R. Gollapudi, R. Valencia, C.T. Stinis, J.P. Levisay, A. Ernst, N.S. Sawhney, R.A. Schatz, P.S. Teirstein, Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation, Eur. Heart J. 29 (8) (2008) 992–1000.
[26] J. Kotani, M. Awata, S. Nanto, M. Uematsu, F. Oshima, H. Minamiguchi, G.S. Mintz, S. Nagata, Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings, J. Am. Coll. Cardiol. 47 (10) (2006) 2108–2111.
[27] V. Henn, J.R. Slupsky, M. Grafe, I. Anagnostopoulos, R. Forster, G. Muller-Berghaus, R.A. Kroczek, CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells, Nature 391 (6667) (1998) 591–594.
[28] C.M. Hawrylowicz, G.L. Howells, M. Feldmann, Platelet-derived interleukin 1 induces human endothelial adhesion molecule expression and cytokine production, J. Exp. Med. 174 (4) (1991) 785–790.
[29] Y. Huo, A. Schober, S.B. Forlow, D.F. Smith, M.C. Hyman, S. Jung, D.R. Littman, C. Weber, K. Ley, Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E, Nat. Med. 9 (1) (2003) 61–67.
[30] A.D. Hingorani, J. Cross, R.K. Kharbanda, M.J. Mullen, K. Bhagat, M. Taylor, A.E. Donald, M. Palacios, G.E. Griffin, J.E. Deanfield, R.J. MacAllister, P. Vallance, Acute systemic inflammation impairs endothelium-dependent dilatation in humans, Circulation 102 (9) (2000) 994–999.
[31] G. Douglas, E. Van Kampen, A.B. Hale, E. McNeill, J. Patel, M.J. Crabtree, Z. Ali, R.A. Hoerr, N.J. Alp, K.M. Channon, Endothelial cell repopulation after stenting determines in-stent neointima formation: effects of bare-metal vs. drug-eluting stents and genetic endothelial cell modification, Eur. Heart J. 34 (43) (2013) 3378–3388.
[32] B.K. Kim, J.S. Kim, C. Oh, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, Major determinants for the uncovered stent struts on optical coherence tomography after drug-eluting stent implantation, Int. J. Card. Imaging 28 (4) (2012) 705–714.
[33] R. Romaguera, J.A. Gomez-Hospital, J. Gomez-Lara, S. Brugaletta, E. Pinar, P. Jimenez-Quevedo, M. Gracida, G. Roura, J.L. Ferreiro, L. Teruel, E. Montanya, A. Fernandez-Ortiz, F. Alfonso, M. Valgimigli, M. Sabate, A. Cequier, A randomized comparison of Reservoir-based polymer-free amphilimus-eluting stents versus everolimus-eluting stents with durable polymer in patients with diabetes mellitus: The RESERVOIR Clinical Trial, J. Am. Coll. Cardiol. Intv. 9 (1) (2016) 42–50.