



Ischaemic stroke despite oral anticoagulant therapy in patients with AF

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What is the risk of recurrence and how to prevent further events?

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Background

- Oral anticoagulation (OAC) prevents ischaemic stroke in patients with atrial fibrillation (AF)
- Patients with AF may have ischaemic stroke despite taking OAC (“treatment failure”?)
- Since several years, Vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) are alternative options for OAC

- 1) Are patients having ischemic stroke despite OAC are at increased risk of recurrent ischaemic stroke (AIS)?
- 2) Is changing the type of anticoagulant (VKA or DOAC or type of DOAC) associated with reduced risk of AIS?

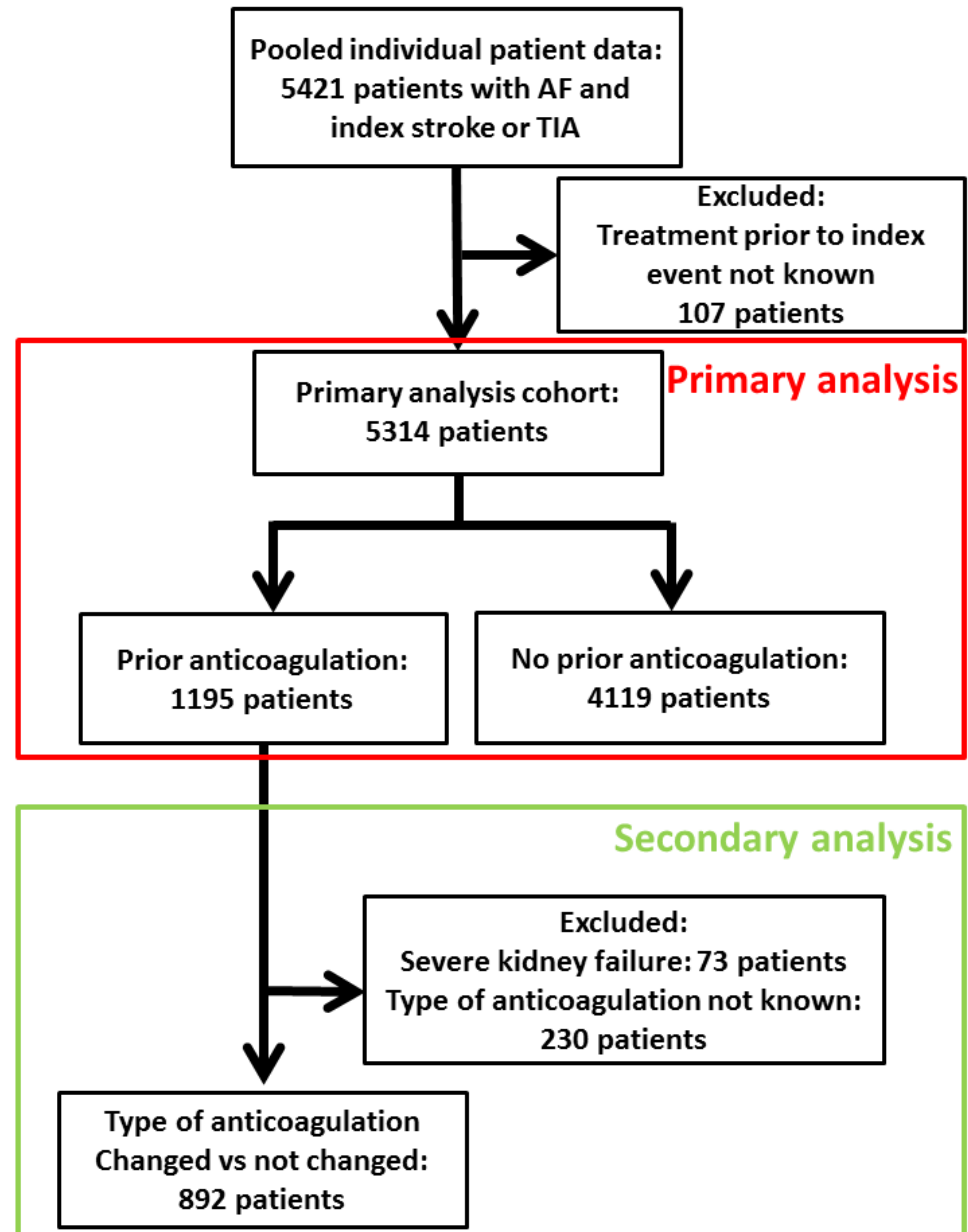
Methods

- Pooled individual patient data analysis of 7 prospective cohorts
- Patients with AF and an index event (ischemic stroke or TIA).
- Primary analysis:
 - Patients taking VKA or DOAC prior to index event (**OAC_{prior}**) vs.
 - Patients without prior anticoagulation (**OAC_{naive}**).
- Secondary analysis:
 - changed the type of OAC (i.e. from VKA to DOAC or vice versa) (**OAC_{changed}**) vs.
 - continued the same OAC (**OAC_{unchanged}**).
- Time-to-endpoint was analysed using multivariate cox proportional hazard regression models with frailty term for study and calculating hazard ratios (HR) with corresponding 95% confidence intervals.

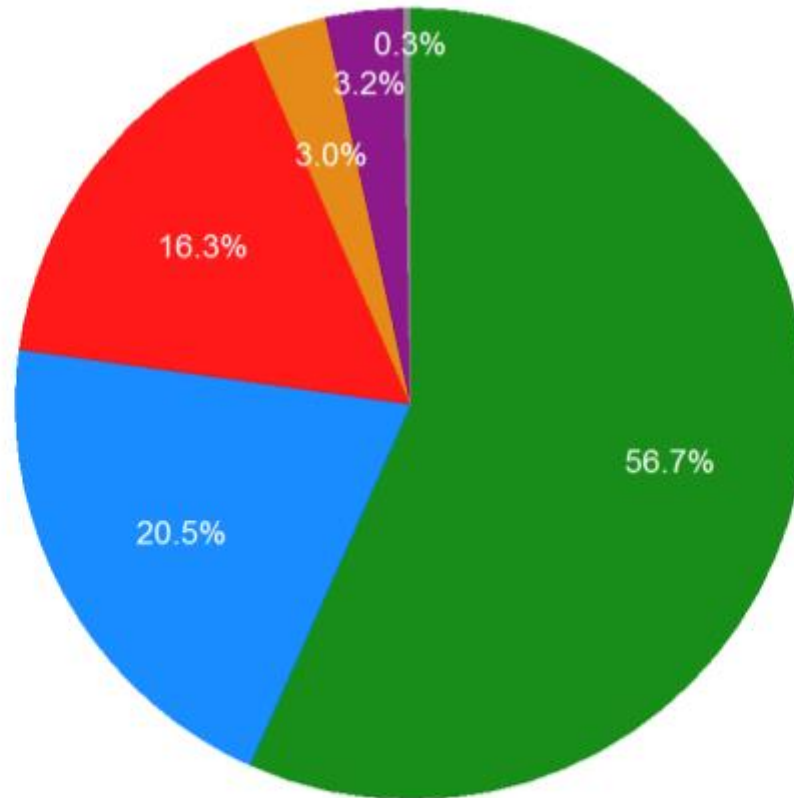


Study flow chart

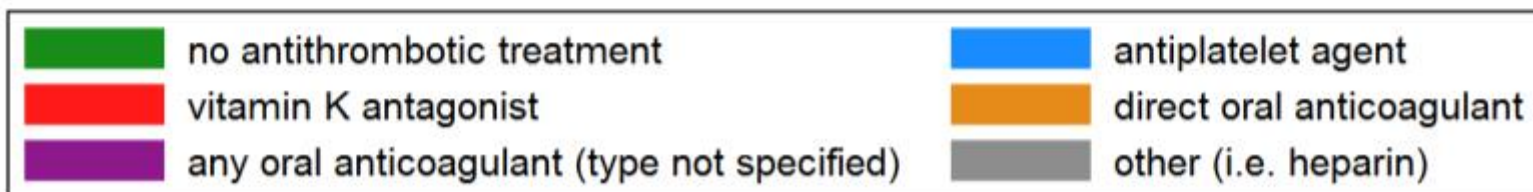
	Study period	Patients
Single Center Studies		
Verona (Italy) ¹	2013-2015	230
Erlangen (Germany)	2011-2013	337
NOACISP (Basel/Switzerland)	2012-2017	540
Multi Center Studies		
RAF (29 centers in Europe/Asia)	2012-2014	854
RAF-NOAC (29 centers in Europe/Asia)	2014-2016	888
SAMURAI-NVAF (18 centers in Japan)	2011-2014	1192
CROMIS-2 (80 centers in the UK and 1 in the Netherlands)	2011-2015	1273



Antithrombotic therapy prior to index event



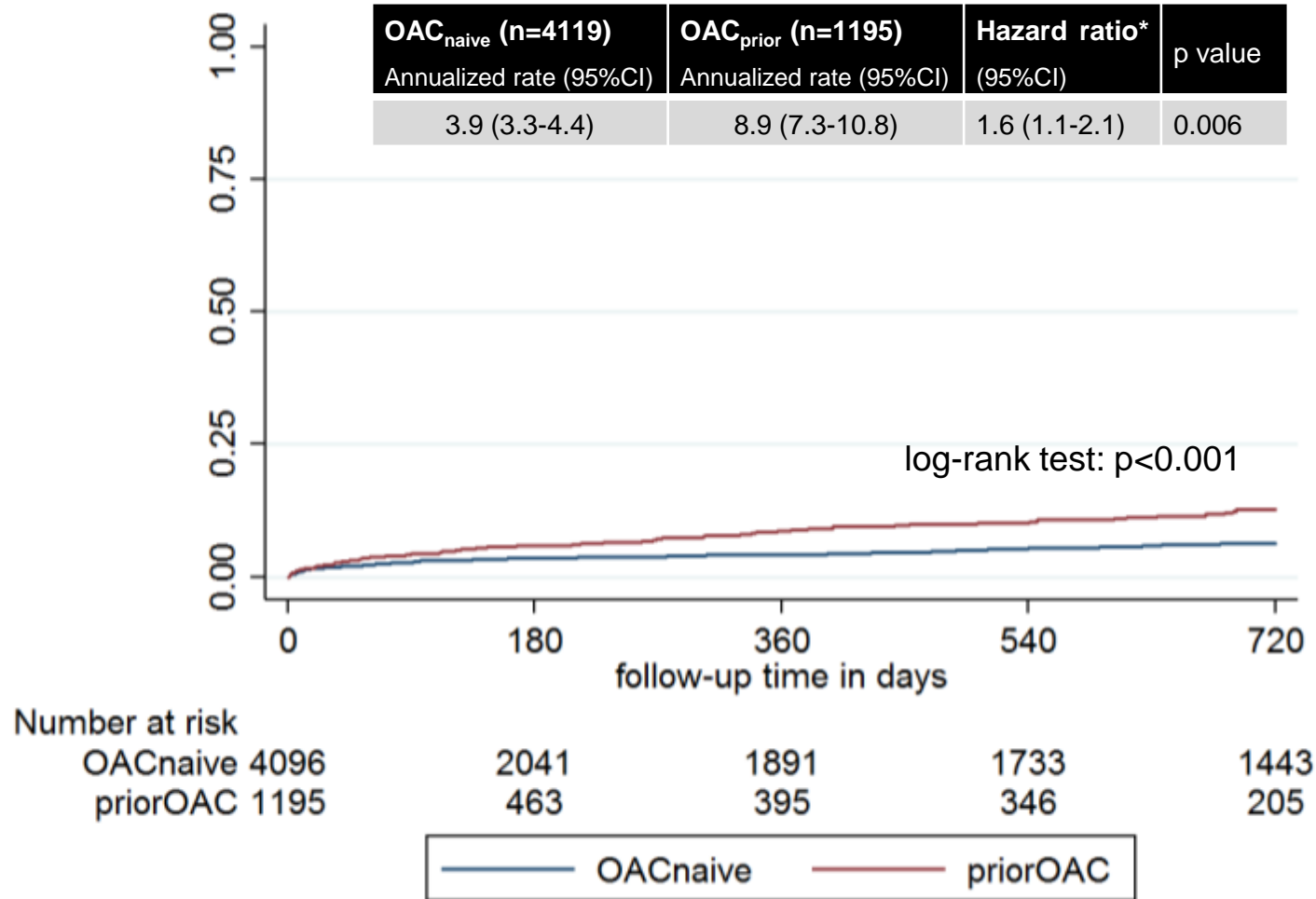
After index event:
92.8% taking any OAC



Primary analysis: Baseline Characteristics

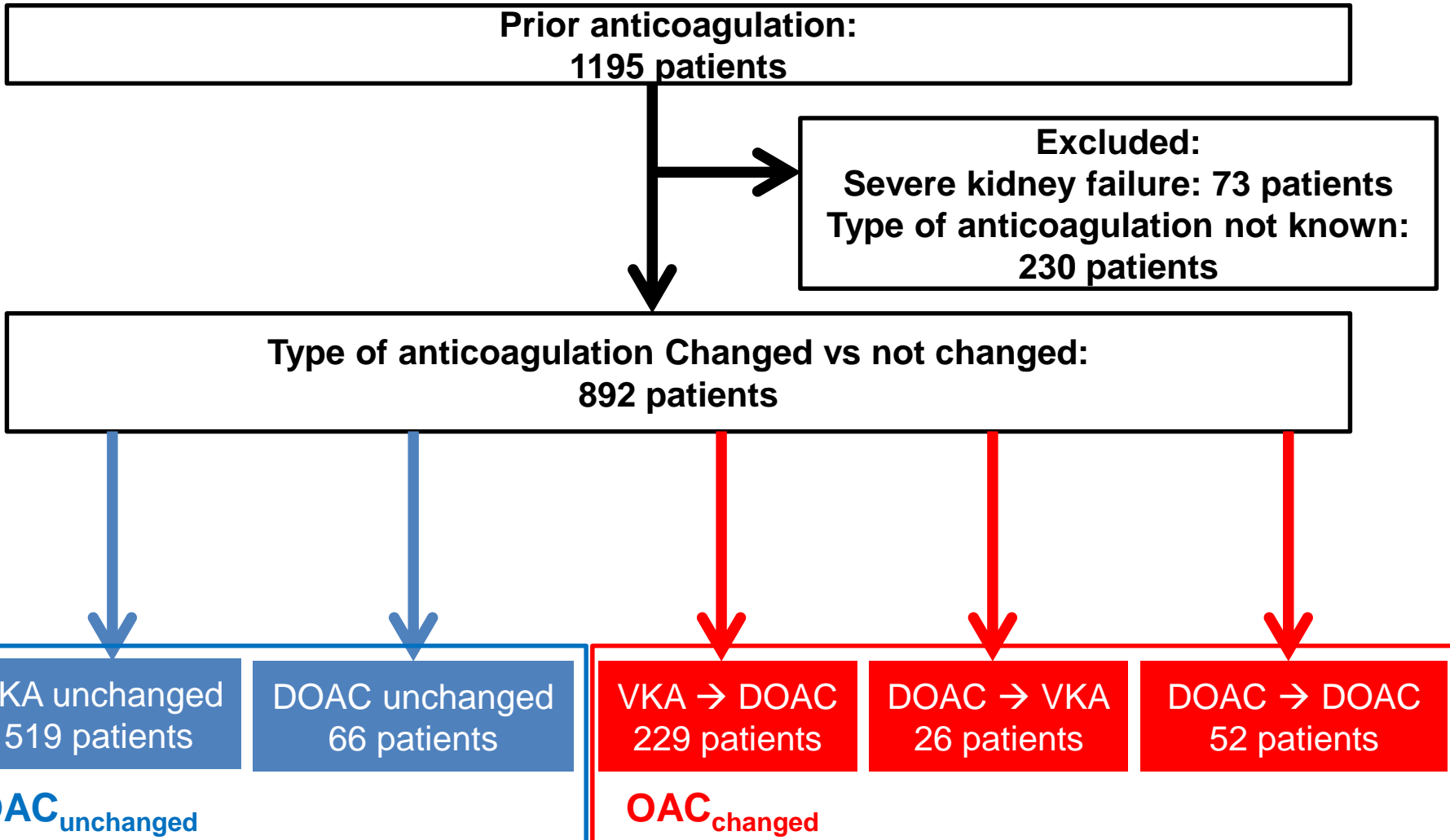
	OAC _{prior} (n=1195)	OAC _{naive} (n=4119)	p value
Age	79 (73-84)	77 (70-84)	<0.001
Female	555 of 1195 (46.4%)	2004 of 4119 (48.7%)	0.178
History of ischemic stroke (other than index event)	458 of 1192 (38.4%)	788 of 4111 (19.2%)	<0.001
History of ICH	17 of 780 (2.2%)	34 of 2769 (1.2%)	0.060
Hypertension	1026 of 1195 (85.9%)	2958 of 4089 (72.3%)	<0.001
Hypercholesterinemia	438 of 1026 (42.7%)	1262 of 3387 (37.3%)	0.002
Smoking	188 of 1150(16.3%)	694 of 4021 (17.3%)	0.505
Diabetes mellitus	442 of 1194 (37.0%)	890 of 4109 (21.7%)	<0.001
Normal renal function (CrCl >50ml/min)	638 of 894 (71.4%)	2638 of 3321 (79.4%)	<0.001
Modest kidney failure (CrCl 30-50ml/min)	185 of 894 (20.7%)	554 of 3321 (16.7%)	
Severe kidney failure (CrCl <30ml/min)	71 of 894 (7.9%)	129 of 3321 (3.9%)	
Intravenous thrombolysis	156 of 1193 (13.1%)	929 of 4095 (22.7%)	<0.001
Intraarterial treatment	48 of 1057(4.5%)	141 of 3897 (3.6%)	0.174
NIHSS on admission	5 (2-11)	6 (2-12)	<0.001
CHADs-VASc	5 (4-6)	5 (4-6)	0.103
HAS-BLED	3 (3-4)	3 (3-4)	0.626

Primary analysis: Recurrent Ischaemic Stroke



* Adjusted for: age, sex, history of ischemic stroke other than index event, hypertension, diabetes mellitus, modest or severe kidney failure (CrCl<50ml/min) and treatment with any oral anticoagulant after index event. Center/study was introduced as shared frailty term in this analysis.

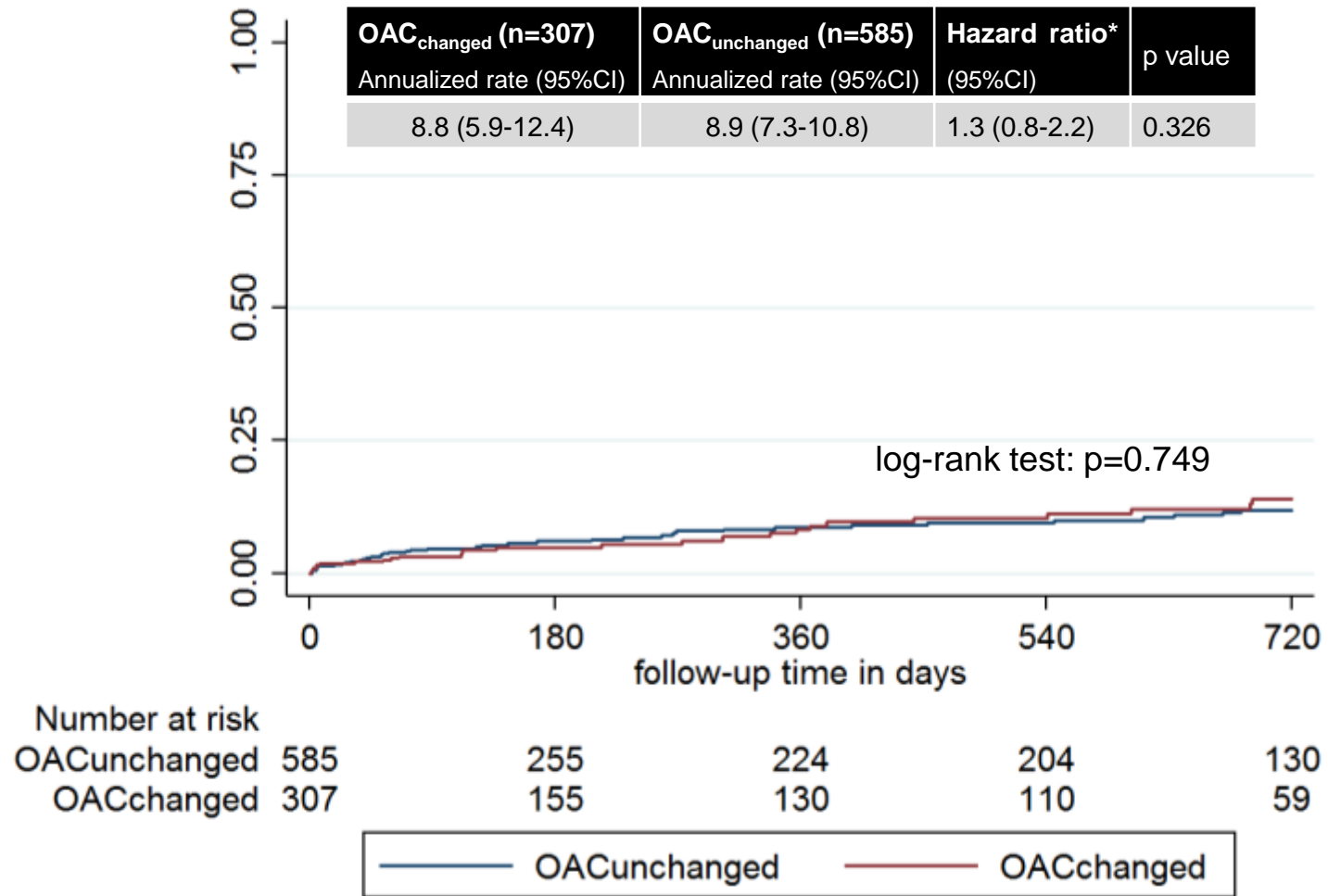
Secondary analysis: OAC changed or unchanged?



Secondary analysis: Baseline Characteristics

	OAC _{changed} (n=307)	OAC _{unchanged} (n=585)	p value
Age	79 (74-84)	79 (72-83)	0.046
Female	155 (50.6%)	249 (42.6%)	0.023
History of ischemic stroke (other than index event)	119 of 306 (38.9%)	222 of 583(38.1%)	0.828
History of ICH	5 of 275 (1.8%)	9 of 414 (2.2%)	1.000
Hypertension	259 of 306 (84.6%)	499 of 584 (85.4%)	0.766
Hypercholesterinemia	145 of 306 (47.4%)	240 of 584 (41.1%)	0.075
Smoking	33 of 286 (11.5%)	80 of 568 (14.1%)	0.336
Diabetes mellitus	109 of 305 (35.7%)	226 of 584 (38.7%)	0.423
Normal renal function (CrCl >50ml/min)	207 of 273 (75.8%)	105 of 305 (74.4%)	0.719
Modest kidney failure (CrCl 30-50ml/min)	66 of 273 (24.2%)	105 of 410 (25.6%)	
Severe kidney failure (CrCl <30ml/min)	0	0	
Intravenous thrombolysis	51 of 304 (16.8%)	60 of 584 (10.3%)	0.007
Intra-arterial treatment	15 of 278 (5.4%)	18 of 483 (3.7%)	0.274
NIHSS on admission	4 (2-10)	5 (2-11)	0.222
CHADs-VASc	6 (4-6)	5 (4-6)	0.014
HAS-BLED	3 (2-4)	3 (3-4)	0.097

Secondary analysis: Recurrent Ischaemic Stroke



* Adjusted for: age, sex, history of ischemic stroke other than index event, hypertension, diabetes mellitus, modest or severe kidney failure (CrCl<50ml/min) and treatment with any oral anticoagulant after index event. Center/study was introduced as shared frailty term in this analysis.

Conclusions

- Patients having a stroke despite anticoagulation therapy are at increased risk of further events.
- Changing anticoagulation was not associated with a decreased risk
- Limitation: No detailed analysis of different agents/dosages or od/bid
- More research is needed to investigate mechanisms of recurrent stroke and improve secondary prevention in these patients



Thank you for your attention!

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