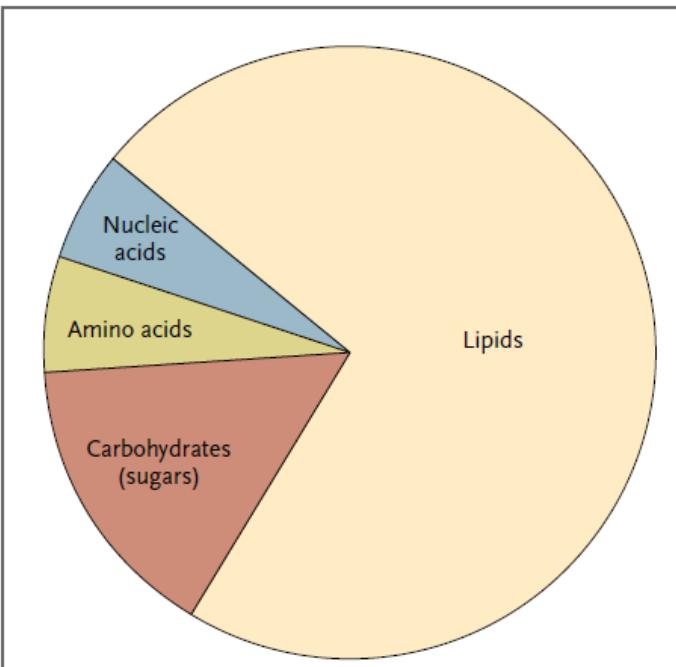


# Lipids and Cerebrovascular Disease

# Objectives

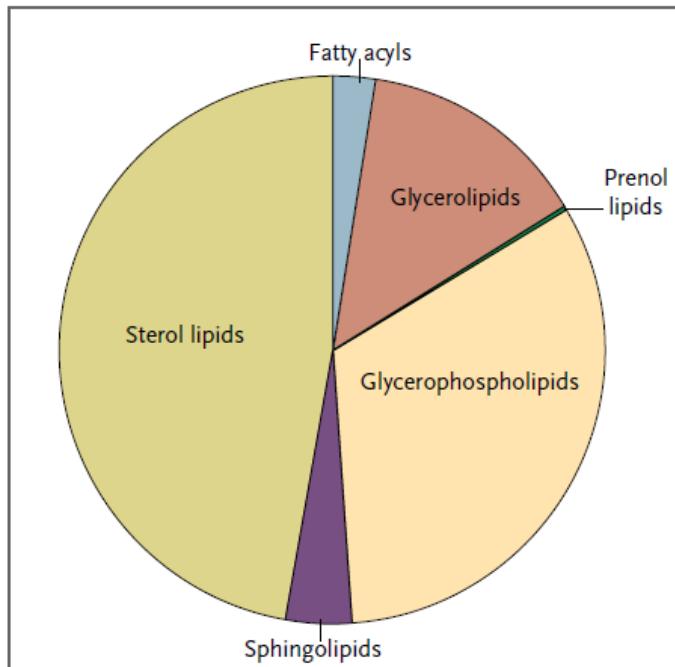
- Review lipoprotein biochemistry
- Lipids and cerebrovascular disease
- Lipid management in stroke
- Emerging lipid biomarkers
- Future directions

# Lipids



**Figure 1. Relative Distribution of Biologic Molecules in Human Plasma.**

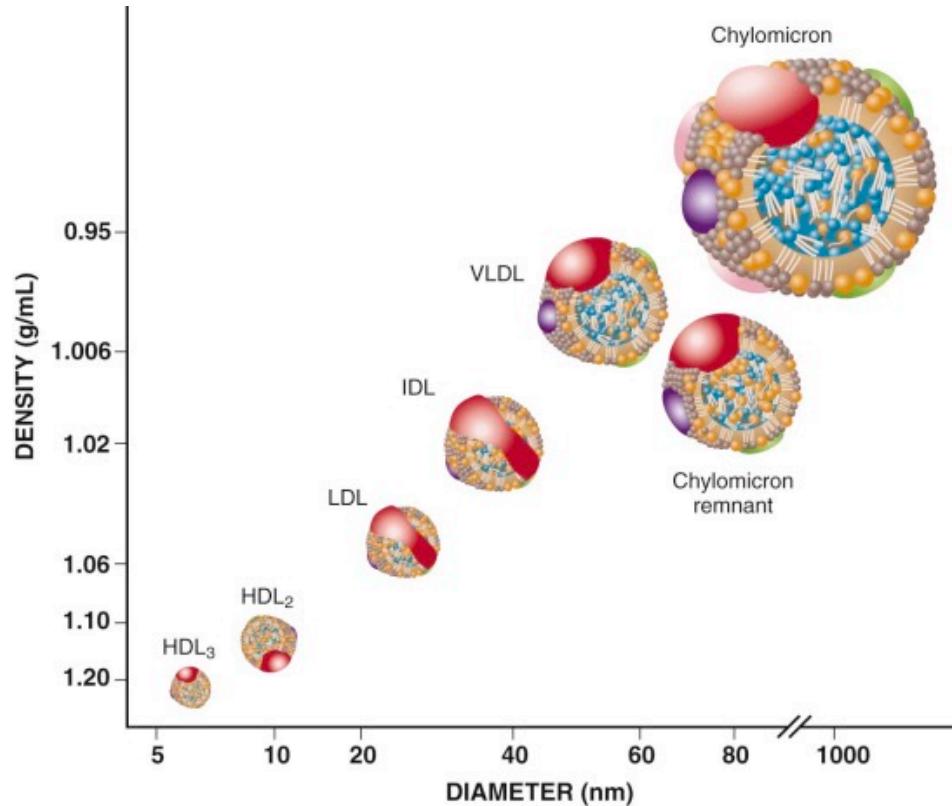
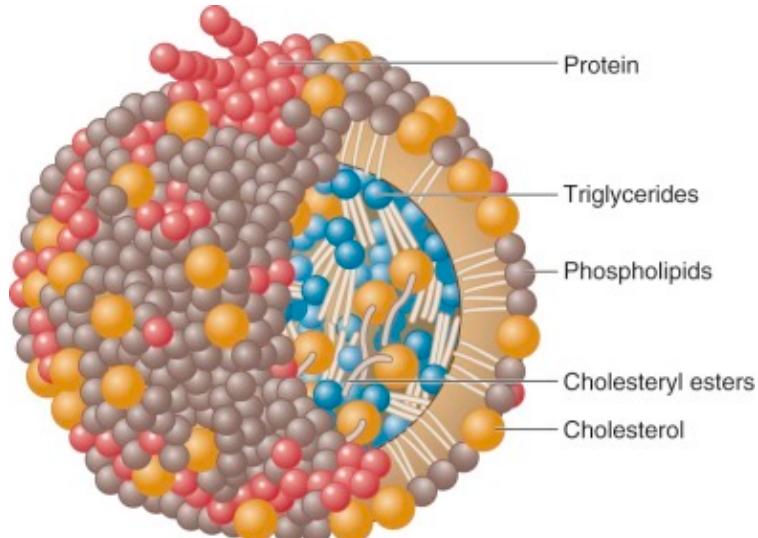
Amino acids and nucleic acids are shown without consideration of the contribution of proteins and DNA or RNA. The relative distribution is based on weight (grams per deciliter). Data were compiled from Lentner,<sup>1</sup> Wishart et al.,<sup>2</sup> and Quehenberger et al.<sup>3</sup>



**Figure 2. Relative Distribution of Lipids in Human Plasma.**

Lipidomic analysis has identified, characterized, and quantified almost 600 lipid molecular species in human plasma.<sup>3</sup> The relative distribution in each category is given on a molar basis. The nomenclature of the lipid categories conforms to the recently developed LIPID MAPS classification system.<sup>6</sup>

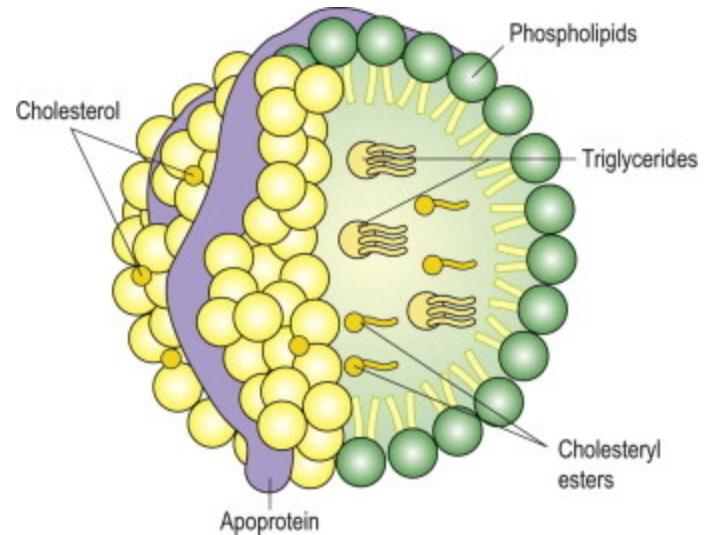
# Lipoproteins



$$\begin{aligned}\text{Friedewald Forumla: } \text{LDL-C} &= \text{TC} - (\text{VLDL} + \text{HDL}) \\ &= \text{TC} - ((\text{Tg}/5) + \text{HDL})\end{aligned}$$

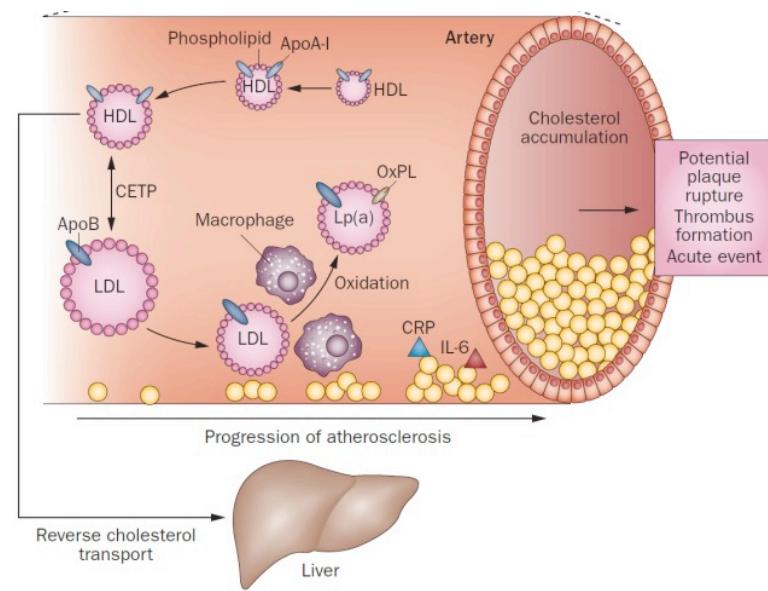
# Apoproteins

- Functions
  - Lipoprotein assembly & secretion
  - Lipoprotein structural integrity
  - Enzyme co-activation or inhibition
  - Binding/docking to specific receptors/proteins

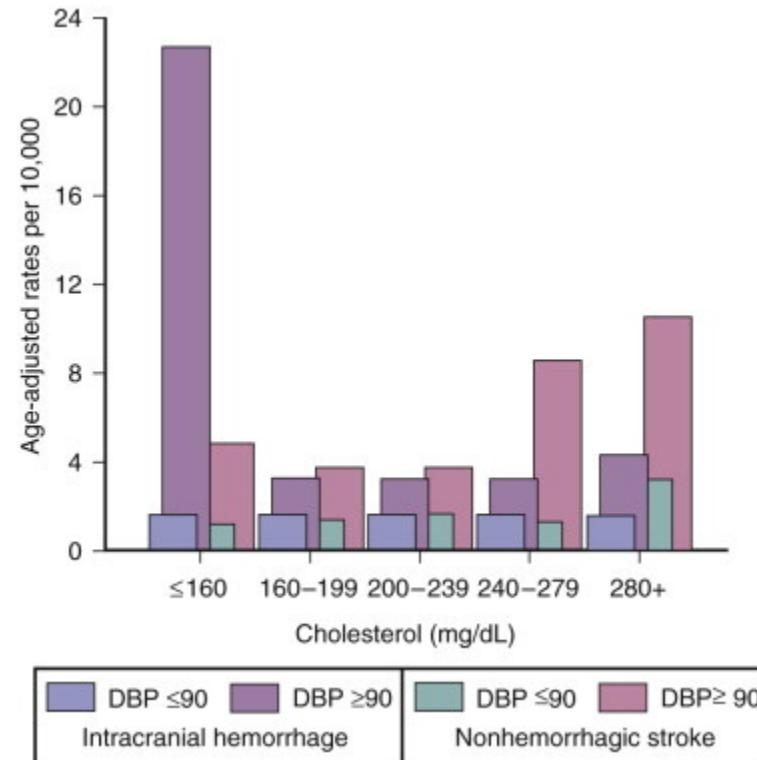
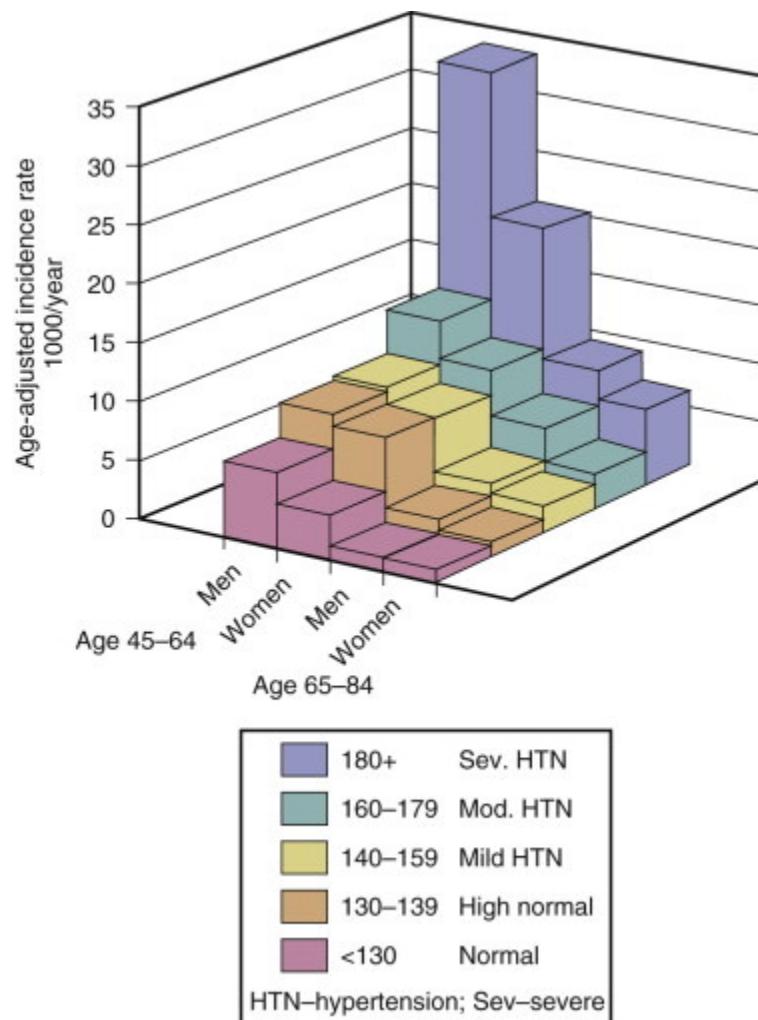


Particle	Density (kg/L)	Main component	Apolipoproteins *	Diameter (nm)
Chylomicrons	0.95	TG	B48 (A, C, E)	75–1200
VLDL	0.95–1.006	TG	B100 (A, C, E)	30–80
IDL	1.006–1.019	TG & cholesterol	B100, E	25–35
LDL	1.019–1.063	Cholesterol	B100	18–25
HDL	1.063–1.210	Protein	AI, AIi (C, E)	5–12

- Apo A1
  - ~70% of HDL protein
  - Role: structural, lecithin-cholesterol acyltransferase activator
  - Marker of HDL concentration
- Apo B100
  - LDL, VLDL/IDL
  - Role: structural, ligand for LDL receptor
  - Marker of LDL + VLDL + chylomicron remnants



# Epidemiology



## Total Cholesterol and LDL-C

Lipid Profile Component	Study	Results	Age-adjusted HR (95% CI)
Total cholesterol	Alpha-Tocopherol, Beta Carotene Cancer Prevention Study <sup>1</sup>	Increased risk of ischemic stroke with a total cholesterol levels $\geq 7$ mmol/L ( $\geq 271$ mg/dL; HR, 1.25; 95% CI, 0.99–1.57)	
	Asia Pacific Cohort Studies Collaboration <sup>2</sup>	For every 1-mmol/L increase in total cholesterol, there was a 25% (95% CI, 13–40) increase in ischemic stroke rate	
	Women's Health Study <sup>3</sup>	Total cholesterol level was associated with ischemic stroke (adjusted HR per 1-mmol/L increase for ischemic stroke of 1.17 (95% CI, 1.06–1.30))	
	Eurostroke Project <sup>4</sup>	No relationship between total cholesterol level and ischemic stroke	
	Women's Pooling Project <sup>5</sup>	Higher total cholesterol was associated with increased risk of ischemic stroke (HR, 1.69; 95% CI, 0.91–3.13, for topmost quintile compared with the lower-most one)	
	Women's Health Study <sup>3</sup>	Serum LDL cholesterol was associated with increased risk of ischemic stroke (HR, 1.74; 95% CI, 1.14–2.66; $P$ (trend across quintiles)=0.003)	
LDL cholesterol	The Atherosclerosis Risk in Communities <sup>5</sup>	Nonsignificant association between LDL cholesterol and ischemic stroke (HR, 1.26; 95% CI, 0.91–1.76, for topmost quintile compared with the lower-most one)	
			<b>Total Cholesterol (mg/dL)<sup>§</sup></b> <179                    1.00 (referent) 179-199                1.69 (1.03-2.77) 200-218                1.78 (1.09-2.88) 219-243                2.20 (1.38-3.49) $\geq 244$ 2.40 (1.52-3.80) P for trend <sup>¶¶</sup> <0.001
			<b>LDL Cholesterol (mg/dL)<sup>§</sup></b> <96                    1.00 (referent) 96-113                1.36 (0.86-2.14) 114-129                1.19 (0.75-1.89) 130-150                1.97 (1.30-2.98) $\geq 151$ 1.85 (1.22-2.80) P for trend <sup>¶¶</sup> <0.001

↑ TChol & LDL-C  $\alpha$  ↑ Ischemic Stroke

Stroke. 2015 Nov;46(11):3322-8.  
 Neurology. 2007 February 20;68(8):556–562.

Lipid Profile Component	Study	Results
Total cholesterol	Multiple Risk Factor Intervention Trial <sup>13</sup>	Three-fold increase in the risk of fatal intracerebral hemorrhage in patients total serum cholesterol <4.13 mmol/L when compared with those with values ≥4.13 mmol/L
	Asia Pacific Cohort Studies Collaboration <sup>2</sup>	For every 1-mmol/L (38.7 mg/dL) increase in total cholesterol, there was a 20% (95% CI, 8–30) reduction in the risk of hemorrhagic stroke
	Korean Medical Insurance Corporation Study <sup>14</sup>	Low serum cholesterol was not associated with intracerebral hemorrhage
LDL Cholesterol	Pooled cohort analysis of the ARIC study and the Cardiovascular Health Study <sup>15</sup>	LDL was inversely associated with hemorrhagic stroke risk (HR for topmost quartile versus lowest 3 quartiles 0.52; 95% CI, 0.31–0.88)

↓ Total Cholesterol & LDL-C α  
↑ Hemorrhagic Stroke

Stroke. 2015 Nov;46(11):3322-8.  
Stroke. 2013 Jul;44(7):1833-9.  
Stroke. 2007;38:2718-2725.

Table 3. Multivariable Adjusted Independent Associations of Baseline Risk Factors With Intraparenchymal Hemorrhage, Combined ARIC/CHS Cohort

Variable (contrast)	Relative Rate	95% CI	P Value
Age per 10 years	2.00	1.69, 2.38	<0.0001
Hypertension Status*			
Normal or High Normal	1.00		
Stage 1 Hypertension	1.43	0.90, 2.26	0.132
Stage 2 Hypertension	2.71	1.58, 4.67	0.0003
Stage 3 Hypertension	5.55	3.07, 10.03	<0.0001
Ethnicity (African-American vs Whites)	1.89	1.28, 2.80	0.0019
Triglycerides per log unit, mg/dL†	0.56	0.37, 0.84	0.0039
LDL-C (top 1/4 vs lower 3/4)	0.52	0.31, 0.88	0.0085

## HDL-C

Copenhagen City Heart Study<sup>7</sup>

47% reduction in the risk of nonhemorrhagic stroke for every 1-mmol/L increase in HDL

Northern Manhattan Stroke Study<sup>8</sup>

Inverse relationship between ischemic stroke and HDL level  $\leq 35$  mg/dL (0.91 mmol/L; OR, 0.53; 95% CI, 0.39–0.72)

Cardiovascular Health Study<sup>9</sup>

Higher HDL cholesterol level was associated with a decreased risk of ischemic stroke in men, but not in women

The Atherosclerosis Risk in Communities<sup>5</sup>

No relationship between HDL cholesterol and ischemic stroke in men and a nonsignificant association in women

### Estimates RR per 10 mg/dl increase in HDL-C

#### **Cohort studies**

- Population-based sample
  - Wallius et al, 2006
  - Simons et al, 2006
  - Psaty et al, 2004
  - Lindstrom et al, 1994
  - Tanne et al, 1997

- Record-based sample
  - Koren-Morag et al, 2002

#### **Case-Control studies**

- Non-nested design
  - Amarenco et al, 2006
  - Milonis et al, 2005
  - Tirschwell et al, 2004
  - Sacco et al, 2001

#### Nested design

- Patel et al, 2005
- Bots et al, 2002

### Estimates RR per HDL-C categories

#### **Cohort studies**

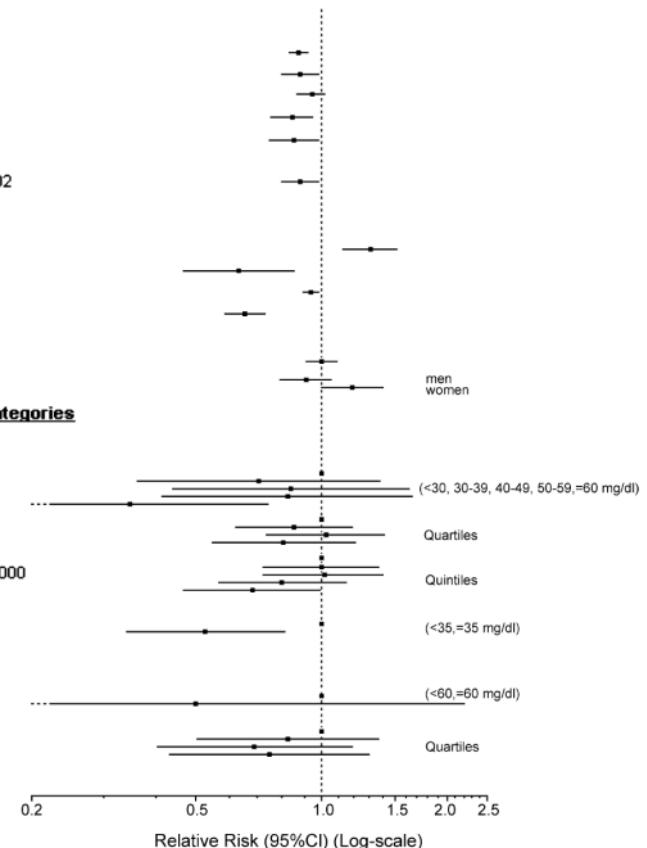
- Population-based sample
  - Soyama et al, 2003
  - Shahar et al, 2003
  - Wannamethee et al, 2000

- Record-based sample
  - Lehto et al, 1996

#### **Case-Control studies**

- Non-nested design
  - Woo et al, 1991

- Nested design
  - Bowman et al, 2003



↑ HDL-C  $\alpha$  ↓ Ischemic Stroke

Stroke. 2015 Nov;46(11):3322-8.

Atherosclerosis. 2008 Feb;196(2):489-96.

## Triglycerides

The Atherosclerosis Risk in Communities <sup>5</sup>	Fasting triglyceride levels were not associated with ischemic stroke
Physicians' Health Study <sup>10</sup>	No association between triglyceride level and ischemic stroke
Copenhagen City Heart Study <sup>11</sup>	15% (95% CI, 9–22) increased risk of ischemic stroke for each 89-mg/dL increase in nonfasting triglycerides
Women's Health Study <sup>12</sup>	The highest tertile of nonfasting but not fasting triglyceride level was associated with increased ischemic stroke risk when compared with lowest tertile
Three City Study <sup>16</sup>	A triglycerides level $\leq 0.94$ mmol/L was associated with an increased risk of hemorrhagic stroke (adjusted HR, 2.35; 95% CI, 1.18–4.70)
Rotterdam study <sup>17</sup>	The highest quartile of triglyceride level had a lower risk of intracerebral hemorrhage than the lowest quartile (HR, 0.20; 95% CI, 0.06–0.69)

Triglycerides  $\alpha \uparrow$  Ischemic Stroke  
 $\downarrow$  Triglycerides  $\alpha \uparrow$  Intracerebral Hemorrhage

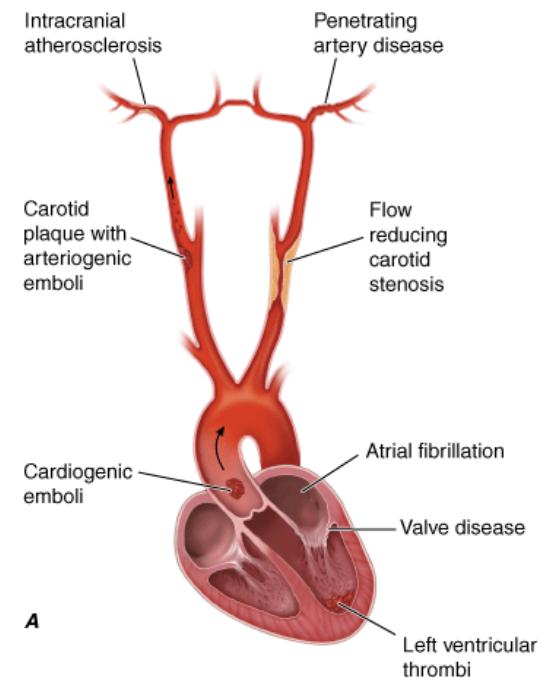
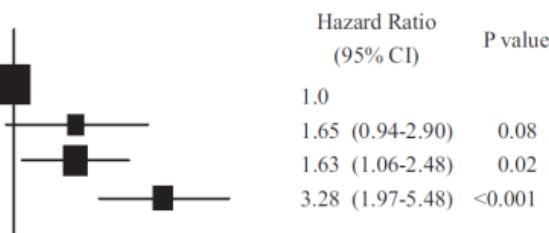
Stroke. 2015 Nov;46(11):3322-8.

Atherosclerosis. 2010 Sep;212(1):9-15.

# Lipids and Ischemic Stroke Subtypes

Table 3 OR (95% CIs) for ischemic stroke by quintile of total and HDL cholesterol

Model	Quintile				
	1	2	3	4	5
<b>All ischemic stroke</b>					
Total cholesterol					
Adjusted for baseline covariates*	1.0 (ref)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.4 (1.2–1.7)
Fully adjusted†	1.0 (ref)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	1.6 (1.3–1.9)
<b>Ischemic stroke subtypes</b>					
Total cholesterol‡					
Lacunar/small artery stroke	1.0 (ref)	1.3 (0.8–2.1)	1.3 (0.8–2.2)	1.1 (0.7–1.8)	2.2 (1.4–3.4)
N cases	34	40	40	33	63
Atherosclerotic/large artery stroke	1.0 (ref)	1.0 (0.5–2.0)	1.8 (1.0–3.4)	1.7 (0.9–3.1)	3.1 (1.7–5.6)
N cases	20	16	28	26	41
Embolic stroke	1.0 (ref)	0.9 (0.6–1.4)	1.1 (0.7–1.6)	0.9 (0.6–1.4)	1.2 (0.8–1.8)
N cases	63	56	59	51	56
Other stroke	1.0 (ref)	0.9 (0.7–1.2)	1.0 (0.7–1.3)	0.9 (0.7–1.2)	1.4 (1.0–1.8)
N cases	117	105	112	113	169



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Ja Harrison's Principles of Internal Medicine, 17th Edition: <http://www.ac>

# Lipids and Carotid Atherosclerosis

**Table 3.** OR (95% CIs) for Lipid Core Presence With Cardiovascular Risk Factors (N=214)

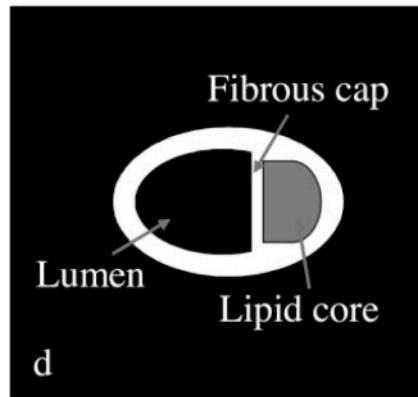
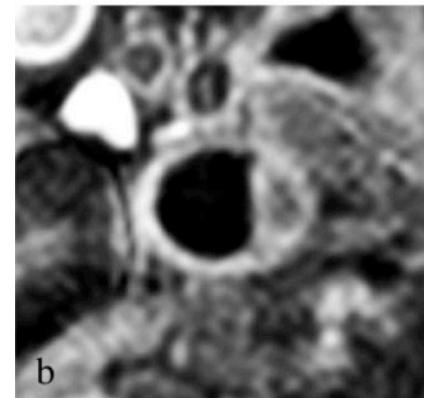
	Adjusted* OR	95% CI
Women vs men	1.35	0.56–3.25
Black vs white	0.52	0.16–1.76
Hispanic vs white	0.77	0.27–2.24
Chinese vs white	2.07	0.49–8.78
Age 45–54 vs >74	0.25	0.06–1.05
55–64 vs >74	0.93	0.28–3.12
65–74 vs >74	0.65	0.20–2.08
Maximum wall thickness per 100 $\mu\text{m}$	1.28	1.18–1.40
Total cholesterol	2.76†	1.01–7.51
181–210 mg/dL vs $\leq 180$ mg/dL		
>210 mg/dL vs $\leq 180$ mg/dL	4.63‡	1.56–13.75
Smoking: current vs never smoked	0.63	0.16–2.49
Former vs never smoked	0.83	0.33–2.10
Diabetes or IFG vs no diabetes or IFG	0.79	0.28–2.18
Hypertension vs nonhypertensives	1.07	0.43–2.67
CRP: 1.14–2.92 mg/L vs <1.14 mg/L	0.53	0.18–1.53
>2.92 mg/L vs <1.14 mg/L	0.97	0.33–2.90

\*Adjusted for all listed variables.

†Reduced to 2.43 (95% CI: 0.87 to 6.75) after adjusting for lipid-lowering medication.

‡Reduced to 4.23 (95% CI: 1.40 to 12.78) after adjusting for lipid-lowering medication.

IFG indicates impaired fasting glucose.



# Lipid-Lowering Therapies and Stroke

Medscape®

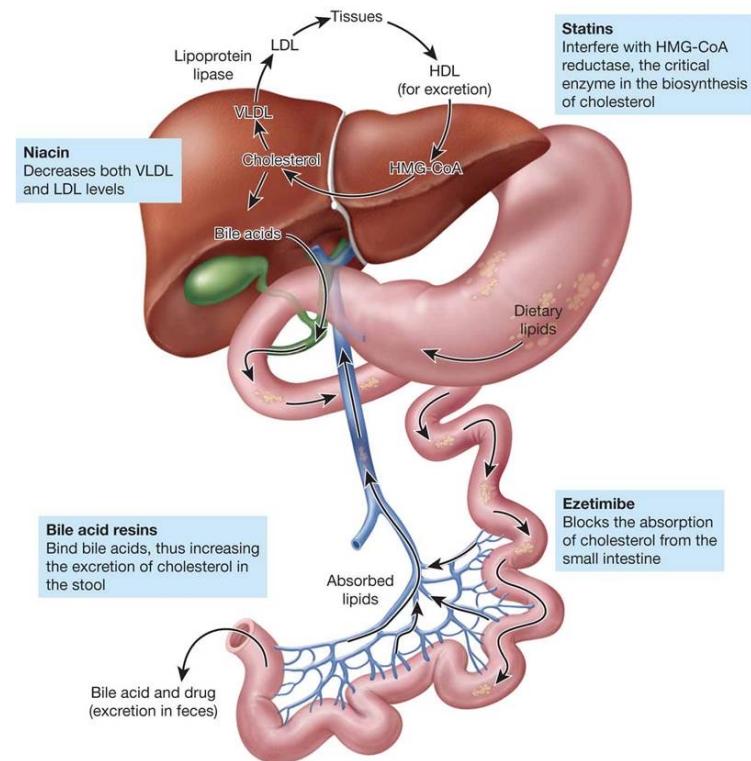
[www.medscape.com](http://www.medscape.com)

## Effect of Lipid-Lowering Drugs on Lipid Profile

	HDL	LDL	TG
Nicotinic acid	↑15 to ↑35%	↓5 to ↓25%	↓20 to ↓50%
Fibric-acid derivatives	↑10 to ↑35%	↓5 to ↓20%	↓20 to ↓50%
Statins	↑5 to ↑15%	↓18 to ↓55%	↓7 to ↓30%
Thiazolidinediones	↑5 to ↑13%	↓4 to ↓16%	↓26 to ↑2%
Bile acid sequestrants	↑3 to ↑5%	↓15 to ↓30%	↓1 to ↑1%
Ezetimibe	↑1 to ↑5%	↓18 to ↓20%	↓5 to ↓11%

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

Source: Cardiosource © 2007 American College of Cardiology Foundation



# Treatment of Dyslipidemia: Primary Stroke Prevention

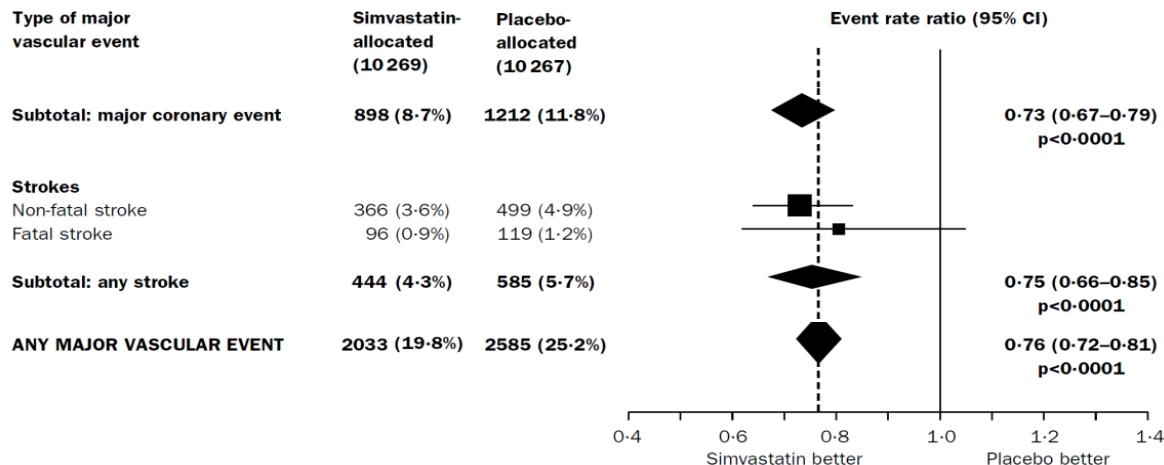
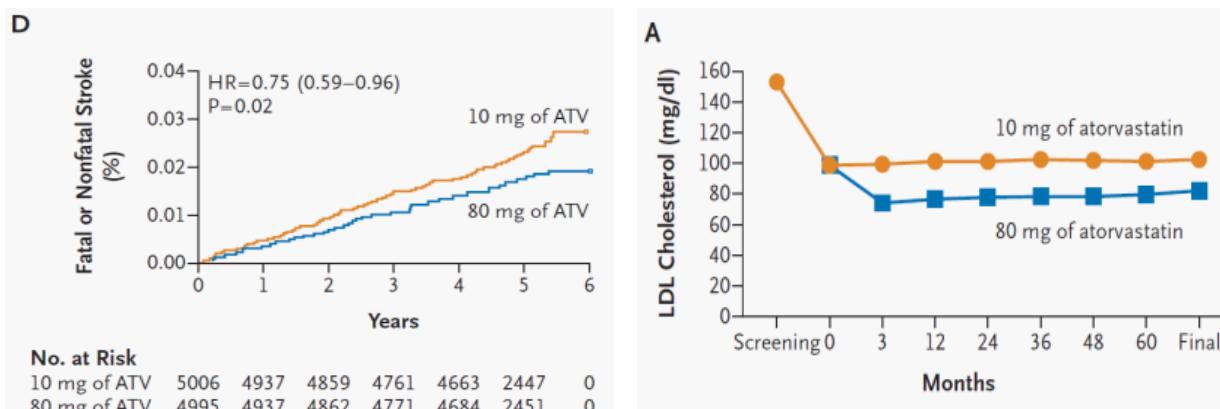


Figure 3: Effects of simvastatin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as "major vascular events")

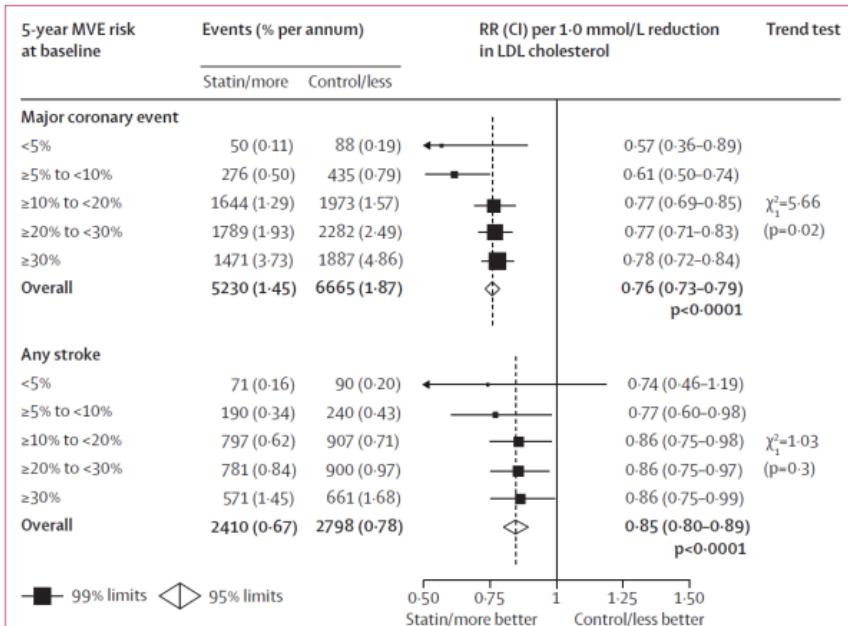


Lancet. 2002 Jul 6;360(9326):7-22.

N Engl J Med. 2005 Apr 7;352(14):1425-35.

**Figure 2.** Major recommendations for statin therapy for ASCVD prevention

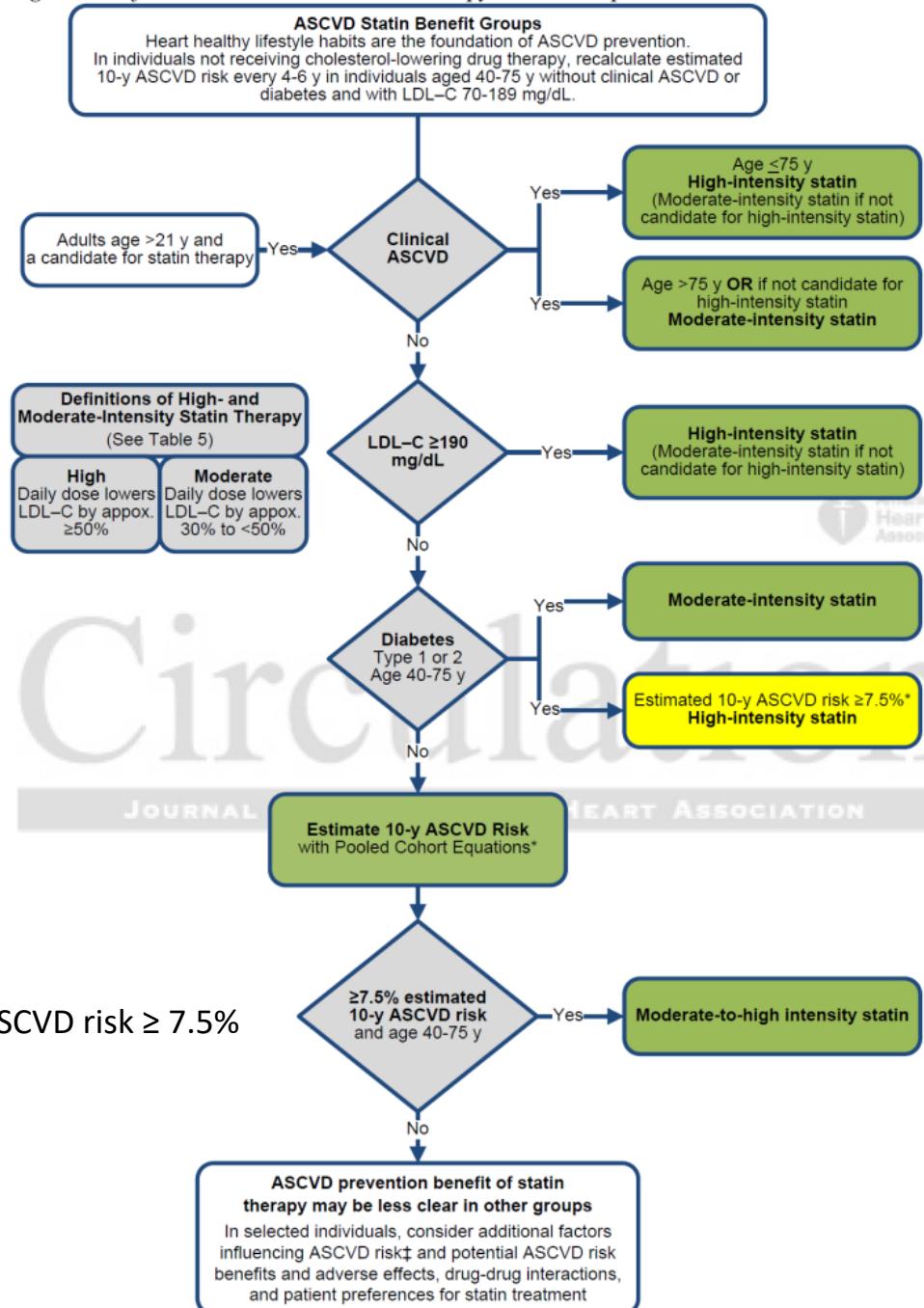
**ASCVD Statin Benefit Groups**  
 Heart healthy lifestyle habits are the foundation of ASCVD prevention.  
 In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.



**Figure 1:** Effects on major coronary events, strokes, coronary revascularisation procedures, and major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk  
 MVE=major vascular event. RR=rate ratio. CI=confidence interval.

### Primary Prevention:

- $LDL-C \geq 190 \text{ mg/dL}$
- Diabetics age 40-75 years &  $LDL 70-189 \text{ mg/dL}$
- Non-diabetics with  $LDL 70-189 \text{ mg/dL}$  and 10-year ASCVD risk  $\geq 7.5\%$



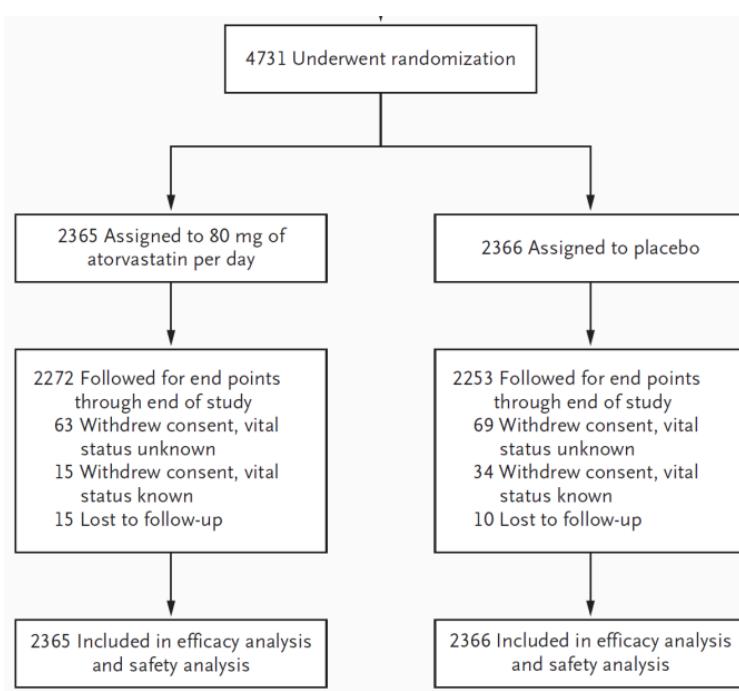
Lancet. 2012 Aug 11;380(9841):581-90.

J Am Coll Cardiol. 2014 Jul 1;63:2889-934.

# Treatment of Dyslipidemia : Secondary Stroke Prevention

## High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators\*



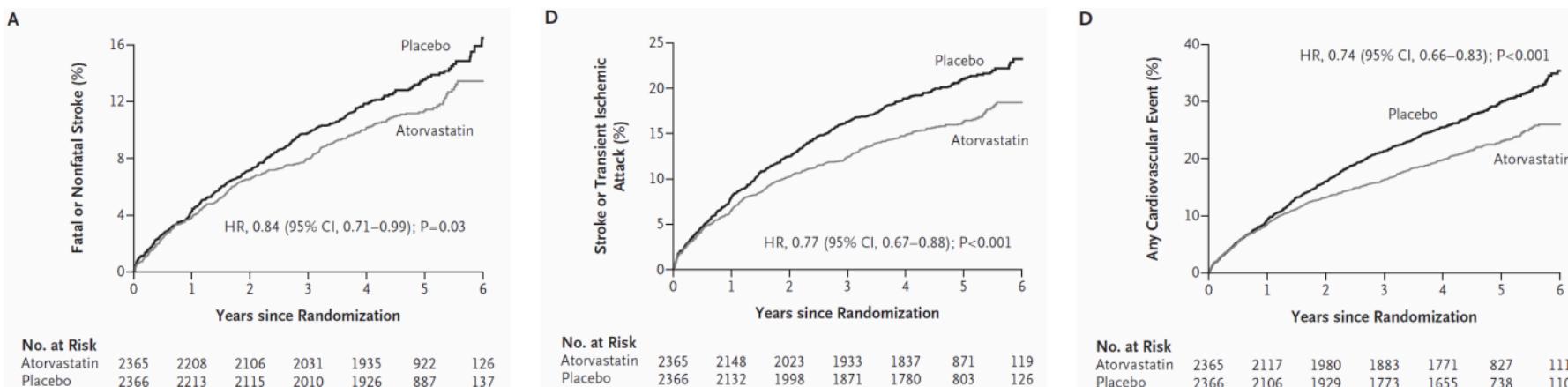
**Table 1.** Baseline Characteristics of the Patients.\*

Characteristic	Atorvastatin (N=2365)	Placebo (N=2366)
Age — yr	63.0±0.2	62.5±0.2
Male sex — no. (%)	1427 (60.3)	1396 (59.0)
Systolic blood pressure — mm Hg	138.9±0.4	138.4±0.4
Diastolic blood pressure — mm Hg	82.0±0.2	81.4±0.2
Body-mass index†	27.5±0.1	27.4±0.1
Entry event — no. (%)		
Stroke	1655 (70.0)	1613 (68.2)
Ischemic	1595 (67.4)	1559 (65.9)
Hemorrhagic	45 (1.9)	48 (2.0)
Other type or not determined	15 (0.6)	6 (0.3)
TIA	708 (29.9)	752 (31.8)
Unknown	2 (0.1)	1 (<0.1)
Time since entry event — days	87.1±1.0	84.3±1.0
Lipids — mg/dl‡		
LDL cholesterol	132.7±0.5	133.7±0.5
HDL cholesterol	50.0±0.3	50.0±0.3
Total cholesterol	211.4±0.6	212.3±0.6
Triglycerides	144.2±1.9	143.2±1.4

**Table 2** Selected outcome data from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study.<sup>6</sup>

Outcome	Atorvastatin n (%) <sup>a</sup>	Placebo n (%) <sup>b</sup>	Hazard ratio (95% CI)	P value
<b>Primary</b>				
All stroke	265 (11.2)	311 (13.1)	0.84 (0.71–0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.87 (0.73–1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.57 (0.35–0.95)	0.03
<b>Secondary</b>				
Stroke or transient ischemic attack	375 (15.9)	476 (20.1)	0.77 (0.67–0.88)	<0.001
Major coronary event	81 (3.4)	120 (5.1)	0.65 (0.49–0.87)	0.003
Any coronary event	123 (5.2)	204 (8.6)	0.58 (0.46–0.73)	<0.001
Revascularization	94 (4.0)	163 (6.9)	0.55 (0.43–0.72)	<0.001
Any cardiovascular event	530 (22.4)	687 (29.0)	0.74 (0.66–0.83)	<0.001
Death	216 (9.1)	211 (8.9)	1.00 (0.82–1.21)	0.98
Death from cardiovascular disease	78 (3.3)	98 (4.1)	0.78 (0.58–1.06)	0.11

<sup>a</sup>Total number of patients = 2,365. <sup>b</sup>Total number of patients = 2,366. Abbreviation: n, number of patients.



# Effects of Statins

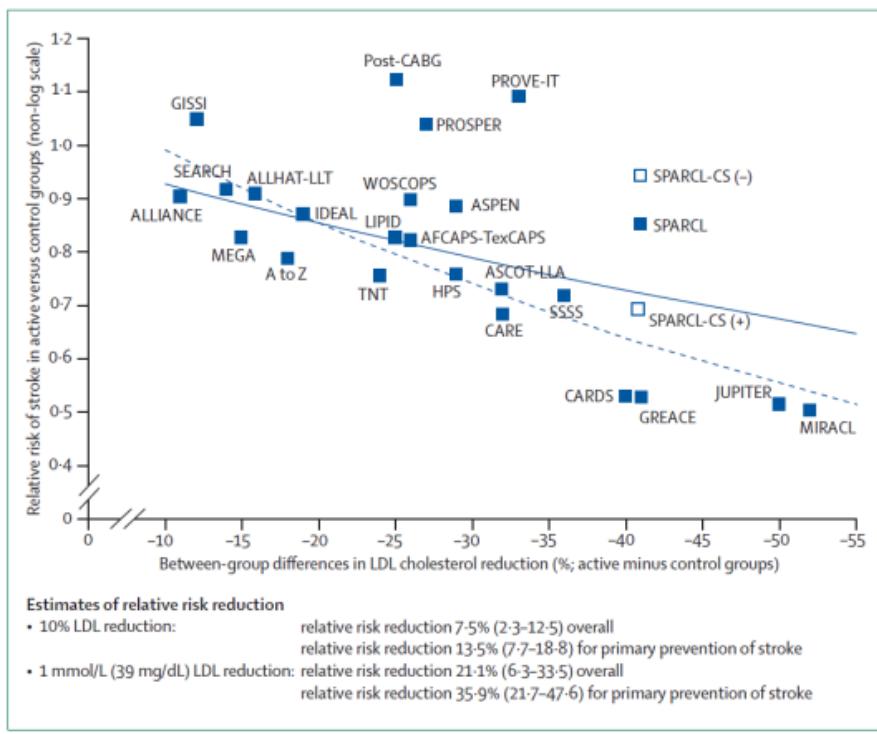


Figure 4: Association between reduction in LDL cholesterol concentration with stroke incidence among the major statins trials

## Box 1 Mechanisms of action attributed to statins.

- Upregulation of LDL receptor activity
- Reduction in the entry of LDL cholesterol into the circulation
- Decrease in serum markers of chronic inflammation
- Upregulation of certain genes
- Improvement in endothelial function
- Plaque stabilization
- Antithrombotic effect
- Antioxidant effect
- Anti-inflammatory effect
- Neuroprotection
- Vasoprotection
- Upregulation of endothelial nitric oxide synthase
- Improvement in HDL cholesterol function

# Statins and Intracerebral Hemorrhage

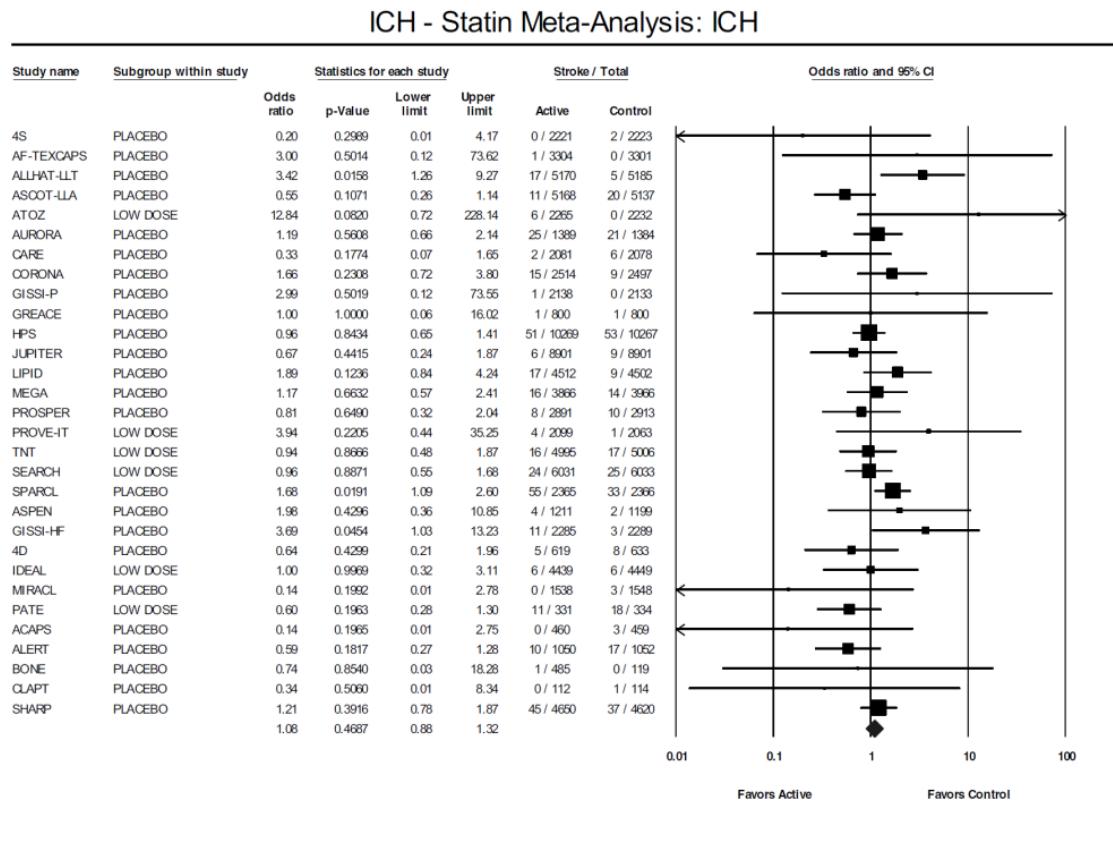
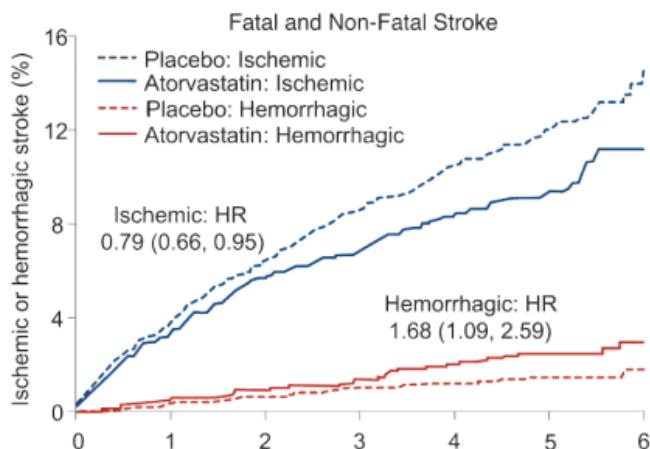
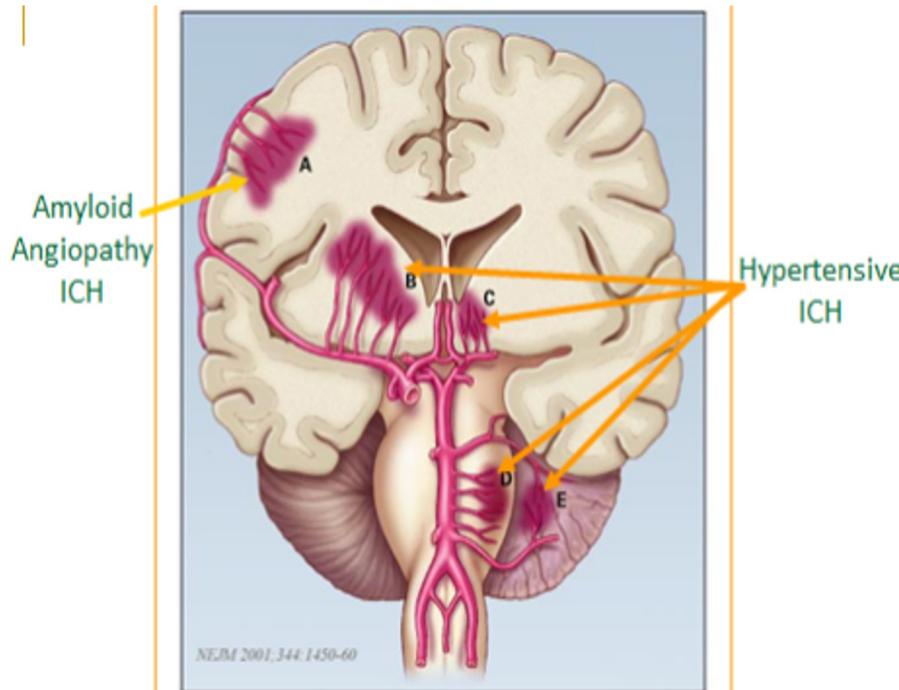


Figure 2. Forrest plot of random-effects meta-analysis of randomized trials of statins and intracerebral hemorrhage.

Neurology. 2008 Jun 10;70(24 Pt 2):2364-70.

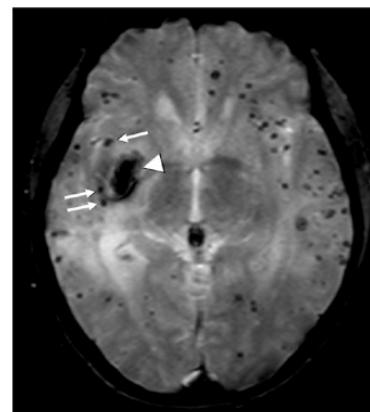
Stroke. 2012 Aug;43(8):2149-56.

# Statins and Lobar Hemorrhage

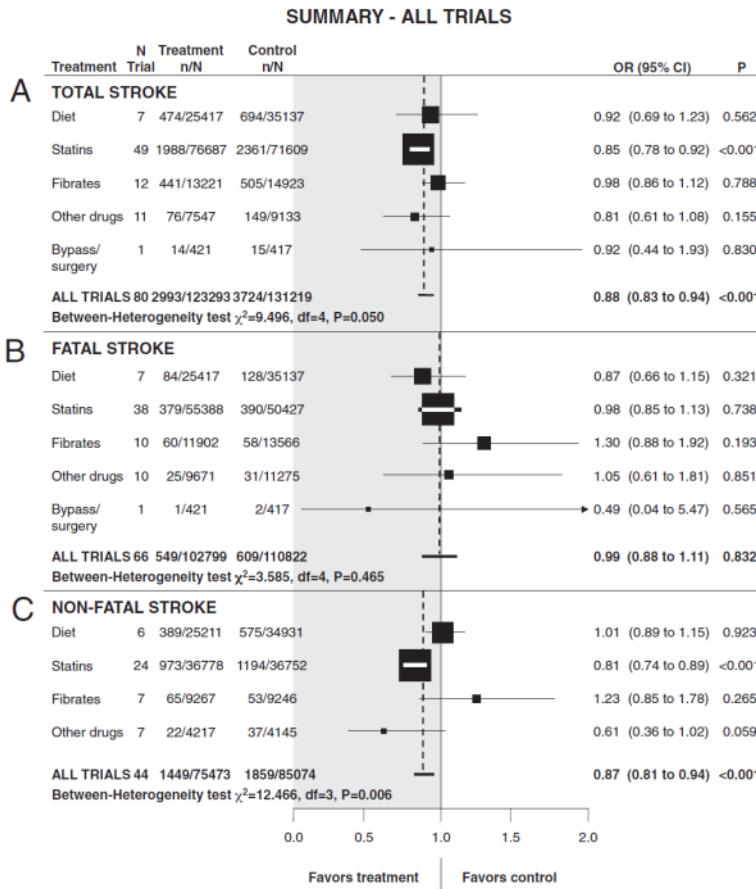


**Table 4. Multivariate Logistic Regression Analysis for Presence of Cortico-Subcortical Microbleed**

Variable	OR	95% CI	P
Age	1.03	1.00–1.06	0.012*
Male	0.66	0.33–1.31	0.240
Hypertension	0.91	0.42–1.94	0.812
Diabetes	0.42	0.15–1.14	0.090
Dyslipidemia	0.72	0.29–1.75	0.471
Coronary artery disease	0.97	0.35–2.69	0.965
Antiplatelet use	0.75	0.33–1.69	0.496
Statin use	4.15	1.54–11.20	0.005*



# Alternative Dyslipidemia Therapies



**Table 2.** Primary, Secondary, and Individual End Points.<sup>a</sup>

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin-Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
<i>no. of patients (%)</i>				
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization $\geq 30$ days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization $\geq 30$ days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points: <sup>b</sup>				
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11

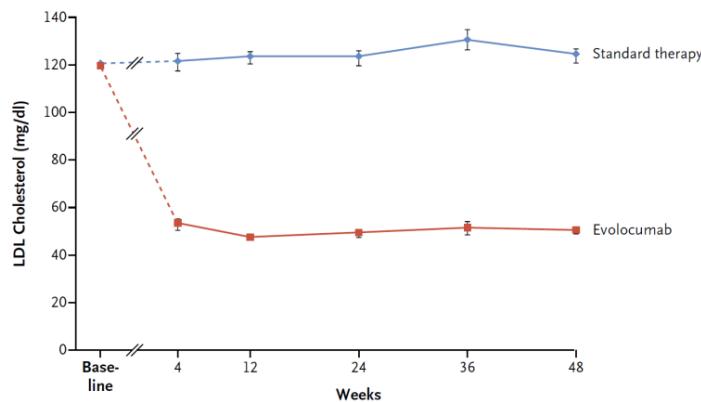
N Engl J Med. 2015 Jun 18;372(25):2387-97.

J Am Coll Cardiol. 2010 Jan 19;55(3):198-211.

# PCSK9 Inhibitors

ORIGINAL ARTICLE

## Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events



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

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.

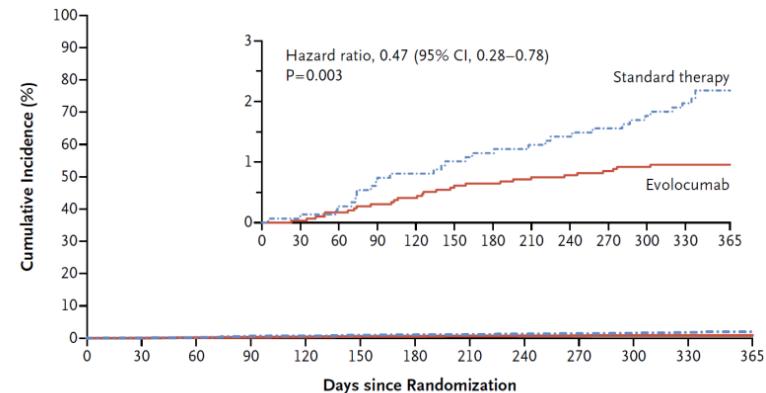


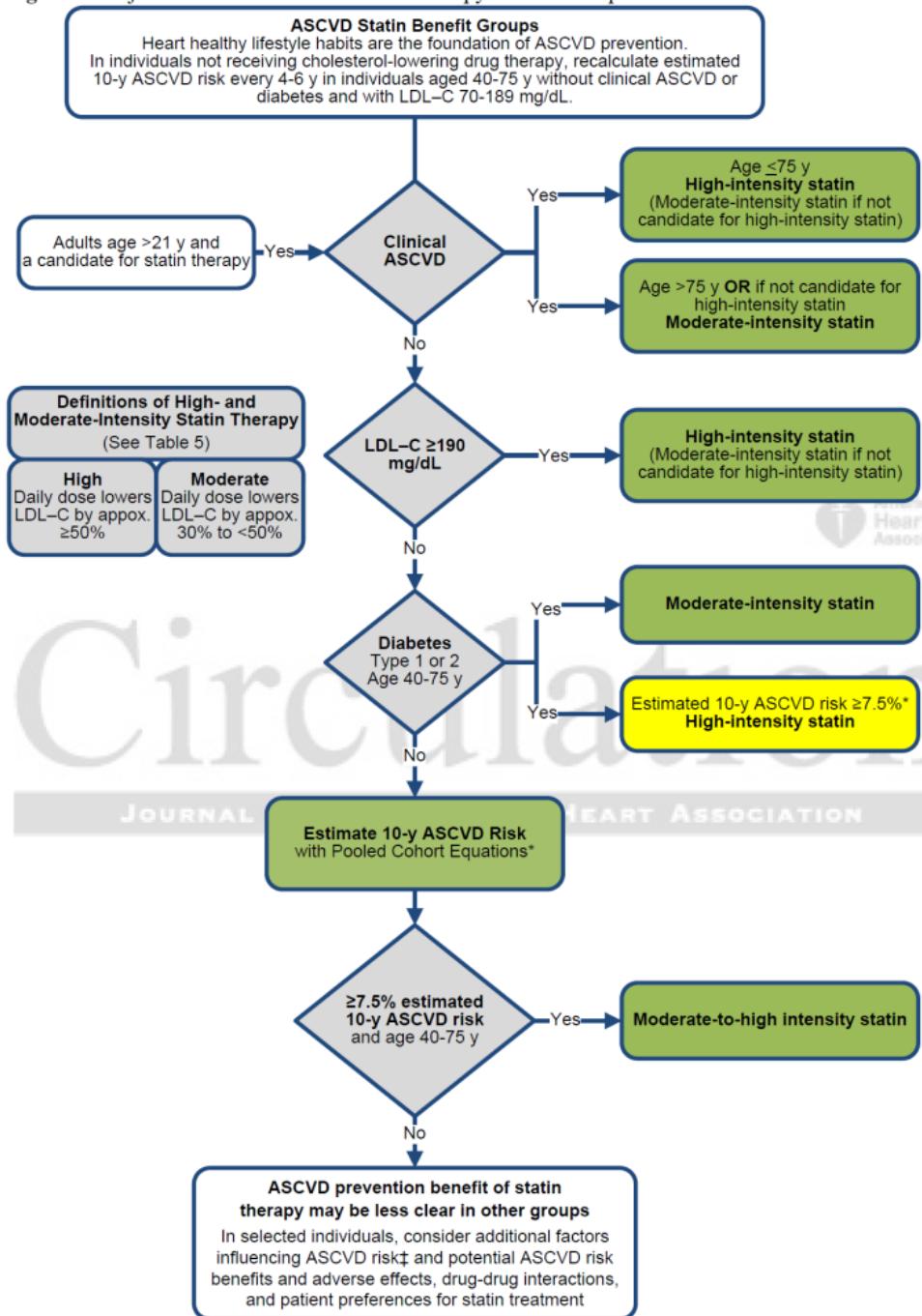
Figure 2. Cumulative Incidence of Cardiovascular Events.

# Guidelines

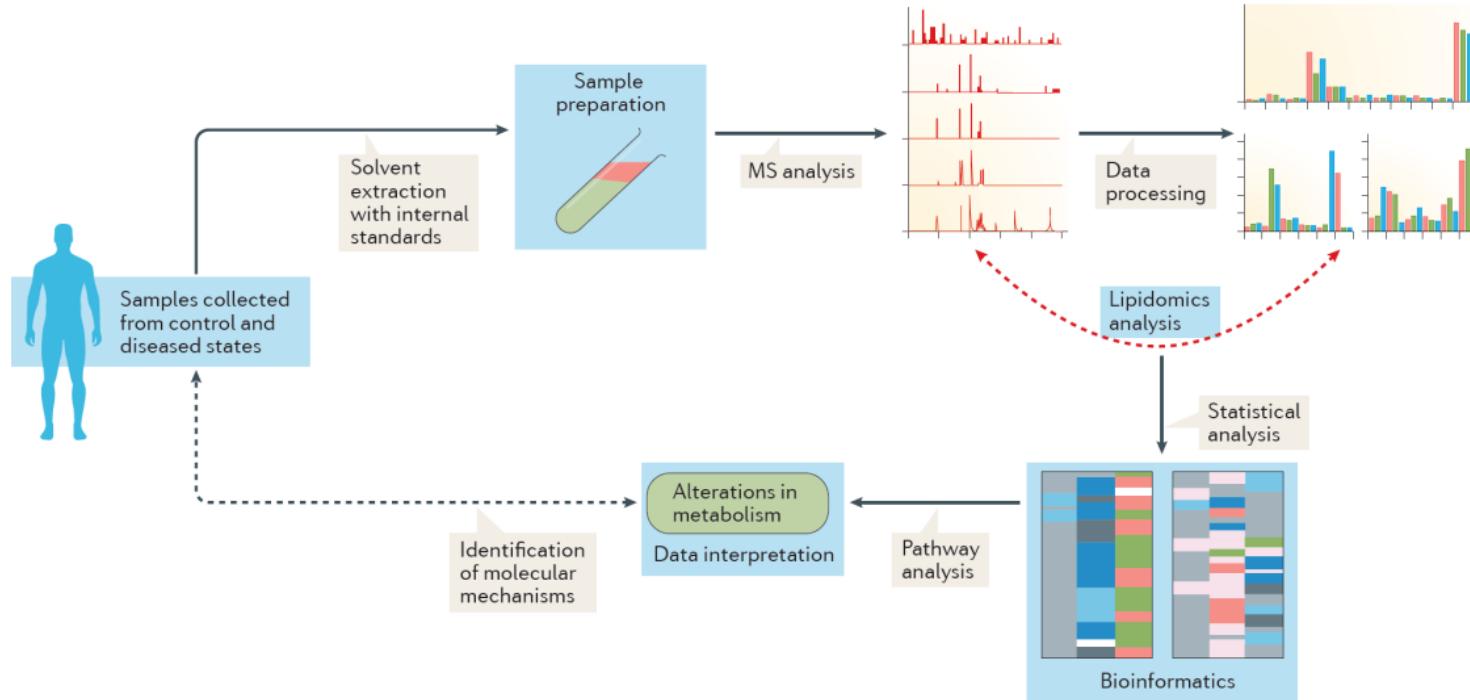
## Dyslipidemia Recommendations

1. 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  $\geq 100$  mg/dL with or without evidence for other clinical ASCVD (*Class I; Level of Evidence B*). (Revised recommendation)
2. 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, an LDL-C level  $< 100$  mg/dL, and no evidence for other clinical ASCVD (*Class I; Level of Evidence C*). (New recommendation)
3. Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines,<sup>16</sup> which include lifestyle modification, dietary recommendations, and medication recommendations (*Class I; Level of Evidence A*). (Revised recommendation)
8. There are insufficient data to recommend restrictions on the use of statins in ICH patients (*Class IIb; Level of Evidence C*). (Unchanged from the previous guideline)

Figure 2. Major recommendations for statin therapy for ASCVD prevention

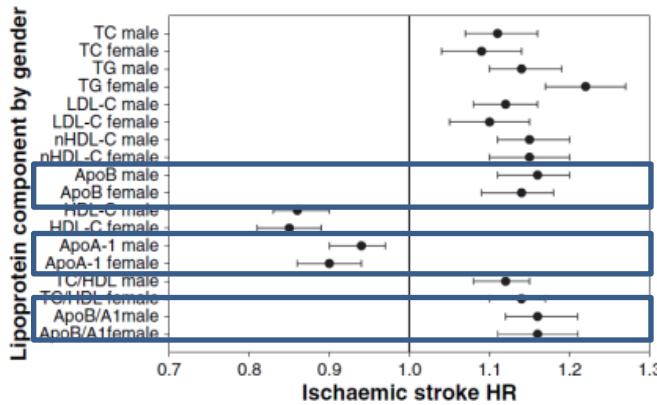


# Emerging Lipid Biomarkers

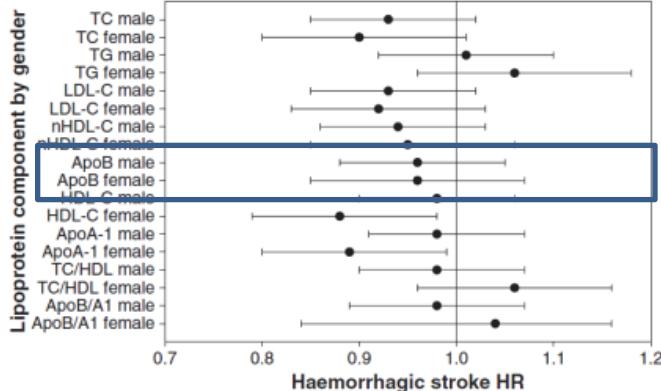


- Apolipoproteins B & A1
- Lipoprotein (a)
- Lipoprotein-associated phospholipase A2
- HDL sub-fractions

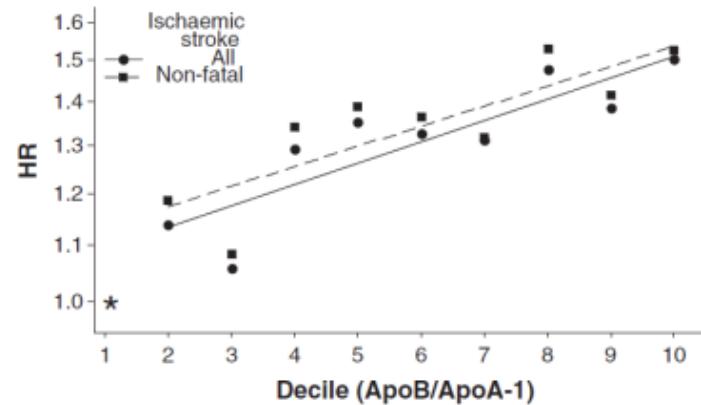
# Apolipoproteins B & A1



**Fig. 1** Ischaemic stroke hazard ratio (HR) for 1 SD difference in lipoprotein components by gender, adjusted for age, acute myocardial infarction, diabetes and hypertension.



**Fig. 2** Haemorrhagic stroke hazard ratio (HR) for 1 SD difference in lipoprotein components by gender, adjusted for age, acute myocardial infarction, diabetes and hypertension.



**Fig. 3** Total and nonfatal ischaemic stroke incidence by apoB/apoA-1 in deciles, adjusted for age, gender, total cholesterol, triglycerides, acute myocardial infarction, diabetes and hypertension. Asterisk represents the reference point and is not included in the regression line fits.

# Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study

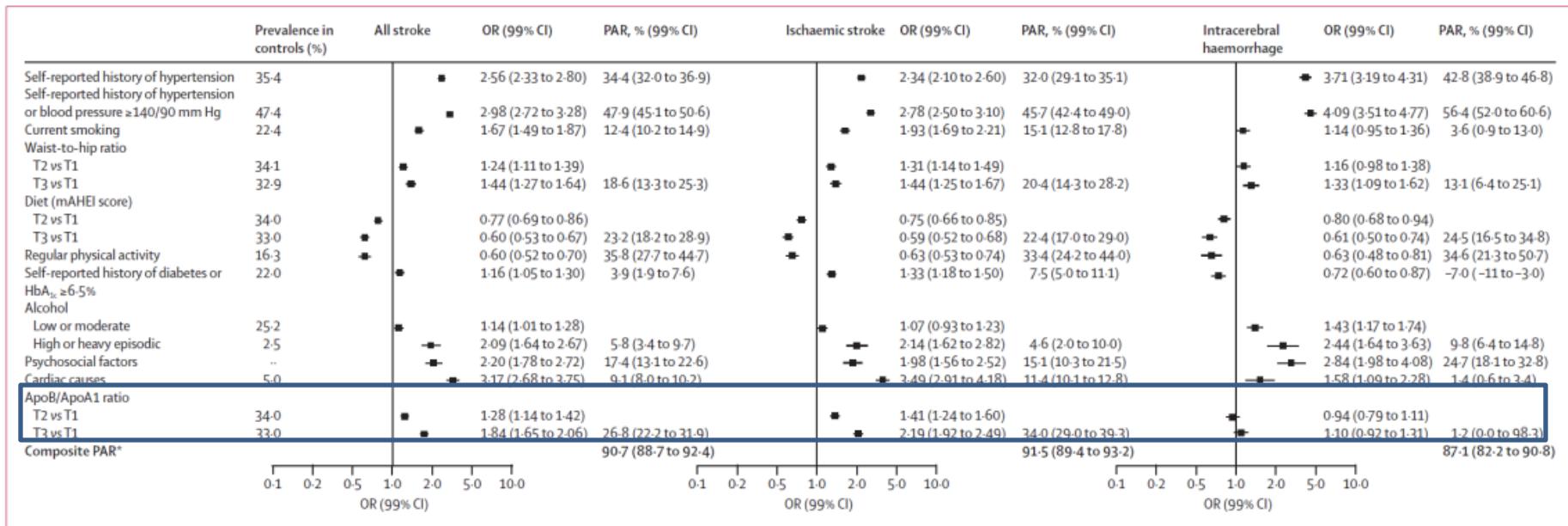


Figure 1: Multivariable analysis of prevalence of risk factors, OR, and PAR for ten risk factors

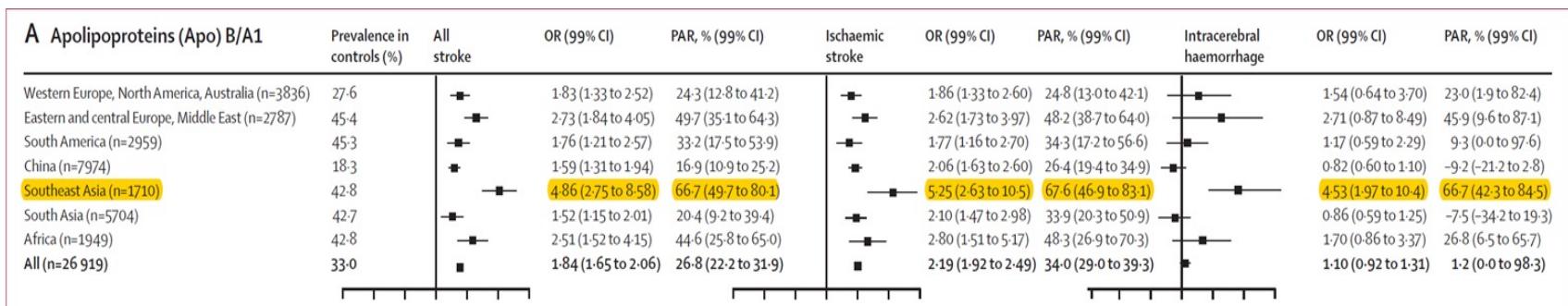
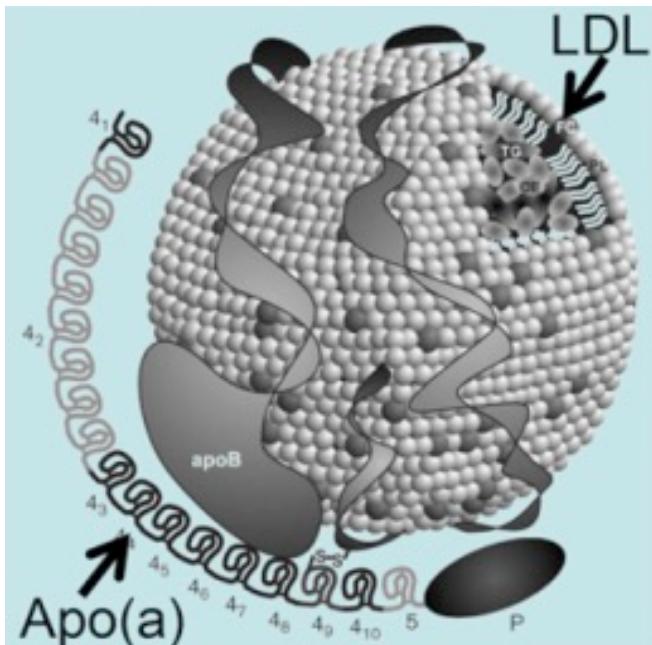


Figure 3: Multivariable analysis by region

# Lipoprotein (a)



**Table 2.** ORs for IS and Lp(a) levels

	OR	95% CI	p value
Lp(a) continuous <sup>1</sup> (per mg/dl)	1.006	1.001–1.01	0.008
Lp(a) continuous <sup>2</sup> (per mg/dl)	1.007	1.002–1.01	0.008
Lp(a) ≥30 mg/dl <sup>1</sup>	1.5	1.1–2.0	0.04
Lp(a) ≥30 mg/dl <sup>2</sup>	1.6	1.1–2.3	0.03
Lp(a) ≥30 mg/dl <sup>3</sup>	1.8	1.2–2.6	0.03

<sup>1</sup> Univariate analysis.

<sup>2</sup> Adjusted for education level and presence of hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD and smoking, and matched for age, gender and ethnicity.

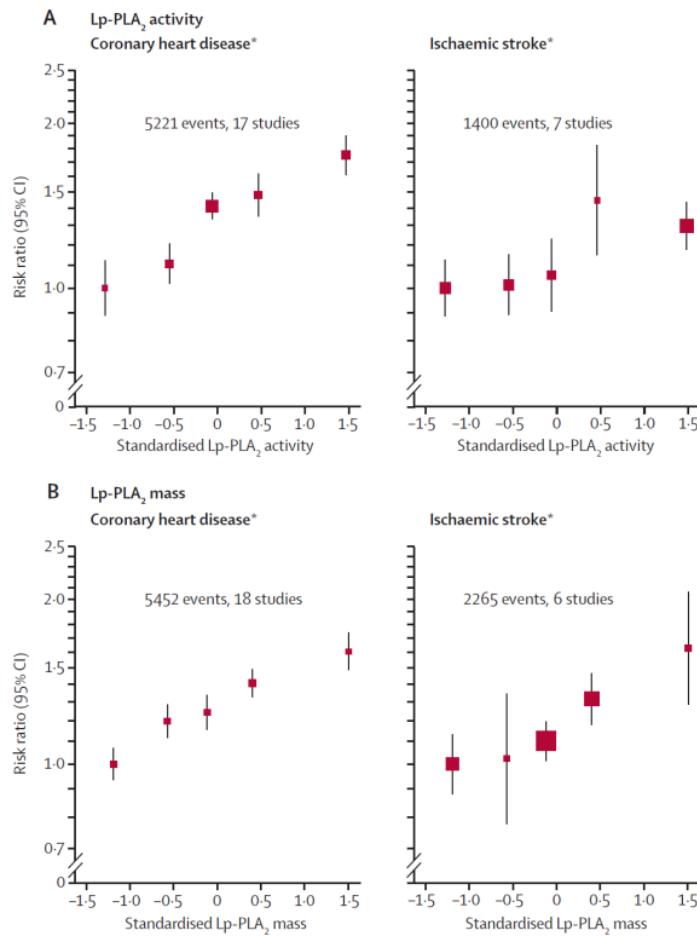
<sup>3</sup> As above but after additional adjustment for fasting lipid and lipoprotein levels.

**Table 3.** Multivariable models for IS and Lp(a) level ≥30 mg/dl stratified by gender and race/ethnicity

	Mean Lp(a) per mg/dl in cases	OR	95% CI	p value
Gender				
Women	47.4 ± 44	1.4	0.9–2.5	NS
Men	46.6 ± 39	2.3	1.3–4.0	0.01
Race/ethnicity				
Whites	31 ± 24	2.1	0.7–6.6	NS
African Americans	66.9 ± 48	2.7	1.2–6.2	0.04
Hispanics	40.8 ± 36	1.5	0.8–2.5	NS

Stratified models were adjusted for education level and presence of hypertension, diabetes mellitus, cardiac disease, waist circumference, EtOH, self-report of PAD, smoking, fasting lipid and lipoprotein levels. NS = Not significant.

# Lipoprotein-Associated Phospholipase A2

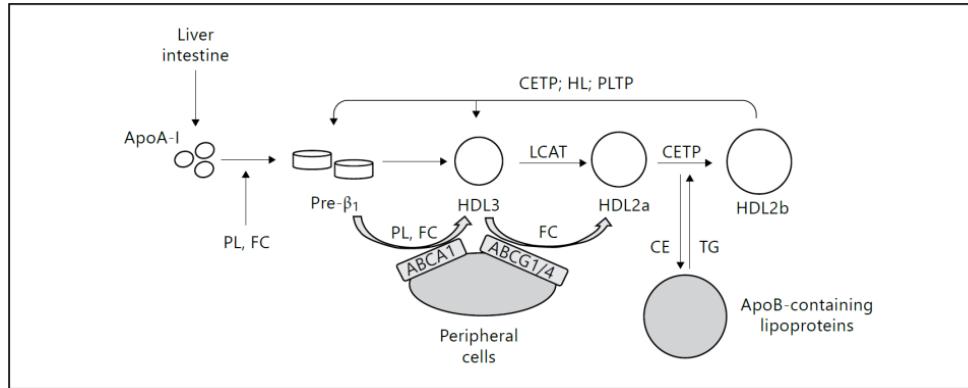


**Table 4** Multivariable analysis of factors associated with primary endpoint (ischemic stroke, MI, or death)

Variable	Hazard ratio (95% CI)	p Value
Age per 10 y	1.15 (1.03-1.28)	0.0138
Male	0.88 (0.69-1.12)	0.2963
BMI	1.03 (0.99-1.07)	0.0977
Systolic blood pressure per 20 mm Hg	1.20 (1.09-1.33)	0.0003
History of hypertension	1.23 (0.94-1.59)	0.1256
History of diabetes	1.42 (1.10-1.85)	0.0081
History of MI	0.14 (0.02-1.02)	0.0519
Lp-PLA <sub>2</sub> -A per 30 nmol/min/mL	1.07 (1.01-1.13)	0.0319

Abbreviations: BMI = body mass index; CI = confidence interval; Lp-PLA<sub>2</sub>-A = lipoprotein-associated phospholipase A<sub>2</sub> activity; MI = myocardial infarction.

# HDL Sub-fractions



**Table 2. Association of HDL2 and HDL3 Subfractions and Total HDL-C With Carotid IMT**

IMT Change per 2 SDs	$\beta$ , SE (n=988)	P Value
<b>HDL2-C</b>		
Model 1	-0.013, 0.005	0.02
Model 2	-0.017, 0.005	0.001
<b>HDL3-C</b>		
Model 1	-0.011, 0.006	0.05
Model 2	0.001, 0.006	0.81
<b>HDL-C</b>		
Model 1	-0.015, 0.006	0.01
Model 2	-0.012, 0.006	0.03

Linear regression model: model 1; adjusted for race/ethnicity, age, sex, low-density lipoprotein-cholesterol, triglycerides, and cholesterol medication use; model 2; adjusted for model 1 and body mass index, smoking, alcohol, physical activity, hypertension, diabetes mellitus, time from baseline to carotid ultrasound. HDL-C indicates high-density lipoprotein-cholesterol; and IMT, intima-media thickness.

**Table 3. Association Between the HDL-C Variables and Carotid IMT Stratified by Diabetes Mellitus Status**

IMT Change per 2 SDs	$\beta$ , SE (n=988)	P Value	Interaction P Value
<b>HDL2-C</b>			
Diabetics	-0.043, 0.014	0.003	0.07
Nondiabetics	-0.012, 0.006	0.04	...
<b>HDL3-C</b>			
Diabetics	0.009, 0.014	0.52	1.00
Nondiabetics	0.002, 0.006	0.81	...
<b>HDL-C</b>			
Diabetics	-0.029, 0.012	0.02	0.07
Nondiabetics	-0.008, 0.006	0.24	...

Linear regression model: fully adjusted for race/ethnicity, age, sex, low-density lipoprotein-cholesterol, triglycerides, and cholesterol medication use, body mass index, smoking, alcohol, physical activity, hypertension, and time from baseline to carotid ultrasound. HDL-C indicates high-density lipoprotein-cholesterol; and IMT, intima-media thickness.

Cardiology. 2013;124(2):116-25.

Stroke. 2016 Jun;47(6):1508-13.

# Summary

- Positive association between elevated cholesterol and ischemic stroke
  - Large artery atherosclerotic, small vessel subtypes
- Inverse association between cholesterol levels and intracerebral hemorrhage
- Statins reduce risk of recurrent stroke after cerebral ischemia

# Future Directions

- Novel lipid-lowering therapies
- Novel lipid biomarkers and cranio-cervical atherosclerosis
- Variation among populations
- Cognitive impairment

# Questions?