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1 **Eds versionTitle**

2 Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease: A Systematic
3 Review and Meta-Analysis

4 **Short title**

5 Oral anticoagulant therapy in kidney disease

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37 **ABSTRACT**

38 **Background:** The effects of oral anticoagulation in chronic kidney disease (CKD) are
39 uncertain.

40 **Purpose:** To evaluate benefits and harms of vitamin K antagonists (VKA) and non-vitamin K
41 oral anticoagulants (NOAC) in patients with CKD stages 3 to 5, including those with
42 dialysis-dependent end-stage kidney disease (ESKD).

43 **Data Sources:** Medline, EMBASE, and Cochrane databases from inception to February 2019
44 with English language restriction; bibliographies of reviews; Clinicaltrials.gov (February 25,
45 2019)

46 **Study selection:** Randomized controlled trials evaluating VKA or NOAC in adult CKD
47 patients for any indication, and reported efficacy and/or bleeding outcomes.

48 **Data Extraction:** Two authors independently extracted data, performed risk of bias
49 assessment, and rated certainty of evidence.

50 **Data Synthesis:** Forty-five trials, involving 34,082 participants anticoagulated for atrial
51 fibrillation ([AF] (eleven trials), venous thromboembolism ([VTE] eleven trials),
52 thromboprophylaxis (six trials), prevention of dialysis-access thrombosis (eight trials), and
53 cardiovascular disease other than AF (nine trials) were included. All but the eight trials
54 involving ESKD patients excluded participants with creatinine clearance <20 mL/min or
55 estimated glomerular filtration rate <15 mL/min/1.73 m². In AF, compared with VKA,
56 NOAC reduced the risks of stroke or systemic embolism (risk ratio 0.79, 95%CI 0.66–0.93;
57 high certainty evidence), and hemorrhagic stroke (0.48, 0.30–0.76; moderate certainty
58 evidence). Compared with VKA, NOAC effects on recurrent VTE or VTE-related death were
59 uncertain (0.72, 0.44–1.17; low certainty evidence). In all trials combined, NOAC reduced
60 major bleeding risk compared to VKA, though the finding was not statistically significant
61 (0.75, 0.56–1.01; low certainty evidence).

62 **Limitation:** Scant evidence among patients with advanced CKD stages or ESKD, data
63 mostly extracted from subgroup analyses of large trials.

64 **Conclusion:** In early stages of CKD, NOAC had a benefit-risk profile superior to VKA with
65 a clear reduction in the risk of stroke or systemic embolism in AF, and reduction in overall
66 major bleeding risk that was not statistically significant. There is insufficient evidence to
67 conclude whether patients with advanced CKD stages or ESKD derive benefit from VKA or
68 NOAC.

69 **Registration:** International Prospective Register of Systematic Reviews PROSPERO 2017
70 CRD42017079709 (December 4, 2017)

71 **Primary Funding Source:** None.

72 **INTRODUCTION**

73 Chronic kidney disease (CKD) is a pro-thrombotic state, associated with substantially
74 increased risks of arterial and venous thromboembolism (VTE) (1). In addition, atrial
75 fibrillation is highly prevalent in this population, affecting 18% of patients with CKD (2), and
76 12-25% of patients with dialysis-dependent end-stage kidney disease (ESKD) (3, 4). The
77 presence of CKD increases the risks of stroke or systemic embolism, congestive heart failure,
78 myocardial infarction, and all-cause death among patients with atrial fibrillation (5, 6).
79 Compared with people with normal kidney function, the risk of VTE is almost two-fold
80 greater among those with estimated glomerular filtration rate (eGFR) between 15 and 59
81 mL/min/1.73 m²) (7), and three-fold greater in patients with dialysis-dependent ESKD (8).
82 VTE in ESKD is also associated with increased risks of bleeding and all-cause death (8).
83 Other common clinical manifestations of increased thrombotic risk in CKD include acute
84 coronary syndrome, stroke, peripheral arterial occlusion, and dialysis access thrombosis (1,
85 9).

86 Anticoagulant therapy is an important intervention in the prevention of cardiovascular
87 thrombotic and VTE events. Evidence-based treatment guidelines recommend
88 anticoagulation for the prevention of stroke in patients with nonvalvular atrial fibrillation and
89 a CHA₂DS₂-VASc score ≥ 2 in men or ≥ 3 in women (10, 11), VTE in major orthopedic or
90 non-orthopedic surgical patients or hospitalized acutely ill medical patients (12), and
91 recurrent VTE in patients with VTE disease (13).

92 Patients with advanced stages of CKD and ESKD with atrial fibrillation are
93 prescribed oral anticoagulant therapy less frequently than those with normal kidney function
94 (3, 14). The use of warfarin in patients on dialysis who have atrial fibrillation varies
95 considerably, ranging from as low as 2% in Germany to 37% in Canada (3). The low rates of
96 anticoagulant therapy use in advanced CKD and ESKD may be due to the increased risk of
97 bleeding, uncertainty regarding potential benefits in this population, warfarin-associated

98 calciphylaxis, and warfarin-related nephropathy (15, 16). In CKD, the risk of major bleeding
99 increases linearly with declining eGFR (17). In patients with dialysis-dependent ESKD, the
100 bleeding risk is further increased with the incremental use of antithrombotic agents such as
101 warfarin and antiplatelet agents (18). The exclusion of CKD patients from nearly 90% of
102 trials evaluating anticoagulant interventions has contributed to uncertainty on the role of
103 anticoagulant therapy in CKD (19).

104 The aim of the current systematic review was to evaluate the benefits and harms of
105 oral anticoagulant (OAC) therapy for a range of clinical indications in patients with CKD
106 stages 3 to 5, including those receiving dialysis.

107

108 **METHODS**

109 The systematic review and meta-analysis was conducted according to the Preferred
110 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (20). The
111 protocol of this review was prospectively registered in the International Prospective Register
112 of Systematic Reviews (PROSPERO; December 4, 2017) and can be accessed at:

113 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79709

114 **Data Sources and Searches**

115 Relevant studies were identified by searching Medline (inception to February 2019),
116 Embase (inception to February 2019), and the Cochrane Central Register of Controlled Trials
117 (January 2019) with English language restriction using search strategy described in
118 **Appendix Table 1**. In addition, reference lists of relevant systematic reviews were searched.

119 Online trial registry Clinicaltrials.gov was searched (February 25, 2019) using the following
120 terms: chronic kidney disease, renal dialysis, atrial fibrillation and anticoagulation.

121 **Study Selection and Outcomes**

122 Studies were eligible for inclusion if they (i) were randomized controlled trials; (ii)
123 included adults with CKD (creatinine clearance [CrCl] <60 mL/min or eGFR <60
124 mL/min/1.73 m²), or dialysis-dependent ESKD; (iii) compared vitamin K antagonist (VKA)
125 or non-vitamin K oral anticoagulant (NOAC) to another oral anticoagulant, placebo, low-
126 molecular weight heparin (LMWH), aspirin, or no study medication; and (iv) reported
127 efficacy and/or bleeding outcomes. All indications for anticoagulation were eligible for
128 inclusion. Two authors (J.T.H. and B.L.N.) independently reviewed each title and abstract,
129 and performed full-text review of shortlisted studies. Disagreements about study eligibility
130 were resolved via consultation with two other authors (S.V.B. and V.P.). If multiple
131 secondary publications of the same trial were identified, the publication with the most
132 complete data was used and additional data from secondary sources were extracted.
133 Incomplete, or unpublished data from trials were requested from the investigators.

134 The outcomes of this systematic review were: stroke or systemic embolism in atrial
135 fibrillation, non-hemorrhagic stroke, hemorrhagic stroke, all-cause or cardiovascular death,
136 VTE or VTE-related death, myocardial infarction, composite cardiovascular events
137 (cardiovascular or all-cause death, nonfatal myocardial infarction, or stroke), dialysis access
138 thrombotic events, major bleeding, major or non-major clinically relevant bleeding, and
139 intracranial hemorrhage.

140 **Data Extraction and Quality Assessment**

141 Data extraction was carried out independently by two authors (J.T.H. and B.L.N.).
142 Disagreements were resolved via consultation with two other authors (S.V.B. and V.P.). The
143 following data were extracted using a standardized form: patient demographic details, study
144 design and conduct, indication for anticoagulation, dose of drug, non-randomized co-
145 interventions, follow-up duration, and outcome and bleeding events. The methodological
146 quality of each study included was assessed at the outcome level independently by two
147 authors (J.T.H. and B.L.N.) using the risk of bias assessment tool developed by the Cochrane
148 Bias Methods Group (21).

149 **Data Synthesis and Analysis**

150 The results were expressed as risk ratios (RR) with 95% confidence intervals (CI). A
151 treatment arm continuity correction was used if there were zero events in one arm in a trial.
152 For trials with three arms comparing two different doses of NOAC with VKA, similar to a
153 previous meta-analysis (22), data from only the high dose NOAC arm were used for the main
154 analyses to avoid potentially uninterpretable results by merging of the benefits and harms of
155 different doses. Additional analyses were conducted by combining data from both high and
156 low dose arms of NOAC. Summary estimates were obtained by random-effects model using
157 the Paule-Mandel method (23). If data on the number of events and participants were not
158 reported, generic inverse variance meta-analysis was performed by calculating log hazard

159 ratio and its standard error from the reported hazard ratio and respective CI. Evidence of
160 statistical heterogeneity across the studies was estimated using the I^2 test. I^2 values of 25%,
161 50%, and 75% were considered to correspond to low, moderate, and high levels of
162 heterogeneity (24). Statistical analyses were performed using Stata/MP, version 15.1
163 (StataCorp College Station, Texas), and R statistical software, version 3.5.3 (R Foundation
164 for Statistical Computing, Vienna, Austria).

165 Certainty in the evidence was summarized using the Grading of Recommendations
166 Assessment, Development and Evaluation (GRADE) approach, considering the following
167 domains: (1) within-study risk of bias, (2) indirectness of evidence, (3) unexplained
168 heterogeneity or inconsistency of results, and (4) imprecision of results by three authors
169 (J.T.H., B.L.N., and L.P.C.) and disagreements were resolved via consultation with two other
170 authors (S.V.B. and M.J.) (25). Because all meta-analyses involved fewer than 10 trials,
171 small study effects (publication bias) was not assessed and publication bias was not included
172 in rating certainty of evidence (26).

173 **Role of the Funding Source**

174 There was no funding source for this study.

175

176 **RESULTS**

177 **Selection and Description of Studies**

178 Forty-five trials involving 34,082 participants (median sample size 276 [range 10-
179 4,168], median follow-up 12 [range 1-36] months) evaluating VKA or NOAC were included
180 in the systematic review (**Figure 1**). Of these trials, eight included 685 participants with
181 dialysis-dependent ESKD (median sample size 91 [range 18-174], median follow-up 12
182 [range 3-36] months) evaluating VKA for the prevention of dialysis access thrombosis in
183 seven trials and one evaluated the effect of VKA on hemostatic factors. The remaining 37
184 trials included 33,397 participants with CKD, who were not receiving dialysis (defined as
185 CrCl 20-60 mL/min, eGFR 15-60 mL/min/1.73 m², or serum creatinine level ≥ 1.5 mg/dL;
186 median sample size 380 [range 10-4,168], median follow-up 12 [range 1-36] months). Eleven
187 trials included 16,787 participants with atrial fibrillation (median sample size 516 [range 12-
188 4,074], median follow-up 14 [range 3-34] months); eleven trials included 2,975 participants
189 with acute VTE (median sample size 162 [range 72-657], median follow-up 12 [range 6-36]
190 months), six trials included 3,908 medically ill or peri-operative patients requiring
191 anticoagulation for thromboprophylaxis (median sample size 380 [range 42-2,197] median
192 follow-up 2 [range 1-6] months); and the remaining nine trials included 9,727 participants
193 with cardiovascular disease other than atrial fibrillation (median sample size 331 [range 72-
194 2197] median follow-up 9 [range 1-36] months). Data from the 37 trials involving patients
195 with non-dialysis CKD were obtained exclusively from CKD subgroup analyses of large
196 trials. Details of included trials are described in **Appendix Table 2**.

197 NOAC was compared with VKA (15 trials, 16,495 participants), placebo (ten trials,
198 11,683 participants), LMWH (five trials, 1,720 participants), and aspirin (four trials, 2,690
199 participants); and VKA was compared with placebo (four trials, 408 participants), no study
200 medication (four trials, 277 participants), LMWH (two trials, 293 participants), and aspirin
201 (one trial, 516 participants). The interventional agents were: rivaroxaban (13 trials),

202 dabigatran (eight trials), apixaban (seven trials), edoxaban (five trials), betrixaban (one trial),
203 fixed-dose [1 or 2 mg] or low-intensity [target international normalized ratio (INR) 1.4-1.9]
204 warfarin (six trials), and adjusted-dose (target INR 1.5-2.5, or 2-3) warfarin or
205 acenocoumarol (five trials).

206 Source of funding was not reported in four trials. Thirty-nine of the remaining 41
207 (95%) trials were sponsored by pharmaceutical companies.

208 **Risk of bias**

209 Risk of bias assessment at outcome level is described in **Appendix Table 3**. Random
210 sequence generation and allocation concealment were reported using low risk methods in
211 80% of trials reporting the outcomes of stroke or systemic embolism, and major bleeding in
212 trials involving participants with atrial fibrillation. Random sequence generation and
213 allocation concealment were reported using low risk methods in all trials reporting the
214 outcome of VTE or VTE-related death in participants with acute VTE or those requiring
215 thromboprophylaxis, and major adverse cardiovascular events in participants with
216 cardiovascular disease other than atrial fibrillation. Trials involving participants with dialysis-
217 dependent ESKD reporting the outcomes of hemodialysis access thrombosis or malfunction,
218 all-cause death, and major bleeding were generally at high or unclear risk of bias in the
219 domains of random sequence generation and allocation concealment.

220 **Effects of interventions**

221 *Trials involving participants with atrial fibrillation*

222 None of the eleven trials involving participants with atrial fibrillation included
223 patients with dialysis-dependent ESKD. Anticoagulation was used for the prevention of
224 stroke or systemic embolism in seven trials, acute coronary syndrome or percutaneous
225 coronary intervention in two trials, and for periprocedural anticoagulation in participants
226 undergoing cardioversion, or catheter ablation, in one trial each. No trial tested a treatment
227 strategy of comparing an OAC to no anticoagulation in atrial fibrillation. Compared with

228 VKA, high dose NOAC reduced the risks of stroke or systemic embolism (RR 0.79, 95% CI
229 0.66–0.93), hemorrhagic stroke (RR 0.48, 95% CI 0.30–0.76), and all-cause death (RR 0.88,
230 95% CI 0.78–0.99); and had no clear effect on non-hemorrhagic stroke though confidence
231 bounds were wide (RR 1.04, 95% CI 0.83–1.30) (**Figure 2, Appendix Figures 1 to 4**).

232 Compared with aspirin, any OAC (VKA or NOAC) reduced the risk of stroke or systemic
233 embolism (RR 0.30, 95% CI 0.19–0.48). Compared with VKA, high dose NOAC reduced the
234 risk of major bleeding (RR 0.80, 95% CI 0.61–1.04), although this finding was not
235 statistically significant (**Appendix Figure 5**). Compared to VKA, the effect of high dose
236 NOAC on the risk of major or non-major clinically relevant bleeding was uncertain (RR 0.97,
237 95% CI 0.76–1.23) (**Appendix Figure 6**). Additional analyses after the inclusion of both
238 high and low doses of NOAC showed that, compared with VKA, NOAC reduced the risks of
239 stroke or systemic embolism (RR 0.87, 95% CI 0.74–1.02), and major bleeding (RR 0.74,
240 95% CI 0.55–1.00), though these findings were not statistically significant as their respective
241 upper limits of confidence intervals crossed 1 (**Appendix Figures 1 and 5**).

242 ***Trials involving participants with acute VTE***

243 NOAC reduced the risk of recurrent VTE or VTE-related death when compared with
244 placebo (RR 0.14, 95% CI 0.04–0.48); but had an uncertain effect when compared with VKA
245 (RR 0.72, 95% CI 0.44–1.17) (**Figure 3, Appendix Figure 7**). There was no difference in the
246 risk of recurrent VTE or VTE-related death between any OAC and LMWH (RR 2.10, 95%
247 CI 0.72–6.15) (**Appendix Figure 7**). None of the NOAC trials reported data on all-cause
248 death. There was no difference in the risk of all-cause death between VKA and LMWH (RR
249 1.01, 95% CI 0.79–1.31). There were no differences in the risk of major bleeding between
250 NOAC and VKA (RR 0.54, 95% CI 0.21–1.43), VKA and LMWH (RR 1.03, 95% CI 0.43–
251 2.51), and any OAC and LMWH (RR 1.24, 95% CI 0.54–2.88) (**Appendix Figure 8**). There

252 was no difference in the risk of major or non-major clinically relevant bleeding between
253 NOAC and VKA (RR 0.84, 95% CI 0.63–1.11) (**Appendix Figure 9**).

254 *Trials involving participants requiring anticoagulation for thromboprophylaxis*

255 There were no clear differences between NOAC and LMWH in the risks of VTE or
256 VTE-related death (RR 0.85, 95% CI 0.40–1.83), major bleeding (RR 3.72, 95% CI 0.79–
257 17.54), and major or non-major clinically relevant bleeding (RR 1.09, 95% CI 0.64–1.85)
258 (**Appendix Figure 10**). There was no difference in the risk of VTE or VTE-related death (RR
259 0.98, 95% CI 0.53–1.82) between NOAC and placebo.

260 *Trials involving participants with dialysis-dependent ESKD*

261 None of the eight trials involving participants with dialysis-dependent ESKD
262 evaluated NOAC (**Appendix Figure 11**). There was no clear difference in the risk of dialysis
263 access thrombosis or catheter malfunction between fixed-dose/low-intensity warfarin and
264 placebo/no study medication (RR 1.04, 95% CI 0.85–1.28) (**Appendix Figure 12**).
265 Compared with no study medication, adjusted-dose warfarin reduced the risk of dialysis
266 access thrombosis or catheter malfunction (RR 0.28, 95% CI 0.16–0.47) (**Appendix Figure**
267 **12**). Compared with placebo or no study medication, the effect of fixed-dose or low-intensity
268 warfarin on all-cause death (RR 0.65, 95% CI 0.34–1.24), and major bleeding (RR 2.66, 95%
269 CI 0.39–18.19) were uncertain (**Appendix Figures 13 and 14**).

270 *Participants with cardiovascular disease other than atrial fibrillation*

271 Compared with placebo, NOAC reduced the risk of major adverse cardiovascular
272 events (defined as a composite of cardiovascular or all-cause death, non-fatal myocardial
273 infarction or stroke), though this finding was not statistically significant as the upper limit of
274 confidence intervals crossed 1 (RR 0.88, 95% CI 0.75–1.04) (**Appendix Figures 15 and 16**).
275 In a single trial involving 4,168 participants with stable coronary or peripheral arterial
276 disease, the risk of major adverse cardiovascular events with low dose NOAC was lower than

277 placebo (RR 0.77, 95% CI 0.62–0.95). Compared with placebo, NOAC significantly
278 increased the risk of major bleeding (2.18, 95% CI 1.10–4.32) (**Appendix Figure 17**).
279 Additional analyses with the inclusion of trials comparing only the low dose NOAC with
280 placebo showed that NOAC reduced the risk of major adverse cardiovascular events (RR
281 0.89, 95% CI 0.77–1.04) although the upper limit of confidence intervals crossed 1, with no
282 difference in major bleeding risk (RR 2.29, 95% CI 0.57–9.18) (**Appendix Figures 16 and**
283 **17**).

284 *Bleeding outcomes from all trials combined*

285 Compared with VKA, high dose NOAC reduced the risk of major bleeding (RR 0.75,
286 95% CI 0.56–1.01), though this finding was not statistically significant as the upper limit of
287 confidence intervals crossed 1 (**Figure 4, Appendix Figure 18**). There was no significant
288 interaction of major bleeding risk by indication for anticoagulation (p=0.84). There was no
289 clear difference in the risk of major or non-major clinically relevant bleeding (RR 0.95, 95%
290 CI 0.83–1.07) between the NOAC and VKA groups (**Appendix Figure 19**). Compared with
291 VKA, high dose NOAC reduced the risk of intracranial hemorrhage (RR 0.49, 95% CI 0.30–
292 0.80) (**Appendix Figure 20**). Compared with placebo, NOAC increased the risks of major
293 bleeding (RR 2.27, 95% CI 1.21–4.26), and major or non-major clinically relevant bleeding
294 (RR 4.03, 95% CI 1.62–10.03). Compared to LMWH, NOAC increased the risk of major
295 bleeding (RR 3.67, 95% CI 1.05–12.89), but not major or non-major clinically relevant
296 bleeding (RR 1.09, 95% CI 0.64–1.85). Additional analysis after the inclusion of high and
297 low doses of NOAC showed clear reduction in major bleeding risk with NOAC compared
298 with VKA (RR 0.71, 95% CI 0.52–0.96) (**Appendix Figure 18**).

299
300

301 **DISCUSSION**

302 This review provides a comprehensive overview of the available data describing the
303 effects of anticoagulation for people with kidney disease and a range of co-morbidities or
304 other risk factors. It identifies some clear findings that can be used to guide treatment
305 decisions, but also a number of areas where the available data are inadequate and further
306 studies are urgently required. A key finding is that in patients with atrial fibrillation and early
307 stage CKD, NOAC were superior to VKA, with 21%, 52% and 51% relative risk reductions
308 in stroke or systemic embolism, hemorrhagic stroke and intracranial hemorrhage,
309 respectively. However, NOAC did not reduce the risk of non-hemorrhagic stroke in atrial
310 fibrillation. In AF, NOAC reduced the risk of major bleeding, though this finding was not
311 statistically significant. Compared with placebo, NOAC reduced the risk of recurrent VTE or
312 VTE-related death in patients with CKD receiving acute VTE treatment; but when compared
313 with VKA, this effect was uncertain. These data suggest that NOAC may be a reasonable
314 option in people with CKD who develop VTE, but further data would be helpful. In all trials
315 combined, compared with VKA, high dose NOAC reduced the risk of major bleeding, though
316 this result was not statistically significant. In contrast, for people with advanced stages of
317 CKD (CrCl <25 mL/min), including dialysis-dependent ESKD, there were no data available
318 regarding the effects of VKA or NOAC on the prevention of stroke or systemic embolism in
319 atrial fibrillation, or on VTE and VTE-related death.

320 Although the rates of ischemic and hemorrhagic stroke, and intracranial hemorrhage
321 were not reported in all trials involving participants with atrial fibrillation, it is possible that
322 the benefit of reduced stroke or systemic embolism with NOAC was mainly driven by a
323 reduction in hemorrhagic stroke. A similar finding was reported in the previously reported
324 systematic review of four randomized trials comparing NOAC with VKA (22). The excess
325 burden of atrial fibrillation, cardiovascular thrombotic events and VTE in patients with
326 advanced CKD contributes to their poor survival (5, 6, 8). Given the greater rates of arterial

327 and venous thrombotic in patients with advanced CKD than those with normal kidney
328 function, the absolute risk reduction with anticoagulation treatment in this population may be
329 greater, but this systematic review highlights the absence of evidence in patients with
330 advanced stages of CKD and ESKD, specifically for the prevention of stroke or systemic
331 embolism in atrial fibrillation, and recurrent VTE or VTE-related death. The potential benefit
332 of anticoagulation treatment needs to be balanced against the risk of bleeding in this
333 population. The rates of major bleeding with apixaban and warfarin in patients with
334 hemodialysis-dependent ESKD (19.7 and 22.9 per 100 person-years, respectively) (27) are
335 substantially greater than those with normal or mildly decreased kidney function (2.13 and
336 3.09 per 100 person-years, respectively) (28). Furthermore, 60-75% of patients with ESKD
337 discontinue oral anticoagulation within one year, possibly due to bleeding (27, 29). Despite
338 the absence of specific evidence, current guidelines suggest warfarin with target INR 2.0-3.0
339 or apixaban (recommendation class: IIa, evidence level: B-NR) (11) and time in therapeutic
340 range >65-70% (ungraded consensus-based statements) (10) in patients CrCl <15 mL/min or
341 dialysis-dependent ESKD with a CHA₂DS₂-VASc score ≥ 2 in men or ≥ 3 in women (11). The
342 lack of evidence-based guidelines strongly suggests that adequately-powered randomized
343 trials are required to address the unmet need in this population.

344 Leveraging their favourable benefit-harm profile, NOAC are now being evaluated for
345 new cardiovascular indications. In early stage CKD, although NOAC did not reduce major
346 cardiovascular events after acute coronary syndrome, the combination of low dose
347 rivaroxaban and aspirin was beneficial for this primary outcome in patients with stable
348 coronary or peripheral arterial disease in a single trial (30). A dose of rivaroxaban far below
349 that required for full anticoagulation may be particularly valuable in patients with advanced
350 CKD and ESKD, who also have an elevated bleeding risk. However, the exclusion of patients

351 with eGFR <15 mL/min/1.73 m² in this trial mandates the testing of this strategy in
352 randomized trials specifically in patients with advanced CKD and ESKD.

353 In contrast to the other recent systematic reviews identified by searching Medline to
354 February 2019, this systematic review demonstrates superiority of NOAC over VKA in
355 reducing the risk of stroke or systemic embolism in atrial fibrillation (31, 32). Furthermore,
356 the broad scope of clinical settings of the present review allows a more comprehensive
357 understanding of effects. Other strengths of this systematic review include inclusion of a
358 large number of participants, robust evaluation of efficacy and bleeding outcomes, and use of
359 the GRADE approach to assess the body of evidence. These strengths should be balanced
360 against its limitations, which are largely due to the limitations of the underlying literature.
361 These include exclusion of patients with dialysis-dependent ESKD and advanced non-
362 dialysis CKD, limited information on demographic characteristics of the CKD subgroup,
363 under-reporting of organ-specific bleeding data (especially gastrointestinal bleeding), lack of
364 individual patient data and suboptimal methodological quality of trials involving participants
365 with dialysis-dependent ESKD. Data on patients with CKD from trials of NOAC were
366 obtained exclusively from subgroup analyses of large trials. The current review was not
367 designed to assess differences between individual NOAC.

368 There are two ongoing trials comparing apixaban to VKA in participants with
369 hemodialysis-dependent ESKD and atrial fibrillation (RENAL-AF trial: NCT02942407 and
370 AXADIA trial: NCT02933697) (33). Another ongoing trial will compare VKA to no oral
371 anticoagulation in participants with hemodialysis-dependent ESKD and atrial fibrillation
372 (AVKDIAL: NCT02886962). Future trials should include not only participants with dialysis-
373 dependent ESKD but also those with creatinine clearance <25 mL/min. Since no trial has
374 evaluated a treatment strategy for comparing an OAC to no anticoagulation in atrial
375 fibrillation, future trials should compare NOAC to placebo.

376 In summary, this systematic review demonstrates that NOAC had a benefit-risk
377 profile superior to VKA in people with early stages of CKD, with significant reductions in
378 stroke or systemic embolism and hemorrhagic stroke in atrial fibrillation, and also reduction
379 in overall major bleeding risk in all trials combined that was not statistically significant,
380 suggesting that these individuals will derive similar or greater benefit than those who do not
381 have CKD. However, there is insufficient evidence to recommend widespread use of VKA or
382 NOAC to improve clinical outcomes in patients with advanced CKD and dialysis-dependent
383 ESKD. Adequately-powered randomized trials are required to evaluate the benefits and
384 harms of anticoagulant therapy in this patient population.

385

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415 All authors had full access to all of the data in the study and take responsibility for the
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446 **Reproducible Research Statement**

447 *Study protocol:* Available from PROSPERO

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449 *Statistical code:* Available from Dr Badve (sbadve@georgeinstitute.org.au)

450 *Data set:* Available from Dr Badve (sbadve@georgeinstitute.org.au)

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591

592 **FIGURE LEGENDS**

593 **Figure 1. PRISMA flow diagram showing selection of studies**

594 PRISMA flow diagram showing selection of studies.

595 Abbreviations: CAD, coronary artery disease; ESKD, end-stage kidney disease; PAD:
596 peripheral artery disease; RCT, randomized controlled trial; VTE, venous thromboembolism.

597 **Figure 2. Summary of treatment effects in trials involving participants with atrial**
598 **fibrillation**

599 Forest plot showing treatment effects in trials involving participants with atrial fibrillation on
600 stroke or systemic embolism, non-hemorrhagic stroke, hemorrhagic stroke, myocardial
601 infarction, all-cause death, and bleeding outcomes.

602 Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of
603 Recommendations Assessment, Development and Evaluation; NOAC, non-vitamin K oral
604 anticoagulants; OAC, oral anticoagulants; RR, risk ratio; VKA, vitamin K antagonists.

605 **Figure 3. Summary of treatment effects in trials involving participants with acute VTE**

606 Forest plot showing treatment effects in trials involving participants with acute VTE on
607 recurrent VTE or VTE-related death, all-cause death, and bleeding outcomes.

608 Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of
609 Recommendations Assessment, Development and Evaluation; LMWH, low molecular weight
610 heparin; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulants; RR, risk ratio;
611 VKA, vitamin K antagonists; VTE, venous thromboembolism.

612 **Figure 4. Summary of treatment effects on bleeding outcomes in all trials combined**

613 Forest plot showing treatment effects in all trials combined on major bleeding, major or non-
614 major clinically relevant bleeding, and intracranial hemorrhage.

615 * The number of events were not reported in one trial; hence generic inverse variance meta-
616 analysis was performed.

617 Abbreviations: ASA, aspirin; CI, confidence intervals; GRADE, Grading of
618 Recommendations Assessment, Development and Evaluation; LMWH, low molecular weight
619 heparin; NOAC, non-vitamin K oral anticoagulants; RR, risk ratio; VKA, vitamin K
620 antagonists.





