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The CERC Chronicle

Special Edition – May 2024

Exploring the Potential of Drug-Coated/Eluting Balloons: A Focus on Some of the Most Impactful Clinical Trials: SELUTION DeNOVO, REVERSE, TRANSFORM II, and MAGICAL SV

Introduction to DCB/DEB "Revolution"

Welcome to the **Special Edition of CERC Chronicle**, dedicated to exploring the latest advancements and insights into the dynamic research of DCB/DEB. We are thrilled to present a compilation of cutting-edge research that will shed light on the transformative potential of DCBs in Percutaneous Coronary Interventions (PCI), either for indications or geographic availability.

The fundamental principle behind DCBs lies in their ability to deliver therapeutic agents directly to the site of arterial lesions, thereby mitigating restenosis and enhancing vessel patency.

DCBs have transformed endovascular procedures with the "Leave nothing behind" approach, turning diffusely infiltrated metallic conduit into a well-functioning artery. While the concept is promising, we must discern the right patient and timing for its use through rigorous clinical trials.

We extend our gratitude to all contributors to this edition of CERC Chronicle. We trust readers will appreciate a comprehensive summary of these trials in one place though we regret not being able to cover all ongoing trials with potential significant impact.

SELUTION DeNovo Clinical Trial

By Steering Committee of SELUTION DeNovo Trial

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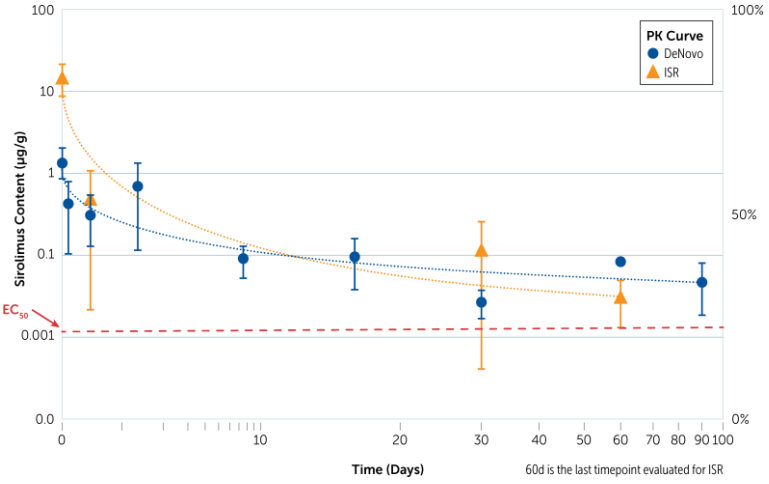
The **SELUTION DeNovo** steering committee is proud of working with CERC on a unique trial with a new drug-eluting balloon (DEB).

Limus drugs are the most widely used for stent-mediated drug delivery, whereas Paclitaxel dominates balloon-mediated delivery. Whilst Sirolimus is more effective in inhibiting neointimal hyperplasia, tissue delivery and retention challenges have so far limited its use in DEBs. The SELUTION SLR™ sirolimus-eluting balloon (SES, MedAlliance/Cordis) successfully addresses these issues. Sirolimus is encapsulated with PGLA into micro-reservoirs which adhere to the balloon surface using a proprietary 3-component phospholipid. Retention of the drug on the balloon during preparation and delivery is high and the concentration in the arterial wall resembles currently available limus-eluting stents (Figure 1).

The SELUTION DeNovo (NCT04859985) compares two strategies: PCI with a SELUTION SLR SEB substituted or followed, when necessary, by implantation of a drug-eluting stent (DES) versus PCI with DES. 3326 patients are planned at more than 50 sites in Europe and Asia. Non-inferiority for TVF will be tested at 1 and 5 years and if achieved, superiority of the SES strategy will be tested at five years. Thanks to the investigator's hard work, we are close to the end of enrollment, with 2778 patients included on May 2nd 2024. Up until now, randomized trials on DEBs have included patients after vessel preparation. In SELUTION DeNovo, patients are randomized before the procedure and selection criteria are broad, excluding only unprotected left main, STEMI and CTO. A high rate of multivessel, complex lesions have been included. The results of this « all comer » study should have major implications on clinical practice.

Figure 1. Pharmacokinetics: Arterial Tissue

Sirolimus concentration in treated coronary arteries: DeNovo and ISR (without BLQ values)

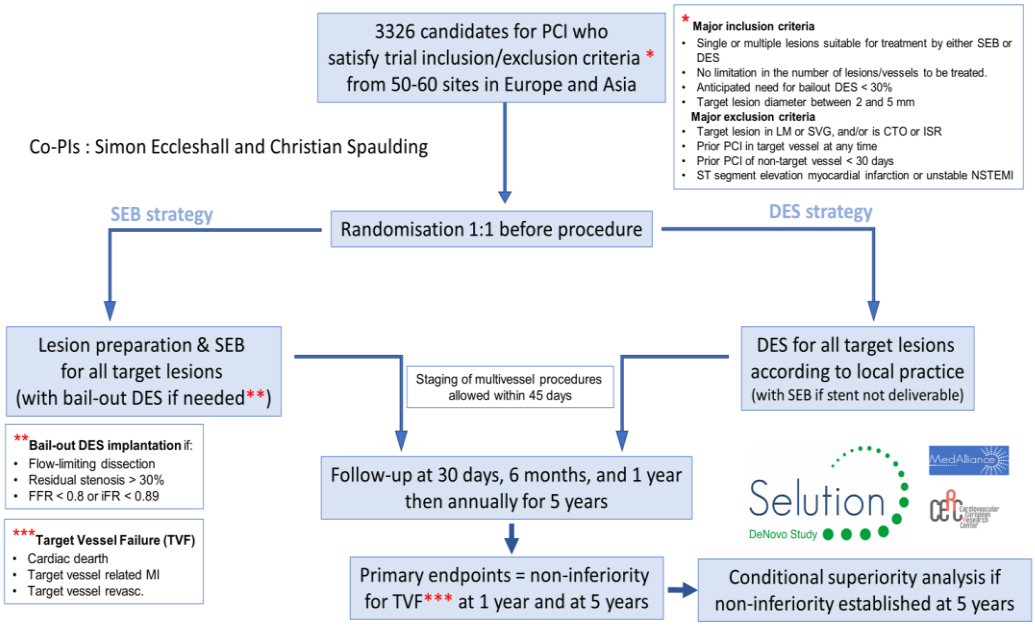


MedAlliance data on file (TRO339); Virmani R, Farb A, Kolodgie FD. Histopathologic alterations after endovascular radiation and antiproliferative stents: similarities and differences. Herz 2002; 27:1–6

Dear Investigators, study teams, industry partners, and friends, the CERC team is looking forward to seeing you!

Come and meet us
CERC Booth M6 Level 2

SELUTION DeNovo – Study Flow



PCI: Percutaneous Coronary Intervention; SEB: Selution Eluting Balloon; DES: Drug Eluting Stent; LM: Left Main; SVG: Saphenous Vein Graft; CTO: Chronic Total occlusion; ISR: In-Stent Restenosis; NSTEMI: Non-ST Segment Elevation Myocardial Infarction; FFR: Fractional Flow Ratio; iFR: instantaneous Flow Ratio; TVF: Target Vessel Failure

REVERSE – DCB leading back to the future of PCI

By Eun-Seok Shin and Philip Steen

The REVERSE trial (NCT05846893) is an international, randomized, multi-center study that evaluates the efficacy of the benchmark drug-coated balloon technology (SeQuent® Please NEO) in comparison to the latest generation of drug-eluting stents for the treatment of large vessel (≥3.0 mm) de novo coronary artery disease (CAD). This pioneering study, sponsored by B.Braun, is a collaborative effort with the Asia Pacific DCB consensus group, led by Chief Principal Investigator Professor Eun-Seok Shin, and CERC serving as the global CRO.

The **REVERSE trial** is actively enrolling and plans to randomize 1,436 patients (1:1) in South Korea, Malaysia, Singapore, and Taiwan.

Patients are randomized after successful lesion preparation and with its deliberate inclusion of patients with multi-vessel disease, the trial will gain important scientific evidence on this frequently underrepresented population. in a broader range of indications and a greater incorporation of this technology into clinical routine.

The primary endpoint of the study is the rate of net adverse clinical events (NACE), a composite including all-cause death, non-fatal myocardial infarction, clinically driven target vessel revascularization, or major bleeding (BARC type 3 to 5) within 12 months.

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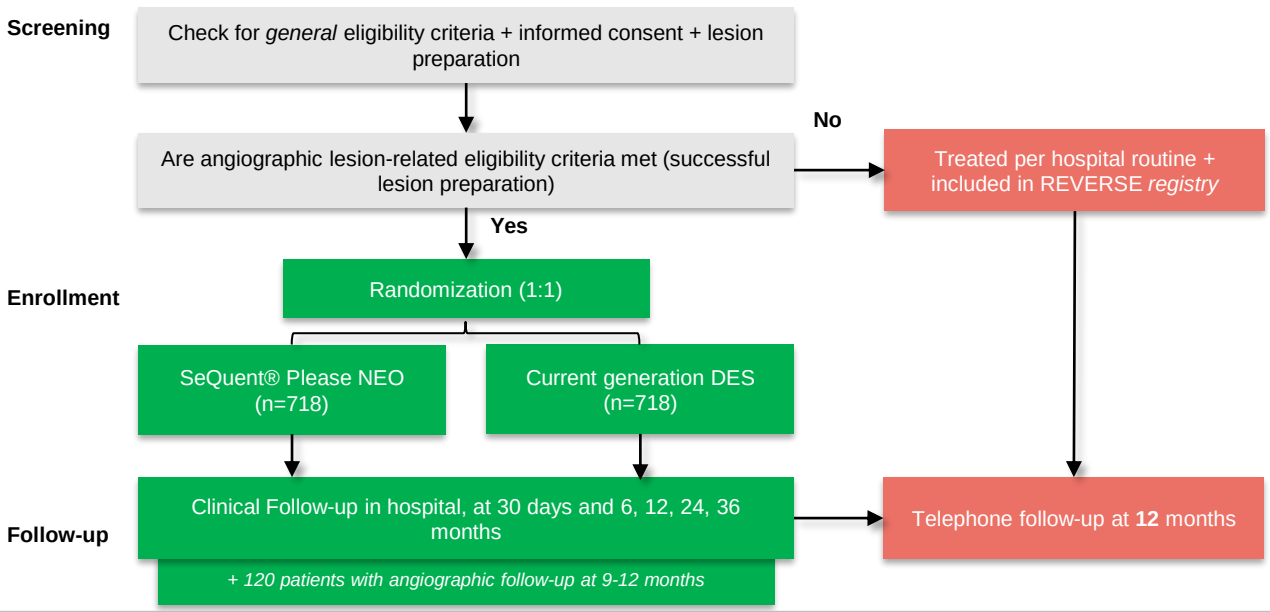
Simplified REVERSE Study Flow



REVERSE Trial continued…

Additionally, a pre-specified subgroup of 120 patients will undergo angiographic follow-up to assess angiographic endpoints at 9 to 12 months.
Patients who are not suitable for randomization will be included in the REVERSE registry, which is an observational sub-study to collect further real-world clinical data and to provide insights into the clinical outcomes in addition to data collected from the randomized study arms.
The REVERSE trial is positioned to significantly contribute to the optimization of future treatment strategies in interventional cardiology, offering important insights into the future role of DCB technology in a broader range of indications and a greater incorporation of this technology into clinical routine.
In summary, REVERSE clearly addresses current evidence gap in the treatment of de novo large vessel disease by providing randomized controlled trial data and is posed offer a more comprehensive understanding of using DCB in real-world clinical practice.

Fondazione Ricerca e Innovazione Cardiovascolare

TRANSFORM II Clinical Trial

TRANSFORM II

By Sylwia Iwanczyk & Bernardo Cortese on behalf of Transform II Investigators

TRANSFORM II is an investigator-initiated, multicenter, noninferiority, randomized clinical trial (NCT04893291) that aims to evaluate the efficacy of a sirolimus-coated balloon (MagicTouch SCB, Concept Medical, USA) compared to new-generation everolimus-eluting stent in the treatment of native coronary vessels. The study promoter is Fondazione Ricerca e Innovazione Cardiovascolare, Milano, Italy.
The primary endpoint of the study is Target Lesion Failure at 12 months, where non-inferiority is expected. As a coprimary endpoint, the superiority of SCB to EES in the 12-month reduction of net adverse cardiovascular events will be evaluated.
The study includes patients with native coronary artery lesions in vessels with diameter >2.0 mm and ≦3.5 mm at visual estimation and maximum lesion length of 50 mm. Main exclusion criteria encompass a creatinine clearance <30 ml/min, a left ventricular ejection fraction <30%, prior stent implantation at the target vessel, a target lesion in the left main stem, and an ST-segment elevation myocardial infarction diagnosis in the previous 48 h. Important, patients can be randomized only after successful lesion preparation. Moreover, in high-volume OCT centers the intracoronary imaging substudy of the first 70 patients undergoing invasive imaging substudy of the first 70 patients undergoing invasive coronary angiography and OCT at a 9-month follow-up will be conducted.
The sample size to encounter the 1-year non-inferiority was calculated for 1825 patients. Another important point is the fact that patients will be followed up for 5 years, and also according to the recent ANDROMEDA meta-analysis (B. Cortese et Al., CRT 2024 LBCT), a possible reduction in hard clinical endpoints could be expected with DCB on the long term.
The study is currently ongoing at 45 sites across Europe (Italy, the Netherlands, Spain, UK, France and Poland), Asia (Bangladesh, Malaysia, Thailand and Brunei) and Brasil, and has enrolled **>50%** of the expected patient population. Drug-coated balloons are emerging as an alternative approach to fulfill the **"leaving nothing behind"** principle and avoid long-term DES-related complications. **TRANSFORM II** study could propose SCB as a first-line treatment in native vessel disease to obtain the benefits of a stentless strategy in the native coronary arteries. Importantly, this study will directly compare a SCB approach vs a DES one, since randomization is carried out after adequate lesion preparation, with any available tool.

TRANSFORM II– Study Flow

PI: Dr. Bernardo Cortese

MAGICAL SV Clinical Trial

By Concept Medical

The MAGICAL SV (NCT06271590) is an FDA IDE trial conducted in the US and Europe. It is a prospective, randomized, two-arm, single-blind, non-inferiority trial to evaluate the safety and efficacy of the MagicTouch™ Sirolimus-Coated Balloon in the treatment of small vessel coronary stenosis.

The study evaluates the safety and efficacy of the Magic Touch™ Drug-Coated Balloon in treating small vessels (≤2.75 mm). Concept Medical INC sponsors the study, and the Cardiovascular Research Foundation (CRF) is responsible for data management and clinical management. Cardiovascular European Research Center (CERC) is the CRO for the European sites, and Cogentech is the CRO for the sites in the United States of America.

The study is chaired by Dr. Martin Leon, and the study PIs are Dr. Azeem Latib and Dr. Ajay Kirtane.

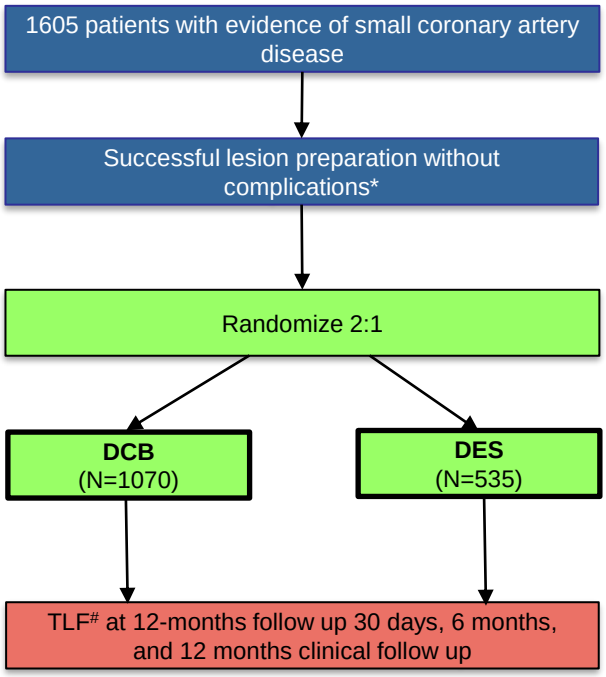
The study plans to randomize 1605 patients (2 Magic Touch: 1 DES) in the US, France, Italy, Switzerland, the United Kingdom, Spain, the Netherlands, Germany, and Poland. Patients are randomized after successful lesion preparation.

The primary endpoint of the study is the rate of target lesion failure (TLF), defined as the composite of cardiovascular mortality, target-vessel myocardial infarction (TVMI), and ischemia-driven target lesion revascularization within 12 months.

In summary

The MAGICAL-SV trial is expected to provide important insights into the future role of DCB technology. Through this randomized study, it could lead to greater incorporation into clinical practice. The trial results are expected to contribute significantly to optimizing future treatment strategies in interventional cardiology in the USA and Europe.

MAGICAL SV– Study Flow



*Adequate lesion preparation described in further in trial protocol

#Primary end point of TLF(Target Lesion Failure): Cardio-Vascular Death, Target Vessel Myocardial Infarction, Ischemia driven Target Vessel Revascularisation

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