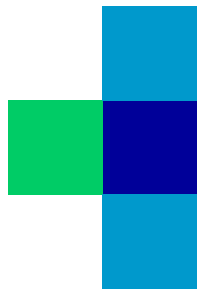


**Anticoagulant Reversal, Blood Pressure Levels,
and Anticoagulant Resumption in Patients
with Anticoagulant Related Intracerebral Hemorrhage**

JAMA. 2015;313(8):824-836

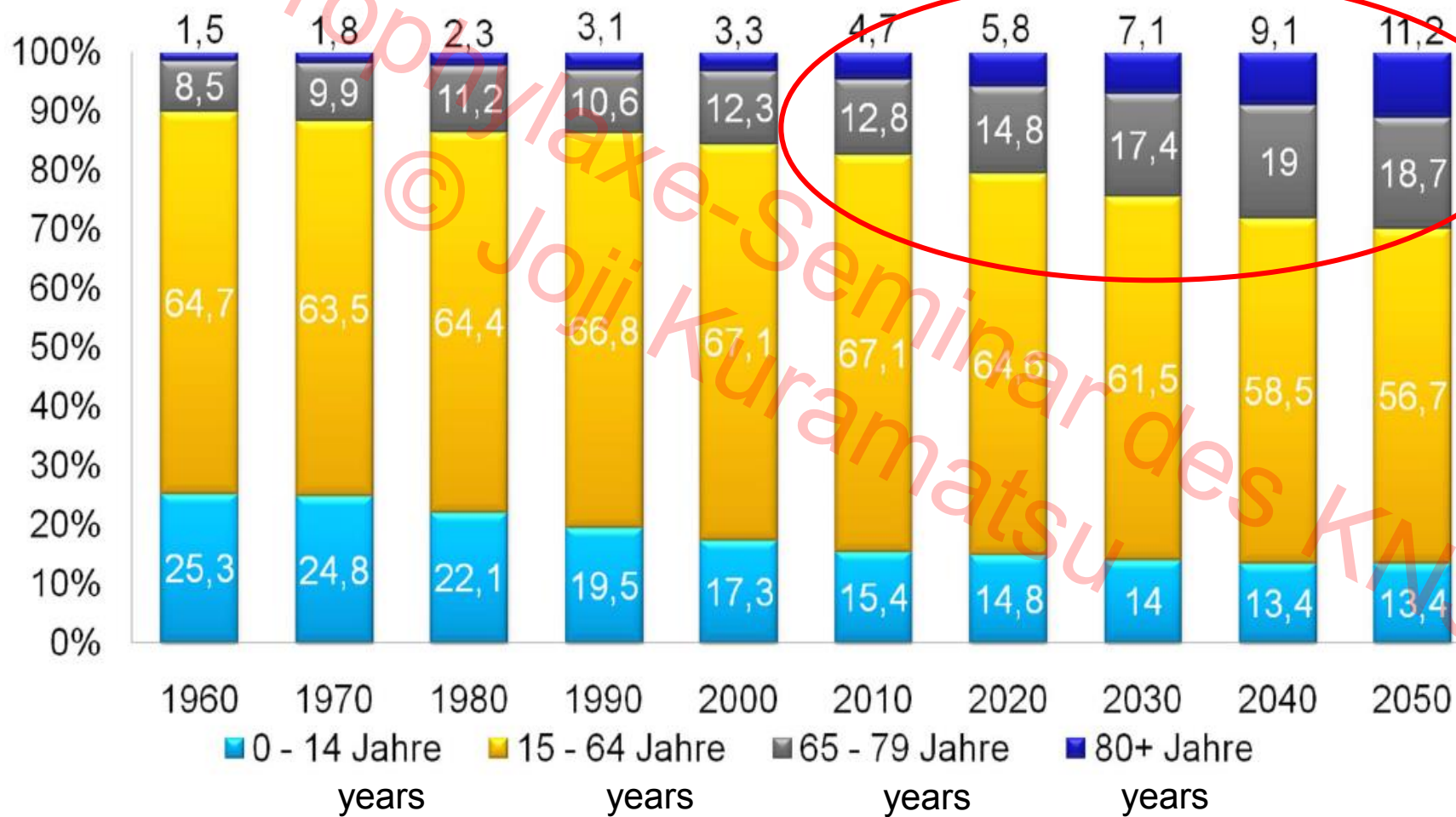
Joji Kuramatsu

Neurologische Univ.- Klinik Erlangen



Epidemiologie der intrazerebralen Blutung unter OAK

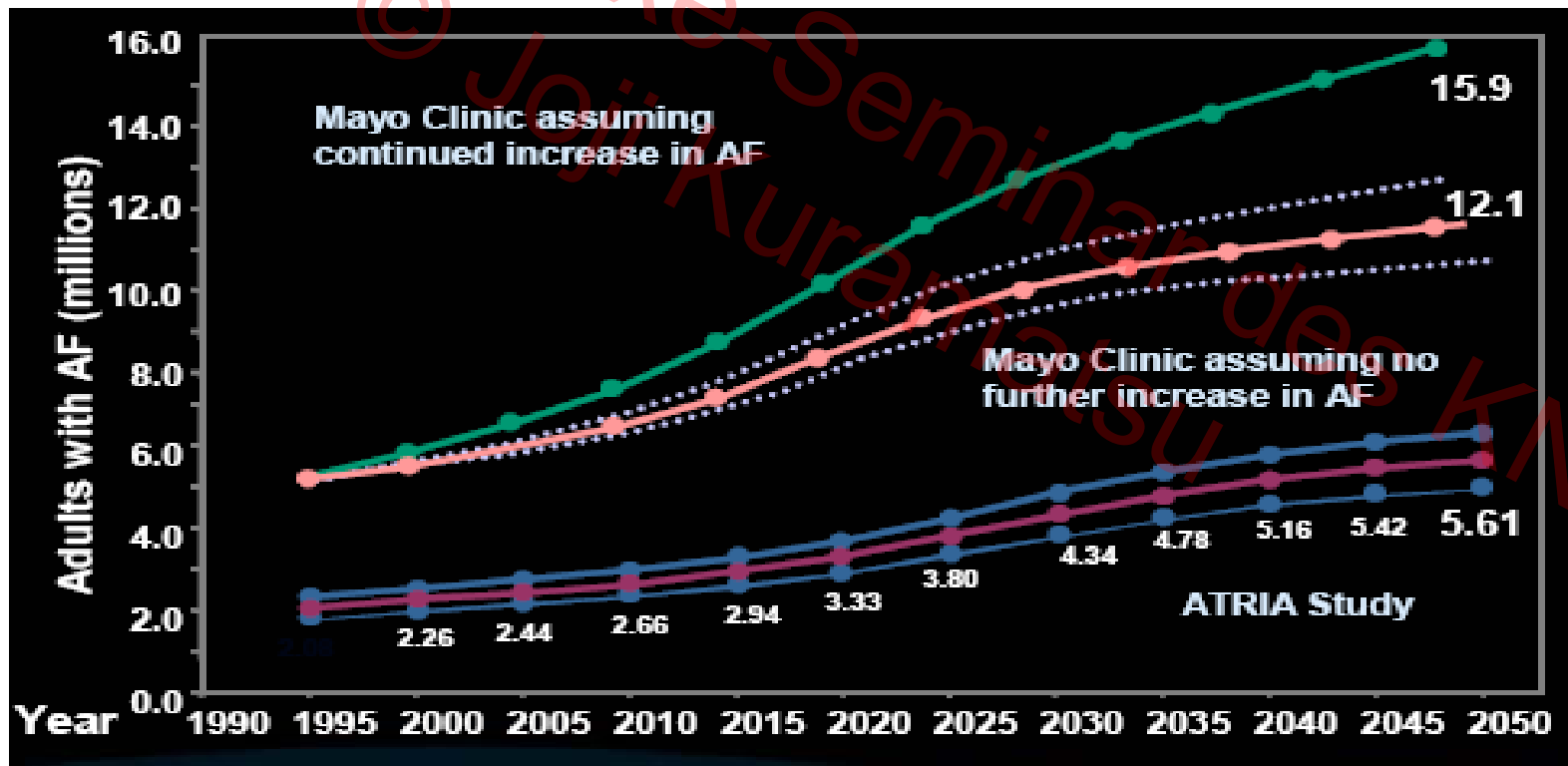
- Demographische Entwicklung in der EU -



Epidemiologie der intrazerebralen Blutung unter OAK

- einige Fakten -

- 1-1.7 % der europäischen Bevölkerung sind auf OAK
- Eurostat: im Jahre 2020 geschätzte 10.7 Mio. mit VHF



Epidemiologie der intrazerebralen Blutung unter OAK

- einige Fakten -

The increasing incidence of anticoagulant-associated intracerebral hemorrhage

M.L. Flaherty, MD; B. Kissela, MD; C.J. M...; P. Sekar, MS; ...erick, MD

Table 1. Incidence of anticoagulant-associated intracerebral hemorrhage (AAICH), and ischemic stroke

	1988	1993–1994	1999
All ischemic stroke	NA	140.0 (133.2–146.8)	142.6 (135.8–149.3)
Cardioembolic ischemic stroke	NA	31.1 (27.9–34.3)	30.4 (27.3–33.5)
Cardioembolic ischemic stroke due to atrial fibrillation	NA	22.0 (19.3–24.7)	20.6 (18.1–23.2)
All ICH	16.5 (14.1–18.9)	22.1 (19.4–24.8)	24.6 (21.8–27.4)
AAICH	0.8 (0.3–1.3)	1.9 (1.1–2.7)	4.4 (3.2–5.5)

Parentheses indicate 95% confidence intervals.

* Age-, sex-, and race-adjusted to the 2000 US population, expressed per 100,000 persons.

NA = not available.

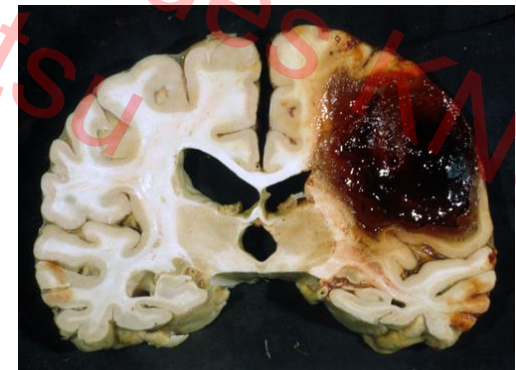
Ca. 80% der OAK assoziierten ICBs sind Patienten mit VHF

Epidemiologie der intrazerebralen Blutung unter OAK

- einige Fakten -

- Unter Antikoagulation bis 10-fach erhöhtes Risiko für eine ICB
- OAK-ICB stellen 13% bis 25% aller ICB dar
- OAK-ICB treten auf mit einer Rate von 2-9 pro 1000 Patienten/Jahr
- Jährliche Inzidenz in den USA

Übertragen auf die BRD konservativ geschätzt ca. 2000 Patienten/Jahr

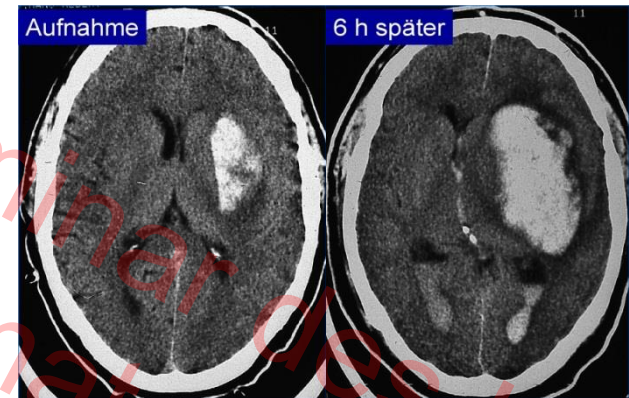


Steiner et al. Stroke 2006
Hart et al. Stroke 1995/2006
Liotta et al. 2013 J Stroke-CVD
Kuramatsu et al. 2015 JAMA

Behandlung der Antikoagulanzen - ICB

Keine Hilfe aus den Guidelines!

- AHA / ASA
- EUSI / ESO
- World Stroke Recommendations



→ **Very low quality of evidence**

→ **Weak recommendations**

ICB unter oraler Antikoagulation (Vitamin-K-Antagonisten)

■ Akutbehandlung

→ Minimierung des Hämatomwachstums

■ Langzeitbehandlung

→ Balance zwischen Blutung und Ischämie



Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

Joji B. Kuramatsu, MD; Stefan T. Gerner, MD; Peter D. Schellinger, MD; Jörg Glahn, MD; Matthias Endres, MD; Jan Sobesky, MD; Julia Flechsenhar, MD; Hermann Neugebauer, MD; Eric Jüttler, MD; Armin Grau, MD; Frederick Palm, MD; Joachim Röther, MD; Peter Michels, MD; Gerhard F. Hamann, MD; Joachim Hüwel, MD; Georg Hagemann, MD; Beatrice Barber, MD; Christoph Terborg, MD; Frank Trostdorf, MD; Hansjörg Bänzner, MD; Aletta Roth, MD; Johannes Wöhrle, MD; Moritz Keller, MD; Michael Schwarz, MD; Gernot Reimann, MD; Jens Volkmann, MD; Wolfgang Müllges, MD; Peter Kraft, MD; Joseph Classen, MD; Carsten Hobohm, MD; Markus Horn, MD; Angelika Milewski, MD; Heinz Reichmann, MD; Hauke Schneider, MD; Eik Schimmel, MD; Gereon R. Fink, MD; Christian Dohmen, MD; Henning Stetefeld, MD; Otto Witte, MD; Albrecht Günther, MD; Tobias Neumann-Haefelin, MD; Andras E. Racs, MD; Martin Nueckel, MD; Frank Erbguth, MD; Stephan P. Kloska, MD; Arnd Dörfler, MD; Martin Köhrmann, MD; Stefan Schwab, MD; Hagen B. Huttner, MD

JAMA. 2015;313(8):824-836. doi:10.1001/jama.2015.0846

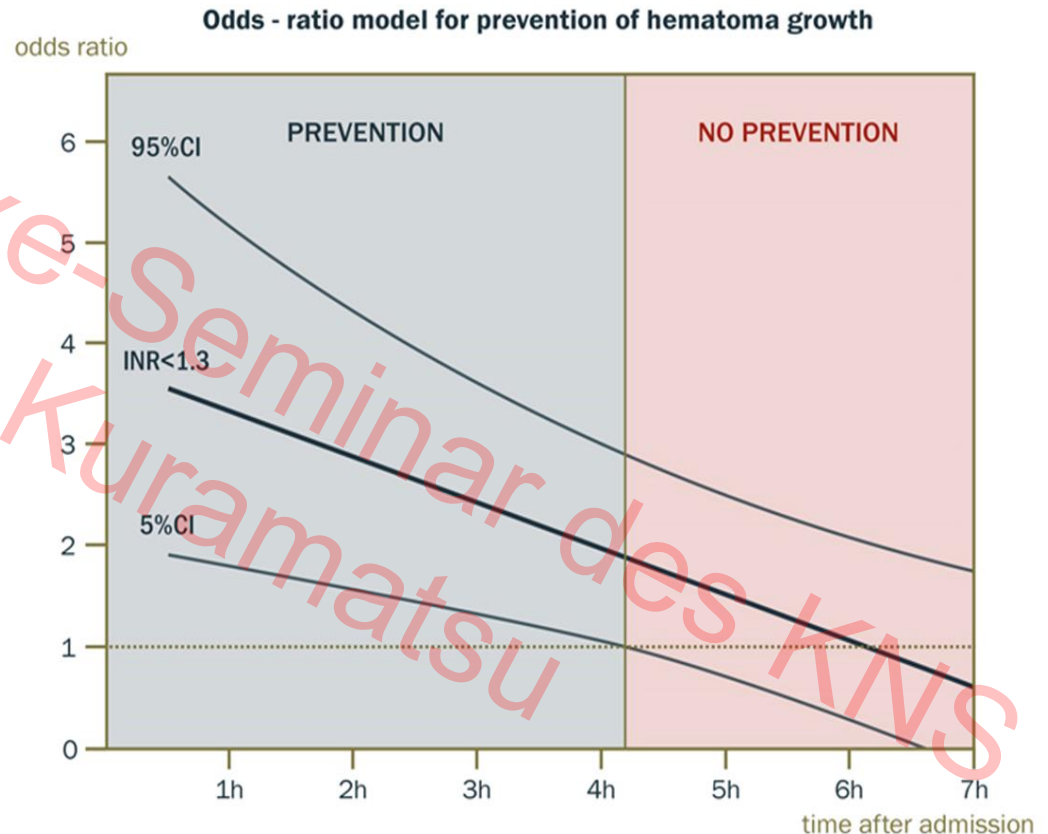


- Fragestellung: Akut und Langzeitbehandlung
- Deutschlandweit-multizentrisch (19 Zentren)
- 1176 Patienten mit OAK-ICB eingeschlossen
- Studien Endpunkte: Vermeidung Hämatomwachstum & Komplikationen im 1 Jahres Follow-up

Akutbehandlung – Antagonisierung OAK- ICB

eTable 2. Multivariable model for factors associated with hematoma enlargement.

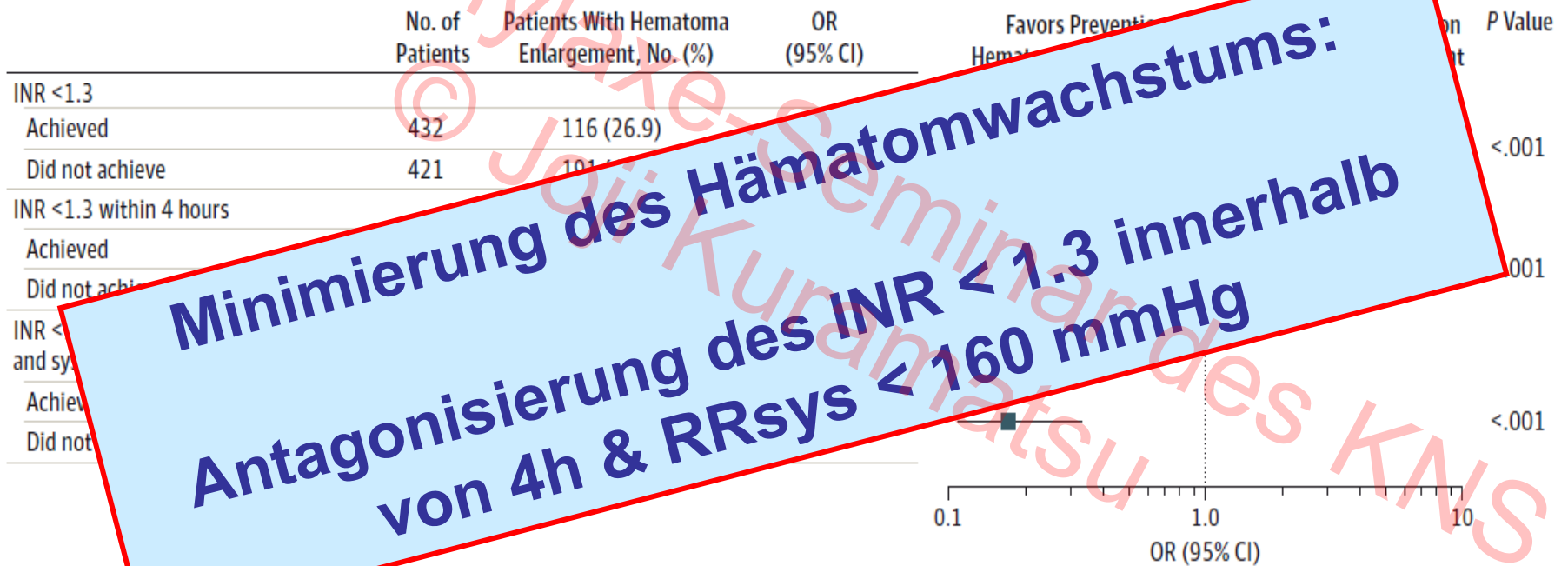
Multivariable - parameters	Risk ratio (95% CI)	P Value (<0.05)
Onset to initial imaging [<130min], n=137/271 (50.6%) [≥130min], n=95/278 (34.2%)	2.284 (1.445-2.949)	<0.001
Diagnosis to treatment [≥80min], n=148/374 (39.6%) [<80min], n=123/371 (33.2%)	1.559 (1.142-2.130)	0.005
Deep ICH present, n=173/406 (42.6%) absent, n=134/447 (30.0%)	1.389 (1.012-1.905)	0.04
1st INR-monitoring after reversal reference increment 0.1	2.294 (1.282-4.098)	0.005
Systolic blood pressure at 4h reference increment 1 mmHg	1.007 (1.002-1.014)	0.02
NIHSS reference increment 1 point	1.017 (0.998-1.036)	0.07
Mechanical heart valve present, n=32/67 (47.8%) absent, n=275/786 (35.0%)	1.037 (0.496-1.961)	0.96
Coronary artery disease present, n=154/379 (40.6%) absent, n=153/474 (32.3%)	1.531 (1.018-2.092)	0.007



Combined effects of INR reversal & blood pressure reduction

Akutbehandlung – Antagonisierung OAK- ICB

Figure 3. Adjusted Graphical Regression Analysis of Combined Associations of INR Reversal, Systolic Blood Pressure, and Timing With Hematoma Enlargement



Multivariable model for the combined associations, ie, extent and timing of international normalized ratio (INR) reversal and systolic blood pressure (BP), with hematoma enlargement. Hematoma enlargement was defined as relative volume increase of >33% on follow-up imaging. Adjustments consisted of all

nonmodifiable parameters associated with hematoma enlargement, ie, time from symptom onset to imaging, deep intracerebral hemorrhage location, National Institutes of Health Stroke Scale score, and comorbidity (eTable 2 in the Supplement). OR indicates odds ratio.

Akutbehandlung – Antagonisierung OAK-ICB Hämatomwachstum & Outcome

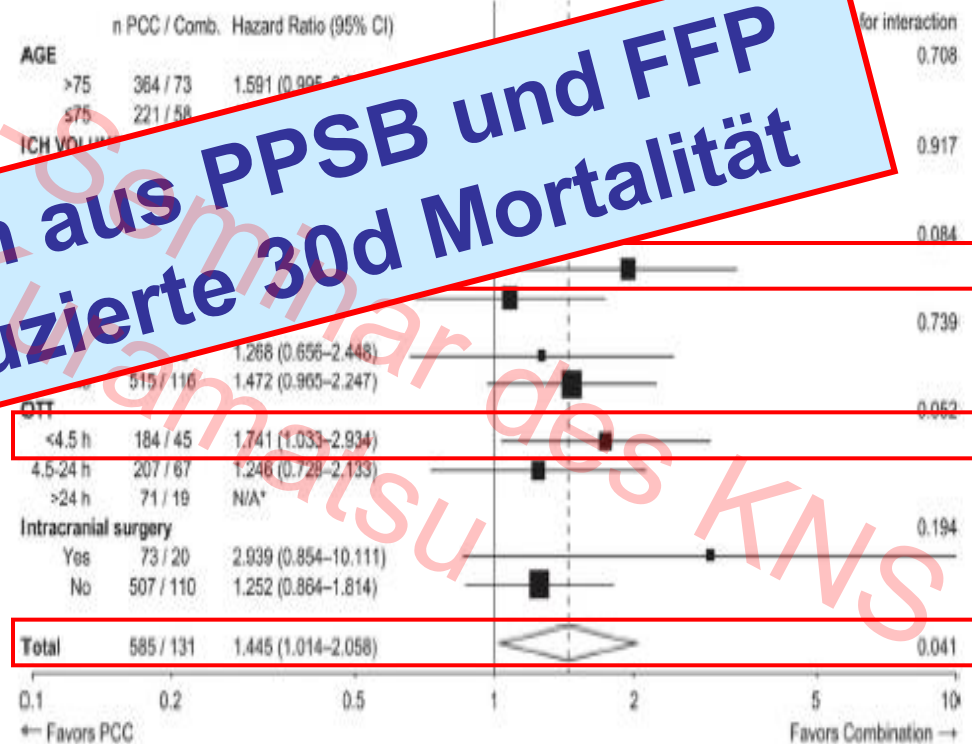
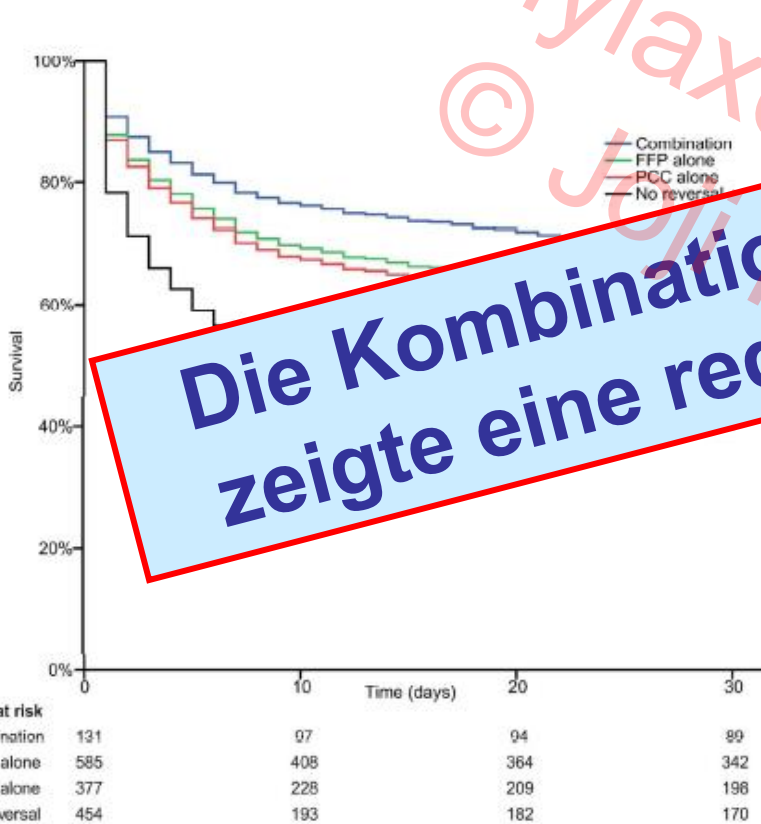
Ann Neurol, 2015 Apr 8. doi: 10.1002/ana.24416. [Epub ahead of print]

Reversal strategies for vitamin K antagonists in acute intracerebral hemorrhage.

Parry-Jones AR¹, Di Napoli M, Goldstein JN, Schreuder FH, Tetri S, Tattisumak T, Yan B, van Nieuwenhuizen KM, Dequatre-Ponchelle N, Lee-Archer M, Horstmann S, Wilson D, Pomero F, Masotti L, Lerpiniere C, Godoy DA, Cohen AS, Houben R, Al-Shahi Salman R, Pennati P, Fenoglio L, Werring D, Veltkamp R, Wood E, Dewey HM, Cordonnier C, Klijn CJ, Meligeni F, Davis SM, Huhtakangas J, Staals J, Rosand J, Meretoja A.

- Fragestellung: Modus der Antagonisierung (PPSB, FFP und Kombinationen)
- International-multizentrisch (9 Länder, 16 Zentren)
- 1547 Patienten mit OAK-ICB eingeschlossen
- Studien Endpunkt 30 Tages-Mortalität

Akutbehandlung – Antagonisierung OAK-ICB Hämatomwachstum & Outcome



Die Kombination aus PPSB und FFP zeigte eine reduzierte 30d Mortalität

FIGURE 3: Cox regression survival curves for 30-day survival

Antagonisierung mit was??

Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial

Lancet 2015; 385: 2077-87

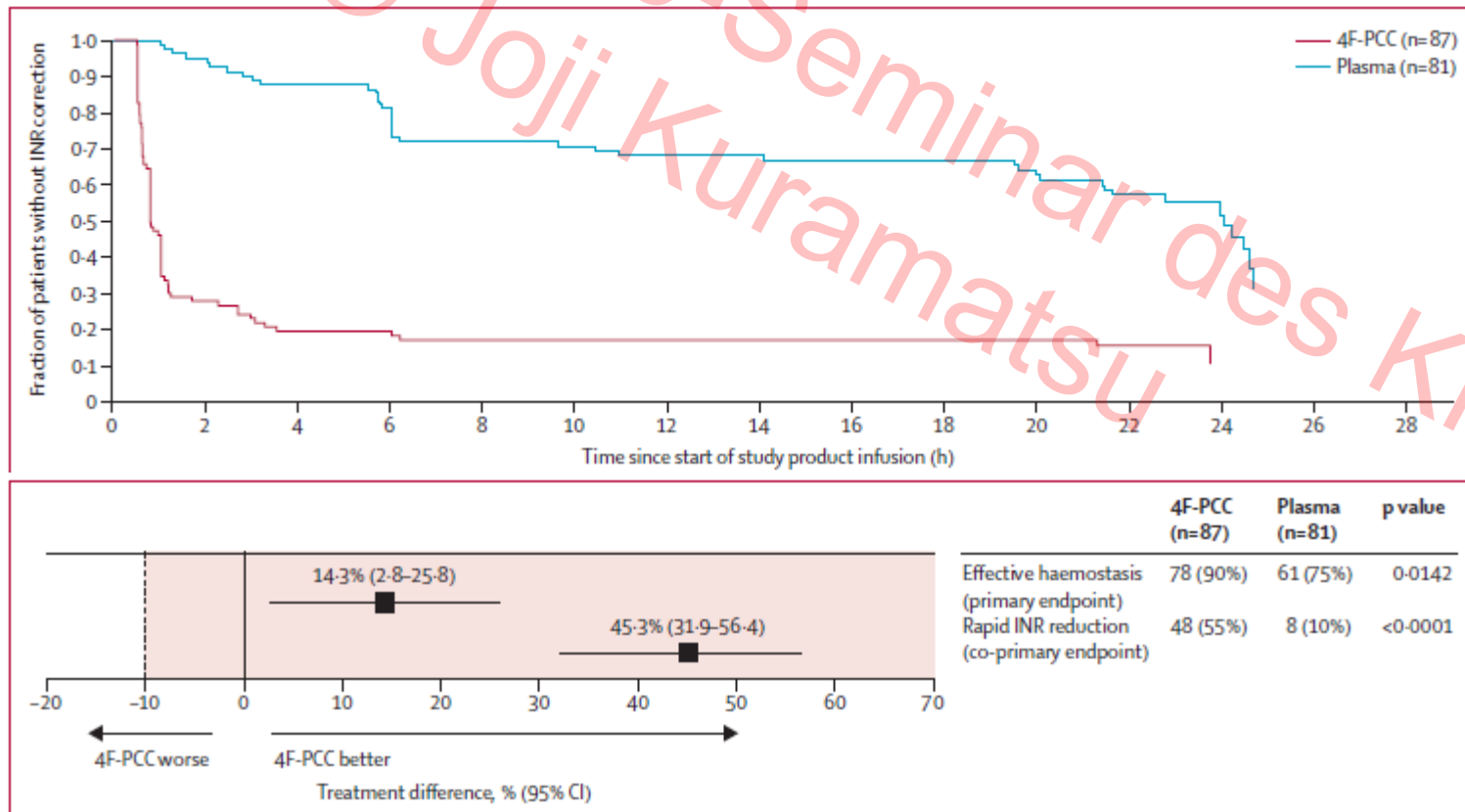


Figure 3: Primary and co-primary endpoints

Zusammenfassung – Akutbehandlung

Minimierung des Hämatomwachstums

- Blutdruck in der Frühphase aggressiv senken
RRsys < 140 mmHg
- OAK-ICB so schnell wie möglich INR ausgleichen
mindestens INR < 1,3 innerhalb von 4h
30-50IE PPSB/kg KG
- PPSB besser als FFP, ggfs. in Kombination
- Symptombeginn? → Risikoabschätzung



7. ICB unter oraler Antikoagulation (Vitamin-K-Antagonisten)

■ Akutbehandlung

→ Minimierung des Hämatomwachstums

■ Langzeitbehandlung

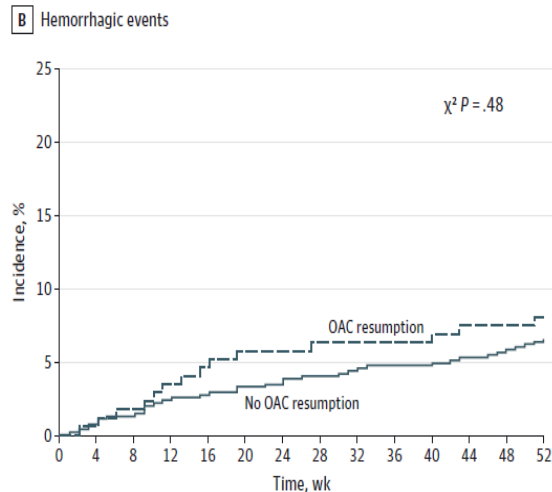
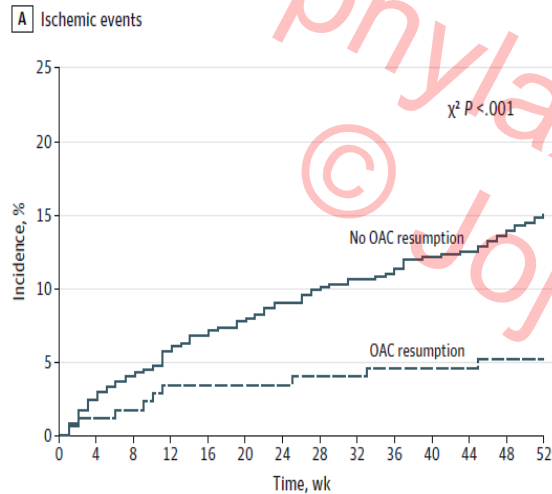
→ Balance zwischen Blutung und Ischämie



Langzeitbehandlung

Erneute Antikoagulation nach ICB

Figure 4. Crude Incidence Rates of Ischemic and Hemorrhagic Complications During 1-Year Follow-up in Patients With and Without OAC Resumption



No. of patients	547	518	481	445	416	399	389	375	362	354	343	336	322	316
No OAC resumption	547	518	481	445	416	399	389	375	362	354	343	336	322	316
OAC resumption	172	172	170	170	169	168	166	166	165	163	161	161	159	157

eTable 7. Analyses of confounders within OAC resumption analysis for A-fib patients – before and after propensity score matching.

OAC-ICH patients with atrial fibrillation (n=566)	OAC resumption (n=110)	No OAC resumption (n=456)	P Value	std. mean diff.
Before propensity matching				
Age† [y]	72.9 (±7.7)	75.5 (±7.8)	0.002	0.35
Prestroke mRS‡	0 (0-1)	0 (0-1)	0.37	0.09
CHADS₂ score‡				
median (IQR)	2 (1-3)	2 (2-3)	0.09	0.18
Admission status‡				
NIHSS‡	7 (3-13)	10 (4-17)	0.002	0.33
Imaging				
ICH volume‡ [cm ³]	11.0 (3.9-22.0)	11.9 (4.8-31.8)	0.10	0.30
Intraventricular hemorrhage*	30 (27.3%)	156 (34.2%)	0.16	0.17
Hematoma enlargement*	22/103 (21.4%)	128/416 (30.8%)	0.06	0.19
Hospital discharge				
mRS‡	3 (2-4)	4 (3-5)	<0.001	0.55
OAC-ICH patients with atrial fibrillation (n=261)				
After propensity matching				
Age† [y]	73.1 (±7.6)	74.2 (±8.8)	0.29	0.07
Prestroke mRS‡	0 (0-1)	0 (0-1)	0.57	0.06
CHADS₂ score‡				
median (IQR)	2 (1-3)	2 (2-3)	0.57	0.04
On admission status‡				
NIHSS‡	7 (3-13)	7 (3-14)	0.97	0.05
Imaging				
ICH volume‡ [cm ³]	10.5 (3.5-20.2)	9.9 (3.6-20.7)	0.98	0.05
Intraventricular hemorrhage*	29 (26.9%)	47 (30.7%)	0.50	0.03
Hematoma enlargement*	22 (20.4%)	31 (20.3%)	0.88	0.04
Hospital discharge				
mRS‡	4 (3-4)	4 (3-4)	0.29	0.01

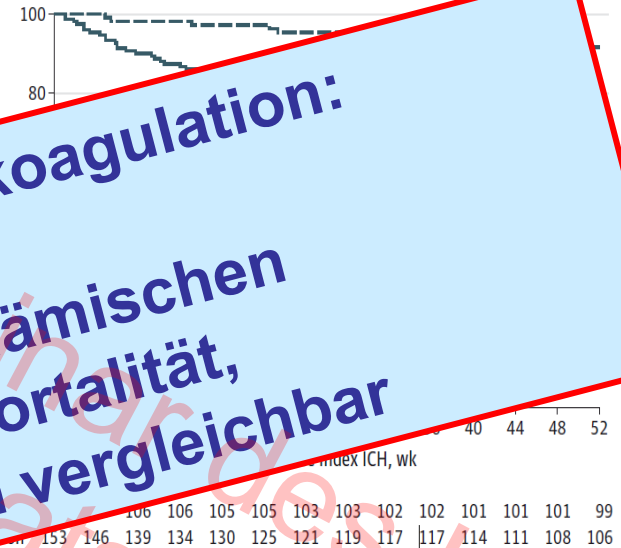
Langzeitbehandlung

Erneute Antikoagulation nach ICB

Table 8. Propensity-matched analysis of event and incidence rates in A-fib patients – new ischemic stroke versus recurrent ICH.

Patients with atrial fibrillation	No. of Patients	No. of events (%)	P Value	Incidence rate per 100 patient years (95%CI)	P Value
New cerebral Infarction	261	20 (7.7%)			
According to treatment					
OAC resumption	108	4 (3.7%)	0.55	3.9 (1.9-5.8)	0.92
No OAC resumption	153	5 (3.3%)		3.9 (2.2-5.7)	
Recurrent ICH					
According to treatment					
OAC resumption	108	4 (3.7%)	0.55	3.9 (1.9-5.8)	0.92
No OAC resumption	153	5 (3.3%)		3.9 (2.2-5.7)	

Figure 5. Kaplan-Meier Survival Rates of Patients With Atrial Fibrillation With and Without OAC Resumption



**Wiederaufnahme einer Antikoagulation:
Niedrigere Rate an ischämischen
Komplikationen & Mortalität,
Blutungskomplikationen vergleichbar**

Table 9. Propensity-matched Cox regression analyses of long-term mortality in A-fib patients.

Patients with atrial fibrillation (n=261)	No. of patients	No. of events (%)	Hazard ratio (95%CI)	P Value	Adjusted Hazard ratio (95%CI)	P Value
Overall	261	56 (21.5%)				
OAC resumption	108	9 (8.3%)	0.233 (0.114-0.476)	<0.001	0.258 (0.125-0.534)	<0.001
No OAC resumption	153	47 (30.7%)	1 (reference)		1 (reference)	

Langzeitbehandlung Erneute Antikoagulation nach ICB

Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding A Nationwide Cohort Study

Peter Brønnum Nielsen, MSc, PhD; Torben Bjerregaard Larsen, MD, PhD;
Flemming Skjøth, MSc, PhD; Anders Gorst-Rasmussen, MSc, PhD;
Lars Hvilsted Rasmussen, MD, PhD; Gregory Y.H. Lip, MD

Circulation August 11, 2015

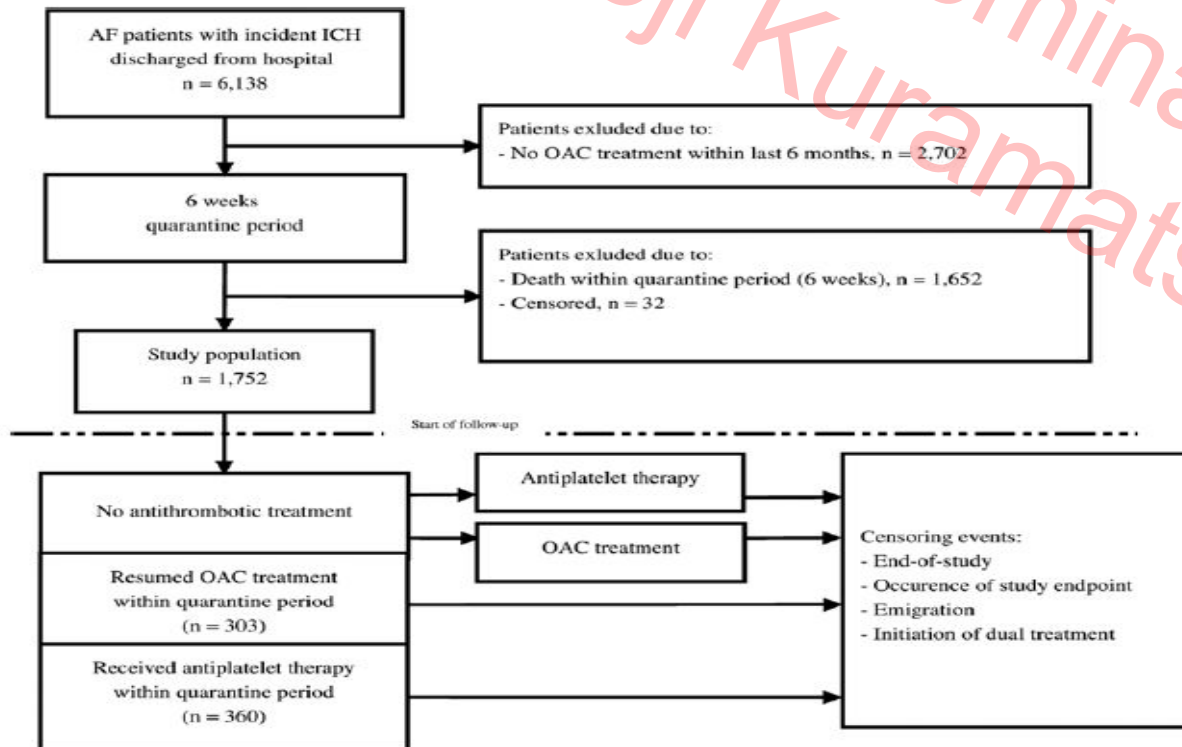


Figure 1. Flowchart of the study design and population. AF indicates atrial fibrillation; ICH, intracranial hemorrhage; and OAC, oral anticoagulation.

Langzeitbehandlung Erneute Antikoagulation nach ICB

Table 2. Event Rates of Various Outcomes According to Stratification on Treatment Regimen Using 1 Year of Follow-Up

Outcome	No Antithrombotic Treatment	OAC Treatment	Antiplatelet Therapy
Ischemic stroke/SE and all-cause mortality			
Events	179	43	83
Person-time (100 y)	655	316	335
Event rate (95% CI)	27.3 (23.6–31.6)	13.6 (10.1–18.3)	
Ischemic stroke/SE			
Events	69		
Person-time (100 y)			
Event rate (95% CI)			
All-cause mortality			
Events			
Person-time (100 y)			
Event rate (95% CI)			
Recurrent ICH			
Events		18	
Person-time (100 y)		316	339
Event rate (95% CI)		8.0 (5.4–11.8)	5.3 (3.3–8.4)
Major extracranial bleeding			
Events	10	5	9
Person-time (100 y)	677	329	349
Event rate (95% CI)	1.5 (0.8–2.7)	1.5 (0.6–3.7)	2.6 (1.3–5.0)

CI indicates confidence interval; ICH, intracranial hemorrhage; OAC, oral anticoagulation; and SE, systemic embolism.

Treatment vs No antithrombotic treatment
Hazard ratio (95% CI)

Outcome / Treatment

Ischemic stroke/SE and all-cause mortality

OAC treatment

Recurrent ICH

OAC treatment

Antiplatelet therapy

Major extracranial bleeding

OAC treatment

Antiplatelet therapy

0.50 (0.37; 0.70)

0.55 (0.39; 0.78)

0.90 (0.69; 1.17)

0.77 (0.67; 1.14)

0.33 (0.23; 0.95)

0.33 (0.23; 1.03)

0.77 (0.55; 1.55)

0.77 (0.55; 1.49)

0.49 (0.33; 0.72)

0.55 (0.37; 0.82)

0.94 (0.70; 1.26)

0.90 (0.67; 1.21)

0.93 (0.57; 1.51)

0.91 (0.36; 1.49)

0.60 (0.37; 1.02)

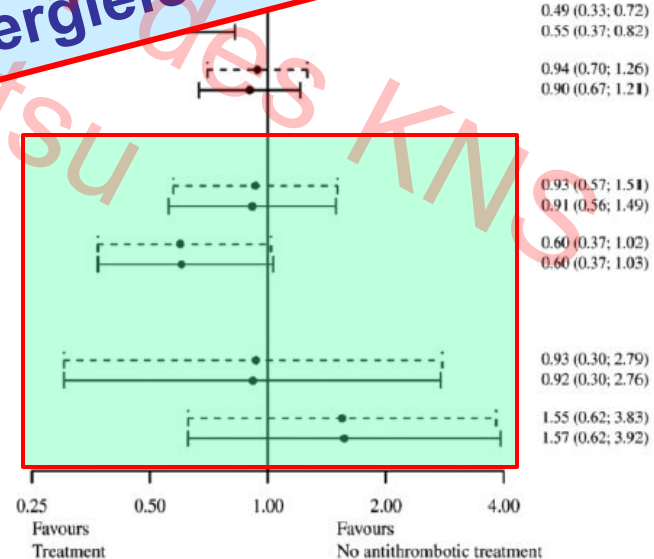
0.60 (0.37; 1.03)

0.93 (0.30; 2.79)

0.92 (0.30; 2.76)

1.55 (0.62; 3.83)

1.57 (0.62; 3.92)



**Wiederaufnahme einer Antikoagulation:
Niedrigere Rate an ischämischen
Komplikationen & Mortalität,
Blutungskomplikationen vergleichbar**

Langzeitbehandlung

Erneute Antikoagulation nach ICB

Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding

A Nationwide Cohort Study

Peter Bronnum Nielsen, MSc, PhD; Torben Borch-Johnsen, MSc, PhD; Flemming Skjøth, MSc, PhD; Anders Gade, MSc, PhD; Lars Hvilsted Rasmussen, MSc, PhD

VORSICHT !!!

**Keine Therapie Empfehlung möglich
anhand observationalen Daten
lediglich Assoziationen gezeigt**

Patients with atrial fibrillation (AF) who have had an intracranial hemorrhage (ICH) are at high risk of recurrent stroke and mortality. We investigated the impact of restarting oral anticoagulation (OAC) treatment after ICH on recurrent stroke, mortality, and bleeding in a nationwide cohort study.

Patients sustaining an ICH were included in the study. The study population comprises a total of 1752 patients. We investigated the impact of restarting OAC treatment in comparison with patients who did not resume OAC treatment on the primary end point of ischemic stroke/systemic embolism and secondary end points of recurrent ICH, all-cause mortality, and bleeding. The adjusted hazard ratios favored OAC treatment versus no antithrombotic treatment (0.39–0.78), whereas antiplatelet therapy did not entail similar associations (0.67–1.14). We calculated the net clinical benefit as a weighted sum of rate differences for the primary end point of ischemic stroke/systemic embolism and all-cause mortality and recurrent ICH. The net clinical benefit for OAC versus no antithrombotic treatment was 14.6 (95% confidence interval, 6.4–22.8), whereas the net clinical benefit was nonsignificant for antiplatelet therapy versus no antithrombotic treatment, 6.5 (95% confidence interval, –2.1 to 15.2). Despite the inherited limitations of observational data (selection bias and confounding by indication), these data support OAC reintroduction post-ICH. Based on these results, future randomized, controlled trials investigating the resumption of OAC treatment post-ICH are encouraged.

Erneut oral antikoagulieren nach intrazerebraler Blutung?

Zusammenfassung

- **Signifikante Reduktion der Ischämischen Komplikationen durch Wiederaufnahme einer oralen Antikoagulation**
Inzidenz (pro 100 Patienten-Jahre): 3.9-5.3 versus 10.3-12.7
- **Signifikante Reduktion der 1-Jahres Mortalität durch Wiederaufnahme einer oralen Antikoagulation**
1-Jahres Mortalität: 8.3-9.7 versus 19.5-30.7
- **Rate an intra- und extra-kraniellen Blutungskomplikationen ohne signifikante Unterschiede im 1-Jahres Follow-up**

Erneut oral antikoagulieren nach intrazerebraler Blutung?

- **Wann?** Keine ausreichenden Daten
- **Wen?** Jüngere Patienten (<75 Jahre)
Stammganglien >> Lobäre ICBs
Patienten mit VHF bei einem CHADS₂ ≥ 2
- **Welche Patienten lieber nicht?**
Schlecht kontrollierbarer Hypertonus
Hohe Last an Mikrobleeds bzw. Amyloid Angiopathie
Mit gleichzeitiger Thrombozytenfunktionshemmung
CAVE: schlechter funktioneller Status
- **Fragen & Outlook?** RCT?, Risk-benefit Analyse, Ischämie vs. ICB, loco typico vs. Lobäre ICB, Zeitpunkt, Einfluss der DOAKs

Wiederbeginn orale Antikoagulation

■ Kooperationen

- R. Veltkamp, Imperial College, London
→ Meta-analyse, n=2452 (Italien, Dänemark, Canada, USA)

Welche Art der sekundäre Prophylaxe?

- A. Biffi, Havard
- K. Sheth, Yale
→ Individual patient data Meta-analyse, n=810

Lokalisations-abhängige Untersuchung (Microbleeds, CAA)



Vielen Dank für Ihre Aufmerksamkeit !

