Comparison of bioresorbable vs durable polymer drug-eluting stents in unprotected left main (from the RAIN-CARDIOGROUP VII Study)

Iannaccone, Mario ; Barbero, Umberto ; et al ; Templin, Christian ; Lüscher, Thomas F

Abstract: BACKGROUND There are limited data regarding the impact of bioresorbable polymer drug eluting stent (BP-DES) compared to durable polymer drug eluting stent (DP-DES) in patients treated with percutaneous coronary intervention using ultrathin stents in left main or bifurcations. METHODS In the RAIN registry (ClinicalTrials NCT03544294, june 2018 retrospectively registered) patients with a ULM or bifurcation stenosis treated with PCI using ultrathin stents (struts thinner than 81 μm) were enrolled. The primary endpoint was the rate of target lesion revascularization (TLR); major adverse cardiovascular events (MACE, a composite of all-cause death, myocardial infarction, TLR and stent thrombosis) and its components, along with target vessel revascularization (TVR) were the secondary ones. A propensity score with matching analysis to compare patients treated with BP-DES versus DP-DES was also assessed. RESULTS From 3001 enrolled patients, after propensity score analysis 1400 patients (700 for each group) were selected. Among them, 352 had ULM disease and 1048 had non-LM bifurcations. At 16 months (12-22), rates of TLR (3.7% vs 2.9%, p = 0.22) and MACE were similar (12.3% vs. 11.6%, p = 0.74) as well as for the other endpoints. Sensitivity analysis of outcomes after a two-stents strategy, showed better outcome in term of MACE (20.4% vs 10%, p = 0.03) and TVR (12% vs 4.6%, p = 0.05) and a trend towards lower TLR in patients treated with BP-DES. CONCLUSION In patients with bifurcations or ULM treated with ultrathin stents BP-DES seems to perform similarly to DP-DES: the trends toward improved clinical outcomes in patients treated with the BP-DES might potentially be of value for speculating the stent choice in selected high-risk subgroups of patients at increased risk of ischemic events. TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03544294. Retrospectively registered June 1, 2018.

DOI: https://doi.org/10.1186/s12872-020-01420-5
Comparison of bioresorbable vs durable polymer drug-eluting stents in unprotected left main (from the RAIN-CARDIOGROUP VII Study)

Mario Iannaccone1†, Umberto Barbero1,*†, Michele De Benedictis1, Yoichi Imori2, Giorgio Quadri3,#4, Daniela Trabattoni5,6, Nicola Ryan7, Giuseppe Venuti8, Andrea Montabone9, Wojciech Wojakowski10, Andrea Rognoni11, Gerard Helft12, Radoslaw Parma13, Leonardo De Luca14, Michele Autelli15, Giacomo Boccuzzi15, Alessio Mattesini19, Christian Templin16, Enrico Cerrato3,#4, Wojciech Waniha10, Grzegorz Smolka10, Zenon Huczek13, Francesco Tomassini3,#4, Bernardo Cortese17, Davide Capodanno8, Alaide Chieffo16, Ivan Nunez-Gil7, Sebastiano Gili5,6, Antonia Bassignana1, Carlo di Mario8, Baldassarre Doronzo1, Pierluigi Omede19, Maurizio D’Amico19, Delio Tedeschi20, Ferdinando Varbella3,#4, Thomas Luscher16, Imad Sheiban21, Javier Escaned7, Mauro Rinaldi19 and Fabrizio D’Ascenzo19

Abstract

Background: There are limited data regarding the impact of bioresorbable polymer drug eluting stent (BP-DES) compared to durable polymer drug eluting stent (DP-DES) in patients treated with percutaneous coronary intervention using ultrathin stents in left main or bifurcations.

Methods: In the RAIN registry (ClinicalTrials NCT03544294, June 2018 retrospectively registered) patients with a ULM or bifurcation stenosis treated with PCI using ultrathin stents (struts thinner than 81 μm) were enrolled. The primary endpoint was the rate of target lesion revascularization (TLR); major adverse cardiovascular events (MACE, a composite of all-cause death, myocardial infarction, TLR and stent thrombosis) and its components, along with target vessel revascularization (TVR) were the secondary ones. A propensity score with matching analysis to compare patients treated with BP-DES versus DP-DES was also assessed.

Results: From 3001 enrolled patients, after propensity score analysis 1400 patients (700 for each group) were selected. Among them, 352 had ULM disease and 1048 had non-LM bifurcations. At 16 months (12–22), rates of TLR (3.7% vs 2.9%, p = 0.22) and MACE were similar (12.3% vs. 11.6%, p = 0.74) as well as for the other endpoints. Sensitivity analysis of outcomes after a two-stents strategy, showed better outcome in term of MACE (20.4% vs 10%, p = 0.03) and TVR (12% vs 4.6%, p = 0.05) and a trend towards lower TLR in patients treated with BP-DES.

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Background
The treatment of unprotected left main and of coronary bifurcation still represents a challenge for interventional cardiologists due to both procedural complications and higher restenosis rates compared with non-bifurcation lesions [1–4].

The complexity of the bifurcation milieu is rooted into the unique flow patterns that characterized them, with local low and oscillatory endothelial shear stress along the lateral walls of the main vessel and of the side branch, whereas high endothelial shear stress develops at the carina. This ultimately leads to a prothrombotic and atherogenic flow-pattern, and even after treatment with percutaneous coronary intervention (PCI), it may increase the failure rate with need for subsequent revascularization on the target lesion (TLR) and an increased risk of stent thrombosis (ST) [4–6].

In the last years, BP-DES (Bioresorbable polymer drug eluting stents) have been introduced with the rationale to potentially decrease ST. Differently from durable polymer stents (DP), after the elution of the antiproliferative drug the biodegradable polymer is going to dissolve leaving behind a bare metal stent, thus reducing the local inflammatory reactions and therefore the risk of thrombosis related to a permanent polymer. Clinically, this translated into lower rates of TLR for BP-DESs implanted in coronary bifurcations in the LEADER-FREE [7], although this RCT was weakened by the comparison with a first generation stent. Regarding currently implanted second generation DES, both in the EVOLVE II trial and in a recent paper of Mennuni et al. [8, 9], BP-DESs were shown to be safe and effective as compared to durable polymer, although coronary bifurcations and LM were underrepresented (respectively about 4 and 15%) [10].

In light of the intrinsic limitations of the above studies, the RAIN study (very thin stents for patients with MAIN or bifurcation in real life: the RAIN, a multicenter study) was designed to evaluate the clinical performance of ultrathin stents in everyday clinical practice. We here present an analysis of the RAIN study aimed to evaluate the safety and efficacy of BP-DES in the bifurcation setting.

Methods
The RAIN is a large multicenter retrospective observational registry (ClinicalTrials NCT03544294, retrospectively registered; see Additional file 1 for enrolling sites).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and are consistent with ICH Good Clinical Practice as well as regulatory requirements. It was approved by an institutional review committee, and all patients provided informed consent.

Inclusion criteria
The RAIN registry included all consecutive patients from June 2015 to January 2017 undergoing complex PCI involving LM and/or bifurcation with ultrathin stents (Promus Element, Xience Alpine, Ultimaster, Synergy, and Resolute Onyx; see Additional file 1 for more details on the stents involved in this study).

Baseline and procedural data
Cardiovascular risk factors, clinical presentation, angiographic features, use of Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT) and Fractional Flow Reserve (FFR) were recorded, along with the characteristics of the implanted stents. IVUS or OCT was used prior to stent implantation to assess the severity of the stenosis and side branch involvement, and post stent implantation to evaluate dissection and the requirement for stent optimisation. The decision to post-dilate, to perform final kissing balloon (FKB), to assess intracoronary imaging and the choice of the stenting technique (provisional versus 2-stent), was at the discretion of the treating physician.

The above data were derived from electronic patient records at each center, while follow-up data were obtained from clinical assessment, telephonic consultations or via primary care physicians and then recorded online (http://www.cardiogroup.org/RAIN/index.php?cat=home).

Endpoints
The rate of TLR was the primary endpoint, while MACE (a composite endpoint of all-cause death, myocardial infarction, TLR and stent thrombosis) and its components, along with TVR were the secondary endpoints. The analyses were performed according to PCI strategy (provisional vs two-stent).
Statistical analysis
Categorical variables are reported as count and percentages, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or not Gaussian distribution was evaluated by Kolmogorov-Smirnov test. The t-test has been used to assess differences between parametric continuous variables, Mann-Whitney U test for non parametric variables, the chi-square test for categorical variables and Fisher’s exact test for 2×2 tables. The a priori statistical significance level was set at \( \alpha = 0.05 \). To account for clustered data among centres we used a normal regression (ANOVA) approach with a fixed effect for cluster and an effect for group when data were normally distributed. For non-normal data, we used the Wilcoxon rank sum test modified to account for clustering. For propensity score, first logistic regression analysis was done for all baseline features that differed between BP-DES and DP-DES, matching was computed after division into quintiles and methods of the 1:1 nearest neighbor on the estimated propensity score \([11]\). Calibration was tested with Hosmer-Lemeshow, and accuracy was assessed with Area Under the Curve. Standardized differences were evaluated before and after matching to evaluate the performance of the model. All statistical analyses were performed with SPSS 21 and differences were considered significant at \( \alpha = 0.05 \).

Results
Before propensity score with matching
At the end of the enrolling period 3001 patients had been recorded: 2120 were treated with DP-DES ad 881 with BP-DES (see Fig. 1).

At baseline patients in the BP-DES were more hypertensive (28.8% vs 23.2% in the DP group, \( p < 0.01 \)), with a higher rate of previous MI (35.3% vs 26.6% in the DP group, \( p < 0.01 \)) and they were more often admitted due to STEMI (19.1% vs 16%, \( p < 0.01 \)). On the other side, patients with DP-DES were more often hyperlipidemic (58.1% vs. 54.6% in the BP group, \( p < 0.01 \); see Additional file 1: Table A).

Patients with BP-DES more frequently presented diffuse coronary disease (55.1% vs 29.9% in the DP group, \( p < 0.01 \)), and with true bifurcation involvement (i.e. Medina 1,1,1 or 0,1,1; 28.1% in the BP group vs 17.5% in the DP group, \( p < 0.001 \)). They were less frequently treated with two-stent technique (76.9% vs 82.4% in the DP group, \( p < 0.01 \)). Finally, there was a similar rate of total ULM disease (30% vs 26.9%, \( p = 0.45 \) (see Additional file 1: Table B).

After propensity score with matching
After multivariate adjustment, 700 patients for each group were selected. Baseline clinical features were comparable, with similar rates of presentation for STEMI (19% in the DP group vs. 18.1% in the BP group, \( p = 0.1 \), see Table 1 and Fig. 1).

At angiography, similar percentages of patients had a LM disease (23.1% in the DP group vs 27.1% in the BP group, \( p = 0.87 \)) and true bifurcation involvement (19.7% in the DP group vs 21.9% in the BP group, \( p = 0.5 \)). Provisional strategy was successfully performed in both groups in the majority of patients (82.1% in the DP group vs. 82.2% in the BP group, \( p = 0.68 \), see Table 2).

At a median follow up of 16 (12–22) months, rates of TLR (3.7% vs 2.9%, \( p = 0.22 \)) and MACE were similar
(12.3% vs. 11.6%, \( p = 0.74 \)), without significant differences among all the secondary endpoint (see Fig. 2).

At sensitivity analysis for patients treated with two stents strategy, patients treated with BP-DES showed a better outcome in term of MACE (20.4% vs 10% in the DP group, \( p = 0.03 \)) and TVR (12% vs 4.6% in the DP group, \( p = 0.05 \), see Fig. 3) and a trend towards TLR (3.7% vs 2.9%, \( p = 0.22 \)).

**Discussion**

Our main findings may be summarised as follows:

- Among patients treated for Left Main disease, the risk of MACE was similar for BP-DES and DP-DES.
- Among patients treated with two stents strategy in both LM and non-LM bifurcation involvement, patients treated with BP-DES showed a better outcome in term of MACE and TVR.
- No differences in ST are evident in BP-DES compared to DP-DES group.

Table 1: Baseline Characteristics Post PSWM

|                  | DP-DES (700 pt.) | BP-DES (700 pt.) | \( p \) |
|------------------|------------------|------------------|--------|
| Age (mean ± SD)  | 70.7 ± 9         | 70.7 ± 10        | 0.97   |
| Female (%)       | 20.5             | 23.1             | 0.24   |
| Hypertension (%) | 77.1             | 73.8             | 0.17   |
| Hyperlipidemia (%) | 62               | 63.8             | 0.5    |
| Diabetes mellitus non ID (%) | 26.2          | 27.8             | 0.5    |
| Diabetes mellitus ID (%) | 6.4            | 9.5              | 0.09   |
| Previous smoker (%) | 31.8           | 30.3             | 0.5    |
| Renal Disease (gfr < 60 ml/min/m2) (%) | 19.7         | 19.9             | 0.71   |
| Previous PCI (%) | 32               | 33.6             | 0.57   |
| Previous CABG (%) | 4.9             | 4.4              | 0.7    |
| Previous MI (%)  | 31.8             | 36               | 0.1    |
| ASA + Clopidogrel (%) | 64.3         | 66.4             | 0.25   |
| ASA + Ticagrelol (%) | 24.2          | 23.8             | 0.22   |
| ASA + Prasugrel (%) | 7.6            | 8.0              | 0.11   |
| Length of DAPT (months) | 11.3        | 11.7             | 0.34   |
| Indication for PCI (%) | - STEMI       | 19               | 18.1   |
|                  | - NSTEMI         | 25.4             | 27.8   |
|                  | - UA             | 18.2             | 14.7   |
|                  | - Stable angina  | 14.9             | 21.6   |
|                  | - Planned angiographic follow up | 7.1        | 4.9    |

Table 2: Interventionsal Characteristics post PSWM

|                  | DP-DES (700 pt.) | BP-DES (700 pt.) | \( p \) |
|------------------|------------------|------------------|--------|
| Radial access (%) | 69.7             | 68.9             | 0.77   |
| Overall LM (%)   | 23.1             | 27.1             | 0.87   |
| Site of lesion:  |                  |                  | 0.11   |
| - Ostial LM      | 23.9             | 25.5             |        |
| - Mid LM         | 46.8             | 49.3             |        |
| - Distal LM      | 19.9             | 16.3             |        |
| Type C lesion (%) | 44.3             | 41.9             | 0.37   |
| Severe calcification (%) | 13.2          | 14               | 0.68   |
| Diffuse disease (%) | 52.5            | 55.9             | 0.23   |
| Bifurcation site (%) | 82.1            | 82.2             | 0.9    |
| True bifurcation (medina 1,1,1 or 0,1,1) | 19.7         | 21.9             | 0.5    |
| Provisional strategy (%) | 82.1          | 82.2             | 0.9    |
| 2 stents technique strategy (%) |                  |                  | 0.1    |
| - Culotte        | 1.7              | 1.6              |        |
| - Mini crush     | 4.1              | 5                |        |
| - Crush          | 0.5              | 0.8              |        |
| - DK-crush       | 0.3              | 0.6              |        |
| - T stent        | 4.4              | 2.8              |        |
| - TAP stent      | 3.9              | 3.7              |        |
| Use of imaging:  |                  |                  | 0.09   |
| - IVUS           | 29.9             | 34.2             |        |
| - OCT            | 0.9              | 1.6              |        |

To the best of our knowledge, this is the first real-world, observational registry evaluating the safety and efficacy profile of different ultrathin stents (struts thinner than 81 μm) in patients with a ULM stenosis treated with PCI using newer-generation abluminal BP-DES as compared to the DP-DES.

BP-DES have been developed to combine the best of both family of metallic stents, i.e. the efficacy of DES and the late safety associated with BMS. However, the available evidences on cardiac death, MI, or stent thrombosis are still scarce [12–17]: network meta-analyses have indicated an excess risk of BP-DES with regard to MI or stent thrombosis when compared with DP-EES (i.e. Xience, Abbott Vascular, Santa Clara, California), though their results were restricted due to heterogeneity of devices in the BP-DES group and to limited follow-up duration [12–14]. Of note, the meta-analyses by Kang et al. [12] and by Navarese et al. [14] included BP-BES trials using the Biosensors BioMatrix device (Biosensors International, Singapore), the meta-analysis of Bangalore et al. [13] included also trials using an other sirolimus-eluting stent (SES) with biodegradable polymer (Yukon Choice PC, Translumina, Hechingen, Germany) while the one by Cassese et al. [15] included
trials on the ultrathin sirolimus-eluting Orsiro device (Biotronik, Bülach, Switzerland).

The principal finding of our current analysis is that BP-DES actually showed a similar safety and efficacy profile at 5 years compared with the DP-DES. Notably - apart from ST - event rates in our study were low keeping into account the clinical and anatomical complexity of the enrolled patients, and similar to previous studies on new-generation DES [16, 17]. These data reflect the global improvement in quality and safety outcomes of these devices mainly due to either the effect of anti-proliferative drug on restenosis and either to the thin struts technology that facilitate the endothelial coverage. However in our study the whole population analysis did
not show differences between patients who received BP-DES compared to DP-DES: this might be due to the overwhelming benefit of the thin strut design over the polymer material: the difference in adverse events is in fact observed during period of time that is shorter than the complete polymers dissolution time. These findings highlight the importance of the overall DES design and biocompatibility on the clinical performance of contemporary DES [3]. The effect of stent’s struts thickness has been well established already, with thinner struts showing to produce less inflammation, vessel injury, neointimal proliferation, as well as thrombus formation when compared with thicker ones [18, 19]. Furthermore, the 5-year analysis of the COMPARE II trial also confirmed the early- and mid-term similar safety and efficacy of the BP-BES and the DP-EES, thus challenging the concept itself of the biodegradable polymer coating [20, 21]. On the other hand, Bayesian analysis in the BIOFLOW-V trial, despite limited by the analysis itself and by the particular thickness of the stent used, is encouraging for an actual role of bioresorbable polymers [22, 23]. Therefore, whether BP-DES are as safe and effective as DP-DES should be proven for each specific stent by an appropriately designed clinical trial.

The second interesting result is the trend towards better outcome in term of MACE and TVR in patients treated with BP-DES and a two stents strategy. The higher risk of subsequent events in this challenging anatomical subset is well known, and it is related either to patient either to technique drawbacks [23, 24]. Despite the low percentage of patients included in this analysis (about 20% of the patients selected by propensity score), we can speculate that in an high risk setting like the one who received the provisional approach, finally, although designed as an all comers study, only 23% of patients undergoing percutaneous interventions were actually enrolled in the study, so selection bias cannot be entirely ruled out.

Conclusion
The main message is that BP-DES look as safe as DP-DES even in high anatomical risk setting like LM disease. Furthermore, the provisional approach confirms itself as the safer on the long term. Finally, when a two-stent strategy is absolutely needed, the trends toward improved clinical outcomes with respect to MACE and TVR we found with BP-DES might potentially be of value to speculate about the stent choice in selected high-risk subgroups of patients at increased risk of ischemic events.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12872-020-01420-5.

Acknowledgements
None.

Authors’ contributions
IM, UB, SG, GQ, EC and FD: design of the study, collection of the data, analysis and writing of the paper. AM1, FT, YL, DT1, AB, PQ, MD8, BD, MD, NR, GV, WW, AR, GH, RP, LDL, MA, GB and AM helped in data collection; CT, WojW, GS, ZH, BC, DC, AC, ING, CdM, FV, TL, IS, JE, MR, DT helped in writing the paper, corrected the analysis and all the authors together reviewed the final version of the paper before submission. The author(s) read and approved the final manuscript.
Funding

None.

Availability of data and materials

On request; personal data are protected according to the law. Please refer to the corresponding author at umberto.barberi@unitn.it.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee by Comitato Etico Interazendale AOUI Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. TO1 and by The University of Zurich Ethics Commission, and retrospectively registered on ClinicalTrials.gov, number NCT03544294. Each enrolled patient signed to provide informed consent.

Consent for publication

Not applicable.

Competing interests

Fabrizio D’Ascenzo is member of the editorial board (Section Editor) of this journal. All the other authors have no competing interests.

Author details
1. Division of Cardiology, SS. Annunziata Hospital, ASL CN1, Savigliano, Italy.
2. Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, Japan.
3. Department of Cardiology, Infermi Hospital, Ravoni, Italy.
4. Department of Cardiology, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy.
5. Department of Cardiovascular Sciences, IRCCS Centro Cardiologico Monzino, Milan, Italy.
6. University of Milan, Milan, Italy.
7. Department of Cardiology, Hospital Clinico San Carlos, Madrid, Spain.
8. Division of Cardiology, Cardio-Thoracic-Vascular Department, Azienda Ospedaliero Universitaria ‘Policlinico-Vittorio Emanuele’, Catania, Italy.
9. Structural Interventional Cardiology, Careggi University Hospital, Florence, Italy.
10. Department of Cardiology, Medical University of Silesia, Katowice, Poland.
11. Coronary Care Unit and Catheterization Laboratory, A.O.U. Maggiore della Carità, Novara, Italy.
12. Division of Cardiology, Pierre and Marie Curie University, Paris, France.
13. University Hospital Clinical, Warsaw, Poland.
14. Pederzoli Hospital, Peschiera del Garda, Italy.
15. Cardioogy Department, Ospedale San Giovanni Bosco, Turin, Italy.
16. Division of Cardiology, Universitätsklinikum of Zurich, Zurich, Switzerland.
17. Interventional Cardiology, ASST Fatebenefratelli-Sacco, Milan, Italy.
18. San Raffaele Scientific Institute, Milan, Italy.
19. Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, Turin, Italy.
20. Interventional Cardiology, Istituto clinico Sant’anna, Brescia, Italy.
21. Interventional Cardiology, Pederzoli Hospital Peschiera del Garda, Verona, Italy.

Received: 16 June 2019 Accepted: 9 March 2020

Published online: 15 May 2020

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