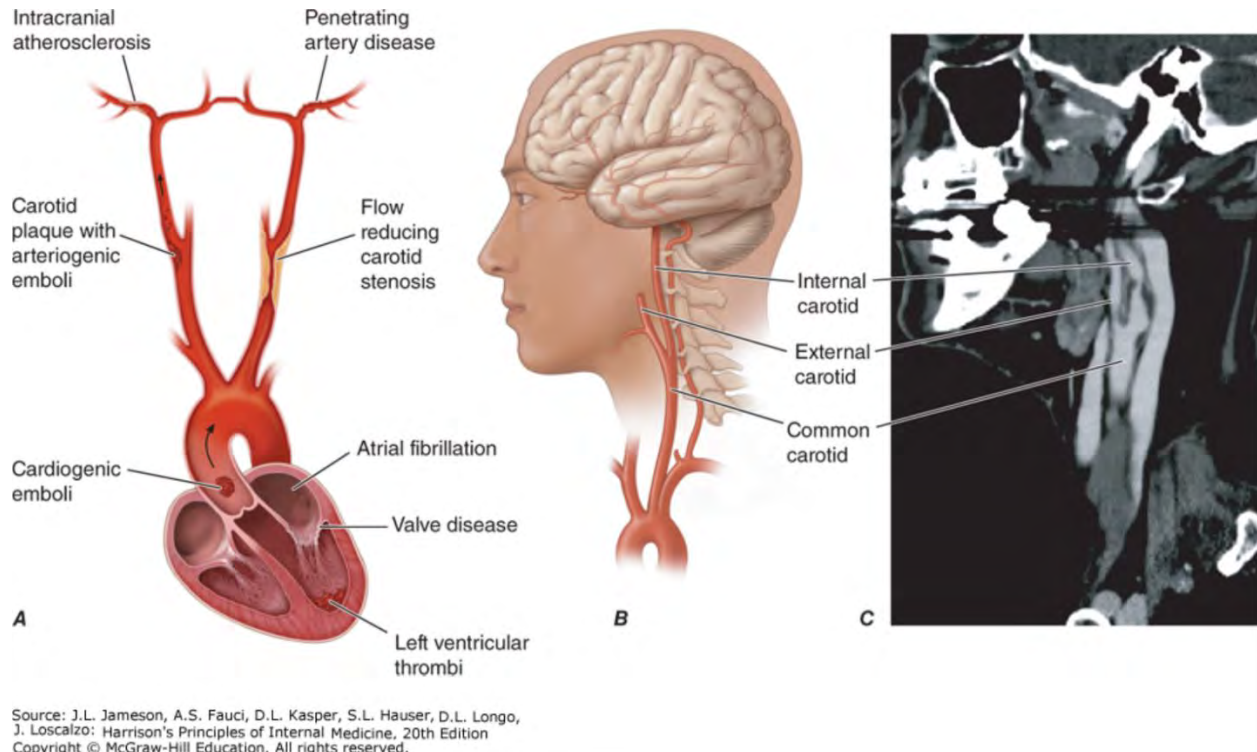


Putting the STAT in Statin: The Potential Role of Statins in Cardioembolic Stroke



Raymond G. Mattes, PharmD
Pharmacotherapy Resident
University of the Incarnate Word
Feik School of Pharmacy

Learning Objectives:

For Pharmacists:

1. Summarize the mechanism of statin drugs including its pleiotropic effects
2. Appraise the currently published literature on the use of statins for cardioembolic stroke
3. Develop a recommendation for a case involving the use of statins for cardioembolic stroke

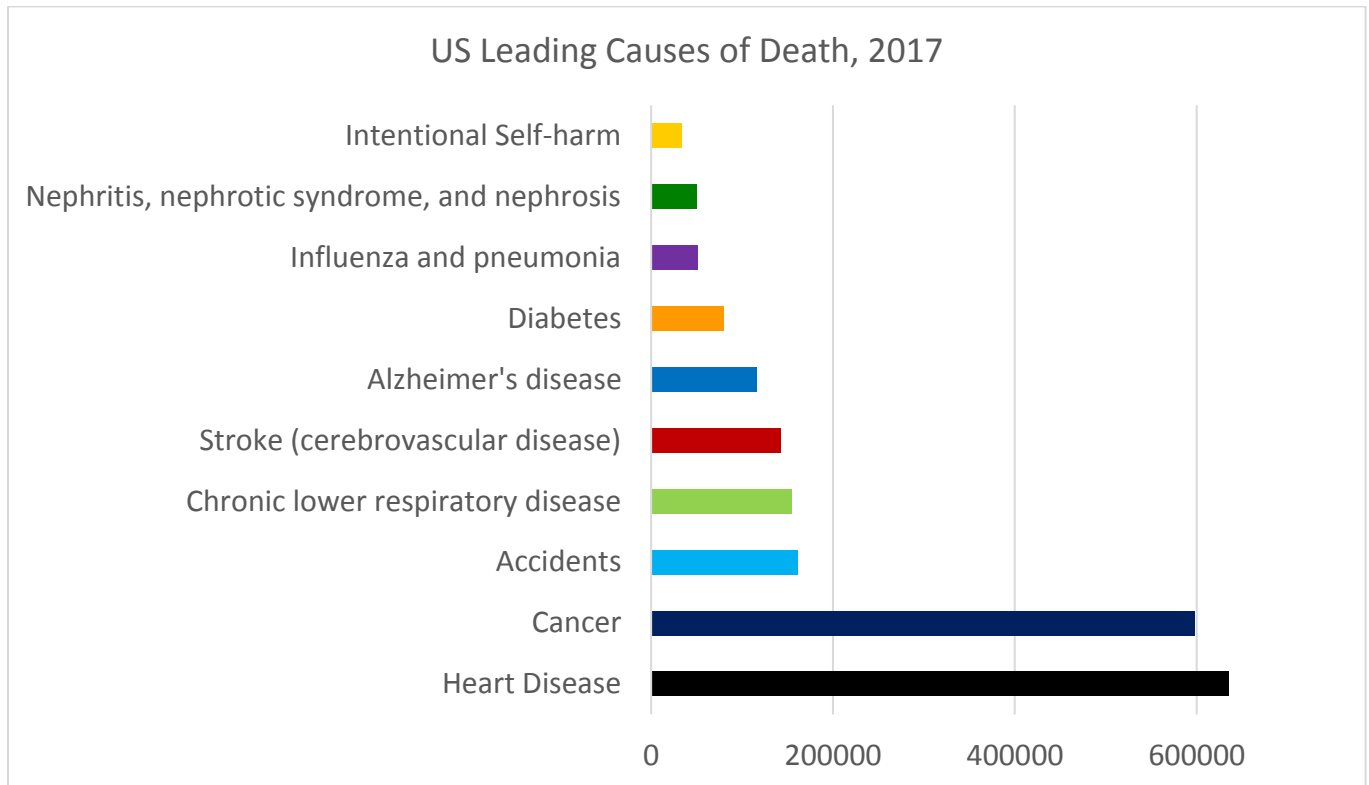
For Pharmacy Technicians:

1. State the mechanism of action of statin medications
2. Recall the definition of cardioembolic stroke
3. Describe the potential benefits of statin therapy for cardioembolic stroke

Background for Statin Treatment in Cardioembolic Stroke

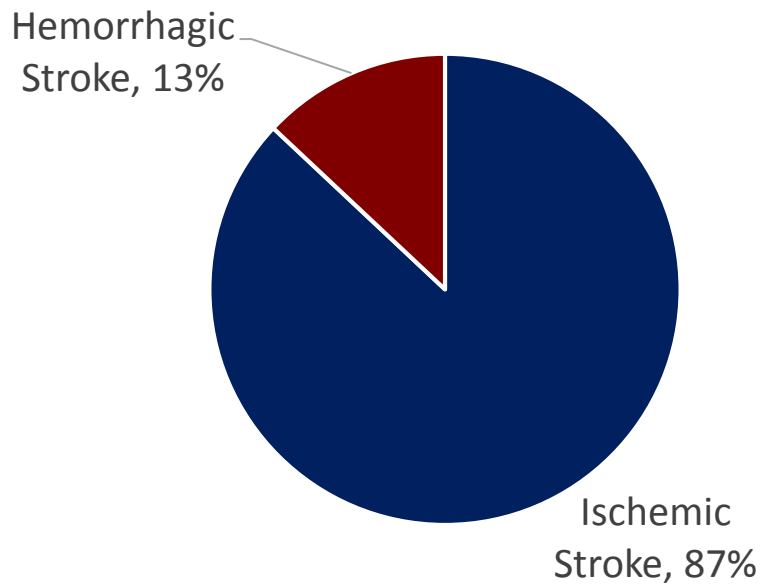
1. Epidemiology ^{1,2}

- Stroke is the 5th leading cause of death in the US
- Most common disabling disease in the US

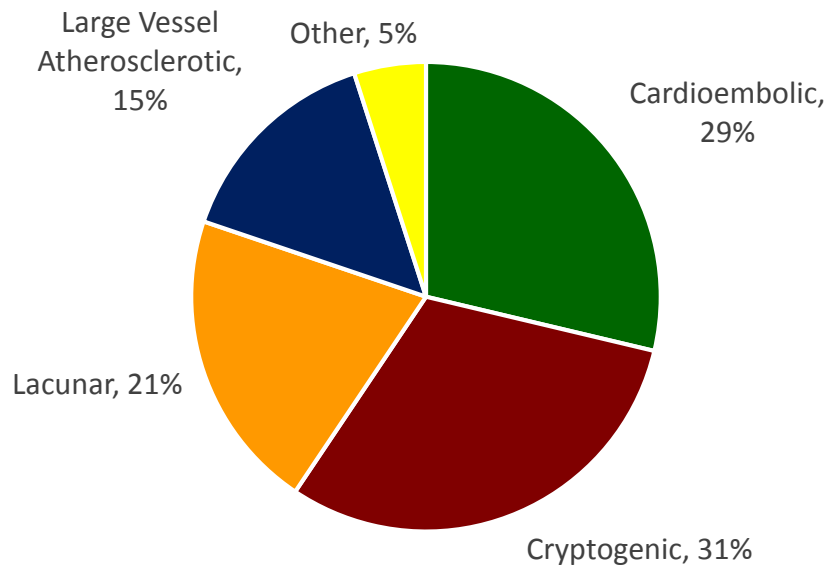


- Cardioembolic Stroke ^{3,4,5,6}
 - Highest in-hospital mortality among ischemic strokes
 - Stroke patients with Atrial Fibrillation have higher complication rates and mortality
- 20-50% of patients die within the first month post-stroke
- Anticoagulation: Prevents 70% of Cardioembolic Strokes

Epidemiology of Stroke by Subtype ^{1, 2}



Epidemiology by Subtypes of Ischemic Stroke ^{6, 7}



2. What is a stroke? ^{7,8}

Stroke/Cerebrovascular Accident (CVA)

- Disease affecting arteries leading to and within the brain that occurs when the artery becomes blocked or ruptures, resulting in brain tissue ischemia or death
- Defined as a neurological deficit which occurred with a sudden onset and persists for >24 hours or confirmed by CT or MRI

Transient Ischemic Attack (TIA)

- Similar symptoms to a stroke, however it only lasts for minutes to hours and always recovers within 24 hours
- Not considered as a stroke, but significant increases the risk of future stroke by ~3-4%
- "Mini-stroke"

Ischemic Stroke

- Ischemia resulting from occlusion of the blood flow that supplies the brain
- Most common subtype of stroke

Cardioembolic Stroke

- Caused primarily by cardiac diseases that predisposes the patient to form a thrombus within the heart wall or left heart valves which may then detach and embolize into the arterial circulation and lodge within a cerebral artery and occlude blood flow
- Most commonly caused by atrial fibrillation

Lacunar Stroke

- Subtype of ischemic stroke that occurs after blockage of small, deep blood vessels within the brain

Cryptogenic Stroke

- Subtype of Ischemic Stroke that has unknown origin

Hemorrhagic Stroke

- Ischemia resulting from rupture of blood vessels within the brain, resulting in increasing intracranial pressure and decreased blood flow
- Includes intracranial hemorrhage and subarachnoid hemorrhage

Subarachnoid Hemorrhage (SAH)

- Subtype of hemorrhagic stroke caused by rupture and bleeding between the brain and the meninges

Intracerebral Hemorrhage (ICH)

- Subtype of hemorrhagic stroke caused by rupture and bleeding within the brain

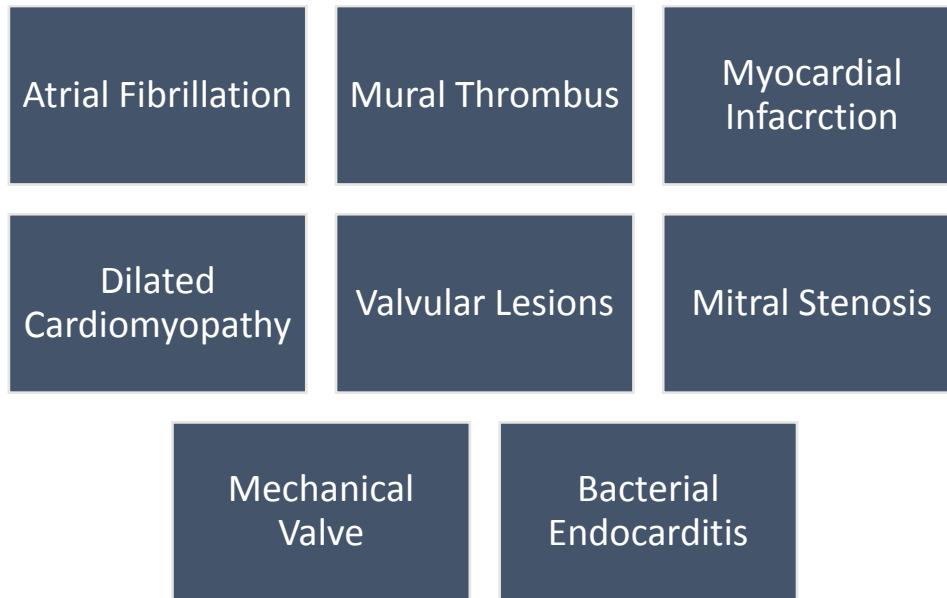
3. Pathophysiology^{5,9}

- Ischemic Stroke:
 - Occurs due to blockage in cerebral vasculature
 - Hypoxia due to interrupted supply of oxygen
 - Types of Ischemic Stroke
 1. Thrombotic Stroke
 - a. Caused by a thrombus that develops within the arteries supplying the brain; typically due to atherosclerosis
 2. Embolic Stroke
 - a. Caused by a blood clot that forms in the body, and then travels to the brain; 15% of embolic strokes are caused by atrial fibrillation
 - b. Cardioembolic stroke = thrombus forms in the heart and travels to the brain

4. Risk Factors for Cardioembolic Stroke^{5,6,10}

Atrial Fibrillation
Heart Failure
Hypertension
Age ≥65 years
Diabetes
Prior Stroke or TIA
Vascular Disease
Sex (females > males)
Dyslipidemia
Atherosclerosis
CKD or RRT
Biomarkers (CRP, IL-6 etc)

5. Causes of Cardioembolic Stroke ^{3, 5, 9}



6. Current Guideline Directed Medical Therapy of Cardioembolic Stroke Prevention

- Primary Cardioembolic Stroke Prevention ¹¹
 - Anticoagulation or antithrombotic therapy per CHADS₂ or CHA₂DS₂-VASc Score
- Secondary Cardioembolic Stroke Prevention ¹²
 - Statin for ischemic stroke or TIA of **atherosclerotic** origin and LDL \geq 100 mg/dL with or without evidence of other ASCVD
 - Anticoagulation or antithrombotic therapy per CHADS₂ or CHA₂DS₂-VASc Score
- 2018 ACC/AHA Multisociety Lipid Guidelines ¹³
 - No mention of Atrial Fibrillation and statin use

- 2018 Antithrombotic Therapy for Atrial Fibrillation Guidelines¹⁰
 - Anticoagulation therapy per CHA₂DS₂-VASc

CHA ₂ DS ₂ -VASc Scoring System	
C-CHF	1
H-HTN	1
A ₂ - Age ≥75 years	2
D- Diabetes	1
S ₂ - Prior Stroke/TIA	2
V- Vascular Disease (prior MI, PAD, aortic plaque)	1
A- Age 65-74 years	1
S- Sex Category, female	1

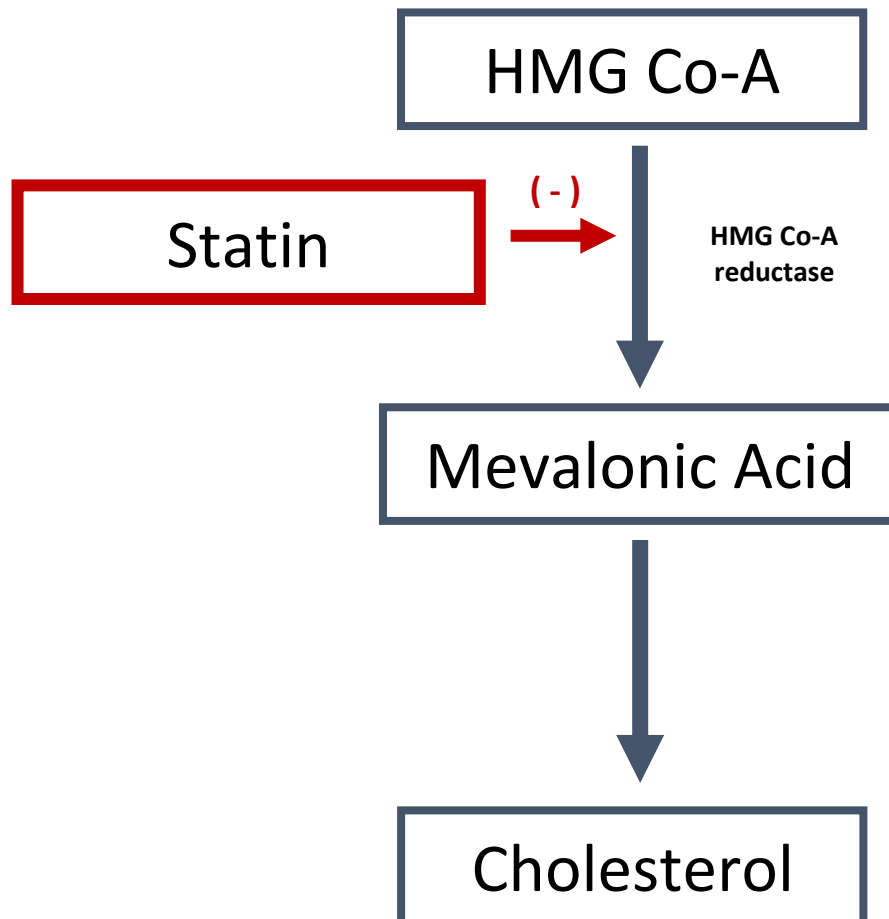
Score 0 → No anticoagulation

Score 1 (not including sex) → Anticoagulation recommended

Score 2+ → Anticoagulation recommended

7. Statin Medications¹⁴

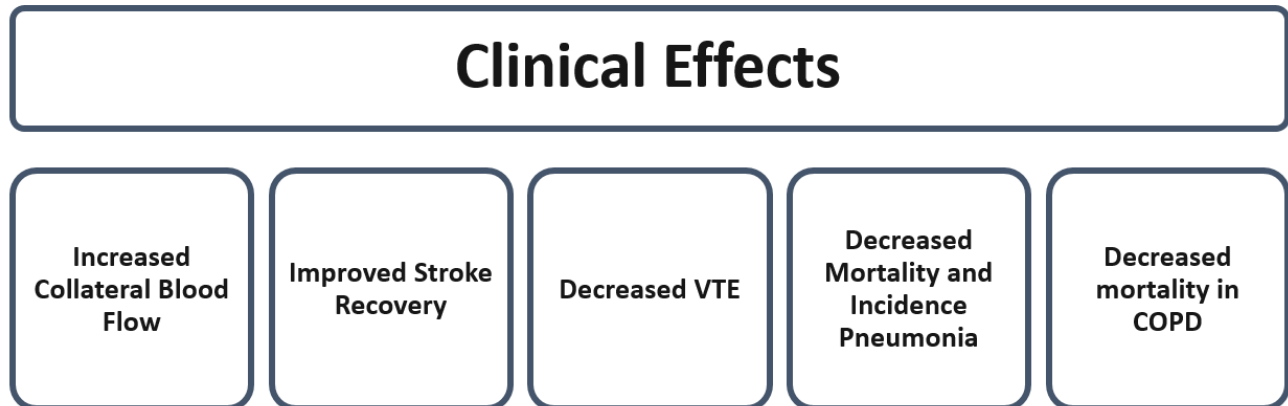
- Primary mechanism (HMG-CoA Reductase Inhibition)
 - ↓ LDL-C, TC, TG, ↑HDL-C



8. Pleiotropic Effects ^{15, 16, 17 18}

Endothelial Cells	↑eNOS expression and activity
	↓ Plasminogen activator 1 expression and ↑ tissue type plasminogen activator expression
	↓ Endothelin 1 synthesis and expression
	↓ ROS
	↑ Peroxisome proliferator activated receptor α and γ expression
	↓ Proinflammatory cytokines expression (IL-1 β , IL-6, and cyclooxygenase-2)
	↓ CD40 expression
Vascular smooth muscle cells	↓ Migration and proliferation
	↓ ROS
	↓ NADPH oxidase activity
	↓ AT1 receptor expression
	↓ Platelet-derived growth factor
Myocardium	↓ NADPH oxidase activity
	↓ ROS
	↓ Left ventricular fibrosis and hypertrophy
	↑ Nitric Oxide
	↓ Apoptosis
Platelets	↓ Platelet reactivity
	↓ Thromboxane A2 biosynthesis
Monocyte/Macrophages	↓ Macrophage growth
	↓ MMP expression and secretion
	↓ tissue factor expression and activity
	↓ Proinflammatory cytokines expression (IL-1 β , IL-6, IL-8, and TNF- α)
	↓ Monocyte chemoattractant protein-1 secretion
Vascular Inflammation	↓ CRP level
	↓ Leukocyte-endothelial cell adhesion
	↓ T-cell activation
	↓ Nuclear factor κ B activation
	↑ Mobilization of stem cells

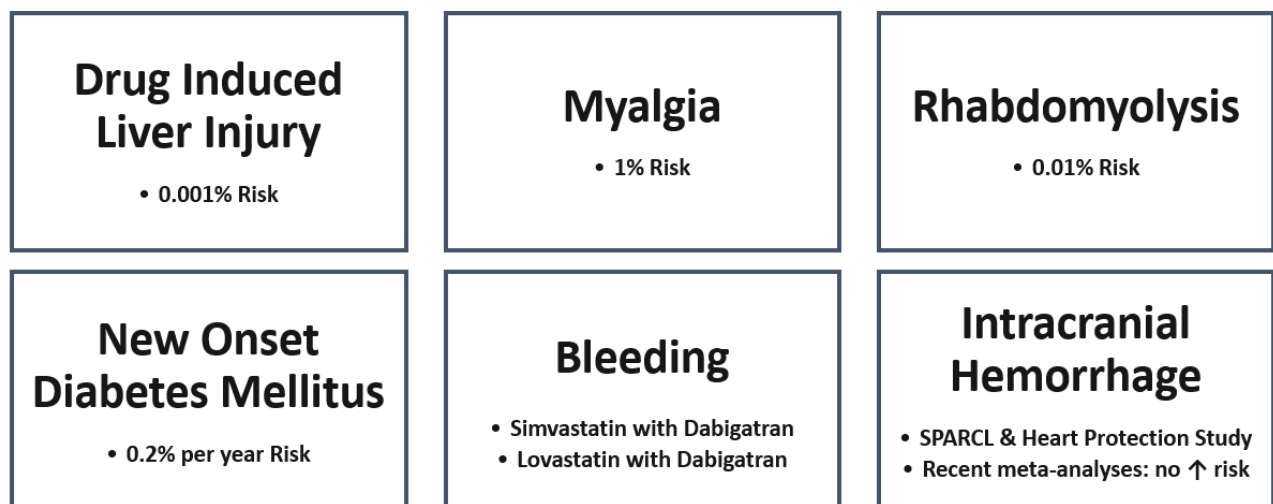
9. Clinical Outcomes Attributed to Statin's Pleiotropic Effects ^{15, 16, 17, 18}



10. Statin Names and Intensities ¹³

Statin Medications and their Relative Intensities		
Low Intensity (Lowers LDL by <30%)	Moderate Intensity (Lowers LDL by 30-50%)	High Intensity (Lowers LDL by ≥50%)
Simvastatin 10 mg Fluvastatin 20-40 mg Lovastatin 20 mg Pitavastatin 1 mg Pravastatin 10-20 mg	Simvastatin 20-40 mg Fluvastatin 80 mg Lovastatin 40 mg Pitavastatin 2-4 mg Pravastatin 40-80 mg Rouvastatin 5-10 mg Atorvastatin 10-20 mg	Rosuvastatin 20-40 mg Atorvastatin 40-80 mg

11. Adverse Effects of Statins ^{19, 20, 21, 22}



12. Clinical Controversy:

- Statin therapy has proven benefit for atherosclerotic stroke recurrence ²³
- What is the role of statin therapy for cardioembolic stroke?

Study	Design	Intervention	Results
Ko (2017) ²⁴	Retrospective Chart Review	30 day Follow Up Statin (n = 400) vs No Statin (n = 630)	↓ Stroke Severity
Choi (2014) ²⁵		22 month Follow Up Statin (n = 240) vs No statin (n = 295) Divided by potency	↓ Mortality No difference for stroke recurrence
Wu (2017) ²⁶		2.4 year Follow Up Statin (n = 1546) vs No Statin (n = 3092) Patients matched	↓ Mortality No difference for Stroke Recurrence, MI, MACE, Ischemic Stroke, and Hemorrhagic Stroke
Flint (2017) ²⁷		3 year Follow Up Patients assessed adherence by PDC PDC85+ (n = 1138) vs PDC<85 (n = 308)	↓ Stroke Recurrence

Literature Review for the Use of Statins in Cardioembolic Stroke

Table 2. Ko D, et al. Influence of Statin Therapy at Time of Stroke Onset on Functional Outcome among Patients with Atrial Fibrillation. *Int J Cardiol.* 2017 January 15; 227:808-812. ²⁴

Objective	Determine the functional outcome of statin use at time of stroke onset																																																																																															
Methods																																																																																																
Study design	Multicentered Retrospective Chart Review including patients from 2006-2010 with 30 day follow-up																																																																																															
Inclusion criteria	Atrial Fibrillation Related Stroke verified via CT or MRI and confirmed by neurologist Atrial Fibrillation confirmed via electrocardiogram at time of admission, during the index hospitalization, or within the prior 6 months																																																																																															
Exclusion criteria	Patients with mechanical heart valves																																																																																															
Intervention	Inclusion into statin vs non-statin group were determined based on whether or not the patient was taking a statin medication at the time of their stroke																																																																																															
Outcomes	Stroke Severity using modified Rankin Score (mRS) Severe stroke was defined as mRS≥4 or resulted in death after discharge but before 30 days																																																																																															
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	Factors Associated with Stroke Severity	
	Characteristic	Adjusted Odds Ratio (95% CI)
	Female Sex	1.36 (1.01-1.83)
	White Race	0.66 (0.47-0.92)
	Age, per year	1.04 (1.02-1.05)
	Diabetes Mellitus	1.41 (1.03-1.92)
	Prior Ischemic Stroke	1.51 (1.07-2.11)
	Prior DVT or PE	1.95 (1.13-3.34)
	Dementia	2.38 (1.41-4.00)
	Statin Use	0.68 (0.50-0.92)
	Warfarin Use	0.92 (0.65-1.30)
Author's Conclusions	Pre-stroke statin use among patient with ischemic stroke in AF is associated with a 32% reduction in the risk of the stroke being severe or fatal at 30 days	
Critique	<p>Strengths:</p> <ul style="list-style-type: none"> • Definition of stroke follows AHA/ASA definition • Ischemic stroke related to AF and confirmed by hypothesis blinded neurologist • Atrial Fibrillation confirmed by electrocardiograph • Severity of stroke measured by mRS • Multivariable logistic analysis adjusted for factors associated with statin use and severity <p>Weaknesses:</p> <ul style="list-style-type: none"> • INR subtherapeutic overall, and not reported between statin groups • Differences in study groups • Specific statin medication and doses used not reported • Duration of statin treatment not reported 	
Take Away Summary	<ul style="list-style-type: none"> • Patients taking a statin at the time of their stroke seem to have more risk factors for stroke and a higher CHA₂DS₂-VASC score with a lower stroke severity compared to patients not taking statins • It is unclear which statins may benefit patients stroke severity and at what doses as they are not reported in this study 	

Table 3. Choi JY, Seo WK, Kang SH et al. Statins Improve Survival in Patients With Cardioembolic Stroke. Stroke. 2014; 45:1849-1852. ²⁵

Objective	Investigate the potential benefits of statin therapy on mortality and stroke recurrence after cardioembolic stroke
Methods	
Study design	Retrospective Observational Multicenter Study including patients from January 2008-December 2012 with a 22 month follow-up
Inclusion criteria	Patients registered in the Korean University Stroke registry (KUSR)
Exclusion criteria	Patients with a previous stroke
Intervention	Inclusion in a group was determined based on stroke subtype (Cardioembolic vs non-cardioembolic) and on whether the patient was taking a statin medication and statin intensity
Outcomes	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Time to mortality by any cause • Time to recurrence of stroke

Results

Baseline	Baseline Characteristics of the Subjects according to statin therapy (Cardioembolic Stroke patients, n=535)									
	Characteristic	Non-Statins n=295	Low-potency statin n=125	High-potency statin* n=115	P value					
	Age	68	71	65	<0.001					
	Sex, male	163 (55.3)	60 (48.0)	72 (62.6)	0.075					
	Hypertension	199 (67.5)	92 (73.6)	79 (68.7)	0.457					
	Diabetes Mellitus	56 (19.0)	34 (27.2)	33 (28.7)	0.049					
	Smoking	76 (25.8)	28 (22.4)	39 (33.9)	0.113					
	CAD	30 (10.2)	25 (20.0)	18 (15.7)	0.021					
	CHF	32 (10.8)	15 (12.0)	8 (7.0)	0.390					
	Cerebral Atherosclerosis	118 (40.0)	55 (44.0)	36 (31.3)	0.117					
	PVD	1 (0.3)	2 (1.6)	2 (1.7)	0.282					
	CKD	12 (4.1)	1 (0.8)	3 (2.6)	0.192					
	WBC, 10 ³ /μL	8.36	7.89	8.32	0.154					
	Total Cholesterol, mg/dL	155.70	178.55	181.18	<0.001					
	HDL Cholesterol, mg/dL	44.80	45.95	43.97	0.414					
	LDL Cholesterol, mg/dL	87.51	106.83	112.34	<0.001					
	C-reactive protein, mg/dL	17.9	4.39	5.47	<0.001					
	NIHSS at admission	7.55	6.04	5.51	0.020					
	IV t-PA thrombolysis	54 (18.3)	23 (18.4)	13 (11.3)	0.100					
	Intra-arterial thrombolysis	17 (5.8)	3 (2.4)	2 (1.7)	0.203					
	Anticoagulation	139 (47.1)	76 (60.8)	60 (59.2)	0.101					
	*atorvastatin 40mg-80mg, rosuvastatin 10mg-20mg, simvastatin/ezetimibe 20/10mg-40/10mg									
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Outcomes	Cox Proportional Hazard Model for Predicting Mortality									
	Variable	Univariable Analysis		Multivariable Analysis						
		HR (95% CI)	P value	HR (95% CI)	P value					
	Age	1.065 (1.033-1.098)	<0.001	1.050 (1.018-1.084)	0.002					
	Hypertension	2.811 (1.184-6.673)	0.019							
	Diabetes Mellitus	1.940 (1.032-3.647)	0.040	2.019 (1.054-3.866)	0.034					
	CHF	2.916 (1.433-5.934)	0.003	3.026 (1.398-6.551)	0.005					
	WBC, 10 ³ /μL	1.196 (1.117-1.280)	<0.001	1.151 (1.062-1.246)	<0.001					
	Total Cholesterol, mg/dL	0.988 (0.980-0.996)	0.005							
	HDL cholesterol, mg/dL	0.964 (0.940-0.989)	0.005							
	C-reactive protein, mg/dL	1.015 (1.011-1.020)	<0.001	1.008 (1.003-1.014)	0.004					
Fibrinogen, mg/dL	1.003 (1.002-1.005)	<0.001								

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Author's Conclusions	<ul style="list-style-type: none"> Statin therapy was associated with reduced mortality Benefit of statin therapy was similar in CE stroke and Non-CE stroke No benefit for stroke recurrence in CE and Non-CE stroke 																																																	
Critique	<p>Strengths:</p> <ul style="list-style-type: none"> All patients were treated per similar hospital protocol Treatment protocol followed guideline recommended medical therapy Large Population Size Inclusion within statin groups well defined within study protocol Compared subgroups of CE and Non-CE stroke Adjusted multivariable analyses <p>Weaknesses:</p> <ul style="list-style-type: none"> Low potency statin medications not defined High potency statins include moderate intensity statins and ezetimibe Different population demographic CHA₂DS₂-VASc Score not reported for patient groups INR not reported between groups Anticoagulation monitoring unlikely to be uniform between patients 																																																	
Take Away Summary	<ul style="list-style-type: none"> Both low-potency and high-potency statin therapy is associated with lower mortality from CE and Non-CE stroke Statins did not have a significant effect on stroke recurrence for CE stroke and Non-CE stroke 																																																	

Table 4. Wu YL, Saver JL, Chen PC, et al. Effect of Statin use on Clinical Outcomes in Ischemic Stroke Patients with Atrial Fibrillation ²⁶

Objective	Determine whether statin therapy can influence the prognosis in recent ischemic stroke patients with atrial fibrillation			
Methods				
Study design	Retrospective cohort study Data from the Taiwan National Health Insurance Research Database from 2001-2012			
Inclusion criteria	<ul style="list-style-type: none"> • Patients >=18 yo • Admitted with primary diagnosis of ischemic stroke for the first time via ICD-9 • Atrial Fibrillation diagnosed prior to stroke, or in list of diagnoses at time of admission 			
Exclusion criteria	<ul style="list-style-type: none"> • Patient with a recurrent stroke ≤ 90 days after the index stroke • Patients on hemodialysis • Follow up ≤ 90 days • Patients receiving some statin therapy but less than 30 days within 90 days of the stroke 			
Intervention	Inclusion within a group based on statin therapy* or no statin therapy Patients treated with statins were matched with non-statin controls on a 1:2 ratio *Defined as receiving a statin for at least 30 days within 90 days post-stroke			
Outcomes	Primary Outcome <ul style="list-style-type: none"> • First event of recurrent stroke (combined endpoint of ischemic and hemorrhagic stroke) Secondary Outcomes <ul style="list-style-type: none"> • In-hospital death • Hemorrhagic Stroke • Ischemic Stroke • Myocardial Infarction • Major Adverse Cardiovascular Events 			
Results				
Baseline	Baseline Characteristics of Included Patients			
	Variable	Statin Group n=1546	Comparison Group n=3092	P-Value
	Male, n, %	759 (49.1)	1528 (49.1)	1.0000
	Age, y, mean	75.6 (7.4)	75.6 (7.4)	0.9487
	HTN, n, %	1493 (96.6)	2986 (96.6)	1.0000
	DM, n, %	518 (33.5)	1036 (33.5)	1.0000
	CAD, n, %	1014 (65.6)	2028 (65.6)	1.0000
	HF, n, %	38 (2.5)	76 (2.5)	1.0000
	Anticoagulant (>=30 days use within 90 days after index stroke)	613 (39.7)	1226 (39.7)	1.0000
	Severity, eNIHSS			1.0000
	0-5	786 (50.8)	1572 (50.8)	
	6-10	219 (14.2)	438 (14.2)	
	11-15	115 (7.4)	230 (7.4)	
	>15	426 (27.6)	852 (27.6)	
Statins and doses				
Atorvastatin	738			
Dose, mg	13.0 +/-9.8			
Fluvastatin	143	N/A	N/A	
Dose, mg	70.7 +/-33.9			
Lovastatin	15			
Dose, mg	17.2+/-8.8			

		Pravastatin Dose, mg	65 24.8+/-15.9		
		Rosuvastatin Dose, mg	350 8.6+/-3.7		
		Simvastatin Dose, mg	152 18.1+/-11.5		
Outcomes	Cox Proportional Hazard Models for Primary and Secondary Outcomes				
	Endpoints	Statin Group n=1546	Comparison Group n=3092	HR (95% CI)	P
	Any Stroke, n, %	324 (21.0)	609 (19,7)	1.01 (0.88-1.15)	0.92
	Ischemic Stroke	292 (18.9)	535 (17.3)	1.04 (0.90-1.20)	0.63
	Intracerebral Hemorrhage	31 (2.0)	73 (2.4)	0.79 (0.52-1.21)	0.27
	Fatal Stroke	15 (1.0)	23 (0.7)	1.21 (0.63-2.32)	0.57
	Myocardial Infarction, n, %	38 (2.5)	58 (1.9)	1.23 (0.81-1.85)	0.33
	MACE, n, %	355 (23.0)	658 (21.3)	1.03 (0.90-1.17)	0.68
In-hospital death, n, %	144 (9.3)	363 (11.7)	0.74 (0.61-0.89)	0.002	
Cardiovascular Death	27 (1.8)	53 (1.7)	0.95 (0.60-1.51)	0.83	
Noncardiovascular Death	117 (7.6)	310 (10.0)	0.70 (0.56-0.86)	0.001	
Author's Conclusions	Statin therapy within the acute to subacute phase is not associated with reduced recurrence of stroke Statin therapy is associated with a lower in-hospital mortality risk, driven by noncardiovascular causes				
Critique	<p>Strengths</p> <ul style="list-style-type: none"> Specified time period of statin therapy for inclusion Baseline characteristics similar due to matching Doses and statins used are reported Long follow-up of 2.4 years Large population size <p>Weaknesses</p> <ul style="list-style-type: none"> Statin may have been discontinued after 30 days Smoking status, lipid panel, and alcohol use not assessed and are risks for stroke Anticoagulation monitoring unlikely to be uniform between patients Different population demographic 				
Take Away Summary	<ul style="list-style-type: none"> Statin had no effect on stroke recurrence, MI, MACE, Intracerebral Hemorrhage, and Ischemic Stroke Statin ↓ in-hospital mortality driven by noncardiovascular death 				

Table 5. Flint AC, Conell C, Ren X, et al. Statin Adherence is Associated with Reduced Recurrent Stroke Risk in Patients With or Without Atrial Fibrillation ²⁷	
Objective	Determine whether statins reduce the risk of recurrent ischemic stroke caused by atrial fibrillation
Methods	
Study design	Retrospective Observational Multicenter Study with a 3 year follow-up Data captured from 2008-2012 from Kaiser Permanente Northern California (KPNC) EMR
Inclusion criteria	<ul style="list-style-type: none"> Age ≥ 18 years Membership to (KPNC) from 2008-2012 Admitted to KPNC hospital with ischemic stroke and discharged with statin prescription (either continued from previous outpatient prescription or initiated at the time of hospitalization) Filled statin prescription within 90 days of discharge

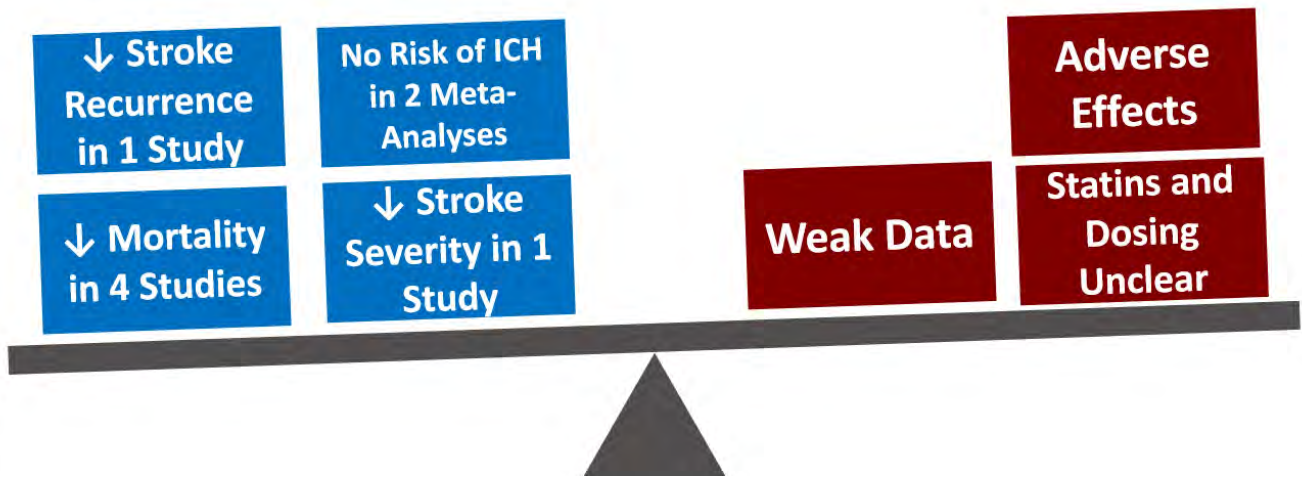
Exclusion criteria	<ul style="list-style-type: none"> Patients discharged to skilled nursing facility or hospice 																																																																																					
Intervention	Retrospective data analysis from 2008-2012 Patients assessed on statin adherence by percent days covered																																																																																					
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Hispanic	256 (13.8)	491 (11.5)	747 (12.2)	0.01																																																																																		
Asian	241 (13.0)	516 (12.1)	757 (12.4)	0.33																																																																																		
Other/Unknown	125 (6.8)	331 (7.8)	456 (7.5)	0.17																																																																																		
Outcomes	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="3" style="text-align: center;">Adjusted Cox Survival Model for 3-year survival free of ischemic stroke</th> </tr> <tr> <th style="text-align: center;">Subgroup</th> <th style="text-align: center;">HR, 95% CI</th> <th style="text-align: center;">P-value</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Atrial Fibrillation N=1446</td> <td style="text-align: center;">0.59 (0.43-0.81)</td> <td style="text-align: center;">0.001</td> </tr> <tr> <td style="text-align: center;">No Atrial Fibrillation N=4669</td> <td style="text-align: center;">0.78 (0.63-0.97)</td> <td style="text-align: center;">0.023</td> </tr> <tr> <td style="text-align: center;">Atrial Fibrillation (controlled for time in therapeutic range) N=1010</td> <td style="text-align: center;">0.61 (0.41-0.90)</td> <td style="text-align: center;">0.012</td> </tr> </tbody> </table> <ul style="list-style-type: none"> The risk of recurrent stroke decreases nonlinearly with increasing adherence Risk of recurrent stroke is high at low levels of statin adherence, irrespective of AFib status 	Adjusted Cox Survival Model for 3-year survival free of ischemic stroke			Subgroup	HR, 95% CI	P-value	Atrial Fibrillation N=1446	0.59 (0.43-0.81)	0.001	No Atrial Fibrillation N=4669	0.78 (0.63-0.97)	0.023	Atrial Fibrillation (controlled for time in therapeutic range) N=1010	0.61 (0.41-0.90)	0.012																																																																						
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Critique	<p>Strengths</p> <ul style="list-style-type: none"> Large patient population Conducted with US population demographic Long follow up time of 3 years Adherence to statin assessed by PDC and validated through LDL measures Outcome controlled for time in therapeutic range for anticoagulated patients <p>Weaknesses</p> <ul style="list-style-type: none"> Adherence assessed by percentage days covered (PDC) is not a perfect measure of adherence Adherence unusually high within cohort 																																																																																					

	<ul style="list-style-type: none"> • Specific statins and potencies used not reported
Take Away Summary	<ul style="list-style-type: none"> • Statin adherence is associated with reduced risk of recurrent stroke for both patients with AFib and without AFib and even when controlled for time in therapeutic range for patients on warfarin

Other Studies:

Study	Methods	Results
Kumagai ²⁸ (2017)	Sub-Analysis of J-RHYTHM Trial Warfarin (n = 1605) vs Warfarin + Statin (n = 4799)	<ul style="list-style-type: none"> ↓ All-cause mortality ↓ thromboembolism in DM patients No effect on Major Hemorrhage No effect on Cardiovascular Mortality
Ntaios ²⁹ (2014)	Retrospective Observational Up to 5 year Follow Up Statin (n = 102) vs Non-statin (n = 302) Post Cardioembolic Stroke	<ul style="list-style-type: none"> ↓ Mortality ↓ Composite Cardiovascular Endpoint No effect on Stroke Recurrence

Final Recommendation:



Consider the use of statin as part of the risk discussion with the patient if they do not meet criteria for statin due to LDL, ASCVD, or Diabetes.

If patient and provider decision is to initiate statin therapy, use one with greater evidence:



Resources for Pharmacists:

- Kamel H, Healey JS. Cardioembolic Stroke. *Circ Res.* 2017;120(3):514-526.
- Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. *Circ Res.* 2017;120:229-243.
- Lip GYH, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guidelines and Expert Panel Report. *Chest.* 2018 Nov;154 (5): 1121-1201

References:

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e229-e445.
2. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics*. 2011;8(3):319-29.
3. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev*. 2010;6(3):150-61.
4. Henninger N, Goddeau RP Jr, et al. Atrial Fibrillation Is Associated With a Worse 90-Day Outcome Than Other Cardioembolic Stroke Subtypes. *Stroke*. 2016 Jun;47(6):1486-92.
5. Kamel H, Healey JS. Cardioembolic Stroke. *Circ Res*. 2017;120(3):514-526.
6. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, Welch SJ, Gutnikov SA, Mehta Z, Rothwell PM; Oxford Vascular Study. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. *Circulation*. 2014;130:1236–1244. doi: 10.1161/CIRCULATIONAHA.114.010942.
7. Adams Jr HP, Bendixen BH, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35-41
8. Sacco RL, et al. An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064-2089.
9. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. *Pathophysiology*. 17 (2010) 197–218
10. Lip GYH, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guidelines and Expert Panel Report. *Chest*. 2018 Nov;154 (5): 1121-1201.
11. Meschia JF, Bushnell C, Boden-Abala B, et al. Guidelines for the Primary Prevention of Stroke- A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3754–3832.
12. Kernan WN, et al. Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160-2236.
13. 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;Nov 10:[Epub ahead of print].
14. Stancu C, Sima A. Statins: mechanism of action and effects. *J Cell Mol Med*. 2001 Oct-Dec;5(4):378-87.
15. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol*. 2005;45:89-118.
16. Kavalipati N, Shah J, Ramakrishan A, Vasawala H. Pleiotropic effects of statins. *Indian J Endocrinol Metab*. 2015;19(5):554-62.
17. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol*. 2005;45:89-118.
18. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. *Circ Res*. 2017;120:229-243.
19. Antonious T, MacDonald EM, et al. Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation. *CMAJ*. 2017; 189:E4-10.
20. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
21. Newman CB, Preiss D, Tobert JA, et al. Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2018;38:e00-e00.
22. McKinney JS, Kostis WJ. Statin Therapy and the Risk of Intracerebral Hemorrhage: A Meta-Analysis of 31 Randomized Controlled Trials. *Stroke*. 2012;43:2149-2156.
23. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
24. D. Ko et al. Influence of statin therapy at time of stroke onset on functional outcome among patients with atrial fibrillation. *International Journal of Cardiology*. 227 (2017) 808–812.
25. Choi JY, et al. Statins Improve Survival in Patients with Cardioembolic Stroke. *Stroke*. 2014; 45: 1849-1852.

26. Wu et al. Effect of statin use on clinical outcomes in ischemic stroke patients with atrial fibrillation. *Medicine* (2017) 96:5
27. Flint AC, et al. Statin Adherence Is Associated With Reduced Recurrent Stroke Risk in Patients With or Without Atrial Fibrillation. *Stroke*. 2017;48:1788-1794.
28. Kumagai N, et al. Effect of Addition of a Statin to Warfarin on Thromboembolic Events in Japanese Patients With Nonvalvular Atrial Fibrillation and Diabetes Mellitus. *Am J Cardiol* 2017; 120:230-235.
29. Ntaios G, et al. Statin treatment is Associated with Improved Prognosis in Patients with AF-related Stroke. *International Journal of Cardiology*. 177 (2014); 129-133.
30. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2007:CD006186.
31. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology*. 2006; 66:641–646.
32. Emberson J, Lees KR, Lyden P, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5.