Annals of Internal Medicine REVIEW

Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease

A Systematic Review and Meta-analysis

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Background: Effects of oral anticoagulation in chronic kidney disease (CKD) are uncertain.

Purpose: To evaluate the benefits and harms of vitamin K antagonists (VKAs) and non–vitamin K oral anticoagulants (NOACs) in adults with CKD stages 3 to 5, including those with dialysis-dependent end-stage kidney disease (ESKD).

Data Sources: English-language searches of MEDLINE, EMBASE, and Cochrane databases (inception to February 2019); review bibliographies; and ClinicalTrials.gov (25 February 2019).

Study Selection: Randomized controlled trials evaluating VKAs or NOACs for any indication in patients with CKD that reported efficacy or bleeding outcomes.

Data Extraction: Two authors independently extracted data, assessed risk of bias, and rated certainty of evidence.

Data Synthesis: Forty-five trials involving 34 082 participants who received anticoagulation for atrial fibrillation (AF) (11 trials), venous thromboembolism (VTE) (11 trials), thromboprophylaxis (6 trials), prevention of dialysis access thrombosis (8 trials), and cardiovascular disease other than AF (9 trials) were included. All but the 8 trials involving patients with ESKD excluded participants with creatinine clearance less than 20 mL/min or estimated glomerular filtration rate less than 15 mL/min/1.73 m^2. In AF, compared with VKAs, NOACs reduced risks for stroke or systemic embolism (risk ratio [RR], 0.79 [95% CI, 0.66 to 0.93]; high-certainty evidence) and hemorrhagic stroke (RR, 0.48 [CI, 0.30 to 0.76]; moderate-certainty evidence). Compared with VKAs, the effects of NOACs on recurrent VTE or VTE-related death were uncertain (RR, 0.72 [CI, 0.44 to 1.17]; low-certainty evidence). In all trials combined, NOACs seemingly reduced major bleeding risk compared with VKAs (RR, 0.75 [CI, 0.56 to 1.01]; low-certainty evidence).

Limitation: Scant evidence for advanced CKD or ESKD; data mostly from subgroups of large trials.

Conclusion: In early-stage CKD, NOACs had a benefit–risk profile superior to that of VKAs. For advanced CKD or ESKD, there was insufficient evidence to establish benefits or harms of VKAs or NOACs.

Primary Funding Source: None. (PROSPERO: CRD42017079709)

Ann Intern Med. 2019;171:181-189. doi:10.7326/M19-0087 **Annals.org**
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This article was published at Annals.org on 16 July 2019.

Chronic kidney disease (CKD) is a prothrombotic state that is associated with substantially increased risks for arterial and venous thromboembolism (VTE) (1). In addition, atrial fibrillation (AF) is highly prevalent in this population, affecting 18% of patients with CKD (2) and 12% to 25% of those with dialysis-dependent end-stage kidney disease (ESKD) (3, 4). The presence of CKD increases risks for stroke or systemic embolism, congestive heart failure, myocardial infarction, and all-cause death among patients with AF (5, 6). Compared with persons with normal kidney function, risk for VTE is almost 2-fold greater among those with an estimated glomerular filtration rate (eGFR) between 15 and 59 mL/min/1.73 m^2 (7) and 3-fold greater in those with dialysis-dependent ESKD (8). Venous thromboembolism in ESKD is also associated with increased risks for bleeding and all-cause death (8). Other common clinical manifestations of increased thrombotic risk in CKD include acute coronary syndrome, stroke, peripheral artery occlusion, and dialysis access thrombosis (1, 9).

Anticoagulant therapy is an important intervention in the prevention of cardiovascular thrombotic and VTE events. Evidence-based treatment guidelines recommend anticoagulation for prevention of stroke in patients with nonvalvular AF and a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women (10, 11), for VTE in patients who have had major orthopedic or nonorthopedic surgery or hospitalized patients with acute illness (12), and for recurrent VTE in patients with VTE disease (13).

Patients with advanced CKD and ESKD who have AF are prescribed oral anticoagulant (OAC) therapy less frequently than those with normal kidney function (3, 14). Use of warfarin in patients receiving dialysis who have AF varies from 2% in Germany to 37% in Canada (3). The low rates of anticoagulant therapy use in advanced CKD and ESKD may be due to the increased risk for bleeding, uncertainty about potential benefits in this population, warfarin-associated calciphylaxis, and warfarin-related nephropathy (15, 16). In CKD, risk for major bleeding increases linearly with decreasing eGFR

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(17). In patients with dialysis-dependent ESKD, bleeding risk is further increased with incremental use of antithrombotic agents, such as warfarin and antiplatelets (18). The exclusion of patients with CKD from nearly 90% of trials evaluating anticoagulants has contributed to uncertainty about the role of anticoagulant therapy in CKD (19). The aim of the current systematic review was to evaluate the benefits and harms of OAC therapy for a range of clinical indications in patients with CKD stages 3 to 5, including those receiving dialysis.

METHODS

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (20). The protocol for this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 4 December 2017 (www.crd.york.ac.uk/prospero/display_record.php?RecordID=79709).

Data Sources and Searches

Relevant studies were identified by performing English-language searches of MEDLINE (inception to February 2019), EMBASE (inception to February 2019), and the Cochrane Central Register of Controlled Trials (January 2019) using the search strategy described in Supplement Table 1 (available at Annals.org). In addition, reference lists of relevant systematic reviews were searched. ClinicalTrials.gov was searched (25 February 2019) using the following terms: *chronic kidney disease*, *renal dialysis*, *atrial fibrillation*, and *anticoagulation*.

Study Selection and Outcomes

Studies were eligible for inclusion if they were randomized controlled trials; included adults with CKD (creatinine clearance [CrCl] <60 mL/min or eGFR <60 mL/min/1.73 m^2) or dialysis-dependent ESKD; compared a vitamin K antagonist (VKA) or non–vitamin K oral anticoagulant (NOAC) with another OAC, placebo, low-molecular-weight heparin (LMWH), aspirin, or no study medication; and reported efficacy, bleeding outcomes, or both. All indications for anticoagulation were eligible for inclusion. Two authors (J.T.H. and B.L.N.) independently reviewed each title and abstract and reviewed the full texts of shortlisted studies. Disagreements about study eligibility were resolved via consultation with 2 other authors (V.P. and S.V.B.). If multiple secondary publications of the same trial were identified, the one with the most complete data was used and additional data from secondary sources were extracted. Incomplete or unpublished trial data were requested from the investigators. The outcomes of this systematic review were stroke or systemic embolism in AF, nonhemorrhagic stroke, hemorrhagic stroke, all-cause or cardiovascular death, VTE or VTE-related death, myocardial infarction, composite cardiovascular events (cardiovascular or all-cause death, nonfatal myocardial infarction, or stroke), dialysis access thrombotic events, major bleeding, major or nonmajor clinically relevant bleeding, and intracranial hemorrhage.

Data Extraction and Quality Assessment

Data were extracted independently by 2 authors (J.T.H. and B.L.N.), and disagreements were resolved via consultation with 2 other authors (V.P. and S.V.B.). A standardized form was used to extract the following data: patient demographic characteristics, study design and conduct, indication for anticoagulation, drug dose, nonrandomized co-interventions, follow-up duration, and outcome and bleeding events. The methodological quality of each included study was assessed at the outcome level independently by 2 authors (J.T.H. and B.L.N.) using the risk-of-bias assessment tool developed by the Cochrane Bias Methods Group (21).

Data Synthesis and Analysis

The results were expressed as risk ratios (RRs) with 95% CIs. A treatment group continuity correction was used if there were 0 events in 1 group in a trial. For trials with 3 groups comparing 2 different doses of NOACs with VKAs, data from only the high-dose NOAC groups were used for the main analyses to avoid potentially uninterpretable results caused by merging of the benefits and harms of different doses; this was similar to the method used in a previous meta-analysis (22). Additional analyses were conducted by combining data from both high- and low-dose groups of NOACs. Summary estimates were obtained with a random-effects model using the Paule–Mandel method (23). If data on the number of events and participants were not reported, a generic inverse variance meta-analysis was performed by calculating the log of the hazard ratio and its SE from the reported hazard ratio and its CI. Statistical heterogeneity across studies was estimated using the I^2 test, with values of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively (24). Statistical analyses were performed using Stata/MP, version 15.1 (StataCorp), and R, version 3.5.3 (R Foundation for Statistical Computing).

Using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, 3 authors (J.T.H., B.L.N., and L.P.C.) summarized the certainty of the evidence based on the following domains: within-study risk of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, and imprecision of results. Disagreements were resolved via consultation with 2 other authors (M.J. and S.V.B.) (25). Because all meta-analyses involved fewer than 10 trials, small-study effects (publication bias) were not assessed and publication bias was not included in ratings of certainty of evidence (26).

Role of the Funding Source

This study received no funding.

RESULTS

Selection and Description of Studies

Forty-five trials that involved 34 082 participants and evaluated VKAs or NOACs were included in the systematic review (median sample size, 276 participants [range, 10 to 4168 participants]; median follow-up, 12 months [range, 1 to 36 months]) (Figure 1). Of

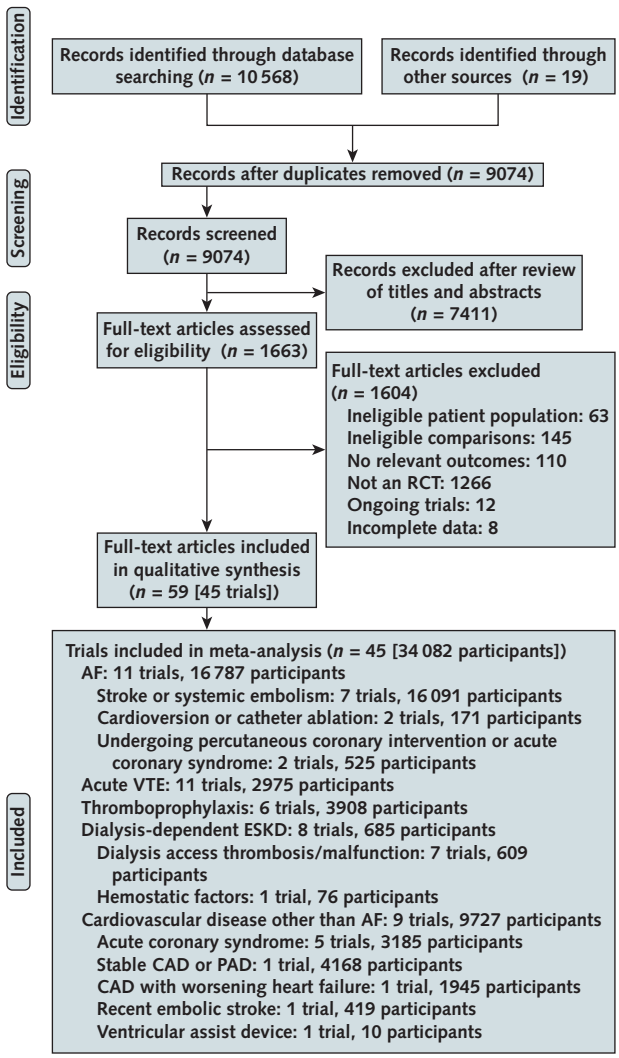
these trials, 8 included 685 participants with dialysis-dependent ESKD (median sample size, 91 participants [range, 18 to 174 participants]; median follow-up, 12 months [range, 3 to 36 months]), with 7 evaluating VKAs for prevention of dialysis access thrombosis and 1 evaluating the effect of VKAs on hemostatic factors. The remaining 37 trials included 33 397 participants with CKD who were not receiving dialysis (defined as CrCl of 20 to 60 mL/min, eGFR of 15 to 60 mL/min/1.73 m^2, or serum creatinine level ≥1.5 mg/dL; median sample size, 380 participants [range, 10 to 4168 participants]; median follow-up, 12 months [range, 1 to 36 months]). Eleven trials included 16 787 participants with AF (median sample size, 516 participants [range, 12 to 4074 participants]; median follow-up, 14 months [range, 3 to 34 months]). Eleven trials involved 2975 participants with acute VTE (median sample size, 162 participants [range, 72 to 657 participants]; median follow-up, 12 months [range, 6 to 36 months]). Six trials included 3908 medically ill or perioperative participants requiring anticoagulation for thromboprophylaxis (median sample size, 380 participants [range, 42 to 2197 participants]; median follow-up, 2 months [range, 1 to 6 months]). The remaining 9 trials involved 9727 participants with cardiovascular disease other than AF (median sample size, 331 participants [range, 72 to 4168 participants]; median follow-up, 9 months [range, 1 to 36 months]). Data from the 37 trials involving patients with nondialysis CKD were obtained exclusively from CKD subgroup analyses of large trials. Details of the included trials are provided in Supplement Table 2 (available at Annals.org).

Non–vitamin K oral anticoagulants were compared with VKAs (15 trials, 16 495 participants), placebo (10 trials, 11 683 participants), LMWH (5 trials, 1720 participants), and aspirin (4 trials, 2690 participants). Vitamin K antagonists were compared with placebo (4 trials, 408 participants), no study medication (4 trials, 277 participants), LMWH (2 trials, 293 participants), and aspirin (1 trial, 516 participants). The interventional agents were rivaroxaban (13 trials), dabigatran (8 trials), apixaban (7 trials), edoxaban (5 trials), betrixaban (1 trial), fixed-dose (1 or 2 mg) or low-intensity (target international normalized ratio, 1.4 to 1.9) warfarin (6 trials), and adjusted-dose (target international normalized ratio, 1.5 to 2.5 or 2 to 3) warfarin or acenocoumarol (5 trials). The funding source was not reported in 4 trials. Thirty-nine of the remaining 41 (95%) trials were sponsored by pharmaceutical companies.

Risk of Bias

Risk-of-bias assessment at the outcome level is summarized in Supplement Table 3 (available at Annals.org). Random sequence generation and allocation concealment were reported using low-risk methods in 80% of trials reporting stroke or systemic embolism and major bleeding in participants with AF. Random sequence generation and allocation concealment were reported using low-risk methods in all trials reporting VTE or VTE-related death in participants with acute VTE or those requiring thromboprophylaxis, and major adverse cardiovascular events in participants with cardiovascular disease other than AF. Trials that involved participants with dialysis-dependent ESKD and reported hemodialysis access thrombosis or malfunction, all-cause death, and major bleeding generally had high or unclear risk of bias in the domains of random sequence generation and allocation concealment.

Figure 1. Evidence search and selection.



AF = atrial fibrillation; CAD = coronary artery disease; ESKD = end-stage kidney disease; PAD = peripheral artery disease; RCT = randomized controlled trial; VTE = venous thromboembolism.

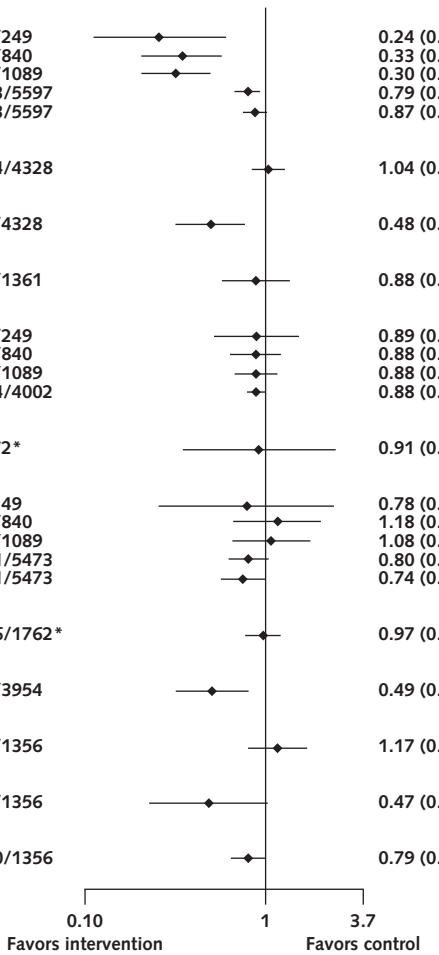
Effects of Interventions

Atrial Fibrillation

None of the 11 trials involving participants with AF included those with dialysis-dependent ESKD. Anticoagulation was used for prevention of stroke or systemic embolism in 7 trials, acute coronary syndrome or percutaneous coronary intervention in 2 trials, and periprocedural anticoagulation in participants undergoing cardioversion or catheter ablation in 1 trial each. No trial compared an OAC with no anticoagulation in patients

Figure 2. Treatment effects in trials involving participants with atrial fibrillation on stroke or systemic embolism, nonhemorrhagic stroke, hemorrhagic stroke, myocardial infarction, all-cause death, and bleeding outcomes.

Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Control	RR (95% CI)	I^2, %	GRADE Certainty of Evidence
Stroke or systemic embolism						
VKA vs. ASA	1	6/267	23/249	0.24 (0.10–0.59)	NA	Very low
NOAC vs. ASA	1	17/857	51/840	0.33 (0.19–0.56)	NA	Very low
Any OAC vs. ASA	2	23/1124	74/1089	0.30 (0.19–0.48)	0	Moderate
High-dose NOAC vs. VKA	5	227/5735	283/5597	0.79 (0.66–0.93)	0	High
High- and low-dose NOAC vs. VKA	5	389/8265	283/5597	0.87 (0.74–1.02)	8	High
Nonhemorrhagic stroke						
High-dose NOAC vs. VKA	3	151/4362	144/4328	1.04 (0.83–1.30)	0	Moderate
Hemorrhagic stroke						
High-dose NOAC vs. VKA	3	27/4362	57/4328	0.48 (0.30–0.76)	0	Moderate
Myocardial infarction						
High-dose NOAC vs. VKA	1	34/1379	38/1361	0.88 (0.56–1.39)	NA	Very low
All-cause death						
VKA vs. ASA	1	21/267	22/249	0.89 (0.50–1.58)	NA	Very low
NOAC vs. ASA	1	59/857	66/840	0.88 (0.62–1.23)	NA	Very low
Any OAC vs. ASA	2	80/1124	88/1089	0.88 (0.66–1.18)	0	Low
High-dose NOAC vs. VKA	3	598/4113	664/4002	0.88 (0.78–0.99)	22	Moderate
Death or ischemic event after PCI/ACS						
High-dose NOAC vs. VKA	2	13/73*	8/72*	0.91 (0.33–2.56)	75	Very low
Major bleeding						
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
Any OAC vs. ASA	2	29/1124	26/1089	1.08 (0.64–1.83)	0	Low
High-dose NOAC vs. VKA	5	402/5600	491/5473	0.80 (0.61–1.04)	75	Low
High- and low-dose NOAC vs. VKA	5	574/8121	491/5473	0.74 (0.55–1.00)	83	Low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	5	401/1792*	396/1762*	0.97 (0.76–1.23)	28	Low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate
Gastrointestinal bleeding						
High-dose NOAC vs. VKA	1	51/1372	43/1356	1.17 (0.79–1.75)	NA	Very low
Fatal bleeding						
High-dose NOAC vs. VKA	1	9/1372	19/1356	0.47 (0.21–1.03)	NA	Very low
Minor bleeding						
High-dose NOAC vs. VKA	1	120/1372	150/1356	0.79 (0.63–0.99)	NA	Very low



ACS = acute coronary syndrome; ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NA = not applicable; NOAC = non–vitamin K oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; RR = risk ratio; VKA = vitamin K antagonist.
* The number of events was not reported in 1 trial; hence, generic inverse variance meta-analysis was performed.

with AF. Compared with VKAs, high-dose NOACs reduced risks for stroke or systemic embolism (RR, 0.79 [95% CI, 0.66 to 0.93]), hemorrhagic stroke (RR, 0.48 [CI, 0.30 to 0.76]), and all-cause death (RR, 0.88 [CI, 0.78 to 0.99]) and had no clear effect on nonhemorrhagic stroke (RR, 1.04 [CI, 0.83 to 1.30]), although CIs were wide (**Figure 2**; **Supplement Figures 1** to **4**, available at Annals.org). Compared with aspirin, any OAC (VKA or NOAC) reduced risk for stroke or systemic embolism (RR, 0.30 [CI, 0.19 to 0.48]). High-dose NOACs reduced risk for major bleeding compared with VKAs (RR, 0.80 [CI, 0.61 to 1.04]), although this finding was not statistically significant (**Supplement Figure 5**, available at Annals.org). The effect of high-dose NOACs compared with VKAs on risk for major or nonmajor clinically relevant bleeding was uncertain (RR, 0.97 [CI, 0.76 to 1.23]) (**Supplement Figure 6**, available at Annals.org). Additional analyses that included both high and low NOAC doses showed that, compared with VKAs, NOACs reduced risks for stroke or systemic embolism (RR, 0.87 [CI, 0.74 to 1.02]) and major bleeding (RR, 0.74 [CI, 0.55 to 1.00]), although these findings were not statistically significant because the upper limits of their CIs crossed 1 (**Supplement Figures 1** and **5**).

Acute VTE

Non–vitamin K oral anticoagulants reduced risk for recurrent VTE or VTE-related death compared with placebo (RR, 0.14 [CI, 0.04 to 0.48]) but had an uncertain effect compared with VKAs (RR, 0.72 [CI, 0.44 to 1.17]) (**Figure 3**; **Supplement Figure 7**, available at Annals.org). There was no difference in risk for recurrent VTE or VTE-related death between any OAC and LMWH

(RR, 2.10 [CI, 0.72 to 6.15]) (Supplement Figure 7). None of the NOAC trials reported data on all-cause death. There was no difference in risk for all-cause death between VKAs and LMWH (RR, 1.01 [CI, 0.79 to 1.31]). Risk for major bleeding did not differ between NOACs and VKAs (RR, 0.54 [CI, 0.21 to 1.43]), VKAs and LMWH (RR, 1.03 [CI, 0.43 to 2.51]), and any OAC and LMWH (RR, 1.24 [CI, 0.54 to 2.88]) (Supplement Figure 8, available at Annals.org). There was no difference in risk for major or nonmajor clinically relevant bleeding between NOACs and VKAs (RR, 0.84 [CI, 0.63 to 1.11]) (Supplement Figure 9, available at Annals.org).

Anticoagulation Required for Thromboprophylaxis

We found no clear differences between NOACs and LMWH in risks for VTE or VTE-related death (RR, 0.85 [CI, 0.40 to 1.83]), major bleeding (RR, 3.72 [CI, 0.79 to 17.54]), and major or nonmajor clinically relevant bleeding (RR, 1.09 [CI, 0.64 to 1.85]) (Supplement Figure 10, available at Annals.org). Risk for VTE or VTE-related death did not differ between NOACs and placebo (RR, 0.98 [CI, 0.53 to 1.82]).

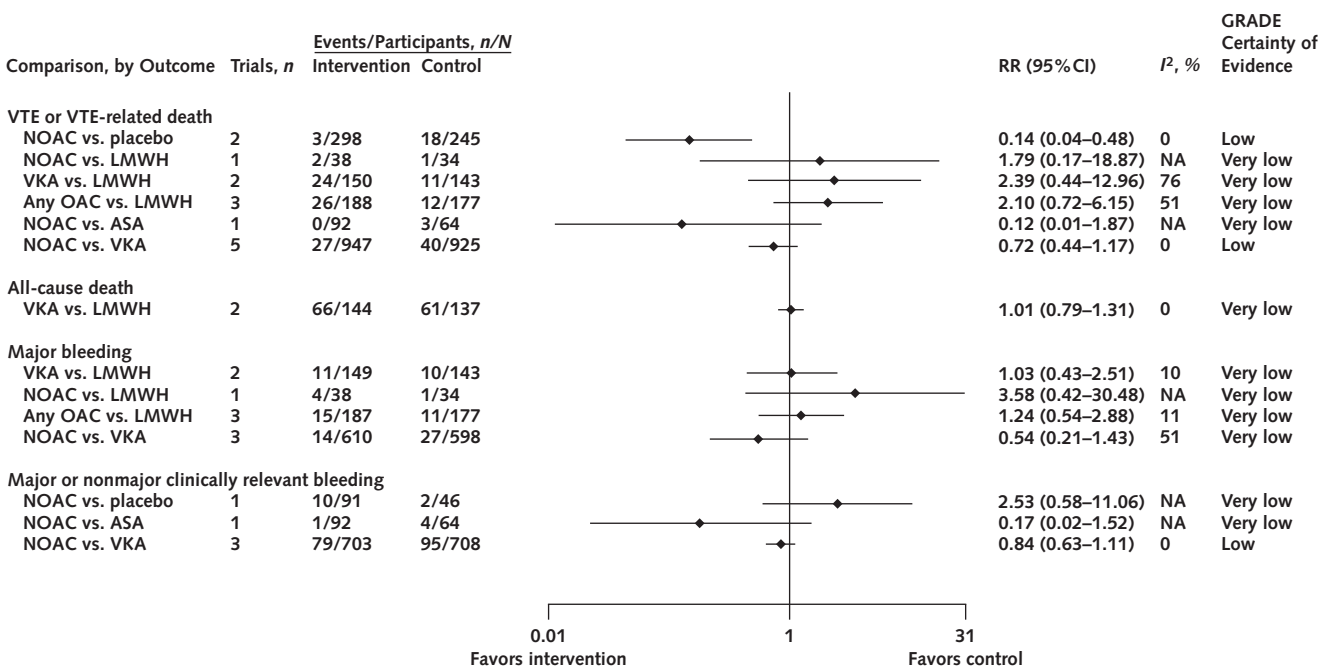
Dialysis-Dependent ESKD

None of the 8 trials involving participants with dialysis-dependent ESKD evaluated NOACs (Supplement Figure 11, available at Annals.org). There was no clear difference in risk for dialysis access thrombosis or catheter malfunction between fixed-dose or low-intensity warfarin and placebo or no study medication (RR, 1.04 [CI, 0.85 to 1.28]) (Supplement Figure 12, available at Annals.org). Compared with no study medication, adjusted-dose warfarin reduced risk for dialysis access thrombosis or catheter malfunction (RR, 0.28 [CI, 0.16 to 0.47]) (Supplement Figure 12). The effects of fixed-dose or low-intensity warfarin compared with placebo or no study medication on all-cause death (RR, 0.65 [CI, 0.34 to 1.24]) and major bleeding (RR, 2.66 [CI, 0.39 to 18.19]) were uncertain (Supplement Figures 13 and 14, available at Annals.org).

Cardiovascular Disease Other Than AF

Compared with placebo, NOACs reduced risk for major adverse cardiovascular events (defined as a composite of cardiovascular or all-cause death, nonfatal myocardial infarction, or stroke), although this finding was not statistically significant because the upper limit of the CI crossed 1.0 (RR, 0.88 [CI, 0.75 to 1.04]) (Supplement Figures 15 and 16, available at Annals.org). In a single trial involving 4168 participants with stable coronary or peripheral artery disease, risk for major adverse cardiovascular events with low-dose NOACs was lower than with placebo (RR, 0.77 [CI, 0.62 to 0.95]). Compared with placebo, NOACs significantly increased risk for major bleeding (RR, 2.18 [CI, 1.10 to 4.32]) (Supplement Figure 17, available at Annals.org). Additional analyses that included trials comparing only low-dose NOACs with placebo showed that NOACs re-

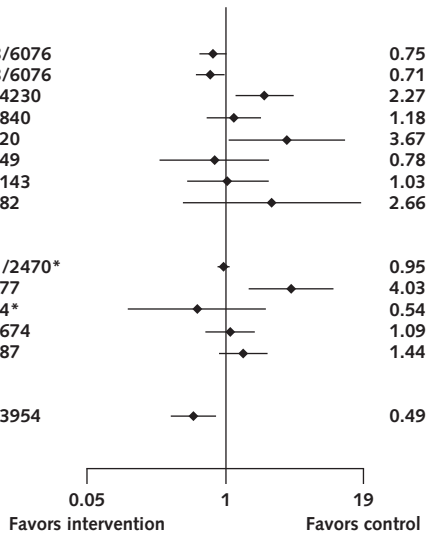
Figure 3. Treatment effects in trials involving participants with acute VTE on recurrent VTE or VTE-related death, all-cause death, and bleeding outcomes.



ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low-molecular-weight heparin; NA = not applicable; NOAC = non–vitamin K oral anticoagulant; OAC = oral anticoagulant; RR = risk ratio; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Figure 4. Treatment effects in all trials combined on major bleeding, major or nonmajor clinically relevant bleeding, and intracranial hemorrhage.

Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Control	RR (95% CI)	I^2, %	GRADE Certainty of Evidence
Major bleeding						
High-dose NOAC vs. VKA	9	416/6215	518/6076	0.75 (0.56–1.01)	67	Low
High- and low-dose NOAC vs. VKA	9	588/8736	518/6076	0.71 (0.52–0.96)	76	Low
NOAC vs. placebo	4	126/4480	68/4230	2.27 (1.21–4.26)	50	Low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
NOAC vs. LMWH	4	12/443	3/420	3.67 (1.05–12.89)	0	Very low
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
VKA vs. LMWH	2	11/149	10/143	1.03 (0.43–2.51)	10	Very low
Low-intensity VKA vs. placebo	2	16/184	7/182	2.66 (0.39–18.19)	48	Very low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	8	480/2495*	491/2470*	0.95 (0.83–1.07)	4	Low
NOAC vs. placebo	3	48/397	5/177	4.03 (1.62–10.03)	0	Very low
NOAC vs. ASA	2	1/92*	4/64*	0.54 (0.12–2.36)	47	Very low
NOAC vs. LMWH	3	27/640	26/674	1.09 (0.64–1.85)	0	Very low
Low-intensity VKA vs. placebo	1	26/87	18/87	1.44 (0.86–2.44)	NA	Very low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate



ASA = aspirin; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low-molecular-weight heparin; NA = not applicable; NOAC = non-vitamin K oral anticoagulant; RR = risk ratio; VKA = vitamin K antagonist.
* The number of events was not reported in 1 trial; hence, generic inverse variance meta-analysis was performed.

duced risk for major adverse cardiovascular events (RR, 0.89 [CI, 0.77 to 1.04]), although the upper limit of the CI crossed 1.0 and no difference was seen in major bleeding risk (RR, 2.29 [CI, 0.57 to 9.18]) (Supplement Figures 16 and 17).

Bleeding Outcomes From All Trials Combined

Compared with VKAs, high-dose NOACs reduced risk for major bleeding (RR, 0.75 [CI, 0.56 to 1.01]), although this finding was not statistically significant because the upper limit of the CI crossed 1.0 (Figure 4; Supplement Figure 18, available at Annals.org). There was no significant interaction of major bleeding risk by indication for anticoagulation (P = 0.84). No clear difference was seen in risk for major or nonmajor clinically relevant bleeding between the NOAC and VKA groups (RR, 0.95 [CI, 0.83 to 1.07]) (Supplement Figure 19, available at Annals.org). High-dose NOACs reduced risk for intracranial hemorrhage compared with VKAs (RR, 0.49 [CI, 0.30 to 0.80]) (Supplement Figure 20, available at Annals.org). Compared with placebo, NOACs increased risks for major bleeding (RR, 2.27 [CI, 1.21 to 4.26]) and major or nonmajor clinically relevant bleeding (RR, 4.03 [CI, 1.62 to 10.03]). Compared with LMWH, NOACs increased risk for major bleeding (RR, 3.67 [CI, 1.05 to 12.89]) but not major or nonmajor clinically relevant bleeding (RR, 1.09 [CI, 0.64 to 1.85]). An additional analysis that included high and low NOAC doses showed a clear reduction in major bleeding risk with NOACs compared with VKAs (RR, 0.71 [CI, 0.52 to 0.96]) (Supplement Figure 18).

DISCUSSION

This review provides a comprehensive overview of available data describing the effects of anticoagulation for patients with CKD and a range of comorbidities or other risk factors. It identifies clear findings that can be used to guide treatment but also several areas where data are inadequate and further studies are urgently required. A key finding was that in patients with AF and early-stage CKD, NOACs were superior to VKAs, with relative risk reductions of 21% for stroke or systemic embolism, 52% for hemorrhagic stroke, and 51% for intracranial hemorrhage. However, NOACs did not reduce risk for nonhemorrhagic stroke in patients with AF, and although they reduced risk for major bleeding, this finding was not statistically significant. Compared with placebo, NOACs reduced risk for recurrent VTE or VTE-related death in patients with CKD receiving acute VTE treatment; however, compared with VKAs, this effect was uncertain. These data suggest that NOACs may be a reasonable treatment option for patients with CKD who develop VTE, but further data would be helpful. In all trials combined, compared with VKAs, high-dose NOACs reduced risk for major bleeding, although this result was not statistically significant. In contrast, for patients with advanced CKD (CrCl <25 mL/min), including dialysis-dependent ESKD, no data were available on the effects of VKAs or NOACs on prevention of stroke or systemic embolism in patients with AF or on VTE and VTE-related death.

Although rates of ischemic and hemorrhagic stroke and intracranial hemorrhage were not reported in all trials involving participants with AF, the benefit of reduced stroke or systemic embolism with NOACs may have been driven mainly by a reduction in hemorrhagic stroke. A similar finding was reported in a previous systematic review of 4 randomized trials comparing NOACs with VKAs (22). The excess burden of AF, cardiovascular thrombotic events, and VTE in patients with advanced CKD contributes to their poor survival (5, 6, 8). Given the greater rates of arterial thromboembolism and VTE in patients with advanced CKD than in patients with normal kidney function, the absolute risk reduction with anticoagulation in this population may be greater. However, this systematic review highlights the absence of evidence in patients with advanced CKD and ESKD, specifically for prevention of stroke or systemic embolism in AF and for recurrent VTE or VTE-related death. The potential benefit of anticoagulation needs to be weighed against the risk for bleeding in this population. The rates of major bleeding with apixaban and warfarin in patients with hemodialysis-dependent ESKD (19.7 and 22.9 per 100 person-years, respectively) (27) are substantially greater than in those with normal or mildly decreased kidney function (2.13 and 3.09 per 100 person-years, respectively) (28). Furthermore, 60% to 75% of patients with ESKD discontinue OAC therapy within 1 year, possibly because of bleeding (27, 29). Despite the absence of specific evidence, current guidelines suggest warfarin with a target international normalized ratio of 2.0 to 3.0 or apixaban (class IIa recommendation, moderate-quality evidence) (11) and a time in the therapeutic range greater than 65% to 70% (ungraded consensus-based statements) (10) in patients with CrCl less than 15 mL/min or those with dialysis-dependent ESKD and a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women (11). The lack of evidence-based guidelines strongly suggests that adequately powered randomized trials are required to address the unmet need in this population.

Because of their favorable benefit–risk profile, NOACs are being evaluated for new cardiovascular indications. In early-stage CKD, although NOACs did not reduce major cardiovascular events after acute coronary syndrome, the combination of low-dose rivaroxaban and aspirin was beneficial for this primary outcome in patients with stable coronary or peripheral artery disease in a single trial (30). A dose of rivaroxaban far below that required for full anticoagulation may be particularly valuable in patients with advanced CKD and ESKD who also have elevated bleeding risk. However, because patients with eGFR less than 15 mL/min/1.73 m^2 were excluded from this trial, this strategy will need to be tested in randomized trials, specifically in patients with advanced CKD and ESKD.

In contrast to the other recent systematic reviews identified in our MEDLINE search, this review demonstrates the superiority of NOACs over VKAs in reducing risk for stroke or systemic embolism in AF (31, 32). Furthermore, the broad scope of clinical settings in this review allows a more comprehensive understanding of effects. Other strengths were the inclusion of a large number of participants, the robust evaluation of efficacy and bleeding outcomes, and the use of the GRADE approach to assess the body of evidence. These strengths should be weighed against the review's limitations, which were largely due to the limitations of the underlying literature. These include exclusion of patients with dialysis-dependent ESKD and advanced nondialysis CKD, limited information on demographic characteristics of the CKD subgroup, underreporting of organ-specific bleeding data (especially gastrointestinal bleeding), lack of individual-patient data, and suboptimal methodological quality of trials involving participants with dialysis-dependent ESKD. Data on patients with CKD from trials of NOACs were obtained exclusively from subgroup analyses of large trials. The current review was not designed to assess differences among NOACs.

Two ongoing trials (the RENAL-AF [RENal Hemodialysis Patients ALlocated Apixaban Versus Warfarin in Atrial Fibrillation] [ClinicalTrials.gov: NCT02942407] and AXADIA [ClinicalTrials.gov: NCT02933697] trials) are comparing apixaban with VKAs in participants with hemodialysis-dependent ESKD and AF (33). Another ongoing trial (AVKDIAL [ClinicalTrials.gov: NCT02886962]) will compare VKAs with no oral anticoagulation in participants with hemodialysis-dependent ESKD and AF. Future trials should include not only participants with dialysis-dependent ESKD but also those with CrCl less than 25 mL/min. Because no trial has evaluated a treatment strategy for comparing an OAC with no anticoagulation in AF, future trials should compare NOACs with placebo.

In summary, this systematic review demonstrates that NOACs had a benefit–risk profile superior to that of VKAs in patients with early-stage CKD, with significant reductions in stroke or systemic embolism and hemorrhagic stroke in AF. This review also showed a reduction in overall major bleeding risk that was not statistically significant in all trials combined, suggesting that these patients will derive similar or greater benefit compared with those who do not have CKD. However, evidence is insufficient to recommend widespread use of VKAs or NOACs to improve clinical outcomes in patients with advanced CKD and dialysis-dependent ESKD. Adequately powered randomized trials are required to evaluate the benefits and harms of anticoagulant therapy in this patient population.

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Acknowledgment: The authors thank Professor John H. Alexander of Duke University School of Medicine for providing unpublished trial data from 1 trial for meta-analyses.

Financial Support: Dr. Ha is supported by a University Postgraduate Award from UNSW Sydney. Dr. Neuen is supported by a John Chalmers PhD Scholarship from The George Institute for Global Health, a University Postgraduate Award from UNSW Sydney, and an Oxford Australia Clarendon Scholarship from Oxford University. Dr. Jun is supported by a Scientia Fellowship from UNSW Sydney. Dr. Toyama is supported by the Japan Society for the Promotion of Science Program for Fostering Globally Talented Researchers. Dr. Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship. Dr. Palmer is supported by a Rutherford Discovery Fellowship from the Royal Society of New Zealand. Dr. Johnson is supported by an Australian Government National Health and Medical Research Council Practitioner Fellowship. Dr. Badve is supported by a John Chalmers Clinical Research Fellowship with the support of Servier from The George Institute for Global Health. These organizations and agencies had no role in the design or conduct of the study, analysis or interpretation of the data, review or approval of the manuscript, or the decision to submit the manuscript for publication.

Disclosures: Dr. Neuen has received travel support from Janssen outside the submitted work. Dr. Jun reports grants from AstraZeneca outside the submitted work. Dr. Gallagher reports personal fees from Amgen and other support from Bayer outside the submitted work. Dr. Jardine reports grants from Baxter, Amgen, Eli Lilly, and MSD and personal fees from Baxter, CSL, Akebia, Boehringer Ingelheim, Vifor Pharma, and Janssen outside the submitted work. All consultancy, honoraria, or travel support is paid to her employing institution. Dr. Mark reports grants from Boehringer Ingelheim; personal fees from Vifor Pharma, AstraZeneca, Pharmacosmos, Janssen, Novartis, Pfizer, and Bristol-Myers Squibb; and nonfinancial support from Pharmacosmos outside the submitted work. Dr. Wheeler reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mitsubishi, Mundipharma, Napp, Ono Pharmaceutical, Vifor Pharma, and MSD outside the submitted work. Dr. Jha reports grants from Baxter Healthcare, GSK, and Biocon and personal fees from NephroPlus outside the submitted work. Dr. Freedman reports grants from Bayer and BMS-Pfizer; personal fees from Bayer, BMS-Pfizer, and Daiichi Sankyo; and nonfinancial support from Bayer, BMS-Pfizer, Daiichi Sankyo, and AliveCor outside the submitted work. Dr. Johnson reports grants from Baxter Healthcare, Fresenius Medical Care, and the National Health and Medical Research Council of Australia; personal fees from Baxter Healthcare, Fresenius Medical Care, and AstraZeneca; and other support from Amgen during the conduct of the study. Dr. Perkovic reports personal fees from Retrophin, Janssen, Merck, Servier, AbbVie, Astellas, AstraZeneca, Bayer, Baxter, BMS, Boehringer Ingelheim, Dimerix, DURECT, Eli Lilly, Gilead, GSK, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Sanofi, Vifor Pharma, and Tricida outside the submitted work. Dr. Badve reports grants from the National Health and Medical Research Council of Australia, personal fees from Bayer AG and Amgen Australia, and nonfinancial support from Bayer AG during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-0087.

Reproducible Research Statement: *Study protocol:* Available at www.crd.york.ac.uk/prospero/display_record.php?RecordID=79709. *Statistical code and data set:* Available from Dr. Badve (e-mail, sbadve@georgeinstitute.org.au).

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