**SUPPLEMENTARY MATERIAL**

**Title:** Direct Oral Anticoagulants versus Vitamin K Antagonists for the Management of Left Ventricular Thrombus after Myocardial Infarction: A Meta-analysis

**METHODS**

**Literature search**

Literature search was conducted in several databases including Cochrane Library, MEDLINE, Pubmed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI) Database and Wanfang Databasefrom inception until 12/2023. Potential gray literature was searched in OpenGrey.eu. Basic keywords used in search strings were (‘’DOACs’’ OR ‘’direct oral anticoagulants’’ OR ‘’NOACs’’ OR ‘’novel oral anticoagulants’’ OR ‘’apixaban’’ OR ’’rivaroxaban’’ OR ‘’dabigatran’’ OR ‘’edoxaban’’ OR ‘’VKAs’’ OR ‘’Vitamin K antagonists’’ OR ‘’warfarin’’ OR ‘’acenocoumarol’’ OR ‘’phenprocoumon’’) and (‘’AMI’’ OR ‘’MI’’ OR ‘’acute myocardial infarction’’ OR ‘’myocardial infarction’’ OR ‘’acute coronary syndrome’’ OR ‘’left ventricular thrombus’’ OR ‘’LV thrombus’’ OR ‘’thrombus’’ OR ‘’apical thrombus’’ OR ‘’complication’’) and (‘’efficacy’’ OR ‘’safety’’ OR ‘’thrombus resolution’’ OR ‘’bleeding’’ OR ‘’outcomes’’ OR ‘’prognosis’’ OR ‘’prognostic value’’ OR ‘’stroke’’ OR ‘’embolism’’ OR ‘’systemic embolism’’ OR ‘’embolic stroke’’) " in both free text and Medical Subject Headings (MeSH) format. Τhe reference lists of the eligible studies and relevant reviews were searched manually to identify any papers not previously detected.

**Data extraction**

Data were independently extracted by two investigators (CG and VA). Pre-specified forms were used to extract the following information: study design, study population, demographic characteristics, anticoagulant therapy, antiplatelet therapy, follow up period, and raw outcome data on pre-specified outcomes of interest.

**Quality assessment**

Τhe methodological quality of the included studies was independently evaluated by two reviewers (VA and SD) using the Quality In Prognosis Studies (QUIPS) tool and classifying the risk of bias as “low”, “moderate” or “high” in the following domains: study participation, study attrition, prognostic factor measurement, outcome adjudication, study confounding and statistical analysis.

**Data synthesis**

Rates of events were recorded for both case (patients under DOACs) and control (patients under VKAs) groups. Random effects meta-analyses were performed using Mantel-Haenszel weighting and the DerSimonian-Laird method. ORs and 95% CIs were calculated for each analysis based on the raw events and sample sizes provided by each study. For both efficacy and safety outcomes of the study, the results are presented as pooled odds ratio and 95% confidence intervals with a two-sided significance level of p <0.05. Evaluation of heterogeneity was conducted by calculating I2 (i.e., <25 %: low heterogeneity; 25% - 50%: moderate heterogeneity; >50 %: high heterogeneity) (1). The possibility of publication bias was investigated via visual examination of the produced funnel plots; the Egger’s test was not applicable due to limited number of eligible studies (less than 10) (2).

Given the expected heterogeneity of the included studies, subgroup analyses were carried out to relate the outcomes with individual study design characteristics [i.e., triple antithrombotic therapy, follow-up duration, DOAC type, restricted sample size, and type of studies (randomized controlled trials or observational studies)]. Meta-regression analyses could not be performed because of the limited number of eligible studies (less than 10). The Review Manager 5.4 software was used for the statistical analysis and visualization of our findings.

The quality of evidence provided by our analyses was assessed through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. The quality of evidence in each domain was assessed by two independent reviewers (ASP and VA) depending on the existence of “very serious”, “serious” or “not serious” concerns. The final outcome (i.e., certainty and importance of the study outcomes) was automatically generated via the GRADE pro Guideline Development Tool [(Software); McMaster University and Evidence Prime, 2023; available from gradepro.org].

**RESULTS**

**Subgroup analyses**

When subgroup analyses were performed for studies using only rivaroxaban (3-5), or studies with ≥1 year follow up (3, 4, 6, 7), or studies with sample of ≥100 patients (4, 6, 7) DOACs retained a higher rate for thrombus resolution, and a lower risk for systemic embolism and the composite outcome (Supplementary Table S3). When subgroup analyses were undertaken for studies where patients received exclusively triple antithrombotic treatment (3, 5, 8-10), or studies using only apixaban (8, 9), or only randomized controlled trials (5, 8, 9) the superiority of DOACs did not reach statistical significance both for efficacy, safety, and the composite outcome (Supplementary Table S3). In terms of bleeding, the DOACs outperformed VKAs only when studies with ≥1 year follow up (3, 4, 6, 7) or studies with sample of ≥100 patients (4, 6, 7) were grouped (Supplementary Table S3). When abstracts (10) and non-English language studies (4) were excluded DOACs lost their superiority for systemic embolism but they retained it for thrombus resolution, bleeding and the composite outcome (Supplementary Table S3).

**Supplementary Figure S1.** Funnel plot to assess risk of bias regarding the likelihood for thrombus resolution based on the received anticoagulation.

**Supplementary Figure S2.** Funnel plot to assess risk of bias regarding the risk for systemic embolism based on the received anticoagulation.

**Supplementary Figure S3.** Funnel plot to assess risk of bias regarding the risk for bleeding based on the received anticoagulation.

**Supplementary Figure S4.** Funnel plot to assess risk of bias regarding the risk for the composite outcome based on the received anticoagulation.

**Supplementary Table S1.** PRISMA checklist as followed in the current systematic review and meta-analysis.

**Supplementary Table S2.** Quality assessment of the included studies using the QUIPS tool.

**Supplementary Table S3.** Subgroup analyses of the included studies.

**Supplementary Table S4.** GRADE appraisal of the quality of evidence.

**FIGURES**

**Supplementary Figure S1.** Funnel plot to assess risk of bias regarding the likelihood for thrombus resolution based on the received anticoagulation. Odds ratio is plotted on the horizontal scale and SE on the vertical axis. The largest and most powerful studies are placed toward the top of the plot. There is no evidence for funnel plot asymmetry on visual assessment. These findings suggest low heterogeneity and small possibility for publication bias.



**Supplementary Figure S2.** Funnel plot to assess risk of bias regarding the risk for systemic embolism based on the received anticoagulation. Odds ratio is plotted on the horizontal scale and SE on the vertical axis. The largest and most powerful studies are placed toward the top of the plot. There is no evidence for funnel plot asymmetry on visual assessment. These findings suggest low heterogeneity and small possibility for publication bias.

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**Supplementary Figure S3.** Funnel plot to assess risk of bias regarding the risk for bleeding based on the received anticoagulation. Odds ratio is plotted on the horizontal scale and SE on the vertical axis. The largest and most powerful studies are placed toward the top of the plot. There is no evidence for funnel plot asymmetry on visual assessment. These findings suggest low heterogeneity and small possibility for publication bias.

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**Supplementary Figure S4.** Funnel plot to assess risk of bias regarding the risk for the composite outcome based on the received anticoagulation. Odds ratio is plotted on the horizontal scale and SE on the vertical axis. The largest and most powerful studies are placed toward the top of the plot. There is no evidence for funnel plot asymmetry on visual assessment. These findings suggest low heterogeneity and small possibility for publication bias.

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**TABLES**

**Supplementary Table S1.** PRISMA checklist as followed in the current systematic review and meta-analysis.

|  |  |
| --- | --- |
| **Efficacy and safety of direct oral anticoagulants for the management of left ventricular thrombus after myocardial infarction: A meta-analysis** |  |
| **Title**  | 1 | Identify the report as a systematic review. | *Page 1: “Title”* |
| **ABSTRACT**  |  |
| **Abstract**  | 2 | See the PRISMA 2020 for Abstracts checklist. | *Page 3: “Abstract”* |
| **INTRODUCTION**  |  |
| **Rationale**  | 3 | Describe the rationale for the review in the context of existing knowledge. | *Page 5: “Introduction.”* |
| **Objectives**  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | *Page 5: “The present meta-analysis ... AMI.”* |
| **METHODS**  |  |
| **Eligibility criteria**  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | *Page 6: “Eligibility criteria”* |
| **Information sources**  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | *Page 5 Supplementary Material: “Literature Search”* |
| **Search strategy** | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | *Page 5 Supplementary Material: “Literature Search”* |
| **Selection process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | *Page 6: “Eligibility criteria”* |
| **Data collection process**  | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | *Page 2 Supplementary Material Supplementary Matrial: “Data extraction”* |
| **Data items**  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | *Pages 6: “Outcomes of interest”* |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | *Page 2 Supplementary Material: “Data extraction”* |
| **Study risk of bias assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | *Page 2-3 Supplementary Material: “Quality assessment”* |
| **Effect measures**  | 12 | Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | *Page 3 Supplementary Material: “Data synthesis”* |
| **Synthesis methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | *Page 3 Supplementary Material: “Data synthesis”* |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | *Page 3 Supplementary Material: “Data synthesis”* |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | *Page 3 Supplementary Material “Data synthesis”* |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | *Page 3 Supplementary Material: “Data synthesis”* |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | *Page 3 Supplementary Material: “Data synthesis”* |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | *Page 3 Supplementary Material: “Data synthesis”* |
| **Reporting bias assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | *Page 3 Supplementary Material: “Data synthesis”* |
| **Certainty assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | *Page 3 Supplementary Material: “Data synthesis”* |
| **RESULTS**  |  |
| **Study selection**  | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | *Page 7: “Search results and study characteristics” + Figure 1* |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | *Figure 1+ Table 1* |
| **Study characteristics**  | 17 | Cite each included study and present its characteristics. | *Table 1*  |
| **Risk of bias in studies**  | 18 | Present assessments of risk of bias for each included study. | *Supplementary Table S2 + Page 7-8: “Quality assessment of the included studies”* |
| **Results of individual studies**  | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | *Table 1* |
| **Results of syntheses** | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | *Pages 7-9* |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | *Pages 7-9* |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | *Page 4 Supplementary Material: “Subgroup analyses”* |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | *Page 4 Supplementary Material: “Subgroup analyses”* |
| **Reporting biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | *Page 7-8: “Publication bias assessment”* |
| **Certainty of evidence**  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | *Page 8-9: “GRADE appraisal of the quality of evidence”* |
| **DISCUSSION**  |  |
| **Discussion**  | 23a | Provide a general interpretation of the results in the context of other evidence. | *Pages 9-12: “Discussion”*  |
| 23b | Discuss any limitations of the evidence included in the review. | *Page 12: “Limitations* |
| 23c | Discuss any limitations of the review processes used. | *Page 12: “Limitations* |
| 23d | Discuss implications of the results for practice, policy, and future research. | *Pages 9-12: “Discussion” + Page 12: “Conclusions”* |
| **OTHER INFORMATION** |  |
| **Registration and protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | *Page 5: “Our systematic review and meta-analysis was prospectively registered on the PROSPERO registry (CRD42023433101).”* |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | *Page 6: “Our systematic review and meta-analysis was prospectively registered on the PROSPERO registry (CRD42023433101).”* |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | *Not applicable.* |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | *Page 13: “Sources of funding”* |
| **Competing interests** | 26 | Declare any competing interests of review authors. | *Page 13: “Disclosure Statement”* |
| **Availability of data, code and other materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | *Page 13: “Data availability”* |

**Supplementary Table S2.** Quality assessment of the included studies using the QUIPS tool.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Year | Study Participation | Study Attrition | Prognostic Factor Measurement | Outcome Measurement | Study Confounding | Statistical analysis and reporting | Overall assessment |
| Chao et al. | 2018 | L | M | M | L | M | M | M |
| Jaidka et al. | 2018 | M | M | L | M | H | M | M |
| Jones et al. | 2020 | L | L | M | L | L | L | L |
| Zhang et al. | 2021 | L | L | M | L | M | L | L |
| Liang et al. | 2022 | M | M | L | L | H | M | M |
| Alcalai et al. | 2022 | L | L | M | L | H | M | M |
| Youssef et al. | 2023 | M | M | M | L | M | L | M |
| Mansouri et al. | 2024 | M | M | M | M | H | M | M |

The Quality in Prognosis Studies (QUIPS) tool evaluates the individual overall risk of bias of the included studies based on 6 different domains. Those consist of study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting.

Abbreviations: H, high; L, low; M, moderate

**Supplementary Table S3.** Subgroup analyses of the included studies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Subgroup** | **Thrombus resolution** | **Bleeding** | **Systemic embolism** | **Composite outcome** |
| **Studies with DAPT+DOAC(5 studies)** | 1.40 (0.67-2.92), I2=0% | 0.79 (0.27- 2.29), I2=0% | 0.29 (0.06-1.43), I2=0% | 0.53 (0.26-1.09), I2=0% |
| **Studies with rivaroxaban(3 studies included)** | 1.87 (1.08-3.24), I2=0% | 0.56 (0.21-1.45), I2=0% | 0.19 (0.05-0.67), I2=0% | 0.32 (0.16-0.64), I2=0% |
| **Studies with apixaban(2 studies included)** | 1.57 (0.24-10.15), I2=0% | 0.22 (0.02-2.08), I2=0% | 0.28 (0.01-7.31), I2=0% | 0.55 (0.13-2.21), I2=0% |
| **RCTs(3 studies included)** | 1.51 (0.54-4.22), I2=0% | 0.22 (0.02-2.08), I2=0% | 0.28 (0.01-7.31), I2=0% | 0.55 (0.13-2.21), I2=0% |
| **Studies with >1y follow up(4 studies included)** | 2.11 (1.28-3.48), I2=0% | 0.39 (0.20-0.76), I2=0% | 0.28 (0.10-0.77), I2=0% | 0.31 (0.18-0.52), I2=0% |
| **Sample >100 patients(3 studies included)** | 2.36 (1.35-4.12), I2=0% | 0.37 (0.18-0.74), I2=0% | 0.30 (0.10-0.93), I2=0% | 0.29 (0.16-0.54), I2=0% |
| **Exclude abstracts (7 studies included)** | 1.98 (1.26-3.11), I2=0% | 0.37 (0.20-0.71), I2=0% | 0.28 (0.11-0.73), I2=0% | 0.33 (0.20-0.54), I2=0% |
| **Excluded non-English language studies (7 studies included)**  | 1.75 (1.00-3.06), I2=0% | 0.44 (0.22-0.89), I2=0% | 0.39 (0.12-1.24), I2=0% | 0.41 (0.24-0.70), I2=0% |
| **Exclude abstracts and non-English language studies (6 studies included)** | 1.78 (1.00-3.16), I2=0% | 0.32 (0.15-0.69), I2=0% | 0.37 (0.11-1.28), I2=0% | 0.35 (0.19-0.62), I2=0% |

Abbreviations: DAPT, dual antiplatelet therapy; DOAC; direct oral anticoagulant; RCTs, randomized controlled clinical trials

**Supplementary Table S4.** GRADE appraisal of the quality of evidence

**Question:** Clinical outcomes of DOACs vs VKA treatment for apical thrombus after AMI

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **Outcome (№ of studies)** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Outcome after DOAC treatment** | **Outcome after VKA treatment** | **OR(95% CI)** | **Absolute(95% CI)** |
| **Thrombus resolution**(8 studies) | non-randomised studies | not serious | not serious | not serious | not serious | strong association | 211/263(80.2%) | 226/321 (70.4%) | **OR 1.95**(1.25 to 3.04) | **119 more** **per 1.000**(from 44 more to 174 more) | ⨁⨁⨁◯Moderate | IMPORTANT |
| **Bleeding** (7 studies) | non-randomised studies | not serious | not serious | not serious | not serious | strong association | 17/240 (7.1%) | 50/312 (16.0%) | **OR 0.46**(0.26 to 0.84) | **80 fewer per 1.000**(from 113 fewer to 22 fewer) | ⨁⨁⨁◯Moderate | IMPORTANT |
| **Systemic embolism**(7 studies) | non-randomised studies | not serious | not serious | not serious | not serious | strong association | 5/240 (2.1%) | 24/310 (7.7%) | **OR 0.30**(0.12 to 0.75) | **53 fewer per 1.000**(from 67 fewer to 18 fewer) | ⨁⨁⨁◯Moderate | IMPORTANT |
| **Composite outcome(7** studies) | non-randomised studies | not serious | not serious | not serious | not serious | strong association | 34/240 (14.2%)  | 88/310 (28.4%)  | **OR 0.37**(0.23 to 0.60) | **156 fewer per 1.000**(from 200 fewer to 92 fewer) | ⨁⨁⨁◯Moderate | IMPORTANT |

**CI:** confidence interval; **OR:** odds ratio

The GRADE tool consists of 8 domains:

1. risk of bias (as assessed through the Newcastle-Ottawa-Scale),
2. inconsistency (i.e., heterogeneity in results across studies),
3. indirectness (i.e., deviation in the research question among the included studies: population characteristics, interventions, or outcome measures),
4. imprecision (i.e., random variation in outcome estimates due to chance based on sample size, number of events and confidence intervals of the effect estimate),
5. probability of publication bias (as assessed via the visual inspection of the funnel plots),
6. plausibility of residual confounding (i.e., unmeasured confounding factors that reduce or increase the association of the pharmacotherapy with the outcomes of interest),
7. dose-response gradient (i.e., existence of a dose-response effect), and
8. magnitude of effect (i.e., large or very large estimates of the magnitude of the pharmacotherapy effect).

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