Real-World Dual Antiplatelet Therapy Following Polymer-Free Sirolimus-Eluting Stent Implantations to Treat Coronary Artery Disease

Florian Krackhardt 1 · Matthias Waliszewski 1,2 · Viktor Kočka 3 · Petr Toušek 3 · Bronislav Janek 4 · Martin Hudec 5 · Fernando Lozano 6 · Koldobika Garcia-San Roman 7 · Bruno García del Blanco 8 · Josepa Mauri 9 · Tay Mok Heang 10 · Tae Hoon Ahn 11 · Myung Ho Jeong 12 · Denny Herberger 2 · Vjekoslav Tomulic 13 · Gilles Levy 14 · Laurent Sebagh 15 · Jérôme Rischner 16 · Michel Pansieri 17

Published online: 24 March 2020
© The Author(s) 2020, corrected publication November/2021

Abstract

Objectives The objective of this post hoc analysis was to analyze real-world dual antiplatelet therapy (DAPT) regimens following polymer-free sirolimus-eluting stent (PF-SES) implantations in an unselected patient population.

Methods Patient-level data from two all-comers observational studies (ClinicalTrials.gov Identifiers: NCT02629575 and NCT02905214) were pooled and analyzed in terms of their primary endpoint. During the data verification process, we observed substantial deviations from DAPT guideline recommendations. To illuminate this gap between clinical practice and guideline recommendations, we conducted a post hoc analysis of DAPT regimens and clinical event rates for which we defined the net adverse event rate (NACE) consisting of target lesion revascularization (TLR, primary endpoint of all-comers observational studies) all-cause death, myocardial infarction (MI), stent thrombosis (ST), and bleeding events. A logistic regression was utilized to determine predictors why ticagrelor was used in stable coronary artery disease (CAD) patients instead of the guideline-recommended clopidogrel.

Results For stable CAD, the composite endpoint of clinical, bleeding, and stent thrombosis, i.e., NACE, between the clopidogrel and ticagrelor treatment groups was not different (5.4% vs. 5.1%, \( p = 0.745 \)). Likewise, in the acute coronary syndrome (ACS) cohort, the NACE rates were not different between both DAPT strategies (9.2% vs. 9.3%, \( p = 0.927 \)). There were also no differences in the accumulated rates for TLR, myocardial infarction (MI), mortality, bleeding events, and stent thrombosis in elective and ACS patients. The main predictors for ticagrelor use in stable CAD patients were age < 65 years, smaller vessels, treatment of ostial and calcified lesions, and in-stent restenosis.

Conclusion Within the framework of a post hoc analysis based on a real-world, large cohort study, there were no differences in the combined endpoint of major adverse cardiac events (MACE), bleeding and thrombotic events for clopidogrel and ticagrelor in stable CAD or ACS patients. Despite the recommendation for clopidogrel by the European Society of Cardiology (ESC), real-world ticagrelor use was observed in subgroups of stable CAD patients that ought to be explored in future trials.

Keywords Dual antiplatelet therapy · Clopidogrel · Ticagrelor · Polymer-free · Sirolimus-eluting stent

Introduction

The current European Society of Cardiology (ESC) guidelines [1] provide recommendations for dual antiplatelet therapy (DAPT) following percutaneous coronary interventions (PCIs). However, this guidance to balance the risks for ischemic events and bleeding episodes provide some latitude. However, in stable coronary artery disease (CAD), there is only one recommended regimen consisting of clopidogrel and aspirin. Since the “ischemic” risks for major cardiac events (MACE) in particular for stent thrombosis (ST) following drug-eluting stent (DES) implantations are multifactorial [2], it is important to control as many of these factors as possible (Fig. 1). Therefore, it seems advantageous to study these
risks in a large patient population which received one particular DES to eliminate stent-related factors. In this case, the effect of DAPT on the outcomes can be better elucidated. Nevertheless, previous studies focused either on different devices (bare metal stents [BMS] vs. DES) and/or different DAPT modalities (duration).

Urban et al. [3] focused on stent-related factors and compared a drug-coated stent to a BMS in patients with high bleeding risk (HBR) while both groups had the same DAPT regimen. They reported that the drug-coated stent with only 1 month of DAPT was superior to its BMS analogue in terms of safety (cardiac death, myocardial infarction, and ST) and efficacy relative to target lesion revascularization (TLR). While this milestone randomized controlled trial (RCT) investigated the risk/benefit ratio of bleeding vs. ischemic events with a drug-coated stent in high-risk patients, other researchers felt also inspired to study shorter DAPT durations in other clinical scenarios.

In the SENIOR trial [4], the study of patient related factors was the objective. Elderly patients with an increased bleeding risk were randomized in two groups to receive either a DES or BMS while the type of DAPT was not specified, i.e., all P2Y12 receptor inhibitors were permissible. A very comprehensive overview of the type of DAPT was given in the ESC guidelines updated in 2017 [1]. In these guidelines, neither ticagrelor nor prasugrel were recommended for patients with stable coronary artery disease (CAD).

The meta-analysis conducted by Palmerini and coworkers [5], once again a mélange of different DAPT agents and various DES technologies, revealed that in stable CAD patients, there were no significant differences in terms of myocardial infarction (MI) and ST, cardiac death, or any bleeding rates between a short and regular DAPT duration (3 vs. 6 months).

Given the favorable clinical outcomes of a polymer-free thin strut sirolimus-eluting stent (PF-SES) in unselected non-HBR patients [6, 7] with postulated rapid strut coverage [8], we decided to pool data from two observational studies having an identical protocol to analyze the data of a large cohort. During the data analysis, we realized that ticagrelor was used even in elective patients. This in turn triggered subsequent analyses why this more aggressive P2Y12 receptor blocker was used in this particular patient group. Due to the fact that sufficiently large patient cohorts were available and only one particular DES was used, we could study the effect of either aspirin + clopidogrel or aspirin + ticagrelor following in patients with stable CAD and acute coronary syndrome (ACS).

Our primary objective was to study these two DAPT regimens (aspirin + clopidogrel or aspirin + ticagrelor) after PF-SES implantation with a defined post hoc composite endpoint, i.e., net adverse coronary event
(NACE) defined as the cumulative event rates of TLR, MI, all-cause mortality, ST, and bleeding rates in “real-world” patients.

Methods

End Points and Definitions

The international ISAR 2000 all-comers registry (ClinicalTrials.gov Identifier NCT02629575) [6, 7] and the ISAR 2000 all-comers extended registry (ClinicalTrials.gov Identifier NCT02905214) prospectively enrolled patients in Europe and Asia. Prior to patient recruitment, all relevant ethics committees approved the study protocol. To accommodate for national differences of follow-up windows, mainly due to reimbursement issues, a timeframe of 9–12 months was permissible. In the original two studies, target lesion revascularization rate (TLR, coronary artery bypass grafting and Re-PCI) at follow-up was the primary end point, whereas the rate of MACE and the corresponding rates of myocardial infarction (MI) were part of the secondary end-points. Cardiac death was only defined in-hospital whereas the all-cause death rate was used to define MACE at 9–12 months (MI, TLR, in-hospital cardiac death, all deaths post discharge).

During the data verification process, we observed substantial deviations from the DAPT guideline recommendations. To illuminate this gap between clinical practice and guideline recommendation, we conducted a post hoc analysis of all patients receiving either clopidogrel or ticagrelor. To account for ischemic and bleeding events, we defined the net adverse event rate (NACE) which was based on the KAMIR-NIH study conducted by Sim and coworkers [9]. NACE is a composite endpoint consisting of target lesion revascularization (TLR, primary endpoint of all-comers observational studies) all-cause death, myocardial infarction (MI), stent thrombosis (ST), and bleeding events. The definition of acute/subacute stent thromboses (ST) was based on the ARC criteria [10]. Bleeding events were defined according to the BARC classification [11] whereas major bleeding episodes were collectively defined as BARC 3a-5.

A glomerular filtration rate (GFR) < 90 mL/min/1.73m² defined renal insufficiency while the cut-off GFR rate for mandatory dialysis was < 15 mL/min/1.73 m². Severe tortuous vessels were defined by the angulation criterion of > 45°.

Centers

Patients were prospectively enrolled in 39 Asian (South Korea, Malaysia) and 43 European (Croatia, Czech Republic, France, Germany, Slovakia, Spain) cardiac centers.

Materials

All patients received PF-SES of identical polymer-free coating consisting of probucol and sirolimus (Coroflex© ISAR or Coroflex© ISAR NEO, B.Braun Melsungen AG, Germany). All PF-SES were implanted in accordance with each institution’s guidelines and preferences. The PF-SES was described in detail by Krackhardt et al. [6].

Inclusion and Exclusion Criteria

Adult patients with stable angina and objective proof of ischemia or patients with acute coronary syndrome (ACS) had to meet the requirements for PCI at the time the study was being conducted [12]. Stenting was allowed in de novo or restenotic lesions of single or multiple vessels with reference diameters from 2.0 to 4.0 mm.

Procedural Approach

Radial or femoral vascular access was permitted with a recommended introducer sheath of at least five French in diameter. Pre-dilatation with a balloon catheter of the operators’ preference or the direct stenting approach could be chosen. Intravenous heparin (70 IU/kg) was given in all patients and supplemented as needed. According to the institutional preferences of the cardiac centers, platelet aggregation inhibitor loading was recommended but not mandatory.

Post-Procedural Medication

Due to the all-comers nature of this assessment which encompassed centers from Europe and Asia, the choice and duration of the P2Y12 receptor inhibitor was defined by the ESC guideline [12], i.e., 6 months of clopidogrel for patients with stable CAD, and 12 months for ACS patients. As previously reported by Krackhardt et al. [6], various antiplatelet inhibition agents (≥ 6 months) such as clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 2 × 90 mg/day were allowed in conjunction with acetylsalicylic acid 100–325 mg/day life long as recommended by the treating physician.

Data Collection

An electronic data capture system [13, 14] was used which has built-in plausibility checks during each stage of the data entry. Each participating country had a national principal investigator who verified the accuracy of the dataset on a national level whenever routinely performed web-based plausibility checks indicated discrepancies.
Statistical Analysis

Continuous variables are expressed in means and standard deviations and compared with the unpaired t test or the Mann-Whitney U test in case the Shapiro-Wilk test revealed a strong deviation from a normal distribution. Dichotomous and categorical variables are described in counts and percentages and evaluated with the two-sided Fisher’s exact test or the chi² statistic whenever applicable.

Moreover, a logistic regression with various covariates (patient, lesion and procedural parameters) was conducted with “ticagrelor use” as the dependent variables. This post hoc analysis was done to study “predictors for ticagrelor use” in elective patients. The significance level α was 0.05 for all tests. SPSS version 24.0 (IBM, Munich, Germany) was used for all statistical analyses.

Ethics Approval

Prior to patient recruitment, all ethics votes were obtained from relevant national and/or local ethics committees. In France, these non-interventional studies were approved by the Comité Consultative sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé (CCTIRS dossier no. 14.613) and the Commission Nationale de l’informatique et des Libertés (CNIL, demande d’autorisation n°915,019). This study was conducted within the framework of the Declaration of Helsinki in its most current form.

Results

Total Study Population

Between November 2014 and December 2017, 7243 patients were enrolled and treated with PF-SES. Patient demographics, lesion morphologies, and procedural details are detailed in Table 1 for those patients who received either clopidogrel or ticagrelor. Of these, 3828 patients had stable CAD and were treated either with clopidogrel (3224, 84.2%) or ticagrelor (604, 15.8%). Likewise in the ACS subgroup, a total of 2569 patients (clopidogrel 1549, 60.3% vs. ticagrelor: 1020, 29.7%) were available for analysis. Patients who were treated with either clopidogrel (n = 3224) or ticagrelor (n = 604) were used for further analyses (Fig. 2).

Overall, elective patients receiving ticagrelor in stable CAD were more frequently treated in ostial lesions (11.1% vs. 6.8%, p = 0.006) and had longer DAPT (10.5 ± 2.6 months vs. 9.9 ± 2.8 months, p < 0.001) and were less frequent on triple therapy (0.1% vs. 1.7%, p = 0.006). Besides the above-mentioned differences, procedural and lesion related characteristics in the stable CAD groups were reasonably similar (Table 2). In terms of clinical event rates, there were no significant differences between patients treated with either clopidogrel or ticagrelor in terms of NACE (5.4% vs. 5.1%, p = 0.745), MACE (2.8% vs. 3.3%), thrombotic events (0.5% vs. 0.9%, p = 0.213), or bleeding episodes (2.8% vs. 2.2%, p = 0.399).

In the ACS cohort, the NACE rates were significantly higher than the corresponding rates in elective patients (clopidogrel: pstable CAD vs. ACS<0.001, ticagrelor: pstable CAD vs. ACS=0.031). Neither MACE, TLR, bleeding, or thrombotic events were significantly different in ACS patients treated with either clopidogrel or ticagrelor. However, the accumulated mortality rate trended higher in the clopidogrel group as compared to the ticagrelor group (2.8% vs. 1.6%, p = 0.060).

Predictors for Ticagrelor Use in Stable CAD

The forest plot of the logistic regression analysis is shown in Fig. 3. Predictors for ticagrelor use were patients < 65 years of age (p < 0.001), hypertension (p < 0.001), smaller reference vessels (p = 0.022), stenting in ostial lesions (p = 0.001), presence of calcification (p = 0.015), the use of more than one stent (p < 0.001), and in-stent restenosis (p = 0.003).

DAPT Length and Follow-Up Duration

A post hoc analysis of DAPT durations was also conducted with the pooled clopidogrel/ticagrelor data (Table 3). Based on an established cut-off value of ≤3 months [1], there were no differences between the short DAPT (≤3 months) and the long DAPT regimen (> 3 months) in terms of NACE, MACE, TLR, all-cause death, and bleeding complications up to the follow-up. The accumulated MI rates between these two groups, however, were borderline significant (0.6% vs. 2.5%, p = 0.043). The time to discharge was shorter in patients that had ≤3 months of DAPT as compared to those with > 3 months (3.4 ± 10.6 vs. 3.9 ± 20.6, p = 0.030). The shorter DAPT duration was strongly associated with triple therapy (11.5% vs. 1.5%, p < 0.001).

A follow-up window of 9–12 months was requested by several European countries (e.g., Belgium) due to local reimbursement requirements. The “a priori” defined subgroup with follow-up data ≥12 months was analyzed to better respond to the documentation needs in these countries. There was a total of 264 patients with a follow-up duration ≥12 months, including premature events, of 13.3 ± 2.8 months. The corresponding NACE rate in the longer follow-up group was 6.6% (33/501) with no differences between the DAPT groups (clopidogrel 5.9% vs. ticagrelor 8.4%, p = 0.303). Further analyses revealed that the accumulated MACE rate in the longer follow-up group was 4.0% (20/501) without differences between patients receiving clopidogrel and ticagrelor (3.1% vs. 6.3%, p = 0.096). However, the MI rates were...
significantly different between both subgroups (0.8% vs. 4.9%, $p = 0.003$) with an overall MI rate of 2.0% (10/501). In the longer follow-up cohort, the accumulated mortality rate was 0.6% (3/501) without differences between DAPT groups (0.8% vs. 0.0%, $p = 0.272$). Likewise there was no difference in the accumulated rates for definite/probably stent thrombosis with an overall rate of 0.9% (4/501) and without differences in patients receiving clopidogrel or ticagrelor (0.6% vs. 1.5%, $p = 0.335$).

### Discussion

There is a plethora of potential factors and confounders (Fig. 1), which may determine the risk for ischemic events and bleeding episodes in patients undergoing stenting procedures. In the updated ESC guidelines [1], ticagrelor and prasugrel are not recommended for patients with stable CAD. Nevertheless, these new P2Y12 receptor inhibitors are being prescribed for stable CAD patients in clinical practice.
Use of Ticagrelor in Stable CAD Patients

The use of new P2Y12 receptor inhibitors (ticagrelor, prasugrel) is only recommended in ACS patients with a class I recommendation. However, despite the data granularity of our all-comers observational study of close to 3800 stable CAD patients, 15.8% of these patients treated were treated with ticagrelor in real-world clinical practice. But why were these patients not treated with clopidogrel? One could speculate that the use of a polymer-free DES and the concomitant prescription of a more effective antiplatelet agent such as ticagrelor followed a “belt and suspenders” strategy in patients with low/moderate bleeding risk. Our regression analysis revealed that ticagrelor is frequently used in stable CAD patients of younger age and/or lesions with smaller vessel diameters and ostial and calcified lesions. In other words, these attributes may have been considered more challenging in terms of their cardiovascular risk factors or culprit lesion morphology. The higher rate of ostial lesions in the ticagrelor DAPT group (11.2% vs. 7.9%, \(p = 0.004\)) may serve as an explanation for this theory. The treatment of smaller vessels \( (p = 0.022) \) and in-stent restenosis \( (p = 0.003) \) support this theory whereas patients with severe vessel tortuosity received more often clopidogrel \( (p = 0.026) \).

Moreover, patients in the ticagrelor group were less frequent on triple therapy as compared to those who had clopidogrel as part of their standard DAPT \( (0.1\% \text{ vs.} 2.0\%, \ p = 0.001) \). Patients on oral anticoagulation were preferably treated with clopidogrel probably due to its safety profile in this subgroup.

Finally, despite our clinical outcomes in stable CAD patients who were treated with ticagrelor, it is not our
### Table 2  Clinical outcomes in patients treated with clopidogrel or ticagrelor and polymer-free sirolimus-eluting stents

| Variable                                | Stable CAD | Ticagrelor | p value | ACS          | Ticagrelor | p value |
|-----------------------------------------|------------|------------|---------|--------------|------------|---------|
| Number of patients                      | 3224       | 604        | –       | 1549         | 1020       | –       |
| Patients with clinical long term follow-up or early event | 2909 (90.2%) | 550 (91.1%) | 0.526   | 1375 (88.8%) | 873 (85.6%) | 0.017   |
| Follow-up time (months)                 | 9.3 ± 2.0  | 9.2 ± 2.2  | 0.058   | 9.3 ± 2.5    | 9.3 ± 2.4  | 0.961   |
| Time to discharge (days)                | 3.9 ± 20.8 | 2.6 ± 10.6 | 0.034   | 3.3 ± 3.7    | 3.2 ± 3.1  | 0.473   |
| Accumulated NACE                        | 158 (5.4%) | 28 (5.1%)  | 0.745   | 126 (9.2%)   | 81 (9.3%)  | 0.927   |
| Accumulated MACE                        | 80 (2.8%)  | 18 (3.3%)  | 0.498   | 83 (6.0%)    | 47 (5.4%)  | 0.518   |
| Accumulated TLR                         | 50 (1.7%)  | 9 (1.6%)   | 0.891   | 37 (2.7%)    | 19 (2.2%)  | 0.446   |
| Re-PCI                                  | 43 (1.5%)  | 9 (1.6%)   | 0.780   | 36 (2.6%)    | 16 (1.8%)  | 0.227   |
| CABG                                    | 9 (0.3%)   | 0 (0.0%)   | 0.191   | 5 (0.4%)     | 8 (0.9%)   | 0.092   |
| Accumulated MI                          | 16 (0.6%)  | 7 (1.3%)   | 0.056   | 25 (1.8%)    | 22 (2.5%)  | 0.257   |
| Accumulated death all causes            | 22 (0.8%)  | 5 (0.9%)   | 0.709   | 39 (2.8%)    | 14 (1.6%)  | 0.060   |
| Accumulated definite/ probable stent thrombosis | 14 (0.5%) | 5 (0.9%)   | 0.213   | 8 (0.6%)     | 7 (0.8%)   | 0.532   |
| Acute stent thrombosis, ≤ 24            | 5 (0.2%)   | 3 (0.5%)   | 0.241   | 4 (0.1%)     | 3 (0.3%)   | 0.351   |
| Subacute stent thrombosis, 1–30 days    | 0 (0.0%)   | 0 (0.0%)   | 0.191   | 2 (0.1%)     | 0 (0.0%)   |        |
| Late stent thrombosis, ≥ 30 days        | 9 (0.3%)   | 2 (0.4%)   | 0.213   | 2 (0.1%)     | 4 (0.5%)   |        |
| Bleeding complications                  | 82 (2.8%)  | 12 (2.2%)  | 0.399   | 46 (3.3%)    | 37 (4.2%)  | 0.274   |
| Minor                                   | 69 (2.4%)  | 9 (1.6%)   | 0.287   | 38 (2.8%)    | 32 (3.7%)  | 0.230   |
| Major                                   | 13 (0.4%)  | 3 (0.5%)   | 0.755   | 8 (0.6%)     | 5 (0.6%)   | 0.978   |

---

**Fig. 3** Forest plot and odds ratios for ticagrelor use for various covariates
intention to promote an off-label use but to merely stimulate critical discussion beneficial for a potential trial design if this strategy were deemed worthwhile.

**Safety and Bleeding Episodes**

In our stable CAD cohort, there were no differences in minor and major bleeding episodes (2.8% vs. 2.2%, \( p = 0.399 \)). However, in the ticagrelor DAPT group, the acceptably low bleeding rate may be explained by the significantly lower frequency of patients on triple therapy.

In the COMPASS trial [15], a different, more aggressive pharmacotherapeutic strategy was investigated in patients with coronary and/or peripheral artery disease with the same objective to reduce cardiovascular event rates. Three groups of patients who received different treatment modalities consisting of aspirin and rivaroxaban were studied. The authors concluded that the rates for the composite primary endpoint were significantly lower in the more aggressive low-dose rivaroxaban plus aspirin treatment groups. This anticoagulant/antithrombotic approach is in line with our observed strategy to use the more effective ticagrelor + aspirin DAPT strategy for those patients and procedures with a low risk of bleeding events.

**DES or Co-Medication?**

It seems that differences between modern generation DES technologies are becoming less important. Acceptably low ST rates and clinical event rates are reported with various DES platforms [16–18]. Therefore, the type of DAPT and its duration chosen on the basis of patient and procedure-related factors are likely to determine the frequency of cardiovascular events. Further enhancements in optimizing the risk/benefit ratio of bleeding vs. ischemic events are determined by an objective algorithm to choose the right patient and lesion with short and/or more aggressive DAPT. The call for DAPT customization is, albeit its renewed interest first initiated by the LEADERS FREE trial [3], not new and was already proposed by Pfisterer et al. [19]. We suspect that our results indicate that the observed ticagrelor use in stable CAD patients suggests a well-balanced benefit/risk ratio for younger patients and those with ostial lesions, calcified lesions within the limitations of our study.

**Limitations**

Within the nature of an observational study of this size, there is data granularity which can be viewed in terms of event underreporting, real-world DAPT modifications during follow-up, and PCI of other vessels following PF-SES implantations just to name a few. To assure that patients not available for clinical follow-up did not have a higher risk profile in terms of lesion morphology and cardiovascular risk factors, we conducted a chi\(^2\) analysis. This did not reveal that patients lost to follow-up had a higher risk profile. We did not attempt to filter those
patients who were converted from ticagrelor to clopidogrel for symptoms of dyspnea. This may have introduced some unknown bias. A classification of the vascular access route (femoral vs. radial) was not within the scope of this clinical assessment and could have had an effect on the severity of post-procedural access site bleeding. This could have left one predictor for access site bleeding events uncovered. Our findings are hypothesis generating and not meant to suggest ticagrelor use in elective patients. Finally, we only had an observational period of 9–12 months which is too short to account for late ischemic events.

Conclusions

There were no differences in either stable CAD or ACS patients treated with either clopidogrel or ticagrelor in terms of NACE or any other clinical event rates. Ticagrelor is frequently used in stable CAD patients of younger age and those having lesions with smaller vessel diameters and/or other lesion morphologies (ostial lesions, calcification, in-stent-restenosis).

The selection process for patients and lesions suitable for ticagrelor DAPT in stable CAD should be further studied in larger dedicated trials with a special focus on our predictors for ticagrelor use.

Acknowledgments All the named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

The authors would like to thank to the following Medical Affairs Team members Ms. Aude Michaud, Ms. Lucie Wachowiak (France), Dr. Ricard Rosique (Spain), Ms. Zoey Hooi (Malaysia), Ms. Yoonni Lee and Ms. Hyejin Lee (South Korea) for their regulatory and logistic support to conduct this study. We also thank the participants of the study who were involved in recruitment, data entry and validation for their efforts.

All the authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. No external medical writing service was used to write the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due proprietary reasons and data protection reasons as stated in the protocol but are available from the corresponding author on reasonable request.

Compliance with Ethical Standards Prior to patient recruitment, all ethics votes were obtained from relevant national and/or local ethics committees. In France, these non-interventional studies were approved by the Comité Consultative sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé (CCTIRS dossier no. 14.613) and the Commission Nationale de l’informatique et des Libertés (CNIL, demande d’autorisation no. 915019). This trial was conducted according to the declaration of Helsinki in its most current form.

Conflicts of interest The authors provide a full disclosure of real or perceived conflicts of interests. Dr. Florian Krackhardt (honoraria speaker fees with B.Braun, AstraZeneca), Denny Herberger and Dr. Matthias Waliszewski (full-time employees B.Braun), all other authors: unrestricted research grant to recruit and document patients on a pay-by-patient basis. Co-authors of previously published DES studies with polymer-free sirolimus-eluting stents (all authors).

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–60.
2. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur J Heart Vase Dis. 2015;36:2608–20.
3. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrière D, Naber C, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373:2038–47.
4. Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrière D, et al. SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018;391:41–50.
5. Palmirini T, Della Riva D, Benedetto U, Bachchi Reggiani L, Feres F, Abizaid A, et al. Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. Eur Heart J. 2017;38:1034–43.
6. Krackhardt F, Kočka V, Waliszewski MW, Utech A, Lustermann M, Hudec M, et al. Polymer-free sirolimus-eluting stents in a large-scale all-comers population. Open Heart. 2017;4:e000592.eCollection 2017.
7. Krackhardt F, Rosli MA, Leschke M, Schneider A, Sperling C, Heang TM, et al. Propensity score matched all-comers population treated with ultra-thin strut bare metal and sirolimus-probuloc coated drug-eluting stents of identical stent architecture. Catheter Cardiovasc Interv. 2018;91:1221–8.
8. Sperling C, Waliszewski MW, Kherad B, Krackhardt F. Comparative preclinical evaluation of a polymer-free sirolimus-eluting stent in porcine coronary arteries. Ther Adv Cardiovasc Dis. 2019;13:1753944719826335.
9. Sim DS, Jeong MH, Kim HS, et al. Clopidogrel versus aspirin after dual antiplatelet therapy in acute myocardial infarction patients undergoing drug-eluting stenting. Korean Circ J. 2019.

10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G, et al. Academic research consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344–51.

11. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials. Circulation. 2011;123:2736–47.

12. Windecker S, Kolh P, Alfons F, et al. 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. 2014;35:2541–619.

13. Wöhrle J, Zadura M, Möbius-Winkler S, Leschke M, Opitz C, Ahmed W, et al. SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol. 2012;60:1733–8.

14. Leschke M, Waliszewski M, Pons M, Champin S, Nait Saidi L, Mok Heang T, et al. Thin strut bare metal stents in patients with atrial fibrillation: is there still a need for BMS? Catheter Cardiovasc Interv. 2016;88:358–66.

15. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219–29.

16. McKavanagh P, Zawadowski G, Ahmed N, Kutryk M. The evolution of coronary stents. Expert Rev Cardiovasc Ther. 2018;16:219–28.

17. Baquet M, Jochheim D, Mehilli J. Polymer-free drug-eluting stents for coronary artery disease. J Interv Cardiol. 2018;31:330–7.

18. Kedhi E, Latib A, Abizaid A, Kandzari D, Kirtane AJ, Mehran R, et al. Rationale and design of the Onyx ONE global randomized trial: a randomized controlled trial of high-bleeding risk patients after stent placement with 1 month of dual antiplatelet therapy. Am Heart J. 2019 Aug;214:134–41.

19. Pfisterer M, Kaiser C, Jeger R. No one-size-fits-all: a tailored approach to antithrombotic therapy after stent implantation. Circulation. 2012;125:471–3.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Affiliations

Florian Krackhardt1, Matthias Waliszewski1,2, Viktor Kočka3, Petr Toušek3, Bronislav Hudec5, Fernando Lozano6, Koldobika Garcia-San Roman7, Bruno Garcia del Blanco8, Josepa Mauri9, Tay Mok Heang10, Tae Hoon Ahn11, Myung Ho Jeong12, Denny Herberger2, Vjekoslav Tomulic13, Gilles Levy14, Laurent Sebagh15, Jérôme Rischner16, Michel Pansieri17

1 Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin, Campus Virchow, Augustenburger Platz 1, D-13353 Berlin, Germany
2 Medical Scientific Affairs, B.Braun Melsungen AG, Berlin, Germany
3 University Hospital Královské Vinohrady, Prague, Czech Republic
4 IKEM, Prague, Czech Republic
5 SÚSCCH, a.s. Banska Bystrica, Slovak Republic
6 Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
7 Hospital Universitario Vall d’Hebron Barcelona, Barcelona, Spain
8 Hospital Universitari Germans Trias i Pujol, Badalona, Spain
9 Hospital Universitari Germans Trias i Pujol, Badalona, Spain
10 Pantai Ayer Keroh Hospital, Malacca, MLK, Malaysia
11 Gachon University Gil Medical Center, Incheon, South Korea
12 Chonnam National University, Gwangju, South Korea
13 Clinical Hospital Center Rijeka, Rijeka, Croatia
14 Clinique du Millénaire, Montpellier, France
15 Clinique Turin Paris, Paris, France
16 Hôpital Albert Schweitzer Colmar, Colmar, France
17 Centre Hospitalier d’Avignon, Avignon, France