Stroke

CLINICAL TRIAL

Anticoagulation Timing in Acute Stroke With Atrial Fibrillation According to Chronic Kidney Disease: The OPTIMAS Trial

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BACKGROUND: Patients with chronic kidney disease (CKD) are at increased risk of ischemic stroke (IS) and intracerebral hemorrhage, so the safety and efficacy of early direct oral anticoagulant (DOAC) initiation in those with CKD are of clinical relevance.

METHODS: OPTIMAS (Optimal Timing of Anticoagulation After Acute Ischemic Stroke With Atrial Fibrillation) was a multicenter, randomized, parallel-group, open-label trial with blinded outcome assessment, recruiting patients with IS and atrial fibrillation from 100 UK hospitals between 2019 and 2024. Participants were randomized 1:1, stratified by stroke severity, to early (within 4 days of onset) or delayed (at days 7–14) DOAC initiation. CKD was defined as a past medical history of known CKD, collected according to trial protocol as part of the case report form. For this prespecified subgroup analysis, the trial cohorts were classified according to the presence or absence of CKD. Whether CKD modified the treatment effect of early DOAC initiation was determined by fitting mixed effects logistic regression models with interaction terms between CKD and treatment group. The primary outcome was a composite outcome of recurrent IS, symptomatic intracranial hemorrhage, and systemic arterial embolism. Key secondary outcomes included the individual components of the primary outcome and all-cause mortality.

RESULTS: We included 3601 patients (mean age, 78±10 years; 45% female), 543 with CKD. There were 116 primary outcome events: 97 (3.2%) in the normal kidney function group and 19 (3.5%) in the CKD group. There was no difference between early and delayed DOAC initiation for the primary outcome in either the normal kidney function group (odds ratio, 1.01 [95% CI, 0.67–1.51]) or the CKD group (odds ratio, 0.90 [95% CI, 0.36–2.25]; $P_{interaction}$=0.822). Similarly, for the secondary outcomes, we detected no modification of the treatment effect according to CKD ($P_{interaction}$ values of 0.637, 0.386, and 0.107 for IS, symptomatic intracranial hemorrhage, and all-cause mortality, respectively).

CONCLUSIONS: Our findings suggest that CKD does not modify the effects of early versus delayed DOAC initiation after acute IS. Based on these results, early DOAC initiation should not be withheld in patients with CKD.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ brain ischemia ■ cerebral hemorrhage ■ ischemic stroke ■ renal insufficiency, chronic

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For Sources of Funding and Disclosures, see page 1978.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CKD	chronic kidney disease
DOAC	direct oral anticoagulant
eGFR	estimated glomerular filtration rate
IS	ischemic stroke
sICH	symptomatic intracranial hemorrhage

Until recently, there has been little high-quality evidence to guide clinicians on the most beneficial time to start anticoagulation after acute stroke in patients with atrial fibrillation (AF). The OPTIMAS trial (Optimal Timing of Anticoagulation After Acute Ischemic Stroke With Atrial Fibrillation)[1] demonstrated that early initiation (within 4 days of stroke onset) of direct oral anticoagulants (DOACs) was safe and noninferior to delayed initiation (7–14 days), regardless of stroke severity at baseline, reperfusion therapies, and prior anticoagulation. This is built on other recent evidence from the TIMING[2] (Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation) and ELAN[3] (Early Versus Later Anticoagulation for Stroke With Atrial Fibrillation) trials, which indicated that early anticoagulation with a DOAC shortly after stroke is safe, and showed a lower proportion of recurrent composite primary outcome events in the early group, without sufficient precision for statistical significance.

Populations with chronic kidney disease (CKD) are at high risk of both ischemic stroke (IS)[4,5] and intracerebral hemorrhage.[6] Therefore, decisions on the initiation of anticoagulation after acute stroke in this high-risk group are even more finely balanced. Reduced estimated glomerular filtration rate (eGFR)[7,8] and albuminuria[9] have been associated with the risk of symptomatic intracranial hemorrhage (sICH) after thrombolysis in observational studies. Whether patients with CKD are at increased risk of early recurrent IS, or sICH after early anticoagulation, is unknown. A recent Global Burden of Diseases report found that the number of disability-adjusted life-years attributed to impaired kidney function as a risk factor for stroke has been increasing from 1990 to 2019,[10] and further study of this relationship should be a research priority. Clinical concerns about increased bleeding risk for those with CKD taking DOACs are supported by the results a subanalysis of the ARISTOTLE trial (Apixaban Versus Warfarin in Patients with Atrial Fibrillation),[11] which showed significantly higher rates of major bleeding, including intracranial hemorrhage, in those with eGFR <50. Indeed, of the 4 commonly used DOACs, only apixaban has marketing authorization in the United Kingdom when calculated creatinine clearance is below 30 mL/min, and none has a license for those with kidney failure (eGFR <15). Although the Food and Drug Administration in the United States has issued a product label for apixaban use at any level of kidney function, including dialysis, this is based on pharmacokinetic data only as those with creatinine clearance <25 were excluded from all the major DOAC trials.[12] Consequently, uptake of DOAC use in those with advanced CKD has been relatively low.[13]

It remains unknown whether there is an increased risk of sICH or hemorrhagic transformation when anticoagulating those with CKD soon after IS. We performed a prespecified subgroup analysis of the OPTIMAS trial, investigating the safety and efficacy of the trial intervention for those participants with a history of CKD. In addition, we investigated whether moderately severe and severe CKD modify the treatment effect.

METHODS

This study is reported according to CONSORT guidelines (Consolidated Standards of Reporting Trials). The data can be requested by other researchers by contacting the corresponding author with a written proposal. A data sharing agreement must be put in place before any data are shared. Written proposals will be assessed by members of the OPTIMAS trial steering committee. The OPTIMAS study protocol[14] and statistical analysis plan[15] have been published. This analysis was prespecified in the statistical analysis plan, and full details are available in the supplement. Briefly, it had a multicenter, randomized, parallel-group, controlled, open label with blinded end point adjudication (PROBE [Prospective, Randomized, Open-Label, Blinded End Point]) design, investigating the effects of early versus delayed anticoagulation with a DOAC, of patients with acute IS with AF. Participants were recruited at 100 UK hospitals by appropriately trained local investigators. Study sites and all investigators are listed in Table S1. Included participants were adult subjects presenting with acute IS, either with a known history of AF, or a new finding of AF on an ECG, eligible for treatment with a DOAC. Those with a contraindication to DOAC therapy were excluded. Full eligibility criteria are published elsewhere.[1,14] Participants were randomized 1:1 to the intervention group, early DOAC (within 4 days of stroke onset) or the control group, and delayed DOAC (at 7–14 days). Exact timing within those windows is at the discretion of the treating clinician. Randomization took place centrally through an independent online service, stratified by stroke severity as measured by the National Institutes of Health Stroke Scale score. Random permuted blocks with randomly varying block lengths were used. Participants and treating teams were not blinded to allocation, but outcome events were adjudicated by an independent panel of expert stroke clinicians, blinded to allocation.

All trial participants provided written informed consent. When patients lacked capacity, consent was obtained by discussion with a personal or nominated consultee. The trial protocol has been approved by the South Central Oxford Research Ethics Committee, reference number 19/SC/0021, in compliance with the Declaration of Helsinki. D.J.W. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

CKD Definition

The OPTIMAS structured data collection form included the history of known CKD as a data point. Because CKD is defined as at least 3 months history of either reduced eGFR or presence of albuminuria,[16] we chose history of CKD as the definition for this analysis, as it is more precise than a one-off eGFR measurement, which would not account for undetected acute kidney injury, which has an incidence of 12% to 34% in acute stroke populations.[17–19] Blood samples were also taken for kidney function as part of the trial protocol. eGFR was determined centrally using the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) equation,[20] without the ethnicity coefficient.[21,22] Those with a creatinine clearance of <15 mL/min (Cockcroft Gault formula) were excluded. For the analysis of outcomes according to CKD severity, we defined stages of CKD according to established Kidney Disease International criteria[16]: eGFR ≥60, normal kidney function; a history of CKD and eGFR ≥60 (stage 2 CKD); eGFR of 45 to 60 (stage 3a CKD); eGFR of 30 to 45 (stage 3b CKD); and eGFR <30 (CKD stage 4-5). Those with reduced eGFR had to have a history of CKD.

Outcomes

The outcomes of the main OPTIMAS trial were the outcomes of interest for this analysis according to the presence or absence of CKD. The primary outcome was a composite of recurrent IS, sICH, unclassified stroke, or systemic arterial embolism. Secondary outcomes were the individual components of the above primary outcome, all-cause mortality, major extracranial bleeding, clinically significant nonmajor extracranial bleeding, a composite of the primary outcome and all-cause mortality, favorable functional outcome (defined as modified Rankin Scale score of 0-2), and a composite of sICH and major extracranial bleeding, as a safety outcome. The outcomes were adjudicated centrally by an independent expert panel, blinded to the treatment allocation.

Sample Size

The target sample size for the main OPTIMAS trial was 3478, giving 80% power to show noninferiority of the intervention using a 2-sided alpha of 5%. This was determined based on a primary outcome event rate of 4.3%

Statistical Analysis

Analyses were performed according to the modified intention-to-treat principle, whereby those without diagnoses of acute IS or AF were excluded.

To assess whether a history of CKD modifies the treatment effect of the OPTIMAS trial intervention, we fitted binary mixed effects logistic regression models with CKD and study group as interaction variables and primary and secondary outcomes as dependent variables. Similar to the main OPTIMAS trial, we included the stratifying variable, National Institutes of Health Stroke Scale score at randomization, as a covariate in each of the models. Study sites were included as random intercept terms to account for clustering. To assess the robustness of the findings for the primary analysis, we fitted models additionally adjusting for potential baseline imbalances between those with and without CKD and examined whether there was evidence for treatment effect modification by subgroup (interactions).

Statistical analyses were performed using STATA (version 18; StataCorp LLC, College Station, TX).

Sensitivity Analyses

To assess the validity of the history of CKD variable collected, we performed sensitivity analyses with an alternative CKD definition: history of CKD and eGFR <60 mL/min per 1.73 m^2. We repeated each of the mixed effects logistic regression models using this definition.

RESULTS

The OPTIMAS trial recruited 3648 participants between July 4, 2019, and January 31, 2024. Recruitment continued for as long as the trial funding allowed. The target sample size was exceeded because of a decision taken by the trial steering committee in November 2023 to extend the recruitment period to maximize statistical power to detect a treatment effect. Last follow-up was on July 10, 2024; 3621 participants were included in the modified intention-to-treat population, as 27 participants did not have a diagnosis of either IS or AF or withdrew their consent to participate in the trial. Twenty participants were excluded from this analysis because they had missing data on kidney function. Patient flow through the trial is shown in the CONSORT diagram in Figure 1; 3601 participants (mean age, 78.0±9.9 years, 45.3% female) were included in the current analysis, 543 with CKD. The characteristics of the randomized groups were well balanced within the subgroups of those with and without CKD, with clear differences in age and rates of hypertension, diabetes, and prior vascular diseases between those with or without CKD. The mean eGFR values were 71±20 mL/min per 1.73 m^2 in the normal kidney function group and 49±20 in the CKD group. Baseline characteristics are shown in Table 1. Adherence to UK DOAC dosing guidelines[23] was good overall at 89% but worse in the CKD group (17% versus 7% non-guidance dosing in CKD and normal kidney function groups, respectively; Table 2).

Primary Composite Outcome According to CKD

A primary outcome event occurred in 19 (3.5%) of those with CKD and 97 (3.2%) of those with normal kidney function. In the mixed effects logistic regression analysis, there was no difference between early and delayed DOAC initiation for the primary outcome in either the normal kidney function group (odds ratio, 1.01 [95% CI, 0.67–1.51]) or the CKD group (odds ratio, 0.90 [95% CI, 0.36–2.25]; $P_{interaction}$=0.822; Table 3). To explore potential interactions further, we fitted a regression model additionally adjusted for age, sex, duration of AF (diagnosed at time of index stroke or preexisting), hypertension, diabetes, hypercholesterolemia, ischemic heart disease, congestive cardiac failure, and previous IS and found no significant change to the estimates for those

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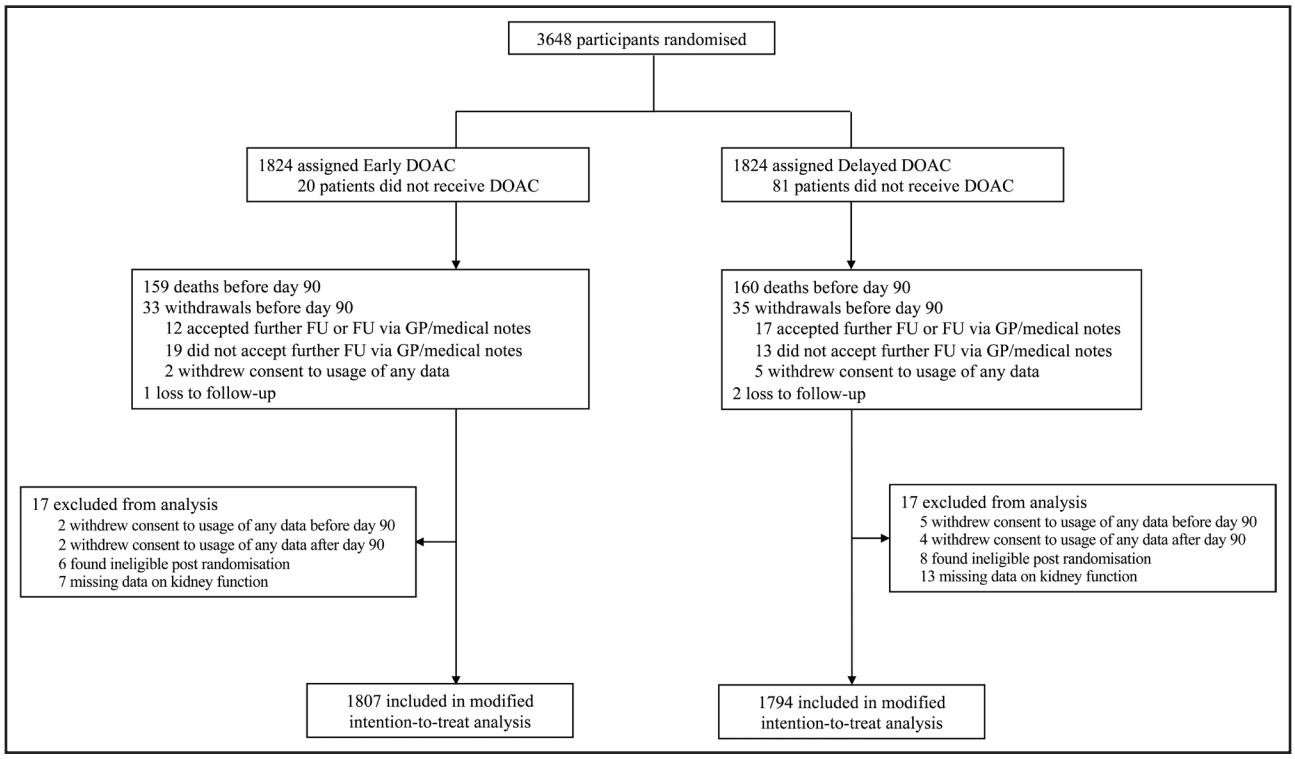

Figure 1. CONSORT diagram (Consolidated Standards of Reporting Trials) showing patient flow through the trial for this OPTIMAS (Optimal Timing of Anticoagulation After Acute Ischemic Stroke With Atrial Fibrillation) subgroup analysis.
DOAC indicates direct oral anticoagulant; FU, follow-up; and GP, general practitioner.

with normal kidney function (odds ratio, 1.01 [95% CI, 0.67–1.53]) or those with CKD (odds ratio, 0.78 [95% CI, 0.30–2.03]). Modification of the intervention according to CKD and CKD severity is shown in Figure 2.

Secondary Outcomes According to CKD

The outcomes according to CKD and treatment allocation are shown in Table 2. Importantly, there were no excess sICH or major extracranial bleeding events in the early DOAC group with CKD. In those with CKD, compared with delayed DOAC initiation, there were numerically more deaths in the early DOAC group, but this was not statistically significant and could not be attributed to excess bleeding events. The subgroup analysis for mortality according to CKD and CKD severity is shown in Figure S1. Outcome events according to CKD severity are shown in Table 4.

Sensitivity Analyses

Using the alternate definition of CKD (eGFR <60 and history of known CKD), the primary and secondary subgroup analyses according to CKD and treatment allocation did not change qualitatively (Table S2).

DISCUSSION

In this prespecified subgroup analysis of the OPTIMAS trial, we found no evidence of change in the risk-benefit ratio from the intervention in patients with acute cardioembolic stroke and all severities of CKD, with the exception of dialysis-dependent kidney failure. This is an important safety finding given existing concerns about bleeding risk, both intracranial and extracranial, in patients with CKD. This finding was consistent across the primary composite outcome and all secondary outcomes, including risk of intracranial and major extracranial hemorrhage. It is notable that there were no excess bleeding events in the CKD group given early DOAC despite a high proportion of pre-stroke anticoagulant use in those with AF and CKD (50%) and 2.5× the rate of non-guideline-recommended DOAC dosages used in the CKD group. We found no evidence to recommend withholding early DOAC initiation in those with CKD not yet requiring dialysis.

The 2 published trials investigating the timing of anticoagulation after acute stroke, TIMING[2] and ELAN,[3] have not reported subgroup analyses according to CKD, so our study provides new evidence suggesting that early anticoagulation after the onset of stroke is safe and noninferior to delayed treatment in this high-risk patient group. There was no indication of harm from the intervention for those with severe CKD (stage 4; eGFR, 15–30 mL/min per 1.73 m^2) although this subgroup was small, so the findings have to be interpreted cautiously. We do not have evidence to support early DOAC initiation in those with kidney failure (eGFR <15), but our trial was limited by UK DOAC licensing rules.

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Table 1. Baseline Characteristics According to Chronic Kidney Disease and Randomized Group

	Normal kidney function			Chronic kidney disease		
	Total (N=3058)	Early DOAC (n=1536)	Delayed DOAC (n=1522)	Total (N=543)	Early DOAC (n=271)	Delayed DOAC (n=272)
Age, y; mean (SD)	77.1 (10.0)	77.1 (9.9)	77.2 (10.1)	82.5 (7.6)	82.5 (8.3)	82.5 (6.9)
Female sex, n (%)	1332 (43.6%)	658 (42.8%)	674 (44.3%)	300 (55.2%)	151 (55.7%)	149 (54.8%)
Ethnicity						
White	2859 (93.5%)	1426 (92.8%)	1433 (94.2%)	514 (94.7%)	257(94.8%)	257 (94.5%)
Black British, African, or Caribbean	45 (1.5%)	25 (1.6%)	20 (1.3%)	13 (2.4%)	6 (2.2%)	7 (2.6%)
South Asian	51 (1.7%)	26 (1.7%)	25 (1.6%)	9 (1.7%)	4 (1.5%)	5 (1.8%)
East Asian or Southeast Asian	37 (1.2%)	21 (1.4%)	16 (1.1%)	3 (0.6%)	2 (0.7%)	1 (0.4%)
Mixed or other ethnicity	66 (2.2%)	38 (2.5%)	28 (1.8%)	4 (0.7%)	2 (0.7%)	2 (0.7%)
Hypertension	1973 (64.5%)	978 (63.7%)	995 (65.4%)	447 (82.3%)	222(81.9%)	225 (82.7%)
Diabetes	575 (18.8%)	296 (19.3%)	279 (18.3%)	188 (34.6%)	93 (34.3%)	95 (34.9%)
Hypercholesterolemia	979 (32.0%)	510 (33.2%)	469 (30.8%)	203 (37.4%)	107 (39.5%)	96 (35.3%)
Type of atrial fibrillation						
Paroxysmal	827 (27.0%)	396 (25.8%)	431 (28.3%)	136 (25.0%)	70 (25.8%)	66 (24.3%)
Persistent	2149 (70.3%)	1096 (71.4%)	1053 (69.2%)	396 (72.9%)	196 (72.3%)	200 (73.5%)
Atrial flutter	81 (2.6%)	43 (2.8%)	38 (2.5%)	11 (2.0%)	5 (1.8%)	6 (2.2%)
Duration of AF						
Newly diagnosed	1598 (52.3%)	802 (52.2%)	796 (52.3%)	178 (32.8%)	93 (34.3%)	85 (31.2%)
Known before stroke	1460 (47.7%)	734 (47.8%)	726 (47.7%)	365 (67.2%)	178 (65.7%)	187 (68.8%)
Myocardial infarction	256 (8.4%)	122 (7.9%)	134 (8.8%)	75 (13.8%)	38 (14.0%)	37 (13.6%)
History of angina	195 (6.4%)	102 (6.6%)	93 (6.1%)	64 (11.8%)	35 (12.9%)	29 (10.7%)
Coronary revascularisation	188 (6.1%)	90 (5.9%)	98 (6.4%)	39 (7.2%)	19 (7.0%)	20 (7.4%)
Congestive heart failure	247 (8.1%)	132 (8.6%)	115 (7.6%)	133 (24.5%)	76 (28.0%)	57 (21.0%)
Peripheral arterial disease	63 (2.1%)	27 (1.8%)	36 (2.4%)	15 (2.8%)	3 (1.1%)	12 (4.4%)
Previous ischemic stroke	415 (13.6%)	230 (15.0%)	185 (12.2%)	115 (21.2%)	60 (22.1%)	55 (20.2%)
Previous intracranial hemorrhage	49 (1.6%)	27 (1.8%)	22 (1.4%)	13 (2.4%)	7 (2.6%)	6 (2.2%)
Dementia	187 (6.1%)	95 (6.2%)	92 (6.0%)	61 (11.2%)	26 (9.6%)	35 (12.9%)
Current smoker	242 (7.9%)	128 (8.3%)	114 (7.5%)	31 (5.7%)	16 (5.9%)	15 (5.5%)
Former smoker	840 (31.2%)	418 (31.2%)	422 (31.2%)	171 (34.8%)	80 (32.7%)	91 (37.0%)
Alcohol >14 units/week	374 (12.2%)	200 (13.0%)	174 (11.4%)	26 (4.8%)	12 (4.4%)	14 (5.1%)
Anticoagulation at baseline	978 (32.0%)	494 (32.2%)	484 (31.8%)	291 (53.6%)	144 (53.1%)	147 (54.0%)
Warfarin	95 (3.1%)	51 (3.3%)	44 (2.9%)	19 (3.5%)	10 (3.7%)	9 (3.3%)
Direct oral anticoagulant	883 (28.9%)	443 (28.8%)	440 (28.9%)	272 (50.1%)	134 (49.4%)	138 (50.7%)
Antiplatelets at baseline	338 (11.1%)	173 (11.3%)	165 (10.8%)	64 (11.8%)	38 (14.0%)	26 (9.6%)
IV thrombolysis	717 (23.4%)	386 (25.1%)	331 (21.7%)	79 (14.5%)	35 (12.9%)	44 (16.2%)
Mechanical thrombectomy	233 (7.6%)	113 (7.4%)	120 (7.9%)	31 (5.7%)	18 (6.6%)	13 (4.8%)
NIHSS on admission, median (IQR)	5 (3–10)	6 (3–11)	5 (3–10)	6 (3–11)	6 (3–11)	6 (4–12)
NIHSS at randomization						
0–4	1811 (59.2%)	900 (58.6%)	911 (59.9%)	265 (48.8%)	137 (50.6%)	128 (47.1%)
5–10	822 (26.9%)	414 (27.0%)	408 (26.8%)	179 (33.0%)	90 (33.2%)	89 (32.7%)
11–15	228 (7.5%)	121 (7.9%)	107 (7.0%)	51 (9.4%)	24 (8.9%)	27 (9.9%)
16–21	148 (4.8%)	76 (4.9%)	72 (4.7%)	32 (5.9%)	14 (5.2%)	18 (6.6%)
>21	49 (1.6%)	25 (1.6%)	24 (1.6%)	16 (2.9%)	6 (2.2%)	10 (3.7%)
NIHSS at randomization, median (IQR)	3 (2–7)	4 (2–7)	3 (2–7)	5 (2–9)	4 (2–8)	5 (2–9)
Systolic blood pressure, mm Hg	134.4 (19.0)	134.2 (19.4)	134.7 (18.6)	134.1 (20.6)	133.3 (21.4)	134.9 (19.7)
Diastolic blood pressure, mm Hg	76.8 (12.7)	76.7 (12.7)	77.0 (12.8)	74.6 (13.3)	74.9 (13.4)	74.2 (13.2)
Prestroke mRS	0 (0–2)	0 (0–1)	0 (0–2)	1 (0–3)	1 (0–3)	1 (0–3)

AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Table 2. Direct Oral Anticoagulant Choice and Dosing According to Treatment Allocation and Kidney Function

	Normal kidney function			Chronic kidney disease		
	Early DOAC (n=1536)	Delayed DOAC (n=1522)	Total participants (N=3058)	Early DOAC (n=271)	Delayed DOAC (n=272)	Total participants (N=543)
Apixaban (any dose)	985 (64.1)	948 (62.2%)	1933 (63.2%)	151 (55.7)	148 (54.4)	299 (55.1%)
Apixaban 5 mg twice daily	857 (55.8%)	817 (53.8%)	1674 (54.7%)	93 (34.3%)	91 (33.5%)	184 (33.9%)
Guideline dosed	837 (97.7%)	786 (96.2%)	1623 (97.0%)	87 (93.5%)	81 (89.0%)	168 (91.3%)
Non-guideline (over) dosed	20 (2.3%)	31 (3.8%)	51 (3.0%)	6 (6.5%)	10 (11.0%)	16 (8.7%)
Apixaban 2·5 mg twice daily	128 (8.3%)	131 (8.6%)	259 (8.5%)	58 (21.4%)	57 (21.0%)	115 (22.2%)
Guideline dose	101 (78.9%)	96 (73.3%)	197 (76.1%)	50 (86.2%)	40 (70.2%)	90 (78.3%)
Non-guideline (under) dosed	27 (21.1%)	35 (26.7%)	62 (23.9%)	8 (13.8%)	17 (29.8%)	25 (21.7%)
Dabigatran (any dose)	32 (2.1%)	27 (1.8%)	59 (1.9%)	6 (2.2%)	4 (1.5%)	10 (1.8%)
Dabigatran 150 mg twice daily	26 (1.7%)	18 (1.2%)	44 (1.4%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Guideline dosed	25 (96.2%)	17 (94.4%)	42 (95.5%)	2 (100%)	1 (50.0%)	3 (75.0%)
Non-guideline (over) dosed	1 (3.8%)	1 (5.6%)	2 (4.5%)	0 (0%)	1 (50.0%)	1 (25.0%)
Dabigatran 110 mg twice daily	6 (0.4%)	9 (0.6%)	15 (0.5%)	4 (1.5%)	2 (0.7%)	6 (1.1%)
Guideline dosed	5 (83.3%)	8 (88.9%)	13 (86.7%)	2 (50.0%)	2 (100%)	4 (66.7%)
Non-guideline (under) dosed	1 (16.7%)	1 (11.1%)	2 (13.3%)	2 (50.0%)	0 (0%)	2 (33.3%)
Edoxaban (any dose)	439 (28.6%)	418 (27.5%)	857 (28.0%)	98 (36.2%)	88 (32.4%)	186 (34.3%)
Edoxaban 60 mg once daily	313 (20.4%)	301 (19.8%)	614 (20.1%)	32 (11.8%)	30 (11.0%)	62 (11.4%)
Guideline dosed	294 (93.9%)	279 (92.7%)	573 (93.3%)	21 (65.6%)	21 (70.0%)	42 (67/7%)
Non-guideline (over) dosed	19 (6.1%)	22 (7.3%)	41 (6.7%)	11 (34.4%)	9 (30.0%)	20 (32.3%)
Edoxaban 30 mg once daily	126 (8.2%)	117 (7.7%)	243 (7.9%)	66 (24.4%)	58 (21.3%)	124 (22.8%)
Guideline dosed	109 (86.5%)	100 (85.5%)	209 (86.0%)	57 (86.4%)	49 (84.5%)	106 (85.5%)
Non-guideline (under) dosed	17 (13.5%)	17 (14.5%)	34 (14.0%)	9 (13.6%)	9 (15.5%)	18 (14.5%)
Rivaroxaban (any dose)	66 (4.3%)	73 (4.8%)	139 (4.5%)	11 (4.1%)	14 (5.1%)	25 (4.6)
Rivaroxaban 20 mg once daily	52 (3.4%)	55 (3.6%)	107 (3.5%)	5 (1.8%)	4 (1.5%)	9 (1.7%)
Guideline dosed	47 (90.4%)	53 (96.4%)	100 (93.5%)	4 (80.0%)	2 (50.0%)	6 (66.7%)
Non-guideline (over) dosed	5 (9.6%)	2 (3.6%)	7 (6.5%)	1 (20.0%)	2 (50.0%)	3 (33.3%)
Rivaroxaban 15 mg once daily	14 (0.9%)	18 (1.2%)	32 (1.0%)	6 (2.2%)	10 (3.7%)	16 (2.9%)
Guideline dosed	11 (78.6%)	14 (77.8%)	25 (78.1%)	6 (100%)	6 (60.0%)	12 (75.0%)
Non-guideline (under) dosed	3 (21.4%)	4 (22.2%)	7 (21.9%)	0 (0%)	4 (40.0%)	4 (25.0%)
Did not commence DOAC	14 (0.9%)	56 (3.7%)	70 (2.2%)	5 (1.8%)	18 (6.6%)	23 (4.2%)
Total guideline dosed	1429 (93.9%)	1353 (92.3%)	2782 (93.1%)	229 (86.1%)	202 (79.5%)	431 (82.9%)
Total non-guideline dosed	93 (6.1%)	113 (7.7%)	206 (6.9%)	37 (13.9%)	52 (20.5%)	89 (17.1%)
Over dosed	45 (3.0%)	56 (3.7%)	101 (3.4%)	18 (6.8%)	22 (8.7%)	40 (7.7%)
Under dosed	48 (3.1%)	57 (3.7%)	105 (3.5%)	19 (7.1%)	30 (11.8%)	49 (9.4%)

Participants were classed as receiving the guideline DOAC dose when the dose received was in line with the UK National Institute for Health and Care Excellence guidance[23] (reduced dose recommended when: for apixaban, creatinine clearance of 15–30 or 2 of 3 of age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 micromol/L; for dabigatran, either age ≥80 years or creatinine clearance of 30–50 mL/min; for edoxaban, either body weight ≤60 kg or creatinine clearance of 30–50 mL/min; and for rivaroxaban, creatinine clearance of 30–50 mL/min). Dosage decisions were made at the discretion of the physicians responsible for the care of each participant at trial sites. DOAC indicates direct oral anticoagulant.

Patients with CKD are at increased risk of a range of adverse health outcomes, including acute coronary syndromes, stroke, cardiovascular death, and death from any cause. A large meta-analysis including data from 3.4 million community-based individuals suggested an independently increased risk of stroke of 73%.[4] A large UK biobank study[6] showed an independent association of CKD with the risk of spontaneous intracerebral hemorrhage. Mendelian allocation in this study suggested a causal association of CKD with intracerebral hemorrhage. This could indicate an increased risk of sICH after anticoagulation after AF-related IS. Another Mendelian allocation study showed increased risk of both IS and intracerebral hemorrhage in those with a history of CKD, reduced eGFR, and albuminuria.[24] A mediation analysis in this study suggested a causal association between CKD and stroke, which was only mediated by hypertension to a limited extent. The increased risk of both major stroke subtypes in those with CKD suggests that clinical decisions on the timing of anticoagulation can be more challenging, and CKD has been associated with the risk of sICH after thrombolysis in 2 cohort studies.[7,9] We did not find increased rates of

CLINICAL TRIAL

Table 3. Outcomes According to Chronic Kidney Disease and Randomized Group

	Normal kidney function (n=3601)			Chronic kidney disease (n=543)			
	Early DOAC (n=1536)	Delayed DOAC (n=1522)	Odds ratio (95% CI)	Early DOAC (n=271)	Delayed DOAC (n=272)	Odds ratio (95% CI)	$P_{interaction}$
Primary composite outcome	49 (3.2%)	48 (3.2%)	1.01 (0.67–1.51)	9 (3.3%)	10 (3.7%)	0.90 (0.36–2.25)	0.822
Recurrent ischemic stroke	35 (2.3%)	35 (2.3%)	0.99 (0.62–1.60)	8 (3.0%)	6 (2.2%)	1.32 (0.45–3.86)	0.637
Symptomatic intracranial hemorrhage	10 (0.7%)	9 (0.6%)	1.05 (0.42–2.62)	1 (0.4%)	3 (1.1%)	0.35 (0.04–3.50)	0.386
Systemic embolism	2 (0.1%)	3 (0.2%)	0.63 (0.10–3.79)	0 (0%)	1 (0.4%)		
Unclassifiable stroke	3 (0.2%)	2 (0.1%)	1.51 (0.25–9.05)	0 (0%)	0 (0%)		
All-cause mortality	120 (7.8%)	129 (8.5%)	0.88 (0.67–1.15)	38 (14.0%)	31 (11.4%)	1.44 (0.84–2.45)	0.107
Primary outcome and mortality	150 (9.8%)	154 (10.1%)	0.93 (0.72–1.18)	44 (16.2%)	35 (12.9%)	1.45 (0.88–2.40)	0.114
Major extracranial bleeding	5 (0.3%)	11 (0.7%)	0.43 (0.15–1.25)	2 (0.7%)	2 (0.7%)	1.01 (0.14–7.38)	0.459
Nonmajor extracranial bleeding	35 (2.3%)	30 (2.0%)	1.13 (0.69–1.87)	10 (3.7%)	6 (2.2%)	1.82 (0.63–5.16)	0.423
All major bleeding (extra and intracranial)	15 (1.0%)	20 (1.3%)	0.71 (0.36–1.40)	3 (1.1%)	5 (1.8%)	0.61 (0.14–2.63)	0.857
Venous thromboembolism	7 (0.5%)	5 (0.3%)	1.38 (0.44–4.38)	0 (0%)	5 (1.8%)		
Functional independence (mRS, 0–2)	748 (56.2%)	728 (55.9%)	1.04 (0.87–1.23)	85 (39.2%)	80 (37.6%)	1.01 (0.66–1.55)	0.921

All logistic regression analyses were adjusted for NIHSS at randomization, and clustering was adjusted for using random effects. DOAC indicates direct oral anticoagulant; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

sICH in those with CKD, and importantly, there was no significant interaction with study group. Our findings are in keeping with the results of a renal subanalysis of the ENCHANTED trial (Low-Dose Versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke).[25]

The strengths of this study include a relatively large sample size, and the multicenter design with patients recruited from over 90 centers increases the generalizability of the findings, as do the broad inclusion criteria. Few patients were lost to follow-up, and there were few missing renal data, minimizing potential bias in the sample. There are limitations to this study. The number of participants and events in the CKD group is modest, and the CIs are wide around both the main effect of randomized

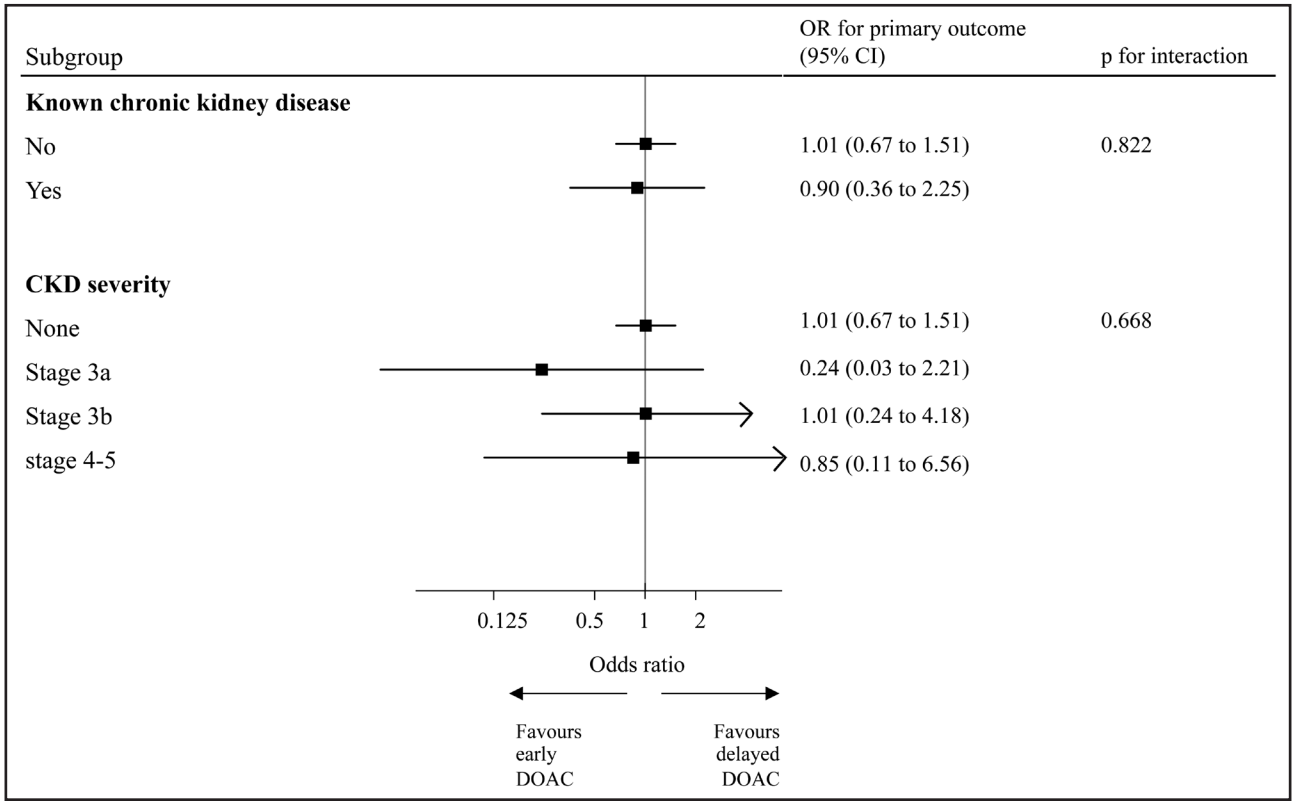

Figure 2. Subgroup analysis for the primary outcome according to chronic kidney disease (CKD) and treatment allocation.
DOAC indicates direct oral anticoagulant; and OR, odds ratio.

Table 4. Outcome Events According to CKD Severity and Treatment Allocation

	No CKD; early DOAC (n=1536)	No CKD; delayed DOAC (n=1522)	CKD stage 2; early DOAC (n=55)	CKD stage 2; delayed DOAC (n=60)	CKD stage 3a; early DOAC (n=91)	CKD stage 3a; delayed DOAC (n=91)	CKD stage 3b; early DOAC (n=91)	CKD stage 3b; delayed DOAC (n=91)	CKD stage 4-5; early DOAC (n=34)	CKD stage 4-5; delayed DOAC (n=30)
Primary composite outcome	49 (3.2%)	48 (3.2%)	2 (3.6%)	0 (0%)	1 (1.1%)	4 (4.4%)	4 (4.4%)	4 (4.4%)	2 (5.9%)	2 (6.7%)
Recurrent ischemic stroke	35 (2.3%)	35 (2.3%)	2 (3.6%)	0 (0%)	1 (1.1%)	2 (2.2%)	3 (3.3%)	4 (4.4%)	2 (5.9%)	0 (0%)
Symptomatic intracranial hemorrhage	10 (0.7%)	9 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (1.1%)	0 (0%)	0 (0%)	2 (6.7%)
Systemic embolism	2 (0.1%)	3 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unclassifiable stroke	3 (0.2%)	2 (0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All-cause mortality	120 (7.8%)	129 (8.5%)	6 (10.9%)	3 (5.0%)	12 (13.2%)	10 (11.0%)	14 (15.4%)	11 (12.1%)	6 (17.6%)	7 (23.3%)
Primary composite outcome and mortality	150 (9.8%)	154 (10.1%)	7 (12.7%)	3 (5.0%)	13 (14.3%)	11 (12.1%)	17 (18.7%)	13 (14.3%)	7 (20.6%)	8 (26.7%)
Major extracranial bleeding	5 (0.3%)	11 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (1.1%)	1 (2.9%)	1 (3.3%)
Nonmajor extracranial bleeding	35 (2.3%)	30 (2.0%)	4 (7.3%)	0 (0%)	1 (1.1%)	2 (2.2%)	2 (2.2%)	4 (4.4%)	3 (8.8%)	0 (0%)
All major bleeding (extracranial and intracranial)	15 (1.0%)	20 (1.3%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	2 (2.2%)	1 (1.1%)	1 (2.9%)	3 (10.0%)
Venous thrombosis	7 (0.5%)	5 (0.3%)	0 (0%)	1 (1.7%)	0 (0%)	1 (1.1%)	0 (0%)	3 (3.3%)	0 (0%)	0 (0%)
Favorable functional outcome (mRS, 0–2)	748 (56.1%)	728 (55.7%)	12 (29.3%)	25 (55.6%)	35 (46.7%)	25 (36.2%)	31 (41.9%)	24 (32.0%)	7 (25.9%)	5 (20.0%)
mRS at follow-up	2 (1–4)	2 (1–3)	3 (2–4)	2 (1–4)	3 (1–4)	3 (2–5)	3 (2–5)	3 (2–4)	4 (2–5)	4 (3–6)

CKD indicates chronic kidney disease; DOAC, direct oral anticoagulant; and mRS, modified Rankin Scale.

treatment in the CKD group and the treatment by CKD status interaction. Our findings, therefore, need to be confirmed in other populations. In particular, the severe CKD group was small (n=64), and this might be in part owing to clinical concerns about DOAC use in this group, a possible selection bias that we acknowledge. In addition, just 6% of the trial population was from a nonwhite ethnicity, possibly limiting the applicability of the results to these patients. However, the proportion of nonwhite participants in our trial was similar to the overall UK proportion of 9% in the most recent Sentinel Stroke National Audit Program.[26]

In conclusion, our findings suggest that CKD does not modify the effects of early versus delayed DOAC initiation after acute IS. Based on these results, early DOAC initiation appears to be safe and should not be withheld in patients with CKD.

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Supplemental Material

Tables S1–S2
Figure S1
Pre-Specified Protocol for OPTIMAS Subgroup Analysis According to Chronic Kidney Disease

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