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Final 5-year outcomes of the Epic02 – RANGO study: A real-world registry of the durable fluoroacrylate polymer-based sirolimus-eluting Angiolite® stent

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ABSTRACT

Background: Clinical results at mid-term of Angiolite, a cobalt-chromium sirolimus-eluting stent, in a non-selected, real-world population were demonstrated to be excellent. 5-year follow-up was planned to exclude late complications.
Methods: We conducted an observational, prospective, multicenter study (RANGO) in different clinical indications with independent event adjudication and data monitoring. All consecutive patients with at least 1 Angiolite stent implanted who gave their informed consent were included. The primary endpoint was the occurrence of target lesion failure (TLF). The secondary endpoints were the individual components of the primary endpoint, Patient-oriented Composite Endpoint (PoCE), and stent thrombosis. We present the 5-year clinical results in the entire population and in 2 predefined subgroups: diabetics and small-vessel disease ($\leq$2.5 mm).
Results: 646 patients with high-risk features (previous MI 18.4 %, previous coronary revascularization 23.4 %, ST-elevation MI 23.1 %, and multivessel disease 47.8 %) were included. Only 18 patients (2.8 %) were lost at 5-years follow-up. The final outcomes were: TLF 8.7 %, PoCE 21.8 %, and stent thrombosis 1.2 %. The small-vessel subgroup showed slightly worse results (TLF, 10.3 %; PoCE, 24.1 %; thrombosis, 0 %), as diabetic subgroup also did (TLF, 11.1 %; PoCE, 29.1 %; thrombosis, 1.0 %). Multivariable analysis showed variables significantly associated with TLF: chronic kidney disease, prior PCI or CABG and lesion calcification; and those associated with PoCE were age, atrial fibrillation, prior PCI, lesion calcification and chronic kidney disease.
Conclusions: The 5-years results of this observational study of Angiolite stent in a real-world population corroborate the outstanding results observed in the mid-term. No signals of late complications were detected.

Abbreviations: DES, drug-eluting stents; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; PoCE, Patient-oriented Composite Endpoint; TLF, target lesion failure; TLR, target lesion revascularization; TVR, target vessel revascularization.

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1. Introduction

Drug-eluting stents (DES) have become the treatment of choice in the percutaneous treatment of coronary artery disease as they have consistently shown lower rates of revascularization in a wide range of clinical situations [1]. Although the second- and further generations DES have almost abolished the fear of (very) late stent thrombosis [2], there is still a bit of concern [3], fueling the need of extended follow-up. Also, the development of neoatherosclerosis is an alarm sign, with earlier presentation and in a high proportion with DES than with older bare metal stents [4]. New DES are designed to overcome these limitations: the Angiolite stent (iVascular, Spain) is a thin-strut cobalt-chromium sirolimus-eluting stent with biostable coating made of 3 layers: acrylate to ensure adhesion to the metal surface, fluoroacrylate loaded with sirolimus (1.4 μg/mm2), and a top layer of fluoroacrylate for drug release control (>75 % elution within the first month).

The Angiolite stent was initially tested in a pre-clinical model with satisfactory results [5] with similar abolition of neointimal proliferation and better healing pattern than the XIENCE stent (Abbott Vascular, United States). The first-in-human study –ANCHOR study– [6] proved a potent inhibition of neointimal hyperplasia as analyzed by OCT; also, late lumen loss at 6 months showed a remarkable mean of 0.07 mm ± 0.37 mm. Finally, the ANGIOLITE study [7] a randomized clinical trial with angiographic follow-up, compared the Angiolite stent to the XIENCE stent in 223 patients. The primary endpoint of the trial was the 6-month in-stent late lumen loss, that was non-inferior with Angiolite stent (0.04 mm ± 0.39 mm) than with XIENCE stent (0.08 mm ± 0.38 mm). The stent received the CE marking (*Conformité Européenne*) for its routine use.

To complete a comprehensive clinical program, we designed an observational, prospective, registry with independent event adjudication and data monitoring to validate the previous results in the routine clinical practice, with wider indications for use. The mid-term (2-years follow-up) results have been published previously [8] with rates of Target Lesion Failure (TLF), Major Adverse Cardiovascular Events (MACE), and stent thrombosis of 3.4 %, 9.6 %, and 0.9 %, respectively. The final follow-up period was established at 5 years to exclude late events. Here we present the results at the final programmed follow-up.

2. Methods

2.1. Study design

The Epic02-RANGO study was designed as a prospective, single-arm, multicenter, international, observational registry for the evaluation of the safety and effectiveness results of the Angiolite stent in unselected patients, representative of the routine clinical practice. The study design was approved by all investigators and the sponsor as well. A reference ethics committee approved the protocol and the informed consent forms; local ethics committees were informed of the participation of their respective centers in compliance with the national and local legislation. To exclude late events, the Steering Committee decided to extend the follow-up to 5 years. The extension of the study was approved by the reference Ethics Committee and informed re-consent was obtained from the participants. A yearly follow-up telephonic visit as well as review of medical records was scheduled.

2.2. Selection of the study population

To be enrolled in the study, subjects should meet all the 3 following inclusion criteria: ≥18 years-old; underwent percutaneous coronary intervention (PCI) with at least 1 Angiolite stent; and have received proper information and signed the corresponding informed consent.

To guarantee a real-world population, non-stringent exclusion criteria were applied. Subjects were only excluded from the study if they met any of the following exclusion criteria: contraindication to dual antiplatelet therapy; established cardiogenic shock; unlikely to complete the scheduled follow-up; or formal refusal to participate in the study.

The PCI (planning and final performance, predilatation, imaging, postdilatation) was left at the discretion of the operator, and was indicative of the real-world use of the stents. Medical treatment during and after the procedure, including antiplatelet regime and duration, also followed the standard local practices; however, we suggested the investigators to follow the guidelines available on the management of these patients [1,9].

2.3. Endpoints

The primary endpoint was Target Lesion Failure (TLF) at 6 months, and 1, 2, and 5 years defined as cardiovascular death, target vessel myocardial infarction (MI) or clinically driven target lesion revascularization (TLR).

The secondary endpoints were:

- Individual components of the primary endpoint: cardiovascular death, target vessel MI, and clinically driven TLR.
- Stent thrombosis, definite or probable, as defined by the ARC criteria [10].
- Patient-oriented Composite EndPoint (PoCE) defined as all-cause mortality, any MI or any revascularization.

In all cases, myocardial infarction refers to spontaneous infarction only. Two subgroups were predefined: patients with diabetes, and patients with Angiolite stents placed in small vessels (stent diameter ≤ 2.5 mm).

2.4. Sample size calculation

We conducted an exploratory analysis that rendered a population of 640 patients (with an estimated loss to follow-up of 10 %). This sample size produces a 2-sided 95 % confidence interval with a precision equal to 1.75 % when the TLF rate is 4.86 %. This value was obtained from the data published from different contemporary stents [8].

2.5. Population analysis

The primary safety and effectiveness analysis considered all patients who received the Angiolite stent only except for those who withdrew their consent. The secondary analysis was performed on all patients included in the study who received, at least, 1 Angiolite stent plus another different stent except for those who withdrew their consent.

2.6. Clinical events committee

All events were remotely monitored by a contract research organization. The independent clinical events committee reviewed, adjudicated, and classified all adverse events. The 5 members of the clinical events committee were not affiliated to the centers that participated in the study.

A total of 90 random patient audits (14 % of the global population) were conducted at 4 centers, including the top 3 recruiters. The result of these audits detected 9 unreported events, most of them corresponded to scheduled procedures that required admission (non-cardiac surgeries and 2 scheduled PCI cases). None of the events associated with these audits were assigned to events classified as primary or secondary endpoints.

2.7. Statistical methods

Regarding the continuous variables, results were expressed as mean ± standard deviation. Variables were compared using an independent *t*-test or the Mann-Whitney test, when applicable. Categorical variables are expressed as counts and percentages and compared using the chi-square test or Fisher's exact test. Variables were compared both for primary (only Angiolite stents) and for secondary (Angiolite plus other stents) populations. Time-to-event hazard curves were expressed as Kaplan-Meier estimates. These methods were applied for the entire cohort and the 2 predefined subgroups, when appropriate: patients with diabetes, and patients with small vessel lesions (stent diameter ≤ 2.5 mm).

Univariate (logistic and Cox regression) and multivariable (stepwise and Cox regression) analyses were conducted to assess independent predictors of TLF and PoCE. The following baseline characteristics were included in the model with an entry/stay criterion of 0.20/0.10: sex (male vs. female), age in years, diabetes mellitus, hyperlipidemia, hypertension, chronic kidney disease, current anticoagulation, atrial fibrillation, clinical presentation (ACS vs. CCS), prior PCI, prior CABG, prior MI, AHA type lesion (B2/C vs. A/B1), LAD lesion, reference vessel diameter in mm, lesion length in mm, stent length in mm, number of vessels treated (Single- vs. multi vessel), number of stents per patient, % diameter stenosis, restenotic lesion treated, calcification (moderate/severe vs. none/mild). All variables are categorized as yes vs. no, unless otherwise indicated.

The statistical software SAS Version 9.4 was used for all statistical analyses, listings, tabulations, and figures.

3. Results

A total of 646 patients who received at least one Angiolite stent were recruited from 16 academic medical centers in Spain and Portugal from June 2017 through July 2018. The primary analysis population consisted of 426 patients treated with Angiolite stents only. The clinical and procedural characteristics are detailed elsewhere [8]. Outstanding high-risk clinical characteristics of the whole sample are high prevalence of previous myocardial infarction (18.4 %), previous coronary revascularization (23.4 %), clinical presentation as ST-segment elevation myocardial infarction –STEMI– (23.1 %), and multivessel disease (47.8 %).

Most of the cases showed complex coronary disease, with a mean ± standard deviation number of treated lesions per patient of 1.68 ± 0.9 (1.80 ± 1.1 stents per patient). Angiolite stents were more frequently used to treat the infarct-related artery in the STEMI scenario compared to other stents. Consequently, lesions with thrombus were more common in the primary population (Angiolite stents only). The procedural and device success rates were 99.7 % and 99.2 %, respectively.

At 5-years follow-up, only 18 patients (2.8 %) were lost, Fig. 1. In the primary analysis population (patients treated with Angiolite stents only) at 5 years, the rates of TLF and PoCE were 7.7 % and 19.7 %, respectively. The rate of definite/probable stent thrombosis was 0.9 %, with only one

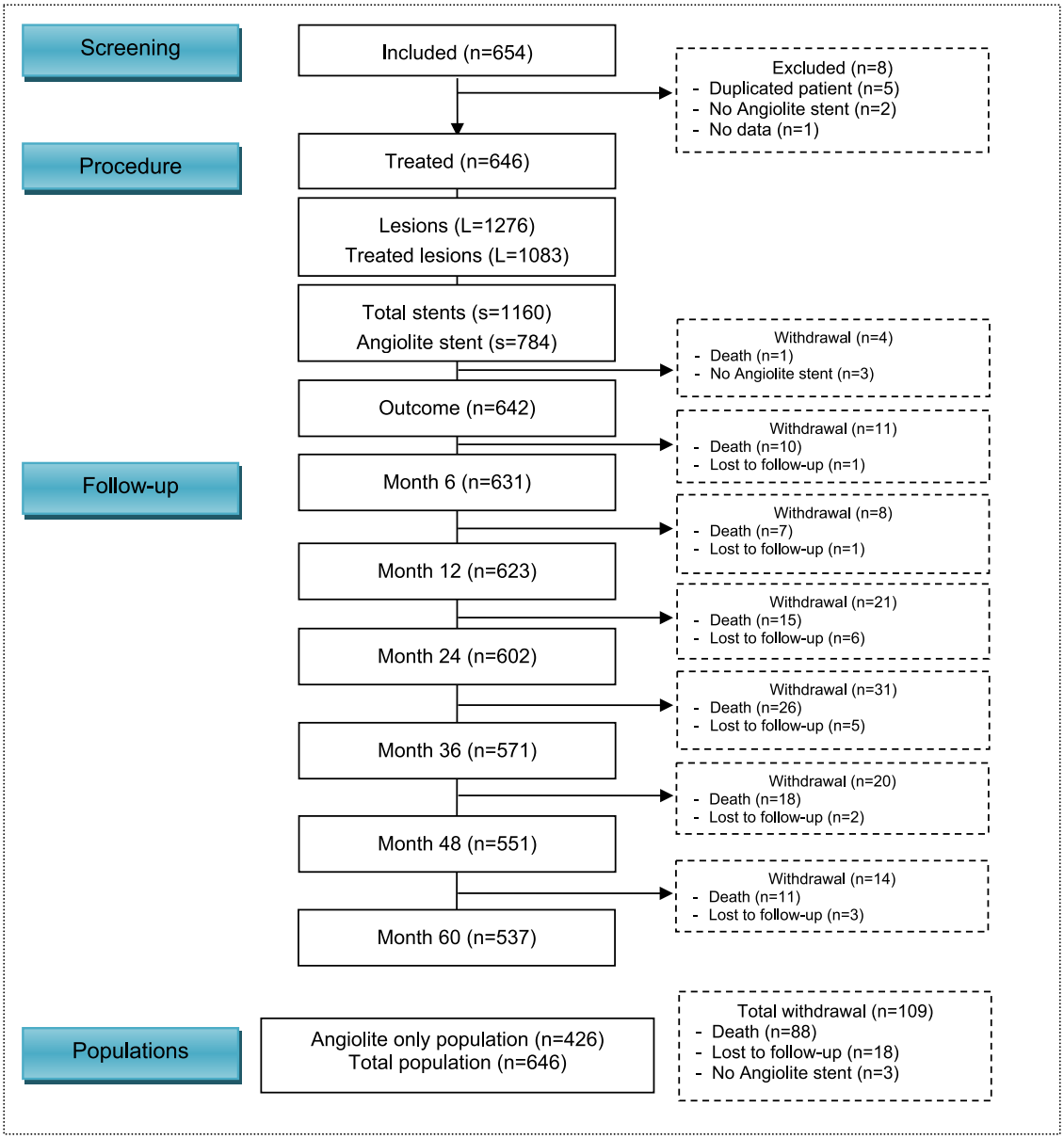

Fig. 1. Flow-chart of the study.

case of stent thrombosis beyond the first 6 months. Table 1 and Fig. 2 summarize the individual event rate and timing.

The rates of TLF and PoCE at 5 years in the global population (secondary analysis) were 8.7 % and 21.8 %, respectively. The rate of definite/probable stent thrombosis was 1.2 %. Only 3 cases of late (at 9 months, 4, and 5 years) stent thrombosis were detected. Table 2 and Fig. 3 summarize the individual event rate and timing.

The subgroup analysis shows 5-year results slightly worse than those observed in the global population:

- –The small vessels ($\leq$2.5 mm stents) subgroup showed rates of TLF and PoCE of 10.3 % and 24.1 %, respectively. No stent thrombosis was found. The description of the event rate and timing are available in Table 1 of the Supplementary data.
- –The diabetic subgroup showed rates of TLF and PoCE of 11.1 % and 29.1 %, respectively. The rate of stent thrombosis was 1.0 %; only 1 case appeared in the primary analysis of patients treated with the Angiolite stent exclusively. The description of the event rate and timing are available in Table 2 of the Supplementary data.
- – Given the high proportion of STEMI cases included, we decided to make a post-hoc analysis of the results in this subgroup: the rates of TLF and PoCE were 8.1 % and 18.8 %, respectively. These figures are slightly lower than those from the global population. However, the rate of stent thrombosis (4.0 %) was significantly ($p = 0.0025$) higher than that observed in the global population (1.2 %). The observed episodes of stent thrombosis appeared acutely, in the same day ($n = 2$); subacute, in the first week (n = 2); and late, after 3 years (n = 2).

Univariate and multivariable analyses were performed to detect variables associated with TLF and PoCE occurrence. Fig. 4 shows the results; Tables 3 and 4 of the Supplementary data detail the analyses. In brief, variables associated with TLF were more related to lesion characteristics (calcification) or specific patient subsets with high incidence of complex disease and lesions (chronic kidney disease, prior PCI or prior CABG). Regarding PoCE, more variables related to clinical characteristics (age, atrial fibrillation) added information beyond the aforementioned variables related to TLF.

4. Discussion

The final results of this real-world registry of the use of Angiolite coronary stent show a sustained safety and effectiveness profile, corroborating the ANCHOR [6] – first-in-human study –, the ANGIOLITE [7] RCT comparison with the XIENCE stent showed, and the 2-year follow-up results previously published from this RANGO study [8]. The population recruited showed a high-risk profile, both from a clinical perspective (18.4 % previous myocardial infarction, 23.4 % previous coronary revascularization, 23.1 % STEMI presentation) and from anatomical characteristics (47.8 % multivessel disease, and 1.8 ± 1.11 stents implanted per patient).

The registry was designed to include all the patients in whom an Angiolite stent was intended to be used. Therefore, we analyze 2 different populations: those in whom only the Angiolite stent was used (primary population) and those who received different stents to treat other lesions (secondary population). These populations were different as Angiolite-only patients showed a better clinical profile. However, some unfavorable prognostic features as STEMI scenario and thrombus-containing lesions were more prevalent in the primary population.

The primary endpoint, TLF at 5 years was consistently low both in the primary population (Angiolite-only), 7.7 %, and in the secondary population, 8.7 %. Target vessel failure, a wider safety variable, was also noticeably low (8.7 % and 9.6 %, respectively). An overview of the TLF results of different stents tested in RCTs and registries is shown on Table 5 of the Supplementary data. The weighed mean TLF value at 5 years is around 13.5 % in published registries and trials, higher than the rate observed in this study.

From a more clinical point of view, using a patient-oriented outcome parameter as PoCE (including all-cause mortality), the results were good either in primary or in secondary populations, with rates of 19.7 % and 21.8 %, respectively. The main driver of this combined endpoint was all-cause death, accounting for 13.4 % and 13.6 %, respectively. Notably, the rates of cardiovascular death were less than half of the total causes of death: 5.9 % in both populations. An overview of previous PoCE results is shown on Table 5 of the Supplementary data. The weighed mean PoCE value at 5 years is 27.4 % in the literature, higher than the rate observed in this study.

The 5-year follow-up confirmed the very low rate of unfavorable cardiac events seen at the mid-term, 2-year, period. The rate of new device-oriented cardiac events, as analyzed with TLF endpoint, was consistently below 2 % per year. The patient-oriented cardiac events, as measured with PoCE, were also low with figures of cardiovascular death around 1 % per year and of new myocardial infarction below that threshold.

Stent thrombosis was of critical relevance in our analysis given the high antiproliferative efficacy of the Angiolite stent demonstrated in both ANCHOR [6] and ANGIOLITE [7] studies, with a mean late lumen loss

Table 1
Final outcomes in the primary analysis population: patients treated with the Angiolite stent only.

Angiolite only population ($N = 426$)	6-months	1-year	2-year	3-year	4-year	5-year
Death	5 (1.2 %)	11 (2.6 %)	19 (4.5 %)	34 (8.0 %)	52 (12.2 %)	57 (13.4 %)
Cardiovascular death[a]	3 (0.7 %)	6 (1.4 %)	9 (2.1 %)	14 (3.3 %)	22 (5.2 %)	25 (5.9 %)
Myocardial infarction (MI)	5 (1.2 %)	7 (1.6 %)	10 (2.3 %)	10 (2.3 %)	15 (3.5 %)	18 (4.2 %)
MI of target vessel	3 (0.7 %)	3 (0.7 %)	5 (1.2 %)	5 (1.2 %)	6 (1.4 %)	6 (1.4 %)
Definite/probable device thrombosis	3 (0.7 %)	3 (0.7 %)	3 (0.7 %)	3 (0.7 %)	4 (0.9 %)	4 (0.9 %)
Revascularization	8 (1.9 %)	12 (2.8 %)	20 (4.7 %)	25 (5.9 %)	27 (6.3 %)	30 (7.0 %)
Target lesion revascularization (TLR)	3 (0.7 %)	4 (0.9 %)	5 (1.2 %)	8 (1.9 %)	9 (2.1 %)	9 (2.1 %)
Target vessel revascularization (TVR)	4 (0.9 %)	7 (1.6 %)	10 (2.3 %)	13 (3.1 %)	14 (3.3 %)	14 (3.3 %)
Non-target vessel revascularization (non-TVR)	4 (0.9 %)	5 (1.2 %)	10 (2.3 %)	12 (2.8 %)	13 (3.1 %)	16 (3.8 %)
Target Lesion Failure (TLF)[b]	6 (1.4 %)	10 (2.3 %)	15 (3.5 %)	24 (5.6 %)	31 (7.3 %)	33 (7.7 %)
Target Vessel Failure (TVF)[c]	7 (1.6 %)	13 (3.1 %)	19 (4.5 %)	28 (6.6 %)	35 (8.2 %)	37 (8.7 %)
Patient oriented Composite endpoint (PoCE)[d]	14 (3.3 %)	25 (5.9 %)	38 (8.9 %)	56 (13.1 %)	77 (18.1 %)	84 (19.7 %)

MI, Myocardial infarction; TVR, Target vessel related; TLR, Target lesion related; TVF, Target vessel failure; TLF, Target lesion failure; PoCE, Patient oriented Composite endpoint.

[a] Cardiovascular death was defined as all deaths due to immediate cardiovascular cause (e.g., MI, low output failure, fatal arrhythmia), unwitnessed death, and death due to unknown cause, as well as all procedure-related deaths, including those related to concomitant treatment.

[b] Target Lesion Failure defined as cardiovascular death, MI not clearly attributable to a non-intervention vessel, and clinically indicated target lesion revascularization.

[c] Target Vessel Failure defined as cardiovascular death, MI not clearly attributable to a non-intervention vessel, and target vessel revascularization. TVF is equivalent to MACE.

[d] PoCE defined as all-cause death, any MI, any revascularization.

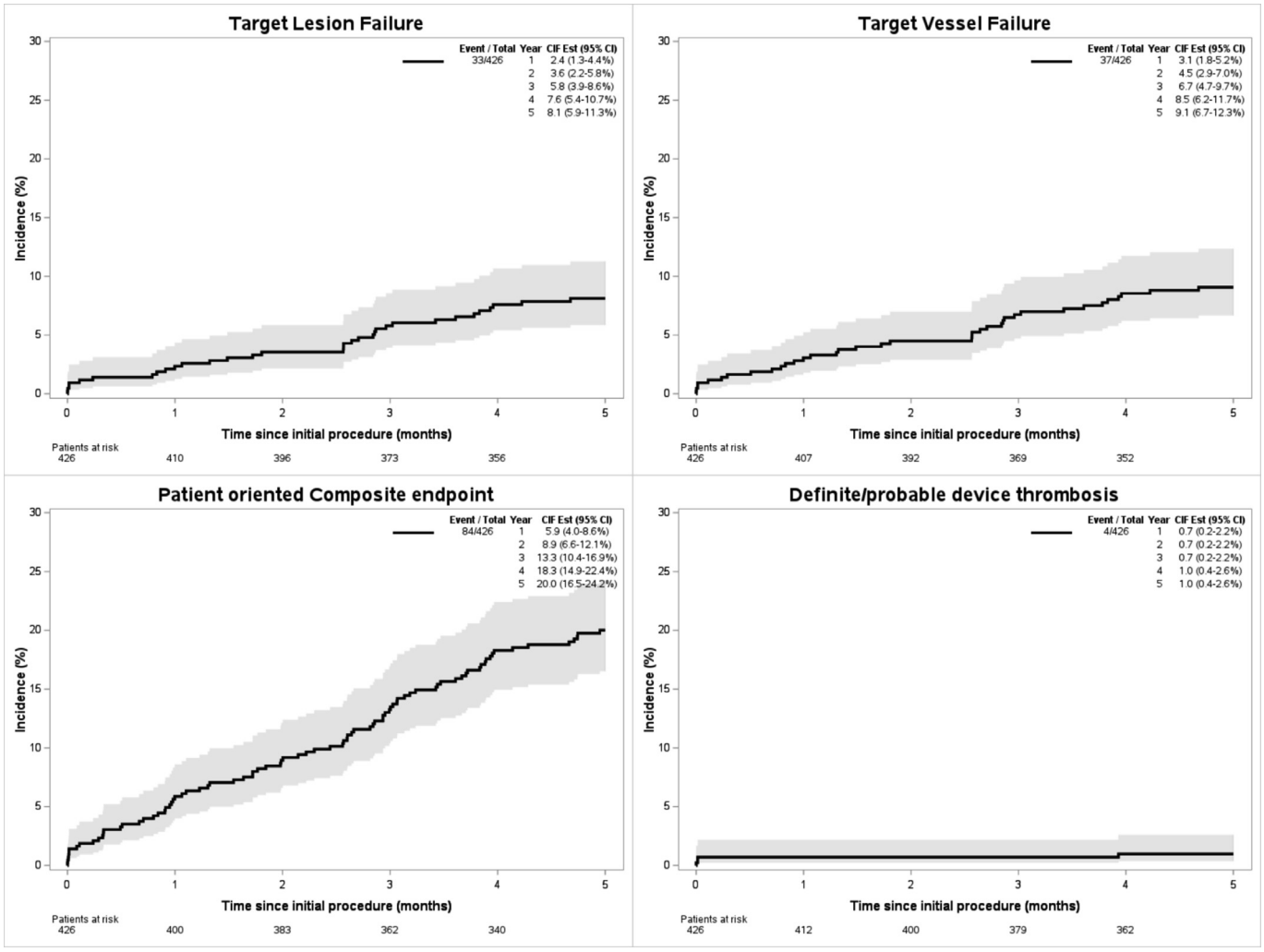

Fig. 2. Five-year cumulative incidence of events in the primary analysis population of patients treated with the Angiolite stent only.

<0.05 mm. The rate of this complication appears very low: 0.9 % in primary analysis, 1.2 % in secondary analysis. The available observational studies showed a mean rate of stent thrombosis ranging from 0.5 % to 2.2 % at the 5-year follow up (Table 5 of the Supplementary data). Also, the very low rate of definite/ probable stent thrombosis beyond the first month (only 3 cases, at 9 months, 4 and 5 years) restates this safety profile.

Table 2
Final outcomes in the global population: Secondary population analysis.

Total population (N = 646)	6-months	1-year	2-year	3-year	4-year	5-year
Death	11 (1.7 %)	18 (2.8 %)	33 (5.1 %)	57 (8.8 %)	77 (11.9 %)	88 (13.6 %)
Cardiovascular death[a]	7 (1.1 %)	11 (1.7 %)	17 (2.6 %)	25 (3.9 %)	34 (5.3 %)	38 (5.9 %)
Myocardial infarction (MI)	11 (1.7 %)	16 (2.5 %)	21 (3.3 %)	22 (3.4 %)	29 (4.5 %)	33 (5.1 %)
MI of target vessel	6 (0.9 %)	7 (1.1 %)	10 (1.5 %)	11 (1.7 %)	12 (1.9 %)	13 (2.0 %)
Definite/probable device thrombosis	5 (0.8 %)	6 (0.9 %)	6 (0.9 %)	6 (0.9 %)	7 (1.1 %)	8 (1.2 %)
Revascularization	14 (2.2 %)	24 (3.7 %)	36 (5.6 %)	45 (7.0 %)	49 (7.6 %)	55 (8.5 %)
Target lesion revascularization (TLR)	6 (0.9 %)	8 (1.2 %)	10 (1.5 %)	16 (2.5 %)	17 (2.6 %)	19 (2.9 %)
Target vessel revascularization (TVR)	7 (1.1 %)	11 (1.7 %)	16 (2.5 %)	22 (3.4 %)	24 (3.7 %)	26 (4.0 %)
Non-target vessel revascularization (non-TVR)	7 (1.1 %)	13 (2.0 %)	20 (3.1 %)	23 (3.6 %)	25 (3.9 %)	29 (4.5 %)
Target Lesion Failure (TLF)[b]	13 (2.0 %)	19 (2.9 %)	28 (4.3 %)	43 (6.7 %)	51 (7.9 %)	56 (8.7 %)
Target Vessel Failure (TVF)[c]	14 (2.2 %)	22 (3.4 %)	33 (5.1 %)	48 (7.4 %)	57 (8.8 %)	62 (9.6 %)
Patient oriented Composite endpoint (PoCE)[d]	26 (4.0 %)	45 (7.0 %)	69 (10.7 %)	99 (15.3 %)	125 (19.3 %)	141 (21.8 %)

MI, Myocardial infarction; TVR, Target vessel related; TLR, Target lesion related; TVF, Target vessel failure; TLF, Target lesion failure; PoCE, Patient oriented Composite endpoint.

[a] Cardiovascular death was defined as all deaths due to immediate cardiovascular cause (e.g., MI, low output failure, fatal arrhythmia), unwitnessed death, and death due to unknown cause, as well as all procedure-related deaths, including those related to concomitant treatment.

[b] Target Lesion Failure defined as cardiovascular death, MI not clearly attributable to a non-intervention vessel, and clinically indicated target lesion revascularization.

[c] Target Vessel Failure defined as cardiovascular death, MI not clearly attributable to a non-intervention vessel, and target vessel revascularization. TVF is equivalent to MACE.

[d] PoCE defined as all-cause death, any MI, any revascularization.

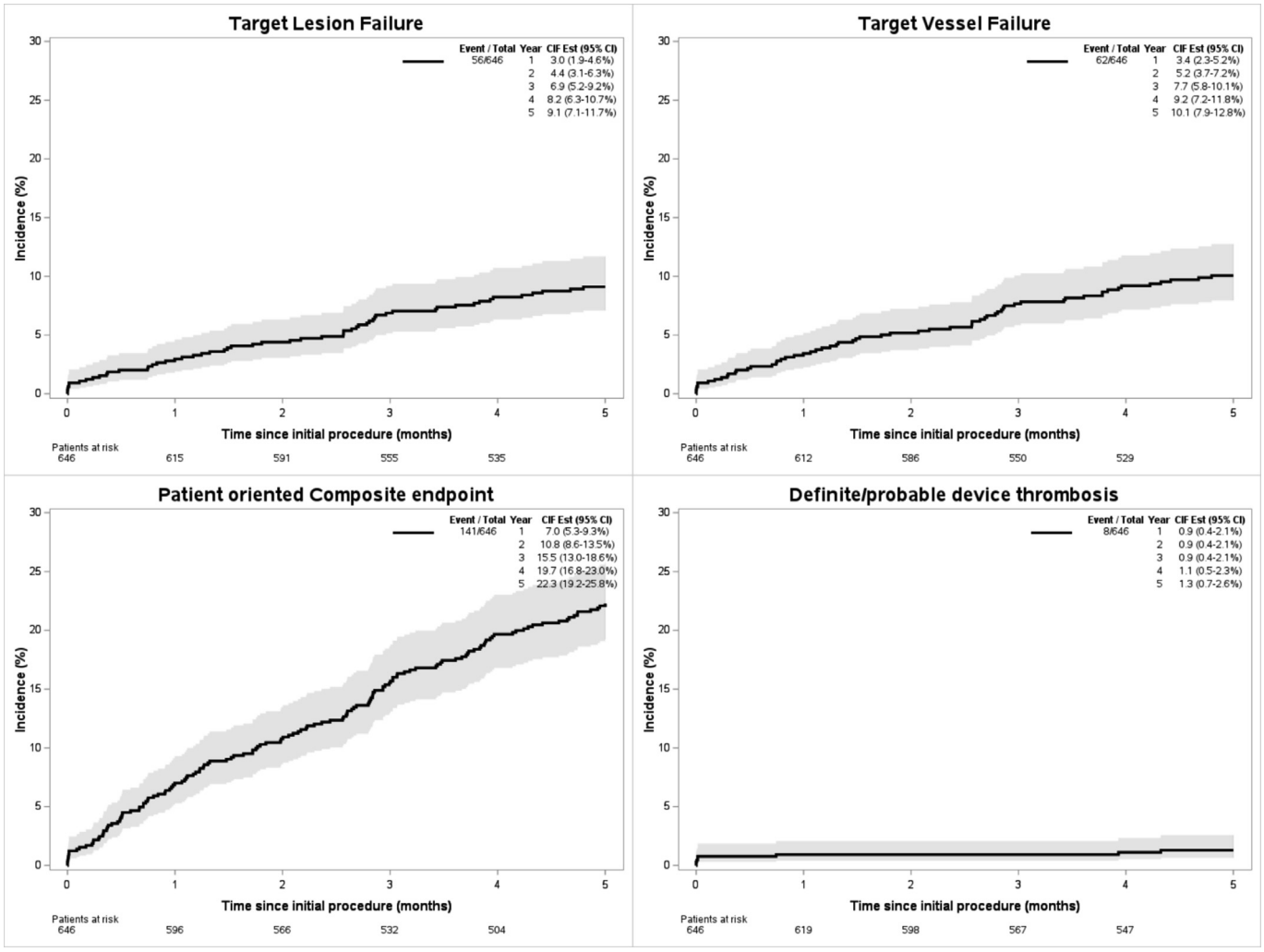

Fig. 3. Five-year cumulative incidence of events in the global population of patients, secondary population analysis.

The predefined subgroup analysis rendered interesting results. Diabetic patients showed higher TLF and PoCE rates at 5 years than the whole population (11.1 % vs 8.7 %, and 29.1 % vs 21.8 %). This finding confirms the worse clinical prognosis of diabetic patients, not only related to the lesion treated but with the remaining coronary artery disease. Our results are consistent with previous data published on the EVOLVE II substudy on diabetes [11] that showed a 2-year TLF rate of 11.2 % and a definite/probable stent thrombosis of 1.1 %.

As expected, the subgroup of small vessel disease ($\leq$2.5 mm) showed slightly higher rates of 5-year TLF and MACE (10.3 % and 24.1 %, respectively) than the global population. The lack of definite/probable stent thrombosis cases could be indicative of detection bias as the thrombosis of these vessels may have a milder clinical expression. The results of this subgroup are usually hard to compare with other data as the definition of small vessel is highly arbitrary, from 2.25 mm to 3.0 mm. However, the results of our study are consistent with those reported in the Basket Small [12] trial.

The results of the *post-hoc* analysis of STEMI patients show rates of TLF (8.1 %) and PoCE (18.8 %) slightly lower than those from the global population. The observed rate of stent thrombosis (4.0 %) may seem worrisome, but it is in line with previously published data: 4.4 % at 2-years of follow-up in the HORIZONS-AMI trial [13]; 4.25 % in 3–5 years of follow-up in the DESERT cooperation [14]. STEMI scenario is a well-known predictor of definite / probable stent thrombosis with HR 3.36 (95 % CI 1.84 to 6.12) [15], especially in the acute / subacute phases, as we observed in this analysis.

4.1. Limitations

The limitations of this study are the well-known issues of real-world observational registries: potential selection bias, reporting bias, and losses to follow-up (not in this case though, with a 97.2 % of the follow-up completed). However, the results are similar to previously reported data and consistent with the results of previous studies with the analyzed device. In the global population (patients who received other stents besides Angiolite stents), endpoints like probable stent thrombosis or cardiovascular death cannot be clearly attributed to a particular stent.

5. Conclusions

In conclusion, the final results at 5 years of this observational multicenter registry on the use of the Angiolite DES in a real-world population confirm the excellent effectiveness and safety profile seen at mid-term follow-up, without observing late events clearly related to the device.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2025.03.015.

CRediT authorship contribution statement

Armando Pérez de Prado: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jeremías Bayón:** Writing – review &

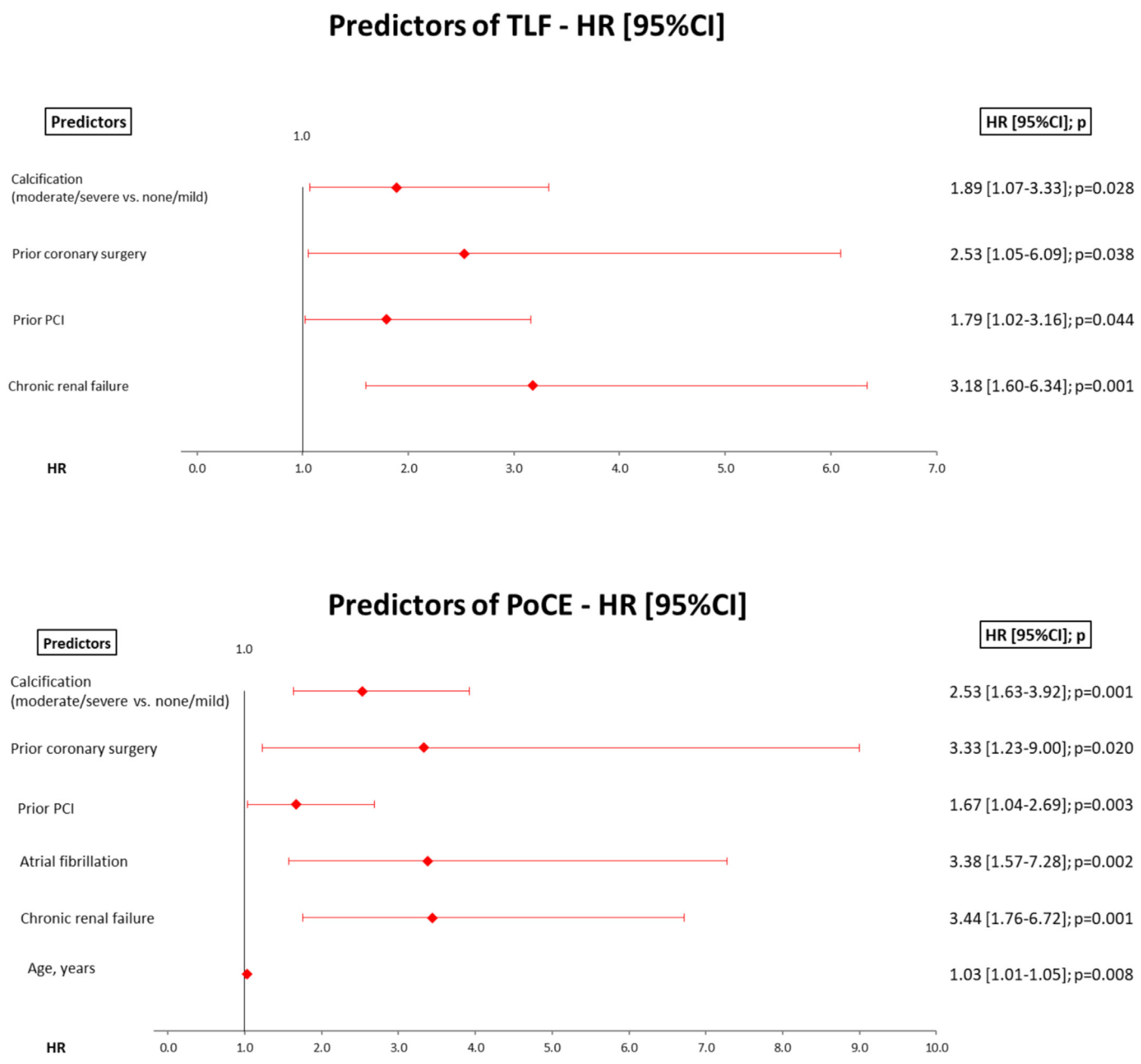

Fig. 4. Predictors of TLF and PoCE in the global population, multivariate Cox regression analysis.

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Declaration of competing interest

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