Nonemergent Percutaneous Coronary Intervention Versus Optimal Medical Treatment for Stable Ischemic Heart Disease: A Rapid Response Literature Review

Rapid Evidence Product

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Investigators:
Rachel McCausland, M.P.H.
Joann Fontanarosa, Ph.D.
Ravi Patel, M.D.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

A representative from AHRQ served as a Contracting Officer's Representative and reviewed the contract deliverables for adherence to contract requirements and quality. AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis, interpretation of data, or preparation or drafting of this report.

Preface

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) is expanding its portfolio to include rapid evidence products. The program has begun to develop a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

In 2014, the AHRQ Evidence-based Practice Center (EPC) Program produced a taxonomy of rapid evidence products produced by leading organizations around the world.[1-4] Based on levels of synthesis, the report classified products as evidence inventories, rapid responses, and rapid reviews. On one end of the spectrum, evidence inventories offer an assessment of the quantity and type of evidence without presenting results. On the other end, rapid reviews adapt and streamline traditional systematic review methods to provide a limited evidence synthesis. Rapid responses fall between the two; through examination of the literature but no formal evidence synthesis, rapid responses aim to offer the end-user a solution to a targeted problem based on the best available evidence.

To shorten timelines, reviewers must make strategic choices about which processes to abridge. Common adaptations include: narrowly focusing questions, limiting the number of databases searched and/or modifying search strategies, using a single reviewer and/or abstractor with a second to provide verification, and restricting to studies published in the English language. However, these adaptations may limit the certainty and generalizability of the review findings, particularly in areas with a large literature base. Transparent reporting of the methods used, the resulting limitations of the evidence synthesis, and the quality of included studies is extremely important. While tradeoffs will likely differ for each topic, they are described so readers can adjudicate the limitations of the findings of the review.

While rapid evidence products are often sufficient for decision making on their own, at other times they can uncover a large, complex literature base that encourages end-users to seek a full review. Rapid evidence products can provide a map of the evidence and assist decisionmakers in targeting resources to areas of highest interest and greatest potential value.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to AHRQ.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Robert Otto Valdez, Ph.D., M.H.S.A.
Director
Agency for Healthcare Research and Quality

Therese Miller, Dr.P.H.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Christine S. Chang, M.D., M.P.H.
Acting Director and Task Order Officer
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Nonemergent Percutaneous Coronary Intervention Versus Optimal Medical Treatment for Stable Ischemic Heart Disease: A Rapid Response Literature Review

Structured Abstract

Aims. There is uncertainty around the optimal role of percutaneous coronary intervention (PCI) for management of chronic coronary syndrome, specifically when patients have disease in multiple coronary vessels and disease in the proximal portion of the left anterior descending coronary artery. This uncertainty was reflected in 2021 guidance from the American College of Cardiology (ACC)/American Heart Association (AHA) on coronary artery revascularization. The Agency for Healthcare Research and Quality has commissioned this rapid response literature review to meet a Congressional request for a summary of recent evidence on the benefits of angioplasties conducted in nonemergency situations.

Methods. This rapid response literature review on the comparative effectiveness of nonemergent PCI followed established best systematic review methods, modified to meet a shortened project timeframe. We searched PubMed®, Embase®, and the Trip© medical database from 2018 through April 2023 for systematic reviews (SRs), clinical practice guidelines, and randomized controlled trials, and summarized the evidence comparing PCI to optimal medical therapy (OMT) for stable ischemic heart disease (SIHD). Our primary outcomes of interest were major objective cardiovascular outcomes, including mortality, myocardial infarction, stroke, urgent revascularization, or composites of one or more of these hard clinical outcomes. Where available, we also abstracted patient reported outcomes (e.g., angina severity and quality of life [QoL]) from included studies.

Findings. Key findings from nine SRs and one primary study include:
- The body of evidence directly comparing PCI to OMT for SIHD has remained largely unchanged since the 2021 ACC/AHA guidance's publication.
- Most studies of revascularization for coronary artery disease do not focus on direct head-to-head comparisons of PCI versus OMT for SIHD but instead either (1) compare OMT to invasive revascularization (PCI and coronary artery bypass graft [CABG] combined cohort); (2) compare PCI to CABG; or (3) compare different PCI techniques.
- Another factor that complicates comparison is that the meta-analyses often included data from CABG and PCI combined cohorts (e.g., the recent landmark ISCHEMIA trial) but reported the outcomes as PCI specific.
- In the general SIHD population, our review did not find evidence to support survival benefit or effect on hard clinical outcomes when PCI is added to OMT.
- Limited evidence indicates there may be a beneficial effect of PCI on angina symptoms and measures of QoL, but most systematic reviews focused on major objective cardiovascular outcomes and did not consider QoL or freedom from angina.
- Both OMT and PCI have evolved significantly during the period of time in which the systematic reviews' included studies were conducted. It is not clear how these changes may have affected the applicability of past studies to current practice.

Conclusions. The evidence directly comparing PCI to OMT for SIHD has remained largely unchanged since publication of the 2021 ACC/AHA guidelines. More research is needed to verify the comparative effectiveness of nonemergent PCI compared to medical treatment for individuals with SIHD, and how the effectiveness varies by certain patient populations and clinical presentation.

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1. Background

Stable ischemic heart disease (SIHD) affects over 20 million Americans and clinically manifests as angina.[1] Approximately every 40 seconds, an American will have an acute myocardial infarction (MI),[1] and the majority of these individuals will have pre-existing SIHD. Due to the high prevalence of SIHD and its associations with cardiovascular (CV) morbidity and symptom burden, treatment strategies to improve mortality, morbidity, and quality of life are of paramount importance. To date, the two foundational options for treatment of SIHD have been (1) optimal medical therapy (OMT) and (2) revascularization of coronary artery disease (CAD) through percutaneous coronary intervention (PCI) or surgical coronary artery bypass grafting (CABG). The specific role of PCI in treatment of SIHD, however, has been complex to decipher.

Discerning the impact of PCI on SIHD carries specific challenges. First of all, the effectiveness of the main alternative to PCI—optimal medical therapy—has improved dramatically over time. Over the past several decades, statins have consistently demonstrated benefit in reduction of CV mortality and MI in low- and high-risk populations and have since become a foundational therapy in SIHD.[2-4] Additional lipid-lowering medications, including cholesterol absorption inhibitors,[5] proprotein convertase subtilisin/kexin type 9 inhibitors,[6,7] and most recently, ATP citrate lyase inhibitors,[8] have reduced clinical events across various populations of CAD. Thus, it is possible that the increased use of effective lipid-lowering therapies in contemporary SIHD populations may reduce any additional benefit from PCI on clinical outcomes (e.g., CV mortality, MI). Similarly, anti-platelet medical therapies, including aspirin and/or P2Y12 inhibitors,[9] and low-dose anticoagulants[10] improve clinical outcomes in SIHD and are widely prescribed, creating further challenges in discerning additional effect from PCI.

A second challenge in discerning the impact of PCI is the evolution of PCI technology. Older trials evaluating the effect of PCI used older generation stents (bare metal) that are known to carry a higher risk of in-stent restenosis over time.[11] Several generations of drug-eluting stents are currently used, which carry lower risks and theoretically, improved efficacy. Furthermore, there have been technological advances in the functional assessment of coronary lesions at the time of PCI (e.g., fractional flow reserve [FFR]) and in non-invasive testing for ischemia.

A third challenge is the wide spectrum of coronary anatomical lesions in SIHD. Patients may have 1-, 2-, or multi-vessel disease, raising the possibility that the effects of PCI may vary by anatomical type.

Finally, some of the studies themselves may distort or obscure the specific effect of PCI. Clinician beliefs about the greater efficacy of PCI may have led to patients with certain CAD anatomy being omitted from randomized trials (i.e., selection bias). The role for PCI in certain high-risk SIHD conditions (e.g., multi-vessel CAD) has been extrapolated from trials of CABG as compared with optimal medical therapy. Since the initial trials of CABG therapy, subsequent trials have evaluated PCI as compared with CABG,[12-14] and direct comparisons of PCI with optimal medical therapy have not been performed in these conditions. Evaluation of the effects of PCI on quality of life and anginal symptoms are difficult to understand because of the lack of patient and investigator blinding and the relative dearth of sham-controlled trials in this space.

The 2021 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for Coronary Artery Revascularization found that, based on evidence from nonrandomized studies, PCI was reasonable in selected patients under some circumstances but areas of uncertainty remain. This uncertainty was around the optimal role of PCI for management of SIHD, specifically when patients have reduced left ventricular ejection fraction

(LVEF), disease in multiple coronary vessels, and/or disease in the proximal portion of the left anterior descending (LAD) coronary artery. The 2021 ACC/AHA Guideline for Coronary Artery Revascularization concluded:[15]

- There are insufficient data to make recommendations for using PCI in patients with SIHD and multivessel CAD with LVEF less than 35 percent.
- The use of PCI in patients with SIHD and multivessel CAD and LVEF 35 to 50 percent requires more study.
- The evidence for a survival advantage for PCI over medical therapy in patients with left main CAD is inferential but plausible.
- The usefulness of PCI to improve survival is uncertain in patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD), and anatomy suitable for PCI.
- The usefulness of coronary revascularization to improve survival is uncertain in patients with SIHD, normal ejection fraction, and significant stenosis in the proximal LAD.

In the Fiscal Year 2023 Federal budget, Congress directed the Agency for Healthcare Research and Quality (AHRQ) to assess the current evidence on the benefits of angioplasties (currently known as PCI) conducted in nonemergency situations. AHRQ subsequently commissioned this rapid response literature review summarizing recent evidence on this topic.

2. Key Question

What is the comparative effectiveness of nonemergent percutaneous coronary intervention compared to medical treatment for individuals with stable ischemic heart disease?

3. Methods

This rapid response on the comparative effectiveness of nonemergent PCI followed established best methods used in systematic review (SR) research while allowing for modifications to meet rapid response project timeframes.[16-18] PICOT (population, intervention, comparison, outcome, time) inclusion criteria (Table 1) were designed to address the 2021 ACC/AHA guideline's uncertainty in the optimal role of PCI for management of SIHD. Populations were excluded if clear evidence-based guidance was already available on PCI in these specific groups of patients. Similarly, harms were not included as an outcome of interest in this rapid response because guidance on the risks (e.g., bleeding, coronary perforation, peri-procedural MI) associated with adding invasive revascularization to medical therapy is available in the 2021 ACC/AHA Guideline for Coronary Artery Revascularization.[15]

Table 1. Inclusion and exclusion criteria

Study Parameter	Inclusion Criteria	Exclusion Criteria
Population	• Adults with SIHD* • CHD/CAD will only be included if outcomes are reported separately for SIHD patients. Subgroups: age, sex, race/ethnicity, anatomical lesion(s), LVEF, symptomatic disease	• ACS • Normal LVEF, and 1- or 2-vessel CAD not involving the proximal LAD[†] • ≥1 coronary arteries that are not anatomically or functionally significant (<70% diameter of non-left main coronary artery stenosis, FFR >0.80)[†]
Intervention	• PCI alone • PCI plus OMT • "Revascularization" (combined study inclusion of CABG or PCI) will only be included if outcomes are reported separately for PCI patients.	• Any intervention other than PCI (e.g., CABG)
Comparison	OMT without PCI	• Comparator other than OMT (e.g., CABG) • No comparator • PCI technique vs. another PCI technique (e.g., FFR- vs. nonFFR-guided PCI, or functional- vs. angiographically-guided PCI, or transradial vs. transfemoral PCI) • PCI stent vs. PCI stent types (e.g., bare metal vs. drug eluting stents)
Outcomes[‡]	• Cardiovascular mortality • MI • Stroke • Urgent revascularization • Composites including ≥1 of the above outcomes as a component	Studies will be excluded if they do not report ≥1 of the specified outcomes, either individually or as a component of a composite.
Timing	Any	None

Study Parameter	Inclusion Criteria	Exclusion Criteria
Setting	Any (US or outside US)	None
Study Design	• SRs/meta-analyses • Clinical practice guidelines, if informed by a systematic review • RCTs published subsequent to included SRs	• RCTs included in or published prior to included SRs • Clinical studies other than RCTs • Non-clinical studies other than guidelines
Language	English language publications.	Non-English language publications.
Publication dates	2018 – April 2023	Prior to 2018

*Stable ischemic heart disease (SIHD) includes adults with known ischemic heart disease, who have stable pain syndromes (i.e., chronic angina), or those with new-onset, low-risk chest pain (i.e., low-risk, unstable angina or UA). Asymptomatic patients diagnosed through non-invasive methods or with symptoms adequately controlled medically or following revascularization are also considered to have SIHD.

†Excluded because clear evidence-based guidance is already available on PCI in these specific groups of patients.

‡Available patient reported outcomes (e.g., angina severity) will be abstracted from otherwise included studies.

Abbreviations: ACS=acute coronary syndrome; CABG=coronary artery bypass graft; CAD=coronary artery disease; CHD=coronary heart disease; FFR=fractional flow reserve; LAD=left anterior descending artery; LVEF=left ventricular ejection fraction; MI=myocardial infarction; OMT=optimal medical treatment; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SIHD=stable ischemic heart disease; SR=systematic review; US=United States.

3.1 Literature Search

We searched for systematic reviews, clinical practice guidelines and randomized controlled trials using the search strategy outlined in Appendix A using the following databases: PubMed®, Embase®, and Trip© medical database. The search was limited to English language publications from 2018 – April 2023.

3.2 Study Selection and Data Extraction

We implemented single screening of titles and abstracts for eligibility against inclusion/exclusion criteria. One reviewer independently screened all titles and abstracts of citations retrieved from literature searches as well as full-text reports of titles and abstracts deemed as potentially relevant after the abstract screening. Once comprehensive SRs were chosen, we supplemented that data with randomized controlled trials (RCTs) published subsequent to the included SRs. All screening was done in DistillerSR and EndNote was used to track citations. Reasons for which full texts were excluded were noted utilizing the eligibility criteria as a benchmark. A project manager provided a final review of inclusions and exclusions.

Following screening, a clinical subject matter expert (SME), a physician specialist, received the list of eligible inclusions, to ensure that influential or landmark publications within the clinical community were not missed, and to identify publications that should be excluded for lack of clinical applicability.

Data was extracted into Word tables and included information about author, year, country, setting, study design, study dates, sample size, follow-up duration, patient characteristics (age, gender, race, co-morbidities), and outcomes of interest (listed in Table 1).

3.3 Quality Assessment

Methodological quality of included SRs and RCTs was assessed using United States Preventive Services Task Force (USPSTF) criteria (Table 2).[19]

Table 2. USPSTF quality rating criteria

Quality Rating	Systematic Reviews	Randomized Controlled Trials
Good	Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.	Comparable groups are assembled initially and maintained throughout the study (follow-up greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used.
Fair	Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.	Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used.
Poor	Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.	Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking.

3.4 Data Synthesis

Data were compiled into evidence tables (Appendix B) and synthesized narratively. Mapping was used to identify which RCTs are included in which SRs via a citation matrix (Table B-3). During review of SRs, attempts were made to exclude data from included trials published prior to the landmark COURAGE trial (2007),[11] due to limited applicability to current care; however, it was ultimately not possible to separate data from specific studies that were included in reviewed meta-analyses. We did not conduct meta-analysis or perform GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Strength of the Evidence Base assessment. The clinical SME reviewed the final report to ensure accurate clinical contextualization of all findings.

4. Results

Our searches for systematic reviews and clinical practice guidelines identified 2,221 potential citations, of which 2,126 were excluded at the title/abstract level. We performed a full-text review of the remaining 95 citations, which resulted in identification of 25 systematic reviews and two clinical practice guidelines that addressed the Key Question and met all PICOT criteria for inclusion. Importantly, although inclusion criteria were limited to SRs or RCTs with hard clinical outcomes (cardiovascular mortality, MI, stroke, urgent revascularization), we did not identify any studies that were excluded for this reason. One of the clinical practice guidelines was excluded from our analysis after we were unable to obtain the details of the SR that informed the guideline, despite multiple efforts to contact the corresponding authors, guideline chairs and publishing society. After analysis of the SRs' included studies and reported outcomes, 16 SRs were further excluded with the most recent and comprehensive SRs chosen for final inclusion in our review. A 2023 SR and meta-analysis of randomized data by Bytyçi et al. evaluated the short- and long-term clinical benefit of PCI compared to OMT in a broad population of adults with chronic coronary syndrome (CCS).[20] To supplement this review, we included an SR of randomized data addressing subgroups of SIHD with chronic kidney disease (CKD),[21] low LVEF,[22] and chronic total occlusion (CTO).[23] We further supplemented this data with additional SRs that investigated different subgroups[24,25] and/or included observational studies.[26-28]

Separate searches for RCTs identified 4,565 potential citations, of which 4,520 were excluded at the title/abstract level. We performed a full-text review of the remaining 45 citations, which resulted in identification of two RCTs that addressed the key question and met all PICOT criteria for inclusion. Both of these RCTs were identified as already included in the reviewed SRs and as a result were excluded from further analysis. Four pivotal RCTs, identified by the SME, were excluded because they overlapped with the SRs' inclusions. One RCT,[29] that met all PICOT criteria but was not captured in our search results and published subsequent to the most recent SR, was identified by the SME and was included in this review.

See Appendix C for more details.

4.1 SIHD General Population

We identified three fair-quality systematic reviews addressing the SIHD general population. Lerman et al.[24] and Radaideh et al.[25] each had distinct inclusion criteria that were more restrictive than the comprehensive meta-analysis by Bytyçi et al.,[20] but the findings across all three SRs were consistent – compared to OMT alone, the addition of PCI does not reduce the risk of all-cause mortality, CV mortality or MI. Notably, all three of these SRs were rated fair-quality because of issues regarding the validity of reported conclusions. In all three SRs, the outcomes were reported by the authors as PCI specific, but the meta-analyses each include data from CABG and PCI combined cohorts (e.g., the recent landmark ISCHEMIA trial[30]). The pooled results and conclusions actually refer to routine revascularization, with no emphasis on patients who have undergone PCI, despite the author's reporting it as PCI specific results. This severely limits the applicability of the studies and must be taken into consideration when reviewing the authors' reported outcomes.

Bytyçi et al. (2023)[20] conducted a fair-quality SR to investigate the benefits of PCI over and above OMT in CCS. This SR included RCTs comparing PCI to OMT in CCS patients, that reported any clinical outcomes. Trials with insufficient statistical data to compare the two

groups, ongoing trials, and non-English language publications were excluded. Fifteen studies (12 original RCTs and three substudies) were included in the meta-analysis with a total of 16,443 CCS patients (PCI N=8307 and OMT N=8136). Mean age ranged from 60 to 80 years, 51 to 85 percent of patients were male, and mean follow-up was 27.7 months (mean range, 1.5 to 60 months). The meta-analysis reported that, compared to OMT alone, the addition of PCI does not reduce the risk of major adverse cardiovascular event (MACE) (risk ratio [RR] 0.95 [95% confidence interval [CI] 0.86–1.05]; p=0.32), all-cause mortality (RR 0.97 [95% CI 0.86–1.09]; p=0.56), CV mortality (RR 0.90 [95% CI 0.73–1.10]; p=0.30), MI (RR 0.90 [95% CI 0.73–1.11]; p=0.32), revascularization (RR 0.54 [95% CI 0.27–1.08]; p=0.08), stroke (RR 1.51 [95% CI 0.93–2.45]; p=0.10), or frequency of hospitalization for angina (RR 0.93 [95% CI 0.67–1.31]; p=0.69). PCI was reported to provide better short-term (<1 year) quality of life (QoL) improvements: Seattle Angina Questionnaire (SAQ) limitation (mean difference [MD] 0.12 [95% CI 0.06–0.19]; p=0.003), angina control (MD 4.64 [95% CI 0.99–8.30]; p=0.01), angina stability (MD 2.62 [95% CI 0.16–5.08]; p=0.04), QoL score (MD 5.56 [95% CI 2.30–8.82]; p=0.0008), and treatment satisfaction (MD 1.98 [95% CI 0.06–3.90]; p=0.04). In the meta-analysis of studies, however, there was no statistically significant difference between the two treatment strategies in their ability to impact symptoms over the long-term (≥1 year) follow-up period.

Lerman et al. (2021)[24] conducted a fair-quality SR to compare PCI plus OMT to OMT alone in stable obstructive CAD. This SR also included RCTs comparing PCI to OMT, but uniquely excluded trials if stent implantation rate was <50% in PCI arms or if statins were used in <50% of PCI and OMT arms. These specific inclusion criteria were intended to clarify whether PCI would improve outcomes when added to OMT in the current cardiac care practice setting by excluding trials that used outdated practices in the majority of patients. Six studies (five original RCTs and one substudy) were included in the meta-analysis with a total of 11,144 CAD patients (PCI N=5,575 and OMT N=5,569). Mean age ranged from 62 to 65 years, 68 to 85 percent of patients were male, and mean follow-up ranged from 2 to 11 years. The meta-analysis reported findings consistent with those reported by Bytyci et al. - compared to OMT alone, the addition of PCI does not reduce the risk of all-cause mortality (OR 0.98 [95% CI 0.86–1.12]; p=0.79), CV mortality (OR 0.91 [95% CI 0.76–1.08]; p=0.27) or MI (OR 0.92 [95% CI 0.81–1.04]; p=0.18) in patients with SIHD.

Radaideh et al. (2020)[25] also conducted a fair-quality study level meta-analysis of RCTs to compare PCI plus OMT to OMT alone in stable CAD patients. In this meta-analysis only RCTs that documented objective evidence of ischemia by either treadmill exercise, myocardial imaging, or FFR were included. Seven RCTs were included in the meta-analysis with a total of 10,043 CAD patients (PCI N=5,033 and OMT N=5,010). Mean age was 62.54 years, 80 percent of patients were male, and mean follow-up was 3.9 years. This meta-analysis also reported that, compared to OMT alone, the addition of PCI does not reduce the risk of all-cause mortality (RR 0.97 [95% CI 0.83–1.12]; p=0.91), CV mortality (RR 0.89 [95% CI 0.72–1.10]); p=0.89) or MI (RR 0.92 [95% CI 0.78–1.09]); p=0.23).

4.2 SIHD and Low LVEF

We identified one good-quality systematic review and one good-quality RCT addressing SIHD and low LVEF. The findings were consistent, and found that compared to OMT alone, the addition of PCI does not provide a survival benefit in patients with SIHD and low LVEF.

4. Results

Yokoyama et al. (2021)[22] conducted a good-quality network meta-analysis comparing OMT, PCI and CABG in patients with CAD and low LVEF. This meta-analysis included RCTs and propensity score matching (PSM) studies comparing at least two of these treatments in patients diagnosed with CAD and LVEF 50 percent or less. Studies that did not report mortality, major adverse cardiac and cerebrovascular event (MACCE), MI, stroke or revascularization were excluded, as well as studies that did not use LVEF to define left ventricular (LV) dysfunction. Thirteen studies (3 RCTs and 10 PSM studies) were included in the meta-analysis with a total of 18,855 CAD patients (PCI N=8,771). Mean age ranged from 50 to 71 years, 69 to 95 percent of patients were male, and follow-up ranged from 2.7 to 15 years. Notably, the PCI versus OMT comparisons were only drawn from two PSM studies, with a total of 735 patients (PCI N=319; OMT N=319, CABG N = 97) and median follow-up periods of 6.2 and 7 years. Patient characteristics were not readily available for these two studies. The pooled analysis demonstrated that, compared to OMT alone, the addition of PCI does not reduce the risk of MACCE (hazard ratio [HR] 1.15 [95% CI 0.89–1.49]; p=NS), all-cause mortality (HR 0.90 [95% CI 0.71–1.15]; p= not significant), CV mortality (HR 0.65 [95% CI 0.33–1.28]; p= not significant), MI (PCI vs. OMT (HR 1.23 [95% CI 0.65–2.31]; p= not significant), revascularization (HR 2.17 [95% CI 0.81–5.80]; p== not significant), or stroke (HR 1.49 [95% CI 0.96–2.30]; p= not significant). A sensitivity analysis limited to patients with LVEF 40 percent or less showed similar results with no significant difference observed between PCI and OMT. A subgroup analysis of patients with drug eluting stents (DES) in the PCI group demonstrated that, compared to OMT, PCI with DES was associated with lower rates of all-cause mortality (HR 0.79 [95% CI 0.64–0.98]; p=0.03) and CV mortality (HR 0.14 [95% CI 0.03–0.58]; p=0.009), while no differences were observed among any other outcome.

Perera et al. (2022)[29] conducted a good-quality multicenter, randomized, open-label trial investigating if revascularization with PCI in addition to OMT for heart failure (HF), as compared with OMT alone, would improve event-free survival in patients with severe ischemic LV systolic dysfunction and demonstrable myocardial viability. This RCT, conducted entirely within the U.K., included adult patients with LVEF 35 percent or less, extensive CAD (British Cardiovascular Intervention Society Jeopardy Score [BCIS-JS] 6 or more), and demonstrable viability in 4 or more dysfunctional myocardial segments amenable to revascularization with PCI. Patients were excluded for MI within the four weeks before randomization, or acute decompensated HF or sustained ventricular arrhythmias within 72 hours before randomization. A total of 700 patients underwent randomization (PCI N=347 and OMT N=353), with baseline patient characteristics well balanced between the two arms (see Table B-2). The primary outcome of interest was a composite of all-cause mortality or hospitalization for HF. Over a median follow-up period of 41 months (interquartile range, 28 to 60 months), the addition of PCI did not significantly reduce the rate of composite events (HR 0.99 [95% CI 0.78–1.27]; p=0.96), all-cause mortality (HR 0.98 [95% CI 0.75–1.27]), or hospitalization for HF (HR 0.97 [95% CI 0.66–1.43]) when compared to OMT alone. Analysis of secondary outcomes also found no significant between group differences for CV mortality, MI or unplanned revascularization. Investigators noted an apparent early benefit of PCI that was observed with respect to QoL, but the between-group difference diminished over time. Overall data from this RCT indicates that among patients with severe ischemic LV systolic dysfunction who received OMT, the addition of revascularization by PCI did not result in a lower incidence of all-cause mortality or hospitalization for HF, nor did it result in a sustained difference in QoL.

4.3 SIHD and Chronic Kidney Disease

We identified one fair-quality systematic review, addressing patients with SIHD and CKD. The authors reported that compared to OMT alone, the addition of PCI reduced the short-term (less than 1 year) and long-term (more than 3 years), but not medium-term (1-3 years) mortality risk in patients with SIHD and CKD. A subgroup analysis of only non-acute myocardial infarction (non-AMI) patients demonstrated a PCI survival benefit that was limited to the long-term (more than 3 years) period.

Yong et al.[21] conducted a systematic review and meta-analysis comparing OMT, PCI and CABG in patients with CAD and CKD. This meta-analysis included RCTs and observational studies comparing at least two of these treatments in patients diagnosed with CAD and stage IV or V CKD (eGFR <30 ml/min/1.73 m^2 or dialysis). Studies that did not report mortality, MI or revascularization were excluded. Thirty-two studies (two RCTs and thirty observational studies) were included in the meta-analysis with a total of 84,598 CAD patients (PCI N= not reported). The specific studies informing the PCI versus OMT comparison were not identified by the authors, resulting in the fair-quality assessment.

In contrast to the Yokoyama et al. (2021) SR, there were no DES-PCI and OMT comparisons included in this SR. Across the entire meta-analysis, mean age ranged from 41 to 77 years, 46% to 88% of patients were male, and follow-up ranged from in-hospital to 8 years. Ten included studies that compared PCI with OMT (PCI N=1480 and OMT N=4422) reported all-cause mortality outcomes. Compared with OMT, PCI was associated with reduced all-cause mortality at 0-1 month (odds ratio [OR] 0.60 [95% CI 0.43–0.82]; p<0.05), 1-12 months (OR 0.60 [95% CI 0.44–0.82]; p<0.05), and >3 years (OR 0.64 [95% CI 0.48–0.85]; p<0.05) of follow-up. During 1-3 years of follow-up, there was no significant difference in all-cause mortality between PCI and OMT (OR 0.82 [95% CI 0.62–1.09]; p = 0.182). Subgroup analyses demonstrated that, compared to OMT, PCI was associated with reduced all-cause mortality at more than3 years of follow-up in non-AMI patients (OR 0.46 [95% CI 0.30–0.72]; p<0.05) and in patients with multi-vessel disease (MVD) at 1-3 years (OR 0.29 [95% CI 0.11–0.77]; p<0.05) and more than 3 years (OR 0.33 [95% CI 0.12–0.93]; p<0.05) of follow-up. Three included studies that compared PCI to OMT reported MACE. Compared to OMT, PCI was associated with a reduced risk of MACE at 1-12 months (OR 0.01 [95% CI 0.01–0.78]; p<0.05) follow-up but not at 1-3 years. Results were similar for the subgroup analysis in non-AMI patients. Three included studies comparing PCI to OMT reported CV mortality and 15 included studies reported MI rates. They reported that results showed "no significant difference in the risk of CV mortality or MI between PCI and OMT" at any follow-up period, including in the subgroup analysis of non-AMI patients, although numerical data was not provided by the authors for this outcome.

4.4 Chronic Total Occlusion

Chronic total occlusion (CTO) is a specific subset of stable ischemic heart disease in which there is a complete or nearly complete blockage in one or more coronary arteries, and this blockage is typically present for at least three months. Patients with CTO are notoriously challenging to manage clinically, as they often suffer from significant angina and have a high risk for cardiovascular events. PCI of CTO lesions, however, is typically more challenging than non-CTO lesions due to the length of time of total occlusion, leading to lesion calcification. Thus, PCI of CTO lesions often carry higher peri-procedural risks. Due to the high-risk nature of these lesions along with procedural complexity, there is a relative lack of randomized clinical

trial data surrounding efficacy of PCI on hard clinical outcomes and quality of life (i.e., anginal improvement) in CTO. Evaluation of reported results should be interpreted in light of the fact that the RCTs of PCI versus OMT in the CTO population are small studies, and the overall patient population of RCTs alone is ~1800 individuals.

Qian et al. (2022)[28] conducted a good-quality systematic review and meta-analysis to compare the results of PCI as compared to medical therapy in CTO lesions. This meta-analysis included RCTs and observational or propensity matched cohorts. Twelve studies (3 original RCTs, 1 long-term extension of an RCT, and 8 observational studies) were included in the meta-analysis with a total of 8,549 CCS patients (PCI N=4288 and OMT N=4261). Mean age, distribution by sex, and follow up time were not reported. The meta-analysis demonstrated that, PCI as compared with medical therapy was associated with reduced risk of MI (RR 0.63 [95% CI 0.45–0.90]; p=0.01) and all-cause mortality (RR 0.51 [95% CI 0.40–0.64]; p<0.00001).

However, three other good-quality meta-analyses have been performed in the CTO population that have either stratified results by study design (RCT vs observational) or only included RCTs. Through these methods, these three other reviews have demonstrated heterogeneity in results by study design. These reviews are described below.

Khan et al. (2021)[26] incorporated 16 studies (4 RCTs, 12 observational studies) with a total of 11,314 patients (PCI N=5,486 and OMT N = 5828). Mean age ranged from 60 to 70 years, 71% to 90% of patients were male, and mean follow-up range was 12 to 60 months. A meta-analysis of all studies demonstrated that, PCI as compared with medical therapy was associated with reduced risk of CV mortality (OR 0.58 [95% CI 0.38–0.39]; p=0.01), MI (OR 0.62 [95% CI: 0.43-0.89]; p=0.009) and all-cause mortality (OR 0.45 [95% CI 0.32–0.63]; p<0.00001). However, upon meta-analysis of RCTs only, there was no significant difference of PCI as compared to optimal medical therapy upon all-cause mortality, CV mortality, or MI.

The findings from Li et al. (2019)[27] are quite similar to Khan et al., but only 3 of the 4 RCTs were included along with additional observational studies. Li et al. (2019) incorporated 17 studies (3 RCTs, 14 observational studies) with a total of 11,493 patients (PCI N= not reported). Mean age ranged from 63 to 69 years, 71 to 90 percent of patients were male, and mean follow-up range was 12 to 60 months. A meta-analysis of all studies demonstrated that OMT as compared with PCI was associated with increased risk of CV mortality (RR 2.36 [95% CI 1.97–2.84]; p<0.00001), all-cause mortality (RR 1.99 [95% CI 1.38–2.86]; p=0.0002), MACE (RR 1.25 [95% CI 1.03–1.51]; p=0.03), and MACCE (RR 2.47 [95% CI 1.52–4.02]; p=0.0003). However, upon meta-analysis of RCTs only, there was no significant difference of OMT as compared to PCI on mortality rates MACE/MACCE.

Finally, a systematic review and meta-analysis of PCI vs. OMT in CTO-SIHD by van Veelan et al. (2021)[23] was performed using only 5 RCTs with a total of 1,790 patients (PCI N = 964, OMT N=826). Mean age ranged from 57 to 65 years and sex was 82 to 89 percent male. The longest weighted follow-up period was 40 months. Meta-analysis of these 5 RCTS demonstrated that PCI, as compared to OMT, was not associated with significant differences in CV mortality at 1 or 4 years, MI at 1 year or 4 years, or all-cause mortality at 1 year or 4 years. PCI was associated with lower rates of subsequent target lesion revascularization at 1 year, but not at 4 years. Finally, PCI was associated with higher rates of freedom from angina at 1 year (RR 0.65 [95% CI 0.50-0.84]; p=0.001).

5. Discussion

As previously mentioned, the 2021 guidance from ACC/AHA on Coronary Artery Revascularization found that while PCI was reasonable in selected patients under some circumstances, there is uncertainty around the optimal role of PCI for management of CCS, specifically when patients have reduced LVEF, disease in multiple coronary vessels and/or disease in the proximal portion of the LAD coronary artery.[15]

In this rapid response, we found a paucity of studies directly comparing PCI to OMT for SIHD. The vast majority of recent trials investigating PCI either 1) compare OMT to invasive revascularization (PCI and CABG combined cohort); 2) compare PCI to CABG; or 3) compare different PCI techniques. Each of these comparisons are outside of the scope of this rapid response SR. For studies that directly compare PCI to OMT, the study populations are very rarely limited to SIHD, but rather typically investigate a broad population of CAD patients including both acute and stable coronary syndromes, with varying levels of ischemia and numbers of diseased vessels. For this reason, although we included nine SRs that are broadly applicable, we did not identify any systematic reviews that only included trials exactly matching our review's defined population, intervention, and comparator (Table 1), which were designed to address the 2021 ACC/AHA guideline's uncertainty. Nevertheless, the findings for each outcome are described below (Table 3).

5. Discussion

Table 3. Outcomes across patient populations

Population	Systematic Review	Included Study Types	All-Cause Mortality	CV Mortality	MI	Revascularization	Stroke	MACE/MACCE Composite	Angina/QoL
General SIHD population	Bytyçi[20]	RCT	No statistical difference	No statistical difference	No statistical difference	No statistical difference	No statistical difference	No statistical difference	PCI benefit, only at <1 year
	Lerman[24]	RCT	No statistical difference	No statistical difference	No statistical difference	NR	NR	NR	NR
	Radaideh[25]	RCT	No statistical difference	No statistical difference	No statistical difference	NR	NR	NR	NR
SIHD + low LVEF	Yokoyama[22]	RCT and Observational	PCI benefit, only DES subgroup	PCI benefit, only DES subgroup	No statistical difference	No statistical difference	No statistical difference	No statistical difference	NR
SIHD + CKD	Yong[21]	RCT and Observational	PCI benefit, only at >3 years for non-AMI subgroup	No statistical difference	No statistical difference	NR	NR	PCI benefit, only at <1 year for non-AMI subgroup	NR
Chronic Total Obstruction (CTO)	Li[27]	RCT and Observational	PCI benefit*	PCI benefit*	PCI benefit*	No statistical difference	No statistical difference	PCI benefit*	NR
	van Veelan[23]	RCT	No statistical difference	No statistical difference	No statistical difference	PCI benefit, only at 1 year	NR	No statistical difference	PCI benefit at 1 year
	Khan[26]	RCT and Observational	PCI benefit*	PCI benefit*	PCI benefit*	No statistical difference	No statistical difference	No statistical difference	NR
	Qian[28]	RCT and Observational	PCI benefit	NR	PCI benefit	No statistical difference	No statistical difference	NR	No statistical difference

*Statistically significant benefit favoring PCI over OMT disappears when observational studies are excluded from the meta-analysis.

Abbreviations: AMI=acute myocardial infarction CKD=chronic kidney disease; CV=cardiovascular; DES=drug eluting stent; LVEF=left ventricular ejection fraction; MACCE=major adverse cardiac and cerebrovascular events; MACE=major adverse cardiac events; MI=myocardial infarction; NR=not reported; OMT=optimal medical therapy; PCI=percutaneous coronary intervention; QoL=quality of life; RCT=randomized controlled trial; SIHD=stable ischemic heart disease

5.1 Composite Major Adverse Cardiac Events (MACE)

Six SRs included a reported composite outcome (MACE and/or MACCE), although the definition and components of MACE/MACCE was variable between each of the SRs' included trials (see Table 3). No statistically significant between group difference was found in four of the SRs,[20,22,23,26] and three did not report a composite outcome.[24,25,28] Li et al. reported a benefit of CTO-PCI, but notably reported that there was no statistically significant difference when the meta-analysis was limited to data from RCTs.[27] Yong et al. reported a benefit of PCI, in patients with SIHD and CKD, at short-term follow-up (1-12 months), but the benefit disappeared at long-term follow-up (1-3 years).[21]

In the REVIVED trial, investigating PCI in patients with severe ischemic LV systolic dysfunction, Perera et al. (2022)[29] reported a composite outcome that included all-cause mortality or hospitalization for HF. No significant between group difference was reported for this composite outcome.

5.2 Mortality

All nine SRs reported all-cause mortality rates (see Table 3). No statistically significant between group survival rate was found in four of the SRs.[20,23-25] Li et al. (2019),[27] Khan et al. (2021)[26] and Qian et al. (2022)[28] all reported a survival benefit of CTO-PCI, but both Li et al. and Khan et al. reported that there was no statistically significant difference when the meta-analyses were limited to data from RCTs. Qian et al. included observational data in the meta-analysis and did not separately analyze the randomized data. Yong et al. (2021)[21] reported a survival benefit of PCI, in patients with SIHD and CKD, at very short-term (0-1 month), short-term (1-12 months), and long-term (more than 3 years) follow-up. No significant between group difference was identified during the medium-term (1-3 years) follow-up period. In subgroup analyses, the survival benefit of PCI was limited to long-term follow-up for non-AMI patients and to medium- and long-term follow-up for patients with MVD. In patients with SIHD and LVEF 50 percent or less, Yokoyama et al. (2021)[22] reported a survival benefit of PCI only in a subgroup analysis that was limited to PCI with DES.

Eight SRs reported CV mortality rates (see Table 3). No statistically significant between group difference was found in five of the SRs,[20,21,23-25] and three reported a benefit limited to a specific subgroup analysis or when observational data was included in the meta-analysis. Li et al. (2019)[27] and Khan et al. (2021)[26] both reported reduced CV mortality rates associated with CTO-PCI, but both again reported that there was no statistically significant difference when the meta-analysis was limited to data from RCTs. In patients with SIHD and LVEF 50 percent or less, Yokoyama et al. (2021)[22] reported a reduced CV mortality rate associated with PCI only in a subgroup analysis that was limited to PCI with DES. Qian et al. (2022)[28] did not report CV mortality rates.

In the REVIVED trial, investigating PCI in patients with severe ischemic LV systolic dysfunction, Perera et al. (2022)[29] reported no significant between group differences for all-cause mortality rates or CV mortality.

5.3 Myocardial Infarction

All nine SRs also reported PCIs' effects on MI (see Table 3). No statistically significant between group difference was reported by six of the SRs, although Yong et. al (2021)[21] only reported these results narratively and did not provide numerical data to support this outcome.

Three of the SRs investigating PCI for CTO,[26-28] which all included observational data in their analysis, reported a benefit favoring CTO-PCI. Both Li et al. (2019)[27] and Khan et al. (2021)[26] reported that there was no statistically significant between group difference when the meta-analysis was limited to data from RCTs.

In the REVIVED trial, investigating PCI in patients with severe ischemic LV systolic dysfunction, Perera et al. (2022)[29] reported no significant between group differences for MI.

5.4 Unplanned Revascularization

Six SRs reported unplanned additional revascularization (see Table 3). No statistically significant between group difference was found in five of the SRs.[20,22,26-28] For CTO-PCI, van Veelan et al. (2021)[23] reported a benefit at 1-year but the between group difference disappeared at the 4-year follow-up period. Three SRs did not report revascularization as an outcome.[21,24,25]

In the REVIVED trial, investigating PCI in patients with severe ischemic LV systolic dysfunction, Perera et al. (2022)[29] reported no significant between group differences for unplanned revascularization.

5.5 Stroke

No statistically significant between group difference was found in the five SRs reporting stroke as an outcome (see Table 3).[20,22,26-28]

5.6 Quality of Life

Only three of the SRs reported angina or other measures of QoL as an outcome (see Table 3).[20,23,28] Bytyçi et al. (2023)[20] reported PCI patients had greater improvement in QoL including physical limitation, angina frequency, stability, and treatment satisfaction at short-term follow-up (less than1 year) but that there were no between group differences for any measures of QoL at long-term follow-up (1 year or more). For CTO-PCI, van Veelan et al. (2021)[23] reported significantly higher rates of freedom from angina at 1 year, compared to OMT alone. In contrast, for CTO-PCI, Qian et al. (2022)[28] reported no significant between group differences in QoL.

In the REVIVED trial, investigating PCI in patients with severe ischemic LV systolic dysfunction, Perera et al. (2022)[29] reported that QoL scores appeared to favor the PCI group at 6 and 12 months, but that the between group differences had diminished by 24 months.

6. Limitations

6.1 Methodology Limitations

To complete this rapid review in a timely fashion, the scope was limited to populations for whom clear evidence-based guidance does not already exist, and the literature search was confined to PubMed, EMBASE, and the Trip medical database. Data were extracted for all included publications but the synthesis of results was limited to a narrative summary. Similarly, time constraints limited this narrative summary to a synthesis of the SRs' reported outcomes. We did not independently analyze each of the SRs' included trials verify accuracy of the reviewed meta-analyses. Risk-of-bias was performed for each included systematic review and the sole RCT, but no overall strength-of-evidence assessment was completed.

6.2 Evidence Base Limitations

Our review had a few other important limitations, directly related to the available evidence.

First, we were unable to create a pure PCI for SIHD data set. Per our protocol, we excluded SRs if the outcomes were not reported for PCI specifically. However, after further reviewing the details of RCTs included in the reviewed SRs, although the outcomes were reported by the authors as PCI specific, the meta-analyses often include data from CABG and PCI combined cohorts (e.g., the recent landmark ISCHEMIA trial[30]). The pooled results and conclusions often refer to routine revascularization with no emphasis on patients who have undergone PCI despite the author's presenting it this way. Similarly, we excluded SRs that only reported results for acute coronary syndromes, but there was often a mix of acute and stable patients in the SRs' included trials and meta-analyses. Furthermore, we were ultimately unable to evaluate the SRs' population characteristics to a level that would have allowed us to exclude the SIHD subgroups of patients for whom clear evidence-based guidance is already available (i.e., normal LVEF, and 1- or 2-vessel CAD not involving the proximal LAD; or 1 or more coronary arteries that are not anatomically or functionally significant (less than70 percent diameter of non-left main coronary artery stenosis, FFR greater than 0.80). These population and intervention discrepancies severely limit the applicability of the studies and must be taken into consideration when reviewing authors' reported outcomes.

Second, there is a relative lack of randomized clinical trial data surrounding efficacy of PCI on hard clinical outcomes and quality of life (i.e., anginal improvement) in CTO. The RCTs of PCI versus OMT in the CTO population are small studies, and the overall patient population of RCTs alone is approximately 1800 individuals. Upon evaluation of RCT data alone within the CTO population, meta-analyses demonstrate that PCI of CTO does not appear to affect CV mortality, MI, or all-cause mortality. However, this is in contrast to statistically significant benefits associated with PCI of CTO when observational studies are included in the meta-analyses. It is unclear to what extent these disparate results may be influenced by the RCT sample size or flaws in observational study designs.

Third, we were faced with many confounding factors that could influence the reported efficacy of OMT. The definition of OMT varied widely between studies and we often did not have access to patients' medication doses as well as data regarding patients' adherence. These variables can of course have a significant impact on efficacy and patients' outcomes.

Fourth, it is unclear to what extent the efficacy outcomes for trials included in the reviewed SRs may be influenced by stent type used. Older trials included in the reviewed meta-analyses

used older generation stents (bare metal) that are known to carry a higher risk of in-stent restenosis over time. Several generations of drug-eluting stents are currently used, which carry lower risks and, theoretically, improved efficacy.

Finally, the majority of the SRs reviewed (67 percent) focused on major objective cardiovascular outcomes and did not take into account the QoL or freedom from angina, which are important treatment goals.

7. Conclusions

The body of evidence directly comparing PCI to OMT for the treatment of stable ischemic heart disease has remained largely unchanged since the 2021 ACC/AHA Guideline for Coronary Artery Revascularization publication. We only identified one additional RCT[29] that was published subsequent to the ACC/AHA guideline. All RCTs included in the reviewed SRs, other than three outdated (and clinically irrelevant) trials published prior to 2007, were included in the 2021 ACC/AHA guidance's evidence base (see Table B-3).

In the general SIHD population, our review did not find evidence to support survival benefit or effect on hard clinical outcomes when PCI is added to OMT. Limited evidence indicates there may be a beneficial effect of PCI on angina symptoms and measures of QoL. Based upon the reviewed meta-analysis of 5 RCTs, CTO-PCI appears to increase the likelihood of freedom from angina at 1 year. Therefore, the overall findings in the CTO cohort are fairly similar to those in the overall SIHD cohort, in which PCI appears to improve symptoms of angina, and therefore may be a therapeutic option to improve quality of life among those with anginal symptoms that clinicians deem secondary to a CTO lesion. The reviewed evidence is inadequate to fully assess which characteristics of the patient, practitioner, or facility predict the most successful patient outcomes from nonemergent PCI.

In the absence of additional randomized data directly comparing PCI to OMT, future analysis of the effectiveness of nonemergent PCI will need to extrapolate from trials of CABG (or CABG and PCI combined cohorts) compared with OMT and trials of CABG compared with PCI. Alternatively, a review of well-conducted studies other than RCTs (e.g., propensity score matched), may help shed light on the utility of nonemergent PCI.

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Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
AMI	Acute myocardial infarction
BCIS	British Cardiovascular Intervention Society
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CI	Confidence interval
CKD	Chronic kidney disease
CTO	Chronic total occlusion
CV	Cardiovascular
DES	Drug eluting stents
eGFR	Estimated glomerular filtration rate
FFR	Fractional flow reserve
HF	Heart failure
HR	Hazard ratio
LAD	Left anterior descending
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular event
MACE	Major adverse cardiac event
MD	Mean difference
MI	Myocardial infarction
MVD	Multi-vessel disease
OMT	Optimal medical therapy
OR	Odds ratio
PCI	Percutaneous coronary intervention
PICOT	Patient, Intervention, Comparison, Outcome, Time
PSM	Propensity score matching
QoL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
SAQ	Seattle Angina Questionnaire
SIHD	Stable ischemic heart disease
SME	Subject matter expert
SR	Systematic review
USPSTF	United States Preventive Services Task Force

Appendix A. Search Strategy

The ICA Medical Librarian conducted searches of the peer-reviewed and grey literature, following established systematic review protocols. Searches were conducted of the following biomedical databases: MEDLINE (PubMed interface) and Embase for practice guidelines, systematic reviews, and randomized controlled trials and Trip Medical Database for practice guidelines. The search strategies used a combination of medical subject headings (i.e., controlled vocabularies) and keywords, and were written in the syntax of each database. The search strategies used terms for the intervention and condition as well as Boolean operators. All search results were limited to the English language and human species. Searches were restricted to the date range of 2018 to 2023 to ensure the literature was relevant to current trends. A customized filter was used to remove unwanted publication types.

Importantly, the search strategy for randomized controlled trials used a narrower set of search terms due to the search yield and the short timeline for this rapid response review. Initial searches with the expanded set of terms used in the search for guidelines and systematic review returned more than 16,000 potential citations for screening. By refining the search terms, we brought the yield down to less than 5,000 potential RCT citations for screening, which was feasible.

Tables A-1 to A-5 depict the search strategies and report results for searches in databases before deduplication.

Table A-1. PubMed search history (guidelines, systematic reviews, meta-analyses)

Search Number	Query	Filters	Results
4	#3 AND (#1 OR #2)	Guideline, Meta-Analysis, Systematic Review, Humans, English, from 2018 - 2023	731
3	"chronic coronary syndrome"[tiab] OR "stable angina"[tiab] OR "angina pectoris"[tiab] OR "ischemic heart disease"[tiab] OR "chronic angina"[tiab] OR "unstable angina"[tiab] OR "Angina Pectoris"[Mesh] OR "Coronary artery Disease"[Mesh] OR "coronary artery disease"[tiab] OR "coronary heart disease"[tiab]	Guideline, Meta-Analysis, Systematic Review, Humans, English, from 2018 - 2023	2,325
2	debulking[tiab] OR atherectomy[tiab] OR brachytherapy[tiab] OR "coronary intravascular lithotripsy"[tiab] OR "cytoreductive surgery"[tiab] OR "Atherectomy, Coronary"[Mesh] OR "Cytoreduction Surgical Procedures"[Mesh] OR "Brachytherapy"[Mesh]	Humans, English, from 2018 - 2023	8,863
1	"percutaneous coronary intervention"[tiab] OR PCI[tiab] OR "coronary revascularization"[tiab] OR (("heart muscle"[tiab] OR myocardial[tiab]) AND revascularization[tiab]) OR "Percutaneous Coronary Intervention"[Mesh] OR "Myocardial Revascularization"[Mesh] OR "percutaneous coronary angioplasty"[tiab] OR PCTA[tiab] OR ((angioplast*[tiab] OR "Angioplasty"[Mesh]) AND (stent*[tiab] OR "Stents"[Mesh]))	Humans, English, from 2018 - 2023	28,165

Table A-2. PubMed Search History (randomized controlled trials)

Search Number	Query	Filters	Results
6	#5 NOT #4	Humans, English, from 2018 - 2023	1,637
5	#1 AND (#2 OR #3)	Humans, English, from 2018 - 2023	2,012

Search Number	Query	Filters	Results
4	comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] OR annual[tiab] OR book[tiab] OR comment[tiab] OR chapter[tiab] OR note[tiab] OR review[tiab] OR symposium[tiab] OR poster[tiab] OR abstract[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab] OR animal[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR goat[tiab] OR goats[tiab] OR pig[tiab] OR pigs[tiab] OR cadaver[tiab] OR dog[tiab] OR dogs[tiab] OR monkey[tiab] OR monkeys[tiab] OR ape[tiab] OR apes[tiab]	Humans, English, from 2018 - 2023	1,157,242
3	debulking[tiab] OR atherectomy[tiab] OR brachytherapy[tiab] OR "coronary intravascular lithotripsy"[tiab] OR "cytoreductive surgery"[tiab] OR "Atherectomy, Coronary"[Mesh] OR "Cytoreduction Surgical Procedures"[Mesh] OR "Brachytherapy"[Mesh]	Humans, English, from 2018 - 2023	8,782
2	"percutaneous coronary intervention"[tiab] OR PCI[tiab] OR "coronary revascularization"[tiab] OR (("heart muscle"[tiab] OR myocardial[tiab]) AND revascularization[tiab]) OR "Percutaneous Coronary Intervention"[Mesh] OR "Myocardial Revascularization"[Mesh] OR "percutaneous coronary angioplasty"[tiab] OR PCTA[tiab] OR ((angioplast*[tiab] OR "Angioplasty"[Mesh]) AND (stent*[tiab] OR "Stents"[Mesh]))	Humans, English, from 2018 - 2023	27,911
1	"chronic coronary syndrome"[tiab] OR "stable angina"[tiab] OR "angina pectoris"[tiab] OR "ischemic heart disease"[tiab] OR "chronic angina"[tiab] OR "unstable angina"[tiab] OR "Angina Pectoris"[Mesh]	Humans, English, from 2018 - 2023	7,917

Table A-3. Embase search history (guidelines, systematic reviews, meta-analyses)

Search Number	Query	Results
5	#4 AND ('meta analysis'/de OR 'precribing guideline'/de OR 'systematic review'/de) AND [humans]/lim AND [english]/lim AND [2018-2023]/py	1889
4	#3 AND (#1 OR #2)	108762
3	'chronic coronary syndrome':ti,ab OR 'stable angina':ti,ab OR 'angina pectoris':ti,ab OR 'ischemic heart disease':ti,ab OR 'chronic angina':ti,ab OR 'unstable angina':ti,ab OR 'angina pectoris'/exp OR 'coronary artery disease'/exp OR 'coronary artery disease':ti,ab OR 'coronary heart disease':ti,ab	584588
2	debulking:ti,ab OR atherectomy:ti,ab OR brachytherapy:ti,ab OR 'coronary intravascular lithotripsy':ti,ab OR 'cytoreductive surgery':ti,ab OR 'atherectomy'/exp OR 'cytoreductive surgery'/exp OR 'brachytherapy'/exp	99067
1	'percutaneous coronary intervention':ti,ab OR pci:ti,ab OR 'coronary revascularization':ti,ab OR (('heart muscle':ti,ab OR myocardial:ti,ab) AND revascularization:ti,ab) OR 'percutaneous coronary intervention'/exp OR 'heart muscle revascularization'/exp OR 'percutaneous coronary angioplasty':ti,ab OR pcta:ti,ab OR ((angioplast*:ti,ab OR 'angioplasty'/exp) AND (stent*:ti,ab OR 'stent'/exp))	227366

Table A-4. Embase search history (randomized controlled trials)

Search Number	Query	Results
6	#5 NOT #4 AND [humans]/lim AND [english]/lim AND [2018-2023]/py	4197
5	#1 AND (#2 OR #3)	33178

Search Number	Query	Results
4	'editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti OR animal:ab,ti OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR goat:ab,ti OR goats:ab,ti OR pig:ab,ti OR pigs:ab,ti OR cadaver:ab,ti OR dog:ab,ti OR dogs:ab,ti OR monkey:ab,ti OR monkeys:ab,ti OR ape:ab,ti OR apes:ab,ti	16594188
3	debulking:ti,ab OR atherectomy:ti,ab OR brachytherapy:ti,ab OR 'coronary intravascular lithotripsy':ti,ab OR 'cytoreductive surgery':ti,ab OR 'atherectomy'/exp OR 'cytoreductive surgery'/exp OR 'brachytherapy'/exp	98713
2	'percutaneous coronary intervention':ti,ab OR pci:ti,ab OR 'coronary revascularization':ti,ab OR (('heart muscle':ti,ab OR myocardial:ti,ab) AND revascularization:ti,ab) OR 'percutaneous coronary intervention'/exp OR 'heart muscle revascularization'/exp OR 'percutaneous coronary angioplasty':ti,ab OR pcta:ti,ab OR ((angioplast*:ti,ab OR 'angioplasty'/exp) AND (stent*:ti,ab OR 'stent'/exp))	226605
1	'chronic coronary syndrome':ti,ab OR 'stable angina':ti,ab OR 'angina pectoris':ti,ab OR 'ischemic heart disease':ti,ab OR 'chronic angina':ti,ab OR 'unstable angina':ti,ab OR 'angina pectoris'/exp	161855

Table A-5. TRIP medical database search history (guidelines)

Search Number	Query	Filters	Results
1	"percutaneous coronary intervention" AND (ischemic OR angina)	Guidelines	273

Appendix B. Evidence Tables

Table B-1. Systematic reviews evidence table

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
General Population	**Reference:** Bytyçi et al. 2023[20] **Country:** Kosovo, Sweden **Purpose:** A systematic review and meta-analysis to evaluate the short- and long-term clinical benefit of PCI compared to OMT in CCS. **Quality Rating:** Fair*- Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; but uncertainty around the validity of reported conclusions. The meta-analysis included data from combined CABG-PCI cohorts but presented conclusions as PCI specific.* **Funding Source:** No external funding	The literature searches included MEDLINE, EMBASE, Scopus, Google Scholar, and Cochrane CENTRAL from inception to July 2022, with English language restrictions. Additional searches included a manual review of related review articles and the abstracts from relevant scientific sessions. **Inclusion/Exclusion Criteria:** Adult, human RCTs and follow-up trials comparing PCI with OMT were included if they reported clinical outcomes. Trials with insufficient statistical data to compare two groups and ongoing trials were excluded. **Included Studies:** Twelve RCTs (Hartigan 1998, Hambrecht 2004, TIME, MASS II, COURAGE, JSAP, BARI 2D, FAME II, Won 2016, ORBITA, Hennigan 2020, ISCHEMIA); three substudies	**Number of Patients:** 15 studies (N=16,443) *PCI: N=8307* *OMT: N=8136* **Diagnosis:** chronic coronary syndrome **Age:** Mean range: 60 to 80 years **Gender:** Range: 51% to 85% male **Intervention/Comparators:** PCI + OMT vs. OMT alone **Follow-up:** Mean range: 1.5 to 60 months; Mean: 27.7 months	**All-cause mortality (11):** PCI 7.5% vs. OMT 7.9% (RR 0.97 [95% CI 0.86–1.09]); p=0.56; I^2= 0% **CV mortality (8):** PCI 8.7% vs. OMT 9.9% (RR 0.90 [95% CI 0.73–1.10]); p=0.30; I^2= 0% **MACE (13):** PCI 18.2% vs. OMT 19.2% (RR 0.95 [95% CI 0.86–1.05]); p=0.32; I^2=40% **MI (11):** PCI 7.7% vs. OMT 8.3% (RR 0.90 [95% CI 0.73–1.11]); p=0.32; I^2=43% **Revascularization (6):** PCI 11.2% vs. OMT 18.6% (RR 0.54 [95% CI 0.27–1.08]); p=0.08; I^2=68% **Stroke (7):** PCI 2.2% vs. OMT 1.4% (RR 1.51 [95% CI 0.93–2.45]); p=0.10; I^2=10% **Hospitalization (6):** PCI 13.5% vs. OMT 13.9% (RR 0.93 [95% CI 0.67–1.31]); p=0.69; I^2=63% **SAQ limitation (3):** *<1 year*: MD 0.12 (95% CI 0.06–0.19); p=0.003; I^2=0% *≥1 year*: MD 1.01 (95% CI -0.84–2.86); p=0.28; I^2=51% **Angina frequency (3):** *<1 year*: MD 4.64 (95% CI 0.99–8.30); p=0.01; I^2=67%

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				≥1 year: MD 1.69 (95% CI -0.84–4.22); p=0.19; I²=61% **Angina stability (2):** *<1 year*: MD 2.62 (95% CI 0.16–5.08); p=0.04; I²=0% *≥1 year*: MD 0.81 (95% CI -1.84–3.46); p=0.55; I²=0% **QoL score (3):** *<1 year*: MD 5.56 (95% CI 2.30–8.82); p=0.0008; I²=77% *≥1 year*: MD 1.52 (95% CI -0.04–3.07); p=0.06; I²=0% **Treatment satisfaction (3):** *<1 year*: MD 1.98 (95% CI 0.06–3.90); p=0.04; I²=72% *≥1 year*: MD 0.58 (95% CI -2.61–3.77); p=0.72; I²=74%
	Reference: Lerman et al. 2021[24] **Country:** Israel **Purpose:** A systematic review and meta-analysis of randomized data comparing PCI plus OMT versus OMT alone in stable obstructive CAD. **Quality Rating:** Fair*- Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; but uncertainty around the validity of reported conclusions. The meta-analysis included data from combined CABG-PCI cohorts but	The literature searches included PubMed, EMBASE, and Cochrane CENTRAL from January 2005 to May 2020, without language restrictions. **Inclusion/Exclusion Criteria:** Adult, human RCTs comparing PCI plus OMT with OMT alone were included. Trials were excluded if stent implantation rate was <50% in PCI arms or if statins were used in <50% of PCI and OMT arms. **Included Studies:** Five RCTs (COURAGE, BARI-2D, MASS II, FAME II, ISCHEMIA); one substudy	**Number of Patients:** 6 studies (N=11,144) *PCI: N=5,575* *OMT: N=5,569* **Diagnosis:** stable obstructive CAD **Age:** Mean range: 62 to 65 years **Gender:** Range: 68% to 85% male **Intervention/Comparators:** PCI + OMT vs. OMT alone **Follow-up:** Range: 2 to 11 years	**All-cause mortality (6):** PCI 9.0% vs. OMT 9.3% (OR 0.98 [95% CI 0.86–1.12]); p=0.79; I²=0% **CV mortality (6):** PCI 4.9% vs. OMT 5.4% (OR 0.91 [95% CI 0.76–1.08]); p=0.27; I²=24% **MI (6):** PCI 9.9% vs. OMT 10.7% (OR 0.92 [95% CI 0.81–1.04]); p=0.18; I²=49%

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
	presented conclusions as PCI specific.* **Funding Source:** NR			
	Reference: Radaideh et al. 2020[25] **Country:** USA **Purpose:** A study-level meta-analysis of randomized data comparing PCI plus MT versus MT alone in stable CAD patients with objective evidence of myocardial ischemia. **Quality Rating:** Fair*- Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; but uncertainty around the validity of reported conclusions. The meta-analysis included data from combined CABG-PCI cohorts but presented conclusions as PCI specific.* **Funding Source:** NR	The literature searches included PubMed, EMBASE, the Cochrane Library. Details regarding search dates and the use of any restrictions were not provided. **Inclusion/Exclusion Criteria:** Adult, human RCTs comparing PCI plus MT to MT alone, utilizing contemporary guideline-directed MT and documented objective evidence of ischemia by either treadmill exercise, myocardial imaging, or FFR were included. **Included Studies:** Seven RCTs (Hambrecht 2004, MASS II, COURAGE, JSAP, BARI 2D, FAME II, ISCHEMIA).	**Number of Patients:** 7 studies (N=10,043) *PCI: N=5,033* *MT: N=5,010* **Diagnosis:** Stable CAD with myocardial ischemia **Age:** Mean 62.54 years **Gender:** 80% male **Intervention/Comparators:** PCI + MT vs. MT alone **Follow-up:** Mean 3.9 years	**All-cause mortality (7):** PCI 6.3% vs. OMT 6.6% (RR 0.97 [95% CI 0.83–1.12]); p=0.91; I^2=0% **CV mortality (6):** PCI 3.3% vs. OMT 3.7% (RR 0.89 [95% CI 0.72–1.10]); p=0.89; I^2=0% **MI (7):** PCI 9.2% vs. OMT 9.9% (RR 0.92 [95% CI 0.78–1.09]); p=0.23; I^2=27%
SIHD and Low LVEF	**Reference:** Yokoyama et al. 2021[22] **Country:** USA **Purpose:** A network meta-analysis comparing CABG, PCI, and OMT in patients with CAD and low LVEF. **Quality Rating:** Good - Recent, relevant review with	The literature searches included MEDLINE and EMBASE from inception to March 2021, without language restrictions. Additional relevant studies were identified through a manual search of secondary sources, including references of initially identified articles, reviews, and commentaries.	**Number of Patients:** 13 studies (N=18,855) *PCI: N=8,771* *CABG: N=9,241* *OMT: N=1,003* **Diagnosis:** CAD and LVEF ≤50% **Age:** Mean range: 50 to 71 years	**All-cause mortality (2):** <u>LVEF ≤50%</u> PCI vs. OMT (HR 0.90 [95% CI 0.71–1.15]); p=0.40 PCI with DES vs. OMT (HR 0.79 [95% CI 0.64–0.98]); p=0.03 <u>LVEF ≤40%</u> PCI vs. OMT (HR 0.91 [95% CI 0.69–1.20]); p=NS **CV mortality (2):** <u>LVEF ≤50%</u>

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
	comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.* **Funding Source:** NR	**Inclusion/Exclusion Criteria:** All adult, human RCTs and PSM studies comparing ≥2 treatments (PCI, CABG, or MT) in patients diagnosed with CAD and LVEF ≤50% were included if they reported mortality, MACCE, MI, stroke, or revascularization. Studies that did not use LVEF to define left ventricular dysfunction were excluded. **Included Studies:** Three RCTs (Yokoyama 1985, STICH, EXCEL); 10 PSM.	**Gender:** Range: 69% to 95% male **Intervention/Comparators:** PCI vs. MT CABG vs. MT PCI vs. CABG **Follow-up:** Range: 2.7 to 15 years	PCI vs. OMT (HR 0.65 [95% CI 0.33–1.28]); p=NS PCI with DES vs. OMT (HR 0.14 [95% CI 0.03–0.58]); p=0.009 LVEF ≤40% PCI vs. OMT (HR 0.69 [95% CI 0.31–1.54]); p=NS **MI (2):** LVEF ≤50% PCI vs. OMT (HR 1.23 [95% CI 0.65–2.31]); p=NS PCI with DES vs. OMT (HR 0.83 [95% CI 0.21–3.28]); p=NS LVEF ≤40% PCI vs. OMT (HR 1.54 [95% CI 0.96–2.45]); p=NS **MACCE (2):** LVEF ≤50% PCI vs. OMT (HR 1.15 [95% CI 0.89–1.49]); p=NS LVEF ≤40% PCI vs. OMT (HR 1.13 [95% CI 0.76–1.67]); p=NS **Revascularization (2):** LVEF ≤50% PCI vs. OMT (HR 2.17 [95% CI 0.81–5.80]); p=NS PCI with DES vs. OMT (HR 1.28 [95% CI 0.23–6.97]); p=NS LVEF ≤40% PCI vs. OMT (HR 2.16 [95% CI 0.80–5.80]); p=NS **Stroke (2):** LVEF ≤50% PCI vs. OMT (HR 1.49 [95% CI 0.96–2.30]); p=NS PCI with DES vs. OMT (HR 1.27 [95% CI 0.36–4.52]); p=NS LVEF ≤40%

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				PCI vs. OMT (HR 1.54 [95% CI 0.91–2.62]); p=NS
SIHD and Chronic Kidney Disease	**Reference:** Yong et al. 2021[21] **Country:** China **Purpose:** A systematic review and meta-analysis to compare PCI, MT, and CABG for the treatment of CAD in patients with CKD. **Quality Rating:** Fair*- Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; but uncertainty around the validity of reported conclusions because of a failure to identify which trials were included in the PCI vs OMT analysis.* **Funding Source:** Capital Health Development Research Project, National Natural Science Foundation of China, Beijing Lab for Cardiovascular Precision Medicine, Beijing Municipal Science and Technology Project, and 2018 Beijing Excellent Talent Fund.	The literature searches included PubMed, and Cochrane CENTRAL from inception to April 2020, without language restrictions. The included manuscripts' reference lists were manually searched as a supplement to the first search. **Inclusion/Exclusion Criteria:** All adult, human RCT and observational studies comparing ≥2 treatments (PCI, CABG, or MT) in patients diagnosed with both CAD and stage IV or V CKD (eGFR <30 ml/min/1.73 m^2 or dialysis) were included if they reported mortality, MI, or revascularization. Meta-analysis, review, study protocol, comments, abstract, case report, or letter were excluded. **Included Studies:** Two RCTs (Manske 1992, ISCHEMIA-CKD); 30 observational.	**Number of Patients:** 32 studies (N=84,598) *PCI: N= NR* *OMT: N= NR* *CABG: N= NR* **Diagnosis:** CAD and advanced CKD **Age:** Mean range: 41 to 77 years **Gender:** Range: 46% to 88% male **Intervention/Comparators:** PCI vs. MT CABG vs. MT PCI vs. CABG **Follow-up:** Range: in-hospital to 8 years	**All-cause mortality (10):** All CAD (AMI and non-AMI combined) *0-1 month:* PCI vs. MT (OR 0.60 [95% CI 0.43–0.82]); p<0.05; I^2=27% *1-12 months:* PCI vs. MT (OR 0.60 [95% CI 0.44–0.82]); p<0.05; I^2=20% *1-3 years:* PCI vs. MT (OR 0.82 [95% CI 0.62–1.09]); p=0.182; I^2=37% *>3 years:* PCI vs. MT (OR 0.64 [95% CI 0.48–0.85]); p<0.05; I^2=49% Non-AMI *1-12 months:* PCI vs. MT (OR 0.54 [95% CI 0.24–1.25]); p=0.151; I^2=0% *1-3 years:* PCI vs. MT (OR 0.63 [95% CI 0.30–1.31]); p=0.213; I^2=57% *>3 years:* PCI vs. MT (OR 0.46 [95% CI 0.30–0.72]); p<0.05; I^2=0% MVD *1-12 months:* PCI vs. MT (OR 0.55 [95% CI 0.21–1.44]); p=0.221 *1-3 years:* PCI vs. MT (OR 0.29 [95% CI 0.11–0.77]); p<0.05 *>3 years:* PCI vs. MT (OR 0.33 [95% CI 0.12–0.93]); p<0.05 **CV mortality (3):** All CAD (AMI and non-AMI combined) *1-12 months:* PCI vs. MT (OR 0.12 [95% CI 0.01–1.30]); p=0.081 *1-3 years:* PCI vs. MT (OR 0.38 [95% CI 0.05–3.19]); p=0.376; I^2=77% Non-AMI *1-12 months:* PCI vs. MT (OR 0.12 [95% CI 0.01–1.30]); p=0.081 *1-3 years:* PCI vs. MT (OR 0.38 [95% CI 0.05–3.19]); p=0.376; I^2=77% **MI (15):**

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				"There was no significant difference in the risk of MI between PCI and MT." no further details reported **MACE (3):** All CAD (AMI and non-AMI combined) *1-12 months:* PCI vs. MT (OR 0.01 [95% CI 0.01–0.78]); p<0.05 *1-3 years:* PCI vs. MT (OR 0.46 [95% CI 0.10–2.17]); p=0.327; I²=62% Non-AMI *1-12 months:* PCI vs. MT (OR 0.01 [95% CI 0.01–0.78]); p=<0.05 *1-3 years:* PCI vs. MT (OR 0.46 [95% CI 0.10–2.17]); p=0.327; I²=62%
Chronic Total Occlusion	**Reference:** Qian et al. 2022[28] **Country:** China **Purpose:** A systematic review and meta-analysis to compare the results of PCI and ODT on CTO lesions or significant coronary artery stenosis. **Quality Rating:** Good - Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.* **Funding Source:** The National Natural Science Foundation of China (No. 81700297), and the Undergraduate Training Program for Innovation and Entrepreneurship, Soochow University (No. 202110285053).	The literature searches included PubMed, Cochrane CENTRAL, Embase, and Web of Science from January 2010 to November 2021, without language restrictions. **Inclusion/Exclusion Criteria:** All adult, human studies comparing PCI with medication were included if they reported mortality, stroke, CVA, MI, revascularization or QoL. **Included Studies:** Three RCTs (EUROCTO, FAME II, COMET-CTO); one long-term; eight observational/PSM.	**Number of Patients:** 12 studies (N=8,549) *PCI: N=4,288* *ODT: N=4,261* **Diagnosis:** coronary CTO or severe coronary artery stenosis **Age:** NR **Gender:** NR **Intervention/Comparators:** PCI vs. ODT **Follow-up:** NR	**All-cause mortality (10):** PCI 6.1% vs. ODT 13.5% (RR 0.51 [95% CI 0.40–0.64]); p<0.00001; I²=49% **MI (9):** PCI 3.3% vs. ODT 5.6% (RR 0.63 [95% CI 0.45–0.90]); p=0.01; I²=41% **Revascularization (8):** PCI 15.6% vs. ODT 23.1% (RR 0.86 [95% CI 0.46–1.62]); p=0.65; I²=97% **Stroke (6):** PCI 1.9% vs. ODT 1.3% (RR 1.33 [95% CI 0.82–2.17]); p=0.24; I²=0% **QoL (2):** MD 10.44 [95% CI -1.84–22.73]); p=0.10; I²=81%
	Reference: van Veelan et al. 2021[23]	The literature searches included MEDLINE, EMBASE, the Cochrane Library from inception	**Number of Patients:** 5 studies (N=1,790) *PCI: N=964*	**All-cause mortality (3):**

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
	Country: The Netherlands **Purpose:** A systematic review and meta-analysis of randomized data, to compare CTO-PCI to OMT alone. **Quality Rating:** Good - Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.* **Funding Source:** NR	to June 2020, without language restrictions. **Inclusion/Exclusion Criteria:** Adult RCTs comparing CTO-PCI with no CTO-PCI or OMT were included. Substudies were included if they described mortality, MACE or ventricular function. Non-randomized studies, observational studies, and studies of non-CTO lesions or treatment with CABG were excluded. **Included Studies:** Five RCTs (DECISION-CTO, EXPLORE, EUROCTO, REVASC, IMPACTOR-CTO); one substudy; one long-term.	*OMT: N=826* **Diagnosis:** coronary CTO **Age:** Mean range: 57 to 65 years **Gender:** Range: 82% to 89% male **Intervention/Comparators:** CTO-PCI vs. no CTO-PCI or OMT **Follow-up:** weighted longest follow-up period of 40 ± 13 months	*1 year:* PCI 1.6% vs. OMT 1.0% (RR 1.70 [95% CI 0.50–5.80]); p=0.40; I^2=0% *4 years:* PCI 5.1% vs. OMT 4.5% (RR 1.14 [95% CI 0.38–3.40]); p=0.81; I^2=75% **CV mortality (3):** *1 year:* PCI 1.2% vs. OMT 0.5% (RR 1.77 [95% CI 0.19–16.06]); p=0.61; I^2=39% *4 years:* PCI 2.7% vs. OMT 2.3% (RR 1.66 [95% CI 0.31–8.79]); p=0.55; I^2=69% **MACE$_{reported}$ (3):** *Weighted 5 months:* PCI 4.8% vs. OMT 3.9% (RR 1.21 [95% CI 0.41–3.60]); p=0.73 *1 year:* PCI 5.9% vs. OMT 9.1% (RR 0.69 [95% CI 0.36–1.33]); p=0.27; I^2=43% *Weighted 4 years:* PCI 17.4% vs. OMT 19.7% (RR 0.85 [95% CI 0.60–1.22]); p=0.38; I^2=53% **MI (4):** *1 year:* PCI 2.6% vs. OMT 2.5% (RR 1.01 [95% CI 0.43–2.36]); p=0.98; I^2=0% *4 years:* PCI 3.0% vs. OMT 3.2% (RR 1.02 [95% CI 0.58–1.81]); p=0.94; I^2=0% **TL Revascularization (4):** *1 year:* PCI 3.1% vs. OMT 12.4% (RR 0.28 [95% CI 0.15–0.52]); p<0.0001; I^2=13% *4 years:* PCI 7.9% vs. OMT 13.2% (RR 0.55 [95% CI 0.28–1.09]); p=0.09; I^2=79% **LV function (2):**

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				LVEF: MD 2.07% (95% CI -1.12–5.25); p=0.20; I^2=45% *LVEF, Δbaseline*: MD 0.28% (95% CI -0.70–1.27); p=0.57 *LVEDV, Δbaseline*: MD 0.03 ml/m^2 (95% CI -2.93–2.99); p=0.98 **SWT in CTO segments (2):** *4-6 months:* MD 5.19% (95% CI -0.47–10.84); p=0.07; I^2=27% **Angina, freedom from (2):** *1 year:* PCI 20.8% vs. OMT 27.3% (RR 0.65 [95% CI 0.50–0.84]); p=0.0010; I^2=0%
	Reference: Khan et al. 2021[26] **Country:** USA **Purpose:** A systematic review and meta-analysis to compare the outcomes of PCI versus OMT for CTO lesions. **Quality Rating:** Good - Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.* **Funding Source:** None	The literature searches included MEDLINE, ClinicalTrials.gov, Google scholar and Cochrane CENTRAL from 2006 to 2019, with English language restrictions. Reference lists of key articles identified by the electronic search were manually reviewed to find other potentially eligible articles. **Inclusion/Exclusion Criteria:** All peer reviewed articles with ≥10 adult, human patients per arm, comparing CTO-PCI with OMT were included if they reported mortality, MI, MACE, revascularization, LVEF or stroke. Review articles and letters to the editor were excluded. **Included Studies:** Four RCTs (DECISION-CTO, EXPLORE, EUROCTO, REVASC); 12 observational studies (7 retrospective, 5 prospective).	**Number of Patients:** 16 studies (N=11,314) *PCI:* N=5,486 *OMT:* N=5,828 **Diagnosis:** coronary CTO **Age:** Mean range: 60 to 70 years **Gender:** Range: 71% to 90% male **Intervention/Comparators:** CTO-PCI vs. OMT **Follow-up:** Mean range: 12 to 60 months	**All-cause mortality (11):** *All studies:* PCI 7.4% vs. OMT 16.6% (OR 0.45 [95% CI 0.32–0.63]); p<0.00001; I^2=67% *Observationals:* PCI 7.8% vs. OMT 17.7% (OR 2.09 [95% CI 0.30–0.56]); p<0.00001; I^2=64% *RCTs:* PCI 4.2% vs. OMT 2.1% (OR 1.61 [95% CI 0.38–6.71]); p=0.52; I^2=25% **CV mortality (11):** *All studies:* PCI 5.2% vs. OMT 8.1% (OR 0.58 [95% CI 0.38–0.89]); p=0.01; I^2=72% *Observationals:* PCI 3.2% vs. OMT 7.1% (OR 0.46 [95% CI 0.31–0.67]); p<0.0001; I^2=53% *RCTs:* PCI 13.08% vs. OMT 13.11% (OR 1.22 [95% CI 0.59–2.54]); p=0.59; I^2=20% **MI (15):** *All studies:* PCI 2.8% vs. OMT 6.8% (OR 0.62 [95% CI 0.43–0.89]); p=0.009; I^2=39%

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				Observationals: PCI 3.0% vs. OMT 7.9% (OR 0.53 [95% CI 0.36–0.77]); p=0.0008; I^2=38% *RCTs:* PCI 2.1% vs. OMT 1.6% (OR 1.25 [95% CI 0.61–2.58]); p=0.54; I^2=0% **Repeat PCI (14):** *All studies:* PCI 15.7% vs. OMT 13.1% (OR 1.24 [95% CI 0.87–1.75]); p=0.23; I^2=87% *Observationals:* PCI 16.3% vs. OMT 13.0% (OR 1.44 [95% CI 0.98–2.12]); p=0.07; I^2=88% *RCTs:* PCI 13.1% vs. OMT 13.6% (OR 0.78 [95% CI 0.32–1.91]); p=0.59; I^2=88% **Stroke (8):** *All studies:* PCI 0.9% vs. OMT 1.3% (OR 0.61 [95% CI 0.32–1.17]); p=0.14; I^2=0% *Observationals:* PCI 0.7% vs. OMT 1.4% (OR 0.56 [95% CI 0.28–1.12]); p=0.10; I^2=0% *RCTs:* PCI 1.2% vs. OMT 1.0% (OR 0.94 [95% CI 0.08–11.17]); p=0.96; I^2=45% **MACE (16):** *All studies:* PCI 17.4% vs. OMT 20.8% (OR 0.82 [95% CI 0.62–1.08]); p=0.16; I^2=84% *Observationals:* PCI 17.7% vs. OMT 21.2% (OR 0.84 [95% CI 0.61–1.17]); p=0.30; I^2=86% *RCTs:* PCI 16.3% vs. OMT 18.7% (OR 0.74 [95% CI 0.38–1.45]); p=0.38; I^2=75%
	Reference: Li et al. 2019[27] **Country:** China, Spain, UK, USA	The literature searches included PubMed and EMBASE, the Cochrane Library from inception	**Number of Patients:** 17 studies (N=11,493) *PCI: N= NR* *OMT: N= NR*	**All-cause mortality (14):** *All studies:* OMT 19.3% vs. PCI 8.8% (RR 1.99 [95% CI 1.38–2.86]); p=0.0002; I^2=89%

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
	Purpose: A systematic review and meta-analysis of RCT and cohort studies involving head-to-head comparisons between PCI and OMT in CTO patients. **Quality Rating:** Good - Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.* **Funding Source:** NR	to March 2019, without language restrictions. **Inclusion/Exclusion Criteria:** Adult, human studies comparing CTO-PCI with no CTO-PCI or OMT were included. Substudies were included if they described mortality, CVA, MI, revascularization, MACE, or MACCE. Both fully published studies and abstracts were included. **Included Studies:** Three RCTs (DECISION-CTO, EUROCTO, REVASC); 14 observational studies.	**Diagnosis:** coronary CTO **Age:** Mean range: 63 to 69 years **Gender:** Range: 71% to 90% male **Intervention/Comparators:** CTO-PCI vs. OMT **Follow-up:** Mean range: 12 to 60 months	*Observationals:* OMT 21.5% vs. PCI 10.3% (RR 2.09 [95% CI 1.40–3.10]); p=0.0003; I^2=91% *RCTs:* OMT 3.6% vs. PCI 2.3% (RR 1.41 [95% CI 0.77–2.61]); p=0.27; I^2=0% **CV mortality (11):** *All studies:* OMT 9.8% vs. PCI 3.6% (RR 2.36 [95% CI 1.97–2.84]); p<0.00001; I^2=23% *Observationals:* OMT 10.7% vs. PCI 4.0% (RR 2.42 [95% CI 2.00–2.91]); p<0.00001; I^2=29% *RCTs:* OMT 2.6% vs. PCI 1.5% (RR 2.36 [95% CI 1.97–2.84]); p=0.27; I^2=0% **MI (10):** *All studies:* OMT 7.3% vs. PCI 3.4% (RR 1.65 [95% CI 0.97–2.78]); p=0.06; I^2=74% *Observationals:* OMT 7.4% vs. PCI 2.4% (RR 2.04 [95% CI 1.31–3.20]); p=0.002; I^2=52% *RCTs:* OMT 6.4% vs. PCI 7.7% (RR 0.73 [95% CI 0.44–1.19]); p=0.21; I^2=2% **TL revascularization (9):** *All studies:* OMT 13.3% vs. PCI 15.4% (RR 0.93 [95% CI 0.67–1.29]); p=0.67; I^2=83% *Observationals:* OMT 13.8% vs. PCI 16.7% (RR 0.85 [95% CI 0.59–1.21]); p=0.36; I^2=84% *RCTs:* OMT 11.2% vs. PCI 9.5% (RR 1.87 [95% CI 0.41–8.58]); p=0.42; I^2=83% **CVA/Stroke (3):**

Population	Study Details	Search Strategy/Evidence Base	Patients/Interventions	Outcomes/Results (No. of Studies)
				All studies (observationals): OMT 1.1% vs. PCI 0.6% (RR 2.10 [95% CI 0.84–5.25]); p=0.11; I^2=0% **MACE (10):** *All studies:* OMT 26.1% vs. PCI 19.7% (RR 1.25 [95% CI 1.03–1.51]); p=0.03; I^2=72% *Observationals:* OMT 28.2% vs. PCI 21.1% (RR 1.25 [95% CI 1.01–1.56]); p=0.04; I^2=76% *RCTs:* OMT 19.6% vs. PCI 16.3% (RR 1.38 [95% CI 0.73–2.60]); p=0.33; I^2=64% **MACCE (2):** *All studies (observationals):* OMT 11.4% vs. PCI 5.1% (RR 2.47 [95% CI 1.52–4.02]); p=0.0003; I^2=56%

*Assessed using United States Preventive Services Task Force criteria (Table 2).[21]

Abbreviations: CABG=coronary artery bypass grafting; CAD=coronary artery disease; CCS=chronic coronary syndrome; CI=confidence interval; CKD=chronic kidney disease; CTO=chronic total occlusion; CV=cardiovascular; CVA=cerebral vascular accident; HR=hazard ratio; ITT=intention to treat; LV=left ventricular; LVEDV=left ventricular end diastolic volume; LVEF=left ventricular ejection fraction; MACCE=major adverse cardiac and cerebrovascular events; MACE=major adverse cardiac events; MD=mean difference; MI=myocardial infarction; MT=medical therapy; NR=not reported; NS=not significant; ODT=optimal drug therapy; OMT=optimal medical therapy; OR=odds ratio; PCI=percutaneous coronary intervention; PSM=propensity score matched; QoL=quality of life; RCT=randomized controlled trial; RR=relative risk; SIHD=stable ischemic heart disease; SWT=segmental wall thickening; TL=target lesion.

Table B-2. Randomized controlled trial evidence table

Study Details	Patients	Interventions	Outcomes, PCI Vs. OMT
Reference: Perera et al. 2022 (REVIVED)[29] **Study Design:** Multicenter, randomized, open-label trial **Country:** U.K. **Purpose:** To investigate if revascularization with PCI in addition to OMT for heart failure, as compared with OMT alone, would improve event-free survival in patients with severe ischemic left ventricular systolic dysfunction and demonstrable myocardial viability. **Quality Rating:** Good - Comparable groups are assembled initially and maintained throughout the study (follow-up greater than or equal to 80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used.* **Funding Source:** The National Institute for Health and Care Research Health Technology Assessment Program.	**Number of Patients:** 700 PCI: 347 OMT: 353 **Diagnosis:** CAD with LVEF ≤35% and demonstrable myocardial viability **Age, years (SD)** PCI: 70.0 (9.0) OMT: 68.8 (9.1) **Gender, male** PCI: 87% OMT: 88% **Baseline Characteristics:** LVEF, % (SD) PCI: 27.0 (6.6) OMT: 27.0 (6.9) Left main CAD, N (%) PCI: 50 (14) OMT: 45 (13) Three-vessel CAD, N (%) PCI: 133 (38) OMT: 148 (42) Two-vessel CAD, N (%) PCI: 178 (51) OMT: 166 (47)	**Intervention:** PCI + OMT **Comparator:** OMT alone **Follow-up:** Median 41 months (IQ range, 28 to 60 months) **Inclusion Criteria:** Adult patients with LVEF ≤35%, extensive CAD (BCIS jeopardy score ≥6), demonstrable viability in ≥4 dysfunctional myocardial segments amenable to revascularization with PCI. **Exclusion Criteria:** MI within the 4 weeks before randomization; acute decompensated HF or sustained ventricular arrhythmias within 72 hours before randomization. **Primary Outcome:** Composite of all-cause mortality or hospitalization for HF.	**All-cause mortality or hospitalization for HF, N (%):** 129 (37.2) vs. 134 (38.0); HR 0.99 (95% CI 0.78–1.27); p=0.96 **All-cause mortality, N (%):** 110 (31.7) vs. 115 (32.6); HR 0.98 (95% CI 0.75–1.27) **Hospitalization for HF, N (%):** 51 (14.7) vs. 54 (15.3); HR 0.97 (95% CI 0.66–1.43) **CV mortality, N (%):** 76 (21.9) vs. 88 (24.9); HR 0.88 (95% CI 0.65–1.20) **MI, N (%):** Total: 37 (10.7) vs. 38 (10.8); HR 1.01 (95% CI 0.64–1.60) Periprocedural: 14 (37.8) vs. 0 (0) Spontaneous: 18 (48.7) vs. 33 (86.8) **Unplanned Revascularization, N (%):** 10 (2.9) vs. 37 (10.5); HR 0.27 (95% CI 0.13–0.53) **LVEF, %Δ from baseline:** 6 months: 1.8 vs. 3.4 12 months: 2.0 vs. 1.1 **KCCQ overall summary score:** 6 months: MD 6.5 (95% CI 3.5–9.5) 12 months: MD 4.5 (95% CI 1.4–7.7) 24 months: MD 2.6 (95% CI -0.7–5.8) **Serious Adverse Event, N (%):** 102 (29.4) vs. 104 (29.5)

*Assessed using United States Preventive Services Task Force criteria (Table 2).[21]

Abbreviations: BCIS=British Cardiovascular Intervention Society; CAD=coronary artery disease; CI=confidence interval; HF=heart failure; HR=hazard ratio; IQ=interquartile; KCCQ=Kansas City Cardiomyopathy Questionnaire; LVEF=left ventricular ejection fraction; MD=mean difference; MI=myocardial infarction; OMT=optimal medical therapy; PCI=percutaneous coronary intervention; SD=standard deviation.

Note: Appendix reference numbers correspond to those in the main section of this report.

Table B-3. Overlap of included studies in systematic reviews

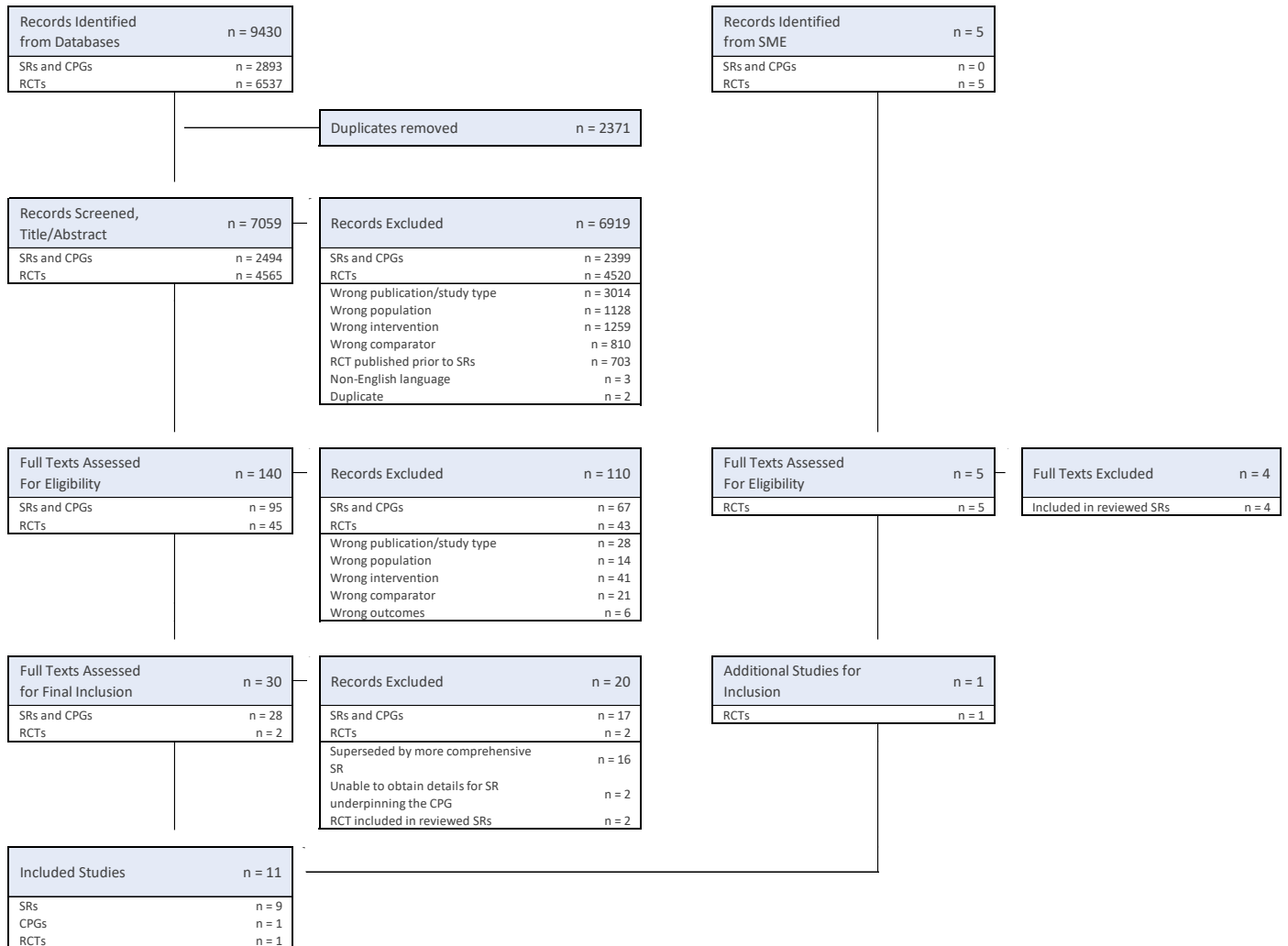| Included Studies	2021 ACC/AHA Guideline[15]	General SIHD Population Bytyçi[20]	General SIHD Population Lerman[24]	General SIHD Population Radaideh[25]	SIHD + Low LVEF Yokoyama[22]	SIHD + CKD Yong[21]	CTO Qian[28]	CTO van Veelan[23]	CTO Khan[26]	CTO Li[27]
Passamani, 1985*[31]	x				x					
Manske, 1992*[32]						x				
Hartigan, 1998*[33]		x								
Hambrecht, 2004*[34]		x		x						
TIME*[35]	x	x								
COURAGE[11]	x	x	X	x						
MASS II[36,37]	x	x	X	x						
JSAP[38]	x	x		x						
BARI 2D[39]	x	x	X	x						
STICH[40]	x				x					
FAME II[41,42]	x	x	X	x				x		
Won, 2016[43]	x	x								
ORBITA[44]	x	x								
Hennigan, 2020[45]	x	x								
EXCEL[46,47]	x				x					
ISCHEMIA[30]	x	x	X	x						
ISCHEMIA CKD[48]	x	x	X			x				
ISCHEMIA QoL[49]		x								
DECISION-CTO[50]	x							x	x	x
EXPLORE[51]	x							x	x	
EURO-CTO[52]	x							x	x	x
REVASC[53]	x							x	x	x
COMET-CTO[54]	x						x			
IMPACTOR-CTO[55]	x						x			
Observational Studies	x				x	x	x		x	x

*Clinically irrelevant, published prior to the landmark COURAGE trial (2007).

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; CKD=chronic kidney disease; CTO=chronic total obstruction; LVEF=left ventricular ejection fraction; SIHD=stable ischemic heart disease

Note: Appendix reference numbers correspond to those in the main section of this report.

Appendix C. PRISMA Flow Diagram

Figure C-1. PRISMA flow diagram

Records Identified from Databases	n = 9430
SRs and CPGs	n = 2893
RCTs	n = 6537

Records Identified from SME	n = 5
SRs and CPGs	n = 0
RCTs	n = 5

Duplicates removed	n = 2371

Records Screened, Title/Abstract	n = 7059
SRs and CPGs	n = 2494
RCTs	n = 4565

Records Excluded	n = 6919
SRs and CPGs	n = 2399
RCTs	n = 4520
Wrong publication/study type	n = 3014
Wrong population	n = 1128
Wrong intervention	n = 1259
Wrong comparator	n = 810
RCT published prior to SRs	n = 703
Non-English language	n = 3
Duplicate	n = 2

Full Texts Assessed For Eligibility	n = 140
SRs and CPGs	n = 95
RCTs	n = 45

Records Excluded	n = 110
SRs and CPGs	n = 67
RCTs	n = 43
Wrong publication/study type	n = 28
Wrong population	n = 14
Wrong intervention	n = 41
Wrong comparator	n = 21
Wrong outcomes	n = 6

Full Texts Assessed For Eligibility	n = 5
RCTs	n = 5

Full Texts Excluded	n = 4
Included in reviewed SRs	n = 4

Full Texts Assessed for Final Inclusion	n = 30
SRs and CPGs	n = 28
RCTs	n = 2

Records Excluded	n = 20
SRs and CPGs	n = 17
RCTs	n = 2
Superseded by more comprehensive SR	n = 16
Unable to obtain details for SR underpinning the CPG	n = 2
RCT included in reviewed SRs	n = 2

Additional Studies for Inclusion	n = 1
RCTs	n = 1

Included Studies	n = 11
SRs	n = 9
CPGs	n = 1
RCTs	n = 1

Abbreviations: CPG=clinical practice guideline; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT=randomized controlled trial; SME=subject matter expert; SR=systematic review