Neues zur Schlaganfallprävention

Matthias Endres

Klinik für Neurologie – Charité
Centrum für Schlaganfallforschung Berlin

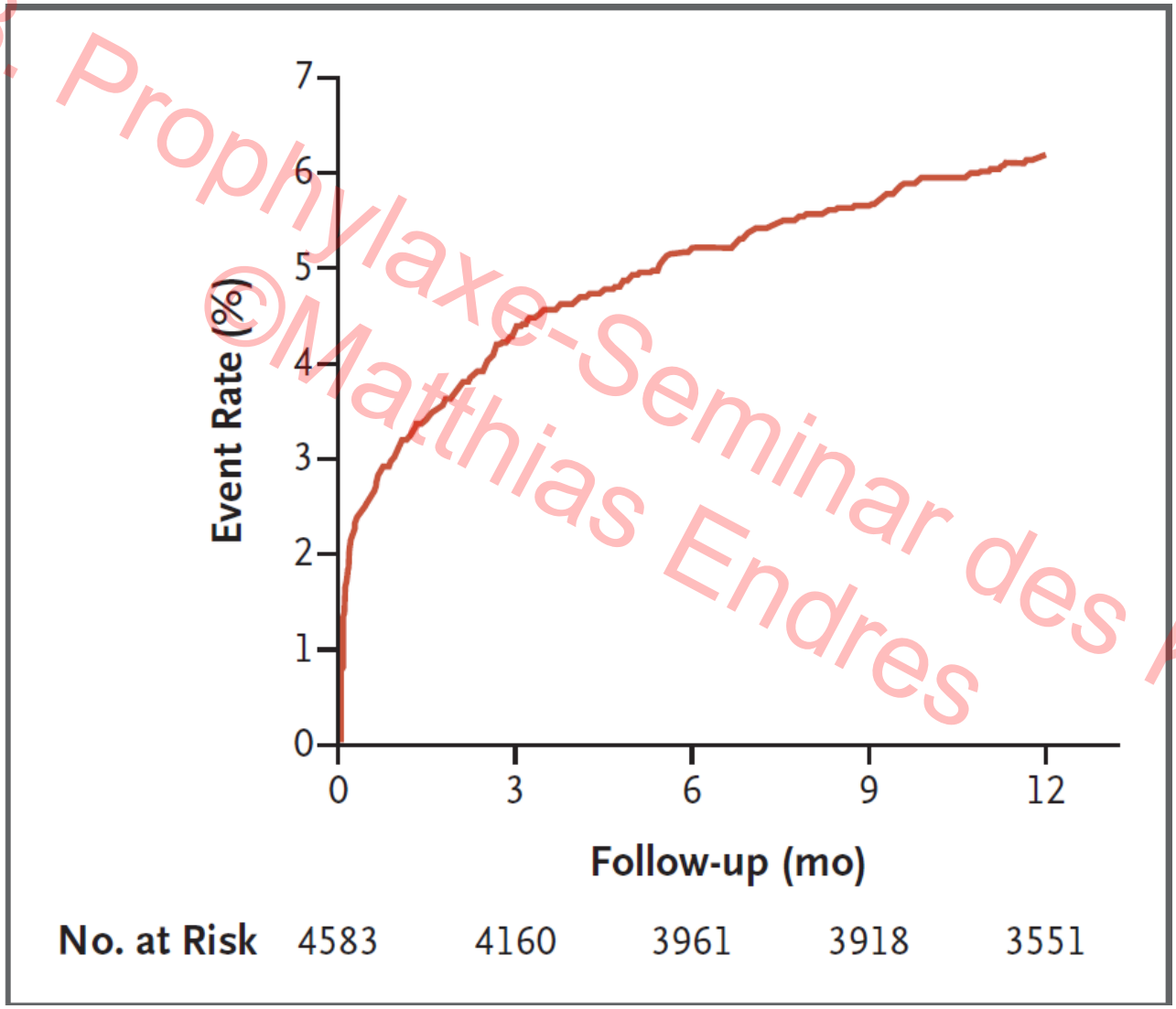
ORIGINAL ARTICLE

One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke

Pierre Amarenco, M.D., Philippa C. Lavallée, M.D., Julien Labreuche, B.S.T., Gregory W. Albers, M.D., Natan M. Bornstein, M.D., Patrícia Canhão, M.D., Louis R. Caplan, M.D., Geoffrey A. Donnan, M.D., José M. Ferro, M.D., Michael G. Hennerici, M.D., Carlos Molina, M.D., Peter M. Rothwell, M.D., Leila Sissani, B.S.T., David Školoudík, M.D., Ph.D., Philippe Gabriel Steg, M.D., Pierre-Jean Touboul, M.D., Shinichiro Uchiyama, M.D., Éric Vicaut, M.D., and Lawrence K.S. Wong, M.D., for the TIAregistry.org Investigators*

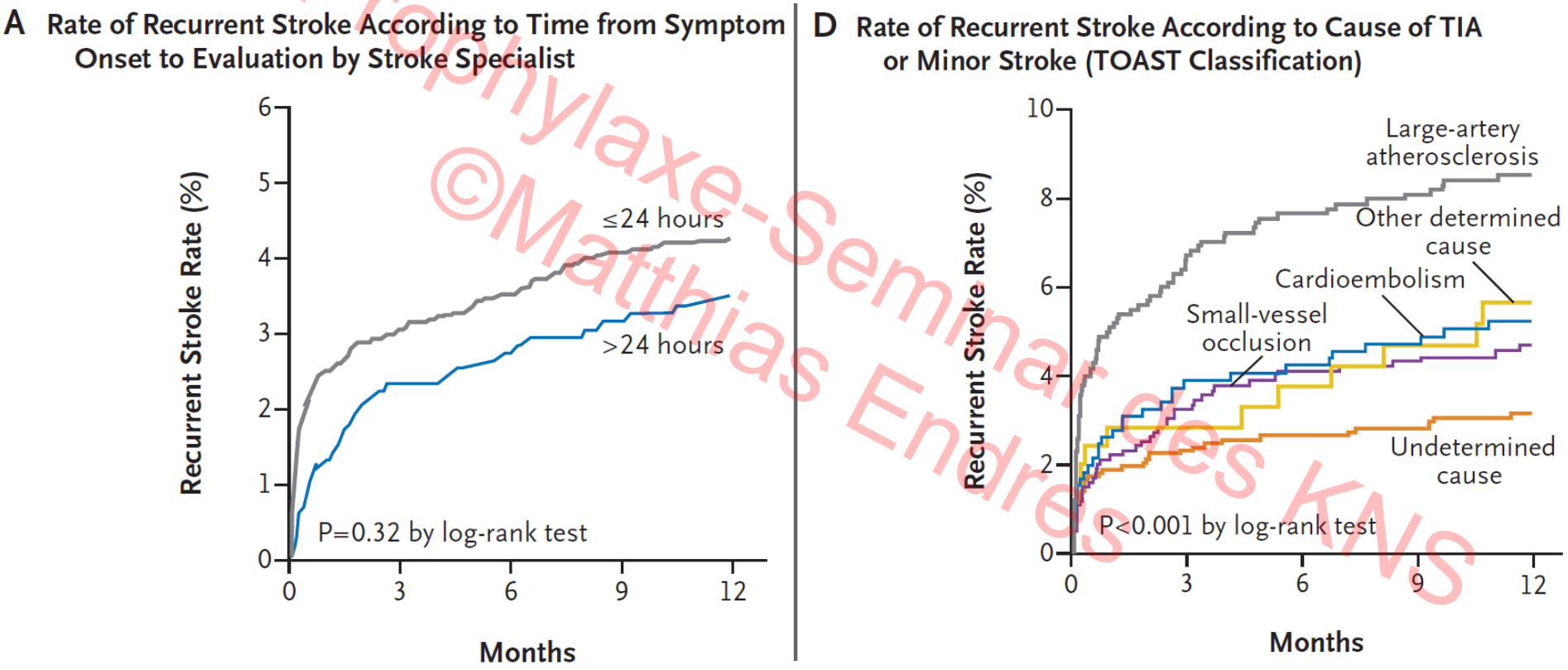
N Engl J Med 2016; 374:1533-1542

Cumulative Incidence



N Engl J Med 2016; 374:1533-1542

Rate of recurrent stroke



N Engl J Med 2016; 374:1533-1542

Sekundärprävention 2017
Evidenzniveau A

-Thrombozytenfunktionshemmung

-Blutdrucksenkung

-Cholesterinsenkung

-Antikoagulation bei kardialer Embolie

-TEA bei symptomatischer Karotisstenose

Sekundärprävention 2017
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-TEA bei symptomatischer Karotisstenose

CSB
Center for Stroke Research Berlin

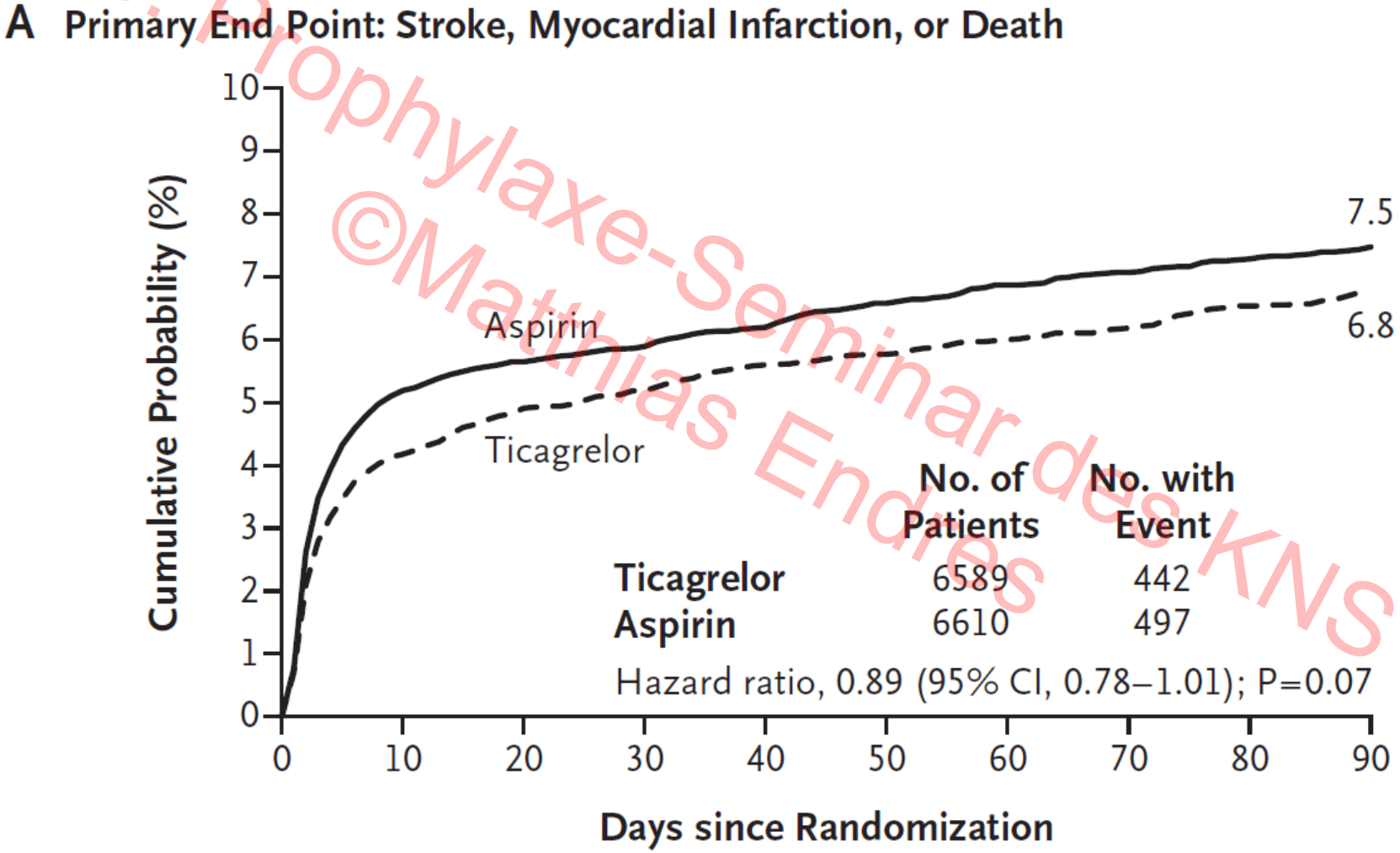
ORIGINAL ARTICLE

Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Gregory W. Albers, M.D., Hans Denison, M.D., Ph.D., J. Donald Easton, M.D., Scott R. Evans, Ph.D., Peter Held, M.D., Ph.D., Jenny Jonasson, Ph.D., Kazuo Minematsu, M.D., Ph.D., Carlos A. Molina, M.D., Yongjun Wang, M.D., and K.S. Lawrence Wong, M.D., for the SOCRATES Steering Committee and Investigators*

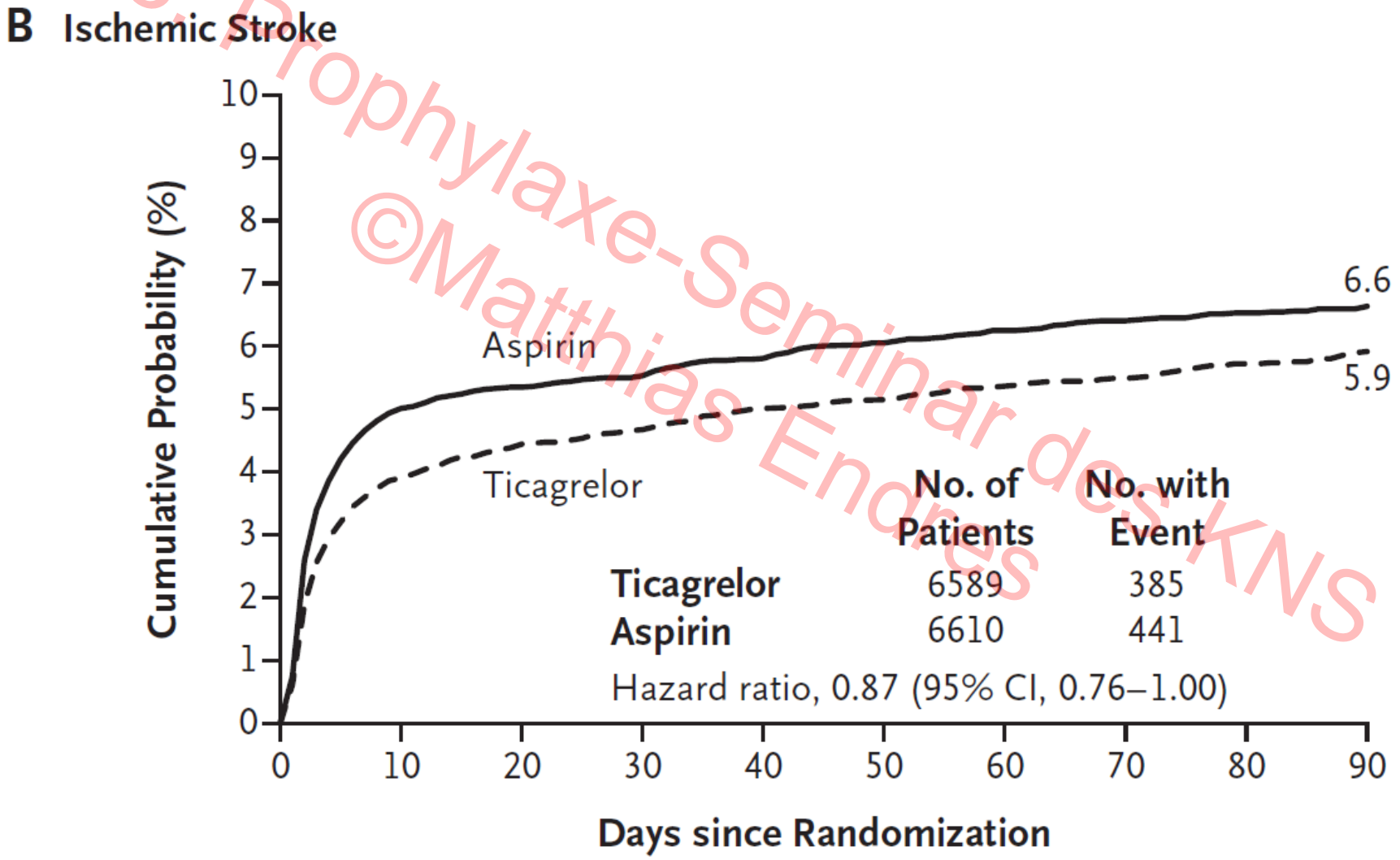
N Engl J Med 2016; DOI: 10.1056/NEJM0a1603060

Primary Endpoint: MACCE



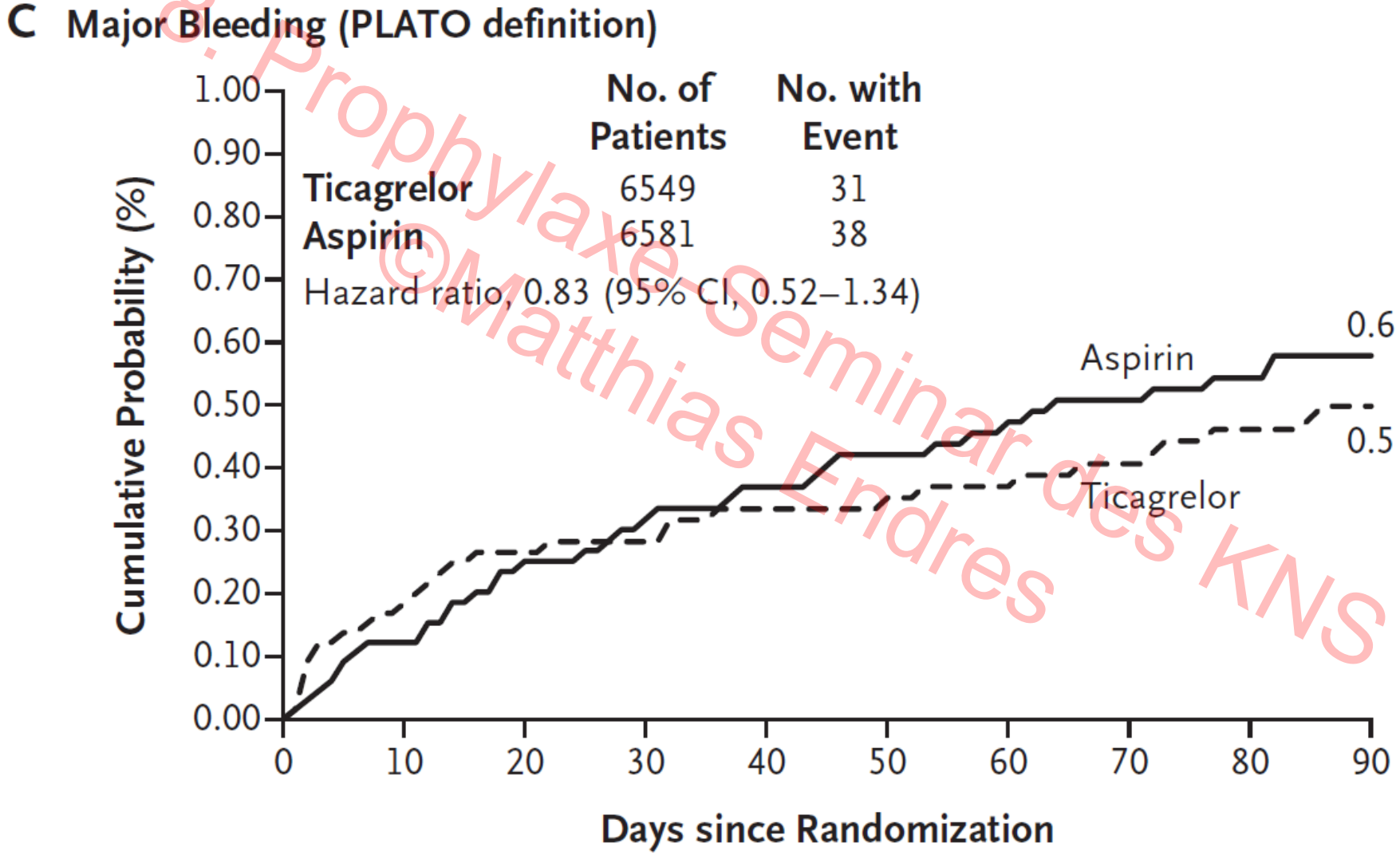
N Engl J Med 2016; DOI: 10.1056/NEJM0a1603060

Secondary endpoint: ischemic stroke



N Engl J Med 2016; DOI: 10.1056/NEJM0a1603060

Safety endpoint: Major bleeds



N Engl J Med 2016; DOI: 10.1056/NEJM0a1603060

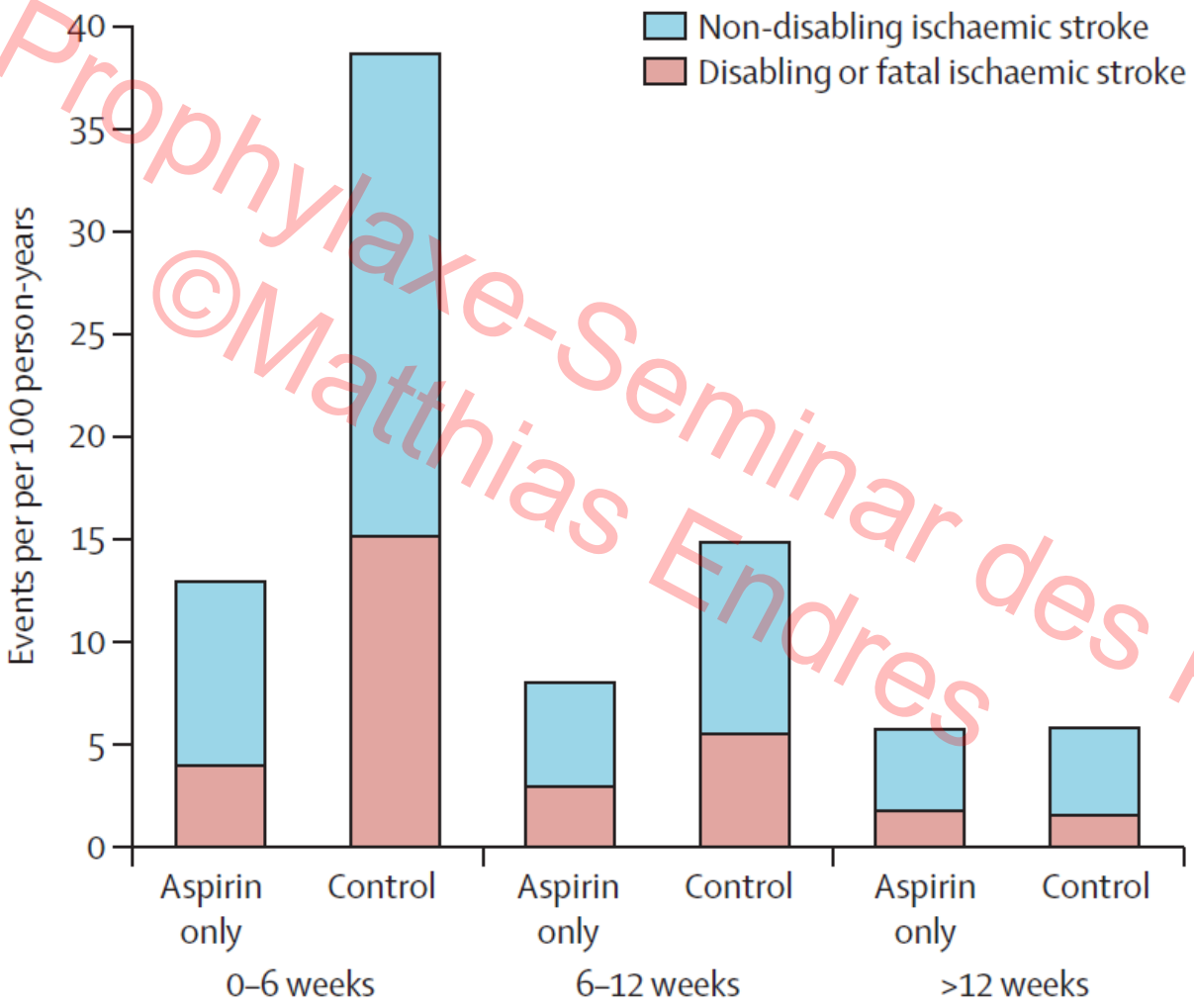
Rate of recurrent stroke

Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials

Peter M Rothwell, Ale Algra, Zhengming Chen, Hans-Christoph Diener, Bo Norrving, Ziyah Mehta

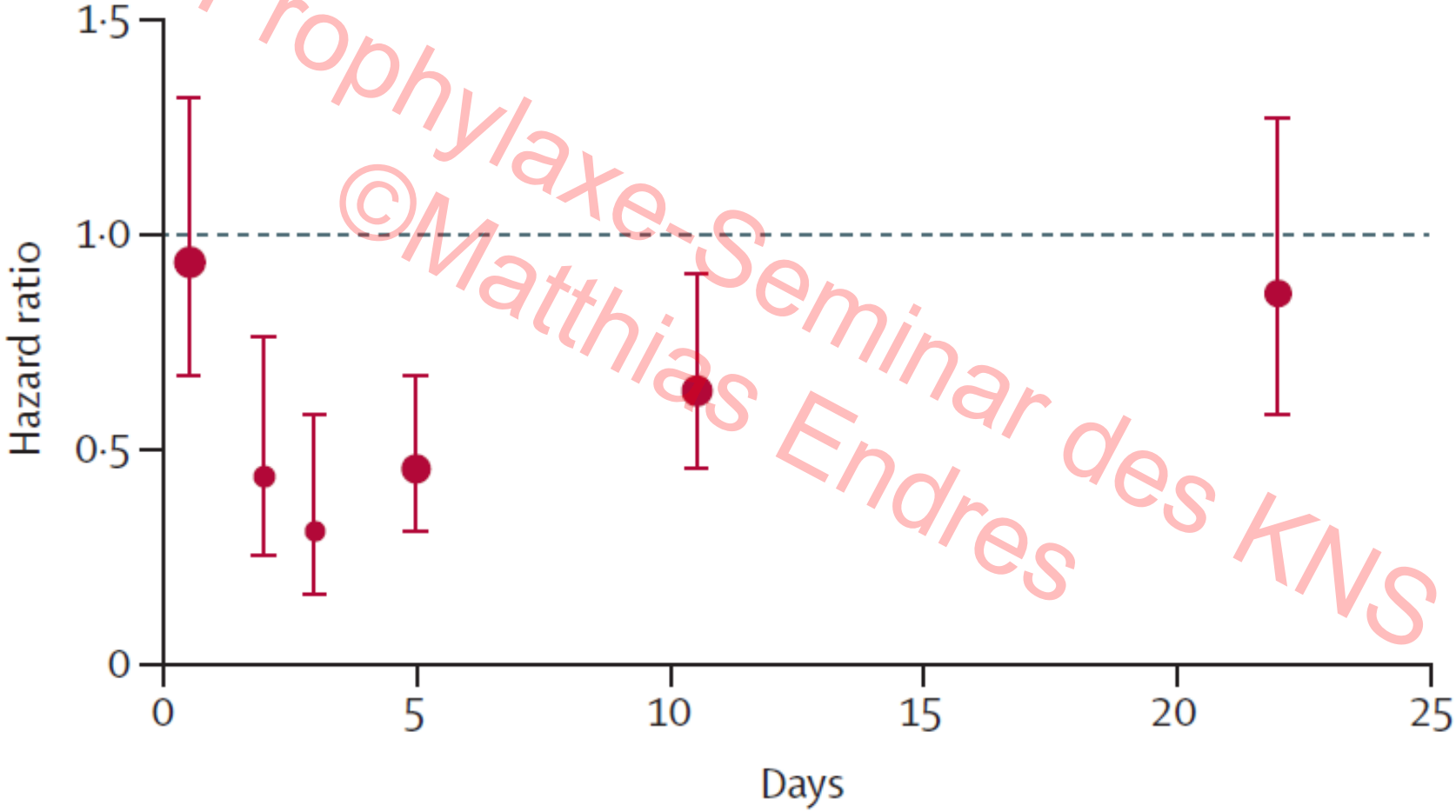
Lancet, online May 18, 2016

Effect of aspirin on recurrent stroke risk and severity



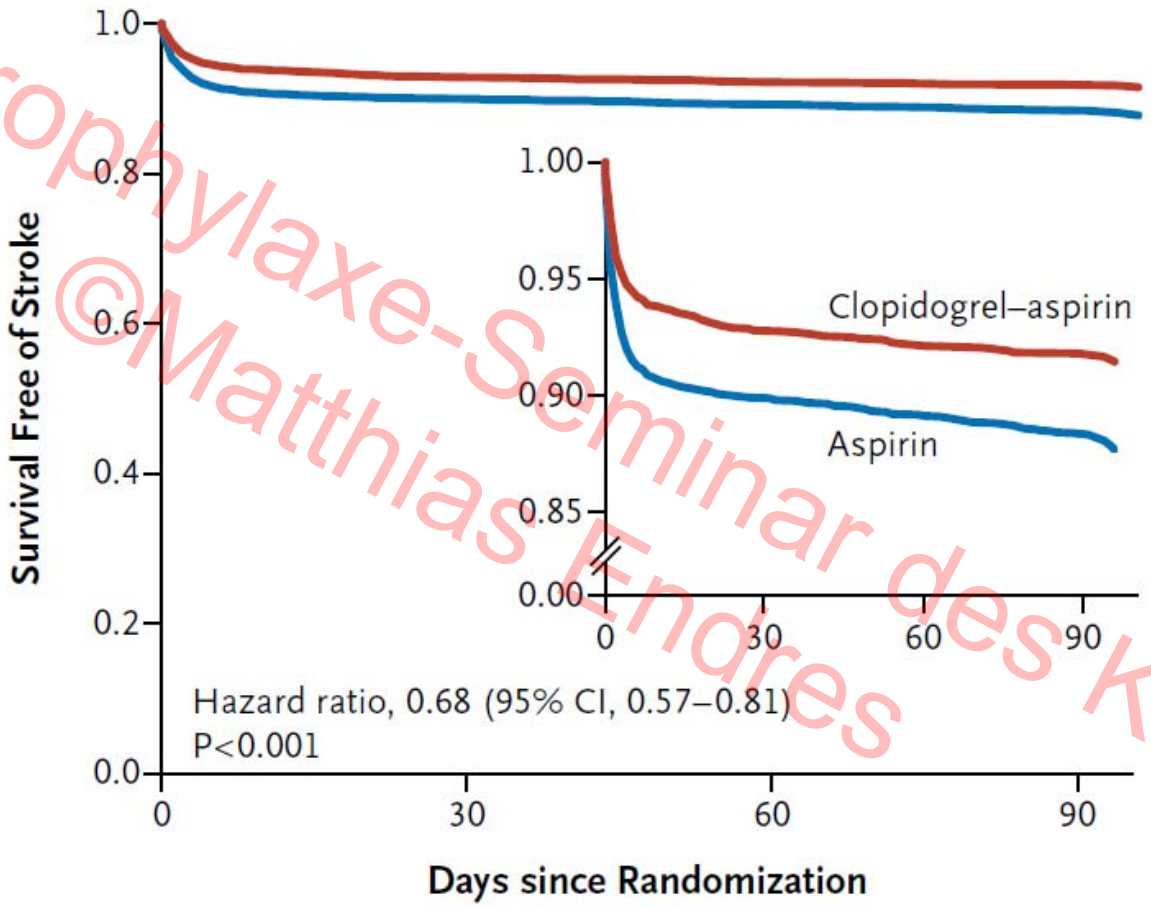
Lancet, online May 18, 2016

Time-dependent effects of aspirin on recurrent stroke risk



Lancet, online May 18, 2016

Doppelte Plättchenhemmung zur frühen Sekundärprävention (CHANCE)



No. at Risk

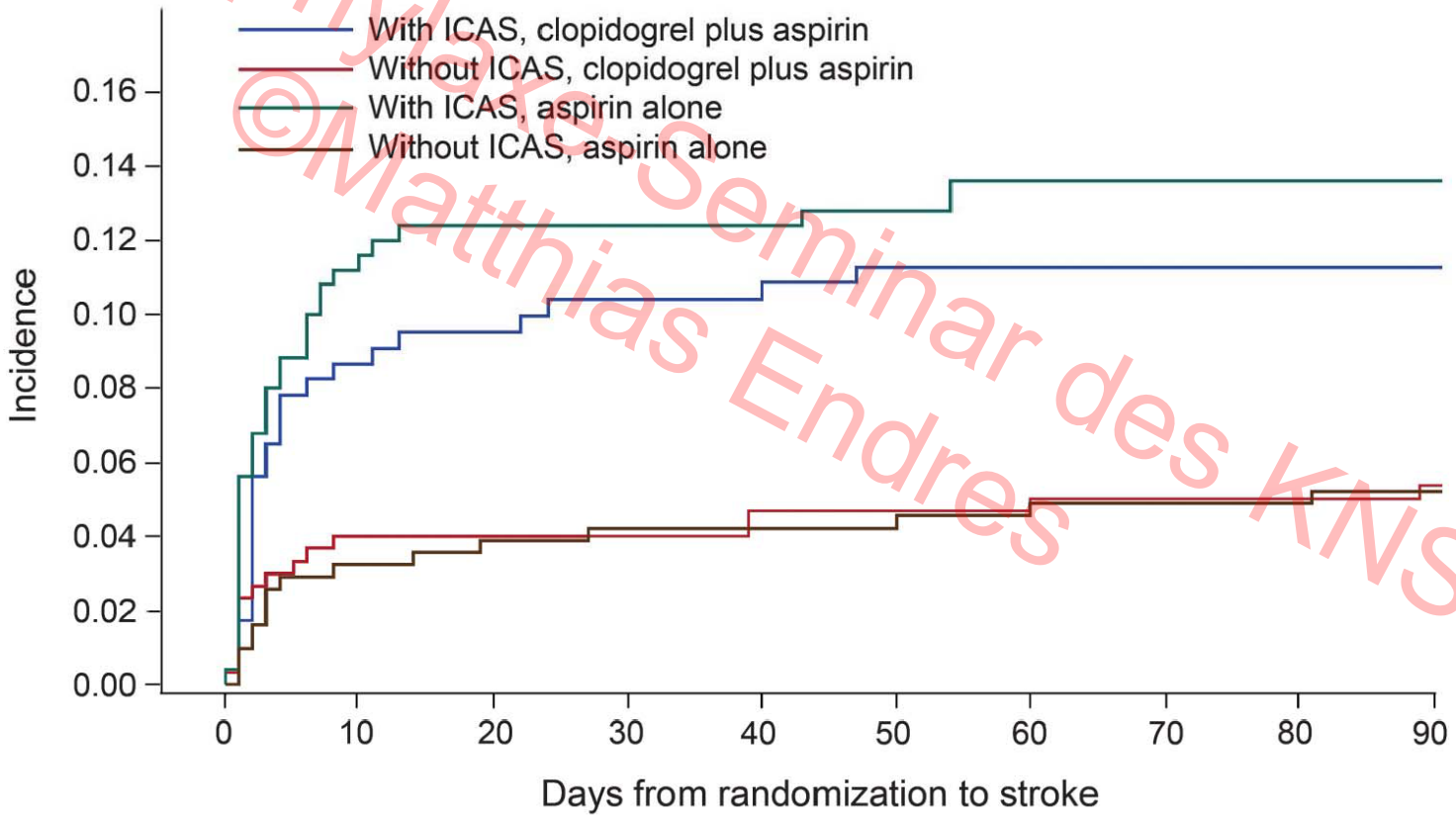
Aspirin	2586	2307	2287	1906
Clopidogrel–aspirin	2584	2376	2361	1989

N Engl J Med 2013, 369:11-19.

Doppelte Plättchenhemmung zur frühen Sekundärprävention (CHANCE)

Subruppenanalyse: intrakranielle Stenosen

Figure 1 Kaplan-Meier curves for the primary efficacy outcome of any stroke



Neurology® 2015;85:1154-1162

Sekundärprävention 2017
Evidenzniveau A

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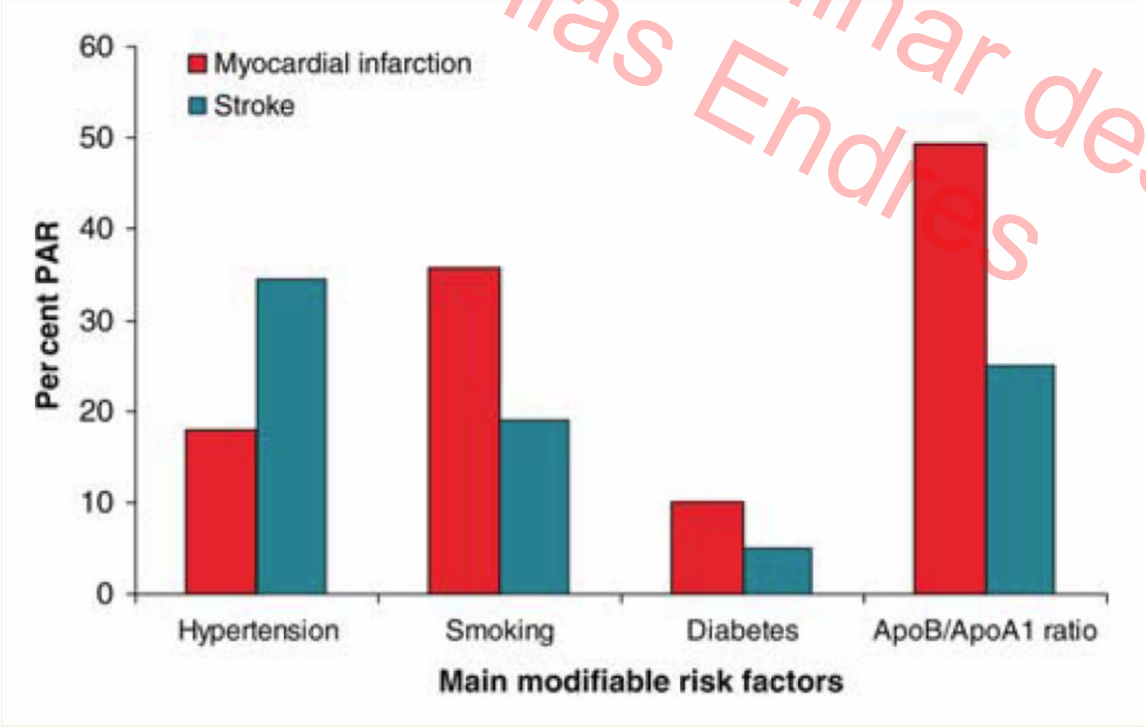
Frontiers in cardiovascular medicine

Primary prevention of stroke: blood pressure, lipids, and heart failure

Matthias Endres[1,2*], Peter U. Heuschmann[2], Ulrich Laufs[3], and Antoine M. Hakim[4]

Attributables Risiko der wichtigsten Risikofaktoren für Schlaganfall und Herzinfarkt



Eur Heart J, 2011

PCSK9 Inhibitoren

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

Robinson et al., N Engl J Med 2015;372:1489-99.
Sabatine et al., N Engl J Med 2015; 372:1500-09.

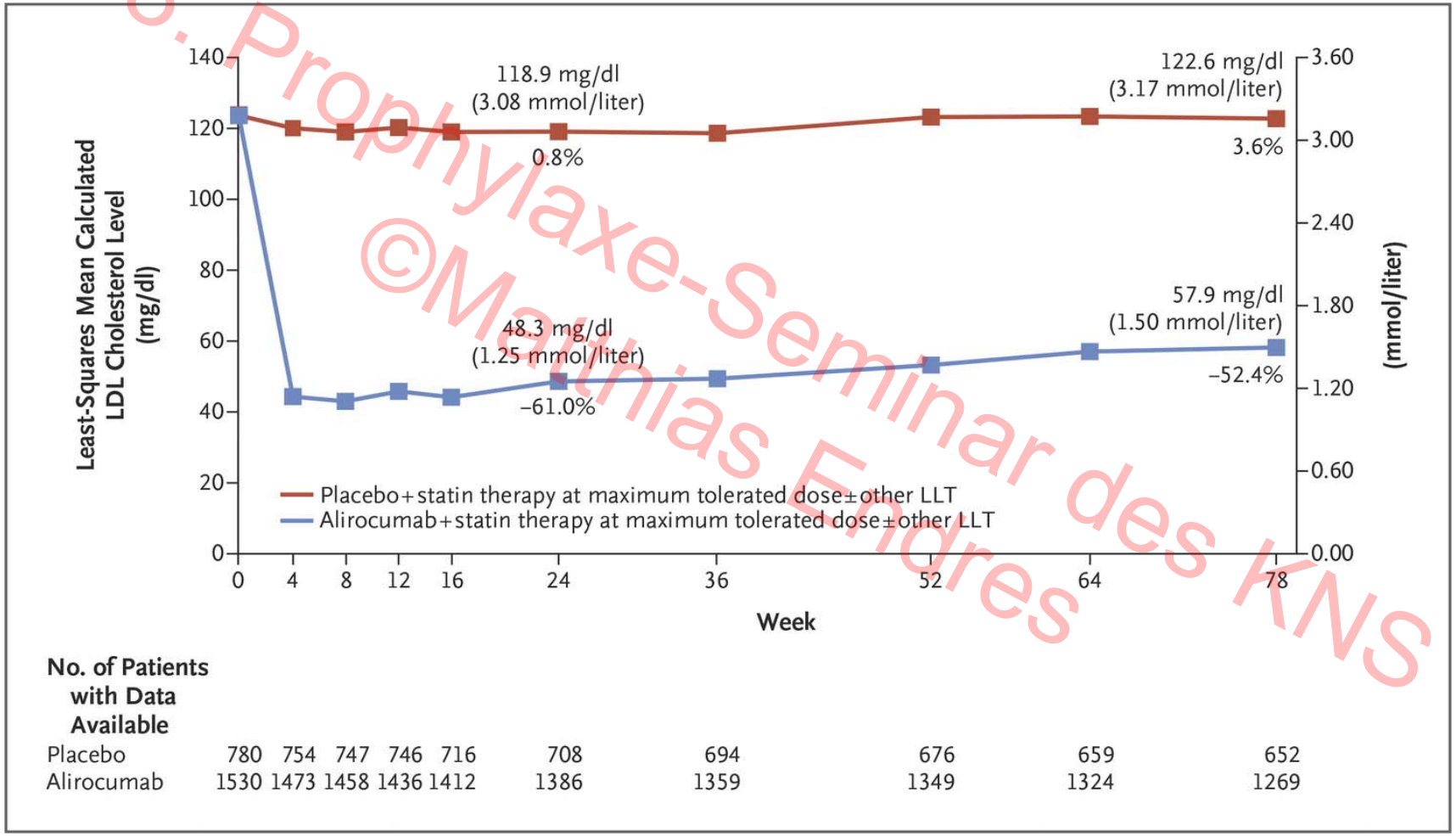
PCSK9 LOF homozygotes show no pathology

- p.Y142X; p.del97Arg compound heterozygote
  - 32 year old African American
  - apparently healthy; LDL-C 0,4 nmol/L / 14 mg/dL

- p.C679X homozygote
  - 21 year old; South African
  - apparently healthy; LDL-C 0,4 nmol/l / 15 mg/dL

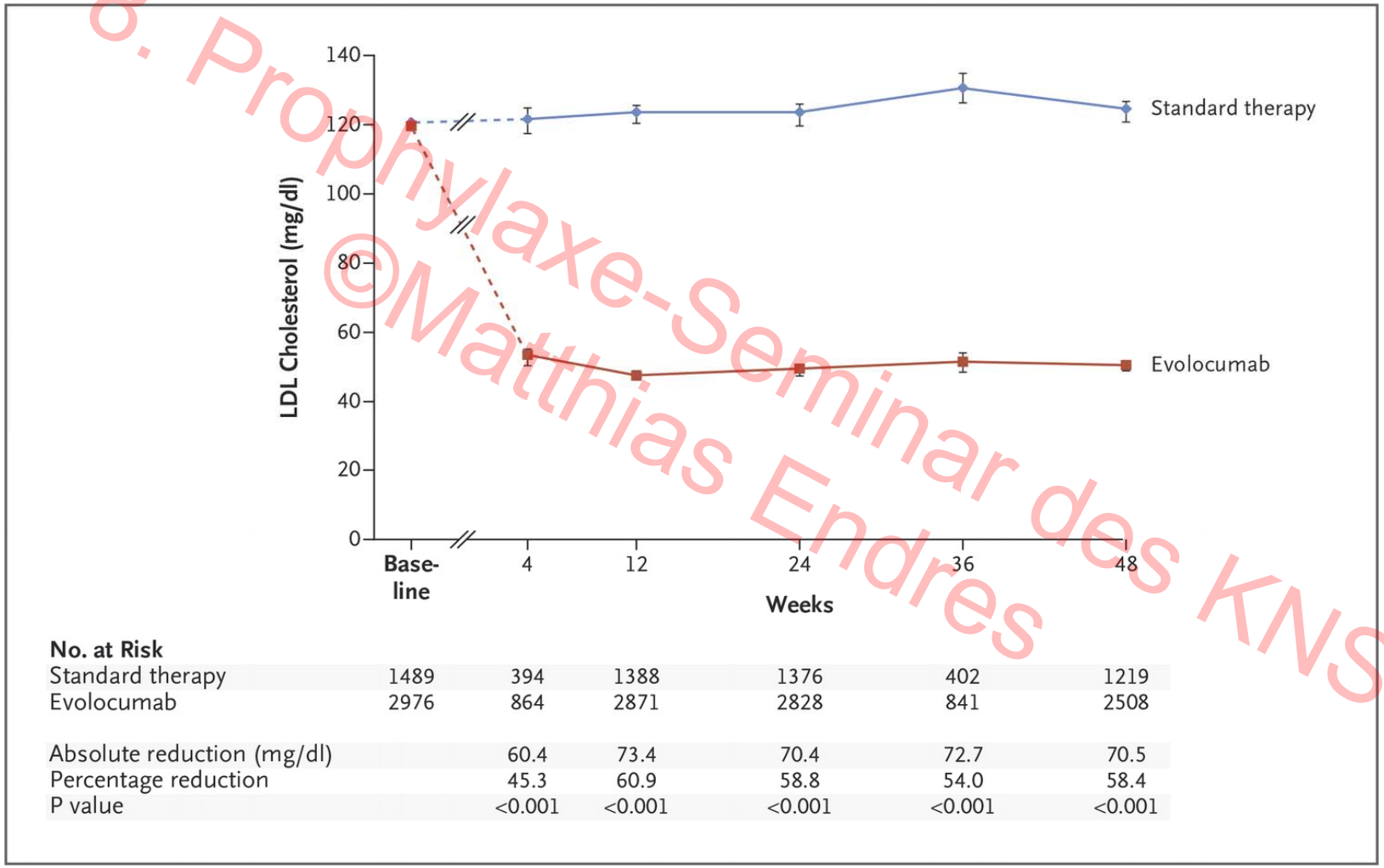
Zhao et al. Am J Hum Genet 2006;79:514-523
Hooper et al. Atherosclerosis 2007;193:445-448

Alirocumab (Odyssey long term): Calculated LDL Cholesterol Levels over Time



Robinson JG et al. N Engl J Med 2015;372:1489-1499.

Evolucomab (Osler): Low-Density Lipoprotein (LDL) Cholesterol Levels.



No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

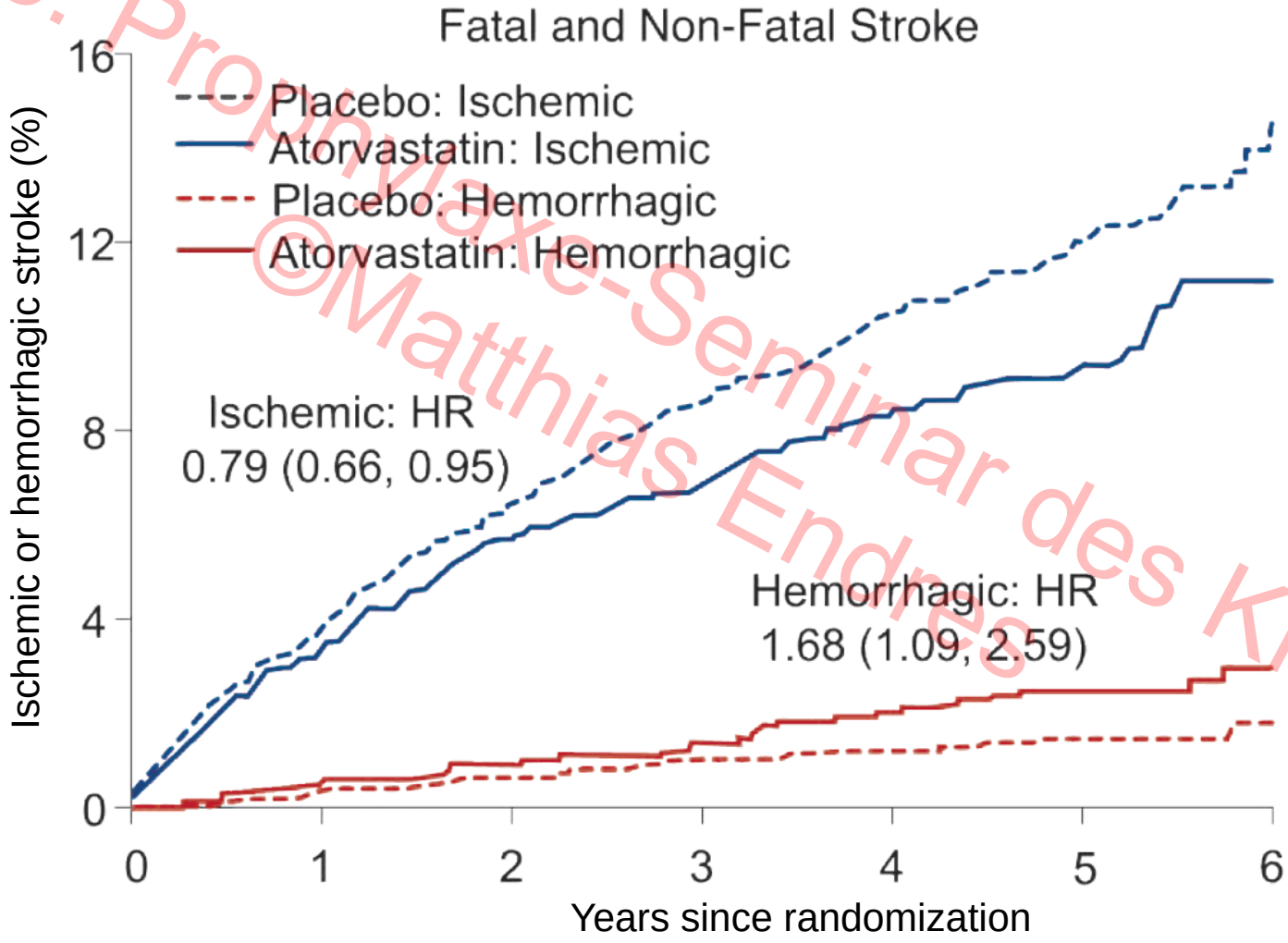
Sabatine MS et al. N Engl J Med 2015;372:1500-1509.

Sind super-niedrige LDL-C Serumkonzentrationen sicher?

Hirnblutungen ?

Kognitive Einschränkungen ?

Hemorrhagic stroke in SPARCL



Goldstein LB, et al. Neurology 2008;70:2364–70.

Alirocumab (Odyssey long term):

Table 3. Adverse Events of Interest and Laboratory Values: Safety Analysis.*

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**	72/556 (12.9)	38/279 (13.6)	0.83

Robinson JG et al. N Engl J Med 2015;372:1489-1499.

Evolocumab (Osler):

Table 3. Adverse Events and Laboratory Results.*

Variable	Evolocumab Group (N = 2976)	Standard-Therapy Group (N = 1489)
	no. (%)	
Adverse events		
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to discontinuation of evolocumab	71 (2.4)	NA
Muscle-related	190 (6.4)	90 (6.0)
Injection-site reaction	129 (4.3)	NA
Neurocognitive event†	27 (0.9)	4 (0.3)
Other‡		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
Laboratory results		
Alanine or aspartate aminotransferase >3 × ULN at any visit after baseline	31 (1.0)	18 (1.2)
Creatine kinase >5 × ULN at any visit after baseline	17 (0.6)	17 (1.1)

Sabatine MS et al. N Engl J Med 2015;372:1500-1509.

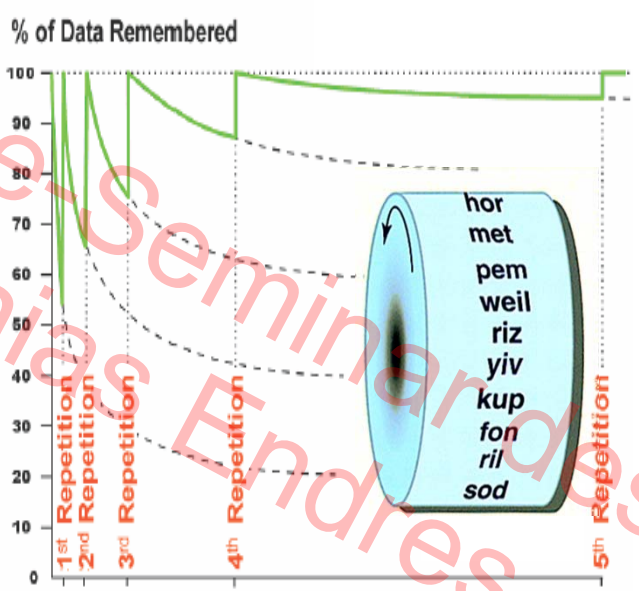
Conclusions

In patients with known cardiovascular disease:

1. **PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy**

2. **Benefit was achieved with lowering LDL cholesterol well below current targets**

ebbinghaus

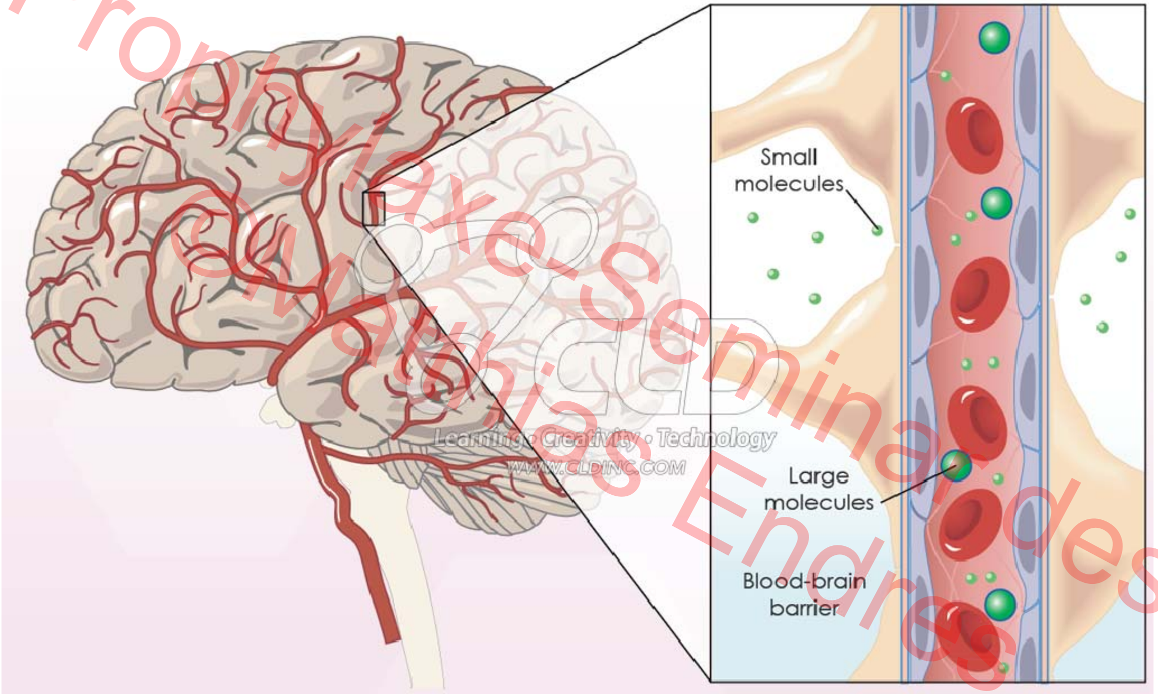


Ebbinghaus, *Über das Gedächtnis*

1885

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-545.

EBBINGHAUS: CANTAB tests

The Cambridge Neuropsychological Test Automated Battery (CANTAB)

Validated neuropsychological test battery in mild cognitive impairment and dementia to measure dysfunctions in:

- Memory executive function
- Visual spatial skills
- Processing speed
- Cognitive flexibility

CANTAB tests used in EBBINGHAUS:

- Spatial Working Memory (SWM)
- Paired Associates Learning (PAL)
- Reaction Time (RTI)

www.cambridgecognition.com (Accessed January 2016).
Egerhazi A, et al. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:746–51.

Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1.No differences btw evolocumab vs placebo

A. A battery of cognitive tests
B. Patient-reported everyday cognition
C. Adverse cognitive events reported by MD

2.No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

N Engl J Med 2016; 374:1321-1331

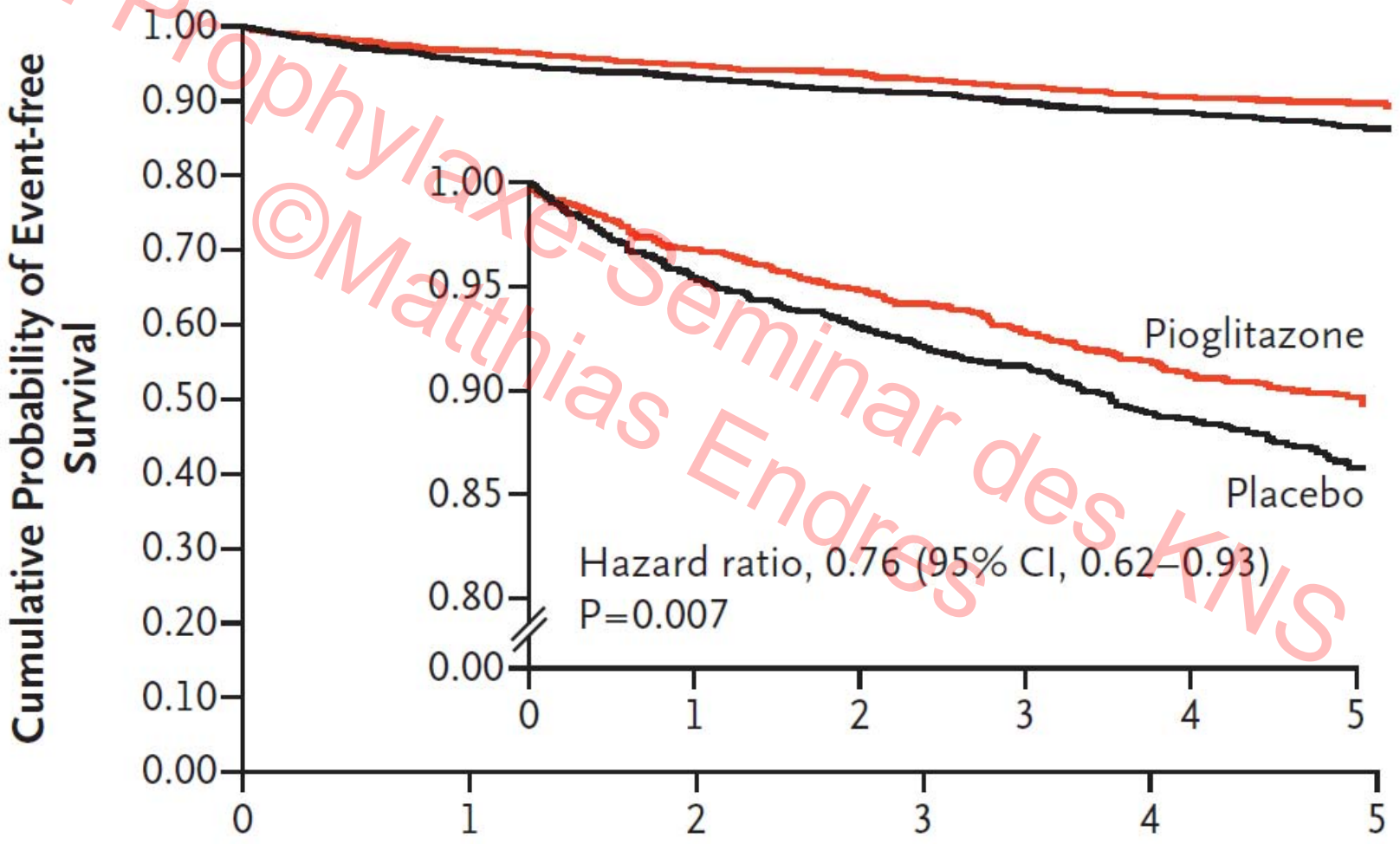
Pioglitazon bei Insulinresistenz

METHODS

In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

N Engl J Med 2016; 374:1321-1331

Primary outcome



N Engl J Med 2016; 374:1321-1331

Adverse effects

	Pioglitazone N=1939	Placebo N=1937	p
Event % (N)			
Bone fracture	5.1% (99)	3.2% (66)	<0.01
Heart failure	2.6% (51)	2.2% (42)	0.35
Incident cancer†	6.9 (133)	7.7 (150)	0.29

N Engl J Med 2016; 374:1321-1331

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-Antikoagulation bei kardialer Embolie

-TEA bei symptomatischer Karotisstenose

Fire and forget?

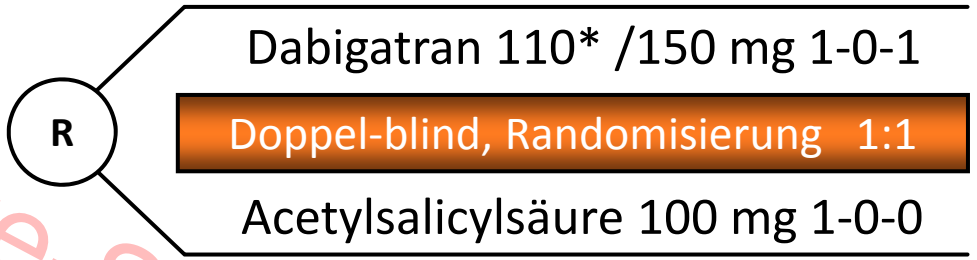
Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

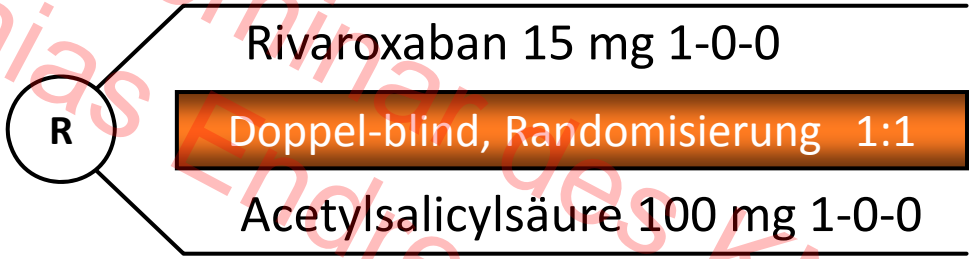
Hart et al. *Lancet Neurology* 2014;13:429–38.

ESUS Trials

RE-SPECT ESUS



NAVIGATE ESUS



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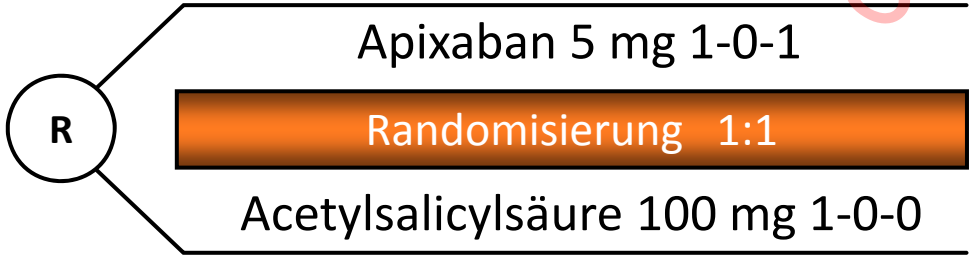


* ≥ 75 Jahre oder eGFR 30-50 mL/min/1.73 m²
Diener et al. *Int J Stroke*, 2015; www.clinicaltrials.gov

Randomized Trials

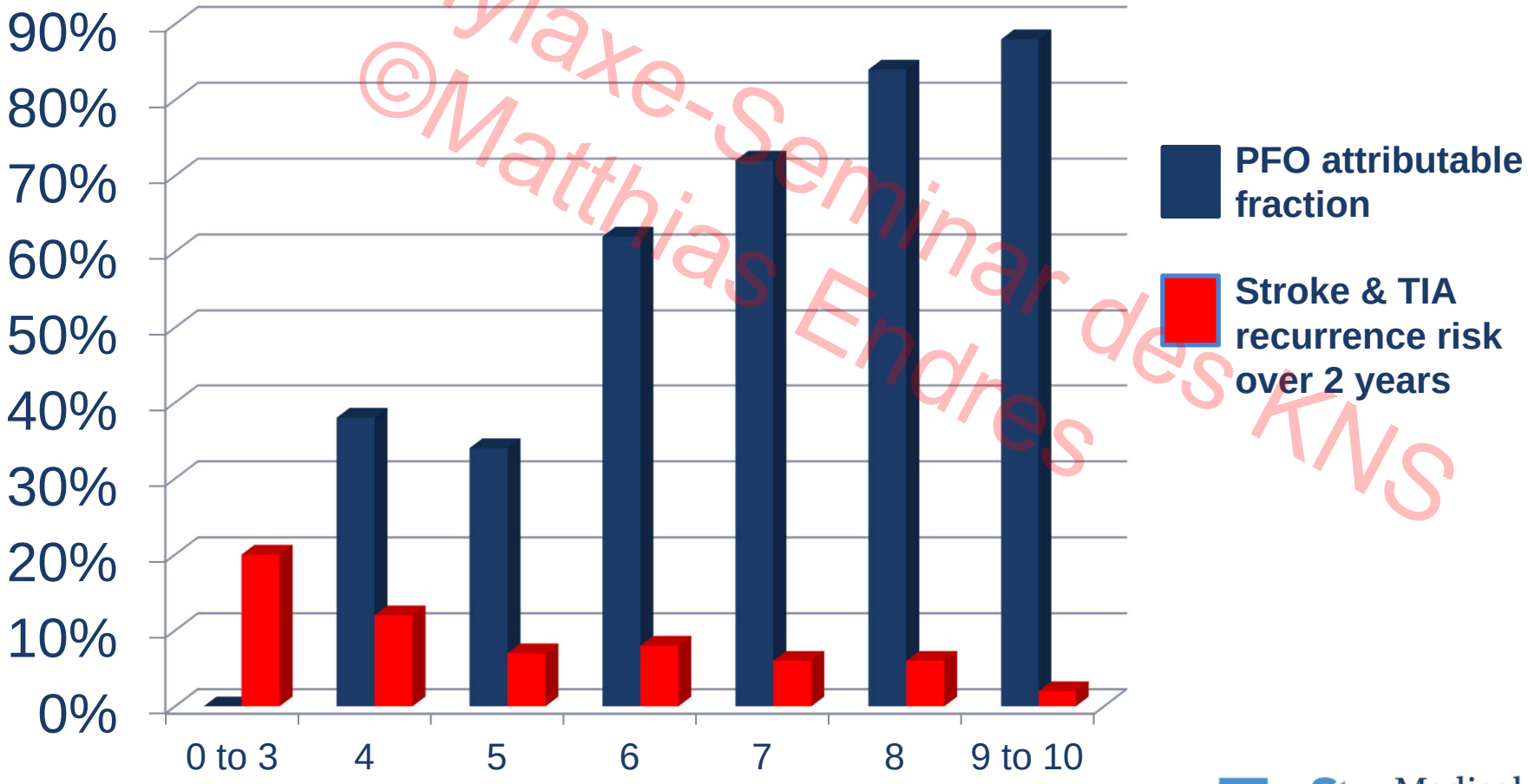
- Closure 2012
- Respect 2013 (long term outcome, Saver et al 2017)
- PC Trial 2013
- Close 2017
- Gore Reduce 2017

ROPE Score: An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke.

Kent DM et al. Neurology 2013; 81: 619-25

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of previous stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (in years): 18-29	5	
30-39	4	
40-49	3	
50-59	2	
60-69	1	
≥ 70	0	
Total score (sum of individual points, max. 10, min 0		

Increasing RoPE score
→ Increasing PFO attributable fraction
→ Decreasing TIA/Stroke recurrence risk

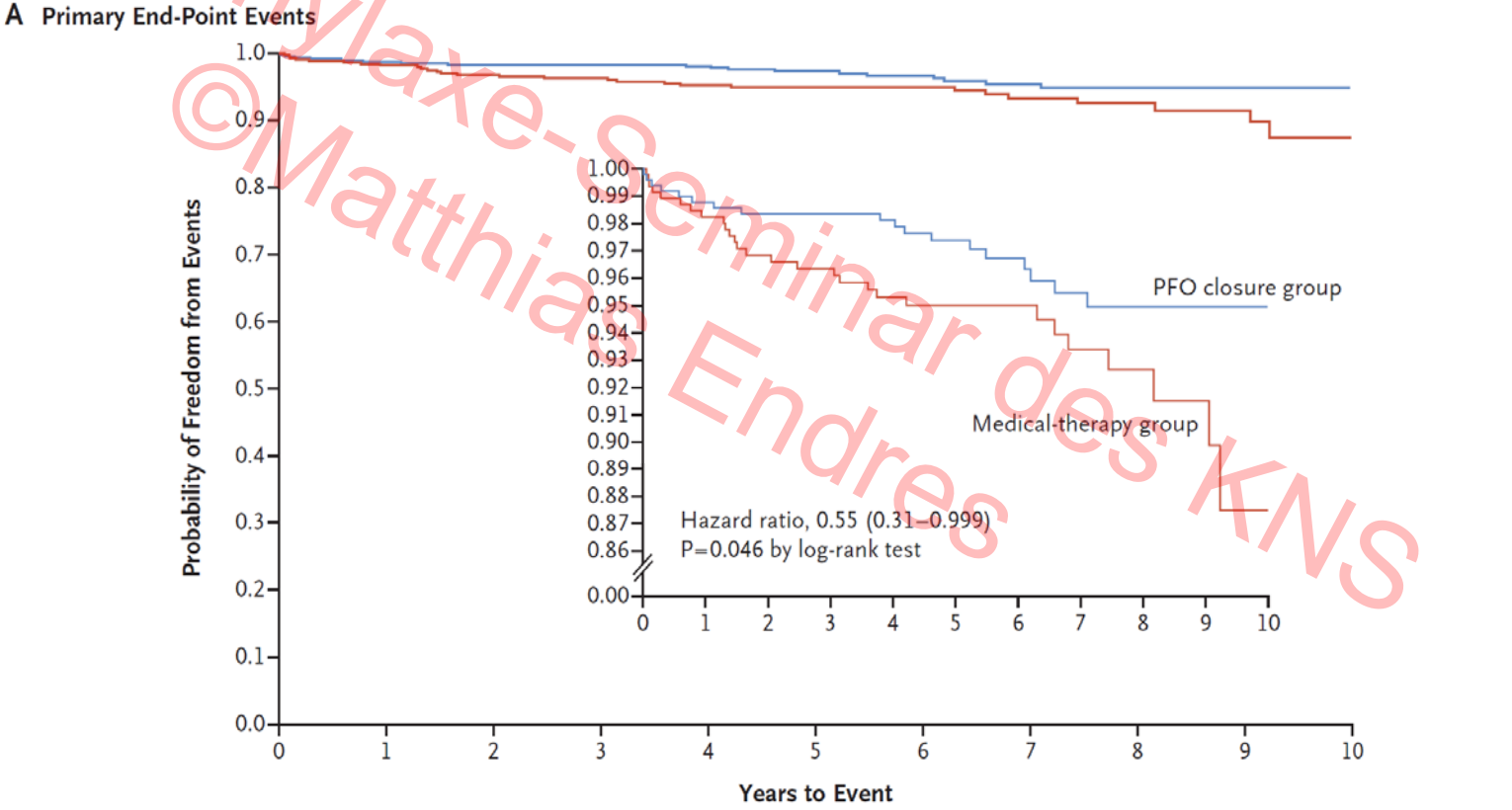


RoPE Study group, Kent D et al. Neurology 2013; 81: 619-25; *graph provided by P Michel*

Tufts Medical Center

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*



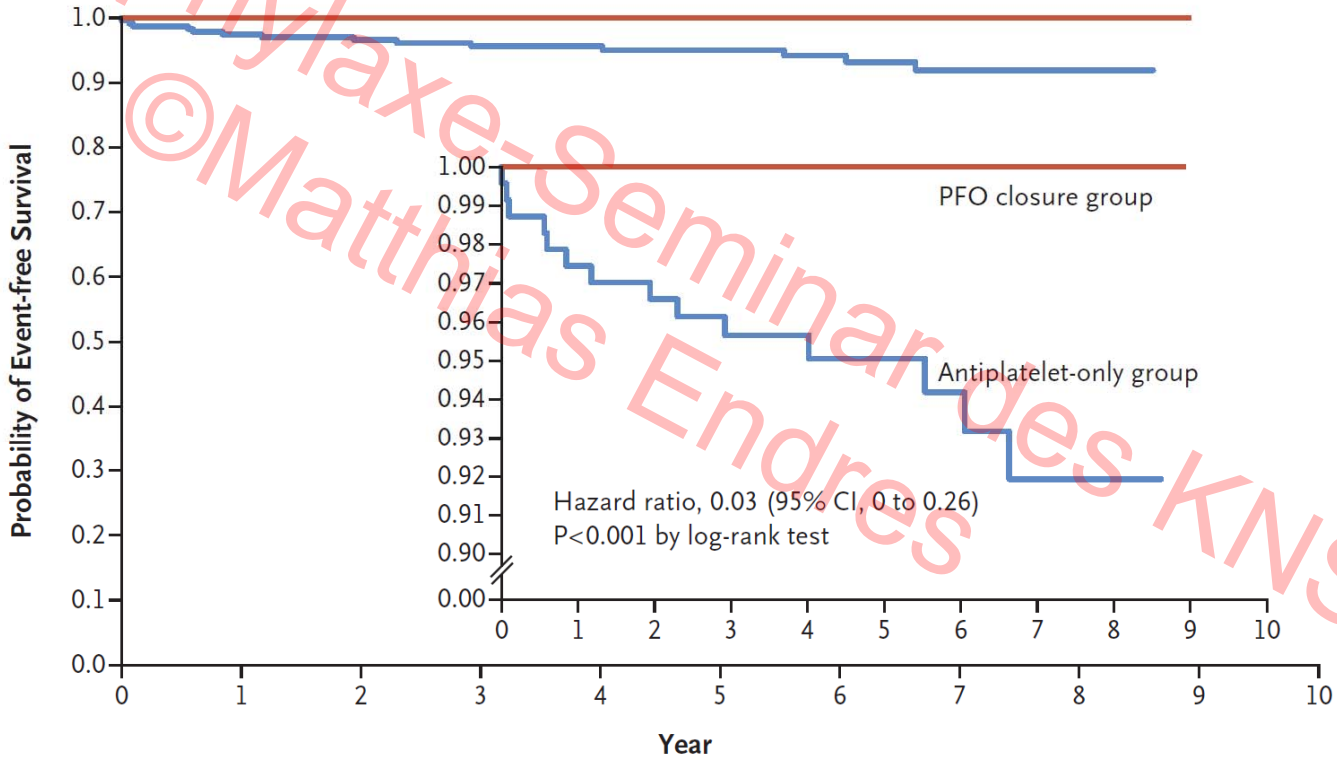
No. at Risk

PFO closure group	499	476	464	447	421	352	262	197	128	77	41
Medical-therapy group	481	433	394	380	354	282	218	150	104	59	31

N Engl J Med 2017;377:1011-21.

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*



No. at Risk											
PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

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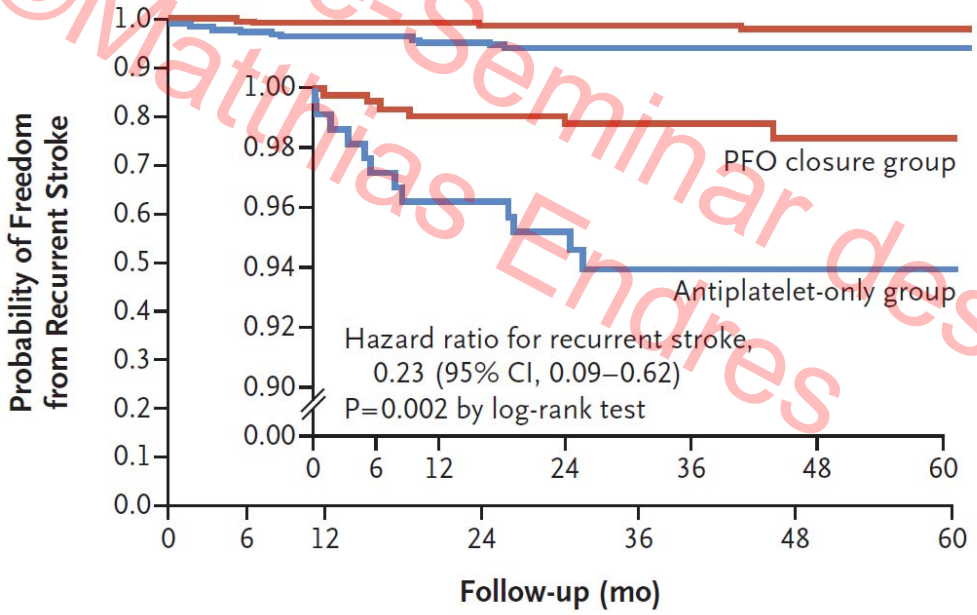
Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*



No. at Risk							
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

N Engl J Med 2017;377:1033-42.

Zusammenfassung

1. **Ticagrelor hat es knapp nicht geschafft**
2. **Aspirin vor allem früh wirksam**
3. **PCSK9 Inhibitor senken Schlaganfallrisiko**
4. **ESUS Studie mit Rivaroxaban negativ**
5. **PFO Verschluss bei jungen Patienten mit kryptogenem Schlaganfall überlegen**