EuroIntervention 2019;15:e382-e388 published online July 2018 published online e-edition July 2019

Coronary artery treatment with a urea-based paclitaxel-coated balloon: the European-wide FALCON all-comers DCB Registry (FALCON Registry)

Julian D. Widder[1]*, MD; Bernardo Cortese[2], MD; Sebastien Levesque[3], MD; Dominik Berliner[1], MD; Simon Eccleshall[4], MD; Kristof Graf[5], MD; Luc Doutrelant[6], MD; Javed Ahmed[7], MD; Erwan Bressollette[8], MD; Dennis Zavalloni[9], MD; Davide Piraino[10], MD; Ariel Roguin[11], MD, PhD; Bruno Scheller[12], MD; Pieter Stella[13], MD; Johann Bauersachs[1], MD; on behalf of the FALCON Investigators

1. Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; 2. Department of Cardiology, ASST Fatebenefratelli-Sacco, Milan, Italy; 3. Department of Cardiology, CHU Poitiers, Poitiers, France; 4. Department of Cardiology, Norfolk and Norwich University Hospital, Norwich, United Kingdom; 5. Department of Cardiology, Jüdisches Krankenhaus Berlin, Berlin, Germany; 6. Department of Cardiology, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France; 7. Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, United Kingdom; 8. Department of Cardiology, Nouvelles Cliniques Nantaises, Nantes, France; 9. Department of Cardiology, Istituto Clinico Humanitas, Rozzano, Italy; 10. Interventional Cardiology, "P. Giaccone" University Hospital of Palermo, Palermo, Italy; 11. Interventional Cardiology, Rambam Medical Center, Haifa, Israel; 12. Clinical and Experimental Interventional Cardiology, University of Saarland, Homburg/Saar, Germany; 13. Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00261

KEYWORDS

- bare metal stent
- drug-coated balloon
- drug-eluting stent
- in-stent restenosis

Abstract

Aims: The aim of this study was to investigate the use of a drug-coated balloon (DCB) in daily clinical practice and provide further evidence on the safety and efficacy of paclitaxel-coated balloon treatment using urea as an inert excipient.

Methods and results: Between December 2013 and December 2015, 757 patients treated for coronary lesions with the IN.PACT Falcon balloon were enrolled in this prospective real-world all-comers registry. The primary outcome was the clinically driven target lesion revascularisation (TLR) rate at 12 months. The secondary outcome was major adverse cardiac events (MACE) defined as cardiac death, myocardial infarction, TLR and target vessel revascularisation (TVR). Out of 805 lesions, 43.1% were *de novo*, and 53.2% drug-eluting stent (DES) or bare metal stent (BMS) in-stent restenosis (ISR). TLR at 12 months was 6.2% and TVR 8.3%. MACE occurred in 9.7% of patients with a composite of cardiac death in 0.8% and myocardial infarction in 2.7% plus TLR/TVR. Subgroup analysis confirmed a TLR rate of 7.5% for ISR (2.1% BMS and 9.5% DES) and 4.9% for *de novo* lesions.

Conclusions: The IN.PACT Falcon urea-based paclitaxel-coated balloon is safe and efficient in *de novo* and ISR lesions with low rates of TLR/TVR. The high proportion of treatment of *de novo* lesions indicates that a DCB-only strategy is nowadays common.

**Corresponding author: Klinik für Kardiologie und Angiologie, Medizinische Hochschule Hannover, Carl-Neuberg-Straße 1, D-30625 Hannover, Germany. E-mail: widder.julian@mh-hannover.de*

SUBMITTED ON 11/03/2018 - REVISION RECEIVED ON 19/06/2018 - ACCEPTED ON 06/07/2018

DOI: 10.4244/EIJ-D-18-00261

Abbreviations

BMS bare metal stent
DCB drug-coated balloon
DES drug-eluting stent
ISR in-stent restenosis
MACE major adverse cardiac events
TLR target lesion revascularisation
TVR target vessel revascularisation

Introduction

Percutaneous coronary interventional revascularisation has improved markedly since the first balloon angioplasty revolutionised coronary revascularisation[1]. Elastic recoil with abrupt vessel closure, subintimal dissection, recoil and restenosis caused by cellular proliferation are major drawbacks of plain angioplasty. The use of intracoronary stents solved the problem of dissection and recoil, though the clinical outcome with bare metal stents (BMS) was limited by neointimal hyperplasia, leading to in-stent restenosis (ISR). The development of drug-eluting stents (DES) significantly attenuated the need for repeat revascularisation, although complex coronary territories such as bifurcations, small vessels, long lesions, saphenous vein grafts and diabetic disease have worse outcomes with DES than simpler lesions. Even with modern DES, late stent thrombosis and continued risk of restenosis remain a severe problem in selected patients[2]. Bioresorbable vascular scaffolds were designed to provide transient support against dissection and acute recoil with the capability of preventing neointimal proliferation by eluting immunosuppressive drugs. However, there are still major problems to overcome with this new technology, especially in the treatment of smaller vessels, and late scaffold thrombosis is of concern[3]. Drug-coated balloons (DCB) represent a potential alternative therapeutic option for ISR treatment and *de novo* stenosis, especially in small vessels or side branches in complex bifurcation stenoses, without implanting a permanent foreign object into the vessel lumen. The mitotic inhibitor paclitaxel was identified as the primary drug for DCB due to its rapid uptake and prolonged retention. According to European clinical practice guidelines, DCB therapy is recommended for the treatment of ISR[4]. This recommendation is based on preclinical and randomised clinical trials which demonstrated the safety and efficacy of DCB technology for patients with ISR with iopromide excipient-based paclitaxel-coated balloons[5-10]. However, no recommendation was given for the use of DCB in broader indications, e.g., in *de novo* lesions in small vessels, side branches in bifurcation stenosis and the increasing use for complex coronary territories or when stent implantation is not an option, as only limited data are available.

While DCB therapy with the urea-based paclitaxel-coated balloon IN.PACT™ Falcon (Medtronic, Minneapolis, MN, USA) for small vessels was superior in terms of late lumen loss and MACE as compared to treatment with the TAXUS™ DES (Boston Scientific, Marlborough, MA, USA)[11], data for real-life situations in which the urea-based paclitaxel-coated balloon IN.PACT Falcon is used are only limited[12]. We therefore conducted the FALCON all-comers DCB Registry to provide further evidence for the safety and efficacy of paclitaxel-coated balloon treatment using urea as an inert excipient and to gain insight into the use of DCB therapy in daily clinical practice in a real-world setting.

Methods

The FALCON Registry was a European-wide, prospective multicentre, observational clinical registry to assess the safety and efficacy of the urea-based paclitaxel-coated balloon IN.PACT Falcon in a real-world setting. Further, the investigators intended to gain more insight into the indications for which DCB is commonly used nowadays. The study procedures were performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The local ethics committee of the Hannover Medical School (as site of the principal investigators), as well as independent ethics committees at each site as per local regulations, approved the study protocol and the patient data release form. Key inclusion criteria were written informed consent, *de novo* lesions, restenosis or ISR in coronaries with a lumen >2.0 and <4.0 mm. As this was a real-world all-comers registry, sites were encouraged to include all patients treated with an IN.PACT Falcon DCB for coronary lesions in their centre during the recruiting period. Key exclusion criteria were patient incompliance, indication for bypass surgery, coronary lesions not treatable by PCI, cardiogenic shock, life expectancy <1 year.

The primary study endpoint was clinically driven target lesion revascularisation (TLR) at 12 months. Key secondary endpoints were major adverse cardiovascular events (MACE), a composite of cardiac death, myocardial infarction and clinically driven TLR or target vessel revascularisation (TVR) at 12 months. Details are shown in **Supplementary Appendix 1**.

STATISTICAL ANALYSIS

Continuous variables are presented as mean±SD. Discrete variables are expressed as counts and percent. Baseline differences between groups were analysed for significance using the Mann-Whitney U test for continuous data and the chi-squared test (or Fisher's exact test where the expected cell value was less than 5) for categorical variables. SPSS statistical software, Version 24 (IBM Corp., Armonk, NY, USA) was used for all statistical calculations.

Results

Between December 2013 and December 2015, 757 patients with a total of 805 lesions treated for all indicated coronary lesions with the IN.PACT Falcon balloon were enrolled at 26 sites in eight countries in this prospective real-world all-comers registry **(Supplementary Table 1)**. Patients had an overall mean age of 66.2±11.2 years and were predominantly male (78.9%). Five hundred and thirty-five (535) patients (70.5%) had hypercholesterolaemia and 567 (74.9%) hypertension; diabetes mellitus was present in 260 (34.3%) and 394 (52.0%) had a history of smoking. Three hundred and ten (310) patients (40.9%) presented with an acute coronary syndrome, of whom 30 had an ST-elevation

myocardial infarction, 159 non-ST-elevation myocardial infarction and 121 unstable angina. A high proportion of patients (326; 43.1%) was treated for *de novo* lesions by a DCB-only strategy, 405 (53.5%) presented with ISR, 102 (13.5%) with BMS-ISR and 223 (29.5%) with DES-ISR. In 81 patients the stent type treated for ISR was unknown. Twenty-two (22) subjects could not be assigned to one of the lesion groups as either numerous different lesion characteristics were detected or the information was unknown **(Table 1)**.

Most lesions presented in the left anterior descending, followed by the left circumflex and right coronary artery. A small number of lesions in bypass grafts were treated, and 16.5% bifurcation stenoses were present. Bifurcation stenoses were significantly more often found in the *de novo* lesion group than in the ISR group. Mean lesion length was 17.9±10.7 mm and reference vessel diameter 2.8±0.5 mm, which was significantly lower in *de novo* lesions (2.5±0.5 mm); 24.9% of lesions were >2.75 mm, while 75.1% were <2.75 mm **(Figure 1)**. Forty-eight (48) patients (6%) were treated for multiple lesions **(Supplementary Table 2)**.

Predilation was performed in nearly all lesions (98%) with a mean inflation pressure of 14.4±5.1 atm. Mean DCB balloon diameter used was 2.73±0.54 mm with a length of 22.0±6.9 mm. Mean inflation pressure was 10.61±3.56 atm. Predilation balloon diameter, inflation pressure and DCB diameter were significantly lower in *de novo* lesions compared to ISR. Procedural device success was high (optimal result 93.9%, suboptimal 5.3%), and in only six lesions (0.7%) was the DCB treatment classified as not successful. In 26 lesions an additional stent implantation was performed, which was significantly more often carried out in the treatment of *de novo* lesions **(Table 2)**.

Follow-up data were available for 745 (98.9%) of the 757 patients at 12 months. Overall clinical TLR was 6.2% in all patients, with 9.5% in patients with DES-ISR, while, as expected, it was lower at 2.1% in BMS-ISR. In *de novo* lesions TLR was 4.9%. Overall MACE was observed in 9.7% of all patients, while MACE was higher in DES-ISR (12.3%) vs BMS-ISR (8.2%) as well as in *de novo* lesions (8.0%). Cardiac death at 0.3% and

Table 1. General patient characteristics.

	All (n=757)	ISR (n=405)	BMS-ISR (n=102)	DES-ISR (n=223)	*de novo* (n=326)	*p*-value BMS-ISR vs DES-ISR	*p*-value ISR vs *de novo*
Age	66.2±11.2	66.9±10.9	69.3±10.9	65.0±10.7	65.1±11.6	<0.01	<0.05
Male	597 (78.9%)	316 (78.3%)	80 (78.4%)	173 (77.6%)	262 (80.4%)	0.743	0.439
Hypercholesterolaemia	535 (70.7%)	311 (76.8%)	75 (73.5%)	170 (76.2%)	204 (62.6%)	0.566	<0.001
Hypertension	567 (74.9%)	324 (80.0%)	79 (77.5%)	176 (78.9%)	224 (68.7%)	0.731	<0.001
Diabetes	260 (34.3%)	134 (33.1%)	28 (27.5%)	85 (38.1%)	117 (35.9%)	<0.05	0.428
Smoking	394 (52.0%)	208 (51.4%)	48 (47.1%)	116 (52.0%)	174 (53.4%)	0.454	0.587
Renal insufficiency	99 (13.1%)	55 (13.6%)	11 (10.8%)	28 (12.6%)	38 (11.7%)	0.670	0.438
Symptoms							
Stable angina	445 (58.9%)	191 (47.2%)	52 (51.0%)	105 (47.1%)	177 (54.3%)	0.569	<0.05
ACS	**(n=310)**	**(n=174)**	**(n=42)**	**(n=93)**	**(n=122)**	**0.985**	**<0.001**
STEMI	30 (4%)	12 (2.7%)	4 (3.9%)	7 (3.1%)	17 (5.2%)		
NSTEM	159 (21.0%)	75 (18%)	19 (18.6%)	43 (19.3%)	75 (23.0%)		
Unstable angina	121 (16.0%)	87 (21.5%)	19 (18.6%)	43 (19.3%)	30 (9.2%)		

Data presented as mean±standard deviation or n (% of patients). ACS: acute coronary syndrome; BMS-ISR: bare metal stent in-stent restenosis; DES-ISR: drug-eluting stent in-stent restenosis; ISR: in-stent restenosis; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction

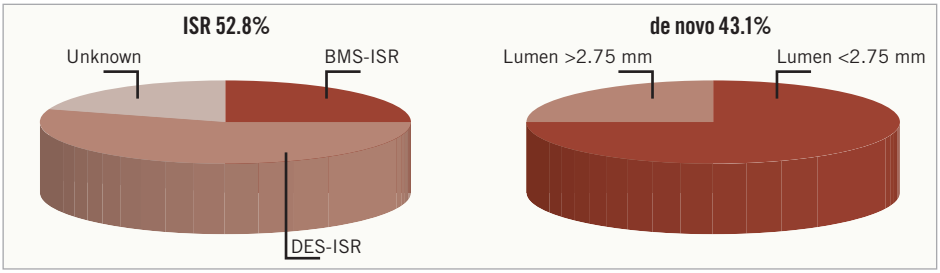

Figure 1. *Indications for drug-coated balloon treatment. In 3.6% indications could not be assigned to one of the groups. BMS: bare metal stent; DES: drug-eluting stent; ISR: in-stent restenosis*

Table 2. Procedural characteristics.

	All (n=805)	ISR (n=428)	BMS-ISR (n=105)	DES-ISR (n=238)	*de novo* (n=346)	*p*-value BMS-ISR vs DES-ISR	*p*-value ISR vs *de novo*
Predilation performed	789 (98.0%)	417 (97.4%)	103 (98.1%)	233 (98.0%)	345 (98.5%)	–	–
Balloon diameter predilation, mm	2.62±0.6	2.86±0.6	2.9±0.5	2.87±0.6	2.31±0.6	0.333	<0.001
Balloon length predilation, mm	16.41±4.67	16.17±4.37	16.85±4.34	16.01±4.57	16.80±5.04	0.57	0.177
Inflation pressure predilation, atm	14.4±5.1	16.5±4.9	16.2±4.5	16.27±5.1	12.1±4.1	0.823	<0.001
Balloon diameter DCB, mm	2.73±0.54	2.95±0.50	3.01±0.47	2.98±0.50	2.46±0.46	0.724	<0.001
Balloon length DCB, mm	22.0±6.9	21.9±6.9	22.7±7.5	21.8±7.0	22.5±7.0	0.311	0.309
Inflation pressure DCB, atm	10.61±3.56	11.93±3.61	11.26±3.67	12.31±3.62	9.08±2.86	<0.05	<0.001
Inflation time, sec	55.3±13.1	55.6±11.5	55.1±12.1	55.8±11.1	55.0±14.7	0.775	0.170
Multiple DCB per lesion	49	27	9	16	19		
Combination with stent	26	8	2	3	17	0.738	<0.05
Device success optimal	756 (93.9%)	409 (95.6%)	103 (98.1%)	224 (94.1%)	323 (92.3%)		
Device success suboptimal	43 (5.3%)	17 (4%)	2 (1.9%)	13 (5.5%)	24 (6.9%)		
Device success no	6 (0.7%)	2 (0.5%)	0 (0%)	1 (0.4%)	3 (0.9%)		

Data presented as mean±standard deviation or n (%). BMS-ISR: bare metal stent in-stent restenosis; DCB: drug-coated balloon; DES-ISR: drug-eluting stent in-stent restenosis; ISR: in-stent restenosis

myocardial infarction at 0.6% were low in patients with *de novo* lesions, and the MACE rate was primarily driven by TLR and TVR (7.4%) **(Figure 2)**.

Discussion

The FALCON Registry reveals several important findings. 1) The IN.PACT Falcon paclitaxel-coated balloon with urea as inert excipient is safe and efficient in a real-world setting. 2) Treatment of ISR with the IN.PACT Falcon shows good clinical results, with TLR/TVR and MACE rates comparable with the outcomes of iopromide-, butyryl trihexyl citrate- or other excipient-based paclitaxel-coated balloon trials. 3) The high rate of successful treatment of *de novo* lesions provides further evidence that the concept of "DCB-only therapy" for *de novo* lesions is nowadays commonly used and provides good results with the urea-based paclitaxel-coated balloon IN.PACT Falcon.

DCB are coated with a layer of antirestenotic drug mixed with an excipient. The mitotic inhibitor paclitaxel was identified as the primary drug for DCB due to its rapid uptake and prolonged retention in the vessel wall; therefore, most commercially available DCB

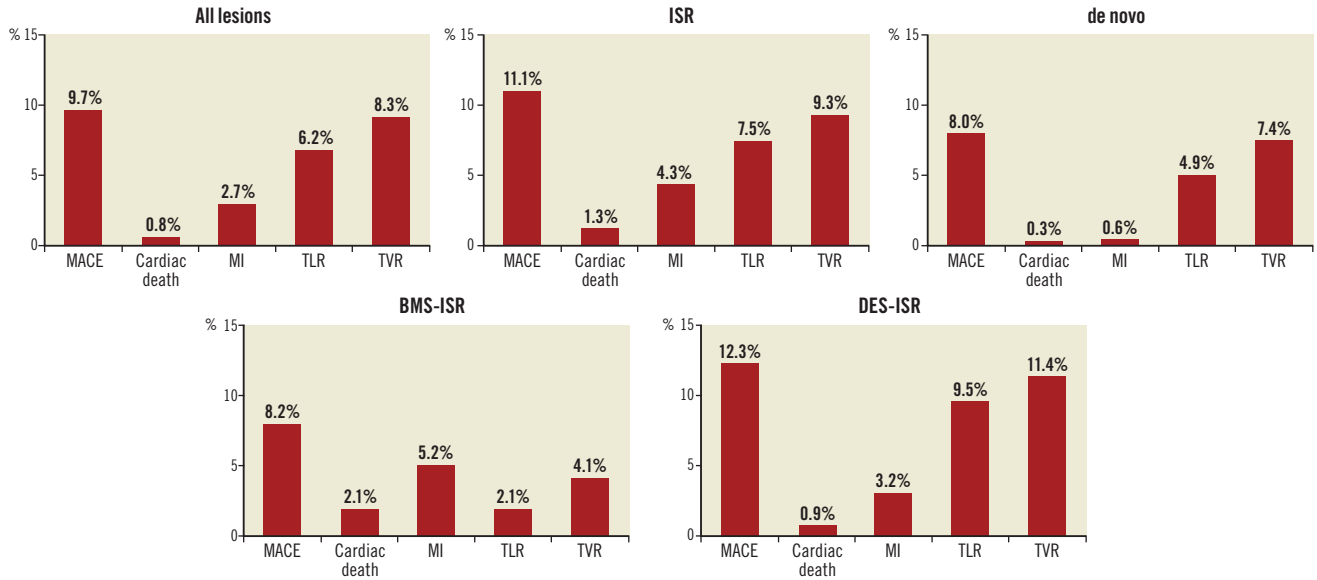

Figure 2. *12-month clinical outcome. Data are shown as % of patients. BMS: bare metal stent; DES: drug-eluting stent; ISR: in-stent restenosis; MACE: major adverse cardiac events; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation*

are coated with paclitaxel. The excipient is needed to facilitate the uptake of the active drug to the vessel wall[13]. Various excipients are used with the contrast agent iopromide, butyryl trihexyl citrate, the film-forming agent shellac or urea. However, evidence exists from preclinical testing that tissue levels of drug following DCB treatment are different among various excipients[14-16]. Therefore, it cannot be presumed that there is a class effect for clinical performance of DCB. The IN.PACT Falcon DCB uses the natural product urea as inert excipient. Urea, due to its hydrophilic nature, dissolves rapidly once hydrated by the blood and water in tissue, facilitating the release of the paclitaxel from the balloon's surface into the vessel wall. The present FALCON Registry proves that the IN.PACT Falcon DCB using urea as excipient provides good clinical 12-month efficacy results with an overall clinical TLR rate at 12 months of 6.2% and is safe with a MACE rate of 9.7% in a real-world setting. Compared to previous registries with other paclitaxel-coated DCB, the FALCON Registry had a different distribution of treated lesion types. While in the SeQuent Please World Wide Registry and the DELUX registry more BMS vs DES-ISR were present[17,18], the ratio of BMS vs DES-ISR shifted to less BMS-ISR (~1/3) and more DES-ISR (~2/3). Furthermore, a higher percentage of patients was treated with a DCB-only strategy for *de novo* lesions in the FALCON Registry. The change of ratio of BMS vs DES-ISR is not surprising given that in recent years more DES have been implanted and, according to the European clinical practice guidelines in 2014, no indication for the use of BMS remains[4]. The first clinical application of DCB was for treatment of BMS-ISR by Scheller et al in the PACCOCATH-ISR trial, demonstrating superiority over plain balloon angioplasty. Other randomised clinical trials and registries comparing DCB vs PES or DCB vs DES followed, confirming the results[5,7,18,19]. The success rate in treatment of ISR might however be dependent on the excipient used, as indicated by data from an optical coherence tomography study which suggested that urea was more efficient than shellac, the coating of the Dior DCB (Eurocor GmbH, Bonn, Germany)[20]. The very low TLR rate at 2.1% in patients treated for BMS-ISR in the present FALCON Registry confirms these initial results seen with the Falcon DCB[11,12]. Treatment of DES-ISR is more challenging, as is known from previous trials[17,18,21-23]. The FALCON Registry with a urea-based paclitaxel-coated balloon shows comparable good results with a TLR rate of 9.5% and a MACE rate of 12.3% **(Supplementary Table 3)**.

Compared with other published all-comers DCB registries, the FALCON Registry has the highest percentage (43.1% of all patients) treated for *de novo* lesions with a DCB-only strategy. Furthermore, over 50% of these lesions were complex (type B2 26.5%, type C 25.3%). However, the procedural success rate with this strategy was good (92.3% optimal result, 6.9% suboptimal and only 0.9% device failure) and safe (MACE 8.0%), with good clinical success after 12 months with a TLR rate of 4.9%. Previous data for treatment of small *de novo* lesions with the IN.PACT Falcon balloon in the randomised BELLO trial showed a low TLR rate of 4.4% and a MACE rate of 10% at six months, though bail-out stenting was carried out in 20%[11]. A significant difference in MACE was reported in favour of DCB therapy in the BELLO trial also after three years[24]. However, the PICCOLETO study with the Dior I paclitaxel-coated balloon showed a higher incidence of MACE in patients who underwent DCB therapy as compared to those who received a first-generation paclitaxel-DES. This divergent result might be due to the lack of excipient used by the first-generation Dior balloon[25]. In the PEPCAD I trial, the procedural success rate with the iopromide-based paclitaxel-coated SeQuent® (B. Braun, Melsungen, Germany) was also high in *de novo* lesions; however, 27% received additional stenting[26]. Numerous observational studies have investigated the DCB-only strategy, mostly for small vessel disease. The rate of additional stenting ranges from 3% to 36%, with evidence that bail-out stenting should be avoided as it seems to have worse outcome[27,28]. In the FALCON Registry, only in 17 cases (4.8%) was a combination with a stent implantation felt to be necessary. This is probably explained by the experience of the centres and the knowledge gained and recommendations for treatment of *de novo* lesions by a DCB-only strategy[29]. The largest registry to date, a prospective "real-world" registry for the use of a "PCB-only" strategy in small vessel *de novo* lesions with the SeQuent Please, had 6% additional stenting and a TLR rate of 3.6% at 9.4±1.7 months[30]. When comparing these previous results, one has to keep in mind that in the FALCON Registry 20.8% of the *de novo* lesions were bifurcation lesions and in 75.1% the lesion had a lumen less than 2.75 mm while in 24.9% the vessel lumen was greater than 2.75 mm, reflecting real-world treatment **(Supplementary Table 4)**.

Study limitations

The FALCON Registry is a clinical registry with clinical follow-up data from office or telephone interviews. No regular angiographic follow-up data after 12 months were obtained and there was no quantitative core laboratory analysis performed on index interventions; therefore, no data on late lumen loss exist. When comparing the outcomes in relation to previous registries and trials, one needs to consider that a possible bias might exist for several reasons. Experience in the use of DCB has increased over recent years, reflected, for example, by the nearly 100% predilation rate in the FALCON Registry influencing the outcome. Further, the characteristics of the cohorts probably vary, as in more recent registries a higher rate of DES-ISR is present and in this group one expects a higher rate of second- or later-generation DES now presenting with ISR.

Conclusions

Treatment with the urea-based IN.PACT Falcon paclitaxel-coated balloon results in good 12-month outcomes in a European-wide all-comers real-world setting. Efficacy and safety are demonstrated by low revascularisation, myocardial infarction and cardiac death rates. The high proportion of successful treatment of *de novo* lesions indicates that the concept of balloon angioplasty with DCB only confirms previous clinical results of this device in small vessels and that using urea as an inert excipient only is nowadays common and safe.

Impact on daily practice

Treatment of *de novo* and ISR coronary lesions with the IN.PACT Falcon urea-based paclitaxel-coated balloon is safe and efficient with low clinical TLR/TVR rates.

Acknowledgements

We would like to thank all other participating centres and all study nurses involved in the FALCON Registry as well as the Hannover Clinical Trial Center for their support.

Funding

This registry was supported by an unrestricted grant from Medtronic to the Hannover Medical School.

Conflict of interest statement

J. Widder is a consultant for Medtronic. S. Eccleshall reports grants and personal fees from B. Braun. A. Roguin is a consultant for Medtronic. B. Scheller is a shareholder of InnoRa GmbH, Berlin, Germany and is named as co-inventor on patent applications by Charite Hospital, Berlin, Germany. J. Bauersachs is a consultant for Medtronic. The other authors have no conflicts of interest to declare.

References

1. Gruentzig A. Results from coronary angioplasty and implications for the future. *Am Heart J.* 1982;103:779-83.

2. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J.* 2015;36:3320-31.

3. Wykrzykowska JJ, Kraak RP, Hofma SH, van der Schaaf RJ, Arkenbout EK, IJsselmuiden AJ, Elias J, van Dongen IM, Tijssen RYG, Koch KT, Baan J Jr, Vis MM, de Winter RJ, Piek JJ, Tijssen JGP, Henriques JPS; AIDA Investigators. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. *N Engl J Med.* 2017;376:2319-28.

4. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

5. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, Böhm M, Speck U. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med.* 2006;355:2113-24.

6. Maier LS, Maack C, Ritter O, Böhm M. Hotline update of clinical trials and registries presented at the German Cardiac Society meeting 2008. (PEPCAD, LokalTax, INH, German ablation registry, German device registry, DES.DE registry, DHR, Reality, SWEETHEART registry, ADMA, GERSHWIN). *Clin Res Cardiol.* 2008;97:356-63.

7. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119:2986-94.

8. Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, Katoh H, Oka N, Fuku Y, Hosogi S, Hirono A, Maruo T, Tanaka H, Shigemoto Y, Hasegawa D, Tasaka H, Kusunose M, Otsuru S, Okamoto Y, Saito N, Tsujimoto Y, Eguchi H, Miyake K, Yoshino M. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv.* 2011;4:149-54.

9. Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Breithardt OA, Schmidt M, Zimmermann S, Lonke S, von Cranach M, Nguyen TV, Daniel WG, Wöhrle J. 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;59:1377-82.

10. Byrne RA, Neumann FJ, Mehilli J, Pinieck S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 investigators. 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;381:461-7.

11. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, Buffoli F, Tamburino C, Varbella F, Menozzi A. 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;60:2473-80.

12. Basavarajaiah S, Latib A, Shannon J, Naganuma T, Sticchi A, Bertoldi L, Costopoulos C, Figini F, Carlino M, Chieffo A, Montorfano M, Colombo A. 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;27:348-55.

13. Byrne RA, Joner M, Alfonso F, Kastrati A. Drug-coated balloon therapy in coronary and peripheral artery disease. *Nat Rev Cardiol.* 2014;11:13-23.

14. Joner M, Byrne RA, Lapointe JM, Radke PW, Bayer G, Steigerwald K, Wittchow E. Comparative assessment of drug-eluting balloons in an advanced porcine model of coronary restenosis. *Thromb Haemost.* 2011;105:864-72.

15. Kelsch B, Scheller B, Biedermann M, Clever YP, Schaffner S, Mahnkopf D, Speck U, Cremers B. Dose response to Paclitaxel-coated balloon catheters in the porcine coronary overstretch and stent implantation model. *Invest Radiol.* 2011;46:255-63.

16. Radke PW, Joner M, Joost A, Byrne RA, Hartwig S, Bayer G, Steigerwald K, Wittchow E. Vascular effects of paclitaxel following drug-eluting balloon angioplasty in a porcine coronary model: the importance of excipients. *EuroIntervention.* 2011;7:730-7.

17. Wöhrle J, Zadura M, Möbius-Winkler S, Leschke M, Opitz C, Ahmed W, Barragan P, Simon JP, Cassel G, Scheller B. SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol.* 2012;60:1733-8.

18. Toelg R, Merkely B, Erglis A, Hoffman S, Bruno H, Kornowski R, Slagboom T, Naber C, Witzenbichler B, Graf K, Richardt G, Hehrlein C; DELUX investigators. Coronary artery treatment with paclitaxel-coated balloon using a BTHC excipient: clinical results of the international real-world DELUX registry. *EuroIntervention.* 2014;10:591-9.

19. Alfonso F, Pérez-Vizcayno MJ, Garcia Del Blanco B, Garcia-Touchard A, Lopez-Minguez JR, Sabaté M, Zueco J, Melgares R, Hernandez R, Moreno R, Dominguez A, Sanchis J, Moris C, Moreu J, Cequier A, Romaguera R, Rivero F, Cuesta J, Gonzalo N, Jiménez-Quevedo P, Cardenas A, Fernandez C; Spanish Society of Cardiology. Usefulness of Drug-Eluting Balloons for Bare-Metal and Drug-Eluting In-Stent Restenosis (from the RIBS IV and V Randomized Trials). *Am J Cardiol.* 2017;119:983-90.

20. Nijhoff F, Stella PR, Troost MS, Belkacemi A, Nathoe HM, Voskuil M, Samim M, Doevendans PA, Agostoni P. Comparative assessment of the antirestenotic efficacy of two paclitaxel drug-eluting balloons with different coatings in the treatment of in-stent restenosis. *Clin Res Cardiol.* 2016;105:401-11.

21. Stella PR, Belkacemi A, Waksman R, Stahnke S, Torguson R, von Strandmann RP, Agostoni P, Sangiorgi G, Silber S; Valentine Investigators. The Valentines Trial: results of the first one week worldwide multicentre enrolment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment. *EuroIntervention.* 2011;7:705-10.

22. Rittger H, Waliszewski M, Brachmann J, Hohenforst-Schmidt W, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Schlundt C, Zimmermann S, Lonke S, von Cranach M, Markovic S, Daniel WG, Achenbach S, Wöhrle J. Long-Term Outcomes After Treatment With a Paclitaxel-Coated Balloon Versus Balloon Angioplasty: Insights From the PEPCAD-DES Study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter). *JACC Cardiovasc Interv.* 2015;8:1695-700.

23. Alfonso F, Pérez-Vizcayno MJ, Cardenas A, Garcia del Blanco B, Garcia-Touchard A, Lopez-Minguéz JR, Benedicto A, Masotti M, Zueco J, Iniguez A, Velazquez M, Moreno R, Mainar V, Dominguez A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernandez C, Macaya C; RIBS IV Study Investigators (under auspices of Interventional Cardiology Working Group of Spanish Society of Cardiology). A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol.* 2015;66:23-33.

24. Latib A, Ruparelia N, Menozzi A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, Buffoli F, Tamburino C, Varbella F, Colombo A. 3-Year Follow-Up of the Balloon Elution and Late Loss Optimization Study (BELLO). *JACC Cardiovasc Interv.* 2015;8:1132-34.

25. Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, Limbruno U. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart.* 2010;96:1291-6.

26. Unverdorben M, Kleber FX, Heuer H, Figulla HR, Vallbracht C, Leschke M, Cremers B, Hardt S, Buerke M, Ackermann H, Boxberger M, Degenhardt R, Scheller B. Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 2010;99:165-74.

27. Richelsen RK, Overvad TF, Jensen SE. Drug-Eluting Balloons in the Treatment of Coronary De Novo Lesions: A Comprehensive Review. *Cardiol Ther.* 2016;5:133-60.

28. Cortese B, D'Ascenzo F, Fetiveau R, Balian V, Blengino S, Fineschi M, Rogacka R, Lettieri C, Pavei A, D'Amico M, Poli A, Di Palma G, Latini RA, Orrego PS, Seregni R. Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE. *J Cardiovasc Med (Hagerstown).* 2018;19:247-52.

29. Kleber FX, Rittger H, Bonaventura K, Zeymer U, Wohrle J, Jeger R, Levenson B, Möbius-Winkler S, Bruch L, Fischer D, Hengstenberg C, Porner T, Mathey D, Scheller B. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol.* 2013;102:785-97.

30. Zeymer U, Waliszewski M, Spiecker M, Gastmann O, Faurie B, Ferrari M, Alidoosti M, Palmieri C, Heang TN, Ong PJ, Dietz U. Prospective 'real world' registry for the use of the 'PCB only' strategy in small vessel de novo lesions. *Heart.* 2014;100:311-6.

Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Table 1. Participating centres.

Supplementary Table 2. Lesion characteristics.

Supplementary Table 3. Data of results for ISR treatment in previous DCB registries vs the FALCON Registry.

Supplementary Table 4. Comparison of previous trials with DCB-only use for *de novo* coronary disease.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00261

Supplementary data

Supplementary Appendix 1. Methods

Procedural strategy and adjuvant medical therapy were left to the discretion of the operators of each site and their routine clinical practice. Handling instructions for use of the IN.PACT Falcon balloon and the recommendation of the German consensus group on DCB treatment [29] were handed out to each centre and adherence to these recommendations was encouraged. In brief, lesion preparation with predilatation using an uncoated balloon and a minimum inflation time of 30-60 seconds for the IN.PACT Falcon DCB were recommended. The balloon surface of the IN.PACT Falcon DCB is homogenously coated with a delivery matrix of 3 μg per mm^2 of paclitaxel, using the natural product urea as an inert excipient. The IN.PACT Falcon DCB was available in lengths of 14 to 40 mm with diameters of 2.25 to 4.0 mm.

Procedural and device success was to be judged by the operator at each individual centre according to the angiographic results. Judgement was made with regard to the recommendation of the German consensus group on DCB treatment [29].

Clinical follow-up was documented at discharge following the index procedure and was performed by way of office visits or telephone contact after 12 months. All centres were monitored online and some centres were randomly visited on site.

Supplementary Table 1. Participating centres.

Centre	Principal investigator	Subjects	ISR	BMS-ISR	DES-ISR	de novo
Hannover Medical School	Widder J/Bauersachs J	61	37	6	21	25
ASST Fatebenefratelli-Sacco, Milan	Cortese B	119	48	10	29	77
CHU Poitiers, Poitiers	Levesque S	96	34	21	13	54
Norfolk and Norwich University Hospital	Eccleshall S	77	13	2	10	66
Jüdisches Krankenhaus Berlin	Graf K	59	55	1	18	6
University Medical Center Utrecht	Stella P	51	28	13	12	25
Centre Hospitalier Sud Francilien, Corbeil-Essonnes	Doutrelant L	39	27	9	12	13
Freeman Hospital, Newcastle upon Tyne	Ahmed J	36	26	0	24	11
Nouvelles Cliniques Nantaises, Nantes	Bressollette E	35	39	15	23	6
Instituto Clinico Humanitas, Rozzano	Zavalloni D	35	27	7	17	9
“P. Giaccone” University Hospital of Palermo	Piraino D	26	7	0	7	19
Rambam Medical Center, Haifa	Roguin A	23	22	5	15	1
University of Saarland, Homburg/Saar	Scheller B	22	19	9	7	4
Schwarzwald-Baar-Klinikum, Villingen-Schwenningen	Jung W	14	11	1	9	2
Klinikum Karlsruhe, Karlsruhe	Schmitt C	13	7	1	6	6
Unfallkrankenhaus Berlin, Berlin	Bruch L	11				12
Asklepios Klinik St. Georg, Hamburg	Meinicke F	9	5		2	3
Kerckhoff Klinik, Bad Nauheim	Möllmann H	7	5	2	1	2
UZ Leuven, Leuven	Dubois P	5	5		5	
CHLN, Lisbon	Canas da Silva P	5	5		3	
Robert-Bosch-Krankenhaus, Stuttgart	Schäuffele T	3	1	1	0	2
Asklepios Klinik Nord - Heidberg	Mletzko N	3	2	1	1	1
Jeroen Bosch Hospital, ’s-Hertogenbosch	Van Eck M	3	1	0	1	1
UKE-Hamburg, Hamburg	Sydow K	2	2	1	1	
Elbe Klinikum Stade	Philip S	2	1			1
Klinikum Ingolstadt	Seidl K	1	1		1	

Supplementary Table 2. Lesion characteristics.

	All lesions (n=805)	ISR (n=428)	BMS-ISR (n=105)	DES-ISR (n=238)	de novo (n=346)	*p*-value BMS-ISR vs. DES-ISR	*p*-value ISR vs. de novo
Length, mm	17.9±10.7	18.2±11.8	18.8±11.2	18.2±13.1	17.7±9.6	0.083	0.685
Reference vessel diameter, mm	2.8±0.5	3.0±0.5	3.0±0.5	3.0±0.5	2.5±0.5	0.743	<0.001
Target lesion							
LMCA	7 (0.9%)	6 (1.4%)	2 (1.9%)	3 (1.3%)	1 (0.3%)		
LAD	348 (43.2%)	181 (42.3%)	46 (43.8%)	92 (38.7%)	154 (44.5%)		
LCX	213 (26.5%)	88 (20.6%)	19 (18.1%)	52 (21.8%)	117 (33.8%)		
RCA	210 (26.1%)	133 (31.1%)	36 (34.3%)	77 (32.4%)	71 (20.5%)		
Graft	27 (3.4%)	20 (4.7%)	2 (1.9%)	14 (5.9%)	3 (0.9%)		
Bifurcation	134 (16.6%)	54 (12.6%)	10 (9.5%)	31 (13.0%)	72 (20.8%)	0.357	<0.01
Single lesion	757 (94%)	405 (94.6%)	101 (96.2%)	223 (93.7%)	326 (94.2%)		
Multiple lesions	48 (6%)	23 (5.6%)	4 (3.8%)	15 (6.3%)	20 (5.8%)		
Lesion type							
A	113 (13.8%)	49 (11.2%)	12 (11.1%)	27 (11.1%)	54 (15.6%)		
B1	303 (37.0%)	174 (40.0%)	48 (44.4%)	90 (37.2%)	118 (34.1%)		
B2	196 (24.0%)	99 (22.8%)	20 (18.5%)	61 (25.5%)	94 (27.2%)		
C	206 (25.2%)	113 (26.0%)	28 (26.0%)	64 (26.4%)	90 (26.0%)		

Data presented as mean±standard deviation or n (%).

BMS-ISR: bare metal stent in-stent restenosis; DES-ISR: drug-eluting stent in-stent restenosis; ISR: in-stent restenosis; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery

Supplementary Table 3. Data of results for ISR treatment in previous DCB registries vs. the FALCON Registry.

Registry name	DCB device	Outcome BMS-ISR (follow-up month)	Outcome DES-ISR (follow-up month)
SeQuent Please World Wide Registry [20]	SeQuent Please	MACE: 5.3% (9) TLR: 5.2% (9)	MACE: 11.6% (9) TLR: 9.6% (9)
DELUX Registry [21]	Pantera Lux	MACE: 11.6% (12) TLR: 4% (12)	MACE: 20.6% (12) TLR: 11.5% (12)
Valentines I [24]	Dior II	MACE: not given TLR: 5.1% (6-9)	MACE: not given TLR: 10.8% (6-9)
FALCON Registry	IN.PACT Falcon	MACE: 8.2% (12) TLR: 2.1% (12)	MACE: 12.3% (12) TLR: 9.5% (12)

DCB: drug-coated balloon; MACE: major adverse cardiac events; TLR: target lesion revascularisation

Supplementary Table 4. Comparison of previous trials with DCB-only use for de novo coronary disease.

Trial	Design DCB device	Number of patients	Vessel size	Outcome (months of follow-up)	Bail-out stenting	Ref.
PICCOLETO	Randomised Dior I vs. DES (TAXUS)	57 (28 DCB)	≤2.75 mm	MACE: 35.7% vs. 13.8% (9) TLR: 32.1% vs. 10.3% (9) Diameter stenosis: 43.6% vs. 24.3% (6)	36%	25
BELLO	Randomised IN.PACT Falcon vs. DES (TAXUS)	182 (90 DCB)	≤2.8 mm	MACE: 10% vs. 16.3% (6) and 14.8% vs. 25.3% (24) TLR 4.4% vs. 7.6% (6) and 6.8% vs. 12.1% (24) LLL 0.08 mm vs. 0.29 mm (6)	20%	11,24
PEPCAD I	Observational SeQuent Please	120	2.25-2.8 mm	MACE: 15.3% (12) TLR: 11.9% (12)	26.7%	26
SeQuent Please Small Vessel ‘‘PCB Only’’ Registry	Observational SeQuent Please	479	≤2.75 mm	MACE: 4.7% (9) TLR: 3.6% (9)	6%	30
SeQuent Please World Wide Registry	Observational SeQuent Please	390	≤2.5 mm	MACE: 2.6% (9) TLR: 1.0% (9)	N/A	17
DELUX Registry	Observational Pantera Lux	105	≤4.0 mm ≤2.75 mm (69.4%)	MACE: 9.4% (12) TLR: 3.1% (12)	22.5%	18
Italian Elutax SV rEgistry-DCB-RISE	Observational Elutax SV	238	not reported	DOCE: 2.6% (13.3±7.4) TLR: 2.6% (13.3±7.4)	12.3%	28
FALCON Registry	Observational IN.PACT Falcon	326	≤4.0 mm (24.9%) ≤2.75 mm (74.9%)	MACE: 7.4% (12) TLR: 4.9% (12)	4.8%	

DCB: drug-coated balloon; DOCE: device-oriented cardiovascular events; LLL: late lumen loss; N/A: not applicable; MACE: major adverse cardiac events; TLR: target lesion revascularisation