Supplemental material

Increase in ticagrelor use over time is associated with lower rates of ischemic stroke following myocardial infarction

Henriksson R, Ulvenstam A, Söderström L, Mooe T.

This supplementary material has been provided for additional information.

Supplemental methods

We performed a number of sensitivity analyses in order to further assess our conclusion that the increased use of ticagrelor vs. clopidogrel is associated with a lower rate of ischemic stroke in unselected AMI patients.

Ticagrelor at discharge as a variable in the multivariate cox regression model

In order to reduce confounding caused by selection bias we compared different time periods with different use of ticagrelor rather than a direct comparison between patients treated with either clopidogrel or ticagrelor. As a sensitivity analysis we performed a multivariable Cox regression analysis using the variable "Ticagrelor at discharge" instead of the variable "Belonging to the late cohort". This was done in the final fun in the multivariable cox regression analysis. In that multivariable Cox regression model ticagrelor at discharge was associated with a significant reduction of ischemic stroke: HR 0.744 (p=0.001). See table IV.

Matched analysis

We also performed a matched analysis based on the most important risk factors from the Cox analysis: age, previous ischemic stroke, CABG during hospitalisation and atrial fibrillation. Based on 25262 matched patients and 455 events of ischemic stroke, the relative risk reduction of ischemic stroke in the late cohort was 35%, using Kaplan-Meier analysis. The analysis was made using "Matchit" software in the statistical package "R".

Sub-analyses within the late cohort

To further evaluate the impact of the switch from clopidogrel to ticagrelor in terms of the risk of ischemic stroke, we compared Kaplan-Meier estimates of the incidence of ischemic stroke in the early cohort vs. the corresponding estimates in first third of the late cohort (Supplemental material, figure I), in which 34.6% of patients used ticagrelor and 65.4% used clopidogrel. Correspondingly, in a second analysis we compared the early cohort vs. the last two thirds of the late cohort (Supplemental material, figure II). Use of ticagrelor rose to 61.1% in the last two thirds of the late cohort, with the use of clopidogrel use falling to 38.9%. Due to a shorter follow-up, and fewer patients in the subgroups of the late cohort, estimated incidence data primarily illustrate a trend towards fewer cases of ischemic stroke among patients treated with ticagrelor vs. clopidogrel at 1 year. The incidence of ischemic stroke in the early cohort was 2.8% compared to 2.5% in the first third, and 2.3% in the last two thirds of the late cohort, respectively.

Table I Medication at admission in the early vs. late cohort.

	Early cohort (% (n=23447))	Late cohort (% (n=24227))	P-value
Aspirin	31.6	30.0	<0.001
ACEI/ARB*	31.6	32.8	0.01
Statins	25.3	24.8	0.16
Beta blockers	31.6	30.9	0.01
Oral Anticoagulants	3.3	3.8	<0.01
Diuretics	20.3	19.0	<0.001
Calcium inhibitors	17.7	18.7	<0.01

* ACEI: Angiotensin converting enzyme-inhibitors; ARB: Angiotensin receptor blockers.

Table II Univariable predictors of ischemic stroke

Name of predictor	HR (95% CI)	P-value
Age 65-74 years*	2.20 (1.83-2.66)	<0.001
Age ≥75 years	4.26 (3.6-5.03)	<0.001
Female sex	1.38 (1.23-1.55)	<0.001
Hypertension	1.98(1.75-2.24)	<0.001
Diabetes	1.60(1.42-1.81)	<0.001
STEMI†	0.93 (0.82-1.05)	0.24
Atrial fibrillation	3.05 (2.7-3.44)	<0.001
Heart failure during hospitalisation	2.21 (1.96-2.5)	<0.001
Smoking	0.62 (0.53-0.72)	<0.001
Previous PCI‡	1.04 (0.85-1.27)	0.73
Previous MI§	1.75 (1.47-2.07)	<0.001
Previous dialysis	1.95 (1.08-3.53)	0.03
Previous PAD**	2 (1.63-2.46)	<0.001
Previous ischemic stroke	5.20 (4.6-5.95)	<0.001
Previous hemorrhagic stroke	2.69 (1.93-3.75)	<0.001
Thrombolysis during hospitalisation	0.91 (0.56-1.50)	0.72
PCI during hospitalisation	0.46 (0.41-0.51)	<0.001
CABG during hospitalisation††	1.73 (1.17-2.58)	0.01
Aspirin at discharge	0.46 (0.37-0.57)	<0.001
ACEI/ARB at discharge‡‡	0.90 (0.79-1.03)	0.13
Statins at discharge	0.41 (0.35-0.47)	<0.001
Oral Anticoagulants at discharge	1.7 (1.39-2.09)	<0.001
Beta-blockers at discharge	0.86 (0.72-1.03)	0.11
Calcium inhibitors at discharge	1.28 (1.11-1.48)	<0.01
Dispensed prescriptions: 2	0.8 (0.63-0.958)	0.02
Dispensed prescriptions: 3	0.96 (0.75-1.23)	0.76
Dispensed prescriptions: 4	0.62 (0.54-0.72)	<0.001
Diuretics at discharge	2.08 (1.85-2.33)	<0.001
eGFR§§	0.98 (0.98-0.98)	<0.001

* Age ≤64 years was used as the reference age for different categories.

† ST-elevation myocardial infarction
‡ Percutaneous coronary intervention
§ Myocardial infarction
** Peripheral artery disease
†† Coronary artery bypass graft surgery
‡‡ ACEI: Angiotensin converting enzyme-inhibitors; ARB: Angiotensin receptor blockers
§§ Estimated glomerular filtration rate

Table III First run of the multivariable Cox regression model.

Predictor Variable	HR (95% Confidence Interval)	P-value
Age 65-74 years*	1.8 (1.43-2.28)	<0.001
Age ≥75 years	2.53 (1.99-3.22)	<0.001
Female sex	1.09 (0.95-1.26)	0.21
Hypertension	1.19 (1.01-1.39)	0.04
Smoking	1.07 (0.88-1.3)	0.5
Diabetes	1.18 (1.01-1.38)	0.04
STEMI†	1.21 (1.04-1.4)	0.02
Atrial fibrillation	1.86 (1.58-2.19)	<0.001
Heart failure during hospitalisation	1.23 (1.05-1.44)	<0.01
PCI during hospitalisation‡	0.77 (0.65-0.9)	<0.01
CABG during hospitalisation§	1.44 (0.72-2.91)	0.31
Previous myocardial infarction	0.93 (0.75-1.16)	0.52
Previous ischemic stroke	3.19 (2.7-3.77)	<0.001
Previous hemorrhagic stroke	1.36 (0.88-2.12)	0.16
Previous peripheral artery disease	1.18 (0.92-1.53)	0.19
Previous dialysis	1.71 (0.83-3.51)	0.15
Statins at discharge	0.84 (0.69-1.02)	0.08
Oral anticoagulants at discharge	0.88 (0.67-1.17)	0.38
Aspirin at discharge	0.8 (0.59-1.07)	0.13
Calcium inhibitors at discharge	0.95 (0.8-1.4)	0.6
Diuretics at discharge	1.05 (0.89-1.23)	0.57
Belonging to the late cohort	0.84 (0.73-0.96)	0.01
Dispensed prescriptions: 2	0.85 (0.67-1.07)	0.16
Dispensed prescriptions: 3	1.11 (0.86-1.44)	0.42
Dispensed prescriptions: 4	0.86 (0.73-1.01)	0.07
eGFR**	0.997 (0.994-1)	0.18

* Age ≤64 years was used as the reference age for different categories.

† ST-elevation myocardial infarction
‡ Percutaneous coronary intervention
§ Coronary artery bypass graft surgery
** Estimated glomerular filtration rate

Table IV Final run of the multivariable cox regression analysis using ticagrelor at discharge as a variable instead of belonging to the late cohort

Predictor Variable	HR (95% Confidence Interval)	P-value
Age 65-74 years*	1.64 (1.36-2.02)	<0.001
Age ≥75 years	2.14 (1.74-2.63)	<0.001
Hypertension	1.17 (1.02-1.34)	0.03
Diabetes	1.23 (1.07-1.41)	0.01
STEMI†	1.29 (1.13-1.48)	<0.001
Atrial fibrillation	1.89 (1.65-2.17)	<0.001
Heart failure during hospitalisation	1.29 (1.13-1.48)	<0.001
PCI during hospitalisation‡	0.74 (0.65-0.86)	<0.001
CABG during hospitalisation§	1.93 (1.28-2.9)	<0.01
Previous ischemic stroke	3.1 (2.68-3.59)	<0.001
Previous hemorrhagic stroke	1.51 (1.06-2.17)	0.02
Statins at discharge	0.8 (0.6-0.95)	0.01
Ticagrelor at discharge	0.744 (0.63-0.86)	0.001
eGFR**	0.996 (0.993-0.999)	0.01

* Age ≤64 years was used as the reference age for different categories.

† ST-elevation myocardial infarction
‡ Percutaneous coronary intervention
§ Coronary artery bypass graft surgery
** Estimated glomerular filtration rate

Figure I Kaplan-Meier estimates of the incidence of ischemic stroke in the early cohort vs. the first third of the late cohort

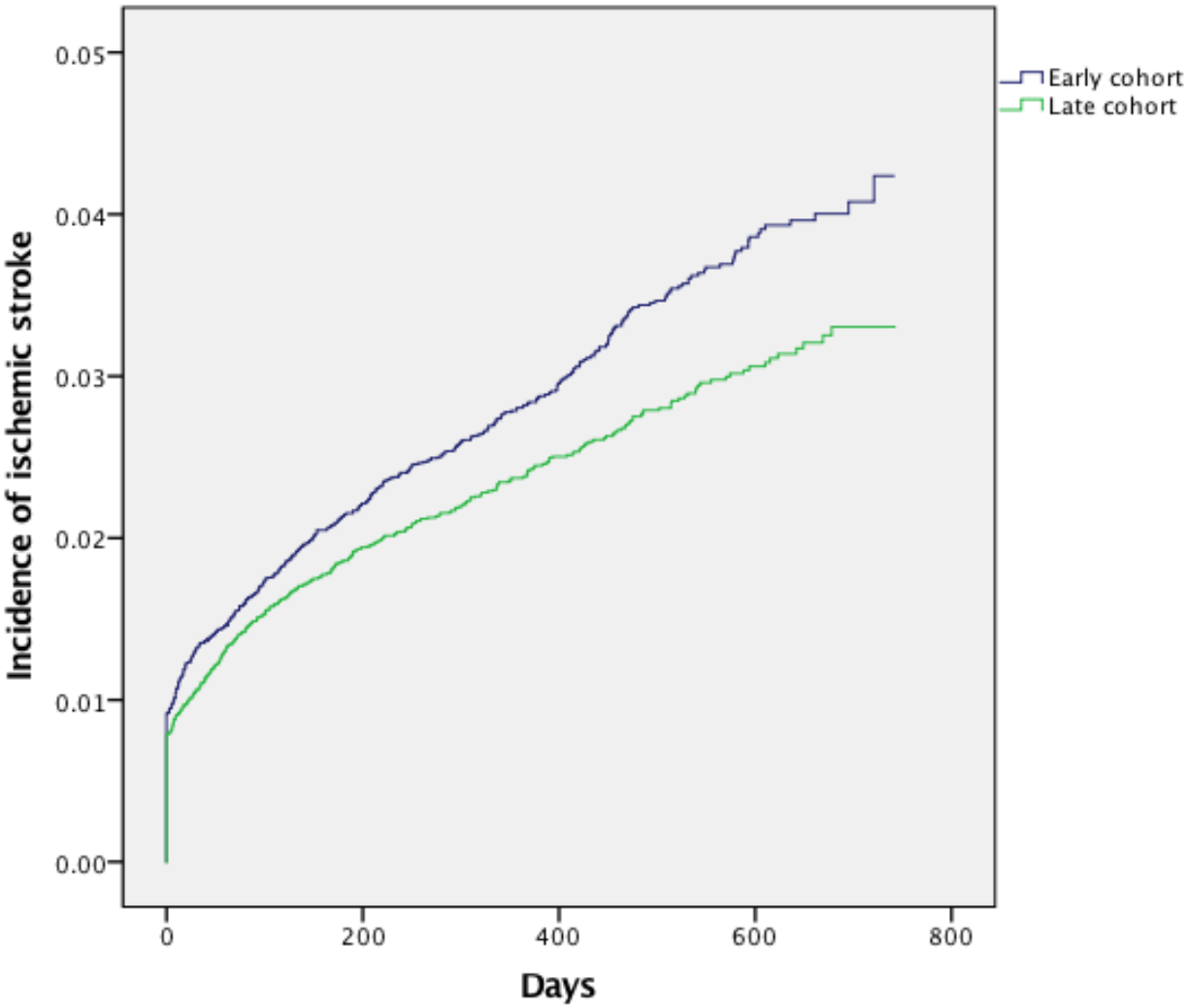

Figure II Kaplan-Meier estimates of the incidence of ischemic stroke in the early cohort vs. the last two thirds of the late cohort