SUPPLEMENTAL MATERIAL

Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled non-inferiority study

Oldgren, Åsberg et al.

Contents

Outcome definition

The primary outcome event was a composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause death within 90 days of index stroke. Recurrent ischemic stroke was defined as a new focal neurological deficit of sudden onset lasting at least 24 h (or < 24 h if following therapeutic intervention, i.e. thrombolysis or thrombectomy, or if the deficit results in death within 24 h), occurring >24 hours after the index ischemic stroke, irrespective of vascular territory, and not attributable to edema, brain shift, hemorrhagic transformation, intercurrent illness, hypoxia, or drug toxicity.[23] Symptomatic intracerebral hemorrhage was defined as a new focal neurological deficit of sudden onset lasting for at least 24 h and with documented intraparenchymal hematoma (≥10mm) on imaging (computed tomography or magnetic resonance imaging), including hemorrhagic transformation of the index ischemic stroke; or a new hospitalization for intracerebral hemorrhage registered in the Swedish Stroke Register. Intracerebral hemorrhage was defined as symptomatic if there was an increase by ≥4 points in total National Institutes of Health Stroke Scale (NIHSS) or ≥2 points in one NIHSS category.[24]

Secondary outcome events included the individual components of the primary outcome event and major bleeding events. Bleedings were considered major if they resulted in death or were life-threatening, which includes all intracranial hemorrhages regardless of size and symptoms, according to the International Society on Thrombosis and Haemostasis definition;[25] or consumed major health-care resources, i.e. bleeding events leading to hospitalization.

Table S1. TIMING sites and Principal investigators.

Site	Principal investigator
Alingsås Hospital	Brita Eklund
Capio S:t Göran Hospital	Ulrika Löfmark
County Hospital Ryhov	Jenny Persson
Danderyd University Hospital	Elisabeth Rooth
Enköping Hospital	Mikael Wiklund
Falun Hospital	Joakim Hambraeus
Gävle Hospital	Ritva Jokela (deceased)
Halland Hospital, Halmstad	Peter Thomasson Sommer
Halland Hospital, Varberg	Henrik Berntsson
Helsingborg Hospital	Maria Macek
Hudiksvall Hospital	Anette Onkenhout
Hässleholm Hospital	Krzysztof Grodon
Kalmar County hospital	Claes Williamsson
Karolinska University Hospital, Huddinge	Fariha Qureshi
Karolinska University Hospital, Solna	Boris Keselman
Kiruna Hospital	Lacramioara Grosu
Kungälv Hospital	Merja Henning
Lindesberg Hospital	Martin Johansson
Motala Hospital	Ulf Rosenqvist
Mälarsjukhuset County Hospital	Bo Danielsson
Mölndal Hospital, Sahlgrenska University Hospital	Carolina Sixt
Nyköping Hospital	Görel Wachtmeister
Oskarshamn Hospital	Bongomin Otto
Sahlgrenska University Hospital	Annika Nordanstig
Skaraborg Hospital Skövde	Björn Cederin
Skåne University Hospital, Malmö	Eva Ask
Sundsvall County Hospital	Fredrick Björck
Södersjukhuset University Hospital	Mihaela Oana Romanitan
University Hospital of Umeå	Per Wester*
Uppsala University Hospital	Signild Åsberg*
Västerås Central Hospital	Hannes Frejd
Västmanland Hospital, Köping	Jan Saaf
Örebro University Hospital	Jakob Ström
Östra Hospital, Sahlgrenska University Hospital	Christina Hedén Ståhl

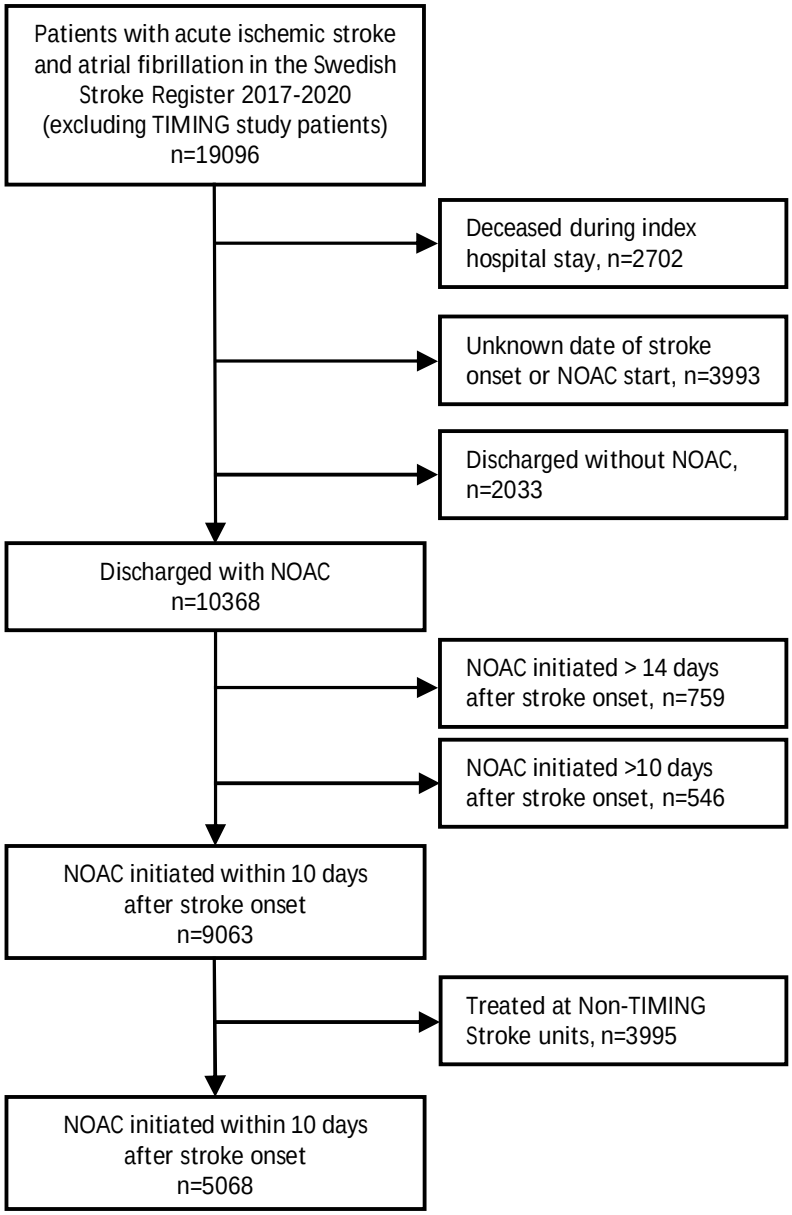
*Steering committee member

Table S2. Baseline characteristics in TIMING study patients and observational cohort

Variable	TIMING study patients n=888	Observational cohort at all stroke units* n=9063	Observational cohort at TIMING units† n=5068
Mean age, years (SD)	78.3 (9.9)	79.5 (9.3)	79.7 (9.5)
Female sex, n (%)	410 (46.2%)	4224 (46.6%)	2418 (47.7%)
Risk factors, n (%)			
Atrial fibrillation			
Previously known	436 (49.1%)	5993 (66.1%)	3521 (69.5%)
Diagnosed on admission	451 (50.8%)	3071 (33.9%)	1548 (30.5%)
Prior stroke	155 (17.5%)	1920 (21.2%)	1087 (21.4%)
Prior TIA	62 (7.0%)	942 (10.4%)	521 (10.3%)
Diabetes	172 (19.4%)	2205 (24.3%)	1224 (24.2%)
Active smoking	71 (8.0%)	700 (7.7%)	397 (7.8%)
ADL-independent before stroke, n (%)	820 (92.3%)	6466 (71.3%)	3489 (68.8%)
Living conditions before stroke, n (%)			
Own home w/o assistance	730 (82.2%)	6566 (72.4%)	3584 (70.7%)
Own home w assistance	113 (12.7%)	1803 (19.9%)	1068 (21.1%)
Nursing home	44 (5.0%)	650 (7.2%)	394 (7.8%)
Drugs on admission, n (%)			
Antihypertensives	671 (75.6%)	7307 (80.6%)	4122 (81.3%)
Statins	327 (36.8%)	3398 (37.5%)	1898 (37.5%)
Antiplatelets			
Single	193 (21.7%)	1677 (18.5%)	877 (17.3%)
Dual	6 (0.7%)	68 (0.8%)	37 (0.7%)
None	689 (77.6%)	6370 (70.3%)	3505 (69.2%)
NOACs			
Apixaban	111 (12.5%)	2685 (29.6%)	1557 (30.7%)
Dabigatran	26 (2.9%)	347 (3.8%)	239 (4.7%)
Edoxaban	2 (0.2%)	68 (0.8%)	35 (0.7%)
Rivaroxaban	36 (4.1%)	643 (7.1%)	394 (7.8%)
Warfarin	65 (7.3%)	722 (8.0%)	382 (7.5%)
Mean initial INR (SD)	1.96 (0.60)	2.40 (1.47)	2.26 (1.06)
NIHSS on admission			
Mean (SD)	6.1 (5.9)	5.4 (5.8)	5.2 (5.7)
Median (IQR)	4 (2-9)	3 (1-8)	3 (1-7)
Reperfusion therapy, n (%)			
Thrombolysis	252 (28.4%)	1021 (11.3%)	531 (10.5%)
Thrombectomy	121 (13.6%)	499 (5.5%)	288 (5.7%)

*Observational cohort, see Figure S1; †Subset of Observational cohort (patients not enrolled in the randomized study) at TIMING stroke units.
The proportion of missing data in the observational cohorts were <1% for all variables except for smoking (14.5% for all units and 10.5% for non-randomized at TIMING units), ADL (1.4 and 1.4%), INR (39.2% and 36.9%) and NIHSS (35.0% and 28.7%).
SD indicates standard deviation; TIA, transient ischemic attack; ADL, activities of daily living; NOAC, Non-vitamin K Antagonist Oral Anticoagulant; INR, international normalized ration; NIHSS, National Institutes of Health Stroke Scale; and IQR, interquartile range.

Figure S1. Study flow chart, observational cohort.



NOAC= Non vitamin K antagonist oral anticoagulant

Figure S2. Time to A) primary composite outcome, B) ischemic stroke, and C) all-cause mortality for early versus delayed initiation of NOAC until 10 days.