

Schlaganfall und Cholesterin

Matthias Endres

*Dept Neurology
Center for Stroke Research Berlin
Charité – Hospital, Germany*

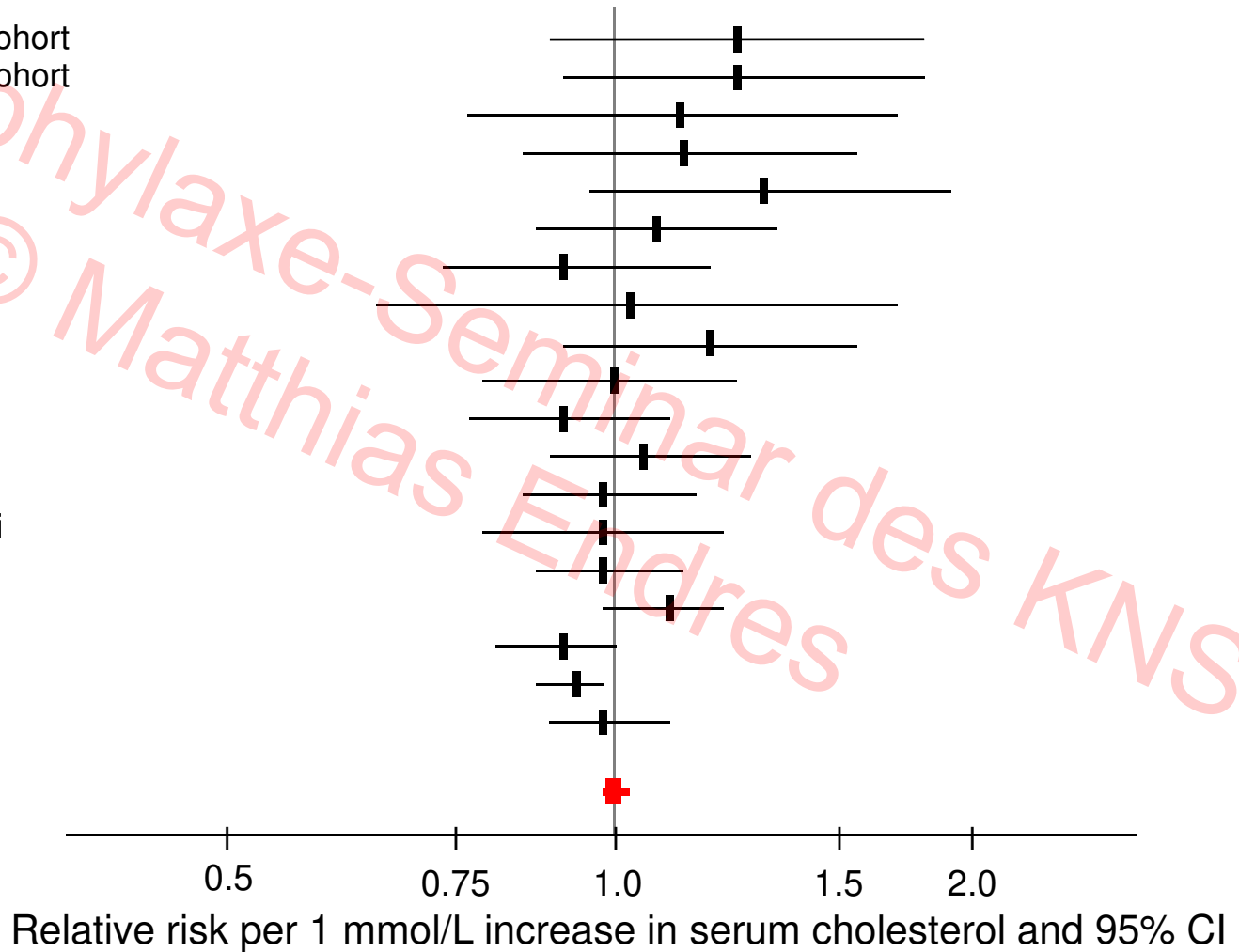
- Cholesterol and ischemic vs hemorrhagic stroke
- Cholesterol lowering and ischemic vs hemorrhagic stroke
- Statins, acute stroke, and risk of thrombolysis
- Statins in patients with ICH
- PCSK9 inhibitors

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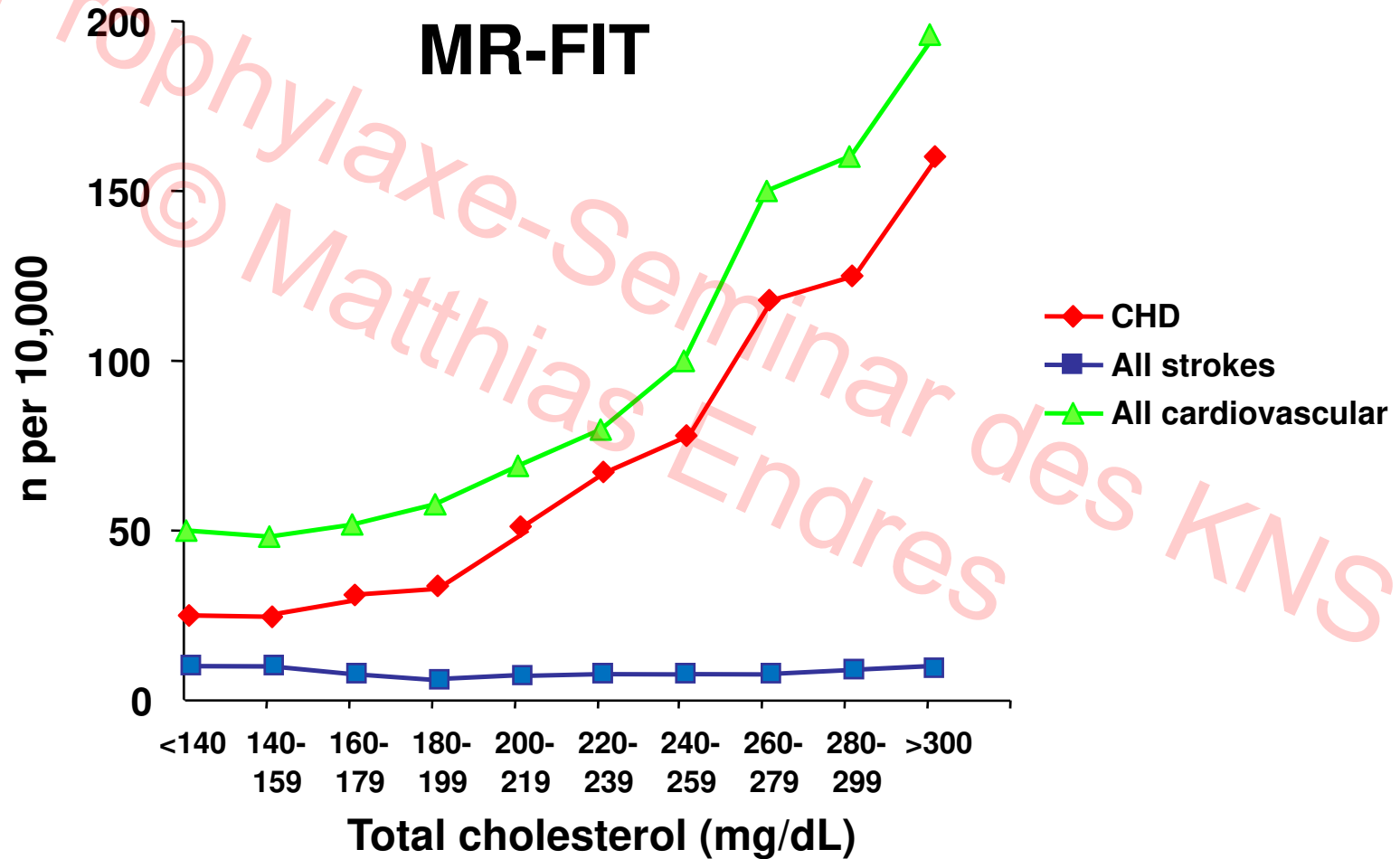
Cholesterol and stroke risk

- Evans County black cohort
- Evans County white cohort
- Norwegian counties
- Rancho Bernardo
- Busselton
- Tecumseh
- Whitehall
- Akita
- Finrisk
- Israel
- Paisley & Renfrew
- Framingham
- Honolulu
- Hiroshima & Nagasaki
- Seven counties
- NHEFS
- Finnish Mobile Clinic
- Varmland
- Other cohorts

TOTAL



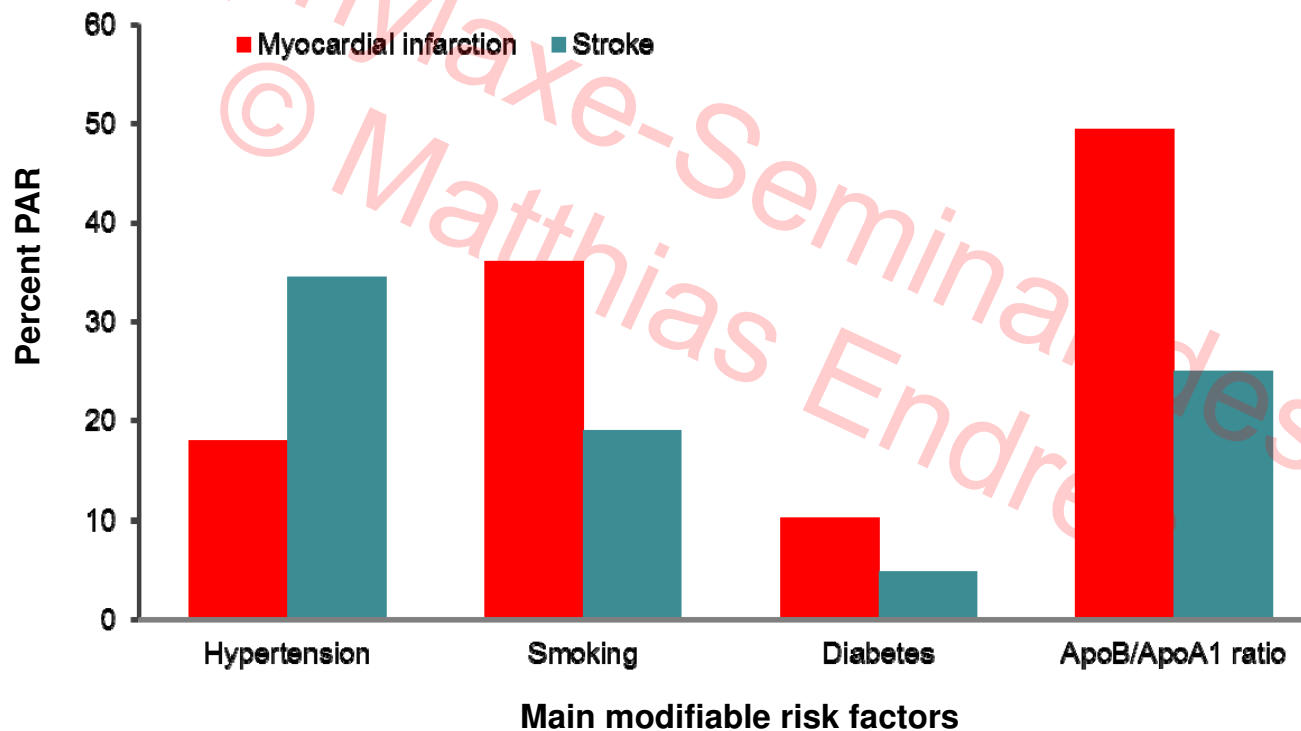
Cholesterol and 6-year mortality



CHD, coronary heart disease;
MR-FIT, Multiple Risk Factor Intervention Trial.

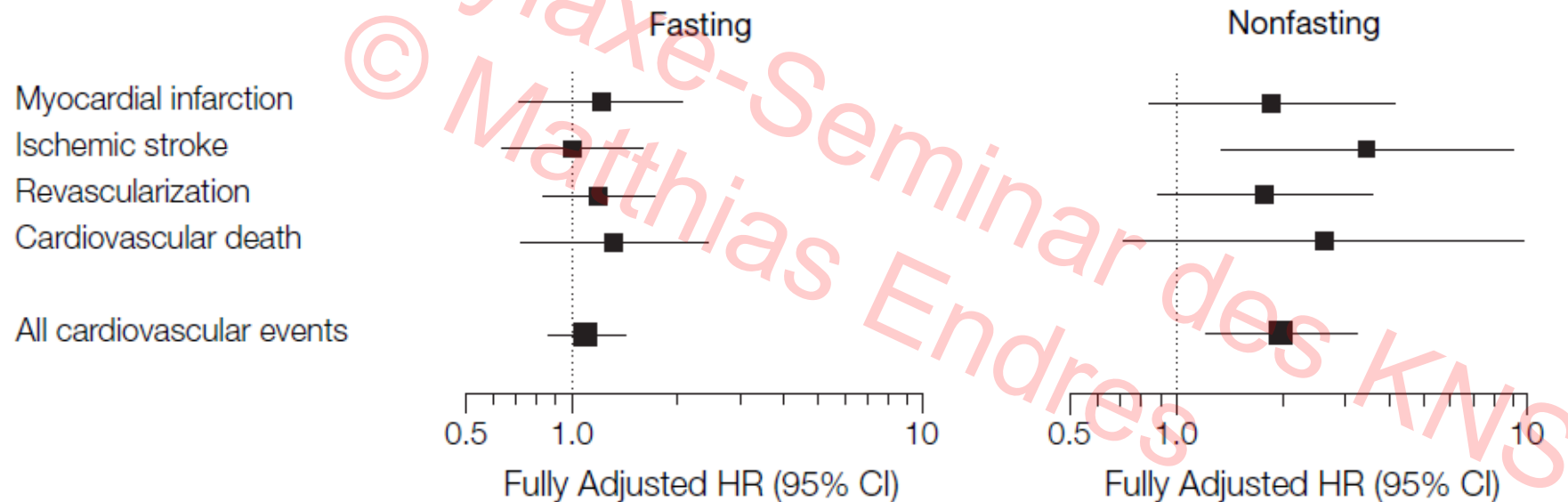
Primary prevention of strokes: blood pressure, lipids and heart failure

Attributable risk for stroke vs myocardial infarction



Apo, apolipoprotein; PAR, population attributable risk.

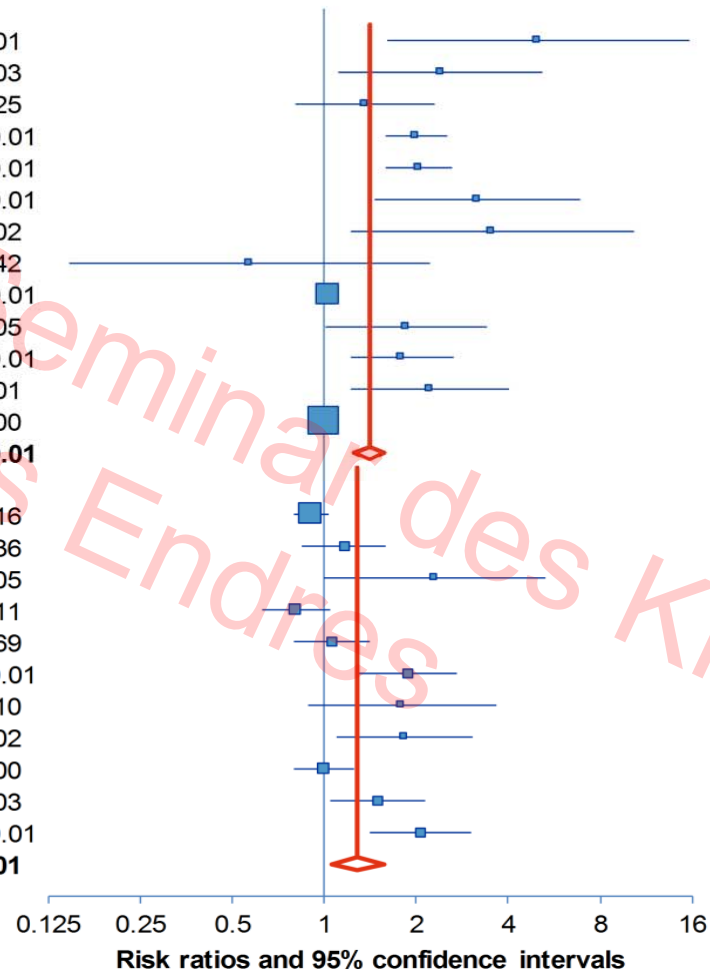
Association of triglyceride levels with individual cardiovascular endpoints, according to fasting status



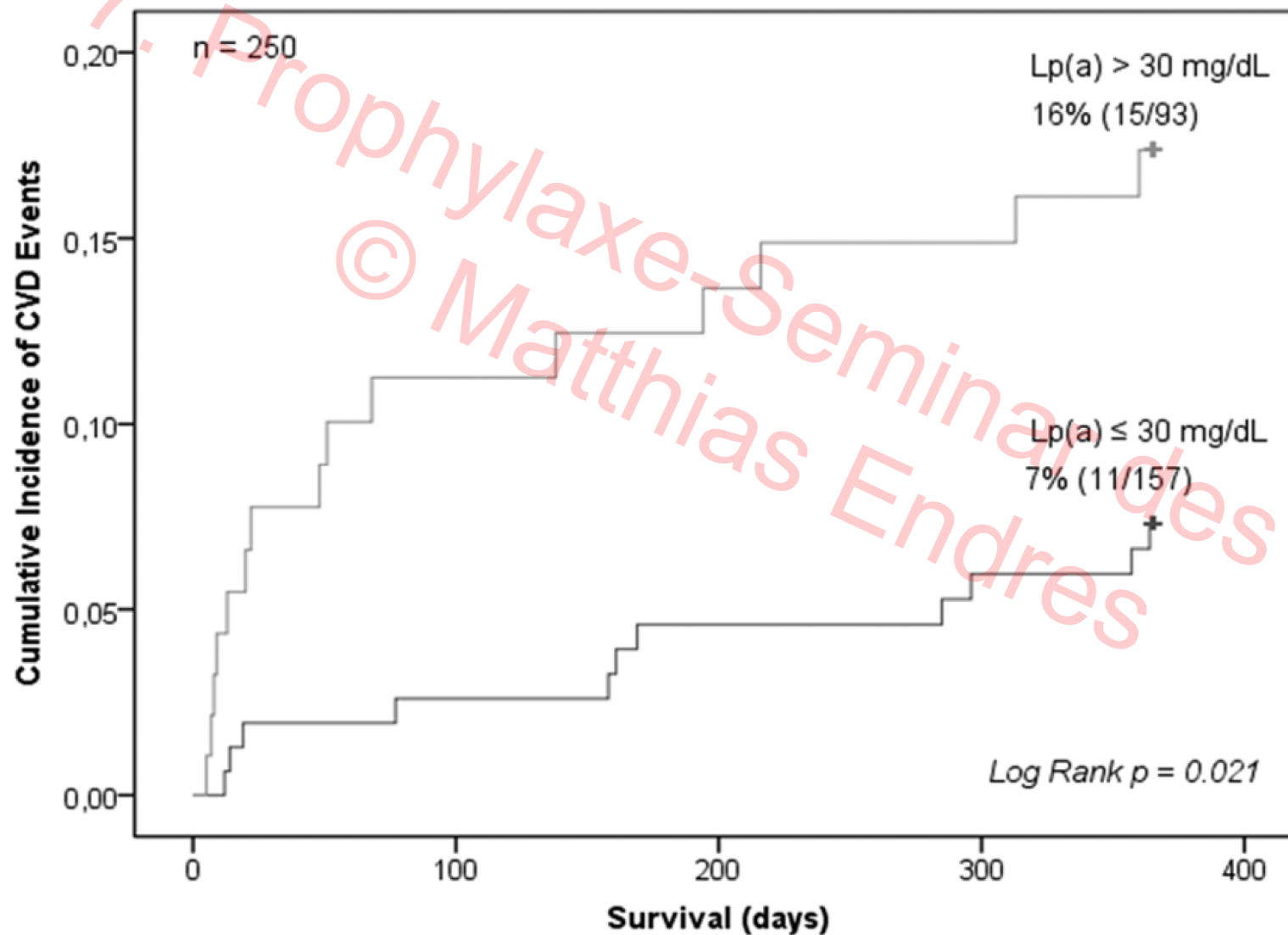
HR and 95% CI for highest vs lowest tertiles of triglyceride level, adjusted for age, blood pressure, smoking, hormone use, levels of total and high-density lipoprotein cholesterol, diabetes mellitus, body mass index and high-sensitivity C-reactive protein level.

Lipoprotein(a) as a risk factor for ischemic stroke: a meta-analysis

Author (year)	n/N	Risk ratio (95% CI)	P
Peynet (1998)	90/174	5.01 (1.60; 15.69)	0.01
Peng (1999)	90/180	2.40 (1.11; 5.17)	0.03
Wityk (1999)	110/326	1.36 (0.80; 2.30)	0.25
Sun ^a (2003)	809/2626	2.00 (1.59; 2.52)	<0.01
Sun ^b (2003)	517/2334	2.05 (1.59; 2.64)	<0.01
Emanuele (2004)	95/200	3.18 (1.47; 6.88)	<0.01
Rigal ^c (2007)	58/116	3.54 (1.22; 10.29)	0.02
Rigal ^d (2007)	42/84	0.57 (0.15; 2.21)	0.42
Petersen (2007)	71/134	1.04 (1.02; 1.07)	<0.01
Jones (2009)	245/684	1.85 (1.01; 3.40)	0.05
Boden-Albaba (2010)	317/730	1.80 (1.22; 2.65)	<0.01
Li (2013)	181/301	2.23 (1.23; 4.05)	0.01
Ma (2013)	124/188	1.00 (0.98; 1.02)	1.00
Pooled estimate	2749/8077	1.41 (1.26; 1.57)	<0.01
Gurdasani (2012)	284/18720	0.91 (0.80; 1.04)	0.16
Berger (2012)	700/1400	1.16 (0.84; 1.60)	0.36
Teo (2013)	50/3414	2.31 (1.00; 5.32)	0.05
Alfthan ^c (1994)	42/190	0.81 (0.63; 1.05)	0.11
Alfthan ^d (1994)	28/149	1.06 (0.80; 1.41)	0.69
Danik (2006)	244/27791	1.87 (1.29; 2.71)	<0.01
Glader (1999)	101/302	1.80 (0.89; 3.65)	0.10
Uchiyama (2009)	70/7832	1.83 (1.10; 3.05)	0.02
Canoui-Poitrine (2010)	98/9711	1.00 (0.80; 1.25)	1.00
Virani ^c (2012)	337/5777	1.50 (1.05; 2.14)	0.03
Virani ^d (2012)	326/7541	2.07 (1.41; 3.03)	<0.01
Pooled estimate	2280/82827	1.29 (1.06; 1.58)	0.01



Lp(a) levels and recurrent vascular events after first ischemic stroke



Total cholesterol levels and risk of hemorrhagic stroke

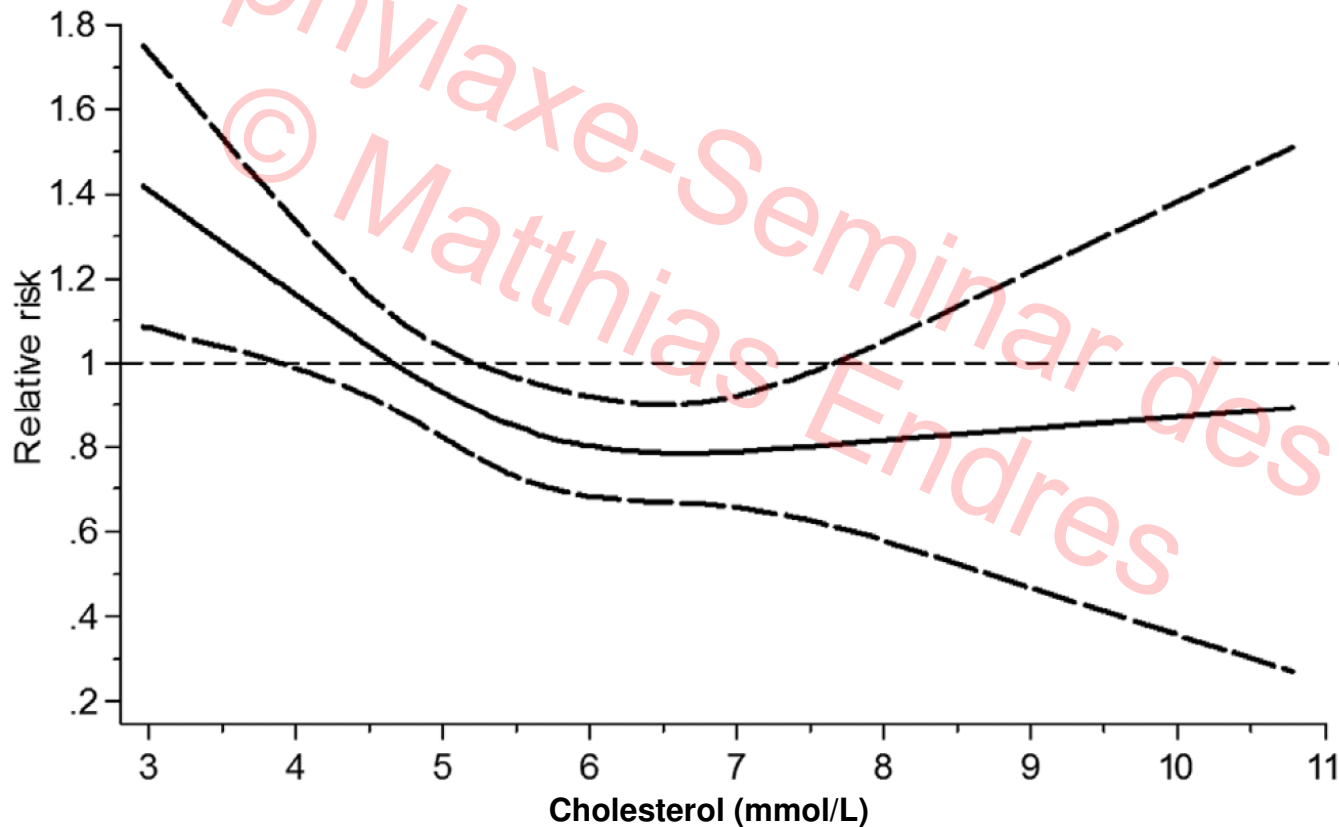
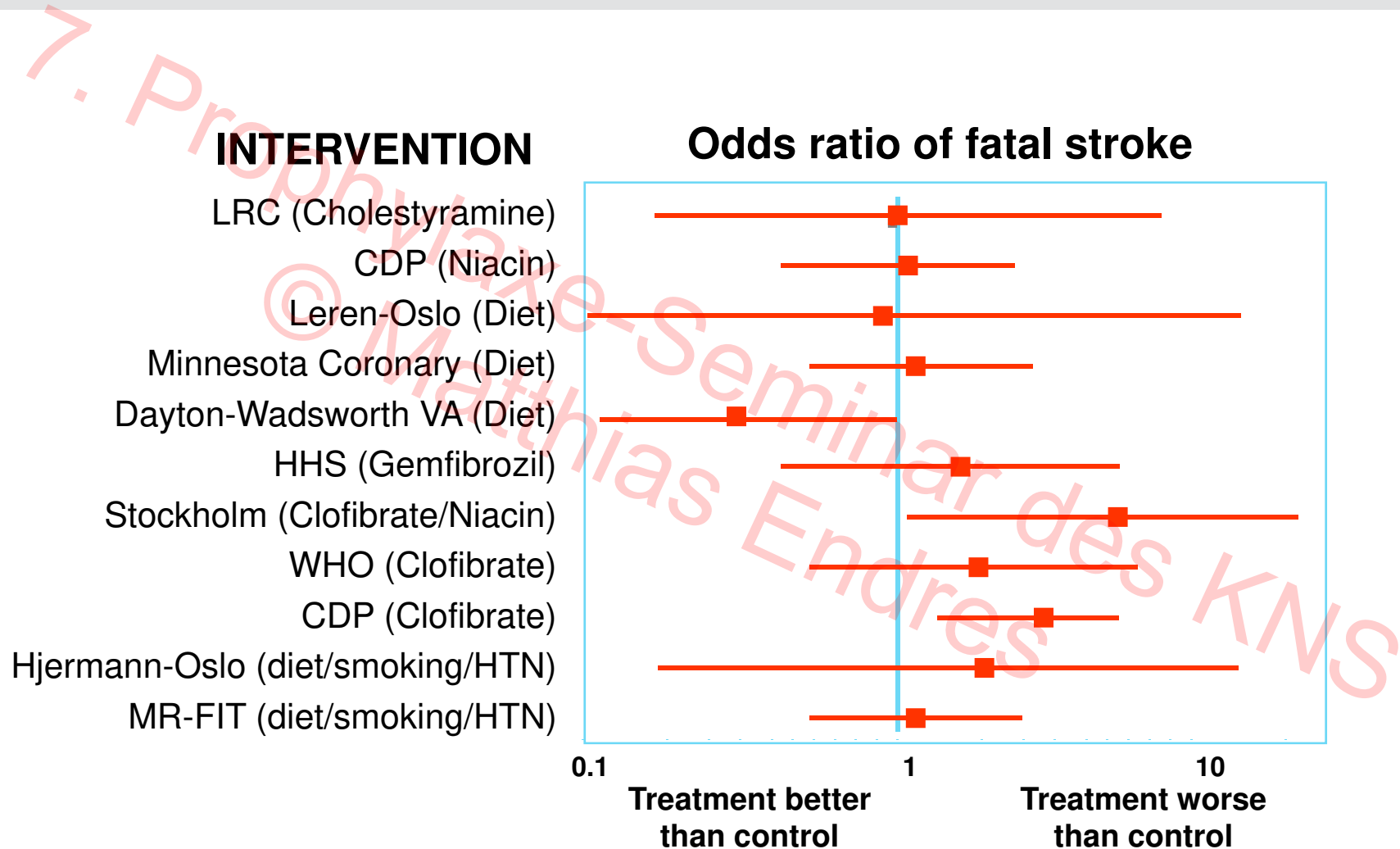


Figure shows relative risk (solid line) with 95% CI (long dashed lines).

- Cholesterol/LDL-C is a risk factor for (atherothrombotic) ischemic stroke
- The attributable risk of cholesterol for stroke is lower than for myocardial infarction
- Low cholesterol/LDL-C levels are associated with hemorrhagic stroke. Some of this association is explained by other comorbidities (i.e. hypertension, alcohol, liver disease)

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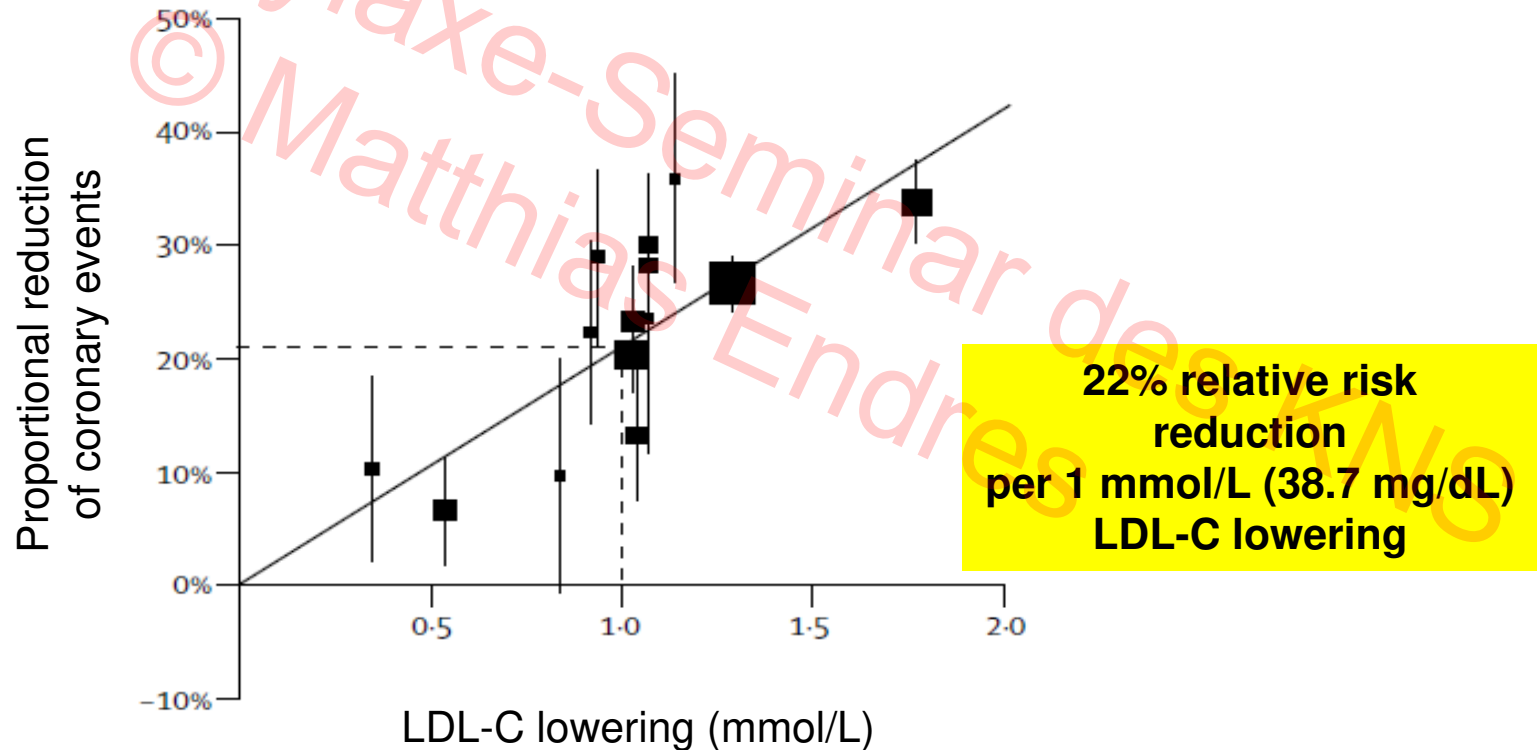


HTN, hypertension.

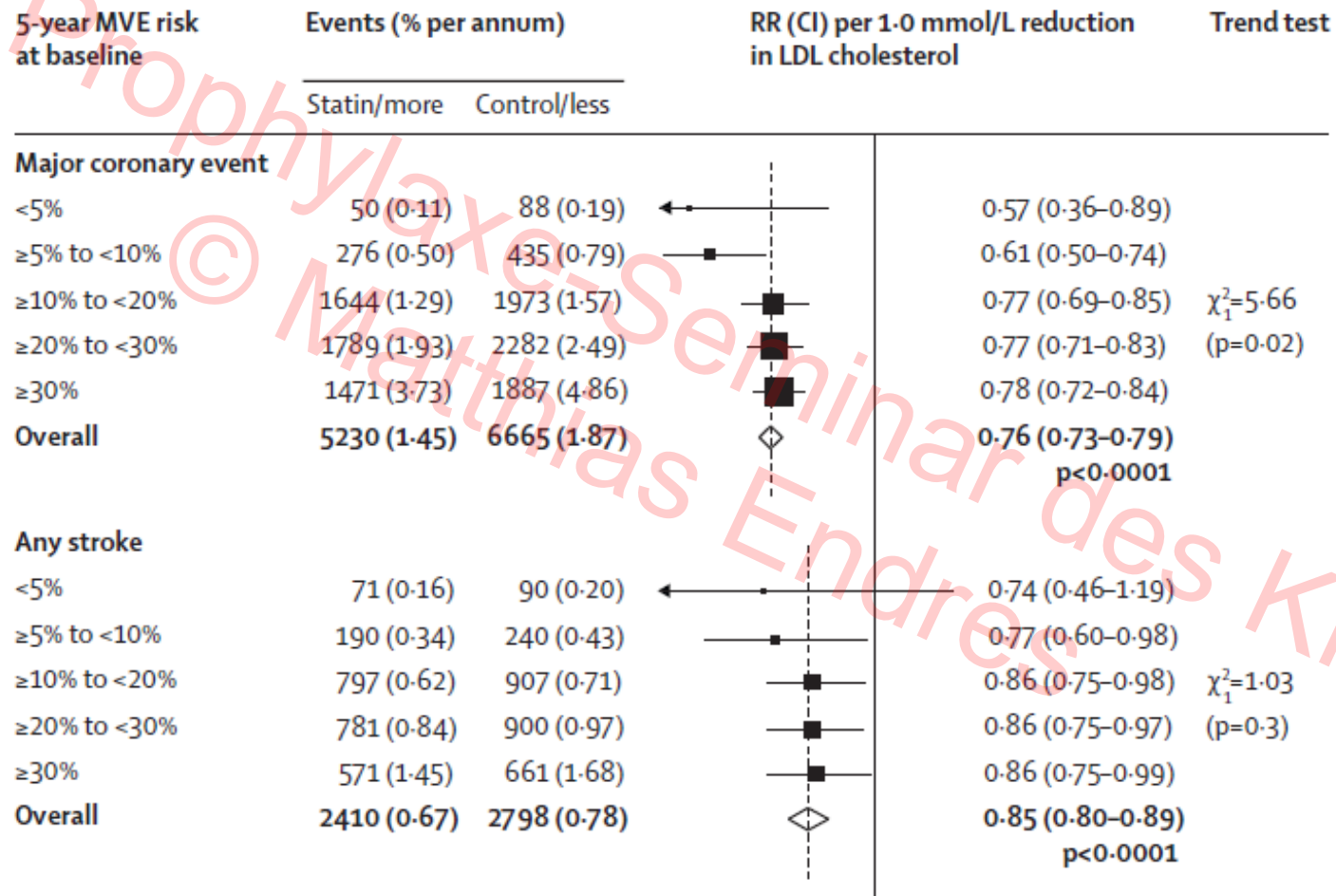
LDL-C lowering with statins reduces cardiovascular events

Cholesterol Treatment Trialists (CTT)

Prospective meta-analysis, 14 randomized studies, n = 90,056



LDL-C lowering with statins also reduces strokes by 15%



MVE, major vascular events; RR, risk reduction.

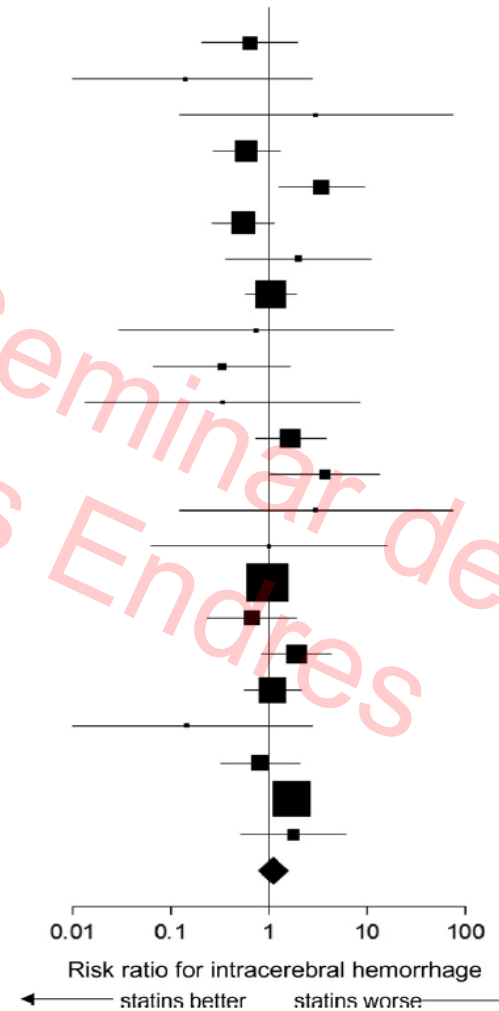


CSB

Center for Stroke Research Berlin

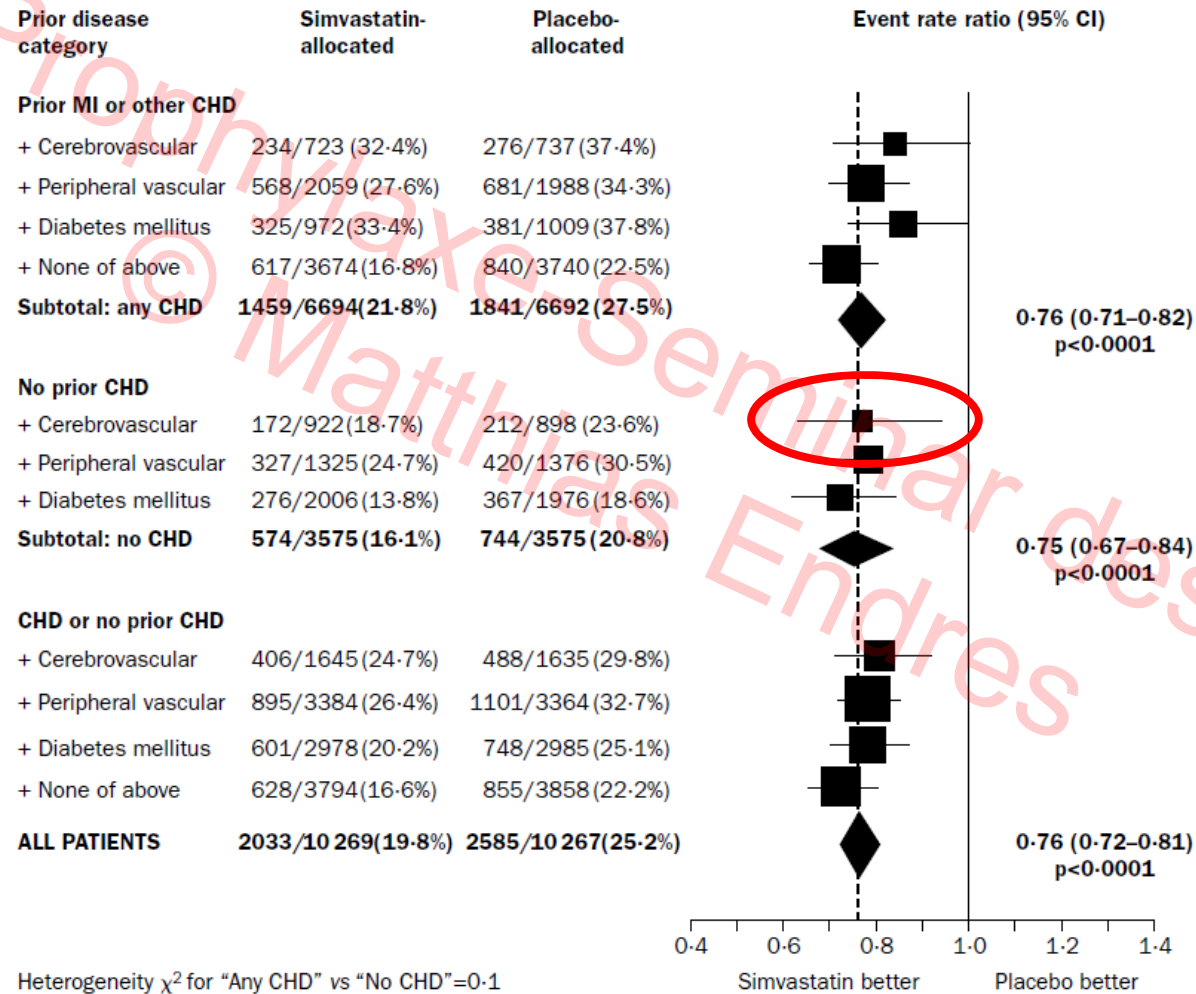
Statins and intracerebral haemorrhage

Trial	RR (95% CI)	Weight
4D	0.64 (0.21 to 1.96)	3.9
ACAPS	0.14 (0.01 to 2.75)	0.7
AFCAPS	3.00 (0.12 to 3.62)	0.6
ALERT	0.59 (0.27 to 1.28)	6.5
ALLHAT	3.42 (1.26 to 9.27)	4.7
ASCOT	0.55 (0.26 to 1.14)	7.0
ASPEN	1.98 (0.36 to 10.9)	1.9
AURORA	1.04 (0.57 to 1.91)	8.8
Bone et al	0.74 (0.03 to 18.3)	0.6
CARE	0.33 (0.07 to 1.65)	2.2
CLAPT	0.34 (0.01 to 8.34)	0.6
CORONA	1.66 (0.72 to 3.80)	6.1
GISSI-HF	3.69 (1.03 to 13.2)	3.2
GISSI-P	2.99 (0.12 to 73.6)	0.6
GREACE	1.00 (0.06 to 16.0)	0.8
HPS	0.96 (0.65 to 1.41)	12.5
JUPITER	0.67 (0.24 to 1.87)	4.4
LIPID	1.89 (0.84 to 4.24)	6.2
MEGA	1.09 (0.56 to 2.11)	7.9
MIRACL	0.14 (0.01 to 2.78)	0.7
PROSPER	0.81 (0.32 to 2.04)	5.2
SPARCL	1.68 (1.09 to 2.60)	11.6
SSSS	1.75 (0.51 to 6.00)	3.4
Overall	1.10 (0.86 to 1.42)	100



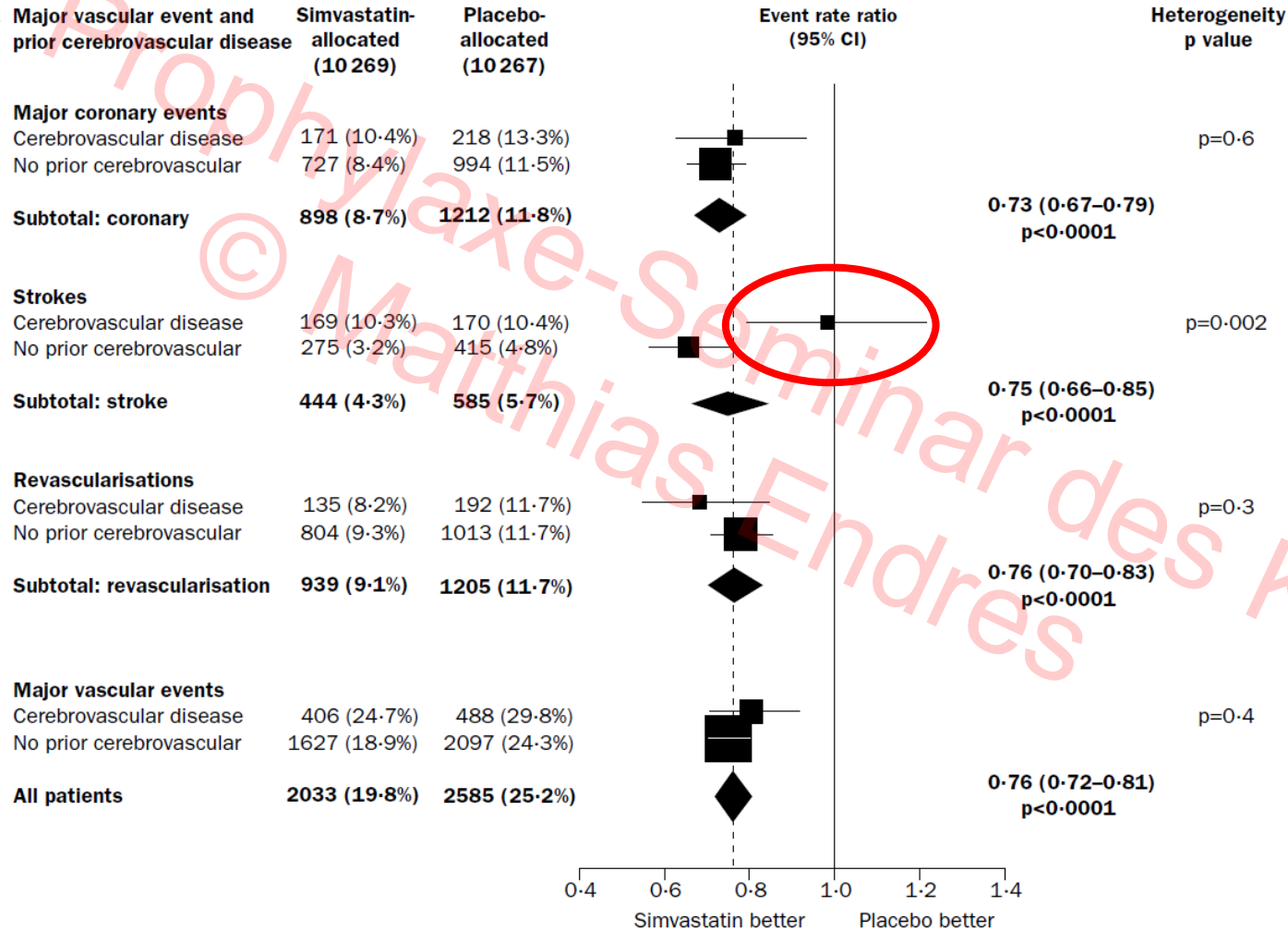
- LDL-C lowering by statins reduces vascular events
- LDL-C lowering by statins also reduces stroke risk
- LDL-C lowering by statins did not increase hemorrhagic stroke risk
- However, these studies were performed in patients with vascular risk. **What about stroke patients?**

Effects of cholesterol lowering with simvastatin on stroke

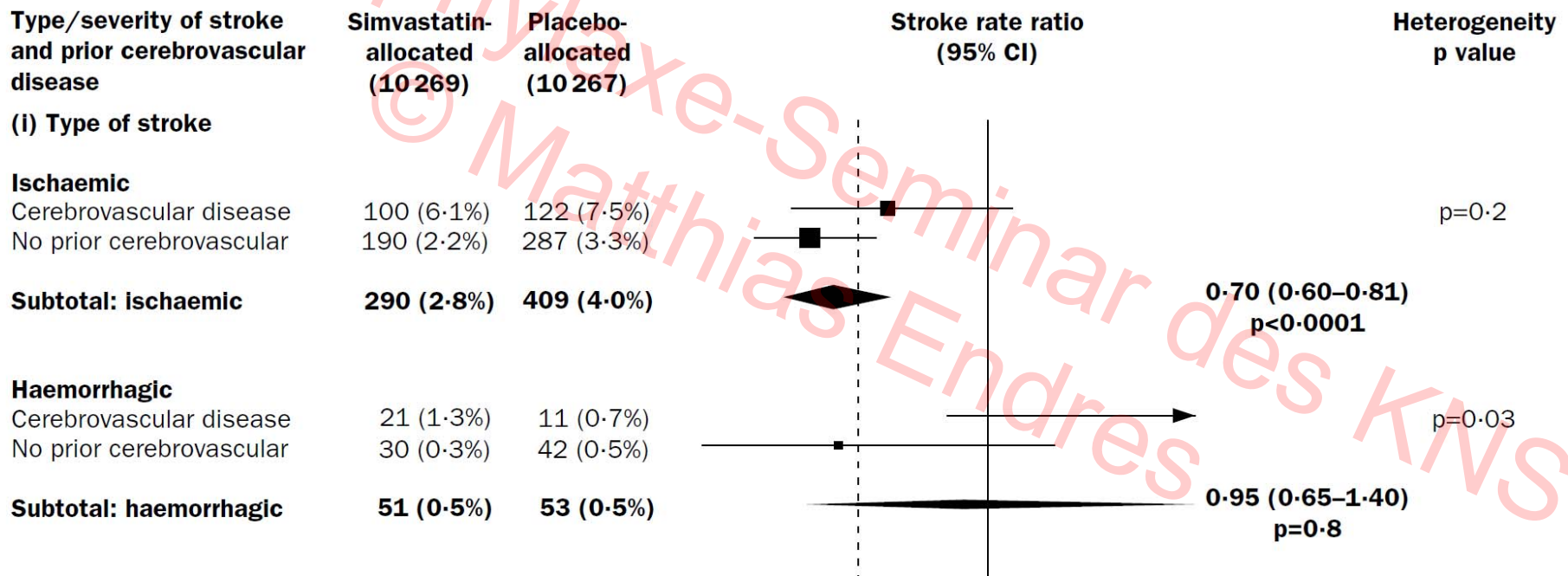


MI, myocardial infarction.

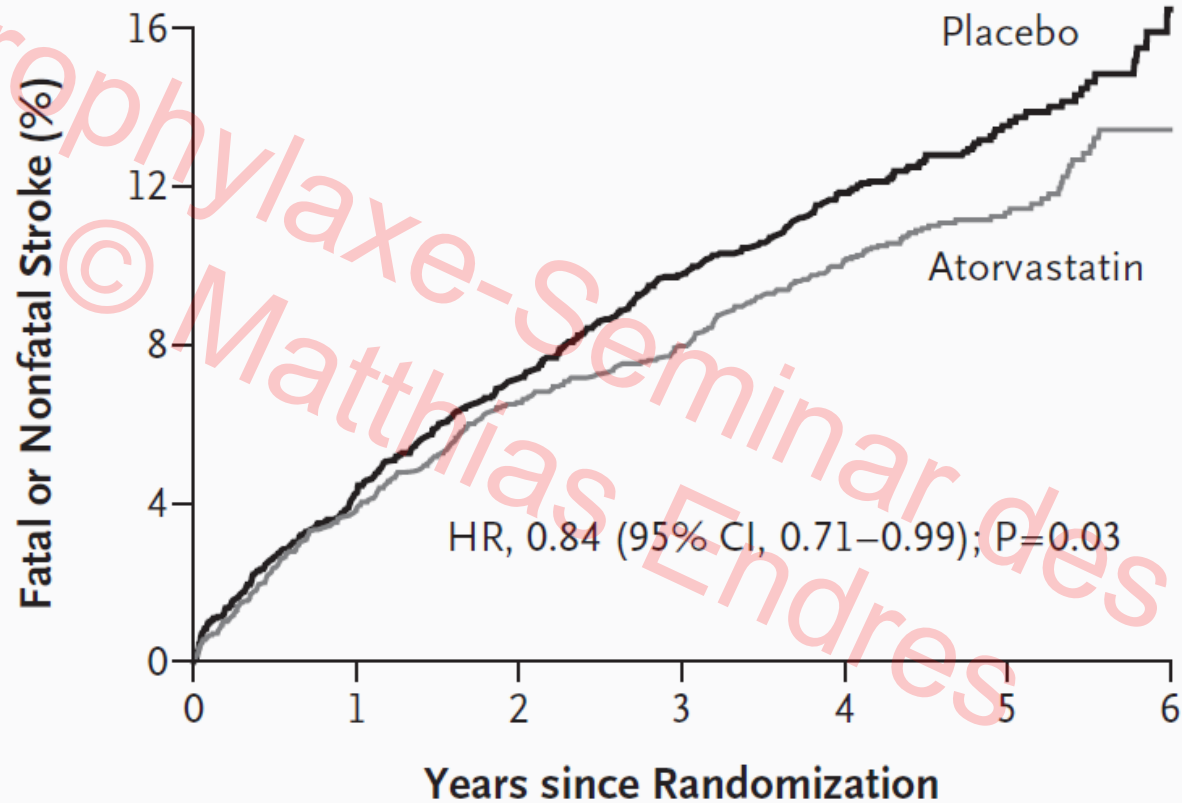
Effects of cholesterol lowering with simvastatin on stroke



Effects of cholesterol lowering with simvastatin on stroke



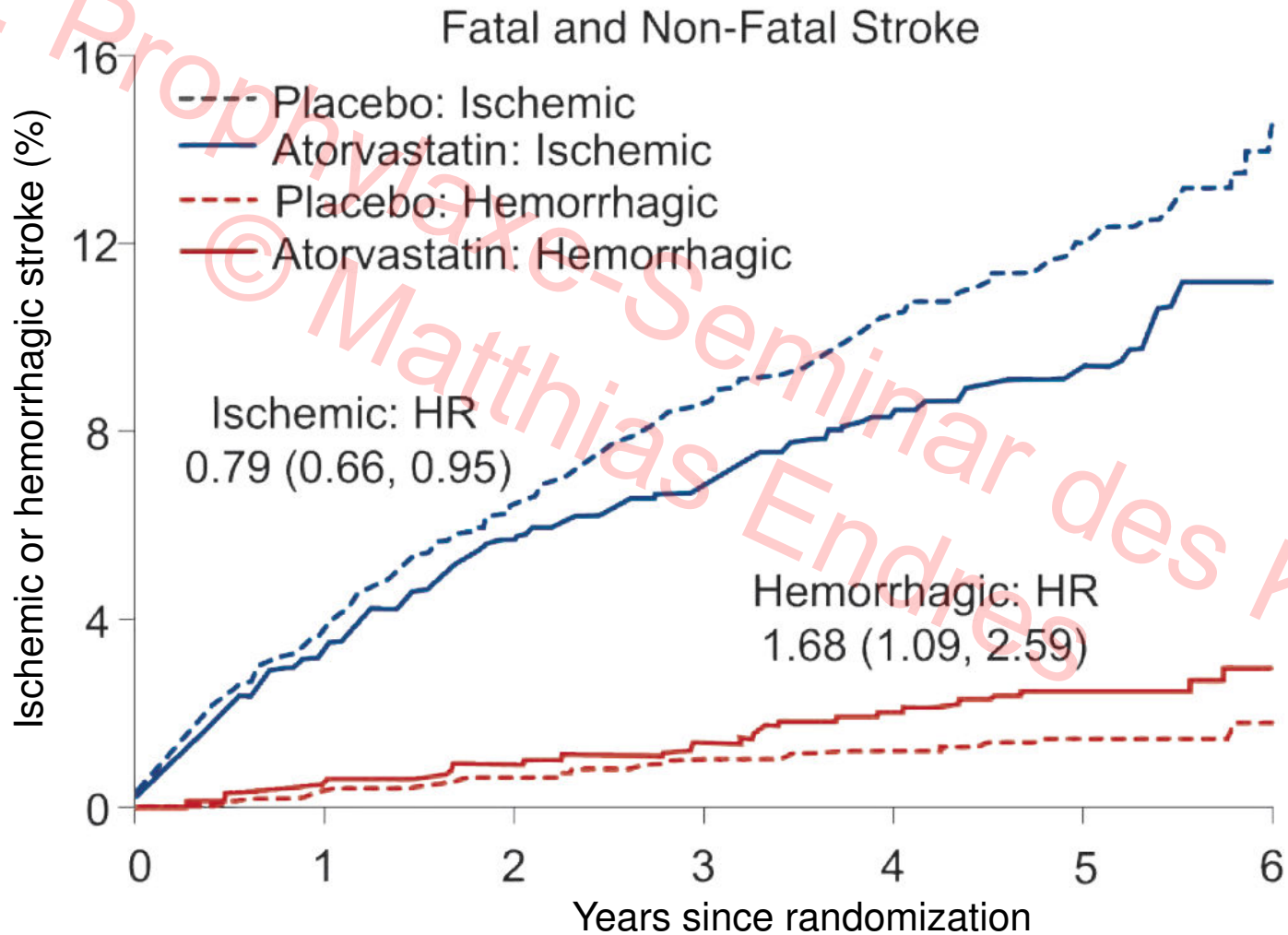
High-dose atorvastatin after stroke or transient ischemic attack (SPARCL)



No. at Risk

Atorvastatin	2365	2208	2106	2031	1935	922	126
Placebo	2366	2213	2115	2010	1926	887	137

Hemorrhagic stroke in SPARCL



In stroke patients (data from HPS and SPARCL)

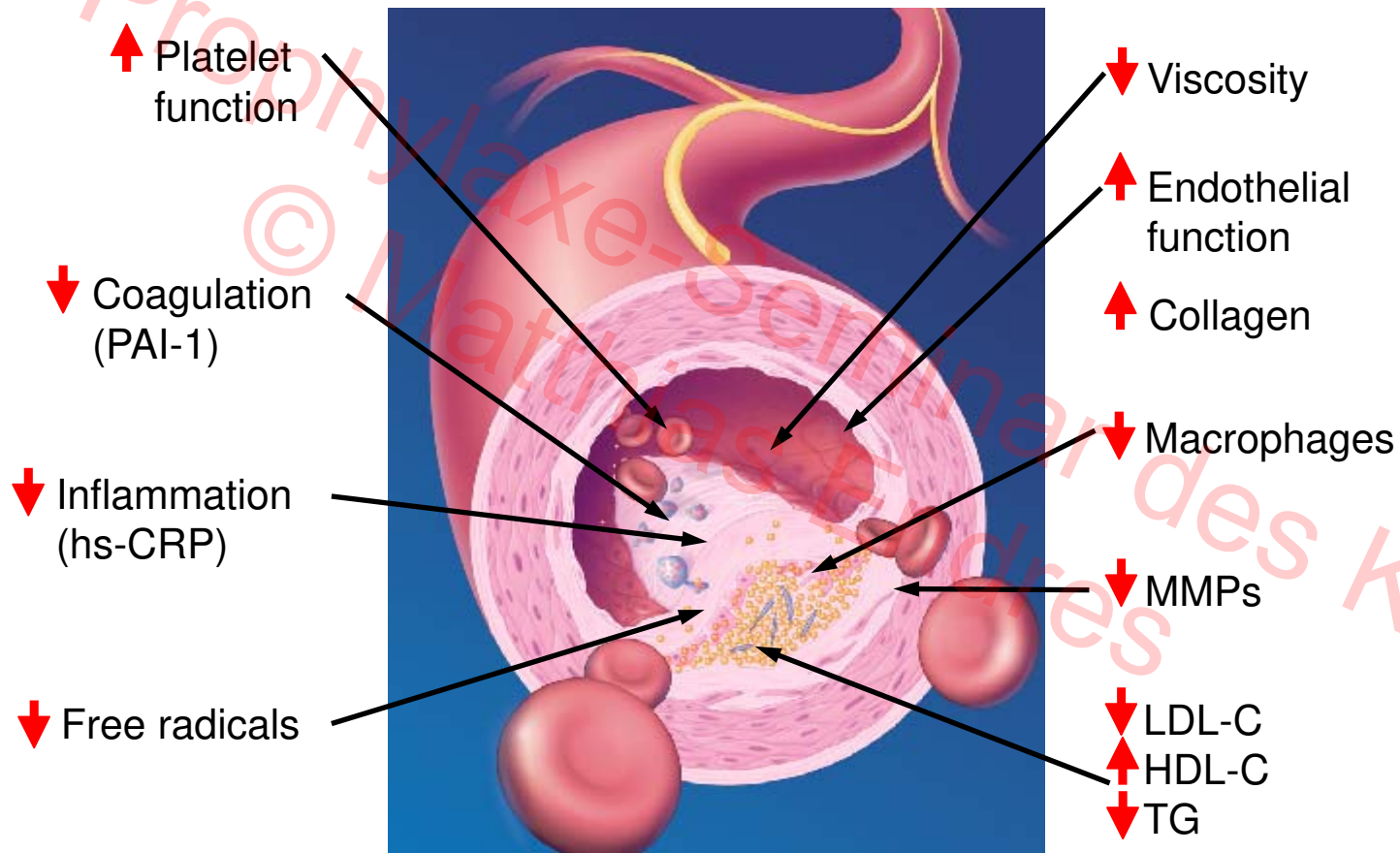
- LDL-C lowering by statins reduces vascular events
- LDL-C lowering by statins also reduces stroke risk
- LDL-C lowering by statins **increases** hemorrhagic stroke risk

Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥ 100 mg/dL with or without evidence for other clinical ASCVD (*Class I; Level of Evidence B*). (Revised recommendation)

ASCVD, atherosclerotic cardiovascular disease;
TIA, transient ischemic attack.

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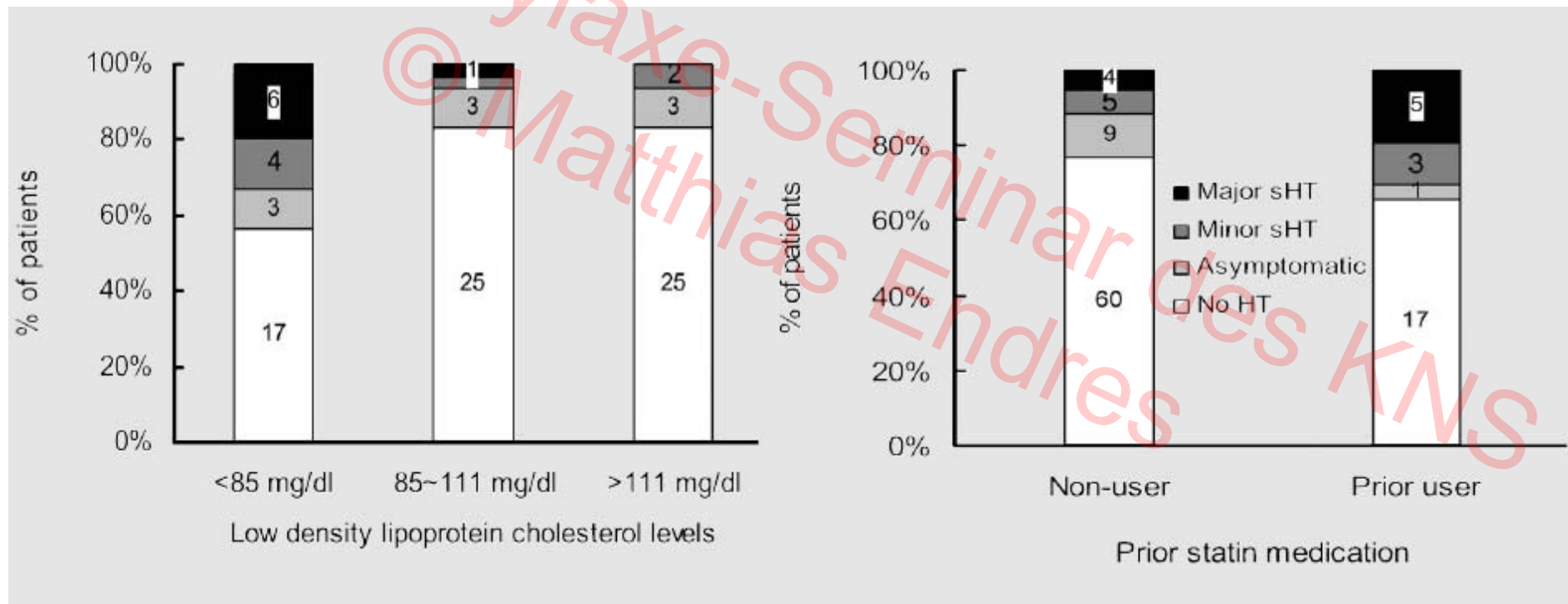
Pleiotropic effects of statins



hs-CRP, high-sensitivity C-reactive protein;
MMPs, matrix metalloproteinases;
PAI-1, plasminogen activator inhibitor-1; TG, triglycerides.

Cholesterol level and symptomatic hemorrhage transformation after ischemic stroke thrombolysis

Severity and type of hemorrhagic transformation after thrombolysis for ischemic stroke by LDL-C and premorbid statin use



HT, hemorrhage transformation; sHT, symptomatic HT.

Dose-related effects of statins on symptomatic ICH and outcome after thrombolysis for ischemic stroke

Two thrombolysis registries from Basel and Berlin, 1446 patients

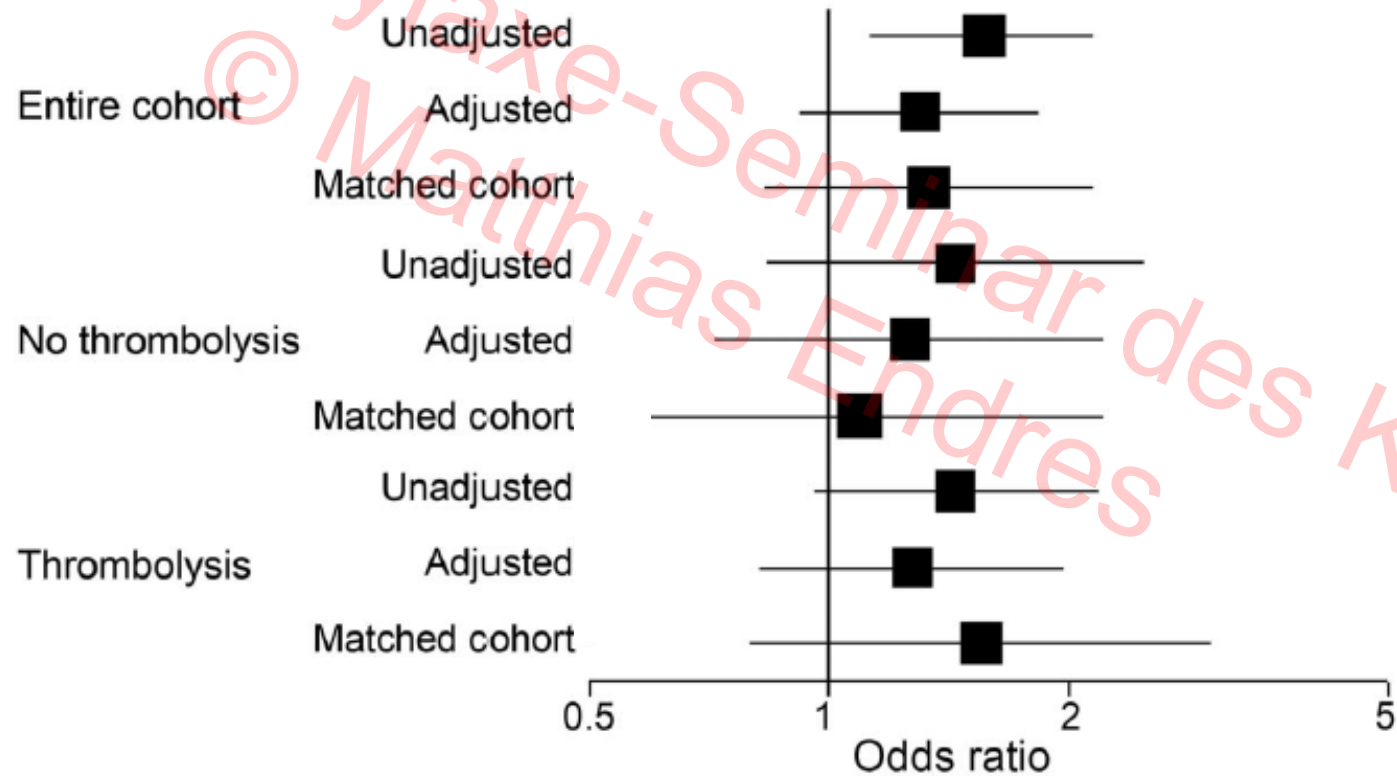
- Symptomatic ICH following thrombolysis higher with pre-stroke statins (i.e., 2%, 6%, and 13% with low-, medium- and high-dose statins, respectively)
- However, 3-month outcome was nevertheless better with pre-stroke statin treatment (OR = 1.8)

OR, odds ratio.

Statins and risk of post-stroke hemorrhagic complications

VISTA database, 8535 patients, propensity score matching

Models of acute symptomatic ICH

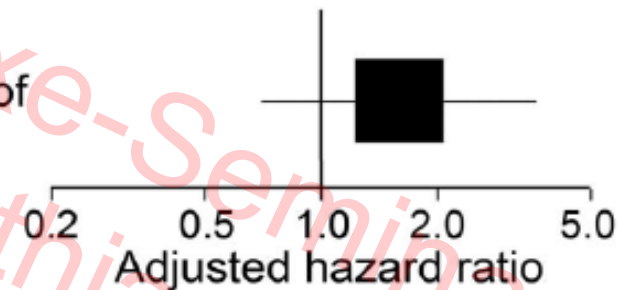


Statins and risk of post-stroke hemorrhagic complications

VISTA database, 8535 patients

Model of postacute ICH within 90 days

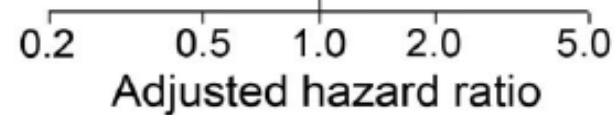
New initiation of statins



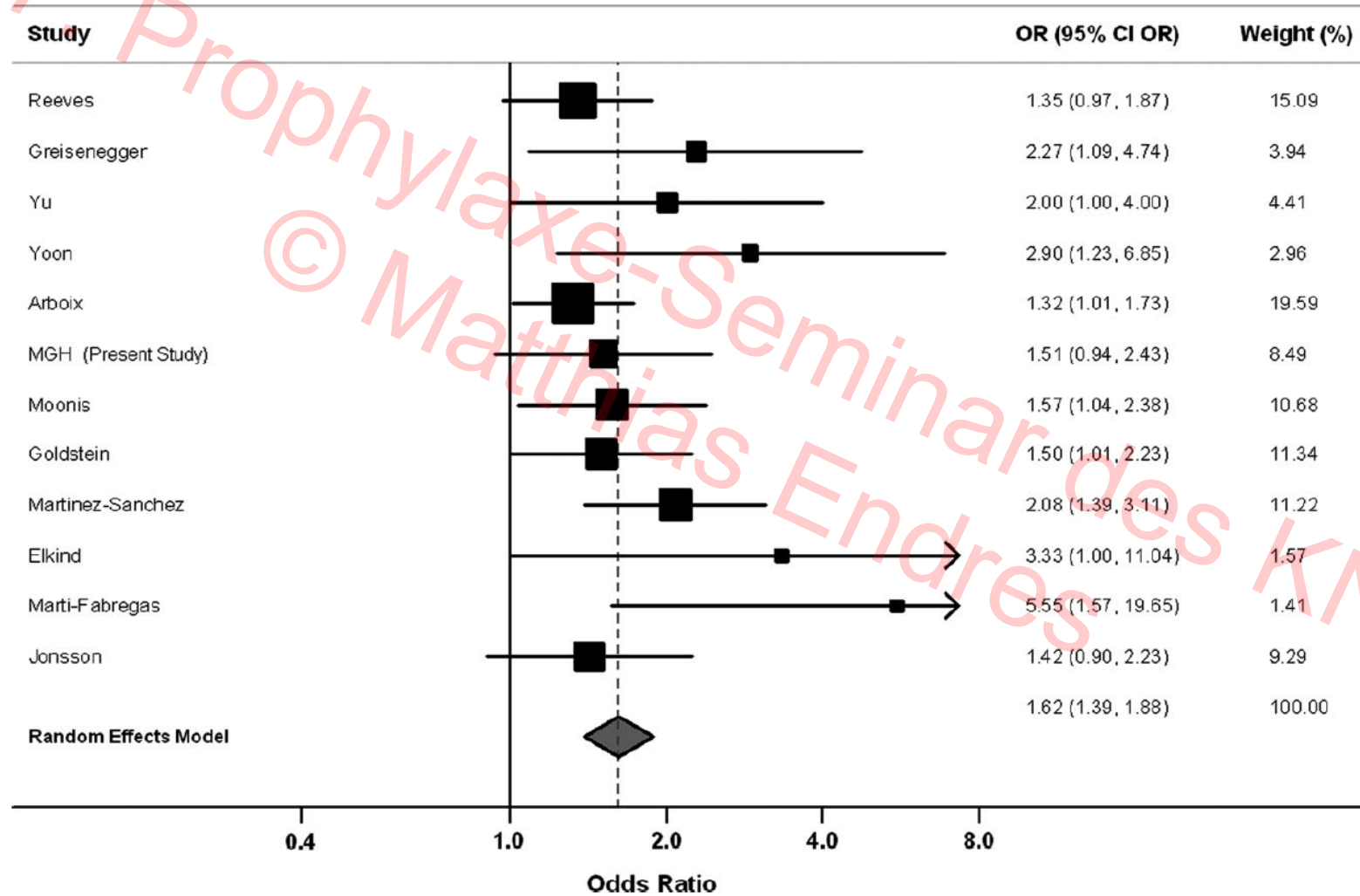
Models of mortality within 90 days

Prior statin use

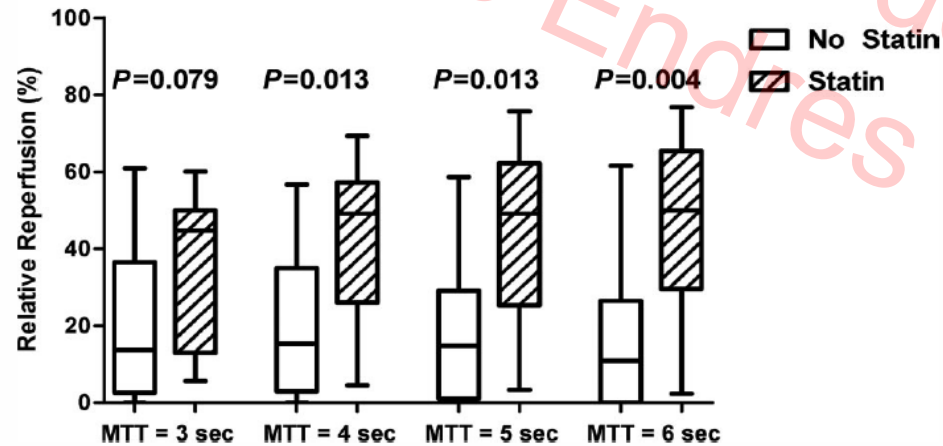
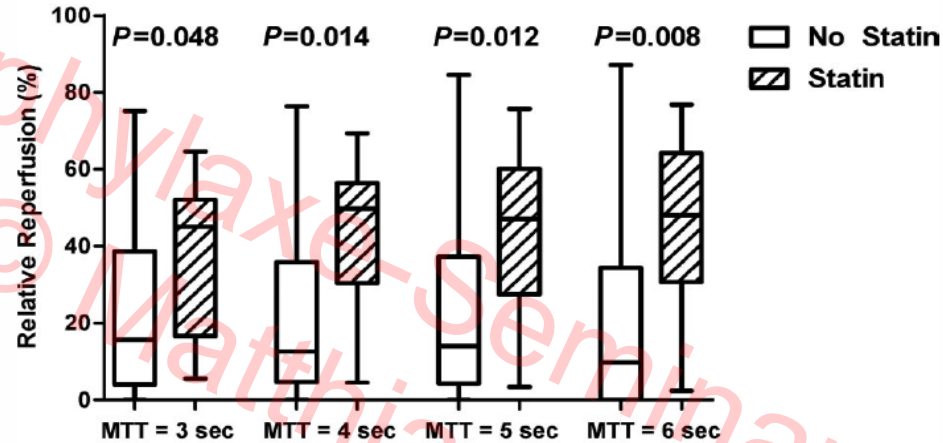
New initiation of statins



Statin treatment and functional outcome after ischemic stroke

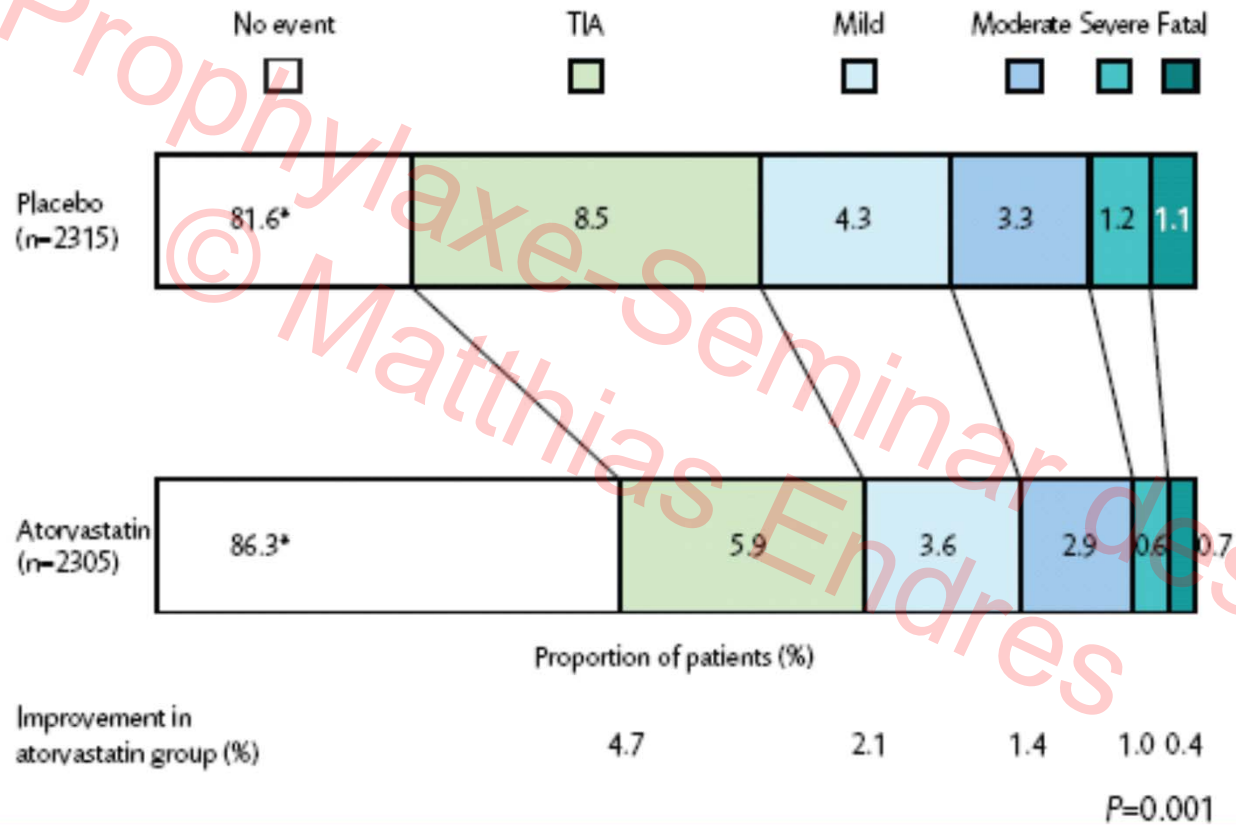


Pre-existing statin use is associated with greater reperfusion in hyperacute ischemic stroke



MTT, mean transit time.

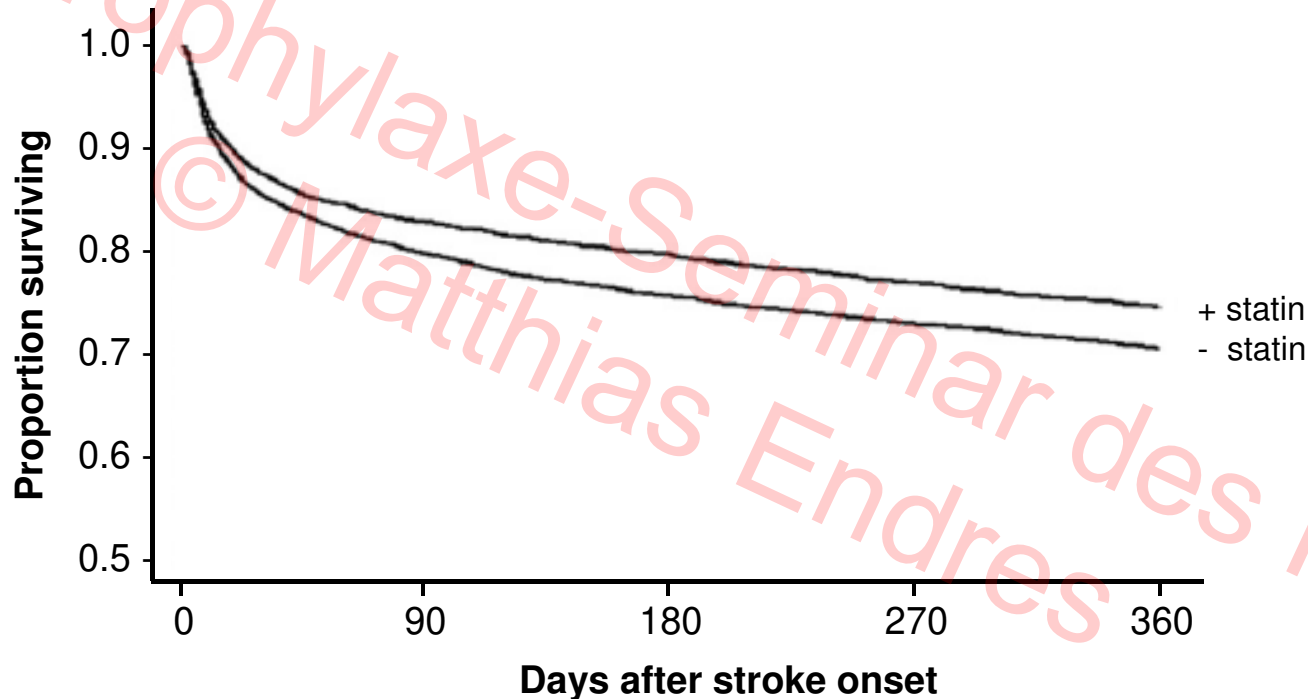
Statin treatment and stroke outcome in the SPARCL trial



*Percent of patients with no recurrent event is not shown to scale. Subjects with missing severity for first event are excluded. Stroke severity determined by Rankin scale: 0/1=mild, 2/3=moderate, 4/5=severe.

Statin use during ischemic stroke hospitalization is strongly associated with improved post-stroke survival

Statin use before stroke

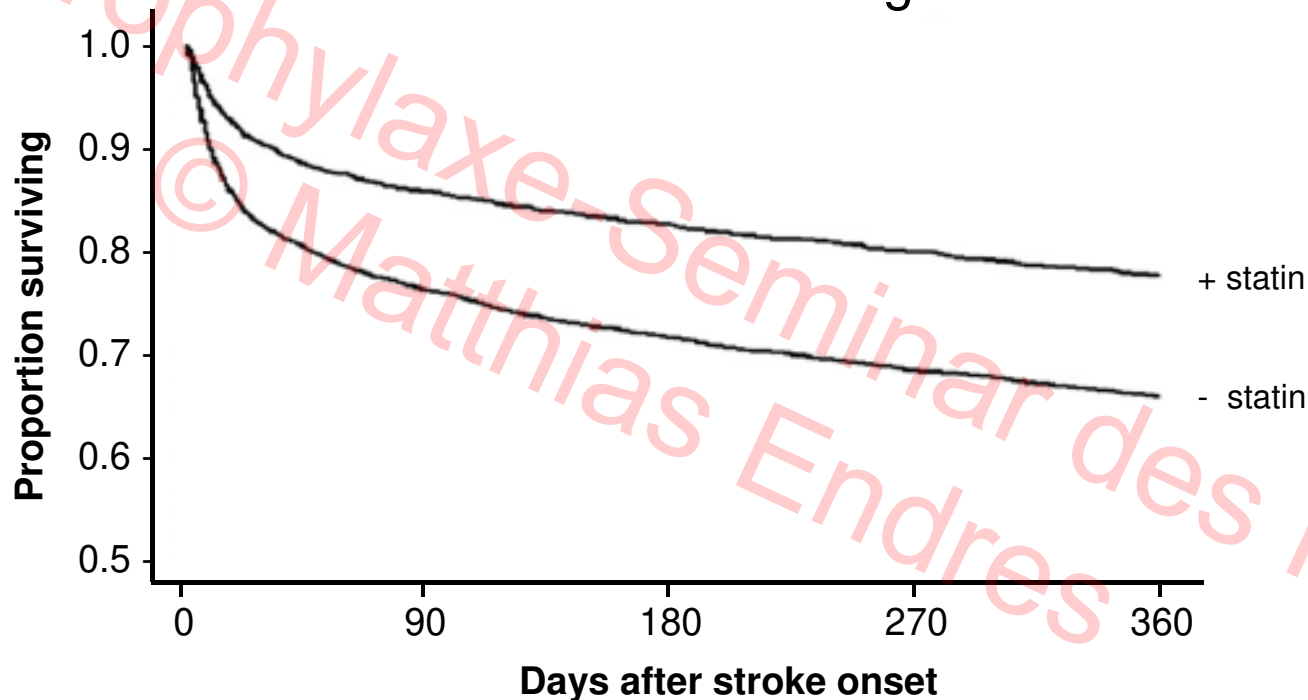


Number at risk

+ statin	3749	3050	2892	2758	2650
- statin	8940	6975	6493	6170	5885

Statin use during ischemic stroke hospitalization is strongly associated with improved post-stroke survival

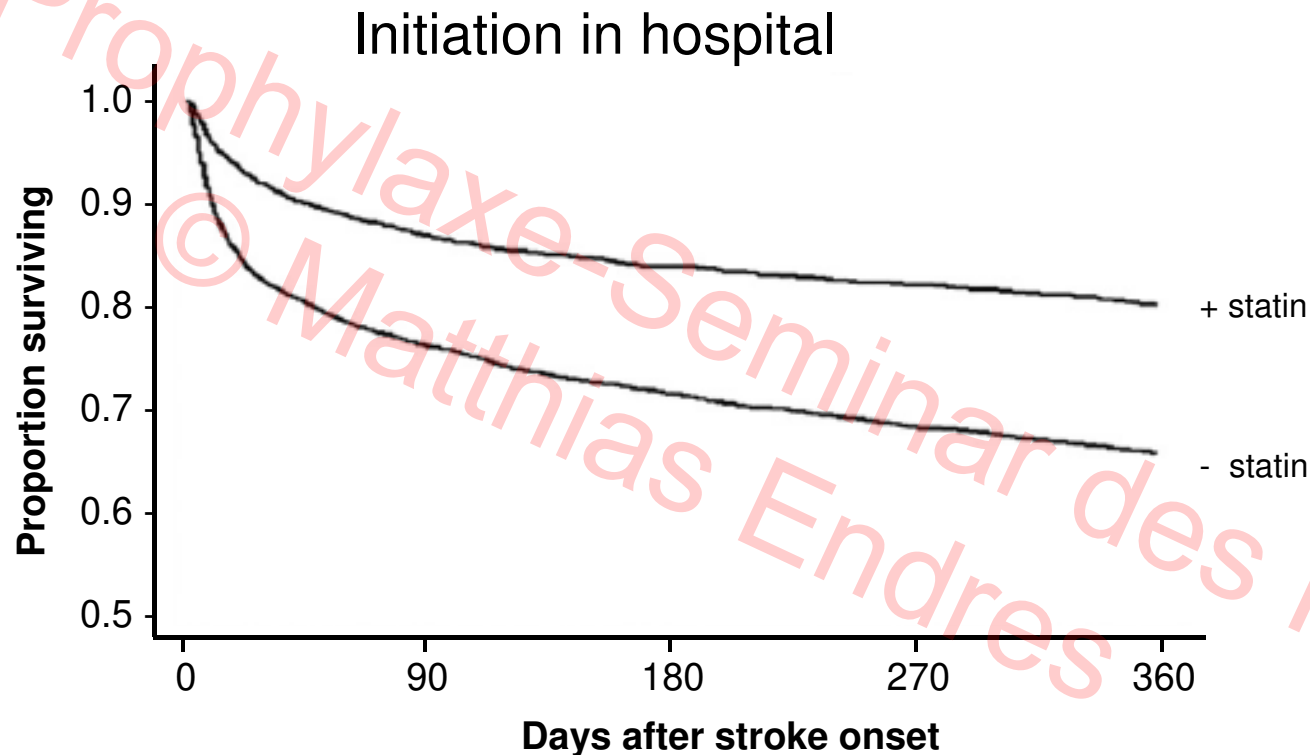
Statin use before and during stroke



Number at risk

+ statin	3280	2773	2634	2517	2418
- statin	5911	4413	4079	3845	3651

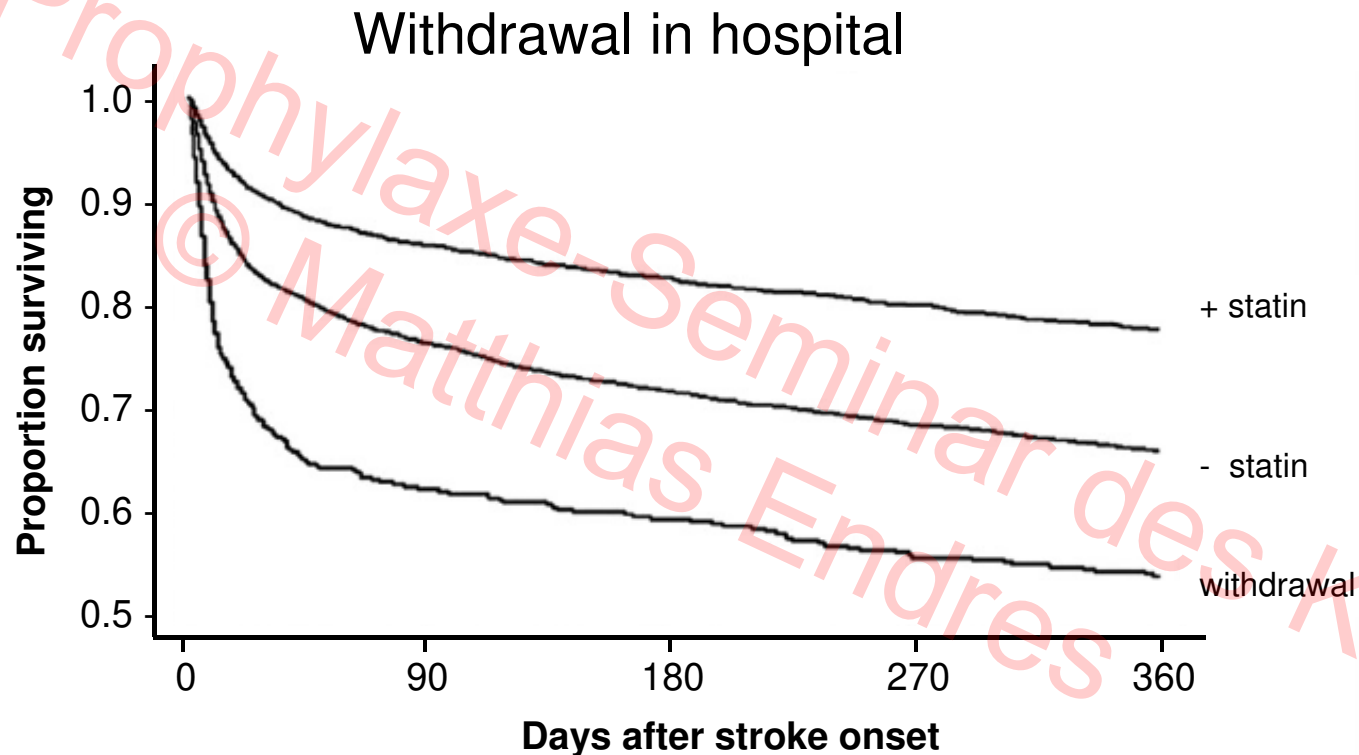
Statin use during ischemic stroke hospitalization is strongly associated with improved post-stroke survival



Number at risk

+ statin	3013	2562	2414	2325	2234
- statin	5911	4413	4079	3845	3651

Statin use during ischemic stroke hospitalization is strongly associated with improved post-stroke survival



	Number at risk				
	0	90	180	270	360
+ statin	3280	2773	2634	2517	2418
- statin	5911	4413	4079	3845	3651
withdrawal	461	277	258	241	232

Discontinuation of statin treatment in stroke patients

Background and Purpose—Statins reduce the risk for myocardial infarctions and stroke which may in part depend on cholesterol-independent (pleiotropic) vasoprotective effects. Here, we review evidence to suggest that the abrupt discontinuation of statin medication exerts negative vascular effects in patients with acute vascular events.

Summary of Review—It is increasingly recognized that statins (HMG-CoA reductase inhibitors) exert rapid cholesterol-independent effects. Cessation of statin treatment confers overshoot activation of heterotrimeric G-proteins Rho and Rac causing production of reactive oxygen species and suppression of NO bioavailability. In humans, discontinuation of statin therapy leads to a proinflammatory, prothrombotic state with impaired endothelium function. In patients with acute coronary syndromes, abrupt discontinuation of statin therapy significantly increases morbidity and mortality, whereas in stable vascular patients discontinuation may be safe. Recent prospective data indicated that the cessation of statin medication in acute ischemic stroke patients confers a significantly higher likelihood of early neurological deterioration and poor outcome.

Conclusions—We propose that in all acute ischemic stroke patients chronically treated with statins before the event, treatment should be continued and the patient should receive medication at the day of the stroke. (*Stroke*. 2006;37:2640-2643.)

NO, nitric oxide.

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Simvastatin and Atorvastatin Improve Neurological Outcome After Experimental Intracerebral Hemorrhage

Kishor Karki, PhD; Robert A. Knight, PhD; Yuxia Han, BS; Dongmei Yang, MD; Jianfeng Zhang, MS; Karyn A. Ledbetter, BS; Michael Chopp, PhD; Donald M. Seyfried, MD

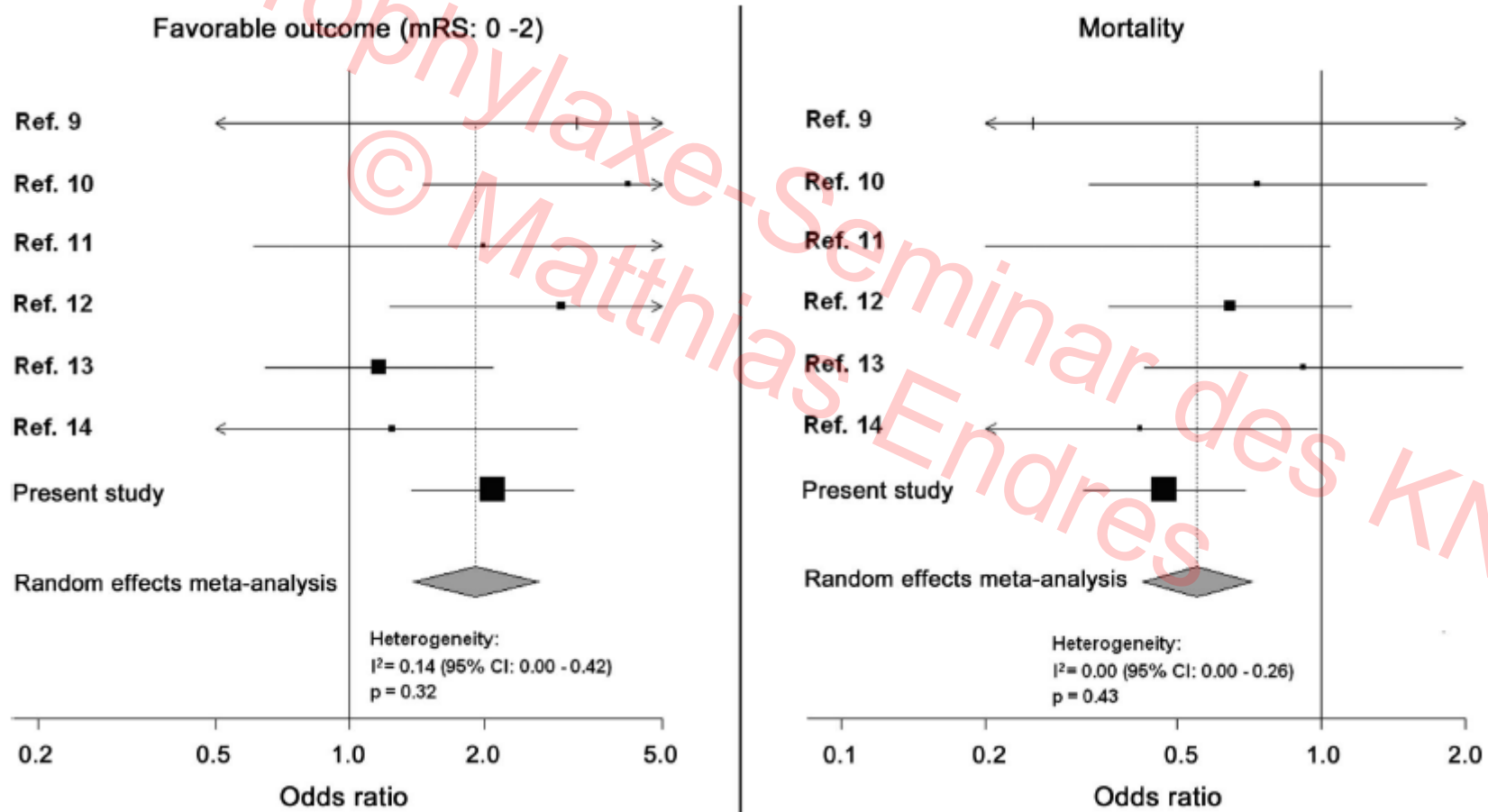
Background and Purpose—This study investigates the effects of statin treatment on experimental intracerebral hemorrhage (ICH) using behavioral, histological, and MRI measures of recovery.

Methods—Primary ICH was induced in rats. Simvastatin (2 mg/kg), atorvastatin (2 mg/kg), or phosphate-buffered saline (n=6 per group) was given daily for 1 week. MRI studies were performed 2 to 3 days before ICH, and at 1 to 2 hours and 1, 2, 7, 14, and 28 days after ICH. The ICH evolution was assessed via hematoma volume measurements using susceptibility-weighted imaging (SWI) and tissue loss using T₂ maps and hematoxylin and eosin (H&E) histology. Neurobehavioral tests were done before ICH and at various time points post-ICH. Additional histological measures were performed with doublecortin neuronal nuclei and bromodeoxyuridine stainings.

Results—Initial ICH volumes determined by SWI were similar across all groups. Simvastatin significantly reduced hematoma volume at 4 weeks ($P=0.002$ versus control with acute volumes as baseline), whereas that for atorvastatin was marginal ($P=0.09$). MRI estimates of tissue loss (% of contralateral hemisphere) for treated rats were significantly lower ($P=0.0003$ and 0.001 , respectively) than for control at 4 weeks. Similar results were obtained for H&E histology ($P=0.0003$ and 0.02 , respectively). Tissue loss estimates between MRI and histology were well correlated ($R^2=0.764$, $P<0.0001$). Significant improvement in neurological function was seen 2 to 4 weeks post-ICH with increased neurogenesis observed.

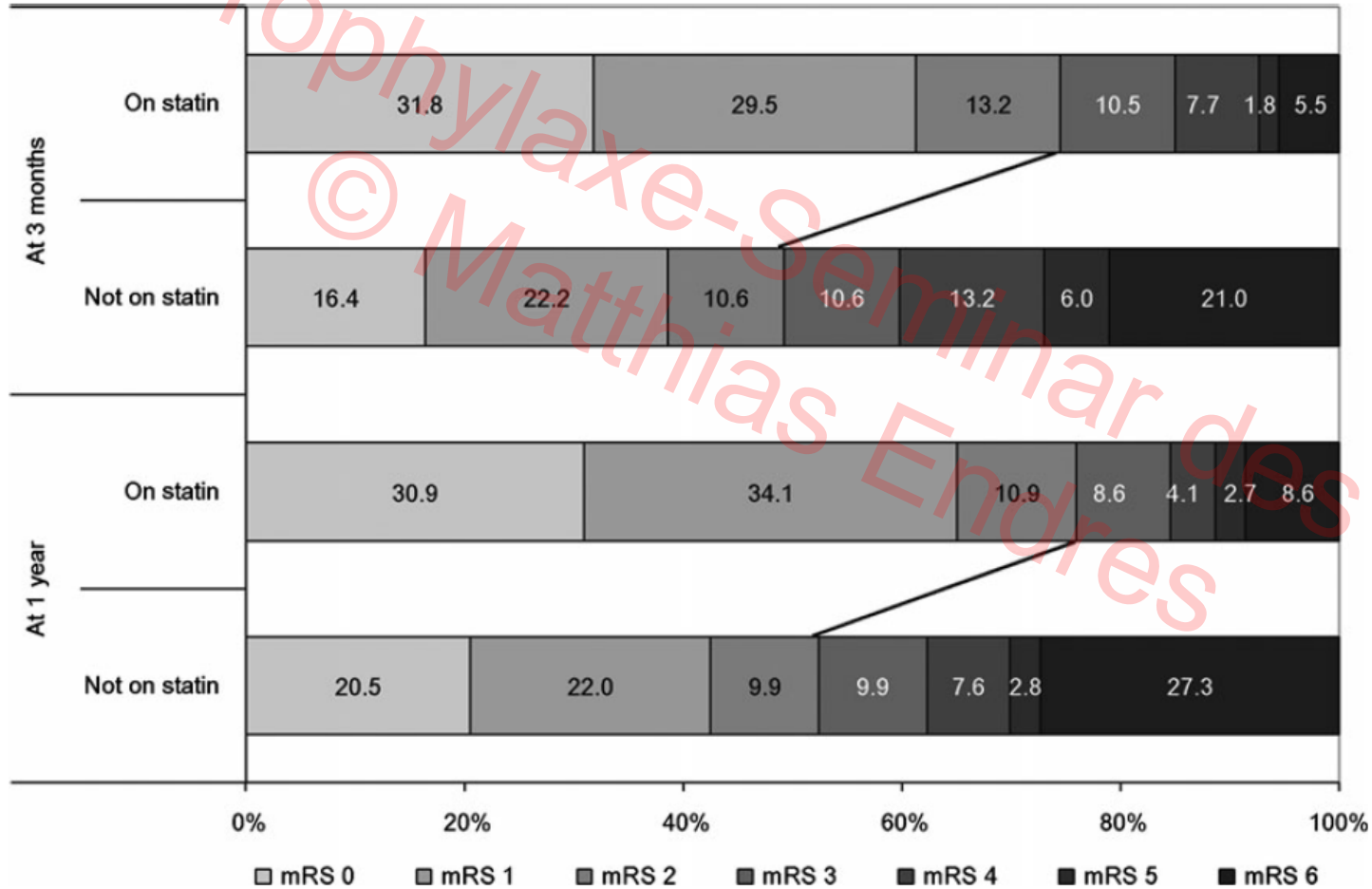
Conclusions—Simvastatin and atorvastatin significantly improved neurological recovery, decreased tissue loss, and increased neurogenesis when administered for 1 week after ICH. (*Stroke*. 2009;40:3384-3389.)

238 pre-ICH statin cases vs. 461 statin-free cases



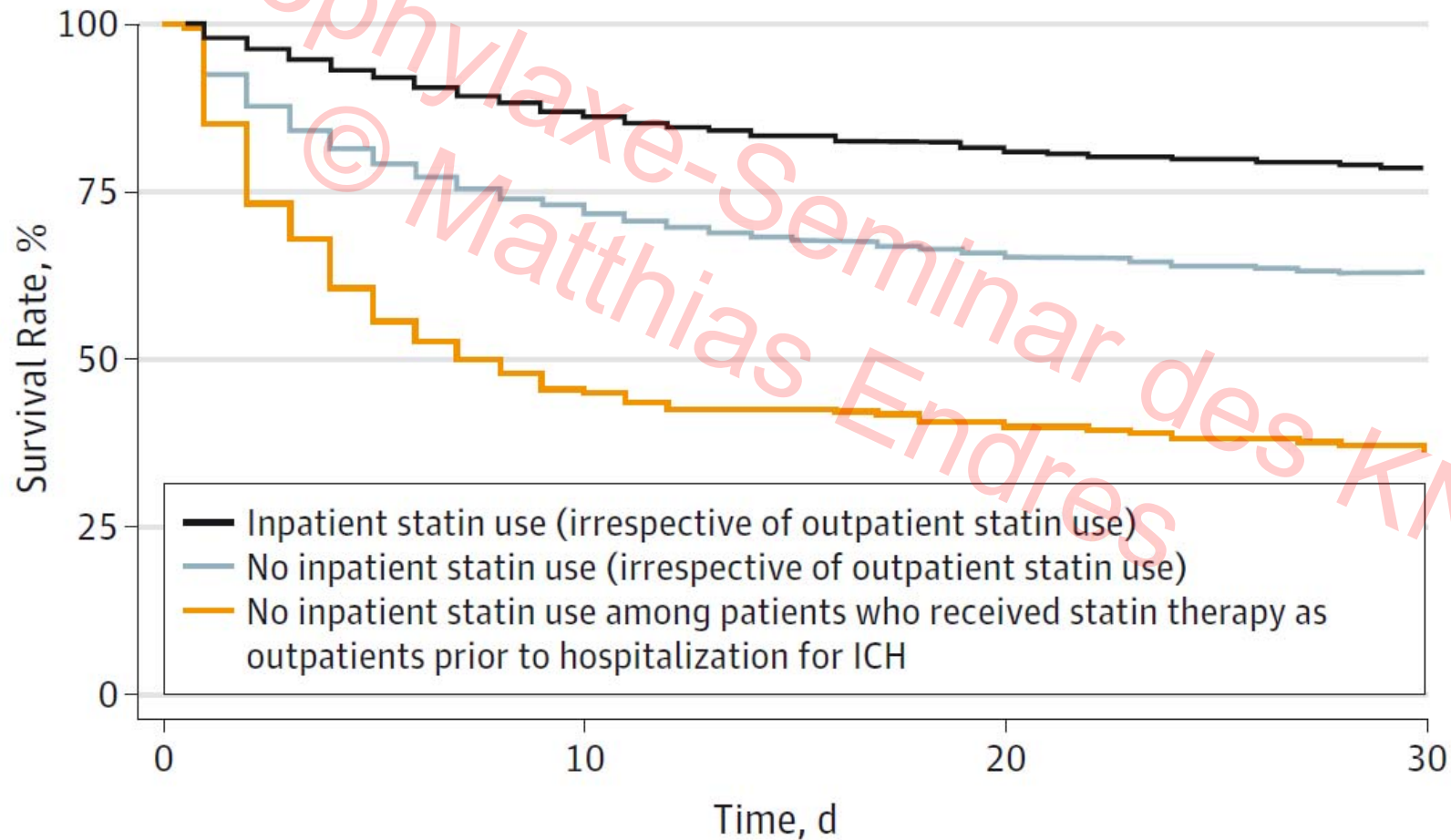
Use of statin during hospitalization improves outcome after ICH

3,218 consecutive ICH patients in China



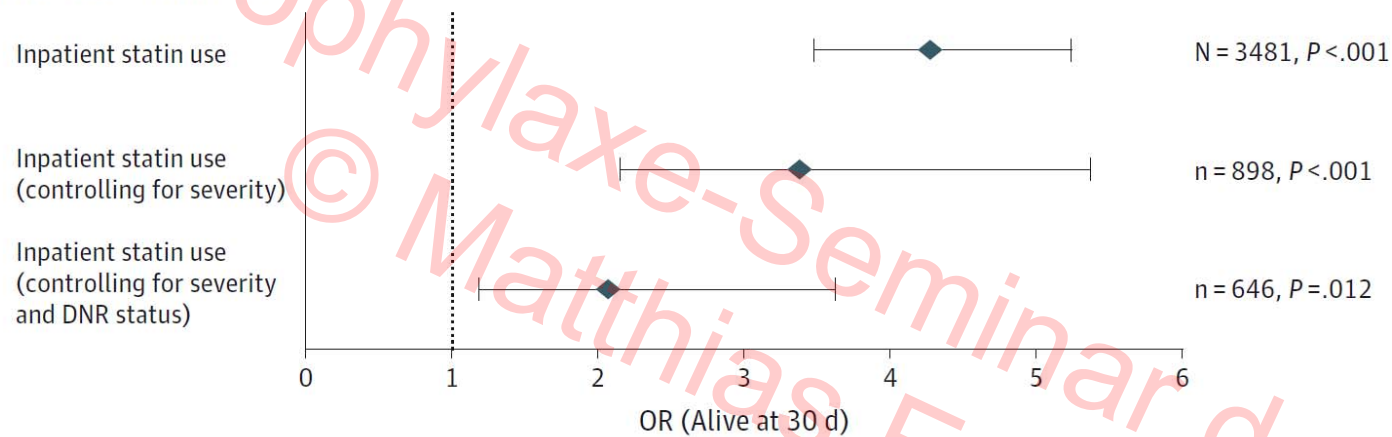
Effect of statin use during hospitalization for ICH on mortality and discharge disposition

3,481 ICH patients in 20 U.S. hospitals

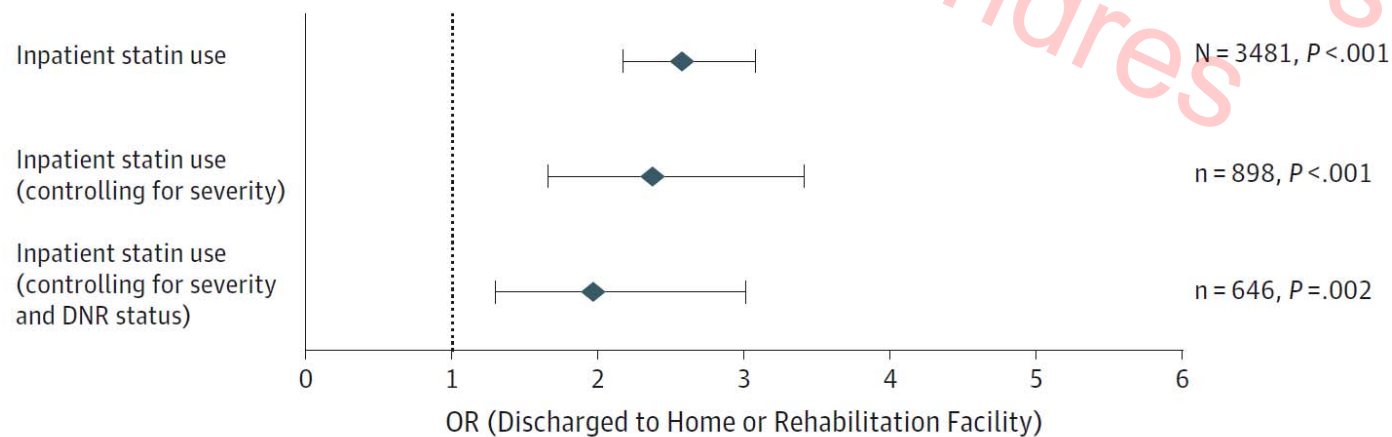


3,481 ICH patients in 20 U.S. hospitals

A Models of survival to 30 d



B Models of discharge to home or inpatient rehabilitation facility



Early statin therapy in patients with acute ICH without prior statin use

8,332 ICH patients in Taiwan

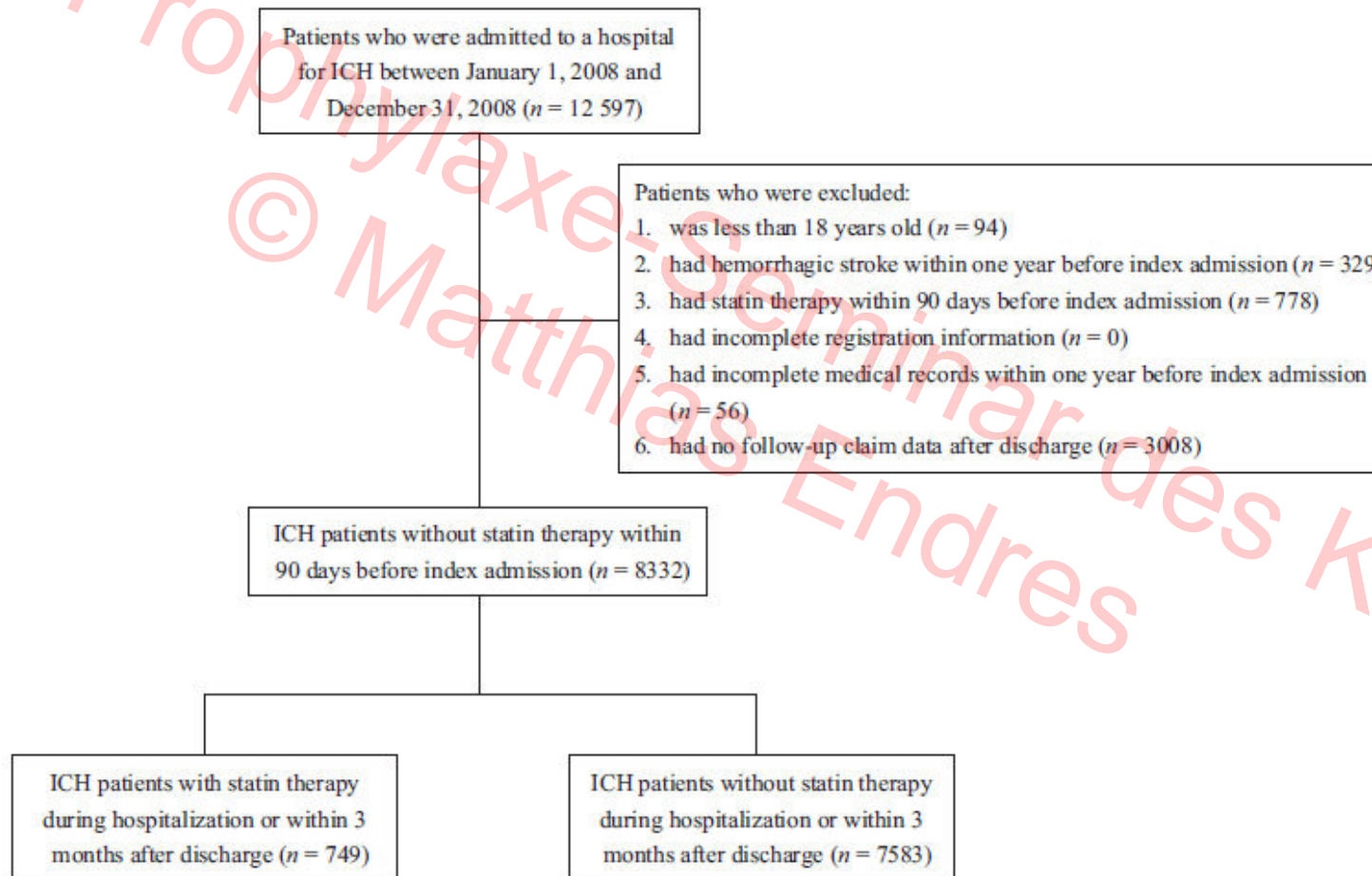
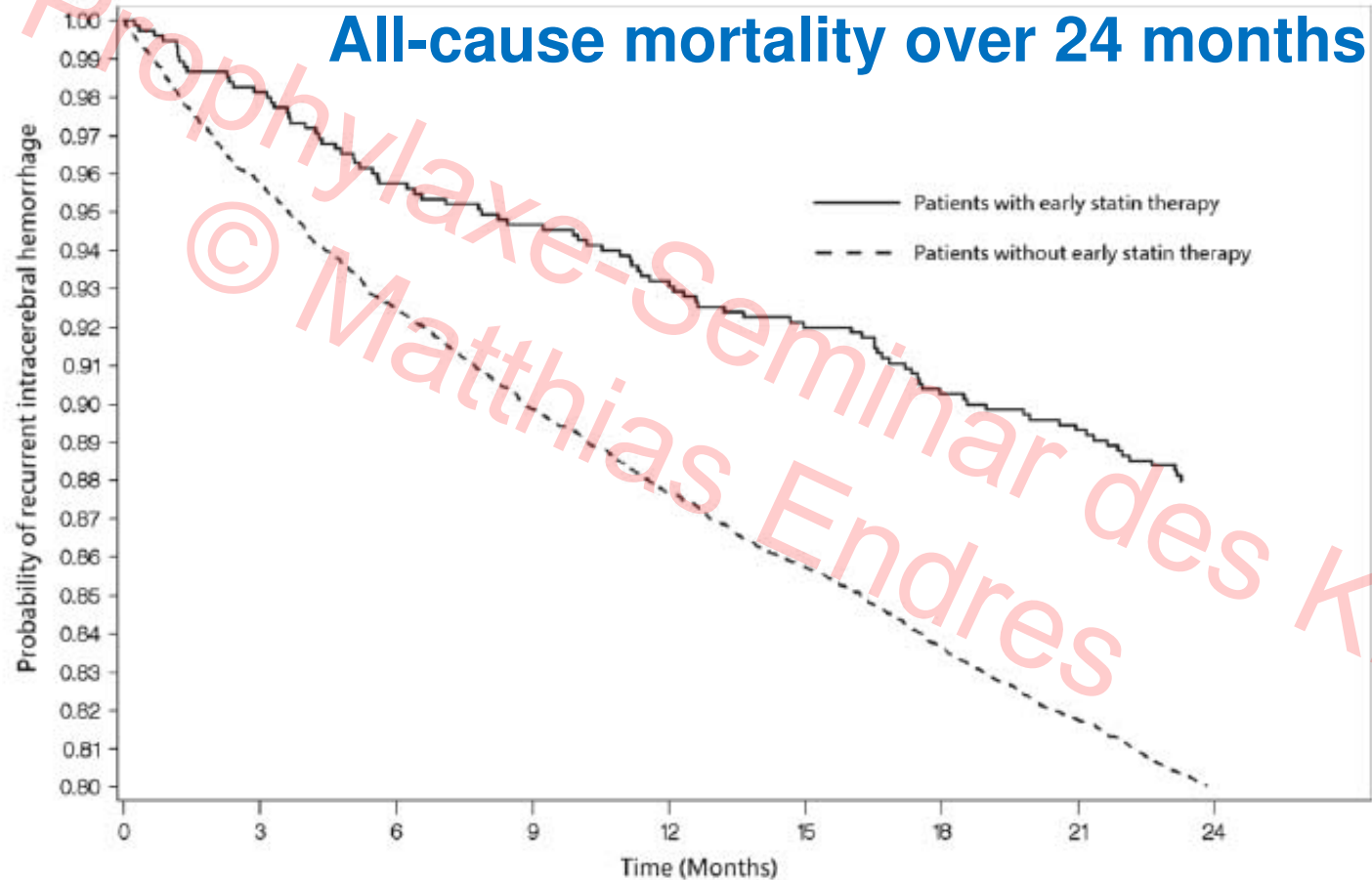


Figure 1 Flow chart for the inclusion and exclusion of study patients.

Early statin therapy in patients with acute ICH without prior statin use

(b)

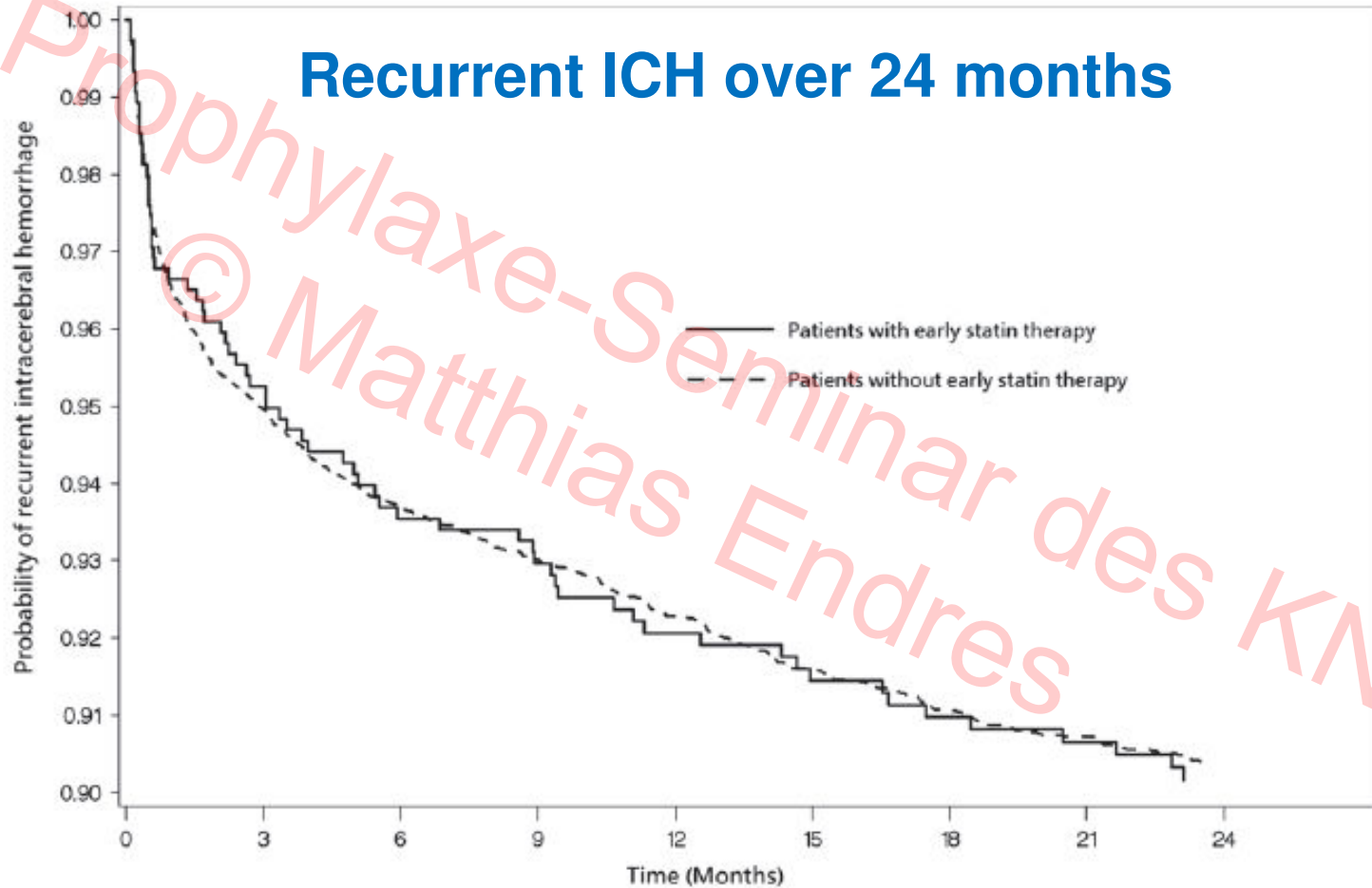


Number at risk

Patients with early statin therapy	735	717	709	698	689	676	669	0
Patients without early statin therapy	7260	7014	6814	6649	6501	6343	6199	0

Early statin therapy in patients with acute ICH without prior statin use

(a)



Number at risk

Patients with early statin therapy	680	648	627	604	589	573	560	0
Patients without early statin therapy	6810	6449	6191	5963	5751	5551	5361	0

- Better outcome and lower mortality with statin pre-treatment
- Better outcome and lower-mortality when statins are given post-event
- Worse outcome and higher mortality when statins are discontinued
- No evidence of increased risk of recurrent ICH over 24 months

Comments and Opinions

Should Statins Be Paused or Discontinued After Thrombolysis or Acute Intracerebral Hemorrhage? No!

Jan F. Scheitz, MD; Christian H. Nolte, MD; Matthias Endres, MD

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Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

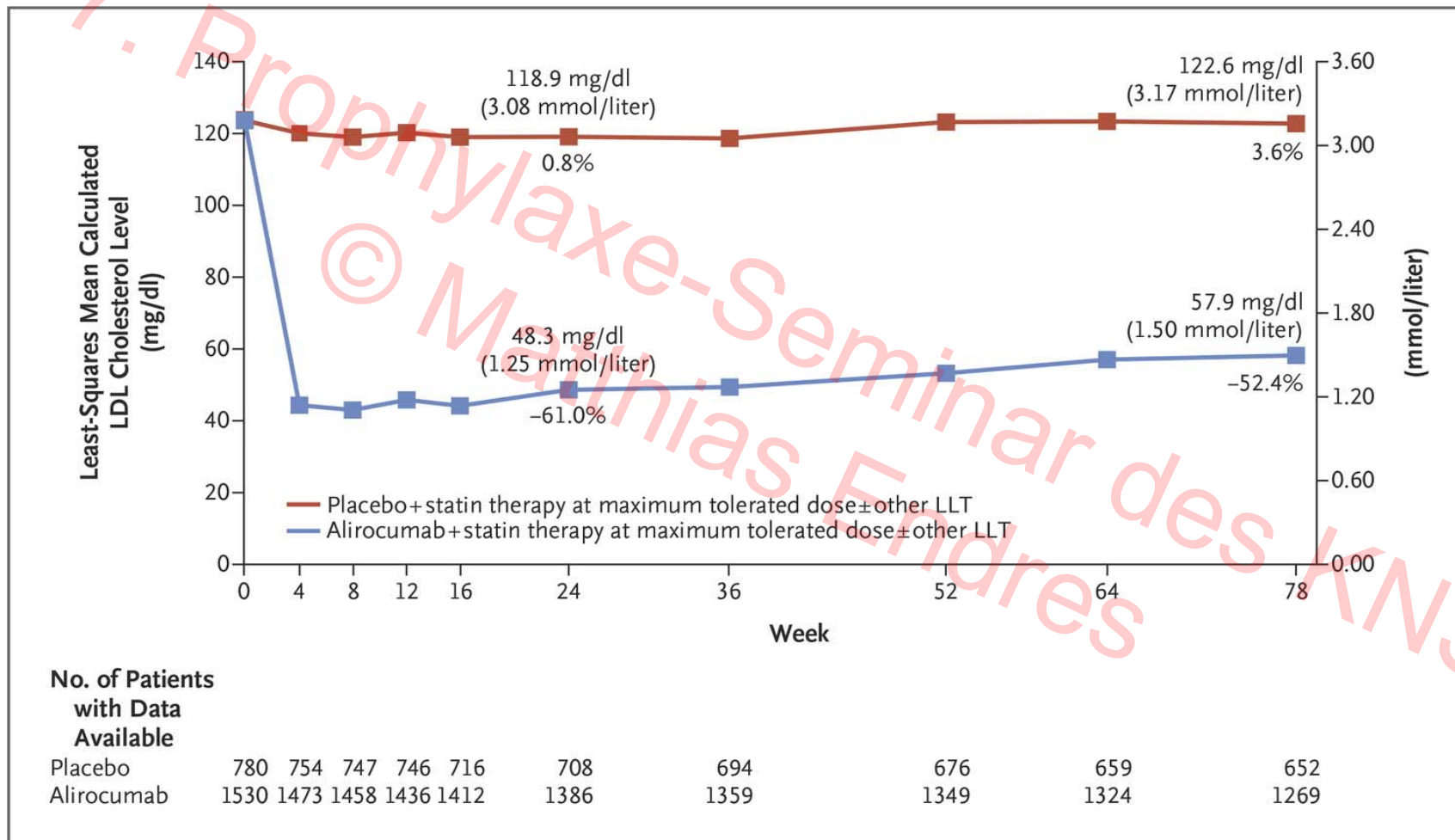
Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., 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

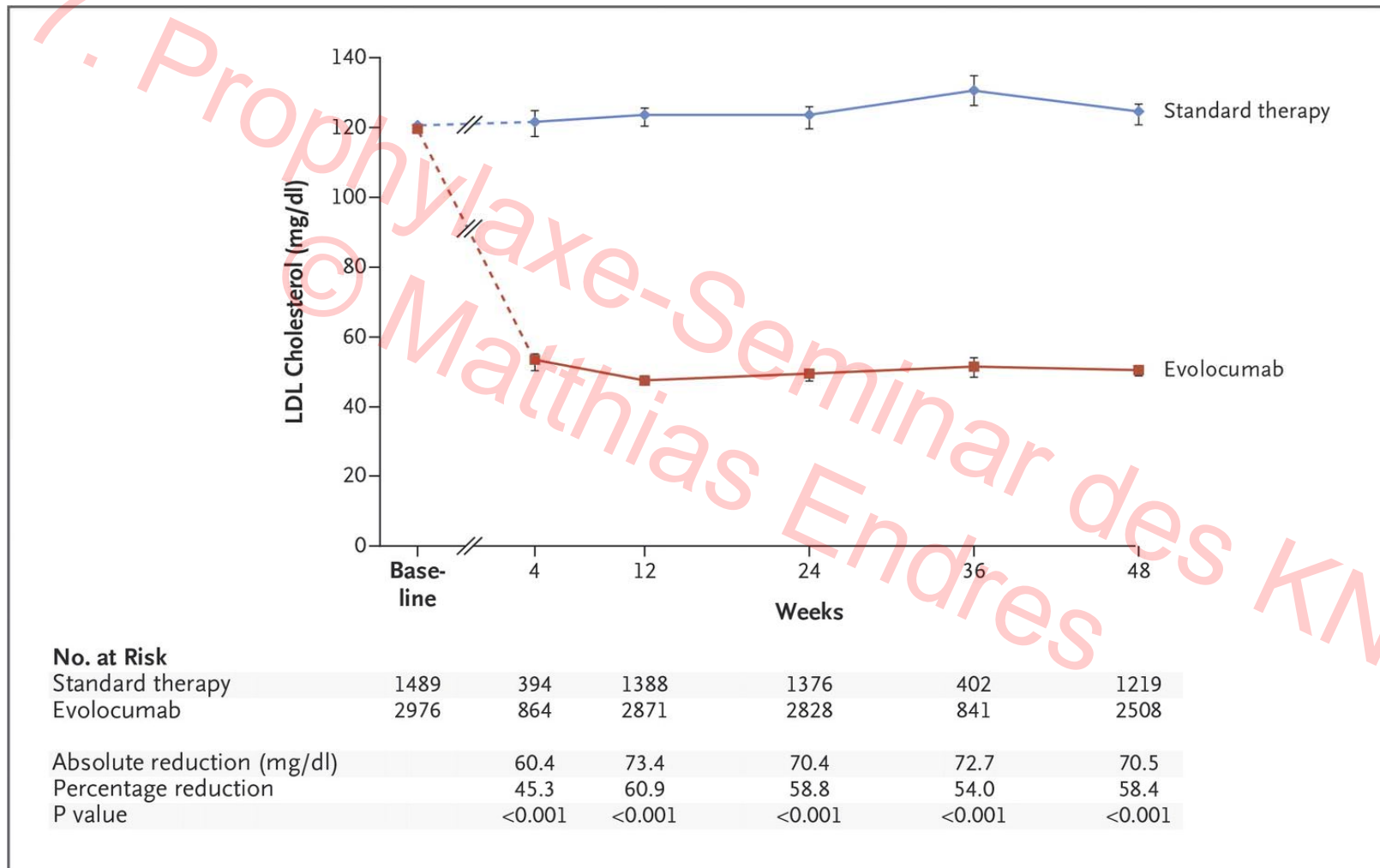
Robinson et al., N Engl J Med 2015;372:1489-99.
Sabatine et al., N Engl J Med 2015; 372:1500-09.

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



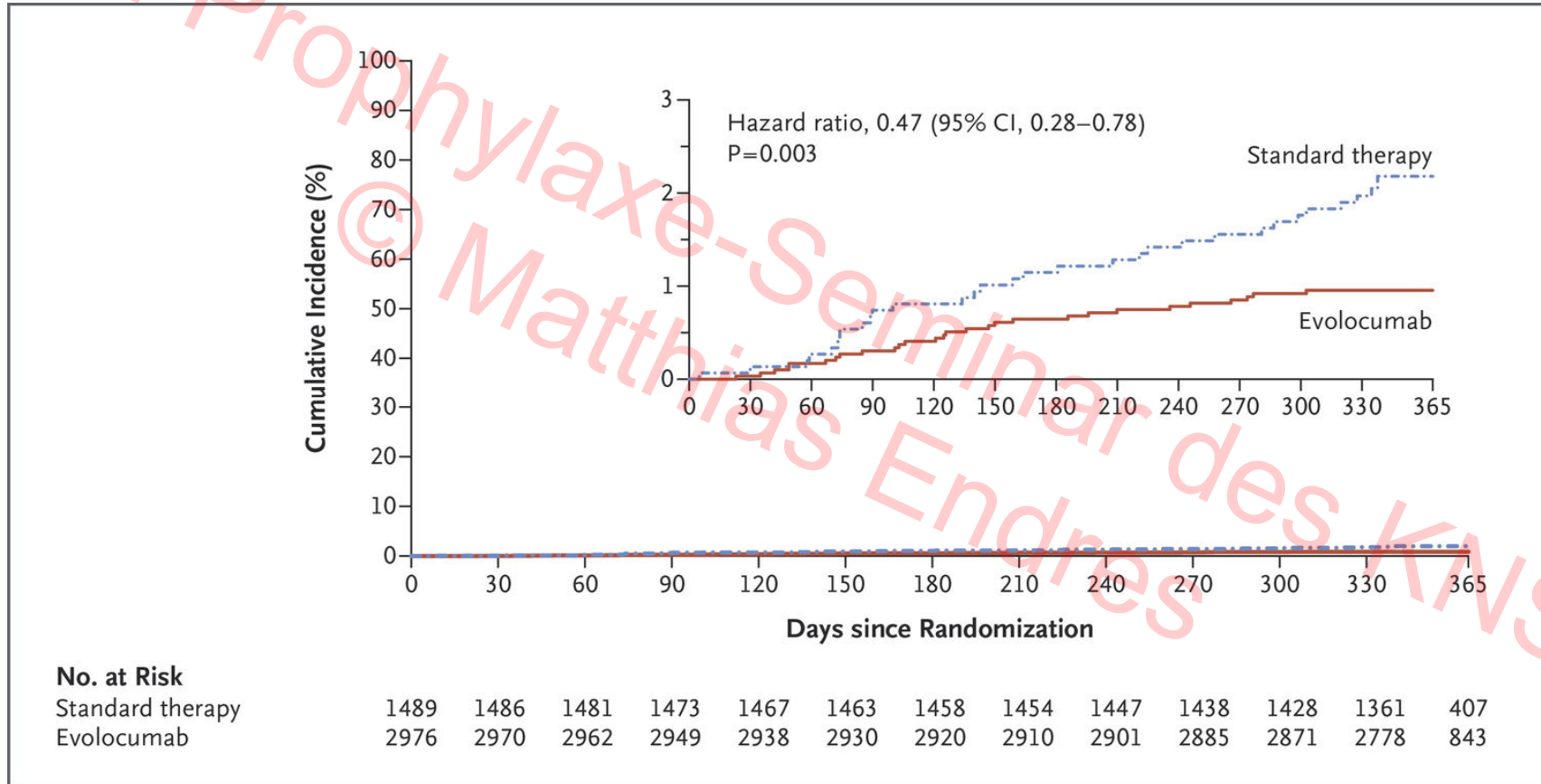
Robinson JG et al. N Engl J Med 2015;372:1489-1499.

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



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

Evolucumab (Osler): Cumulative Incidence of Cardiovascular Events.



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

7. Pro/Contra-Seminar des KNS
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**Sind super-niedrige LDL-C
Serumkonzentrationen sicher?**

Hirnblutungen ?

Kognitive Einschränkungen ?



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

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)

- Cholesterol and ischemic vs hemorrhagic stroke
- Cholesterol lowering and ischemic vs hemorrhagic stroke
- Statins, acute stroke, and risk of thrombolysis
- Statins in patients with ICH
- PCSK9 inhibitors