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Sirolimus-coated balloon versus everolimus-eluting stent in de novo coronary artery disease: Rationale and design of the TRANSFORM II randomized clinical trial

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Abstract

Background: Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is a widely adopted strategy for the treatment of de novo coronary artery disease. DES implantation conveys an inherent risk for short- and long-term complications, including in-stent restenosis and stent thrombosis. Drug-coated balloons are emerging as an alternative approach to fulfill the "leaving nothing behind" principle and avoid long-term DES-related complications.

Design: TRANSFORM II is an investigator-initiated, multicenter, noninferiority, randomized clinical trial, testing a sirolimus-coated balloon (SCB) versus the standard of care for native coronary vessels with a 2–3 mm diameter, in terms of 12-month target lesion failure (TLF; primary endpoint) and net adverse cardiovascular events (coprimary endpoint). Patients undergoing PCI will be randomized to be treated with either SCB or new-generation everolimus-eluting stent and will be followed up clinically for up to 60 months. Assuming a TLF rate of 8% at 12 months with DES, a sample size of 1325 patients was chosen to ensure an 80% power to detect a 1.5% lower incidence in the SCB group with a type I error rate of 0.05. The TRANSFORM II trial is registered on clinicaltrials.gov (identification number NCT04893291). Several substudies, including an optical coherence tomography assessment at 9 months (intracoronary imaging substudy), will investigate the study device in different clinical and lesion settings.

Conclusions: The randomized TRANSFORM II trial will determine whether a novel SCB is noninferior to a current everolimus-eluting stent when adopted for the treatment of de novo lesions in coronary vessels with a diameter between 2 and 3 mm.

KEYWORDS

coronary artery disease, drug-coated balloon, drug-eluting stent, percutaneous coronary intervention, randomized clinical trial, study design

1 | INTRODUCTION

Percutaneous coronary intervention (PCI) is a widespread myocardial revascularization modality for patients with coronary artery disease (CAD), both in the stable and the acute settings.[1] New-generation drug-eluting stents (DES) are currently implanted in a large proportion of patients, eluting an antiproliferative drug suppressing neointima formation.[2,3]

Unfortunately, DES implantation conveys a not negligible risk of in-stent restenosis (ISR) and stent thrombosis (approximately 2% per year) over the long term due to incomplete vascular healing, polymer hypersensitivity, neoatherosclerosis, and stent fracture or malapposition.[4–6] Latest-generation DES are also burdened with a steady annual hazard attributable to the presence of a metallic device that distorts and constrains the coronary vessel, limits vasomotion and positive adaptive remodeling, and leads toward chronic inflammation, neoatherosclerosis, or thrombosis.[7]

To overcome these issues, drug-coated balloons (DCB), combining balloon angioplasty and antiproliferative drug elution, were introduced in clinical practice.[8] Treating CAD with DCB alone defines the concept of DCB-only PCI, which eliminates stent thrombosis and eventually reduces the incidence of restenosis by fulfilling the "leaving nothing behind" principle.[8–11] In addition, another advantage of DCB over DES is the requirement for a shorter course of dual antiplatelet therapy (DAPT) following PCI.[12,13]

Despite these potential advantages of a DCB-based strategy, PCI with DES implantation is often the preferred strategy for the treatment of de novo CAD. Indeed, high-quality evidence about the relative merits of DCB and DES for the treatment of de novo coronary artery lesions is scarce and not conclusive. The aim of the TRANSFORM II trial is to evaluate the efficacy of a sirolimus-coated balloon (SCB) compared to a latest-generation DES in the treatment of native coronary vessels with a diameter between 2 and 3 mm. If a DCB-only strategy will prove to be noninferior to a DES-only strategy in the treatment of small-vessel de novo coronary lesions, DCB could be proposed as a first-line approach to obtain the benefits of the "leaving nothing behind" strategy in this specific setting.

2 | METHODS

2.1 | Study hypotheses and objectives

The TRANSFORM II trial aims at investigating the hypothesis that MagicTouch SCB is noninferior to a gold standard treatment (new-generation everolimus-eluting stent) for native coronary vessels with a diameter between 2 and 3 mm, in terms of target lesion failure (TLF, primary endpoint). In addition, the TRANSFORM II trial will explore whether the MagicTouch SCB is superior to the latest-generation everolimus-eluting stents for the reduction of net adverse cardiovascular events (NACE, coprimary endpoint) at 12 months.

2.2 | Study design

The TRANSFORM II (SCB vs. DES in native coronary vessels) is an investigator-initiated, multicenter, noninferiority, randomized clinical trial (Figure 1) sponsored by "Fondazione Ricerca e Innovazione Cardiovascolare," a nonprofit organization acting in Milan, Italy.

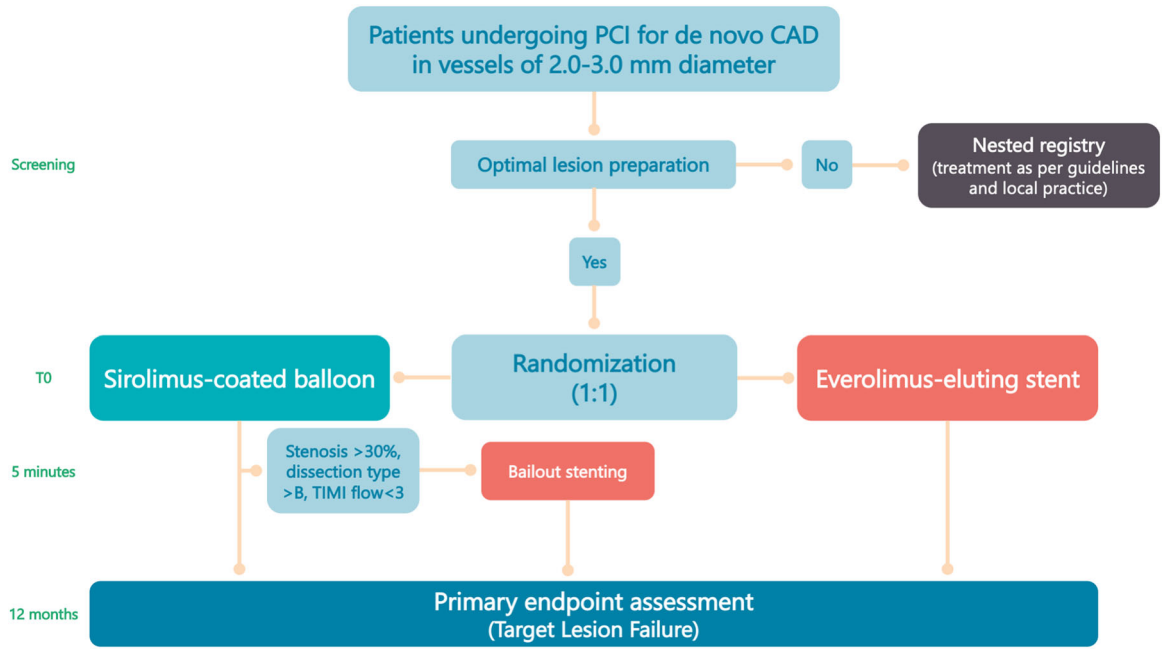

FIGURE 1 Study design. CAD, coronary artery disease; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction. [Color figure can be viewed at wileyonlinelibrary.com]

Patients with de novo lesions of coronary vessels with a diameter >2 and ≤3 mm (by visual estimation) and a clinical indication of PCI (i.e., acute or chronic coronary syndrome) suitable for treatment with either DCB or DES are considered for inclusion in this study. After successful lesion preparation, eligible patients are randomized in a 1:1 ratio to undergo PCI with either MagicTouch SCB (Concept Medical) or a new-generation everolimus-eluting stent. To generate the allocation list, blocked randomization (block size of 4, 6, and 8) stratified by diabetes and clinical presentation (i.e., acute vs. chronic coronary syndrome) is performed via a web-based electronic case report form (eCRF). The list is created by an independent statistician using the software R Studio, package "blockrand" V. 1.5. After randomization, standard PCI is performed according to international guidelines, consensus papers and as per local practice.[12,14,15]

Patients will be followed-up at prespecified timepoints up to 60 months by different modalities (i.e., telephone contact, in-hospital visit, follow-up coronary angiography with intracoronary imaging). The overall expected trial duration for each patient is 60 months. In addition, an intracoronary imaging substudy will be carried out in centers experienced with optical coherence tomography (OCT): the first 70 patients enrolled in such centers will undergo invasive coronary angiography and OCT at a 9-month follow-up.

The TRANSFORM II trial is registered on clinicaltrials.gov (identification number NCT04893291) and is currently ongoing at 31 sites across Europe (Italy, the Netherlands, Portugal, and Spain) and the United Kingdom.

2.3 | Study population and eligibility

Patients with de novo lesions of coronary vessels with a diameter >2 and ≤3 mm and a clinical indication of PCI should be considered for inclusion in this study. Patients will be deemed to be eligible for inclusion in the TRANSFORM II trial if they meet all the inclusion criteria and none of the exclusion criteria. Main inclusion criteria include a native coronary artery lesion in a vessel with a diameter >2.0 and ≤3.0 mm, a lesion length ≤40 mm, and a clinical indication of PCI (i.e., acute or chronic coronary syndrome). Main exclusion criteria encompass a creatinine clearance <30 ml/min, a left ventricular ejection fraction <30%, prior stent implantation in the target vessel, a target lesion in the left main stem coronary artery, and an ST-segment elevation myocardial infarction (MI) diagnosis in the previous 48 h. Detailed inclusion and exclusion criteria are reported in Table 1.

Notably, optimal lesion preparation is encouraged for all study patients; indeed, a thorough assessment of lesion preparation is required before randomization to be sure that an optimal result was reached, especially in patients undergoing PCI with DCB. Should be this condition not met, the patient will be excluded from the study, managed according to guidelines and local practice, and followed-up as a part of a nested registry.

TABLE 1 Eligibility criteria

Inclusion criteria
1. Age ≥18 years old.
2. Clinical indication to PCI (either acute or chronic coronary syndrome).
3. Native coronary artery lesion in a vessel with diameter >2.0 mm and ≦3.0 mm at visual estimation.
4. Maximum lesion length of 40 mm.
5. Written informed consent to participate in the study.
Exclusion criteria
1. Known (and untreatable) hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus, or contrast medium.
2. Patients are already participating in another clinical study.
3. Pregnant or nursing female subject.
4. Creatinine clearance <30 ml/min.
5. Left ventricular ejection fraction <30%.
6. Life expectancy <12 months.
7. ST-segment elevation myocardial infarction diagnosis in the previous 48 h.
8. Visible thrombus at the lesion site.
9. Culprit lesion stenosis >99% and/or TIMI flow <2.
10. Target lesion/vessel with any of the following characteristics:
a. Concomitant PCI in the same vessel as any other device.
b. Predilatation of the target lesion not performed or not successful.
c. Severe calcification of the target vessel (at the lesion site, but also proximally).
d. Highly tortuous vessels potentially impair device delivery to the lesion site.
e. Previous stent implantation in the target vessel.
f. Bifurcation lesion where a two-stent treatment strategy is anticipated.
g. Target lesion in the left main stem.
h. Left main stenosis ≥50%.

Abbreviations: PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

2.4 | Statistical analysis

Study analyses will be performed according to the intention-to-treat and as-treated principles. Categorical variables will be reported as absolute frequencies and percentages. After checking for variables' distribution using the Kolmogorov–Smirnov test, continuous variables will be summarized using means and standard deviation or median and interquartile range, as appropriate. Between-group comparisons will be performed by means of the χ^2 test or Fisher's exact test (categorical variables) or *t*-test for independent data, one-way analysis of variance

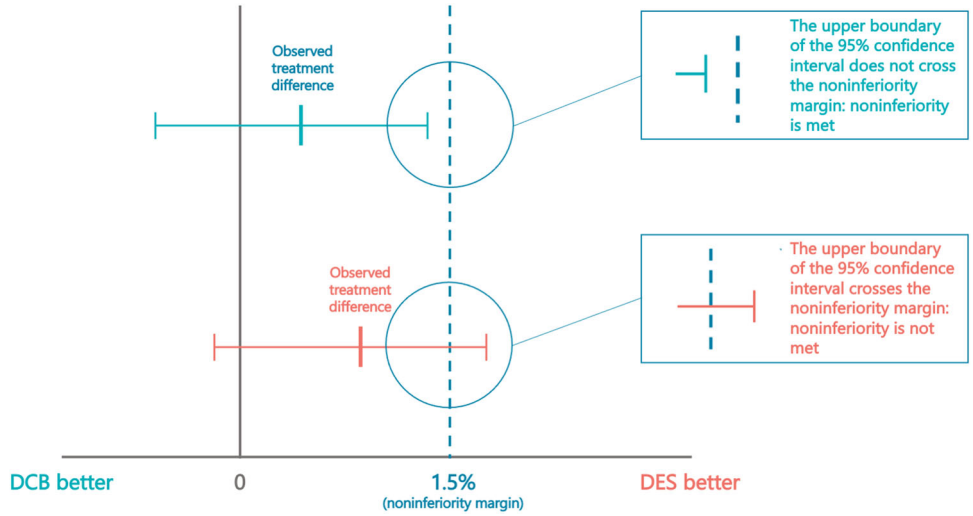

FIGURE 2 Study results interpretation. DCB, drug-coated balloon; DES, drug-eluting stent. [Color figure can be viewed at wileyonlinelibrary.com]

(ANOVA) or Kruskal–Wallis, and Friedman and Mann–Whitney test (continuous variables).

The primary endpoint will be compared with McNemar's test within each group and using the χ^2 test or Fisher's exact test for the between-groups comparisons. Kaplan–Meier analyses will be also performed for all the clinical endpoints.

To explore the association between several factors and study outcomes, binary logistic regression with the enter method will be adopted, both in univariable and multivariable fashions.

OCT analysis is hierarchical as it includes data derived from cross-section level and strut-level evaluations, which are nested into lesions, which, in turn, are nested into patients. OCT variables will be analyzed in a repeated manner for the same patients/lesions generating a correlation structure that also needs to be taken into account. To adjust for the clustered nature of OCT data and the repeated measures in time, the generalized estimating equations (GEE) model or mixed generalized regression model will be used as appropriate. GEE and mixed models account for the nonindependence of struts within lesions and are flexible to adjust for different distributions. The mixed effects model will be used to estimate the correlation coefficient between two variables with repeated observations.

2.4.1 | Sample size calculation

On the basis of previous literature, slightly different TLF rates are expected for DCB and DES groups.[16] The proportion of patients with a TLF event at 12 months was assumed to be 9.5% in the DCB group and 8% in the DES group, allowing a 1.5% maximum difference between the two groups (noninferiority margin). To test the hypothesis of noninferiority of SCB versus DES regarding the primary endpoint of TLF at 12 months, 633 patients per arm will be enrolled. This sample size will enable a power of 80% to be sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the standard group of more than 1.5% (Figure 2). To address a possible withdrawal of 5% of the enrolled patients, the final study population will be 1325 patients.

2.5 | Organizational structure

2.5.1 | Trial oversight

The TRANSFORM II trial organization includes elements of quality, such as a Clinical Events Committee (CEC) and a Data and Safety Monitoring Board (DSMB). CEC is an adjudicating committee reviewing all study endpoints and includes independent cardiologists and neurologists. All members of the CEC are blinded to the patient assignment. The DSMB encompasses four members (three interventional cardiologists and one biostatistician) who will review safety data regarding adverse events to identify potential safety issues. A minimum of 35% of all data entered in the eCRF will be assessed and analyzed by a dedicated independent board for consistency.

2.5.2 | Ethical aspects

The TRANSFORM II study adheres to the ethical principles of the Declaration of Helsinki, the International Conference of Harmonization, and Good Clinical Practice. The study protocol was approved by an independent ethics committee at each participating site. Each patient provided written informed consent before study enrollment and any study procedure.

2.6 | Study interventions

Patients included in the TRANSFORM II study will undergo invasive coronary angiography and PCI as per current guidelines and local practice, according to the study randomization (i.e., using either DCB or DES). Optimal lesion preparation represents a requirement for the DCB group and should achieve the goal of a stenosis <30% of vessel diameter, without flow-limiting dissection (i.e., type C or worse) and with thrombolysis in myocardial infarction (TIMI) flow grade 3.[12] The whole segment involved in lesion preparation should be covered by DCB (or DES), so more than one device can be used for a single lesion if required. The MagicTouch SCB size is selected with a target ratio of 1:1 between distal vessel size and balloon diameter at nominal pressure. Ballooning is performed with a pressure between nominal to rated burst pressure (6–16 atm). The results of PCI should be assessed after 5 min from DCB use in two orthogonal views. Bailout stenting can be performed at the operator's discretion. However, the Steering Committee strongly advises performing bailout stenting only in case of residual >type B coronary dissection and/or TIMI flow < 3. A bailout stenting rate of 10%–12% is expected.

Nonstudy lesion PCI is permitted at the time of index procedure or during another procedure, while study lesion PCI is allowed, independently of timing, only if the target and nontarget lesions are in different segments of the target vessel. The protocol allows nontarget PCI in patients with multivessel disease. However, in the case of multivessel PCI during the index procedure, it is mandatory to treat nontarget lesions first and to assess the efficacy of PCI before starting the treatment of the study lesion. In this scenario, events occurring after the procedure may be due to the target or nontarget lesions, so a clinical events adjudication committee was foreseen to address this issue.

2.7 | Study procedures and follow-up

All study patients are administered antithrombotic drugs according to international guidelines.[17–19] DAPT duration differs according to clinical presentation. In patients presenting with acute coronary syndrome, DAPT is suggested for 12 months in patients randomized to receive DES and for 6 months in patients allocated to the DCB group; both durations can be potentially shortened to 3 months (or even 1 month) if concerns about the bleeding risk prevail.[20] In chronic coronary syndrome patients, DAPT is recommended for 6 months (susceptible to shortening in high-bleeding risk patients) or 1 month in patients randomized to DES or DCB, respectively.[17–19]

2.8 | Study endpoints

The primary endpoint is 12-month TLF, while NACE at 12 months represents the coprimary endpoint. Endpoint definitions are summarized in Table 2. In brief, TLF is defined as the composite of cardiac death, ischemia-driven target-lesion revascularization (TLR), or target-vessel MI. This coprimary endpoint will enable the detection of any difference in the performance of SCB versus DES at the target lesion level. However, since PCI of the target lesion may also indirectly affect a patient's clinical outcomes (e.g., by requiring postprocedural DAPT), NACE represents a more comprehensive endpoint including the occurrence of death, MI, ischemic stroke, and major bleeding (type 3 or 5 according to the Bleeding Academic Research Consortium [BARC] definition).

Secondary endpoints of the TRANSFORM II study include procedural success (defined as technical and angiographic success, with final stenosis <30% in the absence of in-hospital adverse events), all-cause death, cardiac death, any MI, Q-wave MI, TLR, target vessel revascularization (TVR), vessel thrombosis, and fatal or major bleeding (BARC type 3 or 5).

Serial coronary angiographic images will be obtained after intracoronary administration of nitroglycerin (100–200 μg, unless contraindicated) in two orthogonal matching views. Quantitative analyses will be performed by means of validated two-dimensional software for quantitative coronary angiography (QCA) analysis (QAngio XA version 7.2; Medis). The minimal lumen diameter (MLD) and the mean reference diameter (MRD), obtained by averaging 5-mm proximal and distal segments to the target lesion, will be used to calculate the diameter stenosis (DS) as follows: $DS = (1 - MLD/MRD) \times 100$. Acute gain is the change in MLD from baseline to post-device use, while LLL is the change in MLD from the post-PCI angiogram to follow-up. Binary restenosis is defined as stenosis ≥50% at angiographic follow-up. Overall, QCA measurements are defined as "in-stent" (within the stented segment), "in-segment" (spanning the stented segment plus the 5mm proximal and distal), and "outside the stent" (more than 5 mm proximally and distally to the stent).

3 | DISCUSSION

In current-era interventional cardiology, DCB is an established option for the treatment of ISR[21–23] and a valid alternative to DES implantation in small coronary vessel disease.[24–26] On the basis of promising early evidence, DCB can also play a role in other circumstances, such as de novo lesions in large coronary vessels and even complex coronary interventions (Figure 3).[27–31]

Several lesion characteristics act as a marker of risk for mid-to-long-term complications. For instance, an analysis of the GRAND-DES registry showed that lesion length was associated with higher rates of TLF and early stent thrombosis in patients undergoing PCI with stent implantation with newer-generation DES.[32,33] Similarly, small-vessel coronary lesions are associated with worse clinical outcomes and DES implantation in this setting proved to be efficacious but entails a higher relative reduction of the vessel lumen, leading to poorer performances as compared to the treatment of large vessels.[34] The 2-year results of the all-comer DUTCH PEERS (TWENTE II) randomized trial confirmed that the treatment of small-vessel lesions was associated with higher rates of TLF, MI, and TVR,

TABLE 2 Study endpoints and definitions

Study endpoint	Definition
Primary endpoint	
Target lesion failure	Composite of cardiac death, target-vessel myocardial infarction, or ischemia-driven target lesion revascularization
Coprimary endpoint	
Net adverse cardiovascular events (NACEs)	Composite of all-cause death, myocardial infarction, ischemic stroke, and major bleeding
Secondary endpoints	
All-cause death	Composite of cardiac and noncardiac death
Cardiac death	Any death due to a cardiac cause (e.g., myocardial infarction, low-output cardiac failure, fatal arrhythmia), unwitnessed death, death of unknown cause, and all study procedure-related deaths, including those related to concomitant treatment
Ischemia-driven target lesion revascularization	Any repeat percutaneous coronary intervention (PCI) or bypass surgery of the target lesion (from 5 mm proximal and to 5 mm distal to the treated segment) due to the detection of a fractional flow reserve ≤0.80 or an instant wave-free ratio ≤0.89
Ischemic stroke	Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, with pathology or neuroimaging evidence of central nervous system infarction
Major bleeding	BARC type 3 or 5 bleeding
Myocardial infarction	Any acute myocardial injury (rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL) with clinical evidence of acute myocardial ischemia and with detection of at least one of the following: symptoms of myocardial ischemia; new ischemic ECG changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and identification of a coronary thrombus by angiography or autopsy
NACEs	Composite of all-cause death, myocardial infarction, ischemic stroke, and major bleeding
Procedural success	Successful delivery and inflation of the device at the intended target lesion with the achievement of final in-lesion residual stenosis of <30% (DCB) or <20% (DES) without the occurrence of target lesion failure within the hospital stay
Q-wave myocardial infarction	Any myocardial infarction with the development of pathological Q waves at ECG
Target vessel revascularization	Any repeat PCI or surgical bypass of any segment of the target vessel (defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself)
Target-vessel myocardial infarction	Any myocardial infarction not clearly attributable to a nontarget vessel
Vessel thrombosis	Vessel thrombosis included definite (angiographic or pathologic confirmation) and probable thrombosis (any unexplained death within the first 30 days or any myocardial infarction related to documented acute ischemia in the territory of the ballooned segment without angiographic confirmation of thrombosis and in the absence of any other obvious cause)

Abbreviations: BARC, Bleeding Academic Research Consortium; DCB, drug-coated balloon; DES, drug-eluting stent; ECG, electrocardiogram; URL, upper reference limit.

and independently predicted 2-year TLF.[35] These findings paved the way for a number of investigations about alternative strategies, including the use of DCB.

The PICCOLETO study tested a first-generation paclitaxel-coated balloon (PCB) in small coronary vessels and was prematurely discontinued because of the superior performance of the paclitaxel-eluting DES.[36] However, a subsequent analysis of the PICCOLETO study showed that PCB failure was mainly ascribable to the poor performance of the specific device tested and to the low rate of optimal lesion preparation.[37] The BELLO trial revealed that another PCB was associated with improved late loss and similar rates of restenosis and revascularization compared to the first-generation paclitaxel-eluting stent at 6 months, with a lower incidence of 3-year major adverse cardiac events (MACEs) and TLR.[38,39]

More recently, new-generation DCBs have been developed to improve the properties of trackability, deliverability, and drug release, especially in tortuous and small vessels. The BASKET-SMALL 2 trial demonstrated the noninferiority of a novel PCB to DES for the treatment of native vessel disease with a diameter <3 mm, with similar between-groups rates of MACE at 3 years.[24] Similar findings

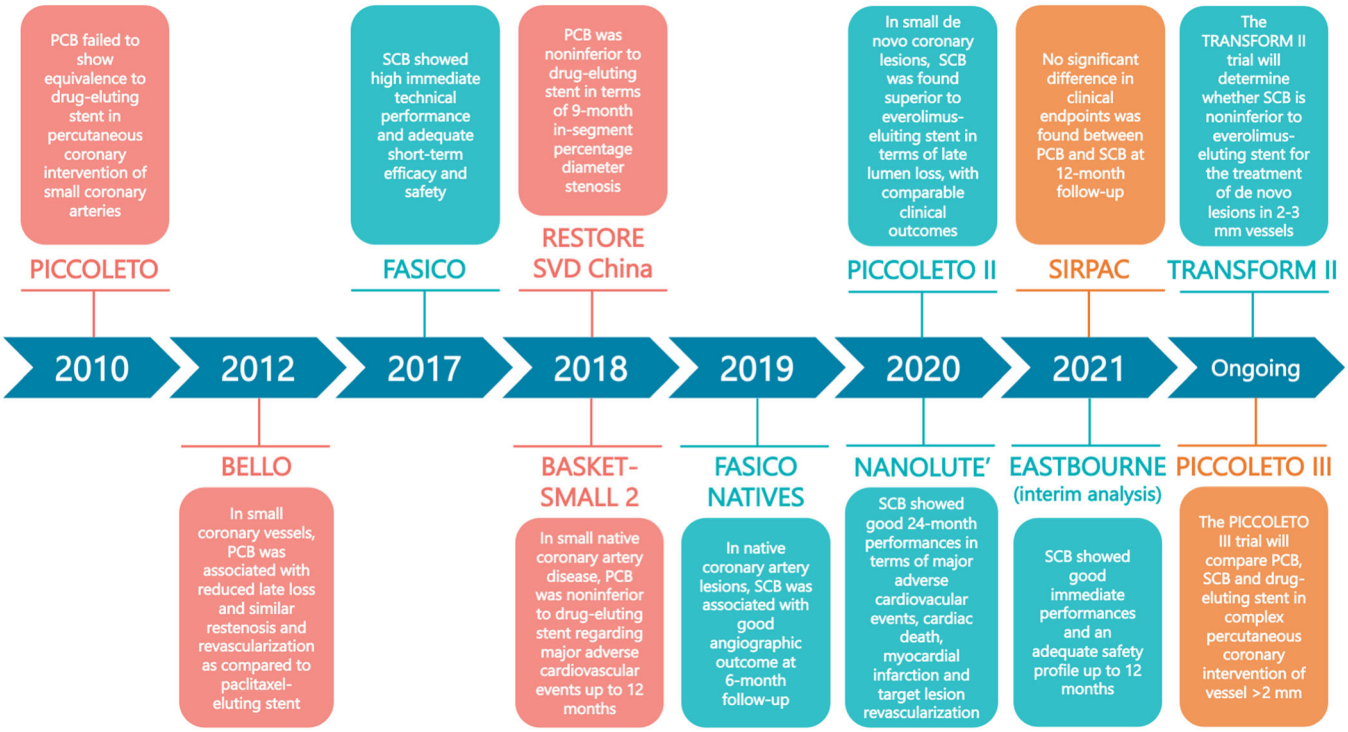

FIGURE 3 Evidence on drug-coated balloon in the treatment of de novo coronary lesion. PCB, paclitaxel-coated balloon; SCB, sirolimus-coated balloon. [Color figure can be viewed at wileyonlinelibrary.com]

were derived from the RESTORE SVD China trial, where PCB was noninferior to DES in terms of TLF for up to 2 years.[40] Finally, in the PICCOLETO II trial, a new-generation PCB was found to be superior to an everolimus-eluting stent for small-vessel disease angioplasty in terms of 6-month late lumen loss, with comparable clinical outcomes at 12 months.[41]

Paclitaxel has long been the drug of choice for DCB due to its easy processing and high lipophilic properties ensuring an adequate bioavailability. However, a major limitation of paclitaxel was its narrow therapeutic window, leading to a number of investigations on alternative drugs to be incorporated in DCB.[42] On this background, the evidence on the use of sirolimus was accruing, but its adoption was limited by its low lipophilicity.[43] To overcome this issue, the Nanoluté technology was developed, consisting in encapsulating sirolimus into a submicron lipophilic platform allowing optimal drug diffusion and penetration into the arterial wall during balloon inflation.[44]

The first study with the MagicTouch SCB was the FASICO, a single-center investigator-driven study that showed the safety and efficacy of MagicTouch SCB in a real-world all-comer population.[45] The FASICO NATIVES is a registry of consecutive patients with native vessel disease treated with the MagicTouch SCB, which showed a core-lab adjudicated late lumen loss of 0.09 ± 0.34 mm at 6 months.[46] In addition, an interim 1-year analysis of the all-comer EASTBOURNE registry, which enrolled 2125 patients with CAD, revealed the safety of the MagicTouch SCB, along with a good midterm performance.[47] Finally, the Nanoluté prospective registry confirmed a low 2-year rate of MACEs in patients undergoing PCI with the MagicTouch SCB.[48] Although the SIRolimus-PAClitaxel study did not show any difference between the latest-generation PCB and the MagicTouch SCB in terms of 1-year clinical outcomes, the optimal DCB treatment has not yet been established.[49] The PICCOLETO III randomized trial will perform a 3-arm comparison among the MagicTouch SCB, a new-generation PCB, and the latest-generation DES in the setting of complex coronary lesions.

No conclusive comparisons are available between the MagicTouch SCB and the latest-generation DES for the treatment of de novo lesions in coronary vessels with a diameter >2.0 and ≤3.0 mm so far. Although an all-comer study without any limitation in vessel size could be of high interest, it would add challenges in the involvement of sites and investigators to enroll such patients and randomize them to eventually undergo DCB-only PCI; we, therefore, used the same upper cutoff of the largest randomized trial on DCB, the BASKET-SMALL 2.[14] The TRANSFORM II, a randomized trial adequately powered for clinical endpoints at a long-term follow-up, will shed some light on the potentialities of this device.

4 | CONCLUSION

In the setting of small- and mid-sized vessel coronary lesions, PCI with DCB is a promising alternative to stent implantation. The MagicTouch SCB adopts a novel technology engineered to effectively

deliver sirolimus to the vessel wall, also aiming to overcome some inherent pharmacokinetic drawbacks of paclitaxel and sirolimus itself.

The randomized TRANSFORM II trial will determine whether the MagicTouch SCB is noninferior to a current-era everolimus-eluting stent, in terms of 12-month TLF and superior in terms of NACE at 1 year when adopted for the treatment of de novo lesions in coronary vessels with a diameter ≤3 mm.

If PCI with the MagicTouch SCB will prove to be noninferior to a DES-based strategy for de novo coronary lesions, this approach could be proposed as a first-line treatment to avoid long-term DES-related complications and to obtain the benefits of a "leaving nothing behind" strategy in this specific setting.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

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