Collaboration on the optimal timing of anticoagulation after ischaemic stroke and atrial fibrillation: a systematic review and prospective individual participant data meta-analysis of randomised controlled trials (CATALYST)

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Summary

Background The optimal timing of oral anticoagulation for prevention of early ischaemic stroke recurrence in people with acute ischaemic stroke and atrial fibrillation remains uncertain. We aimed to estimate the effects of starting a direct oral anticoagulant (DOAC) early (≤4 days) versus later (≥5 days) after onset of ischaemic stroke.

Methods For this systematic review and meta-analysis we searched the electronic databases PubMed, Cochrane Central Register of Controlled Trials, and Embase for randomised controlled trials published from inception until March 16, 2025. We included clinical trials if they were pre-registered, randomised, investigated clinical outcomes, and included participants with acute ischaemic stroke and atrial fibrillation who were assigned to either early or later initiation (≤4 days *vs* ≥5 days) of a DOAC in approved doses. The primary outcome was a composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke within 30 days of randomisation. Secondary outcomes included components of the primary composite within 30 days and 90 days. We did a one-stage individual patient data meta-analysis with the use of a generalised linear mixed-effects model, accounting for between-trial differences, to generate treatment effects, which are presented as odds ratios (ORs) and 95% CIs. This study is registered with PROSPERO, CRD42024522634.

Findings We identified four eligible trials: TIMING (NCT02961348), ELAN (NCT03148457), OPTIMAS (NCT03759938), and START (NCT03021928). After excluding participants who opted out of data sharing or were not randomly assigned to DOAC initiation within 4 days or at day 5 or later, we included 5441 participants (mean age 77·7 years [SD 10·0], 2472 [45·4%] women, median National Institutes of Health Stroke Scale 5 [IQR 3–10]) in the individual patient data meta-analysis. We obtained primary outcome data for 5429 participants. The primary outcome occurred in 57 (2·1%) of 2683 participants who started DOAC early versus 83 (3·0%) of 2746 participants who started later (OR 0·70, 95% CI 0·50–0·98, p=0·039). Early DOAC reduced the risk of recurrent ischaemic stroke (45 [1·7%] of 2683 *vs* 70 [2·6%] of 2746, OR 0·66, 0·45–0·96, p=0·029). There was no evidence of an increase in symptomatic intracerebral haemorrhage with early DOAC initiation (10 [0·4%] of 2683 *vs* 10 [0·4%] of 2746, OR 1·02, 0·43–2·46, p=0·96).

Interpretation For people with acute ischaemic stroke and atrial fibrillation, early DOAC initiation (within 4 days) reduced the risk of the composite outcome of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke within 30 days. These findings support early DOAC initiation in clinical practice.

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Introduction

Atrial fibrillation causes about 20–30% of ischaemic strokes, which are generally more disabling than strokes associated with other causes.[1] Direct oral anticoagulants (DOACs) are highly effective in long-term secondary prevention after ischaemic stroke associated with atrial fibrillation and are associated with about half the risk of intracranial haemorrhage compared with vitamin K antagonists.[2] However, the optimal timing of initiation of anticoagulation after acute ischaemic stroke in atrial fibrillation is a persisting clinical dilemma, since the pivotal DOAC trials excluded participants with recent acute ischaemic stroke (ie, within 7–30 days). Although early DOAC might reduce the risk of early ischaemic

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Research in context

Evidence before this study

Pivotal randomised controlled trials showed that direct oral anticoagulants (DOACs) are highly effective for the prevention of ischaemic stroke in people with atrial fibrillation, but did not include participants soon after acute ischaemic stroke (within about 1–2 weeks). Early DOAC use might reduce the risk of early ischaemic stroke recurrence due to cardiac embolism but might also increase haemorrhagic transformation of the acute infarct that could, if severe, worsen clinical outcomes. We searched the electronic databases PubMed, Cochrane Central Register of Controlled Trials, and Embase on May 16, 2024 (with an additional updated search on March 16, 2025), for randomised controlled trials comparing early versus delayed start of DOAC. The main search terms were "acute ischaemic stroke" AND "atrial fibrillation" AND "anticoagulants" AND "timing" AND "randomised". We identified four published trials (TIMING, ELAN, OPTIMAS, and START). The risk of bias, assessed according to the revised Cochrane risk-of-bias tool for randomised trials, was low. None of the four trials alone provided unequivocal evidence that early DOAC treatment was preferable to delayed initiation.

Added value of this study

We performed an individual patient data meta-analysis including 5441 participants from TIMING, ELAN, OPTIMAS, and START (mean age 77·7 years [SD 10·0], 2472 [45·4%] women, median National Institutes of Health Stroke Scale score at admission 5 [IQR 3–10]) to investigate the effects of early DOAC initiation within 4 days versus later DOAC initiation (at day 5 or later). Our results showed a reduction of the primary outcome, a composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke within 30 days. The primary outcome occurred in 57 (2·1%) of 2683 participants who started a DOAC early versus 83 (3·0%) of 2746 in the delayed DOAC group. The benefits were consistent across key prespecified subgroups including clinical stroke severity, reperfusion treatment, and previous use of oral anticoagulants.

Implications of all the available evidence

Our findings suggest that clinicians should initiate DOAC treatment within 4 days and do not support the practice of delaying DOAC initiation after acute ischaemic stroke with atrial fibrillation. Future CATALYST subgroup analyses will further explore the risks and benefits of early initiation of DOACs.

stroke recurrence due to cardiac embolism, early use of DOACs must be balanced against concerns regarding haemorrhagic transformation of the acute infarct which could, if severe, worsen clinical outcomes. A recent aggregate data meta-analysis[3] including observational and randomised studies suggested that early DOAC treatment might be safe, but these data are limited by potential biases and confounding.

Recently, four randomised controlled trials have provided data on the safety and efficacy of early anticoagulation.[4–7] In TIMING[7] (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation) and OPTIMAS[5] (Optimal Timing of Anticoagulation After Acute Ischaemic Stroke), early anticoagulation within 4 days in people with ischaemic stroke with atrial fibrillation was non-inferior at 90 days compared with a later treatment start (5–10 days in TIMING, 7–14 days in OPTIMAS) for a composite outcome (ie, ischaemic stroke, symptomatic intracerebral haemorrhage, or death in TIMING; and ischaemic stroke, symptomatic intracranial haemorrhage, or systemic embolism in OPTIMAS). In ELAN[6] (Early Versus Late Initiation Of Direct Oral Anticoagulants In Post-Ischaemic Stroke Patients With Atrial Fibrillation), an early treatment start with DOACs (with timings based on infarct size) resulted in a numerically lower primary outcome event rate (ie, a composite outcome of recurrent ischaemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial haemorrhage, or vascular death within 30 days after randomisation) compared with a later treatment start. The START trial used an adaptive design incorporating four different timings of DOAC initiation.[4,8] None of these trials individually showed unequivocally whether early DOAC treatment is effective in reducing the risk of early ischaemic stroke recurrence without increasing the risk of symptomatic intracerebral haemorrhage or major extracranial haemorrhage.

We undertook a collaborative individual patient data meta-analysis (IPDMA) with a prespecified protocol (Collaboration on the Optimal Timing of Anticoagulation After Ischaemic Stroke and Atrial Fibrillation: Prospective Individual Participant Data Meta-Analysis of Randomised Controlled Trials, CATALYST) to determine whether early anticoagulation with DOAC reduces the rate of recurrent ischaemic stroke without increasing symptomatic intracerebral haemorrhage. This collaboration was started prospectively before the results of trials were known; the CATALYST investigators met regularly from August, 2022. The primary aim of this IPDMA was to assess whether early DOAC initiation (within 4 days) is superior to a later treatment start at day 5 or later in reducing a composite outcome of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke at 30 days. Our secondary aims were to investigate individual

components of the primary outcome until 90 days and heterogeneity in effect among clinically important subgroups, including clinical stroke severity.

Methods

Search strategy and selection criteria

Two authors (JD and SA) did a systematic search for randomised controlled trials comparing clinical outcome based on timing of DOAC after acute ischaemic stroke in adult patients with atrial fibrillation. The full search strategy is shown in the appendix (pp 16–17). Records in English were identified from PubMed, Cochrane Central Register of Controlled Trials, and Embase, omitting congress abstracts, up to May 16, 2024. DJW updated the search on March 16, 2025.

We identified four eligible randomised controlled trials: TIMING, ELAN, OPTIMAS, and START. We requested data for individual participants, who had not opted out of data sharing, from chief investigators of completed trials. Risk of bias in the included trials was assessed according to the revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[9] Principal investigators were contacted to clarify eligible participants' cases, particularly regarding data that were unpublished at the time of CATALYST data collection, when needed.

The lead statistician for CATALYST (H-MD) developed a data template to harmonise data collection. Original participant data were extracted by the statisticians of each separate trial from their respective databases. Only the minimum pseudonymised data relevant for this IPDMA were combined. Data were checked for accuracy with respect to the initial publications for ELAN and TIMING. Ethics approval was obtained for data collection from participating centres within each trial or central ethics committees as reported in the respective publications.[4–7] All patients or proxies provided consent for data collection and usage in the original trials.

All outcomes were binary. The prespecified primary outcome was the composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke within 30 days. Definitions of recurrent ischaemic stroke and symptomatic intracerebral haemorrhage for each trial are provided in the appendix (p 22). Secondary outcomes included the primary outcome at 90 days; individual components of the primary outcome within 30 days and 90 days; all-cause mortality within 30 days and 90 days; the composite within 30 days and 90 days of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, unclassified stroke, or all-cause mortality; clinically significant major extracranial haemorrhage within 30 days; and the composite of symptomatic intracerebral haemorrhage or clinically significant major extracranial haemorrhage within 30 days.

In TIMING, early initiation was defined as within 4 days and later (delayed) initiation as between 5 and 10 days after ischaemic stroke onset. In ELAN, the timing depended on stroke severity (defined by infarct size rather than the clinical syndrome). For patients with minor stroke, early initiation was defined as within 48 h and later as 3–4 days. For patients with moderate stroke, the timings were within 48 h versus 6–7 days. In patients with major stroke, the timings were 6–7 days versus 12–14 days. In OPTIMAS, early initiation was defined as within 4 days and later (delayed) initiation was 7–14 days. In START, there were four randomisation arms for patients defined by severity assessed by a combination of clinical syndrome and brain imaging; individuals with mild-to-moderate strokes were assigned to DOAC initiation on days 3, 6, 10, and 14, and patients with severe stroke on days 6, 10, 14, and 21.

In CATALYST, we defined an early DOAC initiation as randomisation to initiation within 4 days of ischaemic stroke onset, and later initiation as randomisation to initiation 5 days or more after ischaemic stroke onset. We were therefore only able to include participants with moderate stroke severity from ELAN (individuals randomly assigned to the early time of 48 h or less were allocated to the early initiation arm of CATALYST and patients randomly assigned to day 6–7 to the later initiation arm). For the START trial, we included participants with mild-to-moderate strokes. Individuals randomly assigned to day 3 were allocated to the early DOAC initiation arm of CATALYST and others (day 6, day 10, and day 14) to the later DOAC initiation arm.

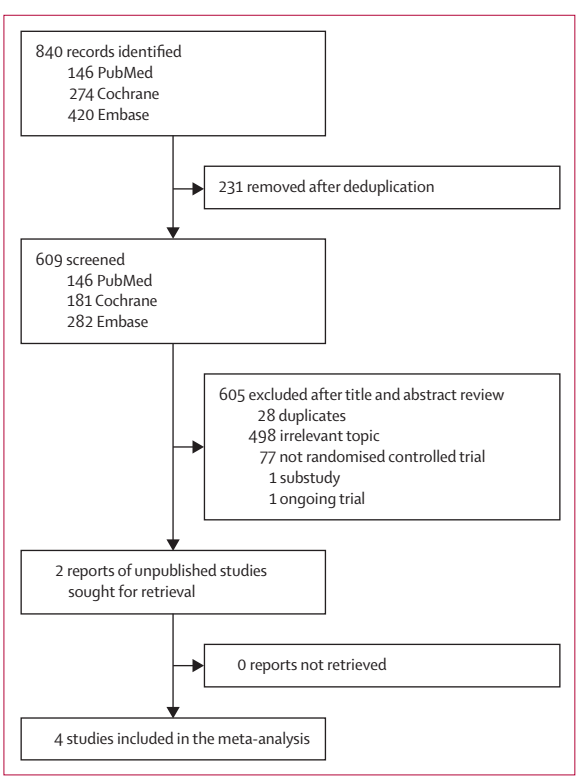

Figure 1: **Study selection**

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See Online for appendix

	Early DOAC	Later DOAC	Total
Number			
Total number (%)	2691 (49·5%)	2750 (50·5%)	5441 (100%)
Age, years			
Mean (SD)	77·7 (10·1)	77·7 (10·0)	77·7 (10·0)
Sex			
Female	1227 (45·6%)	1245 (45·3%)	2472 (45·4%)
Male	1464 (54·4%)	1505 (54·7%)	2969 (54·6%)
NIHSS (admission)			
Median (IQR)	6 (3–11)	5 (3–10)	5 (3–10)
Mild (0–4)	1131 (42·0%)	1196 (43·5%)	2327 (42·8%)
Moderate (5–10)	862 (32·0%)	886 (32·2%)	1748 (32·1%)
Moderate (11–15)	342 (12·7%)	306 (11·1%)	648 (11·9%)
Severe (≥16)	340 (12·6%)	338 (12·3%)	678 (12·5%)
Missing (%)	16 (0·6%)	24 (0·9%)	40 (0·7%)
Hypertension			
No hypertension	840 (31·2%)	818 (29·7%)	1658 (30·5%)
Hypertension	1836 (68·2%)	1923 (69·9%)	3759 (69·1%)
Missing	15 (0·6%)	9 (0·3%)	24 (0·4%)
Diabetes			
No diabetes	2131 (79·2%)	2192 (79·7%)	4323 (79·5%)
Diabetes	553 (20·5%)	548 (19·9%)	1101 (20·2%)
Missing	7 (0·3%)	10 (0·4%)	17 (0·3%)
Mechanical thrombectomy			
No thrombectomy	2375 (88·3%)	2406 (87·5%)	4781 (87·9%)
Thrombectomy	312 (11·6%)	334 (12·1%)	646 (11·9%)
Missing	4 (0·1%)	10 (0·4%)	14 (0·3%)
Intravenous thrombolysis			
No thrombolysis	1950 (72·5%)	2034 (74·0%)	3984 (73·2%)
Thrombolysis	737 (27·4%)	706 (25·7%)	1443 (26·5%)
Missing	4 (0·1%)	10 (0·4%)	14 (0·3%)
Any reperfusion treatment			
No reperfusion	1805 (67·1%)	1854 (67·4%)	3659 (67·2%)
Reperfusion	882 (32·8%)	886 (32·2%)	1768 (32·5%)
Missing	4 (0·1%)	10 (0·4%)	14 (0·3%)
Previous anticoagulation			
No previous anticoagulation	1769 (65·7%)	1715 (62·4%)	3484 (64·0%)
Previous anticoagulation	873 (32·4%)	904 (32·9%)	1777 (32·7%)
Missing	49 (1·8%)	131 (4·8%)	180 (3·3%)
Trial			
ELAN	379 (14·1%)	375 (13·6%)	754 (13·9%)
OPTIMAS	1814 (67·4%)	1807 (65·7%)	3621 (66·6%)
START	49 (1·8%)	131 (4·8%)	180 (3·3%)
TIMING	449 (16·7%)	437 (15·9%)	886 (16·3%)

Data are number (%), unless otherwise indicated. DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale.

Table 1: **Baseline characteristics of included participants**

For CATALYST, there were three prespecified subgroups of interest: presence or absence of reperfusion treatment (thrombolysis, thrombectomy, or both), clinical stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) at admission (categorised as 0–4, 5–10, 11–15, or ≥16), and any anticoagulant use before index stroke, sex, and age (≤75 *vs* >75 years).

Data analysis

After a face-to-face investigator meeting in London on Feb 16, 2024, the CATALYST collaboration policy was finalised on March 12, 2024, and signed by principal representatives of all trials on March 26, 2024. The PROSPERO protocol was published on May 29, 2024 (registration number: CRD42024522634). We did not undertake a formal sample size calculation for this IPDMA. Instead, our intention was to combine all the available data at the patient level to ensure estimation of the effect of early DOAC initiation as precisely as possible.

Given the low event rate for the primary outcome (expected to be <5%), we chose a one-stage IPDMA. For all outcomes, a generalised linear mixed-effects model (with the use of the logit link function), with uncorrelated random slopes and intercepts, was used to take account of between-trial differences. Where the uncorrelated random slopes and intercepts did not converge, we fitted random-intercepts models. Treatment effects are presented as unadjusted odds ratios (ORs) and 95% CIs. For ease of interpretation, the primary outcome is also presented as an absolute risk difference (RD) and 95% CIs. For the primary outcome, we performed sensitivity analyses with the use of a two-stage model in a frequentist and in a Bayesian setting. We had planned to estimate heterogeneity with the use of the between-studies treatment effect variance; however, as only four studies were included, we were not able to estimate it accurately.

Subgroup characteristics were added one at a time as explanatory variables in the model and included an interaction term with timing of DOAC initiation. Interaction p values, treatment effects, and 95% CIs in the separate categories were reported.

Complete case analysis was used because the amount of missing data was minimal. Specific information regarding included participants and amount of missing data is included in the results. For NIHSS data in TIMING, when the score was missing at admission but available at DOAC start or discharge, whichever came first, this score was used for the categorical NIHSS variable (ie, 0–4, 5–10, 11–15, and ≥16), except if the patient received thrombolysis or thrombectomy, in which case the NIHSS score was not replaced.

All analyses were done according to the intention-to-treat principle, defined by the randomised arm from each trial regardless of the actual timing of DOAC initiation achieved. We had planned to examine the presence of small study effects; however, this was not possible with only four studies. All analyses were done with the use of R (version 4.2.2) and its packages lm4 and marginal effects. This study is reported in accordance with the PRISMA guidelines for IPDMA studies.[10]

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After excluding duplicates, the systematic literature database search on March 16, 2024, yielded a total of 609 records, from which the only eligible trials identified were TIMING, ELAN, OPTIMAS, and START. The search was repeated on March 16, 2025, and no additional trials were identified. The flow diagram for the selection and inclusion of studies is presented in figure 1. All available individual participant data from the included trials were retrieved. The trials showed a low risk of bias for the primary outcome (see the risk of bias assessment in the appendix p 18).

For 12 patients in ELAN, the primary outcome was unknown at 30 days, although for seven of these individuals the survival status at 30 days was known. Data from the patients from Norway in ELAN (n=42) could not be shared. In OPTIMAS, 27 patients were removed from the randomised set to form the modified intention-to-treat set because these individuals were found to be ineligible post-randomisation or fully withdrew their consent for their data to be used. In START, 19 patients were lost to follow-up and one patient revoked consent. In TIMING, two participants withdrew consent for the study and were not included in CATALYST. The flowchart of participants included in CATALYST is presented in the appendix (p 23).

In total, this IPDMA included 5441 participants comprising 2691 patients with early DOAC initiation and 2750 patients with later DOAC initiation (mean age 77·7 years [SD 10·0], 2472 [45%] women, median NIHSS at admission 5 [IQR 3–10]). Table 1 reports the baseline characteristics by treatment arm and overall. OPTIMAS accounted for 67% (3621 patients), TIMING for 16% (886 patients), ELAN for 14% (754 patients), and START for 3% (180 patients). We had primary outcome data for 5429 participants. The median time from symptom onset to DOAC initiation was 3·0 days (IQR 2·1–3·7) in the early DOAC arm and 7·2 days (IQR 5·8–8·4) in the later DOAC arm. At admission, 4075 (75%) patients had mild-to-moderate stroke (NIHSS 0–10), 1326 (24%) had moderate-to-severe stroke (NIHSS ≥11), and 40 (1%) had an unknown. More specifically, 2327 (43%) patients had NIHSS scores of 0–4, 1748 (32%) had scores of 5–10, 648 (12%) had scores of 11–15, and 678 (13%) had scores of ≥16. Overall, 33% of patients were taking anticoagulants before admission to hospital for the index stroke. 26% of patients received intravenous thrombolysis, 12% received mechanical thrombectomy, and 33% received any revascularisation treatment (ie, intravenous thrombolysis, mechanical thrombectomy, or both). In the included population, 69% of patients had hypertension and 20% had diabetes (table 1).

The primary outcome occurred in 57 (2·1%) of 2683 participants who started a DOAC early versus 83 (3·0%) of 2746 participants who started a DOAC later. The odds of the primary composite outcome were decreased with early DOAC versus later initiation (OR 0·70, 95% CI 0·50–0·98, p=0·039; table 2, figure 2); the absolute RD was –0·0093 (ie, 0·93 in favour of early DOAC initiation, 95% CI –0·0182 to –0·0004, p=0·039). The corresponding number needed-to-treat to prevent one primary outcome is 108 (95% CI 55–2500). There was no evidence of heterogeneity between trials (p value for heterogeneity 0·66; aggregate data meta-analysis shown in the appendix p 24). Figure 3 shows the primary outcome results overall and for the subgroups of interest

	Early DOAC sample size	Early DOAC number of events	Later DOAC sample size	Later DOAC number of events	OR (95% CI)	p value
Primary composite outcome (ischaemic stroke or sICH or unclassified stroke) at 30 days	2683	57 (2·12%)	2746	83 (3·02%)	0·70 (0·50–0·98)	0·039
Recurrent ischaemic stroke at 30 days	2683	45 (1·68%)	2746	70 (2·55%)	0·66 (0·45–0·96)	0·029
sICH at 30 days	2683	10 (0·37%)	2746	10 (0·36%)	1·02 (0·43–2·46)	0·96
Major extracranial haemorrhage at 30 days	2678	12 (0·45%)	2738	15 (0·55%)	0·82 (0·38–1·75)	0·60
Composite of sICH or major extracranial haemorrhage at 30 days	2678	22 (0·82%)	2738	25 (0·91%)	0·90 (0·51–1·60)	0·72
Mortality at 30 days	2691	99 (3·68%)	2750	120 (4·36%)	0·83 (0·63–1·09)	0·19
Primary composite outcome or mortality at 30 days	2687	138 (5·14%)	2749	173 (6·29%)	0·81 (0·64–1·01)	0·066
Primary composite outcome (ischaemic stroke or sICH or unclassified stroke) at 90 days	2678	83 (3·10%)	2738	96 (3·51%)	0·88 (0·65–1·19)	0·40
Primary composite outcome or mortality at 90 days	2687	252 (9·38%)	2748	265 (9·63%)	0·97 (0·81–1·16)	0·73
Recurrent ischaemic stroke at 90 days	2678	68 (2·54%)	2738	82 (2·99%)	0·85 (0·61–1·17)	0·32
sICH at 90 days	2678	13 (0·49%)	2738	11 (0·40%)	1·22 (0·55–2·72)	0·62
Mortality at 90 days	2687	199 (7·41%)	2748	208 (7·57%)	0·97 (0·79–1·19)	0·78

DOAC=direct oral anticoagulant. OR=odds ratio. sICH=symptomatic intracerebral haemorrhage.

Table 2: **Occurrence of primary and secondary outcomes**

(ie, stroke severity, previous anticoagulation, or reperfusion treatment with thrombolysis, thrombectomy, or both). There were no detectable interactions between the timing of DOAC initiation and any of the subgroup characteristics.

Early DOAC reduced the risk of recurrent ischaemic stroke (45 [1·7%] of 2683 *vs* 70 [2·6%] of 2746, OR 0·66, 95% CI 0·45–0·96, p=0·029). There was no evidence of increase in risk of symptomatic intracerebral haemorrhage with early versus later DOAC (10 [0·4%] of 2683 *vs* 10 [0·4%] of 2746; pooled OR 1·02, 0·43–2·46, p=0·96). There was no evidence of differences between groups in major extracranial bleeding, or the composite outcome of symptomatic intracerebral haemorrhage or major extracranial haemorrhage. For the primary composite outcome at the later timepoint of 90 days, there was a numerical reduction in favour of early DOAC initiation, but with more uncertainty (OR 0·88, 0·65–1·19, p=0·40). There were no differential treatment effects on any of the secondary outcomes with regard to stroke severity, previous anticoagulation, or reperfusion treatment (data not shown).

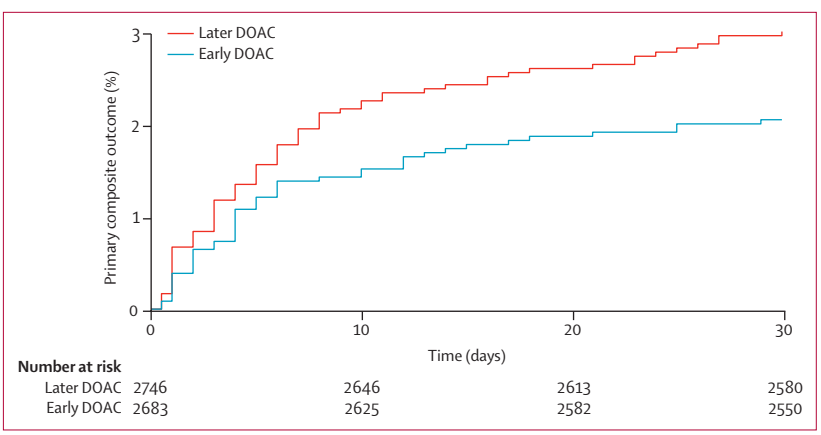

Figure 2: **Primary composite outcome at 30 days by DOAC initiation timing (cumulative hazard)**
Log-rank p value: 0·034. DOAC=direct oral anticoagulant.

Discussion

In this IPDMA, we included individual patient-level data from four randomised clinical trials of early versus later DOAC initiation after acute ischaemic stroke associated with atrial fibrillation. First, our principal finding was a reduction in the primary outcome of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke at 30 days, with no observed heterogeneity in the effect of early DOAC initiation strategy regarding clinical stroke severity. Second, early DOAC initiation reduced the risk of recurrent ischaemic stroke. Third, no increase in symptomatic intracerebral haemorrhage or in major extracranial bleeding was noted. Our results therefore provide some evidence that early DOAC initiation reduces the primary composite outcome and recurrent ischaemic stroke without increasing symptomatic intracerebral haemorrhage. Nonetheless, although our primary outcome is statistically significant at the 5% level, the confidence

	Early DOAC sample size	Early DOAC number of outcomes	Later DOAC sample size	Later DOAC number of outcomes	OR (95% CI)	Interaction p value
All patients	**2683**	**57**	**2746**	**83**	**0·70 (0·50–0·98)**	
NIHSS score						0·54
0–4	1129	24	1194	31	0·82 (0·48–1·40)	
5–10	861	17	885	29	0·60 (0·33–1·09)	
11–15	342	11	306	13	0·75 (0·33–1·70)	
≥16	335	5	337	9	0·55 (0·18–1·67)	
Reperfusion treatment						0·36
No	1800	43	548	57	0·77 (0·52–1·15)	
Yes	879	14	884	26	0·54 (0·28–1·04)	
Previous anticoagulation						0·89
No	1762	33	1714	44	0·72 (0·46–1·14)	
Yes	872	23	901	31	0·76 (0·44–1·31)	
Sex						0·75
Female	1223	32	1244	44	0·73 (0·46–1·16)	
Male	1460	25	1502	39	0·66 (0·39–1·09)	
Age (years)						0·46
≤75	971	13	1008	24	0·56 (0·28–1·10)	
>75	1712	44	1738	59	0·75 (0·51–1·12)	

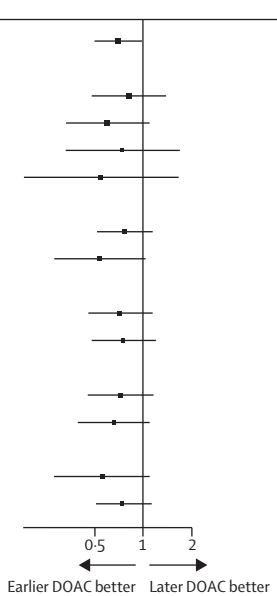

Figure 3: **Primary outcome overall and by subgroups of interest**
Interaction p value refers to the interaction term between early versus later DOAC and the baseline characteristic with respect to the primary outcome. DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio.

interval for the OR is wide, with an upper limit of 0·98. Moreover, adding the competing risk of mortality to the primary outcome increases the point estimate for the effect of early DOAC versus later DOAC to 0·81 (95% CI 0·64–1·01).

Emerging data indicate that early DOAC initiation might be safe and effective in acute ischaemic stroke associated with atrial fibrillation, including narrative reviews[11,12] and a recent systematic review and meta-analysis[3] of randomised controlled clinical trials and observational cohort studies. However, as previous data were limited by potential bias and confounding, these studies could not provide evidence for the superiority of early DOAC treatment. Therefore, the CATALYST large-scale individual patient data meta-analysis of randomised trials has new implications for clinical practice by providing reassurance that early DOAC initiation is safe and reduces the risk of ischaemic stroke within 30 days. Our results suggest that clinicians should initiate DOAC treatment within 4 days and do not support the practice of delaying DOAC initiation after acute ischaemic stroke with atrial fibrillation. Early DOAC initiation also has potential practical advantages for patient adherence and length of hospital stay.

Our secondary outcome for the composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or unclassified stroke at the later timepoint of 90 days did not show a statistically significant difference. The effect of early DOAC initiation would be expected to be greatest within the first 2 weeks, as it could prevent early recurrent cardiac embolism in the acute phase of ischaemic stroke when there might be a pro-thrombotic state. Over time, any advantage of early DOAC might reduce because both study arms will be on an effective prevention treatment and will be at residual risk of further events, including those due to non-cardioembolic mechanisms, such as large artery athero-thromboembolism or small vessel occlusion, which could dilute the treatment effect and account for the smaller and non-significant difference at this later timepoint.

Future CATALYST analyses will explore the associations of DOAC timing as a continuous variable with our outcomes of interest as well as safety and efficacy of an early DOAC start in subgroups with continued clinical uncertainty about the risks and benefits of early DOAC initiation. These analyses will include people with haemorrhagic transformation of the acute infarct on admission,[13] large volume infarcts,[14] or severe cerebral small vessel disease. All four trials enrolled some participants with various degrees of haemorrhagic transformation, whereas three included participants with clinically severe stroke syndromes; START excluded patients with more than 50% infarction in the territory of the middle cerebral artery. Full eligibility details are shown in the appendix (pp 19–20).

The main strength of this IPDMA is the large number of patients included (5441) from well designed randomised controlled trials conducted across multiple hospitals and geographical regions. The results from the population included in CATALYST are likely to be generalisable because the reported clinical stroke severity in this study (NIHSS median 5, IQR 3–10) is comparable with a recent large European multicentre cohort of patients with atrial fibrillation and acute ischaemic stroke treated with DOACs (NIHSS median 4, IQR 2–10)[15] and a Swedish registry observational cohort of 9000 patients (mean NIHSS 5·2 [SD 5·7]).[7] The rate of reperfusion therapy with intravenous thrombolysis in CATALYST (27·4%) is also consistent with that reported in a recent large Swiss observational registry study (29·2%).[16] Moreover, 1326 (24·4%) of 5441 participants in CATALYST had moderate-to-severe stroke syndromes (NIHSS >10) on admission, providing reassurance about the effect of early DOAC initiation in this population in whom early anticoagulation has previously been of clinical concern.[17] In addition, we were able to assess various clinically relevant outcomes, including major extracranial bleeding combined with symptomatic intracerebral haemorrhage as a key safety outcome. Another key strength of CATALYST is our ability to perform subgroup analyses because we had access to individual patient data on clinical stroke severity as well as anticoagulation on admission and revascularisation treatment with thrombolysis, thrombectomy, or both. These data allowed us to answer several important yet unresolved questions about DOAC initiation timing depending on these characteristics.

CATALYST has some potential limitations to consider. First, we used a cutoff of 4 days to define early DOAC initiation. This cutoff was determined by the OPTIMAS and TIMING trial designs, which were planned to address the key clinical uncertainties about DOAC initiation timing; indeed, the OPTIMAS design was based on a UK-wide survey about clinicians' opinions of when to use oral anticoagulant in recent stroke patients with atrial fibrillation.[17] The ongoing trial, Early Versus Late Initiation of Anticoagulation in Mild-to-Moderate Acute Ischaemic Stroke Patients with Non-Valvular Atrial Fibrillation (ASAP, NCT06057467), and additional planned CATALYST analyses with DOAC initiation time as a continuous variable, should provide new information about the optimal initiation point within the full range of timings soon after acute ischaemic stroke and the interaction of DOAC timing with stroke severity. Second, since trials did not randomise all participants to the initiation timings defined in CATALYST, we could not include data from all participants across all trials (eg, we could only include patients with moderate strokes from ELAN and patients with mild-to-moderate strokes from START as some had different timing allocations depending on clinical or radiological measures of stroke severity). Third, only START required radiographical confirmation of all recurrent ischaemic strokes. The three other trials (TIMING, ELAN, and OPTIMAS) based the diagnosis of

recurrent ischaemic stroke on a conventional clinical definition incorporating all available clinical records and brain imaging (appendix p 22),[18] which enabled incorporation of routine clinical care data in the trial designs. Nevertheless, all trials made every effort to minimise the risk of misclassifying suspected outcome events with the use of expert blinded independent outcome event adjudication panels for each trial (appendix p 21). Fourth, the rate of symptomatic intracerebral haemorrhage was low, possibly reducing statistical power to detect any difference between early and later DOAC initiation with our sample size. Finally, we recognise that although the CATALYST population is likely to be generalisable to many patients with acute ischaemic stroke and atrial fibrillation, we did not include a high proportion of patients with very severe stroke (4·6% with an NIHSS >20). All trials specified the exclusion of participants with the most severe type of haemorrhagic transformation (large space-occupying parenchymal haematoma, PH type 2), so our findings cannot be assumed to apply to such patients. Finally, data on ethnicity of participants were only available for one trial (OPTIMAS).

In summary, this large IPDMA provides evidence for the efficacy of early DOAC initiation within 4 days after ischaemic stroke associated with atrial fibrillation without evidence of harm from symptomatic intracerebral haemorrhage. Our data do not support the common practice of delaying anticoagulation for up to 2 weeks due to concerns about intracerebral haemorrhage (mainly haemorrhagic transformation of the infarct) across a wide range of stroke severity. However, participants with very severe stroke, severe space-occupying haemorrhagic transformation, or both, were not well represented in CATALYST, so clinicians must continue to make individualised decisions for these patients. Nevertheless, our data suggest that, apart from in exceptional circumstances, early DOAC initiation seems to be of benefit for a wide range of patients with acute ischaemic stroke and atrial fibrillation, in whom its prompt use can routinely be offered to reduce the risk of early ischaemic stroke recurrence within the first 30 days.

Contributors

H-MD, DJW, and NF prepared the first draft of the report after discussion with all authors about results from prespecified analyses. The CATALYST collaboration was conceptualised by DJW, UF, NF, H-MD, JO, SÅ, BN, and SJW. Database searches and study eligibility assessments were done by SÅ and JD. Data collection was coordinated by H-MD, who prepared a data collection template and liaised with the statisticians and data managers of other trials (MB, TGL, and PL) for data preparation and secure data transfer. The PROSPERO registration (which includes the plan of statistical analyses) was developed by H-MD, with input from all other authors. Data pooling and statistical analysis was conducted by H-MD, with inputs from NF, GS, MB, and TGL. All authors participated in patient enrolment, data collection, curation of the pooled data, and critically reviewed the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

UF reports research support from the Swiss National Science Foundation and the Swiss Heart Foundation; is a principal investigator of the ELAN trial and co-principal investigator of the DISTAL, TECNO, SWIFT DIRECT, SWITCH, ELAPSE, and ICARUS trial; is a steering committee member of the DO_IT trial; declares research grants from Medtronic (BEYOND SWIFT and SWIFT DIRECT), Stryker, Rapid medical, Penumbra, Medtronic, and Phenox (DISTAL), and Boehringer Ingelheim (TECNO) with all fees paid to the institution; reports consultancies for Medtronic, Stryker, and CSL Behring (fees paid to institution); declares participation on an advisory board for AstraZeneca (formerly Alexion/Portola), Boehringer Ingelheim, Biogen, AbbVie, and Acthera (fees paid to institution); is a member of a clinical event committee of the COATING study (Phenox) and a member of the data and safety monitoring committee of the TITAN, LATE_MT, and IN EXTREMIS trials; and is the president of the Swiss Neurological Society and president-elect of the European Stroke Organisation. TJM reports consulting fees from AstraZeneca, CLS Behring, and Octapharma. NF reports grants and contracts from the British Heart Foundation, National Institute for Health and Care Research, Medical Research Council, Cure Parkinson's Trust, and the European Union; declares consulting fees from ALK-Abelló, Sanofi Aventis, Gedeon Richter, Abbot, Galderma, AstraZeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune Therapeutics, and Gilead; and declares participation on a data safety monitoring board (DSMB) for Orion. TG reports research grants from the Austrian Science Fund; speakers' honoraria from Bristol Myers Squibb, Novartis, and AstraZeneca; and participation on advisory boards for Novartis and AstraZeneca. ZH reports research grants from the Swedish Society for Medical Research (S17-0133), the Swedish Heart-Lung Foundation (20200722), and Uppsala University Hospital (Upssala, Sweden); declares lecture and consulting fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, and Roche Diagnostics; and is a member of the Precision Medicine and Diagnostics expert group for SciLifeLab (Uppsala, Sweden). MK reports research support from the Intramural Research Fund (20-4-5) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center, Japan; research funding from Boston Scientific and Nippon Boehringer Ingelheim; research funding and speaker fees from Daiichi-Sankyo; consulting fees from Bristol Myers Squibb/Janssen Pharmaceuticals; and speaker fees from AstraZeneca, Bayer Yakuhin, Bristol Myers Squibb/Pfizer, and Mitsubishi Tanabe Pharma Corporation. PL reports institutional research grants from Lone Star Stroke Consortium. RL reports payments and honoraria to his institution from Boehringer Ingelheim, Bristol Myers Squibb, Medtronic, and Pfizer. GYHL reports consultant and speaker fees for Anthos, Bristol Myers Squibb/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo (paid to institution); and is the senior investigator of the National Institute for Health and Care Research. PSN declares research funding from the British Heart Foundation but declares no competing interests. BN reports payments from Symbec-Orion for participation on the DSMB for the HOVID trial. GT reports grants from the European Union, the German Research Foundation, and the German Innovation Fund; consulting fees and honoraria from Acandis, AstraZeneca, Bayer, and Boehringer Ingelheim; honoraria from Bristol Myers Squibb/Pfizer, Daiichi Sankyo, and Stryker; participation on the DSMB for the TEA-Stroke Study; and is chair of the board of directors for the European Stroke Organisation and Speaker of the Commission Cerebrovascular Diseases of the German Neurological Society. PW reports payments from Abbott for participation in the Clincial Event Adjudication Committee for the PORTICO studies. SJW reports institutional research grants from Lone Star Stroke Consortium and the State of Texas. JO reports institutional research grants from Amgen, AstraZeneca, Bayer, and Roche Diagnostics; and institutional honoraria from Pfizer. JD reports institutional research grants from the Stroke Association for the ELAN and OASIS trials, from National Institute for Health and Care Research for the CLASP study, and a Medicines Development Fellowship from the UK Medical Research Council; speaker fees from Medtronic; participation on the DSMB for INTERACT4; is on an advisory board for AstraZeneca; and is the treasurer of the European Stroke Organisation. DJW reports grant funding from the Stroke Association, British Heart Foundation, and a National Institute for Health and Care Research Senior Investigator Award; speaking honoraria from Bayer; speaking and chairing honoraria from Alexion and Novo Nordisk; consultancy fees from Alnylam, Bayer, and Novo Nordisk; is chief investigator for the PROHIBIT-ICH and

OPTIMAS trials; and participated on DSMB or advisory boards for OXHARP DSMB, and the LACI-2, TICH-2, TICH-3, RESTART, MACE-ICH, and PLINTH Trial Steering Committees. All other authors report no competing interests.

Data sharing

Data from CATALYST are currently not publicly available but we plan to make a de-identified dataset and data dictionary accessible in future at a time decided by the CATALYST Executive Committee.

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