Timing dell’introduzione di anticoagulanti orali diretti dopo ictus ischemico nel paziente con fibrillazione atriale

Risultati dello studio TIMING

Background

- The optimal time point for initiating anticoagulation after acute ischemic stroke is uncertain because the pivotal large-scale studies of NOAC versus warfarin excluded patients with a recent stroke (within 7–30 days).
- Because of the sparse evidence, current international guidelines do not provide specific recommendations on the best time point to start anticoagulation in this setting.
- The risk of ischemic stroke recurrence seems highest in the days immediately after an ischemic stroke, but hemorrhagic transformation of the ischemic lesion or intracerebral hemorrhage could offset the advantages of acute secondary prevention.
- Several observational studies indicate possible clinical benefit of early initiation of NOAC therapy to prevent recurrent ischemic stroke.

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ORIGINAL RESEARCH ARTICLE

Early Versus Delayed Non–Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study

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Methods

- TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation) was a registry-based, randomized, noninferiority, open-label, blinded end-point study at 34 stroke units using the Swedish Stroke Register for enrollment and follow-up.
- Within 72 hours from stroke onset, patients were randomized to early (≤4 days) or delayed (5–10 days) NOAC initiation, with choice of NOAC at the investigators' discretion.
- The primary outcome was the composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality at 90 days.
- The prespecified noninferiority margin was 3%. Secondary outcomes included the individual components of the primary outcome.

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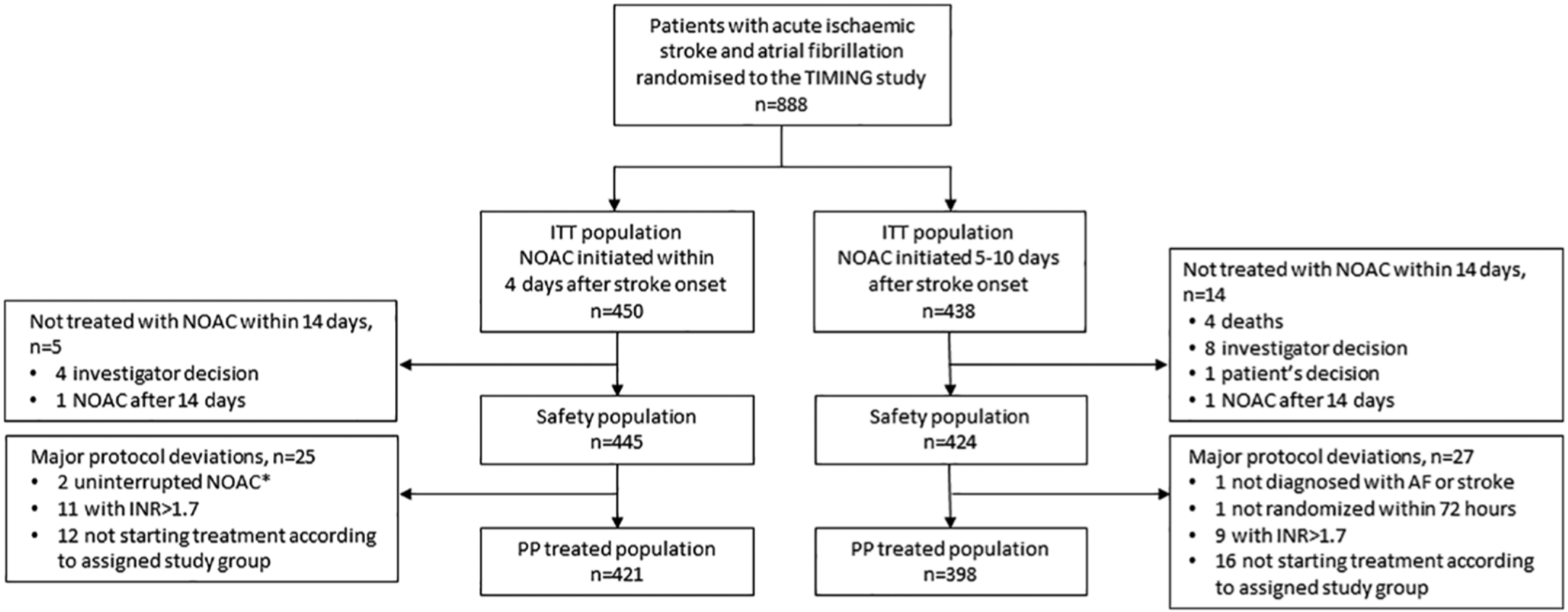
Flow-chart



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Baseline characteristics

Variable	Early start (n=450)	Delayed start (n=438)
Mean age (SD), y	78.4 (10.1)	78.3 (9.7)
Female sex, n (%)	207 (46.0)	203 (46.3)
Risk factors, n (%)		
Atrial fibrillation*		
Previously known	223 (49.6)	213 (48.6)
Diagnosed on admission	227 (50.4)	224 (51.1)
Prior stroke or transient ischemic attack		
Prior stroke	79 (17.6)	76 (17.4)
Prior transient ischemic attack	36 (8.0)	26 (5.9)
Diabetes	81 (18.0)	91 (20.8)
Active smoking	41 (9.1)	30 (6.8)
Activities of daily living independent on admission, n (%)	412 (91.6)	408 (93.2)
Living conditions before stroke, n (%)		
Own home without assistance	367 (81.6)	363 (82.9)
Own home with assistance	61 (13.6)	52 (11.9)
Nursing home	22 (4.9)	22 (5.0)

Variable	Early start (n=450)	Delayed start (n=438)
Drugs on admission, n (%)		
Antihypertensives	333 (74.0)	338 (77.2)
Statins	155 (34.4)	172 (39.3)
Antiplatelets		
Single	100 (22.2)	93 (21.2)
Dual	3 (0.7)	3 (0.7)
None	347 (77.1)	342 (78.1)
Non–vitamin K antagonist oral anticoagulant		
Apixaban	62 (13.8)	49 (11.2)
Dabigatran	12 (2.7)	14 (3.2)
Edoxaban	0 (0.0)	2 (0.5)
Rivaroxaban	16 (3.6)	20 (4.6)
Warfarin	31 (6.9)	34 (7.8)
Mean initial international normalized ratio (SD)	2.07 (0.68)	1.86 (0.50)
National Institutes of Health Stroke Scale score on admission		
Mean (SD)	6.2 (5.8)	5.9 (5.9)
Median (interquartile range)	4 (2–9)	4 (2–8)
Score missing, n (%)	47 (10.4)	48 (11.0)
Acute reperfusion therapy, n (%)		
Thrombolysis	132 (29.3)	120 (27.4)
Thrombectomy	65 (14.4)	56 (12.8)

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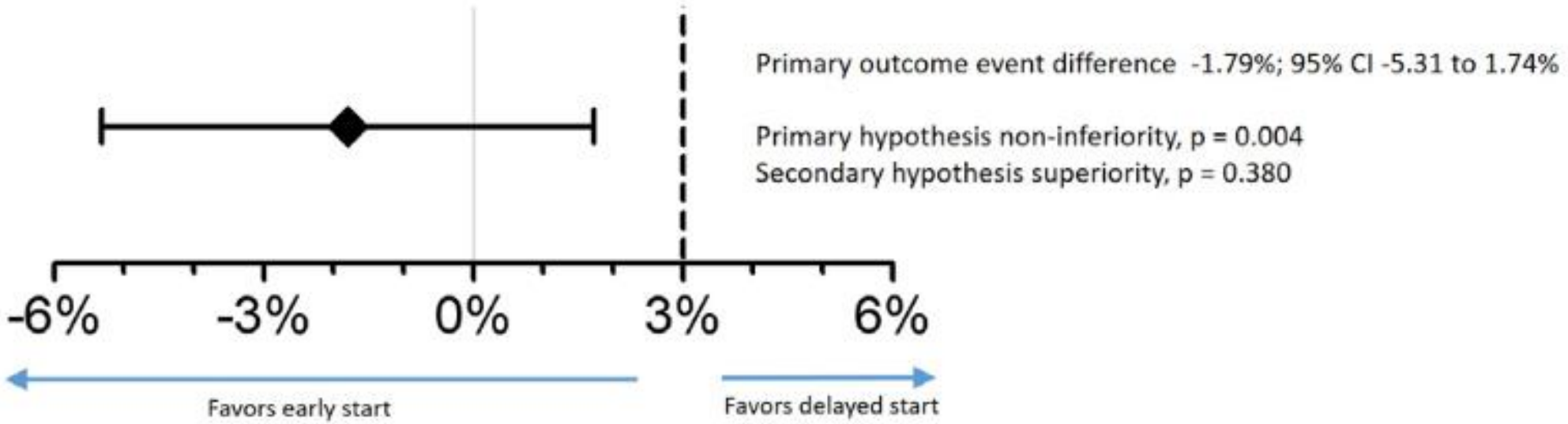
Risk difference in the primary composite outcome for early vs delayed initiation of NOAC at 90 days



Primary outcome was a composite of ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality. Primary hypothesis testing for noninferiority at an absolute 3% margin, and secondary hypothesis testing for

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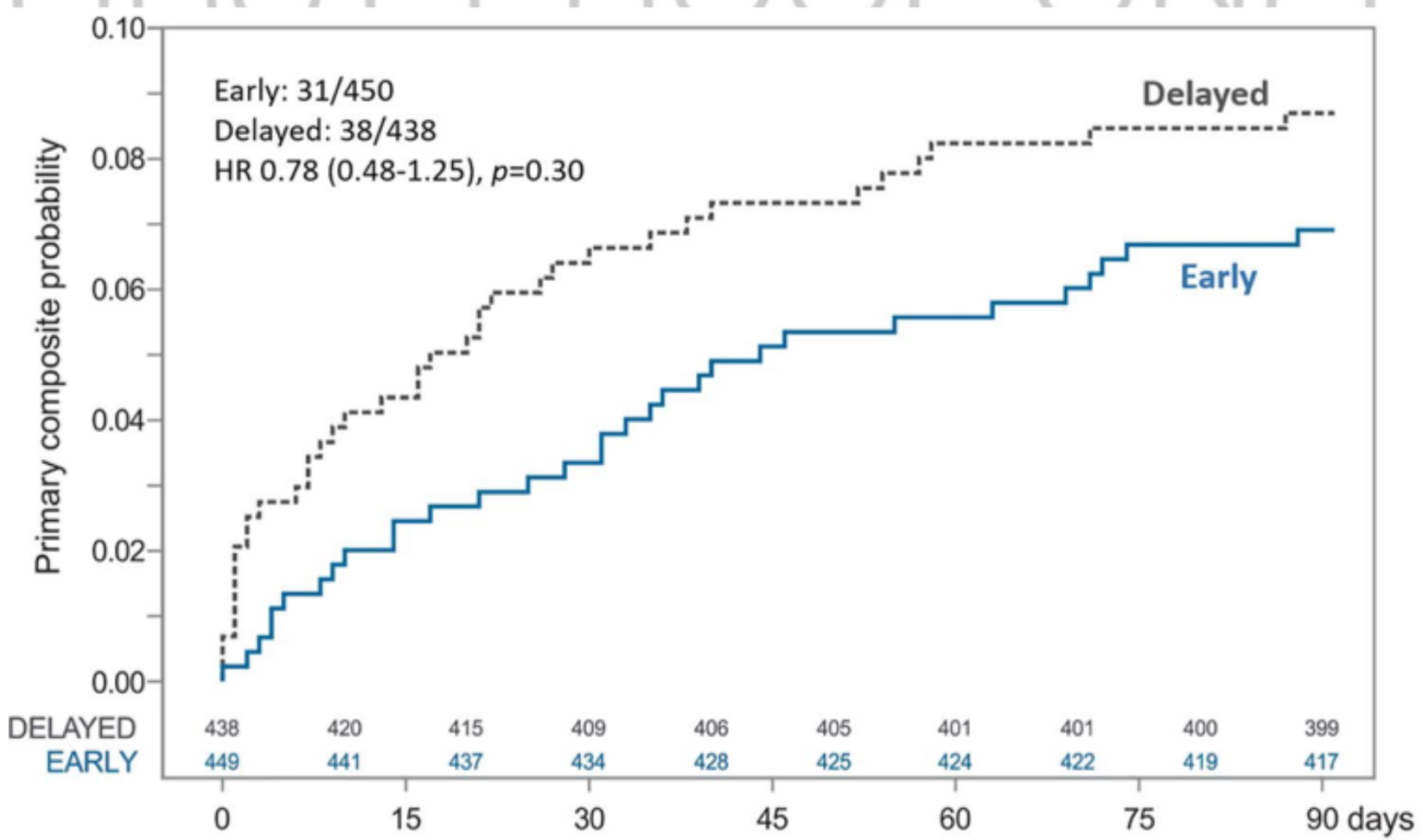
Time to the primary composite outcome and Cox proportional hazards analysis for early vs delayed initiation of NOAC at 90d

The primary outcome occurred in 31 patients (6.89%) assigned to early initiation and in 38 patients (8.68%) assigned to delayed NOAC initiation (absolute risk difference, −1.79% [95% CI, −5.31% to



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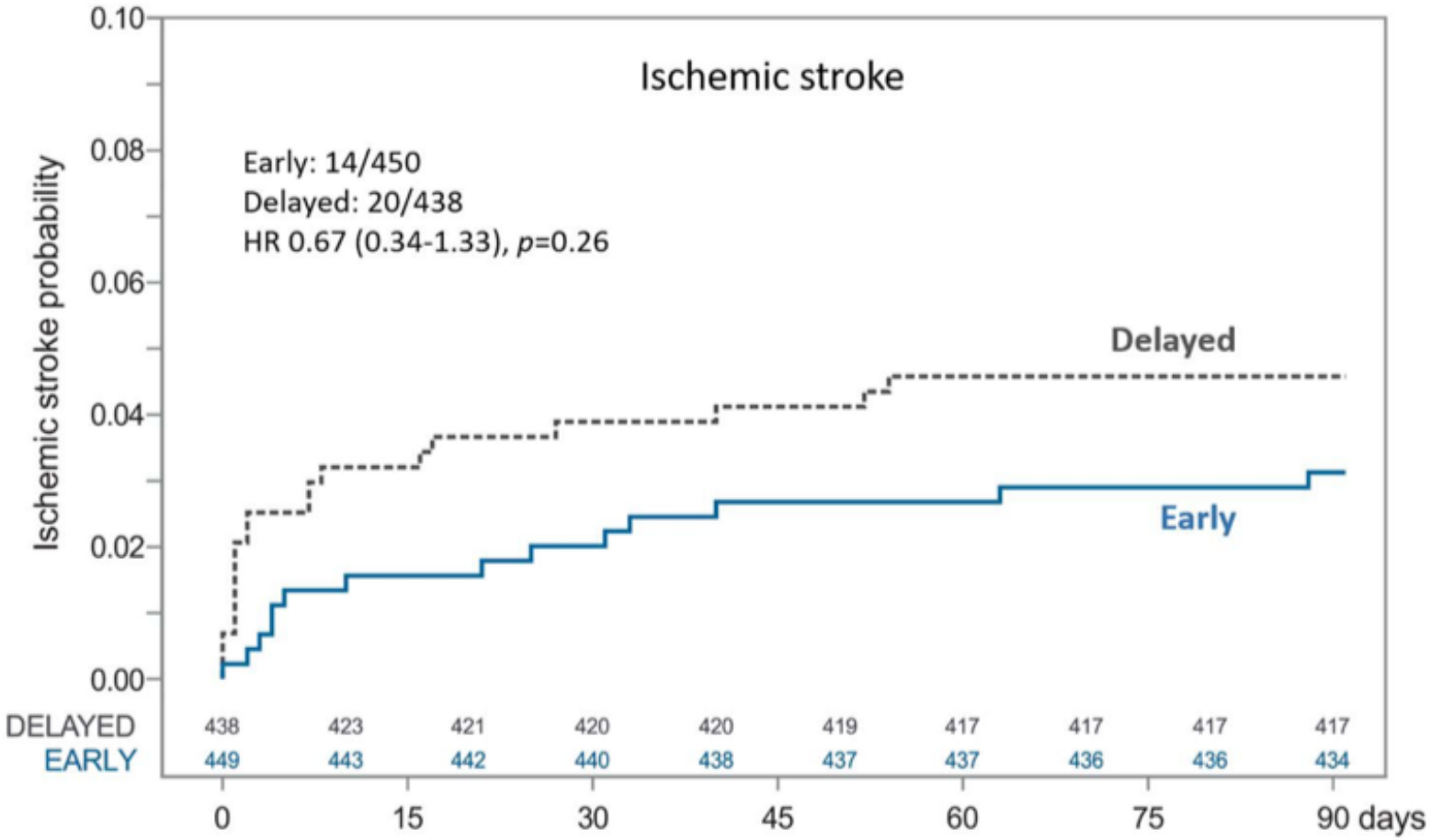
Time to ischemic stroke and Cox proportional hazards analysis for early vs delayed initiation of NOAC until 90 days



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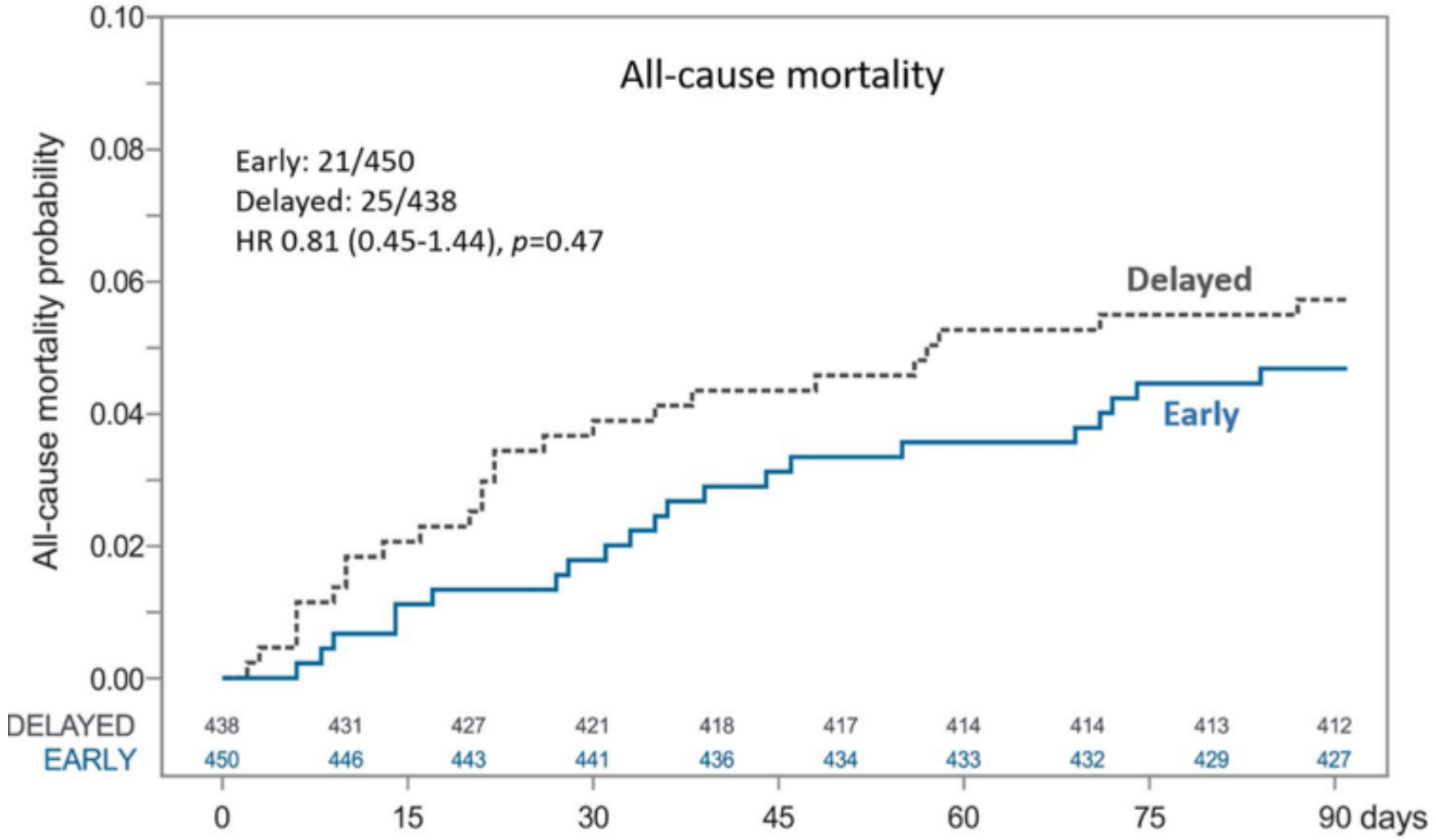
Time to all-cause mortality and Cox proportional hazards analysis for early vs delayed initiation of NOAC until 90 days.



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Major bleeding

- During the first 28 days after randomization, 10 major bleeding events occurred: 7 in the early and 3 in the delayed treatment group.
- Three of these events were intracerebral hemorrhages not fulfilling the symptom criteria in the outcome definition: 2 cases of hemorrhagic transformation in the early group, which occurred 2 and 17 days after randomization (difference in NIHSS scores before and at event, 1 and 0 points), and 1 case of hemorrhagic transformation in the delayed treatment group, which occurred 13 days after randomization (difference in NIHSS scores, 0 points).

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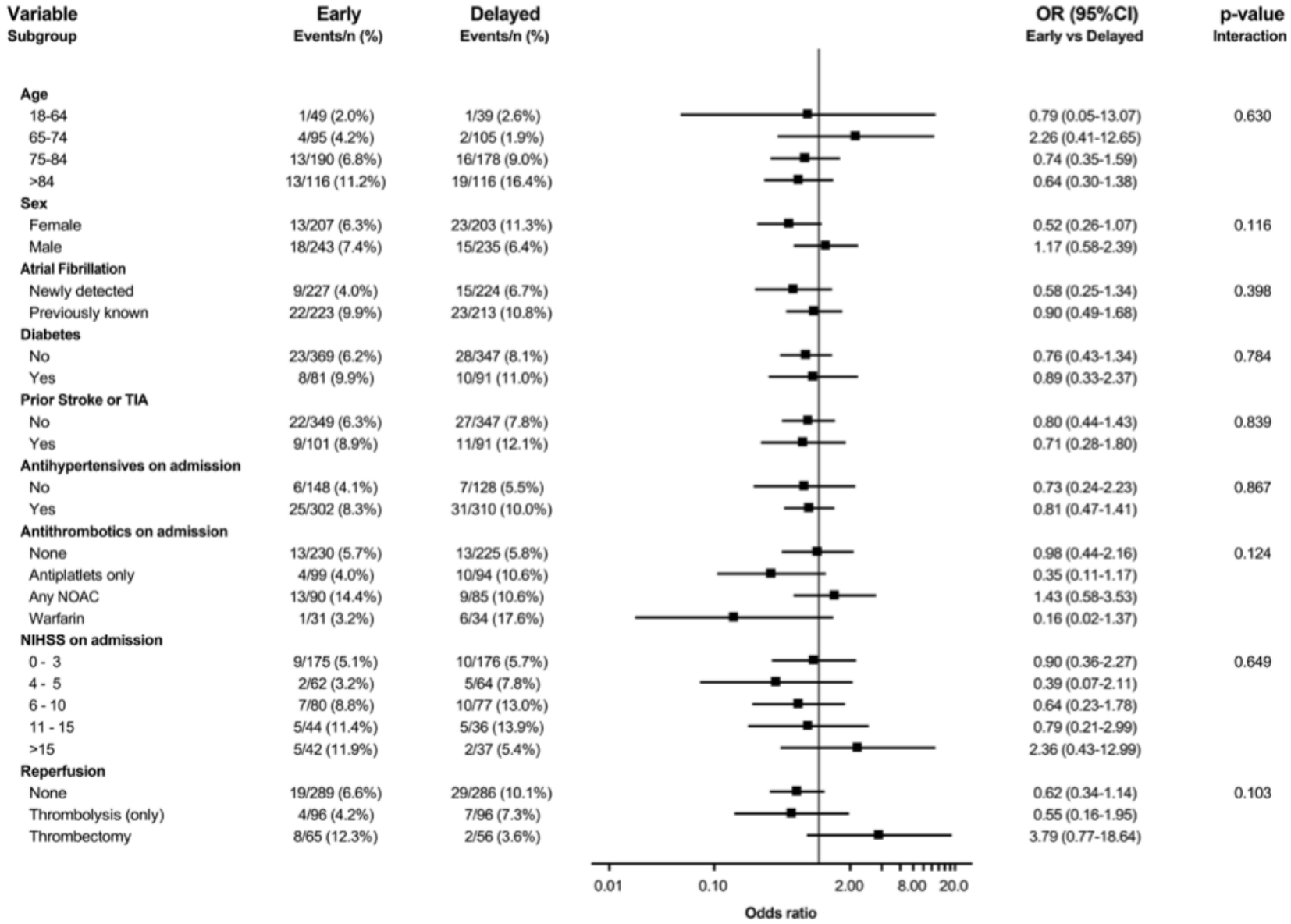
Odds ratio for the primary composite outcome in prespecified subgroups

- Signs of potential harm with early initiation of NOAC were implied only in the small groups of pts who underwent thrombectomy or had admission NIHSS scores >15, that is, pts with more severe strokes.
- There was no sign of interaction with NIHSS score measured at the time of NOAC initiation (data not



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Limitations

- Smaller-than-preplanned study population.
  - Stroke physicians wished to start treatment early to protect their patients from recurrent strokes
  - During the conduct of the TIMING study, several observa- tional studies were published underpinning the potential safety of NOACs early after ischemic stroke, which may have created concerns among investigators in the study.
  - The prevalence of cognitive impairment could undermine the patients' capability to comprehend the study and the ability or willingness to provide written informed consent.
  - COVID-19 pandemic
- Lack of brain imaging data

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Clinical perspective

What Is New?

- The TIMING study (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation) was the first randomized controlled study investigating relevant clinical end points (composite of new ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause death) after initiation of non–vitamin K antagonist oral anticoagulant (NOAC) within the first 10 days after acute ischemic stroke in patients with atrial fibrillation.
- Initiating NOAC treatment within 4 days after ischemic stroke was noninferior to initiation of NOAC between days 5 and 10.
- No patient experienced symptomatic intracerebral hemorrhage in any study group, and rates of ischemic stroke and death were numerically lower in patients randomized to early initiation of NOAC.

What Are the Clinical Implications?

- It seems both safe and reasonable to consider early initiation of NOAC after acute ischemic stroke in patients with atrial fibrillation.
- The TIMING study results may facilitate shared decision making between physicians and patients to ensure adequate acute secondary stroke prevention in the early phase of stroke unit care.
- Whether early initiation is superior to delayed start remains to be established and requires further investigation in ongoing trials (eg, OPTIMAS [Optimal Timing of Anticoagulation After Acute Ischemic Stroke], NCT03759938; ELAN [Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation], NCT03148457; and START [Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation], NCT03021928).

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Conclusions

- Early initiation was noninferior to delayed start of NOAC after acute ischemic stroke in patients with atrial fibrillation.
- The numerically lower rates of ischemic stroke and death, the absence of symptomatic intracerebral hemorrhages, and the overall low rates of major bleedings imply that early initiation of NOAC is safe.
- Patients with acute ischemic stroke and atrial fibrillation should be considered for acute secondary stroke prevention, although it remains to be established whether early is superior to delayed start.

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Ongoing trials

- **OPTIMAS** (Optimal Timing of Anticoagulation After Acute Ischemic Stroke), NCT0375993834
- **ELAN** (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients With Atrial Fibrillation), NCT0314845735
- **START** (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation), NCT03021928.