

THE ANALYSIS STUDY OF EVALUATING THE EFFICACY AND SAFETY OF PERCUTANEUS CORONARY INTERVENTION (PCI) VERSUS EDTA (CHELATION THERAPY) FOR CORONARY ARTERY DISEASE : A COMPREHENSIVE SYSTEMATIC REVIEW

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To Cite This Article: Pangestu, H. P., Swartawan, I. N. I. P., Permatasari, D. I., Trisaputra, T. S., Konoras, H., Sareta, A. A. S. K., & Putri, S. N. (2024). THE ANALYSIS STUDY OF EVALUATING THE EFFICACY AND SAFETY OF PERCUTANEUS CORONARY INTERVENTION (PCI) VERSUS EDTA (CHELATION THERAPY) FOR CORONARY ARTERY DISEASE : A COMPREHENSIVE SYSTEMATIC REVIEW . Journal of Advanced Research in Medical and Health Science (ISSN 2208-2425), 10(9), 16-25. <https://doi.org/10.61841/wtz83z86>

ABSTRACT

Background: Percutaneous coronary intervention (PCI) is a pivotal treatment for patients with stable coronary artery disease (CAD), yet its overall effectiveness remains limited. Despite technological advancements, only about 5% of patients receive PCI, comparable to the 5% who are treated with pharmacological therapies. The ongoing debate between PCI and optimal drug therapy (ODT) continues, with ethylenediaminetetraacetic acid (EDTA) emerging as a notable treatment alternative. This systematic review seeks to compare the outcomes of these interventions and offer guidance for clinical decision-making.

Methods: Adhering to PRISMA 2020 guidelines, this review focused on full-text articles published in English from 2012 to 2024. To ensure the inclusion of high-quality studies, editorial pieces and review articles were excluded unless they included a DOI. A comprehensive literature search was performed across several reputable databases, including ScienceDirect, PubMed, and SagePub, to collect relevant research thoroughly.

Result: The review analyzed over 800 publications from these databases. After an initial screening process, eight studies were selected for detailed examination. These selected studies underwent a rigorous review to ensure comprehensive and precise evaluation.

Conclusion: While both EDTA and PCI represent advanced treatment options for CAD, their effectiveness is contested due to their complexity and high costs. The systematic review indicates that PCI may offer greater benefits for patients with chronic total occlusions (CTO), showing lower mortality and myocardial infarction (MI) rates. Future research should prioritize large-scale clinical trials to further elucidate the comparative efficacy of PCI and EDTA.

Keyword: Coronary artery disease, EDTA, PCI, effectiveness

INTRODUCTION

In patients with stable coronary artery disease (CAD), the presence of complicated chronic total occlusion (CTO) or significant coronary artery stenosis represents a major risk factor for mortality.^{1,2} Notably, approximately 20% of individuals with stable CAD exhibit CTO or severe stenosis.³ Despite advancements in the technology available for coronary CTO interventions, percutaneous coronary intervention (PCI) is administered to only about 5% of these patients, while the majority are managed with pharmacological treatments.⁴ PCI involves enhancing myocardial blood flow by restoring patency to stenosed or occluded coronary arteries through catheter-based techniques. Observational studies have highlighted that PCI can significantly improve patient survival, decrease the necessity for coronary artery bypass grafting (CABG), and lower the incidence of subsequent myocardial infarctions (MI).^{5,6}

Despite these findings, clinical guidelines suggest PCI for CTO patients as a means to enhance survival and quality of life⁷⁻⁹, yet the rate of PCI utilization remains disappointingly low. The debate over whether PCI or optimal drug therapy (ODT) should be the preferred approach for treating CTO patients is ongoing. Several studies have questioned the overall benefits of PCI compared to drug therapy, adding to the controversy surrounding its efficacy.¹⁰⁻¹² This ongoing debate underscores the need for a thorough evaluation of the comparative effectiveness of PCI versus ODT in managing CTO lesions and significant coronary stenosis.

Ethylenediamine-tetraacetic acid (EDTA) is a commonly used chelation agent used to treat excesses of minerals like lead and mercury in CAD patients. Chelation therapy advocates suggest that EDTA extracts calcium from coronary artery lesions, improving coronary artery circulation.¹³ However, evidence regarding the effectiveness of CT in CAD patients is equivocal, with few clinical trials and warnings from the Canadian Cardiovascular Society and the American Heart Association.¹⁴ A considerable number of CAD patients receive chelation therapy annually, but there is no empirical evidence to support its use. Traditional evidence-based therapies are widely available, but patients seek alternatives.¹⁵

To address this issue, the purpose of this meta-analysis is to systematically compare the outcomes associated with PCI and optimal drug therapy (ODT) such as EDTA for CAD. By aggregating and analyzing data from various studies, this systematic review aims to provide a clearer understanding of the relative effectiveness of these treatment options, thereby offering valuable insights for clinical decision-making and potentially guiding future treatment protocols.

METHODS

PROTOCOL

The study adhered meticulously to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, demonstrating a strong commitment to methodological excellence. By following PRISMA 2020 standards, the review process was enhanced in terms of transparency, reproducibility, and rigor. This adherence involved employing detailed strategies for literature searching, data extraction, and synthesis of findings, all meticulously designed to minimize biases and ensure the reliability of the conclusions.

CRITERIA FOR ELIGIBILITY

This study offers a comprehensive analysis of research conducted over the past decade regarding the efficacy and safety of percutaneous coronary intervention (PCI) versus ethylenediaminetetraacetic acid (EDTA) in the treatment of coronary artery disease. By systematically reviewing and integrating data from diverse studies, the research seeks to identify trends and refine patient care strategies for this complex condition.

The main aim of this thesis is to highlight significant themes from a wide array of academic literature, thereby deepening the understanding of PCI and EDTA's effectiveness and safety. To ensure the analysis's rigor and precision, strict inclusion and exclusion criteria were enforced. Only peer-reviewed studies published in English from 2012 to 2024 with a DOI for authenticity were considered. Non-research documents such as reviews, editorials, and duplicate articles were excluded to preserve the focus and integrity of the dataset.

This meticulous approach guarantees that the data analyzed is both pertinent and dependable, forming a solid basis for deriving insightful conclusions and advancing clinical practice.

SEARCH STRATEGY

We used "percutaneous coronary intervention OR PCI OR EDTA OR coronary artery disease." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Table 1. Search Strategy

<i>Database</i>	<i>Search Strategy</i>	<i>Hits</i>
Pubmed	<i>("percutaneous coronary intervention" OR "PCI" AND "EDTA" AND "coronary artery disease")</i>	2
Science Direct	<i>("percutaneous coronary intervention" OR "PCI" AND "EDTA" AND "coronary artery disease")</i>	807
Sagepub	<i>("percutaneous coronary intervention" AND "EDTA" AND "coronary artery disease")</i>	123

DATA RETRIEVAL

The authors conducted a thorough preliminary evaluation of each article by examining its abstract and title to determine its relevance before proceeding to an in-depth analysis. Only studies that met the study’s objectives and adhered to the predefined inclusion criteria were considered for further review. This method facilitated the identification of consistent and clear patterns across the research.

Full-text reviews were confined to articles published in English to maintain uniformity in language. A stringent screening process was applied to ensure that only studies directly relevant to the research focus and compliant with all inclusion criteria were included. Articles that did not meet these criteria were systematically excluded from the detailed analysis and were therefore not part of the final evaluation.

The evaluation process involved a comprehensive review of various elements, including study factors, titles, authors, publication dates, research locations, and methodologies. This meticulous approach ensured that the data incorporated into the analysis was of the highest relevance and quality, thereby strengthening the validity and reliability of the study’s findings.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors performed a thorough review of each article's abstract and title to determine which studies merited further investigation. Following this preliminary screening, documents identified as relevant underwent a detailed examination. The results of this evaluation informed the selection of papers for in-depth review, ensuring that only those with the highest relevance were advanced to comprehensive analysis. This stringent approach refined the selection process, facilitating a more detailed and nuanced assessment of existing research and its context.

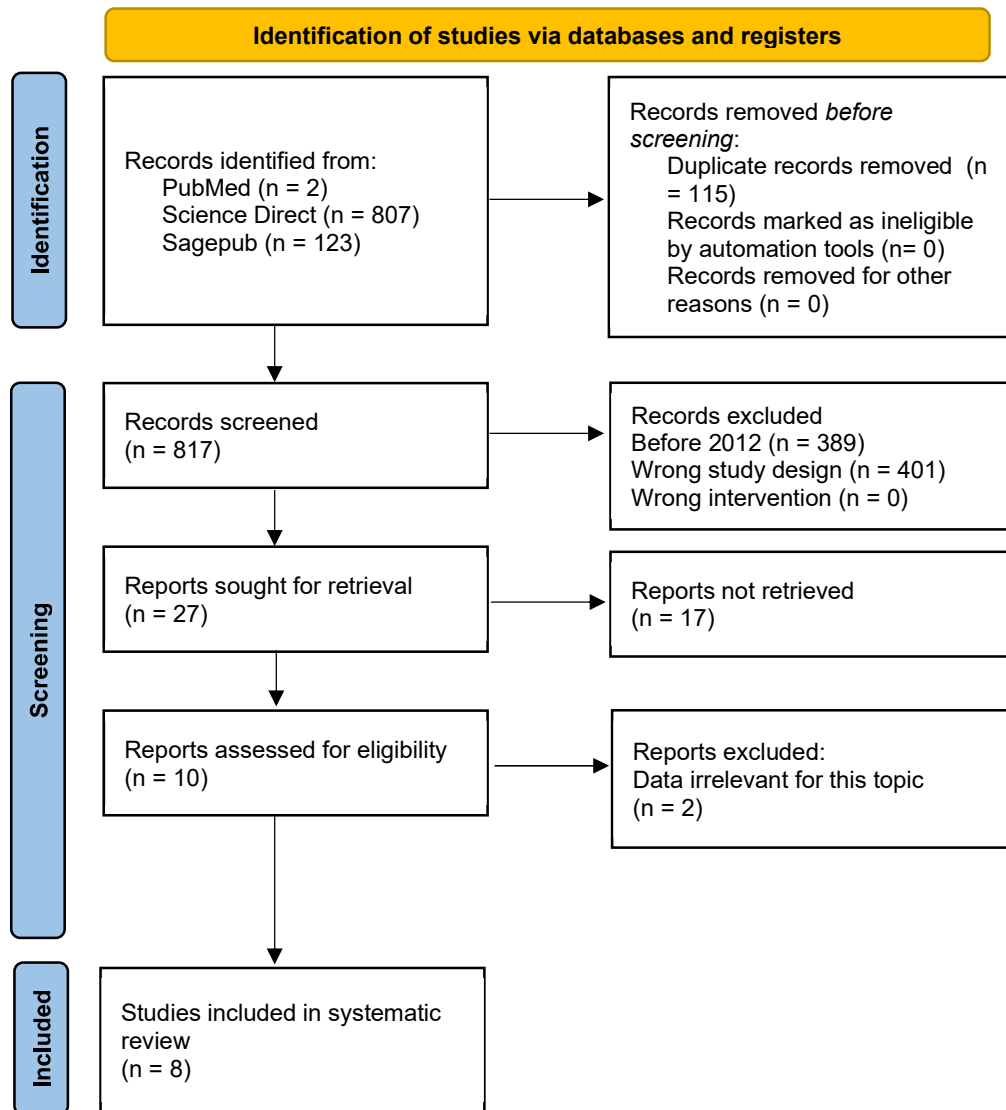


Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(King-Shier et al., 2012)	(Lamas et al., 2013)	(Escobar et al., 2014)	(Sultan et al., 2017)	(Ma et al., 2018)	(Juricic et al., 2021)	(Qian et al., 2022)	(Ravalli et al., 2022)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	No	Yes	Yes	No	No	Yes	No	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	Yes	Yes	Yes	No	No	Yes	No	No
4. Bias related to								

administration of intervention/exposure

Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?

No. Yes. Yes. No. No. Yes. No. No.

5. Bias related to assessment, detection, and measurement of the outcome

Were there multiple measurements of the outcome, both pre and post the intervention/exposure?

No No No No No No No No

Were the outcomes of participants included in any comparisons measured in the same way?

No Yes Yes No Yes Yes Yes Yes

Were outcomes measured in a reliable way?

Yes Yes Yes No Yes Yes Yes Yes

6. Bias related to participant retention

Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?

No Yes Yes No Yes Yes Yes Yes

7. Statistical conclusion validity

Was appropriate statistical analysis used?

Yes Yes Yes No Yes Yes Yes Yes

RESULT

We commenced our investigation by systematically collecting a substantial range of articles from esteemed databases including ScienceDirect, PubMed, and Sage Publications. Following a rigorous three-stage screening process, we identified eight papers that were highly relevant to our systematic review. We then selected specific topics for detailed analysis and conducted a comprehensive evaluation of each report. To streamline our study, we have provided a concise summary of the evaluated findings in Table 3.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
King-Shier et al. ¹³ (2012)	Canada	Cross Sectional	167 participants	Chelation therapy is a treatment that aims to improve heart health by reducing the risk of heart disease. Factors such as previous experience, openness to alternative treatments, satisfaction with traditional care, physician opinion, costs, perceived

				access to a provider, current health state, and desire to do everything for heart health influence the decision to use chelation therapy.
Lamas et al.¹⁶ (2013)	USA	RCT	1708 participants	The study found that EDTA chelation had a similar effect on the components of the primary endpoint other than death, such as myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. The effect was similar to its overall effect, with no effect on total mortality. The study's conclusions were not altered by patient dropout or varying treatment compliance.
Escolar et al.¹⁷ (2014)	USA	RCT	633 participants	EDTA chelation significantly reduced all-cause mortality and secondary end points, but after Bonferroni adjustment for multiple subgroups, the results were no longer significant. The number needed to treat to reduce 1 primary end point over 5 years was 6.5, and there was no reduction in events in non-diabetes mellitus, resulting in a treatment by diabetes mellitus interaction.
Sultan et al.¹⁸ (2017)	USA	Review	-	EDTA, or disodium edetate, is widely used for chelation therapy to prevent cardiovascular disease, but its efficacy remains unclear. Results from the National Institute of Health-sponsored Trial to Assess Chelation Therapy (TACT) in patients after myocardial infarction have sparked renewed interest in its role in treating coronary artery disease. However, the evidence is insufficient to recommend routine use, especially in post-MI diabetic patients.
Ma et al.¹⁹ (2018)	China	Meta Analysis	5 studies	A meta-analysis of five studies found that PCI significantly improved all-cause death, cardiac death, and major adverse cardiac events compared to OMT. However, there were no differences in myocardial infarction (MI) and stroke. The results of the propensity-

				matched subgroup were consistent with the main analysis. In the IRA subgroup, PCI reduced mortality risks but no difference was observed in MI.
Juricic et al.²⁰ (2021)	Serbia	RCT	100 participants	A study randomized 100 patients with CTO into PCI CTO or OMT groups. During the mean follow-up, PCI patients reported less physical activity limitations, less frequent angina episodes, better QoL, greater treatment satisfaction, and borderline differences in angina stability compared to OMT patients. There were no significant differences in SAQ scores in the PCI group.
Qian et al.²¹ (2022)	China	Meta Analysis	12 studies	A study comparing PCI and ODT patients found a significant difference in the probability of myocardial infarction and patient mortality. However, there was no significant difference in stroke, revascularization, or patient quality of life. Performance bias and detection bias were unclear in the included studies, highlighting the need for caution in PCI and ODT procedures.
Ravalli et al.²² (2022)	USA	Systematic Review	24 studies	EDTA treatment has shown improvement in patients with preexistent cardiovascular disease (CVD), with the largest improvements observed in studies with high diabetes and severe occlusive arterial disease prevalence. A meta-analysis of four studies showed an ankle-brachial index improvement of 0.08 from baseline, indicating a significant improvement in treatment outcomes.

DISCUSSION

The incidence of stable coronary heart disease (CHD) varies between genders, with reported rates of 2–11% in men and 3–9% in women, with a notable correlation to advancing age.²³ Advances in percutaneous coronary intervention (PCI) technology and equipment have markedly improved patient outcomes, including symptom relief, quality of life, and overall prognosis.²¹ In parallel, the progress in drug therapies, including the development and clinical application of new medications, has also significantly advanced the management of stable angina pectoris.²⁴⁻²⁶ However, despite the minimally invasive nature of PCI, it is not without risks. Potential complications such as stent shedding, stent thrombosis, and contrast nephropathy, along with the necessity for ongoing medication to mitigate these risks, make PCI more complex and costly compared to drug therapy alone. Consequently, the debate persists regarding whether PCI offers superior

efficacy compared to pharmacological treatments in managing stable coronary heart disease, particularly for patients with chronic total occlusions (CTO).

The definition of stable coronary artery disease (CAD) remains inconsistent across studies. The trials included in this meta-analysis utilized varying angiographic criteria to define significant coronary artery stenosis, and few provided detailed descriptions of clinical symptoms associated with angina. This variability may impact the generalizability of the findings across different patient populations included in other studies. Furthermore, advancements in medical therapy, including high-dose statins and antiplatelet agents, have become standard practice, which could account for the observed lack of significant difference in all-cause mortality between PCI and optimal drug therapy (ODT) treatments such as EDTA in recent trials.^{27,28} This observation highlights the evolving effectiveness of contemporary medical therapies for stable CAD patients, which may influence the perceived advantages of PCI over drug therapy.

Our systematic review, which incorporated data from 8 studies, suggests that PCI may offer greater benefits for patients with CTO compared to EDTA, evidenced by lower mortality and myocardial infarction (MI) rates among those who underwent PCI. These findings are aligned with some previously reported conclusions.^{19,29} Nonetheless, the study is not without limitations. The included studies varied in terms of stent types, medication regimens, and follow-up durations, which introduces potential bias and reduces the robustness of the results. Additionally, some older trials may not accurately reflect the efficacy of current treatments, and variations in disease severity among patients further complicate the analysis. To address these limitations and provide more definitive conclusions, future research should focus on large-scale, multi-center clinical trials that can more accurately assess the comparative efficacy of PCI and EDTA in coronary artery disease management.

CONCLUSION

Coronary artery disease is a prevalent issue, with rates varying between genders. Advances in PCI technology have improved patient outcomes, including symptom relief and quality of life. However, PCI is more complex and costly than drug therapy, and its effectiveness is debated. The definition of stable coronary artery disease (CAD) remains inconsistent across studies, and advancements in medical therapy, such as high-dose statins and antiplatelet agents, have become standard practice. A systematic review suggests that PCI may offer greater benefits for patients with CTO compared to EDTA, with lower mortality and MI rates among those who underwent PCI. Future research should focus on large-scale, multi-center clinical trials to assess the comparative efficacy of PCI and EDTA in coronary artery disease management.

REFERENCES

- [1] Claessen, B. E., Dangas, G. D., Weisz, G., Witzenbichler, B., Guagliumi, G., Möckel, M., Brener, S. J., Xu, K., Henriques, J. P., Mehran, R., & Stone, G. W. (2012). Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *European heart journal*, 33(6), 768–775. <https://doi.org/10.1093/eurheartj/ehr471>
- [2] Hoebers, L. P., Vis, M. M., Claessen, B. E., van der Schaaf, R. J., Kikkert, W. J., Baan, J., Jr, de Winter, R. J., Piek, J. J., Tijssen, J. G., Dangas, G. D., & Henriques, J. P. (2013). The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. *European journal of heart failure*, 15(4), 425–432. <https://doi.org/10.1093/eurjhf/hfs182>
- [3] Azzalini, L., Jolicoeur, E. M., Pighi, M., Millán, X., Picard, F., Tadros, V. X., Fortier, A., L'Allier, P. L., & Ly, H. Q. (2016). Epidemiology, Management Strategies, and Outcomes of Patients With Chronic Total Coronary Occlusion. *The American journal of cardiology*, 118(8), 1128–1135. <https://doi.org/10.1016/j.amjcard.2016.07.023>
- [4] Brilakis, E. S., Banerjee, S., Karpaliotis, D., Lombardi, W. L., Tsai, T. T., Shunk, K. A., Kennedy, K. F., Spertus, J. A., Holmes, D. R., Jr, & Grantham, J. A. (2015). Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC. Cardiovascular interventions*, 8(2), 245–253. <https://doi.org/10.1016/j.jcin.2014.08.014>
- [5] Christakopoulos, G. E., Christopoulos, G., Carlino, M., Jeroudi, O. M., Roesle, M., Rangan, B. V., Abdullah, S., Grodin, J., Kumbhani, D. J., Vo, M., Luna, M., Alaswad, K., Karpaliotis, D., Rinfret, S., Garcia, S., Banerjee, S., & Brilakis, E. S. (2015). Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *The American journal of cardiology*, 115(10), 1367–1375. <https://doi.org/10.1016/j.amjcard.2015.02.038>
- [6] Hoebers, L. P., Claessen, B. E., Elias, J., Dangas, G. D., Mehran, R., & Henriques, J. P. (2015). Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. *International journal of cardiology*, 187, 90–96. <https://doi.org/10.1016/j.ijcard.2015.03.164>
- [7] Levine, G. N., Bates, E. R., Blankenship, J. C., Bailey, S. R., Bittl, J. A., Cercek, B., Chambers, C. E., Ellis, S. G., Guyton, R. A., Hollenberg, S. M., Khot, U. N., Lange, R. A., Mauri, L., Mehran, R., Moussa, I. D., Mukherjee, D., Nallamothu, B. K., & Ting, H. H. (2011). 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary

- Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*, 124(23), e574–e651. <https://doi.org/10.1161/CIR.0b013e31823ba622>
- [8] Kearney, K., Hira, R. S., Riley, R. F., Kalyanasundaram, A., & Lombardi, W. L. (2017). Update on the Management of Chronic Total Occlusions in Coronary Artery Disease. *Current atherosclerosis reports*, 19(4), 19. <https://doi.org/10.1007/s11883-017-0655-0>
- [9] Neumann, F. J., Sousa-Uva, M., Ahlsson, A., Alfonso, F., Banning, A. P., Benedetto, U., Byrne, R. A., Collet, J. P., Falk, V., Head, S. J., Juni, P., Kastrati, A., Koller, A., Kristensen, S. D., Niebauer, J., Richter, D. J., Seferovic, P. M., Sibbing, D., Stefanini, G. G., Windecker, S., ... ESC Scientific Document Group (2019). 2018 ESC/EACTS Guidelines on myocardial revascularization. *European heart journal*, 40(2), 87–165. <https://doi.org/10.1093/eurheartj/ehy394>
- [10] Choi, S. Y., Choi, B. G., Rha, S. W., Baek, M. J., Ryu, Y. G., Park, Y., Byun, J. K., Shim, M., Li, H., Mashaly, A., Jang, W. Y., Kim, W., Choi, J. Y., Park, E. J., Na, J. O., Choi, C. U., Lim, H. E., Kim, E. J., Park, C. G., Seo, H. S., ... Oh, D. J. (2017). Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Chronic Total Coronary Occlusion With Well-Developed Collaterals. *Journal of the American Heart Association*, 6(9), e006357. <https://doi.org/10.1161/JAHA.117.006357>
- [11] Werner, G. S., Martin-Yuste, V., Hildick-Smith, D., Boudou, N., Sianos, G., Gelev, V., Rumoroso, J. R., Erglis, A., Christiansen, E. H., Escaned, J., di Mario, C., Hovasse, T., Teruel, L., Bufo, A., Lauer, B., Bogaerts, K., Goicolea, J., Spratt, J. C., Gershlick, A. H., Galassi, A. R., ... EUROCTO trial investigators (2018). A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *European heart journal*, 39(26), 2484–2493. <https://doi.org/10.1093/eurheartj/ehy220>
- [12] Choo, E. H., Koh, Y. S., Seo, S. M., Lee, J. M., Kim, H. Y., Park, H. J., Kim, P. J., Chang, K., Jeon, D. S., Kim, D. B., Her, S. H., Park, C. S., Yoo, K. D., Chung, W. S., & Seung, K. B. (2019). Comparison of successful percutaneous coronary intervention versus optimal medical therapy in patients with coronary chronic total occlusion. *Journal of cardiology*, 73(2), 156–162. <https://doi.org/10.1016/j.jjcc.2018.08.006>
- [13] King-Shier, K. M., Quan, H., Mather, C., Verhoef, M. J., Knutson, M. L., & Ghali, W. A. (2012). Understanding coronary artery disease patients' decisions regarding the use of chelation therapy for coronary artery disease: descriptive decision modeling. *International journal of nursing studies*, 49(9), 1074–1083. <https://doi.org/10.1016/j.ijnurstu.2012.03.011>
- [14] Seely, D. M., Wu, P., & Mills, E. J. (2005). EDTA chelation therapy for cardiovascular disease: a systematic review. *BMC cardiovascular disorders*, 5, 32. <https://doi.org/10.1186/1471-2261-5-32>
- [15] Lamas, G. A., & Hussein, S. J. (2006). EDTA chelation therapy meets evidence-based medicine. *Complementary therapies in clinical practice*, 12(3), 213–215. <https://doi.org/10.1016/j.ctcp.2006.04.002>
- [16] Lamas GA, Goertz C, Boineau R, Mark DB, Rozema T, Nahin RL, Lindblad L, Lewis EF, Drisko J, Lee KL; TACT Investigators. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. *JAMA*. 2013 Mar 27;309(12):1241-50. doi: 10.1001/jama.2013.2107. PMID: 23532240; PMCID: PMC4066975.
- [17] Escolar, E., Lamas, G. A., Mark, D. B., Boineau, R., Goertz, C., Rosenberg, Y., Nahin, R. L., Ouyang, P., Rozema, T., Magaziner, A., Nahas, R., Lewis, E. F., Lindblad, L., & Lee, K. L. (2014). The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circulation. Cardiovascular quality and outcomes*, 7(1), 15–24. <https://doi.org/10.1161/CIRCOUTCOMES.113.000663>
- [18] Sultan, S., Murarka, S., Jahangir, A., Mookadam, F., Tajik, A. J., & Jahangir, A. (2017). Chelation therapy in cardiovascular disease: an update. *Expert review of clinical pharmacology*, 10(8), 843–854. <https://doi.org/10.1080/17512433.2017.1339601>
- [19] Ma, Y., Li, D., Li, J., Li, Y., Bai, F., Qin, F., Zhou, S., & Liu, Q. (2018). Percutaneous coronary intervention versus optimal medical therapy for patients with chronic total occlusion: a meta-analysis and systematic review. *Journal of thoracic disease*, 10(5), 2960–2967. <https://doi.org/10.21037/jtd.2018.04.140>
- [20] Juricic, S. A., Tesic, M. B., Galassi, A. R., Petrovic, O. N., Dobric, M. R., Orlic, D. N., Vukcevic, V. D., Stankovic, G. R., Aleksandric, S. B., Tomasevic, M. V., Nedeljkovic, M. A., Beleslin, B. D., Jelic, D. D., Ostojic, M. C., & Stojkovic, S. M. (2021). Randomized Controlled Comparison of Optimal Medical Therapy with Percutaneous Recanalization of Chronic Total Occlusion (COMET-CTO). *International heart journal*, 62(1), 16–22. <https://doi.org/10.1536/ihj.20-427>
- [21] Qian X, Deng H, Yuan J, Hu J, Dai L, Jiang T. Evaluating the efficacy and safety of percutaneous coronary intervention (PCI) versus the optimal drug therapy (ODT) for stable coronary heart disease: a systematic review and meta-analysis. *J Thorac Dis*. 2022 Apr;14(4):1183-1192. doi: 10.21037/jtd-22-222. PMID: 35572911; PMCID: PMC9096285.
- [22] Ravalli F, Vela Parada X, Ujueta F, Pinotti R, Anstrom KJ, Lamas GA, Navas-Acien A. Chelation Therapy in Patients With Cardiovascular Disease: A Systematic Review. *J Am Heart Assoc*. 2022 Mar 15;11(6):e024648. doi: 10.1161/JAHA.121.024648. Epub 2022 Mar 1. PMID: 35229619; PMCID: PMC9075296.

- [23] Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., Bravata, D. M., Dai, S., Ford, E. S., Fox, C. S., Franco, S., Fullerton, H. J., Gillespie, C., Hailpern, S. M., Heit, J. A., Howard, V. J., Huffman, M. D., Kissela, B. M., Kittner, S. J., Lackland, D. T., ... American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*, 127(1), e6–e245. <https://doi.org/10.1161/CIR.0b013e31828124ad>
- [24] Fihn, S. D., Gardin, J. M., Abrams, J., Berra, K., Blankenship, J. C., Dallas, A. P., Douglas, P. S., Foody, J. M., Gerber, T. C., Hinderliter, A. L., King, S. B., 3rd, Kligfield, P. D., Krumholz, H. M., Kwong, R. Y., Lim, M. J., Linderbaum, J. A., Mack, M. J., Munger, M. A., Prager, R. L., Sabik, J. F., ... American College of Cardiology Foundation/American Heart Association Task Force (2012). 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*, 126(25), e354–e471. <https://doi.org/10.1161/CIR.0b013e318277d6a0>
- [25] Task Force Members, Montalescot, G., Sechtem, U., Achenbach, S., Andreotti, F., Arden, C., Budaj, A., Bugiardini, R., Crea, F., Cuisset, T., Di Mario, C., Ferreira, J. R., Gersh, B. J., Gitt, A. K., Hulot, J. S., Marx, N., Opie, L. H., Pfisterer, M., Prescott, E., Ruschitzka, F., ... Zamorano, J. L. (2013). 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European heart journal*, 34(38), 2949–3003. <https://doi.org/10.1093/eurheartj/ehs296>
- [26] Risos, L., & Berkenboom, G. (2014). Revascularization versus medical treatments in stable coronary artery disease: predicting the future of novel drug therapies for stable angina. *Journal of cardiovascular pharmacology*, 63(3), 213–217. <https://doi.org/10.1097/FJC.000000000000051>
- [27] Pijls, N. H., Fearon, W. F., Tonino, P. A., Siebert, U., Ikeno, F., Bornschein, B., van't Veer, M., Klauss, V., Manoharan, G., Engström, T., Oldroyd, K. G., Ver Lee, P. N., MacCarthy, P. A., De Bruyne, B., & FAME Study Investigators (2010). Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *Journal of the American College of Cardiology*, 56(3), 177–184. <https://doi.org/10.1016/j.jacc.2010.04.012>
- [28] Pursnani, S., Korley, F., Gopaul, R., Kanade, P., Chandra, N., Shaw, R. E., & Bangalore, S. (2012). Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: a systematic review and meta-analysis of randomized clinical trials. *Circulation. Cardiovascular interventions*, 5(4), 476–490. <https://doi.org/10.1161/CIRCINTERVENTIONS.112.970954>
- [29] Gao, L., Wang, Y., Liu, Y., Cao, F., & Chen, Y. (2017). Long-term clinical outcomes of successful revascularization with drug-eluting stents for chronic total occlusions: A systematic review and meta-analysis. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*, 89(S1), 574–581. <https://doi.org/10.1002/ccd.26934>