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A Prospective Multicenter Randomized Trial to Assess the Effectiveness of the MagicTouch Sirolimus-Coated Balloon in Small Vessels: Rationale and Design of the TRANSFORM I Trial

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ABSTRACT

Aims: The objective of the study is to assess the efficacy and safety of the novel Magic Touch sirolimus coated-balloon (SCB) when compared to the SeQuent Please Neo paclitaxel coated balloon (PCB) for the treatment of de-novo small vessel coronary artery diseases (SVD).
Study design: The TRANSFORM I study is a randomized, multicenter, non-inferiority trial with the intent to enroll a total of 114 patients with a de-novo SVD (≤2.5 mm). Vessel size will be pre-screened by on-line QCA. After successful pre-dilatation without major coronary dissections (type C-F) nor Thrombolysis In Myocardial Infarction trial [TIMI] grade flow ≤2, patients will be enrolled in a 1:1 randomization to receive treatment with either the novel SCB balloon or the comparative PCB balloon. The balloon sizing will be selected according to the lumen-based approach derived from optical coherence tomography (OCT). The primary endpoint is 6-month mean net lumen diameter gain (6-month minimum lumen diameter [MLD] minus baseline MLD) assessed by quantitative coronary analysis (QCA) with non-inferiority margin of 0.3 mm in per-protocol analysis. The clinical follow-up will be conducted up to 1 year. The enrollment started in September 2020 and will complete in April 2021.
Conclusions: The TRANSFORM I trial will assess the efficacy of novel SCB in terms of non-inferiority to conventional PCB with a novel OCT measurement approach in patients with a de-novo SVD.
Clinical Trial Registration URL: https://clinicaltrials.gov.
Unique identifier: NCT03913832.

1. Introduction

The new-generation drug-eluting stents (DES) have shown exceptional anti-proliferative efficacy and excellent long-term results. Their usage, however, results in permanent metallic implants within the vessels and therefore still has some limitations, including risks of in-stent restenosis (ISR), neoatherosclerosis [1], and very late stent thrombosis [2]. Currently, two different technologies, bioresorbable scaffold and drug coated balloon (DCB), have been developed to comply with the "leave nothing behind" strategy [3]. Previous studies have

Abbreviations: DCB, drug coated balloon; DES, drug eluting stent; EEM, external elastic membrane; ITT, intention-to-treat; OCT, optical coherence tomography; PCB, paclitaxel coated balloon; PCI, percutaneous coronary intervention; SCB, sirolimus coated balloon; SVD, small vessel disease; TIMI, Thrombolysis In Myocardial Infarction trial; QCA, quantitative coronary analysis.

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demonstrated the potential adverse effects of a permanent metal prosthesis at very long-term follow-up [4,5].

DCBs first appeared in the European market in 2007, with the aim of being an alternative strategy for ISR instead of DES, and have shown favorable results [6–10]. Thereafter, DCBs have been extensively used for the treatment of de-novo coronary lesions in some specific settings including small vessel disease (SVD) [9–15].

In SVD, the implantation of a metallic prosthesis could further increase the risk of restenosis even more than the large-caliber vessels. Although several past studies attempted the treatment strategy with DCB for SVDs, the results were discordant. This was possibly due to a learning phase during the early years of clinical experience with the DCBs and the fact that multiple different DCB devices were used with different drug dosages (Online Table 1).

Until 2016, all DCBs marketed in Europe eluted paclitaxel due to its favorable pharmacokinetic properties. Paclitaxel is a lipophilic drug that rapidly crosses the cell membrane and binds to microtubules, thus inhibiting cell division and migration, and therefore cell proliferation [16–18]. Conversely, all currently available DES elute sirolimus or analogue drugs (the "-limus" drug class) due to improved outcomes when compared to paclitaxel-eluting stents (PES), including PCI of SVD [19–23]. Compared to sirolimus-eluting stent (SES) the PES had less efficacy in terms of risk reduction of target-lesion revascularization [24]. Moreover, the PES had a possible increased risk in stent thrombosis in comparison to SES or BMS [25]. Therefore, a sirolimus-coated balloon (SCB) may have the potential to reduce the thrombogenicity after the elution and to improve clinical outcomes compared to a conventional paclitaxel-coated balloon (PCB). Although sirolimus has well-recognized antiproliferative properties, it's use on a drug coated balloon was hampered initially due it's low lipophilicity and thus low penetration and retention in the target vessel wall.

The Magic Touch SCB (Concept Medical, Surat, India) was developed with novel technology of an encapsulation of low lipophilicity sirolimus into a protective lipophilic package [26]. The objective of this pilot study is to investigate the efficacy and safety of this novel SCB for de-novo SVD treatment compared to conventional PCB.

2. Methods

2.1. Study design

The TRANSFORM I study (ClinicalTrials.gov unique identifier: NCT03913832) is a prospective, randomized, multicenter, open-label non-inferiority trial, sponsored by the Concept Medicals. The intent is to conduct this trial in 6 interventional cardiology centers in Italy, Poland, the United Kingdom, and Ireland. Additional sites will be included depending on the rate of enrolment. One hundred and fourteen patients with a de-novo SVD will be enrolled in a 1:1 randomization to receive treatment with either the study device (Magic Touch SCB) or the control device (SeQuent Please Neo PCB).

Male or female patients ≥18 years old who have at least one de-novo SVD (reference diameter ≤ 2.50 mm by quantitative coronary angiography [QCA]) with clinical presentation of stable coronary syndrome (CCS) or stabilized acute coronary syndrome (ACS) will be included in this study. The full inclusion and exclusion criteria are as shown in Table 1. Patients will be required to write informed consent before the index procedure to enroll into this study.

The study flowchart is shown in Fig. 1. Vessel size will be pre-screened by on-line QCA pre-procedure. If, based on on-line QCA, the reference vessel size pre-procedure is ≤2.5 mm, using the interpolated reference diameter of the stenotic lesion, if a successful pre-dilatation without major angiographic dissections (type C, D, E, or F) according to the National, Heart, Lung, and Blood Institute (NHLBI) classification [27], without Thrombolysis In Myocardial Infarction trial [TIMI] grade flow ≤2, and without residual angiographically significant stenosis (i.e. >30% stenosis), the patient will be randomized to receive either the

Table 1
Study enrolment criteria.

1. Inclusion criteria
1) Male or female subjects ≥18 years
2) Subject with chronic stable angina or stabilized acute coronary syndromes with normal cardiac biomarker values Note: For subjects showing elevated Troponin (e.g. non-STEMI patients) at baseline (within 72 h pre-PCI) an additional blood sample must be collected prior to randomization to confirm that: • hs-cTn or Troponin I or T levels are stable, i.e. the value should be within 20% range of the value found in the first sample at baseline, or have dropped • CK-MB and CK levels are within normal range If hs-cTn or Troponin I or T levels are stable or have dropped, the CK-MB and CK levels are within normal ranges, and the ECG is normal, the patient may be included in the study.
3) The subject has a planned intervention in one or two separates major epicardial territories (LAD, LCX or RCA) and has at least one de-novo lesion in a small vessel (≤2.5 mm by QCA prior to pre-dilatation)
4) Target lesion length ≤ 30 mm
5) Able to understand and provide informed consent and comply with all study procedures including 6 months angiographic follow-up
6) Subject must have completed the follow-up phase of any previous study
2. Exclusion criteria
Clinical exclusion criteria
1) Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential)
2) Evidence of ongoing acute myocardial infarction (AMI) in ECG and/or elevated cardiac biomarkers (according to local standard hospital practice) have not returned within normal limits at the time of procedure
3) Known contraindication or hypersensitivity to sirolimus, paclitaxel, or to medications such as aspirin, heparin, and all of the following four medications: clopidogrel bisulfate, ticlopidine, prasugrel, ticagrelor
4) Subject suffered from stroke/TIA during the last 6 months
5) LVEF < 30%
6) Platelet count < 100,000 cells/mm^3 or >400,000 cells/mm^3, a WBC of <3000 cells/mm^3, or documented or suspected liver disease (including laboratory evidence of hepatitis)
7) Known renal insufficiency (e.g. creatinine clearance ≤ 30 mL/min), or subject on dialysis, or acute kidney failure (as per physician judgment)
8) Subject undergoing planned surgery within 1 month with the necessity to stop DAPT
9) History of bleeding diathesis or coagulopathy
10) The subject is a recipient of a heart transplant
11) Concurrent medical condition with a life expectancy of less than 12 months
12) The subject is unwilling/not able to return for angiographic recatheterisation at 6-month follow-up
13) Currently participating in another trial and not yet at its primary endpoint.
Angiographic exclusion criteria
14) The subject has a planned intervention in three separates major epicardial territories (3 vessel disease)
15) The subject has a planned intervention in the left-main plus two separates major epicardial territories (left-main plus 2 vessel disease)
16) Target vessel size >2.50 mm (by QCA)
17) Target vessel size <2.00 mm (by QCA)
18) Target lesion has a total occlusion or TIMI flow <2
19) Target lesion in left main stem
20) The target vessel contains a stent or previously treated with DCB (e.g., stenting of the proximal LAD followed by DCB of the diagonal is not allowed)
21) Presence of other 'non-study' lesion (>2.5 mm) in the same epicardial territory or its side branches.
22) The target vessel contains visible thrombus
23) Aorto-ostial target lesion (within 3 mm of the aorta junction)
24) Moderate-severe tortuous, calcified or angulated coronary anatomy of the target vessel that in the opinion of the investigator would result in suboptimal imaging or excessive risk of complication from placement of an OCT catheter
25) Lesion is located within an arterial or saphenous vein graft or distal to a diseased arterial or saphenous vein graft.

STEMI; ST-segment elevated myocardial infarction; hs-cTn: high-sensitivity cardiac troponin; CK: creatine-kinase; ECG: electrocardiogram; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; QCA: quantitative coronary analysis; TIA: transient ischemic attack; LVEF: left ventricular ejection fraction; WBC: white blood cell; DAPT: dual-antiplatelet therapy; DCB: drug-coated balloon; OCT: optical coherence tomography.

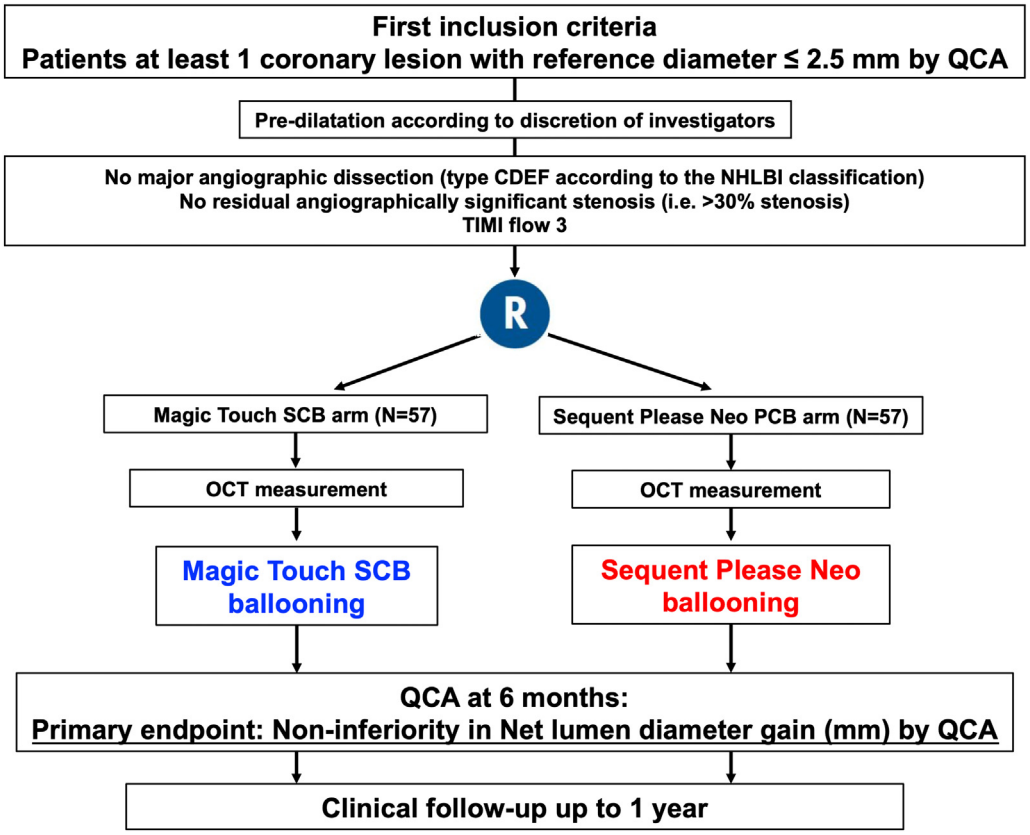


Fig. 1. Study flowchart. QCA: quantitative coronary angiography; SCB: sirolimus-coated balloon: PCB; paclitaxel-coated balloon; OCT: optical coherence tomography.

treatment with Magic Touch SCB or SeQuent Please Neo PCB. Randomization is performed through the central randomization system with electronic case report form (eCRF). Optical coherence tomography (OCT) will be performed after pre-dilatation prior to DCB treatment. If, based on OCT, the vessel size following pre-dilatation is >2.5 mm, the "vessel" will be kept in the study and will be included in the primary analysis, however, one additional non-powered subgroup analysis will be performed excluding those vessels. If applicable, other lesions will be treated with any other commercial devices such as DES.

2.2. Treatment devices

The Magic Touch is a sirolimus-coated balloon with a monorail delivery system compatible with 5-Fr. guiding catheters. The balloon is coated with sirolimus in a uniform manner through the use of a spray coating. The novel Nanolutè technology specifically designed for this device consists in the encapsulation of sirolimus in a protective lipophilic package, which allows drug diffusion, penetration, and mid-term residency in the arterial wall during balloon inflation, overcoming the low lipophilicity of sirolimus (Online Figs. 1 and 2). This package consists of microspheres of 100–300 nm diameter. The total dosage of the drug corresponds to 1.27 μg/mm^2 of surface of the balloon, well within the therapeutic window of sirolimus (Online Fig. 3) [26]. In the Magic Touch SCB, the drug on the balloon is distributed circumferentially over the balloon surface. Approximately 66% of drug remains inside folds while only 34% drug is exposed to blood before dilation of the balloon. Therefore, drug loss during transit could be minimal in the Magic Touch SCB (Online Fig. 4). In a preclinical study of Porcine ISR models, three-overlapping of Magic Touch SCB showed no pharmacokinetic reason for safety concerns (unpublished data).

The comparator device is a commercialized SeQuent Please Neo PCB, coated with 3 μg paclitaxel/mm^2. This device has been widely studied in preclinical and clinical studies and its behavior in terms of paclitaxel release and persistence in the vessel wall has been previously described [16].

2.3. Predilatation

Predilatation will be performed according to the local investigator's discretion. A conventional semi-compliant balloon with size of the balloon-to-vessel ratio 0.8–1.0 and more than nominal inflation pressure will be recommended for the predilatation [28].

2.4. Pre-DCB OCT assessment

OCT assessment will be conducted after the randomization. OCT pullback is performed beyond the target lesion, from a distal landmark (e.g. side-branch) to proximal fiducial landmark. The proximal and distal reference diameters will be measured at the proximal and distal segment of the target lesion, where the healthy 3-layer of the coronary artery is visible in at least 3 quadrants.

2.5. Study balloon size selecting and ballooning

The OCT-derived lumen-based balloon-sizing approach will be adopted in this study (Fig. 2). The diameter of DCBs will be selected according to two different strategies related to the types of DCBs and based on the different balloon compliances in bench tests (Online Table 3). The Magic Touch SCB is less compliant than the SeQuent Please Neo PCB. The purpose of these different approaches in selecting the balloon size for the two respective balloons is to avoid balloon-induced coronary dissection as well as to optimize the wall apposition and the transfer of the drug to the vessel wall from each respective balloon (Online Fig. 4). The Magic Touch SCB size is selected with a diameter larger

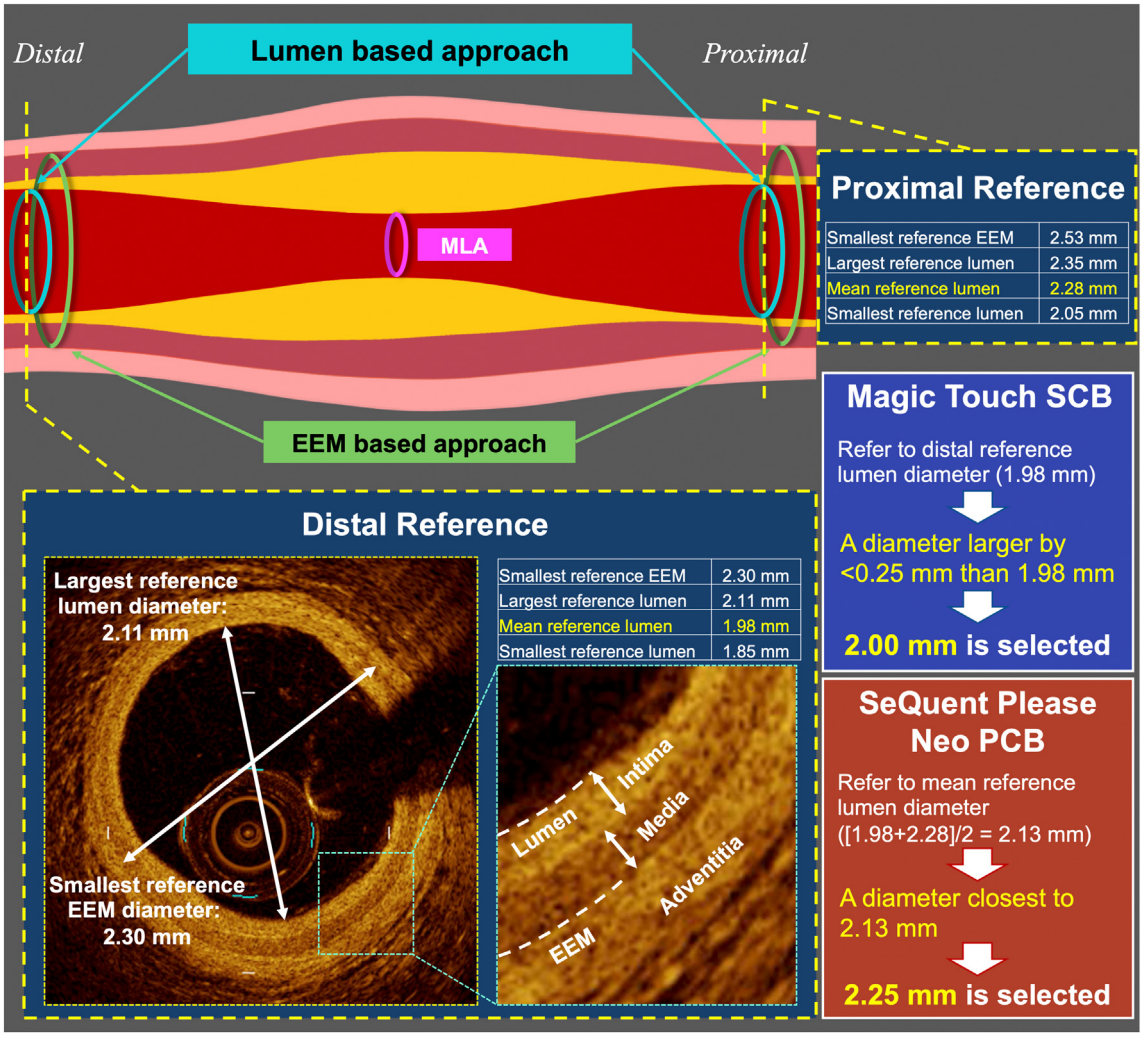


Fig. 2. OCT guided vessel sizing and balloon sizing [46]. The OCT-derived lumen-based approach will be feasible in DCB trials. DCB: drug-coated balloon; SCB: OCT: optical coherence tomography; EEM: external elastic membrane.

by <0.25 mm than the distal reference diameter on OCT. For example, if the distal reference diameter is 1.98 mm, a 2.00 mm balloon will be selected (Fig. 2). Whereas, the SeQuent Please DCB size is selected based on the mean reference diameter on OCT, and a size balloon with the closest to the mean reference diameter is selected. For example, if the mean diameter of proximal and distal reference area is 2.13 mm, a 2.25 mm balloon will be selected (Fig. 2).

Ballooning is performed with a pressure between nominal and rated burst pressure according to each compliance chart (Online Table 2). The DCB should be delivered to the target lesion within 45 s after the DCB get in touch with blood, and a single dilatation of 60 s is recommended, irrespective of types of DCBs (SCB or PCB). If on OCT the lumen diameter tapers >0.25 mm in a lesion with an obstruction lesion length of >20 mm, two same-type DCB (SCB or PCB) with two different balloon sizes (small and large) and appropriate length to minimize the overlap may be used to reduce the cumulative dose of the drug.

2.6. Bail-out procedures

If there is deterioration of blood flow (TIMI grade flow ≤2) after DCB treatment, it is recommended to give intracoronary medication (e.g. nitroprusside, calcium antagonists, or nicorandil) and wait approximately 5 min before making the final assessment and considering a bail-out stenting. Furthermore, only in case of dissection type C or worse, and/or impaired distal flow a strategy of bailout stenting is recommended [11].

For bail-out stenting, any drug-eluting stent is allowed according to the local practice. In case a vessel is too small to implant a stent, a repeat ballooning and administration of nitroprusside [29]/GP IIb/IIIa inhibitors [30] is recommended according to local practice and experience.

2.7. DAPT and follow-up

All subjects must receive DAPT, being aspirin and either clopidogrel, ticagrelor or prasugrel for at least 1 month after index PCI, followed by aspirin monotherapy indefinitely in patients treated with DCB [11]. Detailed pre-procedural and post-procedural antiplatelet regimen are shown in Online Table 3.

Clinical follow-up will occur at 1, 6, and 12 months post-PCI. All patients will undergo repeat angiography at 6-month follow-up. QCA assessment will be performed at pre-, post-procedure, and 6-month follow-up in single or multiple matched angiographic projections.

2.8. Study endpoints

The primary endpoint of this study is set as angiographic in-segment (balloon treated area + 5.0 mm) net lumen diameter gain (mm) at 6 months, which is defined as the 6-month minimum lumen diameter (MLD) minus the baseline MLD. The QCA assessment will be analyzed in

an independent core lab at follow-up by analysis blinded to the assigned treatment. The secondary endpoints are shown in Online Table 4.

2.9. Statistics analysis

The primary analysis of net gain will be based on the Per Protocol (PP) population, which will exclude subjects who do not receive the assigned treatment or receive additional bail-out devices. Whereas, the analysis of clinical secondary endpoints will be performed on the ITT population.

The trial is powered for testing non-inferiority for the primary endpoint at 6-month angiographic follow-up. A net gain of 0.87 ± 0.51 mm is assumed as a reference at 6 months after treatment with DCB in both device groups, based on the net gain at 6-month in lesions treated with SeQuent Please PCB in the PEPCAD study [31]. The non-inferiority margin was set as 0.3 mm. Assuming an attrition rate of 10%, 57 patients per arm is required to achieve more than 85% power to demonstrate non-inferiority with a one-sided type α error of 0.05.

3. Discussion

The TRANSFORM I study is the first trial that randomizes patients with a de-novo SVD to either SCB or PCB.

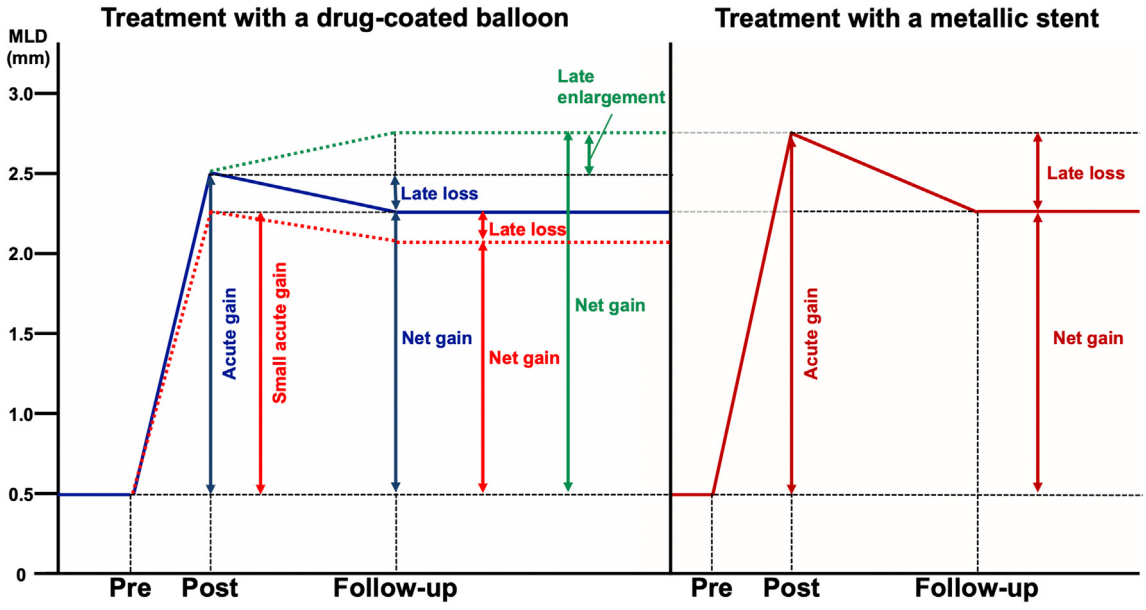
In the field of ISR, the DCB treatment strategy is established and is indicated as class I recommendation in the latest guidelines [32]. Recently, Ali et al. reported that the results of the treatment with SCB (sirolimus-coated SeQuent Neo percutaneous transluminal coronary angioplasty balloon catheter) were equivalent to those with PCB (SeQuent Please Neo) in the QCA analysis at 6 months in patients with ISR [33], indicating the acceptable performance of SCB in this clinical field. For the treatment of de-novo coronary artery lesions, several trials have demonstrated the efficacy and safety of DCB, in some specific settings such as patients with high-bleeding risk [15], ST-segment elevation MI (STEMI) [14], and SVD.

With regard to SVD, the BASKET-SMALL 2 trial was the largest randomized controlled trial to compare PCB and second-generation DES in the all-comers population with de-novo SVD [34]. This trial demonstrated non-inferiority of PCB compared to DES in terms of 12-month major adverse cardiac events (MACE; cardiac death, MI, or target-vessel revascularization). Of note, complete vessel occlusion of the target lesion was seen in 8 patients with DES implantation whereas none was in patients with PCB ($p = 0.009$) at clinically indicated re-angiography analysis of this trial [35]. In the recently published SCAAR registry, in the DCB group most of the target lesion thromboses (94%, 15/16) occurred within the first 6 months, whereas in the DES group the rate of thrombosis gradually increased even after the first 6–-12 months, underscoring the potential thrombogenic nature of the metallic cage in the long-term follow-up [36].

Although the evidence of the clinical efficacy of SCBs for de-novo coronary artery lesions is currently sparse, the results from several registries (Nanolutè [37], FASICO [38]) are quite encouraging for the safety of the Magic Touch SCB. While the first clinical data from the ongoing EASTBOURNE registry (NCT03085823) is also awaited, the TRANSFORM I trial will be worth elucidating the value of this novel SCB for SVD as a randomized controlled trial.

3.1. Advantage of using OCT in balloon sizing

One of the novelties of this trial is the OCT-guided sizing approach for the DCB treatment. OCT has the highest resolution among



	Drug-coated balloon			Metallic stent
	Reference	Small acute gain	Late enlargement	
Pre MLD	0.50 mm	0.50 mm	0.50 mm	0.50 mm
Post MLD	2.50 mm	2.25 mm	2.50 mm	2.75 mm
Follow-up MLD	2.25 mm	2.10 mm	2.25 mm	2.25 mm
Acute gain	2.00 mm	1.75 mm	2.00 mm	2.25 mm
Late lumen loss	**0.25 mm**	**0.15 mm**	**-0.25 mm**	**0.50 mm**
Net gain	**1.75 mm**	**1.60 mm**	**2.25 mm**	**1.75 mm**

Fig. 3. Angiographically changes after treatments with a drug-coated balloon or a metallic stent [47]. Post stenting, there is a predetermined diameter of the metallic cage, implanted with only the biological option to develop intra-stent neointima with reduction of the lumen. However, in the absence of endoluminal prothesis, late enlargement is feasible and will be accounted for, by assessing the net gain (or acute gain + negative late loss) [47]. Therefore, net gain is suitable as a surrogate endpoint in DCB studies. DCB: drug-coated balloon; LLL: late lumen loss.

intracoronary imaging modalities. While IVUS overestimates and QCA underestimates coronary lumen diameter, the measurement by OCT is the closest assessment of true "real dimension" [39,40], resulting in a careful selection of the DCB size. The majority of former drug coated balloon studies in small vessels enrolled patients with lesions assessed by visual angiographic estimation of the vessel size.

The OCT-based sizing approach has been validated in a stent sizing with variety of criteria [41,42]. The balloon dilatation without stenting should be more carefully performed than those with stenting to avoid coronary dissections resulting in bail-out procedures. Therefore, OCT-derived lumen-based approach is particularly suitable for DCB treatments (Fig. 2).

3.2. The endpoint of net gain and the primary analysis

In the treatment with DCB, small late lumen loss evolved somehow in parallel with a small acute gain (the so-called "the more you gain, the more you lose" law) [43]. In addition, late enlargement and remodeling are achievable in a non-caged vessel and will be accounted for after DCB treatments with the measurement of the net gain parameter [44]. Therefore, net gain is considered as more appropriate primary endpoint in this study (Fig. 3). Assuming the net gain of control arm is 0.87 mm [31], non-inferiority margin of 0.3 mm was selected (approximately 34% of absolute net gain) [45].

The primary analysis of this study will be conducted in PP population without undergoing bail-out procedures. In the present trial, bail-out stenting due to complication of drug-coated ballooning in both groups could confound and mislead the interpretation of efficiency of the DCB. If one arm has more complications and therefore results in more usage of drug-eluting stent due to dissection, the net-gain in intention-to-treat analysis could be paradoxically better for the device with more complications and the results could be biased in favor of the poorly performing DCB. Therefore, per-protocol analysis was selected as primary analysis method.

3.3. Limitation

In this study, OCT is performed only during an index procedure following the randomization, not in the follow-up, due to limited financial resources. In addition, the trial will not be able to be powered for clinical endpoints due to limited sample size for angiography endpoint.

4. Conclusions

The TRANSFORM I trial will assess non-inferiority of Magic Touch SCB compared to SeQuent Please PCB in terms of net gain at 6 months after PCI for coronary artery SVD with a novel OCT-based sizing approach. The novel SCB may become a good therapeutic alternative for treatment of SVD.

CRediT authorship contribution statement

Masafumi Ono wrote the first draft of the article and contributed to all revisions.

Yoshinobu Onuma, Patrick W. Serruys, and Bernardo Cortese designed the study, gathered, analyzed and interpreted data and contributed to all revisions.

Faisal Sharif contributed to all revisions.

Hideyuki Kawashima, Hironori Hara, Yuki Katagiri, Kuniaki Takahashi, Norihiro Kogame contributed to revision of the article.

Joanna J. Wykrzykowska, and Jan J. Piek interpreted data and contributed to critical revision of the manuscript.

Manish Doshi and Antonio Colombo designed the study, gathered and interpreted data and contributed to critical revision of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2020.10.004.

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