Comparing a strategy of sirolimus-eluting balloon treatment to drug-eluting stent implantation in de novo coronary lesions in all-comers: Design and rationale of the SELUTION DeNovo Trial

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Background Drug eluting stents (DES) are associated with a 2% to 4% annual rate of target lesion failure through 5-to-10-year follow-up. The presence of a metallic protheses is a trigger for neo-atherosclerosis and very late stent thrombosis. A "leave nothing behind" strategy using Drug Coated Balloons has been suggested; however, paclitaxel coated balloons are only recommended in selected indications. Recently a novel sirolimus eluting balloon, the SELUTION SLR ™ 014 PTCA balloon (SEB) (M.A. MedAlliance SA, Nyon, Switzerland) has been developed.

Hypothesis A strategy of percutaneous coronary intervention (PCI) with SEB and provisional DES is non-inferior to a strategy of systematic DES on target vessel failure (TVF) at one and five years. If non-inferiority is met at 5 years, superiority will be tested.

Design SELUTION DeNovo is a multi-center international open-label randomized trial. Subjects meeting eligibility criteria are randomized 1:1 to treatment of all lesions with either SEB and provisional DES or systematic DES. Major inclusion criteria are PCI indicated for ≥1 lesion considered suitable for treatment by either SEB or DES and clinical presentation with chronic coronary syndrome, unstable angina or non-ST segment elevation myocardial infarction (NSTEMI). There is no limitation in the number of lesions to be treated. Target lesions diameters are between 2 and 5 mm. Major exclusion criteria are lesions in the left main artery, chronic total occlusions, ST segment elevation myocardial infarction and unstable non-ST segment elevation myocardial infarction. Three thousand three hundred twenty six patients will be included in 50 sites in Europe and Asia. TVF rates and their components will be determined at 30 days, 6 months and annually up to 5 years post-intervention. Among secondary endpoints, bleeding events, cost-effectiveness data and net clinical benefits will be assessed.

Summary SELUTION DeNovo trial is an open-label, multi-center international randomized trial comparing a strategy of PCI with SEB and provisional DES to a strategy of PCI with systematic DES on TVF at one and five years. Non-inferiority will be tested at one and five years. If non-inferiority is met at five years, superiority will be tested. (Am Heart J 2023;258:77–84.)

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Take home message: Rationale and design of the Selution De Novo trial which compares a strategy of percutaneous coronary intervention with drug eluting stents (DES) to a strategy of sirolimus eluting stents with DES

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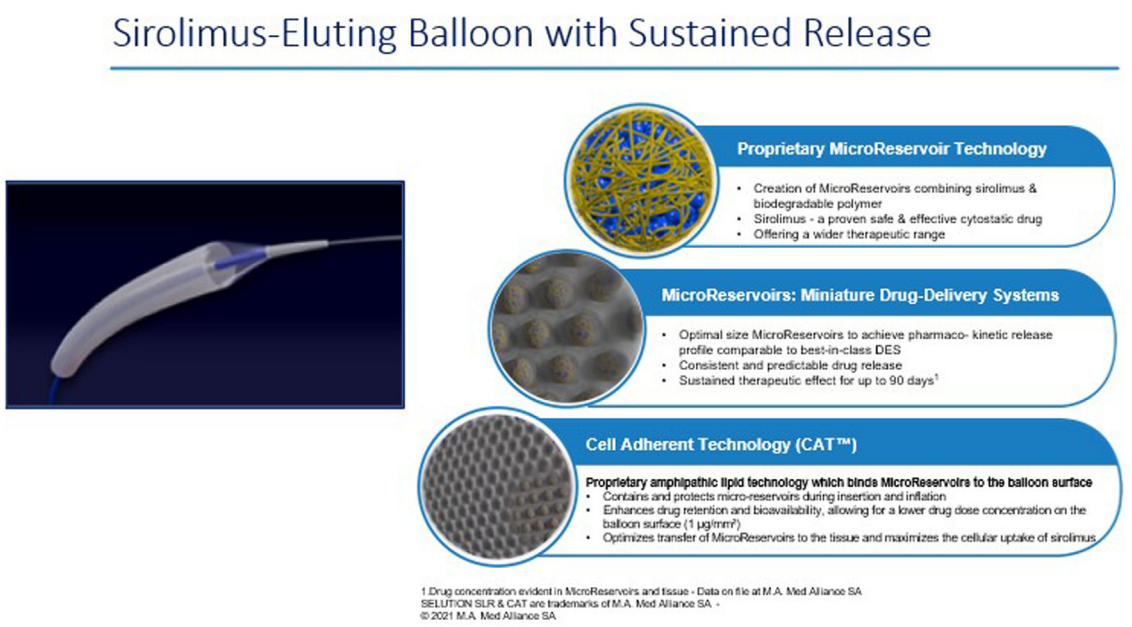
Background

Improvements in coronary stent design such as reduced strut thickness, enhanced polymer biocompatibility and/or resorption have improved short and mid-term clinical outcomes after drug eluting stent (DES) implantation. However, beyond the first year, long-term follow-up of registries and randomized trials have shown a 2 to 4% annual rate of target lesion failure similar to bare metal stents or first-generation DES.[1-3] The presence of a permanent metal scaffold prevents vasomotion and late lumen gain, and provokes inflammation, neo-atherosclerosis and may even be prone to stent fracture. This may contribute to a higher risk of restenosis or very late stent thrombosis. A "leave nothing be-

FIGURE 1



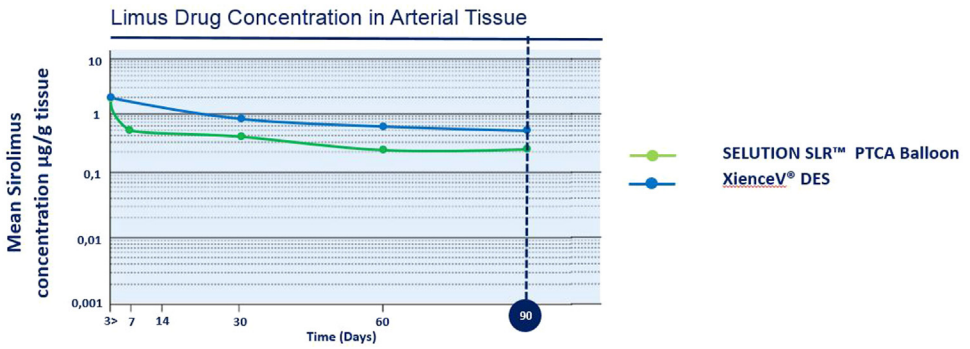
The SELUTION SLR 014 percutaneous transluminal coronary angioplasty (PTCA) balloon.

hind" strategy has been tested with bioabsorbable scaffolds with disappointing results.[4] Drug coated balloons (DCB) are semi-compliant balloons coated with an active drug embedded in a matrix. After inflation of the balloon, the drug is transferred to the vessel wall where the antiproliferative action takes place. Landmark randomized studies have demonstrated the effectiveness of DCBs in selected groups of subjects such as those with de novo lesions in small coronary vessels or in-stent restenosis (ISR) of DES.[5-18] Registries and small randomized trials suggest favorable results with DCBs in large vessels in selected patients.[19-24] However, no large, randomized study has compared DCB to DES in de novo coronary lesions regardless of vessel size.

Because of its lipophilicity, rapid tissue absorption, and durable tissue retention, paclitaxel was the initial drug of choice for balloon-mediated drug delivery. Paclitaxel produces a significant dose-dependent inhibition of neointimal hyperplasia and luminal encroachment in a pig model.[25] However, the bioavailability differs among DCBs currently on the market. One shortcoming of the available DCBs is the amount of the drug lost during preparation and delivery to the target lesion which may exceed 80% of the initially available loading dose on the first generation paclitaxel coated balloons.[26] Lost drug may cause particulate release, distal microembolization and downstream tissue ischemia and infarction. Compared to paclitaxel, sirolimus and related compounds are less cytotoxic, have a broader therapeutic window, and are more effective in inhibiting neointimal hyperplasia.[27] Low lipophilicity and poor tissue retention have limited the use of sirolimus in DCBs. Recently, a new Sirolimus Eluting Balloon, the SELUTION SLR^{TM} 014 percutaneous transluminal coronary angioplasty (PTCA) balloon (SEB) has been developed (Figure 1). The drug coating consists of Sirolimus as the active pharmaceutical ingredient. A biodegradable polymer (Poly-lactic-co-glycolic acid – PLGA) encapsulates Sirolimus into micro-reservoirs, which regulate drug release via matrix degradation. The micro-reservoirs are then sprayed onto the balloon surface and adhered to the balloon surface using a proprietary 3-component phospholipid blend. The drug coating is homogeneously distributed on the cylindrical surface of the balloon with a sirolimus concentration of 1 µg per mm² balloon surface. Retention of the drug on the balloon during preparation and delivery is high and the elution profile is similar to currently available limus DES. (Figure 2).

Lesion preparation using a step-by-step strategy has emerged as a pivotal determinant of DCB angioplasty. Jeger et al[28] summarized the most recent recommendations of the International DCB Consensus Group based on several pivotal studies. A key determinant of success was a ≤30% residual stenosis threshold after lesion preparation to continue with the DCB-only approach. Meticulous lesion preparation is thus highly rec-

FIGURE 2



Elution profile of the SELUTION SL 014 percutaneous transluminal coronary angioplasty balloon. Data on the elution of the SELUTION SLR 014 PTCA balloon on file at M.A. Med Alliance SA. Data on the elution of the Xience DES adapted from reference 33. DES, Drug Eluting Stent; PTCA, percutaneous transluminal coronary angioplasty balloon.

ommended. Provisional stenting with DES can be performed in case of excessive recoil, or flow-limiting dissections.

The Selution De Novo randomized trial will compare a strategy of PCI with SEB and provisional DES to a strategy of PCI with systematic DES. Patients will be randomized before vessel preparation.

Study objectives

Hypothesis

A strategy of percutaneous coronary intervention (PCI) with SEB and provisional DES is non-inferior to a strategy of systematic DES on target vessel failure (TVF) at 1 and 5 years. If noninferiority is met at 5 years, superiority will be tested.

Objectives

The primary objective is to demonstrate non-inferiority at one year for target vessel failure (TVF) of a treatment strategy with SEB and provisional DES versus systematic treatment with DES in PCI of de novo coronary lesions. TVF is a composite endpoint comprised of cardiac death, target vessel myocardial infarction or clinically driven target vessel revascularization.

The secondary objective is to demonstrate non-inferiority at five years for TVF between treatment strategies. If non-inferiority is achieved, a superiority test will be performed.

Study design and methods

Population and procedure

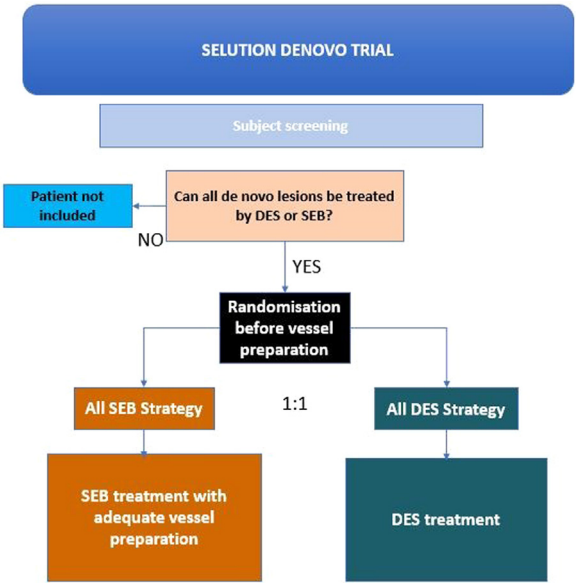
Eligible subjects will be randomized 1:1 to treatment of all lesions requiring PCI with either the SEB strategy or DES strategy. Subjects randomized to the SEB arm will receive lesion preparation according to the 3rd DCB consensus recommendation by Jeger and coworkers[28] (optimal balloon angioplasty with adjunct treatment using high-pressure balloon, lithotripsy, rotational atherectomy or cutting or scoring balloon at the discretion of the operator when necessary to maximize lumen diameter). Subjects with lesions that are then best treated by provisional stenting (flow-limiting dissection, residual stenosis $> 30\%$ or fractional flow reserve (FFR) < 0.8) before or after use of SEB will receive a DES but remain in the SEB group (intention-to-treat ITTanalysis). Subjects randomized to the DES arm will receive treatment with DES, as per standard institutional practice. Subjects with failure to deliver DES can be treated with any other device deemed appropriate, including SEB and will remain in the DES group (ITT analysis). Staged procedures are allowed if they are planned less than 45 days after the index procedure and are done according to the initial treatment allocation for all trial target vessels (SEB if SEB arm, DES if DES arm). Figure 3 shows the flow-chart and Figure 4 summarizes the trial

Main inclusion and exclusion criteria

The inclusion and exclusion criteria and definitions are listed in the supplemental appendix. The main inclusion criteria are patients with at least one native target vessel which is considered for intervention and is suitable for treatment of all lesions with either SEB and provisional stenting or with DES. Target vessels diameters are between 2 and 5 mm, and Thrombolysis in Myocardial Infarction flow 2 or 3. The number of trial target lesions is not limited. If the subject is randomized to the SEB arm, the estimated likelihood of provisional stenting of one or more identified trial target lesions should be less than 30% in the operator's opinion.

The main exclusion criteria are as follows:

FIGURE 3



Flow-chart of the SELUTION DeNovo trial. DES, Drug Eluting Stent; SEB, SELUTION SLR™ 014 PTCA balloon.

- Patients with ST segment elevation myocardial infarction (STEMI)
- Presentation with non-STEMI and ongoing chest pain or hemodynamic instability
- Previous PCI of a trial target vessel at any time
- Previous PCI of a non-trial target vessel within 30 days
- Trial target lesion is located in the left main or any arterial or venous graft
- Trial target lesion is a chronic total occlusion or an ISR
- Patient is not able to tolerate at least 30 seconds of coronary occlusion for each trial target lesion

Sample size calculation

Assuming a 1:1 randomization of SEB + provisional DES strategy vs the systematic DES strategy, a 15% event rate at 5 years in the DES arm and a 13% event rate at 5 years in the DEB arm, 3162 subjects will have 90% power to show non-inferiority in favor of SEB and provisional DES using an absolute non-inferiority margin of 2% and a Z-test at a one-sided alpha of 0.025.[3,29] To account for a 5% loss-to-follow up, 3326 subjects will be randomized. In case noninferiority at 5 years is met, the given sample size will have 80% power to show superiority at 5 years

FIGURE 4

OBJECTIVE	➢ To demonstrate that a strategy of PCI with SEB and provisional DES is non-inferior to a strategy of systematic DES on TVF at one and five years. If non-inferiority is met at 5 years, superiority will be tested.
DESIGN	➢ Prospective randomized open label trial comparing SEB with provisional DES strategy to systematic DES strategy ➢ 3326 patients ➢ 50 sites in Europe, Asia
ENDPOINTS	➢ Primary: TVF (cardiac death, target-vessel related MI or clinically driven TVR) **at 1 year** ➢ Secondary: TVF **at 5 years**
MAJOR INCLUSION AND EXCLUSION CRITERIA	➢ Inclusion ➢ All lesions considered for revascularization are suitable for treatment with either SEB and provisional DES stenting or with systematic DES. ➢ Target vessels diameters are between 2 and 5 mm with TIMI flow 2 or 3. ➢ The number of trial target lesions is not limited. ➢ Exclusion: ➢ STEMI, unstable NSTEMI, CTO, ISR, target lesion in left main or a graft ➢ Previous PCI of a trial target vessel at any time or of a non-trial target vessel within 30 days
FOLLOW-UP	➢ **30 days, 6 months, 1, 2, 3, 4 and 5 years**

Summary of the SELUTION DeNovo trial. CTO, Chronic Total Occlusion; DES, Drug Eluting Stent; ISR, In-Stent Restenosis; MI: myocardial infarction; NSTEMI, Non ST-Segment Elevation Myocardial Infarction; PCI, percutaneous Coronary Intervention; SEB, SELUTION SL 014 PTCA balloon; STEMI, ST-Segment Elevation Myocardial Infarction; TIMI, Thrombolysis In Myocardial Infarction; TVF, Target Vessel Failure; TVR, Target Vessel Revascularization.

in favor of SEB and provisional stenting assuming a 15% event rate at 5 years in the DES arm and a 11.5% event rate in the SEB arm.

Assuming that the event rate at 1 year in both treatment groups will be 6% with a 2% dropout rate, 3260 subjects will have 95% power to show non-inferiority using an absolute non-inferiority margin determined as 50% of the overall rate from both groups combined using a one-sided Z-test at a significance level of 0.025. Hence, assuming that the overall event rate will be 6%, a non-inferiority margin of 3% will be used. In case the overall event rate would be only 5%, a non-inferiority margin of 2.5% will be used and the power will drop to 90%. A minimum of 3326 subjects will be recruited at sites in Europe and Asia. It is anticipated that approximately 50 sites will participate in the study.

Statistical considerations

The hypothesis regarding the first primary clinical endpoint (TVF at 1 year) is formulated as follows:

$$H_0 : p_{A1} - p_{B1} \geq \delta_1 \text{ vs } H_1 : p_{A1} - p_{B1} < \delta_1$$

where p_{A1} and p_{B1} stand for the TVF event rate at one year (365 days) in the SEB and the DES group, respectively, and δ_1 for the non-inferiority margin. δ_1 will be set to 50% of the overall TVF event rate at 1 year. For instance, if the overall TVF rate at 1 year is 6%, the non-inferiority margin will be 3%. The hypothesis regarding the second primary clinical endpoint (TVF at 5 years) is formulated as follows:

$$H_0 : p_{A5} - p_{B5} \geq \delta_2 \text{ vs } H_1 : p_{A5} - p_{B5} < \delta_2$$

where p_{A5} and p_{B5} stand for the TVF event rate at 5 years (1,826 days) in the SEB and DES group, respectively. The non-inferiority margin δ_2 will be set to 2%. In case non-inferiority is shown at 5 years, the TVF event rate will be tested for superiority at 5 years.

The event rates for the primary endpoints at 1 and 5 years are to be determined from a cumulative incidence function in which non-cardiac death will be considered a competing risk. Subjects without an event will be censored at their last known visit date. The non-inferiority analysis will be performed on the full analysis set. The risk difference between the two treatment groups with a one-sided 97.5% confidence interval will be reported. If the upper limit of this interval falls below the non-inferiority margin, non-inferiority at 1 year will be claimed. In addition, a one-sided Z-test at a significance level of 0.025 will be reported. A per protocol analysis will be performed as a sensitivity analysis. The noninferiority analysis at 5 years will be performed similarly.

Primary analyses will be conducted according to the ITT principle meaning that subjects will be analyzed based on the treatment arm to which they were originally allocated to, irrespective of any crossing-over or treatment protocol violations. The primary analysis population is the full analysis set which includes all subjects randomized. Additionally, a per protocol (PP) analysis excluding major protocol violators will be used. The PP analysis set will be determined at a blinded review meeting before the analysis at 1 year will take place. Crossovers for one or more lesions are part of the strategy and allowed by the protocol and hence will not be considered protocol violations. The PP set will be used for sensitivity analyses. Descriptive statistics for baseline characteristics will be presented by treatment group.

Randomization

Subjects who satisfy all clinical and angiographic inclusion and exclusion criteria will be randomized in a 1:1 ratio to be treated for all the identified target lesions with either the SEB and provisional DES strategy or the systematic DES strategy. Each subject will receive one unique randomization number associated with a randomization assignment allocated via the study electronic data capture eCRF. To prevent bias, the blocks and randomization schedules will be predefined prior to the first study enrolment. Once randomized, the subject is considered enrolled in the trial and included in the ITT population. This includes subjects who are randomized but do not receive the SEB or treatments which are not in accordance with the randomization assignment.

Study procedure

Signed written informed consent is obtained for all subjects who are potential study candidates prior to enrolment and completion of index procedure requirements. Assessment of angiographic eligibility criteria is based on visual assessment of the pre-procedure angiogram.

Treatment procedure

Randomization will be done prior to the PCI procedure, ie, before lesion preparation. For subjects randomized to the SEB strategy, all target lesions should be treated with SEB after appropriate lesion preparation, but provisional DES implantation is acceptable if the angiographic result is considered insufficient either after lesion preparation or after SEB treatment (poor flow, dissection type C or higher, residual stenosis >30%). For bifurcation lesions, when both main and side-branch are considered to require treatment, SEB should be used for both.

For subjects randomized to the DES strategy, all target lesions should be treated with DES, but use of a SEB or any other device is acceptable if a DES cannot be delivered to the target lesion. For bifurcation lesions, if the side-branch requires treatment it should be treated with another DES or with plain balloon angioplasty, at the discretion of the operator. The procedure is considered completed when the subject leaves the catheterization laboratory.

When the operator considers it necessary, staging of the index procedure is allowed providing it is planned at the time of the index PCI, takes place within 45 days of the index PCI, and is completed according to the assigned strategy (either SEB and provisional DES or systematic DES). The staged procedure date will then become the date according to which the follow-up visits will be scheduled.

Follow-up visits and data gathering

After discharge, subjects will be contacted by telephone at 30 days, 6 months and then annually for a period of 5 years (supplemental appendix). In case the clinical situation warrants repeat coronary angiography at any time during the five-year follow-up, the angiogram will be uploaded for evaluation by the core laboratory. If target lesion revascularization is considered indicated based on clinical symptoms and visual assessment of a trial target lesion only, the use of fractional flow reserve (FFR) or instantaneous flow reserve (IFR) measurement is highly recommended. Target lesion revascularization should then only be performed when FFR is < 0.8 or IFR < 0.89.

Concomitant medication regimen recommendations

Prior, during and after the index procedure, antiplatelet medication is given according to guidelines,[30] the DCB consensus manuscript[29] and hospital practice.

Peri-procedural intracoronary imaging

Intracoronary imaging is allowed before and during vessel preparation in the DEB arm. Since there is no data on the improvement of outcomes with intracoronary imaging during PCI with DCB, the decision to cross over to stenting should be based on angiographic criteria according to the International DCB consensus[28] and not on intracoronary imaging.

Data collection and safety

All data will be collected in a pseudonymized way (coded) and stored in the Electronic Data Capture system (IBM Clinical Development [IBM-CD], from IBM Watson Health), which is FDA 21 CFR Part 11 compliant. All index and follow-up angiograms will be uploaded and stored in Decidemedical, Hüllhorst, Germany. The patient's data will be managed following European General Data Protection Regulation (EU) 2016/679. Trial organization, data management, Clinical Event Committee (CEC)/Data Safety Monitoring Board (DSMB) coordination, angiographic core laboratory and statistical analysis (in collaboration with the Department of Public Health and Critical Care, KU Leuven, Belgium) will be run independently by the CERC (European Centre for Cardiovascular Research, Massy, France). An independent multidisciplinary CEC will adjudicate all endpoint-related adverse events, and an independent DSMB will regularly assess the data to ensure the safety of the patients. The members of the CEC and DSMB are in the supplemental appendix. All data acquisition and analysis will be performed independently from the study sponsor.

The steering committee meets on a weekly basis to review the first SEB cases of each center and the cases where provisional DES stenting was performed. The steering committee is fully blinded to the accruing events in each arm. The list of the members of the steering committee is in the supplemental appendix

The trial is registered at http://www.clinicaltrials.gov with the unique identifier NCT04859985.

Ethical considerations

All relevant national and local ethics approvals are obtained prior to patient recruitment.

Timelines and current status

The first patient was enrolled on May 15, 2021. On January 4, 2023, 786 patients had been included in the trial. Enrollment is expected to be complete on December 31, 2023. The estimated primary completion date and estimated study completion date are January 1, 2025 and January 1, 2029 respectively.

Discussion

The SELUTION DeNovo trial is an open label multicenter international randomized trial comparing a strategy of PCI with SEB and provisional DES to a strategy of PCI with systematic DES. To our knowledge, this is the largest randomized trial performed with DCBs.

Current data on DCBs is limited to selected patients including ISR and small vessels. There is no limitation to vessel size in our trial provided the lesions can be treated with both techniques. Eligibility criteria are broad, encompassing all clinical situations except those requiring urgent revascularization (STEMI, unstable NTEMI). Angiographic exclusion criteria are limited to left main lesions, chronic total occlusion, and lesions in venous and arterial grafts. The results of this "all comer' trial will therefore be applicable to daily clinical practice.

Randomization will be performed before vessel preparation. Our trial is therefore a comparison of two strategies and not a comparison between devices which contrasts with previous studies on DES and DCB and with the on-going TRANSFORM II randomized trial.[6,31] Our strategy comparison mirrors clinical practice and the information gathered (devices used for vessel preparation, residual stenosis before the use of SEB or DES, provisional DES rate) will be of utmost importance in the future for planning and performing PCI with DCBs.

The SELUTION SLR™ 014 PTCA balloon is a novel DCB with a unique elution profile. Initial data on the use of this device in denovo lesions and ISR are encouraging.[32] Our large, randomized trial will bring major information which will not necessarily be applicable to other DCBs

Despite a wealth of clinical data in de novo native coronary artery disease, the current ESC guidelines[30] limit indication for DCB angioplasty to ISR with a class 1A recommendation. The results of our trial are most likely to impact on guidelines and the use of SEBs in routine practice.

Limitations

Within the nature of any clinical trial, there are several limitations, which must be mentioned. First, the DES strategy treatment arm does not prescribe one particular DES, which may introduce additional variability. However, this closely resembles the clinical reality in the participating centers on a global scale. In addition, participating centers must have experience in DCB angioplasty, which cannot be universally assumed. Lesion preparation is not required in the DES strategy, which may negatively influence the results. However, our trial will provide major information on current vessel preparation before DES implantation and clinical outcomes. Since randomization is performed before vessel preparation, our study compares 2 strategies and not 2 devices. Target vessels of more than 2.5 mm of diameter are included. Our study is not powered to assess the efficacy of the DEB in this subgroup but will gather important information, which may trigger dedicated large randomized trials in this setting.

Conclusion

The SELUTION DeNovo trial is a randomized trial comparing a PCI strategy with SEB and provisional DES to a strategy of PCI with systematic DES implantation. A total of 3326 patients will be included. Non-inferiority for TVF will be tested at 1 and 5 years. If non-inferiority is met at 5 years, superiority will be tested**.** The results of this strategy comparison with broad eligibility criteria will potentially have a major impact on PCI practice.

Author Contributions

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Disclosures

Christian Spaulding reports personal fees from Medtronic, Minnesota, USA, Abbott, Illinois, USA, Edwards, California, USA, Techwald, Italy, The European Cardiovascular Research Center (CERC), France and travelling expenses from MedAlliance, Switzerland. He is a shareholder of Techwald, Valcare, and MedAlliance,

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Philip Urban reports personal fees from Biosensors, Switzerland, from MedAlliance, Switzerland, and from the European Cardiovascular Research Center (CERC), France. He is a shareholder of MedAlliance.

Susanne Meis is a full-time employee of MedAlliance, Switzerland.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.01.007.

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