Long-term safety and effectiveness of the Fantom bioresorbable coronary artery scaffold: final results of the FANTOM II trial

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To overcome the long-term limitations of metallic drug-eluting stents (DES), fully bioresorbable scaffolds (BRS) were developed to restore late vasomotion and adaptive remodelling capability, and reduce the risk of late inflammation, late strut fracture and neoatherosclerosis formation, all of which contribute to restenosis and revascularisation failure. The first-generation bioresorbable scaffolds were launched in Europe in 2012; these were characterised by thick struts (>150 µm) and were derived from a poly-L-lactic acid (PLLA) material. Clinical data from the first-generation PLLA BRS demonstrated their potential for favourable long-term outcomes after their complete bioresorption (~3 years). Before 3 years, however, first-generation BRS were shown to be less safe and effective than DES[1].

The Fantom BRS (REVA Medical) was developed to address the limitations of the first-generation BRS. The Fantom BRS is manufactured from Tyrocore (REVA Medical), a unique desaminotyrosine-based polymer, which improves both material strength and elasticity while allowing for a reduced strut thickness of the scaffold. The first-generation Fantom BRS used in this study had a uniform strut thickness of 125 µm. The Fantom scaffold has an estimated surface-to-artery ratio of 30% and varying strut widths – ranging from approximately 140 µm to 225 µm along the length of the device. The Fantom BRS polymer also incorporates covalently bound iodine into the polymer chain's backbone, making the scaffold radiopaque and allowing for direct visualisation and verification of the implantation results during invasive angiography.

Herein we report the final 60-month clinical outcomes of the FANTOM II study population along with the imaging outcomes from a 24-month follow-up invasive substudy.

The FANTOM II study was a prospective, single-arm, multicentre study assessing clinical and angiographic outcomes after implantation of the Fantom BRS **(Supplementary Figure 1)**. The study population included 240 patients from cohorts A and B, in whom only the Fantom BRS had been implanted. A subset of 36 patients from cohort A completed a 2-year angiography and optical coherence tomography (OCT) imaging follow-up.

During the procedure, lesions were predilated with non-compliant or semi-compliant balloons to within 0.25 mm of the reference vessel diameter (RVD). The Fantom scaffold was deployed at the lesion site with single-step inflation directly to its intended diameter. The decision to perform post-dilation was left to the discretion of the operator. Dual antiplatelet therapy with aspirin plus clopidogrel, ticagrelor, or prasugrel was prescribed to all patients for 12 months.

For analysis, quantitative coronary angiography (QCA) was performed in all patients at either 6- or 9-month follow-up. An additional assessment was performed in a subset of cohort A patients at 24-month follow-up. Angiograms were assessed at an independent angiographic core laboratory (Yale Cardiovascular Research Group, New Haven, CT, USA).

OCT assessments were performed either at the 6- and 24-month or the 9- and 60-month follow-up visits **(Supplementary Figure 2)** and were analysed at an independent core laboratory (Aarhus University Hospital, Denmark).

The primary safety endpoint was the incidence of MACE: a composite of cardiac death, myocardial infarction (MI) or target lesion revascularisation (TLR). A secondary endpoint of target lesion failure (TLF) was defined as the composite of cardiac death, target vessel (TV)-MI, or clinically driven TLR.

A total of 240 patients were included in the modified intention-to-treat analysis (117 patients in cohort A and 123 patients in cohort B) (Supplementary Figure 1). Outcomes at 60 months were also assessed in the 202 patients in the as-treated population. The key baseline characteristics are presented in Supplementary Table 1. The average lesion length was 11.56±3.89 mm. The pre-treatment RVD was 2.71±0.37 mm, and % diameter stenosis was 69.5±11.0%. More detailed baseline angiographic and OCT characteristics have been published previously[2,3].

Clinical outcomes up to 5 years are shown in Central illustration A and Supplementary Table 2. Among the 240 patients, the rates of MACE up to 1 and 2 years were 4.2% and 5.0%, respectively. There were no recorded MACE between 2 and 3 years. After 3 years, only 3 MACE occurred, bringing the 5-year Kaplan-Meier estimated rate of MACE to 6.3%. The TLF rate up to 5 years was 5.8%. Event rates were slightly higher for the 202 patients in the as-treated population (Supplementary Table 2, Supplementary Figure 2, Supplementary Figure 3).

At 5-year follow-up, definite scaffold thrombosis had occurred in 3 patients (1.3%) (Central illustration B). The first event occurred at 5 days post-index procedure due to significant untreated stenoses. The second event occurred at 718 days after implantation in a vessel smaller than the protocol limits. In addition, significant malapposition of the scaffold was present that had not been corrected during the index procedure. The third event occurred at 806 days after implantation and was noticed during clinically driven angiography; no lumen narrowing was observed, but there was a small thrombus at the scaffold's edge.

QCA analysis was performed immediately after the procedure and at 6-, 9- and 24-month angiographic follow-ups. At 24 months, the mean in-scaffold late lumen loss (LLL) was 0.23±0.49 mm, and the mean in-segment LLL was 0.21±0.49 mm. The mean in-scaffold and in-segment % diameter stenosis were 15.1±17.9% and 23.2±16.7%, respectively. There were no significant differences in mean % diameter stenosis between 6-, 9-, and 24-month follow-ups, regardless. While the mean in-scaffold LLL did not show significant differences between different time points, the mean in-segment LLL had increased at 9 and 24 months, compared to 6 months (Supplementary Table 3, Supplementary Table 4 [matched subset]).

At 2 years, a total of 25 patients were available for matched, serial OCT analysis. As shown in Central illustration C and Central illustration D, the mean scaffold area remained stable in this cohort of patients: 7.32±1.14 mm² at baseline (post-implant), 7.43±1.16 mm² at 6 months, and 7.45±1.28 mm² at 24 months. The mean lumen area decreased from 7.09±1.38 mm² at baseline to 6.01±1.32 mm² at 6 months and remained stable thereafter (5.87±0.19 mm² at 2 years). The minimum scaffold area did not change from baseline (6.14±1.09 mm²) to 24-month follow-up (5.99±1.17 mm²). The minimum lumen area (MLA) was 5.58±1.09 mm² at baseline, 4.65±1.10 mm² (p<0.001) at 6 months, and 4.10±1.21 mm² at 24 months (p=0.10). Strut coverage at 6 and 24 months was 98% and 100%, respectively. The mean neointimal thickness covering the struts was 51 µm at 6 months and 79 µm at 24 months (p=0.01). No acquired malapposition nor vessel wall evaginations between struts were detected in any patient during follow-up.

The main findings of the long-term follow-up from the FANTOM II study are as follows: 1) clinical event rates were very low up to 5 years of follow-up with complete scaffold degradation; 2) the rate of stent thrombosis was particularly low (1.3% up to 5 years); 3) 24-month angiographic follow-up showed a modest LLL and low rate of binary restenosis; and 4) serial OCT assessment showed a favourable healing pattern at 24 months.

The objective of BRS is to overcome long-term complications that arise from permanent metallic DES implants. The specific development targets were to improve mechanical properties, reduce strut thickness, improve visibility, and allow for safe resorption. The Fantom BRS is constructed from a completely different material than the 3 first-generation European conformity (CE)-certified scaffolds – Absorb (Abbott), DESolve (Elixir Medical), and Magmaris (Biotronik). In the FANTOM II study, the strut thickness of the Fantom BRS was 125 µm. The strut thickness of the newest generation of BRS (Fantom Encore), which was not included in this study, has been further reduced to 95 µm, while otherwise maintaining the mechanical properties of the first-generation device studied herein.

The present study demonstrates that the Fantom BRS is safe, with low 5-year rates of MACE and scaffold thrombosis when implanted in non-complex lesions. The 5.8% TLF rate at 5 years compares favourably with 6.6% for Magmaris[4] at 3 years and with 11.7% and 12.7% for Absorb at 3 and 5 years, respectively[5].

In addition, the high-resolution 24-month OCT analyses confirmed the scaffold's stable mechanical properties. The lumen area decreased slightly after implantation, as with all DES, due to neointimal proliferation within the implant, but the healing response did not extend beyond 6 months. All acute malappositions were resolved except in one patient, in which nearly half of the scaffold was left severely malapposed after the implantation. No adverse vessel wall reactions were detected at 6 or 24 months, and strut coverage was 98% at 6 months and 100% at 24 months.

Based on these favourable long-term clinical and imaging results, the Fantom BRS may be a safer and more effective implant than first-generation BRS. The present FANTOM II trial results support further evaluation of the Fantom BRS, compared with metallic DES, in a large-scale, randomised clinical outcomes trial.

The results of this study only apply to Fantom BRS implantation in a stable population with non-complex coronary lesions and, therefore, cannot be generalised for more complex lesions or patients at higher risk. The open-label design may have introduced bias, and the low adverse event rates require cautious interpretation given the absence of an active comparator. However, the 2-year angiographic and OCT findings provide objective data supporting the clinical results.

In the prospective, multicentre FANTOM II study, the Fantom BRS was safe and effective during 5-year follow-up after implantation in selected patients and lesions with stable coronary artery disease. With the favourable healing patterns observed during late angiographic and OCT follow-up, the Fantom BRS is a promising alternative to permanent drug-eluting stents, warranting further evaluation in adequately powered randomised trials.

EuroIntervention   Central **Illustration**

Analysis of 60-month clinical data and 24-month OCT.

FANTOM II trial: clinical outcomes
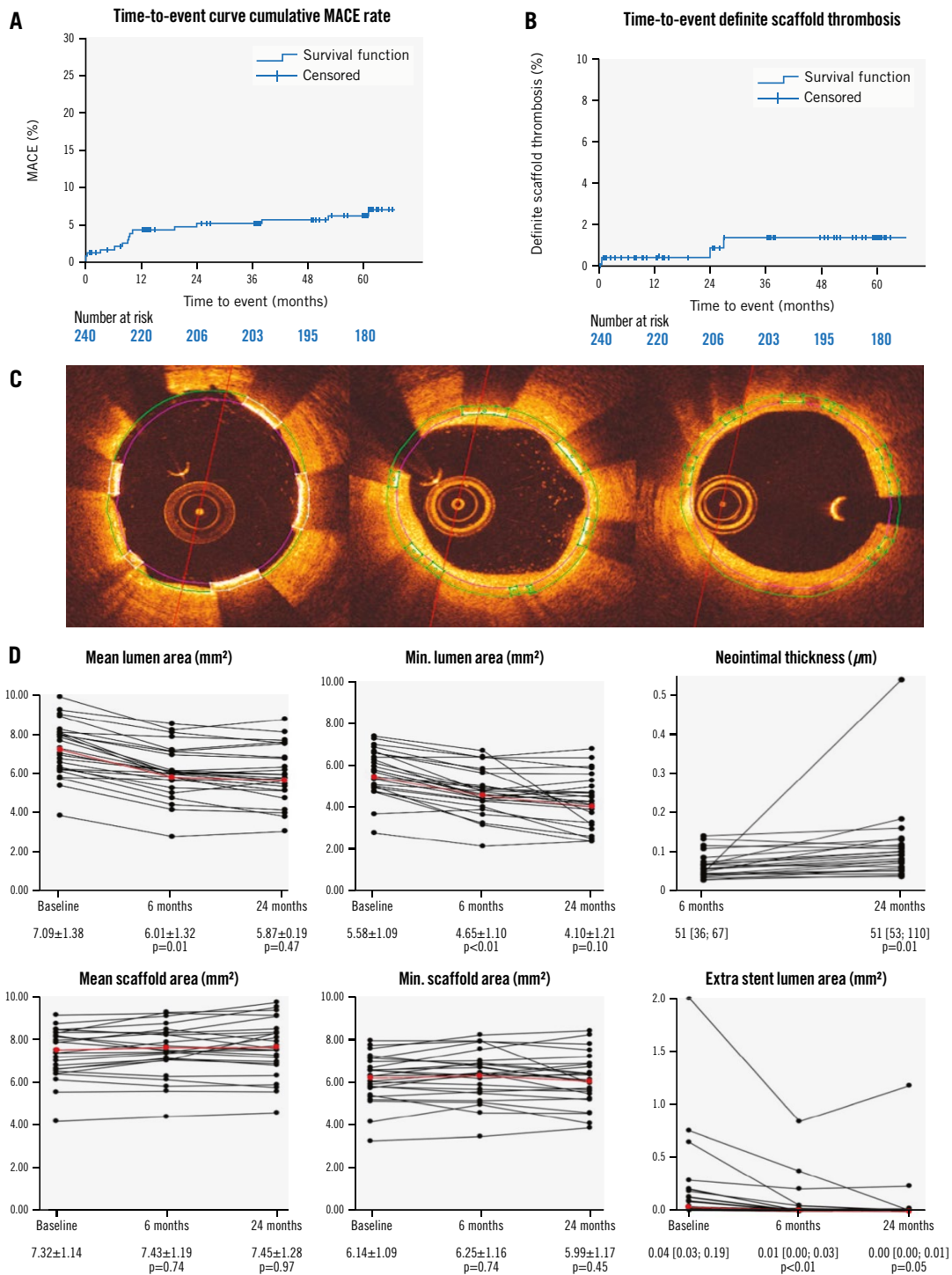
A) Time-to-event curve for cumulative MACE up to 60 months in the intention-to-treat population. B) Time-to-event curve for definite scaffold thrombosis up to 60 months in the intention-to-treat population. C) Representative OCT images of serial analysis at implantation, 6- and 24-month follow-ups. D) Serial OCT results at 6- and 24-month follow-ups. MACE: major adverse cardiac events; min.: minimum; OCT: optical coherence tomography

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Conflict of interest statement

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Supplementary data

Supplementary Table 1. Baseline patient characteristics.
Supplementary Table 2. Clinical outcomes up to 5 years.
Supplementary Table 3. Postprocedural, 6-, 9- and 24-month angiographic follow-up.
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Supplementary Figure 1. Clinical trial design overview.
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Supplementary data

Supplementary Table 1. Baseline patient characteristics.

	N= 240
Age, years	62.7±10.1
Male	169 (70.4)
Risk factors	
Diabetes	57 (23.8)
Cigarette smoking	143 (59.6)
Hypertension	177 (73.8)
Hyperlipidaemia	170 (70.8)
Family history of coronary artery disease	84 (35.0)
Medical history	
Peripheral vascular disease	12/239 (5.0)
Previous myocardial infarction	63 (26.3)
Prior coronary artery bypass graft surgery	7 (2.9)
Left ventricular ejection fraction <40%	0 (0.0)

Supplementary Table 2. Clinical outcomes up to 5 years.

	Modified ITT (n=240)	As-treated (n=202)
Cumulative through 5 years		
MACE	**6.3 (15)**	7.4 (15)
TLF	**5.8 (14)**	6.9 (14)
Death	**5.8 (14)**	6.9 (14)
Cardiac death	**1.7 (4)**	2.0 (4)
Non-cardiac	**4.2 (10)**	5.0 (10)
Device-related	**0.0 (0)**	0.0 (0)
All MI	**1.7 (4)**	2.0 (4)
Target vessel-related MI	**1.3 (3)**	1.5 (3)
Clinically-driven TLR	**3.3 (8)**	4.0 (8)
Scaffold thrombosis (ARC definite or probable)	**1.3 (3)**	1.5 (3)
Definite	**1.3 (3)**	1.5 (3)
Probable	**0.0 (0)**	0.0 (0)
Acute (<24 hours)	**0.0 (0)**	0.0 (0)
Subacute (24 hours to 1 month)	**0.4 (1)**	0.5 (1)
Late (1 month to 1 year)	**0.0 (0)**	0.0 (0)
Very Late (>1 year)	**0.8 (2)**	1.0 (2)
0-1 year		
MACE	**4.2 (10)**	-
Definite (or definite/probable) scaffold thrombosis	**0.4 (1)**	-
1-2 year		
MACE	**0.8 (2)**	-
Definite (or definite/probable) scaffold thrombosis	**0.4 (1)**	-
2-3 year		
MACE	**0.0 (0)**	-
Definite (or definite/probable) scaffold thrombosis	**0.4 (1)**	-
3-4 year		
MACE	**0.4 (1)**	-
Definite (or definite/probable) scaffold thrombosis	**0.0 (0)**	-
4-5 year		
MACE	**0.8 (2)**	
Definite (or definite/probable) scaffold thrombosis	**0.0 (0)**	

Values are expressed as % (n). Data are non-hierarchical. ARC= Academic Research Consortium; MACE= major adverse cardiovascular event(s); MI= myocardial infarction; TLR= target lesion revascularization; TLF=target lesion failure (clinically driven TLR, MI or cardiac death related to the target vessel).

Supplementary Table 3. Post-procedural, 6-, 9- and 24-month angiographic follow-up.

	Post-procedure (n=233 patients and lesions)	Cohort A 6-month follow-up (n=100 patients and lesions)	Cohort B 9-month follow-up (n=105 patients and lesions)	Cohort A 24-month follow-up (n=36 patients and lesions)	P-Value
RVD, mm	2.75 ± 0.38*	2.70 ± 0.36	2.73 ± 0.37	2.67 ± 0.33	-
In-scaffold					
MLD, mm	2.51 ± 0.35 *	2.23 ± 0.41	2.22 ± 0.43	2.18 ± 0.48	-
Diameter stenosis, %	7.2± 9.7 *	15.3 ± 15.2	16.4 ± 14.3	15.1± 17.9	6 mo vs 9 mo = 0.60 Paired: 6 mo vs 24 mo = 0.94
Acute gain, mm	1.68 ± 0.41*	-	-	-	-
Late loss, mm	-	0.25 ± 0.40	0.33 ± 0.36	0.23 ± 0.49	6 mo vs 9 mo = 0.15 Paired: 6 mo vs 24 mo = 0.74
Binary restenosis, % (n)	-	2 (2)	2.9 (3)	2.8 (1)	-
In-segment					
MLD, mm	2.32 ± 0.39*	2.11 ± 0.42	2.08 ± 0.46	2.05 ± 0.52	-
Diameter stenosis, %	17.0 ± 7.2*	21.7 ± 13.2	23.7 ± 14.0	23.2 ± 16.7	6 mo vs 9 mo = 0.29 Paired: 6 mo vs 24 mo =0.63
Acute gain, mm	1.49 ± 0.41*	-	-	-	-
Late loss, mm	-	0.17 ± 0.34	0.29 ± 0.41	0.21 ± 0.49	6 mo vs 9 mo <0.05 Paired: 6 mo vs 24 mo <0.05
Binary restenosis, % (n)	-	2 (2.0)	7.6 (8)	5.6 (2)***	
Acute recoil, % **	4.0 ± 8.3	-	-	-	-

Values are mean ± SD or n (%). ITT = intention to treat.

∗ Data available for 233 patients: the post-implant QCA analysis of five delivery failures was unavailable and two post-procedure angiographic records were not saved at the site.

∗∗ Data available for 156 patients: Not all centers recorded a cine angiogram with the delivery balloon fully inflated. A total of 157 patients provide an adequate assessment of the acute balloon and device recoil. Among 157 subjects who had final balloon measurements, one subject's mean scaffold diameter was not available for acute recoil calculation.

∗∗∗ The % diameter stenosis of these two lesions were 100% (resulted in a TLR) and 55% (resulted in a TVR

Supplementary Table 4. Serial angiographic outcomes – matched set of 36 patients who received angiographic assessments at each time point.

In-Scaffold Analysis	Baseline (Subset n=36)	Cohort A – 6 Mo. (Subset n=36)	Cohort A – 24 Mo. (Subset n=36)
RVD (mm)	2. 68 ± 0.32	2.64 ± 0.29	2.67 ± 0.33
MLD (mm)	0.74 ± 0.30	2.29 ± 0.28	2.18 ± 0.48
Diameter Stenosis (%)	72.3 ± 11.3	11.4 ± 10.1	15.1 ± 17.9
Acute Gain (mm)	1.67 ± 0.43		
Acute Recoil (%)	3.3 ± 8.0		
Mean LLL (mm)		0.18 ± 0.37	0.23 ± 0.49
In-Segment Analysis			
Mean LLL (mm)		0.13 ± 0.38	0.21 ± 0.49
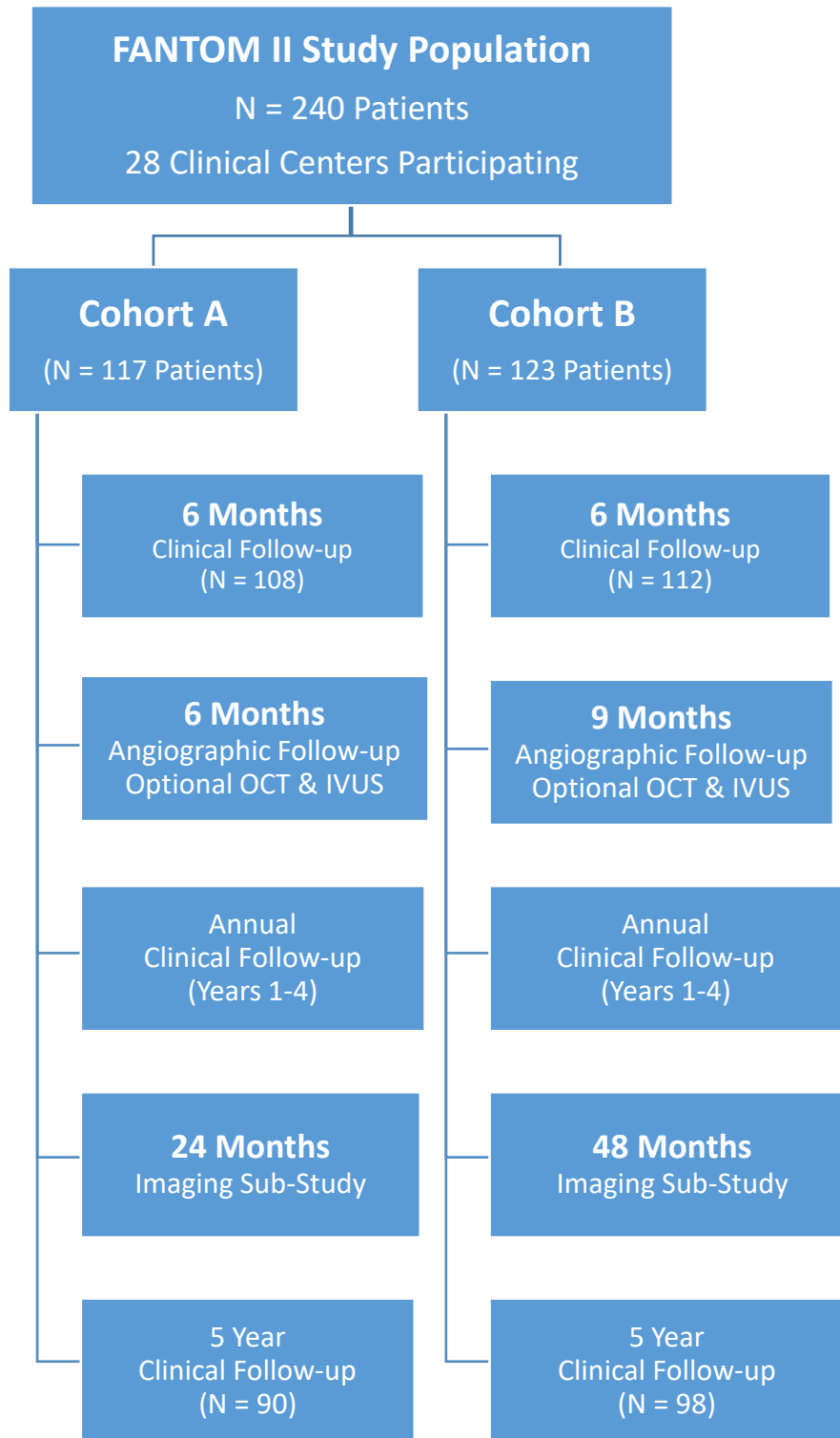
Supplementary Figure 1. Clinical trial design overview.

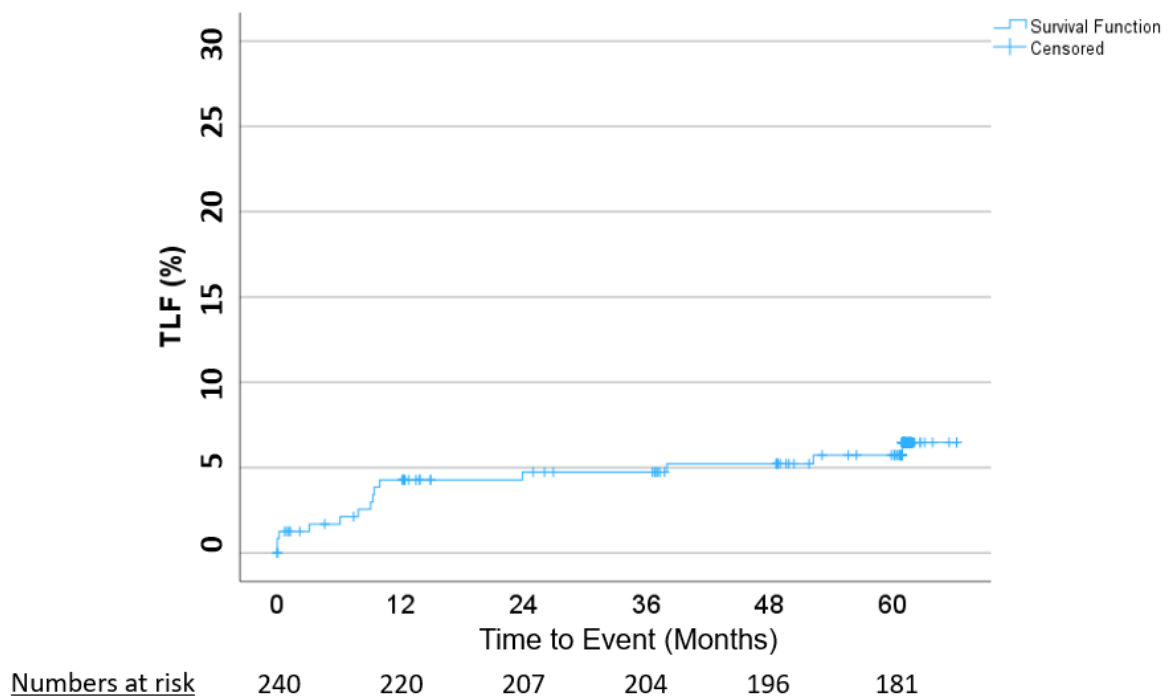Note : The total of 188 patients at 60 months, represents the event free patients that completed their 60-month follow-up clinical visit. This number does not include any loss to follow-up patients.

Clinical follow-up

Modified ITT=240 patients
Enrolled in FANTOM II
(Cohort A=117, Cohort B=123)

As-treated (N=230) at 12 months

As-treated (N=215) at 36 months

As-treated (N=202) at 48 months

As-treated (N=202) at 60 months
38 patients without MACEs did not complete 60 months follow-up due to early study exit, delivery failures, withdrawn consent, bailout, lost to follow up

Angiographic follow-up

Post-Procedure QCA (N-233)
5 delivery failures
2 record not saved

Cohort A: 6 months QCA (N-100)

Cohort B: 9 months QCA (N-105)

Cohort A: 24 months QCA (N-36)

Optional Intravascular Imaging follow-up

OCT analysis (N-25)
35 sets reviewed at baseline, 6 months and 24 months, 10 sets were excluded due to 6 insufficient image quality, 3 missing baseline OCT, and 1 TLR before follow-up

Supplementary Figure 2. FANTOM II trial – clinical analysis summary.

Supplementary Figure 3. Time-to-event TLF curve up to 60 months in the intention-to-treat population.