HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Percutaneous coronary interventions (PCI) for chronic total occlusion (CTO)

Update 2022
Systematic Review

AIHTA Decision Support Document: 64/1. Update 2022
ISSN-online: 1998-0469

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Percutaneous coronary interventions (PCI) for chronic total occlusion (CTO)

Update 2022
Systematic Review

Vienna, March 2022

Project Team

Project leader: Gregor Goetz, MSSc MPH; AIHTA

Authors: Univ. Ass. Mag. rer. nat. Thomas Semlitsch, Carolin Zipp, BA, MA, Mag.a (FH) Christine Loder, MPH; Institute of General Practice and Evidence-Based Health Services Research, Medical University of Graz

Project Support

Systematic literature search: Tarquin Mittermayr, MA; AIHTA

External Review: PD Dr. med. Kambis Mashayekhi; MEDICLIN Herzzentrum Lahr, Lahr, Deutschland

Internal Review: Gregor Goetz, MSSc MPH; AIHTA

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

This report should be referenced as follows

Semlitsch, Th., Zipp, C., Loder, C. Percutaneous coronary interventions (PCI) for chronic total occlusion (CTO). AIHTA Decision Support Documents No. 64/1. Update 2022; 2022. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest

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

Disclaimer

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

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

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

IMPRINT

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

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

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

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

AIHTA Decision Support Documents No.: 64/1.

ISSN online 1998-0469

Content

List of figures

List of tables

List of abbreviations

AMSTAR ..... a measurement tool to assess systematic reviews
AP ..... angina pectoris
CABG ..... coronary artery bypass graft
CHD ..... coronary heart disease
CRD ..... Centre of Review and Dissemination
CTO ..... chronic total occlusion
DES ..... drug-eluting stent
EQ-5D ..... European quality of life-5 dimensions
HrQoL ..... health related quality of life
IQR ..... interquartile range
LAD ..... left anterior descending coronary artery
LCx ..... left circumflex coronary artery
LVEF ..... left ventricular ejection fraction
MACE ..... major adverse cardiac event
MD ..... mean difference
MI ..... myocardial infarction
n.a. ..... not applicable
OMT ..... optimal medical therapy
OR ..... odds ratio
PCI ..... percutaneous coronary intervention
QoL ..... quality of life
RCA ..... right coronary artery
RCT ..... randomised controlled trial
RoB ..... risk of bias
ROBINS-I ..... risk of bias in non-randomised studies – of interventions
RR ..... risk ratio
SAQ ..... Seattle angina questionnaire
SD ..... standard deviation
SF-36 ..... Short form 36
STEMI ..... ST-segment elevation myocardial infarction
TIMI ..... thrombolysis in myocardial infarction
TVR ..... target vessel revascularisation
vs. ..... versus
WHO-ICTRP ..... World Health Organisation – International clinical trial register platform

Executive Summary

Introduction

This report is the first update of the systematic review on "Percutaneous coronary interventions (PCI) for chronic total occlusion (CTO)" initially prepared in March 2013.

Health Problem

Coronary heart disease (CHD) is the most common cause of death in developed countries. Chronic Total Occlusions (CTOs) are defined as completely occluded coronary arteries with an occlusion duration of at least three months. The primary treatment for CHD is a drug therapy. However, coronary bypass surgery (CABG) or percutaneous coronary intervention (PCI) may also be indicated. The selection of a suitable therapy is based on an individual risk stratification.

CTO – chronic total occlusion of coronary artery for ≥ 3 months

Description of Technology

The main purpose of a CTO PCI is to relieve angina pectoris (AP) symptoms and to prolong life expectancy, and to avoid more invasive interventions such as CABG. In contrast to PCIs for only stenosed vessels, reopening of a CTO is much more complex. A microcatheter is used to deliver multiple, special wires to the occluded site to reopen it. After dilation by balloon, the occlusion is treated with stents.

PCI for CTO more complex

Methods

This update report compares efficacy and safety of PCI to medical therapy or CABG in patients with CTO. First, a systematic literature search for systematic reviews on this topic was conducted in four bibliographic databases, to select one or more high-quality and up-to-date systematic reviews from which primary studies were identified. For time periods not covered by a choosen systematic review, a systematic literature search for RCTs and prospective intervention studies were conducted in three databases and three clinical trials registries. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors independently from each other. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. For the rating of the quality of evidence, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used.

systematic literature search

quality of evidence according to GRADE

Domain effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: overall mortality, AP-symptom relief, avoidance of CABG, and health-related quality of life (HrQoL).

efficacy: overall mortality, AP-symptom relief, HrQoL

Domain safety

The following safety-related outcomes were used as evidence to derive a recommendation: procedure-related mortality, major adverse cardiac events (MACE), acute CABG, stent thrombosis, and target vessel revascularisation (TVR).

safety: MACE, acute CABG and TVR

Results

Available evidence

efficacy: PCI vs OMT: 6 RCTs

PCI vs CABG: 1 RCT

Since the previous report in 2013, six RCTs with a total of 1,911 patients comparing PCI to optimal medical therapy (OMT) for CTO have been published. The included patients were predominantly male with a mean age of 57 to 65 years. CTO was located in the right coronary artery in 44% to 100% of the participants. The length of follow-up ranged from nine to 12 months in four RCTs. Two RCTs had a longer follow-up of 47 and 48 months, respectively. In addition, one publication reported 10-year overall mortality results for the subgroup of 460 patients with total occlusion from one RCT comparing PCI to CABG surgery in patients with three-vessel disease (3VD) and/or left main disease (LM) was identified.

safety: 6 additional prospective non-randomised studies

For safety outcomes, additional six prospective non-randomised studies, each including more than 200 participants, were identified. All of them compared PCI to medical therapy, while two of them further compared PCI to CABG. The total number of patients in this studies was 6,618. The mean age of the participants ranged from 62 to 68 years and 70% to 80% were male. Location of the CTO in the right coronary artery in 40% to 50%.

PCI versus OMT

Clinical effectiveness

PCI vs. OMT: no difference in mortality and CABG surgery

AP-symptom relief inconclusive

HrQoL better with PCI

For the comparison of PCI versus medical therapy, a meta-analysis including results from six RCTs after one or four years of follow-up showed no statistically significant difference in overall mortality or avoidance in CABG surgery. In terms of AP-symptom relief, the results were inconclusive. While, based on results from two RCTs, the number of patients with AP-symptoms was statistically significant lower in the PCI arm than the OMT arm after one year, there was no significant difference in the AP frequency after one year and three years assessed by SAQ reported in three RCTs. There were statistically significant advantages in generic HrQoL for PCI compared to medical therapy after one year (mean difference (MD) 2.77 [95% CI 0.74, 4.80]; p=0.008) and after four years of follow-up (MD 3.59 [95% CI 1.18, 6.00]; p=0.004), but no between-group difference in disease-specific QoL.

Safety

PCI vs. OMT: no difference in MACE, MI, stroke, stent thrombosis TVR rate lower with PCI after 1 year, not after 4 years

Peri-procedural mortality rates were very low, with no peri-procedural death reported in five RCTs and two peri-procedural deaths (0.3%) in one prospective non-randomised study. The percentage of patients with MACE during follow-up was reported in four RCTs and five prospective non-randomised studies. Overall, there was no statistically significant difference between PCI and medical therapy after one year (risk ratio (RR) 0.56 [95% CI 0.32, 0.99]; p=0.05) and after four years of follow-up (RR 0.89 [95% CI 0.75, 1.07]; p= 0.21). Single major adverse events reported, were myocardial infarction and stroke, again with no difference between the study groups. There was also no difference in stent thrombosis between PCI and medical therapy. TVR was less frequent in the PCI arm compared to the medical therapy arm after one year follow-up, while there was no statistically significant difference after four years of follow-up.

PCI versus CABG

Clinical effectiveness

For the comparison PCI versus CABG only results on overall mortality and AP-symptom relief were available from one RCT. After 10 years of follow-up, there was no difference in overall mortality between the study groups. The number of patients without AP-symptoms after five years of follow-up was lower in the PCI arm than the CABG arm.

PCI vs CABG: no difference in mortality; AP-symptoms less frequent with CABG

Safety

For the comparison PCI to CABG safety results were only available from two prospective non-randomised studies. One study reported, that the MACE rate (2.6% vs 6.9%) and stroke rate (0.1% vs 5.1%) were lower in the PCI arm than the CABG arm. The percentage of patients with MI during follow-up was reported in two studies, with no difference between PCI and CABG arm. No results were reported on stent thrombosis, TVR or procedure-related mortality.

PCI vs CABG: MACE and stroke rate lower with PCI, no difference in MI

Upcoming evidence

Five ongoing RCTs compare PCI to medical therapy in patients with CTO are listed in clinical trials registries. Two of the RCTs should have been completed in 2021, while the completion date of the remaining three RCTs is between 2023 and 2028. No ongoing RCT could be identified to compare PCI versus CABG in patients with CTO.

5 ongoing RCTs for PCI vs. OMT

Conclusion

Based on the available evidence from six RCTs with 1,911 patients, PCI of CTO compared with medical treatment alone shows no effect on all-cause mortality and thus on overall survival. Still, it indicates a short- and medium-term improvement in AP-symptoms and, consequently, quality of life. At the same time, no increased MACE rates or procedural mortality rates were observed with PCI for CTO. These results are in line with some recently published systematic reviews on this topic. In addition to the available evidence, five ongoing RCTs were identified that investigated PCI of CTO compared with medical therapy in different patient groups. For the comparison of PCI to CABG for CTO, there is currently insufficient evidence to assess efficacy and safety conclusively.

overall some advantage for PCI compared to OMT in terms of symptom relief and HrQoL, while complication rates are comparable

insufficient evidence for PCI vs CABG

The current evidence indicates that the assessed technology PCI for CTO is more effective in terms of AP-symptom relief and improvement of QoL and equally safe than the comparator of medical therapy alone. The technology should thereby be restricted to selected patients and limited to specialised clinical settings.

Zusammenfassung

Einleitung

Dieser Bericht ist das erste Update des systematischen Reviews „Perkutane koronare Interventionen (PCI) bei chronischen Komplettverschlüssen (CTO)“, das im März 2013 erstellt wurde.

Indikation und therapeutisches Ziel

KHK häufigste Todesursache in der westlichen Welt

Die koronare Herzkrankheit (KHK) ist die häufigste Todesursache in den westlichen Ländern. Im Jahr 2020 waren in Österreich 36 % aller Todesfälle durch Herzkreislauferkrankungen verursacht, etwa 13.500 davon durch ischämische Herzkrankheiten. Bei einer KHK kommt es durch Ablagerung von Lipiden an der Gefäßwand zu einer Atherosklerose, die zu einer Verengung in den Herzkranzgefäßen führt. Ein wesentliches Symptom der KHK ist die Angina Pectoris (AP), welche durch Brustschmerzen die meist durch körperliche Belastung oder Stress auslösbar sind, gekennzeichnet ist.

wesentliches Symptom: Angina Pectoris

CTO = Totalverschluss der Koronararterien seit ≥ 3 Monate

Chronische Totalverschlüsse (CTOs) sind definiert als seit mindestens drei Monaten bestehende vollständige Verschlüsse der Koronararterien. Genaue Angaben zur Prävalenz von CTOs sind nicht möglich, da nicht alle Patient*innen mit CTOs Symptome aufweisen. Bei Patient*innen, bei denen aufgrund von KHK Beschwerden eine Koronarangiographie durchgeführt wurde, wurde in etwa 30 % eine oder mehrere CTOs diagnostiziert.

Die primäre Behandlung der KHK ist eine medikamentöse Therapie. Es kann jedoch auch eine koronare Bypass-Operation (CABG) oder eine perkutane Koronarintervention (PCI) angezeigt sein.

Das therapeutische Ziel einer PCI bei Patient*innen mit CTO ist es, Symptome zu lindern und die Lebensqualität zu steigern, kardiale Folgeerkrankungen und invasivere Eingriffe in Form von CABG zu vermeiden sowie die Lebenszeit zu verlängern.

Beschreibung der Technologie

PCI bei CTO aufwändig

Auswahl der Patient*innen entscheidend

Im Gegensatz zu PCIs bei lediglich stenosierten Gefäßen ist die Wiedereröffnung einer CTO deutlich aufwändiger. Die Auswahl geeigneter Patient*innen erfolgt auf der Grundlage einer individuellen Risikostratifizierung. In Abhängigkeit von Lage, Länge und histologischer Beschaffenheit der CTO, wird häufig entweder ein antegrader Zugang oder ein retrograder Zugang gewählt, um die CTO zu eröffnen. Über einen Mikrokatheter werden dabei mehrere, spezielle Drähte an die verschlossene Stelle gebracht und so versucht diese wiederzueröffnen. Nach Durchtritt des Drahtes wird die Engstelle mittels Ballon aufgedehnt und anschließend mittels Stent versorgt. Die PCI eines CTO dauert dabei deutlich länger und verlangt mehr Personal.

Methoden

Dieses Update vergleicht die Wirksamkeit und Sicherheit der PCI mit einer medikamentösen Behandlung oder der CABG bei Patient*innen mit CTO.

systematische Recherche nach Übersichtsarbeiten und Primärstudien

Zunächst erfolgte eine systematische Literatursuche nach systematischen Übersichtsarbeiten zu diesem Thema in vier bibliografischen Datenbanken (Medline, Embase, Cochrane Database of Systematic Reviews, Centre of Re-

view and Dissemination database). Ziel dabei war es, eine oder mehrere hochwertige und aktuelle systematische Übersichtsarbeiten zu identifizieren, die als primäre Quelle für Primärstudien herangezogen werden können. Für jene Zeiträume, die nicht von den ausgewählten systematischen Übersichtsarbeiten abgedeckt wurden, wurde eine systematische Literatursuche nach RCTs und prospektiven nicht-randomisierten Studien in drei Datenbanken (Medline, Embase, Cochrane Clinical Trials Registry) und drei Registern für klinische Studien (ClinicalTrial.gov, WHO-ICTRP und EU Clinical Trials) durchgeführt. Die Selektion relevanter Studien, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autoren unabhängig voneinander durchgeführt. Soweit sinnvoll und möglich, wurden paarweise Meta-Analysen durchgeführt. Zur Berechnung wurde die Cochrane Review Manager Software, Review Manager 5.4 herangezogen. Es wurden die Modelle mit festen oder zufälligen Effekten nach der Mantel-Haenszel-Methode (für dichotome Daten) oder die Inverse-Varianz-Methode (für kontinuierliche Daten) verwendet, wobei das Modell mit zufälligen Effekten bei erhöhter Heterogenität ($I^2 > 30$ %) zur Anwendung kam. Für die Bewertung der Vertrauenswürdigkeit der Evidenz wurde das GRADE-System (Grading of Recommendations Assessment, Development and Evaluation) verwendet.

paarweise Meta-Analysen

Bewertung der Evidenz nach GRADE

Klinische Wirksamkeit

Für die Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte herangezogen: Gesamtmortalität, Linderung von AP-Symptomen, Vermeidung einer CABG und gesundheitsbezogene Lebensqualität (LQ).

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

Sicherheit

Für die Bewertung der Sicherheit wurden folgende Endpunkte herangezogen: interventionsbedingte Mortalität, schwere kardiale Nebenwirkungen, akute CABG Eingriffe, Stent-Thrombosen und Revaskularisationseingriffe im betroffenen Gefäß.

Sicherheit: interventionsbedingte Mortalität, schwere kardiale Nebenwirkungen

Ergebnisse

Verfügbare Evidenz

Seit dem Bericht aus dem Jahr 2013 wurden sechs RCTs mit insgesamt 1.911 Patient*innen veröffentlicht, in denen eine PCI mit der optimalen medikamentösen Therapie (OMT) bei Personen mit CTO verglichen wurde. Die in den RCTs eingeschlossenen Patient*innen waren überwiegend männlich und hatten ein Durchschnittsalter von 57 bis 65 Jahren. Bei 44 % bis 100 % der Teilnehmer befand sich der CTO in der rechten Koronararterie. Die Studiendauer lag in vier RCTs zwischen neun und 12 Monaten. Zwei RCTs wiesen eine längere Studiendauer von 47 bzw. 48 Monaten auf.

PCI vs. OMT: 6 RCTs für Wirksamkeit

Darüber hinaus wurde eine Publikation identifiziert, in der Ergebnisse zur 10-Jahres-Gesamtmortalität für die Subgruppe von 460 Patient*innen mit einem Totalverschluss einer Koronararterie aus einer RCT berichtet wurde, in dem PCI mit der CABG Operation bei Patient*innen mit koronarer Mehrgefäßerkrankung und/oder linker Hauptstammstenose verglichen wurde.

PCI vs CABG: 1 RCT für Wirksamkeit

Zur Bewertung der Sicherheit konnten zusätzlich zu den RCTs sechs prospektive, nicht randomisierte Studien mit jeweils > 200 Teilnehmer*innen identifiziert werden. In diesen Studien wurde eine PCI mit einer medikamentösen Therapie bei Personen mit CTO verglichen, wobei in zwei weiteren Studien auch Ergebnisse zum Vergleich der PCI mit einer CABG berichtet

6 zusätzliche prospektive nicht-randomisierte Studien für Sicherheit

wurden. Die Gesamtzahl der Patient*innen in diesen Studien betrug 6.618. Das Durchschnittsalter der Teilnehmer*innen lag zwischen 62 und 68 Jahren und 70 % bis 80 % waren männlich. In 40 % bis 50 % der Fälle befand sich die CTO in der rechten Koronararterie.

Perkutane Koronarinterventionen versus optimale medikamentöse Therapie

Vertrauenswürdigkeit der Evidenz

Von den sechs eingeschlossenen RCTs wurden drei mit einem niedrigen RoB und drei mit einer moderaten RoB bewertet. Vier der sechs eingeschlossenen nicht-randomisierten Studien zu Sicherheitsergebnissen wurden mit einem mäßigen RoB bewertet, eine mit einem hohen RoB und eine mit einer kritischen RoB. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE für den Vergleich PCI versus OMT als moderat einzustufen.

Klinische Wirksamkeit

PCI vs. OMT: kein Unterschied bei Mortalität und CABG Eingriffen nach max. 4 Jahren

Ergebnisse zu AP-Symptomatik nicht eindeutig

Vorteil für PCI bei LQ nicht jedoch bei erkrankungsspezifischer LQ

Für den wesentlichen Endpunkt zur Bewertung der Wirksamkeit, die Gesamtmortalität, konnten für den Vergleich zwischen PCI und medikamentöser Therapie Ergebnisse aus allen sechs inkludierten RCTs herangezogen werden. Die Meta-Analyse auf Basis dieser RCTs ergab dabei weder nach einem noch nach vier Jahren Follow-up einen statistisch signifikanten Unterschied zwischen PCI und alleiniger medikamentöser Therapie (RR 1,71 [95 % CI 0,54; 5,44]; p=0,40 bzw. RR 1,14 [95 % CI 0,38; 3,40]; p=0,81). Auch in Bezug auf die kardiale Mortalität oder die Vermeidung von CABG-Operationen zeigten sich nach ein bzw. vier Jahren Follow-up keine Unterschiede zwischen den Studiengruppen. Ergebnisse zur Veränderung bzw. Linderung der AP-Symptomatik lagen aus vier RCTs vor und waren nicht eindeutig. In zwei RCTs wurde die Anzahl der Personen mit AP-Symptomen nach einem Jahre Follow-up erhoben. Dabei zeigte sich ein signifikanter Vorteil zu Gunsten der PCI (RR 0,63 [95 % CI 0,49; 0,82]; p=0.0006). Andererseits zeigte sich in der Häufigkeit der AP-Symptome, welche mittels Seattle Angina Fragebogen (SAQ) in drei RCTs erhoben wurde, weder nach einem noch nach drei Jahren in Unterschied zwischen PCI und OMT. Für die allgemeine Lebensqualität ergab sich ein statistisch signifikanter Vorteil für PCI im Vergleich zur medikamentösen Therapie nach einem Jahr (mittlere Differenz (MD) 2,77 [95 % CI 0,74, 4,80]; p=0,008) und nach vier Jahr Follow-up (MD 3,59 [95 % CI 1,18, 6,00]; p=0,004), kein Unterschied zwischen den Gruppen zeigte sich jedoch in der krankheitsspezifischen Lebensqualität nach einem Jahr Follow-up.

Sicherheit

PCI vs. OMT: sehr geringe interventionsbedingte Mortalität; MACE: kein Unterschied nach 1 bzw. 4 Jahren

weniger TVR nach 1 Jahr, kein Unterschied nach 4 Jahren

Die Mortalitätsraten während des Eingriffs waren in den inkludierten Studien insgesamt sehr niedrig. So kam es in fünf RCTs zu keinem einzigen Todesfall während der PCI, während in einer prospektiven nicht-randomisierten Studie zwei peri-prozedurale Todesfälle berichtet wurden (0,3 %). Der Prozentsatz der Patient*innen mit schwerer kardialer Nebenwirkungen im Laufe des Follow-ups wurde in vier RCTs und fünf prospektiven nicht-randomisierten Studien für den Vergleich PCI versus OMT berichtet. Insgesamt zeigte sich dabei kein statistisch signifikanter Unterschied zwischen PCI und medikamentöser Therapie nach einem Jahr (RR 0,56 [95 % CI 0,32; 0,99]; p=0,05) bzw. nach vier Jahren (RR 0,89 [95 % CI 0,75; 1,07]; p=0,21). Einzeln berichtete schwerwiegende unerwünschte Ereignisse waren unter anderem Myokardinfarkt und Schlaganfall, wobei auch hier kein signifikanter Unterschied zwischen den Studiengruppen nach Ende der Studiendauer be-

richtet wurde. Stent-Thrombose traten in den inkludierten Studien insgesamt selten auf, wobei kein Unterschied zwischen PCI und medikamentöser Therapie vorlag (7 vs. 7 Personen). Eine Meta-Analyse nach einem Jahr Follow-up ergab eine signifikant niedrigere Rate an Revaskularisationen im betroffenen Gefäß (TVR) in der PCI-Gruppe im Vergleich zur medikamentösen Therapie (RR 0,28 [95 % CI 0,17; 0,48]; p<0,001), nicht jedoch nach vier Jahren Follow-up (RR 1,11 [95 % CI 0,35; 3,54]; p=0,18).

Perkutane Koronarinterventionen versus koronare Bypass-Operation

Vertrauenswürdigkeit der Evidenz

Der einzige RCT zum Vergleich PCI versus CABG wurde mit einem hohen RoB bewertet. Jene beiden nicht-randomisierten Studien zu Sicherheitsergebnissen die auch Ergebnisse für den Vergleich PCI versus CABG liefern wurden mit einem kritischen RoB bewertet. Insgesamt ist die Vertrauenswürdigkeit der Evidenz nach GRADE für den Vergleich PCI versus CABG als gering bis sehr gering einzustufen.

Klinische Wirksamkeit

PCI vs. CABG: kein Unterschied bei Mortalität nach 10 Jahren;

weniger Patient*innen ohne AP-Symptome in PCI Gruppe

Für den Vergleich PCI versus CABG lagen nur Ergebnisse zu Gesamtmortalität und zur Änderung der AP-Symptomatik aus einem RCT vor. Nach einem Follow-up von zehn Jahren wurde darin kein Unterschied in der Gesamtmortalität zwischen den Studiengruppen berichtet (RR 1,04 [95 % CI 0,56, 1,96]; p=0,90). Ein signifikanter Unterschied zeigte sich jedoch in der AP-Symptomatik nach fünf Jahren. Hier war die Anzahl der Patient*innen ohne AP-Symptome in der PCI-Gruppe geringer als in der CABG-Gruppe (70 % vs. 81 %). Zu allen anderen Endpunkten zur Bewertung der Wirksamkeit lagen für den Vergleich PCI versus CABG bei CTO keine Ergebnisse vor.

Sicherheit

PCI vs. CABG: nur Ergebnisse aus 2 prospektiven nicht-randomisierten Studien;

weniger MACE und Insult in PCI Gruppe, kein Unterschied bei MI

Für den Vergleich zwischen PCI und CABG lagen nur Ergebnisse aus zwei prospektiven, nicht-randomisierten Studien vor. In einer Studie wurde berichtet, dass nach einem Jahr Follow-up sowohl die Rate an schweren kardialen Nebenwirkungen (2,6 % vs. 6,9 %) als auch die Rate an Insulten (0,1 % vs. 5,1 %) im PCI-Studienarm jeweils niedriger war als im CABG-Studienarm. Der Anteil der Patient*innen, die während der Nachbeobachtung von ein bzw. vier Jahren einen Myokardinfarkt erlitten, wurde in zwei Studien berichtet, wobei es keine statistisch signifikanten Unterschiede zwischen dem PCI- und dem CABG-Arm gab (1 % vs. 0,6 % bzw. 8 % vs. 4 %). Zu Stent-Thrombosen, TVR oder Todesfällen im Zusammenhang mit der Intervention wurden keine Ergebnisse berichtet.

Laufende Studien

5 laufende RCTs zu PCI vs. OMT bei CTO

In den Studienregistern sind derzeit fünf laufende RCTs aufgeführt, in denen eine PCI mit einer alleinigen medikamentösen Therapie bei Patient*innen mit CTO verglichen wird. Zwei der RCTs sollten bereits im Jahr 2021 abgeschlossen worden sein, während das geplante Studienende der übrigen drei RCTs zwischen 2023 und 2028 liegt. Für den Vergleich PCI versus CABG bei Patient*innen mit CTO konnte kein laufender RCT identifiziert werden.

Diskussion

keine verlässliche Aussage zu PCI vs CABG möglich

insgesamt leichter Vorteil für PCI im Vergleich zu OMT hinsichtlich Symptomverbesserung bei vergleichbarer Komplikationsrate

Basierend auf den Ergebnissen in retrospektiver Studien zeigt sich, das ein CTO bei Patient*innen mit KHK mit einem erhöhten Mortalitätsrisiko verbunden ist. Für eine PCI bei CTO zeigte sich in rezenten systematischen Reviews auf Basis von Beobachtungsstudien eine signifikant niedrigere Mortalitätsrate im Vergleich zur alleinigen medikamentösen Therapie. Die Meta-Analysen auf Basis der inkludierten RCTs in diesem Bericht können diesen Vorteil jedoch nicht bestätigen. In Hinblick auf die Verbesserung der AP-Symptomatik und die Lebensqualität scheint es insgesamt einen numerischen Vorteil zu Gunsten der PCI zu geben, dieser ist jedoch nicht in allen Fällen statistisch signifikant. Hinsichtlich der Sicherheit einer PCI bei CTO ergibt sich aus der vorliegenden Evidenz keine signifikant erhöhte Rate an kardialen Nebenwirkungen im Vergleich zu einer medikamentösen Behandlung. Limitationen bestehen aufgrund fehlender statistischer Power, heterogener Patient*innengruppen und hoher cross-over Raten in den RCTs. Für den Vergleich PCI versus CABG bei CTO ist die vorliegende Evidenz nicht ausreichend um verlässliche Aussagen zur Wirksamkeit und Sicherheit zu machen.

Empfehlung

Aufnahme in den Leistungskatalog mit Einschränkungen empfohlen

Die derzeitige Evidenz deutet darauf hin, dass die bewertete Technologie PCI bei CTO in Bezug auf die Linderung von AP-Symptomen und die Verbesserung der Lebensqualität effektiver und ebenso sicher ist als die Vergleichsbehandlung einer alleinigen medizinischen Therapie. Die Aufnahme in den Leistungskatalog wird daher mit Einschränkungen empfohlen Die Technik sollte nur bei ausgewählten Patient*innen und nur in spezialisierten klinischen Einrichtungen eingesetzt werden.

Summary of previous assessment 2013

Commissioned by the Austrian Ministry of Health, the HTA-report "Percutaneous coronary interventions (PCI) for chronic total occlusion (CTO)" was initially prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2013 [1]. This chapter summarises the results and the recommendation of this 2013 report.

systematischer Review 2013

Health problem and characteristics of the technology

Overview of the disease, health condition and target population

Coronary heart disease (CHD) is the most common cause of death in developed countries. It mainly affects older people aged 65 and over and to date it has affected more men than women. In 2020, 36% of all deaths in Austria were caused by cardiovascular disease, 13,500 of which were due to ischemic heart disease [2].

KHK häufigste Todesursache in der westlichen Welt

In CHD, atherosclerosis develops due to damage and deposition of lipids in the vessel wall, leading to stenosis in the coronaries. The stenosis can become hemodynamically relevant from a narrowing of the vessel of about 70%. In addition to asymptomatic courses, however, the typical CHD symptoms develop in most cases, which are characterized by a mismatch between oxygen demand and oxygen supply of the myocardial tissue. The leading symptom is angina pectoris (AP), but also cardiac arrhythmias, heart failure, myocardial infarction and sudden cardiac death. In AP, a distinction is made between stable AP, in which chest pain is caused by physical activity or emotional stress but is treatable by medication and physical rest, and unstable AP, characterized by a change in pain symptomatology. This includes the initial onset of symptoms, symptoms under rest and increase in duration or intensity of symptoms, and non-response to rest or medication [3].

Einengung des Gefäßes durch Ablagerung

stabile AP: Brustschmerz auslösbar durch körperliche Aktivität oder Stress

instabile AP: Änderung der Symptomatik

When complete occlusion of the coronary arteries (Thrombolysis in Myocardial Infarction classification (TIMI) flow 0) occurs over a period of at least 3 months, it is referred to as chronic total occlusion (CTO) [4-6]. According to the U.S. National Heart, Lung, and Blood Dynamic Registry, CTOs are most commonly found in the right coronary artery (RCA) [5]. In most cases of CTO, vessels behind the complete occlusion are supplied by collaterals (= bypassing circulation), so acute conditions such as myocardial infarction are rare. However, since the blood supply is insufficient, there is a typical AP symptomatology [7]. Precise information on the prevalence of CTOs is not possible because not all patients with CTOs have symptoms and are therefore not diagnosed. In patients who underwent coronary angiography due to CHD symptoms, one or more CTOs were diagnosed in about 30% [5].

CTO: 100 % Verschluss über mindestens 3 Monate

bei etwa 30 % der Patient*innen mit KHK Symptomen

Current clinical practice

medikamentöse Basistherapie; Bypass-Operation; PCI: Aufdehnung des Gefäßes

In addition to the treatment of risk factors for CHD, such as hypertension, nicotine abuse, diabetes, dyslipidemia, or obesity, drug therapy (e.g., acetylsalicylic acid, beta-blockers, lipid-lowering drugs, calcium antagonists) is the primary treatment for CHD [8]. However, depending on symptoms and anatomic conditions (especially if more than one coronary vessel is affected), coronary bypass surgery (CABG) or less invasive procedures in the form of percutaneous coronary intervention (PCI) may also be indicated [8, 9].

Behandungsziele KHK

The treatment goal for CHD is to decrease mortality and morbidity (myocardial infarction, heart failure) and to improve quality of life by reducing symptoms [8].

Wahl der Therapie: Risikostratifizierung (Alter, Symtome, funktioneller Status und Begleiterkrankungen

Hauptindikation für PCI bei CTO: Eingefäßerkrankung mit AP-Symptomatik trotz medikamentöser Therapie

The selection of a suitable therapy is based on individual risk stratification. In addition to clinical criteria, angiographic and technical considerations are essential. Patient age, the severity of symptoms, functional status and co-morbidities (e.g. diabetes mellitus, chronic renal failure) are important clinical criteria for therapy selection. On angiographic findings, single- or multivessel disease and, in addition, left ventricular function and the presence of valvular disease should be discussed. In contrast, the probability of successful PCI in CTOs, their complication rates, and possible restenosis must be considered as technical criteria [10]. According to current guidelines, the main indication for PCIs in CTOs is a single-vessel disease without further stenosis in patients with evidence of ischemia who are symptomatic despite medical therapy [3, 9]. Patients who are not eligible for CABG are also indicated for CTO [5]. Successful PCIs for CTO can be expected in 50% to 70%, and success rates of ≥ 80% have been reported at specialized centers [11]. CTOs with a length < 20mm have the best probability of success [11].

Features of the intervention

Behandlungsziele PCI bei CTO

The purpose of a CTO PCI is to reopen the occluded site, and thereby:

- relieve symptoms,
- prevent cardiac complications such as heart failure, arrhythmias and myocardial infarction,
- improve left ventricular function,
- prolong life expectancy,
- avoid more invasive interventions such as CABG [5, 11].

PCI bei CTO aufwändiger als bei lediglich verengten Gefäßen

zwei arterielle Schleusen, Führungskatheter und diagnostischer Katheter

antegrader und retrograder Zugang

In contrast to PCIs for only stenosed vessels, reopening of a CTO is much more complex. After diagnostic coronary angiography, two arterial access points (femoral arteries on both sides, radial arteries on both sides, or one in the femoral artery and the other in the radial artery) are often placed initially [11]. To optimally visualize the length of the CTO, as well as its location, a “dual contrast injection” should be performed on both sides of the CTO using guide catheters [11]. Depending on the location, length, and histologic nature of the CTO, either an antegrade approach (in which the guidewire is passed through the coronary vessel) or a retrograde approach (the guidewire is passed through the collaterals to the CTO) is often chosen to open the CTO [11, 12]. However, in addition to these main techniques, there are numerous special procedures such as “true-to-true lumen crossing” or “re-entry”.

A microcatheter is then used to deliver multiple special wires to the occluded site in an attempt to reopen it. After the wire has passed through the CTO, the narrow site is dilated by balloon under continuous fluoroscopy and then treated with stent(s) (usually drug-eluting stents (DES)) [13].

CTO wird aufgebohrt, aufgedehnt und mittels DES versorgt

With an estimated 120 minutes for the procedure and with fluoroscopy times of 60 minutes, CTO PCI takes significantly longer than normal PCIs, and the volume of contrast agent administered is higher. In addition, this procedure also requires more personnel.

Scope and methods

The 2013 report compares the efficacy and safety of PCI to medical treatment or CABG in patients with CTO. A systematic literature search was conducted in four databases (Medline, Embase, Cochrane, Centre of Review and Dissemination (CRD) database). Two review authors independently screened and selected the literature and included eligible studies.

Ziel der Untersuchung 2013

Results

In the absence of (randomised) controlled trials, uncontrolled observational studies with ≥ 200 patients were included as best available evidence, and the quality of evidence was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

keine kontrollierten Studien

Study characteristics

Overall, nine studies comprising 7,299 patients were included [14-22]. Of these, six were registries/databases, and three were case series.

9 einarmige Beobachungsstudien mit 7.299 Patient*innen

On average, patients were aged 58 to 66 years, 19% to 37% had diabetes mellitus, and 18% to 63% had had a previous myocardial infarction. The single-vessel disease was present in 20% to 65%, and 35% to 80% had multivessel disease. In two studies [15, 21], asymptomatic patients were also included (9% and 15%, respectively), and in two others, the majority of those treated had unstable AP (52% to 74% and 63% to 66%, respectively) [21, 22]. In the majority of cases, CTO were located in the RCA (26%-70%).

58-66 Jahre alt

20-65 % Eingefäßerkrankung

If details of intervention were provided in the publications, a DES was used in most cases after the successful reopening of the CTO. One registry mentioned that both antegrade and retrograde approaches were considered [14], and another registry provides information on how often each method was used [15].

Effectiveness

Due to the lack of (randomised) controlled trials, a sufficient assessment of the effectiveness of PCI for CTO was not possible. Therefore, no conclusions can be drawn regarding patient-relevant endpoints such as overall survival, CABG avoidance, AP symptoms reduction, and quality of life.

keine Aussagen zur Wirksamkeit möglich

Safety

Procedure-related mortality rates (in-hospital, max. 30 days) were reported in four studies [14-17] with a total of 2,721 patients and ranged from 0% to 0.5%.

Sicherheit: schwere kardiale Nebenwirkungen bei bis zu 37 %

Major cardiac adverse events (MACE) were reported in seven studies [14, 17-22] involving 4,504 patients. Overall, these adverse events occurred in at least 1.8% [14] and a maximum of 36.9% [20], although the definition of MACE varied across studies. Single major adverse events reported were MIs (1.0%-8.2%) in eight studies [14-20, 22] with a total of 5,436 patients. Coronary artery perforations occurred in two studies [14, 15] in 2.6%-3.1% of 2,138 patients. Data on pericardial tamponades are available from two studies involving 2,116 patients [15, 16], with this adverse event occurring in a maximum of 0.5% of patients.

Revaskularisation in bis zu 31 % nötig

Results on stent thrombosis were available from six publications [15-20], with 0% to 1.8% of 4,945 patients affected. Revascularisation of the affected vessel was necessary for 0.1%-31.1% of a total of 6,194 patients [15, 17-22], with lower rates recorded when DES was used (DES: 9%-18%; BMS: 27%-31%).

akuter CABG: 0 % bis 0,4 %

CABG was required in 0% to 0.4% of all patients, with these data based on a total of three studies [14-16] that included 2,340 patients.

Recommendation

Vertrauenswürdigkeit der Evidenz: nicht beurteilbar für Wirksamkeit, moderat für Sicherheit

Due to methodological limitations of the included studies, the quality of evidence for safety according to GRADE is moderate. For efficacy, the quality of evidence cannot be assessed due to the absence of (prospective) controlled studies.

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

The available evidence is currently insufficient to assess the efficacy and safety of PCI for CTOs in comparison to the respective standard therapies. Therefore, the inclusion into the hospital benefit catalogue is currently not recommended, either for operable or for inoperable patients.

UPDATE 2022

1 Objectives and Scope

1.1 PICO question

PIKO-Frage 2022

Is a percutaneous coronary intervention (PCI) in comparison to optimal medical therapy (OMT) or to coronary bypass graft surgery (CABG) in patients with chronic total occlusion (CTO) of a coronary artery more effective and safe concerning survival, symptoms, quality of life, avoidance of CABG and complication rate?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria

Population	Symptomatic patients with angina pectoris (AP) and chronic total occlusion (CTO), defined as complete occlusion of a coronary artery for at least three months with thrombolysis in myocardial infarction (TIMI) grade 0 flow.
Intervention	Percutaneous coronary intervention (PCI) using drug-eluting or bare-metal stents
Control	Coronary bypass graft surgery (CABG) or conservative medical therapy
Outcomes	
Efficacy	■ Overall mortality ■ AP Symptom relief ■ Avoidance of CABG ■ Health-related QoL ■ LVEF function ■ Late lumen loss ■ Stent restenosis ■ Procedural success
Safety	■ Procedure-related mortality ■ Major adverse cardiac events (MACE) ■ Myocardial infarction (MI) ■ Cardiac tamponade ■ Stroke ■ Acute CABG ■ Coronary perforation ■ Contrast-induced nephropathy ■ Stent-thrombosis ■ Target vessel revascularisation
Study design	
Efficacy	■ Randomised controlled trials
Safety	■ Randomised controlled trials ■ Prospective non-randomised controlled trials (with at least 200 patients)

2 Methods

2.1 Clinical effectiveness and safety

2.1.1 Systematic literature search

systematische Literatursuche nach systematischen Reviews in 4 Datenbanken

A systematic literature search for relevant systematic reviews was conducted on 30.11.2021 in the bibliographic databases MEDLINE, Embase, the Cochrane Database for Systematic Reviews and CRD database. The search was restricted to 2012 to 2022 and to articles published in English or German. The aim was to select one or more high-quality and up-to-date systematic reviews from which primary studies were identified and then selected based on the specific inclusion criteria of the report. After deduplication, overall, 484 citations were included in the search for secondary literature. The specific search strategy employed can be found in the Appendix.

insgesamt 484 Treffer

ergänzende Literatursuche nach Primärstudien in 3 Datenbanken

In addition, for time periods not covered by a choosen up-to-date and of high quality relevant systematic review, systematic literature searches for RCTs and prospective intervention studies were conducted on 02.12.2021 and 23.12.2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library

The systematic search was limited in Medline and Embase to only prospective or randomised controlled trials and to articles published in English or German. After deduplication, 1,763 citations were included. The specific search strategies employed can be found in the Appendix.

insgesamt 1.776 Publikationen identifiziert

By hand-search, 13 publications were found, resulting in overall 1,776 hits in the search for primary studies.

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 20.01.2022 resulting in 335 potential relevant hits.

2.1.2 Flow chart of study selection

Literaturauswahl – systematische Übersichtsarbeiten

In the search for systematic reviews, overall, 597 hits were identified. After de-duplication, 484 references were screened by two independent researchers (TS, CZ, CL), and in case of disagreement, a third researcher (TS, CZ, CL) was involved in solving the differences. The selection process for systematic reviews is displayed in Figure 2-1.

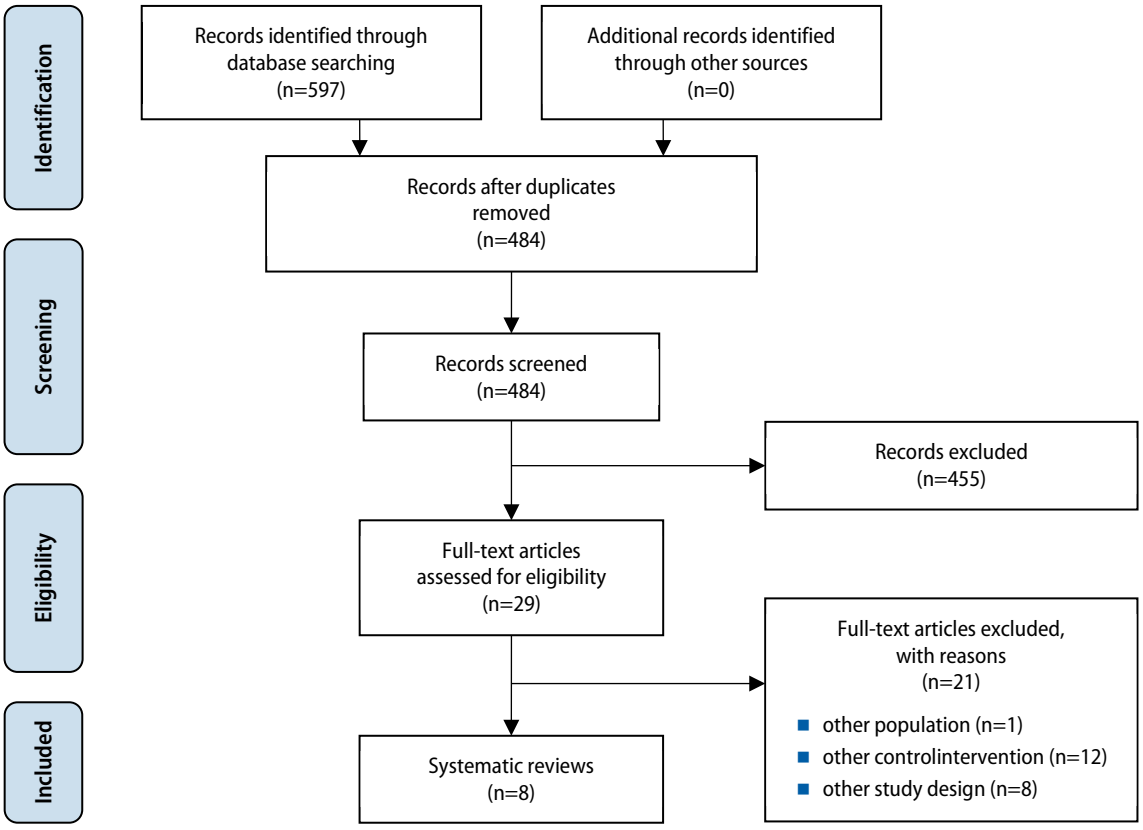

Figure 2-1: Systematic reviews – flow chart of study selection (PRISMA Flow Diagram)

Of the eight systematic reviews included [23-30], two were evaluated as up-to-date and of high quality and were included for the purpose of identifying primary studies [26, 30]. From these systematic reviews, 12 publications on 11 studies (five RCTs [31-37] and four prospective non-randomised studies [38-41]) could be identified as relevant for this review update.

Literaturauswahl – Primärstudien

In the searches for RCTs and prospective non-randomised studies overall 3,645 hits were identified. After deduplications, 1,770 references were screened by two independent researchers (TS, CZ, CL) and in case of disagreement a third researcher (TS, CZ, CL) was involved to solve the differences. The selection process for primary studies is displayed in Figure 2-2.

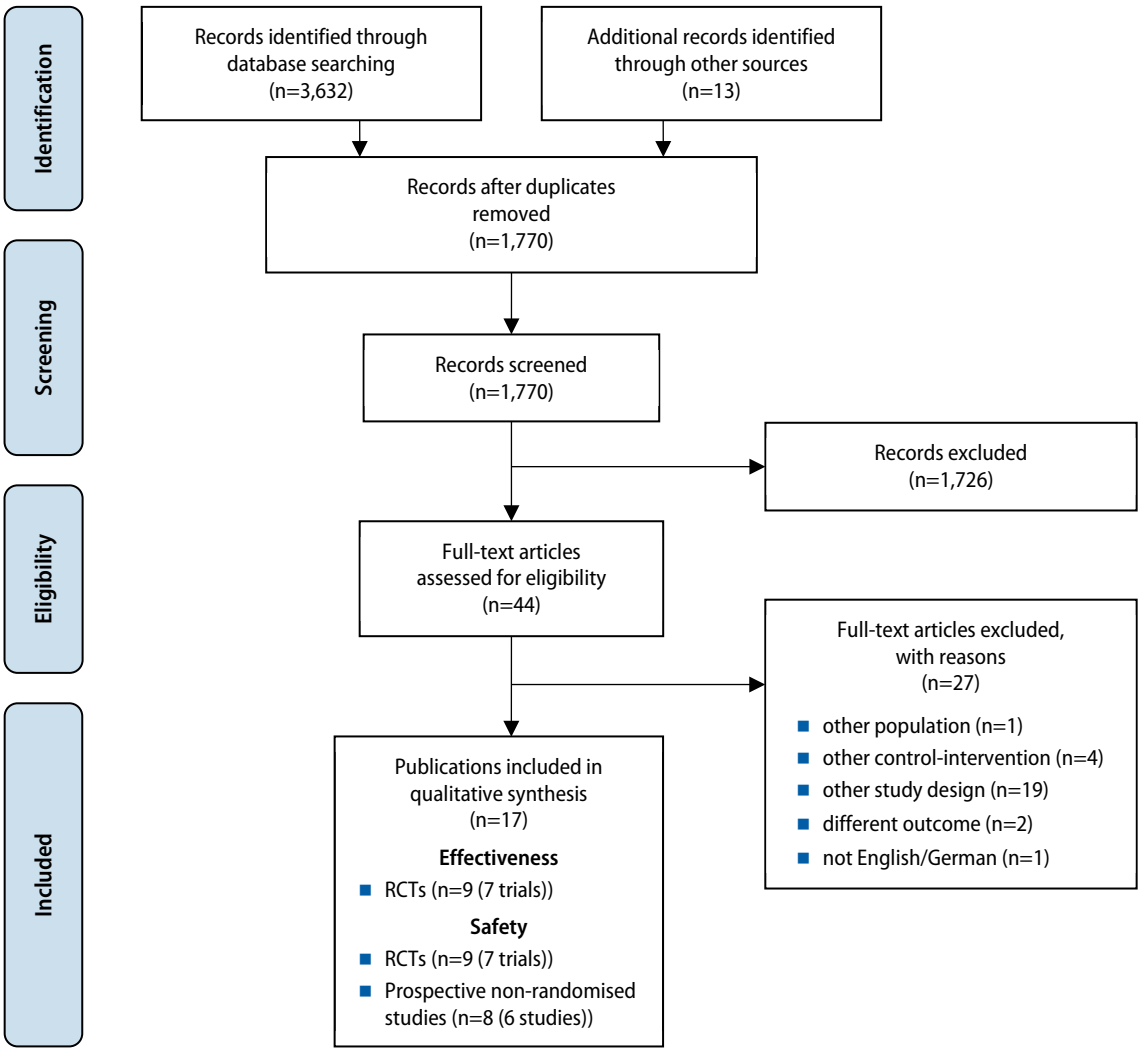

Figure 2-2: Primary studies – flow chart of study selection (PRISMA Flow Diagram)

7 RCTs und 6 nicht-randomisierte Kohortenstudien eingeschlossen

Finally, nine publications on seven RCTs for effectiveness outcomes [31-37, 42, 43] and eight publications on six additional prospective non-randomised studies for safety outcomes [38-41, 44-47] could be included in this review update.

2.1.3 Analysis

Datenextraktion in Tabellen

Relevant information was retrieved from the sources identified. Data from included primary studies were extracted into data extraction tables based on the study design and research question (see Appendix Table A-1). An independent second reviewer (TS) validated the data for accuracy.

Bewertung des Verzerrungspotenzials: Cochrane RoB 2 und ROBINS-I

Two researchers (CZ, TS) conducted risk of bias assessments independently. Differences were resolved by consensus. The methodological quality of the two identified up-to-date systematic reviews was assessed using the AMSTAR-II checklist [48]. The risk of bias (RoB) of the included primary studies was assessed using the Cochrane RoB v.2 tool (for RCTs) [49] and the ROBINS-I tool [50] (for non-randomised studies) (see Table A-3, Table A-4, Table A-5, Table A-6).

2.1.4 Synthesis

Meta-Analysen wenn möglich – Review Manager 5.4

Based on the data-extraction-table (see Appendix Table A-1 and Table A-2), data on each selected outcome were synthesized. If appropriate, pairwise meta-analyses were performed using the Cochrane Review Manager software, Review Manager 5.4. Dichotomous data were expressed as a risk ratio (RR) or odds ratio (OR) with 95% CIs or as the number of events and percentages. Continuous outcomes were given using the mean with standard deviation (SD). We use fixed or random effects model using the Mantel-Haenszel method (for dichotomous data) or Inverse Variance method (for continuous data) to synthesise the results. Thereby, random effects model was used in the case of increased heterogeneity ($I^2 > 30\%$). We identified heterogeneity by visually inspecting the forest plots and by using the I^2 statistic [51]. The level of heterogeneity was taken into account as part of the assessment of the certainty of the evidence (inconsistency).

Bewertung der Vertrauenswürdigkeit der Evidenz mit GRADE

Certainty of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [52]). The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix, results were summarized in Table 6-1.

3 Results: Clinical effectiveness and Safety

3.1 Outcomes

3.1.1 Outcomes effectiveness

Wirksamkeit: entscheidungsrelevante EP: Gesamtsterblichkeit

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

- Overall mortality

Mortality is considered a highly patient-relevant outcome measure when assessing the clinical effectiveness of PCI for CTO. Mortality was reported as overall mortality rates and as cardiac mortality rates in the included RCTs.

Wirksamkeit: wichtige EP: AP Symptomatik, LQ, Verhinderung von CABG

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

- AP- symptom relief
- Avoidance of CABG
- Health-related QoL

The revascularisation of the occluded vessel serves the primary purpose to relieve AP symptoms and improving QoL of the affected patients. In addition, more invasive interventions such as CABG might be avoided.

AP Symptomatik: Seattle Angina Fragebogen

AP symptoms are reported as the percentage of patients without symptoms or are assessed by the Seattle Angina Questionnaire (SAQ), a 19-item questionnaire that measures five domains related to coronary artery disease: angina frequency, physical limitations, quality of life, angina stability, and treatment satisfaction. Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status. A Change of > 20 points predefine clinical relevant improvement in the angina frequency subscale). In addition, the proportion of patients without any AP symptoms was reported in some of the included RCTs [53].

LQ: SF-36 und EQ-5D

Generic HrQoL was assessed by two different questionnaires, the Short Form 36 (SF-36) questionnaire and the European Quality of Life–5 Dimensions (EQ-D) questionnaire. The SF-36 consists of 36 questions and is a general health questionnaire yielding a profile of two health component summary measures through assessing the patient's health status using eight different dimensions (vitality, physical functioning, bodily pain, general health perceptions, role limitations due to physical health, role limitation due to emotional health, social role functioning, mental health). The score ranges from 0 to 100 points, with 0 points representing the greatest possible limitation of health and 100 points representing the absence of health restrictions [54]. The EQ-5D is a five-item measure of mobility, self-care, usual activity, pain or discomfort, and anxiety or depression. Scores range from 0 to 100, with higher scores indicating fewer symptoms and better health status. Disease-specific QoL was assessed using the SAQ. Clinical relevant improvement in the QoL subscale is predefined by > 16 points for the questionnaire [55].

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

3.1.2 Outcomes safety

Sicherheit: entscheidungsrelevante EP: interventionsbedingte Mortalität; schwere kardiale Nebenwirkungen, akuter CABG, Stent Thrombosen

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

- Procedure-related mortality
- Major adverse cardiac events (MACE)
- Acute CABG (in hospital)
- Stent-thrombosis and target vessel revascularisations

schwere kardiale Nebenwirkungen: in den Studien unterschiedlich definiert

The definition of MACE was different in individual studies. MACE was defined as a composition of overall mortality, MI, stroke or revascularisation in two RCTs [31, 37], as a composition of cardiac mortality, MI or ischaemia-driven premature TLR in one RCT [34], or as a composition of cardiac mortality, MI or CABG in the fourth RCT [32, 33, 35]. In the five prospective non-randomised clinical studies, MACE was defined as a composition of cardiac mortality, MI or revascularisation [41, 44], a composition of overall mortality, MI or revascularisation [38, 40] or a composition of cardiac mortality, MI or stroke [39]).

Acute CABG is the proportion of patients with the necessity of a rescue CABG surgery during the hospital stay for CTO-PCI.

Procedure-related mortality was defined as peri-procedural death or death during the hospital stay for CTO-PCI.

Stent thrombosis was defined according to the Academic Research Council criteria [56].

Target vessel revascularisations were defined CABG surgery or repeat PCI performed for symptoms or signs of ischemia in the presence of angiographic stenosis in the CTO vessel.

3.2 Included studies

3.2.1 Included studies effectiveness

6 RCTs zu PCI vs medikamentöse Therapie

1 RCT zu PCI vs CABG

Since the previous report in 2013, six RCTs comparing PCI to OMT for CTO have been published (EXPLORE [32, 33, 35], EUROCTO [34], REVASC [37], IMPACTOR-CTO [36], DECISION-CTO [31] and COMET-CTO [42]). All of them have been included in this report update. In addition, one publication reporting results for the subgroup of patients with total occlusion from one RCT comparing PCI to CABG surgery (SYNTAX) was identified [43].

PCI vs OMT: 1.911 Patient*innen

57-65 Jahre alt

CTO in 44-100 % in der rechten Koronararterie

Three of the six RCTs comparing PCI to OMT were international, multicentre trials [31-35]; the other three were single-centre trials located in Germany [37], Russia [36] and Serbia [42]. All of them were parallel, open-label studies with academic or governmental funding. The six included RCTs enrolled a total of 1,911 patients with CTO, with a sample size ranging from 72 participants [36] to 834 participants [31]. CTO was defined as a complete obstruction of at least one coronary artery (TIMI flow 0) for a minimum of three months in all studies. In one RCT [32, 33, 35], only patients after successful primary PCI for acute STEMI were included and were randomised to PCI for CTO within seven days or medical therapy only (no CTO-PCI within

for months). The included patients were predominantly male (~ 85%) with a mean age between 57 and 65 years. Comorbidities were reported in five of the six included trials, with 15 to 32% of the participants having diabetes mellitus and ten to 64% having a previous MI. CTO was located mostly in the right coronary artery (44% to 100%).

Follow-up: 9 bis 48 Monate

The length of follow-up ranged from nine to 12 months in four RCTs [34, 36, 37, 42]. Two RCTs had a longer follow-up of 47 and 48 months, respectively [31-33, 35]. One RCT was terminated early in 2016, at the request of the executive committee in agreement with the data and safety monitoring board, because of slow enrolment [31]. Procedural success in the PCI group was reported in all six RCTs and ranged from 73% [32, 33, 35] to 97% [37].

PCI vs CABG: Subgruppe mit 460 Patient*innen mit Totalverschluss, nicht nur CTO Patient*innen

mittleres Alter: 65 Jahre

The SYNTAX trial was an academic funded, international multi-centre RCT where 1,800 patients with de novo three-vessel disease (3VD) and/or left main disease (LM) were randomised to PCI or CABG [57]. The publication included in this report update reported results on mortality after ten years of follow-up for a subgroup of 460 patients with total occlusion (TO) (TIMI flow 0) [43]. In this subgroup, patients with CTO (> three months duration) and patients with TO of less duration were included. About 80% of the patients with TO were male, with a mean age of 65 years. Diabetes mellitus was present in 30% and a previous MI in 40% of participants in the subgroup [43]. The procedural success rate of the TO revascularisation or recanalisation was low, with only 43.5% in the PCI arm and 60.5% in the CABG arm, and differed significantly between the two arms.

Study characteristics and results of included studies are displayed in Table A-1.

3.2.2 Additional included studies safety

Sicherheit: zusätzlich 6 nicht-randomisierte Kohortenstudien

PCI vs OMT: 4 Studien mit 3.593 Patient*innen

PCI vs OMT oder CABG: 2 Studien mit 3.025 Patient*innen

In addition to the seven RCTs included for effectiveness outcomes, we identified six prospective non-randomised studies (cohort studies and registries) with at least 200 participants [38-41, 44-47] to be included in the safety analyses. Two of these studies were multi-centre cohort studies [38, 39], two were single-centre cohort studies [41, 45-47], and the last two were single-centre registries [40, 44]. The studies were conducted in the Republic of Korea [38, 40, 44], in Italy [39], in Spain [45-47] and in China [41]. Four of the six studies, including 3,593 patients with CTO compared PCI to medical therapy only [38, 40, 41, 44], while two studies with 3,025 participants compared PCI to medical therapy or to CABG surgery [38, 39, 45-47]. Funding was only reported in two studies [39, 41]; the sponsor was non-commercial. To reduce the impact of selection bias and potential confounding factors, propensity-score-matching was performed in five of the six studies for the comparison PCI versus medical therapy [38-41, 44], but not for the comparison to CABG.

Personen mit CABG ausgeschlossen

mittleres Alter: 62-68 Jahre

All studies included patients with at least one CTO (TIMI flow 0 and minimum duration of three months). Patients with previous CABG procedures were excluded in most of the studies. The mean age of the participants ranged from 62 to 68 years, and 70% to 80% were male. About 30% to 50% of all participants had diabetes mellitus, while a previous MI was presented in about 30%. Location of the CTO was reported in four of the six studies, with 40% to 50% RCA.

Follow-up im Median 4 Jahre

Median length of follow-up was around four years (46 to 52 months) in four studies [40, 41, 44-47], one study had a mean follow-up of 26 months [38], and follow-up in the sixth study was 12 months [39].

Study characteristics and results of included observational studies are displayed in Table A-2 and in the evidence profile inTable A-6.

3.3 Results

3.3.1 PCI for CTO versus medical therapy

Mortality[1]

PCI vs OMT: Gesamtmortalität (6 RCTs) – kein Unterschied nach 1 bzw. 4 Jahren

For the comparison PCI versus OMT, **overall mortality** rates were reported in six RCTs [31, 33, 34, 36, 37, 42]. In summary, there were no significant differences in overall mortality rates between the PCI and OMT groups. A meta-analysis for a follow-up duration of up to one year after intervention, including five RCTs, resulted in a risk ratio (RR) of 1.71 [95% CI 0.54, 5.44] (p=0.40; heterogeneity: I^2=0%; see Figure 3-1). In addition, meta-analyses after a maximum of four years of follow-up including two RCTs with 1,117 patients [31, 33] resulted in RR 1.14 [95% CI 0.38, 3.40]; p=0.81; I^2=75% (see Figure 3-2).

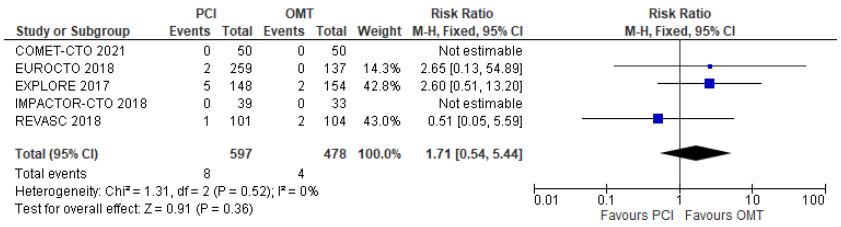

Figure 3-1: PCI versus OMT – Overall mortality at 1 year follow-up

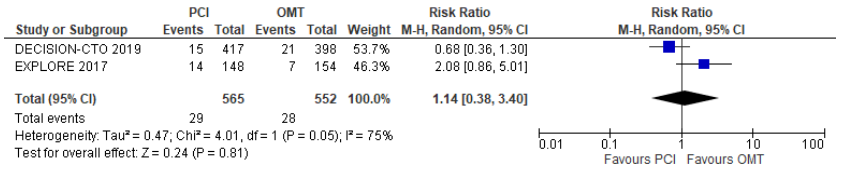

Figure 3-2: PCI versus OMT – Overall mortality at 4 years follow-up

PCI vs OMT: kardiale Mortalität (6 RCTs) – kein Unterschied nach 1 bzw. 4 Jahren

All six RCTs reported results on **cardiac mortality** [31, 33, 34, 36, 37, 42]. After up to one year of follow-up, there was no significant difference between patients treated with PCI for CTO and those treated with OMT in five RCTs, including 1,074 patients (RR 1.77 [95% CI 0.19, 16.06]; p=0.61; I^2=39%; see Figure 3-3). After a maximum of four years of follow-up, including three

[1] **D0001** – What is the expected beneficial effect of PCI for CTO on mortality in comparison to OMT?

RCTs [31, 33, 34] again, no statistically significant differences in cardiac mortality were reported between intervention and comparator (RR 1.64 [95% CI 0.35, 7.66]; p=0.53; I^2=71%; see Figure 3-4).

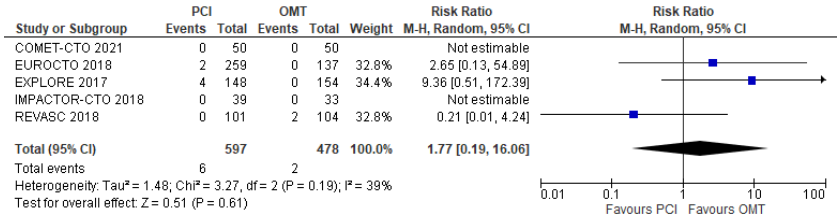

Figure 3-3: PCI versus OMT – Cardiac mortality at 1 year follow-up

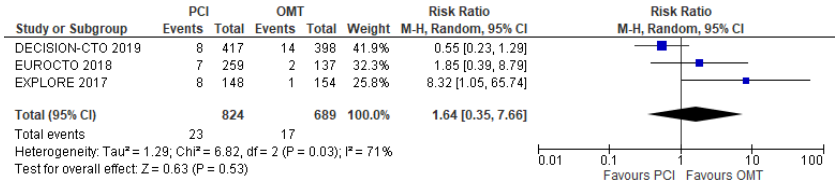

Figure 3-4: PCI versus OMT – Cardiac mortality at 4 years follow-up

Morbidity[2, 3]

PCI vs OMT: AP Symptome – Ergebnisse nicht eindeutig

Two RCTs comparing PCI with OMT reported the number of patients with **AP symptoms** after one year of follow-up [33, 34]. From baseline to follow-up, the percentage of patients with AP symptoms decreased in the PCI and the OMT arms, respectively. A meta-analysis including both RCTs resulted in a statistically significant difference in favour of the PCI arm after one year of follow-up (RR 0.63 [95% CI 0.49, 0.82]; p=0.0006; I^2=0%; see Figure 3-5).

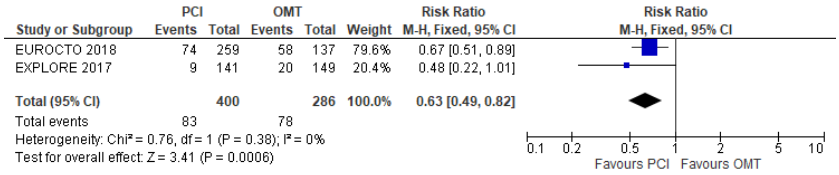

Figure 3-5: PCI versus OMT – Presence of AP symptoms at 1 year follow-up

In addition, in three RCTs, the participants were asked to complete the Seattle Angina Questionnaire (SAQ) after one year of follow-up [31, 34, 42]. A meta-analysis of the mean **SAQ angina frequency score** showed no statistically significant difference between PCI and OMT (mean difference (MD) 4.67 [95% CI -2.21, 11.55]; p=0.18; I^2=85%; see Figure 3-6). On the other hand,

[2] **D0005** – How does PCI for CTO affect angina pectoris symptoms and findings (severity, frequency) in comparison to OMT?

[3] **D0006** – How does PCI for CTO affect progression (or recurrence) of coronary heart disease in comparison to OMT?

the percentage of patients with a clinically relevant improvement of > 20 points in the AP frequency score was significantly higher (p=0.013) in the PCI arm of one RCT [34]. In the DECISION-CTO trial, angina frequency was also assessed after three years of follow up [31], again with no difference between PCI and OMT arm (MD 0.83 [95% CI-0.67 to 2.32]; p=0.27).

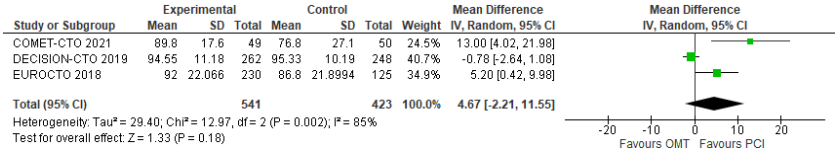

Figure 3-6: PCI versus OMT – SAQ angina frequency score at 1 year follow-up

PCI vs OMT: Verbesserung der LVEF in beiden Gruppen, aber kein Unterschied zwischen den Gruppen

Results on **LVEF** were reported in two RCTs [32, 37]. The REVASC trial [37] reported an improvement from baseline to six months of follow up in both study arms, with no difference between them (median 0.9% [IQR -1.3, 4.1] vs 0.7% [IQR -1.0, 3.7]; p=0.79). In the EXPLORE trial [32], participants' LVEF also improved from baseline to one year of follow-up in the PCI and OMT arm. At one year, the mean LVEF was 45.5% ± 9.1% in the PCI arm and 44.6% ± 10.7% in the OMT arm (p=0.66).

PCI vs OMT: wenige CABG im Follow-up, kein Unterschied zwischen PCI und OMT

The number of patients who underwent **CABG surgery** during follow up was reported in two RCTs [33, 42]. In the EXPLORE trial [33], three patients (2.0%) in the PCI arm and five patients (3.5%) in the OMT arm underwent CABG during 3.9 years of follow-up (p=0.53). In the COMET-CTO trial [42], only one patient in the PCI arm underwent CABG revascularisation during nine months follow-up. No CABG was reported for the OMT arm.

Function[4, 5]

PCI vs OMT: keine Ergebnisse zur Körperfunktion und Aktivitäten des täglichen Lebens

No evidence was found to answer this research question.

Health-related quality of life[6, 7]

PCI vs OMT: LQ – signifikante Vorteil nach 1 und 3 Jahren für PCI

Results on **generic HRQoL** were reported in three RCTs [31, 34, 36]. HrQoL was measured at baseline and at one and three years follow-up, using the SF-36 [36] or EQ-5D generic instruments [31, 34]. A meta-analysis of the two RCTs (885 patients) using the EQ5-D instrument showed a significant improvement in the overall EQ-5D visual analogue scale after 1-year follow-up for patients in the PCI arm compared to the OMT arm (MD 2.77 [95% CI 0.74, 4.80]; p=0.008; I^2=0%; see Figure 3-7). The third RCT, including 72 patients [36], reported significantly better results in all SF-36 subscales for PCI in comparison to OMT after one year (p<0.001). After three years of

[4] **D0011** – What is the effect of PCI for CTO on patients' body functions in comparison to OMT?

[5] **D0016** – How does the use of PCI for CTO affect activities of daily living in comparison to OMT?

[6] **D0012** – What is the effect of PCI for CTO on generic health-related quality of life in comparison to OMT?

[7] **D0013** – What is the effect of PCI for CTO on disease-specific quality of life in comparison to OMT?

follow-up, results on the EQ-5D in the DECISION-CTO trial [31] also showed a statistically significant advantage for PCI versus OMT (MD 3.59 [95% CI 1.18, 6.00]; p=0.004).

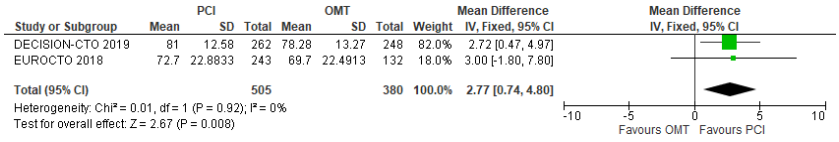

Figure 3-7: PCI versus OMT – HrQoL (EQ-5D VAS) at 1 year follow-up

PCI vs OMT: erkrankungsspezifische LQ – kein Unterschied nach 1 und 3 Jahren

Disease-specific QoL was assessed in three RCTs, using the SAQ-QoL score [31, 34, 42]. Patients were asked to complete the questionnaire at baseline and after one and three years. A meta-analysis including three RCTs and 957 patients showed no significant difference between PCI and OMT arm after one-year follow-up (MD 7.18 [95% CI -1.83, 16.19]; p=0.12; I^2=84%; see Figure 3-8). After three years of follow-up, SAQ-QoL scores after three years in the DECISION-CTO trial [31], including 360 patients, also were comparable between PCI and OMT arm (MD 0.73 [95% CI -3.26; 4.72]; p=0.72).

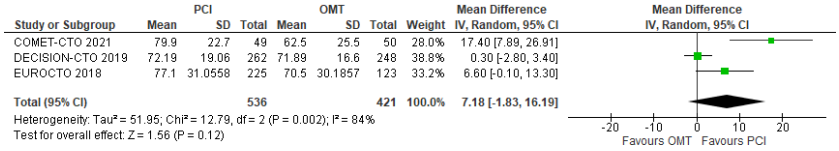

Figure 3-8: PCI versus OMT – Disease-specific QoL (SAQ QoL score) at 1 year follow-up

Patient satisfaction[8]

PCI vs OMT: Behandlungszufriedenheit – kein Unterschied nach 1 Jahr, Vorteil für PCI nach 3 Jahren

Patient satisfaction was assessed in three RCTs using the **SAQ treatment satisfaction score** [31, 34, 42]. Participants were asked to complete the questionnaire after one [31, 34, 42] and three years [31], respectively. A meta-analysis including results of 959 patients after a one-year follow-up showed a non-significant mean difference in SAQ treatment satisfaction score of 3.38 [95% CI -1.03, 7.80] between the PCI and OMT arm (p=0.13; I^2=72%; see Figure 3-9). Results after three years of follow-up from the DECISION-CTO trial (267 patients) [31] showed a significantly increased treatment satisfaction in patients of the PCI arm compared to patients in the OMT arm (MD 3.13 [95% CI 0.38, 5.89]; p=0.03).

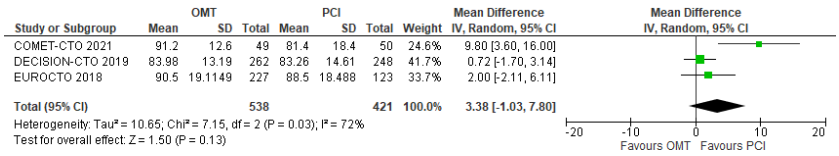

Figure 3-9: PCI versus OMT – SAQ treatment satisfaction score at 1 year follow-up

[8] **D0017** – Was the use of PCI for CTO worthwhile in comparison to OMT?

Patient safety[9, 10]

PCI vs OMT: MACE berichten in 4 RCTs und 5 nicht-randomisierten Studien

MACE – kein Unterschied nach 1 und 4 Jahren

Major adverse cardiac events (MACE) were reported in four RCTs [31, 33, 34, 37] and five prospective non-randomised clinical studies [38-41, 44], including a total of 5,582 patients.

A meta-analysis for a follow-up duration of up to one year after intervention including three RCTs (903 patients) [33, 34, 37] and one prospective non-randomised clinical study (1,238 propensity score matched patients) [39] showed a lower MACE rate in the PCI arm compared to the OMT arm (RR 0.56 [95% CI 0.32, 0.99]; p=0.05; I^2=55%; see Figure 3-10). In the additional meta-analysis including only results from RCTs the difference between PCI and OMT arm was not statistically significant (RR 0.69 [95% CI 0.36, 1.33]; p=0.27; I^2=43%).

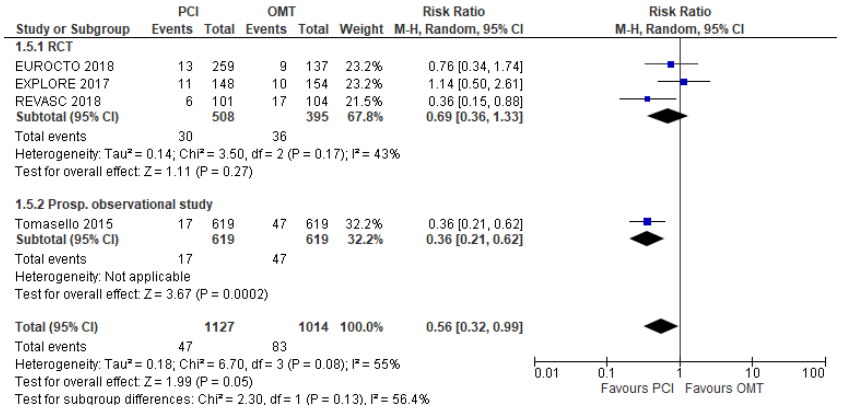

Figure 3-10: PCI versus OMT – MACE at 1 year follow-up

For MACE rates after a maximum of four years of follow-up including three RCTs with 1,513 patients [31, 33, 34] and four prospective non-randomised clinical studies (2,626 patients) [38, 40, 41, 44] the meta-analysis resulted in a non-significant RR of 0.89 [95% CI 0.74, 1.07]; p=0.22; I^2=52% (see Figure 3-11). The meta-analysis including only results from RCTs resulted in a RR of 0.85 [95% CI 0.60, 1.22]; p=0.38; I^2=53%).

[9] **C0008** – How safe is PCI for CTO in comparison to OMT?

[10] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of PCI for CTO in comparison to OMT?

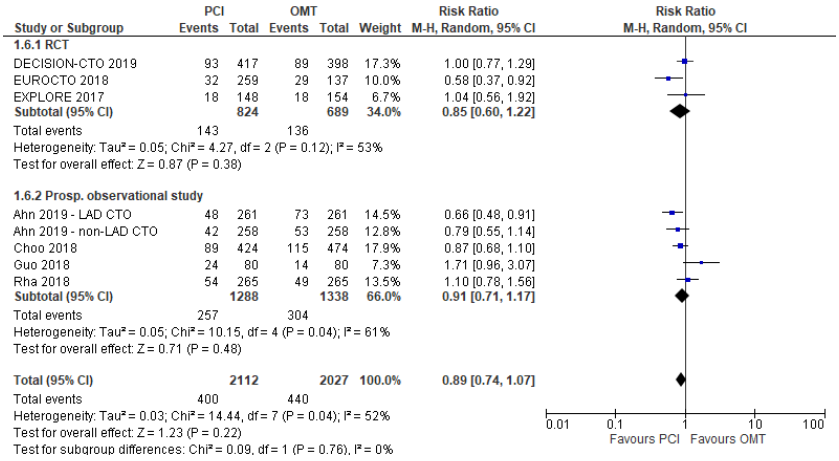

Figure 3-11: PCI versus OMT – MACE at 4 years follow-up

Myocardial infarctions during follow-up were reported in five RCTs [31, 33, 34, 37, 42] and five prospective non-randomised clinical studies [39-41, 44, 45]. A meta-analysis for a follow-up duration of up to one year after intervention including four RCTs (1,003 patients) [33, 34, 37, 42] and one prospective non-randomised clinical study (1,238 propensity score matched patients) [39] showed no significant difference in MI between PCI and OMT arm (RR 0.68 [95% CI 0.29, 1.58]; p=0.37; I^2=30%; see Figure 3-12). The meta-analysis including only results from RCTs (1,002 patients) showed an RR of 1.14 [95% CI 0.51, 2.57]; p=0.75; I^2=0%.

PCI vs OMT: Rate einzelner schwerer Nebenwirkungen wie MI oder Insult nach 1 bzw. 4 Jahren vergleichbar

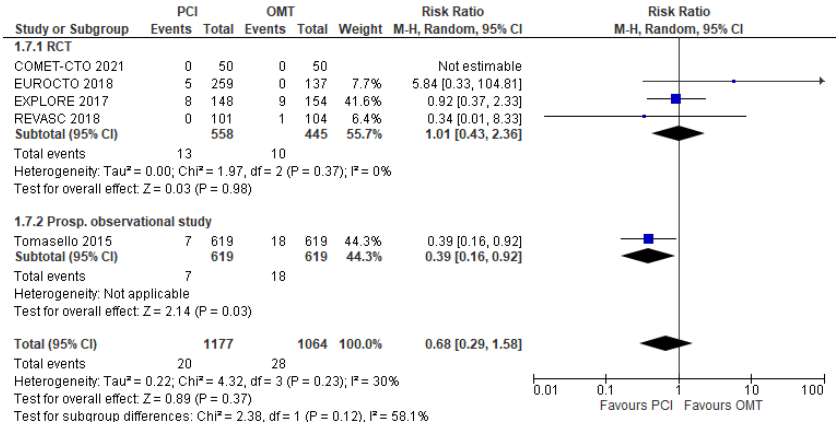

Figure 3-12: PCI versus OMT – MI at 1 year follow-up

A meta-analysis after four years follow-up including three RCTs (1,513 patients) [31, 33, 34] and four prospective non-randomised clinical studies (2,687 patients) [40, 41, 44, 45] resulted in a RR of 1.04 [95% CI 0.80, 1.34]; p=0.80; I^2=0% (see Figure 3-13). Including only RCTs (1,513 patients) resulted in a RR of 1.24 [95% CI 0.87, 1.77]; p=0.23; I^2=0%.

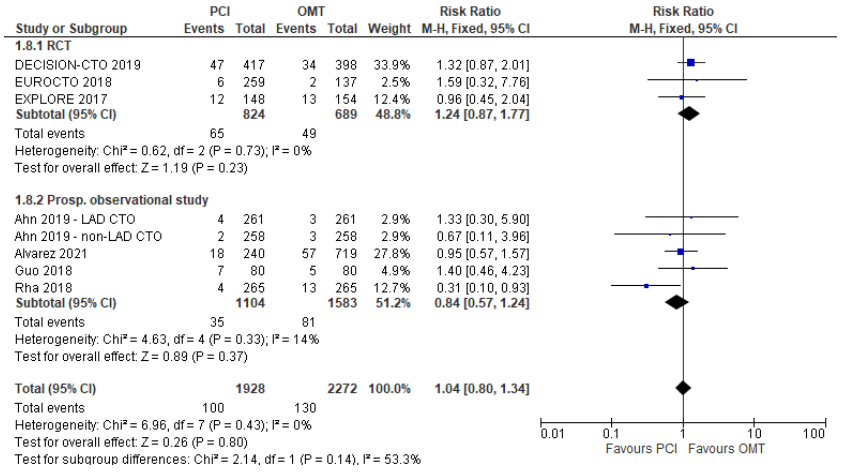

Figure 3-13: PCI versus OMT – MI at 4 years follow-up

Event rates for **stroke** during follow-up were reported in four RCTs [31, 33, 34, 42] and two prospective non-randomised clinical studies [39, 40]. A meta-analysis for a follow-up duration of up to one year after intervention including two RCTs (496 patients) [34, 42] and one prospective non-randomised clinical study (1,238 propensity score matched patients) [39] showed comparable stroke rates in the PCI and the OMT arm (RR 0.55 [95% CI 0.11, 2.69]; p=0.46; I^2=0%; see Figure 3-14). In the meta-analysis including only results from RCTs the RR was 1.06 [95% CI 0.10, 11.56]; p=0.96; I^2=n.a.).

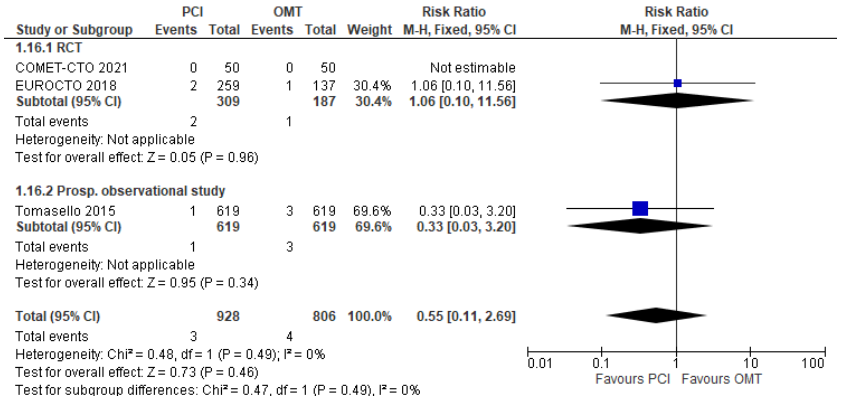

Figure 3-14: PCI versus OMT – Stroke at 1 year follow-up

For stroke rates after a maximum of four years of follow-up including two RCTs with 1,117 patients [31, 33] and one prospective non-randomised clinical study (530 patients) [40] the meta-analysis resulted in a non-significant RR of 0.64 [95% CI 0.30, 1.35]; p=0.24; I^2=0% (see Figure 3-15). The meta-analysis including only results from RCTs resulted in a RR of 0.56 [95% CI 0.24, 1.32]; p=0.18; I^2=0%).

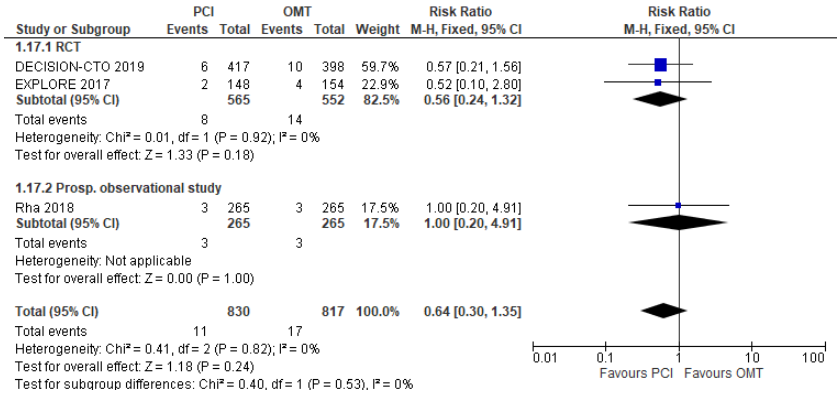

Figure 3-15: PCI versus OMT – Stroke at 4 years follow-up

The occurrence of **stent thrombosis** during follow-up was reported in four RCTs [33, 34, 37, 42]. None of the included prospective non-randomised clinical studies reported results on this outcome. Event rates were generally very low, with no difference between PCI and OMT arms (overall one event in PCI arm and one event in OMT arm during one year follow up six events in PCI and OMT arm, respectively during four years of follow-up).

PCI vs OMT: Stent Thrombosen insgesamt selten, kein Unterschied zwischen den Interventionen

Rates of **target vessel revascularisations** (TVR) during follow-up were reported in all six RCT [31, 33, 36, 37, 42] and in one prospective non-randomised clinical study [40] investigating PCI versus OMT. A meta-analysis after one year follow-up including five RCTs with 1,075 patients [33, 34, 36, 37, 42] showed statistically significant more TVRs in the OMT arm compared to the PCI arm (RR 0.28 [95% CI 0.17, 0.48]; p<0.001; I^2=0%; see Figure 3-16).

PCI vs OMT: Revaskularisationen im betroffenen Gefäß – signifikanter Vorteil für PCI nach 1 Jahr, kein Unterschied nach 4 Jahren

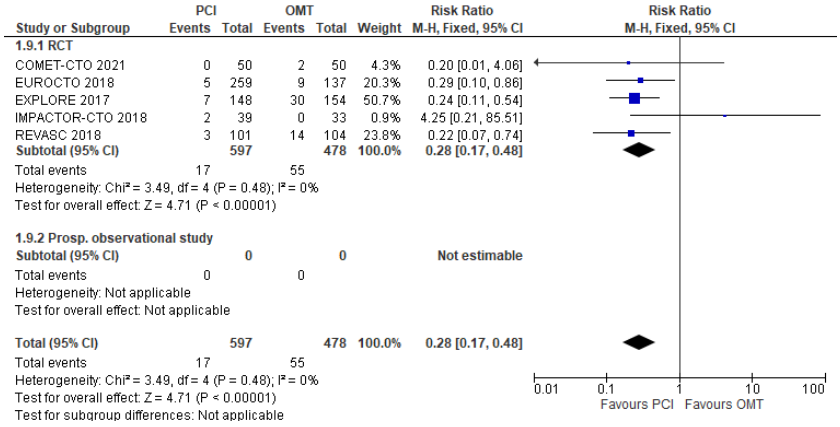

Figure 3-16: PCI versus OMT – TVR at 1 year follow-up

After four years of follow-up, neither the meta-analysis including all studies (two RCTs [31, 33] and one prospective non-randomised clinical study [40]; 1,647 patients) nor the meta-analysis including only RCTs (1,117 patients) resulted in a statistically significant difference between PCI and OMT arm (RR 1.11 [95% CI 0.35, 3.54; p=0.18; I^2=91% and RR 0.64 [95% CI 0.23, 1.75]; p=0.38; I^2=86%, respectively; see Figure 3-17).

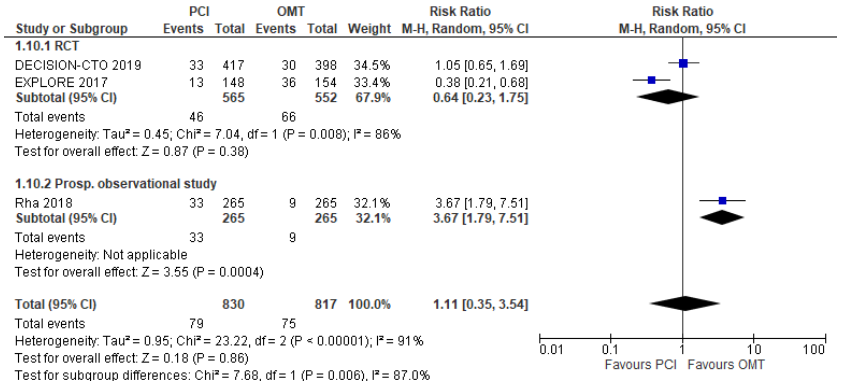

Figure 3-17: PCI versus OMT – TVR at 4 years follow-up

Geringe Mortalität mit Bezug zur PCI der CTO

In the PCI arms of the included studies, there were no **peri-procedural deaths** reported in five RCTs and two peri-procedural deaths (0.3%) in one prospective non-randomised clinical study [39].

Akuter CABG: 0 % bis 0,3 % bei PCI

Data on acute emergency CABG were available from three of the six included RCTs [32, 37, 42]. All of them reported that no emergency CABG procedures occurred. One prospective non-randomised clinical study reported that an emergency CABG surgery was necessary for two patients of the PCI arm (0.3%) [39]

Subgruppen-Analysen aus 2 RCTs und 1 nicht-randomisierten Studie: keine signifikanten Unterschiede

Subgroup analysis with respect to age, gender, CTO location, diabetes status Syntax score or LVEF at baseline in two RCTs [31, 33] comparing PCI to OMT showed no significant increase in MACE or death rates in any of these patient groups. For one prospective non-randomised study, results for the patient group with diabetes mellitus [46] and for older patients [47] were published separately. Both publications reported no increased risk for MI for these selected patients treated with PCI compared to medical therapy [46, 47].

3.3.2 PCI for CTO versus CABG

Mortality[11]

PCI vs CABG: Gesamtmortalität (1 RCT) – kein Unterschied nach 10 Jahren; keine Ergebnisse zur kardialen Mortalität

For the comparison PCI versus CABG, **overall mortality** rates were reported in one RCTs [43]. After ten years of follow-up the subgroup analysis of 460 patients with CTO from the SYNTAX trial showed no significant differences between patients who underwent PCI or those who underwent CABG for the CTO-lesion (patients with 3VD: 29.3% vs 21.0%; hazard ratio (HR) 0.673 [95% CI 0.437 to 1.037]; p=0.073; patients with LM: 30.5% vs 40.9%; HR 1.539 [95% CI 0.814 to 2.911]; p=0.185).

There were no results from RCTs on **cardiac mortality** for the comparison PCI versus CABG.

[11] **D0001** – What is the expected beneficial effect of PCI for CTO on mortality in comparison to CABG?

Morbidity [12, 13]

The number of patients without **AP symptoms** were reported in a subgroup analysis for patients with total occlusion from one RCTs comparing PCI with CABG [43]. In both study arms, the percentage of patients without AP symptoms increased significantly from baseline to five-year follow-up. A comparison of the two study groups showed that there were fewer participants without angina symptoms in die PCI arm compared to the CABG arm after five years of follow-up (121/172 (70.3%) vs 123/152 (80.9%); p=0.03).

PCI vs CABG: Verbesserung in beiden Gruppen, signifikant mehr Patient*innen ohne AP Symptome mit CABG nach 5 Jahren

No results from RCT on change in **LVEF** were reported for the comparison PCI versus CABG.

keine Ergebnisse zur LVEF

Function[14, 15]

No evidence was found to answer this research question.

PCI vs CABG: keine Ergebnisse zur Körperfunktion oder zu Aktivitäten des täglichen Lebens

Health-related quality of life[16, 17]

No Results from RCTs were found to answer this question for the comparison PCI versus CABG.

PCI vs CABG: keine Ergebnisse zur LQ generell oder zur erkrankungsspezifischen LQ

Patient satisfaction [18]

No Results from RCTs were found to answer this question for the comparison PCI versus CABG.

PCI vs CABG: keine Ergebnisse zur Patient*innenzufriedenheit

Patient safety [19, 20]

No results from RCTs on safety outcomes were reported for the comparison PCI versus CABG.

PCI vs CABG: nur Ergebnisse aus nicht-randomisierten Studien

Results on the occurrence of **MACE** were only available from one prospective non-randomised study [39]. After one year of follow-up, the MACE rate was statistically significant lower in the PCI arm (2.6%) compared to the CABG arm (6.9%) (p<0.05, unadjusted results including the entire, unmatched study population. MACE was defined as a combination of cardiac mortality, MI or stroke in this study.

MACE: signifikant geringere Rate mit PCI

---

[12] **D0005** – How does PCI for CTO affect angina pectoris symptoms and findings (severity, frequency) in comparison to CABG?

[13] **D0006** – How does PCI for CTO affect progression (or recurrence) of coronary heart disease in comparison to CABG?

[14] **D0011** – What is the effect of PCI for CTO on patients' body functions in comparison to CABG?

[15] **D0016** – How does the use of PCI for CTO affect activities of daily living in comparison to CABG?

[16] **D0012** – What is the effect of PCI for CTO on generic health-related quality of life in comparison to CABG?

[17] **D0013** – What is the effect of PCI for CTO on disease-specific quality of life in comparison to CABG?

[18] **D0017** – Was the use of PCI for CTO worthwhile in comparison to CABG?

[19] **C0008** – How safe is PCI for CTO in comparison to CABG?

[20] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of PCI for CTO in comparison to CABG?

kein Unterschied bei MI

The rate of **myocardial infarctions** after one or for years of follow-up was reported in two studies [39, 45], with no difference between PCI and CABG arms (1.0% vs 0.6% after one year; 8.0% vs 4.0% after four years).

keine Ergebnisse zu Stent Thrombosen oder Revaskularisation

The number of **stroke** events during follow-up was reported in one study [39], with a statistically significant lower rate in the PCI arm compared to the CABG arm (0.1% vs 5.1%; $p<0.001$).

No results were reported on **stent thrombosis, TVR** or **procedure-related mortality** in any of the included studies.

Subgruppen-Analysen aus 1 nicht-randomisierten Studie: keine signifikanten Unterschiede

For one prospective non-randomised study, results for the patient group with diabetes mellitus [46] and for older patients [47] were published separately. Both publications reported no increased risk for MI for these selected patients treated with PCI compared to CABG [46, 47].

4 Certainty of evidence

Verzerrungspotenzial: Cochrane RoB 2 und ROBINS-I

RoB for individual studies was assessed with the Cochrane RoB v.2 tool (for RCTs) [49] and the ROBINS-I tool (for non-randomised studies) [50] and is presented in Table A-3, Table A-4, Table A-5 and Table A-6 in the Appendix.

Across the seven included RCTs, three were ranked as having low RoB, three as having moderate RoB and one as having a high RoB. Four of the six included non-randomised studies for safety outcomes were ranked as having a moderate RoB, while one was ranked as having a serious RoB and one as having a critical RoB.

RCT: mehrheitlich geringes bis moderates RoB

The main reason for a moderate RoB in two RCTs was the limited information about awareness of the outcome assessors of participants' assignment to intervention. In the RCT with high RoB, reasons for judgement were the general lack of information on the methodology of the study (randomisation process, outcome assessment, statistical considerations) and the patient-reported outcome measures in the absence of blinding. For non-randomised clinical studies, the main reasons for increased RoB were the awareness of the outcome assessors of participants' assignment to intervention and the potential for confounding of the effect of intervention due to unbalanced baseline characteristics.

Vertrauenwürdigkeit der Evidenz nach GRADE

The certainty of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [52] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [52].

GRADE uses four categories to rank the certainty 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 in the evidence profile in Appendix Table A-7 and Table A-8.

Vertrauenwürdigkeit der Evidenz insgesamt moderate für PCI vs OMT und niedrig bis sehr niedrig für PCI vs CABG

Overall the certainty of evidence for the effectiveness and safety of PCI for CTO in comparison to medical therapy is moderate (see Table 4-1. For comparing PCI for CTO and CABG, the overall certainty of evidence for the effectiveness and safety is low to very low (see Table 4-2).

Table 4-1: Summary of findings table of PCI for CTO versus OMT

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with OMT	Risk with PCI for CTO				
EFFECTIVENESS						
Overall mortality – 1 year	8 per 1,000	14 per 1 000 (4 to 49)	RR 1.7 (0.5 to 5.8)	1,075 (5 RCTs)	⨁⨁⨁◯ Moderate	
Overall mortality – 4 years	51 per 1,000	58 per 1 000 (19 to 172)	RR 1.14 (0.38 to 3.40)	1,117 (2 RCTs)	⨁⨁◯◯ Low	
AP symptoms – 1 year	273 per 1,000	177 per 1 000 (136 to 229)	RR 0.65 (0.50 to 0.84)	686 (2 RCTs)	⨁⨁⨁◯ Moderate	
AP frequency – 1 year	The mean SAQ-AP frequency score was 92.14	MD 4.67 higher (2.21 lower to 11.55 higher)	-	964 (3 RCTs)	⨁⨁⨁◯ Moderate	
AP frequency – 3 years	The mean SAQ-AP frequency score was 97.38	MD 0.83 higher (0.67 lower to 2.32 higher)	-	360 (1 RCT)	⨁⨁◯◯ Low	Only 1 RCT
CABG surgery – 9 months to 3.9 years	not pooled			402 (2 RCTs)	⨁⨁◯◯ Low	1 RCT: 2.0% vs 3.5% of patients in 3.9 years of follow-up; 1 RCT: 2.0% vs 0% of patients in 9 months of follow-up.
Generic HrQoL – 1 year	The mean EQ-5D-VAS score was 75.30	MD 2.77 higher (0.74 higher to 4.8 higher)	-	885 (2 RCTs)	⨁⨁⨁◯ Moderate	1 additional RCT (72 participants) showed statistically significant higher SF-36 scores after 1 year of follow-up in the PCI arm compared to OMT arm.
Disease specific QoL – 1 year	The mean SAQ-QoL score was 70.37	MD 7.18 higher (1.83 lower to 16.19 higher)	-	957 (3 RCTs)	⨁⨁◯◯ Low	
SAFETY						
MACE – 1 year	91 per 1,000	63 per 1,000 (33 to 121)	RR 0.69 (0.36 to 1.33)	903 (3 RCTs)	⨁⨁⨁◯ Moderate	Only RCTs included in the analysis
MACE – 4 years	197 per 1,000	168 per 1,000 (118 to 241)	RR 0.85 (0.60 to 1.22)	1,513 (3 RCTs)	⨁⨁⨁◯ Moderate	Only RCTs included in the analysis
MI – 1 year	22 per 1,000	26 per 1,000 (11 to 58)	RR 1.14 (0.51 to 2.57)	1,003 (4 RCTs)	⨁⨁⨁◯ Moderate	Only RCTs included in the analysis
MI – 4 years	71 per 1,000	88 per 1,000 (62 to 126)	RR 1.24 (0.87 to 1.77)	1,513 (3 RCTs)	⨁⨁⨁⨁ High	Only RCTs included in the analysis
Stroke – 1 year	5 per 1,000	6 per 1,000 (1 to 62)	RR 1.06 (0.10 to 11.56)	496 (2 RCTs)	⨁⨁◯◯ Low	Only RCTs included in the analysis
Stroke – 4 years	25 per 1,000	14 per 1,000 (6 to 33)	RR 0.56 (0.24 to 1.32)	1,117 (2 RCTs)	⨁⨁◯◯ Low	Only RCTs included in the analysis
Stent thrombosis – 1 to 4 years	not pooled			1,003 (4 RCTs)	⨁⨁⨁◯ Moderate	Overall 7 events in both study arms during 1 to 4 years of follow up.
Target vessel revascularisation – 1 year	115 per 1,000	32 per 1,000 (20 to 55)	RR 0.28 (0.17 to 0.48)	1,075 (5 RCTs)	⨁⨁⨁⨁ High	Only RCTs included in the analysis
Target vessel revascularisation – 4 years	120 per 1,000	77 per 1,000 (28 to 209)	RR 0.64 (0.23 to 1.75)	1,117 (2 RCTs)	⨁⨁◯◯ Low	Only RCTs included in the analysis

Abbreviations: AP – angina pectoris; CI – confidence interval; CTO – chronic total occlusion; HrQoL – health-related quality of life; MACE – major adverse coronary events; MI – myocardial infarction; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; QoL – quality of life; RCT – randomised controlled trial; RR – risk ratio; vs – versus

Table 4-2: Summary of findings table of PCI for CTO versus CABG

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty	Comments
	Risk with CABG	Risk with PCI for CTO				
EFFECTIVENESS						
Overall mortality – 10 year	247 per 1,000	257 per 1,000 (138 to 483)	RR 1.04 (0.5 to 5.8)	460 (1 RCT)	⨁◯◯◯ Very low	Subgroup-analysis for patients with total occlution from 1 RCT
AP frequency – 5 years	not pooled			324 (1 RCT)	⨁◯◯◯ Very low	Subgroup-analysis for patients with total occlution from 1 RCT: After 5 years of follow-up there were less participants without angina symptoms in the PCI arm compared to the CABG arm (121/172 (70.3%) vs 123/152 (80.9%); p=0.03)
Generic HrQoL	No evidence available					
Disease specific QoL	No evidence available					
SAFETY						
MACE – 1 year	not pooled			903 (1 cohort study)	⨁◯◯◯ Very low	Significant less MACE in PCI arm compared to CABG arm after 1 year follow-up: 20/776 (2.6%) vs 12/175 (6.9%); p<0.05
MI – 1 to 4 years	not pooled			1,480 (2 cohort studies)	⨁◯◯◯ Very low	1 cohort study: 8.0% vs 4.0% of patients in 4 years follow-up; 1 cohort study: 1.0% vs 0,6% of patients in 1 year follow-up. Both results statistically not significant.
Stroke – 1 year	not pooled			903 (1 cohort study)	⨁◯◯◯ Very low	Significant lower stroke rate in PCI arm compared to CABG arm after 1 year follow-up: 1/776 (0.1%) vs 9/175 (5.1%); p<0.001
Stent thrombosis	No evidence available					
Target vessel revascularisation – 4 years	No evidence available					

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CI – confidence interval; CTO – chronic total occlusion; HrQoL – health-related quality of life; MACE – major adverse coronary events; MI – myocardial infarction; PCI – percutaneous coronary intervention; QoL – quality of life; RCT – randomised controlled trial; RR – risk ratio; vs – versus

5 Discussion

Coronary heart disease is the most common cause of death in developed countries. A significant proportion of patients with CHD may have CTOs of the coronary arteries. CTO are defined as completely occluded coronary arteries with an occlusion duration of at least three months. Beside a primary drug therapy for CHD, CABG or PCI may also be indicated for the treatment of CTOs, to relieve AP symptoms and to prolong life expectancy.

The main purpose of this report is to compare the efficacy and safety of PCI to medical treatment or CABG in patients with CTO.

5.1 Summary of findings

6 RCTs zu PCI vs. OMT und 1 RCT zu PCI vs. CABG eingeschlossen

zusätzlich 6 nicht-randomisierte Studien für Sicherheitsendpunkte eingeschlossen

Since the first report on PCI for CTO published in 2013 by the LBI-HTA [1] seven RCTs have been published and included in this 2022 update. Six RCTs, including a total of 1,911 participants with CTO, investigated PCI compared to OMT [31-37, 42], while one RCT with 460 patients with TO investigated PCI compared to CABG [43]. In addition, six larger prospective non-randomised studies (cohort or registry studies) with 6,618 patients were included for the safety endpoints [38-41, 44-47]. The median duration of follow-up for the comparison of PCI versus OMT ranged from nine months to about four years, and for the comparison of PCI versus CABG, it ranged from one to ten years.

Overall, the results on efficacy and safety of PCI for CTO compared with OMT or CABG can be summarized as follows:

kein Unterschied bei Mortalität

- No difference in all-cause mortality at one to four years follow-up for PCI versus OMT or at ten years follow-up for PCI versus CABG
- No difference in terms of avoidance of more invasive procedures (such as CABG) at one to four years follow-up for PCI versus OMT

Trend hinsichtlich Verbesserung der AP-Symptomatik

- A tendency to AP-symptom improvement for PCI compared with OMT at one year, but no difference at three years follow-up; significantly less AP-symptom improvement for PCI compared with CABG at five years follow-up.
- Significant improvement in generic HrQoL for PCI compared with OMT after one to four years, and a tendency in improvement in disease-specific QoL after one year, but without statistical significance; after three years, no difference in disease-specific QoL. No results on QoL for the comparison PCI versus CABG

keine erhöhte Rate an schweren kardialen Nebenwirkungen

- No difference in MACE rates at one to four years follow-up for PCI compared to OMT, but significantly lower MACE rates for PCI compared to CABG at one-year follow-up
- Very low rates of peri-procedural mortality, acute CABG surgery, and stent thrombosis with no difference between PCI and OMT
- Significantly lower TVR rates within one year follow-up for PCI compared to OMT, but no significant difference after four years

5.2 Internal and external validity

CTO mit einem erhöhten Mortalitätsrisiko assoziiert

PCI vs. OMT: Beobachtungsstudien zeigen Senkung des Mortalitätsrisikos durch PCI der CTO

Mortalitätsrate: Senkung durch PCI durch Ergebnisse aus RCTs nicht bestätigt

Limitationen in den RCTs: fehlende statistische Power, hohe Cross-over Raten

Based on the results of retrospective studies, CTO is associated with an increased mortality risk in patients with CHD [58-61]. Revascularisation or recanalization of the affected vessel using PCI or CABG technique in addition to OMT should therefore lead to a short- and long-term reduction of this mortality risk. Some recent systematic reviews based on prospective and retrospective observational studies showed significantly lower mortality rates for PCI of the CTO compared to medical therapy alone [26-28]. However, the meta-analyses based on the included six RCTs in this update report cannot confirm this advantage. However, there are some limitations to these results. First, the study population of the individual RCTs is quite heterogeneous. For example, one RCT included only patients with STEMI after successful PCI [32, 33, 35]. In this trial, the rate of successful PCI of the CTO was comparatively low at 73%. Another RCT included only patients with isolated dominant RCA CTO and stable angina [36]. Secondly, the primary end points in the individual RCTs were quite different – some surrogate end points and some combined end points – and none of the RCTs was calculated for a potential difference in mortality rates. Therefore, the individual RCTs were mostly underpowered with respect to show a mortality difference. One of the trials was also terminated due to insufficient recruitment, resulting in the inclusion of only 834 patients instead of the originally planned 1,284 [31]. There was also a high cross-over rate between groups in this RCT. About 20% of the participants randomised to OMT received PCI, whereas about 7% from the PCI arm did not receive PCI of the CTO.

PCI vs CABG: kein Unterschied bei Mortalität

RCT: nicht nur CTO Patient*innen eingeschlossen

sehr geringe Rate an erfolgreichen Eingriffen: 43 %

Directly comparing PCI of a total occluded coronary artery to the more invasive procedure, CABG, there was neither a disadvantage nor an advantage in the mortality rate for PCI after ten years of follow-up [43]. However, further analyses from this trial comparing patients with successful revascularisation or recanalization of the TO with those without revascularisation or recanalization of the TO showed also no difference in 10-year all-cause mortality [43]. Nevertheless, it should be noted that the results are only a subgroup analysis of an RCT on the treatment of complex CHD (3VD and/or LM), i.e. the patients were not included in the study because of CTO. In addition, the results are only indirectly applicable to patients with CTO, because all subjects with total occlusions of coronary arteries were included in the analysis, irrespective of the duration of the occlusion (i.e., also patients with a duration of total occlusion less than three months). The proportion of individuals with a CTO was not reported in the trial. Also notable in this study is the low success rate of PCI of the TO (43%), which was also significantly different from the success rate in the CABG arm (60%). According to the study authors, this is due to the fact that the RCTs was not focused on the complex treatment of TOs and available of devices and techniques at the time of the study (2007 to 2009), which did not correspond to the state of the art of CTO-PCI treatment nowadays [43].

AP-Symptomatik und LQ: Trend hinsichtlich Vorteil für PCI

subjektiver Endpunkt bei fehlender Verblindung – hohes Verzerrungspotenzial

Another important purpose of PCI of a CTO is the improvement of symptoms and the associated improvement of the quality of life. Based on the included RCTs, the evidence is inconclusive. Overall, there seems to be a numerical advantage in terms of improvement of AP symptoms and quality of life in favour of PCI, but this is not statistically significant in all cases. The reasons for this may be that although a total of six RCTs comparing PCI versus OMT were included, only a few investigated a change in AP symptoms and

quality of life. Furthermore, in some trials, results for these outcomes were only available for a relatively small proportion of study participants, leading to underpowering and potential bias in the results. With regard to the risk of bias, it should also be noted that AP symptoms and quality of life are subjective patient-reported outcomes, which may be considered problematic given the lack of blinding of participants to the intervention in all included RCTs.

Sicherheit: PCI vs. OMT – kein Unterschied in MACE

PCI vs. CABG: keine ausreichende Evidenz

Regarding the safety of PCI for CTO, meta-analyses based on RCTs and additional larger prospective non-randomised studies did not show a significantly increased rate of MACE compared with OMT at one to four years. However, the definitions of MACE used in the individual studies were quite different. Analyses of the individual components of MACE were therefore performed and found no significant difference for MI and stroke. In TVR, however, an advantage for PCI compared with medical therapy alone was found after one year, but this was no longer observed after four years of follow-up. Overall, when interpreting the results on MACE, the same limitations as for mortality should be noted, such as a heterogeneous sample of participants and relatively high cross-over rates in the trials. Compared with CABG, lower MACE rates at one year are reported for PCI of CTO. However, this result is based only on an unmatched analysis of a non-randomised study. Significant differences in individual baseline parameters were reported between patients in the PCI and CABG arms, which means that potential confounding cannot be excluded. In addition, only 175 subjects were included in the CABG arm (compared to 776 subjects in the PCI arm). Therefore the current evidence in insufficient with regard to safety outcomes for PCI versus CABG for CTO.

PCI bei CTO: komplexer, aufwändiger Eingriff

nur von erfahrenen, speziell ausgebildeten Operateuren durchführbar

Patient*innenauswahl sehr wichtig

PCI for CTO is a complex intervention that requires much more time and effort than PCI for only stenosed vessels. While the success rates of CTO-PCI were initially only 50%-70% [11], they could be increased to more than 90% in recent years due to further developments in the devices and the techniques of the intervention, as also shown by the results of the included RCTs. Nevertheless, the procedure requires special knowledge and experience of the physician and should only be performed in specialized centers [62]. A major issue with regard to successful intervention and a good prognosis is the selection of suitable patients using an appropriate risk stratification [62]. While the current American College of Cardiology/American Heart Association guideline on coronary artery revascularisation states that the benefit of PCI of the CTO in terms of symptom improvement is unclear [9], the current guideline of the European Society of Cardiology on revascularisation recommends PCI of the CTO in patients with angina resistant to medical therapy or with a large area of documented ischaemia in the territory of the occluded vessel [63].

5.3 Limitation of the report

Limitationen: nur RCTs und große nicht-randomisierte Vergleichstudie eingeschlossen

This report is limited to RCTs for efficacy outcomes, and to RCTs and non-randomised studies with more than 200 for safety outcomes. Therefore, retrospective studies or registries and uncontrolled single-arm studies were excluded. As a result, not all the full body of evidence was considered. However, since RCTs, if conducted in a methodologically adequate manner and appropriate to the respective research question, are affected by the lowest uncertainty of results, the excluded studies would not have changed the interpretation and the drawn conclusion of the report.

keine individuellen Patient*innendaten

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

5.4 Ongoing sudies

5 laufende RCTs zu PCI vs. OMT; keine zu PCI vs. CABG

Five ongoing RCTs compare PCI to medical therapy in patients with CTO are listed in clinical trials registries. Two of the RCTs should have been completed in 2021, while the completion date of the remaining three RCTs is between 2023 and 2028 (see Appendix).

No ongoing RCT could be identified to compare PCI versus CABG in patients with CTO.

5.5 Conclusion

insgesamt leichter Vorteil für PCI im Vergleich zu OMT hinsichtlich Symptomverbesserung bei vergleichbarer Komplikationsrate

keine verlässliche Aussage zu PCI vs CABG möglich

Overall, on the basis of the available evidence from six RCTs with 1,911 patients, PCI of CTO compared with medical treatment alone shows no effect on all-cause mortality and thus on overall survival, but indicates a short- and medium-term improvement in AP symptoms and consequently in quality of life. At the same time, no increased MACE rates or procedural mortality rates were observed with PCI for CTO. These results are in line with some recently published systematic reviews on this topic [24, 30]. In addition to the available evidence, five ongoing RCTs were identified that investigated PCI of CTO compared with medical therapy in different patient groups. For the comparison of PCI to CABG for CTO, there is currently insufficient evidence to conclusively assess efficacy and safety.

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlung

Table 6-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	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 indicates that the assessed technology PCI for CTO is more effective in terms of AP-symptom relief and improvement of QoL and equally safe than the comparator of medical therapy alone. The technology should thereby be restricted to selected patients and limited to specialised clinical settings.

The re-evaluation is recommended in 2028.

Re-Evaluierung 2028

7 References

[1] Nachtnebel A, Warmuth M. Perkutane koronare Intervention bei chronischen Komplettverschlüssen. Decision Support Document Nr.642013.

[2] Statistik Austria. *Gestorbene 2020 nach Todesursachen, Alter und Geschlecht*. 28.06.2021; Available from: http://www.statistik.at/wcm/idc/idcplg?IdcService=GET_NATIVE_FILE&RevisionSelectionMethod=LatestReleased&dDocName=021987 [cited 15.02.2020].

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

[4] Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010; 31 (20): 2501-55.

[5] Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005; 112 (15): 2364-72.

[6] Di Mario C, Werner GS, Sianos G, et al. European perspective in the recanalisation of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. *EuroIntervention*. 2007; 3 (1): 30-43.

[7] Shah PB. Management of coronary chronic total occlusion. *Circulation*. 2011; 123 (16): 1780-4.

[8] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020; 41 (3): 407-77.

[9] Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022; 145 (3): e18-e114.

[10] Stone GW, Reifart NJ, Moussa I, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation*. 2005; 112 (16): 2530-7.

[11] Whitlow PL, Burke MN, Lombardi WL, et al. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. *JACC Cardiovasc Interv*. 2012; 5 (4): 393-401.

[12] Sumitsuji S, Inoue K, Ochiai M, et al. Fundamental wire technique and current standard strategy of percutaneous intervention for chronic total occlusion with histopathological insights. *JACC Cardiovasc Interv*. 2011; 4 (9): 941-51.

[13] Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005; 26 (8): 804-47.

[14] Kimura M, Katoh O, Tsuchikane E, et al. The efficacy of a bilateral approach for treating lesions with chronic total occlusions the CART (controlled antegrade and retrograde subintimal tracking) registry. *JACC Cardiovasc Interv*. 2009; 2 (11): 1135-41.

[15] Galassi AR, Tomasello SD, Reifart N, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention*. 2011; 7 (4): 472-9.

[16] Barlis P, Kaplan S, Dimopoulos K, et al. An indeterminate occlusion duration predicts procedural failure in the recanalization of coronary chronic total occlusions. *Catheter Cardiovasc Interv*. 2008; 71 (5): 621-8.

[17] Ge L, Iakovou I, Cosgrave J, et al. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur Heart J*. 2005; 26 (11): 1056-62.

[18] Lee SW, Lee JY, Park DW, et al. Long-term clinical outcomes of successful versus unsuccessful revascularization with drug-eluting stents for true chronic total occlusion. *Catheter Cardiovasc Interv*. 2011; 78 (3): 346-53.

[19] Niccoli G, De Felice F, Belloni F, et al. Late (3 years) follow-up of successful versus unsuccessful revascularization in chronic total coronary occlusions treated by drug eluting stent. *Am J Cardiol*. 2012; 110 (7): 948-53.

[20] Mehran R, Claessen BE, Godino C, et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv*. 2011; 4 (9): 952-61.

[21] Han Y, Zhang J, Li Y, et al. Long-term outcomes of drug-eluting versus bare-metal stent implantation in patients with chronic total coronary artery occlusions. *Chinese Medical Journal* 2009; 122 (6): 643-7.

[22] Liu W, Ma C, Kang J, et al. Comparison of drug eluting stent implantation with coronary artery bypass surgery in the treatment of patients with chronic total occlusion and multiple vessel disease. *Chinese Medical Journal*. 2011; 124 (8): 1169-74.

[23] Abo-Aly M, Misumida N, Backer N, et al. Percutaneous Coronary Intervention With Drug-Eluting Stent Versus Optimal Medical Therapy for Chronic Total Occlusion: Systematic Review and Meta-Analysis. *Angiology*. 2019; 70 (10): 908-15.

[24] Barbarawi M, Kheiri B, Zayed Y, et al. Meta-analysis of Percutaneous Coronary Intervention Versus Medical Therapy in the Treatment of Coronary Chronic Total Occlusion. *American Journal of Cardiology*. 2019; 123 (12): 2060-2.

[25] Iannaccone M, D'Ascenzo F, Piazza F, et al. Optimal medical therapy vs. coronary revascularization for patients presenting with chronic total occlusion: A meta-analysis of randomized controlled trials and propensity score adjusted studies. *Catheterization & Cardiovascular Interventions*. 2019; 93 (6): E320-E5.

[26] Khan AA, Khalid MF, Ayub MT, et al. Outcomes of Percutaneous Coronary Intervention Versus Optimal Medical Treatment for Chronic Total Occlusion: A Comprehensive Meta-analysis. *Current Problems in Cardiology*. 2021; 46 (3): 100695.

[27] Khanra D, Mishra V, Jain B, et al. Percutaneous coronary intervention provided better long term results than optimal medical therapy alone in patients with chronic total occlusion: A meta-analysis. *Indian Heart Journal*. 2020; 72 (4): 225-31.

[28] Li KHC, Wong KHG, Gong M, et al. Percutaneous Coronary Intervention Versus Medical Therapy for Chronic Total Occlusion of Coronary Arteries: A Systematic Review and Meta-Analysis. *Current Atherosclerosis Reports*. 2019; 21 (10): 42.

[29] Ma Y, Li D, Li J, et al. Percutaneous coronary intervention versus optimal medical therapy for patients with chronic total occlusion: a meta-analysis and systematic review. *Journal of Thoracic Disease*. 2018; 10 (5): 2960-7.

[30] van Veelen A, Elias J, van Dongen IM, et al. Percutaneous coronary intervention versus medical therapy for chronic total coronary occlusions: a systematic review and meta-analysis of randomised trials. *Netherlands Heart Journal*. 2021; 29 (1): 30-41.

[31] Lee SW, Lee PH, Ahn JM, et al. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. *Circulation*. 2019; 139 (14): 1674-83.

[32] Henriques JPS, Hoebers LP, Råmunddal T, et al. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *Journal of the American College of Cardiology*. 2016; 68 (15): 1622-32.

[33] Elias J, van Dongen IM, Ramunddal T, et al. Long-term impact of chronic total occlusion recanalisation in patients with ST-elevation myocardial infarction. *Heart*. 2018; 104 (17): 1432-8.

[34] Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J*. 2018; 39 (26): 2484-93.

[35] van der Schaaf RJ, Claessen BE, Hoebers LP, et al. Rationale and design of EXPLORE: a randomized, prospective, multicenter trial investigating the impact of recanalization of a chronic total occlusion on left ventricular function in patients after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. *Trials*. 2010; 11: 89.

[36] Obedinskiy AA, Kretov EI, Boukhris M, et al. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv*. 2018; 11 (13): 1309-11.

[37] Mashayekhi K, Nuhrenberg TG, Toma A, et al. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion: The REVASC Trial. *JACC Cardiovasc Interv*. 2018; 11 (19): 1982-91.

[38] Choo EH, Koh YS, Seo SM, et al. Comparison of successful percutaneous coronary intervention versus optimal medical therapy in patients with coronary chronic total occlusion. *Journal of Cardiology*. 2019; 73 (2): 156-62.

[39] Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *European Heart Journal*. 2015; 36 (45): 3189-98.

[40] Rha SW, Choi BG, Baek MJ, et al. Five-Year Outcomes of Successful Percutaneous Coronary Intervention with Drug-Eluting Stents versus Medical Therapy for Chronic Total Occlusions. *Yonsei Med J*. 2018; 59 (5): 602-10.

[41] Guo L, Zhong L, Chen K, et al. Long-term clinical outcomes of optimal medical therapy vs. successful percutaneous coronary intervention for patients with coronary chronic total occlusions. *Hellenic J Cardiol*. 2018; 59 (5): 281-7.

[42] Juricic SA, Tesic MB, Galassi AR, et al. Randomized Controlled Comparison of Optimal Medical Therapy with Percutaneous Recanalization of Chronic Total Occlusion (COMET-CTO). *International Heart Journal*. 2021; 62 (1): 16-22.

[43] Kawashima H, Takahashi K, Ono M, et al. Mortality 10 Years After Percutaneous or Surgical Revascularization in Patients With Total Coronary Artery Occlusions. *Journal of the American College of Cardiology*. 2021; 77 (5): 529-40.

[44] Ahn JH, Yang JH, Song YB, et al. Impact of Chronic Total Coronary Occlusion Location on Long-term Survival After Percutaneous Coronary Intervention. *Revista Espanola de Cardiologia*. 2019; 72 (9): 717-23.

[45] Alvarez-Contreras L, Flores-Umanzor E, Cepas-Guillen P, et al. Clinical Impact of Medical Therapy Versus Revascularization in Patients With Chronic Coronary Total Occlusions. *Journal of Invasive Cardiology*. 2021; 33 (1): E2-E8.

[46] Flores-Umanzor EJ, Cepas-Guillen PL, Vázquez S, et al. Survival benefit of revascularization versus optimal medical therapy alone for chronic total occlusion management in patients with diabetes. *Catheterization and Cardiovascular Interventions*. 2021; 97 (3): 376-83.

[47] Flores-Umanzor EJ, Vazquez S, Cepas-Guillen P, et al. Impact of revascularization versus medical therapy alone for chronic total occlusion management in older patients. *Catheterization & Cardiovascular Interventions*. 2019; 94 (4): 527-35.

[48] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj*. 2017; 358: j4008.

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

[50] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016; 355: i4919.

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

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

[53] Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995; 25 (2): 333-41.

[54] Ware JE, Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000; 25 (24): 3130-9.

[55] EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990; 16 (3): 199-208.

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

[57] Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009; 360 (10): 961-72.

[58] Ramunddal T, Hoebers LP, Henriques JP, et al. Prognostic Impact of Chronic Total Occlusions: A Report From SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *JACC Cardiovasc Interv*. 2016; 9 (15): 1535-44.

[59] Claessen BE, Dangas GD, Weisz G, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J*. 2012; 33 (6): 768-75.

[60] Hoebers LP, Vis MM, Claessen BE, et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. *Eur J Heart Fail*. 2013; 15 (4): 425-32.

[61] Claessen BE, van der Schaaf RJ, Verouden NJ, et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2009; 2 (11): 1128-34.

[62] Mashayekhi K, Bufe A, Werner GS, et al. Behandlung von chronischen Koronarverschlüssen (CTO) – Positionspapier der Deutschen Gesellschaft für Kardiologie. *Der Kardiologe*. 2021; 15: 320-40.

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

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: PCI for CTO: Results for effectiveness and safety outcomes from randomised controlled trials (part 1)

Author, year	EXPLORE [32, 33, 35]	EUROCTO [34]	REVASC [37]
Study description			
Country	International (Netherlands, Belgium, Sweden, Norway, Austria, Canada)	International (France, Germany, Italy, Latvia, Spain, UK)	Germany
Sponsor	Academic Medical Center-University of Amsterdam; Abbott Vascular	Biosensors Europe SA; ASAHI Intecc Co. Ltd; EUROCTO Club e.V.	University Heart Center Freiburg – Bad Krozingen, Germany
Intervention/Product	PCI for the CTO using an approved drug eluting stent	PCI for the CTO with a Biolimus-eluting stent + optimal medical therapy	PCI for the CTO with an "olimus"-eluting stent + optimal medical therapy
Comparator	Standard medical treatment for at least 4 months	Optimal medical therapy	Optimal medical therapy
Study design	Multicentre RCT, 2-arm, parallel, single-blinded (outcome evaluation)	Multicentre RCT, 2-arm, parallel, open-label	Singlecentre RCT, 2-arm, parallel, open-label
Primary endpoint	■ Difference in LVEF at 4 months ■ Difference in LVEDV at 4 months	■ Change in quality of Life (SAQ) from baseline to 12 months ■ MACE (cardiovascular death, non-fatal MI) at 36 months	■ Changes of LVEF from baseline to 9 months ■ Change in SWT in the CTO territory from baseline to 6 months
Number of participants	304 (150 vs 154)	396 (259 vs 137)	205 (101 vs 104)
Follow-up	3.9 (2.1 – 5.0) years	Efficacy: 12 months Safety: 36 months	Efficacy: 6 months Safety: 12 months
Loss to follow-up, n (%)	14 (9) vs 10 (6.5)	0 (12 months)	9 (9) vs 12 (12)
Inclusion criteria	■ Successful primary PCI for acute STEMI ■ Presence of at least one concurrent CTO in a non-infarct-related artery, defined as a 100% luminal narrowing without antegrade flow or with antegrade or retrograde filling through collateral vessels ■ Reference diameter of ≥2.5 mm ■ Amenable to PCI treatment	■ Age ≥ 18 years ■ CTO in native coronary artery ■ Stable angina or myocardial ischaemia in a territory supplied by CTO and viability in akinetic myocardium (<50% transmural late enhancement on MRI or normal resting perfusion scan) ■ CTO located in segments 1-3 (RCA), 6-7 (LAD), 11-12 (LCx) ■ Target artery ≥2.5mm	■ Age ≥ 18 years ■ Stable or unstable AP or a positive functional study for ischemia ■ CTO with TIMI flow 0 (or distal capillary reflow) of a native coronary artery with an estimated reference vessel diameter of 2.5 to 4.0 mm ■ CTO duration > 4 weeks ■ Target vessel has not previously been treated with PCI ■ Target vessel must be feasible for stent implantation ■ Female subjects of childbearing age must have a negative pregnancy test within 7 days before procedure

Author, year	EXPLORE [32, 33, 35]	EUROCTO [34]	REVASC [37]
Exclusion criteria	■ Age > 80 years ■ Persistent or permanent atrial fibrillation ■ Known renal insufficiency (serum creatinin > 265 µmol/L or > 3.5 mg/L) ■ Persistent hemodynamic instability lasting up to 48 hours after primary PCI ■ Cardiac events between primary PCI and randomization ■ Significant left main stenosis ■ Sever CAD, not amenable for PCI but suitable for CABG ■ Severe valvular heart disease requiring cardiac surgery within four months ■ Clinically driven indication for implantable cardioverter defibrillator within 4 months ■ Contraindication for cMRI ■ Serious known concomitant disease with a life expectancy of less than 1 year	■ Acute MI or NSTE-ACS within one months ■ Significant untreated coronary stenosis in a territory other than CTO ■ Multivessel disease and significant non-CTO stenoses where it is deemed unsafe to treat the non-CTO lesion first ■ Unsuitability for 12 month dual anti-platelet therapy ■ Any exclusion criteria for PCI or drug-eluting stents ■ Pregnant or nursing patients and those who plan pregnancy in the period up to 1 year following index procedure	■ Acute MI (>3x normal creatine kinase (CK with presence of CK-MB) within 72 hours preceding the index procedure and CK has not returned to normal limits at the time of the procedure ■ Hypersensitivity or contraindication to aspirin, heparin, clopidogrel, stainless steel or contrast media that cannot be adequately been pre-medicated ■ LVEF < 30% ■ Platelet count of < 100,000 cells/mm^3 or > 700,000 cells/m^3, a white blood cell count of < 3,000 cells/mm^3 or documented or suspected liver disease ■ history of bleeding diathesis or coagulopathy ■ Cerebrovascular accident or transient ischemic attack within the past 6 months ■ Active peptic ulcer or upper gastrointestinal bleeding within the prior 6 months ■ Co-morbidity (i.e. cancer or congestive heart failure) that may cause the patient to be non-compliant with the protocol, or is associated with limited life-expectancy (less than 2 years) ■ Target vessel contains intraluminal thrombus ■ Target vessel or lesson shows angiographic evidence of severe calcification ■ Contraindications to MRI
Population characteristics			
Age of patients (yrs)	PCI: 60 ± 10 OMT: 60 ± 10	PCI: 65.2 ± 9.7 OMT: 64.9 ± 9.9	PCI: 65 (57-72) [a] OMT: 68 (61-74) [a]
Male, n (%)	PCI: 131 (89) OMT: 126 (82)	PCI: 215 (83) OMT: 118 (86)	PCI: 91 (90) OMT: 90 (87)
Diabetes melitus, n (%)	PCI: 22 (15) OMT: 25 (16)	PCI: 85 (33) OMT: 40 (29)	PCI: 32 (32) OMT: 31 (30)
Previous MI/PCI/CABG/stroke, %	PCI: 13/6/0/3 OMT: 16/10/0/4	PCI: 23/56/13/- OMT: 18/52/7/-	PCI: 39/28/12/5 OMT: 37/32/14/9
CTO-related artery: RCA/LCX/LAD, %	PCI: 43/32/24 OMT: 51/24/25	PCI: 64/11/26 OMT: 57/16/27	PCI: 57/20/23 OMT: 68/15/16
Duration of CTO	NR	NR	> 4 weeks
SYNTAX score	PCI: 29 ± 8 OMT: 29 ± 10	NR	PCI: 14 (9-22) [a] OMT: 16 (11-21) [a]

Author, year	EXPLORE [32, 33, 35]	EUROCTO [34]	REVASC [37]
J-CTO score	PCI: 2 ± 1 OMT: 2 ± 1	PCI: 1.82 ± 1.07 OMT: 1.67 ± 0.91	PCI: 2 (1-3) [a] OMT: 2 (1-2) [a]
Baseline LVEF, %	PCI: 41 ± 11 OMT: 42 ± 12	PCI: 55 ± 11 OMT: 56 ± 11	PCI: 55 (43-65) [a] OMT: 60 (46-64) [a]
Outcomes			
Effectiveness			
Overall mortality, n (%)	*1 year:* 5/148 (3.4) vs 2/154 (1.3); p=NR *3.9 years:* 14/148 (12.9) vs 7/154 (6.2); p=0.11	*1 year:* 2/259 (0.8) vs 0/137 (0); p=NR	*1 year:* 1/101 (1.0) vs 2/104 (1.9); p=NR
Cardiac mortality, n (%)	*1 year:* 4/148 (2.7) vs 0/154 (0); p=0.06 *3.9 years:* 8/148 (6.0) vs 1/154 (1.0);p=0.02	*1 year:* 2/259 (0.8) vs 0/137 (0); p=NR *3 years* [b]*:* 7/259 (2.7) vs 2/137 (1.6); p=NR	*1 year:* 0/101 (0) vs 2/104 (1.9); p=NR
AP symptom relief, n (%)	***Freedom of AP:*** *1 year:* 132/141 (94) vs 129/149 (87); p=0.03	***Freedom of AP:*** *1 year:* 185/259 (71) vs 79/137 (58); p=NR ***SAQ AP frequency score:*** *1 year:* 92.0 (89.3 to 94.8) vs 86.8 (83.1 to 90.5); p=0.003 ***% patients AP frequency score change >20:*** *1 year:* 41% vs 28%; p=0.013	NR
Avoidance of CABG, n (%)	***CABG surgery:*** *1 year:* 3/148 (2.0) vs 1/154 (0.6); p=0.36 *3.9 years:* 3/148 (2.0) vs 5/154 (3.5); p=0.53	NR	NR
Quality of life	NR	***EQ-5D visual health state:*** *1 year:* 72.7 (69.9 to 75.5) vs 69.7 (65.9 to 73.5); p=0.104 [c] ***SAQ QoL:*** *1 year:* 77.1 (73.3 to 80.9) vs 70.5 (65.4 to 75.6); p=0.007	NR
LVEF function, %	*1 year:* 45.5 ± 9.1 vs 44.6 ± 10.7; p=0.66	NR	*6 months* [a]*:* 57.0 (45.0 to 65.5) vs 61.0 (51.3 to 66.8); p=0.21 0.9 (-1.3 to 4.1) vs 0.7 (-1.0 to 3.7); p=0.79 [d]
Late lumen loss, mm (SD)	NR	NR	NR
Stent restenosis, n (%)	NR	NR	NR
Patient satistaction	NR	***SAQ treatment satisfaction:*** *1 year:* 90.5 (88.0 to 92.9) vs 88.5 (85.2 to 91.8); p=0.219	NR
Procedural success, n (%)	106 (73) [e]	220 (85)	100 (97)
Safety			
MACE, n (%)	*1 year:* 11/148 (7.4) vs 10/154 (6.5); p=0.82 *3.9 years:* 18/148 (13.5) vs 18/154 (12.3); p=0.93	*1 year:* 13/259 (5.2) vs 9/137 (6.7); p=0.55 *3 years* [b]*:* 32/259 (12.4) vs 29/137 (21.2); p=NR	*1 year:* 6/101 (5.9) vs 17/104 (18.2); p=NR

Author, year	EXPLORE [32, 33, 35]	EUROCTO [34]	REVASC [37]
Myocardial infarction, n (%)	*1 year:* 8/148 (5.8) vs 9/154 (5.8); p=0.79 *3.9 years:* 12/148 (9.2) vs 13/154 (8.7); p=0.74	*1 year:* 5/259 (1.9) vs 0/137 (0); p=NR *3 years* [f]*:* 6/259 (2.3) vs 2/137 (1.6); p=NR	*1 year:* 0/101 (0) vs 1/104 (1.0); p=NR
Stroke, n (%)	*3.9 years:* 2/148 (1.5) vs 4/154 (2.9); p=0.28	*1 year:* 2/259 (0.8) vs 1/137 (0.7); p=0.97	NR
Stent thrombosis, n (%)	*3.9 years:* 6/148 (4.1) vs 6/154 (4.1); p=0.95	*1 year:* 1/259 (0.4) vs 0/137 (0); p=NR	*1 year:* 0/101 (0) vs 1/104 (1.0); p=NR
Target vessel revascularisation, n (%)	*1 year:* 7/148 (4.7) vs 30/154 (19.5); p=NR *3.9 years:* 13/148 (9.9) vs 36/154 (25.5); p=NR	*1 year:* 5/259 (2.0) vs 9/137 (6.7); p=0.04	*1 year:* 3/101 (3.0) vs 14/104 (13.5); p=NR
Contrast-induced nephropathy, n (%)	NR	NR	NR
Procedure-related mortality, n (%)	0 (0)	0 (0)	0 (0)
Cardiac tamponade, n (%)	1 (0.7)	4 (1.6)	0 (0)
Acute CABG (in-hospital), n (%)	0 (0)	NR	0 (0)
Coronary perforation, n (%)	NR	NR	NR

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CTO – chronic total occlusion; EQ-5D – European quality of life-5 dimensions; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MRI – magnet resonance imaging; OMT – optimal medical therapy; NR – not reported; PCI – percutaneous coronary intervention; QoL – quality of life; RCA – right coronary artery; RCT – randomised controlled trial; SAQ – Seattle angina questionnaire; STEMI – ST-segment elevation myocardial infarction; SWT – segmental wall thickening; TIMI – thrombolysis in myocardial infarction; vs – versus; yrs – years.

Explanations:

[a] *Median (IQR)*

[b] *Data from Van Velen et al., 2021 [30]*

[c] *Results from EQ-5D subscales: Mobility: 0 (0 to 0) vs 0 (0 to 0); p=0.005/Self-care: 0 (0 to 0) vs 0 (0 to 0); p=0.242/Activities: 0 (-1 to 0) vs 0 (0 to 0); p<0.001/Pain or discomfort: 0 (-1 to 0) vs 0 (0 to 0); p=0.001/Anxiety or depression: 0 (0 to 0) vs 0 (0 to 0); p=0.872*

[d] *Change from baseline to 6 months*

[e] *Core laboratory adjudicated*

[f] *Data from Khan et al., 2021 [26]*

Table A-1: PCI for CTO: Results for effectiveness and safety outcomes from randomised controlled trials (part 2)

Author, year	IMPACTOR-CTO [36]	DECISION-CTO [31]	COMET-CTO [42]
Study description			
Country	Russia	International (India, Indonesia, Republic of Korea, Taiwan, Thailand)	
Sponsor	NR	CardioVascular Research Foundation, Korea	Ministry of Education and Science of the Republic of Serbia
Intervention/Product	PCI for the CTO + optimal medical therapy	PCI for the CTO using a drug eluting stent + optimal medical therapy	PCI for the CTO using a drug eluting stent + optimal medical therapy
Comparator	Optimal medical therapy	Optimal medical therapy	Optimal medical therapy
Study design	Singlecentre RCT, 2-arm, parallel, open-label	Multicentre RCT, 2-arm, parallel, non-inferiority, open-label	Singlecentre RCT, 2-arm, parallel, open-label
Primary endpoint	■ Change in MIB from baseline to 12 months	■ Composit outcome of all-cause mortality, MI, stroke, and any revaskularisation at 36 months	■ Change in quality of life and overall well-being (SAQ) from baseline to 6 months
Number of pts	72 (39 vs 33)	834 (417 vs 398)	100 (50 vs 50)
Follow-up	12 months	48 months	275 ± 88 days
Loss to follow-up, n (%)	0	Clinical outcomes: 15.7% vs 9.9% (4 years) QoL: 41% (3 years)	1 (2) vs 0
Inclusion criteria	■ Isolated dominant RCA CTO ■ Stable AP	■ Age ≥ 18 years ■ AP or silent ischemia and documented ischemia ■ Eligible for intracoronary stenting ■ De novo lesion CTO ■ Reference vessel size 2.5 mm by visual estimation ■ At least one CTO lesions located in proximal or mid epicardial coronary artery (TIMI flow 0 and estimated duration over 3 months) ■ CTO duration > 3 months	■ CTO of coronary artery (TIMI flow 0) ■ Stable AP and/or evidence of ischemia in the territory of the CTO and/or evidence of viable myocardium in the CTO territory ■ Target coronary artery with a reference diameter of 2.5 mm
Exclusion criteria	■ Unsuccessful CTO PCI attempts ■ Non-compliance with OMT	■ History of bleeding diathesis or coagulopathy ■ Pregnancy ■ Three vessel CTO ■ Hypersensitivity or contra-indication to contrast agent and heparin ■ STEMI requiring primary stenting ■ Characteristics of lesion: 1) Left main disease 2) In-stent restenosis 3) Graft vessels 4) Distal epicardial coronary artery CTO lesions ■ Hematological disease ■ Hepatic dysfunction, liver enzyme elevation 3 times normal ■ Renal dysfunction (creatinine > 2.0 mg/dL) ■ Contraindication to aspirin, clopidogrel or other commercial antiplatelet agent ■ LVEF < 30% ■ Non-cardiac co-morbid conditions are present with limited life expectancy or that may result in protocol non-compliance	■ Acute MI within 1 months ■ contraindications for dual antiplatelet therapy in future 12 months ■ contraindications for drug eluting stents ■ CTO in bypass graft ■ LVEF < 20% ■ Dementia ■ CVI or TIA in past 6 months ■ neutropenia (<1000/mm^3) in past 2 weeks ■ thrombocytopenia (<100 000/mm^3) ■ AST, ALT, alkaline phosphatase > 1.5x the upper limit of normal ■ serum creatine >2 mg/dL ■ Allergy to iodine contrast that cannot be treated medically ■ Life expectancy not longer than 1 year ■ Bleeding diathesis or coagulopathy or will refuse transfusions

Author, year	IMPACTOR-CTO [36]	DECISION-CTO [31]	COMET-CTO [42]
Population characteristics			
Age of patients (yrs)	56.6 ± 8.1	PCI: 62.2 ± 10.2 OMT: 62.9 ± 9.9	PCI: 61 ± 7 OMT: 63 ± 5
Male, n (%)	60 (83)	PCI: 344 (83) OMT: 319 (82)	PCI: 38 (76) OMT: 44 (88)
Diabetes melitus, n (%)	NR	PCI: 132 (32) OMT: 134 (34)	PCI: 14 (28) OMT: 18 (36)
Previous MI/PCI/CABG/stroke, %	NR	PCI: 11/16/1/7 OMT: 9/19/1/8	PCI: 58/-/-/2 OMT: 70/-/-/8
CTO-related artery: RCA/LCX/LAD, %	NR	PCI: 45/10/45 OMT: 48/11/42	PCI: 56/20/24 OMT: 78/12/10
Duration of CTO, months	NR	NR	NR
SYNTAX score	NR	PCI: 20.8 ± 9.2 OMT: 20.8 ± 9.5	PCI: 10.79 ± 4.89 OMT: 9.87 ± 3.41
J-CTO score	NR	PCI: 2.1 ± 1.2 OMT: 2.2 ± 1.2	PCI: 1.48 ± 1.27 OMT: 1.72 ± 1.09
Baseline LVEF	NR	PCI: 57.3 ± 9.8 OMT: 57.6 ± 9.1	PCI: 54.9 ± 9.42 OMT: 51.34 ± 11.28
Outcomes			
Effectiveness			
Overall mortality, n (%)	*1 year:* 0/39 (0) vs 0/33 (0); p=ns	*4 years:* 15/417 (3.6) vs 21/398 (5.3); p=0.30	*9 months:* 0/50 (0) vs 0/50 (0); p=ns
Cardiac mortality, n (%)	*1 year:* 0/39 (0) vs 0/33 (0); p=ns	*4 years:* 8/417 (1.9) vs 14/398 (3.5); p=0.19	*9 months:* 0/50 (0) vs 0/50 (0) ; p=ns
AP symptom relief, n (%)	NR	***SAQ AP frequency:*** *1 year:* 94.55 ± 11.18 vs 95.33 ± 10.19 -0.78 (-2.83 to 1.26); p=0.45 [a] *3 years:* 98.21 ± 5.32 vs 97.38 ± 7.20 0.83 (-0.67 to 2.32); p=0.27 [a]	***SAQ AP frequency:*** *9 months:* 89.8 ± 17.6 vs 76.8 ± 27.1; p=0.006
Avoidance of CABG, n (%)	NR	NR	***CABG surgery:*** *9 months:* 1/50 (2) vs 0/50 (0); p=NR
Quality of life	***SF-36 [b]:*** *1 year:* PF: 45 (45; 70) vs 40 (30; 45); p<0.01 RPF: 75 (50; 75) vs 25 (25; 50); p<0.01 BP: 51 (41; 62) vs 41 (32; 51); p<0.01	***EQ-5D visual health state:*** *1 year:* 81.00 ± 12.58 vs 78.28 ± 13.27 2.72 (0.23 to 5.20); p=0.03 [a] *3 years:* 84.56 ± 9.12 vs 80.97 ± 11.05 3.59 (1.18 to 6.00); p=0.004 [a]	***SAQ QoL:*** *9 months:* 79.9 ± 22.7 vs 62.5 ± 25.5; p=0.001

Author, year	IMPACTOR-CTO [36]	DECISION-CTO [31]	COMET-CTO [42]
Quality of life *(continuation)*	GH: 50 (45; 55) vs 40 (20; 50): p<0.01 V: 45 (40; 50) vs 33 (25; 40); p<0.01 SF: 63 (50; 75) vs 50 (37; 63); p<0.01 RE: 100 (66; 100) vs 67 (33; 67); p<0.01 MH: 52 (32; 48) vs (40 (32; 48); p<0.01	***SAQ QoL:*** *1 year:* 72.19 ± 19.06 vs 71.89 ± 16.6 0.30 (-3.12 to 3.71); p=0.86 [a] *3 years:* 78.26 ± 17.39 vs 77.53 ± 16.69 0.73 (-3.26 to 4.72); p=0.72 [a]	
LVEF function, %	NR	NR	NR
Late lumen loss, mm (SD)	NR	NR	NR
Stent restenosis, n (%)	NR	NR	NR
Patient satisfaction	NR	***SAQ treatment satisfaction:*** *1 year:* 83.98 ± 13.19 vs 83.26 ± 14.61 0.72 (-1.94 to 3.39); p=0.59 [a] *3 years:* 87.13 ± 11.89 vs 84.00 ± 11.59 3.13 (0.38 to 5.89); p=0.03 [a]	***SAQ treatment satisfaction:*** *9 months:* 91.2 ± 12.6 vs 81.4 ± 18.4; p=0.003
Procedural success, n (%)	39 (83)	348 (90.6)	47 (94)
Safety			
MACE, n (%)	NR	*4 years:* 93/417 (22.3) vs 89/398 (22.4); p=0.86	NR
Myocardial infarction, n (%)	NR	*4 years:* 47/417 (11.3) vs 34/398 (8.5); p=0.14	*9 months:* 0/50 (0) vs 0/50 (0); p=ns
Stroke, n (%)	NR	*4 years:* 6/417 (1.4) vs 10/398 (2.5); p=0.33	*9 months:* 0/50 (0) vs 0/50 (0); p=ns
Stent thrombosis, n (%)	NR	NR	*9 months:* 0/50 (0) vs 0/50 (0); p=ns
Target vessel revascularisation, n (%)	*1 year:* 2/39 (5.1) vs 0/33 (0); p=NR	*4 years:* 33/417 (7.9) vs 30/398 (7.5); p=0.63	*9 months:* 0/50 (0) vs 2/50 (4); p=ns
Contrast-induced nephropathy, n (%)	NR	NR	NR
Procedure-related mortality, n (%)	0 (0)	NR	0 (0)
Cardiac tamponade, n (%)	2 (5)	1 (0.3)	nr
Acute CABG (in-hospital), n (%)	NR	NR	0 (0)
Coronary perforation, n (%)	NR	NR	NR

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CTO – chronic total occlusion; EQ-5D – European quality of life-5 dimensions; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MIB – inducible ischemia burden; MRI – magnet resonance imaging; NR – not reported; ns – not significant; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; QoL – quality of life; RCA – right coronary artery; RCT – randomised controlled trial; SAQ – Seattle angina questionnaire; SF-36 – Short form 36; STEMI – ST-segment elevation myocardial infarction; TIMI – thrombolysis in myocardial infarction; vs – versus; yrs – years.

Explanations:

[a] *Between-group-difference PCI vs OMT*

[b] *Median (IQR)*

Table A-1: PCI for CTO: Results for effectiveness and safety outcomes from randomised controlled trials (part 3)

Author, year	SYNTAX (Subgroup – patients with CTO) [43]
Study description	
Country	International (Belgium, Austria, Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Spain, Sweden, UK, France, USA)
Sponsor	Erasmus Medical Center
Intervention/Product	PCI using a drug eluting stent
Comparator	CABG
Study design	Multicentre RCT, 2-arm, parallel, open label
Number of pts	All patients: 1,800 (903 vs 897) TO subgroup: 460 (237 vs 223)
Primary endpoint	■ All-cause mortality at 10 years
Follow-up	11.2 (7.7 to 12.1) years
Loss to follow-up, n (%)	0 (0)
Inclusion criteria	■ 3-vessel disease (3VD), left main disease (LM) or LM equivalent with or without 1, 2 or 3VD ■ De novo lesions with at least 50% stenosis ■ Myocardial ischemia (stable, unstable, silent) ***TO-subgroup:*** ■ At least one TO (≤ 3 months or > 3 months; TMI flow 0)
Exclusion criteria	■ Prior PCI or CABG ■ Acute myocardial infarction (with creatinine kinase > 2-times upper limit of normal) ■ Concomitant cardiac valve disease requiring surgical therapy (reconstruction or replacement)
Population characteristics	
Age of patients (yrs)	PCI: 64.7 ± 70.3 CABG: 64.5 ± 10.5
Male, n (%)	PCI: 188 (79) CABG: 190 (85)
Diabetes melitus, n (%)	PCI: 77 (33) CABG: 57 (26)
Previous MI/PCI/CABG/stroke, %	PCI: 36/0/0/6 CABG: 44/0/0/4
CTO-related artery: RCA/LCx/LAD, %	NR
Duration of CTO, months	NR
SYNTAX score	PCI: 31.3 ± 11.6 CABG: 30.3 ± 9.5
J-CTO score	NR

Author, year	SYNTAX (Subgroup – patients with CTO) [43]
Baseline LVEF	PCI: 55.6 ± 13.3 CABG: 55.7 ± 13.1
Outcomes	
Effectiveness	
Overall mortality, n (%)	***Patients with 3VD:*** *10 years:* 50/176 (29.3) vs 35/173 (21.0); HR 0.673 [0.437 to 1.037]; p=0.073 *Maximum available follow-up:* 57/176 (37.4) vs 45/173 (32.4); HR 0.750 [0.507 to 1.108]; p=0.149 ***Patients with LM:*** *10 years:* 18/61 (30.5) vs 20/50 (40.9); HR 1.539 [0.814 to 2.911]; p=0.185 *Maximum available follow-up:* 20/61 (37.1) vs 24/50 (55.7); HR 1.641 [0.906 to 2.975]; p=0.102
Cardiac mortality, n (%)	NR
AP symptom relief, n (%)	***Freedom of angina:*** *5 years:* 121/172 (70.3) vs 123/152 (80.9); p=0.03
Avoidance of CABG, n (%)	NR
Quality of life	NR
LVEF function, %	NR
Late lumen loss, mm (SD)	NR
Stent restenosis, n (%)	NR
Procedural success, n (%)	NR
Safety	
MACE, n (%)	NR
Myocardial infarction, n (%)	NR
Stroke, n (%)	NR
Stent thrombosis, n (%)	NR
Target vessel revascularisation, n (%)	NR
Contrast-induced nephropathy, n (%)	NR
Procedure-related mortality, n (%)	NR
Cardiac tamponade, n (%)	NR
Acute CABG (in-hospital), n (%)	NR
Coronary perforation, n (%)	NR

Abbreviations: 3VD -3-vessel disease; AP – angina pectoris; CABG – coronary artery bypass graft; CTO – chronic total occlusion; HR hazard ratio; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LM – left main disease; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NR – not reported; PCI – percutaneous coronary intervention; RCA – right coronary artery; RCT – randomised controlled trial; TIMI – thrombolysis in myocardial infarction; TO – total occlusion; vs – versus; yrs – years.

Table A-2: PCI for CTO: Results for safety outcomes from observational studies (part 1)

Author, year	Choo 2018 [38]	Tomasello 2015 [39]	Ahn 2019 [44]
Study description			
Country	Korea	Italy	Korea
Sponsor	NR	Italian Society of Invasive Cardiology (SICI-GISE), Italy	NR
Intervention/Product	PCI for the CTO with drug-eluting stents	PCI for the CTO + optimal medical therapy	PCI for the CTO with drug-eluating stents + optimal medical therapy
Comparator	Optimal medical therapy	Optimal medical therapy (CG 1) or coronary artery bypass grafting (CG2)	Optimal medical therapy
Study design	Prospective multicenter cohort study	Prospective multicentre cohort study	Prospective single-center registry
Primary endpoint	■ All-cause mortality during follow-up	NR	■ Cardiac mortality during follow-up
Number of pts	*Entire cohort:* 898 (424 (PCI) vs 474 (OMT)) *Prospensity matched groups:* 528 (264 (PCI) vs 264 (OMT))	*Entire cohort:* 1,777 (776 (PCI) vs 826 (OMT) vs vs 175 (CABG)) *Prospensity matched groups:* 1,238 (619 (PCI) vs 619 (OMT)	*Entire cohort:* 1,547 pmLAD CTO: 811 (504 (PCI) vs. 307 (OMT)) non-pmLAD CTO: 736 (379 (PCI) vs. 357 (OMT)) *Prospensity matched groups:* pmLAD:522 (261(PCI) vs. 261 (OMT)) non-pmLAD: 516 (258 (PCI) vs. 258 (OMT))
Follow-up	2.2 (1.3-3.6) [a] years	1 year	46.4 (21.8-74.4) [a] months
Loss to follow-up, n (%)	NR	0 (1 year)	0
Inclusion criteria	■ Patients with CTO (complete obstruction > 3 months, TIMI flow 0)	■ At least 1 CTO in a main coronary artery (duration >3 months, TIMI flow 0, vessel size ≥ 2.5 mm).	■ At least 1 CTO detected on a diagnostic coronary angiogram (complete obstruction of a naïve coronary artery > 3 months, TIMI flow 0) ■ Symptomatic angina pectoris and/or a positive functional ischemia study
Exclusion criteria	■ Prior CABG procedure	■ Prior CABG procedure ■ Life expectancy <1 year	■ Previous CABG procedure ■ History of cardiogenic schock or cardiopulmonary resuscitation ■ ST-segment elevation acute MI during the preceding 48 hours
Population characteristics			
Age of patients (yrs)	*Entire cohort:* PCI: 61.3 ± 11.6 OMT: 66.2 ± 11.1	*Entire cohort:* PCI: 67.0 ± 10.6 OMT: 70.1 ± 12.5* CABG: 68.8 ± 8.9	*Entire cohort:* **pmLAD** PCI: 61.9 ± 11.1 OMT:67.3 ± 12.0 **Non-pmLAD** PCI: 61.0 ± 10.4 OMT: 64.8 ± 10.4

Author, year	Choo 2018 [38]	Tomasello 2015 [39]	Ahn 2019 [44]
Age of patients (yrs) *(continuation)*	*Prospensity matched groups:* PCI: 61.5 ± 9.8 OMT: 61.5 ± 10.5	*Prospensity matched groups:* PCI: 68.1 ± 10.3 OMT: 68.5 ± 12.5	*Prospensity matched groups:* **pmLAD** PCI: 65.8 ± 10.3 OMT: 66.1 ± 12.1 **Non-pmLAD** PCI: 63.1 ± 20.2 OMT: 63.1 ± 10.5
Male, n (%)	*Entire cohort:* PCI: 308 (72.6) OMT: 329 (69.4) *Prospensity matched groups:* PCI:199 (75.4) OMT: 201 (76.1)	*Entire cohort:* PCI: 658 (84.8) OMT: 690 (83.5) CABG: 147 (84) *Prospensity matched groups:* PCI: 515 (83.2) OMT: 525 (84.8)	*Entire cohort:* **pmLAD** PCI: 399 (79.2) OMT: 230 (74.9) **Non-pmLAD** PCI: 314 (82.8) OMT: 279 (78.2) *Prospensity matched groups:* **pmLAD** PCI: 196 (75.1) OMT: 199 (76.2) **Non-pmLAD** PCI: 207 (80.2) OMT: 208 (80.6)
Diabetes melitus, n (%)	*Entire cohort:* PCI: 176 (41.5) OMT: 225 (47.5) *Prospensity matched groups:* PCI: 117 (44.3) OMT: 121 (45.8)	*Entire cohort:* PCI: 232 (29.9) OMT: 245 (29.7) CABG: 58 (33.1) *Prospensity matched groups:* PCI: 194 (31.3) OMT: 182 (29.4)	*Entire cohort:* **pmLAD** PCI: 217 (43.1) OMT: 151 (49.2) **Non-pmLAD** PCI: 167 (44.1) OMT: 167 (46.8) *Prospensity matched groups:* **pmLAD** PCI: 125 (47.9) OMT: 124 (47.5) **Non-pmLAD** PCI: 118 (45.7) OMT: 122 (47.3)
Previous MI/PCI/CABG/stroke, %	*Entire cohort:* PCI: 14/NR/NR/11 OMT: 19/NR/NR/10 *Prospensity matched groups:* PCI: 22/NR/NR/10 OMT: 25/NR/NR/9	*Entire cohort:* PCI: 41/32/0/NR OMT: 45/31/0/NR CABG: 47/270/NR *Prospensity matched groups:* PCI: 37/30/0/NR OMT: 40/28/0/NR	*Entire cohort:* **pmLAD** PCI: 21/18/NR/9 OMT: 35/24/NR/11 **Non-pmLAD** PCI: 20/32/NR/6 OMT: 29/38/NR/9 *Prospensity matched groups:* **pmLAD** PCI: 29/23/NR/12 OMT: 30/25/NR/11 **Non-pmLAD** PCI: 22/31/NR/7 OMT: 26/30/NR/8
CTO-related artery: RCA/LCX/LAD, %	*Entire cohort:* PCI: 39/22/42 OMT: 49/29/29 *Prospensity matched groups:* PCI: 47/25/32 OMT: 45/27/30	NR	NR

Author, year	Choo 2018 [38]	Tomasello 2015 [39]	Ahn 2019 [44]
Duration of CTO, months	NR	NR	NR
SYNTAX score	NR	NR	*Entire cohort:* **pmLAD** PCI: 23.8 ± 7.3 OMT: 25.2 ± 8.8 **Non-pmLAD** PCI: 14.0 ± 7.3 OMT: 15.1 ± 7.7 *Prospensity matched groups:* **pmLAD** PCI: 24.7 ± 7.8 OMT: 25.0 ± 8.8 **Non-pmLAD** PCI: 14.4 ± 7.1 OMT: 14.5 ± 7.6
J-CTO score	NR	NR	NR
Baseline LVEF	*Entire cohort:* PCI: 56.0 ± 11.3 OMT: 52.1± 12.6 *Prospensity matched groups:* PCI: 54.8 ± 11.3 OMT: 53.6 ± 12.3	*Entire cohort:* PCI: 52/36/12 [b] OMT: 41/39/21 [b] CABG: 51/27/22 [b] *Prospensity matched groups:* PCI: NR/NR/15 [b] OMT: NR/NR/14 [b]	NR
Outcomes			
Safety			
MACE, n (%)	***2.2 years:*** *Entire cohort:* HR 0.87 [0.68–1.11]; p=0.26 *Prospensity matched groups:* HR 1.12 [0.81–1.55]; p=0.903	***1 year:*** *Entire cohort (PCI vs OMT vs CABG):* 20/776 (2.6) vs 68/826 (8.2) vs 12/175 (6.9); p<0.001 for PCI vs OMT; p<0.05 for PCI vs CABG *Prospensity matched groups:* 17/619 (1.7) vs 47/619 (7.6); p<0.001	***3.9 years:*** *Prospensity matched groups:* **pmLAD:** 48/261 (18.4) vs 73/261 (28.0); p=0.001 **Non-pmLAD:** 42/258 (16.3) vs 53/258 (20.5); p=0.16
Myocardial infarction, n (%)	NR	***1 year:*** *Entire cohort (PCI vs OMT vs CABG):* 8/776 (1) vs 25/826 (3) vs 1/175 (0.6); p<0.05 for PCI vs OMT; p=ns for PCI vs CABG *Prospensity matched groups:* 7/619 (1.1) vs 18/619 (2.9); p=0.03	***3.9 years:*** *Prospensity matched groups:* **pmLAD:** 4/261 (1.5) vs 3/261 (1.3); p=0.76 **Non-pmLAD:** 2/258 (0.8) vs 3/258 (1.2); p=0.62

Author, year	Choo 2018 [38]	Tomasello 2015 [39]	Ahn 2019 [44]
Stroke, n (%)	NR	***1 year:*** *Entire cohort (PCI vs OMT vs CABG):* 1/776 (0.1) vs 6/826 (0.7) vs 9/175 (5.1); p=ns for PCI vs OMT; p<0.001 for PCI vs CABG *Prospensity matched groups:* 1/619 (0.3) vs 3/619 (0.5); p=0.3	NR
Stent thrombosis, n (%)	NR	NR	NR
Target vessel revascularisation, n (%)	NR	NR	NR
Contrast-induced nephropathy, n (%)	NR	NR	NR
Procedure-related mortality, n (%)	NR	*Entire cohort:* 2 (0.3)	NR
Cardiac tamponade, n (%)	NR	*Entire cohort:* 5 (0.6)	*Prospensity matched groups:* **pmLAD:** 32/261 (12.3) vs 45/261 (17.2); p=0.021 **Non-pmLAD:** 32/258 (12.4) vs 41/258 (15.9); p=0.43
Acute CABG (in-hospital), n (%)	NR	*Entire cohort:* 2 (0.3)	NR
Coronary perforation, n (%)	NR	*Entire cohort:* 17 (2.2)	NR

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CG – control group; CTO – chronic total occlusion; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NR – not reported; ns – not significant; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; pmLAD – proximal or middle left anterior descending artery; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction; vs – versus; yrs – years.

Explanations:

[a] *Median (IQR)*

[b] *Proportion of patients with LVEF >50%/50-30%/<30%*

Table A-2: PCI for CTO: Results for safety outcomes from observational studies (part 2)

Author, year	Alvarez-Contreras 2021 [45]	Flores-Umanzor 2019 (subgroup patients ≥ 75 years) [47]	Flores-Umanzor 2021 (subgroupd patients with diabetes) [46]
Study description			
Country	Spain		
Sponsor	NR		
Intervention/Product	PCI for the CTO with drug-eluating stents + optimal medical therapy		
Comparator	Optimal medical therapy (CG 1) or coronary artery bypass grafting (CG2)		
Study design	Single-center prospective cohort study		
Primary endpoint	All-cause mortality during follow-up		
Number of pts	1,248 (240 (PCI) vs 719 (OMT) vs 289 (CABG))	328 (53 (PCI) vs 233 (OMT) vs 42 (CABG)	538 (76 (PCI) vs 326 (OMT) vs 136 (CABG))
Follow-up	4.3 (2.6-4.8) a years	3.5 (2.6-4.8) a years	4.03 (2.6-4.8) a years
Loss to follow-up, n (%)	0 (4.3 years)	0	0
Inclusion criteria	Presence of at least one CTO (total occlution < 3 months, TIMI flow 0)		
Exclusion criteria	No exclusion criteria were considered		
Population characteristics			
Age of patients (yrs)	PCI: 62.8 ± 10.8 OMT: 69.6 ± 10.8 CABG: 65.3 ± 9.5	PCI: 79.2 ± 3.4 OMT: 81.2 ± 3.4 CABG: 78.5 ± 2.2	PCI: 66.8 ± 10.2 OMT: 70.2 ± 10.4 CABG: 66.1 ± 10.2
Male, n (%)	PCI: 203 (85) OMT: 595 (83) CABG: 252 (87)	PCI: 35 (66) OMT: 168 (72) CABG: 35 (83)	PCI: 63 (83) OMT: 259 (79) CABG: 177 (86)
Diabetes melitus, n (%)	PCI: 79 (33) OMT: 323 (45) CABG: 134 (46)	PCI: 24 (45) OMT: 104 (45) CABG: 14 (33)	100%
Previous MI/PCI/CABG/stroke, %	PCI: 27/NR/8/NR OMT: 36/NR/16/NR CABG: 26/NR/2/NR	PCI: 32/NR/13/NR OMT: 38/NR/14/NR CABG: 31/NR/10/NR	PCI: 28/NR/5/NR OMT: 33/NR/14/NR CABG: 28/NR/4/NR
CTO-related artery: RCA/LCX/LAD, %	PCI: 44/18/27 OMT: 52/18/19 CABG: 50/19/23	NR	PCI: 38/1635 OMT: 52/19/18 CABG: 52/22/18
Duration of CTO, months	NR	NR	NR

Author, year	Alvarez-Contreras 2021 [45]	Flores-Umanzor 2019 (subgroup patients ≥ 75 years) [47]	Flores-Umanzor 2021 (subgroupd patients with diabetes) [46]
SYNTAX score	PCI: 20.5 ± 10 OMT: 23.8 ± 12 CABG: 29.8 ± 12	PCI: 25.4 ± 11.3 OMT: 26.1 ± 12.4 CABG: 29.4 ± 11.8	PCI: 22.7 ± 10.5 OMT: 24.3 ± 12.3 CABG: 30.6 ± 12.2
J-CTO score	NR	NR	NR
Baseline LVEF	PCI: 49 ± 13 OMT: 44 ± 14 CABG: 48.1 ± 13	PCI: 47.7 ± 13.5 OMT: 43.8 ± 14.4 CABG: 50.7 ± 11.2	PCI: 46.9 ± 13.1 OMT: 43 ± 14.1 CABG: 48 ± 13
Outcomes			
Safety			
MACE, n (%)	NR	NR	NR
Myocardial infarction, n (%)	*Entire cohort:* ***4.3 years:*** 18/240 (8) vs 57/719 (8) vs 12/289 (4); p=ns for both comparisions	*Entire cohort:* ***3.5 years:*** 4/53 (8) vs 29/233 (12) vs 2/42 (5); p=ns for both comparisions	*Entire cohort:* ***4 years:*** 10/76 (13) vs 24/326 (7) vs 6/136 (4); p=ns for both comparisions
Stroke, n (%)	NR	NR	NR
Stent thrombosis, n (%)	NR	NR	NR
Target vessel revascularisation, n (%)	NR	NR	NR
Contrast-induced nephropathy, n (%)	NR	NR	NR
Procedure-related mortality, n (%)	NR	NR	NR
Cardiac tamponade, n (%)	NR	*Entire cohort (PCI vs CABG):* 1 (2) vs 4 (10); p=0.69	*Entire cohort (PCI vs CABG):* 1 (1) vs 4 (3); p=0.69
Acute CABG (in-hospital), n (%)	NR	NR	NR
Coronary perforation, n (%)	NR	NR	NR

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CG – control group; CTO – chronic total occlusion; LAD – left anterior descending coronary artery; LCx – left circumflex coronary artery; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NR – not reported; ns – not significant; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction; vs – versus; yrs – years.

Explanations:

[a] *Median (IQR)*

Table A-2: PCI for CTO: Results for safety outcomes from observational studies (part 3)

Author, year	Rha 2018 [40]	Guo 2018 [41]
Study description		
Country	Korea	China
Sponsor	NR	Dalian Medical University; Beijing Lisheng Cardiovascular Health Foundation
Intervention/Product	PCI for the CTO with drug-eluating stents + optimal medical therapy	PCI for the CTO with drug-eluting stents + optimal medical therapy
Comparator	Optimal medical therapy	Optimal medical therapy
Study design	Prospective single-center registry	Prospective single-center cohort study
Primary endpoint	All-cause mortality, MI, revascularisation, and MACE during follow-up	MACE (cardiac mortality, MI, repeated revascularisation) during follow-up
Number of pts	*Entire cohort:* 822 (412 (PCI) vs 410 (OMT)) *Prospensity matched groups:* 530 (265 (PCI) vs 265 (OMT))	*Entire cohort:* 326 (125 (PCI) vs 201 (OMT)) *Prospensity matched groups:* 160 (80 (PCI) vs 80 (OMT))
Follow-up	4 ± 1.5 years	47.2 ± 20 months
Loss to follow-up, n (%)	NR	NR
Inclusion criteria	■ At least 1 CTO lesion in the epicardial vessel (complete obstruction ≥ 3 months, TIMI flow 0)	■ At least one CTO detected on diagnostic coronary angiography (complete obstruction > 3 months, TIMI flow 0) ■ Symptomatic angina pectoris and/or functional ischemia
Exclusion criteria	■ CABG procedure ■ CTO located in a small vessel (vessel size ≤2.5 mm) or on side branch vessels	■ Failed CTO-PCI ■ Previous CABG procedure ■ History of cardiogenic shock or cardiopulmonary resuscitation ■ Acute STEMI during the preceding 48 h ■ Malignant tumor
Population characteristics		
Age of patients (yrs)	*Entire cohort:* PCI: 62.1 ± 10.8 OMT: 66.1 ± 10.4 *Prospensity matched groups:* PCI: 64.2 ± 9.8 OMT: 64.5 ± 10.3	*Entire cohort:* PCI: 63.97 ± 9.71 OMT: 64.84 ± 10.47 *Prospensity matched groups:* PCI: 64.76 ± 9.58 OMT: 64.55 ± 11.24
Male, n (%)	*Entire cohort:* PCI: 311 (75.4) OMT: 290 (70.7) *Prospensity matched groups:* PCI:198 (74.7) OMT: 195 (73.5)	*Entire cohort:* PCI: 84 (67.2) OMT: 157 (78.1) *Prospensity matched groups:* PCI: 56 (70) OMT: 58 (72.5)

Author, year	Rha 2018 [40]	Guo 2018 [41]
Diabetes melitus, n (%)	*Entire cohort:* PCI: 184 (44.6) OMT: 179 (43.6) *Prospensity matched groups:* PCI: 113 (42.6) OMT: 119 (44.9)	*Entire cohort:* PCI: 35 (28.0) OMT: 71 (35.3) *Prospensity matched groups:* PCI: 24 (30) OMT: 22 (27.5)
Previous MI/PCI/CABG/stroke, %	*Entire cohort:* PCI: 22/NR/NR/9 OMT:21/NR/NR/13 *Prospensity matched groups:* PCI: 22/NR/NR/NR OMT: 21/NR/NR/NR	*Entire cohort:* PCI: 27/6/0/7 OMT: 30/10/0/12 *Prospensity matched groups:* PCI: 26/6/0/9 OMT: 25/13/0/10
CTO-related artery: RCA/LCX/LAD, %	*Entire cohort:* PCI: 40/27/39 OMT: 54/34/29 *Prospensity matched groups:* PCI: 45/35/30 OMT: 46/31/31	*Entire cohort:* PCI: 42/17/40 OMT: 45/27/29 *Prospensity matched groups:* PCI: 41/23/36 OMT: 42/27/31
Duration of CTO, months	NR	NR
SYNTAX score	NR	*Entire cohort:* PCI: 19.58 ± 7.18 OMT: 23.31 ± 8.91 *Prospensity matched groups:* PCI: 54.73 ± 7.43 OMT: 54.73 ± 7.43
J-CTO score	NR	*Entire cohort:* PCI: 0.86 ± 0.77 OMT: 1.34 ± 0.90 *Prospensity matched groups:* PCI: 1.03 ± 0.82 OMT: 1.01 ± 0.73
Baseline LVEF	*Entire cohort:* PCI: 51.8 ± 11.1 OMT: 48.3 ± 12.8 *Prospensity matched groups:* PCI: 51.0 ± 11.9 OMT: 49.2 ± 12.6	*Entire cohort:* PCI: 54.73 ± 7.43 OMT: 51.75 ± 8.78 *Prospensity matched groups:* PCI: 53.70 ± 8.29 OMT: 53.63 ± 7.21

Author, year	Rha 2018 [40]	Guo 2018 [41]
Outcomes		
Safety		
MACE, n (%)	*Entire cohort:* ***4 years:*** 88/412 (21.4) vs 82/410 (20.0); p=0.353 *Prospensity matched groups:* ***4 years:*** 54/265 (20.4) vs 49/265 (18.5); p=0.302	*Entire cohort:* ***4 years:*** 37/125 (29.6) vs 44/201 (21.9) HR 1.47 [0.95-2.28]; p=0.085 [a] HR 1.76 [1.09-2.82]; p=0.02 [b] *Prospensity matched groups:* ***4 years:*** 24/80 (30.0) vs 14/80 (17.5) HR 1.92 [0.99-3.71]; p=0.052 [a] HR 1.89 [0.96-3.71]; p=0.06 [b]
Myocardial infarction, n (%)	*Entire cohort:* ***4 years:*** 7/412 (1.7) vs 20/410 (4.9); p=0.015 *Prospensity matched groups:* ***4 years:*** 4/265 (1.5) vs 13/265 (4.9); p=0.048	*Entire cohort:* ***4 years:*** 11/125 (8.8) vs 18/201 (9.0) HR 0.98 [0.46-2.09]; p=0.97 [a] HR 1.01 [0.45-2.24; p=0.97 [b] *Prospensity matched groups:* ***4 years:*** 7/80 (8.8) vs 5/80 (6.3) HR 1.41 [0.45-4.45]; p=0.55 [a] HR 1.43 [0.44-4.66]; p=0.55 [b]
Stroke, n (%)	*Entire cohort:* ***4 years:*** 3/412 (0.7) vs 6/410 (1.5); p=0.348 *Prospensity matched groups:* ***4 years:*** 3/265 (1.1) vs 3/265 (1.1); p=0.855	NR
Stent thrombosis, n (%)	NR	NR
Target vessel revascularisation, n (%)	*Entire cohort:* ***4 years:*** 53/412 (12.9) vs 17/410 (4.4); p<0.01 *Prospensity matched groups:* ***4 years:*** 33/265 (12.5) vs 9/265 (3.4); p<0.01	NR
Contrast-induced nephropathy, n (%)	NR	NR
Procedure-related mortality, n (%)	NR	NR
Cardiac tamponade, n (%)	NR	NR
Acute CABG (in-hospital), n (%)	NR	NR
Coronary perforation, n (%)	NR	NR

Abbreviations: see Table A-2

Explanations:

[a] *Unadjusted*

[b] *Adjusted for age, sex, LVEF, LAD-CTO, and SYNTAX score*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers (TS, CZ). In case of disagreement a third researcher was involved to solve the differences (CL). 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 and in the Guidelines of EUnetHTA.

Table A-3: Risk of bias – randomised studies for PCI versus OMT, see [49]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
EXPLORE [32, 33, 35]	Low	Low	Low	Low	Low	Low
EUROCTO [34]	Low	Low	Low	Some concern [a]	Low	Some concern
REVASC [37]	Low	Low	Low	Low	Low	Low
IMPACTOR-CTO [36]	Some concern [b]	Some concern [c]	Low	High [d]	Some concern [e]	High
DECISION-CTO [31]	Low	Low	Low	Low	Low	Low
COMET-CTO [42]	Low	Low	Low	Some concern [a]	Low	Some concern

[a] *Blinding of outcome assessor unclear*
[b] *No information on randomisation process and allocation concealment*
[c] *No information on analysis methods*
[d] *Patient-reported outcomes without blinding of participants to the intervention*
[e] *No study protocol; no information on primary or secondary outcome measures*

Table A-4: Risk of bias of non – randomised studies for PCI versus OMT, see [50]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
Tomasello 2015 [39]	Moderate [a]	Moderate [b]	Low	Low	Low	Moderate [c]	Low	Moderate
Rha 2018 [40]	Serious [d]	Low	Low	Moderate [e]	Low	Moderate [c]	Low	Serious
Choo 2018 [38]	Moderate [a]	Low	Low	Low	Low	Moderate [c]	Low	Moderate
Guo 2018 [41]	Moderate [a]	Low	Low	Low	Low	Moderate [c]	Low	Moderate
Ahn 2019 [44]	Moderate [a]	Low	Low	Low	Low	Low	Low	Moderate
Alvarez-Contreras 2021 [45-47]	Crtiical [f]	Low	Low	Moderate [g]	Low	Moderate [c]	Low	Critical

[a] *Important confounding domains were controlled and measured for (propensity score matching), unmeasured confounding cannot be ruled out.*
[b] *Patients managed with CABG excluded from analysis*
[c] *Outcome assessors were aware of the received intervention.*
[d] *Most important confounding domains were controlled and measured for (propensity score matching), nevertheless a potential for confounding of the effect of intervention in the study, due to unbalances disease severity (angina symptoms and collateral grade) between die study-groups remained. Unmeasured confounding cannot be ruled out.*
[e] *Patients with failed CTO-PCI or with successful CTO-PCI, but with residual CTO in the multi-CTO lesion were included in the OMT study-group*
[f] *There is a potential for confounding of the effect of intervention in the study (e.g. age, disease severity, medical history). No adequate statistical analysis was conducted to control for confounding variables.*
[g] *Patients with failed CTO-PCI were reassigned in the OMT study-group*

Table A-5: Risk of bias – randomised studies for PCI versus CABG, see [49]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
SYNTAX [43]	Low	High [a]	Low	Some concern [b]	Low	High

[a] *Unclear, if PCI or CABG of the TO was done according to the randomised intervention (PCI or CABG) of the primary stenosed vessel*

[b] *Blinding of outcome assessor unclear*

Table A-6: Risk of bias of non – randomised studies for PCI versus CABG, see [50]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of interventiones	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias
Tomasello 2015 [39]	Crtiical [a]	Low	Low	Low	Low	Moderate [b]	Low	Critical
Alvarez-Contreras 2021 [45-47]	Crtiical [a]	Low	Low	Moderate [c]	Low	Moderate [b]	Low	Critical

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

[b] *Outcome assessors were aware of the received intervention.*

[c] *Patients with failed CTO-PCI were reassigned in the OMT study-group.*

Table A-7: Evidence profile: efficacy and safety of PCI for CTO versus OMT

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI for CTO	OMT	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (1 year)											
5	randomised trials	not serious	not serious	not serious	serious [a]	none	597	478	RR 1.7 (0.5 to 5.8)	6 more per 1 000 (from 4 fewer to 40 more)	moderate
Overall mortality (4 years)											
2	randomised trials	not serious	serious [b]	not serious	serious [a]	none	565	552	RR 0.65 (0.50 to 0.84)	98 fewer per 1 000 (from 136 fewer to 122 more)	low
AP symptoms (1 years)											
2	randomised trials	not serious	not serious	not serious	serious [e]	none	400	286	RR 1.14 (0.38 to 3.40)	7 more per 1 000 (from 31 fewer to 44 fewer)	moderate
AP frequency (1 year)											
3	randomised trials	not serious	serious [b]	not serious	not serious	none	541	423	-	MD 4.67 higher (2.21 lower to 11.55 higher)	moderate
AP frequency (3 years)											
1	randomised trials	not serious	NA	not serious	very serious [c]	none	181	179	-	MD 0.83 higher (0.67 lower to 2.32 higher)	low
CABG surgery (9 months to 3.9 years)											
2	randomised trials	not serious	not serious	not serious	very serious [d]	none	198	204	not pooled	1 RCT: 2.0% vs 3.5% of patients in 3.9 years of follow-up; 1 RCT: 2.0% vs 0% of patients in 9 months of follow-up.	low
Generic HrQoL (1 year)											
2	randomised trials	not serious	not serious	not serious	serious [e]	none	505	380	-	MD 2.77 higher (0.74 higher to 4.8 higher)	moderate
Disease specific QoL (1 year)											
3	randomised trials	not serious	serious	not serious	serious [a]	none	536	421	-	MD 7.18 higher (1.83 lower to 16.19 higher)	low
MACE (1 year)											
3	randomised trials	not serious	not serious	not serious	serious [a]	none	508	395	RR 0.69 (0.36 to 1.33)	28 fewer per 1 000 (from 58 fewer to 30 more)	moderate

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI for CTO	OMT	Relative (95% CI)	Absolute (95% CI)	
MACE (4 years)											
3	randomised trials	not serious	serious [b]	not serious	not serious	none	824	689	RR 0.85 (0.60 to 1.22)	30 fewer per 1 000 (from 79 fewer to 43 more)	low
Myocardial infarction (1 year)											
4	randomised trials	not serious	not serious	not serious	serious [a]	none	558	445	RR 1.14 (0.51 to 2.57)	3 more per 1 000 (from 11 fewer to 35 more)	moderate
Myocardial infarction (4 years)											
3	randomised trials	not serious	not serious	not serious	not serious	none	824	689	RR 1.24 (0.87 to 1.77)	17 more per 1 000 (from 9 fewer to 55 more)	high
Stroke (1 year)											
2	randomised trials	not serious	not serious	not serious	very serious [d]	none	309	187	RR 1.06 (0.10 to 11.56)	0 fewer per 1 000 (from 5 fewer to 56 more)	low
Stroke (4 years)											
2	randomised trials	not serious	not serious	not serious	very serious [d]	none	565	552	RR 0.56 (0.24 to 1.32)	11 fewer per 1 000 (from 19 fewer to 8 more)	low
Stent thrombosis (1 to 4 years)											
4	randomised trials	not serious	not serious	not serious	serious [f]	none	558	445	not pooled	Overall 7 events in both study arms during 1 to 4 years of follow up.	moderate
Target vessel revascularisation (1 year)											
5	randomised trials	not serious	not serious	not serious	not serious	none	597	478	RR 0.28 (0.17 to 0.48)	83 fewer per 1 000 (from 96 fewer to 60 fewer)	high
Target vessel revascularisation (4 years)											
2	randomised trials	not serious	serious [b]	not serious	serious [a]	none	565	552	RR 0.64 (0.23 to 1.75)	43 fewer per 1 000 (from 92 fewer to 90 more)	low

Abbreviations: AP – angina pectoris; CI – confidence interval; CTO – chronic total occlusion; HrQoL – health-related quality of life; MACE – major adverse coronary events; NA – not applicable; OMT – optimal medical therapy; PCI – percutaneous coronary intervention; QoL – quality of life; RR – risk ratio; vs – versus

Comments:

[a] *Wide confidence interval*

[b] *Significant heterogeneity*

[c] *Only one study with low number of participants analysed*

[d] *Low event rate and low number of studies*

[e] *low number of studies*

[f] *Very low event rates*

Table A-8: Evidence profile: efficacy and safety of PCI for CTO versus CABG

Certainty assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI for CTO	CABG	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (10 years)											
1	randomised trials	serious [a]	NA	serious [b]	serious [c]	none	237	223	not pooled	Overall mortality rates comparable after 10 years of follow-up: 29% vs 25%; p=0.90	very low
AP frequency (5 years)											
1	randomised trials	serious [a]	NA	serious [b]	serious [c]	none	172	152	not pooled	After 5 years of follow-up there were less participants without angina symptoms in die PCI arm compared to the CABG arm (121/172 (70.3%) vs 123/152 (80.9%); p=0.03)	very low
Generic HrQoL											
No evidence available											
Disease specific QoL											
No evidence available											
MACE (1 year)											
1	cohort study	very serious [d]	NA	not serious	very serious	none	776	175	not pooled	Significant less MACE in PCI arm compared to CABG arm after 1 year follow-up: 20/776 (2.6%) vs 12/175 (6.9%); p<0.05	very low
Myocardial infarction (1 to 4 years)											
2	cohort study	very serious [d]	not serious	not serious	very serious [e]	none	1016	468	not pooled	1 cohort study: 8.0% vs 4.0% of patients in 4 years follow-up; 1 cohort study: 1.0% vs 0,6% of patients in 1 year follow-up. Both results statistically not significant.	very low
Stroke (1 year)											
1	cohort study	very serious [d]	NA	not serious	very serious [e]	none	776	175	not pooled	Significant lower stroke rate in PCI arm compared to CABG arm after 1 year follow-up: 1/776 (0.1%) vs 9/175 (5.1%); p<0.001	very low
Stent thrombosis (1 to 4 years)											
No evidence available											
Target vessel revascularisation (1 year)											
No evidence available											

Abbreviations: AP – angina pectoris; CABG – coronary artery bypass graft; CI – confidence interval; CTO – chronic total occlusion; HrQoL – health-related quality of life; MACE – major adverse coronary events; NA – not applicable; PCI – percutaneous coronary intervention; QoL – quality of life; RR – risk ratio; vs – versus

Comments:

[a] *High RoB, because it is unclear, if PCI or CABG of the TO was done according to the randomised intervention (PCI or CABG) of the primary stenosed vessel*

[b] *Patients with total occlusion of a coronary artery of a duration ≥ 3 months and < 2 months included (not only patients with CTO)*

[d] *Non-randomised study with critical overall RoB* [c] *Only one study* [e] *Low number of studies with low event rate*

Applicability table

Table A-9: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	In the four of the RCTs and all six non-randomised clinical studies, study participants were symptomatic CHD patients with a CTO in a native coronary artery. One RCTs included patients with STEMI after successful primary PCI and CTO situated in a non-infarct related coronary artery or its side branches and one RCTs included only patients with isolated dominant RCA CTO and stable angina. In the RCT comparing PCI to CABG participants were a subgroup of patients with a total occlusion irrespective of the duration from group of patients with de novo three-vessel disease and/or left main disease.
Intervention	In all included studies the intervention was PCI using drug-eluting stents for the CTO in the background of an optimal medical therapy for CHD.
Comparators	Nearly all of the included studies used an optimal medical therpapy for CHD without percutaneous interventions as compatator. In two observational studies CABG surgery was used as an additional comparator, while one RCT used CABG surgery as the only comparator.
Outcomes	For effectiveness outcomes, the crucial outcome mortality was reported in all included RCTs. The important outcomes AP-symptome relieve and HRQoL were reported in five and four RCTs, respectively. The rate of CABG surgery during follow-up was only reported in two RCTs. Regarding safety outcomes, the crucial outcome MACE was reported in five RCTs and five non-randomised clinical studies, but definition of MACE varied between the studies. Target vessel revascularisation was reported in six of the seven included RCTs, but only in one non-randomised clinical study. Results on stent thrombosis were available from four RCTs and no non-randomised clinical study.
Setting	In all studies, the intervention was performed in a clinical setting, corresponding to the utilisation setting in Austria. No applicability issues are expected from the geographical setting of the included studies.

List of ongoing randomised controlled trials

Table A-10: List of ongoing randomised controlled trials of PCI for CTO

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04542460/ The Nordic Baltic Chronic Total Occlusion Arrhythmia Study	Patients with stable CHD and ≥1 CTO lesion amenable to PCI	PCI for CTO and OMT	OMT without PCI	Rate of clinically significant arrhythmias after 1 year follow-up	November 1, 2023	Leif Thuesen
NCT03756870/ REVISE-CTO	Patients with CTO and clinical indication for PCI	PCI for CTO and OMT	OMT without PCI	Ischemic burden assessed with exercise myocardial perfusion SPECT-CT from baseline to 6 months follow-up	January 1, 2021	Academisch Medisch Centrum – Universiteit van Amsterdam (AMC-UvA)
NCT03392415/ NOBLE-CTO	Patients with stable CHD and ≥1 CTO lesion amenable to PCI	CTO PCI attempt as initial strategy with medical optimization simultaneously	OMT and option for crossover after 6 months or ful-fillment of certain conditions	All-cause mortality after 6 moths follow-up QoL after 6 months follow-up (SF-12)	July 1, 2021	Leif Thuesen
NCT03563417/ ISCHEMIA-CTO	Patients with CTO in native coro-nary artery and MI in a territory supplied by CTO	PCI for CTO and OMT	OMT	MACE after 5 years follow-up QoL after 5 years Follow-up	November 1, 2028	Aarhus University Hospital Skejby
NCT05142215/ ORBITA-CTO	Patients with symptoms related to a single vessel CTO	PCI for CTO	Placebo procedure for CTO and OMT	Change in angina symptom ordinal scale score after 24 and 26 weeks	August 1, 2023	Mid and South Essex NHS Foundation Trust & |Imperial College London

Research questions

Table A-11: Research questions – Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of PCI for CTO on mortality?
D0005	How does PCI for CTO affect angina pectoris symptoms and findings (severity, frequency)?
D0006	How does PCI for CTO affect progression of coronary heart disease?
D0011	What is the effect of PCI for CTO on patients' body functions?
D0016	How does the use of PCI for CTO affect activities of daily living?
D0012	What is the effect of PCI for CTO on generic health-related quality of life?
D0013	What is the effect of PCI for CTO on disease-specific quality of life?
D0017	Was the use of PCI for CTO worthwhile?

Table A-12: Research questions – Safety

Element ID	Research question
C0008	How safe is PCI for CTO in comparison to OMT or CABG?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of PCI for CTO?

Literature search strategies

Sytematic reviews – search strategy for Cochrane

Search Name: Revascularisation of CTOs_Update 2022	
Last saved: 01/12/2021 18:01:43	
Comment: MEL (TS)	
ID	Search
#1	MeSH descriptor: [Angina Pectoris] explode all trees
#2	("Angina Pectoris"):ti,ab,kw (Word variations have been searched)
#3	("Angor Pectoris"):ti,ab,kw (Word variations have been searched)
#4	(AP):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Coronary Occlusion] explode all trees
#6	("coronary total occlusion*"):ti,ab,kw (Word variations have been searched)
#7	("coronary chronic total occlusion*"):ti,ab,kw (Word variations have been searched)
#8	(CTO*):ti,ab,kw
#9	MeSH descriptor: [Coronary Stenosis] explode all trees
#10	(coronary NEAR (stenos?s or restenos?s or re-stenos?s)):ti,ab,kw (Word variations have been searched)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (Word variations have been searched)
#12	MeSH descriptor: [Myocardial Revascularization] explode all trees
#13	(revasculari?ation*):ti,ab,kw (Word variations have been searched)
#14	(re-vasculari?ation*):ti,ab,kw (Word variations have been searched)
#15	("percutaneous coronary intervention*"):ti,ab,kw (Word variations have been searched)
#16	(PCI*):ti,ab,kw (Word variations have been searched)
#17	("coronary arter* recanali?ation*"):ti,ab,kw (Word variations have been searched)
#18	("coronary arter* re-canali?ation*"):ti,ab,kw (Word variations have been searched)
#19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	#11 AND #19 with Cochrane Library publication date Between Dec 2012 and Dec 2021, in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)
Total: 19 Hits	

Sytematic reviews – search strategy for CRD

Search Name: Revascularisation of CTOs (MEL Update 2022) TS 021221	
Search date: 02.12.2021	
ID	Search
1	MeSH DESCRIPTOR Angina Pectoris EXPLODE ALL TREES
2	(Angina Pectoris)
3	(Angor Pectoris)
4	MeSH DESCRIPTOR Coronary Occlusion EXPLODE ALL TREES
5	(coronary total occlusion*)
6	(coronary chronic total occlusion*)
7	(CTO*)
8	MeSH DESCRIPTOR Coronary Stenosis EXPLODE ALL TREES
9	(coronary NEAR (stenos* OR restenos* OR re-stenos*))
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	MeSH DESCRIPTOR Myocardial Revascularization EXPLODE ALL TREES
12	(revascularisation*)
13	(revascularization*)

14	(re-vascularisation*)
15	(re-vascularization*)
16	(percutaneous coronary intervention*)
17	(PCI*)
18	(coronary artery recanalisation*)
19	(coronary artery recanalization*)
20	(coronary artery re-canalisation*)
21	(coronary artery re-canalization*)
22	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23	#10 AND #22
24	(#23) WHERE LPD FROM 31/01/2013 TO 02/12/2021
25	(#24) IN DARE
Total: 38 Hits	

Sytematic reviews – search strategy for Medline

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 30, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to November 30, 2021>	
Search date: 01.12.2021	
ID	Search
1	*Angina Pectoris/su [Surgery] (1390)
2	Angina* pectoris.mp. (46036)
3	angor pectoris.mp. (59)
4	AP.ti,ab. (84855)
5	2 or 3 or 4 (130406)
6	Surgery.fs. (2459866)
7	5 and 6 (10421)
8	exp Coronary Occlusion/ (5427)
9	coronary total occlusion*.mp. (198)
10	coronary chronic total occlusion*.mp. (770)
11	CTO*.ti,ab. (11378)
12	*Coronary Stenosis/su [Surgery] (1823)
13	(coronary adj2 (stenos#s or restenos#s or re-stenos#s)).mp. (35509)
14	6 and 13 (6996)
15	1 or 7 or 8 or 9 or 10 or 11 or 12 or 14 (31572)
16	*Myocardial Revascularization/ (7447)
17	re*vascular#ation*.mp. (87938)
18	re-vascular#ation*.mp. (322)
19	percutaneous coronary intervention*.mp. (68552)
20	PCI*.ti,ab. (43937)
21	coronary arter* recanali#ation*.mp. (66)
22	coronary arter* re-canali#ation*.mp. (2)
23	16 or 17 or 19 or 20 or 21 (150176)
24	15 and 23 (9130)
25	limit 24 to (meta analysis or "systematic review") (262)
26	(((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. (851998)

27	24 and 26 (396)
28	25 or 27 (400)
29	limit 28 to dt=20121217-20211201 (332)
30	remove duplicates from 29 (200)
Total: 200 Hits	

Sytematic reviews – search strategy for Embase

Search date: 01.12.2022		
No.	Query Results	Results
#1	'angina pectoris'/mj	27,509
#2	'angina pectoris'	106,530
#3	'angor pectoris'	97
#4	#2 OR #3	106,565
#5	#4 AND 'surgery'/lnk	13,649
#6	'coronary total occlusion*'	226
#7	'coronary chronic total occlusion*'	902
#8	cto*:ti,ab	9,877
#9	'coronary artery occlusion'/mj/dm_su	436
#10	'coronary artery obstruction'/mj/dm_su	3,032
#11	coronary NEAR/1 (stenos*s OR restenos*s OR 'restenos*s')	12,311
#12	#11 AND 'surgery'/lnk	1,002
#13	#1 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #12	52,304
#14	'revascularization'/mj	7,465
#15	revasculari*ation*	126,716
#16	're-vasculari*ation*'	465
#17	'coronary arter* recanali*ation*'	7,157
#18	'coronary arter* re-canali*ation*'	1
#19	'percutaneous coronary intervention'/mj	31,853
#20	'percutaneous coronary intervention*'	96,848
#21	pci*:ti,ab	68,048
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	248,505
#23	#13 AND #22	13,502
#24	#23 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	450
#25	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	1,396,348
#26.	#23 AND #25	855
#27	#24 OR #26	872
#28	#27 AND [17-12-2012]/sd NOT [2-12-2021]/sd	446
#29	#28 AND 'Conference Abstract'/it	106
#30	#28 NOT #29	340

RCTs – search strategy for Cochrane

Search Name: Revascularisation of CTOs_Update 2022_(n)RCTs since 2019	
Last saved: 15/12/2021 16:27:38	
Comment: MEL (TS)	
ID	Search
#1	MeSH descriptor: [Angina Pectoris] explode all trees
#2	("Angina Pectoris"):ti,ab,kw (Word variations have been searched)
#3	("Angor Pectoris"):ti,ab,kw (Word variations have been searched)
#4	(AP):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Coronary Occlusion] explode all trees
#6	("coronary total occlusion*"):ti,ab,kw (Word variations have been searched)
#7	("coronary chronic total occlusion*"):ti,ab,kw (Word variations have been searched)
#8	(CTO*):ti,ab,kw
#9	MeSH descriptor: [Coronary Stenosis] explode all trees
#10	(coronary NEAR (stenos?s or restenos?s or re-stenos?s)):ti,ab,kw (Word variations have been searched)
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (Word variations have been searched)
#12	MeSH descriptor: [Myocardial Revascularization] explode all trees
#13	(revasculari?ation*):ti,ab,kw (Word variations have been searched)
#14	(re-vasculari?ation*):ti,ab,kw (Word variations have been searched)
#15	("percutaneous coronary intervention*"):ti,ab,kw (Word variations have been searched)
#16	(PCI*):ti,ab,kw (Word variations have been searched)
#17	("coronary arter* recanali?ation*"):ti,ab,kw (Word variations have been searched)
#18	("coronary arter* re-canali?ation*"):ti,ab,kw (Word variations have been searched)
#19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	#11 AND #19
#21	#20 in Trials
#22	#21 with Publication Year from 2019 to 2021, in Trials
#23	(conference abstract):pt (Word variations have been searched)
#24	(abstract):so (Word variations have been searched)
#25	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#26	#23 OR #24 OR #25
#27	#22 NOT #26
Total: 437 Hits	

RCTs – search strategy for Medline

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 14, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to December 14, 2021>	
Search date: 15.12.2021	
ID	Search
1	*Angina Pectoris/su [Surgery] (1390)
2	Angina* pectoris.mp. (46088)
3	angor pectoris.mp. (59)
4	AP.ti,ab. (85163)
5	2 or 3 or 4 (130762)
6	Surgery.fs. (2467590)
7	5 and 6 (10455)
8	exp Coronary Occlusion/ (5465)
9	coronary total occlusion*.mp. (202)
10	coronary chronic total occlusion*.mp. (778)
11	CTO*.ti,ab. (11466)
12	*Coronary Stenosis/su [Surgery] (1823)
13	(coronary adj2 (stenos#s or restenos#s or re-stenos#s)).mp. (35663)
14	6 and 13 (7032)
15	1 or 7 or 8 or 9 or 10 or 11 or 12 or 14 (31751)
16	*Myocardial Revascularization/ (7465)
17	re*vascular#ation*.mp. (88302)
18	re-vascular#ation*.mp. (322)
19	percutaneous coronary intervention*.mp. (69011)
20	PCI*.ti,ab. (44226)
21	coronary arter* recanali#ation*.mp. (66)
22	coronary arter* re-canali#ation*.mp. (2)
23	16 or 17 or 19 or 20 or 21 (150918)
24	15 and 23 (9179)
25	limit 24 to randomized controlled trial (587)
26	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1662005)
27	24 and 26 (1195)
28	limit 24 to observational study (497)
29	exp epidemiologic studies/ or exp clinical trial/ or comparative study/ (5860986)
30	((control and study) or program).mp. (3119444)
31	29 or 30 (7778324)
32	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ (10749132)
33	history.fs. or case report.mp. (815639)
34	32 or 33 (11459195)
35	31 not 34 (6502718)
36	24 and 35 (3962)
37	25 or 27 or 28 or 36 (4418)
38	limit 37 to yr="2019 - 2021" (1080)
39	limit 38 to (english or german) (1022)
40	remove duplicates from 39 (513)
Total: 513 Hits	

RCTs – search strategy for Embase

Search date: 15.12.2022		
No.	Query Results	Results
#1	'angina pectoris'/mj	27,510
#2	'angina pectoris'	106,685
#3	'angor pectoris'	97
#4	#2 OR #3	106,720
#5	#4 AND 'surgery'/lnk	13,667
#6	'coronary total occlusion*'	227
#7	'coronary chronic total occlusion*'	903
#8	cto*:ti,ab	9,898
#9	'coronary artery occlusion'/mj/dm_su	439
#10	'coronary artery obstruction'/mj/dm_su	,034
#11	coronary NEAR/1 (stenos*s OR restenos*s OR 'restenos*s')	12,321
#12	#11 AND 'surgery'/lnk	1,196
#13	#1 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #12	,479
#14	'revascularization'/mj	,473
#15	revasculari*ation*	,941
#16	're-vasculari*ation*'	465
#17	'coronary arter* recanali*ation*'	7,167
#18	'coronary arter* re-canali*ation*'	1
#19	'percutaneous coronary intervention'/mj	31,923
#20	'percutaneous coronary intervention*'	97,116
#21	pci*:ti,ab	68,188
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	218,956
#23	#13 AND #22	13,526
#24	#23 AND [randomized controlled trial]/lim	810
#25	'randomized controlled trial'/de	688,654
#26	'controlled clinical trial'/de	435,756
#27	random*:ti,ab,tt	1,730,949
#28	'randomization'/de	92,400
#29	'intermethod comparison'/de	279,894
#30	placebo:ti,ab,tt	334,205
#31	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt	575,361
#32	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,407,516
#33	(open NEXT/1 label):ti,ab,tt	92,683
#34	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	253,088
#35	'double blind procedure'/de	190,923
#36	(parallel NEXT/1 group*):ti,ab,tt	28,532
#37	crossover:ti,ab,tt OR 'cross over':ti,ab,tt	114,082
#38	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	406,217
#39	assigned:ti,ab,tt OR allocated:ti,ab,tt	433,468
#40	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	402,364
#41	volunteer:ti,ab,tt OR volunteers:ti,ab,tt	264,589
#42	'human experiment'/de	563,242
#43	trial:ti,tt	351,264

#44	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR.#39 OR #40 OR #41 OR #42 OR #43	5,641,467
#45	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)	2,772
#46	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)	311,346
#47	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)	19,142
#48	'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)	192,898
#49	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt	17,433
#50	'random field*':ti,ab,tt	2,572
#51	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,509
#52	review:ab AND review:it NOT trial:ti,tt	932,203
#53	'we searched':ab AND (review:ti,tt OR review:it)	39,184
#54	'update review':ab	119
#55	(databases NEAR/5 searched):ab	50,274
#56	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,136,063
#57	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,384,074
#58	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57	3,858,846
#59	#44 NOT #58	5,005,949
#60	#23 AND #59	3,910
#61	#23 AND 'observational study'/de	415
#62	#24 OR #60 OR #61	4,184
#63	(#24 OR #60 OR #61) AND [2019-2021]/py	673
#64	#63 AND 'Conference Abstract'/it	149
#65	#63 NOT #64	524

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH