HTA Austria
Austrian Institute for
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Percutaneous left ventricular assist devices: micro-axial flow pumps

Systematic Review

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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.

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Content

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List of abbreviations

AE ..... Adverse events
AIHTA ..... Austrian Institute for Health Technology Assessment
AMI ..... Acute myocardial infarction
AMSTAR-II ..... A Measurement Tool To Assess Systematic Reviews
AWMF ..... Association of the Scientific Medical Societies of Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
BIVAD ..... Biventricular assist device
CABG ..... Coronary artery bypass grafting
CE ..... Conformité Européenne ("Europäische Konformität")
CERSI ..... Center of Excellence in Regulatory Science and Innovation
CI ..... confidence interval
CI-AKI ..... Contrast-induced acute kidney injury
COPD ..... Chronic obstructive pulmonary disease
COVID-19 ..... Coronavirus disease of 2019
CPI ..... Cardiac power index
CPR ..... Cardiopulmonary resuscitation
CS ..... Cardiogenic shock
cVAD ..... Catheter-based ventricular assist device
DES ..... Drug-eluting stent
ECLS ..... Extracorporeal life support

ECMO ..... Extracorporeal membrane oxygenation
ESRD ..... End-stage renal disease
EUA..... Emergency use authorization
EUnetHTA ..... European network for Health Technology Assessment
FDA..... U.S. Food and Drug Administration
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
HRPCI ..... High-risk percutaneous coronary intervention
HTA ..... Health Technology Assessment
IABP..... Intra-aortic balloon pump
ICD ..... International Classification of Diseases
ICU..... Intensive care unit
INAHTA ..... International Network of Agencies for Health Technology Assessment
ITT ..... Intention-To-Treat
LKF..... Austrian catalogue for medical procedures (Leistungsorientierte Krankenanstaltenfinanzierung)
LV..... Left ventricle
LVAD..... Left ventricular assist device
LVEF..... Left ventricular ejection fraction
LoS ..... Length of stay
MACE ..... Major adverse cardiovascular events
MAE ..... Major adverse events
MCS ..... Mechanical circulatory support
MODS ..... Multiple organ dysfunction score
NA ..... Not available
NIS ..... National inpatient sample
NON-STEMI ... Non-ST segment elevation myocardial infarction
NR ..... Not reported
NRCT..... Non-randomised controlled trial
NSTE-ACS ..... Non-ST segment elevation acute coronary syndrome
P ..... p-Value
PCI ..... Percutaneous coronary intervention
pLVAD ..... Percutaneous left ventricular assist device
pMCS ..... Percutaneous mechanical circulatory support
PP ..... Per-Protocol
PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pts..... Patients
pVAD ..... Percutaneous ventricular assist device
RCT..... Randomised controlled trial
RoB..... Risk of bias
ROBINS-I..... Risk of bias in non-randomized studies of interventions
RVAD..... Right ventricular assist device
SAE ..... Serious adverse events
SC ..... Standard care
SD..... Standard deviation
SOFA ..... Sequential organ failure assessment
SR..... Systematic review
s.s.diff. ..... Statistically significant difference
STEMI ..... ST-elevation myocardial infarction
STIC..... Programme de Soutien aux Techniques Innovantes et Couteuses
SUE ..... Schwere unerwünschte Ereignisse
TIA ..... Transient ischemic attack
UE ..... unerwünschte Ereignisse
VA-ECMO ..... Veno-arterial extracorporeal membrane oxygenation
VV-ECMO ..... Veno-venous extracorporeal membrane oxygenation
YLD ..... Years lost due to disability
YLL ..... Years of life lost

Executive Summary

Introduction

Cardiogenic shock is a life-threatening condition caused by insufficient cardiac pump resulting in reduced cardiac output with inadequate tissue perfusion. Percutaneous coronary interventions (PCI) are minimally invasive procedures for revascularization, primarily achieved by balloon angioplasty and intracoronary stenting. Indications for PCI are myocardial infarction, angina pectoris, and critical coronary artery stenosis. In both of these indications, temporary mechanical circulatory support may, among other interventions, be considered.

cardiogenic shock is a life-threatening condition
PCI: minimally invasive procedure;
temporary mechanical support in cardiogenic shock or PCI

Micro-axial percutaneous left ventricular assist devices (pLVAD) are a type of mechanical circulatory support. Micro-axial pLVAD are inserted percutaneously and consist of a mini heart pump mounted at a catheter, a console, and an infusion system. They aim to improve clinical outcomes such as mortality due to their hemodynamic effects. The Impella® devices are the only micro-axial pLVAD currently available on the market.

micro-axial pLVAD aim to improve hemodynamic support and mortality rates
currently available micro-axial pLVAD: Impella® devices

Methods

This report aimed to assess whether micro-axial pLVAD in patients with a diagnosis of cardiogenic shock or patients undergoing PCI are more effective concerning mortality and equally safe or safer concerning adverse events in comparison to standard care alone. To evaluate the efficacy and safety of micro-axial pLVAD, the evidence from a high-quality HTA report by the Canadian Health Quality Ontario (HQO), published in 2017, was updated. The methodological quality of the HQO HTA was assessed using the AMSTAR-II checklist.

update HTA: Health Quality Ontario report 2017

An update search of the evidence was conducted based on the search strategies from the identified HTA report. The following databases were used for the systematic search from 2015 to 2020: Medline, Embase, The Cochrane Library, CRD, and HTA-INAHTA. In addition, a hand search of reference lists of recent reviews was performed. In total, 1,110 potentially relevant hits were identified.

systematic search: 2015-2020

The study selection, data extraction and assessment of the methodological quality of the studies were performed independently by two researchers. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was further used for the qualitative evidence synthesis.

selection, extraction and quality appraisal: conducted by 2 researchers

Domain clinical effectiveness

For clinical effectiveness, the crucial outcome reduced mortality was used as evidence to derive a recommendation. Additionally, further outcomes such as hemodynamic variables, length of hospital stay as well as rehospitalisation were defined as important.

crucial outcomes effectiveness: mortality

Domain safety

For safety, all (serious) adverse events were defined as crucial outcomes to derive a recommendation.

crucial outcomes safety: all (serious) adverse events

Results: Micro-axial pLVAD in patients with cardiogenic shock

cardiogenic shock: 3 RCTs, 1 observational study; quality of evidence: very low

Three randomised controlled trials (RCTs) with a total of 89 analysed patients and one retrospective cohort study with 18,032 patients investigated the use of the technology in patients with cardiogenic shock. The quality of evidence was very low, mainly due to insufficient precision and a moderate risk of bias (RoB) in two studies and a high RoB in two studies.

Clinical effectiveness

mortality: no stat. significant difference; cardiac index: 1 RCT stat. sign. difference indicating better hemodynamic support in intervention group

Two of the RCTs were not able to detect a statistically significant difference in mortality. One RCT did not report a p-value. Mortality ranged from 28.6 to 46% in the intervention groups and from 0 to 50% in the control groups after one month (in three studies), and 50% in the intervention group and 50% in the control group after six months (in one study). For hemodynamic variables, one of the RCTs detected a statistically significant difference in cardiac index, indicating better hemodynamic support, while one RCT showed no statistically significant difference.

Safety

bleeding complications, additional devices and renal complications: stat.sign. difference detrimental to the intervention group

For bleeding complications, a statistically significant difference detrimental to the intervention group in comparison to the control group was reported in one RCT. Further, the use of additional devices such as extracorporeal membrane oxygenation (ECMO) or intubation showed a statistically significant difference in the intervention group compared to the control group in one observational study, with the use of additional devices more common in the intervention group. For renal complications, there was a statistically significant difference to the disadvantage of the intervention group compared to the control group in one observational study. For major adverse cardiovascular events and other complications, no statistically significant difference between groups was reported.

Results: Micro-axial pLVAD in patients with percutaneous coronary interventions

PCI: 1 RCT, 2 observational studies quality of evidence: very low

One RCT with 448 analysed patients and two retrospective cohort studies with a total of 51,666 patients investigated the use of the technology in patients undergoing PCI. The quality of evidence was very low, mainly due to insufficient precision. There was moderate RoB in two studies and high RoB in one study.

Clinical effectiveness

mortality: no stat. significant difference; cardiac index: 1 RCT stat.sign. difference in indicating better hemodynamic support in intervention group

The RCT was not able to detect a statistically significant difference in mortality. Mortality at one month was reported for 7.6% in the intervention group compared to 5.9% in the control group. After three months, mortality was reported for 12.1% in the intervention group compared to 5.9% in the control group. For hemodynamic variables, the RCT detected a statistically significant difference in cardiac index, indicating better hemodynamic support in the intervention group.

Safety

bleeding complications: stat.sign. difference detrimental to the intervention group

A statistically significant difference in bleeding complications detrimental to the intervention group compared to the control group was reported in two observational studies. For major adverse cardiovascular events and other complications, no statistically significant difference between groups was reported.

Upcoming evidence

In the search for upcoming evidence, five ongoing RCTs were identified. The estimated completion dates range from 2022 to 2027.

5 ongoing RCTs

Reimbursement

Currently, the Austrian hospital benefit catalogue lists a reimbursement code for short-term circulatory support using a centrifugal or axial flow pump. However, the cost for micro-axial pLVAD exceed the reimbursement value of the current code.

current reimbursement does not cover micro-axial pLVAD

Discussion

For both indications, the overall quality of evidence for the clinical effectiveness and safety of micro-axial pLVAD and standard care compared with standard care is very low (GRADE rating). One major limitation of the evidence was an imprecision of data, as all included RCTs had small sample sizes. The overall RoB was considered moderate for observational studies and moderate to high RoB for RCTs.

limitations: imprecision, moderate to high RoB in studies

According to the S3 guideline (2019) of the Association of the scientific medical societies in Germany (AWMF), and the European Society of Cardiology (ESC) guidelines (2018), micro-axial pLVAD may be used for infarct-related cardiogenic shock under certain conditions, but the evidence for micro-axial pLVAD is insufficient to recommend their use. For high-risk PCI, the guidelines describe similar outcomes between pLVAD and IABP.

AWMF S3 guideline, ESC guideline: "may be used" with preconditions, insufficient evidence for recommendation

Currently, the evidence is insufficient to show that micro-axial pLVAD and standard care is superior or inferior to standard care alone. None of the studies were able to find a statistically significant difference in mortality. Some evidence suggests that the technology could improve hemodynamic support. However, safety concerns regarding major bleeding complications were seen that may make the technology a less safe treatment modality in both assessed indications.

insufficient evidence to show a clinical benefit

improved hemodynamic support, but safety concerns

Conclusion

Based on the available evidence, inclusion in the hospital benefit catalogue is currently not recommended. Reevaluation is recommended in 2024 if the larger ongoing randomised trials are published by then.

inclusion currently not recommended

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

kardiogener Schock: lebensbedrohlicher Zustand

Der kardiogene Schock wird durch eine unzureichende Pumpleistung des Herzens verursacht, welche zu einem verminderten Herzzeitvolumen mit Minderperfusion des Gewebes führt. Als häufigste Ursache wird der akute Myokardinfarkt mit Versagen des linken Herzventrikels beschrieben. Der kardiogene Schock ist mit einer hohen Mortalität verbunden.

PCI: minimal-invasives Verfahren

Perkutane Koronarinterventionen (PCI) sind minimal-invasive Verfahren zur Revaskularisierung, die meist mittels Ballonangioplastie und intrakoronaren Stents durchgeführt werden. Häufige Indikationen für PCI sind Myokardinfarkt, Angina pectoris und hochgradige Koronararterienstenosen.

temp. mechanische Kreislaufunterstützung bei kardiogenem Schock oder PCI

Sowohl für Patient*innen mit kardiogenem Schock und unzureichenden Ansprechen auf die pharmakologische Therapie, als auch für Patient*innen während der Durchführung einer Hochrisiko-PCI, kann eine temporäre mechanische Kreislaufunterstützung angewendet werden.

Beschreibung der Technologie

mikro-axiale pLVAD sollen die Hämodynamik und Mortalität verbessern

Mikro-axiale perkutane linksventrikuläre Kreislaufunterstützungssysteme (eng. percutaneous left ventricular assist devices = pLVAD) sind eine Art der mechanischen Kreislaufunterstützung. Diese Systeme werden perkutan eingeführt und bestehen aus einer kleinen Herzpumpe, die an einem Katheter montiert ist, einer Steuerkonsole und einer Infusionsanlage. Mit Hilfe dieser Pumpe kann ein kontinuierlicher Blutfluss von bis zu 5 L/min erzeugt werden. Die Technologie zielt darauf ab, durch verbesserte hämodynamische Effekte die Sterblichkeit zu senken.

bislang verfügbare mikro-axiale pLVAD: Impella® Pumpen

Die Impella®-Pumpen sind die einzigen derzeit erhältlichen mikro-axialen pLVAD mit einer CE-Kennzeichnung für die Behandlung von kardiogenem Schock oder zur Unterstützung während einer Hochrisiko-PCI. Die verschiedenen Impella®-Pumpen unterscheiden sich je nach Kathetergröße sowie maximaler Dauer der mechanischen Kreislaufunterstützung: bei Impella 2.5® und Impella CP® bis zu fünf Tage, bei Impella 5.0/LD® bis zu zehn Tage und bei Impella 5.5® bis zu 30 Tage.

Methoden

update HTA: Health Quality Ontario Bericht aus 2017

Ziel der vorliegenden systematischen Übersichtsarbeit war es, den Einsatz von mikro-axialen pLVAD bei Patient*innen mit kardiogenem Schock oder Patient*innen mit perkutanen Koronarinterventionen im Vergleich zur Standardversorgung zu untersuchen. Die Forschungsfrage war, ob die mikro-axialen pLVAD wirksamer und gleich sicher (oder sicherer) hinsichtlich Patient*innen-relevanter klinischer Endpunkte, wie Reduktion der Mortalität und (schwere) unerwünschte (kardiovaskuläre) Nebenwirkungen ist. Der vorliegende Bericht aktualisiert eine kanadische Evidenzsynthese der Health Quality Ontario (HQO) welcher 2017 publiziert wurde (Stand der systematischen Suche: 2015). Die methodische Qualität des HQO-HTAs wurde anhand der AMSTAR-II Checkliste überprüft.

systematische Suche: 2015-2020

Es wurde eine Update-Suche der Evidenz anhand der Suchstrategien des HQO-Berichts durchgeführt. Dafür wurden folgende Datenbanken im Zeitraum von 2015 bis 2020 für die systematische Suche herangezogen: Medline, Embase, The Cochrane Library, CRD und HTA-INAHTA. Zusätzlich wurde eine Handsuche in Referenzlisten rezenter Übersichtsarbeiten durchgeführt. Nach Deduplizierung konnten insgesamt 1.110 potentielle Treffer identifiziert werden. Eine Suche nach laufenden Studien in drei klinischen Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) ergab 65 potentiell relevante Treffer.

Datenextraktion und GRADE-Bewertung von 2 Personen durchgeführt

Die Studienauswahl, Datenextraktion und Bewertung der methodischen Qualität der Studien wurden von zwei Personen unabhängig voneinander durchgeführt. Die Daten zu jeder ausgewählten Endpunktkategorie wurden studienübergreifend mit Hilfe von GRADE (Grading of Recommendations, Assessment, Development and Evaluation) bewertet.

Endpunkte klinische Wirksamkeit

Endpunkte für Empfehlung hinsichtlich der klinischen Wirksamkeit

Zur Bewertung der klinischen Wirksamkeit wurde die Reduktion der Mortalität als entscheidender Endpunkt für eine Empfehlung herangezogen. Zusätzlich wurden hämodynamische Parameter, die Dauer des Krankenhausaufenthalts sowie die Rehospitalisierung als wichtige Endpunkte definiert.

Endpunkte Sicherheit

Endpunkte für Empfehlung hinsichtlich der Sicherheit

Für die Bewertung der Sicherheit wurden alle (schwerwiegenden) unerwünschten Ereignisse als entscheidende Endpunkte für die Ableitung einer Empfehlung definiert.

Verfügbare Evidenz

Evidenzsynthese aus insgesamt sieben Studien

Im Rahmen dieses Updates des HQO-Berichts (2017) konnten zwei neue randomisierte Kontrollstudien sowie drei neue Beobachtungsstudien identifiziert werden. Die verfügbare Evidenz umfasst damit insgesamt sieben Studien: vier Studien evaluierten mikro-axiale pLVAD bei Patient*innen mit kardiogenem Schock und weitere drei Studien untersuchten den unterstützenden Einsatz von mikro-axialen pLVAD bei PCI.

Ergebnisse: Mikro-axiale pLVAD bei Patient*innen mit kardiogenem Schock

kardiogener Schock: 3 RCTs, 1 Registerstudie Qualität der Evidenz: sehr niedrig

Drei randomisierte kontrollierte Studien (RCTs) mit insgesamt 89 analysierten Patient*innen und eine retrospektive Kohortenstudie mit 18.032 Patient*innen untersuchten die Technologie bei kardiogenem Schock. Die Qualität der Evidenz war sehr niedrig, Gründe dafür waren vor allem eine unzureichende Präzision der Resultate sowie das Verzerrungspotenzial (engl. risk of bias; RoB) der Studien: moderates RoB in zwei Studien, hohes RoB in zwei Studien.

Klinische Wirksamkeit

Mortalität: 3 RCTs konnten keine reduzierte Mortalität nachweisen

Der Endpunkt **Mortalität** wurde in insgesamt drei Studien (n=89) berichtet, wobei keine der Studien eine Reduktion der Mortalität nachweisen konnte. Bei zwei der Studien wurde der Unterschied zwischen Interventions- und Kontrollgruppe als nicht statistisch signifikant berichtet und eine weitere Studie gab keinen p-Wert an. Die Mortalität schwankte zwischen 28,6 und 46 % in den Interventionsgruppen und zwischen 0 und 50 % in den Kontrollgruppen nach einem Monat (in drei Studien), sowie 50 % in der Interventionsgruppe und 50 % in der Kontrollgruppe nach sechs Monaten (in einer Studie).

Aufenthaltsdauer im Krankenhaus, Rehospitalisierung

Die Endpunkte **Aufenthaltsdauer im Krankenhaus und Rehospitalisierung** wurden in einer Studie (n=48) berichtet. Für die Aufenthaltsdauer im Krankenhaus wurde kein statistisch signifikanter Unterschied gefunden (Krankenhaus 16 vs. 10 Tage, davon Intensivstation 7 vs. 7 Tage). Für die Rehospitalisierung wurde kein p-Wert angegeben (21 % vs. 4 %).

Hämodynamik Herzindex: ein RCT zeigte stat.sign. Unterschied zugunsten der Technologie

Hämodynamische Parameter wurden in drei Studien (n=89) berichtet: für die linksventrikuläre Ejektionsfraktion (LVEF) konnten zwei der Studien keinen statistisch signifikanten Unterschied zwischen den Gruppen nachweisen, eine Studie gab keinen p-Wert an. Die LVEF lag zwischen 35 und 46 % in der Interventionsgruppe und zwischen 40,6 und 49 % in der Kontrollgruppe. Der Herzindex wurde in zwei Studien berichtet: Eine Studie fand einen statistisch signifikanten Unterschied zugunsten der Technologie (0,49 ±0,46 l/min/m^2 vs. 0,11 ±0,31 l/min/m^2), eine andere Studie fand keinen statistisch signifikanten Unterschied (-0,02 ±0,25 W/m^2 vs. 0,08 ±0,08 W/m^2).

Sicherheit

Blutungen: ein RCT zeigte stat.sign. Unterschied zuungunsten der Technologie

Blutungen wurden in vier Studien (drei RCTs n=89, eine Registerstudie n=18.033) berichtet, dabei traten in einem RCT Blutungen in der Interventionsgruppe häufiger auf als in der Kontrollgruppe. Ein statistisch signifikanter Unterschied zuungunsten der mikro-axialen pLVAD bei 71,4 % vs. 0 % wurde angegeben. In zwei weiteren RCTs konnte kein statistisch signifikanter Unterschied nachgewiesen werden, mit Blutungsraten zwischen 0-33 % (Interventionsgruppe) vs. 0-8 % (Kontrollgruppe). In der Beobachtungsstudie wurden in der Interventionsgruppe für Hämorrhagie 4,5 % und für Bluttransfusion 30,6 % berichtet. In der Kontrollgruppe wurden für Hämorrhagie 4,4 % und für Bluttransfusion 26 % angegeben.

zusätzliche Interventionen: eine Registerstudie zeigte stat.sign. Unterschied zuungunsten der Technologie

Der Endpunkt **zusätzlich benötigte Interventionen** wurde in drei Studien (zwei RCTs n=61, eine Registerstudie n=18.033) berichtet. In der Beobachtungsstudie wurden bei Patient*innen in der Interventionsgruppe häufiger zusätzliche Interventionen als in der Kontrollgruppe benötigt: Ein statistisch signifikanter Unterschied wurde für die Verwendung von extrakorporaler Membranoxygenierung (ECMO) und Intubation gefunden. Eine ECMO wurde bei 11,4 % in der Interventionsgruppe und bei 5,5 % in der Kontrollgruppe angewandt. Eine Intubation wurde bei 68,2 % in der Interventionsgruppe und 59,7 % in der Kontrollgruppe durchgeführt. Ein RCT konnte keinen statistisch signifikanten Unterschied feststellen, ein weiteres RCT gab keinen p-Wert für Unterschiede bei zusätzlich benötigten Interventionen an.

Nierenkomplikationen: eine Registerstudie zeigte stat.sign. Unterschied zuungunsten der Technologie

Nierenkomplikationen wurden in zwei Studien (ein RCT n=48, eine Registerstudie n=18.033) berichtet: dabei kam es bei Patient*innen in der Interventionsgruppe häufiger zu Nierenkomplikationen als in der Kontrollgruppe. Die Registerstudie gab als statistisch signifikante Unterschiede für akutes Nierenversagen 72,5 % vs. 61,5 %, für Dialyse 15,4 % vs. 10,4 % und für Hämodialyse 16,4 % vs. 12,1 % an. Das RCT gab für Nierenersatztherapie 33 % in der Interventionsgruppe und 29 % in der Kontrollgruppe (ohne p-Wert) an.

Endpunkte ohne stat.sign. Unterschiede

Die Berichterstattung der Sicherheit in Bezug auf **multiple Organversagen** (zwei RCTs, eine Registerstudie) oder **respiratorische Komplikationen** (eine Registerstudie) zeigte keine statistisch signifikanten Unterschiede. Für **vaskuläre Komplikationen** gab es keine statistisch signifikanten Unterschiede in einem RCT und einer Beobachtungsstudie, zwei RCTs gaben keinen p-Wert an. Für **neurologische Komplikationen** wurde in einer Registerstudie kein statistisch signifikanter Unterschied gefunden, zwei RCTs gaben keinen p-Wert an, für **technische Gerätedefekte** (drei RCTs) oder **Folgeeingriffe** (ein RCT) wurden keine p-Werte angegeben.

Ergebnisse: Mikro-axiale pLVAD bei Patient*innen mit perkutanen koronaren Interventionen

PCI: 1 RCT, 2 Registerstudien Qualität der Evidenz: sehr niedrig

Ein RCT mit 448 analysierten Patient*innen und zwei retrospektive Kohortenstudien mit 51.666 Patient*innen untersuchten den Einsatz von mikro-axialen pLVAD während einer PCI. Die Qualität der Evidenz war sehr niedrig: Die Gründe dafür waren vor allem eine unzureichende Präzision der Resultate sowie das Verzerrungspotenzial der Studien: moderates RoB in zwei Studien, hohes RoB in einer Studie.

Klinische Wirksamkeit

Mortalität: 1 RCT konnte keine Reduktion der Mortalität nachweisen

Der Endpunkt **Mortalität** wurde in einer Studie (ein RCT, n=448) berichtet: das RCT konnte keinen statistisch signifikanten Unterschied nachweisen. Die Mortalität nach einem Monat lag bei 7,6 % in der Interventionsgruppe und bei 5,9 % in der Kontrollgruppe. Nach drei Monaten betrug die Mortalität 12,1 % in der Interventionsgruppe und 8,7 % in der Kontrollgruppe.

Aufenthaltsdauer im Krankenhaus, Rehospitalisierung

Der Endpunkt **Aufenthaltsdauer im Krankenhaus** und **Rehospitalisierung** wurde in keiner Studie zu mikro-axialen pLVAD bei PCI erhoben.

Herzschlagleistung: stat. sign. Unterschied zugunsten der Technologie

Hämodynamische Parameter wurden in einer Studie (ein RCT, n=448) erhoben: zur Herzschlagleistung konnte ein statistisch signifikanter Unterschied zugunsten der Technologie nachgewiesen werden (-0,04 ±0,24 W vs. -0,14 ±0,27 W). In Bezug auf die LVEF wurde kein p-Wert angegeben (27 % vs. 33 %).

Sicherheit

Blutungen: 2 Registerstudien stat.sign. Unterschied zuungunsten der Technologie

Blutungen wurden in zwei Registerstudien (n=51.666) berichtet. In beiden traten diese bei Patient*innen in den Interventionsgruppen statistisch signifikant häufiger auf: eine Registerstudie gab ein Odds-Ratio von 1,10 (Konfidenzintervall: 1,00-1,21) an, eine weitere Registerstudie berichtete davon, dass bei 31,3 % in der Interventionsgruppe und bei 16,0 % in der Kontrollgruppe schwere Blutungen auftraten.

neurologische Komplikationen: widersprüchliche Ergebnisse

Der Endpunkt **neurologische Komplikationen** wurde in zwei Studien (ein RCT, n=448; eine Registerstudie, n=48.306) erhoben. Das RCT fand einen statistisch signifikanten Unterschied bei dem Auftreten von Schlaganfällen oder transienten ischämischen Attacken in der Kontrollgruppe nach einem Monat (0 % vs. 1,8 %), jedoch keinen statistisch signifikanten Unterschied nach drei Monaten (0,9 % vs. 2,7 %). Hinsichtlich des Schlaganfallrisikos berichtete die Registerstudie ein Odds-Ratio zuungunsten der Interventionsgruppe von 1,34 (CI: 1,18-1,53).

Endpunkte ohne stat.sign. Unterschiede

Für die Endpunkte **schwerwiegende unerwünschte kardiovaskuläre Ereignisse** (ein RCT), **Folgeeingriffe** (ein RCT), **Nierenkomplikationen** (ein RCT, eine Registerstudie) und **fehlgeschlagene Eingriffe** (ein RCT) wurden keine statistisch signifikanten Unterschiede angegeben, für **Herzklappenschäden** (ein RCT) wurden keine p-Werte berichtet.

Laufende Studien

5 laufende RCTs, davon 3 für kardiogenen Schock und 2 für PCI

Es wurden fünf derzeit laufende RCTs identifiziert, welche voraussichtlich zwischen 2022 und 2027 abgeschlossen sein werden. Zur Indikation des kardiogenen Schocks wurden folgende Vergleichs- bzw. Kontrollinterventionen gewählt: zwei RCTs vergleichen Impella® mit konventioneller Kreislaufunterstützung vs. konventionelle Kreislaufunterstützung allein (insgesamt 440

Patient*innen), ein RCT vergleicht Impella® und VA-ECMO mit VA-ECMO allein (96 Patient*innen). Für die Indikation PCI laufen derzeit zwei RCTs, die Impella®-unterstützte PCI mit der Standard-PCI beziehungsweise Impella CP® und primäre PCI mit primärer PCI allein vergleichen (insgesamt 892 Patient*innen).

Kostenerstattung

derzeitige Kostenerstattung deckt höhere Kosten für mikro-axiale pLVAD nicht ab

Derzeit gibt es im österreichischen stationären LKF-Katalog einen Erstattungscode für die kurzfristige Kreislaufunterstützung mit Zentrifugal- oder Axialflusspumpen. Die Kosten für mikro-axiale pLVAD übersteigen jedoch den angegebenen Erstattungsbetrag dieses Erstattungscodes.

Schlussfolgerung und Diskussion

beide Indikationen mit sehr niedriger Qualität der Evidenz

Für beide Indikationen ist die Gesamtqualität der Evidenz der klinischen Wirksamkeit und Sicherheit der mikro-axialen pLVAD und Standardversorgung im Vergleich zur Standardversorgung sehr niedrig (GRADE-Bewertung).

S3 AWMF Leitlinie, ESC Leitlinie: „kann"-Empfehlung mit Voraussetzungen, unzureichende Evidenz für Empfehlung

Laut einer S3 Leitlinie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF 2019) können mechanische Kreislaufunterstützungssysteme, darunter auch mikro-axiale pLVAD, beim infarktbedingten kardiogenen Schock unter bestimmten Voraussetzungen verwendet werden. Die Europäische Gesellschaft für Kardiologie (ESC) empfiehlt in ihren Leitlinien aus dem Jahr 2018 mikro-axiale pLVAD in ausgewählten klinischen Fällen in Betracht zu ziehen, aber die Evidenz für mikro-axiale pLVAD ist für eine generelle Empfehlung bei kardiogenem Schock unzureichend.

unzureichende Evidenz für klinische Wirksamkeit, laufende Studien abzuwarten

Die derzeitige Evidenz ist unzureichend, um zu zeigen dass mikro-axiale pLVAD und Standardversorgung im Vergleich zur Standardversorgung effektiver und gleich sicher (oder gleich effektiv und sicherer) sind. Keine der Studien konnte eine statistisch signifikante Reduktion der Mortalität nachweisen. Es gibt Anhaltspunkte dass die Technologie die Hämodynamik verbessern könnte, es gibt jedoch Sicherheitsbedenken in Bezug auf schwere Blutungskomplikationen. Aufgrund dieser möglichen Komplikationen könnte die Technologie im Vergleich zur Standardversorgung in beiden Indikationen eine weniger sichere Behandlungsform darstellen. In Anbetracht der verfügbaren Evidenz und der potenziellen Risiken müssen Ergebnisse aus laufenden Studien zu mikro-axialen pLVAD abgewartet werden.

Empfehlung

Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen

Aufgrund der vorliegenden Evidenz wird die Aufnahme in den Leistungskatalog derzeit nicht empfohlen. Eine Re-Evaluierung wird 2024 empfohlen, nach Vorliegen neuer robuster Evidenz.

1 Background

1.1 Overview of the disease, health condition and target population[1]

Percutaneous left ventricular assist devices (pLVAD) offer mechanical circulatory support (MCS) for patients in cardiogenic shock or patients undergoing high-risk percutaneous coronary interventions (PCI) [2]. These pLVAD devices are used to maintain vital organ perfusion by unloading the affected ventricle, reducing myocardial wall stress and myocardial oxygen consumption [3][2].

perkutane linksventrikuläre Flusspumpen bieten bei CS oder PCI mechanische Kreislaufunterstützung

Cardiogenic shock

Cardiogenic shock refers to a circulatory shock caused by an insufficient cardiac pump resulting in reduced cardiac output. The heart is unable to provide the required cardiac output, leading to inadequate tissue perfusion. Causes for cardiogenic shock can be classified as cardiomyopathic, arrhythmic or mechanical [4]. The most common cause of cardiogenic shock is acute myocardial infarction, usually ST-elevation myocardial infarction (STEMI) with left ventricle failure [5] [3].

CS: unzureichende Herz-Kreislauf-Pumpe; meist durch akuten Myokardinfarkt mit Linksherzversagen

Risk factors for cardiogenic shock include, among others [6][4]:

Risikofaktoren für CS:

Alter, kardiovaskuläre und weitere Erkrankungen, Zustand nach medizinischen Leistungen, Geschlecht

- **Age:** Individuals older than 75 years, are at greater risk for cardiogenic shock.
- **Cardiovascular conditions**: Existing cardiovascular diseases can, further, increase the risk of cardiogenic shock. These include, for instance, atherosclerosis, cardiomyopathy (including Takotsubo cardiomyopathy), conduction disorders, heart attack, or heart failure.
- **Other medical conditions**: e.g., high blood cholesterol, diabetes and prediabetes, overweight and obesity, Pneumothorax[5], or sepsis.
- **Medical procedures:** People who have had, for instance, coronary artery bypass grafting are at greater risk for cardiogenic shock
- **Sex:** Men are at greater risk for cardiogenic shock than women.

The target population of this first indication for the use of pLVAD comprises patients of the above-mentioned risk groups suffering from cardiogenic shock with insufficient response to pharmacological therapy[6].

Indikation: CS mit unzureichendem Ansprechen auf pharmakologische Therapie

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1 This section addresses the EUnetHTA Core Model® domain CUR.

2 A0001 – For which health conditions, and for what purposes are micro-axial pLVAD used?

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

4 A0003 – What are the known risk factors for CS and what are the indications for patients requiring PCI? &
A0007 – What is the target population in this assessment?

5 A type of pleural disorder that can lead to a collapsed lung.

6 A0007 – What is the target population in this assessment?

About 5% to 8% of patients with STEMI and 2% to 3% of patients with NON-STEMI can progress to cardiogenic shock [7]. In Germany, the lifetime prevalence for myocardial infarction is 4.7% for ages 40-79 years [8]. About 2% to 5% of patients having cardiac surgery experience cardiogenic shock after surgery [9][7].

in Ö ischämische Herzerkrankung führende Ursache für verlorene Lebensjahre; international hohe Prävalenz und Inzidenz für kardiovaskuläre Erkrankungen

The Global Burden of Disease study found out that deaths due to cardiovascular diseases are, among others, expanding and hence, threats to global health. In Austria, ischemic heart disease is the leading cause of death with years of life lost (measured in thousands) rank of 197 in the year 2010. Globally, in 2017, the prevalence (measured in thousands) for cardiovascular disease was 485,620.9 and the incidence (measured in thousands) was 72,721.2. The years lost to disability (measured in thousands) were 44,311.8 [10-12].

Percutaneous coronary interventions

PCI: minimal invasive Prozedur zur Revaskularisierung

Percutaneous coronary interventions (PCI) are minimally invasive nonsurgical procedures to improve coronary circulation. PCI are increasingly being offered as an alternative to open-heart surgery. The revascularization during a PCI is primarily achieved by balloon angioplasty and intracoronary stenting, further utilized methods are atherectomy and radiation [13].

Indikationen für PCI:

The target population of this second indication for the use of pLVAD includes patients with the following [14][4]:

Myokardinfarkt, Angina pectoris, kritische Koronararterienstenose

- Acute ST-elevation myocardial infarction (STEMI)
- Non-ST-elevation acute myocardial infarction (NSTEMI)
- Stable or unstable angina
- Anginal equivalent (e.g., dyspnea, arrhythmia, dizziness, or syncope)
- Critical coronary artery stenosis, which does not qualify for coronary artery bypass surgery

keine einheitliche Definition der Hoch-Risiko-PCI

There is no general, unifying definition of high-risk PCI, but considered factors include the following [15, 16]:

- Patient-specific factors (e.g., prior myocardial infarction)
- Anatomic-specific factors (e.g., stenosis of the left main artery of the heart)
- Clinical presentation-specific factors (e.g., acute coronary syndrome)

unterstützender Einsatz von pLVAD während PCI

To temporarily support a patient's circulation during high-risk PCI, pLVADs can be used to directly unload the left ventricle. The aim is to support the patient's circulatory system, increase cardiac output and improve blood flow and maintaining hemodynamic stability to minimise myocardial ischemia and reduce the risk of hemodynamic collapse during PCI [17].

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

1.2 Current clinical practice[1]

klinische Diagnose ohne invasive Diagnostik

Cardiogenic shock is diagnosed clinically and does not need invasive diagnostics. The following criteria are used hereby [18][8]:

- **Circulatory dysfunction:** Systolic blood pressure <90 mmHg or drop in mean arterial pressure by ≥30 mmHg or catecholamine requirement or signs of centralization, prolonged recapillary time (>2-3 s), oliguria, i.e. urine output <0.5 mL/kgKG/h
- **Exclusion of volume deficiency**
- **Evidence of primary cardiac dysfunction**: reduced ejection fraction or impairment of ventricular filling

Sofortmaßnahmen bei CS:

Monitoring, Defibrillationsbereitschaft, Sauerstoff-/ Volumentherapie

If a patient presents with a cardiogenic shock, immediate emergency actions are required. These include [18][9]:

- Monitoring (e.g., heart rate, respiration electrocardiogram, blood pressure and urine sample) and depending on the course also arterial access or central venous catheter if required
- Defibrillation readiness
- Oxygen administration
- Evaluation of respiration, non-invasive ventilation or intubation if necessary
- Cautious volume administration
- Transfer to cardiology center (if necessary)

symptomatische Therapie mit Volumensubstitution, medikamentöse Therapie und mechanische Kreislaufunterstützung

Subsequent symptomatic therapy (standard care) includes volume therapy, pharmacological therapy as well as mechanical circulatory support systems:

- **Volume therapy** aims at optimising cardiac functionality while, at the same time, avoiding pulmonary edema
- **Pharmacologic therapy** can be used temporarily for circulatory stabilisation
- **Mechanical circulatory support systems, e.g., pVADs,** are only to be used in individual cases and temporarily in case of insufficient response to pharmacological therapy [18]

AWMF S3 Leitlinie zur Revaskularisation bei CS

For patients with cardiogenic shock, the association of the scientific medical societies of Germany (AWMF) S3 guideline recommends in 2020 early revascularization via primary percutaneous coronary interventions ("strong recommendation" ↑↑, evidence level 1+[10]). In the case of initial shock in the context of infarction (STEMI or NON-STEMI), the time interval from diagnosis to primary PCI should not exceed 90 min ("should" recommendation ↑, evidence level expert consensus[11]). If shock occurs with a time latency to the acute infarction, invasive diagnostics and, if necessary, revascularization

[8] A0024 – How are patients with CS or patients undergoing PCI currently diagnosed according to published guidelines and in practice?

[9] A0025 – How are patients with CS or patients undergoing PCI currently managed according to published guidelines and in practice?

[10] The evidence level 1+ is based on either systematic reviews on RCTs or RCTs with low risk of bias.

[11] The evidence level expert consensus is based on consensus of clinical experts, based on studies and clinical experience or in the interest of patient safety (e.g., monitoring).

should be performed as soon as possible ("strong" recommendation ↑↑, evidence level expert consensus[11]). For revascularization in infarct-related cardiogenic shock, intracoronary stenting using drug-eluting stents should be preferred ("should" recommendation ↑, evidence level expert consensus[11]) [19].

Mechanical circulatory support systems

ESC Leitlinie: bisher wenig Evidenz für pLVADs

In the ESC guideline on myocardial revascularization from 2018, pLVADs are currently limited to two types of devices (including Impella® devices). According to the guideline, the evidence for pLVADs is insufficient to provide a recommendation on their clinical use in cardiogenic shock [20].

AWMF S3 Leitlinie: tepmoräre mechanische Kreislaufunterstützung mit "kann"-Empfehlung

According to a recent AWMF S3 guideline (2019), temporary MCS can be implanted in infarct-related cardiogenic shock if there is a realistic therapeutic goal ("can" recommendation, evidence level expert consensus[11]). The choice of MCS is based on specific characteristics of the circulatory failure and the expertise of the respective cardiac team with the following mandatory prerequisites: a) implantation of MCS without delayed revascularization, ideally in the catheter lab, b) documented realistic therapy goal evaluated by a cardiac team, c) connection to or cooperation with a cardiovascular center, d) implantation before the onset of irreversible organ damage, e) inclusion in an MCS-registry by the professional societies [19].

IABP bisher in Leitlinien empfohlen, Teil der klinischen Praxis

The mechanical circulatory support system intra-aortic balloon pump (IABP) was and is still part of clinical practice to be used in cardiogenic shock complicating acute myocardial infarction (AMI) with guidelines recommending its use especially in the past [21].

neuere AWMF und ESC Leitlinien rücken von Empfehlung für IABP ab

However, two identified guidelines [19, 22] recommend not to use IABP in certain contexts: according to the recent AWMF S3 guideline (2019), IABP with primary PCI should no longer be used in cardiogenic shock complicating acute myocardial infarction ("should not" recommendation, evidence level 1++[12]). For mechanical complications of myocardial infarction, such as ventricular septal rupture or papillary muscle rupture, IABP may be used for hemodynamic stability (open recommendation, evidence level expert consensus[13]) [19]. Another guideline from the ESC (2014) downgraded their recommendation and recommend against the routine use of IABP in the management of cardiogenic shock (class III; level of evidence B). Still, short-term mechanical circulatory support (MCS) may be considered for managing refractory cardiogenic shock in selected patients (class IIb, level of evidence C) [22].

AWMF S3 Leitlinie für ECMO bei kardiovaskulärem Versagen

The current AWMF S3 guideline on ECMO use for cardiovascular failure describes the following [23]:

- In cardiogenic shock, the use of ECMO may be considered[14]
- In shock caused by (drug) intoxication, the use of ECMO may be considered[15]
- During in-hospital resuscitation, ECMO therapy may be considered in selected cases, this decision should be made at an early stage[16]

[12] Evidence level 1++ describes evidence from high quality systematic reviews of RCTs or RCTs with very low risk of bias.

[13] The evidence level EK is based on consensus of clinical experts, based on studies and clinical experience or in the interest of patient safety (e.g., monitoring).

[14] Recommendation level 0, evidence level + to ++

[15] Recommendation level 0, evidence level +

[16] Recommendation level 0 (B), evidence level +++

- In out-of-hospital resuscitation, ECMO therapy may be considered in selected cases. This decision should be made early[17]

In light of these guidelines, the current standard of care, in particular regarding the consideration of applying MCS and choice of MCS type when treating cardiogenic shock, is in a state of flux.

Standardversorgung mit mechanischer Kreislaufunterstützung im Wandel

1.3 Features of the intervention and comparators[18]

Current devices for MCS can be classified according to duration used (short-term or long-term support), location (paracorporeal, extracorporeal or intracorporeal), flow type (pulsatile or continuous flow), degree of support (partial or full support), and type of administration (percutaneous or surgical). A further classification can be made by the supported heart ventricle: left ventricle assist devices (LVAD), right ventricle assist devices (RVAD), or biventricular assist devices (BIVAD) [3]. The pump mechanism used can be classified as pneumatic, centrifugal, or axial flow [1][19].

Klassifikation und Merkmale von Systemen zur mechanischen Kreislaufunterstützung

Intervention: micro-axial pLVAD

For the scope of this assessment, short-term MCS by micro-axial pump, percutaneously placed left ventricular assist devices were chosen as the intervention of interest. Micro-axial pLVADs can replace or be used supplementary to other types of MCS.

untersuchte Intervention: mikro-axiale pLVAD

The Impella® is the only micro-axial pLVAD currently available on the market. It is a ventricular assist device that is inserted percutaneously, usually via the femoral artery. The Impella® system consists of a mini heart pump mounted at a catheter, a console to drive the pump and an infusion system to flush the pump [24]. The different types of Impella® are Impella 2.5®, Impella CP®, Impella 5.0/LD®, Impella 5.5® (for left ventricle support) and Impella RP® (for right ventricle support[20]) [25][19].

bisher nur ein mikro-axiales pLVAD am Markt

The Impella® devices that can be classified as micro-axial pLVAD are placed retrogradely across the aortic valve into the left ventricle, i.e., intracorporeal. They pump blood from the left ventricle to the ascending Aorta with a continuous, axial flow type with blood flow up to 5 L/min [16][21].

Pumpe über die Aortenklappe in den li. Ventrikel eingebracht, bis zu 5 L/min

In Europe, the Impella® devices are CE marked for the treatment of high-risk PCI and cardiogenic shock. Impella 2.5®, Impella CP® are CE marked for treatment up to 5 days; Impella 5.0® and Impella LD® up to 10 days; and Impella 5.5® up to 30 days. In contrast to the other devices, the Impella RP® is CE marked for right heart failure, decompensation following LVAD implantation, myocardial infarction, heart transplantation, open-heart surgery, or refractory ventricular arrhythmia [26]. A possible future direction of Im-

CE-Kennzeichnung für temporäre Kreislaufunterstützung bei CS und PCI

[17] Recommendation level 0 (B), evidence level ++ to +++

[18] This section addresses the EUnetHTA Core Model® domain TEC

[19] B0001 – What are micro-axial pLVAD and the comparator(s)?

[20] Not included in this assessment

[21] B0002 – What is the claimed benefit of micro-axial pLVAD in relation to the comparators?

pella® devices is a decrease in the catheter size. The insertion through smaller sized arterial sheaths could reduce vascular complications [27][22], [23]

FDA: seit 2008 zugelassen

The Impella 2.5® pump device was approved for short-term MCS via 510(k) clearance from the FDA in 2008 [28].

FDA: seit 2020 Notfallgenehmigung für bestimmte COVID-19 Pat.

Additionally, in August 2020, the FDA has granted emergency-use authorization for Impella® device pumps for left ventricle unloading with ECMO in patients with COVID-19. Specifically, temporary use of the Impella 2.5®, Impella CP®, Impella 5.0® and Impella 5.5® are covered for left ventricle unloading in patients with heart failure and pulmonary edema or late decompensation from myocarditis while on ECMO support [29].

Comparators: IABP und ECMO

IABP und ECMO etablierte Maßnahmen zur Kreislaufunterstützung

In this assessment, the eligible comparator interventions were broad and included the management of cardiogenic shock/PCI. This may or may not include other already established types of percutaneous ventricular assist devices such as intra-aortic balloon pumps (IABP) or extracorporeal membrane oxygenation (ECMO) [2][24]. The iVAC 2L® (PulseCath B.V., Amsterdam, The Netherlands) is a device that is available for MCS, although not yet established in widespread use. The iVAC 2L® is a pulsatile mechanical circulatory support system driven by any standard IABP console [30]. Other experimental ventricular assist devices were not considered as eligible comparators.

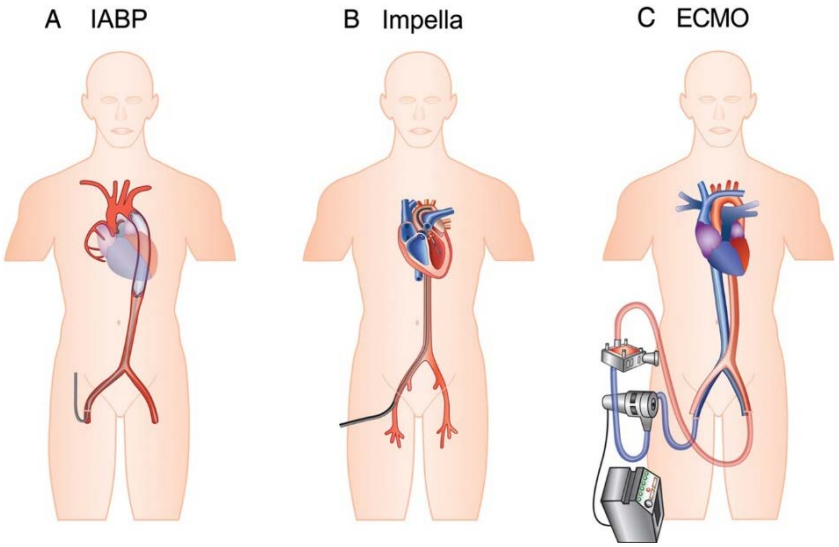

Figure 1-1: Percutaneous ventricular assist devices. Source: [1]

IABP seit 1968, häufiger Einsatz für Kreislaufunterstützung

IABP was first used in 1968. It is the most commonly applied device for short-term MCS[23]. The balloon of the IABP is inflated during the diastole and deflated during the systole using counterpulsation. The timing of the inflation and deflation is according to electrocardiographic or arterial pressure wave-

[22] A0020 – For which indications have micro-axial pLVAD received marketing authorisation or CE marking?

[23] B0003 – What is the phase of development and implementation of micro-axial pLVAD and the comparator(s)?

forms. The IABP is inserted percutaneously and provides pneumatic, pulsatile blood flow and improves cardiac output by 0.5 L/min [31][24].

ECMO: VA-ECMO Systeme bieten mechanische Kreislaufunterstützung

ECMO is used for patients with concomitant respiratory and cardiac failure. Depending on the location of the cannula placement, there are veno-venous extracorporeal membrane oxygenation (VV-ECMO) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) systems. As the VV-ECMO only provides oxygenation support, and the VA-ECMO provides circulatory as well as oxygenation support, only the VA-ECMO system can be used for MCS [2][24].

Vor- und Nachteile der Geräte, Kontraindikationen

The mentioned devices differ according to the type of insertion, cannula size, hemodynamic benefit, mobility of the patient and contraindications. Table 1-1 gives an overview of described advantages, disadvantages and contraindications of the intervention and comparators.

Table 1-1: Features of the intervention micro-axial pLVAD and comparators IABP and ECMO [25, 31-44]

	Intervention	Comparator	Comparator
Name	Micro-axial percutaneous left-ventricular assist devices (pLVAD)	Intraaortic balloon pump (IABP)	Extracorporeal membrane oxygenation (ECMO)
Proprietary name	Impella® devices: ■ Impella 2.5®, ■ Impella CP®, ■ Impella 5.0/LD®, ■ Impella 5.5®	IABP devices: ■ iPulse® ■ ULTRA 7FR® ■ Cardiosave, CS® ■ Corart® ■ AutoCAT2® ■ AC3 Optimus® ■ 7Fr-TAU® ■ Xemex®	ECMO devices: ■ Nautilus Smart ECMO® ■ EOS ECMO® ■ Medos Cardiopulmonary ECMO® ■ iCor® ■ Cardiohelp System® ■ HLS Set Advanced® ■ PLS System®
Manufacturer	Abiomed Europe GmbH	■ Abiomed (iPulse®) ■ Insightra Medical (ULTRA 7FR®) ■ Getinge (Cardiosave, CS®) ■ Senko Medical (Corart®) ■ Teleflex (AutoCAT2®, AC3 Optimus®) ■ Tokai Medical Products (7Fr-TAU®) ■ Zeon Medical (Xemex)®	■ Medtronic (Nautilus Smart ECMO®) ■ LivaNova (EOS ECMO®) ■ Xenios AG (Medos Cardiopulmonary ECMO®, iCor®) ■ Getinge (Cardiohelp System®. HLS Set Advanced®, PLS System®)
Bedside insertion	No	Yes	Yes (peripheral)
Advantages	■ Improved hemodynamics ■ Easy to confirm placement bedside ■ Functions in arrhythmia	■ Ease of insertion ■ Small cannula ■ Decreased risk of peripheral ischemia ■ Potential mobility (with axillary placement)	■ Can support oxygenation and perfusion ■ Full cardiac support ■ Functions in asystole and arrhythmia
Disadvantages	■ Impella 5.0® requires surgical cutdown ■ Increased risk of peripheral ischemia	■ Lower hemodynamic benefit ■ Risk of aortic injury ■ Timing is difficult in arrhythmia or tachycardia ■ Potential immobility with femoral placement	■ Requires systemic anticoagulation ■ Large cannulae increase the risk of peripheral ischemia, venous thrombosis, and upper body hypoxia from incomplete retrograde filling and oxygenation ■ Elevated afterload with consecutive left ventricular distention leading to higher wall stress, impaired myocardial oxygenation and pulmonary edema

[24] B0001 – What are micro-axial pLVAD and the comparator(s)?

	Intervention	Comparator	Comparator
Contraindications	■ Severe aortic stenosis ■ Prosthetic aortic valve ■ Left ventricular thrombus ■ Ventricular septal defect ■ Right ventricular failure ■ Peripheral vascular disease	■ Moderate to severe aortic valve regurgitation ■ Severe aortic disease	■ Severe aortic insufficiency ■ Aortic dissection ■ Inability to tolerate systemic anticoagulation ■ Peripheral vascular disease

Abbreviations: pLVAD – percutaneous left ventricular assist devices, IABP – intra-aortic balloon pump, ECMO – extracorporeal membrane oxygenation

Theoretical benefits of micro-axial pLVAD in comparison to IABP and ECMO

erhoffte Verbesserung der Hämodynamik und Mortalität durch mikro-axiale pLVAD

Micro-axial pLVAD could potentially improve clinical outcomes such as mortality due to its hemodynamic effects: a reduction in left ventricular preload, a decrease of myocardial wall tension and oxygen demand, as well as an increase in cardiac output and systemic perfusion as well as improved hemodynamics compared to other MCS, such as IABP and ECMO. In contrast to IABP, Impella® devices don't require specific timing of balloon inflation and deflation, nor a trigger from an electrocardiographic rhythm or arterial pressure. The cardiac output from Impella® devices is greater than the output from IABP [2, 16][21].

Further devices for mechanical circulatory support

weitere Herzpumpen für mechanische Kreislaufunterstützung (nicht Teil des Assessments)

There are further MCS devices that are beyond the scope of this assessment. The TandemHeart (Cardiac Assist Inc., Pittsburgh, PA, USA), for example, is a centrifugal pump system. In contrast to the other devices, it requires transseptal puncture. After inserting the inflow cannula into the venous circulation, usually via the femoral vein, the inflow cannula is placed from the right atrium to the left atrium by a transseptal puncture. The outflow cannula pumps the blood into the femoral artery. The TandemHeart device can provide up to 4.0 L/min of blood flow [2] The HeartMate II LVAD device uses an axial continuous-flow pump but requires thoracoabdominal placement. The HeartMate III LVAD device uses centrifugal flow by magnetical levitation [45].

Einsatz von pLVAD auf Intensivstationen, interklinische Varianz

In general, all pLVAD devices can be used for temporary MCS as a bridge to recovery, to a durable form of MCS, bridge to transplantation or bridge to decision. MCS by the use of pLVAD, including micro-axial pLVAD, IABP and ECMO, is provided by critical care cardiology units. There is a wide variation between hospitals and the proportion of patients that were treated with temporary MCS – use of newer forms of MCS is more common in tertiary hospital units [46, 47].[25]

Administration, expertise, supplies and reimbursement status of micro-axial pLVAD, IABP and ECMO

Einsatz durch interventionelle Kardiolog*innen/ Kardiochirurg*innen, Expertise erforderlich

Micro-axial pLVADs, IABP and ECMO are used in emergency care and administered by interventional cardiologists or cardiac surgeons, where appropriate in cooperation with anesthesiologists. Specially trained intensive care nursing staff is required during the implantation and duration of the MCS (information provided by clinical correspondence). The frequency of MCS use

[25] B0004 – Who administers micro-axial pLVAD and the comparators and in what context and level of care are they provided? &
B0008 – What kind of special premises are needed to use micro-axial pLVAD and the comparator(s)?

and complication rates vary significantly between hospitals, indicating sufficient expertise as a requirement for the application of these devices [48][25].

Einsatz von mikro-axialen pLVAD zunehmend

The use of micro-axial pLVAD devices has increased over time [48]. According to the proposal of the submitting hospital, micro-axial pLVAD have been used at the submitting hospital 15 times in the previous year with an estimated total use of 25 times per year in Austria[26].

LKF-Katalog: Eintrag für temporäre Kreislaufunterstützung deckt nicht die Kosten der mikro-axialen pLVAD

According to the submitting hospital, the micro-axial pLVAD is to be used in the inpatient setting with an occupancy period of two to 30 days (in usual cases three days) and a frequency of use of one to four times (in usual cases one time). The procedure unit is defined as per application[26]. To use micro-axial pLVAD, coronary angiography, cardiography facility and a recording tripod are needed as supplies[27]. In the 2021 edition of the Austrian catalogue for medical procedures (LKF catalogue) there is an entry for the short-term circulatory support using a centrifugal or axial flow pump (medical procedure code: DL030). According to the proposal of the submitting hospital, the cost of the Impella® device is 12,000€, which is not covered by the medical procedure code DL030. Due to this higher cost of the micro-axial pLVAD, a new entry for the short-term circulatory support using a micro-axial flow pump that is administered percutaneously was proposed [49][28].

LKF-Katalog: Einträge für IABP und ECMO

Comparator procedures (IABP, ECMO) are included in the 2021 edition of the Austrian catalogue for medical procedures (LKF catalogue) and as such are reimbursed [49][28].

[26] A0011 – How many people belong to the target population? &
A0011 – How much are micro-axial pLVAD utilised?

[27] B0009 – What supplies are needed to use micro-axial pLVAD and the comparator(s)?

[28] A0021 – What is the reimbursement status of micro-axial pLVAD?

2 Objectives and Scope

This assessment represents an update of the evidence comprised in the Health Quality Ontario HTA 'Percutaneous Ventricular Assist Devices' (HQO HTA) from 2017 [16].

update der Evidenz eines HTA zu PVAD

2.1 PICO question

Is standard care and short-term mechanical circulatory support with a percutaneous left ventricular assist device (pLVAD) using a micro-axial flow pump in comparison to standard care alone in patients with a diagnosis of cardiogenic shock or patients undergoing high-risk percutaneous coronary interventions (PCI) more effective concerning mortality and equally safe or safer concerning adverse events?

PIKO-Frage

2.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 2-1.

Einschlusskriterien für relevante Studien

Table 2-1: Inclusion criteria

Population	Patients with a diagnosis of cardiogenic shock with insufficient response to pharmacological therapy. OR Patients undergoing high-risk percutaneous coronary interventions. MeSH Terms: Shock, cardiogenic [C14.280.647.500.750, C23.550.513.355.750.750, C23.550.717.489.750.750, C14.907.585.500.750, C23.550.835.550], Heart failure [C14.280.434], Myocardial infarction [C14.280.647.500, C14.907.585.500, [C23.550.513.355.750, C23.550.717.489.750], Cardiovascular surgical procedures [E04.100], Percutaneous coronary intervention [E04.502.382.968, E04.100.814.529.968]
Intervention	Standard care and intervention with short-term pLVAD using a micro-axial flow pump. Product Names: ■ Impella 2.5®, ■ Impella CP/SmartAssist®, ■ Impella 5.5 with SmartAssist®, ■ Impella 5.0/LD® MeSH Terms: Heart-Assist Devices [E04.050.430, E07.695.300.300, E07.858.082.374.300]
Control	Standard care, optional with mechanical circulatory support (MCS), e.g. Intra aortic balloon pump (IABP) or Extra-corporeal membrane oxygenation (ECMO) Rationale: Other HTA reports, systematic reviews and clinical guidelines have compared the short-term percutaneous ventricular assist devices using micro-axial flow pumps to mechanical circulatory support using IABP or ECMO [3, 16, 17, 46]

Outcomes	
Efficacy	Mortality (one month, three months, six months) Hemodynamic stability measured with cardiac index or left ventricular ejection fraction (LVEF) Length of hospitalization Rehospitalization
Safety	Major adverse cardiovascular events (MACE) Serious adverse events (SAE) Adverse events (AE)
Study design	
Efficacy	Randomised controlled trials[29] Prospective non-randomised controlled trials
Safety	Randomised controlled trials[29] Prospective non-randomised controlled trials Observational studies with more than 500 patients with a low or moderate risk of bias[30]
Time period	December 2015 – December 2020
Languages	English, German

[29] Sub-analysis of RCTs were considered as observational evidence and as such excluded if less than 500 patients were analysed.

[30] Assessed with ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions.

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [50].

Table 3-1: Health problem and current use

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

Table 3-2: Description of the technology

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

Table 3-3: Clinical effectiveness

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

Table 3-4: Safety

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

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted on the 16th December 2020 in the following databases:

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

Zeitraum: 2015-2020, deutsche und englische Literatur

The systematic search was limited to the time period December 7th 2015 to December 16th 2020, and in Medline and Embase to articles published in English or German. After deduplication, overall 1,110 citations were included. The specific search strategy employed can be found in the Appendix.

Suche in Referenzlisten von SR

Additionally, a hand-search in the reference lists of three systematic reviews on the use of micro-axial pLVAD was conducted [51-53]. No further studies were hereby identified.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 21st of January 2021 resulting in 65 potential relevant hits.

insgesamt 1.110 Publikationen identifiziert

Overall, 1,110 hits were found (after duplicates were removed). No additional publications were found by hand-search. Two publications that matched the inclusion criteria of this report were identified from the HQO HTA report [16] and included in the qualitative synthesis of this report.

3.2.2 Flow chart of study selection

Overall 1110 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 2-1.

Literaturauswahl: 7 relevante Studien (in 8 Publikationen)

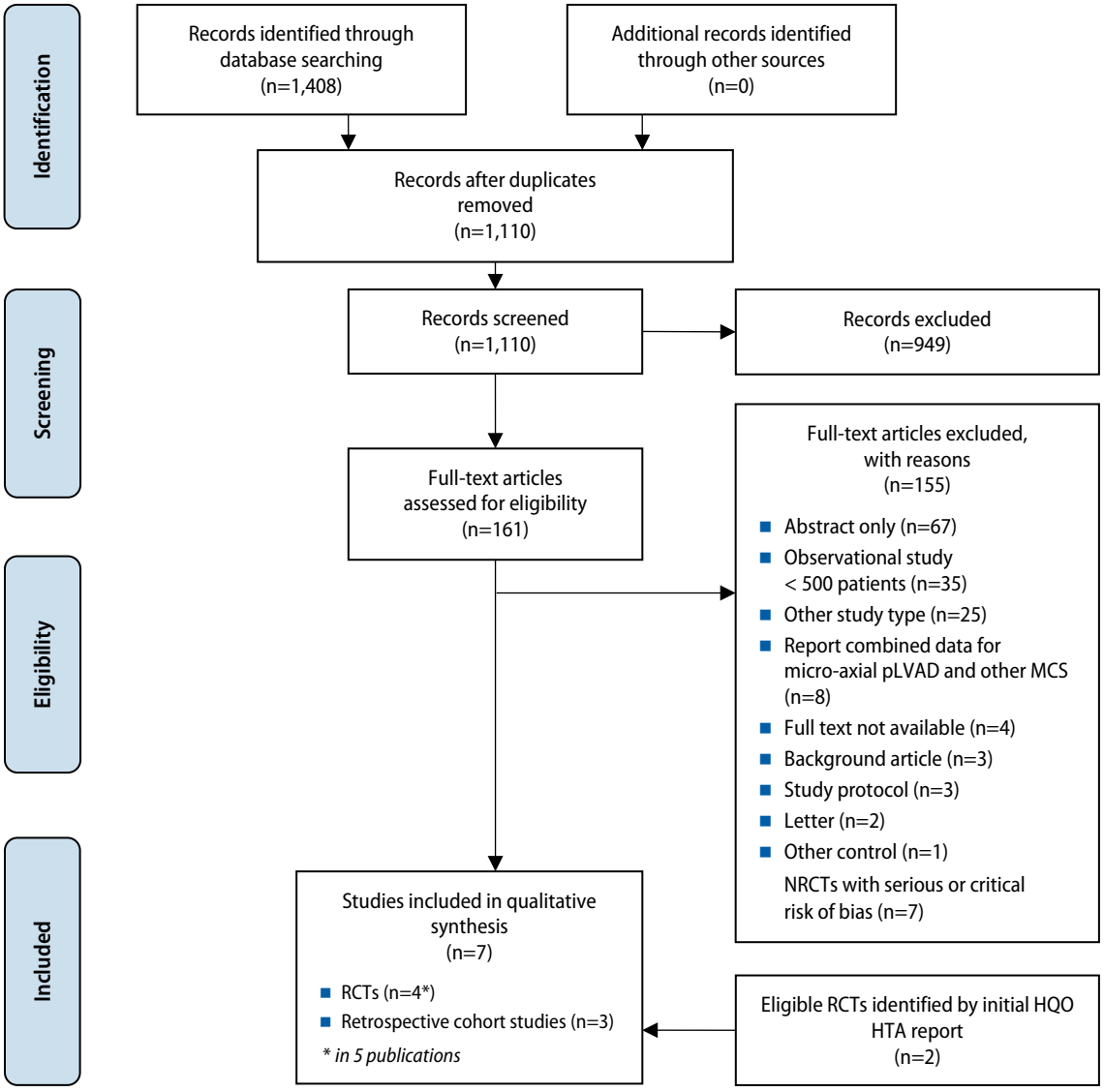

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

update eines HTA Reports aus 2017

The methodological quality of the HQO HTA report [16] was assessed using the AMSTAR-II checklist [54].

Datenextraktion aus Studien

Relevant data from eligible primary studies were systematically extracted into data-extraction tables. One researcher (RJ) extracted the data and another researcher (GG) checked and verified the extracted data.

Qualitätsbeurteilung der Studien mit Cochrane RoB Tool (v.2) und ROBINS-I

Two independent researchers (RJ, GG) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB v.2 tool (for RCTs) [55] and the ROBINS-I tool (for observational studies) [56].

All discrepancies were resolved by consensus.

3.2.4 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

We further used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) scheme to synthesise the identified evidence [57]. GRADE evidence tables and a GRADE summary of findings tables were compiled. No inferential statistical analysis was conducted in the absence of high-quality data derived from RCTs.

4 Results: Clinical effectiveness and safety

4.1 Outcomes

4.1.1 Outcomes clinical effectiveness

entscheidungs-relevanter Endpunkt für die klinische Wirksamkeit: Mortalität

The following outcome was defined as *crucial* to derive a recommendation:

- Mortality

Mortality is considered a highly patient-relevant outcome measure when assessing the clinical effectiveness of these devices.

weitere relevante Endpunkte: li.-ventrikuläre Hämodynamik, Aufenthaltsdauer Rehospitalisierung

Further outcomes were defined as *important*, but not crucial to derive a recommendation:

- Hemodynamic variables (measures of left ventricular systolic function)
- Length of stay (in hospital or intensive care unit)
- Rehospitalization

hämodynamische Parameter: Cardiac output, cardiac index, LVEF

For hemodynamic variables we considered cardiac output, cardiac index and left ventricular ejection fraction (LVEF). Cardiac output is calculated from stroke volume times heart rate; cardiac index describes the cardiac output in relation to body surface area. LVEF is a commonly reported clinical metric and describes the percentage of blood ejected during systole in comparison to the total end-diastolic volume [58].

Length of stay (LoS) in hospital (including intensive care unit length of stay), usually measured in hours or days, were considered as they reflect the disease burden of patients treated for cardiogenic shock or patients undergoing high-risk PCI [59].

Rehospitalization is the proportion of patients being readmitted to the hospital for any condition requiring treatment.

4.1.2 Outcomes safety

entscheidungs-relevante Endpunkte für Sicherheit: MACE, schwere unerwünschte Ereignisse (SUE), unerwünschte Ereignisse (UE)

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

- Major adverse cardiovascular events (MACE)
- Serious adverse events (SAE)
- Adverse events (AE)

MACE: Beschreibung einzelner Ereignisse

For MACE, the included studies did not report the outcomes as a composite. As such. the following individual events were grouped to MACE: refractory heart failure, myocardial (re)infarction, cardiopulmonary resuscitation/ventricular arrhythmia, severe hypotension requiring treatment, cardiac arrest, pericardial effusion, cardiac tamponade and pericardiocentesis.

Definitionen der EC für schwere unerwünschte Ereignisse (SUE) und unerwünschte Ereignisse (UE)

The European Commission guideline on reporting SAE or AE for medical devices defines SAE and AE as following [60]:

SAE is any adverse event that led to a) death, b) serious deterioration in the health of the subjected that resulted in any of the following: i) life-threatening illness or injury, ii) a permanent impairment of a body structure or a body function, iii) in-patient hospitalisation or prolongation of existing hospitali-

sation, iv) medical or surgical intervention to prevent a life-threatening illness or injury, v) chronic disease; c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons (whether or not related to the investigational medical device). Both anticipated, as well as unanticipated events, are included; events relating to the investigational device or in relation to the procedures involved are also included.

keine Beschreibung von SUE und UE in Studien; unerwünschte Ereignisse zur Vergleichbarkeit gruppiert

However, the included studies did not assess safety in terms of composite outcomes like SAEs or AEs, making comparisons across studies difficult. To compare individual safety events across studies, AEs were grouped into the following outcome categories:

- **Bleeding complications:**
  Bleeding, major bleeding, hemorrhage, or blood transfusion
- **Multiple organ complications:**
  Sepsis, septic shock, and multiple organ dysfunction scores[31]
- **Need for an additional device or transplant:**
  ECMO, surgical LVAD placement, Implantation of a biventricular external heart assist device, intubation/mechanical ventilation, artificial heart, or heart transplantation
- **Need for surgery or procedure:**
  Repeated PCI, repeated revascularization, coronary artery bypass grafting, need for cardiac or vascular operation, or other surgeries
- **Vascular complications:**
  Major vascular complications, vascular complications, limb complication, acute limb ischemia, or ischemia
- **Neurological complications:** Stroke (hemorrhagic or ischemic), transient ischemic attack (TIA), or neurological deficit
- **Renal complications:**
  Acute renal dysfunction, acute kidney injury, acute renal failure, acute renal failure requiring dialysis, or hemodialysis
- **Respiratory complications:**
  Pneumonia, respiratory failure, pulmonary embolism, or pulmonary wedge pressure monitoring
- **Valvular damage:**
  Aortic valve damage, aortic valve stenosis, increase in aortic insufficiency, increased aortic valve regurgitation, mitral valve damage, mitral valve stenosis, increased mitral valve regurgitation
- **Device/technical failure:**
  Device-related technical failure, technical failure, device failure requiring extraction, hemolysis requiring extraction of the device
- **Procedural failure:**
  angiographic failure or failure to achieve angiographic success

[31] Such as Multiple organ dysfunction score (MODS) and Sequential organ failure assessment score (SOFA)

4.2 Included studies

4.2.1 Included studies effectiveness

inkludierte Studien für klinische Wirksamkeit: 4 RCTs (2 RCTs aus bisherigem HTA, 2 neue RCTs)

In order to assess the efficacy of micro-axial pLVAD in patients with cardiogenic shock or patients undergoing PCI, we identified two new RCTs [61, 62] to be included in addition to the two RCTs [63, 64] that were included in the initial HQO HTA report [16] being updated. The body of evidence of all four RCTs [61-64] will be described in this evidence synthesis.

Indikationen: 3 RCTs für kardiogenen Schock, 1 RCT für PCI

Three studies enrolled patients with cardiogenic shock to be treated with micro-axial pLVAD [61, 62, 64], whilst one study investigated the use of micro-axial pLVAD during elective PCIs [63].

Study characteristics, patient characteristics as well as outcome measures and length of follow-up of included studies for clinical effectiveness are reported in chapter 4.3.1 (cardiogenic shock) and chapter 4.3.2 (PCI). They are displayed in detail in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

4.2.2 Additional included studies safety

inkludierte Studien für Sicherheit: zusätzlich 3 Registerstudien: 2 Registerstudien für PCI, 1 Registerstudie für CS

To assess the safety of micro-axial pLVAD we identified three further observational studies that met our inclusion criteria [65-67]. Two of these studies were propensity score-matched registry-based retrospective cohort studies and assessed the use of micro-axial pLVAD in comparison to IABP when performing PCIs [65, 66]. One study was a registry-based cohort study assessing the use of micro-axial pLVAD in comparison to IABP when treating cardiogenic shock [67].

Study characteristics, patient characteristics as well as outcome measures and length of follow-up of included studies for safety are reported in chapters 4.3.1 (cardiogenic shock) and 4.3.2 (PCI). They are displayed in detail in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

4.3 Results

4.3.1 Micro-axial pLVAD in cardiogenic shock

Included studies

Study characteristics

CS: 4 Studien (3 RCTs, 1 Registerstudie)

Four studies were included to assess the use of micro-axial pLVAD in patients with cardiogenic shock in AMI. Of these, three were RCTs: the IMPELLA-STIC study, the IMPRESS study and the ISAR-SHOCK study [61, 62, 64]. From the RCTs, effectiveness as well as safety outcomes were included in the analysis. One study was designed as a registry-based retrospective cohort study. From this observational study, only safety outcomes were included in the analysis [67].

Randomised trials

Ein- und Ausschlusskriterien der RCTs; 89 Pts eingeschlossen

All included RCTs enrolled patients that were admitted with cardiogenic shock due to AMI. Differences between RCTs in the inclusion criteria were the requirement for IABP and inotropic drugs as well as a primary angioplasty within 24 hours of the index AMI in the IMPELLA-STIC study [61] or mechanical ventilation before randomization and the setting of immediate PCI in the IMPRESS study [62]. Exclusion criteria differed between RCTs. Shared exclusion criteria were any contraindication to Impella® implantation, prolonged resuscitation, septic conditions, or inclusion in another study or trial. The three RCTs accounted for a total of 89 patients (Intervention group: 44/ Control group: 43) [61, 62, 64].

Durchschnittsalter: IG: 58-65 J.; KG: 53,5-67 J.

männl. Geschlecht: IG: 62-85 % KG: 81-100 %

The mean age of patients was not statistically significant between groups in the included studies, with a range of mean age of 58 (SD: ±9) to 65 (range: 55-71) years in the intervention groups as opposed to a range of 53.5 (SD: ±8.1) to 67 (SD: ±11) years in the control groups. Across studies, men were overrepresented, with a range of 62% to 85.7% and a range of 81.2% to 100% men enrolled in the intervention groups and control groups respectively across studies. Within the included studies, however, there was no statistically significant difference in gender balance. In all three RCTs [61, 62, 64], no statistically significant differences in co-morbidities were reported in baseline characteristics.

primäre Endpunkte: Mortalität (1 RCT), Hämodynamik (2 RCTs) Follow-up: 1 Monat (2 RCTs), 6 Monate (1 RCT)

One of the RCTs assessed one-month all-cause mortality as a primary outcome measure and LoS and rehospitalization as secondary outcome measures [62]. The primary outcomes of the other two RCTs were changes in cardiac power index (CPI) or cardiac index from baseline to 30 minutes or 12 hours after implantation, respectively [61, 64]. Secondary outcome measures of the RCTs were hemodynamic variables, LVEF, all-cause mortality at one month, device-related complications, creatinine clearance, device failure, analyses of the structural integrity of heart valves and left ventricular systolic function measured with echocardiograms, metabolic variables, lactic acidosis, and multiple-organ dysfunction scores. The length of follow-up was up to one month in two RCTs and up to six months in one RCT [61, 62, 64].

Observational studies

CS: Registerstudie mit 18.032 Pts IG: 1.414 KG: 16.619

The retrospective cohort study included patients with a diagnosis of cardiogenic shock that were managed with IABP or PVAD between the years 2010 to 2014. Patients with an AMI or any revascularization procedure during the hospital stay were excluded. Patients that were reported as being managed with both devices were also excluded. A total of 18,032 patients (Intervention group: 1,414/Control group: 16,619) were included according to the selection criteria [67].

durchschnittliches Alter: IG: 55,8 J; KG: 59,5 J männl. Geschlecht: IG: 72 %, KG: 66 %

The mean age of patients was statistically significant between groups in the observational study, with a mean age of 55.8 (±17.2) years in the intervention group and 59.5 (±15.1) years in the control group ($p<0.001$). Men were overrepresented in both groups of the observational study with 1,022 patients (72.3%) in the intervention group compared to 11,030 patients (66.4%) in the control group. Patients in the intervention group had a statistically significant history of LVAD, 25 patients (1.8%) in the intervention group compared to 64 patients (0.4%) in the control group ($p=0.0001$). No other statistically significant differences in co-morbidities in baseline characteristics were reported.

The primary outcome measure of the retrospective cohort study was inpatient mortality and the secondary outcome measure was LoS. The study also reported adverse events and outcomes during the hospital stay. The study's timeframe of analysis was 2010 to 2014 [67].

primärer Endpunkt: stationäre Mortalität, weitere sekundäre Endpunkte; Zeitraum 2010-2014

Mortality

The *crucial* outcome **mortality** was reported in all three included RCTs [61, 62, 64], although only one study [62] defined it as a primary endpoint. Two of the studies were not able to detect a statistically significant difference in mortality between micro-axial pLVAD and IABP, neither at one month nor at six months. One of the studies did not report a p-value[32].

Mortalitätsrate in 3 Studien: 2 Studien ohne stat.sign. Unterschied, 1 Studie ohne p-Wert

Mortality at one month was reported by all included studies: In the IMPRESS RCT, eleven patients (of 24 pts; 46%) in the intervention group with micro-axial pLVAD died compared to twelve patients (of 24 pts; 50%) in the control group with IABP. This finding was not statistically significant (p=0.92) [62]. Of the studies assessing mortality as the secondary outcome measure, the following outcomes were described: In the IMPELLA-STIC RCT, at one month two patients (of 7 pts; 28.6%) in the intervention group died, compared to no patients (of 6 pts; 0%) in the comparison group. This finding was not statistically significant (p=0.46) [61]. In the ISAR-SHOCK RCT, six patients (of 13 pts; 46%) were reported dead at one month in the intervention and control group respectively. No p-value was reported for this finding [64].

Mortalität 1 Monat: Berichterstattung in 3 Studien (n=89): 28,6 %-46 % vs. 0 %-50 %

Mortality at 6 months was reported in the IMPRESS RCT: twelve patients (of 24 pts; 50%) within each group were reported dead at six months. The finding was not statistically significant (p=0.92) [62].

Mortalität 6 Monate: Berichterstattung in 1 Studie (n=48) 50 % vs. 50 %

For the effect of micro-axial pLVAD on mortality due to causes other than cardiogenic shock, no evidence was found[33].

Morbidity

The important outcomes **LoS in hospital** and **rehospitalization** were considered when answering the research questions on morbidity[34]. LoS in hospital and rehospitalization were reported as secondary outcome measures in one RCT [62]. The RCT was not able to detect a statistically significant difference in progression or recurrence of cardiogenic shock.

Morbidität 1 RCT: Aufenthaltsdauer: kein stat.sign. Unterschied; Intensivstation: 7 (3-16) vs. 7 (4-10) Tage

The IMPRESS RCT reported the LoS as median values (25^{th} to 75^{th} percentile): intensive care unit LoS was reported to be seven (3 to 16) days in the intervention group compared to seven (4 to 10) days in the comparison group, hospital LoS was reported to be 16 (3 to 26) days in the intervention group compared to ten (6 to 24) days in the comparison group) [62][34].

Krankenhaus: 16 (3-26) vs. 10 (6-24) Tage Rehospitalisierung: kein p-Wert 21 % vs. 4 %

Further, the proportion of rehospitalised patients was reported in this study. Five out of 24 patients (21%) in the intervention group compared with one out of 24 patients (4%) in the comparison group were rehospitalized. No p-value was reported for this finding [62].

[32] D0001 – What is the expected beneficial effect of micro-axial pLVAD on mortality?

[33] D0003 – What is the effect of micro-axial pLVAD on the mortality due to causes other than CS?

[34] D0005 – How does the micro-axial pLVAD affect symptoms and findings (severity, frequency) of cardiogenic shock? &
D0006 – How does the micro-axial pLVAD affect progression (or recurrence) of CS?

Function

Hämodynamik: 3 RCTs, Herzindex und linksventrikuläre Ejektionsfraktion (LVEF) erhoben

Hemodynamic variables were reported by all three RCTs [61, 62, 64], although only two studies defined them as a primary endpoint [61, 64]. One of the studies was able to detect a statistically significant difference in cardiac index, indicating better hemodynamic support in the intervention group. One of the studies was not able to detect a statistically significant difference in cardiac index. For LVEF, two of the studies were not able to detect a statistically significant difference, and one study did not report a p-value for the difference in LVEF[35].

Herzindex: stat.sign. Unterschied in 1 RCT zugunsten der Technologie: 0,49 ±0,46 l/min/m² vs. 0,11 ±0,31 l/min/m²

The change in cardiac index was reported in two studies, both studies reported cardiac index change as the primary outcome measure. [61, 64]. In one RCT [61], the change in cardiac index was measured as change after 12 hours and reported to be -0.02 ±0.25 W/m² in the intervention group compared to 0.08 ±0.08 W/m² in the comparison group (p=0.4). In the other RCT [64], the change in cardiac index was reported to be 0.49 ±0.46 l/min/m² in the intervention group compared to 0.11 ±0.31 l/min/m² in the control group. This finding was statistically significant (p=0.02).

LVEF: kein stat.sign. Unterschied in 2 RCTs: 35 %-46 % vs. 40,6 %-49 %

LVEF was reported by all three RCTs [61, 62, 64]. In one RCT [61], the LVEF at one month was reported to be 38.6% ±14.4% in the intervention group compared to 40.6% ±12.5% in the comparison group. This finding was not statistically significant (p=0.9). One RCT [62] reported LVEF at six months. In the intervention group, a LVEF of 46% ±11% was reported and in the comparison group of 49% ±9%. No p-value was reported for this finding. One RCT [64] reported the difference of LVEF between groups at discharge. LVEF was reported to be 35% ±17% in the intervention group compared to 45% ±17% in the IABP group. This finding was not statistically significant (p=0.34).

Aktivitäten, QoL, Pat.-Zufriedenheit: keine Evidenz vorhanden

For the effect of micro-axial pLVAD on activities of daily living, generic health-related quality of life, disease-specific quality of life, or patient satisfaction no evidence was found[36].

Patient safety

None of the studies reported on composite outcome measures such as SAEs or AEs, making comparisons across studies difficult[37].

MACE: in 2 RCTs und 1 Registerstudie berichtet kein stat.sign. Unterschied (1 RCT und 1 Registerstudie), kein p-Wert (1 RCT)

Similarly, for MACE no composite was reported. Individual events considered to MACE were reported in two RCTs [61, 62] and one observational study [67]. Two of the studies were not able to detect a statistically significant difference in MACE. One of the studies did not report p-values for the findings.

refraktäre Herzinsuffizienz: 42,9 % vs. 16,7 %
Myokardinfarkt: 4 % vs. 8 %,

In one RCT [61], refractory heart failure was reported in three patients (42.9%) in the intervention group compared to one patient (16.7%) in the comparison group. This finding was not statistically significant (p=0.55). In one RCT [62], myocardial (re)infarction was reported: one patient (4%) in the intervention group compared to two patients (8%) in the comparison group suffered from a re-infarction. No p-value was reported for this finding.

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[35] D0011 – What is the effect of micro-axial pLVAD on patients' body functions?

[36] D0016 – How does the use of micro-axial pLVAD affect activities of daily living? &
D0012 – What is the effect of micro-axial pLVAD on generic health-related quality of life? &
D0013 – What is the effect of micro-axial pLVAD on disease-specific quality of life? &
D0017 – Was the use of micro-axial pLVAD worthwhile?

[37] C0008 – How safe is micro-axial pLVAD in comparison to standard care?

In the observational study, cardiac arrest was reported in 438 patients (31%) in the intervention group compared to 4,609 patients (27.7%) in the comparison group (p=0.21). For pericardial effusion, 74 patients (5.2%) in the intervention group and 556 patients (3.3%) in the comparison group were affected (p=0.107). Cardiac tamponade was found in 59 patients (4.2%) in the intervention group compared to 525 patients (3.2%) in the comparison group (p=0.351). Pericardiocentesis was present in 21 patients (1.5%) in the intervention group compared to 149 patients (0.9%) in the comparison group (p=0.352). The observational study found no statistically significant difference for the described types of MACE [67].

Herzstillstand: 31 % vs. 27,7 %, Perikarderguss: 5,2 % vs. 3,3 %, Herztamponade: 4,2 % vs. 3,2 %, Perikardiozentese: 1,5 % vs. 0,9 %

Bleeding complications were reported as a secondary outcome measure in all three RCTs [61, 62, 64] and one observational study [67]. In the RCTs, bleeding was reported as major bleeding adverse event. In regard to bleeding complications, one RCT was able to detect a statistically significant difference detrimental to the intervention group [61]. Two RCTs and one observational study were not able to detect a statistically significant difference in bleeding complications [62, 64, 67].

Blutungen: in 3 RCTs und 1 Registerstudie berichtet

stat.sign. Unterschied (1 RCT), kein stat.sign. Unterschied (2 RCTs und 1 Registerstudie)

In the IMPELLA-STIC study, five patients (71.4%) in the intervention group treated with micro-axial pLVAD combined with IABP experienced a major bleeding compared to no patients (0%) in the comparison group treated with IABP alone. This finding was reported to be statistically significant (p=0.02) [61].

Blutungen: 0 %-71,4 % vs. 0 %-26 %

In the IMPRESS study, eight patients (33%) in the intervention group treated with micro-axial pLVAD were affected by major bleeding compared to two patients (8%) in the comparison group. No p-value was reported for this finding [62].

In the ISAR-SHOCK study, no major bleeding occurred in 13 patients (0%) in the intervention and control group respectively [64].

The observational study assessed the occurrence of hemorrhage and the need for blood transfusion as bleeding complications. In the intervention group treated with pVAD, hemorrhage occurred in 64 patients (4.5%) and blood transfusion in 433 patients (30.6%). In comparison, in the group treated with standard care or standard care with IABP, hemorrhage occurred in 731 patients (4.4%) and blood transfusion in 4,321 patients (26%). For neither hemorrhage (p=0.904) nor blood transfusion (p=0.096) the differences were statistically significant [67].

Hämorrhagie: 4,5 % vs. 4,4 % Bluttransfusion: 30,6 % vs. 26 %

The **need for an additional device** was reported by two RCTs [61, 62] and one observational study [67]. One RCT [61] found no statistically significant difference between groups, one RCT did not report a p-value for the finding [62], and one observational study [67] found a statistically significant difference in the use of additional devices or transplants in the intervention group.

zusätzliche Interventionen: 2 RCTs und 1 Registerstudie

stat.sign. Unterschied (1 Registerstudie), kein stat.sign. Unterschied (1 RCT), kein p-Wert (1 RCT)

In one RCT [61], ECMO was used in two patients (28.6) of the intervention group compared to one patient (16.7%) in the control group (p=1). In another RCT [62], surgical LVAD placement was reported in no patients in the intervention group, and in one patient (4%) in the control group. No p-value was reported for this finding. No patients in both groups received a heart transplantation, no p-value was reported for this finding.

ECMO: 11,4 %-28,6 % vs. 5.5 %-16,7 %, LVAD: 0 %-13,3 % vs. 4 %-13,3 %, BiVAD: 1 % vs. 0,4 %, Kunstherz: <1 % vs. 0,4 %, Herztransplantation: 3,5 % vs. 4,5 %, Intubation: 68,2 % vs. 59,7 %

One observational study [67] found a statistically significant difference for ECMO and intubation/mechanical ventilation in the intervention group. For biventricular external heart assist, LVAD, artificial heart or heart transplantation the study was not able to detect statistically significant differences. Biventricular external heart assist was used in 14 patients (1%) of the intervention group compared to 70 patients (0.4%) of the control group (p=0.196). LVAD was used in 188 patients (13.3%) in the intervention group compared to 2,211 patients (13.3%) of the control group (p=0.994). Artificial heart was used in < 11 patients (< 1%)[38] in the intervention group compared to 72 patients (0.4%) of the control group (p=0.75). Heart transplant was used in 49 patients (3.5%) in the intervention group compared to 749 patients (4.5%) of the control group (p=0.423)[67].

In the observational study, for the intervention group treated with pVAD, additional treatment with ECMO was given to 161 patients (11.4%) compared to 917 patients (5.5%) in the comparison group. This difference was statistically significant (p<0.001). Intubation or mechanical ventilation was also more common in the intervention group: 965 patients (68.2%) were mechanically ventilated compared to 9,916 patients (59.7%) in the comparison group, this finding was statistically significant (p=0.002) [67].

Nierenkomplikation: in 1 RCT und 1 Registerstudie erhoben

Renal complications were reported in one RCT and one observational study. In the RCT, the authors did not report a p-value for renal complications. The observational study was able to detect a statistically significant difference of renal complications in the intervention group treated with pVAD compared to patients in the control group receiving IABP [62, 68].

stat. sign. Unterschied (1 Registerstudie), kein p-Wert (1 RCT) Nierenersatztherapie: 33 % vs. 29 %, akutes Nierenversagen: 72,5 % vs. 61,5 %, Dialyse: 15,4 % vs. 10,4 %, Hämodialyse: 16,4 % vs. 12,1 %

In the RCT [62], renal replacement therapy was reported for eight patients (33%) in the intervention group compared to seven patients (29%) of the comparison group. The authors did not report a p-value for the rate of renal replacement therapy. In the observational study [67], 1,023 patients (72.5%) of the intervention group compared to 10,206 patients (61.5%) in the comparison group had acute renal failure. This finding was statistically significant (p<0.001). Concerning acute renal failure requiring dialysis, 217 patients (15.4%) in the intervention group were affected compared to 1,734 patients (10.4%) in the control group were reported. This difference was statistically significant (p=0.011). Additionally, hemodialysis was reported in 232 patients (16.4%) in the intervention group compared to 2,008 patients (12.1%) in the comparison group. This finding was statistically significant (p=0.034) [67].

For the following other complications, either no statistically significant difference between groups was found, or p-values were not reported:

multiple Organversagen: kein stat. sign. Unterschied (2 RCTs, 1 Registerstudie) 14,4 %-71,4 % vs. 11,1 %-50,0 % MODS/SOFA: keine Unterschiede

Multiple organ complications were reported in two RCTs [61, 64] and one observational study [67]. The studies did not detect a statistically significant difference for this event group.

In one RCT [61], sepsis was reported in five patients (71.4%) compared to three patients (50.0%) of the control group (p=0.59). In one RCT [64], multiple organ dysfunction score (MODS) and sequential organ failure assessment (SOFA) criteria were reported. No difference between groups in these complex dysfunction scores was reported. In the observational study [67], septic shock was reported in 203 patients (14.4%) of the intervention group compared to 1,852 patients (11.1%) of the control group (p=0.095).

[38] Due to NIS Data Use agreement, cells with small numbers cannot be published.

Vascular complications were reported in three RCTs [61, 62, 64] and one observational study [67]. One of the RCTs and the observational study were not able to detect a statistically significant difference for vascular complications. Two RCTs did not report a p-value for vascular complications.

vaskuläre Komplikationen: kein stat. sign. Unterschied (1 RCT, 1 Registerstudie), kein p-Wert (2 RCTs) 4 %-28,6 % vs. 1,9 %-7,7 %,

One RCT [61] reported limb complications in two patients (28.6%) of the intervention group compared to no patients in the control group (p=0.46). One RCT [62] reported major vascular complications in one patient (4%) of the intervention group compared to no patient in the control group (p=NR). One RCT [64] reported ischemia in no patients in either group and acute limb ischemia in one patient (7.7%) of the intervention group compared to no patient in the control group (p=NR). In the observational study [67], vascular complications were not reported in the intervention group. In the control group, in 310 patients (1.9%) vascular complications were reported (p=0.14).

Neurological complications were reported in two RCTs [62, 64] and one observational study [67]. The two RCTs did not report a p-value for neurological complications. The observational study was not able to detect a statistically significant difference for neurological complications.

neurologische Komplikationen: kein stat. sign. Unterschied (1 Registerstudie), kein p-Wert (2 RCTs) 2,4 %-5,9 % vs. 1,7 %-15,4 %

One RCT [62] reported stroke in one patient (4%) in both the intervention and control group (p=NR). One RCT [64] reported a neurological deficit in no patients of the intervention group and two patients (15.4%) of the control group (p=NR). The observational study [67] reported transient ischemic attack/stroke in 83 patients (5.9%) of the intervention group compared to 878 patients (5.3%) of the control group (p=0.665). All hemorrhagic stroke was reported in 33 patients (2.4%) in the intervention group compared to 278 patients (1.7%) of the control group (p=0.38).

Respiratory complications were reported in one observational study [67]. The observational study was not able to detect a statistically significant difference for respiratory complications.

respiratorische Komplikationen: kein stat. sign. Unterschied (1 Registerstudie) 2,4 %-73,3 % vs. 3 %-68,1 %

The observational study [67] reported pneumonia in 236 patients (16.7%) of the intervention group compared to 3,433 patients (20.7%) of the control group (p=0.107). Respiratory failure was reported in 1,037 patients (73.3%) compared to 11,323 patients (68.1%) in the control group p=0.083). Pulmonary embolism was reported in 34 patients (2.4%) of the intervention group compared to 497 patients (3%) of the control group (p=0.572). Pulmonary wedge pressure monitoring was reported in 345 patients (24.4%) in the intervention group compared to 3,939 patients (23.7%) of the control group (p=0.78).

The need for **surgery or procedure** was reported in one RCT [62], no p-values were reported to the findings.

Folgeeingriffe: kein p-Wert (1 RCT) 0 %-8 % vs. 0 %-13 %

In the RCT [62], repeat PCI was reported in no patients of the intervention group compared to three patients (13%) of the control group (p=NR). Coronary artery bypass grafting was reported in no patients of the intervention group compared to one patient (4%) of the control group (p=NR). Other surgeries were reported in two patients (8%) of the intervention group compared to no patients in the control group (p=NR).

Device/technical failure was reported in three RCTs [61, 62, 64], no p-values were reported for the findings.

technischer Gerätedefekt: kein p-Wert (3 RCTs) 0 %-28,6 % vs. 0 %

In one RCT [61], device failure occurred in two patients (28.6%) in the intervention group compared to no patients in the control group (p=NR). In one RCT [62], hemolysis requiring extraction of the device was reported in two patients (8%) of the intervention group compared to no patients in the

control group (p=NR). In one RCT [64], none of the patients in either group had a device-related technical failure (p=NR).

Herzklappenschäden, fehlgeschlagener Eingriff: nicht erhoben

None of the studies on micro-axial pLVAD in CS reported on **valvular damage** or **procedural failure**.

The results in detail for these other complications are presented in Table A-2 for the RCTs and in Table A-3 for the observational study.

For harms related to dosage or frequency of applying micro-axial pLVAD or the change of frequency or severity of harms over time or in different settings, no evidence was found. For susceptible patient groups that are more likely to be harmed through the use of micro-axial pLVAD, or association to user-dependent harms, no evidence was found. For the kind of data, records or registry to monitor the use of micro-axial pLVAD, no evidence was found[39].

4.3.2 Micro-axial pLVAD in percutaneous coronary interventions

Included studies

Study characteristics

PCI: 3 Studien (1 RCT, 2 Registerstudien)

Three studies were included to assess the use of micro-axial pLVAD in patients undergoing PCI. Of these, one was a RCT: the PROTECT II study [63]. The other two studies were propensity score-matched registry-based retrospective cohort studies, from which only safety outcomes were included in our analysis [65, 66].

Impella/mikro-axiale LVAD als Intervention, IABP als Komparator in allen 3 Studien

The studied interventions were Impella 2.5® in the PROTECT II study [63], all Impella® devices in one retrospective cohort study [65] and intravascular microaxial LVAD in another retrospective cohort study [66]. All three studies had patients treated with IABP in the comparison group [63, 65, 66]. The specified indication was elective PCI in the PROTECT II study [63], any type of PCI in one retrospective cohort study [65], and AMI complicated by cardiogenic shock undergoing PCI in another retrospective cohort study [66].

Randomised trials

Ein- und Ausschlusskriterien des RCT, 448 Pts analysiert (IG: 225, KG: 223)

The PROTECT II study included patients that were scheduled to undergo an elective PCI with a predetermined need for hemodynamic support assessed by the treating physician. Further, either a PCI on an unprotected left main or last patent coronary vessel with a LVEF ≤35%, or a PCI on 3-vessel disease with a LVEF ≤30% was required to be included in the RCT. Patients with recent myocardial infarction with persistent elevation of cardiac enzymes,

[39] C0002 – Are the harms related to dosage or frequency of applying micro-axial pLVAD? &
C0004 – How does the frequency or severity of harms change over time or in different settings? &
C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of micro-axial pLVAD? &
C0007 – Are micro-axial pLVAD or the comparison of standard care with or without IABP associated with user-dependent harms? &
B0010 – What kind of data/records and/or registry is needed to monitor the use of micro-axial pLVAD or the comparison of standard care with or without IABP?

left ventricular thrombus, a low platelet count (≤75000/mm³), high creatinine count (≥4 mg/dL) or severe peripheral vascular disease were excluded from the RCT. The PROTECT II study enrolled a total of 452 patients, of which 448 patients were analysed (Intervention group: 225/Control group: 223) [63].

Durchschnittsalter: IG: 68 J.; KG: 67 J. männl. Geschlecht: IG: 80 %; KG: 81 %

Patients were aged 68 years (SD: ±11) and 67 (SD: ±11) in the intervention and control group respectively. The study enrolled predominantly male participants, with 180 (80%) and 181 (81.2%) men in the intervention and control group respectively. Statistically significant differences in baseline characteristics were reported for a history of heart failure and previous coronary artery bypass grafting. History of heart failure was reported in 91.1% of patients in the intervention group compared to 83.4% of patients in the control group (p=0.014). Previous coronary artery bypass grafting was reported in 38.2% of patients in the intervention group compared to 28.7% of patients in the control group (p=0.033).

primärer Endpunkt: wesentliche unerwünschte Ereignisse, inkl. Mortalität

Follow-up nach 1 und 3 Monaten

The primary outcome measure of the PROTECT II study was a composite rate of intra- and post-procedural major adverse events (MAEs). These included all-cause death, Q-wave or non-Q-wave MI, stroke or transient ischemic attack (TIA), any repeat revascularization (PCI or coronary artery bypass graft surgery), need for cardiac or a vascular operation, acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI. As secondary outcome measures, the PROTECT II study reported the maximal decrease of CPO. Further secondary outcome measures reported were the rate of in-hospital MAEs, analyses of valvular damage measured with echocardiograms, device failure (assessed as Impella® flow <1 L/min for >5 minutes) and creatinine clearance change. The outcome measures were assessed at both one and three months follow-up [63].

Observational studies

Ein- und Ausschlusskriterien der 2 Registerstudien, insgesamt 51.666 Pts (IG: 6.462, KG: 45.204)

The two observational studies [65, 66] included all patients from the registries that were treated with either intravascular micro-axial LVAD (Impella®) or IABP. For one observational study, missing covariate information or the simultaneous use of Impella® and IABP were exclusion criteria. For another observational study, patients with other MCS devices, patients with multiple devices or patients with medical therapy only were excluded from the analysis. Across both studies, a total of 51,666 patients (Intervention groups: 6,462/ Control groups: 45,204) were included according to the selection criteria and after propensity score matching [65, 66].

Durchschnittsalter: IG: 64,3-67,8 J., KG: 64,0-64,2 J. männl. Geschlecht: IG: 71-72 %, KG: 69-71 %

The mean age of patients ranged from 64.3 (SD: ±11.9) to 67.85 (SD: ±12.14) years in the intervention groups compared to a range of 64.0 (SD: ±11.9) to 64.62 (± 12.63) years in the control groups. Across studies, men were overrepresented, with a range of 71.1% to 72.46% in the intervention groups and range of 68.7% to 71.3% in the control groups. Both studies were propensity-matched cohort studies with no statistically significant co-morbidities at baseline characteristics reported.

primäre Endpunkte: Mortalität im Krankenhaus, schwere Blutungen

The primary outcome measures of one of the included observational studies were in-hospital mortality, bleeding requiring transfusion, acute kidney injury and stroke [65]. Primary outcome measures of the other observational study were in-hospital mortality and in-hospital major bleeding [66]. The observational studies did not specify secondary outcome measures. The studies did not report a length of follow-up, as the studies included all data of patients

of the registry that were treated within a timeframe. This timeframe was January 2004 to December 2016 for one observational study [65], and October 1st 2015 to December 31st 2017 for another observational study [66].

Mortality

Mortalitätsrate in 1 RCT: kein stat.sign. Unterschied 1 Monat: 7,6 % vs. 5,9 % 3 Monate: 12,1 % vs. 8,7 %

Mortality was reported by one RCT [63]: The study was not able to detect a statistically significant difference in mortality, neither at one nor at three months[40].

The PROTECT II study assessed mortality at one month and at three months. After one month, 7.6% of patients in the intervention group died compared to 5.9% of patients in the comparison group. This finding was not statistically significant (p=0.473). After three months, 12.1% of patients in the intervention group died compared to 8.7% of patients in the comparison group. This finding was not statistically significant (p=0.244) [63].

For the effect of micro-axial pLVAD on mortality due to causes other than PCI, no evidence was found[41].

Morbidity

Morbidität: keine Evidenz für Aufenthaltsdauer und Rehospitalisierung

The outcomes **LoS** in hospital and **rehospitalization** were considered when answering this research question, but no evidence was found as none of the included studies on micro-axial pLVAD in PCI assessed them[42].

Function

Hämodynamik: 1 RCT, CPO und LVEF erhoben

Hemodynamic variables were reported in one RCT as a secondary endpoint [63]. The study was able to detect a statistically significant difference in CPO, indicative of improved hemodynamic variables in the intervention group. For LVEF, no p-value was reported[43].

CPO: stat. sign. Unterschied in 1 RCT, LVEF kein p-Wert CPO: -0,04 ±0,24 W vs. -0,14 ±0,27 W LVEF: 27 % vs. 33 %

In the PROTECT II study, the drop in cardiac power output from baseline was reported to be -0.04 ±0.24 W in the intervention group compared to -0.14 ±0.27 W in the comparison group. This difference was reported as statistically significant (p=0.001). The LVEF at three months was reported to be 27% ±9% in the intervention group and as 33% ±11% in the comparison group. No p-value was reported for this finding [63].

For the effect of micro-axial pLVAD on activities of daily living, generic health-related or disease-specific quality of life or patient satisfaction, no evidence was found[44].

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40 D0001 – What is the expected beneficial effect of micro-axial pLVAD on mortality?

41 D0003 – What is the effect of micro-axial pLVAD on the mortality due to causes other than percutaneous coronary interventions?

42 D0005 – How does micro-axial pLVAD affect symptoms and findings (severity, frequency) of patients undergoing percutaneous coronary interventions? & D0006 – How does micro-axial pLVAD affect progression (or recurrence) of percutaneous coronary interventions?

43 D0011 – What is the effect of micro-axial pLVAD on patients' body functions?

44 D0016 – How does the use of micro-axial pLVAD affect activities of daily living? & D0012 – What is the effect of micro-axial pLVAD on generic health-related quality of life? & D0013 – What is the effect of micro-axial pLVAD on disease-specific quality of life? & D0017 – Was the use of micro-axial pLVAD worthwhile?

Patient safety

All of the included studies reported on safety outcomes [63, 65, 66]. However, none of the studies reported on composite outcome measures such as SAEs or AEs, making comparisons across studies difficult[45].

Overall complications were reported in one RCT as a primary outcome measure [63]. The RCT was not able to detect a statistically significant difference in overall complications between the groups.

Gesamtkomplikationen in 1 RCT, keine stat. sign. Unterschiede

The PROTECT II study reported on overall complications as MAEs and assessed these complications as a primary outcome measure. The MAE included all-cause death, Q-wave or non-Q-wave MI, stroke or transient ischemic attack, any repeat revascularization (PCI or coronary artery bypass graft surgery, need for cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI. The proportion of overall complications for the intervention group was reported in 35.1% of patients at one month and 40.6% of patients at three months. In the comparison group, the proportion of overall complications was reported to be 40.1% at one month and 49.3% at three months. These findings were reported as not statistically significant (p=0.2777 for one month and p=0.066 for three months) [63].

1 Monat:
35,1 % vs. 40,1 %
3 Monate:
40,6 % vs. 49,3 %

MACE were not reported as a composite by any study, but the RCT reported individual events that can be classified as MACE., but no statistically significant difference in MACE were detected [63].

MACE in 1 RCT, keine stat.sign. Unterschiede

The PROTECT II study reported myocardial infarction in the intervention group in 13.8% of patients at one month and 12.1% of patients at three months. The proportion of myocardial infarction in the comparison group was 10.4% of patients at one month and 14.2% of patients at three months. These differences between the intervention and control group were reported as not statistically significant (of p=0.268 for one month and p=0.512 for three months). For cardiopulmonary resuscitation (CPR) or ventricular arrhythmia, the reported proportions were 2.2% of patients at one month and 2.2% of patients at three months in the intervention group. The proportion of CPR or ventricular arrhythmia was reported in 3.2% of patients at one month and 4.1% of patients at three months in the comparison group. These differences were reported as not statistically significant (p=0.543 for one month and p=0.259 for three months). Further, the PROTECT II study reported severe hypotension requiring treatment, this condition was found in 4.9% of patients at one month and 4.0% of patients at three months in the intervention group. For the comparison group, the proportions were 8.6% at one month and 5.5% at three months. These differences between the intervention group and control group were reported as not statistically significant (p=0.121 for one month and p=0.469 for three months) [63].

1 Monat:
Myokardinfarkt:
13,8 % vs. 10,4 %,
CPR: 2,2 % vs. 3,2 %,
schwere Hypotension:
4,9 % vs. 8,6 %

3 Monate:
Myokardinfarkt:
12,1 % vs. 14,2 %,
CPR: 2,2 % vs. 4,1 %,
schwere Hypotension:
4,0 % vs. 5,5 %

Bleeding was reported as a primary outcome measure in two observational studies [65, 66]. Both were able to detect a statistically significant difference in bleeding events in the intervention group compared to the control group.

Blutungen in 2 Registerstudien, stat. sign. Unterschiede:

[45] C0008 – How safe is micro-axial pLVAD in comparison to the standard care with or without IABP?

Odds ratio 1,10 (1,00-1,21); 31,3 % vs. 16,0 %

In one observational study, the odds ratio for bleeding was reported to be 1.10 (95% CI: 1.00 – 1.21, p=0.0445) [65]. In another observational study, the outcome was reported as major bleeding. In the intervention group, major bleeding occurred in 526 patients (31.3%) compared to 268 patients (16.0%) in the comparison group. The absolute risk difference was reported to be 15.4 (95% CI: 12.5-18.2, p<.001) [66].

neurologische Komplikationen in 1 RCT und 1 Registerstudie

Neurological complications were reported in one RCT and one observational study [63, 65]. In regard to neurological complications, the RCT found a statistically significant difference at one month in the comparison group, but no statistically significant difference between groups at three months [63]. The observational study found a statistically significant difference of neurological complications in the intervention group [65].

RCT: stat. sign. Unterschied nach 1 Monat 0 % vs. 1,8 %, kein stat. sign. Unterschied nach 3 Monaten 0,9 % vs 2,7 %

Registerstudie: stat. sign. Unterschied: Odds ratio 1,34 (1,18-1,53)

In the PROTECT II study, the proportion of stroke or TIA was reported as part of the composite of overall complications as a primary outcome measure. At one month, no patients in the intervention group and 1.8% of patients in the comparison group were affected by either stroke or TIA. At three months, stroke or TIA occurred in 0.9% and 2.7%, in the intervention and control group respectively. This difference was reported to be statistically significant at one month (p=0.043), but not at three months (p=0.144) [63]. One observational study reported an odds ratio for stroke of 1.34 (95% CI: 1.18 – 1.53), reported to be statistically significant (p<0.0001) [65].

For the following other complications, either no statistically significant difference between groups was found, or p-values were not reported:

Folgeeingriffe: kein stat. sign. Unterschied (1 RCT)

The need for surgery or repeat procedure were reported in one RCT [63]. The study was not able to detect a statistically significant difference for this event group.

1 Monat: 0,9 %-1,3 % vs. 1,4 %-4,1 %, 3 Monate: 1,3 %-3,6 % vs. 1,8 %-7,8 %

In the PROTECT II study [63], repeat revascularization or need for cardiac or vascular operation were reported at one and three months. At one month, repeat revascularization was performed in 1.3% of patients in the intervention group compared to 4.1% of patients in the control group (p=0.075). Cardiac or vascular operation at one month was performed in 0.9% of patients in the intervention group compared to 1.4% of patients in the control group (p=0.642). At three months, repeat revascularization was performed in 3.6% of patients in the intervention group compared to 7.8% of patients in the intervention group (p=0.056). Cardiac or vascular operation at three months was performed in 1.3% of patients in the intervention group compared to 1.8% of patients in the control group (p=0.681).

Nierenkomplikationen: kein stat. sign. Unterschied (1 RCT, 1 Registerstudie)

Renal complications were assessed in one RCT [63] and one observational study [65]. The studies were not able to detect a statistically significant difference for renal complications.

1 Monate: 4,0 % vs. 4,5 %, 3 Monate: 4,0 % vs. 4,6 % Odds Ratio 1,08 (CI: 1,00-1,17)

The PROTECT II study [63] reported acute renal dysfunction. At one month, 4.0% of patients in the intervention group compared to 4.5% of patients in the control group had acute renal dysfunction (p=0.792). At three months, 4.0% of patients in the intervention group compared to 4.6% of patients in the control group had this renal complication (p=0.776). In the observational study [65], the odds ratio for acute kidney injury was reported: Odds ratio (95% CI) 1.08 (1.00 – 1.17), p=0.0521.

Valvular damage was assessed in patients from one RCT [63], but the study did not report p-values for the findings.

Herzklappenschäden: kein p-Wert (1 RCT) 0 % vs. 0 %

In the PROTECT II study [63], aortic valve damage or increase in aortic insufficiency was assessed at one and three months. None of the patients in either group had aortic valve damage or an increase in aortic insufficiency, no p-value was reported.

Procedural failure was assessed in one RCT [63]. The study was not able to detect a statistically significant difference in procedural failures.

fehlgeschlagener Eingriff: kein stat. sign. Unterschied (1 RCT)

In the PROTECT II study [63], angiographic failure was reported. At one month, 0.4% of patients in the intervention group compared to 0.5% of patients in the control group had an angiographic failure (p=0.992). At three months, 0.4% of patients in the intervention group compared to 0.0% of patients in the control group had an angiographic failure (p=0.322).

1 Monat: 0,4 % vs. 0,5 %, 3 Monate: 0,4 % vs. 0,0 %

None of the studies on micro-axial pLVAD for PCI reported on the **need for additional device or transplant**, **respiratory complications**, **multiple organ complications**, **vascular complications** or **device failure**.

zusätzliche Interventionen, respiratorische Komplikationen, multiple Organkomplikationen, vaskuläre Komplikationen, technische Fehler: nicht erhoben

The results in detail for these other complications are presented in Table A-2 for the RCT and in Table A-3 for the observational studies.

For harms related to dosage or frequency of applying micro-axial pLVAD or the change of frequency or severity of harms over time or in different settings, no evidence was found. For susceptible patient groups that are more likely to be harmed through the use of micro-axial pLVAD, or association to user-dependent harms, no evidence was found. For the kind of data, records or registry to monitor the use of micro-axial pLVAD, no evidence was found[46].

[46] C0002 – Are the harms related to dosage or frequency of applying micro-axial pLVAD? &
C0004 – How does the frequency or severity of harms change over time or in different settings? &
C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of micro-axial pLVAD? &
C0007 – Are micro-axial pLVAD or the comparison of standard care with or without IABP associated with user-dependent harms? &
B0010 – What kind of data/records and/or registry is needed to monitor the use of micro-axial pLVAD or the comparison of standard care with or without IABP?

5 Quality of evidence

Risk of Bias (RoB) mit Cochrane RoB v.2 und ROBINS-I bewertet

The risk of bias (RoB) for individual studies was assessed with the Cochrane RoB v.2 tool (for RCTs) [55] and the ROBINS-I tool (for observational studies) [56]. RoB is presented in Table A-4 and Table A-5 in the Appendix. Across the four included RCTs, two were ranked as having moderate RoB [62, 63] and two as having a high RoB [61, 64]. The three included observational studies for safety outcomes were ranked as having a moderate RoB [65, 66, 68].

RCTs: moderates bis hohes RoB, Registerstudien: moderates RoB

The main reasons for the risk of bias were in limited information on used randomization tool as well as awareness of the carers delivering the intervention of participants assignment to intervention in the RCTs. The observational studies were limited in the retrospective data collection with differences in events during hospital stay could have influenced the outcome.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [57] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [57].

GRADE uses four categories to rank the strength of evidence:

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

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and the evidence profile in Appendix Table A-6.

insgesamt sehr niedrige Qualität der Evidenz für beide Indikationen (CS und PCI)

Overall, the strength of the body of evidence for the clinical effectiveness and safety of micro-axial pLVAD in comparison to standard care (with IABP) is very low for both indications (cardiogenic shock or patients undergoing PCI).

Table 5-1: Summary of findings table: micro-axial pLVAD in cardiogenic shock

Outcomes	Anticipated effects (SC and micro-axial pLVAD vs. SC with IABP)	Number of analysed pts (studies)	Certainty of the evidence (Importance)	Comments
Efficacy				
Mortality at 1 month	None of the studies were able to detect a s.s.diff. in mortality at 1 month: 2 (28.6) vs. 0 (0); p=0.46 11 (46) vs. 12 (50); p=0.92 6 (46) vs. 6 (46); p=NR	87 (3 RCTs)	⨁⨁◯◯ Low[a, b] (crucial)	-
Mortality at 6 months	The study was not able to detect a s.s.diff. in mortality at 6 months: 12 (50) vs. 12 (50); p=0.92	48 (1 RCT)	⨁⨁◯◯ Low[a, b] (crucial)	-
Hemodynamic variables	One of the studies was able to detect a s.s.diff. in cardiac index: 0.49 ±0.46 l/min/m^2 vs. 0.11 ±0.31 l/min/m^2; p=0.02 One of the studies was not able to detect a s.s.diff. in cardiac index: -0.02 ±0.25 W/m^2 vs. 0.08 ±0.08 W/m^2; p=0.4 Two of the studies were not able to detect a s.s.diff. in LVEF: 38.6% ±14.4% vs. 40.6% ±12.5%; p=0.9 35% ±17% vs. 45% ±17%; p=0.34 One of the studies did not report a p-value for LVEF: 46% ±11% vs. 49% ±9%; p=NR	87 (3 RCTs)	⨁◯◯◯ Very low[a, b] (important)	One study reported cardiac index change after 30 minutes, one study reported cardiac index change after 12 hours One study reported LVEF at discharge, one study reported LVEF at 1 month, one study reported LVEF at 3 months
Length of hospitalization	Hospital LoS: 16 (3-26) vs. 10 (6-24) ICU LoS: 7 (3-16) vs. 7 (4-10)	48 (1 RCT)	⨁◯◯◯ Very low[a, b] (imporant)	Hospital LoS and ICU LoS were reported in days
Rehospitalization	5 (21) vs. 1 (4); p=NR	48 (1 RCT)	⨁⨁◯◯ Low[a, b] (important)	Rehospitalization was reported as number of patients rehospitalized
Safety				
Major adverse cardiovascular events (MACE)	None of the studies were able to detect a s.s.diff. in major adverse cardiovascular events (MACE): Refractory heart failure: 3 (42.9) vs. 1 (16.7); p=0.55 Myocardial (re)infarction: 1 (4) vs. 2 (8); p=NR	61 (2 RCTs)	⨁⨁◯◯ Low[a, b] (crucial)	No composite of major adverse cardiovascular events (MACE) reported
	The study was not able to detect a s.s.diff. in MACE: Cardiac arrest: 438 (31) vs. 4,609 (27.7); p=0.21 Pericardial effusion: 74 (5.2) vs. 556 (3.3); p=0.107 Cardiac tamponade: 59 (4.2) vs. 525 (3.2); p=0.351 Pericardiocentesis: 21 (1.5) vs. 149 (0.9); p=0.352	18,033 (1 observational study)	⨁◯◯◯ Very low[c] (crucial)	No composite of major adverse cardiovascular events (MACE) reported

Outcomes	Anticipated effects (SC and micro-axial pLVAD vs. SC with IABP)	Number of analysed pts (studies)	Certainty of the evidence (Importance)	Comments
Bleeding	One study detected a s.s.diff. in major bleeding: 5 (71.4) vs. 0 (0); p=0.02 Two studies were not able to detect a s.s.diff. in major bleeding: 8 (33) vs. 2 (8); p=NR 0 (0) vs. 0 (0); p=NR	87 (3 RCTs)	⨁⨁◯◯ Low[a, b] (crucial)	-
	The study was not able to detect a s.s.diff. in bleeding complications: Hemorrhage: 64 (4.5) vs. 731 (4.4); p=0.904 Blood transfusion: 433 (30.6) vs. 4,321 (26); p=0.096	18,033 (1 observational study)	⨁◯◯◯ Very low[c] (crucial)	-
Need for additional device or transplant	None of the studies were able to detect a s.s.diff. in need for certain additional devices: ECMO: 2 (28.6) vs. 1 (16.7); p=1 Surgical LVAD placement: 0 (0) vs. 1 (4); p=NR Heart transplantation 0 (0) vs. 0 (0); p=NR	61 (2 RCTs)	⨁◯◯◯ Very low[a, b] (crucial)	-
	One study detected a s.s.diff. in need for certain additional devices: ECMO: 161 (11.4) vs. 917 (5.5); p<.001 Intubation/mechanical ventilation: 965 (68.2) vs. 9.916 (59.7); p=0.002 The study was not able to detect a s.s.diff in certain additional devices or transplants: Biventricular external heart assist: 14 (1) vs. 70 (0.4); p=0.196 LVAD: 188 (13.3) vs. 2,211 (13.3); p=0.994 Artificial heart: < 11 (<1)[47] vs. 72 (0.4); p=0.75 Heart transplant: 49 (3.5) vs. 749 (4.5); p=0.423	18.033 (1 observational study)	⨁◯◯◯ Very low[c] (crucial)	-
Renal complications	One study did not report a p-value for renal complications: Renal replacement therapy: 8 (33) vs. 7 (29); p=NR	48 (1 RCT)	⨁◯◯◯ Very low[a, b] (crucial)	-
	One study detected a s.s.diff. in renal complications: Acute renal failure: 1,023 (72.4) vs. 10,206 (61.4); p<0.001 Acute renal failure requiring dialysis: 217 (15.4) vs. 1.734 (10.4); p=0.011 Hemodialysis: 232 (16.4) vs. 2,008 (12.1); p=0.034	18,033 (1 observational study)	⨁◯◯◯ Very low[c] (crucial)	-
Multiple organ complications, vascular complications, neurological complications, respiratory complications, need for surgery or procedure, device/technical failure	*Multiple organ complications (2 studies):* 71.4% vs. 50.0%, statistically not significant (1 study) MODS/SOFA: no difference between groups reported (1 study) *Vascular complications (3 studies):* 0%-28.6% vs. 0%, statistically not significant (1 study), p-value not reported (2 studies) *Neurological complications (2 studies):* 0%-4% vs. 4%-15.4%, p-value not reported (2 studies)	87 (3 RCTs)	⨁◯◯◯ Very low[a, b, c] (crucial)	Range of patients with at least one (serious) adverse event in %

[47] Due to NIS Data Use agreement, cells with small numbers cannot be published.

Outcomes	Anticipated effects (SC and micro-axial pLVAD vs. SC with IABP)	Number of analysed pts (studies)	Certainty of the evidence (Importance)	Comments
Multiple organ complications, vascular complications, neurological complications, respiratory complications, need for surgery or procedure, device/technical failure *(continuation)*	*Need for surgery or procedure (1 study):* 0%-8% vs. 0%-13%, p-value not reported (1 study) *Device/technical failure (3 studies):* 0%-28.6% vs. 0%, p-value not reported (3 studies)			
	Multiple organ complications (1 study): 14.4% vs. 11.1%, statistically not significant *Vascular complications (1 study):* NR vs. 1.9%, statistically not significant *Neurological complications (1 study):* 2.4%-5.9% vs. 1.7%-5.3%, statistically not significant *Respiratory complications (1 study):* 2.4%-73.3% vs. 3%-68.1%, statistically not significant	18,033 (1 observational study)	⨁◯◯◯ Very low[c] (crucial)	Range of patients with at least one (serious) adverse event in %

Abbreviations: CS – cardiogenic shock, ECMO – extracorporeal membrane oxygenation, GRADE – Grading of Recommendations Assessment, Development and Evaluation, IABP – intra-aortic balloon pump, ICU – intensive care unit, LVAD – left ventricular assist device, LVEF – left ventricular ejection fraction, LoS – length of stay, MACE – major adverse cardiac events, NR – not reported, p – p-value, pLVAD – percutaneous left ventricular assist devices, pts – patients, RCT – randomised controlled trial, s.s.diff. – statistically significant difference, SC – standard care

Explanations:

[a] *The risk of bias was high for the IMPELLA-STIC and the ISAR-SHOCK trial [61, 64]; there was moderate risk of bias for the IMPRESS trial [62]. There were uncertainties in regard to the generation of the randomization sequence as well as carers awareness of the intervention delivered to participants.*

[b] *The studies were statistically underpowered to detect a difference in this outcome due to small number of patients.*

[c] *Retrospective data collection in the study by Ogunbayo et al [67]; differences in events during hospital stay that could have influenced the outcome.*

GRADE Working Group grades of evidence:

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

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

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

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

Table 5-2: Summary of findings table: micro-axial pLVAD in percutaneous coronary intervention

Outcomes	Anticipated effects (micro-axial pLVAD and SC vs. SC with IABP)	Number of analysed pts (studies)	Certainty of the evidence (Importance)	Comments
Efficacy				
Mortality at 1 month	The study was not able to detect a s.s.diff. in mortality 1 month: 7.6% vs. 5.9%; p=0.473	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	-
Mortality at 3 months	The study was not able to detect a s.s.diff. in mortality 3 months: 12.1% vs. 8.7%; p=0.244	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	-
Hemodynamic variables	The study was able to detect a s.s.diff. in drop in cardiac power output from baseline: -0.04 ±0.24 vs. -0.14 ±0.27 W; p=0.001 The study was not able to detect a s.s.diff. in LVEF at 3 months: 27% ±9% vs. 33% ±11%; p=NR	448 (1 RCT)	⨁◯◯◯ Very low[a] (important)	-
Length of hospitalization	-	(0 studies)	-	-
Rehospitalization	-	(0 studies)	-	-
Safety				
Overall complications	The study was not able to detect a s.s.diff. in overall complications (composite of major adverse events): At 1 month: 35.1% vs. 40.1%; p=0.277 At 3 months: 40.6% vs. 49.3%; p=0.066	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	-
Major adverse cardiovascular events (MACE)	The study was not able to detect a s.s.diff. in MACE: Myocardial infarction: At 1 month: 13.8% vs. 10.4%; p=0.268 At 3 months: 12.1% vs 14.2%; p=0.512 Cardiopulmonary resuscitation/ventricular arrhythmia: At 1 month: 2.2% vs. 3.2%; p=0.543 At 3 months: 2.2% vs. 4.1%; p=0.259 Severe hypotension requiring treatment: At 1 month: 4.9% vs. 8.6%; p=0.121 At 3 months: 4.0% vs. 5.5%; p=0.469	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	No composite of MACE reported
Bleeding	The studies detected a s.s.diff. in bleeding: Odds ratio (95% CI): 1.10 (1.00 – 1.21); p=0.0445 526 (31.3) vs. 268 (16.0); p<.001 Absolute Risk Difference (95% CI): 15.4 (12.5-18.2); p<.001	51,666 (2 observational studies)	⨁⨁◯◯ Low[b] (crucial)	-

Outcomes	Anticipated effects (micro-axial pLVAD and SC vs. SC with IABP)	Number of analysed pts (studies)	Certainty of the evidence (Importance)	Comments
Neurological complications	One study detected a s.s.diff. at 1 month, but not at 3 months: At 1 month: 0.0% vs. 1.8%; p=0.043 At 3 months: 0.9% vs. 2.7%; p=0.144	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	-
	One study detected a s.s.diff. in stroke: Odds ratio (95% CI): 1.34 (1.18 – 1.53); p<0.0001	48,306 (1 observational study)	⨁⨁◯◯ Low[b] (crucial)	
Need for surgery or procedure, renal complications, procedural failure, valvular damage	*Need for surgery or procedure (1 study):* Not statistically significant: 1 month: 0.9%-1.3% vs. 1.4%-4.1%, 3 months: 1.3%-3.6% vs. 1.8%-7.8% *Renal complications (1 study):* Not statistically significant: 1 month: 4.0% vs. 4.5%, 3 months: 4.0% vs. 4.6% *Procedural failure (1 study):* Not statistically significant: 1 month: 0.4% vs. 0.5%, 3 months: 0.4% vs. 0.0% *Valvular damage (1 study*): 0% vs. 0%, p-value not reported	448 (1 RCT)	⨁⨁◯◯ Low[a] (crucial)	Range of patients with at least one (serious) adverse event in %
	Renal complications (1 study): Not statistically significant: Odds ratio (95% CI) 1.08 (1.00-1.17)	48,306 (1 observational study)	⨁⨁◯◯ Low[b] (crucial)	-

Abbreviations: CI – confidence interval, GRADE – Grading of Recommendations Assessment, Development and Evaluation, IABP – intra-aortic balloon pump, LVEF – left ventricular ejection fraction, MACE – major adverse cardiac events, NR – not reported, p – p-value, PCI – percutaneous coronary intervention, pLVAD – percutaneous left ventricular assist devices, pts – patients, RCT – randomised controlled trial, s.s.diff. – statistically significant difference, SC – standard care, TIA – transient ischemic attack

Explanations:

[a] *There was moderate risk of bias for the PROTECT II trial [63].*
There was limited information on the randomization tool as well as carers awareness of the intervention delivered to participants.

[b] *Retrospective data collection with appropriate data analysis by propensity score matching in the studies by Amin et al. [65] and Dhruva et al. [66]*

GRADE Working Group grades of evidence:

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

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

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

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

6 Discussion

Micro-axial percutaneous left ventricular assist devices (pLVAD) are a type of mechanical circulatory support (MCS) implanted percutaneously, usually via the femoral artery in patients needing emergency support.

mikro-axiale pLVAD für MCS bei CS oder PCI

This report aimed to assess the clinical effectiveness and safety of micro-axial pLVAD and standard care in patients with cardiogenic shock as well as patients undergoing percutaneous coronary interventions (PCI) in comparison to standard care (including other MCS) concerning patient-relevant outcomes.

Ziel: Synthese der Evidenz für vergleichende klin. Wirksamkeit und Sicherheit

Summary of evidence

In this systematic review evidence from a previous HTA report by the Canadian Health Quality Ontario (HQO) was updated. Concerning patients with cardiogenic shock, four studies (three RCTs and one observational study) were included, further three studies for patients needing PCI (one RCT and two observational studies). All of the included studies compared the use of micro-axial pLVAD to intra-aortic balloon pump (IABP). No studies were comparing micro-axial pLVAD to extracorporeal membrane oxygenation (ECMO) matching the inclusion criteria of this report.

Update HTA HQO

Evidenzsynthese aus 4 Studien zu CS und 3 Studien zu PCI

Komparator in allen Studien: IABP

Micro-axial pLVAD use in the treatment of cardiogenic shock

Overall 18,121 patients were enrolled in the studies assessing the use of micro-axial pLVAD in cardiogenic shock (of whom 18,119 were analysed). Of these, 89 patients (of whom 87 were analysed) were included for clinical effectiveness outcomes.

CS: 3 RCTs und 1 Registerstudie inkludiert

Two included RCTs found no statistically significant difference in mortality between the intervention and comparison groups, one RCT did not report a p-value. For the hemodynamic variable cardiac index, one RCT showed a statistically significant improvement in the micro-axial pLVAD group indicating better hemodynamic support, while one RCT showed no statistically significant difference between groups. For left ventricle ejection fraction, none of the studies found a statistically significant difference between groups. The quality of evidence was assessed as low for mortality and as very low for hemodynamic variables.

klinische Wirksamkeit: Mortalität: keine stat. sign. Unterschiede in 2 RCTs, kein p-Wert in 1 RCT

Hämodynamik: Evidenz deutet auf Verbesserung hin

A statistically significant difference in bleeding complications in the micro-axial pLVAD group was reported. Also, a statistically significant difference in renal complications in the micro-axial pLVAD group was reported. In patients receiving micro-axial pLVAD, there was a statistically significant difference in the use of additional devices such as ECMO or intubation/mechanical ventilation. The quality of evidence for bleeding complications was assessed as low (in RCTs) and very low (in observational studies) for bleeding complications, the quality of evidence for the need for additional devices was assessed as very low, the quality of evidence for renal complications was assessed as low (in RCTs) and very low (in observational studies). For major adverse cardiovascular events (MACE) and other complications, no statistically significant difference between groups was reported. The quality of evidence for MACE and other complications was assessed as low to very low quality.

Sicherheit: in IG stat. sign. Unterschied Blutungen, Nierenkomplikationen sowie Bedarf an zusätzlichen Interventionen

MACE und weitere Kompl.: keine stat. sign. Unterschiede

Micro-axial pLVAD use during percutaneous coronary interventions

PCI: 1 RCT und 2 Registerstudien inkludiert

Overall, 77,062 patients were enrolled in the studies investigating the use of micro-axial pLVAD during percutaneous coronary interventions (of whom 52,114 were analysed). Of these, 452 patients (of whom 448 were analysed) were included for clinical effectiveness outcomes.

klinische Wirksamkeit: Mortalität: kein stat. sign. Unterschied in 1 RCT Hämodynamik: Evidenz deutet auf Verbesserung hin

The included RCT in our qualitative synthesis found no statistically significant difference in mortality between the intervention and comparison group. For the hemodynamic variable cardiac index, the included RCT showed a statistically significant improvement in the micro-axial pLVAD group indicating better hemodynamic support. For left ventricle ejection fraction, the RCT found no statistically significant difference between groups. The quality of evidence was assessed as low for mortality and very low for hemodynamic variables.

Sicherheit: in IG stat. sign. Unterschied Blutungen und neurol. Kompl. MACE und weitere Kompl.: keine stat. sign. Unterschiede

A statistically significant difference in bleeding and neurological complications in the micro-axial pLVAD group was reported. The quality of evidence was assessed as low for both bleeding and neurological complications. For MACE and other complications, no statistically significant difference between groups was reported. The quality of evidence for MACE and other complications was assessed as low to very low quality.

One of the observational studies included in our analysis reported the frequency of mechanical circulatory support to vary significantly across different sites, indicating a requirement of certain expertise when applying micro-axial pLVAD devices [65].

Interpretation of the findings

Ergebnisse decken sich mit anderen SRs

The results of this systematic review are aligned with, and complement the results from other recent systematic reviews:

kardiogener Schock: 3 systematische Reviews und Meta-Analysen (2020): kein stat. sign. Unterschied bei Mortalität

A systematic review and meta-analysis, published in 2020, found no association of improvement in short-term mortality when using micro-axial pLVAD in cardiogenic shock patients. This systematic review describes an association of higher proportions of bleeding and ischemic complications when using micro-axial pLVAD for this population [51].

Another systematic review and meta-analysis, published in 2020, showed that short-term mechanical circulatory support with micro-axial pLVAD improved hemodynamic support by increased cardiac power and cardiac power index, but found no statistically significant difference in mortality with or without the use of micro-axial pLVAD [52].

This is in line with another systematic review and meta-analysis, published in 2020, which found no clear evidence for the clinical benefit of micro-axial pLVAD use in cardiogenic shock complicating acute myocardial infarction [53].

Cochrane Bericht zur mechanischen Kreislaufunterstützung (2020): unzureichende Evidenz für klinischen Nutzen

Further, a recent Cochrane report, published in 2020, assessed the use of mechanical assist devices for cardiogenic shock. The scope of the Cochrane review was broadened to include all mechanical assist devices, including micro-axial pLVAD. The authors state there was little or no effect on survival at 30 days. The quality of the evidence was assessed as very low, due to difficulties in accounting for bias [3].

PCI:
SR (2017): kein stat.sign. Unterschied bei Mortalität

The use of micro-axial pLVAD for use during high-risk PCI was assessed by a systematic review, published in 2017. According to this systematic review, the use of micro-axial pLVAD resulted in improved hemodynamic variables. The systematic review was based on four RCTs, two controlled observational studies and 14 uncontrolled observational studies. In the controlled studies, all-cause mortality and MACE were similar across groups at 30 days. [69].

SR von Health Evidence Review Commission Oregon (2020): kein Vorteil gegenüber IABP

The Health Evidence Review Commission (HERC) Oregon published a systematic review in 2020. According to this report, the use of micro-axial pLVAD for treating ischemic cardiogenic shock or during high-risk PCI did not improve clinical outcomes compared to IABP. The authors state there were no systematic reviews or RCTs evaluating the use of micro-axial pLVAD in the setting of non-ischemic cardiogenic shock [70].

Ergebnisse in Kontrast zu 1 SR (2018), SR ohne RCTs

We identified one systematic review, published in 2018, that was in contrast to our systematic review. The systematic review detailed the outcomes of Impella 5.0/LD® use in cardiogenic shock and found favorable survival outcomes and a high proportion of myocardial recovery in cardiogenic shock patients. However, the systematic review was based on five observational retrospective studies and one prospective single-arm study [71].

Kombination mikro-axiale pLVAD mit ECMO: 2 SRs (2020);

FDA: Notfallzulassung für mikro-axiale pLVAD bei COVID-19 Pts. in ECMO-Behandlung

A new, experimental approach is the combination of micro-axial pLVAD with ECMO. Due to limited evidence, this should be limited to patients included in studies to evaluate this strategy [51]. A systematic review, published in 2020, studied the use of micro-axial pLVAD on top of VA-ECMO compared to VA-ECMO alone. The authors describe a decrease in mortality, increase in hemolysis, neutral bleeding risk, and similar rates of acute kidney injury. However, these findings were based on the results of three retrospective observational studies limiting the quality of evidence [72]. A systematic review, published in 2020, assessed different devices for left ventricle unloading during VA-ECMO. The authors describe a significant reduction in left ventricular preload parameters, most pronounced for micro-axial blood pumps and atrial septostomy. However, results of meta-regression did not indicate an association between the level of left ventricular unloading and mortality [73]. In this regard, however, it should be noted that in August 2020 Impella® devices received an emergency-use-authorization (EUA) from the FDA for left ventricle unloading in COVID-19 patients treated with ECMO [29].

Leitlinien AWMF S3 2019: "kann" Empfehlung für kurzfristige mechanische Kreislaufunterstützung

A recent AWMF S3 guideline, published in 2019, states that in infarct-related cardiogenic shock, temporary MCS such as micro-axial pLVAD can be implanted if there is a realistic therapeutic goal ("can" recommendation, evidence level expert consensus[48]) with mandatory prerequisites. This therapeutic goal should be evaluated by a cardiac team in cooperation with a cardiovascular center and documented in an MCS-registry by the professional societies. Further, the implantation of the MCS device should be implanted without delayed revascularization and before the onset of irreversible organ damage. The choice of MCS is based on the expertise of the respective cardiac team [19].

[48] The evidence level expert consensus is based on consensus of clinical experts, based on studies and clinical experience or in the interest of patient safety (e.g., monitoring).

Leitlinien ESC 2018: Erwägung kurzfristiger mechanischer Kreislaufunterstützung in ausgewählten Pts, aber unzureichende Evidenz für Empfehlung

Even though micro-axial pLVAD appear to have similar short-term mortality compared to IABP and an increase in bleeding complications, guidelines state that their use can be considered in selected clinical cases. According to the guidelines on myocardial revascularization of the European Society for Cardiology (ESC), published in 2018, in selected patients with acute coronary syndrome and cardiogenic shock, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life (class of recommendation IIb, level of evidence C). The guidelines report that recent meta-analysis demonstrated similar short-term mortality between pLVADs and IABP, despite initial beneficial effects on arterial blood pressure and peripheral perfusion. The guidelines also report an increase in bleeding complications (bleeding from vascular access sites and higher incidence of limb ischemia). For high-risk PCI, the guidelines describe similar outcomes between pLVAD and IABP, with no difference in major adverse events at 30 days. The guidelines summarize that the evidence for pLVADs was insufficient to recommend their use in cardiogenic shock [20].

IABP: Leitlinien empfehlen keinen Routineeinsatz mehr, Status der Refundierung zu hinterfragen

The studies included in our qualitative analysis compared with IABP for temporary mechanical circulatory support. IABP is listed in the 2021 edition of the Austrian catalogue for medical procedures (LKF-catalogue) and as such reimbursed. However, the question regarding whether this technology should be reimbursed for clinical practice arises. IABP can be part of standard care for treating cardiogenic shock complicating acute myocardial infarction with a Class I recommendation in European and American guidelines, even though evidence on efficacy by RCTs was lacking [21]. It should be noted that in 2014, the ESC changed the recommendation for routine use of IABP from Class II (may be considered) to Class III (not recommended) after the RCT IABP-SHOCK II, which included 600 patients with cardiogenic shock complicating acute myocardial infarction, showed no statistically significant difference for 30-day mortality [74]. According to a recent AWMF S3 guideline, IABP with primary PCI should no longer be used in cardiogenic shock complicating acute myocardial infarction ("should not" recommendation, evidence level 1++[49]). For mechanical complications of myocardial infarction, such as ventricular septal rupture or papillary muscle rupture, IABP may be used for hemodynamic stability (open recommendation, evidence level EK[50]) [19].

Evidence gaps and ongoing studies

5 laufende RCTs

Five ongoing RCTs were identified with estimated completion dates within the next three years. Of these, the use of micro-axial pLVAD is assessed for the treatment of cardiogenic shock in three RCTs whereas the use during PCI is assessed in two RCTs.

CS: 3 RCTs, abgeschlossen bis 2023

For cardiogenic shock, the DanShock RCT compares Impella CP® to conventional circulatory support. The trial will include 360 patients with the primary outcome of death from all causes. The REVERSE RCT compares VA-ECMO with Impella CP® compared to VA-ECMO alone. The trial will in-

[49] Evidence level 1++ describes evidence from high quality systematic reviews of RCTs or RCTs with very low risk of bias.

[50] The evidence level expert consensus is based on consensus of clinical experts, based on studies and clinical experience or in the interest of patient safety (e.g., monitoring).

clude 96 patients with the primary outcome recovery from cardiogenic shock. The UNLOAD-AMI RCT compares Impella CP® to standard treatment of acute myocardial infarction after PCI. The trial will include 80 patients and assess left ventricular endsystolic volume, left ventricle remodeling and extent of post-infarct scar. All three RCTs are estimated to be completed in 2023 ([NCT01633502], [NCT03431467], [NCT04562272]).

PCI:
2 RCTs
2022 und 2027

During PCI, the Protect Kidney Trial RCT compares Impella®-protected PCI to standard of care PCI. The trial will include 224 patients with the primary outcome contrast-induced acute kidney injury after PCI. The trial is estimated to be completed in 2022 [NCT04321148]. The DTU-STEMI RCT compares Impella CP® placement before reperfusion with primary PCI to primary PCI alone. The trial will include 668 patients and assess infarct size post procedure. The trial is estimated to be completed in 2027 [NCT03947619].

These ongoing trials could potentially influence the effect estimates considerably.

Internal and external validity

RCT mit kleinen Stichprobengrößen

This report is considerably limited by imprecision of data, as all included RCTs had small sample sizes. Another limitation is the retrospective data collection in the observational studies with some differences in events during the hospital stay that could have influenced the outcome.

Registerstudien mit retrospektivem Design

externe Validität: Daten auf österreichischen Kontext übertragbar

The inclusion criteria of the studies reflected the intended patient population for the technology. The data is considered generalizable to the Austrian context. A detailed description of the applicability of the body of evidence to the Austrian context is provided in the Appendix, Table A-8.

Limitations

strenge Einschlusskriterien, Ausschluss mancher kleinerer Studien, kein Einfluss auf Resultate

In this report, we excluded observational studies with fewer than 500 patients or serious or critical RoB (ROBINS-I). This could have led to not capturing the full available body of evidence. However, these studies would not have changed the interpretation of, and drawn conclusion regarding, the comparative clinical effectiveness and safety of micro-axial pLVADs.

aggregierte Berichterstattung mikro-axialer pLVAD Geräte

Further, we considered all micro-axial pLVAD devices as a relevant intervention in our evidence synthesis. Different devices differ in terms of catheter size and maximum treatment duration. It was unclear as to whether these differences do affect clinical outcomes.

Endpunkte ohne definierte minimal klinisch relevante Unterschiede

We further did not define a minimally clinically relevant difference. It may be worthwhile to define what improvement in mortality or hemodynamic variables or what decrease in adverse events are deemed clinically relevant [75]. However and while a minimally clinically relevant difference should be defined with the support of clinicians in the evaluation of invasive medical device evaluations, it would not have changed our interpretation of the currently available evidence.

Conclusion

Schlussfolgerung: unzureichende Evidenz für klinischen Nutzen Sicherheitsrisiken

The available evidence is insufficient to show that micro-axial pLVAD and standard care is superior or inferior to standard care alone. None of the studies were able to find a statistically significant difference in mortality. While some evidence suggests that micro-axial pLVAD could improve hemodynamic support, safety concerns regarding major bleeding were seen that may make micro-axial pLVAD a less safe treatment modality when compared to the intra-aortic balloon pumps in both assessed indications.

laufende Studien sind abzuwarten, Reflexion der Patient*innenselektion in zukünftiger Forschung

Since the evidence was imprecise, continued research, in the form of larger, high-quality randomised controlled trials could change the estimated effects concerning clinical effectiveness and safety. Ongoing studies are to be awaited to shed more light on the benefit-harm-ratio of micro-axial pLVAD. The focus should be shifted towards reflecting on patient selection in future trials to identify the most beneficial type of mechanical circulatory support in specific scenarios.

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 7-1: Evidence-based recommendation

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

Reasoning:

The current evidence is not sufficient to prove that the assessed technology micro-axial percutaneous left ventricular assist devices are more effective and equally safe than the comparator standard care in patients with cardiogenic shock or patients undergoing high-risk percutaneous coronary interventions.

Aufnahme in den Leistungskatalog: derzeit nicht empfohlen

However, new study results (especially results of the DanSchock trial for cardiogenic shock, NCT01633502) could potentially influence the effect estimates considerably.

großes RCT in Durchführung

The re-evaluation is recommended in 2024 if the larger ongoing randomised trials are published.

Re-Evaluierung für 2024 empfohlen

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Appendix

Quality Appraisal of initial HQO HTA report using the AMSTAR-2 assessment tool

Table A-1: AMSTAR-2 assessment of Health Quality Ontario – Percutaneous Ventricular Assist Devices: A Health Technology Assessment [16, 54]

Author, year	**Health Quality Ontario, 2017 [16]**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall Confidence	**High**
Reasoning	No critical flaws suspected. Limitation: Study selection performed in singulate, but not considered a critical flaw.

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: Micro-axial pLVAD: results from randomised controlled trials

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Country	France	Netherlands, Norway	USA, Canada, Europe	Germany
Sponsor	Sponsor: Hospices Civils de Lyon Funding: Programme de Soutien aux Techniques Innovantes et Couteuses (STIC 2009) Abiomed: 20% reduction in the purchase price of the Impella LP5.0® pumps; the company did not intervene in the study.	The study was funded by the Academic Medical Center, Amsterdam. The Academic Medical Center has received research grants and speaker honoraria from Abiomed Inc.	The study was funded by Abiomed (Danvers, MA)	Supported by Abiomed Europe GmbH (Germany)
Intervention/Product	Impella LP5.0® + IABP	Impella CP®	Impella 2.5®	Impella 2.5®
Comparator	IABP	IABP	IABP	IABP
Indication	Cardiogenic shock in acute myocardial infarction	Cardiogenic shock in acute myocardial infarction	Elective percutaneous coronary intervention	Cardiogenic shock in acute myocardial infarction
Study design	RCT (2-center)	RCT (multicenter, open-label)	RCT (multicenter)	RCT (2-center)
Number of pts	15[51]	48	452[52]	26
Analysed pts	7 vs. 6[53]	24 vs. 24	Intention-To-Treat Population: 448[54] (225 vs. 223) Per Protocol Population: 427 (216 vs. 211)	13 vs. 13[55]
Inclusion criteria	All of the following: ■ Admission with CS due to AMI ■ Primary angioplasty within 24 hours of the index AMI	All of the following: ■ Presentation with an AMI with ST-segment elevation complicated by severe CS[56] in the setting of immediate percutaneous coronary intervention (PCI)	All of the following: ■ Predetermined need for hemodynamic support (assessed by the treating physician) ■ Patient age ≥18 years ■ Scheduled to undergo a nonemergent PCI	■ Patients with acute myocardial infarction < 48 h, confirmed by ischemic symptoms for at least 30 min with elevated cardiac markers or ST-segment elevation or left bundle branch block

[51] The study intended to include 60 patients. However, because of slow recruitment and changes to guidelines regarding IABP use, 15 patients were included.

[52] 69% of the planned 654 patient enrollment. After review of interim data of the first 327 patients, the early discontinuation of the study for futility was recommended. An additional 125 patients had been enrolled beyond the 327 patient halfway point which were not included in the interim analysis. Therefore the total final cohort increased to 452 patients.

[53] Of the eight patients in the control IABP group, two patients were excluded (one withdrew consent, the other had non-ischaemic dilated myocardiopathy).

[54] 1 pts died (Impella 2.5 arm) and 3 withdrew consent (IABP arm) before undergoing PCI.

[55] One patient died before Impella implantation. This patient was included in the analysis by assuming a null effect.

[56] Severe CS was defined as systolic blood pressure <90 mm Hg for longer than 30 min or the need for inotropes or vasopressors to maintain a systolic blood pressure >90 mm Hg.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Inclusion criteria *(continuation)*	■ Inotropic drugs required ■ IABP required	■ Mechanically ventilated before randomization	One of the following: ■ PCI on an unprotected left main or last patent coronary vessel with a LVEF ≤35% ■ PCI on 3-vessel disease with a LVEF ≤30%	■ Cardiogenic shock[57]
Exclusion criteria	■ Contraindication to Impella implantation ■ Refractory cardiogenic shock ■ Right ventricular failure ■ Resuscitation for cardiac arrest for > 30 minutes ■ Septic condition	■ Severe aorto-iliac arterial disease impeding placement of either IABP or pMCS ■ Known severe cardiac aortic valvular disease ■ Serious known concomitant disease with a life expectancy of <1 year ■ Known participation in this study or any other trial within the previous 30 days ■ Coronary artery bypass grafting within the preceding week	■ Recent myocardial infarction with persistent elevation of cardiac enzymes ■ Left ventricular thrombus ■ Platelet count ≤75000/mm^3 ■ Creatinine ≥4 mg/dL (patients already on dialysis were eligible) ■ Severe peripheral vascular disease that precluded passage of the Impella 2.5 catheter of IABP	■ Age <18 years ■ Prolonnged resuscitation (>30 minutes) ■ Hypertrophic obstructive cardiomyopathy ■ Definite thrombus in left ventricle ■ Treatment with IABP ■ Severe valvular disease or mechanical heart valve ■ Cardiogenic shock caused by mechanical complications of AMI such as ventricular septal defect, acute mitral regurgitation greater than second degree, or rupture of the ventricle ■ Predominant right ventricular failure or the need for a right ventricular assist device ■ Sepsis ■ Known cerebral disease ■ Bleeding with a need for surgical intervention ■ Pulmonary embolism ■ Allergy to heparin or any known coagulopathy ■ Aortic regurgitation greater than second degree ■ Pregnancy ■ Inclusion in another study or trial
Age of patients, mean±SD (yrs)	60.3 ±12.3 vs. 53.5 ±8.1; p>0.05	58 ±9 vs. 59 ±11; p=NR	68 ±11 vs. 67 ±11; p=0.488	65 (57-71) vs. 67 (55-80); p=NR
Gender male, n (%)	6 (85.7) vs. 6 (100); p>0.05	18 (75) vs. 20 (83); p=NR	180 (80) vs. 181 (81.2); p=0.668	8 (62) vs. 11 (85); p>0.05

[57] CS was defined using both clinical and hemodynamic criteria. Hypotension: systolic blood pressure <90 mm Hg, heart rate >90 bpm or the need for positive inotropic drugs to maintain a systolic blood pressure >90 mm Hg and end-organ hypoperfusion or pulmonary edema. Hemodynamic criteria were either a cardiac index of no more than 2.2 l/min per square meter of body surface area and a pulmonary capillary wedge pressure >15 mm Hg or an angiographically measured left ventricular ejection fraction <30% and left ventricular end diastolic pressure >20 mm Hg. The onset of shock had to be within 24 h.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Reported co-morbidities at baseline, n (%)	No statistically significant differences reported[58]	No statistically significant differences reported	History of heart failure: 91.1% vs. 83.4%, p=0.014 Previous coronary artery bypass grafting: 38.2% vs. 28.7%, p=0.033	No statistically significant differences reported
Primary Outcome Measures	Change in cardiac power index (CPI), from baseline to 12 hours after implantation, measured with a Swan-Ganz catheter	1 month all cause mortality	Composite rate of intra- and post-procedural major adverse events (MAEs)[59]	Change of the cardiac index from baseline to 30 minutes after implantation
Secondary Outcome Measures	■ Hemodynamic and metabolic variables over 96 hours[60] ■ All-cause mortality at 1 month ■ Impella device-related complications, including major bleeding, cerebro-vascular events and limb ischaemia ■ LVEF[61]	6-month mortality Further descriptive endpoints[62]	■ Efficacy of hemodynamic support assessd by maximal decrease of cardiac power output from baseline ■ Creatinine clearance change from baseline 24 hours post-PCI ■ Device failure assessed as Impella flow <1 L/min for >5 minutes ■ Rate of in-hospital MAEs ■ Analyses of structural integrity of heart valves and myocardium and LV systolic function, measured with echocardiograms[63]	■ Haemodynamic and metabolic variables ■ Lactic acidosis ■ All-cause mortality after 1 month ■ Device-related complications including hemolysis, major bleeding, cerebrovascular events, limb ischemia ■ Multiple-organ dysfunction scores[64]
Length of Follow-up	■ Up to 1 month for haemodynamic and metabolic variables[65] ■ Up to 1 month for LVEF	1 month, 6 months	■ 1 month, 3 months ■ Echocardiograms: at baseline, 1 month, 3 months	■ 30 minutes for change of the cardiac index ■ 1 month for all-cause mortality, and multiple-organ dysfunction scores

[58] Numerically more invasive mechanical ventilations in the intervention group, 4 (57.1%) to 0 (0%), p=NR

[59] MAE included all-cause death, Q-wave or non-Q-wave MI, stroke or transient ischemic attack (TIA), any repeat revascularization (PCI or coronary artery bypass graft [CABG] surgery, need for cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency and angiographic failure of PCI.

[60] Measurement at T0 (randomization for the IABP group, time of start of Impella LP5.0 for the Impella LP5.0 + IABP group), and at 3, 6, 9, 12, 24, 48, 72 and 96 hours after T0. Clinical follow-up was scheduled for 6 months.

[61] Measured by echocardiography on randomization, at day 7, day 14 and 1 month.

[62] Descriptive endpoints included duration of mechanical ventilation; the need for and duration of inotropic and vasopressor therapy; renal replacement therapy; length of hospital stay; the amount of blood products needed; additional treatments, such as ICD placement and the need for surgical left ventricular assist device (LVAD) placement or heart transplantation; the occurrence of stroke, myocardial reinfarction, repeat PCI, coronary artery bypass grafting, major vascular complications, major bleeding, or hemolysis requiring extraction of the IABP or pMCS; device failure requiring extraction of the pMCS or IABP; and rehospitalization.

[63] 445 unique subjects with 1114 echocardiograms were analysed.

[64] Using Multiple Organ Dysfunction Score (MODS) and Sepsis-related Organ Failure Assessment (SOFA) criteria.

[65] The follow-up was planned for 6 months. The study was stopped due to futility, reducing the actual follow-up to 1 month.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Loss to follow-up, n (%)	1 month: 0 (0%) vs. 0 (0%) 6 months: NR	0 (0%) vs. 1 (4.2%)[66]	1 month: ITT: 0 (0) vs. 1 (0.45) PP: 0 (0) vs. 0 (0) 3 months: ITT: 1 (0.46) vs. 4 (1.8) PP: 1 (0.46) vs. 1 (0.47)	1 month: 6 (46.1%) vs. 6 (46.1%)
Efficacy outcomes				
Mortality, n (%)	Reported as Death at 1 month: 2 (28.6) vs. 0 (0); p=0.46	1 month all-cause mortality: 11 (46) vs. 12 (50); p=0.92 6-month all-cause mortality: 12 (50) vs. 12 (50); p=0.92	Reported as Death Intention-To-Treat Population: 1 month: 7.6% vs. 5.9%; p=0.473 3 months: 12.1% vs. 8.7%; p=0.244 Per-Protocol Population: 1 month: 6.9% vs. 6.2%; p=0.744 3 months: 11.6% vs. 9.0%; p=0.383	Reported as Death at 1 month: 6 (46) vs. 6 (46); p=NR
Hemodynamic variables	Reported as cardiac index change after 12 hours: -0.02 ±0.25 W/m^2 vs. 0.08 ±0.08 W/m^2; p=0.4 Reported as LVEF at 1 month: 38.6% ±14.4% vs. 40.6% ±12.5%; p=0.9	Reported as LVEF at 6 months: 46% ±11% vs. 49% ±9%; p=NR	Reported as drop in cardiac power output from baseline: -0.04 ±0.24 vs. -0.14 ±0.27 W; p=0.001 Reported as LVEF at 3 months: 27% ±9% vs. 33% ±11%; p=NR[67]	Reported as cardiac index change after 30 minutes: 0.49 ±0.46 l/min/m^2 vs. 0.11 ±0.31 l/min/m^2; p=0.02 Reported as LVEF at discharge: 35% ±17% vs. 45% ±17%; p=0.34
Length of hospitalization	NR	ICU LoS: 7 (3-16) vs. 7 (4-10)[68] Hospital LoS: 16 (3-26) vs. 10 (6-24)	NR	NR
Rehospitalization	NR	Reported as rehospitalization: 5 (21) vs. 1 (4); p=NR	NR	NR
Safety outcomes				
Overall complications, n (%)	NR	NR	Reported as composite of major adverse events[69]: Intention-To-Treat Population: At 1 month: 35.1% vs. 40.1%; p=0.277 At 3 months: 40.6% vs. 49.3%; p=0.066 Per-Protocol-Population: At 1 month: 34.3% vs. 42.2%; p=0.092 At 3 months: 40.0% vs. 51.0%; p=0.023	NR

[66] After 31 days

[67] The study authors state that the improvement in LVEF was similar between the two study groups.

[68] Values are median (25th to 75th percentile)

[69] The composite primary end point components included all-cause death, Q-wave or non-Q-wave myocardial infarction, stroke, or transient ischemic attack, any repeat revascularization procedure (PCI or coronary artery bypass grafting), need for a cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Serious adverse events (SAE), n (%)	NR	NR	NR	NR
Adverse events, n (%)	NR	NR	NR	NR
Major adverse cardiovascular events (MACE), n (%)	Overall: NR Individual events: Refractory heart failure: 3 (42.9) vs. 1 (16.7); p=0.55	Overall: NR Individual events: Myocardial (re)infarction: 1 (4) vs. 2 (8); p=NR	Overall: NR Individual events: Intention-To-Treat Population: Myocardial infarction: At 1 month: 13.8% vs. 10.4%; p=0.268 At 3 months: 12.1% vs 14.2%; p=0.512 Cardiopulmonary resuscitation/ ventricular arrhythmia: At 1 month: 2.2% vs. 3.2%; p=0.543 At 3 months: 2.2% vs. 4.1%; p=0.259 Severe hypotension requiring treatment: At 1 month: 4.9% vs. 8.6%; p=0.121 At 3 months: 4.0% vs. 5.5%; p=0.469 Per-Protocol Population: Myocardial infarction: At 1 month: 13.4% vs. 10.9%; p=0.425 At 3 months: 11.6% vs. 14.8%; p=0.340 Cardiopulmonary resuscitation/ ventricular arrhythmia: At 1 month: 2.3% vs. 3.3%; p=0.531 At 3 months: 2.3% vs. 4.3%; p=0.258 Severe hypotension requiring treatment: At 1 month: 4.6% vs. 9.0%; p=0.072 At 3 months: 3.7% vs. 5.7%; p=0.332	NR
Multiple organ complication, n (%)	Reported as Sepsis: 5 (71.4) vs. 3 (50.0); p=0.59	NR	NR	Reported as MODS and SOFA criteria[70]: No difference between groups in complex dysfunction scores[71]
Bleeding, n (%)	Reported as major bleeding: 5 (71.4) vs. 0 (0); p=0.02	Reported as major bleeding: 8 (33) vs. 2 (8); p=NR	NR	Reported as major bleeding: 0 (0) vs. 0 (0); p=NR
Need for additional device or transplant, n (%)	Reported as ECMO: 2 (28.6) vs. 1 (16.7); p=1	Reported as surgical LVAD placement: 0 (0) vs. 1 (4); p=NR Reported as heart transplantation: 0 (0) vs. 0 (0); p=NR	NR	NR

[70] Multi Organ Dysfunction Score (MODS) and Sepsis-related Organ Failure Assessment (SOFA)

[71] Results presented in a graph.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Need for surgery or procedure, n (%)	NR	Reported as repeat PCI: 0 (0) vs. 3 (13); p=NR Reported as CABG: 0 (0) vs. 1 (4); p=NR Reported as other surgery: 2 (8) vs. 0 (0); p=NR	Reported as repeat revascularization: Intention-To-Treat Population: At 1 month: 1.3% vs. 4.1%; p=0.075 At 3 months: 3.6% vs. 7.8%; p=0.056 Per-Protocol Population: At 1 month: 1.4% vs. 4.3%; p=0.072 At 3 months: 3.7% vs. 8.1%; p=0.055 Reported as need for cardiac or vascular operation[72]: Intention-To-Treat Population: At 1 month: 0.9% vs. 1.4%; p=0.642 At 3 months: 1.3% vs. 1.8%; p=0.681 Per-Protocol Population: At 1 month: 0.9% vs. 1.4%; p=0.634 At 3 months: 1.4% vs. 1.9%; p=0.680	NR
Vascular complications, n (%)	Reported as limb complication: 2 (28.6) vs. 0 (0); p=0.46	Reported as major vascular complication: 1 (4) vs. 0 (0); p=NR	NR	Reported as ischemia: 0 (0) vs. 0 (0); p=NR Reported as acute limb ischemia: 1 (7.7) vs. 0 (0); p=NR
Neurological complications, n (%)	NR	Reported as Stroke: 1 (4) vs. 1 (4); p=NR	Reported as Stroke/TIA Intention-To-Treat Population: At 1 month: 0.0% vs. 1.8%; p=0.043 At 3 months: 0.9% vs. 2.7%; p=0.144 Per-Protocol Population: At 1 month: 0.0% vs. 1.9%; p=0.042 At 3 months: 0.9% vs. 2.4%; p=0.240	Reported as neurological deficit: 0 (0) vs. 2 (15.4); p=NR
Renal complications, n (%)	NR	Reported as renal replacement therapy 8 (33) vs. 7 (29); p=NR	Reported as Acute renal dysfunction: Intention-To-Treat Population: At 1 month: 4.0% vs. 4.5%; p=0.792 At 3 months: 4.0% vs. 4.6%; p=0.776 Per-Protocol Population: At 1 month: 4.2% vs. 4.7%; p=0.774 At 3 months: 4.2% vs. 4.8%; p=0.774	NR
Respiratory complications, n (%)	NR	NR	NR	NR

[72] Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.

Study name, author, year	IMPELLA-STIC Study, Bochaton, 2020 [61]	IMPRESS Study, Ouweneel, 2017 [62]	PROTECT II Study, O'Neill, 2012 [63], Goldstein, 2017 [76]	ISAR-SHOCK Study, Seyfarth, 2008 [64]
Valvular damage, n (%)	NR	NR	Reported as aortic valve damage/increase in aortic insufficiency: Intention-To-Treat Population: 1 month: 0 (0) vs. 0 (0); p=NR 3 months: 0 (0) vs. 0 (0); p=NR Per-Protocol Population: 1 months: 0 (0) vs. 0 (0); p=NR 3 months: 0 (0) vs. 0 (0); p=NR Reported as Mitral valve regurgitation: Mitral valve regurgitation did not worsen after Impella implantation[73] Reported as Mitral valve stenosis: No evidence of significant Mitral valve stenosis at baseline, 1 month and 3 months[73] Reported as Aortic valve regurgitation: Aortic valve regurgitation did not worsen after Impella implantation[73] Reported as Aortic valve stenosis: No cases of structural derangement of the aortic valve after use of the Impella device[73]	NR
Device failure, technical failure, n (%)	2 (28.6) vs. 0 (0); p=NR	Reported as hemolysis requiring extraction of the device: 2 (8) vs. 0 (0); p=NR Reported as device failure requiring extraction: 0 (0) vs. 0 (0); p=NR	NR	Reported as hemolysis: Significantly increased in the Impella group in first 24 hours[74] Reported as device-related technical failure 0 (0) vs. 0 (0); p=NR
Procedural failure, n (%)	NR	NR	Reported as angiographic failure: Intention-To-Treat Population: At 1 month: 0.4% vs. 0.5%; p=0.992 At 3 months: 0.4% vs. 0.0%; p=0.322 Per-Protocol Population: At 1 month: 0.5% vs. 0.5%; p=0.987 At 3 months: 0.5% vs. 0.0%; p=0.322	NR

Abbreviations: AE – adverse events, AMI – acute myocardial infarction, CABG – coronary artery bypass grafting, CI – confidence interval, CPI – cardiac power index, CS – cardiogenic shock, ECMO – extracorporeal membrane oxygenation, GRADE – Grading of Recommendations Assessment, Development and Evaluation, IABP – intra-aortic balloon pump, ICU – intensive care unit, ITT – intention-to-treat, LV – left ventricle, LVAD – left ventricular assist device, LVEF – left ventricular ejection fraction, LoS – length of stay, MACE – major adverse cardiac events, MAE – major adverse events, MCS – mechanical circulatory support, MODS – multiple organ dysfunction syndrome, NR – not reported, p – p-value, pLVAD – percutaneous left ventricular assist devices, pMCS – percutaneous mechanical circulatory support, PP – per-protocol, pts – patients, PVAD – percutaneous ventricular assist device, RCT – randomised controlled trial, s.s.diff. – statistically significant difference, SAE – serious adverse events, SC – standard care, SOFA – sequential organ failure assessment, TIA – transient ischemic attack

[73] Findings presented as echocardiographic measurements.

[74] Results presented as graph.

Table A-3: Micro-axial pLVAD: results from observational studies

Author, year	Amin, 2020 [65]	Dhruva, 2020 [66]	Ogunbayo, 2018 [67]
Country	USA	USA	USA
Sponsor	None	Center of Excellence in Regulatory Science and Innovation (CERSI) grant to Yale University and Mayo Clinic from the FDA (U01FDOO5938)	University of Kentucky and Rochester General Hospital deemed the study exempt as it is a de-identified, publicly available database
Intervention/Product	Impella®	Intravascular microaxial LVAD	PVAD (Impella®)[75]
Comparator	IABP	IABP	IABP
Indication	PCI	AMI complicated by cardiogenic shock undergoing PCI	Cardiogenic shock from non-ischemic etiology
Study design	Propensity score-matched registry-based retrospective cohort study	Propensity score-matched registry-based retrospective cohort study	Registry-based retrospective cohort study
Number of pts	48,306	28,304	18,032
Analysed pts	4,782 vs. 43,524 propensity score-matched patients	1,680 vs. 1,680 propensity score-matched patients	1,414 vs. 16,619
Inclusion criteria	■ MCS with Impella or IABP ■ Availability of covariate information	■ All patients who underwent PCI for AMI complicated by cardiogenic shock between October 1, 2015, and December 31, 2017 ■ Patients with intravascular microaxial left ventricular assist device ■ Patients with IABP	■ Admission with a diagnosis of cardiogenic shock (ICD CM 9 code 785.51) from 2010 to 2014 ■ Patients that were managed with IABP or PVAD (ICD 9 CM codes 37.61 and 37.68 respectively)
Exclusion criteria	■ Did not receive MCS ■ Use of both Impella and IABP ■ Missing covariate information	■ Patients with medical therapy only ■ Patients with other mechnical circulatory support devices or multiple devices	■ AMI or any revascularization procedure during the hospital stay ■ Patients that were reported as being managed with both devices ■ Missing length of stay (LOS) ■ Missing mortality data
Age of patients in yrs, mean (SD)	67.85 (12.14) vs. 64.62 (12.63)	64.3 (11.9) vs. 64.0 (11.9); Standardized Mean Difference=0.03	55.8 ±17.2 vs. 59.5 ±15.1; p<0.001
Gender male, n (%)	3,465 (72.46) vs. 29,903 (68.7)	1,194 (71.1) vs. 1,198 (71.3); Standardized Mean Difference=0.06	1,022 (72.3) vs. 11,030 (66.4)
Reported co-morbidities at baseline, n (%)	Propensity-matched cohort, no statistically significant differences reported[76]	Propensity-matched cohort, no statistically significant differences reported[77]	History of LVAD: 25 (1.8%) vs. 64 (0.4%); p=0.0001

[75] The patient selection flow chart in the appendix shows that patients with Impella were extracted from the database.

[76] Patients in the intervention group had a higher prevalence of diabetes mellitus, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, multivessel disease, greater use of ticagrelor and bivalirudin, but less use of warfarin and glycoprotein Iib/IIIa. The intervention was used less in patients who required mechanical ventilation or who had cardiac arrest or cardiogenic shock.

[77] 74/75 characteristics of the propensity-matched cohorts had standardized mean difference below 0.10.

Author, year	Amin, 2020 [65]	Dhruva, 2020 [66]	Ogunbayo, 2018 [67]
Primary outcome measures	Trends in Impella use, variation in Impella use and its outcomes over 13 years from January 2004 to December 2016 Comparison of clinical outcomes (in-hospital mortality, bleeding requiring transfusion, AKI, and stroke)	In-hospital mortality[78] and in-hospital major bleeding[79]	Inpatient mortality
Secondary outcome measures	NR	NA	Length of stay
Length of follow-up	NA Timeframe of analysis: January 2004 to December 2016	NA Timeframe of analysis: October 1st 2015 to December 31st 2017	NA Timeframe of analysis: 2010 to 2014
Loss to follow-up, n (%)	NA	NA	NA
Efficacy outcomes			
Mortality, n (%)	Reported as in-hospital Mortality: Odds ratio (95% CI): 1.24 (1.13-1.36); p<0.0001[80]	Reported as Mortality during hospitalization: 756 (45.0) vs. 573 (34.1); p<0.001	Reported as Mortality during hospitalization: 734 (51.9) vs. 5,019 (30.2); p<0.001
Hemodynamic variables	NR	NR	NR
Length of hospitalization	Reported as length of stay, ß coefficient (95% CI): 0.04 (-0.08 – 0.16); p=0.524[81] Reported as intensive care unit length of stay, ß coefficient (95% CI): -0.04 (-0.12 – 0.04); p=0.319	NR	Reported as length of stay: 10 (21) vs. 13 (21); p<0.001
Rehospitalization	NR	NR	NR
Safety outcomes			
Overall complications, n (%)	NR	NR	NR
Serious adverse events (SAE), n (%)	NR	NR	NR
Adverse events, n (%)	NR	NR	NR
Major adverse cardiovascular events (MACE), n (%)	NR	NR	Reported as Cardiac arrest: 438 (31) vs. 4,609 (27.7); p=0.21 Reported as Pericardial effusion: 74 (5.2) vs. 556 (3.3); p=0.107 Reported as Cardiac tamponade: 59 (4.2) vs. 525 (3.2); p=0.351 Reported as Pericardiocentesis: 21 (1.5) vs. 149 (0.9); p=0.352
Multiple organ complication, n (%)	NR	NR	Reported as Septic shock: 203 (14.4) vs. 1,852 (11.1); p=0.095

[78] Captured in the Chest Pain-MI Registry.

[79] Defined using the Chest Pain-MI Registry as a decline in hemoglobin level of at least 3 g/dL; transfusion of whole blood or packed red blood cells; procedural intervention/surgery at bleeding site to treat the bleeding; or documented or suspected retroperitoneal bleed, gastrointestinal bleed, genitourinary bleed, or a bleed in a location not specified elsewhere.

[80] The odds ratio and its 95% CI are obtained from a hierarchical, mixed-effects logistic regression model with hospital as a random effect.

[81] Results are from mixed-effects hierarchical models that adjusted for the propensity scores and with hospitals as random effects.
Positive ß coefficients indicate higher values, whereas negative ß coefficients indicate lower values associated with the Impella era in comparison with the pre-Impella era.

Author, year	Amin, 2020 [65]	Dhruva, 2020 [66]	Ogunbayo, 2018 [67]
Bleeding, n (%)	Reported as Bleeding: Odds ratio (95% CI): 1.10 (1.00 – 1.21); p=0.0445	Reported as Major bleeding: 526 (31.3) vs. 268 (16.0); p<.001 Absolute Risk Difference (95% CI): 15.4 (12.5-18.2); p<.001	Reported as Hemorrhage: 64 (4.5) vs. 731 (4.4); p=0.904 Reported as Blood transfusion: 433 (30.6) vs. 4,321 (26); p=0.096
Need for additional device or transplant, n (%)	NR	NR	Reported as ECMO: 161 (11.4) vs. 917 (5.5); p<.001 Reported as biventricular external heart assist: 14 (1) vs. 70 (0.4); p=0.196 Reported as LVAD: 188 (13.3) vs. 2,211 (13.3); p=0.994
Need for additional device or transplant, n (%) *(continuation)*			Reported as Artificial heart: < 11 (<1)[82] vs. 72 (0.4); p=0.75 Reported as Intubation/mechanical ventilation: 965 (68.2) vs. 9916 (59.7); p=0.002 Reported as Heart transplant: 49 (3.5) vs. 749 (4.5); p=0.423
Need for surgery or procedure, n (%)	NR	NR	NR
Vascular complications, n (%)	NR	NR	Reported as vascular complications: NR vs. 310 (1.9); p=0.14
Neurological complications, n (%)	Reported as Stroke: Odds ratio (95% CI): 1.34 (1.18 – 1.53); p<0.0001	NR	Reported as TIA/Stroke: 83 (5.9) vs. 878 (5.3); p=0.665 Reported as All hemorrhagic stroke: 33 (2.4) vs. 278 (1.7); p=0.38
Renal complications, n (%)	Reported as Acute kidney injury: Odds ratio (95% CI): 1.08 (1.00 – 1.17); p=0.0521	NR	Reported as Acute renal failure: 1,023 (72.4) vs. 10,206 (61.4); p<.001 Reported as Acute renal failure requiring dialysis: 217 (15.4) vs. 1,734 (10.4); p=0.011 Reported as Hemodialysis: 232 (16.4) vs. 2,008 (12.1); p=0.034
Respiratory complications, n (%)	NR	NR	Reported as Pneumonia: 236 (16.7) vs. 3,433 (20.7); p=0.107 Reported as Respiratory failure: 1,037 (73.3) vs. 11,323 (68.1); p=0.083 Reported as Pulmonary embolism: 34 (2.4) vs. 497 (3); p=0.572 Reported as Pulmonary wedge pressure monitoring: 345 (24.4) vs. 3,939 (23.7); p=0.78
Valvular damage, n (%)	NR	NR	NR
Device failure, technical failure, n (%)	NR	NR	NR
Procedural failure, n (%)	NR	NR	NR

Abbreviations: *see Abbreviations Table A-2. p. 76*

[82] Due to NIS Data Use agreement, cells with small numbers cannot be published.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers (RJ, GG). In case of disagreement a third researcher (MW) was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [77] and in the Guidelines of EUnetHTA [78].

Table A-4: Risk of bias – study level (randomised studies), see [55]

Trial, Author, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
IMPELLA-STIC, Bochaton, 2020 [61]	High[83]	Moderate[84]	High[85]	Low	Moderate[86]	High
IMPRESS, Ouweneel, 2017 [62]	Low	Moderate[87]	Low	Low	Low	Moderate
PROTECT II, O'Neill, 2012 [63]	Moderate[88]	Low	Low	Moderate[89]	Low	Moderate
ISAR-SHOCK, Seyfarth, 2008 [64]	High[90]	Moderate[91]	Low	Moderate[92]	Low	High

[83] The randomization was performed in blocks while the carers delivering the intervention were unblinded.

[84] The carers delivering the intervention were aware of participants assigned intervention during the trial, no appropriate analysis used to estimate the effect of assignment to intervention.

[85] There was a potential for impact of the failure to analyse participants in the group to which they were randomized, as two of eight patients in the control group were excluded (one withdrew consent, one had non-ischaemic dilated myocardiopathy).

[86] No information on pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis.

[87] The carers delivering the intervention were aware of participants assigned intervention during the trial.

[88] Not enough information on randomization tool, unclear if allocation sequence was concealed.

[89] Outcome assessors were aware of the intervention received by study participants because of the different radiographic appearance. Knowledge of the presence of Impella support led to a greater and more aggressive use of rotational atherectomy in this subgroup.

[90] No information on randomization process, imbalance in baseline characteristics.

[91] No appropiate analysis used to estimate the effect of assignment to intervention.

[92] The duration of mechanical device usage after the primary end point was reached was left to the discretion of the physician.

Table A-5: Risk of bias (observational studies), see [56]

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Alaswad, 2018 [79]	Critical[93]	Serious[94]	Low	Low	Moderate[95]	Serious[96]	Low	Critical	-
Amin, 2020 [65]	Moderate[97]	Moderate[98]	Low	Low	Low	Low	Low	Moderate	included in evidence synthesis
Azzalini, 2020 [80]	Moderate[99]	Low	Low	Low	Serious[100]	Serious[101]	Low	Serious	-
Cohen, 2015 [81]	Moderate[102]	Serious[103]	Low	Low	Moderate[104]	Serious[105]	Low	Serious	-
Dhruva, 2020 [66]	Moderate[106]	Low	Low	Low	Low	Low	Low	Moderate	included in evidence synthesis

[93] There is a potential for confounding of the effect of intervention in the study (e.g., disease severity, medical history, etc.). Further, no adequate statistical analysis was conducted to control for confounding variables.

[94] Selection into the study was related to intervention and outcome, the indication for the PCI, the decision to use MCS before the PCI, and the choice of the MCS device used were made by the primary operator. The cVAD registry is limited to patients who received Impella support; other patients who received other forms of MCS or patients who received HRPCI without support are not included.

[95] 12% (122 patients) were excluded from this analysis because of missing information of baseline left ventricular function.

[96] Outcome assessors were aware of the received intervention.

[97] Important confounding domains were controlled and measured for, unmeasured confounding cannot be ruled out.

[98] The significant variation in outcomes observed among the subset of patients receiving Impella could result from the selection of patients.

[99] No appropriate analysis method that controlled for all the important confounding domains was used, the potential for unmeasured and residual confounding persists.

[100] Follow-up was not available for 25% (one-quarter) of patients.

[101] The assessors were aware of the intervention received by study participants.

[102] There is a potential for confounding of the effect of intervention in the study, no adequate statistical analysis was conducted to control for confounding variables.

[103] Selection into the study was related to intervention and outcome, all patients in the study received the Impella device (the study compared data from the USpella registry with the Impella arm of the PROTECT II trial).

[104] Risk of incosistent documentation in registry.

[105] The assessors were aware of the intervention received by study participants.

[106] Residual confounding whereby patients receiving intravascular microaxial LVADs had greater severity of illness than those receiving IABPs, important confounding domains appropriately measured and controlled for.

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Flaherty, 2020 [82]	Serious[107]	Low	Low	Low	Critical[108]	Critical[109]	Low	Critical	-
Garan, 2019 [83]	Moderate[110]	Low	Low	Critical[111]	Low	Critical[112]	Low	Critical	-
Lemor, 2020 [84]	Serious[113]	Moderate[114]	Moderate[115]	Low	Low	Low	Low	Serious	-
Ogunbayo, 2018 [67]	Moderate[116]	Low	Low	Moderate[117]	Low	Low	Low	Moderate	included in evidence synthesis
Philipson, 2020 [85]	Serious[113]	Low	Low	Low	Low	Low	Low	Serious	-

[107] There is a potential for confounding of the effect of intervention in the study (e.g., disease severity, medical history, etc.). Further, no adequate statistical analysis was conducted to control for confounding variables.

[108] Missing data for 28.9% of patients.

[109] Operators were not blinded to baseline Cr and additional measures to prevent AKI might have been taken.

[110] There is a potential for confounding of the effect of intervention in the study (e.g., disease severity, medical history, etc.). Regression analysis was used to control for confounders, however, the authors probably did not use an appropriate analysis method to control for all (e.g., time varying) confounders.

[111] There were devications from the intended interventions. In some 4/20 pts in the VA-ECMO group, pVAD was added and in some 20/31 pts in the pVAD first group, VA-ECMO was added.

[112] Outcome assessors probably had knowledge regarding and were aware of the intervention received.

[113] The decision on which type of MCS device to use was completely dependent on the operator and their institution preference, those who underwent Impella had higher prevalence of end-stage renal disease (ESRD) and COPD compared to the ECMO cohort.

[114] Use of ECMO more common in teaching hospitals.

[115] Using ICD-10 codes, the study authors were unable to determine if it was central or percutaneous ECMO.

[116] Multivariate analysis was used, but confounding bias cannot be ruled out completely.

[117] Co-interventions not fully balanced (ECMO).

Table A-6: Evidence profile: efficacy and safety of micro-axial pLVAD in cardiogenic shock

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
EFFICACY (Randomized controlled trials)										
Mortality (1 month)										
3 [61, 62, 64]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	44	43	None of the studies were able to detect a s.s.diff. in mortality at 1 month: IMPELLA-STIC: 2 (28.6) vs. 0 (0); p=0.46 IMPRESS: 11 (46) vs. 12 (50); p=0.92 ISAR-SHOCK: 6 (46) vs. 6 (46); p=NR	⊕⊕◯◯ Low
Mortality (6 months)										
1 [62]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	24	24	None of the studies were able to detect a s.s.diff. in mortality at 6 months IMPRESS: 12 (50) vs. 12 (50); p=0.92	⊕⊕◯◯ Low
Hemodynamic variables										
2 [61, 64]	RCT	Very serious[b]	Not serious	Serious[c]	Very serious[a]	none	20	19	One study was able to detect a s.s.diff. in cardiac index: ISAR-SHOCK: 0.49 ±0.46 l/min/m^2 vs. 0.11±0.31 l/min/m^2; p=0.02 One of the studies was not able to detect a s.s.diff. in cardiac index: IMPELLA-STIC: -0.02 ±0.25 W/m^2 vs. 0.08 ±0.08 W/m^2; p=0.4 None of the studies were able to detect a s.s.diff. in LVEF: IMPELLA-STIC: 38.6% ±14.4% vs. 40.6% ±12.5%; p=0.9 ISAR-SHOCK: 35% ±17% vs. 45% ±17%; p=0.34	⊕◯◯◯ Very low
Length of hospitalization										
1 [62]	RCT	Serious[d]	Not serious	Not serious	Very serious[a]	none	24	24	IMPRESS: Hospital LoS: 16 (3-26) vs. 10 (6-24) ICU LoS: 7 (3-16) vs. 7 (4-10)	⊕◯◯◯ Very low
Rehospitalization										
1 [62]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	24	24	IMPRESS: 5 (21) vs. 1 (4); p=NR	⊕⊕◯◯ Low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
SAFETY (Randomized controlled trials)										
Major adverse cardiovascular events (MACE)										
2 [61, 62]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	31	30	IMPELLA-STIC: Refractory heart failure: 3 (42.9) vs. 1 (16.7); p=0.55 IMPRESS: Myocardial (re)infarction: 1 (4) vs. 2 (8); p=NR	⊕⊕◯◯ Low
Multiple organ complication										
2 [61, 64]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	20	19	IMPELLA-STIC: Sepsis 5 (71.4) vs. 3 (50.0); p=0.59 ISAR-SHOCK: Reported as MODS and SOFA criteria: No difference between groups in complex dysfunction scores	⊕⊕◯◯ Low
Bleeding										
3 [61, 62, 64]	RCT	Not serious	Not serious	Not serious	Very Serious[e]	none	44	43	Major Bleeding IMPELLA-STIC: 5 (71.4) vs. 0 (0); p=0.02 IMPRESS: 8 (33) vs. 2 (8); p=NR ISAR-SHOCK: 0 (0) vs. 0 (0); p=NR	⊕⊕◯◯ Low
Need for additional device or transplant										
2 [61, 62]	RCT	Serious[d]	Not serious	Not serious	Very serious[a]	none	31	30	ECMO: IMPELLA-STIC: 2 (28.6) vs. 1 (16.7); p=1 IMPRESS Surgical LVAD placement: 0 (0) vs. 1 (4); p=NR Heart transplantation: 0 (0) vs. 0 (0); p=NR	⊕◯◯◯ Very low
Need for surgery or procedure										
1 [62] IMPRESS	RCT	Serious[d]	Not serious	Not serious	Very serious[a]	none	24	24	Repeat PCI: 0 (0) vs. 3 (13); p=NR CABG: 0 (0) vs. 1 (4); p=NR Other surgery: 2 (8) vs. 0 (0); p=NR	⊕◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
Vascular complications										
3 [61, 62, 64]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	44	43	Major vascular complication: IMPRESS: 1 (4) vs. 0 (0); p=NR Limb complication: IMPELLA-STIC: 2 (28.6) vs. 0 (0); p=0.46 ISAR-SHOCK: 1 (7.7) vs. 0 (0); p=NR Ischemia: ISAR-SHOCK: 0 (0) vs. 0 (0); p=NR	⊕⊕◯◯ Low
Neurological complications										
2 [62, 64]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	37	37	Stroke: IMPRESS: 1 (4) vs. 1 (4); p=NR Neurological deficit: ISAR-SHOCK: 0 (0) vs. 2 (0.33); p=NR	⊕⊕◯◯ Low
Renal complications										
1 [62]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	24	24	Renal replacement therapy IMPRESS: 8 (33) vs. 7 (29); p=NR	⊕⊕◯◯ Low
Device failure, technical failure										
3 [61, 62, 64]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	44	43	Device failure: IMPELLA-STIC: 2 (28.6) vs. 0 (0); p=NR IMPRESS: 0 (0) vs. 0 (0); p=NR ISAR-SHOCK: 0 (0) vs. 0 (0); p=NR Hemolysis: IMPRESS: 2 (8) vs. 0 (0); p=NR ISAR-SHOCK: Significantly increased in the micro-axial pLVAD group in first 24 hours	⊕⊕◯◯ Low
SAFETY (Observational studies)										
Major adverse cardiovascular events (MACE)										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Cardiac arrest: 438 (31) vs. 4609 (27.7); p=0.21 Pericardial effusion: 74 (5.2) vs. 556 (3.3); p=0.107 Cardiac tamponade: 59 (4.2) vs. 525 (3.2); p=0.351 Pericardiocentesis: 21 (1.5) vs. 149 (0.9); p=0.352	⊕◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
Multiple organ complication										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Septic shock: 203 (14.4) vs. 1852 (11.1); p=0.095	⊕◯◯◯ Very low
Bleeding										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Hemorrhage: 64 (4.5) vs. 731 (4.4); p=0.904 Blood transfusion: 433 (30.6) vs. 4321 (26); p=0.096	⊕◯◯◯ Very low
Need for additional device or transplant										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	ECMO: 161 (11.4) vs. 917 (5.5); p<.001 Biventricular external heart assist: 14 (1) vs. 70 (0.4); p=0.196 LVAD: 188 (13.3) vs. 2211 (13.3); p=0.994 Artificial heart: < 11 (<1)[118] vs. 72 (0.4); p=0.75 Intubation/mechanical ventilation: 965 (68.2) vs. 9916 (59.7); p=0.002 Heart transplant: 49 (3.5) vs. 749 (4.5); p=0.423	⊕◯◯◯ Very low
Vascular complications										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Vascular complications: NR vs. 310 (1.9); p=0.14	⊕◯◯◯ Very low
Neurological complications										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	TIAStroke: 83 (5.9) vs. 878 (5.3); p=0.665 All hemorrhagic stroke: 33 (2.4) vs. 278 (1.7); p=0.38	⊕◯◯◯ Very low
Renal complications										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Acute renal failure: 1023 (72.4) vs. 10206 (61.4); p<.001 Acute renal failure requiring dialysis: 217 (15.4) vs. 1734 (10.4); p=0.011 Hemodialysis: 232 (16.4) vs. 2008 (12.1); p=0.034	⊕◯◯◯ Very low

[118] Due to NIS Data Use agreement, cells with small numbers cannot be published.

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
Respiratory complications										
1 [67]	Observational study	Serious[f]	Not serious	Not serious	Not serious	none	1,414	16,619	Pneumonia: 236 (16.7) vs. 3433 (20.7); p=0.107 Respiratory failure: 1037 (73.3) vs. 11323 (68.1); p=0.083 Pulmonary embolism: 34 (2.4) vs. 497 (3); p=0.572 Pulmonary wedge pressure monitoring: 345 (24.4) vs. 3939 (23.7); p=0.78	⨁◯◯◯ Very low

Abbreviations: CABG – coronary artery bypass grafting, CS – cardiogenic shock, ECMO – extracorporeal membrane oxygenation, GRADE – Grading of Recommendations Assessment, Development and Evaluation, IABP – intra-aortic balloon pump, ICU – intensive care unit, ITT – intention-to-treat, LVAD – left ventricular assist device, LVEF – left ventricular ejection fraction, LoS – length of stay, MACE – major adverse cardiac events, MODS – multiple organ dysfunction syndrome, NR – not reported, p – p-value, PCI – percutaneous coronary intervention, pLVAD – percutaneous left ventricular assist devices, pts – patients, RCT – randomised controlled trial, s.s.diff. – statistically significant difference, SC – standard care, SOFA – sequential organ failure assessment, TIA – transient ischemic attack

Explanations:

[a] *Small number of patients, studies were statistically underpowered to detect a difference in this outcome.*

[b] *The duration of mechanical device usage after the primary end point was reached was left to the discretion of the physician.*

[c] *1/2 studies measured this outcome for a duration longer than 30 minutes, limiting generalizability of device effects on duration longer than 30 minutes.*

[d] *The carers delivering the intervention were aware of participants assigned intervention during the trial.*

[e] *Small number of patients, one of the studies included 15 instead of the 60 intended patients (due to slow recruitment and guideline changes regarding IABP use).*

[f] *Retrospective data collection; differences in events during hospital stay that could have influenced the outcome.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or 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)

Table A-7: Evidence profile: efficacy and safety of micro-axial pLVAD in high-risk PCI

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
EFFICACY (Randomized controlled trials)										
Mortality (1 month)										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	The study was not able to detect a s.s.diff. in mortality at 1 month: ITT: 7.6% vs. 5.9%; p=0.473	⨁⨁◯◯ Low
Mortality (3 months)										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	The study was not able to detect a s.s.diff. in mortality 3 months: ITT: 12.1% vs. 8.7%; p=0.244	⨁⨁◯◯ Low
Hemodynamic variables										
1 [63]	RCT	Very serious[b]	Not serious	Not serious	Very serious[a]	none	225	223	The study was able to detect a s.s. diff. in drop in cardiac power output from baseline: -0.04 ±0.24 W vs. -0.14 ±0.27 W; p=0.001 The study was not able to detect a s.s.diff. in LVEF at 3 months: 27% ±9% vs. 33% ±11%; p=NR	⨁◯◯◯ Very low
SAFETY (Randomized controlled trials)										
Overall complications										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Composite of major adverse events: At 1 month: ITT: 35.1% vs. 40.1%; p=0.277 At 3 months: ITT: 40.6% vs. 49.3%; p=0.066	⨁⨁◯◯ Low
Major adverse cardiovascular events (MACE)										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Myocardial infarction: At 1 month: 13.8% vs. 10.4%; p=0.268 At 3 months: 12.1% vs 14.2%; p=0.512 Cardiopulmonary resuscitation/ventricular arrhythmia: At 1 month: 2.2% vs. 3.2%; p=0.543 At 3 months: 2.2% vs. 4.1%; p=0.259 Severe hypotension requiring treatment: At 1 month: 4.9% vs. 8.6%; p=0.121 At 3 months: 4.0% vs. 5.5%; p=0.469	⨁⨁◯◯ Low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
Need for surgery or procedure										
1 [63]	RCT	Serious[c]	Not serious	Not serious	Very serious[a]	none	225	223	Reported as repeat revascularization: Intention-To-Treat Population: At 1 month: 1.3% vs. 4.1%; p=0.075 At 3 months: 3.6% vs. 7.8%; p=0.056 Reported as need for cardiac or vascular operation[119]: Intention-To-Treat Population: At 1 month: 0.9% vs. 1.4%; p=0.642 At 3 months: 1.3% vs. 1.8%; p=0.681	⊕⊕◯◯ Very low
Neurological complications										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Reported as Stroke/TIA Intention-To-Treat Population: At 1 month: 0.0% vs. 1.8%; p=0.043 At 3 months: 0.9% vs. 2.7%; p=0.144	⊕⊕◯◯ Low
Renal complications										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Reported as Acute renal dysfunction: Intention-To-Treat Population: At 1 month: 4.0% vs. 4.5%; p=0.792 At 3 months: 4.0% vs. 4.6%; p=0.776	⊕⊕◯◯ Low
Valvular damage										
1 [63, 76]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Reported as aortic valve damage/increase in aortic insufficiency: Intention-To-Treat Population: 1 month: 0 (0) vs. 0 (0); p=NR 3 months: 0 (0) vs. 0 (0); p=NR Reported as Mitral valve regurgitation: Mitral valve regurgitation did not worsen after Impella implantation[73] Reported as Mitral valve stenosis: No evidence of significant Mitral valve stenosis at baseline, 1 month and 3 months[120]	⊕⊕◯◯ Low

[119] Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.

[120] Findings presented as echocardiographic measurements

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Micro-axial pLVAD + SC	SC with IABP		
1 [63, 76] *(continuation)*									Reported as Aortic valve regurgitation: Aortic valve regurgitation did not worsen after Impella implantation[73] Reported as Aortic valve stenosis: No cases of structural derangement of the aortic valve after use of the Impella device[73]	
Procedural failure										
1 [63]	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	225	223	Reported as angiographic failure: Intention-To-Treat Population: At 1 month: 0.4% vs. 0.5%; p=0.992 At 3 months: 0.4% vs. 0.0%; p=0.322	⊕⊕◯◯ Low
SAFETY (Observational studies)										
Bleeding										
2 [65, 66]	Observational study	Not serious[d]	Not serious	Not serious	Not serious	none	6,462	45,204	Odds ratio (95% CI): 1.10 (1.00 – 1.21); p=0.0445 526 (31.3) vs. 268 (16.0); p<.001 Absolute Risk Difference (95% CI): 15.4 (12.5-18.2); p<.001	⊕⊕◯◯ Low
Neurological complications										
1 [65]	Observational study	Not serious[d]	Not serious	Not serious	Not serious	none	4,782	43,524	Stroke: Odds ratio (95% CI): 1.34 (1.18 – 1.53); p<0.0001	⊕⊕◯◯ Low
Renal complications										
1 [65]	Observational study	Not serious[d]	Not serious	Not serious	Not serious	none	4,782	43,524	Acute kidney injury: Odds ratio (95% CI): 1.08 (1.00 – 1.17); p=0.0521	⊕⊕◯◯ Low

Abbreviations: CABG – coronary artery bypass grafting, CS – cardiogenic shock, ECMO – extracorporeal membrane oxygenation, GRADE – Grading of Recommendations Assessment, Development and Evaluation, IABP – intra-aortic balloon pump, ICU – intensive care unit, ITT – intention-to-treat, LVAD – left ventricular assist device, LVEF – left ventricular ejection fraction, LoS – length of stay, MACE – major adverse cardiac events, MODS – multiple organ dysfunction syndrome, NR – not reported, p – p-value, PCI – percutaneous coronary intervention, pLVAD – percutaneous left ventricular assist devices, pts – patients, RCT – randomised controlled trial, s.s.diff. – statistically significant difference, SC – standard care, SOFA – sequential organ failure assessment, TIA – transient ischemic attack

Explanations:

[a] *The study was statistically underpowered to detect a difference in this outcome.*

[b] *The duration of mechanical device usage was left to the discretion of the physician.*

[c] *The carers delivering the intervention were aware of participants assigned intervention during the trial.*

[d] *Retrospective data collection with appropriate data analysis by propensity score matching.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or 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)

Applicability table

Table A-8: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Cardiogenic shock: Within the included studies, this patient population was covered by three RCTs and one observational study. The inclusion criteria of the studies reflected the intended patient population for the technology. However, differences in inclusion criteria and exclusion criteria across different studies could limit the applicability to the target population. High-risk percutaneous coronary intervention: Within the included studies, this patient population was covered by one RCT and two observational studies. The inclusion criteria of the studies reflected the intended patient population for the technology. However, as there is no general definition of high-risk percutaneous coronary interventions, differences in this patient population within studies could arise.
Intervention	All of the included studies used micro-axial pLVAD as an intervention. Differences were present in the RCTs with specific types of micro-axial pLVAD, e.g., Impella LP5.0®, Impella CP®, or Impella 2.5®. In the registry based observational studies, the used intervention was described as intravascular microaxial LVAD or PVAD (Impella® devices), regardless of device type. The device types differ according to sheath size and maximum duration of mechanical circulatory support, hence comparison between device types is limited.
Comparators	All of the included studies used intra-aortic balloon pumps as comparator. None of the included studies used conservative management as comparator to mechanical circulatory support using micro-axial pLVAD.
Outcomes	For effectiveness outcomes, the crucial outcome mortality was reported by all four RCTs. However, only one of the four RCTs reported mortality as primary outcome measure. Hemodynamic variables were reported by all four RCTs. The length of hospitalization, intensive care unit length-of-stay and rate of rehospitalization was reported by one RCT. Regarding safety outcomes, no standardised reporting of composite adverse events (such as MACE, SAE or AE) was available. Therefore, different definitions for individual adverse outcome events were present and different complications were judged worthwhile to be reported. Hence, the applicability for safety is limited and must be interpreted with caution.
Setting	The included RCTs were conducted as multicenter studies in different geographical regions (one RCT in France, another RCT in the Netherlands and Norway, another RCT in USA, Canada and Europe and another RCT in Germany). The included observational studies were based on registries from the USA. It is not expected that the applicability of the results are limited by geographic settings. The procedures took place in an inpatient setting in operating rooms and cardiac catheterization laboratories, reflecting the clinical setting where the technology is deployed. Clinical expertise with temporary mechanical circulatory support, such as micro-axial pLVAD, is needed. The clinical setting and the need for clinical expertise are applicable to the Austrian context.

Abbreviations: AE – adverse events, LVAD – left ventricular assist device, MACE – major adverse cardiovascular events, pLVAD – percutaneous left ventricular assist device, PVAD – percutaneous ventricular assist device, RCT – randomised controlled trial, SAE – serious adverse events, USA – United States of America

List of ongoing randomised controlled trials

Table A-9: List of ongoing randomised controlled trials of micro-axial pLVAD

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	N of pts planned	Primary completion date	Sponsor
NCT01633502/ DanSchock	Cardiogenic Shock	Impella CP®	Conventional circulatory support	**Death from all causes** [Time Frame: minimum follow-up 6 months]	360	01/2023	Odense University Hospital
NCT03431467/ REVERSE	Cardiogenic Shock	VA-ECMO with early institution of Impella CP® LV venting	VA-ECMO alone per standard clinical protocol	**Recovery from cardiogenic shock.** [Time Frame: At thirty days.]	96	01/2021	University of Pennsylvania
NCT04321148/ Protect Kidney Trial	Pts with induced acute kidney injury undergoing high risk PCI	Impella®-protected PCI	Standard of care PCI	**Incidence rate of Contrast-induced acute kidney injury** (CI-AKI) [Time Frame: 2 days after PCI]	224	03/2022	Heinrich-Heine University, Duesseldorf
NCT03947619/ DTU-STEMI	ST Elevation (STEMI) Myocardial Infarction of Anterior Wall undergoing PCI	Impella CP® placement prior to reperfusion with Primary PCI	Primary PCI	**Infarct Size** [Time Frame: 3-5 days post-procedure]	668	10/2023	Abiomed Inc.
NCT04562272/ UNLOAD-AMI	Myocardial Infarction Remodeling, Ventricular Shock, Cardiogenic	LV mechanical unloading by Impella-CP®	Standard treatment of AMI after PCI according to guidelines	**Difference in the left ventricular end-systolic volume** [Time Frame: LV end-systolic volume measured during the index hospitalization (day 5-7) and at 3 months] **Occurrence of LV remodeling** [Time Frame: LV end-systolic volume measured during the index hospitalization (day 5-7) and at 3 months] **Extent of post-infarct scar** [Time Frame: LV scar extent measured during the index hospitalization (day 5-7) and at 3 months]	80	12/2022	Institute for Clinical and Experimental Medicine

Abbreviations: AMI – acute myocardial infarction, CI-AKI – contrast-induced acute kidney injury, LV – left ventricle, PCI – percutaneous coronary intervention, pts – patients, STEMI – ST-elevation myocardial infarction, VA-ECMO – veno-arterial extracorporeal membrane oxygenation

Literature search strategies

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily <1946 to December 15, 2020>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <2016 to December 15, 2020>	
Search date: 16.12.2020	
ID	Search
1	exp Shock, Cardiogenic/ (10640)
2	(cardiogenic adj shock*).mp. (16128)
3	cardio-genic shock*.mp. (1)
4	((percutaneous adj coronary adj2 (intervention* or revasculari*)) or PCI or Percutaneous transluminal coronary angioplast* or PTCA or Percutaneous transluminal angioplast* or (Coronary adj (angioplast* or stent*)) or balloon angioplast*).mp. (107860)
5	exp Angioplasty/ (67367)
6	(angioplast* or endoluminal repair*).mp. (88454)
7	Percutaneous Coronary Intervention/ (31507)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (167568)
9	exp Heart-Assist Devices/ (18916)
10	(((heart or ventric* or vascular* or percutaneous) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or mechanical circulatory support).mp. (27691)
11	flow pump*.mp. (943)
12	LVAD*.ti,ab. (7321)
13	PVAD*.ti,ab. (243)
14	micro-axial*.mp. (50)
15	microaxial*.mp. (191)
16	mechanic* assist* device*.mp. (428)
17	Impella*.mp. (1543)
18	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (28739)
19	8 and 18 (4177)
20	limit 19 to clinical trial, all (116)
21	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (5470205)
22	19 and 21 (726)
23	20 or 22 (760)
24	limit 19 to (meta analysis or "systematic review") (63)
25	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (756740)
26	19 and 25 (179)
27	24 or 26 (181)
28	limit 19 to observational study (93)
29	limit 19 to multicenter study (191)
30	exp Technology Assessment, Biomedical/ (12869)
31	Technolog* Assessment*.mp. (18800)
32	HTA*.mp. (6920)
33	30 or 31 or 32 (23815)
34	19 and 33 (8)
35	23 or 27 or 28 or 29 or 34 (994)
36	limit 35 to dt=20151207-20201216 (703)
37	limit 36 to (english or german) (693)
38	remove duplicates from 37 (345)
Total hits: 345	

Search strategy for Embase

Search Name: Percutaneous ventricular flow pumps (MEL 2021)		
Search date: 16.12.2020		
No.	Query Results	Results
#35.	#34 AND [7-12-2015]/sd AND ([english]/lim OR [german]/lim)	877
#34.	#33 AND [7-12-2015]/sd	884
#33.	#22 OR #24 OR #25 OR #26 OR #27 OR #32	1,337
#32.	#21 AND #31	11
#31.	#28 OR #29 OR #30	26,923
#30.	hta*:ti,ab,de,lnk,kw	9,421
#29.	'technolog* assessment*':ti,ab,de,lnk,kw	21,151
#28.	'biomedical technology assessment'/exp	15,011
#27.	#21 AND 'multicenter study'/de	203
#26.	#21 AND 'observational study'/de	264
#25.	#21 AND ('meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de)	248
#24.	#21 AND #23	824
#23.	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,663,750
#22.	#8 AND #20 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)	509
#21.	#8 AND #20	8,386
#20.	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	51,764
#19.	impella*:ti,ab,de,lnk,kw,dn	2,807
#18.	'impella'/exp	267
#17.	'left ventricular assist device'/exp	16,624
#16.	'mechanic* assist* device*':ti,ab,de,lnk,kw	508
#15.	'microaxial*':ti,ab,de,lnk,kw	334
#14.	'micro axial*':ti,ab,de,lnk,kw	86
#13.	pvad*:ti,ab	479
#12.	lvad*:ti,ab	13,116
#11.	'flow pump*':ti,ab,de,lnk,kw	1,212
#10.	(((heart OR ventric* OR vascular* OR percutaneous) NEAR/3 assist* NEAR/3 (device* OR pump* OR system* OR treat* OR therap* OR surg*)):ti,ab,de,lnk,kw) OR 'mechanical circulatory support':ti,ab,de,lnk,kw	36,322
#9.	'heart assist device'/exp	42,238
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	201,186
#7.	'percutaneous coronary intervention'/exp	104,748
#6.	angioplast*:ti,ab,de,lnk,kw OR 'endoluminal repair*':ti,ab,de,lnk,kw	99,567
#5.	'angioplasty'/exp	91,778
#4.	(((percutaneous NEAR/1 coronary NEAR/2 (intervention* OR revasculari*)):ti,ab,lnk,de) OR pci:ti,ab,lnk,de OR 'percutaneous transluminal coronary angioplast*':ti,ab,lnk,de OR ptca:ti,ab,lnk,de OR 'percutaneous transluminal angioplast*':ti,ab,lnk,de OR ((coronary NEAR/1 (angioplast* OR stent*)):ti,ab,lnk,de) OR balloon:ti,ab,lnk,de) AND angioplast*:ti,ab,lnk,de,kw	76,272
#3.	'cardio-genic shock*':ti,ab,lnk,de,kw	35
#2.	(cardiogenic NEAR/1 shock*):ti,ab,lnk,de,kw	32,069
#1.	'cardiogenic shock'/exp	28,464
Total hits: 877		

Search strategy for Cochrane

Search Name: Percutaneous ventricular flow pumps (MEL 2021)	
Last Saved: 16/12/2020 20:19:16	
Comment: (RJ/GG) 161220	
ID	Search
#1	MeSH descriptor: [Shock, Cardiogenic] explode all trees
#2	(cardiogenic NEXT shock*) (Word variations have been searched)
#3	(cardio-genic shock*) (Word variations have been searched)
#4	(((percutaneous NEXT coronary NEAR (intervention* OR revasculari*)) OR PCI OR "Percutaneous transluminal coronary angioplast*" OR PTCA OR "Percutaneous transluminal angioplast*" OR (Coronary NEXT (angioplast* OR stent*)) OR "balloon angioplast*")) (Word variations have been searched)
#5	MeSH descriptor: [Angioplasty] explode all trees
#6	(angioplast* OR "endoluminal repair*") (Word variations have been searched)
#7	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH descriptor: [Heart-Assist Devices] explode all trees
#10	((((heart OR ventric* OR vascular* OR percutaneous) NEAR assist* NEAR (device* OR pump* OR system* OR treat* OR therap* OR surg*)) OR "mechanical circulatory support")) (Word variations have been searched)
#11	("flow pump*") (Word variations have been searched)
#12	(LVAD*):ti,ab,kw (Word variations have been searched)
#13	(PVAD*):ti,ab,kw (Word variations have been searched)
#14	(micro-axial*) (Word variations have been searched)
#15	(microaxial*) (Word variations have been searched)
#16	("mechanic* assist* device*") (Word variations have been searched)
#17	(Impella*) (Word variations have been searched)
#18	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#8 AND #18
#20	#19 with Cochrane Library publication date Between Dec 2015 and Dec 2020
#21	#19 with Publication Year from 2015 to 2020, in Trials
#22	#20 OR #21
Total hits: 160	

Search strategy for CRD (DARE, NHS-EED, HTA)

#### Percutaneous circulatory flow pump (Impella) MEL2021 (JR/GG)	
Search date: 16.12.2020	
ID	Search
1	MeSH DESCRIPTOR Shock, Cardiogenic EXPLODE ALL TREES
2	(cardiogenic NEAR shock*)
3	(cardio-genic shock*)
4	((((percutaneous NEAR coronary NEAR (intervention* OR revasculari*)) OR PCI OR "Percutaneous transluminal coronary angioplast*" OR PTCA OR "Percutaneous transluminal angioplast*" OR (Coronary NEAR (angioplast* OR stent*)) OR "balloon angioplast*")))
5	MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES
6	(angioplast* OR "endoluminal repair*")
7	MeSH DESCRIPTOR Percutaneous Coronary Intervention EXPLODE ALL TREES
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	MeSH DESCRIPTOR Heart-Assist Devices EXPLODE ALL TREES

10	(((((heart OR ventric* OR vascular* OR percutaneous) NEAR assist* NEAR (device* OR pump* OR system* OR treat* OR therap* OR surg*)) OR "mechanical circulatory support")))
11	(flow pump*)
12	(mechanic* assist* device*)
13	#9 OR #10 OR #11 OR #12
14	#8 AND #13
15	(LVAD*)
16	(PVAD*)
17	(Impella*)
18	#14 OR #15 OR #16 OR #17
19	(#18) WHERE LPD FROM 07/12/2015 TO 16/12/2020
Total hits: 10	

Search strategy for HTA-INAHTA

Search #19 limited to 2015-2020	
Date of search: 16.12.2020	
Query Nr.	Search query,"Hits","Searched At"
19	("mechanical assist*") OR ("ventricular support*") OR ("ventricular assist*") OR (Impella*) OR (PVAD*) OR (LVAD*) OR ("flow pump*") OR ("mechanical circulatory support*"),"52","2020-12-11T18:48:45.000000Z"
18	"mechanical assist*","0","2020-12-11T18:48:45.000000Z"
17	"ventricular support*","2","2020-12-11T18:48:45.000000Z"
16	"ventricular assist*","42","2020-12-11T18:48:45.000000Z"
15	Impella*,"13","2020-12-11T18:48:45.000000Z"
14	PVAD*,"0","2020-12-11T18:48:45.000000Z"
13	LVAD*,"19","2020-12-11T18:48:45.000000Z"
12	"flow pump*","0","2020-12-11T18:48:45.000000Z"
11	"mechanical circulatory support*","1","2020-12-11T18:48:45.000000Z"
10	("mechanical assist*") OR ("ventricular support*") OR ("ventricular assist*") OR (Impella*) OR (PVAD*) OR (LVAD*) OR ("flow pump*") OR ("mechanical circulatory support*"),"52","2020-12-11T18:46:53.000000Z"
9	("mechanical assist*") OR ("ventricular support*") OR ("ventricular assist*") OR (Impella*) OR (PVAD*) OR (LVAD*) OR ("flow pump*") OR ("mechanical circulatory support*"),"52","2020-12-11T18:46:53.000000Z"
8	"mechanical assist*","0","2020-12-11T18:46:53.000000Z"
7	"ventricular support*","2","2020-12-11T18:46:53.000000Z"
6	"ventricular assist*","42","2020-12-11T18:46:53.000000Z"
5	Impella*,"13","2020-12-11T18:46:53.000000Z"
4	PVAD*,"0","2020-12-11T18:46:53.000000Z"
3	LVAD*,"19","2020-12-11T18:46:53.000000Z"
2	"flow pump*","0","2020-12-11T18:46:53.000000Z"
1	"mechanical circulatory support*","1","2020-12-11T18:46:53.000000Z"
Total Hits: 16	

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