Fully bioresorbable scaffolds for coronary artery disease

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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

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

CONTENT INFORMATION

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Content

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List of abbreviations

ACS ..... acute coronary syndrome
AP ..... angina pectoris
BMS ..... bare metal stent/unbeschichteter Metallstent
BVS ..... bioresorbable vascular scaffold
CABG ..... coronary artery bybass grafting/Bypass-Operation
CAD ..... coronary artery disease
DES ..... drug eluting stent/medikamentenfreisetzender Stent
KHK ..... koronare Herzkrankheit
MI ..... myocardial infarction/Herzinfarkt
MLD ..... minimum lumen diameter
NSTEMI ..... non-ST-Elevation myocardial infarction
PCI ..... percutaneous coronary intervention
PDLLA ..... poly (D, L-lactid)
PLLA ..... poly (L-lactid)
STEMI ..... ST-elevation myocardial infarction
UA ..... unstable angina

Summary

Introduction

Health Problem

Coronary artery disease (CAD), which is a manifestation of atherosclerosis of the coronary arteries, belongs to the most prevalent diseases and it is the leading cause of death in Austria. Apart from an increased mortality risk, CAD is associated with recurring discomfort, impaired quality of life, and repeated hospitalisation.

coronary artery disease (CAD) causes major burden of disease

Description of Technology

Different revascularisation techniques have been developed to restore blood flow. The most common approach today is percutaneous coronary intervention (PCI), which widens stenotic coronary arteries. PCI includes angioplasty and the implantation of a coronary stent or scaffold that holds a blocked vessel open.

PCI most common revascularisation technology

The earliest types of stents were bare metal stents (BMS). Later, drug eluting stents (DES) were developed. The most recent developments in stent technology are fully bioresorbable vascular scaffolds (BVS), designed to slowly disappear over time. To date, two products (ABSORB®, DESolve®) have received CE-mark. This review evaluates whether the implantation of a BVS in patients with CAD has a better benefit-harm profile than other revascularisation approaches.

different stent types

latest development: bioresorbable scaffolds

Methods

The analysis is based on a systematic literature search, complemented by a hand search and manufacturer requests. The studies were systematically assessed for quality and risk of bias. Data on each selected outcome category were synthesised across studies according to the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE).

systematic literature search, data synthesis with GRADE

Results

Available evidence

For evaluating the efficacy of the BVS (ABSORB®), nine- and 12-months interim results from two randomised controlled trials (RCT) with 741 participants were available, comparing the BVS with three types of drug-eluting stents. No evidence was available for evaluating the efficacy of the BVS DESolve®.

efficacy only for ABSORB®: 2 RCTs

For evaluating the safety of the BVS ABSORB®, in addition to the RCTs, ten observational studies (mostly single-arm) fulfilled our inclusion criteria. Overall, safety data from 1,290 patients who received a BVS and from 486 patients with traditional stents were available. For evaluating the safety of the DESolve®, one single-arm observational study (16 patients) was available.

safety ABSORB®: 2 RCTs + 10 observational studies

DESolve: one small case series

Clinical effectiveness

no difference in cardiovascular morbidity, mortality and revascularisation

After 12 months, (cardiac) mortality, myocardial infarction, revascularisation and quality of life did not significantly differ between patients who received a BVS compared to those who received a DES. An equal proportion in both groups was free from angina. The cumulative angina rate was lower in the BVS than in the DES group; however, this is based on a post-hoc analysis.

Safety

short-term safety: very few serious adverse events

Short-term data with moderate strength of evidence showed scaffold thrombosis in <1.5 % of BVS-patients and no stent thrombosis in the control groups. Less than 1 % of participants died from either periprocedural mortality or from cardiovascular mortality in the intervention and control groups respectively.

Upcoming evidence

studies with 32,000 patients ongoing

At least 14 RCTs and 20 single-arm studies are currently registered. They include around 32,120 patients in total and will potentially influence the estimate of effect considerably.

Reimbursement

reimbursement via PCI/stent flat rate

PCI and stenting are hospital based procedures and are therefore reimbursed via the Austrian DRG-system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). The BVS has not received a separate reimbursement code so far. The price per device is currently € 825.

Discussion

limitation of evidence due to study design, limited applicability in routine and short follow-up

The quality of evidence is limited because of study design issues (lack of comparison group, no blinding of outcome assessors or patients, short time-horizon). The results primarily apply to male patients with stable CAD and relatively simple lesions which do not necessarily represent routine CAD patients. Late scaffold thrombosis and its adverse consequences, which are very relevant safety outcomes, require longer follow-up times.

Conclusion

inclusion in benefit catalogue currently not recommended

The current evidence is not sufficient to prove that the BVS is more or at least equally effective and safer than current revascularisation technologies. Hence, the inclusion in the catalogue of benefits is currently not recommended. We suggest re-evaluation in 2018.

Zusammenfassung

Einleitung

Hintergrund

koronare Herzkrankheit (KHK) führt Todesursachenstatistik an

Die koronare Herzkrankheit (KHK) ist eine Manifestation von Atherosklerose der Herzarterien. Die KHK gehört zu den häufigsten Krankheiten in industrialisierten Ländern und führt in Österreich die Todesursachenstatistik an. Neben dem erhöhten Sterblichkeitsrisiko ist die KHK mit erheblichen Einschränkungen (reduzierte körperliche Belastbarkeit, Schmerzen, Depression etc.) und mit wiederholten Spitalsaufenthalten für die PatientInnen verbunden.

Beschreibung der Technologie

PCI oder Bypass als Revaskularisierung

Es wurden mehrere Verfahren entwickelt, um die verengten Blutgefäße offenzuhalten oder operativ mittels eines Bypasses zu überbrücken. Am häufigsten kommt derzeit die perkutane koronare Intervention (PCI) zum Einsatz, bei der das verengte Gefäß mit einem Ballon geweitet und ein Röhrchen aus Drahtgeflecht – ein sogenannter Stent – eingesetzt wird.

mit früheren Stents Restenose- und Stentthromboserisiko

Die ersten Stents waren unbeschichtete Metallstents. Da es durch die physiologische Antwort auf die durch das Implantat entstehende Gefäßverletzung oft zu erneuten Stenosen kam, wurden medikamentenfreisetzende Stents (DES) entwickelt, die durch eine antiproliferative und/oder immunsuppressive Wirkung die Restenose verhindern sollten. Allerdings stellten bei der ersten DES-Generation späte Stentthrombosen ein Sicherheitsrisiko dar.

neu: 2 zugelassene resorbierbare Gefäßgerüste (BVS)

Die neueste Entwicklung sind vollständig resorbierbare Gefäßgerüste (BVS), die nach einiger Zeit gänzlich abgebaut werden. Derzeit sind zwei Produkte (ABSORB®, DESolve®) in Europa zugelassen. Sie bestehen aus einem resorbierbaren Polymer Poly (L-Lactid) (PLLA) Gerüst, das mit einem medikamentenfreisetzenden Polymer beschichtet ist. Die amerikanische Zulassungsbehörde hat bisher noch kein Produkt zugelassen. Zahlreiche weitere resorbierbare Gefäßgerüste werden derzeit in klinischen Studien getestet.

Indikation und therapeutisches Ziel

BVS soll Vorteile von bisherigen Stents kombinieren

Die BVS wurden mit der Intention entwickelt, die Vorteile der unbeschichteten Metallstents und der DES zu kombinieren. Insbesondere soll das späte Thromboserisiko durch die Verhinderung eines permanenten Implantats reduziert werden. Möglicherweise kann die begleitende Therapie mit Gerinnungshemmern verkürzt werden, und in Stent-freien Blutgefäßen ist eine spätere invasive Therapie (Bypass) leichter durchführbar.

indiziert bei KHK, falls PCI sinnvoll, jedoch Gefäße ohne Verkalkung

Die Implantate sind für PatientInnen mit KHK, welche für eine PCI in Frage kommen, indiziert, allerdings dürfen die Gefäße keine hochgradigen Verkalkungen aufweisen. Ein österreichisches Spital empfiehlt, vorrangig DiabetikerInnen unter 75 Jahren zu behandeln.

Methode

systematische Literaturrecherche

Sowohl die Analyse der Wirksamkeit, als auch der Sicherheit basiert auf einer systematischen Literatursuche in medizinischen Datenbanken, die mit einer Handsuche, sowie Anfragen an die Hersteller ergänzt wurde. Relevante Studien wurden nach vorher definierten Ein- und Ausschlusskriterien ausgewählt und auf Qualität und Verzerrungsrisiko überprüft.

relevante Outcomes für Wirksamkeit und Sicherheit

Als relevante Outcomes für die Beurteilung der Wirksamkeit wurden die (kardiovaskuläre) Mortalität und Morbidität (Herzinfarkt, Angina Pectoris), die Lebensqualität und die Revaskularisierungsraten definiert. Für die Beurteilung der Sicherheit wurden die Indikatoren „Stentthrombose inkl. schwerwiegender Konsequenzen", „periprozedurale Mortalität oder Mortalität durch Blutung/Schlaganfall" und „sonstige schweriegende unerwünschte Ereignisse (z.B. Schlaganfall) als entscheidend definiert.

Synthese mit GRADE

Daten zu den als relevant definierten Outcomes wurden mit der Methode „Grading of Recommendations Assessment, Development and Evaluation" (GRADE) zusammenfassend analysiert.

Ergebnisse

Verfügbare Evidenz

Wirksamkeitsdaten nur für ABSORB®: 2 RCTs mit 750 PatientInnen

Die Beurteilung der Wirksamkeit ist lediglich für das Gefäßgerüst ABSORB® möglich. Hierfür standen neun- und 12-Monats Interimsergebnisse zweier randomisiert kontrollierter Studien (RCT) mit insgesamt 741 (primär männlichen) PatientInnen zur Verfügung. In den Studien wurde der BVS mit drei Typen von medikamentenfreisetzenden Stents verglichen. Der Großteil der PatientInnen litt an stabiler CAD, ein kleiner Anteil hatte ein akutes Koronarsyndrom.

Sicherheit ABSORB®: 10 Beobachtungsstudien + 2 RCTs mit 1.800 PatientInnen, primär stabile KHK

Für die Beurteilung der Sicherheit des BVS ABSORB® standen – zusätzlich zu den RCTs – zehn Beobachtungsstudien zur Verfügung. Davon waren acht einarmig und zwei kontrolliert. In acht Beobachtungsstudien litten die PatientInnen unter stabiler KHK, in zwei unter akutem Koronarsyndrom. In Summe standen für die Beurteilung der Sicherheit Daten von 1.290 PatientInnen, die mit dem BVS behandelt wurden und von 486 PatientInnen, die mit herkömmlichen Stents (primär DES) behandelt wurden, zur Verfügung.

DESolve®: 1 Fallserie, 16 PatientInnen

Für die Beurteilung der Sicherheit des BVS DESolve® stand eine einarmige Beobachtungsstudie mit 16 PatientInnen mit stabiler KHK zur Verfügung. Diese untersuchte jedoch einen Myolimus-freisetzenden Prototyp, während das am Markt befindliche Produkt Novolimus freisetzt.

Klinische Wirksamkeit

kein Unterschied bei Morbidität, Sterblichkeit und Revaskularisierung

Nach 12 Monaten waren bei PatientInnen, die das resorbierbare Gefäßgerüst erhielten, die (kardiale) Sterblichkeit, der Anteil der Herzinfarkte und die Häufigkeit von neuerlichen Vaskularisierungsmaßnahmen nicht signifikant geringer als bei jenen, die einen herkömmlichen Stent erhielten. Auch die Lebensqualität wurde nicht höher bewertet. Ein gleicher Anteil von PatientInnen in beiden Gruppen war ohne Angina Pectoris Anzeichen. Die kumulative Angina Rate war in der BVS-Gruppe niedriger, allerdings basiert dieses Ergebnis auf einer post-hoc Analyse.

Sicherheit

kurzfristig kaum schwere Komplikationen

Bei Beobachtung bis zu zwölf Monaten traten in Summe neun BVS-bedingte (<1,5 % der PatientInnen) und keine Stent-bedingten Thrombosen auf. Weniger als 1 % der StudienteilnehmerInnen in beiden Gruppen starben bei der Intervention oder aufgrund späterer kardio-vaskulärer Ursachen.

Laufende Studien

32.000 PatientInnen in 14 RCTs und 30 Beobachtungsstudien untersucht

Derzeit sind zumindest 14 laufende RCTs und 30 einarmige Studien registriert. In diesen Studien sollen in Summe 32.120 PatientInnen teilnehmen. Dadurch kann sich die derzeitige Einschätzung zur Wirksamkeit und Sicherheit noch deutlich verändern.

Kostenerstattung

Bezahlung über PCI/Stent-Pauschale

Preis pro Stück: 825 €

PCI und Stents werden über ein spezifisches Fallpauschale im Rahmen der Leistungsorientierten Krankenanstaltenfinanzierung erstattet. Das vollständig resorbierbare Gefäßgerüst hat derzeit keinen separaten Code und wird daher im Rahmen des PCI/Stent Pauschale refundiert. Der Preis pro BVS liegt laut Auskunft der Hersteller derzeit für das BVS ABSORB® bei 825 €.

Diskussion

derzeit (noch) kein Beleg für überlegenes Nutzen-Schadensprofil des BVS

Nachbeobachtung für späte Thrombosen zu kurz

laufende Studien bringen mehr Gewissheit

Nach den derzeitigen Schlüsselstudien ist die Implantation eines vollständig resorbierbaren Gefäßgerüstes hinsichtlich patientInnenrelevanter Endpunkte nicht wirksamer als herkömmliche Stents. Es konnte bisher auch kein besseres Sicherheitsprofil ausgewiesen werden. Allerdings erfolgten die Nachbeobachtungen in den vergleichenden Studien maximal bis 12 Monate, sodass über die Häufigkeit von sehr späten Stentthrombosen noch keine Aussage möglich ist. Außerdem treten Stentthrombosen, wie auch andere schwerwiegende unerwünschte Ereignisse vergleichsweise selten auf, ein signifikanter Gruppenunterschied ist daher generell schwer nachweisbar. Die große Anzahl laufender Studien mit über 30.000 PatientInnen wird jeoch eine sicherere Aussage über das Nutzen-Schadensprofil ermöglichen.

Limitationen durch Studiendesign

Limitierend für die Aussagekraft der derzeitigen Daten ist das Studiendesign. Es waren teilweise die befundenden Personen und/oder die PatientInnen nicht verblindet. Im Großteil der Beobachtungsstudien gab es keine Kontrollgruppe und die Auswahl der PatientInnen oblag den behandelnden ÄrztInnen. Dadurch könnten genau jene PatientInnen mit dem BVS behandelt worden sein, die die beste Prognose haben.

keine Daten für akute KHK und komplexe Läsionen

Da in den Studien vorwiegend einfache Läsionen bei PatientInnen mit stabiler KHK behandelt wurden, und die TeilnehmerInnen überwiegend männlich waren, sind die Ergebnisse auf klassische RoutinepatientInnen mit komplexeren Läsionen oder mit akuter Erkrankung und auf Frauen nur sehr eingeschränkt übertragbar.

Empfehlung

Aufnahme in Leistungskatalog derzeit nicht empfohlen

Re-Evaluierung 2018

Die derzeitige Evidenz ist nicht ausreichend um zu belegen, dass der BVS wirksamer und sicherer oder zumindest gleich wirksam aber sicher als die herkömmlichen Revaskulaisierungstechnologien sind. Daher wird eine Aufnahme in den Krankenhaus-Leistungskatalog derzeit nicht empfohlen. Aufgrund der zahlreichen laufenden Studien empfehlen wir eine neuerliche Evaluierung im Jahr 2018.

1 Scope

1.1 Research questions

PIKO-Frage

This report addresses the following research question: Is the implantation of a fully bioresorbable scaffold (BVS), in comparison to other revascularisation strategies (permanent stent, coronary artery bypass grafting/CABG) in adult patients with coronary artery disease (CAD) more effective and safe or equally effective but safer concerning cardiovascular mortality, morbidity and health-related quality of life?

1.2 Inclusion criteria

Einschlusskriterien

Inclusion criteria for relevant studies are summarised in Table 1.2-1.

Table 1.2-1: Inclusion criteria

Population	Adult patients with CAD including stable angina, unstable angina, myocardial infarction (ICD-10 code I20-I25) who require and are eligible for myocardial revascularisation *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	Percutaneous coronary intervention (PCI) with implantation of a fully bioabsorbable/biodegradable/bioresorbable vascular scaffold/stent (BVS) Product names: Absorb, DESolve, DREAMS, IDEAL, Igaki-Tamai, Fantom, ART18Z 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]*
Control	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 with implanting a permanent drug eluting or bare metal stents or with a bioresorbable polymer drug eluting stent is currently the main strategy to treat CAD; another alternative for revascularisation is coronary artery bypass grafting (CABG), which may result in more complete revascularisation, yet with a higher procedural risk.
Outcomes	
Efficacy	**Clinical endpoints**: ❖ Mortality (cardiac, all-cause) ❖ Morbidity: angina, myocardial infarction ❖ Quality of life **Composite endpoints:** Major adverse cardiac events (MACE) **Surrogate endpoints:** Re-vascularisation: target vessel revascularisation (TVR), target lesion revascularisation (TLR) 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. Revascularisation should, therefore, ideally prolong life-expectancy, reduce the symptoms and future revascularisations, and increase health-related quality of life.

Safety	**Adverse events** • vascular access-site complication • procedure-related contrast-induced nephropathy **Serious adverse events** • late/very late scaffold/stent thrombosis and its consequences • bleeding from anti-platelet therapy • periprocedural myocardial infarction or mortality • mortality from bleeding/stroke • other serious adverse events Rationale: Compared to 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 anti-platelet 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 due to contrast media used in the coronary angiography.
Study design	
Efficacy	Randomised controlled trials (follow-up ≥6 months)
Safety	Randomised controlled trials (follow-up ≥6 months) Prospective non-randomised controlled trials (follow-up ≥6 months) Prospective (single-arm) observational studies, e.g. case series, registries, (≥15 patients; follow-up ≥1 month)[1]

1.3 Literature search

systematische Literaturrecherche in Datenbanken und Web

The systematic literature search was conducted on the 6th of January 2015 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE – NHS EED – HTA)

Literatursuche: 906 Ergebnisse

Search filters were applied in Medline and Embase to limit the systematic search to clinical trials and systematic reviews. After deduplication, 906 citations overall were included for abstract screening. The specific search strategy employed can be found in the Appendix ("Literature search").

Hersteller: 4 Publikationen

Manufacturers from the two products with CE-marks (ABSORB®, DESolve®) submitted 12 publications, of which four new citations were identified.

mit Handsuche gesamt 966 Zitate

An additional 55 citations were found by handsearch, one additional RCT was published after the literature search and was also added, resulting in 966 hits in total.

[1] Short-term follow-up studies were included to obtain data for immediate/periprocedural complications.

1.4 Flow chart study of selection

Literaturauswahl

Overall 966 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 1.4-1.

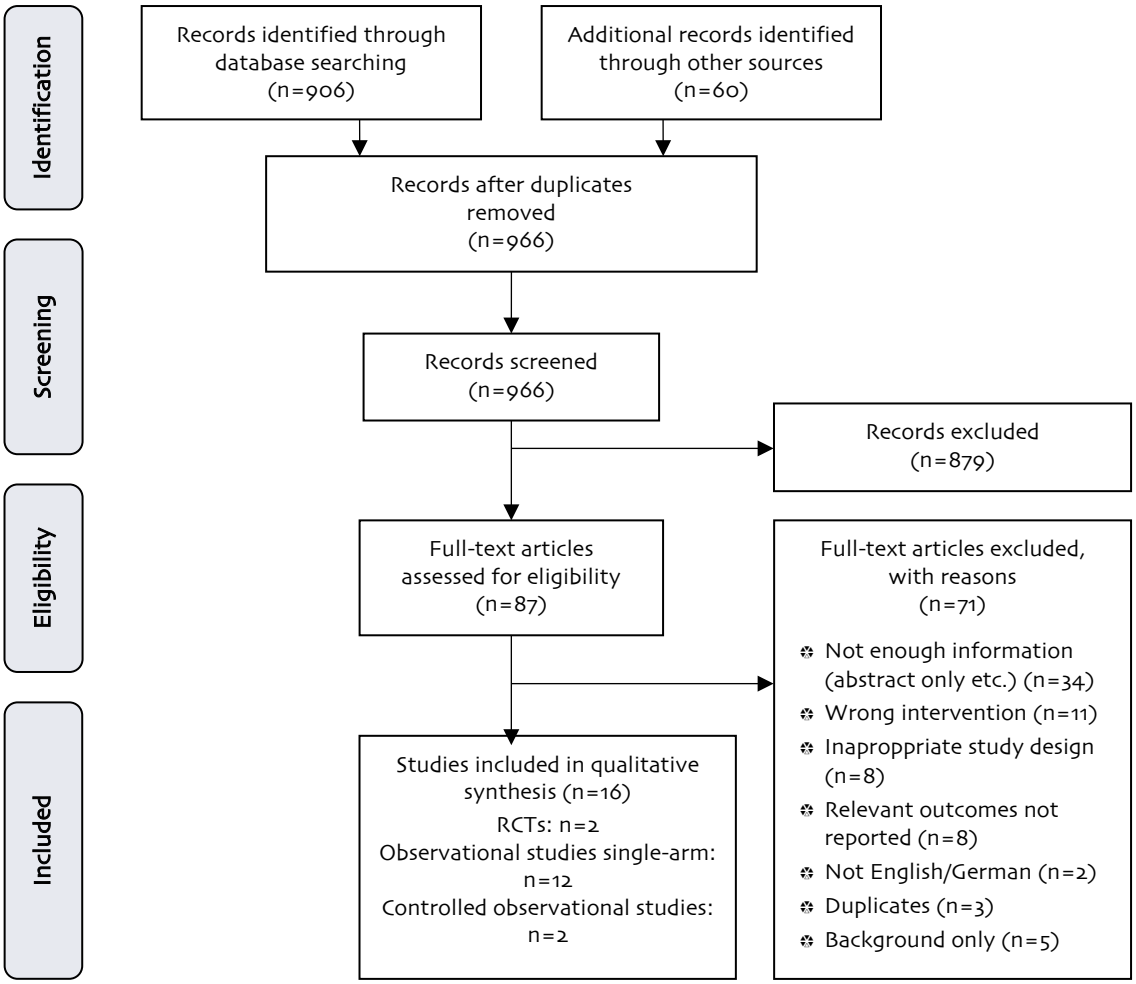

Figure 1.4-1: Flow chart of study selection (PRISMA Flow Diagram)

2 Description and technical characteristics of technology

2.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
B0001	What is the BVS and what are other revascularisation technologies?	2
A0020	For which indications has the BVS received marketing authorisation or CE marking?	2
B0002	What is the claimed benefit of the BVS in relation to other revascularisation techniques?	2
B0003	What is the phase of development and implementation of the BVS and of other revascularisation technologies?	2
B0004	Who administers the use of revascularisation technologies in CAD and in what context and level of care are they provided?	2
B0008	What kind of special premises are needed to use revascularisation technologies in CAD?	1
B0009	Which supplies are needed to use revascularisation technologies in CAD?	1
A0021	What is the reimbursement status of the BVS?	1

Sources

Quellen: systematische Datenbanksuche, Handsuche, Hersteller

The information provided in this chapter is based on different sources: firstly, relevant references identified in the systematic database search (see Chapter 1.3) were used [1-4], supplemented by hand search for clinical guidelines [5-9] and by information provided by clinical experts and by manufacturers on request.

2.2 Results

Features of the technology and comparators

B0001 – What is the BVS and what are other revascularisation technologies?

PCI ist gängige Revaskularisierung

Revascularisation techniques started in the 1960s with the advent of bypass surgery. In the 1970s, the first percutaneous coronary interventions (PCI), which widen stenotic coronary arteries, were performed. They have become one of the most common interventions in the treatment of CAD. PCI includes percutaneous transluminal balloon angioplasty and the implantation of coronary vascular stents or scaffolds that hold a blocked vessel open [2, 7].

inkludiert Stenting mit unterschiedlichen Stenttypen

jüngste Entwicklung: resorbierbare Gefäßgerüste (BVS)

The earliest types of stents were bare metal stents (BMS). Later, drug eluting stents (DES) were developed and have been widely used since then. In the second generation of DES, bioresorbable drug eluting polymers have been used, which, however, leave behind a residual metal platform after six to nine months. The most recent developments in stent technology are fully bioresorbable vascular scaffolds designed to slowly disappear over time. They are composed of either a polymer or metallic alloy. Some of them are drug-coated, while others are not [3] (Table 2.2-1).

Bericht untersucht BVS im Vergleich zu anderen Revaskularisierungsmethoden

This report will evaluate the efficacy and safety of implanting a fully bioresorbable vascular scaffold (sometimes also called bioabsorbable or biodegradable stent/scaffolds) in comparison with other revascularisation techniques: implanting other (permanent) stent types (permanent bare metal or drug eluting stent, bioresorbable polymer drug eluting stent) and coronary artery bypass grafting (CABG).

A0020 – For which indications has the BVS received marketing authorisation or CE marking??

2 Produkte mit CE-Mark:

To date two products (ABSORB®, DESolve®) have received CE-marking for implanting the devices in adult patients with CAD (see Table 2.2-1). None of the products has been approved by the US market authorisation agency (FDA) so far.

ABSORB®

The ABSORB® scaffold (Abbott Vascular) received CE-marking in 2010. It consists of a resorbable polymer poly (L-lactide) (PLLA) scaffold that is coated with an everolimus eluting resorbable poly (D, L-lactide) (PDLLA) polymer. It dissolves completely within several years.

DESolve®

The DESolve® scaffold (Elixir Medical) received CE-marking in 2014. It also consists of a polymer poly (L-lactide) (PLLA) scaffold. Coating consists of a Poly-Lactid-based polymer which elutes novolimus.

weitere in Entwicklung

Several further fully bioabsorbable scaffolds are currently being developed and tested (see Table 2.2-1). This report will cover the CE-marked devices only.

Table 2.2-1: Overview of fully bioresorbable scaffolds

Company	Device Name	Drug	CE-Certificate	FDA Approval	Comment
Polymeric					
Abbott Vascular (IL)	ABSORB®	Everolimus	Yes (2010)	No	ABSORB II trial + further trials
Elixir Medical (CA)	DESolve®	Novolimus	Yes (2014)	No	DESolve Nx Trial
Bioabsorbable Therapeutics Inc. (CA)	IDEAL	Sirolimus	No	No	
Reva Medical Inc. (CA)	Fantom™	Sirolimus	No (expected in 2016)	No	RESTORE trial; First human implants initiated in Dec 2014, first generation product: ReZolve
Amaranth Medical	FORTUTUDE	Sirolimus	No	No	Mend-II trial
Kyoto Medical Planning (Japan)	Igaki-Tamai®	None	No	No	Igaki-Tamai® stent for peripheral artery received the CE mark
Arterial Remodelling Technologies (France)	ART18Z	None	No	No	ARTDIVA trial
Metallic					
Biotronik AG (Germany)	DREAMS	Paclitaxel	No (expected in 2016)	No	BIOSOLVE-II study

Sources: manufacturers, fiercemedicaldevices.com, clinicaltrials.gov

B0002 – What is the claimed benefit of the BVS in relation to other revascularisation techniques?

Vorteil von Stents gegenüber Bypass: weniger Risiko bei Intervention, aber ...

... Restenose und späte Stentthrombosen möglich

Compared with CABG, which is an open heart surgery, the implantation of a stent is less invasive and, thus, associated with lower periprocedural risks [10]. However, in contrast to acute MI, where stent stents improve the prognosis of patients significantly, in patients with stable CAD, stents primarily reduce the symptoms of angina while they do not necessarily prolong life expectancy or reduce the rate of MIs [11]. Furthermore, the problem with stents is that they induce in-stent neointimal hyperplasia, which can result in restenosis and the need for repeated PCI. While DES have been more successful in avoiding restenosis than BMS, their greater risk of late stent thrombosis (> 30 days) has raised safety concerns leading to the development of a further generation of DES using novel anti-proliferative agents, thinner stent struts and biocompatible or biodegradable polymers to minimise inflammation and improve the safety profile [2, 3].

BVS sollen späte Thrombosen verhindern, ermöglichen später Bypass

PatientInnen präferieren befristetes, statt permanentes Implantat

The latest developments are fully BVS. The currently CE-marked products resorb in several stages (hydration of the polymer, depolymerisation by hydrolysis, diffusion of short polymer chains into the body, assimilation of the small particles by phagocytes, conversion into dioxide and water, excretion through kidney or lungs) [12]. They are intended to combine the advantages of both, BMS and DES. Thus, they may reduce the risk of late thrombosis by leaving patients with a treated vessel free of a permanent stent implant. Furthermore, patients need to take anti-platelet medication after stent implantation, and it has been hypothesised [1] that duration of this therapy may be shorter after implanting a BVS in comparison to permanent stents. However, some patients may still need long term anti-platelet therapy because of their

underlying heart condition [1]. Moreover, further invasive therapies (e.g., CABG) will be easier in stent-free vessels and the material allows non-invasive imaging (e.g., stent assessment with coronary computer tomography). Finally, BVS may be more acceptable by patients because of their preference for a temporary implant rather than a permanent one [1].

B0003 – What is the phase of development and implementation of the BVS and of the other revascularisation techniques?

Revaskularisierung kontinuierlich weiterentwickelt

In terms of CABG, the technology was first used in the1960s and has undergone continued advances, in particular with the systematic use of arterial conduits [7]. Implantations of BMS were first reported in 1986. The first DES was launched in 2003. Stenting has become a standard in coronary intervention and DES have accounted for at least two thirds of the implanted stents. In 2010, the first BVS (ABSORB®) was approved in Europe and has increasingly been used since then [1].

Administration, investments, personnel and tools required to use the BVS and other stent types?

B0004 – Who administers the use of revascularisation technologies in CAD and in what context and level of care are they provided?

BVS braucht selbe Infrastruktur wie andere Stents, CABG aufwändiger

According to expert information, implanting a BVS requires the same infrastructure, personnel and equipment as implanting other types of stents. However, implantation of a BVS requires a better preparation of the lesions. Furthermore, because of limited possibilities of device expansion, the dimensions of the affected vessel must be exactly known, which will require invasive imaging more often [13]. The procedure is done in hospitals with an average duration of stay of three to four days. CABG is an open heart surgery that is also done in hospitals, yet it requires a longer hospital stay followed by rehabilitation.

B0008 – What kind of special premises are needed to use revascularisation technologies in CAD?

BVS braucht Katheterlabor

PCI and stenting procedures require a cardiac catheterisation lab and a team consisting of interventional cardiologist, assistant nurses and radiology assistants.

Bypass braucht OP, Intensiv-Einheit

Coronary artery bypass grafting is an open surgery and requires an operating theatre, usually a cardiopulmonary bypass (heart-lung-machine) and an intensive care unit. Concerning personnel, surgeons, nurses, cardio-technicians and anaesthesiologists are required.

B0009 – Which supplies are needed to use revascularisation technologies in CAD?

Equipment

According to the information from clinical experts, in terms of equipment for PCI and stenting, introducer needles, sheath introducers, guiding catheters, balloon catheters and coronary guidewires are needed. Specific imaging technologies (intravascular ultrasound or optical coherence tomography) are occasionally necessary. Materials for general anaesthesia, sternotomy and sewing material along with chest tubes are required for CABG.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of the BVS?

BVS derzeit nicht in MEL-Katalog, Vergütung als herkömmlicher Stent

PCI and stenting are hospital based procedures and are therefore reimbursed via the Austrian DRG-system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). While BMS and DES are specified in the publicly financed benefit catalogue and therefore completely reimbursed per procedure, the BVS has not received a separate code so far. Reimbursement is currently the same as for DES. Because of the higher costs for BVS (according to information from the manufacturer of the ABSORB®-stent, the price per device is € 825 for Austria), reimbursement will very likely currently not cover the full costs.

3 Health Problem and Current Use

3.1 Methods

Research questions

Element ID	Research question	Importance 2=critical 1=optional
A0001	For which health conditions, and for what purposes are BVS used?	2
A0002	What is the disease or health condition in the scope of this assessment?	2
A0003	What are the known risk factors for CAD?	2
A0004	What is the natural course of CAD?	2
A0006	What are the consequences of CAD for society?	2
A0024	How is CAD currently diagnosed according to published guidelines and in practice?	1
A0025	How is CAD currently managed according to published guidelines and in practice?	2
A0007	What is the target population in this assessment?	2
A0023	How many people belong to the target population?	1
A0011	How much are BVS utilised?	1

Sources

Quellen: Leitlinien, Statistiken

The primary sources for this chapter are guidelines on the diagnosis and management of CAD which have been retrieved via handsearch [5-7]. Additionally, data from the Austrian health statistics [14], from international bodies [15] and manufacturer information have been used.

3.2 Results

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes are BVS used?

BVS bei KHK indiziert, Kontraindikation: Verkalkung, komplexe Läsionen

Just like coronary BMS or DES, BVS are indicated in patients with CAD. Yet, certain patients have been deemed unsuitable for the use of BVS, including those with extensive calcifications, with stenoses with large side branches and very large (>4 mm) or small (<2.5 mm) vessels [2]. This is because strut thickness was increased in order to keep the mechanical strength of a conventional stent, and this negatively affects stent deliverability [4].

A0002 – What is the disease or health condition in the scope of this assessment?

KHK = chronisch und akut

CAD which is a manifestation of atherosclerosis of the coronary arteries includes chronic (stable angina) and acute forms (acute coronary syndrome/ ACS). ACS summarises all phases of CAD that are immediately life threatening (e.g. unstable angina, myocardial infarction, heart failure) [5].

KHK ist führende Todesursache

CAD remains the most common cause of death in industrialised countries. Similarly, ischaemic heart disease and acute myocardial infarction in particular are the leading causes of death in Austria, accounting for 12.5 % (9,961) and 6.1 % (4,876) of all deaths in 2013 respectively [14]. The number of coronary events (myocardial infarction and cardiac death) is higher in males than in females and shows a social gradient [5].

A0003 – What are the known risk factors for CAD?

diverse Risikofaktoren

Known risk factors for CAD are hypertension, smoking, sedentary lifestyle, unhealthy diet, obesity, diabetes, genetic factors (family history) and abnormal lipid metabolism [5, 6].

Effects of the disease or health condition on the individual and society

A0004 – What is the natural course of CAD?

stabile KHK erhöht Risiko für kardialen Tod und Infarkt

Patients with stable CAD have an elevated risk of myocardial infarction and premature mortality. The individual risk depends on different risk factors. It is higher in patients with co-morbidity (particularly diabetes) and with severe forms and longer history of angina [5]. Estimates for annual mortality rates range from 1.2–2.4 % per annum with an annual incidence of cardiac death between 0.6 and 1.4 % and of non-fatal myocardial infarction between 0.6 and 2.7 % [6].

eingeschränkte Lebensqualität

Additionally, angina is associated with recurring discomfort, impaired quality of life, reduced physical endurance, mental depression and recurrent hospitalisation [7].

A0006 – What are the consequences of CAD for society?

2 % der Gesundheitsausgaben für KHK

CAD has major human as well as economic costs. According to the European Cardiovascular Disease Statistics [15], CAD accounted for 2 % (€ 489,609,000) of the total health care expenditure or for € 59 per capita in 2009 in Austria. The biggest share (73 %) was attributed to inpatient care (€ 358,277,000).

Gesamtkosten Europa: 60 Mrd.

In Europe, the overall costs for CAD (including direct costs, productivity losses and informal care costs) have been estimated at over € 60 billion.

Current clinical management of the disease or health condition

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

Different diagnostic approaches are used for the chronic and the acute forms of the disease.

Diagnose stabile KHK: Klinik, Labor, EKG, Bildgebung

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 may 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 also offer prognostic information [6].

bei akutem Syndrom Unterscheidung STEMI/NSTEMI

In acute coronary situations, the diagnosis may include clinical evaluation, electrocardiogram, laboratory tests/biomarker and imaging (especially echocardiography). The aim is to differentiate between non-ST-elevation myocardial infarction/NSTEMI or ST-elevation-myocardial infarction/STEMI [8, 9].

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

Management abhängig von klinischer Präsentation

As in the diagnosis, the management of CAD depends on the clinical presentation of CAD (stable, acute), on patient characteristics (age, co-morbidities, etc.) and related risk prognoses and on patient preferences [7].

stabile KHK: konservativ oder Revaskularisierung

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 plus symptomatic medical management only or, additionally, revascularisation, in which case the type of revascularisation has to be determined [6]. Any strategy needs to be accompanied by recommendations for life-style modification [5].

Revaskularisierung eher bei anhaltenden Symptomen

ob Bypass oder PCI hängt vom Nutzen-Risiko Verhältnis ab

Indications for revascularisation are the persistence of symptoms despite medical treatment and/or improvement of prognosis [7]. Patient preferences need to be taken into account [5]. 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, myocardial infarction and stroke against improvements in health-related quality of life, as well as long-term freedom from death, myocardial infarction or repeat revascularisation. Decisions on the most appropriate revascularisation procedure should be guided by clinical judgement, multidisciplinary dialogue and patient preferences. Decisions may be supported by risk stratification models [7]. In general, whether PCI or CABG is more appropriate very much depends of the type and number of affected vessels [5].

bei akutem Syndrom: NSTEMI oder STEMI?

In patients with acute coronary syndrome, management depends on whether patients suffer from NSTEMI or from STEMI [7-9].

NSTEMI: Medikamente und evtl. Revaskularisierung

In patients with NSTEMI (the most frequent manifestation of ACS), treatment includes anti-ischemic therapy (nitrate, beta-receptor blocker etc.), anti-platelet therapy and – potentially – invasive revascularisation. The latter depends on the potential risks associated with invasive and pharmacological

treatments [7]. In the case of a risk stratification that favours revascularisation, early routine angiography followed by revascularisation is favoured against a selective invasive strategy [7, 8]. In stabilised patients, the choice of the revascularisation modality can be made in analogy to patients with stable CAD [7, 8].

STEMI: Reperfusion hat höchste Priorität

Fibrinolyse oder mechanisch mit PCI abhängig von schneller Verfügbarkeit

In the management of patients with STEMI, the timely implementation of reperfusion therapy (fibrinolysis, mechanical reperfusion by primary PCI) is the key issue [7, 9]. 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 [7, 9]. Stenting should be preferred over plain balloon-angioplasty, and new-generation DES have been found to be more effective and safer than BMS [7]. In settings where a timely PCI cannot be performed, fibrinolysis should be considered, particularly if it can be administered pre-hospital [9]. After fibrinolysis, early invasive evaluation is recommended [7].

nach Revaskularisierg. Plättchen- und gerinnungshemmende Therapie

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) [7].

zusätzlich medikamentöse Therapie und Lebensstiländerung

Furthermore, myocardial revascularisation must always be accompanied by medical therapy and other secondary prevention strategies for risk factor modification and permanent lifestyle changes [7].

Target population

A0007 – What is the target population in this assessment?

Zielgruppe: Personen mit KHK und unbehandelten Läsionen

The target population in this assessment includes patients with CAD due to de novo lesions of coronary arteries in whom antithrombotic and/or anticoagulation therapy is not contra-indicated and who do not have aspirin, heparin, bivalirudin, clopidogrel, ticlopidin, prasugrel, ticagrelor, everolimus, PLLA, PDLLA, platin or contrast agent intolerance.

1 Klinik empfiehlt: <75 Jahre, Diabetiker, akutes Koronarsyndrom

According to a guideline from one Austrian clinic on the use of BVS, the primary group of patients includes those who are younger than 75, diabetic and with acute coronary syndromes (particularly with “soft-plaques”). The recommended vessel diameter is 2.5–3.5 mm. The recommended length of the lesion was initially short. In the meantime, the stent has been recommended for longer lesions (e.g. up to 48 mm in the first RCT [16]) to avoid a “full-metal-jacket” and to restore vasomotion. Vessels should only show moderate calcification and should not have strong angulation (< 90°).

A0023 – How many people belong to the target population?

geschätzte ~300,000 Personen mit Angina Pectoris

davon ein Teil PCI mit BVS

The size of the target group can only be approximated. As stable CAD is multi-faceted, its prevalence and incidence have been difficult to assess and numbers vary between studies. The prevalence of angina in population-based studies increases with age in both sexes, from 5–7% in women aged 45–64 years to 10–12% in women aged 65–84 and from 4–7% in men aged 45–64 years to 12–14% in men aged 65–84 years [6]. According to Austrian demographic data [17], these would be equal to 70,730 and 79,460 women aged 45–64 and 65–84 years respectively, and to 63,560 and 74,245 men aged 45–64 and 65–84 years respectively in Austria (~300,000 overall).

As pointed out above, a PCI is indicated only in some patients with stable CAD. Where decisions have been made in favour of a PCI, not all patients are eligible for a BVS.

2005: 16.000 Revaskularisierungen, ein Teil davon für BVS geeignet

With respect to ACS, in 2005 around 24,000 discharges with an ICD-10 diagnosis referring to acute coronary syndrome occurred in Austria in patients up to 75 years. Additionally, around 16,000 revascularisation procedures were reimbursed (80% PCI) in this age group [18]. It is likely that the frequency of revascularisation has risen since then. A proportion of such procedures would in future include implanting a BVS (see next paragraph).

A0011 – How much are the BVS utilised?

geschätzte Häufigkeit: 6000/Jahr

According to the information provided by three hospital providers, the annual Austrian frequency is estimated at 2,000 to 6,000 BVS-procedures. The latter figure seems more realistic, since the three providers themselves already estimated annual frequencies of 230, 400 and 800 BVS-procedures respectively for their individual hospitals.

4 Clinical effectiveness

4.1 Methods

Research questions

Element ID	Research question	Importance 2= critical 1=optional
D0001	What is the expected beneficial effect of the BVS on mortality?	2
D0003	What is the effect of the BVS on the mortality due to causes other than the target disease?	2
D0005	How does the BVS affect symptoms and findings (severity, frequency) of the disease or health condition?	2
D0006	How does the BVS affect recurrence of the disease or health condition?	2
D0016	How does the use of the BVS affect activities of daily living?	2
D0012	What is the effect of the BVS on generic health-related quality of life?	2
D0013	What is the effect of the BVS on disease-specific quality of life?	1
D0017	Was the use of the BVS worthwhile?	1

entscheidende Outcomes Wirksamkeit

The following *crucial* outcomes were used as evidence to derive a recommendation:

- (Cardiac) mortality
- Morbidity: symptoms of angina, MI
- Health-related quality of life
- Recurrent revascularisation

Begründung: BVS sollen kardio-vaskulären Tod und KHK verringern + Lebensqualität verbessern

Revascularisation procedures in patients with CAD are applied to minimise the risk of premature cardiovascular death and to reduce the symptoms of CAD. Hence, the crucial patient relevant outcomes to evaluate the efficacy of any revascularisation technique including BVS are (cardiac) mortality, cardiac morbidity in terms of symptoms of angina or MI and health-related quality of life. This is also supported by the guideline of the European HTA network [19], which points out that endpoints should be long-term or final and all-cause mortality is a preferred clinical endpoint when relevant for the scope of assessment.

möglichst wenig erneute Revaskularisierung

As described in Chapter 2.2, one problem with conventional stents is the need for repeated revascularisation because of re-stenosis. Hence, revascularisation frequency after the implantation has been selected as the fourth crucial outcome.

kombinierter Endpunkt "major adverse cardiac events" (MACE) ungeeignet

One endpoint often used in studies on revascularisation is the composite endpoint "major adverse cardiac events" (MACE). However, according to the EUnetHTA guideline [19], composite endpoints should be avoided for evaluating a technology because the combination often consists of endpoints with very different clinical importance. Instead, a composite endpoint should be disaggregated to the constituent endpoints. In our case, the composite endpoint MACE is inappropriate for the evaluation for two reasons: firstly, MACE is defined differently across studies; secondly, it combines efficacy and safety endpoints. Consequently, the composite endpoint itself was not chosen as relevant outcome parameter, but rather its components.

Sources

Daten aus systematischer Suche + weiteren Quellen

The evidence used in this chapter is based on a systematic literature search in the Medline via Ovid, Embase, Cochrane Library, and CRD (DARE – NHS EED – HTA) databases, and is complemented by a hand search and manufacturer requests according to the PICO question defined in Chapter 1.2.

Analysis

Analyse basiert auf Datenextraktionstabellen und risk of bias Analyse

The data retrieved from the selected studies (see Chapter 1.4) were systematically extracted into a data-extraction-table (Table A1-1). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias using the checklists presented in the Tables A2-1 and A2-4.

Synthesis

Evidenzsynthese mittels GRADE

Based on the data-extraction-table (Table A1-1), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [20]. The results were summarised in evidence-tables (Table 6-1, Table 6-2). The research questions were answered in plain text format.

4.2 Results

Included studies

ABSORB®: 2 RCTs

For evaluating the efficacy of the BVS ABSORB®, 12-months interim results from one RCT with 501 participants [16] and nine-months interim results from an RCT with 240 patients were available. Overall, 415 patients received the BVS (ABSORB®) and 326 a DES (166 Xience Prime®/Everolimus, 80 Promus Element®/Everolimus, 80 Biomatrix Flex®/Biolimus). Study participants were predominantly male with an average age of 61 to 65 years suffering from chronic CAD or ACS (at least one to two de novo lesions affected). Details on anti-platelet therapy were provided in one study: a combination of aspirin (≥100 mg) lifelelong plus either clopidogrel, prasugrel or ticagrelor for at least 6 months was prescribed.

No evidence was available to evaluate the efficacy of the ABSORB® in comparison to other revascularisation technologies and to evaluate the efficacy of the second product with CE-marking (DESolve®).

Study characteristics and results of included studies are displayed in Table A1-1 and summarised inTable 6-1 and Table 6-2.

Mortality

D0001 – What is the expected beneficial effect of the BVS on mortality?

Within nine to 12 months follow-up, there was one cardiac death in the BVS group and no cardiac death in the DES groups. The difference is not statistically significant.

1 kardialer Tod in BVS

D0003 – What is the effect of the BVS on the mortality due to causes other than the target disease?

Within nine to 12 months follow-up four persons (1 %) in the control group died. One death was due cancer; in the other three cases, the causes were not mentioned. There was no death due to causes other than CAD in the BVS group. The difference is not statistically significant.

4 Tote in DES-Gruppe

Morbidity

D0005 – How does the BVS affect symptoms and findings (severity, frequency) of the disease or health condition?

Within nine to 12 months 16 (4%) patients in the BVS groups versus three (1%) in the DES groups had a myocardial infarction. In none of the studies, the difference was statistically significant. Furthermore, three quarters in each group of the 12-months study (227 vs. 113) were angina-free (p=0.98). A post-hoc analysis showed a cumulative angina rate of 72 (22%) in the BVS group and of 50 (30%) in the DES group (p=0.04).

Infarkte und Angina-frei: kein Unterschied zu DES; geringere Angina-Rate in BVS-Gruppe

D0006 – How does the BVS affect recurrence of the disease or health condition?

Within nine to 12 months, 4% to 24% of patients who received the BVS and 7% to 39% of patients who received a DES needed to undergo revascularisation. The difference is not statistically significant in either of the RCTs.

Revaskularisierung: kein Unterschied zu DES

Function

D0016 – How does the use of the BVS affect activities of daily living?

No evidence was found to answer the research question.

Alltagsaktivitäten: keine Evidenz

Health-related quality of life

D0012 – What is the effect of the BVS on generic health-related quality of life?

Data on the quality of life were incompletely presented. The difference between the groups in terms of health-related quality of life was not significant (p=0.55).

Lebensqualität: kein Unterschied

5 Safety

5.1 Methods

Research questions

Element ID	Research question	Importance 2=critical 1=optional
C0008	How safe is the BVS in comparison to other stent types or other revascularisation techniques?	2
C0002	Are the harms related to dosage or frequency of applying the technology?	1
C0004	How does the frequency or severity of harms change over time or in different settings?	1
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	1
C0007	Are the technology and comparator(s) associated with user-dependent harms?	1
B0010	What kind of data/records and/or registry is needed to monitor the use of the BVS and the other revascularisation techniques?	1

The following *crucial* outcomes were used as evidence to derive a recommendation:

entscheidende Sicherheits-Outcomes

- Scaffold/stent-thrombosis and adverse consequences
- Mortality: periprocedural mortality, mortality from bleeding/stroke
- Other serious adverse events (e.g., stroke)

Compared to CABG, one potential advantage of revascularisation with PCI and stent is its lower periprocedural risk. However, stents, in particular first generation DES, have been associated with increased long-term risk of stent thrombosis, which is itself related to increased risk of cardiovascular morbidity and mortality. Furthermore, the anti-platelet therapy patients need to undergo after stenting bears the risk of severe bleeding and mortality. Consequently, scaffold/stent thrombosis, periprocedural mortality and/or mortality from bleeding/stroke have been chosen as crucial safety outcomes.

Begründung: BVS sollten geringeres Re-Interventions- und spätes Thromboserisiko haben

Sources

The evidence used in this chapter is based on a systematic literature search in the Medline via Ovid, Embase, Cochrane Library and CRD (DARE – NHS EED – HTA) databases, complemented by a hand search and manufacturer requests according to the PICO-question defined in Chapter 1.2.

Daten aus systematischer Suche + weiteren Quellen

Analysis

Analyse basiert auf Datenextraktionstabellen und risk of bias Analyse

The data retrieved from the selected studies (see Chapter 1.4) were systematically extracted into data-extraction-tables (Table A1-1, A1-2). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias using the checklists presented in the Tables A2-1, A2-2, A2-3 and A2-4.

Synthesis

Evidenzsynthese mittels GRADE

Based on the data-extraction-tables (Table A1-1, A1-2), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [20]. The results were summarised in evidence-tables (Table 6-1, Table 6-2). The research questions were answered in plain text format.

5.2 Results

Included studies

ABSORB®: 2 RCTs + 10 Beobachtungsstudien, primär einarmig

For evaluating the safety of the BVS ABSORB®, in addition to the RCTs [16, 21] described in Chapter 4.2., ten observational studies presented in 13 publications [22-34] fulfilled our inclusion criteria. Eight studies (eleven publications) [22-32] were single arm and the remaining two [33, 34] were non-randomised controlled studies.

mehrheitlich PatientInnen mit stabiler KHK

Nachbeobachtung 1 bis 36 Monate

Overall, safety data were available from 1,290 patients with BVS and from 486 patients with traditional stents (mainly DES). 364 (30%) BVS-patients suffered from acute coronary syndrome, 740 (61%) from stable CAD, and 186 (15%) from either the former or the latter. 166 DES-patients suffered from stable CAD, 160 from acute coronary syndrome and 160 from either the former or the latter. The follow-up ranged from one month (three studies), six months (four studies) and nine months (one study) to 12 months (three studies) and 36 months (one study).

ø 60–65 Jahre, primär männlich

Patients were on average around 60 to 65 years old and were predominantly male (70-80%). If anti-platelet therapy was described, it was a combination of aspirin (≥75 to 100 mg) plus either clopidogrel, prasugrel or ticagrelor for at least 12 months.

DESolve®: 16 PatientInnen in einarmiger Prototyp-Studie

For evaluating the safety of the DESolve®, one single-arm observational study fulfilled the inclusion criteria [35]. It is a small (16 patients) uncontrolled case series that evaluates a myolimus-eluting BVS prototype, while the product that is currently on sale elutes novolimus. The patients were on average 69 years old and 63% were male.

Study characteristics and results of included studies are displayed in Tables A1-1 and A1-2 and summarised in Tables 6-1 and 6-2.

Patient safety

C0008 – How safe is the BVS in comparison to other stent types or other revascularisation techniques?

ABSORB®

In four studies with a follow-up of six months [26, 30, 32, 33] scaffold thrombosis was observed in four (1.3%) patients. In a nine-month follow-up study one scaffold thrombosis occurred. In three studies with a follow-up of 12 months [16, 27, 31], scaffold thrombosis was observed in another four patients (0.6%). No scaffold thrombosis appeared in the 36 patients with 36 months follow-up [25]. No stent thrombosis occurred in any of the patients in the comparison groups. Where stated, the differences between the groups were not statistically significant.

<1,5 % Thrombosen in BVS-, 0 % in DES-PatientInnen

Where reported, two BVS-patients and two DES-patients died periprocedurally (0.2% and 0.6% respectively) [30, 33, 34].

periprozeduraler Tod <1 % in beiden Gruppen

One patient in the BVS groups versus no patient in the DES groups died from bleeding due to anti-platelet therapy [27].

Blutungstod: 1 vs. 0

Stroke or pneumonia were observed in nine patients (2%) in the BVS groups and in two patients (2%) in the stent groups [27, 30, 32, 34].

jeweils 2 % andere schwere Ereignisse

No evidence on the safety of the BVS in comparison to other revascularisation techniques is available.

Sicherheit gegenüber Bypass unklar

DESsolve®

In the 16 patients who received a prototype of the DESolve® scaffold, one adverse event occurred: one death following a non-target vessel CABG [35].

1 Tod in DESolve® Studie

C0002 – Are the harms related to the frequency of applying the technology?

In theory, the risk of harms increases with the number of scaffolds or stents implanted. The included studies did not analyse whether the frequency of harms was associated with the number of scaffolds implanted.

Zusammenhang Anzahl Implantate-Schaden nicht analysiert

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

Interventional cardiology requires experienced teams. However, whether any harms were associated with volumes of the involved centres or with learning curves has not been part of the research question in the studies.

Zusammenhang Erfahrung/Menge-Schaden nicht analysiert

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

The periprocedural deaths described above occurred in patients with acute coronary syndrome compared to no periprocedural deaths in patients with stable CAD. However, whether or not this was a coincidence cannot be judged on the basis of the current evidence.

ob höheres Risiko bei akutem Syndrom noch unklar

C0007 – Are the technology and comparator(s) associated with user-dependent harms?

keine Nephropathie durch Kontrastmittel, aber kaum berichtet

The accompanying angiography may result in contrast-induced nephropathy which was a reported outcome in one study [26]. Where reported, none of the patients (out of 33) experienced a contrast-induced nephropathy.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of the BVS and the other revascularisation techniques?

RCTs und Register nötig, viele laufen bereits

Firstly, the superior benefit-harm profile of the BVS needs to be demonstrated in robust randomised controlled trials. Indeed, a large number of RCTs are currently ongoing (see Table A4-1 in the Appendix). Because late and very late scaffold thromboses cannot easily be observed in RCTs, registries are additionally recommended to monitor safety. A large number of registries have already be established (see Table A1-2 and Table A4-1) and should be continued [27]. Results from those can be expected from 2016 onwards.

6 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence for each endpoint was individually rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [20]. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of applied criteria can be found in the recommendation of the GRADE Working Group [20]. The ranking according to the GRADE scheme for the research question can be found in the Table 6-1 and Table 6-2.

Schema für Beurteilung

GRADE uses four categories to rank the strength of evidence:

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

Bewertung beginnt mit „hoch" bei RCTs und mit „niedrig" bei Beobachtungsstudien

In outcomes based on randomised controlled trials, the rating starts with "high", however the strength of evidence may be downgraded for several reasons (see GRADE methodology [20]). In observational studies the rating starts with low because the study design of such trials is per se limited with respect to judging on efficacy or safety. The strength of evidence may be downgraded further or upgraded depending on further criteria applied (see Table 6-1 and Table 6-2 and recommendation of the GRADE Working Group [20]).

Stärke der Evidenz Wirksamkeit ABSORB®: mittel

The strength of evidence for the effectiveness of the BVS ABSORB® in CAD in comparison to three types of DES is moderate for the outcomes "(all-cause-)mortality", "morbidity (myocardial infarction, angina)" and "quality of life". Moreover, the strength of evidence for the outcome "revascularisation" is high for a nine-month follow up and low for a 12-month follow-up.

Stärke der Evidenz Sicherheit ABSORB® und DESolve®: moderat bis sehr niedrig

The strength of evidence for the safety of BVS ABSORB ® in comparison to three types of DES in patients with CAD is moderate for short term scaffold/ stent thrombosis. For all other safety outcomes the strength of evidence is very low. Likewise very low is the strength of the evidence for the safety of the BVS DESolve®.

andere Vergleiche: keine Evidenz

No evidence is available for the comparison of BVS and CABG.

Table 6-1: Evidence profile: efficacy and safety of bioresorbable scaffold ABSORB® in patients with coronary artery disease

No of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
All-cause mortality							
1/240	RCT	9 months: 1 (1 %) vs. 3 (2 %)[2]; p=1.00	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
1/501	RCT	12 months: 0 vs. 1 (1 %); p=0.33	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
Cardiac mortality							
1/240	RCT	9 months: 1 (1 %) vs. 0; p=0.33	No serious limitation	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
1/501	RCT	12 months: 0 vs. 0	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
Myocardial infarction							
1/240	RCT	9 months: 1 (1 %) vs. 1 (1 %); p=0.55	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
1/501	RCT	12 months: 15 (4 %) vs. 2 (1 %); p=0.06	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
Angina-free 12 months							
1/501	RCT	74 % vs. 74 %; p=0.98	Serious limitations[4] (-1)	Only 1 trial	Direct, no uncertainty	No	Moderate
Angina rate 12 months							
1/501	RCT	22 % vs. 30 %; **p=0.04**	Serious limitations[5] (-1)	Only 1 trial	Direct, no uncertainty	No	Moderate
Quality of life 12 months							
1/501	RCT	na (p=0.55)	Serious limitations[4] (-1)	Only 1 trial	Direct, no uncertainty	No	Moderate
Revascularisation							
1/240	RCT	9 months: 19 (24 %) vs. 39 (24 %); p=0.99	No serious limitation	Only 1 trial	Direct, no uncertainty	Imprecise data[7] (-1)	Moderate
1/501	RCT	12 months: 12 (4 %) vs. 12 (7 %); p=0.08	Serious limitations[6] (-1)	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Low

[2] Including one cardiac death presented in the following row

[3] Low incidence, study not powered to detect differences

[4] No blinding of outcome assessors, 11% of patients in BVS groups and 3% of patients in DES group were potentially unblinded

[5] No blinding of outcome assessors, 11% of patients in BVS groups and 3% of patients in DES group were potentially unblinded, post-hoc analysis

[6] No blinding of outcome assessors

[7] Study not powered to detect statistically significant differences

No of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety							
Scaffold/stent thrombosis 6 months (definite or probable)							
6 months: 4/306	Observational	4 (1.3 %) vs. 0	Serious limitations[8] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low
9 months: 1/240	RCT	1 (1 %) vs. 0; p=0.33	No serious limitation	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
12 months: 2/283	Observational	1 (1 %) vs. na	Serious limitations[9] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low
12 months: 1/501	RCT	3 (1 %) vs. 0; p=0.55	No serious limitations	Only 1 trial	Direct, no uncertainty	Imprecise data[3] (-1)	Moderate
36 months: 1/36	Observational	0 vs. na	Serious limitations[10] (-1)	Only 1 trial	Direct, no uncertainty	No	Very low
Periprocedural mortality							
10/1475	Observational	2 (0.2 %) vs. 2 (0.6 %)	Serious limitations[11] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low
Mortality from bleeding/stroke							
6 months: 2/175	Observational	0 vs. 0	Serious limitations[12] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low
12 months: 2/283	Observational	1 (0.4) vs. na	Serious limitations[12] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low
36 months. 1/101	Observational	0 vs. na	Serious limitations[10] (-1)	Only 1 trial	Direct, no uncertainty	No	Very low
Other serious adverse events							
4/567	Observational	9 (2 %) vs. 2 (2 %)	Serious limitations[13] (-1)	No important inconsistency	Direct, no uncertainty	No	Very low

BVS: bioresorbable vascular scaffold; na: data not available; significant values in bold

[8] In three studies no control group; treatment with BVS not pre-defined (e.g., according to decision of physician)

[9] No control groups; high risk of selection bias because treatment with BVS not pre-defined

[10] No control group; deviance from study protocol

[11] In seven studies no control group; in five studies high risk of selection bias because treatment with BVS not pre-defined; in one study: analysis combines data from different studies; in 1 study deviance from study protocol

[12] In one study: high risk of selection bias because treatment with BVS not pre-defined (e.g., according to decision of physician)

[13] In three studies: no control group; in one study: treatment with BVS not pre-defined

Table 6-2: Evidence profile: efficacy and safety of bioresorbable scaffold DESolve® in patients with coronary artery disease

No of studies/patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
No evidence							
Safety							
Scaffold thrombosis (12 months)							
1/16	Observational	0	Serious limitations[14] (-1)	Only 1 trial	Direct, no uncertainty	Imprecise data (-1)	Very low
Periprocedural mortality (12 months)							
1/16	Observational	0	Serious limitations[14] (-1)	Only 1 trial	Direct, no uncertainty	Imprecise data (-1)	Very low
Mortality from bleeding/stroke (12 months)							
1/16	Observational	0	Serious limitaitons[14] (-1)	Only 1 trial	Direct, no uncertainty	Imprecise data (-1)	Very low
Other serious adverse events (12 months)							
1/16	Observational	1 (6 %)[15]	Serious limitations[14] (-1)	Only 1 trial	Direct, no uncertainty	Imprecise data (-1)	Very low

[14] Unclear whether all consecutive patients were included

[15] Death following non-target vessel CABG

7 Discussion

nach derzeitiger Evidenz: BVS nicht wirksamer als DES

The currently available evidence (based on two RCTs) shows that concerning patient relevant outcomes the implantation of a BVS is not more efficacious than implanting a DES: After 12 months, (cardiac) mortality, MI, revascularisation and quality of life did not significantly differ between patients who received a BVS compared to those who received a DES. An equal proportion in both groups was free from angina. The cumulative angina rate was lower in the BVS than in the DES group; however, this is based on a post-hoc analysis.

unerwünschte Ereignisse selten, aber große Datenunsicherheit und fehlende Langzeitdaten

In terms of safety, there were in total nine short term scaffold thromboses diagnosed after BVS implantations, while no thrombosis was observed after DES implantation. However, the frequency of scaffold thrombosis was very low (<1.5 %). Less than 1 % of participants died from either periprocedural mortality or from cardiovascular mortality in the intervention and control groups respectively. Except for thrombosis, the strength of the safety evidence is very low and long-term safety outcomes (especially very late scaffold thrombosis incidence) are currently unknown.

endgültiges Nutzen-Schaden Profil noch unklar

In summary, while the current evidence suggests that the BVS is not superior in terms of patient relevant benefits, it is unknown to date whether it is at least equally effective but safer than other stent technologies.

fast nur Daten für ABSORB®

The available evidence is almost entirely related to one of the two CE-marked products (ABSORB®), while the only available study on DESolve® is a very small-scale, uncontrolled case series, which does not evaluate the currently available product but rather a prototype.

limitierte Studienqualität: Untersucher oder Patienten nicht verblindet, für relevante Outcomes zu geringe Studiengröße

The quality of evidence is limited for several reasons. Firstly, while physicians cannot be blinded in this case, patients and outcome assessors could be. However, either outcome assessors or patients were not blinded in the RCTs. This introduces a risk of bias for a number of crucial outcomes (e.g. quality of life, angina symptoms). Secondly, the primary endpoint in the RCT was a surrogate parameter. This means the RCT was not powered for detecting statistically significant differences in the patient-relevant endpoints, so much the more, as many of the crucial outcomes rarely occur (e.g., cardiovascular mortality as a consequence of the implant).

Beobachtungsstudien: meist einarmig, Gefahr Selektionsbias

The most severe limitations in the observational studies are a lack of control groups in most of them and a high risk of selection bias because of the lack of a study protocol or because the decision on implantation of the BVS was based on physicians' judgement. This could have resulted in implanting the BVS predominantly in patients with a good prognosis.

Gültigkeit für ältere PatientInnen mit komplexen Läsionen und akutem Syndrom und für Frauen eingeschränkt

Applicability of the results to routine patients is limited for the following reasons (see Table A3-1): Firstly, the patients in most of the studies were predominantly males with a mean age of around 60 years and with relatively simple lesions. Results are therefore not transferable to patients with complex lesions with wider age ranges frequently encountered in daily practice, which has also been pointed out by study authors [16]. Furthermore, caution is required for transferring the results to females. In addition, most of the patients had stable angina pectoris and very few studies (most of them have a high risk of bias) included patients with acute coronary artery syndrome. The results are, therefore, predominantly valid for a population with stable CAD, while the benefit and safety of the BVS in patients with acute disease has yet to be robustly evaluated.

Unterschied Bildgebung Studie-Routine

Secondly, while the implantation procedure itself does not differ between clinical study setting and routine use, patients in the studies underwent multiple imaging procedures. Adverse consequences of the scaffold may have therefore been better detected than it would be the case in routine care, but it could also have resulted in false-positive results or in negative consequences following the treatment decisions after the imaging results (e.g., adverse events after revascularisation following a positive re-stenosis diagnosis).

Nutzen gegenüber anderen Revaskularisierungsmethoden unklar

Thirdly, the BVS was compared to three types of DES. In routine care, other stent types and other revascularisation strategies will play an important role. The performance of the BVS in comparison to those approaches has not been evaluated so far.

späte Thrombosen bei derzeitiger Studiendauer kaum erkennbar

Furthermore, in terms of scaffold thrombosis, the main interest is in late and very late (> 12 months) thrombosis. However, the results available at the moment are predominantly from a follow-up from six to maximum 12 months.

Studien in spezialisierten Zentren durchgeführt

Finally, while the setting in the studies has not been described precisely, 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 also be limited.

8 Recommendation

In Table 8-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 8-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove that the BVS is more effective and safer or at least equally effective but safer than current stent technologies. No evidence exists to date whether the implantation of a BVS is more effective and/or safer than CABG.

(noch) kein Beleg für besseres Nutzen-Schadenprofil des BVS

A very large number of studies (at least 14 RCTs and 20 single-arm studies, including the ongoing RCT that has been cited in this report [16]) are currently registered (see Chapter "Ongoing studies" of the Appendix for details). They include around 32,120 patients in total and will potentially influence the estimate of effect considerably:

sehr viele laufende Studien

- ABSORB®: ten RCTs (11,107 patients), one non-randomized controlled study (60 patients), nine single arm studies (registries) with 13,323 patients; an overall total of 24,514 patients
- DESolve®: three single-arm studies with 342 patients
- NeoVas: 1 RCT (560 patients), two single-arm studies (855 patients); 1,415 patients overall
- Fortitude: two single-arm studies (170 patients)
- ReZolve: one single-arm study (125 patients)
- ART18Z: one single-arm study (30 patients)
- Biosolve: one single-arm study (121 patients)
- Unspecified devices: three RCTs (2,140 patients), one single-arm registry (1,500 patients), one unspecified study-design (2,000 patients); an overall total of 5,640 patients

A re-evaluation is recommended in 2018. While many of the studies listed in Chapter "Ongoing studies" of the Appendix will still be ongoing at that time, a number of interim results from RCTs and safety data from the registries will very likely be available by then.

neuerliche Evaluierung: 2018

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1-1: Bioresorbable scaffolds: results from randomised controlled trials

Trial, author, year, reference number	ABSORB II; Serruys 2014 [16]	EVERBIO II; Puricel 2015 [21]
Country	Europe, New Zealand	Switzerland
Sponsor	Abbott Vascular	Abbott Vascular, Biosensors International, Boston Scientific
Intervention/Product	Everolimus-eluting bioresorbable scaffold (Absorb®)	Everolimus-eluting bioresorbable scaffold (Absorb®)
Comparator	Everolimus-eluting metallic stent (Xience®)	Everolimus-eluting stent (Promus Element®/Boston Scientific) Biolimus eluting stent (Biomatrix Flex®/Biosensors)
Study design	RCT	RCT
Number of pts	501 (335 vs.166)	240 (80 vs. 80 vs. 80)
Sex (% male)	76 vs. 80	78 vs. 80 vs. 80
Inclusion criteria	18-85 years with evidence of myocardial ischaemia, 1 to 2 de-novo lesions in different epicardial vessels (max. ø 2.25-3.8; max. length 48 mm)	≥18 years, symptomatic CAD or silent ischaemia; no limit for lesion length, number of target lesions or vessels; reference vessel size >4.0 mm
Mean age of patients: yrs (SD)	61.5 (10) vs. 60.9 (10)	65 (11) vs. 65 (11) vs. 65 (10)
Primary endpoint	Vasomotion, Minimum Lumen Diameter (MLD) post nitrate minus MLD post procedure post nitrate	LLL
Follow-up (months)	36; this analysis: 12	60; this analysis: 9
Loss to follow-up, n (%)	6 (2) vs. 2 (1)	9 (12) vs. 8 (10) vs. 5 (6)
Anti-platelet therapy	na	Loading dose of 600 mg clopidogrel, 180 mg ticagrelor or 60 mg prasugrel; lifelong ≥100 mg daily aspirin and 75 mg daily clopidogrel, 90 mg twice daily ticagrelor or 10 mg prasugrel for min. 6 month
Outcomes		
Efficacy		
All-cause mortality; n (%)	0 (0) vs. 1 (1)[16] -0.61 % (95 % CI: -3.35 to 0.65); p=0.33	1 (1) vs. 3 (4) vs. 0; p EES/BES vs. BVS: 1.0
Cardiac mortality; n (%)	0 vs. 0	1 (1) vs. 0 vs. 0
Myocardial infarction[17]; n (%)	15 (4) vs. 2 (1) +3.32% (95% CI: -0.25 to 6.26); p=0.06	1 (1) vs. 1 (1) vs. 0 p EES/BES vs. BVS: 0.55

[16] Due to cancer

Trial, author, year, reference number	ABSORB II; Serruys 2014 [16]	EVERBIO II; Puricel 2015 [21]
Angina; n (%)	Angina-free: 227 (74) vs. 113 (74); p=0.98 Cumulative angina rate: 72 (22) vs. 50 (30); **p=0.04**[18]	na
Quality of life	n: na p=0.55	na
Re-vascularisation	12 (4) vs. 12 (7) -3.65 % (95 % CI: -8.89 to 0.37) p=0.08	19 (24) vs. 24 (30) vs. 15 (19) p EES/BES vs. BVS: 0.99
Composite endpoint (death, MI, revascularisation); n (%)	24 (7) vs. 15 (9) -1.84 % (95 % CI: -7.69 to 2.98); p=0.47	21 (27) vs. 26 (33) vs. 15 (19) p EES/BES vs. BVS: 0.83
Safety		
Overall complications; n (%)	na	
Scaffold/stent thrombosis; n (%)	Definite thrombosis *Acute (0-1 day)* 1 (0.3) vs. 0; p=1 *Sub-acute (2-30 days)* 1 (0.3) vs. 0; p=1 *Late (31-365 days)* 0 vs. 0; p=1 Overall definite or probable thrombosis 3 (0.9) vs. 0; + 0.91 % (95 % CI: -1.45 to 2.65); p=0.55	1 (1) vs. 0 vs. 0 p EES/BES vs. BVS: 0.33
Periprocedural mortality, n (%)	0 vs. 0	na
Periprocedural myocardial infarction; n (%)	na (3-30) vs. na (1-26)[19] p=na	na
Bleeding from anti-platelet treatment	na	na
Procedure-related contrast-induced nephropathy	na	na
Vascular access-site complication	na	na
Mortality from bleeding or stroke	na	na
Other serious adverse events	na	na

BES: biolimus eluting stent; BVS: bioresorbable vascular scaffold; CAD: coronary artery disease; EES: everolimus eluting stent; LLL: late lumen loss; na: data not available; pts: patients; SD: standard deviation; TLR: target lesion revascularisation; TVR: target vessel revascularisation; yrs: years

[17] Defined as development of new pathological Q-wave or creatine kinase rise of two or more times of upper limit of normal accompanied by creatine kinase-MB rise

[18] Post-hoc analysis

[19] Percentage depending on the cardiac biomarker applied for MI

Table A1-2: Bioresorbable scaffolds: results from non-randomized controlled and single-arm trials/1

Trial, author, year, reference number	ABSORB cohort B (B1+B2); Ormiston 2012 [22], Serruys 2010, 2011, 2014 [23-25]	CTO-ABSORB Vaquerizo (2014) [26]	ASSURE registry; Wöhrle 2014 [27]	B-SEARCH; Simsek 2014 [28][20]	BVS STEMI first study; Diletti 2014 [29]	Wiebe 2014 [30]	POLAR-ACS; Dudek 2014 [31]
Country	Europe, New Zealand, USA, Australia	Spain	Germany	The Netherlands	The Netherlands	Germany	Poland
Sponsor	Abbott Vascular	Abbott Vascular	Abbott Vascular	Abbott Vascular	Abbott Vascular	na[21]	na
Intervention/Product	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)
Comparator	-	-	-	-	-	-	-
Study design	Prospective single-arm study	Prospective single-arm study	Prospective single-arm study	Prospective single-arm study	Prospective single-arm study	Prospective single-arm study	Prospective single-arm study
Number of pts	101	33	183	88	49	25	100
Sex (n, % male)	73 (72)	28 (80)	146 (80)	64 (73)	38 (78)	19 (76)	STEMI: 13 (81); NSTEMI: 23 (61); UA: 37 (80)
Mean age of patients: yrs	62 (±9)	61 (±10)	63 (±9)	61 (±9)	60 (±11)	60 (±11)	STEMI: 54 (±9); NSTEMI: 68 (±11); UA: 61 (±10)
Inclusion criteria	Max. 2 de novo native coronary artery lesions (max. ø 3 mm, length ≤14mm, % diameter stenosis ≥50 and <100%	At least 1 chronic total occlusion (CTO), ø 2.5 to 3.5 mm,	18 to 75 years, ischaemic heart disease, 1 or more de novo native coronary artery lesions; ø: ≥2 and ≤3.8 mm	ABSORB cohort A+B: Max. 2 de novo native coronary artery lesions (max. ø 3 mm, length ≤14mm, % diameter stenosis ≥50 and <100%) ABSORB Extend: max. 2 de novo native coronary artery lesions, length: ≤28mm	Patients with STEMI, ≥18 years, vessels ≥2 and ≤3.8 mm	Patients with STEMI	Patients with acute coronary syndrome (STEMI, NSTEMI, UA)
Follow-up (months)	36	6	12	1	1	6	12
Loss to follow-up, n (%)	1 (2)	0	3 (2)	0	0	1 (4)	2 (2)

[20] Includes patients from ABSORB cohort A, ABSORB cohort B and ABSORB EXTEND that were treated in the Netherlands

[21] Author(s) received speaker honoraria from Abbott Vascular

Trial, author, year, reference number	ABSORB cohort B (B1+B2); Ormiston 2012 [22], Serruys 2010, 2011, 2014 [23-25]	CTO-ABSORB Vaquerizo (2014) [26]	ASSURE registry; Wöhrle 2014 [27]	B-SEARCH; Simsek 2014 [28][20]	BVS STEMI first study; Diletti 2014 [29]	Wiebe 2014 [30]	POLAR-ACS; Dudek 2014 [31]
Anti-platelet therapy	Clopidogrel 75 mg for 6 months + aspirin lifelong according to ESC guideline	na	Aspirin 100 mg + clopidogrel 75 mg for 6 months continued with aspirin 100 mg	na	Type: na; duration: 12 months	na	According to ESC guideline for 12 months
Outcomes							
Safety							
Overall complications; n (%)	na	1 (3)	11 (6)	0	0	4 (16)	3 (3)
Scaffold/stent thrombosis; n (%)	0	0	0	0	0	1 (4)[22]	1 (1)[23]
Periprocedural mortality, n (%)	0	0	0	0	0	unclear[24]	0
Periprocedural myocardial infarction; n (%)	na	0	0	0	0	0	2 (2)
Bleeding from anti-platelet therapy; n (%)	na	na	8 (4)	na	na	na	na
Procedure-related contrast-induced nephropathy; n (%)	na	0	na	na	na	na	na
Vascular access site complication; n (%)	na	1 (3)	na	na	na	na	na
Mortality from bleeding or stroke	0	0	1	0	0	na	0
Other serious adverse events	na	na	3 (2)[25]	na	na	3 (12)[26]	na

CTO: chronic total occlusion; ESC: European Society of Cardiology; na: data not available; NSTEMI: non-ST-segment elevation myocardial infarction; pts: patients; STEMI: ST-elevation myocardial infarction; UA: unstable angina; yrs: years

[22] Two days after implantation

[23] Definite stent thrombosis which caused MI

[24] Inconsistency between cases of death in table (1) and text in paper (0)

[25] Stroke/transient ischaemic attack

[26] One stroke, one pneumonia, one ventricular tachycardia

Table A1-3: Bioresorbable scaffolds: results from non-randomized controlled and single-arm trials/2

Trial, author, year, reference number	Jaguszewski 2014 [32]	Prague 19; Kocka 2014 [33]	Gori 2013 [34]	DESolve; Verheye 2014 [35]
Country	Switzerland	Czech Republic	Germany	Belgium, New Zealand,
Sponsor	Abbott Vascular	Public[27]	Public[27]	Elixir Medical
Intervention/Product	Everolimus-eluting bioresorbable scaffold (ABSORB®)	Everolimus-eluting bioresorbable scaffold (ABSORB®)	Everolimus-eluting bioresorbable scaffold (ABSORB ®)	DESolve myolimus eluting bioresorbable coronary scaffold system
Comparator	-	a) Drug eluting or bare metal stent b) no stent	XIENCE PRIME™ metal everolimus eluting stent	-
Study design	Prospective single-arm study	Non-randomised controlled study	Non-randomised controlled study	Prospective single-arm study
Number of pts	106	142 (40 vs. 57 vs. 45)	253 (150 vs. 103)	16
Sex (n, % male)	81 (76)	31 (78) vs. 43 (75) vs. 25 (56)	110 (73) vs. 72 (70)	10 (63)
Age of patients: yrs	61 (±11)	59 (11)[28] vs. 64 (13) vs. 69 (13)	62 (±13) vs. 62 (±11)	69 (±8)
Inclusion criteria	Patients with CAD or ACS, at least 1 coronary artery lesion	Patients with STEMI<24 h from symptom onset	Patients with ACS (UA, STEMI, NSTEMI) with de novo lesions in native coronary artery	Patients with myocardial ischaemia, 1 de novo native coronary artery lesion, ø≤3mm, length ≤10mm
Follow-up (months)	~5	6	6[29]	12
Loss to follow-up, n (%)	8 (8)	23 (58) vs. 32 (56) vs. na[30]	na	1 (6)
Anti-platelet therapy therapy	Aspirin 100 mg + clopidogrel 75 mg, prasugrel 10 mg or ticagrelor 2 x 90 mg for 12 months	Preferred but not mandated: Aspirin + prasugrel, 6 to 12 months	Aspirin 100 mg + clopidogrel, prasugrel or ticagrelor for 12 months	Aspirin ≥75 mg + clopidogrel 75 mg for min. 12 months
Outcomes				
Efficacy				
Overall complications; n (%)	na	2 (5) vs. 4 (7) vs. na	na	2 (13)
Scaffold/stent thrombosis; n (%)	2[31]	1 (3) vs. 0 vs. nr.	1 month definite 3 (2) vs. 3 (3); p=1 1 month probable 1 (0.7) vs. 1 (1); p=1	0

[27] Author(s) received speaker honoraria from Abbott Vascular

[28] Standard deviation

[29] Only one-month data extracted because six-month follow up was not completed at time of publication

[30] Drop-outs inconsistent between figure and text in publication

[31] One acute, one sub-acute

Trial, author, year, reference number	Jaguszewski 2014 [32]	Prague 19; Kocka 2014 [33]	Gori 2013 [34]	DESolve; Verheye 2014 [35]
Periprocedural mortality, n (%)	na	0 vs. 1 (2) vs. na	1 (1) vs. 1 (1) p=1	0
Periprocedural myocardial infarction; n (%)	na	0 vs. 0 vs. na	3 (2) vs. 1 (1) p=0.63	1 (6)
Bleeding from anti-platelet therapy; n (%)	na	na	na	na
Procedure-related contrast-induced nephropathy; n (%)	na	na	na	na
Vascular access site complication; n (%)	na	na	na	na
Mortality from bleeding/stroke	na	0 vs. 0 vs. na	0 vs. 0	0
Other serious adverse events	2 (2)[32]	na	1 month 1 (1) vs. 2 (2)[33]	1(6)[34]

ACS: acute coronary syndrome; CAD: coronary artery disease; na: data not available; nr: not relevant

[32] All-cause death, one of cardiovascular cause

[33] Within 1 month: Bioresorbable scaffold group: 1 sudden death; DES group: 2 sudden deaths (one due to in-stent thrombosis)

[34] Death following non-target vessel coronary artery bypass grafting

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA and in the Guidelines of EUnetHTA [36].

Table A2-1: Risk of bias – study level (randomised studies)

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
ABSORB II [16]	Yes	Yes	(Yes)[35]	No	Yes	No[36]	High
EVERBIO II [21]	Yes	Yes	No[37]	No	Yes	Yes	Low

Table A2-2: Risk of bias – study level (non-randomised controlled studies, see [37])

Study reference/ID	How was the treatment group determined for each patient?	Were treatment groups comparable at baseline?	What steps were taken to minimise bias?	Were all relevant outcomes reported?	Was intention-to-treat appropriately implemented?	Any other problems that could put the study at a high risk of bias
Prague 19; Kocka 2014 [33]	Allocation to groups was based on eligibility of patients	No (better prognosis for control group patients)	None	Partly	Unclear	Selection bias because of non-randomised design
Gori 2013 [34]	Choice was based on availability of scaffolds	No	None	Partly	Unclear	Selection bias because auf non-randomised design

[35] 37 patients in intervention group and five in control group were potentially unblinded through discharge letters to referring physicians, some outcomes (e.g., angina) likely to be influenced by broken blinding

[36] Cumulative angina rate was post-hoc analysis

[37] No blinding, however, the outcomes defined in the study are not likely to be influenced by lack of blinding

Table A2-3: Risk of bias case series (see [38])

	ABSORB cohort B [22-25]	CTO-ABSORB [26]	ASSURE registry[27]	B-SEARCH [28]	BVS STEMI first study [29]	Wiebe 2014 [30]	POLAR-ACS; Dudek 2014 [31]	Jaguszewski 2014[32]	DESolve; Verheye 2014 [35]
Study objective									
Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Study population									
Are the characteristics of the participants included in the study described?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were the cases collected in more than one centre?	yes	no	yes	yes	no	na	yes	yes	yes
Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	yes	yes	yes	yes	yes	no[38]	yes	yes	yes
Were participants recruited consecutively?	yes	yes	yes	no[44]	no[39]	no[39]	yes	no[40]	na[41]
Did participants enter the study at similar point in the disease?	no[42]	no[43]	no[43]	no[44]	no[43]	no[43]	no[45]	no[43]	no[43]
Intervention and co-intervention									
Was the intervention clearly described in the study?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were additional interventions (co-interventions) clearly reported in the study?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Are the outcome measures clearly defined in the introduction or methods section?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were relevant outcomes appropriately measured with objective and/or subjective methods?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were outcomes measured before and after intervention?	na[46]	na[46]	na[46]	na[46]	na[46]	na[46]	na[46]	na[46]	na[46]

[38] Exclusion criteria not defined

[39] Arbitrary allocation to BVS

[40] Selection of patients at discretion of operator

[41] Unclear whether all consecutive patients were included

[42] In 41 from 101 patients BVS was implanted in vessels with ≤2.5 mm diameter while study protocol defined 3mm vessel diameter

[43] Different history of MI, revascularisation, vessel anatomy

[44] Analysis combines data from different studies

[45] Patients with different types of acute coronary syndrome (NSTEMI, STEMI)

[46] For safety outcomes not applicable

	ABSORB cohort B [22-25]	CTO-ABSORB [26]	ASSURE registry[27]	B-SEARCH [28]	BVS STEMI first study [29]	Wiebe 2014 [30]	POLAR-ACS; Dudek 2014 [31]	Jaguszewski 2014[32]	DESolve; Verheye 2014 [35]
Statistical analysis									
Were the statistical tests used to assess the relevant outcomes appropriate?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Results and conclusions									
Was the length of follow-up reported?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was the loss to follow-up reported?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	na[47]	na[47]	na[47]	na[47]	na[47]	na[47]	na[47]	na[47]	na[47]
Are adverse events reported?	partly	partly	partly	partly	partly	partly	partly	partly	partly
Are the conclusions of the study supported by results?	yes	yes	yes	yes	yes	yes	yes	yes	yes
Competing interests and sources of support									
Are both competing interests and sources of support for the study reported?	yes	yes	yes	yes	yes	no[48]	no	yes	yes

Na: data not available

[47] Data reported are absolute counts

[48] Sources of support not reported

Table A2-4: Risk of bias – outcome level

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Efficacy						
All-cause mortality						
ABSORB II [16]	High	Low	Low	Low	Low	Low
EVERBIO II [21]	Low	Low	High	Low	Low	Low
Cardiac mortality						
ABSORB II [16]	High	Low	Low	Low	Low	Low
EVERBIO II [21]	Low	Low	High	Low	Low	Low
MI						
ABSORB II [16]	High	Low	Low	Low	Low	Low
EVERBIO II [21]	Low	Low	High	Low	Low	Low
Composite endpoint (death, MI, revascularisation)						
ABSORB II [16]	High	Low	Low	Low	Low	Low
EVERBIO II [21]	Low	Low	High	Low	Low	Low
Angina						
ABSORB II [16]	High	High	Low	Low	Low	High
Health related quality of life						
ABSORB II [16]	High	High	Low	Low	Low	High
Revascularisation						
ABSORB II [16]	High	High	Low	Low	Low	High
EVERBIO II [21]	Low	Low	High	Low	Low	Low
Safety						
Overall complications						
CTO-ABSORB *[26]*	High	High	High	Low	High	High
ASSURE registry *[27]*	High	High	High	Low	High	High
B-SEARCH *[28]*	High	High	Low	Low	High	High
BVS STEMI first *[29]*	High	High	Low	Low	High	High
Wiebe *[30]*	High	High	Low	Low	High	High
POLAR-ACS *[31]*	High	High	High	Low	High	High
Prague 19 *[33]*	High	High	High	Low	High	High
DESolve *[35]*	High	High	High	Low	High	High

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Scaffold/Stent-thrombosis						
ABSORB II [16]	High	Low	Low	Low	Low	Low
EVERBIO II [21]	Low	Low	High	Low	Low	Low
ABSORB cohort B *[22-25]*	High	High	Low	Low	High	High
CTO-ABSORB *[26]*	High	High	High	Low	High	High
ASSURE registry *[27]*	High	High	High	Low	High	High
B-SEARCH *[28]*	High	High	Low	Low	High	High
BVS STEMI first *[29]*	High	High	Low	Low	High	High
Wiebe *[30]*	High	High	Low	Low	High	High
POLAR-ACS *[31]*	High	High	High	Low	High	High
Jaguszewski *[32]*	High	High	High	Low	High	High
Prague 19 *[33]*	High	High	High	Low	High	High
Gori *[34]*	High	High	High	Low	High	High
DESolve *[35]*	High	High	High	Low	High	High
Procedure-related mortality						
ABSORB II [16]	High	Low	Low	Low	Low	Low
ABSORB cohort B *[22-25]*	High	Low	Low	Low	High	High
CTO-ABSORB *[26]*	High	Low	High	Low	High	High
ASSURE registry *[27]*	High	Low	High	Low	High	High
B-SEARCH *[28]*	High	Low	Low	Low	High	High
BVS STEMI first *[29]*	High	Low	Low	Low	High	High
Wiebe *[30]*	High	Low	Low	Low	High	High
POLAR-ACS *[31]*	High	Low	High	Low	High	High
Prague 19 *[33]*	High	Low	High	Low	High	High
Gori *[34]*	High	Low	High	Low	High	High
DESolve *[35]*	High	Low	High	Low	High	High
Periprocedural myocardial infarction						
ABSORB II [16]	HIgh	Low	Low	Low	Low	Low
CTO-ABSORB *[26]*	High	Low	High	Low	High	High
ASSURE registry *[27]*	High	Low	High	Low	High	High
B-SEARCH *[28]*	High	Low	Low	Low	High	High
BVS STEMI first *[29]*	High	Low	Low	Low	High	High
Wiebe *[30]*	High	Low	Low	Low	High	High

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
POLAR-ACS *[31]*	High	Low	High	Low	High	High
Prague 19 *[33]*	High	Low	High	Low	High	High
Gori *[34]*	High	Low	High	Low	High	High
DESolve *[35]*	High	Low	High	Low	High	High
Bleeding from anti-platelet therapy						
ASSURE registry *[27]*	High	High	High	Low	High	High
Procedure-related contrast-induced nephropathy						
CTO-ABSORB *[26]*	High	High	High	Low	High	High
Vascular access site complication						
CTO-ABSORB *[26]*	High	High	High	Low	High	High
Mortality from bleeding/stroke						
ABSORB cohort B *[22-25]*	High	Low	Low	Low	High	High
CTO-ABSORB *[26]*	High	Low	High	Low	High	High
ASSURE registry *[27]*	High	Low	High	Low	High	High
B-SEARCH *[28]*	High	Low	Low	Low	High	High
BVS STEMI first *[29]*	High	Low	Low	Low	High	High
POLAR-ACS *[31]*	High	Low	High	Low	High	High
Prague 19 *[33]*	High	Low	High	Low	High	High
Gori *[34]*	High	Low	High	Low	High	High
DESolve *[35]*	High	Low	High	Low	High	High
Other serious adverse events						
ASSURE registry *[27]*	High	High	High	Low	High	High
Wiebe *[30]*	High	High	Low	Low	High	High
Jaguszewski *[32]*	High	High	High	Low	High	High
Gori *[34]*	High	High	High	Low	High	High
DESolve *[35]*	High	High	High	Low	High	High

Applicability table

Table A3-1: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The patients in most of the studies were predominantly males with a mean age of around 60 years and with relatively simple lesions in contrast to patients with more complex lesions and wider age ranges frequently encountered in daily practice. The generalisabilty is therefore limited. Furthermore, the study population is predominantly male, hence, generalisability to females is limited. Most of the patients had stable CAD and very few studies, yet with high risk of bias, have included patients with acute coronary artery syndrome. The results are, therefore, only valid for a population with stable CAD.
Intervention	The implantation procedure does not differ from routine use. However, patients in the studies underwent multiple imaging procedures. Compared to routine use, this could have resulted in positive or negative consequences (false-positive, false-negative results etc.)
Comparators	In the only RCT available, the BVS was compared to a DES. 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 BVS is superior to those approaches in terms of benefits and harms.
Outcomes	The primary outcome in the current key study [16] is a surrogate endpoint which does not reflect the most important clinical benefits and harms. The secondary outcomes in this study and the outcomes in the observational studies are patient-relevant, however, the follow-up has mostly been 6 to 12 months only and thus, the superiority of the BVS in term so long-term safety issues (especially late and very late scaffold thrombosis, fatal events) cannot be judged yet.
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.

Ongoing studies

Table A4-1: Ongoing studies

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
ABSORB®							
NCT01986803 (TROFI II Study) Sponsor: ECRI-bv	2015–2017	RCT (single-blind)	190	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	XIENCE Xpedition stent	Acute ST-Elevation myocardial infarction	Healing Score
NCT01425281 (ABSORB II) Sponsor: Abbott Vascular	2011–2018	RCT (single-blind)	501	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE Everolimus Eluting Coronary Stent System	Patients with CAD caused by up to two de novo native coronary artery lesions in separate vessels	Vasomotion, MLD
NCT01751906 (ABSORB III) Sponsor: Abbott Vascular	2012–2019	RCT (single-blind	2250	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE Everolimus Eluting Coronary Stent System	Subjects with de novo native coronary artery lesions	Target lesion failure (TLF) at 1 year (non-inferiority)
NCT01844284 (ABSORB Japan) Sponsor: Abbott Vascular	2013–2019	RCT (single-blind)	400	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE PRIME®/XIENCE Xpedition	Subjects with ischemic heart disease caused by de novo native coronary artery lesions	Target Lesion Failure (TLF), non-inferiority
NCT01858077 (Amsterdam Investigator-initiateD Absorb Strategy All-comers Trial/AIDA) Sponsor: Academisch Medisch Centrum – Universiteit van Amsterdam (AMC-UvA)	2013 -2020	RCT (single-blind)	2690	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE PRIME®/XIENCE Xpedition	Coronary lesions in consecutive all-comers	Target vessel failure (TVF)
NCT02173379 (ABSORB IV) Sponsor: Abbott Vascular	2014–2021	RCT (single-blind)	3000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE Everolimus Eluting Coronary Stent System	Subjects with de novo native coronary artery lesions	Percentage of patients who experienced angina within 1 year, (non-inferiority)
NCT02151929 Sponsor: San Giuseppe Moscati Hospital	2013–2014	RCT (unblinded)	100	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE PRIME®	Patients with ST elevation myocardial infarction	Procedural and Clinical success
NCT01942070 (ISAR- ABSORB MI) Sponsor: Deutsches Herzzentrum Muenchen	2013–2015	RCT (unblinded)	260	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Durable polymer everolimus-eluting metallic stent (EES)	Patients undergoing PCI in the setting of acute MI	Percentage Diameter Stenosis

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
NCT02171065 (PROSPECT ABSORB) Sponsor: Uppsala University	2014–2018	RCT (unblinded)	900	ABSORB BVS + Guideline Directed Medical Therapy	Sham + ABSORB BVS	Patients with acute coronary syndrome	Non-culprit major adverse cardiac event (NC-MACE)
NCT01923740 (ABSORB CHINA RCT) Sponsor: Abbott Vascular	2013–2019	RCT (unblinded)	480	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Abbott Vascular XIENCE Everolimus Eluting Coronary Stent System	Patients with ischemic heart disease caused by up to two de novo native coronary artery lesions in separate vessels	In-segment late loss
NCT02067091 (BVS in STEMI) Sponsor: Haukeland University Hospital	2014–2020	RCT (unblinded)	120	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Xience pro	Patients presenting with ST elevation myocardial infarction for primary PCI (percutaneous coronary intervention)	Coronary stent healing index
NCT02001025 Sponsor: Medical University Vienna	2013–na	Non-randomised controlled trial	60	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	Xience stent	Patients with CAD and multiple lesions to be treated	adverse post-stenting results
NCT01759290 (ABSORB First) Sponsor: Abbott Vascular	2013–2015	Single-arm registry	1801	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	Patients with de novo lesions in previously untreated vessels	Cardiac death/target vessel-MI/ischaemia driven-target lesion revascularisation
NCT02004730 (IT DISAPPEARS) Sponsor: Istituto Clinico Sant'Ambrogio	2013–2015	Single-arm registry	1000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	Patients with diffuse or multivessel coronary artery disease	Major adverse cardiac events
NCT02071342 (ABSORB-ACS) Sponsor: Umberto I Hospital, Frosinone Italy	2013–2015	Single-arm registry (Italian Registry)	300	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	Patients with myocardial infarction	Major adverse cardiac events
NCT01583608 (ASSURE) Sponsor: Medical Care Center Prof. Mathey, Prof. Schofer, Ltd.	2012–2016	Single-arm registry	180	Everolimus-eluting Bioresorbable Vascular Scaffold	-	Patients with de novo native coronary artery lesions in all-day clinical practice	No primary endpoint defined
NCT01915420 (ASSURE-ROT registry) Sponsor: Medical Care Center Prof. Mathey, Prof. Schofer, Ltd.	2013–2017	Single-arm registry	42	Everolimus-eluting Bioresorbable Vascular Scaffold	-	Following rotational atherectomy in patients with complex de novo native coronary artery lesions in all-day clinical practice	Major adverse cardiac event
NCT01977534 (ABSORB UK) Sponsor: Abbott Vascular	2014–2018	Single-arm registry	1000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	Patients with de novo lesions	Acute success: device success (lesion based analysis)

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
NCT02066623 (GABI-R) Sponsor: IHF GmbH-Institut für Herzinfarktforschung	2013–2020	Single-arm German-Austrian registry	5000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	Patients with coronary artery stenosis	Number of serious adverse cardiac events
NCT02298413 (Italian Absorb Registry/BVS RAI) Sponsor: Ospedale Santa Croce-Carle Cuneo	2013–2021	Single-arm registry (Italian Registry)	2000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	All-comers study, and includes all consecutive patients who have been treated with 1 or more BVS	Scaffold thrombosis, target lesion revascularisation
NCT02238054 (FRANCE ABSORB) Sponsor: French Cardiology Society	2014–2022	Single-arm registry	2000	Abbott vascular ABSORB Everolimus Eluting Bioresorbable Vascular Scaffold System	-	All patients with a coronary angioplasty procedure and the implantation of at least one ABSORB BVS	Major adverse cardiac events
DESolve®							
NCT02086006 (DESolve I trial) Sponsor: Elixir Medical Corporation	2011–2016	Single-arm	16	DESolve Myolimus Eluting Bioresorbable Coronary Stent System	-	Patients with de novo coronary artery lesions	Major adverse cardiac events, target vessel failure, target vessel revascularisation, acute success, stent thrombosis
NCT02086045 DESolve Nx Trial Sponsor: Elixir Medical Corporation	2011- 2017	Single-arm	126	DESolve® Novolimus Eluting Bioresorbable Coronary Scaffold System	-	Patients with a single de novo native coronary artery lesion	Clinically-indicated major adverse cardiac events
NCT02013349 (DESolve post approval study) Sponsor: Elixir Medical Corporation	2014–2020	Single-arm	200	DESolve Novolimus Eluting Bioresorbable Coronary Scaffold System	-	Patients with de novo coronary artery lesions	Major adverse cardiac events
NeoVas							
NCT02305485 Sponsor: Lepu Medical Technology (Beijing) Co.,Ltd	2014–2020	RCT (single-blind)	560	NeoVas sirolimus-eluting bioresorbable coronary scaffold	XIENCE PRIME Everolimus Eluting Coronary Stent System	Patients with de novo coronary artery lesion	In-segment late lumen loss
NCT02195414 (NeoVas Bioresorbable Coronary Scaffold first-in-man study) Sponsor: Lepu Medical Technology (Beijing) Co.,Ltd	2014–2019	Single-arm	30	NeoVas sirolimus-eluting bioresorbable coronary scaffold	-	Patients with de novo coronary lesion	Target lesion failure
NCT02305472 Sponsor: Lepu Medical Technology (Beijing) Co.,Ltd	2014–2020	Single-arm registry	825	NeoVas sirolimus-eluting bioresorbable coronary scaffold	-	Patients with de novo coronary artery lesion	Target lesion failure

Study Identifier	Time	Study type	N	Intervention	Comparator	Patient population	Primary endpoints
Fortitude							
NCT02255864 Sponsor: Amaranth Medical	2015–2020	Single-arm	120	Amaranth Medical FORTITUDE Bioresorbable Drug-Eluting Coronary Stent	-	Single, de novo, stenotic native coronary artery lesions in patients undergoing elective percutaneous coronary intervention	In-scaffold late lumen loss, incidence of target vessel failure
NCT02189499 Sponsor: Amaranth Medical Inc.	2014–2020	Single-arm	50	Amaranth Medical FORTITUDE Bioresorbable Drug-Eluting Coronary Stent	-	Single, de novo, stenotic native coronary artery lesions in patients undergoing elective percutaneous coronary intervention	Target vessel failure, in-scaffold late lumen loss
ReZolve							
NCT01845311 RESTORE II Sponsor: REVA Medical, Inc.	2013–2018	Single-arm	125	ReZolve2 Sirolimus-Eluting Bioresorbable Coronary Scaffold	-	na	Major adverse cardiac events, late lumen loss
ART18Z							
NCT01761578 (ARTDIVA) Sponsor: Arterial Remodeling Technologies	2012–2013	Single-arm	30	ART18Z Bioresorbable Stent	-	Patients with single de novo lesion of a native coronary artery	Major adverse cardiac events
Biosolve							
NCT01960504 (BIOSOLVE II) Sponsor: Biotronik AG	2013–2018	Single-arm	121	2nd Generation Drug Eluting Absorbable Metal Scaffold (BIOSOLVE-II)	-	Subjects with de novo lesions in native coronary arteries	In segment Late Lumen Loss
Studies with unspecified products							
NCT02316886 (PREVENT) Sponsor: Seung-Jung Park	2014–2019	RCT(unblinded)	2000	Bioresorbable Vascular Scaffold	Optimal medical Treatment	Patients with functionally insignificant coronary stenosis with vulnerable plaque	Cardiovascular death, non-fatal MI, unplanned hospitalisation
NCT02334826 (RELEASE BVS) Sponsor: Poznan University of Medical Sciences	2015–2022	RCT (unblinded)	140	Bioresorbable Vascular Scaffold	CABG	Patients with advanced stable ischemic heart disease	Extent of ischemia and left ventricular ejection fraction in cardiovascular magnetic resonance
NCT02256449 (REPARA study) Sponsor: Sección Hemodinamica y Cardiologia Intervencionista	2014–2016	Single-arm registry	1500	Bioresorbable coronary device	-	Patients undergoing PCI in de novo coronary artery lesions	Major adverse cardiac events
NCT02162056 (CSI-Ulm-BVS) Sponsor: University of Ulm	2013–2028	na	2000	Bioresorbable Vascular Scaffold	-	Patients with CAD	Major adverse cardiac events

CAD: coronary artery disease

Literature search

Search strategy for Medline (via Ovid)

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 05, 2015>, Ovid MEDLINE(R) Daily Update <November 19, 2014>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	*Angina, Stable/(352)
2	*Angina, Unstable/(5532)
3	*Angina Pectoris/(19222)
4	angina*.mp. (64064)
5	*Myocardial Infarction/(109006)
6	*Myocardial Ischemia/(24154)
7	myocard*.mp. (481367)
8	*Coronary Artery Disease/(33563)
9	*Acute Coronary Syndrome/(7275)
10	*Coronary Disease/(95891)
11	coronary.mp. (416260)
12	*Heart Diseases/(40846)
13	heart*.mp. (1047239)
14	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 (1424379)
15	bioabsorbable*.mp. (1940)
16	bio-absorbable*.mp. (75)
17	biodegradable*.mp. (16737)
18	bio-degradable*.mp. (47)
19	exp Biodegradable Plastics/(61)
20	bioresorbable*.mp. (1439)
21	bio-resorbable*.mp. (21)
22	exp Biocompatible Materials/(77195)
23	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (91178)
24	*Percutaneous Coronary Intervention/(3237)
25	Percutaneous Coronary Intervention*.mp. (21187)
26	PCI*.mp. (16409)
27	*Stents/(34487)
28	*Drug-Eluting Stents/(5387)
29	stent*.mp. (79974)
30	*Tissue Scaffolds/(6664)
31	scaffold*.mp. (56409)
32	*Absorbable Implants/(3543)
33	Absorb.ti,ab. (6732)
34	DEsolve.ti,ab. (1)
35	DREAMS.ti,ab. (3711)
36	IDEAL.ti,ab. (75567)
37	Igaki*.mp. (9)

38	Fantom.ti,ab. (55)
39	ART18Z.mp. (0)
40	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (240647)
41	23 and 40 (16625)
42	14 and 41 (2315)
43	exp Clinical Trial/or double-blind method/or (clinical trial* or randomized controlled trial or multicenter study).pt. or exp Clinical Trials as Topic/or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab. (1248704)

06.01.2015

Search strategy for Embase

No	Query Results	Results	Date
#1.	'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'in vivo study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'methodology'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de AND ('stable angina pectoris'/mj OR 'unstable angina pectoris'/mj OR 'angina pectoris'/mj OR 'angina pectoris' OR 'heart infarction'/mj OR 'heart muscle ischemia'/mj OR myocard* NEAR/1 (infarction* OR ischemia* OR ischaemia*) OR 'coronary artery disease'/mj OR 'acute coronary syndrome'/mj OR 'ischemic heart disease'/mj OR coronary NEAR/1 disease* OR 'heart disease'/mj OR heart NEAR/1 disease*) AND ('biodegradable implant'/mj OR (bioabsorbable OR 'bio-absorbable' OR biodegradable* OR 'bio-degradable' OR bioresorbable* OR 'bio-resorbable') NEAR/5 (stent* OR scaffold* OR implant* OR 'percutaneous coronary intervention' OR 'percutaneous coronary interventions' OR pci*) OR 'bioresorbable vascular stent'/exp OR absorb:dn OR desolve:dn OR dreams:dn OR ideal:dn OR igaki:dn OR 'igaki tamai':dn OR fantom:dn OR art18z:dn) AND 'human'/de OR ('stable angina pectoris'/mj OR 'unstable angina pectoris'/mj OR 'angina pectoris'/mj OR 'angina pectoris' OR 'heart infarction'/mj OR 'heart muscle ischemia'/mj OR myocard* NEAR/1 (infarction* OR ischemia* OR ischaemia*) OR 'coronary artery disease'/mj OR 'acute coronary syndrome'/mj OR 'ischemic heart disease'/mj OR coronary NEAR/1 disease* OR 'heart disease'/mj OR heart NEAR/1 disease* AND ('biodegradable implant'/mj OR (bioabsorbable OR 'bio-absorbable' OR biodegradable* OR 'bio-degradable' OR bioresorbable* OR 'bio-resorbable') NEAR/5 (stent* OR scaffold* OR implant* OR 'percutaneous coronary intervention' OR 'percutaneous coronary interventions' OR pci*) OR 'bioresorbable vascular stent'/exp OR absorb:dn OR desolve:dn OR dreams:dn OR ideal:dn OR igaki:dn OR 'igaki tamai':dn OR fantom:dn OR art18z:dn) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim))	386	6 Jan 2015

Search strategy for CRD

1	(bioabsorbable*)
2	(bio-absorbable*)
3	(biodegradable*)
4	(bio-degradable*)
5	MeSH DESCRIPTOR Biodegradable Plastics EXPLODE ALL TREES
6	(bioresorbable*)
7	(bio-resorbable*)
8	MeSH DESCRIPTOR Biocompatible Materials EXPLODE ALL TREES
9	#1 OR #2 OR #3 OR #5 OR #6 OR #8
10	MeSH DESCRIPTOR Percutaneous Coronary Intervention EXPLODE ALL TREES
11	(Percutaneous Coronary Intervention*)
12	(PCI*)
13	MeSH DESCRIPTOR Stents EXPLODE ALL TREES
14	MeSH DESCRIPTOR Drug-Eluting Stents EXPLODE ALL TREES
15	(stent*)
16	MeSH DESCRIPTOR Tissue Scaffolds EXPLODE ALL TREES
17	(scaffold*)
18	MeSH DESCRIPTOR Absorbable Implants EXPLODE ALL TREES
19	(Absorb)
20	(DEsolve)
21	(DREAMS)
22	(IDEAL)
23	(Igaki*)
24	(Fantom*)
25	(ART18Z)
26	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #21 OR #22 OR #23
27	#9 AND #26
51 Hits	

06.01.2015

Search strategy for The Cochrane Library

Search Name: PCI with bioabsorbable Stents Last Saved: 06/01/2015 19:54:52.818	
ID	Search
#1	MeSH descriptor: [Angina, Stable] explode all trees
#2	MeSH descriptor: [Angina, Unstable] explode all trees
#3	MeSH descriptor: [Angina Pectoris] explode all trees
#4	angina* (Word variations have been searched)
#5	MeSH descriptor: [Myocardial Infarction] explode all trees
#6	MeSH descriptor: [Myocardial Ischemia] explode all trees

#7	myocard* (Word variations have been searched)
#8	MeSH descriptor: [Coronary Artery Disease] explode all trees
#9	MeSH descriptor: [Acute Coronary Syndrome] explode all trees
#10	MeSH descriptor: [Coronary Disease] explode all trees
#11	coronary (Word variations have been searched)
#12	MeSH descriptor: [Heart Diseases] explode all trees
#13	heart* (Word variations have been searched)
#14	#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
#15	bioabsorbable* (Word variations have been searched)
#16	bio-absorbable* (Word variations have been searched)
#17	biodegradable* (Word variations have been searched)
#18	bio-degradable* (Word variations have been searched)
#19	MeSH descriptor: [Biodegradable Plastics] explode all trees
#20	bioresorbable* (Word variations have been searched)
#21	bio-resorbable* (Word variations have been searched)
#22	MeSH descriptor: [Biocompatible Materials] explode all trees
#23	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#25	Percutaneous Coronary Intervention* (Word variations have been searched)
#26	PCI* (Word variations have been searched)
#27	MeSH descriptor: [Stents] explode all trees
#28	MeSH descriptor: [Drug-Eluting Stents] explode all trees
#29	stent* (Word variations have been searched)
#30	MeSH descriptor: [Tissue Scaffolds] explode all trees
#31	scaffold* (Word variations have been searched)
#32	MeSH descriptor: [Absorbable Implants] explode all trees
#33	Absorb (Word variations have been searched)
#34	DEsolve (Word variations have been searched)
#35	DREAMS (Word variations have been searched)
#36	IDEAL (Word variations have been searched)
#37	Igaki* (Word variations have been searched)
#38	Fantom* (Word variations have been searched)
#39	ART18Z (Word variations have been searched)
#40	#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #35 or #36 or #37 or #38
#41	#23 and #40
#42	#14 and #41
273 Hits	