Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

Risultati del trial randomizzato ELAN

Background

- Anticoagulation with direct oral anticoagulants (DOACs) reduces the risk of ischemic stroke and systemic embolism among persons with atrial fibrillation.
- Whether the timing of DOAC initiation influences the risks of stroke recurrence and bleeding after an acute ischemic stroke is unclear.
- The risk of both recurrent ischemic stroke and intracranial hemorrhage is highest in the first few days after acute ischemic stroke, and although studies and small randomized trials suggest that early use of DOACs may be safe, these investigations have had selection bias or small sample sizes.

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ESC guidelines on atrial fibrillation

Continuation of NOACs after ischaemic stroke depends on the infarct size. Clinical study data regarding re-institution of anticoagulation are missing. Some advocate as a rule of thumb the 1-3-6-12 day rule, with re-institution of anticoagulation in patients with a transient ischaemic attack (TIA) after 1 day, with small, non-disabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will be treated not before 2 (or even 3) weeks. If patient compliance and therapeutic effect of coagulation have been assured (i.e. the stroke must have occurred under adequate anticoagulation), alternative causes for ischaemic stroke should be investigated.

Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke	Class[a]	Level[b]
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients.[1125–1130]	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended.[1095]	III	B

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Aim of the study

The Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) randomized trial aimed to estimate the safety and efficacy of early initiation of DOACs as compared with later, guideline-based initiation, using imaging-based selection criteria in persons who have had a recent stroke and have atrial fibrillation.

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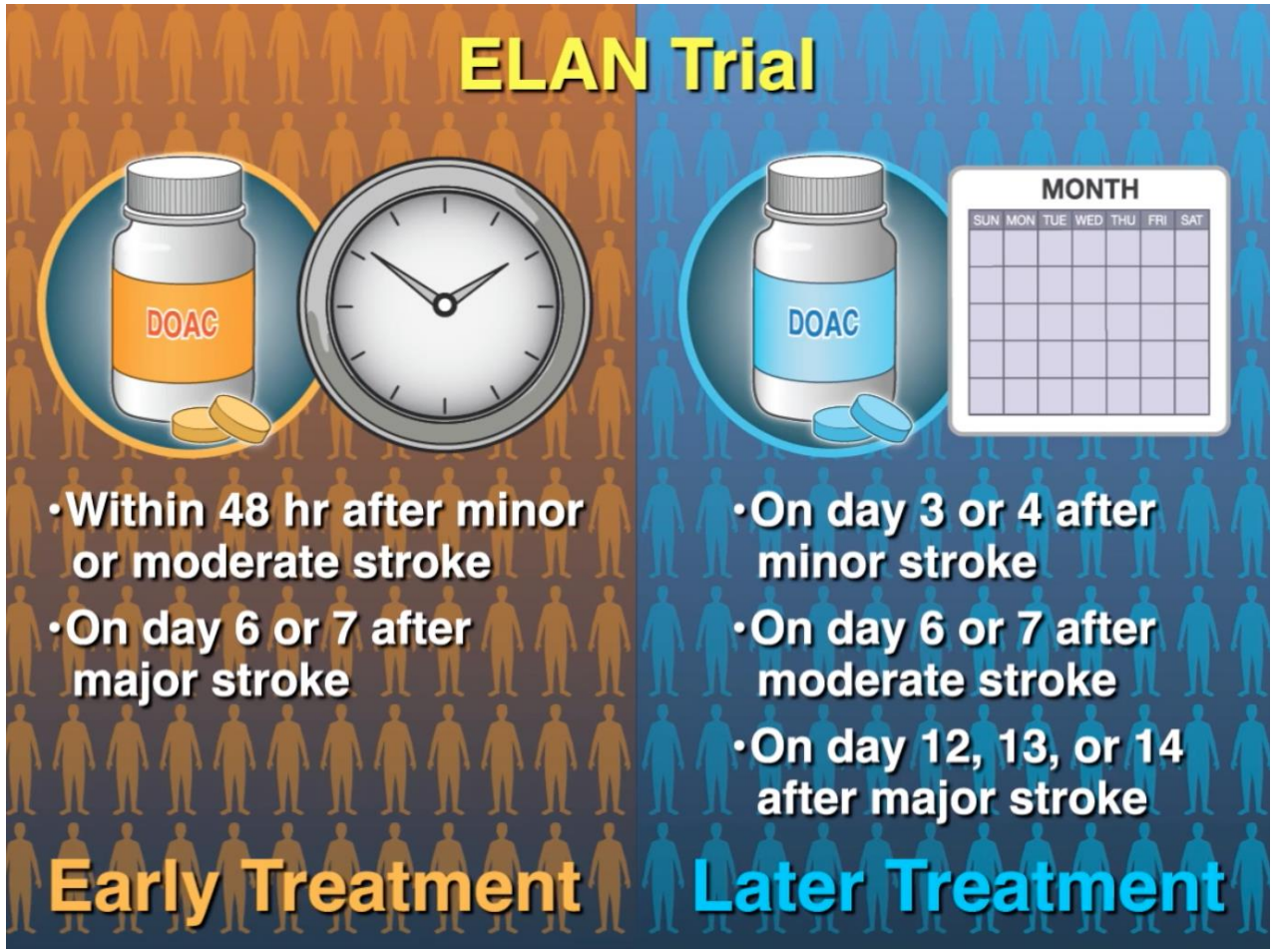
Methods

- Investigator-initiated, open-label trial at 103 sites in 15 countries.
- Assessors were unaware of the trial-group assignments.
- Primary outcome: composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization.
- Secondary outcomes: components of the composite primary outcome at 30 and 90 days

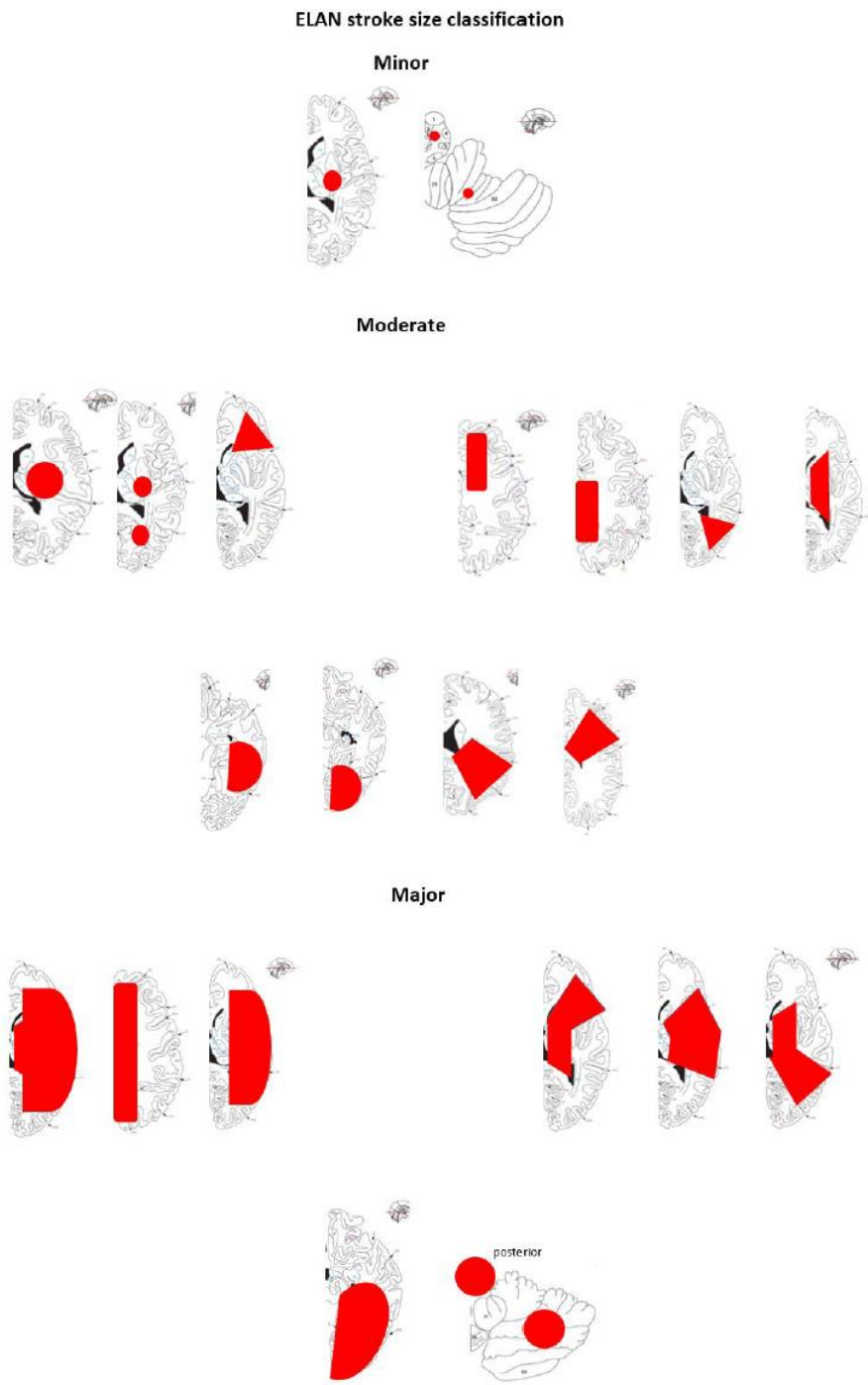


N Engl J Med 2023;388:2411-21.

Stroke size classification

Minor	Moderate	Major
Lesion is ≤ 1.5 cm in anterior or posterior circulation	Lesion is in a cortical superficial branch of the middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of the posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery	Anterior: lesion involves the whole territory of the MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of the MCA associated with the MCA deep branch, or in > 1 artery territory (e.g., MCA associated with anterior cerebral artery territories) Posterior: lesion is ≥ 1.5 cm in the brainstem or cerebellum
Caveat: multiple minor tiny spots (embolic shower) = minor stroke	Caveat: two minor lesions = moderate lesion (the sum of the lesions)	Caveat: two moderate lesions = large lesion

Ischemic stroke size classification is based on recent guidelines [4]



Baseline characteristics

Characteristic	Early-Treatment Group (N = 1006)	Later-Treatment Group (N = 1007)
Median age (IQR) — yr	77 (70–84)	78 (71–84)
Female sex — no. (%)	459 (45.6)	456 (45.3)
Region — no. (%)		
Central Europe	615 (61.1)	618 (61.4)
United Kingdom and Ireland	249 (24.8)	250 (24.8)
Israel	17 (1.7)	17 (1.7)
India	26 (2.6)	29 (2.9)
Japan	99 (9.8)	93 (9.2)
Medical history — no. (%)		
Ischemic stroke	128 (12.7)	140 (13.9)
Transient ischemic attack	45 (4.5)	51 (5.1)
Systemic embolism	19 (1.9)	31 (3.1)
Hypertension	690 (68.6)	673 (66.8)
Myocardial infarction	80 (8.0)	87 (8.6)
Diabetes	185 (18.4)	161 (16.0)
Median CHA_2DS_2-VASc score (IQR)†	5 (4–6)	5 (4–6)
Prestroke score on the modified Rankin scale — no./total no. (%)‡§		
0–2	889/1005 (88.5)	898/1006 (89.3)
3–5	116/1006 (11.5)	108/1007 (10.7)
Stroke severity according to infarct size — no. (%)		
Minor	378 (37.6)	374 (37.1)
Moderate	399 (39.7)	397 (39.4)
Major	229 (22.8)	236 (23.4)
NIHSS score — median (IQR)§		
At admission¶	5 (2–12)	5 (2–11)
At time of randomization	3 (1–6)	3 (1–6)
Initial treatment for stroke — no./total no. (%)¶		
Thrombolysis	391/986 (39.7)	377/987 (38.2)
Thrombectomy	207/986 (21.0)	232/987 (23.5)

N Engl J Med 2023;388:2411-21.

Antiplatelet therapy at baseline and DOAC prescribed after randomization

	Early Treatment (N =1006)	Late Treatment (N = 1007)
Aspirin – no. (%)	457 (45.4)	545 (54.1)
Clopidogrel – no. (%)	57 (93.4)	59 (90.8)
Rivaroxaban 20 mg	43 (4.2)	52 (5.2)
Rivaroxaban 15 mg	2 (0.2)	3 (0.3)
Dabigatran 150 mg bid	127 (12.6)	124 (12.3)
Dabigatran 110 mg bid	42 (4.2)	49 (4.9)
Apixaban 5 mg bid	550 (54.6)	526 (52.2)
Apixaban 2.5 mg bid	80 (8.0)	87 (8.6)
Edoxaban 60 mg	95 (9.4)	98 (9.7)
Edoxaban 30 mg	58 (5.8)	51 (5.1)

N Engl J Med 2023;388:2411-21.

Primary and Secondary Efficacy Outcomes

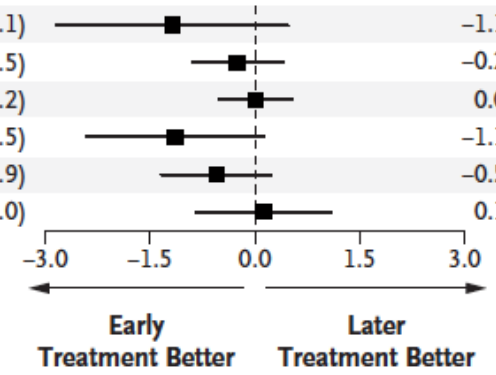
Outcome	Early-Treatment Group (N=1006)	Later-Treatment Group (N=1007)	Adjusted Odds Ratio (95% CI)*
	no./total no. (%)		
Primary outcome: composite outcome at 30 days	29/1006 (2.9)†	41/1007 (4.1)†	0.70 (0.44 to 1.14)‡
Secondary outcomes at 30 days			
Major extracranial bleeding	3/984 (0.3)	5/991 (0.5)	0.63 (0.15 to 2.38)
Symptomatic intracranial hemorrhage	2/984 (0.2)	2/991 (0.2)	1.02 (0.16 to 6.59)
Recurrent ischemic stroke	14/984 (1.4)	25/991 (2.5)	0.57 (0.29 to 1.07)
Systemic embolism	4/984 (0.4)	9/991 (0.9)	0.48 (0.14 to 1.42)
Vascular death	11/984 (1.1)‖	10/991 (1.0)	1.12 (0.47 to 2.65)
Nonmajor bleeding	30/984 (3.0)	27/991 (2.7)	1.13 (0.67 to 1.93)
Modified Rankin scale score ≤2§	624/997 (62.6)	626/1000 (62.6)	0.93 (0.79 to 1.09)
Secondary outcomes at 90 days			
Major extracranial bleeding	3/968 (0.3)	8/965 (0.8)	0.40 (0.10 to 1.31)
Symptomatic intracranial hemorrhage	2/968 (0.2)	2/965 (0.2)	1.00 (0.15 to 6.45)
Recurrent ischemic stroke	18/968 (1.9)	30/965 (3.1)	0.60 (0.33 to 1.06)
Systemic embolism	4/968 (0.4)	10/965 (1.0)	0.42 (0.12 to 1.21)
Vascular death	17/968 (1.8)	16/965 (1.7)	1.04 (0.52 to 2.08)
Death from any cause¶	45/994 (4.5)	48/995 (4.8)	0.93 (0.61 to 1.43)
Nonmajor bleeding	39/968 (4.0)	41/965 (4.2)	0.94 (0.59 to 1.47)
Modified Rankin scale score ≤2§	659/989 (66.6)	654/994 (65.8)	0.93 (0.79 to 1.09)
Any serious adverse event‖	132/947 (13.9)	157/993 (15.8)	

N Engl J Med 2023;388:2411-21.

The Primary Composite Outcome and Its Components at 30 and 90 Days

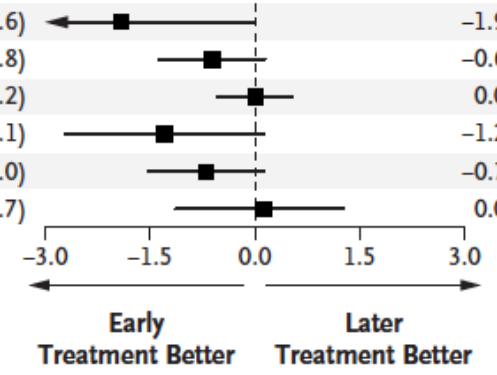
A

Outcome within 30 Days	Early-Treatment Group (N=984)	Later-Treatment Group (N=991)	Adjusted Risk Difference (95% CI)
	no. of events (%)		*percentage points*
Primary-outcome event	29 (2.9)	41 (4.1)	−1.18 (−2.84 to 0.47)
Major extracranial bleeding	3 (0.3)	5 (0.5)	−0.25 (−0.90 to 0.41)
Symptomatic intracranial hemorrhage	2 (0.2)	2 (0.2)	0.01 (−0.52 to 0.53)
Recurrent ischemic stroke	14 (1.4)	25 (2.5)	−1.14 (−2.41 to 0.13)
Systemic embolism	4 (0.4)	9 (0.9)	−0.55 (−1.34 to 0.23)
Death from vascular cause	11 (1.1)	10 (1.0)	0.13 (−0.84 to 1.09)



B

Outcome within 90 Days	Early-Treatment Group (N=968)	Later-Treatment Group (N=965)	Adjusted Risk Difference (95% CI)
	no. of events (%)		*percentage points*
Primary-outcome event	36 (3.7)	54 (5.6)	−1.92 (−3.82 to −0.02)
Major extracranial bleeding	3 (0.3)	8 (0.8)	−0.61 (−1.37 to 0.14)
Symptomatic intracranial hemorrhage	2 (0.2)	2 (0.2)	0.00 (−0.54 to 0.53)
Recurrent ischemic stroke	18 (1.9)	30 (3.1)	−1.29 (−2.72 to 0.13)
Systemic embolism	4 (0.4)	10 (1.0)	−0.70 (−1.53 to 0.13)
Death from vascular cause	17 (1.8)	16 (1.7)	0.07 (−1.13 to 1.27)



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Outcomes

Efficacy:
The incidence of a primary-outcome event was 60 estimated to range from slightly lower to slightly higher (based on the 95% CI) with early use of 40 DOACs than with later use.

Safety:
The incidence of adverse events was similar in the
two groups.

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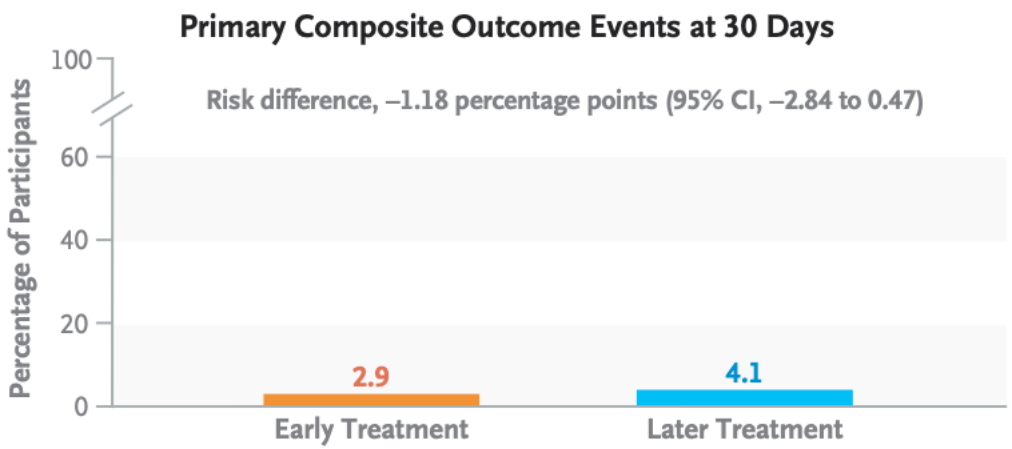

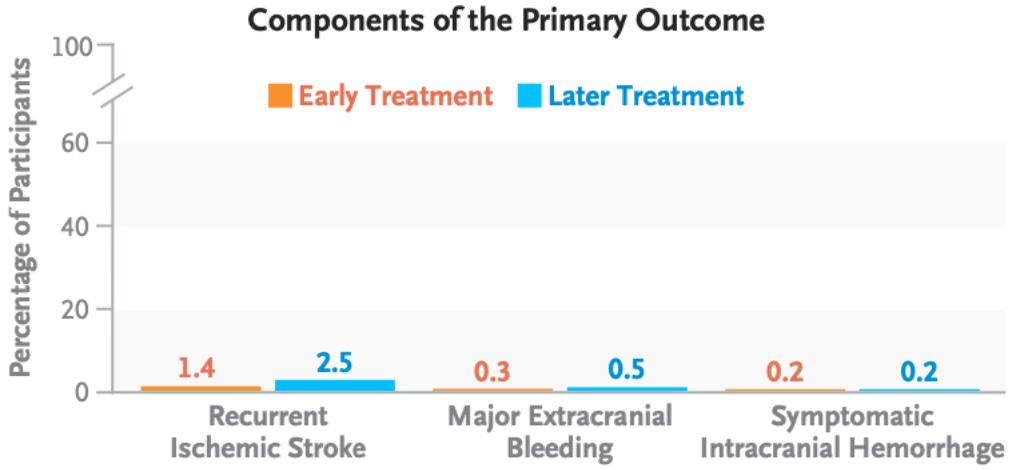

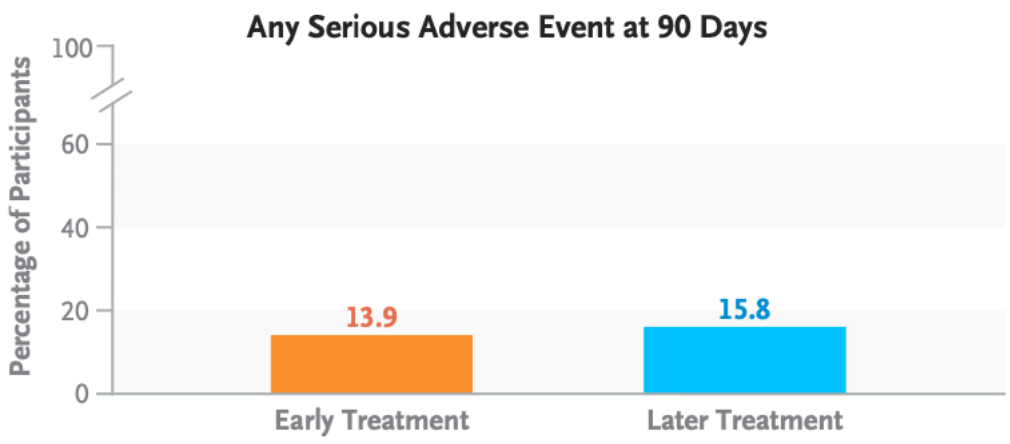

Limitations

- The trial excluded persons who were already receiving therapeutic anticoagulation at baseline.

- Classification of stroke severity was not centrally adjudicated

N Engl J Med 2023;388:2411-21.

Conclusions

In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs.

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