Inflammatory Biomarkers in Acute Stroke and Stroke Prevention

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Photo: Pankaja Ramakrishnan, MD, PhD

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Daiichi-Sankyo; Janssen; Boehringer-Ingelheim

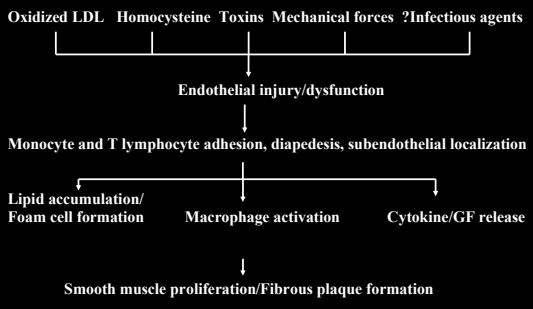
Inflammatory Biomarkers in Acute Stroke and Stroke Prevention

Outline

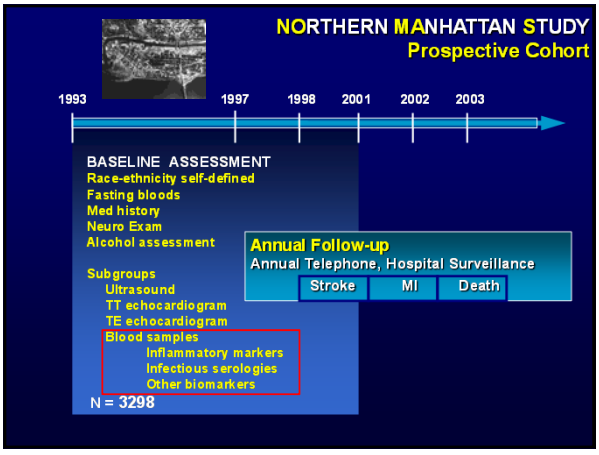
- Inflammatory markers and stroke risk
- Infectious markers and stroke risk
- Acute infection and stroke risk
- Inflammation and acute stroke

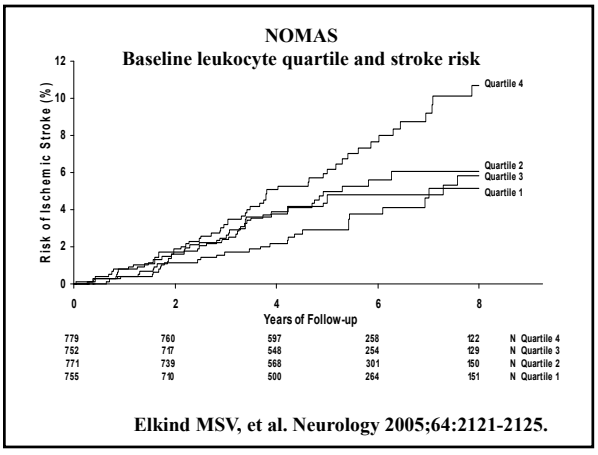
Implications for stroke trials?

The response-to-injury hypothesis of atherosclerosis



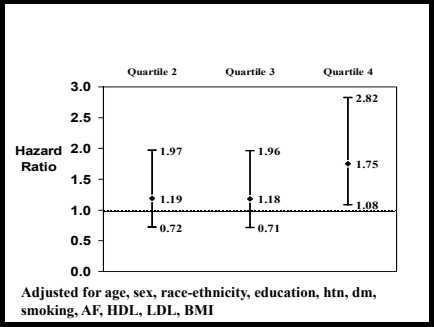
Ross R. N Engl J Med 1999;340:115-26.





Elkind MSV, et al. Neurology 2005;64:2121-2125.

Association between leukocyte count and ischemic stroke risk



Adjusted for age, sex, race-ethnicity, education, htn, dm, smoking, AF, HDL, LDL, BMI

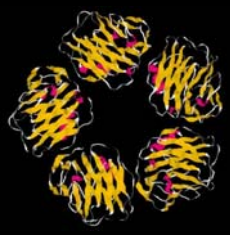
Elkind MSV et al. Neurology 2005;64:2121-2125.

Serum Markers of Inflammation Potentially Associated with Stroke and Vascular Events

- WBC
- Acute Phase Proteins
  - C-reactive protein (CRP)
  - Serum amyloid A (SAA)
  - Haptoglobin
- Cytokines
  - IL-2
  - IL-6
  - IL-8
  - TNF
  - TNF receptors
  - IL-10
  - IL-18
- Cellular adhesion molecules
  - sICAM-1
  - VCAM
  - E-selectin
- Other
  - CD40 Ligand
  - Monocyte Chemoattractant Protein-1
  - ESR
  - Lipoprotein-associated phospholipase A_2

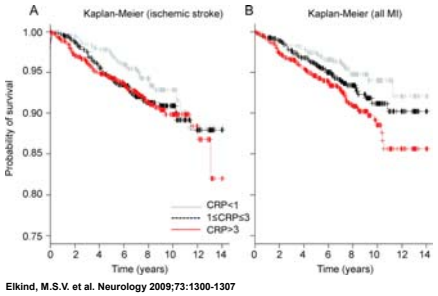
C-Reactive Protein

- Acute phase protein
- Produced in liver and endothelial cells
- Final common pathway of cytokine activation
- Produced in response to a variety of infectious and inflammatory stimuli ("non-specific")
- Predicts incident atherosclerotic and cardiovascular events



Pearson TA et al. Circulation 2003;107:499-511

NOMAS: HsCRP predicts MI but not stroke



Elkind, M.S.V. et al. Neurology 2009;73:1300-1307

Neurology

AMERICAN ACADEMY OF NEUROLOGY

NOMAS: HsCRP predicts MI but not stroke

Characteristics	Mean or Prevalence
Age, mean (± SD), y	68.9 (±10.1)
Male, n (%)	803 (35.9)
Race / Ethnicity, n (%)	
White	420 (18.8)
Black	526 (23.5)
Hispanic	1235 (55.1)
Education Level, n (%)	
≥ High school	996 (44.5)
Smoking Status, n (%)	
Non-Smoker	1071 (47.9)
Past Smoker	784 (35.0)
Current Smoker	383 (17.1)
CAD, n (%)	475 (21.2)
Diabetes Mellitus, n (%)	479 (21.5)

Elkind MSV, et al. Neurology 2009;73:1300-1307

CRP is associated with other risk factors

Increased CRP	Decreased CRP
Hypertension	Alcohol consumption
BMI	Physical activity
Obesity	Weight loss
Diabetes	Medications
Metabolic syndrome	Statins
Smoking	ACEI
Hormone use	

Most studies that have shown an association between hsCRP and risk factors have been done in stroke-free subjects

PRIMARY PREVENTION:
CDC/AHA Consensus On Inflammatory Markers

1. HsCRP assay is optimal inflammatory marker thus far
2. HsCRP may be useful in estimating risk of future cardiovascular events , particularly in persons at intermediate risk based on other risk factors

hsCRP concentration	Risk Level
<1 mg/L	Low
1-3 mg/L	Medium
>3 mg/L	High

Pearson TA et al. Circulation 2003;107:499-511

Lipoprotein-associated phospholipase A2

- 50 kDa, Ca-independent lipase produced by macrophages
- Resides mainly on LDL in human plasma
- Highly upregulated in atherosclerosis
- Lp-PLA2 oxidizes LDL, generating pro-inflammatory mediators:
  - Lysophosphatidylcholine (lyso-PC) and
  - Oxidized fatty acid (oxFA)
- In pre-clinical animal studies, inhibition of Lp-PLA2 attenuates inflammatory process and slows atherosclerotic disease progression.

Laine P et al. Circ. 1999.
Hakkinen T et al. Arterioscler Thromb Vasc Biol. 1999.

Approved by FDA for prediction of risk of first ischemic stroke.

Ballantyne CM et al. Arch Intern Med 2005;165:2479-2484.
Oei HH et al. Circulation 2005;111:570-5.

Darapladib, an inhibitor of LpPLA2, tested in phase 3 trial

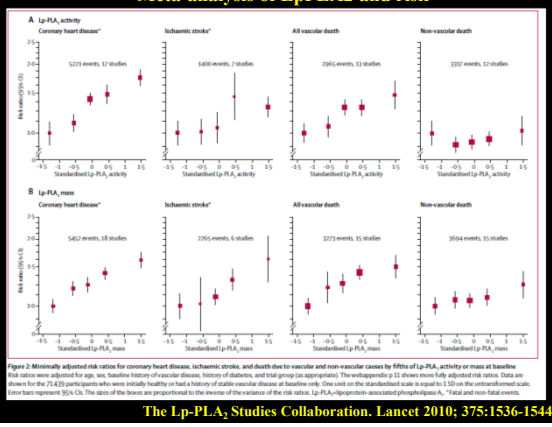
NOMAS: LpPLA2 and atherosclerotic stroke

	Unadjusted HR (95% CI)	Model 1*, HR (95% CI)	Model 2**, HR (95% CI)
LpPLA2-mass (per SD)	1.57 (1.26-1.96)	1.49 (1.18-1.88)	1.55 (1.17-2.04)
LpPLA2-activity (per SD)	1.34 (0.92-1.94)	1.15 (0.76-1.73)	1.17 (0.71-1.92)
LpPLA2-mass levels			
Q1 (28.1-245.6)	Ref.	Ref.	Ref.
Q2 (245.7-307.2)	1.53 (0.26-9.15)	1.42 (0.24-8.52)	1.43 (0.23-8.46)
Q3 (307.2-365.5)	4.63 (1.00-21.44)	4.09 (0.88-19.12)	4.47 (0.93-21.54)
Q4 (365.5-972.6)	6.19 (1.39-27.64)	4.88 (1.06-22.45)	5.07 (1.07-24.06)

Model 1: adjusted age, sex, race-ethnicity, education
Model 2: adjusted for age, sex, race-ethnicity, education, waist circumference, physical activity, moderate alcohol consumption, smoking, diabetes mellitus, systolic blood pressure, coronary artery disease, LDL, HDL

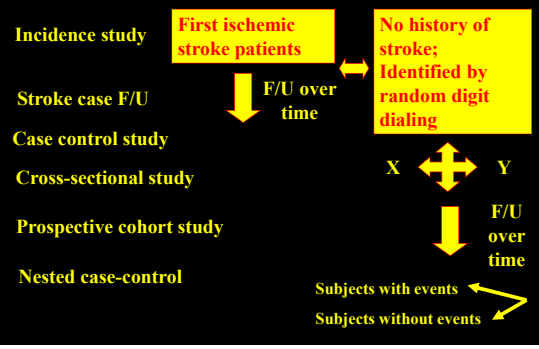
Katan M et al. PLoS One 2014.

Meta-analysis of LpPLA2 and risk



The Lp-PLA$_2$ Studies Collaboration. Lancet 2010; 375:1536-1544.

Northern Manhattan (Stroke) Study
Epidemiological Study Designs



NOMAS stroke survivor follow-up:
HsCRP predicts mortality, Lp-PLA2 predicts recurrent stroke (n=467)

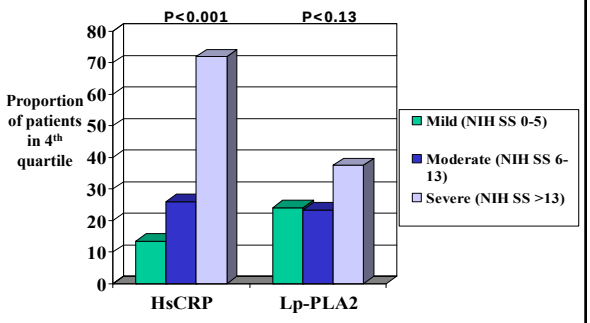
	HsCRP HR (95% CI)	Lp-PLA2 HR (95% CI)
Recurrent stroke (N=80 outcome events)		
Unadjusted	0.86 (0.45-1.65)	2.30 (1.21-4.36)
Adjusted for demographics, risk factors, and both markers	0.68 (0.34-1.35)	2.06 (1.02-4.13)
Recurrent stroke, MI, vascular death (N=122 events)		
Unadjusted	1.86 (1.13-3.08)	2.38 (1.36-4.17)
Adjusted for demographics, risk factors, stroke severity, and both markers	0.98 (0.54-1.78)	1.86 (1.01-3.42)
Death (N=158 outcome events)		
Unadjusted	4.50 (2.83-7.15)	2.29 (1.43-3.67)
Adjusted for demographics, risk factors, stroke severity, and both markers	1.97 (1.13-3.44)	1.41 (0.84-2.38)

Demographics: age, sex, race-ethnicity.

Risk factors: history of CAD, DM, HTN, hyperlipidemia, AF, and smoking.

Elkind MSV et al. Arch Int Med 2006;166:2073-80.

Results:
Inflammatory markers and stroke severity

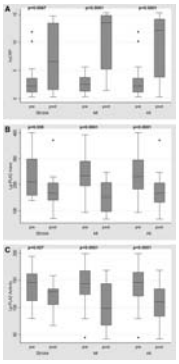


Elkind MSV et al. Arch Int Med 2006;166:2073-80.

NOMAS: Biomarker levels before and after acute stroke/MI

CRP increases at time of stroke/MI

LpPLA2 decreases at time of stroke/MI



N=37

Stroke Elkind MSV et al. Stroke 2009;40:3233-3237.

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Levels of Inflammatory Markers in the Treatment of Stroke
LIMITS

An ancillary prospective cohort study in patients with lacunar stroke in the SPS3 trial

Hypotheses

1. Elevated levels of hsCRP measured after lacunar stroke increase risk of:
   a. recurrent ischemic stroke (IS) and
   b. recurrent IS, MI, or vascular death.

2. Elevated levels of inflammatory markers predict response to dual antiplatelet therapy.

Elkind MSV et al. Stroke 2014; 45:707-716.

Stroke Prevention:
The Secondary Prevention of Small Subcortical Strokes Trial (SPS3)

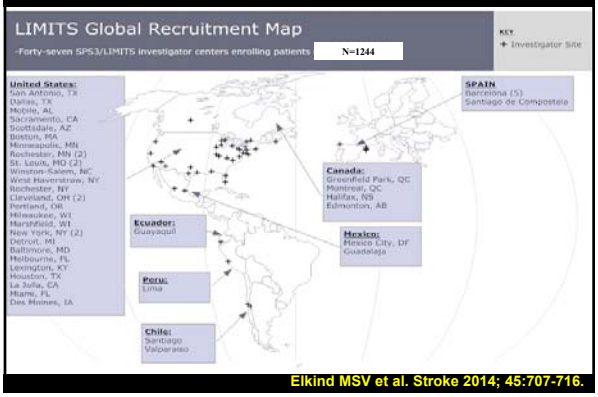
PI: Oscar Benavente
Univ Texas Health Sci Center, San Antonio

Lacunar stroke patients up to 6 months post stroke randomized to:

both

- *Antiplatelet therapy:*
  - aspirin + placebo or aspirin + clopidogrel
- *Target levels of BP:*
  - "usual" 130-149 mmHg syst. or "intensive" <130 mmHg syst.

LIMITS Sites



Elkind MSV et al. Stroke 2014; 45:707-716.

LIMITS: Risk of recurrent ischemic stroke CDC/AHA clinical thresholds (n=1244)

	Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
HsCRP		0.04		0.05		0.06
<1 mg/L (Referent)	--		--		--	
1-3 mg/L	1.75 0.90-3.38		1.82 0.94-3.56		1.82 0.94-3.55	
>3 mg/L	2.20 1.19-4.10		2.22 1.17-4.24		2.16 1.13-4.11	

Model 1: Unadjusted
Model 2: Adjusted for Demographics and Co-morbidities (Hypertension, Smoking, History of Ischemic Stroke, Diabetes, Body mass index, Low-density lipoprotein and High-density lipoprotein)
Model 3: Adjusted for Demographics, Co-morbidities, and Statin use

Elkind MSV et al. Stroke 2014; 45:707-716.

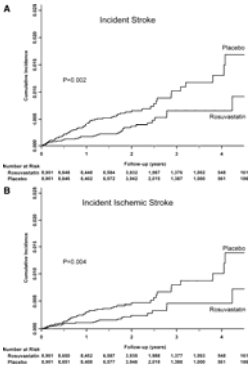
Results

- Approximately 70% of recurrent ischemic strokes were lacunes.
- Results for lacunar stroke consistent with the effect on ischemic stroke (adj HR 2.27, 95% CI 0.90-5.75).
- No interactions with:
  - dual antiplatelet therapy
  - BP targets
  - Statin use

Elkind MSV et al. Stroke 2014; 45:707-716.

JUPITER: Cumulative incidence of stroke according to study group

Rosuvastatin reduced risk of first stroke by 50% among those with hsCRP ≥2 mg/L



Circulation

Copyright ©2010 American Heart Association

Everett BM et al. Circulation 2010;121:143-150

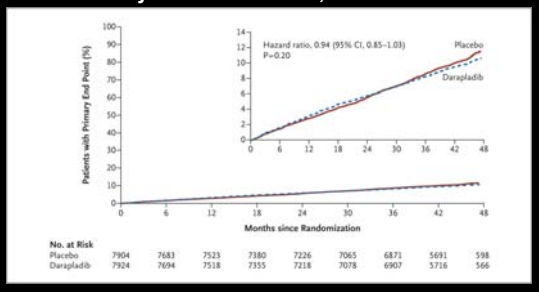
American Heart Association
Learn and Live

- **Use of Inflammatory Biomarkers in Primary Prevention**
  - Unlikely to be of value for general screening or for use in high risk or low risk populations
  - CRP associated with many other risk factors
  - HsCRP and LpPLA2 levels may be of incremental value in identification of patients at increased risk of stroke and other events, particularly for those at intermediate risk
- **Use of Inflammatory Biomarkers in Secondary Prevention**
  - CRP is an acute phase protein and is associated with severity of stroke
  - CRP and LpPLA2 may provide complementary information after stroke in general: CRP may be a better predictor of mortality while LpPLA2 may better predict risk of recurrent stroke and other vascular events
  - HsCRP may be a better prognostic marker in less severe stroke (lacunar stroke), or when measured at an interval of several weeks after stroke
  - Effect of hsCRP has a threshold rather than a continuous relationship.
  - HsCRP levels do not predict response to dual antiplatelet therapy or BP targets.

Inflammation: Potential trials in secondary prevention

1. Use of CRP to stratify patients as being at high risk after lacunar stroke/mild stroke
   a. Improve power when testing an intervention
   b. Limit risks to a high-risk population
2. Anti-inflammatory therapies:
   a. Test for interaction of a therapy with biomarkers
   b. Drugs
      i. Statins
      ii. Methotrexate
      iii. LpPLA2 inhibitor (Darapladib)
      iv. Others

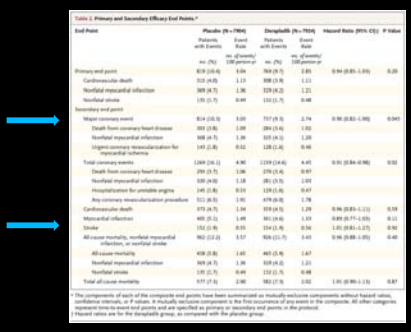
STABILITY: Darapladib Primary End Point of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke



The STABILITY Investigators. N Engl J Med 2014. DOI: 10.1056/NEJMoa1315878

The NEW ENGLAND JOURNAL of MEDICINE

Primary and Secondary Efficacy End Points



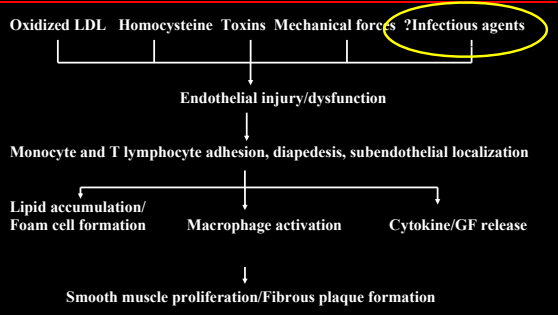
The STABILITY Investigators. N Engl J Med 2014. DOI: 10.1056/NEJMoa1315878

The NEW ENGLAND JOURNAL of MEDICINE

Outline

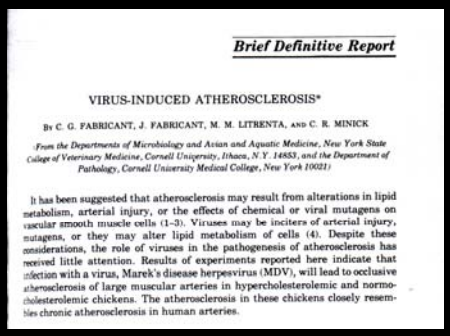
- Inflammatory markers and stroke risk
- Chronic infections and stroke risk
- Acute infection and stroke risk
- Anti-inflammatory treatments

The response-to-injury hypothesis of atherosclerosis



Ross R. N Engl J Med 1999;340:115-26.

Infection and Stroke



Brief Definitive Report

VIRUS-INDUCED ATHEROSCLEROSIS*

By C. G. FABRICANT, J. FABRICANT, M. M. LITRENTA, AND C. R. MINICK

(From the Departments of Microbiology and Avian and Aquatic Medicine, New York State College of Veterinary Medicine, Cornell University, Ithaca, N.Y. 14853, and the Department of Pathology, Cornell University Medical College, New York 10021)

It has been suggested that atherosclerosis may result from alterations in lipid metabolism, arterial injury, or the effects of chemical or viral mutagens on vascular smooth muscle cells (1-3). Viruses may be inciters of arterial injury, mutagens, or they may alter lipid metabolism of cells (4). Despite these considerations, the role of viruses in the pathogenesis of atherosclerosis has received little attention. Results of experiments reported here indicate that infection with a virus, Marek's disease herpesvirus (MDV), will lead to occlusive atherosclerosis of large muscular arteries in hypercholesterolemic and normocholesterolemic chickens. The atherosclerosis in these chickens closely resembles chronic atherosclerosis in human arteries.

J Exp Med 1978

Chlamydia Pneumoniae and Stroke Risk

***C. pneumoniae* is capable of infecting endothelia, monocytes, and smooth muscle cells**

***C. pneumoniae* identified by:**

- **EM in coronary atheroma**

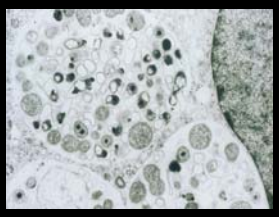
Kuo et al. J Infect Dis 1993.

Ramirez et al. Ann Int Med 1996.

- **PCR/Immunocytochemistry in coronary, aortic, and carotid atheromas**

Grayston et al. Circulation 1995

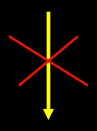
- **Culture in coronary and carotid arteries**



Jackson et al. J Inf Dis 1997

"Burden" of Infectious Disease?

THE "STROKE" BUG



ATHEROSCLEROSIS
STROKE

Elkind MSV. Infect Disord Drug Targets 2010;9(5).

"Burden" of Infectious Disease?

INFLAMMATORY BURDEN

Host factors/genetics
Other environmental risk factors

ATHEROSCLEROSIS
STROKE

Elkind MSV. Infect Disord Drug Targets 2010;9(5).

Results (n=1625)

First stroke

Positive Serology	Adjusted HR* (95 % CI)
C. pneumoniae IgA	1.30 (0.75 – 2.25)
H. pylori IgG	1.13 (0.68 – 1.89)
CMV IgG	2.19 (0.84 – 5.70)
HSV 1 IgG	1.35 (0.59 – 3.07)
HSV 2 IgG	1.59 (0.91 – 2.76)

*Adjusted for age, sex, race-ethnicity, high school education, CAD, systolic BP, HDL, LDL, blood sugar, alcohol, smoking, waist circumference, physical activity

Elkind MSV et al. Arch Neurol 2010;67:33-38.

Results (n=1625)

Serologies	Unadjusted Parameter estimate	*Hypothetical participant* Serologies	Infectious burden index
C. Pneumoniae IgA	0.265	+	0.265
H. Pylori IgG	-0.086	-	0
CMV IgG	0.685	+	0.685
HSV 1 IgG	0.220	-	0
HSV 2 IgG	0.177	+	0.177

Elkind MSV et al. Arch Neurol 2010;67:33-38.

Results (n=1625)

Serologies	Unadjusted Parameter estimate	*Hypothetical participant* Serologies	Infectious burden index
C. Pneumoniae IgA	0.265	+	0.265
H. Pylori IgG	-0.086	-	0
CMV IgG	0.685	+	0.685
HSV 1 IgG	0.220	-	0
HSV 2 IgG	0.177	+	0.177
Total score			1.127

Infectious burden index: mean 1.00 $\pm$ 0.33, median 1.08

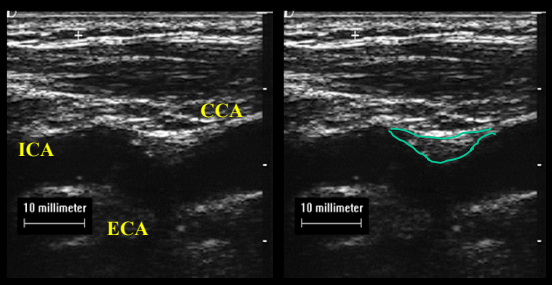
Infectious burden and risk of first stroke

	HR (95 % CI) per SD IBI	
	Among full cohort (n=1625)	Among those without history of MI (n=1525)
Unadjusted	1.39 (1.04 – 1.87)	1.51 (1.08 – 2.11)
Adjusted for demographics*	1.42 (1.04 – 1.94)	1.54 (1.08 – 2.20)
Adjusted for demographics* and risk factors†	1.39 (1.02 – 1.90)	1.50 (1.05 – 2.13)
Adjusted for demographics*, risk factors,† and log hsCRP	1.39 (1.02 – 1.90)	1.52 (1.06 – 2.17)
Adjusted for demographics, risk factors,† and log leukocyte count	1.40 (1.03 – 1.91)	1.51 (1.06 – 2.16)

*Adjusted for age, sex, race-ethnicity, education, history of CAD, BS, SBP, waist circumference, HDL, LDL, cigarette smoking, alcohol consumption, physical activity.

Elkind MSV et al. Arch Neurol 2010;67:33-38.

Maximal Carotid Plaque Thickness (MCPT):



Infectious burden index and MCPT (n=861)

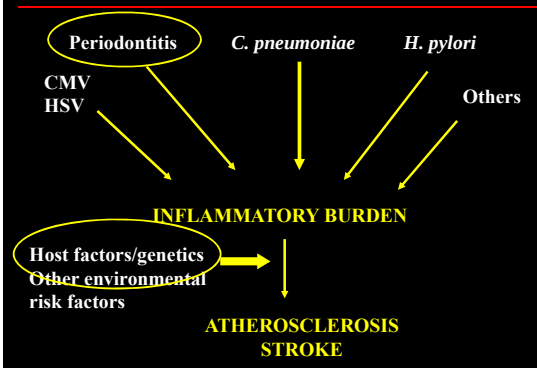
	Change MCPT per SD IBI	p
Unadjusted	0.054 mm	0.07
Adjusted for demographics*	0.079 mm	0.01
Adjusted for demographics and risk factors**	0.087 mm	0.006

*Adjusted for age, sex, race-ethnicity, education

**Adjusted for above and history of CAD, blood sugar, SBP, waist circumference, HDL, LDL, smoking, alcohol consumption, physical activity.

Elkind MSV et al. Stroke 2010;41: e117-e122.

"Burden" of Infectious Disease?



NOMAS: Nested case-control study (n=172 cases/344 controls) Endpoint: all ischemic strokes

- Elevated Procalcitonin and MRproANP levels, but not copeptin, predicted ischemic stroke

Parameter	Hazard Ratio	95% Confidence Interval	
Second Quartile			
Copeptin	0.82	0.43	1.59
MRproANP	1.34	0.70	2.55
Procalcitonin	1.73	0.88	3.43
Third Quartile			
Copeptin	1.15	0.62	2.14
MRproANP	1.57	0.79	3.12
Procalcitonin	1.76	0.89	3.45
Fourth Quartile			
Copeptin	1.14	0.59	2.17
MRproANP	**3.45**	**1.58**	**7.53**
Procalcitonin	**1.98**	**1.02**	**3.83**

• Adjusted for demographics (age, sex, race, education) & medical risk factors (diabetes mellitus, hypertension, coronary artery disease, physical activity, alcohol consumption, smoking, LDL, HDL, eGFR)

Katan M et al. ISC 2014.

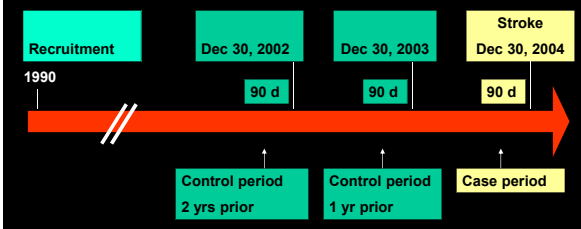
Why *me* versus Why *now*?

Why now? Moving from stroke risk factors to stroke triggers
Mitchell S.V. Elkind

Why does a patient with history of risk factors (or a current risk factor) have a stroke TODAY?
Is this predictable or stochastic?
If predictable, is there something that could have been done to prevent the stroke?

Elkind MSV. Curr Opin Neurol 2007;20:51-57.

Case crossover design



Cardiovascular Health Study

Sponsored by the National Heart, Lung and Blood Institute with additional contribution from the National Institute of Neurological Disorders and Stroke

http://chs-nhlbi.org

Methods

CHS Recruitment and Enrollment

- Multi-center prospective study of vascular risk factors in an elderly population-based cohort
- Random sample of men and women ≥ 65 years recruited from Medicare eligibility lists in four U.S. communities:
  - Sacramento County, California
  - Washington County, Maryland
  - Forsyth County, North Carolina
  - Pittsburgh, Pennsylvania
- The CHS enrolled 5888 participants 1989-93

Fried LP et al. *Ann Epidemiol.* 1991;1:263-276.
Tell GS et al. *Ann Epidemiol.* 1993;3:358-366.

Results

Baseline Characteristic	Case-Crossover Analysis
N (%)	669 (11.4)
Age (years)	74.0 ± 5.7
Women	408 (61.0)
Self-reported race	
Black	101 (15.1)
White	566 (84.6)
Other	2 (0.3)
Current Smoker	74 (11.1)
Diabetes	132 (19.7)
Hypertension	398 (59.5)
Total Cholesterol in mg/dL	213.4 ± 45.2

Elkind MSV et al. Stroke 2011.

Results

General infection class	ICD-9 code(s)	Frequency (%) of infections during 90-day case period	Frequency (%) infections during BOTH 90-day control periods
Respiratory	460-466, 480-487	15	7
Urinary tract	599.0, 595, 590	7	8
Skin and subcutaneous tissue	680-686	2	0
Bacteremia	790.7	1	0
Osteomyelitis	730.0-730.2	1	0
Assorted	001-134	10	6
TOTAL		36	21

Elkind MSV et al. Stroke 2011.

Results

Association of recent hospitalization for infection with ischemic stroke: Case-crossover analysis

Exposure-- Hosp for infection within:	Case intervals, n	Control intervals, n	OR	95 % CI
90 days prior to stroke				
No	631	1179		
Yes	29	17	3.4	1.8-6.5
30 days prior to stroke				
No	655	1193		
Yes	11	3	7.3	1.9-40.9
14 days prior to stroke				
No	660	1194		
Yes	8	2	8.0	1.6-77.3

Elkind MSV et al. Stroke 2011.

Results

Risk of ischemic stroke during the time interval after hospitalization for infection

Time-dependent survival analysis

	Hazard ratio (95% CI)		
	14 days	30 days	90 days
Unadjusted	4.4 (2.2- 9.3)	2.9 (1.6-5.3)	2.9 (2.0-4.2)
Adj for age, sex, race	4.0 (2.0 - 8.2)	2.5 (1.4-4.6)	2.5 (1.7-3.6)
Adj for above, DM, and smoking	3.9 (1.9-8.0)	2.5 (1.4-4.5)	2.4 (1.7-3.5)
Adjusted for above, common carotid IMT	3.9 (1.9-7.9)	2.4 (1.3-4.4)	2.4 (1.6-3.5)

HCUP/AHRQ State Inpatient Databases: California 2007-2009

Acute Influenza-like Illness and Ischemic Stroke

Luna J, et al. Stroke 2014 (ISC).

Exposure: Influenza-like Illness

ICD-9 CODES USED FOR INFLUENZA-LIKE ILLNESS (ILI) IN ESSENCE-1B

079.89	Viral infection NEC	466	Acute bronchitis and bronchiolitis
079.99	Viral infection NOS	466.0	Acute bronchitis
460	Acute nasopharyngitis	466.1	Acute bronchiolitis
462	Acute pharyngitis	466.19	Acute bronchiolitis due to other infectious organism
464	Acute laryngitis and tracheitis	478.9	Other and unspecified diseases of upper resp tract
464.0	Acute laryngitis	480	Viral pneumonia
464.1	Acute tracheitis	487	Influenza
464.10	Acute tracheitis w/o obstruction	487.0	Influenza with pneumonia
464.2	Acute laryngotracheitis	487.1	Influenza with other respiratory manifestation
464.20	Acute laryngotracheitis w/o obstruction	487.8	Influenza with other manifestation
465	Upper resp infection multiple or unspecified sites	490	Bronchitis not specified as acute or chronic
465.0	Acute laryngopharyngitis	780.6	Fever
465.8	Upper resp infection of multiple sites	784.1	Throat pain
465.9	Upper resp infection of unspecified sites	786.2	Cough

Marsden-Haug N, Foster VB, Gould PL, Elbert E, Wang H, Pavlin JA. Code-based syndromic surveillance for influenzalike Illness by International Classification of Diseases, 9th revision. Emerg Infect Dis [serial on the Internet]. 2007 Feb [*date cited*]. Available from http://wwwnc.cdc.gov/eid/article/13/2/06-0557.htm

ESSENCE DOD BIOSURVEILLANCE DETECTION ALGORITHM

ICD-9 groupings used to detect influenza-like illness (ILI) within an automated syndromic system correlate with CDC respiratory virus laboratory test results in the same population (r = 0.71 or 0.86, depending on group).

Results

- Total stroke cases n=41,148
- Median (IQR) age of cases was 74 (62-83) years
- 52.4% were women
- 90-Day ILI Distribution, By Year
  - Year of stroke, 2009 n=439
  - Year prior to stroke, 2008 n=303
  - 2 years prior to stroke, 2007 n=81

Luna J et al ISC 2014

Multivariate Adjusted Results

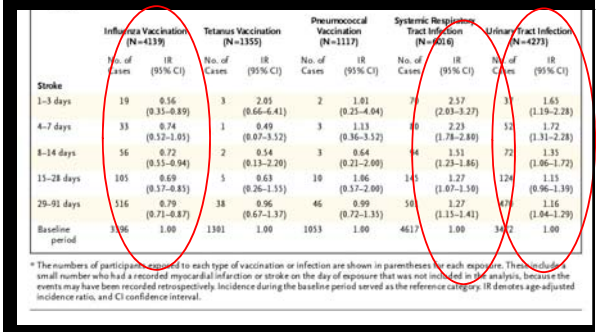
Risk Window	OR	95% CI
15-DAY	6.5	2.2-19.7
30-DAY	3.7	1.8- 8.3
90-DAY	3.3	2.0- 5.8

Age Strata, 30-Day window

	OR	95% CI
<45	16.6	1.0- 267.2
45 to <=65	5.4	1.1- 27.5
>65	2.5	1.0-6.8

Luna J et al ISC 2014

Age-Adjusted Incidence Ratios of a Stroke during Risk Periods after Exposure to Vaccination or Infection



	Influenza Vaccination (N=4139)		Tetanus Vaccination (N=1355)		Pneumococcal Vaccination (N=1117)		Systemic Respiratory Tract Infection (N=6026)		Urinary Tract Infection (N=4273)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Stroke										
1–3 days	19	0.56 (0.35–0.89)	3	2.05 (0.66–6.41)	2	1.01 (0.25–4.04)	71	2.57 (2.03–3.27)	37	1.65 (1.19–2.28)
4–7 days	33	0.74 (0.52–1.05)	1	0.49 (0.07–3.52)	3	1.13 (0.36–3.52)	80	2.23 (1.78–2.80)	52	1.72 (1.31–2.28)
8–14 days	56	0.72 (0.55–0.94)	2	0.54 (0.13–2.20)	3	0.64 (0.21–2.00)	94	1.51 (1.23–1.86)	72	1.35 (1.06–1.72)
15–28 days	105	0.69 (0.57–0.83)	5	0.63 (0.26–1.55)	10	1.06 (0.57–2.00)	145	1.27 (1.07–1.50)	124	1.15 (0.96–1.39)
29–91 days	516	0.79 (0.71–0.87)	38	0.96 (0.67–1.37)	46	0.99 (0.72–1.35)	561	1.27 (1.15–1.41)	478	1.16 (1.04–1.29)
Baseline period	3306	1.00	1301	1.00	1053	1.00	4617	1.00	3412	1.00

* The numbers of participants exposed to each type of vaccination or infection are shown in parentheses for each exposure. These include a small number who had a recorded myocardial infarction or stroke on the day of exposure that was not included in the analysis, because the events may have been recorded retrospectively. Incidence during the baseline period served as the reference category. IR denotes age-adjusted incidence ratio, and CI confidence interval.

Smeeth, L. et al. N Engl J Med 2004;351:2611-2618

The NEW ENGLAND JOURNAL of MEDICINE

Shifting paradigms in prevention

Vulnerable plaque

↓

Vulnerable patient

Naghavi M et al. Circulation 2003.

↓

Vulnerable time period

Infection:

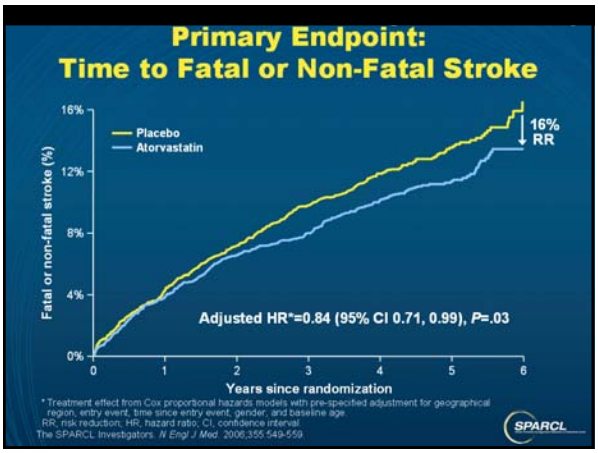
- **Infectious burden may be associated with long-term stroke risk**
- **Acute infections are likely associated with near-term stroke risk (i.e., stroke trigger)**
- **Influenza vaccination can reduce risk of stroke/vascular disease**
  - **AHA/JACC Guidelines**
- **Recognition of this fact could have implications for management of patients presenting with infectious disorders, though this remains to be determined**

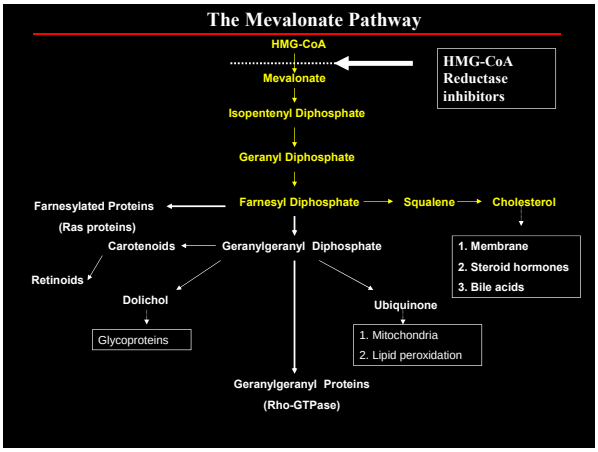
Infection: Potential trials in prevention

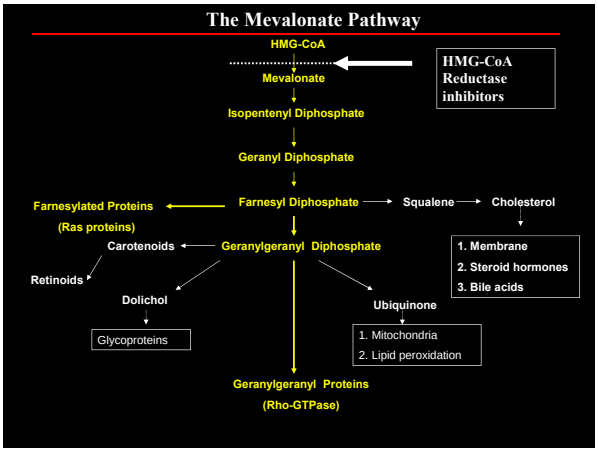
1. **Flu vaccination to prevent stroke (primary/secondary)**
2. **Identification of patients at increased LONG-TERM stroke risk due to infectious burden or related markers for drug therapy**
   a. **Antibiotics**
   b. **Anti-inflammatories**
3. **Identification of patients at increased NEAR-TERM stroke risk due to acute or recent infection (URI, flu, UTI, etc) and treat with vascular protective agent (ASA, statins, etc)**

Outline

- Inflammatory markers and stroke risk
- Infectious markers and stroke risk
- Acute infection and stroke risk
- Acute stroke: Anti-inflammatory treatments
  - Statins
  - Natalizumab







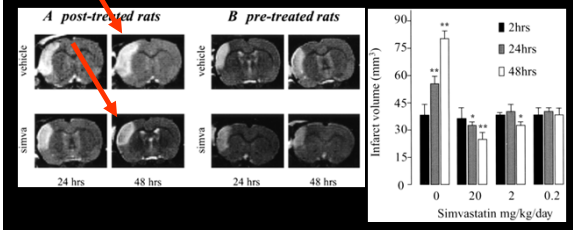
Cholesterol-Independent Effects of the Statins

- **Upregulation of endothelial NOS**
  - **Improves vascular reactivity**
  - **Increased coronary and cerebral blood flow**
- **Anti-inflammatory**
  - **Lowers CRP and LpPLA2**
  - **Inhibits macrophage adhesion and diapedesis**
- **Reduction in free radicals**
- **Decreased platelet activation, thrombus formation**
- **Increased fibrinolysis**
- **Increased angiogenesis**

Neuroprotection

Statins reduce infarct volume in a rat model of stroke

Treatment with simvastatin up 20 mg/kg at 3 hours after MCA occlusion

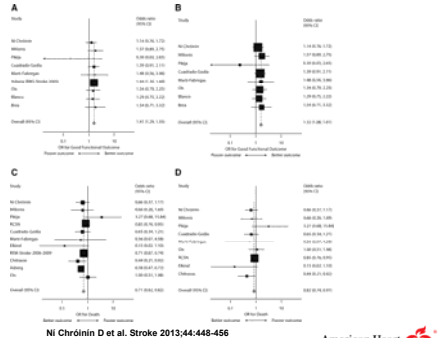


Sironi L et al. Arterioscler Thromb Vasc Biol 2003;23:322-7.

Meta-analysis of statin therapy:
Forest plots of 90-day outcomes (good functional outcome and death) with statin treatment at stroke onset, in observational studies

Functional outcomes

Mortality



Ni Chróinín D et al. Stroke 2013;44:448-456

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Learn and Live

Original Paper

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High-Dose Lovastatin for Acute Ischemic Stroke: Results of the Phase I Dose Escalation Neuroprotection with Statin Therapy for Acute Recovery Trial (NeuSTART)

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NeuSTART Phase 1 RESULTS

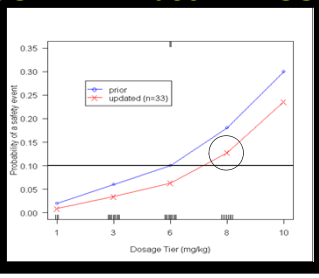


Table 3. Model-based probabilities of dose-limiting toxicity

Dose Tier (mg/kg)	N	Prior P(DLT)	Final P(DLT)	90% posterior interval
1	3	0.02	0.01	0.00, 0.07
3	10	0.06	0.03	0.00, 0.15
6	12	0.10	0.06	0.01, 0.21
8	**8**	**0.18**	**0.13**	**0.03, 0.31**
10	0	0.30	0.24	0.08, 0.44

Elkind MSV et al. Int J Stroke 2008;3:210-218.

NeuSTART Phase 2

Objectives:

- **Primary Aim: To determine whether lovastatin 640 mg daily for 3 days beginning within 24 hours after acute stroke can be administered safely (<10 percentage points higher risk of myotoxicity and/or hepatotoxicity).**
- **Secondary Aim: To assess efficacy of lovastatin administered at high doses.**

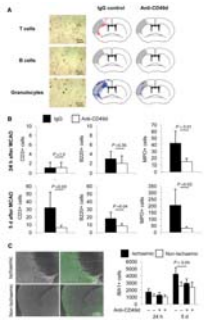
Natalizumab: exploring its potential in acute ischemic stroke

- Natalizumab (BG00002) is a recombinant humanized monoclonal antibody
  - Blocks α4β1-integrin–mediated adhesion of leukocytes to vascular endothelial cells
  - Inhibits transmigration of leukocytes into inflamed parenchymal tissue
  - Well-characterized safety profile and established efficacy in relapsing multiple sclerosis and Crohn's disease[1]
  - Low risk of developing progressive multifocal leukoencephalopathy (PML) from a single dose
- Antibodies targeting α4 reduce infarct volume and improve functional outcomes vs placebo in animal models[2]
- Models of inflammation in stroke indicate an approx 6-hour time window is relevant for natalizumab action[3]

1. Rudick RA, Panzara MA. Biologics 2008;2(2):189-199.
2. Becker K, et al. *Stroke*. 2001;32(1):206-211.
3. Lynch JR, et al. *Stroke*. 2004;35(1):57-63.

72

Anti-CD49d treatment (natalizumab) inhibits leukocyte migration into the ischaemic brain



Liesz A et al. Brain 2011;134:704-720

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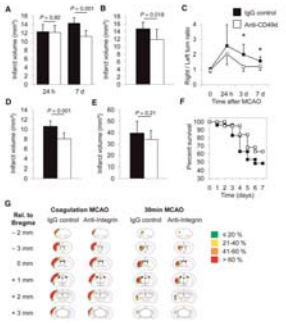
BRAIN A JOURNAL OF NEUROLOGY

Anti-CD49d treatment (natalizumab) improves stroke outcome



Liesz A et al. Brain 2011;134:704-720

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BRAIN A JOURNAL OF NEUROLOGY

What is the ACTION Study?

- Double-blind, randomized, phase II study to assess the efficacy and safety of intravenous natalizumab in reducing infarct volume in acute ischemic stroke
- Randomizing 200 patients with acute ischemic stroke
- Approximately 50 sites in the US and Europe

Primary objective: To determine whether one 300 mg dose of intravenous (IV) natalizumab reduces change in infarct volume from Baseline to Day 5 on magnetic resonance imaging (MRI) in patients with acute ischemic stroke when given at ≤6 hours or at >6 to ≤9 hours from when they were last known normal (LKN).

75

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