Paclitaxel Drug-Coated Balloon for the Treatment of *De Novo* Small-Vessel and Restenotic Coronary Artery Lesions: 12-Month Results of the Prospective, Multicenter, Single-Arm PREVAIL Study

Azeem Latib, MD[1,2]; Pierfrancesco Agostoni, MD, PhD[3]; Jo Dens, MD, PhD[4]; Mark Patterson, MBBS, PhD[5]; Patrizio Lancellotti, MD, PhD[6]; Frankie C.C. Tam, MD[7]; Carl Schotborgh, MD[8]; Elvin Kedhi, MD[9]; Pieter Stella, MD, PhD[10]; Cheryl Shen, MS[11]; Gwenn Wetzels, PhD[11]; Luca Testa, MD[12]; for the PREVAIL Study Investigators

Abstract

Objectives. The PREVAIL study evaluated the safety and effectiveness of a paclitaxel-coated percutaneous transluminal coronary angioplasty balloon catheter for the treatment of coronary *de novo* and in-stent restenosis (ISR) lesions in patients with symptomatic ischemic heart disease. **Methods.** PREVAIL was a prospective, multicenter, single-arm study that enrolled patients with clinical evidence of ischemia who had coronary lesions (*de novo* or first ISR) amenable to treatment with a drug-coated balloon (DCB). The study included 50 subjects (53 target lesions) who were treated with a Prevail DCB (Medtronic) during the index procedure and followed for 12 months. Mean lesion length was 14.5 ± 7.6 mm. The primary endpoint was in-stent (in-balloon) late lumen loss (LLL) by quantitative coronary angiography at 6 months post procedure. If the mean in-stent (in-balloon) LLL was less than the maximum acceptance rate of 0.50 mm at 6 months, then the study was considered successful. **Results.** Mean in-stent (in-balloon) LLL was 0.05 ± 0.44 mm at 6 months post procedure. There were no deaths, myocardial infarctions, or stent (lesion) thrombosis events within 12 months. The incidence of clinically driven target-lesion revascularization was 6.0% at 12 months and clinically driven target-vessel revascularization was 10.0%. **Conclusions.** Paclitaxel DCB treatment of coronary *de novo* and first ISR lesions led to low LLL at 6 months and low rates of revascularization and safety events through 12 months.

J INVASIVE CARDIOL 2021;33(11):E863-E869. Epub 2021 August 19.

Key words: DCB, drug-coated balloon, in-stent restenosis, ischemia, revascularization

As an alternative to drug-eluting stent (DES) options, drug-coated balloons (DCBs) provide targeted delivery of an antirestenotic agent during percutaneous coronary intervention (PCI) without leaving a permanent implant behind. Clinical investigations have evaluated the role of coronary DCBs in the treatment of in-stent restenosis (ISR) and small-vessel lesions, with prospective single-arm trials, retrospective and observational cohort studies, and registries showing that paclitaxel DCBs can safely and effectively treat these lesion types.[1-6] While randomized controlled trials have demonstrated that paclitaxel DCBs are superior to angioplasty with an uncoated balloon and non-inferior to DESs for the treatment of coronary ISR,[7-14] findings have been mixed in patients with small-vessel disease, highlighting that this technology does not have a class effect and not all DCBs are created equally.[15-17]

The aim of the present study was to evaluate the clinical safety and effectiveness of a next-generation paclitaxel-coated percutaneous transluminal coronary angioplasty (PTCA) balloon for the treatment of patients with *de novo* or ISR lesions. Herein, we report 6-month angiographic and 12-month clinical and safety outcomes.

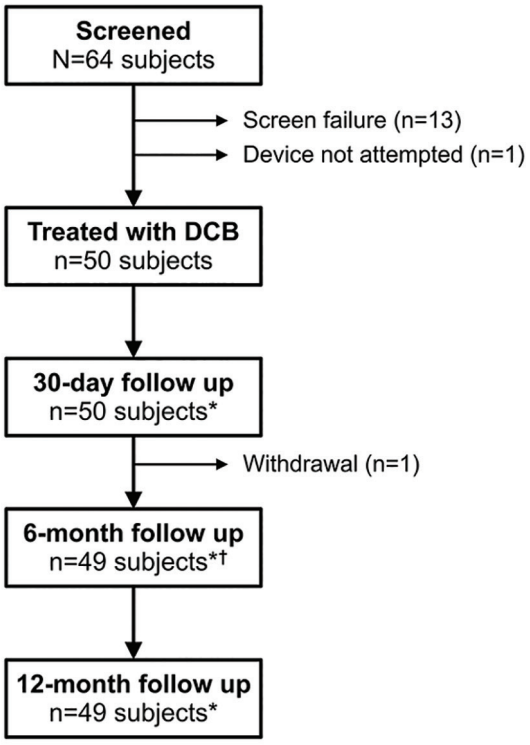

FIGURE 1. Patient flow through 12 months. *Value includes patients who were alive and had not exited the study before the lower window of the visit period. Note that 1 patient withdrew and had a target-lesion revascularization at 73 days post procedure, and therefore was included in the analysis population. †At 6 months, 49 patients underwent a clinical follow-up evaluation and 47 patients had evaluable data for angiographic analysis. DCB = drug-coated balloon.

Methods

Study design. PREVAIL was a prospective, multicenter, single-arm premarket study that evaluated the clinical safety and effectiveness of the Prevail paclitaxel-coated PTCA balloon catheter (Medtronic) for the treatment of coronary de novo lesions, ISR, and small-vessel disease in patients with symptomatic ischemic heart disease. Patients were treated with the DCB during the index procedure and clinical follow-up was performed at 30 days, 6 months, and 12 months post procedure; quantitative coronary angiography (QCA) was performed before and after the procedure, and at 6-month follow-up. All patients provided informed consent.

A clinical events committee reviewed and adjudicated all clinical endpoints (Baim Institute for Clinical Research). A data monitoring committee evaluated safety data over the course of the study (Baim Institute for Clinical Research). An angiography core laboratory analyzed procedural and follow-up images (Beth Israel Deaconess Medical Center).

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice principles outlined in ISO 14155:2011, and applicable laws as specified by all relevant governmental authorities. The protocol was reviewed and approved by all ethics committees and institutional review boards. All patients provided written informed consent prior to enrollment. The study is registered at clinicaltrials.gov (NCT03260517).

Patient population. Patients enrolled had documented stable or unstable angina and/or clinical evidence of ischemia and were deemed acceptable candidates for treatment with a DCB. Major exclusion criteria included previous PCI of the target vessel (<9 months before the index procedure for *de novo* lesions, <3 months for ISR), a stroke/transient ischemic attack <6 months or a myocardial infarction (MI) event <72 hours before the index procedure. Complete inclusion/exclusion criteria are listed in **Supplemental Table S1**. All enrolled patients had angiography to confirm additional angiographic inclusion/exclusion criteria as listed in **Supplemental Table S1**. Of note, target lesions must have been ≤25 mm in length with a reference vessel diameter of 2-4 mm and diameter stenosis ≥50% but <100%.

Index procedure. Successful predilation with semi- and/or non-compliant balloons was required (success being documented by angiographic visual estimation of <30% residual stenosis of the target lesion and no major [> grade B] flow-limiting dissection). Angiography was performed before and after predilation. Adjunctive procedures for lesion preparation, such as cutting/scoring balloons, atherectomy, laser, or thrombectomy, were not permitted. Although 23.4% of lesions had moderate or severe calcification, the study excluded lesions that could not be optimally prepared for DCB with non-compliant balloons, as these are lesions that would be more complex and there are minimal data to support the efficacy of DCB over DES in these lesion types. Since this was the first clinical evaluation of this device, it was important to evaluate the DCB in lesions of moderate complexity where the efficacy and safety would be comparable to studies of other devices. Subjects with successful predilation of the target lesion(s) were treated with the Prevail DCB, a PTCA balloon catheter coated with a target dose of 3.5 μg/mm^2 paclitaxel and the excipient urea. Multiple lesions that individually met the inclusion and exclusion criteria could be treated with a study device. Lesions treated with the DCB were defined as target lesions. A maximum of 4 lesions could be treated during the index procedure (maximum of 3 target vessels). Two lesions in 1 vessel could not be treated with a DCB. A maximum of 2 vessels with 2 lesions was allowed. A unique DCB was to be used for each lesion.

Bailout stenting was permitted for cases of major and/or flow-limiting dissection (grade C or higher) or occlusive complications. Details of the index procedure are provided in **Appendix 1**.

Study endpoints. The primary endpoint was in-stent (in-balloon) late lumen loss (LLL) by quantitative coronary angiography (QCA)

TABLE 1. Baseline demographics and clinical characteristics.

Characteristics	Patients (n = 50)
Age (years)	64.9 ± 9.2
Male	41/50 (82.0%)
Body mass index (kg/m^2)	27.2 ± 3.6
Hyperlipidemia	34/50 (68.0%)
Hypertension	34/50 (68.0%)
Diabetes mellitus	17/50 (34.0%)
Chronic obstructive pulmonary disease	5/50 (10.0%)
Peripheral vascular disease	6/50 (12.0%)
Previous myocardial infarction	20/50 (40.0%)
Prior PCI	39/50 (78.0%)
Prior coronary artery bypass graft	6/50 (12.0%)
Stroke or transient ischemic attack	7/50 (14.0%)
Cardiac admissions within 30 days prior to index procedure	6/50 (12.0%)
Number of diseased major coronary arteries[a]	
1	31/50 (62.0%)
2	11/50 (22.0%)
3	8/50 (16.0%)
Indication for PCI[b]	
Evidence of ischemia	38/50 (76.0%)
Silent ischemia	9/38 (23.7%)
Stable angina	20/38 (52.6%)
Unstable angina	7/38 (18.4%)
Myocardial infarction[c]	2/38 (5.3%)
Positive functional study	15/50 (30.0%)
CASS site of target lesion	
Right coronary artery	15/53 (28.3%)
Left anterior descending artery	20/53 (37.7%)
Left circumflex artery	18/53 (34.0%)
Target lesion type	
De novo	24/53 (45.3%)
Small vessel disease	19/24 (79.2%)
In-stent restenosis	29/53 (54.7%)
Restenosis in bare-metal stent	2/29 (6.9%)
Restenosis in drug-eluting stent	23/29 (79.3%)
Restenosis in unknown stent type	4/29 (13.8%)
Calcification	
Mild	36/47 (76.6%)
Moderate	6/47 (12.8%)
Severe	5/47 (10.6%)
TIMI flow 3	52/52 (100%)
Bifurcation	17/52 (32.7%)[d]
Modified ACC/AHA lesion class B2/C	38/53 (71.7%)
Preprocedural QCA lesion characteristics	
Lesion length (mm)	14.5 ± 7.6
Reference vessel diameter (mm)	2.4 ± 0.6
Minimal lumen diameter (mm)	0.8 ± 0.4
Diameter stenosis by QCA (%)	66.0 ± 12.4

Data presented as mean ± standard deviation or n/total (%).
[a]Diseased major coronary artery defined by >50% stenosis. [b]Subjects could have more >1 indication for PCI. [c]Myocardial infarction (MI) >72 hours prior to the index procedure; subjects with MI <72 hours prior to the index procedure were excluded. [d]Due to protocol violations, 17 target lesions that involved a bifurcation were treated during the index procedure and included in the analysis.
ACC/AHA = American College of Cardiology/American Heart Association; CASS = Coronary Artery Surgery Study; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; TIMI = Thrombolysis in Myocardial Infarction.

at 6 months post procedure. If the mean in-stent (in-balloon) LLL was less than the maximum acceptance rate of 0.50 mm at 6 months, then the study was considered successful. Secondary angiographic endpoints were also measured by QCA at 6 months post procedure and included in-segment LLL, percent diameter stenosis, minimal lumen diameter (MLD), and binary angiographic restenosis (defined as ≥50% diameter stenosis). Besides LLL, all secondary angiographic endpoints were assessed in segment and in stent (in balloon).

Secondary clinical outcomes were assessed at 30 days, 6 months, and 12 months post procedure for the overall population and by lesion type (*de novo* and ISR). Clinical endpoints included: all deaths; target-vessel MI; major adverse cardiac event (MACE), defined as a composite of death, MI (Q-wave and non-Q wave), emergent coronary artery bypass graft surgery, or repeat clinically driven target-lesion revascularization (TLR) by percutaneous or surgical methods; target-vessel failure (TVF), defined as cardiac death, target-vessel MI, or clinically driven target-vessel revascularization (TVR) by percutaneous or surgical methods; target-lesion failure (TLF), defined as cardiac death, target-vessel MI, or clinically driven TLR by percutaneous or surgical methods; and stent (lesion) thrombosis, defined according to the Academic Research Consortium.[18] MI is defined in detail in **Appendix 1**.

The following procedural outcomes were assessed: device success (attainment of <50% residual stenosis of the target lesion

TABLE 2. Procedure characteristics and outcomes.

Characteristics	Patients (n = 50) Target Lesions (n = 53)
Mean total lesions (TL and non-TL) treated per patient	1.4 ± 0.6
Total lesions (TL and non-TL) treated per patient	
1	32/50 (64.0%)
2	14/50 (28.0%)
≥3	4/50 (8.0%)
Target lesions treated per patient	
1	47/50 (94.0%)
2	3/50 (6.0%)
≥3	0/50 (0.0%)
Vascular access site	
Femoral access	8/50 (16.0%)
Radial access	42/50 (84.0%)
Total procedure time (min)	42.7 ± 27.7
Total contrast administered (mL)	154.5 ± 74.0
Predilation performed	53/53 (100%)
Predilation balloon used (first dilation)	
Compliant	10/53 (18.9%)
Semicompliant	33/53 (62.3%)
Non-compliant	10/53 (18.9%)
Duration of DCB inflation of first dilation (sec)	19.3 ± 13.3
Postprocedural QCA lesion characteristics	
Reference vessel diameter (mm)	2.4 ± 0.5
In-stent diameter stenosis after index procedure (%)	21.0 ± 16.5
In-stent minimal lumen diameter (mm)	1.9 ± 0.6
In-stent acute gain (mm)	1.1 ± 0.5
In-segment acute gain (mm)	1.0 ± 0.5
Bailout stenting procedure	2/53 (3.8%)
Flow-limiting dissection	1/53 (1.9%)
Other	1/53 (1.9%)[a]
Device success[b]	50/53 (94.3%)
Lesion success[c]	50/53 (94.3%)
Procedure success[d]	48/50 (96.0%)

Data presented as mean ± standard deviation or n/total (%).
[a]Subject had 2 target lesions in 1 vessel and a grade B dissection post procedure (not confirmed by angiography core lab). [b]Attainment of <50% residual stenosis of the target lesion using only the study device. [c]Attainment of <50% residual stenosis of the target lesion using any percutaneous method. [d]Attainment of <50% residual stenosis of the target lesion and no in-hospital major adverse cardiac events. QCA = quantitative coronary angiography; TL = target lesion.

using only the study device); lesion success (attainment of <50% residual stenosis of the target lesion using any percutaneous method); and procedural success (attainment of <50% residual stenosis of the target lesion and no in-hospital MACE).

Statistical analysis. Categorical variables were reported as percentages and counts, and continuous variables were reported as means ± standard deviations. Statistical analyses were performed with SAS, version 9.1 or higher (SAS Institute).

Results

Baseline demographics and clinical characteristics. The study flow chart is depicted in **Figure 1**. The intent-to-treat population included 50 patients with 53 target lesions. Baseline demographic, clinical, and lesion characteristics are reported in **Table 1**. The mean age was 64.9 ± 9.2 years and 82.0% were men. Comorbidities were prevalent, including hyperlipidemia (68.0%), hypertension (68.0%), and diabetes (34.0%). Most patients (38/50; 76.0%) had evidence of ischemia, with stable angina being the most prevalent indication for PCI (20/38; 52.6%). The mean lesion length was 14.5 ± 7.6 mm, 45.3% were *de novo* lesions (of which 79.2% were in small vessels) and the remaining (54.7%) were ISR lesions.

Procedural characteristics and outcomes. Procedural characteristics and outcomes are reported in **Table 2**. Most patients (94.0%) had 1 target lesion treated during the index procedure, and the remaining patients (6.0%) had 2 target lesions treated. Two lesions (3.8%) required bailout implantation of a DES, 1 for a flow-limiting dissection and 1 with a grade B dissection without compromise of distal flow. Device success was achieved in 50/53 lesions (94.3%), lesion success was achieved in 50/53 lesions (94.3%), and procedural success occurred in 48/50 patients (96.0%).

Angiographic outcomes. The study was successful, with a mean in-stent (in-balloon) LLL of 0.05 ± 0.44 mm at 6 months post procedure, below the predefined performance goal of 0.50 mm. When analyzed by lesion type, the mean in-stent (in-balloon) LLL at 6 months was –0.04 ± 0.41 mm for *de novo* lesions and 0.12 ± 0.45 mm for ISR lesions. The mean in-stent (in-balloon) diameter stenosis by QCA at 6 months for all target lesions was 23.23 ± 17.77%, and the rate of in-stent (in-balloon) binary angiographic restenosis was 10.0%. Angiographic outcomes are summarized in **Table 3**.

Clinical outcomes. There were no deaths, MIs, or stent (lesion) thrombosis events within 12 months (**Figure 2**). The incidence of MACE at 12 months was 6.0%, TVF was 10.0%, and clinically driven TLR was 6.0%. Clinical outcomes by lesion cohort are reported in **Supplemental Table S2**.

TABLE 3. Angiographic outcomes at 6 months.

Outcome	In Segment Subjects (n = 50) Lesions (n = 53)	In Stent (In Balloon) Subjects (n = 50) Lesions (n = 53)[a]	In Stent (In Balloon) *De novo* Lesions Subjects (n = 22) Lesions (n = 24)	In Stent (In Balloon) *De novo* Small Lesions Subjects (n = 17) Lesions (n = 19)[b]	In Stent (In Balloon) ISR Lesions Subjects (n = 28) Lesions (n = 29)
Late lumen loss (mm)	0.06 ± 0.39	0.05 ± 0.44[c]	-0.04 ± 0.41	-0.04 ± 0.36	0.12 ± 0.45
Diameter stenosis by QCA (%)	28.21 ± 17.15	23.23 ± 17.77	20.91 ± 20.14	22.71 ± 21.44	25.05 ± 15.80
Minimal lumen diameter (mm)	1.76 ± 0.64	1.87 ± 0.63	1.75 ± 0.52	1.64 ± 0.52	1.97 ± 0.71
Binary angiographic restenosis[d]	8/50 (16.0%)	5/50 (10.0%)	3/22 (13.6%)	3/17 (17.6%)	2/28 (7.1%)

Data presented as mean ± standard deviation or n/total (%).
[a]A total of 47 subjects with 50 lesions had 6-month angiographic data available. [b]The small *de novo* lesions are a subset of the overall *de novo* lesions. [c]Primary endpoint. [d]Defined as >50% restenosis. ISR = in-stent restenosis; QCA = quantitative coronary angiography.

Discussion

PREVAIL was a prospective, multicenter, single-arm study of the paclitaxel-coated Prevail DCB for the treatment of *de novo* and ISR lesions. The study met the primary endpoint of in-stent (in-balloon) LLL at 6 months post procedure, and the incidence of clinical events within 12 months was low, including no deaths, MIs, or stent (lesion) thromboses. The incidence of clinically driven TLR was also low.

While results cannot be directly compared between studies or specific devices without a head-to-head comparison, clinical outcomes with the Prevail DCB compare favorably to what has been reported for other paclitaxel DCBs at 12 months in similar populations with mixed lesion types, including coronary *de novo* lesions, ISR lesions, and small-vessel disease.[1,5,19,20] While the overall 12-month incidence of MACE in PREVAIL (6.0%) was in the range of what has been reported in these studies (5.7%-21.7%),[1,5,19] there was no all-cause death, MI, or stent (lesion) thrombosis in PREVAIL, which is less than what was reported in any of the other studies (4.9%-5.8% for all-cause death, 1.6%-1.7% for MI, and 0.5%-0.9% for stent thrombosis).[1,19,20] The MACE rate in PREVAIL was solely due to clinically driven TLR (6.0%), which itself was at the low end of what has been reported for paclitaxel DCBs for mixed lesion types (4.0%-17.8%).[1,5,19,20] The DCBs from these previous studies were coated with paclitaxel concentrations of 2 μg/mm² (Agent; Boston Scientific) or 3 μg/mm² (SeQuent Please, [B. Braun], IN.PACT Falcon [Medtronic]; Pantera Lux [Biotronik]),[1,5,19,20] which is lower than the concentration used in the Prevail DCB (3.5 μg/mm²), suggesting that increased paclitaxel exposure was not associated with worse clinical outcomes through 12 months. More recently, a meta-analysis for randomized controlled trials comparing DCB with non-DCB devices for the treatment of ISR or *de novo* lesions demonstrated a trend toward lower mortality with paclitaxel-coated balloons.[21] Similarly, a recent multicenter, randomized, open-label registry of 2289 patients with symptomatic peripheral artery disease demonstrated no difference in 1-year mortality between patients treated with paclitaxel-coated devices and those with uncoated devices.[22]

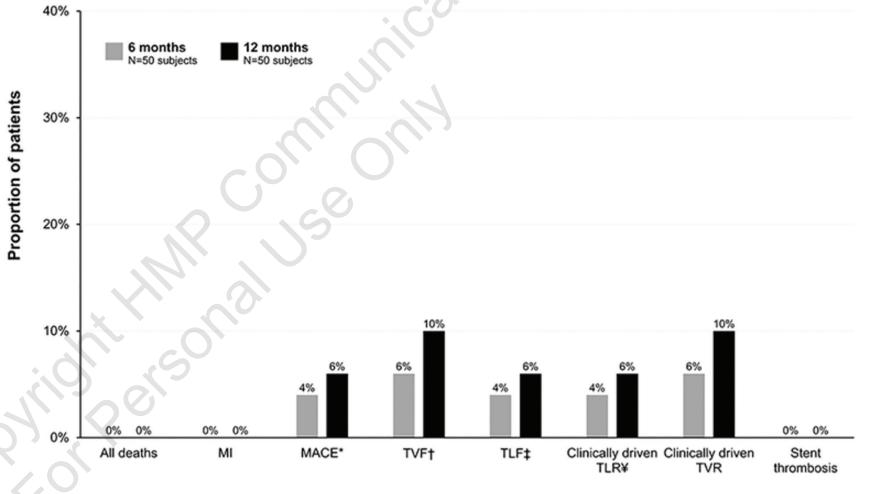

FIGURE 2. Clinical outcomes at 6 and 12 months for the overall population. *Defined as death, myocardial infarction (Q-wave and non-Q wave), emergent coronary bypass surgery, or repeat clinically driven target-lesion revascularization (TLR) by percutaneous or surgical methods. †Defined as cardiac death, target-vessel myocardial infarction (MI), or clinically driven target-vessel revascularization (TVR) by percutaneous or surgical methods. ‡Defined as cardiac death, target vessel MI, or clinically driven TLR by percutaneous or surgical methods. ¥All treated with percutaneous coronary intervention. MACE = major adverse cardiac events; TLF = target-lesion failure; TVF = target-vessel failure.

In addition to differing doses of paclitaxel, DCBs vary in terms of balloon technology, drug-coating process, and how the drug is actually delivered to the vessel wall, which may result in different clinical outcomes. For example, the IN.PACT Falcon DCB, coated with 3 µg/mm^2 of paclitaxel, was evaluated in the BELLO study, which randomized patients to the DCB and provisional bare-metal stenting vs a paclitaxel-eluting stent. The primary endpoint of in-stent (in-balloon) LLL was met (P<.01 for superiority), and the DCB was associated with similar rates of restenosis and revascularization as the paclitaxel-eluting stent.[16] However, similar results were not achieved in the PICCOLETO trial, where the Dior paclitaxel-coated balloon (also 3 µg/mm^2 of paclitaxel; Palex Medical) was randomized to the Taxus DES (Boston Scientific), and the trial stopped early when the superiority of the DES was noted. As such, the primary endpoint of percent diameter stenosis at 6 months was not met, with higher rates of both percent diameter stenosis and angiographic restenosis noted in the Dior balloon group. Regardless of the balloon technology used, optimizing lesion preparation and DCB technique are critical to improving clinical outcomes. Tanaka and colleagues[23] showed how an optimal angiographic result after predilation predicts better clinical outcomes. As a result, in PREVAIL, patients were only enrolled after the operators were able to achieve an optimal angiographic result as recommended by the recently published International DCB Consensus.[24] Angiographic outcomes also compared favorably to those from other DCBs, such as the SeQuent Please DCB, which was recently evaluated in the AGENT ISR randomized trial.[25] The 6-month in-stent LLL in that study was 0.39 ± 0.54 mm, compared with 0.12 ± 0.45 mm in this study for ISR patients.

The Prevail DCB, which received CE mark approval in July 2020, leverages technology from the IN.PACT Falcon catheter, SC Euphora Balloon, and FreePac drug coating (all from Medtronic) and incorporates the same key design features of the Euphora platform, including the hydrophilic coating. Prevail DCB incorporates improvements over the first-generation IN.PACT Falcon DCB but is expected to deliver similar clinical performance (ie, no change in clinical effect and intended purpose). Prevail DCB shares the same proven FreePac coating with IN.PACT Falcon DCB, but differs in the delivery system (PowerTrac technology), coating process, target drug dose on the balloon, and size matrix (33 sizes available). The hydrophilic coating is applied to the distal section of the balloon, between the proximal balloon bond and the rapid exchange joint, to allow for optimized application of the FreePac drug coating. The same FreePac drug formulation is used in all IN.PACT DCBs, with the dose density differing. For the Prevail DCB, a target paclitaxel dose density of 3.5 µg/mm^2 is applied, compared with 3.0 µg/mm^2 used on the IN.PACT Falcon. The angiographic and clinical outcomes reported here for the Prevail DCB are comparable to those reported in the BELLO study from IN.PACT Falcon (for *de novo* small-vessel disease)[16] and a separate study for ISR lesions.[26]

Despite the inherent limitations when comparing outcomes across studies, the outcomes of the PREVAIL study compare favorably with what has been reported and support the conclusion that the Prevail DCB is safe and effective for the treatment of coronary artery disease, including cases that are associated with lesions that can be challenging to treat, such as ISR and small-vessel disease. As a premarket study with a small sample size and no comparator group, further investigation is needed to support these findings.

Study limitations. Limitations include those typical of a premarket study, including small sample size and a single-arm design without a comparator group. The findings of the present study therefore cannot be directly compared with other coronary DCBs in the absence of a head-to-head comparison.

Conclusion

In a prospective, multicenter, single-arm study of patients with symptomatic ischemic heart disease, treatment of coronary *de novo* or ISR lesions with the paclitaxel-coated Prevail DCB was associated with favorable LLL at 6 months and low rates of safety events and revascularization at 12 months. While further investigation is required, results of this premarket study suggest that the Prevail paclitaxel DCB is a safe and effective option for the treatment of coronary *de novo* and ISR lesions.

Acknowledgments. The authors thank the patients involved with the study for their participation. Jessica Dries-Devlin, PhD, CMPP, of Medtronic, and Zachary Harrelson, PhD, provided medical writing support in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

References

1. Basavarajaiah S, Latib A, Shannon J, et al. Drug-eluting balloon in the treatment of in-stent restenosis and diffuse coronary artery disease: real-world experience from our registry. *J Interv Cardiol.* 2014;27:348-355.
2. Hehrlein C, Dietz U, Kubica J, et al. Twelve-month results of a paclitaxel releasing balloon in patients presenting with in-stent restenosis first-in-man (PEPPER) trial. *Cardiovasc Revasc Med.* 2012;13:260-264.
3. Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 2010;99:165-174.
4. Unverdorben M, Kleber FX, Heuer H, et al. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter in the PEPCAD I study: are lesions clinically stable from 12 to 36 months? *EuroIntervention.* 2013;9:620-628.
5. Widder JD, Cortese B, Levesque S, et al. Coronary artery treatment with a urea-based paclitaxel-coated balloon: the European-wide FALCON all-comers DCB registry (FALCON registry). *EuroIntervention.* 2019;15:e382-e388.

6. Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuent Please world wide registry: clinical results of SeQuent Please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol.* 2012;60:1733-1738.
7. Baan J Jr, Claessen BE, Dijk KB, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. *JACC Cardiovasc Interv*. 2018;11:275-283.
8. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet*. 2013;381:461-467.
9. Jensen CJ, Richardt G, Tölg R, et al. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BIOLUX randomised controlled trial. *EuroIntervention*. 2018;14:1096-1103.
10. Pleva L, Kukla P, Kusnierova P, Zapletalova J, Hlinomaz O. Comparison of the efficacy of paclitaxel-eluting balloon catheters and everolimus-eluting stents in the treatment of coronary in-stent restenosis: the treatment of in-stent restenosis study. *Circ Cardiovasc Interv.* 2016;9:e003316.
11. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol.* 2012;59:1377-1382.
12. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119:2986-2994.
13. Wong YTA, Kang DY, Lee JB, et al. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: a randomized RESTORE trial. *Am Heart J.* 2018;197:35-42.
14. Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv.* 2014;7:204-211.
15. Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392:849-856.
16. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (balloon elution and late loss optimization) study. *J Am Coll Cardiol.* 2012;60:2473-2480.
17. Tang Y, Qiao S, Su X, et al. Drug-coated balloon versus drug-eluting stent for small-vessel disease: the RESTORE SVD China randomized trial. *JACC Cardiovasc Interv.* 2018;11:2381-2392.
18. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-2351.
19. Toelg R, Merkely B, Erglis A, et al. Coronary artery treatment with paclitaxel-coated balloon using a BTHC excipient: clinical results of the international real-world DELUX registry. *EuroIntervention.* 2014;10:591-599.
20. Uhlemann M, Möbius-Winkler S, Adam J, et al. The Leipzig prospective drug-eluting balloon-registry — outcome of 484 consecutive patients treated for coronary in-stent restenosis and *de novo* lesions using paclitaxel-coated balloons. *Circ J*. 2016;80:379-386.
21. Scheller B, Vukadinovic D, Jeger R, et al. Survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol.* 2020;75:1017-1028.
22. Nordanstig J, James S, Andersson M, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med.* 2020;383:2538-2546.
23. Tanaka A, Latib A, Jabbour RJ, et al. Impact of angiographic result after predilatation on outcome after drug-coated balloon treatment of in-stent coronary restenosis. *Am J Cardiol.* 2016;118:1460-1465.
24. Jeger RV, Eccleshall S, Wan Ahmad WA, et al. Drug-coated balloons for coronary artery disease: third report of the International DCB Consensus Group. *JACC Cardiovasc Interv.* 2020;13:1391-1402. Epub 2020 May 27.
25. Hamm CW, Dorr O, Woehrle J, et al. A multicentre, randomised controlled clinical study of drug-coated balloons for the treatment of coronary in-stent restenosis. *EuroIntervention.* 2020;16:e328-e334.
26. Basavarajaiah S, Naganuma T, Latib A, et al. Treatment of drug-eluting stent restenosis: comparison between drug-eluting balloon versus second-generation drug-eluting stents from a retrospective observational study. *Catheter Cardiovasc Interv.* 2016;88:522-528.

From the [1]Ospedale San Raffaele – Milano, Milano, Italy; [2]Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, New York, New York; [3]St. Antonius Ziekenhuis, Nieuwegein, the Netherlands and HartCentrum, Ziekenhuis Netwerk Antwerpen (ZNA) Middelheim, Antwerp, Belgium; [4]Ziekenhuis Oost Limburg – Campus Sint-Jan, Genk, Belgium; [5]Onze Lieve Vrouwe Gasthuis – Locatie Oosterpark, Amsterdam, the Netherlands; [6]University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology, CHU SartTilman, Liège, Belgium, and Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, and Anthea Hospital, Bari, Italy; [7]Queen Mary Hospital, University of Hong Kong, Hong Kong; [8]HagaZiekenhuis, Den Haag, the Netherlands; [9]Isala Hartcentrum, Zwolle, the Netherlands; [10]University Medical Center Utrecht, Utrecht, the Netherlands; [11]Medtronic PLC, Santa Rosa, California; and [12]IRCCS Policlinico San Donato, San Donato, Italy.

Funding: This study was supported by Medtronic.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Latib reports honoraria/consultation fees from Abbott, Edwards Lifesciences, CorFlow, ICS, Medtronic, Nuvera, Philips, Supira Medical, NeoChord, and Venus Medtech. Dr Kedhi is a consultant for Medtronic and Abbott. C. Shen and Dr Wetzels are full-time employees and shareholders of Medtronic. Dr Testa reports consultant fees, advisory board, medical proctor, and speaker's fee honoraria from Abbott, Medtronic, Boston Scientific, Meril Life Sciences, and Concept Medical. The remaining authors report no conflicts of interest regarding the content herein.

Manuscript accepted April 28, 2021.

Address for correspondence: Azeem Latib, MD, Montefiore-Einstein Center for Heart and Vascular Care, 111 East 210th Street, Bronx, NY 10467. Email: alatib@gmail.com

Supplemental Materials

APPENDIX 1. Index procedure and study definitions.

Index Procedure:

Vascular access was obtained, and anticoagulation administered according to investigator standard of care. Predilation with a non-drug coated standard semicomplaint balloon was required. For *de novo* lesions, the balloon was required to be the same length as the lesion; for in-stent restenosis (ISR) lesions, the balloon was to be shorter than the previously placed stent. Two rounds of predilation were required. Angiography was performed before and after predilation. Successful predilation of the target lesion(s) was required to confirm eligibility for the study, with success defined as no major flow-limiting dissections (grade C or higher) and <30% residual stenosis of the target lesion by visual estimate on angiography. In cases of unsuccessful predilation of the target lesion(s), the patient was considered a screen failure and was treated as per standard of care.

Subjects who had successful predilation of the target lesion(s) were treated with the Prevail drug-coated balloon (DCB), a percutaneous transluminal coronary angioplasty (PTCA) balloon catheter coated with 3.5 µg/mm^2 paclitaxel and the excipient urea. For each target lesion, DCB size was selected based on a length that could extend ≥2.5 mm beyond the proximal and distal edges of the predilated area, and a balloon:artery diameter ratio of 0.8:1.0 for *de novo* lesions and 1.0:1.0 for ISR. After inflation, DCBs were held at nominal pressure for 30-60 seconds, with a recommendation to maintain the longest possible balloon inflation time without exceeding 60 seconds. Multiple lesions were permitted for treatment. If 2 lesions were present in the same target vessel and could be treated by a single DCB, this was considered a single target lesion. If 2 lesions were present in separate target vessels, and each were planned for DCB treatment, the first lesion must have been treated successfully and the subject determined to be clinically stable before treatment of the second lesion. If 2 lesions were present in separate target vessels, and only 1 was planned for DCB treatment, the lesion planned for DCB was to be treated second.

Adjunctive therapies were avoided if possible. In cases of suboptimal procedure result (>50% residual stenosis, perforation, recoil, or flow-limiting dissection), prolonged balloon inflation could be attempted. Bailout stenting was permitted for cases of major dissection (grade C or higher) or occlusive complication (as evidenced by decreased target-vessel flow, chest pain, or ischemic electrocardiographic (ECG) changes that did not respond to standard rescue techniques). Treatment with other adjunctive procedures was not permitted, including but not limited to cutting/scoring balloons, atherectomy, laser, or thrombectomy.

Patients were prescribed a minimum of 75 mg aspirin within 24 hours prior to the procedure, and a loading dose of antiplatelet therapy within 24 hours prior to the procedure or immediately post procedure. No loading dose was required if the subject had taken at least 3 maintenance doses within 72 hours prior to the procedure. After the procedure, patients were prescribed dual-antiplatelet therapy for a minimum of 4 weeks, with continuation on at least 75 mg aspirin indefinitely. Heparin was used during the procedure for anticoagulation and after the procedure as needed.

Definition of Myocardial Infarction:

Definition of Q-wave myocardial infarction (QWMI) required 1 of the following criteria:

• Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q-waves in 2 or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the circulating endothelial cell (CEC) count, in the absence of timely cardiac enzyme data.

• New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data, the CEC may adjudicate Q-wave MI based on the scenario and appropriate cardiac enzyme data.

Definition of non-Q wave myocardial infarction (NQWMI):

• Elevated creatine kinase (CK) ≥2x the laboratory upper limit of normal with the presence of an elevated CK-MB (any amount above the laboratory upper limit of normal) in the absence of new pathological Q-waves.

Index Procedure by Clinical Presentation

I. PCI (PERCUTANEOUS CORONARY INTERVENTION)

Ia. Baseline biomarkers of myocardial damage (CK and CK-MB and troponin <1x URL) and non-acute MI in progress.
PERIPROCEDURAL <48 HOURS POST PCI
A. New pathologic Q-waves in ≥2 contiguous ECG leads AND:
• any CK-MB > 1x URL or
• in the absence of CK-MB: Troponin >1x URL or
• in the absence of CK-MB and Troponin: CK >1x URL or
• in the absence of CK-MB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data (respecting top-down hierarchy, b1 to b3):
b1. CK ≥2x URL confirmed by:
• CK-MB >1x URL or
• in the absence of CK-MB, Troponin >1x URL or
• in the absence of CK-MB and Troponin: CEC decision upon clinical scenario or
b2. in the absence of CK: CK-MB >3x URL or
b3. in the absence of CK and CK-MB: Troponin >3x URL
Note: URL = upper reference limit, defined as 99th percentile of normal

(Continued)

APPENDIX 1. Index procedure and study definitions. *(continued)*

Ib. If baseline biomarkers of myocardial damage: CK and/or CK-MB >1x URL or acute MI in progress
MYOCARDIAL INFARCTION, REINFARCTION (EXTENSION) <48 HOURS POST PCI
A. If CK (or CK-MB) from index MI has not yet reached its maximum level:
• Recurrent thoracic chest pain or ischemia equivalent >20 minutes (or new ECG changes consistent with MI) AND
• Appropriate cardiac enzyme data:
- A rise in CK within 24 hours of the index event >2x URL (confirmed by either CK-MB or Troponin >1x URL) and >50% above the previous level or
-In absence of CK: a (post-PCI) rise in CK-MB within 24 hours of the index event >3x URL and >50% above the previous level or
-In absence of CK and CK-MB: a (post PCI) rise of Troponin within 24 hours of the index event >3x URL and >50% above the previous level
B. If elevated CK (or CK-MB) following the index MI has peaked AND CK level has returned < URL then any new rise in:
• CK >2x URL (confirmed by either CK-MB > URL or Troponin >URL) or
• In the absence of CK: CK-MB >3x URL or
• In the absence of CK and CK-MB, Troponin >3x URL
C. If CK (or CK-MB) following the index MI has peaked AND CK level has NOT returned to < URL:
• A rise in CK >50% above the previous level and >2x URL confirmed by either CK-MB > URL or Troponin > URL or
• In absence of CK, when CK-MB has NOT returned < URL, a rise in CK-MB >50% above the previous level and >3x URL or
• In absence of CK, when CK-MB and Troponin has not returned < URL a rise in Troponin > 50% above the previous level and >3x URL
SPONTANEOUS MI >48 HOURS (PCI)
A. Recurrent thoracic chest pain or ischemic equivalent AND
• New pathologic Q-waves in ≥2 contiguous ECG leads AND any CK-MB >1x URL or
• In the absence of CK-MB: Troponin >1x URL or
• In the absence of CK-MB and Troponin: CK >1x URL or
• In the absence of CK-MB and Troponin and CK: CEC, decision based upon clinical scenario
B. Appropriate cardiac enzyme data (respecting top-down hierarchy):
b1. CK ≥2x URL confirmed by:
• CK-MB >1x URL or
• In the absence of CK-MB: Troponin >1x URL or
• In the absence of CK-MB and Troponin: CEC decision based upon clinical scenario or
b2. In the absence of CK: CK-MB >3x URL or
b3. In the absence of CK and CK-MB: Troponin >3x URL or
b4. In the absence of CK, CK-MB, and Troponin, clinical decision based upon clinical scenario
IIa. Baseline biomarkers of myocardial damage (CK and CK-MB and Troponin <1x URL) and non-acute MI in progress.
PERIPROCEDURAL <72 HOURS POST CABG
A. New pathologic Q-waves in ≥2 contiguous ECG leads or recurrent signs or symptoms consistent with myocardial ischemia AND
• CK-MB >5x URL or
• In the absence of CK-MB: Troponin >5x URL or
• In the absence of CK-MB and Troponin: CK >5x URL or
• in the absence of CK-MB and Troponin and CK: CEC decision based upon clinical scenario
B. Appropriate cardiac enzyme data
• CK-MB ≥10x URL or
• In the absence of CK-MB: Troponin >10x URL or
• In the absence of CK-MB and Troponin: CK >10x URL
IIb. If baseline biomarkers of myocardial damage: CK and/or CK-MB >1x URL or acute MI in progress:
MYOCARDIAL INFARCTION, REINFARCTION (EXTENSION) <72 HOURS POST CABG
A. If Peak CK (or CK-MB) from index MI has not yet reached its maximum level:
• Signs or symptoms consistent with recurrent myocardial ischemia AND
• Appropriate cardiac enzyme data:
-A rise in CK-MB within 24 hours of the index event >10x URL and URL ≥50% above the previous level
-In absence of CK-MB: a rise in Troponin within 24 hours of the index event >10x URL and ≥50% above the previous level
-In absence of CK-MB and Troponin: a rise in CK within 24 hours of the index event >10x URL and ≥50% above the previous level
B. If elevated CK (or CK-MB) following the index MI has peaked AND CK-MB level has returned < URL, any new rise in:
• CK-MB >10x URL or
• In the absence of CK-MB: Troponin >10x URL or
• In the absence of CK-MB and Troponin: CK >10x URL
C. If elevated CK (or CK-MB) following the index MI has peaked AND CK-MB level has NOT returned < URL:
• A rise in CK-MB ≥50% above the previous level and >10x URL or
• In absence of CK-MB: a rise in Troponin ≥50% above the previous level and >10x URL or
• In absence of CK-MB and Troponin: a rise in CK ≥50% above the previous level and >10x URL

Supplemental Table S1. Inclusion/exclusion criteria.

Inclusion Criteria	**Subject must meet all of the following criteria to be eligible for participation in the study:** 1. Subject age is ≥18 years or minimum legal age as required by local regulations, and ≤85 years. 2. Female subjects of childbearing potential have a negative pregnancy test ≤7 days before the procedure and are willing to use a reliable method of birth control for the duration of study participation. Subjects will be exempted from this requirement in case they are sterile, infertile, or have been post menopausal for at least 12 months (non menses). 3. Subject with documented stable or unstable angina, and/or clinical evidence of ischemia. 4. Subject is an acceptable candidate for treatment with a drug-coated coronary balloon in accordance with the applicable guidelines on percutaneous coronary interventions, manufacturer's Instructions for Use and the Declaration of Helsinki. 5. Successful predilation of the (entire) target lesion(s) that will be treated with the investigational device. Success being documented by angiographic visual estimate of <30% residual stenosis of the target lesion and no major (> grade B) flow-limiting dissection. 6. Subject has a life expectancy >1 year in the investigator's opinion. 7. Subject is willing and able to cooperate with study procedures and required follow-up evaluations. 8. Subject has been informed of the nature of the study and agrees to its provisions and has provided an ethics committee (EC) approved written informed consent.
Angiographic Inclusion Criteria	**After the patient is enrolled in the study, additional evaluation is required to determine angiographic eligibility. In addition to the above general inclusion criteria, patients and each target lesion/vessel must meet all of the following angiographic inclusion criteria for the patient to be considered to be eligible for participation in the study:** **Angiographic Inclusion** 1. The patient requires treatment of either: A. At least a single lesion* amenable to treatment with the Medtronic coronary drug-coated balloon (*if 2 lesions can be treated by one DCB covering both lesions, it will be considered as a single target lesion). OR B. A maximum of 4 lesions in a maximum of 3 vessels. In case 3 vessels require to be treated, at least 1 should receive a non-DCB treatment, ie, treatment with a drug-eluting stent (DES); this will be called a non-target lesion. Lesions (maximum 3) treated with the DCB are considered target lesions. Note: For subjects with a planned treatment of 2 to 4 lesions, the first lesion must be treated successfully and the subject must be clinically stable before treatment of the following 1 to 3 lesions are attempted. The lesion(s) in each vessel that is/are planned to be treated with the DES should be treated first. 2. Target lesion(s) must be ≤25 mm in length. 3. Target lesion(s) must have a stenosis of ≥50% and <100%. 4. Target lesion(s) to be treated with the investigational device must have an reference vessel diameter between 2.0 and 4.0 mm in diameter. 5. Target vessel(s) must have a Thrombolysis in Myocardial Infarction (TIMI) flow ≥2. **Note: Measurements may be made by careful visual estimate, online quantitative coronary angiography (QCA), intravascular ultrasound (IVUS), or optical coherence tomography (OCT).**
Exclusion Criteria	**Patients will be excluded from the clinical study if any of the following criteria are met:** 1. Known hypersensitivity or contraindication to aspirin; heparin; bivalirudin; clopidogrel; prasugrel; ticagelor and structurally related compounds; or a sensitivity to contrast media that cannot be adequately premedicated. 2. History of an allergic reaction or significant sensitivity to paclitaxel or any other analogue or derivative. 3. Platelet count <100,000 cells/mm^3 (ie, 100 x 10^9/L) or >700,000 cells/mm^3 (ie, 700 x 10^9/L), or a white blood cell (WBC) count <3000 cells/mm^3 within 7 days prior to index procedure. 4. Serum creatinine level >2.5 mg/dL (ie, 221 µmol/L) within 7 days prior to index procedure. 5. Evidence of an acute MI within 72 hours of the study procedure: A. Q-wave myocardial infarction (QWMI); OR B. Elevated cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following: i. Symptoms of ischemia. ii. New or presumed significant ST-segment T-wave changes or new left bundle-branch block (LBBB).

(Continued)

SUPPLEMENTAL TABLE S1. Inclusion/exclusion criteria. ***(continued)***

Exclusion Criteria	**Patients will be excluded from the clinical study if any of the following criteria are met:** iii. Development of pathological Q-waves in the ECG. iv. Imaging evidence of new loss of viable myocardium or new regional wall. **Note: Patients with evidence or suspicion of an acute MI (per investigator or sub-investigator determination) must have normal cardiac enzyme results documented by the investigator prior to enrollment.** 6. Planned treatment of the left main coronary artery, internal mammary artery, aorto-ostial, and sapheneous vein grafts with the investigational device. 7. Planned treatment of more than 1 lesion in 1 target vessel, or more than 2 lesions in 2 target vessels. 8. Planned treatment involves a bifurcation 9. Previous percutaneous coronary intervention (PCI) of the target vessel(s) - Within 3 months prior to the procedure for in-stent restenosis. - Within 9 months prior to the procedure for *de novo* lesions. 10. Planned PCI of any vessel within 30 days post index procedure and/or planned PCI of the target vessel within 6 months post procedure. **11. During the index procedure, the target lesion(s) require(s) treatment with a cutting/scoring balloon, atherectomy, laser, or thrombectomy procedure.** **12. History of a stroke or transient ischemic attack (TIA) within the prior 6 months (any prior stroke or TIA, if prasugrel is used).** **13. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months.** **14. History of bleeding diathesis or coagulopathy or will refuse blood transfusions.** **15. Any previous treatment of the target vessel for restenosis, including brachytherapy.** **16. Pregnant or breastfeeding woman.** **17. Documented left ventricular ejection fraction (LVEF) <30% at the most recent evaluation, within 3 months.** **18. Any condition increasing the likelihood that the patient will not be able to adhere to all the follow-up procedures, including compliance with the required study antiplatelet regimen and follow-up angiography and imaging.** **19. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints; or requires coronary angiography, intravascular ultrasound, or other coronary artery imaging procedures.** **Note: Studies requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.** **After the patient is consented for the study, additional evaluation is required to determine angiographic eligibility. In addition to the above general exclusion criteria, patients will be excluded from the study if any of the following angiographic exclusion criteria are met:**
Angiographic Exclusion Criteria	**1. Target lesion(s) is/are located in a bypass graft (including but not limited to saphenous vein graft or a left/right internal mammary artery.** **Note: A target lesion distal to a graft may be accessed through the graft unless the graft has more than 40% diameter stenosis anywhere within the graft.** **2. Target vessel(s) has/have other lesions with >40% diameter stenosis based on visual estimate or online QCA.** **3. Target vessel(s) has/have evidence of thrombus.** **4. Target vessel(s) is/are excessively tortuous (any bend >90° to reach the target lesion).** **5. Target lesion(s) has/have any of the following characteristics:** **a. Lesion location is aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX)** **b. Involves a side branch >2.0 mm in diameter** **c. Is at a >45° bend in the vessel** **d. Is severely calcified** **6. Unprotected left main coronary artery disease is present (an obstruction >50% in the left main coronary artery).**

(Continued)

SUPPLEMENTAL TABLE S1. Inclusion/exclusion criteria. *(continued)*

Angiographic Exclusion Criteria	7. Lesion that is planned to be treated is longer than 25 mm in length or RVD is smaller than 2 mm. A maximum of 4 lesions can be treated during the index procedure (with a maximum of 3 target vessels). Two lesions in 1 vessel can be included only if 1 lesion is treated with DES and the second with the DCB. It is not allowed to treat 2 lesions with a DCB in 1 vessel. A maximum of 2 vessels with 2 lesions is allowed. For subjects with planned treatment of 2 or more lesions, the first lesion must be treated successfully and the subject must be clinically stable before treatment of the next lesion is attempted. Successful treatment of the first lesion is defined as: • <10% residual diameter stenosis result is achieved (visual assessment); • TIMI 3 flow is present post treatment; and • No evidence of dissection (NHLBI type C, D, E or F), thrombus or distal embolization at the first study lesion site post treatment. Prior to attempted treatment of the next study lesion, subjects must be clinically stable without angina or ECG changes consistent with coronary ischemia. If the subject is not clinically stable, or shows signs or symptoms of possible coronary ischemia following treatment of the previous study lesion, treatment of the next lesion should be deferred, if possible. In case only 1 out of a maximum of 4 lesions will be treated with the investigational device, the lesion that is planned to be treated with the investigational device should be treated last. Any other lesion in the target vessel(s) can only be treated after 6 months post procedure. Any lesions in other (non-target) vessels can be treated after 30 days post procedure with any approved PCI treatment.

SUPPLEMENTAL TABLE S2. Clinical outcomes at 12 months, by lesion type.

Outcome	*De Novo* Lesions Subjects (n = 22)	In-Stent Restenosis Lesions Subjects (n = 28)
All deaths	0/22 (0.0%)	0/28 (0.0%)
Myocardial infarction	0/22 (0.0%)	0/28 (0.0%)
Major adverse cardiac event[a]	1/50 (4.5%)	2/28 (7.1%)
Target-vessel failure[b]	2/22 (9.1%)	3/28 (10.7%)
Target-lesion failure[c]	1/22 (4.5%)	2/28 (7.1%)
Clinically driven target-lesion revascularization[d]	1/22 (4.5%)	2/28 (7.1%)
Clinically driven target-vessel revascularization	2/22 (9.1%)	3/28 (10.7%)
Stent thrombosis	0/22 (0.0%)	0/28 (0.0%)

Data presented as mean ± standard deviation or n/total (%).
Subjects with *de novo* lesions or in-stent restenosis could have also had small-vessel disease.
[a]Defined as a composite of death, myocardial infarction (Q-wave and non-Q wave), emergent coronary artery bypass graft surgery, or repeat clinically driven target-lesion revascularization by percutaneous or surgical methods.
[b]Defined as cardiac death, target-vessel myocardial infarction, or clinically driven target-vessel revascularization by percutaneous or surgical methods.
[c]Defined as cardiac death, target-vessel myocardial infarction, or clinically driven target-lesion revascularization by percutaneous or surgical methods.
[d]All treated with percutaneous coronary intervention.