Endovascular embolization of unruptured intracranial aneurysms with flow diverters

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No.: 83
ISSN online: 1998-0469

Endovascular embolization of unruptured intracranial aneurysms with flow diverters

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2015

Project Team

Project leader: Agnes Kisser, PhD

Authors: Agnes Kisser, PhD

Andreas Kirisits, MD, MSc

Project Support

Systematic literature search: Tarquin Mittermayr, BA

External Review: the reviewers preferred to remain anonymous

Internal Review: PD Dr. Claudia Wild

Correspondence

Agnes Kisser, agnes.kisser@hta.lbg.ac.at

This report should be referenced as follows:

Kisser A & Kirisits A. Endovascular embolization of unruptured intracranial aneurysms with flow diverters. Decision Support Document No. 83; 2015. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

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).

Reviewer Prof. Steiner declares a conflict of interest: he is/has been working as a consultant for Covidien.

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

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
http://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at
http://eprints.hta.lbg.ac.at

Decision Support Document No.: 83

ISSN -online: 1998-0469

Content

List of figures

List of tables

List of abbreviations

CE..... Conformité Européenne
CRD ..... Centre for Reviews and Dissemination
CTA..... Computed Tomography Angiography
DSA..... Digital Subtraction Angiography
FD ..... Flow Diverter
FDA..... Food and Drug Administration
HRQoL ..... Health-Related Quality of Life
HTA ..... Health Technology Assessment
IA..... Intracranial Aneurysm(s)
ICD ..... International Classification of diseases
ICH ..... Intracranial Haemorrhage
ISUIA..... International Study of Unruptured Intracranial Aneurysms
mo..... months
MRA..... Magnetic Resonance Angiography
MRI ..... Magnetic Resonance Imaging
mRS..... modified Rankin Scale
PED..... Pipeline Embolization Device
PFED ..... Pipeline Flex Embolization Device
pts ..... patients
QOL ..... Quality of Life
RCT..... Randomised Controlled Trial(s)
SAH..... Subarachnoid Haemorrhage
TIA ..... Transient Ischemic Attack
y ..... year(s)

Summary

Introduction

Health Problem

Hochrisiko-aneurysmen: Coiling oder Clipping als präventive Maßnahmen

nicht möglich in einem Teil der IA

Intracranial aneurysms (IA) are localised abnormal dilatations of the wall of brain arteries and are estimated to be prevalent in 3% of the adult population. Most IA are asymptomatic and have a low risk of rupture and thus a treatment is not indicated. Larger aneurysms and IA located in the posterior circulation present a higher risk of rupture and thus may warrant a preventive treatment. Current treatment options are microsurgical clipping and endovascular coiling; however, these options are not satisfactory or even unfeasible for a subset of IA (e.g., wide-necked, fusiform or giant aneurysms), leaving surgical parent vessel occlusion as a last resort.

Description of Technology

Flow Diverter sind schlauchförmige Metallgeflechte

Verschluss des IA durch Diversion des Blutflusses & Rekonstruktion des Ursprungsgefäßes

Flow diverters are tubular, braided metallic stents, that are deployed intravascularly in the parent artery across the aneurysm neck using a microcatheter approach. Through their dense mesh structure, they re-direct the blood flow leading to thrombosis and occlusion within the aneurysm sac. The stent is subsequently overgrown leading to reconstruction of the parent artery. As of 2008, several flow diverters have received marketing authorisation in Europe for the treatment of any intracranial aneurysms. In particular, however, flow diverters are claimed to allow occlusion of otherwise untreatable aneurysms with parent vessel preservation. We, therefore, assessed the efficacy and safety of the treatment with flow diverters in two distinct populations: a) any unruptured IA that are indicated for preventive treatment and b) unruptured IA, that are indicated but not amenable for preventive treatment.

Methods

Methode: basierend auf EuNetHTA Core Model; systematische Literatursuche in 4 Datenbanken; GRADE

The EuNetHTA Core Model for Rapid Relative Effectiveness was the main source for selecting relevant assessment elements. We conducted a systematic literature search (without restriction on publication date) in bibliographic databases, in the Cochrane Library and in the database of the Centre for Reviews and Dissemination, complemented by a SCOPUS hand search, to answer the research questions in the domains effectiveness and safety. Selection of relevant documents (in English and German) was done by two persons independently. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for qualitatively summarising the results for the domains: “Safety” and “Clinical effectiveness”.

Domain effectiveness

Einschlusskriterien für Wirksamkeit

For analysing the clinical effectiveness in population a) only randomised controlled trials were included; in population b) also prospective uncontrolled studies with follow-up ≥6 months and ≥50 participants were included, provided that any of the defined outcomes were reported. The crucial outcomes to derive a recommendation were: overall mortality, disability/dependency, health-related quality of life, aneurysm retreatment rate and angiographic surrogate parameters (aneurysm occlusion and parent vessel stenosis).

Domain safety

Einschlusskriterien für Sicherheit

For analysing the safety of the treatment with flow diverters, prospective controlled and uncontrolled studies with follow-up ≥6 months were included. Uncontrolled studies were included only, if they either reported ≥200 participants or ≥50 participants and reported mortality and further adverse events. The crucial outcomes to derive a recommendation were: neurological death, haemorrhage (total and early), ischemic stroke (total and early), new or worsened disability/dependency.

Results

Available evidence

5 prospektive, multizentrische, unkontrollierte Studien

Five prospective, multi-centre single-group studies were identified that analysed efficacy and safety of the treatment with flow diverters in unruptured intracranial aneurysms with varying definitions of "difficult to treat" (large, wide-necked, unfavourable dome-to-neck ration, fusiform, etc.). In total, results from 494 patients that were treated with flow diverters were reported.

Clinical effectiveness

Mortalität 0 bis 8 %; Aneurysmaverschluss 49–85,7 % (6 mo)

Overall mortality ranged from 0 to 8%. Retreatment was reported in two studies in 0 and 4.5%. Angiography efficacy was in the range 49–85.7% after 6 months and 81–86.6% after 1 year; however, parent artery stenosis ≥50% occurred in 0 to 16.3%. Improved function was reported in two studies in 8.4% and 19.6%. No direct evidence on relative effectiveness of flow diverters in comparison to alternative treatment options was available.

Safety

Nebenwirkungen: Tod, Hämorrhagie, Schlaganfall

After 6 months, neurological death was reported in 5 studies to occur in a range between 0 to 2.8%. Haemorrhage occurred in 0–6.2% of the participants, late haemorrhage (≥30 days) in a range of 0–2%. Ischemic stroke was reported in the range of 0–3.7%. Worsened function was reported in a range of 2.7–14% of the participants. No direct evidence on relative safety of flow diverters in comparison to alternative treatment options was available.

Upcoming evidence

5 laufende RCTs

Five RCTs using flow diversion as an intervention are currently registered, 4 of which target "difficult to treat" aneurysms with varying inclusion criteria (e.g., wide-necked or large). The FIAT trial is expected to provide efficacy and safety results of flow diversion versus standard treatment following the study completion date in April 2016.

Discussion

keine klare Definition von „unbehandelbaren" Aneurysmen

Flow diverters are claimed to provide a treatment option to otherwise untreatable aneurysms. In practice, however, there is no agreed definition of an "untreatable" aneurysm, as underlined by the heterogeneous inclusion criteria of the studies. In most patients, a standard treatment alternative likely exists and the trade-off of procedural risks with long-term beneficial outcomes will need to be established in RCTs.

Conclusion

There is moderate evidence for efficacy using the angiographic surrogate parameter aneurysm occlusion in a large percentage of treated aneurysms.

Surrogatparameter Aneurysmaverschluss: moderate Evidenz

The current evidence is, however, not sufficient to prove, that the assessed technology of endovascular embolization with flow diverters is more effective and safe with regards to clinical outcomes than no treatment, endovascular coiling or surgical clipping.

ungenügende Evidenz hinsichtlich klinischer Endpunkte im Vergleich zu Behandlungsalternativen

The re-evaluation is recommended in 2017, provided that data from randomised controlled trials will be available at that time.

Re-evaluierung 2017

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Hochrisiko-aneurysmen: Coiling oder Clipping als präventive Maßnahmen

Intrakranielle Aneurysmen (IA) sind lokalisierte abnorme Dilatationen der Wand der Hirnarterien. Sie treten mit einer geschätzten Prävalenz von 3 % der erwachsenen Bevölkerung auf. Die meisten IA sind asymptomatisch und weisen ein geringes Rupturrisiko auf: eine Behandlung ist somit nicht indiziert. Größere Aneurysmen und IA der posterioren Zirkulation haben ein höheres Rupturrisiko, das eine präventive Behandlung rechtfertigen kann. Aktuelle Behandlungsmöglichkeiten sind das mikrochirurgische Clipping und das endovaskuläre Coiling ; diese Optionen sind jedoch für eine Teilmenge der IA (z. B. breithalsige IA oder Riesenaneurysmen) nicht zufriedenstellend oder sogar unmöglich durchzuführen, so dass der chirurgische Verschluss des Ursprungsgefäßes als letzte Option verbleibt. Flow Diverter versprechen hier eine minimalinvasive Alternative, die einen Aneurysmaverschluss bei Erhalt des Gefäßes ermöglicht.

nicht möglich in einem Teil der IA

Beschreibung der Technologie

Flow Diverter sind schlauchförmige Metallgeflechte

Flow Diverter sind schlauchförmige Metallgeflechte, die endovaskulär über dem Aneurysmahals eingesetzt werden. Durch ihre dichte Netzstruktur lenken sie die Durchblutung um, was zu Thrombose und Verschluss des Aneurysmasacks führt. Der Stent wird anschließend überwachsen, was die Rekonstruktion der Stammarterie ermöglicht. Seit dem Jahr 2008 haben mehrere Flow Diverter die Zulassung in Europa für die Behandlung jedweder intrakranieller Aneurysmen erhalten. Insbesondere werden Flow Diverter jedoch für den Verschluss jener Aneurysma angeboten, für die es keine Behandlungsalternativen gibt. Wir haben deshalb die Wirksamkeit und Sicherheit der Behandlung mit Flow Divertern in zwei unterschiedlichen Patientengruppen untersucht: a) alle unrupturierten IA, die für eine präventive Behandlung indiziert sind und b) unrupturierte IA, die zwar indiziert, aber für die Behandlung mit Coiling oder Clipping nicht zugänglich sind.

Verschluss des IA durch Diversion des Blutflusses & Rekonstruktion des Ursprungsgefäßes

Methoden

Methode: basierend auf EuNetHTA Core Model; systematische Literatursuche in 4 Datenbanken; GRADE

Das EUnetHTA Core-Modell war die Hauptquelle für die Auswahl der jeweiligen Bewertungselemente. Wir führten eine systematische Literaturrecherche in Literaturdatenbanken, in der Cochrane Library und in der Datenbank des CRD, ergänzt durch eine SCOPUS Handsuche durch, um die Forschungsfragen in den Bereichen Wirksamkeit und Sicherheit zu beantworten. Die Auswahl der relevanten Studien (in Deutsch und Englisch) wurde von zwei Personen unabhängig voneinander durchgeführt. Die qualitative Zusammenfassung der Ergebnisse erfolgte nach der GRADE Methodik.

Klinische Wirksamkeit

Einschlusskriterien für Wirksamkeit

Für die Analyse der klinischen Wirksamkeit in der primären Studienpopulation a) wurden nur randomisierte kontrollierte Studien einbezogen; in der sekundären Studienpopulation b) wurden auch prospektive unkontrollierte Studien mit Follow-up ≥6 Monaten und ≥50 Teilnehmer eingeschlossen, vorausgesetzt, dass sie die festgelegten Endpunkte behandelten. Die entscheidenden Endpunkte, anhand derer eine Empfehlung abgeleitet wurde, sind:

Gesamtmortalität, Behinderung/Abhängigkeit, gesundheitsbezogene Lebensqualität, Wiederbehandlungsrate und angiographische Surrogatparameter (Aneurysmaverschluss und Stammgefäßverengung).

Sicherheit

Einschlusskriterien für Sicherheit

Für die Analyse der Sicherheit der Behandlung mit Flow Divertern wurden prospektive, kontrollierte und unkontrollierte Studien mit Follow-up ≥6 Monaten eingeschlossen. Unkontrollierte Studien wurden nur eingeschlossen, wenn sie entweder ≥200 Teilnehmer hatten, oder ≥50 Teilnehmer und außer der Mortalität weitere Nebenwirkungen berichteten. Die entscheidenden Endpunkte, anhand derer eine Empfehlung abgeleitet wurde, sind: neurologischer Tod, Hämorrhagie (gesamt und früh), ischämischer Schlaganfall (gesamt und früh), neue oder verschlechterte Behinderung/Abhängigkeit.

Ergebnisse

Verfügbare Evidenz

5 prospektive, multizentrische, unkontrollierte Studien

Fünf prospektive, multizentrische, unkontrolliert Studien wurden identifiziert, die die Wirksamkeit und Sicherheit der Behandlung mit Flow Divertern in rupturierten intrakraniellen Aneurysmen untersuchten, wobei unterschiedliche Einschlusskriterien für „schwer zu behandelnde" Aneurysmen herangezogen wurden (große, breithalsige, fusiforme IA, etc.). Insgesamt wurden Ergebnisse von 494 Patienten, die mit Flow Divertern behandelt wurden, berichtet.

Klinische Wirksamkeit

Mortalität 0 bis 8 %; Aneurysmaverschluss 49-85,7 % (6 mo)

Die Gesamtmortalität lag in den fünf Studien bei 0 bis 8 %. Eine erneute Behandlung der Aneurysmen war laut zwei Studien in 0 bis 4,5 % erforderlich. Angiographische Wirksamkeit lag bei 49 bis 85,7 % nach sechs Monaten und 81 bis 86,6 % nach einem Jahr; gleichzeitig kam es zu Stammgefäßverengungen ≥50 % in 0 bis 16,3 %. Eine verbesserte Funktion wurde in zwei Studien in 8,4 % and 19,6 % der TeilnehmerInnen berichtet. Direkte Evidenz zur Überlegenheit der Flow Diverter im Vergleich zu alternativen Behandlungsmöglichkeiten hinsichtlich der Wirksamkeitsendpunkte steht nicht zur Verfügung.

Sicherheit

Nebenwirkungen: Tod, Hämorrhagie, Schlaganfall

Nach 6 Monaten berichteten die 5 Studien das Auftreten neurologischen Todes in 0 bis 2,8 %. Hämorrhagien traten bei 0–6,2 % der TeilnehmerInnen auf, wobei späte Blutung (≥30 Tage) 0 bis 2 % betrafen. Ischämischer Schlaganfall trat in 0 bis 3,7 % auf. Eine verschlechterte Funktion wurde für 2,7 bis 14 % der Teilnehmer berichtet. Direkte Evidenz zur Überlegenheit der Flow Diverter im Vergleich zu alternativen Behandlungsmöglichkeiten hinsichtlich der Sicherheitsendpunkte steht nicht zur Verfügung.

Laufende Studien

5 laufende RCTs

Fünf RCTs mit Flow Divertern als Intervention sind derzeit registriert: vier davon zielen auf die Behandlung „schwer zu behandelnder" Aneurysmen mit unterschiedlichen Einschlusskriterien (z. B. breithalsig, groß). Die frühesten Ergebnisse zur Wirksamkeit und Sicherheit der Flow Diverter im Vergleich zur Standardbehandlung werden nach dem Abschluss der FIAT Studie im April 2016 erwartet.

Diskussion

keine klare Definition von „unbehandelbaren" Aneurysmen

Flow Diverter werden als Behandlungsoption für ansonsten unheilbare Aneurysmen angepriesen. In der Praxis jedoch gibt es keine einheitliche Definition „unheilbarer" Aneurysmen, wie die heterogenen Einschlusskriterien der Studien unterstreichen. Bei den meisten Patienten ist eine alternative Standardbehandlung tatsächlich möglich und der Trade-off der Verfahrensrisiken gegenüber der langfristigen klinischen Ergebnisse muss anhand von RCTs ermittelt werden.

Empfehlung

Surrogatparameter Aneurysmaverschluss: moderate Evidenz

Es gibt moderate Evidenz für die Wirksamkeit basierend auf dem angiographischen Surrogatparameter Aneurysmaverschluss in einem großen Prozentsatz der behandelten Aneurysmen.

ungenügende Evidenz hinsichtlich klinischer Endpunkte im Vergleich zu Behandlungsalternativen

Die aktuellen Erkenntnisse sind jedoch nicht ausreichend, um zu zeigen, dass die endovaskuläre Embolisation mit Flow Divertern in Bezug auf die klinischen Ergebnisse wirksamer und sicher ist als gar keine Behandlung, endovaskuläres Coiling oder operatives Clipping.

Re-evaluierung 2017

Die Neubewertung wird im Jahr 2017 empfohlen, vorausgesetzt, dass die Daten aus randomisiert kontrollierten Studien zu diesem Zeitpunkt zur Verfügung stehen.

1 Scope

1.1 Research questions

PIKO-Frage

Is the endovascular embolization with flow diverters in comparison to endovascular coiling, microsurgical clipping or no treatment in adult patients with a) unruptured intracranial aneurysms (IA) and b) unruptured large/giant, fusiform or wide-necked IA more effective and safe concerning overall mortality, disability-free survival and treatment-associated morbidity?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1.2-1: Inclusion criteria

Population	A) First-line treatment in adult patients with unruptured intracranial aneurysms. International classification of diseases (ICD)-10-CM code: I67.1 Cerebral aneurysm, unruptured MeSH terms: Intracranial aneurysm B) First- or second-line treatment in adult patients with unruptured large/giant, wide-necked and fusiform intracranial aneurysms, for whom stent-assisted coil embolization and/or neurosurgical techniques are not considered feasible (de novo or repeat treatment). ICD-10-CM code: I67.1 Cerebral aneurysm, unruptured MeSH terms: giant intracranial aneurysm, intracranial aneurysm Patients with ruptured aneurysms and paediatric patients are excluded from the scope.
Intervention	Therapeutic embolization of the aneurysm by endovascular (catheter-based) implantation of a flow diverter/flow modulating device across the neck of the aneurysm alone or in association with embolization coils. MeSH terms: E02.520.360 or E02.926.500
Comparators[1]	Observation (natural course of the disease) Endovascular coiling Neurosurgical clipping
Outcomes	
Efficacy	Overall mortality Disability/Dependency Health-related quality of life (HRQoL) Primary surrogate parameter: Aneurysm occlusion Parent artery stenosis Aneurysm recurrence/retreatment rate
Safety	Peri-operative and post-operative therapy-associated mortality Peri-operative and post-operative therapy-associated morbidity Disability/Dependency

[1] Comparators were selected based on recommended treatment options included in Austrian/German guidelines for unruptured intracranial aneurysms.

Study design	
Efficacy	RCTs with follow-up ≥6 months (Only for Population B: prospective non-randomised controlled trials and prospective single-group studies with follow-up ≥6 months if ≥50 patients
Safety	RCTs with follow-up ≥6 months Prospective non-randomised controlled studies ≥6 months Prospective single-group studies with follow-up ≥6 months if a) ≥200 patients or b) ≥50 patients and reporting of mortality AND further adverse events

1.3 Literature search

systematische Literatursuche in vier Datenbanken

The systematic literature search was conducted on the 12th of December 2014 in the following databases:

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

and complemented with a Scopus Search in the references of key articles.

Search filters were applied (in MEDLINE and Embase) to limit the results to Clinical Trials and Systematic Reviews/Meta-Analyses. After deduplication, 389 citations were included for abstract screening. The specific search strategies employed can be found in the Appendix.

insgesamt 390 Referenzen identifiziert

The manufacturers of all marketed products were asked to submit further publications. One (Covidien, Pipeline Embolization Device) submitted 88 publications of which one new relevant citation was identified, resulting in 390 hits overall.

1.4 Flow chart of study selection

Literaturauswahl

Overall, 390 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.

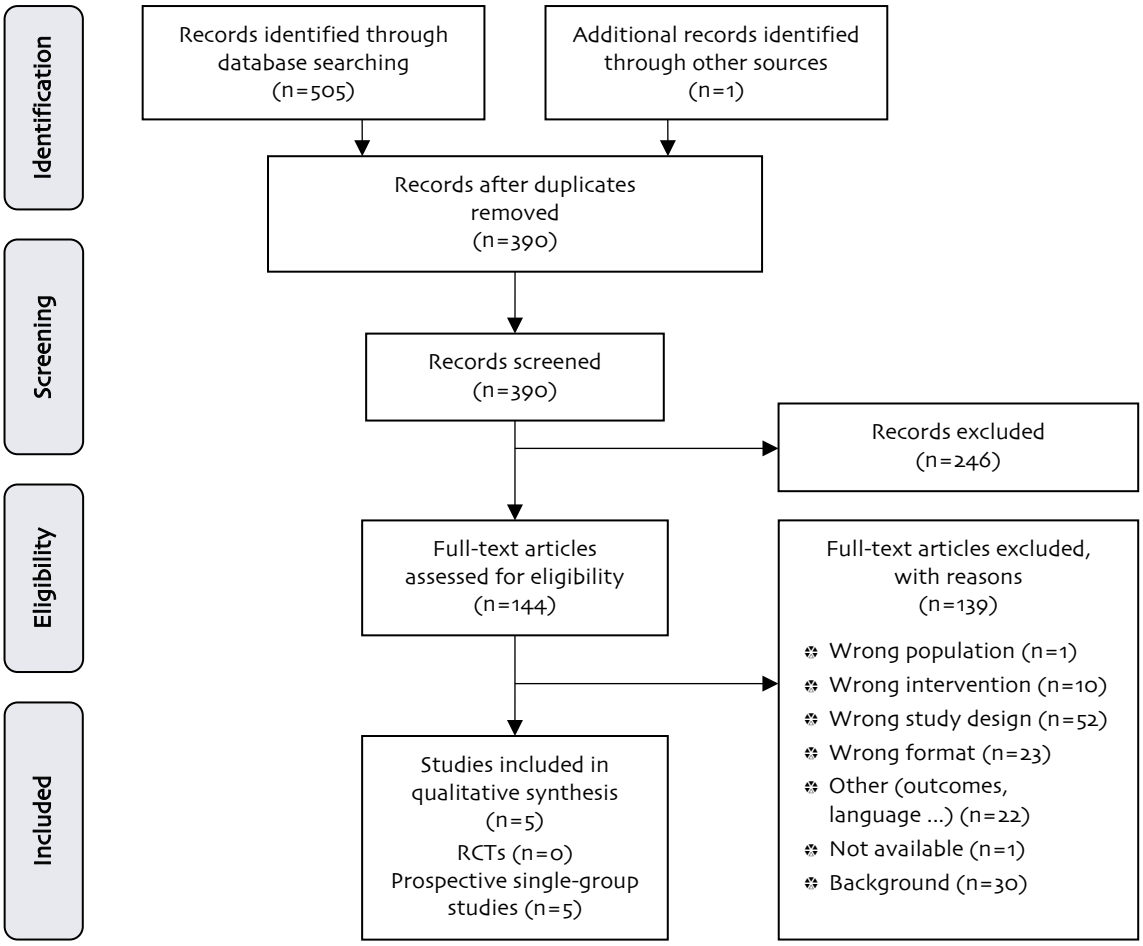

Figure 1.4-1: Flow chart of study selection (PRISMA Flow Diagram)

2 Description and technical characteristics of technology

2.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
B0001	What are flow diverters and what are the alternative standard treatment options?	2
A0020	For which indications have flow diverters received marketing authorisation or CE marking?	2
B0002	What is the approved indication and claimed benefit of flow diverters in relation to the comparators?	2
B0003	What is the phase of development and implementation of flow diverters and the comparator(s)?	2
B0004	Who performs or administers flow diverters and the comparators and in what context and level of care are they provided?	2
B0008	What kind of special premises are needed to use flow diverters and the comparator(s)?	2
B0009	What supplies are needed to use flow diverters and the comparator(s)?	2

Sources

Quellen

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 1.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

2.2 Results

Features of the technology and comparators

B0001 – What are flow diverters and what are the alternative standard treatment options?

Flow diverters are tubular, braided metallic stents that are deployed endovascularly to treat aneurysms [1, 2] through two mechanisms:

1. Flow diverters are placed in the parent artery across the aneurysm neck rather than in the aneurysm sac. There, through their dense mesh structure, they re-direct the blood flow at the aneurysm/parent vessel interface to induce thrombosis and occlusion within the aneurysm sac.
2. The stent is subsequently overgrown, leading to endoluminal reconstruction of the parent artery.

FD: schlauchförmige Stents aus einem Metallgeflecht.
Wirkungsmechanismus:
1) Ableitung des Blutflusses aus Aneurysma
2) Rekonstruktion des Ursprungsgefäßes

Verschluss erst nach einiger Zeit

Flow diverter techniques thereby lead to aneurysm occlusion over time rather than immediately after the intervention.

Stärke der Blutflussableitung abhängig von Porosität und Porendichte des FD

Important metrics for flow diversion efficacy are the porosity/metal coverage (proportion of open metal-free and closed metal-covered area across the aneurysm neck, respectively) and pore density (number of pores per area), with lower porosity and higher pore density being optimal conditions for aneurysm occlusion [2].

Another class of flow diverters (e.g., Woven EndoBridge, WEB, LUNA AES) are placed intrasaccularly (within the aneurysm sac) rather than intravascularly (in the parent vessel) and are not within the scope of this review.

Marketed products

mehrere Produkte mit Marktzulassung

Several endovascular flow diverters have received marketing authorisation in Europe and/or in the USA (Table 2.2-1):

Pipeline™ Embolization device

The Pipeline™ Embolization device (PED) consists of a braided, multi-alloy, mesh cylinder implant woven from cobalt/chromium/molybdenum/nickel and platinum/tungsten alloy wires. It has a porosity of 65-70% [1]. A delivery system is provided with the implant mounted on a micro-guidewire and compressed inside an introducer sheath. The Pipeline™ Flex Embolization device (PFED) is an iteration of the PED with a modified delivery system allowing repositioning of the device (information from the manufacturer).

SILK

The SILK device is a self-expanding flow diverter composed of a braided mesh cylinder with flared ends, made of 48 braided nickel-titanium (nitinol) alloy and platinum microfilament strands [2]. It has a porosity of 45–60% [1]. It is provided with a delivery system. The SILK+ is an iteration of the SILK device with higher radio-opacity and the possibility for repositioning (information from the manufacturer).

Surpass

The Surpass device is a self-expanding flow diverter constructed of cobalt chromium braids with 12 platinum-tungsten wires, shaped in a tubular, low porosity mesh. It is provided with a delivery system composed of a delivery catheter and a pusher [2]. It has a porosity of 70% [1].

FRED™

The FRED™ device has a self-expandable stent-within-a-stent design. The device consists of a paired, dual-layer design with an outer high-porosity stent and a narrower inner flow-diverter mesh composed of 48 braided nitinol strands. It can be partially deployed, retrieved and repositioned (information from the manufacturer).

p64 modulation device

The p64 flow modulation device is composed of a 64 nitinol wire braid. It allows repositioning even after full deployment and is provided with a delivery system (information from the manufacturer).

Derivo® embolization device

The Derivo® embolization device is a nitinol wire braid equipped with a nitinol transport wire and can be recaptured and repositioned. It is provided with a delivery system (information from the manufacturer).

Microsurgical clipping

operatives Clipping: Setzen einer Metallklammer um den Hals des IA

Surgical clipping involves placing a small metal clip across the aneurysm's neck with preservation of the parent vessel and arterial branches. It requires craniotomy and brain retraction. This has been the historical definitive standard for the treatment of IA [3].

Endovascular coiling

endovaskuläres Coiling: Zugang über Mikrokatheter und Auffüllung des Aneurysmasacks mit Platinumspiralen

A variety of endovascular treatments have been developed in the past years. They are all based on the use of a percutaneous catheter system to repair the aneurysm from within the vessel, sparing the need for a craniotomy. A micro-catheter is introduced in the intracranial circulation, usually from a femoral artery approach, and positioned within the aneurysm. Through the micro-catheter a first coil is introduced in the aneurysm sac, forming a basket apposed to the aneurysm wall. Additional coils are introduced until the sac is densely packed and the micro-catheter can be removed [4].

A0020 – For which indications have flow diverters received marketing authorisation or CE marking?

Zulassungshistorie der FD Produkte

Table 2.2-1: Regulatory history of flow diverter products

Product name	Manufacturer	Date	Indication for use	Date	Indication for use
Pipeline™ Embolization Device	(ev3/Covidien) Medtronic, Dublin, IE	Jun 2008: 489211A	The PED is intended for endovascular embolization of cerebral aneurysms.	Apr 2011: P100018	Endovascular treatment of adults (age 22 and above) with large or giant wide-necked IAs in the internal carotid artery from the petrous to the superior hypophyseal segments.
Pipeline Flex Embolization Device	(ev3/Covidien) Medtronic, Dublin, IE	Mar 2014: 489211A	The PFED is intended for endovascular embolization of cerebral aneurysms.	Feb 2015	Endovascular treatment of complex intracranial aneurysms that are not amenable to treatment with surgical clipping and are attached to parent vessels measuring 2.5 to 5.0 mm in diameter
Silk flow diverter	Balt Extrusion, Montmorency, FR	Jan 2008	The treatment of intracranial aneurysms in association with embolization coils	Not approved	
Surpass flow diverter	Stryker Neurovascular, Fremont, Cal, US	Aug 2011	Saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter of ≥2 mm and ≤5.3 mm	Not approved	
Fred™ (Flow redirection endoluminal device)	MicroVention, Tustin, Cal, US	Dec 2013	Information not available	Not approved	
P64 Flow Modulation Device	Phenox, Bochum, DE	Oct 2012	Information not available	Not approved	
Derivo® Embolization Device	Acandis, Pforzheim, DE	Oct 2012	The DERIVO® Embolization Device is intended for the treatment of intracranial aneurysms. It is suitable for vessel diameters from 3 to 6 mm	Not approved	

B0002 – What is the claimed benefit of flow diverters in relation to the comparators?

nicht durch Clipping oder Coiling behandelbare IA: ungedeckter Bedarf. Nutzen liegt in Prävention der Ruptur

The treatment of IA with flow diverters responds to an unmet need in clinical situations not amenable to existing treatments (surgical clipping or endovascular coiling) or associated with a major risk of morbidity and mortality. In these situations, the claimed benefit consists in the stable occlusion of the aneurysm and, thereby, the decreased risk of rupture and prevention of functional impairment or death following subarachnoid haemorrhage (SAH) as compared to the untreated aneurysm.

bei nur durch operative Verfahren behandelbaren IA: Nutzen durch geringere prozedurale Risiken

In comparison to surgical clipping, the claimed benefits of the treatment with flow diverters are comparable occlusion and recurrence rates and fewer procedural risks.

For IA that can be treated by endovascular coiling, treatment of IA with flow diverters responds to a medical need that is already met.

B0003 – What is the phase of development and implementation of flow diverters and the comparator(s)?

FD: erste CE-Zertifizierung 2008, vorläufige FDA Zulassung 2011

The first flow diverters received a CE mark in 2008, and FDA pre-market approval in 2011 (Table 2.2-1). It is a novel technology that has not previously been used for other purposes and is not yet established in use. Iterations of the products are currently emerging, allowing, for example, the repositioning or retraction of the device. No RCT has so far been completed and published on flow diverters; five RCT are currently registered (Table A3-1).

operatives Clipping: etablierte Standardmethode

Surgical clipping: The first aneurysm ever treated by surgical clipping was performed in 1937. Microsurgical clipping is now a well-established standard technique.

endovaskuläres Coiling: etablierte Standardmethode

Endovascular coiling: Endovascular treatment of IA has evolved over the past 30 years. Initially, detachable balloons were used, but they were replaced by fibre coils, allowing a better adaptation to the aneurysm shape. The endovascular treatment of IA with detachable flexible platinum coils is now a well-established standard technique.

Administration, investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers flow diverters and the comparators and in what context and level of care are they provided?
B0008 – What kind of special premises are needed to use flow diverters and the comparator(s)?
B0009 – What supplies are needed to use flow diverters and the comparator(s)?

IA Behandlung in Zentren mit Expertise in Neuroradiologie und Neurochirurgie

The treatment of IA is performed in university hospitals and specialised centres with expertise in both interventional neuroradiology and neurosurgery. To ensure the selection of the most appropriate treatment approach, patients should be evaluated by an interdisciplinary team including both a neurosurgeon and an endovascular specialist.

The endovascular embolization (either with coils or with flow diverters) is performed under general anaesthesia by using biplane angiography units and a transfemoral artery approach. Frequently the flow diverters are used in addition to endovascular coiling. Similar to conventional stenting, patients receive dual antiplatelet therapy (aspirin and clopidogrel) to prevent stent thrombosis prior to the procedure and for at least six months after the procedure [5].

endovaskuläre Behandlung benötigt Zweiebenen-Angiographie-Einheiten

begleitend: Therapie mit Thrombozyten-aggregationshemmern

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 flow diverters indicated?	2
A0002	What indications of flow diverters are in the scope of this assessment?	2
A0003	What are the known risk factors for the development and rupture of intracranial aneurysms?	2
A0004	What is the natural course of intracranial aneurysms?	2
A0005	What is the burden of disease for patients with unruptured intracranial aneurysms?	2
A0006	What is the burden of intracranial aneurysms for society?	2
A0024	How are intracranial aneurysms currently diagnosed according to published guidelines and in practice?	2
A0025	How are intracranial aneurysms 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?	2
A0011	What is the expected annual utilisation of flow diverters?	2

Sources

- Hand search in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background literature identified during systematic literature search: see Section 1.3
- Hand search for clinical guidelines on the websites of the Austrian Society of Neurology (www.oegn.at) and the German Society of Neurology (www.dgn.at), on BMJ Best practice [6] and UptoDate® (http://www.uptodate.com).
- Questionnaire completed by the submitting hospitals

3.2 Results

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes are flow diverters indicated?
A0002 – What indications of flow diverters are in the scope of this assessment?

Europa: indiziert für endovaskuläre Embolisation aller IA

rupturierte IA ausgeschlossen

In Europe, flow diverters have a broad indication for the endovascular embolization of any IA (without anatomic limitation). Ruptured aneurysms would probably not be amenable to the treatment with flow diverters because dual platelet therapy (aspirin and clopidogrel) would be needed with the therapy and the use of anticoagulation medications is relatively contraindicated in cases of ruptured aneurysm. In the scope of this assessment, therefore, only unruptured IA in adults are included.

A0004 – What is the natural course of intracranial aneurysms?

IA: lokalisierte Aussackungen der Blutgefäße

IA (also termed cerebral aneurysms or brain aneurysms) are localised abnormal dilations of the wall of arteries that supply blood to the brain which usually develop from a weakness in the blood vessel wall. They are classified according to morphology, size and location [6, 7]:

Morphology

sakkulär

Saccular (also: berry) aneurysms are IA with a rounded outpouching attached by a neck or stem to the brain artery. They usually arise from arterial bifurcation points.

fusiform

Fusiform (also: atherosclerotic) aneurysms form as tunica media damage leads to arterial stretching and elongation.

Aortendissektion

Dissecting IA arise from arterial dissections where an intramural hematoma extends into the subadventitial plane, forming a sac-like outpouching. They may arise spontaneously, but more commonly they are induced by a trauma or an underlying vasopathy.

Size

Diameter ≥ 25 mm: Riesenaneurysma

Aneurysms with a diameter ≥25mm are classified as giant aneurysms. They are thought to represent about 5–8% of all saccular IA.

Diameter ≥ ca. 10 mm: großes Aneurysma

In contrast to giant aneurysms, there are no standardised cut-offs for small and large aneurysms (sometimes classifications include a “medium” category.). Classification as ‘small’ aneurysms may include aneurysms with maximum diameters of 7mm up to 12mm; classification as ‘large’ aneurysms may include aneurysms with minimum diameters of 10mm up to 20mm (but below 25mm). The majority of IA (>90%) are <10mm [8, 9].

Location

>85 % der IA: vordere Zirkulation

The majority of IA (>85%) develop in the anterior part of the Circle of Willis and involve the internal carotid arteries and their major branches [9].

IA der hinteren Zirkulation schwerer zugänglich

IA located in the basilar artery bifurcation and the remaining posterior circulation arteries are less common and more difficult to treat due to their limited accessibility.

Small, unruptured IA are usually asymptomatic. In larger IA, symptoms may be caused by the compression of adjacent structures, e.g. the oculomotor nerve.

IA üblicherweise asymptomatisch

The mortality and morbidity of an unruptured IA depends mainly on its risk of rupture, resulting in SAH as the major rupture manifestation or parenchymal haemorrhage. In a major study with >4,000 patients (International Study of Unruptured Intracranial Aneurysms, ISUIA) the risk of rupture was estimated to be 1.2% per year [10], but it increases in relation to aneurysm size and location and whether or not the patient has already had a SAH from another aneurysm (Table 3.2-1).

Mortalität und Morbidität aufgrund des Rupturrisikos: subarachnoidale Blutung (SAH)

Table 3.2-1: Five-year cumulative rupture rates for patients with untreated IA

Size	Cavernous carotid artery (%)	Anterior circulation (%)	Posterior circulation (%)
<7mm and previous SAH	0	1.5	3.4
<7mm no previous SAH	0	0	2.5
7–12mm	0	2.6	14.5
13–24mm	3.0	14.5	18.4
>24mm	6.4	40	50

Source: [10] SAH = Subarachnoid Haemorrhage

SAH is bleeding into the fluid-filled spaces surrounding the brain. 32–67% of SAH result in death with more than 20% long-term dependency in survivors [7]. The Hunt and Hess classification is used to grade the clinical status of a patient with SAH (Table 3.2-2).

SAH: hohes Risiko für Tod oder Pflegebedürftigkeit

Table 3.2-2: Hunt and Hess classification of the clinical status of patients with SAH

Grade	Clinical condition at presentation
0	Unruptured aneurysm
1	Asymptomatic or minimal headache, slight nuchal rigidity
2	Moderately severe or severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund appearance

Source: [11] SAH = Subarachnoid Haemorrhage

A0003 – What are the known risk factors for the development and rupture of intracranial aneurysms?

Known risk factors for the development of an IA are a family history of aneurysm, certain inherited disorders (e.g. autosomal dominant polycystic kidney disease), atherosclerosis, age greater than 50 years, female gender, current cigarette smoking and use of cocaine [8, 9].

Risikofaktoren für Entstehung

In addition to larger size, location in the posterior circulation and the IA being symptomatic, age of the patients >60 years, female gender, hypertension, certain behavioural aspects (smoking and drinking habits) are risk factors for rupture. Finnish or Japanese populations also have a higher risk of rupture [12-14].

Risikofaktoren für Ruptur

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

A0005 – What is the burden of disease for patients with unruptured intracranial aneurysms?

Mehrheit der IA asymptomatisch, geringes Rupturrisiko

Most unruptured IA are asymptomatic and the risk of rupture is low. Many unruptured IA are detected incidentally by brain imaging obtained for another condition. No major impact on QOL, anxiety, and depression was found associated with being aware of having an untreated, unruptured IA [15, 16]; however a minor impact is possible.

10–15 % der IA verursachen Symptome durch Gehirnnerven-kompression

Some unruptured IA can become symptomatic [17]. Symptoms include headache (which may be severe and comparable to the headache of SAH), visual acuity loss, cranial neuropathies (particularly third nerve palsy), pyramidal tract dysfunction, and facial pain; these are explained with the mass effect of the aneurysm (i.e. the compression of adjacent structures and nerves). Ischemia can occur as a result of emboli originating from within an aneurysm. 10-15% of IA are symptomatic [10, 18].

modifizierte Rankin Skala: Ausmaß der neurologischen Beeinträchtigung

A variety of functional assessment scales are used to measure the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disabilities [11]. The most widely used clinical outcome measure is the modified Rankin Scale (mRS) (Table 3.2-3).

Table 3.2-3: Modified Rankin Scale (mRS)

Score	Description
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

A0006 – What is the burden of intracranial aneurysms for society?

Prävalenz der IA: ca. 3 %

The overall prevalence of IA for adults without specific risk factors is approximately 3% [9]. Most IA are small, asymptomatic and have a low risk of rupture.

Current clinical management of the disease or health condition

A0024 – How are intracranial aneurysms currently diagnosed according to published guidelines and in practice?

unrupturierte IA: häufig Zufallsbefunde

Most cerebral aneurysms go unnoticed until they rupture or are detected by brain imaging that may have been obtained for another condition. Unruptured IA may be differentiated as:

- incidental aneurysms: true incidental finding without SAH or other symptoms
- symptomatic aneurysms (e.g., compression of oculomotor nerve)
- additional aneurysms (found in patients following rupture of another aneurysm)

The accepted reference standard method for the identification of intracranial aneurysms is intra-arterial digital subtraction angiography [19].

Referenzstandard: intraarterielle digitale Subtraktions-angiographie

Both magnetic resonance angiography (MRA) and the computed tomography angiography (CTA) using contrast dyes have an overall accuracy of ~90% for aneurysms >4-6mm diameter [19]. Smaller aneurysms are less reliably detected. Use of multi-detector CTA or MRA at 3.0 Tesla may improve sensitivity for smaller aneurysms. In the absence of SAH, findings of aneurysms <7mm have a higher likelihood of being false positives and require confirmation [19].

Diagnose auch mittels MRA oder CTA

A0025 – How are intracranial aneurysms currently managed according to published guidelines and in practice?

Unruptured IA are treated electively, with the three major treatment options being observation, surgical clipping and endovascular coiling [20]. The risks of each treatment option need to be weighed against the natural history risks. These vary depending on factors specific both to patients (age, co-morbidities, etc.) and to the aneurysm (size, location, morphology, previous rupture).

Behandlungsoptionen: Beobachtung, operatives Clipping oder endovaskuläres Coiling

Observation

The indication for treatment of very small, unruptured IA is controversial, as the risk of SAH is small [21]. The risk of perforation during endovascular treatment is higher in very small IA (<3mm). Therefore, these IA are sometimes managed conservatively through periodic fluoroscopic and angiographic surveillance, together with treatment for risk factors such as hypertension or smoking.

Beobachtung: bei IA mit niedrigem Rupturrisiko, höherem Alter der PatientInnen

Age is a crucial element in deciding whether to treat an unruptured aneurysm [10]. While age has relatively little effect on the natural course of unruptured aneurysms, morbidity and mortality are increased with open surgery in patients ≥50 years and with endovascular procedures in patients ≥70 years. In contrast, young (<50 years) patients should be considered for treatment due to the higher life-time risk of rupture [22].

Surgical clipping

A systematic review and meta-analysis of 60 observational studies with 9,845 patients and 10,845 aneurysms found that the overall mortality associated with surgical clipping of unruptured aneurysms was 1.7 percent and unfavourable outcomes occurred in 6.7 percent of the patients [23]. Risk factors for poor safety outcomes include advanced age, larger aneurysm size, and location in the posterior circulation; the association with these risk factors is more consistently observed in surgically rather than endovascularly treated patients [10, 24].

operatives Clipping: steigendes Risiko für ungünstigen Ausgang bei zunehmendem Alter der PatientInnen, Größe der IA, IA der hinteren Zirkulation

Surgical treatment of IA in the posterior circulation is particularly challenging due to the proximity of the brain stem and cranial nerves [7].

Endovascular treatment

The main endovascular technology used to treat IA is embolization with detachable flexible platinum coils.

endovaskuläre Behandlung möglicherweise komplikationsärmer als Clipping

In the ISUIA dataset, rates of poor neurologic outcome at one year were 12.6 percent and 9.8 percent for those treated surgically and endovascularly respectively [10]. A meta-analysis of the literature from 2003 to 2011 on the

treatment-related risks of endovascular treatment for unruptured, saccular IA, found a procedure-related unfavourable outcome, including mortality, in 4.7% (99% CI, 3.8% to 5.7%) of the patients and a mortality rate of 1.8% (fixed-effect weighted average: 99% CI, 1.4% to 2.4%) [25]. However, in the absence of randomisation, differences in mortality and morbidity between endovascular treatment and surgical clipping are likely to be distorted by selection bias, as patients with more difficult aneurysms may preferentially be referred to surgery.

Coiling nicht möglich für breithalsige IA, Riesenaneurysmen

Wide-necked aneurysms are traditionally treated with surgical clipping, as standard coiling could result in coil herniation and parent artery occlusion [7]. Giant aneurysms or fusiform aneurysms may neither be treated by simple coiling approaches nor by surgical clipping, due to the neck morphology of these aneurysms [7]. Therefore, the remaining – surgical – approaches are parent vessel occlusion with or without bypass.

Target population

A0007 – What is the target population in this assessment?
A0023 – How many people belong to the target population?

In Europe, flow diverters have received CE marking for the treatment of intracranial aneurysms without further specification.

primäre Zielpopulation: Erwachsene mit unrupturierten IA

Thus, we chose all adult persons with unruptured intracranial aneurysms as our primary target population. Referring to an estimated prevalence of 3% [9], this would correspond to roughly 200,000 affected adult persons in Austria. It must not be forgotten in this context that a large proportion of these aneurysms would be subclinical and likely undiagnosed.

sekundäre Zielpopulation: Erwachsene mit unrupturierten IA, Einschränkung auf große, breitbasige, fusiforme IA oder Riesen-IA

In the USA and Canada, flow diverters have received more restrictive marketing authorisations, limiting their use to "endovascular treatment of adults with large or giant wide-necked IAs in the internal carotid artery from the petrous to the superior hypophyseal segments" (Pipeline Embolization Device) and "endovascular treatment of complex intracranial aneurysms that are not amenable to treatment with surgical clipping" (Pipeline Flex Embolization Device), consistent with the respectively claimed benefit. We therefore defined a second target population restricted to adult patients with unruptured large/giant, wide-necked saccular or fusiform intracranial aneurysms, for whom stent-assisted coil embolization and/or neurosurgical techniques are not considered feasible (de novo or repeat treatment). The percentage of aneurysms ≥10mm is estimated to be 7% [9], reducing their prevalence to roughly 1 in 500 subjects.

A0011 – What is the expected annual utilisation of flow diverters?

ca. 40 Behandlungen jährlich erwartet

In 2013, 10 treatments with flow diverters were recorded. The expected annual utilisation in Austria is estimated to be 40 treatments (estimates provided by the submitting hospital).

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 flow diverters on mortality?	2
D0002	What is the expected beneficial effect of flow diverters on disease-specific mortality?	2
D0003	What is the effect of flow diverters on the mortality due to causes other than the target disease?	1
D0005	How do flow diverters affect symptoms and findings (severity, frequency) of intracranial aneurysms?	2
D0006	How do flow diverters affect progression (or recurrence) of intracranial aneurysms?	2
D0011	What is the effect of flow diverters on patients' body functions?	2
D0016	How does the use of flow diverters affect activities of daily living?	2
D0012	What is the effect of flow diverters on generic health-related quality of life?	2
D0013	What is the effect of flow diverters on disease-specific quality of life?	2
D0017	Was the use of flow diverters worthwhile?	1

Flow diverters are used for the preventive treatment of unruptured IA; hence, long-term outcomes are required to assess the reduced risk of rupture and associated reduction in mortality and morbidity.

FD für Präventivbehandlung: langfristige Endpunkte notwendig

Endpoints for assessing clinical effectiveness were derived from the three main categories of endpoints "mortality", "morbidity" and "quality of life" that have been defined in the EUnetHTA guideline on clinical endpoints [European Network for Health Technology Assessment (EUnetHTA) 2013a].

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

entscheidende Endpunkte:
- **Mortalität**
- **Pflegebedürftigkeit**
- **Lebensqualität**

- Overall mortality (1 year/5 years)
- Disability/Dependency (1 year/5 years)
- Health related quality of life (HRQoL)
- Primary surrogate parameters:
  - Complete aneurysm occlusion (1 year/5 years)
  - Parent artery stenosis (1 year/5 year)
- Aneurysm recurrence/retreatment rate (1 year/5 years)

The most commonly used tool to evaluate the clinical outcomes of IA interventions is the modified Rankin Scale (mRS, Table 3.2-3), which measures the presence of symptoms, the degree of a patient's functional disability, neurological disability or death with acceptable inter-rater variability [26].

- angiographische Endpunkte als Surrogatparameter

Angiographic endpoints (aneurysm occlusion and parent artery stenosis) were considered, but in the knowledge that they are surrogate endpoints and the relation to the final therapeutic objective (prevention of rupture) cannot be directly extrapolated. Apart from that, relevant inter-observer variability might be an issue [27]. Angiographic aneurysm occlusion is measured by digital subtraction angiography (DSA) as the gold standard (alternatively by MRA or CTA) and classified according to the Raymond or Montreal scale in the classes "complete", "residual neck" or "residual aneurysm" [28]. Parent artery stenosis is measured by the method of Samuels [29].

- Wiederbehandlungsrate

Angiographic efficacy should be complemented by measures for the recurrence of the successfully treated (i.e. occluded) aneurysm. In the absence of an agreed definition for recurrence/recanalisation we selected the retreatment rate as an endpoint [30].

Sources

Quellen: systematische Literatursuche

Results from a systematic literature search (see Section 1.3 and "Literature search strategies" of the Appendix) were used to answer the research questions in the domain "clinical effectiveness". The selection of relevant documents was done by two people independently (Figure 1.4-1).

nur Einschluss von prospektiven Studien, Follow-up ≥ 6 Monate

In terms of study design, only randomised controlled trials with a follow-up of ≥6 months were included to assess clinical effectiveness in a population with unruptured IA that are amenable to endovascular or surgical treatment.

To assess clinical effectiveness in a population with unruptured IA not eligible for standard treatment, all prospective studies with a follow-up ≥6 months and with ≥50 patients were included, provided that any of the defined outcomes were reported. The rationale is that the annual risk of rupture for intracranial aneurysms without treatment is known and the spontaneous occlusion of intracranial aneurysms is an unlikely event. An implicit comparison might therefore be meaningful, depending on the magnitude of the effect and the study population [31].

Analysis

keine quantitative Synthese

No additional data analysis/quantitative synthesis were performed. The internal validity of the studies was assessed using the 18 criteria checklist for single-group studies (Table A2-1).

Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Table 6-1.

4.2 Results

Included studies

None of the studies fulfilled the inclusion criteria to answer research questions related to the primary target population (unruptured intracranial aneurysms without further specification).

0 Studien zu primärer Zielpopulation

From the systematic review, five studies were included [32-36] to address research questions of the second target population ("untreatable" unruptured intracranial aneurysms).

5 Studien zu sekundärer Zielpopulation

Study characteristics and results of included studies are displayed in Table A1-1 and in the evidence profile in Table 6-1.

All five were prospective, multi-centre, single-group studies that analysed mortality, angiographic efficacy and major safety endpoints such as ischemic stroke and haemorrhage. All studies had defined inclusion criteria restricting the study population to aneurysms with unfavourable characteristics (large, wide-necked, fusiform, recurrent after previous treatment, etc.) and all but one [34] excluded ruptured aneurysms. Inclusion criteria and cut-off values showed some heterogeneity leading to differences between studies with regards to the proportion of large/fusiform/wide-necked aneurysms. Similarly, the proportion of patients presenting with symptoms or functional disability varied between the studies.

alle Studien: prospektiv, multi-zentrisch, unkontrolliert

Clinical follow-up in all studies was up to six months, with the exception of [32], which presented clinical follow-up after one year and three years.

Mortality

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

In five prospective single group studies (reporting results from 494 patients in total), overall mortality ranged from 0–8% [32-36].

Mortalität: 0–8 %

Morbidity

D0005 – How do flow diverters affect symptoms and risk of rupture (severity, frequency) of intracranial aneurysms?

Three studies reported mRS scores at baseline and follow-up. One study (150 pts.) indicated no significant overall change in neurologic outcomes based on the Wilcoxon signed rank test [36]. An improvement of symptoms was reported by two studies (250 pts.) in 8.4% [32] and 19.6% [35] of the patients; the proportion of patients with a worsening of symptoms following the procedure ranged from 2.7% to 14% [32, 34-36].

verbesserter mRS: 8,4 bis 19,6 %
verschlechterter mRS: 2,7 bis 14 %

As a surrogate parameter for a reduced risk of rupture, complete aneurysm occlusion was analysed. After six months it ranged between 49% and 85.7% as reported by all five studies (502 aneurysms) [32-36]. After one year, aneurysm occlusion ranged between 81% [32] and 86.8% [35]. The occurrence of parent artery stenosis >50% ranged between 0% and 16.3% [32-36].

vollständiger Aneurysmaverschluss: 49 bis 85,7 % nach 6 Monaten

D0006 – How do flow diverters affect recurrence of intracranial aneurysms?

Wiederbehandlungsrate 0 bis 4,5 % nach 6 Monaten

Two studies (142 pts.) provided information on the retreatment rate of the treated aneurysms (0% after one year of follow-up, [32] and 4.5% after a median follow-up of six months [34]).

Function

D0011 – What is the effect of flow diverters on patients' body functions?
D0016 – How does the use of flow diverters affect activities of daily living?

The results on changes in disability/dependence based on the mRS scores are described in D0005.

Health-related quality of life

D0012 – What is the effect of flow diverters on generic health-related quality of life?
D0013 – What is the effect of flow diverters on disease-specific quality of life?

keine Ergebnisse zu Lebensqualität

Quality of life was not addressed in any of the five prospective studies.

Patient satisfaction

D0017 – Was the use of flow diverters worthwhile?

keine Ergebnisse zu PatientInnen-zufriedenheit

Patient satisfaction was not addressed in any of the five prospective studies.

5 Safety

5.1 Methods

Research questions

Element ID	Research question	Importance 2 = critical 1 = optional
C0008	How safe are flow diverters in comparison to observation only, endovascular coiling or surgical clipping?	2
C0002	Are the harms related to the dosage or the frequency of applying flow diverters?	2
C0004	How does the frequency or severity of harms change over time or in different settings?	2
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of flow diverters?	2
C0007	Are flow diverters and comparator(s) associated with user-dependent harms?	2
B0010	What kind of data/records and/or registry are needed to monitor the use of flow diverters and the comparator?	1

thromboembolische Komplikationen

As any stent implant, the treatment with flow diverters is associated with the risk of thromboembolic complications (with the major consequence being ischemic stroke), that can be caused for example by the occlusion of perforator vessels or the flow diverter stent itself. This complication can occur peri-procedurally, as well as in a delayed manner.

Ruptur des Zielaneurysmas

Another reported complication is the rupture of the target aneurysm, leading to intracranial haemorrhage. Ruptures are often caused by procedural perforations; however, delayed aneurysm ruptures and ruptures/bleeding events remote from the treated aneurysms have also been reported. Delayed aneurysm rupture has led to a medical device alert issued by Balt Extrusion instructing practitioners not to use the Silk flow diverter without coils, owing to the potential for patient death [37].

entscheidende Sicherheitsendpunkte:
- neurologischer Tod
- Hämorrhagie
- ischämischer Schlaganfall
- Pflegebedürftigkeit

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

- Neurological death
- Haemorrhage (total and early, ≤30d)
- Ischemic stroke (total and early, ≤30d)
- New or worsened disability/dependency

Sources

Quellen: systematische Literatursuche

Results from a systematic literature search (see Section 1.3 and "Literature search strategies" of the Appendix) were used to answer the research questions in the domain "Safety". The selection of relevant documents was done by two people independently (Figure 1.4-1).

nur Einschluss von prospektiven Studien, Follow-up ≥ 6 Monate

In terms of study design, RCTs with a follow-up ≥6 months and prospective non-randomised controlled studies ≥6 months were included. In addition, prospective single group studies with a follow-up ≥6 months were included if a) ≥200 patients or b) ≥50 patients and the reporting of mortality AND further adverse events were included.

Analysis

keine quantitative Synthese

The sources were sufficient to answer the questions. We did not perform additional data analysis. Quality was assessed using the 18 criteria checklist for single-group studies (Table A2-1).

Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Table 6-1.

5.2 Results

Included studies

0 Studien zu primärer Zielpopulation

None of the studies fulfilled the inclusion criteria to answer research questions related to the primary target population (unruptured intracranial aneurysms without specification).

5 Studien zu sekundärer Zielpopulation

From the systematic review, five studies were included [32-36] to address research questions regarding the second target population ("untreatable" unruptured intracranial aneurysms).

Study characteristics and results of included studies are displayed in Table A1-1 and in the evidence profile in Table 6-1.

In all of the studies, the treatment with flow diverter was accompanied by a dual antiplatelet regimen and occasionally an adjuvant treatment with coils.

Patient safety

C0008 – How safe are flow diverters in comparison to observation only, endovascular coiling or surgical clipping?

neurologischer Tod: 0 bis 3 %
Hämmorrhagie: 0 bis 6,2 %
ischämischer Schlaganfall: 0 bis 3,7 %
verschlechterter mRS: 2,7 bis 14 %

Neurologic death was reported in all five studies (511 pts.) ranging from 0% to 3.0% [32-36]. Haemorrhages were reported in five studies (494 pts.) and occurred in a range of 0% to 6.2% [32-36]; two cases of late haemorrhage (≥30d) were reported in two studies [32, 34]. Ischemic strokes were reported in 5 studies (494 pts.), within a range of 0% to 3.7%, with no cases reported later than 30 days [32-36]. The proportion of patients with worsening symptoms following the procedure was reported in four studies (450 pts.) and ranged from 2.7% to 14% [32, 34-36].

C0002 – Are the harms related to the dosage or the frequency of applying flow diverters?

No evidence was identified to answer the research question.

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

No evidence was identified to answer the research question.

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

No evidence was identified to analyse the susceptibility of subgroups of patients (aneurysms) to specific complications.

C0007 – Are flow diverters and comparator(s) associated with user-dependent harms?

No evidence was identified to answer the research question.

6 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [38] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendation of the GRADE Working Group [38].

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.

Primary target population:

primäre Zielpopulation: keine Evidenz

No evidence is available for the effectiveness and safety of the endovascular embolization of intracranial aneurysms with flow diverters for the treatment of unruptured intracranial aneurysms without morphological specification.

Secondary target population:

sekundäre Zielpopulation:
- Nutzen und Sicherheit im indirekten Vergleich zu Beobachtung: sehr niedrige Evidenz
- wirksamer Aneurysmaverschluss: moderat

Overall, the strength of evidence for the effectiveness and safety of the endovascular embolization of large, giant, fusiform or wide-necked intracranial aneurysms with flow diverters in indirect comparison to no treatment is very low. Moderate evidence is available for the efficacy of flow diverters to occlude large, giant, fusiform or wide-necked aneurysms.

For comparison with no treatment, endovascular coiling or surgical clipping no direct evidence is available.

Table 6-1: Evidence profile: efficacy and safety of flow diverters in intracranial aneurysms

No of studies/patients	Study design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Overall mortality (6mo)							
5/494 pts.	Prospective case series	Range 0–8%	-1	-1	-1[2]	0	Very low
Retreatment rate (1y)							
2/142 pts.	Prospective case series	0–4.5%	0	0	0	0	Very low
Angiographic efficacy (Total occlusion)							
5/502 an. (6mo) 2/166 an. (1y)	Prospective case series	Range 49–85.7% (6mo) Range 81–86.8% (1y)	-1 0	-1 0	-1[2] 0	0 +2[3]	Very low Moderate
Parent artery stenosis ≥50%							
5/489 pts./an.	Prospective case series	Range 0–16.3%	-1	-1	-1[2]	0	Very low
Function/Disability, dependence (% improved)							
2/250 pts.	Prospective case series	Range 8.4–19.6%	0	0	-1[2]	0	Very low
Safety							
Neurological death							
5/511 pts. (6mo FU)	Prospective single-group studies	Range 0–2.8%	-1	0	-1[2]	0	Very low
1/134 pts. (1y FU)	Prospective single-group studies	2.2%	0	0	0	0	Very low
Haemorrhage							
5/494 pts.	Prospective single-group studies	Range 0–6.2%	-1	0	-1[2]	0	Very low
Haemorrhage ≥30d							
4/387 pts.	Prospective single-group studies	Range 0–2%	-1	0	0	0	Very low
Ischemic stroke							
5/494 pts.	Prospective single-group studies	Range 0–3.7%	-1	0	-1[2]	0	Very low
Ischemic stroke ≥30d							
4/387 pts.	Prospective single-group studies	0%	-1	0	0	0	Very low
Function/Disability, dependence (% worsened)							
4/450	Prospective single-group studies	Range 2.7–14%	-1	0	-1[2]	0	Very low

mo = months, an = aneurysms, pts = patients, y = year, FU = Follow-Up

Nomenclature for GRADE Table:

Limitations: *0: no limitations; no serious limitations; -1: serious limitations*

Inconsistency: *NA: not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency*

Indirectness: *0: direct, no uncertainty; -1: some uncertainty; -2 major uncertainty*

Other modifying factors: *publication bias likely (-1); imprecise data (-1); strong or very strong association (+1 or +2); dose-response gradient (+1); Plausible confounding (+1)*

[2] Follow-up too short

[3] Large effect in comparison to no treatment

7 Discussion

Zusammenfassung bestehender systematischer Reviews

The efficacy and safety of flow diverters in the treatment of unruptured IA has already extensively been reviewed in previous systematic reviews [25, 39-44], including the many retrospective case series available on the topic (Table 7-1). For this assessment, therefore, we have restricted our analysis on prospective studies as the best available evidence, of which we could identify five.

Table 7-1: Overview of results from systematic reviews and meta-analyses on flow diverters

	Number of included studies (patients)	Procedure-related Mortality	Procedure-related Morbidity	Haemorrhage	Ischemic stroke	Aneurysmal occlusion rate
Murthy 2014b [44]	13 (905)[6]	2.3% (95% CI, 1.3–3.3%)	Early: 5.7% (95% CI, 4.2–7.2%) Late: 1.9% (95% CI, 1–2.8%)	ICH: 1.1% (95% CI, 0.4–1.8%) SAH: 2.3% (95% CI, 1.3–3.3%).	1.9% (95% CI, 1–2.8%)	79.7% (95% CI, 76.8–82.6%)
Murthy 2014a [43]	8 (285)[4]	4.9% (95% CI, 2.4–7.4%)	Early: 12.5% (95% CI, 8.7–16.3%) Late: 9.9% (95% CI, 6.4–13.4%)	ICH: 1.4% (95% CI, 0.04–2.8%) Late SAH: 3.5% (95% CI, 1.4–5.6%)	7.7% (95% CI, 4.6–10.8%)	81.8% (95% CI, 77.1–86.5%)
Brinjikji 2013 [40]	29 (1,451)	4% (95% CI, 3–6%)	5% (95% CI, 4–7%)	SAH: 3% (95% CI, 2–4%).	6% (95% CI, 4–9%)	76% (95% CI, 70–81%
Arrese 2013 [39]	15 (897)	Early: 2.8% (95% CI, 1.7–3.8%) Late: 1.3% (95% CI, 0.2–2.3%)	Early: 7.3% (95% CI, 5.7–9%) Late: 2.6% (95% CI, 1.1–4%)	Early Haemorrhage: 0.9% (95% CI, 0.2–1.6%)	Early: 3.6% (95% CI, 2.3–4.9%)	76.2% (95% CI, 72.1–80.2%)
Murthy 2013a [42]	13 (796)[6]	2.4% (95% CI, 1.3–3.5%).	Early: 2–22% Late: 0–13%	Haemorrhage: 1.6% (95% CI, NR)	1.4% (95% CI, NR)	85.5% (95% CI, 82.7–88.4%)
Naggara 2012 [25]	6 (104)[5]	Unfavourable outcomes incl. death 11.5% (99% CI, 4.9–24.6%)		NR	NR	NR
Leung 2012 [41]	10 (414)[6]	2.2% (95% CI, NR)	Overall Morbidity: 10.3% (95% CI, NR)	NR	NR	NR

CI = confidence interval, ICH = intracranial haemorrhage, SAH = subarachnoid haemorrhage, NR = not reported

Overall, the results on mortality, haemorrhage, ischemic stroke and aneurysmal occlusion from the systematic reviews are comparable to the results from our assessment.

nur unkontrollierte Studien: indirekter Vergleich

None of the five studies in our review included a control group, so conclusions on relative effectiveness can only be drawn from indirect comparisons.

moderate Evidenz zu hohen Verschlussraten

Here, the studies provide moderate evidence that flow diverters may lead to high rates (>80%) of complete occlusion of large, giant, fusiform or wide-necked aneurysms after one year.

[4] Silk Flow Diverter only

[5] Subgroup of studies on flow diverters

[6] Pipeline Embolization Device only

Beständigkeit des Verschlusses aufgrund kurzer Follow-ups unklar

The relevance of this outcome to the clinical benefit of the patients is unclear. The purpose of the treatment of unruptured IA is the sustainable prevention of rupture, SAH and ensuing disability or death. Only two studies provided data after a follow-up of one year. The sustainability of the occlusion has not been addressed; the provided evidence on recurrence of the aneurysms is insufficient. Moreover, the rating of the grade of occlusion is subjective and prone to bias.

Wiederbehandlung in 0 bis 4,5 %

Retreatment is an issue with endovascular treatments in comparison to surgical clipping and has been estimated to occur in ~9% of aneurysms treated by endovascular coiling [25]. Two studies in the present assessment addressed this issue and reported retreatment rates of 0% and 4.5% respectively. The first estimate, however, was determined with a follow-up in only 75/143 patients.

keine Evidenz zur Verringerung des Rupturrisikos im indirekten Vergleich mit unbehandelten IA

As demonstrated in the ISUIA study, the risk of rupture varies in dependence of the size, the location of the aneurysm and the history of SAH in the patient (Table 3.2-1). Heterogeneity in the results may be caused by heterogeneous study populations, including different proportions of high-risk aneurysms, which make indirect comparisons challenging. A systematic review of studies analysing the risk of rupture in unruptured IA found a range of 0 to 8.7% SAH per person-year [14]. In the studies identified in this assessment, the range of haemorrhage was 0 to 6.2%. Thus, no beneficial effect of flow diverters on the risk of rupture in comparison to no treatment can be deduced from the present evidence base.

Vergleich mit Rupturrisiko ohne Behandlung nur in wenigen Fällen zulässig keine klare Definition „unbehandelbarer" IA, meist Behandlungsoptionen vorhanden

Abwägung von Behandlungsrisiko und -nutzen nur über RCTs möglich

The indirect comparison with the natural course of disease is only valid under the assumption that flow diverters are used for the treatment of aneurysm for which no alternative treatment is available. In practice, however, there is no agreed definition of an "untreatable" aneurysm, as underlined by the heterogeneous inclusion criteria defined in the studies. In fact, the notion of "untreatable" aneurysm may be true only in rare cases with a combination of unfavourable patient characteristics and aneurysm characteristics. In most patients, however, a more conventional, conservative, or validated approach such as coiling, parent vessel occlusion, or surgical clipping likely exists. Mortality and morbidity rates for endovascular coiling are estimated at 1.7% and 7.7% respectively in unruptured aneurysms, with the two most frequent complications being thromboembolic complications and intraoperative rupture [45]. Overall mortality and morbidity for surgical treatment was estimated at 12.6% [10]. Due to the small differences and the variability in dependence of the aneurysm type, location and history, the trade-off of procedural risks with long-term beneficial outcomes in comparison to standard treatment needs to be established in randomised clinical trials.

5 registrierte RCTs FIAT Studie: Wirksamkeits und Sicherheitsdaten nach Studienende April 2016 zu erwarten

Five RCTs using flow diversion as an intervention are currently registered (Table A3-1). With the exception of the MARCO POLO trial, all have defined inclusion criteria based on some notion of "difficult" aneurysms (e.g. large or wide-necked). Notably, the FIAT trial is expected to provide efficacy and safety outcomes of flow diversion versus standard treatment following the study primary completion date in April 2016.

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:

There is moderate evidence that treatment with flow diverters leads to aneurysm occlusion in a large percentage of treated aneurysms.

moderate Evidenz zu Aneurysmaverschluss

The current evidence is, however, not sufficient to prove, that the assessed technology of endovascular embolization with flow diverters is more effective and safe with regards to clinical outcomes than no treatment, endovascular coiling or surgical clipping.

ungenügende Evidenz hinsichtlich Überlegenheit der FD im Vergleich zu Standardbehandlung

The re-evaluation is recommended in 2017, provided that data from randomised controlled trials will be available at that time.

Re-evaluierung 2017 oder sobald RCT Daten verfügbar

9 References

[1] Alderazi YJ, Shastri D, Kass-Hout T, Prestigiacomo CJ, Gandhi CD. Flow diverters for intracranial aneurysms. Stroke research and treatment. 2014;2014:415653. Epub 2014/06/27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24967131.

[2] Zuckerman SL, Eli IM, Morone PJ, Dewan MC, Mocco J. Novel technologies in the treatment of intracranial aneurysms. Neurological Research. 2014;36(4):368-82. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372620378; http://dx.doi.org/10.1179/1743132814Y.0000000318.

[3] Chicoine MR. Microsurgery and clipping: the gold standard for the treatment of intracranial aneurysms. Journal of neurosurgical anesthesiology. 2003;15(1):61-3. Epub 2002/12/25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12499987.

[4] Gemmete JJ, Elias AE, Chaudhary N, Pandey AS. Endovascular methods for the treatment of intracranial cerebral aneurysms. Neuroimaging Clinics of North America. 2013;23(4):563-91. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52598758; http://dx.doi.org/10.1016/j.nic.2013.03.007.

[5] Armoiry X, Paysant M, Hartmann D, Aulagner G, Turjman F. Interest of flow diversion prostheses in the management of unruptured intracranial aneurysms. Int J Vasc Med. 2012;2012:654627. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=prem&AN=22121490.

[6] BMJ. Best practice. Available from: http://bestpractice.bmj.com/best-practice/monograph/490/basics/classification.html.

[7] Alaraj A, Ti J, Dashti R, Aletich V. Patient selection for endovascular treatment of intracranial aneurysms. Neurological Research. 2014;36(4):283-307. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L372620368; http://dx.doi.org/10.1179/1743132814Y.0000000328.

[8] Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29(1):251-6. Epub 1998/01/28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9445359.

[9] Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. The Lancet Neurology. 2011;10(7):626-36. Epub 2011/06/07. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21641282.

[10] Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-10. Epub 2003/07/18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12867109.

[11] UT Southwestern Medical Center Department of Neurology and Neurotherapeutics. The Internet Stroke Center. [cited 2015 20.Feb.]; Available from: http://www.strokecenter.org/professionals/stroke-diagnosis/stroke-assessment-scales/.

[12] Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773-80. Epub 2005/11/12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16282541.

[13] Rinkel GJ. Natural history, epidemiology and screening of unruptured intracranial aneurysms. Revue neurologique. 2008;164(10):781-6. Epub 2008/09/06. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18771787.

[14] Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38(4):1404-10. Epub 2007/03/03. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17332442.

[15] van der Schaaf IC, Wermer MJ, Velthuis BK, Buskens E, Bossuyt PM, Rinkel GJ. Psychosocial impact of finding small aneurysms that are left untreated in patients previously operated on for ruptured aneurysms. J Neurol Neurosurg Psychiatry. 2006;77(6):748-52. Epub 2006/05/18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16705198.

[16] Buijs JE, Greebe P, Rinkel GJ. Quality of life, anxiety, and depression in patients with an unruptured intracranial aneurysm with or without aneurysm occlusion. Neurosurgery. 2012;70(4):868-72. Epub 2011/09/23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21937934.

[17] Raps EC, Rogers JD, Galetta SL, Solomon RA, Lennihan L, Klebanoff LM, et al. The clinical spectrum of unruptured intracranial aneurysms. Archives of neurology. 1993;50(3):265-8. Epub 1993/03/01. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8442705.

[18] Friedman JA, Piepgras DG, Pichelmann MA, Hansen KK, Brown RD, Jr., Wiebers DO. Small cerebral aneurysms presenting with symptoms other than rupture. Neurology. 2001;57(7):1212-6. Epub 2001/10/10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11591837.

[19] White PM, Teadsale E, Wardlaw JM, Easton V. What is the most sensitive non-invasive imaging strategy for the diagnosis of intracranial aneurysms? J Neurol Neurosurg Psychiatry. 2001;71(3):322-8. Epub 2001/08/21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11511704.

[20] Leitlinien der Deutschen und Österreichischen Gesellschaft für Neurologie. Unrupturierte intrakranielle Aneurysmen. Leitlinien für Diagnostik und Therapie in der Neurologie,. 2012. Available from: http://www.dgn.org/leitlinien/2314-ll-25-2012-unrupturierte-intrakranielle-aneurysmen.

[21] Johnston SC, Wilson CB, Halbach VV, Higashida RT, Dowd CF, McDermott MW, et al. Endovascular and surgical treatment of unruptured cerebral aneurysms: comparison of risks. Ann Neurol. 2000;48(1):11-9. Epub 2000/07/14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10894211.

[22] Mahaney KB, Brown RD, Jr., Meissner I, Piepgras DG, Huston J, 3rd, Zhang J, et al. Age-related differences in unruptured intracranial aneurysms: 1-year outcomes. J Neurosurg. 2014;121(5):1024-38. Epub 2014/08/30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25170670.

[23] Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. J Neurol Neurosurg Psychiatry. 2013;84(1):42-8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=23012447.

[24] Ogilvy CS, Carter BS. Stratification of outcome for surgically treated unruptured intracranial aneurysms. Neurosurgery. 2003;52(1):82-7; discussion 7-8. Epub 2002/12/21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12493104.

[25] Naggara ON, Lecler A, Oppenheim C, Meder J-F, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: a systematic review of the literature on safety with emphasis on subgroup analyses. Radiology. 2012;263(3):828-35. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=22623696.

[26] Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38(3):1091-6. Epub 2007/02/03. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17272767.

[27] Tollard E, Darsaut TE, Bing F, Guilbert F, Gevry G, Raymond J. Outcomes of endovascular treatments of aneurysms: observer variability and implications for interpreting case series and planning randomized trials. AJNR Am J Neuroradiol. 2012;33(4):626-31. Epub 2011/12/24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22194386.

[28] Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke. 2001;32(9):1998-2004. Epub 2001/09/08. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11546888.

[29] Samuels OB, Joseph GJ, Lynn MJ, Smith HA, Chimowitz MI. A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol. 2000;21(4):643-6. Epub 2000/04/27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10782772.

[30] Byrne JV. Tutorials in Endovascular Neurosurgery and Interventional Neuroradiology. p. 156ff.

[31] Ip S, Paulus JK, Balk EM, Dahabreh IJ, Avendano EE, Lau J. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. Rockville (MD)2013.

[32] Yu SC-H, Kwok C-K, Cheng P-W, Chan K-Y, Lau SS, Lui W-M, et al. Intracranial aneurysms: midterm outcome of pipeline embolization device – a prospective study in 143 patients with 178 aneurysms. Radiology. 2012;265(3):893-901. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=22996749.

[33] McAuliffe W, Wycoco V, Rice H, Phatouros C, Singh TJ, Wenderoth J. Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. AJNR Am J Neuroradiol. 2012;33(1):164-70. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=21979492.

[34] Byrne JV, Beltechi R, Yarnold JA, Birks J, Kamran M. Early experience in the treatment of intra-cranial aneurysms by endovascular flow diversion: a multicentre prospective study. PLoS ONE. 2010;5(9):e12492 Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=20824070.

[35] Becske T, Kallmes DF, Saatci I, McDougall CG, Szikora I, Lanzino G, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology. 2013;267(3):858-68. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=23418004.

[36] Wakhloo AK, Lylyk P, de Vries J, Taschner C, Lundquist J, Biondi A, et al. Surpass flow diverter in the treatment of intracranial aneurysms: a prospective multicenter study. AJNR Am J Neuroradiol. 2015;36(1):98-107. Epub 2014/08/16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25125666.

[37] Medicines and Healthcare Products Regulatory Agency. 2010; Available from: https://www.gov.uk/drug-device-alerts/medical-device-alert-intracranial-stent-don-t-use-to-treat-intracranial-aneurysms-without-embolisation-coils.

[38] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64:383-94.

[39] Arrese I, Sarabia R, Pintado R, Delgado-Rodriguez M. Flow-diverter devices for intracranial aneurysms: systematic review and meta-analysis. Neurosurgery. 2013;73(2):193-9; discussion 9-200. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=23624409.

[40] Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis. Stroke. 2013;44(2):442-7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=23321438.

[41] Leung GKK, Tsang ACO, Lui WM. Pipeline embolization device for intracranial aneurysm: a systematic review. Clin Neuroradiol. 2012;22(4):295-303. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=23124329.

[42] Murthy S, Shah S, Rao CV, Bershad E, Suarez J. Treatment of intracranial aneurysms with pipeline embolization device: A systematic review of literature. Neurology. 2013;80(1). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71130571.

[43] Murthy SB, Shah S, Shastri A, Venkatasubba Rao CP, Bershad EM, Suarez JI. The SILK flow diverter in the treatment of intracranial aneurysms. J Clin Neurosci. 2014;21(2):203-6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=24128768.

[44] Murthy SB, Shah S, Venkatasubba Rao CP, Bershad EM, Suarez JI. Treatment of unruptured intracranial aneurysms with the pipeline embolization device. J Clin Neurosci. 2014;21(1):6-11. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medl&AN=24055205.

[45] Pierot L, Wakhloo AK. Endovascular treatment of intracranial aneurysms: Current status. Stroke. 2013;44(7):2046-54. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L369278262; http://dx.doi.org/10.1161/STROKEAHA.113.000733.

[46] Gartlehner G. Internes Manual. Abläufe und Methoden. Teil 2 (2. Aufl.). Wien: Ludwig Boltzmann Institut für Health Technology Assessment, 2009.

[47] EUnetHTA Joint Action 2 WP. Levels of evidence: Internal validity (of randomized controlled trials). 2013. Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[48] Moga C GB, Schopflocher D, C H. . Development of a quality appraisal tool for case series studies using a modified Deplhi technique. Methodology Paper. Edmonton AB: Institute of Health Economics, 2012.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A1-1: Flow diverters: Results from observational studies

Author, year,	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
Country	US, AR, NL, DE, FR, HU, JP, IE, CL, IT, UK	US, HU, TK	HK	AU	worldwide (details NR)
Sponsor	NR	Chestnut Medical and ev3 (Covidien)	NR	ev3	Balt Extrusion
Intervention/Product	Surpass Flow Diverter	Pipeline Embolization Device	Pipeline Embolization Device	Pipeline Embolization Device	SILK Flow Diverter
Concomitant medication and therapy	Dual antiplatelet therapy Coil treatment (36 aneurysms)	Dual antiplatelet therapy Coil treatment (1 aneurysm)	Dual antiplatelet therapy Coil treatment (9 aneurysms)	Dual antiplatelet therapy Coil treatment (6 patients)	Dual antiplatelet therapy Coil treatment (10 patients)
Comparator	-	-	-	-	-
Study design	Prospective, multi-centre, single- group study	Prospective, multi-centre, single-group study (PUFs)	Prospective, multi-centre, single-group study	Prospective multi-centre, single-group study	Prospective, multi-centre, single-group study
Number of patients	165	108	143	54	70
Number of aneurysms	190	108 (+2 qualifying contralateral aneurysms in 2 patients)	178	57	70
Inclusion criteria	Aneurysms of any size located in the anterior or posterior circulation with neck diameter >4mm or dome-to-neck ratio ≤2	Presence of an aneurysm arising from the internal carotid artery (petrous through the superior hypophyseal segments) with aneurysm diameter ≥ 10mm and neck diameter ≥ 4 mm	a) Saccular or fusiform aneurysms; b) Untreated unruptured aneurysms or recurrent aneurysms after previous treatment; c) Aneurysm diameter ≥10mm or dome-to-neck ratio ≤1 or neck diameter ≥4mm or multiple aneurysms within a 1cm distance; d) Parent vessel diameter 2.5-5mm	Aneurysms with neck diameter >4mm or dome-to-neck ratio <1.6 or aneurysm diameter >10mm or fusiform or failed treatment	"Patients were selected for treatment locally on the basis that the target aneurysm was unsuitable for conventional treatment."

Author, year,	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
Exclusion criteria	SAH associated with ruptured aneurysm within previous 30d; contraindication or non-responders to dual antiplatelet therapy, non-treated brain arteriovenous malformation	SAH within previous 60d, any intracranial haemorrhage or major surgery within previous 42d, history of bleeding disorder or low platelet count, previously placed stent at the target aneurysm, contraindication to CT or MRI, allergy to platinum/cobalt/chromium alloys, active infection, major stenosis of ipsilateral carotid artery + indwelling stent previously placed across the neck of target IA	a) Dissecting aneurysm; b) SAH within previous 50d; c) Intracranial arteriovenous malformation; d) Parent artery stenosis of ≥50%	Acute SAH	Any contraindication to antiplatelet drugs, pregnancy, breast feeding, and aneurysms considered treatable with coils alone
Patient characteristics					
Mean age of patients (y)	57.1 (range 28–82)	57± 11.3 (range 30.2–75.1)	54.9±11.4 (range 27–82)	55.7 (range 30–83)	Not collected
Sex	72.4% female	88.9% female	74.8% female	81.5% female	Not collected
Risk factors	NR	55.6% hypertension, 57.4% smoker, history of SAH 7.4%	NR	NR	NR
Clinical presentation	Asymptomatic or chronic headache: 31.8%, cranial nerve palsy/mass effect: 18.6%	71/108 (65.7%) presented with neuropathy of cranial nerves 2-6	Asymptomatic: 81.1%, headache: 9.1%, cranial nerve palsy: 9.8%	Asymptomatic: 70.4%, cranial nerve palsy/mass effect: 29.6%	Asymptomatic: 43%, symptomatic with no or mild disability: 44%, moderate or significant disability: 13%. Ruptured aneurysms: 10 (14.3%)
Baseline functional score	mRS: NR	mRS≤ 1 in 87.1%	mRS ≤ 1 in 96.5%	mRS: NR	mRS ≤ 1 in 70%
Aneurysm characteristics					
Type	125 wide-neck saccular (67.2%), 54 fusiform/dissecting (29.0%), 7 blister-like (3.8%)	NR	173 saccular aneurysms (97.2%); 5 fusiform (2.8%)	46 saccular/berry (80.7%), 11 fusiform (19.3%)	44 saccular (62.9%), 26 fusiform (37.1%)
Recurrent/ prior failed treatment	Recurrent aneurysms in 24% of the patients	8 recurrent aneurysms (7.4%)	34 recurrent aneurysms (19.1%)	Recurrent aneurysms in 29.6% of the patients	NR
Location	27 posterior circulation (14.5%)	0 posterior circulation (0%)	6 posterior circulation (3.4%)	11 posterior circulation (19.3%)	26 posterior circulation (37.1%)
Measurements	Mean size 10.4 ± 0.7mm, mean neck diameter 6.0 ± 0.4mm, mean dome-to-neck ratio 1.6 ± 0.08%	Mean size 18.2± 6.4mm, mean neck diameter 8.8 ± 4.3mm		Mean size 13.1mm	

Author, year,	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
	Size ≥ 10mm: 69 (37.1%)	Size ≥ 10mm: 107 (99.1%); Neck ≥ 6mm: 85 (78.7%)	Size ≥10mm: 33 (18.5%); Neck ≥4mm: 96 (53.9%)	Size ≥ 10mm: 39 (68.4%); Dome-to-neck<1.6 or neck>4mm: 57 (100%)	Size ≥ 10mm: 52 (74.3%); Neck ≥ 4mm: 38 (73.1%)[7]
Follow-up	Clinical and angiography: Median, 6mo (range 1-38mo)	Clinical: 6mo Angiography: 6mo and 1y	Clinical and angiography: Median, 18.2 mo (range 3-39.2mo) Clinical: 1y, 3y Angiography: 6mo, 1y, 18mo	Clinical: 6mo Angiography: 6mo	Clinical and angiography: Median, 119d (range 9-528d)
Loss to follow-up, n (%)	Clinical: 15/165 (9.1%) (4 failed treatment, 11 refused) Angiography: 32/190 (16.8%) (4 failed treatment)	Clinical @6mo: 5/108 (4.6%) (1 failed treatment, 4 FU by phone) Angiography @6mo: 11/108 (10.2%) (1 failed treatment, 3 excluded, 3 dead, 4 refused) Angiography @1y 19/108 (17.6%) (11 see above, 7 NR)	Clinical @1y: 9/143 (6.3%) Clinical @3y: 95/143 (66.4%) – data not extracted Angiography @6mo: 38/178 (21.3%) Angiography @1y: 103/178 (57.9%)	Clinical @6mo: 1/54 (1.9%) Angiography @6mo: 1/57 (1.8%)	Clinical: 20/70 (29%) (3 failed treatment) Angiography: 21/70 (30%) (3 failed treatment)
Outcomes					
Efficacy					
Overall mortality, n (%)	7/150 (4.7%)[8]	3/107 (2.8%) (6mo FU)	2/134 (1.5%) (6mo FU) 3/134 (2.2%) (1y FU)	0/53 (0%) (6mo FU)	4/50 (8%)[8]
Retreatment rate, n (%)	NR	NR	0/75 (0%) aneurysms (1y FU)	NR	3/67 (4.5%)[8]
Angiographic efficacy (Total occlusion), n (%)	118/158 (74.7%) aneurysms[8]	78/99 (78.8%) aneurysms (6mo FU) 79/91 (86.8%) aneurysms (1y FU)	78/140 (55.7%) aneurysms (6mo FU) 61/75 (81%) aneurysms (1y FU)	48/56 (85.7%) aneurysms (6mo FU)[9]	24/49 (49%) aneurysms[8]
Parent artery stenosis ≥ 50%	8/150 (5.3%)[8]	2/97 (2.0%) (6mo FU)	0/140 (0%) aneurysms	2/53 (3.5%)	8/49 (16.3%)[10,8]

[7] Measured for 43 saccular aneurysms

[8] No fixed follow-up time point

[9] Occlusion grade not specified

[10] Parent artery occlusion or "severe" degree of arterial narrowing

Author, year,	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
Function/Disability, dependence (mRS)	Wilcoxon matched pairs signed rank test indicates no significant change in neurologic outcomes (P=.55); worse in 4/150 (2.7%)[8]	Improved in 21/107; unchanged 70/107; worse 10/107 (9.3%), unavailable in 6/107 (6mo FU)	Improved in 12/143; unchanged in 119/143; worse in 12/143 (8.4%) (30d FU)	NR	Worse in 7/50 (14%)[11,8]
Safety					
Neurologic death	4/150 (2.7%)[8]	3/107 (2.8%) (6mo FU)	2/134 (1.5%) (6mo FU) 3/134 (2.2%) (1y FU)	0/53 (0%) (6mo FU)	2/67 (3.0%)[8]
Haemorrhage	10/150 (6.2%)	6/107 (5.6%)	5/134 (3.7%)[12] (1y FU)	0/53 (0%)	1/50 (2%)
Haemorrhage ≥ 30d	0/150 (0%)	NR	1/134 (0.7%)[12] (1y FU)	0/53 (0%)	1/50 (2%)
Ischemic stroke	3.7%[12]	4/107 (3.7%)	1/134 (0.7%)[12] (1y FU)	0/53 (0%)	1/50 (2%)
Ischemic stroke ≥ 30d	0/150 (0%)[12]	NR	0/134 (0%)[12] (1y FU)	0/53 (0%)	0/50 (0%)
Serious adverse events	NR	44 events	12/134 (9.0%)[13] (1y FU)	5/53 (9.4%)[14]	12/50 (24%)

d = day(s); FU = Follow-Up; mo = months; IS = Ischemic Stroke; mRS = modified Rankin Scale; NR = not reported; SAH = Subarachnoid Haemorrhage; TIA = Transient Ischemic Attack; y = year(s)

[11] Baseline measured with Glasgow Coma Score, follow-up scores NR

[12] Only major stroke reported, n NR

[13] Only neurological complications reported

[14] Only TIA, stroke, SAH or mass effect documented

Risk of bias tables

The 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 [46] and in the Guidelines of EUnetHTA [47].

Table A2-1: Risk of bias – Study level

18 criteria checklist: critical appraisal single-group studies	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
Study objective					
Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes
Study population					
Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes	Yes
Were the cases collected in more than one centre?	Yes	Yes	Yes	Yes	Yes
Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Yes	No
Were participants recruited consecutively?	Yes	Yes	Yes	Yes	No
Did participants enter the study at similar point in the disease?	Yes	Yes	Yes	Yes	No[15]
Intervention and co-intervention					
Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes
Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	Yes	Yes
Are the outcome measures clearly defined in the introduction or methods section?	No	Yes	Yes	No	No
Were relevant outcomes appropriately measured with objective and/or subjective methods?	No[16]	Yes	Yes	Unclear	No[16]
Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes
Statistical analysis					
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes[18]	Yes[17,18]	Yes[18]	Yes[18]	Yes[18]

[15] Study population included patients with ruptured aneurysms.

[16] Outcomes were measured at variable time-points (no minimum follow-up)

[17] Statistical effectiveness analysis versus fixed threshold was not considered in this report

18 criteria checklist: critical appraisal single-group studies	Wakhloo (2014)	Becske (2013)	Yu (2012)	McAuliffe (2012)	Byrne (2010)
Results and conclusions					
Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes
Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?[18]	No	Yes	Yes	No	No
Are adverse events reported?	Yes	Yes	Yes	Yes	Yes
Are the conclusions of the study supported by results?	Yes	Yes	No[19]	Yes	Yes
Competing interests and sources of support					
Are both competing interests and sources of support for the study reported?	No	Yes	Yes	Yes	Yes
Overall risk of bias at study level	**High**	**Low**	**Low**	**High**	**High**

Source: [48]

[18] Data reported are absolute counts.

[19] Authors recommend considering PED "a first choice for treatment of unruptured IA"

Applicability table

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

Domain	Description of applicability of evidence
Population	Study populations represent a wide spectrum of aneurysms in terms of size, morphology, location and stage of disease. The inclusion criteria do not reflect truly "untreatable" aneurysms, but rather "challenging" aneurysms.
Intervention	The studies include three marketed products (Surpass, Silk and Pipeline). All had concomitant anti-platelet therapy. Applicability might be limited due to some studies using adjuvant endosaccular coiling and others not.
Comparators	None of the studies included a comparison group.
Outcomes	Outcomes most frequently reported are aneurysm occlusion, mortality, neurological death and stroke. Only two studies presented follow-up >6 months. Thus, long-term stability and preventive effect of aneurysm rupture may not be assessed.
Setting	All of the studies included were multi-centre studies, with clinical centres based in Europe, Australia, South America and Asia. Therefore, it can be assumed that the results reflect a wide spectrum of clinical routines both with regard to patient selection and treatment modalities and, therefore, that results are transferable to the Austrian setting. The surgeon's technical expertise likely determines the risk of local side effects. If introduced as a new treatment method in European hospitals, the treatment with flow diverters will certainly be accompanied by a learning curve.

List of ongoing randomised controlled trials

Table A4-1: List of ongoing randomised controlled trials of flow diverters

Identifier/Trial name	Patient population	Intervention	Comparison	Outcome	Primary completion date	Sponsor
NCT01762137 LARGE aneurysm randomized trial: flow diversion versus traditional endovascular coiling therapy (LARGE)	Patients aged 21–75 internal carotid artery aneurysms (petrous, cavernous, and paraophthalmic) with neck and fundus morphologies amenable to either traditional endovascular treatments using coils or reconstruction with the flow diversion. Aneurysm neck ≥4 mm. Fundus ≥10 mm	Flow diversion	Endovascular coil embolization	Non-inferiority with regard to efficacy and safety at 180 days after procedure.	April 2018	Medical University of South Carolina, US
NCT01349582 Flow diversion in intracranial aneurysm treatment (FIAT) trial	Any patient with a "difficult" intracranial aneurysm in whom flow diversion is considered an appropriate, if not the best yet unproved therapeutic option by the participating clinician	Flow diversion	Standard treatment of any of the following: (1) conservative management, (2) coil embolization with or without high porosity stent, (3) parent vessel occlusion, or (4) surgical clipping	Efficacy and safety	April 2016	Centre hospitalier de l'Université de Montréal, CA
NCT01811134 Endovascular treatment of intracranial aneurysm with pipeline versus coils with or without stents (EVIDENCE) trial	Unruptured saccular intracranial aneurysms >7 mm	Pipeline embolization device	Endovascular coil embolization with or without balloon remodelling, with or without stent assistance	Efficacy	Nov 2015	Hospices Civils de Lyon, FR
NCT01084681 Multi-centre randomised trial on selective endovascular aneurysm occlusion with coils versus parent vessel reconstruction using the SILK flow diverter (MARCO POLO)	Patients with at least one documented untreated, unruptured intracranial aneurysm suitable for occlusion with an intracranial device	SILK flow diverter without coils	Endovascular coil embolization with or without balloon remodelling or stent assistance	Efficacy and safety	Oct 2012	Balt International
ChiCTR-TRC-13003127 Parent artery reconstruction for large or giant cerebral aneurysms using Tubridge flow diverter	Patients with unruptured carotid or vertebral artery aneurysms (including saccular or recanalized aneurysms. Neck ≥4mm, size ≥10mm	Tubridge flow diverter +/- bare coils	Enterprise stent combined with bare coils	Efficacy and safety	NR	MicroPort NeuroTech (Shanghai) Co., Ltd.

Literature search strategies

Search strategy for Cochrane

Search Name: Flow Diverters for Intracranial Aneurysm Last Saved: 12/12/2014 15:21:33.840	
ID	Search
#1	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#2	intracranial aneurysm* (Word variations have been searched)
#3	intra-cranial aneurysm* (Word variations have been searched)
#4	#1 or #2 or #3
#5	flow diverter* (Word variations have been searched)
#6	flow diversion* (Word variations have been searched)
#7	flow-diverting (Word variations have been searched)
#8	pipeline embolization device* (Word variations have been searched)
#9	silk near diver* (Word variations have been searched)
#10	surpass near diver* (Word variations have been searched)
#11	endoluminal reconstruction* (Word variations have been searched)
#12	flow redirection endoluminal device* (Word variations have been searched)
#13	FRED (Word variations have been searched)
#14	MeSH descriptor: [Therapeutic Occlusion] this term only
#15	aneurysm* next occlusion* (Word variations have been searched)
#16	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #13 or #14 or #15
#17	#4 and #16
40 Hits	

12.12.2014

Search strategy for CRD

Search Name: Flow Diverters (MELs 2015) AK	
1	(flow diver*)
2	(pipeline emboli*ation device*)
3	(silk NEAR diver*)
4	(surpass NEAR diver*)
5	(endoluminal reconstruction*)
6	(aneurysm occlusion*)
7	(flow redirection endoluminal device*)
8	#1 OR #2 OR #3 OR #6
10 Hits	

12.12.2014

Search strategy for EMBASE

Query Results
'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'feasibility study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de AND ('intracranial aneurysm'/mj OR 'intracranial aneurysm' OR 'intracranial aneurysms' OR 'intra-cranial aneurysm' OR 'intra-cranial aneurysms') AND ('flow diverter' OR 'flow diverters' OR 'flow diversion' OR 'flow diversions' OR 'flow-diverting' OR 'pipeline embolization device'/exp OR 'pipeline embolisation device' OR 'pipeline embolisation devices' OR 'pipeline embolization devices' OR 'pipeline embolization device' OR silk:dn OR surpass:dn OR 'endoluminal reconstruction' OR 'endoluminal reconstructions' OR 'aneurysm occlusion' OR 'aneurysm occlusions' OR 'flow redirection endoluminal device' OR fred:dn OR 'therapeutic occlusion' OR 'therapeutic occlusions') AND 'human'/de
338 Hits

12 .12.2014

Search strategy for OVID Medline

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 10, 2014>, Ovid MEDLINE(R) Daily Update <November 19, 2014>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Intracranial Aneurysm/(22204)
2	intracranial aneurysm*.mp. (23741)
3	1 or 2 (23741)
4	flow diverter*.mp. (267)
5	flow diversion*.mp. (289)
6	flow-diverting.mp. (149)
7	pipeline emboli#ation device*.mp. (190)
8	(silk adj5 diver*).mp. (64)
9	(surpass adj5 diver*).mp. (9)
10	endoluminal reconstruction*.mp. (22)
11	aneurysm occlusion*.mp. (469)
12	flow redirection endoluminal device*.mp. (2)
13	FRED.mp. (747)
14	*Therapeutic Occlusion/(49)
15	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1871)
16	3 and 15 (675)
17	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. (1237296)
18	((systematic adj3 literature) or systematic review* or meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*)).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or "cochrane database of systematic reviews".jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. (216677)
19	17 or 18 (1379293)
20	16 and 19 (121)
21	remove duplicates from 20 (117)
117 Hits	

11.12.2014