HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Percutaneous transluminal coronary angioplasty (PTCA) with drug-eluting balloon (DEB) in patients with coronary artery disease (CAD)

3. Update 2024
Systematic Review

AIHTA Decision Support Document: 24/3 Update 2024
ISSN-online: 1998-0469

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Percutaneous transluminal coronary angioplasty (PTCA) with drug-eluting balloon (DEB) in patients with coronary artery disease (CAD)

3. Update 2024
Systematic Review

Vienna, March 2024

Project Team

Project leader: Gregor Goetz, MSSc MPH; AIHTA

Authors: Univ. Ass. Mag. rer. nat. Thomas Semlitsch &
Cornelia Krenn, MSc; Institute of General Practice and Evidence-Based Health Services Research, Medical University of Graz

Project Support

Systematic literature search: Tarquin Mittermayr, MA; AIHTA

External Review: PD Dr. Markus Stühlinger, Interne Medizin III, Kardiologie, Universitätsklinik, Innsbruck

Internal Review: Priv. Doz. Dr.phil. Claudia Wild, AIHTA

Correspondence: Gregor Goetz, MSSc MPH, Gregor.Goetz@aihta.at

This report should be referenced as follows:

Semlitsch, Th., Krenn C. Percutaneous transluminal coronary angioplasty (PTCA) with drug-eluting balloon (DEB) in patients with coronary artery disease (CAD). AIHTA Decision Support Documents No. 24/3. Update 2024; 2024. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: [HTA Core Model®, Version 4.2]. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr. phil. Claudia Wild, managing director

AIHTA Decision Support Documents do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 24/3 Update 2024

ISSN online 1998-0469

Content

List of figures

List of tables

List of abbreviations

AP.....angina pectoris
BMS.....bare metal stent
CABG.....coronary artery bypass craft
CHD.....coronary heart disease
CI.....confidence interval
CRD .....Centre of Review and Dissemination
DCB/DEB .....drug-coated balloon/ drug-eluting balloon
DES .....drug-eluting stent
EACTS .....European Association for Cardio-Thoracic Surgery
EES.....everolimus-eluting stent
EP .....Endpunkt
ESC .....European Society of Cardiology
EQ-5D .....European quality of life-5 dimensions
GoR .....grade of recommendation
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HrQoL.....health-related quality of life
HTA .....Health Technology Assessment
ICD .....International Statistical Classification of Diseases and Related Health Problems
ICH .....International Conference of Harmonization
ISR.....in-stent restenosis
LLL .....late lumen loss
LoE.....level of evidence
MACE .....major adverse cardiac event
MI.....myocardial infarction
MLD .....mean lumen diameter
OR .....odds ratio
PCI .....percutaneous coronary intervention
PEB .....paclitaxel-eluting balloon
PES.....paclitaxel-eluting stent
POBA .....plain old balloon angiography
PTCA .....percutaneous transluminal coronary angioplasty
RCT.....randomized controlled trial
RoB.....risk of bias
ROBIS.....risk of bias in systematic reviews
RR .....risk ratio
RVD .....reference vessel diameter
SAE .....serious adverse event
SD.....standard deviation
SEB.....sirolimus-eluting balloon
SES .....sirolimus-eluting stent
SF-36.....Short form 36
SR.....systematic review
STEMI .....ST-elevation myocardial Infarction
SVD.....small vessel disease
TLR.....target lesion revascularization
TVR.....target vessel revascularization
vs .....versus
WHO-ICTRP .....World Health Organization – International clinical trial register platform

Executive Summary

Introductio

This report is the third update of the systematic review on "Medikamenten-beschichteter Ballonkatheter" initially prepared in 2009 and updated in 2013 and 2016.

3rd Update of 2009, 2013 and 2016 report

Health Problem

Cardiovascular diseases such as atherosclerosis often lead to partial (stenosis) or complete blockage (occlusion) of blood vessels. Atherosclerosis is a narrowing of the blood vessels due to deposits of blood fats, connective tissue, calcium, or even blood clots. The leading symptom is angina pectoris (AP), but also cardiac arrhythmias, heart failure, myocardial infarction and sudden cardiac mortality. Coronary heart disease is the most common cause of death in developed countries. It mainly affects older people aged 65 and over and to date it has affected more men than women.

atherosclerosis: Narrowing of coronary vessel due to deposition or damage

Description of Technology

The main purpose of a percutaneous transluminal coronary angioplasty (PTCA) is to relieve AP symptoms and to prolong life expectancy, and to avoid more invasive interventions such as coronary artery bypass grafting (CABG). Beside stent implantation also drug-eluting balloon (DEB) catheters can also be used for treatment. DEB are designed to deliver a high concentration of an anti-proliferative agent to the vessel wall of the target lesion to inhibit vasoconstriction. The two antiproliferative agents currently used in DEBs are paclitaxel and sirolimus.

PTCA with DEB

Methods

This update report compares the efficacy and safety of PTCA with DEB to uncoated balloon catheters (plain old balloon angiography/POBA) or drug-eluting stents (DES) in patients with in-stent restenosis (ISR), de novo lesions, small vessel disease (SVD), or ostium stenosis.

A focused literature search for systematic reviews was conducted in MEDLINE, to identify at least one up-to-date high quality systematic review that can be used as primary source for relevant randomized controlled trials (RCTs). A supplementary search for RCTs was conducted in three bibliographic databases for time periods not covered by the systematic reviews. In addition three clinical trial registries were search for unpublished or ongoing trials. The study selection, data extraction and assessing the methodological quality of the studies were performed by two review authors independently from each other. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. For the rating of the quality of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used.

focused literature search for systematic reviews

additional systematic search for RCTs

quality of evidence according to GRADE

Domain efficacy

The following efficacy-related outcomes were used as evidence to derive a recommendation: AP symptom relief, avoidance of CABG, revascularization rates (target lesion revascularization/TLR; target vessel revascularization/TVR), and health-related quality of life (HrQoL).

efficacy: AP symptoms, revascularization, HrQoL

Domain safety

The following safety-related outcomes were used as evidence to derive a recommendation: overall mortality, cardiac mortality, major cardiac adverse events (MACE), myocardial infarction (MI), stent thrombosis, and serious adverse events (SAE).

safety: mortality, MACE, MI, stent thrombosis, SAE

Results

Available evidence

Two recently published systematic reviews on DEB in patients with ISR and three systematic reviews on DEB in patients with de novo coronary lesions including patients with SVD were included as basic information sources in this update report. Six additional RCTs were identified through supplementary database search and hand search. All together 14 RCTs could be included in the analyses for DEB versus POBA or DES in patients with ISR, 29 RCTs in the analyses for DEB versus POBA or DES in patients with de novo lesions irrespective of vessel diameter, and 10 RCTs in the analyses for DEB versus POBA or DES in patients with SVD. No systematic reviews or RCTs could be identified for PTCA with DEB in patients with ostium stenosis.

DEB for ISR:
2 SR; 14 RCTs

DEB for de novo:
2 SR; 29 RCTs

DEB for SVD:
2 SR; 10 RCTs

Clinical efficacy

There were no results for the efficacy outcomes AP symptom release, avoidance of CABG, and change in HrQoL in any of the included RCTs.

efficacy: no results for AP symptoms, avoidance of CABG, and HrQoL

In patients with ISR, PTCA with DEB showed statically significant lower revascularization rates (TLR and TVR) in comparison to POBA, but no difference in comparison to DES during long term follow-up up to 10 years.

ISR: TLR and TVR lower compared to POBA; no difference compared to DES

In patients with de novo lesions irrespective of vessel diameter, PTCA with DEB in comparison to POBA showed statically significant lower TLR rates, but no difference in TVR rates. Comparted to DES implantation, PTCA with DEB showed higher TLR and TVR rates in long term follow-up up to three years.

de novo: TLR lower compared to POBA; higher compared to DES

In the subgroup of patients with SVD, PTCA with DEB compared to PTCA with an uncoated balloon, showed statically significant lower TLR rates in a follow-up up to three years, but no difference in TVR rates. Compared to DES implantation, there were no statistically significant differences in the revascularization rates.

SVD: TLR lower compared to POBA; no difference compared to DES

Safety

In patients with ISR, PTCA with DEB showed statically significant lower MACE rates in comparison to POBA, but no differences in overall or cardiac mortality, MI, or stent thrombosis during long term follow-up up to 10 years. Comparted to DES implantation, there was no statistically significant differences in any of the investigated safety outcomes – death, MACE, MI, and stent thrombosis – during 10 years follow-up.

safety:
ISR: no difference in mortality; MACE lower compared to POBA; no difference compared to DES

In patients with de novo lesions irrespective of vessel diameter, PTCA with DEB in comparison to POBA or in comparison to DES showed no statically significant differences in any of the investigated safety outcomes – death, MACE, MI, and stent thrombosis – during three years follow-up.

de novo and SVD: no difference in MACE or mortality compared to POBA or DES

In the subgroup of patients with SVD, PTCA with DEB in comparison to POBA or in comparison to DES showed no statically significant differences in any of the investigated safety outcomes – death, MACE, MI, and stent thrombosis – during three years follow-up.

Upcoming evidence

There are six RCTs listed in clinical trial registries, investigating PTCA with DEB versus PTCA with POBA or DES implantation in patients with ISR. Estimated primary completion dates range from 10/2023 to 09/2025. 14 additional RCTs are listed for the comparison of the PTCA with DEB versus PTCA with POBA or DES implantation in patients with de novo coronary lesions. Estimated primary completion dates of these trials range from 11/2022 to 05/2027. No ongoing RCT could be identified for PTCA with DEB versus PTCA with POBA or DES implantation in patients with ostium stenosis.

6 ongoing RCTs for ISR
14 ongoing RCTs for de novo

Evidence-based conclusion

According to the available evidence, in patients with ISR, the evaluated technology PTCA with DEB is shown to be more effective and safe than the comparator PTCA with POBA, and comparably effective and safe than the comparator DES implantation. The certainty of the evidence for these comparisons is largely moderate. For patients with de novo lesions, the evaluated technology PTCA with DEB is shown to be more effective and safe than the comparator PTCA with POBA, but less effective and equally safe than the comparator DES implantation. The certainty of the evidence for these comparisons is low to moderate. Overall, the evidence base does not appear sufficient for a conclusive judgement of the efficacy and safety of PTCA with DEB in comparison to PTCA with POBA or DES implantation in patients with SVD. New study results will potentially influence the effect estimate considerably. For patients with ostium stenosis no evidence from RCTs is currently available.

ISR: DEB more effective and safe than POBA and equally effective and safe as DES

de novo: DEB more effective and safe than POBA but less effective and equally safe than DES

SVD: evidence not sufficient

Therefore, the current evidence indicates an added benefit only in specific indications. A re-evaluation for de novo lesions and small vessel disease is recommended in 2027.

conclusion: added benefit only in specific indications

Zusammenfassung

Einleitung

3. Update der 2009, 2013 und 2016 Berichte

Dieser Bericht ist das dritte Update des systematischen Reviews „Medikamentenbeschichteter Ballonkatheter“, der erstmals im Jahr 2009 vom Ludwig-Boltzmann-Institut für Health Technology Assessment im Auftrag des österreichischen Bundesministeriums für Gesundheit und in Kooperation mit dem Medizinischen Dienst des Spitzenverbandes/MDS (Deutschland) erstellt wurde und in den Jahren 2013 und 2016 aktualisiert wurde.

Indikation und therapeutisches Ziel

Arteriosklerose: Verengung der Gefäße durch Ablagerungen oder Beschädigungen

wesentliches Symptom: Angina Pectoris

Kardiovaskuläre Erkrankungen wie Arteriosklerose führen häufig zu teilweisen (Stenosen) bzw. vollständigen Verschlüssen (Okklusion) von Blutgefäßen. Bei Arteriosklerose handelt es sich um eine Verengung der Gefäße durch Ablagerungen von Blutfetten, Bindegewebe, Kalk oder auch Thromben. Arteriosklerose im Bereich der Herzkranzgefäße wird auch mit dem Begriff Koronare Herzkrankheit (KHK) bezeichnet. Ein wesentliches Symptom der KHK ist die Angina Pectoris (AP), welche durch Brustschmerzen die meist durch körperliche Belastung oder Stress auslösbar sind, gekennzeichnet ist. Eine okkludierende Veränderung, etwa im Bereich der Herzkranzarterien, hat eine mangelhafte Sauerstoffversorgung des Herzmuskels zur Folge und kann zu einem akuten Myokardinfarkt oder auch zu chronisch-ischämischer Herzkrankheit führen.

Behandlung: Medikamente, PCI oder Bypass-Operation

Zur Behandlung einer KHK stehen neben einer medikamentösen Therapie grundsätzlich auch die Bypass-Operation als chirurgische Maßnahme, sowie die perkutane Koronarintervention (PCI) mit Stent Implantation mittels Herzkatheter zur Verfügung.

Die therapeutischen Ziele einer PCI bei Patient*innen mit KHK sind es, Symptome zu lindern und die Lebensqualität zu steigern, kardiale Folgeerkrankungen und invasivere Eingriffe in Form von CABG zu vermeiden sowie die Lebenszeit zu verlängern.

In-Stent-Restenosen: neuerliche Verengung nach Stent Implantation

Bei der Behandlung mittels Stent Implantation, kann es trotz des Einsatzes moderner medikamentenfreisetzender Stents bei bestimmten Patientengruppen zum einer neuerlichen Verengung des Gefäßes – einer In-Stent-Restenosen (ISR) – kommen. In-Stent-Restenosen haben eine erhöhte Morbidität nach Stentimplantation zur Folge.

Beschreibung der Technologie

DEB mögliche Alternative zu Stent

Neben der PCI mit Stent Implantation, können zur Behandlung können auch nicht beschichtete oder medikamentenbeschichtete Ballonkatheter eingesetzt werden. Diese stellen vor allem an Stellen, wo Stents nicht eingesetzt werden können, eine grundsätzlich interessante Alternative dar.

DEB: Beschichtung mit antiproliferativen Wirkstoffen

Bei der Dilation mittels medikamentenbeschichtetem Ballonkatheter (Freisetzung von Substanzen, die die Gefäßwiederverengung inhibieren) wird ein Ballonkatheter von variabler Länge (10 mm–30 mm) und Durchmesser (2,0-4,0 mm) durch die Aorta bis an die Stelle der identifizierten Verengung eingeführt und dort etwa 60 Sekunden lang aufgeblasen. Dies führt zu einer Ausdehnung des Gefäßes und zum Auftragen des Medikaments bzw. des Wirkstoffs auf die Innenseite der Gefäßwand. Die beiden derzeit bei medikamentenbeschichtetem Ballonkatheter eingesetzten antiproliferativen Wirkstoffe sind Paclitaxel und Sirolimus.

Methoden

Dieses Update vergleicht die Wirksamkeit und Sicherheit der perkutanen transluminalen koronaren Angioplastie (PTCA) mit einem medikamentenfreisetzenden Ballonkatheter (engl. drug-eluting balloon/DEB) einer PTCA mit einem nicht beschichteten Ballonkatheter (engl. plain old balloon agiography/POBA) oder der Implantation eines medikamentenfreisetzenden Stents (engl. drug-eluting stent/DES) bei Patient*innen mit erstmaligen Verengung der Herzkranzgefäße (de novo Läsionen), Ostiumstenosen, Verengung kleiner Herzkranzgefäße (engl. small vessel disease/SVD) und mit Rezidiven nach Stent Implantation (In-Stent-Restenosen/ISR).

fokussierte Recherche nach Übersichtsarbeiten und systematische Recherche nach RCTs

Zunächst erfolgte eine fokussierte Literatursuche nach systematischen Übersichtsarbeiten zu diesem Thema in der bibliografischen Datenbank Medine. Ziel dabei war es, eine oder mehrere hochwertige und aktuelle systematische Übersichtsarbeiten zu identifizieren, die als primäre Quelle für Primärstudien herangezogen werden können. Für jene Zeiträume, die nicht von den ausgewählten systematischen Übersichtsarbeiten abgedeckt wurden, wurde eine systematische Literatursuche nach randomisierten kontrollierten Studien (RCTs) in drei Datenbanken (Medline, Embase, Cochrane Clinical Trials Registry) und drei Registern für klinische Studien (ClinicalTrial.gov, WHO-ICTRP und EU Clinical Trials) durchgeführt. Die Selektion relevanter Studien, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autor*innen unabhängig voneinander durchgeführt. Soweit sinnvoll und möglich, wurden paarweise Meta-Analysen durchgeführt. Zur Berechnung wurde die Cochrane Review Manager Software, Review Manager 5.4 herangezogen. Es wurden die Modelle mit festen oder zufälligen Effekten nach der Mantel-Haenszel-Methode (für dichotome Daten) oder die Inverse-Varianz-Methode (für kontinuierliche Daten) verwendet, wobei das Modell mit zufälligen Effekten zur Anwendung kam. Für die Bewertung der Vertrauenswürdigkeit der Evidenz wurde das GRADE-System (Grading of Recommendations Assessment, Development and Evaluation) verwendet.

paarweise Meta-Analysen

Bewertung der Evidenz nach GRADE

Klinische Wirksamkeit

Wirksamkeit: AP-Symptomatik, Vermeidung von CABG, Revaskularisation, LQ

Für die Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte herangezogen: Linderung von AP Symptomen, Vermeidung einer Koronararterien-Bypass-Operation (CABG), In-Segment-Revaskularisationsraten (engl. target lesion revascularization/TLR bzw. target vessel revascularization/TVR) und gesundheitsbezogene Lebensqualität (LQ).

Sicherheit

Sicherheit: Mortalität, schwere kardiale Nebenwirkungen, Stent-Thrombosen

Für die Bewertung der Sicherheit wurden folgende Endpunkte herangezogen: Gesamtmortalität, kardiale Mortalität; schwere kardiale Nebenwirkungen (engl. major cardiac adverse events/MACE), Myokardinfarkte, Stent-Thrombosen und schwere unerwünschte Ereignisse.

Ergebnisse

Verfügbare Evidenz

Seit der letzten Aktualisierung des Berichts zu PTCA mit DEB bei Patient*innen mit KHK im Jahr 2016 wurden zahlreiche RCTs veröffentlicht, die eine PTCA mit DEB mit der DES-Implantation bei Patient*innen mit ISR sowie eine PTCA mit DEB mit der PTCA mit POBA oder der DES-Implantation bei Patient*innen mit de novo Läsionen (inklusive Patient*innen mit SVD) verglichen. Basierend auf dem MEL-Bericht von 2016, fünf hochwertigen und aktuellen systematischen Übersichten sowie einer ergänzenden Recherche nach RCTs konnten insgesamt 14 RCTs für die Indikation ISR, 29 RCTs für de novo Läsionen unabhängig vom Zielgefäßdurchmesser und 10 RCTs für die Subgruppe der Patient*innen mit SVD in die Meta-Analysen des Berichts-Updates eingeschlossen werden. Für die PTCA mit DEB bei Patient*innen mit Ostiumstenosen konnten keine systematischen Übersichten oder RCTs identifiziert werden. Die Nachbeobachtungsdauer der RCTs lag bei Patient*innen mit ISR bei sechs Monate bis 10 Jahren. Bei Patient*innen mit de novo Läsionen (inkl. SVD) bei sechs Monaten bis drei Jahren. In einer der inkludierten RCTs wurde ein experimenteller Biolimus-freisetzender Ballonkatheter als Intervention eingesetzt. In allen anderen RCTs wurde ein Paclitaxel-freisetzender Ballonkatheter untersucht. Als Vergleichsintervention kamen nicht beschichtete Ballonkatheter (10 RCTs) bzw. medikamenten-freisetzende Stents – hauptsächlich mit den Wirkstoffen Paclitaxel, Everolimus und Sirolimus – (24 RCTs) zum Einsatz. Ergebnisse aus RCTs mit Sirolimus-freisetzenden Ballonkathetern liegen aktuell nicht vor.

DEB bei ISR:
2 SR; 14 RCTs

DEB bei de novo Läsionen:
2 SR; 29 RCTs

DEB bei SVD:
2 SR; 10 RCTs

keine RCTs oder SR zu Ostiumstenosen

Langzeit-Follow-up bis 10 Jahre

Klinische Wirksamkeit

Für drei wesentliche Endpunkte zur Bewertung der Wirksamkeit – Linderung von AP Symptomen, Vermeidung einer CABG und gesundheitsbezogene Lebensqualität – wurden in keiner der insgesamt 43 eingeschlossenen RCTs Ergebnisse berichtet.

Wirksamkeit:
keine Ergebnisse zu AP-Symptomatik, Vermeidung von CABG und LQ

Für den Vergleich zwischen PTCA mit DEB und PTCA mit POBA bei **Patient*innen mit ISR** lagen Ergebnisse aus fünf RCTs zu In-Segment-Revaskularisationsraten vor. Die Meta-Analysen zu TLR und TVR auf Basis dieser RCTs ergaben nach einem Follow-up von sechs Monaten bis 10 Jahren einen statistisch signifikanten Vorteil für PTCA mit DEB gegen über PTCA mit POBA. Für den Vergleich der PTCA mit DEB versus DES Implantation ergaben die Meta-Analysen zu TLR und TVR mit sieben bzw. acht RCTs nach einem Follow-up von sechs Monaten bis 10 Jahren keinen statistisch signifikanten Unterschied.

ISR:
TLR und TVR niedriger im Vergleich zu POBA; kein Unterschied im Vergleich zu DES

Bei **Patient*innen mit de novo Läsionen** (kleine und große Gefäße) lagen für den Vergleich PTCA mit DEB und PTCA mit POBA Ergebnisse aus fünf RCTs vor. Auch hier zeigte sich in der Meta-Analyse zu TLR nach einem Follow-up von sechs bis 12 Monaten ein statistisch signifikanter Vorteil für PTCA mit DEB, nicht jedoch in der Meta-Analyse zu TVR. Für den Vergleich der PTCA mit DEB versus DES Implantation bei Patient*innen mit de novo Läsionen ergaben die Meta-Analysen mit 21 bzw. 15 RCTs nach einem Follow-up von sechs Monaten bis drei Jahren deutlich höhere TLR- und TVR-Raten bei der Verwendung des medikamentenfreisetzenden Ballonkatheters, wobei dieser Unterschied bei TVR statistisch signifikant war, bei TLR gerade nicht.

de novo Läsionen:
TLR niedriger im Vergleich zu POBA aber höher im Vergleich zu DES

Bei **Patient*innen mit SVD** lagen für den Vergleich PTCA mit DEB versus PTCA mit POBA Ergebnisse zu Revaskularisationsraten aus drei RCTs vor. Auch hier ergab die Meta-Analyse auf Basis dieser RCTS nach einem Follow-up von sechs bis 12 Monaten einen statistisch signifikanten Vorteil für PTCA mit DEB bei den TLR-Raten. TVR-Raten wurden nur in einer RCT berichtet, wobei kein Unterschied zwischen PTCA mit DEB und PTCA mit POBA vorlag. Für den Vergleich der PTCA mit DEB mit einer DES Implantation ergaben die Meta-Analysen zu TLR und TVR mit sechs bzw. fünf RCTs nach einem Follow-up von sechs Monaten bis drei Jahren keinen statistisch signifikanten Unterschied zwischen den beiden Interventionen.

SVD: TLR niedriger im Vergleich zu POBA; kein Unterschied im Vergleich zu DES

Sicherheit

Für den Vergleich zwischen PTCA mit DEB und PTCA mit POBA bei **Patient*innen mit ISR** lagen Ergebnisse aus fünf RCTs zur Gesamtmortalität und aus vier RCTs zur kardialen Mortalität vor. Die Meta-Analysen auf Basis dieser RCTs ergaben nach einem Follow-up von sechs Monaten bis 10 Jahren keine statistisch signifikanten Unterschiede zwischen den beiden Interventionen hinsichtlich der Mortalitätsraten. Ergebnisse zu schweren kardialen Ereignissen, zu Myokardinfarkten sowie zu Stent Thrombosen wurden ebenfalls in fünf RCTs berichtet. Hier ergaben die Meta-Analysen nach einem Follow-up von sechs Monaten bis 10 Jahren statistisch signifikant niedrigere MACE-Raten bei einer PTCA mit DEB im Vergleich zu einer PTCA mit POBA, bei der Häufigkeit von Myokardinfarkten bzw. Stent Thrombosen zeigte sich hingegen kein Unterschied zwischen den beiden Interventionen. Für den Vergleich der PTCA mit DEB versus DES Implantation zeigten die Meta-Analysen zu Gesamtmortalität, kardialer Mortalität, MACE, Myokardinfarkten sowie Stent Thrombosen auf Basis von neun bzw. 10 RCTs nach einem Follow-up von sechs Monaten bis 10 Jahren keine statistisch signifikanten Unterschiede zwischen den beiden Interventionen.

Sicherheit: ISR: kein Unterschied zu POBA oder DES bei Mortalität und Stent Thrombosen

MACE niedriger im Vergleich zu POBA; kein Unterschied im Vergleich zu DES

Bei **Patient*innen mit de novo Läsionen** (kleine und große Gefäße) lagen zu den Endpunkten zur Bewertung der Sicherheit für den Vergleich PTCA mit DEB und PTCA mit POBA Ergebnisse aus fünf RCTs vor. Die Meta-Analysen auf Basis dieser RCTs ergaben nach einem Follow-up von sechs bis 12 Monaten keine statistisch signifikanten Unterschiede zwischen den beiden Interventionen hinsichtlich der Mortalitätsraten. Die Meta-Analyse statistisch zu MACE ergab nach einem Follow-up von sechs bis 12 Monaten eine signifikant niedrigere Ereignisrate bei einer PTCA mit DEB im Vergleich zu einer PTCA mit POBA, bei der Häufigkeit von Myokardinfarkten bzw. Stent Thrombosen zeigte sich hingegen kein Unterschied zwischen den beiden Interventionen. Für den Vergleich der PTCA mit DEB versus DES Implantation zeigten die Meta-Analysen zu Gesamtmortalität, kardialer Mortalität, schweren kardialen Ereignissen, Myokardinfarkten sowie Stent Thrombosen auf Basis von 22 bzw. 23 RCTs nach einem Follow-up von sechs Monaten bis drei Jahren keine statistisch signifikanten Unterschiede zwischen den beiden Interventionen.

de novo Läsionen: kein Unterschied zu POBA oder DES bei Mortalität, MACE oder Stent Thrombosen

Bei **Patient*innen mit SVD** lagen für den Vergleich PTCA mit DEB und PTCA mit POBA zur Gesamtmortalität und kardialen Mortalität Ergebnisse aus drei RCTs vor. Dabei wurde berichtet, dass im Zeitraum bis zu 12 Monaten in keiner der drei Studien eine Person verstarb. Ergebnisse zu MACE, zu Myokardinfarkten sowie zu Stent Thrombosen wurden ebenfalls in drei RCTs berichtet. Hier ergaben die Meta-Analysen nach einem Follow-up von sechs bis 12 Monaten signifikant niedrigere Raten an schweren kardialen Ereignissen bei einer PTCA mit DEB im Vergleich zu einer PTCA mit POBA,

SVD: kein Unterschied zu POBA oder DES bei Mortalität, MACE oder Stent Thrombosen

bei der Häufigkeit von Myokardinfarkten bzw. Stent Thrombosen zeigte sich hingegen kein Unterschied zwischen den beiden Interventionen. Für den Vergleich der PTCA mit DEB versus DES Implantation zeigten die Meta-Analysen zu Gesamtmortalität, kardialer Mortalität, schweren kardialen Ereignissen, Myokardinfarkten auf Basis von sechs RCTs nach einem Follow-up von sechs Monaten bis drei Jahren keine statistisch signifikanten Unterschiede zwischen den beiden Interventionen. Bei Stent Thrombosen zeigte die Meta-Analyse auf Basis von sieben RCTs nach einen Follow-up von sechs Monaten bis drei Jahren deutlich niedrigere Raten bei PTCA mit DEB im Vergleich zu einer DES Implantation, der Unterschied war jedoch nicht statistisch signifikant.

Zu schweren unerwünschten Ereignissen lagen keine Ergebnisse aus den 43 inkludierten RCTs vor.

Keine Ergebnisse zu SAE

Vertrauenswürdigkeit der Evidenz

Bei Patient*innen mit ISR die Vertrauenswürdigkeit der Evidenz für die Wirksamkeit und Sicherheit der PTCA mit DEB im Vergleich zur PTCA mit POBA als gering bis moderat, und für den Vergleich PTCA mit DEB versus DES Implantation mit moderat bis hoch einzustufen. Bei Patient*innen mit de novo Läsionen (kleine und große Gefäße), ist die Vertrauenswürdigkeit der Evidenz für die Wirksamkeit und Sicherheit der PTCA mit DEB im Vergleich zur PTCA mit POBA sehr gering bis hoch und für den Vergleich der PTCA mit DEB versus DES Implantation sehr gering bis moderat. Bei Patient*innen mit SVD ist die Vertrauenswürdigkeit der Evidenz für die Wirksamkeit und Sicherheit der PTCA mit DEB im Vergleich zur PTCA mit POBA sehr gering bis moderat zu bewerten, und für den Vergleich zur PTCA mit DEB mit einer DES Implantation als gering bis moderat.

GRADE: überwiegend moderate Evidenz für ISR

mehrheitlich moderate bis geringe Evidenz bei de novo Läsionen und SVD

Laufende Studien

In den Studienregistern sind derzeit 20 laufende RCTs zu PTCA mit DEB im Vergleich zu PTCA mit POBA oder DES Implantation aufgeführt. Sechs RCTs untersuchen dabei Patient*innen mit ISR und 14 RCTs Patient*innen mit de novo Läsionen. In sieben dieser Studien wird ein Sirolimus-freisetzender Ballonkatheter untersucht Vier der RCTs sollten bereits in den Jahren 2022 oder 2023 abgeschlossen worden sein, während das geplante Studienende der übrigen RCTs zwischen 2024 und 2027 liegt.

6 laufende RCTs zu ISR
14 laufende RCTs zu de novo Läsionen

Schlussfolgerung

Die derzeitige Evidenz belegt, dass bei Patient*innen mit In-Stent Restenosen die bewertete Technologie PTCA mit DEB wirksamer und sicherer als die Vergleichsbehandlung PTCA mit einem nicht beschichteten Ballonkatheter ist. Im Vergleich zu einer Implantation eines medikamenten-freisetzenden Stent ist die bewertete Technologie PTCA mit DEB bei Patient*innen mit In-Stent Restenosen vergleichbar wirksam und sicher.

ISR:
DEB wirksamer und sicherer als POBA und vergleichbar wirksam und sicher wie DES

Bei Patient*innen mit de novo Läsionen deutet die derzeitige Evidenz darauf hin, dass die bewertete Technologie PTCA mit DEB wirksamer und sicherer als die Vergleichsbehandlung PTCA mit einem nicht beschichteten Ballonkatheter, jedoch tendenziell weniger wirksam und ebenso sicher wie die Vergleichsbehandlung einer Implantation eines medikamenten-freisetzenden Stents ist, welcher den derzeitigen Goldstandard in der Therapie von de novo Läsionen darstellt.

de novo Läsionen:
DEB wirksamer und sicherer als POBA aber weniger wirksam, aber gleich sicher wie DES

SVD: Evidenz immer noch nicht ausreichend für Empfehlung

Für die Subgruppe der Patient*innen mit Verengung kleiner Herzkranzgefäße (SVD) zeigt die aktuelle Evidenz, dass die bewertete Technologie PTCA mit DEB ebenso wirksam und sicher ist wie die Vergleichsverfahren PTCA mit einem nicht beschichteten Ballonkatheter bzw. einer Implantation eines medikamenten-freisetzenden Stent. Insgesamt scheint die Evidenzbasis jedoch nicht ausreichend für eine abschließende Beurteilung der Wirksamkeit und Sicherheit der PTCA mit DEB bei Patient*innen mit SVD. Neue Studienergebnisse werden die Effektschätzung möglicherweise erheblich beeinflussen. Für Patient*innen mit Ostiumstenosen gibt es derzeit keine Evidenz aus RCTs.

Schlussfolgerung: zusätzlicher Nutzen nur für bestimmte Indikationen

Daher weisen die derzeitigen Belege insgesamt nur bei bestimmten Indikationen auf einen zusätzlichen Nutzen hin.

Eine neuerliche Evaluierung im Jahr 2027 wird für Patient*innen mit de novo Läsionen bzw. für Patient*innen mit Verengung kleiner Herzkranzgefäße (SVD) vorgeschlagen.

Summary of previous assessment 2016

systematischer Review 2016

An initial HTA-report "Medikamentenbeschichteter Ballonkatheter" was prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in 2009 [1] and twice updated in 2013 [2] and 2016 [3]. This chapter summarizes the results and the recommendation of the last 2016 update report.

Health problem and characteristics of the technology

Overview of the disease, health condition and target population

Arteriosklerose: Einengung des Gefäßes durch Ablagerung

verminderte Sauerstoffversorgung

Angina pectoris ist häufigstes Symptom

Cardiovascular diseases such as atherosclerosis often lead to partial (stenosis) or complete blockage (occlusion) of blood vessels. Atherosclerosis is a narrowing of the blood vessels due to deposits of blood fats, connective tissue, calcium, or even blood clots. Atherosclerosis in the coronary arteries is also known as coronary heart disease (CHD). The stenosis can become hemodynamically relevant from a narrowing of the vessel of about 70%. In addition to asymptomatic courses, however, the typical CHD symptoms develop in most cases, which are characterized by a mismatch between oxygen demand and oxygen supply of the myocardial tissue. The leading symptom is angina pectoris (AP), but also cardiac arrhythmias, heart failure, myocardial infarction and sudden cardiac mortality. In AP, a distinction is made between stable AP, in which chest pain is caused by physical activity or emotional stress but is treatable by medication and physical rest, and unstable AP, characterized by a change in pain symptomatology. This includes the initial onset of symptoms, symptoms under rest and increase in duration or intensity of symptoms, and non-response to rest or medication [4].

KHK häufigste Todesursache in der westlichen Welt

CHD is the most common cause of death in developed countries. It mainly affects older people aged 65 and over and to date it has affected more men than women. In 2021, a total of 12,461 patients (male: 6,828, female: 5,633) died of ischemic heart disease (ICD-10 codes: I20-I25) in Austria, accounting for 13.6% of all deaths. More than a third of these deaths (34.5%) were caused by myocardial infarction (MI) (ICD-10 code: I21-I22) [5].

In-Stent-Restenosen: neuerliche Verengung nach Stent Implantation

Despite the use of modern drug-eluting stents (DES), in certain lesions and patient groups, 2-10% of percutaneous coronary interventions (PCI) in Germany result in a new progressive narrowing of the coronary lesion previously treated with a stent, a so-called in-stent restenosis (ISR). ISR leads to an increase in morbidity after stent implantation – acute MI occurs in around 5-10% of cases. Compared to patients with de novo lesions, patients with ISR also show symptoms of unstable angina pectoris more frequently [6].

Current clinical practice

primäre Therapieziele

The primary therapeutic goals of various interventions in the treatment of CHD are

- Increasing the disease-related quality of life, among other things by
  - Prevention of AP symptoms,
  - Maintaining the physical strength,
  - Reduction of CHD-associated mental illnesses (depression, anxiety disorders)
- Reduction of cardiovascular morbidity, in particular prevention of heart attacks of heart attacks and the development of heart failure
- Reduction in mortality

Therapie der KHK mittels Bypass Chirurgie oder mit perkutanen Interventionstechniken

To achieve the therapeutic goals, bypass surgery and PCI with stent implantation via cardiac catheterization are available. In 2013, approximately 2,500 PCIs were performed per 1 million inhabitants in Austria [7].

Drug-eluting balloon catheters can also be used for treatment. These may be an interesting alternative, especially in places where stents cannot be used.

In the 2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines for myocardial revascularization, both drug-eluting balloons and DES are recommended for the treatment of in-stent restenosis (GoR I, LoE A) [8].

Features of the intervention

Gefäßdehnung und Wirkstoffapplikation durch Aufblasen des Ballonkatheters

Wirkstoffe: Paclitaxel und Sirolimus

In drug-eluting balloon (DEB) dilatation, a balloon catheter of variable length (10 mm to 30 mm) and diameter (2.0 to 4.0 mm) is inserted through the aorta to the site of the identified narrowing and inflated for approximately 60 seconds. This causes the vessel to dilate, delivering the drug to the inside of the vessel wall. DEB are balloon catheters with a drug coated surface. They are designed to deliver a high concentration of an anti-proliferative agent to the vessel wall of the target lesion to inhibit vasoconstriction. The two anti-proliferative agents currently used in DEBs are paclitaxel and sirolimus. In 2023, the following DEB were available in the European market [9]:

- SeQuent Please (B. Braun) – paclitaxel
- Restore (Cardionovum) – paclitaxel
- Agent (Boston Scientific) – paclitaxel
- Prevail (Meditronic) – paclitaxel
- Pantera Lux (Biotronik) – paclitaxel
- Elutax SV (Aachen Resonance) – paclitaxel
- MagicTouch (Concept Medical) – sirolimus
- Selution (Med Alliance) – sirolimus
- SeQuent SCB (B. Braun) – sirolimus

In addition to the anti-proliferative agents, DEB differ in the excipients (mainly polymers) that transport the drug into the vessel wall. There has been debate as to whether the type of excipient has a significant role in the efficacy of DEB. Recently published trials directly comparing paclitaxel-eluting DEBs with different excipients (triglyceride, acetyl tri-butyl citrate, or iopromide matrix) in the treatment of ISR have not shown significant differences [70,71].

The balloon catheter is intended for the treatment of in-stent restenosis. Balloon dilatation is used in CHD for in-stent restenosis, ostium stenosis and the treatment of very small vessels. The primary goals of using drug-eluting balloon catheters are to reduce restenosis rates in patients with CHD, prevent heart attacks and strokes, and improve quality of life.

Scope and methods

Ziel des systematischen Reviews 2016

The aim of this systematic review was to assess the efficacy and safety of percutaneous transluminal coronary angioplasty (PTCA) with drug-eluting balloon (DEB) compared to PTCA with uncoated balloon (plain old balloon angioplasty/POBA) or implantation of a drug-eluting stent (DES) for the treatment of in-stent restenosis (ISR), de novo lesions of coronary vessels, small coronary vessel disease (SVD), and ostium stenosis.

Overview of Reviews

Since numerous systematic reviews on the topic of DEB versus POBA or versus DES had been published, for the 2016 report update, an overview of reviews was performed including systematic reviews (SRs) and meta-analyses relevant on this topic. For SVD and ostium stenosis an additional search for randomized controlled trials (RCTs) was conducted.

Recherche in 4 Datenbanken

A systematic literature search for reviews and RCTs in four databases (Medline, Embase, Cochrane, CRD) was complemented by a search in trial registries an unsystematic hand search. The methodologic quality of systematic reviews was assessed using the quality-index by Oxman & Guyatt [10-12]. The overall judgement on the quality of evidence was done according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [13].

Results

insgesamt 13 systematische Reviews: 11 SR zu DEB bei ISR 3 SR + 1 RCT zu DEB bei de novo Läsionen

2 RCTs zu SVD

A total of 13 systematic reviews were included in the 2016 MEL report. Ten reviews evaluated the efficacy and safety of DEB for in-stent restenosis. In the three reviews on de novo lesions, the results of RCTs on de novo lesions in large and small coronary vessels were analyzed together. During the screening of the trial registers, the publication of one additional RCT was identified and included in the evidence analysis. In one of the SRs on de novo lesions, subgroup results based on two RCTs on stenosis of small coronary vessels (small vessel disease) were reported. The supplementary search for RCTs concerning small vessel disease yielded two additional publications for one of the two studies included in the SR, reporting results on further outcomes and longer follow-up.

ISR: signifikanter Vorteil für DEB vs POBA bei TLR und MACE; heterogene Ergebnisse bei Gesamtmortalität

For ISR, all included SRs showed superiority of PTCA with DEB over PTCA with POBA based on the results of a maximum of five RCTs with a total of 749 patients. This was mainly based on consistently significantly lower target lesion revascularization (TLR) rates and major adverse cardiac event (MACE) rates with DEB. With regard to all-cause mortality, the results of the meta-analyses were inconsistent. However, the two most recent reviews that included all relevant RCTs in their meta-analyses reported a (small) significant advantage of DEB over POBA. Myocardial infarction (MI) and stent

thrombosis also tended to be less frequent after PTCA with DEB, but these results were not statistically significant in any of the included reviews.

In contrast, the comparison of DEB versus DES, which was recommended as the treatment of choice for in-stent restenosis in the 2016 guidelines [14], did not show a significant difference for any of the outcomes examined in the SRs based on up to six RCTs with a total of 1,160 patients. TLR rates, MACE rates and stent thrombosis rates actually tended to be higher in the

ISR: kein signifikanter Unterschied zwischen DEB und DES bei allen Endpunkten; ...

DEB groups. The control intervention was an everolimus-eluting stent (EES) in three RCTs included in the reviews and a paclitaxel-eluting stent (PES) in the other three trials. To assess subgroup effects, separate meta-analyses were performed for these two control interventions in one review. This showed a disadvantage for DEB, especially compared to EES, which was even statistically significant for TLR rates. Both the subgroup analyses from this review of DEB versus PES and the reviews that included only RCTs with PES as the comparison intervention reported no disadvantage but also no advantage for DEB.

... TLR, MACE und Stent Thrombosen tendenziell höher mit DEB

For de novo lesions in large and small coronary vessels, results from three SRs were available. In the two SRs with meta-analyses, no difference was found between PTCA with DEB and DES implantation based on a maximum of seven RCTs (4-7 included RCTs depending on the outcome) involving up to 1,267 patients. However, there was a trend toward a higher event rate for all patient-relevant endpoints and thus a disadvantage for DEB compared to DES. For the TLR rate, this disadvantage was even statistically significant in one SR. An additional RCT with 108 patients also showed a significantly higher TLR rate in the DEB group.

de novo Läsionen: TLR höher bei DEB im Vergleich zu DES; kein Unterschied bei anderen Endpunkten

A subgroup analysis of patients with SVD in one SR based on two RCTs and a total of 242 patients showed no statistically significant difference between DEB and DES for MACE. For this indication, results from SRs on other patient-relevant outcomes were not available. There were two publications on one of the two RCTs included in the review with results on further outcomes at six and 24 months. Again, there was no statistically significant difference between DEB and DES. However, this study tended to report fewer MACE with DEB compared to DES at 24 months.

SVD: kein signifikanter Unterschied zwischen DEB und DES bei allen Endpunkten

No reviews or trials were identified for PTCA with DEB in patients with ostium stenosis.

Keine SR oder RCTs zu DEB bei Ostiumstenosen

Recommendation

Based on the 2016 evidence, the inclusion of PTCA with DEB into the hospital benefit catalogue was not recommended. The evidence suggested a benefit for PTCA with DEB versus PTCA with POBA in patients with ISR, but no difference in efficacy and safety of PTCA with DEB and DES implantation – the first line therapy recommended in 2016 guidelines – in ISR or de novo lesions. For patients with SVD the evidence was insufficient to assess the efficacy and safety of PTCA with DEB in comparison to DES implantation.

Aufnahme in den Leistungskatalog nicht empfohlen

A re-evaluation was recommended for SVD in 2020. For ISR, de novo lesions and ostium stenosis a re-evaluation was not recommended.

UPDATE 2024

1 Objectives and Scope

1.1 PICO question

PIKO-Frage 2024

Is percutaneous transluminal coronary angioplasty (PTCA) with a drug-eluting balloon (DEB) in comparison to PTCA with an uncoated balloon (plain old balloon angioplasty/POBA) or in comparison to drug-eluting stent (DES) implantation in patients with de novo lesions of the large coronary arteries, with narrowing of the small coronary arteries (small vessel disease/SVD), with ostium stenosis, or with recurrence after stent implantation (in-stent restenosis/ISR) more effective and safe concerning revascularization rate, avoidance of coronary bypass surgery, quality of life, morbidity and mortality?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Adults ≥18 years with coronary artery diseases with: ■ in-stent-restenosis ■ ostium stenosis ■ stenosis of small coronary vessels, as defined in the studies ■ de novo lesion of coronary vessels
Intervention	Percutaneous transluminal coronary angioplasty (PTCA) with drug-eluting balloon (DEB)/paclitaxel-eluting balloon (PEB) or sirolimus-eluting balloon (SEB)
Control	Percutaneous transluminal coronary angioplasty (PTCA) with conventional uncoated balloon (plain old balloon angioplasty/POBA) AND/OR drug-eluting stent (DES) implantation
Outcomes	
Efficacy	Clinical outcomes ■ Angina pectoris (AP) symptom relief ■ Avoidance of coronary artery bypass grafting (CABG) ■ Revascularization rate (target lesion revascularization/TLR; target vessel revascularization/TVR) ■ Health-related quality of life (HRQoL) Angiographic outcomes ■ Late lumen loss (LLL) ■ Restenosis rate
Safety	■ Overall mortality ■ Cardiac mortality ■ Major adverse cardiac events (MACE) ■ Myocardial infarction (MI) ■ Stent thrombosis ■ Serious adverse events (SAE)
Study design	■ Systematic reviews (SR), meta-analyses or Heath Technology Assessment (HTA) reports ■ RCTs (limited to indications/interventions/timeframes without published SR/HTA)

2 Methods

2.1 Research questions

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customized to the specific objectives of this assessment [15].

2.2 Clinical effectiveness and safety

2.2.1 Systematic literature search

fokussierte Literatursuche nach systematischen Reviews: Identifikation von Basis-Reviews als primäre Quelle für RCTs

As a first step a focused search for systematic reviews in the MEDLINE database (including the Cochrane Database of Systematic Reviews) was conducted on the 19th December 2023. The search was restricted to the last 3 years before 2024 and to articles published in English or German It was checked whether at least one high-quality and up-to-date systematic review was available whose information retrieval could be used as a basis for the synthesis (hereafter: basic review). The specific search strategy of the focussed search for systematic reviews can be found in the Appendix.

ergänzende systematische Literatursuche nach RCTs in vier Datenbanken ab März 2020

If one or more such basic reviews were available, an additional search for RCTs for the period not covered by the basic reviews was conducted in a second step. Otherwise, the search for RCTs was conducted without time period restriction.

An additional systematic literature search for RCTs was conducted on the 23rd January 2024 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

The systematic search was limited to the timeframe of March 2020 to January 2024, and in Medline and Embase to only prospective or randomized controlled trials and to articles published in English or German. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 7th February 2024, resulting in 125 hits. Four additional relevant ongoing RCTs were identified by correspondence with an expert in the field.

2.2.2 Flow chart of study selection

Literaturauswahl – systematische Reviews

All references were screened by two independent researchers (CK, TS) and in case of disagreement a third researcher was involved to solve the differences.

The focused search for systematic reviews resulted in 70 hits. Overall 13 relevant systematic reviews were identified [16-28]. Of these 13 systematic reviews, five systematic reviews [19, 21, 26-28] were assessed to be up to date and of high quality and were included as basic reviews for the purpose of primary study identification. The selection process for systematic reviews is displayed in Figure 2-1.

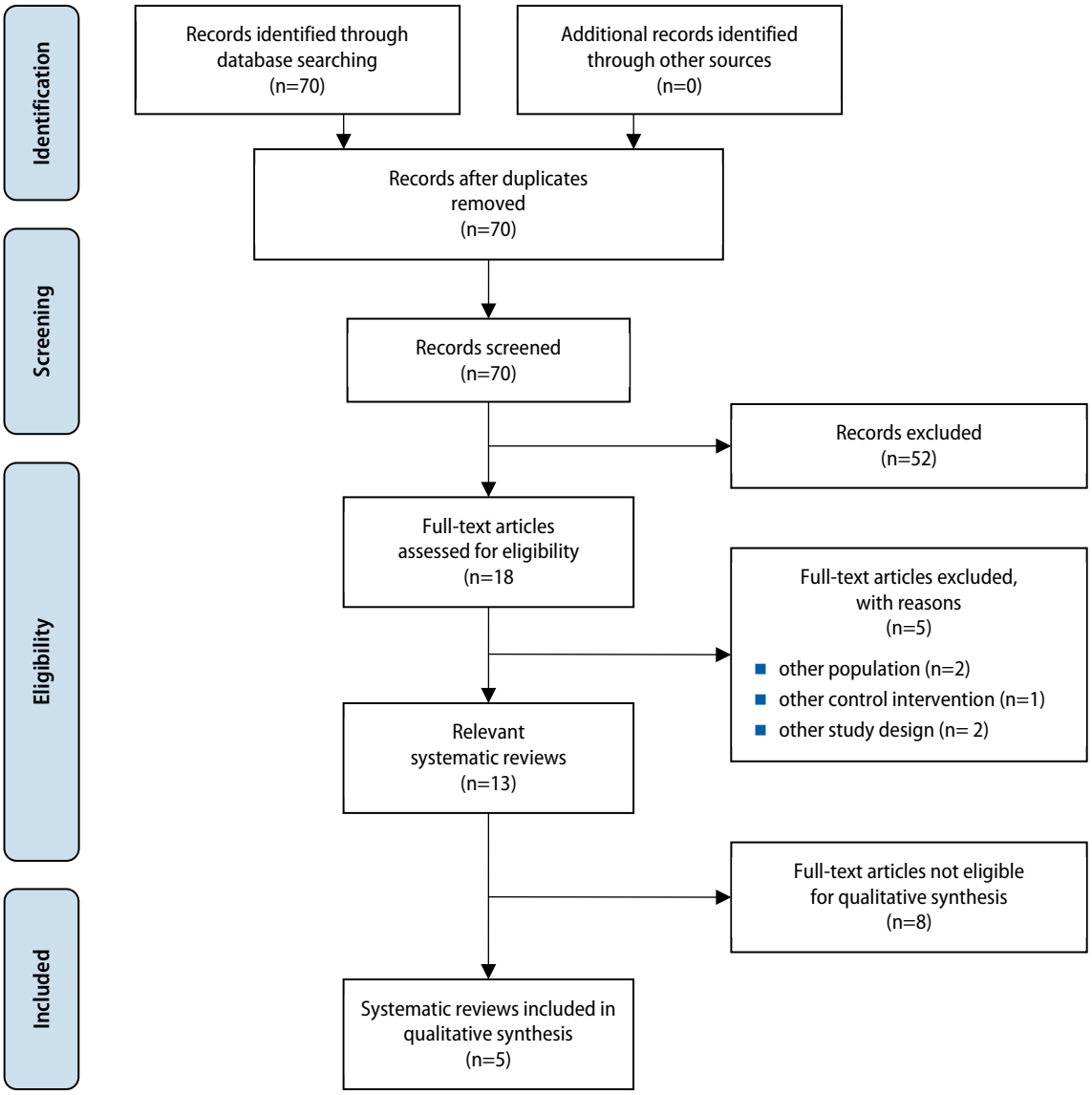

Figure 2-1: Systematic reviews: Flow chart of study selection (PRISMA Flow Diagram)

Literaturauswahl – RCTs

insgesamt 43 RCTs inkludiert

From the 2016 MEL report [3] and the five included basic reviews, a total of 46 publications on 37 RCTs were identified as relevant. In addition, the reference lists of the eight relevant but not included reviews were screened. From these, four additional RCTs were included [29-32]. The systematic additional search for primary studies for the time periods that were not covered by the basic reviews resulted in a total of 524 hits. Finally, two further RCTs [33, 34] and two additional recent publications with long-term results from studies already included from other sources were identified [35, 36]. Overall, 54 publications involving 43 RCTs were included in this updated report. The selection process for RCTs is displayed in Figure 2-2.

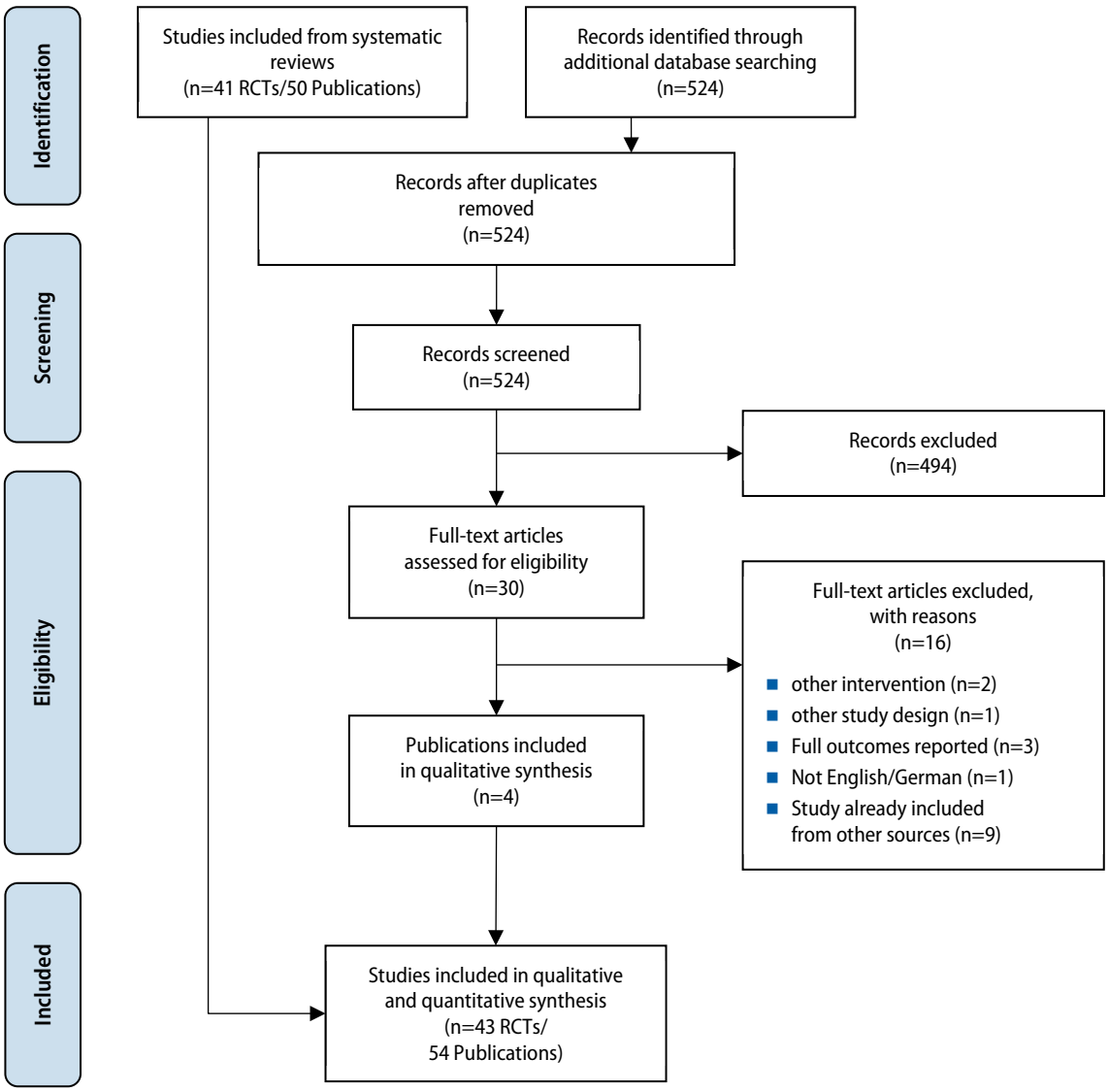

Figure 2-2: RCTs: Flow chart of study selection (PRISMA Flow Diagram)

2.2.3 Analysis

Datenextraktion in Tabellen

Relevant information was retrieved from the sources identified. Data from included systematic reviews and primary studies were extracted into data extraction tables based on the study design and research question (see Appendix Table A-1 to Table A-5). An independent second reviewer (CK or TS) validated the data for accuracy. For RCTs included in the five basic reviews, all results were retrieved from these systematic reviews. The primary publications of these RCTs were not taken into account for the analysis. For all other RCTs identified in the hand search or supplemental electronic search, data were extracted and analysed based on the primary publication.

Bewertung des Verzerrungs-potenzials: ROBIS und Cochrane RoB 2

Two researchers (CK, TS) conducted risk of bias assessments independently. Differences were resolved by consensus. The risk of bias (RoB) of the included systematic reviews has been evaluated using the ROBIS tool [37] (see Appendix Table A-6). For RCTs included in the basic reviews, the RoB assessment was directly taken from these reviews. The RoB of the additional RCTs has been evaluated using the Cochrane RoB v.2 tool [38] (see Appendix Table A-7).

2.2.4 Synthesis

Meta-Analysen wenn möglich – Review Manager 5.4

Based on the data-extraction-table (see Appendix Table A-1 toTable A-5), data on each selected outcome were synthesized. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. Dichotomous data were expressed as a risk ratio (RR) with 95% CIs or as the number of events and percentages. Continuous outcomes were given using the mean with standard deviation (SD). We use the fixed or random effects model to synthesise the results using the Mantel-Haenszel method (for dichotomous data) or Inverse Variance method (for continuous data). Thereby, the random effects model was used in the case of increased heterogeneity ($I^2 > 30\%$). We identified heterogeneity by visually inspecting the forest plots and by using the I^2 statistic [39]. The level of heterogeneity was taken into account as part of the assessment of the certainty of the evidence (inconsistency).

Bewertung der Vertrauenswürdigkeit der Evidenz mit GRADE

Certainty of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [13]). The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix, results were summarized in Table 4-1 to Table 4-6.

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

Wirksamkeit: entscheidungsrelevante EPs: AP Symptomatik, Vermeidung von CABG, TLR/TVR, LQ

As in the previous versions of this report, following clinical outcomes were defined as *crucial* to derive a recommendation:

- Angina pectoris (AP) symptom relief
- Avoidance of coronary artery bypass grafting (CABG)
- Revascularization rate
- Health-related quality of life (HrQoL)

A PTCA with balloon dilatation or stent implantation serves the primary purpose to relieve AP symptoms and improving HrQoL of the affected patients. In addition, more invasive interventions such as CABG might be avoided.

Subjective outcomes like AP symptom relief or HrQoL are taken into account if they were recorded using valid measurement instruments, e.g. validated scales like Seattle Angina Questionnaire (SAQ), Short Form 36 (SF-36) questionnaire, or the European Quality of Life–5 Dimensions (EQ-D) questionnaire.

Avoidance of CABG is reported as the percentage of patients having a CABG surgery during follow-up.

Revascularization of the narrowed target vessel in the event of renewed stenosis (restenosis) after PTCA or stent implantation has already been performed remains a common procedure in real word practice. The avoidance of revascularization is therefore seen as a crucial effectiveness outcome for PTCA with balloon dilatation or stent implantation. Revascularisation rates are reported as target lesion revascularisation (TLR) or target vessel revascularisation (TVR) within studies. TLR or TVR were defined as any CABG surgery or repeat PCI performed for symptoms or signs of ischemia in the presence of angiographic stenosis in target lesion or vessel.

Angiographic outcomes (e.g. LLL, restenosis rate) were considered less important and are therefore not considered to derive a recommendation. For completeness, results for angiographic outcomes are provided in the evidence tables in the Appendix.

3.1.2 Outcomes safety

Sicherheit: entscheidungsrelevante EPs: Mortalität, schwere kardiale Ereignisse, Myokardinfarkt, Stent Thrombosen, SAE

As in the previous versions of this report, following outcomes were defined as *crucial* to derive a recommendation:

- Overall mortality
- Cardiac mortality
- Major adverse cardiac events (MACE)
- Myocardial infarction (MI)
- Stent Thrombosis
- Serious adverse events (SAE)

Mortality is considered a highly patient-relevant outcome measure. Mortality was reported as overall mortality rates and as cardiac mortality rates in the included RCTs.

The definition of MACE was different in individual studies. MACE was mostly defined as a composition of cardiac mortality, MI or revascularisation. In some studies, all-cause mortality was considered instead of cardiac mortality. Other RCTs also included stroke or thrombosis.

Stent thrombosis was defined according to the Academic Research Council criteria [40].

According to International Conference of Harmonization (ICH) Guideline for Clinical Safety Data Management [41] an SAE is an adverse event that led to a death, to a serious deterioration in health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

3.2 Included studies

3.2.1 Included studies effectiveness

Patients with in-stent restenosis (ISR)

ISR:
2 SR mit 4 neuen RCTs

insgesamt 14 RCTs zu DEB vs POBA oder DES bei ISR

2 zusätzliche Publikationen zu RCTs mit 3 bzw. 10 Jahren Follow-up

Two systematic reviews investigating DEB compared to DES for the treatment of ISR were included as basic reviews [26, 28]. In addition to the already included RCTs in the previous 2016 MEL report, these two reviews provide results from four recent RCTs [42-45], published in 2016 and 2018. Two additional publications reporting long-term results after three-year follow-up and 10-year follow-up to two already included RCT (RIBS IV [35] and ISAR-DESIRE III [36]) were identified in the supplementary search. No further RCTs were identified through other sources. Therefore, overall 14 RCTs investigating DEB compared to POBA or DES in patients with ISR were included in the analysis of this report update. Table 3-1 (on the next page) presents an overview of all included RCTs and the corresponding sources.

SR Xi 2019: 8 RCTs mit 1.576 Patient*innen

Alter: 62-68 Jahre

65 %-87 % Männer

Maximales Follow-up: 36 Monate

Beside nine observational studies, the systematic review Xi 2019 [26] included eight RCTs with a total number of 1,576 patients. The number of patients in the individual RCTs ranged from 50 to 309. The average age of study participants was 62 to 68 years. The majority of patients in the RCTs were men, ranging from 65% to 87%. Information on cardiovascular risk factors was reported in the review (see Appendix Table A-1). Information on the target lesion type or the classification of in-stent restenosis was not provided. MACE, MI, TLR or TVR, all-cause mortality, cardiac mortality and stent thrombosis were evaluated as clinical endpoints in the review. In addition, the results of the angiographic endpoints late lumen loss (LLL), minimal lumen diameter (MLD) and diameter stenosis were analysed. The results of the RCTs were pooled in a meta-analysis. The maximum follow-up was six to 12 months for angiographic endpoints and 12 to 36 months for clinical endpoints.

Table 3-1: Study pool: RCTs included in different sources comparing drug-eluting balloon angioplasty with other devices in patients with ISR

RCT	Type of device used in controlgroups	Systematic review			Supplementary database search for RCTs 2024	Hand search 2024
		MEL report 2016	Xi 2019	Zhu 2021		
Habara 2011	POBA	x				
PACCOCATH-ISR I + II 2012	POBA	x				
PEPCAD-DES 2012	POBA	x				
Habara 2013	POBA	x				
ISAR-DESIRE III 2013	POBA/PES	x	x	x	x[b]	
PEPCAD II 2009	PES	x	x			
PEPCAD-China ISR 2014	PES	x	x	x		
RIBS V 2014	EES	x	x			
SEDUCE 2014	EES	x	x			
RIBS IV 2015	EES	x	x	x	x[b]	
TIS 2016	EES		x			
BIOLUX 2018	SES			x		
DARE 2018	EES		x			
RESTORE 2018	DES[a]			x		

Abbreviations: DES – drug elution stent; EES – everolimus eluting stent; PES – paclitaxel eluting stent; POBA – plain old balloon angioplasty; RCT – randomized controlled trial; SES – sirolimus eluting stent

Explanations:

[a] *no specification*

[b] *additional publication with long-term results*

The second review Zhu 2021 [28] included five RCTs with a minimum follow-up of one year comparing DEB to DES comprising a total of 1,193 patients with ISR. The number of patients in the individual RCTs ranged from 172 to 309. The average age of study participants was 62 to 68 years. Again, the majority of patients in the RCTs were men, ranging from 71.5% to 83%. Information on cardiovascular risk factors and on the target lesion type was reported in the review (see Appendix Table A-1). Information on the classification of in-stent restenosis was not provided. TLR was defined as the primary endpoint of this review. Further clinical outcomes reported were TVR, MACE, cardiac mortality, MI, and stent thrombosis at a maximum follow-up of 12 to 36 months. Angiographic outcomes reported were LLL, MLD, diameter stenosis, and binary restenosis rate, respectively (six to nine months follow-up).

SR Zhu 2021: 5 RCTs mit 1.193 Patient*innen

Alter: 62-68 Jahre

72 %-83 % Männer

Maximales Follow-up: 36 Monate

Study characteristics and results of the two systematic reviews are displayed in Table A-1.

Patients with de novo lesions

One basic systematic review investigated DEB compared to DES for the treatment of patients with de novo lesions in large vessels [21]. The second basic review compared DEB to other devices (POBA, bare metal stent/BMS or DES) in patients with de novo lesions irrespective of the vessel size [27]. In addition to the already included RCTs in the previous 2016 MEL report, these two reviews provide information from 14 recent RCTs [46-59], published between 2016 and 2022. Two additional RCTs [33, 34] published in 2021 and 2024 were identified in the supplementary search, and four further RCTs were identified by hand search [29-32]. Therefore, overall 29 RCTs

de novo Läsionen: 2 SR mit 14 neuen RCTs

insgesamt 29 RCTs zu DEB vs POBA oder DES bei de novo Läsionen

investigating DEB compared to POBA or DES in patients with de novo lesions irrespective of vessel size were included in the analysis of this report update. Table 3-2 presents an overview of al included RCTs and the corresponding sources.

Table 3-2: Study pool: RCTs included in different sources comparing drug-eluting balloon angioplasty with other devices in patients with de novo lesions

RCT	Type of device used in controlgroups	Systematic review			Supplementary database search for RCTs 2024	Handsearch 2024
		MEL report 2016	Sun 2023	Zhang 2023		
BEYOND 2020	POBA			x	x	
PEPCAD-BIF 2016	POBA			x		
BIO-RISE CHINA 2022	POBA			x	x	
PEPCAT Japan 2017	POBA			x		
PEPCAD China SVD 2022	POBA			x	x	
BELLO 2012	PES	x		x		
PICCOLETO 2010	PES	x		x		
PICCOLETO II 2020	EES			x	x	
BASKET-SMALL 2 2020	PES/EES			x	x	
RESTORE SVD China 2018	DES*			x	x	
The D5 study 2022	EES					x
Liu 2024	DES*				x	
Herdeg 2009	PES	x				
PEPCAD III 2009	SES	x				
PEPCAD IV 2011	PES	x				
Liistro 2011	EES	x				
DEB-AMI 2012	PES	x				
DEBIUT 2012	PES	x				
BABILON 2014	EES	x		x		
Poerner 2014	EES					x
Zurakowski 2015	PES					x
Nishiyama 2016	EES		x	x		
Chae 2017	ZES					x
Gobic 2017	SES		x	x		
Hao 2021	EES		x		x	
PEBSI-2 2021	SES				x	
REVELATION 2022	DES[a]		x	x	x	
Yu 2022	EES		x	x	x	
Wang 2022	SES		x			

Abbreviations: DES – drug elution stent; EES – everolimus eluting stent; PES – paclitaxel eluting stent; POBA – plain old balloon angioplasty; RCT – randomized controlled trial; SES – sirolimus eluting stent; ZES – zotarolimus eluting stent

Explanations:

[a] *no specification*

The systematic review Sun 2023 [21] included six relevant RCTs comparing DEB to DES with a total number of 680 patients with de novo lesions in large vessels. A reference vessel diameter > 2.5 mm was defined as inclusion criterion. The number of patients in the individual RCTs ranged from 60 to 184. The average age of study participants was 50 to 71 years. The majority of patients in the RCTs were men, ranging from 72% to 96%. Information on cardiovascular risk factors and on the target lesion type was reported in the review (see Appendix Table A-2). The primary endpoint of the review was the occurrence of MACE, defined as a composite outcome of cardiac mortality, re-infarction, or TLR. Further clinical outcomes reported were target lesion failure (TLF), cardiac mortality, MI, and TLR, respectively. In addition, the results of the angiographic endpoints LLL and MLD were reported. The maximum follow-up was six to 12 months for angiographic endpoints and six to 24 months for clinical endpoints.

SR Sun 2023: 6 RCTs mit 680 Patient*innen

Alter: 50-71 Jahre

72 %-96 % Männer

Maximales Follow-up: 24 Monate

The systematic review Zhang 2023 [27] included 15 RCTs comparing DEB to POBA (five RCTs) or DES (10 RCTs) with a total of 2,899 patients with de novo lesions. There were no restrictions on the diameter of the target vessels. The number of patients in the individual RCTs ranged from 60 to 758. The average age of study participants was 54 to 68 years. The majority of patients in the RCTs were men, ranging from 65% to 87%. Information on cardiovascular risk factors was only partially reported in the review (see Appendix Table A-2). Information on the target lesion type was not provided. MACE (as defined in the individual RCTs included) was defined as the primary clinical endpoint, and in-segment LLL as the primary angiographic endpoint of this review. Secondary endpoints included TLR, all-cause or cardiac mortality, MI, binary restenosis rate, MLD, and diameter stenosis. Maximum follow-up ranged from six to 36 months for clinical endpoints, and from six to nine months for angiographic endpoints. Results from subgroup analysis on vessel diameter (reference vessel diameter/RVD ≤ 2.75 mm vs RVD > 2.75 mm) were reported for the two primary endpoints.

SR Zhang 2023: 15 RCTs mit 2.899 Patient*innen

Alter: 54-68 Jahre

65 %-87 % Männer

Maximales Follow-up: 36 Monate

Study characteristics and results of the two systematic reviews are displayed in Table A-2.

Six additional RCTs [29-34] from other sources were included for the comparison of DEB versus DEB in patients with de novo lesions, with two studies limited to patients with lesions in small vessels [30, 34]. The number of included patients ranged from 42 to 247, with a mean age of 57 to 71 years. The proportion of men among the study participants ranged from 69% to 83%. Primary endpoints in the RCTs were angiographic measures (LLL, MLD, binary restenosis) [33], in-segment LLL [29], in-stent LLL [32], endothelial stent coverage [31], endothelial function [30], and in-segment diameter stenosis [34], respectively. The mean follow-up ranged from three to 12 months.

6 zusätzliche RCTs zu DEB vs DES bei de novo Läsionen

Maximales Follow-up: 12 Monate

Study characteristics and results of the six RCTs are displayed in Table A-3 to Table A-5.

Patients with small vessel disease (SVD)

SVD:
2 SR mit 6 neuen RCTs

1 zusätzliche RCT

insgesamt 10 RCTs zu DEB vs POBA oder DES bei SVD

As mentioned above, the systematic review Zhang 2023 [27] comparing DEB to other devices (POBA, BMS or DES) included also results from RCTs with patients with SVD. A second review [19] investigated DEB versus DES only in patients with SVD. In addition to the already included RCTs in the previous 2016 MEL report, these two reviews provide information from six recently published RCTs for SVD [46, 47, 50, 54, 55, 58], published between 2017 and 2022. One additional RCT [34] published in 2024 was identified in the supplementary search, and one further RCT on SVD was identified by hand search [30]. Therefore, overall 10 RCTs investigating DEB compared to POBA or DES in patients with SVD were included in the analysis of this report update. Table 3-3 presents an overview of al included RCTs and the corresponding sources.

Table 3-3: Study pool: RCTs included in different sources comparing drug-eluting balloon angioplasty with other devices in patients with SVD

RCT	Type of device used in controlgroup	Systematic review			Supplementary database search for RCTs 2024	Handsearch 2024
		MEL report 2016	Sanz Sanchez 2021	Zhang 2023		
BIO-RISE CHINA (Xu) 2022	POBA			x		
PEPCAT Japan (Funatsu) 2017	POBA			x		
PEPCAD China SVD (Qian) 2022	POBA			x		
PICCOLETO 2010	PES	x	x	x		
BELLO 2012	PES	x	x	x		
RESTORE SVD China 2018	DES*		x	x		
PICCOLETO II 2020	EES		x	x		
BASKET-SMALL 2 2020	PES/EES		x	x		
The D5 study 2022	EES					x
Liu 2024	DES[a]				x	

Abbreviations: DES – drug elution stent; EES – everolimus eluting stent; PES – paclitaxel eluting stent; POBA – plain old balloon angioplasty; RCT – randomized controlled trial

Explanations:

[a] *no specification*

The characteristics of the systematic review Zhang 2023 [27] are already descripted earlier in the report. For SVD the review included eight RCTs comparing DEB to POBA (three RCTs) or DES (five RCTs) with a total of 2,077 patients. The number of patients in the individual RCTs ranged from 60 to 758. The average age of study participants was 60 to 68 years. The majority of patients in the RCTs were men, ranging from 72% to 79%.

SR San Sanchez 2021:
5 RCTs mit
1.459 Patient*innen

Alter: 60-68 Jahre

72 %-79 % Männer

The systematic review San Sanchez 2021 [19] included five RCTs with a minimum follow-up of six months comparing DEB to DES with a total number of 1,459 patients with SVD. A RVD < 3.0 mm was defined as inclusion criterion. The number of patients in the individual RCTs ranged from 60 to 758. The average age of study participants was 60 to 68 years. The majority of patients in the RCTs were men, ranging from 72% to 79%. Information on cardiovascular risk factors was reported in the review (see Appendix Table A-2). Information on the target lesion type was not provided. TVR was the primary endpoint of this review. Secondary clinical outcomes were TLR, MI, all-cause mortality, cardiac mortality, and stent thrombosis, respectively. Secondary

angiographic endpoints were in-segment restenosis rate, in-segment diameter stenosis, in-segment LLL, in segment net luminal gain, and in-segment MLD. The maximum follow-up was six to nine months for angiographic endpoints and six to 12 months for clinical endpoints.

Maximales Follow-up: 12 Monate

Study characteristics and results of the two systematic reviews are displayed in Table A-2.

The characteristics of the two additional RCTs for SVD [30, 34] are already descripted earlier in the report. Study characteristics and results of the two RCTs are displayed in Table A-3.

3.2.2 Additional included studies safety

Results from the systematic reviews and RCT included for effectiveness outcomes were also included in the safety analyses. No additional studies were included.

3.3 Results

3.3.1 Patients with in-stent-restenosis (ISR)

Morbidity[1,2]

Angina pectoris (AP) symptom relief

There were no results concerning AP symptom relief for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ISR.

ISR: keine Evidenz zu AP-Symptomatik bzw. Vermeidung von CABG

Avoidance of coronary artery bypass grafting (CABG)

There were no results concerning the avoidance of CABG for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ISR.

Revascularization rate

DEB vs POBA

For the comparison of DEB versus POBA in patients with ISR, revascularization rates were reported as TLR in five RCTs including 745 patients and as TVR in three RCTs including 422 patients.

ISR: signifikanter Vorteil für DEB vs POBA bei TLR und TVR

Meta-analyses resulted in a statistically significant lower TLR rate with DEB compared to POBA after six months to 10 years (RR 0.28 [95% CI 0.11 to 0.67]; p=0.004; I^2=85%; see Figure 3-1) as well as statistically significant

[1] **D0005** – How does PTCA with DEB in comparison to PTCA with POBA or DES affect symptoms and findings (severity, frequency) of patients with ISR?

[2] **D0006** – How does PTCA with DEB in comparison to PTCA with POBA or DES affect progression (or recurrence) of patients with ISR?

lower TVR rate with DEB compared to POBA after six to 12 months (RR 0.39 [95% CI 0.24 to 0.64]; p=0.0002; I^2=41%; see Figure 3-2).

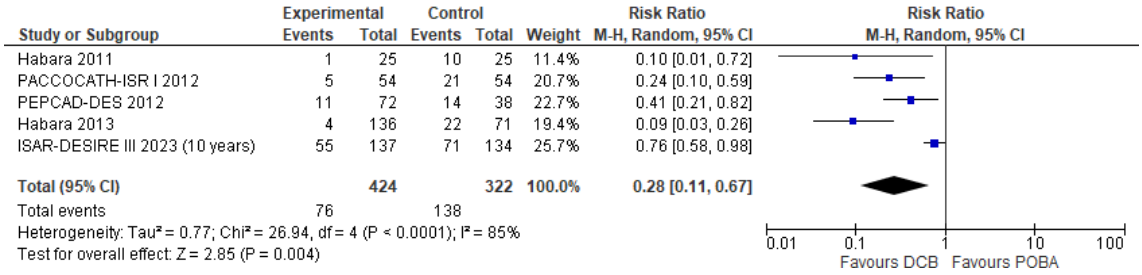

Figure 3-1: DEB versus POBA in patients with ISR – Target lesion revascularization (TLR)

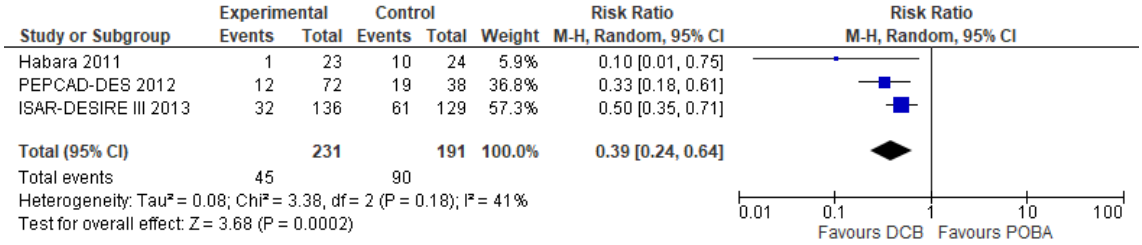

Figure 3-2: DEB versus POBA in patients with ISR – Target vessel revascularization (TVR)

DEB vs DES

ISR: kein Unterschied zwischen DEB und DES bei TLR und TVR

For the comparison of DEB versus DES in patients with ISR, revascularization rates were reported as TLR in eight RCTs including 1,467 patients and as TVR in eight RCTs including 1,610 patients.

Meta-analyses showed no statistically significant differences between DEB and DES in the TLR rate after 12 months to 10 years (RR 1.33 [95% CI 0.90 to 1.95]; p=0.15; I^2=37%; see Figure 3-3) and in the TVR rate after 12 months to three years (RR 1.25 [95% CI 0.89 to 1.76]; p=0.19; I^2=33%; see Figure 3-4).

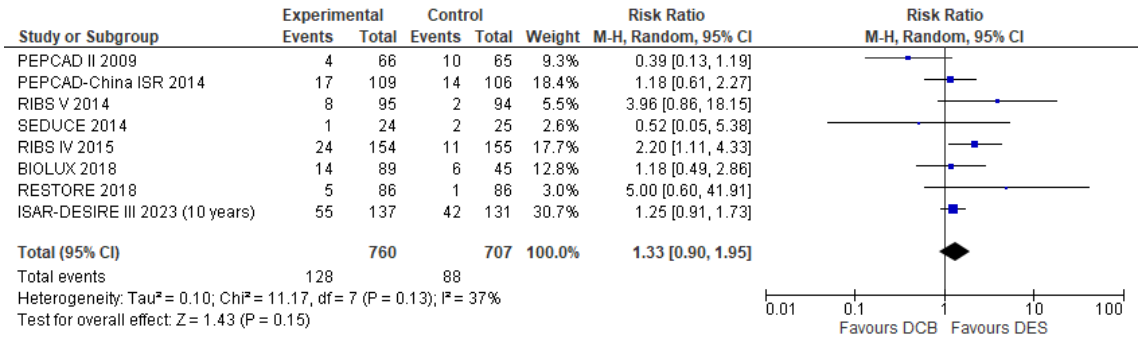

Figure 3-3: DEB versus DES in patients with ISR – Target lesion revascularization (TLR)

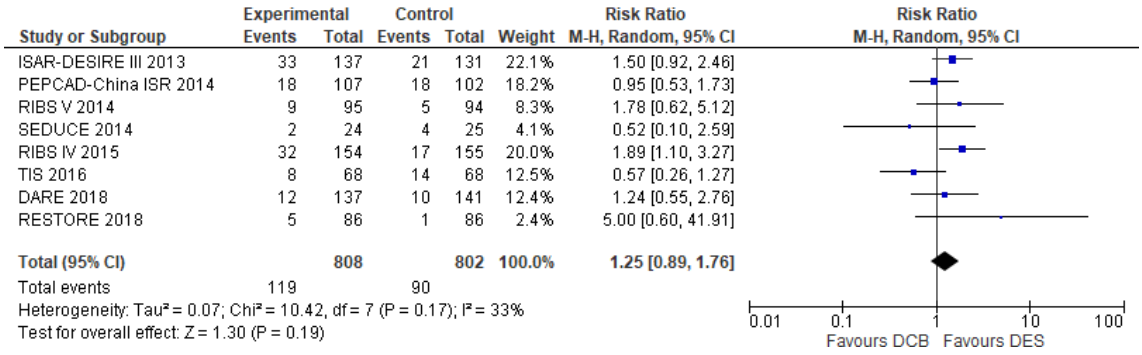

Figure 3-4: DEB versus DES in patients with ISR – Target vessel revascularization (TVR)

Health-related quality of life[3,4]

There were no results concerning the generic health-related or disease-specific quality of life for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ISR.

ISR: keine Evidenz zu LQ

Mortality[5,6]

DEB vs POBA

For the comparison of DEB versus POBA in patients with ISR, results on overall mortality were reported in five RCTs including 746 patients, while results on cardiac mortality were reported in four RCTs with a total of 638 patients.

ISR: kein Unterschied zwischen DEB und POBA bei Gesamtmortalität und kardialer Mortalität

The meta-analysis including results on overall mortality after six months to 10 years follow-up showed no significant difference in the overall mortality rates between DEB and POBA (RR 0.68 [95% CI 0.34 to 1.37]; p=0.28; I^2=40%; see Figure 3-5). The meta-analysis for cardiac mortality also showed no significant difference between DEB and POBA within the same follow-up period (RR 0.45 [95% CI 0.08 to 2.57]; p=0.37; I^2=64%; see Figure 3-6).

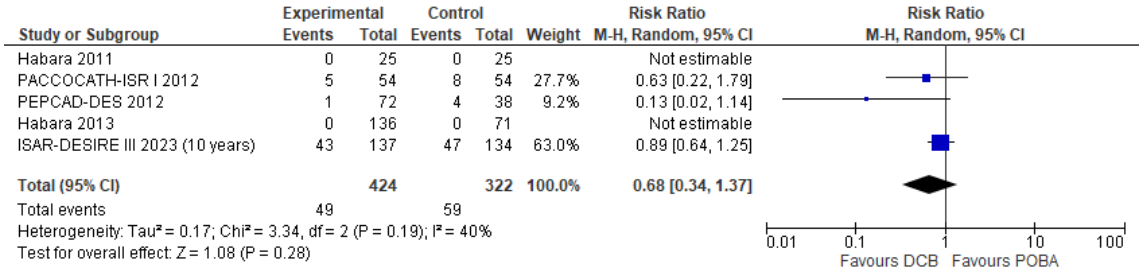

Figure 3-5: DEB versus POBA in patients with ISR – Overall mortality

[3] **D0012** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on generic health-related quality of life in patients with ISR?

[4] **D0013** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on disease-specific quality of life in patients with ISR?

[5] **D0001** – What is the expected beneficial effect of PTCA with DEB versus PTCA with POBA or DES on mortality in patients with ISR?

[6] **D0003** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on the mortality due to causes other than the target disease in patients with ISR?

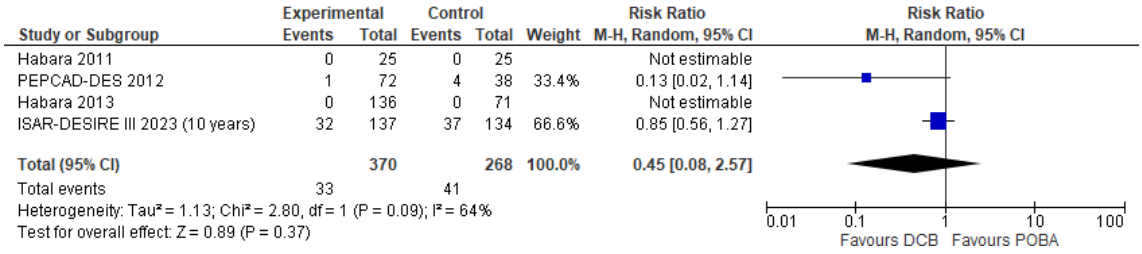

Figure 3-6: DEB versus POBA in patients with ISR – Cardiac mortality

DEB vs DES

ISR: kein Unterschied zwischen DEB und DES bei Gesamtmortalität und kardialer Mortalität

For the comparison of DEB versus DES in patients with ISR, results on overall mortality were reported in nine RCTs including 1,741 patients, and on cardiac mortality in 10 RCTs including 1,875 patients.

Meta-analyses after 12 months to 10 years showed no significant differences between DEB and DES in the overall mortality rates (RR 0.82 [95% CI 0.62 to 1.07]; p=0.15; I^2=0%; see Figure 3-7) as well as in cardiac mortality rates (RR 0.83 [95% CI 0.58 to 1.18]; p=0.29; I^2=0%; see Figure 3-8)

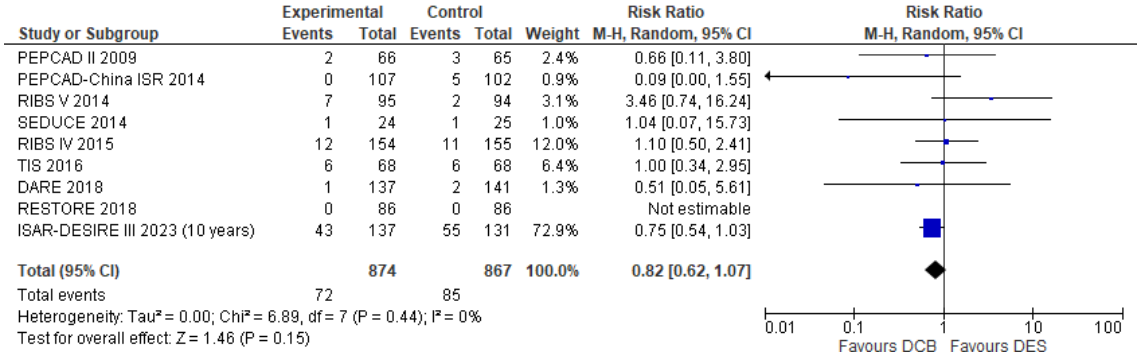

Figure 3-7: DEB versus DES in patients with ISR – Overall mortality

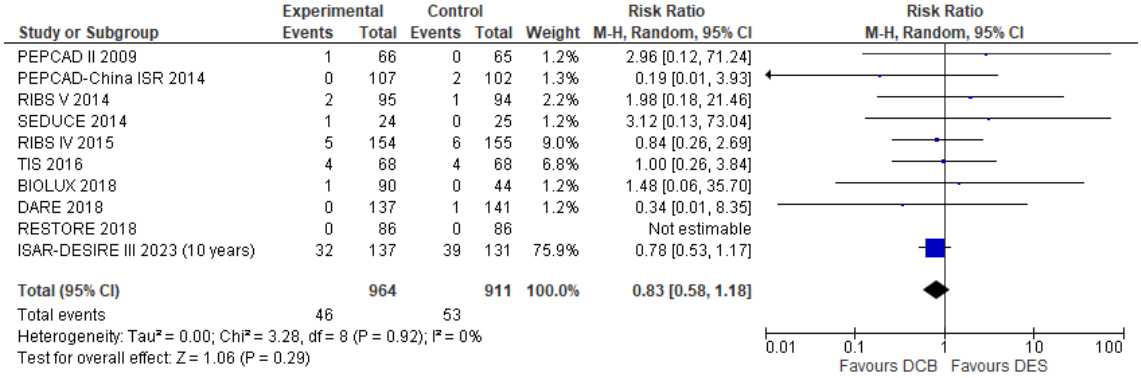

Figure 3-8: DEB versus POBA in patients with ISR – Cardiac mortality

Patient safety[7],[8],[9]

Major adverse cardiac events (MACE), myocardial infarction (MI), and stent thrombosis

DEB vs POBA

ISR: signifikanter Vorteil für DEB vs POBA bei MACE; kein Unterschied zwischen DEB und POBA bei MI und Stent Thrombosen

For the comparison of DEB versus POBA, results on MACE, MI, and stent thrombosis were reported in five RCTs including 746 patients with ISR. Follow-up ranged from six months to 10 years.

The meta-analysis for MACE resulted in a statistically significant advantage for DEB compared to POBA (RR 0.38 [95% CI 0.20 to 0.73]; p=0.004; I^2=86%; see Figure 3-9), while those for MI (RR 1.42 [95% CI 0.72 to 2.79]; p=0.31; I^2=0%) and stent thrombosis (RR 0.38 [95% CI 0.05 to 2.71]; p= 0.33; I^2=46%) showed no significant difference between the two interventions (see Figure 3-10 and Figure 3-11).

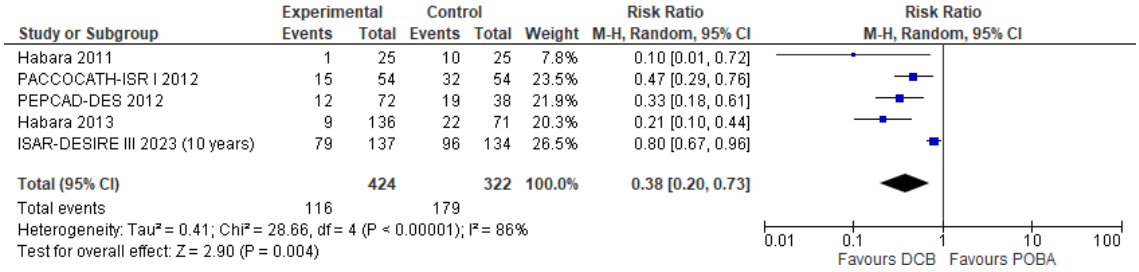

Figure 3-9: DEB versus POBA in patients with ISR – Major adverse cardiac events (MACE)

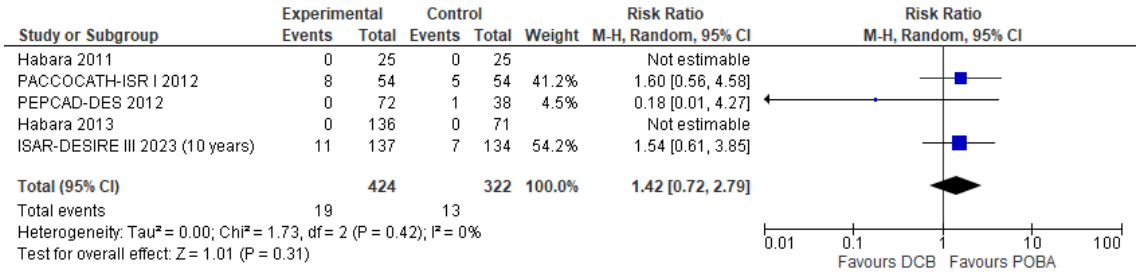

Figure 3-10: DEB versus POBA in patients with ISR – Myocardial infarction (MI)

[7] C0008 – How safe is PTCA with DEB in comparison to PTCA with POBA or DES in patients with ISR?

[8] C0004 – How does the frequency or severity of harms change over time or in different settings?

[9] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of PTCA with DEB?

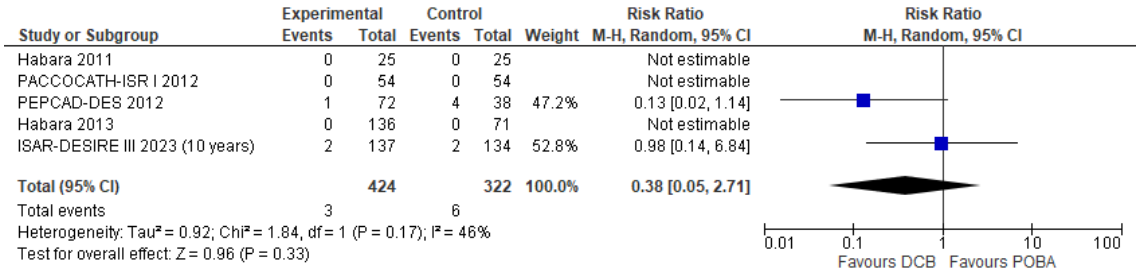

Figure 3-11: DEB versus POBA in patients with ISR – Stent Thrombosis

DEB vs DES

ISR: kein Unterschied zwischen DEB und DES bei MACE, MI und Stent Thrombosen

For the comparison of DEB versus DES, results on MACE were reported in nine RCTs including 1,828 patients with ISR and on MI or stent thrombosis in 10 RCTs including 1,877 and 1,874 patients with ISR, respectively. Follow-up ranged from 12 months to 10 years.

All meta-analyses resulted in no statistically significant difference between DEB and DES (MACE: RR 0.98 [95% CI 0.78 to 1.24]; p=0.87; I^2=36%; MI: RR 0.94 [95% CI 0.60 to 1.46]; p=0.77; I^2=0%); stent thrombosis: RR 1.01 [95% CI 0.41 to 2.49]; p=0.99; I^2=0%; see Figure 3-12, Figure 3-13, and Figure 3-14).

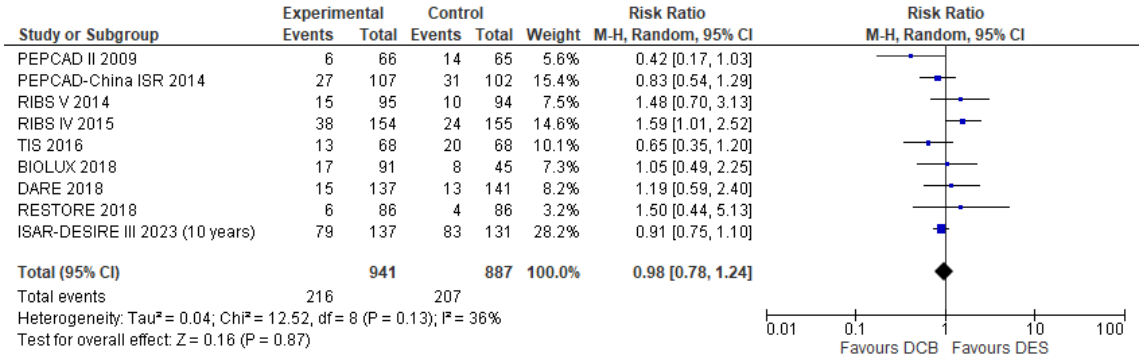

Figure 3-12: DEB versus DES in patients with ISR – Major adverse cardiac events (MACE)

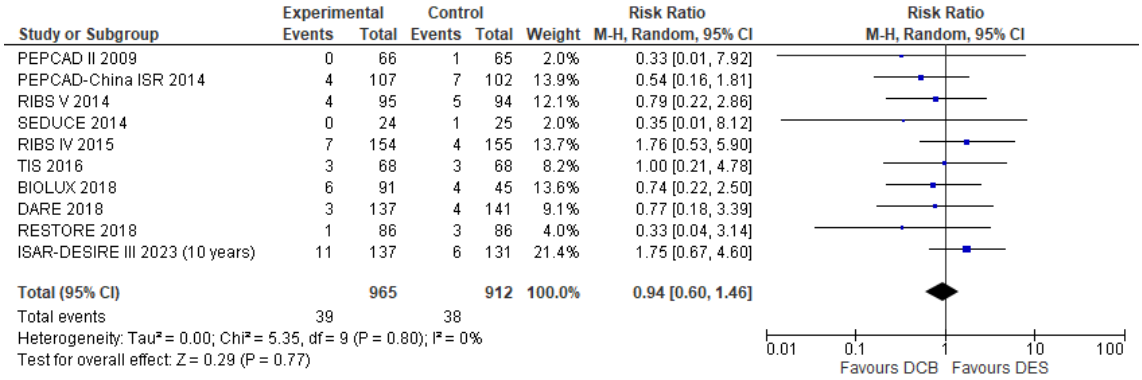

Figure 3-13: DEB versus DES in patients with ISR – Myocardial infarction (MI)

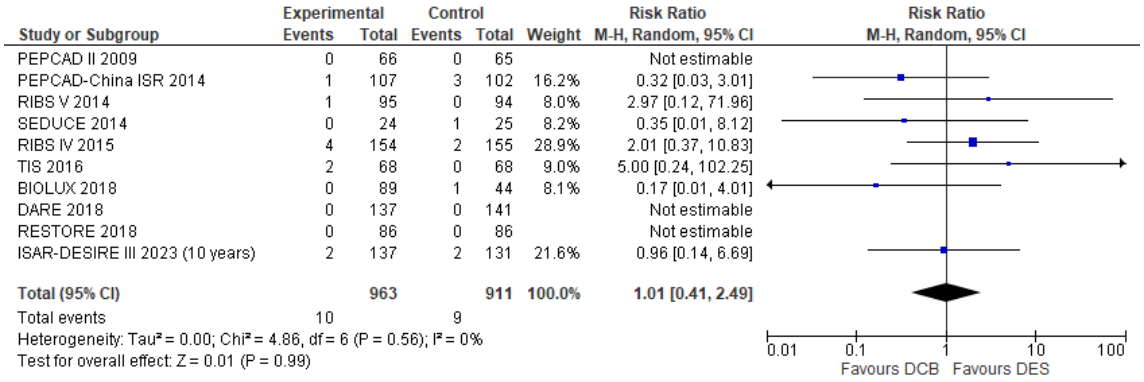

Figure 3-14: DEB versus DES in patients with ISR – Stent Thrombosis

Serious adverse events (SAE)

There were no results concerning **(serious) adverse events** for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ISR.

ISR: keine Evidenz zu SAE

3.3.2 Patients with de novo lesions of large or small coronary vessels

Morbidity[10,11]

Angina pectoris (AP) symptom relief

There were no results concerning AP symptom relief for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with de novo lesions.

de novo Läsionen: keine Evidenz zu AP-Symptomatik bzw. Vermeidung von CABG

Avoidance of coronary artery bypass grafting (CABG)

There were no results concerning the avoidance of CABG for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with de novo lesions.

Revascularization rate

DEB vs POBA

For the comparison of DEB versus POBA in patients with de novo lesions of large or small coronary vessels, revascularization rates were reported as TLR in five RCTs including 887 patients and as TVR in two RCTs including 490 patients. Meta-analyses resulted in a statistically significant lower TLR rate with DEB compared to POBA after six to 12 months (RR 0.46 [95% CI 0.24 to 0.86]; p=0.01; I^2=0%; see Figure 3-15), but no statistically significant difference in the TVR rate after nine to 12 months (RR 0.48 [95% CI 0.19 to 1.24]; p=0.13; I^2=na; see Figure 3-16).

de novo Läsionen: signifikanter Vorteil für DEB vs POBA bei TLR; kein Unterschied zwischen DEB und POBA bei TVR

[10] **D0005** – How does PTCA with DEB versus PTCA with POBA or DES affect symptoms and findings (severity, frequency) of patients with de novo lesions in coronary vessels?

[11] **D0006** – How does PTCA with DEB versus PTCA with POBA or DES affect progression (or recurrence) of patients with de novo lesions in coronary vessels?

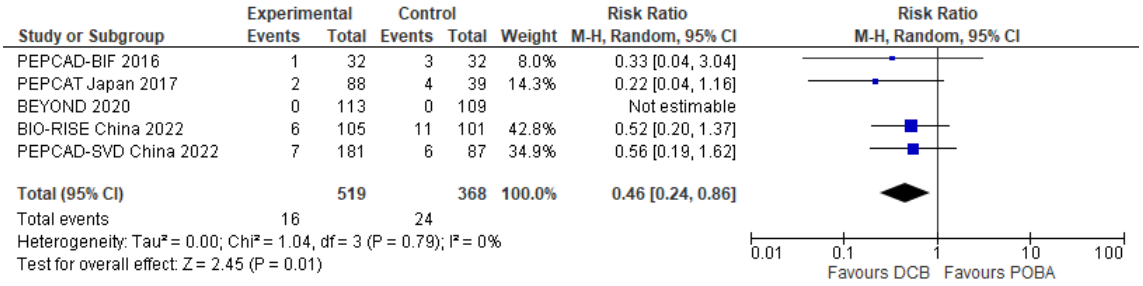

Figure 3-15: DEB versus POBA in patients with de novo lesions – Target lesion revascularization (TLR)

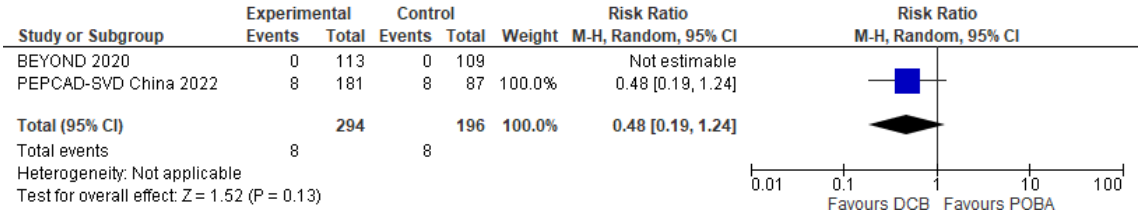

Figure 3-16: DEB versus POBA in patients with de novo lesions – Target vessel revascularization (TVR)

DEB vs DES

For the comparison of DEB versus DES in patients with de novo lesions of large or small coronary vessels, revascularization rates were reported as TLR in 21 RCTs including 3,151 patients and as TVR in 15 RCTs including 3,292 patients.

Meta-analyses showed higher rates of TLR for DEB compared to DES after six months to three years, although the difference was just not statistically significant (RR 1.46 [95% CI 1.00 to 2.15]; p=0.05; I^2=40%; see Figure 3-17).

de novo Läsionen: kein signifikanter Unterschied zwischen DEB und DES bei TLR; signifikanter Nachteil für DEB vs DES bei TVR

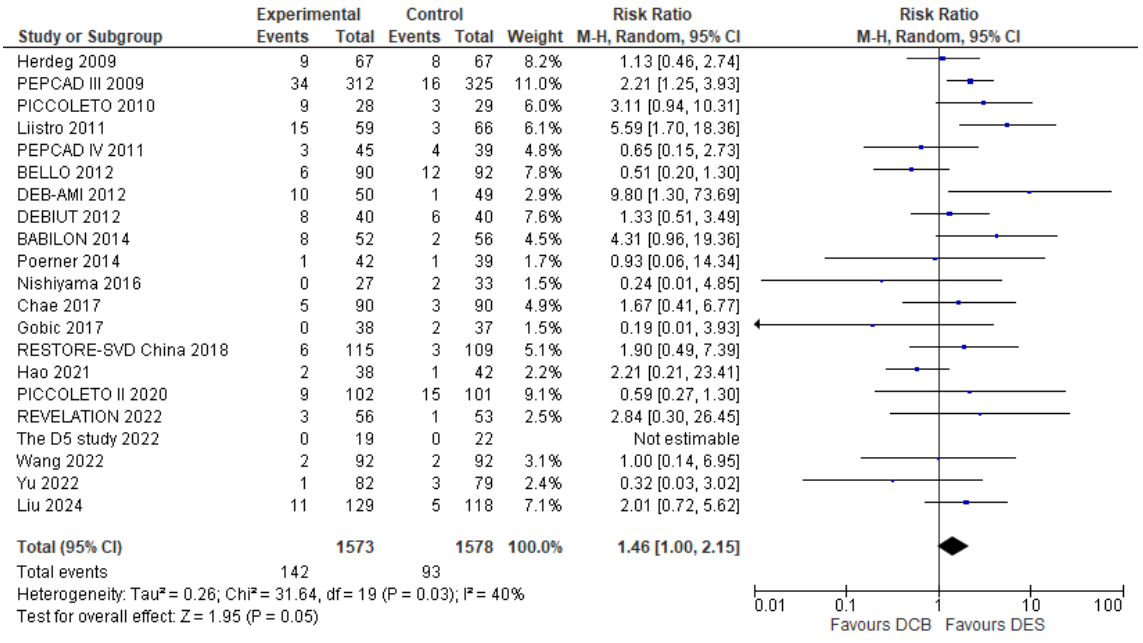

Figure 3-17: DEB versus DES in patients with de novo lesions – Target lesion revascularization (TLR)

For TVR there was a statistically significant disadvantage for DEB compared to DES (RR 1.51 [95% CI 1.05 to 2.16]; p=0.03; I^2=48%; see Figure 3-18).

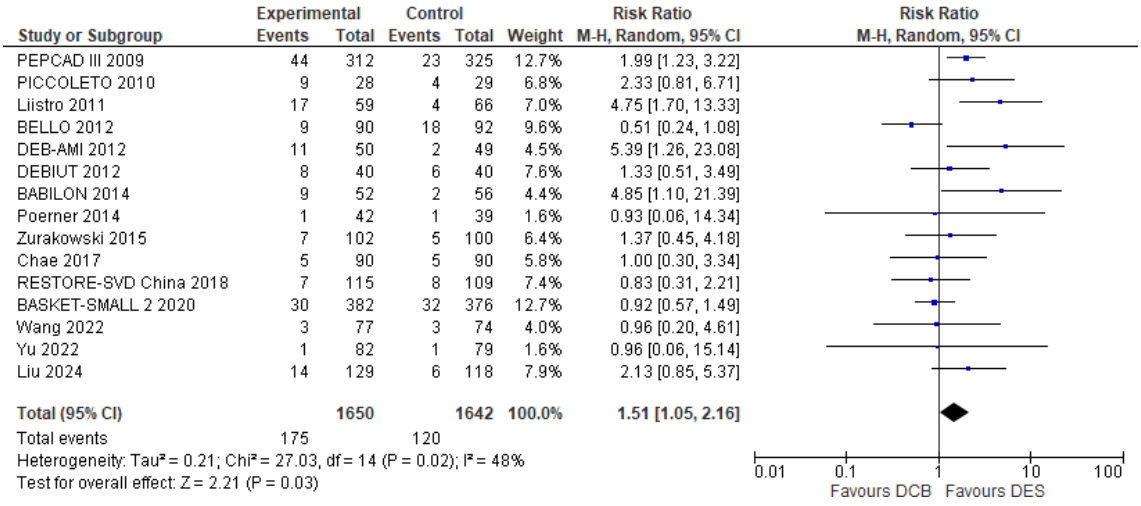

Figure 3-18: DEB versus DES in patients with de novo lesions – Target vessel revascularization (TVR)

Health-related quality of life[12,13]

There were no results concerning the generic health-related or disease-specific quality of life for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with de novo lesions.

de novo Läsionen: keine Evidenz zu LQ

[12] **D0012** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on generic health-related quality of life in patients with de novo lesions in coronary vessels?

[13] **D0013** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on disease-specific quality of life in patients with de novo lesions in coronary vessels?

Mortality[14,15]

DEB vs POBA

de novo Läsionen: keine Todesfälle in 4 RCTs zu DEB vs POBA; 0 vs 2 Todesfälle in 1 RCT

For the comparison of DEB versus POBA in patients with de novo lesions of large or small coronary vessels, results on overall mortality and cardiac mortality were reported in five RCTs including 887 patients.

Overall, there were no death reported in four of these five RCTs within a follow-up period of six to 12 months. In the fifth trial two patients died within 12 months in the POBA group, while there was no death in die DEB group. Both death were of cardiac origin.

DEB vs DES

de novo Läsionen: kein Unterschied zwischen DEB und DES bei Gesamtmortalität und kardialer Mortalität

For the comparison of DEB versus DES in patients with de novo lesions of large or small coronary vessels, results on overall mortality were reported in 23 RCTs including 4,089 patients, while results on cardiac mortality were reported in 22 RCTs with a total of 3,485 patients.

The meta-analysis including results on overall mortality after six months to three years follow-up showed no significant difference in the overall mortality rates between DEB and DES (RR 1.04 [95% CI 0.69 to 1.55]; p=0.86; I^2=0%; see Figure 3-19). The meta-analysis for cardiac mortality also showed no significant difference between DEB and DES within the same follow-up period (RR 1.14 [95% CI 0.65 to 2.03]; p=0.65; I^2=0%; see Figure 3-20).

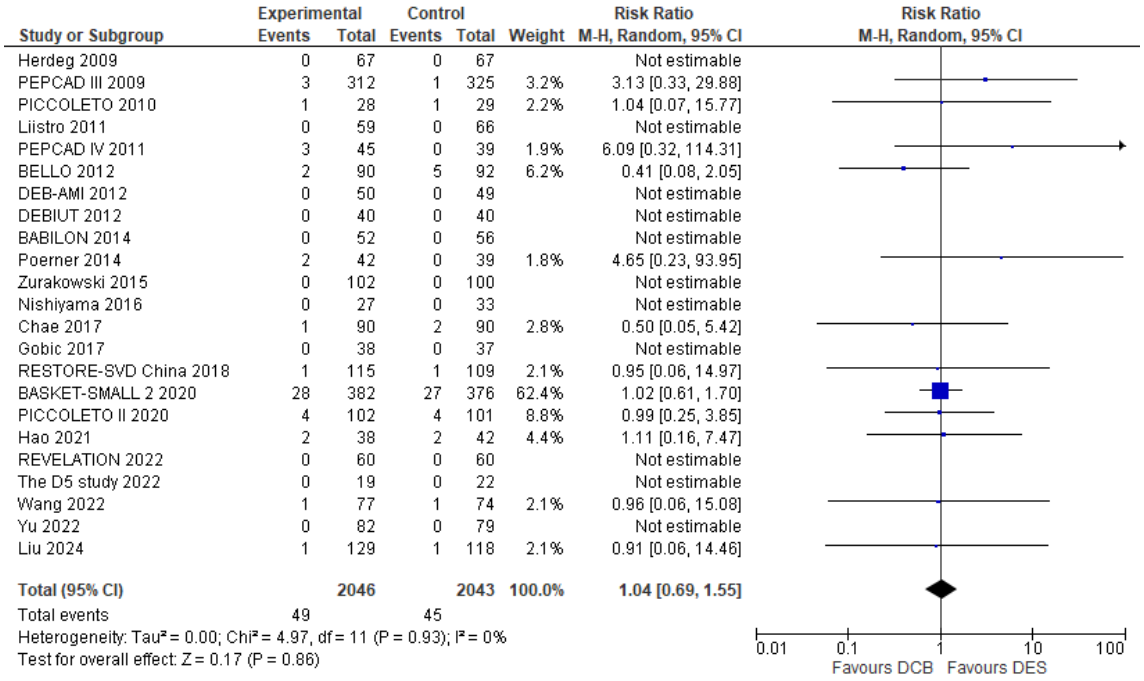

Figure 3-19: DEB versus DES in patients with de novo lesions – Overall mortality

[14] **D0001** – What is the expected beneficial effect of PTCA with DEB versus PTCA with POBA or DES on mortality in patients with de novo lesions in coronary vessels?

[15] **D0003** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on the mortality due to causes other than the target disease in patients with de novo lesions in coronary vessels?

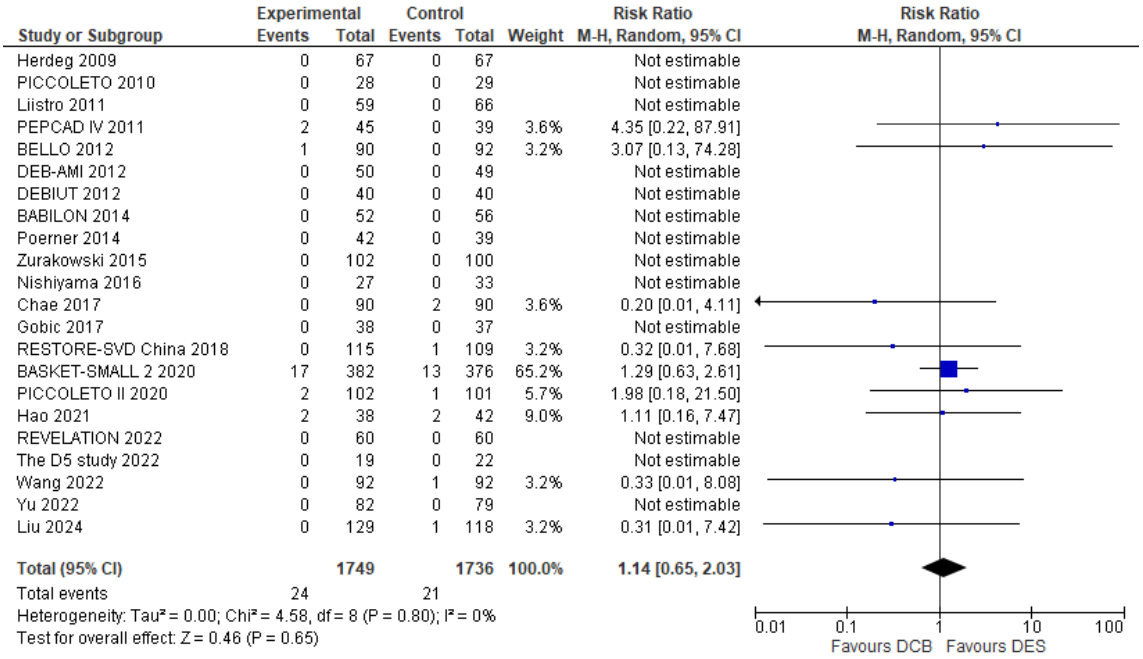

Figure 3-20: DEB versus DES in patients with de novo lesions – Cardiac mortality

Patient safety[16,17,18]

Major adverse cardiac events (MACE), myocardial infarction (MI), and stent thrombosis

DEB vs POBA

de novo Läsionen: signifikanter Vorteil für DEB vs POBA bei MACE; kein Unterschied zwischen DEB und POBA bei MI; keine Stent Thrombosen

For the comparison of DEB versus POBA in patients with de novo lesions of large or small coronary vessels, results on MACE were reported in four RCTs including 823 patients, results on MI were reported in five RCTs including 887 patients, and results on stent thrombosis were reported in three RCTs including 617 patients. Follow-up ranged from six to 12 months.

The meta-analysis for MACE resulted in statistically significant lower event rates for DEB compared to POBA (RR 0.63 [95% CI 0.43 to 0.92]; p=0.02; I^2=0%; see Figure 3-21), while the meta-analysis for MI showed no significant difference between the two interventions (RR 0.39 [95% CI 0.15 to 1.02]; p= 0.06; I^2=0%; see Figure 3-22). No stent thrombosis after PTCA with DEB or POBA occurred in three RCTs within 6 to 12 months follow-up.

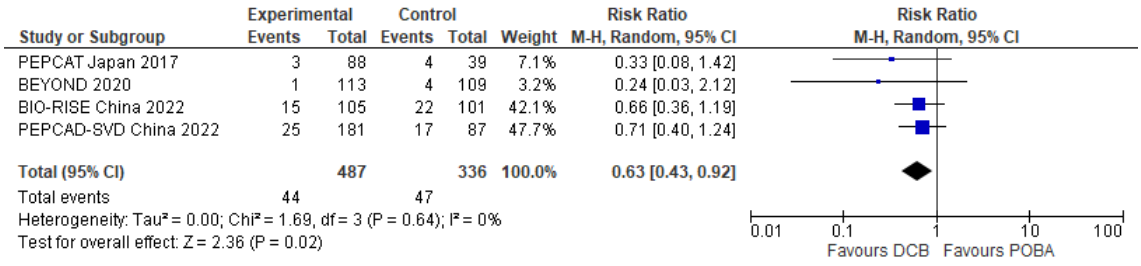

Figure 3-21: DEB versus POBA in patients with de novo lesions – Major adverse cardiac events (MACE)

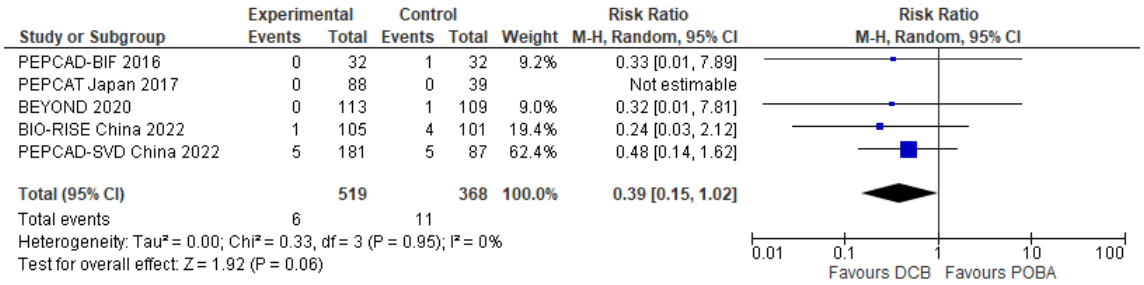

Figure 3-22: DEB versus POBA in patients with de novo lesions – Myocardial infarction (MI)

[16] C0008 – How safe is PTCA with DEB in comparison to PTCA with POBA or DES in patients with de novo lesions in coronary vessels?

[17] C0004 – How does the frequency or severity of harms change over time or in different settings?

[18] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of PTCA with DEB?

DEB vs DES

de novo Läsionen: kein Unterschied zwischen DEB und DES bei MACE, MI und Stent Thrombosen

For the comparison of DEB versus DES in patients with de novo lesions of large or small coronary vessels, results on MACE were reported in 23 RCTs including 4,078 patients, results on MI were reported in 22 RCTs including 4,003 patients, and results on stent thrombosis were reported in 15 RCTs including 2,698 patients. Follow-up ranged from six months to three years.

All meta-analyses resulted in no statistically significant difference between DEB and DES (MACE: RR 1.15 [95% CI 0.88 to 1.51]; p=0.30; I^2=53%; MI: RR 0.91 [95% CI 0.61 to 1.36]; p=0.64; I^2=2%); stent thrombosis: RR 0.75 [95% CI 0.36 to 1.56]; p=0.44; I^2=0%; see Figure 3-23 Figure 3-24, and Figure 3-25).

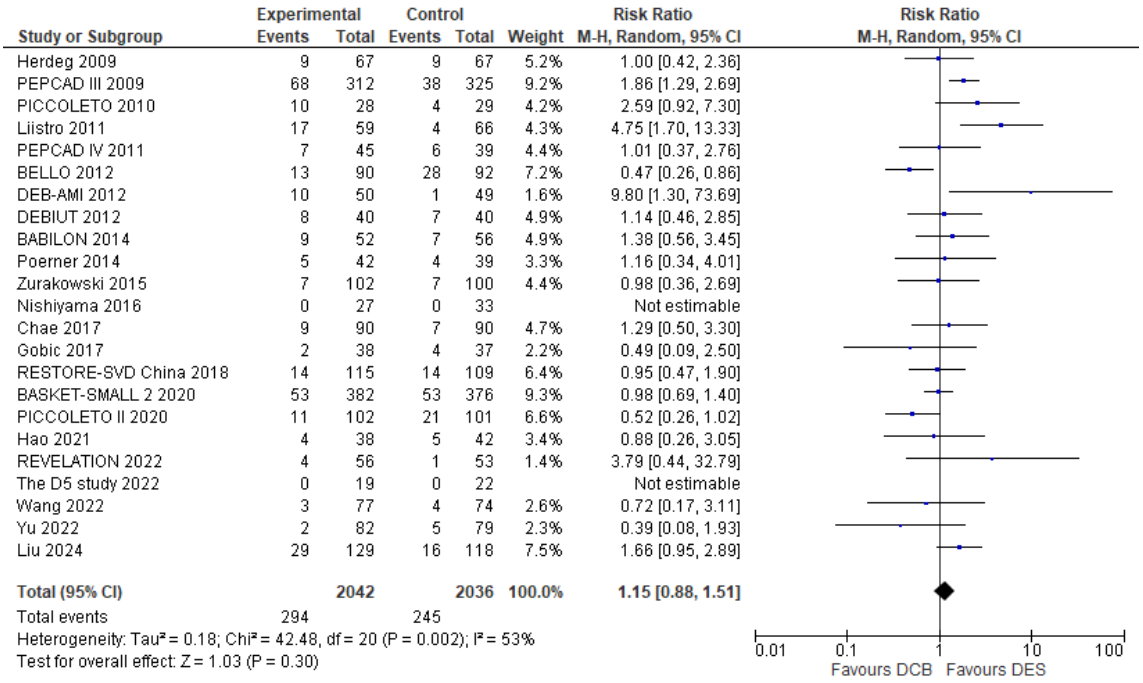

Figure 3-23: DEB versus DES in patients with de novo lesions – Major adverse cardiac events (MACE)

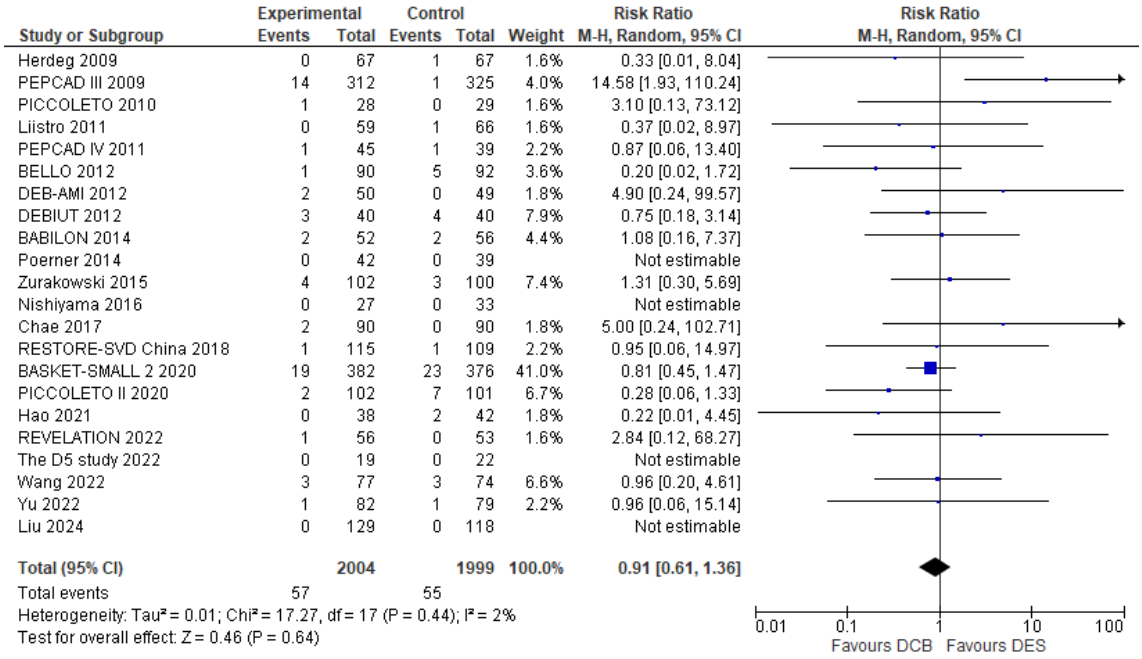

Figure 3-24: DEB versus DES in patients with de novo lesions – Myocardial infarction (MI)

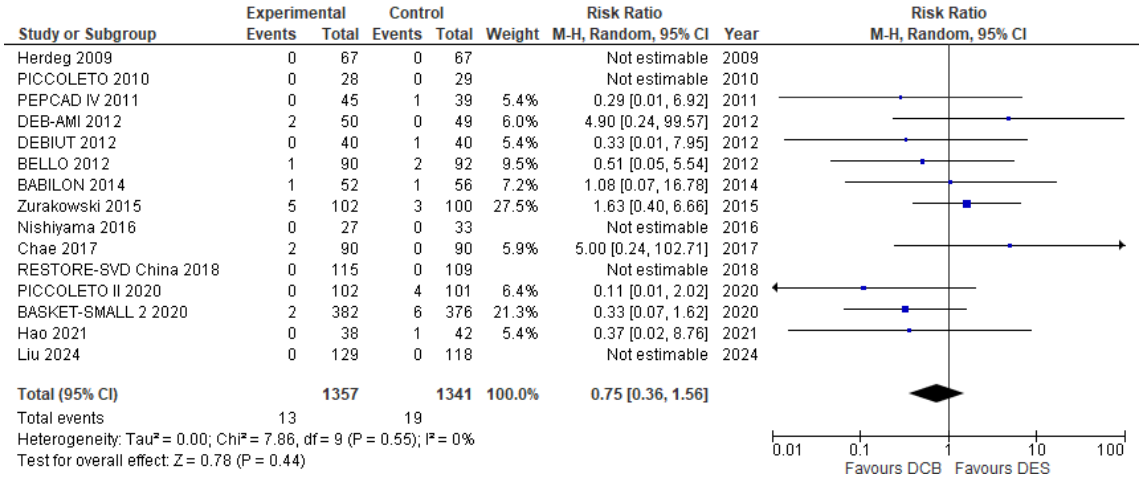

Figure 3-25: DEB versus DES in patients with de novo lesions – Stent Thrombosis

Serious adverse events (SAE)

There were no results concerning (serious) adverse events for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with de novo lesions.

de novo Läsionen: keine Evidenz zu SAE

3.3.3 Patients with small vessel disease (SVD)

Morbidity[19,20]

Angina pectoris (AP) symptom relief

There were no results concerning AP symptom relief for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with SVD.

SVD: keine Evidenz zu AP-Symptomatik bzw. Vermeidung von CABG

Avoidance of coronary artery bypass grafting (CABG)

There were no results concerning the avoidance of CABG for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with SVD.

Revascularization rate

DEB vs POBA

For the subgroup of patients with de novo lesions of small coronary vessels (SVD) comparing DEB to POBA, revascularization rates in were reported as TLR in three RCTs including 601 patients. The meta-analysis for TLR resulted in a statistically significant lower rate with DEB compared to POBA after six to 12 months (RR 0.47 [95% CI 0.25 to 0.90]; p=0.02; I^2=0%; see Figure 3-26). Results on TVR were only reported in one RCT including 268 patients, showing no statistically significant difference between the two interventions after 12 months (RR 0.48 [95% CI 0.19 to 1.24]; p=0.13).

SVD: signifikanter Vorteil für DEB vs POBA bei TLR; kein Unterschied zwischen DEB und POBA bei TVR

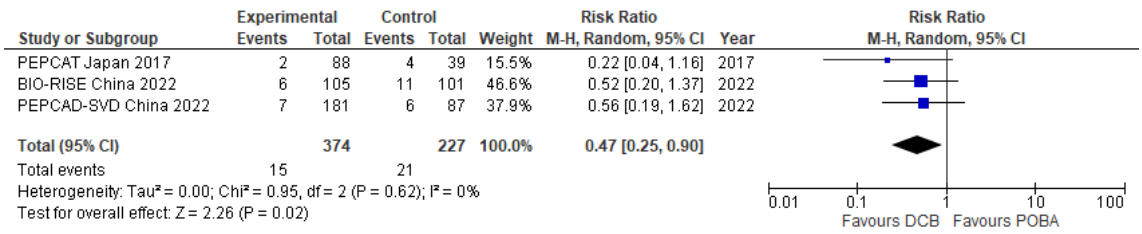

Figure 3-26: DEB versus POBA in patients with SVD – Target lesion revascularization (TLR)

DEB vs DES

For the comparison of DEB versus DES in patients with SVD, revascularization rates were reported as TLR in six RCTs including 954 patients and as TVR in five RCTs including 1,468 patients.

SVD: kein Unterschied zwischen DEB und DES bei TLR und TVR

Meta-analyses showed no statistically significant differences between DEB and DES in the TLR rate after eight months to three years (RR 1.18 [95% CI 0.57 to 2.43]; p=0.65; I^2=59%; see Figure 3-27) and in the TVR rate after nine months to three years (RR 1.06 [95% CI 0.63 to 1.78]; p=0.82; I^2=52%; see Figure 3-28).

[19] **D0005** – How does PTCA with DEB versus PTCA with POBA or DES affect symptoms and findings (severity, frequency) of patients with SVD?

[20] **D0006** – How does PTCA with DEB versus PTCA with POBA or DES affect progression (or recurrence) of patients with SVD?

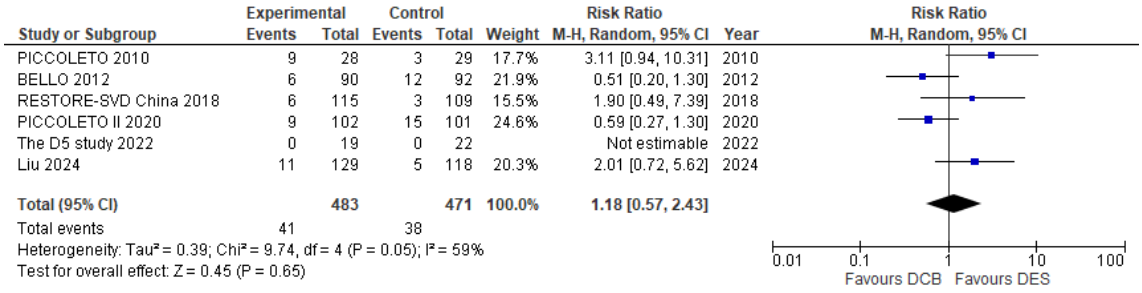

Figure 3-27: DEB versus DES in patients with SVD – Target lesion revascularization (TLR)

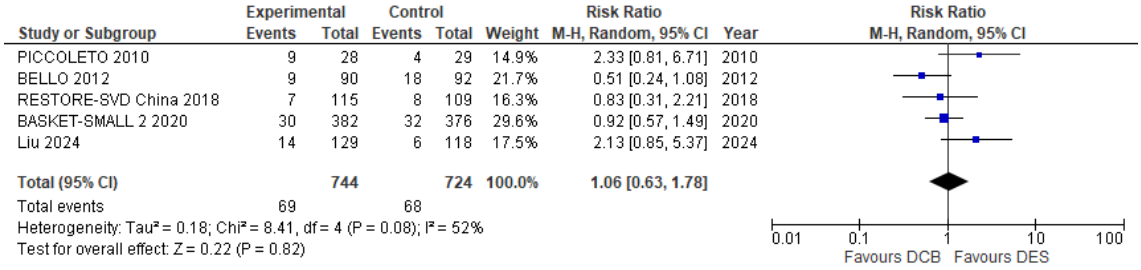

Figure 3-28: DEB versus DES in patients with SVD – Target vessel revascularization (TVR)

Health-related quality of life[21,22]

There were no results concerning the generic health-related or disease-specific quality of life for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with SVD.

SVD: keine Evidenz zu LQ

Mortality[23,24]

DEB vs POBA

For the comparison of DEB versus POBA in patients with SVD, results on overall mortality and cardiac mortality were reported in three RCTs including 601 patients.

SVD: keine Todesfälle in 2 RCTs zu DEB vs POBA; 0 vs 2 Todesfälle in 1 RCT

Overall, there were no death reported in two of these three RCTs within a follow-up period of six to 12 months. In the third trial two patients died within 12 months in the POBA group, while there was no death in die DEB group. Both death were of cardiac origin.

[21] **D0012** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on generic health-related quality of life in patients with SVD?

[22] **D0013** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on disease-specific quality of life in patients with SVD?

[23] **D0001** – What is the expected beneficial effect of PTCA with DEB versus PTCA with POBA or DES on mortality in patients with SVD?

[24] **D0003** – What is the effect of PTCA with DEB versus PTCA with POBA or DES on the mortality due to causes other than the target disease in patients with SVD?

DEB vs DES

SVD: kein Unterschied zwischen DEB und DES bei Gesamtmortalität und kardialer Mortalität

For the comparison of DEB versus DES in patients with SVD, results on overall and cardiac mortality were reported in seven RCTs including 1,712 patients.

The meta-analysis including results on overall mortality after eight months to three years follow-up showed no significant difference in the overall mortality rates between DEB and DES (RR 0.95 [95% CI 0.61 to 1.47]; p=0.81; I^2=0%; see Figure 3-29). The meta-analysis for cardiac mortality also showed no significant difference between DEB and DES within the same follow-up period (RR 1.23 [95% CI 0.65 to 2.32]; p=0.53; I^2=0%; see Figure 3-30).

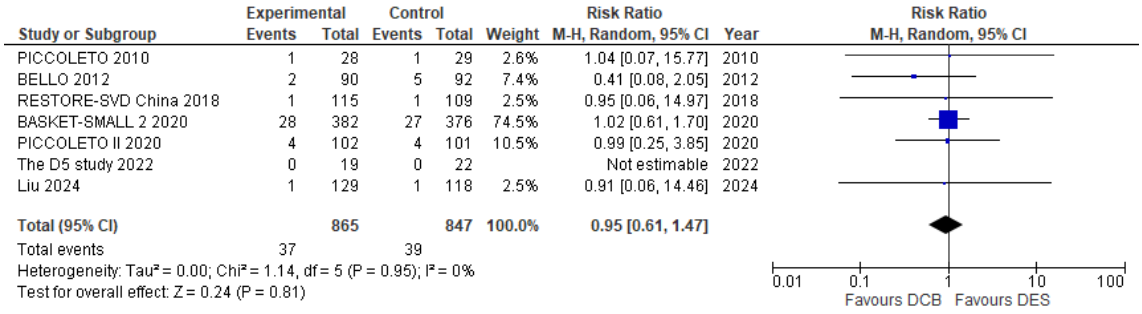

Figure 3-29: DEB versus DES in patients with SVD – Overall mortality

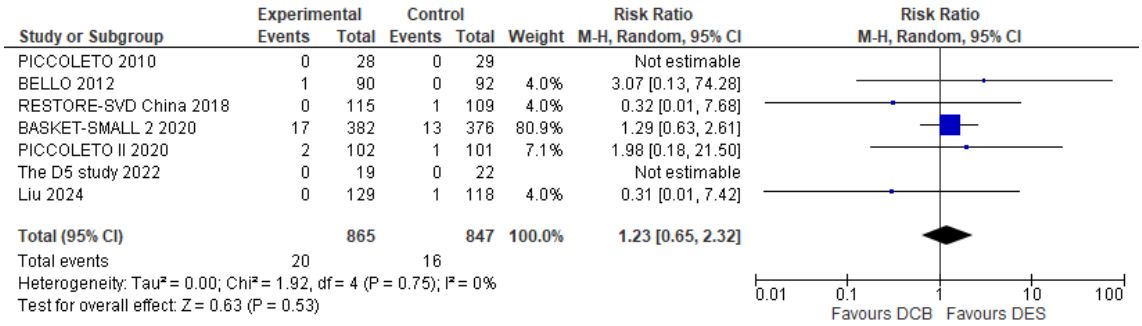

Figure 3-30: DEB versus DES in patients with SVD – Cardiac mortality

Patient safety[25,26,27]

Major adverse cardiac events (MACE), myocardial infarction (MI), and stent thrombosis

DEB vs POBA

SVD: signifikanter Vorteil für DEB vs POBA bei MACE; kein Unterschied zwischen DEB und POBA bei MI; keine Stent Thrombosen

For the comparison of DEB versus POBA in patients with SVD, results on MACE and MI were reported in three RCTs including 601 patients. Results on stent thrombosis were reported in two RCTs including 395 patients. Follow-up ranged from six to 12 months.

The meta-analysis for MACE resulted in statistically significant lower event rates for DEB compared to POBA (RR 0.65 [95% CI 0.44 to 0.96]; p=0.03; I^2=0%; see Figure 3-31), while the meta-analysis for MI showed no significant difference between the two interventions (RR 0.41 [95% CI 0.14 to 1.18]; p=0.10; I^2=0%; see Figure 3-32). No stent thrombosis after PTCA with DEB or POBA occurred in three RCTs within six to 12 months follow-up.

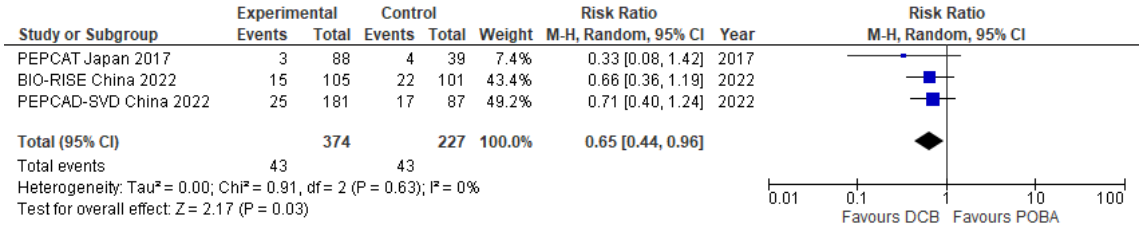

Figure 3-31: DEB versus POBA in patients with SVD – Major adverse cardiac events (MACE)

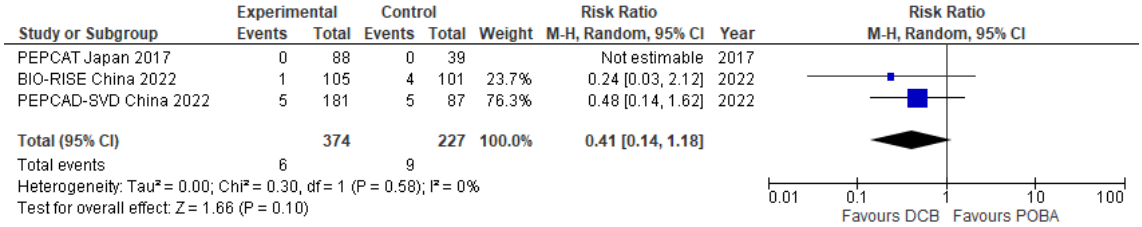

Figure 3-32: DEB versus DES in patients with de novo lesions – Myocardial infarction (MI)

DEB vs DES

SVD: kein Unterschied zwischen DEB und DES bei MACE, MI und Stent Thrombosen

For the comparison of DEB versus DES in patients with SVD, results on MACE and MI were reported in seven RCTs including 1,712 patients. Follow-up ranged from eight months to three years. Results on stent thrombosis were reported in six RCTs including 1,671 patients and a follow-up of nine months to three years.

---

[25] C0008 – How safe is PTCA with DEB in comparison to PTCA with POBA or DES in pa-tients with SVD?

[26] C0004 – How does the frequency or severity of harms change over time or in different settings?

[27] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of PTCA with DEB?

All meta-analyses resulted in no statistically significant difference between DEB and DES (MACE: RR 0.95 [95% CI 0.61 to 1.47]; p=0.81; I^2=68%; MI: RR 0.69 [95% CI 0.41 to 1.16]; p=0.17; I^2=0%); stent thrombosis: RR 0.30 [95% CI 0.09 to 1.02]; p=0.05; I^2=0%; see Figure 3-33, Figure 3-34, and Figure 3-35).

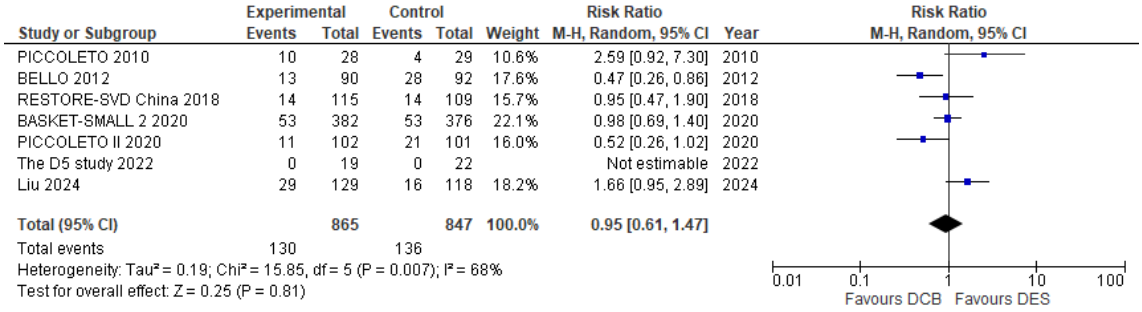

Figure 3-33: DEB versus DES in patients with SVD – Major adverse cardiac events (MACE)

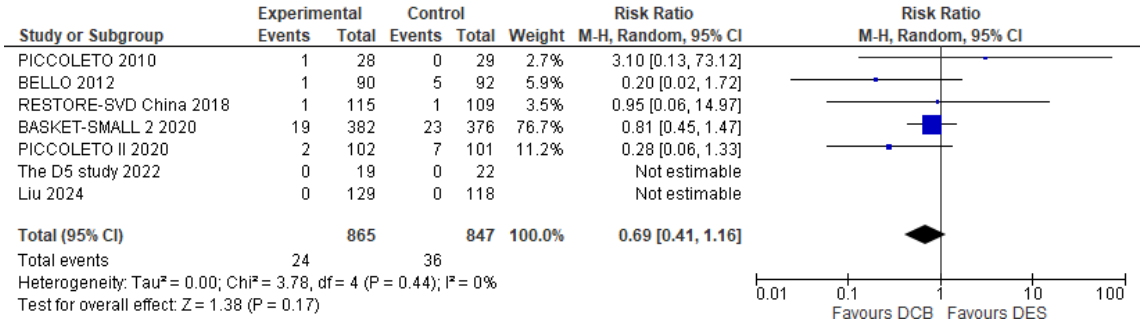

Figure 3-34: DEB versus DES in patients with SVD – Myocardial infarction (MI)

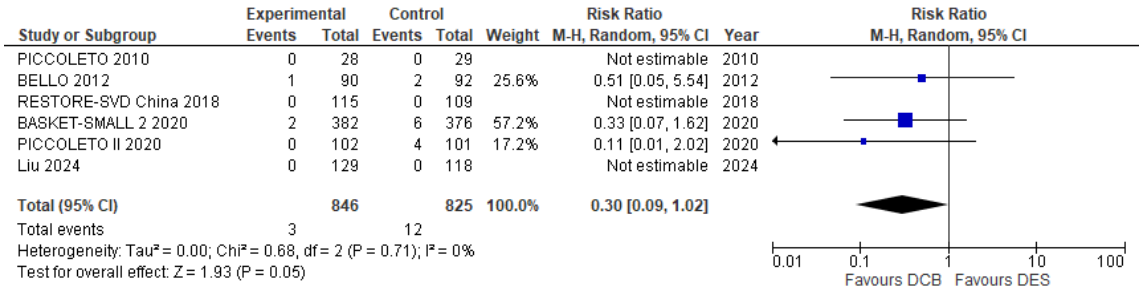

Figure 3-35: DEB versus DES in patients with SVD – Stent thrombosis

Serious adverse events (SAE)

There were no results concerning (serious) adverse events for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with SVD.

SVD: keine Evidenz zu SAE

3.3.4 Patients with ostium stenosis

Morbidity[28,29]

Ostiumstenosen: keine Evidenz aus SR oder RCTs vorhanden

There were no results concerning AP symptom relief for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

There were no results concerning the avoidance of CABG for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

There were no results concerning revascularisation rate (TLR or TVR) for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

Health-related quality of life[30,31]

There were no results concerning the generic health-related or disease-specific quality of life for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

Mortality[32,33]

There were no results concerning overall or cardiac mortality for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

---

28 **D0005** – How does PTCA with DEB in comparison to PTCA with POBA or DES affect symptoms and findings (severity, frequency) of patients with ostium stenosis?

29 **D0006** – How does PTCA with DEB in comparison to PTCA with POBA or DES affect progression (or recurrence) of patients with ostium stenosis?

30 **D0012** – What is the effect of PTCA with DEB in comparison to PTCA with POBA or DES on generic health-related quality of life in patients with ostium stenosis?

31 **D0013** – What is the effect of PTCA with DEB in comparison to PTCA with POBA or DES on disease-specific quality of life in patients with ostium stenosis?

32 **D0001** – What is the expected beneficial effect of PTCA with DEB in comparison to PTCA with POBA or DES on mortality in patients with ostium stenosis?

33 **D0003** – What is the effect of PTCA with DEB in comparison to PTCA with POBA or DES on the mortality due to causes other than the target disease in patients with ostium stenosis?

Patient safety[34,35,36]

There were no results concerning MACE for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

There were no results concerning MI, or stent thrombosis for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

There were no results concerning (serious) adverse events for the comparison of PTCA with DEB versus PTCA with POBA or DES for patients with ostium stenosis.

[34] C0008 – How safe is PTCA with DEB in comparison to PTCA with POBA or DES in patients with ostium stenosis?

[35] C0004 – How does the frequency or severity of harms change over time or in different settings?

[36] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of PTCA with DEB?

4 Quality of evidence

Qualität der SR: ROBIS

RoB der zusätzlichen RCTs: Cochrane RoB 2

RoB for systematic reviews was assessed with the ROBIS tool [37] and is presented in Table A-6 in the Appendix. For RCTs already included in the 2016 MEL report or included in these five basic reviews, the results of the RoB assessment have been taken directly from systematic reviews. In the systematic reviews, RoB was assessed using the Cochrane RoB v.1 tool or the Jadad score. RoB for the additional RCTs (from electronic supplementary search or hand search) was assessed with the Cochrane RoB v.2 tool [38] and is presented in Table A-7 in the Appendix.

Vertrauenswürdigkeit der Evidenz nach GRADE

RoB for the included systematic reviews was low for one review (San Sanchez 2021 [19]) and unclear for the other for reviews [21, 26-28]. Overall, some concerns occurred in the domain "Identification and selection of studies", as most reviews used only electronic sources in their search process.

According to the review authors, RoB of the 37 RCTs included in the 2016 MEL report or in the five basic reviews, was low in 17 trials, moderate in 13 trials, and high in seven trials.

RoB for the six additional RCTs [29-34] was judged as low for three trials, as moderate for one trial, and as high for two trials. The main reasons for the moderate RoB were some concerns regarding the randomization process and the selection of reported results. In the two RCTs with a high RoB, the reasons for the judgment were again the sparse data on the methodology of the study (randomization procedure, allocation concealment) and the shortcomings due to missing outcome data.

The certainty of evidence was rated according to GRADE [13] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [13].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings tables below (see Table 4-1 to Table 4-6) and in the evidence profile in Appendix Table A-8 to Table A-13.

Overall in patients with ISR the certainty of evidence for the effectiveness and safety of PTCA with DEB in comparison to PTCA with POBA is low to moderate, and moderate to high comparing PTCA with DEB to PTCA with DES. In patients with de novo lesions irrespective of the vessel diameter, the certainty of evidence for the effectiveness and safety of PTCA with DEB in comparison to PTCA with POBA is very low to high, and very low to moderate comparing PTCA with DEB to PTCA with DES. In patients with de novo lesions in small vessels – small vessel disease – the certainty of evidence for the effectiveness and safety of PTCA with DEB in comparison to PTCA with POBA is very low to moderate, and low to moderate comparing PTCA with DEB to PTCA with DES. For the comparison of PTCA with DEB to PTCA with POBA or DES in patients with ostium stenosis no evidence is available.

Vertrauenswürdigkeit der Evidenz niedrig bis hoch für DEB bei ISR, und sehr niedrig bis hoch für DEB bei de novo Läsionen und sehr niedrig bis moderat für DEB bei SVD

Table 4-1: Summary of findings table of DEB compared to POBA in patients with ISR

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with POBA	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	429 per 1,000	120 per 1,000 (47 to 287)	RR 0.28 (0.11 to 0.67)	746 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of inconsistancy
TVR	471 per 1,000	184 per 1,000 (113 to 302)	RR 0.39 (0.24 to 0.64)	422 (3 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
HrQoL	No evidence available					
Overall mortality	183 per 1,000	125 per 1,000 (62 to 251)	RR 0.68 (0.34 to 1.37)	746 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Cardiac mortality	153 per 1,000	69 per 1,000 (12 to 393)	RR 0.45 (0.08 to 2.57)	638 (4 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of inconsistancy and imprecision
MACE	556 per 1,000	211 per 1,000 (111 to 406)	RR 0.38 (0.20 to 0.73)	746 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of inconsistancy
Myocardial infarction	40 per 1,000	57 per 1,000 (29 to 113)	RR 1.42 (0.72 to 2.79)	746 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Stent thrombosis	19 per 1,000	7 per 1,000 (1 to 50)	RR 0.38 (0.05 to 2.71)	746 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; POBA: Plain old balloon angiography; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

***High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.*

***Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

***Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.*

***Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

Table 4-2: Summary of findings table of DEB compared to DES in patients with ISR

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DES	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	124 per 1,000	166 per 1,000 (112 to 243)	RR 1.33 (0.90 to 1.95)	1 467 (8 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
TVR	112 per 1,000	140 per 1,000 (100 to 198)	RR 1.25 (0.89 to 1.76)	1 610 (8 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
HrQoL	No evidence available					
Overall mortality	98 per 1,000	80 per 1,000 (61 to 105)	RR 0.82 (0.62 to 1.07)	1 741 (9 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
Cardiac mortality	58 per 1,000	48 per 1,000 (34 to 69)	RR 0.83 (0.58 to 1.18)	1 875 (10 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
MACE	233 per 1,000	229 per 1,000 (182 to 289)	RR 0.98 (0.78 to 1.24)	1 828 (9 RCTs)	⊕⊕⊕⊕ High	
Myocardial infarction	42 per 1,000	39 per 1,000 (25 to 61)	RR 0.94 (0.60 to 1.46)	1 877 (10 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
Stent thrombosis	10 per 1,000	10 per 1,000 (4 to 25)	RR 1.01 (0.41 to 2.49)	1 874 (10 RCTs)	⊕⊕⊕◯ Moderate	downgraded one level because of imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; DES: drug-eluting stent; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

High certainty: *we are very confident that the true effect lies close to that of the estimate of the effect.*

Moderate certainty: *we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

Low certainty: *our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.*

Very low certainty: *we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

Table 4-3: Summary of findings table of DEB compared to POBA in patients with de novo lesions (large and small vessels)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with POBA	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	65 per 1,000	30 per 1,000 (16 to 56)	RR 0.46 (0.24 to 0.86)	887 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
TVR	41 per 1,000	20 per 1,000 (8 to 51)	RR 0.48 (0.19 to 1.24)	490 (2 RCTs)	⨁◯◯◯ Very low	downgraded three levels because of RoB and serious imprecision
HrQoL	No evidence available					
Overall mortality	5 per 1,000	1 per 1,000 (0 to 22)	RR 0.19 (0.01 to 3.96)	887 (5 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
Cardiac mortality	5 per 1,000	1 per 1,000 (0 to 22)	RR 0.19 (0.01 to 3.96)	887 (5 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
MACE	140 per 1,000	88 per 1,000 (60 to 129)	RR 0.63 (0.43 to 0.92)	823 (4 RCTs)	⨁⨁⨁⨁ High	
Myocardial infarction	30 per 1,000	12 per 1,000 (4 to 30)	RR 0.39 (0.15 to 1.02)	887 (5 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Stent thrombosis	0 per 235 with POBA versus 0 per 382 with DEB		na	617 (3 RCTs)	⨁◯◯◯ Very low	downgraded three levels because of RoB and serious imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; POBA: Plain old balloon angiography; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

High certainty: *we are very confident that the true effect lies close to that of the estimate of the effect.*

Moderate certainty: *we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

Low certainty: *our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.*

Very low certainty: *we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

Table 4-4: Summary of findings table of DEB compared to DES in patients with de novo lesions (large and small vessels)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DES	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	59 per 1,000	86 per 1,000 (59 to 127)	RR 1.46 (1.00 to 2.15)	3 151 (21 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
TVR	73 per 1,000	110 per 1,000 (77 to 158)	RR 1.51 (1.05 to 2.16)	3 292 (15 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of inconsistancy
HrQoL	No evidence available					
Overall mortality	22 per 1,000	23 per 1,000 (15 to 34)	RR 1.04 (0.69 to 1.55)	4 089 (23 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Cardiac mortality	12 per 1,000	14 per 1,000 (8 to 25)	RR 1.14 (0.65 to 2.03)	3 485 (22 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
MACE	120 per 1,000	138 per 1,000 (106 to 182)	RR 1.15 (0.88 to 1.51)	4 087 (23 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of inconsistancy and imprecision
Myocardial infarction	28 per 1,000	25 per 1,000 (17 to 37)	RR 0.91 (0.61 to 1.36)	4 003 (22 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Stent thrombosis	14 per 1,000	11 per 1,000 (5 to 22)	RR 0.75 (0.36 to 1.56)	2 698 (15 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; DES: drug-eluting stent; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

High certainty: *we are very confident that the true effect lies close to that of the estimate of the effect.*

Moderate certainty: *we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

Low certainty: *our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.*

Very low certainty: *we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

Table 4-5: Summary of findings table of DEB compared to POBA in patients with SVD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with POBA	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	93 per 1,000	43 per 1,000 (23 to 83)	RR 0.47 (0.25 to 0.90)	601 (3 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
TVR	92 per 1,000	44 per 1,000 (17 to 114)	RR 0.48 (0.19 to 1.24)	268 (1 RCT)	⨁◯◯◯ Very low	downgraded three levels because of RoB and serious imprecision
HrQoL	No evidence available					
Overall mortality	9 per 1,000	2 per 1,000 (0 to 35)	RR 0.19 (0.01 to 3.96)	601 (3 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
Cardiac mortality	9 per 1,000	2 per 1,000 (0 to 35)	RR 0.19 (0.01 to 3.96)	601 (3 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
MACE	189 per 1,000	123 per 1,000 (83 to 182)	RR 0.65 (0.44 to 0.96)	601 (3 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Myocardial infarction	40 per 1,000	16 per 1,000 (6 to 47)	RR 0.41 (0.14 to 1.18)	601 (3 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
Stent thrombosis	0 per 126 with POBA versus 0 per 269 with DEB		na	395 (2 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; POBA: Plain old balloon angiography; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 4-6: Summary of findings table of DEB compared to DES in patients with SVD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DES	Risk with DEB				
AP symptom relief	No evidence available					
Avoidance of CABG	No evidence available					
TLR	81 per 1,000	95 per 1,000 (46 to 196)	RR 1.18 (0.57 to 2.43)	954 (6 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of inconsistancy and imprecision
TVR	94 per 1,000	100 per 1,000 (59 to 167)	RR 1.06 (0.63 to 1.78)	1 468 (5 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of inconsistancy and imprecision
HrQoL	No evidence available					
Overall mortality	46 per 1,000	44 per 1,000 (28 to 68)	RR 0.95 (0.61 to 1.47)	1 712 (7 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Cardiac mortality	19 per 1,000	23 per 1,000 (12 to 44)	RR 1.23 (0.65 to 2.32)	1 712 (7 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
MACE	161 per 1,000	153 per 1,000 (98 to 236)	RR 0.95 (0.61 to 1.47)	1 712 (7 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of inconsistancy and imprecision
Myocardial infarction	43 per 1,000	29 per 1,000 (17 to 49)	RR 0.69 (0.41 to 1.16)	1 712 (7 RCTs)	⨁⨁⨁◯ Moderate	downgraded one level because of imprecision
Stent thrombosis	15 per 1,000	4 per 1,000 (1 to 15)	RR 0.30 (0.09 to 1.02)	1 671 (6 RCTs)	⨁⨁◯◯ Low	downgraded two levels because of serious imprecision
(Serious) adverse events	No evidence available					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: AP: Angina pectoris; CABG: coronary artery bypass grafting; CI: confidence interval; DEB: Drug-eluting balloon; DES: drug-eluting stent; HrQoL: Health-related quality of life; MACE: Major cardiac adverse event; MD: mean difference; RR: risk ratio; TLR: target lesion revascularization; TVR: Target vessel revascularization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

5 Discussion

Summary of findings

Since the last report update on the PTCA with DEB for coronary artery disease (CAD) published in 2016, various RCTs comparing PTCA with DEB to DES implantation in patients with ISR as well as for PTCA with DEB compared to PTCA with POBA or DES implantation in patients with de novo lesions have been published. Using the 2016 MEL report [3], five recently published topic related systematic reviews [19, 21, 26-28], and a supplementary search for RCTs as primary sources, we could include results from 14 RCTs for ISR, results from 29 RCTs for de novo lesions irrespective of the target vessel diameter, and results from 10 RCTs for the subgroup of patients with SVD in this report update. Still no systematic reviews or RCTs could be identified for PTCA with DEB in patients with ostium stenosis.

5 SR zu DEB vs POBA oder DES als primäre Quelle für RCTs inkludiert

6 zusätzliche rezente RCTs

insgesamt 43 RCTs

For **patients with ISR**, the results on efficacy and safety of PTCA with DEB, focusing on critical outcomes can be summarized as follows:

- Compared to PTCA with an uncoated balloon, PTCA with DEB showed statistically significant lower revascularization rates (TLR and TVR) and lower MACE rates in short and long term follow-up (up to 10 years). No significant difference between the two interventions was found for overall or cardiac mortality, MI, and stent thrombosis.
- Comparted to DES implantation, there was no statistically significant difference in any of the investigated critical efficacy and safety outcomes – revascularisation rates (TLR and TVR), death, MACE, MI, and stent thrombosis – in short and long term follow-up (up to 10 years).
- There were no results for the efficacy outcomes AP symptom relieve, avoidance of CABG, and change in HrQoL.

ISR: Vorteil für DEB vs POBA bei TLR, TVR und MACE; kein Unterschied bei anderen EPs;

kein Unterschied zwischen DEB und DES in allen EPs;

keine Evidenz zu AP-Symptomatik, Vermeidung von CABG und LQ

For **patients with de novo lesions irrespective of the target vessel diameter**, the results on efficacy and safety of PTCA with DEB, focusing on critical outcomes can be summarized as follows:

- Compared to PTCA with an uncoated balloon, PTCA with DEB showed statistically significant lower TLR rates and lower MACE rates in short and long term follow-up (up to 12 months). Overall the event rates were also lower in DEB compared to POBA for MI. However, the difference was just not statistically significant. No difference between the two interventions was found for overall or cardiac mortality, TVR, and stent thrombosis, but results on TVR and stent thrombosis are not very reliable.
- Compared to DES implantation, PTCA with DEB showed statistically significant higher TVR rates in short and long term follow-up (up to three years). Overall, the event rates were also higher in DEB compared to DES for TLR. However, the difference was just not statistically significant. No difference between the two interventions was found for overall or cardiac mortality, MACE, MI, and stent thrombosis.
- There were no results for the efficacy outcomes AP symptom relieve, avoidance of CABG, and change in HrQoL.

de novo Läsionen: Vorteil für DEB vs POBA bei TLR und MACE sowie MI tendenziell geringer;

Nachteil für DEB vs DES bei TVR, auch TLR tendenziell höher; kein Unterschied zwischen DEB und DES in anderen EPs;

keine Evidenz zu AP-Symptomatik, Vermeidung von CABG und LQ

For the subgroup of **patients with de novo lesions in small vessels (SVD)**, the results on efficacy and safety of PTCA with DEB, focusing on critical outcomes can be summarized as follows:

- Compared to PTCA with an uncoated balloon, PTCA with DEB showed statistically significant lower TLR and MACE rates in short and long term follow-up (up to 12 months). Overall the event rates were also lower in DEB compared to POBA for MI. However, the difference was just not statistically significant. No difference in TVR, overall or cardiac mortality, and stent thrombosis – in short and long term follow-up (up to three years)
- Compared to DES implantation, there was no statistically significant difference in any of the investigated critical efficacy and safety outcomes – revascularisation rate, death, MACE, MI, and stent thrombosis – in short and long term follow-up (up to three years), although event rates tended to be lower with DEB for MI and stent thrombosis.
- Overall the results for DEB compared to POBA or DES are not sufficient reliable because the number of RCTs is still limited and optimal information size is not met for any investigated outcome.
- There were no results for the efficacy outcomes AP symptom relieve, avoidance of CABG, and change in HrQoL.

SVD:
Vorteil für DEB vs POBA bei TLR und MACE sowie MI tendenziell geringer;

kein Unterschied zwischen DEB und POBA in anderen EPs;
MI und Stent Thrombosen tendenziell geringer bei DEB vs DES;

kein Unterschied zwischen DEB und DES in anderen EPs;

Evidenz insgesamt nicht noch nicht ausreichend;

keine Evidenz zu AP-Symptomatik, Vermeidung von CABG und LQ

Further considerations

In patients with ISR, the type of restenosed stent might play an important role in the treatment effect. Of the 10 RCTs for the comparison of DEB versus DES in patients with ISR, four RCTs included patients with BMS-ISR [44, 72-74], while four other RCTs included patients with DES-ISR only [35, 36, 45, 75]. The remaining two RCTs investigated both, patients with BMS-ISR and DES-ISR [42, 43]. Subgroup-analyses with respect to the index procedure (BMS or DES) showed no difference between DEB and DES in any of the safety outcomes. While in patients with BMS-ISR there was also no difference between DEB and DES in TLR (RR 0.94 [95% CI 0.19 to 4.61]; p=0.94), in patients with DES-ISR there was a statistically significant higher TLR-rate with DEB compared to DES after a maximum 10-year follow-up (RR 1.44 [95% CI 1.02 to 2.05]; p=0.04).

Within the indication of patients with de novo coronary lesions, RCTs with different study populations were summarized. This includes six RCTs investigating DEB versus DES in patients with acute STEMI [33, 48, 49, 56, 57, 60], as well as each two RCTs investigating DEB versus POBA [51, 52] and DEB versus DES [61, 62] in patients with bifurcation lesions. Subgroup meta-analyses including RCTs with STEMI patients only, showed comparable results to those from the meta-analyses including all patients with de novo lesions, with no statistically significant differences between DEB and DES in overall or cardiac mortality, revascularization rates, MACE, MI, or stent thrombosis. For the subgroup of patients with bifurcation lesions, no death occurred in the two RCTs comparing DEB to DES. For all other reported clinical outcomes, there was also no statistically difference between DEB and DES. For the comparison of DEB versus POBA in patients with bifurcation lesions, results also showed no difference between the two interventions in any of the investigated clinical outcomes. Overall data on patients with bifurcation lesions are not sufficient to draw a reliable conclusion on efficacy and safety of DEB either in comparison to POBA or in comparison to DES.

de novo Läsionen: unterschiedliche Studienpopulationen in den RCTs

Subgruppe für STEMI: kein Unterschied zwischen DEB und DES

Evidenz für DEB vs POBA oder DES bei Bifurkationsstenosen unzureichend

Subgruppen in 1 RCT zu DEB vs DES bei SVD: Kein Einfluss durch Geschlecht, Diabetes mellitus, Blutungsrisiko bzw. chronische Nierenerkrankung

For the comparison of DEB to DES in patients with SVD, results on various subgroups from one RCT (BASKET-SMALL 2) have recently been published. Thus, when comparing women and men in this study, there was no statistically significant effect of sex on the results for DEB versus DES with respect to MACE up to 36 months [63]. A second publication focussed on patients with diabetes mellitus, since these patients have a higher risk for MACE, especially restenosis, MI, and stent thrombosis, compared to non-diabetic patients. The analyses after 3 years of follow-up showed similar rates of MACE, MI, and cardiac mortality between DEB and DES in diabetic and non-diabetic patients, while, TVR-rates were significantly lower with DEB in diabetic patients, but not in non-diabetic patients [64]. Further publications analysed patients with and without high bleeding risk [65] or patients with and without chronic kidney disease [66] within the participants of the BASKET-SMALL 2 RCT. Both analyses indicated that the long-term efficacy and safety of DEB compared to DES is similar in patients with or without high-bleeding risk and with or without chronic kidney disease, respectively.

Internal validity

interne Validität: große Anzahl an RCTs zu ISR und de novo Läsionen; Patient*innenzahlen in RCTs zu SVD nicht ausreichend

mehrjähriges Follow-up

RoB großteils gering bis moderat

The number of published RCTs investigating PTCA with DEB in patients with ISR, de novo lesions in large or small vessels is high, although the overall number of analysed participants seems to be insufficient in some outcomes in these indications and in general for patients with SVD. In addition, all information in this report update refer only to paclitaxel-coated balloons. For the new sirolimus-coated balloons no results from RCTs are published to date. The length of follow-up in the majority of included studies is sufficient for the evaluation of effects on patient-relevant outcomes such as morbidity or mortality. Overall, the RoB of the included RCTs is low to moderate, with only nine of 43 RCTs been judged as having a high RoB. Therefore, the certainty of evidence for the comparison of PTCA with DEB versus DES implantation in patients with ISR or de novo lesions as well as for the comparison of PTCA with DEB versus PTCA with POBA in patients with ISR is moderate for most outcomes. For the comparison of PTCA with DEB versus PTCA with POBA in patients with de novo lesions including patients with SVD the certainty of evidence is moderate to low, since data are sparse for some outcomes. Downgrading resulted mostly from the imprecision of the results due to wide confidence intervals of the effect estimator or because the total number of patients included in the meta-analysis does not meet the optimal information size criterion, and/or increased heterogeneity in the meta-analyses.

External validity

externe Validität: weitgehende Übereinstimmung mit anderen rezenten systematischen Reviews

For external validity, there are no limitations in terms of applicability of the study results in terms of study population, intervention or setting (see Appendix Table A-14).

Beside the five systematic reviews included in this report update as information source, there are several recent systematic reviews investigating PTCA with DEB especially in patients with de novo lesions in large vessels or patients with SVD. Overall, the results of these reviews are comparable to those of this update-report.

The systematic review Felbel 2023 [17] investigated DEB as an alternative to DES in patients with SVD, defined as RVD ≤ 3.0 mm. Summarizing the results of 37 RCTs and observational studies with a total of 31,835 patients,

the results showed comparable TLR, MACE, MI, and mortality rates for DEB and DES treatment. Therefore, the authors concluded, that DEB is non-inferior to DES as treatment for SVD and may be an effective alternative to stent therapy.

A second systematic review (Lin 2021 [18]) analysed the efficiency and safety of DEB versus DES in de novo coronary lesions in large vessels (RVD > 2.5 mm). The review included three RCTs and one non-randomized study with a total of 321 patients. With respect to the primary clinical endpoint TLR and the primary angiographic endpoint LLL, meta-analyses showed no difference between DEB and DES treatment. DEB therefore appears be a stentless alternative for the treatment of de novo coronary lesions in large vessels, although additional well-designed large RCTs with long follow-up periods are needed to confirm the results.

Verdoia et al published a systematic review on DEB in comparison to conventional revascularization strategies for the treatment of coronary and non-coronary arterial disease in 2021 [23]. For patients with CAD – ISR and de novo lesions including SVD, 27 RCTs were included in the meta-analyses. DEB compared to DES or uncoated devices (POBA or BMS) showed no difference in mortality and TLR rates, and a statistically significant advantage regarding MI rates. The authors of this review also concluded, that DEB for PTCA is associated to a comparable risk compared to other revascularization strategies.

Limitations of the report

Limitationen: keine unkontrollierten oder nicht-randomisierten Studien eingeschlossen

This report is limited to RCTs for efficacy and safety outcomes. Therefore, non-randomized controlled studies, registries and uncontrolled single-arm studies were excluded. As a result, not the full body of evidence was considered. However, since RCTs, if conducted in a methodologically adequate manner and appropriate to the respective research question, are affected by the lowest uncertainty of results, the excluded studies would not have changed the interpretation and the drawn conclusion of the report.

nur publizierte Daten

Only published study data were used for this report; unpublished raw data from the included trials and individual patient data were not available.

nur Publikationen in englischer und deutscher Sprache

This report includes only RCTs published in English or German language. Since there an increased number of RCTs were recently conducted in East-Asia, especially China, there is a possibility that additional studies may be available in other languages which have not been taken into account in this report.

Ongoing studies

24 laufende RCTs: 6 RCTs bei ISR und 18 RCTs bei de novo Läsionen

Screening the 125 hits of the search in clinical trials registries, we identified 20 relevant ongoing trials, investigating DEB versus POBA or DES in patients with coronary disease. In addition, four relevant ongoing RCTs were identified by correspondence with an expert. Six RCTs comprising a total of 2,256 participants investigate different types of DEB in patients with ISR, in three of these trials, with a total of 1,060 participants a sirolimus-eluting balloon is used in the intervention groups. Estimated primary completion dates range from 10/2023 to 09/2025. In addition, 18 ongoing RCTs, including 16,572 patients, compare DEB to DES or POBA in patients with de novo lesions. In four trials of these trials with 6,186 participants, a sirolimus-eluting balloon

is the active comparator. Estimated primary completion dates range from 11/2022 to 07/2027 (see Appendix Table A-15 and Table A-16). For three ongoing RCTs, the study protocols have already been published [67-69]. No study registry entries for RCTs investigating DEB in patients with ostium stenosis were found.

6 Evidence-based conclusion

In Table 6-1 the scheme for the evidence-based conclusion is displayed and the according choice is highlighted.

Schlussfolgerung

Table 6-1: Evidence-based conclusion for DEB in patients with CAD

	Strong evidence for added benefit in routine use
X	**Evidence indicates added benefit only in specific indications**
	Less robust evidence indicating an added benefit in routine use or in specific indications
	No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest
	Strong evidence indicates that intervention is ineffective and or harmful

Reasoning:

In patients with in-stent restenosis (ISR) after BMS or DES implantation, the current evidence proves that the assessed technology PTCA with DEB is more effective and safe than the comparator PTCA with POBA, and equally effective and equally safe than the comparator DES implantation. The certainty of the evidence for these comparisons is largely moderate.

zusätzlicher Nutzen nur für bestimmte Indikationen

In patients with de novo coronary lesions irrespective of the vessel diameter, the current evidence indicates that, the assessed technology PTCA with DEB is more effective and safe than the comparator PTCA with POBA, but tends to be less effective and equally safe than the comparator DES implantation, which is the current gold standard therapy for treatment of de novo lesions. The certainty of the evidence for these comparisons is very low to moderate. In the subgroup of patients with small vessel disease, the current evidence indicates that, the assessed technology PTCA with DEB is equally effective and safe than the comparators PTCA with POBA and DES implantation, respectively. The certainty of the evidence for this comparison is very low to moderate. Overall, the evidence base does not appear sufficient for a conclusive judgement of the efficacy and safety of PTCA with DEB in patients with small vessel disease. New study results will potentially influence the effect estimate considerably.

For patients with ostium stenosis no evidence from RCTs is currently available.

The re-evaluation for patients with de novo lesions and small vessel disease is recommended in 2027.

Re-Evaluierung für de novo Läsionen und SVD 2027

7 References

[1] Adlbrecht C. Drug coated balloon catheter. Systematic Review. 2009. Ludwig Boltzmann Institut for Health Technology Assessment.

[2] Hintringer K, Warmuth M. Perkutane transluminale koronare Angioplastie (PTCA) mit drug-eluting balloon (DEB). Decision Support Dokument Nr.: 24/Update 2013. 2013. Ludwig Boltzmann Institut for Health Technology Assessment.

[3] Semlitsch T, Horvath K. Perkutane transluminale koronare Angioplastie (PTCA) mit drug-eluting balloon (DEB). Decision Support Dokument Nr.: 24/Update 2016. 2016. Ludwig Boltzmann Institut for Health Technology Assessment.

[4] Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2012; 59 (9): 857-81.

[5] Statistik Austria. *Jahrbuch der Gesundheitsstatistik 2021;* [cited 12.02.2024]. Available from: https://www.statistik.at/fileadmin/user_upload/Gesundheitsstatistik-JB_2021_Web-barrierefrei.pdf.

[6] Ulrich H, Olschewski M, Muenzel T, et al. Coronary in-stent restenosis – predictors and treatment. *Dtsch Arztebl Int*. 2021; 118: 637-44.

[7] Mühlberger V, Kaltenbach L, Ulmer H, et al. Herzkathetereingriffe in Österreich im Jahr 2013 (mit Audit 2014). *ournal für Kardiologie – Austrian Journal of Cardiology*. 2015; 22 (1-2): 22-6.

[8] Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019; 40 (2): 87-165.

[9] Cortese B, Kalkat H, Bathia G, et al. The evolution and revolution of drug coated balloons in coronary angioplasty: An up-to-date review of literature data. *Catheter Cardiovasc Interv*. 2023; 102 (6): 1069-77.

[10] Jadad AR, Murray WE. Randomized controlled trials: questions, answers and musings. 2nd ed. Malden: BMJ Books; 2007.

[11] Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol*. 1991; 44 (11): 1271-8.

[12] Oxman AD, Guyatt GH, Singer J, et al. Agreement among reviewers of review articles. *J Clin Epidemiol*. 1991; 44 (1): 91-8.

[13] Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011; 64 (4): 383-94.

[14] Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014; 35 (37): 2541-619.

[15] European Network for Health Technology Assessment (EUnetHTA). *The HTA Core Model® for Rapid Relative Effectiveness Assessments*. 30.11.2015; [cited 03.03.2023]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.

[16] Bai X, Shen C, Zhang W, et al. Efficacy and risks of drug-coated balloon treatment for coronary artery disease: A meta-analysis. *Heliyon*. 2023; 9 (11): e22224.

[17] Felbel D, Bozic F, Mayer B, et al. Drug-coated balloon: an effective alternative to stent strategy in small-vessel coronary artery disease-a meta-analysis. *Frontiers in Cardiovascular Medicine*. 2023; 10: 1213992.

[18] Lin Y, Sun X, Liu H, et al. Drug-coated balloon versus drug-eluting stent for treating de novo coronary lesions in large vessels: a meta-analysis of clinical trials. *Herz*. 2021; 46 (3): 269-76.

[19] Sanz Sanchez J, Chiarito M, Cortese B, et al. Drug-Coated balloons vs drug-eluting stents for the treatment of small coronary artery disease: A meta-analysis of randomized trials. *Catheterization & Cardiovascular Interventions*. 2021; 98 (1): 66-75.

[20] Scheller B, Vukadinovic D, Jeger R, et al. Survival After Coronary Revascularization With Paclitaxel-Coated Balloons. *Journal of the American College of Cardiology*. 2020; 75 (9): 1017-28.

[21] Sun B, Zhang XT, Chen RR. Comparison of Efficacy and Safety Between Drug-Coated Balloons Versus Drug-Eluting Stents in the Treatment of De Novo Coronary Lesions in Large Vessels: A Study-Level Meta-Analysis of Randomized Control Trials. *Cardiovascular Drugs & Therapy*. 2023; 24: 24.

[22] Sun K, Liu Z, Wang H. Drug-Coated Balloon vs Stent for de novo Non-small Coronary Artery Disease: A Systematic Review and Meta-Analysis. *Frontiers in Cardiovascular Medicine*. 2021; 8: 700235.

[23] Verdoia M, Negro F, Kedhi E, et al. Benefits with drug-coated balloon as compared to a conventional revascularization strategy for the treatment of coronary and non-coronary arterial disease: a comprehensive meta-analysis of 45 randomized trials. *Vascular Pharmacology*. 2021; 138: 106859.

[24] Wang D, Wang X, Yang T, et al. Drug-Coated Balloons for De Novo Coronary Artery Lesions: A Meta-Analysis of Randomized Clinical Trials. *Yonsei Medical Journal*. 2023; 64 (10): 593-603.

[25] Wu X, Li L, He L. Drug-Coated Balloon versus Drug-Eluting Stent in Patients with Small-Vessel Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. *Cardiology Research & Practice*. 2021; 2021: 1647635.

[26] Xi Y, Chen J, Bi Y, et al. Long-term clinical safety and efficacy of drug-coated balloon in the treatment of in-stent restenosis: A meta-analysis and systematic review. *Catheterization & Cardiovascular Interventions*. 2020; 96 (2): E129-E41.

[27] Zhang W, Zhang M, Tian J, et al. Drug-Coated Balloon-Only Strategy for De Novo Coronary Artery Disease: A Meta-analysis of Randomized Clinical Trials. *Cardiovascular therapeutics*. 2023; 2023: 3121601.

[28] Zhu Y, Liu K, Kong X, et al. Comparison of Drug-Coated Balloon Angioplasty vs Drug-Eluting Stent Implantation for Drug-Eluting Stent Restenosis in the Routine Clinical Practice: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Cardiovascular Medicine*. 2021; 8: 766088.

[29] Chae IH, Yoon CH, Park JJ, et al. Comparison of Drug-Eluting Balloon Followed by Bare Metal Stent with Drug-Eluting Stent for Treatment of de Novo Lesions: Randomized, Controlled, Single-Center Clinical Trial. *J Korean Med Sci*. 2017; 32 (6): 933-41.

[30] Kawai T, Watanabe T, Yamada T, et al. Coronary vasomotion after treatment with drug-coated balloons or drug-eluting stents: a prospective, open-label, single-centre randomised trial. *EuroIntervention*. 2022; 18 (2): e140-e8.

[31] Poerner TC, Otto S, Gassdorf J, et al. Stent coverage and neointimal proliferation in bare metal stents postdilated with a Paclitaxel-eluting balloon versus everolimus-eluting stents: prospective randomized study using optical coherence tomography at 6-month follow-up. *Circ Cardiovasc Interv*. 2014; 7 (6): 760-7.

[32] Zurakowski A, Buszman PP, Milewski KP, et al. Stenting and Adjunctive Delivery of Paclitaxel Via Balloon Coating Versus Durable Polymeric Matrix for De Novo Coronary Lesions: Clinical and Angiographic Results from the Prospective Randomized Trial. *J Interv Cardiol*. 2015; 28 (4): 348-57.

[33] García-Touchard A, Gonzalo N, Goicolea J, et al. Early coronary healing in ST segment elevation myocardial infarction: Sirolimus-eluting stents vs drug-coated balloons after bare-metal stents. The PEBSI-2 optical coherence tomography randomized study. *Coronary Artery Disease*. 2021; 32 (8): 673-80.

[34] Liu S, Zhou Y, Shen Z, et al. Comparison of Drug-Coated Balloon and Drug-Eluting Stent for the Treatment of Small Vessel Disease (from the Dissolve SVD Randomized Trial). *American Journal of Cardiology*. 2024; 211: 29-39.

[35] Alfonso F, Pérez-Vizcayno MJ, Cuesta J, et al. 3-Year Clinical Follow-Up of the RIBS IV Clinical Trial: A Prospective Randomized Study of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis in Coronary Arteries Previously Treated With Drug-Eluting Stents. *JACC: Cardiovascular Interventions*. 2018; 11 (10): 981-91.

[36] Giacoppo D, Alvarez-Covarrubias HA, Koch T, et al. Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial. *European Heart Journal*. 2023; 44 (15): 1343-57.

[37] Whiting P, Savovic J, Higgins JP, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 2016; 69: 225-34.

[38] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; 366: l4898.

[39] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327 (7414): 557-60.

[40] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007; 115 (17): 2344-51.

[41] European Medicines Agency. *ICH Topic E 2 A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*. 06.1995; [cited 12.2.2024]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-topic-e-2-clinical-safety-data-management-definitions-and-standards-expedited-reporting-step_en.pdf.

[42] Baan J, Jr., Claessen BE, Dijk KB, et al. A Randomized Comparison of Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent for the Treatment of Any In-Stent Restenosis: The DARE Trial. *JACC Cardiovasc Interv*. 2018; 11 (3): 275-83.

[43] Jensen CJ, Richardt G, Tolg R, et al. Angiographic and clinical performance of a paclitaxel-coated balloon compared to a second-generation sirolimus-eluting stent in patients with in-stent restenosis: the BIOLUX randomised controlled trial. *EuroIntervention*. 2018; 14 (10): 1096-103.

[44] Pleva L, Kukla P, Zapletalova J, et al. Long-term outcomes after treatment of bare-metal stent restenosis with paclitaxel-coated balloon catheters or everolimus-eluting stents: 3-year follow-up of the TIS clinical study. *Catheter Cardiovasc Interv*. 2018; 92 (6): E416-E24.

[45] Wong YTA, Kang DY, Lee JB, et al. Comparison of drug-eluting stents and drug-coated balloon for the treatment of drug-eluting coronary stent restenosis: A randomized RESTORE trial. *Am Heart J*. 2018; 197: 35-42.

[46] Cortese B, Di Palma G, Guimaraes MG, et al. Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease: PICCOLETO II Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2020; 13 (24): 2840-9.

[47] Funatsu A, Nakamura S, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon with plain balloon angioplasty in patients with small vessel disease. *Clin Res Cardiol*. 2017; 106 (10): 824-32.

[48] Gobic D, Tomulic V, Lulic D, et al. Drug-Coated Balloon Versus Drug-Eluting Stent in Primary Percutaneous Coronary Intervention: A Feasibility Study. *Am J Med Sci*. 2017; 354 (6): 553-60.

[49] Hao X, Huang D, Wang Z, et al. Study on the safety and effectiveness of drug-coated balloons in patients with acute myocardial infarction. *J Cardiothorac Surg*. 2021; 16 (1): 178.

[50] Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018; 392 (10150): 849-56.

[51] Jing QM, Zhao X, Han YL, et al. A drug-eluting Balloon for the trEatment of coronarY bifurcatiON lesions in the side branch: a prospective multicenter ranDomized (BEYOND) clinical trial in China. *Chin Med J (Engl)*. 2020; 133 (8): 899-908.

[52] Kleber FX, Rittger H, Ludwig J, et al. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. *Clin Res Cardiol*. 2016; 105 (7): 613-21.

[53] Nishiyama N, Komatsu T, Kuroyanagi T, et al. Clinical value of drug-coated balloon angioplasty for de novo lesions in patients with coronary artery disease. *Int J Cardiol*. 2016; 222: 113-8.

[54] Qian J, Wu Y, Li C, et al. Drug-coated balloon for the treatment of small vessel disease: 9 months of angiographic results and 12 months of clinical outcomes of the PEPCAD China SVD study. *Catheter Cardiovasc Interv*. 2023; 101 (1): 33-43.

[55] Tang Y, Qiao S, Su X, et al. Drug-Coated Balloon Versus Drug-Eluting Stent for Small-Vessel Disease: The RESTORE SVD China Randomized Trial. *JACC Cardiovasc Interv*. 2018; 11 (23): 2381-92.

[56] Vos NS, Fagel ND, Amoroso G, et al. Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction: The REVELATION Randomized Trial. *JACC Cardiovasc Interv*. 2019; 12 (17): 1691-9.

[57] Wang Z, Yin Y, Li J, et al. New Ultrasound-Controlled Paclitaxel Releasing Balloon vs Asymmetric Drug-Eluting Stent in Primary ST-Segment Elevation Myocardial Infarction – A Prospective Randomized Trial. *Circ J*. 2022; 86 (4): 642-50.

[58] Xu K, Fu G, Tong Q, et al. Biolimus-Coated Balloon in Small-Vessel Coronary Artery Disease: The BIO-RISE CHINA Study. *JACC Cardiovasc Interv*. 2022; 15 (12): 1219-26.

[59] Yu X, Wang X, Ji F, et al. A Non-inferiority, Randomized Clinical Trial Comparing Paclitaxel-Coated Balloon Versus New-Generation Drug-Eluting Stents on Angiographic Outcomes for Coronary De Novo Lesions. *Cardiovasc Drugs Ther*. 2022; 36 (4): 655-64.

[60] Belkacemi A, Agostoni P, Nathoe HM, et al. First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. *J Am Coll Cardiol*. 2012; 59 (25): 2327-37.

[61] Lopez Minguez JR, Nogales Asensio JM, Doncel Vecino LJ, et al. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. *EuroIntervention*. 2014; 10 (1): 50-7.

[62] Stella PR, Belkacemi A, Dubois C, et al. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. *Catheter Cardiovasc Interv*. 2012; 80 (7): 1138-46.

[63] Rubini Gimenez M, Scheller B, Farah A, et al. Sex-specific inequalities in the use of drug-coated balloons for small coronary artery disease: a report from the BASKET-SMALL 2 trial. *Clinical Research in Cardiology*. 2023; 26: 26.

[64] Wohrle J, Scheller B, Seeger J, et al. Impact of Diabetes on Outcome With Drug-Coated Balloons Versus Drug-Eluting Stents: The BASKET-SMALL 2 Trial. *Jacc: Cardiovascular Interventions*. 2021; 14 (16): 1789-98.

[65] Scheller B, Rissanen TT, Farah A, et al. Drug-Coated Balloon for Small Coronary Artery Disease in Patients With and Without High-Bleeding Risk in the BASKET-SMALL 2 Trial. *Circulation: Cardiovascular Interventions*. 2022; 15 (4): e011569.

[66] Mahfoud F, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease in patients with chronic kidney disease: a pre-specified analysis of the BASKET-SMALL 2 trial. *Clinical Research in Cardiology*. 2022; 111 (7): 806-15.

[67] Greco A, Sciahbasi A, Abizaid A, et al. Sirolimus-coated balloon versus everolimus-eluting stent in de novo coronary artery disease: Rationale and design of the TRANSFORM II randomized clinical trial. *Catheterization & Cardiovascular Interventions*. 2022; 100 (4): 544-52.

[68] Spaulding C, Krackhardt F, Bogaerts K, et al. 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. *American Heart Journal*. 2023; 258: 77-84.

[69] Yeh RW, Bachinsky W, Stoler R, et al. Rationale and design of a randomized study comparing the agent drug coated balloon to plain old balloon angioplasty in patients with In-stent restenosis. *American Heart Journal*. 2021; 241: 101-7.

[70] Liu S, Zhou Y, Shen Z, et al. A Randomized Comparison of 2 Different Drug-Coated Balloons for In-Stent Restenosis. JACC Cardiovasc Interv. 2023; 16 (7): 759-67.

[71] Hamm CW, Dorr O, Woehrle J, et al. A multicentre, randomised controlled clinical study of drug-coated balloons for the treatment of coronary in-stent restenosis. EuroIntervention. 2020; 16 (4): e328-e34.

[72] Adriaenssens T, Dens J, Ughi G, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug elUting balloon in Coronary artery rEstenosis) randomised clinical trial. EuroIntervention. 2014; 10 (4): 439-48.

[73] Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). J Am Coll Cardiol. 2014; 63 (14): 1378-86.

[74] Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation. 2009; 119 (23): 2986-94.

[75] Xu B, Gao R, Wang J, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. JACC Cardiovasc Interv. 2014; 7 (2): 204-11.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: In-stent restenosis – Results from systematic reviews

Author, year	Zhu 2021	Xi 2019
Titel	Comparison of Drug-Eluting Balloon Angioplasty vs Drug-Eluting Stent Implantation for Drug-Eluting Stent Restenosis in the Routine Clinical Practice: A Meta-Analysis of Randomized Controlled Trials.	Long-term clinical safety and efficacy of drug-eluting balloon in the treatment of in-stent restenosis: A meta-analysis and systematic review
Registry number	NR	NR
Country	China	China
Sponsor	National Key Research and Development Program of China; Beijing Municipal Administration of Hospitals Ascent Mission Plan; Beijing Municipal Health Commission Project of Science and Technology Innovation	Guandong Innovative and Entrepreneurial Research Team Program; International S&T Cooperation Project of Dongguan, China
Intervention/Product	Drug-eluting balloon (Paclitaxel)/SeQuent Please; Pantera LUX	Drug-eluting balloon (Paclitaxel)/SeQuent Please
Comparator/Product	Drug-eluting stent (Paclitaxel, Everolimus or Sirolimus)/Taxus Libertè; Xience Prime; Orsiro	Drug-eluting stent (Paclitaxel or Everolimus)/Taxus Libertè; Xience Prime; PromusElement
Study design	Systematic review and meta-analysis	Systematic review and meta-analysis
Search/search date	PubMed, Embase, Cochrane Library; reference lists of eligible studies and reviews/ 19. June 2021	PubMed, Embase, Cochrane Library, ClinicalTrials.gov without language restriction/ 19. March 2019
Inclusion criteria	Patients with DES In-stent resteosis; comparing PCI with DEB vs PCI with DES; RCTs; follow-up ≥ 1 year; reporting clinical or angiographic outcomes	Patients with In-stent resteosis; comparing PCI with DEB vs PCI with DES; RCTs or observational studies; reporting at least one of the following safety and efficacy outcomes: major adverse cardiovascular events (MACEs), target lesion revascularization (TLR), target vessel revascularization (TVR), myocardial infarction, stent thrombosis; cardiac mortality, all-cause death, or coronary angiography outcomes included late lumen loss (LLL), minimum luminal diameter (MDL), % diameter stenosis (DS%)
Primary endpoints SR	Target lesion revascularization	NR
Number of relevant RCTs/pts	5 RCTs/1193 pts	8 RCTs/1576 pts
Follow-up (months)	12 to 36 months	12 to 36 months
Indication	In-stent restenosis	In-stent restenosis
Age of patients (yrs)	62 to 68 years	62 to 68 years
Male, %	71.5 to 83%	65 to 87%
Reference vessel diameter (mm)	NR	NR

Author, year	Zhu 2021	Xi 2019
Cardiac risk factors, n studies (% patients)		
Diabetes mellitus	37 to 47%	14 to 46%
Arterial hypertension	68 to 94.5%	62 to 82%
Family history CAD	NR	NR
Hyper-/Dyslipidemia	34 to 86%	34 to 96%
Smoking	12.5 to 62%	12.5 to 67%
BMI, kg/m^2	NR	NR
Unstable angina, n (%)	NR	NR
Stable angina, n (%)	NR	NR
STEMI, n (%)	NR	NR
Target lesion, n studies (% patients)		NR
LAD	32 to 58%	
LCX	14 to 33.5%	
RCA	26 to 36%	
Single-vessel disease, n studies (% patients)	NR	NR
Multi-vessel disease, n studies (% patients)	NR	3 RCTs: 30 to 93.5%
Classification of ISR, n studies (% patients)	NR	NR
Outcomes		
Efficacy clinical endpoints		
AP symptom relief, n (%)	NR	NR
Avoidance of CABG, n (%)	NR	NR
Target lesion revascularization (TLR), RR (95 %CI)	5 RCTs: 1.53 [1.15 to 2.04]; p=0.003; I^2=0%	6 RCTs: 1.38 [0.78 to 2.43]; p=0.26; I^2=55%
Target vessel revascularization (TVR), RR (95 %CI)	4 RCTs: 1.50 [1.11 to 2.04]; p=0.009; I^2=28%	7 RCTs: 1.19 [0.85 to 1.68]; p=0.32; I^2=30%
Quality of life	NR	NR

Author, year	Zhu 2021	Xi 2019
Efficacy angiographic endpoints		
Late lumen loss, [mm] MD (95 %CI)	4 RCTs: 0.02 [-0.06 to 0.10]; p=0.62; I^2=24%	8 RCTs: -0.10 [-0.21 to 0.00]; p=0.06; I^2=74%
Binary restenosis rate of target lesion, OR (95 %CI)	4 RCTs: 1.28 [0.90 to 1.81]; p=0.17; I^2=51%	NR
In-segment diameter stenosis, [%] MD (95 %CI)	4 RCTs: 3.25 [-1.26 to 7.77]; p=0.16; I^2=53%	8 RCTs: 1.04 [0.89 to 1.22] [a]; p=0.64; I^2=0%
In-segment minimum lumen diameter, [mm] MD (95 %CI)	4 RCTs: -0.12 [-0.27 to 0.03]; p=0.12; I^2=59%	8 RCTs: -0.15 [-0.29 to -0.02]; p=0.02; I^2=76%
Safety		
Overall mortality, RR (95 %CI)	NR	7 RCTs: 0.83 [0.40 to 1.72]; p=0.61; I^2=14%
Cardiac mortality, n (%)	5 RCTs: 0.49 [0.23 to 1.04]; p=0.06; I^2=0%	7 RCTs: 0.63 [0.27 to 1.47]; p=0.29; I^2=0%
MACE, RR (95 %CI)	5 RCTs: 1.10 [0.89 to 1.36]; p=0.37; I^2=13%	8 RCTs: 0.99 [0.72 to 1.35]; p=0.93; I^2=36%
Myocardial infarction, RR (95 %CI)	5 RCTs: 0.96 [0.55 to 1.69]; p=0.90; I^2=0%	7 RCTs: 1.23 [0.82 to 1.86]; p=0.32; I^2=36%
Stent thrombosis, RR (95 %CI)	5 RCTs: 0.69 [0.26 to 1.86]; p=0.46; I^2=0%	8 RCTs: 1.01 [0.36 to 2.83]; p=0.99; I^2=0%
Serious AE, n (%)	NR	NR

Abbreviations: AE – adverse events; AP – angina pectoris; CABG – coronary artery bypass graft; DEB – drug-eluting balloon; DES – drug-eluting stent; MACE – major cardiac adverse events; MD – mean difference; na – not applicable; NR – not reported; PCI – percutaneous coronary intervention; pts – patients; RCT – randomized controlled trial; RR – risk ratio; STEMI – ST elevation myocardial infraction

Explanations:

[a] *Risk ratio*

Table A-2: De novo lesions including small vessel disease – Results from systematic reviews

Author, year	Sun 2023	Zhang 2023	Sanz Sanchez 2021
Titel	Comparison of Efficacy and Safety Between Drug‐Eluting Balloons Versus Drug‐Eluting Stents in the Treatment of De Novo Coronary Lesions in Large Vessels: A Study‐Level Meta‐Analysis of Randomized Control Trials	Drug-Eluting Balloon-Only Strategy for De Novo Coronary Artery Disease: A Meta-analysis of Randomized Clinical Trials	Drug-Eluting balloons vs drug-eluting stents for the treatment of small coronary artery disease: A meta-analysis of randomized trials
Registry number	CRD42022383512	CRD42020158856	CRD42019137500
Country	China	China	Italy
Sponsor	Tang Du Yin Feng program	Beijing Lab for Cardiovascular Precision Medicine	Fundación Alfonso Martin Escudero (Madrid, Spain)
Intervention/Product	Drug-eluting balloon (Paclitaxel)/NR	Drug-eluting balloon (Paclitaxel)/SeQuent Please; IN.PACT Falcon; Bingo; BA9; Dior; Elutax SV/Emperor; Restore; Pantera Lux	Drug-eluting balloon (Paclitaxel)/SeQuent Please; IN.PACT Falcon; Dior; Elutax SV/Emperor; Restore
Comparator/Product	Drug-eluting stent (Everolimus or Sirolimus)/NR	Drug-eluting stent or uncoated balloon /NR	Drug-eluting stent (Paclitaxel, Everolimus or Sirolimus)/Xience; Taxus Libertè; Resolute integrity
Study design	Systematic review and meta-analysis	Systematic review and meta-analysis	Systematic review and meta-analysis
Search/search date	PubMed, Embase, Cochrane Library, ClinicalTrials.gov/1. August 2023	PubMed, Embase, Web of Science, Cochrane Library without language restriction/6. May 2023	Medline, Embase, Cochrane Library, ClinicalTrials.gov; Handsearch: abstracts from 2017 to 2019 presented at relevant scientific meetings (American Heart Association, American College of Cardiology, European Society of Cardiology, EuroPCR, and Transcatheter Cardiovascular Therapeutics); contact of authors/September 2019
Inclusion criteria	Patients with de novo coronary leasions in large vessels (RVD > 2.5 mm) and successful PCI; comparing PCI with DEB only versus PCI with DES; RCTs; reporting any efficacy or safety outcomes	Patients with de novo de novo coronary artery disease; comparing PCI with DEB only vs PCI other conventional options (POBA/BMS/DES); RCTs; availability of clinical outcome data without follow-up duration restriction	Patients with de novo small coronary artery disease (RVD < 3.0 mm); comparing PCI with DEB versus PCI with DES; RCTs; availability of clinical outcome data; minimum follow-up of 6 months
Primary endpoints SR	Major adverse cardiovascular events (cardiac mortality, reinfarction, target lesion revascularization)	Major adverse cardiac events (MACE); late lumen loss (LLL)	Target vessel revascularization (TVR)
Number of relevant RCTs/pts	6 RCTs/680 pts	DEB vs POBA: 5 RCTs/901 pts DEB vs DES: 10 RCTs/1998 pts	5 RCTs/1459 pts
Follow-up (months)	6 to 24 months	6 to 36 months	6 to 12 months
Indication	De novo lesions in large coronary vessels	De novo lesions in large and small coronary vessels	Small vessel diease
Age of patients (yrs)	50 to 71 years	54.3 to 68.4 years	60 to 68 years
Male, %	72 to 96%	65 to 87%	72 to 79%
Reference vessel diameter (mm)	2.5 to 4.0 mm	1.99 to 3.11 mm	2 to 3 mm
Cardiac risk factors, n studies (% patients)			
Diabetes mellitus	8 to 82%	8 to 47%	33 to 42%
Arterial hypertension	25 to 84%	NR	66 to 87%
Family history CAD	NR	NR	NR
Hyper-/Dyslipidemia	15 to 80%	15 to 78%	50 to 79%

Author, year	Sun 2023	Zhang 2023	Sanz Sanchez 2021
Smoking	30 to 81%	14 to 60%	14 to 30%
BMI, kg/m²	NR	NR	NR
Unstable angina, n (%)	NR	NR	12 to 81%
Stable angina, n (%)	NR	NR	NR
STEMI, n (%)	NR	NR	2 RCTs: 2 to 10% 3 RCTs: excluded
Target lesion, n studies (% patients)		NR	NR
LAD	5 RCTs: 36 to 55%		
LCX	5 RCTs: 16.5 to 25%		
RCA	5 RCTs: 12 to 37%		
Single-vessel disease, n studies (% patients)	NR	NR	NR
Multi-vessel disease, n studies (% patients)	NR	NR	NR
Outcomes			
Efficacy clinical endpoints			
AP symptom relief, n (%)	NR	NR	NR
Avoidance of CABG, n (%)	NR	NR	NR
Target lesion revascularization (TLR), RR (95 %CI)	7 RCTs: 0.83 [0.36 to 1.88]; p=0.65; I^2=0%	**DEB vs DES:** [a] *large vessels:* 4 RCTs: 1.29 [0.30 to 5.52]; p=0.73; I^2=45% *SVD:* 4 RCTs: 1.04 [0.45 to 2.39]; p=0.93; I^2=61% **DEB vs POBA:** [a] *large vessels:* 1 RCT: 0.33 [0.04 to 3.04]; p=0.33; I^2=na *SVD:* 3 RCTs: 0.47 [0.25 to 0.90]; p=0.01; I^2=0%	4 RCTs: 1.74 [0.57 to 5.28] [b]; p=0.33; I^2=NR
Target vessel revascularization (TVR), RR (95 %CI)	NR	NR	5 RCTs: 0.97 [0.56 to 1.68] [b]; p=0.92; I^2=NR
Quality of life	NR	NR	NR
Efficacy angiographic endpoints			
Late lumen loss, [mm] MD (95 %CI)	6 RCTs: -0.13 [-0.22 to -0.05]; p=0.003; I^2=60%	**DEB vs DES:** [a] ***SMD:*** *large vessels:* 4 RCTs: -0.13 [-0.61 to 0.34]; p=nr *SVD:* 4 RCTs: -0.37 [-0.69 to -0.06]; p=nr **DEB vs POBA:** [a] ***SMD:*** *large vessels:* 2 RCTs: -0.74 [-1.01 to -0.47]; p<0.001; I^2=0% *SVD:* 3 RCTs: -0.59 [-0.90 to -0.27]; p<0.001; I^2=65%	4 RCTs: -0.18 [-0.39 to 0.03] [c]; p=0.09; I^2=NR

Author, year	Sun 2023	Zhang 2023	Sanz Sanchez 2021
Binary restenosis rate of target lesion, RR (95 %CI)	NR	**DEB vs DES:** [a] *large vessels:* 1 RCT: 0.92 [0.34 to 2.51]; p=0.88; I^2=na *SVD:* 5 RCTs: 1.09 [0.73 to 1.64]; p=0.67; I^2=11% **DEB vs POBA:** [a] *large vessels:* 1 RCT: 0.20 [0.05 to 0.85]; p=0.03; I^2=na *SVD:* 3 RCTs: 0.33 [0.22 to 0.49]; p<0.001; I^2=0%	5 RCTs: 1.12 [0.69 to 1.84] [b]; p=0.64; I^2=NR
In-segment diameter stenosis, [%] MD (95 %CI)	NR	NR	5 RCTs: 0.27 [0.12 to 0.41] [c]; p<0.01; I^2=NR
In-segment minimum lumen diameter, [mm] MD (95 %CI)	6 RCTs: -0.21 [-0.34 to -0.07]; p=0.003; I^2=52%	NR	5 RCTs: -0.52 [-0.86 to -0.18] [c]; p=0.003; I^2=NR
Safety			
Overall mortality, RR (95 %CI)	NR	**DEB vs DES:** [a] *large vessels:* 5 RCTs: 0/225 vs 0/258 *SVD:* 5 RCTs: 0.95 [0.61 to 1.48]; p=0.82; I^2=0% **DEB vs POBA:** [a] *large vessels:* 2 RCTs: 0/145 vs 0/141 *SVD:* 3 RCTs: 0.19 [0.01 to 3.96]; p=0.29; I^2=na	4 RCTs: 1.03 [0.14 to 7.48] [b]; p=0.98; I^2=NR
Cardiac mortality, n (%)	7 RCTs: 0.68 [0.22 to 2.06]; p=0.49; I^2=0%		NR
MACE, RR (95 %CI)	NR	**DEB vs DES:** [a] *large vessels:* 5 RCTs: 1.48 [0.40 to 5.47]; p=nr *SVD:* 4 RCTs: 0.81 [0.52 to 1.24]; p=nr **DEB vs POBA:** [a] *large vessels:* 1 RCT: 0.24 [0.03 to 2.12]; p=nr *SVD:* 3 RCTs: 0.65 [0.44 to 0.96]; p=0.03; I^2=0%	NR
Myocardial infarction, RR (95 %CI)	7 RCTs: 0.67 [0.26 to 1.71]; p=0.40; I^2=0%	**DEB vs DES:** [a] *large vessels:* 4 RCTs: 1.27 [0.31 to 5.20]; p=0.74; I^2=0% *SVD:* 4 RCTs: 0.75 [0.44 to 1.28]; p=0.29; I^2=0% **DEB vs POBA:** [a] *large vessels:* 2 RCTs: 0.33 [0.03 to 3.10]; p=0.33; I^2=0% *SVD:* 3 RCTs: 0.41 [0.14 to 1.18]; p=0.10; I^2=0%	5 RCTs: 0.49 [0.23 to 1.03] [b]; p=0.06; I^2=NR
Stent thrombosis, RR (95 %CI)	NR	NR	4 RCTs: 0.12 [0.01 to 0.94] [b]; p=0.04; I^2=NR
Serious AE, n (%)	NR	NR	NR

Abbreviations: AE – adverse events; AP – angina pectoris; BMS – bare metal stent; CABG – coronary artery bypass graft; DEB – drug-eluting balloon; DES – drug-eluting stent; MACE – major cardiac adverse events; MD – mean difference; na – not applicable; NR – not reported; PCI – percutaneous coronary intervention; POBA – plain old balloon angiography; pts – patients; RCT – randomized controlled trial; RR – risk ratio; RVD – reference vessel diameter; STEMI – ST elevation myocardial infraction

Explanations:

[a] *Own calculation based on the absolute event rates from the review*

[b] *Odds ratio*

[c] *Standardized mean difference*

Table A-3: De novo lesions – Results from additional randomized controlled trials (Part 1)

Author, year	Chae 2017	Garcia-Touchard 2021
Titel	Comparison of Drug-Eluting Balloon Followed by Bare Metal Stent with Drug-Eluting Stent for Treatment of de Novo Lesions: Randomized, Controlled, Single-Center Clinical Trial	Early coronary healing in ST segment elevation myocardial infarction: sirolimus-eluting stents vs drug-eluting balloons after bare-metal stents. The PEBSI-2 optical coherence tomography randomized study
Country	South Korea	Spain
Sponsor	Ministry of Trade, Industry and Energy, Korea	Biotronik
Intervention/Product	Drug-eluting balloon (DEB) followig bare metal stent implantation (BMS) (Paclitaxel)/SeQuent® Please, (B. Braun, Melsungen, Germany)	Drug-eluting ballon (DEB) following bare metal stent implantation (BMS) (Paclitaxel)/Pantera Lux (Biotronik, Berlin, Germany)
Comparator/Product	Drug-eluting stent (DES) (Zotarolimus)/ZES, Resolute Integrity™ (Medtronic, Brooklyn Park, MN, USA)	Drug-eluting stent (DES) (Sirolimus)/Orsio (Biotronik, Berlin, Germany)
Study design	prospective, open-label RCT, single-center, 2 study arms (DEB+BMS vs DES)	prospective, single-blind RCT, multicenter, 2 study arms (DEB+BMS vs DES)
Inclusion criteria	Patients of at least 18 years of age with stable angina or acute coronary syndrome (unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) of documented ischemia due to a significant lesion in a native coronary artery; patients with native coronary lesion greater than 50% diameter stenosis by visual estimation of the coronary angiogram with reference diameter between 2.5 mm and 4.0 mm and lesion length less than 28.0 mm	Patients older than 18 years of age, presenting within the first 12h of STEMI onset and undergoing primary coronary intervention; patients with a single culprit lesion in the infarcted territory
Primary endpoints	In-segment late loss	Vessel diameter, lesion length, minimal lumen diamter, binary restenosis, late lumen loss
Number of pts	180 pts DEB+BMS (I) 90 pts DES (C) 90 pts	53 pts DEB+BMS (I) 27 pts DES (C) 26 pts
Follow-up (months)	clinical follow-up: 1, 3, 9, 12 months routine angiographic follow-up: 9 months	angiographic follow-up: 1, 3 months
Loss to follow-up, n (%)	I 16 (18) vs C 18 (20)	I 0 vs C 1 (4)
Indication	De novo lesions in large coronary vessels	De novo lesions in large coronary vessels
Age of patients (yrs)	I 61.2 (11.1) vs C 62.4 (11.9), p=0.457	I 59.2 (9.7) vs C 56.9 (10.8), p=0.42
Male, %	I 75.6% vs C 70%, p=0.503	I 85.1% vs C 80.1%, p=0.46
Cardiac risk factors, n (%)	I vs C	I vs C
Diabetes mellitus	28 (31.1%) vs 26 (28.9%), p=0.871	3 (11.1%) vs 1 (3.8%), p=0.473
Arterial hypertension	25 (27.8%) vs 40 (44.4%), p=0.029	10 (37.03%) vs 15 (57.7%), p=0.275
Family history CAD	3 (3.3%) vs 5 (5.6%), p=0.72	NR
Hyper-/Dyslipidemia	15 (16.7%) vs 18 (20%), p=0.70	NR
History of smoking	27 (30%) vs 19 (21.1%), p= 0.211	*Active*: 16 (59.2%) vs 16 (61.5%), p=NR *Previous*: 7 (9.25%) vs 6 (23%), p=NR
BMI, kg/m²	25.6 (3.1%) vs 25.7 (3.2%), p=0.805	26.9 (3.9) vs 27.7 (6.1), p=0.57
Unstable angina, n (%)	20 (22.2%) vs 28 (31.1%), p=NR	NR
Stable angina, n (%)	42 (46.7%) vs 43 (47.8%), p=NR	NR
STEMI, n (%)	NR	NR

Author, year	Chae 2017	Garcia-Touchard 2021
Target lesion, n (%)	I vs C, p=0.72	I vs C, p=0.7
LAD	37 (41.1%) vs 42 (46.7%)	11 (NR) vs 10 (NR)
LCX	26 (28.9%) vs 25 (27.8%)	5 (NR) vs 4 (NR)
RCA	27 (30%) vs 23 (25.6%)	11 (NR) vs 12 (NR)
Single-vessel disease, n (%)	NR	NR
Multi-vessel disease, n (%)	45 (50%) vs 55 (61.1%), p=0.324	NR
Outcomes (I vs C)		
Efficacy clinical endpoints		
AP symptom relief, n (%)	NR	NR
Avoidance of CABG, n (%)	NR	NR
Target lesion revascularization (TLR), RR (95 %CI)	5 (5.6%) vs 3 (3.3%), p=0.72	NR
Target vessel revascularization (TVR), RR (95 %CI)	5 (5.6%) vs 5 (5.6%), p=1.0	NR
Quality of life	NR	NR
Efficacy angiographic endpoints		
Late lumen loss, [mm] MD (95 %CI)	*9 months (in-stent):* 0.54 (0.48) vs 0.28 (0.43), p=0.001 *9 month (in-segment):* 0.50 (0.46) vs 0.21 (0.44), p=<0.001	*3 months:* 0.21 (0.22) vs 0.10 (0.22), p=0.075
Binary restenosis rate of target lesion, RR (95 %CI)	*9 months (in-stent):* 8 (10.8%) vs 2 (2.8%), p=0.098 *9 months (in-segment):* 9 (12.2%) vs 2 (2.8%), p=0.056	*3 months:* 0 vs 0, p=1
In-segment diameter stenosis, [%] MD (95 %CI)	*9 months:* 29.5 (16.1) vs 16.5 (10.6), p=< 0.001	*3 months:* 10.54 (9.39) vs 7.88 (7.49), p=0.276
In-segment minimum lumen diameter, [mm] MD (95 %CI)	*9 months:* 1.93 (0.59) vs 2.34 (0.47), p=<0.001	*3 months:* 2.66 (0.46) vs 2.66 (0,42), p=0.994
Safety		
Overall mortality, RR (95 %CI)	1 (1.1%) vs 2 (2.2%), p=1.0	NR
Cardiac mortality, n (%)	0 vs 2 (2.2%), p=0.497	NR
MACE, RR (95 %CI)	9 (10%) vs 7 (7.8%), p=0.794	NR
Myocardial infarction, RR (95 %CI)	2 (2.2%) vs 0, p=0.497	NR
Stent thrombosis, RR (95 %CI)	2 (2.2%) vs 0, p=0.497	NR
Serious AE, n (%)	NR	*3 months:* 0 vs 0

Abbreviations: AE – adverse events; AP – angina pectoris; BMS – bare metal stent; C: control group; CABG – coronary artery bypass graft; DEB – drug-eluting balloon; DES – drug-eluting stent; I: intervention group; MACE – major cardiac adverse events; MD – mean difference; na – not applicable; NR – not reported; PCI – percutaneous coronary intervention; pts – patients; RCT – randomized controlled trial; RR – risk ratio; RVD – reference vessel diameter; STEMI – ST elevation myocardial infraction

Table A-4: De novo lesions – Results from additional randomized controlled trials (Part 2)

Author, year	Poerner 2014	Zurakowski 2015
Titel	Stent coverage and neointimal proliferation in bare metal stents postdilated with a Paclitaxel-eluting balloon versus everolimus-eluting stents: prospective randomized study using optical coherence tomography at 6-month follow-up	Stenting and Adjunctive Delivery of Paclitaxel Via Balloon Coating Versus Durable Polymeric Matrix for De Novo Coronary Lesions: Clinical and Angiographic Results from the Prospective Randomized Trial
Country	Germany	Poland
Sponsor	NR	B.Braun; American Heart of Poland Inc.
Intervention/Product	Drug-eluting balloon (DEB) following bare metal stent implantation (BMS) (Paclitaxel)/SeQuent® Please (B. Braun, Melsungen, Germany)	Drug-eluting balloon (DEB) following bare metal stent implantation (BMS) (Paclitaxel)/Sequent Please™ (B. Braun, Melsungen, Germany)
Comparator/Product	Drug-eluting stent (DES) (Everolimus)/Xience V (Abbott Vascular, IL)	Drug-eluting stent (DES) (Paclitaxel)/Coroflex Please™ (B. Braun, Melsungen, Germany)
Study design	prospectice, single-blind RCT, single-center, 2 study arms (DEB+BMS vs DES)	prospective, double-blind RCT, multicenter, 2 study arms (DEB+BMS vs DES)
Inclusion criteria	Patients with elective percutaneous coronary intervention according to current guidelines with a native coronary lesion suitable for stent placement and optical coherence tomography imaging	Patients aged 18 years or older with chronic stable coronary artery disease, unstable angina or silent ischemia; patients with single lesions (type A, B1, B2 according to AHA/ACC) in the native coronary arteries along with a diameter stenosis of 50% or more that was suitable for stent implantation in a vessel with a reference vessel diameter ranging from 2.25 mm to 3.5 mm
Primary endpoints	Endothelial stent coverage	In-stent late lumen loss
Number of pts	90 pts/150 lesions DEB+BMS (I) 54 pts DES (C) 51 pts	202 pts DEB+BMS (I) 102 pts DES (C) 100 pts
Follow-up (months)	6 months	9 months
Loss to follow-up, n (%)	Invasive follow-up: I 10 (20%) vs C 3 (6%)	I (0) vs C (0)
Indication	De novo lesions in large coronary vessels	De novo lesions in large coronary vessels
Age of patients (yrs)	I 68.9 (9.5) vs C 68.2 (8.5), p=0.702	I 64.1 (8.5) vs C 62.9 (9.3), p=0.35
Male, %	I 70.6% vs C 75%, p=0.622	I 67% vs C 70%, p=0.72
Cardiac risk factors, n (%)	I vs C	I vs C
Diabetes mellitus	22 (43.1%) vs 25 (52.1%), p=0.373	25 (25%) vs 20 (20%), p=0.55
Arterial hypertension	51 (100%) vs 48 (100%), p=0.999	90 (89%) vs 79 (79%), p=0.11
Family history CAD	NR	NR
Hyper-/Dyslipidemia	39 (76.5%) vs 34 (70.8%), p=0.379	NR
History of smoking	14 (27.5%) vs 18 (37.5%), p=0.761	17 (16%) vs 22 (22%), p=0.43
BMI, kg/m²	NR	28.9 (4.14%) vs 27.5 (3.4%), p=0.53
Unstable angina, n (%)	NR	46 (45%) vs 48 (48%), p=0.79
Stable angina, n (%)	NR	56 (55%) vs 52 (52%), p=0.79
STEMI, n (%)	NR	NR
Target lesion, n (%)	I vs C	I vs C
LAD	25 (46.2%) vs 20 (39.2%), p=NR	46 (45.1%) vs 41 (42%), p=0.66
LCX	17 (31.5%) vs 15 (29.4%), p=NR	18 (17.6%) vs 19 (19%), p=0.95
RCA	12 (22.2%) vs 16 (31.2%), p=0.558	36 (35.2%) vs 40 (40%), p=0.29

Author, year	Poerner 2014	Zurakowski 2015
Single-vessel disease, n (%)	NR	NR
Multi-vessel disease, n (%)	NR	NR
Outcomes (I vs C)		
Efficacy clinical endpoints		
AP symptom relief, n (%)	NR	NR
Avoidance of CABG, n (%)	NR	NR
Target lesion revascularization (TLR), RR (95 %CI)	*All patients*: 1 (2%) vs 2 (4.2%), p=0.522 *No device overlap*: 1 (2.4%) vs 1 (2.6%), p=0.959	NR
Target vessel revascularization (TVR), RR (95 %CI)	*All patients:* 1 (2%) vs 2 (4.2%), p=0.522 *No device overlap*: 1 (2.4%) vs 1 (2.6%), p=0.959	1.42 [0.45 to 4.41] [a], p=0.54
Quality of life	NR	NR
Efficacy angiographic endpoints		
Late lumen loss, [mm] MD (95 %CI)	*Quantitative coronary angiography:* 0.24 (0.21) vs 0.16 (0.15), p=0.034	0.21 (0.5) vs 0.30 (0.7), $p_{non\text{-}inf}$=<0.05
Binary restenosis rate of target lesion, RR (95 %CI)	*Quantitative coronary angiography:* 0 vs 0, p=1	11% vs 15.4%, p=0.29
In-segment diameter stenosis, [%] MD (95 %CI)	*Quantitative coronary angiography:* 22.8 (11.9) vs 16.9 (10.4), p=0.014	no differences between the groups
In-segment minimum lumen diameter, [mm] MD (95 %CI)	*Quantitative coronary angiography:* 2 (0.44) vs 2.16 (0.39), p=0.065 *Optical coherence tomography:* 1.91 (0.44) vs 2.15 (0.43), p=0.015 [b]	no differences between the groups
Safety		
Overall mortality, RR (95 %CI)	*All patients*: 2 (3.9%) vs 0, p=0.166 *No device overlap*: 2 (4.8%) vs 0, p=0.167	0 vs 0, p=1.0
Cardiac mortality, n (%)	NR	0 vs 0, p=1.0
MACE, RR (95 %CI)	*All patients*: 5 (9.8%) vs (5 (10.4%), p=0.919 *No device overlap*: 5 (11.9%) vs 4 (10.3%), p=0.182	1.0 [0.3 to 2.8] [a], p=0.99
Myocardial infarction, RR (95 %CI)	0 vs 0, p=1.0	1.93 [0.52 to 7.19] [a], p=0.32
Stroke, n (%)	NR	NR
Stent thrombosis, RR (95 %CI)	NR	2.01 [0.54 to 7.46] [a], p=0.29
Serious AE, n (%)	NR	NR

Abbreviations: ACC – American College of Cardiology; AE – adverse events; AHA – American Heart Association; AP – angina pectoris; BMS – bare metal stent; C – control group; CABG – coronary artery bypass graft; DEB – drug-eluting balloon; DES – drug-eluting stent; I – intervention group; MACE – major cardiac adverse events; MD – mean difference; na – not applicable; NR – not reported; PCI – percutaneous coronary intervention; pts – patients; RCT – randomized controlled trial; RR – risk ratio; STEMI – ST elevation myocardial infraction

Explanations:

[a] *Hazard ratio*

[b] *Optical coherence tomography (OCT) measurements for proliferation and stent strut coverage after 6 months; per-protocol analysis: non-inferiority p-value I vs C with 5% margin: 0.04*

Table A-5: Small vessel disease – Results from additional randomized controlled trials

Author, year	Kawai 2022	Liu 2024 (Dissolve SVD)
Titel	Coronary vasomotion after treatment with drug-eluting balloons or drug-eluting stents: a prospective, open-label, single-centre randomised trial	Comparison of Drug-Eluting Balloon and Drug-Eluting Stent for the Treatment of Small Vessel Disease (from the Dissolve SVD Randomized Trial)
Country	Japan	China
Sponsor	Osaka Heart Club (Osaka, Japan)	DK Medical Technology (Suzhou, China)
Intervention/Product	Drug-eluting balloon (DEB) (Paclitaxel)/SeQuent® Please (B. Braun Melsungen, Germany)	Drug-eluting balloon (DEB) (Paclitaxel)/Dissolve (DK Medical, SuZhou, China)
Comparator/Product	Drug-eluting stent (DES) (Everolimus)/Synergy™ (Boston Scientific, Marlborough, MA, USA)	Drug-eluting stent (DES) (Zotarolimus)/Endeavor Resolute (Medtronic, Santa Rosa, CA, USA)
Study design	prospective, open-label RCT, single-center, 2 study arms (DEB vs DES)	prospective, randomized, multicenter, noninferiority trial; 2 study arms (DEB vs DES)
Inclusion criteria	Patients aged ≥20 years with stable angina or documented silent ischaemia with de novo coronary lesions; patients with a RVD of 2.0-3.0 mm and a lesion length of ≤25 mm	Patients aged 18 to 80 years with only 1 target lesion in a small vessel; RVD ≥2.25 and ≤2.75 mm, lesion length <26 mm, % of diameter stenosis: ≥70% or ≥50% with documented myocardial ischemia
Primary endpoints	Endothelial function	In-segment percent diameter stenosis at 9 months
Number of pts	42 pts DEB (I) 19 pts DES (C) 23 pts	247 pts DEB (I) 129 pts DES (C) 118 pts
Follow-up (months)	8 months	12 months
Loss to follow-up, n (%)	I 0 vs C 2 (9%)	0 vs 0
Indication	Small vessel disease	Small vessel disease
Age of patients (yrs)	I 69 (8) vs C 73 (8), p=0.176	60.2 (9.5) vs 60.1 (9.3)
Male, %	I 79% vs C 74%, p=0.711	72.9% vs 69.5%
Cardiac risk factors, n (%)	I vs C	
Diabetes mellitus	5 (26%) vs 8 (35%), p=0.566	46 (35.7%) vs 45 (38.1%)
Arterial hypertension	17 (89%) vs 21 (91%), p=0.845	95 (73.6%) vs 89 (75.4%)
Family history CAD	NR	10 (7.8%) vs 22 (18.6%); p=0.01
Hyper-/Dyslipidemia	15 (79%) vs 19 (83%), p=0.77	58 (45.0%) vs 64 (54.2%)
History of smoking	10 (53%) vs 12 (52%), p=0.977	60 (46.5%) vs 56 (47.5%)
mean BMI, kg/m² (SD)	25 (4%) vs 24 (4%), p=0.237	25.8 (3.4%) vs 25.2 (3.0%)
Unstable angina, n (%)	NR	82 (63.6%) vs 77 (65.3%)
Stable angina, n (%)	12 (63%) vs 18 (78%), p=0.499	26 (20.6%) vs 30 (25.4%)
STEMI, n (%)	NR	NR
Target lesion, n (%)	I vs C, p=0.074	
LAD	8 (42%) vs 4 (17%)	29 (22.5%) vs 28 (23.5%)

Author, year	Kawai 2022	Liu 2024 (Dissolve SVD)
LCX	5 (26%) vs 14 (61%)	67 (51.9%) vs 57 (47.9%)
RCA	6 (32%) vs 5 (22%)	33 (25.6%) vs 34 (28.6%)
Single-vessel disease, n (%)	NR	71 (55.0%) vs 66 (55.9%)
Multi-vessel disease, n (%)	NR	58 (45.0%) vs 52 (44.1%)
Outcomes (I vs C)		
Efficacy clinical endpoints		
AP symptom relief, n (%)	NR	NR
Avoidance of CABG, n (%)	NR	NR
Target lesion revascularization (TLR), RR (95 %CI)	0 vs 0, p=1	11 (8.5%) vs 5 (4.3%); p=0.17
Target vessel revascularization (TVR), RR (95 %CI)	NR	14 (10.9%) vs 6 (5.1%); p=0.10
Quality of life	NR	NR
Efficacy angiographic endpoints		
Late lumen loss, [mm] MD (95 %CI)	*8 months:* -0.07 (0.43) vs 0.37 (0.40), p=0.002	*9 months: 117 vs 98 pts* 0.22 (0.35) vs 0.31 (0.38); p=0.09
Binary restenosis rate of target lesion, RR (95 %CI)	*8 months:* 3 (16) vs 1 (5), p=0.321	*9 months: 117 vs 98 pts* 11 (9.4) vs 10 (10.2); p=0.84
In-segment diameter stenosis, [%] MD (95 %CI)	*8 months:* 20 (22) vs 15 (21), p=0.405	*9 months: 117 vs 98 pts* 29.9 (17.4) vs 25.7 (19.8); p=0.10
In-segment minimum lumen diameter, [mm] MD (95 %CI)	*8 months:* 1.78 (0.64) vs 1.83 (0.63), p=0.772	*9 months: 117 vs 98 pts* 1.55 (0.43) vs 1.72 (0.50); p=0.008
Safety		
Overall mortality, RR (95 %CI)	NR	1 (0.8%) vs 1 (0.8%); p=1.0
Cardiac mortality, n (%)	0 vs 0, p=1.0	0 vs 1 (0.8%); p=0.48
MACE, RR (95 %CI)	0 vs 0, p=1.0	27 (20.9%) vs 16 (13.6%); p=0.12
Myocardial infarction, RR (95 %CI)	0 vs 0, p=1.0	0 vs 0
Stent thrombosis, RR (95 %CI)	NR	0 vs 0
Serious AE, n (%)	NR	NR

Abbreviations: AE – adverse events; AP – angina pectoris; C – control group; CABG – coronary artery bypass graft; DEB – drug-eluting balloon; DES – drug-eluting stent; I – intervention group; MACE – major cardiac adverse events; MD – mean difference; na – not applicable; NR – not reported; PCI – percutaneous coronary intervention; pts – patients; RCT – randomized controlled trial; RR – risk ratio; RVD – reference vessel diameter; STEMI – ST elevation myocardial infraction

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-6: ROBIS results for included systematic reviews, see [37]

Systemativ Review	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Sun 2023	Low	Unclear	Unclear	Unclear	Unclear
Zhang 2023	Low	Unclear	Unclear	Low	Unclear
Zhu 2021	High	Unclear	Low	Low	Unclear
San Sanchez 2021	Low	Low	Low	Low	Low
Xi 2020	Unclear	Unclear	Unclear	Unclear	Unclear

Table A-7: Risk of bias – study level (randomized studies), see [1]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Poerner 2014	Some concerns	Low	High	Low	Some concerns	High
Zurakowski 2015	Some concerns	High	High	Low	Some concerns	High
Chae 2017	Low	Low	Low	Low	Low	Low
Garcia-Touchard 2021	Low	Low	Low	Low	Low	Low
Kawai 2022	Some concerns	Low	Low	Low	Some concerns	Some concerns
Liu 2024	Low	Low	Low	Low	Low	Low

Table A-8: Evidence profile: efficacy and safety of DEB compared to POBA in patients with ISR

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	POBA	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
5	randomised trials	not serious	serious [a]	not serious	not serious	none	76/424 (17.9%)	138/322 (42.9%)	RR 0.28 (0.11 to 0.67)	309 fewer per 1,000 (from 381 fewer to 141 fewer)	⨁⨁⨁◯ Moderate
TVR											
3	randomised trials	not serious	not serious	not serious	serious [b]	none	45/231 (19.5%)	90/191 (47.1%)	RR 0.39 (0.24 to 0.64)	287 fewer per 1,000 (from 358 fewer to 170 fewer)	⨁⨁⨁◯ Moderate
HrQoL											
No evidence available											
Overall mortality											
5	randomised trials	not serious	not serious	not serious	serious [b]	none	49/424 (11.6%)	59/322 (18.3%)	RR 0.68 (0.34 to 1.37)	59 fewer per 1,000 (from 121 fewer to 68 more)	⨁⨁⨁◯ Moderate
Cardiac mortality											
4	randomised trials	not serious	serious [a]	not serious	serious [b]	none	33/370 (8.9%)	41/268 (15.3%)	RR 0.45 (0.08 to 2.57)	84 fewer per 1,000 (from 141 fewer to 240 more)	⨁⨁◯◯ Low
MACE											
5	randomised trials	not serious	serious [a]	not serious	not serious	none	116/424 (27.4%)	179/322 (55.6%)	RR 0.38 (0.20 to 0.73)	345 fewer per 1,000 (from 445 fewer to 150 fewer)	⨁⨁⨁◯ Moderate
Myocardial infarction											
5	randomised trials	not serious	not serious	not serious	serious [b]	none	19/424 (4.5%)	13/322 (4.0%)	RR 1.42 (0.72 to 2.79)	17 more per 1,000 (from 11 fewer to 72 more)	⨁⨁⨁◯ Moderate
Stent thrombosis											
5	randomised trials	not serious	not serious	not serious	serious [b]	none	3/424 (0.7%)	6/322 (1.9%)	RR 0.38 (0.05 to 2.71)	12 fewer per 1,000 (from 18 fewer to 32 more)	⨁⨁⨁◯ Moderate
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; POBA – plain old balloon angiography; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *Significant heterogeneity*

[b] *Optimal information size criterion is not met*

Table A-9: Evidence profile: efficacy and safety of DEB compared to DES in patients with ISR

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	DES	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
8	randomised trials	not serious	not serious	not serious	serious [a]	none	123/760 (16.2%)	88/707 (12.4%)	RR 1.33 (0.90 to 1.95)	41 more per 1,000 (from 12 fewer to 118 more)	⊕⊕⊕◯ Moderate
TVR											
8	randomised trials	not serious	not serious	not serious	serious [a]	none	119/808 (14.7%)	90/802 (11.2%)	RR 1.25 (0.89 to 1.76)	28 more per 1,000 (from 12 fewer to 85 more)	⊕⊕⊕◯ Moderate
HrQoL											
No evidence available											
Overall mortality											
9	randomised trials	not serious	not serious	not serious	serious [b]	none	72/874 (8.2%)	85/867 (9.8%)	RR 0.82 (0.62 to 1.07)	18 fewer per 1,000 (from 37 fewer to 7 more)	⊕⊕⊕◯ Moderate
Cardiac mortality											
10	randomised trials	not serious	not serious	not serious	serious [b]	none	46/964 (4.8%)	53/911 (5.8%)	RR 0.83 (0.58 to 1.18)	10 fewer per 1,000 (from 24 fewer to 10 more)	⊕⊕⊕◯ Moderate
MACE											
9	randomised trials	not serious	not serious	not serious	not serious	none	216/941 (23.0%)	207/887 (23.3%)	RR 0.98 (0.78 to 1.24)	5 fewer per 1,000 (from 51 fewer to 56 more)	⊕⊕⊕⊕ High
Myocardial infarction											
10	randomised trials	not serious	not serious	not serious	serious [c]	none	39/965 (4.0%)	38/912 (4.2%)	RR 0.94 (0.60 to 1.46)	3 fewer per 1,000 (from 17 fewer to 19 more)	⊕⊕⊕◯ Moderate
Stent thrombosis											
10	randomised trials	not serious	not serious	not serious	serious [c]	none	10/963 (1.0%)	9/911 (1.0%)	RR 1.01 (0.41 to 2.49)	0 fewer per 1,000 (from 6 fewer to 15 more)	⊕⊕⊕◯ Moderate
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; DES – drug-eluting stent; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *CI fails to exclude important harm*

[b] *CI fails to exclude important benefit*

[c] *CI fails to exclude important benefit or harm*

Table A-10: Evidence profile: efficacy and safety of DEB compared to POBA in patients with de novo lesions (large and small vessels)

Certainty assessment							Nº of patients		Effect		Certainty
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	POBA	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
5	randomised trials	not serious	not serious	not serious	serious [a]	none	16/519 (3.1%)	24/368 (6.5%)	RR 0.46 (0.24 to 0.86)	35 fewer per 1,000 (from 50 fewer to 9 fewer)	⨁⨁⨁◯ Moderate
TVR											
2	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	8/294 (2.7%)	8/196 (4.1%)	RR 0.48 (0.19 to 1.24)	21 fewer per 1,000 (from 33 fewer to 10 more)	⨁◯◯◯ Very low
HrQoL											
No evidence available											
Overall mortality											
5	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/519 (0.0%)	2/368 (0.5%)	RR 0.19 (0.01 to 3.96)	4 fewer per 1,000 (from 5 fewer to 16 more)	⨁⨁◯◯ Low
Cardiac mortality											
5	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/519 (0.0%)	2/368 (0.5%)	RR 0.19 (0.01 to 3.96)	4 fewer per 1,000 (from 5 fewer to 16 more)	⨁⨁◯◯ Low
MACE											
4	randomised trials	not serious	not serious	not serious	not serious	none	44/487 (9.0%)	47/336 (14.0%)	RR 0.63 (0.43 to 0.92)	52 fewer per 1,000 (from 80 fewer to 11 fewer)	⨁⨁⨁⨁ High
Myocardial infarction											
5	randomised trials	not serious	not serious	not serious	serious [d]	none	6/519 (1.2%)	11/368 (3.0%)	RR 0.39 (0.15 to 1.02)	18 fewer per 1,000 (from 25 fewer to 1 more)	⨁⨁⨁◯ Moderate
Stent thrombosis											
3	randomised trials	serious [b]	not serious	not serious	very serious [e]	none	0 per 235 with POBA versus 0 per 382 with DEB				⨁◯◯◯ Very low
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; POBA – plain old balloon angiography; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *Optimal information size criterion is not met*

[b] *RCTs with increased RoB*

[c] *Optimal information size criterion is not met and CI fails to exclude important benefit*

[d] *CI fails to exclude important benefit*

[e] *Optimal information size criterion is not met and very low event rate*

Table A-11: Evidence profile: efficacy and safety of DEB compared to DES in patients with de novo lesions (large and small vessels)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	DES	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
21	randomised trials	not serious	not serious	not serious	serious [a]	none	142/1573 (9.0%)	93/1578 (5.9%)	RR 1.46 (1.00 to 2.15)	27 more per 1,000 (from 0 fewer to 68 more)	⨁⨁⨁◯ Moderate
TVR											
15	randomised trials	not serious	serious [b]	not serious	not serious	none	175/1650 (10.6%)	120/1642 (7.3%)	RR 1.51 (1.05 to 2.16)	37 more per 1,000 (from 4 more to 85 more)	⨁⨁⨁◯ Moderate
HrQoL											
No evidence available											
Overall mortality											
23	randomised trials	not serious	not serious	not serious	serious [c]	none	49/2046 (2.4%)	45/2043 (2.2%)	RR 1.04 (0.69 to 1.55)	1 more per 1,000 (from 7 fewer to 12 more)	⨁⨁⨁◯ Moderate
Cardiac mortality											
22	randomised trials	not serious	not serious	not serious	very serious [d]	none	24/1749 (1.4%)	21/1736 (1.2%)	RR 1.14 (0.65 to 2.03)	2 more per 1,000 (from 4 fewer to 12 more)	⨁⨁◯◯ Low
MACE											
23	randomised trials	not serious	serious [b]	not serious	serious [a]	none	294/2042 (14.4%)	245/2036 (12.0%)	RR 1.15 (0.88 to 1.51)	18 more per 1,000 (from 14 fewer to 61 more)	⨁⨁◯◯ Low
Myocardial infarction											
22	randomised trials	not serious	not serious	not serious	serious [c]	none	57/2004 (2.8%)	55/1999 (2.8%)	RR 0.91 (0.61 to 1.36)	2 fewer per 1,000 (from 11 fewer to 10 more)	⨁⨁⨁◯ Moderate
Stent thrombosis											
15	randomised trials	not serious	not serious	not serious	very serious [d]	none	13/1357 (1.0%)	19/1341 (1.4%)	RR 0.75 (0.36 to 1.56)	4 fewer per 1,000 (from 9 fewer to 8 more)	⨁⨁◯◯ Low
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; DES – drug-eluting stent; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *CI fails to exclude important harm*

[b] *Increased heterogeneity*

[c] *CI fails to exclude important benefit or harm*

[d] *CI fails to exclude important benefit or harm and very low event rate*

Table A-12: Evidence profile: efficacy and safety of DEB compared to POBA in patients with SVD

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	POBA	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
3	randomised trials	not serious	not serious	not serious	serious [a]	none	15/374 (4.0%)	21/227 (9.3%)	RR 0.47 (0.25 to 0.90)	49 fewer per 1,000 (from 69 fewer to 9 fewer)	⨁⨁⨁◯ Moderate
TVR											
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	8/181 (4.4%)	8/87 (9.2%)	RR 0.48 (0.19 to 1.24)	48 fewer per 1,000 (from 74 fewer to 22 more)	⨁◯◯◯ Very low
HrQoL											
No evidence available											
Overall mortality											
3	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/374 (0.0%)	2/227 (0.9%)	RR 0.19 (0.01 to 3.96)	7 fewer per 1,000 (from 9 fewer to 26 more)	⨁⨁◯◯ Low
Cardiac mortality											
3	randomised trials	not serious	not serious	not serious	very serious [c]	none	0/374 (0.0%)	2/227 (0.9%)	RR 0.19 (0.01 to 3.96)	7 fewer per 1,000 (from 9 fewer to 26 more)	⨁⨁◯◯ Low
MACE											
3	randomised trials	not serious	not serious	not serious	serious [a]	none	43/374 (11.5%)	43/227 (18.9%)	RR 0.65 (0.44 to 0.96)	66 fewer per 1,000 (from 106 fewer to 8 fewer)	⨁⨁⨁◯ Moderate
Myocardial infarction											
3	randomised trials	not serious	not serious	not serious	very serious [c]	none	6/374 (1.6%)	9/227 (4.0%)	RR 0.41 (0.14 to 1.18)	23 fewer per 1,000 (from 34 fewer to 7 more)	⨁⨁◯◯ Low
Stent thrombosis											
2	randomised trials	not serious	not serious	not serious	very serious [d]	none	0 per 126 with POBA versus 0 per 269 with DEB				⨁⨁◯◯ Low
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; POBA – plain old balloon angiography; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *Optimal information size criterion is not met*

[b] *RCT with increased RoB*

[c] *Optimal information size criterion is not met and CI fails to exclude important benefit or harm*

[d] *Optimal information size criterion is not met and very low event rate*

Table A-13: Evidence profile: efficacy and safety of DEB compared to DES in patients with SVD

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEB	DES	Relative (95% CI)	Absolute (95% CI)	
AP symptom relief											
No evidence available											
Avoidance of CABG											
No evidence available											
TLR											
6	randomised trials	not serious	serious [a]	not serious	serious [b]	none	41/483 (8.5%)	38/471 (8.1%)	RR 1.18 (0.57 to 2.43)	15 more per 1,000 (from 35 fewer to 115 more)	⨁⨁◯◯ Low
TVR											
5	randomised trials	not serious	serious [a]	not serious	serious [b]	none	69/744 (9.3%)	68/724 (9.4%)	RR 1.06 (0.63 to 1.78)	6 more per 1,000 (from 35 fewer to 73 more)	⨁⨁◯◯ Low
HrQoL											
No evidence available											
Overall mortality											
7	randomised trials	not serious	not serious	not serious	serious [b]	none	37/865 (4.3%)	39/847 (4.6%)	RR 0.95 (0.61 to 1.47)	2 fewer per 1,000 (from 18 fewer to 22 more)	⨁⨁⨁◯ Moderate
Cardiac mortality											
7	randomised trials	not serious	not serious	not serious	serious [b]	none	20/865 (2.3%)	16/847 (1.9%)	RR 1.23 (0.65 to 2.32)	4 more per 1,000 (from 7 fewer to 25 more)	⨁⨁⨁◯ Moderate
MACE											
7	randomised trials	not serious	serious [a]	not serious	serious [b]	none	130/865 (15.0%)	136/847 (16.1%)	RR 0.95 (0.61 to 1.47)	8 fewer per 1,000 (from 63 fewer to 75 more)	⨁⨁◯◯ Low
Myocardial infarction											
7	randomised trials	not serious	not serious	not serious	serious [c]	none	24/865 (2.8%)	36/847 (4.3%)	RR 0.69 (0.41 to 1.16)	13 fewer per 1,000 (from 25 fewer to 7 more)	⨁⨁⨁◯ Moderate
Stent thrombosis											
6	randomised trials	not serious	not serious	not serious	very serious [d]	none	3/846 (0.4%)	12/825 (1.5%)	RR 0.30 (0.09 to 1.02)	10 fewer per 1,000 (from 13 fewer to 0 fewer)	⨁⨁◯◯ Low
(Serious) adverse events											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass grafting; CI – confidence interval; DEB – drug-eluting balloon; DES – drug-eluting stent; HrQoL – health-related quality of life; MACE – major cardiac adverse event; MD – mean difference; RR – risk ratio; TLR – target lesion revascularization; TVR – target vessel revascularization

Comments:

[a] *Increased heterogeneity*

[b] *CI fails to exclude important benefit or harm*

[c] *CI fails to exclude important benefit*

[d] *CI fails to exclude important benefit and very low event rate*

Applicability table

Table A-14: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	14 RCTs enrolled patients with ISR after BMS or DES implantation. Patients with native coronary lesions in large vessels were included in nine RCTs, four RCTs investigated patients with bifurcation lesions and 6 RCTs patients with acute STEMI. Patients with de novo lesions in small coroary vessels were investigated in 10 RCTs. Most common comorbidities in the participants were arterial hypertension and diabetes mellitus.
Intervention	In all included RCTs the intervention was PTCA with a drug-eluting balloon. In all but one RCT, paclitaxel was used as the active substance. One RCT investigated a novel, experimental biolimus-eluting balloon. In the RCTs for the treatment of ISR, DEB was used as the only intervention, while in most studies for de novo lesions or SVD, bailout treatment using a BMS, in some cases also DES, was allowed in case of residual stenosis or flowlimiting dissection. In 11 RCTs DEB dillation was combined with a bare metal stenting in the intervention group. Additional medical therapy followed current guideline recommendations in all included RCTs. No results from RCTs investigating a sirolimus-eluting balloon is curently available.
Comparators	The comparators used in the included RCTs were POBA in 10 RCTs and DES in 34 trials. Most RCTs used paclitaxel- or everolimus-eluting stents in the control groups. Sirolimus-eluting stents were used as comparators in four RCTs. Additional medical therapy followed current guideline recommendations in all included RCTs.
Outcomes	The most frequent clinical outcomes in the RCTs were TLR, overall mortality and MACE. The most frequent angiographic outcomes in the RCTs were LLL, in-segment diameter stenosis and binary re-stenosis rates; AP-symptome relief and QoL were not assessed in any of the included RCTs.
Setting	In all studies, the intervention was performed in a clinical setting, corresponding to the utilisation setting in Austria. No applicability issues are expected from the geographical setting of the included studies.

List of ongoing randomised controlled trials

Table A-15: List of ongoing randomized controlled trials of PTCA with DEB vs PTCA with POBA or DES in patients with ISR

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05908331/ MAGICAL ISR	*Clinical inclusion criteria:* ■ Subject is at least 18 years old ■ Patient with an indication for PCI due to suspected in-stent restenosis *Angiographic inclusion criteria:* ■ In-stent restenosis after drug-eluting stent implantation(s) in the target lesion ■ Target lesion must have visually estimated stenosis ≥ 50% and less than 100% diameter stenosis in symptomatic patients; or a visually estimated target lesion diameter stenosis of ≥ 70%, or by evidence of ischemia by coronary physiology (fractional flow reserve [FFR] ≤0.80 or non-hyperemic pressure ratio [NHPR] ≤ 0.89) in absence of symptoms ■ Successful lesion preparation (residual stenosis < 30%), without complications (no or slow flow, flow-limiting dissection, perforation, distal embolization) and without plan for stenting ■ Target lesion in a native coronary artery ■ Thrombolysis In Myocardial Infartction (TIMI) grade flow ≥1 in target lesion ■ Target reference vessel diameter (visual estimation) >2.0 and ≤ 4.0 mm ■ Target lesion length (including tandem lesions) ≤36.0 mm (visual estimation) and can be covered by only one balloon ■ One ISR target lesion (overlapping stents are allowed) to be treated per patient and in single major coronary artery or side branch (reference vessel diameter > 2.0 mm) ■ Other coronary lesions (ISR or non-ISR) in non-target vessel are allowed and may be treated by any approved interventional device, but must be treated successfully prior to randomization	Magic Touch™ (sirolimus eluting ballon)	Plan balloon angioplasty (POBA)	Target Lesion Failure	September 2025	Concept Medical Inc.
NCT04647253/ AGENT IDE	*Clinical inclusion criteria:* ■ Subject must be at least 18 years of age ■ Subject is eligible for PCI ■ Women of child-bearing potential must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure *Angiographic inclusion criteria:* ■ In-stent restenosis in a lesion previously treated with either a drug-eluting stent or bare metal stent, located in a native coronary artery with a visually estimated reference vessel diameter (RVD) > 2.0 mm and ≤ 4.0 mm ■ Target lesion length must be < 26 mm (by visual estimate) and must be covered by only one balloon	Agent DEB (paclitaxel eluting PTCA balloon catheter)	PTCA balloon catheter	Target Lesion Failure	October 2023	Boston Scientific Corporation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04647253/ AGENT IDE *(continuation)*	■ Target lesion must have visually estimated stenosis > 50% and < 100% in symptomatic patients (>70% and <100% in asymptomatic patients) prior to lesion pre-dilation ■ Target lesion must be successfully pre-dilated ■ If a non-target lesion is treated, it must be treated first and must be deemed a success					
NCT04280029/ SELUTION SLR	*Clinical inclusion criteria:* ■ Subject age is ≥ 18 years or minimum legal age as required by local regulations ■ Female subjects of childbearing potential have a negative pregnancy test ≤ 7 days before the procedure ■ Documented stable or unstable angina including non-ST-elevation MI or functional testing demonstrating ischemia ■ Subject is eligible for dual antiplatelet therapy (DAPT) treatment with aspirin plus either, Clopidogrel, Prasugrel, or Ticagrelor ■ Life expectancy >1 year in opinion of investigator *Angiographic Inclusion Criteria:* ■ Target lesion is within a previously placed BMS or DES and does not extend > 5.00 mm beyond proximal or distal edge ■ Target lesion is < 36 mm in length ■ Target lesion has diameter stenosis of > 50% and < 100% with distal flow at least Thrombolysis in Myocardial Infarction (TIMI) 2 ■ RVD is ≥ 2.00 mm and ≤ 4.50 mm ■ Target lesion is within a native coronary artery or major branch ■ Up to two (2) non-target lesions in non-target vessels may be treated, but successful percutaneous coronary Intervention (PCI) must be completed before treatment of target lesion	SELUTION SLR™ DEB (sirolimus eluting balloon)	commercially available DES or alternativeyl POBA	Target Lesion Failure	November 2023	M.A. Med Alliance S.A.
NCT04862052/ OPEN ISR	■ Patients admitted for intervention of drug eluting stent restenosis ■ Restenosis suitable for all three treatment arms as per 'instructions for use' of the devices ■ Optional enrollment in the optical coherence tomography sub-study (10-20% of patients)	Emperor (paclitaxel eluting balloon) Magic Touch (sirolimus eluting balloon)	Xience (chromium-cobalt everolimus eluting stent)	Target vessel myocardial infarction Target vessel revascularizatino of failure Target lesion revascularization	January 2024, but no data has been published to date	Semmelweis University Heart and Vascular Center
NCT05544864/ ISAR-DESIRE 5	■ Patients with ischemic symptoms and/or evidence of myocardial ischemia ■ Presence of ≥ 50% restenosis after prior implantation of drug-eluting stents in native coronary vessels ■ Availability of an OCT-pullback of the target lesion ■ Age ≥ 18 years	Agent (paclitaxel eluting balloon)	Xience (everolimus eluting stent)	Major adverse cardiac event	September 2026	Deutsches Herzzentrum Muenchen
NCT04119986/ UNIQUE-DEB 2	■ Patients with coronary in-stent restenosis and QFR<0.8 of target lesion in the coronary stent	Drug eluting balloon (no further information provided)	Drug eluting stent (no further information provided)	Late lumen loss	December 2026	Nanjing First Hospital, Nanjing Medical University

Table A-16: List of ongoing randomized controlled trials of PTCA with DEB vs PTCA with POBA or DES in patients with de novo lesions

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05946629/ SELUTION 4	*Clinical inclusion criteria:* ■ Subject is ≥ 18 years (or the minimum legal age as required by local regulations) ■ Female subjects of childbearing potential must have a negative pregnancy test ≤ 7 days before the procedure or are using a contraceptive device or drug ■ Subject presents with chronic coronary syndromes [CCS] (manifest as documented angina or positive functional testing), unstable angina or stabilized non-ST elevation myocardial infarction (NSTEMI) (biomarkers stabilized or down trending) with an indication for PCI and planned intervention ■ Subject can tolerate dual antiplatelet therapy with aspirin, plus either Clopidogrel, Prasugrel, or Ticagrelor. (Note: For subjects requiring oral anticoagulation, aspirin may be omitted based on investigator discretion) ■ Subject has life expectancy > 1 year in the opinion of the investigator *Imaging inclusion criteria:* ■ A single, target lesions that meet criteria can be treated in a single vessel. No non-target lesions can be treated within the target vessel in the index procedure. Non-target lesions within the target vessel can be staged for treatment > 30 days from the index procedure ■ Up to two (2) non-target lesions in up to two (2) non-target vessels may be treated, but successful PCI of the non-target lesions must be completed before randomization and treatment of the target lesion ■ Target lesion is ≤ 36 mm in length ■ Target lesion has diameter stenosis > 50% and ≤ 99% with distal flow at least thrombolysis in myocardial infarction (TIMI) 2 ■ Target vessel has RVD of ≥ 2.00 mm and ≤ 2.75 mm [by visual assessment] ■ Target lesion is within a native coronary artery or major branch ■ A target lesion within or near a bifurcation is allowed only if a single vessel (either main vessel or side branch) is to be treated ■ The identified target lesion has high probability (> 70%) for successful treatment with approved pre-treatment techniques and DEB alone	SELUTION SLR 014 (sirolimus eluting balloon)	FDA approved "limus-based" drug eluting stent	Target lesion failure	August 2025	M.A. Med Alliance S.A.
NCT04859985/ SELUTION DeNovo	*Subjects must meet all the following criteria to participate in the trial:* ■ Subject age is ≥ 18 years (or 21 according to countries legal age) ■ Female subjects of childbearing potential have a negative pregnancy test ≤7 days before the procedure or are using a contraceptive device or drug. ■ Documented angina and/or positive functional testing or unstable angina or stabilized NSTEMI presentation. ■ Life expectancy >1 year ■ Written informed consent by the subject or her/his legally authorized representative for participation in the study ■ One or more native target vessel (LAD, LCX or RCA) is considered to require intervention and is suitable for treatment of all lesions with either DEB + provisional stenting or with DES and is identified as such.	SELUTION SLR 014 (sirolimus eluting balloon)	Drug eluting stent (no further information provided)	Target vessel failure (cardiac mortality, target-vessel related myocardial infarction (MI) or clinically driven target vessel revascularization) at 1 and 5 years	December 2024	M.A. Med Alliance S.A.

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04859985/ SELUTION DeNovo *(continuation)*	■ The number of trial target lesions is not limited, but in the operator's opinion, if the subject is randomized to the DEB arm, the likelihood of the subject requiring provisional stenting of any of the identified trial target lesions is < 30%, and if randomized to the systematic DES arm, all lesions are considered amenable to stenting. ■ All target lesions: diameter between 2.0 and 5 mm, and diameter stenosis > 50% and < 100% with distal flow at least TIMI 2					
NCT05516446/ DEBATE	■ Patients with silent ischemia, stable angina, unstable angina, or non-Q wave myocardial infarction ■ A de Novo lesion on a never treated native artery ■ A reference artery diameter between 2 mm and 4 mm	SeQuent® Please NEO (paclitaxel eluting balloon)	Promus Premier (everolimus eluting platinum chromium alloy coronary stent)	Late lumen loss	November 2022, but no data has been published to date	General Administration of Military Health, Tunisia
NCT05846893/ REVERSE	■ Patient must be ≥ 18 years of age ■ Patient is able to verbally confirm understanding of the study aim, risks, benefits, and treatment alternatives of receiving DEB or DES and he/she or his/her legally authorized representative provides written informed consent prior to any study-related procedure ■ (i) Clinical evidence of angina, and/or (ii) an abnormal functional study demonstrating myocardial ischemia due to the target lesion(s), or (iii) acute coronary syndrome [unstable angina or non-ST-elevation myocardial infarction (NSTEMI) or uneventful STEMI (≥ 48 hours after primary PCI and no sign of thrombus in lesion(s) to treat)] ■ Patient with lesions suitable for PCI with a DEB (and/or DES) according to the Instructions for Use ■ Patient is able to comply with the study protocol and agrees to undergo the clinical follow-up of 30 days, 6 months, 12 months, 24 months, and 36 months ■ Presence of significant de novo large vessel coronary artery disease (reference vessel diameter ≥ 3.0 mm by visual estimation) with either ≥ 70% diameter stenosis or intermediate ≥ 50% to < 70% diameter stenosis with abnormal functional test or symptom of ischemia ■ Successful lesion preparation. For randomisation, the lesion must satisfy the following criteria after optimal balloon angioplasty: no flow-limiting dissection (TIMI=3), and residual stenosis is ≤ 30% ■ Multivessel disease with two or more vessels showing diameter stenosis of 50% or more is not an exclusion as long as it fulfills all study's eligibility criteria ■ In diffuse lesion, inclusion is possible if the proximal reference vessel diameter is 3.0 mm or more	SeQuent® Please NEO (paclitaxel eluting balloon)	Current-generation DES	Net Adverse Clinical Event	October 2026	B. Braun Medical Industries Sdn. Bhd.
NCT05674630/ TITAN-DEB	■ Adult patients (≥ 18 years old) with chronic coronary syndrome deemed suitable for PCI ■ At least one significant de novo coronary lesion (defined as diameter stenosis > 50% on angiography, with flow limiting features, confirmed with FFR ≤0.80 or iFR ≤ 0.89 and intended implantation of a long (≥ 30 mm) DES based on IVUS findings	Magic Touch (sirolimus eluting balloon)	Drug eluting stent (no further information provided)	Absolute change of fractional flow reserve values	June 2026	Cardiocentro Ticino

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05961787/ LARGE-ONE	*Cinical inclusion criteria:* ■ Age of subject 18-75 years old ■ The subject (or legal guardian) understands and provides written informed consent to the test requirements and treatment procedures prior to performing any specific tests or procedures in the study ■ The subject is suitable for PCI ■ The subject had symptomatic coronary artery disease with objective evidence or asymptomatic ischemia *Angiographic inclusion criteria:* ■ At Maximum 2 target lesions with stenosis ≥50%, located in no more than 2 vessels with a visual reference vessel diameter (RVD) of ≥ 3.00 mm and ≤4.00 mm ■ The length of the target lesion must be≤35 mm (visually) and can be covered by one study stent or drug balloon ■ The first target lesion must be successfully predilated/pretreated without: ■ Vascular tears affecting hemodynamics (TIMI blood grade ≤2) ■ Coronary dissection classified as D, E and F(ARC) ■ Residual stenosis > 30% after lesion preparation	SeQuent® Please (paclitaxel eluting balloon)	Firehawk family drug eluting stent	Value of luminal loss	January 2025	Shanghai MicroPort Medical (Group) Co., Ltd.
NCT05550233/ DEB-LVD	■ Over 18 years old ■ Asymptomatic myocardial ischemia, stable or unstable angina ■ The subject (or legal guardian) understands the trial requirements and treatment process, and signs a written informed consent before performing any prescribed inspection or operation ■ Willing to undergo all follow-up evaluations requested by the trial, including admission angiographic evaluation at 12 months ■ The target lesion must be the de novo lesion, and the diameter of the reference vessel is ≥3.0mm	Drug eluting balloon (no further information provided)	Drug eluting stent (no further information provided)	Late lumen loss	December 2024	Beijing Hospital
NCT05209412/ CAGE-FREE 3	■ 18y ≤ age ≤ 80y ■ De novo coronary artery lesions with an indication for PCI ■ Target lesion diameter stenosis ≥ 70% (visual) or ≥ 50% (visual) with evidence of ischemia ■ Target lesion reference vessel diameter (2.5mm-4.0 mm), Length of a single target lesion ≤ 35mm; Total treated lesion length ≤ 60 mm ■ Vessels treated ≤ 2; only one DEB/DES is allowed for each target vessel ■ ≤ 2 non-target lesions (non-TL) are allowed, and can not be in the same vessel as the target lesion (randomization should be implemented only after the successful treatment of all non-TL) ■ Patients who are able to complete the follow-up and compliant to the prescribed medication	Lepu (paclitaxel eluting balloon)	Resolute (zotarolimus eluting stent)	Coronary fraction flow reserve	February 2024	Xijing Hospital

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04937803/ DEB-ACS	■ Age ≥18 years and < 80 years ■ Acute coronary syndrome patients eligible for PCI ■ Successful preparation is defined as ≤ 30% residual stenosis with Thrombolysis in Myocardial Infarction (TIMI) Grade III flow and not evidence of type C-F dissection ■ Vessel diameter from 2.25 mm-4.0 mm ■ Lesion length ≤ 28 mm ■ A single culprit lesion or 1 lesion in each of two vessels	Drug eluting balloon (no further information provided)	Zotarolimus eluting stent	Fractional flow reserve	February 2023[3]	Harbin Medical University
NCT04893291/ TRANSFORM 2	■ Age >18 years ■ All patients with a clinical indication to PCI (stable coronary artery disease or acute coronary syndromes) ■ Native coronary artery lesion in a vessel with diameter > 2.0 mm and ≦ 3.5 mm at visual estimation ■ Maximum lesion length: 50 mm	Sirolimus eluting balloon	Everolimus eluting stent	Target lesion failure Net adverse clinical events	November 2024	Fondazione Ricerca e Innovazione Cardiovascolare ETS
NCT04814212/ DEBATE	■ Age ≥ 18 years ■ At least one major or two minor bleeding risk criteria of Academic Research Consortium (ARC)	SeQuent® Please (paclitaxel eluting balloon) + tailored antithrombotic regimen	Biofreedom, Synergy, Ultimaster Tansei and Integrity Onyx, Xience Pro S or Promus Elite or any other DES	Major Adverse Cardiac Event	January 2026	North Karelia Central Hospital
NCT04561739/ CAGE-FREE 1	■ Patients with an indication for PCI due to acute or chronic coronary syndrome ■ Patients with de novo, non-complex lesion and underwent successful pre-dilation ■ Patients who are able to complete the follow-up and compliant to the prescribed medication	Paclitaxel eluting balloon	Sirolimus eluting stent	Device-oriented Composite Endpoint of Cardiac cause death, Target vessel myocardial infarction and Clinically indicated target lesion revascularization	May 2024	Xijing Hospital
NCT05750771	■ Patients older than 60 years of age ■ Patients meeting the indications for coronary intervention ■ IVUS examination suggests severe calcified lesions (calcification angle > 270° at the target lesion) or OCT examination suggests severe calcified lesions (calcification angle > 180° and/or length > 5 mm and/or thickness > 0.5 mm) ■ Target lesion vessel diameter > 2.5 mm	Drug-coated balloon with paclitaxel as drug coating	Second-generation drug-eluting stents	Late lumen loss (LLL) of the target lesion segment at 12 months	February 2024	Henan Institute of Cardiovascular Epidemiology
NCT05731687/ Hybrid DEB	■ Age ≥ 18 years ■ Significant de novo bifurcation lesion (main vessel and side branch diameter ≥ 2.5mm, diameter stenosis of the main vessel ≥ 70% and of the side branch ≥ 50% or in intermediate stenosis FFR ≤ 0.80 or iFR ≤ 0.89) ■ Stable coronary artery disease or stabilized acute coronary syndrome ■ Acceptable candidate for treatment with a drug eluting stent	Hybrid DEB approach with drug-eluting balloon	Two-stent strategy	Composite of all-cause death, periprocedural or spontaneous myocardial infarction (MI) and/or target vessel revascularization (TVR)	March 2026	Cathreine BV

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT06084000/ STENTLESS	■ Age ≥18 years ■ De novo lesions of large coronary vessels with the diameter of target lesion reference vessel > 2.75 mm ■ Single- or multi-vessel disease with only 1 lesion meeting the definition of severe stenosis and anatomically amenable to coronary revascularization using DCB alone judged by physician. ■ Other coronary artery lesions are not recommended for coronary revascularization by current guidelines and are not likely need to be treated within the next 1 year judged by physician (e.g., visual stenosis with severity between 50-70% and FFR > 0.8) ■ The prospective subject is agreed on participating the study with a formal written consent	Drug-coated balloon (Bingo© [Paclitaxel-coated Balloon], Yinyi Ltd., China)	Drug-eluting stent	Incidence of a composite of cardiac death, target-vessel myocardial infarction and clinically indicated target vessel revascularization	December 2025	China National Center for Cardiovascular Diseases
NCT05221931/ DCB-HBR	■ Subject must be at least 19 years of age ■ Subject who is able to understand risks, benefits and treatment alternatives and sign informed consent voluntarily. ■ Patients with at least one lesion with greater than 50% diameter stenosis or fractional flow reserve ≤0.80 requiring revascularization in de novo coronary artery of reference vessel size ≥2.25 mm ■ Patients with high bleeding risk	Drug eluting balloon (Agent, Prevail, or SeQuent Please/SeQuent Please NEO)	Second-generation drug-eluting stents	Target vessel failure (TVF)	July 2027	Samsung Medical Center
JPRN-UMIN000052443/ NEO D5	■ Age ≥ 20 years ■ Patients with stable or unstable angina or documented silent ischemia with de novo coronary lesions scheduled to undergo PCI ■ Patients with lesions with a reference vessel diameter between 2.0 mm-3.0mm and a lesion length of = or < 25 mm	Drug eluting balloon (no further information provided)	Drug eluting stent (no further information provided)	Coronary microcirculation	May 2027	not indicated
ChiCTR2200061611	■ Aged 40-75 years ■ Patients clinically diagnosed as coronary atherosclerotic heart disease, coronary angiography showed that PCI was needed, OCT confirmed that lesion is coronary artery intimal calcification, OCT score ≧ 2, and the lesion after pre-treatment is suitable for drug-eluting stent and drug-eluting balloon ■ For patients with diabetes and hypertension, blood sugar and blood pressure were up to standard before operation ■ Patients and their families signed the informed consent, and were willing to cooperate with the follow-up until 12 months after operation	Drug eluting balloon (no further information provided)	Drug eluting stent (no further information provided)	Late lumen loss	December 2025	Fuwai Central China Cardiovascular Hospital

Research questions

Table A-17: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-18: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-19: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A-20: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Literature search strategies

Search strategy for systematic reviews – Medlinie

Database: Ovid MEDLINE(R) ALL <1946 to December 19, 2023	
Search date: 19.12.2023	
ID	Search
1	exp Coronary Restenosis/ (8718)
2	restenos*.mp. (28374)
3	re-stenos*.mp. (754)
4	((ostium or ostial) adj5 stenos*).mp. (1431)
5	(de novo adj5 (lesion* or stenos*)).mp. (2571)
6	((stenos* or occlusion*) adj2 coronary).ti,ab. (26241)
7	1 or 2 or 3 or 4 or 5 or 6 (56273)
8	exp Angioplasty, Balloon, Coronary/ (36290)
9	Percutaneous transluminal coronary angioplast*.mp. (6869)
10	PTCA*.mp. (6716)
11	balloon*.mp. (126559)
12	8 or 9 or 10 or 11 (128929)
13	drug eluting balloon*.mp. (662)
14	DEB*.ti,ab. (293041)
15	drug coated balloon*.mp. (1753)
16	coated balloon catheter*.mp. (87)
17	exp Paclitaxel/ (31252)
18	exp Sirolimus/ (23490)
19	((paclitaxel* or sirolimus*) adj5 (eluting or coated)).mp. (4996)
20	DIOR.mp. (46)
21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (347878)
22	12 and 21 (6748)
23	7 and 22 (3249)
24	limit 23 to (meta analysis or "systematic review") (165)
25	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (737474)
26	23 and 25 (267)
27	24 or 26 (268)
28	limit 27 to ed=20201201-20231220 (48)
29	limit 27 to dt=20201201-20231220 (55)
30	28 or 29 (72)
31	limit 30 to (english or german) (71)
32	remove duplicates from 31 (70)
Total hits: 70	

Search strategy for RCTs – Medlinie

Database: Ovid MEDLINE(R) ALL <1946 to December 19, 2023	
Search date: 19.12.2023	
ID	Search
1	exp Coronary Restenosis/ (8732)
2	restenos*.mp. (28432)
3	re-stenos*.mp. (755)
4	((ostium or ostial) adj5 stenos*).mp. (1431)
5	(de novo adj5 (lesion* or stenos*)).mp. (2577)
6	exp Cerebral Small Vessel Diseases/ (9897)
7	small vessel* disease*.mp. (6239)
8	SVD*.ti,ab. (3968)
9	((stenos* or occlu*) adj2 coronar*).mp. (40385)
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (85241)
11	exp Angioplasty, Balloon, Coronary/ (36307)
12	Percutaneous transluminal coronary angioplast*.mp. (6871)
13	PTCA*.mp. (6720)
14	balloon*.mp. (126859)
15	11 or 12 or 13 or 14 (129234)
16	drug eluting balloon*.mp. (666)
17	DEB*.ti,ab. (294231)
18	drug coated balloon*.mp. (1774)
19	coated balloon catheter*.mp. (87)
20	exp Paclitaxel/ (31319)
21	exp Sirolimus/ (23535)
22	((paclitaxel or sirolimus) adj5 (eluting or coated)).mp. (5006)
23	DIOR.mp. (46)
24	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (349196)
25	15 and 24 (6778)
26	10 and 25 (3502)
27	limit 26 to randomized controlled trial (455)
28	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1495448)
29	26 and 28 (1098)
30	27 or 29 (1098)
31	limit 30 to dt=20200301-20240122 (183)
32	limit 30 to ed=20200301-20240122 (178)
33	31 or 32 (220)
34	limit 33 to (english or german) (219)
35	remove duplicates from 34 (219)
Total hits: 219	

Search strategy for RCTs – Embase

Search Name: PTCA mit DEBs_Trials (MEL-Update 2024)		
Search date: 22.01.2024		
No.	Query Results	Results
#48.	#46 NOT #47	273
#47.	#46 AND 'Conference Abstract'/it	80
#46.	#45 AND ([english]/lim OR [german]/lim)	353
#45.	#42 OR #44	360
#44.	#41 AND #43	349
#43.	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,306,788
#42.	#41 AND [randomized controlled trial]/lim	167
#41.	#40 AND [01-03-2020]/sd NOT [20-01-2024]/sd	1,651
#40.	#11 AND #39	5,406
#39.	#16 AND #38	8,993
#38.	#17 OR #18 OR #19 OR #24 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	19,014
#37.	dior:tn,dn	103
#36.	'dior'/exp	11
#35.	(paclitaxel OR sirolimus) NEAR/1 (eluting OR coated)	10,535
#34.	'sirolimus coated balloon'/exp	17
#33.	'paclitaxel coated balloon catheter'/exp	334
#32.	#30 AND #31	4,806
#31.	balloon*	178,987
#30.	#25 OR #26 OR #27 OR #28 OR #29	197,654
#29.	'sirolimus eluting stent'/exp	256
#28.	'sirolimus eluting coronary stent'/exp	2,489
#27.	'sirolimus'/exp	66,309
#26.	'paclitaxel eluting coronary stent'/exp	1,340
#25.	'paclitaxel'/exp	138,090
#24.	#20 AND #23	2,306
#23.	#21 OR #22	212,602
#22.	coated	160,981
#21.	eluting	56,619
#20.	'balloon catheter'/exp	34,466
#19.	'drug coated balloon*'	4,023
#18.	deb:ab,ti	3,620
#17.	'drug eluting balloon*'	1,564
#16.	#12 OR #13 OR #14 OR #15	206,997
#15.	'percutaneous transluminal coronar* angioplast*'	8,451
#14.	balloon*	178,987
#13.	ptca*	10,854
#12.	'transluminal coronary angioplasty'/exp	29,282
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	134,704
#10.	svd*:ti,ab	6,360
#9.	'small vessel* disease*'	10,166
#8.	'small vessel disease'/exp	119
#7.	(stenos* OR occlu*) NEAR/2 coronar*	70,648
#6.	'de novo' NEAR/4 (lesion* OR stenos*)	4,424

#5.	'in-stent restenosis'/exp	14,459
#4.	(ostium OR ostial) NEAR/4 stenos*	2,135
#3.	're-stenos*'	1,379
#2.	restenos*	51,877
#1.	'coronary restenosis'/exp	71
Total hits: 273		

Search strategy for RCTs – Cochrane (CENTRAL)

Search Name: PTCA mit DEBs_Trials (MEL-Update 2024)	
Search date: 22.01.2024	
Comments: TS/CW	
ID	Search
#1	MeSH descriptor: [Coronary Restenosis] explode all trees
#2	(restenos*) (Word variations have been searched)
#3	re-stenos* (Word variations have been searched)
#4	((coronar* OR ostium OR ostial OR (small NEXT vessel*)) NEAR (stenos* or occlu* or obstruct*)) (Word variations have been searched)
#5	(de novo NEAR (lesion* OR stenos*)) (Word variations have been searched)
#6	MeSH descriptor: [Cerebral Small Vessel Diseases] explode all trees
#7	(small NEXT vessel* NEXT disease*)
#8	(SVD*):ti,ab,kw (Word variations have been searched)
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	MeSH descriptor: [Angioplasty, Balloon, Coronary] explode all trees
#11	"Percutaneous transluminal coronary angioplasty":ti,ab,kw (Word variations have been searched)
#12	PTCA*
#13	balloon* (Word variations have been searched)
#14	#10 or #11 or #12 or #13
#15	"drug eluting balloon" (Word variations have been searched)
#16	DEB*:ti,ab,kw (Word variations have been searched)
#17	"drug coated balloon" (Word variations have been searched)
#18	"coated balloon catheter" (Word variations have been searched)
#19	MeSH descriptor: [Paclitaxel] explode all trees
#20	MeSH descriptor: [Sirolimus] explode all trees
#21	((paclitaxel OR sirolimus) NEAR (eluting OR coated OR releasing)) (Word variations have been searched)
#22	DIOR (Word variations have been searched)
#23	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	#14 AND #23
#25	#9 AND #24
#26	#9 AND #24 with Publication Year from 2020 to 2024, in Trials
#27	English:la
#28	German:la
#29	#27 OR #28
#30	#26 AND #29
#31	(conference proceeding):pt
#32	(abstract):so

#33	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#34	#31 OR #32 OR #33
#35	#30 NOT #34
Total hits: 142	

Search strategy for RCTs – INAHTA

Search Name: PTCA mit DEBs_Trials (MEL-Update 2024)	
Search date: 22.01.2024	
Search step #: "Search query,""Hits"",""Searched At"""	
ID	Search
28	"(((((DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) AND ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])))) AND (((stenos* OR occlu*) AND (coronar*)) OR (SVD*) OR (small vessel disease*) OR (""Cerebral Small Vessel Diseases""[mhe]) OR ((de novo) AND (lesion* OR stenos*)) OR ((ostium OR ostial) AND (stenos*)) OR (re-stenos*) OR (restenos*) OR (""Coronary Restenosis""[mhe]))) FROM 2020 TO 2024) AND (English OR German)[Language],""1"",""2024-01-22T16:43:02.000000Z"""
27	"((((DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) AND ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])))) AND (((stenos* OR occlu*) AND (coronar*)) OR (SVD*) OR (small vessel disease*) OR (""Cerebral Small Vessel Diseases""[mhe]) OR ((de novo) AND (lesion* OR stenos*)) OR ((ostium OR ostial) AND (stenos*)) OR (re-stenos*) OR (restenos*) OR (""Coronary Restenosis""[mhe]))) FROM 2020 TO 2024,""1"",""2024-01-22T16:42:43.000000Z"""
26	"(((DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) AND ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])))) AND (((stenos* OR occlu*) AND (coronar*)) OR (SVD*) OR (small vessel disease*) OR (""Cerebral Small Vessel Diseases""[mhe]) OR ((de novo) AND (lesion* OR stenos*)) OR ((ostium OR ostial) AND (stenos*)) OR (re-stenos*) OR (restenos*) OR (""Coronary Restenosis""[mhe])),""29"",""2024-01-22T16:42:10.000000Z"""
25	"(((DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) AND ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])))) AND (((stenos* OR occlu*) AND (coronar*)) OR (SVD*) OR (small vessel disease*) OR (""Cerebral Small Vessel Diseases""[mhe]) OR ((de novo) AND (lesion* OR stenos*)) OR ((ostium OR ostial) AND (stenos*)) OR (re-stenos*) OR (restenos*) OR (""Coronary Restenosis""[mhe])),""29"",""2024-01-22T16:42:01.000000Z"""
24	"((DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) AND ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])),""204"",""2024-01-22T16:41:30.000000Z"""
23	"(DIOR) OR ((paclitaxel OR sirolimus) AND (eluting OR coated OR releas*)) OR (""Sirolimus""[mhe]) OR (""Paclitaxel""[mhe]) OR (drug coated balloon*) OR (DEB) OR (drug eluting balloon*) OR ((balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe])) OR (balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe]),""299"",""2024-01-22T16:41:08.000000Z"""
22	"DIOR,""0"",""2024-01-22T16:40:20.000000Z"""
21	"(paclitaxel OR sirolimus) AND (eluting OR coated OR releas*),""26"",""2024-01-22T16:39:58.000000Z"""
20	"""Sirolimus""[mhe],""37"",""2024-01-22T16:39:11.000000Z"""
19	"""Paclitaxel""[mhe],""58"",""2024-01-22T16:38:54.000000Z"""
18	"drug coated balloon*,""11"",""2024-01-22T16:36:56.000000Z"""

17	"DEB,""10"",""2024-01-22T16:36:19.000000Z"""
16	"drug eluting balloon*,""12"",""2024-01-22T16:35:23.000000Z"""
15	"(balloon*) OR (PTCA*) OR (""Percutaneous transluminal coronary angioplasty"") OR (""Angioplasty Balloon Coronary""[mhe]),""204"",""2024-01-22T16:34:45.000000Z"""
14	"balloon*,""153"",""2024-01-22T16:34:30.000000Z"""
13	"PTCA*,""37"",""2024-01-22T16:33:41.000000Z"""
12	"""Percutaneous transluminal coronary angioplasty"",""26"",""2024-01-22T16:33:26.000000Z"""
11	"""Angioplasty Balloon Coronary""[mhe],""23"",""2024-01-22T16:33:04.000000Z"""
10	"((stenos* OR occlu*) AND (coronar*)) OR (SVD*) OR (small vessel disease*) OR (""Cerebral Small Vessel Diseases""[mhe]) OR ((de novo) AND (lesion* OR stenos*)) OR ((ostium OR ostial) AND (stenos*)) OR (re-stenos*) OR (restenos*) OR (""Coronary Restenosis""[mhe]),""153"",""2024-01-22T16:32:36.000000Z"""
9	"(stenos* OR occlu*) AND (coronar*),""65"",""2024-01-22T16:32:16.000000Z"""
8	"SVD*,""2"",""2024-01-22T16:31:31.000000Z"""
7	"small vessel disease*,""8"",""2024-01-22T16:31:13.000000Z"""
6	"""Cerebral Small Vessel Diseases""[mhe],""16"",""2024-01-22T16:30:36.000000Z"""
5	"(de novo) AND (lesion* OR stenos*),""24"",""2024-01-22T16:27:33.000000Z"""
4	"(ostium OR ostial) AND (stenos*),""2"",""2024-01-22T16:26:54.000000Z"""
3	"re-stenos*,""0"",""2024-01-22T16:25:52.000000Z"""
2	"restenos*,""59"",""2024-01-22T16:25:40.000000Z"""
1	"""Coronary Restenosis""[mhe],""41"",""2024-01-22T16:24:35.000000Z"""
Total hits: 1	

Search strategy in clinical trial registries

Search date: 07.02.2024

ClinicalTrials.gov (Expert search)

AREA[StudyType] EXPAND[Term] COVER[FullMatch] "Interventional" AND AREA[ConditionSearch] (instent stenosis OR in-stent OR ostium OR ostial OR capillaries OR small vessels OR small blood vessels OR capillary OR re-stenosis OR restenosis OR re-stenotic OR restenotic) AND AREA[InterventionSearch] (balloon OR DEB OR Paclitaxel OR Sirolimus) AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[03/01/2020, 02/07/2024]

73 studies identified

WHO-ICTRP (Advanced search)

coronary OR instent stenosis OR in-stent OR ostium OR ostial OR capillaries OR small vessel OR small blood vessels OR capillary OR re-stenosis OR restenosis OR re-stenotic OR restenotic in the Condition eluting balloon OR coated balloon OR releasing balloon OR DEB OR Paclitaxel OR Sirolimus in the Intervention

Date of registration is between 01/03/2020 and 07/02/2024

59 (52 additional) studies identified

EU Clinical Trials Register (EudraCT) (Basic search)

("instent stenosis" OR in-stent OR ostium OR ostial OR capillaries OR "small vessel" OR "small blood vessels" OR capillary OR re-stenosis OR restenosis OR re-stenotic OR restenotic) AND ("eluting balloon" OR "coated balloon" OR "releasing balloon" OR DEB)

Selected Date Range: 2020-03-01 to 2024-02-07

No studies identified

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH