**Supplementary material**

**Switching from vitamin K antagonists to direct oral anticoagulants in frail elderly patients with atrial fibrillation: Systematic review and meta-analysis**

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**Supplemental Table S1.** Search strategy for MEDLINE (Pubmed)

| |
|---|
| ("Atrial Fibrillation"[MeSH Terms] OR "Atrial Fibrillation"[Title/Abstract] OR "AF"[Title/Abstract]) AND ("Warfarin"[MeSH Terms] OR "Warfarin"[Title/Abstract] OR "acenocoumarol"[Title/Abstract] OR "phenprocoumon"[Title/Abstract] OR "fluindione"[Title/Abstract] OR "vitamin k antagonist*"[Title/Abstract] OR "VKA"[Title/Abstract] OR "VKAs"[Title/Abstract]) AND ("Rivaroxaban"[MeSH Terms] OR "Dabigatran"[MeSH Terms] OR "Edoxaban"[Supplementary Concept] OR "apixaban"[Title/Abstract] OR "Rivaroxaban"[Title/Abstract] OR "Dabigatran"[Title/Abstract] OR "Edoxaban"[Title/Abstract] OR "DOAC"[Title/Abstract] OR "DOACs"[Title/Abstract] OR "NOAC"[Title/Abstract] OR "NOACs"[Title/Abstract] OR "direct oral anticoagulant*"[Title/Abstract] OR "non vitamin k antagonist oral anticoagulant*"[Title/Abstract] OR "novel oral anticoagulant*"[Title/Abstract]) AND ("switch*"[Title/Abstract] OR "switching"[Title/Abstract] OR "switched"[Title/Abstract] OR "transition*"[Title/Abstract] OR "convert*"[Title/Abstract] OR "conversion"[Title/Abstract] OR "change*"[Title/Abstract] OR "continu*"[Title/Abstract] OR "remain*"[Title/Abstract]) AND ("frail"[Title/Abstract] OR "frailty"[Title/Abstract] OR "elderly"[Title/Abstract] OR "older"[Title/Abstract] OR "geriatric*"[Title/Abstract] OR "Frail Elderly"[Title/Abstract] OR "older adult*"[Title/Abstract] OR "older patient*"[Title/Abstract] OR "Frail Elderly"[MeSH Terms] OR "Aged"[MeSH Terms]) |

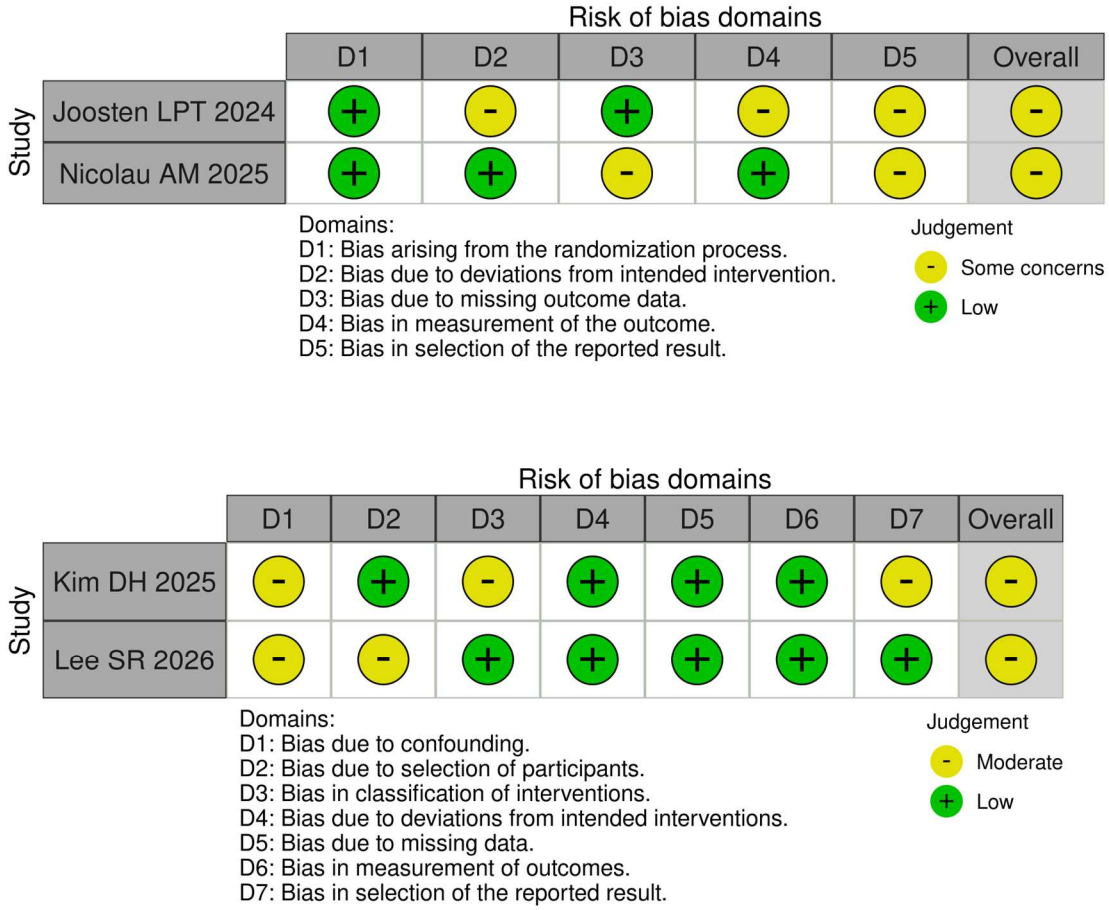
**Supplemental Table S2.** Search strategy for Cochrane library

| ID | Search |
|---|---|
| #1 | warfarin |
| #2 | acenocoumarol |
| #3 | phenprocoumon |
| #4 | fluindione |
| #5 | "vitamin K antagonist*" |
| #6 | VKA |
| #7 | VKAs |
| #8 | MeSH descriptor: [Warfarin] explode all trees |
| #9 | apixaban |
| #10 | rivaroxaban |
| #11 | dabigatran |
| #12 | edoxaban |
| #13 | DOAC |
| #14 | DOACs |
| #15 | NOAC |
| #16 | NOACs |
| #17 | "direct oral anticoagulant*" |
| #18 | "non-vitamin K antagonist oral anticoagulant*" |
| #19 | "novel oral anticoagulant*" |
| #20 | MeSH descriptor: [Apixaban] explode all trees |
| #21 | MeSH descriptor: [Rivaroxaban] explode all trees |
| #22 | MeSH descriptor: [Dabigatran] explode all trees |
| #23 | MeSH descriptor: [Atrial Fibrillation] explode all trees |
| #24 | atrial fibrillation |
| #25 | AF |
| #26 | switch* |
| #27 | transition* |
| #28 | convert* |
| #29 | conversion |

| |
|---|
| #30 change* |
| #31 continu* |
| #32 remain* |
| #33 frail |
| #34 frailty |
| #35 elderly |
| #36 older |
| #37 geriatric* |
| #38 "frail elderly" |
| #39 "older adult*" |
| #40 "older patient*" |
| #41 MeSH descriptor: [Frail Elderly] explode all trees |
| #42 MeSH descriptor: [Aged] explode all trees |
| #43 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #44 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 |
| #45 #23 OR #24 OR #25 |
| #46 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 |
| #47 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 |
| #48 #43 AND #44 AND #45 AND #46 AND #47 |

**Supplemental Table S3.** Search strategy for Scopus

| |
|---|
| TITLE-ABS-KEY("atrial fibrillation" OR AF)<br>AND TITLE-ABS-KEY(warfarin OR acenocoumarol OR phenprocoumon OR fluindione OR "vitamin K antagonist*" OR VKA OR VKAs)<br>AND TITLE-ABS-KEY(apixaban OR rivaroxaban OR dabigatran OR edoxaban OR DOAC OR DOACs OR NOAC OR NOACs OR "direct oral anticoagulant*" OR "non-vitamin K antagonist oral anticoagulant*" OR "novel oral anticoagulant*")<br>AND TITLE-ABS-KEY(switch* OR switching OR switched OR transition* OR convert* OR conversion OR change* OR continu* OR remain*)<br>AND TITLE-ABS-KEY(frail OR frailty OR elderly OR older OR geriatric* OR "frail elderly" OR "older adult*" OR "older patient*") |




**Supplemental Figure S1**. Risk-of-bias assessments of included studies. The upper panel presents the RoB 2 assessment for randomized trials, organized across the following domains: D1, bias arising from the randomization process; D2, bias due to deviations from intended interventions; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; and D5, bias in selection of the reported result. The lower panel presents the ROBINS-I assessment for non-randomized studies, organized across the following domains: D1, bias due to confounding; D2, bias due to selection of participants; D3, bias in classification of interventions; D4, bias due to deviations from intended interventions; D5, bias due to missing data; D6, bias in measurement of outcomes; and D7, bias in selection of the reported result. For RoB 2, green indicates low risk of bias and yellow indicates some concerns. For ROBINS-I, green indicates low risk of bias and yellow indicates moderate risk of bias. The overall judgement for each study is shown in the rightmost column.

**Supplemental Table S4**. PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Title page (p. 1) |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract (p. 1) |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Introduction (pp. 3–4) |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | End of Introduction (p. 4) |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Methods, Section 2.2 (pp. 4–5) |
| 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. | Methods, Section 2.1 (p. 4) |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Supplemental Tables 1–3 |
| 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. | Methods, Section 2.4 (p. 5) |
| 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. | Methods, Section 2.5 (p. 5) |
| 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. | Methods, Sections 2.3 and 2.5 (pp. 5–6) |
| | 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. | Methods, Section 2.5 (p. 5) |
| 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. | Methods, Section 2.6 (p. 6) |
| 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. | Methods, Section 2.7 (p. 6) |
| 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)). | Methods, Sections 2.2, 2.3, and 2.7 (pp. 4–6) |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Methods, Section 2.7 (p. 6) |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Methods, Sections 2.5 and 2.7 (pp. 5–6) |
| | 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. | Methods, Section 2.7 (pp. 6–7) |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Methods, Section 2.7; sensitivity analyses described (p. 7) |

| | | | |
|---|---|---|---|
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Methods, Section 2.7 (p. 7) |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Methods, Section 2.7 (p. 7) |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | NA |
| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| **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. | Results, Section 3.1 (p. 7); Figure 1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | NA |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Results, Section 3.1 (pp. 7–8); Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Results, Section 3.1 (p. 8); Supplemental Figure 1 |
| 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. | Figures 2–4; Table 1 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Results, Sections 3.1–3.4 (pp. 7–11) |
| | 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. | Results, Sections 3.2–3.4 (pp. 8–11); Figures 2–4 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Results, Sections 3.3–3.4 (pp. 9–11) |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Results, Sections 3.3–3.4 (pp. 9–11); Figures 3–4 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Not assessed; fewer than 10 studies included (Results not applicable; Methods, Section 2.7, p. 7) |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | NA |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion, Section 4 (pp. 11–14) |
| | 23b | Discuss any limitations of the evidence included in the review. | Section 4.1 (p. 14) |
| | 23c | Discuss any limitations of the review processes used. | Section 4.1 (p. 14) |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Discussion, |

| | | | |
|---|---|---|---|
| | | | Section 4 (pp. 13–14); Conclusions (p. 15) |
| **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. | Methods, Section 2 (p. 4); Protocol statement (p. 15) |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Methods, Section 2 (p. 4); Protocol statement (p. 15) |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Methods, Section 2: "no departures from the original methodological plan" (p. 4) |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Acknowledgements / Conflict of interest p. 15) |
| Competing interests | 26 | Declare any competing interests of review authors. | Conflict of interest (p. 15) |
| 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. | Data availability (p. 15) |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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