Bioresorbierbare Stents zur Behandlung von kardiovaskulären Indikationen (Koronare Herzkrankheit)

EUnetHTA-Report

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Ludwig Boltzmann Institut
Health Technology Assessment

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Vienna, March 2019

Zusammenfassung

Einleitung

Beschreibung der Technologie

BRS:
abbaubares Material,
medikamentenbeschichtet
oder unbeschichtet

Intention: um dem Risiko
von Spätkomplikationen
der myokardialen
Revaskularisation
vorzubeugen

5 CE-zertifizierte Produkte
für CAD PatientInnen
zugelassen

Vollständig bioresorbierbare Stents oder Scaffolds (BRS/ bioresorbable scaffold oder BVS/ bioabsorbable vascular scaffold) stellen die neueste Generation von Stents zur myokardialen Revaskularisation dar. Sie bestehen aus einem abbaubaren Material, meist einem Polymer wie Polymilchsäure oder einer Magnesiumlegierung und sind entweder medikamentenbeschichtet oder unbeschichtet. Sie werden hauptsächlich verwendet, um das Risiko von Spätkomplikationen wie Gerüstthrombose (ScT) oder Restenose vorzubeugen, die auftreten können, wenn das starre geflochtene Gerüst eines herkömmlichen Metallstents dauerhaft im kranken Gefäß verankert bleibt. Bislang haben fünf Produkte (Absorb®, DESolve®, ART Pure, Fantom® und Magmaris) das CE-Zertifikat zur Implantation in erwachsenen PatientInnen mit koronarer Herzkrankheit (KHK) erhalten. Absorb® (bioresorbable vascular scaffolds, BVS) wurde 2016 auch von der US-amerikanischen Zulassungsbehörde FDA zugelassen. Absorb® ist nun aber nicht mehr auf dem Markt erhältlich, da der Hersteller den Verkauf im Mai 2017 eingestellt hat.

myokardiale
Revaskularisationstechniken:
PCI und CABG

Stents:
BMS,
DES,
BRS

Myokardiale Revaskularisation bei PatientInnen mit CAD kann verschiedene Arten erfolgen: mittels einer perkutanen koronaren Intervention (PCI) oder einer koronaren Bypass-Operation (CABG). Die erste PCI-Technik war die Ballonangioplastie (PTA). Die Koronarstenose konnte zwar mit PTA erfolgreich behandelt werden, führte aber auch zu einer hohen Rate an akuten Gefäßverschlüssen und Restenosen. Die Entwicklung von unbeschichteten Metallstents (Bare metal stents, BMS) leitete daraufhin eine Revolution ein. Die Implantation des BMS reduzierte den Gefäßrückstoß und führte deswegen zu besseren akuten Ergebnissen. Der Nachteil ist, dass das Metallgerüst dauerhaft im Gefäß verbleibt und einen dauerhaften Reiz durch Gefäßschädigung mit Risiko für Thrombose und Restenose darstellt. Um die neointimale Hyperplasie und dadurch die Rate der Restenose zu reduzieren, wurden Medikamente freisetzende Stents (Drug Eluting Stents, DES) entwickelt. Bei DES wird das Metallgerüst mit einem immunsuppressiven oder zytotoxischen Wirkstoff beschichtet, der freigesetzt wird. Thrombozytenaggregationshemmer (TAH) sind aufgrund des Stent-Thrombose Risikos erforderlich, allerdings können sie zu Blutungskomplikationen führen. Stents mit bioresorbierbarer Polymer-Beschichtung wurden entwickelt, um das Risiko für Polymer-induzierte Entzündungsreaktionen zu reduzieren und auf diese Weise arterielle Heilungsprozesse zu beschleunigen.

CABG: Operation am
offenen Herzen

PCI: häufigste
Revaskularisationstechnik

Stents: am wenigsten
invasiv

Die koronaren Bypass-Operation (CABG) ist eine Operation am offenen Herzen, die den Blutfluss zum Herzen verbessert. Bei der CABG wird eine gesunde Arterie oder Vene mit der blockierten Koronararterie verbunden, sodass die transplantierte Arterie oder Vene den blockierten Teil der Koronararterie umgeht. Obwohl die perkutane Koronarintervention (PCI, auch: perkutane transluminale koronare Angioplastie, PTCA) derzeit die am häufigsten eingesetzte Revaskularisationstechnik ist, spielt CABG nach wie vor eine wichtige Rolle bei der Behandlung von PatientInnen mit fortgeschrittener

obstruktiver Koronarerkrankung. Im Vergleich zur Implantation eines Stents, ist CABG invasiver und damit mit höheren periprozeduralen Risiken verbunden.

Indikation und therapeutisches Ziel

KHK: häufigste Krankheit und Todursache in Europa

Die koronare Herzkrankheit (KHK) ist eine Manifestation der Arteriosklerose in den Koronararterien und gehört zu den häufigsten Krankheiten. KHK ist die häufigste Todesursache in Europa. Zu den Risikofaktoren gehören Rauchen, hoher Alkoholkonsum, Bewegungsmangel, hoher Cholesterinspiegel im Blut, Übergewicht oder Fettleibigkeit, Diabetes mellitus, Bluthochdruck und psychosoziale Belastungen wie Stress oder Depressionen. Menschen mit KHK haben ein erhöhtes Risiko für Myokardinfarkt (MI), Herzrhythmusstörungen wie Vorhofflimmern, Herzinsuffizienz und vorzeitige Mortalität. Symptome für KHK sind typischerweise Kurzatmigkeit und Brustschmerzen (Angina pectoris). Bei PatientInnen mit stabiler Angina pectoris ändern sich die Symptome über einen längeren Zeitraum nicht, während bei PatientInnen mit instabiler Angina pectoris die Symptome ohne körperliche Anstrengung plötzlich zunehmen oder sich die Belastungsschwelle ändert.

KHK erhöht das Risiko für MI, Herzrhythmusstörungen und Mortalität

in Europa fast 17 Millionen Männer und 13 Millionen Frauen mit KHK

Im Jahr 2015 lebten in Europa fast 17 Millionen Männer und mehr als 13 Millionen Frauen mit KHK: die Gesamtkosten (einschließlich direkter Gesundheitskosten, Produktivitätsverluste und informeller Pflegekosten) wurden auf über 59 Milliarden Euro geschätzt.

Diagnose und Abklärung von KHK durch Identifizierung von biochemischen Risikofaktoren und kardiale Untersuchungen

Die Diagnose und Bewertung von stabiler KHK beinhaltet die klinische Abklärung, einschließlich der Identifizierung von signifikanter Dyslipidämie, Hyperglykämie oder anderen biochemischen Risikofaktoren und spezifischer kardialer Untersuchungen wie Stresstests oder koronare Bildgebung. Bei vermutetem akutem koronarem Syndrom (ACS) werden zur Differentialdiagnostik aus dem klinischen Erscheinungsbild (d.h. Symptome, Vitalparameter) verschiedene Merkmale mittels 12-Kanal-Elektrokardiogramm (EKG) und Biomarkern (insbesondere Troponin) erhoben. Eine nichtinvasive Bildgebung, wie die transthorakale Echokardiographie, kann zur Diagnose beitragen.

Methoden

Verwendung von HTA Core Model® für REA

Der Bericht wurde im EUnetHTA HTA Core Model® REA Version 4.2 erstellt und basiert auf der systematischen Übersichtsarbeit zum gleichen Thema vom LBI-HTA 2015 (DSD 81: http://eprints.hta.lbg.ac.at/1060). Die systematische Suche wurde in mehreren Datenbanken durchgeführt (Medline, PubMed, Embase, Cochrane Central Register of Controlled Trials, und Cochrane Database for Systematic Reviews). Weitere Informationen wurden durch Handsuche nach potentiell relevanten Primärstudien, Informationen des Herstellers, systematische Suche nach klinischen Leitlinien in der G-I-N Datenbank sowie der Suche nach laufenden Studien (Clinical Trials Registry Platform [ICTRP] und Clinicaltrials.gov) gewonnen.

Suche in mehreren Datenbanken

Einschluss von Studie
für Wirksamkeit: RCTs, nRCTs
für Sicherheit: auch Beobachtungsstudien

Für die Beurteilung der klinischen Wirksamkeit wurden nur randomisierte kontrollierte Studien (RCTs) und nicht randomisierte kontrollierte Studien (nicht-RCTs) eingeschlossen. Für die Beurteilung der Sicherheit wurden neben RCTs und nicht-RCTs prospektive unkontrollierte Studien mit mindestens 50 PatientInnen berücksichtigt.

Zur Beurteilung der internen Validität der eingeschlossenen RCTs wurde das Cochrane Risk of Bias (RoB) Tool verwendet. Die IHE-20-Checkliste wurde zur Bewertung der internen Validität der eingeschlossenen Studien ohne Kontrollgruppe verwendet. Die Qualität der Evidenz wurde mit der GRADE-Methode (Grading of Recommendations, Assessment, Development and Evaluation) bewertet.

Cochrane RoB Tool, IHE-20 Checkliste GRADE

Ergebnisse

Verfügbare Evidenz

Es wurden acht RCTs mit insgesamt 5.863 PatientInnen für die Bewertung der Wirksamkeit eingeschlossen. Alle RCTs bewerteten den **Absorb® BVS**. In sieben RCTs war ein Stent mit permanenter Everolimusbeschichtung (Xience® oder Synergy®) der Komparator. Eine Studie verwendete zwei verschiedene Komparatoren: ein Stent mit permanenter Everolimusbeschichtung (Promus Element, DES) und ein Stent mit permanenter Biolimusbeschichtung (Biomatrix Flex, DES). Für die Beurteilung der Sicherheit wurden noch zusätzlich 45 prospektive unkontrollierte Studien eingeschlossen. Von denen untersuchten drei Studien (345 PatientInnen) **DESolve®**, zwei Studien (184 PatientInnen) **Magmaris**, eine Studie (mit einem Follow-Up von 6 Monaten bei 117 von 240 PatientInnen) **Fantom®**, und 39 Studien (insgesamt mehr als 15.000 PatientInnen) Absorb®. Keine Studie konnte identifiziert werden, die den **ART Pure** Stent untersuchte.

8 RCTs für die Bewertung der Wirksamkeit: 5.863 Pts

45 unkontrollierte Studien zusätzlich für die Bewertung der Sicherheit

Klinische Wirksamkeit

Die wichtigsten Endpunkte zur Wirksamkeit waren schwerwiegende unerwünschte koronare Komplikationen (MACE, major adverse cardiac events), Gesamtmortalität, Koronarmortalität, Angina pectoris, MI, Lebensqualität, Aktivitäten des täglichen Lebens. Darüber hinaus wurden die Surrogatendpunkte Zielgefäß-Revaskularisation (TVR) und Zielläsion-Revaskularisation (TLR) bewertet.

Wirksamkeitsendpunkte

Die Meta-Analyse zeigte…

- keinen signifikanten Unterschied zwischen Absorb® und dem DES mit permanenter Beschichtung für die Gesamtmortalität und Herzmortalität (RR 0.84 [95% CI 0.63 - 1.11] und RR 0.91 [95% CI 0.60 - 1.39]),

Gesamtmortalität, Koronarmortalität: kein signifikanter Unterschied

- ein signifikant erhöhtes Risiko für MACE (RR 1.36 [95% CI 1.06 – 1.73]), MI (RR 1.49 [95% CI 1.21 – 1.84]) und TLR (RR 1.36 [95% CI 1.08 – 1.71]) für PatientInnen, die mit dem Absorb® BVS behandelt wurden, und

MACE und TLR: signifikant erhöhtes Risiko mit Absorb®

- keinen Unterschied zwischen Absorb® und dem DES mit permanenter Beschichtung für die Lebensqualität und die Aktivitäten des täglichen Lebens.

LQ: kein Unterschied im Vergleich zu DES

Es wurde keine Evidenz für die Beantwortung der Forschungsfragen zur Wirksamkeit der weiteren (CE-zertifizierten) vollständig bioresorbierbaren Stents DESolve®, Magmaris, ART Pure und Fantom® gefunden.

keine vergleichende Evidenz zu DESolve®, Magmaris, ART Pure und Fantom®

Sicherheit

Sicherheitsendpunkte

Um die Sicherheit der vollständigen BRS zu beurteilen, wurden schwerwiegende unerwünschte Ereignisse (SAEs), wie periprozeduraler MI oder Mortalität, Gerüstthrombose (ScT), die nach mindestens einem Jahr Follow-up auftraten, Mortalität als Folge von Blutungen oder Schlaganfällen oder unerwünschte Ereignisse, wie Blutungen als Folge einer Antiplättchentherapie, Komplikationen beim Gefäßzugang oder verfahrensbedingte kontrastmittelinduzierte Nephropathie, berücksichtigt.

- **Absorb®**

periprozedurale MI:
kein Unterschied in RCTs

Die RCTs zeigten keinen statistischen Unterschied für periprozeduralen MI im Vergleich zu DES mit permanenter Beschichtung [RR 1.22 (95% CI 0.82-1.82)]. In acht unkontrollierten Studien trat während oder kurz nach der Implantation des Absorb® BVS kein MI auf, in weiteren 20 unkontrollierten Studien betrug die Medianrate der periprozeduralen MI 2.8%. Periprozeduraler Tod wurde nur in zwei RCTs und 22 unkontrollierten Studien berichtet, wobei in 21 Studien, einschließlich der beiden RCTs, keine PatientInnen während des Verfahrens starben. In den übrigen drei unkontrollierten Studien betrugen die Raten der periprozeduralen Mortalität 0.04%, 0.5% bzw. 1.3%. Die Gesamtrate von ScT, die nach mindestens 1-Jahres Follow-up auftrat, war in den eingeschlossenen Studien gering. Dennoch führte die Meta-Analyse aus RCTs im Vergleich zu DES mit permanenter Beschichtung zu einem statistisch signifikant höheren Risiko für sehr später ScT bei PatientInnen, die mit dem Absorb® BVS behandelt wurden [RR 5.09 (95% CI 1.9-13.17)]. In sieben unkontrollierten Studien kam es zu keiner sehr späten ScT. In 13 unkontrollierten Studien lag die Rate der sehr späten ScT zwischen 0.2% und 1.7%. Blutungen als Folge der Thrombozytenaggregationshemmung wurden nur in fünf unkontrollierten Studien (Ereignisrate: 1%-4.4%) und Mortalität als Folge von Blutungen oder Schlaganfällen in elf Studien berichtet, wobei in neun Studien keine und in den verbleibenden beiden Studien jeweils ein Todesfall auftraten. Komplikationen beim vaskulären Zugang wurden nur aus zwei unkontrollierten Studien abgeleitet (Ereignisrate: 0.09% und 0.7%). Es wurden keine Hinweise auf verfahrensbedingte kontrastmittelinduzierte Nephropathie gefunden. Es wurde kein Unterschied in Bezug auf die Rate der Sicherheitsereignisse aus RCTs oder prospektiven unkontrollierten Studien mit überwiegend PatientInnen mit stabiler Angina im Vergleich zu Studien mit überwiegend PatientInnen mit ACS festgestellt.

periprozedurale Mortalität:
keine Todesfälle in 21 Studien,
0.04-1.3% in 3 Studien

späte ScT:
signifikant erhöhtes Risiko mit Absorb® im Vergleich zu DES mit permanenter Beschichtung

Mortalität:
keine Todesfälle in 9 Studien, jeweils ein Todesfall in 2 Studien

- **DESolve®**

keine periprozeduralen Todesfälle,
keine MIs,
keine sehr späten ScTs

Es lagen keine Sicherheitsergebnisse aus RCTs vor. In drei unkontrollierten Studien wurden periprozedurale Todesfälle oder periprozedurale MIs berichtet, wobei kein/e PatientIn während oder kurz nach dem Eingriff starb und nur bei einem/r PatientIn ein periprozeduraler MI auftrat. Darüber hinaus starb kein/e PatientIn an Blutungen oder Schlaganfällen. Sehr späte ScTs konnten nur aus einer Studie abgeleitet werden, ohne dass Ereignisse gemeldet wurden. Es wurden keine Hinweise auf Blutungen als Folge von Antiplättchentherapie, Komplikationen des Gefäßzugangs oder verfahrensbedingte kontrastmittelinduzierte Nephropathie gefunden.

- **Magmaris (Dreams 2G)**

Es lagen keine Sicherheitsergebnisse von RCTs vor. In zwei unkontrollierten Studien wurden periprozedurale Todesfälle oder periprozedurale MIs berichtet. In beiden Studien starb kein/e PatientIn und es erlitt kein/e PatientIn während oder kurz nach dem Eingriff einen MI. Darüber hinaus starb kein/e PatientIn an Blutungen oder Schlaganfällen. Eine Studie berichtete, dass keine sehr späten ScTs auftraten. Es wurden keine Hinweise auf Blutungen als Folge von Antiplättchentherapie, Komplikationen des Gefäßzugangs oder verfahrensbedingte kontrastmittelinduzierte Nephropathie gefunden.

keine periprozeduralen Todesfälle,
keine MIs,
keine sehr späten ScTs

- **Fantom®**

Es konnte nur eine unkontrollierte Studie mit 6 Monaten Follow-up identifiziert werden. In dieser Studie starb kein/e PatientIn während oder kurz nach dem Eingriff und es trat ein Fall von periprozeduralem MI auf. Darüber hinaus starb kein/e PatientIn während der 6-monatigen Nachbeobachtung an Blutungen oder Schlaganfällen. Da die Publikation nur über 6 Monate Follow-up-Ergebnisse berichtete, waren sehr späte ScT-Raten für Fantom® nicht verfügbar. Es wurden keine Hinweise auf Blutungen als Folge von Antiplättchentherapie, Komplikationen des Gefäßzugangs oder verfahrensbedingte kontrastmittelinduzierte Nephropathie gefunden.

keine periprozeduralen Todesfälle, keine MIs

Laufende Studien

Es konnten zehn laufende RCTs und 21 Beobachtungsstudien identifiziert werden. Neun der RCTs und 12 der Beobachtungsstudien untersuchen Absorb® BVS, ein RCT und vier Beobachtungsstudien untersuchen Magmaris (Dreams 2G) BRS, zwei Beobachtungsstudien untersuchen DESolve® BRS und weitere zwei Beobachtungsstudien untersuchen Fantom® BRS. In einer Beobachtungsstudie war unklar, welches BRS Modell untersucht wurde. Die geplanten Studienabschlusstermine für die RCTs lagen zwischen Dezember 2018 und April 2024. Darüber hinaus gab es sieben beendete oder derzeit eingestellte RCTs und zwei beendete oder eingestellte Beobachtungsstudien des Absorb® BVS sowie eine eingestellte Beobachtungsstudie des DESolve® BRS und eine weitere der Magmaris BRS. Gründe für die Aussetzung oder Beendigung der Studie waren eine langsame PatientInnenrekrutierung, Sicherheitsprobleme oder die Nichtverfügbarkeit des BRS.

laufende Studien:
10 RCTs,
21 Beobachtungsstudien

11 eingestellte Studien:

9 mit Absorb®
1 mit DESolve®
1 mit Magmaris

Diskussion

Die Qualität der Evidenz für das Absorb® BVS wurde als hoch bis mittelgradig für die Wirksamkeitsergebnisse und mittelgradig bis sehr niedrig für die Sicherheitsergebnisse beurteilt. Hauptgründe für die niedrige Qualität der Evidenz waren sehr niedrige Ereignisraten in den Studien und/oder ein hohes Verzerrungsrisiko. Sieben Jahre nach der CE-Zulassung des Absorb® BVS zeigten die Ergebnisse von acht RCTs, darunter fast 6.000 PatientInnen, eine geringere Wirksamkeit in Bezug auf patientenrelevante Endpunkte im Vergleich zur 2. Generation von DES mit permanenter Beschichtung. Dies zeigte sich an den höheren Raten der Revaskularisation, MI und MACE, des kombinierten patienten-relevanten Endpunkts, der alle Todesfälle, alle MI und alle Revaskularisation umfasst. Bezüglich Sicherheitsendpunkte zeigten die Ergebnisse aus diesen RCTs ein signifikant höheres Risiko für sehr späte ScT nach 1-Jahres Follow-up oder länger bei PatientInnen, die mit Absorb® BVS behandelt wurden, als bei PatientInnenen, die mit DES mit permanenter Beschichtung behandelt wurden. Alle diese Ergebnisse basieren ausschließlich auf Daten von Absorb BVS® Studien und können daher nicht direkt auf andere BRS übertragen werden.

Qualität der Evidenz für Absorb® als hoch bis mittelgradig für Wirksamkeit, als mittelgradig bis sehr niedrig für Sicherheit beurteilt

Wirksamkeitsendpunkte: Absorb® ist DES mit permanenter Beschichtung unterlegen

Sicherheitsendpunkte: Absorb® ist DES mit permanenter Beschichtung unterlegen

Für alle anderen CE- zertifizierten BRS (DESolve®, Magmaris, ART Pure und Fantom®) liegen derzeit keine Ergebnisse aus RCTs oder zumindest aus nicht randomisierten kontrollierten Studien vor. Sicherheitsergebnisse für diese andere CE- zertifizierten BRS sowie für Absorb® lagen nur aus wenigen unkontrollierten Kurzzeitstudien vor. Daher wird die derzeit verfügbare Evidenz für diese Produkte als sehr niedrig erachtet und man kann keine zuverlässigen Schlussfolgerungen auf ihre klinische Wirksamkeit und Sicherheit ziehen.

DESolve®, Magmaris, ART Pure und Fantom®: keine vergleichenden Studien, Schlussfolgerung möglich

Im Prinzip wurden vollständige BRS entwickelt, um unerwünschte Ereignisse wie Thrombose oder Restenose vorzubeugen, die durch das permanente Vorhandensein von Metallstents in den Gefäßen entstehen können. Nun, zehn Jahre nach ihrer Implementierung, zeigt die Evidenz aus Langzeit-RCTs genau das Gegenteil, nämlich mehr späte Thrombosen und höhere TLR-Raten für PatientInnen, die mit BRS behandelt werden. Aufgrund dieser Erkenntnisse hat der Hersteller des Absorb® BVS dessen Produkt im Mai 2017 vom Markt genommen. Alle anderen BRS sind deutlich weniger gut untersucht. Da es jedoch erhebliche Unterschiede zwischen den einzelnen CE- zertifizierten Stents sowohl in Bezug auf das Grundgerüstmaterial, das freigesetzte Medikament, die Strebendicke und die Zeitdauer bis zum vollständigen Abbau des Materials gibt, ist die Übertragbarkeit der Ergebnisse aus den Studien zur Untersuchung des Absorb® BVS auf die klinische Wirksamkeit und Sicherheit anderer Produkte begrenzt.

Absorb® wurde vom Markt genommen aufgrund schlechter Ergebnissen von Langzeit-RCTs

andere BRS weniger gut untersucht, Übertragbarkeit der Absorb® Studienergebnisse auf andere BRS begrenzt

Darüber hinaus ist die Anwendbarkeit der Ergebnisse aus den vorliegendenklinischen Studien eingeschränkt. Die meisten PatientInnen innerhalb der Studien waren Männer (60% oder mehr) im Alter zwischen 60 und 70 Jahren, mit - in den meisten Fällen - einer oder maximal zwei einfachen Läsionen. Die Ergebnisse dürfen auf weibliche Patientinnen, ältere PatientInnen oder PatientInnen mit komplexeren Läsionen nur mit großer Vorsicht übertragen werden. Darüber hinaus hatten in den ersten RCTs die meisten der eingeschlossenen PatientInnen eine stabile Angina, hingegen umfassten einige neuere RCTs überwiegend PatientInnen mit ACS. Jedoch sind die Ergebnisse sowohl für PatientInnen mit stabiler Angina Pectoris als auch für PatientInnen mit ACS anwendbar, da die Subgruppenanalysen, die RCTs mit mehr PatientInnen mit stabiler KHK mit jenen, mit mehr PatientInnen mit

eingeschränkte Anwendbarkeit der Studienergebnisse

instabiler KHK verglichen, keinen Unterschied in wichtigen Endpunkten zeigten.

Aktuelle Guideline zur myokardialen Revaskularisation legen dar, dass die Evidenz für andere BRS als Absorb® BVS begrenzt ist und dass BRS *nicht* außerhalb gut kontrollierter klinischer Studien verwendet werden sollte. Die Ergebnisse aus RCTs für andere BRS als Absorb® BVS werden dringend benötigt. Eine große Anzahl laufender Studien ist derzeit in ClinicalTrials.gov und der WHO-ICTR-Datenbank registriert, aber es wurde nur ein RCT identifiziert, der nicht Absorb® BVS (sondern Magmaris) untersucht.

aktuelle Guidelines empfehlen BRS nicht außerhalb kontrollierter klinischer Studien

RCT-Ergebnisse für andere BRS als Absorb® dringend benötigt

Schlussfolgerung

Basierend auf der verfügbaren Evidenz aus acht RCTs gilt der vollständig bioresorbierbare Everolimus-eluierende Stent Absorb® BVS als weniger wirksam und hat ein schlechteres Sicherheitsprofil als Stents mit permanenter Everolimus- oder Biolimusbeschichtung. Diese Schlussfolgerung basiert auf einem statistisch höherem Risiko für MI, TLR und sehr späte Thrombosen (nach einem Jahr oder länger) bei PatientInnen, die mit Absorb® BVS innerhalb von bis zu vier Jahren behandelt wurden, und es konnte kein Nutzen für alle anderen Wirksamkeits- oder Sicherheitsendpunkte gezeigt werden.

Absorb® ist weniger wirksam und sicher als Stents mit permanenter Beschichtung

Es gibt keine ausreichende Evidenz, um festzustellen, ob Absorb® BVS als weniger wirksam oder weniger sicher als andere Revaskularisationsstrategien angesehen wird.

keine Aussage möglich zu… …Absorb® im Vergleich zu anderen Revaskularisationsstrategien

Es gibt keine ausreichende Evidenz, um festzustellen, ob die anderen vier derzeit CE-zertifizierten BRS (DESolve®, Magmaris, Art Pure oder Fantom®) effektiver als (oder mindestens so effektiv wie) und/oder mit besseren (oder mindestens ähnlichen) Sicherheitsprofilen als DES mit permanenter Beschichtung oder andere Revaskularisationsstrategien sind.

…DESolve®, Magmaris, Art Pure oder Fantom® im Vergleich zu DES mit permanenter Beschichtung oder anderen Revaskularisationsstrategien

Es besteht ein dringender Bedarf an RCTs oder zumindest nichtrandomisierten kontrollierten Studien mit einer höheren PatientInnenzahl und Langzeit-Follow-up, um feststellen zu können, ob die CE-zertifizierten BRS (DESolve®, Magmaris, Art Pure oder Fantom®) geeignete Alternativen zu DES mit permanenter Beschichtung oder anderen Revaskularissationsstrategien sind.

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

BIORESORBABLE STENTS FOR THE TREATMENT OF CARDIOVASCULAR INDICATIONS (CORONARY ARTERY DISEASE)

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Disclaimer

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Assessment team

Author(s)	Institute for General Practice and Evidence-based Health Service Research, Medical University of Graz (IAMEV)/Austria
Co-Author(s)	National School of Public Health, Management and Professional Development Bucharest (SNSPMPDSB)/Romania
Dedicated Reviewer(s)	French National Authority for Health (HAS)/France Health Service of Canary Islands (SESCS)/Spain

Consultation of the draft Rapid Assessment

External experts	PD Dr Herwig Schuchlenz, Landeskrankenhaus Graz West, Austria
Manufacturer(s) (factual accuracy check)	Reva Medical, San Diego, CA, USA Biotronik, Bülach, Switzerland
Medical editor	Compuscript Ltd/Ireland
Project Manager	Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)/Austria

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
ARC	Academic Research Consortium
BES	Biolimus-eluting stent
BMS	Bare metal stent
BRS	Bioresorbable scaffold
BVS	Bioresorbable vascular scaffold
CA	California
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CE	Conformité Européenne (European Conformity)
CFR	Coronary flow reserve
CI	Confidence interval
CVD	Cardiovascular disease
DES	Drug-eluting stent
DOCE	Device-oriented composite endpoint
DRG	Diagnosis Related Group
EACTS	European Association for Cardio-Thoracic Surgery
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiography
EES	Everolimus-eluting stent
EF	Ejection fraction
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
GIN	Guidelines International Network
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard ratio
ICD	International Classification of Diseases
ID-TLR	Ischaemic-driven target lesion revascularisation
ID-TVR	Ischaemic-driven target vessel revascularisation
IHD	Ischaemic heart disease
IHE	Institute of Health Economics
IMR	Index of microvascular resistance
IVUS	Intravascular ultrasound
LL	Lumen loss
LLL	Late lumen loss

MACE	Major adverse cardiac events
MeSH	Major Subject Headings
MI	Myocardial infarction
MIT	Massachusetts Institute of Technology
MLD	Minimum lumen diameter
na	Not applicable
NICE	National Institute for Health and Care Excellence
nr	Not reported
NSTEMI	Non-ST-segment elevation myocardial infarction
OCT	Optical coherence tomography
OR	Odds ratio
PCI	Percutaneous coronary intervention
PDLLA	Poly(D,L-lactic acid)
PLLA	Poly(L-lactic acid)
POCE	Patient-oriented composite endpoint
PTA	Percutaneous transluminal angioplasty
QCA	Quantitative coronary angiography
RCT	Randomised controlled trial
REA	Relative effectiveness assessment
RMS	Resorbable magnesium scaffold
RR	Risk ratio
RUTTS	Ratio of uncovered to total stent struts per cross-section score
RVD	Reference vessel diameter
SAE	Serious adverse event
ScT	Scaffold thrombosis
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularisation
TV-MI	Target vessel myocardial infarction
TVF	Target vessel failure
TVR	Target vessel revascularisation
USA	United States of America
WHO-ICTRP	World Health Organisation – International Clinical Trials Registry Platform

SUMMARY OF THE RELATIVE EFFECTIVENESS OF BIORESORBABLE STENTS FOR THE TREATMENT OF CARDIOVASCULAR INDICATIONS (CORONARY ARTERY DISEASE)

Scope

The scope can be found here: Scope.

Introduction

Description of technology and comparators

The technology

Fully bioresorbable stents or scaffolds (BRS) represent the latest generation of devices for myocardial revascularisation strategies [1]. They comprise a degradable material, most commonly a polymer, such as poly(L-lactic acid) (PLLA) or a magnesium alloy, and are either drug coated or drug free. They are mainly built to overcome the risk of late complications, such as scaffold thrombosis or restenosis, which can occur when the rigid metal backbone of a conventional metal stent remains permanently embedded in the diseased vessel [2, 3]. To date, five devices (Absorb®, DESolve®, ART Pure, Fantom® and Magmaris) have received Conformité Européenne (CE) marking for their use in adult patients with coronary artery disease (CAD). Absorb® was also approved by the US market authorisation agency (Food and Drug Administration; FDA) in 2016. However, it has not been available on the market since the manufacturer stopped sales in May 2017 [4].

The comparators

The two main options currently available for revascularisation in patients with CAD are percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) [5]. The first PCI technique developed was balloon angioplasty (percutaneous transluminal angioplasty; PTA). Although coronary stenosis could be treated successfully with PTA, it also led to a high rate of acute vessel closures and restenosis. The next step was the introduction of bare metal stents (BMS). The implantation of such stents reduced vessel recoil, leading to better acute results, but restenosis, resulting from neointimal hyperplasia, remained an issue [2]. To reduce this neointimal hyperplasia, so-called ‘drug-eluting stents’ (DES) were developed. With these stents, the metal scaffold is coated with an immunosuppressant or cytotoxic drug. A polymer coating is usually used for drug loading and control of elution kinetics. Sustained release of the drug reduces neointimal hyperplasia, leading to a reduction in the rate of restenosis. However, because stent implantation can also lead to stent thrombosis with potentially deleterious consequences, it necessitates potent antiplatelet therapy with a combination of aspirin and P2Y12 inhibitors, thus leading to potential bleeding complications. A consequence of the implantation of metal stents is that the metal cage remains in the vessel, providing a permanent stimulus for thrombosis and restenosis [2]. Nevertheless, permanent metallic stents with metallic cages remain the standard treatment technique for PCI [5].

CABG is a type of open-heart surgery that improves blood flow to the heart. During CABG, a healthy artery or vein is connected to the blocked coronary artery, so that the grafted artery or vein bypasses the blocked portion of the coronary artery. Although PCI is currently the most commonly used revascularisation intervention, CABG still has an important role in the management of patients with advanced obstructive coronary disease. Compared with the implantation of a stent, CABG is more invasive and, thus, associated with higher periprocedural risk [2].

Health problem

The target population for this assessment was patients with stable or unstable CAD. CAD is a prevalent disease defined as the manifestation of arteriosclerosis in the coronary arteries and is the leading cause of death in Europe [6]. Risk factors for CAD that can be controlled are smoking, high alcohol consumption, lack of physical activity, high blood cholesterol levels, overweight or obesity, diabetes mellitus, hypertension and psychosocial burden, such as stress or depression [7-9]. Patients with CAD have an elevated risk for myocardial infarction (MI), cardiac arrhythmias, such as atrial fibrillation, heart failure and premature mortality [7]. Symptoms for CAD typically include shortness of breath and chest pain (angina pectoris). In patients with stable angina pectoris, the symptoms do not change over a long time period, whereas, in patients with unstable angina pectoris, either the symptoms suddenly increase without physical exertion or the exertion threshold changes [10].

In 2015, almost 17 million men and more than 13 million women were living with CAD in Europe. The overall costs for CAD (including direct healthcare costs, productivity losses and informal care costs) have been estimated at over €59 billion [11].

The diagnosis and assessment of stable CAD involves clinical evaluation, including identifying significant dyslipidaemia, hyperglycaemia, or other biochemical risk factors, and specific cardiac investigations, such as stress testing or coronary imaging. For suspected acute coronary syndromes (ACSs), initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation (i.e., symptoms and vital signs), 12-lead electrocardiography (ECG) and biomarkers (especially cardiac troponin). Non-invasive imaging, such as transthoracic echocardiography, can aid diagnosis [9].

Methods

The HTA Core Model Application for Rapid Relative Effectiveness Assessment (REA; 4.2) was the primary source for selecting assessment elements. This assessment was based on a systematic review of the same topic authored by Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA) in 2015 [12]. To identify primary studies for Effectiveness (EFF) and Safety (SAF) domains fulfilling the predefined inclusion criteria outlined in the Scope of this assessment, we conducted systematic literature searches on the 10th September 2018 of the bibliographic databases Medline, PubMed, Embase and the Cochrane Central Register of Controlled Trials. In addition, we searched the Cochrane Database for Systematic Reviews for topic-related review articles. References from relevant original articles and reviews were hand-searched to identify additional primary studies. Furthermore, a search for relevant ongoing studies was carried out of the clinical trial registries ClinicalTrials.gov and World Health Organisation (WHO)-International Clinical Trials Registry Platform (ICTRP). Information for the 'Description and technical characteristics of technology' (TEC) and 'Health problem and current use of technology' (CUR) domains was derived from current clinical guidelines on the topics 'management of stable/unstable CAD' or 'revascularisation strategies' identified through a systematic search of the Guidelines International Network (GIN) database, and from consultations with the manufacturers of relevant devices and with clinical experts.

For TEC and CUR domains, no quality assessment tool was used, but multiple sources were used to validate individual, possibly biased, sources. Descriptive analyses of different information sources were performed. For the EFF and SAF domains, we applied EUnetHTA guidelines to the selection of quality-rating tools. Risk of bias at the study level and endpoint level for randomised

controlled trials (RCTs) was assessed using the Cochrane risk of bias tool [13]. Risk of bias at the study level for the single-arm studies was assessed using the Institute of Health Economics (IHE) 20-Criteria checklist [14, 15]. Two reviewers performed the risk of bias assessment independently. Disagreements were resolved by consensus. The quality of the body of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology [16].

Results

Available evidence

The inclusion criteria for assessing the clinical effectiveness of fully BRS were exclusively restricted to studies with a comparison group, including RCTs and non-RCTs. The inclusion criteria for assessing safety considered in addition to RCTs and non-RCT studies were prospective studies without a control group (single-arm studies, case series and registry studies) with at least 50 patients. In our systematic literature search, eight relevant RCTs, reported in 18 publications, were identified [17-34]. All studies assessed the everolimus-eluting Absorb® bioresorbable vascular scaffold (BVS) as intervention. In seven RCTs, an everolimus-eluting permanent metal stent (Xience® or Synergy®) was the comparator device. One study used two different comparators: an everolimus-eluting permanent metallic stent (Promus Element) and a biolimus-eluting permanent metal stent (Biomatrix Flex) [22, 33]. The total number of patients included in the eight RCTs was 5863. All but one study [28] included patients with stable or unstable CAD. In these studies, the percentage of patients with stable angina ranged from 20% to 65%. One RCT included only patients with acute ST-segment elevation MI (STEMI) [28]. Most study participants were male (70–80%), with a mean age range of 57–67 years.

For safety outcomes, we additionally identified 45 prospective single-arm studies (observational studies and registries) [35-105], that met our inclusion criteria. Three of the 45 prospective studies, with 345 patients, investigated the DESolve® device [37, 61, 76] and two studies, totalling 184 patients, investigated the Magmaris (Dreams 2G) device [35, 56, 58, 82], one with published results at 12 months and the other at 24 months of follow-up. One publication reported results at 6 months follow-up for 117 of 240 patients treated with the Fantom® device [52]. No relevant study was identified for the ART Pure bioresorbable stent. In the remaining 39 prospective uncontrolled studies with a total of more than 15,000 patients, the Absorb® BVS was the investigated device [36, 38-51, 53-55, 57, 59, 60, 62-75, 77-81, 83-105]. Most of these studies had a mean duration of follow-up of 12 to 24 months [38, 39, 41, 43, 45, 47, 50, 53-55, 57, 59, 64, 65, 67-69, 71-75, 77, 79-81, 83, 84, 87-89, 94, 100-104]. Six studies reported results for a longer follow-up [36, 40, 44, 46, 60, 66, 70, 78, 85, 86, 92, 93, 95-99, 105].

In all 45 uncontrolled studies included, the study population was predominately male (60–90%) with a mean age range of 54–66 years. In 22 studies (two for DESolve®, one for Magmaris and 19 for Absorb®), most patients had stable angina at study inclusion [36, 41, 44, 46-48, 53-55, 58-61, 65-67, 69-71, 74, 76, 77, 79-82, 86, 87, 91, 92, 100, 102, 103, 105], whereas, in another 19 studies, all investigating the Absorb® BVS, the patients predominantly had an ACS [38-40, 42, 43, 45, 49-51, 57, 62-64, 68, 72, 73, 77, 83-85, 88-90, 94, 95, 99, 101, 104]. In the remaining four studies details on the indication for stent implantation were not reported [35, 37, 52, 56, 78, 93, 96-98].

Clinical effectiveness

To describe the clinical effectiveness of fully BRS, the following patient-relevant outcomes were considered: major adverse cardiac events (MACE), all-cause mortality, cardiac mortality, angina, MI, quality of life, and daily functioning. In addition, the surrogate endpoints target vessel revascularisation (TVR) and target lesion revascularisation (TLR) were assessed. Whereas meta-analyses for all-cause mortality and cardiac mortality showed no significant difference between Absorb® BVS and permanent metal DES {risk ratio (RR) 0.84 [95% confidence interval (CI) 0.63–1.11] and RR 0.91 (95% CI 0.60–1.39)}, there was a significant increased risk for MACE [RR 1.36 (95% CI 1.06–1.73)], MI [RR 1.49 (95% CI 1.21–1.84)], and TLR [RR 1.36 (95% CI 1.08–1.71)] for patients treated with the Absorb® BVS. For quality of life and daily functioning, no differences between Absorb® BVS and permanent metal DES were reported.

No evidence was identified to answer the research questions regarding the effectiveness for the other four CE-marked fully BRS (DESolve®, Magmaris, ART Pure and Fantom®).

Safety

To assess the safety of fully BRS, serious adverse events (SAEs), such as periprocedural MI or mortality, scaffold thrombosis (ScT) that occurred after at least 1 year of follow-up, mortality as a result of bleeding or stroke, or adverse events, such as bleeding as a result of antiplatelet therapy, vascular access-site complications, or procedure-related contrast-induced nephropathy, were considered.

For the Absorb® BVS, results from RCTs showed no statistically difference for periprocedural MI compared with permanent metal DES [RR 1.22 (95% CI 0.82–1.82)]. No MIs occurred during or shortly after the implantation of the Absorb® BVS in eight single-arm studies, whereas, in a further 20 single-arm studies, the median rate of periprocedural MI was 2.8% (range 0.2%–12%). Results of periprocedural death were published only in two RCTs and 22 single-arm studies, with no patients dying during index procedure in 21 studies, including the two RCTs. In the remaining three single-arm studies, the rates of periprocedural mortality were 0.04%, 0.5%, and 1.3%, respectively. The overall rate of ScT that occurred after at least 1 year of follow-up was low in the included studies. Nevertheless, compared with permanent metal DES, the meta-analysis from RCTs resulted in a statistically significant higher risk for very late ScT in patients treated with the Absorb® BVS [RR 5.09 (95% CI 1.9–13.17)]. In seven single-arm studies investigating the Absorb® BVS, no very late ScT occurred. In 13 single-arm studies, the rate of very late ScT ranged from 0.2% to 1.7%. Bleeding resulting from antiplatelet therapy was reported only in five single-arm studies (event rate: 1%–4.4%) and mortality as a result of bleeding or stroke in 11 single-arm studies, with no events in nine studies and one death each in the remaining two studies. Results of vascular access site complications were derived from only two single-arm studies (event rate: 0.09% and 0.7%). No evidence was found for the endpoint of procedure-related contrast-induced nephropathy. Comparing the results from RCTs or prospective uncontrolled studies including predominantly patients with stable angina to those studies including predominantly patients with ACS, no difference was found regarding the rates of safety events.

For the DESolve® device, no safety results were available from RCTs. Periprocedural death or periprocedural MIs were reported in three uncontrolled studies, with no patient dying during or shortly after the procedure and only one case of periprocedural MI occurred. In addition, no patient died from bleeding or stroke. Very late ScTs could be derived only from one study, with no events reported. No evidence was found for the endpoints bleeding as a result of antiplatelet therapy, vascular access site complication, or procedure-related contrast-induced nephropathy.

For the Magmaris (Dreams 2G) device, no safety results were available from RCTs. Periprocedural death or periprocedural MIs were reported in the two uncontrolled studies. In both studies, no patient died or had a MI during or shortly after the procedure. In addition, no patient died from bleeding or stroke. Very late ScTs could be derived only from one study, with no events reported. No evidence was found for the endpoints bleeding as a result of antiplatelet therapy, vascular access site complication, or procedure-related contrast-induced nephropathy.

For the Fantom® device, no RCTs and only one publication reporting data at 6 months follow-up from an uncontrolled study could be identified. In this study, no patient died during or shortly after the procedure and one case of periprocedural MI occurred. In addition, no patient died from bleeding or stroke during the 6 months follow-up. Given that the publication reported only 6 months follow-up results, very late ScT rates were not available for the Fantom® device. No evidence was found for the endpoints bleeding as a result of antiplatelet therapy, vascular access site complication, or procedure-related contrast-induced nephropathy.

Upcoming evidence

Searches of ClinicalTrial.gov and WHO-ICTRP for fully BRS identified ten ongoing RCTs and 21 ongoing observational studies. Nine of the RCTs and 12 of the observational studies are investigating the Absorb® BVS, one RCT and four observational studies were investigating the Magmaris (Dreams 2G) device, two observational studies were investigating the DESolve® and another two observational studies were investigating the Fantom® device. In one observational study, the type of the investigated BRS was unclear. Planned study completion dates for the RCTs ranged from December 2018 to April 2024. In addition, there were seven terminated or currently suspended RCTs and two terminated or suspended observational studies of the Absorb® BVS, and a suspended observational study of the DESolve® device and another of the Magmaris device listed. Reasons for study suspension or termination were slow enrolment, BRS safety issues, or unavailability of the BRS device.

Discussion

The overall quality of evidence for the Absorb® BVS is high to moderate for effectiveness outcomes and moderate to very low for safety outcomes (Table 1:). Main reasons for the low quality of evidence were very low event rates in the studies and/or a high risk of bias. Seven years after the CE approval of the Absorb® BVS, the results of eight RCTs, together including nearly 6000 patients, indicated a lower effectiveness in terms of patient-relevant outcomes compared with the second generation of permanent metal DES. This was apparent from the higher rates of target-lesion revascularisation, all MI, and MACE, and of the combined patient-oriented composite endpoint (POCE), which includes all death, all MI, and all revascularisation. Regarding safety outcomes, the evidence from these RCTs showed a significantly higher risk of very late ScT after 1 year of follow-up or longer for patients treated with Absorb® BVS compared with patients treated with drug-eluting permanent metal stents. All these results are exclusively based on Absorb BVS® data and, therefore, cannot directly be transferred to other BRS devices.

For all other CE-marked BRS devices (DESolve®, Magmaris, ART Pure and Fantom®), no results from randomised or at least nonrandomised controlled trials are currently available. Safety results for these other CE-market devices in addition to Absorb® were available only from some individual single-arm short-term studies. Therefore, the evidence currently available for these products is very low and does not allow reliable conclusions to be drawn with regard to their clinical effectiveness and safety (Table 2, Table 3 and Table 4).

In principle, fully BRS have been developed to overcome adverse events, such as device thrombosis or restenosis that can arise from the permanent presence of metallic stents in the vessels. Now, ten years after their implementation, the evidence from long-term RCTs shows exactly the opposite, namely more late ScT and higher rates of TLRs for patients treated with BRS devices. Based on this evidence, the manufacturer of the Absorb® BVS withdrew the device from the market in May 2017. All other BRS are less well studied. However, given that there are considerable differences between the individual CE-marked devices with regard to both the backbone material, the drug released, the strut thickness and the time to full mass loss, the transferability of the results from the studies investigating the Absorb® BVS to the clinical effectiveness and safety of other products is limited.

Beyond that, applicability of the results from both current clinical trials and current single-arm studies to routine patients is limited. Most of the patients within the studies were males (60% or more) aged between 60 and 70 years, with, in most cases, one or a maximum of two simple lesions. Therefore, caution is required when transferring the results to female patients, patients with a wider age range, or patients with more complex lesions. Whereas, in initial RCTs, most of the included patients had stable angina, some recent RCTs predominantly included patients with ACS. Subgroup analyses comparing RCTs including more patients with stable CAD with those including more patients with unstable CAD showed no difference in key endpoints. Therefore, the results are applicable for both patients with stable angina pectoris and patients with ACS.

Current guidelines on myocardial revascularisation state that evidence for BRS other than Absorb® BVS is limited and any BRS should not be used outside well-controlled clinical studies. Results from RCTs for BRS other than the Absorb® BVS are urgently needed to investigate the technology of fully BRS. A large number of ongoing studies are currently registered on ClinicalTrials.gov and the WHO-ICTR database, but there is only one RCT among them that examines a device (Magmaris) other than the Absorb® BVS.

Conclusion

Based on evidence from eight RCTs, the fully bioresorbable everolimus-eluting stent Absorb® BVS is considered to be less effective and to have a worse safety profile compared with everolimus- or biolimus-eluting permanent metal stents. This conclusion is based on a statistically higher risk for MI, TLR and very late ScT (after 1 year of follow-up or longer) for patients treated with Absorb® BVS within a follow-up of up to 4 years, with no benefit in all other effectiveness or safety endpoints.

There is insufficient evidence to determine whether Absorb® BVS is considered less effective or less safe than other revascularisation strategies.

There is insufficient evidence to determine whether the other four currently CE-certificated fully bioresorbable sent systems [DESolve®, Magmaris (Dreams 2G), Art Pure or Fantom®] are more effective than (or at least as effective as) and/or have better (or at least similar) safety profiles compared with drug-eluting permanent metal stents or other revascularisation strategies.

There is an urgent need for RCTs, or at least nonrandomised controlled trials, with a higher number of patients and long-term follow-up to be able to determine whether the CE-certificated fully BRS systems (DESolve®, Magmaris, Art Pure or Fantom®) are suitable alternatives to drug-eluting permanent metal stents or other revascularisation strategies.

Table 1: Summary of findings table of Absorb® BVS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with DES	Risk with Absorb® BVS				
Effectiveness						
All-cause mortality (2–4 years follow-up)	38 per 1000	32 per 1000 (24–43)	RR 0.84 (0.63–1.11)	5645	⊕⊕⊕⊙ moderate[1]	—
All-cause mortality (≥3 years follow-up)	41 per 1000	34 per 1000 (26–46)	RR 0.82 (0.62–1.10)	5001	⊕⊕⊕⊙ moderate[a]	—
Cardiac mortality (6 months–4 years follow-up)	16 per 1000	15 per 1000 (10–23)	RR 0.91 (0.60–1.39)	5830	⊕⊕⊕⊙ moderate[a]	—
Cardiac mortality (≥3 years follow-up)	18 per 1000	16 per 1000 (11–25)	RR 0.89 (0.58–1.38)	5185	⊕⊕⊕⊙ moderate[a]	—
MI (1–4 years of follow-up)	49 per 1000	73 per 1000 (60–91)	RR 1.49 (1.21–1.84)	5845	⊕⊕⊕⊕ high	—
MI (≥3 years follow-up)	53 per 1000	77 per 1000 (62–96)	RR 1.44 (1.16–1.80)	5001	⊕⊕⊕⊕ high	—
Safety						
Periprocedural mortality	—	—	—	419	⊕⊕⊙⊙ low[2]	No events of periprocedural mortality occurred in either the BRS or DES groups in two RCTs
Periprocedural MI	60 per 1000	73 per 1000 (49–109)	RR 1.22 (0.82–1.82)	5503	⊕⊕⊕⊙ moderate[a]	—
Mortality as a result of bleeding or stroke (6–60 months follow-up)	—	—	—	1402	⊕⊙⊙⊙ very low[3]	Two deaths from bleeding or stroke occurred in 11 single-arm observational studies with Absorb® BVS in 6–60 months follow-up
Very late ScT (after at least 1 year of follow-up)	1 per 1000	7 per 1000 (3–17)	RR 5.09 (1.97–13.17)	5549	⊕⊕⊕⊙ moderate[4]	—

Abbreviations: BRS=bioresorbable scaffold; BVS=bioresorbable vascular scaffold; CI=confidence interval; DES=drug-eluting stent; MI=myocardial infarction; RR=risk ratio; ScT=scaffold thrombosis.

[1] Downgraded by by 1 point because of imprecision.

[2] Downgraded by by 2 points because of imprecision.

[3] Downgraded by by 3 points because of risk of bias and imprecision.

[4] Downgraded by by 1 point because of imprecision.

Table 2: Summary of findings table for the DESolve® Scaffold System

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with DES or other revascularisation strategies	Risk with DESolve® Scaffold System				
Effectiveness						
All-cause mortality	—	—	—	—	—	Outcome not reported
Cardiac mortality	—	—	—	—	—	Outcome not reported
MI	—	—	—	—	—	Outcome not reported
Safety						
Periprocedural mortality	—	—	—	345	⊕⊙⊙⊙ very low[5]	No events of periprocedural mortality occurred in three single-arm observational studies of the DESolve® Scaffold System
Periprocedural MI	—	—	—	345	⊕⊙⊙⊙ very low[e]	One periprocedural MI occurred in three single-arm observational studies of the DESolve® Scaffold System
Mortality as a result of bleeding or stroke (12 months follow-up)	—	—	—	219	⊕⊙⊙⊙ very low[e]	No death from bleeding or stroke occurred in two single-arm observational studies of the DESolve® Scaffold System in 12 months follow-up
Very late ScT (after at least 1 year of follow-up)	—	—	—	126	⊕⊙⊙⊙ very low[e]	No very late ScT after at least 1 year of follow-up occurred in one single-arm observational study of the DESolve® Scaffold System

Abbreviations: CI=confidence interval; DES=drug-eluting stent; MI=myocardial infarction; ScT=scaffold thrombosis.

[5] Downgraded by by 3 points because of risk of bias and imprecision.

Table 3: Summary of findings table for RMS Magmaris

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with DES or other revascularisation strategies	Risk with RMS Magmaris				
Effectiveness						
All-cause mortality	—	—	—	—	—	Outcome not reported
Cardiac mortality	—	—	—	—	—	Outcome not reported
MI	—	—	—	—	—	Outcome not reported
Safety						
Periprocedural mortality	—	—	—	184	⊕⊙⊙⊙ very low[6]	No events of periprocedural mortality occurred in two single-arm observational studies of RMS Magmaris
Periprocedural MI	—	—	—	184	⊕⊙⊙⊙ very low[f]	No periprocedural MI occurred in two single-arm observational studies of RMS Magmaris
Mortality as a result of bleeding or stroke (24 months follow-up)	—	—	—	184	⊕⊙⊙⊙ very low[f]	No death from bleeding or stroke occurred in two single-arm observational studies of RMS Magmaris in 24 months follow-up
Very late ScT (after at least 1 year of follow-up)	—	—	—	123	⊕⊙⊙⊙ very low[f]	No very late ScT occurred after at least 1 year of follow-up in one single-arm observational study of RMS Magmaris

Abbreviations: CI=confidence interval; DES=drug-eluting stent; MI=myocardial infarction; RMS=resorbable magnesium scaffold; ScT=scaffold thrombosis.

[6] Downgraded by by 3 points because of risk of bias and imprecision.

Table 4: Summary of findings table for Fantom® BRS

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with DES or other revascularisation strategies	Risk with Fantom® BRS				
Effectiveness						
All-cause mortality	—	—	—	—	—	Outcome not reported
Cardiac mortality	—	—	—	—	—	Outcome not reported
MI	—	—	—	—	—	Outcome not reported
Safety						
Periprocedural mortality	—	—	—	117	⊕⊙⊙⊙ very low[7]	No events of periprocedural mortality occurred in two single-arm observational studies of Fantom® BRS
Periprocedural MI	—	—	—	117	⊕⊙⊙⊙ very low[9]	One periprocedural myocardial infarction occurred in one single-arm observational study of Fantom® BRS
Mortality as a result of bleeding or stroke (24 months follow-up)	—	—	—	117	⊕⊙⊙⊙ very low[9]	No death from bleeding or stroke occurred in two single-arm observational studies of Fantom® BRS in 6 months follow-up
Very late ScT (after at least 1 year of follow-up)	—	—	—	—	—	Outcome not reported

Abbreviations: BRS=bioresorbable scaffold; CI=confidence interval; DES=drug-eluting stent; MI=myocardial infarction; ScT=scaffold thrombosis.

[7] Downgraded by by 3 points because of risk of bias and imprecision.

1 SCOPE

Description	Project Scope
Population	Adult patients with CAD, including stable angina, unstable angina, and/or MI [International Classification of Diseases (ICD)-10 code I20-I25] who require, and are eligible for, myocardial revascularisation *Major Subject Heading (MeSH) terms: Heart Disease [C14.280], Myocardial Ischemia [C14.280.647], Acute Coronary Syndrome [C14.280.674.124] Angina Pectoris [C14.280.647.124], Coronary Disease [C14.280.647.250], Coronary Artery Disease [C14.280.64], Myocardial Infarction [C14.280.674.7.250.260]*
Intervention	PCI with implantation of a fully bioabsorbable, biodegradable or bioresorbable vascular scaffold or stent (BRS) Product names: Absorb, DESolve®, MAGMARIS (DREAMS), ART Pure (ART18Z), Fantom® Trials: ABSORB, BIOSOLVE, DESolve Nx-Trial, ARTDIVA, RESTORE *MeSH terms: Percutaneous Coronary Intervention [E04.100.814.529.968], Stents [E07.695.750], Drug-Eluting Stents [E07.695.750.500]*
Comparison	PCI with implantation of other stent types or other revascularisation strategies *MeSH-terms: Percutaneous Coronary Intervention [E04.100.814.529.968], Stents [E07.695.750], Drug-Eluting Stents [E07.695.750.500], Coronary Artery Bypass [E04.100.376.719.332]* Rationale: PCI by implanting a permanent DES or BMS or with a bioresorbable polymer DES is currently the main strategy to treat CAD [7, 9, 106]; another alternative for revascularisation is CABG, which can result in more complete revascularisation, but with a higher procedural risk [7, 9, 106].
Outcomes	***Effectiveness:*** **Clinical endpoints** • Mortality (cardiac, all-cause) • Morbidity: angina, MI • Quality of life • Daily functioning **Composite endpoints:** • MACE **Surrogate endpoints:** • Revascularisation: TVR, TLR **Other endpoints:** • Duration of procedure **Long-term results** • ≥3 years of follow-up Rationale: CAD is associated with an increased risk of mortality and with impaired quality of life, reduced physical endurance, mental depression and recurrent hospitalisation or outpatient visits [7]. Therefore, revascularisation should ideally prolong life expectancy, reduce symptoms and future revascularisations, and increase health-related quality of life. ***Safety:*** **Adverse events (AEs)** • vascular access site complication • procedure-related contrast-induced nephropathy

	SAEs • late/very late (after ≥1 year) ScT and/or stent thrombosis and its consequences • bleeding as a result of antiplatelet therapy • periprocedural MI or mortality • mortality as a result of bleeding and/or stroke • other SAEs **Long-term results** • ≥1 year of follow up Rationale: compared with CABG, PCI + stenting has lower periprocedural risks but bears the risk of late stent thrombosis with potentially severe consequences. Furthermore, the treatment requires long-term antiplatelet therapy, which bears the risk of potentially life-threatening bleeding. Finally, PCI + stenting can be associated with complications at the vascular access site or with nephropathy because of the contrast media used in the coronary angiography [107, 108].
Study design	***Effectiveness:*** RCTs ***Safety:*** RCTs; prospective nonrandomised controlled trials; prospective (single-arm) observational studies (e.g., case series), registries with at least 50 patients

Abbreviations: AE=adverse event; BMS=bare metal scaffold; BRS=bioresorbable scaffold; CABG=coronary artery bypass graft surgery; CAD=coronary artery disease; DES=drug-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; PCI=percutaneous coronary intervention; RCT=randomised controlled trial; SAE=serious adverse event; ScT=scaffold thrombosis; TLR=target lesion revascularisation; TVR=target vessel revascularisation.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

Description of the distribution of responsibilities and the workload between authors and co-authors:

IAMEV (author):

- Develop first draft of the project plan; amend the project plan following comments of co-authors, dedicated reviewers and external experts.
- Perform the literature search, study selection, data extraction and risk of bias assessment; meta-analyses and the quality of the body of evidence assessment; check the discrepancies from study selection with the co-author and resolve via third reviewer
- Answer assessment elements for TEC and CUR domains
- Develop first draft of assessment
- Send draft versions to co-authors, dedicated reviewers and external experts, and perform amendments according to comments
- Prepare final assessment, including an executive summary.

SNSPMPDSB (co-author):

- Review and comment on the draft project plan
- Check and approve literature search
- Perform study selection
- Check all data extractions and risk of bias assessments for included studies
- Review the draft assessment, propose amendments if necessary and provide written feedback

2.2 Source of assessment elements

The HTA Core Model Application for rapid REA (4.2) is the primary source for selecting assessment elements. The selected assessment elements (generic questions) were translated into specific research questions.

2.3 Search

To identify primary studies fulfilling the inclusion criteria for EFF and SAF domains, systematic literature searches were conducted on the 10th September 2018 of the following databases:

- Medline via Ovid
- PubMed
- Embase
- Cochrane Central Register of Controlled Trials
- Cochrane Database for Systematic Reviews

In addition to the electronic search, references from relevant original articles and reviews (identified by a search of the Cochrane Database for Systematic Reviews) were assessed.

Furthermore, a search for relevant ongoing studies was carried out of the following clinical trials registries:

- ClinicalTrials.gov
- WHO-ICTRP

Current clinical guidelines on the topics ‘management of stable/unstable CAD’ or ‘revascularisation strategies’ were searched in the GIN database, to retrieve information for the TEC and CUR domains.

We contacted manufacturers, particularly for information regarding CE marks, marketing, availability and current use of the technology. Manufacturers were also asked about unpublished trial results.

Detailed tables on search strategies are included in Appendix 1.

2.4 Study selection

The systematic literature searches of bibliographic databases yielded 4408 citations. After removal of duplicates, 2376 references remained. One additional reference was identified through the search of study registries. Two researchers independently screened the 2377 citations for eligibility. In case of disagreements, a third researcher was involved to resolve the differences. In a first step, 2192 citations were excluded based on their titles and abstracts and, in a second step, 96 of the remaining 185 articles were excluded after reviewing the full texts. This left 89 articles meeting the inclusion criteria, of which 18 reported on eight RCTs [17-34] and 71 on 45 prospective cohort studies [35-105] (Figure 1). Hand searches of the reference lists of the included studies or topic-related systematic reviews and enquiries to the device manufacturers resulted in no additional relevant studies.

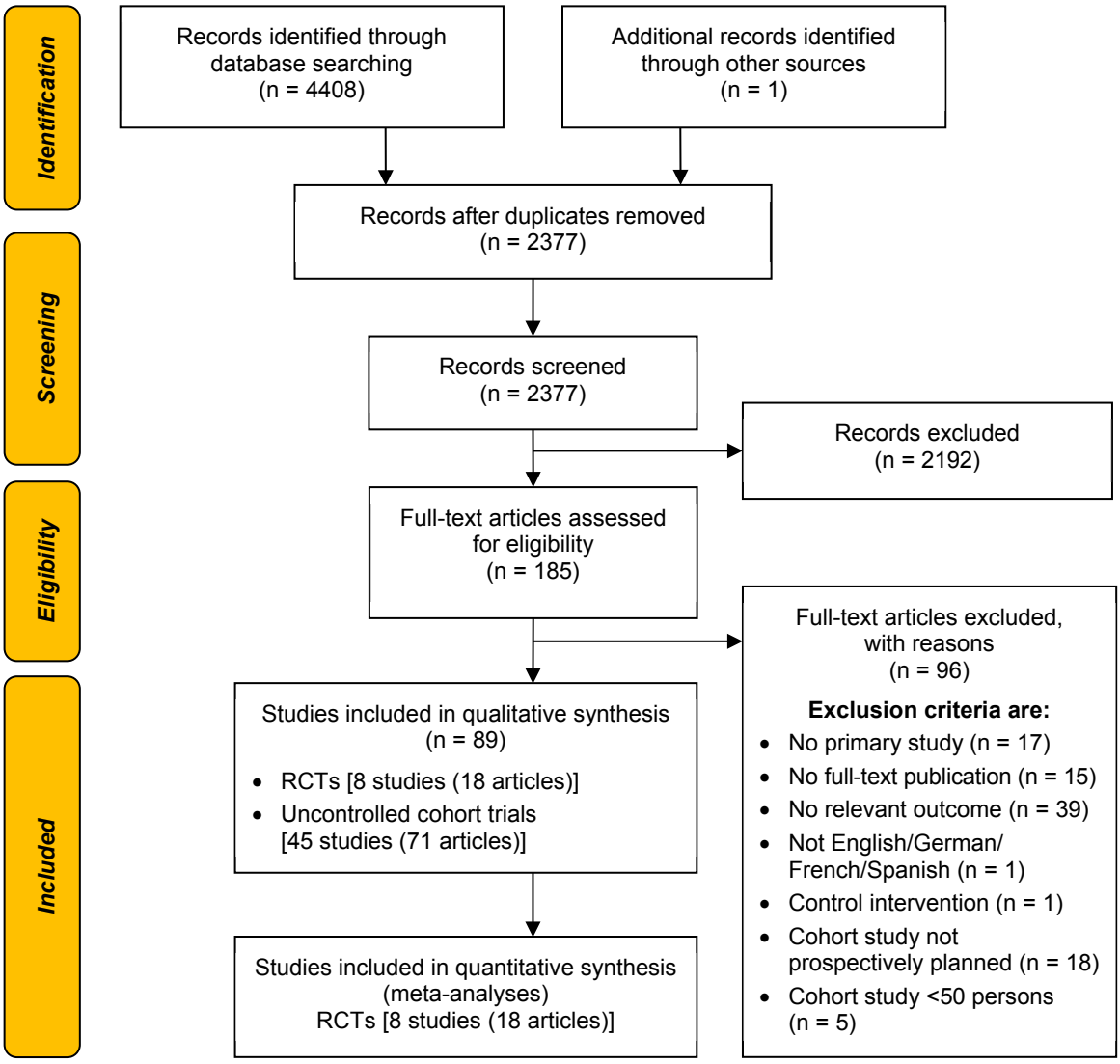

Figure 1: Flow chart of literature review process.

Searches of the study registries ClinicalTrial.gov and WHO-ICTRP identified 267 potentially relevant entries after the removal of duplicates. Two researchers independently screened the registry entries for eligibility. In case of disagreements, a third researcher was involved to resolve the differences. At the end of the study selection process, 57 relevant studies investigating fully BRS remained. These include five completed trials, three of which were already included from the search of bibliographic databases, with the other two without published results, and ten ongoing RCTs. In addition, there were seven terminated or currently suspended RCTs listed. In all but one RCT, the Absorb® BVS was the investigated device. Details of the characteristics of ongoing RCTs are presented in the Appendix 1.

2.5 Data extraction and analyses

The following characteristics and all reported results regarding the predefined outcomes from all included studies were extracted in evidence tables by one reviewer and checked independently by another reviewer:

- Study characteristics (authors, year of publication, setting/country, objective, inclusion criteria, study design, study duration, primary study endpoint, clinical trial identification number/ registry identifier and funding source)
- Participant/patient characteristics (number of participants in the trial, age, sex, and condition)
- Intervention and control characteristics (name/type of the device, comparator, description of procedure, antiplatelet co-therapy, length of follow-up and loss to follow-up)

Dichotomous data were expressed as a RR or odds ratio (OR) with 95% CIs or as the number of events and percentages. Continuous outcomes were given using the mean with standard deviation (SD). For endpoints reported in at least two included RCTs, meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.3 [109]. Subgroup analyses were planned for the type of eluted drug, the indication for stent implantation (stable/unstable condition) or type of antiplatelet therapy after stent implantation. Given that the included RCTs only investigated the everolimus-eluting Absorb® BVS with nearly the same postprocedural antiplatelet therapy, including patients with stable and unstable disease, these subgroup analyses were not possible.

2.6 Quality rating

For the TEC and CUR domains, no quality assessment tools were used, but multiple sources were used to validate individual, possibly biased, sources. Descriptive analyses of different information sources were performed.

For the EFF and SAF domains, we applied EUnetHTA guidelines to the selection of quality-rating tools. Risk of bias at the study level and endpoint level for RCTs was assessed using the Cochrane risk of bias tool [13]. Risk of bias at the study level for the single-arm studies was assessed using the IHE 20-Criteria checklist [14, 15]. Two reviewers performed the risk of bias assessment independently. Disagreements were resolved by consensus.

The quality of the body of evidence was assessed using the GRADE methodology [16]. The authors performed the GRADE assessment and the co-authors checked it.

2.7 Description of the evidence used

For the EFF domain, data from eight RCTs were analysed, and for the SAF domain, in addition to the already mentioned RCTs, data from 45 prospective single-arm cohort studies were included (Table 5).

2.8 Deviations from project plan

The Xlimus® bioresorbable stent (Cardionovum Corporate, Bonn, Germany), which was considered relevant in the project plan, was not included in the assessment because it is not a fully BRS but a bioresorbable polymer-coated metal stent [2, 110].

Table 5: Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
Absorb II [19, 20, 23, 27, 32, 34]	RCT, superiority	501 (335 vs. 166)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience®	Vasomotion; MLD post nitrate minus MLD postprocedure post nitrate by QCA	4 years	Effectiveness and safety
Absorb III [24, 30]	RCT, non-inferiority	2008 (1322 vs. 686)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience®	Number of patients with TLF (cardiac death, TV-MI or ID-TLR) at 1 year	3 years	Effectiveness and safety
Absorb Japan [26, 31]	RCT, non-inferiority	400 (266 vs. 134)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience Prime or Xience Xpedition®	Number of patients with TLF (cardiac death, TV-MI or ID-TLR) at 1 year	3 years	Effectiveness and safety
Absorb China [17, 29]	RCT, non-inferiority	480 (242 vs. 239)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience®	Angiographic in-segment LL after 1 year	3 years	Effectiveness and safety
AIDA [18, 25]	RCT, non-inferiority	1845 (924 vs. 921)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience Prime or Xience Xpedition®	TVF (cardiac death, TV-MI or TVR) at 2 years	3 years	Effectiveness and safety
Trofi II [28]	RCT, non-inferiority	191 (95 vs. 96)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent metallic stent/Xience Prime®	Optical frequency domain imaging-derived healing score at 6 months	3 years	Effectiveness and safety
Everbio II [22, 33]	RCT, non-inferiority	238 (78 vs. 80 vs. 80)	Everolimus-eluting BRS/Absorb® vs. Everolimus-eluting permanent metallic stent/Promus Element vs. Biolimus-eluting metallic stent/Biomatrix Flex	LLL at 9 months	24 months	Effectiveness and safety
Hernandez 2017 [21]	RCT	200 (100 vs. 100)	Everolimus-eluting BRS/Absorb® vs. everolimus-eluting permanent platinum chromium stent/Synergy®	Fluoroscopy time, median dose-area product, contrast agent volume, periprocedural troponin release	12 months	Effectiveness and safety
Gunes 2017 [61]	Single-centre, cross-sectional study	117	Novolimus-eluting BRS/DESolve®	nr	12 months	Safety

[8] Maximum length of follow-up of published results

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
DESolve Nx 2016 [76]	Prospective, multicentre, single-arm study	126	Novolimus-eluting BRS/DESolve®	MACE (cardiac death, TV-MI or clinically indicated TLR) at 6 months, LLL at 6 months	24 months	Safety
DESolve PMCF [37]	Prospective, multicentre, single-arm registry	102	Novolimus-eluting BRS/DESolve®	MACE (cardiac death, TV-MI or clinically indicated TLR) at 1, 6, 12 months, 2, 3, 4, and 5 yr	12 months	Safety
Fantom II [52]	Prospective multicentre, single-arm study	240	Sirolimus-eluting coronary BRS/Fantom®	MACE (cardiac death, MI or TLR) at 6 months, LLL at 6 months	6 months	Safety
Biosolve II [35, 56, 58, 82]	Prospective multicentre, single-arm study	123	Sirolimus-eluting absorbable magnesium scaffold system/DREAMS 2G	In-segment LLL at 6 months	24 months	Safety
Biosolve III [35, 56]	Prospective multicentre, single-arm study	61	Sirolimus-eluting absorbable magnesium scaffold system/DREAMS 2G	Procedure success	12 months	Safety
Fam 2016 [72]	Single-centre, cohort study	151	Everolimus-eluting BRS/Absorb® BVS	nr	18 months	Safety
Maes 2018 [38]	Single-centre, cohort study	118	Everolimus-eluting BRS/Absorb® BVS	Procedural success	12 months	Safety
Costopoulos 2014 [91]	Single-centre cohort study	92	Everolimus-eluting BRS/Absorb® BVS	Clinical efficacy	6 months	Safety
Panolas 2016 [69]	Single-centre cohort study	70	Everolimus-eluting BRS/Absorb® BVS	MACE	12 months	Safety
Jamshidi 2016 [74]	Observational single-centre single-arm study	65	Everolimus-eluting BRS/Absorb® BVS	Composite endpoint of TLR, ScT, MI, or death at 6 or 12 months	12 months	Safety
Grimfjard 2017 [50] (SCAAR)	Prospective multicentre registry	460	Everolimus-eluting BRS/Absorb® BVS	Incidence of definite ScT	24 months	Safety
Teeuwen 2015 [104]	Prospective single-centre registry	108	Everolimus-eluting BRS/Absorb® BVS	nr	24 months	Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
Felix 2016 [68] (BVS Expand)	Investigator-initiated, prospective, single-centre, single-arm study	249	Everolimus-eluting BRS/Absorb® BVS	MACE (cardiac death, MI or TLR)	18 months	Safety
Kraak 2015 [90]	Prospective single-centre registry	135	Everolimus-eluting BRS/Absorb® BVS	nr	6 months	Safety
Remkes 2017 [47]	Prospective single-centre registry	105	Everolimus-eluting BRS/Absorb® BVS	TLF (cardiac death, nonfatal TV-MI, clinically indicated TLR)	19.8 months	Safety
Alfonso 2017 [53] (RIBS VI)	Investigator-initiated, prospective, multicentre, single-arm study	141	Everolimus-eluting BRS/Absorb® BVS	In-segment MLD at 6 and 9 months	12 months	Safety
PRAGUE 19 [73, 83]	Prospective multicentre open-label single-arm study	114	Everolimus-eluting BRS/Absorb® BVS	Combination of death, MI and TVR	24 months	Safety
Iwanczyk 2017 [18, 25]	Prospective, multicentre registry	165	Everolimus-eluting BRS/Absorb® BVS	nr	12 months	Safety
Gil 2016 [79]	Prospective multicentre open-label single-arm study	139	Everolimus-eluting BRS/Absorb® BVS	MACE (cardiac death, MI and clinically driven TLR)	12 months	Safety
Dudek 2014 [94]	Prospective multicentre single-arm registry	100	Everolimus-eluting BRS/Absorb® BVS	MACE (cardiac death, MI, and clinically driven TLR) at 12 months	12 months	Safety
Rzeszutko 2016 [48] (ORPKI Registry)	Prospective multicentre single-arm registry	2258	Everolimus-eluting BRS/Absorb® BVS	nr	Peri-procedural	Safety
Briede 2018 [41]	Prospective single-centre single-arm registry	187	Everolimus-eluting BRS/Absorb® BVS	MACE (death, MI, cerebral infarction, CABG major bleeding, ScT, in-scaffold restenosis, TLR, and TVR)	24 months	Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
GABI-R registry [42, 72]	Prospective, observational, multicentre study	3231	Everolimus-eluting BRS/Absorb® BVS	MACE (death, MI, clinically motivated TVR), MACCE (MACE + stroke), stent thrombosis	6 months	Safety
Cortese 2017a [55]	Prospective single-centre registry	122	Everolimus-eluting BRS/Absorb® BVS	LLL at 1 year, ID-TLR at 2 years	24 months	Safety
Cortese 2017b [63]	Prospective multicentre single-arm study	67	Everolimus-eluting BRS/Absorb® BVS	DOCE (cardiac death, MI or TLR)	7 months	Safety
MICAT Absorb Substudy) [40, 85, 99]	Prospective single-centre registry	657	Everolimus-eluting BRS/Absorb® BVS	MACE (death, cardiac death, MI or TLR)	3 years	Safety
ISAR-Absorb [59, 71, 80]	Prospective multicentre single-arm study	419	Everolimus-eluting BRS/Absorb® BVS	MACE (death, MI or TLR)	24 months	Safety
Absorb Extend [44, 46, 66, 86, 92]	Prospective, single-arm, open-label clinical study	812	Everolimus-eluting BRS/Absorb® BVS	MACE (cardiac death, MI or ID-TLR) at 7, 30, 180 and 360 days	3 years	Safety
Wöhrle 2015 [88] (ASSURE)	Prospective multicentre, observational registry	183	Everolimus-eluting BRS /Absorb® BVS	MACE (cardiac death, MI or ID-TLR) at 24 months	12 months	Safety
Khamis 2016 [102]	Uncontrolled cohort study	264	Everolimus-eluting BRS/Absorb® BVS	MACE (cardiac death, MI or ID-TLR)	24 months	Safety
Tanaka 2017 [65] Kawamoto 2015 [103]	Uncontrolled cohort study	264	Everolimus-eluting BRS/Absorb® BVS	TLF, MACE	12 months	Safety
Moscarella 2015 [100] Moscarella 2016 [75]	Uncontrolled cohort study	116	Everolimus-eluting BRS/Absorb® BVS	Procedural success defined as successful delivery and use of BVS at target lesion with <30% final residual stenosis and without in-hospital MACE and/or cerebrovascular events; DOCE (cardiac death + target vessel MI + TLR)	15 months	Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
Maggio 2016 [77]	Prospective, single-centre registry	112	Everolimus-eluting BRS/Absorb® BVS	MACE	12 months	Safety
Regazzoli 2018 [36]	Prospective multicentre registry	573	Everolimus-eluting BRS/Absorb® BVS	TLF, definite and probable ScT	4 years	Safety
Naganuma 2017 [54]	Cohort study	147	Everolimus-eluting BRS/Absorb® BVS	TLF	24 months	Safety
Azzalini 2016 [67]	Multicentre registry	153	Everolimus-eluting BRS/Absorb® BVS	TVF	24 months	Safety
Testa 2017 [57]	Multicentre, prospective registry	1002	Everolimus-eluting BRS/Absorb® BVS	Cumulative hierarchical incidence of MACE defined as: cardiac death, nonfatal TV-MI, or clinically driven target lesion revascularisation	12 months	Safety
Ielasi 2017 [51]	Multicentre, prospective registry	505	Everolimus-eluting BRS/Absorb® BVS	Device-oriented composite endpoint of cardiac death, any MI (STEMI or NSTEMI) clearly attributable to intervention culprit vessel (TV-MI) and ID-TLR within 30 days after index procedure	1 month	Safety
RAI registry [43, 45, 64, 84, 89, 101]	Multicentre, prospective registry	1505	Everolimus-eluting BRS/Absorb® BVS	TLR, definite/probable device thrombosis	21.6 months	Safety
Robaei 2016 [81, 87]	Multicentre, prospective registry	100	Everolimus-eluting BRS/Absorb® BVS	nr	24 months	Safety
CSI-Ulm-BVS [60, 70]	Prospective single-centre study, registry	319	Everolimus-eluting BRS/Absorb® BVS	Cardiac death, MI not clearly related to a nontarget vessel and ID-TLR	36 months	Safety
Hellenkamp 2017 [62]	Nonrandomised observational registry study, single centre	204	Everolimus-eluting BRS/Absorb® BVS	MACE (all-cause death and/or MI)	834 days	Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Length of follow-up [8]	Included in clinical effectiveness and/or safety domain
Gori 2014 [95]	Nonrandomised design, registry, single centre	150	Everolimus-eluting BRS/Absorb® BVS	MACE, including death, non-fatal MIR (with or without STE), or need for revascularisation (target or nontarget lesion/vessel, including planned staged revascularisations)	6 months	Safety
Absorb Cohort B [78, 93, 96-98]	Multicentre, uncontrolled cohort study	101	Everolimus-eluting BRS/Absorb® BVS	Ischaemic-driven MACE (ID-TLR, MI or cardiac death)	5 years	Safety

Abbreviations: BES=biolimus-eluting stent; BRS=bioresorbable scaffold; BVS=bioresorbable vascular scaffold; CABG=coronary artery bypass graft surgery; DOCE=device-oriented composite endpoint; EES=everolimus-eluting stent; ID-TLR=ischaemic-driven target lesion revascularisation; LL=lumen loss; LLL=late lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; MLD=minimum lumen diameter; NSTEMI=non-ST-segment elevation myocardial infarction; nr=not reported; QCA=quantitative coronary angiography; RCT=randomised controlled trial; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TLF=target lesion failure; TLR=target lesion revascularisation; TVF=target vessel failure; TV-MI=target vessel myocardial infarction; TVR=target vessel revascularisation.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What are fully BRS and the comparators (other stent types or other revascularisation strategies)?
A0020	For which indications have fully BRS received marketing authorisation or CE marking?
B0002	What is the claimed benefit of fully BRS in relation to the comparators (other stent types or other revascularisation strategies)?
B0003	What is the phase of development and implementation of fully BRS and the comparators (other stent types or other revascularisation strategies)?
B0004	Who administers fully BRS and the comparators (other stent types or other re-vascularisation strategies) and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use fully BRS and the comparators (other stent types or other revascularisation strategies)?
B0009	What equipment and supplies are needed to use fully BRS and the comparators (other stent types or other revascularisation strategies)?
A0021	What is the reimbursement status of fully BRS?

3.2 Results

Features of the technology and comparators

[B0001] – What are fully BRS?

Fully BRS, also called BVS, represent the latest generation of devices for myocardial revascularisation strategies [1]. Instead of using a permanent metal backbone, as in other stent types, they comprise a degradable material, most commonly a polymer, such as PLLA or a magnesium alloy [2]. Therefore, fully BRS are designed to be absorbed by the body over time (1–3 years) [3]. Conventional metal stents, where the rigid metal backbone remains permanently embedded in the diseased vessel, are associated with an increased risk of ScT or restenosis [2]. The aims of fully BRS are to overcome the risk of these late complications and to reduce the need for long-term antiplatelet drugs, with their risk of bleeding complications [2, 3]. As permanent metal stents, BRS can be either drug coated or drug free.

To date, five products (Absorb®, DESolve®, ART Pure, Fantom® and Magmaris) have received CE marking for implanting in adult patients with CAD Table 6), although Absorb® has not been available on the market since the manufacturer stopped sales in May 2017. Absorb® was also approved by the FDA in 2016 [4].

The Absorb® scaffold (Abbott Vascular) comprises a resorbable polymer PLLA scaffold that is coated with an everolimus-eluting resorbable poly(D,L-lactic acid) (PDLLA) polymer. It dissolves completely within ~3 years [4].

The DESolve® scaffold (Elixir Medical) received CE marking in May 2014. It also comprises a PLLA scaffold with a strut thickness of 150 µm and coat thickness of <3 µm/side. Coating comprises a PLLA-based polymer, which elutes novolimus. It dissolves completely within ~1 year [4].

The ART Pure (Arterial Remodelling Technologies and Terumo) scaffold received CE marking in May 2015. This stent is drug free and comprises a PDLLA scaffold with a strut thickness of 150 µm and coat thickness of 8 µm/side. It dissolves completely within ~1 year.

Fantom® (Reva Medical) is a sirolimus-eluting scaffold comprising tyrosine polycarbonate. CE marking was granted in April 2017. According to the manufacturer, the key differentiating features of Fantom® compared with other polymeric BRS technologies include its 125-µm thickness after coating, DES-like radiographic visibility, single-step inflation, good expansion range and no special storage or handling requirements. It dissolves completely within ~4 years [4].

The sirolimus-eluting magnesium drug-eluting absorbable metal scaffold was CE approved in June 2016 and is currently marketed as Magmaris (Biotronik). It has a strut thickness of 150 µm and a coat thickness of 8 µm/side. It is the only metal-based BRS. According to the manufacturer, its key features are single-step inflation, good expansion range, no special storage or handling requirements, and electropolished struts for better laminar blood flow. In addition, the use of a metal backbone should result in reduced thrombogenicity, and accelerated endothelialisation compared with polymeric scaffolds. The Magmaris scaffold dissolves completely within ~1 year [4, 111, 112].

Table 6: Features of the technology

Feature	Fully BRS system				
Name	Absorb® BVS	DESolve® Scaffold System	RMS Magmaris	ART Pure BRS	Fantom® BRS
Manufacturer	Abbott Vascular	Elixir Medical	Biotronik	Arterial Remodelling Technologies/Terumo	Reva Medical
Eluted drug	Everolimus	Novolimus	Sirolimus	Drug free	Sirolimus
Stent material	PLLA	PLLA	Magnesium	PDLLA	Tyrosine polycarbonate
Strut/coat thickness	150 µm/3 µm per side	150 µm/<3 µm per side	150 µm/8 µm per side	170 µm/uncoated	125 µm after coating
CE certificate	Yes (2011)[9]	Yes (2014)	Yes (2016)	Yes (2015)	Yes (2017)
FDA approval	Yes (2016)	No	No	No	No

Abbreviations: BRS=bioresorbable stent; BVS=bioresorbable vascular scaffold; CE=Conformité Européenne; FDA=Food and Drug Administration; RMS=resorbable magnesium scaffold.

Source: [4].

Current European Society of Cardiology (ESC) guidelines do not recommend the use of BRS outside of scientific studies [5].

What are other stent types (permanent BMS or DES, bioresorbable polymer DES) or other revascularisation strategies?

The current two principal options for revascularisation in patients with CAD are PCI and CABG.

[9] Manufacturer stopped selling the first-generation Absorb® BVS on 14th September 2017.

The indication, timing and modality of myocardial revascularisation is dependent on several factors, including risk stratification and risk factors, clinical presentation, comorbidities and life expectancy [5].

The most commonly used revascularisation intervention is PCI [5].

Historically, the first PCI technique was balloon PTA. With PTA, coronary stenosis is treated by insufflation of a balloon, thus compressing and dissecting atherosclerotic plaques. Although coronary stenosis can be treated successfully with PTA, it also leads to a high rate of acute vessel closures (caused by vessel dissection and recoil) and restenosis [2].

The next step was the introduction of BMS. The implantation of such stents reduces vessel recoil, leading to better acute results. Additionally, they also reduce restenosis by abolishing late constrictive remodelling. Nevertheless, restenosis, resulting from neointimal hyperplasia, is a problem with BMS [2].

To reduce this neointimal hyperplasia, so-called DES were developed. With these stents, the metal scaffold is coated with an immunosuppressant or cytotoxic drug. Usually, a polymer coating is used for drug loading and control of the elution kinetics. Initially, permanent polymer coatings were used, which can provoke inflammatory responses and delayed arterial healing. Therefore, biodegradable polymer and polymer-free coating technologies were developed to reduce these adverse events [2]. Sustained release of the drugs reduces neointimal hyperplasia, leading to a reduction in the rate of restenosis [2]. However, because stent implantation can also lead to stent thrombosis with potentially deleterious consequences, it necessitates potent antiplatelet therapy with a combination of aspirin and P2Y12 inhibitors, thus leading to potential bleeding complications. A consequence of the implantation of metal stents is that the metal cage remains permanently in the vessel, providing a permanent stimulus for thrombosis and restenosis [2]. Currently, permanent metallic stents with metallic cages are the standard treatment technique with PCI [5].

CABG is a type of open-heart surgery that improves blood flow to the heart. During CABG, a healthy artery or vein is connected to the blocked coronary artery, such that the grafted artery or vein bypasses the blocked portion of the coronary artery [113]. Although PCI is currently the most commonly used revascularisation intervention, CABG still has an important role in the management of patients with advanced obstructive coronary disease [2].

This report evaluates the efficacy and safety of PCI in patients with CAD using implantation of a fully BRS compared with other revascularisation techniques: implanting other (permanent) stent types (permanent BMS or DES, or bioresorbable polymer-covered DES) and CABG.

[A0020] – For which indications have fully BRS received marketing authorisation or CE marking?

Fully BRSs have received CE marking for the treatment of coronary artery lesions in patients with CAD. The regulatory status of all five BRS systems, including the verbatim wording of the indications, is presented in Table A17 in Appendix 2. Contraindications are described only for the Absorb® BVS and include patients with contraindications for procedural anticoagulation or postprocedural antiplatelet therapy and patients with contraindications to the eluted drug.

[B0002] – What is the claimed benefit of fully BRS in relation to the comparators (other stent types or other revascularisation strategies)?

Compared with CABG, the implantation of a stent is less invasive and, thus, associated with lower periprocedural risks [5]. However, in contrast to acute MI (AMI), where stents improve the prognosis of patients significantly, in patients with stable CAD, stents primarily reduce the symptoms of angina and do not necessarily prolong life expectancy or reduce the rate of MIs [5]. Furthermore, the residual metal cage of metallic stents is associated with a substantial risk for late failure in the form of in-stent thrombosis and restenosis. This is believed to be a consequence of accelerated atherosclerosis developing inside the stent and of a loss of vasomotor function in the stented vessel segment. In addition, stents might break [2]. One study found very late adverse events to occur up to 20 years after implantation [114]. Thus, stents comprising fully biodegradable material (e.g., polymers of PLLA and magnesium alloys) were thought to reduce the risk for very late failure because no permanent residue would remain in the coronary vessel [2].

[B0003] – What is the phase of development and implementation of fully BRS and the comparators (other stent types or other revascularisation strategies)?

First attempts to develop fully bioresorbable devices for treating CAD began during the 1990s [115]. The first commercially available device was the Abbott Absorb® BVS, which uses PLLA as stent material and everolimus as the eluded drug. In 2010, Absorb® BVS was approved in Europe and has been used increasingly since then [12]. Other companies have also developed and tested BRS using different stent materials. Currently, five BRS have received CE-market approval (Table 6) and more than ten further devices are in development [4, 115]. In 2017, the commercial use of Absorb® BVS was stopped. This stop was initiated by the manufacturer as a result of low commercial sales [116].

BMS and DES with permanent metal scaffolds are considered standard revascularisation treatments for most patients with CAD. In addition, CABG surgery is a routine procedure with an important role, especially in patients with advanced CAD [2, 5].

[B0004] – Who administers fully BRS and the comparators (other stent types or other revascularisation strategies) and in what context and level of care are they provided?

PCI is provided in hospitals. Specialised cardiologists implant stents supported by radiology assistants and nurses. Implanting a BRS requires the same infrastructure, personnel and equipment as implanting other types of stent. However, stenting with BRS (except the metal-based Magmaris device) requires more extensive preparation of the lesion and invasive imaging. The latter is because the dimension of the affected vessel must be exactly known because of the expansion limits of BRS.

CABG is open-heart surgery requiring the use of a heart-lung machine. The team comprises surgeons, anaesthesiologists, cardiotechnicians and nurses. CABG is performed in hospitals [117].

[B0008] – What kind of special premises are needed to use fully BRS and the other stent types or other revascularisation strategies?

Institutions providing PCI need a cardiac catheterisation lab and a team comprising an interventional cardiologist, assistant nurses and radiology assistants.

CABG is open surgery and requires an operating theatre, usually a cardiopulmonary bypass machine (heart-lung machine) and an intensive care unit. In terms of personnel, surgeons, nurses, cardiotechnicians and anaesthesiologists are required [5, 12].

[B0009] – What equipment and supplies are needed to use fully BRS and the comparators (other stent types or other revascularisation strategies)?

To perform PCI with the implantation of stent, whether BRS or permanent metallic, balloon catheters, coronary guidewires, sheath introducers, introducer needles and guiding catheters are essential equipment. Some BRS require special storage facilities.

Equipment for general anaesthesia, sternotomy and sewing material, along with chest tubes, are necessary for CABG [12].

[A0021] – What is the reimbursement status of fully BRS?

The implantation of a fully BRS into the coronary vessels is currently not recommended for reimbursement in some European countries (Appendix 2). Nevertheless, the implantation of fully BRS is listed with a separate reimbursement code in the Austrian Diagnosis Related Group (DRG) System [118]. The status of reimbursement is not known for other countries.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is CAD?
A0003	What are the known risk factors for CAD?
A0004	What is the natural course of CAD?
A0005	What are the symptoms and the burden of CAD for the patient?
A0006	What are the consequences of CAD for society?
A0024	How is CAD currently diagnosed according to published guidelines and in practice?
A0025	How is CAD 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 is fully BRS utilised?

4.2 Results

Overview of the disease or health condition

[A0002] – What is CAD?

CAD is defined as the manifestation of arteriosclerosis in the coronary arteries. Atherosclerotic plaque causes a narrowing of the coronary vessel, reducing blood flow to the heart muscle and resulting in an imbalance between oxygen demand and supply. CAD is usually progressive [3, 7].

CAD is one of the most prevalent diseases, and is the leading cause of death in Europe [6].

[A0003] – What are the known risk factors for CAD?

Known risk factors for CAD that can be controlled are: smoking, high alcohol consumption, lack of physical activity, high blood cholesterol level, overweight or obesity, diabetes mellitus, hypertension and psychosocial burden, such as stress or depression. Risk factors that cannot be controlled are age, sex (men are generally at greater risk), family history and race [7-9]

[A0004] – What is the natural course of CAD?

Patients with CAD have an elevated risk for MI, cardiac arrhythmias, such as atrial fibrillation, heart failure and premature mortality [7]. Additionally, angina is associated with recurring discomfort, impaired quality of life, reduced physical endurance, mental depression and recurrent hospitalisation [5]. CAD is usually progressive [3].

CAD is a chronic disease that can appear for the first time as angina pectoris, but it can also lead to a heart attack without any previous symptoms [10].

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of CAD for the patient?

The symptoms of CAD typically include shortness of breath and chest pain (angina pectoris) usually exacerbated by exertion. These symptoms are typically associated with a feeling of anxiety or fear and can radiate into the arms, neck, back, upper abdomen or jaw.

In patients with stable angina pectoris, symptoms do not change over an extended period of time.

In patients with unstable angina pectoris, the symptoms suddenly increase without physical exertion or the exertion threshold changes. This can mean that the pain occurs earlier, lasts longer and/or becomes more frequent or stronger. Any angina pectoris that occurs for the first time is unstable angina pectoris. In contrast to the stable form, unstable angina pectoris should be treated as an emergency [10].

[A0006] – What are the consequences of CAD for society?

CAD has major human as well as economic costs. According to the European Cardiovascular Disease Statistics [11], ischaemic heart disease (IHD) accounted for 1% (€ 509,647,000) of the total healthcare expenditure or for € 59 per capita in 2015 in Austria. The biggest share (72%) was attributed to inpatient care (€ 368,901,000). In Europe, the overall costs for IHD (including direct healthcare costs, productivity losses and informal care costs) have been estimated at over € 59 billion.

Current clinical management of the disease or health condition

[A0024] – How is CAD currently diagnosed according to published guidelines and in practice?

The diagnosis and assessment of stable CAD involves clinical evaluation, including identifying significant dyslipidaemia, hyperglycaemia or other biochemical risk factors, and specific cardiac investigations, such as stress testing or coronary imaging. These investigations can be used to confirm the diagnosis of ischaemia in patients with suspected stable CAD, to identify or exclude associated conditions or precipitating factors, assist in stratifying risk associated with the disease and to evaluate the efficacy of treatment. In practice, diagnosis and prognostic assessments are conducted simultaneously, rather than separately, and many of the investigations used for diagnosis offer prognostic information [9].

In patients with suspected ACS, the initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation (i.e., symptoms and vital signs), 12-lead ECG and biomarkers (especially cardiac troponin). Non-invasive imaging, such as transthoracic echocardiography, can add to the diagnosis [119].

[A0025] – How is CAD currently managed according to published guidelines and in practice?

As in the diagnosis of CAD, the management of CAD depends on its clinical presentation (stable or acute), on patient characteristics (age, comorbidities, etc.) and related risk prognoses, and on patient preferences [5].

In patients with stable CAD, management decisions after the diagnosis depend on the severity of symptoms, on the patient's risk factors for adverse cardiac events and on patient preferences. The choice is between preventive medication and symptomatic medical management only or, additionally, revascularisation, in which case the type of revascularisation has to be determined [9]. Any strategy needs to be accompanied by recommendations for life-style modification [7].

Indications for revascularisation are the persistence of symptoms despite medical treatment and/or improvement of prognosis [5]. Patient preferences also need to be taken into account [7]. In terms of revascularisation, whether PCI or CABG is preferred should depend on the risk:benefit ratios of these treatment strategies, weighing the risks of procedural death, MI and stroke against improvements in health-related quality of life, as well as long-term freedom from death, MI or repeat revascularisation. Decisions on the most appropriate revascularisation procedure should be guided by clinical judgement, multidisciplinary dialogue and patient preferences. Risk stratification models can support decisions [5]. In general, the choice of suitable revacularisation strategy (PCI or CABG) depends on the number of affected vessels (single-vessel or multivessel disease) and on the anatomical complexity of coronary lesions, whereby CABG appears to be advantageous in terms of mortality, MI and the need for reintervention in patients with multivessel CAD and intermediate-to-high anatomical complexity [5, 7].

In patients with ACS, management depends on whether patients have non-STEMI (NSTEMI) or STEMI [5].

In patients with NSTEMI (the most frequent manifestation of ACS), treatment includes anti-ischaemic therapy (nitrate, beta-receptor blockers, etc.), antiplatelet therapy and, potentially, invasive revascularisation. The latter depends on the potential risks associated with invasive and pharmacological treatments [5]. In the case of a risk stratification that favours revascularisation, early routine angiography followed by revascularisation is favoured against a selective invasive strategy [5]. In patients who are stable, the choice of the revascularisation modality can be made in analogy to patients with stable CAD [5].

In the management of patients with STEMI, the timely implementation of reperfusion therapy (fibrinolysis or mechanical reperfusion by primary PCI) is key [5]. PCI (without prior fibrinolysis) has replaced fibrinolysis as the preferred reperfusion strategy, provided it can be performed in a timely manner in high-volume PCI centres with experienced operators [5]. Stenting should be preferred over plain balloon angioplasty, and new-generation DES have been found to be more effective and safer than BMS [5]. In settings where a timely PCI cannot be performed, fibrinolysis should be considered, particularly if it can be administered prehospital. After fibrinolysis, early invasive evaluation is recommended [5].

In general, patients need to undergo antithrombotic treatment after revascularisation. The choice, initiation, combination and duration of antithrombotic treatment depend on various factors (e.g., mode of revascularisation) [5].

Furthermore, myocardial revascularisation must always be accompanied by medical therapy and other secondary prevention strategies for risk factor modification and permanent lifestyle changes [5, 12].

Target population

[A0007] – What is the target population of this assessment?

The target population in this assessment includes patients with CAD including stable angina, unstable angina and/or MI (ICD-10 code I20-I25) who require, and are eligible for, myocardial revascularisation.

This topic was chosen based on a request from the Austrian Federal Ministry of Labour, Social Affairs, Health and Consumer Protection who commissioned our agency to do an HTA on PCI with implantation of a fully BRS. The relevance of the topic lies in the fact that CAD, which is a manifestation of atherosclerosis of the coronary arteries, is one of most prevalent diseases and the leading cause of death in Europe [6].

[A0023] – How many people belong to the target population?

According to the 2017 edition of European Cardiovascular Disease Statistics, in 2015 almost 17 million men (41% of all CVD) and more than 13 million women (30% of all CVD) were living with CAD in Europe [11]. The total number of new cases for CAD was 5.75 million in Europe in 2015, with slightly more cases among males. Age-standardised prevalence CAD rates were lower in the European Union (EU; 20 per 1000 males, 11 per 1000 females) than in Europe as a whole (30 per 1000 males, 17 per 1000 females). Changes in age-standardised prevalence rates were reported only for CVD in total. On average, in Europe, these rates had decreased from 137 per 1000 inhabitants in 1990 to 128 per 1000 inhabitants in 2015 [11].

Inpatient admission rates for all CVD or for AMI were available for several European countries. On average, admission rates for CVD were 30% higher for males, and admission rates for AMI were more than twice as high for males than for females. Within Europe, admission rates for all CVD were lowest in Cyprus (6.1 per 1000 males, 2.9 per 1000 females) and highest in Lithuania (45.4 per 1000 males, 50.1 per 1000 females) [11]. For AMI, high inpatient admission rates were observed in Norway (5.7 per 1000 males, 2.9 per 1000 females), Sweden (4.1 per 1000 males, 2.5 per 1000 females) and Lithuania (4.1 per 1000 males, 2.3 per 1000 females), whereas lowest rates were found in Cyprus (0.7 per 1000 males, 0.2 per 1000 females), Turkey (0.9 per 1000 males, 0.4 per 1000 females) and Romania (1.1 per 1000 males, 0.6 per 1000 females) [11].

CAD is the leading single cause of death in Europe. Data from 2009 to 2014 suggest that, in Europe, approximately 1.8 million people per year die from CAD, with nearly the same rates for men and women (~20% of all deaths) [11]. Across the various European countries, age-standardised mortality rates from CAD ranged from 77 per 100,000 males and 32 per 100,000 females in France to 700 per 100,000 males and 429 per 100,000 females in Lithuania [11].

[A0011] – How much is fully BRS utilised?

Data about the number of implantations of fully BRS in Europe are not available. For all coronary stenting procedures, the latest data for the whole of Europe come from a paper published in 2007. The authors reported that 769,766 stenting procedures were carried out in Europe in 2004, which was an increase of 22% compared with 2003 [120]. Data that are more recent were available from the Austrian Cardiovascular Disease Report. According to this report, a total of 6950 coronary stent implantations were registered in 2010 in Austria (0.8 implantations per 1000 inhabitants) [121].

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of fully BRS on mortality?
D0005	How does fully BRS affect symptoms and findings (severity and frequency) of CAD?
D0006	How does fully BRS affect progression (or recurrence) of CAD?
D0011	What is the effect of fully BRS on patients' body functions?
D0016	How does the use of fully BRS affect activities of daily living?
D0012	What is the effect of fully BRS on generic health-related quality of life?
D0013	What is the effect of fully BRS on disease-specific quality of life?

5.2 Results

Included studies

The inclusion criteria to assess the clinical effectiveness of fully BRS were restricted to RCTs. In the systematic literature search, eight relevant RCTs, reported in 18 publications, were identified [17-34] (Table 5). All studies assessed the everolimus-eluting BRS Absorb® as intervention. In seven RCTs, an everolimus-eluting permanent metal stent (Xience® or Synergy®) was the comparator device. One study used two different comparators: an everolimus-eluting metallic stent (Promus Element) and a biolimus-eluting permanent metal stent (Biomatrix Flex) [22, 33].

Four of the included RCTs were multicentre trials and were sponsored by the device manufacturer [17, 19, 20, 23, 24, 26, 27, 29-32, 34], two were international trials and the other two were located in China and Japan, respectively. The other four RCTs [18, 21, 22, 25, 28, 33] were investigator initiated. Two of them were multicentre and two were single-centre trials, all located in Europe. Half of the included RCTs have been completed [19-23, 27, 28, 32-34], whereas the other four trials are ongoing and the publications included in this assessment report only interim results. The maximum time of follow-up reported in the study publications were 4 years [19, 20, 23, 27, 32, 34], 3 years [17, 18, 24, 25, 29, 30] 2 years [22, 26, 31, 33], 1 year [21] and 6 months [28]. In addition, results from 3-year follow up for the Absorb Japan and Trofi II trial were reported in two recently published systematic reviews [122, 123].

The total number of patients included in the eight RCTs was 5863. All but one study [28] included patients with stable or unstable CAD. In these studies, the percentage of patients with stable angina ranged from 20% to 65%. One RCTs included only patients with acute STEMI [28]. Patients with previous MI were included in all RCTs and the percentage ranged from 2% to 30%. Most study participants were male (70%–80%), with a mean age range of 57–67 years. After stent implantation, dual antiplatelet therapy was given for at least 12 months in five RCTs [17, 18, 24-26, 28-31] and for at least 6 months in two studies [19, 20, 22, 23, 27, 32-34]. Afterwards aspirin was maintained for at least 5 years [17, 29] or indefinitely [22, 24, 26, 30, 31, 33]. One trial did not report any details about antiplatelet therapy [21]. Details of the characteristics of the included studies and the results are presented in the evidence tables included in Appendix 1.

In our literature search, we could not identify any RCTs investigating one of the other CE-certificated fully BRS (DESolve®, Magmaris, ART Pure or Fantom®).

Mortality

[D0001] – What is the expected beneficial effect of fully BRS on mortality?

Two outcomes were considered relevant to assess the effect of fully BRS on mortality: all-cause mortality and cardiac mortality. All-cause mortality was reported in seven RCTs [17-20, 22-34]. A meta-analysis including results from the maximum length of follow-up in seven RCTs showed no significant difference between Absorb® BVS and permanent metal DES [RR 0.84 (95% CI 0.63–1.11); p=0.22; 0% heterogeneity] (Figure 2). Including only studies with at least 3 years of follow-up did not change the results [RR 0.82 [(95% CI 0.62–1.10); p=0.19; 0% heterogeneity].

In terms of cardiac mortality, results from all eight RCTs were available [17-34]. Again, the meta-analysis including all trials [RR 0.91 (95% CI 0.60–1.39); p=0.68; 0% heterogeneity] (Figure 3) or only trials with at least 3 years of follow-up [RR 0.89 (95% CI 0.58–1.38); p=0.61; 0% heterogeneity] resulted in no significant difference between Absorb® BVS and permanent metal DES.

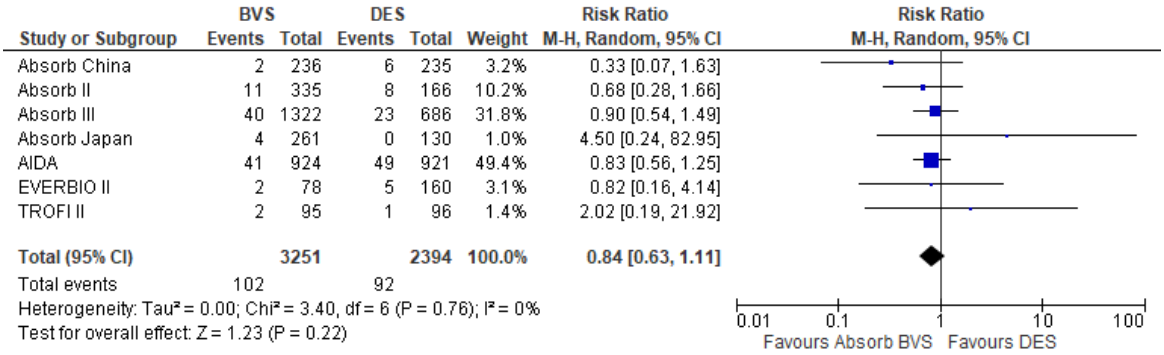

Figure 2: Meta-analysis for all-cause mortality (maximum length of follow-up).

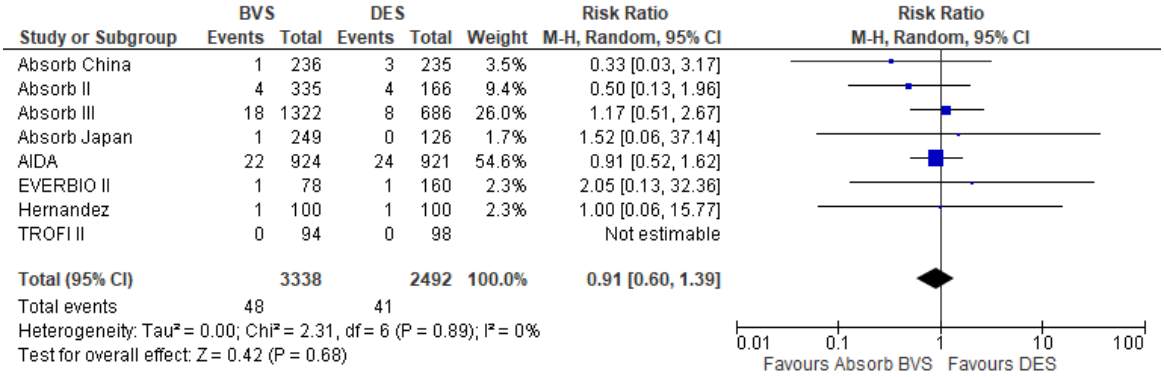

Figure 3: Meta-analysis for cardiac mortality (maximum length of follow-up).

No evidence was identified to answer these research questions for the fully BRS DESolve®, Magmaris ART Pure and Fantom®.

Morbidity

[D0005] – How does fully BRS affect symptoms and findings (severity and frequency) of CAD?

Two outcomes were considered relevant to assess this research question: occurrence of MI and of angina. MI during follow-up was reported in all eight trials [17-34]. The meta-analysis for maximum length of follow-up showed statistically significant higher rates of MIs for patients treated with Absorb® BVS compared with patients treated with permanent metal DES [RR 1.49 (95% CI 1.21–1.84); p=0.0002; 0% heterogeneity] (Figure 4). Including only studies with at least 3 years of follow-up (five RCTs), the result remained significant against the Absorb® BVS [RR 1.44 (95% CI 1.16–1.80); p=0.001; 0% heterogeneity].

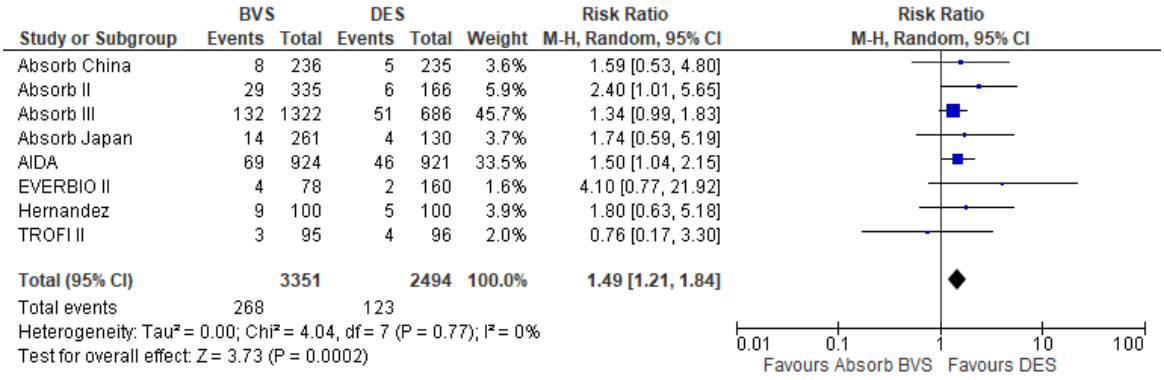

Figure 4: Meta-analysis for all MI (maximum length of follow-up).

Angina as an endpoint was reported in three studies [19, 20, 23, 24, 27, 28, 30, 32, 34]. In one study, the percentage of patients reporting angina after 1 year of follow-up was 18.3% in the Absorb® BVS group and 18.4% in the permanent metal DES group [24, 30]. In the other two RCTs, the percentage of patients free of angina was assessed using the Seattle Angina Questionnaire, with no difference between the study groups (74% vs. 73% after 3 years [19, 20, 23, 27, 32, 34] and 91.4% vs. 91.7% after 6 months [28], respectively).

Beside individual outcomes, most of the trials also reported results for combined endpoints. In four RCTs [17, 19, 20, 22-24, 27, 29, 30, 32-34], MACE was reported, which comprises cardiac death, all MI, and ischaemic-driven TLR (ID-TLR). The meta-analysis for maximum length of follow-up showed statistically significant higher rates for patients treated with Absorb® BVS compared with patients treated with permanent metal DES [RR 1.36 (95% CI 1.06–1.73); p=0.01; 0% heterogeneity] (Figure 5).

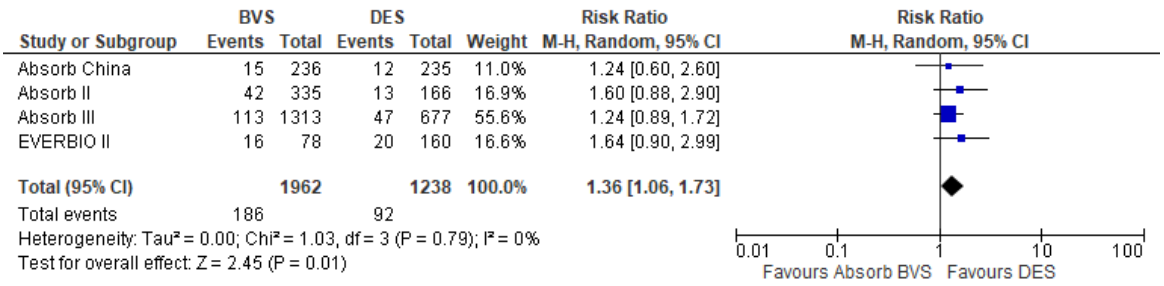

Figure 5: Meta-analysis for MACE (maximum length of follow-up).

In addition, a POCE, comprising all death, all MI, and all revascularisations, was reported in the RCTs. The meta-analysis for maximum length of follow-up including results from five RCTs showed statistically significant higher rates for patients treated with Absorb® BVS compared with patients treated with permanent metal DES [RR 1.13 (95% CI 1.01–1.26); p=0.04; 3% heterogeneity] (Figure 6).

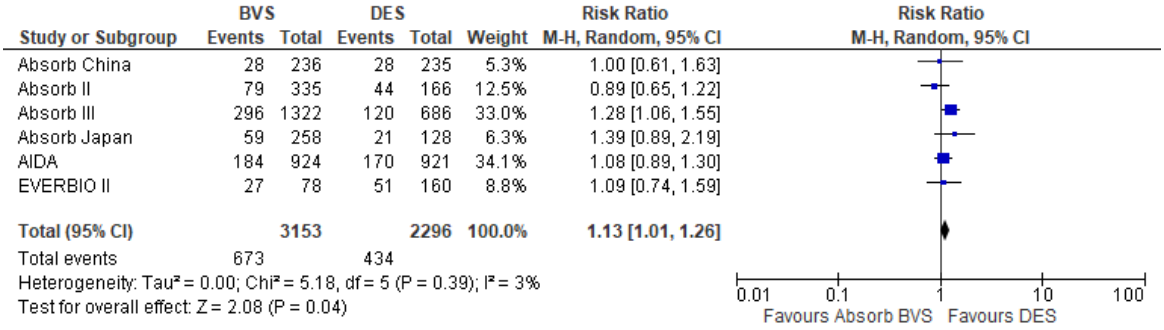

Figure 6: Meta-analysis for POCE (maximum length of follow-up).

No evidence was identified to answer this research question for the fully BRS DESolve®, Magmaris, ART Pure and Fantom®.

[D0006] – How does fully BRS affect progression (or recurrence) of CAD?

The surrogate endpoints TLR and TVR were considered eligible to answer this research question. In a meta-analysis for all-TLR after a maximum length of follow-up (eight RCTs [17-34]), the TLR rate was significant higher in the Absorb® BVS group than in the DES group [RR 1.36 (95% CI 1.08–1.71); p=0.009; 0% heterogeneity] (Figure 7). By contrast, the meta-analysis for TVR (eight RCTs) did not show any significant difference between Absorb® BVS and DES [RR 1.18 (95% CI 0.98–1.41); p=0.08; 0% heterogeneity] (Figure 8).

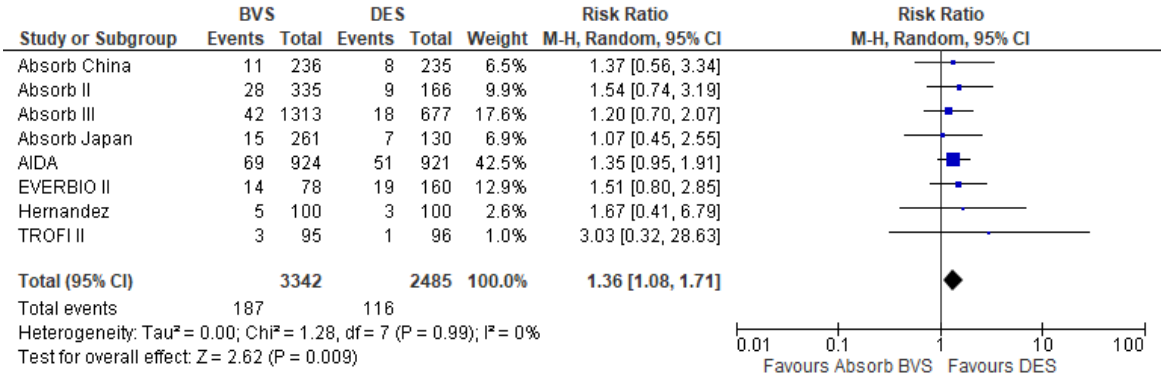

Figure 7: Meta-analysis for all TLR (maximum length of follow-up).

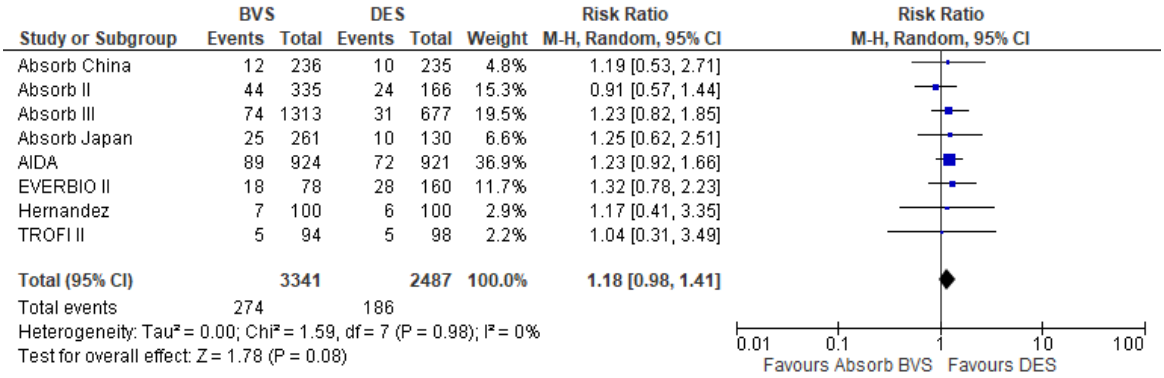

Figure 8: Meta-analysis for all TVR (maximum length of follow-up).

No evidence was identified to answer this research question for the fully BRS DESolve®, Magmaris, ART Pure and Fantom®.

[D0011] – What is the effect of fully BRS on patients' body functions?

No evidence was identified to answer the research question 'patients' body functions' for the fully BRS.

[D0016] – How does the use of fully BRS affect activities of daily living?

The endpoint 'daily functioning' was considered eligible to answer the second research question. Only one RCTs reported results for this outcome [19, 20, 23, 27, 32, 34]. In the Absorb II trial, the domain score for 'physical limitation' in the Seattle Angina Questionnaire increased in both study groups from baseline (75 pts vs. 72 pts; p=0.77) to 1-year follow-up (87 pts vs. 86 pts; p=0.48), and remained constant for the following 2 years (at 3-year follow-up: 87 pts vs. 86 pts; p=0.54). There was no significant difference between patients in the Absorb® BVS group and patients in the DES group.

No evidence was identified to answer this second research question for the fully BRS DESolve®, Magmaris, ART Pure and Fantom®.

Health-related quality of life

[D0012] – What is the effect of fully BRS on generic health-related quality of life?

[D0013] – What is the effect of fully BRS on disease-specific quality of life?

Disease-specific quality of life was defined as an outcome in three RCTs [18, 20, 23-25, 27, 30, 32, 34], but published results were only available from two trials [20, 23, 24, 27, 30, 32, 34]. Both trials used the Seattle Angina Questionnaire, with no difference between the Absorb® BVS and DES groups after 1, 2 or 3 years (76 pts vs 74 pts; p=0.47) [19, 20, 23, 27, 32, 34] and 1 year [24, 30] (87 pts vs. 86 pts; p=nr), respectively. No evidence was identified in any of the trials to answer the research question on generic health-related quality of life.

No evidence was identified to answer either of these research questions for the fully BRS DESolve®, Magmaris, ART Pure and Fantom®.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is fully BRS in relation to the comparators (other stent types or other revascularisation strategies)?
C0004	How does the frequency or severity of harm 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 fully BRS?
B0010	What kind of data/records and/or registry is needed to monitor the use of BRS and the comparators (other stent types or other revascularisation strategies)?

6.2 Results

Included studies

The inclusion criteria to assess the safety of fully BRS differed from those used for assessing clinical effectiveness. In addition to RCTs, we also included prospective studies with or without control groups with at least 50 patients. In the systematic literature search, the same eight relevant RCTs were identified [17-34]. In addition, we identified 45 prospective single-arm studies (observational studies and registries) [35-105] that met our inclusion criteria (Table 5). For details of the RCTs, see Section 5 (Clinical Effectiveness) and the evidence tables included in Appendix 1.

Three of the 45 prospective studies, with a total of 345 patients, investigated the DESolve® device [37, 61, 76] and two studies, with a total of 184 patients, investigated the Magmaris (Dreams 2G) device [35, 56, 58, 82], one with published results at 12 months of follow-up and the other at 24 months of follow-up. One publication reported results at 6 months of follow-up for 117 of 240 patients treated with the Fantom® device [52]. No relevant study was identified for the ART Pure bioresorbable stent. In the six studies investigating DESolve® BVS, Magmaris (Dreams 2G) or Fantom®, the study participants were predominately male (70%–85%, 63%, and 70%, respectively). The mean age ranged from 60 to 65 years and most patients had stable angina.

The Absorb® BVS was the investigated device in the remaining 39 prospective uncontrolled studies, with a total of more than 15,000 patients [36, 38-51, 53-55, 57, 59, 60, 62-75, 77-81, 83-105]. The mean duration of follow-up was 12 months in 12 studies and 24 months in ten studies. Six studies reported results for a longer follow-up (four studies with 3-year follow-up, one study with 4-year follow-up and one study with 5-year follow-up). As in all other included studies, the study population was predominately male (60%–90%) with a mean age range of 54–66 years. In 19 studies, most patients had stable angina at study inclusion [36, 41, 44, 46-48, 53-55, 59, 60, 65-67, 69-71, 74, 77, 79-81, 86, 87, 91, 92, 100, 102, 103], whereas, in another 19 studies, the patients predominately had ACS (unstable angina, STEMI or NSTEMI) [38-40, 42, 43, 45, 49-51, 57, 62-64, 68, 72, 73, 77, 83-85, 88-90, 94, 95, 99, 101, 104]. In the remaining study, details of the indication for treatment were not reported [78, 93, 96-98]. Details of the characteristics of the included prospective studies and the results are presented in the evidence tables included in Appendix 1.

Patient safety

[C0008] – How safe is fully BRS in relation to the comparators (other stent types or other revascularisation strategies)?

Absorb® BVS

RCTs

Results from RCTs were available for four (ScT ≥1 year, periprocedural MI, periprocedural mortality and all SAEs) of the eight predefined safety endpoints.

Results of periprocedural death were published in two trials [17, 28, 29]. Both RCTs reported that no patients died during the index procedure either in the Absorb® BVS group or in the DES group.

The occurrence of periprocedural MI was reported in seven of the eight trials [17-21, 23-32, 34]. The meta-analysis showed no statistically difference between Absorb® BVS and permanent metal DES [RR 1.22 (95% CI 0.82–1.82); p=0.32; 0% heterogeneity] (Figure 9).

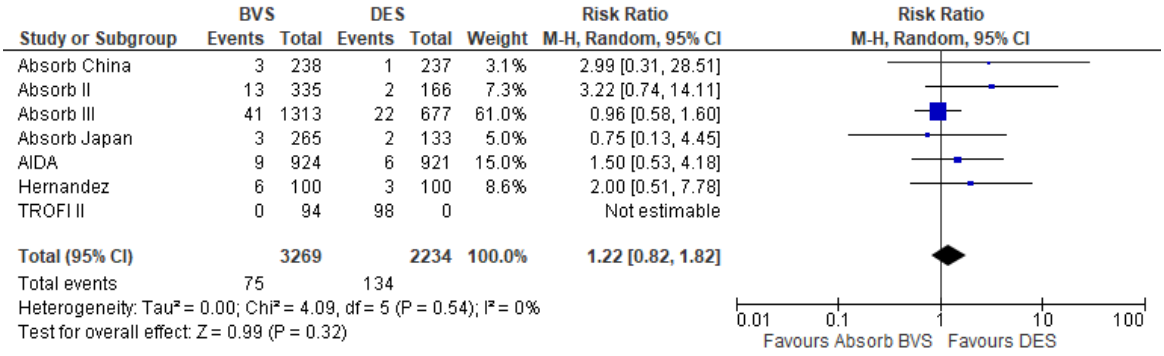

Figure 9: Meta-analysis for periprocedural MI.

ScT that occurred after at least 1 year of follow-up (very late ScT) was reported in all six RCTs with a follow-up longer than 1 year [17-20, 22-27, 29-34]. Overall, the rate was very low, with ScT in 35 of 3152 patients in the Absorb® BVS groups of the studies. Nevertheless, compared with permanent metal DES, the meta-analysis resulted in a statistically significant higher risk for very late ScT in patients treated with the Absorb® BVS [RR 5.09 (95% CI 1.97–13.17); p=0.0008; 0% heterogeneity] (Figure 10).

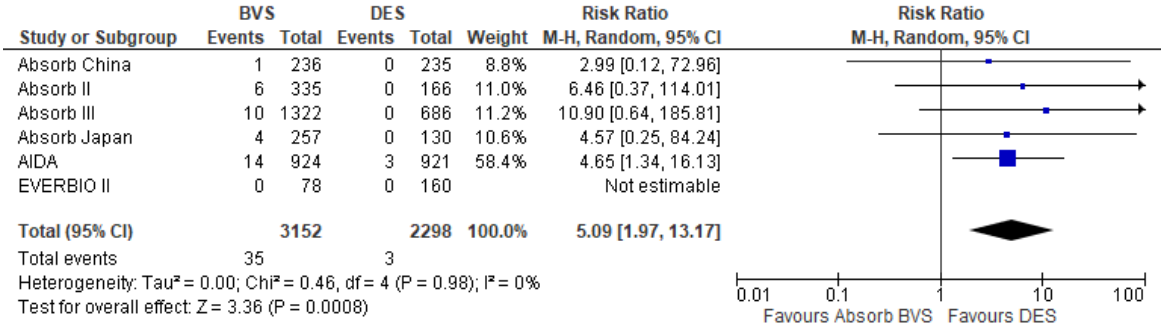

Figure 10: Meta-analysis for very late ScT (≥1 year).

Results for all SAEs were derived from the results section of the ClinicalTrials.gov study registry entry of two RCTs [17, 24, 29, 30]. In the Absorb III trial, the rates of SAEs were 30.1% versus 28.9% after 1 year of follow-up. For the Absorb China trial, SAE rates of 18.7% versus 19.6% after 3 years of follow-up were reported.

No evidence from RCTs was found for the following endpoints:

- Vascular access site complications
- Procedure-related nephropathy
- Bleeding as a result of antiplatelet therapy
- Mortality as a result of bleeding and/or stroke

Other studies

Periprocedural mortality was reported in 22 of 39 studies assessing the Absorb® BVS device, with 19 studies reporting that none of the 3733 patients included died during or shortly after the index procedure. In the three remaining studies, with 2258, 187, and 1505 patients, respectively, the rate of periprocedural mortality was 0.04%, 0.5%, and 1.3%, respectively.

Periprocedural MIs were reported in 28 of 39 studies assessing the Absorb® BVS device. Whereas eight studies (3206 participants) reported that no MI occurred during or shortly after the index procedure, the median rate of periprocedural MI was 2.8% (range 0.2%–12%) in the other 20 studies, which included a total of 9069 patients.

From the 20 studies with follow-up duration of more than 1 year, all reported rates of very late ScT (≥1 year). As in the RCTs, the rates were very low. In seven studies, with a total of 1026 patients, no very late ScT occurred. In the other studies, with a total of 5515 patients, the rate ranged from 0.2% to 1.7%.

Bleeding as a result of antiplatelet therapy was reported in five studies, with a total of 1989 participants (event rate: 1%–4.4%) and mortality as a result of bleeding or stroke in 11 studies, with no events in nine studies (1105 patients) and one death each in the remaining two studies, with 114 and 183 patients, respectively [83, 89].

Results on vascular access site complications were derived from only two of the 39 studies [two in 2258 participants (0.09%) and one in 153 participants (0.7%), respectively] [48, 67].

No published results were found for procedure-related nephropathy.

All AEs reported in RCTs are presented in Table 7 categorised by study and severity.

For other SAEs reported in uncontrolled studies, see results in the evidence tables included in Appendix 1.

DESolve®

RCTs

No evidence from RCTs was found for any of the safety endpoints.

Other studies

Periprocedural death or periprocedural MIs were reported in all three uncontrolled studies (a total of 345 patients) investigating the DESolve® device [37, 61, 76]. In all studies, no patient died during or shortly after the procedure and only one case of periprocedural MI occurred. In addition, no patient died from bleeding or stroke in two studies with a total of 219 participants and 12 months follow-up [37, 61]. The remaining study did not report this endpoint. The very late ScT rate could be derived only from one study (126 patients) at 24 months of follow-up [76], with no events reported. For other SAEs reported in uncontrolled studies, see results in the evidence tables included in Appendix 1.

For all other safety outcomes, no evidence was available.

Magmaris (Dreams 2G)

RCTs

No evidence from RCTs was found for any of the safety endpoints.

Other studies

Periprocedural death or periprocedural MIs were reported in two uncontrolled studies, with a total of 187 patients, investigating the Magmaris (Dreams 2G) device [35, 56, 58, 82]. In both studies, no patient died or had a MI during or shortly after the procedure. In addition, no patient died from bleeding or stroke in two studies with 12 and 24 months of follow-up. The very late ScT rate could be derived only from one study, with 123 patients and 24 months of follow-up [35, 56, 58, 82], with no events reported. For other SAEs reported in uncontrolled studies, see results in the evidence tables included in Appendix 1.

For all other safety outcomes, no evidence was available.

Fantom®

RCTs

No evidence from RCTs was found for any of the safety endpoints.

Other studies

In the only study reporting 6-month follow-up results on the Fantom® device [52] for 117 patients, no patient died during or shortly after the procedure and only one case of periprocedural MI occurred. In addition, no patient died from bleeding or stroke during the 6 months follow-up. Given that the publication reported only 6-month follow-up results, very late ScT rates were not available for the Fantom® device. For other SAEs reported in uncontrolled studies, see results in the evidence tables included in Appendix 1.

For all other safety outcomes, no evidence was available.

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

No evidence from RCTs was found to answer this research question.

From results reported in prospective uncontrolled studies, no association could be found between the rate of bleeding as a result of antiplatelet therapy or the rate of death as a result of bleeding or stoke and the length of follow-up.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of fully BRS?

Comparing the results from RCTs or prospective uncontrolled studies including predominantly patients with stable angina to those studies including predominantly patients with ACS, no difference was found regarding the rates of safety events. A subgroup analysis on very late ScT comparing those RCTs where most of the included patients (60% or more) had stable angina and those in which most patients had ACS (60% or more) showed no statistically significant subgroup differences (Figure 11).

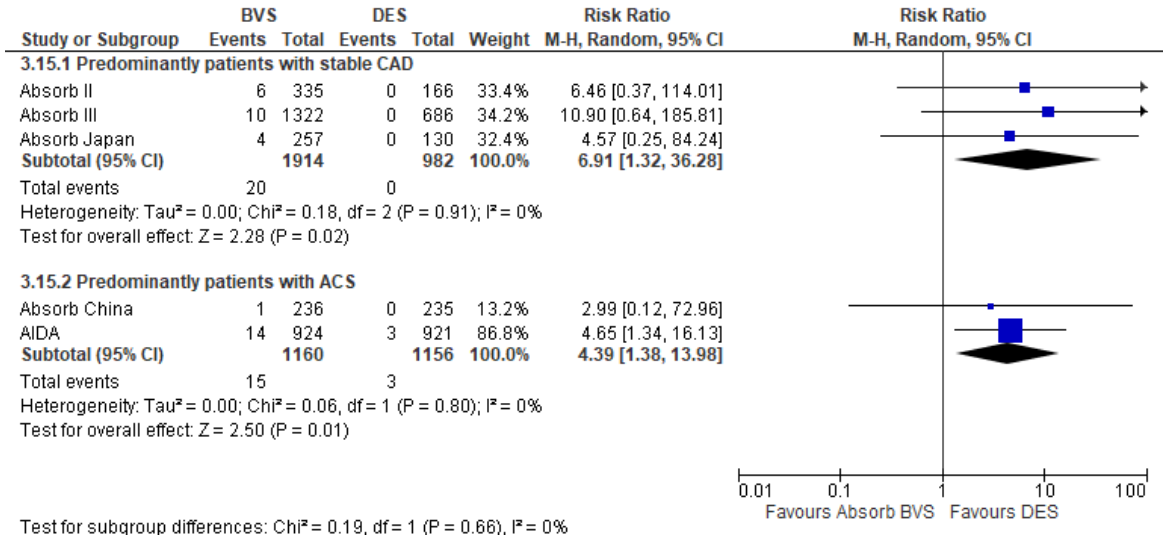

Figure 11: Subgroup analysis of different patient groups (stable angina vs. ACS) for very late ScT (≥1 year).

[B0010] – What kind of data/records and/or registry is needed to monitor the use of BVS and the comparators (other stent types or other revascularisation strategies)?

No evidence was found to answer this research question.

Table 7: Frequency and severity of adverse events in comparative studies

RCT	Absorb II [19, 20, 23, 27, 32, 34]		Absorb III [24, 30]		Absorb Japan [26, 31]		Absorb China [17, 29]	
Adverse events	**Absorb® BVS (N = 335)**	**EES (N = 166)**	**Absorb® BVS (N = 1322)**	**EES (N = 686)**	**Absorb® BVS (N = 266)**	**EES (N = 134)**	**Absorb® BVS (N = 241)**	**EES (N = 239)**
All grades								
Vascular access site complication, n (%)	—	—	—	—	—	—	—	—
Procedure-related contrast-induced nephropathy, n (%)	—	—	—	—	—	—	—	—
Grades ≥3								
Very late (after ≥1 year) ScT and/or stent thrombosis and its consequences, n (%)	6 (1.8)	0	10 (0.8)	0	4 (1.6)	0	1 (0.4)	0
Bleeding as a result of antiplatelet therapy, n (%)	—	—	—	—	—	—	—	—
Periprocedural MI, n (%)	13 (4)	2 (1)	41 (3.1)	22 (3.2)	3 (1.1)	2 (1.5)	3 (1.3)	1 (0.4)
Periprocedural mortality, n (%)	—	—	—	—	—	—	0	0
Mortality as a result of bleeding and/or stroke, n (%)	—	—	—	—	—	—	—	—
Total SAEs, n (%)	—	—	398 (30.1)	198 (28.9)	—	—	45 (18.7)	46 (19.3)
Total deaths, n (%)	11 (3.2)	8 (4.7)	40 (3.1)	23 (3.4)	4 (1.5)	0	2 (0.8)	6 (2.6)

Abbreviations: BVS=bioresorbable vascular scaffold; EES=everolimus-eluting stent; MI=myocardial infarction; SAE=serious adverse events; ScT=scaffold thrombosis.

Table 7: Frequency and severity of adverse events in comparative studies (continued)

RCT	AIDA [18, 25]		TROFI II [28]		Everbio II [22, 33]			Hernandez [21]	
Adverse events	**Absorb® BVS (N = 924)**	**EES (N = 921)**	**Absorb® BVS (N = 95)**	**EES (N = 96)**	**Absorb® BVS (N = 78)**	**EES (N = 80)**	**BES (N = 80)**	**Absorb® BVS (N = 100)**	**EES (N = 100)**
All grades									
Vascular access site complication, n (%)	—	—	—	—	—	—	—	—	—
Procedure-related contrast-induced nephropathy, n (%)	—	—	—	—	—	—	—	—	—
Grades ≥3									
Very late (after ≥1 year) ScT and/or stent thrombosis and its consequences, n (%)	14 (1.5)	3 (0.3)	—	—	0	0	0	—	—
Bleeding as a result of antiplatelet therapy, n (%)	—	—	—	—	—	—	—	—	—
Periprocedural MI, n (%)	9 (1.0)	6 (0.7)	0	0	—	—	—	—	—
Periprocedural mortality, n (%)	—	—	0	0	—	—	—	—	—
Mortality as a result of bleeding and/or stroke, n (%)	—	—	—	—	—	—	—	—	—
Total SAEs, n (%)	—	—	—	—	—	—	—	—	—
Total deaths, n (%)	41 (4.4)	49 (5.3)	2 (2.1)	1 (1.0)	2 (3)	4 (5)	1 (1)	1 (1)	1 (1)

Abbreviations: BES=biolimus-eluting stent; BVS=bioresorbable vascular scaffold; EES=everolimus-eluting stent; MI=myocardial infarction; SAE=serious adverse events; ScT=scaffold thrombosis.

7 DISCUSSION

As a consequence of progress in vessel stent development, the introduction of fully BRS was received with high levels of expectation not only from patients, but also from the scientific community, especially in terms of higher safety and clinical effectiveness. Seven years after the CE approval of the first BRS (Absorb®), results from eight RCTs (two international trials, and two trials located in Asia and four in Europe) and more the 40 single-arm studies (mostly registries from all over the world) are available. Current evidence from these eight RCTs (altogether including nearly 6000 patients) now indicates a lower effectiveness in terms of patient-relevant outcomes for fully BRS compared with the second generation of permanent metal DES. This is apparent from the higher rates of target-lesion revascularisation (63/1000 vs. 47/1000), of all MI (73/1000 vs. 49/1000), of MACE (101/1000 vs. 74/1000), and of the combined POCE, which includes all death, all MI, and all revascularisation (214/1000 vs. 189/1000) after a maximum of 4 years of follow-up. For other endpoints, such as all-cause mortality, cardiac mortality, occurrence of angina pectoris symptoms, quality of life or physical functioning, no significant difference was found between patients who received a fully BRS and those who received a permanent metal DES. However, this evidence is entirely based only on studies of one single product, namely Absorb® BVS. Regarding safety outcomes, the evidence from these RCTs showed a significant higher risk of very late ScT after 1 year of follow-up or longer for patients treated with Absorb® BVS compared with patients treated with permanent metal DES (7/1000 vs. 1/1000). This rate in patients who received fully BRS is consistent with the results from 20 single-arm studies with at least 2 years of follow-up, which reported very late ScT in 6–7 per 1000 patients. Periprocedural MI occurred in ~2% of all patients, with no difference between Absorb® BVS and permanent metal DES. For all other safety outcomes, the evidence was low or very low with, for example, only a few single-arm studies reporting on bleeding as a result of antiplatelet therapy or death as a result of bleeding or stroke. In most of the studies, antithrombotic medication after the intervention comprised dual antiplatelet therapy for 12 months and aspirin indefinitely thereafter. However, all these results are exclusively based on Absorb® BVS data and, therefore, cannot directly be transferred to other BRS devices.

For all of the other CE-marked BRS devices (DESolve®, Magmaris, ART Pure and Fantom®), no results from RCTs or at least nonrandomised controlled trials are currently available. Safety results for the CE-mark devices besides Absorb were available only from some individual single-arm short-term studies. Therefore, the currently available evidence for these products is very low and does not allow reliable conclusions to be drawn with regard to their clinical effectiveness and safety.

The risk of bias on outcome level for the included RCTs was judged to be low in most cases. Although a blinding of the investigator performing the procedure was not possible, patients were masked to the treatment group for the whole study duration in most of the trials, whereas in-clinical events were adjudicated by an independent clinical events committee, which was unaware of treatment assignment in all but one RCT. For some outcomes, such as occurrence of angina pectoris or quality of life, risk of bias has to be judged as high, because of inadequate realisation of the intention-to treat (ITT) principle. For these outcomes, only some of the patients were analysed, which does not rule out the possibility that patients with poor outcomes might not have been considered. For all of the observational studies, a high risk of bias results from the lack of control groups and of a study protocol.

In principle, fully BRS have been developed to overcome adverse events such as device thrombosis or restenosis that can arise from the permanent presence of metallic stents in the vessels. Now, 10 years after their implementation, the evidence from long-term RCTs shows exactly the opposite, namely more late ScT and higher rates of TLRs for patients treated with BRS devices.

Based on the results of some of these RCTs, in March 2017, the FDA issued a safety alert for the Absorb® device, investigating an increased risk for major cardiac adverse events [124]. In addition, in Europe, a Task Force of the ESC and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) recommended that BRS should not be used preferentially to the current generation of permanent metal DES [125]. This led to the indefinite market withdrawal of the Absorb® device by the manufacturer in 2017 [126]. In February 2018, the Massachusetts Institute of Technology (MIT) analysed the microstructure of BRS to determine why these stents failed. With one exception (Magmaris), all of the bioresorbable stents are polymer based. The researches at MIT found that, on a microscopic level, these polymer stents have a very heterogeneous structure. Whereas the stents have a smooth crystalline structure externally, the inner layers are less ordered. Therefore, when the stent is inflated, these inner regions might be disrupted, leading to structural collapse and deformation of the stent as a result of non-uniform degradation. This can then block the blood flow and might lead to an increased rate of ScT or MI [127].

As mentioned earlier, the current evidence for fully BRS is almost exclusive based on results from studies investigating the no-longer-available Absorb® device. The other BRS are less well studied. However, given that there are considerable differences between the individual CE-marked devices with regard to both the backbone (PDLLA, PLLA, tyrosine polycarbonate or magnesium), the drug released (everolimus, novolimus, sirolimus or no drug), the strut thickness (170 µm–125 µm) and the time to full mass loss (3 years for Absorb®, 1 year for all other products), the transferability of the results from studies investigating the Absorb® device to the clinical effectiveness and safety of the other products is limited. Current guidelines on myocardial revascularisation state that any BRS should not be used outside well-controlled clinical studies [5]. Therefore, it is all the more important that results from long-term RCTs are also available for these other devices. Looking at ClinicalTrials.gov or the WHO-ICTR database, a large number of ongoing studies are currently registered, including ten RCTs and 21 observational studies. However, there is only one RCT among them that examines a device other than Absorb® BVS (Magmaris) (Table A6 in Appendix 1).

In addition, the applicability of the results from both current clinical trials and current single-arm studies to routine patients is limited. Most of the patients within the studies were males (60% or more) aged between 60 and 70 years, with, in most cases, one or a maximum of two simple lesions. Therefore, caution is required when transferring the results to female patients, patients with a wider age range, or patients with more complex lesions. Although most of the patients included in initial RCTs had stable angina, some recent RCTs predominantly included patients with ACS. Subgroup analyses comparing RCTs including more patients with stable CAD with those including more patients with unstable CAD showed no difference in key endpoints, such as all-cause mortality, cardiac mortality, all MI, TLR or very late ScT. Therefore, the results are applicable for both patients with stable angina pectoris and patients with ACS. With regard to the comparative treatment, only results from RCTs on BRS versus everolimus- or biolimus-eluting permanent metal stents were available. In routine care, other stent types and other revascularisation strategies are also used. The effectiveness and safety of fully BRS compared with those approaches have not yet been evaluated.

This report has some limitations. First, only results published in full-text articles were included; therefore, some results from studies only presented at conferences might be missing. Given that some very recent study results have been presented at 2017 and 2018 international conferences, we would recommend a further update of this report when journal publications of these results are available. Second, in the case of results from single-arm registries, especially the different Italian registries, it was not always clear whether the patients evaluated in the individual publications came from the same or different patient populations. Thus, it was not always clear whether indi-

vidual publications referred to the same study or reported results from different studies. Therefore, we only assigned publications to the same study if this was clearly evident. Otherwise, we assumed that the publications reported results from separate studies. This could have led to some publications being be presented as individual studies when in fact they referred to the same patient population, which, therefore, was counted more than once.

8 CONCLUSION

Based on the current evidence from eight RCTs, the fully bioresorbable everolimus-eluting stent Absorb® BVS is considered less effective than everolimus- or biolimus-eluting permanent metal stents. This conclusion is based on a statistically higher risk for MI and for TLR for patients treated with Absorb® BVS within a follow-up of up to 4 years, with no benefit for any other effectiveness endpoints.

Based on the current evidence from eight RCTs, the fully bioresorbable everolimus-eluting stent Absorb® BVS is considered to have a worse safety profile than everolimus- or biolimus-eluting permanent metal stents. This conclusion is based on a statistically higher risk for very late ScT (after 1 year of follow-up or longer) for patients treated with Absorb® BVS.

There is insufficient evidence to determine whether Absorb® BVS is less effective or less safe than other revascularisation strategies.

There is also insufficient evidence to determine whether the other four currently CE-certificated fully BRS systems (DESolve®, Magmaris, Art Pure or Fantom®) are more effective than (or at least as effective as) permanent metal DES or other revascularisation strategies.

There is insufficient evidence to determine whether the other four currently CE-certificated fully BRS systems (DESolve®, Magmaris, Art Pure or Fantom®) have better (or at least similar) safety profiles than permanent metal DES or other revascularisation strategies.

There is an urgent need for RCTs or at least nonrandomised controlled trials with a higher number of patients and long-term follow-up to be able to determine whether the CE-certificated fully BRS systems (DESolve®, Magmaris, Art Pure or Fantom®) are suitable alternatives to permanent metal DES or other revascularisation strategies.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Medline Ovid

Date of search: 10.09.2018

Databases: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to August 20, 2018

# ▲	Searches	Results
1	*Heart Diseases/	48220
2	*Myocardial Ischemia/	26561
3	*Coronary Disease/	96306
4	*Coronary Artery Disease/	45659
5	*Coronary Stenosis/	8377
6	*Coronary Occlusion/	2348
7	*Acute Coronary Syndrome/	11181
8	*Angina Pectoris/	19735
9	*Angina, Stable/	794
10	*Angina, Unstable/	5797
11	exp Myocardial Infarction/	165258
12	((coronar* or heart* or cardiac*) adj4 (arteri* or artery*) adj4 (disease* or stenos* or occlusi* or narrow* or block* or restrict*)).ab,ot,ti.	96234
13	"angina*".ab,ot,ti.	52005
14	"myocardial infarct*".ab,ot,ti.	177793
15	CAD.ab,ot,ti.	33441
16	CHD.ab,ot,ti.	22320
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	499417
18	exp Stents/	69508
19	exp Tissue Scaffolds/	17318
20	exp Myocardial Revascularization/	87980
21	exp Percutaneous Coronary Intervention/	47528
22	(stent* or tube* or graft* or scaffold* or implant*).ab,ot,ti.	1156589
23	(percutaneous adj1 coronary adj1 intervention*).ab,ot,ti.	27967
24	(percutaneous adj1 transluminal adj1 coronary adj1 angioplasty).ab,ot,ti.	6594
25	(pci or ptca).ab,ot,ti.	27768
26	"angioplasty*".ab,ot,ti.	40790
27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1243959
28	exp Absorbable Implants/	7857
29	exp Biodegradable Plastics/	372
30	exp Biocompatible Materials/	95794
31	(bioresorbable* or bio-resorbable* or bioabsorbable* or bio-absorbable* or absorbable* or biocompatible* or bio-compatible* or biodegradable* or bio-degradable* or temporar*).ab,ot,ti.	126007
32	28 or 29 or 30 or 31	209014
33	(Absorb or DESolve or Magmaris or Dreams or Fantom or "Art Pure" or ArtPure or ART18Z or Xlimus).ab,ot,ti.	13381

34	(prospect* and (studi* or study* or trial*)).ti,ab,ot.	559244
35	exp prospective study/	481866
36	34 or 35	739741
37	(randomised controlled trial or controlled clinical trial).pt. or randomi?ed.ti,ab. or placebo.ti,ab. or drug therapy.fs. or randomly.ti,ab. or trial.ti,ab. or groups.ti,ab.	4345301
38	exp animals/ not humans.sh.	4495487
39	37 not 38	3761288
40	exp clinical trial/	807207
41	exp Clinical Trials as Topic/	317484
42	clinical trial.pt.	512330
43	40 or 41 or 42	1045822
44	27 and 32	63338
45	17 and 44	3172
46	39 and 45	1109
47	43 and 45	661
48	36 and 45	538
49	46 or 47 or 48	1370
50	17 and 33	359
51	49 or 50	1526
52	limit 51 to yr="2008 -Current"	1109
53	limit 52 to (English or French or German or Spanish)	1085

EMBASE

Date of search: 10.09.2018

Databases: Ovid Embase 1974 to 2018 September 7

# ▲	Searches	Results
1	*Heart Diseases/	10646
2	*Myocardial Ischemia/	20822
3	*Coronary Disease/	17169
4	*Coronary Artery Disease/	80571
5	*Coronary Stenosis/	7554
6	*Coronary Occlusion/	53
7	*Acute Coronary Syndrome/	20370
8	*Angina Pectoris/	22191
9	*Angina, Stable/	1317
10	*Angina, Unstable/	3690
11	exp Myocardial Infarction/	339261
12	((coronar* or heart* or cardiac*) adj4 (arteri* or artery*) adj4 (disease* or stenos* or occlusi* or narrow* or block* or restrict*)).ab,ot,ti.	143135
13	"angina*".ab,ot,ti.	69862
14	"myocardial infarct*".ab,ot,ti.	246061
15	CAD.ab,ot,ti.	56807
16	CHD.ab,ot,ti.	34166
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	616969
18	exp Stents/	153915
19	exp Tissue Scaffolds/	13458
20	exp Myocardial Revascularization/	28766

21	exp Percutaneous Coronary Intervention/	88952
22	(stent* or tube* or graft* or scaffold* or implant*).ab,ot,ti.	1413639
23	(percutaneous adj1 coronary adj1 intervention*).ab,ot,ti.	48533
24	(percutaneous adj1 transluminal adj1 coronary adj1 angioplasty).ab,ot,ti.	7516
25	(pci or ptca).ab,ot,ti.	56859
26	"angioplasty*".ab,ot,ti.	55988
27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1543258
28	exp Absorbable Implants/	5566
29	exp Biodegradable Plastics/	223
30	exp Biocompatible Materials/	46568
31	(bioresorbable* or bio-resorbable* or bioabsorbable* or bio-absorbable* or absorbable* or biocompatible* or bio-compatible* or biodegradable* or bio-degradable* or temporar*).ab,ot,ti.	156303
32	28 or 29 or 30 or 31	197283
33	(Absorb or DESolve or Magmaris or Dreams or Fantom or "Art Pure" or ArtPure or ART18Z or Xlimus).ab,ot,ti.	15833
34	(prospect* and (studi* or study* or trial*)).ti,ab,ot.	829265
35	exp prospective study/	465924
36	34 or 35	945008
37	(randomised controlled trial or controlled clinical trial).pt. or ran-domi?ed.ti,ab. or placebo.ti,ab. or drug therapy.fs. or randomly.ti,ab. or trial.ti,ab. or groups.ti,ab.	6335489
38	exp animals/ not humans.sh.	23017400
39	37 not 38	535104
40	exp clinical trial/	1323478
41	exp Clinical Trials as Topic/	272254
42	clinical trial.pt.	0
43	40 or 41 or 42	1580427
44	27 and 32	55838
45	17 and 44	4022
46	39 and 45	97
47	43 and 45	1065
48	36 and 45	659
49	46 or 47 or 48	1472
50	17 and 33	669
51	49 or 50	1844
52	limit 51 to yr="2008 -Current"	1630
53	limit 52 to (English or French or German or Spanish)	1608
54	*Heart Diseases/	10646
55	*Myocardial Ischemia/	20822
56	*Coronary Disease/	17169
57	*Coronary Artery Disease/	80571
58	*Coronary Stenosis/	7554
59	*Coronary Occlusion/	53
60	*Acute Coronary Syndrome/	20370
61	*Angina Pectoris/	22191
62	*Angina, Stable/	1317
63	*Angina, Unstable/	3690
64	exp Myocardial Infarction/	339261
65	((coronar* or heart* or cardiac*) adj4 (arteri* or artery*) adj4 (disease* or stenos* or occlusi* or narrow* or block* or restrict*)).ab,ot,ti.	143135

66	"angina*".ab,ot,ti.	69862
67	"myocardial infarct*".ab,ot,ti.	246061
68	CAD.ab,ot,ti.	56807
69	CHD.ab,ot,ti.	34166
70	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69	616969
71	exp Stents/	153915
72	exp Tissue Scaffolds/	13458
73	exp Myocardial Revascularization/	28766
74	exp Percutaneous Coronary Intervention/	88952
75	(stent* or tube* or graft* or scaffold* or implant*).ab,ot,ti.	1413639
76	(percutaneous adj1 coronary adj1 intervention*).ab,ot,ti.	48533
77	(percutaneous adj1 transluminal adj1 coronary adj1 angioplasty).ab,ot,ti.	7516
78	(pci or ptca).ab,ot,ti.	56859
79	"angioplasty*".ab,ot,ti.	55988
80	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79	1543258
81	exp Absorbable Implants/	5566
82	exp Biodegradable Plastics/	223
83	exp Biocompatible Materials/	46568
84	(bioresorbable* or bio-resorbable* or bioabsorbable* or bio-absorbable* or absorbable* or biocompatible* or bio-compatible* or biodegradable* or bio-degradable* or temporar*).ab,ot,ti.	156303
85	81 or 82 or 83 or 84	197283
86	(Absorb or DESolve or Magmaris or Dreams or Fantom or "Art Pure" or ArtPure or ART18Z or Xlimus).ab,ot,ti.	15833
87	crossover-procedure/ or double-blind procedure/ or randomised controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.	2032770
88	*clinical trial/ or *clinical study/ or *"clinical trial (topic)"/ or *comparative study/ or controlled clinical trial/ or *"controlled clinical trial (topic)"/ or *controlled study/ or *major clinical study/ or *multicentre study/ or *clinical article/	553099
89	(prospect* and (studi* or study* or trial*)).ti,ab,ot.	829265
90	exp prospective study/	465924
91	89 or 90	945008
92	80 and 85	55838
93	70 and 92	4022
94	87 and 93	894
95	88 and 93	255
96	91 and 93	659
97	94 or 95 or 96	1343
98	70 and 86	669
99	97 or 98	1734
100	limit 99 to yr="2008 -Current"	1562
101	limit 100 to (English or French or German or Spanish)	1537

NLM PubMed

Date of search: 10.09.2018

Databases: PubMed NLM

Limits:

- Language (English, German, French, Spanish)
- Date of Publication: 01.01.2008 to current

Search	Query	Items found
#62	Search #55 OR #56 OR #36 Filters: Publication date from 2008/01/01; English; French; German; Spanish	1209
#57	Search #55 OR #56 OR #36	1845
#56	Search #34 AND #54	1108
#55	Search #34 AND #47	1306
#54	Search #50 or #53	1622290
#53	Search #51 OR #52	1044857
#52	Search "Clinical Trial" [Publication Type]	806499
#51	Search "Clinical Trials as Topic"[Mesh]	317223
#50	Search #48 OR #49	739164
#49	Search "Prospective Studies"[Mesh]	481238
#48	Search prospect*[tiab] AND (studi*[tiab] OR study*[tiab] OR trial*[tiab])	559260
#47	Search #45 NOT #46	3763310
#46	Search animals [Mesh] NOT humans [Mesh]	4493104
#45	Search #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	4347005
#44	Search groups [tiab]	1856579
#43	Search trial [tiab]	518155
#42	Search randomly [tiab]	297224
#41	Search drug therapy [sh]	2044853
#40	Search placebo [tiab]	196729
#39	Search randomised [tiab] OR randomised [tiab]	541486
#38	Search controlled clinical trial[pt]	555872
#37	Search randomised controlled trial [pt]	468108
#36	Search #17 AND #35	383
#35	Search Absorb[tiab] or DESolve[tiab] or Magmaris[tiab] or Dreams[tiab] or Fantom[tiab] or "Art Pure"[tiab] or ArtPure[tiab] or ART18Z[tiab]	13765
#34	Search #17 AND #33	4549
#33	Search #27 AND #32	59321
#32	Search #28 OR #29 OR #30 OR #31	189641
#31	Search bioresorbable*[tiab] OR bio-resorbable*[tiab] OR bioabsorbable*[tiab] OR bio-absorbable*[tiab] OR absorbable*[tiab] OR biocompatible*[tiab] OR bio-compatible*[tiab] OR biodegradable*[tiab] OR bio-degradable*[tiab] OR tempo-rar*[tiab]	126948
#30	Search "Biocompatible Materials"[Mesh]	74230
#29	Search "Biodegradable Plastics"[Mesh]	369
#28	Search "Absorbable Implants"[Mesh]	7843
#27	Search #18 OR #19 OR #20 OR #21 OR #22 or #23 OR #24 OR #25 OR #26	1214975
#26	Search "angioplasty"[tiab]	41727
#25	Search pci[tiab] OR ptca[tiab]	28223
#24	Search percutaneous[tiab] AND transluminal[tiab] AND coronary[tiab] AND angio-plasty[tiab]	7405
#23	Search percutaneous[tiab] AND coronary[tiab] AND intervention*[tiab]	32672
#22	Search stent*[tiab] OR tube*[tiab] OR graft*[tiab] OR scaffold*[tiab] OR im-plant*[tiab]	1127092
#21	Search "Percutaneous Coronary Intervention"[Mesh]	47492
#20	Search "Myocardial Revascularization"[Mesh]	87947
#19	Search "Tissue Scaffolds"[Mesh]	17253
#18	Search "Stents"[Mesh]	69466
#17	Search #1 OR #2 Or #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 Or #11	1015707

	OR #12 OR #13 OR #14 OR #15 OR #16	
#16	Search CHD[tiab]	22706
#15	Search CAD[tiab]	33981
#14	Search "myocardial infarct*"[tiab]	19551
#13	Search angina*[tiab]	53067
#12	Search (coronar*[tiab] OR heart*[tiab] OR cardiac*[tiab]) AND (arteri*[tiab] OR artery*[tiab]) AND (disease*[tiab] OR stenos*[tiab] OR occlusi*[tiab] OR narrow*[tiab] OR block*[tiab] OR restrict*[tiab])	186171
#11	Search "Myocardial Infarction"[Mesh]	165179
#10	Search "Angina, Stable"[Majr]	794
#9	Search "Angina, Unstable"[Majr]	7208
#8	Search "Angina Pectoris"[Majr]	27262
#7	Search "Acute Coronary Syndrome"[Majr]	11168
#6	Search "Coronary Occlusion"[Majr]	2339
#5	Search "Coronary Stenosis"[Majr]	12867
#4	Search "Coronary Artery Disease"[Majr]	45607
#3	Search "Coronary Disease"[Majr]	161657
#2	Search "Myocardial Ischemia"[Majr]	330405
#1	Search "Heart Diseases"[Majr]	890159

Cochrane Library

Date of search: 10.09.2018

Databases: Cochrane Library - CCTR (Wiley)

Search	Query	Items found
#1	MeSH descriptor: [Heart Diseases] this term only	1850
#2	MeSH descriptor: [Myocardial Ischemia] this term only	3201
#3	MeSH descriptor: [Coronary Disease] this term only	6936
#4	MeSH descriptor: [Coronary Artery Disease] this term only	5007
#5	MeSH descriptor: [Coronary Stenosis] this term only	680
#6	MeSH descriptor: [Coronary Occlusion] this term only	95
#7	MeSH descriptor: [Acute Coronary Syndrome] this term only	1530
#8	MeSH descriptor: [Angina Pectoris] this term only	3224
#9	MeSH descriptor: [Angina, Stable] this term only	230
#10	MeSH descriptor: [Angina, Unstable] this term only	976
#11	MeSH descriptor: [Myocardial Infarction] explode all trees	10037
#12	(((coronar* or heart* or cardiac*) and (arteri* or artery*) and (disease* or stenos* or occlusi* or narrow* or block* or restrict*))):ti,ab,kw	27191
#13	(angina*):ti,ab,kw	10812
#14	("myocardial infarct*"):ti,ab,kw	466
#15	(CAD):ti,ab,kw	3623
#16	(CHD):ti,ab,kw	2419
#17	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	48461
#18	MeSH descriptor: [Stents] explode all trees	3806
#19	MeSH descriptor: [Tissue Scaffolds] explode all trees	68
#20	MeSH descriptor: [Myocardial Revascularization] explode all trees	8869
#21	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees	4957
#22	(stent* or tube* or graft* or scaffold* or implant*):ti,ab,kw	73791
#23	(percutaneous and coronary and intervention*):ti,ab,kw	7798
#24	(percutaneous and transluminal and coronary and angioplasty):ti,ab,kw	1196
#25	(pci or ptca):ti,ab,kw	6732

#26	("angioplasty*"):ti,ab,kw	7114
#27	#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26	82722
#28	MeSH descriptor: [Absorbable Implants] explode all trees	622
#29	MeSH descriptor: [Biodegradable Plastics] explode all trees	4
#30	MeSH descriptor: [Biocompatible Materials] explode all trees	2037
#31	(bioresorbable* or bio-resorbable* or bioabsorbable* or bio-absorbable* or absorbable* or biocompatible* or bio-compatible* or biodegradable* or bio-degradable* or temporar*):ti,ab,kw	9085
#32	#28 or #29 or #30 or #31	9409
#33	#27 and #32	3522
#34	(Absorb or DESolve or Magmaris or Dreams or Fantom or "Art Pure" or ArtPure or ART18Z):ti,ab,kw	870
#35	#17 and #33	697
#36	#17 and #34	142
#37	#36 or #35 with Publication Year from 2008 to present, in Trials	**577**

ClinicalTrials.gov

Date of search: 27.09.2018

Age Groups: Adult (18–64); Older Adult (65+)

Study Type: All studies

Search terms:

Condition or disease: „Angina, Unstable OR Angina, Stable OR Angina Pectoris OR Coronary Disease OR Coronary Artery Disease OR Cardiovascular Disease OR Coronary Stenosis OR Coronary Occlusion OR Acute Coronary Syndrome OR Myocardial Infarction OR Myocardial Ischemia“
Other Terms: (bioresorbable OR bio-resorbable OR bioabsorbable OR bio-absorbable OR biodegradable OR bio-degradable) AND (stent OR scaffold) OR (Absorb OR Magmaris OR DESolve OR Dreams OR Fantom OR ART18Z OR "Art Pure")

WHO-ICTRP

Date of search: 27.09.2018

Recruitment status is ALL

ALL Phases

Title: (bioresorbable OR bio-resorbable OR bioabsorbable OR bio-absorbable OR biodegradable OR bio-degradable) AND (stent OR scaffold) OR (Absorb OR Magmaris OR DESolve OR Dreams OR Fantom OR ART18Z OR "Art Pure")
AND
Condition: „Angina, Unstable OR Angina, Stable OR Angina Pectoris OR Coronary Disease OR Coronary Artery Disease OR Cardiovascular Disease OR Coronary Stenosis OR Coronary Occlusion OR Acute Coronary Syndrome OR Myocardial Infarction OR Myocardial Ischemia“
OR
Condition: „Angina, Unstable OR Angina, Stable OR Angina Pectoris OR Coronary Disease OR Coronary Artery Disease OR Cardiovascular Disease OR Coronary Stenosis OR Coronary Occlusion OR Acute Coronary Syndrome OR Myocardial Infarction OR Myocardial Ischemia“

AND
Intervention: (bioresorbable OR bio-resorbable OR bioabsorbable OR bio-absorbable OR biodegradable OR bio-degradable) AND (stent OR scaffold) OR (Absorb OR Magmaris OR DESolve OR Dreams OR Fantom OR ART18Z OR "Art Pure")

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A1: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
European Society of Cardiology (ESC) European Association for Cardio-Thoracic Surgery (EACTS)	2018	Europe	BRS are currently not recommended for clinical use outside of clinical studies.	C / III
National Institute for Health and Care Excellence (NICE)	2014	United Kingdom	Current evidence on the short-term safety and efficacy of bioresorbable stent implantation for treating coronary artery disease is adequate, but the quantity of evidence on the safety and efficacy of the procedure in the long term is inadequate. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.	-/-

Abbreviations: BRS=bioresorbable scaffold; EACTS=European Association for Cardio-Thoracic Surgery; ESC=European Society of Cardiology; NICE=National Institute for Health and Care Excellence

Sources: [3, 5]

Evidence tables of individual studies included for clinical effectiveness and safety

Table A2: Characteristics of randomised controlled studies – Absorb® BVS

Author, year	ABSORB II			
	Chevalier 2018 [20]	Serruys 2016 [23]	Chevalier 2016 [27]	Serruys 2015 [34]
Study-ID	NCT01425281			
Study design	Single-blind, parallel two-group, multicentre RCT (2:1 ratio; superiority design)			
Country	46 sites in Europe and New Zealand			
Sponsor	Abbott Vascular, Santa Clara, CA, USA			
Intervention/Product	Everolimus-eluting BRS/Absorb®			
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience®			
Anti-platelet therapy	Dual-antiplatelet therapy for a minimum of 180 days: 75 mg aspirin daily after the index procedure and throughout the length of the clinical investigation + maintenance at a minimum of 75 mg of clopidogrel daily or a minimum of 10 mg of prasugrel daily for a minimum of 180 days after the procedure; in case of sensitivity to clopidogrel or prasugrel: switch to ticlopidine according to standard hospital practice.			
Main inclusion criteria	• Age 18 to <85 years; • Evidence of myocardial ischaemia (e.g., stable or unstable angina; silent ischemia); • 1 to 2 de-novo lesions each located in a different epicardial vessel (maximum ø 2.25-3.8 mm; maximum length 48 mm)			
Primary endpoint	• Vasomation • Minimum Lumen Diameter (MLD) post nitrate minus MLD post procedure post nitrate by quantitative coronary angiography (QCA)			
Maximumfollow-up	Primary outcomes: 3 years Clinical outcomes: 5 years			
Number of patients; (n)	501 (335 vs. 166)			
Patients lost to follow-up, timepoint; n (%)	at 4 years: 28 (8.4) vs. 18 (10.8)			
Mean age of patients (years)	61.5 (10.0) vs. 60.9 (10.0)			
Sex (% male)	76% vs. 80%			
Previous MI; n (%)	94 (28) vs. 48 (29)			
Stable angina; n (%)	214 (64) vs. 107 (64)			

Author, year	ABSORB II			
	Chevalier 2018 [20]	**Serruys 2016 [23]**	**Chevalier 2016 [27]**	**Serruys 2015 [34]**
Unstable angina; n (%)	68 (20) vs. 37 (22)			
Silent ischemia; n (%)	42 (13) vs. 19 (11)			
Outcomes: Efficacy	4 year follow-up	3 year follow-up	2 year follow-up	1 year follow-up
MACE; n (%)	42 (12.4) vs. 13 (8.0); p=0.1545	nr	25 (7.6) vs. 7 (4.30); RR = 1.79 (0.79 - 4.04); p=0.155	17 (5) vs. 5 (3); Δ = 2.11% (-2.20 to 5.51); p=0.28
POCE; n (%)	79 (23.6) vs. 44 (26.7); p=0.4682	68 (21) vs. 39 (24); RR = 0.86 (0.61 - 1.22); p=0.41	39 (11.6) vs. 21 (12.8); RR = 0.90 (0.55 - 1.49); p=0.6947	24 (7) vs. 15 (9); Δ = -1.84% (-7.69 to 2.98); p=0.47
TVF; n (%)	47 (14.0) vs. 23 (14.0); p=0.997	nr	28 (8.5) vs. 11 (6.7); RR = 1.27 (0.65 - 2.49); p=0.4789	18 (5) vs. 8(5); Δ = 0.59% (-4.26 to 4.41); p=0.78
All-cause mortality; n (%)	11 (3.2) vs. 8 (4.7); p=0.4268	8 (2) vs. 6 (4); RR = 0.66 (0.23 -1.87); p=0.57	4 (1.2) vs. 1 (0.6); RR = 2.00 (0.23 - 17.75); p=0.699	0 vs. 1 (0.6); Δ = -0.61% (3.35 to 0.65); p=0.33
Cardiac mortality; n (%)	4 (1.3) vs. 4 (2.7); p=0.2795	3 (1) vs. 3 (2); RR = 0.50 (0.10 - 2.43); p=0.40	2 (0.6) vs. 0; p=0.554	0 vs. 0; Δ = 0%; p=1.0
All myocardial infarction; n (%)	29 (8.6) vs. 5 (3.3); p=0.0363	27 (8) vs. 5 (3); RR = 2.68 (1.05 - 6.82); p=0.0295	18 (5.5) vs. 4 (2.4); RR = 2.25 (0.77 - 6.54); p=0.123	15 (4) vs. 2 (1); Δ = 3.32% (-0.25 to 6.26); p=0.06
Angina; n (%)	nr	*free of angina:* 230 (74) vs. 113 (73); p=0.33 *N = 313 vs. 155*	*free of angina:* 244 (78) vs. 119 (77); p=0.82 *N = 313 vs. 155*	*free of angina:*227 (74) vs. 113 (74); p=0.98 *N = 307 vs. 153*
TVR; n (%)				
All-TVR	44 (13.1) vs. 24 (14.6); p=nr	33 (10) vs. 19 (12); RR = 0.86 (0.51 - 1.46); p=0.58		8 (2) vs. 8 (5); Δ = -2.43% (-7.01 to 0.86); p=0.15
ID-TVR	nr		8 (2.4) vs. 7 (4.3); RR = 0.57 (0.21 - 1.55); p=0.265	
TLR; n (%)				
All-TLR	28 (8.3) vs. 9 (5.3); p=0.2545	24 (7) vs. 8 (5); RR = 1.49 (0.68 - 3.23); p=0.31		4 (1) vs. 3 (2); Δ = -0.61% (-4.08 to 1.60); p=0.69
ID-TLR	22 (6.7) vs. 3 (2.0); p=0.0330		5 (1.5) vs. 3 (1.8); RR = 0.83 (0.20 - 3.44); p=1.0	
Quality of life; points (SD)	nr	N =313 vs. 155: 76 pts (nr) vs. 74 pts (nr); p=0.47 *N = 313 vs. 155*	76 pts (nr) vs. 78 pts (nr); p=0.60 *N = 313 vs. 155*	76 pts (nr) vs. 74 pts (nr); p=0.55 *N = 313 vs. 155*

Author, year	ABSORB II			
	Chevalier 2018 [20]	**Serruys 2016 [23]**	**Chevalier 2016 [27]**	**Serruys 2015 [34]**
Daily functioning; points (SD)	nr	87 pts (nr) vs. 86 pts (nr); p=0.54 *N = 313 vs. 155*	87 pts (nr) vs. 86 pts (nr); p=0.53 *N = 313 vs. 155*	87 pts (nr) vs. 86 pts (nr); p=0.48 *N = 313 vs. 155*
Duration of procedure; min (SD)	nr			
Outcomes: Safety	4 year follow-up	3 year follow-up	2 year follow-up	1 year follow-up
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	13 (4) vs. 2 (1); p=nr			
Periprocedural mortality; n (%)	nr			
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	6 (1.8) vs. 0; p=0.1851	6 (1.8) vs. 0; p=0.1851	2 (0.6) vs. 0; p=0.554	na
Other SAEs; n (%)	nr	nr	nr	nr

Abbreviations: BRS=bioresorbable scaffold; CA=California; EES=everolimus-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; MLD=minimum lumen diameter; na=not applicable; nr=not reported; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; RR=risk ratio; SAE=serious adverse event; SD=standard deviation; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	ABSORB III	
	Kereiakes 2017 [24]	**Ellis 2015 [30]**
Study-ID	NCT01751906	
Study design	Single-blind, parallel two-group, multicentre RCT (2:1 ratio; noninferiority design)	

Author, year	ABSORB III	
	Kereiakes 2017 [24]	Ellis 2015 [30]
Country	202 sites in USA and Australia	
Sponsor	Abbott Vascular, Santa Clara, CA, USA	
Intervention/Product	Everolimus-eluting BRS/Absorb®	
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience®	
Anti-platelet therapy	Loading dose of at least 300 mg aspirin within 24 hours before the procedure; dual antiplatelet therapy was continued for at least 1 year, and aspirin (at a dose of at least 81 mg daily) was continued indefinitely	
Main inclusion criteria	• ≥18 years of age • Evidence of myocardial ischaemia (e.g., stable or unstable angina; postinfarct angina, silent ischemia) suitable for elective PCI; • 1 to 2 de-novo lesions each located in a different epicardial vessel (maximum ø 2.50-3.75 mm; maximum length ≤24 mm)	
Primary endpoint	• Number of patients with TLF (cardiac death, MI in target vessel or ID-TLR) at 1 year	
Maximumfollow-up	5 years	
Number of patients; (n)	2008 (1322 vs. 686)	
Patients lost to follow-up, timepoint; n (%)	at 3 years: 46 (3.5) vs. 25 (3.6)	
Mean age of patients (years)	63.5 (10.6) vs. 63.6 (10.3)	
Sex (% male)	70.7% vs. 70.1%	
Previous MI; n (%)	282 (21.5) vs. 150 (22.0)	
Stable angina; n (%)	757 (57.3) vs. 417 (60.8)	
Unstable angina; n (%)	355 (26.9) vs. 168 (24.5)	
Silent ischemia; n (%)	132 (10.2) vs. 70 (10.2)	
Outcomes: Efficacy	3 year follow-up	1 year follow-up
MACE; n (%)	nr	113 (8.6) vs. 47 (6.9); p=nr [a]
POCE; n (%)	296 (22.7) vs. 120 (17.8); HR = 1.31 (1.06 - 1.62); p=0.01	184 (14) vs. 78 (11.5); p=nr [a]
TVF; n (%)	229 (17.7) vs. 86 (12.8); HR = 1.41 (1.10 - 1.81); p=0.006	131 (10) vs. 53 (7.8) [a]

Author, year	ABSORB III	
	Kereiakes 2017 [24]	**Ellis 2015 [30]**
All-cause mortality; n (%)	40 (3.1) vs. 23 (3.4); HR = 0.90 (0.54 - 1.51); p=0.70	15 (1.1) vs. 3 (0.4); RR = 2.58 (0.75 - 8.87); p=0.12
Cardiac mortality; n (%)	18 (1.4) vs. 8 (1.2); HR = 1.17 (0.51 - 2.69); p=0.71	8 (0.6) vs. 1 (0.1); RR = 4.12 (0.52 - 32.91); p=0.29
All myocardial infarction; n (%)	132 (10.2) vs. 51 (7.6); HR = 1.36 (0.98 - 1.88); p=0.06	90 (6.9) vs. 38 (5.6); RR = 1.22 (0.85 - 1.76); p=0.28
Angina; n (%)	nr	*patient reported angina:* 238 (18.3) vs. 125 (18.4) 0.99 (0.82 - 1.21); p=0.93
TVR; n (%)		
All-TVR	nr	74 (5.6) vs. 31 (4.6) [a]
ID-TVR	148 (11.6) vs. 51 (7.7); HR = 1.54 (1.12 - 2.11); p=0.008	66 (5.0) vs. 25 (3.7); RR = 1.36 (0.87 - 2.14); p=0.18
TLR; n (%)		
All-TLR	nr	42 (3.2) vs. 18 (2.7) [a]
ID-TLR	92 (7.2) vs. 39 (5.9); HR = 1.23 (0.85 - 1.79); p=0.27	40 (3.0) vs. 17 (2.5); RR = 1.21 (0.69 - 2.12); p=0.50
Quality of life; points (SD)	nr	87.05 pts (13.91) vs. 86.42 pts (14.45); p=nr [a] N = 1014 vs. 514
Daily functioning; points (SD)	nr	nr
Duration of procedure; min (SD)	42.2 (23.1) vs. 38.3 (20.9); p<0.001	
Outcomes: Safety	3 year follow-up	2 year follow-up
Vascular-access-site complication; n (%)	nr	nr
Procedure-related nephropathy; n (%)	nr	nr
Periprocedural MI; n (%)	41 (3.1) vs. 22 (3.2); RR = 0.96 (0.58 - 1.60); p=0.88	
Periprocedural mortality; n (%)	nr	
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr

Author, year	ABSORB III	
	Kereiakes 2017 [24]	**Ellis 2015 [30]**
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr
ScT ≥1 year; n (%)	10 (0.8) vs. 0; p=0.02	na
Other SAEs; n (%)	nr	398 (30.1) vs. 198 (28.9); p=nr [a]

[a] Results from ClinicalTrials.gov

Abbreviations: BVS=bioresorbable vascular scaffold; CA=California; EES=everolimus-eluting stent; HR=hazard ratio; ID-TLR=ischaemic driven target lesion revascularisation; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; PCI=percutaneous coronary intervention; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; RR=risk ratio; SAE=serious adverse event; SD=standard deviation; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	ABSORB Japan		
	Ali 2018 [122]; meta-analysis	**Onuma 2016 [26]**	**Kimura 2015 [31]**
Study-ID	NCT01844284		
Study design	Single-blind, parallel two-group, multicentre RCT (2:1 ratio; noninferiority design)		
Country	38 sites in Japan		
Sponsor	Abbott Vascular, Santa Clara, CA, USA		
Intervention/Product	Everolimus-eluting BRS/Absorb®		
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience Prime or Xience Xpedition®		
Anti-platelet therapy	Thienopyridine for at least 12 months and aspirin indefinitely		
Main inclusion criteria	• ≥20 years of age; • Evidence of myocardial ischaemia (e.g., stable or unstable angina, silent ischemia) suitable for elective PCI • 1 to 2 de-novo lesions each located in a different epicardial vessel (maximum ø 2.50-3.75 mm; maximum length ≤24 mm)		
Primary endpoint	• Number of patients with TLF (cardiac death, MI in target vessel or ID-TLR) at 1 year		
Maximumfollow-up	Up to 5 years		
Number of patients; (n)	400 (266 vs. 134)		

Author, year	ABSORB Japan		
	Ali 2018 [122]; meta-analysis	Onuma 2016 [26]	Kimura 2015 [31]
Patients lost to follow-up, timepoint; n (%)		at 2 years: 8 (3.0) vs. 4 (3.0)	
Mean age of patients (years)		67.1 (9.4) vs. 67.3 (9.6)	
Sex (% male)		78.9% vs. 73.9%	
Previous MI; n (%)		42 (16.0) vs. 32 (23.9)	
Stable angina; n (%)		170 (63.9) vs. 88 (65.7)	
Unstable angina; n (%)		26 (9.8) vs. 22 (16.4)	
Silent ischemia; n (%)		70 (26.3) vs. 24 (17.9)	
Outcomes: Efficacy	3 year follow-up	2 year follow-up	1 year follow-up
MACE; n (%)	nr	nr	nr
POCE; n (%)	59 (22.9) vs. 21 (16.4); RR = 1.39 (0.89 - 2.19); p=nr	52 (19.9) vs. 16 (12.3); RR = 1.62 (0.96 - 2.72); p=0.06	26 (9.8) vs. 11 (8.3); RR = 1.19 (0.60 - 2.33); p=0.62
TVF; n (%)	nr	29 (11.1) vs. 9 (6.9); RR = 1.60 (0.78 - 3.29); p=0.19	16 (6) vs. 7 (5.3); RR = 1.15 (0.48 - 2.72); p=0.75
All-cause mortality; n (%)	nr	4 (1.5) vs. 0; p=0.31	2 (0.8) vs. 0; p=0.55
Cardiac mortality; n (%)	1 (0.4) vs. 0; p=nr	1 (0.4) vs. 0; p=1.0	0 vs. 0; p=1.0
All myocardial infarction; n (%)	nr	14 (5.4) vs. 4 (3.1); RR = 1.74 (0.59 - 5.19); p=0.31	9 (3.4) vs. 3 (2.3); RR = 1.51 (0.41 - 5.47); p=0.76
Angina; n (%)	nr	nr	nr
TVR; n (%)			
All-TVR	nr	25 (9.6) vs. 10 (7.7); RR = 1.25 (0.62 - 2.51); p=0.54	13 (4.9) vs. 6 (4.5); RR = 1.09 (0.42 - 2.80); p=0.86
ID-TVR	nr	24 (9.2) vs. 7 (5.4); RR = 1.71 (0.76 - 3.86); p=0.19	13 (4.9) vs. 5 (3.8); RR = 1.30 (0.48 - 3.58); p=0.60
TLR; n (%)			
All-TLR	nr	15 (5.7) vs. 7 (5.4); RR = 1.07 (0.45 - 2.55); p=0.88	7 (2.6) vs. 5 (3.8); RR = 0.70 (0.23 - 2.17); p=0.55

Author, year	ABSORB Japan		
	Ali 2018 [122]; meta-analysis	**Onuma 2016 [26]**	**Kimura 2015 [31]**
ID-TLR	17 (6.8) vs. 4 (3.2); RR = 2.14 (0.74 - 6.23); p=nr	14 (5.4) vs. 3 (2.3); RR = 2.32 (0.68 - 7.94); p=0.16	7 (2.6) vs. 3 (2.3); RR = 1.17 (0.31 - 4.46); p=1.00
Quality of life; points (SD)	nr	nr	nr
Daily functioning; points (SD)	nr	nr	nr
Duration of procedure; min (SD)	49.8 (24.8) vs. 44.9 (21.7); p=0.04		
Outcomes: Safety	3 year follow-up	2 year follow-up	1 year follow-up
Vascular-access-site complication; n (%)	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr
Periprocedural MI; n (%)	3 (1.1) vs. 2 (1.5); RR = 0.75 (0.13 - 4.45); p=1.0		
Periprocedural mortality; n (%)	nr		
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr
ScT ≥1 year; n (%)		4 (1.6) vs. 0; p=0.31	na
Other SAEs; n (%)	nr	nr	nr

Abbreviations: BRS=bioresorbable scaffold; CA=California; EES=everolimus-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; RR=risk ratio; SAE=serious adverse event; SD=standard deviation; TLF=target lesion failure; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	ABSORB China

	Xu 2018 [17]	ClinicalTrials.gov (online)	Gao 2015 [29]
Study-ID	NCT01923740		
Study design	Open-label, parallel two-group, multicentre RCT (1:1 ratio; noninferiority design for primary endpoint)		
Country	24 sites in China		
Sponsor	Abbott Vascular, Santa Clara, CA, USA		
Intervention/Product	Everolimus-eluting BRS/Absorb®		
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience®		
Anti-platelet therapy	Loading dose of at least 300 mg aspirin and either clopidogrel (≥300 mg) or ticagrelor (180 mg) 6 to 24 h before the procedure; following PCI, aspirin 100 mg daily for at least 5 years, with clopidogrel (75 mg daily) or ticagrelor (90 mg twice a day) for a minimum of 12 months. Prasugrel was not available for use during this study.		
Main inclusion criteria	• ≥18 years of age; • Evidence of myocardial ischaemia (e.g., stable or unstable angina; postinfarct angina, silent ischemia) suitable for elective PCI • 1 to 2 de-novo lesions each located in a different epicardial vessel (maximum ø 2.50-3.75 mm; maximum length ≤24 mm)		
Primary endpoint	• Angiographic in-segment late loss (LL) after 1 year		
Maximumfollow-up	5 years		
Number of patients; (n)	480 (241 vs. 239 (randomised)) 475 (238 vs. 237 (ITT population))		
Patients lost to follow-up, timepoint; n (%)	at 3 years: 5 (3.5) vs. 4 (1.8) [a]		
Mean age of patients (years)	57.2 (11.4) vs. 57.6 (9.6)		
Sex (% male)	71.8% vs. 72.6%		
Previous MI; n (%)	40 (16.8) vs. 38 (16.0) [b]		
Stable angina; n (%)	53 (22.3) vs. 40 (16.9) [c]		
Unstable angina; n (%)	154 (64.7) vs. 152 (64.1) [d]		
Acute MI; n (%)	18 (7.6) vs. 28 (11.8)		
Outcomes: Efficacy	3 year follow-up N = 236 vs. 235	2 year follow-up N = 226 vs. 232	1 year follow-up N =238 vs. 237
MACE; n (%)	15 (6.4) vs. 12 (5.1); RR = 1.24 (0.60 - 2.60); p=0.56	10 (4.4) vs. 11 (4.7); p=nr [e]	9 (3.8) vs. 10 (4.2); Δ = -0.4% (-4.3 to 3.3); p=0.81
POCE; n (%)	28 (11.9) vs. 28 (11.9); RR = 1.00 (0.61 - 1.63); p=0.99	22 (9.7) vs. 26 (11.2); p=nr [e]	19 (8.0) vs. 23 (9.7); Δ = -1.7% (-7.0 to 3.5); p=0.51

Author, year	ABSORB China		
	Xu 2018 [17]	**ClinicalTrials.gov (online)**	**Gao 2015 [29]**
TVF; n (%)	16 (6.8) vs. 16 (6.8); RR = 1.00 (0.51 - 1.94); p= 0.99	11 (4.9) vs. 15 (6.5); p=nr [e]	10 (4.2) vs. 14 (5.9); Δ = -1.7% (-5.9 to 2.4); p=0.40
All-cause mortality; n (%)	2 (0.8) vs. 6 (2.6); RR = 0.33 (0.07 - 1.63); p=0.18	1 (0.4) vs. 5 (2.1); p=nr [e]	0 vs. 5 (2.1); Δ = -2.1% (-4.4 to -0.1); p=0.03
Cardiac mortality; n (%)	1 (0.4) vs. 3 (1.3); RR = 0.33 (0.03 - 3.17); p=0.37	nr	0 vs. 3 (1.3); Δ = -1.3% (-3.7 to 0.5); p=0.50
All myocardial infarction; n (%)	8 (3.4) vs. 5 (2.1); RR = 1.59 (0.53 - 4.80); p=0.40	5 (2.2) vs. 5 (2.1); p=nr [e]	5 (2.1) vs. 4 (1.7); Δ = 0.4% (-2.4 to 3.3); p=1.0
Angina; n (%)	nr	nr	nr
TVR; n (%)			
All-TVR	14 (5.9) vs. 13 (5.5); RR = 1.07 (0.52 - 2.23); p=0.85	11 (4.9) vs. 13 (5.6); p=nr [e]	9 (3.8) vs. 12 (5.1); Δ = -1.3% (-5.3 to 2.6); p=0.5
ID-TVR	12 (5.1) vs. 10 (4.3); RR = 1.19 (0.53 - 2.71); p=0.67	nr	7 (2.9) vs. 9 (3.8); Δ = -0.9% (-4.5 to 2.6); p=0.61
TLR; n (%)			
All-TLR	11 (4.7) vs. 8 (3.4); RR = 1.37 (0.56 - 3.34); p=0.49	9 (4.0) vs. 8 (3.5); p=nr [e]	7 (2.9) vs. 7 (3.0); Δ = 0.0% (-3.4 to 3.4); p=0.99
ID-TLR	10 (4.2) vs. 6 (2.6); RR = 1.66 (0.61 - 4.49); p=0.31	nr	6 (2.5) vs. 5 (2.1); Δ = 0.4% (-2.6 to 3.5); p=0.77
Quality of life; points (SD)	nr	nr	nr
Daily functioning; points (SD)	nr	nr	nr
Duration of procedure; min (SD)	nr		
Outcomes: Safety	3 year follow-up	2 year follow-up	1 year follow-up
Vascular-access-site complication; n (%)	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr
Periprocedural MI; n (%)	3 (1.3) vs. 1 (0.4); p=0.62 [e]		

Author, year	ABSORB China		
	Xu 2018 [17]	ClinicalTrials.gov (online)	Gao 2015 [29]
Periprocedural mortality; n (%)	0 vs. 0		
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr
ScT ≥1 year; n (%)	1 (0.4) vs. 0; p=1.0	1 (0.4) vs. 0; na; p=1.0 [e]	na
Other SAEs; n (%)	45 (18.7) vs. 46 (19.3); p=nr [e] *N = 241 vs. 239*	nr	nr

[a] Summary of withdrawals and lost to follow up
[b] Data from Gao 2015 [29]; Discrepant data in Xu 2018 [17]: 40 (16.8%) vs. 40 (16.9%)
[c] Data from Gao 2015 [29]; Discrepant data in Xu 2018 [17]: 53 (22.3%) vs. 41 (17.3%)
[d] Data from Gao 2015 [29]; Discrepant data in Xu 2018 [17]: 156 (65.5%) vs. 153 (64.6%)
[e] Results from ClinicalTrials.gov

Abbreviations: BRS=bioresorbable scaffold; CA=California; EES=everolimus-eluting stent; ITT=intention-to treat; LL=lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; MLD=minimum lumen diameter; na=not applicable; nr=not reported; PCI=percutaneous coronary intervention; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; RR=risk ratio; SAE=serious adverse event; SD=standard deviation; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	AIDA	
	Tijssen 2018 [18]	Wykrzykowska 2015 [25]
Study-ID	NCT01858077	
Study design	Single-blind, parallel two-group, multicentre RCT (1:1 ratio; noninferiority design)	
Country	5 sites in the Netherlands	
Sponsor	Academisch Medisch Centrum - Universiteit van Amsterdam	
Intervention/Product	Everolimus-eluting BRS/Absorb® revision 1.1	
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience Prime or Xience Xpedition®	
Anti-platelet therapy	Dual antiplatelet therapy was administered before the procedure in accordance with the ESC guidelines; dual-antiplatelet therapy (75-100 mg aspirin daily and 75 mg clopidogrel or 10 mg prasugrel or 180 mg ticagrelor daily) for a minimum of 1 year after the index procedure	

Author, year	AIDA			
	Tijssen 2018 [18]			Wykrzykowska 2015 [25]
Main inclusion criteria	• ≥18 years of age • Evidence of coronary artery disease suitable for treatment with DES in accordance with guidelines • 1 or more target lesions (Maximumø 2.50-4.00 mm; maximum length ≤70 mm)			
Primary endpoint	• TVF (cardiac death, MI in target vessel or TVR) at 2 years			
Maximumfollow-up	5 years			
Number of patients; (n)	1845 (924 vs. 921)			
Patients lost to follow-up, timepoint; n (%)	at 2 years: 35 (3.8) vs. 24 (2.6)			
Mean age of patients (years)	64.3 (10.6) vs. 64.0 (10.5)			
Sex (% male)	72.5% vs. 76.0%			
Previous MI; n (%)	166 (18.0) vs. 172 (18.7)			
Stable angina; n (%)	361 (39.1) vs. 370 (40.2)			
Unstable angina; n (%)	70 (7.6) vs. 87 (9.4)			
STEMI; n (%)	240 (26.0) vs. 225 (24.4)			
NSTEMI; n (%)	185 (20.0) vs. 192 (20.8)			
Outcomes: Efficacy	~3 year follow-up (median 1092 days) [a]	2 year follow-up	1 year follow-up	30 months follow-up
MACE; n (%)	nr	nr	nr	nr
POCE; n (%)	184 (19.9) vs. 170 (18.5); p=nr	155 (17.0) vs. 140 (15.3); HR = 1.09 (0.88 - 1.34); p=0.352	107 (11.6) vs. 97 (10.6); HR = 1.09 (0.88 - 1.34); p=0.481	161 (17.8) vs. 149 (16.1); HR = 1.08 (0.87 - 1.35); p=0.49
TVF; n (%)	120 (12.9) vs. 103 (11.2); p=nr	100 (11.0) vs. 90 (9.9); HR = 1.12 (0.94 - 1.49); p=0.436	70 (7.6) vs. 56 (6.1); HR = 1.26 (0.88 - 1.78); p=0.204	105 (11.7) vs. 94 (10.7); HR = 1.12 (0.85 - 1.48); p=0.43
All-cause mortality; n (%)	41 (4.4) vs. 49 (5.3); p=nr	30 (3.3) vs. 37 (4.1); HR = 0.81 (0.50 - 1.31); p=0.385	19 (2.1) vs. 23 (2.5); HR = 0.82 (0.45 - 1.51); p=0.528	32 (3.5) vs. 43 (4.3); HR = 0.74 (0.47 - 1.17); p=0.19
Cardiac mortality; n (%)	22 (2.4) vs. 24 (2.6); p=nr	17 (1.9) vs. 20 (2.2); HR = 0.85 (0.44 - 1.62); p=0.618	12 (1.3) vs. 11 (1.2); HR = 1.09 (0.48 - 2.47); p=0.841	18 (2.0) vs. 23 (2.7); HR = 0.78 (0.42 - 1.44); p=0.43
All myocardial infarction; n (%)	69 (7.5) vs. 46 (5.0); p=nr	59 (6.5) vs. 37 (4.1); HR = 1.61 (1.07 - 2.42); p=0.022	40 (4.4) vs. 28 (3.1); HR = 1.43 (0.89 - 2.32); p=0.141	62 (7.1) vs. 41 (4.2); HR = 1.52 (1.02 - 2.25); p=0.04
Angina; n (%)	nr	nr	nr	nr
TVR; n (%)				

Author, year	AIDA			
	Tijssen 2018 [18]			Wykrzykowska 2015 [25]
All-TVR	89 (9.6) vs. 72 (7.8); p=nr	74 (8.2) vs. 63 (7.0); HR = 1.18 (0.84 - 1.65); p=0.333	48 (5.2) vs. 38 (4.2); HR = 1.27 (0.83 - 1.94); p=0.278	76 (8.7) vs. 65 (7.5); HR = 1.16 (0.84 - 1.62); p=0.37
ID-TVR	nr	nr	nr	nr
TLR; n (%)				
All-TLR	69 (7.5) vs. 51 (5.5); p=nr	59 (6.5) vs. 44 (4.8); HR = 1.35 (0.91 - 1.99); p=0.133	38 (4.2) vs. 27 (3.0); HR = 1.41 (0.86 - 2.31); p=0.171	60 (7.0) vs. 45 (5.2); HR = 1.33 (0.90 - 1.96); p=0.15
ID-TLR	nr	nr	nr	nr
Quality of life; points (SD)	nr	nr	nr	nr
Daily functioning; points (SD)	nr	nr	nr	nr
Duration of procedure; min (SD)	49 (26) vs. 44 (23); p<0.001			
Outcomes: Safety	~3 year follow-up (median 1092 days) [a]	2 year follow-up	1 year follow-up	30 months follow-up
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	9 (1.0) vs. 6 (0.7); HR = 1.50 (0.53 - 4.20); p=0.44			
Periprocedural mortality; n (%)	nr			
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	14 (1.5) vs. 3 (0.3); p=nr [b]	9 (1) vs. 2 (0.2); p=nr	na	10 (1.1) vs. 2 (0.2); p=nr

Author, year	AIDA			
	Tijssen 2018 [18]			Wykrzykowska 2015 [25]
Other SAEs; n (%)	nr	nr	nr	nr

[a] Total number of events reported before data lock on 28 February 2018, no full analysis
[b] up to 5 years follow-up

Abbreviations: BRS=bioresorbable scaffold; CA=California; DES=drug-eluting stent; EES=everolimus-eluting stent; HR=hazard ratio; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; sAE=Serious adverse event; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	TROFI II	
	Felix 2018 [123]; meta-analysis	Sabate 2016 [28]
Study-ID	NCT01986803	
Study design	Single-blind, parallel two-group, multicentre RCT (1:1 ratio; noninferiority design for primary endpoint)	
Country	8 sites in the Netherlands, Denmark, Spain and Switzerland	
Sponsor	European Cardiovascular Research Institute Abbott Vascular, Santa Clara, CA, USA Terumo Europe N.V.	
Intervention/Product	Everolimus-eluting BRS/Absorb®	
Comparator/Product	Everolimus-eluting permanent metallic stent/Xience Prime®	
Anti-platelet therapy	It was recommended that patients received a loading dose of aspirin and a P2Y12 inhibitor pre-procedure, followed by dual antiplatelet therapy for at least 12 months.	
Main inclusion criteria	• ≥18 years of age • ST-segment elevation of >1mm in >2 contiguous leads, or (presumably new) left bundle branch block, or true posterior MI with ST depression of >1 mm in >2 contiguous anterior leads • Primary PCI within 24 hours of symptom onset • 1 or more acute infarct artery target vessel with one or more coronary artery stenoses in a native coronary artery (Maximumø 2.50-3.80 mm)	
Primary endpoint	• Optical frequency domain imaging-derived healing score at 6 months	
Maximumfollow-up	Angiographic: 6 months Clinical: 36 months	
Number of patients; (n)	191 (95 vs. 96)	

Author, year	TROFI II	
	Felix 2018 [123]; meta-analysis	Sabate 2016 [28]
Patients lost to follow-up, timepoint; n (%)	at 6 months: 2 (2.1) vs. 0	
Mean age of patients (years)	59.1 (10.7) vs. 58.2 (9.6)	
Sex (% male)	76.8% vs. 87.5%	
Previous MI; n (%)	2 (2.1) vs. 3 (3.1)	
Stable angina; n (%)	0 vs. 0	
Unstable angina; n (%)	0 vs. 0	
STEMI; n (%)	95 (100) vs. 95 (100)	
Outcomes: Efficacy	3 year follow-up	6 months follow-up
MACE; n (%)	nr	nr
POCE; n (%)	nr	nr
TVF; n (%)	nr	nr
All-cause mortality; n (%)	2 (2.1) vs. 1 (1.0); OR = 2.04 (0.18 - 22.92); p=nr	0 vs. 0; p=1.0
Cardiac mortality; n (%)	nr	0 vs. 0; p=1.0
All myocardial infarction; n (%)	3 (3.2) vs. 4 (4.2); OR = 0.75 (0.16 - 3.44); p=nr	1 (1.0) vs. 0; p=nr
Angina; n (%)	nr	*free of angina:* 87 (91.4) vs. 88 (91.7); p=0.94
TVR; n (%)		
All-TVR	nr	5 (5.3) vs. 5 (5.2); p=1.0
ID-TVR	nr	nr
TLR; n (%)		
All-TLR	3 (3.2) vs. 1 (1.0); OR = 3.10 (0.32 - 30.32); p=nr	2 (2.1) vs. 1 (1.0); p=nr
ID-TLR	nr	nr

Author, year	TROFI II	
	Felix 2018 [123]; meta-analysis	Sabate 2016 [28]
Quality of life; points (SD)	nr	nr
Daily functioning; points (SD)	nr	nr
Duration of procedure; min (SD)	nr	
Outcomes: Safety	3 year follow-up	6 months follow-up
Vascular-access-site complication; n (%)	nr	nr
Procedure-related nephropathy; n (%)	nr	nr
Periprocedural MI; n (%)	0 vs. 0; p=1.0	
Periprocedural mortality; n (%)	0 vs. 0; p=1.0	
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr
ScT ≥1 year; n (%)	nr	na
Other SAEs; n (%)	nr	nr

Abbreviations: BRS=bioresorbable scaffold; CA=California; EES=everolimus-eluting stent; OR=odds ratio; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; SAE=serious adverse event; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation; USA=United States of America

Table A2: Characteristics of randomised controlled studies – Absorb® BVS (continued)

Author, year	Everbio II		
	Arroyo 2017 [22]	Puricel 2015 [33]	Hernandez 2017 [21]

Author, year	Everbio II		Hernandez 2017 [21]
	Arroyo 2017 [22]	Puricel 2015 [33]	
Study-ID	NCT01711931		-
Study design	Assessor-blind, parallel three-group, single-centre RCT (1:1:1 ratio; noninferiority design for primary endpoint)		Parallel two-group, single centre RCT (1:1 ratio); blinding unclear
Country	1 site in the Switzerland		1 site in Spain
Sponsor	University of Fribourg, Switzerland Fonds Scientifique Cardiovasculaire, Fribourg, Switzerland		Hospital Universitario Marques de Valdecilla, Department of Cardiology, Interventional Cardiology Unit, Santander, Spain
Intervention/Product	Everolimus-eluting BRS/Absorb® (BRS)		Everolimus-eluting BRS/Absorb®
Comparator/Product	1) Everolimus-eluting permanent metallic stent/Promus Element (EES) 2) Biolimus-eluting permanent metallic stent/Biomatrix Flex (BES)		Everolimus-eluting permanent Platinum Chromium stent/Synergy®
Anti-platelet therapy	Loading dose of either a minimum 600 mg clopidogrel, 180 mg of ticagrelor, or 60 mg prasugrel before or immediately after the procedure. Lifelong ≥100 mg daily aspirin and either 75 mg daily clopidogrel, or 90 mg twice-daily ticagrelor or 10 mg prasugrel for a minimum of 6 months.		nr
Main inclusion criteria	• ≥18-70 years of age • Evidence of coronary artery disease (unstable angina, non-ST segment MI, ST-elevated MI) suitable for elective PCI		• ≥18 years and ≤70 years of age • Indication for percutaneous revascularisation (excluding STEMI or NSTEMI) and reasonable candidates for BRS • Target lesions with ø ≥2.50 mm)
Primary endpoint	• Lumen Late Loss (LLL) at 9 months		• Fluoroscopy time • Median dose-area product • Contrast agent volume • Periprocedural troponin release
Maximumfollow-up	5 years		12 months
Number of patients; (n)	238 (BRS vs. EEs vs. BES: 78 vs. 80 vs. 80)		200 (100 vs. 100)
Patients lost to follow-up, timepoint; n (%)	at 2 years: BRS 1 (1) vs. EES 3 (4) vs. BES 0		nr
Mean age of patients (years)	BRS 65 (11) vs. EES 65 (11) vs. BES 65 (10)		60.8 (11) vs. 61.3 (12)
Sex (% male)	BRS 78.0% vs. EES 80.0% vs. BES 80.0%		79.0% vs. 76.0%
Previous MI; n (%)	BRS 11 (14) vs. EES 14 (18) vs. BES 16 (20)		18 (18) vs. 22 (22)
Stable angina; n (%)	BRS 41 (53) vs. EES 47 (59) vs. BES 27 (34)		nr
Unstable angina; n (%)	BRS 6 (8) vs. EES 5 (6) vs. BES 9 (11)		55 (55) vs. 51 (51)

Author, year	Everbio II		Hernandez 2017 [21]
	Arroyo 2017 [22]	Puricel 2015 [33]	
STEMI; n (%)	BRS 9 (12) vs. EES 6 (8) vs. BES 8 (10)		nr
Outcomes: Efficacy	2 year follow-up	9 months follow-up	1 year follow-up
MACE; n (%) [a]	BRS vs. EES: 16 (20.5) vs. 13 (16.3); p=0.54 BRS vs. BES: 16 (20.5) vs. 7 (8.8); p=0.04 BRS vs. EES & BES: 16 (20.5) vs. 20 (12.5); p=0.12	BRS vs. EES: 9 (11.5) vs. 11 (13.8); p=0.68 BRS vs. BES: 9 (11.5) vs. 4 (5); p=0.14 BRS vs. EES & BES: 9 (11.5) vs. 15 (9.4); p=0.60	nr
POCE; n (%)	BRS vs. EES: 27 (34.6) vs. 30 (37.5); p=0.74 BRS vs. BES: 27 (34.6) vs. 21 (26.3); p=0.30 BRS vs. EES & BES 27 (34.6) vs. 51 (31.9); p=0.67	BRS vs. EES: 21 (26.9) vs. 26 (32.5); p=0.44 BRS vs. BES: 21 (26.9) vs. 15 (18.8); p=0.22 BRS vs. EES & BES: 21 (26.9) vs. 41 (25.6); p=0.83	nr
TVF; n (%)	nr	nr	nr
All-cause mortality; n (%)	BRS vs. EES: 2 (3) vs. 4 (5); p=0.68 BRS vs. BES: 2 (3) vs. 1 (1); p=0.62 BRS vs. EES & BES: 2 (3) vs. 5 (3); p=1.00	BRS vs. EES: 1 (1) vs. 3 (4); p=0.62 BRS vs. BES: 1 (1) vs. 0; p=0.49 BRS vs. EES & BES: 1 (1) vs. 3 (2); p=1.0	nr
Cardiac mortality; n (%)	BRS vs. EES: 1 (1) vs. 1 (1); p=1.00 BRS vs. BES: 1 (1) vs. 0; p=0.49 BRS vs. EES & BES: 1 (1) vs. 1 (1); p=0.55	BRS vs. EES: 1 (1) vs. 0; p=0.49 BRS vs. BES: 1 (1) vs. 0; p=0.49 BRS vs. EES & BES: 1 (1) vs. 0; p=0.33	1 (1) vs. 1 (1); p=1.0
All myocardial infarction; n (%)	BRS vs. EES: 4 (5) vs. 2 (3); p=0.44 BRS vs. BES: 4 (5) vs. 0 (0); p=0.06 BRS vs. EES & BES: 4 (4) vs. 2 (1); p=0.09	BRS vs. EES: 1 (1) vs. 1 (1); p=1.0 BRS vs. BES: 1 (1) vs. 0; p=0.49 BRS vs. EES & BES: 1 (1) vs. 1 (1); p=0.55	9 (9) vs. 5 (5); p=nr
Angina; n (%)	nr	nr	nr
TVR; n (%)			
All-TVR	BRS vs. EES: 18 (23) vs. 17 (21); p=0.85 BRS vs. BES: 18 (23) vs. 11 (14); p=0.15 BRS vs. EES & BES: 18 (23) vs. 28 (18); p=0.38	BRS vs. EES: 11 (14.1) vs. 14 (17.5); p=0.56 BRS vs. BES: 11 (14.1) vs. 8 (10); p=0.43 BRS vs. EES & BES: 11 (14.1) vs. 22 (13.8); p=0.94	7 (7) vs. 6 (6); p=nr [b]
ID-TVR	nr	nr	nr
TLR; n (%)			
All-TLR	BRS vs. EES: 14 (18) vs. 12 (15); p=0.67 BRS vs. BES: 14 (18) vs. 7 (9); p=0.10 BRS vs. EES & BES: 14 (18) vs. 19 (12); p=0.23	BRS vs. EES: 8 (10) vs. 11 (14); p=0.50 BRS vs. BES: 8 (10) vs. 4 (5); p=0.21 BRS vs. EES & BES: 8 (10) vs. 15 (9); p=0.83	5 (5) vs. 3 (3); p=0.7
ID-TLR	nr	nr	nr
Quality of life; points (SD)	nr	nr	nr
Daily functioning; points (SD)	nr	nr	nr

Author, year	Everbio II		
	Arroyo 2017 [22]	Puricel 2015 [33]	Hernandez 2017 [21]
Duration of procedure; min (SD)	nr		nr
Outcomes: Safety	2 year follow-up	9 months year follow-up	1 year follow-up
Vascular-access-site complication; n (%)	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr
Periprocedural MI; n (%)	nr		6 (6) vs. 3 (3); p=0.49 [c]
Periprocedural mortality; n (%)	nr		nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	
ScT ≥1 year; n (%)	BRS vs. EES vs. BES: 0 vs. 0 vs. 0	na	na
Other SAEs; n (%)	nr	nr	nr

[a] Device-oriented MACE (composite of cardiac death, myocardial infarction, and target-lesion revascularisation)
[b] TVR = TLR + non-target lesion TVR
[c] All MI = peri-procedural MI + 12 months follow up MI

Abbreviations: BES=biolimus-eluting stent; BRS=bioresorbable scaffold; EES=everolimus-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; POCE=patient-oriented composite endpoint; RCT=randomised controlled trial; SAE=serious adverse event; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation

Table A3: Characteristics of other relevant studies – DESolve®, Fantom®

Author, year	Gunes 2017 [61]	Abizaid 2016 [76] (DESolve Nx)	Nef 2018 [37] (DESolve PMCF)	Abizaid 2017 [52] (Fantom II)
Study-ID	-	NCT02086045	NCT02013349	NCT02539966
Study design	Single center, cross sectional study	Prospective, multicenter, single-arm study	Prospective, multicenter, single-arm registry	Prospective multi-centre, single arm study
Country	Turkey	13 sites in Belgium, Brazil, Denmark, Germany, New Zealand and Poland	10 sites in Germany and Italy	28 sites in Australia, Belgium, Brazil, Denmark, France, Germany, Netherlands, Poland
Sponsor	Elixir Medical Corporation	Elixir Medical Corporation	Elixir Medical Corporation	REVA Medical, Inc.
Intervention/Product	Novolimus-eluting BRS/DESolve®	Novolimus-eluting BRS/DESolve®	Novolimus-eluting BRS/DESolve®	Sirolimus-Eluting Coronary BRS/Fantom®
Comparator/Product	none	none	none	none
Anti-platelet therapy	ASA + P2Y12 inhibitor n=63 (55.8%); ASA + Clopidogrel n= 50 (44.2%) Aspirin-native patients were treated with upstream clopidogrel (300 mg) followed with daily oral aspirin of 100 mg. Patients free from chronic antiplatelet therapy were treated with clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (180 mg) loading doses before PCI followed with daily doses of clopidogrel (75 mg) or prasugrel (10 mg) or ticagrelor (180 mg) for 12 months. All of the patients were anticoagulated with unfractionated heparin during the procedure.	Loading dose of aspirin (≥300 mg) and clopidogrel (≥300 mg) if not on long-term use. Post-procedure: aspirin (≥75 mg) indefinitely and clopidogrel (75 mg daily) for a minimum of 12 months.	ASA: n=101 (99%); Clopidogrel: n=68 (66,7%); Ticagrelor: n=21 (20.6%) Prasugrel: n=12 (11.8%) Ticlopidine: n=1 (1.0%)	Dual antiplatelet therapy with aspirin plus clopidogrel, ticagrelor, or prasugrel for 12 months
Main inclusion criteria	• Reference vessel diameter ≥2.5 mm, stentable lesions • Stable coronary artery disease, or unstable angina or non-ST segment elevation myocardial infarction	• >18 years of age; • Symptoms of stable or unstable angina pectoris; • Presence of a single, de novo coronary lesion (ø 2.75-3.50 mm; MaximumLength 14 mm); • Stenosis between 50% and 90%	• >18 years of age; • Evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study or electrocardiogram changes consistent with ischemia); • De novo coronary lesions (ø 2.75-3.50; Maximumlength 24 mm); • Stenosis between 50% and 90%	• >18 years of age; • Patients with coronary artery disease and evidence of myocardial ischemia; • Presence of a single, de novo coronary lesion (ø 2.5-3.50; MaximumLength 20 mm); • Stenosis between 50% and 100%

Author, year	Gunes 2017 [61]	Abizaid 2016 [76] (DESolve Nx)	Nef 2018 [37] (DESolve PMCF)	Abizaid 2017 [52] (Fantom II)
Primary endpoint	nr	MACE (cardiac death, target vessel MI or clinically indicated TLR) at 6 months and annually up to 5 years Late lumen loss (LLL) at 6 months	MACE (cardiac death, target vessel MI or clinically indicated TLR) at 1, 6, 12 mo, 2, 3, 4, 5 yrs	MACE (cardiac death, MI or TLR) at 6 months Late Lumen Loss (LLL) at 6 months
Maximumfollow-up	12 months	5 years	5 years	6 months
Number of patients; (n)	117	126	102	240 (all) 117 (Cohort A)
Patients lost to follow-up, timepoint; n (%)	0	at 12 months: 4 (3.2)	at 12 months: 1 (1)	at 6 months: 9 (7.7)
Mean age of patients (years)	57.6 (10.6)	62 (10)	62.0 (12.9)	62.7 (9.7)
Sex (% male)	85.5%	68%	77.5%	70.1%
Previous MI; n (%)	20 (17.1)	56 (44)	35 (34.3)	31 (26.5)
Stable angina; n (%)	101 (86.3)	95 (75)	nr	nr
Unstable angina; n (%)	16 (13.7)	16 (13)	nr	nr
STEMI; n (%)	nr	nr	nr	nr
NSTEMI; n (%)	nr	nr	nr	nr
ACS; n (%)	nr	nr	nr	nr
Outcomes: Safety	**12 months follow-up**	**24 months follow-up**	**12 months follow-up**	**6 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	1 (0.9)	0	0	1 (0.85)
Periprocedural mortality; n (%)	0	0	0	0
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	0	nr	0	0
ScT ≥1 year; n (%)	na	0	na	na

Author, year	Gunes 2017 [61]	Abizaid 2016 [76] (DESolve Nx)	Nef 2018 [37] (DESolve PMCF)	Abizaid 2017 [52] (Fantom II)
Other SAEs; n (%)	MACE: 1 (0.9)	MACE: 9 (7.4)	MACE: 3 (3.0)	MACE: 3 (2.6)

Abbreviations: ACS=acute coronary syndrome; ASA=acetylsalicylic acid; BRS=bioresorbable scaffold; LLL=late lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation

Table A4: Characteristics of other relevant studies – Magmaris (DREAMS 2G), Absorb® BVS

Author, year	Haude 2016 [58] Haude 2016 [82] Haude 2018 [35] Haude 2017 [56] (Biosolve II)	7 Haude 2018 [35] Haude 2017 [56] (Biosolve III)	Fam 2016 [72]	Maes 2018 [38]
Study-ID	NCT01960504	NCT02716220	-	-
Study design	Prospective multi-centre, single arm study	Prospective multi-centre, single arm study	Single center, cohort study	Single center, cohort study
Country	13 sites in Belgium, Brazil, Denmark, Germany, Singapore, Spain, Switzerland, and the Netherlands	8 sites in Europe, South America, and Asia	The Netherlands	Canada
Sponsor	Biotronik AG, Switzerland.	Biotronik AG, Switzerland.	Abbott Vascular	Internal funding
Intervention/Product	Sirolimus-eluting absorbable magnesium scaffold system/DREAMS 2G	Sirolimus-eluting absorbable magnesium scaffold system/DREAMS 2G	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS /Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	Dual antiplatelet treatment was recommended for a minimum of 6 months after the procedure	Dual antiplatelet treatment was recommended for a minimum of 6 months after the procedure	Dual antiplatelet therapy for 12 months	nr
Main inclusion criteria	• >18 years and <80 years of age; • Stable or unstable angina or documented silent ischaemia; • Maximum of two de-novo coronary lesion in two separate coronary arteries (ø 2.2-3.7 mm; MaximumLength 21 mm); • Stenosis between 50% and 99%	• >18 years and <80 years of age; • Stable or unstable angina or documented silent ischaemia; • Maximum of two de-novo coronary lesion in two separate coronary arteries (ø 2.7-3.8 mm; MaximumLength 21 mm); • Stenosis between 50% and 99%	• >18 years of age • STEMI	• Patients undergoing percutaneous coronary intervention (PCI)

Author, year	Haude 2016 [58] Haude 2016 [82] Haude 2018 [35] Haude 2017 [56] (Biosolve II)	7 Haude 2018 [35] Haude 2017 [56] (Biosolve III)	Fam 2016 [72]	Maes 2018 [38]
Primary endpoint	In segment LLL at 6 months	Procedure success, defined as final diameter stenosis of <30% by quantitative coronary angiography without occurrence of in-hospital death, Q-wave or non-Q-wave myocardial infarction or repeat target lesion revascularisation	nr	Procedural success
Maximumfollow-up	36 months	36 months	18 months	12 months
Number of patients; (n)	123	61	151	118
Patients lost to follow-up, timepoint; n (%)	at 24 months: 3 (2.4)	0	6 (3.9)	0
Mean age of patients (years)	65.2 (10.3)	66.3 (11.8)	56.3 (10.22)	59 (11)
Sex (% male)	63.4%	63.9%	72.2%	83%
Previous MI; n (%)	29 (24)	14 (23)	nr	20 (17)
Stable angina; n (%)	88 (72)	nr	na	43 (36)
Unstable angina; n (%)	17 (14)	nr	na	46 (39)
STEMI; n (%)			151 (100)	11 (9.3)
NSTEMI; n (%)			na	18 (15)
ACS; n (%)	nr	nr	na	nr
Outcomes: Safety	**24 months follow-up**	**12 months follow-up**	**18 months follow-up**	**12 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	0	0	nr	nr
Periprocedural mortality; n (%)	0	0	nr	0
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr

Author, year	Haude 2016 [58] Haude 2016 [82] Haude 2018 [35] Haude 2017 [56] (Biosolve II)	7 Haude 2018 [35] Haude 2017 [56] (Biosolve III)	Fam 2016 [72]	Maes 2018 [38]
Mortality as a result of bleeding and/or stroke; n (%)	0	0	nr	nr
ScT ≥1 year; n (%)	0	na	2 (1.5)	na
Other SAEs; n (%)	All-cause mortality: 4 (3.3)	All-cause mortality: 2 (3.3)	nr	MACE: 12 (10)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; LLL=late lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction

Table A5: Characteristics of other relevant studies – Absorb® BVS

Author, year	Costopoulos 2014 [91]	Panolas 2016 [69]	Jamshidi 2016 [74]	Grimfjard 2017 [50] (SCAAR)
Study-ID	-	-	-	-
Study design	Single center cohort study	Single center cohort study	Observational single-centre single arm study	Prospective multi-centre registry
Country	Italy	Italy	Switzerland	Up to 74 sites in Sweden
Sponsor	nr	nr	nr	nr
Intervention/Product	Everolimus-eluting BRS /Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	Dual antiplatelet therapy (aspirin + clopidogrel) for 12 months (complex lesions aspirin + prasugrel or ticagrelor first 3 months)	Dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor or prasugrel) for 12 months	Patients with stable CAD: aspirin and clopidogrel; Patients with ACS: ticagrelor or prasugrel in addition to aspirin. dual antiplatelet therapy was recommended for 12 months.	nr
Main inclusion criteria	• Patients undergoing percutaneous coronary intervention	• Stable angina	• Symptomatic stable CAD or acute coronary syndrome; • Target lesion (ø 2.5->4,0 mm)	• All patients treated with the Absorb® or any of the twelve most commonly used modern DES
Primary endpoint	Clinical efficacy	Major acute cardiovascular events (MACE)	Composite endpoint of TLR, ScT, MI, or death at 6 or 12 months	Incidence of definite ScT

Author, year	Costopoulos 2014 [91]	Panolas 2016 [69]	Jamshidi 2016 [74]	Grimfjard 2017 [50] (SCAAR)
Maximumfollow-up	6 months	12 months	12 months	24 months
Number of patients; (n)	92	70	65	460
Patients lost to follow-up, timepoint; n (%)	0	0	16 (25)	0
Mean age of patients (years)	64.2 (11.8)	64.5 (10.3)	66.0 (10.7)	59.3 (nr)
Sex (% male)	89.1%	91.4%	86%	79.3%
Previous MI; n (%)	26 (28.3)	17 (28.3)	27 (42)	75 (16.3)
Stable angina; n (%)	82 (89.1)	70 (100)	47 (72)	115 (25)
Unstable angina; n (%)	nr	na	6 (9)	52 (11.3)
STEMI; n (%)	nr	na	1 (2)	98 (21.3)
NSTEMI; n (%)	nr	na	11 (17)	182 (39.6)
ACS; n (%)	10 (10.9)	na	nr	nr
Outcomes: Safety	**6 months follow-up**	**12 months follow-up**	**12 months follow-up**	**24 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	8 (8.7)	5 (7.1)	0	nr
Periprocedural mortality; n (%)	0	0	0	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	0	nr
ScT ≥1 year; n (%)	na	na	na	3 (0.7)
Other SAEs; n (%)	MACE: 3 (3.3)	nr	All-cause mortality: 2/49 (4.1)	All-cause mortality: 5 (1.0) at 12 months

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable stent; CAD=coronary artery disease; DES=drug-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, year	Teeuwen 2015 [104]	Felix 2016 [68] (BVS Expand)	Kraak 2015 [90]	Remkes 2017 [47]
Study-ID	-	-	-	-
Study design	Prospective single centre registry	Investigator-initiated, prospective, single-center, single-arm study	Prospective single centre registry	Prospective single centre registry
Country	The Netherlands	The Netherlands	The Netherlands	The Netherlands
Sponsor	nr	Abbott Vascular	Abbott Vascular	nr
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	Stable angina: dual anti-platelet therapy prior to treatment with aspirin 100 mg and 75 mg clopidogrel daily ACS: prasugrel 5/10 mg daily or 90 mg ticagrelor twice daily DAPT was advised for at least 12 months.	Stable angina: 300 mg aspirin and 600 mg clopidogrel acute coronary syndrome: 300 mg aspirin and 60 mg prasugrel or 180 mg ticagrelor.	Patients received dual antiplatelet therapy (DAPT) for at least 12 months.	Dual antiplatelet therapy for at least 12 months
Main inclusion criteria	• All patients with stable angina, acute coronary syndromes, high-risk lesions like ST-segment elevated myocardial infarction (STEMI) or BMS and DES in-stent restenosis • Target lesion (ø 2.5->3,5mm)	• Patients with NSTEMI, stable or unstable angina or silent ischemia; • De-novo lesion (ø 2.0-3,8mm)	• Patients with a wide range of indications, ranging from stable angina to acute coronary syndrome, and with a diverse range of lesion characteristics	• All patients who underwent PCI with at least one E-BRS implantation
Primary endpoint	MACE	MACE (cardiac death, MI or TLR)	nr	TLF (cardiac death, non-fatal target vessel MI, clinically-indicated TLR)
Maximumfollow-up	24 months	18 months	6 months	mean 19,8 (10) months
Number of patients; (n)	108	249	135	105
Patients lost to follow-up, timepoint; n (%)	3 (2.7)	0	3 (3)	0
Mean age of patients (years)	59.4 (12.0)	61.3 (10.2)	59 (11)	60 (11)
Sex (% male)	69.4%	73.5%	73.0%	71.4%
Previous MI; n (%)	nr	17.7	34 (25)	12 (11.4)
Stable angina; n (%)	54 (50)	40.6	63 (47)	62 (59.1)
Unstable angina; n (%)	10 (9.3)	16.1	13 (10)	13 (12.3)

Author, year	Teeuwen 2015 [104]	Felix 2016 [68] (BVS Expand)	Kraak 2015 [90]	Remkes 2017 [47]
STEMI; n (%)	20 (18.5)	0	17 (13)	9 (8.6)
NSTEMI; n (%)	24 (22.2)	43.0	36 (27)	21 (20.0)
ACS; n (%)	-	-	-	-
Outcomes: Safety	**24 months follow-up**	**18 months follow-up**	**6 months follow-up**	**19.8 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	1 (0.9)	2 (0.8)	0	2 (1.9)
Periprocedural mortality; n (%)	0	nr	0	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	0	0	0	nr
ScT ≥1 year; n (%)	0	1 (0.4)	na	0
Other SAEs; n (%)	MACE: 11 (10.9) All-cause mortality: 3 (2.7)	MACE: 6.8 All-cause mortality: 4 (1.8)	Cardiac morality: 1 (0.8)	All-cause mortality: 2 (1.9) Cardiac mortality: 0

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable stent; CAD=coronary artery disease; DES=drug-eluting stent; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	Alfonso 2017 [53] (RIBS VI)	Widimsky 2015 [83] Tousek 2016 [73] (Prague 19)	Iwanczyk 2017 [39]	Gil 2016 [79]
Study-ID	-	-		
Study design	Investigator-initiated, prospective, multi-center, single-arm study	Prospective multicenter open-label single arm study	Prospective, multi-centre registry	Prospective multicenter open-label single arm study
Country	19 sites in Spain	2 sites in Poland	2 sites in Poland	5 sites in Poland

Author, **year**	**Alfonso 2017 [53] (RIBS VI)**	**Widimsky 2015 [83] Tousek 2016 [73] (Prague 19)**	**Iwanczyk 2017 [39]**	**Gil 2016 [79]**
Sponsor	Sociedad Española de Cardiología; Abott Vascular	Charles University Research program P 35 and UNCE 20410	nr	nr
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	Dual antiplatelet therapy was recommended for 1 year	Dual antiplatelet therapy for 12 months with prasugrel or ticagrelor	Daily dose of 75 mg ASS and 75 mg clopidogrel or prasugrel 60 mg p.o. Continued with 10 mg daily dose (n = 3; 1.8%) or ticagrelor 180 mg loading dose and continued with 2 × 90 mg daily dose (n = 121; 73.3%). Duration of dual antiplatelet therapy was recommended for a minimum of 12 months.	All patients received acetylsalicylic acid (75 mg/24 h) and clopidogrel (75 mg/24 h) at least 72 h before PCI. This dual antiplatelet therapy was planned for one year
Main inclusion criteria	• Patients with angina or objective evidence of ischemia; • In-stent restenosis (>50% diameter stenosis on visual assessment) • Target lesion (ø >2.5 mm; Maximumlength <32 mm)	• Consecutive patients with STEMI • STEMI duration <24 hours	• Patients with ACS; • At least 1 coronary artery stenosis (ø >2.3-<3.7 mm)	• Age ≥18 years and ≤65 years; • Stable coronary artery disease; • De novo coronary lesions
Primary endpoint	In-segment minimal lumen diameter at 6 and 9 months	Combination of death, myocardial infarction and TVR	nr	MACE (cardiac death, MI, and clinically-driven TLR)
Maximumfollow-up	12 months	mean 730 days (± 275)	12.4 months	12 months
Number of patients; (n)	141	114	165	139
Patients lost to follow-up, timepoint; n (%)	0	1 (0.9)	14 (8.5)	0
Mean age of patients (years)	65 (10)	60 (11)	59.9 (10.6)	59.5 (5.5)
Sex (% male)	89%	65%	75.1%	65.5%
Previous MI; n (%)	88 (62)	4/70 [a]	44 (26.7)	30 (21.6)
Stable angina; n (%)	72 (51)	0	0	139 (100)
Unstable angina; n (%)	69 (49)	0	95 (57.6)	0
STEMI; n (%)	0	114 (100)	26 (15.7)	0
NSTEMI; n (%)	0	0	45 (27.3)	0

Author, **year**	**Alfonso 2017 [53] (RIBS VI)**	**Widimsky 2015 [83] Tousek 2016 [73] (Prague 19)**	**Iwanczyk 2017 [39]**	**Gil 2016 [79]**
ACS; n (%)	-	114 (100)	165 (100)	0
Outcomes: Safety	**12 months follow-up**	**24 months follow-up**	**12 months follow-up**	**12 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	nr	0	0	1 (0.7)
Periprocedural mortality; n (%)	0	0	0	0
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	0	1 (0.9)	nr	0
ScT ≥1 year; n (%)	na	0 (after mean 730 days follow up)	na	na
Other SAEs; n (%)	All-cause mortality: 0 Cardiac mortality: 0 MACE: 20 (14.2)	All-cause mortality: 5 (4.4) (after mean 730 days follow up)	All-cause mortality: 4 (2.42)	MACE: 2 (1.4) All-cause mortality: 1 (0.7)

[a] Data reported in Widimsky 2015 [83] only for 70 patients

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation; TVR=target vessel revascularisation;

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	**Dudek 2014 [94]**	**Rzeszutko 2016 [48] (ORPKI Registry)**	**Briede 2018 [41]**	**Wöhrle 2018 [42] Nef 2017 [72] (GABI-R)**
Study-ID	-	-	-	NCT02066623
Study design	Prospective multicenter single arm registry	Prospective multicenter single arm registry	Prospective single center single arm registry	Prospective, observational, multi-centre study
Country	12 sites in Poland	151 sites in Poland	Latvia	92 sites in Germany and Austria

Author, **year**	**Dudek 2014 [94]**	**Rzeszutko 2016 [48] (ORPKI Registry)**	**Briede 2018 [41]**	**Wöhrle 2018 [42]** **Nef 2017 [72] (GABI-R)**
Sponsor	nr	No funding	National Research Program "Biomedicine for Public Health" (BIO-MEDICINE); grant from the corporation "Sistemu Inovacijas"	Abbott Vascular, Santa Clara, CA, USA
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	Dual antiplatelet therapy for 12 months according to the current ESC guidelines	nr	Dual antiplatelet therapy was prescribed at least for 12 months for all patients.	Dual antiplatelet therapy was prescribed for at least one year in all patients
Main inclusion criteria	• Consecutive patients with ACS (STEMI, NSTEMI or unstable angina)	• Patients with stable angina or ACS; • De novo lesion	• Patients with stable angina or ACS; • Target lesion (ø 2.5-4.0 mm)	• >18 years of age; • Absorb® BVS implant scheduled
Primary endpoint	MACE (cardiac death, MI, and clinically-driven TLR) at 12 months	nr	MACE (death, MI, cerebral infarction, CABG major bleeding, ScT, in-scaffold restenosis, TLR, TVR)	MACE (death, MI, clinically motivated TVR) MACCE (MACE + stroke) Stent thrombosis
Maximumfollow-up	12 months	Periprocedural	24 months	5 years
Number of patients; (n)	100	2258	187	3231
Patients lost to follow-up, timepoint; n (%)	2 (2)	0	7 (3.8)	86 (2.6)
Mean age of patients (years)	All: 62.7 (nr) [a]	59.97 (10.6)	56.74 (11.85)	60.9 (11.0)
Sex (% male)	73%	70.7%	78.6%	76.8%
Previous MI; n (%)	39 (39)	645 (28.6)	65 (34.8)	713 (22.4)
Stable angina; n (%)	0	1169 (52)	148 (79.1)	1075 (33.3)
Unstable angina; n (%)	46 (46)	562 (25)	11 (5.9)	379 (11.7)
STEMI; n (%)	16 (16)	256 (11.4)	18 (9.6)	560 (17.3)
NSTEMI; n (%)	38 (38)	260 (11.6)	6 (3.2)	724 (22.4)
ACS; n (%)	100 (100)	-	-	1663 (51.5)
Outcomes: Safety	**12 months follow-up**	**Periprocedural**	**24 months follow-up**	**6 months follow-up**

Author, **year**	**Dudek 2014 [94]**	**Rzeszutko 2016 [48] (ORPKI Registry)**	**Briede 2018 [41]**	**Wöhrle 2018 [42] Nef 2017 [72] (GABI-R)**
Vascular-access-site complication; n (%)	nr	2 (0.09)	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	2 (2)	0	0	8 (0.2)
Periprocedural mortality; n (%)	0	1 (0.04)	1 (0.5)	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	2 (1.1)	nr
Mortality as a result of bleeding and/or stroke; n (%)	0	nr	nr	nr
ScT ≥1 year; n (%)	na	na	0	na
Other SAEs; n (%)	MACE: 4 (4)	nr	All-cause mortality: 7 (3.9)	All-cause mortality: 40 (1.2) MACE: 131 (4.1)

[a] Mean age: 54.3 years (STEMI), 68.4 years (NSTEMI), 60.9 years (unstable angina)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; CABG=coronary artery bypass graft surgery; ESC=European Society of Cardiology; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; SAE=serious adverse event; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation; TVR=target vessel revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	**Cortese 2017a [55]**	**Cortese 2017b [63]**	**Anadol 2017 [40] Gori 2015 [85] Anadol 2018 [99] (MICAT Absorb Substudy)**	**Wiebe 2017 [203] Hoppmann 2016 [475] Wiebe 2016 [408] (ISAR-Absorb)**
Study-ID	-	-	NCT02180178	-
Study design	Prospective single-centre registry	Prospective multicentre single arm study	Prospective single-centre registry	Prospective multicentre single arm study
Country	Italy	6 or 7 sites in Europe	Germany	2 sites in Germany
Sponsor	nr	nr	Johannes Gutenberg University Mainz	nr

Author, **year**	**Cortese 2017a [55]**	**Cortese 2017b [63]**	**Anadol 2017 [40] Gori 2015 [85] Anadol 2018 [99] (MICAT Absorb Substudy)**	**Wiebe 2017 [203] Hoppmann 2016 [475] Wiebe 2016 [408] (ISAR-Absorb)**
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none
Anti-platelet therapy	During the procedure, patients received anticoagulation according to standard hospital practice. Glycoprotein IIb/IIIa inhibitors were used at the physician's discretion. All patients received dual antiplatelet therapy for at least 12 months after intervention.	All patients were treated according to international guidelines but following local practice. (Specifically, all patients were pretreated with aspirin (chronically or with endovenous bolus of 250–500 mg) plus clopidogrel or ticagrelor or prasugrel. During the procedure the anticoagulant of choice was unfractionated heparin given with a bolus of 70–100 IU/kg at the beginning of the procedure, with additional boluses given according to the activated clotting time.)	Dual antiplatelet therapy for 12 months (aspirin plus clopidogrel for stable disease; aspirin plus prasugrel/ticagrelor for acute coronary syndromes) was recommended.	All patients received a loading dose of aspirin and an adenosine diphosphate receptor antagonist according to the clinical presentation and guidelines, followed by aspirin indefinitely and 12 months of the selected adenosine diphosphate receptor antagonist
Main inclusion criteria	• Consecutive patients with all types of clinical settings and coronary lesions, including ACS, in-stent restenosis, small vessels, long lesions, and calcified vessels	• Consecutive patients with any clinical indication including stable angina or ACS treated with BVS for de novo lesions	• Consecutive patients treated with one or more Abott BVS®	• Consecutive patients with de novo lesions undergoing single-vessel or multivessel PCI with Absorb® BVS • Stenosis of at least 50% diameter stenosis • Angina symptoms and/or pathological functional testing
Primary endpoint	LLL at 1 year ID-TLR at 2 years	DOCE (cardiac death, MI or TLR)	MACE (death, cardiac death, MI or TLR)	MACE (death, MI or TLR)
Maximumfollow-up	24 months	7 months (± 2)	3 years	24 months
Number of patients; (n)	122	67	657	419
Patients lost to follow-up, timepoint; n (%)	nr	0	nr	0
Mean age of patients (years)	61.72 (10.38)	58 (11)	63 (12)	66.6 (10.9)
Sex (% male)	85.2%	nr	79.0%	76.6%
Previous MI; n (%)	nr	10 (15)	nr	109 (26.0)
Stable angina; n (%)	86 (70.5)	30 (44.8)	219 (33.3)	256 (61.1)
Unstable angina; n (%)	nr	10 (14.9)	78 (11.9)	48 (11.5)

Author, **year**	**Cortese 2017a [55]**	**Cortese 2017b [63]**	**Anadol 2017 [40] Gori 2015 [85] Anadol 2018 [99] (MICAT Absorb Substudy)**	**Wiebe 2017 [203] Hoppmann 2016 [475] Wiebe 2016 [408] (ISAR-Absorb)**
STEMI; n (%)	13 (10)	9 (13.5)	166 (25.3)	35 (8.4)
NSTEMI; n (%)	nr	18 (26.9)	191 (29.1)	80 (19.1)
ACS; n (%)	36 (29.5)	-	-	-
Outcomes: Safety	**24 months follow-up**	**7 months follow-up**	**3 years follow-up**	**24 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	nr	6 (8.9)	nr	4 (0.95)
Periprocedural mortality; n (%)	0	0	nr	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	0	nr	nr
ScT ≥1 year; n (%)	1	na	9 (1.7)	6 (1.4)
Other SAEs; n (%)	All-cause mortality: 1 (0.8) MACE: 23 (18.8)	All-cause mortality: 0 DOCE: 3 (4.5)	All-cause mortality: 43 (6.5)	All-cause mortality: 26 (6.3) MACE: 91 (21.6)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; DOCE=device-oriented composite endpoint; ID-TLR=ischaemic driven target lesion revascularisation; LLL=late lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	**Costa 2018 [105] Costa 2018 [44] Campos 2018 [46] Costa 2016 [66] Costa 2015 [86] Abizaid 2015 [92] (Absorb EXTEND)**	**Wöhrle 2015 [88] (ASSURE)**	**Tanaka 2017 [65]**	**Kawamoto 2015 [103]**
Study-ID	NCT01023789	NCT01583608	-	

Author, **year**	**Costa 2018 [105] Costa 2018 [44] Campos 2018 [46] Costa 2016 [66] Costa 2015 [86] Abizaid 2015 [92] (Absorb EXTEND)**	**Wöhrle 2015 [88] (ASSURE)**	**Tanaka 2017 [65]**	**Kawamoto 2015 [103]**
Study design	Prospective, single-arm, open-label clinical trial	Prospective multi-centre, observational registry	Uncontrolled cohort study	
Country	56 international sites outside USA	6 sites in Germany	Italy	
Sponsor	Abbott Vascular, Santa Clara, CA, USA	Medical Care Center Prof. Mathey, Prof. Schofer, Ltd. Abbott Vascular, Germany GmbH.	nr	
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	
Comparator/Product	none	none	none	
Anti-platelet therapy	All patients were to be pretreated with a loading dose of 300 mg of clopidogrel and 300 mg of aspirin, followed by 75 mg of clopidogrel daily for a minimum of 6 months and 75 mg of aspirin daily indefinitely.	All patients were maintained on 75 mg clopidogrel daily and 100 mg aspirin for a minimum of six months. Aspirin 100 mg daily was continued thereafter.	Dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor or prasugrel) for 12 months	
Main inclusion criteria	• ≥18 years of age; • Up to two de novo lesions, each located in a separate native epicardial vessel (ø 2.0-3.3 mm, Maximumlength = 28 mm) [a] • Stenosis: ≥50% and <100%	• Consecutive patients aged between 18 and 75 years with ischaemic heart disease • One or more de novo native coronary artery lesions (ø 2.0-3.8 mm) • Stenosis: ≥50%	• Patients undergoing percutaneous coronary intervention with bifurcation lesions	
Primary endpoint	MACE (cardiac death, MI or ID-TLR) at 7, 30, 180 and 360 days	MACE (cardiac death, MI or ID-TLR) at 24 months	Target lesion failure	MACE
Maximumfollow-up	3 years	24 months	24 months	12 months
Number of patients; (n)	812	183	264	119
Patients lost to follow-up, timepoint; n (%)	14 (1.7)	3 (1.6)	0	0
Mean age of patients (years)	61.1 (10.7)	63.5 (9.3)	63.5 (10.5)	62.5 (11.1)
Sex (% male)	74.3%	79.80%	236 (89.4)	106 (89.1)
Previous MI; n (%)	230 (29)	48 (27.1)	72 (27.3)	31 (26.1)
Stable angina; n (%)	461 (56.8)	65 (35.5)	228 (86.4)	105 (88.2)
Unstable angina; n (%)	215 (26.5)	39 (21.3)	31 (11.7)	12 (10.1)
STEMI; n (%)	nr	nr	STEMI or NSTEMI: 5 (1.9%)	2 (1.7)

Author, **year**	**Costa 2018 [105] Costa 2018 [44] Campos 2018 [46] Costa 2016 [66] Costa 2015 [86] Abizaid 2015 [92] (Absorb EXTEND)**	**Wöhrle 2015 [88] (ASSURE)**	**Tanaka 2017 [65]**	**Kawamoto 2015 [103]**
NSTEMI; n (%)	136 (16.7%)	nr		nr
ACS; n (%)	-	nr	36 (13.6)	14 (11.8)
Outcomes: Safety	**3 years follow-up**	**12 months follow-up**	**24 months follow-up**	**12 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	22 (2.7)	0	nr	15 (12.6)
Periprocedural mortality; n (%)	0	0	nr	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	8 (4.4)	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	1 (0.5)	nr	nr
ScT ≥1 year; n (%)	10 (1.2)	na	0	na
Other SAEs; n (%)	All-cause mortality: 7 (0.86) MACE: 74 (9.2) All SAE: 295 (36.3)	Stroke/TIA: 3 (1.7) MACE: 9 (5.0)	All-cause mortality: 7 (3.5)	All-cause mortality: 1 (1.4)

[a] Costa 2018 [105]: Inclusion criteria = reference vessel diameter (RVD) ≥2.0 mm and ≤3.8 mm

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; CA=California; ID-TLR=ischaemic driven target lesion revascularisation; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; RVD= reference vessel diameter; SAE=serious adverse event; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TIA=transient ischemic attack; USA=United States of America

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	**Moscarella 2015 [100]**	**Moscarella 2016 [75]**	**Maggio 2016 [77]**	**Regazzoli 2018 [36]**
Study-ID	-		-	-
Study design	Uncontrolled cohort study		Prospective, single center registry	Prospective multicenter registry

Author, **year**	**Moscarella 2015 [100]**	**Moscarella 2016 [75]**	**Maggio 2016 [77]**	**Regazzoli 2018 [36]**
Country	Italy		Italy	Italy, India
Sponsor	nr		nr	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Intervention/Product	Everolimus-eluting BRS/Absorb®		Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none		none	none
Anti-platelet therapy	Dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor or prasugrel) for at least 12 months		nr	Dual antiplatelet therapy (aspirin + clopidogrel) for 12 months; complex lesions aspirin + ticagrelor/prasugrel for 12 months
Main inclusion criteria	• Patients with either DES or BMS in-stent restenosis lesions		• Patients undergoing percutaneous coronary intervention (PCI) • ≥18 years of age	• Patients undergoing percutaneous coronary intervention (PCI)
Primary endpoint	Procedural success defined as the successful delivery and deployment of the BVS at the target lesion with less than 30% final residual stenosis and without in-hospital major adverse cardiac and/or cerebrovascular events	DOCE (cardiac death + target vessel myocardial infarction + target lesion revascularisation)	Major adverse cardiac events (MACE)	Target-lesion failure (TLF) and definite and probable scaffold thrombosis (ScT)
Maximumfollow-up	7 months	15 months	12 months	48 months
Number of patients; (n)	83	116	112	573
Patients lost to follow-up, timepoint; n (%)	0 (0)	0 (0)	12 (11.6)	0 (0)
Mean age of patients (years)	65.2 (10.0)	66.04 (10)	55.5 (12.4)	59.1 (11)
Sex (% male)	84.3%	84.5%	89.3%	89.9%
Previous MI; n (%)	51 (61.4)	71 (61.2)	5 (4.5)	112 (19.5)
Stable angina; n (%)	44 (53.0)	65 (56.0)	13 (11.6)	400 (69.8)
Unstable angina; n (%)	18 (21.7)	24 (20.7)	15 (13.4)	146 (25.5)
STEMI; n (%)	5 (6.0)	7 (6.0)	43 (38.4)	STEMI + NSTEMI: 27 (4.7)
NSTEMI; n (%)	16 (19.3)	20 (17.2)	31 (27.7)	
ACS; n (%)	39 (47.0)	51 (44.0)	89 (79.5)	173 (30.2)
Outcomes: Safety	**7 months follow-up**	**15 months follow-up**	**12 months follow-up**	**48 months follow-up**

Author, **year**	**Moscarella 2015 [100]**	**Moscarella 2016 [75]**	**Maggio 2016 [77]**	**Regazzoli 2018 [36]**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	6 (7.2)	nr	nr	nr
Periprocedural mortality; n (%)	nr	nr	nr	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	1 (1)	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	na	1 (0.8)	na	1 (0.2)
Other SAEs; n (%)	All-cause mortality: 2 (2.4)	All-cause mortality: 4 (3.4)	nr	All-cause mortality: 15 (4.4)

Abbreviations: ACS=acute coronary syndrome; BMS=bare metal stent; BRS=bioresorbable scaffold; DES=drug-eluting stent; DOCE=device-oriented composite endpoint; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; ScT=scaffold thrombosis; STEMI=ST-segment elevation myocardial infarction; TLF=target lesion failure

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, **year**	**Naganuma 2017 [54]**	**Azzalini 2016 [67]**	**Testa 2017 [57]**	**Ielasi 2017 [51]**
Study-ID	-	-	NCT02004730	NCT02601781
Study design	Cohort study	Multicenter registry	Multicenter, prospective registry	Multicenter, prospective registry
Country	Italy	5 international sites	Italy	Italy (22 sites)
Sponsor	no funding	nr	The Italian Society of Interventional Cardiology (SICI-GISE) has promoted this study. Abbott Vascular provided an unrestricted grant to SICI-GISE.	nr
Intervention/Product	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none	none	none	none

Author, **year**	**Naganuma 2017 [54]**	**Azzalini 2016 [67]**	**Testa 2017 [57]**	**Ielasi 2017 [51]**
Anti-platelet therapy	Dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor or prasugrel) for at least 12 months	nr	Aspirin + according to guideline; P2Y12 receptor antagonist was administered before the procedure or within one hour after the procedure	Aspirin indefinitely + clopidogrel or ticagrelor or prasugrel for at least 12 months
Main inclusion criteria	• Patients undergoing percutaneous coronary intervention (PCI) with non-left main bifurcation lesions	• Chronic total occlusion	• Patient must have indication to percutaneous coronary intervention for: multivessel disease (at least two significant stenoses in two different segments NOT as a bifurcation lesion; for patients with two vessel disease at least 1 lesion must be >24 mm and must be treated with the BVS; for patients with 3 vessel disease a hybrid approach is acceptable provided that 2 vessels are treated with BVS), • Long (>24 mm) single vessel disease following: Stable angina or evidence of myocardial ischemia with stress echocardiography/ myocardial SPECT/exercise test, or Unstable angina / non ST-elevation myocardial infarction ST-elevation myocardial infarction with de novo culprit lesion.	• Patients with STEMI (<75 years of age with symptom onset <12 h)
Primary endpoint	Target lesion failure	Target-vessel failure	The cumulative hierarchical incidence of major adverse cardiac events (MACE) defined as: cardiac death, non-fatal target vessel myocardial infarction, or clinically driven target lesion revascularisation.	A device oriented composite end-point of cardiac death, any myocardial infarction (STEMI or NSTEMI) clearly attributable to the intervention culprit vessel and ischemic driven TLR within 30 days after the index procedure
Maximumfollow-up	24 months	24 months	12 months	1 month
Number of patients; (n)	147	153	1002	505
Patients lost to follow-up, timepoint; n (%)	nr	0	46 (4.6)	0
Mean age of patients (years)	62.7 (10.6)	60.0 (9.3)	60 (10.4)	56.6 (9.4)

Author, **year**	**Naganuma 2017 [54]**	**Azzalini 2016 [67]**	**Testa 2017 [57]**	**Ielasi 2017 [51]**
Sex (% male)	89.8%	89.5%	85.1%	81.2%
Previous MI; n (%)	nr	50 (32.7)	208 (20.8)	22 (4.4)
Stable angina; n (%)	131 (89.1)	nr	267 (26.7)	0
Unstable angina; n (%)	14 (9.5)	nr	126 (12.6)	0
STEMI; n (%)	2 (1.4)	nr	218 (21.8)	505 (100)
NSTEMI; n (%)	0	nr	255 (25.5)	0
ACS; n (%)	16 (10.9)	14 (9.7)	599 (59.8)	505 (100)
Outcomes: Safety	**24 months follow-up**	**24 months follow-up**	**12 months follow-up**	**1 month follow-up**
Vascular-access-site complication; n (%)	nr	1 (0.7)	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	13 (8.8)	nr	28 (2.8)	1 (0.2)
Periprocedural mortality; n (%)	nr	nr	0	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	21 (2.1)	7 (1.4)
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	0	1 (0.7)	na	na
Other SAEs; n (%)	nr	nr	All-cause mortality: 12 (1.2) stroke: 2 (0.2)	All-cause mortality: 2 (0.4)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction;

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

	RAI registry			
Author, **year**	**Cortese 2017 [64]**	**Tarantini 2018 [45]**	**Tarantini 2018 [101]**	**Moscarella 2018 [43]**
Study-ID	NCT02298413			

Author, **year**	**RAI registry**			
	Cortese 2017 [64]	**Tarantini 2018 [45]**	**Tarantini 2018 [101]**	**Moscarella 2018 [43]**
Study design	Multicenter, prospective registry			
Country	Italy			
Sponsor	No funding			
Intervention/Product	Everolimus-eluting BRS/Absorb®			
Comparator/Product	none			
Anti-platelet therapy	Aspirin indefinitely + clopidogrel or ticagrelor or prasugrel for at least 12 months			
Main inclusion criteria	• Patients undergoing percutaneous coronary intervention (PCI) with stable or unstable coronary artery disease (including ST-elevation myocardial infarction)			
Primary endpoint	Target lesion revascularisation (TLR) Definite/probable device thrombosis			
Maximumfollow-up	unclear			
Number of patients; (n)	1505	1384	1384	317
Patients lost to follow-up, timepoint; n (%)	0	0	13 (0.9)	0
Mean age of patients (years)	59 (10.4)	58.5 (10)	58.4 (10.2)	55.5 (10.6)
Sex (% male)	82%	82.2%	82.2%	81%
Previous MI; n (%)	423 (28.1)	315 (22.8)	315 (22.8)	38 (12.0)
Stable angina; n (%)	610 (40.4)	320 (23.1)	438 (31.7)	na
Unstable angina; n (%)	210 (14)	186 (13.4)	186 (13.4)	na
STEMI; n (%)	317 (21)	328 (23.7)	337 (24.4)	317 (100)
NSTEMI; n (%)	364 (24.2)	341 (24.6)	339 (24.5)	na
ACS; n (%)	891 (59.2)	948 (68.5)	862 (62.3)	317 (100)
Outcomes: Safety	**unclear**	**21.6 months follow-up**	**12 months follow-up**	**12 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	nr	21 (1.5)	21 (1.5)	nr

Author, year	RAI registry			
	Cortese 2017 [64]	**Tarantini 2018 [45]**	**Tarantini 2018 [101]**	**Moscarella 2018 [43]**
Periprocedural mortality; n (%)	20 (1.3)	nr	nr	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	nr	4 (0.3)	4 (0.3)	nr
Other SAEs; n (%)	All-cause mortality: 2 (0.13)	All-cause mortality: 19 (1.4)	All-cause mortality: 13 (1.0)	All-cause mortality: 5 (1.6)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; MI=myocardial infarction; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TLR=target lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, year	RAI registry (continued)		Robaei 2016 [81] Robaei 2015 [87]
	Cortese 2015 [84]	**Ielasi 2015 [89]**	
Study-ID	NCT02298413		-
Study design	Multicenter, prospective registry		Multicenter, prospective registry
Country	Italy		Australia (2 sites)
Sponsor	No funding		Funding for the Absorb® BVSused in the registry was sourced internally.
Intervention/Product	Everolimus-eluting BRS/Absorb®		Everolimus-eluting BRS/Absorb®
Comparator/Product	none		none
Anti-platelet therapy	Aspirin indefinitely + clopidogrel or ticagrelor or prasugrel for at least 12 months		Dual antiplatelet therapy (aspirin + clopidogrel or ticagrelor or prasugrel)
Main inclusion criteria	• Patients undergoing percutaneous coronary intervention (PCI) with stable or unstable coronary artery disease (including ST-elevation myocardial infarction)		• Patients undergoing percutaneous coronary intervention (PCI)

Author, **year**	RAI registry (continued)		Robaei 2016 [81] Robaei 2015 [87]
	Cortese 2015 [84]	**Ielasi 2015 [89]**	
Primary endpoint	Cumulative occurrence of POCE (a composite of patient-oriented MACE, including death, MI, TLR) and device thrombosis at 6-month follow-up	Procedural success, defined as BVS implantation at the "culprit" lesion site with less than 30% final stenosis and TIMI 3 flow without in-hospital major adverse cardiovascular events (MACE: cardiac death, MI or need for emergent revascularisation)	nr
Maximumfollow-up	unclear		24 months
Number of patients; (n)	122	74	100
Patients lost to follow-up, timepoint; n (%)	0	6 (8.1)	1 (1)
Mean age of patients (years)	54 (48-60)	54.4 (10.5)	62.1 (12.4)
Sex (% male)	74.6%	78.4%	68%
Previous MI; n (%)	15 (12.3)	8 (10.8)	15 (15)
Stable angina; n (%)	na	na	56 (56)
Unstable angina; n (%)	na	na	25 (25)
STEMI; n (%)	122 (100)	74 (100)	4 (4)
NSTEMI; n (%)	na	na	15 (15)
ACS; n (%)	122 (100)	74 (100)	(44)
Outcomes: Safety	**6 months follow-up**	**6 months follow-up**	**24 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr
Periprocedural MI; n (%)	nr	nr	4 (4.0)
Periprocedural mortality; n (%)	nr	nr	0
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr
ScT ≥1 year; n (%)	na	na	1 (1.0)
Other SAEs; n (%)	All-cause mortality: 1 (0.8)	nr	All-cause mortality: 3 (3.0)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; POCE=patient-oriented composite endpoint; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TIMI=thrombolysis in myocardial infarction; TLR=target lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, year	CSI-Ulm-BVS		Hellenkamp 2017 [62]	Gori 2014 [95]
	Markovic 2017 [60]	Markovic 2016 [70]		
Study-ID	NCT02162056		-	-
Study design	Prospective single-center study, registry		Non-randomised observational registry study, single center	Non-randomised design, registry, single center
Country	Germany		Germany	Germany
Sponsor	Research grant from Abbott Wiesbaden, Germany		nr	Grant from the German Ministry of Education and Research
Intervention/Product	Everolimus-eluting BRS/Absorb®		Everolimus-eluting BRS/Absorb®	Everolimus-eluting BRS/Absorb®
Comparator/Product	none		none	none
Anti-platelet therapy	Stable coronary artery disease: aspirin plus clopidogrel(for 6 months). ACS: Prasugrel, ticagrelor, acetylsalicylic acid plus clopidogrel (12 months); triple therapy		nr	Dual antiplatelet therapy with aspirin 100 mg plus clopidogrel, prasugrel or ticagrelor for 12 months.
Main inclusion criteria	• Stable or unstable coronary artery disease including NSTEMI or STEMI • Patients had to be in a haemodynamically stable condition, with left ventricular ejection fraction of more than 30% with a life expectancy of at least 5 years		• Aged ≥18 years, who received at least one everolimus-eluting bioresorbable vascular scaffold (Absorb® BVS; Abbott Vascular) for treatment of coronary artery lesion.	• Culprit lesion in the setting of an acute coronary syndrome (lesions had to be de novo, in a native coronary artery with a reference vessel diameter compatible with the use of a 2.5, 3.0 or 3.5 mm BVS)
Primary endpoint	Cardiac death, MI not clearly related to a nontarget vessel and ischemia-driven target lesion revascularizirtion (TLR)		All-cause death and/or myocardial infarction (MACE)	Major adverse cardiac events (MACE) including death, non-fatal myocardial infarction (with or without ST-segment elevation), or need for revascularisation (target or non-target lesion/vessel, including planned staged revascularisations)
Maximumfollow-up	36 months		unclear	6 months
Number of patients; (n)	319	236	204	150

Author, **year**	**CSI-Ulm-BVS**		**Hellenkamp 2017 [62]**	**Gori 2014 [95]**
	Markovic 2017 [60]	**Markovic 2016 [70]**		
Patients lost to follow-up, timepoint; n (%)	20 (6.2)	nr	9 (4.4)	nr
Mean age of patients (years)	62.0 (10.7)	62.7 (9.9)	64.0 (10)	61.7 (12.5)
Sex (% male)	76.8%	78.4%	66.8%	73%
Previous MI; n (%)	nr	nr	nr	15 (10)
Stable angina; n (%)	180 (56.4)	132 (55.9)	49 (25.0)	na
Unstable angina; n (%)	nr	46 (19.5)	24 (12.2)	24 (16)
STEMI; n (%)	nr	16 (6.8)	63 (32.1)	66 (44)
NSTEMI; n (%)	nr	42 (17.8)	60 (30.6)	60 (40)
ACS; n (%)	139 (43.5)	104 (44.1)	147 (75.0%)	150 (100)
Outcomes: Safety	**36 months follow-up**	**12 months follow-up**	**median: 834 days follow-up**	**1 & 6 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	nr	21 (6.8)	nr	nr
Periprocedural mortality; n (%)	nr	nr	nr	nr
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr	nr	nr	nr
ScT ≥1 year; n (%)	2 (0.6)	0	nr	na
Other SAEs; n (%)	nr	Cardiac death: 0	All-cause mortality: 21 (10.8), Cardiac mortality: 17 (8.7)	All-cause mortality at 1 month:2 (1.4) Stroke: 0

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; TLR=taget lesion revascularisation

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, year	Absorb Cohort B			
	Serruys 2016 [78]	**Diletti 2013 [96]**	**Diletti 2011 [98] Nakatani 2015 [93]**	**Serruys 2011 [97]**
Study-ID	NCT00856856			
Study design	Multicenter, uncontrolled cohort study			
Country	Australia, Belgium, Denmark, France, Netherlands, New Zealand, Poland, Switzerland			
Sponsor	Abbott Vascular, Santa Clara, CA, USA			
Intervention/Product	Everolimus-eluting BRS/Absorb® revision 1.1			
Comparator/Product	none			
Anti-platelet therapy	Clopidogrel 75 mg daily for a minimum of 6 months, aspirin lifelong			
Main inclusion criteria	• ≥18 years, stable or unstable angina or silent ischaemia, lesions (maximum of two) in separate native coronary arteries with a visually estimated diameter of 3.0 mm, a length <14 mm and a diameter stenosis ≥50% and <100% • [major exclusion criteria: acute myocardial infarction, unstable arrhythmias, left ventricular ejection fraction <30%, restenosis, lesions located in the left main coronary artery]			
Primary endpoint	Ischemia-driven major adverse cardiac events (ID-TLR, MI, or cardiac death)			
Maximumfollow-up	5 years			
Number of patients; (n)	101			Cohort B2: 56
Patients lost to follow-up, timepoint; n (%)	At 5 years: 1			0
Mean age of patients (years)	62 (9)			60 (8)
Sex (% male)	72%			71%
Previous MI; n (%)	25 (25)			9 (16)
Stable angina; n (%)	nr			nr
Unstable angina; n (%)	15 (14.9)			
STEMI; n (%)	nr			
NSTEMI; n (%)	nr			
ACS; n (%)	nr			
Outcomes: Safety	**5 years follow-up**	**12 and/or 24 months follow-up**	**6 months follow-up**	**12 months follow-up**
Vascular-access-site complication; n (%)	nr	nr	nr	nr

Author, year	Absorb Cohort B			
	Serruys 2016 [78]	Diletti 2013 [96]	Diletti 2011 [98] Nakatani 2015 [93]	Serruys 2011 [97]
Procedure-related nephropathy; n (%)	nr	nr	nr	nr
Periprocedural MI; n (%)	2	nr	1 (1)	1 (1.8)
Periprocedural mortality; n (%)	60 months: 0	24 months: 0 (of 101 (B1+B2))	nr	0
Bleeding as a result of antiplatelet therapy; n (%)	nr	nr	nr	nr
Mortality as a result of bleeding and/or stroke; n (%)	60 months: 0	24 months: 0 (of 101 (B1+B2))	nr	0
ScT ≥1 year; n (%)	60 months: 0	24 months: 0 (of 101 (B1+B2))	na	nr
Other SAEs; n (%)	at 5 years: Cardiac mortality 0; All-cause mortality 3 (3.0)	All-cause mortality: 0 (24 months)	nr	nr

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; CA=California; ID-TLR=ischaemic driven target lesion revascularisation; MACE=major adverse cardiac events; MI=myocardial infarction; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction; USA=United States of America

Table A5: Characteristics of other relevant studies – Absorb® BVS (continued)

Author, year	Khamis 2016 [102]
Study-ID	-
Study design	Prospective, single-centre, single arm, open label study
Country	Egypt
Sponsor	nr
Intervention/Product	Everolimus-eluting BRS/Absorb®
Comparator/Product	none
Anti-platelet therapy	All patients received aspirin and clopidogrel as guidelines for DES
Main inclusion criteria	• ≥18 and ≤65 years of age • stable coronary artery disease • PCI for de novo coronary lesions

Author, year	Khamis 2016 [102]
Primary endpoint	MACE (cardiac death, MI or ID-TLR)
Maximumfollow-up	12 months
Number of patients; (n)	99
Patients lost to follow-up, timepoint; n (%)	0
Mean age of patients (years)	57.75 (9.6)
Sex (% male)	60.6%
Previous MI; n (%)	26 (26.2)
Stable angina; n (%)	99 (100)
Unstable angina; n (%)	0
STEMI; n (%)	0
NSTEMI; n (%)	0
ACS; n (%)	0
Outcomes: Safety	**12 months follow-up**
Vascular-access-site complication; n (%)	nr
Procedure-related nephropathy; n (%)	nr
Periprocedural MI; n (%)	0
Periprocedural mortality; n (%)	0
Bleeding as a result of antiplatelet therapy; n (%)	nr
Mortality as a result of bleeding and/or stroke; n (%)	nr
ScT ≥1 year; n (%)	na
Other SAEs; n (%)	MACE: 2 (2)

Abbreviations: ACS=acute coronary syndrome; BRS=bioresorbable scaffold; DES=drug-eluting stent; ID-TVR=ischaemic driven target vessel revascularisation; MACE=major adverse cardiac events; MI=myocardial infarction; na=not applicable; nr=not reported; NSTEMI=non-ST-segment elevation myocardial infarction; SAE=serious adverse event; STEMI=ST-segment elevation myocardial infarction

List of ongoing and planned studies

Table A6: List of ongoing controlled clinical trials with BRS for the treatment of cardiovascular indications (CAD)

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01844284	May 2019	RCT (non-inferiority)	400	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE PRIME®/XIENCE Xpedition™)	• At least 20 years of age. • Evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia) suitable for elective percutaneous coronary intervention (PCI). • Acceptable candidate for coronary artery bypass graft (CABG) surgery. • Able to take dual antiplatelet therapy for up to 1 year following the index procedure and anticoagulants prior/during the index procedure.	Primary: • Target Lesion Failure (TLF), non-inferiority against the active control [Time Frame: 12 months] Secondary: • Late Loss (LL) at 13 Months (Non-inferiority) [Time Frame: 13 months] • Change in average lumen diameter, between pre- and post-nitrate injection by angiography (superiority) [Time Frame: 3 years] • Change in average lumen area, from post-procedure to 3 years by IVUS (superiority) [Time Frame: 3 years] • Percentage of treated segments (in scaffold or in-stent) that show ACh induced vaso-dilatation by angiography. [Time Frame: 4 years]
NCT03234348	March 2019	RCT (non-inferiority)	151	Magnesium-based sirolimus-eluting BRS (Magmaris)	Biodegradable polymer sirolimus-eluting stent (Orsiro)	• At least 18 years of age. • ST-segment elevation Myocardial Infarction documented in an ambulance or in a Cathlab, with ≥2 mm ST segment elevation in at least two contiguous leads, presenting in the Cathlab <12 hours after the onset of symptoms lasting ≥20 min requiring primary PCI. • Target lesion must be a de-novo lesion located in a native vessel. • Vessel size should match available M-BRS scaffold sizes (≥2.75 mm, and ≤3.7 mm by visual assessment). • Lesion preparation by either manual thrombectomy or pre-dilatation has been successful, with opening of the vessel and TIMI ≥2 and residual stenosis <20%.	Primary: • In-stent/scaffold vasodilatory endothelium independent response [Time Frame: 12 months follow-up] Secondary: • Device success [Time Frame: Immediate after the procedure] • Procedure success [Time Frame: Up to 7 days] • Device-oriented Composite Endpoint (DOCE) [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Cardiac death [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Target vessel MI [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Clinically driven target lesion

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							revascularization [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Stent/scaffold thrombosis [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Patient oriented endpoint (POCE) [Time Frame: 1, 6 months, 1,2,3,4,5 years] • All-cause death [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Any repeat myocardial infarction [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Any revascularisation [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Target lesion revascularisation [Time Frame: 1, 6 months, 1,2,3,4,5 years] • Target vessel revascularisation [Time Frame: 1, 6 months, 1,2,3,4,5 years] • MLD [Time Frame: Baseline and 1 year follow-up] • %DS [Time Frame: Baseline and 1 year follow-up] • Acute gain [Time Frame: Baseline] • Late loss [Time Frame: 1 year] • Binary restenosis [Time Frame: 1 year] • Lumen area [Time Frame: 1 year follow-up] • Mean lumen volume [Time Frame: 1 year follow-up] • % strut malapposition [Time Frame: 1 year follow-up] • Tissue Prolapse [Time Frame: 1 year follow-up] • Neointimal hyperplasia [Time Frame: 1 year follow-up] • Healing index [Time Frame: 1 year follow-up] • Strut coverage [Time Frame: 1 year follow-up] • RUTTS [Time Frame: 1 year follow-

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							up]
NCT01923740	July 2019	RCT (non-inferiority)	480	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE V EECSS)	• At least 18 years of age • Evidence of myocardial ischemia (e.g., stable angina, unstable angina, post-infarct angina or silent ischemia) suitable for elective percutaneous coronary intervention (PCI). Subjects with stable angina or silent ischemia and <70% diameter stenosis must have objective sign of ischemia as determined by one of the following, echocardiogram, nuclear scan, ambulatory ECG or stress ECG. In the absence of noninvasive ischemia, fractional flow reserve must be done and indicative of ischemia. • Acceptable candidate for coronary artery bypass graft (CABG) surgery.	Primary: • In-segment Late Loss (LL) - Per Subject Analysis [Time Frame: At 1 year] • In-segment Late Loss (LL) - Per Lesion Analysis [Time Frame: At 1 year] Secondary: • Acute Device Success [Time Frame: <or = 1 day] • Number of Participants With Acute Procedural Success [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced Death (Cardiac, Vascular, Non-cardiovascular) [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants With Myocardial Infarction [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants With Target Lesion Revascularisation (TLR) [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants With Target Vessel Revascularisation (TVR) [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants With All Coronary Revascularisation (PCI and CABG) [Time Frame: up to 7 days in

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							hospital, 3-37days, 0-208days, 0.393days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced Death/All MI [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced Cardiac Death/All MI [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced All Death/All MI/All Revascularisation [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced Cardiac Death/TV-MI/ID-TLR [Target Lesion Failure (TLF)] [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants Experienced Cardiac Death/All MI/ID-TVR [Target Vessel Failure (TVF)] [Time Frame: up to 7 days in hospital, 3-37days, 0-208days, 0.393days, 0-758 days, 0-1123days, 4 years, 5 years] • Number of Participants Experienced Cardiac Death/All MI/ID-TLR (Major Adverse Cardiac Event [MACE]) [Time Frame: up to 7 days in hospital, 3-37 days, 0-208 days, 0-393 days, 0-758 days, 0-1123 days, 4 years, 5 years] • Number of Participants With Stent/Scaffold Thrombosis (Per Academic Research Consortium Definition)

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT01751906	September 2021	RCT (non-inferiority)	2008	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro and XIENCE ProX)	• 18 years of age. • Evidence of myocardial ischemia. In the absence of noninvasive ischemia, fractional flow reserve must be done and indicative of ischemia. • Acceptable candidate for coronary artery bypass graft (CABG) surgery.	Primary: • Number of Participants With Cardiac Death/TV-MI/ID-TLR (TLF) [Time Frame: 1 year] Secondary: • Acute Success- Device Success (Lesion Level Analysis) [Time Frame: On day 0 (the day of procedure)] • Acute Success: Procedural Success (Subject Level Analysis) [Time Frame: On day 0 (the day of procedure)] • Number of Participants With Powered Secondary Endpoint: Angina [Time Frame: 1 yea] • Number of Participants With Powered Secondary Endpoint: All Revascularisation [Time Frame: 1 year] • Number of Participants With Powered Secondary Endpoint: Ischemia Driven Target Vessel Revascularisation (ID-TVR) [Time Frame: 1 year] • Number of Participants With Death (Cardiac, Vascular, Non-cardiovascular) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With All Myocardial Infarction (MI) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With All Target Lesion Revascularisation (TLR) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With All

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							Target Vessel Revascularisation (TVR) Excluding Target Lesion Revascularisation (TLR) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With All Revascularisation [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Death/All MI [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Cardiac Death/All MI [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Cardiac Death/TV-MI/ID-TLR (TLF) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Cardiac Death/All MI/ID-TLR (Major Adverse Cardiac Events-MACE) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Target Vessel Failure (TVF) [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5 years] • Number of Participants With Death/All MI/All Revascularisation [Time Frame: up to 7 days in hospital, 0-30 days, 0-180 days, 0-1 year, 2 years, 3 years, 4 years, 5

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							years] • Number of Participants With Scaffold/Stent Thrombosis (Per ARC Definition)
NCT01858077	December 2020	RCT (non-inferiority)	1845	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE PRIME®/XIENCE Xpedition™)	• 18 Years and older • Subject is an acceptable candidate for treatment with a drug-eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the ABSORB® BVS strategy and XIENCE family.	Primary: • Target Vessel Failure (TVF) [Time Frame: 2 years] Secondary: • Device success [Time Frame: 1 day] • Procedural success [Time Frame: 1 day] • Target vessel failure (TVF) [Time Frame: 30 days, and 1, 3, 4 and 5 years] • Target lesion failure [Time Frame: 30 days, and 1, 2, 3, 4 and 5 years] • All revascularisations [Time Frame: 5 year] • All-cause mortality [Time Frame: 30 days, 1 year, 2, 3, 4 and 5 years] • Myocardial Infarction [Time Frame: 30 days, 1, 2, 3, 4 and 5 years] • Target Lesion Revascularisation (TLR) [Time Frame: 30 days, 1 year, 2, 3, 4 and 5 years] • Target Vessel Revascularisation (TVR) [Time Frame: 30 days, 1 year, 2, 3, 4 and 5 years] • Non-Target Vessel Revascularisation [Time Frame: 30 days, 1 year, 2, 3, 4 and 5 years] • Scaffold/Stent Thrombosis [Time Frame: 30 days, 1, 2, 3, 4 and 5 years] • Seattle Angina Questionnaire [Time Frame: 1 year and 2 years] • Quality of Life Questionnaire [Time Frame: 1 year and 2 years]
NCT02796157	May 2019	RCT	950	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE EES)	• Age 19-85 years • Patients with ischemic heart disease requiring PCI	Primary: • Incidence of composite of major adverse cardiovascular events [Time

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						• Significant coronary de novo lesion (stenosis >50% by quantitative angiographic analysis) requiring stent ≥28 mm in length based on angiographic estimation • Reference vessel diameter of 2.5 to 3.75 mm by operator assessment	Frame: 1 year after PCI] Secondary: • Not reported
NCT02173379	April 2024	RCT (non-inferiority)	2610	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE V, XIENCE PRIME, XIENCE Xpedition, XIENCE Alpine, XIENCE Pro and XIENCE ProX)	• At least 18 years of age. • Evidence of myocardial ischemia (e.g., silent ischemia, stable or unstable angina, non-ST-segment elevation MI (NSTEMI), OR recent ST-segment elevation MI (STEMI). Patients with stable coronary syndromes can be enrolled any time after symptom onset if eligibility criteria are otherwise met. Patients with acute coronary syndrome can be enrolled under the following conditions: ○ Unstable angina or NSTEMI within 2 weeks of the index procedure. ○ STEMI >72 hours ≤2 weeks prior to the index procedure. • Suitable for PCI. Subjects with stable angina or silent ischemia and <70% diameter stenosis must have objective signs of ischemia as determined by one of the following: abnormal stress echocardiogram, nuclear scan, electrocardiogram, positron emission tomography, magnetic resonance imaging, and/or fractional flow reserve. • Subject must be an acceptable candidate for coronary artery bypass graft (CABG) surgery. • Treatment of up to three de novo lesions in a maximum of two epicardial vessels, with a maximum of two lesions per epicardial vessel. If only a single lesion is to be treated, it must be a target lesion. Up to one non-target lesion can be treated. Non-target lesion treatment can occur only in a non-target vessel.	Primary: • Number of Participants With Target Lesion Failure (TLF) [Time Frame: 30 days] Secondary: • Powered TLF, Tested for Non-inferiority of Absorb® BVS to XIENCE [Time Frame: 1 year] • Number of Participants With Powered Angina [Time Frame: 30 days] • Percentage of Target Lesion With Acute Success- Device Success (Lesion Level Analysis) [Time Frame: In-hospital (≤7days)] • Number of Participants With Acute Success- Procedural Success (Subject Level Analysis) [Time Frame: In-hospital (≤7days)] • Number of Participants Experienced Death (Cardiac, Vascular, Non-cardiovascular) [Time Frame: In-hospital (≤7 days post index procedure), 30 days, 90 days, 180 days, 270 days, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years] • Number of Participants With Myocardial Infarction (MI) [Time Frame: In-hospital (≤7 days post index procedure), 30 days, 90 days, 180 days, 270 days, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years] • Number of Participants With Target

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						• Target lesion(s) must be located in a native coronary artery with a visually estimated or quantitatively assessed %DS of ≥50% and <100%, with a thrombolysis in myocardial infarction (TIMI) flow of ≥1, and one of the following: stenosis ≥70%, an abnormal functional test (e.g., fractional flow reserve ≤0.80 AND/OR a positive stress test), or presentation with an acute coronary syndrome (unstable angina or NSTEMI within 2 weeks of index procedure, or STEMI >72 hours but ≤2 weeks prior to the index procedure). ○ Target lesion(s) must be located in a native coronary artery with reference vessel diameter (RVD) by visual estimation of ≥2.50 mm and ≤3.75 mm. ○ Target lesion(s) must be located in a native coronary artery with length by visual estimation of ≤24 mm.	Lesion Revascularisation (TLR) [Time Frame: In-hospital (≤7 days post index procedure), 30 days, 90 days, 180 days, 270 days, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years] • Number of Participants With Target Vessel Revascularisation (TVR) [Time Frame: In-hospital (≤7 days post index procedure), 30 days, 90 days, 180 days, 270 days, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years] • + over 100 additional secondary endpoints
NCT03076476	December 2018	RCT	50	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE EES)	• Age >18 years, <75 years. • Lesion suitability for BVS deployment: target vessel calibre >2.3mm and <3.8mm reference diameter, without significant tortuosity or calcification. • Listed for single-vessel PCI procedure. • Lesion length≤28mm (to accommodate single BVS/DES) • Preserved left ventricular ejection fraction (EF≥50%).	Primary: • Change in IMR between baseline and post-stent/scaffold implantation. [Time Frame: During procedure] • Change in CFR between baseline and post-stent/scaffold implantation. [Time Frame: During procedure] Secondary: • Incidence of troponin elevation post-PCI (MI4a). [Time Frame: Measured 6 hours after stent insertion] • Changes in IMR between baseline, post-implant and subsequent timepoints in sub randomised group. [Time Frame: 3 months follow up] • Incidence of post-PCI angina and quality of life by standardised Seattle angina questionnaire at telephone follow-up. [Time Frame: Up to 12 months] • Incidence of stent & scaffold expansion & malapposition adjudged

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
							by strut-level OCT analysis. [Time Frame: During index procedure and at 3 month follow up] • Incidence of stent/scaffold strut coverage/endothelialisation adjudged by strut-level OCT analysis. [Time Frame: During index procedure and at 3 month follow up] • Nature/phenotype of underlying target lesion plaque by OCT analysis. [Time Frame: During index procedure and at 3 month follow up] • Adverse events [Time Frame: At time points 1, 3, 6 & 12 months post-PCI] • Serious adverse events [Time Frame: At time points 1, 3, 6 & 12 months post-PCI]
NCT01942070	March 2019	RCT (non-inferiority)	262	Everolimus-eluting BRS (Absorb™ BVS)	Everolimus-eluting permanent metal stent (XIENCE EES)	• 18 years or older with acute ST-elevation myocardial infarction or non ST-elevation myocardial infarction with angiographically confirmed thrombus • Planned stent implantation in de novo lesions in native vessels or coronary bypass grafts with reference vessel diameter ≥2.5 mm and ≤3.9 mm	Primary: • Percentage Diameter Stenosis [Time Frame: 6-8 months] Secondary : • Device-oriented composite endpoint [Time Frame: 12 months] • Patient-oriented composite endpoint [Time Frame: 12 months] • Composite of death or MI [Time Frame: 12 months] • Stent thrombosis [Time Frame: 12 months]
NCT02171065	June 2020	Multicentre Prospective Natural History Study combined with a RCT	902	Everolimus-eluting BRS (Absorb™ BVS)	Sham device	• Troponin positive ACS (STEMI >12 h or NSTEMI) occurring within the prior 2 weeks of enrollment, with symptoms consistent with acute ischemia lasting >10 minutes, intended for angiography and Percutaneous Coronary Intervention (PCI) if appropriate. • Patient must have one-vessel, two-vessel or three-vessel disease in native coronary arteries requiring PCI. • Successful PCI Additional for RCT:	Primary: • Patient level non-culprit lesion related Non-Culprit Major Adverse Cardiac Event through 2 years adjudicated to an originally untreated non-culprit lesion [Time Frame: 2 years]

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						• The lesion has an angiographic diameter stenosis <70%, and is not intended for revascularisation based on angiographic criteria and Fractional Flow Reserve/Instantaneous wave-free ratio. • The lesion has a site-determined IVUS plaque burden in at least one frame ≥70%. Note: Such a lesion may or may not be angiographically evident; i.e., the visually estimated angiographic diameter stenosis may range between 0% - <70%. • The reference vessel diameter of an eligible lesion is ≥2.5 mm - ≤4.0 mm (visually estimated) capable of being treated with a 2.5 mm, 3.0 mm, or 3.5 mm diameter BVS. • The lesion length of an eligible lesion is ≤50 mm (visually estimated), capable of being treated by no more than two BVS (maximum length of each BVS 28 mm), allowing for 2 mm BVS overlap and 2 mm of "normal" reference segment treatment at each edge. • The lesion must be at least 10 mm from a previously implanted stent/scaffold and an intervening 10 mm segment must not have plaque burden (PB) >50% • A bifurcation lesion may be enrolled only if the side branch is a) ≤2.5 mm in reference vessel diameter, AND b) has either no lesion requiring treatment, or atherosclerotic disease limited to within 5 mm of its origin from the parent vessel such that the operator believes that the side branch can be successfully treated with balloon angioplasty only (without a stent). If a stent subsequently becomes necessary, only a permanent metallic drug-eluting stent (DES; XIENCE	

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						strongly recommended) may be used to treat the side branch with a T-stent technique.	

Abbreviations: ACS=acute coronary syndrome; ARC=Academic Research Consortium; BRS=bioresorbable scaffold; BVS=bioresorbable vascular scaffold; CABG=coronary artery bypass graft surgery; CFR=coronary flow reserve; DOCE=device-oriented composite endpoint; ECG=electrocardiography; EES=everolimus-eluting stent; EF=ejection fraction; ID-TLR=ischaemic driven target lesion revascularisation; ID-TVR=ischaemic driven target vessel revascularisation; IMR=index of microvascular resistance; IVUS=intravascular ultrasound; LL=lumen loss; MACE=major adverse cardiac events; MI=myocardial infarction; MLD=minimum lumen diameter; NSTEMI=non-ST-segment elevation myocardial infarction; OCT=optical coherence tomography; PCI=percutaneous coronary intervention; RCT=randomised controlled trial; RUTTS=ratio of uncovered to total stent struts per cross-section score; STEMI=ST-segment elevation myocardial infarction; TIMI=thrombolysis in myocardial infarction; TLF=target lesion failure; TLR=target lesion revascularisation; TVF=target vessel failure; TVR=target vessel revascularisation

Sources: ClinicalTrials.gov; WHO-ICTRP (http://www.who.int/ictrp/en/)

Risk of bias tables

Table A7: Risk of bias – study level (RCTs) – Absorb® BVS

Trial	Random sequence generation	Allocation concealment	Blinding of		Selective outcome reporting	Incomplete outcome data (short-term, long-term)
			Participants	Medicinal personnel		
Absorb II	Low	Low	Low	High[a]	Low	Low
Absorb III	Low	Low	Low	Low[b]	Low	Low
Absorb China	Low	Low	High[a]	High[a]	Low	Low
Absorb Japan	Low	Low	Low	Low[c]	Low	Low
AIDA	Low	Low	Low	High[a]	Low	Low
Trofi II	Low	Low	Low	High[a]	Low	Low
Everbio II	Low	Low	High[a]	High[a]	Low	Low
Hernandez	Unclear[d]	Unclear[e]	Unclear[f]	Unclear[f]	Low	Low

Comments:

[a] Not blinded
[b] Investigators doing the procedure not blinded; follow-up personnel were unaware of study-group assignments
[c] blinded site personnel were assigned to conduct scheduled clinical follow-up
[d] Method of randomization not described
[e] Method of allocation concealment not described
[f] No information about blinding

Sources: [17-34]

Table A8: Risk of bias – outcome level (RCTs) – Absorb® BVS

Outcome Trial	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
All-cause mortality					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low

Outcome Trial	**Blinding – outcome assessors**	**ITT principle adequately realised**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
Cardiac mortality					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low
Hernandez	Unclear	Low	Low	Low	Unclear
Angina					
Absorb II	Low	High[a]	Low	Low	High
Absorb III	Low	High[b]	Low	Low	High
Trofi II	Low	Unclear	Low	Low	Unclear
Myocardial infarction					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low
Hernandez	Unclear	Low	Low	Low	Unclear
MACE					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low
TVR					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low
Hernandez	Unclear	Low	Low	Low	Unclear

Outcome Trial	**Blinding – outcome assessors**	**ITT principle adequately realised**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
TLR					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low
Hernandez	Unclear	Low	Low	Low	Unclear
Quality of Life					
Absorb II	Low	High[a]	Low	Low	High
Absorb III	Low	High[b]	Low	Low	High
Daily Functioning					
Absorb II	Low	High[a]	Low	Low	High
Duration of Procedure					
Absorb III	High[c]	Low	Low	Low	High
Absorb Japan	High[c]	Low	Low	Low	High
AIDA	High[c]	Low	Low	Low	High
Peri-procedural MI					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Hernandez	Unclear	Low	High[d]	Low	High
Peri-procedural mortality					
Absorb China	Low	Low	Low	Low	Low
Trofi II	Low	Low	Low	Low	Low
Very late scaffold thrombosis (≥1 year)					
Absorb II	Low	Low	Low	Low	Low
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Absorb Japan	Low	Low	Low	Low	Low
AIDA	Low	Low	Low	Low	Low
Everbio II	Low	Low	Low	Low	Low

Outcome Trial	**Blinding – outcome assessors**	**ITT principle adequately realised**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
All Serious Adverse Events					
Absorb III	Low	Low	Low	Low	Low
Absorb China	Low	Low	Low	Low	Low
Comments: [a] only patients with 3 year clinical follow-up analysed [b] only patients with 1 year clinical follow-up analysed [c] Investigators doing the procedure not blinded [d] only reported, that rates are not significant different					

Abbreviations: ITT=intention to treat

Sources: [17-34]

Table A9: Risk of bias – single-arm studies – DESolve® and Fantom® (IHE 20-Criteria checklist)

Study	Gunes 2017 [61]	Abizaid 2016 [76] (DESolve Nx)	Nef 2018 [37] (DESolve PMCF)	Abizaid 2017 [52] (Fantom II)
Study objective				
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	partially
Study population				
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	no	yes	yes	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	unclear
5. Were participants recruited consecutively?	unclear	unclear	unclear	unclear
6. Did participants enter the study at similar point in the disease?	no	no	no	unclear
Intervention and co-intervention				
7. Was the intervention clearly described in the study?	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	yes
Outcome measures				
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na
Statistical Analysis				
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes
Results and Conclusions				
13. Was the length of follow-up reported?	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	no	no	no	no
16. Are adverse events reported?	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes
Competing interest and source of support				
18. Are both competing interest and source of support for the study reported?	no	yes	yes	yes
Overall Risk of bias	moderate	moderate	moderate	moderate

Abbreviations: na=not applicable

Table A10: Risk of bias – single-arm studies – Magmaris (Dreams 2G) (IHE 20-Criteria checklist)

Study	Haude 2016 [58] Haude 2016 [82] Haude 2018 [35] Haude 2017 [56] (Biosolve II)	7 Haude 2018 [35] Haude 2017 [56] (Biosolve III)
Study objective		
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes
Study population		
2. Are the characteristics of the participants included in the study described?	yes	yes
3. Were the cases collected in more than one centre?	yes	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes
5. Were participants recruited consecutively?	unclear	unclear
6. Did participants enter the study at similar point in the disease?	no	no
Intervention and co-intervention		
7. Was the intervention clearly described in the study?	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes
Outcome measures		
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes
11. Were outcomes measured before and after intervention?	na	na
Statistical Analysis		
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes
Results and Conclusions		
13. Was the length of follow-up reported?	yes	yes
14. Was the loss to follow-up reported?	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	no	no
16. Are adverse events reported?	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes
Competing interest and source of support		
18. Are both competing interest and source of support for the study reported?	yes	yes
Overall Risk of bias	moderate	moderate

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (IHE 20-Criteria checklist)

Study	Fam 2016 [72]	Maes 2018 [38]	Costopoulos 2014 [91]	Panolas 2016 [69]	Tanaka 2017 [65] Kawamoto 2015 [103]	Moscarella 2015 [100] Moscarella 2016 [75]
Study objective						
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	no	yes	yes	yes	yes	yes
Study population						
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	no	no	yes	no	no	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes	yes	yes
5. Were participants recruited consecutively?	unclear	yes	yes	yes	unclear	yes
6. Did participants enter the study at similar point in the disease?	yes	no	no	yes	no	no
Intervention and co-intervention						
7. Was the intervention clearly described in the study?	yes	yes	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	yes	yes	yes
Outcome measures						
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na	na
Statistical Analysis						
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes
Results and Conclusions						
13. Was the length of follow-up reported?	yes	yes	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	no	no	no	no	no
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes
Competing interest and source of support						
18. Are both competing interest and source of support for the study reported?	yes	yes	no	no	yes	no
Overall Risk of bias	moderate	low	low	low	moderate	low

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Maggio 2016 [77]	Regazzoli 2018 [36]	Naganuma 2017 [54]	Azzalini 2016 [67]	Testa 2017 [57]	Ielasi 2017 [51]
Study objective						
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes	yes
Study population						
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	no	yes	yes	yes	yes	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes	yes	yes
5. Were participants recruited consecutively?	yes	yes	unclear	yes	unclear	unclear
6. Did participants enter the study at similar point in the disease?	no	no	no	no	no	no
Intervention and co-intervention						
7. Was the intervention clearly described in the study?	yes	yes	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	yes	yes	yes
Outcome measures						
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na	na
Statistical Analysis						
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes
Results and Conclusions						
13. Was the length of follow-up reported?	yes	yes	yes	yes	yes	yes
14. Was the loss to follow-up reported?	no	no	no	no	no	no
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes
Competing interest and source of support						
18. Are both competing interest and source of support for the study reported?	no	yes	yes	no	yes	no
Overall Risk of bias	low	low	moderate	low	moderate	moderate

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	RAI registry					
	Moscarella 2017 [43]	Tarantini 2018 [45]	Tarantini 2018 [101]	Cortese 2017 [64]	Cortese 2015 [84]	Ielasi 2015 [89]
Study objective						
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes	yes
Study population						
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	yes	yes	yes	yes	yes	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes	yes	yes
5. Were participants recruited consecutively?	unclear	unclear	yes	yes	yes	unclear
6. Did participants enter the study at similar point in the disease?	no	yes	no	no	yes	yes
Intervention and co-intervention						
7. Was the intervention clearly described in the study?	yes	yes	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	yes	yes	yes
Outcome measures						
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na	na
Statistical Analysis						
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes
Results and Conclusions						
13. Was the length of follow-up reported?	yes	no	yes	no	yes	yes
14. Was the loss to follow-up reported?	no	no	yes	no	no	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes
Competing interest and source of support						
18. Are both competing interest and source of support for the study reported?	no	yes	yes	yes	yes	yes
Overall Risk of bias	moderate	moderate	low	low	low	moderate

Abbreviations: na: not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Robaei 2016 [81] Robaei 2015 [87]	Markovic 2017 [60] Markovic 2016 [70]	Hellenkamp 2017 [62]	Gori 2014 [95]	Teeuwen 2015 [104]
Study objective					
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes
Study population					
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	yes	no	no	no	no
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes	partially
5. Were participants recruited consecutively?	yes	unclear	yes	yes	unclear
6. Did participants enter the study at similar point in the disease?	no	no	no	no	no
Intervention and co-intervention					
7. Was the intervention clearly described in the study?	yes	yes	yes	yes	no
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	no	no	yes	yes
Outcome measures					
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na
Statistical Analysis					
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes
Results and Conclusions					
13. Was the length of follow-up reported?	yes	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes
Competing interest and source of support					
18. Are both competing interest and source of support for the study reported?	yes	yes	no	no	no
Overall Risk of bias	low	moderate	moderate	low	moderate

Abbreviations: na: not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Absorb B Diletti 2011 [98] Nakatani 2015 [93] Serruys 2011 [97] Diletti 2013 [96] Serruys 2016 [78]	Jamshidi 2016 [74]	Grimfjard 2017 [50] (SCAAR)	Widimsky 2015 [83] Tousek 2016 [73] (Prague 19)	Iwanczyk 2017 [39]	Gil 2016 [79]
Study objective						
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes	yes
Study population						
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	partially	yes	yes
3. Were the cases collected in more than one centre?	yes	no	yes	yes	yes	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	partially	partially	yes	yes	yes
5. Were participants recruited consecutively?	unclear	unclear	unclear	yes	unclear	unclear
6. Did participants enter the study at similar point in the disease?	no	no	no	yes	no	no
Intervention and co-intervention						
7. Was the intervention clearly described in the study?	yes	yes	no	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	no	yes	yes	yes
Outcome measures						
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	partially	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na	na
Statistical Analysis						
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes
Results and Conclusions						

13. Was the length of follow-up reported?	yes	yes	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes
Competing interest and source of support						
18. Are both competing interest and source of support for the study reported?	yes	no	no	yes	partially	partially
Overall Risk of bias	moderate	high	high	low	low	low

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Felix 2016 [68] (BVS Expand)	Kraak 2015 [90]	Remkes 2017 [47]	Alfonso 2017 [53] (RIBS VI)	Cortese 2017a [55]	Cortese 2017b [63]	Anadol 2017 [40] Gori 2015 [85] Anadol 2018 [99] (MI-CAT Absorb Substudy)
Study objective							
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes	yes	yes
Study population							
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	no	no	no	yes	no	yes	no
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	partially	partially	yes	partially	no	no
5. Were participants recruited consecutively?	unclear	yes	yes	unclear	yes	yes	yes
6. Did participants enter the study at similar point in the disease?	no	no	no	no	no	no	no
Intervention and co-intervention							
7. Was the intervention clearly described in the study?	yes	yes	yes	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	partially	partially	partially	yes	yes	partially
Outcome measures							
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes	yes	yes

10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na	na	na	na
Statistical Analysis							
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes	yes
Results and Conclusions							
13. Was the length of follow-up reported?	yes	yes	yes	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes	no	yes	no
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes	yes
Competing interest and source of support							
18. Are both competing interest and source of support for the study reported?	yes	yes	partially	yes	partially	partially	yes
Overall Risk of bias	low	moderate	moderate	low	moderate	moderate	moderate

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Dudek 2014 [94]	Rzeszutko 2016 [48] (ORPKI Registry)	Briede 2018 [41]	Wöhrle 2018 [42] Nef 2017 [72] (GABI-R)
Study objective				
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes
Study population				
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	yes
3. Were the cases collected in more than one centre?	yes	yes	no	yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	partially	partially	yes	partially
5. Were participants recruited consecutively?	yes	yes	no	yes
6. Did participants enter the study at similar point in the disease?	no	no	no	no
Intervention and co-intervention				
7. Was the intervention clearly described in the study?	partially	no	no	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	partially	no	partially	yes

Outcome measures				
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	no	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	unclear	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na
Statistical Analysis				
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	unclear	yes
Results and Conclusions				
13. Was the length of follow-up reported?	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes
Competing interest and source of support				
18. Are both competing interest and source of support for the study reported?	no	yes	yes	yes
Overall Risk of bias	high	high	moderate	low

Abbreviations: na=not applicable

Table A11: Risk of bias – single-arm studies – Absorb® BVS (continued) (IHE 20-Criteria checklist)

Study	Wiebe 2017 [59] Hoppmann 2016 [80] Wiebe 2016 [71] (ISAR-Absorb)	Costa 2018 [105] Costa 2018 [44] Campos 2018 [46] Costa 2016 [66] Costa 2015 [86] Abizaid 2015 [92] (Absorb EXTEND)	Wöhrle 2015 [88] (ASSURE)	Khamis 2016 [102]
Study objective				
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes
Study population				
2. Are the characteristics of the participants included in the study described?	yes	yes	yes	partially
3. Were the cases collected in more than one centre?	yes	yes	yes	no
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes
5. Were participants recruited consecutively?	yes	no	yes	unclear

6. Did participants enter the study at similar point in the disease?	no	no	no	yes
Intervention and co-intervention				
7. Was the intervention clearly described in the study?	yes	yes	yes	yes
8. Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	partially
Outcome measures				
9. Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes
11. Were outcomes measured before and after intervention?	na	na	na	na
Statistical Analysis				
12. Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes
Results and Conclusions				
13. Was the length of follow-up reported?	yes	yes	yes	yes
14. Was the loss to follow-up reported?	yes	yes	yes	yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	yes	yes	yes	yes
16. Are adverse events reported?	partially	partially	partially	partially
17. Are the conclusions of the study supported by results?	yes	yes	yes	yes
Competing interest and source of support				
18. Are both competing interest and source of support for the study reported?	partially	yes	yes	partially
Overall Risk of bias	low	low	low	moderate

Abbreviations: na=not applicable

Table A12: GRADE assessment of Absorb® BVS (critical endpoints)

Quality assessment							Summary of findings				
							Number of patients	Effect			Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations		Relative (95% CI)	Absolute (95% CI)		
									Absorb® BVS	DES	
All-cause mortality (2 to 4 years follow-up)											
7	RCTs	Not serious	Not serious	Not serious	Serious[a]	No	5645	RR 0.84 (0.63 to 1.11)	32 per 1000 (24 to 43)	38 per 1000	⊕⊕⊕⊙ moderate
All-cause mortality (≥3 years follow-up)											
5	RCTs	Not serious	Not serious	Not serious	Serious[a]	No	5001	RR 0.82 (0.62 to 1.10)	34 per 1000 (26 to 46)	41 per 1000	⊕⊕⊕⊙ moderate
Cardiac mortality (6 months to 4 years follow-up)											
8	RCTs	Not serious	Not serious	Not serious	Serious[a]	No	5830	RR 0.91 (0.60 to 1.39)	15 per 1000 (10 to 23)	16 per 1000	⊕⊕⊕⊙ moderate
Cardiac mortality (≥3 years follow-up)											
5	RCTs	Not serious	Not serious	Not serious	Serious[a]	No	5185	RR 0.89 (0.58 to 1.38)	16 per 1000 (11 to 25)	18 per 1000	⊕⊕⊕⊙ moderate
MI (1 to 4 years of follow-up)											
8	RCTs	Not serious	Not serious	Not serious	Not serious	No	5845	RR 1.49 (1.21 to 1.84)	73 per 1000 (60 to 91)	49 per 1000	⊕⊕⊕⊕ high
MI (≥3 years follow-up)											
5	RCTs	Not serious	Not serious	Not serious	Not serious	No	5001	RR 1.44 (1.16 to 1.80)	77 per 1000 (62 to 96)	53 per 1000	⊕⊕⊕⊕ high
Periprocedural mortality											
2	RCTs	Not serious	Not serious	Not serious	Very serious[b]	No	419	No events of periprocedural mortality occurred either in BRS groups or in DES groups in 2 RCTs			⊕⊕⊙⊙ low
Periprocedural MI											
7	RCTs	Not serious	Not serious	Not serious	Serious[a]	No	5503	RR 1.22 (0.82 to 1.82)	73 per 1000 (49 to 109)	60 per 1000	⊕⊕⊕⊙ moderate
Mortality as a result of bleeding and/or stroke (6 to 60 months follow-up)											

Quality assessment							Summary of findings				
							Number of patients	Effect			Quality
Number	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations		Relative (95% CI)	Absolute (95% CI)		
11	Single-arm observational studies	Very serious[c]	Not serious	Not serious	Serious[d]	No	1402	2 death as results of bleeding and/or stroke occurred in 11 single-arm observational studies with Absorb® in 6 to 60 months follow-up			⊕⊙⊙⊙ very low
Very late ScT (after at least 1 year of follow-up)											
6	RCTs	Not serious	Not serious	Not serious	Serious[d]	No	5549	RR 5.09 (1.97 to 13.17)	7 per 1000 (3 to 17)	1 per 1000	⊕⊕⊕⊙ moderate

comments:

[a] Imprecision was down-graded by 1 point because of a non-significant effect estimate with wide CI
[b] Imprecision was down-graded by 2 points because of low number of studies and a very low event rate
[c] Risk of bias was down-graded by 2 points because of study design and study quality (observational single-arm studies with predominantly moderate to high risk of bias
[d] Imprecision was down-graded by 1 point because of a very low event rate

Abbreviations: BRS=bioresorbable scaffold; BVS=bioresorbable vascular scaffold; CI=confidence interval; DES=drug-eluting stent; MI=myocardial infarction; RCT=randomised controlled trial; RR=risk ratio; ScT=scaffold thrombosis;

Table A13: GRADE assessment of DESolve® Scaffold System (critical endpoints)

Quality assessment							Summary of findings				
							Number of patients	Effect			Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations		Relative (95% CI)	Absolute (95% CI)		
									DESolve® Scaffold System	comparator	
All-cause mortality											
Outcome not reported											
Cardiac mortality											
Outcome not reported											
MI											

Quality assessment							Summary of findings			
Number	Study design	Risk of	Inconsistency	Indirectness	Impression	Other	Number of patients	Effect		Quality
								Relative	Absolute (95% CI)	
Outcome not reported										
Periprocedural mortality										
3	Single-arm observational studies	Very serious[a]	Not serious	Not serious	Serious[b]	No	345	No events of periprocedural mortality occurred 3 single-arm observational studies with DESolve® Scaffold System		⊕⊙⊙⊙ very low
Periprocedural MI										
3	Single-arm observational studies	Very serious[a]	Not serious	Not serious	Serious[b]	No	345	One periprocedural MI occurred 3 single-arm observational studies with DESolve® Scaffold System		⊕⊙⊙⊙ very low
Mortality as a result of bleeding and/or stroke (12 months follow-up)										
2	Single-arm observational studies	Very serious[a]	Not serious	Not serious	Serious[b]	No	219	No death as a result of bleeding and/or stroke occurred in 2 single-arm observational studies with DESolve® Scaffold System in 12 months follow-up		⊕⊙⊙⊙ very low
Very late ScT (after at least 1 year of follow-up)										
1	Single-arm observational study	Very serious[a]	Not serious	Not serious	Very serious[c]	No	126	No very late ScT after at least 1 year of follow-up occurred in 1 single-arm observational studies with DESolve® Scaffold System		⊕⊙⊙⊙ very low

comments:

[a] Risk of bias was down-graded by 2 points because of study design and study quality (observational single-arm studies with moderate risk of bias
[b] Imprecision was down-graded by 1 point because of a very low event rate
[c] Imprecision was down-graded by 2 points because results were only available from 1 study and because of a very low event rate

Abbreviations: CI=confidence interval; MI=myocardial infarction; ScT=scaffold thrombosis;

Table A14: GRADE assessment of RMS Magmaris (critical endpoints)

Quality assessment							Summary of findings			
Number	Study design	Risk of	Inconsistency	Indirectness	Impression	Other	Number of patients	Effect		Quality
								Relative	Absolute (95% CI)	

of studies		bias				considerations		(95% CI)	RMS Magmaris	comparator	
All-cause mortality											
Outcome not reported											
Cardiac mortality											
Outcome not reported											
MI											
Outcome not reported											
Periprocedural mortality											
2	Single-arm observational studies[a]	Very seri-ous	Not serious	Serious	Serious[b]	No	184	No events of periprocedural mortality occurred 2 single-arm observational studies with RMS Magmaris			⊕⊙⊙⊙ very low
Periprocedural MI											
2	Single-arm observational studies[a]	Very seri-ous	Not serious	Not serious	Serious[b]	No	184	No periprocedural MI occurred 2 single-arm observational studies with RMS Magmaris			⊕⊙⊙⊙ very low
Mortality as a result of bleeding and/or stroke (24 months follow-up)											
2	Single-arm observational studies[a]	Very serious	Not serious	Not serious	Serious[b]	No	184	No death as a result of bleeding and/or stroke occurred in 2 single-arm observational studies RMS Magmaris in 24 months follow-up			⊕⊙⊙⊙ very low
Very late ScT (after at least 1 year of follow-up)											
1	Single-arm observational study[a]	Very serious	Not serious	Not serious	Very serious[c]	No	123	No very late ScT after at least 1 year of follow-up occurred in 1 single-arm observational studies with RMS Magmaris			⊕⊙⊙⊙ very low

comments:

[a] Risk of bias was down-graded by 2 points because of study design and study quality (observational single-arm studies with moderate risk of bias
[b] Imprecision was down-graded by 1 point because of a very low event rate
[c] Imprecision was down-graded by 2 points because results were only available from 1 study and because of a very low event rate

Abbreviations: CI=confidence interval; MI=myocardial infarction; RMS=resorbable magnesium scaffold; ScT=scaffold thrombosis;

Table A15: GRADE assessment of Fantom® BRS (critical endpoints)

Quality assessment							Summary of findings				
							Number of patients	Effect			Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations		Relative (95% CI)	Absolute (95% CI)		
									Fantom® BRS	comparator	
All-cause mortality											
Outcome not reported											
Cardiac mortality											
Outcome not reported											
MI											
Outcome not reported											
Periprocedural mortality											
1	Single-arm observational study[a]	Very serious	Not serious	Not serious	Very serious[b]	No	117	No events of periprocedural mortality occurred 2 single-arm observational studies with Fantom® BRS			⊕⊙⊙⊙ very low
Periprocedural MI											
1	Single-arm observational study[a]	Very serious	Not serious	Not serious	Very serious[b]	No	117	One periprocedural MI occurred 1 single-arm observational study with Fantom® BRS			⊕⊙⊙⊙ very low
Mortality as a result of bleeding and/or stroke (6 months follow-up)											
1	Single-arm observational study[a]	Very serious	Not serious	Not serious	Very serious[b]	No	117	No death as a result of bleeding and/or stroke occurred in 2 single-arm observational study with Fantom® BRS in 6 months follow-up			⊕⊙⊙⊙ very low
Very late ScT (after at least 1 year of follow-up)											
Outcome not reported											
comments: [a] Risk of bias was down-graded by 2 points because of study design and study quality (observational single-arm study with moderate risk of bias [b] Imprecision was down-graded by 2 points because results were only available from 1 study and because of a very low event rate											

Abbreviations: BRS=bioresorbable scaffold; CI=confidence interval; MI=myocardial infarction; ScT=scaffold thrombosis;

Applicability tables

Table A16: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The patients in the included studies (RCTs and single-arm studies) were predominantly male with a mean age of 60 to 70 years. Hence, generalisability to females and other age groups is limited. In addition, the majority of the included study population had relatively simple lesions in contrast to patients with more complex lesions frequently encountered in daily practice. Both patients with stable CAD and patients with ACS were included in the studies in sufficiently large numbers. Subgroup-analyses from RCTs showed no different results between these groups. Therefore, the results are valid for both groups.
Intervention	The implantation procedure does not differ from routine use. Valid results are only available for the Absorb® BVS. Since the other BRS devices are essentially different from the Absorb® BVS in their structure (backbone material, strut thickness, eluted drug), generalisability to all fully BRS is limited.
Comparators	All currently available RCTs compare BRS to a DES (mostly EES). In routine practice, other stent types and further revascularisation strategies (CABG) will be taken into consideration. From the current evidence, we do not know whether the BRS is non-inferior to those approaches in terms of benefits and harms.
Outcomes	The primary outcomes in most of the RCTs were surrogate endpoints, which do not reflect the most important clinical benefits and harms. Patient-relevant outcomes such as TLF, TVF were MACE or cardiac death were the primary outcomes in two RCTs and in most of the included single-arm observational studies. In addition, they were secondary outcomes in all other RCTs. Long-term results with a follow-up of three or more years were available from 4 RCTs, in all other studies, maximum length of follow-up was about two years. For safety, valid results are limited to ScT and periprocedural cardiac events. All other safety outcomes, especially those related to the anti-thrombotic therapy, were rarely reported.
Setting	The setting in the studies has not been described precisely but most of the procedures seem to have been undertaken in highly specialised university units. The transferability to a low-volume cardiac catheterisation lab with less experienced cardiologists may be limited.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A17: Regulatory status

Device	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch
Absorb® BVS	EU	CE mark	Yes	…improving coronary luminal diameter in patients with ischemic heart disease due to de novo native coronary artery lesions[1]	Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or the post-procedural antiplatelet regimen.	January 2011 / May 2015 (Absorb GT1)	Yes[k]
Absorb® BVS	USA	FDA	Yes		Patients with hypersensitivity or contraindication to everolimus or structurally-related compounds, or known hypersensitivity to scaffold components (poly (L-lactide), poly (D,L-lactide), platinum) or with contrast sensitivity.[j]	July 2016	Yes[b]
DESolve® Scaffold System	EU	CE mark	Yes	…treatment of patients with CAD[l]	-	May 2014	Yes
RMS Magmaris	EU	CE mark	Yes	…treating CAD[m]	-	June 2016	Yes
ART Pure Bioresorbable Scaffold	EU	CE mark	Yes	…to treat CAD[n]	-	May 2015	Yes
Fantom® BRS	EU	CE mark	Yes	…treatment of CAD[o]	-	April 2017	Yes

Abbreviations: BRS=bioresorbable scaffold; BVS=bioresorbable vascular scaffold; CE=Communauté Européenne; EU=European Union; RMS=resorbable magnesium scaffold; USA=United States of America;

Table A18: Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions	Source
NICE, England	This procedure should only be used with special	Current evidence on the short-term safety and	https://www.nice.org.uk/ guidance/ipg492

[j] https://www.vascular.abbott/us/products/coronary-intervention/absorb-bioresorbable-scaffold-dissolving-stent.html

[k] Manufacturer stopped selling the first-generation Absorb® BVS on 14th September 2017

[l] http://elixirmedical.com/index.php?mact=News,cntnt01,detail,0&cntnt01articleid=26&cntnt01origid=56&cntnt01returnid=56

[m] https://www.biotronik.com/en-au/newsroom/press-releases/press-release-magmaris-ce-mark-june15-en

[n] http://art-stent.com/wp-content/uploads/2015/05/ART-News-150518.pdf

[o] https://globenewswire.com/news-release/2018/02/26/1387381/0/en/REVA-Announces-CE-Mark-and-First-Implant-of-the-Fantom-Encore-Bioresorbable-Scaffold.html

Country and issuing organisation	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions	Source
	arrangements for clinical governance, consent and audit or research.	efficacy of BRS implantation for treating coronary artery disease is adequate, but the quantity of evidence on the safety and efficacy of the procedure in the long term is inadequate.	
LBI-HTA, Austria	The inclusion in the catalogue of benefits is currently not recommended.	The current evidence is not sufficient to prove that the BRS is more or at least equally effective and safer than current revascularisation technologies.	http://eprints.hta.lbg.ac.at/1060/
HAS, France	The performance is insufficient for registration of the Absorb® device on the list of products and services provided in Article L.165-1 of the Social Security Code.	The therapeutic value of the Absorb® stent cannot be established in the indications claimed.	https://www.has-sante.fr/portail/upload/docs/evamed/CEPP-5281_ABSORB%205281_occultations%20accept%C3%A9es%20par%20HG%20le%2025%2010%202017.pdf

Abbreviations: HAS=Haute Autorité de Santé; LBI-HTA=Ludwig Boltzmann Institute for Health Technology Assessment; NICE=National Institute for Health and Care Excellence

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	No
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the MAH/manufacturer(s) (fact check), as well as responses from authors, is available on the EUnetHTA website.